POPULATION HEALTH AND INFECTIOUS DISEASE

NOTES

PRE-SUMMARIZED
READY-TO-STUDY
HIGH-YIELD NOTES

FOR THE TIME-POOR
MEDICAL, PRE-MED,
USMLE OR PA STUDENT

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Table Of Contents:

What's included: Ready-to-study summaries of population health and infectious diseases presented in succinct, intuitive and richly illustrated downloadable PDF documents. Once downloaded, you may choose to either print and bind them, or make annotations digitally on your iPad or tablet PC.

Free Bonus: 'Community Health' and 'Infectious Diseases' chapters of Toronto Notes for reference and further detailed reading.

File List:

Chronic Disease & Risk Factors

Australia's Health:

- **Trends:**
  - **Living Longer:**
    - Men – 78yrs
    - Women – 83yrs
  - **Declining:**
    - ↓CVD Death-Rates
    - ↓Cancer Death-Rates
    - ↓Smoking Rates
  - **Increasing:**
    - ↑Diabetes Prevalence Doubled (Over Last 20yrs)
    - ↑Overweight & Obesity
- **Major Causes of Mortality:**
  - Injury & Poisoning (1-45yrs)
  - Cancer (45-84yrs)
- **Major Causes of Morbidity:**
  - Mental Illnesses (Depression/Anxiety/Sleep-Disorders)

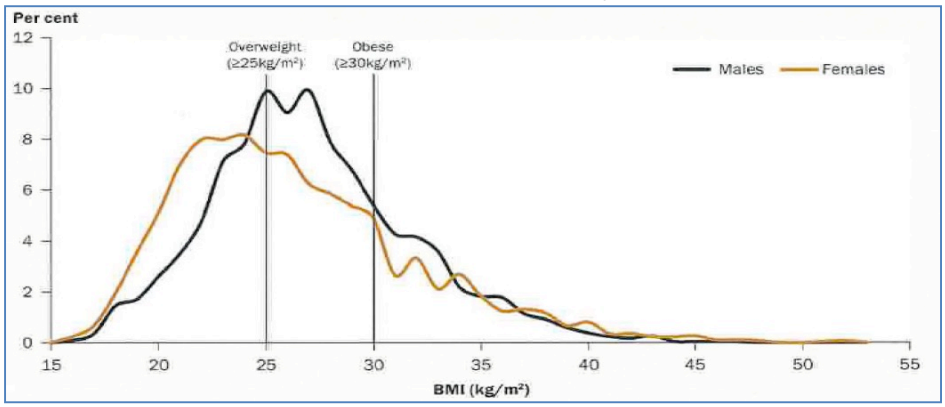
Chronic Disease:

- **Definition:**
  - **A Disease with One/More of the Following Characteristics:**
    - It is Permanent (Ie. Incurable) and Leaves Residual Disability (Morbidity).
    - Caused by Non-Reversible Pathological Alteration
    - Requires long-term Observation/Management /Care.
- **Burden of Chronic Disease:**
  - **Australia's Biggest Contributors to DALY:**
    - Cardiovascular Disease
    - Anxiety/Depression
    - Diabetes
    - Chronic Kidney Disease
- **Causes of Chronic Disease:**
  - **Patients Presenting to Doctors:**
    - ≈20% are Smoking (Decreasing)
    - ≈55% are Overweight/Obese (Increasing)
    - ≈65% Do Less than Recommended Levels of Exercise (30mins x 5days/week)
    - ≈25% Drink at Risky Levels
  - **Risk Factors:**
    - **Things to Remember:**
      - Risk Factors are often Associated with Many Diseases
      - Risk Factors shouldn't be considered in Isolation.
        - Risk Factors Interact → Multiplies Risk.
      - Most Risk Factors are Completely Avoidable.

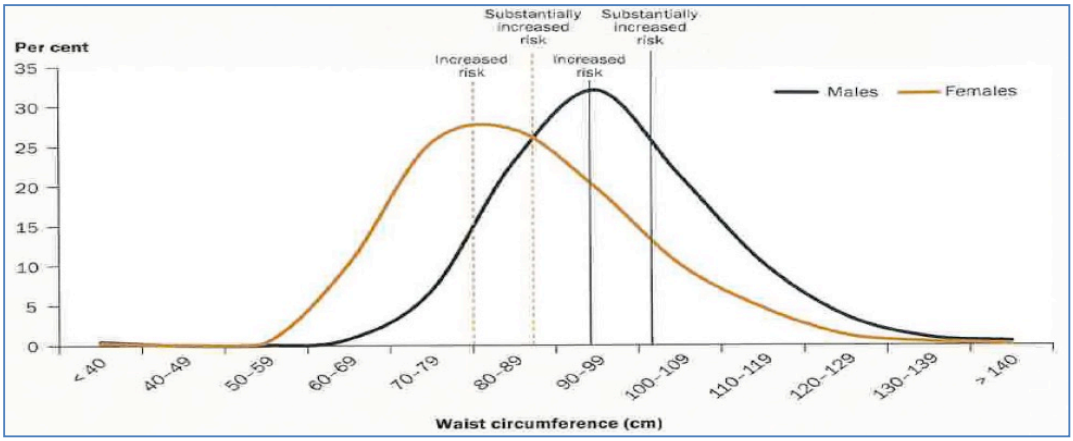
Table 2.1: Relationships among cardiovascular disease, Type 2 diabetes and chronic kidney disease and risk factors

Risk factor	Cardiovascular disease	Type 2 diabetes	Chronic kidney disease
Overweight and obesity	✘	✘	✘
Physical inactivity	✘	✘	✘
Poor diet	✘	✘	✘
Tobacco smoking	✘	✘	✘
Excessive alcohol	✘		
High blood pressure	✘		✘
High blood cholesterol	✘	✘	

- **Risk Factors:**
  - **Overweight & Obesity:**
    - **Trend:**
      - ≈55% are Overweight/Obese
      - Rates are Increasing
    - **BMI:**
      - **Calculation:**
        - Kg/Height in m^2
      - **Ranges:**
        - Underweight <18.5
        - Normal 18.5 – 25
        - Overweight 25 – 30
        - Obese >30
      - **Limitations:**
        - Limited Sensitivity – Some people who are clearly overweight may be tall → False Negatives.
        - Limited Specificity – Extremely muscular people will have a high BMI → False Positives.
        - Hence, should be used in Conjunction with Waist Circumference.



    - **Waist Circumference:**
      - Males:
        - > 94cm → Increased Risk
        - > 102cm → High Risk
      - Females:
        - >80cm → Increased Risk
        - >88cm → High Risk



  - **Physical Inactivity:**
    - Ie. Sedentary Lifestyle
    - Recommended Levels of Exercise (30mins x 5days/week)
    - Est. ≈65% of people don't do enough exercise.
    - NB: Sedentary Lifestyle increases with Age.

- **Poor Diet:**
  - Inadequate Fruit & Vegetable Intake
  - Most prevalent in Low Socioeconomic Status groups.
- **Tobacco Smoking:**
  - Smoking rates are ≈20% spread evenly across all agegroups.
  - Most prevalent in Low Socioeconomic Status groups.
- **Excessive Alcohol:**
  - Approx. ≈25% Drink at Risky Levels.
  - Rates among adults are consistent with age.
  - Most prevalent in Rural & Remote Areas.
- **High Blood Pressure:**
  - Approx 30% of Adults over 25yrs.
  - Most prevalent in Males
  - **What is High?**
    - Systolic above 140mmHg
    - Diastolic above 90mmHg
- **High Blood Cholesterol:**
  - Approx 50% of Population have High Cholesterol. (Rates are stagnant)
  - ≈60% of Indigenous (Rates are stagnant)
  - **What is High?**
    - LDL:HDL Ratio

- **Disease Determinants:**
  - **NB: The Above Risk Factors aren't the *Only* Factors in our Burden of Disease – Eg:**
    - Genetics
    - Illicit drugs
    - Social norms & culture
    - Busy life → Time-poor → ↓Exercise & ↑Fast Foods
  - **Social Determinants of Health:**
    - **Socioeconomic Status:**
      - High SES people tend to live longer.
      - **Why? – They can Afford Better:**
        - Nutrition
        - Medical Care
        - Education → ↓Risky behaviours.
    - **Early Life:**
      - Eg. Low Birth Weight (ie. From maternal smoking)
      - Eg. Poor Nutrition
      - Eg. Neonatal Infections
      - Eg. Breastfed Vs. Non-Breastfed
    - **Stress:**
      - Money
      - Family
      - Relationship
      - Job Security
    - **Employment:**
      - Eg. Occupational Hazards
      - Eg. Bad influences of Workmates (Eg. Drinking/Smoking)
      - Eg. Fast foods for lunches
    - **Social Networks:**
      - Or Lack of → Depression
      - Social Exclusion (eg. Minorities – Racial/SES/Sexuality/Weight/etc)
    - **Drug Addiction:**
      - Direct impact on health (eg. Hep-B/HIV/Substance-Dependence)
      - Indirect impact through:
        - Crime
        - Compromise on nutrition etc. To save money for drugs.

- **Treating Chronic Disease:**
  - **Prevention Approach:**
    - Diagnosing Chronic Disease early →
      - Better Prognosis for patient
      - Better Quality of Life for Patient
      - Prevents progression of disease.
      - Better for the Economy
  - **Prevention Levels:**
    - **Primary Prevention:**
      - Preventing the disease from developing in the first place by modifying removing risk factors.
        - Eg. Changing eating habits to prevent obesity.
        - Eg. Immunisation
        - Eg. Fitting vehicles with seat-belts.
    - **Secondary Prevention:**
      - Prevent disease progression by early detection of disease & Early Intervention.
        - Eg. Identifying someone with hypertension → early treatment to prevent CVD.
    - **Tertiary Prevention:**
      - Interventions to prevent or minimise complications with an Established disease.
        - Eg. Bariatric surgery for morbidly obese people with poor diabetic control to avoid needing insulin therapy.
  - **Public Vs. Individual Prevention:**
    - **1. "High Risk" Prevention Strategies:**
      - Selecting individuals at high risk of a disease → Medical Intervention.
      - Opportunistic Screening.
      - **Advantages:**
        - Appropriate for the individual
        - Cost-Effective
        - Good Risk-Benefit Ratio.
      - **Disadvantages:**
        - Problems with screening
          - Who
          - How
          - When
          - Borderline Cases
          - Behaviourally Inappropriate (eg. Papsmears)
          - $Costs$
        - Difficult to predict the *Absolute Risk* of disease in an individual:
          - Some people with risk factors don't get the disease.
        - Many people with the disease, don't have the risk factors.
    - **2. "Population" Prevention Strategies:**
      - Where you attempt shift the whole *distribution* of an exposure in a favourable direction by controlling the determinants of the disease (Environmental/Behavioural/etc).
      - Ie. Trying to reduce the underlying causes of a disease across an entire population.
      - **Advantages:**
        - A small change can make a huge difference when it occurs across an entire population.
      - **Disadvantages:**
        - Low Benefit-Risk ratio:
          - Limited benefit to the individual (Eg. Immunisation – even @ low risk of disease)
          - Poor motivation
  - **Modifying Lifestyle Behaviour:**
    - See GLS section.

- **Prevention of Chronic Diseases You Will See as a Doctor:**
  - **Hypertension:**
    - **Primary Prevention:**
      - ↑Exercise
      - Lose weight
      - ↓Salt intake
      - ↓Saturated Fats
      - ↓Stress
      - Coping Strategies
    - **Secondary Prevention:**
      - Screening for Hypertension
      - Early Diagnosis
      - Review for other risk factors
      - Lifestyle Counselling
    - **Tertiary Prevention:**
      - Antihypertensive Drug Interventions
      - Follow-up Monitoring
  - **Depression:**
    - **Primary Prevention:**
      - Address Social Isolation/Greif/Family Problems
      - Strategies for Coping with Stress
      - Build good support networks
      - Physical Exercise → ↓Stress
    - **Secondary Prevention:**
      - Screening for signs of depression
      - Early Diagnosis
      - Early Intervention
    - **Tertiary Prevention:**
      - Appropriate Therapy/Counselling
      - Monitoring & Support
      - Refer to Therapist
  - **Diabetes:**
    - **Primary Prevention:**
      - Physical Activity
      - Weight Control & Diet
      - Find out Family History
    - **Secondary Prevention:**
      - Screening blood tests in *At-Risk* patients.
    - **Tertiary Prevention:**
      - Referral to Diabetes Educator
      - Initiation of Treatment
      - Ongoing Monitoring
  - **Lipid Disorder:**
    - **Primary Prevention:**
      - Diet
      - Exercise
      - Family History
    - **Secondary Prevention:**
      - Screening
      - Risk Factor Profile
      - Dietary Counselling
    - **Tertiary Prevention:**
      - Start Treatment (Monitor Effects & Side-Effects)

- **Osteoarthritis:**
  - **Primary Prevention:**
    - Avoidance of Injuries in Early Life
  - **Secondary Prevention:**
    - Diagnose from Other Rheumatological Disorders
    - Provide Early Intervention
  - **Tertiary Prevention:**
    - Medication
    - Physical Therapies
    - Devices & Aids
    - Surgical Referral

GLS – Changing Behaviour

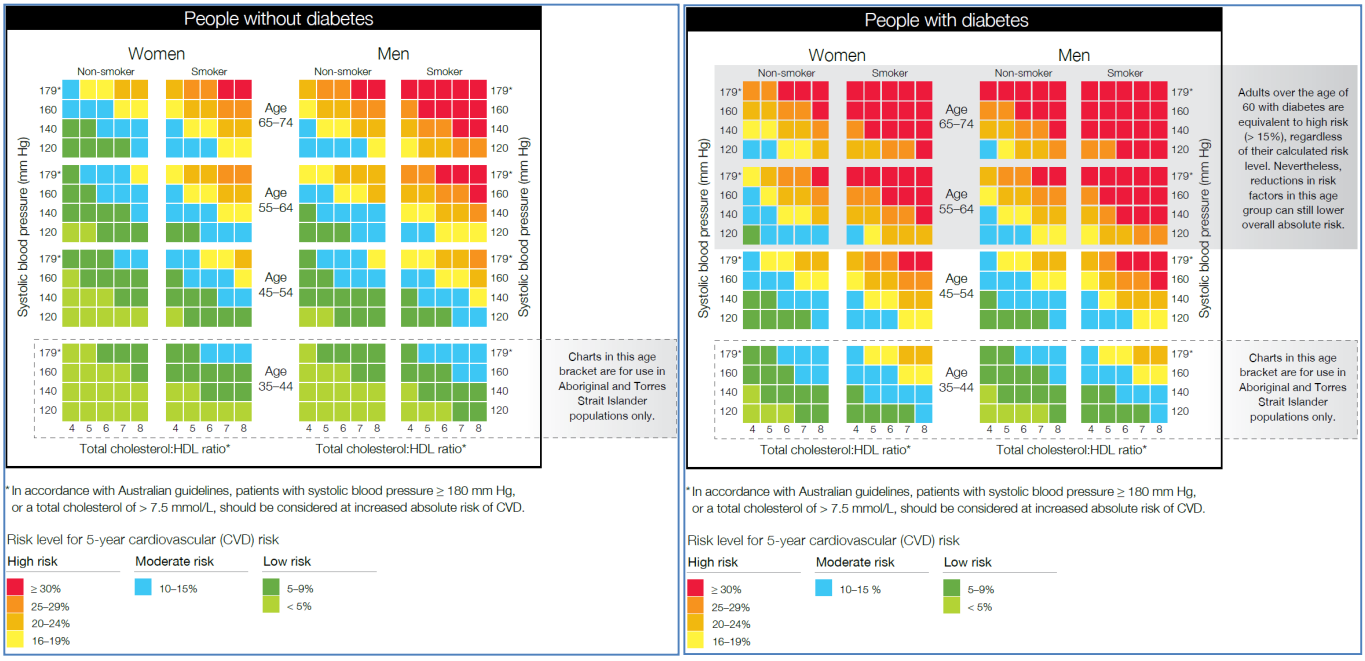
How People Change:

- **NB: Patients don't change just because you say so.**
  - Ambivalence, Resistance & Defence Mechanisms are Normal.
  - **Intentional Change Occurs Gradually**
- **Requirements for Change:**
  - Change in Thinking/Feeling about an Issue
  - Planned Steps
  - Time

"SNAP": – Guidelines for Managing Lifestyle Risk Factors:

- **What are the Risk Factors?**
  - **Smoking**
  - **Nutrition**
  - **Alcohol**
  - **Physical Exercise**
- **5 A's Approach to SNAP:**
  - **1. Ask:**
    - Ask which Risk Factors apply to Patient.
    - Eg. Do you Smoke/Eat Healthily/Drink/Exercise?
  - **2. Assess:**
    - Assess Level of Risk & Relevance to Patient's Health.
      - Ie. Behaviour History (Smoking/Diet/Drinking/Exercise History)
      - BMI
      - ***Cardiovascular Risk Calculator** – Work out absolute risk level for CVD.
    - Assess Readiness to Change
  - **3. Advise:**
    - Advise with Written Information (Eg. Pamphlets)
    - Advise with a Lifestyle Prescription (Life Script)
    - Advise with a Brief Intervention & Motivational Interviewing.
  - **4. Assist:**
    - Assist with Pharmacotherapy.
    - Assist with Self-Monitoring (Suggest Keeping a Diary)
  - **5. Arrange:**
    - Arrange Referral to:
      - Specialist Services (Eg. Dietician/Exercise Physiologist/'ATODs')
        - NB: ATODs = Alcohol, Tobacco & Other Drugs
      - Support Groups
      - Helplines
      - Counselling
    - Arrange Follow-Up

Cardiovascular Risk Calculator:



A Useful Tool: "The 5 Stages of Change Model":

- **1. Precontemplation:**
  - No intention to change behaviour.
  - **Precontemplation → Contemplation:**
    - Make the patient aware of the problem (Link their Behaviour to their Health)
    - Encourage them to take ownership of the problem
    - Explain the Negative Aspects of Problem (Convince patient that the behaviour *Is* a problem)
- **2. Contemplation:**
  - Person is thinking about changing behaviour.
  - **Contemplation → Preparation:**
    - Get patient to Think How the Behaviour is Affecting Others.
    - Change how they think & feel about the Issue.
    - NB: Pushing People to Change can be Counterproductive → Resentment.
    - 3 Strong Motivators:
      - Health
      - Money
      - Relationships
- **3. Preparation:**
  - Person prepares to make the change:
  - **Preparation → Action:**
    - Gathers information
    - Finds out how to achieve the change
    - Set Firm Goals & Priorities
    - Acquiring Skills Necessary for change.
- **4. Action:**
  - Person makes changes (may be small steps at first)
  - **Action → Maintenance:**
    - Self-Efficacy is very important.
    - Keep focussed
    - Acknowledge that Change is Difficult & Potential Relapse is Normal.
- **5. Maintenance:**
  - Consistently practices new/altered behaviour.
  - Acknowledge that Change is Difficult & Potential Relapse is Normal.
- **//Relapse:**
  - Person relapses back to original behaviour.
  - Move back to Contemplation if Relapse Occurs.

Figure 2. The contemplation ladder[20,21]

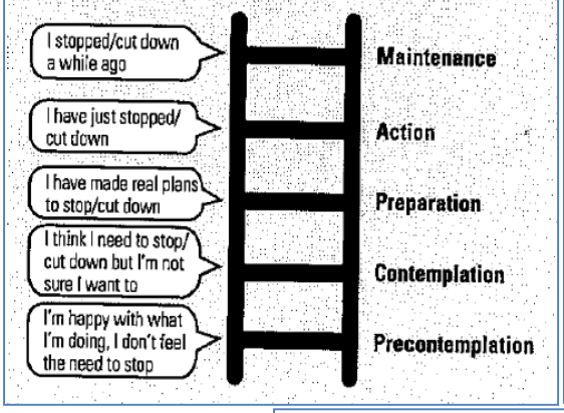
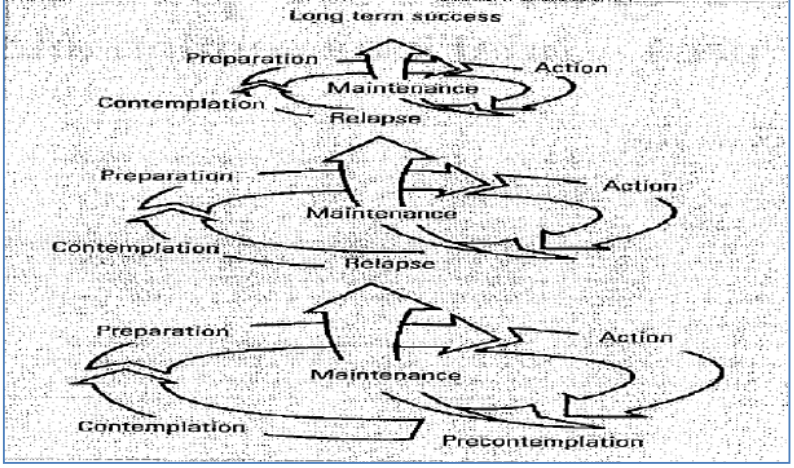
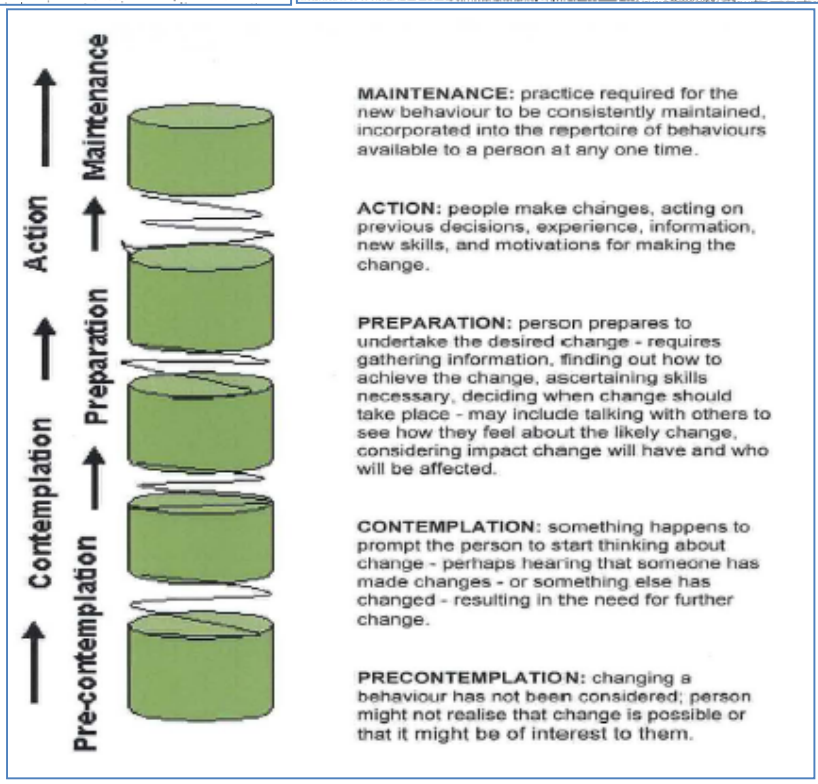


Figure 1. The spiral of change





SS – Lowering Lipid Levels:

Heart Foundation Guidelines for Lowering Lipid Levels:

- **Initial Assessment:**
  - All adults need ongoing Risk-Assessment & Lifestyle Advice.
  - Mass screening ISN'T Recommended.
  - Test Lipid Profile & Blood-Sugar Levels before any Treatment:
    - Test all over 45yrs
    - Test all 'High Risk' adults Annually (eg. ATSI)
- **High Risk Criteria:**
  - Known Coronary Heart Disease
  - Other known Atherothrombotic Disease/Peripheral Artery Disease.
  - Diabetes Mellitis
  - Renal Failure
  - ATSI Populations
  - Familial Hypercholesterolaemia
  - **Predicted Absolute 5yrly Risk** of Cardiovascular Disease using **Cardiovascular Risk Calculator.**
  - **Risky Cholesterol Levels:**
    - LDL Greater Than 4.0mmol/L; OR
    - HDL Less Than 1.0mmol/L; OR
    - Total Cholesterol Greater than 6mmol/L
- **Target Levels:**
  - **LDL** - Less than 2.5mmol/L
  - **HDL** - Greater Than 1.0mmol/L
  - **Total Cholesterol** - Less Than 4.0mmol/L
  - **Triglycerides** - Less Than 2.0mmol/L
  - **Total Cholesterol:HDL Ratio** – Less than 5
  - **NB:** Any of lowering of Total Cholesterol or LDL levels; Or raising of HDL levels is advantageous, even if target levels aren't achieved.
- **Starting Treatment:**
  - Use High Risk Criteria
  - Diet for 6 weeks (↓Sat.Fats)
    - NB: if they have CVD, commence treatment straight away, in addition to a diet.
    - If levels aren't improved after 6 weeks of diet, commence pharmacotherapy.
    - Re-Test every 2 Months until Target Levels are achieved.
  - **PBS Criteria for Lipid-Lowering Drugs:**
    - Symptomatic CVD
    - High Risk Diabetes
    - Microalbuminuria (Indicative of Vascular Disease)
    - ATSI
    - Family history of Symptomatic Coronary Heart Disease (2x Aged <55yrs; or 1x Aged <45yrs)

Introduction To Disease Prevention

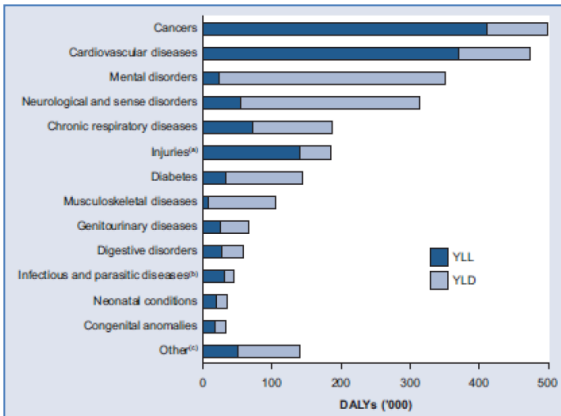
Basic Glossary:

- **Aetiology** = The Cause of disease or study of factors involved in development of disease
- **Epidemiology** = The study of distribution and determinants of disease in human population
- **Risk factor** = Something associated with an increased risk of developing a particular disease or condition.
    - Demographic
    - Behavioural
    - Biomedical
    - Genetic
    - Environmental
    - Social
    - Other factors which may interact to increase or reduce effect
- **DALY** = Disability Adjusted Life Years - an indicator of the time lived with a disability and the time lost due to premature mortality
- **YLL** = (years of life lost) Years Lost due to premature death
- **YLD** = Years Lost to Disability

Burden of Disease in Australia:

- **Causes of Mortality (by Age):**

Age	Cause of Death
Infants	**1. Perinatal Conditions** 2. Congenital Defects
1-44 yrs	**1. Injury & Poisoning** 2. Cancer
45-84 yrs	**1. Cancer** 2. CVD
85+ yrs	**1. CVD** 2. Cancer



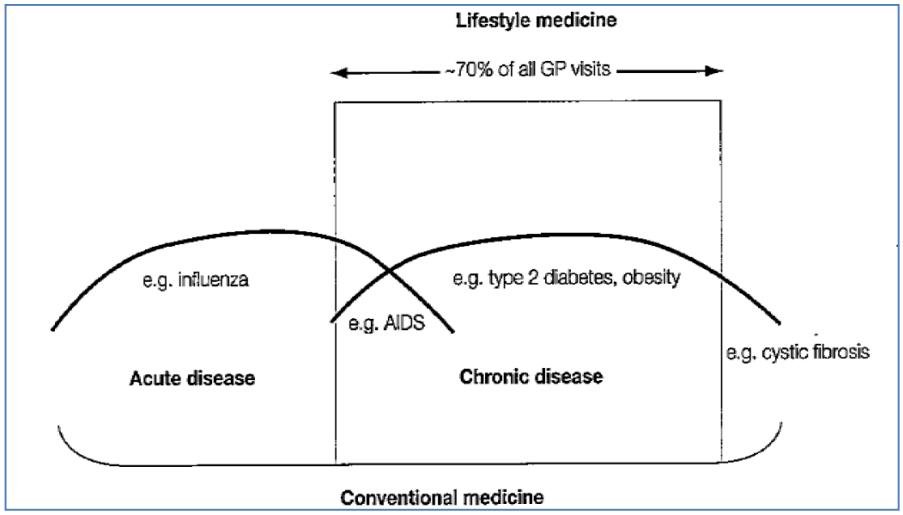
(a) Includes intentional and unintentional injuries.
(b) Excludes acute respiratory infections.
(c) Includes maternal conditions, nutritional deficiencies, non-malignant neoplasms, skin diseases, oral health conditions, acute respiratory infections and ill-defined conditions.
Source: Begg et al. 2007.
Figure 2.17: Burden (YLL, YLD and total DALYs) of major disease groups, 2003

- **Risk Factor Contribution to DALYs:**

Risk factor	Percentage
Overweight	8.6
Tobacco smoking	7.9
High blood pressure	7.3
Physical inactivity	6.7
High cholesterol	6.1
Alcohol harm	3.8
Alcohol benefit	-1.8
Occupational exposure	2.0
Illicit drugs	1.9
Lack of fruit and vegetables	1.0

Why Prevent Disease?:

- Beneficial for patient
- Prevents disability/mortality
- Some diseases aren't curable (eg. AIDs), but are preventable.
- Cheaper than treating chronic disease – Some 70% of all GP visits are due to Chronic Disease:



Types of Prevention:

- **Primary Prevention:**
  - Preventing the disease from developing in the first place by modifying removing risk factors.
    - Eg. Changing eating habits to prevent obesity.
    - Eg. Immunisation
    - Eg. Fitting vehicles with seat-belts.
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Prevention Strategies:

- **1. "High Risk" Prevention Strategies:**
  - Selecting individuals at high risk of a disease → Medical Intervention.
  - Opportunistic Screening.
  - **Advantages:**
    - Appropriate for the individual
    - Cost-Effective
    - Good Risk-Benefit Ratio.
  - **Disadvantages:**
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      - When
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      - Behaviourally Inappropriate (eg. Papsmears)
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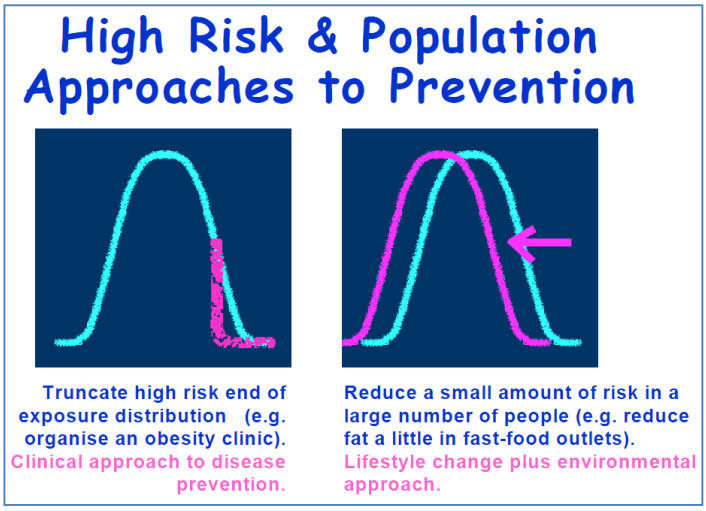


The Prevention Paradox:

- A Preventative measure which benefits the population, offers little to each individual. (Eg. Seat Belts)

Success Stories:

- **Vaccination →**
    - Eradication of Smallpox/Polio
    - Control of Measles/Rubella/Tetanus/HiB
- **Car Safety →**
    - Personal Behaviour Change (Seat-belts/Helmets/Drink-Driving)
    - ↑Engineering of Roads & Vehicles
    - → Large Reduction in Deaths.
- **Occupational Hazards →**
    - Injury reductions due to legislation (Health & Safety at all sites/Smoking Ban)
    - → ↓ "Black Lung"/Asbestosis/Workplace Deaths/etc.
- **Communicable Disease Control →**
    - Clean Water & sanitation
    - Antibiotics
    - Vector control
- **CardioVascular Disease →**
    - Risk factor reduction
    - BP Control
    - Smoking Cessation
    - Earlier Detection
    - Safer, more-effective treatment.
- **Food Safety →**
    - ↓Microbial Content (Eg. Pasteurisation)
    - ↑Nutritional Content (Eg. Food fortification – eg. Iodised Table Salt)
    - Food safety legislation for handlers.
    - Elimination of major nutritional deficiency diseases (Rickets, Goiter, Pellagra)

- **Mothers' & Babies' Health →**
  - Hygeine & Nutrition
  - Antibiotics
  - Access to healthcare
  - Technology
  - → Infant & maternal mortality decreased by 90%$^{+}$.
- **Flouridation of Water →**
  - Entire population benefits
  - 40% Reduction in adult tooth-loss
  - 60% Reduction in Child Tooth Decay
- **Antismoking Campaigns →**
  - Recognition of tobacco as a health hazard.
  - Legislation – Sales to minors, Advertising banned, No Smoking in Public/Work-Places.
  - Smoking reduced from 40% → 20%.

Maggie's Lecture – Measuring Health Concepts:

- **Sensitivity Vs. Specificity:**
  - **Sensitivity:**
    - The ability of a test to pick up people who truly have the disease of interest.
    - Ie. No False Negatives
    - **Calculating Sensitivity:**

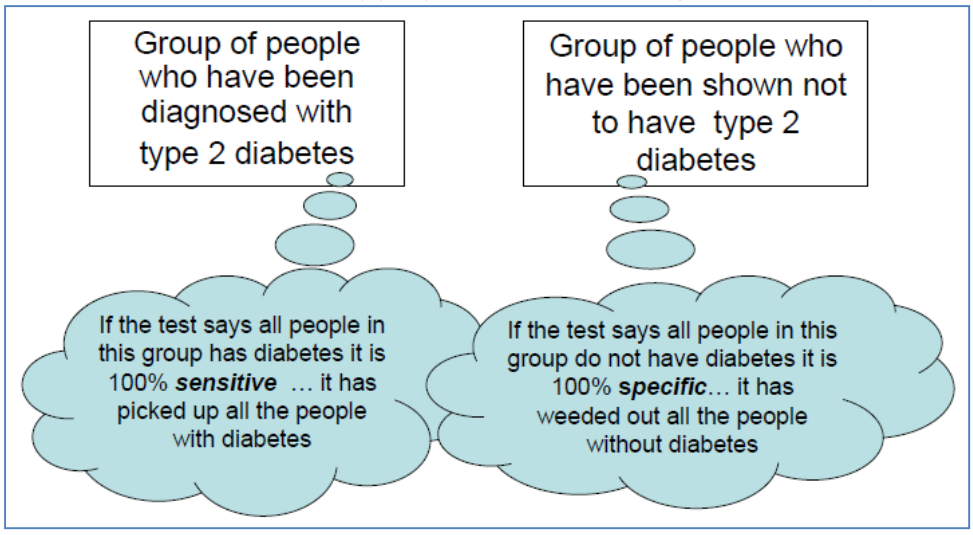
$$Sensitivity = \frac{Number\ of\ True\ Test\_Positives}{Actual\ Positives}$$

Ie. The % of the diseased people that the test recognised as diseased.

  - **Specificity:**
    - The ability of a test to weed out people who are truly Free of the disease of interest.
    - Ie. No False Positives
    - **Calculating Specificity:**

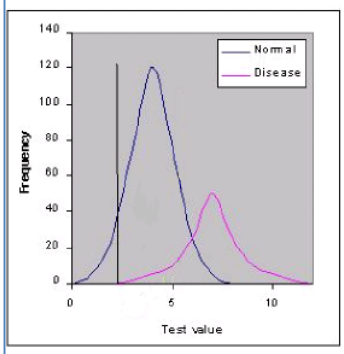
$$Specificity = \frac{Number\ of\ True\ Test\_Negatives}{Actual\ Negatives}$$

Ie. The % of the healthy people that the test recognised as healthy.

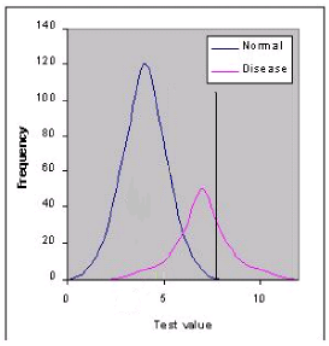


- **Why can't some tests be both 100% Sensitive *AND* Specific?:**
  - Certain diseases have a distribution in a population.

This T4 distribution shows these is no point where the test is 100% sensitive and 100% specific

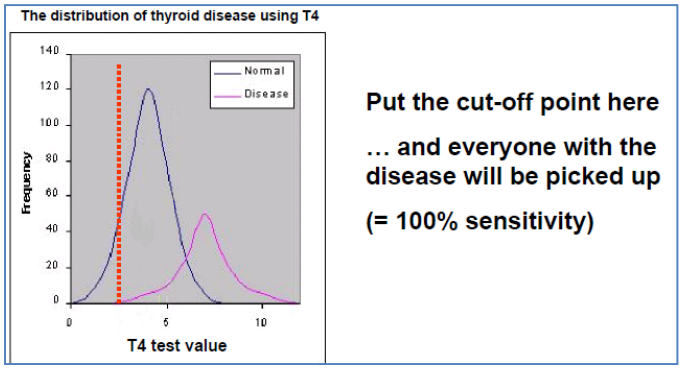


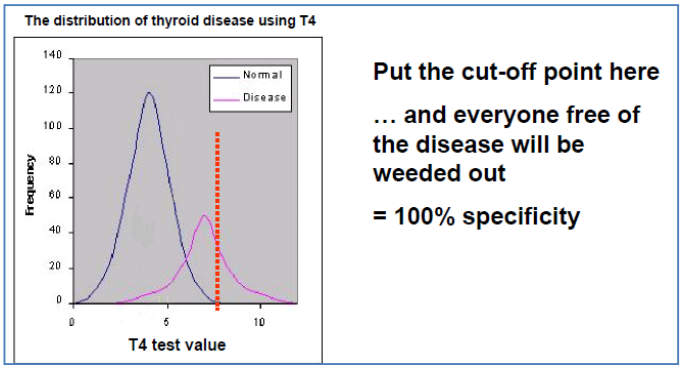
100% sensitive; lots of false positives



100% specific; lots of false negatives

  - **So where do you draw the line? Answer – Depends on the disease in question**.
  - **NB: When 'drawing the line', you trade Sensitivity for Specificity and vice versa:**
    - Eg. If the disease has extreme morbidity/mortality, and the treatment is cheap and harmless, then you want a highly *Sensitive* test to pick up every possible case.
    - Eg. However, if the consequences of the disease are minor, but the treatment is extremely costly/invasive/risky, you want a highly *Selective* test so you only treat actual cases.





- **Positive Predictive Value (PPV):**
  - Tells us how likely a Positive Test will be a True Positive.
    - Ie. The % of Positives that were *True*.
  - **Calculating PPV:**

$$PPV = \frac{True\ Positives}{True\ Positives + False\ Positives}$$

- **Relative Risk:** "The risk of getting a disease when comparing one group to another"
  - Eg. Relative risk of lung-cancer in smokers is 2x that of non-smokers.
  - **Rate Ratio:**
    - Derived from Cohort Studies.
    - Compares the incidence ***rates*** of a disease in 2 groups of people (With/Without Exposure).
    - **Calculating Rate Ratio:**

$$Rate\ Ratio = \frac{Incidence\ Rate\ in\ Exposed}{Incidence\ Rate\ in\ Unexposed}$$

- **Odds Ratio:**
  - Supposedly tells you what your ***Odds*** are of getting a disease if you are exposed to a certain risk factor.
  - **Calculating Odds Ratio:**

$$Odds\ Ratio = \frac{The\ \%\ of\ people\ with\ the\ disease\ who\ had\ Exposure}{The\ \%\ of\ people\ without\ the\ disease\ who\ had\ Exposure}$$

  - **Maggie's Way:**

	With CHD	Without CHD	Total
Smokers	a. 80	b. 10	90
Non-smokers	c. 20	d. 90	110
Total	100	100	200

OR = a/c (odds people with CHD were smokers compared to non-smokers
b/d (odds people without CHD were smokers compared to non-smokers

- **Absolute Risk:**
  - The actual risk of getting the disease, over a period of time.
  - Eg. Assuming you live to 90, your risk of getting breast cancer is ≈12%.
  - This is based on the prevalence of that specific disease in that population.
- **Numbers Needed to Treat (NNT):**
  - The number of patients you need to treat to prevent one additional bad outcome.
  - Gives insight to the effectiveness & cost of a treatment.
  - Ideal NNT = 1 Ie. Everyone treated improves.
  - Eg. A drug with an NNT of 5 → you have to treat 5 people with the drug to get 1 cure.
- **Validity & Reliability:**
  - **Validity =** The ability of a test to test what it's meant to be testing.
    - (eg. How well IQ measures intelligence)
  - **Reliable =** The degree of consistency of results despite changes in external factors
    - (eg. Different testers, different times, different places)

Screening:

- "Identifying individuals who are *More Likely To Be HELPED THAN HARMED* by further tests/treatment"

- **Criteria for Selecting Diseases to Screen for:**
  - **1.** It should be an obvious burden for the Individual/Community.
    - Deaths
    - Suffering
    - Economic/Social Costs
  - **2.** It should have an initial Latent Stage, or be determined by risk factors, which can be detected by tests.
  - **3.** The Tests should be simple, safe, precise, socially-acceptable & validated.
  - **4.** Treatment/Intervention is crucial to prognosis.
  - **5.** Early intervention must provide a BETTER prognosis. (Mortality/Morbidity/QOL)

- **The RACGP "Redbook" – Guidelines for Preventative Activities in General Practice:**
  - **Using the RedBook:**
    - 'Preventative Activities Chart':

Preventive activities over the lifecycle – adults

Patient name DOB Date

Activity/topic	Frequency	Notes	Page no.	Years											
				10–14	15–17	18–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–64	65+
Prevention of chronic disease															
(S) Smoking	Opportunistically, ideally every visit		33	■	■	■	■	■	■	■	■	■	■	■	■
(N) Weight	Every 2 years	Every 12 months for Indigenous Australians, diabetes, CVD, stroke, gout, liver or gallbladder disease	34	■	■	■	■	■	■	■	■	■	■	■	■
Nutrition	Every 2 years	Every 6 months for overweight, obese, high CV AR, family history CVD, type 2 diabetes	36	■	■	■	■	■	■	■	■	■	■	■	■
(A) Alcohol – early detection of problem drinking	Every 3–4 years	Opportunistically for other risk factors	37		■	■	■	■	■	■	■	■	■	■	■
(P) Physical activity	Every 2 years	Every visit adolescent girls, Indigenous Australians, NESB, chronic disease or CVD	39	■	■	■	■	■	■	■	■	■	■	■	■
Prevention of vascular disease															
Absolute cardiovascular risk assessment	Every 2 years	More frequently if change of treatment indicated	41									■	■	■	■
Blood pressure	Every 2 years	Every 12 months with increased age and CV risk. Every 6 months for high CV risk. From 15 years of age for Indigenous Australians	42		▫	■	■	■	■	■	■	■	■	■	■
Cholesterol and lipids	Every 5 years	Every 2 years >45 years of age and increased risk. Every 12 months with increased CV risk and existing chronic disease	43									■	■	■	■
Type 2 diabetes	Every 3 years	Start at 18 years of age for Indigenous Australians	44			▫	▫	▫	▫	▫	■	■	■	■	■
Stroke	Every 12 months with risk factors	Every 12 months with AF and risk factors, previous stroke or MI or chronic kidney disease	45									■	■	■	■
Kidney disease	Every 5 years	Every 12 months with HTN, diabetes, family history or presence of kidney disease. From 35 years of age for Indigenous Australians	46							▫	▫	▫	■	■	■
Cancer															
Skin cancer examination	Opportunistically	With increased risk – up to every 3 months for high risk	48						■	■	■	■	■	■	■
Cervical cancer	Every 2 years	Women with a cervix from 18 years of age, or 1–2 years after becoming sexually active. Ceasing at age 69 years if two normal smears in previous 5 years	51			■	■	■	■	■	■	■	■	■	■
Breast cancer	Every 2 years	Women aged 50–69 years	52										■	■	■
Colorectal cancer	Every 2 years	Earlier for high risk	54					▫	▫	▫	▫	▫	■	■	■
Preconception															
Preconception care	Opportunistically	Consider for all women aged 15–49 years	11		■	■	■	■	■	■	■	■			
Sexual health															
Chlamydia	Opportunistically	All sexually active females aged <25 years	30		■	■	■								
Psychosocial															
Depression	Opportunistically	When there is effective treatment and follow up	58			■	■	■	■	■	■	■	■	■	■
Intimate partner violence	Opportunistically	For pregnant and adolescent women	60	▫	▫	▫	▫	▫	▫	▫	▫	▫			
Elderly															
Falls risk	Every 12 months	Every 6 months with history of falls or risk factors	24												■
Vision and hearing	Every 12 months		25												■

■ Population based activity ▫ Increased risk (eg. Aboriginal people and Torres Strait Islanders)

    - **Coding for Evidence Level & Strength of Recommendations:**

Level of evidence

Level	Explanation
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly designed randomised controlled trial
III	Evidence obtained from any of the following: • well designed pseudo randomised controlled trials (alternate allocation or some other method) • comparative studies with concurrent controls and allocation not randomised (cohort studies), case control studies, or interrupted time series with a control group • comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test and post-test
V	Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees
No evidence	After thorough searching no evidence was found regarding recommendations in general practice for the target disease or condition

Strength of recommendation

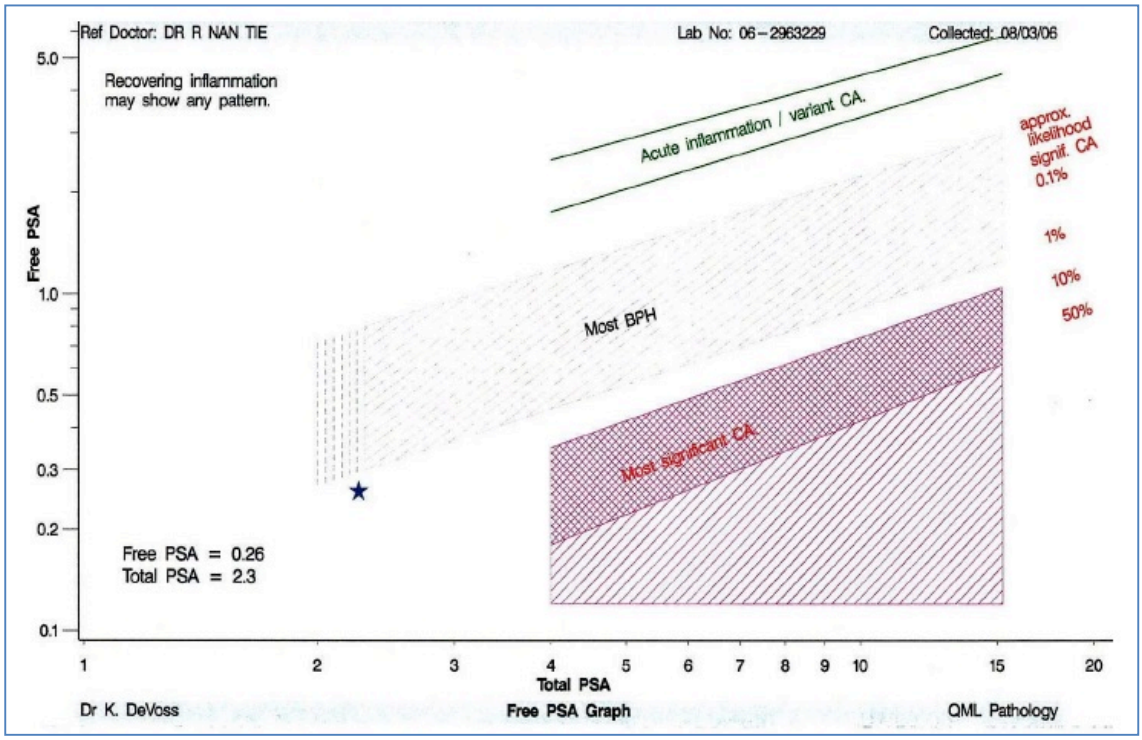
Strength	Explanation
A	There is good evidence to support the recommendation
B	There is fair evidence to support the recommendation
C	There is poor evidence regarding the inclusion or exclusion of the recommendation but recommendations may be made on other grounds
D	There is fair evidence against the recommendation
E	There is good evidence against the recommendation

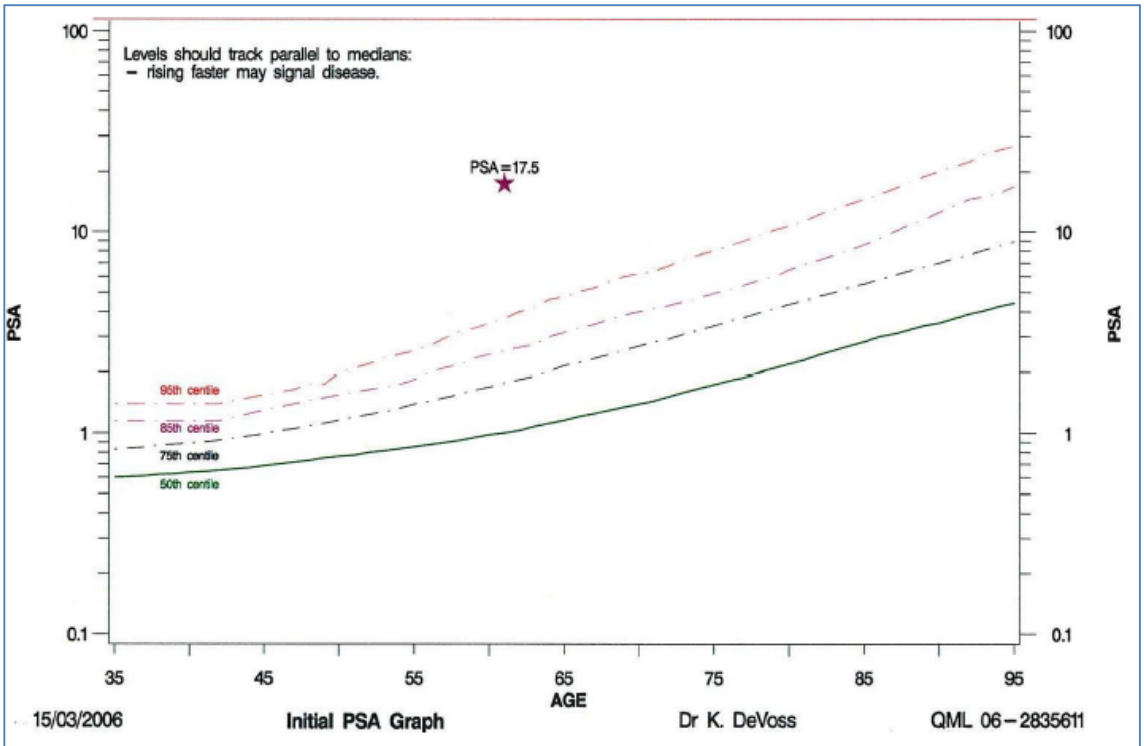
Summarising the GLS:

- **Workbook:**
  - **Pregnancy:**
    - **Folic Acid (Folate) Supplemtation –** Prevents Neural Tube Defects (Eg. Spina Bifida)
    - **Get Genetic Testing for Fragile X**
    - **Check Rubella Immunity**
    - **Stop Smoking**
    - **Stop Drinking**
    - **Prevent Listeriosis –** A bacterial infection typically contracted from 'Deli-foods'.
      - Unpasteurised Dairy Products
      - Soft Cheeses
      - Cold Meets
      - Raw Seafood
      - Maintain good Personal/Food-Hygiene
  - **Breast Cancer:**
    - **Screening not necessary until 50yrs.**
    - **If 50^{+}, screen every 2 years – Mammogram & Breast Examination.**
  - **Cervical Cancer:**
    - **Screen 2yrly.**
    - **Pap-smear**
    - **Immunisation (Gardosil)**
  - **Overweight & Obesity:**
    - **Screen 12mthly for:**
      - **Blood Pressure**
      - **Cholesterol & Lipids**
      - **Diabetes**
    - **Screen 6mthly for:**
      - **Nutritional Advice.**
    - **Ideal Waist Circumference = <94cm.**
  - **Alcohol:**
    - **Reduce consumption as much as possible.**
    - **Ensure 2x 'Alcohol-Free Days' per week.**
  - **Falls:**
    - **Common in elderly due to:**
      - Vision Problems (eg. Glaucoma – screen @ 55^{+}yrs.)
      - Inner Ear Problems → ↓Balance
      - Multiple Meds → Nauseating
      - Gait
    - **Screening Procedures:**
      - Check all of above.
      - Suggest Installation of handles/non-slip surfaces in their home.
      - Suggest having a carer.
  - **Dementia:**
    - **Screen the elderly:**
      - Family History
      - "Clock-Drawing Test"
      - Mini-mentals test.

Synthesis Session:

- **Prostate Cancer:**
  - **Risk Factors:**
    - #1 – Family History. (The closer the affected relatives, the more likely one is to be affected)
    - Age – Typically seen in men over 50yrs. (40% of men over 50yrs have prostate cancer)
    - Race: Highest = African American; Lowest = Chinese
  - **Screen 2yrly for 50^{+}yrs**
  - **NB:** 85% of cases have a 20yr survival rate with no treatment → Most die with it, not of it.
  - **NB:** Early surgery only saves 1:12 (NNT=12)
  - **Screening Procedures:**
    - Digital Rectal Exam (DRE)
    - Prostate Speficic Antigen (PSA) blood test.
  - **PSA Screening:**
    - **↑PSA occurs with:**
      - Carcinoma – (The purpose of the test)
      - However, also with:
        - Benign prostatic hypertrophy
        - Prostatitis/UTI
        - Recent Ejaculation
        - Bike Riding
    - **Sensitivity =** Relatively Sensitive (A Few false negatives)
      - Ie. ≈99% of *Normal* PSAs are Not Cancer.
    - **Specificity =** Poorly Specific (Many false positives)
      - Ie. ≈33% of *Abnormal* PSAs Are Cancer.
      - NB: False positives → Anxiety, further tests & possible treatment → ↓QOL.
  - **Best Treatment:**
    - Uncertain.
    - Can't predict who will benefit from early treatment (Ie. No way of knowing which cancers are fatal)
    - **Options:**
      - Wait & Watch
      - Radical Prostatectomy
      - Radiation Therapy
      - Hormone Therapy
    - **Side Effects:**
      - Infection
      - Urinary Incontinence (Very Common)
      - Chronic Diarrhoea & Rectal Bleeding (From radiation)
      - Impotence.





- **Send for biopsy!**

Health Behaviour

Health Promotion:

- Promote healthy behaviours through education
- Monitor individual wellbeing and risk-taking behaviours.
- **Doctor's Role:**
  - Advise the most effective way to a healthy lifestyle
  - Monitor patient's behaviour
  - Skill training
  - Reinforcement of behaviour
  - Role modelling
  - Provision of information
  - Give "expert" opinions
- **Psychologist's Role:**
  - Develop interventions at individual & community levels
- **Mass Media's Role:**
  - Educate people about health risks (AIDs, smoking, alcohol)
- **Role of Legislation:**
  - Rules enforcing healthy behaviour (seatbelts/drink-driving/smoking)

Role of Behavioural Factors in Disease & Disorder

- **Health Behaviours:**
  - Behaviours that promote/maintain individual wellbeing. (eg. Exercise/healthy diet)
  - Either **Habitual or Intentional**
  - **Health Habits:**
    - Seatbelt/cleaning teeth etc.
- **Risk Behaviours:**
  - Behaviours which are proven to increase susceptibility to a specific disease/illness.

Primary Prevention:

- Instilling good health habits & changing poor ones
- **Strategies:**
  - Change current health behaviour
  - Prevent the uptake of poor health habits in the first place

Obstacles to Changing Health Behaviours:

- Pleasure (being high)
- Addiction (drugs)
- Behaviour is now habitual
- Relapse
- Factors influencing behaviour (stress → smoking)

Urealistic Optimism & Irrational Risk Perception:

- Inaccurate perceptions of risk
- Inaccurate perceptions of susceptibility
- Lack of personal experience with problem
- There's no problem now so there won't be in the future
- Belief that problem is infrequent.

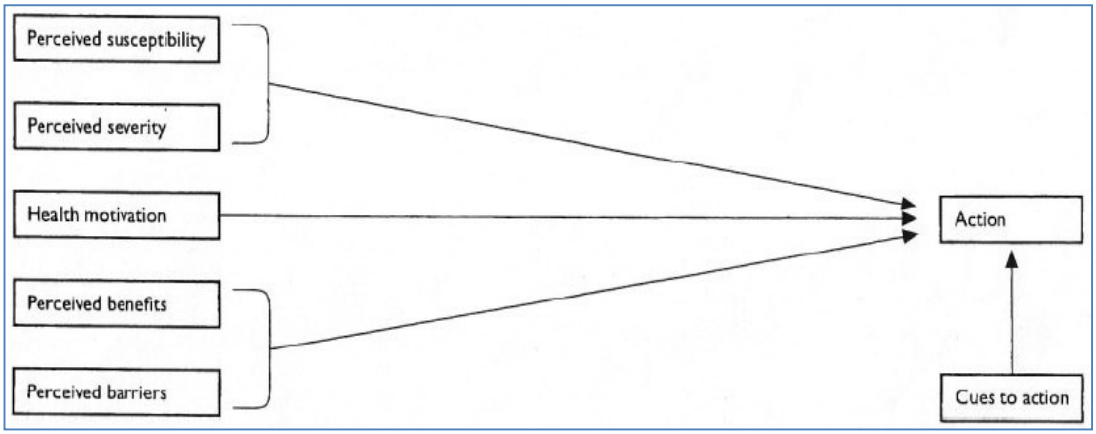
Components of Motivation:

- **Willing**
  - Perceived importance of change
- **Able**
  - Self efficacy
- **Ready**

Health Belief Model

5 Factors determining health behaviour:

1. **Perceived Threat:**
   a. **Perceived Susceptibility:** One's perceived risk of contracting a health condition.
   b. **Perceived Severity:** One's opinion of the seriousness of getting/having the condition.
2. **Perceived Benefits:** The believed effectiveness of preventative measures
3. **Perceived Barriers:** Potential negative consequences of taking the preventative measures.
4. **Cues To Action:** Events (symptoms/media/social) that motivate people to take action.
5. **Self-Efficacy:** One's confidence in being able to undertake the preventative measure successfully.



Theory of Planned Behaviour

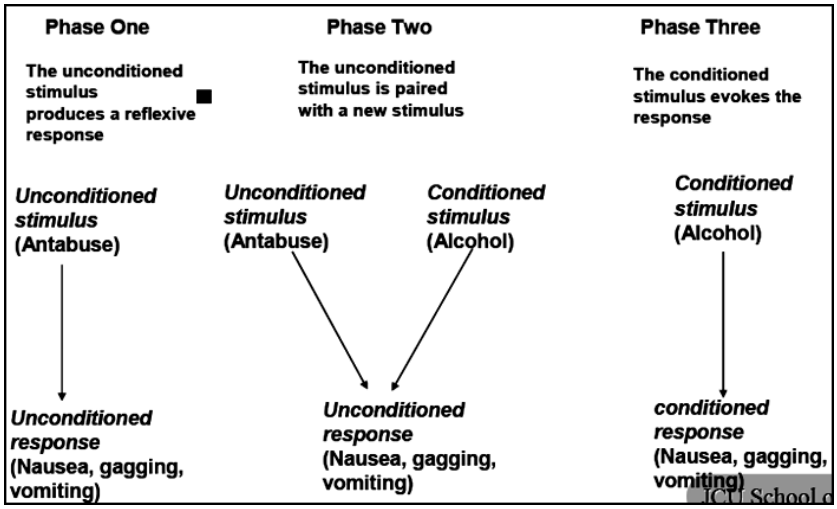
- Assumes that behaviour is a direct result of a person's intentions.
- **3 Behavioural Intentions:**
  1. **Attitude Toward Behaviour**
     - Evaluation of outcomes: Positive / Negative
     - "If I diet, I'll lose weight, improve my health & be more attractive.
       - Being healthy & looking good are desirable.
  2. **Subjective Norms**
     - The individual's perception of social standard pressures
     - Pressures of significant others (family/friends/girlfriend) to change behaviour.
  3. **Perceived Behavioural Control**
     - One's perceived confidence in being able to change their behaviour.
     - "I think I can diet."
  - **Results in an Intention:**
    - **Change** behaviour
    - Or **Continue** behaviour
    - **Results in Behaviour**

Cognitive-Behavioural Therapy

- Behaviour = the outcome of an interaction between the way one thinks and environmental events.
- Behaviour is governed by the individual's expectations about the outcomes of engaging in it.
  - Eg. Hot Stove Vs. Smoking
- **Focus on:**
  - **The behaviour itself:** Ie. The conditions that elicit/maintain/& reinforce it.
  - **Individual's Beliefs about their health habits:** "I will never be able to quit smoking."
  - **Self-observation & monitoring:** Record & chart behaviour.

Classical Conditioning

- Where a natural stimulus acquires the ability to evoked by another stimulus.
- Ie. Unacquiring a 'taste' for something.
- Eg. Using 'antabuse' to treat alcoholism:



Operant Conditioning

AKA: *Instrumental* conditioning.

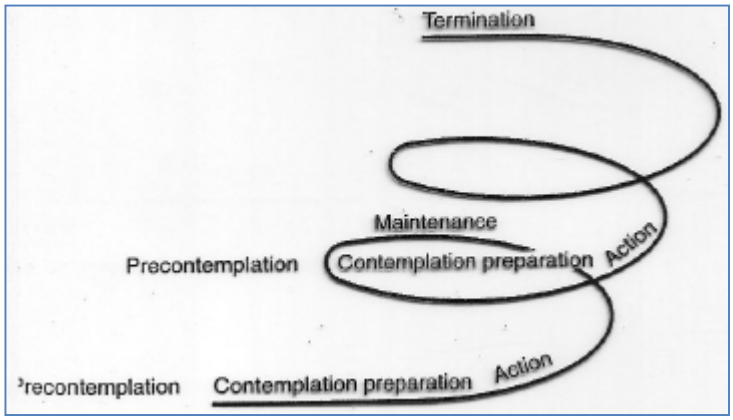
- Assumes that an individual's behaviour is a consequence of **positive** or **negative reinforcement.**
- If positive, the behaviour is more likely to occur again.
- If negative, it is less likely.

Other Methods:

- **Role Modelling**
- **Self-rewarding**

Stages of Change:

- **Precontemplation**
  - No intent to change
- **Contemplation**
  - Considering a change
- **Preparation**
  - Making small changes
- **Action**
  - Actively engaging/abstaining from behaviour
- **Maintenance**
  - Sustaining the behaviour
- **Possible Relapse**
  - Going back to previous behaviours.



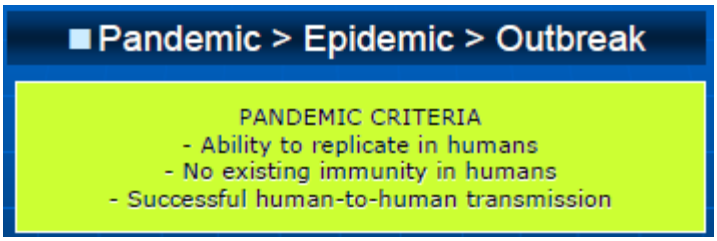
Relapse Prevention

- Common with addictive disorders (smoking, drinking, gambling, etc)
- More likely to occur in times of stress, anxiety, depression
- Once relapse has occurred, it is just as hard to 'quit' the 2nd time as it was for the 1st.

Pandemics: Influenza

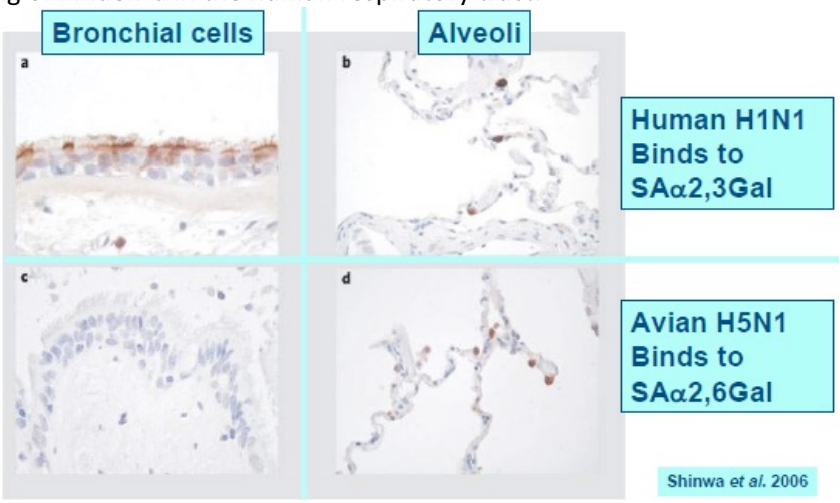
What is a Pandemic?

- **World Health Organization (WHO) – 3 Criteria:**
  - Disease is **New** to a population; (Ie. NO Existing Human Immunity)
  - Agents infect **Humans**, causing serious illness; and
  - Agents **Spread Easily** and among humans.
- **It is not a pandemic just because it is widespread or kills many people; it must also be infectious.**
  - Eg. Cancer kills many people, but is not a pandemic because it is not infectious or contagious.
- **Excludes "seasonal influenza" –not a new disease**



Eg. Avian flu H5N1:

- Case fatality rate >**50%**
- Very severe disease even in fit young people
- BUT NOT person to person transmission (luckily, so far!)
- **Pathogenesis of Influenza:**
  - Binding of influenza in the human respiratory tract:



NB: Human H1N1 is present in Bronchial Cells, but Avian H5N1 is not.

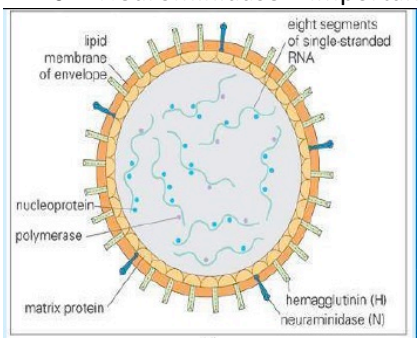
- **WHAT DOES THIS MEAN?**
  - If human to human transmission for H5N1?
    - → Would Become a Pandemic

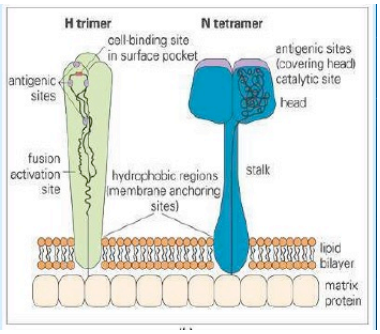
Eg. H1N1 (Swine Flu):

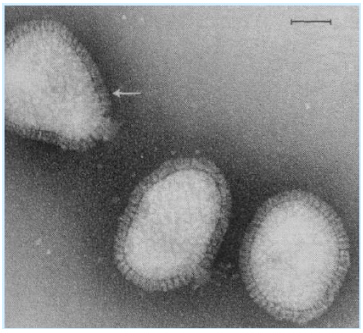
- **Usually mild infection with low case fatality rate,**
  - Many were Fit, Healthy, Young People.
- **Usually uncomplicated except in "high risk" groups:**
  - COAD (chronic obstructive airways Disease)
  - CCF (Chronic cardiac failure)
  - Pregnancy
- **Rapid spread**
- ***→ Pandemic***

Orthomyxovirus (Influenza) Morphology:

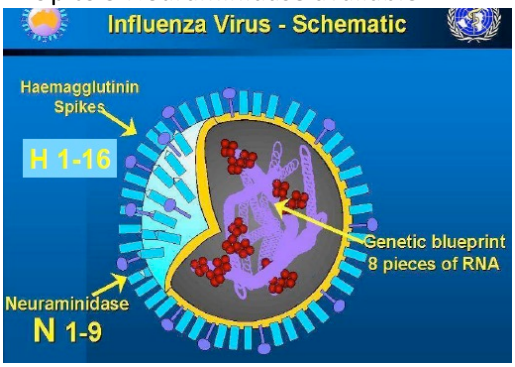
- **Surface Glycoproteins:**
  - Haemagglutinin
  - Neurominidase – Important in the release of the virus from the cell

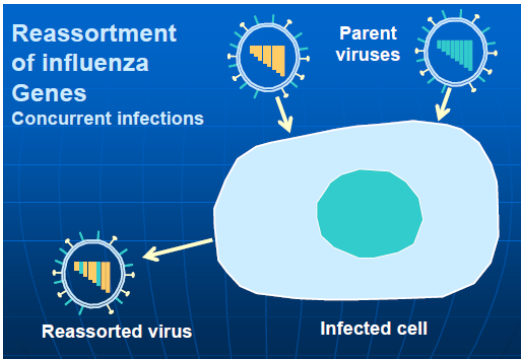




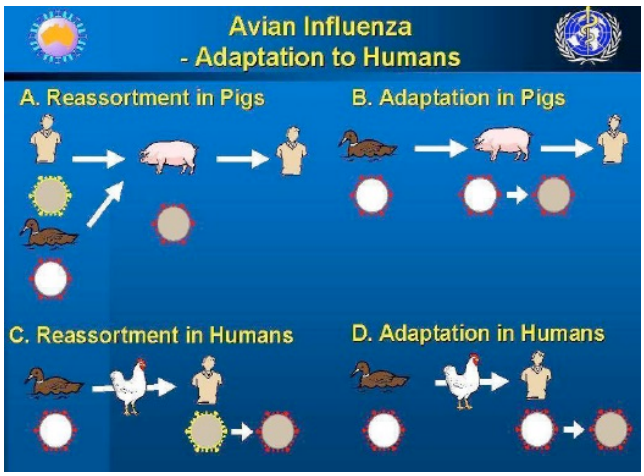


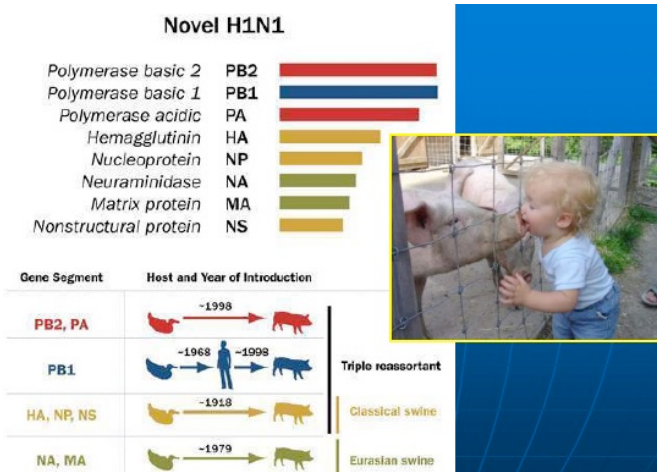
- **Replication:**
  - Virus attaches to receptors via the H Protein
  - There are 8 Discrete Segments of –ve-ssRNA and each Functions as a Separate Gene
  - Virions bud from the infected cells and require **neuraminidase** for **release of the virus**
  - The **haemagglutinin** must be Proteolytically Cleaved from a larger precursor to become active.
- **Influenza Viruses Change!!!:**
  - Up to 16 Haemagglutinins available
  - Up to 9 Neuraminidase available





  - **Antigenic SHIFT:**
    - Infection with 2 parent viruses
    - Reassortment of viral genes
    - → Brand-new virus created
  - **Antigenic DRIFT:**
    - Gradual Change in Genome due to MUTATIONS
    - → New '*Strain*' of Virus
    - → Annual outbreaks & Epidemics
- **How Can This Reassortment Occur?**





- **Immune responses to Influenza:**
  - **The Main Resonse: Cytotoxic T-Cells:**
    - →Responsible for the lysis of infected cells
  - **Helper T-cells** → Responsible for the cytokine production that activates and recruits the Tc-cells.
  - **IgA-Antibodies** in Respiratory Mucus →Prevention or Reduction in the *Severity* of *Reinfection*

Pandemic Management:

- Potential Solutions Depend on phase of pandemic
- **Australian Phase Descriptions**
  - **ALERT:**
    - A novel zoonotic virus with **pandemic potential** causes severe disease in humans.
    - There is no Human-Human Transmission
    - Novel virus has not arrived in Australia.
  - **DELAY:**
    - Novel virus still not in Australia.
    - OS4 Small cluster of cases in one country overseas.
    - OS5 Large cluster(s) of cases in only one or two countries overseas.
    - OS6 Large cluster(s) of cases in more than two countries overseas.
  - **CONTAIN:**
    - Pandemic Virus Arrives in Australia
    - Small Number of Cases
  - **SUSTAIN:**
    - Pandemic virus Established in Australia and Spreading in the community.
  - **CONTROL:**
    - Customised Vaccine widely available
    - Beginning to bring the Pandemic under control.
  - **RECOVER:**
    - Pandemic controlled in Australia but further waves may occur if the virus drifts and/or is re-imported into Australia.

- **Triage?**
  - **Clinical symptoms:**
    - Fever + Cough → Treat like they have the Flu.
  - **Age groups at risk:**
  - **Exposure of Staff & Other Patients:**
    - It's impossible to isolate patients in an ED

HOW DO YOU DIAGNOSE? – (Ie. Differentiating it from a common Viral URTI):

- Clinical Findings (Poor Specificity/Sensitivity)
- **Rely on Laboratory & Contact history (Assume they're infected)**

Who do you treat?

- **Depends on phase-**
  - **Early phase**, treat everyone
    - Reduce disease transmission
  - **Later phases**, treat at risk groups
- **Who pays for it?**
  - If you treat everyone, it gets very expensive.

Anti-Influenza Drugs:

- **M2 Blockers: Amantadine and rimantadine target the M2 protein**
  - they have a limited spectrum of activity
  - **resistance readily develops**
- **Neuraminidase Blockers: Zanamivir (Relenza) and Oseltamivir target the neuraminidase enzyme**
  - (NB: Neuraminidase is essential for viral budding & therefore transmission)
  - Effective against both influenza A and B
  - Early drug treatment reduces the severity and duration of the disease

Influenza Prophylaxis: Becomes Available At "Control" Phase:

- **Vaccines - The #1 Method of Choice:**
  - **Who Gets it?**
    - *High Risk Individuals* (eg. old, debilitated, chronic heart/respiratory/renal disease)
    - *People in closed institutions* (Eg. Prisons)
    - *Groups in community service* (Eg. Doctors/Hospital Staff)
- **Types:**
  - **Inactivated Vaccines** are prepared from the appropriate strain of virus
  - **Subunit Vaccines** are prepared to reduce the content of extraneous proteins

- **New Generation Vaccines:**
  - **Live Attenuated Vaccines:**
    - These vaccines could be administered as a nasal spray
    - This would encourage the development of appropriate immune responses based on mucosal immunity
  - **Recombinant Vaccines:**
    - Based on Recombinant DNA Technologies

ETHICAL ALLOCATION OF SCARCE RESOURCES?

- **Single biggest question is how to ration scarce life saving resources:**
  - "who shall live when not all can ?"
- **WHO GETS IT ?** ***(Fleming, BMJ 2005)***
  - Blind Justice? (1st come or lottery)
  - **High risk given priority ?**
    - (old, chronic disease)
  - **Healthcare workers ?**
  - **Essential services?**
    - (Policemen/Firemen)
  - Children?
  - Global perspective

Eg. In the Recent H1N1 (Swine) Outbreak:

- Massive access block (Where there are insufficient beds for new patients)
- →ED overcrowding
- Not enough ICU beds
- →More beds were created by:
  - →Cancellation of elective surgery
  - →Esp cancellation of elective major surgery needing ICU.
- ***And this was only a MILD disease!***

MANAGEMENT of PANDEMIC?

- **Therapeutic countermeasures**
  - stockpiling of resources
    - vaccines
    - antiviral medications
  - access to care
  - health care workers
- **Non therapeutic countermeasures**
  - infection control
  - surveillance and contact tracing
  - social separation
  - quarantine and containment
  - international boundaries, duties and foreign nationals

ISOLATION AND QUARANTINE – Essential In Early Phase:

- **Isolation** = Separation (for the period of communicability) of known **infected persons** to prevent or limit the spread of infection.
- **Quarantine =** Restriction of activities of **healthy persons who have been exposed,** to prevent disease transmission during the incubation period.


SURVEILLANCE & CONTACT TRACING:

- **Contact Tracing** = Identification of cases by Name.
- **Surveillance** is more intrusive than simply reporting names:
    - daily temperatures, health questionnaires
    - complete daily certificates

Conflicts of Interest:

- **CLINICAL MEDICINE**
    - Doctors Promote best interests of a Patient
        - (Respect patients Liberty & Autonomy)
- **PUBLIC HEALTH**
    - Promotes best interest of the Population
    - Liberty and Autonomy of the Patient may be Overridden for the good of the public.
        - Quarantine
        - Isolation
        - Closing International Borders

What will the future hold?

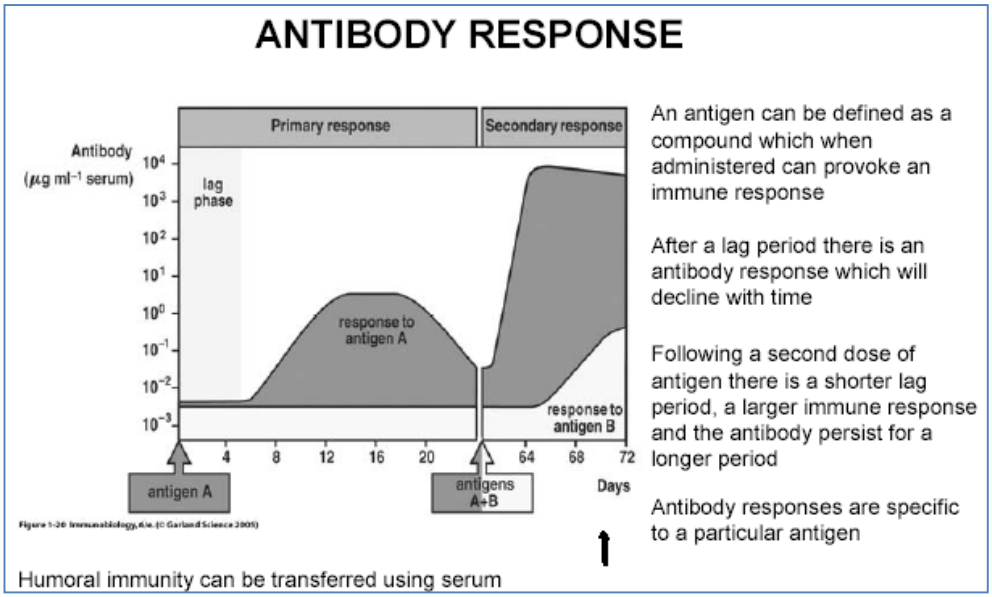
- Will there be another pandemic – **Yes!!**
- What serotype of virus will be responsible - ??
- How well are we prepared ?? - NOT
- How much warning will we get??
- What should I be doing to prepare ?

Vaccination/Immunisation

WHO: "The most successful & cost-effective public health intervention in history"

How Vaccines Work:

- **Individual Protection:**
  - They stimulate the immune system to create Antibodies/Memory-Cells in the absence of Disease Symptoms.
  - Once immune, if the body is subjected to the actual pathogen, it mounts an even stronger attack (Secondary Immune Response) against it.
- **Herd Immunity:**
  - Protects those who aren't vaccinated in the community, providing there is a high rate of vaccination within the population.



Principals of Vaccine Development & Use:

- 1. Separate the Disease-Causing effects from the Immune-Generating effects in an organism.
- 2. Give it to susceptible individuals to provoke an immune response.
- 3. Result is non-susceptible, immune individuals.
- 4. Eventually results in herd immunity.

Contraindications to Vaccination:

- **Absolute:**
  - Anaphylactic response to vaccine or component
- **Relative:** (Ie. Risks Vs. Benefits)
  - Immunocompromised (Live Vaccines)
  - Pregnant or Suspected Pregnancy (Live Vaccines
  - Fever of >38.5°C
  - Recent Live Vaccine (4 weeks)
  - Recently received blood/blood products
  - Guillian Barre Syndrome (GBS)
  - Influenza
- NB: All other *excuses* are not good reasons not to vaccinate!

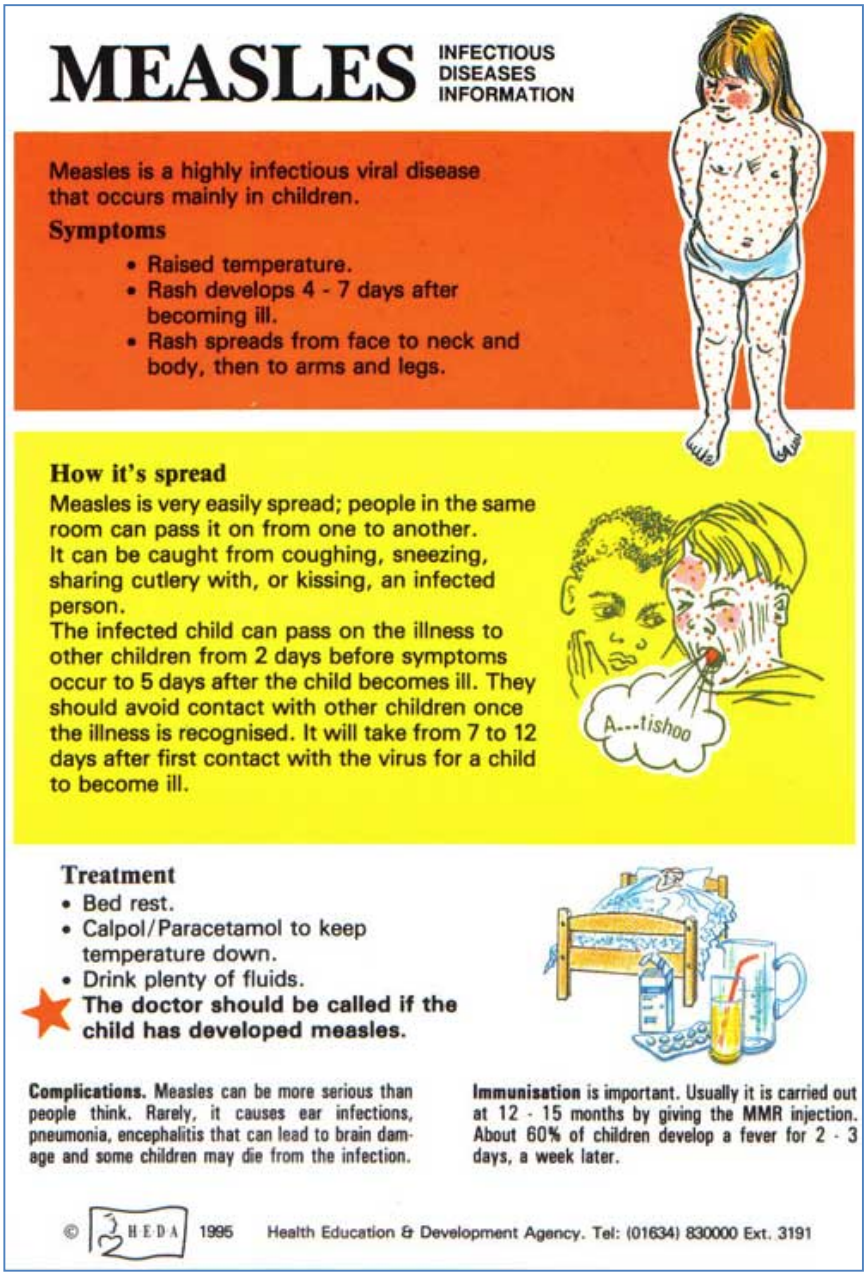
Types of Vaccines:

- **Live Attenuated vaccines:**
  - Live organisms that have been de-pathogenised
  - **Advantages:**
    - Robust Immune Response
    - Lifetime Immunity with 1 or 2 doses.
  - **Disadvantages:**
    - Potential to cause disease (can't give to immunocompromised or pregnant women)
    - Potential for Adverse Events/Side-Effects.
- **Inactivated/killed vaccines:**
  - Dead organisms containing relevant proteins but unable to replicate
  - **Advantages:**
    - No Ability to cause disease
    - Fewer Adverse Events/Side-Effects
  - **Disadvantages:**
    - Less robust immune response
    - Waning Immunity → Requires multiple doses & may require booster.
- **Acellular/Toxoid/Subunit:**
  - Artificially synthesised non-toxic antigens.
  - **Advantages:**
    - No Ability to cause disease
    - Fewer Adverse Events/Side-Effects
  - **Disadvantages:**
    - May require Adjuvants or Conjugation
    - Less robust immune response
    - Waning Immunity → Requires multiple doses & may require booster.

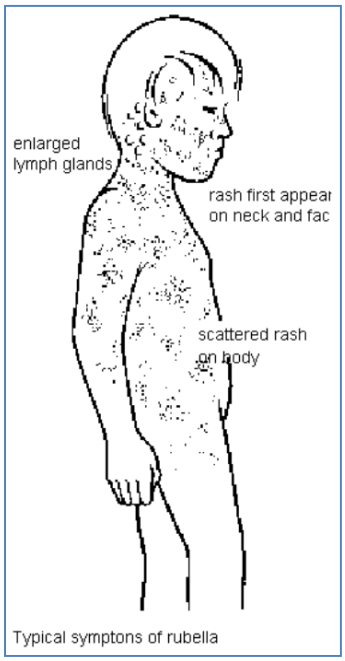
2 Important Vaccine-Preventable Diseases:

- **Measles:**
  - **Extremely Virulent: –** One of the most infectious (easily Spread) Diseases known to man.
  - **Genus: –** Morivillivirus
  - **Occurrence:**
    - Prior to Immunisation = >100Million cases/year → 6 Million Deaths/year. (Worldwide)
    - Post-Immunisation = 99% drop in cases.
  - **Transmission: -** Airborne Droplet Spread
  - **Incubation Period:**
    - ≈10 days to onset of fever
    - ≈14 days to onset of rash
  - **Period of Communicability:**
    - From 'Prodrome' (Time before symptoms) to 4 days after onset of rash.
  - **Susceptibility:**
    - Everyone un-sensitised people.
    - Survival of Illness → Lifetime immunity
    - 1st Vaccine → 95% Immune
    - 2nd Vaccine → 99% Immune
    - Maternal Antibodies protect infant for 6-9 months.
    - Malnutrition is a problem – as measles causes diarrhoea in children.
  - **Symptoms:**
    - Fever
    - Malaise
    - Cough
    - 'Coryza' – ("Overflowing Head")
    - Conjunctivitis
    - Rash – starting on face → Spreading to rest of body
    - Koplic Spots (Unique to Measles) – White/Blueish spots on buccal mucosa.

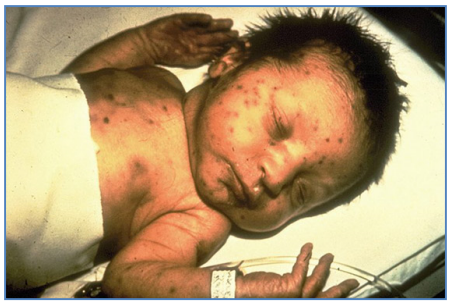
- **Complications:**
  - Otitis Media (Middle ear infection)
  - Pneumonia
  - Diarrhoea
  - Acute Encephalitis (Rare)
- **Measles Vaccine:**
  - **Type: -** Live Attenuated Vaccine (Given in combination with Mumps, Rubella & Varicella)
  - **NB:** It interferes with other live vaccines.
  - **NOT given during Pregnancy**
  - **Adverse Reactions:**
    - Fevers – common
    - Faint red rash
    - Local swelling
    - Local Knot in muscle
  - **Dosing:**
    - **1st Dose @ 12mths**
    - **2nd Dose @ 18mths**
- **Measles in Australia:**
  - No longer endemic
  - Outbreaks are due to imported cases.



- **Rubella:**
  - **Genus: -** Rubivirus
  - **Occurrence:**
    - Pre-Vaccine = Worldwide Endemic
      - Epidemics every 5-9yrs
    - Post-Vaccine = Elimination of Rubella
  - **Transmission:**
    - Airborne Droplet Spread
    - Contact with Mucus Membranes
  - **Incubation Period:**
    - 14-21 Days
  - **Period of Communicability:**
    - 1 Week Before & 4 Days after Rash
  - **Susceptibility:**
    - Universal Without Vaccine/Prior Infection
    - Immunity after single dose (95-100%)
    - Maternal Antibodies protect infant for 6-9mths.
  - **Symptoms:**
    - 50% Asymptomatic
    - Low-Grade Fever
    - Headache
    - Malaise
    - Coryza ("Overflowing Head")
    - Conjunctivitis
    - Lymphadenopathy
    - Arthralgia
    - Rash



Typical symptons of rubella



  - **Complications:**
    - Post Viral Encephalitis (Uncommon)
    - **Congenital Rubella Syndrome (CRS)
      - Occurs in 90% of babies whose mother had Rubella during 1st Trimester
      - Multiple Defects are common (Eg. Blindness, Deafness, many more...)
      - Hence ALL WOMEN OF CHILD-BEARING AGE MUST BE IMMUNISED.
  - **Rubella Vaccine:**
    - **Type: -** Live Attenuated Vaccine (Given in combination with Measles, Mumps & Varicella)
    - **NB:** It interferes with other live vaccines.
    - **NOT given during Pregnancy**
    - **Adverse Reactions:**
      - Fevers – common
      - Faint red rash
      - Local swelling
      - Local Knot in muscle
    - **Dosing:**
      - **1st Dose @ 12mths**
      - **2nd Dose @ 18mths**
    - **ALL WOMEN OF CHILD-BEARING AGE MUST BE IMMUNISED.**
  - **Rubella in Australia:**
    - Incidence has fallen considerably since vaccine.
    - Mass vaccination of school-girls → ↓CRS.

Other Vaccines & the Diseases they Prevent:

- **Hep B:**
  - **Hepatitis B:**
    - An Infectious illness caused by Hep-B-Virus
    - Infects the Liver
    - Causes Vomiting, Jandice, Liver Cirrhosis & Liver Cancer. (Rarely death)
- **DTP:**
  - **Diptheria:**
    - Upper Respiratory Tract illness
    - Characterised by sore throat, low fever & a pseudomembrane on tonsils/pharynx/nasal cavity.
  - **Tetanus:**
    - Gram-Positive anaerobic bacteria infection – occurs through skin wound.
    - Bacteria secrete a neurotoxin → Prolonged contraction of skeletal muscle fibres ("Tetany")
  - **Pertussis:**
    - Whooping Cough – A highly contagious disease spread by droplet transmission.
    - Bacterial Infection
    - Droplet Transmission
- **Hib:**
  - **Haemophilus Influenzae B:**
    - Actually a Bacteria (Despite the 'viral' name)
    - Cause opportunistic infections.
    - Leads to Bacteraemia, Pneumonia, Bacterial Meningitis.
- **IPV:**
  - **Inactivated Poliomyelitis (Polio):**
    - AKA: Infantile Paralysis
    - An acute viral infection
    - Faecal-Oral Transmission
    - 90% of infections are asymptomatic.
    - If the virus enters the CNS, it preferentially destroys motor neurons → Muscle Weakness, Paralysis & Muscle Wasting.
- **$_{7v}$PCV:**
  - **Pneumococcal Conjugate:**
    - Bacterium →
      - Pneumonia, Sinusitis, Otitis Media
      - Meningitis (Most common cause of bacterial meningitis)
      - Bacteraemia → Sepsis
      - Endocarditis
      - Pericarditis
- **Rotavirus:**
  - Leading cause of Severe Diarrhoea among infants & young children.
    - Also causes gastroenteritis & dehydration
  - Known as *Stomach Flu* (But no relation to influenza)
  - Faecal-Oral Route
- **MMR:**
  - **Measles:** See Above
  - **Mumps:**
    - Viral Disease
    - Droplet Transmission
    - Typically presents as painful swelling of the Salivary Glands, fever & headache.
    - Can also cause painful testicular swelling & rash.
  - **Rubella**: See Above
- **MenCCV:**
  - **Meningococcal C:**
    - Bacterium
    - Typically causes Meningitis & Fever, but is most dangerous when infection becomes septic.

GLS - *Cold chain*

1. **What is the *cold chain*?**
   - Is the transport and storage of a vaccine b/w the temperature of 2-8^{oC}. It includes the vaccine equipment, people and the procedures

2. **What are the *stages* in the cold chain?**
   - Manufacture
   - Supply
   - Distribution
   - Clinic
   - Fridge
   - Patient

3. **Name 5 Vaccines that are damaged or destroyed by *freezing*?**
   - Tetanus
   - DTP
   - Hib
   - Hep A & B
   - Influenza
   - Mneumococcal

   Which vaccines are damaged by exposure to *heat or light*?
   - BCG
   - Oral polio
   - MMR

4. **What is the main requirement for *vaccine fridge thermometers*?**
   - Can measure max & min temperature for the previous 24 hrs

5. **Which are the *best types of thermometers*?**
   - Mercury and digital thermometers

6. **Where in the fridge would you place the temperature probe?**
   - In the centre of the fridge
   - In the case of a multiple purpose fridge (eg. If food is stored with it), then is best located with the immunisations in the foam box within the fridge

7. **What *monitoring device* is included in vaccine transportation of vaccine supplies?**
   - Temperature monitors → heat & freeze cards (charts)

8. **How would you *pack* vaccines for transport and what other *precautions* would you take for transportation?**
   - Vaccine package
     - Good icebox with a tight fitting lid
     - Store immunisations with ice block that is "sweating"
     - Shredded newspaper is recommended to allow air to circulate around vaccines
     - Layers: ice block - shredded newspaper – immunisations – shredded newspaper – piece foam – ice block
   - Transport
     - Whenever being transported don't place in direct sunlight
     - Minimise duration of journey
     - Record temperature whenever vaccines are put in/ taken out
     - Place securely in boot
     - Only deliver to surgery if someone is there
     - Check the temperature of the fridge at surgery before put new immunisations in

9. **What are the *requirements of a surgery vaccine fridge*?**
    - Have a safe lockable fridge
    - Try to keep immunisations in a proper immunisation fridge – if not possible separate the immunisation from the other things that are being stored in the fridge (eg. Have separate shelf for immunisation and separate shelf for medications)
    - Check the temperature of the immunisation fridge daily
    - When placing new vaccines in fridge, rotate stock
    - Use older vaccines first, don't use the most recent – will prevent vaccines going out of date
    - Use only 50% of available space in fridge – allow air to circulation around the vaccines in the fridge
    - Place immunisation in correct location in fridge – the bottom shelf and door shelves should no be used
        - recommended to place salty water in these draws to prevent shelves from being used and the water from being drank
    - Don't co-store non-vaccine items in the fridge (eg food) – this will ↑ fridge door opening and may interfere with temperature

    - If it is thought that cold chain may have been broken or vaccine has been tampered with contact supplier 1st before throwing out. Isolate in the fridge in with clear label stating "do not use" until ascertained whether should be thrown out

Allaying parents fears – potential q's a parent might ask

Will the actual needle given for immunisation hurt my baby?

- It will hurt a bit, but it can be compared to a bee sting and will only hurt for a short period of time

Why do you need to give the same needle a couple times, months/years apart if your already had it?

- To improve the immune response. When give a 2nd time, the immune system will be able to cope much better than if only given once. (Primary vs secondary immunity)

Why do you need to give my child so many different needles all @ once?

- Only injecting a small amount for each immunisation
- You are protecting the child against many different diseases at once

Why immunise for diseases if they are not even present in Australia anymore?

- Eg. With polio, many people thing that the disease has totally been eradicated – this is not true, as it is still very common in other countries.
- As long as the disease is present anywhere in the world it is still highly possible to catch the disease.

Is it true that your actually injecting the disease into people with certain types of immunisation. Can I catch the disease?

- The sx. assoc with naturally catching the disease and from an immunisation vary. If catch naturally the severity can vary, however it is generally more severe.
- Eg. If don't get chickenpox till later in life as adult, the effects of the disease can be quite severe, and potentially fatal

I heard MMR causes autism. Should I still immunise my child?

- Essentially is an old wives tale - There is no conclusive evidence from any of the studies
- Poor study design - Confounding variables of all children being immunised and a child getting diagnosed with autism at the same time.

Why not just depend on immunity developed naturally from infection, rather than having a needle to develop immunisation

- Problems if catch at older age
- Avoid more disease complications
- More controlled – know exactly whats going in.
- Giving to healthy child, when immune system is competent.

THINGS TO REMEMBER:

- Be confident – parent feel better
- Allay all parents fears
- Check they fully understand, and ask if they have any further questions.

Synthesis Session: Smallpox & Influenza:

Smallpox:

- Disfiguring → Scarring
- Claimed Millions
- Affected Aborigines worst
- Quarantine was common
- **Variola Viruses:**
  - Major (30% Mortality)
  - Minor (15% Mortality)
- **Old-School 'Vaccines' = Variolation:**
  - Dried, Crushed up smallpox scabs were blown into the patient's nose.
  - 98% were immunised.
  - 2% got the disease – Was a worthwhile risk to take.
- **The Smallpox Vaccine Discovery:**
  - Cowpox (A benign pox virus) is used to create an immune response to the Smallpox Virus.
- **WHO decided to eradicate Smallpox** → Succeeded in 1979; 2 years after last naturally-occurring case.

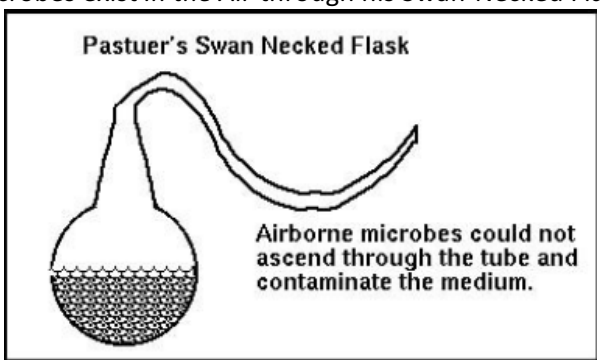
Influenza:

- **Massive *Pandemic* during WWI (1918)** → Killed 500,000,000 people.
  - 3 Waves, each increasing in Death Rate.
  - NB: all pandemics since are genetic descendants from the 1918 pandemic
- **Seasonal Influenza**
  - Annual Epidemics
  - Typically influenza-A (one of the 3 types – A/B/C)
  - Annual global death toll of up to 1 million. (Mostly elderly/debilitated) – Hence Flu-Vax for elderly.
- **Droplet Transmission** – Enhanced by overcrowding.
- **'Orthomyxovirus':**
  - **3 Types:** A/B/C
  - **Exhibit 2 Types of Glycoproteins – Used to identify different strains:**
    - **Haemagglutinin:** "H"
    - **Neuraminidase:** "N"
    - *Hence – H1N1*
- **Clinical Presentation:**
  - Abrupt onset (within 6hrs)
  - Fever (sore joints, muscles, prostration)
  - Acute Respiratory symptoms
  - Cough
  - Children get GI-Symptoms (Nausea/Vomiting/Diarrhoea)
- **Complications:**
  - Pneumonia (1^{o} Viral)
  - Pneumonia (2^{o} Bacterial)
  - Sinusitis
  - Acute Bronchitis/Asthma Exacerbation
  - Croup
  - Post-Viral Encephalitis
- **Vaccines – Seasonal** – New one each year.
  - H1N1 (A)
  - H3N2 (A)
  - B
  - NB: mismatch still provides some protection.
  - 75% effectiveness
  - NB: It Is a Good Idea to give Flu-Vax to pregnant women, because if they *do* get the flu, they have a higher risk of pneumonia (due to their higher fluid volume)

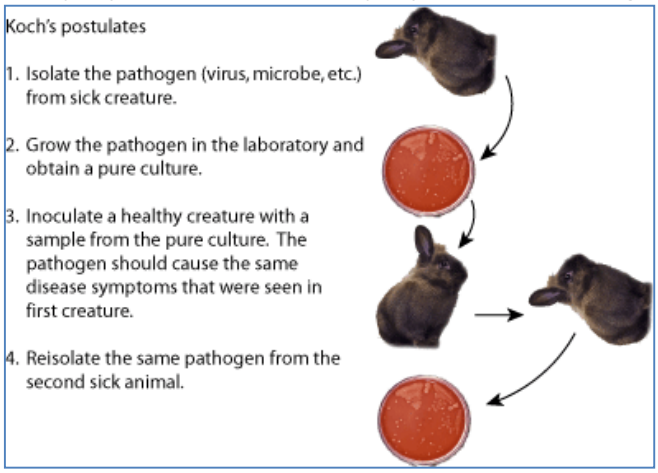
Basic Concepts of Infectious Diseases

Germ Theory:

- People recognised that meat broth became cloudy and overgrown with microbes.
- But *where did these microbes come from?* – 2 Schools of Thought:
  - 1. Spontaneous Generation
  - 2. Formed from Seeds/Germs.
- **Pasteur** Proved that Microbes exist *In the Air* through his Swan-Necked Flask experiment.

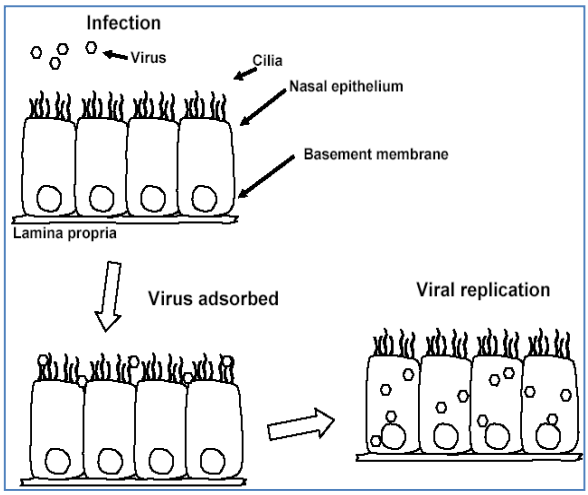


- **Robert Koch** Proved that *Specific Microbes* caused *Specific Diseases* through 'Koch's Postulates':

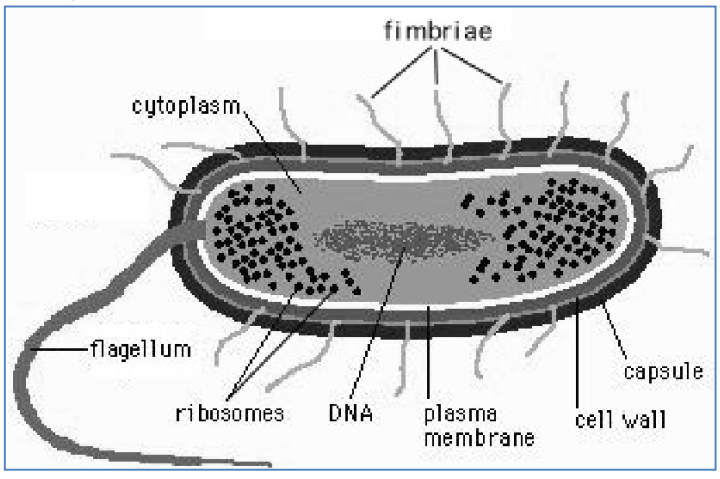


Revision of Microbial Diversity:

- **Viruses:**
  - Very small
  - Nucleic acid inside protein coat (DNA or RNA)(ss or ds)
  - Complete parasitic dependency
  - Replicates inside cell - but metabolically inert in external environment.
  - Need close/direct contact
  - Need a moist environment
  - Respiratory route / oral / inoculation / sexual transmission.

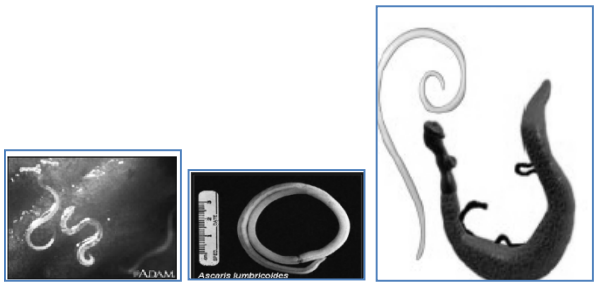


- **Prokaryotes:**
  - **Bacteria:**
    - Larger than viruses
    - Visible under light microscope
    - Living → replicate by binary fission
      - (Therefore Can be killed)
    - Intracellular or extracellular
    - Motile
    - Can produce toxins
    - Contain DNA, Ribosomes + Inclusions – no true nucleus
    - Resulting disease often more severe.

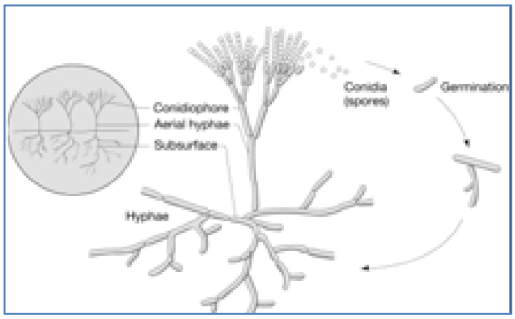


- **Eukaryotes:**
  - **Protozoa:**
    - Single-Celled **Animals**
    - Larger than bacteria – still small enough to live intracellularly.
      - Can also live extracellularly.
    - Vectors / faecal-oral route →most infections occur tropically.

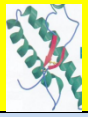
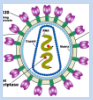
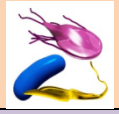
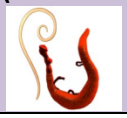
  - **Helminths:**
    - Multi-celled, often macroscopic organisms.
    - Complex body organisation and reproduction (some have sexual dimorphism)
    - Difficult for immune system to destroy – too big.
    - Cause inflammation
    - Are often never eliminated.



  - **Fungi**
    - Thousands of species
    - Few are pathogenic to humans
      - 20ish are fatal.
    - Resulting Mycoses (diseases) Depend on site of infection:
      - Superficial
      - Cutaneous
      - Subcutaneous
      - Systemic
      - Opportunistic – seen in compromised hosts
    - Exist as branched filamentous forms, or yeasts
    - Asexual spores (conidia)
    - Spores commonly inhaled & cause infection.

