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AN OVERVIEW ON COVID-19 VACCINES IN INDIA

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ABSTRACT
This review article outlines the key concepts of differences between corona virus and flu and current status of vaccine discovery process in India. There is a new public health crises threatening the world with the emergence and spread of 2019 novel corona virus (2019-nCoV) or the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2).Corona viruses are enveloped positive sense RNA viruses ranging from 60 nm to 140 nm in diameter with spike like projections on its surface giving it a crown like appearance under the electron microscope; hence the name corona virus. The disease is transmitted by inhalation or contact with infected droplets and the incubation period ranges from 2 to 14 d. Influenza is an acute respiratory disease caused by the influenza A or B virus. It often occurs in outbreaks and epidemics worldwide, mainly during the winter season. Significant numbers of influenza virus particles are present in the respiratory secretions of infected persons, so infection can be transmitted by sneezing and coughing via large particle droplets. The mean duration of influenza virus shedding in immune competent adult patients is around 5 days but may continue for up to 10 days. The pandemic declaration of Covid-19 disease by World Health Organization (WHO) and subsequent widespread morbidities and mortalities in almost all countries of the world led to the research and development to find out a vaccine against SARS-CoV2 virus. Normally any new vaccine development takes 10–15 y time but the search for vaccine against SARS-CoV2 is going on at a very fast pace resulting in almost breakthrough in vaccine development by several research institutions and vaccine manufacturers. In India, there are three vaccine developers are currently working on vaccine discovery with large number of scientist. The article ends with the vaccine development phases and present scenario on development of corona vaccine in India and improves health outcomes through life course.

KEYWORDS: Corona virus, Flu, Clinical stages, Vaccine status.

INTRODUCTION
In December 2019, a novel corona virus called SARS-CoV-2 has resulted in the outbreak of a respiratory illness known as COVID-19.Corona virus disease (COVID-19) is an infectious disease caused by a newly discovered corona virus. Most people who fall sick with COVID-19 will experience mild to moderate symptoms and recover without special treatment. There is a new public health crises threatening the world with the emergence and spread of 2019 novel corona virus (2019-nCoV) or the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). Corona viruses are enveloped positive sense RNA viruses ranging from 60 nm to 140 nm in diameter with spike like projections on its surface giving it a crown like appearance under the electron microscope; hence the name corona virus. The disease is transmitted by inhalation or contact with infected droplets and the incubation period ranges from 2 to 14 d.[1] Influenza is an acute respiratory disease caused by the influenza A or B virus. It often occurs in outbreaks and epidemics worldwide, mainly during the winter season. Significant numbers of influenza virus particles are present in the respiratory secretions of infected persons, so infection can be transmitted by sneezing and coughing via large particle droplets. The mean duration of influenza virus shedding in immune competent adult patients is around 5 days but may continue for up to 10 days.

Entry of Corona virus is mediated by S-glycoprotein which protrudes from the viral surface as homotrimeric trans membrane protein. S-glycoprotein assembled into trimetric conformation on the surface of the virus to form the typical “corona”, or crown-like appearance. S-glycoprotein is essential for membrane fusion, receptor binding, internalization, tissue tropism, and host range. S-glycoprotein consists of two functional subunits S1, required for the attachment to cellular receptors and S2, involved in viral and cell membrane fusion. The S-glycoprotein is cleaved from the interface of S1 and S2

subunits that remains non-covalently linked in perfusion conformation. S1 subunit is required for the stability of perfusion conformation of membrane linked S2 subunit. To activate the S-glycoprotein, host proteases are involved in the processing of spike protein specifically at the S2′ site present at the upstream fusion peptide which ultimately requires for its membrane fusion activity.

It is often stated that vaccination has made the greatest contribution to global health of any human intervention apart from the introduction of clean water and sanitation, but this is a claim that needs some qualification. Study of the pattern of infectious diseases in industrialized countries from the end of the nineteenth century onwards shows that there was a large and progressive decline in child mortality, owing largely to a reduction in mortality from infectious diseases, prior to the development and deployment of vaccines.

As per the recent nation-wide survey data, of the targeted annual cohort of 26 million infants in India, only 61 per cent had received all due vaccines. In India, till 1850, the vaccine was imported from Great Britain. However, there were real logistic challenges in transport of vaccine to India. The increased demand in later years led to the shortage of vaccine or lymph in the country and mandated the Government of India to find alternatives for increasing sustained vaccine supply.[2]

Serious symptoms of corona virus

Difficulty breathing or shortness of breath, chest pain or pressure, loss of speech or movement seek immediate medical attention if you have serious symptoms. Always call before visiting your doctor or health facility. People with mild symptoms who are otherwise healthy should manage their symptoms at home.

