EDITORIAL

Vaccine development: a time-consuming process

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Development of a successful vaccine is a time consuming and a complex process that may take 10-15 years. During the 20th century, standardized procedures and regulations have been adopted for developing, testing, and regulating vaccines development.

Although at the end of the 19th century, for humans several vaccines were developed, such as smallpox, rabies, plague, cholera and typhoid vaccines but there were no regulations for vaccine production.

In the US, in 1902, the first legislation to control the quality of drugs was made which was later named as "Biologics Control Act" that regulates the sale of viruses, serums, toxins, and analogous products. Infect this act was developed in response to contamination of smallpox vaccine and diphtheria antitoxin. The objective of the Act was to oversee hygienic conditions of the Public Health Service laboratory of manufacture of biological drugs which was eventually designated as National Institutes of Health. By virtue of this Act government's right to control the establishments of vaccines was made. Later Public Service Act of 1944 authorized federal government to issue licenses for biological products, including vaccines. However, in 1954, due to the incidence of poliovirus vaccine, Division of Biologics Standards was made to observe vaccine safety and regulation that finally emerged as Food and Drug Administration (FDA).

In the European Union, there is European Medicines Agency which supervises vaccines and other drugs regulation. However, World Health Organization has made recommendations for the biological products which have been adopted internationally by many countries [1].

Stages of Vaccine Development

The initial stages are exploratory in nature. Regulation and oversight increase as the candidate vaccine makes its way through the process.

Early steps: laboratory and animal studies

It consists of basic laboratory research which may be up to 2-4 years where natural or synthetic antigens are identified to prevent or treat the disease. These antigens could be bacteria, virus, their toxins or weakened forms of bacteria or viruses, etc.

Pre-clinical stage

This stage often lasts for 1-2 years that uses tissue-culture technique and laboratory animal testing to assess the safety or ability to mount an immune response. By virtue of this scientists may have an idea about cellular immune responses in humans. In this way, safe dose and method of vaccine administration can be suggested for the next phase of the research.

Researchers may take up challenge studies, e.g., animals are vaccinated followed by infection of these animals with the target pathogen. If the candidate vaccine fails to produce the desired immune response they do not go to the next stage [2].

Investigational new drug (IND) application

IND is often submitted by a private company (sponsor) to the U.S. FDA. Here, the sponsor is bound to provide details of its manufacturing, testing process, laboratory reports, and the proposed study. The application must have approval of the

protocol from the institutional review board where clinical trial is supposed to be carried out. After the approval of IND application, the candidate vaccine undergoes three phases of testing [3].

Clinical studies with human subjects

Phase I vaccine trials

This phase includes a small group of human adults usually 20-80 to assess the candidate vaccine. If the tested vaccine is for children, the researchers will first test it on the adults, and if the results are encouraging then they gradually decrease the age of the subjects until target population is tested. This stage is normally non-blinded, i.e., the researchers and the subjects are aware whether a vaccine or placebo is used.

Phase I assesses the safety, the type and extent of immune response provoked by the candidate vaccine. In some Phase I vaccine trials, researcher uses challenge model where the experimental group is vaccinated and then they are infected with the pathogen. For a challenge study, normally an attenuated, or modified, version of the pathogen is used. These participants are carefully monitored. Encouraging results of this phase will allow the progress of candidate vaccine into next stage.

Phase II vaccine trials

In this phase a larger group, i.e., several hundred individuals participate. Here, some of the subjects may belong to the risk of acquiring the disease. Normally these are randomized trials and include a placebo group as well. The aim of this phase is to study safety, immunogenicity, proposed doses, schedule of immunizations, and method of delivery of the candidate vaccine. Successful results of this phase lead the vaccine to the next stage.