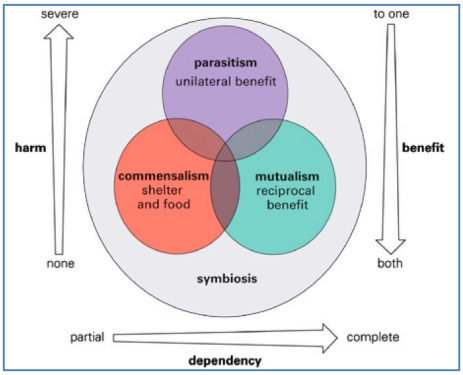


- **+ My Diagram of differential features of Microbes:**

Pathogen:	**Visible Via:**	**Cellular?**	**Nuclear Material:**	**Nuclear Organisation:**	**Structural Constituents:**	**Outer Surface:**
Prions 	Electron Microscope	Acellular	No Nucleic Acid – Just Protein.	No Nucleus	No Membrane. No Cellular Machinery. No Cytoplasm.	No Membrane
Viruses 			DNA or RNA			'Enveloped' Or 'Non-Enveloped'
Bacteria (Prokaryotes) 	Light Microscope	Single Cell	DNA	No Distinct Nucleus. Single, Circular Chromosome. Simultaneous Transcription & Translation.	Membrane-Bound. Cellular Machinery. Cytoplasm.	Bi-lipid membrane is covered by a thick Cell Wall. Gram Pos = Peptidoglycan Gram Neg = Lipopolysaccharide
Protozoan Parasites (Eukaryotes) 				Distinct Nucleus. Several Linear Chromosomes. Transcription in the Nucleus. Translation on Ribosomes in the Cytoplasm.		Simple Bi-lipid Membrane.
Metazoan (Eukaryotic) Parasites (Helminths) 	Naked Eye	Multi-Cell				

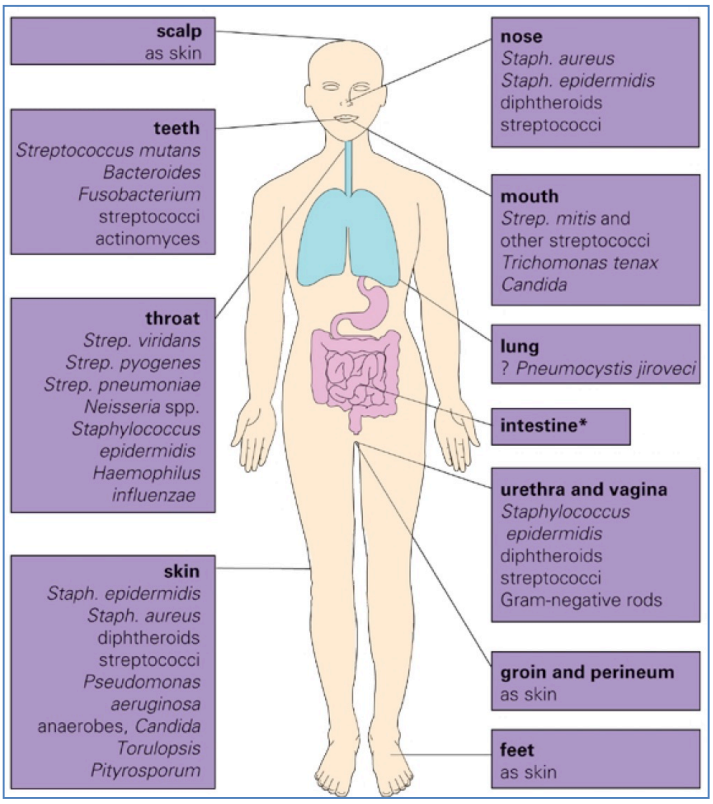
Host-Parasite Relationships:

- **Commensalism:**
  - Colonised; But No Disease.
  - (Eg. E.Coli in stomach)
- **Mutualism:**
  - Colonised; No Disease; Mutually Beneficial.
  - (Eg. Digestive Bacteria in Colon; Lactobacillus in Vaginal → Acidity)
- **Parasitism:**
  - Colonised; With Disease/Damage.
  - (Eg. Hookworm; Plasmodium Malariae)



Normal Flora Vs. Pathogens:

- **Normal Flora (Commensals):**
  - **Can be Beneficial:**
    - Can be *Protective* by outcompeting potential pathogens for Space/Nutrients.
    - If they are washed away (Eg. Vaginal Antibiotics), pathogens can colonise the area → Disease
  - **Heavily Colonise Skin:**
    - Armpit, Perineum, Interdigital areas
    - Nose and oropharynx
    - GI Tract
    - Uro-genital tract.
  - **Heavily Colonise the GIT:**
    - *Density* of Microbes *Increases* Towards the Rectum. (Stomach Acid → Low Numbers)
    - *Species* of Microbes change throughout due to different environments.
  - **Some Areas are Sterile:**
    - Bladder
    - Blood
    - Organs
  - **Location depends on Aerobic/Anaerobic Species:**
    - Aerobic – Likes Oxygen (Eg. In Respiratory Tract)
    - Anaerobic – Cannot stand Oxygen (Eg. Found in Bowel/Necrotic Tissue/Etc)
  - **Nosocomial Infection (Opportunism):**
    - If Commensals Colonise somewhere they shouldn't, they cause disease.
    - Often occurs in Hospitals → Typically Highly Resistant to Antibiotics.



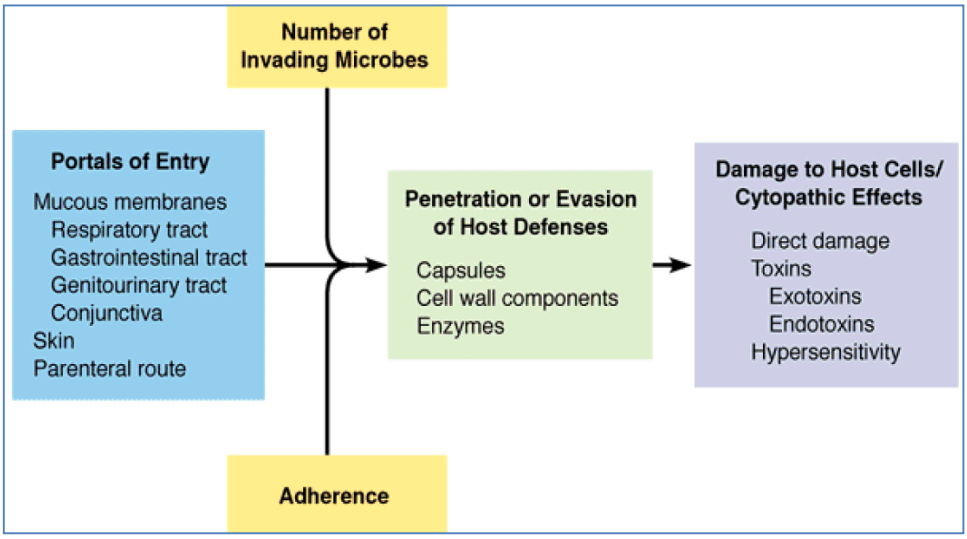
- **Pathogens (4 Features of a "Pathogen"):**
  - **Pathogens =** Organisms capable of causing disease.
  - ***They *MUST* do *ALL 4* of the Following:**
    - 1. Gain Entry to Host
    - 2. Attach & Multiply
    - 3. Evade Host Defences
    - 4. Cause Damage to Cells/Tissues
  - **Primary Vs. Secondary Pathogens:**
    - **1° Pathogens:**
      - Can produce an Infection without the help of other organisms.
      - →Also Encourage 2° Pathogens.
      - (Eg. HIV → Immunocompromise)
    - **2° Pathogens (Aka: Opportunistic Pathogens):**
      - Only produce an Infection due to damage caused by 1° Pathogens.

"Mixed Infections:

- Most infections severe enough to cause symptoms aren't caused by a singular pathogen.
- Rather, the effects of *2 or more* Pathogens are responsible for disease.
  - Effects are *Additive*
  - May also be *Synergistic*

Pathogenesis (4 Stages to Infection):

- **Pathogenesis =** The biochemical sequence of events whereby microbes (bacteria, fungi, parasites & viruses) causes disease.
- **4 Stages to Infection:**
  - **1. Gain Entry to Host:**
    - **Needs a *Portal of Entry & Exit*. Egs:**
      - **(For Exogenous Organisms) -** Oral/Skin/Trans-placental/Inhalation/Inoculation (wound/skin penetration)/Sexual
      - **(For Endogenous Organisms)** – Organisms already present On/In Body. – Requires Immunocompromise.
  - **2. Attach & Multiply:**
    - **Attachment Via:**
      - Adhesion Receptors (Eg. Glycoproteins on Viruses)
      - Cellular Extensions (Eg. Fimbriae/Pili on Bacteria)
      - Physical Structures (Eg. Hooks/Suckers on Helminths)
    - **Multiplication/Spread of Infection:**
      - Local (Abscesses/Mucosal/Nerves/CSF)
      - Systemic (Blood/Sepsis)
    - **Factors Affecting Spread:**
      - **Organism Factors:**
        - Virulence Factors
      - **Host Factors:**
        - Genetic Susceptibility
        - Immune Status
        - (Age, Pregnancy, Nutrition, Etc)
  - **3. Evade Host Defences:**
    - Beat Physical Barriers (Eg. Flushing, Mucous + Cilia, Stomach pH, Lysosomes)
    - Beat Innate Cellular Defences (Eg. Inflammation, Phagocytosis, NK Cells)
    - Beat Adaptive Defences (Eg. Antibodies, Cell-Mediated Immunity)
  - **4. Cause Damage to Cells/Tissues:**
    - Physical Disruption
    - Toxic Damage
    - Aberrant Cell Activity
    - Immune-Mediated Damage.



Virulence:

- **Short Definition:** The propensity of a microbe to cause infection → disease in a Definitive Host.
- **Long Definition:** The degree of pathogenicity of an infectious agent, indicated by:
  - Case-fatality rates
  - Ability of the agent to invade and damage tissues of the host.
  - Toxicity.
  - Ability to overcome/evade body defences.
- **(*'Avirulence' = Antonym*)**
- **Virulence Factors:**
  - Molecules Expressed/Secreted by Pathogens that enable them to achieve the following:
    - Colonisation of a Niche in the host (this includes adhesion to cells)
    - Immunoevasion, evasion of the host's immune response
    - Immunosuppression, inhibition of the host's immune response
    - Entry into & Exit out of cells (if the pathogen is an intracellular one)
    - Obtain nutrition from the host.
  - Eg. Endotoxin (LPS) – Potent antigen
  - Eg. Exotoxins (eg. Tetanus Toxin) → Tetanus
  - Eg. Fungal Mycotoxins (eg. Aspergillis) → Severe Liver Damage
  - Eg. Ig-Proteases (eg. Strep. Pyogenes) → Break down Antibodies.
  - Eg. Capsules (eg. Bacterial cell walls) → Inhibits Phagocytosis.

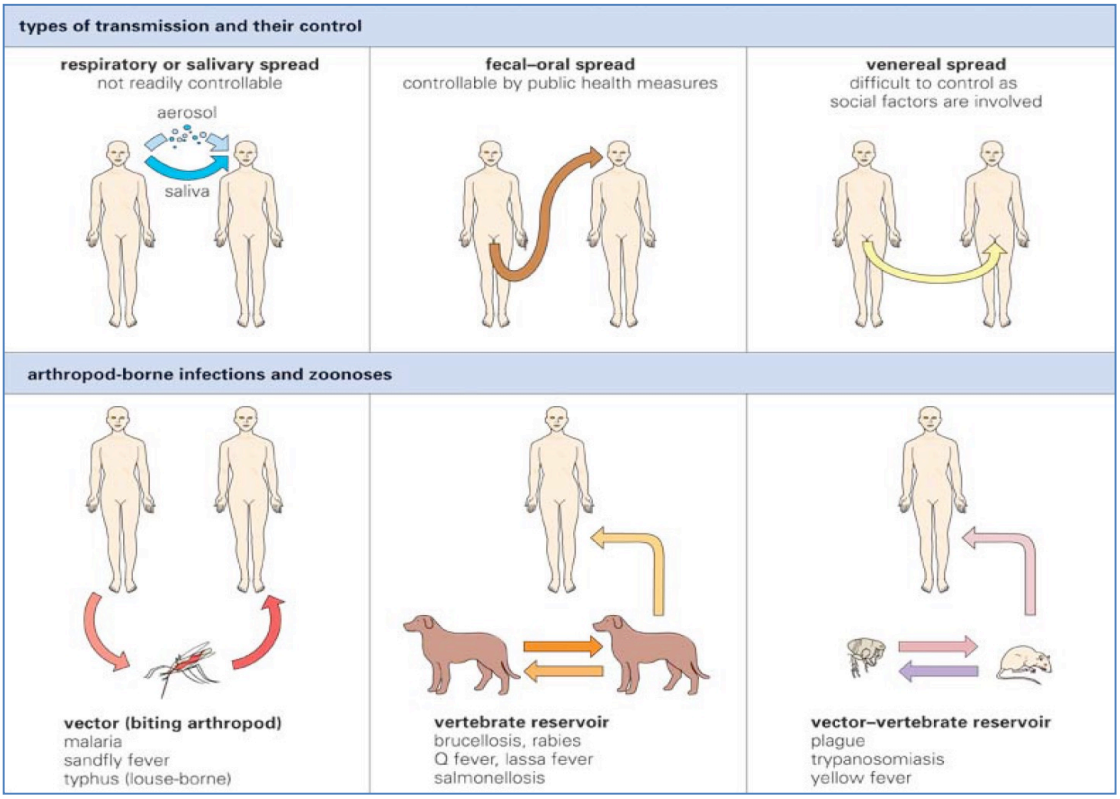
Immune Evasion Strategies:

- **Viruses:**
  - Persist as Latent Infections
  - →Reactivation/Recrudescence following Immunosuppression/Stress.
  - Superantigens → Inappropriate Immune Response
  - Inhibition of MHC-I Synthesis/Assembly/Ag-Loading
- **Bacteria:**
  - Depression of phagocytosis by neutrophils
  - Depress cellular immunity
  - Induction of apoptosis
  - Killing of alveolar macrophages
  - Superantigens → Inappropriate Immune Response
  - Produce superoxide dismutase, catylase or oxidase → protect it from the hydrogen peroxide of the respiratory burst of Neutrophils.
  - Intracellular bacterial evasion:
    - Travel b/w cells without being exposed to extracellular fluid
    - Escape into vacuole in the cytoplasm
    - Prevent fusion of lysosomes with phagosomes

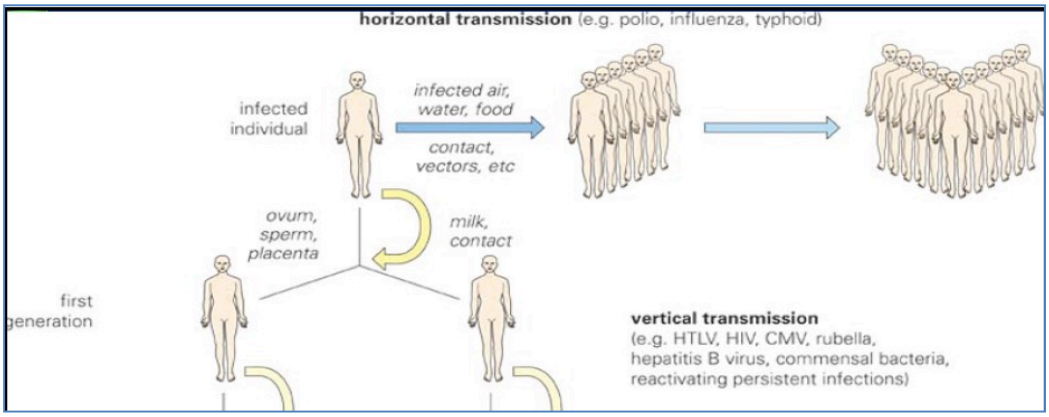
- **Parasites:**
  - **Protozoan Parasites:**
    - Antigenic Variation
    - Antigenic Drift
    - Molecular Mimicry (Expression of Host Proteins)
    - Intracellular Localisation
    - Self-Isolation in Membrane-bound Vesicle.
    - Prevent fusion of lysosomes with phagosomes
    - Sequestration in privileged sites
    - Regulation of host functions.
  - **Helminth Parasites:**
    - Antigen Shedding
    - Protease production → Neutralise some immune components. (Eg. Antibodies)
    - Superoxide Dismutase → Neutralise Respiratory Burst by Neutrophils.
    - Regulation of host functions (Immunosuppression/Maladaptive Response)
    - Skew the T-Helper Response to Favour Th1-Cells:
      - Favouring Th1→ Reduced class-switching to IgE, the AntiParasitic Ab.
    - Use Host Cytokines as Parasitic Growth Factors

Transmission - (Exiting the infected host & Spread of Infection):

- **Successful Microbes must Exit the body →Transmit to a new host. They are Either:**
  - Shed in Secretions/Excretions.
  - Taken up by Vectors (Eg. Mosquitoes) from the blood.
- **Transmission Depends On:**
  - Number of Organisms Shed (High Numbers Needed)
  - Activities of the host (Eg. Coughing, Sneezing, Diarrhoea, Intercourse)
  - Stability in the Environment (Eg. Amebic Cysts resist drying & heat →Survive)
  - # Required for Infective Dose. (Depends on organism & route)
  - Virulence/Pathogenicity
- **Types of Transmission:** - (Requires a "*Vehicle*")
  - Airborne – (Must survive outside the host & in Dry Conditions)(Eg. Influenza)
  - Waterborne – (Eg. Cholera)
  - Food-borne – (Spoilage, Preformed Toxins, Faecal-Oral)



- **Vertical Transmission:** Parent →Offspring
- **Horizontal Transmission:** Person → Person
- **Zoonotic Transmission:** Animal → Human (Via Contact/Inhalation/Ingestion/Bites/Scratches)



Epidemiology:

- **Epidemiology =** "The relationship between factors determining the frequency & distribution of infectious disease in a population"
- **Factors Influencing Epidemiology (Eg. Δ in # of susceptible/environment/organism/new organism):**
  - **The Organism:**
    - Δ in Properties of the Endemic Organism (Eg. Persistence; Transmissibility)
    - New Organism
  - **The Host:**
    - Δ in # of Susceptible Hosts
    - Δ in Conc. Of Susceptible Hosts
    - Δ in Behaviour
  - **The Environment:**
    - Δ in Climate (eg. Cold → People crowd indoors → ↑Droplet Transmission)
    - Δ in # of Vectors (Eg. Rainy season → ↑Mosquitoes)

Prions, Viruses & Parasites

Prions:

- **What are they?**
  - **Abnormally folded Host-Proteins** that accumulate in the brain → Spongiform Encephalopathies.
  - NB: **All** known Prion Diseases **affect the Brain** and are **currently Untreatable** & **Universally Fatal**.
  - The precise structure of the Prion is Unknown.
  - **Derivation of the term "prion":** Proteinaceous, Infectious + 'on'

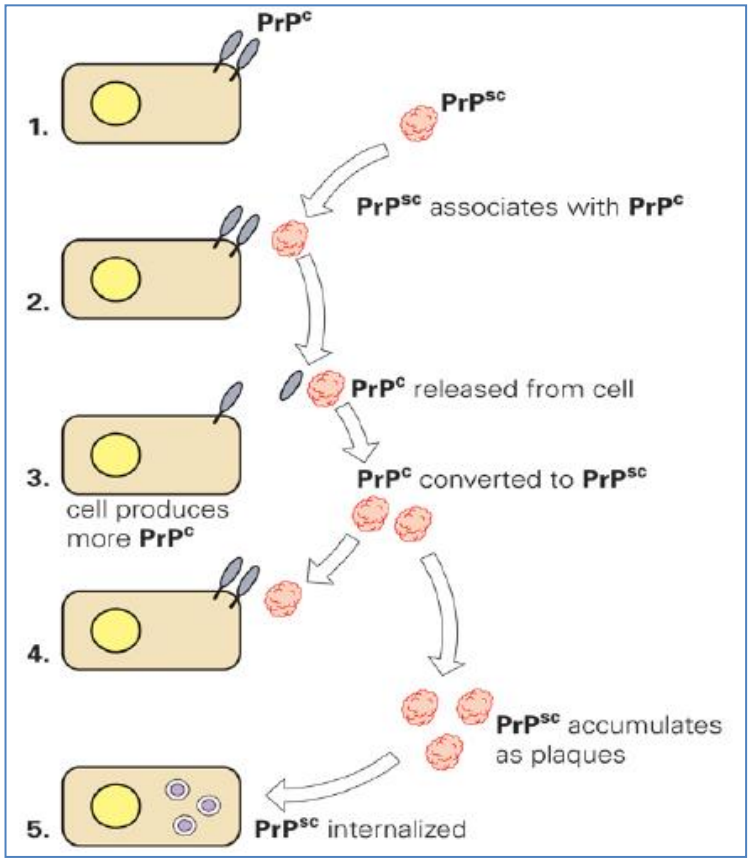
- **TSE's – (Transmissible Spongiform Encephalopathies):**
  - **TSE's =** A *group* of slow, fatal Neuro-Degenerative Diseases.
  - **The Infectious Agent = A *Prion* Protein (PrP) –** Abnormally folded Host-protein (no nucleic acid).
  - Prions cause Neurodegenerative Disease by aggregating Extra-Cellularly in the CNS → form amyloid plaques → Plaques are Internalised → Vacuole formation in Neurons → Spongy Architecture.
  - **Symptoms:**
    - Convulsions (Myoclonus)
    - Dementia
    - Ataxia, Dysarthria, Dysphagia, Nystagmus
    - Behavioural/Personality Changes

- **Human Prion Diseases:**
  - **CJD - *Creutzfeldt-Jakob disease*:**
    - The most common prion-caused disease (1/1M people)
    - 3 Forms: (Sporadic, Variant (mainly younger period), Familial)
  - **GSS - *Gerstmann–Sträussler–Scheinker syndrome*:**
    - Extremely Rare TSE.
    - Familial – Autosomal Dominant.
  - **FFI – *Familial Fatal Insomnia*:**
    - Extremely Rare TSE.
    - Familial – Autosomal Dominant.
  - **Kuru-Kuru:**
    - Found in PNG who had consumed the brains of their relatives.

- **Non-Human Prion Diseases:**
  - **Bovine Spongiform Enecphalopathy ("Mad Cow Disease"):**
    - Neurodegenerative Prion-based Disease in Cattle.
    - Causes spongy degeneration in the CNS like human TSEs.
    - May be transmitted to humans by eating contaminated meat.

- **PrP, PrP^{c}, PrP^{sc}:**
  - ***Prion* Proteins (PrP):**
    - **Normal Form = PrP^{c} (Cellular)**
      - Found throughout the body (Also in mammals).
      - Anchored to the cell membrane by a Glycophosphoinositol (GPI) anchor.
      - Normal α-Helix form. (Functional & Denaturable)
    - **Abnormal Form = PrP^{sc} (Scrapie)**
      - Accumulates in plaque deposits in the brain of affected individuals → Tissue Damage & Cell Death.
      - Abnormal β-Sheet form. (Non-Functional & Non-Denaturable)
      - *EXTREMELY STABLE* – Resists denaturation by Chemicals/Heat/Autoclaving/UV.
        - *Therefore, disposal of prions is VERY DIFFICULT.*

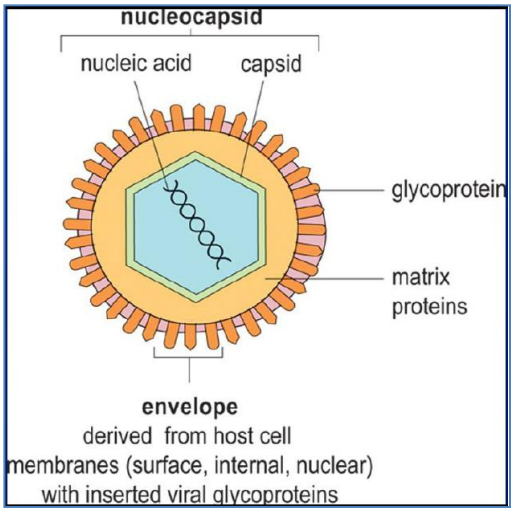
- **Propagation: Conversion of Normal Proteins (α-helix → β-sheet):**
    - Prions propagate by transmitting a ***Mis-Folded Protein State,*** Instead of replicating.
    - Ie. They convert *Pre-Existing, Normal* forms of the protein to the *Abnormal Form*.
    - Due to small differences in PrP between different animals, it is unusual for a prion disease to be transmitted zoonotically.
        - However, The human Prion Disease, ***variant Creutzfeldt-Jakob disease***, is believed to be transmitted from cattle with ***Bovine Spongiform Encephalopathy*** through infected meat.



- **Transmission:**
    - **Acquired, Familial, or Sporadic.**
    - **Current Theory –** Primarily infected through ingestion. Prions may be deposited in the environment through Animals Carcases, Urine, Saliva, other body fluid; and may linger in the soil.

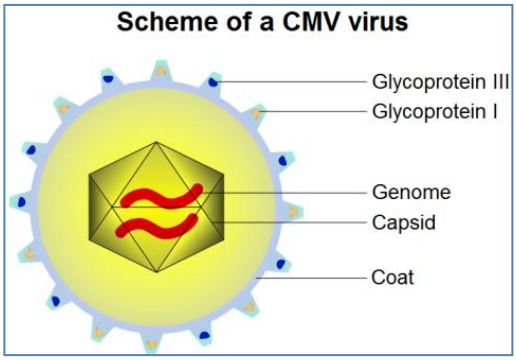
Viruses:

- **Nomenclature:**
  - **Virion –** A Complete Viral Particle
  - **Capsid** – The Protein Coat made up of smaller structural Subunits (Capsomeres)
  - **Capsomeres** – The Subunits of the Capsid
  - **Nucleocapsid** – The Capsid + Nucleic Acid + Associated Nucleoproteins
  - **Envelope** – Lipid Bilayer of *Host-Cell Origin*, imbedded with Viral Lipoproteins.



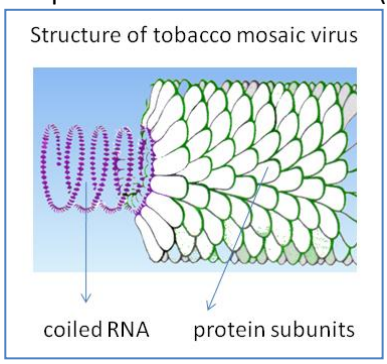
- **Properties Distinguishing Viruses from other Microorganisms:**
  - Acellular
  - No Cell Membrane
  - No Cytoplasm
  - Can have a DNA *or* RNA Genome. (All others only have DNA)
  - No Cellular Synthetic Machinery (Metabolically Inert)
  - Can Only Replicate in Living Cells

- **Viral Envelopes - (Construction/Origin/Proteins):**
  - **Origin:** Some viruses envelop themselves in a modified piece of host cell membrane (Either the Plasma Membrane, or Organelle Membranes).
  - **Construction:** This membrane is studded with Viral & Host Proteins. Most enveloped viruses depend on the envelope for infection.
  - **Proteins:** Viral envelopes are studded with **Glycoproteins –** Serve to identify and bind to receptor sites on the host's membrane. The viral envelope then fuses with the host's membrane, allowing the capsid and viral genome to enter and infect the host.

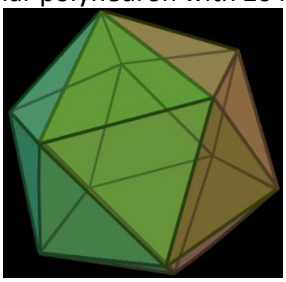


- **Structural Vs. Non-Structural Proteins:**
  - **Structural Proteins:**
    - Proteins Encoded by a Virus that form Structural Components of the end Viral Particle.
  - **Non-Structural Proteins:**
    - Proteins Encoded by a Virus, but NOT part of the Viral Particle.

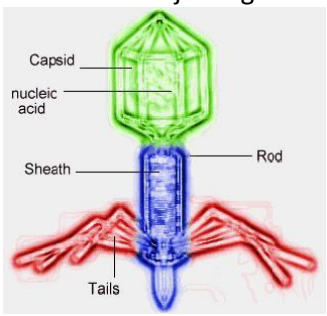
- **Symmetry:**
  - **Helical Symmetry:**
    - Composed of a single type of capsomere stacked around a central, coiled Nucleic Acid →form a helical structure.
      - Results in rod-shaped or filamentous virions: (Short and Rigid, or Long and Flexible.)



  - **Cubic (Icosahedral) Symmetry:**
    - Icosahedron = a regular polyhedron with 20 identical equilateral triangular faces.

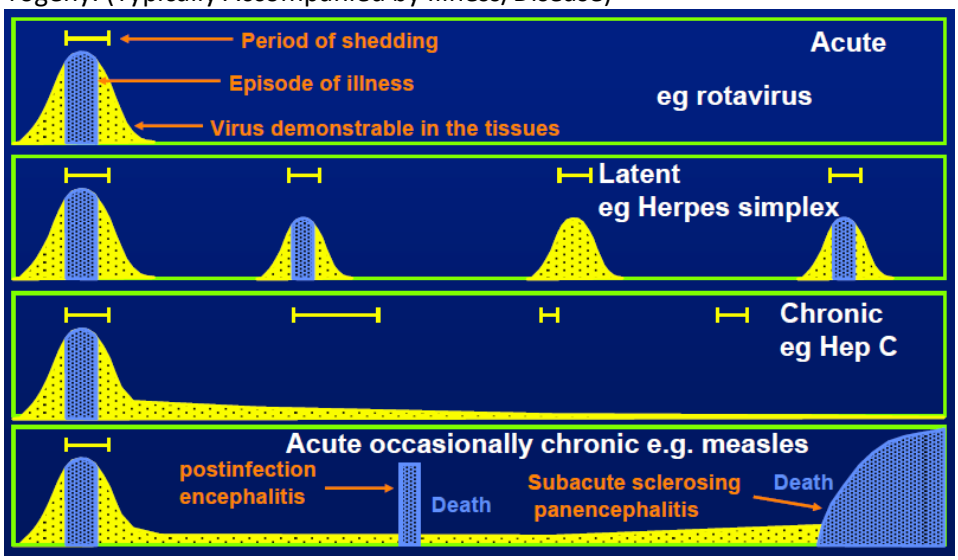


  - **Complex Symmetry:**
    - Capsid is neither purely helical, nor purely icosahedral, and that may possess extra structures such as protein tails or a complex outer wall.
    - Some have a Cubic head bound to a Helical tail, with protruding protein tail fibres that attach to the host cell and then injecting the viral genome into the cell.

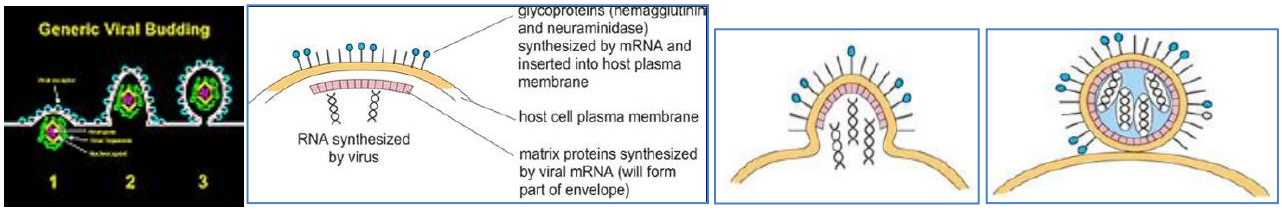


- **Requirements for Viability & Culturing Viruses:**
  - **Viability Requires:**
    - **1. *Must* Retain an Intact Protein Coat.**
      - (NB: Enveloped Viruses are Inactivated by Detergents → Disperses Lipid Bilayer)
    - **2. *Must* Retain an Intact Genome.**
  - **Culturing Viruses Requires:**
    - Living Cells – (Because Viruses lack the cellular machinery for replication)

- **“Shedding” & Disease:**
  - **Viral Shedding =** The Successful Reproduction, Expulsion & Host-Cell Infection caused by Virus Progeny. (Typically Accompanied by Illness/Disease)

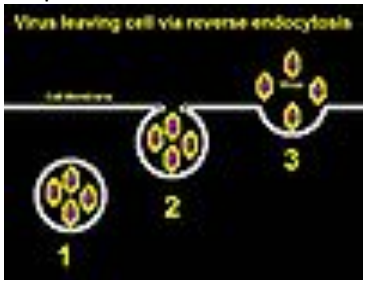


  - **Via Budding:**
    - “Budding” through the cell membrane, using it to form the viral Envelope.
    - Primarily Enveloped Viruses

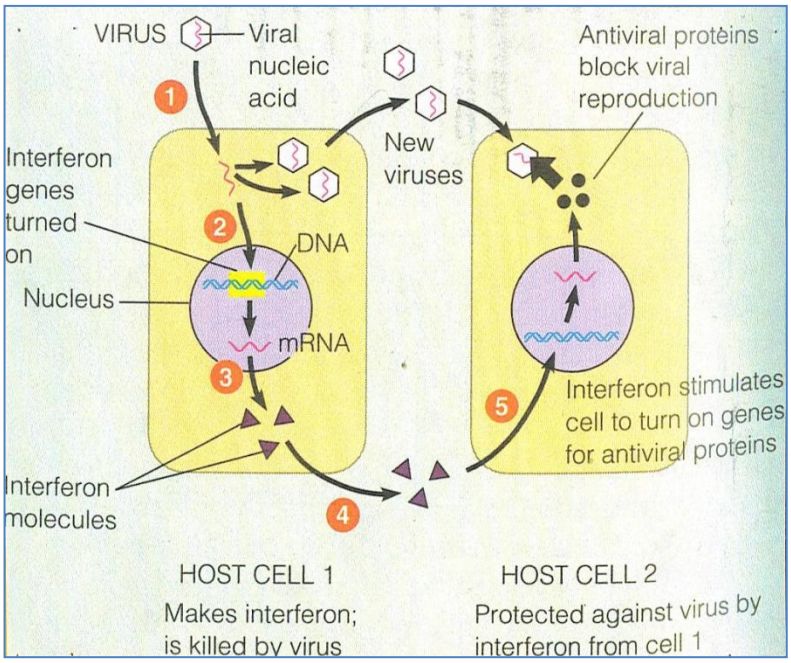


  - **Via Apoptosis:**
    - Forcing cell into Apoptosis → Release of progeny into Extracellular Space within apoptotic bodies. Macrophages phagocytose the apoptotic bodies → Become Infected.
    - Primarily Non-Enveloped Viruses

  - **Via Exocytosis:**
    - Exocytotic release of Viral Progeny into the Extracellular Space.
    - Primarily Non-Enveloped Viruses.



- **Innate Defences against Viruses:**
  - ***Interferons (IFNs):**
    - Non-specific Anti-Viral Proteins (Particularly IFN-γ) secreted by Virally Infected Cells to protect nearby cells that haven't yet been infected.
    - → **IFN results in Synthesis of Gene Products, which:**
      - Cleaves Viral mRNA → Inhibits Viral Protein Synthesis & Reproduction.
      - Prevents viral growth in Macrophages
      - Prevents Elongation of Viral dsRNA
      - Can inhibit the Transcription & Translation of some viral mRNA.
    - →**Also Activates Natural Killer-Cells.**

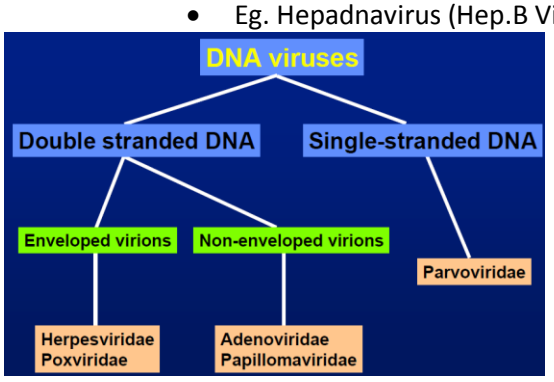


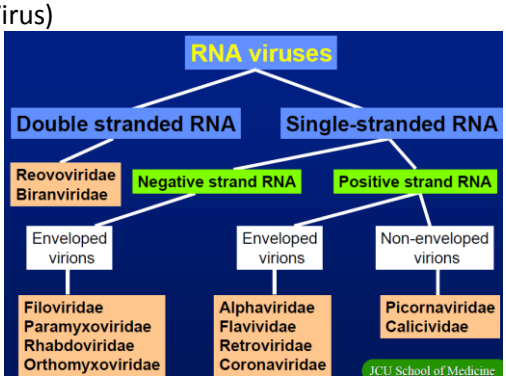
  - **Natural Killer Cells:**
    - (Activated by IFN-γ)
    - Lyse some Virally-Infected Cells.
  - **Compliment Activation (Alternate Pathway) & Phagocytosis of Extracellular Viruses**:
    - C3b opsonisation → Phagocytosis
  - **Lysozyme:**
    - (in Tears/Saliva/Mucus/Neutrophils)
  - **Stomach Acid:**
    - Denatures some viruses.
  - **Intestinal Enzymes:**
    - Degrade some viruses.

- **Immune Evasion Strategies:**
  - Persist as Latent Infections
  - →Reactivation/Recrudescence following Immunosuppression/Stress.
  - Superantigens → Inappropriate Immune Response
  - Inhibition of MHC-I Synthesis/Assembly/Ag-Loading

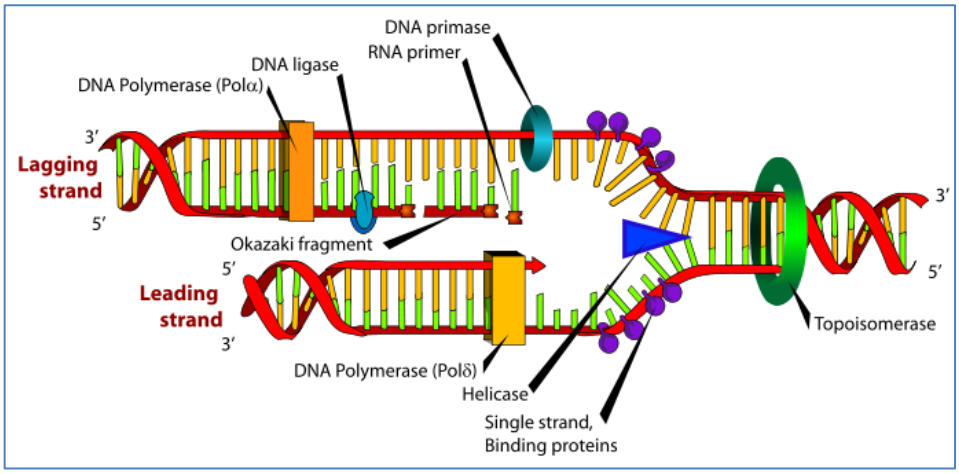
- **Latency (Recurrence & Recrudescence):**
  - **Latency = The Ability of a Pathogenic Virus to lie Dormant within a cell.**
  - **Virus *Production* Ceases:**
    - NO active Viral Shedding
    - NO Pathologies/Symptoms
  - **However, Latency is still an *Active* Process:**
    - Maintaing latency requires expression of viral genes which may function to:
      - Keep the viral genome from being digested by cellular *Ribozymes*.
      - Downregulate MHC-I to hide from the immune system.
      - Inhibit Apoptosis
      - Induce Cell Growth/Division
  - **2 Types of Latency:**
    - **Episomal Latency:**
      - Viral genes are left floating in the Cytoplasm or Nucleus.
      - (Eg. Herpes Virus)
    - **Proviral Latency:**
      - Virus genome Integrates into the Host Genome → Becomes a Provirus.
      - (Eg. HIV)
  - **Reactivation/Recrudescence:**
    - A Latent Virus can Reactivate
    - Triggers include Stress, Sunlight.

- **Classification of Viruses:**
  - **The ICTV Classification:**
    - **Family** ("-viridae")
      - **Genus** ("-virus")
        - **Species**
    - (Ie. Binomial Nomenclature isn't used)
  - **The Baltimore Classification:**
    - (7 Groups of viruses based on DNA/RNA, Strandedness (Single/double), Sense/Nonsense, & Method of Replication.)
    - **1. dsDNA Viruses** **(double-stranded DNA Viruses)**
      - Eg. Herpesvirus, Poxvirus, Adenovirus
    - **2. ssDNA Viruses** **(single-stranded DNA Viruses)**
      - Eg. Parvovirus
    - **3. dsRNA Viruses** **(double-stranded RNA Viruses)**
      - Eg. Reovirus
    - **4. (+)ssRNA Viruses** **(positive [sense] single-stranded RNA Viruses)**
      - Eg. Picornavirus, Togavirus
    - **5. (-)ssRNA Viruses** **(negative [nonsense] single-stranded RNA Viruses)**
      - Eg. Orthomyxovirus, Rhabdovirus.
    - **6. ssRNA-RT Viruses** **(single-stranded RNA Reverse Transcriptase Viruses)**
      - Eg. Retroviruses (HIV)
    - **7. dsDNA-RT Viruses** **(double-stranded DNA Reverse Transcriptase Viruses)**
      - Eg. Hepadnavirus (Hep.B Virus)

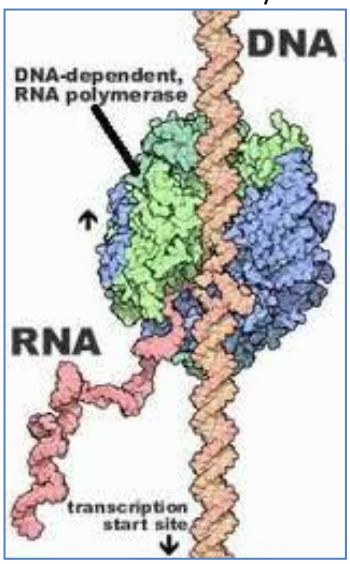


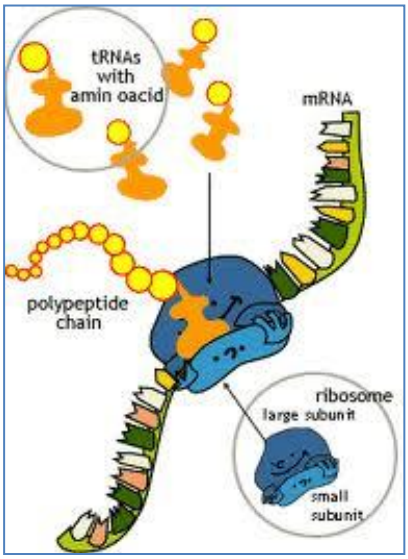


- **Revision of DNA Replication/Transcription/Translation & Enzymes (For Viral Replication Cycles):**
  - **DNA Replication:**
    - **DNA Replication** **DNA → DNA** (Via DNA Polymerase)



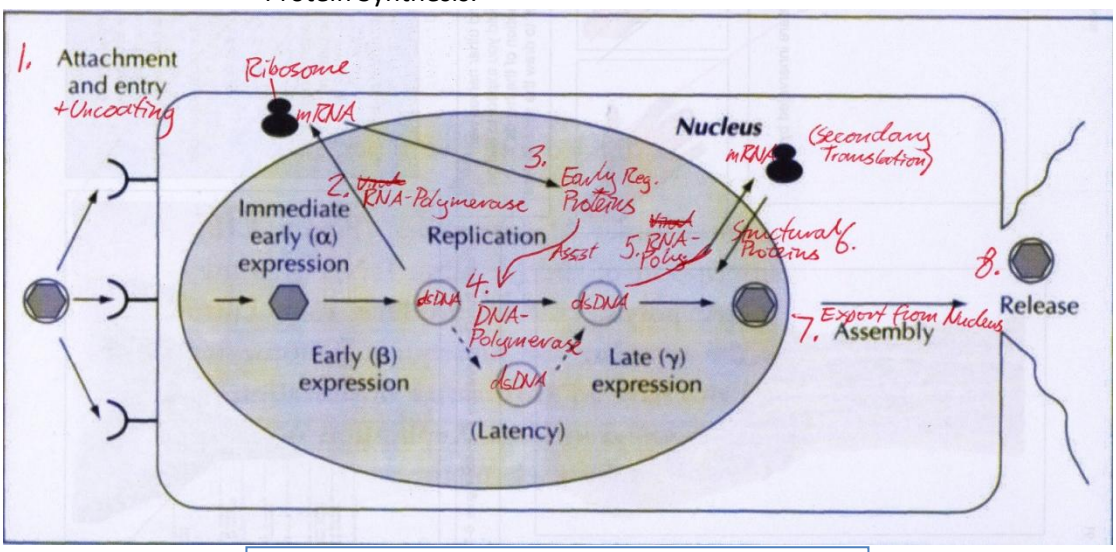
  - **Protein Synthesis:**
    - **1. Transcription:** **DNA → mRNA** (Via RNA Polymerase)
      - mRNA Exits the Nucleus → Cytosol.
    - **2. Translation:** **mRNA → Protein** (Via Ribosomes)
      - Occurs in the Cytosol.

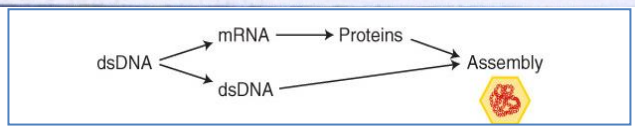




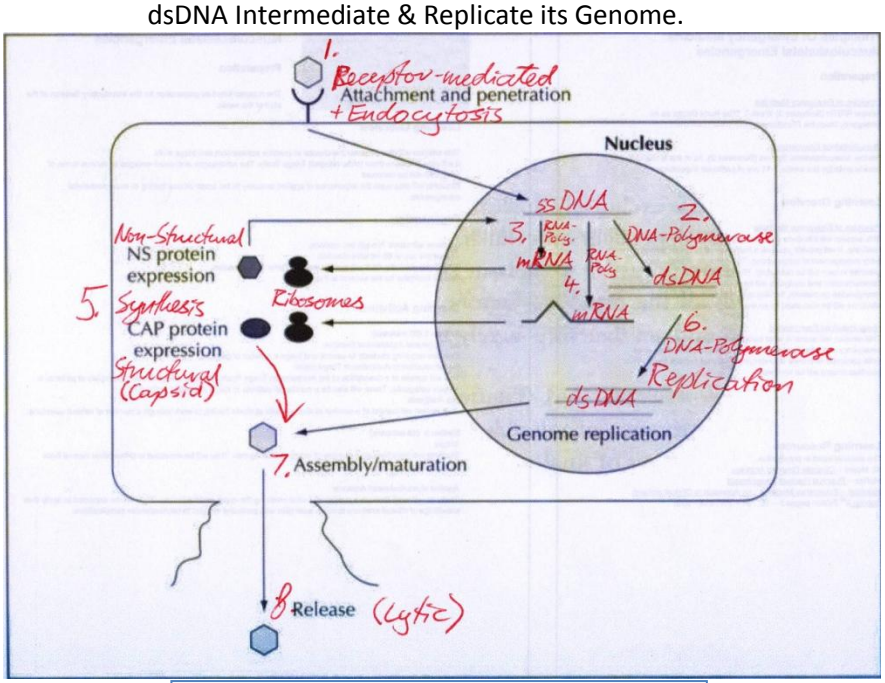
  - **Enzymes: (Host Enzymes) (Viral Enzymes):**
    - **DNA Polymerase** – Synthesizes new DNA from DNA.
    - **(DNA-Dependent) RNA Polymerase** – Synthesizes mRNA from DNA.
    - **RNA-Dependent RNA Polymerase (Transcriptase)** – Synthesizes new mRNA from mRNA.
    - **RNA-Dependent DNA Polymerase (Rev.Transcriptase)** – Converts mRNA back to dsDNA.
    - **Retroviral Integrase** – Allows viral DNA to be *integrated* into the DNA.

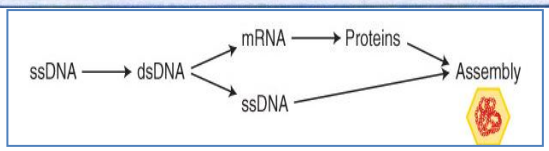
- **Replication Cycles:**
  - **1. dsDNA Viruses (double-stranded DNA Viruses)**
    - Eg. Herpesvirus, Poxvirus, Adenovirus
    - **Replication Features:** (In the Nucleus (As with all DNA Viruses))
      - Requires *Host-Cell* ***DNA Polymerase*** (& hence Host-Cell Division) to Replicate its Genome.
      - Also Requires *Host-Cell* ***RNA Polymerase*** to transcribe dsDNA → mRNA for Protein Synthesis.



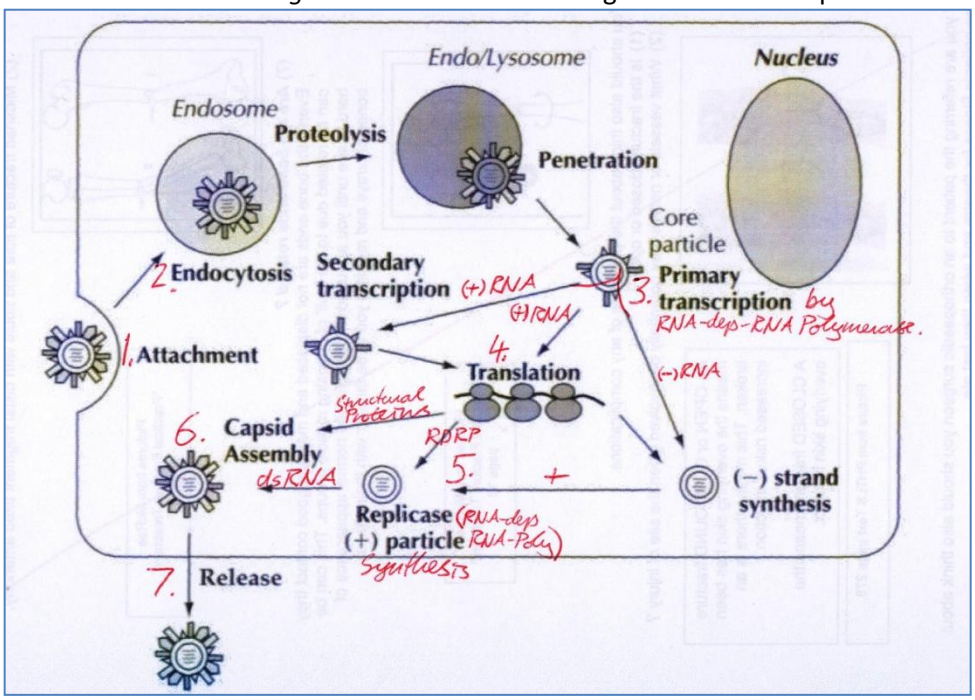


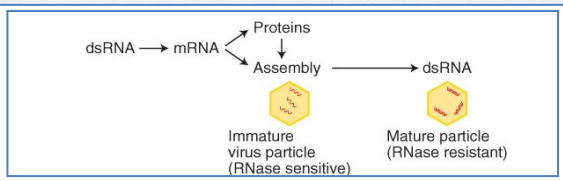
  - **2. ssDNA Viruses (single-stranded DNA Viruses)**
    - Eg. Parvovirus
    - Replication
    - **Replication Features:** (In the Nucleus (As with all DNA Viruses))
      - Requires *Host-Cell* ***DNA Polymerase*** (& hence Host-Cell Division) to form a dsDNA Intermediate & Replicate its Genome.



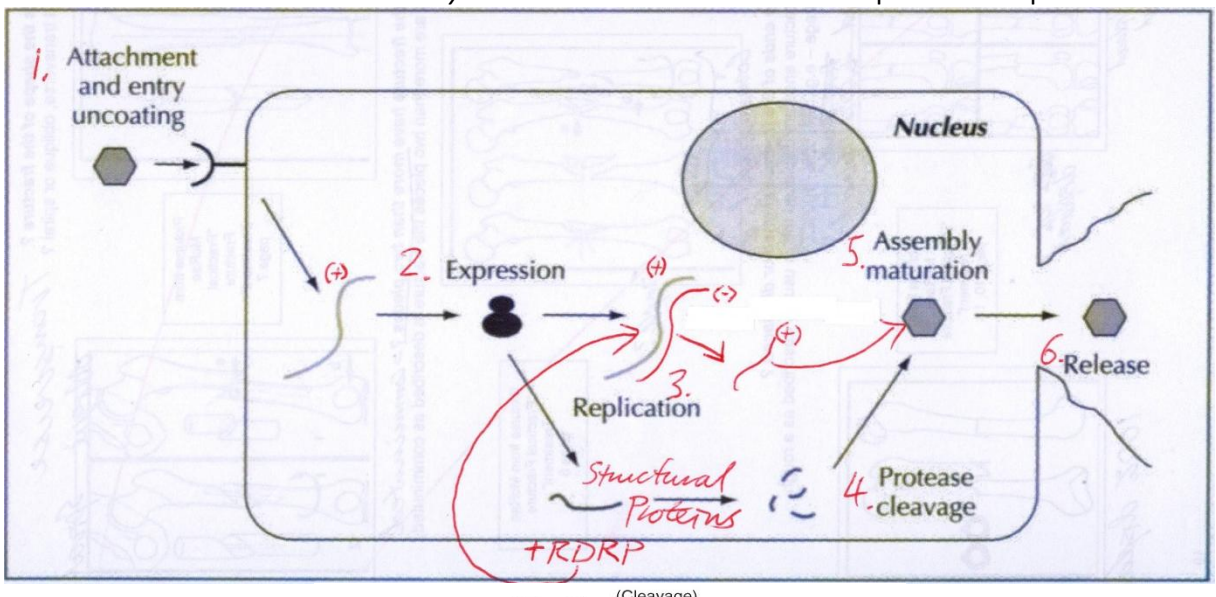


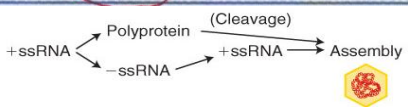
- **3. dsRNA Viruses (double-stranded RNA Viruses)**
  - Eg. Reovirus
  - **Replication Features:** (In the Cytoplasm (As with all RNA Viruses))
    - Supplies its *Own* ***RNA-dependent-RNA-Polymerase*** for RNA Replication.
      - (As opposed to RNA Polymerase which transcribes DNA → RNA)
    - Have *Segmented Genomes* – each gene codes for 1x protein.



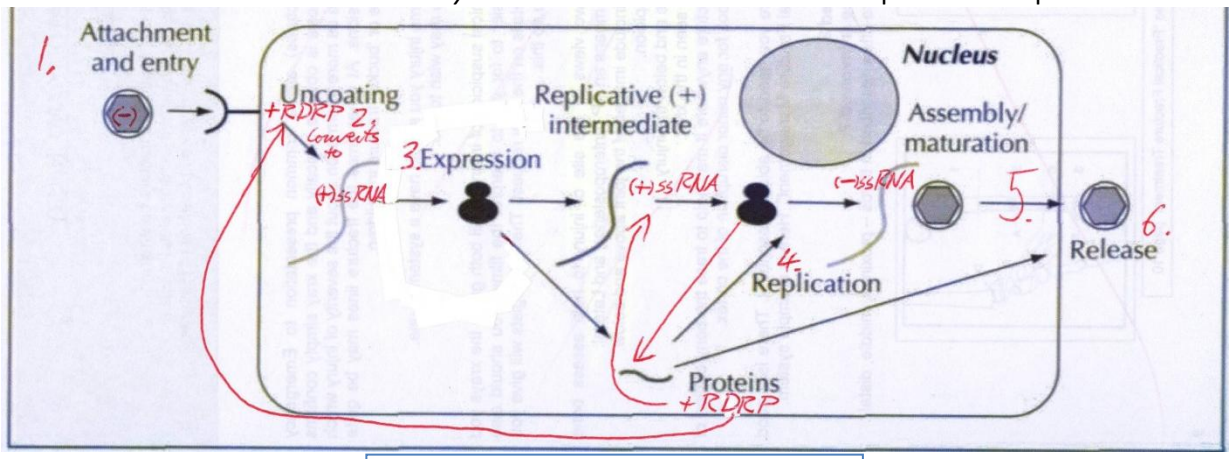


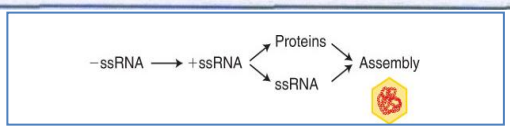
- **4. (+)ssRNA Viruses (positive [sense] single-stranded RNA Viruses)**
  - Eg. Picornavirus, Togavirus
  - **Replication Features:** (In the Cytoplasm (As with all RNA Viruses))
    - Supplies its *Own* ***RNA-dependent-RNA-Polymerase*** for RNA Replication.
    - Directly access *Host* ***Ribosomes*** → Viral *Poly*-Protein Synthesis.
      - *Poly-Proteins* are cleaved to form multiple different proteins.



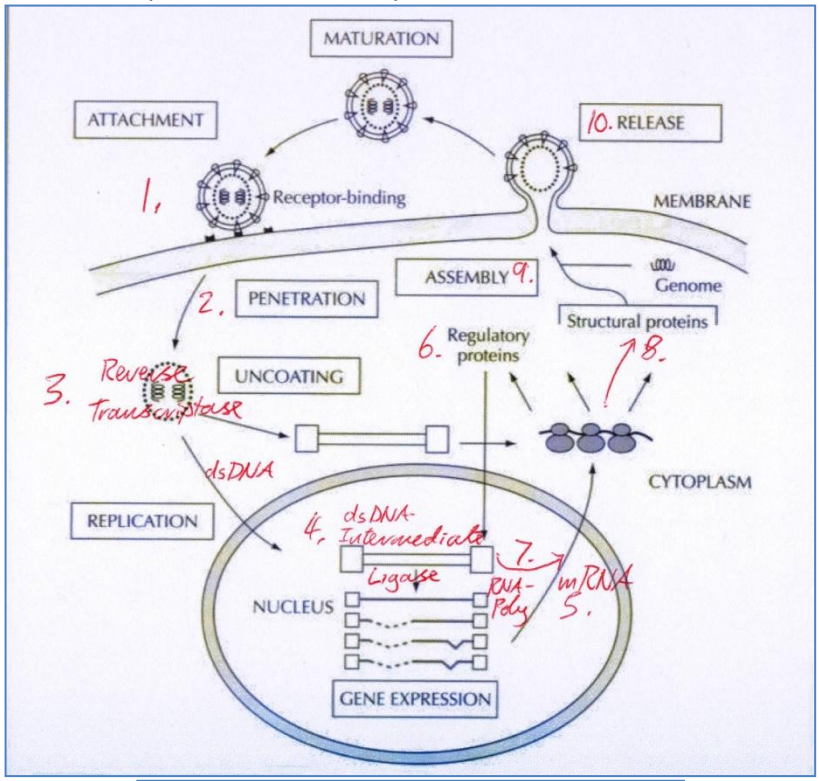


- **5. (-)ssRNA Viruses (negative [nonsense] single-stranded RNA Viruses)**
  - Eg. Orthomyxovirus, Rhabdovirus.
  - **Replication Features:** (In the Cytoplasm (As with all RNA Viruses))
    - Can't directly access *Host Ribosomes* – Because it is a *Nonsense* Strand.
    - Must first use its *Own* ***RNA-dependent-RNA-Polymerase*** to transcribe a *Positive (Sense)* Strand.
    - Positive Strand → Accesses ***Ribosomes*** → Viral *Poly*-Protein Synthesis.
      - *Poly-Proteins* are cleaved to form multiple different proteins.

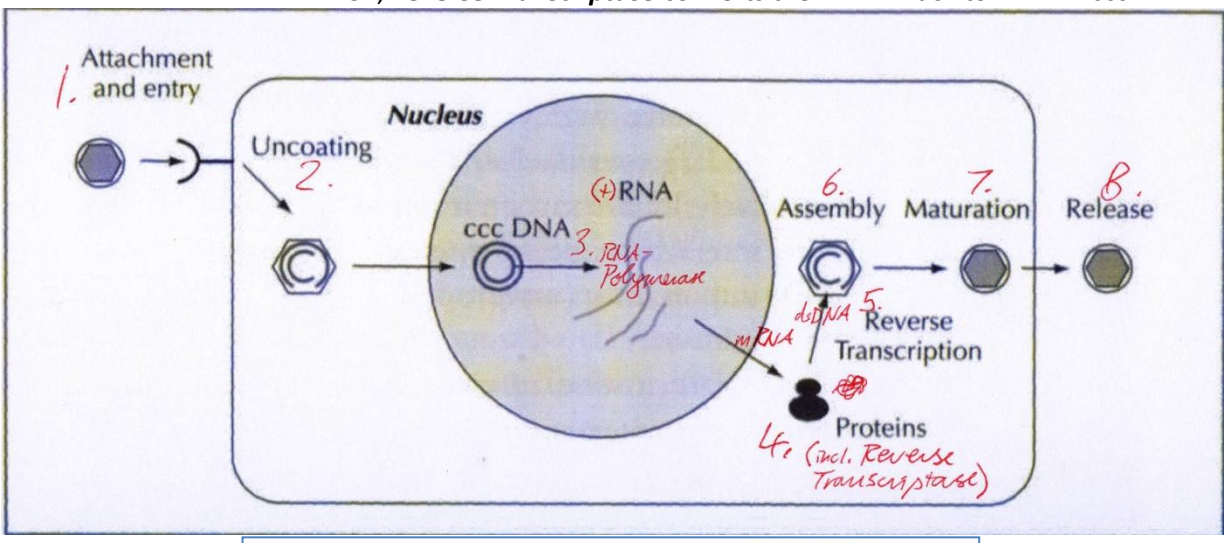


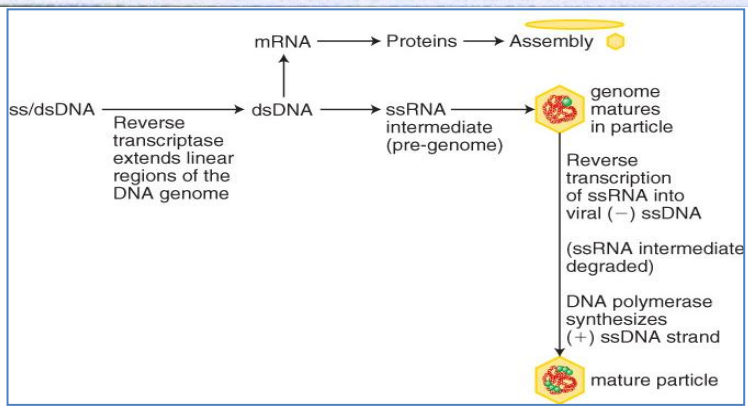


- **6. ssRNA-RT Viruses (single-stranded RNA Reverse Transcriptase Viruses)**
  - Eg. Retroviruses (HIV)
  - **Replication Features:** (In the Cytoplasm *AND* the Nucleus)
    - Instead of using the +ssRNA to make proteins, it converts the +ssRNA → dsDNA via ***Reverse Transcriptase***.
    - The resulting DNA is spliced into the *Host Genome* using ***Integrase***.
    - Replication & Protein Synthesis then comes from the viral DNA in the Nucleus.



- **7. dsDNA-RT Viruses (double-stranded DNA Reverse Transcriptase Viruses)**
  - Eg. Hepadnavirus (Hep.B Virus)
  - **Replication Features:** (In the Cytoplasm *AND* the Nucleus)
    - Genome is a '*covalently closed circle*' (cccDNA) → Nucleus
      - →Transcribed to mRNA (Via ***RNA-Polymerase***)
    - mRNA exits Nucleus → Protein Synth. In Cytoplasm.
    - *Then*, ***Reverse Transcriptase*** converts the mRNA *Back* to DNA → cccDNA.





- **Viral Assembly:**
  - **Assembly =** When all of the components of the virus are assembled into a particle.
    - Occurs when an appropriate conc. Of Virus Proteins & Nucleic Material is reached.
    - (NB: Some particles self-assemble)

- **Viral Maturation:**
  - **Maturation =** Stage in the Virus Life-Cycle when it becomes infectious.
    - Involves proteolytic cleavage of capsid or envelope poly-proteins into functional proteins.

- **Targets for Antiviral Therapies:**
  - **1. Attachment**
  - **2. Penetration**
  - **3. Uncoating**
  - **4. Replication**
  - **5. Assembly**
  - **6. Maturation**
  - **7. Release**

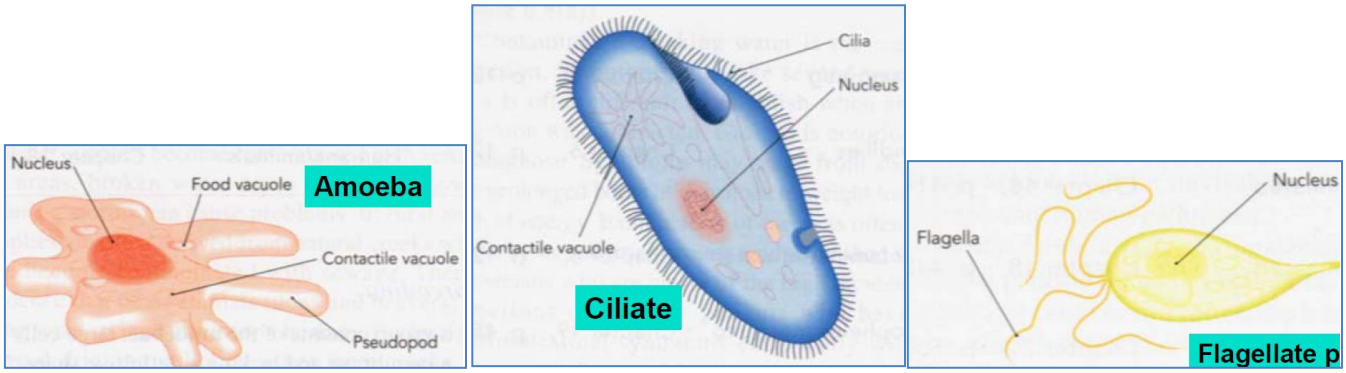
- **Quasispecies:**
  - A substrain of an organism that develops in an individual by the process of evolutionary selection

Parasites:

- **General Features:**
  - Live at the expense of their host → Acquires Nutrients/Other Benefits without Reciprocal Benefits
  - Complex Life-Cycle involving 2 or More Hosts (Definitive Host & Intermediate Host/s)

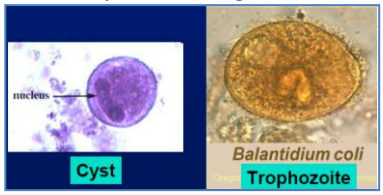
- **Hosts (Definitive Vs. Intermediate):**
  - **Definitive Host:**
    - - Harbours the Mature, Adult Form of the Parasite.
  - **Intermediate Host:**
    - - Harbours the Immature, Larval Form of the Parasite.

- **Grouping: Protozoan Vs. Metazoan:**
  - **Protozoan Parasites:**
    - (Single-Celled Parasites)
    - **3 Categories of Locomotion:**

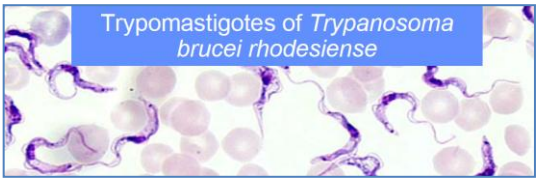


- **Amoeba** – (Move by Crawling) (Eg. Entamoeba Histolytica)

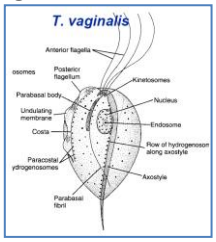
- **Ciliate** – (Move by Swimming – via cilia) (Eg. Balantidium Coli)



- **Flagellate** – (Move by Swimming – Via Flagella) (Eg. Giardia Lamblia)



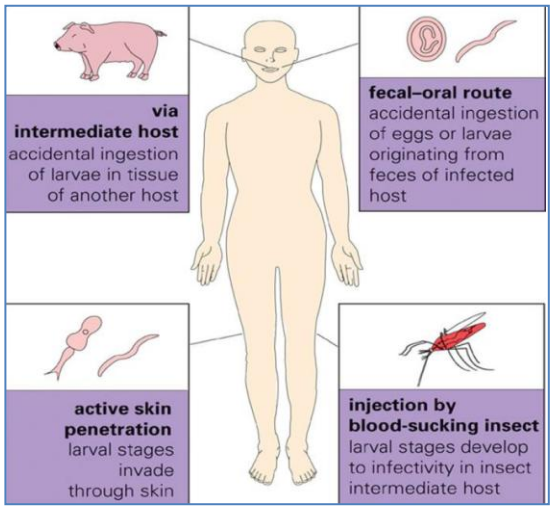
trichomonads:



- **(Sporozoa) –** (No motile structures) (Eg. Plasmodium Malariae; Toxoplasma)

- **Metazoan Parasites – (Helminths & Arthropods):**
  - (Multi-Celled Parasites)
  - **Helminths:**
    - **3 'Phyla':**
      - **Platyhelminthes** (Flat worms)
        - ***Trematodes*** (Flukes)
        - ***Cestodes*** (Tapeworms)
      - **Nematoda** (Round Worms)
      - **Acanthocephala** (Spiny-headed worms)
  - **Arthropods:** (Animals with segmented bodies, exoskeletons and jointed appendages)

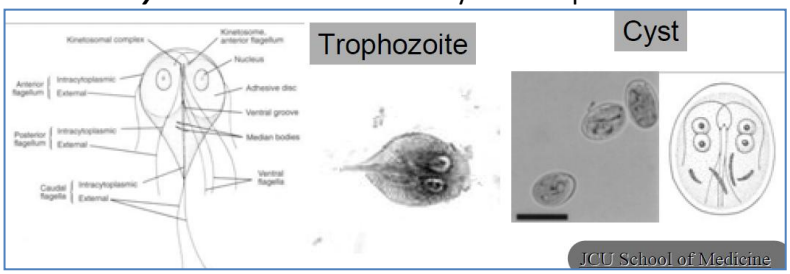
- **Routes of Entry of Helminths:**



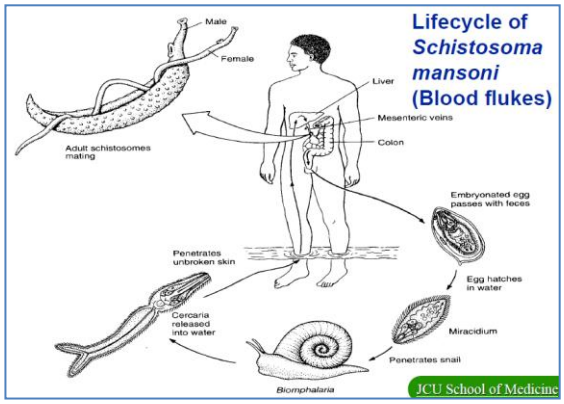
- **Innate Defences against Parasites:**
  - **Lysozyme:**
    - (in Tears/Saliva/Mucus/Neutrophils)
  - **Eosinophils (Eosinophil Granulocytes):**
    - Degranulate → Release Reactive Oxygen Species → to kill parasites.
  - **Complement Activation:**
    - By Alternate/MB-Lectin Pathway
  - **Phagocytes in Spleen:**
    - Recognise Infected RBCs in the Spleen & Remove them from blood.

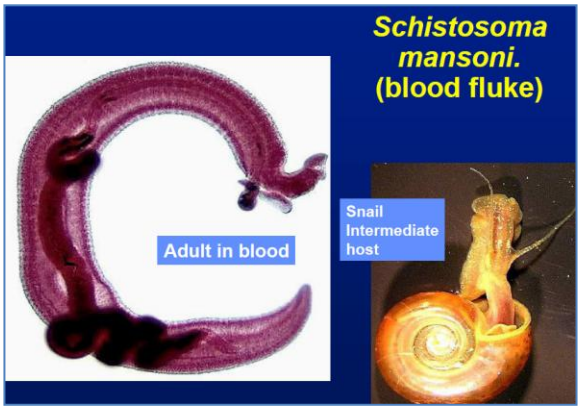
- **Immune Evasion Strategies:**
  - **Protozoan Parasites:**
    - Antigenic Variation
    - Antigenic Drift
    - Molecular Mimicry (Expression of Host Proteins)
    - Intracellular Localisation
    - Self-Isolation in Membrane-bound Vesicle.
    - Prevent fusion of lysosomes with phagosomes
    - Sequestration in privileged sites
    - Regulation of host functions.
  - **Helminth Parasites:**
    - Antigen Shedding
    - Protease production → Neutralise some immune components. (Eg. Antibodies)
    - Superoxide Dismutase → Neutralise Respiratory Burst by Neutrophils.
    - Regulation of host functions (Immunosuppression/Maladaptive Response)
    - Skew the T-Helper Response to Favour Th1-Cells:
      - Favouring Th1→ Reduced class-switching to IgE, the AntiParasitic Ab.
    - Use Host Cytokines as Parasitic Growth Factors

- **Replication Cycles:**
  - **Protozoan Parasites:**
    - **Trophozoite Stage:** ("Tropho" = Feeding)
      - Infective, Proliferative Stage – Lives in the definitive host.
      - Trophozoites *Actively* Feed.
      - Protozoa can reproduce by *Fission, Sexual Reproduction,* or be *Hermaphroditic*.
      - ***Encystation*** = Conversion of Trophozoite → Cyst.
    - **Cysts Stage:**
      - Hardy, thick-walled spore able to survive for lengthy periods **outside a host**. (Organisms that create oocysts include *Cryptosporidium* and *Toxoplasma*.)
        - Resistant to heat, harmful chemicals.
        - Can survive without access to nutrients, water, or oxygen.
      - Often shed in the faeces (Eg. Giardia)
      - ***Excystation*** = Conversion of Cyst → Trophozoite.

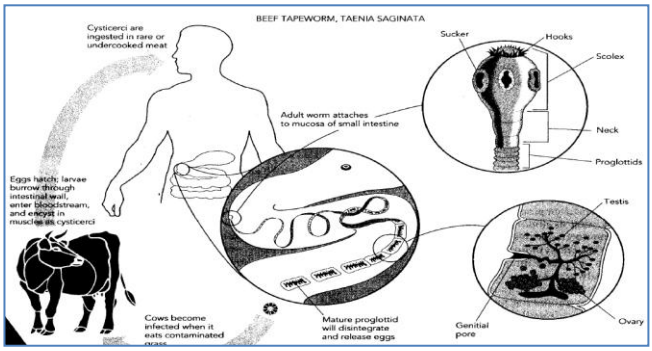


  - **Metazoan Parasites: (Platyhelminthes, Nematodes & Acanthocephala)**
    - **Platyhelminthes:**
      - **Trematodes (Flukes):**
        - The Eggs of Trematodes (Flukes) pass out in the Faeces, develop into larvae, which MUST PASS THROUGH THE SNAIL (Intermediate Host) and develop into *Cercaria* before the parasite is again infective to humans.

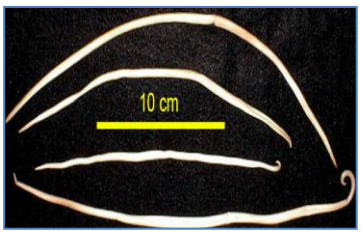


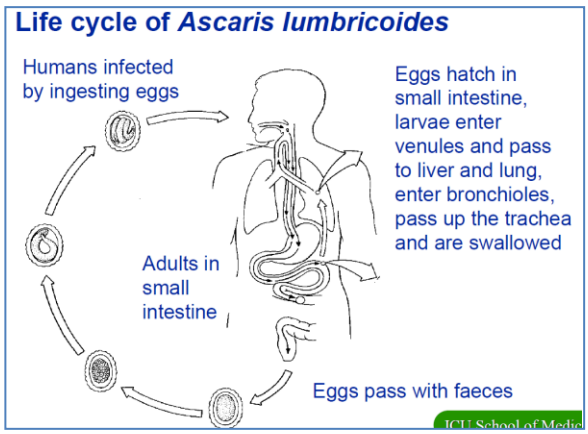


      - **Cestodes (Tapeworms):**
        - Cysts are shed in Human Faeces → Grass → Eaten by Cow or Pig (Intermediate Hosts). Humans are infected by eating Contaminated Beef. Adult worm attaches to SI-Mucosa.

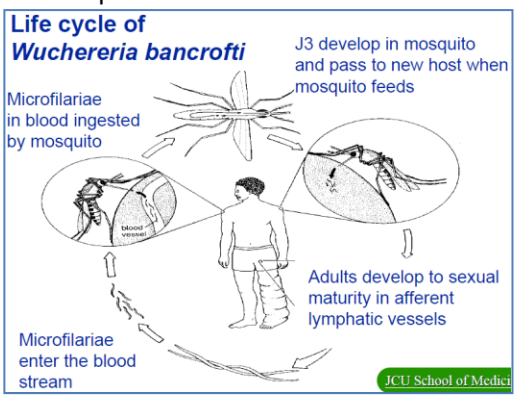


- **Nematodes (Round worms):**
  - **Intestinal Nematodes:**
    - Direct Life-cycle. (Horizontal Transmission *Without* Intermediate Hosts)
    - Faecal Oral – Eggs in Faeces → Ingested → Hatch in SI → Burrow into Bloodstream → Exit blood in lungs → Pass up the Trachea & are Swallowed → Adults mature in Small Intestine.

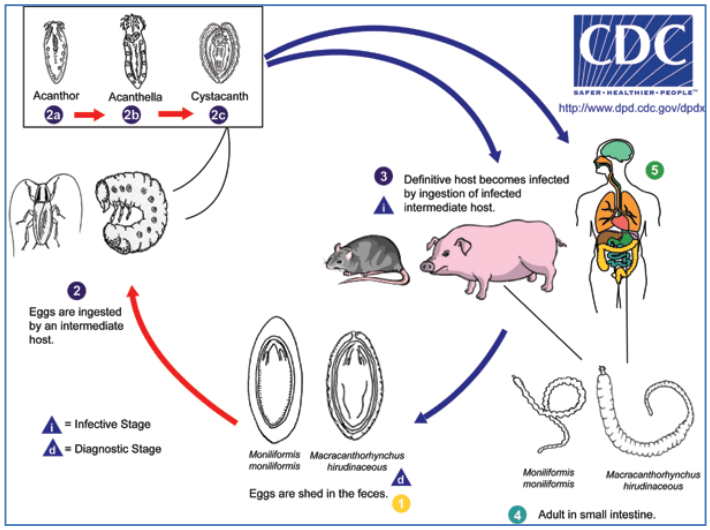




  - **Filarial Nematodes:**
    - Microfilariae in the blood are infective to Mosquitoes → Pass on the infection to other people.
    - Most Common = *Wuchereria Bancrofti* → Lymphatic Filariasis & Elephantiasis.



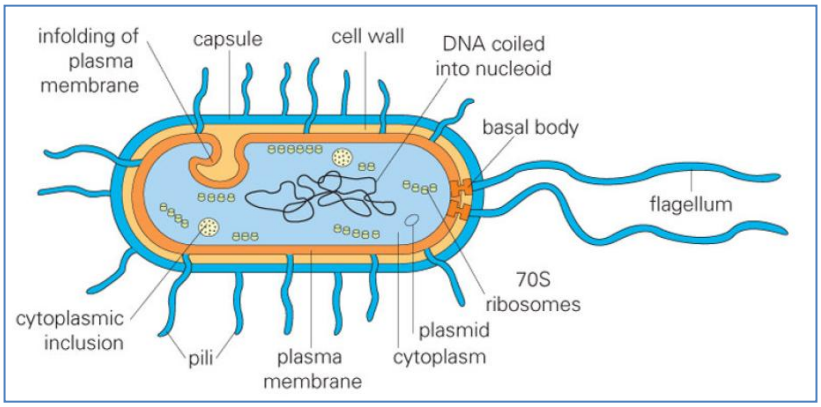
- **Acanthocephala:**
  - (A Phylum of parasitic worms known as Thorny-headed/Spiny-Headed Worms.)
  - Complex Life-Cycles involving a number of hosts:
    - Embryo is released in faeces → Ingested by a Crustacean (eg. A Mollusc) (the Intermediate Host) → Encystation occurs → Intermediate Host is Ingested by the Definitive Host → Excystation in the gut → Reproduction



Intro to Bacterial Pathogenesis

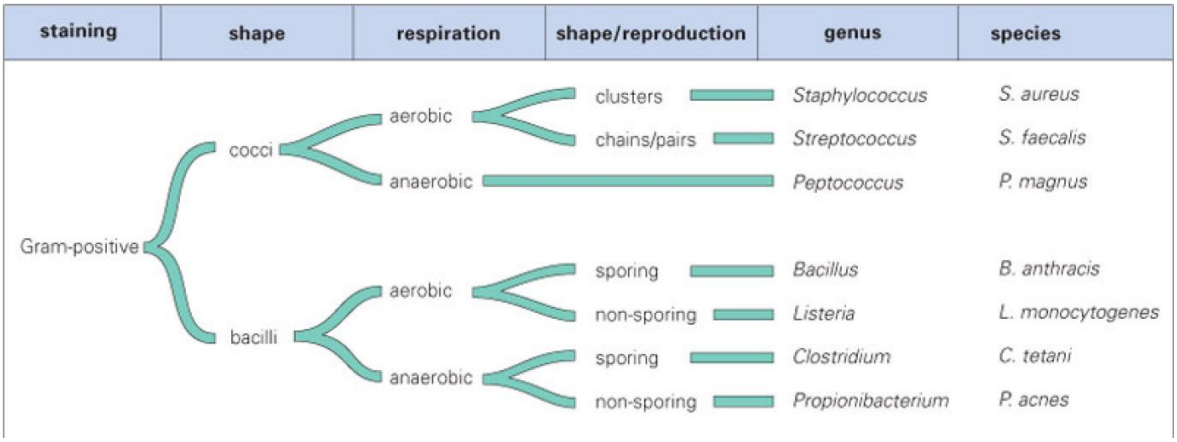
Structure of the Bacterial Cell:

- Prokaryotic
- Single-Celled Organisms
- DNA Based Genome, but *No Distinct Nucleus*. (Circular Chromosome)
- **3 Layers:**
  - Plasma Membrane
  - A Thick Cell Wall covers the Plasma Membrane (Composition depends on Gram -/+)
    - **Gram Positive:**
      - Thick Peptidoglycan Layer
      - & Teichoic Acid.
    - **Gram Negative:**
      - Primarily Lipid-Based (Including Lipopolysaccharide – LPS)
      - (+Thin Peptidoglycan Layer)
  - A Polysaccharide Capsule covers the Cell Wall. (Considered a Virulence Factor – Resists Phagocytosis, Detergents & Dehydration.)
- **Pili/Fimbriae:**
  - For Adherance to Cells or Other Bacteria.
- **Flagellum:**
  - For Mobility.



Taxonomy & Classification:

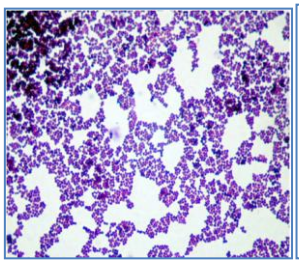
- **Uses a 'Binomial Nomenclature' – (*Genus + Species*):**
  - **Genus =** Eg. Staphylococcus
  - **Species** = Eg. Aureus
  - *(Staphylococcus Aureus)*

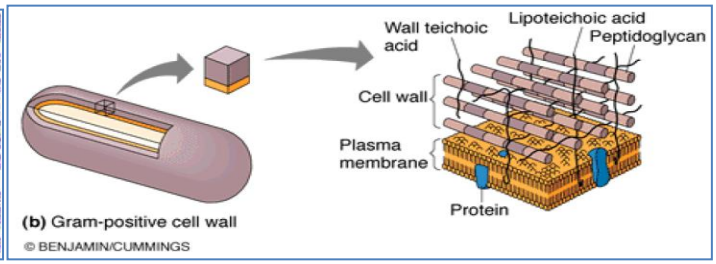


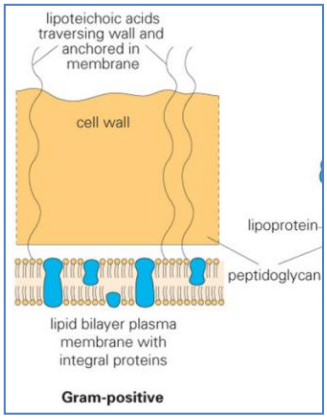
(NB: Don't need to memorise the genus & species listed above)

Classification of Bacteria:

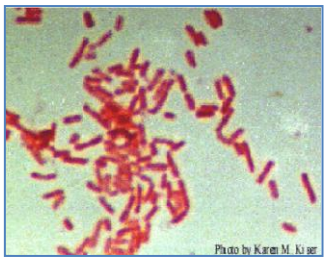
- **Staining of Cell Wall Structure:**
  - **Gram Stain:**
    - **Gram Positive:**
      - (Stain Blue/Purple)
      - Thick Peptidoglycan Layer
        - (The Site of Action of β-Lactam Antibiotics)
      - & Teichoic Acid.

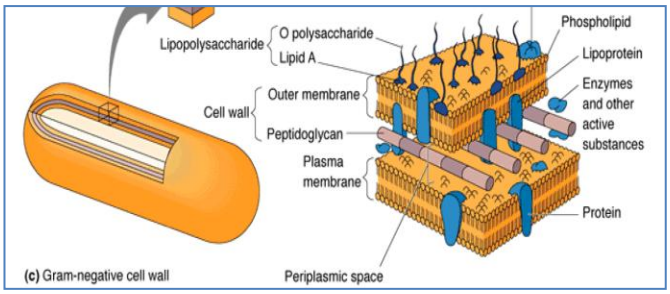


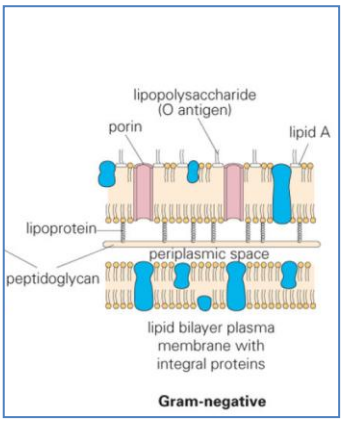




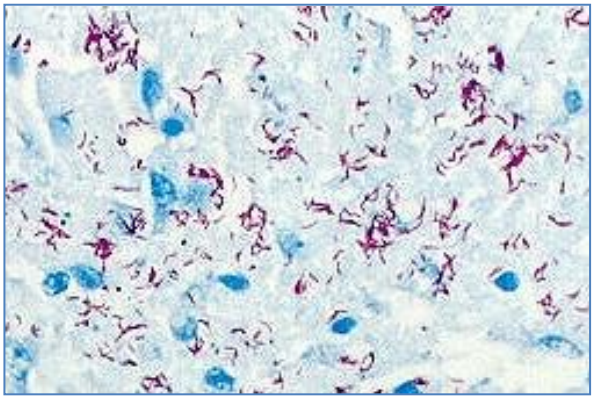
    - **Gram Negative:**
      - (Stain Pink/Red)
      - Primarily Lipid-Based (Including Lipopolysaccharide – LPS)
        - (NB: LPS = Endotoxin; can → *Septic* Shock)
      - (+ 'Lipid A' = Endotoxin; can →*Septic Shock*)
      - (+Thin Peptidoglycan Layer)





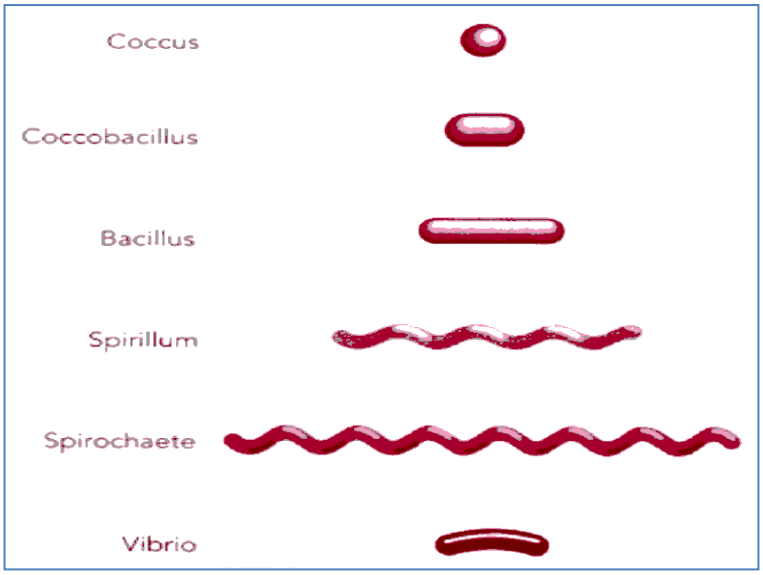


  - **Acid-Fast Stain:**
    - (Eg. Mycobacterium Tuberculosis)
    - Doesn't Stain with Gram.
    - Similar Cell-Wall to Gram + Bacteria, but different type of Peptidoglycan.
    - Stains with the *"Ziehl Neelsen Stain"* ('Acid-Fast Stain')
      - "Acid-Fast" Bacilli stain bright red in contrast to a blue background.

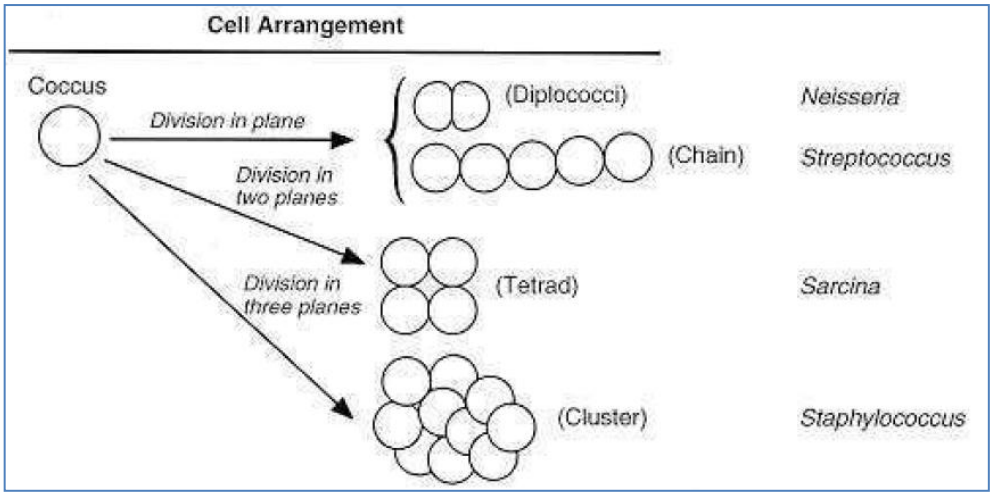


- **Respiration:**
  - Aerobic Vs. Anaerobic

- **Cellular Morphology (Shape):**



- **Grouping:**
  - Single
  - Pairs (Diplo-)
  - Chains (Strepto-)
  - Clusters (Staphylo-)



- **Innate Defences Against Bacteria:**
  - Physical Barriers
  - Lysozyme (Saliva/Tears)
  - Acid (Stomach/Vagina)
  - Phagocytosis (Macrophages/Neutrophils)
  - Fever
  - Complement (Opsonisation/Lysis)
  - Acute Phase Proteins

- **Adaptive Defences Against Bacteria:**
  - Antibodies (Toxin Neutralisation/Bacterial Opsonisation)
  - CD4-Th-Cells (Activate Macrophages & B-Cells)
  - CD8-Tc-Cells (Kill infected cells)

- **Bacterial Virulence Factors:**
    - Molecules Expressed/Secreted by Pathogens that enable them to achieve the following:
        - Colonisation of a Niche in the host (this includes adhesion to cells)
        - Immunoevasion, evasion of the host's immune response
        - Immunosuppression, inhibition of the host's immune response
        - Entry into & Exit out of cells (if the pathogen is an intracellular one)
        - Obtain nutrition from the host.
    - Eg. Endotoxin (LPS) – Potent antigen
    - Eg. Exotoxins (eg. Tetanus Toxin) → Tetanus
    - Eg. Ig-Proteases (eg. Strep. Pyogenes) → Break down Antibodies.
    - Eg. Capsules (eg. Bacterial cell walls) → Inhibits Phagocytosis.

- **Bacterial Immune Evasion Strategies:**
    - Antigenic Variation
    - Inhibition of Complement Activation.
    - Resistance to Phagocytosis
    - Produce Superoxide Dismutase → Scavenge Free Radicals from respiratory burst of Neutrophils.
    - Intracellular bacterial evasion:
        - Travel b/w cells without being exposed to extracellular fluid
        - Escape into vacuole in the cytoplasm
        - Prevent fusion of lysosomes with phagosomes
    - Depress cellular immunity
    - Superantigens → Inappropriate Immune Response

Pathological Consequences - Damage due to:

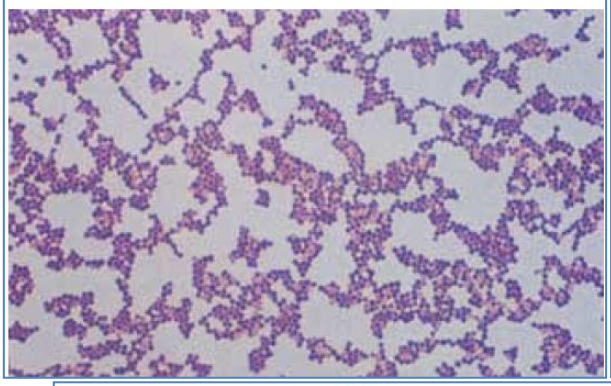
- **Exotoxins:**
    - **= Toxins Secreted from the Bacteria into the system.**
        - (:. Organisms need not be invasive to produce illness)
    - **Typically from *Gram Positive* bacteria.**
        - Eg. Botulinum Toxin
        - Eg. Tetanus Toxin
    - **Toxic Shock Syndrome:**
        - Some bacteria produce Superantigens → Widespread, Non-Specific activation of Th-Cells → Massive secretion of Pro-Inflammatory Cytokines → Massive Vasodilation/↑Capillary Permeability/Hypotension → Toxic Shock Syndrome.
            - – High Fever
            - – Hypotension
            - – Potential Multi-Organ Failure → Death.
- **Endotoxins:**
    - **= Structural (Cell-Wall) Components of the Bacteria that are Antigenic.**
        - They are *Not Secreted* and are *Not Directly Toxic*.
        - They are released into the system during *Lysis/Death* of Gram Negative Bacteria.
    - **Typically from *Gram Negative* bacteria.**
        - Eg. *Lipopolysaccharide* (LPS)
    - **Septic Shock:**
        - Bacteraemia & :. ↑LPS → LPS binds to TLR-4 on Macrophages & Dendritic Cells → Secretion of Pro-Inflammatory Cytokines & Nitric Oxide → Massive Vasodilation/↑Capillary Permeability/Hypotension → Septic Shock.
            - – Fever
            - – Tachypnea
            - – Tachycardia
            - – Hypotension
            - – Potential Multi-Organ Failure → Death
- **Hypersensitivity Reactions:**
    - Due to immune response.

GLS WORKBOOK STUFF

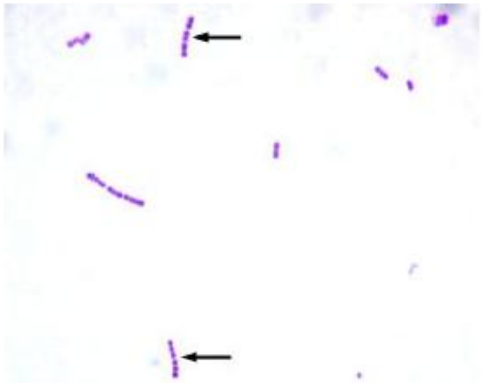
Microbial Identification & Gram staining

- **Use the slides and microscopes provided to complete the following table:**

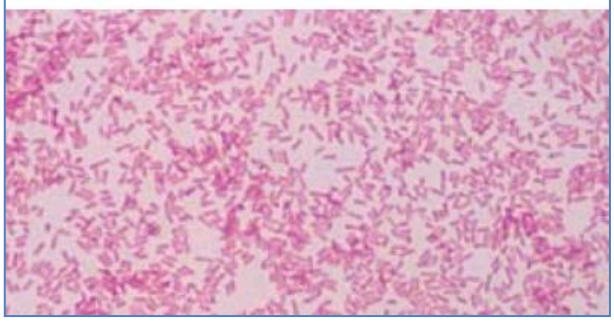
SLIDE 1



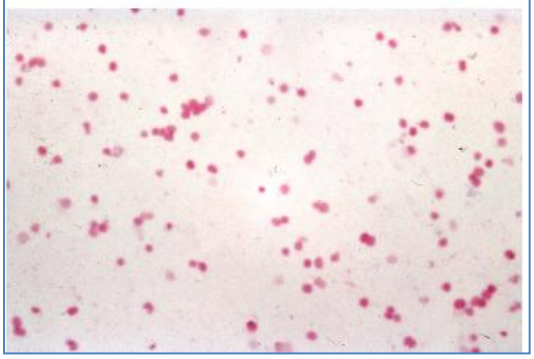
SLIDE 2



SLIDE 3



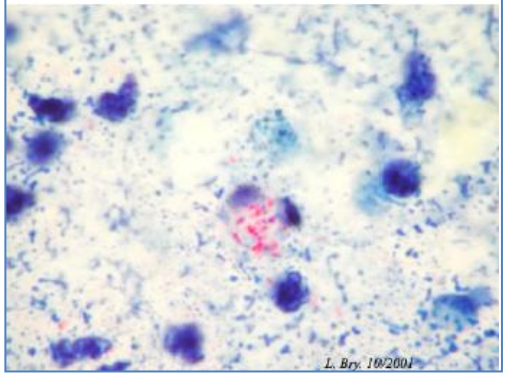
SLIDE 4



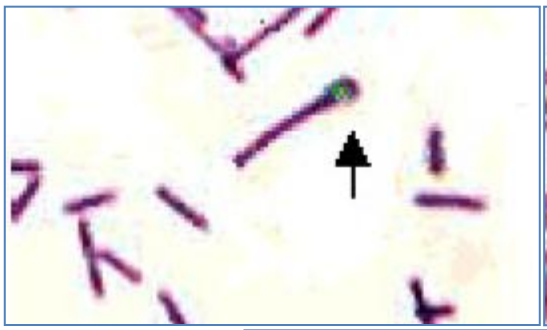
Slide	Gram Reaction	Cellular Morphology	Possible Identity
Eg.	Negative	Spiral Rods	Campylobacter, Helicobacter
1	Positive	Cocci	Staphylococcus
2	Positive	Cocci	Streptococcus
3	Negative	Bacillus	Bacillus Subtilis
4	Negative	Cocci	Diplococcus

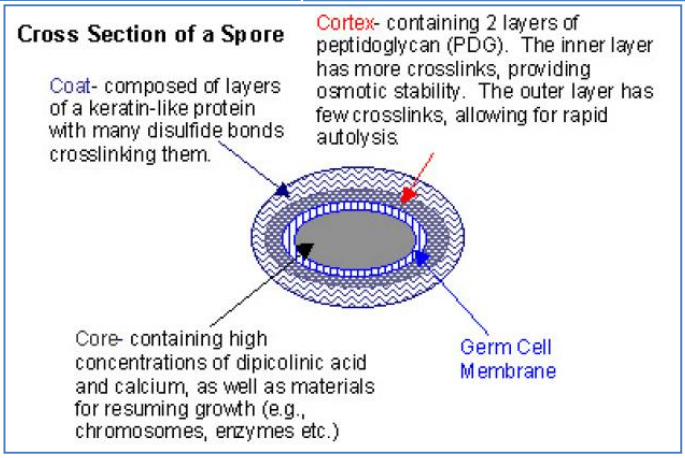
- **Look at the slide of the sputum sample which has been stained with the Ziehl-Neelson stain for acid fast bacteria. Which species is potentially demonstrated?**
  - Mycobacterium (Possibly tuberculosis)

Acid fast stain of un-lysed sputum

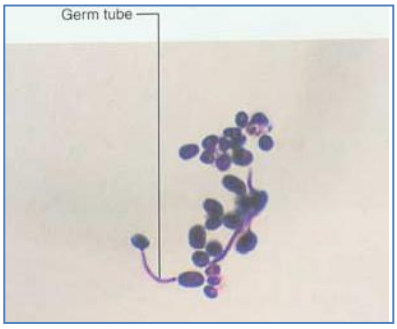


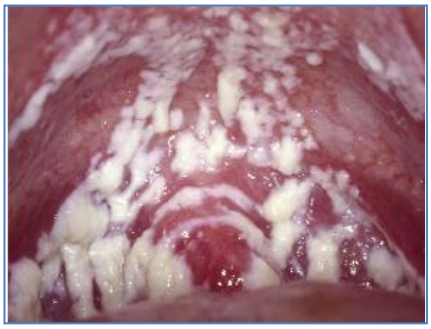
- **Look at the *Bacillus* and *Clostridium* slides which have been stained with a special stain to show the bacterial spores. What is the purpose of these structures and what is their importance in human disease?**
    - **Bacterial Spores:** The dormant form of an organism, and hence, exhibit no metabolic activity.
        - They are similar to 'cysts' in that they are resistant to heat, desiccation and freezing.
    - **Importance of Bacterial Spores:** Allow the organism to survive until environmental conditions improve.





- **Look at the slide of *Candida albicans*. Which broad taxonomic category does this organism fit into?**
    - A Diploid Fungus (a form of yeast)





- **What is the primary structural difference between this and the previous organisms you have looked at today? (Bacteria Vs. Fungal)**
    - Bacteria are prokaryotic, and have no nucleus, whereas fungi are eukaryotic, and have a distinct nucleus.

- **Why is this important in relation to treatment of the fungal infections?**
    - Antifungals have to exploit the differences between mammalian and fungal cells to achieve selective toxicity. Since fungi & human cells are both eukaryotes, it is more difficult to find a drug that targets fungi without affecting human cells.

Microbial pathogenesis: Entry:

3.1: Innate Defences:

Pathogens must able to grow and multiply in the host, since the initial dose is usually insufficient for disease. **Organisms enter the body via one of five routes (skin, oropharynx, respiratory tract, GI tract, urogenital tract).** Each of these sites has Defensive Mechanisms to prevent infection. However, microbes have developed mechanisms for overcoming these defences.

Complete the following table

Body Site	Host Defence Mechanisms	Examples of Breaches & Evasion Mecahanisms.	Examples of Commensal Flora at Site
Skin	Stratified Keratinocytes Lactic acid and fatty acids in sweat and sebaceous secretion & low pH.	Wounds Abrasions Burns Insect Bites	Staph. Aureus Streptococci Pseudomonas Candida
Oropharynx	Mucus inhibits adherence of bacteria to epithelial cells. Lysozyme in nasal secretions & saliva. (And Tears) Tonsils – Lymphoid Tissue	Inhibiting Cilia →Attachment	Streptococci Trichomonas Candida
Respiratory Tract	Mucus inhibit adherence of bacteria to epithelial cells. Mechanical removal of microbes in mucus (Ciliary Action, Coughing, Sneezing) Alveolar Macrophages	Inhibiting Cilia →Attachment Avoid Phagocytosis or survive inside Mϕ	Staph Aureus Streptococci
GI Tract	Gastric acid Vomiting IgA Secreted Antibodies Diarrhoea	Attachment to Epithelium Motile Microbes Survive Enzymes & Acid	Lactobacilli (Stomach) Strep (Duodenum) E.Coli (LI) Staph. Aureus (LI) Strep (LI)
Urogenital Tract	Flushing action of urine. Lactic acid (Vagina) due to Lactobacilli + Glycogen.	Invasion from Exterior Attachment	Staph. Epidermis Streptococci Gram-Neg Rods

3.2 Exit/Transmission:

Successful organisms should not be lethal to the host and should have an Exit Strategy so it can be transmitted to fresh hosts.

Transmission Depends on Three Factors

1) number of organisms shed
2) the stability of the organism in the environment
3) the efficiency of infection.

Complete the following table:

Method of Transmission	Examples of Organisms Using this Route	Populations at Risk of Infection	Potential Control Measures
Respiratory/Aerosols	Influenza Virus Myco.Tuberculosis Pertussis	Crowded Populations Schools/Offices/Military	Ventilation Less Crowding
Faecal-Oral	Cholera Typhoid	Developing Countries Contaminated Water	Clean Food Preparation Clean Disposal of Faeces
Venereal	Gonococci Chlamydia Herpes Simplex	Unsafe Sex Prostitutes Developing Countries	Condoms Promotion of Safe Sex Monogamy

GLS LECTURE STUFF

Antibiotic Susceptibility:

- **Selective Toxicity:**
  - **Critical to Efficacy & Safety of Anti-Microbials**
  - **Exploits Differences in Cell Biology between *Host* & *Pathogen* Cells.**
  - **Aim → Kill only the Pathogen Cells**

- **Antibiotic Action: Key Steps:**
  - 1. Active drug (Ie. The metabolically active form)
  - 2. Present at site of infection
  - 3. Bind to bacterial cell surface. **X**
  - 4. Uptake into bacterial cell. **X**
  - 5. Bind to target – molecular interaction with bacterial cell components. **X**
  - 6. Lysis and death or growth inhibition of bacterial cell. **X**
    - (**X** = steps where bacterial activity leads to resistance.)

- **Classification of Antibiotics:**
  - **1. Bactericidal or bacteriostatic:**
    - Bactericidal →kill bacteria (Ie. Makes the organism unviable)
    - Bacteriostatic →inhibit growth → Host defences kill static population
    - NB: Some agents can be both -e.g.chloramphenicol with *Ecoli*and *Haemophilus*.
  - **2. Target site:**
    - **Cell wall synthesis**
      - Beta lactams
      - Glycopeptides
    - **Protein synthesis**
      - Aminoglycosides
      - Tetracyclines
      - Macrolides
    - **Nucleic acid synthesis**
      - Quinolones
      - **Folic Acid Pathway:**
        - Sulphonamides
        - Trimethoprim
    - **Cell membrane function**
      - Polymixins
      - Colistin
  - **3. Chemical structure**
    - Beta lactams
    - Glycopeptides
    - Aminoglycosides
    - Tetracyclines
    - Macrolides
    - Quinolones
    - Sulphonamides
    - Trimethoprim

Antibacterial Drugs:

NB: The Suffix "-Mycin" simply means an antibiotic derived from the fungus: *'Erythromycin'*.
It is irrelevant to classes of antibiotics.

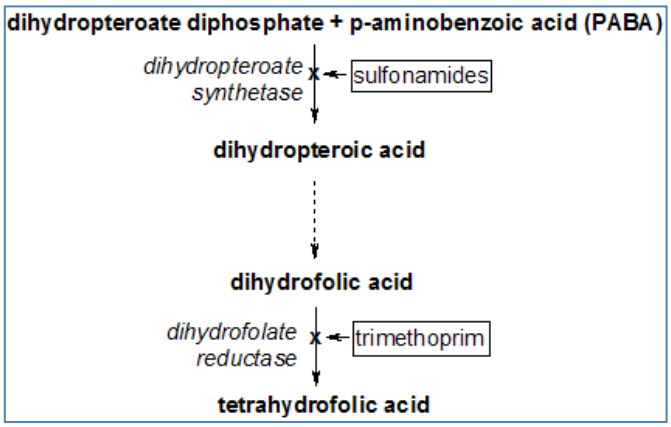
- **1. Anti Cell-Wall Synthesis Antibiotics – (Bacteriocidal):**
  - Target Peptidoglycan Synthesis on Gram-Positive Bacteria.

Classical Agents:	Common Uses:	Mechanism of Action:	Side Effects:
β-Lactam Antibiotics:			
Penicillins: Penicillins 'G' & 'V' Amoxicillin & Ampicillin Flucloxacillin Methocillin Ticarcillin **(Suffix = "-Cillin")**	Gram Positive Bacteria (NB: Bacteria Producing β-Lactamase are resistant) (NB: Fluclox – for β-Lactamase Resistant)	Block "Penicillin-Binding Proteins" (Enzymes) →Inhibit Synthesis of the Peptidoglycan Layer of the Bacterial Cell Wall.	GI Upset & Diarrhoea Allergic Rash Anaphylaxis (Need Adrenaline Handy)
Cephalosporins: (Ceftriaxone)	(NB: Cephalosporins – for *Non*-β-Lactamase Risistant)		(As above) + Mild Renal Toxicity
β-Lactamase Inhibitors: Augmentin	(In Combination with Penicillins) for Penicillin-Resistant Gram Positive Bacterial Infections	Inhibits β-Lactamase → Allows β-Lactams to work on Penicillin-Resistant Bacteria.	
Glycopeptide Antibiotics:			
Vancomycin Teicoplanin Telavancin	Gram Positive Bacteria (*As a LAST RESORT for MRSA*) (Also if Pt. is allergic to β-Lactams)	Prevents incorporation of specific Peptide Subunits into the Peptidoglycan Layer of the Bacterial Cell Wall.	Local Pain Phlebitis (Vein Inflam) Kidney Damage Hearing Loss

- **2. Anti Protein-Synthesis Antibiotics – (Bacteriostatic):**
  - Exploits differences between Eukaryotic (Human) Ribosomes & Prokaryotic Ribosomes.
  - **Selective Toxicity –** Due to specific binding to Prokaryotic Ribosomes.
  - **NB: Aminoglycosides are *Solely* eliminated by the Kidneys & Are Nephrotoxic.** (Need to assess renal function first, then Dose Accordingly)

Classical Agents:	Common Uses:	Mechanism of Action:	Side Effects:
Aminoglycoside Antibiotics:			
Gentamicin **Streptomycin** **Tobramycin**	Gram Negative Bacteria (Used *Synergistically* with β-Lactams to ↑ drug entry into Bacteria)	Bind Specifically to *Prokaryotic Ribosomal* Subunits → Causes Misreading of mRNA → Inhibits Synthesis of Proteins vital to Bacteria.	Ototoxic (Hearing Loss & Vertigo) Nephrotoxic (Kidney Damage)
Tetracycline Antibiotics:			
Doxycycline **Tetracycline** **(Suffix = 'Cycline')**	Gram Negative Bacteria Syphilis (G^-), Chlamydia (G^-), Lyme Disease (G^-) (And *Malaria* - Protazoa)	Bind Specifically to *Prokaryotic Ribosomal* Subunits → Inhibits Binding of tRNA to mRNA → Inhibits Synthesis of Proteins vital to Bacteria.	Nausea/Vom/Diarr. Photosensitivity Staining of Teeth Renal/Liver Toxicity.
Macrolides:			
Erythromycin, **Azithromycin**	Gram Negative Bacteria Syphilis, Lyme Disease.	Bind Specifically to *Prokaryotic Ribosomal* Subunits →Inhibits release of tRNA → Inhibits Synthesis of Proteins vital to Bacteria.	Nausea/Vom/Diarr. Jaundice

- **3. Anti Nucleic-Acid Synthesis Antibiotics – (Bacteriostatic):**
    - **Exploits differences in the Metabolic Pathways of DNA Synthesis – (Humans rely solely on *Dietary Folate*, while Bacteria have to make their own):**
        - Eg. Competitive Inhibition of *Dihydropteroate-Synthase*, a key Enzyme involved in Folate Synthesis in Bacteria.
        - Eg. Competitive Inhibition of *Dihydrofolate-Reductase*, a key Enzyme involved in Folate Synthesis in Bacteria. (NB: Humans share this pathway, but bacteria require it 100x more than humans)
        - Eg. Inhibition of Bacterial DNA Gyrase/Topoisomerase → Stops DNA Replication/Transcrib.



