

VACCINES: THE WAY FORWARD

Abstract

Vaccination has its roots since 18th century and is a time tested, safe and cost-effective preventive tool against many infectious diseases. Over time, the 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 that vaccines are not only effective in preventing infections or reducing the severity and duration of illness, but also effective in preventing malignancies attributed to pathogens (E.g., Cervical cancer

Human Papilloma virus, Burkitt's lymphoma – Epstein Barr Virus, etc.). Yet there remains a threat of emerging, reemerging, or novel infectious pathogens, sometimes even leading to pandemics like COVID-19 Pandemic Global vaccination drives were in place to curtail the pandemic. This chapter focuses on these very trends in vaccination development: historic roots and evolution, newer forms, newer methods, forms of vaccines and a way forward.

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I. INTRODUCTION

Vaccination has a proven record of enhancing global health and development and saving numerous lives. It can increase societal production, safeguard communities against developing and existing health risks, and increase people's chances of survival. 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 targeting variety of diseases and remains one of the powerful strategies of tackling new and re-emerging 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 smallpox would never get re-infected⁶. The Chinese realized in the fifteenth century that people who had previously experienced smallpox were resistant to infection.⁶ In 18th the small pox vaccine was developed by Edward Jenner which is of historical significance ⁶. Louis Pasteur created effective rabies and anthrax vaccines in the 19th century.⁷ A tuberculosis vaccine (BCG Vaccine) was developed in the early 20th century by Albert Calmette and veterinarian Camille Guerin. ⁸ The Salk and Sabin vaccines Produced around 1950s.⁹

In 1974, WHO's Expanded Programme on Immunization (EPI) was established. In 1980 thirty-third World Health Assembly officially declared smallpox eradication.¹⁰ In 1999, the Global Alliance for Vaccines and Immunization (GAVI) was established to improve the health of children in the poorest countries.¹¹ Polio has reached its end of eradication. Many other diseases like maternal and neonatal tetanus have also been eliminated in many countries.^{12,13} Vaccines played a significant role in the prevention and control of Ebola, Covid Pandemics. Vaccines are available for travelers visiting endemic countries 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 sustainable development goals, etc. Conceptualization, production, storage, delivery, immunization, and public reception are all guided by evidence-based policies, guidelines, and methods with the ultimate goal of providing fair and equitable immunization for everyone.

Vaccines are available for all age groups, including infants, adults,¹⁴ elderly people. Vaccines not only prevent the disease but there exist therapeutic vaccines which work with the patient's own immune system to fight to cure an existing illness. Therapeutic vaccines are targeted against both infectious (e.g., HIV, H. Pylori infection, tuberculosis) and non-infectious conditions which include autoimmune disorders, addictions, cancers.

The therapeutic cancer vaccine (Immunotherapy) can be directed against the tumour directly or to boost the anti-tumour immune response. Vaccines for autoimmune or allergy disorders are being developed to turn off unnecessary immune responses (referred to as "negative vaccination") rather than turning on the necessary immunologic response required for infections and cancer.¹⁵

Covid vaccines have brought forth a new era in the vaccinology. They needed to be developed in a shorter amount of time after several clinical trials. There are more candidate vaccines under trial. Issues pertaining to the efficacy, immunogenicity, antigenicity, 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:

1. **Live-attenuated vaccines**¹⁶- Use of the attenuated Strains. E.g. MMR Vaccine
2. **Inactivated vaccines**¹⁷- Killed pathogens are used. E.g. Salk polio vaccine
3. **Toxoid vaccines**¹⁸- Use of chemically inactivated toxins produced by the pathogen. E.g. Tetanus Toxoid
4. **Subunit vaccines**¹⁹- Use of purified fragments of the pathogen. E.g. Pertussis Vaccine, pneumococcal polysaccharide vaccine (PPV), pneumococcal conjugate vaccine (PCV).
5. **Virus-like particles (VLP) vaccines**²⁰- They are more immunogenic compared to other subunit vaccines. These multiprotein complexes resemble viruses but do not contain the genetic material of viruses, making them immune system recognizable. Examples include the hepatitis B (Engerix) and human papillomavirus (Cervarix).
6. **Bacterial outer membrane vesicle (OMV) vaccines**²¹ Nonreplicated copies of parent bacterial cell which utilise 'bubble-like' structures from the bacterial surface have antigenicity that is equivalent to and a superior safety profile than intact yet attenuated bacterial cells. E.g., Bexsero MenB vaccine,

