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The doubtful effectiveness of the COVID-19 vaccine

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Abstract

A COVID-19 pandemic has erupted around the world. World Health Organization (WHO) and allies are racing to create and deploy safe and effective vaccines as they work together to monitor the pandemic, advise on crucial measures, and distribute essential medical resources to those in need. Vaccines save millions of lives, by training the body's natural defenses, the immune system, to identify and combat the viruses and bacteria they are intended to combat. This review article presents the status of COVID-19 vaccines evaluated by the WHO Emergency Use Listing (EUL) assessment process and those liberated as well. Data was obtained from the WHO, Gavi – The Vaccine Alliance from Bill & Melinda Gates Foundation, Oxford Vaccine Group, Serum Institute of India, AstraZeneca, European Medicines Agency EMA among others. As can be seen, there is still no totally effective vaccine, and many clinical trials are still needed, and even immunized citizens are still at risk of recontagion. Virus mutation is a recurring problem and different vaccine production methodologies are still being studied.

Keywords: COVID-19; Pandemic; Vaccines; World Health Organization.

1. Introduction

Several vaccines are currently in use, according to data from the World Health Organization (WHO). The first mass vaccination campaign began in early December 2020, and 175.3 million vaccine doses had been administered as of February 15, 2021. At least seven different vaccines (from three different platforms) have been given out. On December 31, 2020 WHO released an Emergency Use Listing (EUL) for the Pfizer COVID-19 vaccine (BNT162b2). WHO released another EUL for two variants of the AstraZeneca/Oxford COVID-19 vaccine, manufactured by the Serum Institute of India and SKBio, on February 15, 2021. Other vaccine products are on track to be EUL by June 2021 [1].

2. Methodology

Vaccines must be licensed by national authorities, produced to exacting standards, and administered after they have been shown to be safe and reliable. WHO is collaborating with partners all over the world to help organize crucial steps in the process, such as ensuring equal access to safe and reliable COVID-19 vaccines for the billions of people who will need them. COVID-19 vaccines have already started to be distributed in some countries. Until COVID-19 vaccines can be administered, the following requirements must be met:

- In phase III of clinical trials, the vaccines must be proved safe and reliable. Many potential COVID-19 vaccine candidates have completed phase III trials, and many more are being produced;

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- Before WHO considers a vaccine candidate for prequalification, independent evaluations of effectiveness and safety evidence are required for each vaccine candidate, as well as regulatory review and approval in the country where the vaccine is produced. The Global Advisory Committee on Vaccine Safety (GACVS) is also involved in this operation;
- In addition to reviewing the data for regulatory purposes, the facts must be checked in order to make policy decisions on how vaccines can be used;
- The WHO's Strategic Advisory Committee of Experts on Immunization (SAGE) reviews the outcomes of clinical trials, as well as evidence on the disease, age groups affected, disease risk factors, programmatic use, and other data. After that, SAGE makes suggestions on when and how vaccines can be used [2];
- SAGE analyses clinical trial findings, as well as evidence on the disease, affected age groups, disease risk factors, programmatic use, and other data. After that, SAGE makes suggestions on when and how vaccines can be used [2];
- Officials in individual countries determine whether to allow the vaccines for national use and establish policies based on WHO guidelines on how to use the vaccines in their country;
- The vaccines must be produced in vast quantities, which is a significant and unprecedented undertaking – even while continuing to manufacture all of the other critical life-saving vaccines currently in use;
- Finally, all licensed vaccines must be distributed through a complex logistical process that includes strict stock management and temperature regulation.

The status of COVID-19 vaccines in the WHO EUL/PQ assessment process is shown in Table 1.

