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" COVID flood, can vaccines withstand (Review paper)"

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Abstract:

Coronavirus disease (COVID-19) is a worldwide pandemic started in Wuhan city, China, in December 2019, resulting in huge economic and social consequences globally. Numerous variants of SARS-COV-2 virus are being tracked in the United States (US) and globally during this pandemic. Variants of Concern (VOCs) include B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta). These variants are characterized by genetic mutations of the spike protein (S protein) of the virus. These mutations can minimize the neutralization activity of antibodies by post vaccination sera and consequently affecting the immune response of the body against the virus. With this rapid rate of variants emergence, a lot of studies and updated reports were published to document the ongoing changes of the virus circulation and to study the effectiveness of available vaccines on these variants. This review showed that the currently available vaccines are of acceptable effectiveness against all possible clinical outcomes of COVID-19 infection caused by the VOCs, even delta variant. So full immunization with at least two doses is still highly recommended for all indicated groups of population to ensure acceptable protection against symptomatic disease, hospitalization and deaths.

Background

Coronavirus disease (COVID-19) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a worldwide pandemic caused by a virus that was first detected in Wuhan city, China, in December 2019 and then spreads worldwide. The World Health Organization (WHO) announced this disease as being a new pandemic on 11 March 2020. As reported in August 2021, over 216 million confirmed cases and 4.49 million deaths have been documented; so it is considered one of the lethal pandemics in the history. The pandemic also has resulted in huge economic and social upheaval globally [1].

Patients with COVID-19 experience many symptoms ranging from mild symptoms to severe disease. Symptoms usually appear about 2 to 14 days after getting the virus (what is called Incubation period). The commonest reported symptoms are fever, cough, difficult breathing, fatigue, bony aches, headache, loss of taste or smell, sore throat, rhinorrhea, nausea, vomiting and diarrhea. Elderly and chronic illnesses' patients as heart or lung disease or diabetes are found to be at higher risk for experiencing more critical outcomes from COVID-19 illness [2].

As Viruses continuously change through mutation, and new mutants of a virus are expected to appear, numerous variants of SARS-COV-2 virus are being tracked in the United States (US) and globally since this pandemic starts [2]. The US Department of Health and Human Services established an Interagency Group of SARS-COV2 that developed a classification system including variants of interest, of concern, and of high consequence. The variants of concern - which are defined as variants containing one or more mutations that can alter some of the virus properties as enhancement of the transmissibility of the virus and increasing the resistance to the immune response of the body- include Alpha, Beta, Gamma, and Delta variants. [3].

The development of SARS-CoV-2 vaccines is a major asset to slow down the progress of COVID-19 pandemic. At the current time, more than 100 vaccines have been developed, and 22 vaccines have been evaluated in phase III clinical trials according to the World Health Organization (WHO) [4]. The evolution of new virus variants is a point of interest by now as studies showed that genetic mutations of the spike protein of the virus, especially E484K and P1 can minimize the neutralization activity of antibodies by post vaccination sera and consequently affecting the immune response of the body against the virus [5].

With the ongoing evolution of new variants of concern of SARS-COV 2 virus and the effect of mutations on how will vaccines work against the virus, a lot of studies were published and daily updated reports are still needed to cope with the ongoing changes of the virus circulation and to develop new vaccines that are able to target new variants and improve the immune response of the body against the virus.

Methods

Electronic searches for studies were conducted using terms of “SARS-CoV-2”, “COVID-19”, “vaccine efficacy”, “effectiveness”, “variants of concern”, “delta variant” in addition to the scientific or commercial name of the vaccines reported by WHO in phase III/IV. Vaccines included in this review were approved in at least one country by FDA (The Food and Drug Administration) according to the authorization of emergency use -named as (EUA)- for the emergency usage of the vaccine for prophylaxis against COVID-19 and based on phase III randomized placebo-controlled trials.

