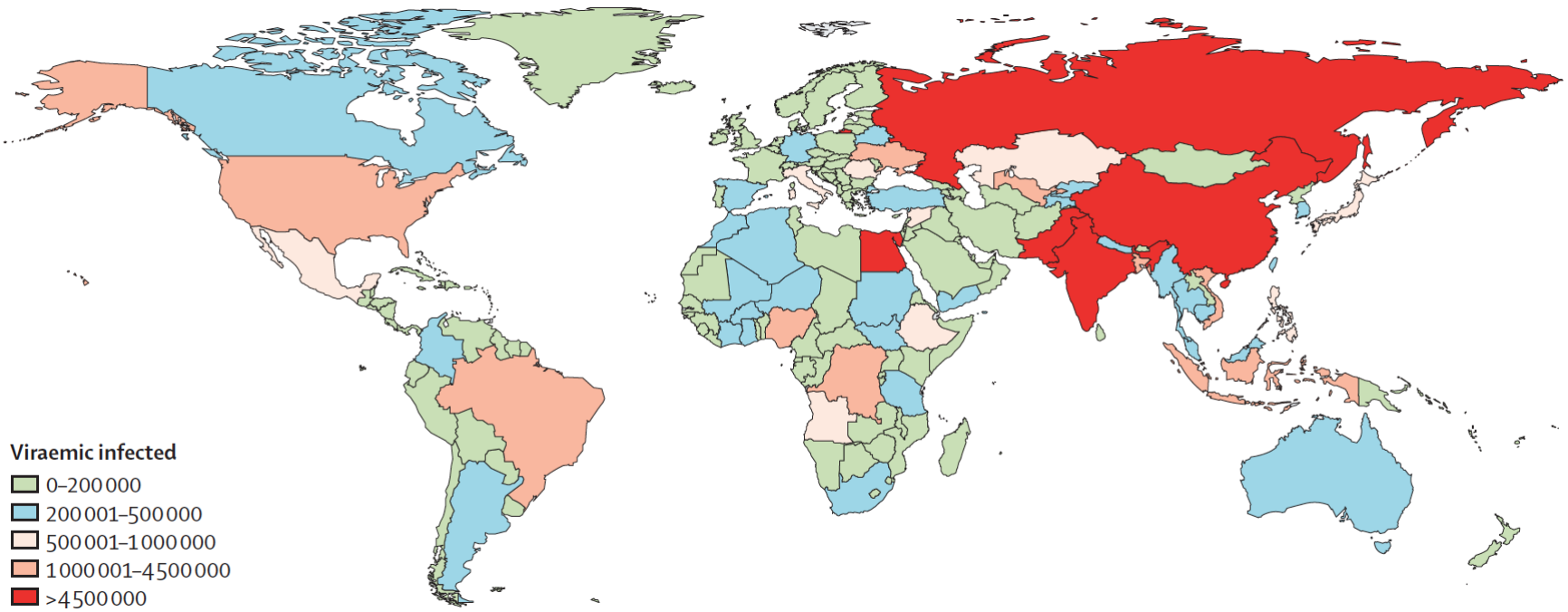
A hepatitis C virus vaccine update

Andrea L. Cox, MD,PhD

Professor of Medicine, Oncology, and Immunology

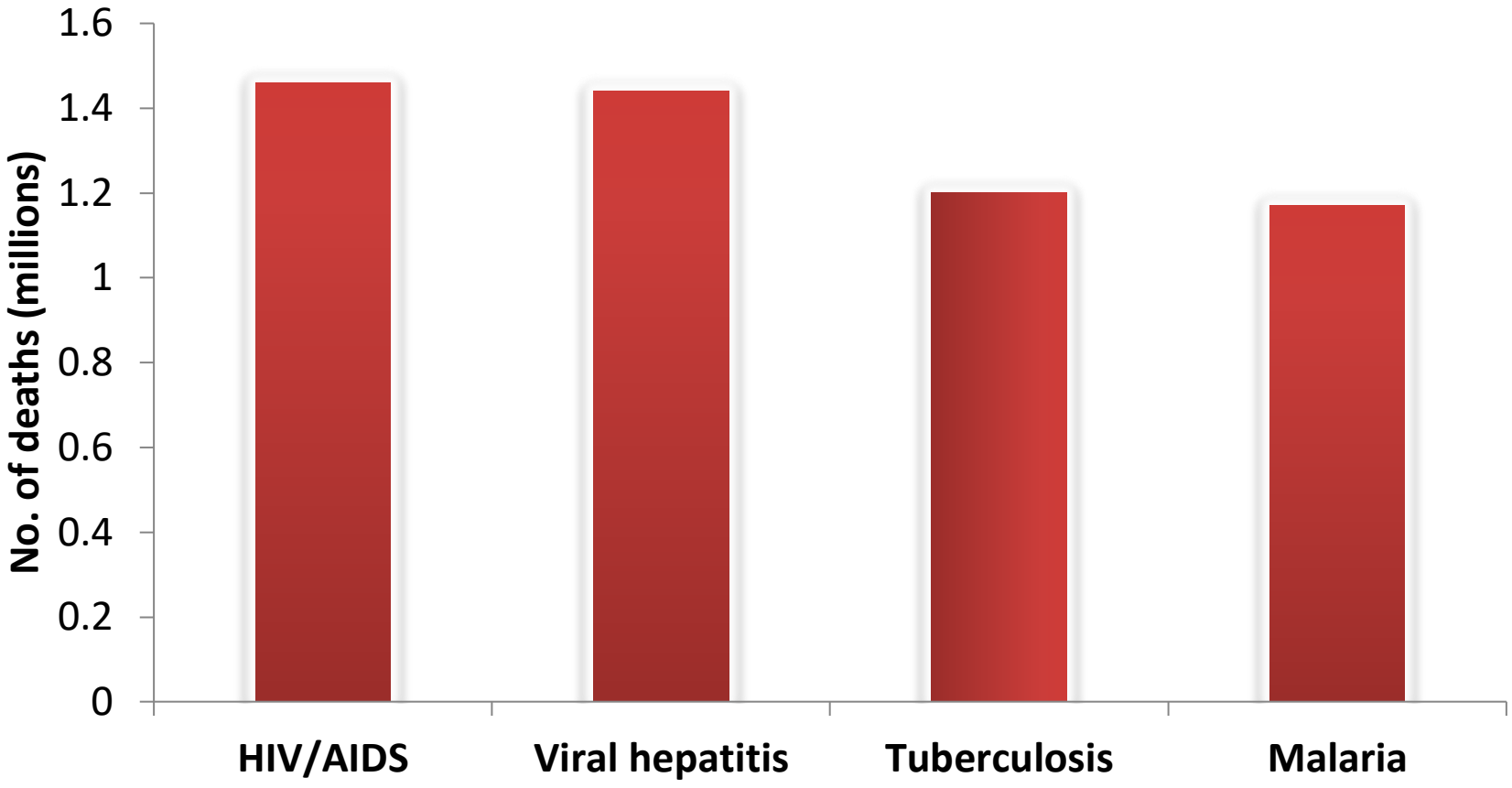
JOHNS HOPKINS
MEDICINE

Global Distribution of 71 million HCV infections



Polaris observatory HCV collaborators, Lancet Gastro Hepatol, 2017

Global number of deaths in 2010 – Hepatitis B and C ≈ other big killers



Global Burden of Disease Study 2010 Lozano et al, Lancet 2012

Challenges in HCV vaccine development

- Lack of focus on problem
- New treatments will be sufficient
- No protective immunity to HCV
- Hepatitis C virus too diverse

HCV elimination is an important goal

- There has been important progress in breaking the silence
