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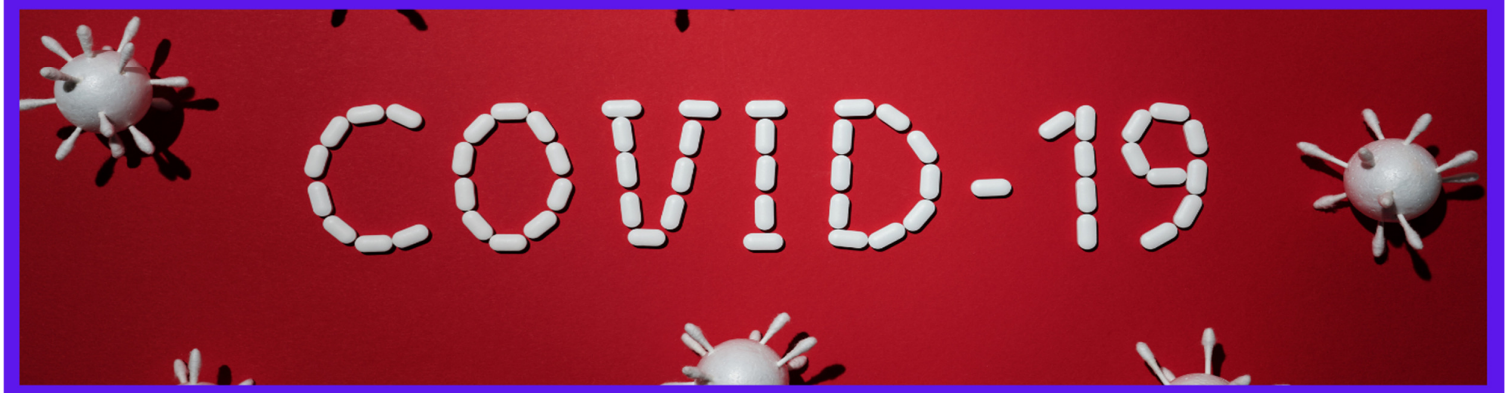

Genetic Variation of COVID-19 and Vaccine Development

Different Vaccines and their effects

Plant-Based Adjuvanted Covid-19

Moderna Vaccine Shot Against the Flu and COVID

PharmaMedical Trend Analysis

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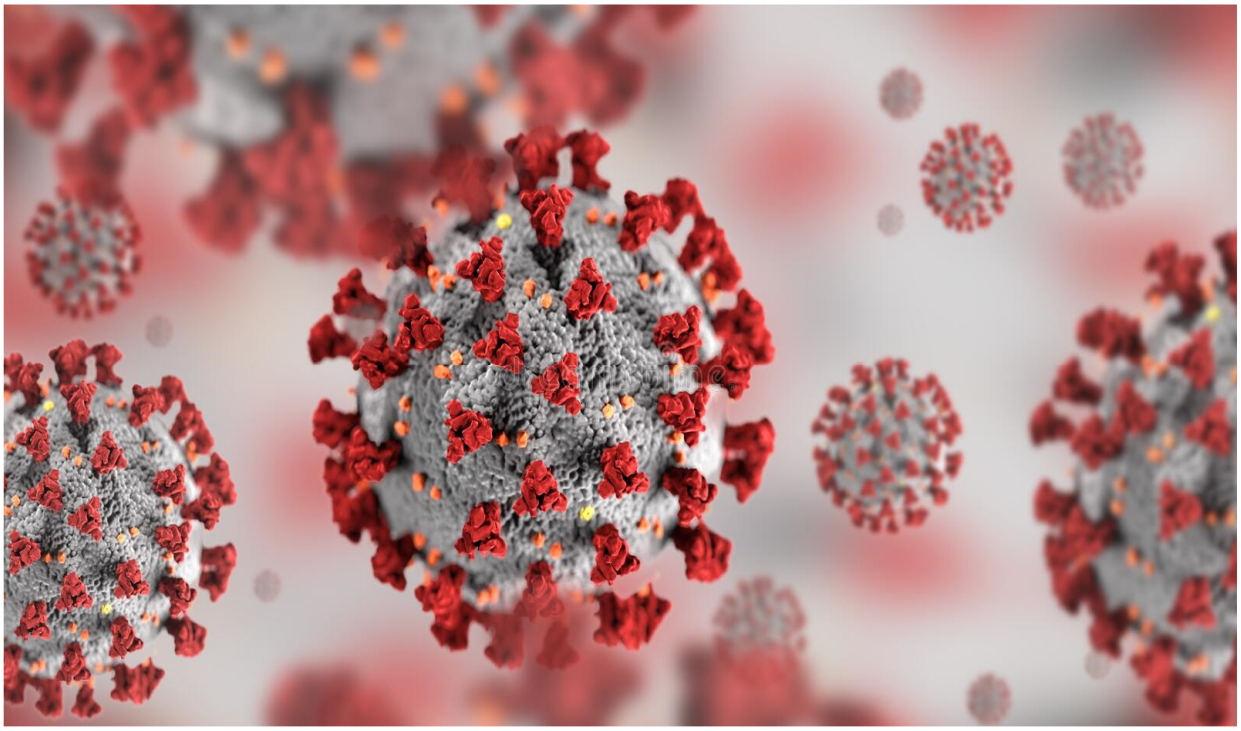

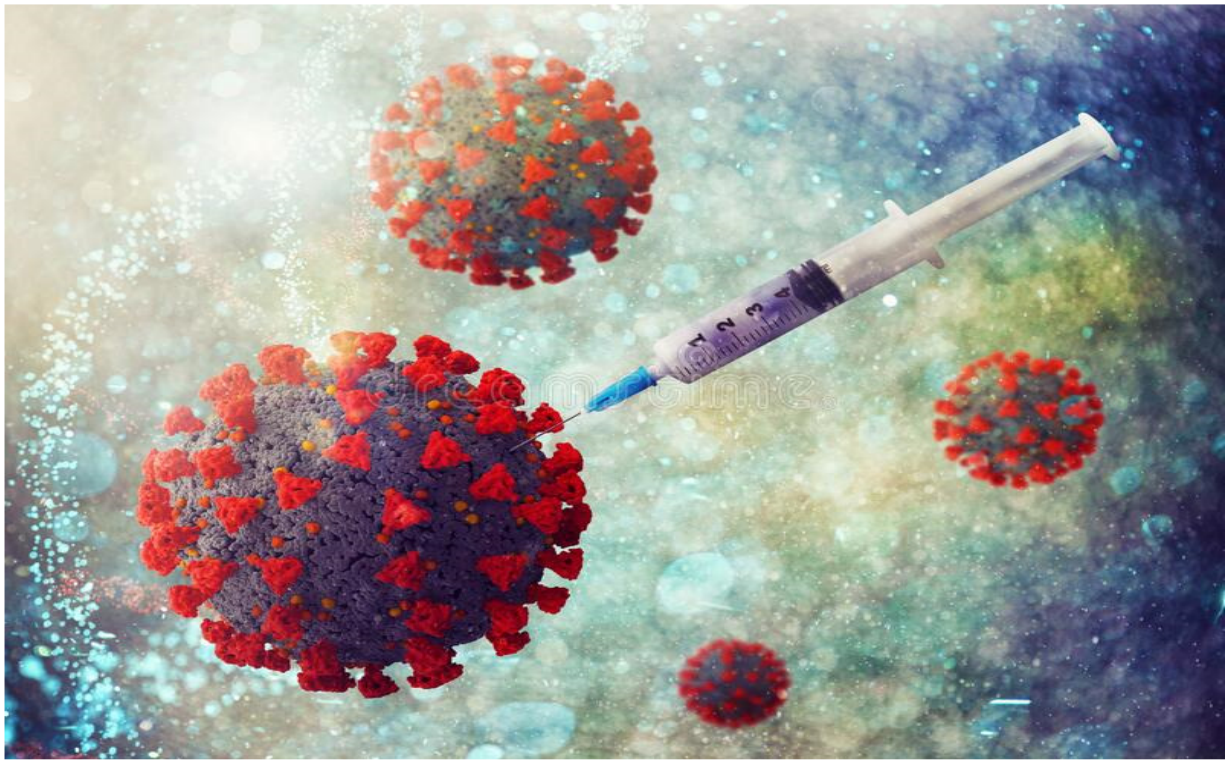

Covid-19 (Source: Dreamstime.com)