It usually takes 10-15 years to reach the market by using the above technology and for the multiplication or development of pathogens or their parts, they need biological systems (such as chicken eggs, cell cultures of bacteria or yeast, or plant or animal cells), which demands for the use of suitable biocontainment levels to prevent their environmental contamination.²²

V. THE NEWER VACCINES

1. **Platform-based vaccines**²³: The most recent platform-based immunizations for humans are given directly to the body in a variety of methods and are based on the genetic information of the pathogen.

Examples are:

- **DNA vaccines:** They make use of DNA from the pathogen. Once injected into the body, this might be duplicated as mRNA, which the body would then "read" to

produce pathogen proteins and start an immune reaction. 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 ZyCoV-D COVID-19 vaccine in India is the first DNA-based vaccine to be licenced for use in humans in an emergency.

- **mRNA vaccines:** Using the 'ready to read' mRNA to trigger the immune system's activation and the synthesis of a pathogen's protein 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.
- **Viral vector vaccines²⁶:** In this vaccine, a modified form of a virus delivers the genetic material encoding a particular antigen into the recipient's host cells. These platforms are used as a quick response to newly developing infectious diseases since they are quickly manipulated by modifying the genetic information they carry. However, not all ailments benefit favourably from these therapies. Ensure that we are ready for any risks in the future, vaccination technology must continue to evolve. As an illustration, most bacterial vaccinations are polysaccharide-based (as opposed to protein-based). Examples include the AstraZeneca COVID-19 vaccine and the rVSV-ZEBOV Ebola vaccine.
- **Live recombinant vaccines as vectors²⁷:** An immunogenic protein from another infectious agent is transported by a virus or bacteria from one disease. This strategy is sometimes used to stimulate the immune system, and other times it is applied when administering the actual substance as a vaccination would result in disease. For example, experimental recombinant vaccinia strains have been created to offer defence against a range of diseases, including as hepatitis B, rabies, and influenza.

VI. CURRENT DEVELOPMENTS

1. **Newer technologies:** New technologies in development will simplify and increase the efficacy of vaccine delivery.²⁸ Multiple shots might not be necessary due to emerging technologies and alternate adjuvants, which are currently being developed. Multiple antigens can now be delivered in single injection without affecting the immune response to every other. Less needles for patients and more effective vaccination administration overall result from this.²⁹⁻³²
2. **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
3. **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. 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

- 4. Preparation technique:** The vaccine provider would be able to prepare the component (with a fluid medium within the syringe) and deliver the vaccine simultaneously by placing it in a holder that could be attached to a syringe. With a stabilising strategy like this, widespread immunisation campaigns are also possible in previously difficult-to-reach areas.
- 5. 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.³⁸ A smartphone app called Electronic Vaccine Intelligence Network (eVIN) uses cloud computing to digitise data on vaccine stockpiles and temperatures across the nation.³⁹
- 6. Vaccine records:** Vaccine passport—a portable form of health data—can be a potential tool for health monitoring and notifications while preserving individual privacy.⁴⁰ Demographic data, the name and production information of the vaccine received, the date of vaccination, any acute adverse effects, and the length of protection are all included in the vaccine-related data of recipients. It serves as proof for the people who are vaccinated especially for the international travellers. The Ministry of Health and Family Welfare in India owns and operates CoWIN (Covid Vaccine Intelligence Network), a government web service for COVID-19 vaccination registration.⁴¹
- 7. Need of vaccines:** Most effective vaccines offer protection against acute (short-lived) illnesses primarily through the generation of antibodies, but chronic (long-lasting) infections, particularly those caused by HIV, TB, and malaria, continue to be difficult to treat. We do not yet have a vaccine for several illnesses that are linked to substantial long-term consequences. e.g. Streptococcal Infection & Rheumatic Fever