  - WHO/UN: 2008 to 2017
    - ✓ 2015 UN General Assembly adopts Sustainable Development Goals ‘to combat’ hepatitis
    - ✓ 2016: WHO global health sector strategy for elimination
    - ✓ 2017: Global Hepatitis Report

WHO Goal for 2030: Reduce HCV infected people by 80%

Achieving control

- The reduction in HCV infected people must substantially exceed new HCV cases.

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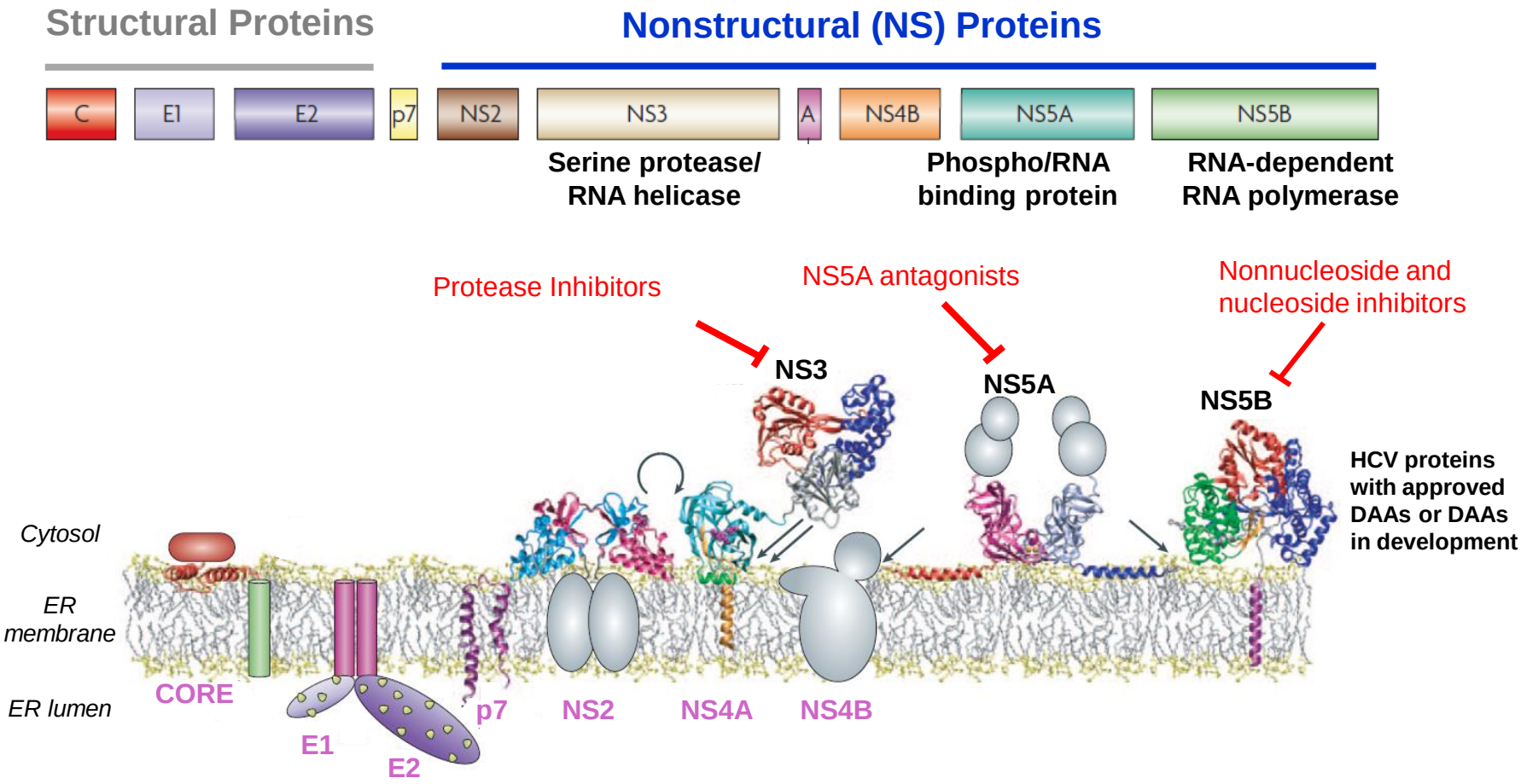
Cure (+ death) > New infection

Substantial focus on and progress with cure

Cure

New infection

Multiple HCV Proteins Can Serve as Targets for DAAs



Adapted from Moradpour et al. *Nat Rev Microbiol*. 2007;5:453-463.

