Addressing the Rapidly Evolving Vaccine Development Landscape

Highlights:

- The history of vaccine development shows scientific innovation
- Tenets of vaccine development and COVID-19's impact
- Operational considerations are always a factor, but even more critical during times of rapid change
- Expanding technologies and new considerations impact vaccine development

Introduction

Among all the rapid changes in clinical research initiated by COVID-19, none is quite as intensely focused as vaccine development. The history of vaccine development has been driven by scientific innovation and discovery, learning from successes — and failures — over the years. From 1796, when Edward Jenner used cowpox pustules to inoculate against smallpox, to the first true virus vaccines created at the turn of the 20th century to the polio vaccine in 1955 to the 2020 race for a coronavirus vaccination, vaccine development has undergone constant change responding to population health crises.

One thing has been constant, however: Vaccine development takes time. On average, it takes about 10 years to make a vaccine. One of the fastest ever was for Ebola, which took five years. On the other hand, the vaccine for HIV has been in the works for 36 years. Yet today, researchers are tasked with developing a vaccine in record speed to tackle a major pandemic.

One reason vaccine development typically takes a long time is because the highest levels of safety are required. The general public has low tolerance for adverse events; since vaccines are typically administered to healthy persons, there can be some reluctance to become vaccinated because of perceived "exposure" to a virus.

National regulatory authorities (NRAs) rigorously ensure quality, safety, and effectiveness of vaccines. Prior to being introduced, vaccines are thoroughly assessed in clinical trials. Once introduced, vaccines are exhaustively and continuously reviewed. NRAs monitor and investigate adverse events following immunization (AEFIs) to ensure safety for the population.

With the current landscape, urgency to speed the process is being escalated under pressure to control the pandemic, but safety and efficacy still must remain a priority.

Types of Vaccines

Understanding COVID-19 vaccine development is predicated on understanding the four main types of vaccines:

Live attenuated (LAV), or weakened virus: Typically, these have long-lasting response; one drawback is they need to be kept cool, limiting their use in certain areas of the world. Examples include tuberculosis, oral polio, measles, and rotavirus.

Inactivated (killed antigen): These generally have fewer side effects, but they're not quite as strong, necessitating booster shots. Examples include whole-cell pertussis and inactivated polio.

Subunit (purified antigen): Using a specific piece of the virus, a strong response is seen but a booster is often necessary. Examples include hepatitis B and pneumococcal.

Toxoid (inactivated toxins): This uses a toxin made by virus to create immunity, but again, it may necessitate a booster. One example is tetanus.

Tenets of Vaccine Development

In vaccine development, the ultimate goal is to develop a vaccine that is effective in preventing or reducing the severity of an infectious disease — and ensuring the vaccine itself does not make a situation worse. As researchers press timelines with COVID vaccine development, this premise is paramount. Other tenets that vaccine developers strive to include:

- Achieve immunity with a minimal number of doses
- Cause no or mild adverse events
- Make available for general use through mass production
- Provide durable, long-term protection against disease
- Provide maximum number of antigens to confer broadest protection against infection
- Remain stable at extremes of storage conditions over prolonged periods of time
- Are affordable to populations at risk for the targeted infectious disease

Questions that arise with the accelerated vaccine development of COVID-19 are among these tenets — for example, will a booster be needed in six months? Will the vaccine be stable in extreme storage conditions, ensuring it is useful throughout the world's climate zones? Will it be affordable?

Operational Considerations

Especially in the high-speed, high-stakes landscape of vaccine development during a pandemic, operational considerations can have a profound impact.

Choosing the right sites is critical:

- Geography and regulatory environment are critical; if you are doing an outcomes trial, it should be done in an area with a high incidence and prevalence — if you are looking for antibodies, it can be done in other locations
- Consider the incidence of the virus; looking for naive versus previously exposed patients factors into site selection
- Can the sites deliver endpoints, and do they have the bandwidth to take on the trial?

Another consideration is patient recruitment and patient retention:

- Sites, CROs, and sponsors need to have enough resources to deal with high patient throughput
- For pediatric patients, parental commitment is needed, along with clear/concise diaries
- Elderly patients may need caregiver support and transportation
- Depending on the progression of the vaccine and current conditions, patients may need long-term follow up, such as immunogenicity testing and booster vaccinations

Again, safety is paramount. Preset quality checks are necessary after a set number of patients are enrolled, ensuring safety and allowing for issues to be addressed and mitigated.

Beyond operational considerations, some logistical considerations include immunogenicity testing (such as sample collection timing and processing and shipping), CMI response/PBMC testing/biopsies (including site training and the many months to train local labs), and cold chain considerations (for example, some vaccines must be maintained at -70 degrees Celsius, and distribution to sites and patients is a factor).

Impact of COVID-19 on Vaccine Development Process

COVID-19 is a watershed moment for vaccine development, accelerating timelines under great pressure. The impact includes:

- Changes to all future vaccine development
- Interaction with regulators
- Adaptive designs
- Manufacturing at risk

The disruption continues across all areas of development — for example, accelerated timelines mean sponsors are starting Phase I while already looking ahead for sites for Phase II and Phase III studies. And there are potential bottlenecks on the manufacturing side, including complications that previously did not exist, such as a shortage of glass vials and stoppers, or locating facilities that have the required sterile environment for manufacturing and fills.

New Considerations for Vaccine Development

Pressing onward with vaccine development in the current challenging and high-pressure climate leads to focus on Phase II and Phase III considerations regarding patient recruitment and surveillance — the importance of following patients for safety and continued serology testing. And it throws open wide the opportunity for virtual or decentralized trials to minimize risk and increase patient convenience and access.

While the ultimate impact of COVID-19 is still unknown, it has undeniably changed the landscape of vaccine development. Drawing from lessons of the past while employing the technology of today, innovation and perseverance will be the key to successfully developing and implementing a COVID-19 vaccine.