VII. CHALLENGES AND OPPORTUNITIES

Developments in fundamental research, animal testing, clinical trial design and approval, manufacturing, and distribution are among the challenges and possibilities for vaccine R&D. The vaccine hesitancy among the people poses the biggest challenge in vaccination which can be reduced by appropriate information and updates regularly. Learning everything there is to know about infections, the immune system, and the effects of a disease on the population (i.e., "epidemiology") is one of the most difficult tasks in vaccine research and development. The difficulty among older persons has been linked to an increased vulnerability to pathogenic pathogens and suboptimal vaccination responses due to the age-related dysregulation and immune system loss, commonly referred to as "immunosenescence."⁴²

VIII. RECENT INNOVATIONS IN FUNDAMENTAL RESEARCH FOR VACCINES

- 1. System-approaches in biology and immunology:** Instead of concentrating on individual components, these methods depend on a variety of experimental procedures integrated

with computational tools to gain knowledge of biological systems such as whole. For example, reverse vaccinology examines the pathogen's whole genetic material to determine the appropriate antigens to stimulate a potent immune response.⁴³ This approach may generate vaccines against complicated diseases, such as Meningococcus B (MenB).⁴⁴ It is possible to analyse genomes and a person's immune system to learn more about how they react to diseases or why some people have negative side effects from vaccination while others do not⁴⁵ and this would enable the creation of "personalised" vaccinations that are catered to the immune system of a particular person.⁴⁶

- 2. Structural biology approaches:** These want to comprehend how the immune system recognises antigens and their three-dimensional structure. By easing the choice of the optimal antigens, they improve efficient vaccine design when used in conjunction with computational approaches.⁴⁷ When dealing with complicated infections, this may be very beneficial. One of the first products made using this method was the respiratory syncytial virus (RSV) vaccine, which was first created for veterinary usage.^{48,49} The effectiveness of current vaccinations may be increased by utilising various adjuvants or other delivery systems as a result of a greater understanding of how to elicit the immune response.^{50,51} For example mucosal vaccinations (such as the nasal influenza vaccine for kids) cause an immune reaction at the mouth and nose level, guaranteeing the virus is halted 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 cells^{55,56}.

Vaccinations for animals and research with animals before beginning clinical trials, vaccination safety and effectiveness must be established in animal models, therefore having access to top-notch animal testing facilities is essential.

Clinical trial infrastructure that is flexible and Innovative clinical trial designs, such those that permit the trial's protocol or sample size to be modified when new data become available, have a role in hastening the development of vaccines.⁵⁷ Phases may be merged (for example, Phase 2 and Phase 3 may be combined), allowing data on vaccination immune response levels, adverse effects, and effectiveness to be gathered concurrently. Additionally, a strong infrastructure supporting clinical trials can facilitate quick resource allocation and participant recruiting.

- 3. Human challenge trials:** Human challenge trials can be used to show vaccine effectiveness in a limited group when a disease is not prevalent enough in the community to allow for the testing of vaccinations in traditional large-scale studies. To better explore correlates of protection, show that vaccinations offer protection, and compare various vaccines (allowing advancement of just those vaccines that look promising), healthy volunteers are "challenged" with small amounts of pathogen in a controlled setting throughout these studies.⁵⁸ Trials on humans aided in the creation of vaccines against cholera, malaria, influenza, and typhoid fever.⁵⁹⁻⁶² Human challenge trials must meet stringent safety and quality standards in order to be morally acceptable.

Innovation licencing in Clinical trial data is evaluated as they become available without waiting for the conclusion of the study using a "rolling-review strategy," which

has been used to simplify this process. Vaccination approval for COVID-19 is an example.^{4,63-65}

IX. THE WAY FORWARD

Vaccines are commonly viewed as being crucial for preventing the spread of communicable disease outbreaks and other emerging infectious disorders, like antibiotic resistance. Countries Should Prioritise and maintain the Important services including the immunization services when the threat rise. The benefits of immunisation are not distributed equitably due to stark differences in coverage across and within nations. In unstable, conflict-torn settings the most vulnerable, poor, and Marginalised people have limited access to immunisation programmes.

To ensure that everyone has access to immunisation services, vaccines must be distributed to marginalised populations such as refugees, migrants, those impacted by conflicts and natural disasters, as well as to geographically, culturally, socially, or otherwise isolated areas. It is important to recognise and address the low vaccination rates in order to increase public demand for immunisation services. 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 to offer immunisation services that are connected to primary healthcare, new strategies are required.

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