Classical Agents:	Common Uses:	Mechanism of Action:	Side Effects:
		Sulphonamides:	
Sulfasalazine **(Prefix = "Sulfa")**	Urinary Tract Infections	Competitive inhibition of *Dihydropteroate-Synthase*, a key Enzyme involved in Folate Synthesis. (Folate is necessary for Nucleic Acid Synthesis → & Hence DNA Synthesis.	Nausea/Vom/Diarr Allergy Precipitation in Urine –Kidney Failure Leukopaenia Photosensitivity
		Trimethoprim:	
Trimethoprim	Urinary Tract Infections	Competitive inhibition of *Dihydrofolate-Reductase*, a key Enzyme involved in Folate Synthesis. (Folate is necessary for Nucleic Acid Synthesis → & Hence DNA Synthesis.	Nausea/Vom/Diarr Allergy Precipitation in Urine –Kidney Failure Leukopaenia Photosensitivity (BIRTH DEFECTS)
		Quinolones:	
Ciprofloxacin (Systmc) **Norfloxacin (for UTI)** **(Suffix = "Floxacin")**	Urinary Tract Infections Comm.Acq. Pneumonia Bacterial Diarrhoea Gonorrhea	Inhibits bacterial DNA Gyrase or Topoisomerase → Inhibits DNA Replication & Transcription.	

- **Antibiotic Resistance:**
  - **= "Bacteria *Isn't* Inhibited/Killed by an Antibacterial @ Normal Dosage Concentrations."**
  - **NB: Bacterial "Resistance Genes" exist**, and *Mutation Potential* is HIGH!
    - (Due to huge numbers of rapidly proliferating bacteria)
  - **Antibiotic Usage *Preferentially Selects* these resistant strains** → Transmission of "Resistance Genes" to offspring.
  - ***THEREFORE –*** "*Restraint of antimicrobial use is the best way to ensure their efficacy*".

- **Categories of Organism Susceptibility:**
  - ***Susceptible*:**
    - Pt. is likely to respond to treatment with that Antibiotic @ Normal Doses.
    - (Ie. Organism is Killed/Inhibited by the drug @ Normal Doses)
  - ***Resistant*:**
    - Pt. *NOT* likely to respond to treatment with that Antibiotic @ Normal Doses.
    - (Ie. Organism *NOT* Killed/Inhibited by the drug @ Normal Doses)
  - ***Intermediate*:**
    - *Higher Doses are Needed* to ensure treatment success.

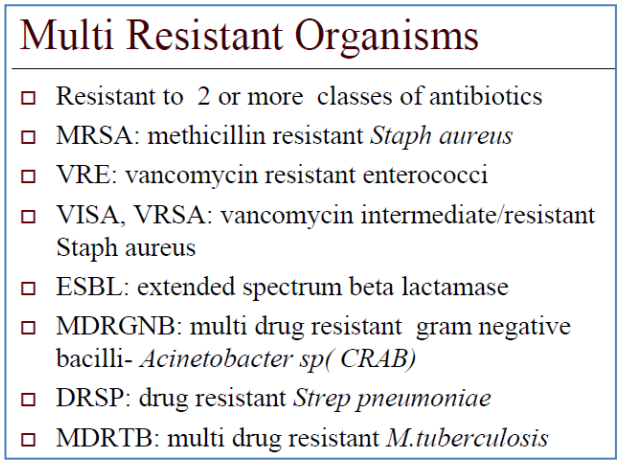
- **Intrinsic Vs. Acquired Resistance:**
  - **1. Intrinsic resistance**
    - Normal genetic, structural or physiologic state -lack target site or impermeable to agent.
    - Predictable within genus or species
    - Eg. All Gram Neg bacilli are intrinsically resistant to Vancomycin.
    - Eg. Bacteria secreting β-Lactamase are resistant to β-Lactams.
  - **2.Acquired resistance**
    - Changes in usual genetic state of bacteria > altered cellular physiology or structural changes.
    - Unpredictable > why laboratory methods are necessary to detect resistance.
    - Resistance arises from:
      - 1) chromosomal mutation
      - 2) transmissible plasmids
      - 3) Combination of mutation and gene transfer events
    - Multiple mechanisms may exist in 1 organism

Common Acquired Resistance

- Penicillin – *Staph aureus*: 90% R.
- Ampicillin – *Ecoli:* 45% R
- Tetracycline- Group B Strep: 91% R
- Methicillin -*Staph aureus* : 29%
- Timentin- *Pseudomonas* 19% R
- Nitrofurantoin- *Kleb pneumoniae*: 54% R

This is why you need to test for resistance to ensure efficacy of drugs.

- **Multi-Resistant Organisms:**
  - (Definition = "Resistant to 2 or more classes of Antibiotics.")



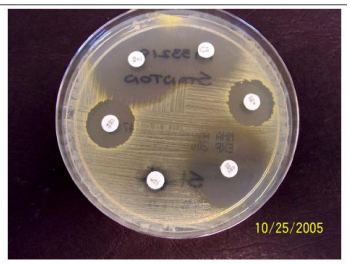
- **Common Resistant Orgainsms:**
  - **MRSA:**
    - (Methicillin Resistant Staphylococcus Aureus)
    - Due to an alteration in PBP (Penecillin binding protein) in cell wall.
    - Also produce β-Lactamase (therefore resistant to all β-lactams, including β-lactamase Inhibitors)
    - Nosocomial (hospital) strains – Typically Multi-Resistant
    - Community Acquired – Typically not Multi-Resistant
  - **VRE:**
    - (Vancomycin resistant Enterococci)
    - Due to altered Target Site
    - 2 Types:
      - Van A – Resistant to both Vanc. And Teicoplanin
      - Van B – Just resistant to Vanc.
  - **VISA:**
    - (Vancomycin Intermediate/Resistant Staph. Aureus)
    - Have Thick Cell walls → Trap Vancomycin
    - Very difficult to detect
  - **ESBL:**
    - (Extended Spectrum Beta Lactamase)
    - Resistance due to β-Lactamase enzymes
      - → Hydrolyse β-lactam ring → Inactivate β-Lactam Antibiotics
    - Now many ESBLs exist → influence affinity for β-Lactams.
  - **MDR-GNB:**
    - (Multi Drug Resistant Gram Negative bacilli)
    - Resistant to all commonly used antibiotics → limited treatment options

- **Laboratory Methods for Detection of Antibiotic Resistance:**
  - **Aim:** To measure an organism's acquired resistance to a select panel of Antibiotics.
  - **Antibiotic Panel is Determined by:**
    - Organism
    - Site of Infection (eg. Drugs for UTI vs. Systemic)
    - Availability of Antibiotic (and Cost)

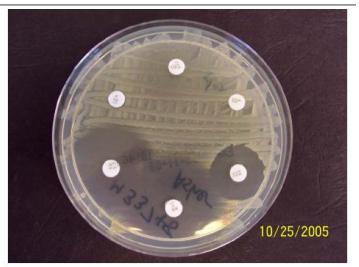
Three Test Methods:

- **1. Measuring Antibiotic Activity:**
  - Organism grown in presence of antibiotic
  - Determines impact of drug on the organism's growth and viability
    - Will it survive?
    - Will it die?
  - Organism's resistance or susceptibility to each antibiotic is reported to clinician.
  - **3 methods:**
    - **A) Disc diffusion**
      - Filter paper discs impregnated with known concentration of different antibiotics.
      - Discs placed on surface of an agar plate seeded with a lawn of bacteria. Incubated.
      - Antibiotic diffuses from the disc into the agar as the bacteria is growing.
      - Bacterial growth inhibited >Zones of inhibition around each disc.
      - Zone sizes measured in mm.
        - Resistant organisms have small zones (of inhibition)
        - Susceptible organisms have large zones (of inhibition).
      - Zone sizes relate to MIC (minimum inhibitory concentration)
      - Report as Susceptible, Resistant or Intermediate(rare)

Disc diffusion: S aureus

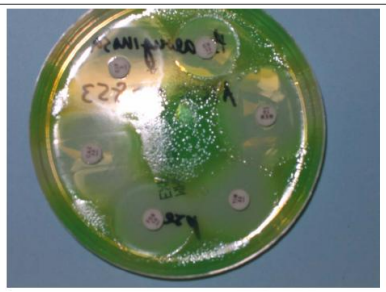


Disc diffusion: MRSA

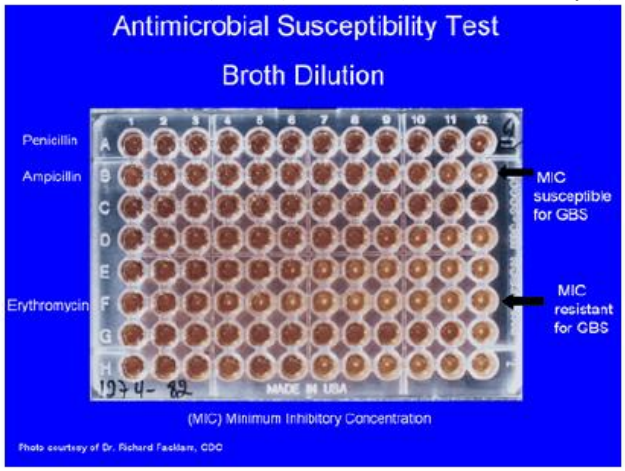


Disc diffusion: Streptococcus

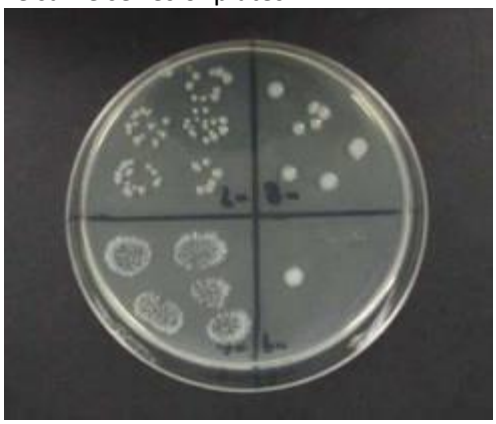
Disc diffusion: Pseudomonas



- **B) Broth and agar dilution**
  - Broth dilution: organism added to a series of broths with ***increasing concentration of antibiotic*** tested. Test one organism per series of broth.
    - Macro (tubes) or micro(microtitre trays) methods



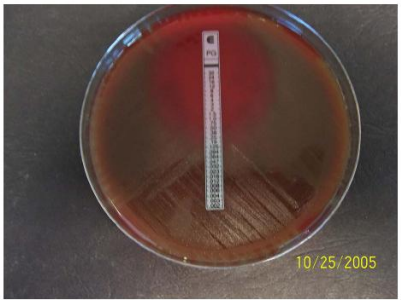
  - Agar dilution: antibiotic at increasing concentration dissolved in a series of agar media. Organism spot inoculated onto agar surface. Can test multiple organisms on the same series of plates.



  - E-test (AB Biodisc)
    - Gradient concentration on plastic strip.
    - Placed onto agar plate with lawn of bacteria.
    - Incubate
    - Read at point where organism growth intersects plastic strip
    - MIC

Etest: GNB

Etest: S pneumoniae

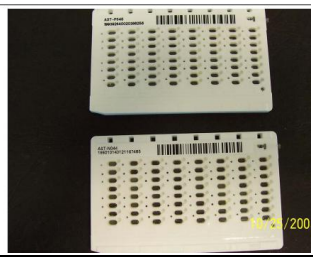


- **(MIC result (Minimal inhibitory concentration** = Lowest concentration of antibiotic that completely inhibits bacterial growth *as detected visually*.

- **C) Automated methods:**
  - Variations of conventional disc or dilution methods.
    - Vitek 2 (bioMerieux)
      - Closed cards with specified concentrations of multiple antibiotics.
      - Card filled with suspension of test organism.
      - Incubated in instrument, optical density readings to measure growth of organism every 15 minutes.
      - Reported as MIC with category interpretation (S,I or R)

Automated system: Vitek

Vitek AST cards.



    - MicroscanWalkaway(Dade)
    - Phoenix system (BD)

- **2. Detecting Specific Resistance Mechanisms:**
  - Detects resistance mechanism (Not activity of antibiotic against bacteria)
  - Most common: detect Beta-lactamase enzymes present in bacteria.
    - Uses chromogenic substrate-colour change if enzyme present.
  - Molecular methods to detect genes encoding for resistance. (*mecA*in MRSA)

Beta lactamase

- **3. Special Methods for Complex Antibiotic-Organism Interactions:**
  - Measure bactericidal activity: MBC
  - Time kill studies: measure *kill rate over time*.
  - Serum bactericidal effect: uses patient serum to detect the dissolved antibiotic activity.
  - Measure effect of antibiotics used in combination.

When to test

- Only do it on
  - clinically significant organisms
  - Organisms with unpredictable susceptibility profile
- Time since last test. Usually do not test if isolated twice in 5 days.
- Only if reliable standardised test available.

Time taken for testing

- At least 18 hours for cultures
- Then approx. another day for Identification and susceptibility testing.
- Expected time from receipt of specimen to final report: at least 24 hours (some urine isolates only). Average is 2-3 days.
- Can take up to 5 days or even longer for unusual or slow growing organisms.

Pathology Reports:

- Provide results for a range of antibiotics tested against the pathogenic organism.
- Each antibiotic reported as:
    - "R" resistant
    - "S" susceptible
    - "I" intermediate.
- Provide alternative agents which may be used e.g. –if patient develops adverse reaction
- Provide information to enable clinician to direct treatment toward most narrow spectrum, least expensive agent to which the organism will respond.

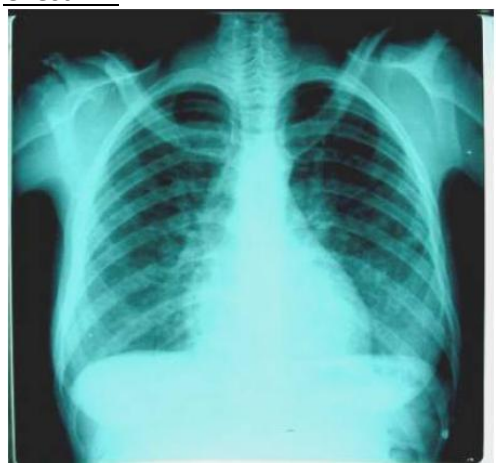
Synthesis Session: Case Study:

Symptoms:

19 year old previously healthy male
Chills, headache, myalgia, abdominal pain, bloody sputum
Reported tenderness in the calves for previous 5 days
Admission examination:
High fever
No rash
No conjunctivitis
No spleno- or hepatomegaly
Mild jaundice

- **Red Flags:**
  - Bloody Sputum – Implies a form of Lung Disease
  - High Fever – Implies a Bacterial Infection
  - Mild Jaundice – Implies possible Haemolysis or Liver Dysfunction.
- **Differential Diagnoses:**
  - TB
  - Flu
  - Viral Pneumonia
  - Bacterial Pneumonia
  - Viral Hepatitis
  - Typhoid
  - Melioidosis

Chest XR:



- Patchy

Patient History:

- Recently returned from camping trip to Tully
- Hiking, white water rafting
- No injuries
- Doesn't remember being bitten by anything

Samples Taken:

- Blood Culture
- Sputum Culture
- Paired Sera
  - If Acute → High IgM
  - If Convalescent → High IgG
- Urine & CSF – Just to be sure.

Lab Results:

- Nothing on Gram Stain
- Nothing on Routine Cultures
- (But NB: Some don't show up on normal stains – ie. Need acid-fast stain)

Requested Serologies:

- EBV
- Dengue Virus
- Flu
- Hep A,B,C
- (→ All Negative.)

NB: Then a Lab Tech did a Dark-Field Microscopy → Found lots of Spirochaete bacteria → Leptospirosis Diagnosis

Leptospirosis:

- Natural host/Reservoir Host = Rats.
- Humans are 'Dead-End' Hosts – Typically clear organisms without transmission.
- Common in Tropical & Subtropical Climates.
- **Risk Groups:**
    - Rice Field Workers
    - Cane Cutters
    - Swine Herds
    - Dairy Farmers
    - Mud Contact
- **Treatment:**
    - Antibiotics
        - Penicillin
        - Doxycytline
        - Amoxycillin
        - Ampicillin

Bacteraemia & Intravascular Infection

LECTURE

A few definitions…

- **Bacteraemia:** The Presence of viable Bacteria in the Bloodstream.
- **Septicaemia:** (old term) The *Spread* of Microbes from Wound →Lymphatics→Bloodstream.
- **Sepsis:** Physiological term; A condition where Bacteremia is Associated with an Inflammatory Response from the body (→systemic inflammatory response syndrome), characterised by Fever or Hypothermia, Tachypnoea, Tachycardia and Hypotension.

The Human Eco-system:

- **Commensal Flora Exist on:**
  - Skin (eg. Staphylococus)
  - Pharynx & bronchial tree (eg. Streptococcus)
  - Gut (eg. E.Coli)
  - Vagina (eg. Lactobacilli)
- **Sterile Sites:**
  - Lungs
  - Uterus & fallopian tubes
  - Urethra, bladder, Ureters & Kidneys
  - Peritoneal Cavity
  - Solid organs and tissues
  - Blood
  - CSF

The Bloodstream Can be a Home for Microbes:

- **Favourable Conditions:**
  - Contains Oxygen, Water & Nutrients
    - (all things required for life – [except. For anaerobes])
  - Has a neutral pH
  - Appropriate temperature for Microbial Growth
    - (Ie. Most cultures are incubated at 37 degrees)
- **Unfavourable Conditions: (To balance out those favorable conditions)**
  - Blood is Constantly Moving
    - →Inhibits Adherence
  - Antimicrobial Defence Mechanisms
    - Phagocytes
    - Complement
    - Antibodies
    - Interferon
  - Blood recirculates through spleen & liver
    - →Foreign things Get filtered out

Origins of Organisms in Blood Infections:

- Commensal Flora (Ie. Opportunistic Endogenous Organisms)
  - Skin
  - Nose and pharynx
  - Gut
- Sites of infection/Introduction of Pathogens (Ie. Exogenous Organisms)

Things that Can Cause Bacteraemia:

- Chewing food/Brushing Teeth/Dental work (e.g. fillings, extractions):
  - Can Introduce mouth flora into blood.
- Minor injuries:
  - Can Introduce Skin Flora into blood.
- G-I Endoscopy, Polypectomy:
  - Can introduce Intestinal Flora into blood.
- Urinary Catheterisation:
  - Can introduce perineal flora into blood.
- Abscess Rupture:
  - Skin and soft tissues
  - Bone
  - Visceral abscesses
- Significant infection anywhere:
  - Pneumonia
  - UTI
  - Wound Infection
- Contaminated IV lines or catheters.

Conditions Required for Infection:

1. Large Numbers of Organisms
2. Anatomical Defect Facilitating Colonization:
   a. Eg. Faulty Heart Valves – Slows down local blood flow, or increases turbulence, giving the organisms more chance to hang on.
   b. Eg. Break in Epithelium – No barrier to infection.
3. Organisms have protective mechanism/s:
   a. Ie. Virulence Factors:
      i. Eg. A Capsule [polysaccharide layer outside normal cell wall] → Not Immunogenic & Resists Phagocytosis.
      ii. Eg. Secrete Proteinases → Aid in penetrating into tissues.
4. Impaired host defence (Ie. Immunocompromise)

At risk patients (May require some form of prophylaxis against infection)

1. Disruption or penetration of anatomical barriers (Ie. Bypassed physical barriers):
   a. Wounds
   b. IV catheters
   c. Contaminated IV drugs
2. Devitalised tissue:
   a. Eg. Necrotic tissue has no blood supply (Ie. No way the immune system can get to that area)
3. Defective granulocyte function:
   a. Eg. In Chemotherapy/Diabetes
   b. (NB. Chemo pts. Don't have many polymorphonucleocytes)
4. Complement defects/deficiency (Immunodeficiencies)
5. Splenic Malfunction/Absence:
   a. Ie. Poor filtering of bacteria out of the blood (Especially Encapsulated Bacteria)

Safe havens for bacteria

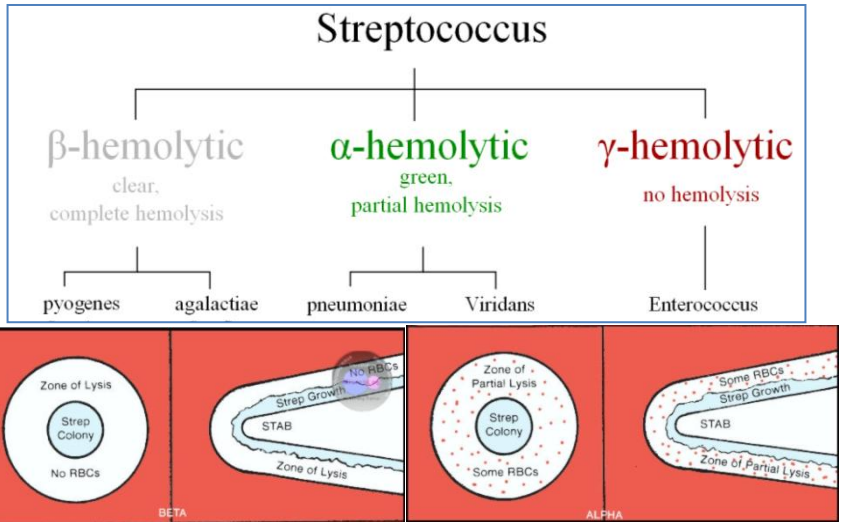
- Damaged Heart Valves & Endocardium
- Organisms can form Bio-films on foreign material because there is no immune system to prevent their growth. Eg.
  - Catheters
  - Prosthetic valves, joints

Diagnosis of bacteraemia

- Blood culture (off antibiotics) (The best)
- Imaging to identify primary & secondary foci of infection
- Histology / Culture of any pathological foci

Common Bacteria to Know:

- **Gram +ve Bacteraemia:**
  - ***Staphylococcus***
    - ***-Aureus*** (Common flora of Skin & Nasopharynx)(NB: Has many Virulence Factors – Eg. a capsule, toxins, antioxidants)
    - ***-Epidermidis*** (Common skin flora)
    - **(Coagulase Positive Vs. Coagulase Negative):**
      - **Coagulase Positive Staphylococcus: (Eg. Aureus)**
        - Ie. Produce Coagulase → Converts Fibrinogen to Fibrin → Forms a Fibrin Coat around Bacteria → Resists Phagocytosis → More Virulent.
      - **Coagulase Negative Staphylococcus: (Eg. Epidermidis)**
        - Ie. Don't Produce Coagulase.
  - ***Streptococcus***
    - ***(α-Haemolytic)(αHaemolysis = Oxidation of Haemoglobin → Greenish colour on Blood-Agar)***
      - ***-Pneumoniae*** (a Leading cause of Bacterial Pneumonia)(Occasionally causes meningitis)
      - ***-Viridans*** (Common flora of Mouth)(Can cause Endocarditis in Bacteraemia)
    - **(β-Haemolytic)(β-Haemolysis = Complete rupture of RBCs → Wide, clear areas around bacterial colonies on Blood-Agar)**
      - Further Grouped by Serotyping (Based on Cell wall Antigens) – Types: A/B/C/D
      - **Group A Streptococcus** – (Implicated in Rheumatic Fever and Post-Strep Glomerulonephritis)
    - **(Non-Haemolytic/γ-Haemolytic)**
      - Enterococcus



  - ***Enterococcus*** (Normal in bowel; doesn't have many virulence factors, but has high antibiotic resistance)

- **Gram –ve Bacteraemia:**
  - ***Neisseria:***
    - ***Meningitides*** (a common URT/Epithelial flora; cocci)(The only cause of Bacterial Meningitis → Headache & Neck Stiffness)
    - ***Gonorrhoeae*** (Responsible for the STI: Conorrhea)
  - ***Escherichia Coli*** (a common Intestinal Flora)(Usually harmless, but can cause Food Poisoning)
  - ***Klebsiella Pneumonia*** (Gram Negative Rods)(Normal Flora of Skin, Mouth & Intestines)(Can cause Pneumonia)

SEPSIS & SHOCK:

Clinical features of Sepsis:

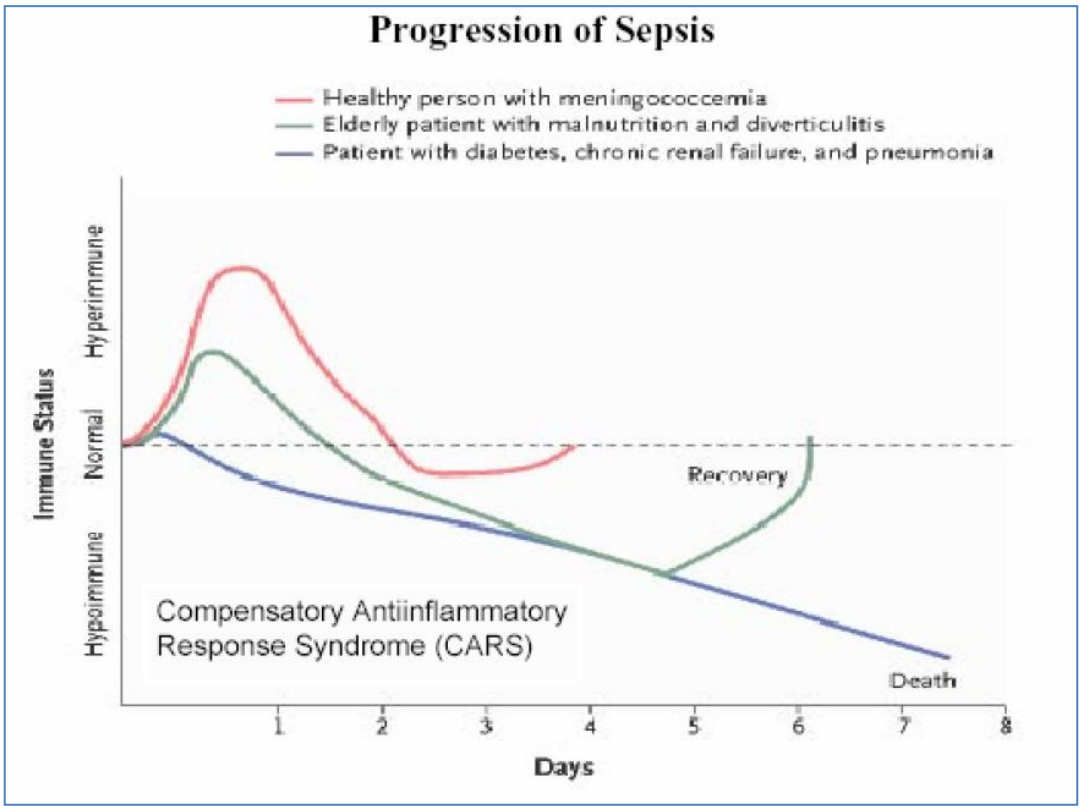
(Remember, **Sepsis =** A condition where Bacteremia is Associated with an Inflammatory Response)

(* Extremely variable* - Relate to the organism causing the sepsis)

1. Patient has high, spiking fever
2. Often severe alternating shaking chills & sweats
3. Symptoms may be intermittent, with periods of improvement
4. →**Shock**: low BP, vascular collapse
    a. Toxic Shock (If Gram Positive)(From Superantigens/Exotoxins)
    b. Or Septic Shock (If Gram Negative)(From Endotoxins – eg. LPS)

- **What role does the bacterial capsule play in the pathogenesis of sepsis?**
    - The bacterial Capsule isolates the bacterium from the immune system, allowing higher numbers of organisms in the blood before immune activation. → Promotes Bacteraemia (which can lead to sepsis & Shock).
- **Name Three Gram Negative Organisms commonly Involved in Bacterial Sepsis:**
    - **(Enterobacteria** (in Soil, Water, vegetation, Intestinal Flora) – Responsible for 35% of all cases of sepsis) a large family of Gram negative bacilli Bacteria**):**
        - **a.** Salmonella Typhi
        - **b.** Escherichia Coli.
        - **c.** Shigella

- **Possible Outcomes of Sepsis:**
    - **Red – Eg. Healthy person with meningococcaemia** → Immune system goes into overdrive → then slows down after infection is dealth with. (Good outcome)
    - **Green – Eg. Elderly person with malnutrition & diverticulitis** → Immune response is slightly depressed → The slows earlier & goes down further → Eventually deals with infection.
    - **Blue – Eg. Pt with diabetes, CKD, & Pneumonia** → Immune system never really responds → Immune function deteriorates → Pt Dies.



Differences between Endotoxins and Exotoxins?

- **Endotoxins:**
  - = Structural components of Gram Negative bacteria
  - (Eg. LPS; NB: Lipid A is the toxic part of LPS)

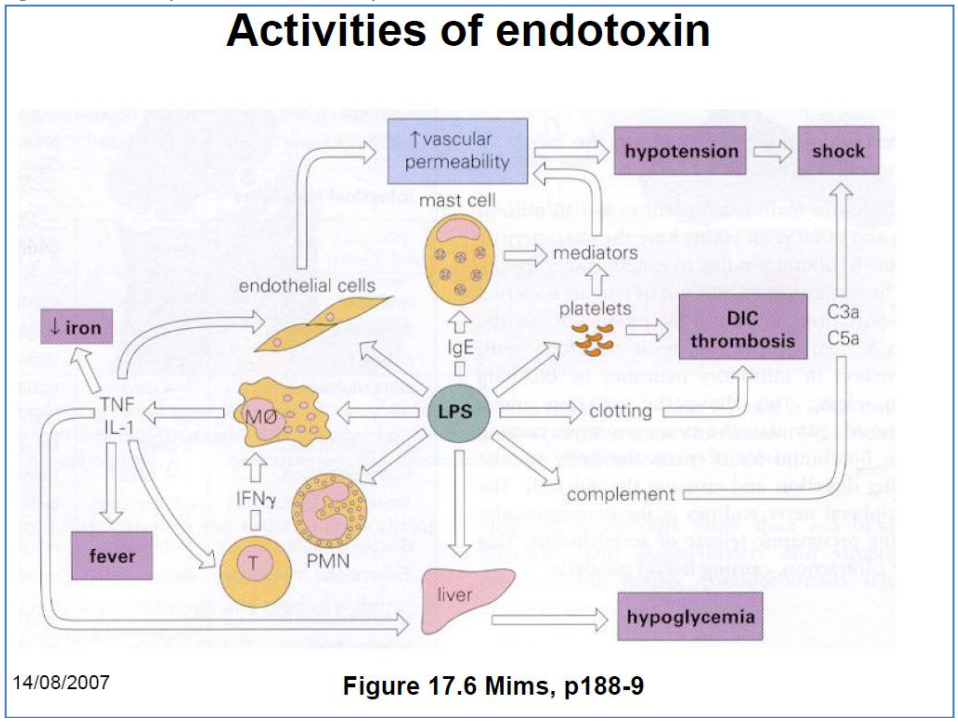
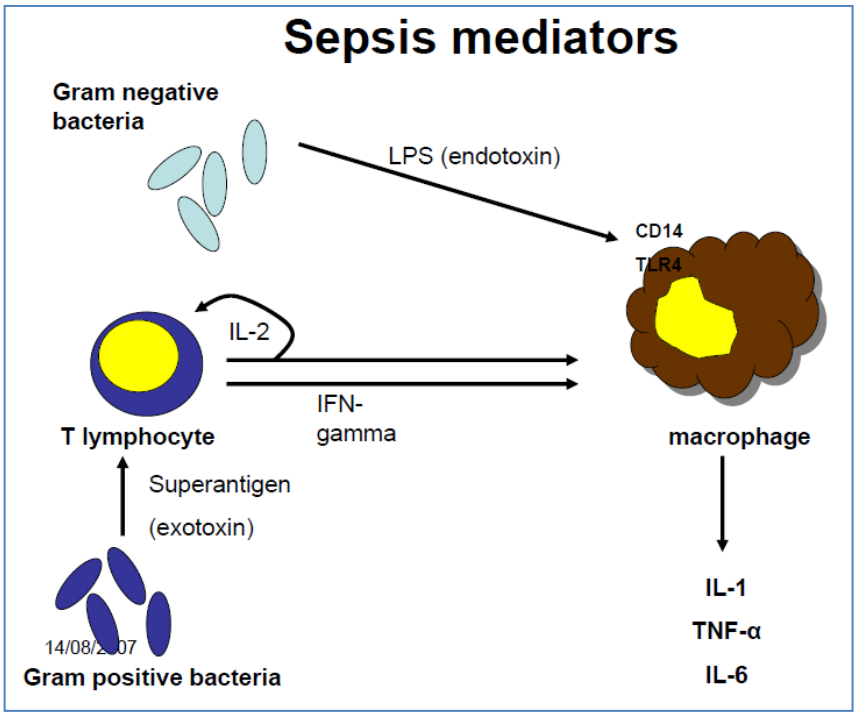


Figure 17.6 Mims, p188-9

  - The above diagram shows every possible symptom of sepsis: (NB: most are due to the immune response rather than the organism)
- **Exotoxins:**
  - = Secreted toxins typically from Gram Positive Bacteria
  - (Eg. Lipoteichoic acid)
  - (Eg. Superantigens (Staph TSST - Toxic Shock Syndrome Toxin; SPE – Strep Pyrogenic Exotoxin))

The Difference between *Septic Shock* and *Toxic Shock*:

- **Septic Shock:**
  - From ***Gram Negative Bacteria***
  - (Mediated by ***Liberated Endotoxin*** from dead organisms – LPS (Lipid A = the toxic part of LPS) → Directly Activates CD14 & TLR-4 on Macrophages → *Cytokine Storm* (including IL-1, IL-6, IL-8, TNF-alpha and PAF) → Shock)
  - – Therefore shouldn't be treated by Bacteriocidals (As they would liberate more Endotoxin)
  - **NB: Septic Shock can be fatal even after Antibiotic Treatment. Explain why?:**
    - 1. If the Antibiotics were *Bacteriocidal*, they will liberate more Endotoxin from lysed bacteria and further exacerbate the septic shock → Death.
      - :. In Septic Shock, Bacteriostatic Antibiotics are most useful, as they slow bacterial growth without lysing them.
    - 2. Conversely: If the shock is in the irreversible stage, no amount of antibiotics (Even bacteriostatic) will do any good. (As there is irreversible organ failure)
- **Toxic Shock:** (Eg. From Staph/Strep)
  - From ***Gram Positive Bacteria*** (Don't contain Endotoxin – Cell walls are primarily Peptidoglycan)
    - (Mediated by ***Superantigens*** secreted from live organisms → Widespread non-specific MHC-II:TCR interaction → Widespread CD4-T-Cell activation → Stimulates macrophages by γ-IFN → *Cytokine Storm* (including IL-1, IL-6, IL-8, TNF-alpha and PAF) → Shock)
  - – Therefore should be treated by bacteriocidals (Don't need to worry about Endotoxin)


Sepsis mediators
Gram negative bacteria
LPS (endotoxin)
CD14
TLR4
IL-2
IFN-gamma
T lymphocyte
macrophage
Superantigen (exotoxin)
IL-1
TNF-α
IL-6
Gram positive bacteria

VARIOUS BACTERIAL DISEASES:
(ENDOCARDITIS, VALVE VEGETATIONS, RHEUMATIC HEART DISEASE, MYOCARDITIS, PERICARDITIS)

Safe havens for bacteria

- Damaged Heart Valves & Endocardium
- Organisms can form Bio-films on foreign material because there is no immune system to prevent their growth. Eg.
    - Catheters
    - Prosthetic valves, joints

ENDOCARDITIS:

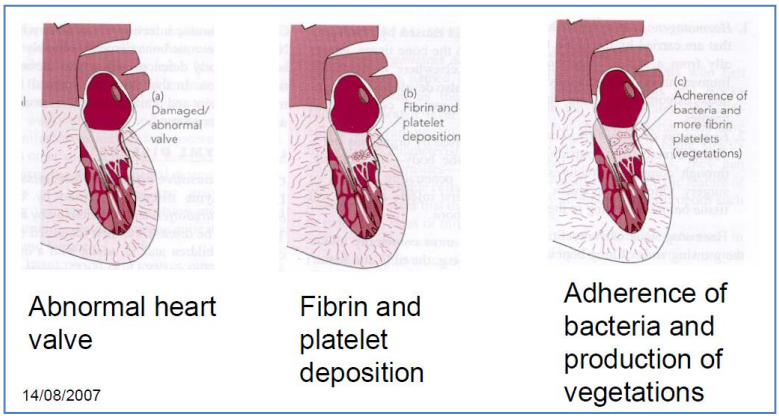
- **= Inflammation of the Endocardium:**
    - Usually Involves the Heart Valves
    - NB: Heart Valves don't have a dedicated Blood Supply →Immune Mechanisms (WBCs) can't reach the valves via the bloodstream.

- **Probability of Infecting Organism depends on:**
    - 1) Condition of valve (abnormal, prosthetic):
        - #1. Oral Streptococci
        - #2. Or Staph. Aureus (Introduced @ time of Valve Surgery)
        - Eg. If Prosthetic Valve:
            - (within 2 moths of prosthetic – these will have probably come from surgery):
            - (after 2 months of prosthetic – typically community acquired organisms):
    - 2) IV drug user (will have normal skin flora injected into themselves):
        - #1. Staph. Aureus / Epidermidis
        - #2. Oral Streptococci
        - #3. Enteric Gram Neg. Bacteria
    - 3) No underlying condition

- **Clinical Presentation:**
    - **Clinical Presentation tells us Aetiology (Organism):**
        - **1. Sub-acute Endocarditis (~60% non/α haemolytic Streptococccci):**
            - Poorly defined onset (Slow onset)
            - Symptoms lasting weeks/months before presentation
        - **2. Acute Endocarditis (~60% S. aureus):**
            - Acute onset of symptoms (Rapid Onset)
            - Symptoms occurring days before presentation

- **Microbiological Diagnosis**
    - Blood Culture – positive in 85-95% cases
    - Isolation of Organism for Antibiotic Sensitivity Testing
    - Acute: 3 bloods @ separate sites, 15-30 min intervals over 1-2 hrs
    - Sub-acute: 3 bloods over 24-48 hours
        - (Why at different intervals? – eg. For subacute infections where organisms are hiding in vegetations, they only break off into the blood occasionally)
    - Positive result: 3 blood cultures positive for same organism

- **Pathogenesis:**



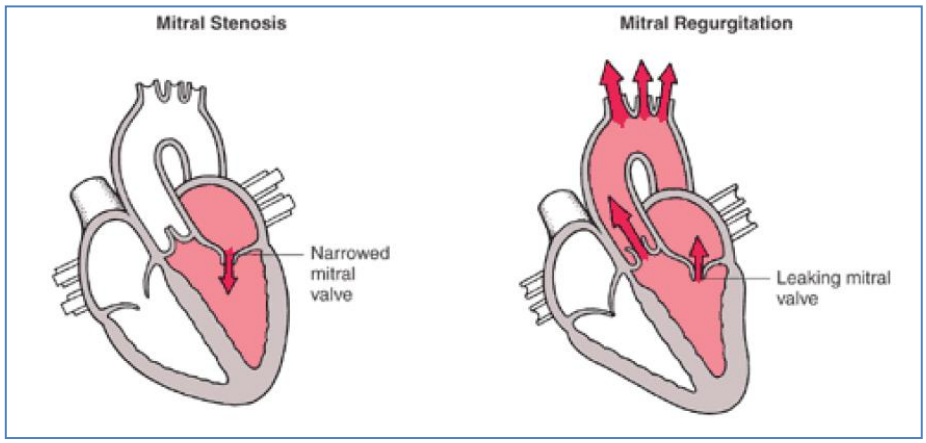
  - Typcailly starts with a damaged or abnormal heart valve
  - Then the body's repair system (fibrin & platelet deposition) → produces 'vegetations'
  - Vegetations are great for bacterial colonization.

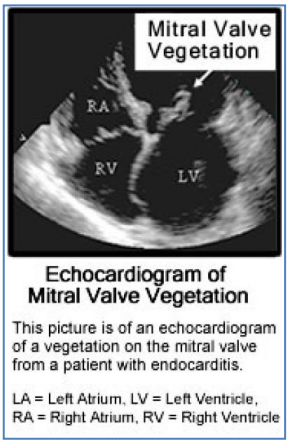
  - **Why is a History of Rheumatic Fever Relevant to the Development of Bacterial Endocarditis?**
    - Normally blood flows smoothly through heart valves. If they have been damaged (Eg. From rheumatic fever) the risk of bacterial attachment & formation of Bacterial Vegetations is higher.

- **Treatments:**
  - **Acute Endocarditis** - Empirical Antibiotic Therapy is started Immediately. (Typically Oxacilin and Gentamicin (IV)) until culture sensitivity report comes back. Then Specific Antibiotic Therapy.
  - **Subacute Endocarditis** – Specific Antibiotic Therapy based on microbe involved (requiring culture report)

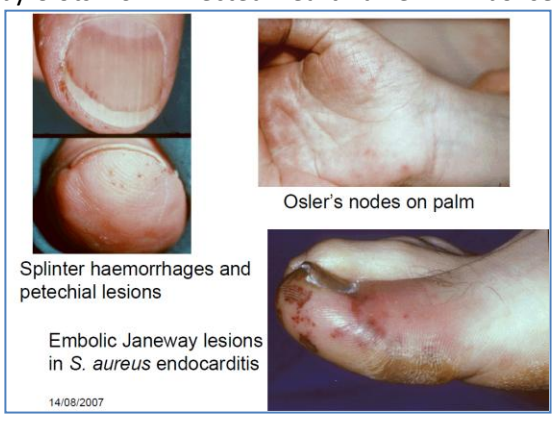
- **Bacterial Endocarditis →Mitral Valve Vegetations:**
  - **Clinical Features:**
    - Extremely variable
    - Can reflect one or more of:
      - **1. Damage/deformation of heart valves**
        - → stenosis, regurgitation
      - **2. Embolisation of vegetations with necrosis**
        - (IE. Vegetations breaking off under high mechanical forces → Emboli)
      - **3. Deposition of Ag-Ab complexes**

  - **Heart Murmers Occur in 85% of Cases – Due to:**
    - Stenosis – (Narrowed Mitral (Stenosis) → Slower ventricular filling)
    - Or Regurgitation – (Leaking mitral valve → Regurgintation back into atria)





  - **Osler's Nodes:**
    - (Painful subcutaneous lesions on hands and feet)
    - - Caused by Immune Complex (Ag:Antibody complex) Deposition in Skin.
  - **Embolic Janeway Lesions:**
    - (Painless hemorrhagic cutaneous lesions on the palms and soles)
    - - Caused by Deposition of Septic Emboli → Microabscesses → Necrosis & Inflammation.
  - **Splinter haemorrhages:**
    - (tiny lines that run vertically under nails)
    - - Caused by Clots from Affected Heart Valve →Embolise to finger→Capillary Damage.



- **Treatment**
  - **Antibiotic therapy** (Including Prophylaxis for @ risk patients – eg. Those going in for surgery)
    - Usually focussed after organism is isolated
    - Broad-spectrum if cultures are negative
  - **Cardiac surgery on valve**
    - Early if infection is uncontrolled and life threatening
    - Late if valve damage is progressive

GAS & RHEUMATIC HEART DISEASE:

- **Pathogenesis:**
  - **= A Complication of GAS infection characterised by Inflammatory changes in the Heart:**
    - 1. Pharyngitis due to Group-A Streptococcus
    - 2. Antibody response against **M-Protein** on Bacterium (Which mimics cardiac myosin)
    - 3. Antibodies Cross-React with Heart Tissue → Promotes Complement Deposition & Inflammation → Damages Heart Tissue.
      - Anti-M-Protein Antibodies *Cross-React* with Cardiac Myosin →
        - → Valvular Thickening
        - →Thickening/Fusion of Chordae Tendonae
        - → Diffuse fibrosis
        - →Focal Fibrinoid Necrosis
    - 4. Healing of Damaged Heart Tissue → Scarring, Deformity & Dysfunction.
    - Rheumatic Heart Disease is a *Consequence* of the lasting, *Cross-Reactive, Adaptive Immune Response* to a Previous GAS Infection.

- ***What is the difference between Rheumatic Fever (RF) & Rheumatic Heart Disease (RHD)?***
  - **(NB: Neither RF or RHD is an Infection, and *Both* can affect the Heart.)**
    - **(The Distinction is whether it is *Reversible* (RF) or *Irreversible* (RHD).)**
  - **Rheumatic Fever:**
    - An Acute, *Post*-GAS-Infection Inflammatory Disease.
    - Occurs a few weeks *After* a GAS Infection.
    - If not treated aggressively →Acute Rheumatic Carditis → Valvular Deformities.
  - **Rheumatic Heart Disease:**
    - The Chronic Stage which causes Irreversible Myocardial Damage & Heart Valve Damage.

- **Major Manifestations:**
  - Carditis – (Inflammation of the Heart)
  - Erythema (Erythematous Rash) – (pink rings on the trunk, arms &/or legs) – due to immune complexes depositing in the Vessels.
  - Polyarthritis
  - Chorea – (spasmodic movements of the body and limbs)
  - Subcutaneous Nodules
- **Minor Manifestations:**
  - Fever
  - Prolonged PR-Interval (Cardiac Fibrosis → Disruption in the Heart's Conduction Pathway)
  - **Lab Tests:**
    - Presence of Anti-Strep Antibodies – (Definitive)
    - Anti-DNA Antibodies.

- **Treatment:**
  - **Eradication Treatment:**
    - Antibiotic Treatment to treat the Initial Strep Infection & prevent the *Development* of RF.
    - If commenced within 9 days of onset → Prevents progression to Acute Rheumatic Fever.
  - **Secondary Prophylaxis:**
    - Long-Term Antibiotic Treatment to prevent Re-Infection → Prevents progression to RHD.

MYOCARDITIS:

- **What is Myocarditis?**
  - = Infection of the Heart, with Inflammatory Infiltrate, Myocardial Damage, *without* Coronary Occlusion.
    - May include Necrosis of Heart Tissue.

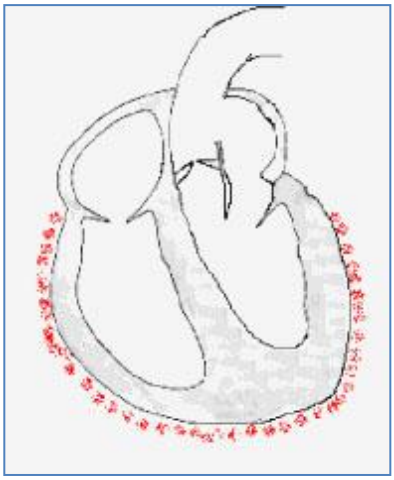
- **Pathogenesis:**
  - **Is often an Autoimmune Complication of Viral, Bacterial or Parasitic Infections:**
    - Eg. **Streptococcal M-Protein** and **Coxsackie Virus B** have Epitopes that mimic cardiac myosin.
  - (Most Commonly due to Viral Infection (enteroviruses being the most important))

- **Presentation of *Viral* Myocarditis:**
  - Resembles a *heart attack* but coronary arteries are not blocked.
  - Heart Failure
    - (leading to oedema, breathlessness and hepatic congestion)
    - May rapidly deteriorate even with supportive care.
    - Young children have higher mortality rates than older patients.
  - Chest pain:
    - May be due to ischemia or concurrent pericarditis
  - Arrhythmia:
    - Including AV-Conduction Blocks.
    - Sinus Tachycardia
  - Sudden Death
  - Fever

- **Long Term Outcomes of Myocarditis:**
  - **Good Prognoses:**
    - If MI-like syndrome with normal coronary arteries →Good Prognosis.
    - If Heart failure, even with dilated left ventricle →Good prognosis.
  - **Poor Prognoses:**
    - Ventricular Arrhythmias and Severe Heart Block → Poor prognosis.
    - Loss of R-Ventricular Function →Strong Predictor of Death.

PERICARDITIS:

- **Presentation:**
  - Chest Pain, (Radiating to the Back) - Relieved by Sitting Forward/Worsened by Lying Down
    - Pain may resemble Angina/MI
    - May also worsen during a Deep Breath.
  - Other symptoms of pericarditis may include:
    - Dry Cough
    - Fever
    - Fatigue
    - Anxiety.
- **Common Causative Organisms:**
  - **Acute Pericarditis – Typically Viral**
    - **Coxsackie B Virus**
    - (Also immune mediated – Eg. SLE (lupus), or rheumatoid)
    - (Also iatrogenic – from surgery)
  - **Acute Purulent Pericarditis – Typically Bacterial**
    - Streptococcus Pneumonia
    - Staphylococcus Aureus
    - Neisseria Gonorrhoeae
    - Neisseria Meningitidis
    - Mycoplasma Pneumoniae
  - **Chronic Pericarditis – Typically Mycobacterium Tuberculosis**
- **Diagnosis:**
  - Symptomatic Differential diagnosis
  - **The classic Sign: "**Friction Rub".
  - **Other signs include:**
    - ST-Elevation on ECG
    - PR-Depression on ECG
    - Cardiac Tamponade
    - And Congestive Heart Failure (Elevated JVP with Peripheral Oedema).
  - **Organism Identification:**
    - Gram Staining Microscopy
    - Bacterial Cultures
    - PCR or other genetic means.



MENINGITIS:

- **Organism Responsible:**
  - ***Neisseria Meningitidis***
  - Gram Negative
  - Diplococci
- **Antibiotic Therapies For Meningococcemia? (*Neisseria Meningitidis)***
  - **Primary Care Setting:** IM *Benzylpenicillin*,
  - **Hospital Setting:** IV Broad Spectrum *Cephalosporins*, (Eg. Cefotaxime or Ceftriaxone (β-Lactams))
- **Criteria For Prophylaxis against Bacterial Meningitis?**
  - Health Care People should have Routine Immunisation against meningococcal.
    - (including lab personel).
  - If Vaccination is unavailable, High Risk People are given Antibiotic Prophylaxis (Oral Rifampin; IM Ceftriaxone; or oral Ciprofloxacin)

SS Case Study:

Chief complaint:

- A 21 year old woman in shock with a temperature of 41oC.

History:

- The patient was well until three days ago, when mild frontal headaches began. On the morning of admission she felt very hot and had a shaking chill. That afternoon she became confused and fainted, at which time she was brought to hospital.

Physical Exam:

- Temp 41C,
- BP 70/30,
- Pulse 140
- The patient was intermittently alert

Pertinent findings include:

- **Skin:** Several ecchymoses on the trunk and bleeding from the nose and mouth
- **Neck:** Supple; no signs of meningeal irritation
- **Lungs:** Clear
- **Heart:** No murmur
- **Abdomen:** Negative except for surgical scar in left upper quadrant, indicating splenectomy
- **Neurologic:** No localised signs

Laboratory:

Blood: (Know the normal ranges)

Measure:	**Case Patient:**	**Normal:**
Haematocrit	0.22 (22%)	0.4-0.5 (40-50%)
WBC Count	2,800	4300-10800/mm^3
Neutrophilic Band Forms	15%	3-5%
PMNLs (Polymorphs)	60%	50-70%
Lymphocytes	22%	25-45%
Eosinophils	3%	1-7%
Platelets	20,000/L	150Billion-450Billion/L

Urine:

- 2+ protein
- occasional WBC and RBC

Chest X-ray:

- Lungs and heart normal

Culture results:

- Gram positive diplococci were seen in blood culture. (:. Possibly Staphylococcus Aureus/Streptococcus)
- Subculture to blood agar revealed small, translucent, alpha-haemolytic Colonies.
    - – (Since it's α-Haemolytic, it's strep – either pneumonia or viridans)(NB: β-Haemolytic streps are grouped –A,B,C,D based on cell wall antigens)

Question:

What was the single most important factor contributing to overwhelming sepsis in this patient?

- The fact that she had a splenectomy!

Question:

Which three organisms are most likely to cause sepsis in an Asplenic Patient?

- Organisms with a capsule (eg. Strep Pneumoniae; Neisseria Meningitidis; Haemophilis Influenzae)
- Others (E.Coli & Staph. Aureus)

Question:
How would you distinguish among these three in the laboratory?

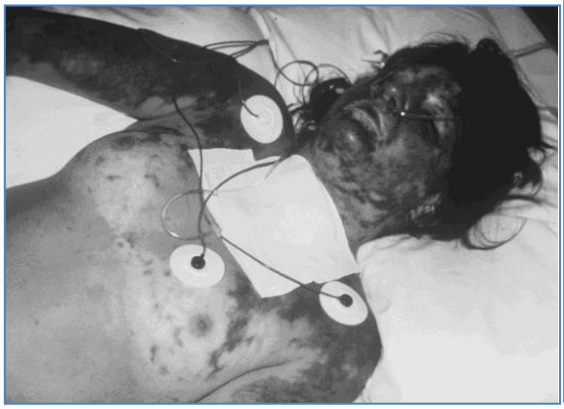
- **Gram Stain**
  - (Eg. Gram Negative, Diplococci – The only clinically important example is Neisseria Meningiditis)
  - (Eg. Gram Negative, small rods – Haemophylis Influenzae)
  - (Eg. Gram Positive, Diplococci – Strep. Pneumoniae – The organism in this case)
- **Culture**
  - To see whether a/b/y haemolytic
- **Quellung Reaction**
  - A Reaction in which Antibodies bind to the Bacterial Capsule of:
    - *Streptococcus pneumoniae*,
    - *Klebsiella pneumoniae*
    - *Neisseria meningitidis*
    - Or *Haemophilus influenzae*
  - → Capsule becomes Opaque and Swollen →Allowing them to be seen under a Microscope.

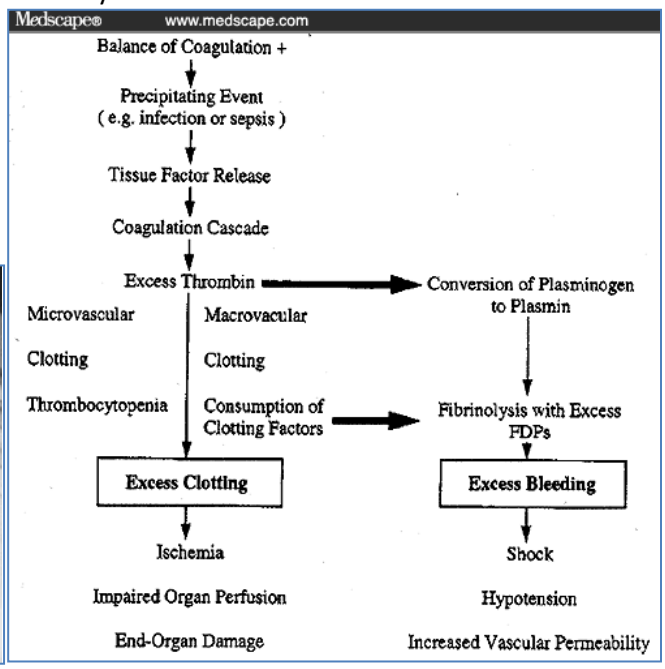
Question:
What was the likely source of this patient's bacteraemia?

- Sepsis from Strep. Pneumoniae
- Could have got it from a pneumonia (But cxr was clear)
- However, they are also normal flora of the nasopharynx.
  - :. Opportunistic Infection + Asplenic → Sepsis.

Question:
Why was the patient bleeding into the skin (ecchymoses) and from the mouth and nose?

- DIC (Disseminated Intravascular Coagulation)
- Due to consumption of clotting factors → Many microclots in the bloodstream.





Patient Course:

- Four hours after admission, the patient became comatose and hypotensive despite antibiotics, transfusions and Vasopressors. Cardiac arrest occurred two hours later → Died.

Question:
How could this infection have been prevented?

- Should have been educated about infection @ time of splenectomy.
    - Vaccines (Pneumococcal Vaccine) – Should be given to all patients with splenectomy.
        - (Composed of capsular polysaccharides for antigen)

Question:
Which drugs would you have given this patient shortly after her arrival at the hospital?

- G-Pos; therefore it's desirable to kill the organism → Penecillin (for pneumococcus & meningococcus)
- (If G-Neg; therefore statics are required → Eg. Aminoglycosides)

Question:
Is drug resistance a problem with the causative organism? (Strep Pneumoniae)

- Yes. Now up to 50% are resistant to penicillin (therefore may require cephalosporin + Vancomycin)

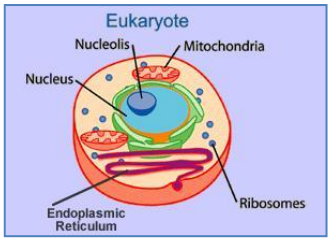
Question:
What is the mode of action of the drugs you would use?

- **Penecillin** – a β-Lactam – Stops linking of Peptidoglycan in the Cell Wall (Therefore more effective against gram positive)
- **Aminoglycosides** – Inhibit protein Synthesis by binding to bacterial ribosomal subnit (Eg. Gentamicin) – (This can therefore be used in Gram-Negative sepsis – as it is bacteriostatic)
- **Glycopeptides** – inhibits late stage of cell wall synthesis (eg. Vancomycin)

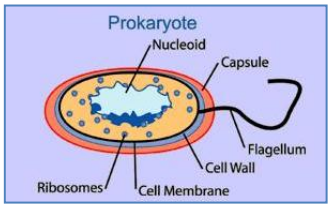
Antimicrobial Therapy: Selective Toxicity

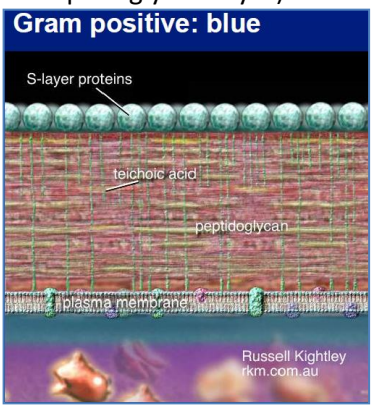
Review of Microbial Cell Biology:

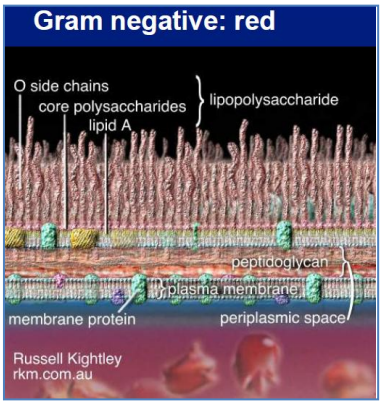
- **Host:**
  - **Eukaryotes**



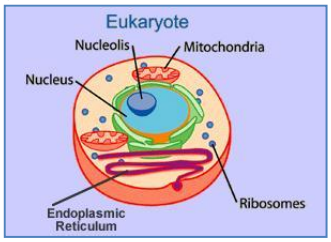
- **Bacteria:**
  - **Prokaryotes** – (Very different from Eukaryotic Host Cells – Therefore Selective Toxicity is easy)
  - (Therefore, Antibacterials are safer (Have less side effects) than Antifungals)
  - **NB: Gram Positive & Gram Negative Bacteria Differ by their Cell Wall Structures:**
    - **Gram Positive:**
      - Thick Peptidoglycan Layer
    - **Gram Negative:**
      - Primarily Lipid-Based (Including Lipopolysaccharide – LPS)
      - (Negligible Peptidoglycan Layer)



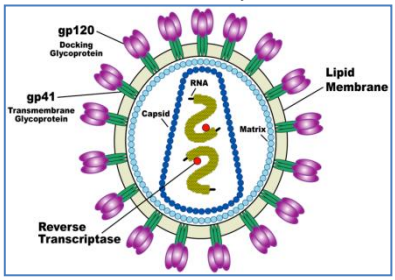




- **Fungi/Parasites:**
  - **Eukaryotes** – (Very similar to Eukaryotic Host-Cells – Therefore Selective Toxicity is Difficult)
  - (Therefore, Antibacterials are safer (Have less side effects) than Antifungals)



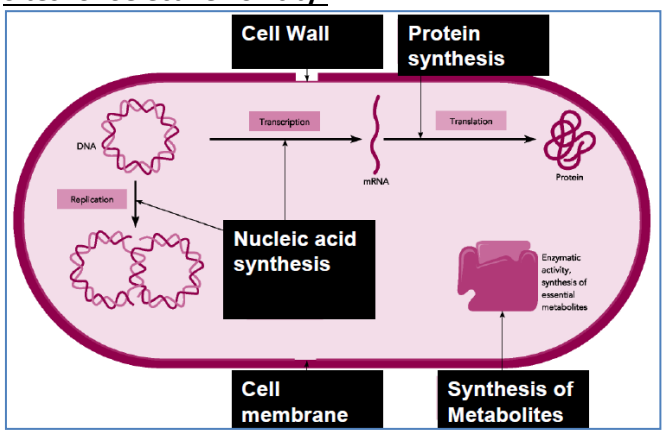
- **Viruses:**
  - **Encapsulated DNA/RNA –** (Very different from Eukaryotic Host Cells)
  - *However* – they are "*Obligate Intracellular Pathogens*" – Ie. Hijack Host-Cell Machinery to Replicate.
    - Therefore, Selective Toxicity is Difficult, because you have to inhibit Host-Cell machinery in order to stop the virus.



Principle of Antimicrobial Therapy:

- **Origins of Antimicrobial Therapy:**
  - NB: Most Anti-Microbials are derived from other Organisms.
  - Eg. Penecillin's Anti-Bacterial property was discovered by Alexander Fleming as it was killing his Bacterial Cultures.
- **Selective Toxicity:**
  - **Critical to Efficacy & Safety of Anti-Microbials**
  - **Exploits Differences in Cell Biology between *Host* & *Pathogen* Cells.**
  - **Aim → Kill only the Pathogen Cells**
- **Scope of Activity:**
  - **Specific to Class of Microbe:**
    - Ie. Antibacterials aren't effective against Viruses.
  - **The *Effect* on the Microbes:**
    - Eg. Bacterio-*Cidal* → Kills Bacteria (Eg. Penecillin)
    - Eg. Bacterio-*Static* → Slows Bacterial Growth (Eg. Tetracycline)
    - (FYI: Bacteriostatic drugs are more useful than Bacteriocidal drugs for Sepsis – Because bacteriocidal drugs will liberate the bacteria's *Endotoxin*s → Further Sepsis)
  - **Synergy:**
    - Some antibacterial agents can amplify each-other's mechanism of action.
    - **Eg. Aminoglycosides + β-Lactams:**
      - Aminoglycosides Inhibit Protein Synthesis, but need to gain access into cell.
      - β-Lactams inhibit Cell Wall Synthesis → ↓Cell wall Integrity → ↑Access into cell.
  - **Broad Spectrum Antibiotics – ("*Empirical Therapy*"):**
    - Compounds active against a wide range of bacteria.
    - Eg. Gram + & Gram – Bacteria.
  - **Narrow Spectrum – ("*Directed Therapy*"):**
    - Compounds active against a specific class/type of bacteria.
    - Eg. Gram + only.
- **Antimicrobial Therapy Should be *EVIDENCE BASED*:**
  - **Ie. *KNOW* what organism you are dealing with before treatment – (Unless Emergency):**
    - Allows treatment to be ***"Directed"*** rather than ***"Empirical"***.
    - → Maximises Efficacy
    - → Minimises Antibiotic Resistance.
- **Antimicrobial Resistance:**
  - **NB: Bacteria employ *'Antibiosis'* of their own to potentiate their *Own* Survival.**
    - **They also develop *Resistance* to Antibiosis from other bacteria to potentiate survival.**
    - **- *THIS CAN WORK AGAINST US* – As Bacteria develop *Resistance* to *Our* Drugs!**
  - **NB: Also, Bacterial "Resistance Genes" exist, and *Mutation Potential* is HIGH!**
    - (Due to huge numbers of rapidly proliferating bacteria)
  - **Antibiotic Usage *Preferentially Selects* these resistant strains, giving them a Competitive Advantage over the rest → Transmission of "Resistance Genes" to offspring.**
  - ***THEREFORE* – "***Restraint of antimicrobial use is the best way to ensure their efficacy*".

Sites for Selective Toxicity:



Antibacterial Drugs:

NB: The Suffix "-Mycin" simply means an antibiotic derived from the fungus: *'Erythromycin'*.
It is irrelevant to classes of antibiotics.

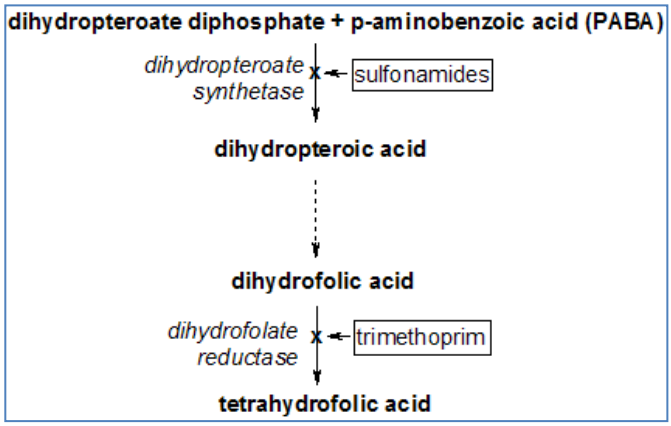
- **1. Anti Cell-Wall Synthesis Antibiotics – (Bacteriocidal):**
  - Target Peptidoglycan Synthesis on Gram-Positive Bacteria.

Classical Agents:	Common Uses:	Mechanism of Action:	Side Effects:
β-Lactam Antibiotics:			
Penicillins: Penicillins 'G' & 'V' Amoxicillin & Ampicillin Flucloxacillin Methocillin Ticarcillin **(Suffix = "-Cillin")**	Gram Positive Bacteria (NB: Bacteria Producing β-Lactamase are resistant) (NB: Fluclox – for β-Lactamase Resistant)	Block "Penicillin-Binding Proteins" (Enzymes) →Inhibit Synthesis of the Peptidoglycan Layer of the Bacterial Cell Wall.	GI Upset & Diarrhoea Allergic Rash Anaphylaxis (Need Adrenaline Handy)
Cephalosporins: (Ceftriaxone)	(NB: Cephalosporins – for *Non*-β-Lactamase Risistant)		(As above) + Mild Renal Toxicity
β-Lactamase Inhibitors: Augmentin	(In Combination with Penicillins) for Penicillin-Resistant Gram Positive Bacterial Infections	Inhibits β-Lactamase → Allows β-Lactams to work on Penicillin-Resistant Bacteria.	
Glycopeptide Antibiotics:			
Vancomycin Teicoplanin Telavancin	Gram Positive Bacteria (*As a LAST RESORT for MRSA*) (Also if Pt. is allergic to β-Lactams)	Prevents incorporation of specific Peptide Subunits into the Peptidoglycan Layer of the Bacterial Cell Wall.	Local Pain Phlebitis (Vein Inflam) Kidney Damage Hearing Loss

- **2. Anti Protein-Synthesis Antibiotics – (Bacteriostatic):**
  - Exploits differences between Eukaryotic (Human) Ribosomes & Prokaryotic Ribosomes.
  - **Selective Toxicity –** Due to specific binding to Prokaryotic Ribosomes.
  - **NB: Aminoglycosides are *Solely* eliminated by the Kidneys & Are Nephrotoxic.** (Need to assess renal function first, then Dose Accordingly)

Classical Agents:	Common Uses:	Mechanism of Action:	Side Effects:
Aminoglycoside Antibiotics:			
Gentamicin **Streptomycin** **Tobramycin**	Gram Negative Bacteria (Used *Synergistically* with β-Lactams to ↑ drug entry into Bacteria)	Bind Specifically to *Prokaryotic Ribosomal* Subunits → Causes Misreading of mRNA → Inhibits Synthesis of Proteins vital to Bacteria.	Ototoxic (Hearing Loss & Vertigo) Nephrotoxic (Kidney Damage)
Tetracycline Antibiotics:			
Doxycycline **Tetracycline** **(Suffix = 'Cycline')**	Gram Negative Bacteria Syphilis (G^-), Chlamydia (G^-), Lyme Disease (G^-) (And *Malaria* -Protazoa)	Bind Specifically to *Prokaryotic Ribosomal* Subunits → Inhibits Binding of tRNA to mRNA → Inhibits Synthesis of Proteins vital to Bacteria.	Nausea/Vom/Diarr. Photosensitivity Staining of Teeth Renal/Liver Toxicity.
Macrolides:			
Erythromycin, **Azithromycin**	Gram Negative Bacteria Syphilis, Lyme Disease.	Bind Specifically to *Prokaryotic Ribosomal* Subunits →Inhibits release of tRNA → Inhibits Synthesis of Proteins vital to Bacteria.	Nausea/Vom/Diarr. Jaundice

- **3. Anti Nucleic-Acid Synthesis Antibiotics – (Bacteriostatic):**
    - **Exploits differences in the Metabolic Pathways of DNA Synthesis – (Humans rely solely on *Dietary Folate*, while Bacteria have to make their own):**
        - Eg. Competitive Inhibition of *Dihydropteroate-Synthase*, a key Enzyme involved in Folate Synthesis in Bacteria.
        - Eg. Competitive Inhibition of *Dihydrofolate-Reductase*, a key Enzyme involved in Folate Synthesis in Bacteria. (NB: Humans share this pathway, but bacteria require it 100x more than humans)
        - Eg. Inhibition of Bacterial DNA Gyrase/Topoisomerase → Stops DNA Replication/Transcrib.



Classical Agents:	Common Uses:	Mechanism of Action:	Side Effects:
		Sulphonamides:	
Sulfasalazine **(Prefix = "Sulfa")**	Urinary Tract Infections	Competitive inhibition of *Dihydropteroate-Synthase*, a key Enzyme involved in Folate Synthesis. (Folate is necessary for Nucleic Acid Synthesis → & Hence DNA Synthesis.	Nausea/Vom/Diarr Allergy Precipitation in Urine –Kidney Failure Leukopaenia Photosensitivity
		Trimethoprim:	
Trimethoprim	Urinary Tract Infections	Competitive inhibition of *Dihydrofolate-Reductase*, a key Enzyme involved in Folate Synthesis. (Folate is necessary for Nucleic Acid Synthesis → & Hence DNA Synthesis.	Nausea/Vom/Diarr Allergy Precipitation in Urine –Kidney Failure Leukopaenia Photosensitivity (BIRTH DEFECTS)
		Quinolones:	
Ciprofloxacin **Norfloxacin** **(Suffix = "Floxacin")**	Urinary Tract Infections Comm.Acq. Pneumonia Bacterial Diarrhoea Gonorrhea	Inhibits bacterial DNA Gyrase or Topoisomerase → Inhibits DNA Replication & Transcription.	

Antimycobacterial Drugs:

- **Mycobacterial Infections in Humans:**
  - **2 Main Types:**
    - **Tuberculosis**
    - **Leprosy**
  - **Why are they a Problem?**
    - Because Mycobacteria can live inside Macrophages following Phagocytosis.
    - Also, Multi-Drug-Resistant strains are on the rise.
  - **Compound Drug Therapy:**
    - A frequent strategy to decrease the probability of the emergence of resistant organisms.
    - Also requires Long-Term Therapy.

Classical Agents:	Common Uses:	Mechanism of Action:	Side Effects:
		Isoniazid:	
Isoniazid	Combination Treatment of M. Tuberculosis	MOA unknown. (Bacteriostatic & Bacteriocidal)	Allergic Skin Eruptions Fever Hepatotoxicity Haemolysis (in G6PD Deficiency)
		Rifampicin:	
Rifampicin	Combination Treatment of M. Tuberculosis	Binds to & Inhibits DNA-Dependent *Prokaryotic RNA-Polymerase* → Inhibits DNA Transcription & therefore Inhibits Protein Synthesis. (Bacteriostatic & Bacteriocidal)	Allergic Skin Eruptions Fever Hepatotoxicity
		Ethambutol:	
Ethambutol	Combination Treatment of M. Tuberculosis	MOA Unknown. (Bacteriostatic)	Optic Neuritis Visual Disturbances Colour Blindness.
		Pyrazinamide:	
Pyrazinamide	Combination Treatment of M. Tuberculosis	Active in Low pH–(In Phagolysosomes) (Bacteriostatic)	Gout GI Upset Hepatotoxicity

Antifungal Drugs:

- **NB: Fungi are Eukaryotic:**
  - Therefore Selective Toxicity is Difficult.
- **Drug Targets:**
  - **1. Difference in Lipid Composition of Cell Membrane:**
    - Fungi – Ergosterol
    - Humans – Cholesterol.
  - **2. Inhibition of Ergosterol Synthesis:**
    - Fungal Cell Cytochrome Enzymes
  - **3. Inhibition of DNA & RNA Synthesis:**
    - Intracellular Conversion to Inhibition Substances.
- **Routes of Administration:**
  - **Systemic (Oral/Parenteral) –** For Systemic Fungal Infections
  - **Oral –** For Mucocutaneous Infections.
  - **Topical –** For Mucocutaneous Infections. (Selective Toxicity is less important)

Antiviral Drugs:

- **Viruses are "*Obligate Intracellular Pathogens*" – Ie. Hijack Host-Cell Machinery to Replicate:**
  - Therefore, Selective Toxicity is Difficult, because you have to inhibit Host-Cell machinery in order to stop the virus.
- **Mechanisms of Antiviral Selective Toxicity:**
  - **Nucleoside Reverse Transcriptase Inhibitors.**
  - **Non- Nucleoside Reverse Transcriptase Inhibitors.**
  - **Protease Inhibitors**
  - **Viral DNA Polymerase Inhibitors**
  - **Inhibitors of Fusion with Host Cells**
  - **Inhibitors of Viral Coat Disassembly**
  - **Biologics & Immunomodulators (Eg. Interferon)**

Antiparasitic Drugs:

- **NB: Parasites are Eukaryotic:**
  - Therefore Selective Toxicity is Difficult.
- **Drug Targets:**
  - **1. Unique Enzymes**
  - **2. Shared Enzymes – but those Indispensable for Parasite.**
  - **3. Common Pathways with Different Properties.**

- **NB: Antimalarial Drugs & G6P-Dehydrogenase Deficiency:**
  - **Eg. Chloroquine/Primaquine/Pamaquine:**
    - Must NOT be given to Pts with Glucose-6-Phosphate Dehydrogenase Deficiency, as they can cause Fatal Haemolysis.
    - (NB: G6PD is an essential enzyme in RBC Metabolism)

Bali Belly (Traveller's Diarrhoea)

Definitions:

- **Diarrhoea:** 3-4 unformed stools/day + 1x Enteric Symptom
- **Persistent Diarrhoea:** 14 Days
- **Chronic Diarrhoea:** 30 Days

Possible Causes of Traveller's Diarrhoea:

- **Bacterial:**
  - **E. Coli (Particularly Enterotoxigenic E.Coli)**
  - **Campylobacter**
  - **Shigella**
  - **Salmnoella**
  - **Vibrio Cholerae**
- **Viral:**
  - **Rotavirus**
  - **Norovirus**
  - **Adenovirus**
  - **Astrovirus**
  - **Calcivirus**
- **Parasites:**
  - **Giardia Lamblia**
  - **Cryptosporidium**
  - **Entamoeba Histolytica (Amoebic Dysentery)**
- **Chemicals:**
  - **Poisons**
  - **Mercury**
  - **Arsenic**
  - **Cyanide**

****ETEC – Enterotoxigenic E.Coli:**

- **Responsible for 80% of all Cases of Traveller's Diarrhoea**
- **Microbiology:**
  - Gram Negative – (LPS Endotoxin)
  - **Virulence Factors:**
    - **Has Fimbriae** (For Attachment)
    - **Produces 2 Exo-Toxins:**
      - **Heat Labile Enterotoxin** → Disrupts Chloride Channels → Increases Fluid Secretion in SI
      - **Heat Stable Enterotoxin** → Disrupts Chloride Channels→ Increases Fluid Secretion in SI
- **Infection Via Faecal Oral Transmission:**
  - Usually Food-Borne:
    - Raw Food
    - Contaminated Food (Commonly by Hawker Food Stalls)
    - Unreliable Refrigeration
    - Inadequate food storage/transport.
    - No pasteurisation
  - Contaminated Water
  - (NB: Require High Numbers for Infection)
  - "If you can't cook it, boil it, or peel it…don't eat it!"

- **High Risk Groups in Travelers:**
  - People eating from roadside stalls
  - Vegetarians
  - Infants
  - Pregnant Women
  - Immunocompromised
- **Timescale:**
  - Incubation 12-72 hrs (1-3 days)
  - →Brief illness (5 days)
- **Prevention:**
  - Organisms killed by heat

Traveller's Diarrhoea. AKA "Bali Belly":

- Usually Self-Limiting
- Caused by ingesting contaminating food/water
- Higher in places where sanitation & hygiene standards are poor.
- **Scenario:**
  - Student on a 4 week placement in Indonesia. 2 Days after arrival, he develops severe abdominal pain & watery Diarrhoea.
  - **Is this 'Traveller's Diarrhoea'?**
- **Patient History:**
  - Travel History
  - What have they been eating
  - Where have they been eating
  - Diarrhoea:
    - Duration
    - Severity
    - Number/day
    - Presence of Blood/Mucous (Dysentery?)
  - Other Symptoms:
    - Vomiting
    - Abdominal Pain
  - Medications
- **Signs/Symptoms of Dehydration:**
  - **Mild Dehydration:**
    - Thirst
    - Dry Mouth
  - **Moderate Dehydration:**
    - Loss of Skin Elasticity
    - Sunken Eyes
    - Dry Mouth
  - **Severe Dehydration:**
    - Lethargy
    - Confusion
    - Dizziness
    - Faintness
    - Cold/Clammy skin
    - Shock

- **Patient Management Goals:**
    - **Rehydration or Prevent Dehydration:**
        - **If Mild:**
            - No Treatment
        - **If Mild-Moderate:**
            - Symptomatic Treatment
            - Anti-Diarrhoeal Agents?
        - **Dysentery:**
            - As Above + **Antimicrobial Therapy.
        - **If Pt. is an Infant:**
            - ***Oral Rehydration Therapy:
                - Rehydration:
                    - Getting them back to square 1.
                - + Maintenance:
                    - Replacing what they lose over time.
            - Kids have a higher fluid:body-weight ratio.
                - Ie. Loose more fluid in diarrhea per body weight.
                - :. Require proportionally higher amounts of rehydration.
            - If at Home:
                - Make your own ORT
                    - 1x Salt
                    - 8x Sugars
                    - 1L Clean, Boiled Water.
                - Breast Feeding.
    - **How ORT Works:**
        - Na^+ Absorption is impaired in Diarrhoea.
        - However, Glucose/Na^+ Co-Transport is Unaffected.
            - This is a 1:1 ratio.
        - :. You need to add Glucose to the ORT in order to absorb Na^+.
- **Indications for Stool Sample:**
    - Enteric Symptoms – Cramps/Vomiting/etc.
    - Persistent Diarrhoea (Diarrhoea for >14 Days)
    - Fever (>38.5^{o}C)
    - Dysentery/Bloody Stools
- **Vaccination?:**
    - None Available
    - Desired Vaccine:
        - Oral
        - Induce *Mucosal Immunity* – (ie. Induces IgA)
        - Long Lasting

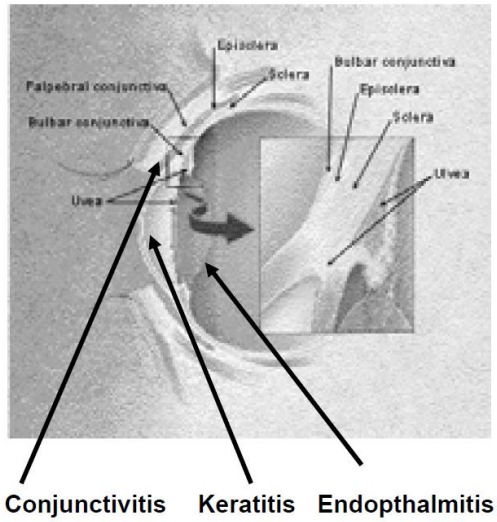
Patient Travel Advice:

- Don't Drink from Mountain Streams
- Don't buy food from local street vendors
- Don't handle the local fauna

INFECTIOUS DISEASE HEALTH Pathology:
Eye & ENT Infections

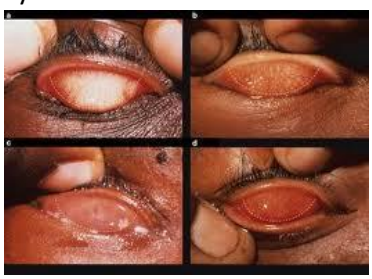
EYE INFECTIONS:

- **Bacterial Conjunctivitis:**
  - **Aetiology:**
    - Can be Infectious or Non-Infectious
    - **Major Pathogens in Acute Bacterial Conjunctivitis:**
      - *Streptococcus*
      - *Staphylococcus* (*S. aureus*, *S. epidermidis*)
      - *(Chlamydia Trachomatis – in Trachoma)*
  - **Presentation:**
    - Inflammation of the orbital and/or palpebral conjunctivae
    - Itching
    - Discharge:
      - If Serous (watery) – viral, allergic
      - If Mucoid – allergy, dry eyes
      - If Purulent – bacterial, often associated with morning crusting



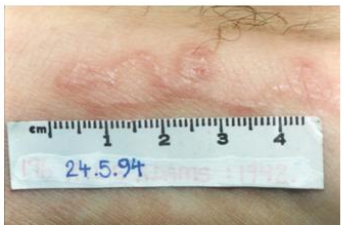
- **Trachoma:**
  - **Organism:**
    - *Chlamydia Trachomatis*
  - **Pathophysiology:**
    - Infection with C.Trachomatis → Chronic Inflammation of the Upper tarsal conjunctiva → Scarring of the Conjunctiva → Retraction of scarring → Pulls eyelid inwards → Eyelashes abrade the cornea → scarring of the cornea → Opacity & Blindness.

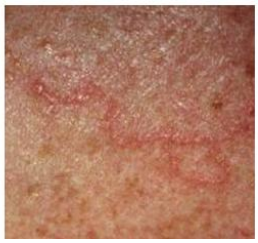




INFECTIOUS DISEASE HEALTH Pathology:
Helminths

- **Cutaneous Larval Migrans (CML):**
  - **Organism:**
    - Infective larvae of ***Hookworms***
    - →penetrate the skin and wander aimlessly until they die
  - **Presentation:**
    - →***Well-Defined*** Serpigenous, Inflammed tract appears
      - Itchy, moves slowly
      - Lasts about 6 weeks
  - **Treatment:**
    - Spontaneous Resolution
    - Can be treated with Ivermectin.



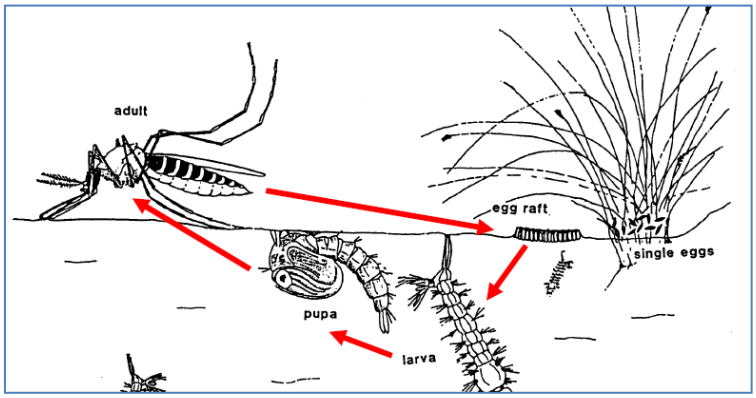


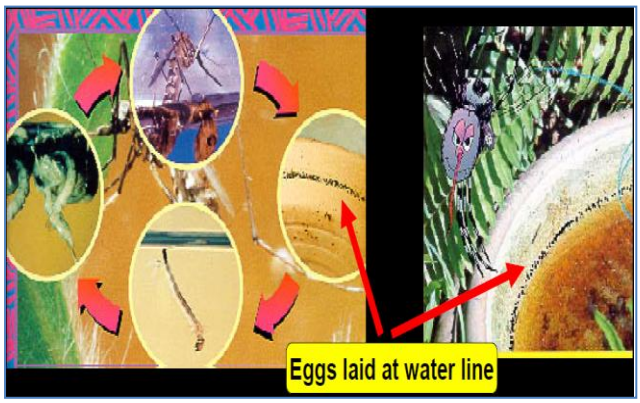
- **Larva Currens (LC):**
  - **Organism:**
    - Autoinfective larvae of ***Strongyloides Stercoralis*** **(Threadworm)**
    - Normally lives in the small intestine.
  - **Pathogenesis:**
    - Autoinfective larvae invade the body (from the intestines), wander randomly and sometimes come up to the skin
  - **Presentation:**
    - →***Urticarial*** Red line that moves rapidly (>5 cm/day)

Intro to Tropical Diseases & Dangerous Creatures

Medical Entomology:

- (study of insects/arthropods in the cause of disease in humans)
- **Micropredators Vs. Ectoparasites:**
    - **Micropredators:**
        - Arthropods that feed on animals, but *don't live on* them.
        - Eg. Mosquitos
    - **Ectoparasites:**
        - Arthropods that feed on animals, AND have to live on them to survive.
        - Eg. Ticks/Fleas/Head-Lice
- Most Important Vector = **MOSQUITO:**
- **Mosquito:**
    - **Life-Cycle:**
        - 1. Lays Eggs in Water
            - Eggs resistant to dehydration → Will hatch after rain after being dry for long time.
        - 2. Eggs Hatch
        - 3. Larvae → Pupa
        - 4. Pupa → Adult



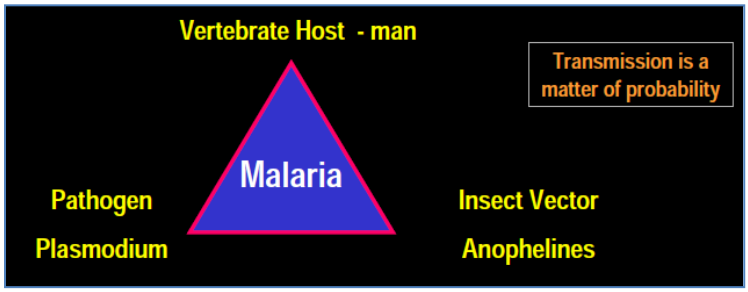


    - **Ecology:**
        - **Eg. Aedes Aegypti (Dengue Vector):**
            - Urban Environment (Pots/Gutters/Puddles/Around the house)

        - **Eg. RRV Vector:**
            - Open Environment (Marshlands/Swamps/Tidal Flats/Etc)

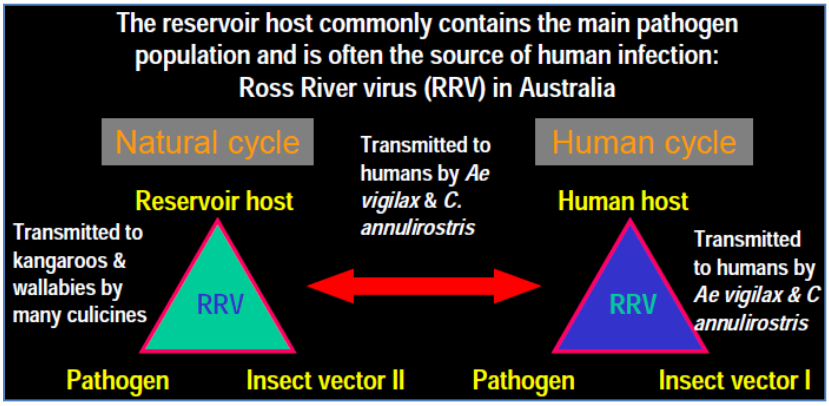
    - **Pre-Feeding Activity:**
        - Feed @ Dawn & Dusk – Activity stimulated by dim light.
        - Attracted by Visual & Chemical Cues (up to 20m away).
        - Mosquito Lands, Ascertains its safety, then finds a suitable site to probe.
    - **Feeding:**
        - Probes several times before finding a capillary.
        - Feeding only takes a few minutes
        - 'Pool Feeding' – Waits until sufficient blood has collected, then ingests it.
        - NB: Only the *Female* needs to feed on blood (necessary to lay eggs)

- **Normal Vector-Host Interaction:**

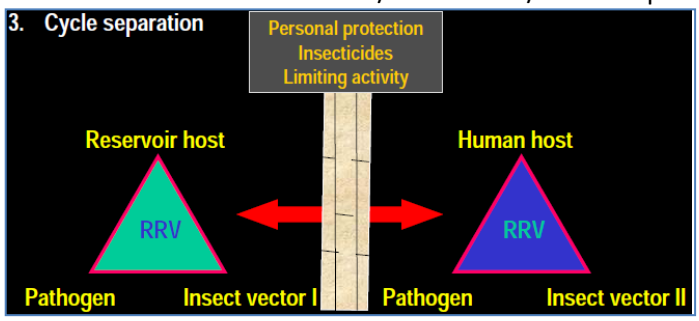


  - **Vector-Bourne Disease Control Strategies:**
    - **1. Break Host-Vector Contact:**
      - Eg. Protective Clothing/Insect Repellant
    - **2. Break Host-Pathogen Contact:**
      - Ie. Personal Medication/Immunisation.
    - **3. Eliminate The Vector:**
      - Ie. Use of Insecticides

- **"Reservoir Host"-Vector-Human Interaction:**



  - **Reservoir Host-Vector-Bourne Disease Control Strategies:**
    - **1. Treat Human Hosts**
      - Ineffective control strategy – as incidence is maintained by reservoir cycle.
    - **2. Reservoir Elimination:**
      - Ineffective – as it is unacceptable to kill all the animal reservoir hosts.
    - **3. **Cycle Separation:**
      - Via Personal Protection/Insecticides/Insect Repellant.



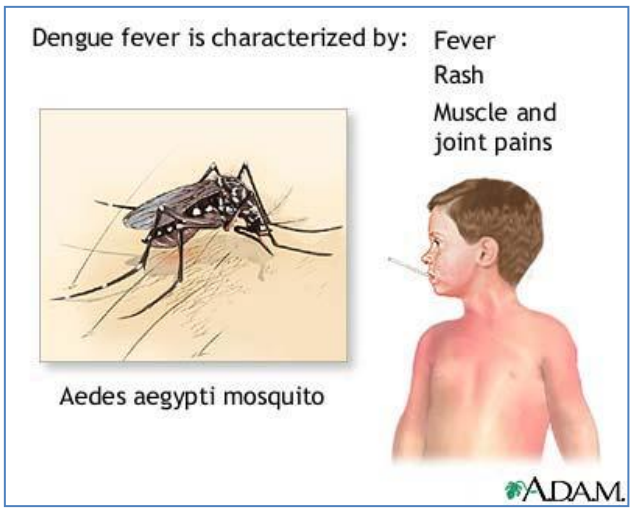
Examples of Vector-Bourne Diseases:

- Dengue - Mosquitos
- Ross River Virus - Mosquitos
- Japanese Encephalitis - Mosquitos
- Malaria - Mosquitos
- Lymphatic Filariasis - Mosquitos
- Leishmaniasis - Sandflies
- Plague - Flea

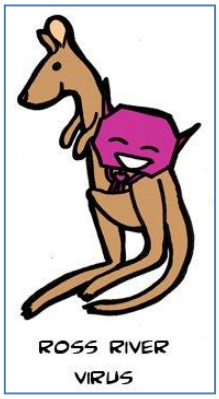
Tropical Diseases:

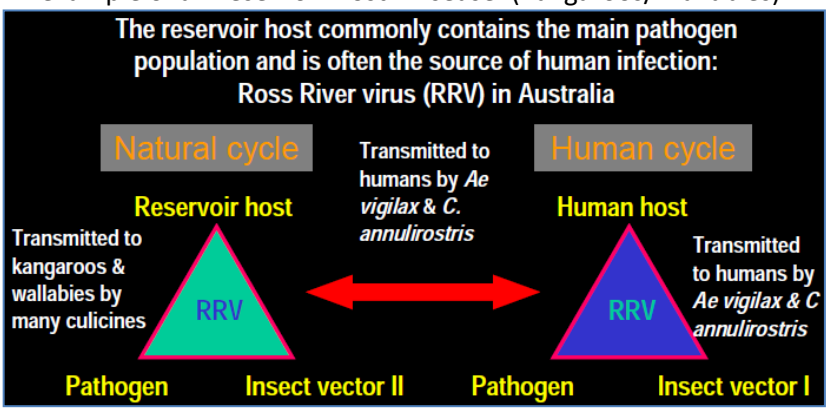
Viral:

- **Dengue Fever:**
  - **Pathogen:**
    - Dengue Virus
  - **Vector:**
    - Mosquito – (2 Specific Species – "Aegypti" & "Albopictus")
    - Disease only occurs where these vectors are.
  - **Life Cycle:**
    - "Peridomestic" = Vectors Breed around the home.
    - Ie. In Urban Environments
  - **In Australia?:**
    - Not Endemic
    - Some "Imported" Cases
  - **Symptoms:**
    - Fever
    - Muscle Pain
    - Photophobia (fear of light)
    - Headache
    - Rash
    - Minor Bleeding
    - **Dengue Haemorrhagic Fever:**
      - Severe Bleedng
      - Leaky Capillaries
      - Shock



- **Ross River Virus:**
  - **Infection:**
    - Via Infected Mosquito Vector
      - Breeds in Open Environment (Marshlands/Swamps/Tidal Flats/Etc)
      - - Incidence increases after significant Tides/Floods/Rain/etc.
    - RRV – An example of a "Reservoir Host" Disease. (Kangaroos/Wallabies)



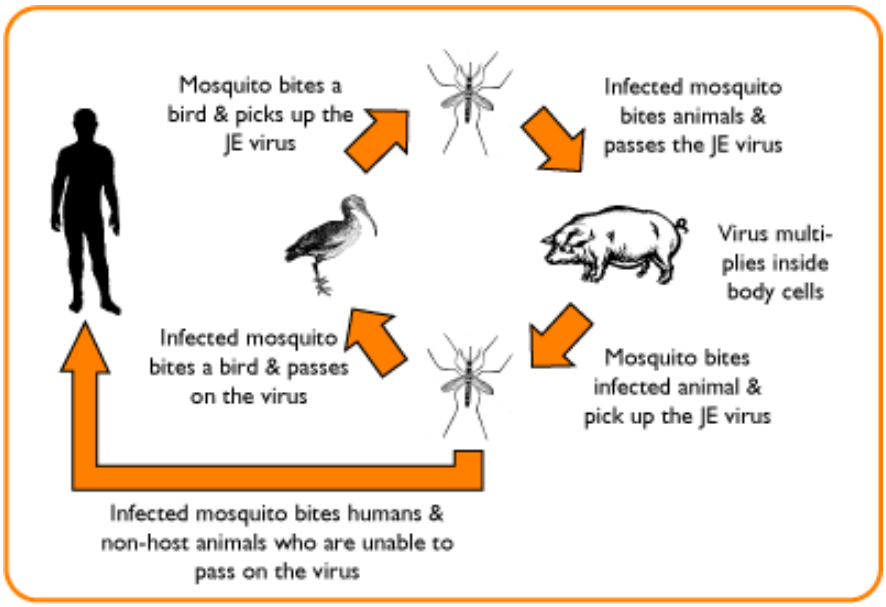


  - **Symptoms:** (Similar to "Barmah Forest Disease")
    - PolyArthritis
    - Fever
    - Arthralgia (Sore Joints)- Due to Arthritis
    - Rash (Red & Spotty – not Itchy)
    - Lethargy
    - Fatigue

- **Hepatitis A/B/C:**
  - **Complications:**
    - Hepatitis
    - Hepatomas (liver cancer)

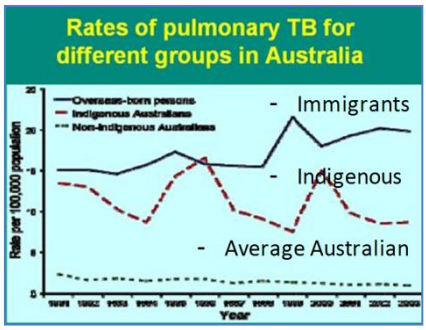
- **HIV/AIDS:**
  - **Virus:**
    - Human Immunodeficiency Virus
    - RNA Virus →Host cell forced to make DNA Copies → DNA inserted into Genome
  - **Prevalence:**
    - Mostly in Tropical/Developing Countries.
    - 50% Patients in African Hospitals Infected.
  - **Symptoms:**
    - Weight Loss
    - Opportunistic Infections

- **Japanese Encephalitis:**
  - **Vector:**
    - Mosquitos
    - Birds = Reservoir Hosts
    - Pigs = Amplifier Hosts
  - **Pathogen:**
    - Flavivirus
  - **Symptoms:**
    - Encephalitis = Inflammation of the Brain.
  - **In Australia?:**
    - 1x Clinical case in 1998

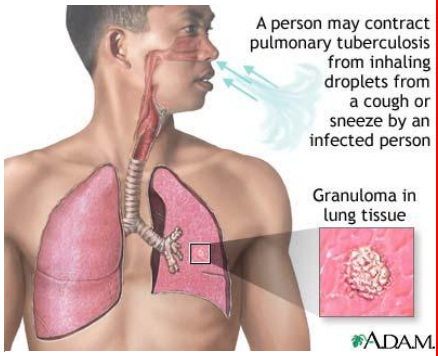


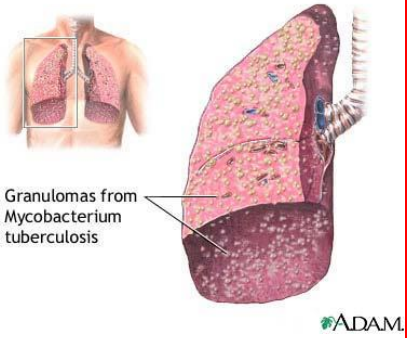
Bacterial:

- **Tuberculosis:**
  - **Infection** - Via Droplet-Transmission
    - Contaminated Droplets Inhaled → Deposit in Alveoli
    - Catalysed by Poor Sanitation & Overcrowding.
    - Augmented by HIV (Immunocompromise)
  - **Can infect all ages.**
    - Infection may be acquired in childhood → sits in lymph nodes until ↓Host Immunity
    - Hence most Aus. TB Cases are Middle-Aged Immigrants.
    - 2nd Highest = Aboriginals.
  - **Minimising Risk:**
    - Handwashing
    - Protective Equipment (eg. PC2 Masks)
    - Keep Distance
    - Ventilate Room (or Negative Pressure Rooms)
    - Air Filtering
    - Separation of Patients
    - Safe Disposal of Waste



  - **Diagnosis:**
    - Sputum Microscopy
    - Culture of Sputum → Detection of TB Bacteria in Sputum.
    - X-Ray – inadequate.
  - **Symptoms** = **Pulmonary Disease**
    - **Early Stages:**
      - Chronic Cough
      - Sputum (phlegm)
      - Haemoptysis (Coughing up blood)
      - Weight Loss
      - Night Sweats.
      - Fevers
    - **Terminal Stages:**
      - Severe Lung Damage
      - Spticaemia
      - Some Spread to **Other Organs.**
        - TB Meningitis
        - TB Osteomyelitis
        - TB Arthritis
        - TB Lymph Node Infection

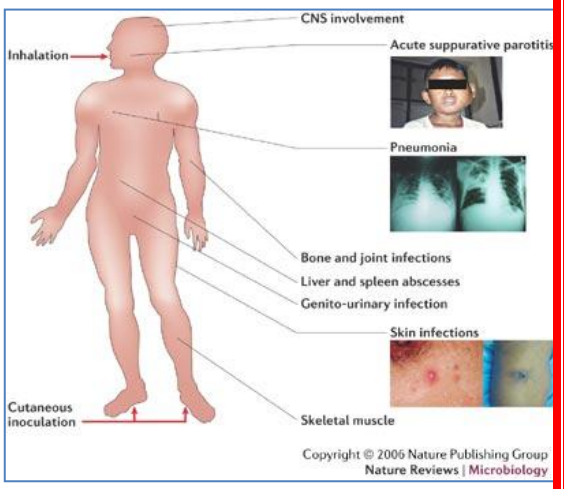




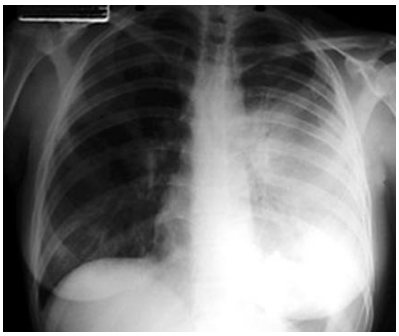
  - **Mechanics of Disease:**
    - Bacteria form little tubercles in lung tissue.
    - Tubercles burst into airways
    - Extensive damage → Result = Many Massive Cavities within lung.
      - Impaired Gaseous Exchange
    - Tubercles may burrow into Major Blood Vessels → Haemoptysis → Death.
  - **Complications:**
    - Severe Respiratory Compromise
    - Haemoptysis
    - Miliary TB – Spread of Bacterium → Other Tissues → Disseminated Tubercles.
      - Multiorgan Failure
      - Septic Shock

- **Cholera:**
  - Bacteria Lives in Contaminated Water
  - When epidemic starts → Gains Virulence
  - Infection via Consumption of Contaminated Water
    - High dose needed.
    - Bacteria *Doesn't* penetrate Intestinal Cell (colonises within intestine lumen)
  - Uncommon in Aus – Due to $^{++}$Sanitation.
  - **Symptoms:**
    - Toxins → Interfere with Na^+ Channels → ↑H_2O Secretion → Diarrhoea.
  - **Complications:**
    - Severe Dehydration
  - **Management**:
    - Replace all the fluids lost through stools. → Patient will survive.
    - - With Oral Rehydration Solution (ORS) = Sugar, Salt & Water.
  - **Treatment:**
    - Antibiotics.
  - **Mortality:**
    - If incorrectly/not treated, 50$^+$% Mortality.

- **Melioidosis:**
  - Bacterium that lives in Soil & Water – Only In Tropics
  - Relatively Common in Northern Australia.
  - Infected via Ingestion/Wound.
  - Most infections – Asymptomatic.
  - Some Infections – Fatal!
    - Abscesses Everywhere
    - Pneumonia
    - Septicaemia → Sore throat/Fever/Headaches/ Chest Pain/Upper Quadrant Abdo. Pain/Sputum → Death.

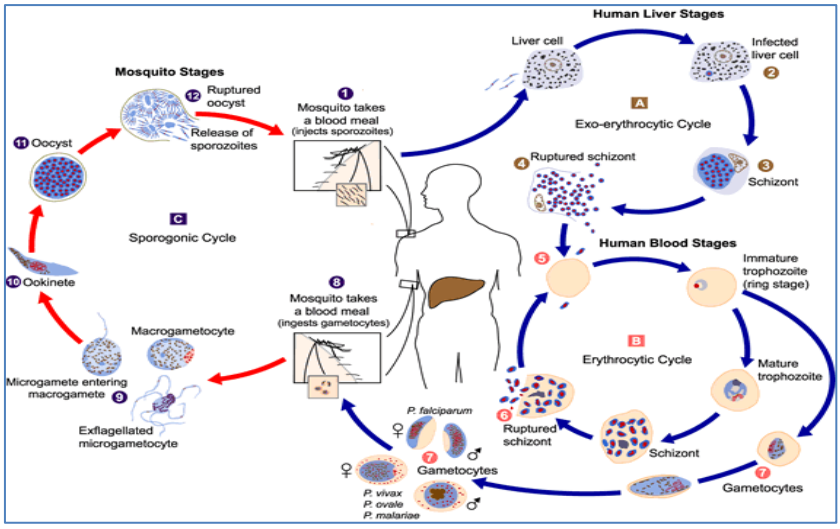


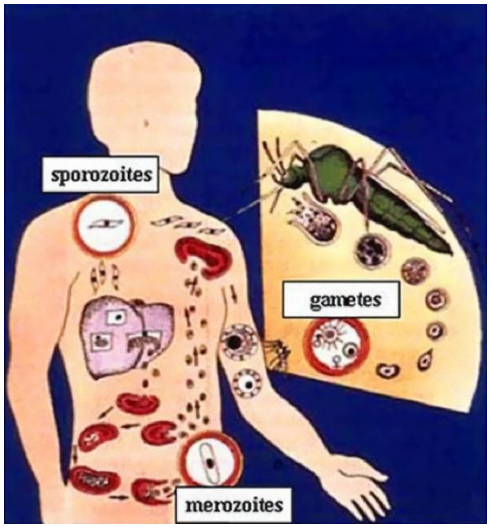
- **Plague:**
  - **Vector:**
    - Flea = Vector
    - Black Rat = Reservoir Host
  - **Pathogen:**
    - Bacterium – Yersinea Pestis
  - **Symptoms:**
    - **Bubonic:**
      - Swelling + Inflammation of lymph nodes – 'Buboes'
      - Fever
    - **Pneumonic:**
      - Infection of lung → Severe Acute Pneumonia.
      - Cough
      - Dyspnoea
      - Fever
      - Shock



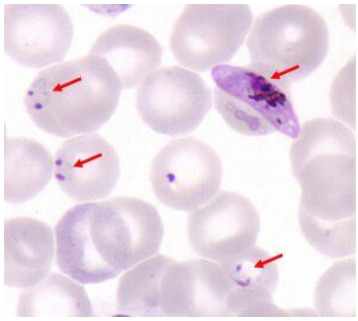
Protozoan:

- **Malaria:**
  - **Big Killer!**
    - Affects Mostly Poor Countries
    - Vector Present In Aus, But Disease is Eradicated
    - Still have 600-1000 'Imported' cases/year.
  - **Mosquito Vector: Lifecycle:**
    - 1. Mosquito Bites Human → Sporozites into blood → Liver → Infects RBCs
      - Sporozites → Gametocytes.
    - 2. Mozzie sucks blood → Gametocytes grows in Mosquito's gut → Sporozoites in salivary gland injected into human.
      - This stage takes up to 14days before re-infection can occur.