On average it takes 5–6 days from when someone is infected with the virus for symptoms to show, however it can take up to 14 days.[3]

How corona virus spreads

The virus that causes COVID-19 is mainly transmitted through droplets generated when an infected person coughs, sneezes, or exhales. These droplets are too heavy to hang in the air, and quickly fall on floors or surfaces. You can be infected by breathing in the virus if you are within close proximity of someone who has COVID-19, or by touching a contaminated surface and then your eyes, nose or mouth.[3]

COVID-19 affects different people in different ways. Most infected people will develop mild to moderate illness and recover without hospitalization.

It may be possible that a person can get infected by physical human contact (e.g. shaking hands) or by touching a surface or object that has virus on it and then touching his or her own mouth, nose, or possibly their eyes.

Both flu virus and the virus that causes COVID-19 may be spread to others by people before they begin showing symptoms, with very mild symptoms or who never developed symptoms (asymptomatic).[4]

Influenza (Flu) Viruses

There are two main types of influenza (flu) virus: Types A and B. The influenza A and B viruses that routinely spread in people (human influenza viruses) are responsible for seasonal flu epidemics each year.[5]

While seasonal influenza (flu) viruses are detected year-round, flu viruses are most common during the fall and winter. The exact timing and duration of flu seasons can vary, but influenza activity often begins to increase in October. Most of the time flu activity peaks between December and February, although activity can last as late as May.[6]

How Flu Spreads

People with flu can spread it to others up to about 6 feet away. Most experts think that flu viruses spread mainly by droplets made when people with flu cough, sneeze or talk. These droplets can land in the mouths or noses of people who are nearby or possibly be inhaled into the lungs. Less often, a person might get flu by touching a surface or object that has flu virus on it and then touching their own mouth, nose, or possibly their eyes.

People with flu are most contagious in the first three to four days after their illness begins. Most healthy adults may be able to infect others beginning 1 day **before** symptoms develop and up to 5 to 7 days **after** becoming sick. Children and some people with weakened immune systems may pass the virus for longer than 7 days.

Symptoms can begin about 2 days (but can range from 1 to 4 days) after the virus enters the body. That means that you may be able to pass on the flu to someone else before you know you are sick, as well as while you are sick. Some people can be infected with the flu virus but have no symptoms. During this time, those people may still spread the virus to others.

You may be able to pass on flu to someone else before you know you are sick, as well as while you are sick.

- People with flu are most contagious in the first 3-4 days after their illness begins.
- Some otherwise healthy adults may be able to infect others beginning 1 day **before** symptoms develop and up to 5 to 7 days **after** becoming sick.
- Some people, especially young children and people with weakened immune systems, might be able to infect others with flu viruses for an even longer time.[7]

Both COVID-19 and flu can spread from person-to-person, between people who are in close contact with one another (within about 6 feet). Both are spread mainly

by droplets made when people with the illness (COVID-19 or flu) cough, sneeze, or talk. These droplets can land in the mouths or noses of people who are nearby or possibly be inhaled into the lungs.

What is the difference between Influenza (Flu) and COVID-19?

Influenza (Flu) and COVID-19 are both contagious respiratory illnesses, but they are caused by different viruses. COVID-19 is caused by infection with a new coronavirus (called SARS-CoV-2) and flu is caused by infection with influenza viruses.

There are some key differences between flu and COVID-19. COVID-19 seems to spread more easily than flu and causes more serious illnesses in some people. It can also take longer before people show symptoms and people can be contagious for longer. Another important difference is there is a vaccine to protect against flu. There is currently no vaccine to prevent COVID-19. The best way to prevent infection is to avoid being exposed to the virus. More information about differences between flu and COVID-19 is available in the different sections below.

Because some of the symptoms of flu and COVID-19 are similar, it may be hard to tell the difference between them based on symptoms alone, and testingmay be needed to help confirm a diagnosis. Flu and COVID-19 share many characteristics, but there are some key differences between the two.[8]

Here are some similarities and differences explained between common cold and flu.

