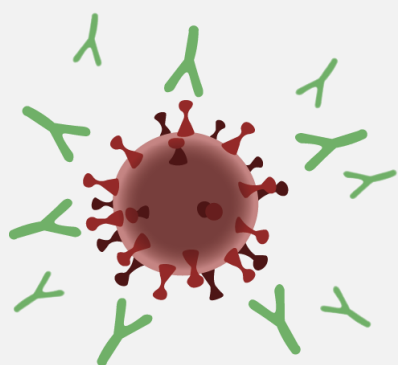


Science & Technology Policy Brief

Vaccines



Vaccination is a critical measure for safeguarding public health and is an essential element of healthcare programs worldwide. This brief outlines the science behind vaccines, their role in public health, vaccine development process, and related concerns.

Summary

- Vaccines simulate some features of a low-intensity infection to prepare the immune system to respond to future infections.
- Mass vaccination breaks the chain of transmission, protecting not just the vaccinated, but also a wider populace.
- Improvement in understanding of disease-determinants has led to development of new vaccine design approaches and technologies.
- Effective vaccine design needs to account for the evolution of the pathogen and variability in the immune response.
- Continuous surveillance and research are critical to vaccine development.

Introduction

Vaccines are critical in preventing infectious diseases caused by microorganisms such as bacteria and viruses. Some diseases are highly transmissible, causing public health emergencies, such as the Measles outbreak in Maharashtra in 2022, the COVID-19 pandemic in 2020, the Japanese Encephalitis outbreak in Bihar in 2019, and the Nipah virus outbreak in Kerala in 2018.^{1,2,3,4} The impact is seen in terms of loss of life, significant expenses on treatments, strained health systems, and negative economic consequences.

Vaccines are an important feature of public health policy. Vaccines have helped eradicate diseases such as smallpox (across the globe) and polio (across many countries). As per a Lancet study, vaccination against COVID-19 is estimated to have lowered the death toll by two-thirds at the global level in 2021.⁵

Vaccine and the Immune System

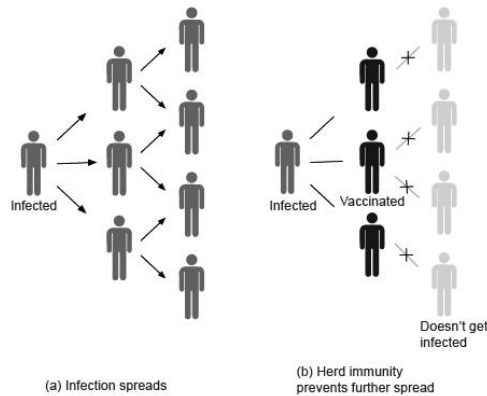
Microorganisms such as viruses and bacteria can be several times smaller than the human cells.⁶ This means that these pathogens (disease causing microorganisms) can enter the human body and replicate themselves within a human cell or outside of a cell. These may enter the body through air, water, skin cracks, and the bloodstream through vectors such as mosquitoes.⁷ The presence of a pathogen inside a healthy human body and its replication inside the host is called infection.⁸ If an infection cannot be controlled, damage to the body starts resulting in illness or disease. The human

body has an elaborate mechanism, called the immune system, to fight infections. The immune system has three key properties:^{9,10}

- **Distinction between self and foreign:** It possesses the ability to recognise and destroy foreign microorganisms such as bacteria and viruses, while leaving its own cells unharmed.
- **Memory:** After it eliminates a pathogen when encountered for the first time, the system remembers the pathogen and keeps itself ready to mount a rapid and effective response for subsequent infections.
- **Specificity:** The response is specific to the pathogen with different infections resulting in different responses.

Vaccines leverage the above properties to prevent an infection from developing into a disease.⁹ Vaccines introduce a pathogen in whole or in part to the body of a healthy person.¹¹ This triggers the immune system to prepare a response and build memory to fight any future infections effectively.

Mass vaccination protects the vaccinated as well as unvaccinated.¹² When a sufficiently large proportion of the population develops immunity either through vaccination or through prior infection, the chances of any infected person coming into contact with a person without immunity is low. Consequently, the pathogen has difficulty in finding susceptible hosts in the population, thus reducing the degree of transmission. This is referred to as herd immunity.¹² This makes vaccination an effective measure for protecting the population at large against some infectious diseases.

