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ADVANCEMENTS IN VACCINE TECHNOLOGY AND THEIR ROLE IN IMMUNIZATION STRATEGIES: A COMPREHENSIVE REVIEW

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ABSTRACT

Immunization and vaccine development have advanced significantly, revolutionizing the fight against illness. Inactivated, live-attenuated, and toxoid vaccines were the mainstays of traditional vaccine development and have proven effective in the battle against a wide range of illnesses. Rapid vaccine development, however, has been transformed by contemporary technologies such as mRNA, DNA, and viral vector vaccines, particularly in times of global health emergencies like COVID-19. Researchers are now able to find possible vaccine targets and improve vaccine design thanks to the greater acceleration of vaccine research brought about by artificial intelligence and machine learning. By prioritizing promising vaccine candidates through the analysis of genomic data, reverse vaccinology has also expedited the development process. The Universal Immunization Program (UIP) of the Indian government, which offers vital immunizations to expectant mothers, children, and newborns, is a model for international immunization campaigns. Integrating cutting-edge technologies, such as artificial intelligence, will be essential to bolstering vaccination campaigns and guaranteeing readiness for upcoming pandemics as the world deals with changing health issues.

KEYWORD:- WHO, Immunization, Vaccine, UIP.

INTRODUCTION

Public health has undergone a revolution thanks to vaccines, which are biological treatments intended to boost immunity against particular illnesses. Infectious disease control has benefited greatly from the use of conventional vaccination technologies, such as live-attenuated and inactivated vaccines. Nevertheless, more recent developments in biotechnology have produced additional vaccine methods, such as subunit, viral vector, and mRNA vaccines. These cutting-edge methods provide quicker development times, more efficacy, and safety. Governments and international health organizations establish immunization programs, which are essential for preventing diseases that can be prevented by vaccination. Coordinating international vaccination campaigns and encouraging the use of vaccines have been made possible in large part by the World Health Organization (WHO) and regional health organizations. One noteworthy example of a widespread immunization program that has considerably decreased the prevalence of vaccine-preventable diseases in the nation is India's Universal Immunization Program (UIP). Machine learning and artificial intelligence (AI) are becoming increasingly potent instruments in vaccine development as technology develops. These technologies can potentially increase clinical trial efficiency, expedite research, and optimize vaccine creation. Scientists can predict immune responses, find possible vaccine targets, and create innovative vaccine formulations by using AI to examine enormous volumes of biological data.

Different types of immunity: The body's defence mechanism against dangerous substances is known as the immunological response. Lines of defense against the majority of microorganisms and very specific, specialized reactions to specific offenders are part of the response. There are two types of this immune response: innate and adaptive. The innate reaction protects the body from a pathogen and is frequently our first line of defence against anything alien. These natural mechanisms include the skin barrier, saliva, tears, cytokines, complement proteins, lysozyme, bacterial flora, and numerous cells, including neutrophils, basophils, eosinophils, monocytes, macrophages, reticuloendothelial system, natural killer cells, epithelial cells, endothelial cells, red blood cells, and platelets. The adaptive immune response uses the ability of particular lymphocytes and their byproducts, such as cytokines and immunoglobulins, to react against the invasive bacteria.[1]

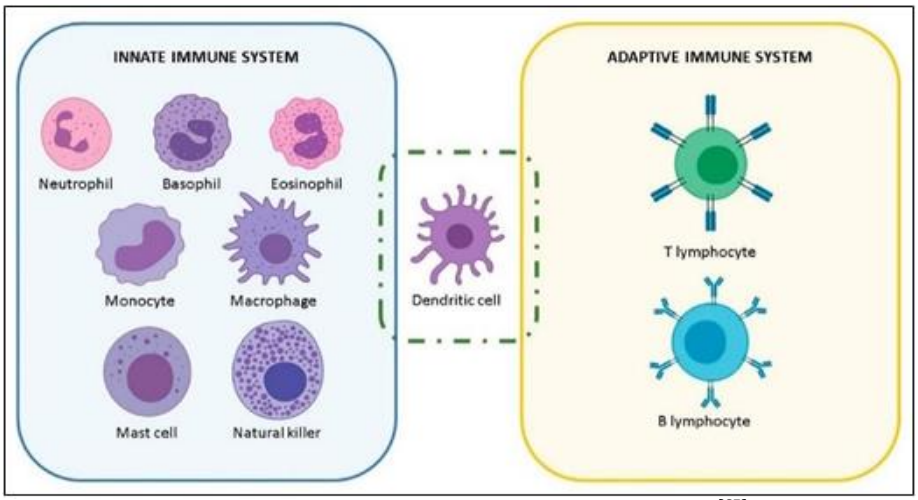

Figure No. 01: Cells involved in immune system.[65]

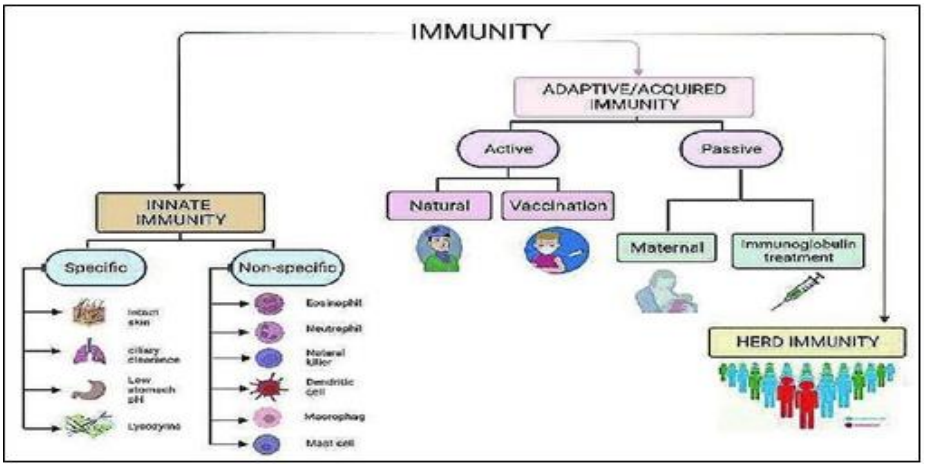

Figure No. 02: Types of immunity.[63]

Vaccine: By definition, vaccines are biological agents that trigger an immune response to a particular antigen obtained from a pathogen that causes infectious diseases. A vaccine is a medical treatment that contains either the killed or attenuated microorganism or a portion of it that causes the host to become antigenic and develop acquired immunity. Before being authorized in the US, they must pass stringent safety testing and review. Vaccines aid in providing the body with protection against illnesses. The mechanisms in which various vaccines function vary. B-cells produce protective antibodies against the antigen following vaccination. In the event that the body becomes infected again, these antibodies aid the cells in remembering this specific antigen so they can combat it.[2,3,4]

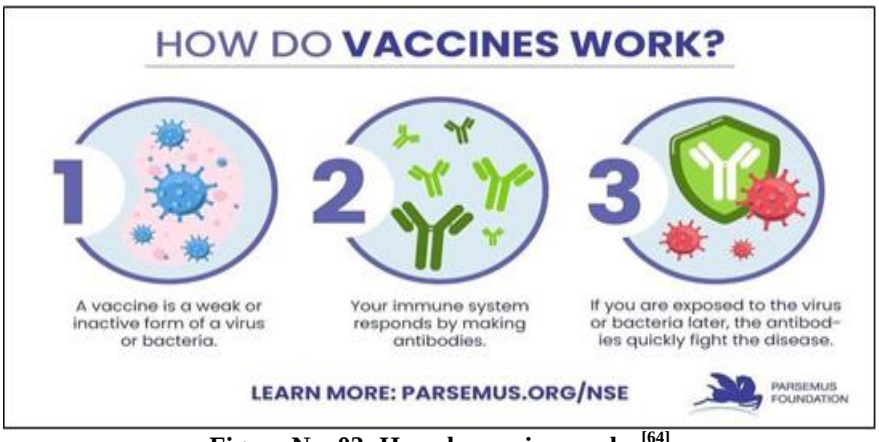

Figure No. 03: How do vaccine works.[64]

History of vaccine: The term vaccine was first described in the 18th century by Edward Jenner. It is derived from Vacca, a Latin word for cow.[6,7,8]

Table No. 01: History of vaccine.

