**Vaccines: The Way Forward**

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 **ABSTRACT**

‘Vaccination’ since the roots from the first safe and reliable vaccine in 18th century has time-tested proven to be one of the most safe and cost-effective ways against infections. Overtime, with advent of molecular techniques and whole genome sequencing for infectious pathogens have exponentially propelled this field with safer and very effective vaccines replacing the older ones. Research has proven vaccines are not only effective in preventing infections or curtailing the illness severity and duration, but also effective in preventing malignancies attributed to pathogens (Eg. Cervical cancer – Human Papilloma virus, Burkitt’s lymphoma – Epstein Barr Virus, etc.). Yet there remains a threat of emerging or remerging or novel infectious pathogens sometimes even leading to pandemics as witnessed by the COVID-19 Pandemic that arisen from Wuhan, China in 2019. Global vaccinations drives were in places to curtail the pandemic. This chapter focuses on these very trends in vaccination development: the historic roots and evolution, newer forms, newer methods, forms of vaccines and a way forward.

**I. INTRODUCTION**

Vaccination encompasses a proven record of enhancing global health and development and saving numerous lives. It can improve people’s chances of survival, protect communities from new and reemerging health threats, and enhance societal productivity. A minimum of 26 diseases which will be prevented by vaccinations are being developed, and vaccination can currently prevent over 20 of those diseases.1,2,3 These include vaccines for fatal diseases like meningitis, typhoid, cholera, cervical cancer, and pneumonia.4 Thus, vaccination may be a safe and cost-effective preventive tool to reduce mortality and morbidity because of variety of diseases and remains one of the powerful strategies of tackling new and re-remerging health threats in the form of epidemics and pandemics.5

**II. HISTORY AND EVOLUTION OF VACCINATION**

From as far back as 496 B.C, Greek historian Thucydides observed that those that survived small pox would never get re-infected6. In 15 century, the Chinese recognized that people who had contracted smallpox once were immune to reinfection.6 In 18th century British physician Edward Jenner who is credited with developing the first safe and reliable smallpox vaccine6. In 19th century, Louis Pasteur developed successful vaccines against anthrax and rabies. 7In the early 20th century, Albert Calmette and veterinarian Camille Guérindeveloped a tuberculosis vaccine(BCG Vaccine).8 The Salk and Sabin vaccines Produced around 1950s.9

In 1974 WHO's Expanded Programme on Immunization (EPI) is established. In the 1980 Thirty-third World Health Assembly officially declares smallpox eradication.10 In 1999, the Global Alliance for Vaccines and Immunization (GAVI) was established to improve health of children in the poorest countries.11 Polio has reached near end eradication. Many other diseases like maternal and neonatal tetanus have also been eliminated in many countries.12,13Vaccines played a significant role in the prevention and control of Ebola, Covid Pandemics. Vaccines are available for travelers visiting endemic countries in order to prevent acquaintance of infection.

**III. ASPECTS OF VACCINATION**

There are different aspects of vaccination that are universal when considering vaccinating any community. Globally and regionally, there are certain commitments undertaken just like the sustainable development goals, etc. Evidence based policies, guidelines and strategies direct the conceptualization, manufacturing, storage, delivery, vaccination, and reception by public, with an underlying theme of fair and equitable vaccination for all.

Vaccines are available for all age groups including infants, adults,14 elderly people. Vaccines even have the potential to be used to treat diseases, instead of preventing them. Such therapeutic vaccines are being targeted at persistent infections, like shingles and those due to human papilloma virus (Cervarix, Gardasil vaccine). They are also being targeted at non-infectious conditions, including autoimmune disorders, tumours, allergies, and drug addiction.

In the case of tumours, the vaccine can either be directed against the tumour itself or be designed to amplify the anti-tumour immune response. For autoimmune or allergic disorders, vaccines are being designed to change off unwanted immune responses (so-called ‘negative vaccination’), instead of switching on the useful immunologic response needed for infections and cancer.15

Covid vaccines have brought forth a new era in vaccinology. They need been developed over a reduced time span after conducting several clinical trials. There are more candidate vaccines under trial. Issues pertain to the efficacy, immunogenicity, reactogenicity, adjuvants, platform of delivery, cost of the vaccines and also the emerging Covid-19 variants are the biggest Challenges.

**IV. FORMS OF VACCINES**

Vaccines depending upon the process of manufacturing are of different types. These are mainly listed as following:

* **Live-attenuated vaccines**16- Use of the attenuated Strains. Eg. MMR Vaccine
* **Inactivated vaccines**17- Killed pathogens are used. Eg. Salk polio vaccine
* **Toxoid vaccines**18- Use of chemically inactivated toxins produced by the pathogen. Eg.Tetanus Toxoid
* **Subunit vaccines**19- Use of purified fragments of the pathogen. Eg. Pertussis Vaccine pneumococcal polysaccharide vaccine (PPV), pneumococcal conjugate vaccine (PCV).
* **Virus-like particles (VLP) vaccines**20-Human papillomavirus (HPV) vaccine, use structures similar to viruses, but without the virus’ genetic material, that are recognised by the immune system.
* **Bacterial outer membrane vesicle (OMV) vaccines**21 - Bexsero Meningitis B vaccine, use ‘bubble-like’ structures from the bacterial surface

It usually takes 10-15 years to reach the market by using the above technology. They require biological systems (such as chicken eggs, cell cultures of bacteria or yeast, or plant or animal cells) for multiplication or propagation of pathogens or their parts, necessitating the employment of adequate biocontainment levels to avoid their release into the surrounding environment.22

**V. THE NEWER VACCINES**

**Platform-based vaccines**23

The most recent platform-based vaccinations for human use are based on the genetic information of the pathogen and are administered directly to the body in various ways.