Figure 1: Herd Immunity

Immune Response

Improvements in the understanding of the immune response to a pathogen has been key to development of vaccines. There are two key types of immune responses against a pathogen.^{13,14} These work together to prevent an infection from developing into a disease or illness.^{15,16,17}

Innate immune response is the first line of defence against an invading pathogen.^{14,16} This response is immediate and non-specific, i.e., the response does not differ based on the type of the pathogen. Innate response is a culmination of a variety of cells performing certain specific functions. These cells populate all tissues and blood in a human body.¹⁷ They have receptors which can identify a molecular pattern associated with a pathogen or an infected cell.^{10,16} These patterns are distinct from uninfected human cells, resulting in identification of foreign entities.

There are cells called natural killer cells which identify infected cells using the above mechanism, and give them instructions to self-destruct in a controlled manner.¹³ Two other types of cells, called macrophages and neutrophils, can identify, and ingest a pathogen or a dead human cell. Thus, these cells eliminate pathogens, which have not yet entered a human cell, or the ones killed by the natural killer cells. Macrophages, as well as another set of cells called dendritic cells, release cytokines (type of proteins which act as messengers to the different parts of immune system) and other chemicals to cause inflammation.¹⁷ Inflammation results in more of these cells to reach the site of an infection, and intensify the immune response.^{16,17}

If a pathogen invades in large numbers, the innate immune response might not be enough.¹⁷ Certain pathogens have also evolved to have the ability to evade the innate response.^{10,16} This is where another type of response called adaptive immune response comes into picture, which complements the innate immune response.¹⁵

Adaptive immune response: This response mechanism identifies the pathogen and develops a special counter to it. Two sub-types of White

Blood Cells, B-cells, and T-cells, play a central role in the adaptive immune response.^{18,19} These cells can identify antigen, which are substances such as protein or complex sugar molecules found on the surface of pathogens. The body produces a large number of B-cells and T-cells, with diversified receptors to identify different antigen.¹³ The number of different types of receptors is estimated to be of the order of a billion.¹⁷ If an antigen were to be considered to be a lock, by producing a wide variety of B-cells and T-cells with different receptors, the body is producing a wide variety of keys hoping that one of these might be able to open the lock.

Once presented with an antigen, those B-cells and T-cells, which have receptors that can recognise that antigen, clone themselves rapidly to increase their number for mounting the response.^{16,17} Certain cells from the innate response such as macrophages and dendritic cells help T-cells identify the antigen.^{11,17} B-cells differentiate and proliferate into short lived Plasma cells which produce antibodies.^{20,21} Antibodies are a kind of protein which specifically bind to the antigen. This binding marks the pathogen for ingestion and destruction by macrophages and certain other cells.¹⁷ T-cells identify the infected cells, they either help such cells to kill pathogens inside them or eliminate them in a similar manner as the killer cells of the innate response.¹³

Some B-cells differentiate into long-lived plasma cells and memory cells.²² Memory B-cells persist for longer. They have a 10-100 times higher antibody production capability on antigen exposure.^{16,17} T-cells also differentiate into memory cells with a relatively longer lifespan, providing capability for a rapid response on subsequent infections.²³

The adaptive immune response can take days to develop, increasing the chances of an infection developing into a disease.⁹ As mentioned earlier, vaccines prevent this by simulating a low-intensity infection to stimulate the adaptive immune response in advance, thereby building immune memory. Vaccines target adaptive immune response to fight against the pathogen. Immune response may vary with factors such as age, genetics, and environmental factors.¹⁹

Types of Vaccines

Vaccines aim to stimulate the immune system by exposing it to a pathogen or a part of it.²⁴ This can be achieved by administering: (i) whole pathogen (weakened or dead), (ii) sub-unit of a pathogen, i.e., protein or carbohydrates found on its surface, or (iii) genetic material such as DNA or RNA to provide instruction to human cells to synthesise protein associated with the pathogen. Proteins or carbohydrates derived from the pathogen can also trigger immune response similar to introduction of a full pathogen in the human body.^{25,26,27,28,29,30,31}

Table 1: Common vaccine types

Type	Administered Material	Examples
Live Attenuated	Alive but weakened pathogen	BCG, Rotavirus
Inactivated	Dead pathogen	Polio, COVAXIN
Sub-Unit	Protein or carbohydrate on surface of pathogen	HPV, Tetanus, Novovax
DNA	DNA with information for synthesising protein associated with targeted pathogen	Zydu Cadila COVID Vaccine
mRNA	RNA with instruction for synthesising protein associated with targeted pathogen	Pfizer and Moderna COVID vaccines
Viral Vecteded	A weakened, generally non replicating live virus carrying genetic material of targeted pathogen	AstraZeneca COVID Vaccine, Ervebo (Ebola Vaccine)

Sources: Types of Vaccines, University of Oxford; PRS.