Year	Name of vaccine
1796	Smallpox vaccine
1881	Anthrax vaccine
1885	Rabies vaccine
1914	Pertussis, or whooping cough, vaccine
1926	Diphtheria vaccine
1938	Tetanus vaccine
1948	Pertussis, diphtheria and tetanus vaccines combined as DTP vaccine
1955	Polio vaccine based on a dead poliovirus.
1963	Measles vaccine
1967	Mumps vaccine
1969	Rubella vaccine
1981	Hepatitis B vaccine
1996	Chickenpox vaccine
1998-1999	Rotavirus vaccine
2000	Hepatitis A vaccine
2001	Pneumococcal vaccine
2003	Nasal influenza vaccine, vaccine for Argentine hemorrhagic fever
2006	Vaccine for Human Papillomavirus
2011	Vaccine for non-small-cell lung carcinoma
2012	Vaccine for hepatitis E
2013	Vaccine for enterovirus 71
2015	Vaccine for malaria
2019	Vaccine for Ebola
2020	Vaccine for COVID-19

Types of vaccine: Vaccines come in a variety of forms. Each sort teaches your immune system how to combat specific types of germs and the dangerous illnesses they might cause.[9]

a. **Inactivated vaccines**
b. **Live-attenuated vaccinations**
c. **Vaccines using messenger RNA (mRNA)**
d. **Polysaccharide, conjugate, Recombinant and Subunit vaccines**
e. **Toxoid vaccinations**
f. **Vaccines against viral vectors**

a. **Inactivated vaccinations:** These vaccinations employ the disease-causing bacterium that has been killed. Booster shots were necessary for continued immunity against illnesses. For example, rabies, polio, flu, and hepatitis A.
b. **Live-Attenuated vaccinations:** Live vaccinations employ a pathogen that has been weakened or attenuated. They provide a robust and enduring immunological response. Most live vaccinations provide lifetime protection with just one or two doses. Examples include rotavirus, smallpox, chickenpox, yellow fever, measles, mumps, and rubella (MMR combination vaccine).
c. **mRNA vaccines:** These vaccines use the production of proteins to elicit an immune response. Its production periods are shortened, and since it doesn't contain a live virus, there is no chance that the recipient would become ill. For example, COVID-19.
d. **Polysaccharide, conjugate, Recombinant and Subunit vaccines:** These vaccines target important components of the germ and produce a powerful immune response by using specific parts of the germ, such as its protein, sugar, or capsid (the shell surrounding the germ). For continued disease prevention, booster shots can be required. Haemophilus influenzae type B, Hepatitis B, HPV, whooping cough, pneumococcal disease, and meningococcal disease are among the illnesses it is used to prevent.
e. **Toxoid vaccines:** These vaccines employ a toxin, which is a toxic substance produced by the pathogen. They develop immunity to the disease-causing components of the germ rather than the germ itself. This indicates that the toxin, rather than the entire germ, is the target of the immune response. Tetanus and diphtheria are prevented with toxoid vaccinations.
f. **Viral vector vaccines:** To provide protection, viral vector vaccines employ a modified form of an alternative virus. Adenovirus, which causes the common cold, influenza, measles virus, and vesicular stomatitis virus (VSV) are among the viruses that have been utilized as vectors.

Ex. COVID-19vaccination

General procedure for development of vaccine[10]

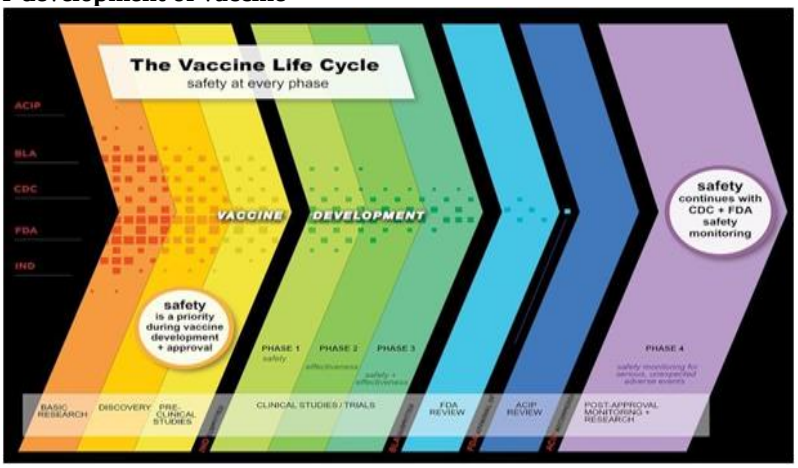

Figure No. 04: General procedure for development of vaccine.[10]

General procedure for development of vaccine

1. Research and discovery
2. Pre-clinical trials
3. Clinical trials
4. FDA review and approval
5. Manufacturing and distribution
6. Post-licensure surveillance

1. Research and Discovery (2-10 Years)

- Identify need for vaccine
- Develop vaccine concept
- Collaborate with researchers, universities, and industry

2. Pre-Clinical Trials (1-3 Years)

- Test vaccine in laboratory
- Evaluate safety and effectiveness
- Animal studies

3. Clinical Trials (5-10 Years)

- Phase I: Small human trials (safety, tolerability)
- Phase II: Larger trials (immunogenicity, efficacy)
- Phase III: Large-scale trials (confirm efficacy, safety)

4. FDA Review and Approval (1-2 Years)

- Submit clinical trial data
- Review by FDA
- Approval for licensure

5. Manufacturing and Distribution

- Scale-up production
- Quality control and assurance
- Distribution to healthcare providers

6. Post-Licensure Surveillance

- Monitor adverse events
- Evaluate vaccine effectiveness
- Post marketing studies

Vaccine as dosage form: Biological preparations known as vaccines trigger an immune response against particular diseases. Usually, they are given in different dose forms to guarantee efficient delivery and the best possible immunological response.[46]

Typical vaccine dosage forms[47]

1. Injections

a. Intramuscular: Enter the muscle directly. such as the tetanus and hepatitis B vaccines.

b. Subcutaneous: administered immediately below the epidermis. Vaccination against rubella, mumps, and measles.

c. Intradermal: Administered directly into the epidermis. BCG vaccine for tuberculosis, for example.

2. Oral

a. Liquids: Oral polio vaccine (OPV) liquid vaccine administered orally.

b. Tablets: Some rotavirus vaccines are administered in tablet form.

c. Nasal: Nasal influenza vaccines are administered as a nasal spray.