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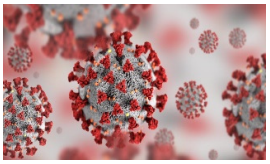

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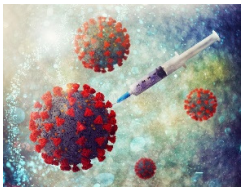

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Genetic Variation of COVID-19 and Vaccine Development

Dr Hossain Md Anawar

Several variants of Coronavirus have been identified from the onset of the COVID-19 outbreak. The severity of these variants is different. Some variants have intensive and deadly effects such as Delta variant, while some variants have extensive and widespread, but less deadly effects such as Omicron. The Delta variants in the beginning of the pandemic caused more death cases. However, subsequent variant, Omicron showed less deadly effects.

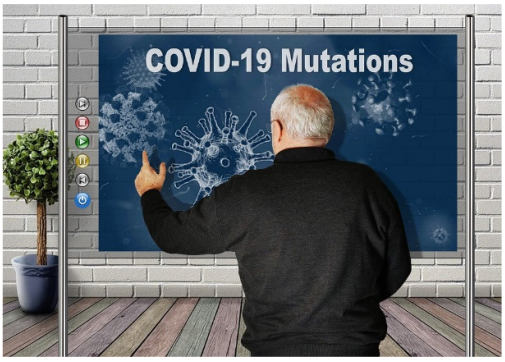
Why a virus changes to a new variant?

The wide circulation of viral infections in the population increases the possibility of virus mutation (WHO, 2021). Most of the viral mutations don't significantly affect the ability of virus to cause infections and disease. But it may affect a virus's properties. As for example, mutation may increase the ability of virus to spread more or less. After mutation, new variant can cause more severe or less severe disease. New variants may have wider spreading and infections among the population.

Source: Pixabay

The mutation or change of virus's genes creates new variants of viruses with slightly different characteristics. Thus, different distinct variants are evolved depending on the geographic differences, climate and demography. It is characteristics of RNA viruses which undergo mutation over time. Some undergo minor mutation and some do more mutation to their genes (Bollinger et al., 2022).

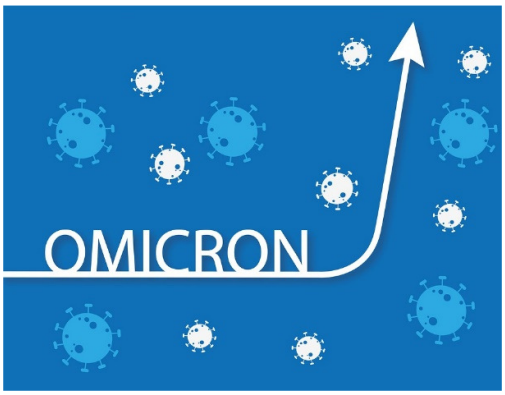
The Coronavirus variants have specific genetic characteristics which impart high transmissibility, evasion of immunity or diagnostic testing, and cause more severe disease or death.



Source: Pixabay

COVID-19 variants

Mutations to genes are monitored every year for development of flu virus vaccines. Similarly, we need to keep an eye on the Coronavirus and track it (Bollinger et al., 2022) to accommodate the changes in vaccine development process. The Omicron variants including a subvariant called BA.2 are highly contagious which have caused surges of COVID-19, especially in less protected areas. The Omicron has over 50 mutations and it's very different from earlier variants, including Delta. But luckily, Omicron caused less severe disease than the Delta variant. Omicron virus can exist in the air in indoor settings. The Delta and Omicron variants have caused the widespread severe infections and deaths including increased number of cases in children. At the start of Omicron, the people were very scared, because it rapidly increased the surge of COVID-19 case. Later the people could breathe in open air when they realized that the number of cases admitted into hospital and ICU (intensive care unit) decreased compared to the earlier variants.



Source: Pixabay

At the beginning there was lack of sufficient information about COVID-19 virus and its variants. Therefore, some COVID-19 vaccines were approved before they completed all the rigorous clinical trials. However, currently we have much more information about COVID-19 variants than we knew at the beginning of the pandemic. That's why, the extent of transmission and the rate of deaths has drastically decreased and under control in some areas. The January and March 2022 report of the CDC research also demonstrated that COVID-19 vaccine boosters were effective in preventing severe COVID-19 and reduced the risk and hospitalization of COVID-19 cases (Bollinger et al., 2022).

Vaccine may stop the transmission of viral infection for long time, but it may appear again, although it is rare (Santos, 2021). Some vaccines may induce the long-lasting immunity, while others may not do it. There was possibility of evolution of new variants when the infections by the delta and omicron variant families continued among the people. Therefore, all people should strive to prevent viral transmission, by practicing safety measures and getting vaccinated including booster doses as early as possible.

How to stop new variants of COVID-19

We need to prevent the transmission of virus to stop the evolution of new variants. We can do it by practising the current process of safety measures such as frequent hand washing, wearing a mask, physical distancing, good ventilation and avoiding crowded places or closed settings. Vast production of COVID-19 vaccines and wider distribution in different segments of people and countries are essential to protect the people before they are exposed to the virus and enhance the risk of new variants. Most of the people irrespective the rich and poor, wealthy countries or poor nations should get equal access to vaccination, which would decrease virus circulation leading to fewer mutations of COVID-19 virus.

Vaccine development

There are a couple of vaccines developed in different countries to combat the infection of COVID-19. Among them, the Pfizer-BioNTech vaccine, Moderna, Johnson & Johnson, Novavax, Oxford-AstraZeneca, Sinopharm and Sinovac are more popular and widely administered globally. Pfizer and Moderna are the messenger RNA (mRNA) vaccines. These vaccines use a genetic code called RNA, which induce human body's cells to produce the coronavirus' specific spike protein. Then body's immune system cells recognise the spike protein as a threat and start to build an immune response against it. Our body's DNA is not damaged by the RNA from the vaccine, and our body quickly breaks it down. These vaccines do not have any live virus.

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Different COVID-19 Variants and Their Mutations

The SARS-CoV-2 virus has changed its gene and did some mutations generating several variants that are circulating globally at the current time. The SARS-CoV-2 virus was first emerged in Wuhan, China in late 2019. After that, this virus is performing a lot of changes to it genes creating new variants. Some of these variants may have almost similar properties, while other variants may have severe impacts on human health. They may spread infection faster than other variants and have more dangerous and deadly effects (Geddes et al., 2021).

A variant of concern

A variant of concern is more contagious, causes more severe disease, and less susceptible to public health measures, vaccines, diagnostic tests and/or therapeutics. Some of the COVID-19 variants of concern seem to partially evade the immunity generated by vaccination. However, double dose or booster dose can still help to reduce the spread of COVID-19 and are highly effective at reducing hospitalisation and deaths associated with the disease. The following variants of concern have been identified all over the world. These include Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529).

Alpha (B.1.1.7)

It was first identified in the United Kingdom in December 2020. Now Alpha variant has been detected in 192 locations worldwide (as of 7 December 2021). It has undergone several key mutations in the spike protein and mark it out from the original Wuhan strain. Alpha is considered to about 50% more contagious than the original Wuhan strain. Alpha (or Alpha plus) variant had three mutations (E484K, N501Y, and D614G).

N501Y mutation improves spike protein binding to cellular receptors making the virus more contagious.