Phase III vaccine trials

It involves larger population, i.e., thousands to tens of thousands of subjects for candidate vaccine. It is randomized and double blind and includes the experimental vaccine being tested against a placebo. Here vaccine safety is assessed in a large group of subjects. In the earlier phase, on small subjects, certain rare side effects might not be detected. It is suggested that to detect a significant difference for a rare side effect of low frequency, the trial should have 60,000 subjects and half of them should be in the control group [4].

At the end of this phase, the researcher has answers to the following questions:

1) Does the candidate vaccine prevent disease? 2) Does it prevent infection with the pathogen? 3) Does it lead to produce antibodies or immune responses related to the pathogen?

Approval and licensure

If the results of the Phase III trial are successful, the sponsor will submit a Biologics License Application to the FDA. After satisfactory inspection report of the factory, FDA will approve the application of that vaccine. FDA can carry out its own testing of manufacturers' vaccines. Even after issuance of licensure, FDA continues to monitor the production of vaccine, i.e., inspection of facilities and test potency, safety, and purity of the vaccine.

Post-licensure monitoring of vaccines

Once the vaccine is approved by the FDA, there are still different ways for the surveillance of the vaccine e.g., Phase IV trials, the vaccine adverse event (VAERS) reporting system, and the vaccine safety datalink (VSD).

Phase IV trials

After the release of a vaccine in the market, there comes phase IV trial which is optional for the drug companies. Here, the manufacturer intent to test safety, efficacy, and other potential uses of the vaccine [4].

Vaccine adverse event reporting system (VAERS)

In 1990, the VAERS was established by The Centre for Disease Control (CDC) and FDA. The CDC mentioned the purpose of VAERS as "to detect possible signals of adverse events associated with vaccines." Each year around 30,000 events are reported and among these 10%-15% are serious medical events which need hospitalization, life-threatening illness, disability, or death.

This system is open to everyone and anyone can report to this system, i.e., health care provider, even a friend of the patient, who thinks that vaccination causes an adverse effect, may report it to VAERS. Then comes the role of CDC to investigate the event and confirm or discard the claim.

The CDC states that they monitor VAERS data to

- Detect new, unusual, or rare vaccine adverse events
- Monitor increases in known adverse events
- Identify potential risk factors for particular types of adverse events
- Identify vaccine lots with increased numbers or types of reported adverse events
- Assess the safety of newly licensed vaccines

It is noted that all the adverse events reported to VAERS are not due to vaccination and not all the adverse events caused by the vaccination are reported to this system. The CDC admits that serious adverse events are likely to be reported while minor events such as swelling at the injection site are seldom reported.

Followings are the rare adverse events to vaccination identified by the VAERS [2]:

- In 1999, after the first vaccine for rotavirus, an intestinal problem
- Neurologic and gastrointestinal diseases due to yellow fever vaccine
- Need for investigation of association of MMR with a blood clotting disorder, encephalopathy and syncope

Vaccine Safety Datalink (VSD)

In 1990, VSD was established by the CDC. It is a linked databases of information from medical groups. It facilitates officials to collect data regarding vaccination from people observed by the medical groups.

Like all other systems, VSD also have some drawbacks e.g., unvaccinated children are also entered, medical groups provide information that may not be true representative of large populations. Further, data is from actual medical practice and it is not from randomized, controlled, blinded trials, therefore data cannot be evaluated.

In 2005, another program of VSD by the name of "Rapid Cycle Analysis" was started that compares the rate of adverse events in vaccinated with the unvaccinated subjects. It is used to monitor new vaccines such as conjugated meningococcal vaccine, rotavirus vaccine, MMRV vaccine, Tdap vaccine, and HPV vaccine. Under this program possible associations between adverse events and vaccination are studied further [5].

Conclusion

Similar to drugs, vaccines are also manufactured, tested, and regulated in the same way. Rather, the criterion for vaccines is more stringent as more humans are involved clinical trials for vaccines. Furthermore, even after issuance of license, monitoring of vaccines is closely performed by the CDC and the FDA.

Conflict of interest

None to declare.

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