Variants of SARS-COV2

As viruses widely spread, they continuously change via mutations to their genetic code. Although most mutations of the SARS-CoV-2 genome do not influence the functioning of the virus, mutations of the spike protein (S protein) of SARS-CoV-2 virus -which binds to receptors on cells lining the human respiratory tract- may enable the virus to spread easily or affect the way vaccines work against the virus. Other mutations may lead to reducing the response of COVID-19 patients to the treatments for the disease [6].

Variant of concern (VOC) are defined by CDC (Centers for Disease Control and Prevention) as being a variant with one mutation or more that enable the virus to infect people or spread from someone to another more easily, make the virus more resistant to treatments, or change the effectiveness of the vaccine against the virus”. The definition of Variant of high consequence is stated as being a variant for which there is clear prove that “prevention measures such as available vaccines and treatments have a significant reduced effectiveness as compared to previously circulating variants,” resulting in more severe illness and more hospitalizations”. By now, no variants of high consequence have been reported globally [7].

Recently, the VOCs were renamed by the WHO as Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1) and Delta (B.1.617.2). All of them have common mutations in the S gene as compared with the original (Wuhan) virus [8], details are shown in (Table 1) [5].

Since late March 2021, India has experienced rush in number of cases of Covid-19, reaching about 400,000 cases and more than 4 thousand deaths reported daily in May 2021. Which in turn led to overwhelming the available hospital services and to a deficiency of oxygen supplies. Only a small number of specimens have been sequenced. However, Delta variant of SARS-CoV-2 has dominated [9]. The Delta variant is characterized by a wide variant of S protein mutations, many of these mutations can affect the immune reactions directed toward the main antigens of 452 and 478 receptor binding proteins and partial removal of the N-terminal domain. Strains with mutations at the P681R site which is at the S1–S2 cleavage site,

may express over replication, that consequently results in elevation of viral loads and more viral spread [10].

Due to these mutations and compared to the alpha variant, delta variant is estimated to have a 60% over transmission rate, and the CDC has estimated its main reproduction rate (R0) - which represents the calculated number of infections' secondary cases that occur through transmission of infection from a confirmed case of infection to a vulnerable people - is within the range of 5 and 8. As an easy estimation to clarify the impact of this elevation in theR0, If a virus with a 2.5 R0 spreads within vulnerable people, about 9536 cases of infection would result through 10 transmission cycles, What a disaster?! [11].

On 30 August 2021, WHO's watchlist was added a new variant of concern named as Mu (B.1.621) variant after being reported in more than 40 countries worldwide. It was first identified in Colombia in January 2021 and since then sporadic cases and larger outbreaks caused by it have been reported globally. According to the weekly reports of WHO on the pandemic, this variant is found to possess a collection of genetic mutations that give the virus potential characteristics of immune defenses escape as the Beta variant when it was first discovered in south Africa, but further research is needed to confirm these data [12].

Vaccine end points (efficacy& effectiveness)

In the field of vaccine research and to define efficacy, various endpoints are used depending on the pathogen, infection outcomes and transmission dynamics [13]. In WHO's Vaccines Explained series, the vaccine's **efficacy** is defined as" a measure of how much the vaccine lowered the risk of getting sick". It is measured in phase III randomized controlled trials (RCTs) based on how many vaccinated people developed the disease in comparison to people who got the placebo (dummy vaccine). At the end of the study, the numbers of sick people in each group are compared, in order to calculate the relative risk (RR) of getting the disease depending on whether or not the study subjects received the vaccine. Vaccine's **effectiveness** is defined as "a measure of how well vaccines work in the real world by observing how well the vaccines work to protect communities as a whole". Real life clinical trials (phase IV RCTs) include a wide range of people with a broad age range, both sexes, different ethnicities and those with known medical conditions. Although, they cannot be a perfect representation of the whole population [14].

For COVID-19, efficacious and effective vaccine might protect against viral spread, getting the infection or experiencing the disease (Figure 1). COVID-19 infection has variable consequences based on a lot of factors as age, gender, ethnicity and chronic illnesses. So individually, the outcome of infection can range from asymptomatic conditions to hospitalization, need for oxygen support, or death [15].