D614G mutation seems to enhance viral replication and a P681H mutation, the function of which is unclear.

Beta (B.1.351)

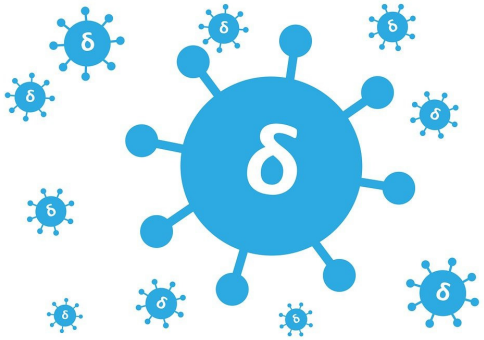
The Beta variant was first identified in South Africa in December 2020. It was also detected in 139 locations worldwide (as of 3 December 2021). Beta contains a K417N mutation and seems to be around 50% more contagious than previous variants, but there is no clear evidence about its severity.

Gamma (P.1)

Gamma was first identified in Brazil, but has now been verified in 98/239 locations worldwide (as of 3 December, 2021). It contains E484K, N501Y, D614G, K417T and H655Y mutations.

Delta (B.1.617.2)

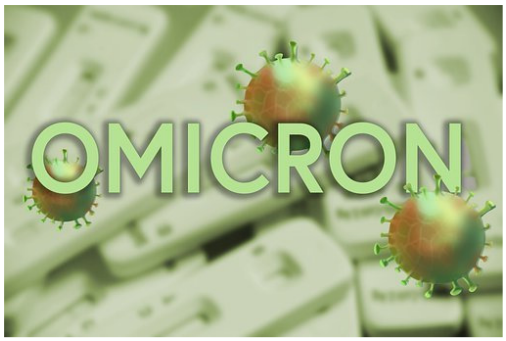
The Delta variant was first identified in India in May 2021 and has now been verified in 176 locations worldwide. It was a dominant variant and overtook existing variants in many countries.

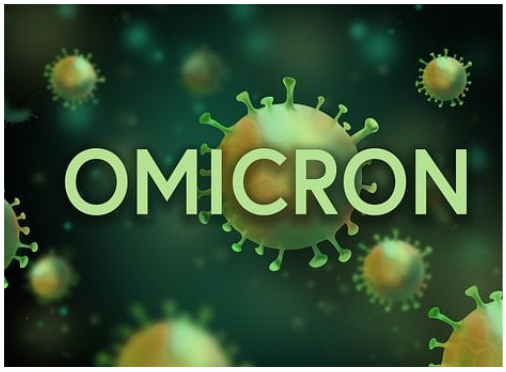


Delta contains the D614G, L452R, T478K and P681R mutations. This variant is estimated to be 40-60% more contagious than the Alpha variant, and about two times higher contagious than the original Wuhan strain of SARS-CoV-2.

Omicron (B.1.1.529)

It was quickly detected in numerous countries in November 2021. It had been verified at 22 locations worldwide, including parts of North and South America, Europe, Africa, Asia and Australia (As of 3 December 2021).





Omicron had many mutations such as N501Y, D614G, K417N and T478K and some of them are concerning. However, it also contains many other mutations which have not yet been characterised. It has increased risk of reinfection compared to other variants of concern.

Sourced from Geddes et al. (2021)

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Effectiveness of COVID-19 Vaccines on Different Variants

Dr Hossain Md Anawar

COVID-19 vaccines will protect us from illness, deaths, social isolation, economic slowdown, educational disruptions of children, and prevent severe diseases. A good number of vaccines have been developed all over the world. Some of these vaccines are less effective against some of these variants, while the others have demonstrated satisfactory performance to reduce the number of hospitalization and deaths. Furthermore, the COVID-19 booster doses are recommended for the people for added protection against infection and severe disease (Bollinger et al., 2022).

The currently developed and approved COVID-19 vaccines have demonstrated their ability to protect the people and reduce the spread of infections. These vaccines are anticipated to provide at least some protection against the new virus variants because these vaccines increase the immunity response in human body involving a range of antibodies and cells (WHO, 2021). Different vaccines have shown the various level of performance against the infection and severity of disease.

Mutations of virus can not completely annul the effectiveness of these vaccines. However, the currently developed and approved vaccines may be less effective against some new variants. Therefore, it is important to monitor the variants and change the composition of the vaccines to protect against the new variants. Vaccination and precautions may stop the spread of virus and subsequently prevent the mutations of virus and protect the effectiveness of existing vaccines.

Source: Pixabay

There are different strains of COVID-19 affecting the people worldwide. Therefore, vaccine development may need to incorporate more than one strain, and other vaccine changes may be needed as well. Sufficient extent of trials must also be designed and conducted to determine the effectiveness and impact of the vaccines.

The research group of WHO is continuously working to identify, monitor and assess the variants of concern and evaluate their impact on diagnostics, therapeutics and vaccines. Different vaccine manufacturers and countries can get new information on changes that may be needed for COVID-19 vaccine development.

Source: Pixabay

The B.1.617.2 (Delta) coronavirus variant caused the severe acute respiratory syndrome which had contributed to a surge in cases in India, the United Kingdom and across the globe. The effectiveness of the different vaccines currently available in the market, especially BNT162b2 and ChAdOx1 nCoV-19 vaccines against this variant was mysterious. Therefore, Bernal et al. (2001) investigated the effectiveness of these vaccines against the Delta variant and Alpha variant. After application of one dose of vaccine, both vaccines (BNT162b2 or ChAdOx1 nCoV-19) demonstrated notably lower effectiveness among persons with the Delta variant than among those with the Alpha variant. The two doses of the BNT162b2 vaccine showed 93.7% effectiveness among persons with the Alpha variant and 88.0% among those with the Delta variant. Double doses of the ChAdOx1 nCoV-19 vaccine showed 74.5% effectiveness among persons with the Alpha variant and 67.0% among those with

the Delta variant. Double doses of the vaccines (BNT162b2 or ChAdOx1 nCoV-19) showed only very small or modest differences in effectiveness against the Delta variant as compared with the Alpha variant. Absolute differences in vaccine effectiveness were noted after application of one dose. After application of two doses of vaccines showed the higher levels of vaccine effectiveness against symptomatic disease with the Delta variant.

The Delta (B.1.617.2) variant is nearly twice as contagious as earlier variants and might cause more severe illness (Mayo Clinic Staff, 2022). The greatest risk of transmission is among the unvaccinated people. But it appeared that the vaccinated people spread COVID-19 for a shorter period than do the unvaccinated people. Although research suggested that COVID-19 vaccines were slightly less effective against the Delta variant, the vaccines still appeared to provide some protection against severe COVID-19 (Mayo Clinic Staff, 2022).

The Omicron (B.1.1.529) variant spreads more easily than the original virus that causes COVID-19 and the Delta variant (Mayo Clinic Staff, 2022). However, Omicron appears to cause less severe disease. But the COVID-19 vaccines effectively prevented severe illness. The Omicron variant and its subvariant BA.2 have attacked the vast population of unvaccinated people all over the world (Katella, 2022). It is even causing infections in some vaccinated people. This variant spread more rapidly and widely than other variants of COVID-19. However, it was good news that this variant was not deadly and severe compared to the other variants. The COVID-19 vaccines are still expected to be effective at preventing severe disease, hospitalization, and death from COVID-19 (Katella, 2022).