DAAs- the good and the bad

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  - is well tolerated

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- Treatment
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  - is effective: >95% cured of HCV infection when given DAAs (SVR)
  - Led to widespread notion that a vaccine was no longer needed

Challenges to cure

- Treatment remains expensive

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- Treatment remains expensive
- We have already treated many of those easiest to treat- ~$60 billion USD on DAAs 2014-2017, but numbers of new patients initiating DAAs declining

Challenges to cure

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- We have already treated many of those easiest to treat
- Finding the people who need treatment remains challenging

Identification of HCV Infected people is challenging

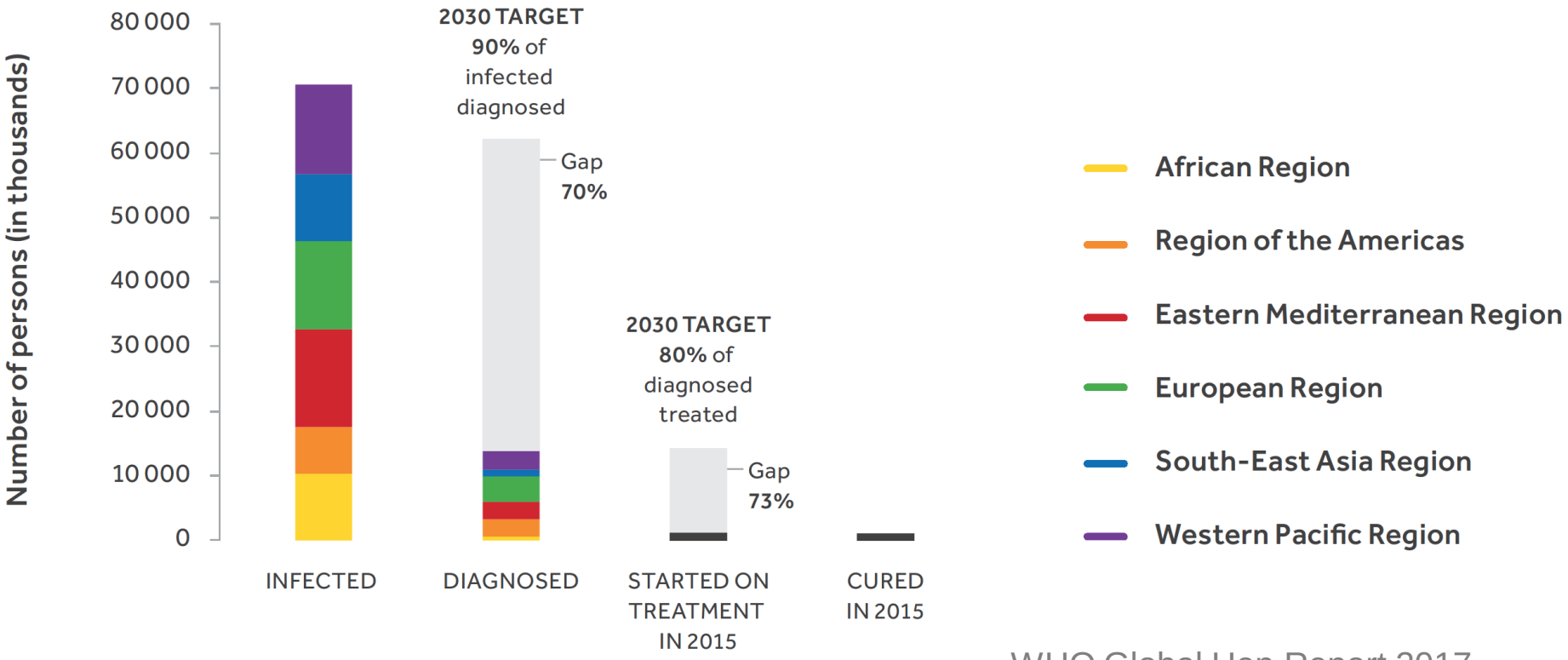
- Infection usually silent until ESLD present

Identification of HCV Infected people is challenging

- Infection usually silent until ESLD present
- Knowledge of infection status limited

Centers for Disease Control and Prevention MMWR Recomm. Rec. 47 (RR-19), 1-39 (1998), Nature Outlook Hepatitis C vol 474, 7350, S2

HCV care cascade varies worldwide



WHO Global Hep Report 2017

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- Drugs do not provide protection against reinfection- HCW, PWID, MSM

Challenges to cure

- Treatment remains expensive
- We have already treated many of those easiest to treat
- Finding the people who need treatment remains challenging
- Drugs do not provide protection against reinfection
- Treatment in the later stages doesn’t reverse all disease