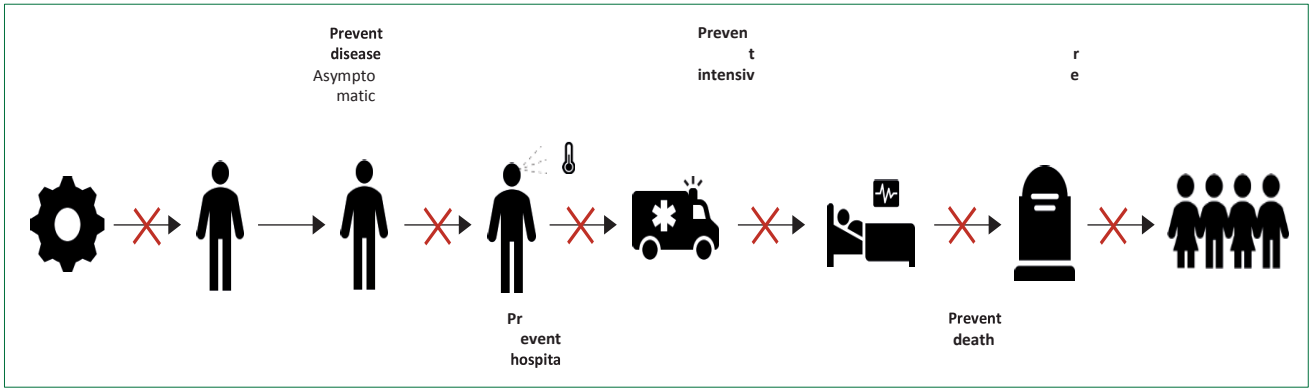
COVID-19 vaccines

GISAID (Global Initiative on Sharing All Influenza Data) in January 2020 published the data of genetic sequencing of SARS-CoV-2 virus and by the end of March, the international pharmaceutical industry started the process of vaccine manufacturing [16].

An efficacy of about 95% in preventing SARS-CoV-2 symptomatic infections have been reported in Phase III RCTs of the process of vaccines' production. FDA approved about 22 vaccines in at least one country for public use. Categories and names of vaccines are shown in (Table 2) [17].

Figure (1): Potential endpoints of an efficacious COVID-19 vaccine.

An efficacious COVID-19 vaccine could reduce the possibility of infection of an individual, severity of disease in an individual, or degree of transmission within a population.



The Pfizer BioNTech vaccine was approved on 21 December 2020 and since then vaccination against COVID-19 virus using it began to be given worldwide. Moderna vaccine was approved on 6 January 2021 and the AstraZeneca on 29 January of the same year [18]. Sinopharm and the Chinese Academy of Science has developed The Wuhan vaccine which is a β- propiolactone-inactivated vaccine based on WIV04 strain that was derived from a patient in the Jinyintan Hospital, Wuhan city [19].

Table (1): COVID-19 variants

SARS-CoV-2 variants	B1.1.7 501Y.V1	B.1.351 501Y.V2	B.1.1.28.1. P1 501Y.V3	B.1.617.2
WHO nomenclature	**Alpha**	**Beta**	**Gamma**	**Delta**
Key spike mutations	69/70del, 144del, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H	D80A, D215G, 241/243del, K417N, E484K, N501Y, D614G, A701V	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G H655Y, T1027I, V1176F	T19R, T95I, G142D, E156-, F157-, R158G, , L452R, T478K, D614G, P681R, D950N ± (V70F, A222V, W258L, K417N)
First detection	United Kingdom	South Africa	Brazil and Japan	India
Transmission compared to non-VOC/VOI	+56% in the UK +56-74% in Denmark, Switzerland, US 43-100% higher reproductive number	+50% in South Africa	+160% in Brazil	+40 to 60% in the UK (compared to Alpha) +97% higher reproductive number
Risk of mortality	Increased 61-64%mortality in the UK	Under investigation	Under investigation	Under investigation

VOC: Variant of Concern, VOI: Variant of Interest, UK: United Kingdom, US: United States.