DNA, mRNA, and viral vectored vaccines are relatively newer approaches to vaccine development, and are categorised as **platform-based technologies**.²⁴ In these, a standardised platform is used to deliver genetic material inside human cells to stimulate the immune response.³² Genetic information carried by these delivery platforms can easily be modified, allowing for quicker development and adaptation of vaccines against the evolution of the pathogen.³³ These methods are limited to use against protein-based antigens as the body can only synthesise proteins from an external instruction, and will not work against bacteria, which are carbohydrate-based.³⁴

Trials

As vaccines are given to healthy persons, the efficacy as well as safety of vaccines must be demonstrated. These aspects are tested in phased trials. Efficacy is defined as the observed reduction in incidence (number of cases of infection) in vaccinated persons as compared to the same in those unvaccinated.³⁵ If the incidence in an unvaccinated group of 500 persons is 100, and that in a vaccinated group of 500 persons is 40, then the incidence reduction rate is 60%, which is the efficacy. Regulatory authorities across the globe typically require a proven efficacy of more than 50% to approve a vaccine.³⁶

Table 2: Clinical Trials for Vaccines³⁷

Phase	Sample Size	Purpose
I	5 to 50	Assessing safety, immune response, optimising dose schedule
II	25 to 1,000	Expanding study for safety, immune response, and optimising dose schedule
III	100 to 10,000	Assessing efficacy and safety at a bigger scale
IV	100,000 to millions	Assessing the side effects caused over time by a vaccine after approval

Sources: Vaccines and Immunization, CDC; PRS.

Box 1: Vaccines against COVID-19

The COVID-19 pandemic was caused by a member of the SARS virus family called SARS-CoV-2.¹ Herd immunity achieved via mass vaccination was seen as a way out of pandemic. This led to extensive government programs funding the research and development of vaccines globally.³⁸ The first vaccine was approved by WHO in December 2020, one year into the pandemic.³⁹ Adoption of COVID-19 vaccines was expedited through emergency use authorisation, an accelerated process for regulatory approval.

As on May 31, 2023, India has recorded 4.5 crore COVID-19 cases with 5.3 lakh deaths.⁴⁰ A fully public-funded mass vaccination programme against COVID-19 has been running in India since January 2021.⁴¹ The program is estimated to have cost Rs 36,405 crore over three years.⁴² The COVID Suraksha Mission, with an estimated cost of about Rs 900 crore, was launched in November 2020 to accelerate the development of COVID-19 vaccines domestically.⁴³ As of January 2023, this program has yielded four approved COVID-19 vaccines.⁴⁴

Early-stage studies on humans

Before a vaccine goes for clinical trials, animal trials are done to study response to a vaccine.³⁷ These trials however have certain limitations.⁴⁵ The host-parasite interaction in animals may not be similar to that in humans. Clinical trials are also cost and time intensive. Controlled Human Infection Model Studies (CHIM) are expected to aid current mechanisms to address these issues.⁴⁵

In CHIM studies, the subject is intentionally infected with the pathogen under a controlled environment.⁴⁶ These studies help in narrowing down a suitable vaccine candidate and speeding up vaccine development.⁴⁵ They can also help in developing vaccines particular to a population as efficacy changes with genetic complexities, environmental factors, and nutritional status.⁴⁶ While these studies may be useful, they present ethical concerns as it involves infecting healthy people at an experimental stage.⁴⁷ Currently, India does not have any framework for CHIM studies.⁴⁶

Surveillance

As pathogens may keep evolving and evade the vaccine induced immune response, surveillance of variants and mutations becomes critical. From a safety perspective, it is also critical to continue monitoring for any adverse events (any minor or major illness after vaccination). This makes surveillance systems an essential pillar of the public health system.⁴⁸ A 2020 report by NITI Aayog observed that India's surveillance system is not well integrated, with different monitoring agencies working in silos.⁴⁹ As a result, the data collected is patchy. The report also observed that there is a dearth of human resource for public health surveillance.⁴⁹

Another challenge is increasing incidences of zoonotic diseases, i.e., diseases jumping from animals to humans. As per WHO, 75% of emerging infections in humans are zoonotic in

nature.⁵⁰ Hence, strengthening disease surveillance in animals has the added advantage of protecting humankind through the early detection, prevention, and control of zoonotic diseases.⁵¹ In 2021, the Department of Biotechnology of the central government had launched One Health Mission to monitor the prevalence of zoonotic diseases.⁵²