Pfizer-BioNTech

The Pfizer-BioNTech vaccine is manufactured by the Pfizer and BioNTech companies. It is a messenger RNA (mRNA) vaccine, which is a new type of vaccine (Katella, 2022). It must be stored in freezer-level temperatures, which can make it more difficult to distribute than some other vaccines. Although two doses of this vaccine were effective against the Omicron virus, additional booster dose was highly recommended for enhancing immunity capacity in the body. But the Center for Disease Control and Prevention (CDC) suggests an eight-week interval between the two shots to reduce the risk of myocarditis, an uncommon side effect according to the FDA warnings. But this inflammation, in most cases, gets better on its own without treatment. There are a few more side effects reported e.g., pain, redness, or swelling at the site where the shot was administered, and/or tiredness, headache, muscle pain, chills, fever, or nausea throughout the rest of the body. These side effects generally should go away in a few days. Another serious side effect (very rare) such as anaphylaxis is treatable with epinephrine (the drug in Epipens®) (Katella, 2022).

Moderna

Both Moderna and Pfizer-BioNTech uses the same mRNA technology and showed a similarly high efficacy, about 95% efficacy, to protect the people against the COVID-19 symptomatic disease. This vaccine also needs to be stored in freezer-level temperatures (Katella, 2022).

Source: Pixabay

The primary series (two shots) of this vaccine is taken 28 days apart. This vaccine is fully effective after two weeks of the second shot. For some people older than 12, especially boys and men between ages 12 and 39, the CDC suggests an eight-week interval between the two shots to reduce the risk of myocarditis, an uncommon side effect. After five months of primary series (two-shot), anyone aged 18 or older should get a booster shot.

According to FDA and CDC, the possible side effects are similar to Pfizer-BioNTech's vaccine**.**

According to the CDC, the mRNA booster shots provided significant protection against hospitalization from Omicron.

Johnson & Johnson (brand name: Janssen)

Johnson & Johnson's coronavirus vaccine is a carrier, or virus vector, vaccine, a type of vaccine similar to other flu vaccine (Katella, 2022). This one-shot vaccine is easier and the most convenient to distribute and administer to people. It is fully effective after two weeks of vaccination. It showed 67% efficacy in preventing moderate to severe/critical disease by 14 days after vaccination—and 66% effective by 28 days after vaccination (Source: FDA). The preliminary study results from South Africa showed a J&J booster to be 85% effective against hospitalization at a time when Omicron was the dominant variant in that country.

Janssen has almost similar side effects to Moderna and Pfizer-BioNTech vaccines, which are pain, redness, swelling in the arm, tiredness, headache, chills, fever, nausea, muscle pain throughout the rest of the body. But these side effects normally go away in a few days. There are a few rare cases of the neurological disorder (Source: FDA) in vaccination recipients occurred within 42 days after vaccination (Katella, 2022).

Some restrictions were imposed on this vaccine due to concerns of rare occurrence of blood clots associated with the vaccine (FDA and CDC source). Adults 18 and older, who specifically request the J&J vaccine or who cannot have the other available vaccines for medical reasons, can get the Janssen vaccine. After at least 2 months of a single J&J primary shot, the people should get a Pfizer-BioNTech or Moderna vaccine booster dose.

Novavax

The Novavax vaccine (brand names: Nuvaxovid and Covovax) showed its high effectiveness in clinical trials. Unlike the mRNA and vector vaccines, this vaccine is a protein adjuvant. It can be stored in a refrigerator, making it easier to distribute (Katella, 2022).

When the vaccine is injected, this stimulates the immune system to

produce antibodies and T-cell immune responses. It is 90% effective against lab-confirmed, symptomatic infection and 100% against moderate and severe disease in phase 3 trial results. Novavax is an effective booster vaccine against the variant following the primary series of other vaccines (Source: University of Oxford).

Possible side effects are injection site tenderness, fatigue, headache, muscle pain.

Oxford-AstraZeneca

This Oxford-AstraZeneca vaccine is cheaper due to its lower manufacturing cost per dose. This vaccine can be stored in normal refrigeration for at least six months, making it easier to distribute. Two doses need to be administered four to twelve weeks apart (Katella, 2022).

Similar to the Johnson & Johnson vaccine, this is a carrier vaccine. Scientists engineer a harmless adenovirus as a shell to carry genetic code on the spike proteins to the cells. Once the code is inside the cells, the cells produce a spike protein to train the body's immune system, which creates antibodies and memory cells to protect against an actual SARS-CoV-2 infection.

This vaccine is 76% effective at reducing the risk of symptomatic disease by 15 days or more after receiving the two doses, and 100% against severe disease. It was also 85% effective in preventing COVID-19 in people over 65.

There are some possible side effects, which include tenderness, pain, warmth, redness, itching, swelling or bruising at the injection site, all of which generally resolve within a day or two. However, some very rare side effects of unusual blood clots with low blood platelets are also reported such as 8.1 cases per million in those who received a first dose of the vaccine, and 2.3 per million after the second dose (Katella, 2022).

Source: Information from Yale Medicine articles.

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Production and Distribution of COVID-19 Vaccines Around the World

Dr Hossain Md Anawar

Vaccines can significantly fight against some diseases. But it is very difficult to affordably, reliably and successfully develop and bring a vaccine to the market in spite of significant scientific advancement. Vaccine development needs a lot of financial investments, knowledge, capacity building, time and efforts. In some cases, the anticipated results may not come in spite of great efforts. After development of vaccines, sometimes, supply shortages of existing vaccines can fail to improve human health. The vaccine development in low-resource countries faces a lot of challenges.

Vaccine development

Developing new vaccines takes a long time and high cost. However, innovation in technologies, platforms, processes, and business models can bring success to accelerate timelines and reduce costs in vaccine development. It is also particularly important that we understand how to prioritize our efforts. We can bring more success in vaccine development by applying deep expertise in the vaccine manufacturing process, quality control, and clinical evaluation, because it will advise on more effective vaccine development programs and identify new areas of innovation to benefit multiple disease programs.

Source: Pixabay

COVID-19 vaccine production and distribution

More than 12 billion doses of COVID-19 vaccine were estimated to be produced in 2021 and if this amount were produced, sold and distributed equitably across the world's population, the majority of the world's needs would be fulfilled in 2021. The vaccine developers projected and assumed this total of vaccine

production. About 11 billion doses are needed to vaccinate 70 percent of the world's population and reach herd immunity. However, the requirement of the global demand for COVID-19 vaccines may change depending on the spread of the new variants and immunity levels of the double doses and booster. We may need to have regular booster doses (every six months or every year). The approval of one or more vaccines for children can also change the demand and supply of vaccines.

The vaccine manufacturers had to drastically increase their production capacity to meet the global needs of more than 12 billion doses for the year 2021, which were dominantly made and distributed by the Pfizer-BioNTech, Oxford-AstraZeneca and Moderna. But in 2022, more companies can dominantly produce and supply COVID-19 vaccines. Sinopharm and Sinovac are also significantly increasing manufacturing capacity of their inactivated virus vaccines. In both China and Russia, the people depend on their domestic vaccines for their national supply, but there is the lack of publicly available information on purchases or doses allocated to domestic supply in either country.

Source: Pixabay

Vaccine Production in Africa

The global support is needed for a robust and reliable vaccine capacity in Africa and for a global public good (Georgieva, 2022). The Institut Pasteur in Dakar has attracted and trained international and regional specialists to address Africa's immediate COVID-19 challenge. They are also building the region's capacity to fight future pandemics and meet Africa's more routine immunization needs. But they need help for the tools and the necessary funds to build capacity to produce and manufacture vaccines considering the overall low COVID vaccination rate on the continent, still below 10 percent. It is also very important to ensure the sufficient deliveries of vaccine to every African country through COVAX and the African Vaccine Acquisition Trust (AVAT).