Conventional vaccine development technologies: Toxoid and inactivated or live attenuated vaccines are among the vaccines created using conventional technologies.[11]

1. Inactivated vaccines

Because inactivated vaccines use microorganisms that have been killed or rendered inactive, they provide weakened immunity that necessitates booster injections. For example, vaccinations against rabies, polio, HPV, Hepatitis A, and flu. microorganisms that have been rendered inactive by injection. Immune cells are able to identify these pathogens. As a result, antibodies are created to neutralize the pathogens and destroy the infected cells, and T-cells and B-cells are activated. The memory cells are then formed so that they can react quickly when exposed again.[12,13]

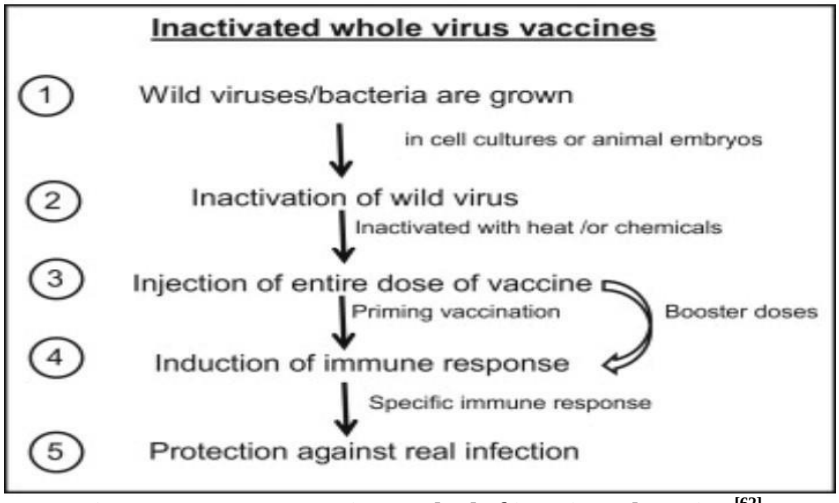

Figure No. 05: Preparation method of inactivated vaccine.[62]

2. Live attenuated vaccines

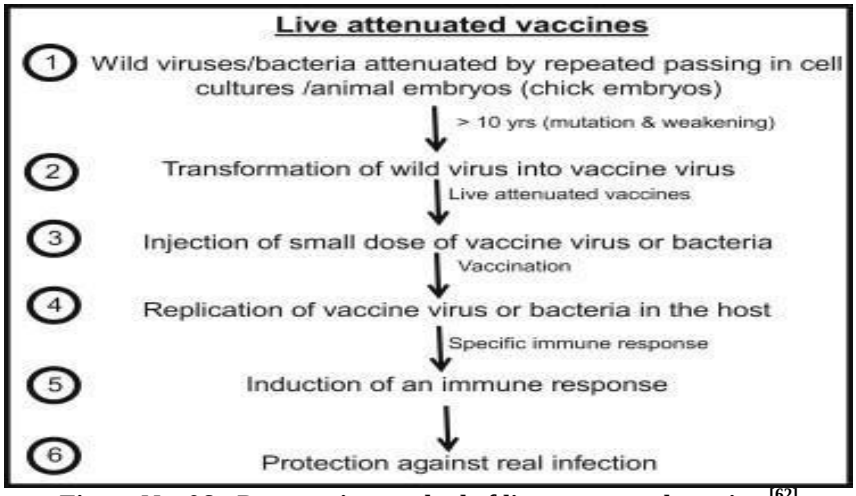

Figure No. 06: Preparation method of live attenuated vaccine.[62]

Live attenuated vaccines use weakened pathogens to provide strong, long-lasting immunity. It requires only 1-2 doses. Examples are MMR, chickenpox, and rubella vaccines. These vaccines are highly effective in preventing disease. Attenuated vaccines function by encouraging the body to create antibodies and memory immune cells in response to the specific pathogen.[14,15]

Toxoid vaccine

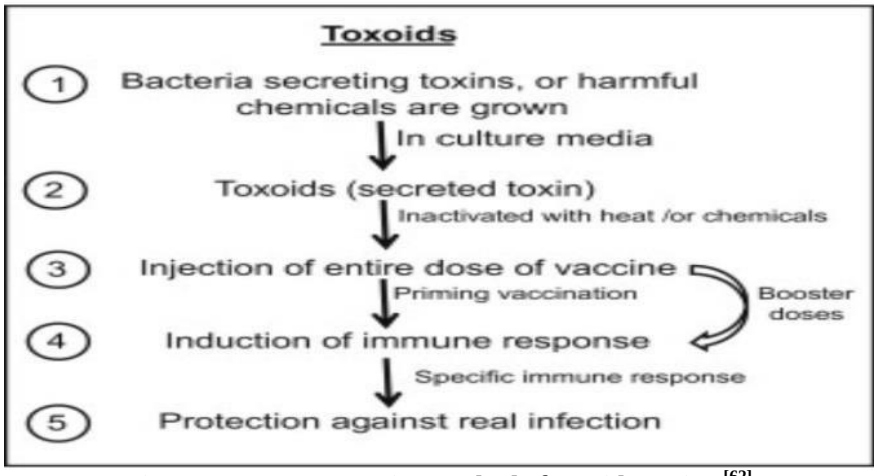

Figure No 07: Preparation method of toxoid vaccine.[62]

Modified toxins from pathogenic bacteria are used in toxoid vaccinations to elicit immunity. They defend by offering focused and efficient defence. The immune system learns to combat the natural toxin when it is vaccinated with a harmless toxoid. The bacterial poisons are opsonized by antibodies produced by the immune system. The best examples of toxoid vaccinations are those that prevent tetanus and diphtheria.[62]

Modern technologies of vaccine development: Recent years have seen tremendous progress in the creation of vaccines, with new technologies developing to efficiently target specific infections. These developments seek to increase vaccination accessibility and overcome the drawbacks of conventional vaccines, especially in low- and middle-income nations.

1. DNA Vaccine

DNA vaccines work by using modified DNA to trigger an immune response against viruses, bacteria, and parasites. launched less than ten years ago.[16] Compared to conventional immunizations, DNA vaccines function differently. To elicit an immunological response, scientists employ genetically modified DNA plasmids rather than introducing weakened viruses or bacteria. Offer defence against particular illnesses.[17]

How Do DNA Vaccines Work?[48,49]

DNA vaccines use a DNA plasmid that codes for a pathogen-derived protein to trigger an adaptive immune response.

a. DNA vaccination given intradermally, subcutaneously, or intramuscularly.
b. Myocytes are penetrated by pDNA.
c. Programmed cell death occurs in transfected cells.
d. Endocytosis is triggered by released membrane-bound fragments.
e. The production of exogenous antigens is started by endocytosis.
f. Helper T cells are presented with antigen.
g. Activating helper T cells.
h. Antibodies are produced by activated B cells.
i. T cell production is made possible by the humoral response.

Benefits[17]

1. Broad immune response and long-term immunity
2. Safety: No live pathogens or toxins
3. Flexibility: Easy to design and manufacture

Disadvantages of DNA Vaccines[17]

1. The risk of affecting genes that control cell growth.
2. Repeated doses are required.

2. mRNA Vaccine

A messenger ribonucleic acid (mRNA) vaccine is a biological substance given in a series of shots to protect from developing a disease.[18] mRNA Vaccine Mechanism.[19,50]

1. RNA vaccine is administered via injection intramuscularly.
2. mRNA is uptake by immune cells, such as dendritic cells and macrophages.
3. mRNA is translated into protein within the cell.
4. Protein is processed and presented to T-cells.
5. T-cells recognize the antigen and become activated.
6. Activated T-cells stimulate B cells to produce antibodies.
7. Activated T-cells directly kill infected cells.

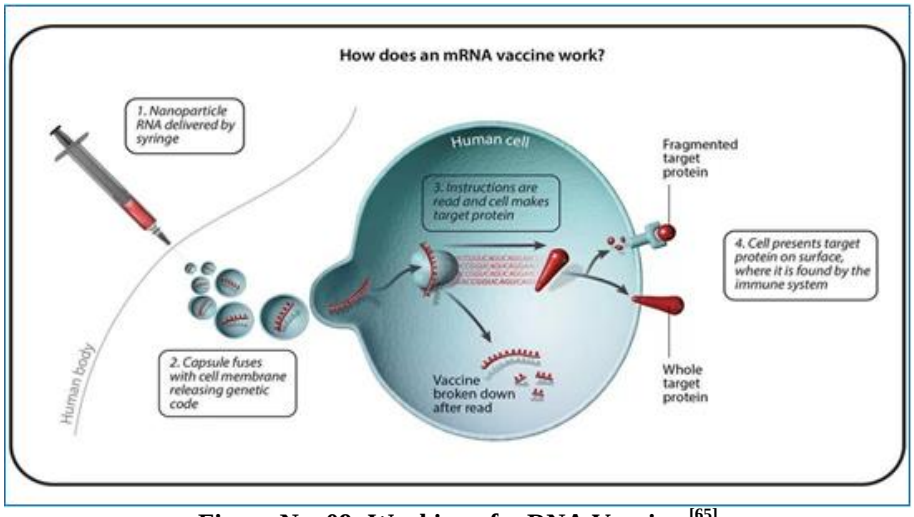

Figure No. 09: Working of mRNA Vaccine.[65]