Achieving control- a challenge

- Epidemiological data extracted for 210 countries for 2016

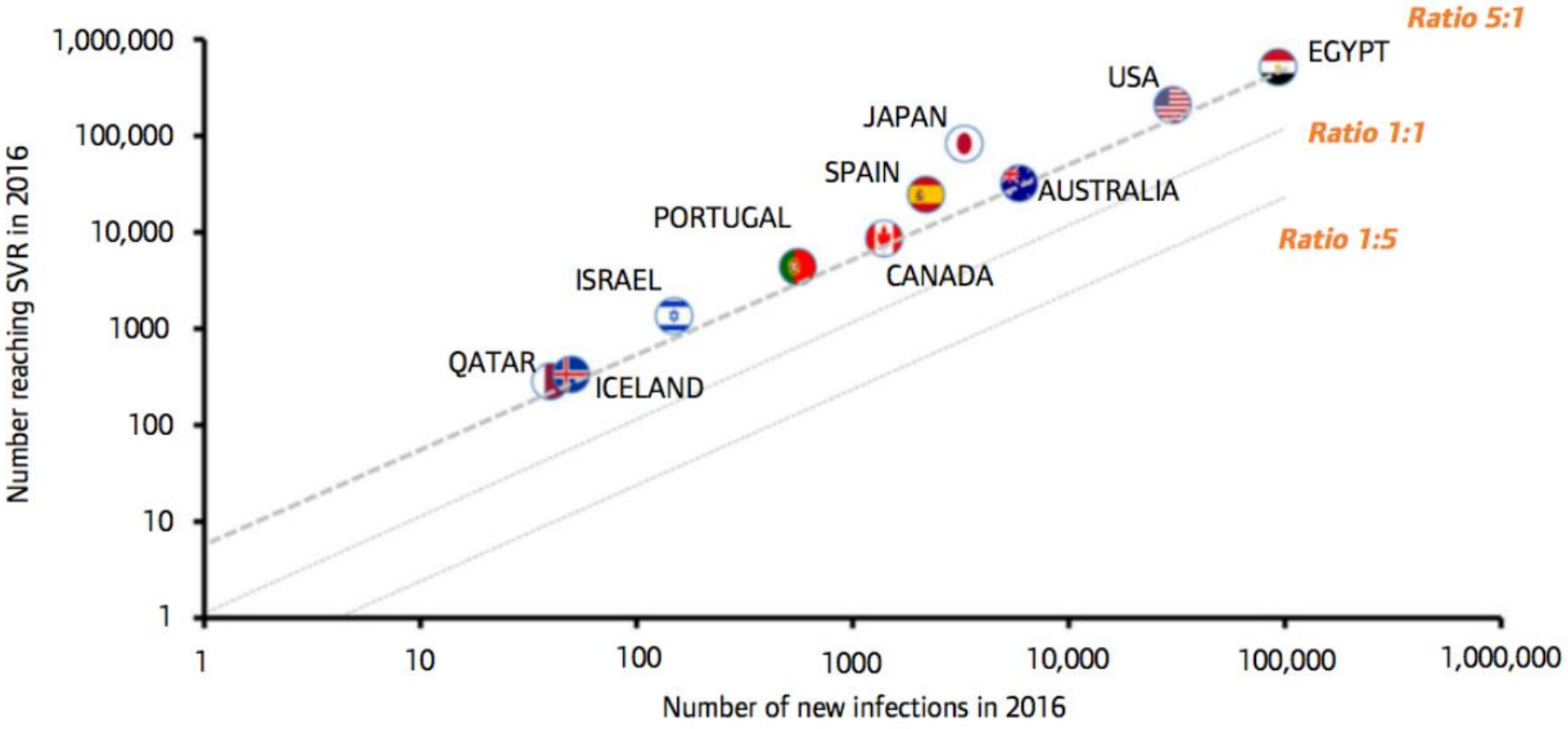
Hill J Virus Erad 2017

Achieving control- a challenge

- Epidemiological data extracted for 210 countries for 2016
- 91 countries with data on SVR, HCV-related deaths, and new infections available for analysis

Hill J Virus Erad 2017

Cure rates must substantially exceed new infection rates



Hill J Virus Erad 2017

Achieving control- a challenge

- 47 of 91 countries: more new HCV infections than SVR in 2016.

Hill J Virus Erad 2017

Globally, rates of SVR aren't significantly higher than new infection rates

- Net HCV in 91 countries dropped from 57.3 to 56.9 million people- 0.7% reduction.

Hill J Virus Erad 2017

Consider some additional focus on prevention…

Cure

Focus on decreasing new infection

WHO New Infection Goal 2016

Called for **90%** reduction in new HCV infections by 2030

2015 HCV incidence: 1.75 million and highly variable

WHO region	Estimated incidence	Uncertainty (X1000)
African	309,000	222-544
Americas	63,000	59-69
Eastern Mediterranean	409,000	363-426
European Region	565,000	460-603
South-East Asia Region	287,000	243-524
Western Pacific Region	111,000	104-124
Global	**1,751,000**	**1,572-2,210**

WHO Global Hepatitis Report 2017

Risk factors for incident HCV vary globally

Source of new HCV infection	Resource rich	Resource poor
Unsafe medical practices	eliminated	**dominant**
Transfusion	eradicated	uncontrolled
Injection drug use	**dominant**	uncontrolled
Sexual esp MSM	uncontrolled	uncontrolled
Perinatal	uncontrolled	uncontrolled

WHO Global Hepatitis Report 2017

Prevention Strategies- Vaccine

- Prevention regardless of risk factors

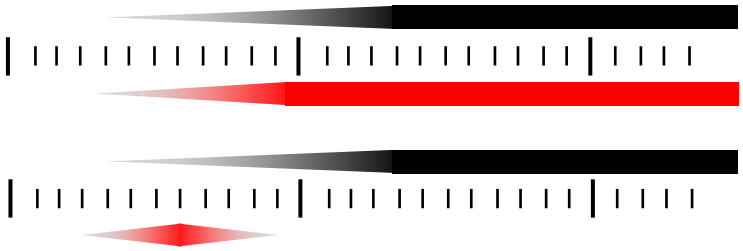
Is protective immunity possible?

