While healthcare organisations across the globe have launched the quest for a vaccine for Covid 19, let us try to understand the basics of how vaccines are produced and how they work.

THE RACE TO DFEVELOP THE COVID VACCINE

Are we there yet?

Dr Lalit Singh

Introduction

We are seeing intense research activity across several laboratories and major pharma/biotech companies, who are all trying to be the first to launch a vaccine against Covid-19. As per WHO data, more than 100 such R&D efforts are currently underway across dozens of labs and sites. Every small or big news from these efforts is received with a lot of enthusiasm and gives people greater hope for an early breakthrough.

Several eminent people have predicted that a vaccine for Covid-19 could be available by or before end of this year. Can there be any truth in these claims? Russian media has reported that the local regulatory bodies are all set to launch a vaccine for masses by August 12th. Is that really possible? And how, if so?

Let's try and explore if we can really have a vaccine for Covid-19 in such a quick timeframe! But, before we get to the point, let's start by understanding what is a vaccine, how do vaccines build immunity in individuals, why ensuring large scale immunization in a population is required for deriving the real benefits from a vaccine and how are vaccines actually developed. A deeper understanding of these aspects will give us the right context to analyse and evaluate some of these sensational news/sentiments about a vaccine for Covid-19.

What is a vaccine?

According to Oxford Vaccine Group, "a vaccine is a type of medicine that trains the body's immune system so that it can fight a disease it has not come into contact with before."

A vaccine stimulates human immune system to produce antibodies against the disease causing organism in the same way as it would do if it were infected with the real live organism. Thus on being vaccinated for a certain disease, one develops immunity to that disease without having to get the disease first. In other words, a vaccine prevents a disease by harnessing the natural activity of human immune system.

The immune response of human body can be viewed as immediate/ primary response of body's immune system to first introduction of the microorganism, which is led by T-cells, and a secondary response of body's immune system to repeated exposure to the same microorganism, which is led by memory B-cells. Vaccination helps trigger long term immunity in the body without the need for an initial exposure to the disease-causing microorganism, but still leading to generation of memory B-cells.

As per WHO, we now have vaccines for over twenty life-threatening diseases, like diphtheria, tetanus, pertussis, influenza, and measles, immunization for which helps prevent approximately 2-3 million deaths every year.

How do vaccines help an individual build immunity?

There are a few different types of vaccines –

1. **Live attenuated vaccines** – These vaccines contain the live disease-causing organisms, but in extremely weakened form which upon introduction in human body, trigger appropriate and sufficient immune response, but do not induce full blown disease. Example – Measles, Mumps, Rubella and Influenza vaccines.
2. **Inactivated vaccines** – These vaccines contain killed disease-causing organisms, which trigger an appropriate and sufficient immune response, but again do not cause full blown disease. Example – Polio IPV, Hepatitis A and Rabies vaccines.
3. **Subunit/conjugate vaccines** – Some newer vaccines don't contain entire organism, but only a specific protein/carbohydrate molecule of that organism, which when introduced in human body, triggers the

appropriate immune response without causing the disease. Example – Hepatitis B, Pneumococcal, HPV and Influenza vaccines.

4. **Toxoid vaccines** – Some bacteria cause harm to human body by secreting toxins. It's possible to deactivate such natural toxins and use them to trigger an appropriate immune response in human beings without causing any harm to the body. Example – Diphtheria and Tetanus vaccines.
5. **Nucleotide (DNA/RNA) Vaccines** – Unlike in traditional vaccines, where we introduce an antigen (dead/attenuated disease-causing organism or a protein/carbohydrate molecule from this organism) in human body to trigger an immune response, in case of DNA/RNA based vaccines, we introduce only a specific portion of DNA/RNA of the causative organism in human body and that leads to production of the antigen in human body itself. This technique is still experimental, but, if successful, this technique can help develop efficient, cheaper and easier to produce vaccines for mass usage. This technique is currently being used to develop vaccines for Influenza and Herpes, both of which are in human testing phases.
6. **Recombinant vector vaccines** – These are another group of experimental vaccines, which are similar to nucleotide vaccines as these also rely on the DNA/RNA of the harmful pathogen to trigger the desired immune response in human body. But, these vaccines also use an attenuated virus or bacterium as a vehicle to introduce pathogen's DNA/RNA in human body. In other words, this technique involves dressing up a harmless bacterium/virus with the DNA/RNA of a disease-causing organism for introduction into human body with an intent to trigger an appropriate immune response to build immunity. This technique is currently being tried to develop vaccines for HIV, Rabies, and Measles.