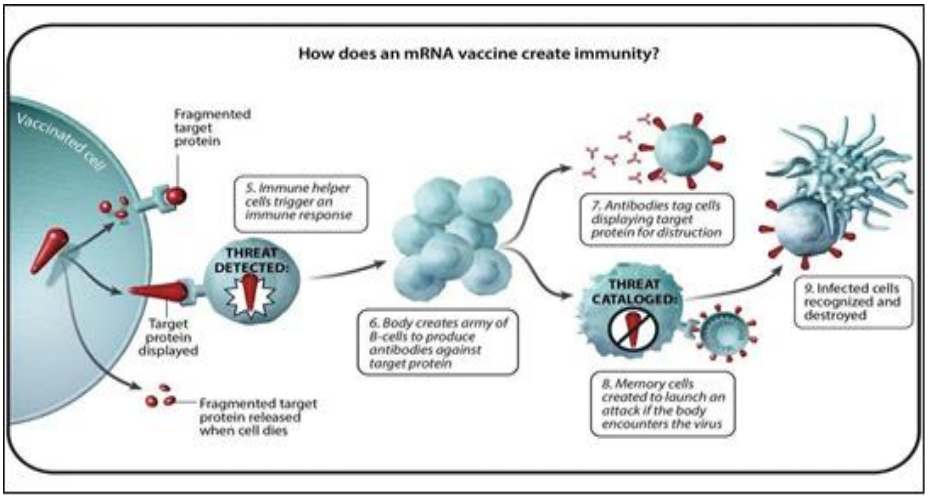

Figure No. 10: mRNA Vaccine Creating Immunity.[65]

Method of Preparation for mRNA Vaccines[20]

1. First, researchers design and clone the mRNA sequence encoding the antigenic protein into a plasmid vector.
2. Next, the plasmid is linearized using restriction enzymes and purified.
3. In vitro transcription (IVT) follows, where the linearized plasmid is mixed with RNA polymerase, nucleotide triphosphates and pH buffer, then incubated at 37°C for 2-4 hours.
4. Subsequent mRNA purification removes impurities through chromatography or filtration and precipitates mRNA using ethanol or isopropanol.
5. The mRNA then undergoes capping, either co-transcriptionally using cap analogues during IVT or post-transcriptionally with vaccinia capping enzyme and methyl donor.
6. Formulation with lipid nanoparticles (LNPs) involves mixing mRNA with lipids and forming LNPs via microfluidics or extrusion.
7. Finally, fill-to-finish processing fills LNPs into vials or syringes, followed by lyophilization or storage at -20°C.
8. This process enables the production of messenger RNA vaccines.

Advantages[51]

1. **Flexibility:** Easy to design and manufacture.
2. **Safety:** No live viruses or toxins.

Side Effects of mRNA Vaccines[52]

1. Pain, swelling or redness, Muscle pain where you got the shot.
2. Chills, Fever, Fatigue, Headache, Nausea, vomiting or diarrhoea.

Viral like particle vaccine

VLP stands for virus-like particles. Virus-like particles are molecules that mimic viruses but are not infectious. They are a very effective way of creating vaccines against diseases such as human papillomavirus (HPV), hepatitis B, malaria, and more.[21]

Antigen presentation

VLPs are picked up by antigen-presenting cells (APCs), such as dendritic cells. APCs digest the VLP antigens and deliver them to T cells.

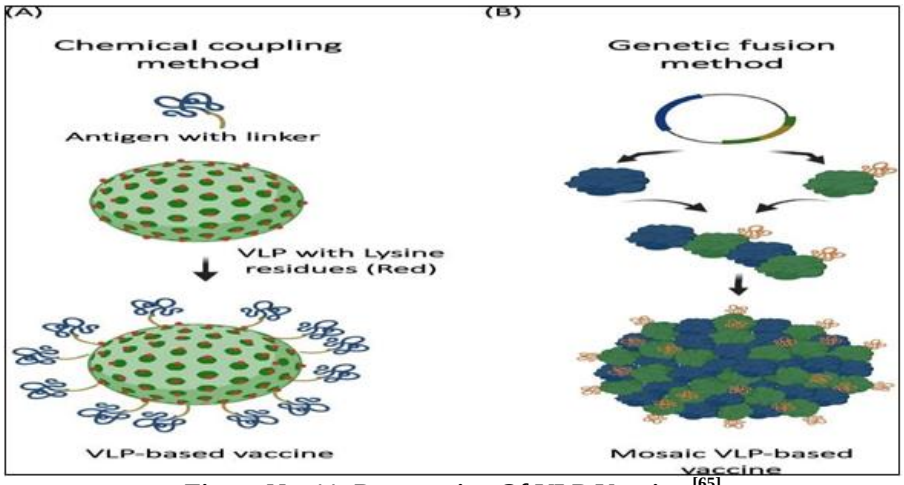

Figure No. 11: Preparation Of VLP Vaccine.[65]

Immune response activation

a. **Humoral immunity:** Antibodies specific to the VLP antigen are produced as a result of T cells activating B cells. If the person is infected again, these antibodies can neutralize the pathogen.
b. **Cellular immunity:** T cells, particularly cytotoxic T cells, are activated to directly kill virus-infected cells.
c. **Memory immune response:** To provide long-lasting immunity, the immune system produces memory cells, which can identify and react to viruses when they are re-exposed.

3. Viral vector vaccine

A weakened, altered form of another virus, known as a vector, is used in a viral vector vaccination.[22] Through the use of a modified virus, viral vector vaccines transfer genetic code into human cells, instructing them to create antigens that elicit an immune response.[23]

Method for preparing viral vector vaccines[55,56]

1. The first step in upstream processing is choosing an appropriate cell line, like Vero or HEK293, then cultivating these cells in a bioreactor. After that, transfection is used to introduce the viral vector genome into the cells. The virus takes two to seven days to produce.
2. Harvest and clarity then entail gathering the cell culture supernatant and filtering or centrifuging the cell debris out.
3. Next comes purification, which involves concentrating and separating viral vectors using methods like ultrafiltration, chromatography, and ultracentrifugation.
4. Filling vaccines into vials or syringes, combining viral vectors with excipients, and possibly freeze-drying for stability are all part of formulation and fill-finish.
5. Lastly, sterility testing, viral titre determination, infectivity tests, safety testing, and immunogenicity testing are used in quality control and testing to guarantee the safety and effectiveness of vaccines.

How does a viral vector vaccine works?

