Development, Testing & Regulation of a Vaccine

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VACCINES are biological materials designed to generate active immunity against a particular disease. Vaccines mimic the infectious bacteria or viruses responsible for a disease. Inoculation of vaccines stimulates the immune system in the human body to build a defence against the infectious micro-organism (antigens) without causing the disease.

There are different kinds of vaccines available currently out of which few contain weakened versions of a bacteria or virus; others contain a specific part of the bacteria or virus, while a few vaccines contain only the genetic material for a specific protein (mRNA vaccines). In mRNA vaccines, the genetic material (a specific protein) asks the body to produce the required protein by itself stimulating the body to generate an immune response against the micro-organism.

After vaccination, our immune system reacts in two ways — direct immune response and adaptive immune response. Direct immune response generates antibodies. Antibodies are proteins that bind to specific parts of the bacteria or virus and prevent them from entering our cells. In adaptive immune response, the body generates memory cells (T-cells and B-cells). T-cells are a kind of white blood cells produced by our immune system which directly kill the infected host cells and activate other immune cells. B-cells produce an army of antibodies to fight bacteria or viruses when needed. Vaccination prepares our immune system to respond quickly and forcefully whenever the body is attacked with real bacteria or viruses.

Vaccines have existed since the late 19th century (*e.g.* plague, cholera, typhoid, etc.) but there was no regulation of vaccine production back then. On 1 July 1902, the American Congress passed an act 'to regulate the sale of viruses, serums, toxins and analogous products' which was later termed as the *Biologics Control Act* (BCA). The main reason for the formulation of this law were the contaminated smallpox and diphtheria vaccines that appeared in St. Louis and Camden (USA). It was the first law to control the quality of drugs. Much later, after the 1954 Cutter incident when a polio vaccine, manufactured by the California-based family firm of Cutter Laboratories, caused 40,000 cases of polio, leaving 200 children with varying degrees of paralysis and killing 10. Subsequently, the Division of Biologics Standards was founded, which became a part of *Food and Drug Administration* (FDA), USA, and is now known as the *Center for Biologics Evaluation and Research*.

In modern times, vaccine development and testing process follow several compulsory steps. The first stage is the exploratory stage involving the basic laboratory research and identification of synthetic antigens which have the potential to prevent or treat the disease. It may be virus-mimicking particles, attenuated viruses or bacteria, or other materials derived from pathogens. The second stage is the pre-clinical stage during which vaccine candidates are evaluated with the help of tissue culture and cell-culture systems followed by animal testing (on mice, rabbit or macaques primates, etc.) to assess their preliminary safety and immunogenicity. For COVID-19 vaccine candidates, most of the preliminary studies were performed on *macaques* – a species of old world monkeys.

Pre-clinical studies provide crucial information regarding cellular response in animals. In these tests, the initial dose of vaccine is also estimated in terms of safety. Several vaccine candidates fail to generate the immune response and are excluded from the process due to safety issues. After this procedure, the vaccine candidates are approved for clinical trials with human subjects by the Indian Council of Medical Research (in India) just like the Food and Drug Administration (in the USA). After this approval, the vaccine candidates are subjected to clinical trials with human subjects.

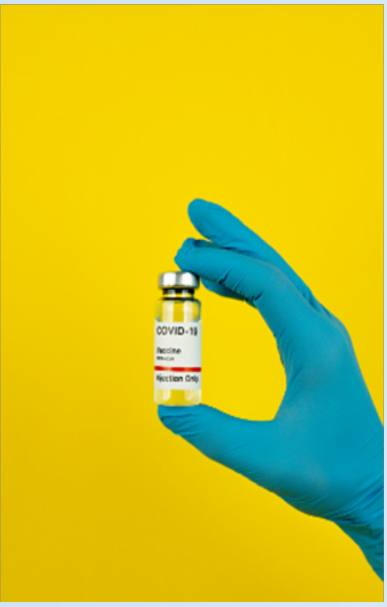
Clinical trial with human subjects is performed in three phases. In phase-I vaccine trial, small groups of adult healthy humans (with 20-80 people) are involved. The main goal of phase-I trial is to assess the safety of the vaccine candidate

and to determine the type and extent of immune response. The phase-I trial may be non-blinded which means the volunteer knows that he or she has been given the vaccine candidate or placebo (a saline solution, vaccine for another disease or some other non-harmful substance). After careful monitoring of volunteers in controlled conditions, the results of phase-I trials are analyzed. Sometimes, the vaccine candidate is modified according to need at this stage. On achieving promising results in phase-I, the trial moves to phase-II.