How do vaccines work at community/population level?

So, now that we know how vaccines help build immunity among vaccinated individuals, we need to also understand how vaccination helps control diseases at a larger scale and at community/ population levels. It is also important because an individual's vaccine-induced immunity for some of the diseases may actually fade with time, and this requires booster immunization at required frequency/times. If booster immunization is not done in a timely manner, some of these previously vaccinated individuals may still get the disease on being exposed to the pathogen in future. A community or herd level immunity towards the given pathogen provides additional protection to individuals in such cases.

Herd immunity essentially means immunity at a herd/population level. We can say that herd immunity has been attained against a given pathogen when a significant portion of the given population becomes immune against that pathogen. Attainment of herd immunity essentially means that the further person-to-person spread of the disease will not take place, or in other words, the entire community is now protected against that particular disease. Several deadly communicable diseases, like smallpox, polio, diphtheria, and rubella have been controlled globally by mass vaccination using the concept of herd immunity.

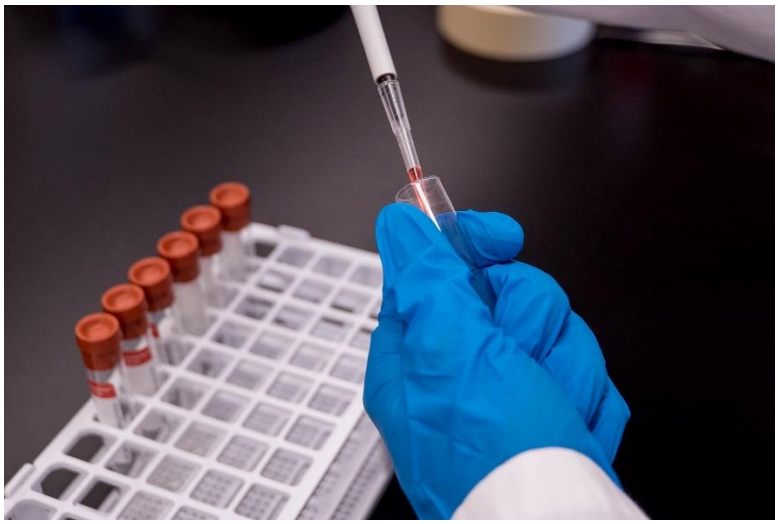
However, a minimum percentage of the given population needs to develop immunity against a particular disease before herd immunity can set in. This minimum percentage, also known as "herd immunity threshold", varies from one to another disease condition and basically depends upon the infectivity of the pathogen in question. In general, higher the infectivity of the pathogen, higher is its "herd immunity threshold", which simply means that a larger portion of the population needs to develop immunity against this disease at individual levels before the immunity can set in at a population level. For example, Measles is a highly contagious disease and thus the "herd immunity threshold" value for Measles is 94%.

While the evidence on the infectivity of Covid-19 is still evolving, it is estimated that one infected individual typically spreads the disease to 2-3 uninfected individuals. This means that the "herd immunity threshold" for Covid-19 is close to 65-70%, or that at least 65-70% of a given population will need to develop immunity against Covid-19 before we could say that further spread of disease would now be minimal or that the population has attained herd immunity against Covid-19.

There are two ways for a population to develop herd immunity against a given pathogen — vaccination and natural infection. Vaccination is always a safer and preferred route to herd immunity as it doesn't require the community to have active infection and disease. Vaccination would be preferred and an ideal approach to build herd immunity against Covid-19 also. However, until we have a vaccine available for mass consumption and we are able to immunise 65-70% of each of the sub-populations, natural infection would remain the main route to build herd immunity, which essentially means that individuals will get naturally infected – while most will remain asymptomatic or have minimal discomfort before they recover and get immune to Covid-19, some people with lower immunity will get full blown disease also.

What is the process of vaccine development?