Table 1 Status of COVID-19 vaccines in the WHO EUL/PQ assessment process

Manufacturer	Vaccine	National Regulatory Authorities (NRA) of record	Platform	Expression of Interest (EOI) accepted	Pre-submission meeting held	Dossier accepted for review*	Status of assessment**	Anticipated decision date***
Pfize, Biontech	BNT162b2/COMIRNATY Tozinameran (INN)	EMA	Nucleoside modified mRNA	Yes	Yes	Yes	Finalized	31/12/20
AstraZeneca, Oxford	AZD1222	Core– EMA Non-COVAX	Recombinant ChAdOx1 adenoviral vector encoding the Spike protein antigen of the SARS-CoV-2.	Yes	Yes	Accepted core data of AZ – non-Covax Data for Covax expected in March 2021	Non-Covax Core data. Awaited	NA March – April 2021
SK Bio, Astrazeneca, Oxford	AZD1222	MFDS KOREA	Recombinant ChAdOx1 adenoviral vector encoding the Spike protein antigen of the SARS-CoV-2.	Yes	Yes	Yes	Finalized	15 Feb 2021
Serum Institute of India	Covishield (ChAdOx1_nCoV19)	DCGI	Recombinant ChAdOx1 adenoviral vector encoding the Spike protein antigen of the SARS-CoV-2.	Yes	Yes	Yes	Finalized	15 Feb 2021

Sinopharm, Beijing Bio-Institute of Biological Products Co-Ltd	SARS-CoV-2 Vaccine (Vero Cell), Inactivated (lnCoV)	NMPA	Inactivated, produced in Vero cells	Yes	Yes	Yes	In progress	Earliest March
Sinovac	SARS-CoV-2 Vaccine (Vero Cell), Inactivated	NMPA	Inactivated, produced in Vero cells	Yes	Yes	Additional expected end of Feb 2021	No data	Earliest March
Moderna	mRNA-1273	EMA	mRNA-based vaccine encapsulated in lipid nanoparticle (LNP)	Yes	Yes	Additional data expected week starting 15 Feb 2021	No data	Estimated end of Feb 2021
Janssen	Ad26.COV2.S	EMA	Recombinant, replication incompetent adenovirus type 26 (Ad26) vectored vaccine encoding the (SARS-CoV-2) Spike (S) protein	Additional information submitted	Several meetings held	Rolling data to EMA – Dec, 29 Jan and 15 Feb 2021 To submit for EUL on 19 Feb 2021	Not yet started. Use abridged procedure relying on EMA	March - April 2021
The Gamaleyea National Center	Sputnik V	Russian NRA	Human Adenovirus Vector-based Covid-19 vaccine	Yes	Yes	Rolling data started 09 and additional data expected week starting 15 Feb 2021	No data	No data
CanSinoBio	Ad5-nCoV	NMPA	Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector)	Letter received not EOI. Reply sent on 15/01/2021	No data	Rolling data starting April 2021	No data	No data
Vector State Research Centre of Virology and Biotechnology	EpiVacCorona	Russian NRA	Peptide antigen	Response to Second EOI sent 29 Jan 2021. Additional information requested.	No data	No data	No data	No data
Zhifei Longcom, China	Recombinant Novel Coronavirus Vaccine	NMPA	Recombinant protein subunit	Not accepted, still under initial development	No data	No data	No data	No data

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IMBCAMS, China	SARS-CoV-2 Vaccine, Inactivated (Vero Cell)	NMPA	Inactivated	No data	No data	No data	No data	No data
Sinopharm, Wuhan Institute of Biological Products Co Lt	Inactivated SARS-CoV-2 Vaccine (Vero Cell)	NMPA	No pre-submission meeting yet	No data	No data	No data	No data	No data
Novavax	No data	EMA	No pre-submission meeting yet	Awaiting decision on submission	No data	No data	No data	No data

* Dossier Submission dates: more than one date is possible because of the rolling submission. Dossier is accepted for submission after screening of received submission; ** Status of assessment: 1. under screening; 2. under assessment; 3. Waiting responses from the applicant. 4. Risk-benefit decision 5. Final decision made; *** anticipated decision date: this is only an estimate because it depends on when all the data is submitted under rolling submission and when all the responses to the assessors' questions are submitted.