Phase IV studies evaluate the vaccine real-life effectiveness in an observational design among general population, unlike phase III trials which assess the efficacy in controlled conditions only. Real-world studies provide crucial information about short and long-term effects, the prevention of asymptomatic infection, the severity of COVID-19 illness, hospitalization and death related to the disease. Moreover, these studies evaluated vaccine effectiveness in a real-world setting and have shown encouraging results in several countries -as will be discussed later- suggesting a potent effect of the vaccines on the transmissibility of SARS-CoV-2 and the control of the pandemic [5].

Table (2): COVID-19 vaccines

Type of the vaccine	No.	Nam e
DNA vaccines	1	ZyCoV-D
RNA vaccines	2	Pfizer– BioNTech , Moderna
conventional inactivated vaccines	9	BBIBP-CorV, Chinese Academy of Medical Sciences "Sinopharm", CoronaVac, Covaxin, CoviVac, COVIran Barekat, Minhai- angtai, QazVac, and WIBP-CorV
viral vector vaccines	5	Sputnik Light, Sputnik V, Oxford AstraZeneca, Convidecia, and Janssen
protein subunit vaccines	5	Abdala, EpiVacCorona, MVC-COV1901, Soberana 02, and ZF2001

Starting with **ChAdOx1 nCoV-19 vaccine (Astrazeneca)**, a lot of studies were conducted to assess the efficacy of this vaccine in real life. An analysis of four RCTs in Brazil, South Africa, and the UK was done among subjects aged 18 years and older on the use of ChAdOx1 nCoV-19 vaccine, showing an overall efficacy of 70.4% regardless number of administered doses. It also has been proved for its effectiveness to protect against symptomatic COVID-19, serious disease outcomes, hospitalization and deaths [20].

As a comparative study with **BNT16b2 (Pfizer– BioNTech) vaccine**, VIVALDI study was conducted among elderly in the UK showing that Single-dose vaccination with either of both vaccines can potently protect against infection in elderly about 4 to 7 weeks after vaccination and can also minimize COVID-19 spread. Despite these findings, the infection risk is found not to be full eradicated, as mean PCR cycle threshold values when compared between infections occurring about 28 days after getting the vaccine and those occurring before the vaccination were found to be higher. The point which highlights the potential need for non-pharmacological measures to inhibit viral transmission in establishments of long-term care [21].

Bernal JL *et al*. have conducted the same comparison through a test negative case control study, concluding that one dose vaccination with either BNT162b2 or ChAdOx1-S could lead to a remarkable reduction in the incidence of symptomatic covid-19 in older adults, and with subsequent protection against critical illness. Also, as a conclusion, an effectiveness against hospitalization of about 80% and of 85% against deaths of a single dose of either vaccine was reported [22].

Public Health England (PHE) published the same results in their updated report in February 2021 [23]. Similar findings were reported in Scotland as being the both vaccines sharing the same reducing effect on severity of symptomatic COVID-19 disease, need for hospitalization and COVID-19 related death rates [24].

Several papers were published discussing the effectiveness of **BNT16b2 (Pfizer– BioNTech) vaccine** on COVID-19 illness. A prospective cohort study (SERIN study) was conducted in UK reporting an effectiveness of 72% about 21 days after the first dose and 86% about 7 days after the second dose [25]. Different percentages were reported in Qatar as vaccine efficacy being around 39.4% after single dose and 97.4% after full vaccination [26].

Along with BNT16b2 (Pfizer– BioNTech) vaccine, **mRNA-1273 (Moderna) vaccine** was the first vaccine to be approved by FDA in US [18]. Regarding the Real-life effectiveness of both vaccines on the clinical sequence of SARS-CoV-2 illness, studies showed an overall effectiveness of about 80% after a single dose of either vaccine and 90% after full immunization [27]. Puranik A. *et al* reported near results with more potent effect on the hospitalization rates, need for ICU admission and disease related deaths. Although, they noticed decreased effectiveness with time of breakthrough from January to July 2021 [28].