BBAASH Cohort

Baltimore Before and After Acute Study of Hepatitis

18-35yo Active PWID
HCV EIA & RNA neg

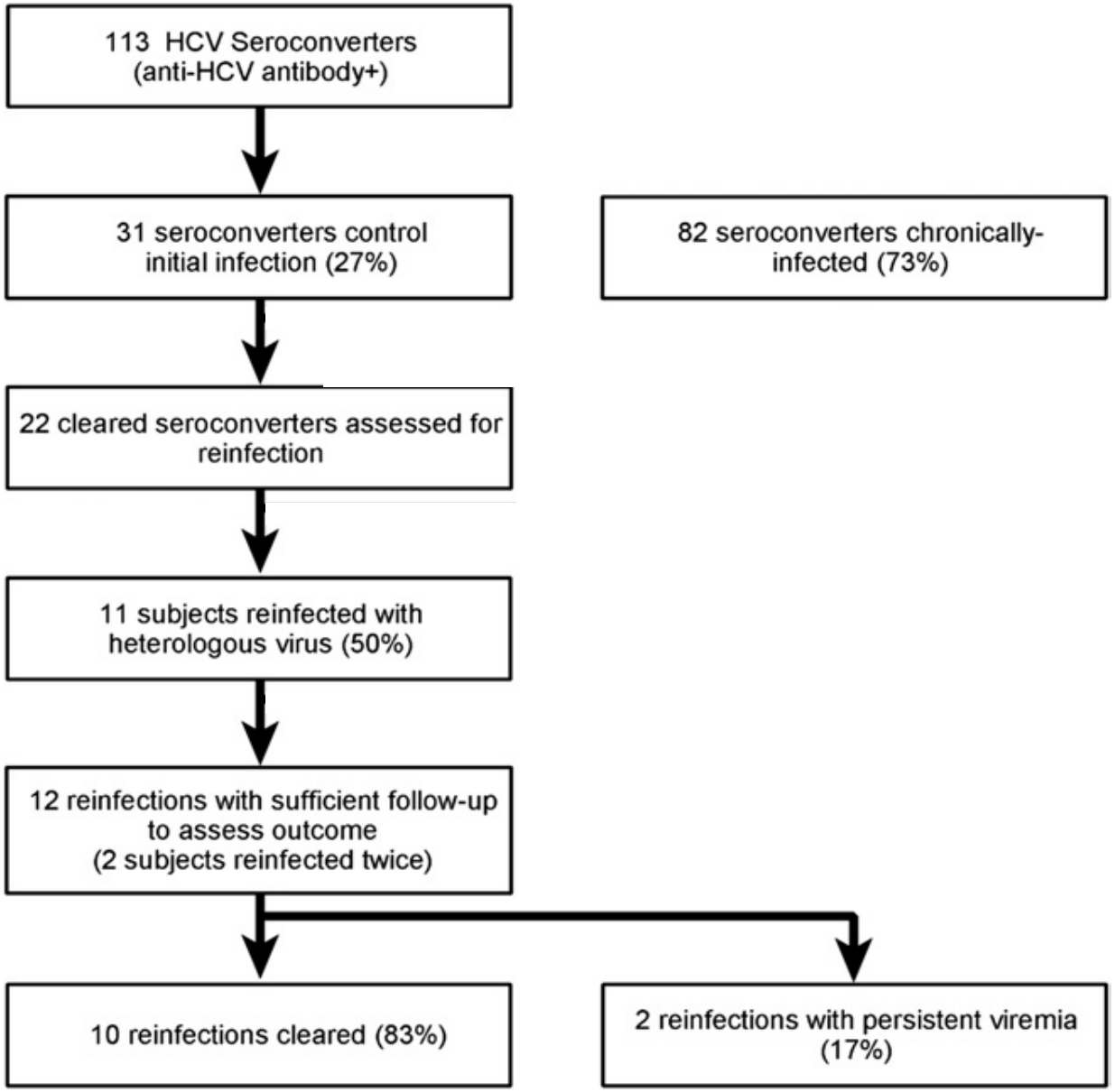
Anti-HCV Ab = black bar **HCV = red bar**