In phase-II trial of a vaccine candidate, a larger number of volunteers are involved and the trials are randomised and controlled. In phase-II, a few volunteers are also recruited who have more risk of acquiring the disease. The goals of phase-II trials are to assess the vaccine candidate's safety, immunogenicity, the appropriate drug dose, the number of vaccine shots needed and the method of vaccine delivery. After promising results in phase-II, the vaccine trial moves on to phase-III.

In phase-III trials, tens of thousands of volunteers are involved and the trials are randomised and double-blinded. It assesses the safety of the vaccine candidate among a very large number of randomised people and seeks the rare side-effects in diversified groups of volunteers. Phase-III seeks to find the side effects which were not visible in smaller groups of volunteers in controlled conditions. The vaccine efficacy is also assessed in a better way in these trials. The vaccine candidate is assessed on several parameters as to whether it prevents the disease or pathogen from infecting the person, whether antibodies are generated, whether T-cells are generated?

After successful phase III trials, the vaccine candidate is approved by an authorised agency in respective countries. In India, Central Drugs and Standards control organization (CDSCO) has the authority to approve a vaccine candidate. This committee approves the usage of a vaccine candidate on the recommendation by a Subject Expert Committee (SEC) of Technical Experts. This committee also approves whether the vaccine candidates will be used in emergency conditions or in normal conditions. The CDSCO continues to monitor the production of the vaccine material by inspecting the manufacturing facilities and analysing/reviewing batches of vaccines for their potency, safety and purity even after approval. It also has the right to test the vaccines of different batches in its own testing facilities to maintain the required parameters. Upon recommendation, the drug companies may conduct a phase-IV vaccine trial too after the release of a vaccine, if needed.



It is very important to gain public confidence in a vaccine and avoid/overcome the adverse side effects of the vaccines. In the USA, the *Vaccine Adverse Event Reporting System* (VAERS) was established in 1990 by CDC and FDA to detect possible signals of adverse events associated with vaccines. In the US, around 30,000 events are reported to VAERS every year out of which around 10-15% of cases are related to serious medical events for all available vaccines. VAERS is open to all the volunteers such as patient, family members, friends, doctors, and any other related person. VAERS was able to detect several adverse events like intestinal problems due to the first rotavirus vaccine in 1999 and neurologic and gastrointestinal diseases related to the yellow fever vaccine and many more.

Vaccine-making involves several crucial, costly and exhaustive steps which make it eligible for patenting and earning profit. Patenting of vaccines sometimes makes its availability hard for common people when they need it the most. However, many experts say that it is not the patenting laws but the management of patents that restrict the availability of a vaccine.

In 1995, *World Trade Organization* (WTO) formulated the *Trade Related Intellectual Property Rights* (TRIPS) which protects the patents and copyrights including for vaccines and other medical supplies. However, there is a provision to temporarily suspend these patenting laws in emergency situations. In the case of temporary suspension of patent laws, the rights of vaccine makers and the needs of the common public are balanced through 'compulsory licensing' as per the *Doha Declaration on TRIPS and Public Health*.

Under compulsory licensing, the legal authority in a country can grant specific permission to a person (who is not the rights holder) to exploit the patent-protected product under specific circumstances or in an emergency. During the COVID-19 crisis, the need to relax the patenting laws corresponding to several medical drugs and upcoming vaccines was realised. In October 2020, India and South Africa requested WTO TRIPS to consider a temporary waiver to suspend the TRIPS obligations on all medical products to control the COVID-19 pandemic. However, the proposal was discussed by 40 WTO members and opposed by most of the developed countries that own most of the patents related to the needed drugs.

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