Source: Pixabay

Manufacturing COVID vaccines in lower-income countries

Drug companies and wealthy countries are not interested to make partnership with developing and south countries although they are facing increased pressure to do that. Many people are not getting COVID-19 vaccines in the poor, developing countries and global south. The countries in the global south, poor, and developing countries should be enabled to make their own production to ensure equitable access to COVID-19 vaccines (Maxmen, 2021). Different

international health and advocacy organizations including WHO are sending proposal, request and pressure to the pharmaceutical companies (Moderna, Pfizer, BioNTech, Johnson & Johnson (J&J)) and their native governments that developed highly effective vaccines to share their patented knowledge and technology with drug manufacturers that could produce them for poorer countries. Some of the pharmaceutical companies in the developing countries of Asia, Africa, Central and South America have advanced manufacturing capacity and facilities. They can produce high quality vaccines through their rigorous quality control processes in procurement, manufacturing, quality check, packaging, storage and distribution. But they need only patent and partnership with the patent developing companies. This partnership manufacturing process can accelerate the production and distribution of vaccines in the poor and developing countries. Through this process, the patent developing companies can get their financial benefit and help the global people to protect from COVID-19 disease, illness and death.

A great partnership production of COVID-19 vaccine started in India in collaboration with Oxford/ AstraZeneca (Horner, 2021). The Serum Institute of India manufactured Covishield, which is a version of the Oxford/AstraZeneca vaccine. They distributed several millions of vaccines to Bangladesh, Myanmar and Iran by October 2021 through vaccine friendship initiative. This initiative of India was highly appreciated by international communities. But soon after the initiative started, India postponed the exporting of vaccines in March 2021 when the second wave of COVID-19 dangerously attacked the people killing thousands of people in India and they focused on meeting their domestic needs. The Serum Institute anticipated to export a large volume of vaccines to Covax by January 2022 and continue their export to reach a billion doses to Covax by the end of 2022. But there were a lot of uncertainties of India's exporting vaccines to reach target until 2022. The institute also signed a deal with Novavax to manufacture vaccine.

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How Do Natural and Hybrid Immunity Work for Protection Against SARS-CoV-2?

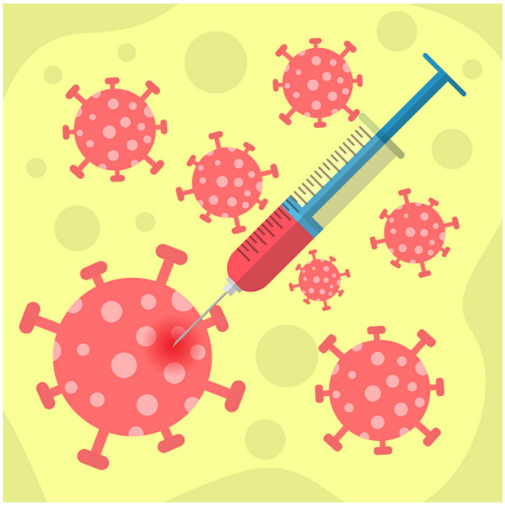
Vaccination provides people with immunity capacity. Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) also provides natural immunity against reinfection. However, the immunity level wanes with time. Therefore, the researchers have investigated how the natural and hybrid immunity wanes with passage of time (Goldberg et al., 2022). How do natural and vaccination immunity work alone and together? How long do natural, vaccination and hybrid immunity last in human body?

Natural Immunity and Elapse

The unvaccinated persons, who had infection 1 year ago and had recovered from infection, is more vulnerable to reinfection than those who had been infected 4 to less than 6 months ago indicating that the natural immunity decreases with the elapsing of time. Among the people who had received a single dose of vaccine after previous infection, the reinfection rate was lower who received vaccination less than 2 months previously than those who received vaccination at least 6 months previously. These results indicate that the hybrid immunity level of the people increases after receiving the vaccination, but the immunity level decreases when time elapses. The previously uninfected persons vaccinated with double doses of vaccine less than 2 months ago had lower risk of reinfection than those who had been vaccinated at least 6 months ago.

Hybrid Immunity

Among the people who was either previously infected with SARS-CoV-2 or received any dose of vaccine before or after infection, protection against reinfection decreased as the time increased since the last immunity-conferring event. A single dose of vaccine after infection reinforced protection against reinfection. The previously infected and recovered people obtain natural immunity. The previous infection provides natural immunity to people, but this immunity decreases with passing of time. Therefore, they should get vaccination of single dose, double dose and booster or more. It is evident that vaccination provides additional protection against reinfection by COVID-19.



The vaccination provides the previously infected people with hybrid immunity and higher protection against the reinfection than the unvaccinated people. But the immunity level waned in all cases across all age groups when time elapses. The rates of reinfection among the recovered, previously infected, unvaccinated group were lower than those among the group with vaccination of two-dose when the time since the last immunity-conferring event was similar. However, the booster dose can restore the protection in the two-dose cohort. The protection against the Delta variant decreased over time in both vaccinated and previously infected persons. But an additional vaccine dose restored protection.

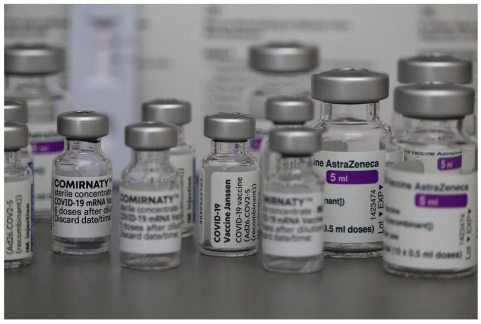
Reference

Goldberg Y, Mandel M, Bar-On Y M, Bodenheimer O, Freedman L S, Ash N, Alroy-Preis S, Huppert A, Milo R, Protection and Waning of Natural and Hybrid Immunity to SARS-CoV-2. N Engl J Med 2022; 386:2201-2212, June 9, 2022.

Are Homologous and Heterologous COVID-19 Boosters Equally Effective Against Omicron?

For the Ad26.COV2.S vaccine (Johnson & Johnson–Janssen) recipients, heterologous boosting was more effective than homologous boosting for protection against Omicron infection. However, there was not enough data from the general adult population, and vaccine effectiveness over time was also lacking (Accorsi et al., 2022). That's why a booster dose of a messenger RNA (mRNA) vaccine at least 2 months after the primary dose of Ad26.COV2.S vaccine (Johnson & Johnson–Janssen) was recommended for better protection against coronavirus disease 2019 (COVID-19). The people who received Ad26.COV2.S for both the primary and booster doses, they may receive a second booster dose of an mRNA COVID-19 vaccine at least 4 months after the first Ad26.COV2.S booster dose.

A booster dose provided more protection against symptomatic Omicron infection as compared with no vaccination. The vaccine effectiveness was the highest for the cases who received a booster dose of an mRNA vaccine and was lowest who received the homologous Ad26.COV2.S/Ad26.COV2.S (Janssen) vaccine. A single booster dose of an mRNA COVID-19 vaccine after primary vaccination with a single-dose Ad26.COV2.S provided protection close to that of the three-dose mRNA vaccine regimen.



A booster dose of mRNA vaccine is recommended at least 2 months after primary vaccination with single-dose Ad26.COV2.S or at least 4 months after an Ad26.COV2.S booster dose.

Reference

Accorsi E K., Britton A, Shang N, Fleming-Dutra K E, Link-Gelles R, Smith Z R, Derado G, Miller J, Schrag S J, Verani J R, 2022. Effectiveness of Homologous and Heterologous COVID-19 Boosters against Omicron. Editorial, N Engl J Med, May 25, 2022.

Suitability of mRNA-1273 (Moderna) COVID-19 Vaccine for Children Aged 6 to 11 Years

Since the onset of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), we noticed that mostly, adult people were infected by COVID-19. Therefore, the adult people were predominantly vaccinated. However, gradually children infection started to be noticed also. Therefore, the vaccination of children to prevent coronavirus disease 2019 (COVID-19) became an urgent public health issue. Creech et al. (2022) investigated the safety, immunogenicity, and efficacy of the mRNA-1273 (Moderna) vaccine in children 6 to 11 years of age.