Development of a novel vaccine – the first vaccine developed for a disease – is a fairly complex and elaborate process and goes through multiple stages. The process of vaccine development can broadly be divided into preclinical and clinical stages. Preclinical phase of development basically involves laboratory experiments and animal studies, and the clinical phases of development include human trials. A very small percentage of candidate vaccines actually progress from laboratory/animal studies to clinical trials on human beings.



The clinical (human) phase of vaccine development is further divided into three phases - Phase I, Phase II, and Phase III, which typically take place in that order only. After successful completion of Phase III trials and following required regulatory approvals, the vaccine is made available for mass inoculation. But, even then the phase IV studies, also known as post-marketing surveillance studies (PMS), continue to monitor the vaccine for safety and effectiveness at a population level. This requires precise data capture, collation, analysis and reporting for adverse effects of the vaccine using standard tools and techniques.

1. **Phase I clinical studies**

The phase I clinical studies involve administration of a candidate vaccine to human beings with a primary objective to evaluate its safety, tolerability and reactogenicity. These are typically small trials and are conducted in otherwise healthy adults who are at low risk of acquiring a vaccine induced infection. The volunteers in Phase I trials are kept under close observation and are thoroughly investigated using pre-approved protocols. These volunteers are carefully monitored, preferably in tertiary clinical settings, to watch out for any clinical signs of infection.

Adult studies can then be followed up with further phase I studies in other target populations, like children or elderly etc. in order to find out any potential differences in dosage, safety, schedule, or route of administration of the vaccine.

2. **Phase II clinical studies**

A candidate vaccine which has been found to be safe enough in a phase I clinical study progress to phase II studies. Phase II studies are typically conducted on a larger and pre-defined set of human beings (hundreds to a few thousands), located across multiple sites in order to have the desired statistical power. Therefore, these studies deliver a stronger and more reliable report on safety, immunogenicity, and efficacy of the candidate vaccine.

The primary objective of phase II clinical trial is to identify the vaccine preparation, dosage, schedule of administration, and duration of follow up for further validation in Phase III studies. Phase II studies also help to identify different types of adverse effects and detect any differences in adverse effects between different groups of population. The specific adverse effects are then further evaluated in larger Phase III studies. Sometimes multiple phase II studies need to be conducted for more conclusive answers to these questions.

The study population can comprise adults, adolescents, children, or pregnant women, depending on the study objective. The study population is typically also diverse enough to take care of gender, ethnic, and racial variances in response.

3. Phase III clinical studies

The phase III vaccine trials are statistically strong population level studies, which involve thousands of people from the target population to allow testing for as many population variables as possible.

The main focus of phase III vaccine studies is to evaluate its efficacy and safety in the target population. Many a times, phase III studies continue for a longer period of time to study the likely long-term protection benefits of the vaccine and identify the need for a booster dose for continued protection. Therefore, these studies are conducted in "real-life" conditions, under which the vaccine, if the trial is successful, would be administered.

The most accepted way to conduct a phase III trial for a candidate vaccine is to conduct a Prospective Randomised Controlled Trial (RCT), typically across multiple sites to include as much diversity in samples as possible. The participants of a typical multicentric, prospective, randomised controlled trial are randomly allocated to two groups – the participants in the "study" group receive the candidate vaccine, whereas those belonging to the "control" group receive a control vaccine, or a placebo, or nothing at all. The construct of the RCT ensures that there is no bias in selection of "study" group and multicentricity ensures a wider spectrum of members from target population get represented in the trial. A single study may not be able to address all questions; therefore it is often necessary to test the vaccine under different conditions, disease patterns, and populations.

4. Phase IV clinical studies

Successful RCT is mandatory for applying for required regulatory approvals for a wide-scale usage of any candidate vaccine. Clinical studies on the vaccine continue even after successful completion of phase III studies and regulatory approvals for mass adoption. This phase of clinical study is also known as phase IV study or simply "Post-marketing surveillance (PMS)". PMS allows researchers to study an approved vaccine over an even longer term and over a much larger population for its longer term safety, efficacy and effectiveness.