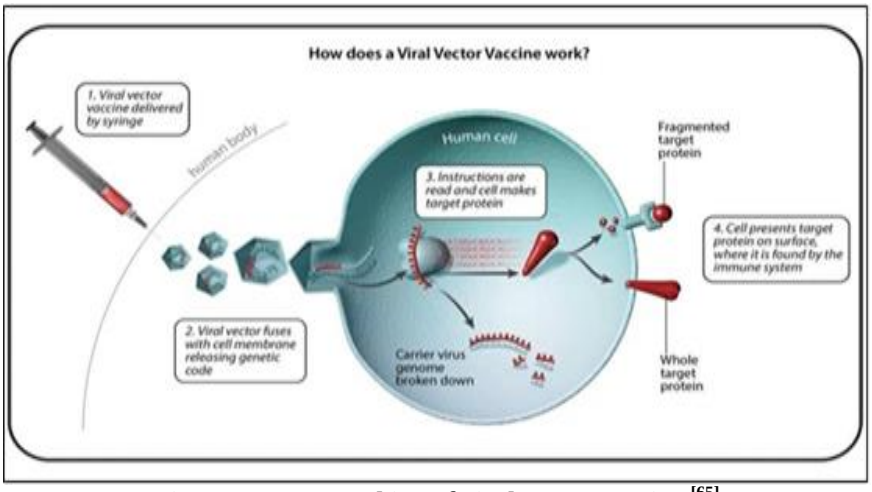

Figure No. 12: Working of viral vector vaccine.[65]

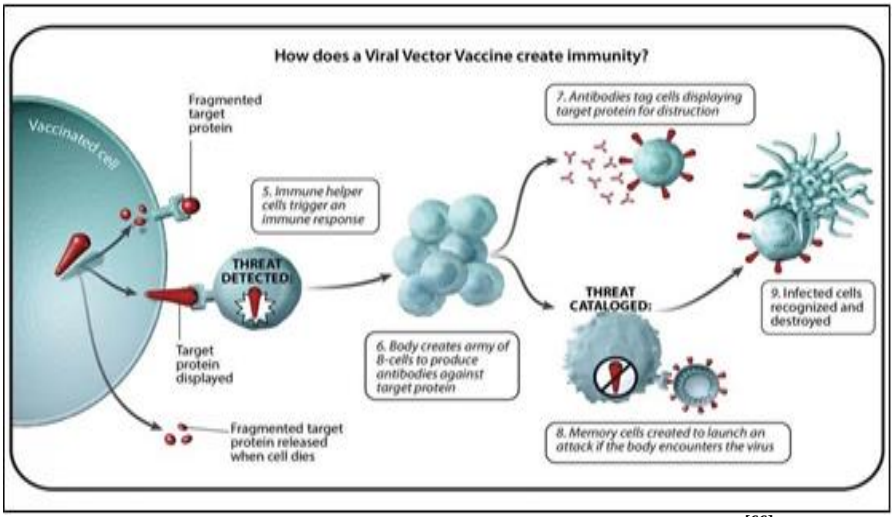

Figure No. 13: Viral vector vaccine creating immunity.[66]

Advantages of viral vector vaccines[56]
1. A robust immunological reaction
2. Excellent Versatility and Efficiency
3. T cells initiate the immunological response, and B cells produce antibodies.

Disadvantages of viral vector vaccines[56]
1. Manufacturing challenges
2. Potential for vector-induced disease

Example: rVSV-ZEBOV vaccine against Ebola.

4. Protein subunit vaccines

Using recombinant technology or protein isolation and purification, protein subunit vaccines are made up of certain isolated proteins from harmful bacteria or viruses.[25]

Mechanism
a. The antigen is taken up by antigen-presenting cells (APCs)
b. Adjuvants activate APCs;
c. APCs deliver the antigen to adaptive immune cells.
d. The immune reaction produced

Advantages
1. Eliminates risk of severe adverse effects
2. Reduced risk of infection
3. Can be designed to target specific epitopes
4. Can be combined with adjuvants to enhance immunogenicity

Limitations
1. Require adjuvants to stimulate immune response
2. Need booster doses for sustained immunity
3. Poor inducers of CD8+ T cell responses
4. Repeated administration required

Examples: Hepatitis B vaccine and COVID-19 subunit vaccines.

5. Artificial Intelligence and Machine Learning

AI is used by "intelligent" computers to think like people and carry out tasks independently. The process by which a computer system becomes intelligent is called machine learning.[26]

AI/ML Applications in Vaccine Development[27,28,29]
1. Antigen Design and Prediction: AI/ML finds possible antigens and improves their structure for increased immunogenicity.
2. Epitope Discovery: By predicting immunogenic epitopes, AI/ML facilitates the development of tailored vaccines.
3. Optimization of Vaccine Composition: AI/ML optimizes the composition of vaccines, including the choice of adjuvants.
4. Predictive modelling: AI/ML models the behaviour of vaccines to forecast their safety and effectiveness.
5. Protein Structure Prediction: AI/ML helps with antigen design by predicting protein structures.
6. Data Integration and Analysis: AI and ML combine and examine massive datasets to find trends and connections.
7. Personalized Vaccines: AI and ML allow for the creation of customized vaccines according to each person's unique genetic profile.
8. Vaccine Formulation and Stability: AI/ML improves vaccine formulation and stability.
9. Regulatory Compliance: By anticipating and reducing possible risks, AI/ML support regulatory compliance.
10. Real-time Monitoring and Surveillance: AI/ML make it possible to track the effectiveness and safety of vaccines in real-time.

Benefits of AI/ML In Vaccine Development[27,28,29]
1. Accelerated development timeline
2. Improved vaccine efficacy and safety and Reduced costs.
3. Enhanced personalized medicine and Increased accuracy.

Real-World Examples[27,28,29]
1. BioNTech's COVID-19 vaccine development using AI/ML
2. Google's DeepMind predicting protein structures for vaccine design
3. IBM's Watson Health accelerating vaccine development

6. Reverse vaccinology

This contemporary method of vaccine development finds possible vaccine candidates by using bioinformatics tools and computational techniques. Instead than depending on empirical approaches, this strategy starts with the pathogen's genome sequence, reversing the conventional vaccine development process. By facilitating the quick and precise identification of possible vaccine candidates, reverse vaccinology has completely changed the vaccine development process. Fighting infectious diseases will be greatly aided by its ongoing development.[58,59]

Key Steps[58,59]
1. Genome sequencing: Get the target pathogen's entire genome sequence.
2. Bioinformatics analysis: Examine the genomic sequence and find putative antigens using computer methods. Antigen prediction: Use ML models and algorithms to forecast putative antigens.
3. Finding immunogenic epitopes within the anticipated antigens is known as epitope mapping.
4. Vaccine design: Create vaccine candidates using the epitopes and antigens that have been discovered.
5. Experimental validation: Use experimental research to confirm the vaccination candidates.

Advantages
1. Quick identification of possible candidates for vaccines

2. Less time and money spent than with conventional techniques
3. Increased precision, specificity, and capacity to recognize new antigens and epitopes

4. Tools and Techniques

1. Tools for genome assembly and annotation (such as GenBank and RefSeq)
2. Bioinformatics databases, such as Pfam and UniProt
3. Algorithms for antigen prediction (such as VaxiJen and AntigenProfiler)
4. Epitope mapping technologies, such as NetMHC and EPIMHC
5. Simulations of molecular dynamics (such as GROMACS and AMBER)

Achievements

1. Meningococcal B vaccine development (MenB)
2. Development of COVID-19 vaccines (e.g., Moderna, Pfizer-BioNTech)
3. Studies on influenza vaccinations, HIV, and TB

Challenges

1. The availability and quality of data
2. Validation and correctness of algorithms
3. Combining information from several sources
4. Converting in silico forecasts into in vivo effectiveness
5. Regulatory structures and public approval

7. Nanoparticle based vaccine

Vaccinations that use nanoparticles to introduce antigens or genetic information into the body and stimulate an immune response are known as nanoparticle-based vaccinations. Metals, polymers, lipids, and proteins are among the components that can be used to create these nanoparticles.[30]

Development Process of Nanoparticle-Based Vaccines[31,32,33]

a. Nanoparticle selection: Choosing or creating nanoparticles is the first stage. Lipid nanoparticles, liposomes, virus-like particles (VLPs), and synthetic polymers are a few examples of these. Certain benefits, like stability, biocompatibility, and regulated antigen release, are provided by each variety.

b. Incorporation of antigen: The pathogen's protein or peptide, known as the antigen, is integrated into or secured to the nanoparticle. Because it affects the immune response, the antigen loading technique is essential. While some nanoparticles encapsulate the antigen inside, others permit surface binding.

c. Adjuvant integration: Often, adjuvants are included to enhance the immune response. Nanoparticles can serve as carriers for both the antigen and the adjuvant, improving the vaccine's efficacy by directing the immune system to respond more vigorously.

d. Immune response optimization: Nanoparticles enhance the delivery of antigens to antigen-presenting cells (APCs) like dendritic cells, which are crucial for initiating an immune response. These particles improve the transport of antigens to lymph nodes and enhance antigen presentation, thereby stimulating both humoral (antibody) and cellular immune responses.

e. Formulation and Stability: The formulation process aims to ensure that the nanoparticles are stable during storage and maintain their structural integrity to preserve the antigen. This often involves controlling size, charge, and surface properties of the nanoparticles.

f. Preclinical testing: After development, the nanoparticle vaccine undergoes preclinical testing in animal models to assess its safety, immunogenicity, and ability to provoke a strong immune response. g. Clinical Trials: If preclinical results are promising, the vaccine progresses to clinical trials, where its safety and efficacy are tested in humans in three phases before approval. h. Regulatory Approval: Finally, the vaccine is reviewed by regulatory agencies for approval and licensing based on its performance in clinical trials.