2.1. Status of COVID-19 vaccines within WHO EUL/PQ evaluation process [Source: WHO (2021)]

A COVID-19 pandemic has erupted around the world. WHO and allies are racing to create and deploy safe and effective vaccines as they work together to monitor the pandemic, advise on crucial measures, and distribute essential medical resources to those in need. Vaccines save millions of lives, by training the body's natural defenses, the immune system, to identify and combat the viruses and bacteria they are intended to combat.

If the body is later exposed to such disease-causing germs after vaccination, the body is able to kill them right away, avoiding illness. At least seven separate vaccines across three channels have been carried out in countries as of February 18, 2021. Vaccination is prioritized for vulnerable groups in all countries.

Simultaneously, more than 200 additional vaccine candidates are being studied, with more than 60 of them in clinical trials [3]. COVAX is a component of the ACT Accelerator, which WHO and collaborators launched in 2020. COVAX, the ACT Accelerator vaccines pillar convened by CEPI, Gavi, and WHO, aims to end the COVID-19 pandemic's acute period by:

- collaborating with governments and manufacturers to ensure equal and equitable allocation of vaccines for all countries;
- speeding up the production of safe and reliable COVID-19 vaccines;
- promoting the development of manufacturing capabilities;
- working with governments and manufacturers to ensure fair and equitable allocation of vaccines for all countries.

Vaccines are an important weapon in the fight against COVID-19, and the fact that so many vaccines are proving to be effective and are being developed is extremely promising. Scientists from all over the world are working and innovating as rapidly as they can to develop experiments, medications, and vaccines that can save lives and put an end to the pandemic.

Safe and reliable vaccinations will change the game, but for the time being, we must continue to wear masks, keep a safe distance, and avoid crowds. The degree to which vaccinations can protect not only against disease but also against infection and transmission is still unknown, so by being vaccinated does not mean we can throw caution to the wind and put ourselves and others at risk.

Data from a major clinical trial of Oxford University and AstraZeneca's COVID-19 vaccine candidate indicates that a halved first dose followed by a maximum second dose could be up to 90% effective [4-5]. This regimen will result in more people being vaccinated earlier because it uses less vaccine for the first doses. Gavi has now secured 200 million vaccine doses, with the option of securing many times more.

Any of the first doses may be available by the end of 2020, pending complete licensure or WHO prequalification of the vaccine. More than 23,000 people from the United Kingdom and Brazil were included in the interim findings from phase 3 clinical trials. So far, 131 participants in these studies have produced COVID-19, the majority of whom were in groups that got the placebo, followed by a dose of MenACWY meningococcal conjugate vaccine and a dose of saline solution.

After obtaining the candidate vaccine, none of the participants who acquired COVID-19 developed serious disease or needed hospitalization for their symptoms. Based on weekly nose and throat swabs from trial participants, preliminary evidence suggests that the vaccine could reduce the rate of asymptomatic COVID-19 cases.

If confirmed, this may suggest that the vaccine is preventing SARS-CoV-2 transmission as well as disease symptoms. So far, no significant side effects from the vaccine have been reported. The new findings come after phase 2 trial results were published in The Lancet, indicating that the vaccine is safe and induces a similar immune response in both old and young adults (including those aged over 70). However, the duration of defense against SARS-CoV-2 is unknown [6].

For the duration of the pandemic, Oxford University and AstraZeneca have committed to providing the vaccine on a not-for-profit basis to low- and middle-income countries, as well as higher-income countries [4-5].

AstraZeneca has formed collaborations with partner manufacturers in ten countries to ensure global supply of the vaccine, with three billion doses anticipated by the end of 2021. It was also the first company to join COVAX, a global initiative led by Gavi, CEPI, and WHO to ensure equal access to COVID-19 vaccines. According to a memorandum signed in June, AstraZeneca will guarantee up to 300 million doses of its vaccine to the 188 economies now involved in the global system, based on licensure or WHO prequalification.