Recommendation of Advisory Committee on Immunization Practices (ACIP) on December 2020 for those who are indicated for vaccination were arranged in three phases based on prioritization [29]:

1- **Phase Ia**: includes healthcare personnel and residents of long-term care facility.
2- **Phase 1b**: includes people aged 75 years and more and non–healthcare essential workers as military members.
3- **Phase 1c**: includes people aged 65 to 74 years, people aged 16 to 64 years with high-risk medical comorbidities, and essential workers not included in the Phase 1b [29].

On August 13,2021, CDC states recommendations of administering a third dose of COVID-19 vaccines to immunocompromised persons about 28 days after the second dose. Immunocompromised individuals are those diagnosed with malignancy and on active treatment, organ transplant recipients receiving post transplantation immunosuppressive drugs, cases of severe HIV infection and primary immunodeficiency and those who are on treatments with high dose steroids, chemotherapy, immunosuppressive drugs, antimetabolites and other immunosuppressive biological agents [30].

Regarding Sinopharm vaccine, Phase I and II trials showed this vaccine's efficacy depends mainly on the production of neutralizing antibodies [31]. Antibody levels were found to be measurable enough in about 90% of persons aged below 50, but these levels were found to be lower and

lower with increasing age [32]. Phase III trials done in Bahrain, China, Pakistan, and the United Arab Emirates reported an effectiveness of about 72.8% against SARS-CoV-2 infection about 14 days after full vaccination with two doses [33].

COVID-19 vaccines and delta variant

With updated scientific research, the immunity provided by the currently available COVID-19 vaccines against the Delta variant is about to be illustrated [5]. Data from England suggests that protection against symptomatic infection with the Delta variant couldn't be provided by just one dose of either the Pfizer-BioNTech (BNT162b2) or the AstraZeneca-Oxford (ChAdOx1 nCoV-19) vaccine, but full vaccination with two doses increase effectiveness to about 88% and 67% respectively. These percentages are still lower than those for the Alpha variant (93.7% and 74.5% respectively) [34]. Similar results were reported in Canada with a lower effectiveness of partial vaccination against the Delta variant compared to the Alpha one for mRNA-1273 (Moderna) vaccine (72% vs. 83%) and BNT162b2 (Pfizer- BioNTech) vaccine (56% vs. 66%), but was similar to Alpha for ChAdOx1(Astrazeneca) vaccine (67% vs. 64%). Two doses of BNT162b2 vaccine offered an over immunity against Delta (87%) reaching comparable values to Alpha (89%) and Beta (84%) [35].

Results among vaccinated population in Iceland showed that all vaccinated people who became infected have been recovered without serious illnesses. Number of reported COVID-19 related deaths were the same among all cases regardless the causative variant. This study concluded that even if herd immunity due to vaccination can't be achieved for COVID-19 caused by delta variant, high vaccination levels minimize rates of hospitalization and deaths [36].

In India, effectiveness of Covaxin vaccine against delta variant was studied showing a 2-fold drop in sero neutralization caused by the vaccine in cases of delt variant compared to alpha and beta variants [37].

Conclusion

According to the global updated reports, only 6 months passed between the announcement of COVID-19 as being a pandemic and the launch of the first phase III vaccine trials. Overall, COVID-19 vaccines appear to be safe and effective tools to prevent symptomatic and severe disease, hospitalization and death against all VOCs, confirming the results from phase III clinical trials. However, as discussed in details before, available data vary greatly depending on the vaccines considered. All reported data showed that mRNA vaccines have a reducing effect on the incidence of asymptomatic COVID-19 and viral load and subsequently transmission [4].

What is obvious enough is that breakthrough infections are still infrequent but are linked with the Delta variant; despite this fact, the currently available vaccines are of acceptable effectiveness against severe illness, hospital admission and death rates. In US, most of severe cases occur among unvaccinated individuals [11].

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