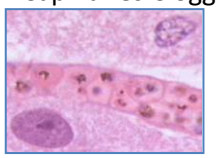




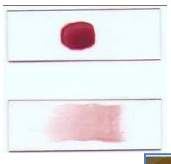
  - **Pathogen:**
    - 4 Species Infective to Humans...
    - **#1 - Plasmodium Falciparum (The Lethal One)
    - Lives in Human RBC's

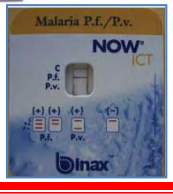


  - **Symptoms:**
    - Rupture of RBC's → Disease.
      - Fever
      - Rigors
      - Headache
      - Severe Anaemia
      - Haemoglobinuria (Hb in Urine)
    - RBC's Become 'Sticky' → Adhere to Endothelium → Capillaries Clogged → Tissue Hypoxia → Multiorgan Failure.
      - Cerebral Malaria
      - Pulmonary Oedema
      - Renal Failure



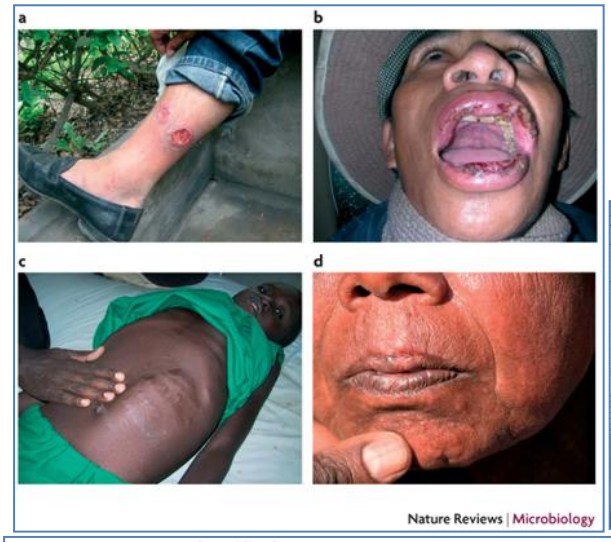
  - **High Risk People:**
    - Infants
    - Non-Immunes: eg. Tourists.
  - **Diagnosis:**
    - Blood Smear
      - Thin Blood Smear:
        - To diagnose the species
      - Thick Blood Smear:
        - To diagnose malaria
        - Gets the most amount of RBCs on the slide
          - (if infection is scant)

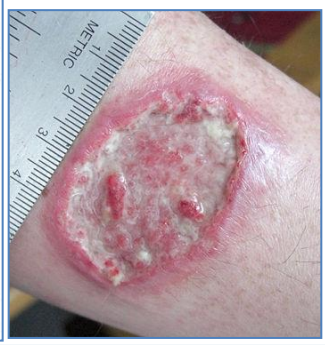


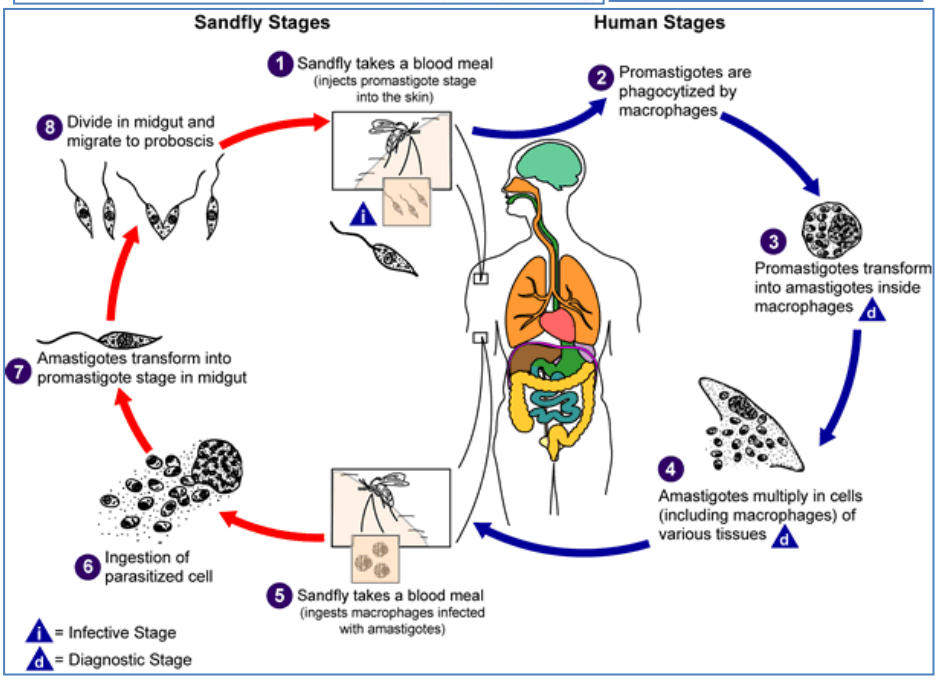


    - Card Test
    - PCR

- **Leishmaniasis:**
  - **Vector:**
    - Transmitted Via Ectoparasites (Namely Sandflies)
  - **Pathogen:**
    - Leishmania Parasites
    - **2 Forms in Lifecycle:**
      - Amastigotes – In man (mostly Intracellular)
      - Promastigotes – In the Sandfly
  - **Disease:**
    - **Visceral Leishmaniasis – AKA- Kala Azar:**
      - Fever
      - Weight loss
      - Anaemia
      - Swelling of liver & spleen
      - Patient Turns Black
    - **Cutaneous Leishmaniasis:**
      - Nodular & Ulcerated Skin Lesions.
    - **MucoCutaneous Leishmaniasis:**
      - Destructive Nasopharyngeal Lesions



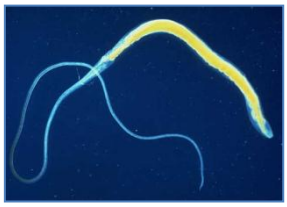




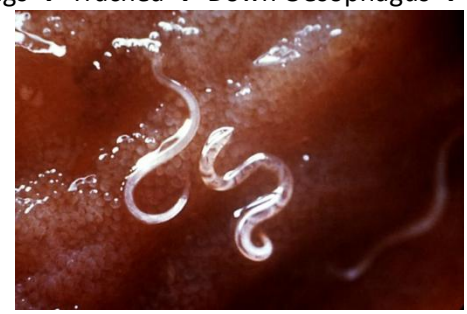
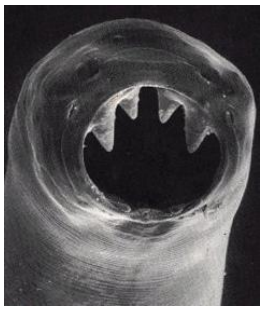
Metazoan Parasites:

- **Soil Transmitted Helminths:**
  - Live in GIT
  - Pass Progeny in the Faeces (Usually Eggs, Sometimes larvae)
  - Use soil for Development from Early Stage (Egg/Larvae) → Infective Stage → Host.
  - Common in tropical Climates – Warmth & Humidity Critical.
  - **Roundworm ("Ascaris"):**
    - Lives in Small Intestine.
    - Feeds on Intestinal Contents
    - Strong Swimmer (has no 'attachment organ')

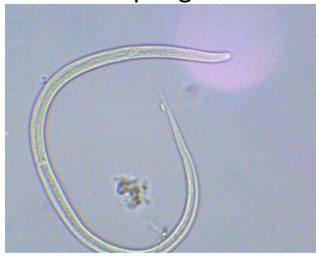

  - **Whipworm:**
    - Lives in Large Intestine
    - Whip-like Tail Anchors to L.Intestine Wall.



  - **Hookworm:**
    - Live in Small Intestine
    - Uses Mouth to Attach to Intestine Wall → Feed on Blood.
    - Eggs → Soil → *Hatches in Soil* → Larvae Chase *Heat* → Burrow Through Skin → Circultion → Lungs → Trachea → Down Oesophagus → Stomach → Small Intestine.

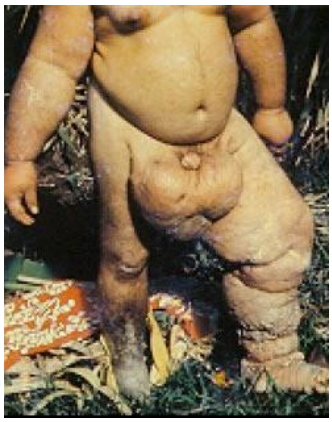



  - **Strongyloides:**
    - Lives in Small Intestine
    - Eggs → Soil → *Hatches in Soil* → Larvae Chase *Heat* → Burrow Through Skin → Circultion → Lungs → Trachea → Down Oesophagus → Stomach → Small Intestine.



- **Lymphatic Filariasis:**
  - **Vector:**
    - Mosquitos
  - **Pathogen:**
    - Filarial Worms (Parasite)
    - Live in Lymphatics + Nodes
  - **Life Cycle:**
    - Adults in Lymphatics → Release Baby Worms (Microfilaria)
    - Microfilaria → Sucked up By Mosquito → Develops inside mosquito
    - New Host Next Bite.
  - **Results in *Morbidity*, not *Mortality*.**
    - Extensive Lymphatic Damage
    - Suppresses Immune System → Recurrent Infections
    - Fevers
    - Genital Disease
    - Elephantiasis – Massive Oedema
    - Social Isolation/Stigmatisation/Depression
  - **4 Aspects of Management:**
    - 1. Preventative Chemotherapy (Prevention)
      - 1x Dose every year for 5 years = good protection
    - 2. Hygeine
      - Care of Entry Lesions (wounds)
      - Wash affected limb with Soap + Water
      - Prevents Secondary Infections
    - 3. Elevation:
      - To Maximise Lymphatic Drainage.
    - 4. Exercise:
      - To Maximise Lymphatic Drainage.
  - **Acute Attack of Filariasis:**
    - Caused by secondary bacterial infection
      - Increased swelling
      - Fever
      - Sore Glands
      - Headach
      - Nausea
    - **Treatment:**
      - 1. Cool leg with cold, clean water
      - 2. Take medicines for Fever + Drink More Water.
      - 3. Keep Washing as per Usual
      - 4. Rest.

Elephantiasis of the legs due to filariasis (CDC).



Tropical Diseases in Australia:

- **Dengue**
- **Tuberculosis**
- **Rotaviral Disease**
- **Hepatitis A/B/C**
- **HIV**
- **Soil-Transmitted Helminths**
- **Melioidosis**

Disease of Poverty (in Tropical Countries):

- Many "Tropical" Disease are more *Diseases of Poverty* than 'Tropical' – As many developing countries are in the tropics.
- **HIV/AIDS**
- **Hepatitis A/B/C**
- **Cholera**
- **Parasites**
- **Tuberculosis**

"TRUE" "TROPICAL" Disesases:

- **Melioidosis**
- **Soil Transmitted Helminths**
- **Shistosomiasis**
- **Vector Borne Diseases**
    - **Dengue**
    - **Malaria**
    - **Trypanosomiasis**
    - **Leishmaniasis**
    - **Filariasis**

The Scourge of Malaria (PNG)

Extent of the Malaria Problem:

- In the top 5 causes of childhood mortality worldwide
  - (as well as pneumonia, diarrhoea, measles, neonatal)
  - Causes 10% of Child Deaths in PNG
- 1/3 of the PNG Population are Treated for Malaria @ Health Centres/Hospitals each year.
  - Commonest Outpatient Presentation
  - 3rd Commonest cause of admission
- **Millennium Development Goal #6 – Combat HIV/AIDS & Malaria:**
  - Goal = To halt and reverse incidence of malaria by 2015.
- **So why a scourge there and not here?? (Despite close geography) – Many Factors.**

Effects of Uncontrolled Malaria on a Community:

- ↑Child Death Rates
- ↓Productivity
- ↑Disease Susceptibility
- ↑Maternal Mortality – due to increased anaemia
- ↑Malnutrition
- ↑Costs to Health System.

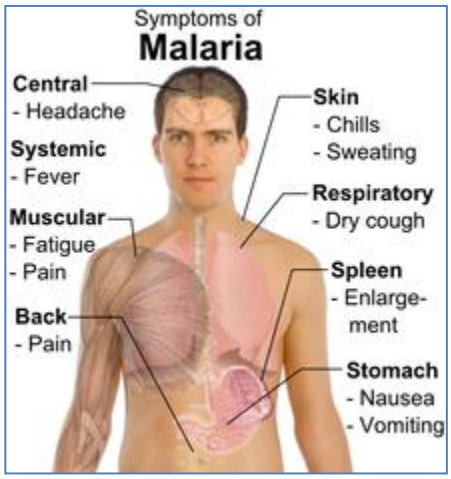
Clinical Stuff:

- **Pathophysiology:**
  - Infectious, Mosquito-Borne Disease
  - **Organism = *Plasmodium***
    - Eukaryotic Protozoan Parasite.
    - Widespread in Tropical & Subtropical regions.
    - **5 Species:**
      - *Plasmodium Falciparum* (Most Serious) (Not Persistent in Liver)(80% of Cases)
      - *Plasmodium Vivax* (Less Serious) (Persistent in Liver)
      - *Plasmodium Ovale* (Less Serious) (Persistent in Liver)
      - *Plasmodium Malariae* (Less Serious) (Not Persistent in Liver)
      - (*Plasmodium Knowiesi – Mostly* A Zoonosis)
  - Commonly Associated with Poverty (Can be the *Effect or* the *Cause*)
  - **Lifecycle:**
    - By the bite of a female *Anopheles Mosquito*.
    - 1. Bites an Infected Person (Blood contains malaria *Gametocytes*)
    - 2. *Gametocytes* develop in the *Anopheles Mosquito* → *Oocysts* in the Gut Wall.
    - 3. *Oocysts* rupture → Sporozoites Released → Migrate to Mosquito's Salivary Glands
    - 4. *Sporozoites* are injected in the *Anopheles Mosquito's* Saliva → Into the Human Host.
    - 5. *Sporozoites* in Bloodstream → Infect Liver & Multiply → Thousands of *Merozoites*.
    - 6. *Merozoites* lyse Hepatocytes → Infect RBCs & Multiply
    - 7. *Merozoites* → Form *Gametocytes* → Sucked up by *Anopheles Mosquito*.
  - **Incubation:**
    - Between 2wks and several months.

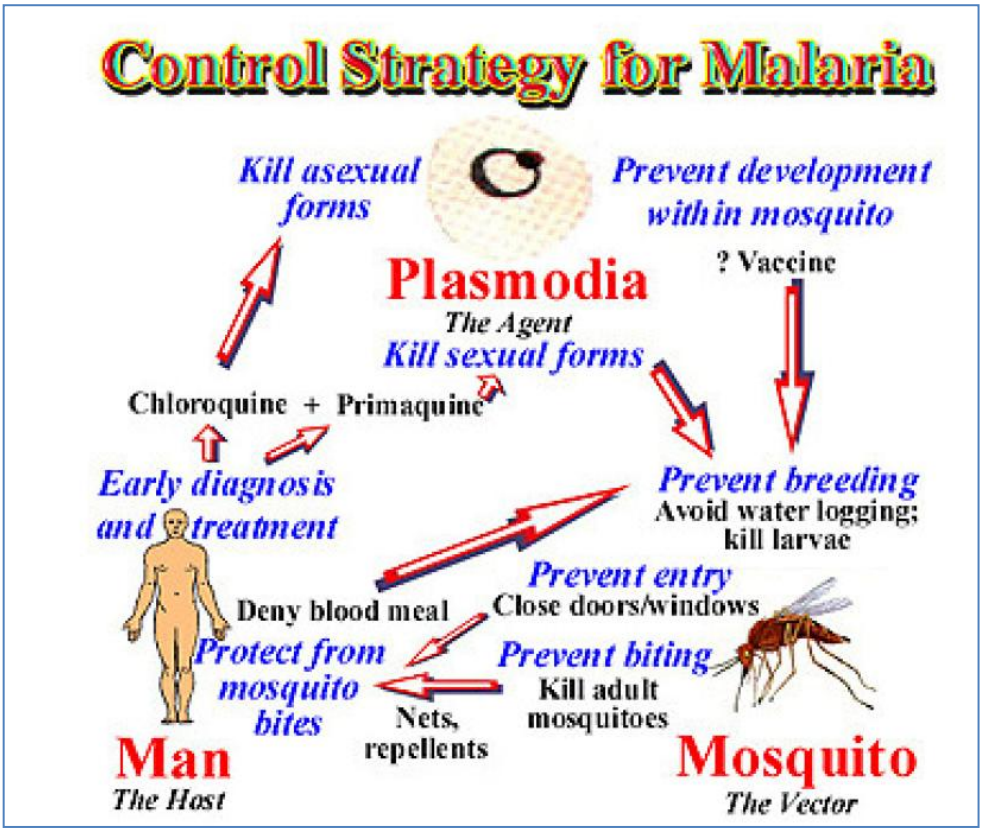
- **Two Patterns of Transmission:**
  - **1. Stable Transmission:**
    - Constant Endemic Rates.
      - Eg. Year-round high level of mosquitoes, and people continually get reinfected.
    - Over time adults develop partial immunity.
      - (Ie. Have parasitaemia and anaemia, but less severe)
      - (Or may not have symptoms)
    - Children/pregnant women/HIV - At risk of severe disease.
  - **2. Unstable Transmission:**
    - – Periodic Epidemic Outbreaks
      - (Eg. In wet seasons due to mosquitoes)
    - No partial immunity – All Adults at risk of Severe Disease
  - **(PNG has areas of each..)**

- **Epidemiology (contributing factors):**
  - **Environmental:**
    - Tropical regions most affected – Wet weather promotes Mosquito Vector Growth.
    - Rugged terrain hinders transport of Patients & Meds
  - **Social:**
    - Commonly associated with poverty (Also a cause of poverty)
      - Poor don't have access to prevention or treatment.
      - Overcrowding in Houses (With no protection against Mosquitoes)
    - Poor Health-Seeking Behaviour
    - Giving Sub-optimal Dosages of Antimalarials to Conserve Medication → Resistance.
    - Poor Access to Health Care
    - Regional hospitals are "Fee for service" – Most can't afford.

- **Classical Presentations – *Complicated* Vs. *Uncomplicated*:**
  - **"Complicated Malaria" (Acute) – Exclusively by *P.Falciparum* (80% of Cases; 90% of Deaths):**
    - Severe Headache/Nausea/Vomiting
    - Cerebral Ischaemia/Hallucinations
    - Severe Anaemia (Hb of 10-20)
    - Haemoglobinuria (+ Renal Failure)
    - Hepatomegaly/Splenomegaly
    - Hypoglycaemia/Acidosis
    - Seizures
    - Coma
    - Death (Fatality Rate ≈20% *with Treatment; 100% without treatment*)(Within hours/days)
    - **Treated with Artemisinins** – Target Gametocytes in the blood (kills active infection & prevents transmission)
  - **"Uncomplicated Malaria" (Chronic) – With *P.Vivax & P.Ovale*:**
    - Headache
    - Fever, Chills, Sweating
      - NB: Fever may be periodic
    - Muscle Fatigue/Joint Pain.
    - Dry Cough
    - Splenomegaly/Haemolytic Anaemia/Jaundice
    - Nausea/Vomiting
    - (Relapses can occur months/years after exposure – Due to *Latent Hypnozoites in Liver*)
    - **Treated with Primaquine** - Targets Hypnozoites in Liver (Which can lie dormant and cause recurrences)→Preventing recurrence of P Vivax.

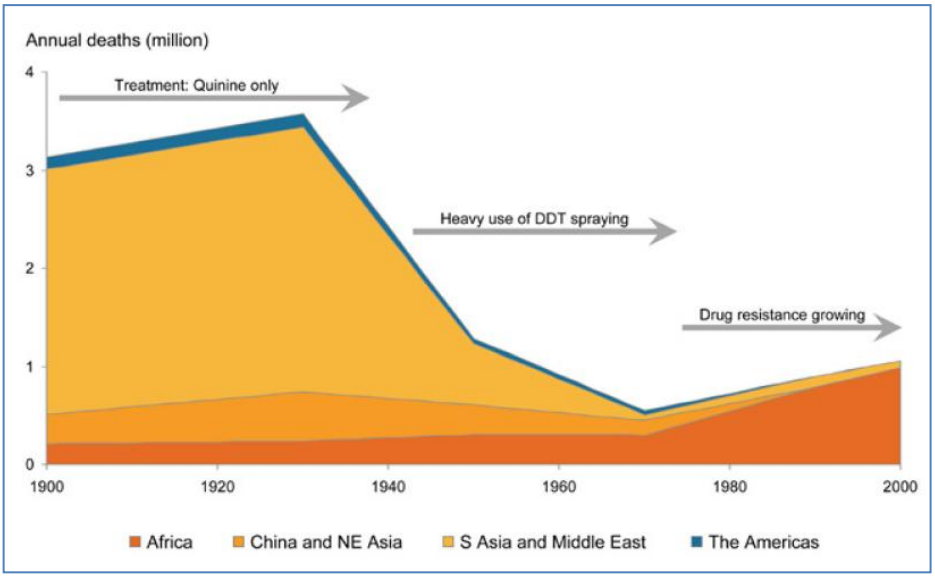


- **Diagnosis:**
  - Symptomatic Diagnosis – (Classical Symptoms + Endemic Area ≈ Malaria)
  - Old way - Microscopic Examination of Blood (Thick & Thin Films)(Still highly Effective)
  - New way – RDTs (Rapid Diagnostic Tests) – Antigen Tests Similar to Pregnancy Test.
- **Possible Treatments:**
  - Artemisinin (or Derivative = Artesunate)
  - Quinine
  - Chloroquine
- **Disease Prevention:**
  - Prophylactic Drugs
  - Mosquito Nets & Repellants
  - Indoor Residual Spraying (Insecticides) in houses.
  - Vector Control (DDT Spraying, Poisoning Breeding Grounds)
  - Public Education about Disease Epidemiology.



Approaches to Malaria Control/Eradication:

- ***Past* Vector Control - DDT Insecticide Spraying 1950-70's:**
  - Dramatically Reduced Deaths from Malaria.
  - However, DTT spraying was abandoned in the 70's → Incidence Rapidly Increased Again.
  - **Factors contributing to the increase in malaria since then include:**
    - Resistance of Parasites to commonly used anti-malarial drugs
    - Resistance of Mosquitoes to Insecticides
    - Unstable Political and Economic Conditions



- ***Current* Vector Control – (Two Methods)**:
  - **1. IRS (Indoor residual spraying)**
    - Reduces transmission by reducing the survival of malaria vectors entering houses or sleeping units.
    - Logistical Difficulties:
      - Cost
      - Labour intensive
      - People get sick of respraying
  - **2. ITN(Insecticide treated Nets)(Because Anopheles Mosquitoes are '*Night biters*'):**
    - If used by the total population, have shown to be able to lower transmission by 90%, malaria incidence by 50% and all case child mortality by 18 %.
    - Logistical Difficulties:
      - Cost
      - Distribution
      - Nets get holes in them – (need a system to replace them)
      - Need replacement when the insecticides run out.
      - Getting everyone to use them
- **Better Diagnosis - RDT's(Rapid diagnostic tests):**
  - Antigen Tests Similar to Pregnancy Test
- **New Drugs:**
  - **NB: However Resistance to new treatments already emerging.**
    - :. Role of combination of Artemesinins with other anti-malarial drugs (To prevent resistance)
    - :. Appropriate use of drugs (To prevent resistance)
  - **(ACT's) Artemesinin Combination Therapy** (Typically synthetic versions: artemether /artesunate) – (Based on a Chinese traditional herb)
    - Target the sporozoites (in the blood) rather than the Gametocytes.
    - Very Effective & Rapid Acting
    - Very Safe
    - Combination Therapy (Artemesinin + Traditional Antimalarials) → To combat resistance.

- **Prophylactic Drugs in Pregnancy and Infancy:**
  - (Ie. Treating those most at risk in order to reduce morbidity)
- **Prophylactic Intermittent Treatment – (In Pregnancy):**
  - NB: Different to Dose given for International Travelers)
  - These are intermittent (Eg. Every 2 months), *Full-Dose* treatments for high Risk people (Pregnant) in Highly Endemic areas.
    - Reduces Maternal Mortality
    - Reduces Infant Mortality
    - Reduces Anaemia and other Complications.
- **Gametocidal Drugs:**
  - **Artemethers** – Target Gametocytes in the blood (The form that's infective to mosquitoe)
  - (Single Dose Primaquine is also effective)
- **Drugs Targeting Hypnozoites – (in the Liver):**
  - **Primaquine** - Targets Hypnozoites in Liver (Which can lie dormant and cause recurrences)→Preventing recurrence of P Vivax.
- **Vaccine Development:**
  - Some currently in trial phases and offer partial protection:
    - Seem to be showing partial protection, but not total prevention.
    - Short lived nature of natural immunity
    - Parasites' able to mutate

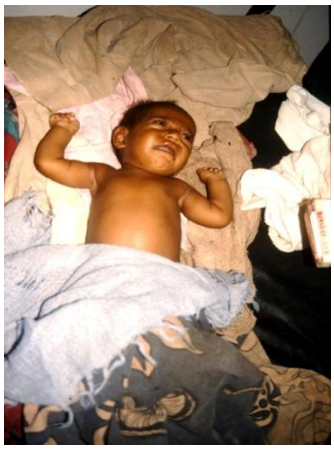
Factors Affecting Management Options:

- **Social:**
  - Culture
  - Poverty
- **Environmental:**
  - Geography
  - Weather
- **Economic/Political situation:**
  - Health care system
  - Availability of medicines
  - Access to care
  - Facilities and staff
  - Investigations

Malaria in PNG: Case Study

Patient:

- 2 old boy, brought in by mother,
- Lives near large coastal river,
- Swampy area,
- Unwell 3/7 with fever, shakes,
- Now cough, SOB, weak, lethargic
- Not feeding
- Lives in grass house, a few hundred metres elevation above the Yuat River in Madang Province




- Very Pale for PNG – Obviously very anaemic.

- **Presenting Complaint**
  - High fevers, 3/7
  - Listless, not feeding
  - Now has cough, SOB,
- **Past History**
  - Previously well, normal village birth
  - Probable malaria a number of times, treated in village
  - No medications,
  - Had an immunization once at age 6/12 when visiting immunization team came by.
- **Examination**
  - Pale, lethargic, looks unwell,
  - Tachypneoic
  - Tender RUQ, probable splenomegaly
- **Investigations:**
  - Possible use of RDT's (Eg. The Malaria Card) but *unlikely*.
- **Differential Diagnosis?**
  - Malaria,
  - Malaria,
  - Malaria!
  - NB: If it isn't, and you give antimalarials, it doesn't matter

  - Bacterial infections – (Eg. Meningitis, pneumonia, UTI)
  - Viral infections – (Dengue, other viruses, flu, measles)
  - HIV, AIDS
  - Others – (filariasis? Rheumatic fever?)
  - NB: But if it is one of these, it's still not going to matter as you can't treat them anyway.

Treatment:

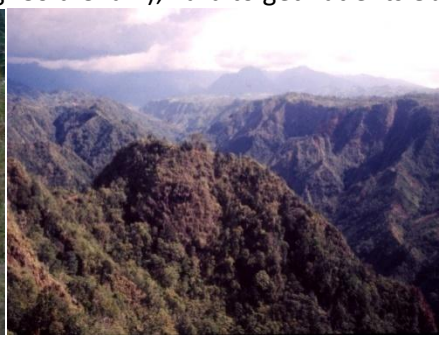
- **What would we do in Australia?**
  - Admit
  - Blood smears, blood cultures, viral serology,
  - Lumbar puncture? Urine culture? CXR?
  - IV fluids, Antimalarials, IV antibiotics, urgent blood transfusion.

- **PNG Health Care – Limited:**
  - Malaria endemic area
  - Village Aid Post with a small supply of medicines
  - Health care provided by village aide with grade 6 education and brief "introductory" health care training
  - **What can the village aide do? Not very much.**
    - Don't have any IVs
    - Don't have any equipment
    - May have 1 doctor or nurse.

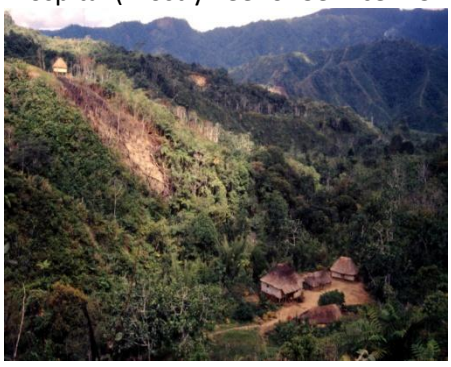
  - **Treatment Options:**
    - 1. Treat the child in village aide post, with antimalarial medication
      - Probably has chloroquine and fansidar,
      - May have artemether (many have this now)
    - 2. Should you Arrange transfer to nearby health centre?
      - Flight? (In *What??*)
      - Walking? (3 days walk!)
    - 3. Arrange transfer to District Hospital?
      - (5 days walk)
      - Plane flight, but patient has no money,
      - District hospital may have budget for flights for patients?
    - **NB: Without adequate treatment this child will probably die, so we'd probably just give antimalarials and hope for the best.**

Factors Influencing Treatment:

- **Geography**
  - Very steep terrain
  - No roads
  - Very few airstrips
  - → Hard to get medications *In* (Eg. Cold Chain), hard to get Patients *Out*.

- **Access to care**
  - Village health facility (Poorly Equipped)
  - Aid Posts (Poorly Equipped)
    - (Most Likely, all they'll have is an aid post and it will be 2 days walk.)
  - Health Centre
  - Hospital (Mostly Fee for Service – Unaffordable)

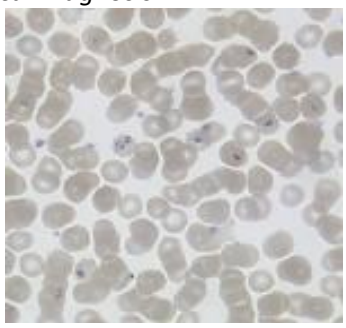



(This is a typical aid post)

- **Weather**
  - Rain, Clouds,
  - Lightning
  - Dangerous flying conditions
  - Granito-cumulus (Hail)
  - :. Hard to get Meds *In*, hard to get Patients *Out*.

- **Facilities and staff**
  - Village Aide (Little Training)
  - Nurse (Rare)
  - Doctor (Very Rare)

- **Investigations**
  - Power Microscopes are expensive & :. Rare (Existing microscopes haven't been serviced and many are not functional)
    - Do you have Slides?
    - Do you have Reagents?
  - Even if you have all of the above, do you have a skilled Technician who can recognise malaria.
  - :. In PNG, Malaria is a *Clinical Diagnosis*.



- **Availability of Medicines**
  - A major problem
  - Has improved a lot due to "Aus Aid"

- **Poverty**
  - Can't afford travel
  - Can't afford investigations
  - Can't afford medicines
  - Dependent on existing health care services

Summary

- **How do these factors affect the likelihood of adequate treatment?**
  - These factors dramatically reduce the likelihood of the kid getting adequate treatment.
  - Without adequate treatment, the child will probably die
  - Therefore, it is attractive to prevent malaria.
- **How can we prevent malaria?**
  - Vector Control
    - Mosquito Nets
    - Mosquito Spraying
  - Prophylaxis
  - Treatment – To Prevent Mosquito Infection & Spread of Disease.

Mosquito Borne Infections: (Arboviruses, Malaria and Lymphatic Filariasis)

Epidemiology of vector borne disease – This is VERY IMPORTANT FOR EXAMS:

- **Vector Transmission is dependent on 4 Things:**
  - **1. Abundance of Vector:**
    - Appropriate Environment & Weather (rain/temp/humidity/etc)
    - Appropriate food sources
    - Eg. Aedes Aegypti – (Require suitable breeding vessels – Ie. Pots, water tanks, gutters)
    - Eg. Aedes Vigilax (the Ross-River Vector) – (Breeds in salt water – Ie. Tidal flats)
    - (↑Abundance → ↑Probability of Transmission.)
  - **2. Survival of Vector:**
    - Natural Predators?
    - Insecticide Use?
    - Resistance to Insecticides
    - Appropriate Environment (Temp/Humidity/Etc)
    - Food Sources
    - (↑Survival of Vectors → ↑Probability of Transmission)
  - **3. Feeding habits (do they feed on humans or other animals?)**
    - Humans *and* Animals = Reservoir Hosts.
    - If they feed at Night, then Humans who sleep outdoors are at Risk.
    - If they feed *only* on Animals, (not humans) then there'll be no Human Disease.
  - **4. Vector competence (ability to infect the host):**
    - (↑Vector Competence → ↑Transmission of Vector-Borne Disease)

Examples of Vector-Bourne Diseases:

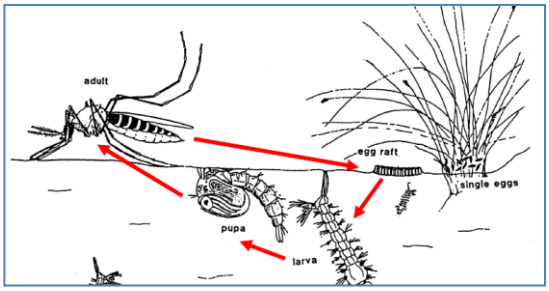
- Ross River Virus	- Alphavirus	- Mosquitoes	- Febrile + Rash + Arthritis
- Barmah Forest Virus	- Alphavirus	- Mosquitoes	- Febrile + Rash + Arthritis
- Dengue	- Flavivirus	- Mosquitoes	- Haemorrhagic Fevers
- Yellow Fever	- Flavivirus	- Mosquitoes	- Haemorrhagic Fevers
- Murray Valley Encephalitis	- Flavivirus	- Mosquitoes	- Encephalitic
- Japanese Encephalitis Virus	- Flavivirus	- Mosquitoes	- Encephalitic
- West Nile Virus	- Flavivirus	- Mosquitoes	- Encephalitic
- Malaria	- Parasite	- Mosquitoes	
- Trypanosomiasis	- Parasite	- Tsetse Flie (African); Kissing Bug (Sth. American)	
- Lymphatic Filariasis	- Parasite	- Mosquitoes	

OVERVIEW OF IMPORTANT DISEASES THIS WEEK:

- **VECTOR BORNE VIRUSES**
  - **ALPHAVIRUSES:**
    - **→ Febrile Illness + Rash + Arthritis – (*Ross River & Barmah Forest*):**
  - **FLAVIVIRUSES:**
    - **→ Haemorrhagic – (*Dengue, Yellow Fever*)**
    - **→ Encephalitic – (*MVE, JEV, West Nile*)**
- **VECTOR BORNE PARASITES:**
  - **Malaria:**
    - ***P.Falciparum***
    - ***P.Vivax***
  - **Trypanosomiasis:**
    - **African Trypanosomiasis ("African Sleeping Sickness"):**
    - **South American Trypanosomiasis ("Chagas' Disease"):**
  - **Lymphatic Filariasis:**

The Mosquito:

- **Life-Cycle:**
  - 1. Lays Eggs in Water
    - Eggs resistant to dehydration → Will hatch after rain after being dry for long time.
  - 2. Eggs Hatch
  - 3. Larvae → Pupa
  - 4. Pupa → Adult

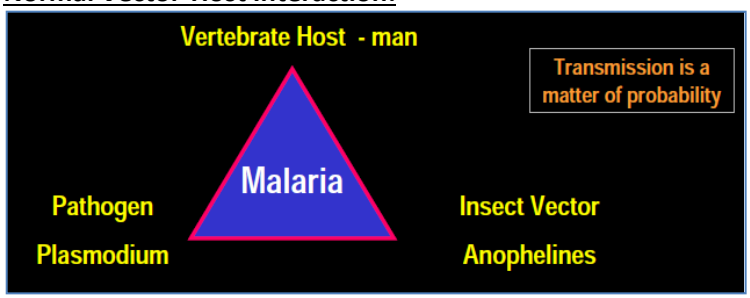


- **Ecology:**
  - **Eg. Aedes Aegypti & Aedes Albopictus (Dengue Vectors):**
    - Urban Environment (Pots/Gutters/Puddles/Around the house)

  - **Eg. Aedes Vigilax & Culex Annulirostris (RRV, Yellow Fever, MVE, & Barmah Forest Vectors):**
    - Open Environment (Marshlands/Swamps/Tidal Flats/Etc)
    - **Aedes Vigilax –** Breeds in stagnant Salt Water (Mudflats/Mangroves/Tidal Flats/Etc)
    - **Culex Annulirostris –** Breeds in freshwater pools/ponds/wetlands/lakes/dams/etc)

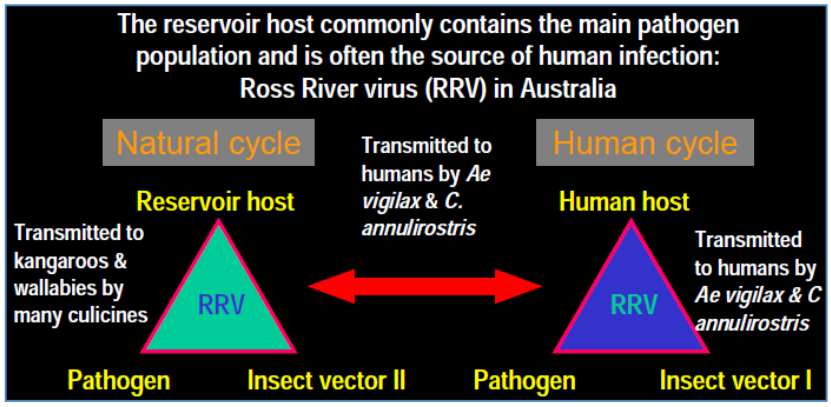
  - **Eg. Anopheles & Culex Annulirostris (Wuchereria Bancrofti Vectors):**
    - **Anopheles -** breeds in shaded, heavily vegetated permanent water
    - **Culex Annulirostris –** Breeds in freshwater pools/ponds/wetlands/lakes/dams/etc)

- **Normal Vector-Host Interaction:**



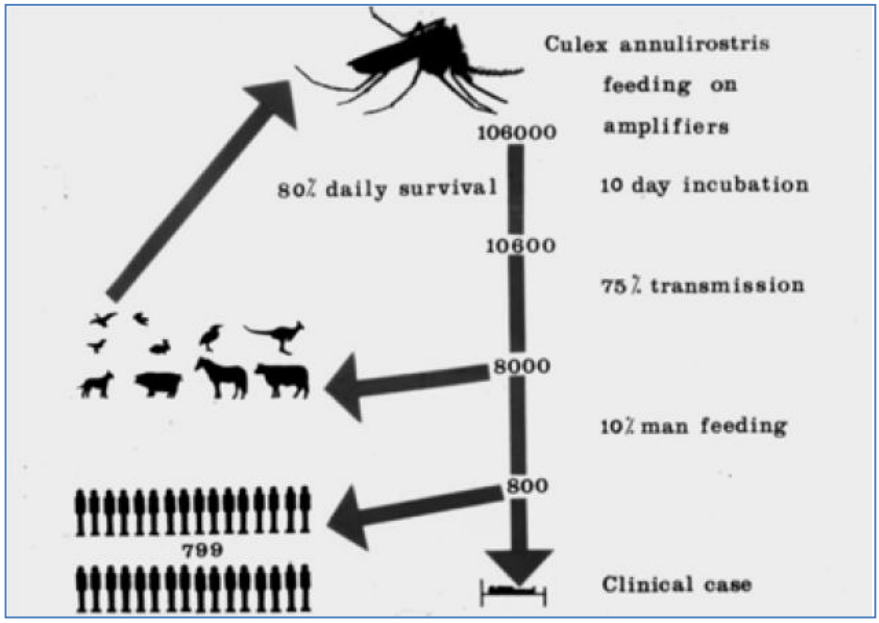
  - **Control Strategies:**
    - **1. Break Host-Vector Contact:**
      - Eg. Protective Clothing/Insect Repellant
    - **2. Break Host-Pathogen Contact:**
      - Ie. Personal Medication/Immunisation.
    - **3. Eliminate The Vector:**
      - Ie. Use of Insecticides

- **"Reservoir Host"-Vector-Human Interaction:**



  - **Control Strategies:**
    - **1. Treat Human Hosts**
      - Ineffective control strategy – as incidence is maintained by reservoir cycle.
    - **2. Reservoir Elimination:**
      - Ineffective – as it is unacceptable to kill all the animal reservoir hosts.
    - **3. **Cycle Separation:**
      - Via Personal Protection/Insecticides/Insect Repellant.

- **Monitoring Prevalence of Vector Borne Diseases:**
  - **Monitoring Human Clinical Cases:**
    - Ie. Reporting clinical cases to the CDC.
    - (NB: However, this is NOT a sensitive measure of Pathogen Prevalence, since only ≈1/800 are symptomatic, and the Pathogen may be *Well Established* in Reservoir Populations)
      - Therefore, you need a *more Sensitive* system (Ie. One where you'll definitely find disease if it is there) – (Ie. Animal Sentinels or Direct Vector Monitoring)
  - **Monitoring Animal Sentinels:**
    - Monitoring caged/wild reservoir animals for presence of the Pathogen.
    - (NB: Mosquito must feed from *Both Humans & Animals* for this system to be effective)
  - **Monitoring Vectors:**
    - Catch vectors and Check for presence of the Pathogen.
    - This is a good *Direct* way of assessing presence of Pathogen.



VECTOR BORNE VIRUSES

"Arboviruses":

- **A group of viruses which are "*Biologically Transmitted*" between hosts by biting arthropods**
  - ("**Ar**thropod-**Bo**rne" Viruses)
  - **Arthropods** = Invertebrate animals with exoskeletons (Incl. Insects/Spiders/Crustaceans)
- **NB: Biological Vs. Mechanical Transmission:**
  - (***Biological Transmission*** – Involves Infection of The Vector → Intermediate development/replication of the pathogen occurs inside the Vector)
  - (***Mechanical Transmission*** – NO Infection of the Vector & NO development/replication of the pathogen in the Vector – Ie. The Vector is simply a vehicle)

Reservoir Hosts:

- **Natural reservoirs =** Animals, Birds and Reptiles.
- NB: Man is only infected by insects which normally bite other species.
  - Although, Some man to man transmission occurs

Viral families

- **ALPHAVIRUSES:**
  - → **Febrile Illness + Rash + Arthritis – (*Ross River & Barmah Forest*):**
- **FLAVIVIRUSES:**
  - → **Haemorrhagic – (*Dengue, Yellow Fever*)**
  - → **Encephalitic – (*MVE, JEV, West Nile*)**

The 3x Disease Syndromes: (NB: Some overlap)

- **1. Febrile illness (Fever) (+ Rashes and Arthritis):**
  - **(*Ross River Fever/Barmah Forest*)**
  - (NB: *ALL ARBOVIRUSES → Fever*)
- **2. Haemorrhagic Fevers:**
  - **(*Dengue/Yellow Fever*)**
  - →Initial Febrile Period; Then Bleeding into Skin/Mucus Membranes →High Mortality Rates
    - Sometimes Haemorrhage from Body Orifices
    - Can be Haemorrhagic Rashes
  - Can →Thrombocytopaenia (As a result of Disseminated Intravascular Coagulation)
- **3. CNS Infection (Encephalitis):**
  - **(*Murray Valley Encephalitis/Japanese Encephalitis/ West Nile*)**
  - Virus invades CNS during initial Viraemia →Neurons are lysed
  - →Febrile Illness followed by Neck Rigidity, Convulsions and Disturbances of Consciousness
    - →Sequelae include motor, sensory and psychological defects

Pathogenesis and Immunity:

- **Pathogenesis:**
  - **1. Bite of an arthropod → Infection**
  - **2. Virus may replicate in the endothelium and lymphatics**
  - **3. Viraemia and infection of Target Organs → Fever and malaise (Often due to cytokines)**
- **Immunity:**
  - **Immunity to Viral Infections is Cell Mediated (Tc-Cells, NK-Cells)**
  - **Immunity to Viral Re-Infection is via Humoral Response (Antibodies & Complement)**
    - Prevent Re-Infection by neutralising free viruses in blood & preventing Fusion with Cells.
- **Humans are Often "Dead End Hosts" for Arboviruses:**
  - This means that the infection is eliminated by the human host before it has a chance to be spread to other hosts.

Control Measures for Arboviruses:

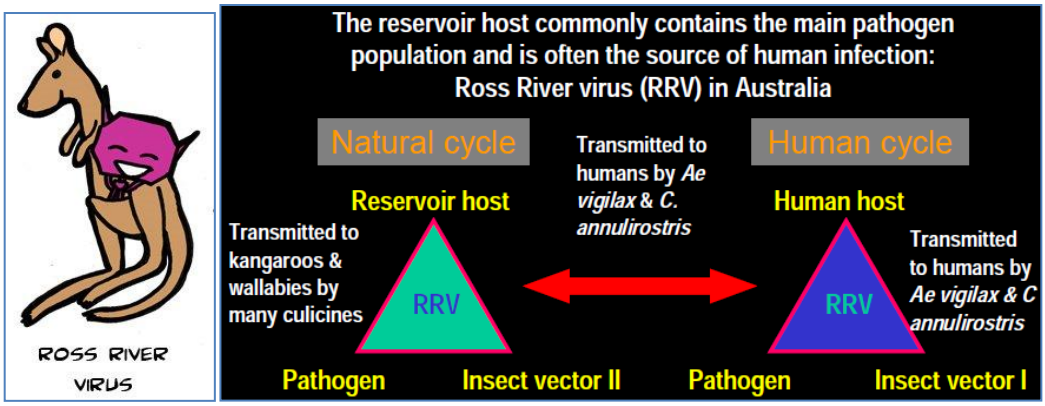
- **1. Eradication of vectors:**
  - Especially those with an urban man made habitat
- **2. Vaccination for the humans:**
  - An attenuated yellow fever vaccine 17D is effective for yellow fever
  - Dengue vaccines are being developed
  - Vaccines against Japanese encephalitis and other encephalitis viruses are recommended in endemic areas

ALPHAVIRUSES:

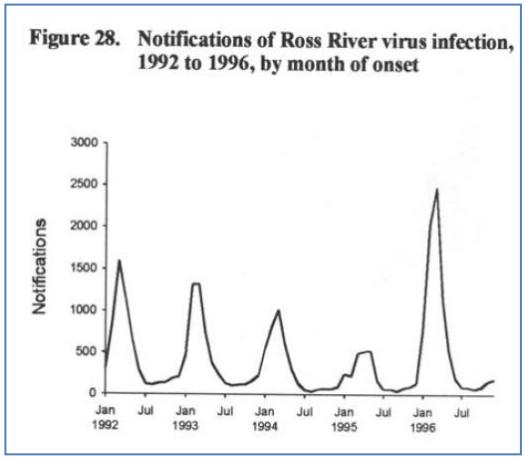
→Febrile + Rash + Arthritis – (*Ross River & Barmah Forest*):

- **1. Ross River Virus (RRV)**
  - **Causative Organism:**
    - Ross River Virus
    - (RRV is an Alphavirus)
  - **Vectors:**
    - **Aedes Vigilax –** Breeds in stagnant Salt Water (Mudflats/Mangroves/Tidal Flats/Etc)
    - **Culex Annulirostris –** Breeds in freshwater pools/ponds/wetlands/lakes/dams/etc)

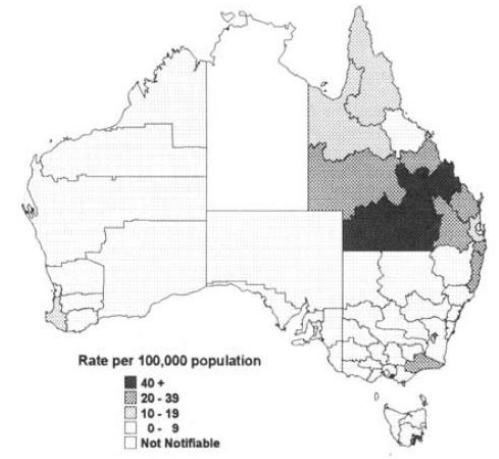
  - **Reservoir Hosts:**
    - Kangaroos & Wallabies



  - **Symptoms:** (Similar to "Barmah Forest Disease")
    - **95% Polyarthritis** in small, joints, fingers, hands, feet & wrist.
    - **30-50% suffer fever**
    - **Maculopapular Rash** (Red/Raised – but not itchy)
    - **Arthralgia** (sore joints)
    - **Nausea, myalgia, anorexia & lethargy**
    - Symptoms can last from 30 weeks to 2 years. (Esp. Arthritic Symptoms)
  - **Infections are Epidemic/Seasonal:**
    - Seasonal Rainfall (affects breeding environment of vector)
    - Lunar influences on the tides → flooded marshlands (affects breeding environment of vector)
    - Temperature & Humidity changes

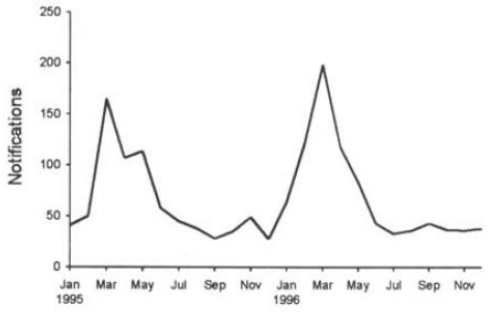


- **2. Barmah Forest Virus:**
  - **(Similar Symptoms to *Ross River Virus*)**
  - **NOTIFICATION RATE OF BFV INFECTION IN 1996**



  - **NOTIFICATION RATE OF BFV INFECTION IN 1996**

Figure 26. Notifications of Barmah Forest virus infection, 1995 to 1996, by month of onset



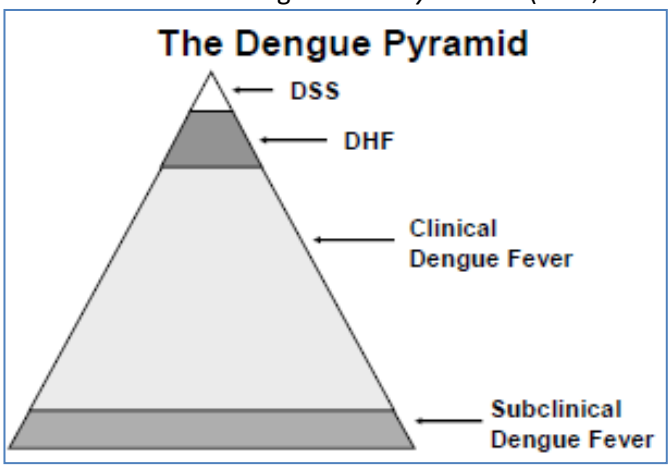
Late summer – Majority of infections

FLAVIVIRUSES – (*Dengue, Yellow Feve; MVE, JEV, West Nile*):
(NB: Flaviviruses have common Epitopes and are hard to differentiate Serotypes Via ELIZAs)

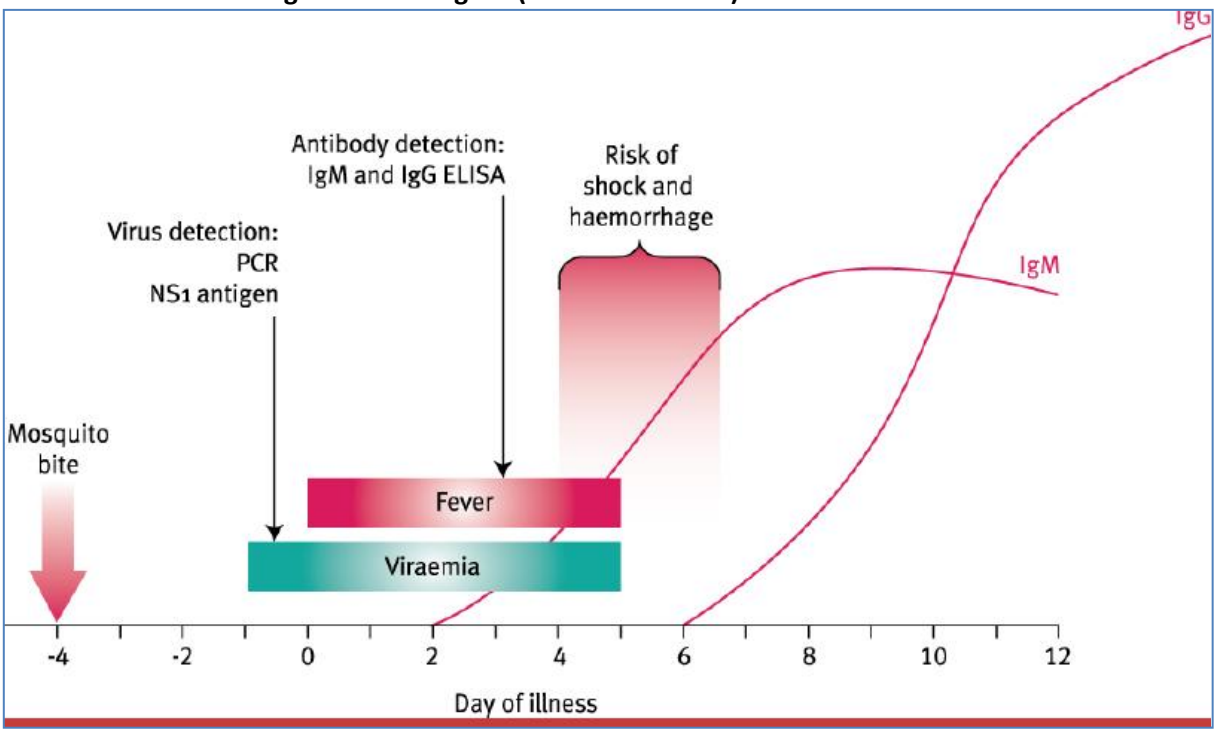
→ Haemorrhagic Flaviviruses – (*Dengue, Yellow Fever*)

1. **Dengue Virus:**
   - **Causative Organism:**
     - **Dengue Virus (A Flavivirus)**
     - **4x Serotypes:**
       - (Ie. Different epitopes on the envelope → Specific for adaptive responses)
   - **Vector:**
     - ***Aedes Aegypti***
       - Urban Environment (Pots/Gutters/Puddles/Around the house)
       - Infective Vector radius of ~200m from breeding ground.

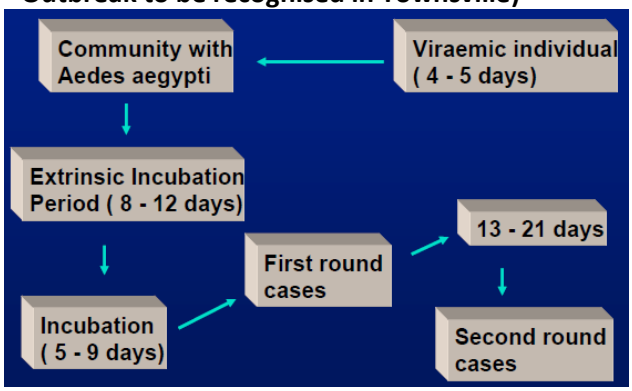
   - **General:**
     - It is Extremely Common
     - Its Incidence is Increasing
   - **Presentation: -** (NB: Most present *Before Immune Response*)
     - **Typical Presentation:**
       - **Fever & Malaise** (Death warmed up/"Breakbone Fever")
       - **Polyarthritis** (Muscle & Joint Pain)
       - **Haemorrhagic Rash**
     - ***Dengue Haemorrhagic Fever (DHF)*:**
       - Severe Bleeding
       - Leaky Capillaries
       - Shock
     - **Children may suffer from Dengue *Haemorrhagic Shock Syndrome (DHSS)(DSS)*:**
       - A result of Immune Enhancement due to a *Second Infection* with a different Serotype.
     - **(The Dengue Pyramid):**
       - Some infected will be Sub-Clinical.
       - Most infected will be Clinically Obvious
       - Some will have Dengue *Haemorrhagic Fever* (DHF)
       - A few will have Dengue *Shock Syndrome* (Rare, but high mortality rate)



- **Pathophysiology:**
  - **→Dengue Haemorrhagic Fever (DHF):**
    - **1. Primary Infection** →Production of Antibody to *Non-Neutralising Epitopes*
    - **2. Secondary Infection** →Binding of Ab to *Non-Neutralising Epitopes* →↑Fc-Mediated Uptake of Dengue Virus by Macrophages.
      - **3. →Activated Macrophages** →Massive Cytokine Production (Esp. TNFα, TNFβ and IFNγ)
      - **4. Cytokines + Complement** → ↑Vessel Permeability → Vascular Leakage & Haemorrhage
  - **→Dengue Shock Syndrome (DSS)**:
    - **Due to Immune Enhancement** following a second infection with a different Dengue Serotype.
    - **Secondary Infection**→Binding of Ab to *Non-Neutralising Epitopes* →↑Fc-Mediated Uptake of Dengue Virus by Macrophages.
      - **→Activated Macrophages** → Massive Cytokine Production (Esp. TNFα, TNFβ and IFNγ)
      - **Cytokines + Complement** → ↑Vessel Permeability → Vascular Leakage & Haemorrhage → **If Severe →SHOCK!**
- **Disease Progression & Diagnostic Tests:**
  - **-** (NB: Most present *Before Immune Response*)
    - NB:Early negative serology is irrelevant because there may not be antibodies yet.
    - NB: Also difficult to distinguish between Antibodies against different serotypes.
  - ***- Dengue Non-Structural Protein 1 (NS1) (detected via ELISA)**
    - **RDT's Available.**
  - - **High IgG Titre to Flaviviruses**
  - **- Dengue Virus Antigens (detected via PCR)**



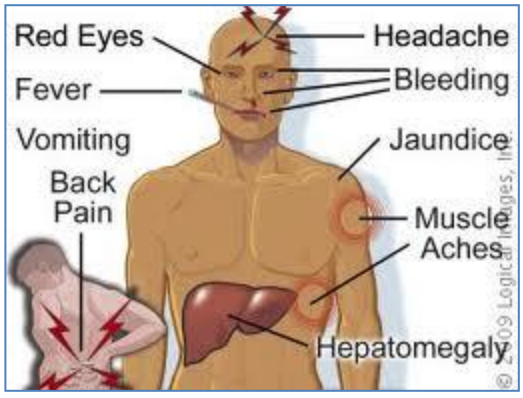
- **Epidemiology & Transmission**:
  - **Endemic and epidemic where vectors present:**
    - **Vector = *Aedes Aegypti*** (Mosquito)
      - Urban Environment (Pots/Gutters/Puddles/Around the house)
      - Infective Vector radius of ~200m from breeding ground.
    - **Reservoir Host =** Monkeys
  - **Events Leading to Dengue Epidemic:**
    - 1. Viraemic Individual
    - 2. Community must have *Aedes Aegypti*
    - 3. Extrinsic Incubation Period (Time from infection of vector, to when it can transmit it to others)
    - 4. Intrinsic Incubation (Time from infection of human host, to onset of symptoms)
    - 5. First Cases
    - **(NB: Cycle takes 13-21 Days – Hence it may take several weeks for a Dengue Outbreak to be recognised in Townsville)**



- **Treatment:**
  - **Fluid therapy** (usually very effective)
  - **(Avoid Aspirin or Brufen – Ie. Stuff that makes bleeding worse)**
  - **NO Vaccines present.**

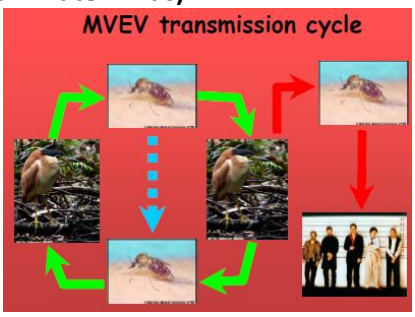
2. **Yellow Fever:**
    - **Causative Organism:**
        - Yellow Fever Virus (A Flavivirus)
    - **Vector:**
        - ***Aedes Aegypti***
            - Urban Environment (Pots/Gutters/Puddles/Around the house)
            - Infective Vector radius of ~200m from breeding ground.
    - **Pathophysiology:**
        - **Virus Infects Viral Organs (Especially the Liver):**
            - **→Liver Necrosis →Jaundice**
        - The virus **also damages the kidney and heart.**
    - **Presentation:**
        - Characterised by Jaundice
        - **High case fatality rate**
    - **Transmission**
        - ***Urban cycle:***
            - Requires man to man transmission
        - ***Sylvatic cycle:***
            - Involves other animals/environment (Esp. monkeys)

    - **GLS: What are the factors that make Townsville a potential site for an outbreak of yellow fever?**
        - Transmission by Aedes Aegypti (Present in Townsville)
        - Townsville has heavy wet-seasons → Puddles, Stagnant water around the house (Perfect Breeding Grounds for Aedes Aegypti).
        - **What might be important factor in ensuring that this does not happen?**
            - Removing Breeding Grounds for Aedes Aegypti.
            - Mosquito Nets & Spray

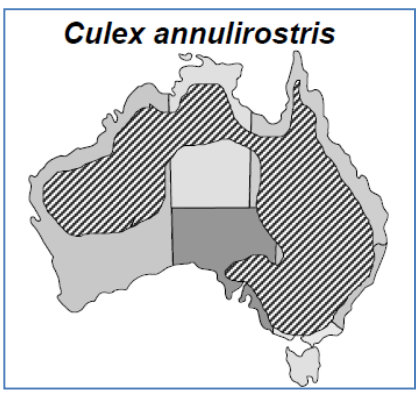


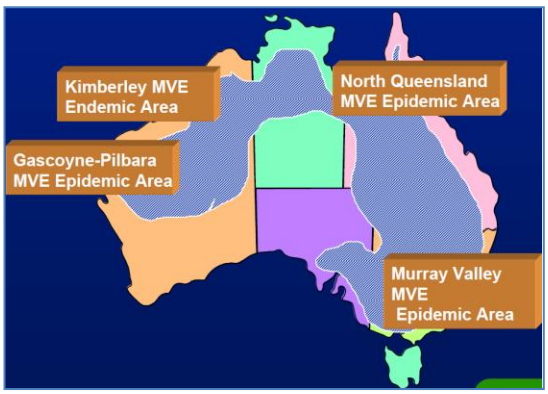
→ **Encephalitic Flaviviruses – (*MVE, JEV, West Nile*):**

- **1. Murray Valley Encephalitis:**
  - **Causative Organism:**
    - Murray Valley Virus
    - (A Flavivirus)
  - **Vector:**
    - ***Culex Annulirostris* –** Breeds in freshwater pools/ponds/wetlands/lakes/dams/etc.
    - **(Reservoir Host = Water Birds)**

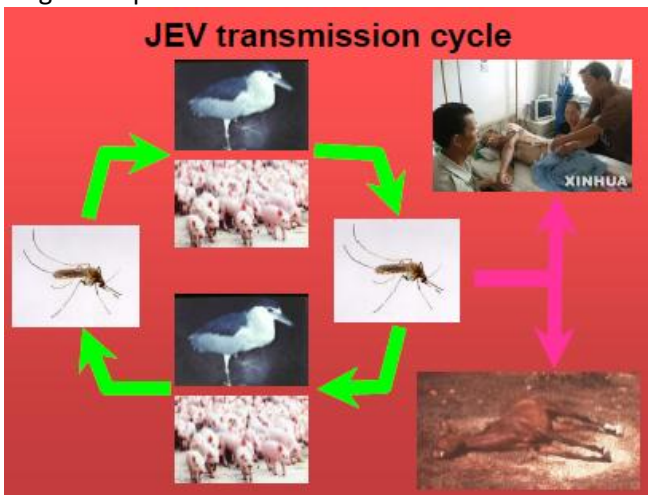


  - **Potentially Fatal CNS infection:**
    - **Virus crosses the Blood Brain Barrier during initial Viraemia**
      - → CD8-Tc-Cells invade the CNS → Attack infected *Glial Cells* → Damages brain.
    - **NB: Knockout Mice with *No Cell-Mediated Immunity* (Tc-Cell Cytotoxins: Perforins/Granzymes), do not get Encephalitis associated with Infection. Why?**
      - Lack of CD8-Tc-Cell Cytotoxic Enzymes → No cytotoxicity of Tc-Cells → No cell-mediated damage of Virally-Infected Glial Cells in the brain → NO Encephalitis.
  - **Presentation:**
    - Fever
    - Headaches
    - Nausea & Vomiting
  - **Severity of brain damage varies:**
    - Complete Recovery
    - Mild Residual Neurological Symptoms
    - Severe Neurological Damage
    - Death
  - **Prognosis of Encephalitis:**
    - ~20% fatal
    - ~50% of survivors have significant neurological disabilities
  - **Distribution in Australia:**
    - ***Requires Culex Annulirostris*** (Which breeds in freshwater/ponds/etc)
    - ***Endemic*** in Wet, Tropical Areas of the Northern Territory:
      - Eg. Kimberly
    - **(Epidemic in NQ & Murray Valley) – An Epidemic Requires:**
      - Very wet summer
      - Massive growth of the organism
      - Susceptible individuals & reservoir & amplificatory hosts & Migratory Birds
      - Continuous channels of water

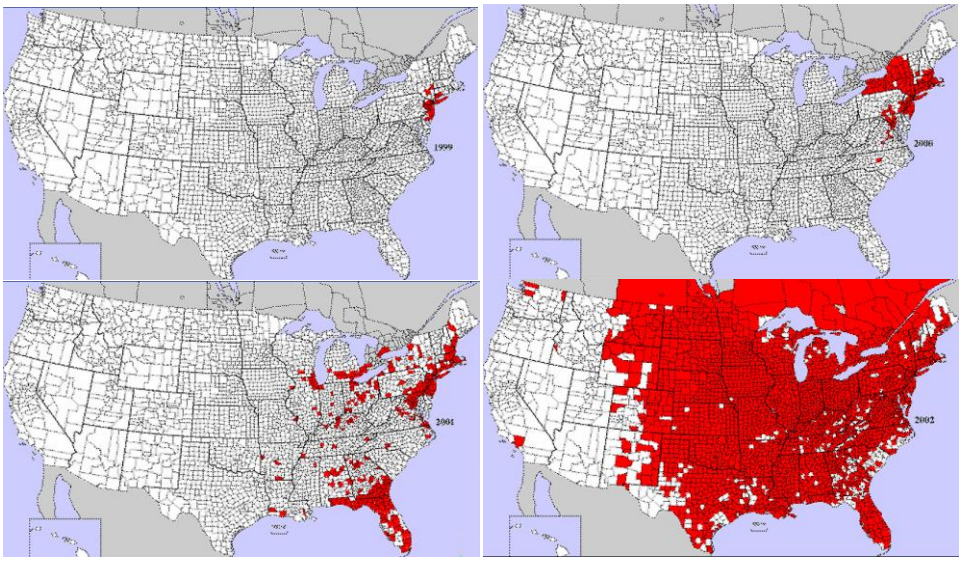




- **2. Japanese Encephalitis Virus:**
  - **Epidemiology:**
    - Leading cause of encephalitis in SE Asia
    - Majority in China
    - Mainly in children
    - Primarily a rural disease
  - **Prognosis of Encephalitis:**
    - ~20% fatal
    - ~50% of survivors have significant neurological disabilities
  - **Transmission:**
    - Mosquito = Vector
    - Bird & Pigs = Amplifier Hosts



- **3. West Nile Virus:**
  - West Nile virus has recently been introduced into the USA
  - It has spread from New York to most of USA
  - The implications for introduction into Australia are interesting



VECTOR BORNE PARASITES: (Malaria, Trypanosomiasis, Lymphatic Filariasis):

Introduction:

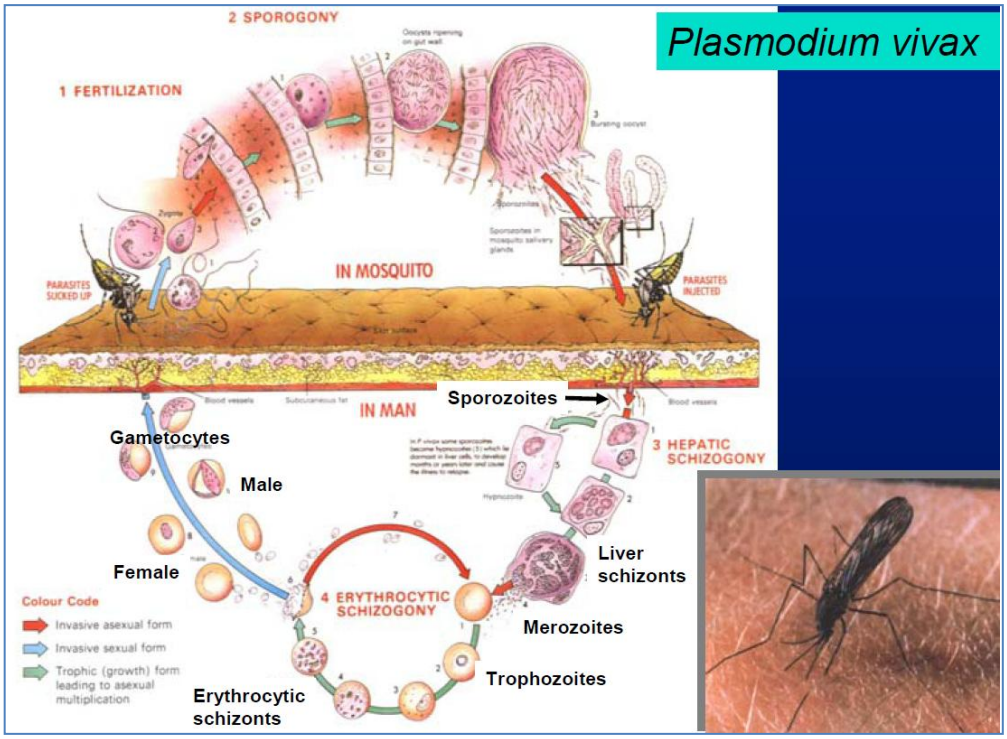
- **Major cause of mortality in developing world**
  - ***Plasmodium* (Malaria)**
  - ***Trypanosomes* (Trypanosomiasis) (African Sleeping Sickness & Chaga's Disease)**
    - In Africa and South America
  - ***Filarial Worms* (Lymphatic Filariasis – Nematode infection of lymph vessels)**
  - ***Leishmania* (Leishmaniasis)**
    - Asia / Africa / Americas

Blood Borne Parasites: Australia

- None are Endemic in Australia
- Neighboring Countries are Endemic for:
  - Malaria &
  - Lymphatic Filariasis
- Poses concern for Travel medicine! (Most of these that present in Australia are imported)
- Hospitals in urban, developed cities must be on Guard

Malaria

- **Organism:**
  - ***Plasmodium***
  - (Protozoan Intracellular Parasite)
  - Widespread in Tropical & Subtropical regions.
  - **5 Species:**
    - ***Plasmodium Falciparum*** (Most Serious) (Not Persistent in Liver)(80% of Cases)
    - ***Plasmodium Vivax*** (Less Serious) (Persistent in Liver)
    - *Plasmodium Ovale* (Less Serious) (Persistent in Liver)
    - *Plasmodium Malariae* (Less Serious) (Not Persistent in Liver)
    - (*Plasmodium Knowiesi – Mostly* A Zoonosis in Monkeys)
- **Vector:**
  - ***Anopheles* Mosquito**:
    - (A Night Biter)
    - Breeds in shaded, heavily vegetated permanent water
- **Two Patterns of Transmission:**
  - **1. Stable Transmission:**
    - Constant Endemic Rates.
  - **2. Unstable Transmission:**
    - – Periodic Epidemic Outbreaks
- **Life-Cycle:**
  - **Infected By the bite of a female *Anopheles Mosquito*.**
    - 1. Bites an Infected Person (Blood contains malaria *Gametocytes*)
    - 2. *Gametocytes* develop in the *Anopheles Mosquito* → *Oocysts* in the Gut Wall.
    - 3. *Oocysts* rupture → Sporozoites Released → Migrate to Mosquito's Salivary Glands
    - 4. *Sporozoites* are injected in the *Anopheles Mosquito's* Saliva → Into the Human Host.
    - 5. *Sporozoites* in Bloodstream → Infect Liver & Multiply → Thousands of *Merozoites*.
    - 6. *Merozoites* lyse Hepatocytes → Infect RBCs & Multiply
    - 7. *Merozoites* → Form *Gametocytes* → Sucked up by *Anopheles Mosquito*.
  - (NB: Extrinsic Incubation period ≈14 Days – Before Reinfection can occur)
  - **NB: Plasmodium *Vivax* – Can Produce Recurrent Infections:**
    - It can stay dormant inside hepatocytes and recrudesce at later stages.
    - Some of the sporozoites remain in a dormant, hypnozoite stage for weeks or months.
    - Even if you eliminate all Vivax from the blood, there may still be cycling in the liver.

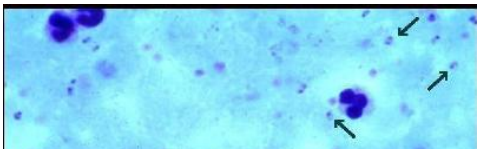
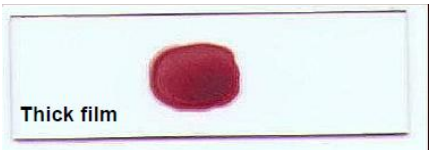


- **Pathogenesis:**
  - **RBC Invasion and Lysis →**
    - Release of Pyrogens → Fever
    - Extravascular haemolysis – (in spleen)
      - Haemoglobinuria
      - →Anaemia
    - Headache
  - **RBCs Become Sticky to Avoid Phagocytosis in the Spleen→**
    - Adherence of RBCs to Capillaries → Blocks Capillaries → Tissue Hypoxia → Multi-Organ Failure (brain/kidneys/liver/etc)
    - May alter blood/brain barrier permeability → Malarial Encephalitis.
  - **Cytokine induction**
    - TNF → Tissue damage
  - **Immune Complex Deposition(Type III Hypersensitiviy):**
    - Glomerulonephritis
    - Arthritis
- **Genetic Protection Against Malaria:**
  - **Sickle Cell Trait (heterozygotes) is Protective from Malaria:**
    - In a Sickle Cell carrier, Infected Sickle RBCs rupture prematurely → Plasmodium is Unable to Reproduce
    - ↓O2 → ↓Plasmodium Growth
    - ↑Macrophage Phagocytosis of the Infected Sickle Cells (Eliminates the parasites in the sickle cell population)
  - **Others:**
    - Lack of the Duffy Antigen (A RBC surface receptor which makes a RBC susceptible to P.Vivax)
    - G6-phosphate dehydrogenase deficiency
    - Thallasemias
- **Immunity to Malaria:**
  - **Immunes:**
    - After Repeated exposure over many years in an endemic area
    - →Malaria episodes are brief and rarely severe
  - **Non-immunes:**
    - Infants/children
    - Travellers from non-malarious areas
    - →Very symptomatic
    - →Susceptible to severe, life-threatening malaria
  - **Loss of Immunity to Malaria:**
    - Pregnant women
    - Previously immune residing outside of endemic areas
    - →also susceptible to severe, life-threatening malaria

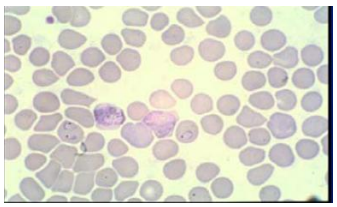
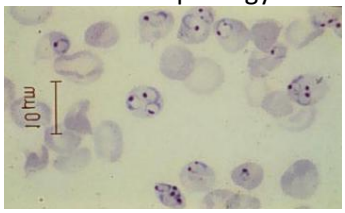
- **Presentations:**
  - **(The Common Symptoms):**
    - **Episodic Fever** (6-8hrs) – Due to consecutive *Waves* of Merozoites Escaping from RBCs & Reinfecting Other RBCs.
      - May be *'Tertian'* (Every 2nd day)
      - May be '*Quartan*' (Every 3rd day)
    - Vomiting/Headache/Diarrhoea
  - **"Complicated Malaria" (Acute) – Exclusively by *P.Falciparum* (80% of Cases; 90% of Deaths):**
    - Severe Anaemia (Hb of 10-20)
      - Haemoglobinuria (+ Renal Failure)
    - Cerebral Ischaemia
      - Hallucinations
      - Seizures
      - Coma
    - Hepatomegaly/Splenomegaly
    - Hypoglycaemia/Acidosis
    - **Death** (Fatality Rate ≈20% *with Treatment; 100% without treatment*)(Within hours/days)
      - **NB: *Falciparum* can kill very quickly (within 1 day of symptoms) if not treated.**
      - **:. Fever in a Returned Traveller (despite mild symptoms) must be taken seriously.**
    - **Treated with Artemisinins** – Target Gametocytes in the blood (kills active infection & prevents transmission)
  - **"Uncomplicated Malaria" (Chronic) – With *P.Vivax & P.Ovale*:**
    - Muscle Fatigue/Joint Pain.
    - Dry Cough
    - Splenomegaly/Haemolytic Anaemia/Jaundice
    - (Relapses occur months/years after exposure – Due to *Latent Vivax Hypnozoites in Liver*)
    - **Treated with Primaquine** - Targets Hypnozoites in Liver (Which can lie dormant and cause recurrences)→Preventing recurrence of P Vivax.

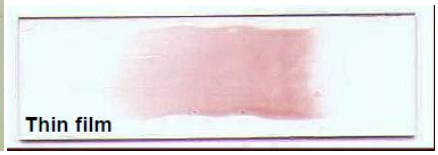
- **Diagnosis:**
  - ELISA / Immuno –chromatography (Detect Antigens or Antibody)
  - PCR (genome detection)
  - **Blood film (**The Mainstay**):**

    - **Thick Film:**
      - Used to ID (non-specific)
      - More blood = More sensitive

    - **Thin Film:**
      - Used to specify
      - Less Blood = less sensitive
      - Reveals:
        - Red cell morphology
        - Parasite morphology



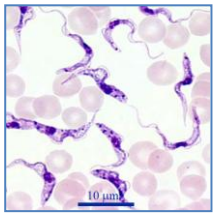
Vivax **Falciparum**

- **Treatment:**
  - Cloroquine
  - (+ Primaquine if P.Vivax – Kills Hypnozoites in Liver)
    - (NB: Primaquine is Contraindicated in G6P-Deficiency; can → RBC Haemolysis)

Trypanosomiasis:

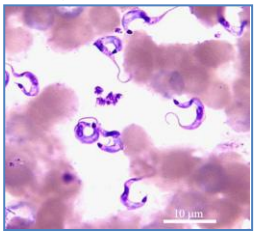
- **African Trypanosomiasis ("African Sleeping Sickness"):**
  - **Causative Organism:**
    - *Trypanosoma brucei*
  - **Vector:**
    - *Tsetse Fly*.
  - **Transmission:**
    - **Mechanically Transmitted** – (Ie. NO Infection of the Vector & NO development/replication of the pathogen in the Vector – Ie. The Vector is simply a vehicle)

  - **Presentation:**
    - A Cutaneous Condition:
      - Erythema
      - Oedema
      - Angioedema
  - **Trypomastigotes of *Trypanosoma brucei*:**
    - (Trypomastigotes = "Developmental stage of Trypanosomatidae living mostly free in the blood of vertebrate hosts.")



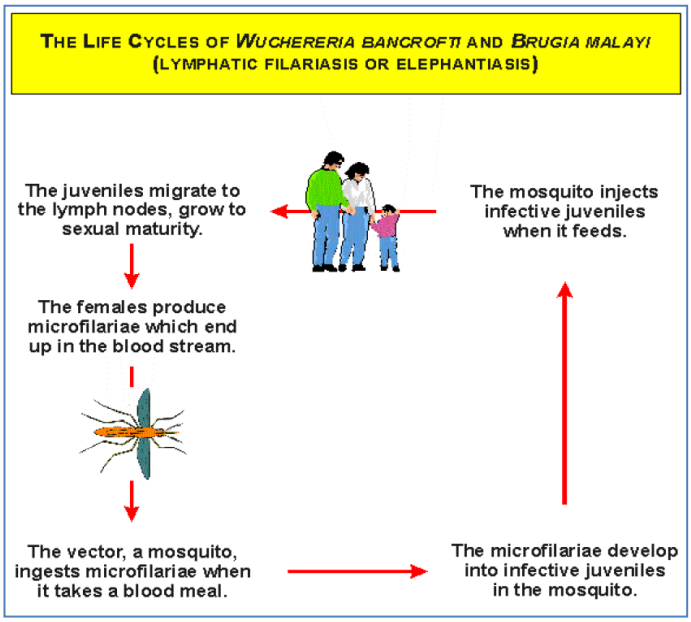
- **South American Trypanosomiasis ("Chagas' Disease"):**
  - **Causative Organism:**
    - *Trypanosoma cruzi*
  - **Vector:**
    - Reduviid bug (the kissing bug – in thatched roofs)

  - **Presentation:**
    - A Cutaneous Condition:
      - Erythema
      - Oedema
      - Angioedema
  - **Trypomastigotes of *Trypanosoma cruzi*:**
    - (Trypomastigotes = "Developmental stage of Trypanosomatidae living mostly free in the blood of vertebrate hosts.")

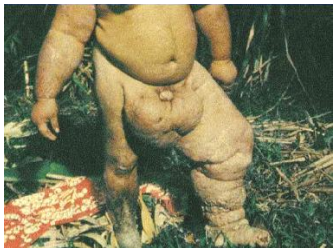


Lymphatic Filariasis:

- **Causative Organisms:**
  - ***Wuchereria Bancrofti*** (A Human Filarial Nematode)
  - Live in Lymphatics + Nodes
  - Active in bloodstream after 10PM (since its Vector – *Anopheles* – is a *Night Biter*)
- **Transmission & Vector:**
  - **Mosquitoes:** (Night Biters)
    - ***Anopheles*** **-** breeds in shaded, heavily vegetated permanent water
    - ***Culex Annulirostris*** **–** Breeds in freshwater pools/ponds/wetlands/lakes/dams/etc)
  - **Periodic Parasitaemia Corresponds with the Feeding Habits of their Vector:**
    - Eg. ***Anopheles*** – A *Night Biter*
    - If you take a peripheral blood sample at midday – you won't see anything
    - You need to take peripheral blood at night
- **Lifecycle:**
  - Adults in Lymphatics → Release Baby Worms (Microfilaria)
  - Microfilaria → Sucked up By Mosquito → Develops inside mosquito
  - New Host Next Bite.



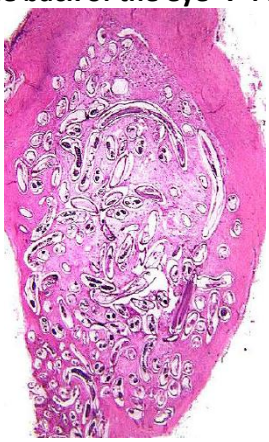
- **Pathogenesis & Presentation:**
  - **Filarial Nematodes living in the hosts lymphatic system → Extensive Lymphatic Damage**
  - **Suppress Immune System:**
    - Decreased MHC-II Processing
    - Inhibit Neutrophil Proteases
    - Downregulate inflammatory responses
    - → ↑Susceptibility to other diseases + Recurrent Infections:
      - (Eg. TB/other intracellular pathogens)
  - **Can clog up Lymphatics & cause Reactive Changes in Lymph Nodes→**
    - Can →Oedema → Elephantiasis

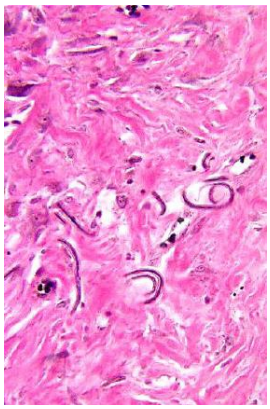


- **Diagnosis:**
  - Via Microscopy
  - Or ELISA (Ag. Detection)

Onchocerciasis ("River Blindness"):

- **Causative Organism:**
  - *Onchocerca volvulis*
- **Vector:**
  - The Biting fly
- **Can occur in the back of the eye → Press on optic nerve → blindness**

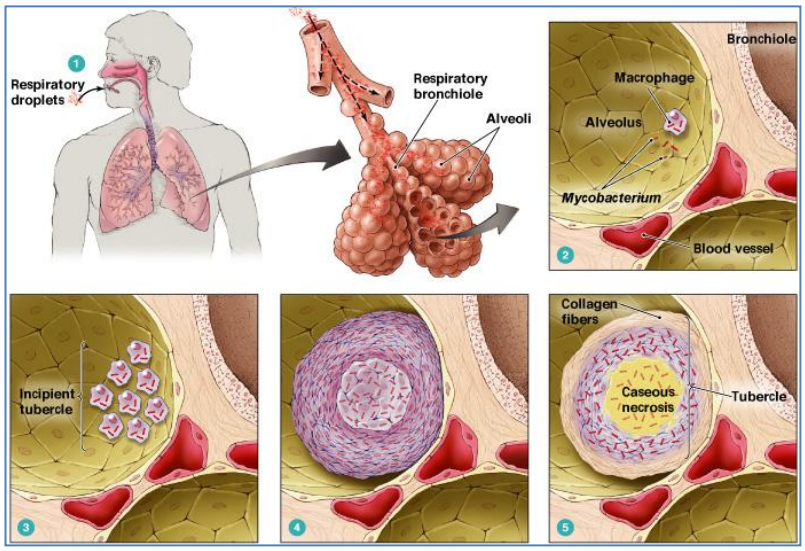




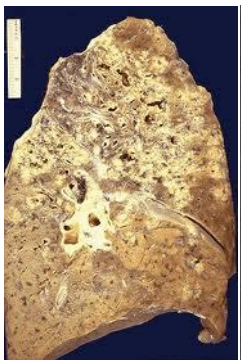
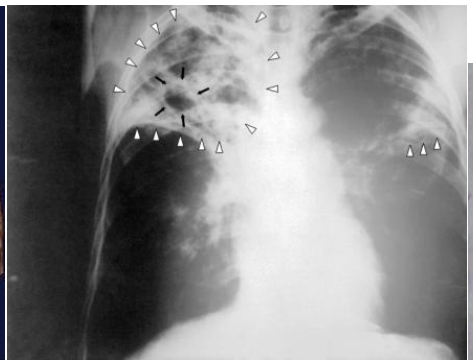
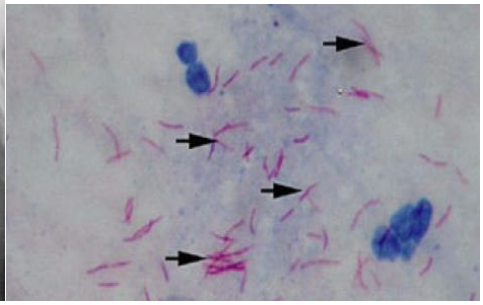
INFECTIOUS DISEASE HEALTH Pathology:
MYCOBACTERIUM

PULMONARY TUBERCULOSIS:

- **Aetiology:**
  - Infection with *Mycobacterium Tuberculosis* (An Acid-Fast Bacilli) (Droplet Transmission)
- **Pathogenesis:**
  - **Pulmonary Tuberculosis:**
    - M.Tuberculosis Inhaled → Reaches Alveoli
    - → **Invade & Replicate within Alveolar Macrophages**
    - **(3wks Later) T-Cell Sensitization → Chronic Hypersensitivity** reaction to TB Antigens.
      - Th-Cells Secrete IFNy → Activate Macrophages → Caseating Granulomatous Inflammation

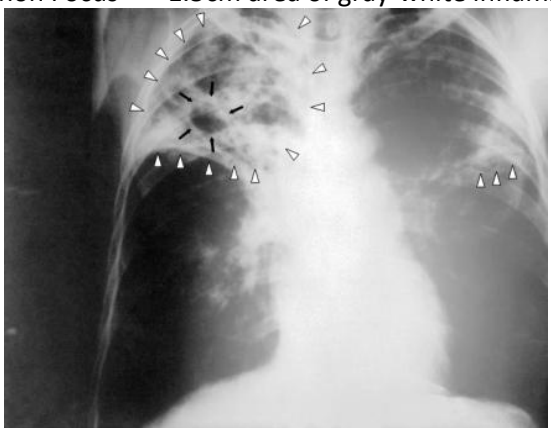


  - **Miliary Tuberculosis:**
    - M.tuberculosis overrun draining Lymph Nodes and enter the Circulation.
    - Organisms are 'seeded' back into the lung → Forming Many lesions
    - Miliary lesions Coalesce & Erode the lung parenchyma → Pleural Effusion/Haemoptysis/ Empyema.
- **Morphology:**
  - **Typically Affects Upper Lung Lobes First**
  - **Caseating Granulomas** (Pulmonary or Miliary/Systemic)
    - Nodular, Cavitating, Fibrosing
    - T/B-Lymphocytes, Macrophages, Langerhan's Giant Cells & Fibroblasts
    - Caseating Necrosis (looks like soft, white cheese)
    - Rim = Fibroblastic + Lymphocytes
    - Centre = Multinucleated Langerhan's Giant Cells
  - **Ghon Focus:**
    - 1-1.5cm area of Gray-white inflammation with consolidation.
    - Central Caseous Necrosis
  - **Ghon Complex:**
    - Ghon Focus + Nodal Involvement

- **Clinical Features:**
  - May be Asymptomatic/Latent.
  - **Classic Symptoms:**
    - Chronic Cough
    - Fever, Night Sweats
    - Weight Loss
    - Pleuritic Chest Pain
    - Cavitation & Erosion can → Pleural Effusion &/or Haemoptysis
    - Extrapulmonary Symptoms – Depend on the Organ Affected.
  - **Miliary Tuberculosis:**
    - M.tuberculosis overrun draining Lymph Nodes and enter the Circulation.
    - Organisms are 'seeded' back into the lung → Forming Many lesions
    - Miliary lesions Coalesce & Erode the lung parenchyma
  - **Diagnosis:**
    - **Mantoux Test (Tuberculin Test):**
      - Intradermal Hypersensitivity test to injected PPD (Purified Protein Derivative)
      - Only works after 2-4wks post infection; but once infected, will be positive for life.
      - Signifies T-Cell Sensitivity to Mycobacterial Antigens.

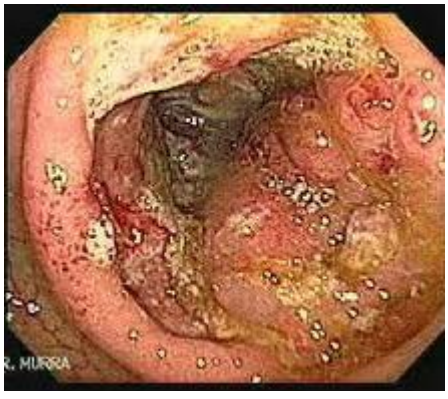

    - **CXR:**
      - Upper Lobe Consolidation
      - "Ghon Focus" - ≈1.5cm area of gray-white inflammation with Caseous Necrosis

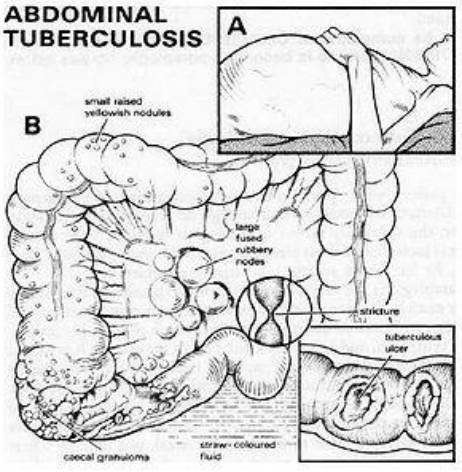


    - **Serology:**
      - PCR Amplification (Much more sensitive)
    - **Microscopy:**
      - Acid-Fast Sputum Smears
      - Culture & Sensitivity
  - **Treatment:**
    - Combined Antibiotics
      - Pyrazinamide
      - Ethambutol
      - Isoniazid
      - Rifampicin.

INTESTINAL TUBERCULOSIS:

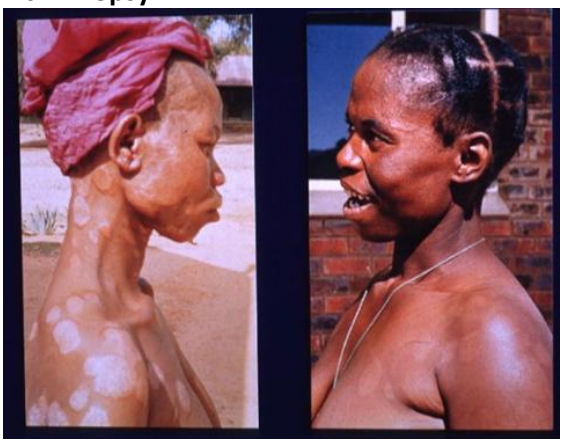
- **Aetiology:**
  - Reactivation of Primary Mycobacterium tuberculosis (Typically from Pulmonary TB).
  - Typically in Immunocompromised (HIV/Drugs)
- **Pathogenesis:**
  - Spread/Reactivation of Tuberculosis:
    - (i) hematogenous spread from the primary lung focus
    - (ii) ingestion of bacilli in sputum from active pulmonary focus;
    - (iii) direct spread from adjacent organs;
    - (iv) through lymph channels from infected nodes.
- **Morphology:**
  - Mesenteric Thickening
  - Lymphadenopathy
  - Ulceration of Transverse Colon
  - Multiple Granulomas in Lymph Nodes or Below Ulcers
  - Fibrosis, Thickening and Stricturing of the bowel wall
- **Clinical Features:**
  - **Symptoms/Signs:**
    - **Fever + Night Sweats
    - **Weight Loss
    - *Ileocaecal Area is most commonly affected → RIF Abdominal Pain, Palpable Masses
    - Generalised Peritonitis
    - Anaemia
    - Obstruction
  - **Diagnosis:**
    - Histology & Culture
    - CXR (50% have evidence of Pulmonary TB)
  - **Treatment:**
    - **Combination Antibiotics:**
      - Rifampicin
      - Isoniazid
      - Pyrazinamide
      - Ethambutol

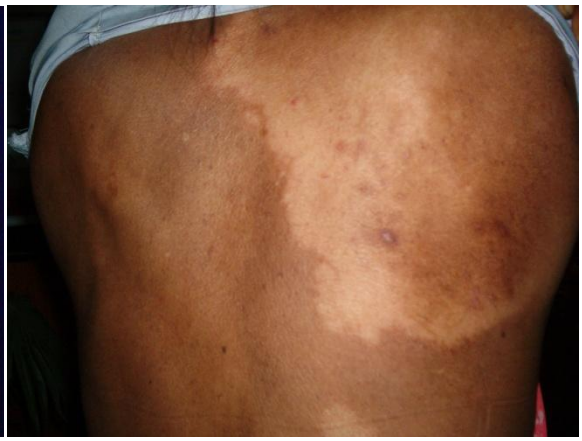




LEPROSY:

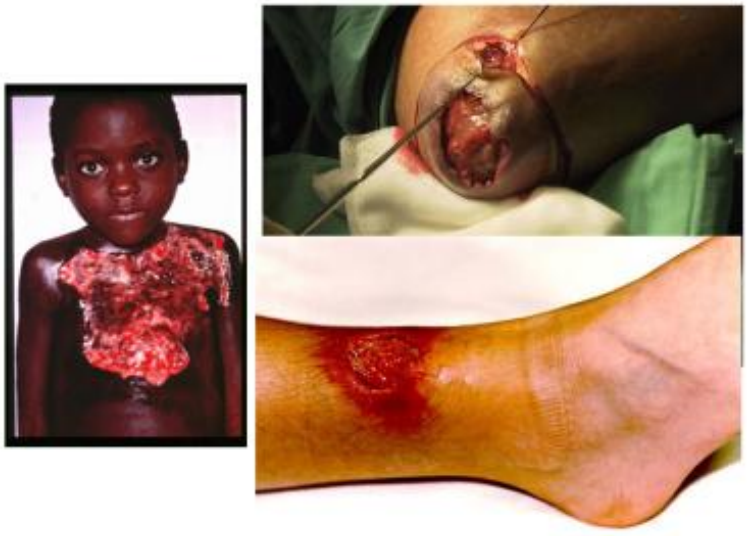
- **Organism:**
  - *Mycobacterium leprae*
- **Pathogenesis:**
  - Chronic disease of skin and nerves
- **Presentation:**
  - Some skin lesions of leprosy can look like dermatophytosis
  - Decreased sensation and no sweating
  - Lesions can be:
    - Depigmented or Reddish/Copper-coloured
    - flat or raised
    - do not itch/hurt
    - Can appear anywhere.
- **Differential Diagnoses:**
  - Birthmark
  - Vitiligo
  - Contact Dermatitis
  - Lichenoid Dermatitis
  - Tinea Versicolor
- **Diagnosis Of Leprosy:**
  - **Clinical**
    - Skin lesions
    - Thickening of cutaneous nerves
    - Loss of sensation
  - **Split Skin Smears**
    - Acid fast bacilli (AFB)
  - **Biopsy**





MYCOBACTERIUM ULCERANS:

- **Organism:**
  - *Mycobacterium ulcerans*
- **Epidemiology:**
  - Occurs in Mossman / Cooktown area
- **Pathophysiology:**
  - Chronic ulcerative disease of skin and subcutaneous tissue (Buruli ulcer)
  - Probably starts from minor trauma
- **Presentation:**
  - Ulcers are always much smaller in area than subcutaneous infection underlying them
  - Usually not painful



- **Diagnosis:**
  - Clinical
  - Swab for AFB, culture and PCR
  - Skin biopsy
- **Treatment:**
  - Surgical resection
  - Intravenous amikacin + oral rifampicin + oral clarithromycin or azithromycin
  - Local heat

Other Tropical Diseases

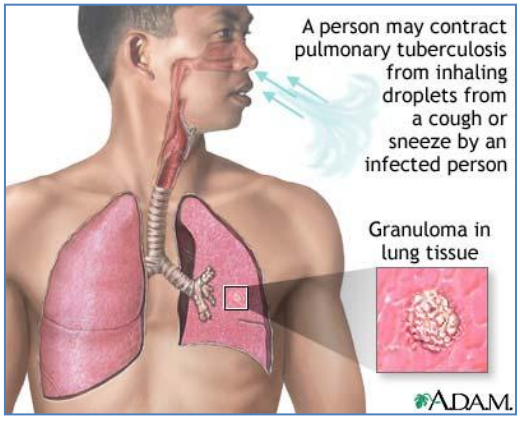
Overview:

- **Bacterial:**
  - Tuberculosis
  - Melioidosis
- **Protazoan:**
  - Malaria (Plasmodium Vivax)
  - Giardia
  - Toxoplasmosis (Toxoplasma Gondii)
- **Metazoan:**
  - Helminths (NB: Schistosomiasis is mentioned separately in another document)
  - Filarial Worms

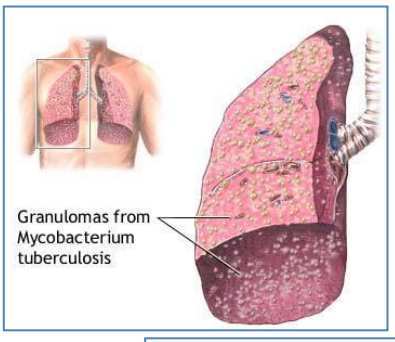
Tropical Diseases:

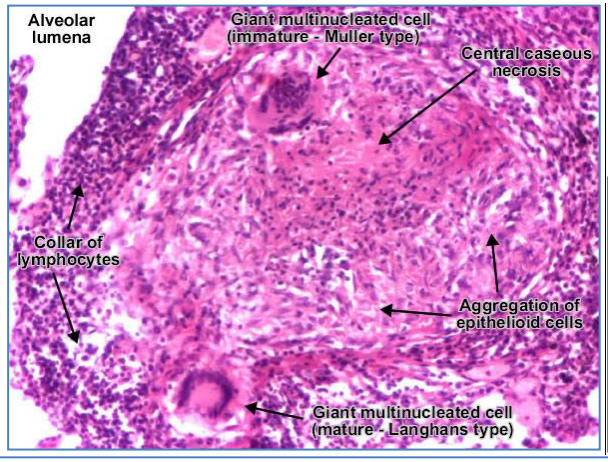
Bacterial:

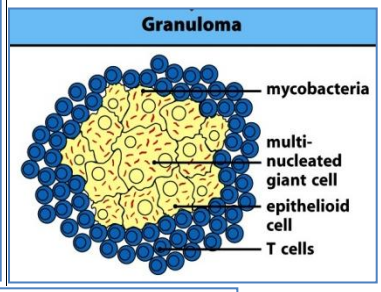
- **Tuberculosis:**
  - **Bacterium:**
    - Mycobacterium Tuberculosis.
    - Aerobic
    - Non-Motile
    - Live Intracellularly (Inside Macrophages)
    - Wax-like coating on Cell Surface
      - (Consists of *High-Molecular-Weight Fatty Acids* ('Mycolic Acids'))
    - Is *Neither* Gram Positive *Or* Negative.
      - Instead, Ziehl-Neelsen Staining (or 'Acid-Fast' Staining) is used.
      - → Red, Rod-Shaped.
    - **NB:** No known Toxins or Proteolytic Enzymes → All 'damage' is due to host immune system.
    - *ONLY infects Humans.*
  - **Infection - Via Droplet-Transmission:**
    - **Primary Infection:**
      - **1.** Inhalation of Bacteria → Deposit in Alveoli → Alveolar Macrophages (1st Target).
      - **2.** Infection is then established in the draining Lymph Nodes (2nd Target).
      - **3.** 5% of cases Disseminate → Cause Miliary (Blood-borne) Disease.
      - NB: Typically leads to formation of a "**Gohn Complex**" – A calcified lesion in the lung.
    - **Secondary/Post-1° Infection (Ie. Reactivation):**
      - Reactivation of a Latent TB Infection.
      - Typically due to Immunocompromise.
        - (HIV, Old age, Malnutrition, Aolcohol, Immunodeficiency, corticosteroids)
      - NB: Typically Presents as Cavitation in Apex of the Lung, with Caseous Necrosis.
    - NB: HIV (Immunocompromise) → ↑Susceptibility.
    - NB: Growth is Slow (4-6 weeks) – Reaches an *Equilibrium* between Bacterium & Host.
    - NB: Multi-Drug Resistance is a big problem.

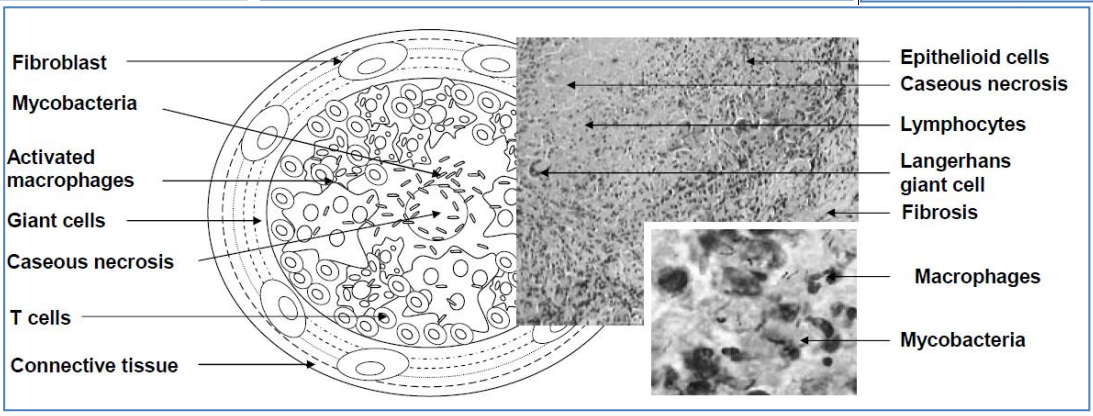


- **Symptoms** = **Pulmonary Disease**
  - **Latent TB:**
    - No Symptoms
  - **Early Stages:**
    - Fevers
    - Weight Loss
    - Chronic Cough
    - Sputum (phlegm)
    - Haemoptysis (Coughing up blood)
    - Night Sweats.
  - **Terminal Stages:**
    - Severe Lung Damage
    - Septicaemia
    - Some Spread to **Other Organs.**
      - TB Meningitis
      - TB Osteomyelitis
      - TB Arthritis
      - TB Lymph Node Infection
- **Mechanics of Disease – Granuloma Formation:**
  - **Most of the Tissue Damage is by the Immune System:**
    - Macrophages secrete lots of Proteases → Breaks down Extracellular Matrix.
      - →lots of Caseous Necrosis
    - Extensive damage → Result = Many Massive Cavities within lung.
      - Impaired Gaseous Exchange
    - Granulomas may burrow into Major Blood Vessels → Haemoptysis → Death.
  - **Bacteria form Granulomas in lung tissue – Consist of:**
    - Central Caseous Necrosis
    - Giant Multinucleated 'Langhan's' Cells.
    - Epithelioid Cells (Macrophage-derived cells with an epithelial-like phenotype)
    - T-Cells & Fibrous Tissue Surround the Granuloma.

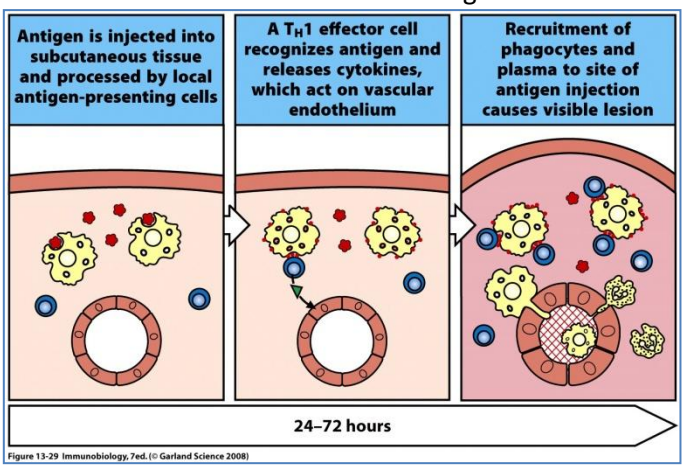


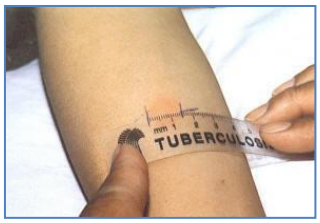






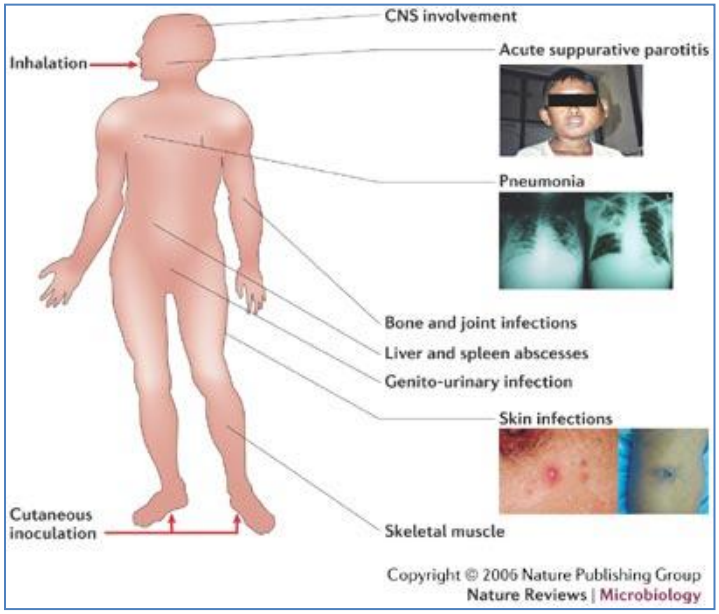
- **Immune Mechanisms Against Tuberculosis:**
  - **Phagocytosis – By Macrophages:**
    - TLRs on Macrophages recognise PAMPs on TB →
      - Phagocytosis
      - Release of Pro-Inflammatory Cytokines.
  - **Complement Activation:**
    - Alternate Pathway
    - →Opsonisation of bacteria for Phagocytosis.
  - **CD4-T-Cells:**
    - → Help Activate Macrophages Via IFN-γ→ Kill Intracellular TB.
    - → Help Activate B-Cells → ~~Produce Antibodies against Extracellular TB~~.
      - NB: Antibodies play NO role in immunity against TB.
    - → Help Activate CD8-T-Cytotoxic cells → Kill infected Cells (incl. Macrophages)
- **Evasion of Immune Mechanisms by Tuberculosis:**
  - TB inhibits Fusion of Lysosome with Phagosome.
  - TB is Resistant to Lysosomal Enzymes (& Oxidative Killing)
  - TB can *Escape* from Phagosome into Macrophage Cytoplasm.
  - Binds to TLR-2 (Instead of TLR-4) on Macrophages → Secretes IL-10 (An Anti-inflammatory)
- **Diagnosis:**
  - Sputum Microscopy (NB: Not definitive)
  - Culture of Sputum → Detection of TB Bacteria in Sputum. (Takes Ages – Poor test)
  - **PCR-Amplification of sputum samples (Detects Tuberculosis genes →Definitive)**
  - **Quantiferon-TB Assay:**
    - Addition of TB-Antigens to a Whole-Blood sample.
    - Samples with Memory Lymphocytes will show Secretion of IFNγ.
  - **Mantoux Test**:
    - Subcutaneous introduction of TB Antigen → Look for Visible Lesion within 3days:
      - Lesion = Positive Mantoux – (Suggests pre-exposure to TB & presence of memory T-Cells in tissues)
      - No Lesion = Negative Mantoux.