COMMON COLD vs. FLU

Signs and Symptoms	**Cold**	**Influenza (Flu)**
Symptom onset	Gradual	Abrupt
Fever	Rare	Usual; lasts 3-4 days
Aches	Slight	Usual; often severe
Chills	Uncommon	Fairly common
Fatigue, weakness	Sometimes	Usual
Sneezing	Common	Sometimes

Symptoms of Corona virus and Flu

Both COVID-19 and flu can have varying degrees of signs and symptoms, ranging from no symptoms (asymptomatic) to severe symptoms. Anyone can have mild to severe symptoms. **Older adults and people who have severe underlying medical conditions** like heart or lung disease or diabetes seem to be at higher risk for developing more serious complications from COVID-19 illness. People with COVID-19 have had a wide range of symptoms reported – ranging from mild symptoms to severe illness. Symptoms may appear **2-14 days after exposure to the virus.** People with these symptoms may have COVID-19.Influenza (flu) can cause mild to severe illness, and at times can lead to death. Flu is different from a cold. Flu usually comes on suddenly. People who have flu often feel some or all of these symptoms.

CORONA vs. FLU

Signs and Symptoms	
CORONA	**Influenza (Flu)**
Fever or chills	Fever or feeling feverish/chills.It's important to note that not everyone with flu will have a fever.
Cough	Cough
Sore throat	Sore throat
Congestion or runny nose	Runny or stuffy nose
Muscle or body aches	Muscle or body aches
Headache	Headaches
Fatigue	Fatigue (tiredness)
Diarrhea	Some people may have vomiting and diarrhea, though this is more common in children than adults.
New loss of taste or smell	------
Nausea or vomiting	------
Shortness of breath or difficulty breathing	------

This list does not include all possible symptoms.[9]

Approved Treatments

People at high-risk of complications or who have been hospitalized for **COVID-19 or flu** should receive supportive medical care to help relieve symptoms and complications.

Flu: Prescription influenza antiviral drugs are FDA-approved to treat flu.

People who are hospitalized with flu or at high-risk of flu complications with flu symptoms are recommended to be treated with antiviral drugs as soon as possible.

COVID-19: The National Institutes of Health (NIH) has developed guidance on treatment of COVID-19external icon, which will be regularly updated as new evidence on treatment options emerges.

While remdesivir is an antiviral agent that is being explored as a treatment for COVID-19 and is available under an Emergency Use Authorization (EUA), there are currently no drugs or other therapeutics approved by the Food and Drug Administration (FDA) to prevent or treat COVID-19.

Vaccine

Flu: There is multiple FDA-licensed influenza vaccines produced annually to protect against the 3 or 4 flu viruses that scientists anticipate will circulate each year.

COVID-19: Currently there is no vaccine to prevent COVID-19. Vaccine developers and other researchers and manufacturers are expediting the development of a vaccine to prevent COVID-19.[9]

Globally, as of 5:58pm CET, 21 December 2020, there have been 75,704,857 confirmed cases of COVID-19, including 1,690,061 deaths, reported to WHO.[10]

CURRENT SCENARIO OF VACCINES IN INDIA

In INDIA, there are three manufacturers in an event to strive down by defeating or establishing superiority over corona virus. The various producers of corona vaccine which are in pipeline are listed here.

a. **Serum Institute of India Pvt. Ltd. (Pune, Maharashtra, INDIA - 411028)**
b. **Bharat Biotech (Hyderabad, Telagana INDIA – 500 078)**
c. **Zydus Cadila Healthcare Ltd. (Ahmadabad, Gujarat, INDIA – 382225)**

(1) Serum Institute of India Pvt. Ltd. is now the world's largest vaccine manufacturer by number of doses produced and sold globally (more than 1.5 billion doses) which includes Polio vaccine as well as Diphtheria, Tetanus, Pertussis, Hib, BCG, r-Hepatitis B, Measles, Mumps and Rubella vaccines. It is estimated that about 65% of the children in the world receive at least one vaccine manufactured by Serum Institute. Vaccines manufactured by the Serum Institute are accredited by the World Health Organization, Geneva and are being used in around 170 countries across the globe in their national immunization programs, saving millions of lives throughout the world.

(2) Bharat Biotech creates innovative vaccines and bio-therapeutics trusted by physicians around the world. We own 160 global patents and our products help people in over 65 countries live to their fullest potential. Their manufacturing facilities are approved by USFDA, KFDA and WHO. They have delivered over 3 billion vaccine doses all over the world and their key priority is to solve the health challenges of the developing world by developing innovative vaccines and therapeutics.