Companies and Their Nanoparticle-Based Vaccines

1. Moderna: mRNA-1273 COVID-19 vaccine
2. Pfizer: BNT162b2 COVID-19 vaccine
3. Novavax: NVX-CoV2373 COVID-19 vaccine

Examples of Nanoparticle-Based Vaccines Include

1. **mRNA vaccines:** These vaccines use lipid nanoparticles to deliver mRNA into cells, which then produces the antigen. Two examples of mRNA vaccines are the Pfizer and Moderna COVID-19 vaccines.[34]
2. **DNA vaccines:** These vaccines use nanoparticles to deliver DNA into cells, which then produces the antigen. One example of a DNA vaccine is the ZyCoV-D COVID- 19 vaccine.[35]
3. **Protein subunit vaccines:** These vaccines use nanoparticles to deliver protein antigens into the body. One example of a protein subunit vaccine is the Novavax COVID-19 vaccine.[36]

Table No. 02: Comparison Between Traditional and Modern Technologies.

Characteristics	Traditional Vaccines	Modern Vaccines
Development Time	Years to decades	Months to year
Production cost	High	Lower
Efficacy	Variable	High

Scalability	Limited	Scalable
Contamination risk	Higher	Lower
Infection risk	Yes	No
Booster shoots	Required	Potential single dose
Side effects	High risk	Low risk
Immunogenicity	Variable	Enhanced
Flexibility	Limited	Adaptable
Storage condition	Refrigeration	Ultra cold storage
Examples	Live-attenuated, toxoid vaccine, inactivated vaccines, subunit vaccines	mRNA vaccines, DNA vaccines

Comparison between Traditional and Modern technologies[200,23,24,26]

Immunization program

Immunization is the process whereby a person is made immune or resistant to an infectious disease, typically by the administration of a vaccine. Immunization Programme in India was introduced in 1978 as 'Expanded Programme of Immunization' (EPI) by the Ministry of Health and Family Welfare, Government of India. In 1985, the programme was modified as 'Universal Immunization Programme' (UIP) to be implemented in phased manner to cover all districts in the country by 1989-90 with the one of largest health programme in the world. Ministry of Health and Family Welfare, Government of India provides several vaccines to infants, children and pregnant women through the Universal Immunisation Programme.[37]

Objectives[38]

1. Prevent and reduce infectious disease outbreaks
2. Protect vulnerable populations (e.g., children, elderly)
3. Reduce disease transmission and spread
4. Promote herd immunity
5. Eliminate or eradicate diseases

8. Full immunization

If a kid receives every vaccination listed in the national immunization schedule within their first year of life, they are said to be fully vaccinated. Vaccines against 12 diseases, such as diphtheria, pertussis, tetanus, polio, measles, rubella, tuberculosis, hepatitis B, meningitis, and pneumonia, are given away for free by the Indian government (UIP). Other vaccinations guard against pneumococcal pneumonia, Japanese encephalitis, and rotavirus diarrhea. Through Mission Indradhanush, the initiative seeks to achieve a 90% complete immunization coverage rate.[39]

9. Awareness and Education on health creation about vaccination

By addressing parental concerns and outlining the advantages of vaccines, healthcare professionals—especially hospital and healthcare workers—play a critical role in promoting childhood vaccinations. Future initiatives should use information, education, and communication (IEC) to raise awareness and educate the public.[39]

10. Reasons for not getting vaccinated

With over 26.7 million babies and 30 million pregnant women vaccinated, the immunization program is among the biggest in the world. An estimated 38% of children did not obtain all of the recommended vaccinations during their first year of life in 2016, despite consistent progress. Large mobile and isolated groups that are hard to reach, low demand from ignorant and misled populations that fear side effects, and those influenced by anti-vaccination messaging are some of the causes limiting vaccine coverage. The main causes of non-vaccination are listed below, according to a recent study by Gurnani and colleagues that was based on their examination of the Intensified Mission Indradhanush strategy in India. They discovered that 62% of Indian children aged 12 to 23 months had received all recommended vaccinations during the 2015–16 study. It was projected that 69% of children have full immunization coverage in 2018 following Intensified Mission Indradhanush.[39]

Table No. 03: Major Reasons for Non-Vaccination.[39]

Reasons for non-vaccination	Percentage (%)
Lack of awareness	45
Apprehension about adverse events	24
Vaccine resistance (reluctance to receive the vaccine for reasons other than fear of adverse events)	11
Child travelling	8
Programme related gaps	4
Others	9

Types of immunization program[40,41]

a. Supplementary immunization

All targeted individuals receive vaccinations through supplemental immunization, regardless of their prior immunization history. In order to control disease, the goal is to quickly increase population-level immunity

and decrease the number of vulnerable.

b. Routine immunization

This method is used to increase vaccination awareness and give routine vaccinations to groups that are under vaccinated. National Vaccination Weeks, Child Health Weeks, and Child Health Days are a few examples. Here, the doses given are documented on vaccination cards and registers, and the individuals are checked for eligibility based on their age and history of vaccinations.

c. Catch UP Immunization

The process of vaccinating a person who, for whatever reason, has not received doses of vaccines for which they are eligible according to the national immunization schedule is known as "catch up immunization."

History of immunization program

As part of the National Tuberculosis Programme, the BCG vaccine was the first to be made available in India in 1962. Numerous milestones have been reached and numerous new vaccines have been introduced over time. The following are some significant turning points in India's vaccination program:[60,61]

Table No. 04: History of immunization program.[60,61]

Year	Event
1978	Expanded Program of Immunization (EPI) launched, including BCG, DPT, OPV, and typhoid (urban areas)
1983	TT vaccine introduced for pregnant women
1990	Vitamin-A supplementation initiated
1995	Polio National Immunization Days started
1997	Vaccine Vial Monitor (VVM) introduced in UIP
2002	Hepatitis B vaccine introduced as a pilot in 33 districts and cities of 10 states.
2005	National Rural Health Mission launched
2005	Auto-Disable (AD) Syringes introduced in UIP
2006	Japanese Encephalitis (JE) vaccine introduced in endemic districts
2007-2008	Hepatitis B expanded to all districts in 10 states, schedule revised to 4 doses
2010	Measles second dose introduced in high-risk states
2011	Hepatitis B universalized, Pentavalent vaccine introduced in 2 states, Open Vial Policy implemented
2013	Pentavalent vaccine expanded to 9 states, second dose of JE vaccine introduced
2014	India and South East Asia Region certified polio-free
2015	India validated for Maternal and Neonatal Tetanus elimination, Pentavalent vaccine expanded to all states, Inactivated Poliovirus Vaccine (IPV) introduced, Rotavirus vaccine introduced in 4 states
2016	Switch from trivalent oral poliovirus vaccine (tOPV) to bivalent OPV (bOPV), Phased introduction of fractional IPV, Phased launch of Rotavirus vaccine
2017	Measles-Rubella (MR) vaccine introduced; Pneumococcal Conjugate Vaccine (PCV) introduced (phased launch)

India's Immunization program, per the government of india

National Immunization Program (NIP)[42]

Launched in 1985, NIP aims to prevent and control vaccine-preventable diseases.