Persistent Infection

Spontaneous Clearance

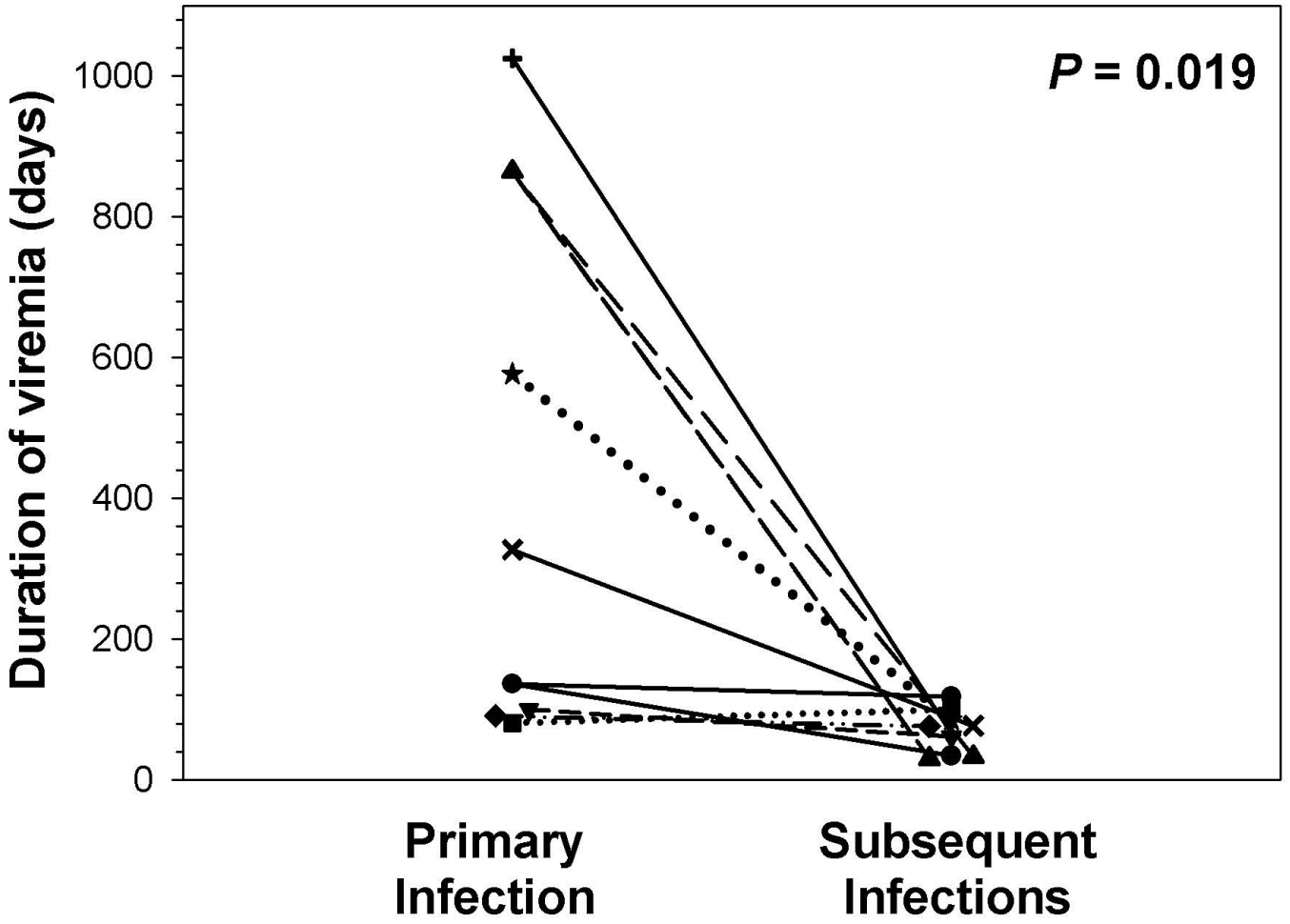
Protection from Persistent HCV



(*P =.001)*

Osburn et. al. Gastroenterolgy 2010;138:315–324

Shorter duration of viremia during reinfection



Osburn et. al. Gastroenterolgy 2010;138:315–324

Evidence of protective immunity

- Peak HCV RNA level significantly lower during reinfection than primary infection
  - Mehta et. al. Lancet 2002,
  - Grebely et. al. Hepatology 2006
  - Osburn et. al. Gastroenterolgy 2010
  - Sacks-Davis et. al. JID 2015

Broadening of T cell responses in HCV Reinfection

- Demonstrated in BBAASH
- Confirmed in Montreal Acute Hepatitis C Injection Drug User Cohort

Osburn et. al. Gastroenterolgy 2010;138:315–324
Abdel-Hakeem, M et. al. Gastroenterolgy 2014, 147;870-881

HCV- Can we make an effective vaccine?

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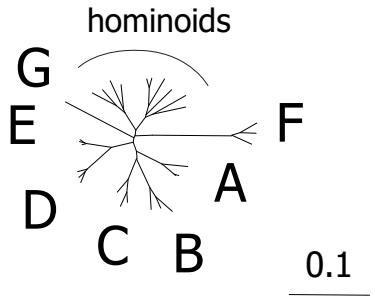
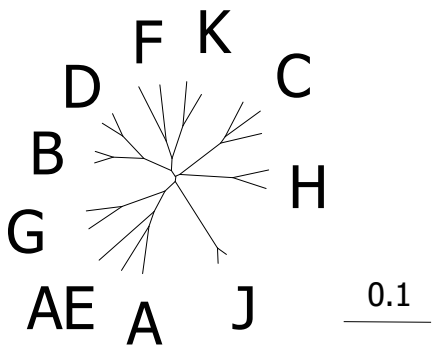
- Viral diversity is a challenge