(3) Zydus Cadila Healthcare Ltd. is one of the largest privately-held pharmaceutical companies in India. Over the past six decades, they have been developing and manufacturing affordable medicines for patients around the world. Their innovation-led drug discovery processes ensure the health and well-being of people around the world. Their enhanced investment in innovation and a strong track record in research and development have produced medical miracles that have changed lives and made a profound impact on real life.

CLINICAL STAGES OF VACCINE DEVELOPMENT

Preclinical stage: This stage of development uses a platform of tissue-culture or cell-culture systems and animal testing to assess the safety of the candidate vaccine and its immunogenicity. Animal studies using mice, rabbits, guinea pigs, monkeys etc., according to the antigens, are used to find out the immune response and also side-effects related to the candidate vaccine. These studies provide researchers an idea of the cellular responses they might expect in humans. They may also suggest the safest starting dose for the next phase of research as well as the safest method of administering the vaccine. Many researchers in this stage try challenging the animals with the offending organisms to find out the efficacy in preventing the infection or severity of the disease. This stage usually takes 1–2 y and out of 100 potential candidates, 6 usually pass through this stage. The regulatory authority is informed about the candidate vaccine with full data and the sponsor company for manufacturing and undertaking the next clinical stages is identified.

Clinical stages of development consist of at least 3 stages and the 4th post-marketing safety assessment is also mandatory.

Clinical trial **phase I:** In Phase I, a small number of healthy adult volunteers usually between 20 and 80 subjects are administered the candidate vaccine. If the vaccine is intended for children, researchers will first test adults, and then gradually step down the age of the test subjects until they reach their target. Phase I trial is usually an open label trial where both researchers and subjects are aware of what vaccine has been given. The aim of phase I trial is to assess the safety as well the type of immune response the candidate vaccine may produce. In some of the instances, in this stage, the participants are challenged with the pathogens under carefully monitored and controlled environment to find the real effect of the vaccine. The data is analyzed and if it shows promising result, the trial progresses to the next phase.

In **Phase II** vaccine trial, a larger group of several hundred individuals participate in testing. Some of the individuals may belong to the groups at risk of acquiring the disease. These trials are randomized and well controlled, and include a placebo group.

The goals of **Phase II** testing are to study the candidate vaccine's safety, immunogenicity, proposed doses, schedule of immunization, and route of administration.

In **Phase III** of the trial, vaccine safety in a large group of people is tested. If the chance of side-effects is 1:1000, then a sample size of approximately 60,000 subjects is to be included in the trial. In this stage the immunogenicity of the trial vaccine is tested, e.g., production of critical level of antibodies/cell-mediated immunity and also whether it prevents infection by the infecting agent as well as protects from the disease.

After a successful Phase III trial, the vaccine manufacturer shall submit application for biological license of the product to the licensing authority (in India, it is Drug Controller General of India). The licensing authority then physically verifies the vaccine and if satisfied, gives permission.[11]

Latest Keynotes

(1) Serum Institute of India Pvt. Ltd.

Serum Institute of India (SII), the world's largest vaccine manufacturer by volume, and **Indian Council of Medical Research (ICMR)**, the apex body in India for biomedical research, announce completion of enrolment of phase 3 clinical trials for COVISHIELD in India. ICMR and SII have further collaborated for clinical development **COVOVAX (Novavax)** developed by Novavax, USA and up scaled by SII. The partnership is a stellar example of private-public institutes collaborating to mitigate the dire consequences of the pandemic outbreak.

ICMR has funded the clinical trial site fees while SII has funded other expenses for **COVISHIELD**. At present, SII and ICMR are conducting Phase 2/3 clinical trial of COVISHIELD at 15 different centers, across the country. It has completed the enrolment of all 1600 participants on 31 Oct 2020. COVISHIELD has been developed at the SII Pune laboratory with a master seed from Oxford University/Astra Zeneca. The vaccine made in UK is currently being tested in large efficacy trials in UK, Brazil, South Africa and USA. The promising result of the trials so far gives confidence that **COVISHIELD** could be a realistic solution to the deadly pandemic. **COVISHIELD** is by far the most advanced vaccine in human testing in India. Based on the Phase 2/3 trial results, SII with the help of ICMR will pursue the early availability of this product for India. SII has already manufactured 40 million doses of the vaccine, under the at-risk manufacturing and stockpiling license from DCGI.[12]

(2) Bharat Biotech

COVAXIN, India's indigenous COVID-19 vaccine by Bharat Biotech is developed in collaboration with the Indian Council of Medical Research (ICMR) - National Institute of Virology (NIV). The indigenous, inactivated vaccine is developed and manufactured in Bharat Biotech's BSL-3 (Bio-Safety Level 3) high containment facility.