Injection of Moderna vaccine did not cause any significant side effects in children. Two injections of mRNA-1273 (50 µg each) vaccine caused mainly low-grade, transient adverse effects, most commonly injection-site pain, headache, and fatigue. But it did not cause any serious adverse events, multisystem inflammatory syndrome in children (MIS-C), myocarditis, or pericarditis as of the data-cutoff date (Creech et al., 2022). Two 50-µg doses of the mRNA-1273 vaccine induced immune responses in children safely and effectively and prevented COVID-19 in children 6 to 11 years of age; these responses were noninferior to those in young adults.

The mRNA-1273 vaccine (Moderna) showed high efficacy to prevent COVID-19, and it had mainly low-grade transient adverse effects in persons of 12 years of age or older including adults. The older adults and populations, who have pre-existing conditions, have the highest risk of illness and death from COVID-19. But the children are also at risk for COVID-19 infection that can lead to severe COVID-19–related health issues such as, hospitalization, the use of life-supporting interventions, and death. The pandemic of COVID-

19 created some social issues such as school interruptions, academic development and well-being for children.

Some studies have demonstrated that vaccination of 12-to-17-year-old adolescents reduced the risks of MIS-C and hospitalization. The Food and Drug Administration (FDA) approved urgently the use of COVID-19 BNT162b2 vaccine (Pfizer–BioNTech) for adolescents and children 5 to 11 years of age. The mRNA-1273 vaccine also received provisional approval in some countries for use in children of 6 to 11 years of age.

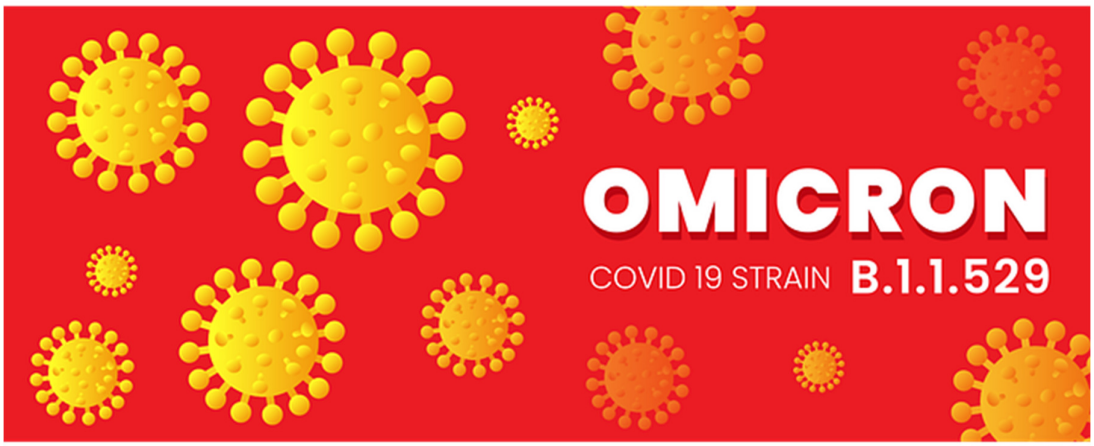
Creech et al. (2022) reported that the vaccination of children (6 to 11 years of age) with two 50-μg doses of the mRNA-1273 vaccine administered 28 days apart showed safety, immunogenicity, and vaccine efficacy that were consistent with those previously observed in adolescents and adults. These results provided support for the use of mRNA-1273 vaccine to prevent COVID-19 in children.

Reference

Creech C B, Anderson E, Berthaud V, Yildirim I, Atz A M, Baez I M, Finkelstein D, Pickrell P, Kirstein J, Yut C, Blair R, Clifford R A, et al., 2022. Evaluation of mRNA-1273 COVID-19 Vaccine in Children 6 to 11 Years of Age. N Engl J Med 2022; 386:2011-2023, May 26, 2022.

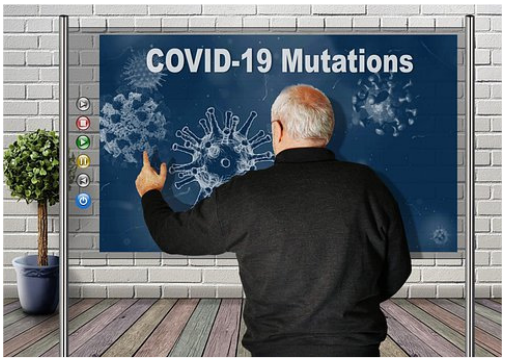
Neutralization of the SARS-CoV-2 Deltacron and BA.3 Variants

The B.1.1.529 (Omicron) variant has undergone continuing evolution generating the emergence of the BA.1, BA.2, and BA.3 sublineages and has created serious concern over the durability of vaccine- and infection-induced immunity during the coronavirus disease 2019 (COVID-19) pandemic (Evans et al., 2022). The health concern of viral evolution through the recombination of the Omicron variant with the B.1.617.2 (Delta) variant has created serious health issues, because this new "Deltacron" variants have the ability to evade immunity induced by either vaccination or previous infection.

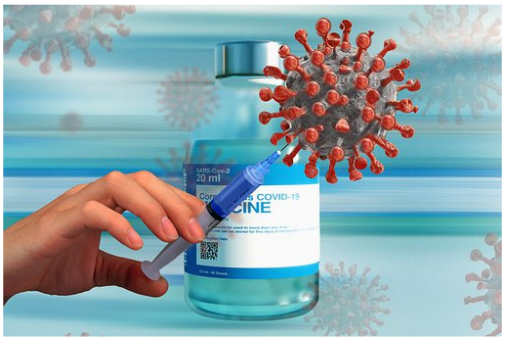


Delta variant and Omicron variant have undergone some mutations over time generating some new variants of SARS-CoV-2. Among these variants, some of them are resistant to vaccines currently available in the market such as

Pfizer, Moderna, AstraZeneca, etc., while most of them can be neutralized by these vaccines. Therefore, Evans et al. (2022) examined the neutralizing-antibody titers in serum samples of health care workers receiving the mRNA-1273 vaccine (Moderna) and the BNT162b2 vaccine (Pfizer–BioNTech). The neutralizing-antibody titers were 3.3 times as low against the BA.3 variant and 44.7 times as low against the Deltacron variant as compared with the response against the D614G variant. However, after receiving the booster dose by the same health workers, their neutralizing-antibody titers increased; they were 2.9 times as low against the BA.3 variant and 13.3 times as low against the Deltacron variant as against the D614G variant. The Deltacron variant showed similar neutralizing-antibody resistance to the BA.1 and BA.2 variants. However, the BA.3 variant showed higher sensitivity to both two-dose and booster due to absence of many critical mutations in the receptor-binding domain, whereas other variants of Omicron had more mutations.

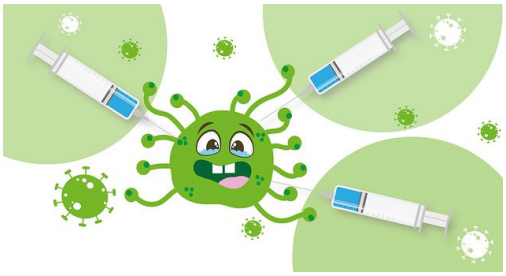


For the other group of 18 patients from ICU during the Delta wave of the pandemic, the neutralization escape of the Deltacron variant paralleled that of the BA.1 and BA.2 variants, whereas the BA.3 variant remained largely sensitive to neutralization. The vaccinated cases had substantially higher titers against the D614G and BA.3 variants than the unvaccinated patients.



For the other 31 hospitalized patients during the Omicron wave (not admitted to the ICU), the neutralization of the Deltacron and BA.3 variants was similar to that of the D614G variant, for which titers were much lower than those in samples obtained during the Delta wave. Neutralization of both the Deltacron and BA.3 variants was similar to that of the BA.1 and BA.2 variants; the Delta variant had the most resistance to serum obtained during the Omicron wave. This similar neutralization of Omicron

sublineages occurred regardless of vaccination status.