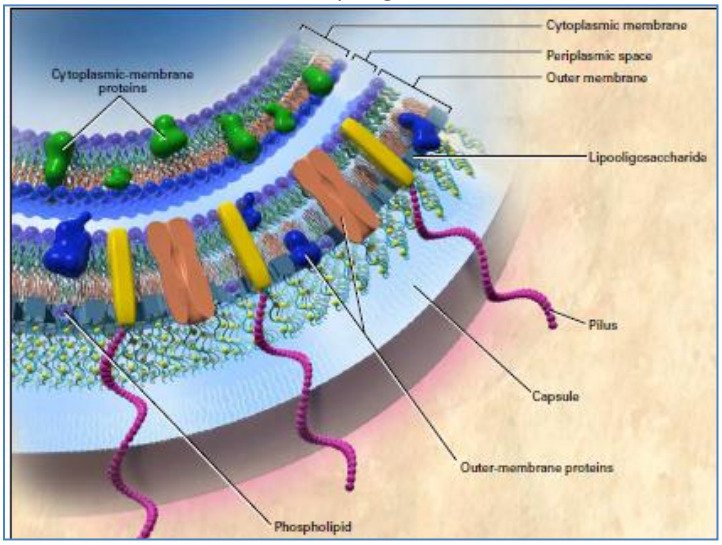


- **Treatment:**
  - **BCG Vaccine:**
    - (Attenuated strain of M.Bovis – 'cow TB')
    - Reduces risk of all forms of TB by ≈ 50%.
    - Often given to young children in places of Endemic TB.
  - **Combined Antibiotic Therapy:**
    - TB requires Long Courses of Treatment (6-24mths)
    - Multiple Antibiotics are used to prevent Resistant Strains.

- **Melioidosis:**
  - **Bacterium – "*Burkholderia Pseudomallei*":**
    - Bacterium that lives in Soil & Water – Only In Tropics
    - Intracellular
    - Gram Negative
    - Resistant to some antibiotics.
  - **Mode of Infection:**
    - Ingestion
    - Open Wound
  - **Symptoms**:
    - **Most infections:**
      - Asymptomatic.
    - **Some Infections – Fatal!:**
      - Fever, Pain, Cough
      - Pneumonia
      - Systemic Abscesses
      - If Septic → Sore throat/Fever/Headaches/Chest Pain/Upper Quadrant Abdo.Pain
      - → Death.
    - **Chronic:**
      - Chronic Skin Infection
      - Skin Ulcers
      - Lung Nodules
      - Chronic Pneumonia
  - **Immune Mechanisms Against Melioidosis:**
    - (Pseudomallei lives *Intracellularly* – determines Immune Mechanisms)
    - - **Cell-Mediated Immunity = Most Important:**
      - **Macrophages** – (NB: Bacteria can survive within macrophages)
      - **CD4-T-Helper Cells –** Activate Macrophages to kill intracellular bacteria.
      - **CD8-T-Cytotoxic Cells –** Recognises & Kills Infected Cells
    - **NB: Humoral Immunity is *Ineffective*.**
  - **Evasion of Immune Mechanisms by Melioidosis:**
    -
  - **Diagnosis:**
    - *Culture Samples – (Definitive Diagnosis)
    - Serological (Immunofluorescence/Monoclonal Antibodies/Agglutination Tests)
  - **Treatment:**
    - NB: Organism is resistant to *Broad Spectrum Antibotics*.
    - Long-Course Antibiotic Therapy.

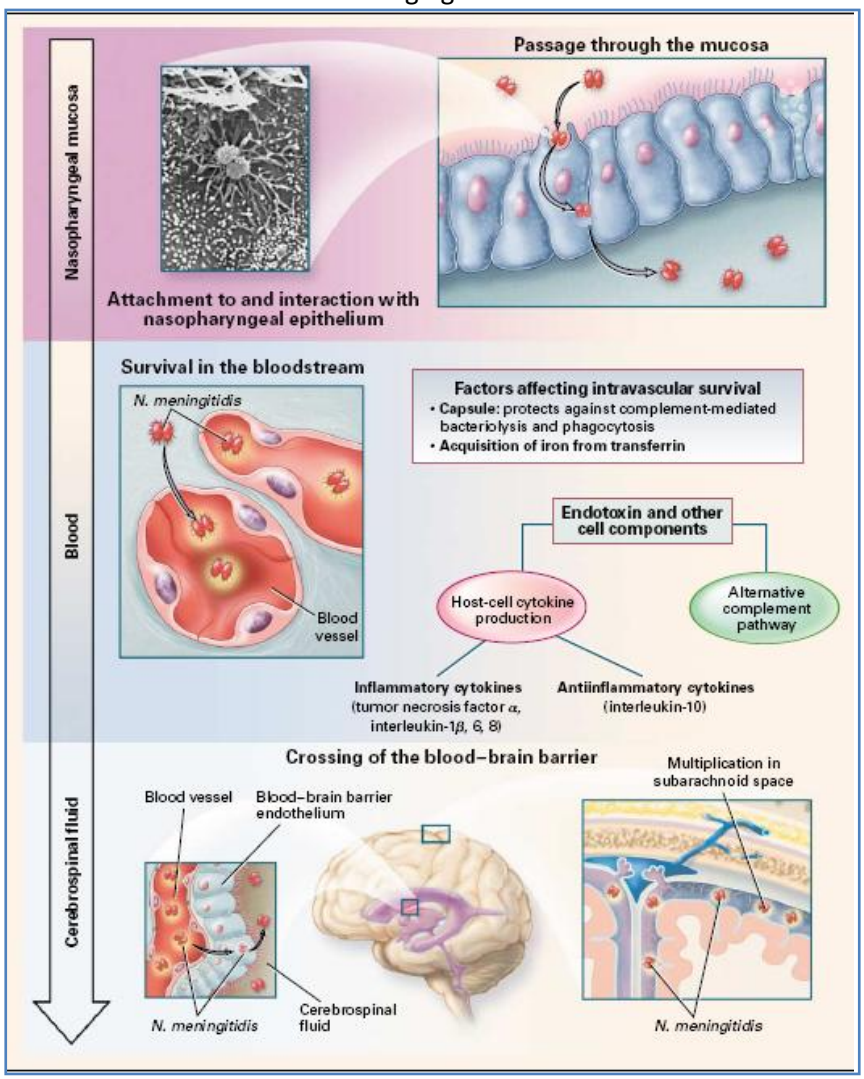


- **Meningococcal Disease:**
  - **Bacterium – "*Neisseria Meningitidis*":**
    - Extracellular
    - Gram Negative Aerobic Bacteria
    - Humans are the Only Host.
    - Colonises the Nasopharynx
    - **6 Important 'Serotypes':**
      - A, B, C, Y, W135 & X.
  - **Virulence Factors:**
    - **The Capsule:**
      - Protects the organism
      - Prevents Phagocytosis
      - Prevents Opsonisation
      - Prevents Complement Activation
      - Can "Capsule Switch" to Evade the Immune System.
    - **Pili:**
      - Facilitates Attachment to Nasopharyngeal Surfaces
    - **IgA Protease:**
      - Secreted to evade Mucosal-IgA.
      - → Cleaves Dimeric IgA.
    - **Lipopolysaccharide (LPS) Endotoxin:**
      - Binds to TLR-4 on Macrophages → Stimulates release of Pro-Inflam.Cytokines.



  - **Mode of Infection:**
    - Aerosol-Droplet Transmission
    - Occurs Mainly during Winter/Spring (Rainy Seasons)
    - Serotype B is the Most Common (70% of all infections)
  - **Symptoms**:
    - Meningitis
      - Headache
      - Nausea
      - Photophobia
    - Petechiae/Rashes
    - Leg Stiffness
    - Coolness of Extremities.
    - Pneumonia
    - Pericarditis
    - Arthritis
    - Conjunctivitis
    - Septic Shock
    - Tissue Gangrene

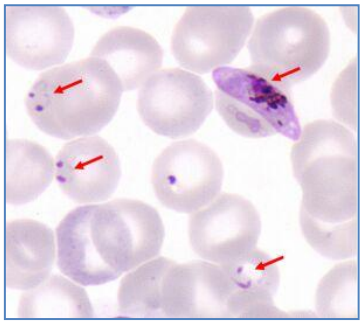
- **Contribution of the Immune System to Disease:**
  - **Cytokine Production →Septic Shock:**
    - TNF, IL-1, Il-6.
  - **Clotting Pathways → DIC:**
    - (Disseminated Intravascular Coagulation)
    - Activation of Clotting Pathways & Down-regulation of Fibrinolysis.
    - → Petechial Haemorrhaging.



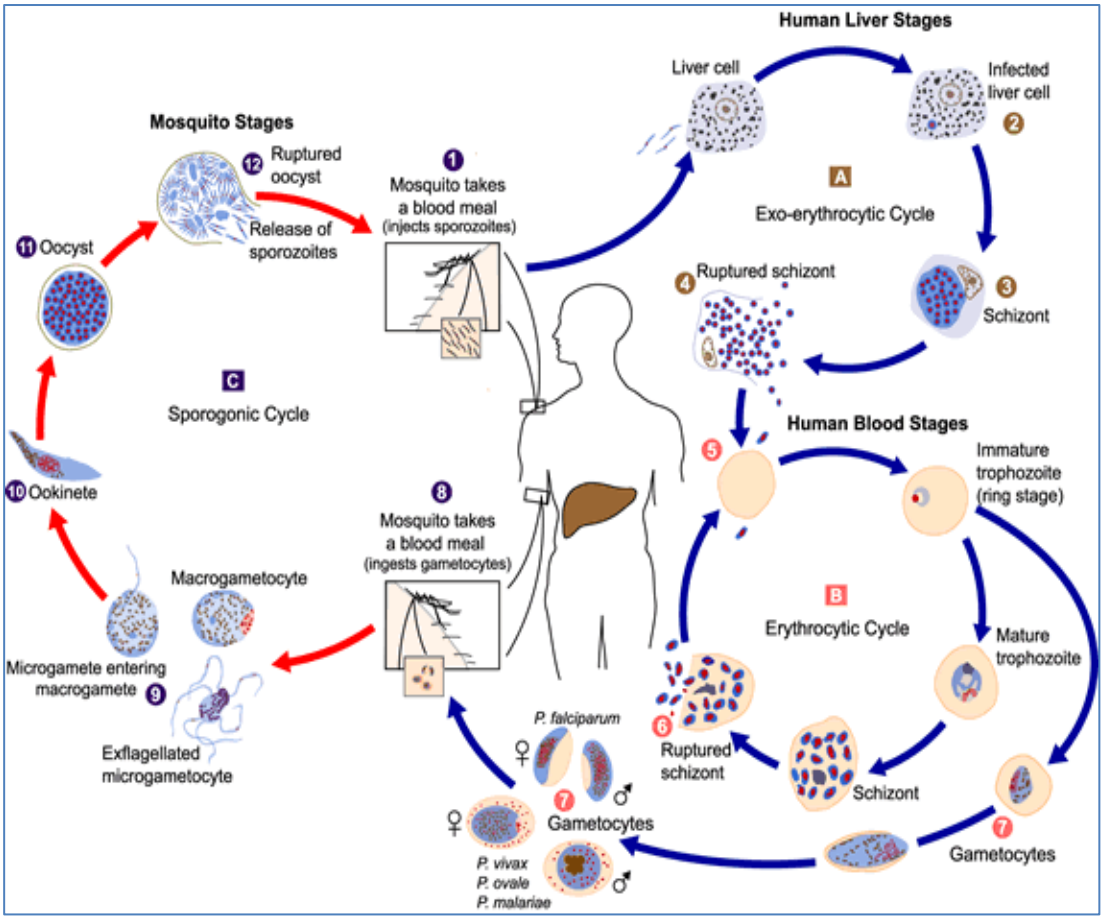
- **Immune Mechanisms Against Melioidosis:**
  - **IgG –** The Only Effector Mechanism
  - **(CD8-T-Helper Cells):**
    - Still required to fully activate B-Cells → Secrete IgG.
- **Evasion of Immune Mechanisms by Melioidosis:**
  - Can "Capsule Switch" to Evade the Immune System.
- **Diagnosis:**
  - #1 - Clinical Suspicion (Very Important since the infection can lead to sepsis within hours)
  - Blood Cultures
  - CSF Cell Counts (requires spinal tap)
  - PCR Amplification
- **Treatment:**
  - EARLY Antibiotic Treatment.
    - Penicillin (or penicillin derivatives)
  - 10% mortality rate.
  - NB: Some Vaccines are available – (Not 100% effective)

Protozoans:

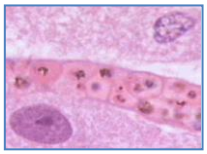
- **Malaria (Plasmodium Vivax):**
  - **Pathogen:**
    - 4 Species Infective to Humans...
    - **#1 - Plasmodium Falciparum (The Lethal One)
    - Intracellular Parasite (Inside Human RBC's)



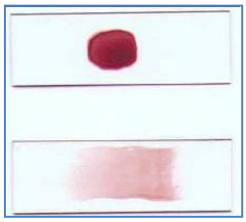
  - **Big Killer!**
    - Affects Mostly Poor Countries
    - Vector Present In Aus, But Disease is Eradicated
    - Still have 600-1000 'Imported' cases/year.
  - **Mosquito Vector: Lifecycle:**
    - **1. Mosquito Bites Human → Sporozites into blood → Liver → Infects RBCs**
      - Sporozites → Gametocytes.
    - **2. Mozzie sucks blood → Gametocytes grows in Mosquito's gut → Sporozoites in salivary gland injected into human.**
      - This stage takes up to 14days before re-infection can occur.



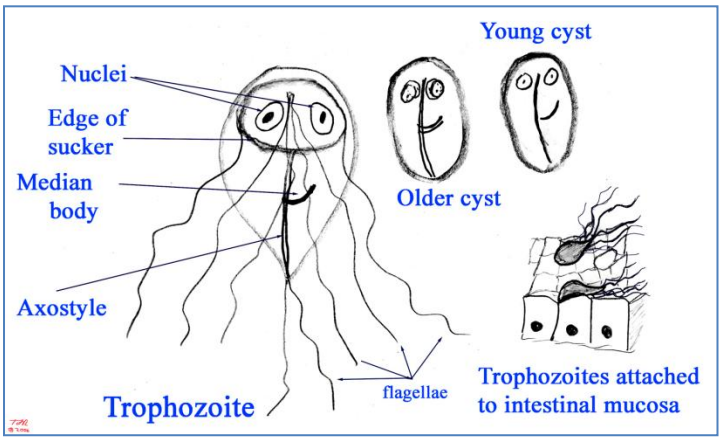
- **Symptoms:**
  - Rupture of RBC's → Disease.
    - Fever
    - Rigors
    - Headache
    - Severe Anaemia
    - Haemoglobinuria (Hb in Urine)
  - RBC's Become 'Sticky' → Adhere to Endothelium → Capillaries Clogged → Tissue Hypoxia → Multiorgan Failure.
    - Cerebral Malaria
    - Pulmonary Oedema
    - Renal Failure



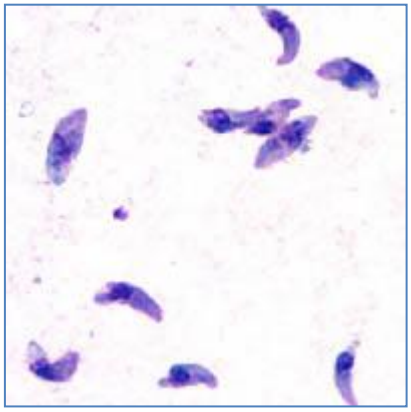
- **High Risk People:**
  - Infants
  - Non-Immunes: eg. Tourists.
- **Diagnosis:**
  - Blood Smear
    - Thin Blood Smear:
      - To diagnose the species
    - Thick Blood Smear:
      - To diagnose malaria
      - Gets the most amount of RBCs on the slide
        - (if infection is scant)
  - Card Test
  - PCR



- **Giardia:**
  - **What is it?**
    - A Common Intestinal Parasite found throughout the world.
  - **Exists in 2 Forms:**
    - **Trophozoite:**
      - The Infective Stage
      - Trophozoites have 4 pairs of Flagella.
      - Has a Sucker – Allows it to attach to the Intestine Wall.
    - **Cyst:**
      - The Resistant Stage
      - Cysts are shed in Faeces
      - Can survive for weeks in a Moist Environment.

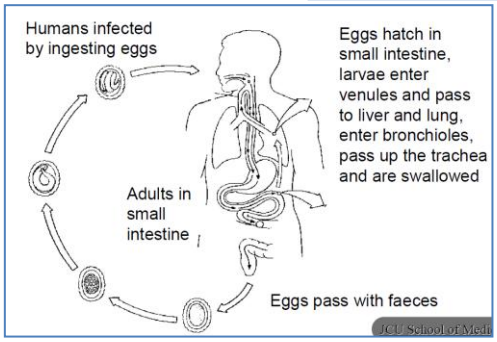


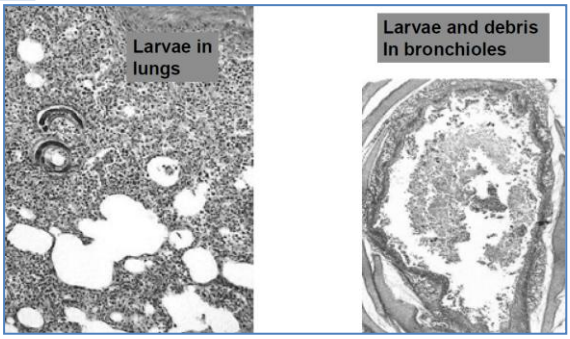
- **Toxoplasmosis (Toxoplasma Gondii):**
  - **Tachyzoites free in blood are susceptible to the Immune System:**
    - Antibodies
    - Complement
    - Phagocytes
  - **Tachyzoites Invade Normal Macrophages.**
    - However, Lysosomes fail to fuse with Phagosomes.
    - Inside the macrophage, they are sheltered from the immune system.
  - **NB: Infections can be Acute (Flu-like symptoms) or Latent (Asymptomatic):**
    - In the latent stage, Cysts may form → No Immune Response.



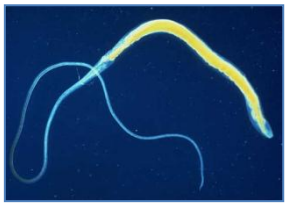
Metazoan Parasites:

- **Soil Transmitted Helminths:**
  - Live in GIT
  - Pass Progeny in the Faeces (Usually Eggs, Sometimes larvae)
  - Use soil for Development from Early Stage (Egg/Larvae) → Infective Stage → Host.
  - Common in tropical Climates – Warmth & Humidity Critical.
  - **Roundworm ("Ascaris Lumbricoides"):**
    - Larvae grow in the Lungs
    - Adults Live in Small Intestine.
      - Feeds on Intestinal Contents
      - Strong Swimmer (has no 'attachment organ')

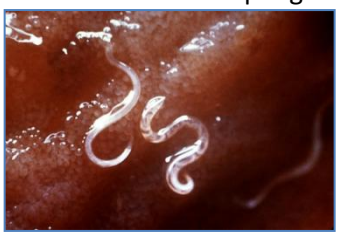





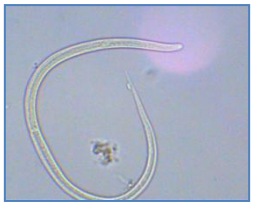
  - **Whipworm:**
    - Lives in Large Intestine
    - Whip-like Tail Anchors to L.Intestine Wall.



  - **Hookworm:**
    - Live in Small Intestine
    - Uses Mouth to Attach to Intestine Wall → Feed on Blood.
    - Eggs → Soil → *Hatches in Soil* → Larvae Chase *Heat* → Burrow Through Skin → Circultion → Lungs → Trachea → Down Oesophagus → Stomach → Small Intestine.

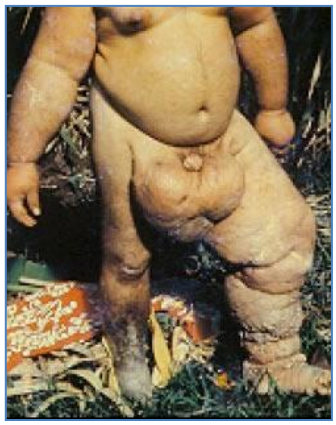


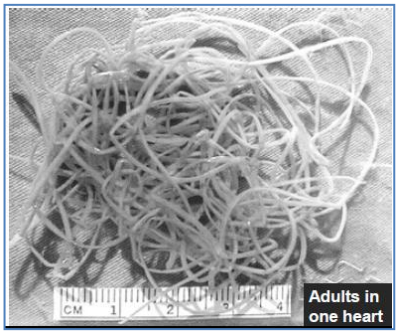

  - **Strongyloides:**
    - Lives in Small Intestine
    - Eggs → Soil → *Hatches in Soil* → Larvae Chase *Heat* → Burrow Through Skin → Circultion → Lungs → Trachea → Down Oesophagus → Stomach → Small Intestine.



- **Lymphatic Filariasis:**
  - **Vector:**
    - Mosquitos
  - **Pathogen:**
    - Filarial Worms (Parasite)
    - Live in Lymphatics + Nodes
  - **Life Cycle:**
    - Adults in Lymphatics → Release Baby Worms (Microfilaria)
    - Microfilaria → Sucked up By Mosquito → Develops inside mosquito
    - New Host Next Bite.
  - **Results in *Morbidity*, not *Mortality*.**
    - **Elephantiasis – Massive Oedema**
      - Extensive Lymphatic Damage
      - Suppresses Immune System → Recurrent Infections
      - Fevers
      - Genital Disease
      - Social Isolation/Stigmatisation/Depression
  - **4 Aspects of Management:**
    - 1. Preventative Chemotherapy (Prevention)
      - 1x Dose every year for 5 years = good protection
    - 2. Hygeine
      - Care of Entry Lesions (wounds)
      - Wash affected limb with Soap + Water
      - Prevents Secondary Infections
    - 3. Elevation:
      - To Maximise Lymphatic Drainage.
    - 4. Exercise:
      - To Maximise Lymphatic Drainage.
  - **Acute Attack of Filariasis:**
    - Caused by secondary bacterial infection
      - Increased swelling
      - Fever
      - Sore Glands
      - Headach
      - Nausea
    - **Treatment:**
      - 1. Cool leg with cold, clean water
      - 2. Take medicines for Fever + Drink More Water.
      - 3. Keep Washing as per Usual
      - 4. Rest.

Elephantiasis of the legs due to filariasis (CDC).





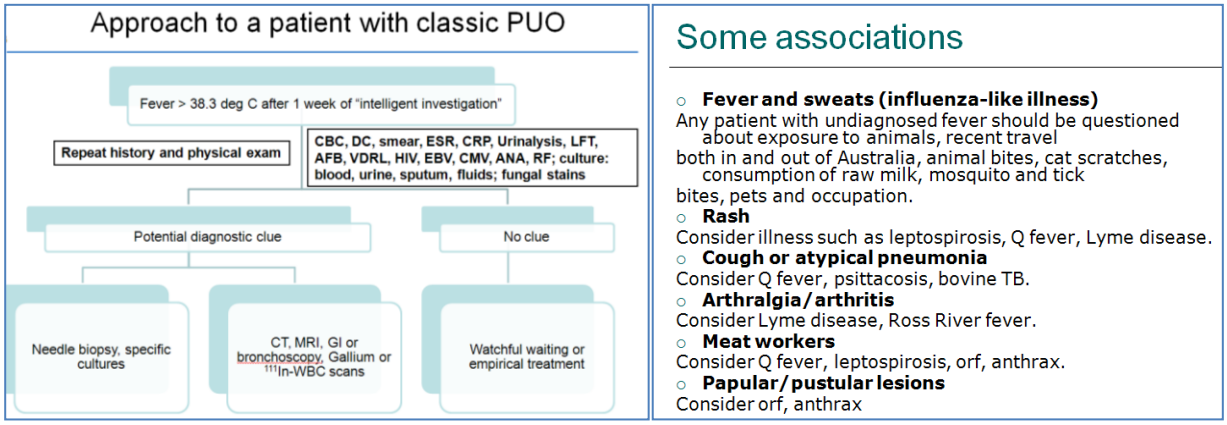
PUOs & Tropical Diseases

Overview:

- **Pyrexia of Unknown Origin:**
- **Arboviruses:**
- **Arboparasite – Eg. Malaria:**
- **Melioidosis**
- **Leptospirosis ("Weil's syndrome", "Canefield Faver", "7-Day Fever", "Rat Catcher's Fever"):**
- **Q-Fever (Query Fever):**
- **Brucellosis (AKA: Mediterranean Fever):**

Pyrexia of Unknown Origin:

- **Aetiology:**
  - **Infective**
    - **Viral –**
      - EBV, CMV, HIV, HepB, HHV, Mumps, RRV, Dengue,
    - **Parasitic –**
      - Cryptosporidium, Malaria
    - **Bacterial –**
      - TB, Leptospirosis, Brucellosis, QFever (coxiella burnettii), UTIs
      - **NB: UTIs:**
        - **UTI in Elderly:** Confusion, Behaviour Disturbance, + PUO. Risk Factors – faecal incontinence, immobility, incomplete urinary emptying.
        - **Complicated UTI:** is commonly caused by Pseudomonas aeruginosa
        - **Recurrent/Chronic UTI:** May indicate organism is resistant to antibiotics
  - **Malignant –**
    - Cancer, Leukaemia, Lymphoma
  - **Connective Tissue Disease –**
    - Rheumatoid, SLE, Vasculitis, Sarcoidosis, Crohn's Disease
  - **Drugs –**
    - Amphetamines
  - **Endocrine Causes –**
    - Hyperthyroidism
  - **Inherited Causes –**
  - **Factitious –**
    - Munchausen Syndrome, Fakers, Psychosomatic
- **Pathogenesis:**
  - **Immune Activation** (to Infection, Cancer, Inflammatory Disease) → Release of Cytokines → Fever
  - **Endocrine** (Eg. Hyperthyroidism/Stress/Addison's) → ↑Basal Metabolic Rate → Fever
- **Clinical Features:**
  - **Classic PUO:**
    - Temp of >38.3
    - For >3wks Duration
    - Failure to Diagnose after 3days of Hospitalisation.
  - **Nosocomial PUO:**
    - Temp of >38.3 in a Hospitalised Patient
    - No Fever on Admission
  - **Ix:**
    - Cultures – Blood, Urine, Sputum, Stool, LP
    - FBC, Smear, ESR, U&E, CRP, LFT, ANA, VDRL, HIV, EBV, CMV, Rh Factor, TFT.
- **Treatment:**
  - Unless the Pt is Acutely Unwell, or Neutropaenic, DON'T Treat Empirically.
  - Otherwise, Determine the Cause...Then TREAT THE CAUSE.



Some associations

- **Fever and sweats (influenza-like illness)**

Any patient with undiagnosed fever should be questioned about exposure to animals, recent travel both in and out of Australia, animal bites, cat scratches, consumption of raw milk, mosquito and tick bites, pets and occupation.

- **Rash**

Consider illness such as leptospirosis, Q fever, Lyme disease.

- **Cough or atypical pneumonia**

Consider Q fever, psittacosis, bovine TB.

- **Arthralgia/arthritis**

Consider Lyme disease, Ross River fever.

- **Meat workers**

Consider Q fever, leptospirosis, orf, anthrax.

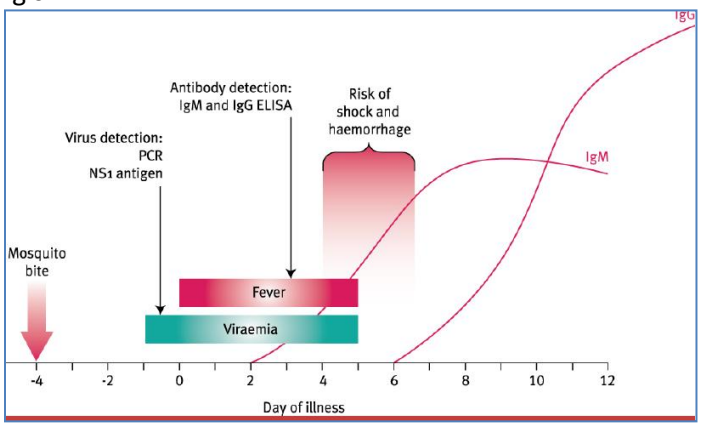
- **Papular/pustular lesions**

Consider orf, anthrax

Tropical Infections

Arboviruses:

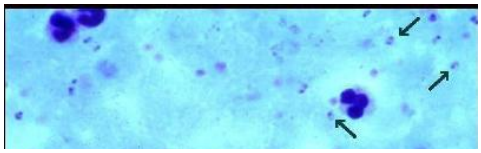
- **Aetiology:**
  - **Alphaviruses:**
    - **Ross River Virus** - Alphavirus - Mosquitoes - **Fever + Rash + Arthritis**
    - Barmah Forest Virus - Alphavirus - Mosquitoes - Indistinguishable from RRV
  - **Flaviviruses:**
    - **Dengue (4x Serotypes)** - Flavivirus - **Aedes Aegypti** - ***Haemorrhagic*** Fevers
    - **Murray Valley Encephalitis** - Flavivirus - Mosquitoes - ***Encephalitic*** Fevers
- **Pathogenesis:**
  - **1. Bite of an arthropod → Infection**
  - **2. Virus may replicate in the endothelium and lymphatics**
  - **3. Viraemia and infection of Target Organs → Fever and malaise (Often due to cytokines)**
  - **4. Adaptive Immunity to Viral Infections is Cell Mediated (Tc-Cells, NK-Cells)**
  - **5. Long-Term Immunity to Re-Infection is via Humoral Response (Antibodies & Complement)**
    - Prevent Re-Infection by neutralising free viruses in blood & preventing Fusion with Cells.
- **Clinical Features:**
  - **3x Typical Presentations:**
    - **Ross River Virus & Barmah Forest Virus:**
      - (Fever)
      - *Rash (Maculopapular) (On Trunk)
      - *Arthritis (Symmetrical Polyarthritis)
      - Lethargy
      - **(Barmah Forest –** Indistinguishable from RRV)
    - **Dengue Fever:**
      - (Fever)
      - *Rash (Haemorrhagic/Petechial – due to DIC → Thrombocytopaenia)
      - *Myalgia ("Breakbone Fever" – Severe Muscle Pain)
      - (+/- Vom, Diarr, Abdo Pain)
      - **If 2nd Infection with *Different Serotype* → *Dengue Haemorrhagic Fever/Shock (DHF)***
        - Severe Bleeding
        - Leaky Capillaries
        - Shock
    - **Murray Valley Encephalitis:**
      - (Fever)
      - *CNS Involvement → Headache, Neck Rigidity, Nausea, Convulsions, ALOC.
      - ~20% Mortality; 50% of survivors have significant neurological disabilities
      -
- **Diagnosis:**
  - Serology for Ab's Test
  - PCR for viral Ag's

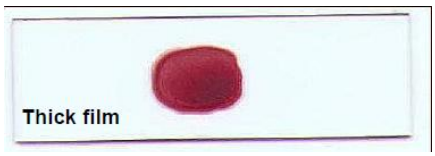


- **Treatment:**
  - Supportive Treatment

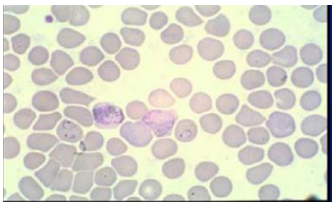
Arboparasite – Eg. Malaria:

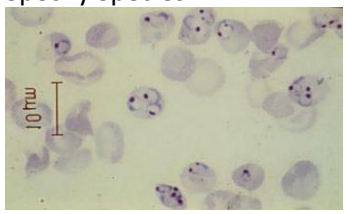
- **Aetiology:**
  - ***Plasmodium***
  - (Protozoan Intracellular Parasite)
  - **5 Species:**
    - ***Plasmodium Falciparum*** (Most Serious) (Not Persistent in Liver)(80% of Cases)
    - ***Plasmodium Vivax*** (Less Serious) (Persistent in Liver)
    - *Plasmodium Ovale* (Less Serious) (Persistent in Liver)
    - *Plasmodium Malariae* (Less Serious) (Not Persistent in Liver)
    - (*Plasmodium Knowiesi – Mostly* A Zoonosis in Monkeys)
- **Pathogenesis:**
  - **Vector:**
    - ***Anopheles* Mosquito**:
      - (A Night Biter)
      - Breeds in shaded, heavily vegetated permanent water
  - **Life-Cycle:**
    - 1. Person-Person Transmission via Anopheles Mosquito
    - 2. Parasitaemia → Plasmodium Infects Liver & Multiplies →
      - → **Hepatomegaly**
    - 3. Hepatocyte Lysis → Plasmodium Infects RBCs & Multiplies
    - 4. **Intravascular Haemolysis:** Cyclical *RBC Lysis & Further RBC Infection* →
      - → **Cyclical Fevers**
      - → **Haemolytic Anaemia & Jaundice**
    - 5. **Extravascular Haemolysis:** Spleen Removes Infected RBCs from Circulation →
      - → **Anaemia**
      - → **Splenomegaly**
    - **NB: 6. Plasmodium *Vivax* – Can Produce Recurrent Infections:**
      - - By staying dormant inside hepatocytes and reactivating at later stages.
      - - :. Even after eliminating Vivax from the blood, there may still be cycling in the liver.
- **Morphology:**
  - **Blood Films:**
    - **Thick Film:**
      - More blood = More sensitive

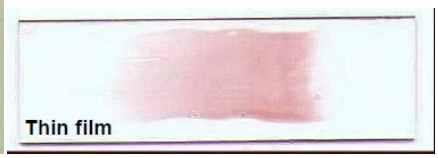




    - **Thin Film:**
      - Used to Specify Species





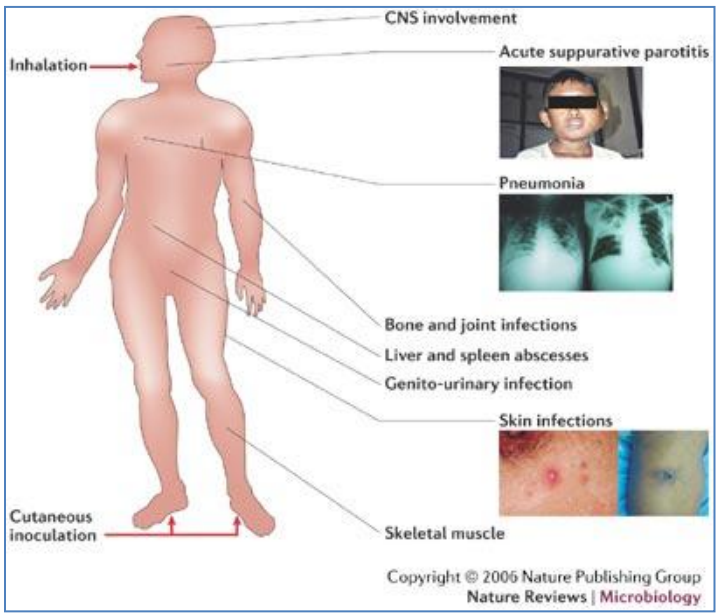


Vivax **Falciparum**

- **Clinical Features:**
  - Not endemic in Australia
  - **Symptoms:**
    - Cyclical Fevers – (May be *'Tertian'* (Every 2nd day), or '*Quartan*' (Every 3rd day))
    - Headache
    - Myalgia/Arthralgia
    - Vomiting/Diarrhoea
    - Anaemia → SOB, Palpitations
  - **Signs:**
    - Fever
    - Tachycardia
    - Anaemia & Jaundice
    - Hepatomegaly & Splenomegaly
  - **Complications:**
    - Haemolytic Anaemia
    - Liver Failure & Jaundice
    - Immune Complex Deposition → (Glomerulonephritis, Arthritis)
- **Diagnosis:**
  - **Blood Films (**The Mainstay**):**
  - **RDTs** (Rapid Diagnostic Tests)
  - **ELISA** (Detect Antigens or Antibody)
  - **PCR** (Genome detection)
- **Treatment:**
  - **Artemisinins** – Kills Plasmodium in the blood (kills active infection & prevents transmission)
  - **Primaquine** – Kills Active/Latent Plasmodium in the Liver (Prevents Recurrence of P Vivax)

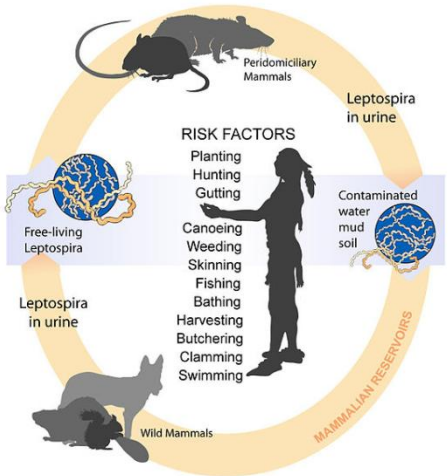
Melioidosis

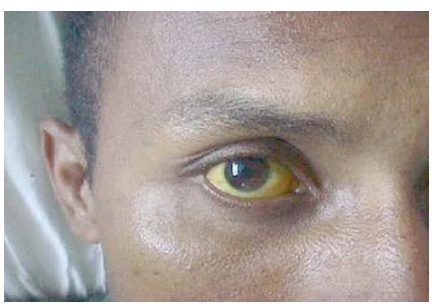
- **Aetiology:**
  - Burkholderia Pseudomallei (Intracellular Gram Negative Bacteria)
  - Lives in soil & fresh surface water (Seasonal in wet seasons)
- **Pathogenesis:**
  - **Transmission** – Percutaneous Inoculation from Wet Soils/Surface Water. Or inhalation.
    - Risk factors – Immunosuppression, chronic lung disease.
  - **Immune Mechanisms -** Pseudomallei lives *Intracellularly*:
    - Cell-Mediated Immunity = Most Important
    - Humoral Immunity is *Ineffective*
- **Morphology:**
  - **Macro:**
    - Cavitatory Lesions in Upper Lung Lobes
    - Skin Abscesses
  - **Micro:**
    - Flourescence stain – Rod-shaped, gram negative, bacilli.
- **Clinical Features:**
  - **Typical Presentation - Pneumonia:**
    - Pneumonia + (Cavitatory Lesions in the upper lung lobes (SIMILAR TO TB))
      - :. Cough, Sputum, Respiratory Distress
    - + PUO (Fever), Chills, Rigors.
    - + Skin Ulcers/Abscesses
  - (May → Sepsis → Death)
- **Diagnosis:**
  - Cultures
- **Treatment:**
  - NB: Organism is resistant to *Broad Spectrum Antibotics*.
  - Long-Course Antibiotic Therapy.

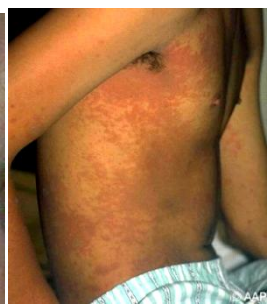


Leptospirosis ("Weil's syndrome", "Canefield Faver", "7-Day Fever", "Rat Catcher's Fever"):

- **Aetiology:**
  - Spirochaete Bacteria – Leptospira spp.
- **Pathogenesis:**
  - **Zoonotic Disease** – (Mammals, Rats, Birds, Reptiles) – Transmission through water, food, soil containing urine of infected animals.
    - NO person to person transmission.
  -
- **Morphology:**
  - **Micro:**
    - Spirochaete Bacteria
- **Clinical Features:**
  - **Symptoms – NB: *Biphasic Presentation*:**
    - **1st Phase (First 7-10 Days):**
      - Flu like symptoms – Fevers, Chills, Myalgias, Headache & Leptospiral rash. NB: Resolves after 1 wk.
    - ***Brief Asymptomatic Period...then**
    - **2nd Phase (After 10 Days):**
      - Meningitis (*Photophobia), Liver Damage (*jaundice), Renal Failure, Red Eyes (Uveitis)
  - **Signs:**
    - Fever (PUO)
    - Palmar Erythema
    - Leptospiral rash
    - Jaundice
    - Hepatomegaly/Splenomegaly
    - Costovertebral Angle Tenderness (Nephritis)
  - **Complications:**
    - Myocarditis, Pericarditis
    - Meningitis
    - Liver Failure
    - Renal Failure
    - Respiratory Distress
- **Diagnosis:**
  - Blood Cultures – if in 1st phase
  - **Urine Cultures or Serology – if in 2nd phase
  - (DDX's: Dengue, Hepatitis, Meningitis, Malaria, Typhoid)
- **Treatment:**
  - Penicillin/Cephalosporins

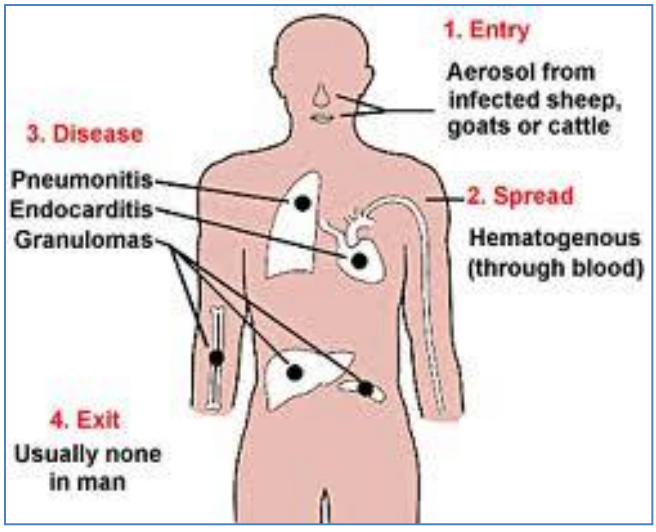






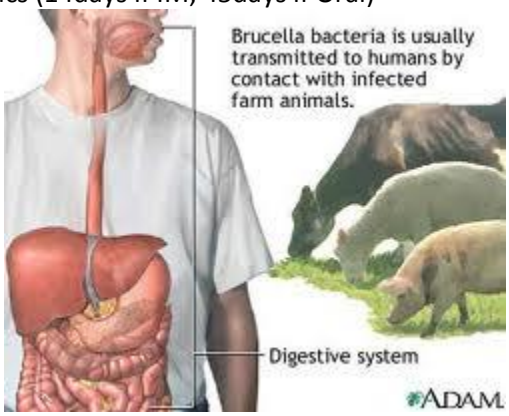
Q-Fever (Query Fever):

- **Aetiology:**
  - *Coxiella Burnettii* - (Obligate, Intracellular Bacteria)
- **Pathogenesis:**
  - (NB: the most infectious disease in the world – 1 Single Bacterium is Sufficient for Infection)
  - Transmitted from Cattle, Sheep, Goat & other livestock.
- **Clinical Features:**
  - (2-3wk Incubation)
  - **Typical Presentation:**
    - Acute PUO (++Fever, ++Malaise)
      - +Nausea, Vomiting, Diarrhoea
      - +Severe Headache, Myalgia, Arthralgia
    - *Atypical Pneumonia (Dry Cough, Pleuritic Pain, Chills) & ARDS
  - **Signs:**
    - Fever
    - Pneumonia (Consolidation)
    - Signs of Endocarditis
    - Hepatomegaly, Splenomegaly
  - **Complications:**
    - (Can → Hepatitis → Hepatomegaly & RUQ-Pain)
    - (Can → Endocarditis)
- **Diagnosis:**
  - **Serology
  - Culture
  - PCR
  - (+ LFT & Echo)
- **Prevention:**
  - Q-Vax (Whole-cell Attenuated Intradermal Vaccine)
    - NB: Vaccine + Pre-existing Immunity can → Severe Local Reaction
- **Treatment:**
  - Antibiotics (Doxy, Tetra, Cipro, Quinolones)



Brucellosis (AKA: Mediterranean Fever):

- **Aetiology:**
  - "Brucella Suis" (Gram Negative Intracellular Bacteria)
- **Pathogenesis:**
  - Zoonotic (Pigs = main hosts)
- **Clinical Features:**
  - Malaise, weakness, sweating, headache, myalgia
  - **Symptoms:**
    - Intermittent Fever
    - **Profuse Sweating**
    - **Myalgia**, Weakness, Arthralgia
    - Headache/Depression/Irritability
  - **Signs:**
    - Intermittent Fever
    - Hyperhydrosis (Profuse Sweating)
    - Splenomegaly, Hepatomegaly, Lymphadenopathy
    - Rashes
    - Anaemia
  - **Complications:**
    - Anaemia, Leukopaenia, Thrombocytopaenia
    - Endocarditis
    - Granulomatous Hepatitis
    - Brucellic Spondylitis
    - Orchitis
- **Diagnosis:**
  - Blood Cultures
  - Serology
  - Hepatic Biopsy (Granulomatous Hepatitis)
  - XRay – Brucellic Spondylitis
- **Treatment:**
  - Long-Course Antibiotics (14days if IM; 45days if Oral)



A 23-year-old man presents with a 6-day history of fever, sore throat, swollen lymph nodes, weight loss, and fatigue. Physical examination shows generalized lymphadenopathy, most prominent in the cervical lymph nodes, and mild hepatosplenomegaly. The peripheral blood smear shows 65% atypical lymphocytes. A Paul-Bunnell antigen test (heterophile antibody test) is +ve.

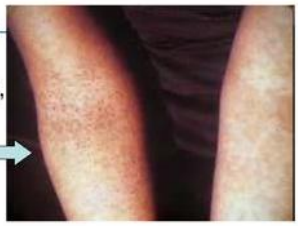
The atypical lymphocytes in this patient's are…

A. Activated T cells
B. Immature B cells
C. Mature B cells
D. Natural killer (NK) cells
E. Plasma cells

Which of the following is the most likely complication for the patient described in the previous Question?

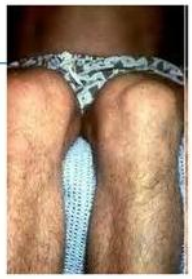
A. Burkitt lymphoma
B. Cirrhosis of liver
C. Encephalitis
D. Laryngeal stricture
E. Rupture of spleen.

56y male from Cairns, high fever, headache, myalgia, arthralgia, retro-orbital pain, nausea since 2 days. Positive tourniquet test. Platelets 13,700, WBC 2,200, albumin 2.1g/dl.



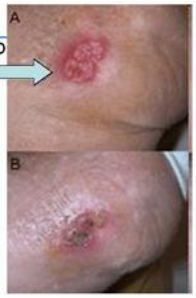
A. Ross river fever.
B. Melioidosis.
C. Encephalitis
D. Leptospirosis.
E. Dengue Fever.

35y male from Mackay, mild fever, severe pains in hands & knee, and severe fatigue since 3 weeks. Few cervical lymphnodes are enlarged. What is the most likely diagnosis?



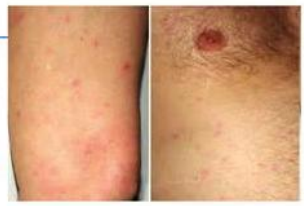
A. Ross river fever.
B. Melioidosis.
C. Encephalitis
D. Leptospirosis.
E. Dengue Fever.

51y male Diabetic presents with high fever, chills, cough one week following fishing trip on Ross River. Examination reveals skin wound on right elbow. Chest X-ray shows cavitary lesions in the upper lobe. What is the most likely diagnosis?



A. Ross river fever.
B. Melioidosis.
C. Encephalitis
D. Leptospirosis.
E. Dengue Fever.

45y male Banana farmer from Tully presents with high fever, rash and flu like symptoms. 3 weeks later develops renal failure. What is the most likely diagnosis?



A. Ross river fever.
B. Melioidosis.
C. Encephalitis
D. Leptospirosis.
E. Dengue Fever.

Parasites – An Introduction to Schistosomes (The Quintessential Metazoan Parasites)

Properties of Parasites:

- **Parasites in General:**
  - Lives at the expense of their host → Acquires Nutrients/Other Benefits without Reciprocal Benefits.
  - Are Successful if:
    - Produces minimal disturbance
    - Not regarded by host as foreign
  - Parasite infections tend to be Long-Term (As opposed to Bacteria/Viruses)
  - Many make use of the Host's growth-factors to promote their *own* growth.
  - **(Incl. Protozoa, Metazoa [Helminths/Worms] & Arthropods):**

Protozoa
Unicellular, either intracellular (for example, malaria) or extracellular (for example, African trypanosomes).
Malaria kills over 1 million per year.

Leishmania mexicana

Helminths
Multicellular, metazoan worms; includes round-worms (nematodes), schistosomes and tape-worms.
Over 25% of global population infected.

Heligmosomoides polygyrus

Ixodes hexagonus

Ectoparasites
Lice, mites, ticks and other arthropods.

Taxonomy:

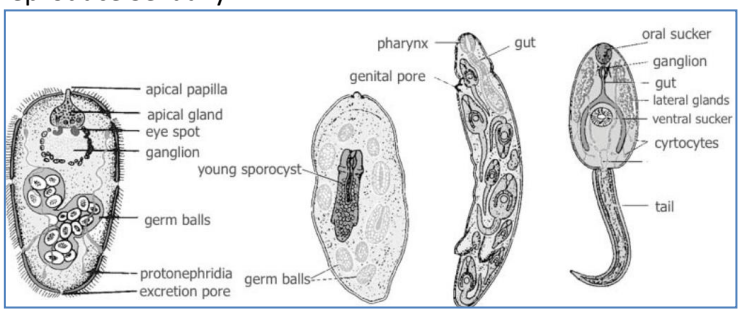
- **Subphylum Neodermata:**
  - Free-Swimming Larval Stages with Ciliated Surface
  - Epidermis is Sloughed Off during Penetration into the Host → & a *New Dermis* ("Neodermis") is formed.
  - **Class Digenea:**
    - **"Digenea"** = "Two" "Descent/Creation/Genes"
      - Ie. Have a 2-Stage (Digenetic) Lifecycle
      - Lifecycle Consists of 2 Intermediate Hosts. (Mostly Gastropods/Fish/Crustaceans)
      - Lifecycle depends on Water (Fresh/Sea)
    - **Multiplication in Larval Stages** (via Asexual replication).
    - **Are Parasites of Vertebrates** (Vertebrates = the 'definitive' hosts)
      - Localisation = Primarily in the Gut
      - Adults reproduce Sexually.

Suphylum Neodermata

Infraphylum Trematoda

Class Aspidogastrea

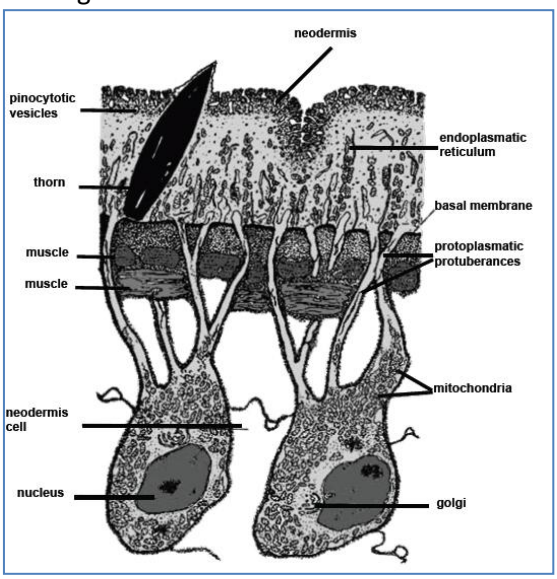
Class Digenea



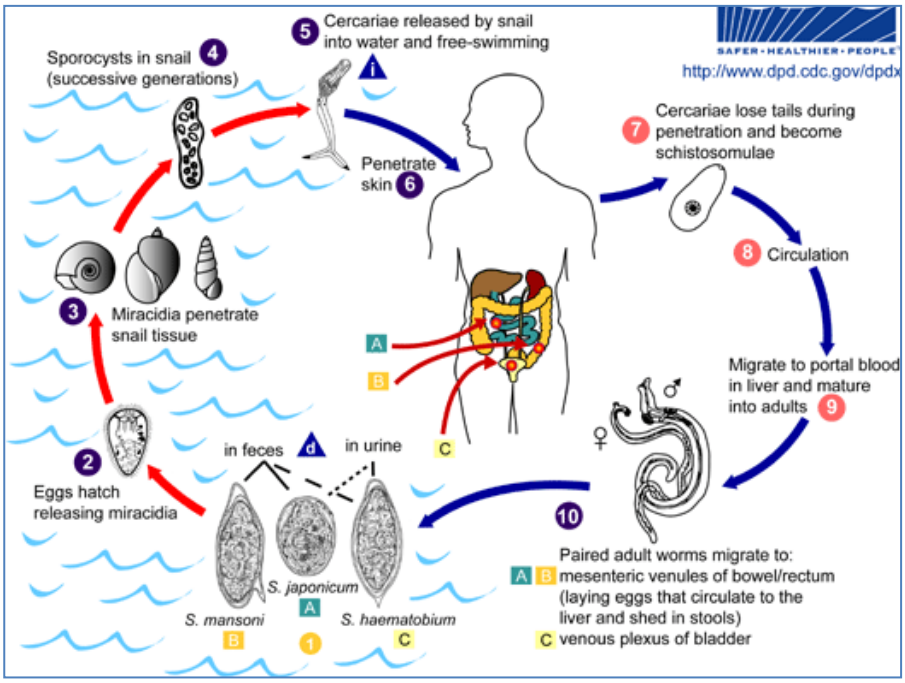
Our Focus = The Schistosoma Species – "Schistosomiasis":

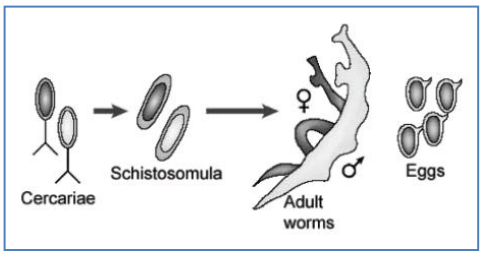
- **Epidemiology:**
  - The 2nd most Important Parasite Infection (After Malaria)
  - Most common in Tropics & Subtropics
  - Majority of patients are under 14yrs.

- **Surface of the Worms:**
  - **Double Layered Cell Membrane**
    - Outer membrane has High Lipid content (Poorly permeable)
    - Outer membrane can fuse with Host-Cell Membranes → Masking.
  - **Has *Thorns* –** For Anchorage.



- **Lifecycle:**
  - **NB: Cercariae are the larval stage that infects humans.**
  - **Penetration:**
    - Cercariae are attracted to hosts (in water) by a) Temperature; and b) Fatty-Acids from skin.
    - Epidermis is penetrated Mechanically.
    - Dermis is penetrated Chemically (By lytic enzymes from *'Acetabular Glands'*)
    - Cercariae Shed their tails.
    - Full Penetration/Invasion takes about ≈30mins.

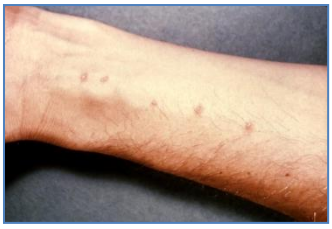
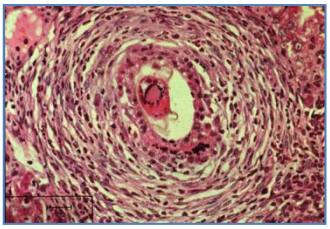




NB: Wild & Domestic Animals act as *Reservoir Hosts* for Schistosomiasis.

- **Interaction between Males & Females:**
  - Females depend on Permanent Association with males.
    - Females wrap around the males.
  - Germ-line Stem-Cells in the Female are stimulated to Proliferate/Differentiate by "Interaction" with male worm.

- **Symptoms:**
  - **Dermatitis** (@ Site of Cercariae Penetration)
  - **Pseudopapillomas** in the Colon → Obstruction/Bleeding.
  - **Granulomas** in the Liver → Destruction of Organ Tissue → Fibrosis.
    - NB: Can alter blood-flow in liver → Portal Hypertension:
      - → Hepatosplenomegaly)
      - → Ascites
      - →Varicose Veins in Stomach/Oesophagus. (Bleeding from these is most common cause of death)

- **Diagnosis:**
  - Parasite Eggs in Faeces/Urine.
  - Serological Tests (Eg. Immunoflourescence/ELISAs/etc)
  - Clinical Diagnosis
  - Ultrasound

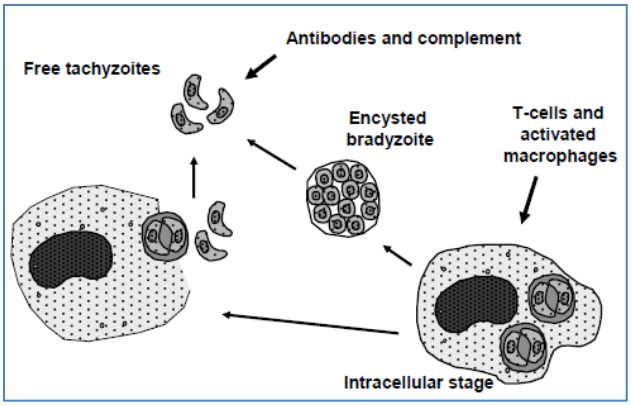
- **Treatment/Prevention:**
  - Treatment via Chemotherapy (MOA – Unknown)
  - (NB: Liver Damage cannot be reversed)
  - Supply of Cercaria-Free Water (Sewage plants/Hygiene/Education)

- **Vaccine Development:**
  - Chemotherapy treatment is impractical & doesn't confer lasting immunity.
  - Therefore, strong push for a Vaccine.
  - Recombinant Parasite Antigens = The basis for Vaccine Development. (But little progress so far)

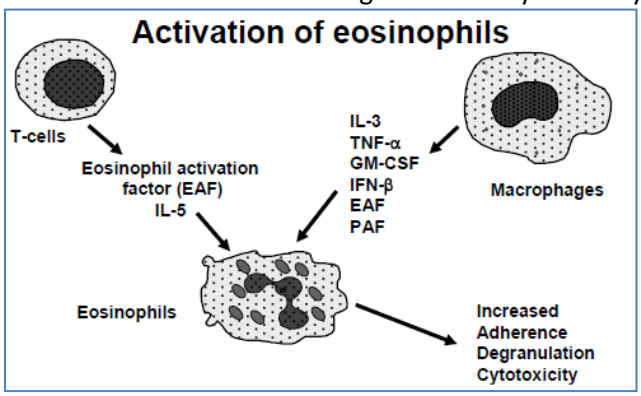
REVISION OF IMMUNITY

Immunity Against Parasites:

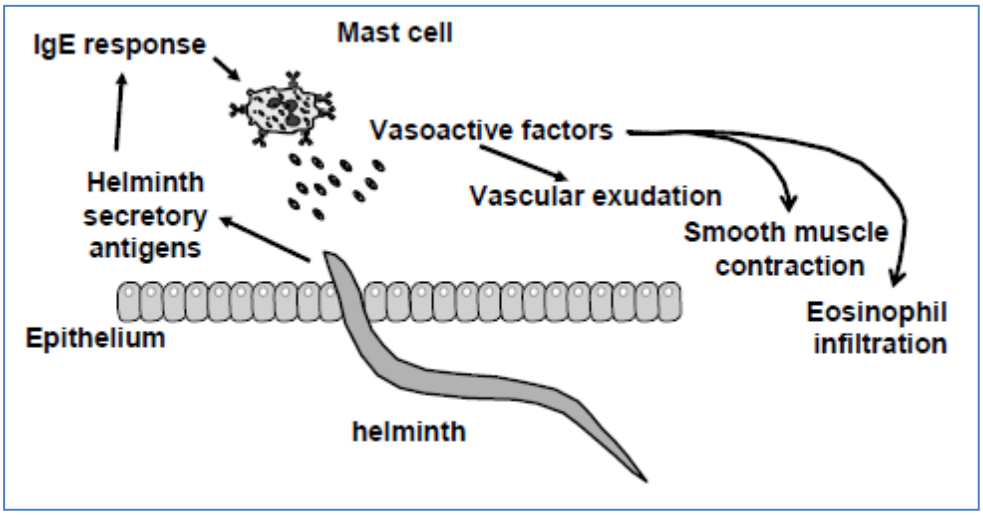
- **Innate Immunity:**
  - **Lysozyme:**
    - (in Tears/Saliva/Mucus/Neutrophils)
    - Some parasites are susceptible.
  - **Eosinophils (Eosinophil Granulocytes):**
    - Combat multicellular Parasites.
    - Degranulate → Release Reactive Oxygen Species → to kill parasites.
  - **Complement Activation:**
    - By Alternate Pathway – Complement Activation by Binding to Pathogen Surface
    - By MB-Lectin Pathway – Complement Activation by Binding to Lectin on Pathogen Surface.
    - (NB: Classical Pathway is Adaptive – Complement Activation by Ab's on Pathogen Surface)
  - **Phagocytes in Spleen:**
    - Infected RBCs express specific Parasite Antigens which are opsonised by antibody/complement → Recognised & Removed by Phagocytes in the Spleen.
- **Adaptive Immunity:**
  - **Antibodies (B-Cells):**
    - **Typically for Extracellular Infections (in blood/Tissues)**
    - **IgE** is the Major Isotype (Important in eliminating many helminth infections)
      - → (Hence, many infections are associated with **Type-1 Hypersensitivity** reactions.)
        - →Oedema, Asthma, Urticaria.
    - **- Can destroy Tachyzoites (young parasites) in blood.**
    - - Can neutralise *Proteases* used by parasites to enter tissues.
    - - Can block 'Anal Pores' of parasites.
    - - Can block enzyme pathways of some helminths (Can arrest egg production)
    - (NB: However, Many parasites are unaffected by antibodies)
  - **Complement Activation (By Classical Pathway):**
    - Complement Activation by Ab's on Pathogen Surface
    - - Can destroy Tachyzoites (young parasites) in blood.
  - **Cell-Mediated:**
    - **Typically for Intracellular Infections.**
    - **Th1-Cells Activate Macrophages:**
      - Macrophages become more Phagocytic and Destroy Intracellular Parasites.
      - (NB: Typically only Protazoan parasites are small enough to live intracellularly)
    - **Th2-Cells Help B-Cells produce Antibodies:**
      - (Th2 is the predominant response)
    - **Tc-Cells Destroy Infected Cells:**
      - May also directly destroy larvae.



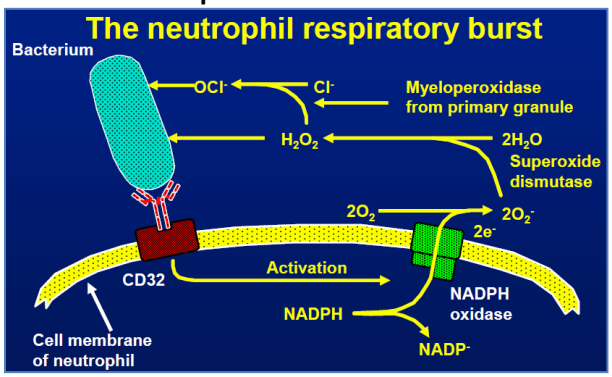
- **Eosinophils (In 'adaptive' due to dependence on Antibodies):**
  - **NB: They are the MAIN Effector Cell against Helminth Infections.**
  - **Activated by:**
    - Th-Cells (IL-5) & Macrophages (TNF-α, IFN-β, IL-3)
    - → Increased Adherence & Degranulation Cytotoxicity.



  - **Eosinophils have Fc receptors (Allow binding to Parasites covered with IgE-Antibodies)**
    - Binding of Antigen to Eosinophil-Bound-IgE → Degranulation.
    - **Similar to Mast Cells:**



  - **Release Granules onto the worm:**
    - ***Major Basic Protein** (Damages Cuticle of Helminths)
    - Eosinophil-Cationic Protein (A Ribonuclease – Toxic to Helminths)
    - Lysophospholipase
    - Phospholipase D
  - **Respiratory Burst:**
    - Superoxide
    - Chloride Ions
    - Hydrogen Peroxide
    - **Similar to Neutrophils:**



REVISION OF IMMUNE EVASION

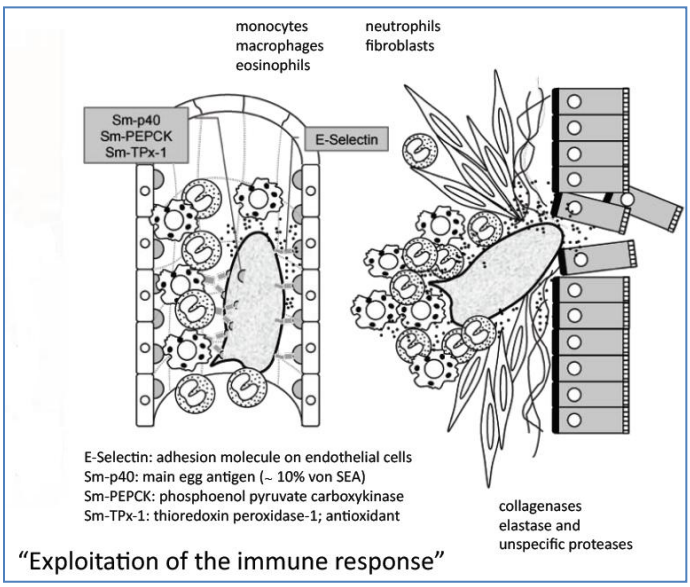
Immune Evasion by Parasites:

- **Resistance to Immune Effector Mechanisms:**
  - **Eg. Molecular Mimicry:**
    - **Eg. Expression of Host-Proteins:**
      - **Eg. Some Schistosomes** cover themselves with *Host Proteins* (Eg. Blood-Group Antigens & MHC products)
        - → **Avoids Recognition by Effector Immune Mechanisms**
  - **Eg. Protease Production to Neutralise Anti-Parasite Immune Components:**
    - **Eg. Shistosomula (Helminth)** Produces Proteases → Cleave Antibodies
      - They also Inhibit Macrophage Function.
    - **Host Proteases may be Inactivated by Protease Inhibitors.**

- **Immunosuppression or Inappropriate Immune Responses:**
  - **Eg. Helminths – Secrete Soluble Immunosuppressant Factors:**
    - **→Inhibit Lymphocyte Function.**
    - **→Inhibit Mast-Cell Degranulation.**

- **Sheltering in Immune-Privileged Sites:**
  - **Eg. RBCs:**
    - ***Plasmodium Falciparum* (Malaria) – lives inside RBCs which don't express MHC-I:**
      - → Can't be recognised by CD8-T-Cells.
      - → Are Shielded from Antibodies.
    - However, Infected RBCs *Can* be recognised/destroyed in the spleen:
      - To avoid this, Malaria Parasites cause the RBCs to become *Sticky* →
      - RBCs adhere to endothelium in peripheral organs.
      - (NB: Can lead to peripheral vasculopathies & ischaemic organ failure)

- **Exploiting The Immune System to Aid in Life-Cycle:**
  - **Eg. Some Helminths Exploit the Increased Expression of Cell-Adhesion-Molecules in Inflammation:**
    - **Eg. Helminths which lay eggs need to get the eggs out of the Blood Vessels.**
      - Therefore, by causing Inflammation, Endothelial Cells Increase CAM Expression.
      - → Eggs use these Adhesion Molecules to adhere to the Endothelium.
      - → They then secrete Collagenases/Elastases/Proteases → to Exit the Blood Vessel.



"Exploitation of the immune response"

Tropical & Indigenous Health Issues

Aims Of This Module

- **Describe: Appearance & Pathophysiology of the following Tropical Cutaneous Diseases:**
  - **Parasitic:**
    - Scabies
    - Pediculosis – (Lice)
    - Wandering Worms: Cutaneous Larval Migrans & Larva Currans
  - **Fungal:**
    - Tinea/Ringworm
  - **Bacterial:**
    - **Gram+ Cocci (Strep/Staph):**
      - Impetigo (Staph/Strep)
    - **Mycobacterium:**
      - Leprosy
      - Ulcers due to *Mycobacterium ulcerans*
    - **Other Bacteria:**
      - Tropical Phagedenic Ulcer
- **Describe Diagnosis.**
- Discuss the Epidemiology and Impact in rural and remote ATSI communities.
- Discuss the role of community based programs in the control of hyperendemic scabies and skin sores in rural Aboriginal and Islander communities.

Are Skin Diseases Different In The Tropics?

- **Infectious and Neoplastic Diseases are More Common:**
  - Particularly Fungal and Parasitic Diseases
  - but also Bacterial Diseases due to Gram Positive Cocci (Staph/Strep)
  - Higher Neoplastic Diseases due to higher doses of UV Radiation

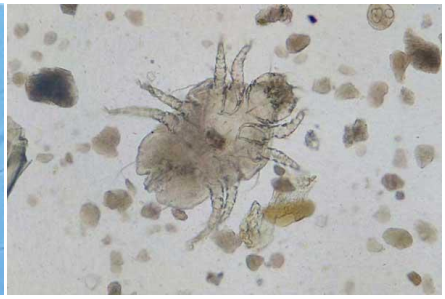
Diseases In This Presentation

- **Parasitic:**
  - Scabies
  - Pediculosis – (Lice)
  - Wandering Worms: Cutaneous Larval Migrans & Larva Currans
- **Fungal:**
  - Tinea/Ringworm
- **Bacterial:**
  - **Gram+ Cocci (Strep/Staph):**
    - Impetigo (Staph/Strep)
  - **Mycobacterium:**
    - Leprosy
    - Ulcers due to *Mycobacterium ulcerans*
  - **Other Bacteria:**
    - Tropical Phagedenic Ulcer

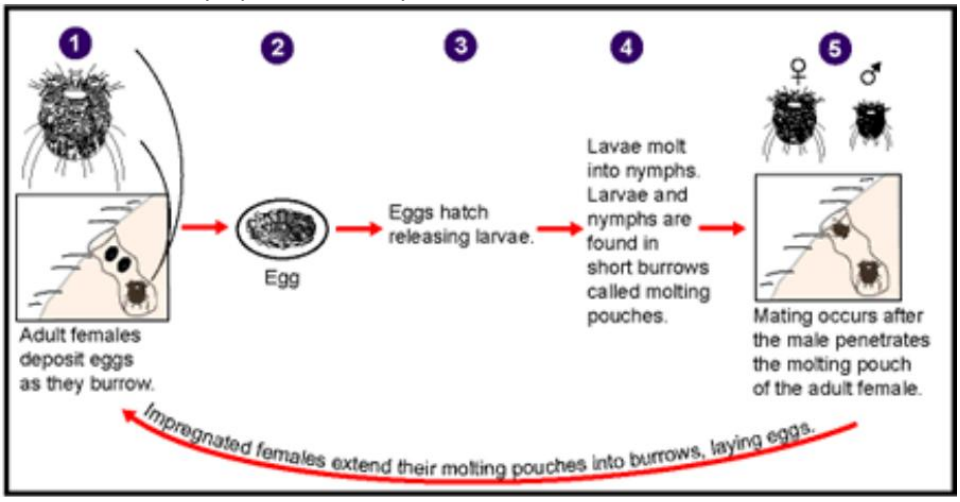
PARASITIC SKIN INFECTIONS:

SCABIES:

- **Organism:**
  - **The Mite: Sarcoptes Scabiei**

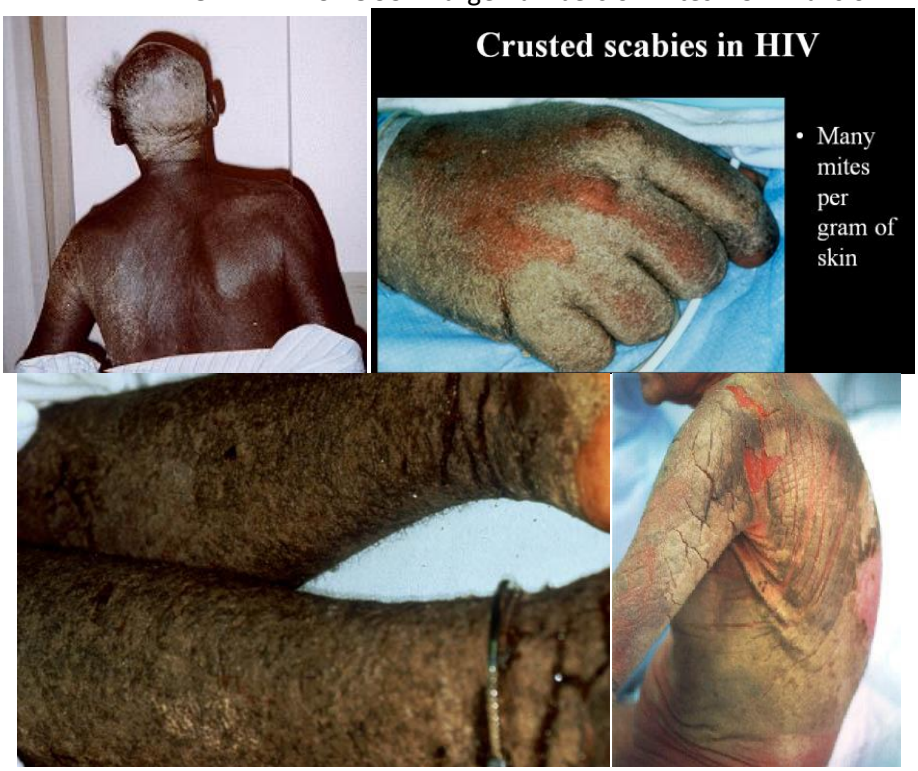
  - **Life Cycle**
    - Mites live in stratum corneum (Don't get any deeper)
    - Eat stratum corneal Keratinocytes
    - Make "tunnels" by eating
    - Female lays eggs
      - Eggs hatch in 3 days
      - Larvae moults 3 days
      - Nymphs x 2 x 3 days



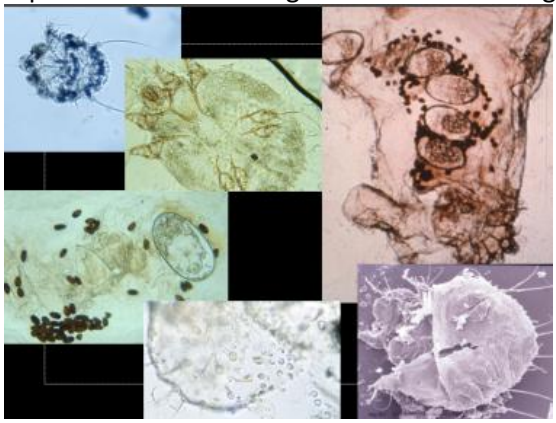
- **Epidemiology In Indigenous Communities?:**
  - High prevalence in children (50%) and adults (25%) in tropical remote communities
  - Secondary bacterial infection is very common - Streptococcus
  - Acute glomerulonephritis is a serious sequelae
- ***Secondary Problems*:**
  - **Bacterial Infection -** particularly common in rural ATSI communities
    - Streptococcus pyogenes
    - →Acute glomerulonephritis may follow GAStreptococcal infection
  - **Mental Health Issues:**
    - Psychoses, particularly depression, may be precipitated by persistent scabies
- **Diagnosis:**
  - **Clinical Diagnosis**
    - Chronic itch with Symmetrical Rassh
    - Burrows
  - **Skin Scrape, Bathe in KOH (10%) & Look for Scabies Mites.**
    - Intact larvae, nymphs or adults
    - Unhatched or hatched eggs
    - Moulted skins of mites
    - Fragments of moulted skins
    - Mite faeces

- **3 CLINICAL TYPES OF SCABIES:**
  - **1. Typical Scabies:**
    - **Pathogenesis:**
      - = Widespread Cutaneous Allergic Reaction (Hypersensitivity)
      - Why? The Allergic Component is a reaction to Mite *Saliva*, which penetrates into the dermis. (NB: Can also enter circulation → Generalised Reaction)
        - NB: Takes 1mth to become allergic to scabies.
    - **Presentation:**
      - Itch, Rash, Papules
      - Rarely - Blisters & Nodules
      - **NB: Inflammation doesn't always occur Near the Scabies Mites:**
        - Scabes Mites live ONLY in the *Stratum Corneum*
        - The Allergic Inflammatory Reaction is primarily in the *Dermis*
      - ***Look for symmetry*:**
        - Allergic lesions of scabies are distributed in a symmetrical pattern
        - Papules are the most common lesion in the tropics
        - "Burrows" are very rare in tropical cases

- **2. Crusted Scabies:**
  - **Pathogenesis:**
    - = More Severe Scabies
    - NOT an Allergic Response
    - :.There is NO protective Allergic Reaction → Severe Epidermal Hyperkeratosis
  - **Presetation:**
    - Hyperkeratosis (Buildup of Stratum Corneum)
      - + Mites
      - + Eggs
      - + Shed Skins, Mite Faeces
      - + Bacteria
    - HIGHLY INFECTIOUS – Large numbers of Mites + Skin falls off in large Flakes.



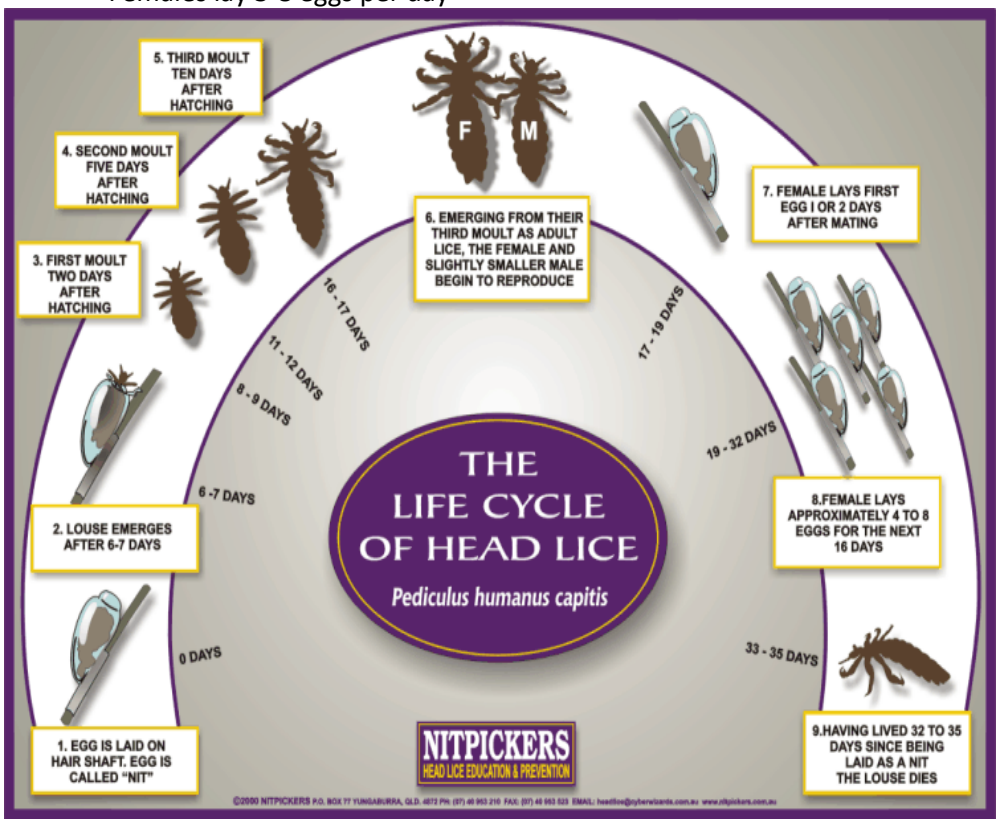
- **3. Transient Scabies (AKA: "Pseudoscabies"):**
  - **Pathophysiology:**
    - = Cutaneous Allergic Response, but mites do not become established
    - Occurs in people who are allergic to *Sarcoptes scabiei*
    - Mite burrows into skin – BUT does not survive
      - → Spontaneous Resolution
  - **Examples:**
    - Nurses in nursing homes – itch goes away at weekends
    - People in contact with dogs with scabies – itch goes when dog is cured



- **<u>Treatment:</u>**
  - **Topical**
    - Benzyl Benzoate (NB: Can't be applied to the face)
    - Permethrin
  - **or Oral Ivermectin.** (The best)
    - NB: Not Registered in Australia (Not on the PBS - :. Very Expensive)
    - Cost – Hampers effective treatment in poor families.
  - (NB: Always treat the head)
  - **Environmental Measures:**
    - Mites can contaminate bedding, chairs, floors, and even walls
      - (Usually only a problem with crusted scabies)
    - Wash, sun, vacuum, surface insecticide
  - **Community Prevention:**
    - Treat all close contacts – Esp. in Indigenous Communities
    - Simultaneous Effective Treatment
  - ***TREAT AGAIN IN 7 DAYS***

PARASITIC LICE - PEDICULOSIS:

- **Organism:**
  - ***Pediculus Humanus***
- **Life-Cycle:**
  - Egg ("Nit") laid close to scalp on Hair Shaft
    - Egg hatches in 7 days → Louse Emerges
  - 3 Nymphs (Moults)
  - Adult is mature after 3rd Moult (10 days after hatching)
    - Mating of Males & Females (Females are Bigger)
    - Adult lives 30 days
    - Females lay 3-8 eggs per day

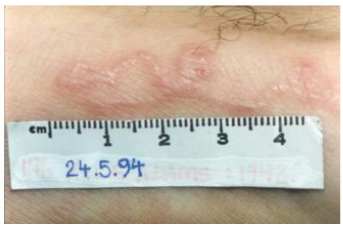


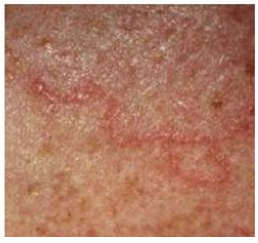
- **3 Types:**
  - **1. Head Lice: *Pediculus Humanus Capitis***
    - **Epidemiology:**
      - Common in Primary School Children in the Tropics
      - Higher prevalence in Aboriginal Children
    - **Diagnosis:**
      - Conditioner + Fine-Tooth Come
      - Wipe combings on white tissue paper
  - **2. Body Lice: *Pediculus Humanus Corporis***
    - Live on clothes, and come to the body to feed.
  - **3. Pubic Lice: *Phthirus Pubis***
    - Largely sexually transmitted
    - Blood Feeder
    - Can infect any Body Hair (Pubic/Trunk/Legs/Axilla/Beard) but rarely head.
- **Diagnosis:**
  - Do not rely on itching & scratching
  - Use Strong Light and Look for Eggs on Hair Sharfts.
  - **Best Method = *'Conditioner & Comb Technique'*:**
    - Very Practical for parents
    - Cost Effective
    - High Sensitivity
    - Conditioner 'Stuns' the lice by suffocating them → Prevents them from running away

- **<u>Management/Treatment:</u>**
  - Conditioner & Nit Comb
  - Physical Removal
  - Cut Hair
  - Topical Insecticidal Cream
  - Good idea to wash pillows and hats though – Hot Wash
  - (Treat all body hair – for Pubic lice)
  - **Reasons for Treatment Failure:**
    - Inadequate application of the product
    - Lice are resistant to insecticide
    - Failure to retreat to kill nymphs emerged from eggs
    - Reinfection.

SKIN LESIONS CAUSED BY WANDERING WORMS:

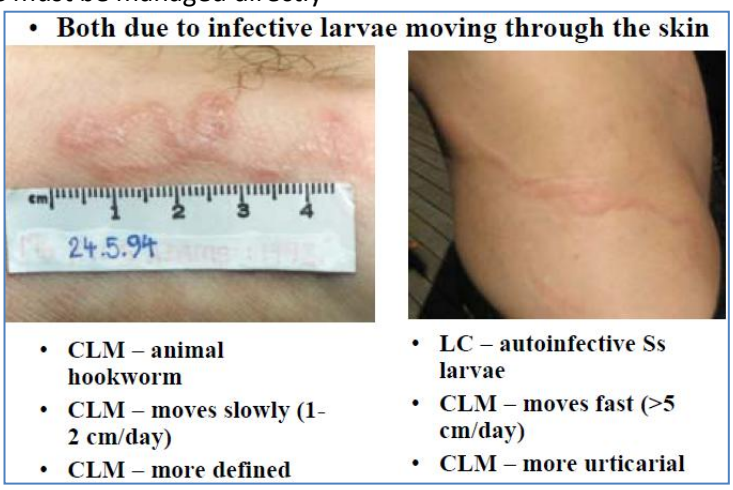
- **Cutaneous Larval Migrans (CML):**
  - **Organism:**
    - Infective larvae of ***Hookworms***
    - →penetrate the skin and wander aimlessly until they die
  - **Presentation:**
    - →***Well-Defined*** Serpigenous, Inflammed tract appears
      - Itchy, moves slowly
      - Lasts about 6 weeks
  - **Treatment:**
    - Spontaneous Resolution
    - Can be treated with Ivermectin.





- **Larva Currens (LC):**
  - **Organism:**
    - Autoinfective larvae of ***Strongyloides Stercoralis*** **(Threadworm)**
    - Normally lives in the small intestine.
  - **Pathogenesis:**
    - Autoinfective larvae invade the body (from the intestines), wander randomly and sometimes come up to the skin
  - **Presentation:**
    - →***Urticarial*** Red line that moves rapidly (>5 cm/day)

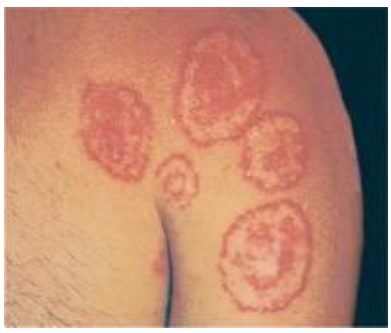
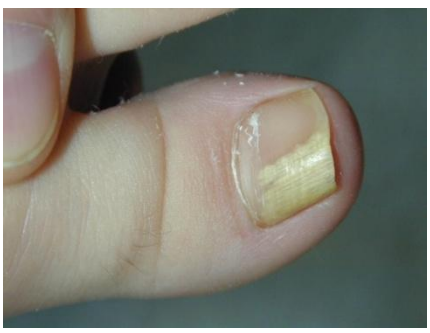
- **Differentiating Between CLM Vs Larva Currens (LC):**
  - **NB: Both Have different implications**
    - CML will resolve itself
    - LC must be managed directly

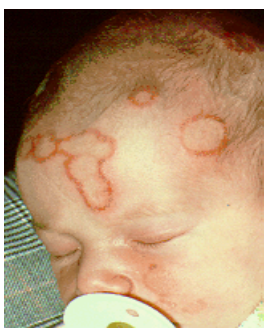


FUNGAL SKIN INFECTIONS:

DERMATOPHYTOSIS - "Ringworm"/"Tinea":

- **Organism:**
  - **3 Genera Are Important:**
    - *Trichophyton*
    - *Microsporum*
      - NB: Microsporum Canis – (From Dogs/other animals)
      - NB: Flourescent under Wood's Lamp
    - *Epidermophyton*
- **Pathogenesis:**
  - **Fungi ONLY Metabolizes Keratin:**
    - :. Only infect the Stratum Corneum
    - NB: Can Also Invade Hair Shafts
- **Epidemiology:**
  - Common In Rural Indigenous Populations
- **Conditions Named Based On Location of Infection:**
  - Tinea Corporis (On Body)
  - Tinea Capitis (On Head)
  - Tinea Crura (Pubic Area)
- **Symptoms:**
  - Well Circumscribed lesions with central clearing.
  - Focal hair loss due to infection of Hair Follicle.
  - Focal pityriasis (Skin Flaking)
  - Usually not pruritic
  - Can infect any keratinised structure
  - Nail infections can be severe
  - "Tinea Versicolor" (Depigmentation of the Skin)
  - "Tinea Imbricata/Concentricum" (As the ringworm grows, it produces concentric silvery rings)
    - Caused by Trichophyton Concentricum
- **Diagnosis Of Dermatophytosis:**
  - Clinical Diagnosis
  - Woods lamp – only *Microsporum canis* fluoresces
  - Microscopy of hairs/nail shavings/skin shavings
  - Culture for dermatophyte on Sabouraud's agar
- **Treatment**:
  - **Topical Antifungals:**
    - Clotrimazole
    - Miconazole
    - Econazole
    - Tolnaftate
    - Terbinafine
  - **Oral Antifungals:**
    - Griseofulvin for 4 weeks
    - Itraconozole
    - Fluconazole
    - Terbinafine



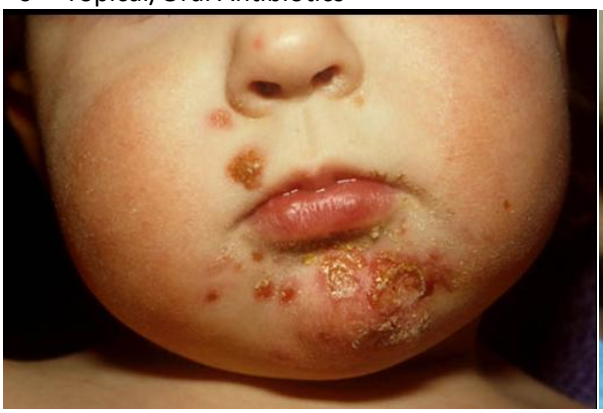
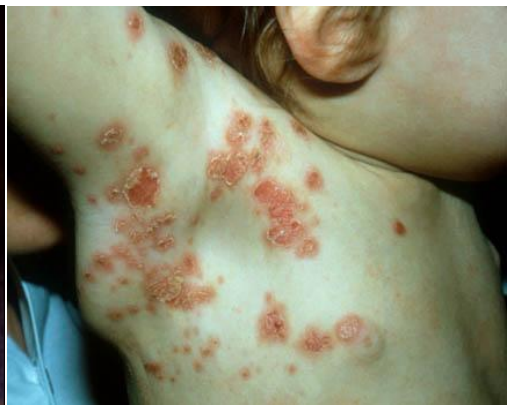
BACTERIAL SKIN INFECTIONS:

GRAM POSITIVE COCCI IN TROPICAL INDIGENOUS COMMUNITIES:

- **Gram Positive Cocci – *Streptococcus* & *Staphylococcus***
- **Streptococcal Diseases**
  - *Infection – **impetigo**, invasive disease*
  - *Autoimmune – **acute glomerulonephritis, rheumatic fever** and **rheumatic heart disease***
- **Staphylococcal Diseases**
  - Infection – **impetigo**, **abscesses**, invasive disease
  - Toxin diseases – scalded skin syndrome, **toxic shock**, gastroenteritis
  - **Emergence of drug resistant *Staphyloccus Aureus* (MRSA)**
    - Particularly in rural Indigenous Communities

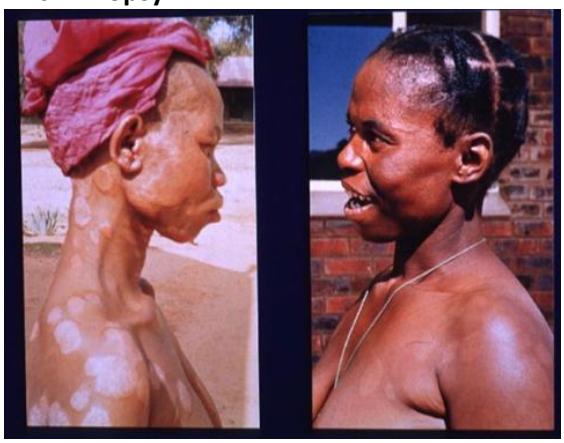
IMPETIGO – "SCHOOL SORES":

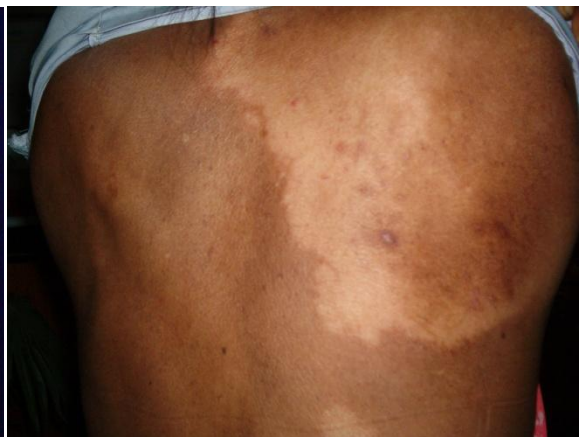
- **Organism/s:**
  - *Streptococcus pyogenes* or *Staphyloccocus aureus*
- **Transmission:**
  - VERY Contagious
  - Direct Contact with Lesions
  - Scratching Spreads Lesions
- **Presentation:**
  - Thin-Walled Vesicles → Rupture →Honey-Coloured Crusted Lesions
  - Erythematous
  - Well Demarcated
  - Flu-Like Symptoms (Fatigue, Myalgia, Headaches, Vomiting)
- **Treatment:**
  - Antiseptic
  - Topical/Oral Antibiotics

LEPROSY:

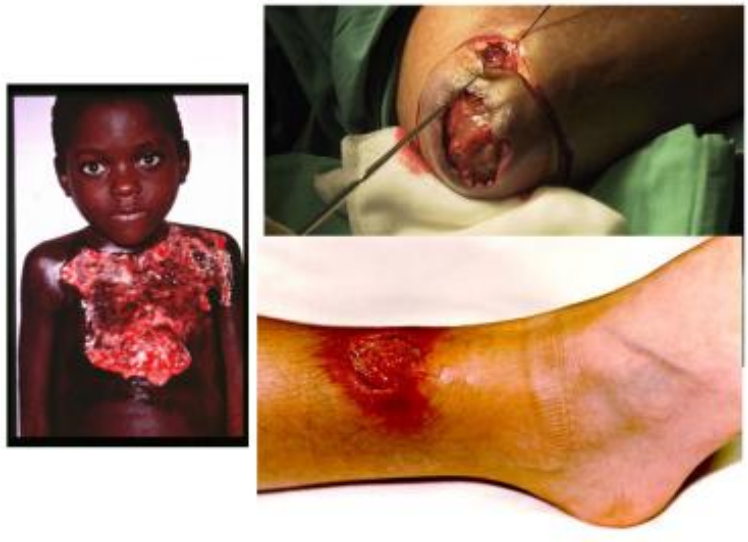
- **Organism:**
  - *Mycobacterium leprae*
- **Pathogenesis:**
  - Chronic disease of skin and nerves
- **Presentation:**
  - Some skin lesions of leprosy can look like dermatophytosis
  - Decreased sensation and no sweating
  - Lesions can be:
    - Depigmented or Reddish/Copper-coloured
    - flat or raised
    - do not itch/hurt
    - Can appear anywhere.
- **Differential Diagnoses:**
  - Birthmark
  - Vitiligo
  - Contact Dermatitis
  - Lichenoid Dermatitis
  - Tinea Versicolor
- **Diagnosis Of Leprosy:**
  - **Clinical**
    - Skin lesions
    - Thickening of cutaneous nerves
    - Loss of sensation
  - **Split Skin Smears**
    - Acid fast bacilli (AFB)
  - **Biopsy**





MYCOBACTERIUM ULCERANS:

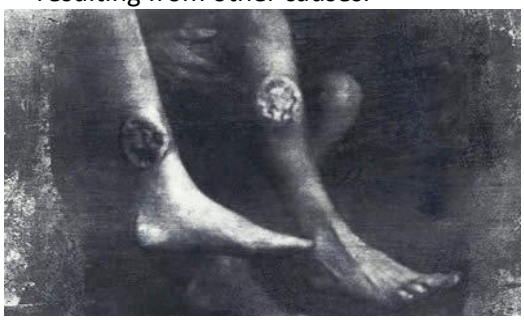
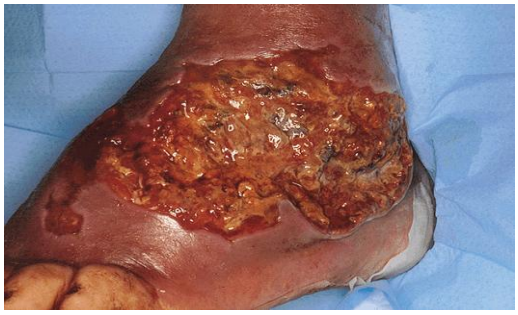
- **Organism:**
  - *Mycobacterium ulcerans*
- **Epidemiology:**
  - Occurs in Mossman / Cooktown area
- **Pathophysiology:**
  - Chronic ulcerative disease of skin and subcutaneous tissue (Buruli ulcer)
  - Probably starts from minor trauma
- **Presentation:**
  - Ulcers are always much smaller in area than subcutaneous infection underlying them
  - Usually not painful



- **Diagnosis:**
  - Clinical
  - Swab for AFB, culture and PCR
  - Skin biopsy
- **Treatment:**
  - Surgical resection
  - Intravenous amikacin + oral rifampicin + oral clarithromycin or azithromycin
  - Local heat

TROPICAL ULCER:

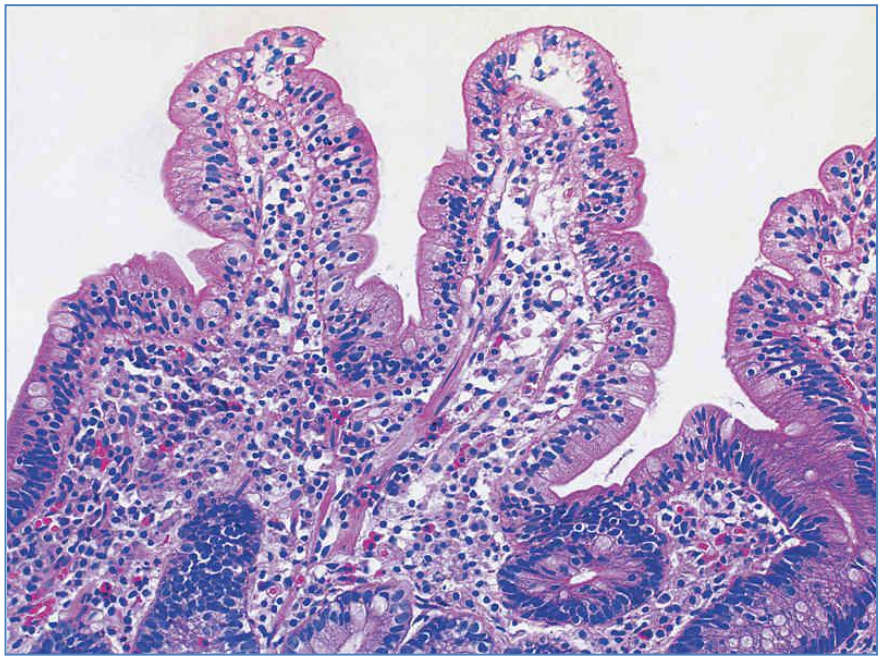
- **Organisms:**
  - Fusiform bacilli and Spirochaetes
- **Pathophysiology:**
  - Specific acute ulcerative skin disease limited to tropical and subtropical regions
  - **Can follow minor trauma**
    - Manage coral cuts effectively
    - Manage minor wounds
- **Presentation:**
  - Characteristic slough containing, in its early stages, numerous fusiform bacilli and spirochaetes.
  - Rapidly growing
  - Usually on leg
  - May develop into a chronic non-specific ulcer which is indistinguishable from indolent ulceration resulting from other causes.

- **Diagnosis:**
  - Clinical
  - Culture
    - *Fusobacterium*
    - Mixed bacteria
  - Biopsy
    - *Fusobacterium*
    - No mycobacteria
- **Treatment:**
  - Antibiotics – systemic and broad-spectrum including metronidazole
  - Rest

INFECTIOUS DISEASE HEALTH Pathology:
TROPICAL SPRUE

- **Tropical Sprue**
  - = "Severe Malabsorption, Accompanied by Diarrhoea & Malnutrition"
  - **Aetiology:**
    - Infective – But Unknown Agent.
  - **Pathogenesis:**
  - **Morphology:**
    - *Partial* Villous Atrophy *Throughout the Whole SI*
      - (As opposed to Coeliac Disease → Total Villous Atrophy in Proximal SI)
    - Inflammatory Infiltrate
  - **Clinical Features:**
    - **Epidemiology:**
      - Residents/Visitors of Affected Tropical Areas (Asia, Caribbean, S.America)
    - **Symptoms:**
      - **Chronic Diarrhoea + Malabsorption
      - Anorexia, Weight Loss
      - Abdo Distension
    - **Diagnosis:**
      - Exclude Acute Infective Diarrhoeas – esp. *Giardia*
      - Demonstrate Malabsorption – esp. *Fat & VitB12*
      - Jejunal Mucosal Biopsy – Partial Villous Atrophy *Throughout the Whole SI.*
    - **Treatment:**
      - Fluid Resuscitation (if Severe)
      - VitB12 & Folate Supplements
      - Long-Course Antibiotics (6mths Tetracycline)
    - **Prognosis:**
      - Excellent
      - Mortality only due to Dehydration/Electrolyte Depletion.

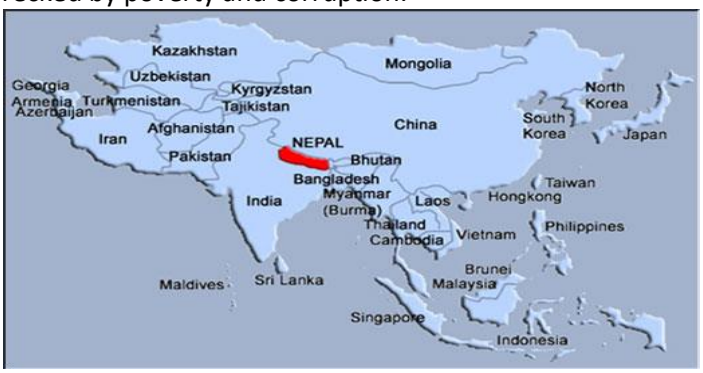


NB: Inflammatory Infiltrate & Villous Blunting

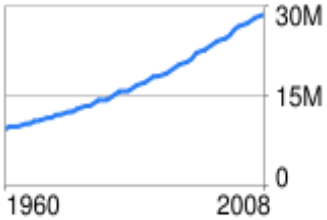
International Health Notes
TB in Nepal

Overview of Nepal:

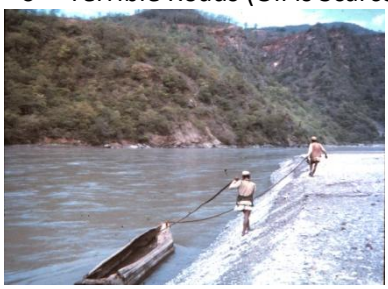
- Sandwiched between Chinese Tibet and India
- Beautiful country wrecked by poverty and corruption.



- **4th poorest country**
- **POPULATION CRISIS:**
  - Early marriage
  - poor contraception
  - high fertility (5.4)
  - male preponderance



- **Poverty:**
  - Poor food security
  - Poor housing standards
  - Poor communication
  - Corruption effect on service delivery
- **Poor Transport:**
  - **Walking
  - No River or Sea Ports
  - No Motor Boats
  - No Railways
  - Terrible Roads (Oil is Scarce)



- **Geology:**
  - Monsoons
  - (Tectonic Plate) Seizmic Activity
  - Landslides
  - Floods

Learning objectives – (With Respect to Nepal):

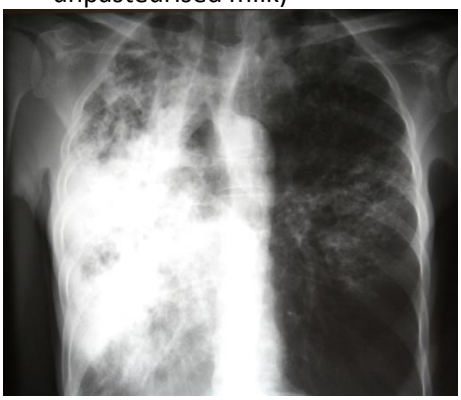
- Understand pathological and clinical parameters of Tuberculosis
- Understand social determinants of Tuberculosis
    - Identity the impacts of Tuberculosis on the lives of the poor
- Identify the MDG specific to TB
- Understand the DOTS and DOTS Plus systems of management of Tuberculosis in regions of high prevalence
- Understand the part played by WHO, National TB organization, and NGOs in TB control

Millennium Development Goals.

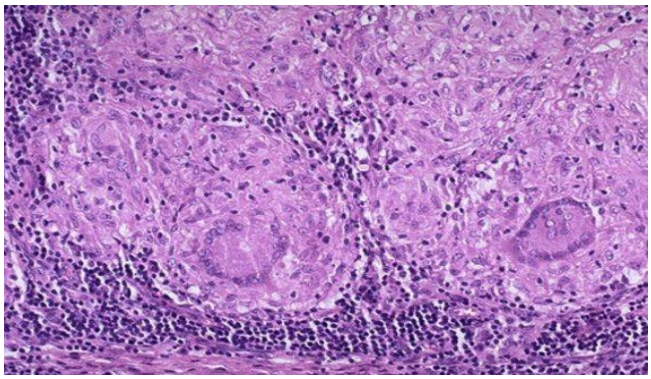
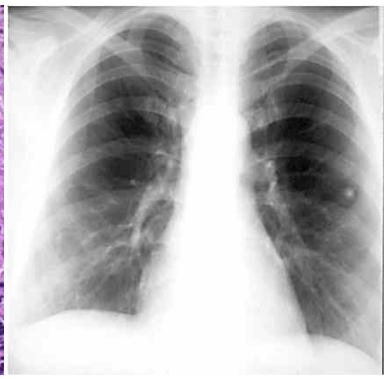
- For tackling extreme poverty
- Goal N0 6- Combat HIV/AIDS malaria and other diseases (including TB)

TUBERCULOSIS IN NEPAL:

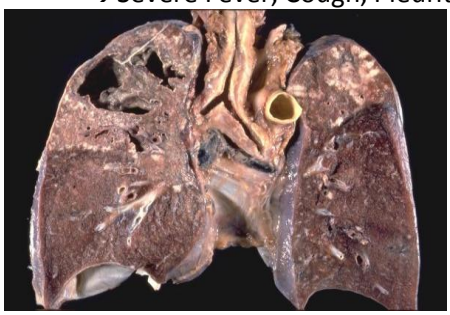
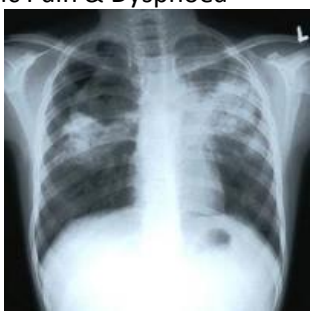
- **Tuberculosis:**
    - **Organism:**
        - A Mycobacterium
        - Requires a Ziehl Nielsen Acid-Fast Stain
        - Found in many animals (Eg. Cattle - Bovine TB - Common in children after consuming unpasteurised milk)



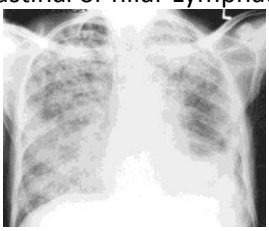

    - **Epidemiology:**
        - TB Accounts for 99% of the Deaths
    - **Histology:**
        - Tuberculosis follicle consists of central ***Caseous Necrosis***
        - Surrounded by lymphocytes, ***multi-nucleate giant cells*** and epitheloid macrophages
        - Organisms may be identified within the macrophages
        - **"Gohn Focus" (Gohn Complex):**
            - a sub-pleural lesion
            - in an immunocompetent individual
            - usually occurs in an upper region of the lung

- **Types of TB:**
  - **Pulmonary TB →:**
    - Cavitation
    - Caseation
    - Consolidation
    - May cause Pleurisy with Pleural Effusion
    - →Severe Fever, Cough, Pleuritic Pain & Dyspnoea

  - **Pulmonary TB in AIDs:**
    - The immune system is no longer able to mount a granulomatous reaction
    - →Diffuse, patchy transbronchial spread without definite granuloma formation
    - may be mediastinal or hilar Lymphadenopathy

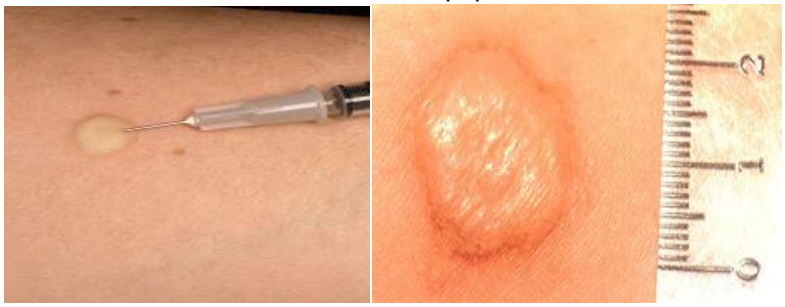


  - **Extrapulmonary TB:**
    - **Tuberculous Spondylitis:**
      - Systemic symptoms are often absent. Initial symptoms include back pain and stiffness.
      - Disease progression may lead to leg weakness or paraplegia.
      - Anterior wedging of two adjacent vertebrae with destruction of the intervening disc causes a tender prominence of the spine (gibbus).
    - **Peripheral osteoarticular TB**
      - Pain in affected bone or joint, with swelling and restricted movements of the involved joint. and (Arjun,) ****
      - Bone marrow involvement may cause pancytopenia.
    - **Tuberculous meningitis**
      - Initially presents with fatigue, malaise, intermittent headaches and low-grade fever.
      - Progresses over a few weeks to cause headaches, altered mental state and vomiting, and then to meningism. Focal neurological signs due to involvement of cranial nerves and vasculitis.
      - Tuberculous meningitis may present with sudden severe meningitis progressing rapidly to coma and death.
    - **Scrofula,**
      - Mesenteric lymphadenitis
      - Tuberculous abdominal lymphadenopathy is common in HIV-positive patients
      - May present with fever, abdominal pain and gastrointestinal (GI) obstruction. A mass may be palpable.
    - **Renal TB**
      - May present with dysuria, pyuria, haematuria, urinary frequency, and back and loin pain.