Status of Vaccination in India

The central government-funded universal immunisation programme in India provides children with free vaccines against 12 diseases.^{53,54} The percentage of children who got all vaccines under this program has significantly improved over the years (referred to as immunisation coverage). The coverage has increased from 35% in 1992-93 to 76% in 2019-21, which is well short of achieving universal coverage.⁵⁵ There is also significant variation across states. The North-eastern states barring Sikkim, fare poorly, with Nagaland having 58% coverage and coverage in others in the range of 60-70%.⁵⁶ Certain large states including Uttar Pradesh, Maharashtra, and Bihar have their coverage around 70%, while the large states with highest coverage are Odisha (91%), Tamil Nadu (89%), and West Bengal (88%).⁵⁷

Table 3: Adoption of vaccines in India^{58,59,60}

Category	Diseases
Vaccines covered under the Universal Immunisation Program	Nationally: Diphtheria, Pertussis, Tetanus, Polio, Measles, Rubella, severe Tuberculosis, Hepatitis B, Meningitis, Pneumonia, Rotavirus Diarrhoea, Pneumococcal Pneumonia, Sub-Nationally: Japanese Encephalitis
Vaccines approved in India, but not covered under government programs	HPV, Hepatitis A, Typhoid, Rabies, Influenza, Herpes zoster, Varicella zoster
Vaccines approved by WHO, but not approved in India	Dengue (under phase 3 trials in India)
Prevalent diseases in India for which no vaccines are approved globally	Tuberculosis in adults, AIDS, Hepatitis C, Malaria variety dominant in India

Sources: National Health Mission, World Health Organisation; PRS.

Developing vaccines for India

India has a significant presence in the vaccine manufacturing ecosystem through its private players. In 2021, Serum Institute and Bharat Biotech of India were amongst the top 10 manufacturers of vaccines by volume (excluding COVID-19 vaccines), with 20% and 7% share in the global market, respectively.⁶¹ Existence of these manufacturing capabilities within the country helped India in securing vaccine supplies for COVID-19. However, their share by value in the global market is much lower (< 2% in 2021).⁶¹

Box 2: New Frontiers in Vaccine Technology^{62,63}

Universal Vaccines: These aim to target common elements shared across multiple strains or species of pathogens, to provide broader protection against a family of pathogens, such as flu virus or coronavirus families.

Therapeutic Vaccines: These aim to treat instead of prevent diseases such as cancer or Alzheimer's disease.

Personalised Vaccines: These aim to customise vaccine to factor an individual's genetics to improve immune response.

This may indicate limited presence and capability in developing newer and higher-value vaccines.

Vaccine development is cost intensive as research and development (R&D) requires sophisticated infrastructure and a long timeframe due to regulatory requirements.^{61,64} There may not be a guarantee of a vaccine candidate reaching the market or assured procurement from government. These uncertainties limit the investments by the private sector towards R&D. Development of a relatively higher number of vaccines for COVID-19 were spurred by government incentives for R&D as well as assured procurement globally.³⁵

There could be diseases prevalent only in India, due to environment and other factors. Other countries may not have the incentive to invest in vaccines for them. WHO (2022) observed that diseases associated with markets of little commercial value have remained neglected, have seen suboptimal investment, and have only a few products in the development pipeline.⁶¹ These include diseases referred to as **neglected tropical diseases**.⁶⁵ Some of these diseases such as dengue and lymphatic filariasis are prevalent in India. Hence, India may need a sustained directed effort towards R&D in vaccines.

Public funding may also become necessary to widely administer vaccines against certain diseases. Given limited resources and a range of diseases to protect against, decisions such as funds for R&D or mass vaccination need to take various factors into account. These could include susceptibility, transmissibility, disease burden, and geographical spread. These may help in deciding the scale of mass vaccination.⁶⁶ For example, Polio vaccine is given across India, while Japanese Encephalitis is given only in some states.⁵⁴ The Rabies vaccine is given only to people bitten by a rabid animal and not everyone.⁶⁷ The trade-off between treatment and the cost of vaccination and morbidity of a disease helps government decide roll out of a vaccine. Chickenpox has a vaccine but vaccination is usually not recommended.⁶⁸ There are diseases such as hepatitis-A and cervical cancer, for which vaccines are available but not given freely through the public health system.⁶⁹

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