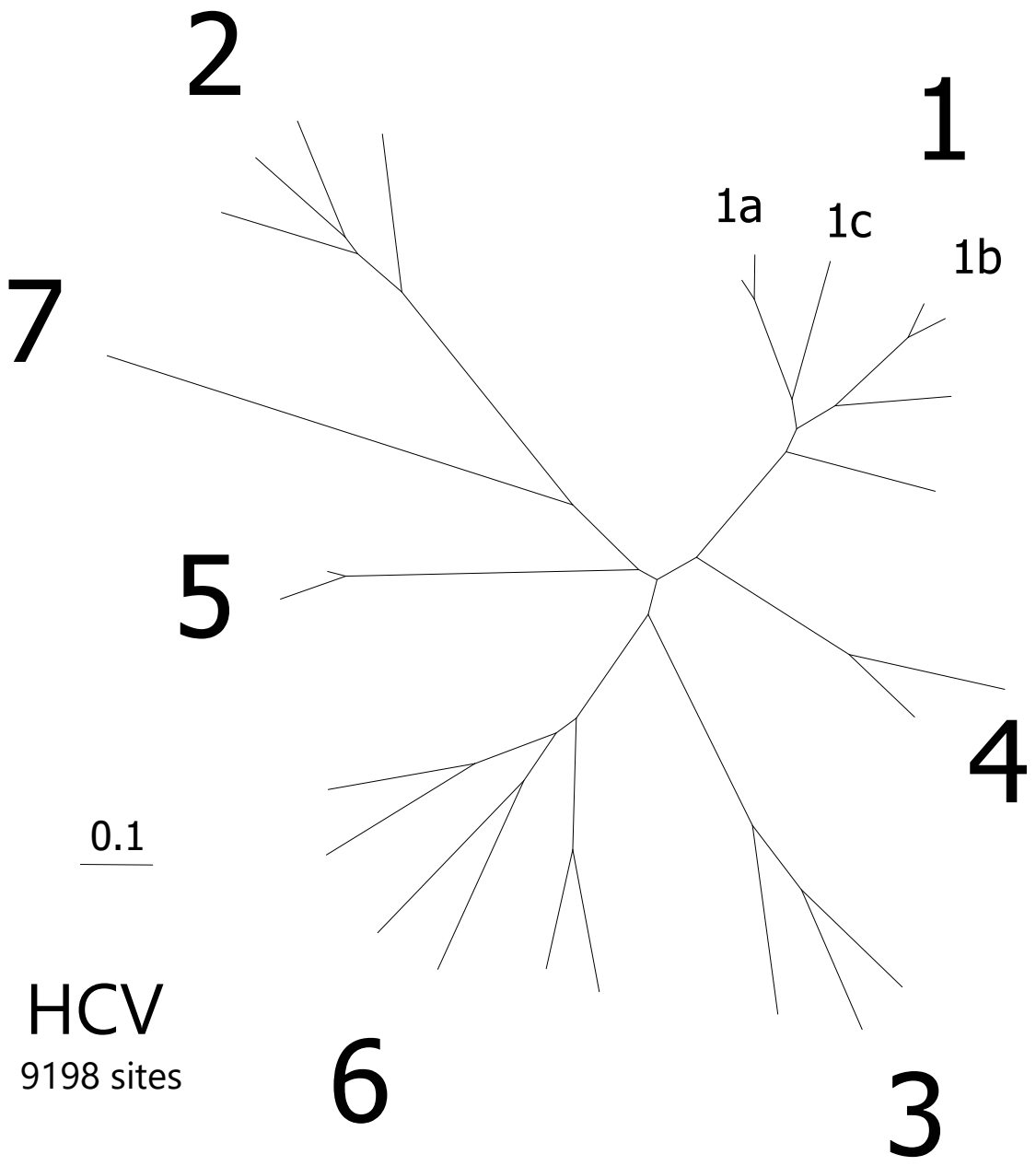
HBV

3181 sites



HIV

8316 sites

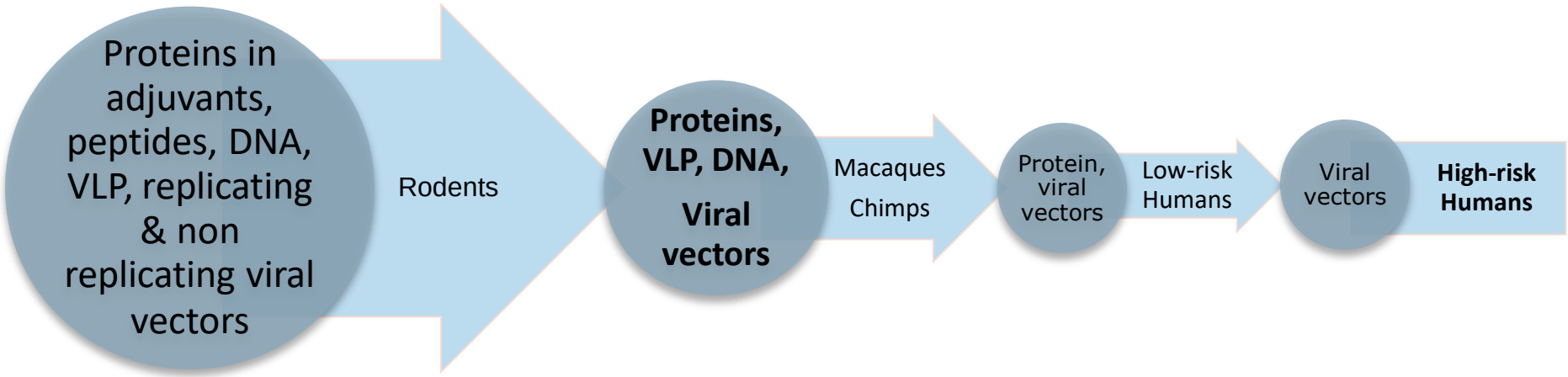


HCV

9198 sites

Ray SC and Thomas DL. *PPID* 7th ed, Chapter 154 2009

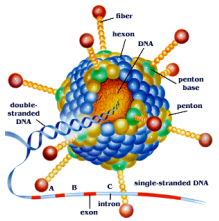
Efforts to develop a prophylactic HCV vaccine



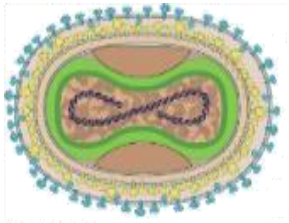
Cox AL, Vaccines for Hepatitis C, 25 Years After the Discovery of Hepatitis C, Springer, 2016

Prophylactic vaccine to generate T cell immunity based on viral vectors

- Prime: Low seroprevalence chimpanzee derived Adenovirus – ChAd3

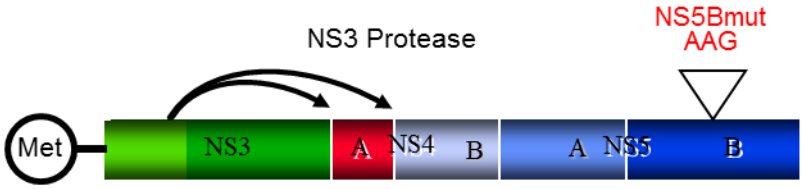


- Boost: MVA attenuated strain, non-replicating in mammalian cells



Prophylactic vaccine to generate T cell immunity based on viral vectors: the antigen

- Vectored HCV antigen: Genotype 1 NS3-NS5B (NS = 1985 aa)



HCV Vaccine Healthy Volunteer Trial Summary

- AdCh3NSmut prime with MVANSmut boost is a highly potent inducer of T cell responses.
- T cells responses across genotypes detected.
- Vaccines safe and well tolerated.

Swadling L et al., S*cience Translational Medicine;* 5 November 2014; 6:(261)

VIP: Vaccine is Prevention

- **Design:** Double blind, randomized, placebo controlled at JHU, UCSF, UNM

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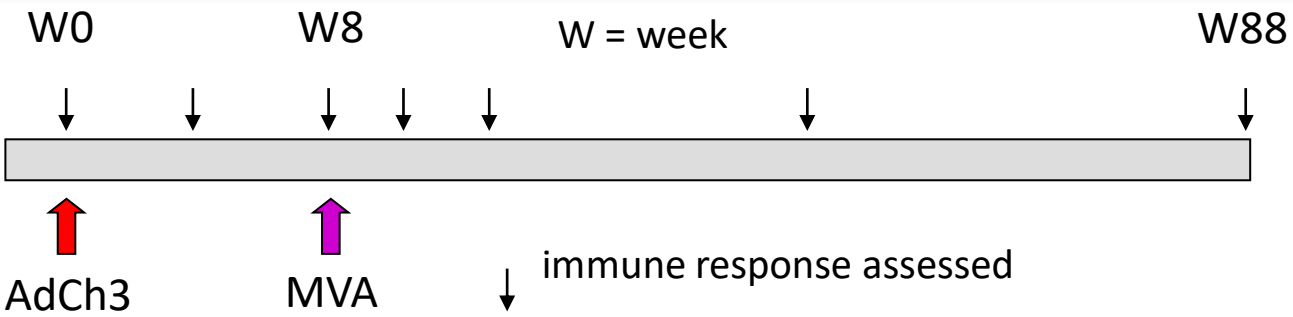
- **Population**: 18-45 yo PWID actively injecting at high risk for but not infected with HCV at screening
- **Enrollment completed in 2016:** 545
- **Goal:** assessment of safety, induction of HCV specific immune responses, and efficacy in preventing chronic HCV infection