- **Gastrointestinal TB:**
  - after swallowing of respiratory secretions
  - or drinking of unpasteurised milk (M. bovis)
  - Oral TB may cause non-healing ulcers of the mouth or tongue
  - **May present with:**
    - dysphagia
    - massive haematemesis
    - abdominal pain
    - anorexia
    - diarrhea
    - obstruction
    - haemorrhage
    - a palpable mass.
- **TB Peritonitis:**
  - Fever, weight loss and anorexia, with abdominal pain and swelling (ascites).
- **Pericardial TB:**
  - **Non-specific symptoms:**
    - Fever
    - weight loss
    - night sweats
  - **Local Symptoms:**
    - Cough
    - Dyspnoea
    - Orthopnoea
    - ankle swelling
    - chest pain.
    - Cardiac tamponade
    - cardiac constriction
- **TB Otitis:**
  - Hearing loss
  - Painless discharge.
  - May present as facial nerve palsy
- **Genital TB**
  - More common in women and may present with menstrual irregularity, abdominal pain and infertility. Ectopic pregnancies

- **Disseminated Miliary TB:**
  - Presentation usually non-specific with fever, anorexia, weight loss, night sweats and weakness
  - pulmonary involvement
  - altered mental state, meningismus
  - wasting
  - hepatosplenomegaly
  - lymphadenopathy

- **Diagnosis:**
  - **Chest X-Rays**
  - **Sputum Microscopy**
  - **Biopsy**
  - **Skin tests (Mantoux & Heaf):**
    - Delayed hypersensitivity reaction used to diagnose tuberculosis
    - **In the Mantoux test** 0.1 ml of purified protein derivative is injected intradermally
      - Positive reaction is a papule of > 5 mm diameter at 72 hours



    - **In the Heaf test** purified protein derivative is placed on the skin
      - A gun is used to produce multiple punctures
      - Positive reaction is more than 4 papules at puncture sites at 72 hours
    - **Positive skin test =**
      - Active infection
      - or previous BCG vaccination

- **Social determinants**
  - Poverty , War, Civil strife
  - Malnutrition, poor housing, unemployment
  - Female gender inequality
  - Poor housing sputum/droplet close contact
  - Poor nutrition
  - Long working hours
  - Unable to access treatment due to distance, transport, money, time off work.
  - No free Hospitals

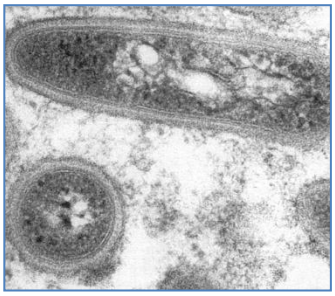
- **Prevention Strategy: "DOTS" (Directly Observed Treatment Short-Course):**
  - **1. Sustained political and financial commitment.**
    - TB can be cured and the epidemic reversed if adequate resources and administrative support for TB control are provided.
  - **2. Diagnosis by quality ensured sputum-smear microscopy.**
    - Chest symptomatics examined this way helps to reliably find infectious patients.
  - **3. Standardized short-course anti-TB treatment (SCC) given under direct and supportive observation (DOT).**
    - Helps to ensure the right drugs are taken at the right time for the full duration of treatment.
  - **4. A regular, uninterrupted supply of high quality anti-TB drugs.**
    - Ensures that a credible national TB programme does not have to turn anyone away.
    - **Anti-Mycobacterial Drugs:**
      - *Rifampicin
      - Isoniazid
      - Pyrazinamide
      - Ethambutol
    - (4 for 2 months, or 2 for 4 months)
  - **5. Standardized recording and reporting**
    - Helps to keep track of each individual patient and to monitor overall programme performance.

- **ROLE OF NGO'S IN TB CONTROL:**
  - 1 Providing TB treatment services
  - 2 Supporting Existing Health Services for TB Control
  - 3 Educating community about TB treatment
  - 4 Providing Community-based Care
  - 5 Advocating for and mobilizing enhanced TB control effort
  - 6 Conducting and supporting operational research ...

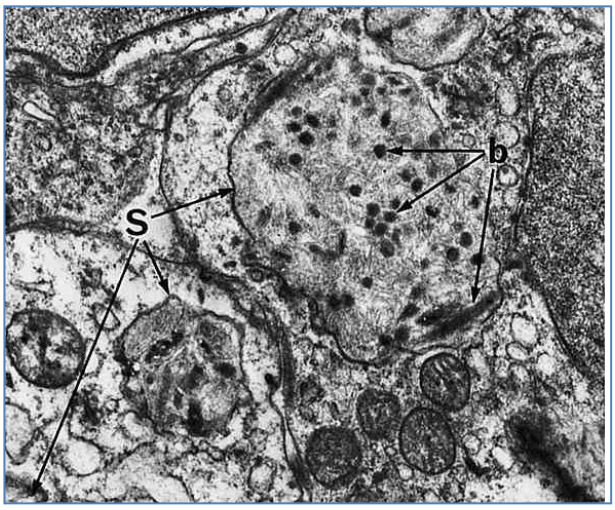
- **Impact on the economy:**
  - Costs of care.
  - Drugs, contact tracing, clinics and hospitals
  - Costs of lost work.
  - Low output, time off
  - Costs of support of families and orphans
  - Costs of prevention, BCG of babies etc

INFECTIOUS DISEASE HEALTH Pathology:
WHIPPLES DISEASE

- **Whipples**
  - **Aetiology:**
    - Chronic Infection with Bacterium: ***Tropheryma Whipplei***
  - **Pathogenesis:**
    - *Tropheryma Whipplei* is a Relative of Mycobacteria → :. Intracellular (in Macrophages)
    - Systemic Infection → Systemic Disease
  - **Morphology:**
    - Endoscopy – Pale, Shaggy Duodenal Mucosa + Eroded, Red Friable Patches
    - **Biopsy – Characteristic 3-Layered Cell Wall of *T.whipplei Within Foamy Macrophages.*
  - **Clinical Features:**
    - **Symptoms/Signs:**
      - Initially – Arthritis & Arthralgia (but in Middle Aged)
      - Progression to – Weight Loss, Diarrhoea, Abdo Pain, Fever
      - Involvement of – Lymphnodes, Heart, Lung, Joints & Brain (Neuro Symptoms)
    - **Investigations:**
      - Blood Tests – Features of Chronic Inflammation & Malabsorption
      - Endoscopy – Pale, Shaggy Duodenal Mucosa + Eroded, Red Friable Patches
      - **Biopsy – Characteristic 3-Layered Cell Wall of *T.whipplei Within Macrophages.*
      - Immunohistochemistry - *T.whipplei* Antibodies
      - PCR
    - **Treatment:**
      - Long-Course Antibiotics that Cross the BBB – Eg. Trimethoprim or Co-Trimoxazole
    - **Prognosis:**
      - Fatal if untreated.



Electron Micrograph showing the Tri-Laminar Cell Wall of *Trophyrema.whipplei*



NB: S = Spherical Sacs inside Macrophages containing B= Dense Rod-Shaped Bodies (Bacteria).

Continue Reading For Bonus Supplementary Study Materials…

PH

Population Health and Epidemiology

Catherine R. L. Brown, chapter editor
Lindsey Chapman and **Meghna Rajaprakash,** associate editors
Shany Gertzbein, EBM editor
Dr. Allison Chris and **Dr. Katherine Bingham,** staff editors

For more detail on topics covered in this chapter, use this website as a resource: http://phprimer.afmc.ca/

Acronyms

AR	attributable risk
CAS	Children's Aid Society
CBA	cost benefit analysis
CEA	cost effectiveness analysis
CFR	case fatality rate
CPHO	Chief Public Health Officer
DALY	disability adjusted life years
EBM	evidence based medicine
HC	Health Canada
FP	false positives
FN	false negatives
IMR	infant mortality ratio
ITT	intention to treat analysis
LICO	low income cut-off
LR	likelihood ratio
MHO	Medical Health Officer
MOH	Medical Officer of Health
MMR	maternal mortality ratio
MSDS	Material Safety Data Sheets
NNH	number needed to harm
NNT	number needed to treat
NPV	negative predictive value
OR	odds ratio
PHAC	Public Health Agency of Canada
PP	per protocol analysis
PPV	positive predictive value
PYLL	potential years of life lost
QALY	quality adjusted life years
QI	quality improvement
RCT	randomized controlled trial
RR	relative risk
SMR	standardized mortality ratio
SN	sensitivity
SP	specificity
TP	true positives
TN	true negatives
WHMIS	Workplace Hazardous Materials Information System
WHO	World Health Organization
WSIB	Workplace Safety and Insurance Board

Public Health Context

- see Ethical, Legal, and Organizational Medicine, ELOAM2 *Overview of Canadian Healthcare System* for the organization of health care in Canada including the legal foundation and historical context

Definitions

- **population health**
  - health of the population as measured by health status indicators (e.g. life expectancy, low birth weight rates)
  - influenced by: physical, biological, social, environmental, and economic factors; personal health behaviours; health care services
  - refers to the prevailing or desired level of health in the population of a specific country/region/subset of population
  - considered to be more complex than the aggregate health status of individuals within a population
- **public health**
  - organized collective efforts of society to protect, promote, and restore the health of the public and prevent illness, injury, and premature death
  - refers to the practices, programs, policies, institutions, and disciplines required to achieve the desired state of population health
- **epidemiology**
  - study of the distribution and determinants of health-related states or events in a specified populations
  - application of this study to the control of health problems
- **public health and preventive medicine** (formerly called community medicine)
  - the postgraduate study of health and disease in the population or a specified community
  - five-year Royal College specialty training
  - goal: to identify and address health problems and evaluate the extent to which health services and others address these issues (see http://www.royalcollege.ca for more information)

Preparing for the LMCC
The AFMC Primer on Population Health is the core text for the LMCC and is available as an online resource on the AFMC website (http://phprimer.afmc.ca)
For the LMCC exam, it is recommended that you also read Chapter 15 in Shah CP. Public health and preventive medicine in Canada, 5th ed. Toronto: Elsevier, 2003

Historical Perspective
Over the last century, Public Health has evolved through three main epidemiological phases:
- **Infectious diseases:** controlled in the more developed world but an issue in less developed countries (e.g. polio, malaria)
- **Chronic diseases:** chronic diseases and other noncommunicable conditions have increased morbidity and mortality (e.g. heart disease and cancer due to risk factors and/or exposures)
- **Re-emerging infectious diseases:** new or re-emergent infections emerge due to unfamiliar or new pathogens, inefficient or inappropriate antibiotic use, travel, and global warming (e.g. HIV, drug resistant TB and malaria)

Public Health Services in Canada

Mission: to promote and protect the health of Canadians, and reduce health inequities through leadership, partnership, innovation, and action in public health

- local public health units and services within regional health authorities (in most provinces except Ontario, where local public health units are either autonomous or within local government) provide programs and activities for health protection, promotion, and disease prevention at local and regional levels
- catchment-area populations range from hundreds to thousands of people, covering areas of 15 km^2 to 1.5 million km^2
- the "core functions" of public health include six essential activities:
  1. **health protection**: ensure safe water, air, and food; advise on food and drug safety regulations; maintain regulatory framework for control of infectious diseases and protection from environmental threats
  2. **health surveillance**: using routinely collected health data to monitor and predict health events or determinants
  3. **disease and injury prevention**: reduce risk of infectious disease by investigation, partner notification, and development of preventative and control measures such as immunization programs; reduce preventable illness and injuries by promoting safe, healthy lifestyles
  4. **population health assessment**: understand the health of communities/specific population to produce better policies and services
  5. **health promotion**: maintain and improve health through public policy, community-based interventions, active public participation, and advocacy
  6. **emergency preparedness and response**: planning for natural (e.g. floods, earthquakes) and man-made (e.g. radioactive substances) threats

CPHO of Canada
- Responsible for the PHAC and reports to the Minister of Health
- As the federal government's lead public health professional, provides advice to the Minister of Health and Government of Canada on health issues
- Collaborates with other governments, jurisdictions, agencies, organizations, and countries on health matters
- Communicates public health information to health professionals, stakeholders, and the public
- In an emergency, such as an outbreak or natural disaster, provides direction to PHAC staff, including medical professionals, scientists, and epidemiologists, as they plan and respond to the emergency

Source: Public Health Agency of Canada. http://www.phac-aspc.gc.ca/cpho-acsp/cpho-acsp-role-eng.php

Legislation and Public Health in Canada

Table 1. Legislation and Public Health in Canada

Federal	Provincial	Municipal (Ontario)

• Health Canada
  • Provides health services to First Nations, Aboriginal peoples, the Canadian military, and veterans
  • Approves new drugs and medical devices
• Canadian Food Inspection Agency
  • Monitors food products
  • Deals with animal-related infections
  • Regulates food labeling
• Public Health Agency of Canada (main Government of Canada agency responsible for public health)
  • An independent body created to strengthen public health capacity
  • Focuses on preventing chronic diseases, preventing injuries, and responding to public health emergencies and infectious disease outbreaks
  • Oversees immigration screening, protects Canadian borders (e.g. airport health inspection)
  • Liaises with the World Health Organization (WHO) on global health issues
	• Legislation is in the form of Acts and Regulations
	• Each province has its own Public Health Act or equivalent (e.g. the *Health Protection and Promotion Act* in Ontario)
	  • Designates the creation of geographic areas for the provision of public health services
	  • Gives powers to the Chief Medical Officer of Health to control public health hazards
	  • Specifies infectious diseases to be reported to public health units by physicians, laboratories, and hospitals (see *Appendix*, PH25)
	  • Has the ability to mandate programs that address public health issues, environmental health, and chronic disease prevention
		• Local boards of health deliver programs mandated by provincial and municipal or regional legislation
		• Boards of health are responsible for the delivery of most public health services, such as:
		  • Infectious disease control, including the follow-up of reported diseases and management of outbreaks
		  • Inspection of food premises including those in hospitals, nursing homes, and restaurants
		  • Family health services including pre-conception, preschool, school-aged, and adult health programs
		  • Tobacco control legislation enforcement
		  • Assessment and management of local environmental health risks
		  • Collection and dissemination of local health status reports
		  • Public dental health services to children
		• By-laws may be approved by municipal governments to facilitate public health issues

Medical Officer of Health (MOH) (Ontario)
- May be called "Medical Health Officer" (MHO) in other provinces
- Appointed to each public health unit by the board of health
- Held by a licensed physician with public health training
- Responsibilities include:
  - Collection and analysis of epidemiological data
  - Occupational and environmental health surveillance
  - Implementation of health programs, including:
    - Counseling
    - Family planning services
    - Parenting programs, prenatal courses
    - Preschool and school health services
    - Disease screening programs
    - Tobacco use prevention programs
    - Nutrition services to schools and seniors' centres
- The Medical Officer of Health can require an individual/premise/agency to take or refrain from any action due to a public health hazard

Determinants of Health

Concepts of Health

- **wellness**: state of dynamic physical, mental, social, and spiritual well-being that enables a person to achieve full potential and have an enjoyable life
- **disease:** abnormal, medically-defined changes in the structure or function of the human body
- **illness:** an individual's experience or subjective perception of a lack of physical or mental well-being and consequent inability to function normally in social roles
- **illness behaviour:** an individual's actions in response to their illness, including whether they seek health care and whether they comply with the subsequent recommendations
- **sickness:** socially and culturally held conceptions of health conditions that may influence how the patient reacts
- **impairment:** any loss or abnormality of psychological, physiological, or anatomical structure or function
- **disability:** any restriction or lack of ability to perform an activity within the range considered normal for a human being
- **handicap:** the disadvantage for an individual arising due to impairment and disability
  - limits or prevents the fulfillment of an individual's normal role as determined by society and depends on age, sex, social, and cultural factors
  - changes the individual's relationship with the physical and social environment
- **health equity:** when all people have "the opportunity to *attain their full health potential*" and no one is "disadvantaged from achieving this potential because of their social position or other socially determined circumstance." Differs from health equality. Health inequities are those which are considered unjust and/or avoidable
- **health equality:** defined as where populations have equal or similar health status. Health inequalities are systematic differences in health status that occur among population groups

Determinants of Health

- 1974: the Honourable Marc Lalonde, federal Minister of Health, presented the health field concept entitled *A New Perspective on the Health of Canadians* which included four areas that interact to determine health: human biology, environment, lifestyle, and health care. This concept has been expanded to include numerous determinants of health

Definitions of Health
- First multidimensional definition of health, as defined by the WHO in 1948: "state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"
- WHO updated the definition (socio-ecological definition) of health in 1986: "The ability to identify and to realize aspirations, to satisfy needs, and to change or cope with the environment. Health is therefore a resource for everyday life, not the objective of living. Health is a positive concept emphasizing social and personal resources, as well as physical capacities" (Ottawa Charter for Health Promotion)
- Other definitions of health have since been proposed that incorporate other dimensions of health (e.g. "Health is a social, economic, and political issue and above all a fundamental human right" – The People's Charter for Health)

Determinants of Health
- Income and social status
- Social support networks
- Education and literacy
- Employment and working conditions
- Social and work environments
- Physical environment
- Personal health practices and coping skills
- Healthy child development
- Biology, genetics, and epigenetics
- Health services
- Gender
- Culture

Source: Public Health Agency of Canada

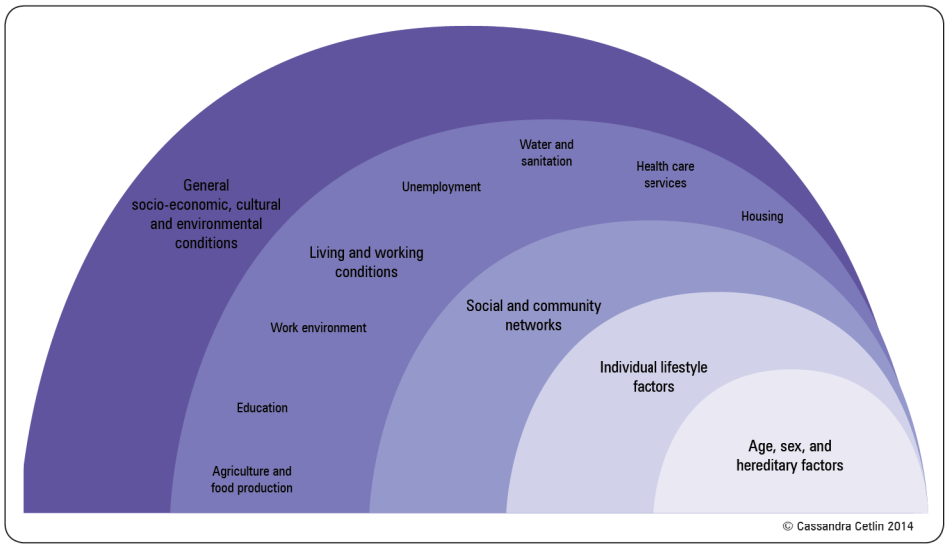


Figure 1. Population health model
Adapted from Dahlgreen G, Whitehead M. European strategies for tackling social inequities in health: Leveling up Part 2. World Health Organization, 2006.

Vulnerable Populations

Table 2. Health Determinants of Vulnerable Populations

	Definition	Psychosocial/ Socioeconomic	Physical Environment	Individual Behaviour	Population-Specific Interventions
Aboriginal Peoples	Four specific groups: First Nations Status Indians (registered under the *Indian Act*), non-Status Indians, Métis, and Inuit	Low income Family violence Low education status Unemployment Homelessness Longer length of disability	Crowded housing Inefficient ventilation Environmental toxins (botulism) TB declining but prevalence higher than rest of population	Smoking Substance misuse Excessive gambling Poor nutrition Sedentary lifestyle High BMI Higher risk of suicide	Mental health awareness Aboriginal-specific DM initiatives Substance abuse treatment programs
Isolated Seniors	Individuals >65 yr	Elder abuse Lack of emotional support Isolation	Low hazard tolerance Institutionalization Mobility issues	Inactivity Polypharmacy Medical comorbidities	Aging in place of choice Falls and injury prevention Mental health promotion Preventing abuse and neglect
Children in Poverty	Based on Low Income Cut Offs (LICO) LICO is an income threshold below which a family will likely devote a larger share of its income on the necessities of food, shelter and clothing than the average family	Low income Family dysfunction Lack of educational opportunities	Housing availability Unsafe housing Lack of recreational space	Poor supervision Food insecurity High risk behaviours	Improvements in family income most significant Early childhood education
People with Disabilities	Includes impairments, activity limitations, and participation restrictions	Low income Low education status Discrimination Stigma	Institutionalization Barriers to access Transportation challenges	Substance misuse Poor nutrition Inactivity Dependency for ADLs	Transportation support Multidisciplinary care Unique support for individuals with specific disabilities (e.g. Trisomy 21)
New Immigrants	Person born outside of Canada who has been granted the right to live in Canada permanently by immigration authorities	Access to community services Cultural perspectives (including reliance on alternative health practices)	Exposure to diseases and conditions in country of origin (e.g. smoke from wood fires, incidence of TB, etc.)	Employment, ESL Healthy Newcomer Effect (health worsens over time to match that of the general population) Cultural or religious expectations	Women's health Mental health Infectious diseases (syphilis blood test, CXR, HIV) Dental and vision screening Vaccinations Cancer screening

Social Determinants: Indigenous People's Health in Canada
- **Colonization:** subjugation of Indigenous peoples by the Europeans, leading to the loss of lands, cultural practices, and self-government
- **Residential schools:** placement of children from Indigenous groups in church-run, government-funded schools for the purpose of assimilation, resulting in loss of identity, alienation, and abuse, with long-lasting consequences of higher rates of addictions, abusive relationships, and suicide
- **Treaties and Land Claims:** inadequate services for those living on reserves leading to poverty and poor quality infrastructure, reflected in disproportionate burden of infectious diseases (e.g. pertussis, Chlamydia, hepatitis, shigellosis)
- **Traditional Approach to Healing:** restoring balance in the four realms of spiritual, emotional, mental and physical health of a person acting as an individual, as well as a member of a family, community and nation
  - Ideas represented by medicine wheel of First Nations peoples, the Learning Blanket of Inuit peoples, and the Metis tree model of Holistic Lifelong Learning
  - Contrast to Western medicine focus of treating illness, leading to challenges for practitioners of Western medicine to meet Aboriginal patients' needs
  - National Aboriginal Health Organization (NAHO) offers 8 guidelines on practicing culturally safe health care for Aboriginal patients including need to allow Aboriginal patients access to ceremony, song, and prayer; the need for information and for family support; guidelines for the appropriate disposal of body parts and for handling death

New Immigrants to Canada
- Mandatory medical exams on entry to Canada by a designated medical practitioner:
  - Complete medical examination for all persons of all ages
  - Chest x-ray and report for persons 11 yr of age and over
  - Urinalysis for persons 5 yr of age and over
  - Syphilis serology for persons 15 yr of age and over
  - HIV testing for applicants 15 yr of age and over, as well as for those children who have received blood or blood products, have a known HIV-positive mother, or have an identified risk. An ELISA HIV screening test should be done for HIV 1 and HIV 2
  - Serum creatinine if the applicant has hypertension (resting blood pressure greater than 140/90 mmHg), a history of treated hypertension, DM, autoimmune disorder, persistent proteinuria, or kidney disorder

Citizenship and Immigration Canada Handbook.http://www.cic.gc.ca

Table 2. Health Determinants of Vulnerable Populations (continued)

	Definition	Psychosocial/ Socioeconomic	Physical Environment	Individual Behaviour	Population-Specific Interventions
Homeless Persons	An individual who lacks permanent housing	Low income Food insecurity Mental illness	Exposure to temperature extremes Infections such as West Nile Virus	Substance misuse Violence	Safe housing Addictions support Mental health
Refugee Health	Forced to flee country of origin because of a well-founded fear of persecution and given protection by the Government of Canada *Refugee claimant:* Arrive in Canada and ask to be considered refugee	Post-traumatic stress disorders Depression Adjustment problems Partial health coverage via Interim Federal Health Program	Diseases and conditions in country of origin (e.g. malaria, TB, onchocerciasis, etc.) Direct and indirect effects of war	Employment ESL Longstanding prior lack of access to health care (chronically neglected problems) Cultural or religious expectations	Vaccinations Women's health Mental health Infectious diseases Dental and vision screening Political advocacy

Note: this chart delineates the major challenges faced by each group, but the issues listed are not unique to each population

Disease Prevention

Natural History of Disease

- course of a disease from onset to resolution
  1. pathological onset
  2. presymptomatic stage: from onset to first appearance of symptoms/signs
  3. clinically manifest disease: may regress spontaneously, be subject to remissions and relapses, or progress to death

Disease Prevention Strategies

- measures aimed at preventing the occurrence, interrupting through early detection and treatment, or slowing the progression of disease/mitigating the sequelae

Table 3. Levels of Disease Prevention

Level of Prevention	Goal	Sample Strategies
Primary	Protect health and prevent disease onset	Immunization programs (e.g. measles, diphtheria, pertussis, tetanus, polio, see Pediatrics, P3) Smoking Cessation Seatbelt use
Secondary	Early detection of disease to minimize morbidity and mortality	Mammography Routine Pap smears
Tertiary	Treatment and rehabilitation of disease to prevent progression and permanent disability	DM monitoring with HbA1c, eye exams, foot exams Medication

Passive prevention, measures that operate without the person's active involvement (e.g. airbags in cars) are more effective than active prevention, measures that a person must do on their own (e.g. wearing a seatbelt)

Example of Primary Prevention
Gardasil Vaccine and Its Efficacy in the Prevention of Cervical Cancer
Gardasil® is a quadrivalent HPV vaccine covering strains 6,11,16,18. The efficacy of Gardasil® was studied in 4 randomized, double-blind, placebo controlled trials on females between 16 and 26 yr of age and was found to prevent nearly 100% of precancerous cervical changes for up to 4 yr after vaccination

Screening (Secondary Prevention)

- presumptive identification (not diagnosis) of unrecognized disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly
- **types of screening**
  - mass screening: screening all members of a population for a disease (e.g. phenylketonuria (PKU) and hypothyroidism in all newborns)
  - selective screening: screening of a specific subgroup of the population at risk for a disease (e.g. mammography in women >50 yr old)
  - multiphasic screening: the use of many measurements and investigations to look for many disease entities (e.g. periodic health exam)
- **bias in screening**
  - **lead-time:** time between early diagnosis with screening, and when diagnosis would have been made without screening
  - **lead-time bias:** over-estimation of survival when the estimate is made from the time of screening, instead of the later time when the disease would have been diagnosed without screening
  - **length-time bias:** overestimation of the survival time due to the sampling of prevalent as opposed to incident cases
    - selection of prevalent cases will favour the over-inclusion of longer-living cases rather than newly-diagnosed incident cases, some of whom may have short survival times

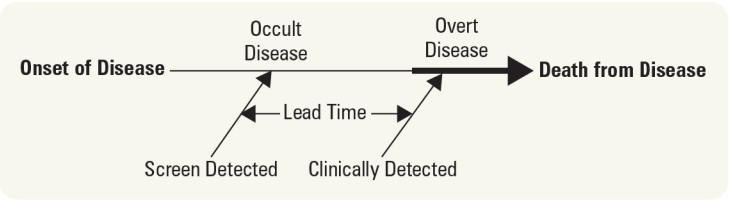


Figure 2. Lead-time bias

Table 4. Ideal Criteria for Screening Tests

Disease	Test	Health Care System
Causes significant suffering and/or death Natural history must be understood Must have an asymptomatic stage that can be detected by a test Early detection and intervention must result in improved outcomes Incidence is not too high or too low	High specificity and sensitivity Safe, rapid, easy, relatively inexpensive Acceptable to providers and to population	Adequate capacity for reporting, follow-up, and treatment of positive screens Cost effective Sustainable program Clear policy guidelines

Ottawa Charter for Health Promotion (1986)

- Health promotion: the process of enabling people to increase control over and improve their health
- The charter states that governments and health care providers should be involved in a health promotion process that includes:
  1. Building healthy public policy
  2. Creating supportive environments
  3. Strengthening community action
  4. Developing personal skills
  5. Re-orienting health services

Health Promotion Strategies

Table 5. Disease Prevention vs. Health Promotion Approach

Disease Prevention	Health Promotion
Health = absence of disease	Health = positive and multidimensional concept
Medical model (passive role)	Participatory model of health
Aimed mainly at high-risk groups in the population	Aimed at the population in its total environment
One-shot strategy, aimed at a specific pathology	Diverse and complementary strategies aimed at a network of issues/determinants
Directive and persuasive strategies enforced in target groups	Facilitating and enabling approaches by incentives offered to the population
Focused mostly on individuals and groups of subjects	Focused on a person's health status and environment
Led by professional groups from health disciplines	Led by non-professional organizations, civic groups, local, municipal, regional, and national governments

Source: Shah CP. Public Health and Preventive Medicine in Canada, 5th ed. Toronto: Elsevier, 2003

Example of Harm Reduction Strategy
Summary of Findings from the Evaluation of a Pilot Medically Supervised Safer Injecting Facility
CMAJ 2006;175:1399-1404
Background: This study discusses the outcomes among a population of illicit injection drug users (IDUs) after initiating a supervised safe injecting facility in Vancouver, September 2003. Legal exemption by the Canadian government was granted such that an evaluation of its results be conducted over a 3 yr period.
Study Population: IDUs of the Vancouver area were allowed to inject previously obtained illicit drugs under the supervision of nurses and physicians. IDUs were offered addiction counseling and supports for appropriate community resources. A random sample of 670 IDUs was recruited and monitored from Dec 2003-July 2004.
Results: Characteristics of IDUs who used the safe injecting facility included age <30 yr, history of public drug use, homelessness, daily heroin and/or cocaine injection, and recent history of overdose. Mean measures of public order problems were taken 6 wk before and 12 wk after initiation of the safer injection facility. It was found that the mean number of IDUs injecting daily in public, along with the mean number of publically discarded syringes were reduced by approximately half.
Conclusions: Overall it has been found that the safer injecting facility in Vancouver has been successful in attracting IDUs at increased risk of HIV, overdose, and public injection of substances. This has resulted in lower incidences of public drug use, publicly discarded syringes and sharing of needles. Other studies associated with this one have demonstrated that there has been no increase in the drug dealing, drug related crimes, or rates of new IDUs in the area surrounding the safer injecting facility.

Healthy Public Policy

- characterized by an explicit concern for health and equity in all areas of policy and by an accountability for health impact
- main aim: to create a supportive environment to enable people to lead healthy lives, thereby making healthy choices easier for citizens
- government sectors must take into account health as an essential factor when formulating policy and should be accountable for the health consequences of their policy decisions
- methods
  - fiscal: imposing additional costs (e.g. taxes on tobacco and alcohol)
  - legislative: implementing legal deterrents (e.g. smoking bans, legal alcohol drinking age)
  - social: improving health beyond providing universally funded health care (e.g. providing affordable housing)

Source: International Conference on Health Promotion, Adelaide, South Australia (1998)

Behaviour Change

- health education serves to
  - increase knowledge and skills
  - encourage positive behaviour changes and discourage unhealthy choices
- health education is an important component of eliciting behaviour change
- behaviour is a result of three factors
  1. predisposing factors: knowledge, attitude, beliefs, values, intentions
  2. enabling factors: skills, supports
  3. reinforcing factors: health care professionals and the social context of family and community
- **Health Belief Model** (1975)
  - behaviours undertaken by individuals in order to remain healthy are a function of a set of interacting beliefs
  - beliefs include an individual's perception of his or her susceptibility to a disease, the severity of the disease, and the benefits and costs of health-related actions
  - beliefs are modified by socio-demographic and psychosocial variables

- individuals must believe that the action will have positive consequences
- individuals must be in a state of readiness
- behaviour can be stimulated by cues to action, which are specific events that can encourage preventive health decisions and actions (e.g. physician recommendation, public advertising)

- **Stages of Change Model**
  - provides a framework in which the Health Belief Model is applied to facilitating behaviour change (e.g. quitting smoking)

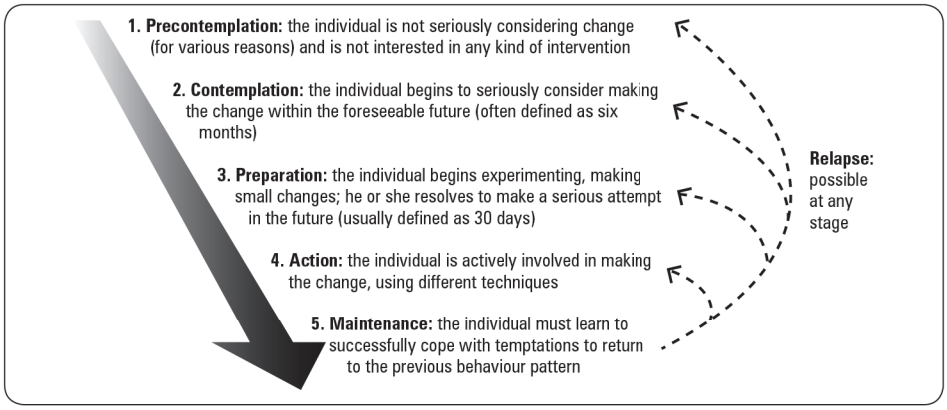


Figure 3. Stages of change model
Source: Prochaska JO, DiClemente CC, and Norcross JC. In Search of How People Change. Applications to Addictive Behaviours. Am Psychol 1992;47:1102-1114

Risk Reduction Strategies
- **risk reduction:** lower the risk to health without eliminating it (e.g. avoiding sun to lower risk of skin cancer)
- **harm reduction:** tolerance of some degree of risk behaviour, while aiming to minimize the adverse outcomes associated with these behaviours (e.g. needle exchange programs)

Measurements of Health and Disease in a Population

MEASURES OF DISEASE RATES

Incidence Rate
- number of new cases in a population over a defined period of time

Prevalence
- *total number* of cases in a population over a defined period of time
- two forms of prevalence
  - **point prevalence:** attempts to measure the frequency of all disease at one specific point in time, therefore knowledge of the time of onset of disease is not required
  - **period prevalence:** measure constructed from prevalence at a point in time, plus new cases and recurrences over a defined period of time
- depends on **incidence rate** and disease duration from onset to termination (cure or death)
- favours the inclusion of chronic over acute cases and may be used to present a biased picture of the disease
- prevalence studies are cross-sectional and cannot be used for causal inferences
- prevalence figures are useful for determining the extent of a disease and can aid in the rational planning of facilities and services

Age Standardized Rate
- adjustment of the crude rate of a health-related event using a "standard" population
- standard population is one with a known number of persons in each age and sex group
- standardization prevents bias which could be made by comparing crude rates from two dissimilar populations (e.g. crude death rates over a number of decades are not comparable as the population age distribution has changed with time)

MEASURES OF MORTALITY

Life Expectancy
- the expected number of years that an individual will live based on standardized death rates for the population
- usually qualified by country, gender, and age

Incidence and Prevalence

$$\text{Incidence} = \frac{\#\text{ of new cases in a time interval}}{\text{total population at risk}}$$
(measures the rate of new infections)

$$\text{Prevalence} = \frac{\#\text{ of existing cases at a point in time}}{\text{total population at risk}}$$
(measures the frequency of disease at a point in time)

e.g. For Canada in 2011:
HIV incidence rate is 9.5 per 100,000 people
HIV prevalence is 213 per 100,000 people

Top 5 Causes of Mortality in Canada, 2012, by Sex

Female
- Cancer
- Heart disease
- Stroke
- COPD/chronic lower respiratory disease
- Alzheimer's

Male
- Cancer
- Heart disease
- Accidents
- Stroke
- COPD/chronic lower respiratory disease

Source: Statistics Canada. *CANSIM*, 2012. Table 102-0561 and 102-0562 and catalogue no.84-215-X

Principles of Standardization
- When comparing an outcome (e.g. mortality) in two populations that differ in terms of characteristics known to influence that outcome (e.g. age), standardization is used to control for the effect of that factor
- **Standardization is either direct or indirect**
  - **Indirect standardization** is expressed as standardized outcome ratio. For example, Standardized Mortality Ratio (SMR) is calculated using age specific rates for a reference population, as well as age structure and total cases for a sample/known population. (e.g. an SMR of 100 signifies that deaths are at the expected level, a SMR of 110 indicates a death rate 10% higher than expected)
  - **Direct standardization** is expressed as a rate. (i.e. using age specific rates in a known/sample population against a standard population)

Crude Death Rate
- mortality rate from all causes of death per 1,000 in the population

Infant Mortality Rate (IMR)
- number of deaths among children under 1 yr of age reported during a given time period divided by the number of live births reported during the same time period and expressed per 1,000 live births per year

Maternal Mortality Rate (MMR)
- number of deaths of women during pregnancy and due to puerperal causes per 100,000 live births per year

Standardized Mortality Rate (SMR)
- the ratio of the observed (actual) number of deaths to the expected number of deaths for a group (e.g. age, race, gender, etc.)
- useful for comparing populations that are significantly different in some aspect (e.g. the causes of death in more and less developed countries)

MEASURES OF DISEASE BURDEN

Potential Years of Life Lost (PYLL)
- calculated for a population using the difference between the actual age at death and a standard/expected age at death
- increased weighting of mortality at a younger age

Disability Adjusted Life Year (DALY)
- quantitative indicator of the burden of diseases that reflects the total amount of disability-free life years lost
- includes loss from premature mortality and loss due to a degree of disability over a specific period of time; these disabilities can be physical or mental

Quality Adjusted Life Year (QALY)
- a value from 0 to 1 assigned to a year of life based on perceived quality of life; a yr in "perfect" health is considered equal to 1 QALY, the value of a year in ill health would be lowered based on the burden of disease
- it is possible to have "states worse than death" for example QALY <0 for extremely serious conditions

For additional rate calculations see *Outbreak of Infectious Diseases*, PH19

Consult the Public Health Agency of Canada for examples and latest statistics
http://www.phac-aspc.gc.ca/cphorsphc-respcacsp/2008/fr-rc/cphorsphc-respcacsp06b-eng.php

Epidemiology

Population
- a collection of individuals who share a common trait (most commonly applied to a geographic area but it could be another factor such as ethnic group)

Sample
- a selection of individuals from a population or set of observations
- types
  - random: all are equally likely to be selected
  - systematic: an algorithm is used to select a subset
  - stratified: separate representations of more than one subgroup
  - cluster: grouped in space/time to reduce costs
  - convenience: non-random inclusion, usually volunteers

Sample Size
- sample size contributes to the statistical precision of the observed estimate
- increasing the sample size decreases the probability of type I and type II errors (see *Data Analysis*, PH14)

Bias

- non-random error leading to a deviation of inferences or results from the truth
- any trend in the collection, analysis, interpretation, publication, or review of data that can lead to conclusions that are systematically different from the truth
  - **sampling bias:** occurs with the selection of a sample that does not truly represent the population
    - sampling procedures should be chosen to prevent or minimize bias
  - **measurement bias:** systematic error arising from inaccurate measurements of subjects
  - **recall bias:** when individuals with a disease are more prone to recalling or believing they were exposed to a possible causal factor than those who are free of disease

SPIN: use a **SP**ecific test to rule **IN** a hypothesis. Note that specific tests have very few false positives. If you get a positive test, it is likely a true positive

SNOUT: use a **SEN**sitive test to rule **OUT** a hypothesis. Note that sensitive tests have very few false negatives. If you get a negative test, it is likely a true negative

Confounder

- a variable that is related to both the exposure and outcome but is not measured or is not distributed equally between groups
- distorts the apparent effect of an exposure or risk because it may not be possible to separate/control for the contribution of a single causal factor to an effect (e.g. late maternal age could be a confounder in an investigation of birth order >4 and risk of developing Trisomy 21)

Interpreting Test Results

TP = True positive TN = True negative FP = False positive FN = False negative

		Disease	
		Present	Negative
Test Result	Positive	TP	FP
	Negative	FN	TN

Sensitivity = TP/(TP+FN)
Specificity = TN/(TN+FP)

Likelihood Ratio (LR)

- Likelihood that a given test result would be expected in a patient with disease compared with the likelihood that the same result would be expected in a patient without disease
- LR+ indicates how much the probability of disease increases if the test is positive
- LR- indicates how much the probability of disease decreases if the test is negative

$$\textbf{LR+} = \frac{\text{Sensitivity}}{1 - \text{Specificity}} = \frac{[TP/TP+FN)]}{[FP/(TN+FP)]} \qquad \textbf{LR–} = \frac{1 - \text{Sensitivity}}{\text{Specificity}} = \frac{[FN/(TP+FN)]}{[TN/(TN+FP)]}$$

Positive Predictive Value (PPV)

- Proportion of people with a positive test who have the disease

$$\textbf{PPV} = \frac{TP}{TP + FP}$$

Negative Predictive Value (NPV)

- Proportion of people with a negative test who are free of disease

$$\textbf{NPV} = \frac{TN}{TN + FN}$$

		Advanced Neoplasia	
		Present	Negative
Test Result	Positive	68	147
	Negative	216	2234
	Total	284	2381

Sensitivity = 68/284 = 23.9%
Specificity = 2234/2381 = 93.8%

$$\textbf{LR+} = \frac{0.239}{1 - 0.938} = 3.85$$

$$\textbf{LR–} = \frac{1 - 0.239}{0.938} = 0.81$$

$$\textbf{PPV} = \frac{68}{(68+147)} = 31.6\%$$

$$\textbf{NPV} = \frac{2234}{(2234+216)} = 91.2\%$$

Figure 5. Interpreting test results: Practical example using FOBT testing in advanced colon cancer
Source: Numbers from Collins J, Lieberman D, Durbin T, et al. Accuracy of screening for fecal occult blood on a single stool sample obtained by digital rectal examination: a comparison with recommended sampling practice. *Ann Intern Med* 2005;142:81-85

Figure 4. Understanding sensitivity and specificity

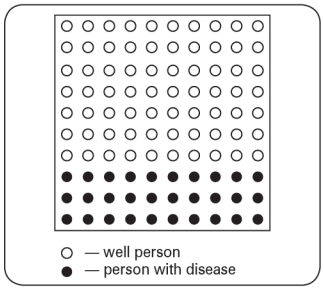


Figure 4a. Hypothetical population

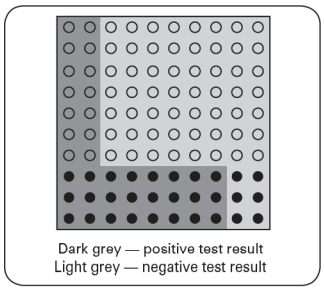


Figure 4b. Results of diagnostic test on hypothetical population

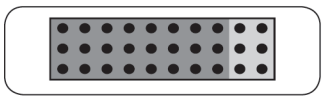


Figure 4c. Sensitivity of test (e.g. 24/30 = 80% sensitive)

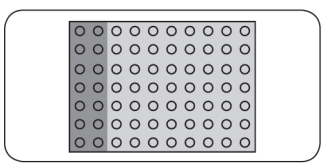


Figure 4d. Specificity of test (e.g. 56/70 = 80% specific)

Source: Loong TW. Understanding sensitivity and specificity with the right side of the brain. *BMJ* 2003;327:716-719

Sensitivity
- proportion of people with disease who are correctly identified by having a positive test

Specificity
- proportion of people without disease who are correctly identified by having a negative test

Pre-Test Probability
- an estimate of the likelihood a particular patient has a given disease based on known factors

Post-Test Probability
- a revision of the probability of disease after a patient has been interviewed and examined
- calculation process can be more explicit using results from epidemiologic studies, knowledge of the accuracy of tests, and Bayes' theorem
- the post-test probability from clinical examination is the basis of consideration when ordering diagnostic tests or imaging studies
  - after each iteration the resultant post-test probability becomes the pre-test probability when considering new investigations

Effectiveness of Interventions

Effectiveness, Efficacy, Efficiency
- three measurements indicating the relative value (beneficial effects vs. harmful effects) of an intervention
  - **efficacy:** the extent to which a specific intervention produces a beneficial result under ideal conditions
    - ideally, based on the results of a randomized control trial (the theoretical impact)
  - **effectiveness:** measures the benefit of an intervention under usual conditions of clinical care
    - considers both the efficacy of an intervention and its actual impact on the real world, taking into account access to the intervention, whether it is offered to those who can benefit from it, its proper administration, acceptance of intervention, and degree of adherence to intervention
  - **efficiency:** a measure of economy of an intervention with known effectiveness
    - considers the optimal use of resources (e.g. money, time, personnel, equipment, etc.)

Disease (e.g. lung CA)

Exposure (e.g. smoking)	**Present**	**Absent**	**Total**
Present	A	B	A + B
Absent	C	D	C + D
Total	A + C	B + D	A + B + C + D

Case-Control Study

$$\text{odds ratio (OR)}^* = \frac{A \times C}{B \times D} = \frac{A \times D}{B \times C}$$

Cohort Study

$$\frac{A}{A+B} = \text{incidence rate of health outcome in exposed} \qquad \frac{C}{C+D} = \text{incidence rate of health outcome in non-exposed}$$

$$\text{relative risk (RR)}^{**} = \frac{A}{A+B} \div \frac{C}{C+D} \qquad \text{attributable risk (AR)}^{***} = \frac{A}{A+B} - \frac{C}{C+D}$$

*Ratio of the odds in favour of the health outcome among the exposed to the odds in favour among the unexposed
**Ratio of the risk of a health outcome among exposed to the risk among the unexposed
***Rate of health outcome in exposed individuals that can be attributed to the exposure

Figure 7. Measures of effect by study type

Sensitivity and specificity are characteristics of the test

LR depends on the test characteristics, not the prevalence

PPV and NPV depend on the prevalence of the disease in the population

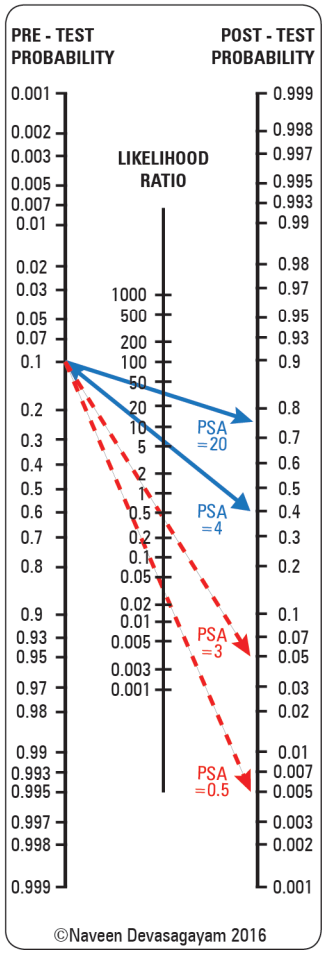


Figure 6. Fagan's likelihood ratio nomogram: Practical example using PSA levels to calculate post-test probability of prostate cancer
Source: Modified from Holmstrom B, Johansson M, Bergh A, et al. Prostate specific antigen for early detection of prostate cancer: longitudinal study. BMJ 2009;339:b3537

Equations to Assess Effectiveness
CER = control group event rate
EER = experimental group event rate
RR = EER/CER
AR = CER – EER
NNT = 1/ARR

Beware
Do not be swayed by a large RR, as it may appear to be large if event rate is small to begin with. In these cases AR is more important (e.g. a drug which lowers an event which occurs in 0.1% of a population to 0.05% can boast a RR of 50%, and yet the AR is only 0.05%, which is not nearly as impressive)

Number Needed to Treat (NNT)
- number of patients who need to be treated to achieve one additional favourable outcome
- only one of many factors that should be taken into account in clinical or health system decision making (e.g. must take into account cost, ease, feasibility of intervention)
  - a condition with death as a potential outcome can have a higher NNT (and be acceptable), as compared to an intervention to prevent an outcome with low morbidity, in which a low NNT would be necessary

NNT
Consult http://www.thennt.com for quick summaries of evidence-based medicine (includes NNT, LR, and risk assessments)

Number Needed to Harm (NNH)
- number of patients who, if they received the experimental treatment, would lead to one additional patient being harmed, compared with patients who received the control treatment

Adherence (formerly compliance)
- degree to which a patient follows a treatment plan

Coverage
- extent to which the services rendered cover the potential need for these services in a community

Types of Study Design

Qualitative vs. Quantitative

Table 6. Qualitative vs. Quantitative Study Designs

Qualitative	Quantitative
Generates hypothesis (Why? What does it mean?)	Tests hypothesis (What? How much/many?)
Inductive (specific to general): "bottom up" Observation → pattern → tentative hypothesis → theory	Deductive (general to specific): "top down" Theory → hypothesis → observation → confirmation
Sampling approach to obtain representative coverage of ideas or concepts	Sampling approach to obtain representative coverage of people in the population
Narrative: rich, contextual, and detailed information from a small number of participants	Numeric: frequency, severity, and associations from a large number of participants

Source: Adapted from http://phprimer.afmc.ca

Quantitative Research Methods

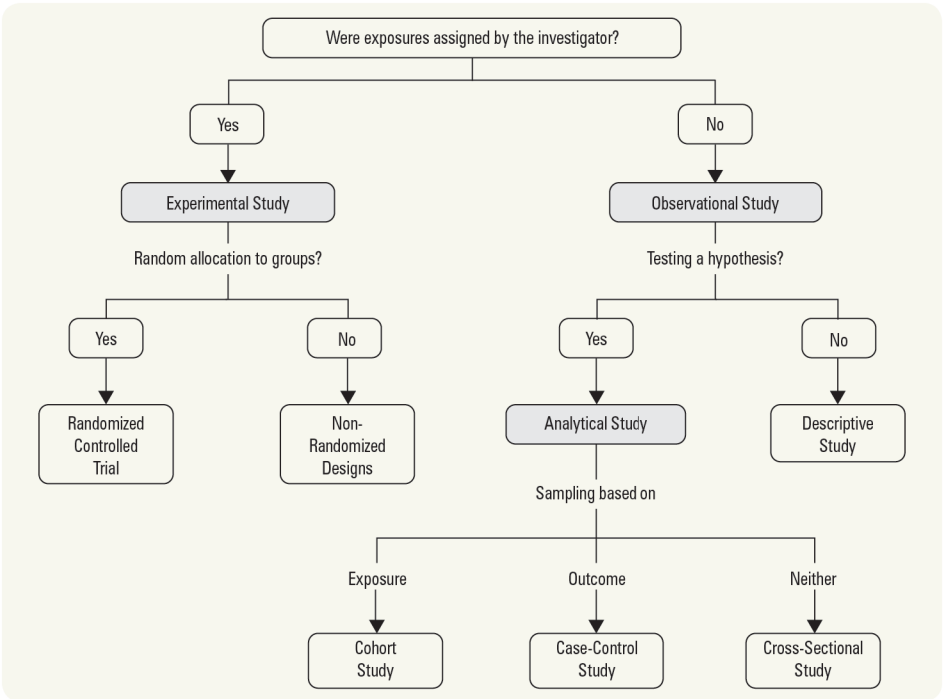


Figure 8. Quantitative study designs

Source: Adapted from http://phprimer.afmc.ca

Formulating a Research Question

PICO
Patient Characteristics
Intervention of Interest
Comparison Group or Control Group
Outcome that you are trying to prevent or achieve

Observational Study Designs

- observational studies involve neither the manipulation of the exposure of interest nor randomization of the study subjects
- there are two main subtypes of observational studies: descriptive and analytic studies

An example of an ecological fallacy would be concluding that red wine drinking leads to lower risk of death from CVS disease after an ecological study shows that France has a higher rate of red wine consumption and a lower rate of death from CVS causes

Descriptive Studies

- describe the events and rates of disease with respect to person, place and time and to estimate disease frequency and time trends
- first sets of studies and are used to generate an etiologic hypothesis, not test a hypothesis

Analytic Studies

- observational studies used to test a specific hypothesis
- includes ecological studies, cohort studies, case-control studies, and cross-sectional studies

Table 7. Observational Study Designs

Type of Study	Ecological	Cross-Sectional	Case-Control	Cohort
Definition	Units of analysis are populations or groups of people, rather than individuals	Assessment of individuals with respect to presence and absence of exposures and diseases at the same point in time	Samples a group of people who already have a particular outcome (cases) and compares them to a similar sample group without that outcome (controls)	Subjects are sampled and, as a group, classified on the basis of presence or absence of exposure to a particular risk factor
Subjects	Population (e.g. geographic areas)	Population (sample)	Two study sample populations are compared: cases and controls	One or more cohorts Cohort: group of people with common characteristics (e.g. year of birth) Divided into measured exposed vs. non-exposed groups
Methods	Descriptions of the average exposure or risk of disease for a population	Collect information from each person at one particular time Tabulate the numbers in groups (e.g. by presence or absence of disease/factor of interest) Make 2 x 2 table and compare groups Estimate prevalence	Ask cases and controls about exposures Select all the cases of a specific disease during a specific time frame Representative of spectrum of clinical disease Select control(s) Represent the general population To minimize risk of bias, may select more than one control group and/or match controls to cases (e.g. age, gender) Association can be concluded between the risk factor and the disease (odds ratio) Estimate incidence	Subjects are followed for a specific period of time to determine development of disease in each exposure group Prospective: measuring from the exposure to the future outcomes – looking forward Retrospective: measuring from outcomes to possible risk factors or protective factors – looking back Collect information on factors from all persons at the beginning of the study Tabulate the number of persons who develop the disease or other measured outcomes of morbidity Provides estimates of incidence, relative risk, attributable risk
Advantages	Quick, easy to do Uses readily available data Generates hypothesis	Determines association between variables Quick and uses limited resources Surveys with validated questions allows comparison between studies	Used when disease in population is rare (less than 10% of population) due to increased efficiency Less costly and time consuming	Shows an association between a factor and an outcome/several outcomes Stronger evidence for causation
Disadvantages	Poor generalizability to individual level (not direct assessment of causal relationship) Ecological fallacy: an incorrect inference about individuals in the population	Does not allow for assessment of temporal relationship or causation between variables Recall bias (see *Bias*, PH9)	Recall bias (see *Bias*, PH9) Confounding Selection bias for controls Only one outcome can be measured	By itself, cannot establish causation Confounding factors are common as the cohort self-selects the exposure, or unknown/unmeasured factors are associated with the measured exposure Cost and duration of time needed to follow cohort
Examples	A study looking at the association between smoking rates and lung cancer rates in different countries at the population level without individual data on both factors	A study that examines the distribution of BMI by age in Ontario at a particular point in time	A famous case control study is by Sir Richard Doll who demonstrated the link between tobacco smoking exposure and lung cancer cases at the individual level	A famous cohort study is the Framingham Heart Study, which assessed the long-term cardiovascular risks of diet, exercise, medications such as ASA, etc.

Experimental Study Designs

- not discussed here are non-randomized control trials (e.g. allocation by clinic or other non-random basis – performed when randomization is not possible) and clinical trials (e.g. test treatments or laboratory tests in human subjects)

RANDOMIZED CONTROLLED TRIAL (RCT)

Definition
- subjects are assigned by random allocation to two or more groups, one of which is the control group, the other group(s) receive(s) an experimental intervention

Subjects
- individuals are separated into groups by a random process to ensure as much as possible equal distribution of known and unknown factors except for the experimental exposure (e.g. the treatment)

Methods
- random allocation of individuals into two or more treatment groups through a centralized concealed process
- method of assessment to reduce bias
  - **single-blind:** subject does not know group assignment (intervention or placebo)
  - **double-blind:** subject and observer both unaware of group assignment
  - **triple-blind:** subject, observer, and analyst unaware of group assignment (rarely done)
- one group receives placebo or standard therapy
- one or more groups receive(s) the intervention(s) under study
- the outcome is measured and the groups are compared
- all other conditions are kept the same between groups

Advantages
- "gold standard" of studies, upon which the practice of EBM is founded
- provides the strongest evidence for effectiveness of intervention
- with sufficient sample size and appropriate randomization, threats to validity are minimized
- allows prospective assessment of the effects of intervention while minimizing bias

Disadvantages
- some exposures are not amenable to randomization (e.g. cannot randomize subjects to poverty/wealth or to harmful exposures such as smoking) due to ethical or feasibility concerns
- difficult to randomly allocate groups (e.g. communities, neighbourhoods)
- difficult to study rare events, since RCTs would require extremely large sample sizes
- costly

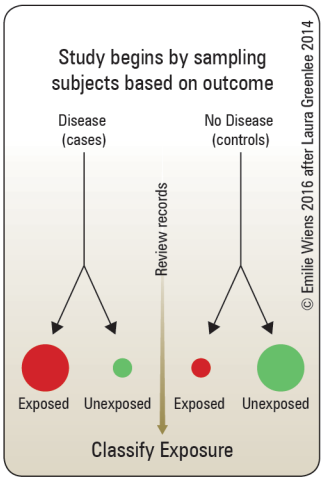


Figure 9. Case-control study
Adapted from http://phprimer.afmc.ca

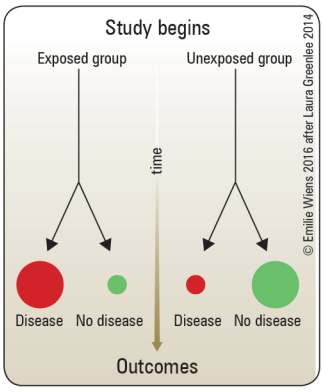


Figure 10. Cohort study
Adapted from http://phprimer.afmc.ca

Analysis
Per-Protocol Analysis (PP)
Strategy of analysis in which only patients who complete the entire study are counted towards the results
Intention-to-Treat Analysis (ITT)
When groups are analyzed exactly as they existed upon randomization (i.e. using data from all patients, including those who did not complete the study)

An example of an RCT is the SPARCL trial, which demonstrated intense lipid-lowering with atorvastatin reduces the risk of cerebro- and cardiovascular events in patients with and without carotid stenosis when compared to placebo

Summary Study Designs

META-ANALYSIS

Definition
- a form of statistical analysis that combines the results of independent studies addressing a common research hypothesis, as identified through systematic review, into one large study

Subjects
- combination of all the subjects used in original studies

Methods
- selection of relevant studies from the published literature which meet quality criteria
- statistical models used to combine the results of each independent study
- provides a summary statistic of overall results as well as graphic representation of included studies

Advantages
- attempts to overcome the problem of reduced power due to small sample sizes of individual studies
- ability to control for inter-study variation

Disadvantages
- sources of bias may not be controlled for
- reliance on published studies may increase the potential conclusion of an effect as it can be difficult to publish studies that show no significant results (publication bias)
- the decision to include/reject a particular study is subjective

An example of a meta-analysis is one that compares the effects of ACE inhibitors, CCBs, and other antihypertensive agents on mortality and major cardiovascular events by compiling and analyzing data from a full set of reported RCTs

Consult the Cochrane Library of Systematic Reviews (http://www.cochranelibrary.com) for high-quality systematic reviews and meta-analyses

Methods of Analysis

Distributions

- distribution describes the probability of events
- normal (Gaussian) or non-normal (skewed, bimodal, etc.)
- characteristics of the normal distribution
  - mean = median = mode
  - 67% of observations fall within one standard deviation of the mean
  - 95% of observations fall within two standard deviations of the mean
- measures of central tendency
  - **mean:** sum of all observations divided by total number of variables
  - **median:** value at the 50th percentile, this is a better reflection of the central tendency for a skewed distribution
  - **mode:** most frequently observed value in a series
- measures of dispersion
  - **range:** the largest value minus the smallest value
  - **variance:** a measure of the spread of data
  - **standard deviation:** the average distance of data points from the mean (the positive square root of variance)
- given the mean and standard deviation of a normal or binomial distribution curve, a description of the entire distribution of data is obtained

Example Calculation
Data set: 17, 14, 17, 10, 7
Mean = (17 + 14 + 17 + 10 + 7) ÷ 5 = 13
Median (write the list in order, median is the number in the middle) = 7, 10, 14, 17, 17 = 14
Mode (number repeated more often) = 17
Range = 17- 7 = 10
Variance = $[(17-13)^2 + (14-13)^2 + (17-13)^2 + (10-13)^2 + (7-13)^2] \div 5 = 15.6$
Standard Deviation = 3.95
√variance = √15.6 = 3.95

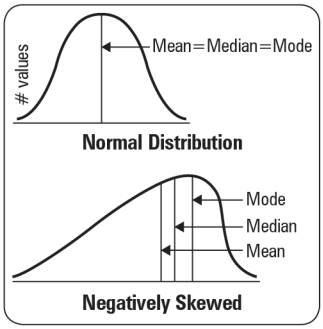


Figure 11. Distribution curves

Data Analysis

Statistical Hypotheses

- **null (H_o)**
  - no relationship exists between the two stated variables (i.e. no association between the hypothesized exposure and the outcome)
- **alternative (H_1)**
  - a relationship does exist between the two stated variables

Type I Error (α Error)

- the null hypothesis is falsely rejected (i.e. concluding an intervention X is effective when it is not, or declaring an observed difference to be real rather than by chance)
- the probability of this error is denoted by the p-value
- studies tend to be designed to minimize this type of error, since a type I error can have larger clinical significance than a type II error

Type I (α) Error
"**T**here **I**s **A**n **E**ffect" where in reality there is none

Type II Error (β Error)

- the null hypothesis is falsely accepted (i.e. stating intervention X is not effective when it is, or declaring an observed difference/effect to have occurred by chance when it is present)
- higher level of error is acceptable for most studies
- can also be used to calculate statistical power

Power

- probability of correctly rejecting a null hypothesis when it is in fact false (i.e. the probability of finding a specified difference to be statistically significant at a given p-value)
- power increases with an increase in sample size
- power = 1 – β, and is therefore equal to the probability of a true positive result

Statistical Significance

- the probability that the statistical association found between the variables is due to random chance alone (i.e. that there is no association)
- the preset probability is set sufficiently low that one would act on the result; frequently p=0.05
- when statistical tests result in a probability less than the preset limit, the results are said to be statistically significant (i.e. $p<0.05$)

Clinical Significance

- measure of clinical usefulness (e.g. 1 mmHg BP reduction may be statistically significant, but may not be clinically significant)
- depends on factors such as cost, availability, patient compliance, and side effects in addition to statistical significance

Trend

- an observed directional relationship that does not meet criteria for statistical significance and thus should be interpreted with caution

Confidence Interval (CI)
- provides a range of values within which the true population result (e.g. the mean) lies
- frequently reported as 95% CI (i.e. one can be 95% certain that the true value is within this data range)
- bounded by the upper and lower confidence limits

A wider confidence interval implies more variance than a tighter confidence interval

Data
- information collected from a sample of a population
- there are 2 overall classes of data listed with examples
  - **discrete**
    - categorical (e.g. gender, marital status)
    - ordinal (e.g. low, medium, high)
  - **continuous** (e.g. serum cholesterol, hemoglobin, age)

Accuracy
- how closely a measurement approaches the true value

Reliability
- how consistent a measurement is when performed by different observers under the same conditions or by the same observer under different conditions

Validity
- extent to which a measurement approaches what it is designed to measure
- determined by the accuracy and reliability of a test

Internal Validity
- degree to which the findings of the sample truly represent the findings in the study population
- dependent on the precision and accuracy

External Validity (i.e. Generalizability)
- degree to which the results of the study can be generalized to other situations or populations

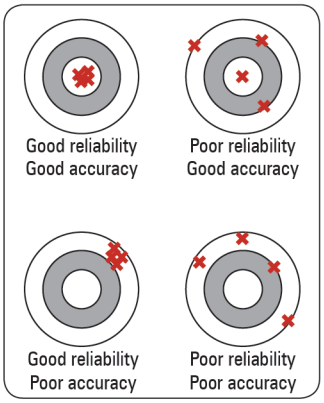


Figure 12. Accuracy vs. reliability

Common Statistical Tests

Table 8. Statistical Tests

	Z-Test (known as t-test for samples <30)	Analysis of Variance (ANOVA)	Chi-Squared Test (χ^2)	Linear Regression	Logistic Regression
What are you trying to show?					
	Compare the mean values of an outcome variable between two groups (e.g. difference in average BP between men and women)	Compare the mean values of an outcome variable between two or more groups (e.g. difference in average BP between persons in three towns)	Test the correspondence between a theoretical frequency distribution and an observed frequency distribution (e.g. if one sample of 20 patients is 30% hypertensive and another comparison group of 25 patients is 60% hypertensive, a chi-squared test determines if this variation is more than expected due to chance alone)	Looks at associations between two or more continuous variables (e.g. age and blood pressure)	Shows how a change in one explanatory variable affects the status (e.g. ill vs. non-ill) of the outcome variable
What kind of data do you have in your study?					
	Data on two groups	Mean of groups (one or more) Overall mean of an entire sample	Data on two or more populations and two or more outcome measures	Data on at least one population	Data on at least one population
What kind of variables do you measure?					
Dependent Variable	Continuous data	Continuous data	Categorical (2 or more)	Continuous	Categorical (discrete outcomes usually dichotomous)
Independent Variable	Categorical (2 only)	Categorical (2 or more)	Categorical (2 or more)	Continuous	Continuous/categorical
Assumptions		"Normal" distribution	None	Dependent variable has "normal" distribution Linear relationship between variables	None

Causation

Criteria for Causation (Sir Bradford Hill)

1. **strength of association:** the frequency with which the factor is found in the disease and the frequency with which it occurs in the absence of disease
2. **consistency:** is it the same outcome with different populations or study design?
3. **specificity:** is the association particular to your intervention and measured outcome?
4. **temporal relationship**: did the exposure occur before the onset of the disease?
5. **biological gradient:** finding a quantitative relationship between the factor and the frequency (e.g. dose response relationship)
6. **biological plausibility**: does the association/causation make biological sense?
7. **coherence**: can the relationship be explained/accounted for based on what we know about the laws of science, logic, etc.?
8. **experimental evidence:** experiment that investigates what happens when the suspected offending agent is removed (e.g. is there improvement?)
9. **analogy:** do other established associations provide a model for this type of the relationship?

Note: Not all criteria must be fulfilled to establish scientific causation, and the modern practice of EBM emphasizes 'experimental evidence' as superior to other criteria for experimental causation review. However many causation questions in health cannot be answered with experimental methods.

Beware
Correlation ≠ Causation
e.g. There is evidence of a direct correlation between the amount of ice cream sold and the amount of deaths in swimming pools. Of course, ice cream does not cause drowning, rather, they both increase in the summer

Criteria for Causation
ACCESS PTB
Analogy
Consistency
Coherence
Experimental evidence
Strength of association
Specificity
Plausibility
Temporal relationship
Biological gradient

Assessing Evidence

- critical appraisal is the process of systematically examining research evidence to assess validity, results, and relevance before using it to inform a decision

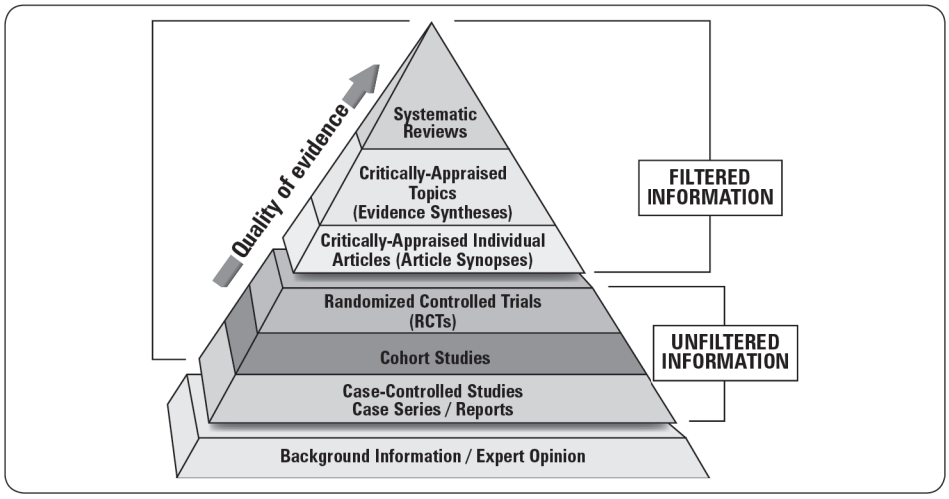


Figure 13. Pyramid of pre-appraised evidence

A. Are the results of the study valid?
- see below for classifications of evidence that has already been assessed; see sidebar for assessing primary studies

B. What are the results?
- what was the impact of the treatment effect?
- how precise was the estimate of treatment effect?
- what were the confidence intervals and power of the study?

C. Will the results help me in caring for my patients?
- are the results clinically significant?
- can I apply the results to my patient population?
- were all clinically important outcomes considered?
- are the likely treatment benefits worth the potential harm and costs?

Validity
- The degree to which the outcome observed in the study can be attributed to the intervention

5 Questions About the Validity of Primary Studies
- Were the patients randomized?
- Was the follow-up of patients sufficiently long and complete?
- Were all patients analyzed in the groups to which they were randomized?
- Were the groups treated equally except for the intervention?
- Were the patients and clinicians kept blind to treatment?

Other Questions to Consider
- Were the groups similar (i.e. demographics, prognostic factors) at the start of the trial?
- Were the appropriate and valid exposure and outcome measures obtained?
- Were outcome assessors aware of group allocation?
- Was contamination reported?
- Were ethical issues continuously upheld?

Levels of Evidence: Classifications Cited in Guidelines/Consensus Statements

Level I evidence: based on RCTs (or meta-analysis of RCTs) big enough to have low risk of incorporating FP or FN results

Level II evidence: based on RCTs too small to provide Level I evidence; may show positive trends that are non-significant, or have a high risk of FN results

Level III evidence: based on non-randomized, controlled or cohort studies; case series; case-controlled; or cross-sectional studies

Level IV evidence: based on opinion of respected authorities or expert committees, as published consensus conferences/guidelines

Level V evidence: opinions of the individuals who have written/reviewed the guidelines (i.e. Level IV evidence), based on experience/knowledge of literature/peer discussion

Notes: These 5 levels of evidence are not direct evaluations of evidence quality or credibility; they reflect the nature of the evidence. While RCTs tend to be most credible (with <III), level III evidence gains credibility when multiple studies from different locations and/or time periods report consistent findings. Level IV and V evidence reflects decision-making that is necessary but in the absence of published evidence.

Figure 14. Levels of evidence classifications
Note: This is only one method of classifying evidence. Various systems exist, but operate within the same premise that certain types of evidence carry more weight than others

Health Services Research

Continuous Quality Improvement

Quality Improvement (QI)
- method of evaluating and improving processes; focusing more on systems and systematic biases, which are thought to be the cause of variation in quality, as opposed to individuals
- taking measures to increase efficiency of action with the purpose of achieving optimal quality

Quality Assurance
- management system to assure the quality of health care provided by workers and received by patients
- constantly aims to improve standards and the frequency of attaining those standards
- **five-stage process of quality assurance**
  1. establishment of functional goals
  2. implementation of procedures to achieve those goals
  3. regular assessment of performance relative to the goals
  4. proposal of solutions to close the gap between performance and goals
  5. documentation and reporting of this assessment activity

Quality Control
- method of maintaining standards by reviewing the quality of all factors involved in the process

Continuous Quality Improvement
- management approach to improve and maintain quality via continuous assessment of potential defects, followed by action to improve process, avoid decrease in quality or correcting process in early stages
- continuous feed-forward process

Quality Management
- encompasses quality assurance, quality control, and quality improvement to achieve consistent quality

Total Quality Management
- management philosophy for improving quality while controlling costs
- focusing on the system rather than the individual, to ensure decisions are made to support quality and remove barriers to quality inherent in bureaucratic, hierarchical systems

Audit
- process of systematic examination of a quality system carried out by internal or external quality auditors
- to determine whether quality processes and results comply with goals, and whether processes have been implemented effectively

Systems Analyses Tools
1. **5 Whys:** brainstorming to simplify the process of change; continue asking 'why' until the root of the problem is discovered
2. **Ishikawa Diagrams (i.e. Fishbone Diagrams):** identify generic categories of problems that have an overall contribution on the effect

Canadian Task Force on Preventive Health Care Grading of Health Promotion Actions
- **A:** *Good evidence* to *recommend* the preventive health measure
- **B:** *Fair evidence* to *recommend* the preventive health measure
- **C:** *Existing evidence* is *conflicting* and does not allow making a recommendation for or against use of the clinical preventive action, however other factors may influence decision-making
- **D:** *Fair evidence* to *recommend against* the preventive health measure
- **E:** *Good evidence* to *recommend against* the preventive health measure
- **I:** *Insufficient evidence* (in quantity and/or quality) to make a recommendation, however other factors may influence decision-making

Source: Canadian Task Force on Representative Health Care. Canadian task force on preventive new grades for recommendations *CMAJ* 2003;169:207-208

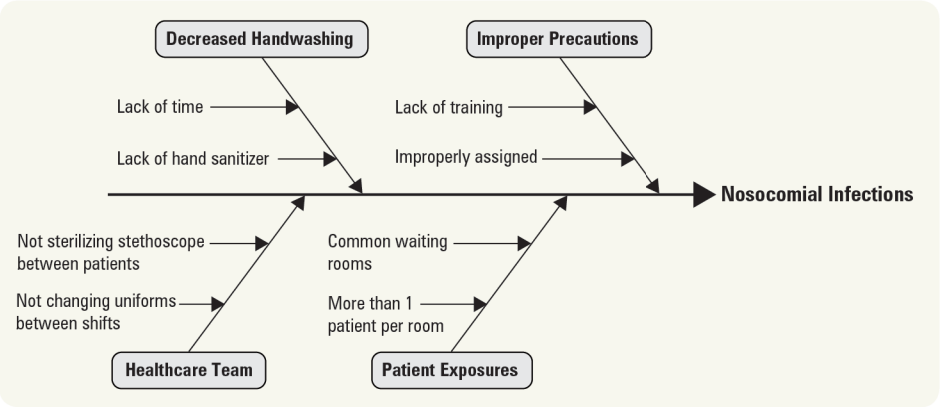


Figure 15. Ishikawa diagram

3. **Defect check sheets:** consider all defects and tally up the number of times the defect occurs
4. **Pareto Chart**: x vs. y chart; x-axis = defect categories, y-axis = frequency; plot cumulative frequency on the right y-axis
   - purpose is to highlight most important among large set of factors contributing to defects/ poor quality

Precede-Proceed Model

- tool for designing, implementing, and evaluating health interventions/programs

Table 9. Precede-Proceed Model

PRECEDE Phase	PROCEED Phase
Phase 1 – Identify the ultimate desired result	Phase 5 – Implementation (design and conduct the intervention)
Phase 2 – Identify and set priorities among health issues and their behavioural and environmental determinants	Phase 6 – Process Evaluation (determine if the program is implemented as planned)
Phase 3 – Identify the predisposing, enabling, and reinforcing factors that affect the behaviours and envrionmental determinants	Phase 7 – Impact Evaluation (measure intermediate objectives – predisposing, enabling, and reinforcing factors)
Phase 4 – Identify the administrative and policy factors that influence what can be implemented	Phase 8 – Outcome Evaluation (measure desired result)

Cost Analysis

Cost Benefit Analysis (CBA)

- a process of, either explicitly or implicitly, weighing the total expected costs against the total expected benefits of one or more actions in order to choose the best or most profitable option
- all costs are adjusted for the time value of money so that costs that may change over time are expressed on a common basis in terms of their present value

Cost Effectiveness Analysis (CEA)

- a comparison of the relative expenditure (costs) and outcomes (effects) of two or more courses of action
- cost effectiveness analysis is often used where a full cost benefit analysis is inappropriate
- a CEA is commonly expressed in terms of a ratio: the denominator is a gain in health from a measure (e.g. years of life, premature births averted, sight-years gained) and the numerator is the cost of the health gain
- the most commonly used outcome measure is quality-adjusted life years (QALY) (see *Quality Adjusted Life Year*, PH8)

Outbreak of Infectious Diseases

Definitions

Endemic
- constant presence of disease or infectious agent in a given geographic area or population subgroup (i.e. usual rate of disease)

Outbreak
- occurrence of new cases clearly in excess of the baseline frequency of the disease in a defined community or population over a given period of time
- synonymous with epidemic, although generally considered to be an epidemic that is localized, has an acute onset, or is relatively short in duration

Epidemic
- any disease, infectious or chronic, occurring at a greater frequency than usually expected in a defined community or institutional population over a given time period (i.e. excessive rate of disease)

Pandemic
- epidemic over a wide area, crossing international boundaries, and affecting a large number of people

Attack Rate
- cumulative incidence of infection within a defined group observed during a specific period of time in an epidemic
- calculated by dividing the total number of people who develop clinical disease by the population at risk, usually expressed as a percentage

Secondary Attack Rate
- number of cases among contacts occurring within the incubation period following exposure to the primary case, in relation to the total exposed contacts
- infectiousness reflects the ease of disease transmission and is usually measured by the secondary attack rate

Virulence
- severity of the disease produced by the organism in a given host
- expressed as the ratio of the number of cases of severe and fatal infection to the total number of clinically affected

Case-Fatality Rate (CFR)
- proportion of individuals contracting a disease who die as a result of that disease
- most frequently applied to a specific outbreak of acute disease in which all patients have been followed for an adequate period of time to include all attributable deaths
- must be clearly differentiated from the mortality rate

Mortality Rate/Crude Death Rate
- estimation of the portion of the population that dies during a specified period from all causes of death

Infection Control Precautions
(see Infectious Diseases, ID6)

Contact (impetigo, chicken pox, warts)
- Wash hands
- Gloves
- Gown
- Wipe equipment after use

Airborne (TB)
- Contact precautions PLUS
- N95 mask (fit tested)
- Negative pressure room

Droplet (influenza, mumps, pneumonia)
- Contact precautions PLUS
- Goggles/face shield
- Surgical mask

Source: Public Health Ontario. http://www.publichealthontario.ca/en/eRepository/IPAC_Clinical_Office_Practice_2013.pdf http://www.oahpp.ca/resources/documents/pidac/Routine%20Practices%20and%20Additional%20Precautions.pdf

Steps to Control an Outbreak

1. Define the Problem
- is it an outbreak?

2. Appraise Existing Data and Institute a Surveillance System
- **case definition:** formulated from the most common symptoms or signs; definition includes the likely date of onset of illness of the first case (e.g. any person with onset of fever higher than 38.5°C and cough within past 28 d)
- **active surveillance:** identify those who may have been exposed to the infectious agent and who fit the case definition through active efforts, including
  - contacting emergency rooms, physicians' offices, local schools
  - obtaining records from health units, such as mortality or laboratory records

Active Surveillance
Outreach such as visits or phone calls by the public health/surveillance authority to detect unreported cases (e.g. an infection control nurse goes to the ward and reviews temperature charts to see if any patient has a nosocomial infection)

Passive Surveillance
A surveillance system where the public health/surveillance authority depends on others to submit standardized forms or other means of reporting cases (e.g. ward staff notify infection control when new cases of nosocomial infections are discovered)

3. Formulate Hypotheses and Implement Initial Control Measures
- track outbreak evolution to develop hypotheses about potential source and populations at risk
- case management depends on symptoms, suspected agent, population at risk, and location
- population management requires public health services in the community and infection control teams in hospitals to initiate initial control measures:
  - disseminate information about risk reduction
  - ensure adherence to personal preventative measures (e.g. hand hygiene, personal protective equipment)
  - prevent new cases (e.g. vaccination, post-exposure prophylaxis)
  - decrease risk of propagation (e.g. quarantine)
  - treat existing cases (e.g. antibiotics, antivirals, supportive care)

4. Test the Hypothesis through Analysis of Surveillance Data or Special Studies
- analyze outbreak surveillance data
- generate epidemic curves
  - usually a frequency histogram, with the number of cases plotted on the vertical axis and dates or times of onset along the horizontal axis
  - curve can indicate whether the epidemic (outbreak) has a common source or whether it is propagated
  - **point source epidemic:** exposure is brief and essentially simultaneous
  - **extended source epidemic**: exposure lasts for a period of days to weeks and may be continuous (no irregular peaks) or intermittent (irregularly spaced peaks)
  - **propagated epidemic:** begins with only a few exposed persons but is maintained by person-to-person transmission (e.g. measles/influenza); epidemic curve shows a series of peaks
- use epidemic curves, cross-sectional studies, and/or case-control studies to evaluate hypotheses about cause of outbreak

5. Draw Conclusions and Re-Adjust Hypothesis and Control Measures
- establish cause of outbreak with further epidemiologic investigation and revise initial control measures accordingly

6. Plan for Long-Term Prevention and Control
- implement prevention measures to avoid similar future incidents
  - strengthen resistance of hosts (e.g. immunization)
  - interrupt modes of transmission in environment (e.g. improvements in food processing)
- communicate outbreak prevention and control strategies to the public

For specific examples, see "Communicable Diseases" section in: Shah CP. Public Health and Preventive Medicine in Canada Toronto: Elsevier, 5th edition, 2003

Figure 16. Epidemic curves

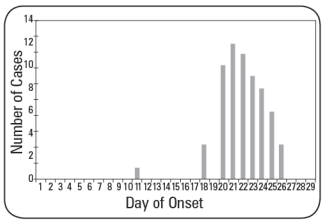


Figure 16a. Point source epidemic curve

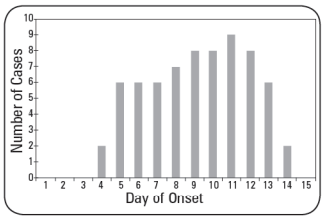


Figure 16b. Extended continuous source epidemic curve

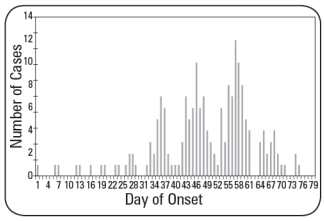


Figure 16c. Propagated source epidemic curve

Infection Control Targets

- interventions should target host, agent, environment, and their interactions

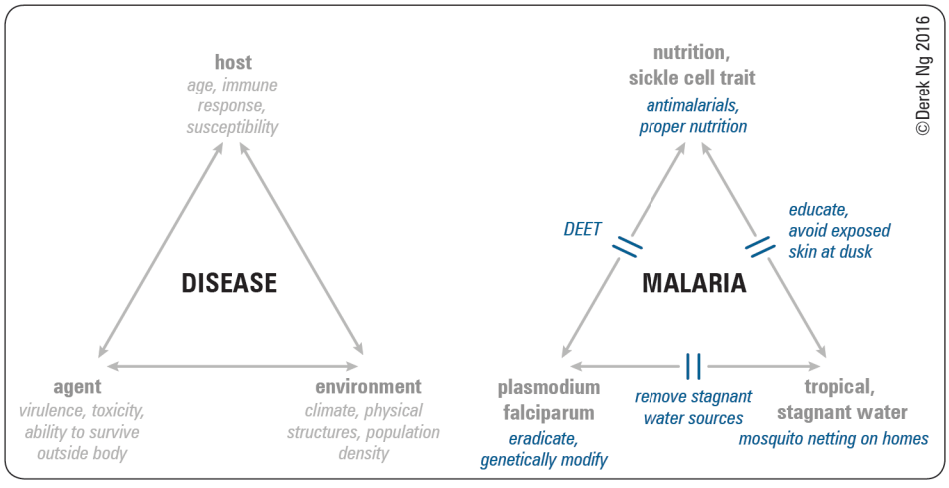


Figure 17. Epidemiology triad as framework for infection control interventions: Practical example using malaria

Environmental Health

Definition
- study of conditions in the natural and human-made environment that influence human health and well-being
- environmental exposures
  - four common hazards: chemical, biological, physical, and radiation
  - four main reservoirs: air, food, water, and soil
  - three main routes: inhalation, ingestion, or absorption (skin)
  - usually divided into two main settings
    - workplace (including schools): may see high level exposure in healthy individuals (see *Occupational Health*, PH23)
    - non-workplace: generally low level but chronic exposure; population at risk includes extremes of age, developing fetuses, and ill or immunocompromised individuals
- health impacts of the environment also include factors such as urban planning and how individuals interact with the built environment (e.g. safe pedestrian and bicycle paths are neighbourhood features that can facilitate more active lifestyles among residents)

Environmental Health Jurisdiction

Table 10. Environmental Health Jurisdiction

Public Health Unit	Enforcement of water and food safety regulations (including restaurant food safety) Sanitation Assessment of local environmental risks Monitoring and follow-up of reportable diseases
Municipal Government	Waste disposal Recycling Water and sewage treatment/collection/distribution
Provincial and Territorial Government	Water and air quality standards Industrial emission regulation Toxic waste disposal
Federal Government	Designating and regulating toxic substances Regulating food products (e.g. Health Canada) Setting policy for pollutants that can travel across provincial boundaries
International	Multilateral agreements (e.g. Kyoto Protocol, UN Convention on Climate Change, International Joint Commission)

Taking an Environmental Health History

CH_2OPD_2
Community
Home
Hobbies
Occupation
Personal habits
Diet
Drugs

Risk Assessment

Hazard Identification
- what is the hazard involved?
- assess potential hazards by taking an environmental health history

Risk Characterization
- is the identified agent likely to elicit the patient's current symptoms?
- review known health impacts of the hazard and identify specific properties that contribute to or diminish adverse effects (e.g. evaluate threshold levels)

Exposure Assessment
- is the patient's exposure to the environmental agent sufficient to have caused the current symptoms?
- quantify exposure through direct measurement or by reviewing frequency and nature of contact with hazard

BPA, the Toxin Concern of 2009
Bisphenol A (BPA) is a chemical compound found in some hard, clear, lightweight plastics and resins. According to the NIH, animal studies suggest that ingested BPA may imitate estrogen and other hormones. In October 2008, Canada became the first country in the world to ban the import and sale of polycarbonate baby bottles containing BPA, stating that although exposure levels are below levels that cause negative effects, current safety margins need to be higher. The US FDA does not consider normal exposure to BPA to be a hazard, however the NIH has some concern that fetuses, infants, and children exposed to BPA may be at increased risk for early-onset puberty, prostate, and breast cancer

Air

Biological Hazards
- moulds thrive in moist areas; 10-15% of the population allergic
- bacteria survive as spores and aerosols, can be distributed through ventilation systems (e.g. *Legionella*)
- dust mites (year-round) and pollens (seasonal) can trigger upper and lower-airway symptoms

Chemical Hazards
- ground-level ozone
  - main component of smog with levels increasing in major cities
  - worsens asthma, irritates upper airway
- carbon monoxide (fossil fuel-related, common byproduct of combustion)
  - aggravates cardiac disease at low levels
  - headache, nausea, dizziness at moderate levels
  - fatal at high levels
- sulphur dioxide (fossil fuel-related), nitrogen oxides
  - contribute to acid rain and exacerbate breathing difficulties
- organic compounds at high levels (e.g. benzene, methylene chloride, tetrachloroethylene)
  - tend to be fat-soluble, easily absorbed through skin and difficult to excrete
- heavy metals emissions (e.g. nickel, cadmium, chromium)
  - variety of health effects: upper airway disease, asthma, decreased lung function
- second-hand tobacco smoke
  - respiratory problems, increase risk of lung cancer
  - particulates associated with decreased lung function, asthma, upper airway irritation

Radiation Hazards
- sound waves
  - ionizing radiation
  - radon is naturally produced by soil containing uranium or radium, can contaminate indoor air and is associated with a small proportion of lung cancers
- ultraviolet radiation is increasing due to ozone layer destruction and increases risk of skin cancer
  - non-ionizing radiation
  - visible light, infrared, microwave

Effects of Ionizing Radiation
α-particles are larger and damage the skin and bronchial lining (airway irritation)

β-particles are smaller and cause deeper damage (alveoli)

Water

Biological Hazards
- mostly due to human and animal waste
- Aboriginal Canadians, rural Canadians at higher risk
- bacteria: *Escherichia coli* (e.g. Walkerton, ON), *Salmonella, Pseudomonas, Shigella*
- protozoa: *Giardia*, *Cryptosporidium* (e.g. North Battleford, SK)

Chemical/Industrial Hazards
- chlorination by-products (e.g. chloroform can cause cancer at high levels)
- volatile organic compounds, heavy metals, pesticides, and other industrial waste products can be present in groundwater
- fluoride at high levels (greater than that of municipal fluoridation) can cause skeletal fluorosis

To Fluoridate or Not
At the recommended concentration of 0.8-1.0 mg/L, fluoride reduces cavities by 18-40%, and there is little risk of fluorosis unless other exposures (e.g. toothpaste, rinses, mouthwash, etc.) are swallowed. Opposition raises concerns that the intake is not easily controlled, and that children, and others may be more susceptible to health problems. However, public health experts strongly support fluoridation as an effective measure to prevent dental caries at the community level and reduce dental health inequities

Soil

Biological Hazards
- biological contamination: tetanus, *Pseudomonas*

Chemical Hazards
- contamination sources: rupture of underground storage tanks, use of pesticides and herbicides, percolation of contaminated water runoffs, leaching of wastes from landfills, dust from smelting and coal burning power plants, residue of industrial waste/development (e.g. urban agriculture), lead deposition, leakage of transformers
- most common chemicals: petroleum hydrocarbons, solvents, lead, pesticides, motor oil, other industrial waste products
- health effects
- infants and toddlers at highest risk of exposure due to hand-mouth behaviours
- dependent on contaminant: leukemia, kidney damage, liver toxicity, neuromuscular blockade, developmental damage to the brain and nervous system, skin rash, eye irritation, headache, nausea, fatigue

The Walkerton Tragedy
In May 2000, the drinking water system in the town of Walkerton, ON, became contaminated with *Escherichia coli* O157:H7 and *Campylobacter jejuni*. Over 2,300 individuals became ill; 27 people developed hemolytic uremic syndrome and 7 individuals died in the outbreak

Source: Ministry of the Attorney General. Report of the Walkerton inquiry. Ontario, 2002

Food

Biological Hazards

Table 11. Comparison of Select Biological Contaminants of Food and Effects on Human Health

	Source	Effects
Salmonella	Raw eggs, poultry, meat	GI symptoms
Campylobacter	Raw poultry, raw milk	Joint pain, GI symptoms
Escherichia coli	Various including meat, sprouts Primarily undercooked hamburger meat	Watery or bloody diarrhea Hemolytic uremic syndrome (esp. children)
Listeria monocytogenes	Unpasteurized cheeses, prepared salads, cold cuts	Listeriosis: nausea, vomiting, fever, headache, rarely meningitis or encephalitis
Clostridium botulinum	Unpasteurized honey, canned foods	Dizziness, weakness, respiratory failure, GI symptoms: thirst, nausea, constipation
Prion (BSE*)	Beef and beef products	Creutzfeldt-Jakob disease

*BSE = bovine spongiform encephalopathy

- other biological food contaminants include
  - viruses, mould toxins (e.g. aflatoxin has been associated with liver cancer), parasites (e.g. Toxoplasmosis, tapeworm), paralytic and shellfish poisoning (rare), genetically modified organisms (controversial as to health risks/benefits)

Honey and Botulism
Although exceedingly rare, infant botulism has been documented as a form of food poisoning from *C. botulinum* found in honey. When an infant swallows spores of this bacterium, they grow and produce a toxin in the baby's intestine. By the time an infant is 1, its gut has a healthy colony of "good" bacteria that prevents this from occurring

Organic Foods
- Foods designated as "organic" in Canada must conform to the Organic Products Regulations enforced by the Canadian Food Inspection Agency
- Organic foods are not free of synthetic pesticide residues but typically contain smaller amounts compared to conventionally grown foods
- Currently, there has not been strong evidence to suggest that eating organic foods is safer or more nutritious compared to eating conventionally grown food

Source: Organic foods. *Ann Intern Med 2012;157:348-66.* Health Canada. Pesticides and food, 2011. UpToDate. Organic foods and children, 2009

Chemical Hazards

many persistent organic pollutants are fat-soluble and undergo bioamplification

- drugs (antibiotics, hormones)
- inadequately prepared herbal medications
- food additives and preservatives
  - nitrites highest in cured meats; can be converted to carcinogenic nitrosamines
  - sulphites commonly used as preservatives; associated with sulphite allergy (hives, nausea, shock)
- pesticide residues
  - older pesticides (e.g. DDT) have considerable human health effects
- polychlorinated biphenyls (PCBs)
  - effects (severe acne, numbness, muscle spasm, bronchitis) much more likely to be seen in occupationally exposed individuals than in the general population
- dioxins and furans
  - levels highest in fish and marine mammals, also present in breast milk
  - can cause immunosuppression, liver disease, respiratory disease

Occupational Health

- occupational health is the maintenance and promotion of health in the work environment
- services encompass health promotion and protection (primary prevention), disease prevention (secondary prevention), and treatment and rehabilitation (tertiary prevention)
- general bias towards reporting occupational injuries versus occupational disease, as occupational disease is harder to identify

Taking an Occupational Health History

- current and previous job duties
- exposures
  - identification: screen for chemical, metal, dust, biological, and physical hazards as well as psychological stressors; review relevant workplace MSDS
  - assessment: duration, concentration, route, exposure controls (e.g. ventilation, personal protective equipment)
- temporal relationship: changes in symptoms in relationship to work environment
- presence of similar symptoms in co-workers
- non-work exposures: home, neighbourhood, hobbies

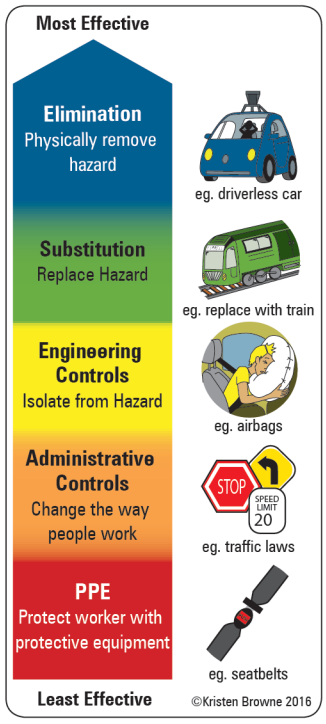


Figure 18. Hierarchy of controls for reduction of occupational exposures
Source: Modified from CDC. 2015. Hierarchy of controls. http://www.cdc.gov/niosh/topics/hierarchy/

Occupational Hazards

Table 12. Occupational Hazards

Physical	Chemical	Biological	Psychosocial

• Trauma (e.g. fractures, lacerations)
• Noise (e.g. hearing loss)
• Temperature
  • heat cramps, heat exhaustion, heat stroke
  • hypothermia, frostbite
• Air pressure (barotrauma, decompression sickness)
• Ergonomic
  • repetitive use/overuse injuries, excessive force, awkward postures, poorly designed physical work environment
  • tenosynovitis, bursitis, carpal tunnel syndrome
• Radiation
  • non-ionizing: visible light, infrared
  • ionizing: UV, x-rays, γ rays
• Electricity
	• Organic solvents (e.g. benzene, methyl alcohol; most toxic is carbon tetrachloride)
	• Mineral dusts (e.g. silica leads to silicosis and predisposition to TB, asbestos leads to diffuse fibrosis and mesothelioma, coal leads to pneumoconiosis)
	• Heavy metals (e.g. nickel, cadmium, mercury, lead)
	• Gases (e.g. halogen gases, sulphur dioxide, carbon monoxide, nitrogen oxides)
	• Second-hand smoke (causal factor for lung cancer, lung disease, heart disease, asthma exacerbations; may be linked to miscarriage)
	• Skin diseases (major portion of compensations, e.g. contact dermatitis, occupational acne, pigmentation disorders)
		• Exposure to bacteria, viruses, fungi, protozoa, Rickettsia
		• Blood should be considered a potentially toxic substance due to blood-borne infectious diseases (e.g. HIV, hepatitis B)
		• Consider exposure to disease in endemic countries, travelers from endemic countries, or recent travel history in the setting of acute onset of symptoms (e.g. malaria, SARS, TB)
			• Workload stressors
			  • responsibility
			  • fear of job loss
			  • geographical isolation
			  • shift work
			  • bullying
			  • harassment (sexual/non-sexual)
			• Incurs high cost from absenteeism, poor productivity, mental illness (e.g. post-traumatic stress disorder)

Workplace Legislation

- universal across Canada for corporate responsibility in the workplace: due diligence, application of Workplace Hazardous Materials Information System (WHMIS), existence of joint health and safety committees in the workplace with representatives from workers and management
- jurisdiction in Canada is provincial (90% of Canadian workers), except for 16 federally regulated industries (e.g. airports, banks, highway transport) under the *Canada Labour Code*
- Ontario's *Occupational Health and Safety Act*
  - sets out rights of workers and duties of employers, procedures for dealing with workplace hazards, and law enforcement
  - workers have the right to
    - **participate** (e.g. have representatives on joint health and safety committees)
    - **know** (e.g. be trained and have information about workplace hazards)
    - **refuse work** (e.g. workers can decline tasks they feel are overly dangerous)
      - note: For some occupations, this right is restricted if, for example, danger/risk is normal part of work or refusal would endanger others (e.g. police, firefighters, some health care workers)
    - **stop work** (e.g. 'certified' workers can halt work they feel is dangerous to other workers)
  - employers must take precautions to protect the health and safety of employees and investigate concerns
  - enforced by Ministry of Labour via inspectors
- *Health Protection and Promotion Act* (HPPA) (Ontario)
  - Medical Officer of Health has right to investigate and manage health hazards where workplace exposures may impact non-workers (e.g. community members living close to the work site)

Ontario's *Workplace Safety and Insurance Act* (Each province will have their own similar legislation)

- Establishes Workplace Safety and Insurance Board (WSIB), an autonomous government agency that oversees workplace safety training and administers insurance for workers and employers
- WSIB decides benefits for workers, which may include reimbursement for
  - Loss of earned income
  - Non-economic loss (e.g. physical, functional, or psychological loss extending beyond the workplace)
  - Loss of retirement income
  - Health care expenses (e.g. first-aid, medical treatment)
  - Survivor benefits (e.g. dependents and spouses can receive benefits)
- Employers pay for costs (e.g. no government funding)
- No-fault insurance (e.g. worker has no right to sue the employer) in return for guaranteed compensation for accepted claims
- Negligence is not considered a factor
- Physicians are required to provide the WSIB with information about a worker's health without a medical waiver once a claim is made

For more information: http://www.wsib.on.ca/en/community/WSIB

Workplace Health Promotion and Protection

- take action in the workplace so the worker is protected from injury or illness
  - identifying workplace hazards (e.g. through material safety data sheets [MSDS])
  - assessing risk
  - reducing exposure : changes to work environment including elimination, substitution, and isolation of hazard (e.g. engineering controls) more effective than changes to how people work (e.g. administrative controls) and personal protective equipment

Workplace Disease Prevention and Identification

- monitor workers' health to prevent the development of disease
  - periodic examinations to facilitate pre-symptomatic diagnosis
    - PFT for asthma (e.g. occupational dust exposure)
    - audiograms for hearing loss (e.g. occupational noise exposure)
  - substance misuse screening where performance impairment is suspected
- work up and diagnose presenting occupational health problems with appropriate laboratory and radiologic investigations

Occupational Health Statistics

- 1 in 68 employed workers in 2010 received workers compensation due to injury or harm on the job
- 4,405 fatal work injuries in the United States in 2013; rate = 3.2/100,000 workers

Source: Employment and Social Development Canada. Work-related injuries, 2015

U.S. Bureau of Labour Statistics. Census of Fatal Occupational Injuries Charts, 1992-2013, 2014

Workplace Treatment and Rehabilitation

- treat injury or illness with safe return to the workplace
- may require rehabilitation, retraining, change in job duties, and/or workers' compensation (WSIB)
- advise relevant authorities if necessary (e.g. report notifiable diseases to public health, conditions impeding driving to Ministry of Transportation, see *Appendix*, PH25)

Taking an Occupational Health Hx

WHACS
What do you do?
How do you do it?
Are you concerned about any particular exposures on or off the job?
Co-workers or others with similar problems?
Satisfied with your job?