So, we can see that the whole process of vaccine development for human beings - starting with phase I trial till regulatory approval of the vaccine – is rather long process, that too for all good reasons. It's important to have any candidate vaccine go through these phases to ensure safety, efficacy, and effectiveness of the vaccine before it gets approved for large populations of otherwise healthy individuals. Well done phase III trials (powerful enough multicentric randomized controlled studies) are required to prove that the candidate vaccine is actually safe for use and triggers required immunity against the pathogen and also for studying the duration this immunity lasts so as to plan the appropriate booster schedule for the vaccine.

Where are we with a vaccine for Covid-19?

There are a few different routes being taken by different groups of researchers –

1. The first candidate vaccine to get into limelight was from Moderna Therapeutics, which produced a candidate vaccine for clinical trials within just 42 days of the release of genetic sequence of Covid-19 virus. While this certainly was a commendable effort from the scientists involved in this work, we have to also remember that the underlying technology behind its development – putting virus's DNA/RNA into human cells, where this DNA/RNA induces production of the protein that, in turn, triggers an immune response by the human body (please refer to nucleotide vaccines described above) – has been known for last 30 years and is yet to deliver a working vaccine for any human disease. While it's quicker to produce DNA/RNA based candidate vaccines and such vaccines have shown potential in animal models, they haven't ever delivered the results in human trials.
2. AstraZeneca and J&J have taken the alternative Recombinant vector vaccine approach. As described above, this technique involves stitching the DNA encoding the "full-length spike protein" of Covid-19 into the common-cold virus, which acts as the vector for the Covid-19 DNA. This presumably is a more efficient approach to transport the spike-protein DNA into human cells, where it stimulates immune response to Covid-19. The phase II trial using this technique has delivered promising results in the study carried out by AstraZeneca at Oxford University, although the study was conducted on a homogeneous population. We will know more about the success of this approach as the phase III trials are now underway.
3. A group of researchers in China have been working on the time-tested "inactivated virus vaccine" model, which involved using the inactivated virus to trigger immune response in human subjects. The initial results of the phase II clinical study using this approach have been encouraging, and this candidate vaccine is now entering phase III clinical study.

Can we fast track development of Covid-19 vaccine?

There have been suggestions from several media and policy experts to fast track the process of vaccine development to get a Covid-19 vaccine out for mass usage at the earliest. Let's examine how the process could be fast tracked and what could fast tracking of process mean for us.

Some good and productive ways to fast track the development of vaccine would include –

1. Fast tracking administrative steps in the process to design/approve trials.
2. Collaboration and information/data sharing across labs, corporations and governments.
3. Pooling of funds, research capabilities and infrastructure during research phase so that trials on multiple candidate vaccines can be conducted in parallel, rather than in series.
4. Pooling of capital, manufacturing capacities and supply chain for quicker and more efficient manufacturing and distribution of the approved vaccine.
5. Avoiding "vaccine nationalism" once we finally get a vaccine in order to allow vaccine induced herd immunity to settle in faster.

Not so good ways to fast track development of vaccine include –

1. Let it become an ego issue for specific research labs, nations or politicians and not allow the scientists to do their job in the most efficient and scientific manner.
2. Fall for the temptation to skip steps in vaccine development process. For example:
    a. "Human-challenge" trials – "Human-challenge" trials include giving the candidate vaccine to healthy people and then deliberately exposing these people to the disease to see if they exhibit any immunity. These trials should only be conducted in cases where the safety of the vaccine has been established and there is a highly effective treatment already available for the

disease. Example, these trials are ethically permissible for some of the candidate vaccines for Malaria. These are a clear "No" for Covid-19 because we still do not have a definitively curative treatment for Covid-19.

b. Skipping critical phase III trials altogether – If the unverified news reports coming from Russia are to be believed, the regulators there are planning to allow one of the candidate vaccines for immunizing large populations on successful completion of phase II trials. As explained in the vaccine development process above, such an approach can prove to be disastrous.

There is no denying the fact that if all the nations and corporates come together to fast track the vaccine development in the right manner, the research can certainly be fast tracked and we can surely hope to get an effective vaccine out within next 12 months. And, such a collaborative approach could actually set a new, more effective, and quicker model of advancing medical science.

What should we do in the meantime?

