VACCINES: HOW AND WHY THEY WORK

Since the start of this pandemic, not only have we searched for "a cure" for SARS-CoV-2, the world's top health experts and scientists have also sought to develop a vaccine (or multiple vaccines) to immunize and protect the public (CDC, 2020). Ideally, a perfect vaccine will prevent an individual from getting COVID-19 without any harmful/deleterious effects (e.g., think of childhood vaccines that protect against Rubella, Measles/Mumps, etc.).

The purpose of a vaccine is not only to protect an individual; but, once many others are also vaccinated, it will create a "herd immunity" that protects those individuals who are unable to be vaccinated due to health reasons, age, etc. (WHO, 2020; Figure 1).

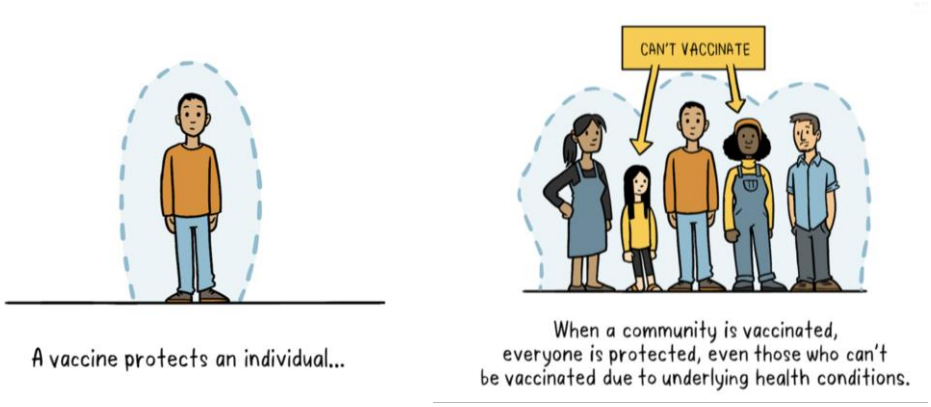

Figure 1. Vaccine protection (Source: WHO, 2020)

However, to ensure that the COVID-19 vaccine (or any vaccine) is safe, the process of development until implementation can be lengthy and time/resource consuming due to the need to carefully study, evaluate, and test not only the vaccine's efficacy (how well the vaccine works against SARS-CoV-2) but also its safety (ensuring it doesn't cause bodily harm).

In that way, vaccine development does not happen in a vacuum; companies, researchers, and governmental organizations worldwide have teamed up and collaborated on developing various types of vaccines. For example, the World Health Organization (WHO) began the COVAX Initiative as a means of pooling the purchasing power and research knowledge of all participating countries to ensure rapid access to safe and effective doses of vaccines upon receiving regulatory approval.

Vaccines go through a number of stages before being approved for general use, as depicted in the New York Times graphic below (Figure 2). The article also reported that (as of December 02, 2020) 58 vaccines were in clinical trials on humans and at least 87 preclinical vaccines under investigation (being tested with animals).

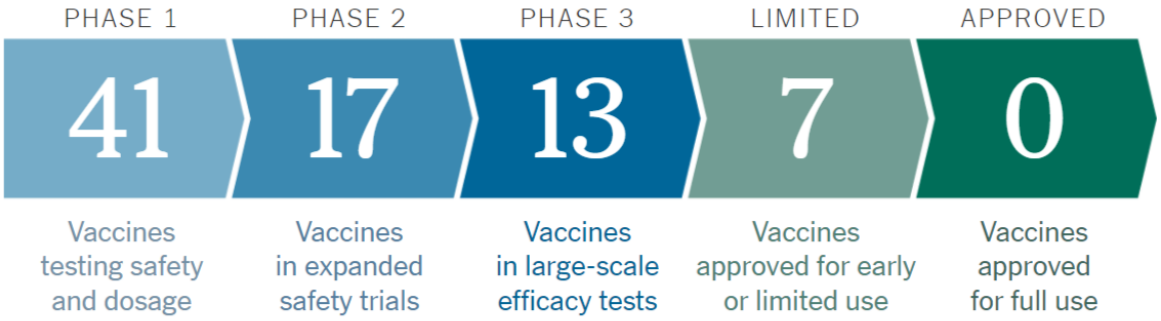

Figure 2. Vaccine phases updated on December 02, 2020 (Source: New York Times)

In a recent COVID-19 Recommendations for Industry article, TAG also provided a summary of the top three vaccines currently in trial periods. What exactly does all this mean?

The Trials and Tribulations of a Vaccine's Lifespan

All vaccine development must undergo a series of phases (Vaccine Testing Process) before the vaccine can be considered effective, safe, and widely distributed to the public (Figure 3).