J Occup Environ Med 1998;40:680-684

Appendix – Mandatory Reporting

Reportable Diseases

As an essential part of the health system, physicians in Canada are required by law to report certain diseases to public health for the following reasons

1. to control the outbreak
   - if the disease presents an outbreak threat (e.g. measles, *Salmonella*, respiratory diseases in institutions)
2. to prevent spread
   - if the disease presents a significant threat to individuals or a subset of the population (e.g. Lassa Fever)
3. for surveillance
   - if the disease is preventable with immunization (e.g. polio, diphtheria, congenital rubella)
4. if infected individuals require education, treatment and/or partner notification (e.g. gonorrhea, TB)
5. reporting details (website, office etc.)
   - some are more urgent than others (must contact MOH)
   - physicians should also report unlisted diseases that appear in clusters

The following list is based on the reportable diseases in Ontario for 2014. Each province will have similar legislation
Source: Health Protection and Promotion Act, O. Reg. 559/91, amended to O. Reg.49/07

Acquired Immunodeficiency Syndrome (AIDS)
Acute flaccid paralysis <15 yr
Amoebiasis
Anthrax

Botulism
Brucellosis

Campylobacter enteritis
Chancroid
Chickenpox (Varicella)
Chlamydia trachomatis infections
Cholera
Clostridium difficile associated disease (CDAD) outbreaks in public hospitals
Cryptosporidiosis
Cyclosporiasis
Cytomegalovirus infection, congenital

Diphtheria

Encephalitis, including:
i. Primary, viral
ii. Post-infectious
iii. Vaccine-related
iv. Subacute sclerosing panencephalitis
v. Unspecified

Food poisoning, all causes

Gastroenteritis, institutional outbreaks
Giardiasis, except asymptomatic cases
Gonorrhea

Haemophilus influenzae b disease, invasive
Hantavirus pulmonary syndrome
Hemorrhagic fevers, including:
i. Ebola virus disease
ii. Marburg virus disease
iii. Other viral causes
Hepatitis, viral:
i. Hepatitis A
ii. Hepatitis B
iii. Hepatitis C
iv. Hepatitis D (Delta hepatitis)
Herpes, neonatal
Human Immunodeficiency Virus (HIV)

Influenza

Lassa Fever
Legionellosis
Leprosy
Listeriosis
Lyme Disease

Malaria
Measles
Meningitis, acute:
i. Bacterial
ii. Viral
iii. Other
Meningococcal disease, invasive
Mumps

Ophthalmia neonatorum

Paralytic shellfish poisoning
Paratyphoid fever
Pertussis (whooping cough)
Plague
Pneumococcal disease, invasive
Poliomyelitis, acute
Psittacosis/Ornithosis

Q Fever

Rabies
Respiratory infection outbreaks in institutions
Rubella
Rubella, congenital syndrome

Salmonellosis
Severe Acute Respiratory Syndrome (SARS)
Shigellosis
Smallpox
Streptococcal infections, Group A invasive
Streptococcal infections, Group B neonatal
Syphilis

Tetanus
Transmissible spongiform encephalopathy, including:
i. Creutzfeldt-Jakob disease, all types
ii. Gerstmann-Sträussler-Scheinker syndrome
iii. Fatal familial insomnia
iv. Kuru
Trichinosis
Tuberculosis, active and latent
Tularemia
Typhoid Fever

Verotoxin-producing *E. coli* infection indicator conditions, including Hemolytic Uremic Syndrome (HUS)

West Nile Virus illness, including:
i. West Nile fever
ii. West Nile neurological manifestations

Yellow Fever
Yersiniosis

Other Reportable Conditions

In addition to reporting diseases, physicians have a legal responsibility to report certain conditions. The list below highlights some reportable conditions for Ontario, but is not exhaustive. See your jurisdiction's regulatory body for the full list

Child Abuse – to local Children's Aid Society (CAS)
- all child abuse and neglect where reasonable grounds to suspect exist (including physical harm, emotional harm, sexual harm, and neglect)
- duty to report is ongoing: if additional reasonable grounds are suspect, a further report to CAS is necessary

Unfit to Drive – to provincial Ministry of Transportation
- all patients with a medical condition (e.g. dementia, untreated epilepsy) that may impede their driving ability
- if a physician does not report and the driver gets into an accident, the physician may be held liable

Unfit to Fly – to federal Ministry of Transportation
- all patients believed to be flight crew members or air traffic controller with a medical or optometric condition that is likely to constitute a hazard to aviation safety

Gunshots Wounds – to local police service
- all patients with a gunshot or stab wounds
- self-inflicted knife wounds are not reportable

Source: CPSO. Mandatory and Permissive Reporting. 2012. Available from: http://www.cpso.on.ca/policies-publications/policy/mandatory-and-permissive-reporting

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ID

Infectious Diseases

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Acronyms

AFB	acid-fast bacilli	ETEC	enterotoxigenic *E. coli*	HDV	hepatitis D virus	MERS	Middle Eastern respiratory syndrome	Sn	sensitivity
AIDS	acquired immune deficiency syndrome	FDP	fibrinogen degradation products	HEV	hepatitis E virus			Sp	specificity
ANC	absolute neutrophil count			HHV	human herpes virus	MDR	multidrug resistance	spp.	species
AOM	acute otitis media	FUO	fever of unknown origin	Hib	*Haemophilus influenzae* b	MMR	measles/mumps/rubella	SRI	severe respiratory illness
ARV	anti-retroviral	GAS	group A *Streptococcus*	HIV	human immunodeficiency virus	MRSA	methicillin-resistant *S. aureus*	STEC	Shiga toxin-producing *E. coli*
ART	anti-retroviral therapy	GBS	group B *Streptococcus*	HPF	high power field	MSM	men who have sex with men	STI	sexually transmitted infection
BAL	bronchoalveolar lavage	GC	gonococcus	HRIg	human rabies immunoglobulin	O&P	ova and parasites	TB	mycoplasma tuberculosis
BCG	Bacille Calmette-Guérin	GNB	Gram negative bacilli	HSV	herpes simplex virus	PCR	polymerase chain reaction	TIg	tetanus immune globulin
C&S	culture and sensitivity	GP	Gram positive	HUS	hemolytic uremic syndrome	PMN	polymorphonuclear leukocytes	TMP/SMX	trimethoprim-sulfamethoxazole
CFU	colony forming units	H. flu	*Haemophilus influenzae*	IE	infective endocarditis	PNS	peripheral nervous system	TNF	tumour necrosis factor
CMV	cytomegalovirus	HAART	highly active anti-retroviral treatment	IFN	interferon	PPD	purified protein derivative	TORCH	toxoplasmosis, other, rubella, cytomegalovirus, HSV
CNS	central nervous system			Ig	immunoglobulin	RSV	respiratory syncytial virus		
CSF	cerebrospinal fluid	HAV	hepatitis A virus	INH	isoniazid	RTI	respiratory tract infection	TSS	toxic shock syndrome
DEET	N,N-Diethyl-meta-toluamide	HBc	HBV core antigen	IVDU	intravenous drug use	RT-PCR	reverse transcription-PCR	URTI	upper respiratory tract infection
DM	diabetes mellitus	HBeAg	HBV envelope antigen	KOH	potassium hydroxide	SARS	severe acute respiratory syndrome	UTI	urinary tract infection
DVT	deep vein thrombosis	HBsAg	HBV surface antigen	KSHV	Kaposi's sarcoma-associated herpes virus			VRE	vancomycin-resistant *Enterococcus*
EBV	Epstein-Barr virus	HBV	hepatitis B virus			sBP	systolic blood pressure		
EHEC	enterohemorrhagic *E. coli*	HCC	hepatocellular carcinoma	LOC	level of consciousness	SIADH	syndrome of inappropriate antidiuretic hormone secretion	VZV	varicella-zoster virus
EIEC	enteroinvasive *E. coli*	HCV	hepatitis C virus	LP	lumbar puncture				

Principles of Microbiology

Bacteriology

Bacteria Basics

- bacteria are prokaryotic cells that divide asexually by binary fission
- Gram stain divides most bacteria into two groups based on their cell wall
  - Gram positive (GP): thick, rigid layer of peptidoglycan
  - Gram negative (GN): thin peptidoglycan layer + thicker outer membrane composed of lipoproteins and lipopolysaccharides
  - clinical significance: GN thick outer membrane makes it resistant to penicillin's mechanism of action
- acid-fast bacilli (AFB): high mycolic acid content in cell wall, "acid fast" as washout phase with acid-alcohol is ineffective in acid-fast bacteria, e.g. *Mycobacteria, Nocardia*
- "atypical" bacteria: not seen on Gram stain and difficult to culture
  - obligate intracellular bacteria: e.g. *Chlamydia, Chlamydophilia*
  - bacteria lacking a cell wall: e.g. *Mycoplasma*
  - spirochetes: e.g. *Treponema pallidum*
- O_2 can be either vital or detrimental to growth
  - obligate aerobes: require O_2
  - obligate anaerobes: require environment without O_2
  - facultative anaerobes: can survive in environments with or without O_2

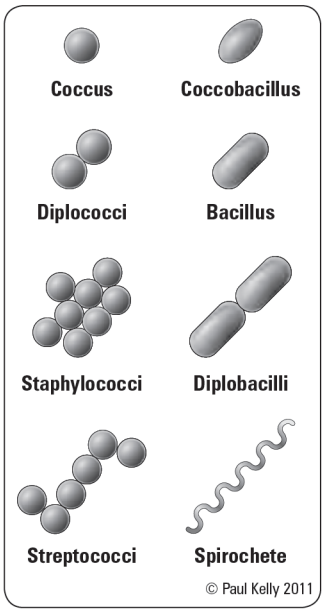


Figure 1. Bacteria morphology

Mechanisms of Bacterial Disease

1. adherence to and colonization of skin or mucous membranes
   - e.g. fimbriae (pili): microfilaments extending through the cell wall – like burrs sticking to your clothes, they attach to epithelial cells e.g. *E. coli* in the urinary tract
2. invasion or crossing normal epithelial barriers
3. evasion of host defense system through inhibition of
   - phagocytic uptake via polysaccharide capsule (*S. pneumoniae, N. meningitidis, H. influenzae*) or surface proteins (*Staphylococcus, Streptococcus*)
4. toxin production
   - exotoxins are secreted by living pathogenic bacteria and cause disease even if the bacteria is not present (e.g. *Clostridium*)
   - endotoxins are structural components of GN bacterial cell walls, and may be shed by live cells or released during cell lysis
5. intracellular growth
   - obligate intracellular: *Rickettsia, Chlamydia, Chlamydophilia*
   - facultative intracellular: *Salmonella, Neisseria, Brucella, Mycobacteria, Listeria, Legionella*
6. biofilm
   - an extracellular polysaccharide network forming mesh around the bacteria (e.g. *S. epidermidis*) which can coat prosthetic devices like IV catheters

Table 1. Common Bacteria

	Gram-Positive Bacteria		Gram-Negative Bacteria		Not Seen on Gram Stain	
	Cocci	**Bacilli (rods)**	**Diplococci**	**Bacilli (rods)**	**Acid Fast**	**Others**
Aerobes	*Staphylococcus* *S. aureus* *S. saprophyticus* *S. epidermidis* *Streptococcus* *S. pneumoniae* *S. pyogenes (GAS)* *S. agalactiae (GBS)* *Enterococcus* *E. fecalis*	*Bacillus* *B. anthracis* *Listeria* *Nocardia* (modified acid fast positive)	*Neisseria* *N. meningiditis* *N. gonorrhoeae* *Moraxella* *M. catarrhalis*	*Enterobacteriaceae* *E. coli, Salmonella, Shigella, Campylobacter, Yersinia* *Klebsiella* *Legionella* *Pseudomonas* *Haemophilus* *H. influenzae*	*Mycobacteria* *M. tuberculosis* *M. leprae* *M. avium complex* *M. bovis*	Obligative intracellular *Rickettsiae* *Chlamydia* *C. trachomatis* *Chlamydophila* *C. pneumoniae* No cell wall *Mycoplasma* Spirochaete (spiral) *Treponema pallidum*
Anaerobes	*Peptostreptococcus*	*Clostridium* *C. difficile, C. tetani, C. botulinum, C. perfringens*		*Bacteroides* *B. fragilis*		

Table 2. Commensal Flora

Site	Organisms
Skin	Coagulase-negative staphylococci, *Corynebacterium, Propionibacterium acnes, Bacillus, S. aureus*
Oropharynx	Viridans group streptococci, *Haemophilus, Neisseria*, anaerobes (*Peptostreptococcus, Bacteroides, Veillonella, Fusobacterium, Actinomyces, Prevotella*)
Small Bowel	*E. coli*, anaerobes (low numbers)
Colon	*E. coli, Klebsiella, Enterobacter, Enterococcus*, anaerobes (*Bacteroides, Peptostreptococcus, Clostridium*)
Vagina	*Lactobacillus acidophilus*, viridans group streptococci, coagulase-negative staphylococci, facultative Gram-negative bacilli, anaerobes

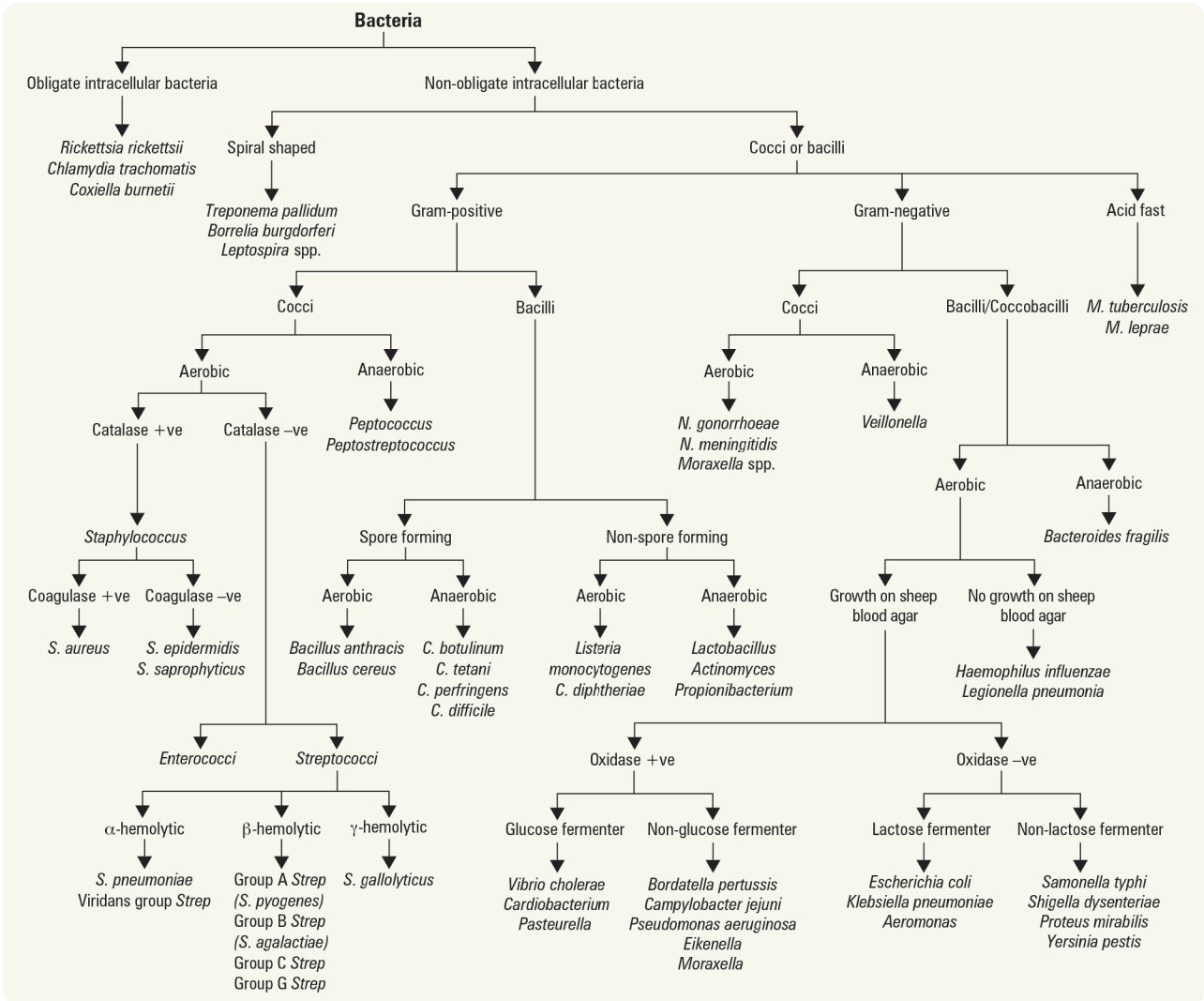


Figure 2. Laboratory identification of bacterial species

Virology

Viral Basics

- viruses are infectious particles consisting of RNA or DNA covered by a protein coat
  - infect cells and use host metabolic machinery to replicate
  - nucleic acid can be double stranded (ds) or single stranded (ss)
  - can be enveloped or naked
- virions are mature virus particles that can be released into the extracellular environment
- host susceptibility is governed by the host cell and virus surface proteins (viral tropism) and cellular immunity

Viral Disease Patterns

1. acute infections (e.g. adenovirus)
   - host cells are lysed in the process of virion release
   - some produce acute infections with late sequelae (e.g. measles virus → subacute sclerosing panencephalitis)
2. chronic infections (>6 mo): (e.g. HBV, HIV)
   - host cell machinery is used to produce and chronically release virions
3. latent infections
   - viral genome remains latent in host cell nucleus
   - can reactivate (e.g. HSV, VZV)

Table 3. Common Viruses

Nucleic Acid	Enveloped	Virus Family	Major Viruses	Medical Importance
dsDNA	N	*Adenoviridae*	Adenovirus	URTI Conjunctivitis Gastroenteritis
	N	*Papillomaviridae*	HPV1,4 HPV6,11 HPV16,18, etc.	Plantar warts Genital warts Cervical/anal dysplasia and cancer
	Y	*Herpesviridae*	HHV1=HSV1 HHV2=HSV2 HHV3=VZV HHV4=EBV HHV5=CMV HHV6* HHV8=KSHV	Oral, ocular, and genital herpes; encephalitis Genital, oral, and ocular herpes; encephalitis Chicken pox, shingles Mononucleosis, viral hepatitis Retinitis, pneumonitis, hepatitis, encephalitis Roseola Kaposi's sarcoma, multicentric Castleman's disease, body cavity lymphoma
	N	*Polyomaviridae*	JC virus	Progressive multifocal leukoencephalopathy
	Y	*Hepadnaviridae* *Poxviridae*	Hepatitis B Variola	Hepatitis Smallpox
ssDNA	N	*Parvoviridae*	Parvovirus B19	Erythema infectiosum (Fifth disease)
(+) ssRNA	N	*Caliciviridae*	Norwalk Hepatitis E	Gastroenteritis Acute hepatitis
	N	*Picornaviridae*	Poliovirus Echovirus Rhinovirus Coxsackie virus Hepatitis A	Poliomyelitis URTIs, viral meningitis URTIs Hand-foot-and-mouth, viral meningitis, myocarditis Acute hepatitis
	Y	*Coronaviridae*	Coronavirus	URTIs, SARS, MERS
	Y	*Flaviviridae*	Yellow fever Dengue fever Hepatitis C West Nile	Yellow fever Dengue fever Hepatitis Encephalitis, flaccid paralysis
	Y	*Togaviridae*	Rubella	Rubella (German measles)
(+) ssRNA-RT	Y	*Retroviridae*	HIV HTLV-1	AIDS T-cell leukemia and lymphoma
(+) ssRNA	Y	*Arenaviridae*	Lassa fever	Lassa fever
	Y	*Filoviridae*	Ebola, Marburg	Hemorrhagic fever
	Y	*Orthomyxoviridae*	Influenza A, B, C	Influenza
	Y	*Paramyxoviridae*	Measles Mumps Parainfluenza RSV	Measles Mumps URTIs, croup, bronchiolitis Bronchiolitis, pneumonia
	Y	*Rhabdoviridae*	Rabies	Rabies
dsRNA	N	*Reoviridae*	Rotavirus	Gastroenteritis

Note: ___**viridae** = family, ___**virus** = genus, # = species (e.g. Retroviridae HIV-2)
*Roseolovirus, Herpes lymphotropic virus

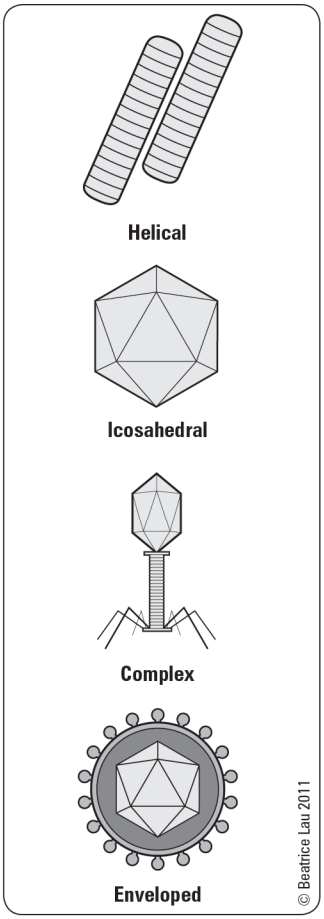


Figure 3. Virus morphology

DNA Viruses: Families

HHAPPPPy
H*epadnaviradae*
H*erpesviridae*
A*denoviridae*
P*apillomaviridae*
P*arvoviridae*
P*olyomaviridae*
P*oxviridae*

Mycology

Fungal Basics

- fungi are eukaryotic organisms, they can have the following morphologies
  1. yeast (unicellular)
  2. molds (also known as filamentous fungi) (multicellular with hyphae)
  3. dimorphic fungi (found as mold at room temperature but grow as yeast-like forms at body temperature)

Table 4. Membrane and Cell Wall Compositions

	Membrane Sterol	Cell Wall
Bacteria	–	Peptidoglycan
Human Cell	Cholesterol	–
Fungi	Ergosterol	Chitin (complex glycopolysaccharide)

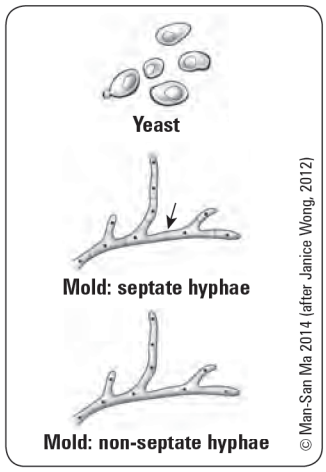


Figure 4. Common fungus morphology

Mechanisms of Fungal Disease

- primary fungal infection by
  - overgrowth of normal flora (e.g. *Candida* species)
  - inhalation of fungal spores
  - traumatic inoculation into skin
- toxins produced by fungi (e.g. ingestion aflatoxins)
- allergic reactions to fungi (e.g. bronchopulmonary aspergillosis)

Parasitology

Parasite Basics

- **parasite**: an organism that lives in or on another organism (host) and damages the host in the process
- parasites with complex life cycles require more than one host to reproduce
  - reservoir host: maintains a parasite and may be the source for human infection
  - intermediate host: maintains the asexual stage of a parasite or allows development of the parasite to proceed through the larval stages
  - definitive host: allows the parasite to develop to the adult stage where reproduction occurs
- 2 major groups of parasites: protozoa and helminths
- see Tables 26 and 27 for examples of clinically important parasites

Table 5. Differences Between Protozoa and Helminths

Protozoa	Helminths
Unicellular	Multicellular
Motile trophozoite → inactive cyst	Adult → egg → larva
Multiplication	No multiplication
Eosinophilia unusual	Eosinophilia (proporticnal to extent of tissue invasion)*
Indefinite life span	Definite life span

*Adult *Ascaris* (roundworm) does not cause eosinophilia; migratory larval phases of *Ascaris*, however, cause high-grade eosinophilia

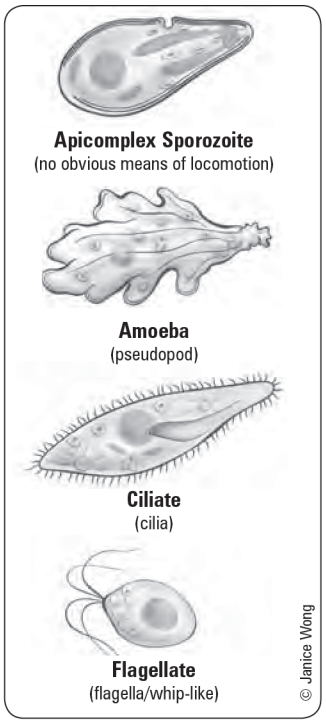


Figure 5. Classification of protozoa based on movement

Characteristics of Parasitic Disease

- symptoms are usually proportional to parasite burden
- tissue damage is due to the parasite and host immune response
- chronic infections may occur with or without overt disease
- immunocompromised hosts are more susceptible to manifestations of infection, reactivation of latent infections, and more severe disease
- eosinophilia may suggest a parasitic infection

Mechanisms of Parasitic Disease

1. mechanical obstruction (e.g. ascariasis, clonorchiasis)
2. competition with host for resources (e.g. anemia in hookworm disease, vitamin B_{12} deficiency in diphyllobothriasis)
3. cytotoxicity leading to abscesses and ulcers (e.g. amoebiasis, leishmaniasis)
4. inflammatory
   - acute hypersensitivity (e.g. pneumonitis in Loeffler's syndrome)
   - delayed hypersensitivity (e.g. egg granulomas in schistosomiasis)
   - cytokine-mediated (systemic illness of malaria, disseminated strongyloidiasis)
5. immune-mediated injury
   - autoimmune (e.g. myocarditis of Chagas disease, tissue destruction of mucocutaneous leishmaniasis)
   - immune complex (e.g. nephritis of malaria, schistosomiasis)

Parasite sampling may need to be repeated on a number of occasions before infection can be ruled out

Transmission of Infectious Diseases

Table 6. Mechanism of Transmission

Mechanism	Mode of Transmission	Examples	Preventative Measure
Contact	Direct physical contact, or indirect contact with a fomite	Skin-to-skin (MRSA) Sexual (*N. gonorrhoeae, C. trachomatis*, HSV, HIV) Blood-borne (HIV, HBV, HCV)	For patients in health care facilities: Contact precautions Barrier precautions Safe needlestick/sharp practices
Droplet/Contact	Respiratory droplets (>5 μm) can be projected short distances (≤2 m) and deposit on mucosal surfaces of the recipient (e.g. by coughing, sneezing, or talking); transmission can also occur by direct physical contact of respiratory fluids or indirect contact with a fomite contaminated with respiratory fluids	Influenza, mumps *N. meningitidis, Bordetella pertussis*	For patients in health care facilities: Contact/droplet precautions
Airborne	Airborne droplet nuclei (<5 μm) remain infectious over time and distance	*M. tuberculosis*, VZV, measles	For patients in health care facilities: Airborne precautions
Food/ Waterborne	Ingestion of contaminated food or water	*V. cholerae, Salmonella,* HAV, HEV	Prophylactic vaccinations where available Ensure clean food/water supply For patients in health care facilities: Contact precautions used for admitted patients with fecal incontinence when stool is unable to be contained in diapers
Zoonotic	Disease transmission from animals to humans either directly or via an insect vector	Animals (rabies, Q fever) Arthropods (malaria, Lyme disease)	Prophylactic medications, vaccinations Protective clothing, insect repellent, mosquito nets, tick inspection
Vertical	Spread of disease from parent to offspring	Congenital syndromes (TORCH infections) Perinatal (HIV, HBV, GBS)	Prenatal screening Prophylactic treatment

Nosocomial Infections

- **nosocomial infectio**: infections acquired >48 h after admission to a healthcare facility or within 30 d from discharge
- risk factors: prolonged hospital stay, antibiotic use, surgery, hemodialysis, intensive care, colonization with a resistant organism, immunodeficiency
- patients with nosocomial infections have higher mortality, longer hospital stays, and higher healthcare costs
- hand hygiene is an essential precaution

Table 7. Common Nosocomial Infectious Agents

Bacteria	Characteristics	Manifestation	Investigations	Management
Methicillin-Resistant *S. aureus* (MRSA)	Gram-positive cocci	Skin and soft tissue infection Bacteremia Pneumonia Endocarditis Osteomyelitis	Admission screening culture from nares and peri-anal region identifies colonization Culture of infection site CXR	Contact precautions For infection: vancomycin or daptomycin or linezolid To decolonize: 2% chlorhexidine wash OD (+ rifampin + (doxycycline or TMP/SMX) + mupirocin cream bid to nares) x 7 d
Vancomycin-Resistant *Enterococcus* (VRE)	Majority are *E. faecium* Resistant if minimum inhibitory concentration of vancomycin is ≥32 μg/mL	Rarely causes disease in healthy people UTI Bacteremia Endocarditis Meningitis	Rectal or perirectal swab OR stool culture for colonization Culture of infected site	Contact precautions* Ampicillin if susceptible Otherwise, linezolid, tigecycline, or daptomycin depending on site of infection No effective decolonization methods identified

Table 7. Common Nosocomial Infectious Agents (continued)

Bacteria	Characteristics	Manifestation	Investigations	Management
Clostridium difficile **(*C. difficile*)**	Releases exotoxins A and B Hypervirulent strain has been responsible for increase in incidence and severity	Fever, nausea, abdominal pain Watery diarrhea ± occult blood Pseudomembranous colitis Severe: toxic megacolon Risk of bowel perforation Associated with antibiotic use Leukocytosis	Stool PCR for toxin B gene Stool immunoassay for toxins A and B (less sensitive than PCR) AXR (may see colonic dilatation) Sigmoidoscopy for pseudomembranes; avoid if known colonic dilatation	Contact precautions Stop culprit antibiotic therapy Supportive therapy (IV fluids) Mild-moderate disease: metronidazole PO x 10-14 d Severe disease: vancomycin PO x 10-14 d Toxic megacolon: metronidazole IV + vancomycin PO (as above) and general surgery consult
Extended Spectrum β-lactam Producers (ESBL producing *E. coli, K. pneumoniae*)	Resistant to most β-lactam antibiotics except carbapenams e.g. penicillins, aztreonam, and cephalosporins	UTI Pulmonary infection Bacteremia Liver abscess in susceptible patients Meningitis	Blood, sputum, urine, or aspirated body fluid culture Imaging at infection site (CXR, CT, U/S)	Carbapenems or non-β-lactam antibiotics can be used for empiric therapy

*the use of contact precautions for VRE varies depending on institutional policies

Respiratory Infections

Pneumonia

- see Pediatrics, P88
- see Family Medicine, FM20

Definition
- infection of the lung parenchyma

Etiology and Risk Factors
- impaired lung defenses
  - poor cough/gag reflex (e.g. illness, drug-induced)
  - impaired mucociliary transport (e.g. smoking, cystic fibrosis)
  - immunosuppression (e.g. steroids, chemotherapy, AIDS/HIV, DM, transplant, cancer)
- increased risk of aspiration
  - impaired swallowing mechanism (e.g. impaired consciousness, neurologic illness causing dysphagia, mechanical obstruction)
- no organism identified in 75% of hospitalized cases, and >90% of ambulatory cases

When *Klebsiella* causes pneumonia; see red currant jelly sputum

3 As of *Klebsiella*

Aspiration pneumonia
Alcoholics and diabetics
Abscess in lungs

Aspiration pneumonias more commonly manifest as infiltrates in the right middle or lower lobes due to the larger caliber and more vertical orientation of the right bronchus

Table 8. Common Organisms in Pneumonia

Community-Acquired	Nosocomial	Aspiration	Immunocompromised Patients	Alcoholic
Typical Bacteria *Streptococcus pneumoniae* *Moraxella catarrhalis* *Haemophilus influenzae* *Staphylococcus aureus* GAS Atypical Bacteria *Mycoplasma pneumoniae* *Chlamydophila pneumoniae* *Legionella pneumophila* Viral *Influenza* virus *Adenovirus*	Enteric GNB *(e.g. E. coli)* *Pseudomonas aeruginosa* *S. aureus* (including MRSA)	Oral anerobes *(e.g. Bacteroides)* Enteric GNB *(e.g. E. coli)* *S. aureus* Gastric contents (chemical pneumonitis)	*Pneumocystis jiroveci* Fungi (e.g. Cryptococcus) *Nocardia* CMV HSV TB	*Klebsiella* Enteric GNB *S. aureus* Oral anaerobes (aspiration) TB

*See Pediatrics P90, Table for Common Causes and Treatment of Pneumonia at Different Ages

Clinical Features
- cough (± sputum), fever, pleuritic chest pain, dyspnea, tachypnea, tachycardia
- elderly often present atypically; altered LOC is sometimes the only sign
- evidence of consolidation (dullness to percussion, bronchial breath sounds, crackles)
- features of parapneumonic effusion (decreased air entry, dullness to percussion) (see Respirology, R23)
- complications: ARDS, lung abscess, parapneumonic effusion/empyema, pleuritis ± hemorrhage

Investigations

- pulse oximetry to assess severity of respiratory distress
- CBC and differential, electrolytes, urea, Cr, ABG (if respiratory distress), troponin/CK, LFTs, urinalysis
- sputum Gram stain/C&S, blood C&S, ± serology/viral detection, ± pleural fluid C&S (if effusion >5 cm or respiratory distress)
- CXR±CT chest shows distribution (lobar consolidation or interstitial pattern), extent of infiltrate ± cavitation
- bronchoscopy ± washings for
  - (1) severely ill patients refractory to treatment and (2) immunocompromised patients

Treatment

- ABC, O_2, IV fluids, consider salbutamol (nebulized or MDI)
- determine prognosis and need for hospitalization and antibiotics

Criteria for Hospitalization

Table 9. CURB 65 Score – Pneumonia Clinical Prediction Tool

Component	Measurement(s)	Points	Total Score	Mortality	Disposition
Confusion	Altered mental status	1	0-1	<5%	Can treat as outpatient
Urea/BUN	Urea >7 mmol/L or BUN >20 mg/dL	1	2-3	5-15%	Consider hospitalization
Respiratory Rate	>30 breaths/min	1	4-5	15-30%	Consider ICU
Blood Pressure	Systolic <90 or diastolic <60 mmHg	1			
Age	**65** or older	1			

Table 10. IDSA/ATS Community Acquired Pneumonia Treatment Guidelines 2007

Setting	Circumstances	Treatment
Outpatient	Previously well No antibiotic use in last 3 mo	Macrolide[1] OR Doxycycline
	Comorbidities[2] Antibiotic use in last 3 mo (use different class)	Respiratory fluoroquinolone[3] OR β-lactam[4] + Macrolide[1]
Inpatient	Ward	Respiratory fluoroquinolone[3] OR β-lactam[4] + Macrolide[1]
	ICU	β-lactam[4] + (Macrolide[1] OR Respiratory fluoroquinolone[3])

1. Macrolide: azithromycin, clarithromycin, erythromycin
2. Comorbidities: chronic heart, lung, liver, or renal disease, DM, alcoholism, malignancy, asplenia, immunocompromised
3. Respiratory fluoroquinolone: moxifloxacin, gemifloxacin, levofloxacin
4. β-lactam: cefotaxime, ceftriaxone, ampicillin-sulbactam
IDSA: Infectious Diseases Society of America
ATS: American Thoracics Society

Table 11. IDSA/ATS Hospital/Ventilator/Healthcare-Associated Pneumonia Treatment Guidelines 2005

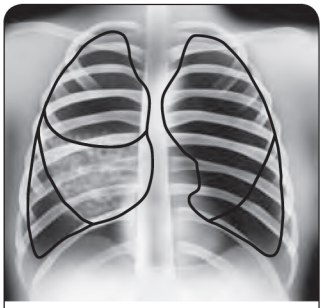
Setting	Treatment
No risk factors for multidrug resistance (MDR) Early onset (<5 d)	ceftriaxone OR levofloxacin, moxifloxacin, or ciprofloxacin OR ampicillin/sulbactam OR ertapenem
Late onset disease (≥5 d) or With risk factors for MDR: Antibiotic use in last 3 mo High frequency of antibiotic resistance in the community or in the specific hospital unit Hospitalization >1 d in past 3 mo Residence in a nursing home or extended care facility Dialysis within 30 d Home wound care Family member with multidrug-resistant pathogen Immunosuppressive disease and/or therapy	antipseudomonal cephalosporin (cefepime or ceftazidime) OR antipseudomonal carbepenem (imipenem or meropenem) OR β-lactam/β-lactamase inhibitor (piperacillin/tazobactam) PLUS antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) OR aminoglycoside (amikacin, gentamicin, or tobramycin) PLUS for MRSA linezolid or vancomycin PLUS for *Legionella* ensure regime includes either a macrolide or a fluoroquinolone

Note: Always use directed therapy against specific organism if one is found on culture (e.g. blood, sputum, etc.)
Note: These guidelines may be less applicable in Canada given lower rates of antibiotic resistance among common nosocomial pathogens

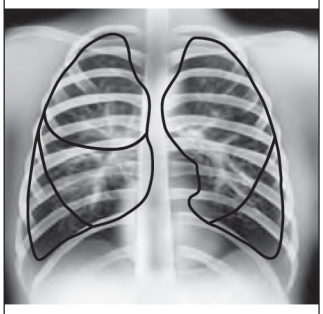
Prevention

- Public Health Agency of Canada recommends the following
  - vaccine for influenza A and B annually for all ages ≥ 6 mo
  - pneumococcal polysaccharide vaccine (Pneumovax®) for all adults >65 yr and in younger patients 24 mo of age and older at high risk for invasive pneumococcal disease (e.g. functional or anatomic asplenia, congenital or acquired immunodeficiency)

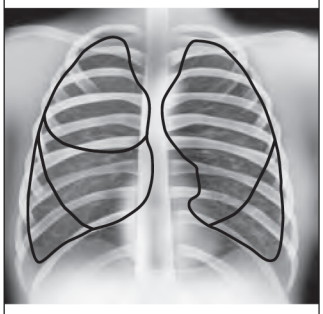
Does This Patient Have Ventilator-Associated Pneumonia?
JAMA 2007;297:1583-1593
Study: Systematic review of articles describing the precision and accuracy of clinical, radiographic, and laboratory data to diagnose bacterial ventilator-associated pneumonia, which is the most common and fatal nosocomial complication of intensive care.
Results: The presence of a new infiltrate on radiography with 2 or more of purulent sputum, fever, or increased white blood cell count increases the likelihood of ventilator-associated pneumonia (LR 2.8, 95% CI 0.97-7.9). Fewer than 50% neutrophils on the cell count of lower pulmonary secretions make ventilator-associated pneumonia unlikely (LR 0.05-0.10).
Conclusions: Routine bedside evaluation with radiographic information provides suggestive, but not definitive, evidence of ventilator-associated pneumonia. Clinicians need to consider additional tests to provide further evidence for ventilator-associated pneumonia.



Lobar Pneumonia



Bronchopneumonia



Interstitial Pneumonia

Figure 6. Lobar, broncho, and interstitial pneumonia

- pneumococcal conjugate vaccine (Prevnar-13®) for all children <5 yr, and for children and adolescents at high risk for invasive pneumococcal disease who are 5-17 yr and who have not previously received Prevnar-13® (CDC recommends giving Prevnar-13® to all adults at high risk for invasive pneumococcal disease)

Influenza

Definitions and Etiology
- influenza viruses A and B
- influenza A further divided into subtypes based on envelope glycoproteins
  - hemagglutinin (H) and neuraminidase (N)
- seasonal (epidemic) influenza
  - main circulating influenza viruses: human-origin A (H1N1) and B (H3N2) subtypes
  - associated with antigenic drift (gradual, minor changes due to random point mutations)
  - may create a new viral subtype resulting in a seasonal epidemic (disease prevalence is greater than expected)
  - outbreaks occur mainly during winter months (late December to early March)
- pandemic influenza
  - associated with antigenic shift: abrupt, major changes due to mixing of two different viral strains from different hosts
  - may create a new viral strain resulting in a pandemic outbreak (worldwide)
  - antigenic shift occurs only in type A
- transmission: droplet, possibly airborne

Table 12. Difference Between Influenza Strains

	Influenza A	Influenza B
Host(s)	Humans, birds, mammals	Humans only
Antigenic drift	Yes, new strains	Yes, new strains
Antigenic shift	Yes, new subtypes	No
Epidemics	Yes	Yes
Pandemics	Yes	No

Clinical Features
- incubation period 1-4 d
- acute onset of systemic (fever, chills, myalgias, arthralgias, H/A, fatigue) and respiratory symptoms (cough, dyspnea, pharyngitis)
- complications: respiratory (viral pneumonia, secondary bacterial pneumonia, otitis media, sinusitis), muscular (rhabdomyolysis, myositis), neurologic (encephalitis, meningitis, transverse myelitis, Guillain-Barré syndrome)

Investigations
- diagnosis is primarily clinical based on symptoms during the influenza season
- nasopharyngeal swabs for rapid antigen detection, DFA (Direct Fluorescent Antigen) detection, RT-PCR (gold standard)
- serology: rarely used for clinical management

Treatment and Prevention
- primarily supportive unless severe infection or high-risk of complications (e.g. elderly, pulmonary or cardiac disease)
- neuraminidase inhibitors: zanamivir (Relenza®) and oseltamivir (Tamiflu®) for treatment and prophylaxis against types A and B
  - decreases duration (by 1-2 d) and severity of symptoms if given within 48 h of onset
  - treatment beyond 48 h time window may be warranted in immunosuppressed and critically ill patients
- M2-inhibitors: amantidine/rimantidine for treatment and prophylaxis against type A only no longer recommended due to increased resistance
- vaccine for influenza A and B viruses is recommended annually for all ages ≥ 6 mo
  - vaccine is reformulated each year to reflect circulating influenza A and B strains

Does This Adult Patient Have Pneumonia? From The Rational Clinical Examination
JAMA 2009; http://www.jamaevidence.com/content/3485708
Study: Systematic review of articles assessing the sensitivity and specificity of clinical exam maneuvers for the diagnosis of adult community acquired pneumonia.
Results: The presence of fever or immunosuppression had a positive likelihood ratio (+LR) of 2, while a history of dementia had a +LR of 3; however, these traits are not confirmatory. The presence of an abnormality in any vital sign, including tachycardia, tachypnea, or fever had a +LR ranging from 2-4, which was not significantly affected by different cut-points. The absence of vital sign abnormality had a –LR ranging from 0.5-0.8. The combination of respiratory rate <30/min, heart rate <100/min, and temperature <37.8°C had a –LR of 0.18. Findings on chest exam raised the likelihood of diagnosis, but were uncommonly seen in studies. For example, presence of asymmetric respirations essentially confirmed the diagnosis, but was only present in 4% of patients. In patients with a clinical diagnosis, but normal radiograph, only ~10% will develop radiographic findings in 72 h.
Conclusions: Evidence suggests no single item on clinical history or physical exam is sufficient to rule in or out pneumonia without chest x-ray. Vital sign abnormalities were correlated with a diagnosis of pneumonia. Findings on chest exam significantly raised the likelihood of pneumonia, but were uncommonly seen in studies.

Beware! Do Not Confuse *H. influenzae* with Influenza Virus
H. influenzae: a bacterium (Types A, B, C, D, E, F, refer to capsule)
Influenza: a virus (Types A and B refer to strain)

Vaccines for Preventing Influenza in Healthy Adults
Cochrane DB Syst Rev 2014;CD001269
Study: Meta-analysis of 90 RCTs and quasi-RCTs evaluating influenza vaccines compared to placebo in healthy individuals aged 16-65 yr.
Results: The preventative effect of inactivated influenza vaccine on healthy adults is small: 40 people would need a vaccination to avoid one influenza-like illness and 71 people would need a vaccination to prevent one case of influenza. 15.6% of unvaccinated versus 9.9% of vaccinated people developed influenza-like symptoms: of these participants, only 2.4% and 1.1%, respectively, developed laboratory-confirmed influenza. Vaccination had a modest effect on working days lost, but no effects on hospitalization or complications. The effectiveness of live aerosol vaccinations on healthy adults is similar to that of inactivated influenza vaccines: 46 people would need a vaccination to avoid one influenza-like illness.
Conclusions: Influenza vaccines have a very modest effect in reducing influenza-like illness and working days lost in the general population.

Skin and Soft Tissue Infections

Cellulitis

Definition
- acute infection of the skin principally involving the dermis and subcutaneous tissue

Etiology
- common causative agents: *S. aureus*, β-hemolytic streptococci
- immunocompromised patients or water exposure: may also include GN rods and fungi
- risk factors
  - trauma with direct inoculation, recent surgery
  - peripheral vascular disease, lymphedema DM, cracked skin in feet/toes (tinea pedis)

Clinical Features
- pain, edema, erythema with indistinct borders ± regional lymphadenopathy, systemic symptoms (fevers, chills, malaise)
- can lead to ascending lymphangitis (visible red streaking in skin along lymphatics proximal to area of cellulitis)

Investigations
- CBC and differential, blood C&S if febrile
- skin swab ONLY if open wound with pus

Treatment
- antibiotics: cephalexin (broader coverage if risk factors for GN rods)
- if extensive erythema or systemic symptoms, consider cefazolin IV
- if MRSA is suspected, alternative therapy should be prescribed (see *A Simplified Look at Antibiotics*, ID47)
- limb rest and elevation may help reduce swelling

Necrotizing Fasciitis

Definition
- life- and limb-threatening infection of the deep fascia characterized by rapid spread

Etiology
- Two main forms
  - Type I: polymicrobial infection – aerobes and anaerobes (e.g. *S. aureus, Bacteroides, Enterobacteriaceae*)
  - Type II: monomicrobial infection with GAS, and less commonly *S. aureus*

Clinical Features
- pain out of proportion to clinical findings and beyond border of erythema
- edema, ± crepitus (subcutaneous gas from anaerobes), ± fever
- infection spreads rapidly
- patients may rapidly become very sick (tachycardia, hypotension, lightheadedness)
- late findings
  - skin turns dusky blue and black (secondary to thrombosis and necrosis)
  - induration, formation of hemorrhagic bullae

Investigations
- clinical/surgical diagnosis – do NOT wait for results of investigations before beginning treatment
- blood and tissue C&S
- serum CK (elevated CK usually means myonecrosis – a late sign)
- plain film x-ray (soft tissue gas may be visualized)
- surgical exploration for debridement of infected tissue

Treatment
- resuscitation with IV fluids
- emergency surgical debridement to confirm diagnosis and remove necrotic tissue (may require amputation)
- IV antibiotics
  - unknown organism: meropenem or piperacillin/tazobactam + clindamycin IV ± vancomycin if MRSA is considered
  - Type I (polymicrobial): piperacillin/tazobactam + clindamycin IV
  - Type II (monomicrobial): cefazolin (or cloxacillin) + clindamycin IV; with confirmed GAS infection, penicillin G + clindamycin IV
  - with Type II, evaluate for streptococcal toxic shock syndrome and the need for IVIg

Gastrointestinal Infections

Acute Diarrhea

- see Gastroenterology, G15
- see Pediatrics, P35

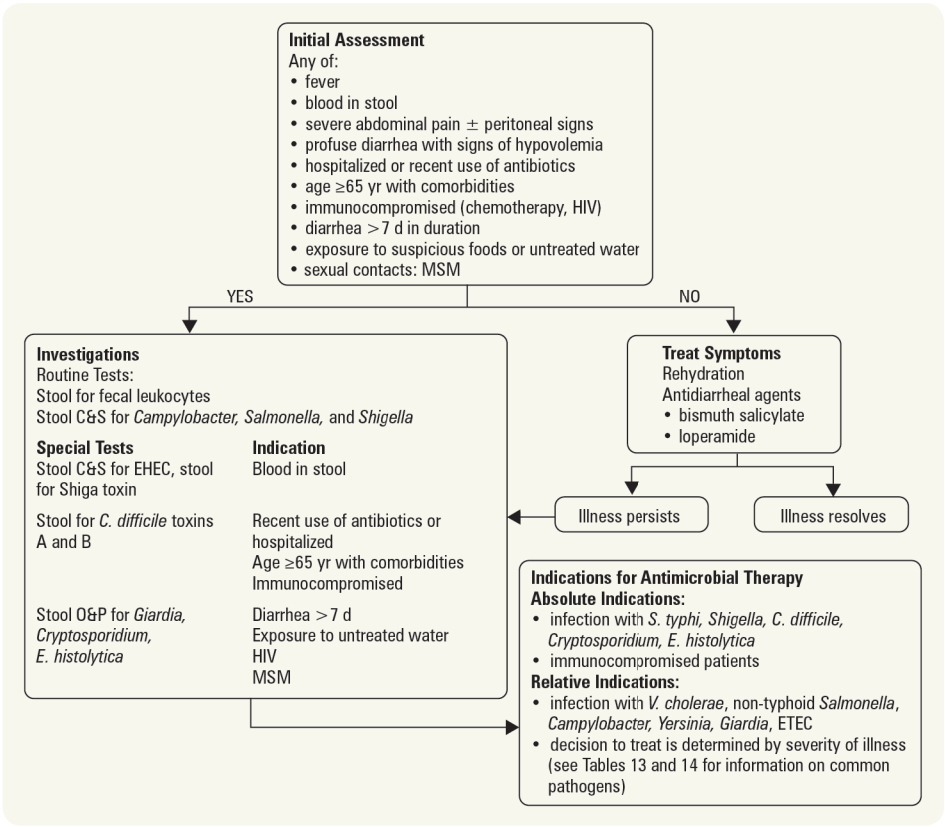
Epidemiology
- one of the top five leading causes of death worldwide, according to the World Health Organization
- significant morbidity in developed countries (over 900,000 hospitalizations in the United States each year)

Definition
- passage of ≥3 loose or liquid stools/d OR >200 g stool/d for >2 d but ≤14 d

Approach to Acute Diarrhea
- rationale
  - the vast majority of acute diarrhea is caused by infection
  - in most cases, acute diarrheal illness is viral and/or self-limited, and lasts <3 d
  - investigations are costly and are necessary only in certain circumstances
- therefore, the evaluation of acute diarrhea involves
  - identifying characteristics of the illness or patient that warrant further investigation
  - assessing volume status to determine appropriate method of rehydration
- see Figure 7

Physical Exam
- volume status: appearance, level of alertness, pulse, BP, orthostatic vitals, JVP, mucous membranes, skin turgor, capillary refill
- abdominal exam: pain, guarding, peritoneal signs

Treatment
- rehydration is mainstay of treatment
  - oral rehydration therapy
  - IV rehydration if oral intake insufficient to replace fluid loss
- antidiarrheal agents reduce duration of diarrhea: loperamide, bismuth salicylate
  - delays excretion of causative pathogens
  - contraindications: diarrhea with fever, bloody stool or diarrhea caused by *C.difficile*
- antibiotic therapy is rarely indicated because
  - most acute diarrheal illness is viral and self-limited
  - antibiotics can eradicate normal gut flora, predisposing patient to *C. difficile* infection
  - antibiotics prolong the shedding of *Salmonella* and other causes of bacterial diarrhea
  - in EHEC infection, antibiotics may increase the risk of HUS
  - indications for antibiotic therapy are shown in Figure 7



Causes of Acute Bloody Diarrhea

Campylobacter
Hemorrhagic *E. coli* (e.g. O157:H7)
Entamoeba histolytica
Salmonella
Shigella

Figure 7. Approach to acute diarrhea

Table 13. Bacteria in Infectious Diarrhea

Pathogen	Source or Mode of Transmission	Incubation	Clinical Features				Duration	Antimicrobial Therapy	Notes
			Fever	Bloody Stool	Abdo Pain	N/V			
B. cereus – Type A (emetic)	Rice dishes	1-6 h	–	–	–	+	<12 h	None	Preformed exotoxin
B. cereus – Type B (diarrheal)	Meats, vegetables, dried beans, cereals	8-16 h	–	–	–	–	<24 h	None	Secondary endotoxin
Campylobacter jejuni	Uncooked meat, especially poultry	2-10 d	+	±	+	±	<1 wk	Macrolide or fluoroquinolone if diarrhea >1 wk, bloody diarrhea, or immunocompromised	Most common bacterial cause of diarrhea in Canada Associated with Guillain-Barré syndrome
Clostridium difficile	Can be normally present in colon in small numbers (primary risk factor for disease is exposure to antimicrobials)	Unclear	±	±	±	–	Variable	Stop culprit antibiotic therapy, if possible Supportive therapy (IV fluids) Mild-moderate disease: metronidazole PO x 10-14 d Severe disease: vancomycin PO x 10 - 14 d Toxic Megacolon: metronidazole IV + vancomycin PO (as above) and general surgery consult	Usually follows antibiotic treatment (especially clindamycin, fluoroquinolones, penicillins, cephalosporins) Can develop pseudomembranous colitis
Clostridium perfringens	Contaminated food, especially meat and poultry	8-12 h	±	–	+	–	<24 h	None	Clostridium spores are heat resistant Secondary enterotoxin
Enteroinvasive *E. coli* (EIEC)	Contaminated food/water	1-3 d	+	±	+	–	7-10 d	None	Relatively uncommon
Enterotoxigenic *E. coli* (ETEC)	Contaminated food/water	1-3 d	–	–	+	–	3 d	Fluoroquinolone or azithromycin for moderate to severe symptoms	Most common cause of traveller's diarrhea Heat-labile and heat-stable toxins
Enterohemorrhagic *E. coli* (EHEC/STEC) i.e. O157:H7	Contamination of hamburger, raw milk, drinking, and recreational water	3-8 d	–	+	+	±	5-10 d	None: antibiotics increase risk of HUS	Shiga toxin production Monitor renal function: 10% develop HUS Antidiarrheals increase risk of HUS
Salmonella typhi *S. paratyphi* (i.e. Enteric Fever, Typhoid)	Fecal-oral Contaminated food/water, travel to endemic area	10-14 d	+	±	+	±	<5-7 d	Empiric treatment with ceftriaxone or azithromycin Fluoroquinolone resistance is increasing	*Salmonella typhi*: "Rose spot" rash (on anterior thorax, upper abdomen), fever, and abdominal pain precedes diarrhea
Non-typhoidal Salmonellosis *S. typhimurium,* *S. enteritidis*	Contaminated animal food products, especially eggs, poultry, meat, milk	12-72 h	+	±	+	+	3-7 d	Ciprofloxacin only in severe illness, extremes of age, joint prostheses, valvular heart disease, severe atherosclerosis, cancer, uremia	
Shigella dysenteriae	Fecal-oral Contaminated food/water	1-4 d	+	±	+	+	<1 wk	Fluoroquinolone	Very small inoculum needed for infection Complications include toxic megacolon, HUS Antidiarrheals may increase risk of toxic megacolon
Staphylococcus aureus	Unrefrigerated meat and dairy products (custard, pudding, potato salad, mayo)	2-4 h	–	–	+	+	1-2 d	None	Heat-stable preformed exotoxin
Vibrio cholerae	Contaminated food/water, especially shellfish	1-3 d	–	–	–	–	3-7 d	Tetracycline or quinolones (ciprofloxacin)	Massive watery diarrhea (1-3 L/d) Mortality <1% with treatment
Yersinia	Contaminated food Unpasteurized milk	5 d	+	±	+	±	Up to 3 wk	Fluoroquinolone only for severe illness	Majority of cases in children 1-4 yr Mesenteric adenitis and terminal ileitis can occur without diarrhea, mimicking appendicitis

Table 14. Parasites in Infectious Diarrhea

Pathogen	Source or Mode of Transmission	Incubation	Clinical Features				Duration	Antimicrobial Therapy	Notes
			Fever	Bloody Stool	Abdo Pain	N/V			
Cryptosporidium	Fecal-oral	7 d	±	–	–	+	1-20 d	Paromomycin + nitazoxanide	Immune reconstitution if immunosuppressed
Entamoeba histolytica	Worldwide endemic areas Fecal-oral	2-4 wk	±	+	–	+	Variable	Metronidazole + iodoquinol or paromomycin if symptomatic infection Only iodoquinol or paromomycin for asymptomatic cyst passage	If untreated, potential for liver abscess Sigmoidoscopy shows flat ulcers with yellow exudates
Giardia lamblia	Fecal-oral Contaminated food/water	1-4 wk	–	–	+	+	Variable	Metronidazole or nitazoxanide Treatment of asymptomatic carriers not recommended	Higher risk in: day care children, intake of untreated water ("beaver fever"), MSM, immunodeficiency (decreased IgA) May need duodenal biopsy

Table 15. Viruses in Infectious Diarrhea

Pathogen	Source or Mode of Transmission	Incubation	Clinical Features				Duration	Antimicrobial Therapy	Notes
			Fever	Bloody Stool	Abdo Pain	N/V			
Norovirus	Fecal-oral	24 h	–	–	+	+	24 h	None	Noroviruses includes Norwalk virus
Rotavirus	Fecal-oral	2-4 d	±	–	–	±	3-8 d	None	Can cause severe dehydration Virtually all children are infected by 3 yr of age Oral vaccine given at 2 and 4 mo of age

Traveller's Diarrhea

- see *Acute Diarrhea,* ID10

Epidemiology
- most common illness to affect travellers
- up to 50% of travellers to developing countries affected in first 2 wk and 10-20% after returning home

Etiology
- bacterial (80-90%): *E. coli* most common (ETEC), *Campylobacter, Shigella, Salmonella, Vibrio* (non-cholera); wide regional variation (e.g. *Campylobacter* more common in Southeast Asia)
- viral: norovirus, rotavirus, and astrovirus account for 5-8%
- protozoal (rarely): *Giardia*, *Entamoeba histolytica*, *Cryptosporidium*, and *Cyclospora* for ~10% in long-term travellers
- pathogen-negative traveller's diarrhea common despite exhaustive microbiological workup

Treatment
- rehydration is the mainstay of therapy
  - rehydrate with sealed beverages
  - in severe fluid loss use oral rehydration solutions (1 package in 1 L boiled or treated water)
- treat symptoms: antidiarrheal agents (e.g. bismuth salicylate, loperamide)
- empiric antibiotics in moderate or severe illness: ciprofloxacin or azithromycin or rifaximin
  - note: there is increasing fluoroquinolone resistance in causative agents, especially in Southeast Asia

Prevention
- proper hygiene practices
  - avoid consumption of: foods or beverages from establishments with unhygienic conditions (e.g. street vendors), raw fruits or vegetables without a peel, raw or undercooked meat and seafood
  - avoid untreated water
- bismuth salicylate (Pepto-Bismol®): 60% effective (2 tablets qid according to CDC website)
- CDC Guidelines: antibiotic prophylaxis not recommended
  - increased risk of infection with resistant organisms
  - high risk groups (e.g. immunocompromised) likely to be infected with pathogen not covered by standard antimicrobial agents

Bismuth salicylate (Pepto-Bismol®) can cause patients to have black stools, which may be mistaken for melena

- Dukoral®: oral vaccine that offers protection against *V. cholerae* (efficacy ~80%) and ETEC (efficacy ~50-67%). Not recommended for routine use in travellers, but the PHAC recommends that it may be considered in short-term travellers >2 yr old who are high-risk (e.g. chronic illness) for whom there is an increased risk of serious consequences for traveller's diarrhea (e.g. chronic renal failure, CHF, type 1 DM, inflammatory bowel disease), immunosuppressed, history of repeat traveller's diarrhea, increased risk of acquiring traveller's diarrhea (gastric hypochlorhydria or young children >2 yr), or travellers to cholera endemic countries at increased risk of exposure

Chronic Diarrhea

- see Gastroenterology, G16

Peptic Ulcer Disease *(H. pylori)*

- see Gastroenterology, G12

Bone and Joint Infections

Septic Arthritis

Routes of Infection
- hematogenous
  - contiguous osteomyelitis common in children
- direct inoculation via skin/trauma
- iatrogenic (surgery, arthroscopy, arthrocentesis)

Etiology
- gonococcal
  - *N. gonorrhoeae:* previously accounted for 75% of septic arthritis in young sexually active adults
- non-gonococcal
  - *S. aureus:* affects all ages, rapidly destructive, accounts for most non-gonococcal cases of septic arthritis in adults (especially in those with rheumatoid arthritis)
  - *Streptococcus* species (Group A and B)
  - Gram-negatives: affect neonates, elderly, IV drug users, immunocompromised
  - *S. pneumoniae*: affects children
  - *Kingella kingae:* affects children aged <2 yr of age
  - *Haemophilus influenzae* type B (Hib) now rare due to Hib vaccine: consider in unvaccinated children
  - *Salmonella* spp.: characteristic of sickle cell disease
  - coagulase-negative *Staphylococcus* species: prosthetic joints
- if culture negative: partially-treated infection (prior to oral antibiotics), reactive arthritis, rheumatic fever, less common bacterial causes such as *Borrelia* spp. (Lyme disease) or *Tropheryma whipplei* (Whipple's disease), and non-infectious causes

Medical Emergency
Septic arthritis is a medical emergency! If untreated, rapid joint destruction will occur

Risk Factors
- gonococcal
  - age (<40 yr), multiple partners, unprotected intercourse, MSM
- non-gonococcal
  - most affected children are previously healthy with no risk factors: occasionally preceding history of minor trauma
  - bacteremia (extra-articular infection with hematogenous seeding, endocarditis)
  - prosthetic joints/recent joint surgery
  - underlying joint disease (rheumatoid arthritis, osteoarthritis)
  - immunocompromise (DM, chronic kidney disease, alcoholism, cirrhosis)
  - loss of skin integrity (cutaneous ulcer, skin infection)
  - age >80 yr

Disseminated Gonococcal Infection Triad
- Migratory arthralgias
- Tenosynovitis next to inflamed joint
- Pustular skin lesions

Clinical Features of Gonococcal Arthritis
- two forms (although often overlap)
  - bacteremic form
    - systemic symptoms: fever, malaise, chills
    - gonococcal triad: migratory polyarthralgias, tenosynovitis, dermatitis (pustular skin lesions)
  - septic arthritis form
    - local symptoms in involved joint: swelling, warmth, pain, inability to bear weight, marked decrease in range of motion (see Rheumatology, RH3 for differential diagnosis)

Clinical Features of Non-Gonococcal Arthritis
- acute onset of pain, swelling, warmth, decreased range of motion ± fever and chills
- most often in large weight-bearing joints (knee, hip, ankle) and wrists
- usually monoarticular (polyarticular risk factors: rheumatoid arthritis, endocarditis, GBS)

Investigations
- consider rheumatologic causes for monoarthritis (see Rheumatology, RH3)
- gonococcal: blood C&S, as well as endocervical, urethral, rectal, and oropharyngeal testing
- non-gonococcal: blood C&S
- arthrocentesis (synovial fluid analysis) is mandatory: CBC and differential, Gram stain, C&S, examine for crystals
  - infectious = opaque, increased WBCs (>15,000/mm^3: likelihood of infection increases with increasing WBCs), PMNs >90%, culture positive
  - growth of *N. gonorrhoeae* from synovial fluid is successful in <50% of cases
- ± plain x-ray: assess for osteomyelitis, provides baseline to monitor treatment

Treatment
- medical
  - empiric IV antibiotics: specific choice depends on clinical scenario; for most adults, vancomycin + ceftriaxone is reasonable; for fully vaccinated children, cefazolin or cloxacillin IV unless MRSA is a consideration – delay may result in joint destruction
  - Gram stain and cultures guide subsequent treatment
  - gonococcal: ceftriaxone + azithromycin, for concurrent treatment of *C. trachomatis*
  - non-gonococcal: antibiotics against *Streptococcus* spp. (2-3 wk IV f/b PO), *S. aureus* (4 wk IV minimum), or GNB (4 wk)
- surgical drainage if (see Orthopedics, OR10)
  - persistent positive joint cultures on repeat arthrocentesis
  - hip joint involvement
  - prosthetic joint
- daily joint aspirations until culture sterile; no need to give intra-articular antibiotics
- physiotherapy

Intra-articular steroids are contraindicated until septic arthritis has been excluded

Prognosis
- gonococcal: responds well after 24-48 h of initiating antibiotics (usually complete recovery)
- non-gonococcal: in children, generally good outcome if treated promptly; in adults, up to 50% morbidity (decreased joint function/mobility)

Diabetic Foot Infections

Etiology
- neuropathy, peripheral vascular disease, and hyperglycemia contribute to foot ulcers that heal poorly, and are predisposed to infection
- organisms in mild infection: *S. aureus, Streptococcus* spp.
- organisms in moderate/severe infection: polymicrobial with aerobes (*S. aureus, Streptococcus, Enterococcus*, GNB) and anaerobes (*Peptostreptococcus, Bacteroides, Clostridium*)

Clinical Features
- not all ulcers are infected
- consider infection if: probe to bone (see below), ulcer present >30 d, recurrent ulcers, trauma, PVD, prior amputation, loss of protective sensation, renal disease, history of walking barefoot
- diagnosis of infected ulcer: ≥2 of the cardinal signs of inflammation (redness, warmth, swelling, pain) or the presence of pus
- ± crepitus, osteomyelitis, systemic toxicity
- visible bone or probe to bone → osteomyelitis
- infection severity
  - mild = superficial (no bone/joint involvement)
  - moderate = deep (beneath superficial fascia, involving bone/joint) or erythema >2 cm
  - severe = infection in a patient with systemic toxicity (fever, tachypnea, leukocytosis, tachycardia, hypotension)

Does this Patient with Diabetes have Osteomyelitis of the Lower Extremity?
JAMA 2008;299:806-813
Study: Systematic literature review. 21 studies.
Population: 1,027 adult patients with DM being investigated for osteomyelitis.
Intervention: Various aspects of history, physical exam, laboratory tests, and diagnostic imaging studies versus bone biopsy.
Primary Outcome: Diagnostic utility.
Results: No studies examined any part of history taking. Temperature, ulcer characteristics (erythema, swelling, purulence), elevated WBC, skin swabs, and soft tissue cultures were not useful. Nuclear imaging has poor specificity for osteomyelitis (62%-88.5%), and MRIs have greater accuracy in detecting osteomyelitis.

Finding	(+) LR	(–) LR
Visualization of bone	9.2	0.70
Ulcer area >2 cm^2	7.2	0.48
Probe-to-bone	6.4	0.39
Clinical judgment	5.5	0.54
ESR >70 mm/h	11	NS*
Plain radiographs	2.3	0.63
MRI	3.8	0.14

*NS = not significant

Investigations
- curettage specimen from ulcer base, aspirate from an abscess or bone biopsy (results from superficial swabs do not represent organisms responsible for deeper infection)
- blood C&S if febrile
- assess for osteomyelitis by x-ray (although not sensitive in early stages) or MRI if high clinical suspicion
  - if initial x-ray normal, repeat 2-4 wk after initiating treatment to increase test sensitivity

Treatment
- evaluate for early surgical debridement ± revascularization or amputation
- eliminate/reduce pressure and provide regular local wound care
- mild: cephalexin or clindamycin
- moderate: clindamycin + ciprofloxacin or moxifloxacin PO, ceftriaxone or ertapenem IV ± MRSA coverage
- severe: piperacillin/tazobactam or meropenem IV ± vancomycin if MRSA known or suspected
- encourage glycemic control

Osteomyelitis

- see Orthopedics, OR10

Cardiac Infections

Infective Endocarditis

Definition
- infection of cardiac endothelium, most commonly the valves
- classifications: acute vs. subacute, native valve vs. prosthetic valve, right sided vs. left sided
- leaflet vegetations are made of platelet-fibrin thrombi, WBCs, and bacteria

Risk Factors and Etiology
- predisposing conditions
  - **high risk**: prosthetic cardiac valve, previous IE, congenital heart disease (unrepaired, repaired within 6 mo, repaired with defects), cardiac transplant with valve disease (surgically constructed systemic-to-pulmonary shunts or conduits)
  - moderate risk: other congenital cardiac defects, acquired valvular dysfunction, hypertrophic cardiomyopathy
  - low/no risk: secundum ASD or surgically repaired ASD < VSD, PDA, MV prolapse, ischemic heart disease, previous CABG
  - opportunity for bacteremia: IVDU, indwelling venous catheter, hemodialysis, poor dentition, DM, HIV
- frequency of valve involvement MV >> AV > TV > PV
  - but in 50% of IVDU-related IE the tricuspid valve is involved

Etiology of Culture-Negative Endocarditis
- **HACEK (fastidious Gram-negative bacilli)**
  - ***H****aemophilus parainfluenzae*
  - ***A****ggregatibacter aphrophilus/* ***A****ggregatibacter actinomycetemcomitans*
  - ***C****ardiobacterium hominis*
  - ***E****ikenella corrodens*
  - ***K****ingella kingae*
- *Coxiella burnetii*
- *Bartonella* species
- *Tropheryma whipplei*
- Fungi
- Mycobacteria

Table 16. Microbial Etiology of Infective Endocarditis Based on Risk Factors

Native Valve	Intravenous Drug Users (IVDU)	Prosthetic Valve (recent surgery <2 mo)	Prosthetic Valve (remote surgery >2 mo)
Streptococcus[1] **(36%)**	***S. aureus* (68%)**	***S. aureus* (36%)**	***Streptococcus* (20%)**
***S. aureus* (28%)**	***Streptococcus* (13%)**	***S. epidermidis* (17%)**	***S. aureus* (20%)**
Enterococcus (11%)	*Enterococcus*	Other	***S. epidermidis* (20%)**
S. epidermidis	GNB	*Enterococcus*	***Enterococcus* (13%)**
GNB	*Candida*	GNB	Other[2]
Other[2]	Other[3]	Other[2]	

Organisms in bold are the most common isolates.
1. *Streptococcus* includes mainly viridans group *streptococci*
2. Other includes less common organisms such as:
   - *Streptococcus gallolyticus* (previously known as *S. bovis*; usually associated with underlying GI malignancy, cirrhosis)
   - Culture-negative organisms including nutritionally-deficient *streptococci*, HACEK, *Bartonella, Coxiella, Chlamydia, Legionella, Brucella*
   - *Candida*
3. IVDU endocarditis pathogens depend on substance used to dilute the drugs (i.e. tap water = *Pseudomonas*, saliva = oral flora, toilet water = GI flora)

Clinical Features
- systemic
  - fever (80-90%), chills, weakness, rigors, night sweats, weight loss, anorexia
- cardiac
  - dyspnea, chest pain, clubbing (subacute)
  - regurgitant murmur (new onset or increased intensity)
  - signs of CHF (secondary to acute MR, AR)
- embolic/vascular
  - petechiae over legs, splinter hemorrhages (linear, reddish-brown lesion within nail bed)
  - Janeway lesions (painless, 5 mm, erythematous, hemorrhagic pustular lesions on soles/palms)
  - focal neurological signs (CNS emboli), H/A (mycotic aneurysm)
  - splenomegaly (subacute)
  - microscopic hematuria, flank pain (renal emboli) ± active sediment
- immune complex
  - Osler's nodes (painful, raised, red/brown, 3-15 mm on digits)
  - glomerulonephritis
  - arthritis
  - Roth's spots (retinal hemorrhage with pale centre)

Clinical Features of Infective Endocarditis

FROM JANE
Fever
Roth's spots
Osler's nodes
Murmur
Janeway lesions
Anemia
Nail-bed hemorrhages (i.e. splinter hemorrhages)
Emboli

Diagnosis
- Modified Duke Criteria, see Table 17
  - definitive diagnosis if: 2 major, OR 1 major + 3 minor, OR 5 minor
  - possible diagnosis if: 1 major + 1 minor, OR 3 minor

Table 17. Modified Duke Criteria

Major Criteria (2)
1. Positive blood cultures for IE • Typical microorganisms for IE from 2 separate blood cultures (*Streptococcus viridans*, HACEK group (see ID16), *Streptococcus gallolyticus* (previously known as *S. bovis*), *Staphylococcus aureus*, community-acquired *enterococci*) OR • Persistently positive blood culture, defined as recovery of a microorganism consistent with IE from blood drawn >12 h apart OR • All of 3 or a majority of 4 or more separate blood cultures, with first and last drawn >1 h apart OR • Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titer >1:800
2. Evidence of endocardial involvement • Positive echocardiogram for IE (oscillating intracardiac mass on valve or supporting structures, or in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation OR abscess OR new partial dehiscence of prosthetic valve) OR • New valvular regurgitation (insufficient if increase or change in preexisting murmur)
Minor Criteria (5)
1. Predisposing condition (abnormal heart valve, IVDU)
2. Fever (38.0°C/100.4°F)
3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysms, ICH, conjunctival hemorrhages, Janeway lesions
4. Immunologic phenomena: glomerulonephritis, rheumatoid factor, Osler's nodes, Roth's spots
5. Positive blood culture but not meeting major criteria OR serologic evidence of active infection with organism consistent with IE

Investigations

- serial blood cultures: 3 sets (each containing one aerobic and one anaerobic sample) collected from different sites >1 h apart
  - persistent bacteremia is the hallmark of endovascular infection (such as IE)
- repeat blood cultures (at least 2 sets) after 48 to 72 h of appropriate antibiotics to confirm clearance
- blood work: CBC and differential (normochromic, normocytic anemia), ESR (increased), RF (+), BUN/Cr
- urinalysis (proteinuria, hematuria, red cell casts) and urine C&S
- ECG: prolonged PR interval may indicate perivalvular abscess
- Echo findings: vegetations, regurgitation, abscess
  - TTE (poor sensitivity) inadequate in 20% (obesity, COPD, chest wall deformities)
  - TEE indicated if TTE is non-diagnostic in patients with at least possible endocarditis or if suspect prosthetic valve endocarditis or complicated endocarditis (e.g. paravalvular abscess/perforation) (~90% sensitivity)

TEE transesophageal echo
TTE transthoracic echo

Treatment

- medical
  - usually non-urgent and can wait for confirmation of etiology before initiating treatment
  - empiric antibiotic therapy if patient is unstable; administer ONLY after blood cultures have been taken
    - first-line empiric treatment for native valve: vancomycin + gentamicin OR ceftriaxone
    - first line empiric treatment for prosthetic valve: vancomycin + gentamicin + cefepime + rifampin
  - targeted antibiotic therapy: antibiotic and duration (usually 4-6 wk) adjusted based on valve, organism, and sensitivities
  - monitor for complications of IE (e.g. CHF, conduction block, new emboli) and complications of antibiotics (e.g. interstitial nephritis)
  - prophylaxis only for high risk individuals listed above with dental procedures that may lead to bleeding OR invasive procedure of the respiratory tract that involves incision or biopsy of the respiratory mucosa, such as tonsillectomy and adenoidectomy OR procedures on infected skin, skin structure, or musculoskeletal tissue
    - dental/respiratory: amoxicillin single dose 30-60 min prior; clindamycin if penicillin-allergic
    - skin/soft tissue: cephalexin single dose 30-60 min prior; clindamycin if penicillin-allergic (modify based on etiology of skin/soft tissue infection)
- surgical
  - most common indication is refractory CHF
  - other indications include: valve ring abscess, fungal etiology, valve perforation, unstable prosthesis, ≥2 major emboli, antimicrobial failure (persistently positive blood cultures), mycotic aneurysm, *Staphylococci* on a prosthetic valve

Prognosis

- adverse prognostic factors: CHF, prosthetic valve infection, valvular/myocardial abscess, embolization, persistent bacteremia, altered mental status prognostic factors: CHF, prosthetic valve infection, valvular/myocardial abscess
- mortality: prosthetic valve IE (25-50%), non-IVDU *S. aureus* IE (30-45%), IVDU *S. aureus* or streptococcal IE (10-15%)

CNS Infections

Meningitis

• see Pediatrics, P60

Definition
• inflammation of the meninges

Etiology

Table 18. Common Organisms in Meningitis

Bacterial			Viral	Fungal	Other
Age 0-4 wk	Age 1-23 mo	Age >2 yr			
GBS *E. coli* *L. monocytogenes* *Klebsiella*	*GBS* *E. coli* *S. pneumoniae* *N. meningitidis* *H. influenzae*	*S. pneumoniae* *N. meningitidis* *L. monocytogenes* (age >50 and comorbidities)	HSV-1, 2 VZV Enteroviruses Parechoviruses West Nile	*Cryptococcus* *Coccidioides*	Lyme disease Neurosyphilis TB

Risk Factors
• lack of immunization against *S. pneumoniae, H. influenzae type b* in children
• hematogenous spread after invasion from a mucosal surface (nasopharynx)
• parameningeal focus (otitis media, infection, sinusitis)
• penetrating head trauma
• anatomical meningeal defects – CSF leaks
• previous neurosurgical procedures, shunts
• immunodeficiency (corticosteroids, HIV, asplenia, hypogammaglobulinemia, complement deficiency)
• contact with colonized or infected persons

Clinical Features
• neonates and children: fever, lethargy, irritability, vomiting, poor feeding
• older children and adults: fever, H/A, neck stiffness, confusion, lethargy, altered level of consciousness, seizures, focal neurological signs, N/V, photophobia, papilledema
• petechial rash in meningococcal meningitis, seen more frequently on trunk or lower extremities

Investigations
• blood work: CBC and differential, electrolytes (for SIADH), blood C&S
  ▪ CSF: opening pressure, cell count + differential, glucose, protein, Gram stain, bacterial C&S
  ▪ AFB, fungal C&S, cryptococcal antigen in immunocompromised patients, subacute illness, suggestive travel history or TB exposure
  ▪ PCR for HSV, VZV, enteroviruses; in infants <6 mo, parechoviruses
  ▪ WNV serology in blood and CSF during summer and early fall if viral cause suspected
• imaging/neurologic studies: CT, MRI, EEG if focal neurological signs present

Table 19. Typical CSF Profiles for Meningitis

CSF Analysis	Bacterial	Viral
Glucose (mmol/L)	Decreased	Normal
Protein (g/L)	Markedly Increased	Increased
WBC	500-10,000/μL	10-500/μL
Predominant WBC	Neutrophils	Lymphocytes

Treatment
• bacterial meningitis is a medical emergency: **do not delay antibiotics for CT or LP**
• empiric antibiotic therapy
  ▪ age <6 wk: ampicillin + cefotaxime IV OR ampicillin ± an aminoglycoside IV; add vancomycin if suspect S. pneumoiae
  ▪ 6 wks-3 mo: ampicillin + cefotaxime + vancomycin
  ▪ age >3 mo: vancomycin + cefotaxime OR ceftriaxone IV
    ◆ add ampicillin IV if risk factors for infection with *L. monocytogenes* present: age >50, alcoholism, immunocompromised
• steroids in acute bacterial meningitis: dexamethasone IV within 20 min prior to or with first dose of antibiotics
  ▪ continue in those patients with proven pneumococcal meningitis
  ▪ not recommended for patients with suspected bacterial meningitis in some resource-limited countries
  ▪ not recommended for neonatal meningitis

Brudzinski's Sign
Passive neck flexion causes involuntary flexion of hips and knees

Kernig's Sign
Resistance to knee extension when hip is flexed to 90°

Jolt Accentuation of H/A
Headache worsens when head turned horizontally at 2-3 rotations; more sensitive than Brudzinski's and Kernig's

CSF Gram Stain Findings
• *S. pneumoniae* – GP diplococci
• *N. meningitidis* – GN diplococci
• *H. influenzae* – Pleiomorphic GN coccobacilli
• *L. monocytogenes* – GP rods

Does this Adult Patient Have Acute Meningitis? From The Rational Clinical Examination
JAMA 2009; http://www.jamaevidence.com/content/3482857
Study: Systematic review of articles assessing the sensitivity and specificity of clinical exam maneuvers for the diagnosis of adult meningitis.
Results: In retrospective studies, sensitivity for headache was 68%, and 52% for nausea and vomiting. Sensitivity for physical exam findings is similarly low (fever: 87%, neck stiffness: 80%, altered mental status: 69%). Sensitivity for the combination of the classic triad of fever, neck stiffness, and altered mental status was 46%. In prospective studies, sensitivity of H/A was 92%, while sensitivity of N/V could not be pooled, and ranged from 32-70%. Brudzinski's and Kernig's signs had a sensitivity of 5% and Kernig's sign only 5-9%. Jolt accentuation had a sensitivity of 97%.
Conclusions: Data were heterogeneous, and lacked standardization of clinical exams. No single item on clinical history or physical exam was sufficient to rule out meningitis, including Kernig's and Brudzinski's signs, or the absence of the classic triad of fever, neck stiffness, and altered mental status meningitis. Jolt accentuation has high sensitivity, but further research is needed. LP may be performed safely without CT head in patients without altered LOC, no recent seizure, no history of CNS disease, not immunocompromised, and <60 yr.

Prevention
- see Pediatrics, P3
- immunization
  - children: immunization against *H. influenzae* type B (Pentacel®), *S. pneumoniae* (Synflorix®, Prevnar-13®), *N. meningitidis* (Menjugate®, Menactra®, Bexsero®)
  - adults: immunization against *N. meningitidis* in selected circumstances (outbreaks, travel, epidemics) and *S. pneumoniae* (Pneumovax®) for high-risk groups
- prophylaxis: close contacts of patients infected with *H. influenzae* type B should be treated with rifampin if they live with an inadequately immunized (<4 yr) or immunocompromised child (<18 yr); ciprofloxacin, rifampin, or ceftriaxone if close or household contact of a patient with *N. meningitidis*

Public Health Agency of Canada Indications for Adult Immunization

Pneumococcal Polysaccharide Vaccine (i.e. Pneumovax®)
- >65 yr
- >2 yr, with chronic cardiovascular/respiratory/hepatic/renal disorders, asplenia, sickle cell, or immunosuppression (8 wk after pneumococcal conjugate vaccine if <18 yr)

Meningococcal Quadrivalent Vaccine (Menactra® or Menomune®)
- Healthy young adults
- Asplenia
- Travellers to high-risk areas
- Military recruits or laboratory personnel
- Complement, factor D, or properdin deficiency or acquired terminal complement deficiency through receipt of eculizumab

Multicomponent meningococcal serogroup B vaccine (Bexsero®)
- Asplenia
- Military recruits or laboratory personnel
- Complement, factor D, or properdin deficiency, or acquired terminal complement deficiency through receipt of eculizumab

Prognosis
- complications
  - H/A, seizures, cerebral edema, hydrocephalus, SIADH, residual neurological deficit (especially CN VIII), deafness, death
- mortality
  - *S. pneumoniae* 25%; *N. meningitidis* 5-10%; *H. influenzae* 5%
  - worse prognosis if: extremes of age, delays in diagnosis and treatment, stupor or coma, seizures, focal neurological signs, septic shock at presentation

Encephalitis

Definition
- inflammation of the brain parenchyma

Etiology
- identified in only 40-70% of cases
  - when cause is identified, the most common etiology is viral: HSV, VZV, EBV, CMV, enteroviruses, West Nile, HIV, mumps, measles, rabies, polio
  - bacteria: *L. monocytogenes*, Mycobacteria, spirochetes (Lyme, syphillis), *Mycoplasma pneumoniae*
  - parasites: protozoa (e.g. *Toxoplasma*) and helminths (rare)
  - fungi: e.g. *Cryptococcus*
  - post-infectious (e.g. acute disseminated encephalomyelitis [ADEM])
  - auto-antibody mediated encephalitis
    - anti-N-methyl-D-aspartate (NMDA) receptor encephalitis most common
    - in adults, most autoantibody-mediated encephalitis cases are associated with malignancy

Pathophysiology
- acute inflammatory disease of the brain due to direct invasion or pathogen-initiated immune response
- viruses may reach the CNS via peripheral nerves (e.g. rabies, HSV)
- herpes simplex encephalitis
  - acute, necrotizing, asymmetrical hemorrhagic process with lymphocytic and plasma cell reaction which usually involves the medial temporal and inferior frontal lobes
  - associated with HSV-1, but can also be caused by HSV-2
- influenza and other respiratory viruses are associated with acute necrotizing encephalopathy (ANE); likely mediated by pathogen-initiated immune response

Meningitis and encephalitis patients can be distinguished based on their cerebral function. Cerebral function is abnormal in encephalitis patients (e.g. altered mental status, motor or sensory deficits, altered behaviour, speech or movement disorders), but may be normal in patients with meningitis. Note however, that there is considerable overlap between the two syndromes ("meningoencephalitis")

Clinical Features
- constitutional: fever, chills, malaise, N/V
- meningeal involvement (meningoencephalitis): H/A, nuchal rigidity
- parenchymal involvement: seizures, altered mental status, focal neurological signs
- herpes simplex encephalitis
  - acute onset (<1 wk) of focal neurological signs: hemiparesis, ataxia, aphasia, focal or generalized seizures
  - temporal lobe involvement: behavioural disturbance
  - usually rapidly progressive over several days and may result in coma or death
  - common sequelae: memory and behavioural disturbances

Investigations
- CSF: opening pressure, cell count and differential, glucose, protein, Gram stain, bacterial C&S, PCR for HSV, VZV, EBV, enteroviruses/parechoviruses, *M. pneumoniae*, and selectively for other less common etiologies
- serology: may aid diagnosis of certain causes of encephalitis (e.g. EBV, West Nile virus, rabies, *Bartonella henslae*)
- imaging/neurologic studies: CT, MRI, EEG to define anatomical sites affected

- invasive testing: brain tissue biopsy may be required for culture, histological examination, and immunocytochemistry (if diagnosis not clear via non-invasive means)
- findings in herpes simplex encephalitis (must rule out due to high mortality)
  - CT/MRI: medial temporal lobe necrosis
  - EEG: early focal slowing, periodic discharges

Treatment
- general supportive care
- monitor vital signs carefully
- IV acyclovir empirically until HSV encephalitis ruled out

Generalized Tetanus

- see Pediatrics, P4

Etiology and Pathophysiology
- caused by *Clostridium tetani*: motile, spore forming, anaerobic GP bacillus
- found in soil, splinters, rusty nails, GI tract (humans and animals)
- traumatic implantation of spores into tissues with low oxygenation (e.g. puncture wounds, burns, nonsterile surgeries or deliveries)
- upon inoculation, spores transform into *C. tetani* bacilli that produce tetanus toxin
  - toxin travels via retrograde axonal transport to the CNS where it irreversibly binds presynaptic neurons to prevent the release of inhibitory neurotransmitters (e.g. GABA)
  - net effect is the disinhibition of spinal motor reflexes which results in tetany and autonomic hyperactivity

Clinical Features
- generalized tetanus
  - initially present with painful spasms of masseters (trismus or "lockjaw")
  - sustained contraction of skeletal muscle with periodic painful muscle spasms (triggered by sensory stimuli, e.g. loud noises)
  - paralysis descends to involve large muscle groups (neck, abdomen)
  - apnea, respiratory failure, and death secondary to tonic contraction of pharyngeal and respiratory muscles
- autonomic hyperactivity
  - diaphoresis, tachycardia, HTN, fever as illness progresses

Investigations
- primarily a clinical diagnosis, often although not always with a history of a traumatic wound and lack of immunization
- culture wounds, CK may be elevated

Treatment
- stop toxin production
  - wound debridement to clear necrotic tissue and spores
  - antimicrobial therapy: IV metronidazole; IV penicillin G is an effective alternative
- neutralize unbound toxin with tetanus immune globulin (TIg)
- supportive therapy: intubation, spasmolytic medications (benzodiazepines), quiet environment, cooling blanket
- control autonomic dysfunction: α- and β-blockade (e.g. labetalol), magnesium sulfate

Antimicrobial therapy (e.g. metronidazole) may fail to treat *C. tetani* unless adequate wound debridement is performed

Prevention
- infection with *C. tetani* does not produce immunity – vaccinate patients on diagnosis
- tetanus toxoid vaccination (see Pediatrics, P4 and Emergency Medicine, ER17)

Rabies

Definition
- acute progressive encephalitis caused by RNA virus (genus *Lyssavirus* of the *Rhabdoviridae* family)

Etiology and Pathophysiology
- any mammal can transmit the rabies virus
  - most commonly transmitted by raccoon, skunk, bat, fox, cat, and dog; monkeys also a risk in the developing world
- transmission: breaching of skin by teeth or direct contact of infectious tissue (saliva, neural tissue) with skin or mucous membranes
  - almost all cases due to bites
- virus travels via retrograde axonal transport from PNS to CNS
- virus multiplies rapidly in brain, then spreads to other organs, including salivary glands
- development of clinical signs occurs simultaneously with excretion of rabies virus in saliva
  - infected animal can transmit rabies virus as soon as it shows signs of disease

Clinical Features
- five stages of disease
  1. incubation period
     - 1-3 mo on average (can range from days to years)
  2. prodrome (<1 wk)
     - influenza-like illness: low-grade fever, malaise, anorexia, N/V, H/A, sore throat
     - pain, pruritus, and paresthesia may occur at wound site
     - once prodromal symptoms develop, there is rapid, irreversible progression to death
       - progression from prodrome to coma and death may occur without an intervening acute neurologic syndrome
  3. acute neurologic syndrome: 3 types (<1 wk)
     a. encephalitic (most common): hyperactivity, fluctuating LOC, hydrophobia, aerophobia, hypersalivation, fever, seizures
        - painful pharyngeal spasms on encountering gust of air or swallowing water cause aerophobia and hydrophobia, respectively
     b. paralytic: quadriplegia, loss of anal sphincter tone, fever
     c. atypical: rare
  4. coma
     - complete flaccid paralysis, respiratory and cardiovascular failure
  5. death (within days to weeks of initial symptoms)

Investigations
- purpose of diagnosis by investigations is to limit patient contact with others and to identify others exposed to the infectious source
- ante-mortem: direct immunofluorescence or PCR on multiple specimens: saliva, skin biopsy, serum, CSF
- post-mortem: direct immunofluorescence in nerve tissue, presence of Negri bodies (inclusion bodies in neurons)

Treatment
- post-exposure prophylaxis depends on regional prevalence (contact Public Health) and circumstances surrounding injury
- 3 general principles
  - wound care: clean wound promptly and thoroughly with soap and running water
  - passive immunization: HRIg infiltrated into wound site, with any remaining volume administered IM in anatomical site distant from vaccine administration
  - active immunization: inactivated human diploid cell rabies virus vaccine (series of 4 shots post-exposure if not pre-immunized)
- treatment is supportive once victim manifests signs and symptoms of disease

Prevention
- pre-exposure vaccination
  - recommended for high risk persons: laboratory staff working with rabies, veterinarians, animal and wildlife control workers, long-term travellers to endemic areas
  - eliminates need for HRIg following an exposure, and reduces number of HDCV PEP shots from 4 to 2

Systemic Infections

Sepsis and Septic Shock

- see Respirology, R33

Definitions
- systemic inflammatory response syndrome (SIRS): 2 or more of
  1. temperature <36°C/96.8°F or >38°C/100.4°F
  2. heart rate >90 beats/min
  3. respiratory rate >20 breaths/min or $PaCO_2$ <32 mmHg
  4. WBC <4 x 10^9/L or >12 x 10^9/L or >10% bands
- sepsis: SIRS + proven or provable infection
- severe sepsis: sepsis + signs of end-organ dysfunction and hypoperfusion
- septic shock: severe sepsis + hypotension (<90 mmHg sBP), despite adequate fluid resuscitation

Pathophysiology
- causative agents are identified in only 50-70% of cases
- when organisms are identified, GP and GN organisms are the cause in 90% of cases
- primary bloodstream infection or secondary bacteremia → local immune response → immune cells release pro-inflammatory cytokines → immune response spreads beyond local environment → unregulated, exaggerated systemic immune response → vasodilation and hypotension → involvement of tissues remote from the site of injury/infection resulting in multiple major organ dysfunction → periodic immunoparalysis

Clinical Features
- history: fever, chills, dyspnea, cool extremities, fatigue, malaise, anxiety, confusion
- physical: abnormal vitals (fever, tachypnea, tachycardia, hypotension), local signs of infection

Investigations
- CBC and differential, electrolytes, BUN, creatinine, liver enzymes, ABG, lactate, INR, PTT, FDP, blood C&S x2, urinalysis, urine C&S and cultures of any wounds or lines
- CXR (other imaging depends on suspicion of focus of infection)

Treatment (see Respirology, R33)
- respiratory support: O_2 ± intubation
- cardiovascular support: IV fluids, ± norepinephrine + ICU
- IV antibiotics (empirical, depends on suspected source)
  - start with broad spectrum antibiotics (piperacillin/tazobactam or meropenem) ± additional agents depending on patient risk factors, suspected etiology of infection, and local microbial susceptibilities (± aminoglycoside for drug-resistant GNs or vancomycin for MRSA)
  - narrow once susceptibilities are known
- hydrocortisone IV in patients with septic shock unresponsive to fluid resuscitation and vasopressors

Leprosy (Hansen's Disease)

Etiology
- *Mycobacterium leprae*: obligate intracellular bacteria, slow-growing (doubling time 12.5 d), survives in macrophages
- bacteria transmitted from nasal secretions, potentially via skin lesions
- invades skin and peripheral nerves leading to chronic granulomatous disease

Clinical Features
- lesions involve cooler body tissues (e.g. skin, superficial nerves, nose, eyes, larynx)
- spectrum of disease determined by host immune response to infection

i. paucibacillary "tuberculoid" leprosy (intact cell-mediated immune response)
  - ≤5 hypoesthetic lesions, usually hypopigmented, well-defined, dry
  - early nerve involvement, enlarged peripheral nerves, neuropathic pain
  - may be self-limited, stable, or progress over time to multibacillary "lepromatous" form

ii. multibacillary "lepromatous" leprosy (weak cell-mediated immune response)
  - ≥6 lesions, symmetrical distribution
  - leonine facies (nodular facial lesions, loss of eyebrows, thickened ear lobes)
  - extensive cutaneous involvement, late and insidious nerve involvement causing sensory loss at the face and extremities

iii. borderline leprosy
  - lesions and progression lies between tuberculoid and lepromatous forms

Investigations
- skin biopsy down to fat or slit skin smears for AFB staining, PCR
- histologic appearance: intracellular bacilli in spherical masses (lepra cells), granulomas involving cutaneous nerves

Treatment (WHO Treatment Regimens)
- paucibacillary: dapsone + rifampin monthly x 6 mo
- single skin lesion paucibacillary: single dose of rifampicin, ofloxacin, and minocycline
- multibacillary and borderline: dapsone + rifampin monthly + clofazimine monthly x 12 mo AND low dose clofazimine once daily x 12 mo
- treatment of leprosy can cause an immune reaction to killed bacteria (e.g. erythema nodosum leprosum and reversal reaction): symptomatic management with NSAIDs if mild, prednisone with 6-12 wk taper if severe; thalidomide for erythema nodosum leprosum

Prognosis
- curable with WHO-approved treatment regimens
- complications: muscle atrophy, contractures, trauma/superinfection of lesions, crippling/loss of limbs, erythema nodosum leprosum, social stigmatization due to clofazimine hyperpigmentation
- long post-treatment follow-up warranted to monitor for relapse and immune reactions

Lyme Disease

Etiology/Epidemiology
- spirochete bacteria: *Borrelia burgdorferi* (N. America), *B. garinii, B. afzelii* (Europe and Asia)
- transmitted by Ixodes tick
- reported in 49 of the 50 U.S. states, but most cases occur in the Northeast, the Midwest, and Northern California
- in Canada, reported in southern and southeastern Quebec, southern and eastern Ontario, southeastern Manitoba, New Brunswick and Nova Scotia, as well as southern British Columbia
- small rodents (mice) serve as primary reservoir, while larger animals (white-tailed deer) serve as hosts for ticks
- human contact usually May-August in fields with low brush near wooded areas
- infection usually requires >36 h tick attachment

Clinical Features
- stage 1 (early localized stage: 7-14 d post-bite)
  - malaise, fatigue, H/A, myalgias
  - erythema migrans: expanding, non-pruritic bulls-eye (target) lesions (red with clear centre) on thigh/groin/axilla
- stage 2 (early disseminated stage): weeks post-infection
  - CNS: aseptic meningitis, CN palsies (CN VII palsy), peripheral neuritis
  - cardiac: transient heart block or myocarditis
- stage 3 (late persistent stage: months to years post-infection)
  - may not have preceding history of early stage infection
  - MSK: chronic monoarticular or oligoarticular arthritis
  - acrodermatitis chronicum atrophicans (due to *B. afzelii*)
  - neurologic: encephalopathy, meningitis, neuropathy

BAKE a Key Lyme Pie

Bell's palsy
Arthritis
Kardiac block
Lyme
Erythema chronicum migrans

Investigations
- serology: ELISA, Western blot

Prevention
- use of protective clothing (tuck pants into socks), insect repellent, inspection for ticks and prompt removal of tick
- doxycycline prophylaxis within 72 h of removal of an engorged, *Ixodes scapularis* tick in hyperendemic area (local rate of infection of ticks ≥20%) for patients >8 yr who are not pregnant or lactating

Treatment
- stage 1: doxycycline/amoxicillin/cefuroxime
- stage 2-3: ceftriaxone

Toxic Shock Syndrome

Etiology
- superantigens produced by some strains of *S. aureus* or GAS cause widespread T-cell activation and pro-inflammatory cytokine release (IL-1, IL-6, TNF)
- course of disease is precipitous and leads to acute fever, shock, multiorgan failure
- Staphylococcal TSS involves the production of superantigen TSST-1 (toxic shock syndrome toxin 1)
- Streptococcal TSS involves the production of superantigens SPEA, SPEB, SPEC

Risk Factors
- Staphylococcal: tampon use, nasal packing, wound infections (e.g. postpartum vaginal or Cesarean or other surgical infections)
- Streptococcal: minor trauma, surgical procedures, preceding viral illness (e.g. chickenpox), use of NSAIDs

Clinical Features and Investigations
- acute onset
- Staphylococcal TSS
  - T >38.9°C
  - sBP <90 mmHg
  - diffuse erythroderma with subsequent desquamation, especially on palms and soles
  - involvement of 3 or more organ systems: GI (vomiting, diarrhea), muscular (myalgia, increased CK), mucous membranes (hyperemia), renal, hepatic, hematologic (thrombocytopenia), CNS (disorientation)
  - isolation of *S. aureus* is not required for diagnosis (*S. aureus* is rarely recovered from blood in TSS)

- Streptococcal TSS
  - sBP <90 mmHg
  - isolation of GAS from a normally sterile site (e.g. blood, pleural, tissue biopsy, or surgical wound)
  - ≥2 of coagulopathy, liver involvement, ARDS, soft tissue necrosis (necrotizing fasciitis, myositis, gangrene), renal impairment, erythematous macular rash that may desquamate

Treatment
- supportive: fluid resuscitation
- Staphylococcal: for methicillin-susceptible *S. aureus*: clindamycin + cloxacillin (IV); for MRSA: clindamycin + vancomycin x 10-14 d
- Streptococcal: IV penicillin and clindamycin and ± IVIg

Cat Scratch Disease

Etiology
- *Bartonella henselae:* intracellular bacteria
- cat-to-human transmission via cat scratch/bite

Clinical Features
- skin lesion appears 3-10 d post-inoculation
- may be followed by fever, tender regional lymphadenopathy
- in some patients, organism may disseminate causing fever of unknown origin, hepatosplenomegaly, retinitis, encephalopathy
- usually self-limited

Investigations
- serology, PCR, lymph node biopsy

Treatment
- supportive in most cases
- azithromycin x 10-14 d with lymphadenitis in patients with moderate-severe disease or immunodeficiency

Rocky Mountain Spotted Fever

Etiology
- *Rickettsia rickettsii:* obligate intracellular GN organism
- reservoir hosts: rodents, dogs
- vectors: *Dermacentor* ticks
- organisms cause inflammation of endothelial lining of small blood vessels, leading to small hemorrhages and thrombi
- can cause widespread vasculitis leading to H/A, and CNS changes; can progress to death if treatment is delayed

Clinical Features
- usually occurs in summer following tick bite
- influenza-like prodrome: acute onset fever, H/A, myalgia, N/V, anorexia
- macular rash appearing on day 2-4 of fever
  - begins on wrists and ankles, then spreads centrally to arms/legs/trunk/palms/soles
  - occasionally "spotless" (10% of patients)

Investigations
- skin biopsy and serology (indirect fluorescent antibody test)

Treatment
- doxycycline, usually 5-7 d (treat for 3 d after defervescence)

West Nile Virus

Epidemiology
- virus has been detected throughout the United States and much of southern Canada
- overall case-fatality rates in severe cases are ~10%

Transmission
- primarily from mosquitoes that have fed on infected birds (crows, blue jays)
- transplacental, blood products (rare), organ transplantation

Clinical Features
- most are asymptomatic
- most symptomatic cases are mild (West Nile fever): acute onset of H/A, back pain, myalgia, anorexia, maculopapular non-pruritic rash involving chest, back, arms
- severe complications: encephalitis, meningoencephalitis, and acute flaccid paralysis (especially in those >60 yr)

Investigations
- IgM antibody in serum or CSF (cross reactivity with yellow fever and Japanese encephalitis vaccines, and with dengue fever and St. Louis virus infection); may not reflect current illness as IgM antibody can last for >6 mo
- viral isolation by PCR from CSF, tissue, blood, and fluids (all have low sensitivity)
- CSF: elevated lymphocytes and protein if CNS involvement

Treatment and Prevention
- treatment: supportive
- prevention: mosquito repellant (DEET), drain stagnant water, community mosquito control programs

Syphilis

Etiology
- *Treponema pallidum:* thick motile spirochetes historically detectable by dark-field microscopy
- transmitted sexually, vertically, or parenterally (rare)

Clinical Features
- see Dermatology, D32 and Gynecology, GY30
- multi-stage disease
  1. primary syphilis (3-90 d post-infection)
     - painless chancre at inoculation site (any mucosal surface)
     - regional lymphadenopathy
     - acute disease lasts 3-6 wk, 25% progress to secondary syphilis without treatment
  2. secondary syphilis = systemic infection (2-8 wk following chancre)
     - maculo-papular non-pruritic rash including palms and soles
     - generalized lymphadenopathy, low grade fever, malaise, H/A, aseptic meningitis, ocular/otic syphilis
     - condylomata lata: painless, wart-like lesion on palate, vulva, or scrotum (highly infectious)
  3. latent syphilis
     - asymptomatic infection that follows untreated primary/secondary syphilis
     - early latent (<1 yr post-infection) or late latent/unknown duration (>1 yr post-infection)
     - increased transmission risk with early latent; longer treatment duration required for late latent
  4. tertiary syphilis (1-30 yr post-infection)
     - gummatous syphilis: nodular granulomas of skin, bone, liver, testes, brain
     - aortic aneurysm and aortic insufficiency
     - neurosyphilis: dementia, personality changes, Argyll-Robertson pupils, tabes dorsalis
  5. congenital syphilis
     - causes spontaneous abortions, stillbirths, congenital malformations, developmental delay, deafness
     - most infected newborns are asymptomatic
     - clinical manifestation in early infancy include rhinitis (sniffles), lymphadenopathy, hepatosplenomegaly, pseudoparalysis (bone pain associated with osteitis)
     - late onset manifestations (>2 yr of age) include saddle nose, saber shins, Glutton joints, Hutchinson's teeth, mulberry molars, ragades, CN VIII deafness, interstitial keratitis, juvenile paresis

Investigations
- screening tests: CMIA, CLIA, EIA (treponemal), RPR, or VDRL (non-treponemal)
- confirmatory tests: TPPA, FTA-ABS, MHA-TP, TPI, dark field microscopy with silver stain (rarely)
- LP for neurosyphilis if: seropositive and symptoms of neurosyphilis or treatment failure/other tertiary symptoms, or with HIV and late latent/unknown duration syphilis; consider in others
- for congenital syphilis, LP is essential; long bone x-rays may also be helpful

Treatment
- for 1°, 2°, early latent: benzathine penicillin G 2.4 million units IM x 1
- for 3°, late latent: benzathine penicillin G 2.4 million units IM weekly x 3
- if allergic to penicillin: doxycycline 100 mg PO bid x 14 d
- neurosyphilis: aqueous Penicillin G 18-24 million units/d IV x 14 d
- for congenital syphilis, penicillin G IV x 10 d
- see Family Medicine, FM45 for generalized STI workup

Argyll Robertson Pupil
Accommodates but does not react to light

Those with Untreated 1° or 2° Syphilis
1/3 cure
1/3 latent indefinitely
1/3 3° syphilis

Causes of False Positive VDRL and RPR Tests

Viruses (mononucleosis, hepatitis)
Drugs and substance abuse
Rheumatic fever
Lupus and leprosy

Patients with 2° or 3° syphilis treated with penicillin may experience a Jarisch-Herxheimer reaction. Lysis of organisms release pyrogens thought to cause fever, chills, myalgia, flu-like symptoms may last up to 24 h

VDRL	Venereal Disease Research Laboratory
RPR	Rapid Plasma Reagin
EIA	Enzyme Immunoassay
CLIA	ChemiLuminescent ImmunoAssay
CMLA	ChemiLuminescent Microparticle ImmunoAssay
FTA-ABS	Fluorescent *Treponema* Antibody-Absorption
MHA-TP	Microhemagglutination Assay *T. pallidum*
TPPA	*T. pallidum* Particle Agglutination Assay

Tuberculosis

Etiology, Epidemiology, and Natural History

- 1/3 of the world's population is infected with TB
- contracted by aerosolized inhalation of *Mycobacterium tuberculosis*, a slow growing aerobe (doubling time = 18 h) that can evade innate host defenses, survive, and replicate in macrophages
- inhalation and deposition in the lung can lead to one of the following outcomes
  1. immediate clearance of the pathogen
  2. latent TB: asymptomatic infection contained by host immune defenses (represents 95% of infected people)
  3. primary TB: symptomatic, active disease (represents 5% of infected people)
  4. secondary TB: symptomatic reactivation of previously dormant TB (represents 5-10% of those with latent TB, most often within the first 2-3 yr of initial infection) at a pulmonary or extrapulmonary site

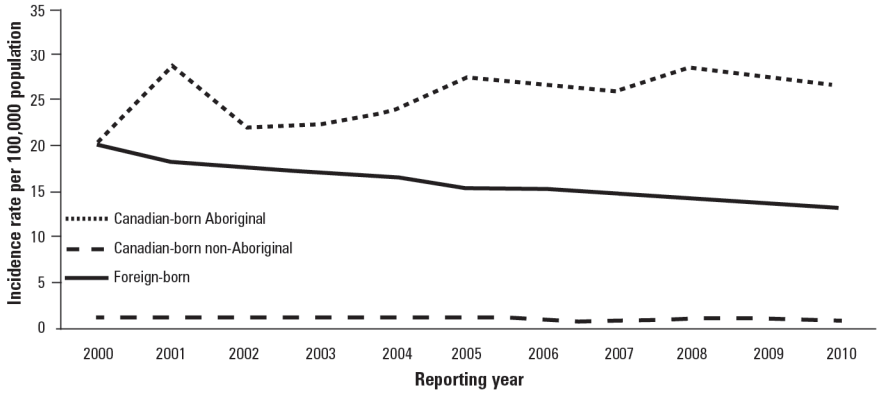


Figure 8. Tuberculosis statistics
Canadian Tuberculosis Standards, 7th ed.

Tuberculous Polyserositis
pleural + pericardial + peritoneal effusions (usually from granuloma breakdown that spills TB into pleural cavity – very rare)

Risk Factors

- social and environmental factors
  - travel or birth in a country with high TB prevalence (e.g. Asia, Latin America, Sub-Saharan Africa, Eastern Europe)
  - Aboriginal (particularly Inuit), crowded living conditions, low SES/homeless, IVDU
  - personal or occupational contact
- host factors
  - immunocompromised/immunosuppressed (especially HIV, including extremes of age)
  - silicosis
  - chronic renal failure requiring dialysis
  - malignancy and chemotherapy
  - substance abuse (e.g. drug use, alcoholism, smoking)

Clinical Features

- primary infection usually asymptomatic, although progressive primary disease may occur, especially in children and immunosuppressed patients
- secondary infection/reactivation usually produces constitutional symptoms (fatigue, anorexia, night sweats, weight loss) and site-dependent symptoms

1. pulmonary TB
   - chronic productive cough ± hemoptysis
   - CXR consolidation or cavitation, lymphadenopathy
   - non-resolving pneumonia despite standard antimicrobial therapy
2. miliary TB
   - widely disseminated spread especially to lungs, abdominal organs, marrow, CNS
   - CXR: multiple small 2-4 mm millet seed-like lesions throughout lung
3. extrapulmonary TB
   - lymphadenitis, pleurisy, pericarditis, hepatitis, peritonitis, meningitis, osteomyelitis (vertebral = Pott's disease), adrenal (causing Addison's disease), renal, ovarian

Investigations

- screening for latent TB
  - PPD/Mantoux skin tests
    - both tests diagnose prior TB exposure; neither can diagnose or exclude active disease
  - IFN-γ release assay (IGRA)
    - in patients previously infected with TB, T-cells produce increased amounts of IFN-γ when re-exposed to TB antigen
    - detects antigen not present in the BCG vaccine or in most types of non-tuberculous-mycobacteria (NTM), therefore fewer false positives
  - Canadian and American guidelines treat IGRAs as equivalent to the TB skin test and preferable in patients with a history of BCG vaccination or who may not return for a skin test reading
- diagnostic tests/investigations for active pulmonary TB
  - three sputum specimens (either spontaneous or induced) should be collected for acid-fast bacilli smear and culture; the three specimens can be collected on the same day, a minimum of 1 hour apart
  - BAL
  - CXR
    - nodular or alveolar infiltrates with cavitation (middle/lower lobe if primary, apical if secondary)
    - pleural effusion (usually unilateral and exudative) may occur independently of other radiograph abnormalities
    - hilar/mediastinal adenopathy (especially in children)
    - tuberculoma (semi-calcified well-defined solitary coin lesion 0.5-4 cm that may be mistaken for lung CA)
    - miliary TB
    - evidence of past disease: calcified hilar and mediastinal nodes, calcified pulmonary focus, pleural thickening with calcification, apical scarring

Positive PPD Test
If induration at 48-72 h
>5 mm if immunocompromised, close contact with active TB
>10 mm all others; positive PPD → CXR; decision to treat depends on individual risk factors
False(–): poor technique, anergy, immunosuppression, infection <10 wk or remotely
False(+): BCG after 12 mo of age in a low-risk individual, NTM
Booster effect: initially false(–) result boost to a true(+) result by the testing procedure itself (usually if patient was infected long ago so had diminished delayed type hypersensitivity reaction or if history of BCG)

Prevention

- primary prevention
  - airborne isolation for active pulmonary disease
  - BCG vaccine
    - ~80% effective against pediatric miliary and meningeal TB
    - effectiveness in adults debated (anywhere from 0-80%)
    - recommended in high-incidence communities in Canada for infants in whom there is no evidence of HIV infection or immunodeficiency; widely used in other countries
- secondary prevention (defer in pregnancy unless mother is high risk)
  - likely INH-sensitive: isoniazid (INH) + pyridoxine (vit B_6 to help prevent INH-associated neuropathy) x 9 mo
  - likely INH-resistant: rifampin x 4 mo

Treatment of Active Infection

- empiric therapy: INH + rifampin + pyrazinamide + ethambutol + pyridoxine
- pulmonary TB: INH + rifampin + pyrazinamide + ethambutol + pyridoxine x 2 mo (initiation phase), then INH + rifampin + pyridoxine x 4 mo in fully susceptible TB (continuation phase), total 6 mo
- extrapulmonary TB: same regimen as pulmonary TB but increase to 12 mo in bone/joint, CNS, and miliary/disseminated TB + corticosteroids for meningitis, pericarditis
- empiric treatment of suspected MDR (multidrug resistant) or XDR (extensively drug-resistant) TB requires referral to a specialist
  - MDR = resistance to INH and rifampin ± others
  - XDR = resistance to INH + rifampin + fluoroquinolone + ≥1 of injectable, second-line agents
    - very difficult to treat, global public health threat, 5 documented cases in Canada from 1997-2008
  - suspect MDR TB if previous treatment, exposure to known MDR index case, or immigration from a high-risk area
- note: TB is a reportable disease to Public Health (please see Public Health Agency of Canada website for more information: www.phac-aspc.gc.ca/tbpc-latb/pubs/tb-canada-7/index-eng.php)

HIV and AIDS

Epidemiology

Canadian Situation (Public Health Agency of Canada, 2013)

- estimated 71,300 Canadians living with HIV infection at the end of 2011, 25% unaware of HIV-positive status
- 2,090 new infections were reported in2013: MSM account for 49.3% of cases, IVDU 12.8%

Global Situation (WHO and UNAIDS Core Epidemiology Slides, July 2014)

- estimated 35 million people living with HIV/AIDS in 2013
- estimated 2.1 million newly infected in 2013
- estimated 1.5 million AIDS-related deaths in 2013

HIV-1 is the predominant type in North America and most of the world

HIV-2 is found mainly in West Africa

Both lead to AIDS but HIV-2 is generally less virulent

Definition and Pathophysiology

- HIV is a retrovirus that causes progressive immune system dysfunction which predisposes patients to various opportunistic infections and malignancies
- HIV virion includes an envelope (gp41 and gp120 glycoproteins), matrix (p17) and capsid (p24) enclosing 2 single-stranded copies of RNA + enzymes in its core
- virion glycoproteins bind CD4 and CXCR4/CCR5 on CD4+ T lymphocytes (T-helper cells) to fuse and enter the cells
- RNA converted to dsDNA by reverse transcriptase; dsDNA is integrated into host genome
- virus DNA transcribed and translated using host cell machinery, post-translational modifications include proteolytic activity of virally encoded protease enzymes
- newly produced virions bud out of host cell, incorporating host cell membrane; additional maturation steps are required before virion is considered infectious
- exact mechanisms of CD4 depletion incompletely characterized but likely include direct viral cytopathic effects, apoptosis, and increased cell turnover

p24 = capsid protein
gp41 = fusion and entry
gp120 = attachment to host T-cell

Homozygosity for A32 mutation in CCR5 gene confers relative resistance to HIV infection
Heterozygosity for A32 mutation in CCR5 gene associated with slower disease course

Modes of Transmission

Table 20. Modes of Transmission by Site and Medium

HIV Invasion Site	Sub-Location	Transmission Medium	Transmission Probability per Exposure Event
Female genital tract	Vagina, ectocervix, endocervix	Semen	1 in 200 to 1 in 2,000
Male genital tract	Inner foreskin, penile urethra	Cervicovaginal and rectal secretions and desquamations	1 in 700 to 1 in 3,000
Intestinal tract	Rectum Upper GI tract	Semen Semen Maternal blood/genital secretions (intrapartum) Breastmilk	1 in 20 to 1 in 300 1 in 2,500 1 in 5 to 1 in 10 1 in 5 to 1 in 10
Placenta	Chorionic villi	Maternal blood (intrauterine)	1 in 10 to 1 in 20
Blood stream		Contaminated blood products Sharp/needlestick injuries	95 in 100 1 in 150

Adapted with permission from Macmillan Publishers Ltd. *Nat Rev Immunology* 2008;8:447-457

NOTE: these estimates are for "all comers" i.e. they estimate transmission risk for anyone with HIV infection and do not take into account treatment status of the HIV+ person (in contrast to results of PARTNER study)

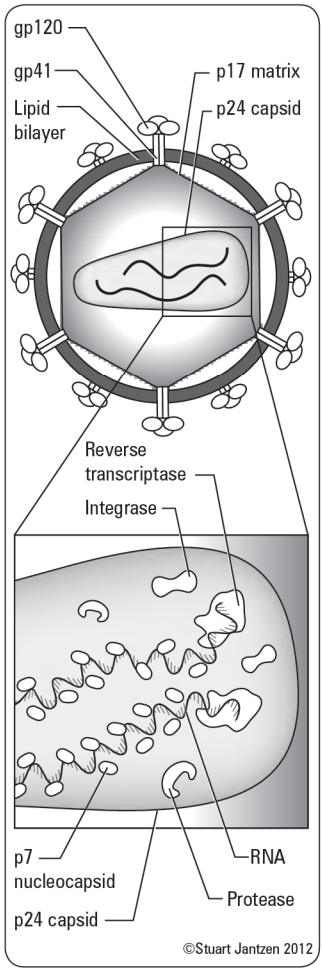


Figure 9. HIV viral particle

Natural History

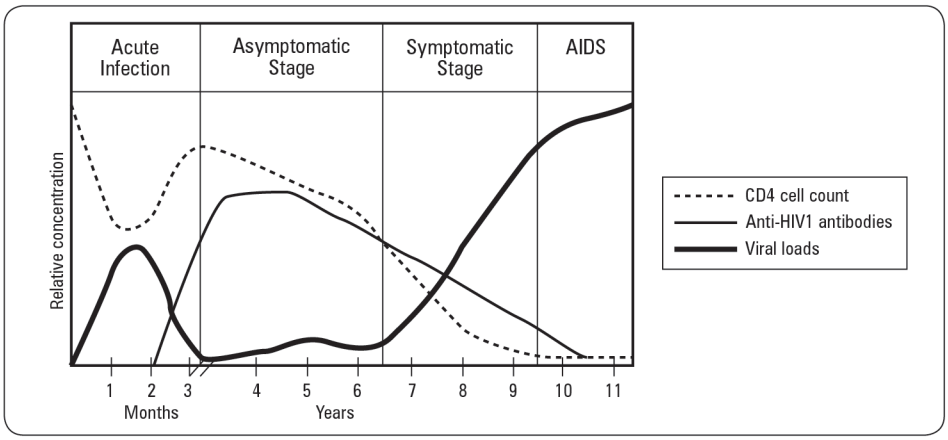


Figure 10. Relationships between CD4 T-cell count, viral load, and anti-HIV antibodies

Acute (Infection) Retroviral Syndrome

- 40-90% experience an acute "flu-like" illness (may include fever, pharyngitis, lymphadenopathy, rash, arthralgias, myalgias, H/A, GI symptoms, oral ulcers, weight loss) 2-6 wk post-exposure lasting 10-15 d
- hematologic disturbances (lymphopenia, thrombocytopenia)
- 10-20% present with aseptic meningitis; HIV RNA and/or p24 may be detected in CSF
- associated with a high level of plasma viremia and therefore high risk of transmission

Asymptomatic (Latent) Stage

- during latent phase, HIV infects and replicates in CD4+ T lymphocytes (lymph nodes)
- normal CD4 count: 500-1,100 cells/mm^3
- CD4 count drops 60-100 cells/mm^3 per year
- by 10 yr post-infection, 50% have AIDS, 30% demonstrate milder symptoms, and <20% are asymptomatic if left untreated

AIDS Definition in Canada

- HIV-positive AND
- one or more of the clinical illnesses that characterize AIDS, including: opportunistic infections (e.g. PJP (previously PCP), esophageal candidiasis, CMV, MAC, TB, toxoplasmosis), malignancy (Kaposi's sarcoma, invasive cervical cancer), wasting syndrome OR
- CD4 <200 (or <15%); this is largely historical since ART can reverse CD4 count decline

Table 21. Symptomatic Stage (CD4 count thresholds for classic clinical manifestations)

CD4 Counts	Possible Manifestations
<500 cells/mm^3	Often asymptomatic Constitutional symptoms: fever, night sweats, fatigue, weight loss Mucocutaneous lesions: seborrheic dermatitis, HSV, VZV (shingles), oral hairy leukoplakia (EBV), candidiasis (oral, esophageal, vaginal), Kaposi's sarcoma (KS) Recurrent bacterial infections, especially pneumonia Pulmonary and extrapulmonary tuberculosis Lymphoma
<200 cells/mm^3	*Pneumocystis jiroveci* pneumonia (formerly PCP) KS Oral thrush Local and/or disseminated fungal infections: *Cryptococcus neoformans*, *Coccidioides immitis, Histoplasma capsulatum*
<100 cells/mm^3	Progressive multifocal leukoencephalopathy (PML) – JC virus CNS toxoplasmosis
<50 cells/mm^3	CMV infection: retinitis, colitis, cholangiopathy, CNS disease Mycobacterium avium complex (MAC) Bacillary angiomatosis (disseminated *Bartonella*) Primary central nervous system lymphoma (PCNSL)

PARTNER Study: Risk of HIV Transmission Between Serodiscordant Couples with HIV+ Partner on ART

Preliminary results presented at Conference on Retroviruses and Opportunistic Infections 2014 (CROI 2014); final results due 2017

Participants: 740 serodiscordant heterosexual (60% of couples) and homosexual couples (40% of couples) that engage in sex without using condoms. The HIV- partner cannot be using pre- or post-exposure prophylaxis and the HIV+ partner must be on ART with an undetectable viral load.