Until a vaccine against Covid-19 gets approved and is made available for global consumption, we need to continue to take all measures to minimise person-to-person transmission of disease. We have to always remember that a large number of people who get Covid-19 infection actually will not show any symptoms while they could still be spreading the infection. It is especially important to safeguard the most vulnerable people in our society, like the elderly people, toddlers and other people with chronic debilitating illness, whose overall immunity is lower.

Some of the simple preventive measure we all can take include –

- Staying at home as far as possible and encouraging work from home, wherever possible.
- Maintaining "social distancing" (a safe distance of 6 feet) while in public spaces or while dealing with anyone who has got Covid-19 symptoms.
- Not organizing/attending large events such as wedding functions and religious gatherings.
- Frequent and proper handwashing with soap and water or using alcohol-based hand sanitizers for cleaning hands.
- Wearing a face mask covering both mouth and nose, while we are out in public spaces.
- Covering our mouth and nose with elbow or disposable tissue while coughing or sneezing.
- Not touching our eyes, nose or mouth repeatedly.
- Cleaning all frequently touched surfaces like doorknobs, light switches, kitchen counters, etc. on a regular basis.

In case someone has symptoms suggestive of Covid-19, they should, in addition to abovementioned steps, also take following additional precautions –

- Isolate themselves at home and avoid contact with others in the family/neighbourhood.
- Keep themselves hydrated and consult a doctor immediately for potential testing/treatment.

- Avoiding travelling unless going out for medical attention, and especially avoid using public transport as far as possible.

- Always wear a face mask - one that covers both mouth and nose, and avoid touching the mask repeatedly.

Conclusion

While new scientific developments can surprise us any time and we could actually have a vaccine for Covid-19 very soon, going by the previous data and our accumulated knowledge about the process of vaccine development over last several decades, it's difficult to reliably predict if we will have a safe and effective vaccine for Covid-19 even in next one year.

We also need to keep in mind that vaccine trials are far more complex than drug trials because unlike drugs, which are given to people having a specific disease, vaccines are given to otherwise healthy individuals. Therefore, we need to ensure we allow adequate testing of the candidate vaccines for their safety profile during early phases of the trials, else the results can be disastrous. For example, the candidate vaccine for SARS (a related coronavirus), actually enhanced the disease during experiments on animal models, and thus had to be dumped.

Hopefully with collaboration among scientists, corporations and countries, and with availability of required funds to fast track the clinical trials, we will see this record getting broken without really compromising on the quality and scientific rigor of the development process, but even then we need to be a little more pragmatic in our forecasts. And till the time we get a vaccine, we need to stay alert and exercise all preventive measures to avoid contracting/ disseminating the disease.

About the Author

Dr Lalit Singh

Managing Director – McGraw Hill Education, India

Dr Lalit Singh is a senior executive with over eighteen years of cross-functional experience in Healthcare and Education industries. He firmly believes that both Healthcare and Education are core social sectors, which will play the most crucial role in transforming India into a developed country.

Dr Lalit is passionate about application of appropriate technology to drive a real transformation in Healthcare and Education in India. He strongly believes that technology is the means and not the outcome; technology has to be intelligent and not indulgent - ultimately here to solve on-ground real time problems in both Healthcare and Education spaces. This passion along with an innate ability to challenge the status quo drove Dr Lalit to change his career track from an accomplished clinician to a technocrat and eventually a management professional.

Dr Lalit is currently the Managing Director at McGraw Hill India and is driving digital transformation of the Education business for this 50-year strong brand in India. Prior to McGraw Hill, he has led several initiatives in Medical Education, Research and Clinical Solutions at Elsevier over a period of ten years and, prior to that, also served as a Senior Resident doctor in Trauma Surgery at All India Institute of Medical Sciences, New Delhi. Dr Lalit has been consistently recognized for his innovative, human-centric approach to management. He was voted as “Person of the year” by staff at McGraw Hill India in January 2020. Earlier, Dr Lalit received the CEO’s “Lead the way” award for “Developing best in class talent” in year 2017. He was also recognized as “Innovation Champion”, and “Strategy Champion” for his product leadership at Elsevier.

Dr Lalit completed his MBBS and MS (General Surgery) from JN Medical College, Aligarh Muslim University and then earned a full-time MBA from the prestigious National University of Singapore.