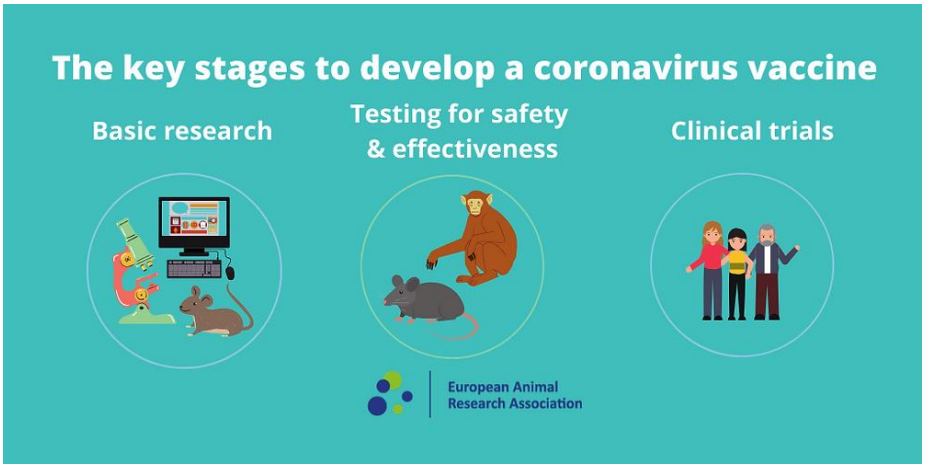

Figure 3. Process by which vaccines are developed. (Source: European Animal Research Association, 2020)

Think of these as "hurdles" that need to be successfully attained to move to the next step, with all focused on efficacy and safety:

- Pre-clinical Testing – In this "pre-phase" scientists test a new vaccine on cells and then on animals (e.g., mice, monkeys, hamsters) to see if an immune response (in which the body develops a resistance and protects against the bad bug) is triggered. It is important to understand the vaccine's potential toxicity levels, approximate dosage ranges, and drug formulations. If a positive immune response is produced, then the vaccine may move to Phase 1.
- Phase 1 – In this phase, the test for the vaccine is on safety. The vaccine will be given to a limited number of individuals who will be assessed for a stimulated immune system (e.g., antibody production ability to fight the virus if the body encounters the virus). Safety trials seek to assess the vaccine's safety (no negative affects to the person) and determine viable dosages. In Phase 1 trials, one small subset of people will be given the trial vaccine while another group (the "control") is given

a placebo. The purpose of this is to determine if there are any differences between the two groups. If this phase is successful, the vaccine development moves to Phase 2.

- Phase 2 – With the data from Phase 1 showing that the vaccine should be safe to proceed, Phase 2 expands the study to include many more individuals who are also studied based on specific demographics (e.g., gender, age) to see if the vaccine affects different populations in different ways. This phase continues to test the safety and ability to stimulate the immune system (e.g. to produce antibodies that will fight the virus if your body encounters it). If Phase 2 is promising, then the study expands into the largest phase, Phase 3.
- Phase 3 – Thousands of individuals are vaccinated in the Phase 3 trials which determine the ultimate efficacy of the vaccine. In this phase, researchers determine how effective the vaccine is when individuals are exposed (either deliberately or through their daily lives) and compare the vaccine's efficacy in producing an immune response in vaccinated individuals to those given only a placebo. Ideally, a vaccine is determined efficacious when at least 50% of vaccinated individuals are protected. Since Phase 3 includes many more people than the previous phases, this is also where negative side affects may become more evident.

After the phases are completed, the vaccine must go through an approval process. Normally, the Vaccine Development Phases will take many years and undergo multiple rounds or review, discussion, and scrutiny. However, in special circumstances, such as the COVID-19 pandemic which has, itself, been swift, some of the phases are combined to hasten the rate of development. Additionally, in the United States, the approval process can be shortened as an *Emergency Use Authorization*.

If at any time something goes wrong or negative side affects occur, a vaccine process can and will be paused at any phase (as have been at least three COVID-19 vaccine trials) so researchers can ascertain the root of the problem.

What is Being Used to Make the Vaccines?

Vaccines can be made in a variety of ways. However, all vaccines require something to activate a body's immune system (e.g., to trigger and prime our bodies to fight the virus). Currently, for viruses, vaccine development falls into two groups: protein-based or gene-based (Abbasi, 2020).