Methods: Partners enrolled in the study are asked to independently complete a questionnaire on sexual behaviour with their partner every 3-6 mo. Additionally, if the HIV- partner seroconverts, a blood sample will be taken from each partner and the viruses genotyped for comparison. To remain in the study, the requirements for participation must be maintained.

Results: No HIV transmissions within couples from a partner with an undetectable viral load in an estimated 16,400 occasions of sex in MSM and 28,000 occasions of sex in the heterosexual couples. If the HIV+ partners had not been on treatment in this group, 50-100 (median: 86) transmissions would have been expected in the MSM group and 15 transmissions in heterosexual couples. In a couple whose sexual activity is considered as average for the group studied, there was a 95% chance that the greatest-possible risk of transmission from a partner was 0.45% per year as well as 1% per year from anal sex.

Laboratory Diagnosis

- anti-HIV antibodies detectable after a median of 3 wk, virtually all by 3 mo (therefore 3 mo window period)
- initial screening test (3rd generation antibody test): enzyme linked immunosorbent assay (ELISA) detects serum antibody to HIV; sensitivity >99.5%

- increasingly, combination p24 antigen/HIV antibody tests (4th generation) used for screening; improved sensitivity in early or acute infection and sensitivity/specificity approach 100% for chronic infection
- confirmatory test: if positive screen, Western blot confirmation by detection of antibodies to at least two different HIV protein bands (p24, gp41, gp120/160); specificity >99.99%
- rapid (point of care) antibody tests: higher false positives, therefore need to confirm positive results with traditional serology
- p24 antigen: detection by ELISA may be positive during "window period"

Management of the HIV-Positive Patient

- verify positive HIV test
- complete baseline history and physical exam, then follow-up every 3-6 mo
- laboratory evaluation
  - routine CD4 count to measure status of the immune system
  - routine HIV-RNA levels (viral load)
    - also important indicator of effect of ART
  - baseline HIV resistance testing to guide ARV therapy
  - HLA-B*5701 genetic test to screen for abacavir hypersensitivity
  - baseline tuberculin skin test (PPD): induration greater than 5 mm is positive
  - baseline serologies (hepatitis A, B, and C, syphilis, toxoplasma, CMV, VZV)
  - routine biochemistry and hematology, CXR
  - annual fasting lipid profile and fasting glucose (due to HAART side effects)
- education
  - regular follow-up on CD4 counts and viral loads (q3-6mo) as well as strict adherence to ART improves prognosis
  - prevention of further transmission through safer sex and clean needles for injection drug use
  - HIV superinfection (transmission of different HIV strains from another HIV+ person) does rarely occur so barrier protection during sex is still recommended
  - discuss importance of disclosing HIV status to partners including risk of criminal prosecution of non-disclosure in jurisdictions where applicable
  - connect to relevant community groups and resources
- health care maintenance
  - assessment of psychosocial concerns and referral to psychiatry or social work if appropriate
  - vaccines: influenza annually, 23-valent pneumococcal every 5 yr, HBV (if not immune), HAV (if seronegative)
  - annual screening (PAP smear, STIs)
  - management of comorbid conditions and provision of general primary care

Table 22. Prophylaxis Against Opportunistic Infections in HIV-infected Patients

Pathogen	Indication for Prophylaxis	Prophylactic Regimen
Pneumocystis jiroveci	CD4 count <200 cells/mm^3 or history of oral candidiasis	TMP-SMX 1 SS or DS OD
Toxoplasma gondii	IgG antibody to *Toxoplasma* and CD4 count <100 cells/mm^3	As per prophylaxis for pneumocystis
Mycobacterium tuberculosis	PPD reaction >5 mm or contact with case of active TB	INH + pyridoxine daily x 9 mo
Mycobacterium avium complex	CD4 count <50 cells/mm^3	Azithromycin 1,200 mg q1wk

SS = single strength; DS = double strength
See 2002 USPHS/IDSA guidelines for preventing opportunistic infections among HIV-infected persons. Available from: http://aidsinfo.nih.gov/

Anti-Retroviral Treatment

Overall Treatment Principles

- recommended that all HIV+ patients initiate HAART to prevent disease progression and transmission; strength of evidence supporting this recommendation changes depending on CD4 count and sexual practices (AI evidence that CD4 <350 should be on HAART)
- patients starting HAART should be committed to treatment and understand the importance of adherence; poor compliance can lead to viral resistance; may defer treatment on the basis of clinical and psychosocial factors on case by case basis
- initiate ART if opportunistic infection/malignancy, pregnancy, HIV-associated nephropathy, HIV-associated thrombocytopenia, need for hepatitis B therapy in HBV co-infected patients
- consider starting treatment early if HCV co-infection, high HIV viral load, comorbid conditions (e.g. cardiovascular disease)
- consider results of baseline resistance testing and complete ART history before (re-)initiating HAART
- goal: keep viral load below limit of detection i.e. <40 copies/mL (undetectable); viral load should decrease 10-fold within 4-8 wk, be undetectable by 6 mo, and restore immunological function
- strong evidence against intermittent HAART or 'drug holidays'
- ART leads to 96% reduction in risk of transmitting HIV to sexual partners

Seroconversion: Development of detectable anti-HIV antibodies

Window Period: Time between infection and development of anti-HIV antibodies; when serologic tests (ELISA, Western blot) are negative

All infants born to HIV infected mothers have positive ELISA tests because of circulating maternal anti-HIV antibodies, which disappear by 18 mo; early diagnosis is made by detection of HIV RNA in plasma

HIV Status
- CD4 count: progress and stage of disease
- Viral load: rate of progression

1° and 2° prophylaxis may be discontinued if CD4 count is above threshold for ≥6 mo while on ART

HLA-B*5701 Testing
Abacavir hypersensitivity reactions usually only occur in individuals carrying this HLA allele (~5-7% of Caucasians, lower prevalence in other ethnic groups). Routine screening for HLA-B*5701 at baseline and definitely prior to abacavir use

Reasons for Deterioration of a Patient with HIV/AIDS
- Opportunistic infections
- Neoplasms
- Medication-related toxicities
- Co-infections (e.g. HBV, HCV, STIs)
- Non-AIDS-related comorbidities (e.g. cardiovascular, renal, hepatic, neurocognitive, bone disease)

HAART Recommendations for Treatment of Naïve Patients

- 2 NRTIs + 1 INSTI/NNRTI/PI (boosted with ritonavir or cobicistat)

Treatment Failure

- defined clinically (HIV progression), immunologically (failure to increase CD4 count by 25-50 over first yr of treatment or CD4 decrease >100 over 1 yr), or virologically (failure to achieve viral load <40 copies/mL after 6 mo)
- ensure that viral load >40 is not just a transient viremia or 'blip'; confirm medication adherence, assess drug interactions, perform resistance testing

Treatment Failure
- Assess adherence
- Assess drug interactions
- Resistance testing
- Rule out opportunistic infections
- Rule out marrow suppression
- Construct new 3-drug regimen

Table 23. Anti-Retroviral Drugs

Class	Drugs	Mechanism	Adverse Effects
Nucleoside reverse transcriptase inhibitors (NRTIs)	zidovudine (AZT) lamivudine (3TC) stavudine (d4T) didanosine (ddI) abacavir (ABC) emtricitabine (FTC) tenofovir disoproxil fumurate (TDF) **Combination Tablets:** AZT/3TC (Combivir®) AZT/3TC/ABC (Trizivir®) ABC/3TC (Kivexa®) TDF/FTC (Truvada®)	Incorporated into the growing viral DNA chain, thereby competitively inhibiting reverse transcriptase and terminating viral DNA growth	Lactic acidosis Lipodystrophy Rash N/V/diarrhea Bone marrow suppression (AZT) Peripheral neuropathy (ddI, d4T) Drug-induced hypersensitivity (ABC) Pancreatitis (ddI/d4T) Myopathy (AZT)
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	efavirenz (EFZ) nevirapine (NVP) delavirdine (DLV) etravirine (ETR) rilpivirine (RPV)	Non-competitively inhibit function of reverse transcriptase, thereby preventing viral RNA replication	Rash, Stevens-Johnson syndrome CNS: dizziness, insomnia, somnolence, abnormal dreams (efavirenz) Hepatotoxicity (nevirapine – avoid in females with CD4 >250, men with CD4 >400) CYP3A4 interactions
Protease inhibitors (PIs)*	ritonavir (RTV) saquinavir (SQV) amprenavir (APV) nelfinavir (NFV) indinavir (IDV) atazanavir (ATV) fosamprenavir (FPV) lopinavir/ritonavir (Kaletra®) tipranavir (TPV) darunavir (DRV)	Prevent maturation of infectious virions by inhibiting the cleavage of polyproteins	Lipodystrophy, metabolic syndrome N/V/diarrhea Nephrolithiasis (indinavir) Rash (APV) Hyperbilirubinemia (atazanavir, indinavir) CYP3A4 interactions Hyperlipidemia
Fusion inhibitor	enfuvirtide (T-20)	Inhibit viral fusion with T-cells by inhibiting gp41, preventing cell infection	Injection site reactions, rash, infection, diarrhea, nausea, fatigue
CCR5 antagonist	maraviroc	Inhibit viral entry by blocking host CCR5 co-receptor	Fever, cough, dizziness
Integrase strand transfer inhibitors (INSTIs)	raltegravir elvitegravir dolutegravir	Inhibits integration of HIV DNA into the human genome thus preventing HIV replication	

*Standard of care is to pharmacologically boost most PIs with ritonavir to increase concentrations

Lactic Acidosis
- Occurs secondary to mitochondrial toxicity
- Symptoms include abdominal pain, fatigue, N/V, muscle weakness

Lipodystrophy
Body fat redistribution (mainly with old ARVs)
- Lipohypertrophy (e.g. dorsal fat pad, breast enlargement, increased abdominal girth) thought to be caused primarily by protease inhibitors
- Lipoatrophy (e.g. facial thinning, decreased adipose tissue in the extremities) is thought to be caused by thymidine analogue NRTIs such as d4T and AZT
- Metabolic abnormalities: lipids (increased LDL, increased TGs), glucose (insulin resistance, type 2 DM), increased risk of CVD

Single Tablet ART Regimens

- reduces pill burden and increases adherence
- generally better tolerated

Table 24. Single Tablet HAART Regimens

Name	Contents	Common Side Effects
Atripla®	efavirenz/tenofovir/emtricitabine	psychiatric events, vivid dreams
Complera®	rilpivirine/emtricitabine/tenofovir	good side effect profile
Stribild®	elvitegravir/cobicistat/emtricitabine/tenofovir	good side effect profile
Triumeq®	Dolutegravir/abacavir/lamivudine	good side effect profile; use only in HLAB*5701 negative patients

Pharmacologic Boosting
- The goal of pharmacologic boosting is to increase the plasma exposure to the boosted drug
- PI boosting traditionally achieved by administering low-dose ritonavir along with the PI
- Ritonavir inhibits the metabolism of other PIs primarily by inhibiting cytochrome P450 3A4, the enzyme systems responsible for metabolism of the PIs
- Cobicistat is a new non-ARV pharmacologic booster, presently co-formulated with elvitegravir, darunavir, or atazanavir

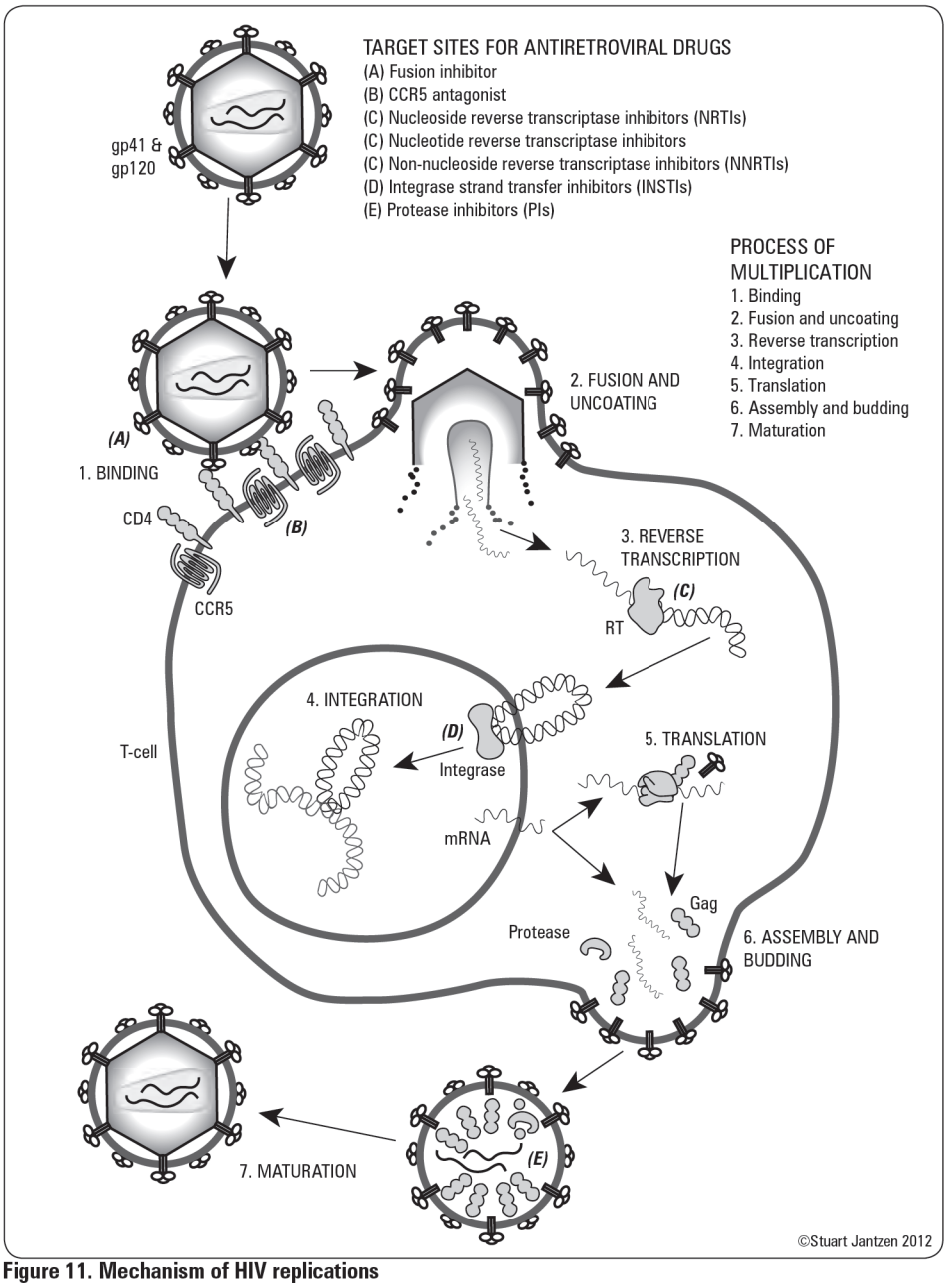


Figure 11. Mechanism of HIV replications

Prevention of HIV Infection

- education, including harm-reduction
  - safer sexual practices: condoms for vaginal and anal sex, barriers for oral sex
  - harm reduction for injection drug users: avoid sharing needles
- treatment of HIV+ women with HAART during the 2nd and 3rd trimester of pregnancy and AZT during delivery followed by treatment of the infant for 6 wk (decreases maternal-fetal transmission from 25% to <3%)
- universal blood and body precautions for health care workers
  - post-exposure prophylaxis (PEP) after occupational (e.g. needle-stick injury) and non-occupational (e.g. consensual sex, sexual assault) exposure to HIV: 2- or 3-drug regimen initiated immediately (<72 h) after exposure and continuing for 4 wk
- recent data has demonstrated efficacy of pre-exposure prophylaxis (oral PrEP or topical microbicides) in preventing HIV although additional data needed
- ART associated with 96% reduction in risk of transmitting HIV to sexual partners
- screening of blood and organ donation

Types of Testing

1. Nominal/Name-Based HIV Testing
- person ordering the test knows the identity of the person being tested for HIV
- HIV test is ordered using the name of the person being tested
- person ordering the test is legally obligated to notify Public Health officials if test results are positive for HIV
- test result is recorded in the health care record of the person being tested

2. Non-Nominal/Non-Identifying HIV Testing
- similar to nominal/name-based testing on all points except:
- HIV test is ordered using a code or the initials of the person being tested

3. Anonymous Testing
- available at specialized clinics
- person ordering the HIV test does not know the identity of the person being tested
- HIV test is carried out using a unique non-identifying code that only the person being tested for HIV knows
- test results are not recorded on the health care record of the person being tested
- patient identification and notification of Public Health required to gain access to ART

Early identification of HIV is essential for patients to receive the maximal benefit from ART

HIV Pre- and Post-Test Counselling

- a diagnosis of HIV can be overwhelming and is often associated with stigma and discrimination
- consider pre- and post-test counselling, regardless of the results
- goals include: assessing risk, making informed decision to be tested, education to protect themselves and others from virus exposure, where to go for more information and support
- HIV+ patients should be connected with local support services

Fungal Infections

Skin and Subcutaneous Infections

Superficial Fungal Infections

- see Dermatology, D27

Dermatophytes

- see Dermatology, D27

Subcutaneous Fungal Infection

Pathophysiology
- fungi that naturally reside in soil and enter skin via traumatic break
- *Sporothrix schenckii*: most commonly affects gardeners injured by a rose thorn or splinter
  - causes subcutaneous nodule at point of entry
  - fungi may migrate up lymphatic vessels creating nodules along the way – "nodular lymphangitis"

Treatment
- oral azole (e.g. itraconazole)
- IV amphotericin B for severe or disseminated infection

Endemic Mycoses

Basics
- three major endemic mycoses in North America
  - histoplasmosis
  - blastomycosis
  - coccidioidomycosis

Histoplasmosis is commonly associated with exposure to chicken coops, bird roosts, and bat caves

- thermally dimorphic organisms: mold in cold temperature (e.g. soil) and yeast at higher temperature (e.g. tissue)
- infection occurs through inhalation of spores (soil, bird droppings, vegetation) or inoculation injury
- all can cause pneumonia and may disseminate hematogenously
- may reactivate or disseminate during immunocompromised states

High Risk for Dissemination
- Immunocompromised (e.g. HIV, steroids, TNF-α inhibitors, transplantation)
- Pregnancy (3rd trimester)
- DM

Treatment
- common to all endemic mycoses
  - oral azole (e.g. itraconazole for mild-moderate local infection)
  - IV amphotericin B for systemic infection

Table 25. Endemic Mycoses

Disease	Endemic Region	Clinical Features	Investigations
Histoplasma capsulatum	Ohio and Mississippi River valleys in central USA, Ontario, Quebec; widespread	Asymptomatic (in most people) Primary pulmonary • Fever, cough, chest pain, H/A, myalgia, anorexia • CXR (acute): pulmonary infiltrates ± hilar lymphadenopathy • CXR (chronic): pulmonary infiltrates, cavitary disease Disseminated (rare) • Occurs primarily in immunocompromised patients • Spread to bone marrow (pancytopenia), GI tract (ulcers), lymph nodes (lymphadenitis), skin, liver, adrenals, CNS	Fungal culture, fungal stain Antigen detection (urine and serum) Serology
Blastomyces dermatitidis	States east of Mississippi River, Northern Ontario and along the Great Lakes	May be asymptomatic Primary: acute or chronic pneumonia • Fever, cough, chest pain, chills, night sweats, weight loss • CXR (acute): lobar or segmental pneumonia • CXR (chronic): lobar infiltrates, fibronodular interstitial disease Disseminated • Spread to skin (verrucous lesions that mimic skin cancer, ulcers, subcutaneous nodules), bones (osteomyelitis, osteolytic lesions), GU tract (prostatitis, epididymitis)	Sputum smear and culture Direct examination of clinical specimens for characteristic broad-based budding yeast (sputum, tissue, purulent material)
Coccidioides immitis	Deserts in southwest USA, northwest Mexico	Primary • "Valley fever": subacute fever, chills, cough, chest pain, sore throat, fatigue that lasts for weeks to months • Can develop hypersensitivity with arthralgias, erythema nodosum Disseminated • Rare spread to skin (ulcers), joints (synovitis), bones (lytic lesions), meninges (meningitis) • Common opportunistic infection in patients with HIV	Sputum culture Direct examination of clinical specimens for characteristic yeast (sputum, tissue, purulent material)

Opportunistic Fungi

Pneumocystis jiroveci (formerly *P. carinii*) Pneumonia: PJP or PCP

Microbiology
- unicellular fungi
- previously classified as a protozoa

Transmission
- rarely person-to-person transmission
- most disease is due to reactivation of latent infection acquired by the respiratory route or reinfection by a different genotype
  - causes clinical disease in immunocompromised patients (steroid use, HIV)
  - 80% lifetime risk without prophylaxis (TMP/SMX) in HIV patients with CD4 count <200 cells/mm^3

CXR in *P. jiroveci*
- Bilateral, diffuse opacities
- CXR may be normal (20-30% cases)
- CT shows cysts (hence the name Pneumo"cystis") but almost never pleural effusions

Clinical Features
- symptoms of pneumonia: fever, nonproductive cough, progressive dyspnea
- classic CXR

Investigations
- demonstration of organism in induced sputum, bronchoalveolar lavage, or endotracheal aspirate (if intubated)

Treatment and Prevention
- oxygen to keep SaO_2 >90%
- antimicrobial options
  - TMP/SMX (PO or IV)
  - dapsone and TMP
  - clindamycin and primaquine
  - pentamidine (IV)
  - atovaquone
- corticosteroids used as adjuvant therapy in those with severe hypoxia (pO_2 <70 mmHg or A-a gradient O_2 >35 mmHg)
- prophylactic TMP/SMX for those at high risk of infection (HIV patients when CD4 <200 cells/mm^3 or non-HIV immunocompromised patients under specific conditions)

Cryptococcus spp.

Microbiology
- encapsulated yeast found worldwide
- 2 human pathogenic species: *C. gattii*, *C. neoformans*

C. gattii sees limited geographical distribution including Vancouver Island, Northern Australia, and Papua New Guinea

Transmission
- inhalation of airborne yeast from soil contaminated with pigeon droppings (*C. neoformans*) or certain tree species such as Eucalyptus or Douglas fir (*C. gattii*) → may cause local infection in lung → asymptomatic or pneumonia
- may also spread hematogenously to the CNS, skin, bones, and other organs
- *C. neoformans* tends to affect immunocompromised hosts
- *C. gattii* tends to affect immunocompetent hosts

Clinical Features
- pulmonary
  - usually asymptomatic or self-limited pneumonitis
  - only 2% of HIV+ patients present with pulmonary symptoms including productive cough, chest tightness, and fever
- disseminated
  - frequently disseminates in HIV+ population
  - CNS: meningitis (leading cause of meningitis in patients with HIV)
  - skin: umbilicated papules that resemble large lesions of *Molluscum contagiosum*

India-ink sensitivity for cryptococcus is only 50% (higher in HIV patients); now replaced by cryptococcal antigen test in most laboratories

Investigations
- serum cryptococcal antigen
- CSF for meningitis: India-ink stain, cryptococcal antigen test, culture to confirm

Treatment
- in patients with HIV who have cryptococcal meningitis or severe pulmonary disease:
  - amphotericin B (+ flucytosine) is used in the first 2 wk for induction therapy; limited duration due to side effects
  - switch to fluconazole for at least 8 wk as consolidation therapy, then continue at lower dose for prolonged maintenance

Candida albicans

Microbiology
- yeast forms with pseudohyphae germ tube formation at 37°C

Transmission
- normal flora of skin, mouth, vagina, and GI tract
- risk factors for overgrowth:
  - immunocompromised state (DM, corticosteroids)
  - ICU patients (broad-spectrum antibiotic use, central venous catheters, TPN)
  - obesity → maceration and moisture in intertriginous areas, pannus, under breasts

Clinical Features
- mucocutaneous
  - oral thrush, esophagitis (chest pain, odynophagia), vulvovaginitis (see Gynecology, GY27), balanitis, cutaneous (diaper rash, skin folds, folliculitis), chronic mucocutaneous
  - small satellite lesions beyond the margin of the rash
- invasive
  - candidemia, endophthalmitis, endocarditis, UTI (upper tract), hepatosplenic disease

Treatment
- thrush: nystatin suspension or pastilles for mild disease, fluconazole for severe disease
- vulvovaginal candidiasis: topical agents (imidazole or nystatin), oral fluconazole for recurrent disease
- cutaneous infection: topical imidazole
- opportunistic infections in HIV, other systemic infections: fluconazole or echinocandin
- chronic mucocutaneous: azoles

Aspergillus spp.

Microbiology
- branching septate hyphae
- common species causing disease include *A. fumigatus, A. flavus*

Transmission
- ubiquitous in the air and the environment
- *Aspergillus* produces a toxin called aflatoxin that contaminates nuts, grains, and rice

Clinical Features
- allergic bronchopulmonary aspergillosis (ABPA)
  - IgE-mediated asthma-type reaction with dyspnea, high fever, and transient pulmonary infiltrates
  - occurs more frequently in patients with asthma and allergies
- aspergilloma (fungus ball)
  - ball of hyphae in a preexisting lung cavity
  - symptoms range from asymptomatic to massive hemoptysis
  - CXR: round opacity surrounded by a thin lucent rim of air, often in upper lobes ("air crescent" sign)
- invasive aspergillosis
  - associated with prolonged and persistent neutropenia or transplantation
  - pneumonia – most common
  - may disseminate to other organs: brain, skin
  - severe symptoms with fever, cough, dyspnea, cavitation; fatal if not treated early and aggressively
  - CXR: local or diffuse infiltrates ± pulmonary infarction, pulmonary nodules with surrounding ground glass ("halo" sign)
- mycotoxicosis
  - aflatoxin produced by *A. flavus* (nuts, grains, rice)
  - results in liver hemorrhage, necrosis, and hepatocellular carcinoma formation

Treatment Options
- for invasive aspergillosis: voriconazole or amphotericin B
- surgical resection for aspergilloma
- corticosteroids ± itraconazole for ABPA

Parasitic Infections

Protozoa – Intestinal/Genitourinal Infections

Entamoeba histolytica (Amoebas)

Transmission
- reservoir: infected humans
- cysts by fecal-oral and food/waterborne transmission in areas of poor sanitation
- seen in immigrants, travellers, institutionalized individuals, Aboriginal Canadians, MSM

Clinical Features
1. asymptomatic carriers
2. amoebic dysentery
   - abdominal pain, cramping, colitis, dysentery, low grade fever with bloody diarrhea secondary to local tissue destruction and ulceration of large intestine
3. amoebic abscesses
   - most common in liver (hematologic spread); presents with RUQ pain, weight loss, fever, hepatomegaly
   - can also occur in lungs and brain

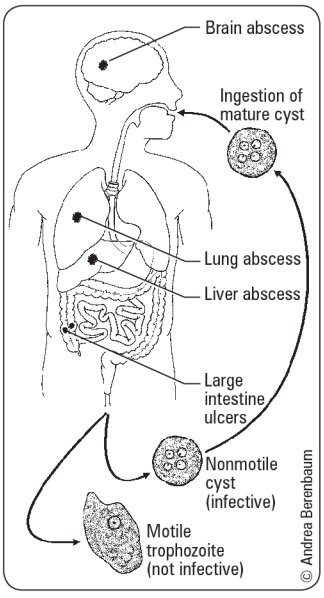


Figure 12. Entamoeba life cycle

Investigations
- serology, fecal/serum antigen testing, stool exam (for cysts and trophozoites), colon biopsy
- *E. histolytica* indistinguishable microscopically from the non-pathogen *E. dispar* (distinguish by specific stool antigen detection)

Treatment and Prevention
- metronidazole
- for invasive disease or cyst elimination: follow with iodoquinol or paromomycin
- aspiration of hepatic abscess if risk of cyst rupture, poor response to medical therapy, or diagnostic uncertainty
- asymptomatic cyst shedding: iodoquinol or paromomycin alone
- good personal hygiene, purification of water supply by boiling, filtration (not chlorination)

Giardia lamblia

Transmission
- reservoir: infected humans and other mammals
- food/waterborne (especially in the Rockies) and fecal-oral transmission of infectious cysts
- risk factors: travel, camping, institutions, day care centres, MSM

Clinical Features
- giardiasis ("beaver fever")
  - symptoms vary from asymptomatic to self-limited mild watery diarrhea to malabsorption syndrome (chronic giardiasis where the parasite coats the small intestine and thus prevents fat absorption)
  - nausea, malaise, abdominal cramps, bloating, flatulence, fatigue, weight loss, steatorrhea
  - no hematochezia (no invasion into intestinal wall), no mucous in stool

Investigations
- multiple stool samples (daily x 3 d) for microscopy, stool antigen used occasionally
- occasionally small bowel aspirate or biopsy

Treatment and Prevention
- metronidazole; nitazoxanide if symptomatic
- good personal hygiene and sanitation, water purification (iodine better than chlorination), outbreak investigation

Trichomonas vaginalis

Trichomonas causes 25% of vaginitis

Transmission
- sexual contact

Clinical Features
- often asymptomatic (10-50%), especially males (occasionally urethritis, prostatitis)
- trichomonas vaginitis (see Gynecology, GY27)
  - vaginal discharge (profuse, malodourous, yellow-green or grey, frothy), pruritus, dysuria, dyspareunia

Investigations
- wet mount (motile parasites), antigen detection, culture
- urine PCR to detect in males

Treatment
- metronidazole for patient and partner(s)

Cryptosporidium spp.

Transmission
- reservoir: infected humans and a wide variety of young animals
- fecal-oral transmission by ingestion of cysts; waterborne
- risk factors: summer and fall, young children (day care), MSM, contact with farm animals, immunodeficiency

Clinical Features
- range from self-limited watery diarrhea (immunocompetent) to chronic, severe, non-bloody diarrhea with N/V, abdominal pain, and anorexia resulting in weight loss and death (immunocompromised)

Investigations
- modified acid-fast stain of stool specimen, microscopic identification of oocysts in stool or tissue, stool antigen detection by direct fluorescent antibody

Treatment and Prevention
- supportive care
- in HIV, try HAART to restore immunity; if fails, try nitazoxanide
- good personal hygiene, water filtration

Blood and Tissue Infections

Plasmodium spp. (Malaria)

Microbiology
- species include: *P. falciparum* (most common and most lethal), *P. vivax, P. ovale, P. malariae, P. knowlesi* (new species isolated from primates in Malaysia, potentially fatal)
- complex life cycle: human host for asexual reproduction and mosquito for sexual reproduction
- sporozoites from mosquitoes infect human liver cells, where they multiply and are released as merozoites; merozoites infect RBCs and cause disease
- *P. ovale* and *P. vivax* can produce dormant hypnozoites in the liver that may cause relapsing malarial attacks by reactivating (entering the erythrocytic cycle) after many months

Transmission
- reservoir: infected human
- transmission by the night-biting female *Anopheles* mosquito, vertical transmission, and blood transfusion
- occurs in tropical/subtropical regions (sub-Saharan Africa, Oceania, South Asia, Central America, Southeast Asia, South America)

Clinical Features
- flu-like prodrome
- paroxysms of high spiking fever and shaking chills (due to synchronous systemic lysis of RBCs) (lasts several hours)
  - *P. vivax* and *P. ovale*: chills and fever x48h but can be variable
  - *P. malariae*: chills and fever x72h but can be variable
  - *P. falciparum*: less predictable fever interval, can be highly variable (>90% ill within 30 d)
- abdominal pain, diarrhea, myalgia, H/A, and cough
- hepatosplenomegaly and thrombocytopenia without leukocytosis

Complications
- *P. falciparum*: CNS involvement (cerebral malaria = seizures and coma), severe anemia, acute kidney injury, ARDS, primarily responsible for fatal disease
- *P. knowlesi*, and rarely *P. vivax*, can be fatal

Investigations
- microscopy: blood smear q12-24h (x3) to rule out infection
  - thick smear (Giemsa stain) for presence of organisms
  - thin smear (Giemsa stain) for species identification and quantification of parasites
- rapid antigen detection tests

Treatment and Prevention
- *P. vivax, P. ovale*: chloroquine (and primaquine to eradicate liver forms)
- *P. vivax*, chloroquine resistant: atovaquone/proguanil + primaquine or quinine and doxycycline + primaquine
- *P. malariae, P. knowlesi*: chloroquine
- *P. falciparum*: most areas of the world show chloroquine resistance – check local resistance patterns
  - artemisinin combination therapy (e.g. artesunate + doxycycline or clindamycin or atovaquone/proguanil)
  - atovaquone/proguanil combination (Malarone®)
  - quinine + doxycycline or clindamycin
  - mefloquine and artemisinin resistance increasing in southeast Asia (check local resistance)
- prevention with antimalarial prophylaxis, covering exposed skin, bed nets, insect repellant

Malaria is the most common fatal infectious disease worldwide

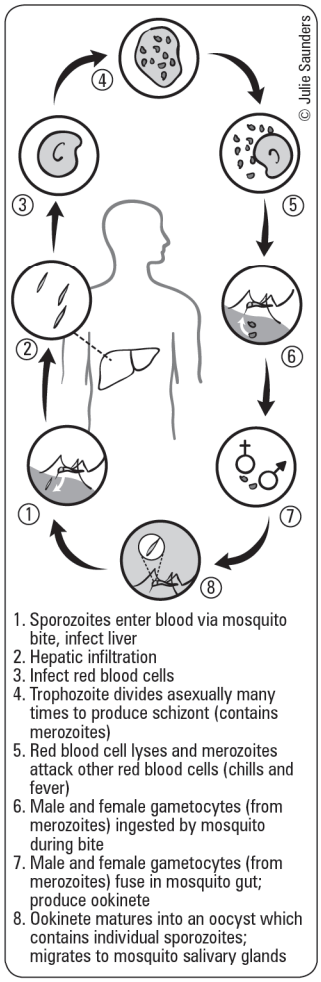


Figure 13. Life cycle of *Plasmodium* spp.

Drugs for Preventing Malaria in Travellers
Cochrane DB Syst Rev 2009;CD006491
Study: Cochrane Systematic Review. 8 RCTs.
Population: 4,240 non-immune adults and children traveling to regions with *P. falciparum* resistance to chloroquine.
Intervention: Atovaquone-proguanil, doxycycline, mefloquine, chloroquine-proguanil, or primaquine used for malaria prophylaxsis.
Outcome: Efficacy, safety, and tolerability.
Results: Atovaquone-proguanil and doxycycline had similar adverse events. Atovaquone-proguanil had fewer overall (RR 0.72), GI (RR 0.54), and neuropsychiatric events (RR 0.49) than mefloquine. Doxycycline also had fewer neuropsychiatric events than mefloquine (RR 0.84).
Conclusion: Atovaquone-proguanil or doxycycline as prophylaxis against malaria is best tolerated in terms of adverse effects and mefloquine is associated with adverse neuropsychiatric outcomes.

Trypanosoma cruzi

Transmission
- found in Mexico, South America, and Central America
- transmission by Reduviid insect vector ("Kissing Bug"), which defecates on skin and trypomastigotes in the stool are rubbed into bite site by host
- also transmitted via placental transfer, organ donation, blood transfusion, and ingestion of contaminated food containing Reduviid insects (especially cane juice)

Clinical Features
- American trypanosomiasis (Chagas disease)
  - acute: usually asymptomatic, local swelling at site of inoculation ("Romana's sign"; usually around one eye) with variable fever, lymphadenopathy, cardiomegaly, and hepatosplenomegaly
  - chronic indeterminate phase: asymptomatic but increasing levels of antibody in blood; most infected persons (60-70%) remain in this phase, and do not go on to manifest a determinate form of Chagas disease
  - chronic determinate: leads to chronic dilated cardiomyopathy, esophagomegaly, and megacolon 10-25 yr after acute infection in 30-40% of infected individuals

Investigations
- wet prep and Giemsa stain of thick and thin blood smear, serology, PCR

Treatment and Prevention
- acute: nifurtimox or benznidazole
- indeterminate: increasing trend to treat as acute infection
- chronic determinate: symptomatic therapy, surgery as necessary including heart transplant, esophagectomy, and colectomy; there may be a benefit to antiparasitic treatment
- insect control, bed nets

1/3 of Ontario's population is infected with *Toxoplasma gondii*

Toxoplasma gondii

Transmission
- acquired through exposure to cat feces (oocysts), ingestion of undercooked meat (tissue cysts), vertical transmission, organ transplantation, gardening without gloves (cat oocyst exposure), whole blood transfusions

Clinical Features
- congenital
  - result of acute primary infection of mother during pregnancy (TORCH infection – see Obstetrics, OB31)
  - stillbirth (rare), chorioretinitis, blindness, seizures, severe developmental delay, microcephaly
  - initially asymptomatic infant may develop reactivation of chorioretinitis as adolescent or adult → blurred vision, scotoma, ocular pain, photophobia, epiphora, hearing loss, developmental delay
- acquired
  - usually asymptomatic or mononucleosis-like syndrome in immunocompetent patient
  - infection remains latent for life unless reactivation due to immunosuppression
- immunocompromised (most commonly AIDS with CD4 <200)
  - encephalitis with focal CNS lesions seen as single or multiple ring-enhancing masses on CT (H/A and focal neurological signs)
  - lymph node, liver, and spleen enlargement and pneumonitis
  - chorioretinitis

Investigations
- serology, CSF Wright-Giemsa stain, antigen or DNA detection (PCR); pathology provides definitive diagnosis
- immunocompromised patients: consider CT scan (ring-enhancing lesion in cortex or deep nuclei) and ophthalmologic examination
- negative serology in many AIDS patients (false negative due to decreased lymphocyte population)

Treatment and Prevention
- no treatment if: immunocompetent, not pregnant, no severe organ damage
- pregnancy: spiramycin to prevent transplacental transmission or pyrimethamine + sulfadiazine (add folinic acid), avoid undercooked meat and refrain from emptying cat litter boxes
- HIV: pyrimethamine + sulfadiazine (see *Prophylaxis*, ID31)
- eye disease, meningitis: corticosteroids
- proper hand hygiene, cook meat thoroughly to proper temperature

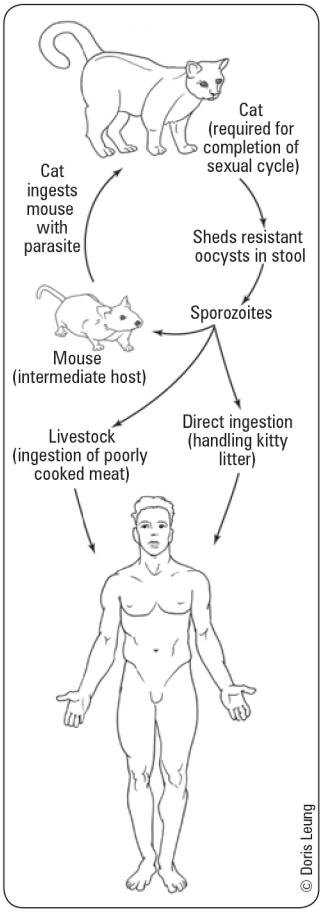


Figure 14. Life cycle of *Toxoplasma gondii*

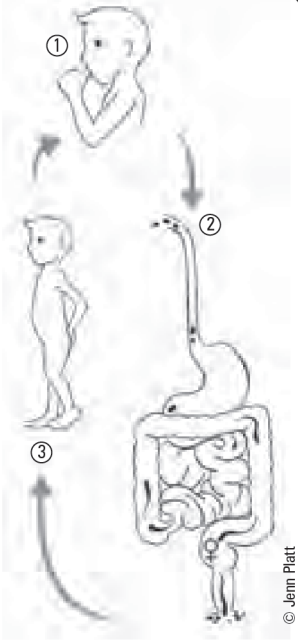
Classic Triad of Congenital Toxoplasmosis
- Chorioretinitis
- Hydrocephalus
- Intracranial calcifications

Helminths

Roundworms – Nematodes

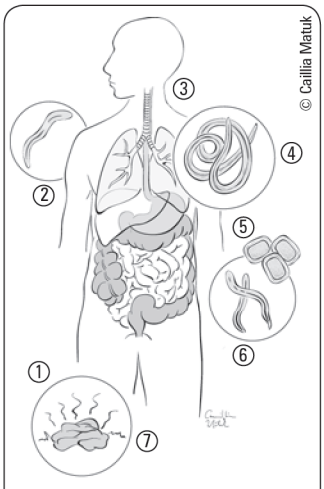
Table 26. Nematodes (Roundworms)

Nematode	Epidemiology	Transmission	Medical Importance	Treatment
Ascaris lumbricoides	Tropics	Human feces, ingestion of contaminated food or water containing eggs	Abdominal pain and intestinal obstruction from high worm burden Cough, dyspnea, pulmonary infiltrates from larval migration through lungs (Löffler's syndrome)	Mebendazole OR albendazole OR pyrantel pamoate
Trichuris trichiura (whipworm)	Tropics	Ingestion of eggs in soil	Diarrhea (± mucous, blood), abdominal pain, rectal prolapse, stunted growth	Mebendazole OR albendazole
Onchocerca volvulus	Africa, Latin America	Blackfly bite	River blindness (onchocerciasis), dermatitis	Ivermectin + doxycycline
Wuchereria bancrofti	Tropics	Mosquito bite	Damage to lymphatics resulting in lymphadenopathy, lymphedema, and elephantiasis Tropical pulmonary eosinophilia	Diethylcarbamazine + doxycycline
Loa Loa	Central Africa	Deer fly bite	Subcutaneous migration of worm, hyperresponsiveness in travellers	Diethylcarbamazine
Enterobius vermicularis (Pinworm)	Worldwide	Human host: fecal-oral self-inoculation and fomite person-to-person transfer Adult worms live in cecum and deposit eggs in perianal skin	Asymptomatic carriers or severe nocturnal perianal itching (pruritus ani) Occasional vaginitis, ectopic migration to appendix or other pelvic organs Abdominal pain, N/V with high worm burden	Sticky tape test: eggs adhere to tape applied to perianal skin (need 5-7 tests to rule out) Examination of perianal skin at night may reveal adult worms Usually no eosinophilia as no tissue invasion Mebendazole, albendazole; pyrantel in pregnancy Change underwear, bathe in morning, pajamas to bed, wash hands, trim fingernails Treat all family members simultaneously Reinfection common
Strongyloides stercoralis (Threadworm)	Subtropical, tropical, and temperate (including southern US)	Fecal contamination of soil: transmission via unbroken skin, walking barefoot Autoinfection: penetration of larvae through GI mucosa or perianal skin Adult worms live in mucosa of small intestine	One of few worms able to multiply in human host Mostly asymptomatic infection or can have pruritic dermatitis at site of larval penetration Transient pulmonary symptoms during pulmonary migration of larvae (eosinophilic pneumonitis = Löffler's syndrome) Abdominal pain, diarrhea, pruritis ani, larva currens (itchy rash) Hyperinfection: occasional fatal cases caused by massive auto-infection in immunocompromised host; immunoablative therapy, including high-dose corticosteroids, is the most common risk factor for disseminated infection	Ivermectin, 200 μg/kg/d PO x 2 doses (albendazole 400 mg PO bid x 7 d, less effective)



1. Embryonated eggs ingested by humans
2. Larvae hatch in small intestine
3. Females migrate out anus at night

Figure 15. Life cycle of *Enterobius*



1. Step on stool containing larvae
2. Larvae migrate to lungs via bloodstream
3. Larvae crawl up trachea and down to GI tract (cough/swallow)
4. Adult worms in intestine
5. Eggs produced in bowel
6. Larvae
7. Bowel movement containing larvae

Figure 16. Life cycle of *Strongyloides*

Flatworms

Cestodes/Trematodes

Table 27. Cestodes/Trematodes (Flatworms)

	Epidemiology	Transmission	Medical Importance	Treatment
CESTODES				
Taenia solium	Developing countries	Undercooked pork (larvae), human feces (eggs)	Taeniasis: mild abdominal symptoms Cysticercosis: mass lesions in CNS, eyes, skin, seizures	Corticosteroids + albendazole for cysticercosis Antiepileptics if seizures Praziquantel for adult tapeworm in gut (taeniasis)
Taenia saginata	Developing countries	Undercooked beef (larvae)	Mild GI symptoms	Praziquantel
Diphyllobothrium latum	Europe, North America, Asia	Raw fish	B_{12} deficiency leading to macrocytic anemia and posterior column deficits	Praziquantel
Echinococcus granulosus	Rural areas Sheep-raising countries	Dog feces (eggs)	Liver/lung cysts (enlarge between 1-20 yr; may cause mass effect or rupture) Risk of anaphylaxis if cystic fluid released during surgical evacuation	Albendazole ± praziquantel alone Surgery + perioperative albendazole Percutaneous aspiration + perioperative albendazole
TREMATODES				
Clonorchis sinensis	Japan, Taiwan, China, SE Asia	Raw fish	Exists in bile ducts, causes inflammation and sometimes cholangiocarcinoma	Praziquantel
Schistosoma spp.	Africa, SE Asia, focal in Western Hemisphere	Fresh water exposure	Chronic sequelae secondary to long-term infection (e.g. chronic liver disease, SCC of the bladder)	Praziquantel

Trematodes/Flukes

Schistosoma spp.

Species
- *S. mansoni, S. hematobium, S. japonicum*

Transmission
- larvae (cercariae), released from snails, penetrate unbroken skin in infested fresh water
- adult worms live in terminal venules of bladder/bowel passing eggs into urine/stool
- eggs must reach fresh water to hatch; schistosomes cannot multiply in or pass between humans
  - more common in individuals from sub-Saharan Africa, South America, Asia, Caribbean, Eastern Mediterranean/North Africa

Clinical Features
- most asymptomatic; symptoms seen in travellers (nonimmune)
- swimmer's itch: pruritic skin rash at site of penetration (cercarial dermatitis)
- acute schistosomiasis (Katayama fever): hypersensitivity to migrating parasites (4-8 wk after infection)
  - fever, hives, H/A, weight loss, cough, abdominal pain, chronic diarrhea, high-grade eosinophilia

Complications of Chronic Infection
- *S. mansoni, S. japonicum*
  - worms in mesenteric vein, eggs in portal tracts of liver and bowel
  - heavy infections: intestinal polyps, portal and pulmonary HTN, splenomegaly (2° to portal HTN), hepatomegaly
- *S. hematobium*
  - worms in vesical plexus, eggs in distal ureter and bladder induce granulomas and fibrosis
  - hematuria and obstructive uropathy; associated with squamous cell bladder cancer
- neurologic complications: spinal cord neuroschistosomiasis (transverse myelitis), cerebral or cerebellar neuroschistosomiasis (increased ICP, focal CNS signs, seizures)
- pulmonary complications: granulomatous pulmonary endarteritis, pulmonary HTN, cor pulmonale; especially in patients with hepatosplenic involvement

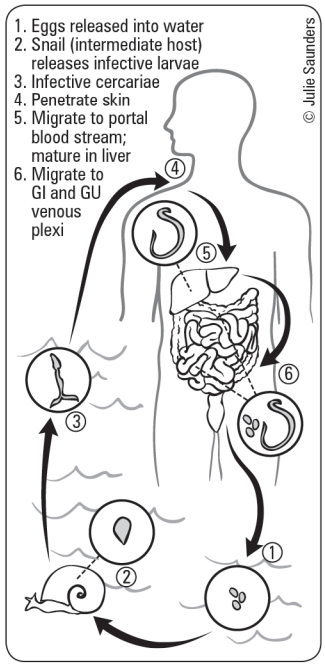


Figure 17. Life cycle of *Schistosoma*

Investigations
- serology (high sensitivity and specificity), CBC (eosinophilia, anemia, thrombocytopenia)
- *S. mansoni, S. japonicum*: eggs in stool, liver U/S shows fibrosis, rectal biopsy
- *S. hematobium*: bladder biopsy, eggs in urine and occasionally stool, kidney and bladder U/S

Treatment and Prevention
- praziquantel
- add glucocorticoid if acute schistosomiasis or neurologic complications develop
- proper disposal of human fecal waste, molluscicide, avoidance of infested water
- do not swim in Lake Malawi

For up to date information on geographic and seasonal patterns of disease and travel advisories, check the website for the United States Centers for Disease Control and Prevention (wwwvnc.cdc.gov/travel) or Foreign Affairs Canada (travel.gc.ca)

Ectoparasites

- scabies, lice
- see Dermatology, D28

Travel Medicine

General Travel Precautions
- vector-borne: long sleeves, long pants, hats, repellents (containing permethrin) applied to clothes, belongings, and bed nets, and skin repellents (such as DEET) applied to exposed skin
- food/water: avoid eating raw meats/seafood, uncooked vegetables, and milk/dairy products; drink only bottled beverages, chlorinated water, boiled water
- recreation: caution when swimming in schistosomiasis-endemic regions (Lake Malawi), fresh water rafting/kayaking, beaches that may contain human/animal waste products, near storm drains, after heavy rainfalls
- prophylaxis: malaria (chloroquine, mefloquine, atovaquone + proguanil, doxycycline), traveller's diarrhea (bismuth salicylate)
- standard vaccines up to date (hepatitis B, MMR, tetanus/diphtheria, varicella, pertussis, polio, influenza)
- travel vaccines: hepatitis A/B, Japanese encephalitis, typhoid fever, yellow fever, rabies, ETEC, cholera
- sexually transmitted and blood-borne infections: safe sex practices, avoidance of percutaneous injury through razors, tattoos, piercings

Infectious Diseases to Consider
- vector borne: malaria, dengue fever, Chikungunya fever, yellow fever, spotted fever rickettsioses, West Nile virus, trypanosomiasis, Japanese encephalitis, tick-borne encephalitis, *leishmaniasis*
- sexually transmitted: HIV, HBV, acute HSV, syphilis, usual STIs
- zoonotic: rabies, hantavirus, tularemia, Q fever, anthrax, brucellosis
- airborne: TB
- food/water: HAV, HEV, brucellosis, typhoid, paratyphoid, amoebiasis, dysentery, traveller's diarrhea, cholera, *Campylobacter* spp.
- soil/water: schistosomiasis, strongyloidiasis, leptospirosis, cutaneous larva migrans, histoplasmosis, paracoccidioidomycosis

Important Exposures

Insect Bites	
Mosquito	• *Plasmodium* spp. (Malaria) • Dengue • Lymphatic filariasis (Elephantiasis) • West Nile Encephalitis • Yellow Fever • Japanese Encephalitis
Tick	• *Borrelia burgdorferi* (Lyme Disease) • *Rickettsia rickettsii* (Rocky Mountain Spotted Fever)
Fly	• *Trypanosoma brucei* spp. (African sleeping sickness) • *Leishmania* spp. (Leishmaniasis) • *Bartonella bacilliformis* (Bartonellosis)
Flea	• *Yersinia* (Plague) • *Tunga penetrans* (Tungiasis)
Mammal Bites	
Dog/Cat	• Rabies, *Pasteurella*, anaerobes, *Streptococcus, S. aureus*
Human	• *Streptococcus, S. aureus*, oral anaerobes, *Eikenella*
Oral Exposures	
Unpasteurized Milk	• *Brucella* spp., non-tuberculous mycobacteria, *Salmonella, E. coli, Listeria*
Undercooked Meat/Fish	• Enteric bacteria, helminths, protozoa
Water	• Hepatitis A/E, Norwalk, cholera, *Salmonella, Shigella, Giardia*, poliovirus, *Cryptosporidium, Cyclospora*
Environmental Exposures	
Freshwater	• *Leptospira* spp., schistosomes, Acanthamoeba, *Naegleria fowleri*
Soil	• Hookworms, *Toxocara* spp. (visceral larva migrans), *Leptospira interrogans* (leptospirosis)

Adapted with permission from *Lancet* 2003;361:1459-69

Fever in the Returned Traveller

Etiology
- commonly identified causes of fever in returning traveller
  - parasitic: malaria (20-30%)
  - viral: non-specific mononucleosis-like syndrome (4-25%), dengue (5%), viral hepatitis (3%)
  - bacterial: typhoid from *Salmonella* (2-7%), rickettsioses (3%)
  - diverse group of causative pathogens: traveller's diarrhea (10-20%), RTI (10-15%), UTI/STI (2-3%)
- febrile illness in travellers can be caused by routine infections that are common in nontravellers (e.g. URTI, UTI)
- less commonly, fever can be due to non-infectious causes (e.g. DVT, PE)

History
- pre-travel preparation
- travel itinerary: when, where, why, what, who, how?
  - dates of travel (determine incubation period)
  - season of travel: wet or dry
  - destination: country, region (urban or rural), environment (jungle, desert, etc.)
  - purpose of trip

Fever in traveller from malaria endemic area is malaria until proven otherwise

- persons visiting friends and family more likely to be exposed to local population and pathogens
  - style of travel: lodgings, camping, adventure travelling
  - local population: sick contacts
  - transportation: use of animals
- exposure history
  - street foods, untreated water: increased risk of traveller's diarrhea, enteric fever
  - uncooked meat/unpasteurized dairy: increased risk of parasitic infection
  - body fluids (sexual contacts, tattoos, piercings, IVDU, other injections)
  - increased risk of HBV, HCV, HIV, GC, *C. trachomatis*, syphilis
  - animal/insect bites: increased risk of malaria, dengue, rickettsioses, rabies
- fever pattern
- incubation period: use the earliest and latest possible dates of exposure to narrow the differential diagnosis and exclude serious infections
  - <21 d: consider malaria, typhoid fever, dengue fever, rickettsioses; exclude HBV, TB
  - >21 d: consider malaria, TB; exclude dengue fever, traveller's diarrhea, rickettsioses
- body systems affected: GI, respiratory, CNS, skin

Investigations

- all travellers with fever should undergo the following tests
  - blood work: CBC and differential, liver enzymes, electrolytes, creatinine, thick and thin blood smears x3 (for malaria), blood C&S
  - urine: urinalysis, urine C&S if dysuria or other localizing signs
- special tests based on symptoms, exposure history, and geography
  - stool: C&S, O&P
  - CXR
  - dengue serology for IgM

Table 28. Fever in the Returned Traveller

Illness	Geography/ Timing	Pathogen	Incubation Period	Clinical Manifestations	Diagnosis	Treatment
Malaria	Africa India C. and S. America SE Asia Usually rural, night-biting mosquitoes	*Plasmodium falciparum* *Plasmodium vivax* *P. malaraie* *P. ovale* *P. knowlesi*	10 d to 40 yr	Fever and flu-like illness, (shaking chills, H/A, muscle aches, and fatigue) N/V and diarrhea Anemia and jaundice *Plasmodium falciparum*: (severe) kidney failure, seizures, mental confusion, prostration, coma, death, respiratory failure	Blood smear (thick and thin) x3 Antigen detection PCR (mostly a research tool)	Artesunate (for severe disease) + malarone, doxycycline, or clindamycin Quinine sulfate + doxycycline or clindamycin Chloroquine + primaquine
Dengue	South East Asia Caribbean Usually urban, day-biting mosquitoes	Dengue viruses	3 d to 2 wk	Sudden onset of fever, H/A, retro-orbital pain, myalgias, and arthralgias Leukopenia Thrombocytopenia Hemorrhagic manifestations (rare in travellers)	Anti-dengue IgM positivity	Symptom relief: Acetaminophen (avoid using NSAIDs because of anticoagulant properties)
Typhoid (enteric fever)	Global but mostly Indian subcontinent	*Salmonella typhi* *Salmonella paratyphi*	3 to 60 d	Sustained fever 39°-40°C (103°-104°F) Abdominal pain, H/A, loss of appetite, cough, constipation	Stool, urine, or blood sample positive for *S. typhi* or *S. paratyphi*	Quinolone antibiotic (e.g. ciprofloxacin), ceftriaxone, or macrolide
Tick Typhus	Mediterranean South Africa India	*Rickettsia*	1 to 2 wk	Fever, H/A, fatigue, muscle aches, occasionally rash Eschar at site of tick bite Thrombocytopenia Elevated liver enzymes	Serology Presence of classic tick eschar	Doxycycline
TB	Global	*M. tuberculosis*	Variable	Fever, cough, hemoptysis	CXR Sputum culture and acid-fast stain	Ethambutol, isoniazid, pyrazinamide, rifampin
Mononucleosis	Caribbean, C. and S. America	EBV or CMV	30 to 50 d	Malaise, fatigue, pharyngitis, lymphadenopathy, splenomegaly	Atypical lymphocytes on blood smear and positive heterophilic antibody (monospot) test	Acetaminophen or NSAIDs, fluids

Fever of Unknown Origin

Table 29. Classification of Fever of Unknown Origin (FUO) – Temp >38.3°C/101°F on several occasions

Classical FUO	Nosocomial FUO	Neutropenic FUO	HIV-associated FUO
Duration >3 wk	Hospitalized patient Infection not present/ incubating on admission	Neutrophil count <500/mL or is expected to fall to that level in 1-2 d	HIV infections Duration >4 wk for outpatients, >3 d for hospitalized patients
Diagnosis uncertain after 3 outpatient visits or 3 d in hospital or 1 wk of intensive ambulatory investigation	Diagnosis uncertain after 3 d of investigation, including at least 2 d incubation of cultures	Diagnosis uncertain after 3 d of investigation, including at least 2 d incubation of cultures	Diagnosis uncertain after 3 d of investigation, including at least 2 d incubation of cultures

Causes of Nosocomial FUO

B, C, D, E
Bacterial and fungal infections of respiratory tract and surgical sites
Catheters (intravascular and urinary)
Drugs
Emboli

Etiology of Classic FUO

- infectious causes (~30%)
  - TB: extra-pulmonary (most common), miliary, pulmonary (if pre-existing disease)
  - abscess: subphrenic, liver, splenic, pancreatic, perinephric, diverticular, pelvis, psoas
  - osteomyelitis
  - bacterial endocarditis (culture negative)
  - uncommon: viral (CMV, EBV), fungal (histoplasmosis, cryptococcosis), parasitic (toxoplasmosis, leishmaniasis, amoebiasis, malaria)
- neoplastic causes (~20%)
  - most commonly lymphomas (especially non-Hodgkin's) and leukemias, also multiple myeloma, myelodysplastic syndrome
  - solid tumours: RCC (most common), also breast, liver (hepatoma), colon, pancreas, or liver metastases
- collagen vascular diseases (~30%)
  - SLE, RA, rheumatic fever, vasculitis (temporal arteritis, PAN), JRA, Still's disease
- miscellaneous (~20%)
  - drugs, factitious fever
  - sarcoidosis, granulomatous hepatitis, IBD
  - hereditary periodic fever syndromes (such as familial Mediterranean fever)
  - venous thromboembolic disease: PE, DVT
  - endocrine: thyroiditis, thyroid storm, adrenal insufficiency, pheochromocytoma
- unknown in 30-50% despite detailed workup

Drugs that may Cause Fever

- Anti-microbials (sulfonamides, penicillins, nitrofurantoin, antimalarials)
- Anti-hypertensives (hydralazine, methyldopa)
- Anti-epileptics (barbiturate, phenytoin)
- Anti-arrythmics (quinine, procainamide)
- Anti-inflammatories (NSAIDs)
- Anti-thrombotics (ASA)
- Anti-histamines
- Anti-thyroid

Approach to Classic FUO

- careful history: travel, environmental/occupational exposures, infectious contacts, medication history, immunizations, TB history, sexual history, past medical history, comprehensive review of systems (including symptoms that resolved before interview)
- thorough physical exam: fever pattern, rashes (skin, mucous membranes), murmurs, arthritis, lymphadenopathy, organomegaly
- initial investigations as appropriate
  - blood work: CBC and differential, electrolytes, BUN, Cr, calcium profile, LFTs, ESR, CRP, muscle enzymes, RF, ANA, serum protein electrophoresis (SPEP), blood smear
  - cultures: blood (x2 sets), urine, sputum, stool C&S, O&P, other fluids as appropriate
  - serology: HIV, monospot, CMV IgM
  - imaging: CXR, abdominal imaging
- if there are diagnostic clues from any of the above steps, proceed with directed exam, biopsies or invasive testing as required, followed by directed treatment once a diagnosis is established
- if no diagnosis with the above, consider empiric therapy vs. watchful waiting
  - without intervention: patients that remain undiagnosed despite extensive workup have good prognosis

Infections in the Immunocompromised Host

- immunocompromised hosts have increased susceptibility to infections from pathogens that are typically low virulence, commensal, or latent
- type of immunodeficiency predicts probable spectrum of agents

Factors that Compromise the Immune System

- general: age (very young or elderly), malnutrition
- immune disease: HIV/AIDS, malignancies, asplenia (functional or anatomic), hypogammaglobulinemia, neutropenia
- DM
- iatrogenic: corticosteroids, chemotherapy, radiation treatment, anti-TNF therapy, other immunosuppressive drugs (e.g. in transplant patients)

Infections Associated with Asplenia
- *Haemophilus influenzae* type b
- *Streptococcus pneumoniae*
- *Neisseria meningitidis*
- *Salmonella*
- *Babesiosis*
- *Malaria*
- *Capnocytophaga canimorsus* (dog bite)

Table 30. Types of Immunodeficiency

Type	Conditions	Vulnerable To
Cell-Mediated Immunity	HIV, Hodgkin's, hairy cell leukemia, cytotoxic drugs, SCID, DiGeorge syndrome	Latent viruses Fungi Parasites
Humoral Immunity	CLL, lymphosarcoma, multiple myeloma, nephrotic syndrome, protein-losing enteropathy, burns, sickle cell anemia, asplenia, splenectomy, selective Ig deficiencies, Wiskott-Aldrich syndrome	Encapsulated organisms (*S. pneumoniae, H. influenzae, N. meningitidis, Salmonella typhi,* GBS)
Neutrophil Function	Myelodysplasia, paroxysmal nocturnal hemoglobinuria, radiation, cytotoxic drug therapy, C3 or C5 deficiencies, chronic granulomatous disease	Catalase-producing organisms (*Staphylococcus*, *Serratia, Nocardia, Aspergillus*)

Febrile Neutropenia

Definition

- fever (≥38.3°C/101°F or ≥38.0°C/100.4°F for ≥1 h) and one of
  - ANC <0.5 OR
  - ANC <1.0 but trending down to 0.5

ANC (absolute neutrophil count) = WBC x (%neutrophils + %bands)

Pathophysiology

- decreased neutrophil production
  - marrow: infection, aplastic/myelophthisic anemia, leukemia, lymphoma, myelodysplastic syndromes
  - iatrogenic: cancer chemotherapy, radiation, drugs
  - deficiencies: vitamin B_{12}, folate
- increased peripheral neutrophil destruction
  - autoimmune: Felty's syndrome, SLE, antineutrophil antibodies
  - splenic sequestration

Usual signs and symptoms of infection may be diminished because neutrophils are required for a robust inflammatory response; exam and x-ray findings may be more subtle

Epidemiology/Etiology

- most common life-threatening complication of cancer therapy
- 8 cases per 1,000 cancer patients per yr in the U.S.
- causative organism identified only 1/3 of the time
- GN (especially *Pseudomonas*) historically most common
- GP more common now
- fungal superinfection if neutropenia prolonged or if concurrent antibiotic use (especially *Candida, Aspergillus*)

WBC is lowest between 5-10 d after last chemotherapy cycle

Investigations

- examine for potential sites of infection: mucositis and line infections are most common
- do NOT perform DRE; examine perianal region
- blood C&S (x2 sets), urine C&S, culture all indwelling catheter ports, ± sputum C&S and NP swab for respiratory viruses
- CBC and differential, Cr, BUN, electrolytes, AST/ALT, total bilirubin

Treatment

- most hospitals have their own specific protocol; one example is presented below

Prophylaxis against FN with G-CSF (granulocyte colony-stimulating factor) and GM-CSF (granulocyte-macrophage colony-stimulating factor) decreases hospitalization without affecting mortality (indicated if risk of FN 20% or if FN has occurred in a previous chemotherapy cycle)

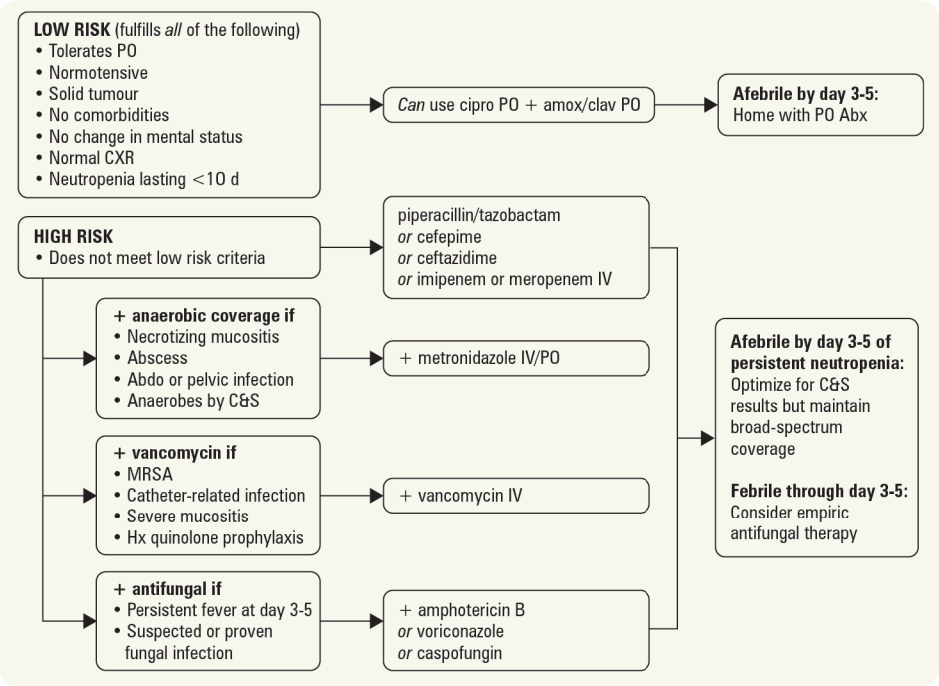


Figure 18. Example of treatment protocol for febrile neutropenia

Infections in Solid Organ Transplant Recipients

- infection is a leading cause of early morbidity/mortality in transplant recipients
- infection depends on degree of immunosuppression
- common infections <1 mo post-transplant
  - bacterial infection of wound/lines/lungs, herpetic stomatitis
- common infections >1 mo post-transplant
  - viral (especially CMV, EBV, VZV)
  - fungal (especially *Aspergillus, Cryptococcus, P. jiroveci*)
  - protozoan (especially *Toxoplasma*)
  - unusual bacterial/mycobacterial infections (especially TB, *Nocardia, Listeria*)

Prophylactic Vaccinations Given Before Transplant

- to all transplant patients: DTaP, pneumococcal, influenza, hepatitis A and B vaccines
- if low titre or poor documentation: MMR, polio, varicella vaccination (with booster 4-8 wk later)

Immune Reconstitution Syndrome

Definition

- a harmful inflammatory response directed against a previously acquired infection following a recovery of the immune system

Etiology

- paradoxical worsening of a successfully or partially treated opportunistic infection
- new onset response to a previously unidentified opportunistic infection
- the majority of cases are in HIV/AIDS or immunosuppressed patients starting anti-retroviral therapy or discontinuing immunosuppressive therapy; sudden recovery from an immunosuppressive state towards a pro-inflammatory state directed towards subclinical infection results in fever and inflammation
- can occur in response to multiple infections
  - *Mycobacteria* (*tuberculosis, avium* complex)
  - *Cryptococcus*
  - *Pneumocystis*
  - *Toxoplasma*
  - HBV and HCV
  - Herpes viruses (VZV reactivation, HSV, CMV)
  - JC virus (progressive multifocal leukoencephalopathy)
  - *Molluscum contagiosum*

- clinical features are dependent on the type and location of the pre-existing infection
- thought to be worse with quick increase in CD4 count and with lower pre-treatment CD4 count
- non-HIV conditions with documented IRS: solid organ transplant recipients, post-partum women, neutropenic patients, anti-TNF therapy

Epidemiology
- in HIV patients starting HAART, IRS reported to affect ~10%

Investigations
- IRS is a diagnosis of exclusion
- rule out drug reaction, patient non-adherence, drug resistance

Treatment
- continue HAART therapy in HIV patients with mild-moderate symptoms, but consider discontinuation if symptoms are life-threatening or potentially irreversible
- treat underlying infection; initiate treatment for some infections prior to HAART initiation
- consider starting corticosteroids/NSAIDs to decrease inflammatory response

A Simplified Look at Antibiotics

- general overview, see Table 31 for more details

1. Penicillins

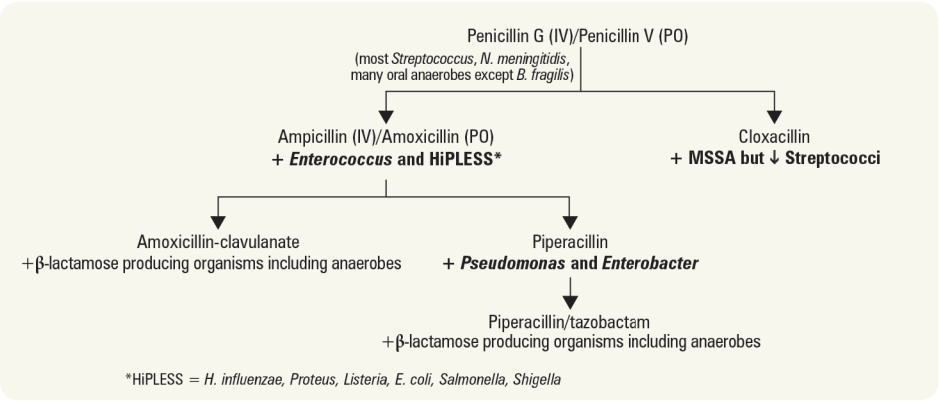


Figure 19. Penicillins

2. Cephalosporins (PO/IV)
- 1st generation: cephalexin/cefazolin (mostly GP, some GN)
- 2nd generation: cefuroxime/cefprozil (some GP and some GN, *anaerobes)
- 3rd generation: cefixime/cefotaxime, ceftriaxone (good *Streptococcal* coverage, mostly GN), and ceftazidime (no GP, mostly GN, *Pseudomonas*)
- 4th generation: --/cefepime (most GP, most GN, *Pseudomonas*)

3. Aminoglycosides (GN aerobic bacilli)
- gentamicin
- tobramycin
- amikacin

4. Macrolides (GP, *Haemophilus*, and atypical bacteria [*Legionella, Chlamydophila, Mycoplasma*])
- erythromycin
- clarithromycin
- azithromycin

5. Fluoroquinolones (GN – although resistance becoming a huge problem)
- ciprofloxacin (+ *Pseudomonas*)
- norfloxacin (for UTI only)
- respiratory fluoroquinolones (some GP, GN, "atypicals", *Legionella, Mycoplasma, Chlamydophila, Mycobacteria*)
  - levofloxacin
  - moxifloxacin (+ anaerobes)

6. Carbapenems (broad coverage: GP, GN, and anaerobes)
- imipenem (+ *Pseudomonas*)
- meropenem (+ *Pseudomonas*)
- ertapenem

7. Others
- doxycycline/tetracycline (GP, syphilis, *Chlamydophila, Rickettsia, Mycoplasma*)
- tigecycline (for resistant GP infections, GN, anaerobes, *Chlamydophila, Rickettsia, Mycoplasma*)
- vancomycin (all GP and *C. difficile* – the oral form)
- linezolid (for resistant GP infections)
- daptomycin (for resistant GP infections)
- clindamycin (most GP, GN anaerobes)
- TMP/SMX (most *S. aureus* including: MRSA, GN aerobes, *Pneumocystis*)
- nitrofurantoin (GN bacilli, *S. saprophyticus, Enterococcus*)
- metronidazole (anaerobes including: *C. difficile; Trichomonas, Entamoeba*)
- treatment for *C. difficile*: metronidazole OR oral vancomycin; consider both in serious infection

Antimicrobials

Antibiotics

- empiric antibiotic therapy
  - choose antibiotic(s) to cover for most likely and lethal organisms for the type of infection prior to obtaining laboratory results (usually reserved for serious infections)
  - adjust antibiotic(s) based on C&S
    - if causative organism identified, use antibiotic to which organism is sensitive
    - if causative organism not identified, re-evaluate need for ongoing antimicrobial therapy (and continue with empiric antibiotic(s) if indicated)

Reasons for Combination Therapy
- Polymicrobial infection
- Empiric therapy pending culture results
- Synergy for difficult to treat pathogens (e.g. *Enterococcus* spp. causing endocarditis)
- To prevent emergence of resistance

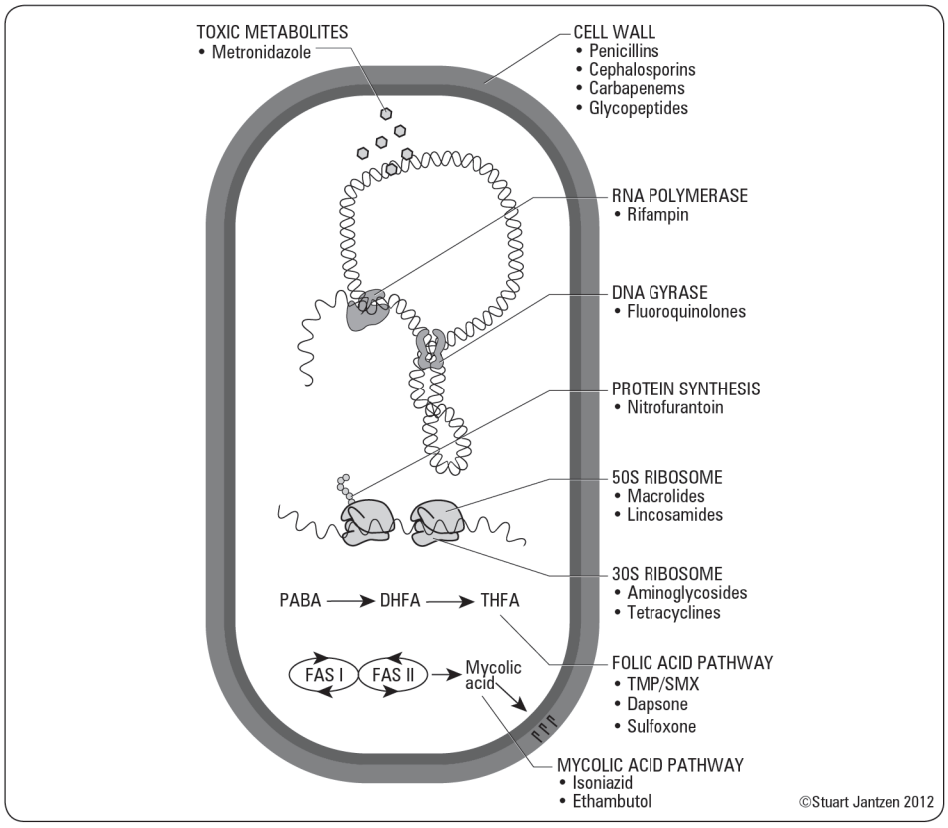


Figure 20. Mechanism of action of antibiotics

Bactericidal Antibiotics	Bacteriostatic Antibiotics
"**V**ery **F**inely **P**roficient **A**t **CC**ell **M**urder"	"**ECSTaTiC**"
Vancomycin	**E**rythromycin (and other macrolides)
Fluoroquinolones	**C**lindamycin
Penicillin	**S**ulfamethoxazole
Aminoglycosides	**T**rimethoprim
Cephalosporins	**T**etracyclines
Carbapenems	**C**hloramphenicol
Metronidazole	
Daptomycin	

Table 31. Antibiotics

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Indications	Contraindications
CELL WALL INHIBITORS					
Penicillins					
Benzyl penicillin - penicillin G IV/IM - penicillin V PO	GP except *Staphylococcus*, *Enterococcus* Oral anaerobes Syphilis	Bactericidal: β-lactam inhibits cell wall synthesis by binding penicillin binding protein (PBP) preventing cross-linking of peptidoglycan	Immediate allergy (IgE): anaphylaxis, urticaria Late-onset allergy (IgG): urticaria, rash, serum sickness Interstitial nephritis Dose related toxicity: seizures Diarrhea	Mild to moderately severe infections caused by susceptible organisms including actinomycosis, streptococcal pharyngitis, streptococcal skin and soft tissue infections, pneumococcal pneumonia, syphilis	Hypersensitivity to penicillin
Aminopenicillin - ampicillin IV - amoxicillin PO (Amoxil®)	Same as penicillin AND *Enterococcus* *Listeria*	See above	See above	Bacterial meningitis and endocarditis (IV ampicillin), acute otitis media (AOM), streptococcal pharyngitis, sinusitis, acute exacerbations of COPD, part of multidrug therapy for *H. pylori* treatment, Lyme disease, pneumococcal pneumonia; UTI (amoxicillin and ampicillin) for most enterococci and susceptible gram-negative pathogens	Hypersensitivity to penicillin or β-lactam antibiotics
Isoxazyolyl penicillin - cloxacillin - methicillin - nafcillin - oxacillin	Methicillin-sensitive *Staphylococcus aureus;* streptococci	See above	See above	Bacterial infections caused by staphylococci and streptococci including skin soft-tissue infections	Hypersensitivity to cloxacillin or any penicillin
β-lactam/β-lactamase inhibitor combinations - amoxicillin-clavulanate (Clavulin®, Augmentin®) - piperacillin/tazobactam (Tazocin®)	Same as penicillin AND *Staphylococcus* *H. influenzae* *Enterococcus* Anaerobes (oral and gut)	β-lactamases prduced by certain bacteria inactivate β-lactams Lactamase inhibitors prevent this process, preserving antibacterial effect of β-lactams	See above	Various β-lactamase producing bacteria, Clavulin® sensitive bacteria including RTI, sinusitis, AOM, skin and soft tissue infections, UTI, and severe intra-abdominal and pelvic infections	Hypersensitivity to penicillin or cephalosporin History of Clavulin®-associated jaundice or hepatic dysfunction
Cephalosporins					
PO / **IV**	**GP**	**GN**			
1° cephalexin (Keflex®) / cefazolin (Ancef®)	Good with the exception of *Enterococcus* and MRSA	*E. coli*, *Klebsiella*, *Proteus*, *H. influenzae* (not all isolates)	Bactericidal: β-lactam inhibits PBP, prevents cross-linking of peptidoglycan, less susceptible to penicillinases	10% penicillin allergy cross-reactivity Nephrotoxicity	Skin and soft tissue infections, prevention of surgical site infections (cefazolin); infections caused by susceptible organisms (especially *Staph* and *Strep* infections)	Hypersensitivity to cephalosporins or other β-lactam antibiotics
2° cefuroxime (Ceftin®) cefprozil (Cefzil®) / cefuroxime (Zinacef®) cefoxitin[A]	Weaker activity than 1°	More coverage than 1° ([A]includes anaerobes)	See above	See above	Upper and lower respiratory tract infections; pneumococcal pneumonia; soft tissue infections	See above
3° cefixime (Suprax®) / ceftriaxone (Rocephin®) cefotaxime (Claforan®) ceftazidime[B] (Fortaz®)	*S. aureus* + *streptococcal* coverage (cefotaxime and ceftriaxone) especially *S. pneumoniae*	Broad coverage ([B]includes *Pseudomonas* for ceftazidime only)	See above	~1% penicillin allergy cross-reactivity	Community-acquired pneumonia (cefotaxime, ceftriaxone), gonorrhea (use ceftriaxone), community-acquired bacterial meningitis (ceftriaxone, cefotaxime); abdominal and pelvic infections (cefotaxime or ceftriaxone in combination with metronidazole); once-daily administration makes ceftriaxone convenient for outpatient IV therapy	Severe hypersensitivity (Type I) to other β-lactam antibiotics
4° / cefepime (Maxipine®)	Broad spectrum	Broad coverage including *Pseudomonas*	See above	See above	Empiric therapy for febrile neutropenia	See above

Table 31. Antibiotics (continued)

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Indications	Contraindications
CELL WALL INHIBITORS					
Carbapenems					
imipenem (Primaxin®)	GP except MRSA GN including *Pseudomonas* + *Enterobacter,* ESBLs, anaerobes	β-lactam inhibits PBP and prevents cross-linking of peptidoglycan	Penicillin allergy cross-reactivity Seizures	Treatment of infections caused by GNB producing extended-spectrum β-lactamases, serious infections caused by susceptible organisms	Hypersensitivity to imipenem
meropenem (Merrem®)	See above; does not cover *Enterococcus*	See above	See above	See above	Hypersensitivity to β-lactams
ertapenem (Invanz®)	GP except *Enterococcus*, MRSA GN including *Enterobacter* (but not *Pseudomonas*), anaerobes	See above	See above	See above; once-daily administration makes it convenient for outpatient IV therapy	Hypersensitivity to β-lactams
Glycopeptides					
Vancomycin (Vancocin®)	GP including MRSA, not VRE *C. difficile* if PO	Glycopeptide sterically inhibits cell wall synthesis	Red Man Syndrome Nephrotoxicity Ototoxicity Thrombocytopenia	Severe or life-threatening GP infections, patients with β-lactam allergy May only be taken orally for severe *C. difficile* infection	Hypersensitivity to vancomycin
PROTEIN SYNTHESIS INHIBITORS (50S RIBOSOME)					
Macrolides					
erythromycin (Erybid®, Eryc®) *This agent is rarely used due to GI upset	GP except *Enterococcus* GN: *Legionella, B. pertussis* "Atypicals": *Chlamydophila, Mycoplasma*	Binds to 50S ribosomal subunit inhibiting protein synthesis	GI upset Acute cholestatic hepatitis Prolonged QT	Susceptible RTI, pertussis, diphtheria, Legionnaires' disease, skin and soft tissue infections	Hypersensitivity to erythromycin Concurrent therapy with astemizole, terfenadine
clarithromycin (Biaxin®)	See above	See above	See above	Susceptible RTI, skin infections, non-tuberculous mycobacterial infections, part of mulitdrug therapy for *H. pylori* treatment	Hypersensitivity to macrolides
azithromycin (Zithromax®)	See above	See above	See above	Susceptible RTI, acute exacerbations of COPD, community-acquired pneumonia, skin infections, *Campylobacter* infections if treatment indicated, chlamydia	Hypersensitivity to macrolides
Lincosamides					
clindamycin (Dalacin®)	GP except *Enterococcus*, most community-acquired MRSA Anaerobes	Inhibits peptide bond formation at 50S ribosome	Pseudomembranous colitis GI upset	Treatment of suspected or proven infections caused by GP, anaerobes including skin and skin structure infections, oropharyngeal infections, in combination with GN coverage for intra-abdominal and pelvic infections	Hypersensitivity to clindamycin Infants <30 d
chloramphenicol	GP GN Anaerobes	Inhibits peptidyl transferase action of tRNA at 50S ribosome	Aplastic anemia Grey Baby Syndrome	Serious infections by susceptible organisms when suitable alternatives are not available including meningococcal disease in patients with anaphylaxis to β-lactams	Hypersensitivity to chloramphenicol
linezolid (Zyvoxam®)	GP including VRE + MRSA	Binds 50S ribosome and prevents functional 70S initiation complex	HTN (acts as MAOI) Risks with prolonged use: myelosuppression optic neuropathy, peripheral neuropathy	Vancomycin-resistant *Enterococcus faecium* infections including intra-abdominal, skin and skin structure, and urinary tract infections, MRSA infections as outpatient therapy	Hypersensitivity to linezolid

Table 31. Antibiotics (continued)

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Indications	Contraindications
PROTEIN SYNTHESIS INHIBITORS (30S RIBOSOME)					
Aminoglycosides					
gentamicin tobramycin amikacin (Amikin®)	GN (includes *Pseudomonas*)	Binds 30S subunit of ribosome inhibiting protein synthesis	Nephrotoxicity (reversible) Vestibular and ototoxicity (irreversible) Vestibular toxicity is the most important aminoglycoside toxicity	GN infections when alternatives do not exist, UTIs, used in low doses for synergy with β-lactams or with vancomycin for the treatment of serious enterococcal infections	Pre-existing hearing loss and renal dysfunction
Tetracyclines					
tetracycline (Apo-Tetra®, Nu-TetraT®) minocycline (MinocinT®) doxycycline (Doxycin®) tigecycline (Tygacil®)	GP Anaerobes "Atypicals": *Chlamydophila, Mycoplasma, Rickettsia, Borrelia burgdorferi Treponema* Malaria prophylaxis (doxycycline) Tigecycline has activity against MRSA, VRE, and ESBL-producing *E. coli/K. pneumoniae*	Binds 30S subunit of ribosome inhibiting protein synthesis	GI upset Hepatotoxicity Fanconi's syndrome Photosensitivity Teratogenic Yellow teeth and stunted bone growth in children	Rickettsial infections, *Chlamydophila*, acne (tetracycline, minocycline), PID (step-down), malaria prophylaxis (doxycycline)	Severe renal or hepatic dysfunction Pregnancy or lactation Children under 8 yr
TOPOISOMERASE INHIBITORS					
Fluoroquinolones (FQs)					
ciprofloxacin (Cipro®) norfloxacin (Apo-Norflox®) ofloxacin (Floxin®) Respiratory FQs: levofloxacin (Levaquin®) moxifloxacin (Avelox®)	Poor GP activity GN (includes *Pseudomonas*) Atypicals Moxifloxacin also covers many anaerobes	Inhibits DNA gyrase	H/A, dizziness Allergy Seizures Prolonged QT Dysglycemia (levofloxacin, moxifloxacin)	Upper and lower RTI (not ciprofloxacin unless susceptible organism isolated), UTI, prostatitis (not moxifloxacin), bone and joint infections for susceptible organisms, skin and soft tissue infections (levofloxacin, moxifloxacin), infectious diarrhea, meningococcal prophylaxis, intra-abdominal infections (moxifloxacin, ciprofloxacin in combination with metronidazole or clindamycin), febrile neutropenia prophylaxis (ciprofloxacin, levofloxacin) or ciprofloxacin in combination with amoxicillin-clavulanate low management of "low-risk" febrile neutropenia	
OTHER					
Rifampin	GP cocci *N. meningitidis* *H. influenzae* *Mycobacteria*	Inhibits RNA polymerase	Hepatic dysfunction, P450 enzyme induction Orange tears/saliva/urine	Part of multidrug treatment for active TB, alone for treatment of latent TB, part of multidrug treatment of other mycobacterial infections, endocarditis involving prosthetic valve or other prosthetic device infections in combination with other antibiotic agents, prophylaxis for those exposed to people with *N. meningitidis* or HiB meningitis	Jaundice Not to be used as monotherapy (except for prophylaxis)
Metronidazole (Flagyl®)	Anaerobes Protozoa	Forms toxic metabolites in bacterial cell which damage microbial DNA	Disulfiram-type reaction with EtOH Seizures Peripheral neuropathy	Protozoal infections (trichomoniasis, amoebiasis, giardiasis), bacterial vaginosis, anaerobic bacterial infections	
Daptomycin	GP, including MRSA and VRE	Hypothesized to bind to cell wall and form channels leading to intracellular K^+ depletion	Skeletal muscle injury at high doses (elevated CPK) Peripheral neuropathy	Bacteremia, endocarditis, skin and soft tissue, and other infections due to resistant GP infections including MRSA and VRE	Known hypersensitivity

Table 31. Antibiotics (continued)

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Indications	Contraindications
ANTI-METABOLITE					
Trimethoprim-Sulfamethoxazole (TMP/SMX) (Septra®, Bactrim®)	GP, especially *S. aureus* (including most MRSA) GN: enteric *Nocardia* Other: *Pneumocystis, Toxoplasmosis*	Inhibits folic acid pathway (TMP inhibits DHFR and SMX competes with PABA)	Hepatitis Stevens-Johnson syndrome Bone marrow suppression Hyperkalemia Drug toxicity (increases free levels of many drugs, including glyburide, warfarin)	Susceptible UTI, RTI, GI infections, skin and soft tissue infections caused by staphylococcal species, treatment and prophylaxis of *P. jiroveci* pneumonia	Hypersensitivity to TMP-SMX, sulfa drugs
nitrofurantoin (MacroBID®, (Macrodantin®)	*Enterococcus, S. saprophyticus* GN (coliforms)	Reactive metabolites inhibit ribosomal protein synthesis	Cholestasis, hepatitis Hemolysis if G6PD deficiency Interstitial lung disease with chronic use	Lower UTI; not pyelonephritis or bacteremia	Hypersensitivity to nitrofurantoin Anuria, oliguria, or significant renal impairment Pregnant patients during labour and delivery or when labour imminent Infants <1 mo of age
ANTI-MYCOBACTERIALS					
isoniazid (INH)	*Mycobacteria*	Inhibits mycolic acid synthesis	Hepatotoxicity Hepatitis Drug-induced SLE Peripheral neuropathy	Part of multidrug treatment for active TB, alone for treatment of latent TB	Drug-induced hepatitis or acute liver disease
rifampin (RIF)	*Mycobacteria*	Inhibits RNA polymerase	Hepatotoxicity P450 enzyme inducer Orange tears, saliva, urine	Part of multidrug treatment for active TB, alone for treatment of latent TB, part of multidrug treatment of other mycobacterial infections	Jaundice Not to be used monotherapy (except for prophylaxis)
ethambutol	*Mycobacteria*	Inhibits mycolic acid synthesis	Loss of central and colour vision	Part of multidrug treatment for active TB and other mycobacterial infections	Renal failure
pyrazinamide (PZA)	*Mycobacteria*	Unknown	Hepatotoxicity Gout Gastric irritation	Part of multidrug treatment for active TB	Severe hepatic damage or acute liver disease Patients with acute gout
SULFONES					
dapsone sulfoxone	*M. leprae, P. jiroveci, Toxoplasma*	Inhibit folic acid synthesis by competition with PABA	Rash Drug fever Agranulocytosis	Part of multidrug treatment for *M. leprae*, part of treatment for *P. jiroveci* pneumonia (with TMP), *P. jiroveci* pneumonia prophylaxis, toxoplasmosis prophylaxis with pyrimethamine	

Table 32. Antibiotics for Selected Bacteria

Pseudomonas	*S. aureus*	*Enterococcus*	*H. influenzae*	Anaerobes
ciprofloxacin	cloxacillin (MSSA)	ampicillin	amoxicillin-clavulanate	metronidazole
gentamicin, tobramycin	1º cephalosporin (MSSA)	amoxicillin	2º/3º cephalosporin	clindamycin
piperacillin/tazobactam	clindamycin	vancomycin	macrolides (clarithromycin, azithromycin)	amoxicillin-clavulanate
ceftazidime	vancomycin (including MRSA)	nitrofurantoin (lower UTI)	levofloxacin	cefoxitin
cefipime	linezolid (including MRSA)	linezolid for VRE	moxifloxacin	piperacillin/tazobactam
meropenem	daptomycin (including MRSA)	daptomycin for VRE		moxifloxacin
imipenem	tigecycline (including MRSA)	tigecycline for VRE		ertapenem, imipenem, meropenem

Rifampin
- Good adjunct for treating prosthetic device infection (bacterial biofilm)
- Always used in combination with other antibiotics to reduce emergence of resistance

Antivirals

Table 33. Antivirals

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Contraindications
ANTI-HERPESVIRUS				
acyclovir valacyclovir (Valtrex®) (prodrug of acyclovir)	HSV-1,2 VZV	Guanosine analog inhibits viral DNA polymerase	PO well-tolerated IV: nephrotoxicity, CNS	Hypersensitivity to acyclovir or valacyclovir
famciclovir (Famvir®) penciclovir	HSV-1,2 VZV	See above	H/A, nausea	Hypersensitivity to famciclovir or penciclovir
ganciclovir (Cytovene®) valganciclovir (prodrug of ganciclovir)	CMV HSV-1,2, VZV, HHV-6, EBV	See above	Heme: neutropenia, thrombocytopenia, anemia	Hypersensitivity to ganciclovir or valganciclovir Possible cross-hypersensitivity between acyclovir and valacyclovir
foscarnet	CMV Acyclovir-resistant HSV, VZV	Pyrophosphate analog inhibits viral DNA polymerase	Nephrotoxicity Anemia Electrolyte disturbance	Hypersensitivity to foscarnet
OTHER ANTIVIRALS				
(pegylated) interferon-α-2a or-2b	Chronic hepatitis B or C HPV	Inhibits viral protein synthesis	"Flu-like" syndrome Depression Bone marrow suppression	Hypersensitivity to any interferon Cannot use in combination with ribavirin if renal impairment
ribavirin (Virazole®)	Chronic hepatitis C RSV Lassa fever	Guanosine analog with multiple postulated mechanisms of action	Hemolytic anemia Rash, conjunctivitis Highly teratogenic	Pregnancy, women who may become pregnant or their partners Renal impairment
Cidofovir	Adenovirus CMV retinitis Acyclovir and foscarnet resistant HSV	Deoxycitidine analogue Inhibits DNA snythesis	Nephrotoxicity (proximal tubule dysfunction)	Renal failure; probenecid can reduce renal toxicity
lamivudine (Epivir®)	Chronic hepatitis B HIV	See *HIV and AIDS*, ID28	See *HIV and AIDS*, ID28	See *HIV and AIDS*, ID28
Tenofovir	Chronic hepatitis B HIV	See *HIV and AIDS*, ID28	See *HIV and AIDS*, ID28	See *HIV and AIDS*, ID28
Neuraminidase inhibitors: zanamivir (Relenza®) oseltamivir (Tamiflu®)	Influenza A and B: treatment and prophylaxis	Inhibits neuraminidase, an enzyme required for release of virus from infected cells and prevention of viral aggregation	GI: N/V, diarrhea Bronchospasm in zanamavir	Hypersensitivity to the neuraminidase inhibitors

Antifungals

Table 34. Antifungals

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Contraindications
POLYENES				
amphotericin B	Endemic mycoses: Histoplasmosis Blastomycosis Coccidioidomycosis Pulmonary: Aspergillosis CNS: Cryptococcus	A polyene antimicrobial: inserts into fungal cytoplasmic membrane causing altered membrane permeability and cell death	Nephrotoxicity Hypo/hyperkalemia Infusion reactions: chills, fevers, H/A Peripheral phlebitis	Renal impairment
nystatin (oral, topical)	Candidiasis: mucocutaneous, GI, oral (thrush), vaginal	See above Not absorbed from the GI tract	GI: N/V, diarrhea Highly toxic if given IV	
IMIDAZOLES				
clotrimazole (Canesten®)	Oral and vulvovaginal candidiasis Dermatomycoses	All azoles: inhibit ergosterol synthesis and thereby alter fungal cell membrane permeability	Pruritis, skin irritation	
miconazole (Monistat®, Micozole®)	Vulvovaginal candidiasis Dermatomycoses		Vaginal burning N/V	
IMIDAZOLES				
ketoconazole (Nizoral®)	Dermatomycoses Seborrheic dermatitis		Pruritis, skin irritation GI nonspecific Results in decreased androgen and testosterone synthesis	Coss-sensitivity with other azoles possible Hepatic dysfunction Pregnant women or those that may become pregnant

Table 34. Antifungals (continued)

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Contraindications
TRIAZOLES				
fluconazole (Diflucan®)	Candida infections (mucosal and invasive) Cryptococcal meningitis (step-down therapy)	All azoles: inhibit ergosterol synthesis and thereby alter fungal cell membrane permeability	Elevated liver enzymes GI nonspecific	Cross-sensitivity with other azoles unknown
itraconazole (Sporanox®)	Sporotrichosis Onychomycoses Endemic mycoses: Histoplasmosis Blastomycosis Coccidioidomycosis		Elevated liver enzymes Rash GI nonspecific HTN Hyperkalemia Peripheral edema	Cross-sensitivity with other azoles unknown Severe ventricular dysfunction
voriconazole (Vfend®)	Aspergillosis Candidiasis		Visual disturbance (30%) Hepatotoxicity Cutaneous photosensitivity Cutaneous squamous cell carcinoma with long-term use in immunosuppressed patients Prolonged QT Periostitis Neurologic toxicity	Cross-sensitivity with other azoles unknown May avoid or alter doses if co-administered with other CYP3A4 substrates, rifampin, carbamazepine, long-acting barbiturates, ritonavir, efavirenz, sirolimus, rifabutin, ergot alkaloids
posaconazole (Posanol®, Noxafil®)	Candidiasis Aspergillosis Mucormycosis		Elevated liver enzymes H/A Prolonged QT	Coadministration of cisapride, ergot alkaloids, pimozide, quinidine, or sirolimus
ALLYLAMINES				
terbinafine (Lamisil®)	Dermatomycoses Onychomycoses	Inhibits enzyme needed for ergosterol synthesis	Rash, local irritation GI nonspecific, transaminitis	Active liver disease
ECHINOCANDINS				
caspofungin micafungin anidulafungin	Refractory aspergillosis, candidemia (azole-resistant)	Inhibits 1-3 β-D-glucan synthesis (needed for fungal cell wall)	Hepatotoxicity Infusion and injection site reactions	

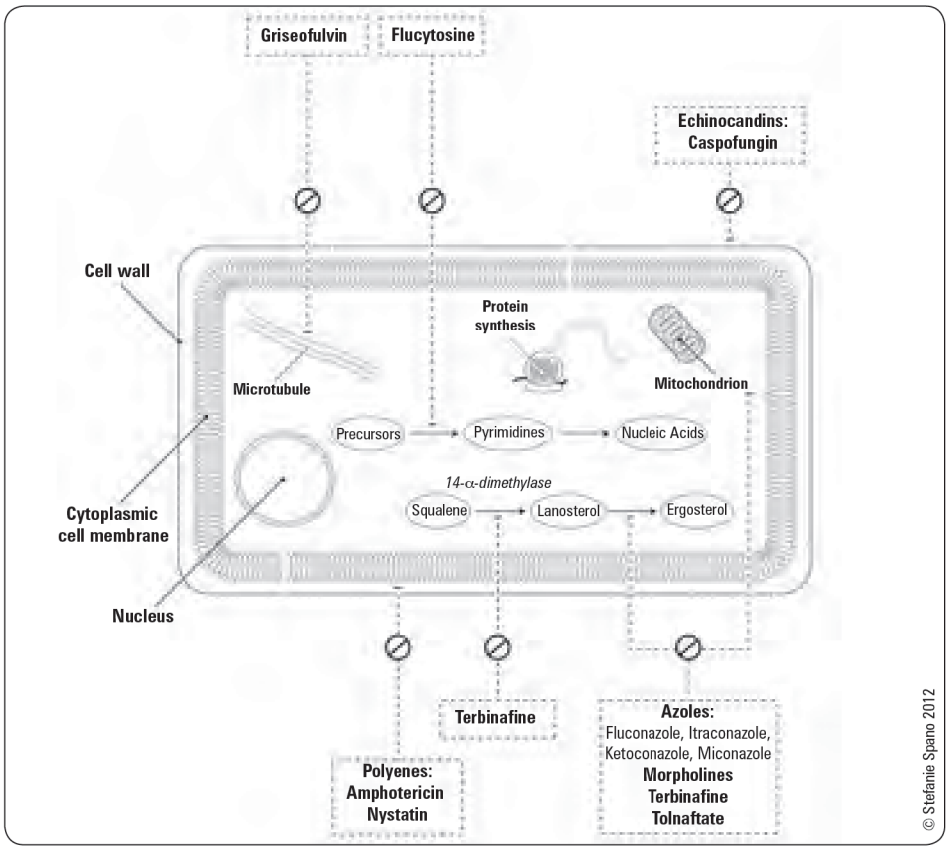


Figure 21. Mechanism of action of antifungals

Antiparasitics

Table 35. Antiparasitics

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Contraindications
ANTIMALARIALS				
chloroquine	Malaria: treatment of erythrocytic phase of all five species of *Plasmodium* that infect humans Note: High resistance of *P. falciparum* and *P. vivax* in certain geographic areas	Inhibits parasite heme polymerase	CNS: blurred vision, retinopathy, dizziness Nonspecific GI (rare with prophylaxis)	Hypersensitivity to chloroquine or other 4-aminoquinoline Retinal or visual field changes due to 4-aminoquinoline
quinine	Malaria: treatment of all five species of *Plasmodium* that infect humans, including chloroquine-resistant *P. falciparum*		Cinchonism: ears (tinnitus, vertigo), eyes (visual disturbance), GI (N/V, diarrhea), CNS (H/A, fever) Hypoglycemia	Hypersensitivity to quinine, may have cross-sensitivity with quinidine Patients with G6PD deficiency, tinnitus, optic neuritis, hypoglycemia, history of blackwater fever or thrombocytopenic purpura due to quinine use
mefloquine (Lariam®)	Malaria: prophylaxis		CNS/Psych: irritability, nightmares, psychoses, suicide, depression, seizures, H/A	History of seizures, psychosis, severe anxiety or depression
primaquine	Malaria: treatment of liver hypnozoites of *P. vivax* and *P. ovale*; prophylaxis of all *Plasmodium* spp. *Pneumocystis jiroveci* (with clindamycin)	Interferes with mitochondrial function	Hemolytic anemia in G6PD deficient GI upset (take with food)	GI nonspecific G6PD deficiency Concurrent or recent use of quinacrine Pregnancy
atovaquone/proguanil (Malarone®)	Malaria: treatment and prophylaxis of *P. falciparum*	Inhibits mitochondrial electron transport and dihydrofolate reductase	N/V, anorexia, diarrhea, abdominal pain (take with food)	Hypersensitivity to atovaquone or proguanil Severe renal impairment
artemisinin derivatives (artemether, artesunate, etc.) Note: marketed primarily in endemic countries	Malaria: treatment of all *Plasmodium* species Severe malaria (IV artesunate) Typically used in combination with a longer-acting agent from above	Binds iron, leading to formation of free radicals that damage parasite proteins	Transient neurologic deficits (nystagmus, balance disturbance) Transient neutropenia (at high doses of oral artesunate) Transient neutropenia (at high doses of oral artesunate) Delayed hemolysis	Hypersensitivity to artemisinins
OTHER ANTI-PROTOZOAL				
iodoquinol (Diodoquin®)	Amoebiasis: *E. histolytica, Dientamoeba fragilis, Balantidium coli, Blastocystis hominis*	Contact amoebicide that acts in intestinal lumen by uncertain mechanism	GI: N/V, diarrhea, abdominal pain CNS: H/A, seizures, encephalitis	Hypersensitivity to any 8-hydroxy-quinoline or iodine Patients with hepatic damage or optic neuropathy Pregnancy
metronidazole	Amoebiasis, *T. vaginalis,* giardiasis, *D. fragilis*	See *Antibiotics*, ID48		
nitazoxanide	*Cryptosporidium,* giardiasis, cyclosporiasis	Interferes with parasite anaerobic metabolism	N/V, diarrhea, abdominal pain, H/A	Hypersensitivity to nitazoxanide
ANTI-HELMINTHICS				
praziquantel	*Schistosomiasis* and other flukes Tapeworms	Increases Ca^{2+} permeability of helminth cell membrane, causing paralysis and detachment	N/V, fever, dizziness	Ocular cysticercosis
albendazole	Intestinal roundworms *Neurocysticercosis* *Echinococcus* → Hydatid disease	Inhibits glucose uptake into susceptible parasites	Elevated liver enzymes Alopecia GI nonspecific Agranulocytosis	Pregnancy Ocular cysticercosis or intraventricular cysticercosis
mebendazole (Vermox®)	Intestinal roundworms: pinworm, whipworm, hookworm, roundworm (e.g. *Ascaris*)	Inhibits microtubule formation and glucose uptake	Nonspecific GI	Pregnancy, infants
ivermectin	*Strongyloidiasis* *Onchocerciasis* Scabies	Interferes with polarization of nerve and muscles cells in susceptible parasites leading to paralysis	Nausea, bloating, diarrhea, myalgias, lightheadedness, H/A	Hypersensitivity to ivermectin Pregnancy
diethylcarbamazine	*Wuchereria bancrofti* *Loa loa*		Anorexia, N/V, H/A, drowsiness, encephalitis, retinal hemorrhage Mazzotti reaction if coinfected with onchocerciasis	Pregnancy Onchocerciasis

Quick Reference: Common Infections and Their Antibiotic Management

• see Family Medicine, FM52

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