Table No. 05: National immunization schedule for pregnant women.[42]

Vaccine	Due age	Max age	Dose	Diluent	Route	Site
For pregnant women						
TT-1	Early in pregnancy	Give as early as possible in pregnancy	0.5 ml	No	Intramuscular	Upper arm
TT-2	4 weeks after TT 1		0.5 ml	No	Intramuscular	Upper arm
TT-Booster	If received two TT doses in a pregnancy within the last 3 years		0.5 ml	No	Intramuscular	Upper arm

Table No. 06: National immunization schedule for infants.[42]

Vaccine	Due age	Max dose	Dose	Diluent	Route	Site
For infants--						
BCG	At birth	Till one year of age	(0.05 ml until 1 month) 0.1ml Beyond age 1 month	YES Manufacturer supplied diluent (Sodium chloride)	Intra- dermal	Upper Arm- Left
Hepatitis dose	At birth	Within 24 hours	0.5 ml	No	Intra-muscular	Anterolateral Side of mid Thigh-left
OPV 0	At birth	Within first 15 days	2 drops	-	Oral	Oral
OPV 1,2 & 3	At 6 week 10 weeks & 14 weeks	Till 5 years of age	2 drops	-	Oral	Oral
Penta-valent 1 & 3(Diph-theria+ Pertussis + Tetanus + Hepatitis B +Hib)	At 6 weeks,10 weeks &14 weeks	1 year of age	0.5 ml	No	Intra-muscular	Anterolateral Side of mid Thigh-left
Fractional IPV	At 6 & 14 weeks	1 year of age	0.1 ml	No	Intra-dermal	Upper arm – Right
Rotavirus	At 6 weeks, weeks & 14 weeks	1 year of age	5 drops	No	Oral	Oral
Pneum-ococcal conjugate Vaccine (PCV)	At 6 weeks & 14 weeks At 9 completed months – booster	year of age	0.5 ml	No	Intra-muscular	Anterolateral Side of mid Thigh- left
Measles / Rubella 1st dose	At 9 weeks Complete & 12 months	5 years of age	0.5 ml	Yes- Manufacturer Supplied Diluent (Sterile water)	Sub-cutaneous	Upper arm – right
Japanese Encephalitis –1 @ (Were applicabl e)	At 9 months-12 months	15 year of age	0.5 ml	YES - Manufacturer supplied diluent (Phosphate Buffer Solution)	Sub-cutaneous	Upper arm – Left
Vitamin A (1st dose)	At 9 months	5years of age	1 ml		Oral	Oral

Table No. 07: National immunization schedule for children.[42]

Vaccine	When to Give	Max age	Dose	Diluent	Route	Site
For children						
DPT Booster-1	16-24 Months	7 years of age	0.5 ml	No	Intra-muscular	Antero-lateral Side of mid Thigh- Right
Measles / Rubella 2nd dose ##	16-24 Months	5 years of age	0.5 ml	Yes Manufacturers Supplies diluent (Sterile water)	Sub-cutaneous	Upper arm – Right
OPV Booster	16-24 Months	5 years	2 drops	No	Oral	Oral

Japanese Encephalitis2 (where applicable)	16-24 Months	Till 15 Years of Age	0.5 ml	Yes Manufacturers Supplies diluent (Phosphate buffer solution)	Sub-cutaneous	Upper arm – Left
Vitamin A $ (2nd to 9th dose)	At 16 months Then one Dose every 6 months	Up to the Age of 5 Years	2 ml	-	Oral	Oral
DPT Booster-2	5-6 years	7 years of Age	0.5 ml	No	Intra-muscular	Upper arm
TT	10 years and 16 years	16 years	0.5 ml	No	Intra-muscular	Upper arm

Universal Immunization Program (UIP)[39]

In India, the Universal Immunization Programme (UIP) is a crucial public health program that attempts to lower the death and morbidity rates from diseases that can be prevented by vaccination. One of the biggest public health initiatives, UIP was first introduced in 1978 as the enlarged Programme of Immunization (EPI) and then enlarged in 1985. Its annual target population is 2.67 crore infants and 2.9 crore pregnant women. If a child receives all recommended vaccinations within their first year of life, they are deemed completely immunized. The eradication of polio in 2014 and maternal and neonatal tetanus in 2015 are significant achievements of UIP.[39]

1. **Penta-valent Vaccine (2011):** Reduces the number of needle pricks while providing protection against tetanus, diphtheria, pertussis, hepatitis B, and Haemophilus influenza B.
2. **Inactivated Polio Vaccine (IPV) (2015):** The Global Polio end-game strategy includes the 2015 Inactivated Polio Vaccine (IPV).
3. **Rotavirus Vaccine (RVV) (2016):** Lowers Rotavirus diarrhoea mortality.
4. **The 2017 Measles Rubella (MR) Vaccine:** aims to control rubella and eradicate measles.
5. **Pneumococcal Conjugate Vaccine (PCV) (2017):** Lowers infant pneumonia-related morbidity and mortality.

Immunization schedule

1. BCG (Birth)
2. DTP (6, 10, 14 weeks)
3. Hepatitis B (6, 10, 14 weeks)
4. Haemophilus influenzae type b (Hib) (6, 10, 14 weeks)
5. Polio (birth, 6, 10, 14 weeks)
6. Rotavirus (6, 10, 14 weeks)
7. MMR (9-15 months)
8. Japanese Encephalitis (JE) (9-15 months)
9. TT (10-16 years)

Additional vaccines

- HPV (9-14 years, girls only)
- Rubella (9-15 months)
- PCV (Pneumococcal Conjugate Vaccine) (6, 10, 14 weeks)

Table No. 08: Immunization schedule in tamil nadu: Primary vaccination.[39]

Age	Vaccine	Dose	Route	Site
At birth	BCG	0.1 ml	Intradermal	Left upper arm
	OPV zero dose	2 drops	Oral	Oral
	Hep B birth dose	0.5 ml	Intramuscular	Anterolateral Aspect of mid thigh
6th week	Penta-1	0.5 ml	Intramuscular	Anterolateral Aspect of mid thigh
	OPV-1	2 drops	Oral	Oral
	IPV-1	0.1 ml	Intradermal	Right upper arm
	Rota-1	5 drops	Oral	Oral
10th week	Penta-2	0.5 ml	Intramuscular	Anterolateral Aspect of mid thigh
	OPV-2	2 drops	Oral	Oral
	Rota-2	5 drops	Oral	Oral
14th week	Penta-3	0.5 ml	Intramuscular	Anterolateral aspect of mid thigh
9 month	OPV-3	2 drops	Oral	Oral
	IPV-2	0.1 ml	Intradermal	Right upper arm
	Rota-3	5 drops	Oral	Oral
	MR 1st dose	0.5 ml	Subcutaneous	Right upper arm
	JE 1	0.5 ml	Subcutaneous	Left upper arm

Table No. 09: Immunization schedule in tamil nadu: Booster vaccination.[39]

Age	Vaccine	Dose	Route	Site
16-24 months	DPT 1st booster	0.5 ml	Oral	Anterolateral Aspect of mid-thigh
	OPV booster	2 drops	Subcutaneous	Oral

	MR 2nd dose	0.5 ml	Subcutaneous	Right upper arm
	JE 2	0.5 ml	Intramuscular	Left upper arm
5-6 years	DPT 2nd booster	0.5 ml	Intramuscular	Upper arm
10th year	Td single dose	0.5 ml	Intramuscular	Upper arm
16th year	Td single dose	0.5 ml	Intramuscular	Upper arm
Pregnant women	Td 1early in Pregnancy	0.5 ml	Intramuscular	Upper arm
	Td 2 four weeks After Td 1	0.5 ml	Intramuscular	Upper arm
	Td booster If received 2nd dose in a pregnancy within last 3 years	0.5 ml	Intramuscular	Upper arm