The hospitalized patients during the Omicron wave had broader neutralization of all the tested Omicron variants than did those hospitalized during the Delta wave. The Deltacron variant retains the strong resistance of other Omicron sublineages and has no enhanced sensitivity to serum obtained during the Delta wave. Recombination of SARS-CoV-2 variants and the potential emergence of a more virulent variant with strong immune escape poses a serious threat to public health, which needs ongoing monitoring.

Reference

John P. Evans, Panke Qu, Cong Zeng, Yi-Min Zheng, Claire Carlin, Joseph S. Bednash, Gerard Lozanski, Rama K. Mallampalli, Linda J. Saif, Eugene M. Oltz, Peter J. Mohler, Richard J. Gumina, Shan-Lu Liu, Neutralization of the SARS-CoV-2 Deltacron and BA.3 Variants. The New England Journal of Medicine, May 18, 2022.

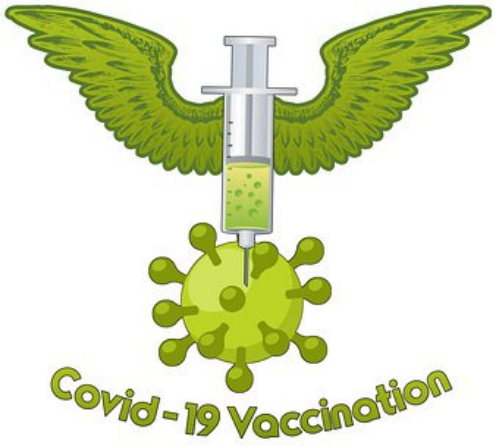
Necessity of New COVID-19 Vaccines in the World

There was a global shortage of COVID-19 vaccines in 2021. There will be abundant supply of vaccines by middle of 2022 to provide more equitable coverage. As of April 19, 2022, approximately 11.5 billion COVID-19 vaccine doses have been administered globally (Nohynek and Wilder-Smith, 2022). Speedy and high manufacturing capacity of the currently available vaccines by vaccine producers through the COVAX (COVID-19 Vaccines Global Access) program and beyond should secure the coverage target projected by the World Health Organization (WHO) for 70% of the world population by mid 2022.

Therefore, some questions are circulating around whether we still need to develop new type of COVID-19 vaccines. Globally the researchers have developed and are still working to develop a total of 344 COVID-19 vaccine candidates. Out of these, manufacturers are now producing 31 vaccine products in large-scale use after conditional

approval by national regulatory authorities or under the WHO Emergency Use Listing.

These vaccine products are applying at least five different technology platforms such as messenger RNA [mRNA], viral-vectored, inactivated whole-virus, protein subunit, and plasmid DNA approaches. Some important reasons have been underscored for the development of a range of COVID-19 vaccines for use across the world and ending of the pandemic. Each vaccine product has different attributes, advantages and disadvantages. Therefore, different countries, health care facilities, different subpopulations and age groups, may benefit from different vaccine products developed on different platforms.



Although there are a couple of vaccines available for the safe and effective protection against the COVID-19 virus, the development of further two new vaccines is recommended which are produced on new technology platforms (Nohynek and Wilder-Smith, 2022). As for example, Hager et al. described a plant-based coronavirus-like particle vaccine, and Dai et al., a receptor-binding domain (RBD)–dimer–based vaccine. These two vaccines have some advantages. They don't need extreme cold-chain procedures for storage. They are user-friendly in primary health care settings as well as in low- and middle-income countries. In the trial of these vaccines, low- and middle-income countries were included in the phase 3 trials of these vaccines. The trial period of these vaccines encountered the circulation of several SARS-CoV-2 variants.

Based on the phase 3 trial conducted in Argentina, Brazil, Canada, Mexico, the United Kingdom, and the United States, the recombinant plant-based vaccine showed the average efficacy of 69.5% against confirmed symptomatic infection. In a post hoc analysis, the overall vaccine efficacy against preventing moderate-to-

severe disease was 78.8%, and among participants who were seronegative at baseline, vaccine efficacy against any severity of disease was 74.0%.

Based on the phase 3 trial data conducted in Ecuador, Indonesia, Uzbekistan, and Pakistan (efficacy and safety assessments) and in China (safety assessment only), the RBD-dimer–based COVID-19 vaccine (as a three-dose regimen) showed average efficacy of 75.7% against confirmed symptomatic disease and 87.6% against severe to critical COVID-19. Most of the incident cases occurred during period in which B.1.617.2 (Delta) was the dominant variant.

For trials, above two new vaccines used mostly working-age adults; but there is no information available on their efficacy against older persons, the most vulnerable and highest priority-use group. The vaccines already in use are lacking in data on durability of protection and safety in subpopulations such as older persons, pregnant women, and persons with immunosuppression. After application, it is also highly significant to monitor the effectiveness of different vaccines including the above two new vaccines over time and against different virus variants and in various subpopulations and health care settings.

Although the vaccines currently in use are playing a key role to tackle the COVID-19 pandemic, but there are disadvantages regarding their durability of protection against COVID-9, storage condition and supply chain; and they do not have the best long-lasting solution. Therefore, further research and development of new vaccines are essential which will have broader epitope coverage to provide cross-immunity against SARS-CoV-2 variants, a longer duration of protection, and be easy to update in a timely manner for protection against any new variants.

Reference

Nohynek H., Wilder-Smith A, Does the World Still Need New COVID-19 Vaccines? N Engl J Med 2022; 386:2140-2142. June 2, 2022.

A Sustainable Recombinant Plant-Based Adjuvanted COVID-19: How Effective and Safe?

From the beginning of out-break of COVID in 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused more than 497 million cases of coronavirus disease 2019 (COVID-19) and 6.1 million deaths globally (Hager et al., 2022). The researchers across the world have jumped into the stream of huge research and developed different types of vaccines. Most of these vaccines have the spike (S) glycoprotein as the antigen, and S-specific neutralizing antibodies have been correlated with protection against infection. The trial of these vaccines conducted in early in the pandemic generally showed high efficacy against the original Wuhan-Hu-1 strain of SARS-CoV-2 except rare, platform-related adverse events. But there had been some mutations of original virus, that generated some new variants over time such as Delta (B.1.617.2), Omicron (B.1.1.529), and Deltacron. These variants have also some sublineages. As for example, Omicron (B.1.1.529) variant has encountered further mutation creating the emergence of the BA.1, BA.2, and BA.3 sublineages. The health experts were anxious about the effectiveness and efficacy of the currently developed vaccines against the infection caused by these variants. Therefore, global research is continuing to improve the efficacy of the vaccines and also develop new vaccines.

However, new and recent research has identified that the currently available and used vaccines have reduced protection due to waning immunity and the emergence of new variants. Therefore, the booster doses are highly recommended to restore levels of neutralizing antibodies and improve cross-protection against a range of variants. Therefore, new type of vaccine development is recommended to meet the global demand, which have stability at refrigerator temperatures and can overcome concerns in vaccine-hesitant populations.

A coronavirus-like particle (CoVLP) vaccine can be produced in a plant leaves, which can be used to generate a number of viral vaccines that have shown substantial immunogenicity and efficacy. The expression of the SARS-CoV-2 S protein in the cells of the plant leaves can form virus-like particles measuring 100 to 150 nm. After harvesting and purification, these particles are stable for at least 6 months at 2 to 8°C. These Coronavirus-like particles (CoVLP), which display the prefusion spike glycoprotein of the original strain of SARS-CoV-2, are combined with an adjuvant (Adjuvant System 03

[AS03]) to form the candidate vaccine.