The vaccine received DCGI approval for Phase I & II Human Clinical Trials and the trials commenced across India from July, 2020.

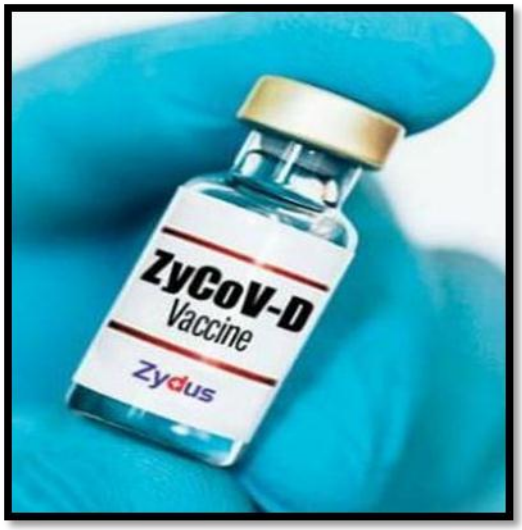
After successful completion of the interim analysis from the Phase 1 & 2 clinical trials of **COVAXIN**, Bharat Biotech received DCGI approval for Phase 3 clinical trials in 26,000 participants in over 25 centres across India.[13]

(3) Zydus Cadila Healthcare Ltd.

Ahmadabad-based pharmaceutical major Zydus Cadila's COVID-19 candidate vaccine **ZyCov-D** is likely to enter Phase III final stage of clinical trials by December. If all goes well, the vaccine should be ready for launch by March, next year. Further, Zydus is working on a second vaccine for COVID-19 and its pre-clinical data will be ready by January.

ZyCov-D is currently undergoing second phase of clinical trials in India among 1,048 volunteers and trial data is likely to be available next month. "So far it has been progressing smooth and solid and it is not fair to comment on the results until we complete the trials," said Pankaj Patel Chairman, Zydus Cadila. Zydus is planning to start the final phase trial by December among 30,000 volunteers, which will be the largest COVID-19 trial in India.

The company has created an in-house manufacturing capacity of 100 million doses per year and has roped in a contract manufacturer to make additional capacities to make about 150 million doses a year. Regulatory agencies worldwide, including the Indian regulator the Drug Controller General of India (DCGI), are expected to clear COVID-19 vaccines with an 'emergency use authorization' to start immunization, once the vaccines successfully undergo trials. The phase I dosing of **ZyCoV-D** was to establish safety and the phase II clinical trials are to evaluate the safety and immunogenicity of the vaccine in a larger population. Unlike the dead and live virus vaccines being tried by many vaccine makers, **ZyCov-D** is a plasmid DNA vaccine. In this, plasmid DNA, a small circular piece of DNA found in the cells would be introduced into the host cells, where it would be translated into the viral protein and elicits a strong immune response in the human immune system.[14]



CONCLUSION

In India, from Jan 3 to 5:34pm to 20 December 2020, there have been 10,031,223 confirmed cases of COVID-19 with 145,477 deaths. The success of immunization depends highly on the level of cold chain maintenance. Immunization is one of the best efforts that India is putting forward currently to fight against various vaccine preventable diseases. India had started its Universal Immunization Program (UIP) in 1985 focusing more on infants and pregnant mothers. The country spends a lot of money every year on immunization. The success of this program depends highly on the level of cold chain maintenance of the vaccines right from the site of manufacturing up to its administration. Urban Health Centers (UHCs), set up under various Municipal Corporations, have been the backbone for delivering services related to immunization in urban areas in India. It is thereby important that cold chain system be adequately maintained at these centers. Masks should be used as part of a comprehensive strategy of measures to suppress transmission and save lives; the use of a mask alone is not sufficient to provide an adequate level of protection against COVID-19.If COVID-19 is spreading in your community, stay safe by taking some simple precautions, such as physical distancing, wearing a mask, keeping rooms well ventilated, avoiding crowds, cleaning your hands, and coughing into a bent elbow or tissue. Check local advice where you live and work.

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