Mission indradhanush

Launched on December 25, 2014, Mission Indradhanush is a state-wide vaccination campaign that aims to vaccinate pregnant women and all children under two who were previously excluded or abandoned from the regular immunization program. Twelve deadly illnesses are the focus of the mission: polio, hepatitis B, pneumonia, meningitis, measles, rubella, Japanese encephalitis, rotavirus diarrhoea, polio, pertussis, tetanus, TB, and diphtheria. All Indian districts are now included in the program. Madhya Pradesh, Rajasthan, Uttar Pradesh, Bihar, Gujarat, Odisha, Maharashtra, and Assam are a few of the states that are heavily covered. Over 5.06 crore children and 1.25 crore pregnant women had received vaccinations through Mission Indradhanush as of October 2023. a 5-7% increase in the coverage of all vaccinations. led to an annual increase in vaccine coverage of 6.7%.[43]

Intensified Mission Indradhanush (IMI)

Improving immunization coverage for children and pregnant women not covered by regular programs is the goal of Intensified Mission Indradhanush (IMI). By December 2018, the target vaccination rate is expected to surpass 90%. Since 2014, Mission Indradhanush has vaccinated more than 5.06 million children and 1.25 crore pregnant women. The phases of IMI are:[43]

a. **IMI 3.0:** Introduced in February and March of 2021, it focused on regions with significant immunization gaps and targeted 250 districts.
b. **IMI 4.0:** Introduced in February 2022, this initiative focuses on missed vaccines and targets 416 districts in 33 states and UTs.
c. **IMI 5.0:** Introduced from August to October 2023, it included children up to age five, enhanced MR immunization, and made use of the U-WIN online platform for monitoring.

Immunization initiatives

1. National Vaccine Policy (2011)
2. National Immunization Strategy (2013)
3. Electronic Vaccine Intelligence Network (eVIN)
4. Immunization Management System (IMS)

Implementation

1. Ministry of Health and Family Welfare (MoHFW)
2. National Health Mission (NHM)
3. State/UT governments
4. District health authorities
5. Frontline workers (ASHAs, ANMs, etc.)

WHO Immunization Program

Thirteen vaccines are recommended for the WHO's Essential Programme on Immunization (EPI). These include COVID-19 (adult), polio, measles, rubella, pneumococcal disease (PNC), rotavirus (Rota), human papillomavirus (HPV), diphtheria, pertussis, tetanus, Haemophilus influenzae type B (Hib), Hepatitis B (HepB), and Bacillus Calmette-Guérin (BCG). EPI is dedicated to ensuring that everyone at risk has access to all necessary vaccines, and it keeps collaborating with other public health initiatives to prevent infectious diseases and improve the health of all people worldwide.[44]

Case Study

Table No. 10: Immunization Program Who Adopted Recent Advancement of Vaccine Technology.

Sr.no.	Vaccine name	Used against	Immunization program	Technology
1	ZyCoV-D	Covid 19	National covid 19Vaccination Program	DNA technology
2	Covishield	Covid 19	National covid 19 Vaccination Program	Recombinant Technology
3	Pneumococcal Conjugate Vaccine	Pneumococcal Disease	National Immunization Program	Conjugate Technology
4	Cervavax	Human B Papilloma Virus	National Immunization Program	Viral like particle Technology

5	Measles-rubella Vaccine	Measles and Rubella	Expanded Immunization Program	Recombinant Technology
6	Tdap vaccine	Tetanus & diphtheria	Expanded Immunization Program	Combination Technology

How the government can be ready for a pandemic in the future

1. **Planning for preparation:** Planning for pandemic preparation entails simulating past outbreaks at different scales (continents, nations, hospitals, intensive care units). The necessity to identify key targets was highlighted by WHO's influenza simulation, which exposed weaknesses in pandemic plans. While influenza is the main focus of most simulations, COVID-19 brought attention to important but often ignored elements like face shields and super pollutants. Developing a variety of scenarios, models, and simulations based on transmission channels is essential for effective pandemic preparation in order to improve response tactics.[45]

2. **Early warning system:** Early pandemic detection requires a strong surveillance system. It entails locating contacts, detecting cases quickly, and putting isolation measures in place. People with chronic illnesses and the elderly are high-risk groups that need special treatment. Preventing pandemics requires prompt data reporting, robust laboratory infrastructure, and quick diagnosis procedures.[45]

3. **Competence of Healthcare Workers and External Support to Them:** Because they interact closely with patients during pandemics, healthcare personnel are particularly vulnerable. In order to reduce dangers and safeguard their physical and mental health, proper training, high-quality PPE, and fair compensation are essential. Their general safety and motivation can be increased by addressing issues including knowledge gaps, a lack of personal protective equipment (PPE), physical demands, and unpredictable work hours.[45]

Table No. 11: Vaccine and Their manufacturing companies based on modern technologies.

Company Name	Product	Technology
Cadila Healthcare	ZyCov-D	DNA Vaccine
Moderna Tx, Inc	Spikevax (moderna covid 19 vaccine)	mRNA Vaccine
Serum Institute	Genevac B	VLP Vaccine
AstraZeneca	Oxford–AstraZeneca vaccine	Viral vector vaccine
Novavax, Inc	Novavax COVID-19 vaccine	Protein subunit vaccine
CytoDyn Inc.	CYT-0851 (Hepatitis B Vaccine)	Artificial intelligence and Machine learning
MenB	GSK plc	Reverse vaccinology

Role of Artificial Intelligence in Immunization Program[10]

1. **AI-Assisted Vaccine Development:** By speeding up vaccine research, improving disease tracking, and streamlining distribution, artificial intelligence is revolutionizing vaccination systems. AI can anticipate antigen architectures, find therapeutic targets, and expedite clinical trials by evaluating large amounts of genetic and proteomic data. Additionally, AI-powered solutions track vaccination rates, identify at-risk individuals, and improve vaccine delivery. Immunization programs are more successful and efficient because to this integrated strategy, which also improves global health and saves lives.

2. **AI-Driven Analytics**: Vaccine distribution is being revolutionized by AI-powered analytics and data management solutions that optimize supply chain logistics, demand forecasting, and resource allocation. These methods guarantee the efficient and equitable delivery of vaccines, especially to vulnerable groups, by examining healthcare infrastructure, geographic regions, and population demographics.

3. **AI-Enabled Surveillance Systems**: AI-powered surveillance systems monitor internet disinformation, vaccine hesitancy, and disease outbreaks. Algorithms using natural language processing identify and refute false information about vaccines, encouraging factual information. To guarantee the accuracy and dependability of AI-driven vaccination efforts, however, issues with algorithmic bias, data privacy, and ethical ramifications must be resolved.

CONCLUSION

In public health, vaccines—biological preparations intended to boost immunity against particular illnesses—have proved crucial. Their history began with the invention of vaccination by Edward Jenner in the 18th century. With the enormous advancements in vaccine technology, safer and more effective choices are now available. Conventional vaccinations, including subunit, inactivated, and live-attenuated vaccines, have been in use for many years. They can have adverse effects, have varied efficacy, and frequently call for several dosages. Modern vaccines, such as mRNA and DNA vaccines, on the other hand, have a number of benefits, including improved scalability, lesser side effects, faster

development, and higher efficacy. In order to distribute vaccines to the populace, governments and international organizations such as the WHO conduct immunization programs. For example, India's Universal Immunization Program has achieved notable progress in preventing diseases that can be prevented by vaccination. To protect against a variety of diseases, the WHO's Essential Program on Immunization (EPI) suggests a full range of immunizations. Governments must make investments in the creation of new vaccines, bolster production capacity, and guarantee fair distribution in order to combat the threat of pandemics in the future. Through epidemic prediction, vaccination schedule personalization, and vaccine delivery optimization, artificial intelligence has the potential to completely transform immunization programs

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