A trial of this vaccine was conducted using a total of 24,141 participants, whose median age was 29 years. The CoVLP+AS03 vaccine was effective to prevent COVID-19 disease. It can protect the people against the infection of different variants, with efficacy ranging from 69.5% against symptomatic infection to 78.8% against moderate-to-severe disease. No trial participants group faced any severe cases of COVID-19. Solicited adverse events were mostly mild or moderate and transient and were more frequent in the vaccine group than in the placebo group; local adverse events occurred in 92.3% and 45.5% of participants, respectively, and systemic adverse events in 87.3% and 65.0%. The incidence of unsolicited adverse events was similar in the two groups up to 21 days after each dose (22.7% and 20.4%) and from day 43 through day 201 (4.2% and 4.0%).

References

Karen J. Hager, Gonzalo Pérez Marc, Philipe Gobeil, Ricardo S. Diaz, Gretchen Heizer, Conrado Llapur, Alexander I. Makarkov, Eduardo Vasconcellos, Stéphane Pillet, Fernando Riera, Pooja Saxena, Priscila Geller Wolff, et al., Efficacy and Safety of a Recombinant Plant-Based Adjuvanted COVID-19 Vaccine. N Engl J Med 2022; 386:2084-2096. June 2, 2022.

Intramuscular AZD7442 (Tixagevimab–Cilgavimab) for Prevention of COVID-19

The development of different vaccines and their wide application have reduced and combated the severe attack of COVID-19 (Levin et al., 2022). But there are some immunocompromised people, who can't get vaccine, are at high risk of COVID-19 infection.

Monoclonal antibodies have high capacity to provide the rapid protection against disease irrespective of their immune system status. Therefore, these antibodies are considered as a potential candidate for COVID-19 immunoprophylaxis. Some combinations of monoclonal antibodies are already in use through emergency or temporary authorization for preexposure or postexposure prophylaxis against COVID-19 or treatment of mild-to-moderate disease.

Two fully human, SARS-CoV-2–neutralizing monoclonal antibodies (tixagevimab and cilgavimab) are separated from antibodies isolated from B cells obtained from persons infected with SARS-CoV-2. These two monoclonal antibodies are combined to prepare AZD7442 that has been shown to neutralize SARS-CoV-2 and its variants of concern in vitro and has prophylactic and therapeutic effects in animal models/nonhuman primates. Pharmacokinetic data in humans indicate that AZD7442 has an extended half-life of approximately 90 days.

The 35.3% of participants in the AZD7442 group reported having at least one adverse event, most of which were mild or moderate in severity. The 0.2% of participants showed symptomatic COVID-19 after administering the AZD7442. A single dose of AZD7442 had efficacy for the prevention of COVID-19, without evident safety concerns.

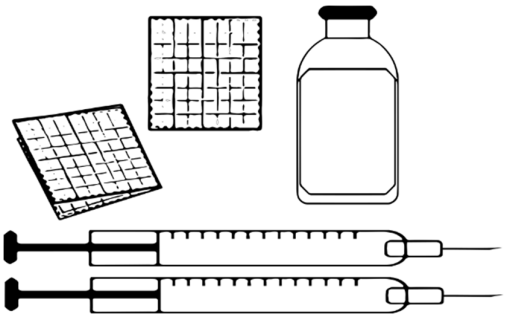
References

Levin M J, Ustianowski A, De Wit S, Launay O, Avila M, Templeton A, Yuan Y, Seegobin S, Ellery A, Levinson D J, Ambery P, Arends R H, et al., Intramuscular AZD7442 (Tixagevimab–Cilgavimab) for Prevention of COVID-19. N Engl J Med 2022; 386:2188-2200. June 9, 2022.

Dual action single dose Moderna vaccine shot against the flu and COVID

Moderna is endeavouring to develop a single-shot vaccine for COVID-19 and the flu in near future. This product will be made at its Victorian manufacturing facility (Koehn, 2022).

Moderna has been developing a new vaccine that specifically target the Omicron virus, which is coming to the market by the start of August 2022 (ABC news, 2022; Collins, 2022). In the persons not affected by COVID-19, this new vaccine produced 1.75 times the level of antibodies against Omicron than the existing Moderna vaccine. Moderna's Chief Medical Officer, Paul Burton said that a new booster was necessary to address waning immunity. Therefore, they are developing a single dose super vaccine that will work to protect against the flu and COVID-19 (ABC news, 2022).



Moderna's Chief medical officer, Paul Burton, told *The Age* and *The Sydney Morning Herald* that the government bodies of the different countries around the world have shown great interest to develop a single vaccine that can tackle multiple respiratory diseases.

COVID-19 has severely affected the people since the end of 2019. Recently, the case number of influenza/flu is surging all over the place. Therefore, Moderna is currently running trials of a combined flu and COVID vaccine (Collins, 2022; Koehn, 2022). They will soon start a phase-one study of a single dose shot to protect against influenza, coronavirus and respiratory syncytial virus (RSV).

References

ABC news Australia, 21/06/2022

Collins J**,** Aussies Will Soon Get A Super Vaccine That Will Cover COVID-19 And Flu. Ladbible publisher, Published 7:39, 21 June 2022 BST| Last updated 7:39, 21 June 2022 BST. Link: https://www.ladbible.com/news/latest-aussies-will-soon-get-a-super-vaccine-COVID19-and-flu-20220621. Accessed on 22/06/2022.

Koehn E, 'One and done': Moderna could make combined COVID-19, flu jab in Melbourne. The Sunday Morning Herald, June 21, 2022 — 5.00 am.

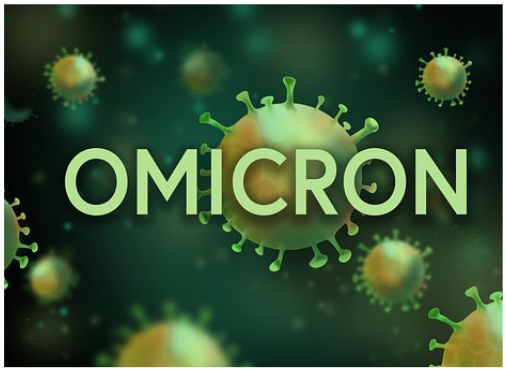
End of the COVID-19 Pandemic

Dr Hossain Md Anawar

The number of COVID-19 cases is decreasing all over the world and the severity of the new variants is relatively lower than the earlier variants. Therefore, the people are wondering that the pandemic will end and change to localised problems or flu-like disease.

Trend of Omicron

The Omicron variant hit the people showing a rapid increase in the number of cases and also spread very quickly all over the world. It was more infectious than any previous variants and evades the immunity of the people provided by single dose or incomplete vaccination. But it was less severe than the Delta variant except some worst case scenarios. After the Omicron variant declines, the pandemic phase of COVID-19 started to end for most locations, unless a significant and severe new variant emerges. Omicron has spread around the world in less than three months, the case number skyrocketed in many places. But the case number luckily declined just as quickly.



After the Omicron, another variant was affecting the people sporadically and locally indicating that the pandemic phase of COVID-19 is moving to be as endemic (Charumilind et al., 2022). After the Omicron, the public-health measures and restrictions were relaxed in some areas, which was not seen before. Public health precautions, social responses, up-to-date vaccinations and booster doses of vaccination were very effective against the Omicron wave and changed the pandemic situation to endemic.

Post-Omicron COVID-19 Situation

After the Omicron infection wanes and is almost over, there appears a new sub-variant that is also affecting the people locally. Now the questions are roaming around whether and

when future variants will emerge. Some other variants of COVID-19 may appear seasonally and locally in any part of the world resulting in endemic.

The different parts of the world will experience the coming phase differently depending on seasonal variations (north and south hemisphere), age, demography of populations and government policy. Countries with high rates of current immunity and widespread booster uptake will be better protected (Charumilind et al., 2022).

Reference

Charumilind S, Craven M, Lamb J, Sabow A, Singhal S, Wilson M, 2022. When will the COVID-19 pandemic end? March 1, 2022. Link: https://www.mckinsey.com/industries/healthcare-systems-and-services/our-insights/when-will-the-COVID-19-pandemic-end. Accessed on 19/05/2022.