VIP Design

- **Two injections administered at 0 and 8 weeks:**

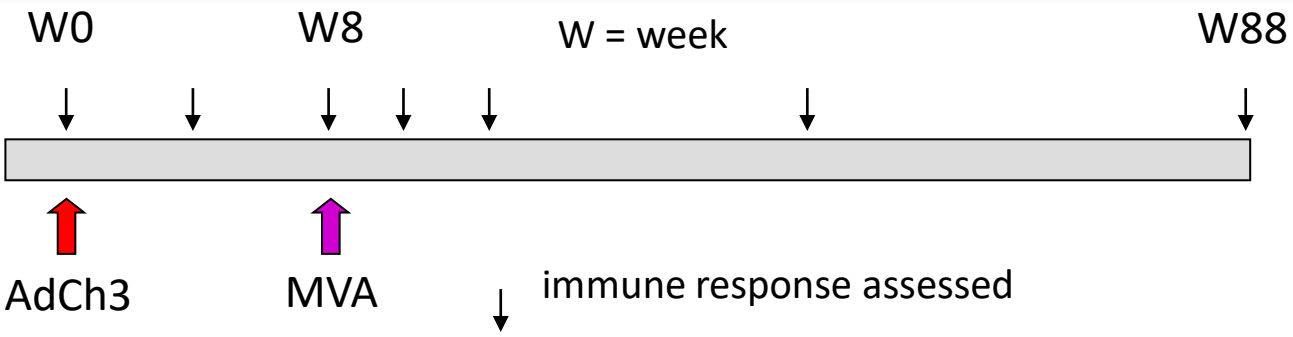
  AdCh3NS$_{mut1}$ & MVA-NS$_{mut}$

- Immune responses assessed



VIP Design

- **Two injections administered at 0 and 8 weeks:**
  AdCh3NS$_{mut1}$ & MVA-NS$_{mut}$
- Immune responses assessed
- HCV RNA tested monthly



VIP Results

- Aiming for release in Fall 2018

Conclusions

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  - Comprehensive strategy
    - Prevention, harm reduction
    - Diagnosis
    - Treatment

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- Protective immunity likely exists *in vivo*.

Conclusions

- A prophylactic HCV vaccine is needed.
- Protective immunity likely exists *in vivo*.
- A new prophylactic vaccine is in trials for the first time in at risk subjects- data due out in fall of 2018

Acknowledgements

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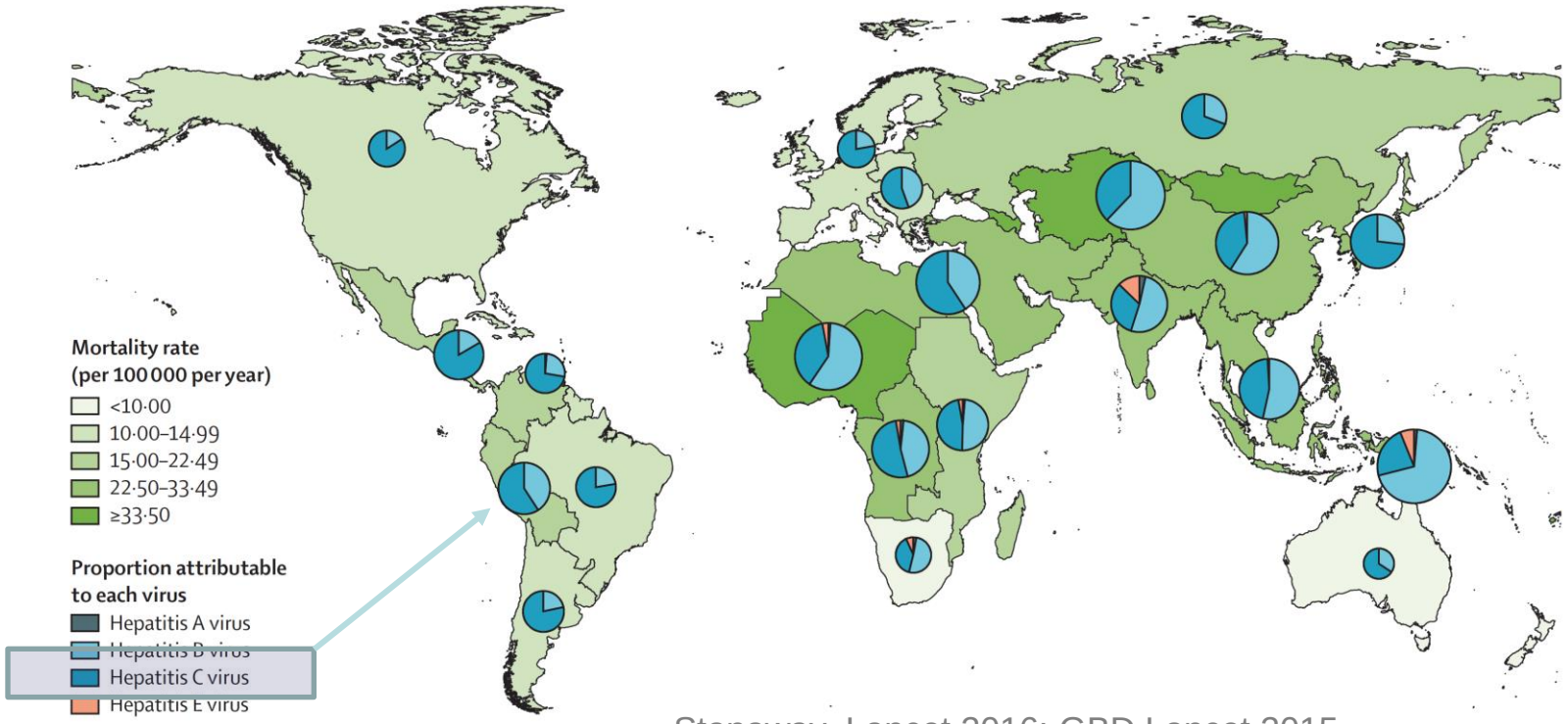
Antonella Folgori
Stefania Capone
Alfredo Nicosia
Stefano Colloca
Ventzislav Vassilev
Lan Lin

Thank you!!!

- Questions?

Global distribution of 600,000 HCV-related deaths – 2013

Regional distribution of deaths shown by size of pie charts



Stanaway, Lancet 2016; GBD Lancet 2015