Examples are:

**A. DNA vaccines**24:

They utilise the pathogen’s DNA. Once administered in the body, this may be replicated within the body as mRNA, which the body will then "read" to form pathogen's proteins and trigger an immunologic response. The first DNA-based vaccine to be approved to be used in humans in an emergency is that the ZyCoV-D COVID-19 vaccine in India.

**B. mRNA vaccines**25**:**

Using the ‘ready to read’ mRNA to induce the production of a pathogen's protein and to activate the immune system. mRNA vaccines are typically more effective than DNA vaccines because of their "readable" form, requiring lower doses and fewer shots per person. Like the COVID-19 vaccines from Moderna and Pfizer/BioNTech.

**C. Viral vector vaccines**26**:**

The harmless virus (the vector) modified to contain a part of DNA of the target pathogen. The COVID-19 University of Oxford/AstraZeneca vaccine is an example.

These platforms are often used as a quick response to emerging infectious diseases since they can be easily modified by altering the genetic information they carry. However, not all diseases respond well to these methods. For example, bacterial vaccines are frequently polysaccharide-based (as opposed to protein-based), hence advancement altogether vaccine technologies continues to be required to assure preparedness for potential threats within the future.

**D. Live recombinant vaccines use attenuated viruses (or bacterial strains) as vectors**27**:**

 A virus or bacterium from one disease acts as a delivery device for an immunogenic protein from another infectious agent. In cases, this approach is employed to boost the immune response; in others, it is used when giving the actual agent as a vaccine would cause disease. Eg. Experimental recombinant vaccinia strains have been developed to provide protection against a variety of illnesses, including hepatitis B, rabies, and influenza.

**VI. CURRENT DEVELOPMENTS**

**A. Newer Technologies:**

New technologies in development will improve the effectiveness of vaccine delivery and make it simpler.28Multiple shots might not be necessary due to emerging technologies and alternate adjuvants, which are currently being developed. Multiple antigens can now be delivered in one injection without affecting the immune response to every other. Less needles for patients and more effective vaccination administration overall result from this.29–32

**B. Delivery Technique**:

It is feasible to administer some vaccines without using a needle, like live oral vaccines (e.g. rotavirus), as a nasal spray (Flu vaccine).33 Patch application34 uses a patch that contains a matrix of incredibly small needles distributes a vaccine without the utilization of a syringe. Given that its administration wouldn't necessitate a qualified medical professional, as is typically required for vaccines administered via syringe injection, this mode of delivery could be very helpful in distant locations. 35

**C. Storage Technique:**

For long-term vaccine storage, a small membrane that was like a filter, coated it with an ultrathin sugar glass coating was used, then virus particles trapped inside of it. The viruses the researchers used could be kept in this state for six months at temperatures as high as 113°F without losing their capacity to elicit an immunological response.36. Passive cooling storage technology, Computational Fluid Dynamics, Coloured Petri Net for monitoring are some of the new innovations.37

**D. Preparation Technique:**

The researchers also showed that the vaccine component could be put in a holder that could be attached to a syringe, enabling a vaccine provider to prepare the component (with a fluid medium within the syringe) and administer the vaccine nearly simultaneously. Widespread immunisation campaigns is also feasible in previously hard to reach locations with a stabilising technique like this.

**E. Monitoring:**

The biometric tracking technique(the iris and fingerprints) shows an innovative way to coordinate vaccination distribution in developing nations, which are frequently more prone to contagious diseases.38Electronic Vaccine Intelligence Network (eVIN) is a smartphone and cloud technology-based app that digitizes information on vaccine stocks and temperatures across the country.39

**F. Vaccine Records:**

Vaccine passport, as a form of portable health data, with adoption of blockchain technology40, can be a promising tool for health monitoring and alerts while protecting personal privacy. Vaccine-related information of importance, say recipients’ demographics, name and manufacturing details of the vaccine received, vaccination date, immediate side effects, duration of protection and so on, can also be included. Without excessive disclosure of personal identification, databases stored in blockchain are useful for data analytics. CoWIN (Covid Vaccine Intelligence Network)41 is an Indian government web portal for COVID-19 vaccination registration, owned and operated by India's Ministry of Health and Family Welfare.

**G. Need of Vaccines for chronic and emerging infections**

Most successful vaccines protect against acute (short-lived) infections largely through the production of antibodies. Vaccines for chronic (long-lasting) infections, especially for HIV, tuberculosis and malaria, remain a challenge. There are some infections related to serious long-term complications that we don’t yet have a vaccine for. For eg, infection with the bacterium Helicobacter pylori means patients are more likely to develop stomach cancer, and group A streptococcus infection is responsible for rheumatic fever, which remains a significant cause of death and disability in developing countries.