- **Protein-based vaccines** are made from whole inactivated (killed/dead) viruses or virus-like protein particles (pieces and parts of a once-whole virus). There is no genetic material from the coronavirus in protein-based vaccines. Some current protein-based vaccines are polio, flu, Hepatitis B, and HPV. Protein-based vaccines deliver a part of the virus to the body's immune system, which learns what that virus might "look like" and is stimulated to develop antibodies to fight against that "print" (Abbasi, 2020).
- **Gene-based vaccines** bring the genetic blueprint of the virus parts to the body (in COVID's case, it's the spiky surface proteins that gives the virus its corona ["crown"] name). The goal is for the body to understand how this spiky protein is made and develop an antibody response to protect *against* it in the future (Abbasi, 2020). This may include providing the body with a live-attenuated virus (a not-so-virulent version of a virus), viral vectors, DNA, or mRNA. In the latter three, researchers make and "insert genetic instructions from the pathogen of interest to induce immune responses" (Abbasi, 2020). In this case, measles, mumps, and rubella are examples of live-attenuated virus.

Currently, both protein-based and gene-based vaccines are being developed and tested.

- Within gene-based **Genetic Vaccines,** both **mRNA** (messenger RNA) and **DNA**-based vaccines seem to be gaining traction and moving into Phase 3 trials.

    - Originally started as an idea, COVID-19 has catalyzed the fruition and development of **mRNA vaccines**. mRNA vaccines are looked upon as an exciting venture as they are unlikely to cause an infection (Abbasi, 2020). The mRNA vaccine "teaches our cells how to make a protein" that will then go on to trigger an immune response inside our bodies (CDC, 2020)! Additionally, long-term risks are assumed to be mitigated as the human body quickly breaks down mRNA. However, because of the quick breakdown, mRNA vaccines are given in two doses. Two companies, Moderna and Pfizer, are in Phase 3 trials with mRNA vaccines (with Pfizer reporting a 90% efficacy); two mRNA vaccines are in Phase 2; and at least three are in Phase 1 or a Pre-clinical Phase.
    - **DNA**-based vaccines incorporate the DNA sequence "encoding the antigen(s) against which an immune response is sought" and relies on the body to produce the target antigen (WHO, 2020). Currently, there are two DNA-based vaccines (one through skin absorption) being tested in Phase 2, four in Phase 1, and others in Pre-clinical.
- In the gene-based vaccines sector, **Viral Vector Vaccines** also are proving to be effective. In these, the vaccines contain viruses that themselves carry coronavirus genes. Some of these viral vectors will enter the body's cells causing them to make viral proteins; others will replicate in the body and present coronavirus proteins on the surface to which the body can then develop antibodies and "learn" to attack/evade during a true infection.
    - There are currently four viral-vector based vaccines in Phase 3 (and approved for limited use). They include those developed by CanSino Biologics in China (with limited use in China); Gamaleya Research Institute in Russia (with limited use in Russia); a collaboration with Johnson & Johnson (with results expected by end of year); and a collaboration with AstraZeneca.
    - Eight DNA-based vaccines are currently in Phase 1, and many more are still in Pre-clinical Phases.
- Within the **Protein-Specific Vaccines**, in which proteins are used, there is currently only one vaccine that has made it to Phase 3. Manufactuered by Novavax, it launched Phase 3 trials in the UK in November and will begin Phase 3 trials in the US in December. Five (5) protein-based vaccines are in Phase 2 (2/1) trials, while 12 are in Phase 1, and many more are in Preclinical Stages.
- Finally, there are a number of vaccines being developed through **Inactivated (Dead/Killed) or Attenuated (Weakend)** coronaviruses. There are currently four vaccines in Phase 3 (with some approved limited use). Although some vaccine volunteers have developed side effects, in the U.A.E., two such vaccines produced with Sinopharm and Wuhan Institute of Biological Products and Sinopharm with Beijing Institute of Biological Products are allowed for limited use by health care workers. Sinovac Biotech's vaccine, in Phase 3, has also achieved emergency approval for limited use within China. Finally, Bharat Biotech, an India-based and supported company, will soon begin Phase 3 trials on their vaccine. Two vaccines are in Phase 2 development, four (4) in Phase 1, and a few others in Pre-clincial stages.

In the attempt to develop new vaccines, some that were developed for other purposes and diseases are being repurposed to determine their efficacy and protection against coronavirus. For example, the Bacillus Calmette-Guerin vaccine (for protection against tuberculosis) is in Phase 3 testing through the Murdoch Children's Institute.

Ultimately, the race to develop vaccines against COVID-19 is enabling the world to explore and chart new territories and utilize technologies that, until now, have not all been wholly proven to be effective. While this will take time, patience, understanding, and collaboration, together we are ensuring that we can continue to protect everyone around us.