**VII. CHALLENGES AND OPPORTUNITIES**

Challenges and opportunities for vaccine R&D include progress in fundamental research, animal testing, clinical trial design and approval, and manufacturing and distribution. One amongst the most important challenges in vaccine R&D is developing a complete understanding of pathogens, the immune system, and a disease’s impacts on the population (i.e., ‘epidemiology’).The age-related dysregulation and decline of the immune system—collectively termed “immunosenescence”—has been generally related to an increased susceptibility to infectious pathogens and poor vaccine responses in older adults is that the challenge among them.42

**VIII. RECENT INNOVATIONS IN FUNDAMENTAL RESEARCH FOR VACCINES**

**A. System-approaches in biology and immunology**

These depends upon on a series of experimental techniques, combined with computational tools, to develop an understanding of biological systems in all their parts rather than focusing on single components. For eg., reverse vaccinology uses the entire genetic information of the pathogen to identify the effective antigens to trigger a strong immune response.43 eg.Meningococcus B (MenB) and it can be used to develop vaccines against complex pathogens.44 Similarly, genomes and individuals’ immune responses can be analysed to understand better how they respond to infections or why some show adverse effects following vaccination and others do not.45This would allow the development of ‘personalised’ vaccines, tailored to a specific individual’s immune system.46

**B. Structural biology approaches**

These seek to understand the three-dimensional structure of antigens and how they are recognised by the immune system. Combined with computational methods, they enhance effective vaccine design by facilitating selection of the best antigens.47 This could be particularly helpful with complex pathogens. The respiratory syncytial virus (RSV) vaccine, first developed for veterinary use, is one of the first examples developed using this approach.48,49 A better understanding of way to stimulate the immune response has the potential to extend the efficacy of existing vaccines, for instance by using different adjuvants or alternative administration routes.50,51 For example, mucosal vaccines (such as the nasal spray influenza vaccine for children) trigger an immune response at the level of the nose and the mouth, ensuring the pathogen is stopped as soon as it tries to enter the body.50–54 Vaccines can also be used as therapeutics to treat non-communicable diseases, such as some cancers, by stimulating the immune system to attack cancer cells55,56.

Animal research and veterinary vaccines Demonstration of vaccine safety and efficacy in animal models is required before starting clinical trials, and so access to high quality, laboratory capacity for animal testing is critical.

Flexible clinical trials and clinical trial infrastructure Innovative clinical trial designs, such as those that allow for the trial’s protocol or sample size to be adapted as data emerge, have a task in speeding up vaccine development.57 For instance, phases can be mixed (for example, Phase 2 and 3 can be combined), allowing information about vaccine immune response levels, side effect and efficacy to be collected at the same stage. In addition, a well-established clinical trial infrastructure, can allow for rapid resource allocation and the recruitment of trial participants.

Human challenge trials When a disease isn’t widely circulating within a population and thus vaccines cannot be tested with conventional largescale trials, human challenge trials can be used to demonstrate vaccine efficacy in a small population. During these trials, healthy volunteers are ‘challenged’ with minimal quantities of pathogen in a controlled environment to: better study correlates of protection; demonstrate that vaccines confer protection; compare different vaccines (enabling progressing of only those vaccines that appear promising).58 Human challenge trials contributed to the development of vaccines for cholera, malaria, influenza and typhoid fever.59–62 High safety and quality standards are key requirements for human challenge trials to be ethically acceptable.

Licensing innovation A ‘rolling-review approach’, where clinical trial data are assessed as they become available without waiting for the end of the trial, has been used to streamline COVID-19 vaccine approval.4,63–65

**IX. THE WAY FORWARD**

Vaccines are commonly viewed as being crucial for preventing the spread of Communicable disease outbreaks and other developing infectious disorders, like antibiotic resistance. Countries should prioritise and maintain important services while also acting promptly and providing missing immunizations when infectious disease threats rise. Long-term prevention of recurrences is predicted to need substantial, collaborative investments in research and development as well as an equal sharing of new vaccines. Even though, there are still significant obstacles. The benefits of immunisation are not distributed equitably due to the stark differences in coverage across and within nations. In unstable, conflict-torn settings, some populations—often the poorest, most marginalised, and most vulnerable—have limited access to immunisation programmes.

To ensure that everyone has access to immunisation services, vaccines must be distributed to marginalised populations such as displaced people and migrants, those affected by conflict, political instability, and natural disasters, as well as to geographically, culturally, socially, or otherwise isolated areas. To raise public demand for immunisation services, the causes of low vaccination rates must be acknowledged and addressed. Stock-outs at service delivery locations must be minimised, and sufficient, dependable supplies of pertinent, cost-effective vaccines with guaranteed quality must be accessible. To understand and remove immunisation barriers, particularly those caused by the gender of caregivers and healthcare workers, targeted interventions are necessary. To reach older age groups and offer immunisation services that are connected to primary healthcare, new strategies are required.

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