If the vaccine is approved, it should be deployed quickly, especially if only a half dose is needed for the first shot. AstraZeneca's Vice President of Operations, Pam Cheng, stated that the company could send complete or half vials of vaccine with no major effect on the supply chain. A new agreement between Gavi, the Serum Institute of India, and the Bill & Melinda Gates Foundation [7-8] could secure up to 200 million vaccine doses of either the AstraZeneca or a Novavax vaccine for lower-income countries at a ceiling price of US$ 3 per dose, with the option to secure many times that amount if the COVAX Facility sees a need.

Importantly, adenovirus vaccines are relatively stable and can be transported and stored at 2-8 degrees Celsius in a domestic refrigerator. This means that, rather than needing specialized storage facilities, the vaccine could be administered using existing cold chains and delivered alongside regular vaccination services, such as at doctor's offices, community centers, and local pharmacies.

These interim findings, along with safety details, will now be sent to regulators around the world for independent review and product approval. AstraZeneca has already announced that it would apply to the WHO for an Emergency Use Listing, which would expedite vaccine access in low-income countries.

Meanwhile, as the pandemic progresses, the clinical trial participants will be tracked, providing more data on vaccine effectiveness and period of safety. Additional vaccine trials are being performed in the United States, Kenya, Japan, and India, with about 60,000 people projected to be enrolled.

When administered as a half dose followed by a full dose at least one month later, the vaccine had a 90 percent efficacy; when given as two full doses at least one month apart, it shows 62 percent efficacy. According to AstraZeneca's interim trial results, the vaccine is 80% effective in preventing COVID-19 among those aged 65 and up, who made up 20% of trial participants. The number of cases of COVID-19 observed in this cohort is not stated in the press release, but Falsey stated on Monday that there were enough infections in the older age group to make a statistically relevant comparison [9].

At its extraordinary meeting on March 18, 2021, the European Medicines Agency's (EMA) safety committee, known as the Pharmacovigilance Risk Assessment Committee (PRAC), concluded its preliminary examination of a signal of blood clots in people vaccinated with AstraZeneca's COVID-19 vaccine [10].

The Committee has confirmed:

- the vaccine's benefits in mitigating the still-present danger of COVID-19 (which causes clotting issues and can be fatal) appear to outweigh the risk of side effects;

- The vaccine has not been related to an increased risk of blood clots (thromboembolic events) in those who receive it;
- There is no evidence of an issue with individual batches of the vaccine or manufacturing facilities;
- however, the vaccine can be related to extremely rare cases of blood clots associated with thrombocytopenia, or low levels of blood platelets (elements in the blood that make it clot), with or without bleeding, including very rare cases of clots in the brain's blood vessels (CVST).

As of March 16, nearly 20 million people in the UK and EEA had received the vaccine, and the EMA had only reviewed seven cases of blood clots in multiple blood vessels (disseminated intravascular coagulation, or DIC) and eight cases of CVST. While a causal link to the vaccine has not been identified, it is probable and warrants further investigation.

In conducting its study, the PRAC consulted with experts in blood disorders and collaborated closely with other health agencies, including the UK's MHRA, which has experience administering this vaccine to over 11 million people. Overall, the number of thromboembolic events recorded after vaccination was lower than anticipated in the general population, both in studies before licensing and in findings after vaccination campaigns (469 reports, 191 from the EEA). This helps the PRAC to ensure that the overall risk of blood clots has not risen. However, there are some concerns among younger patients, especially in these rare cases.

The experts on the Committee reviewed in great detail reports of DIC and CVST cases identified by Member States, nine of which resulted in death. The bulk of these happened to people under the age of 55, and the majority of them were women. The bulk of these happened to people under the age of 55, and the majority of them were women. It's difficult to predict a background rate for these events in people who haven't had the vaccine because these events are uncommon, and COVID-19 itself often triggers blood clotting disorders in patients.

However, based on pre-COVID results, less than 1 confirmed case of DIC among people under 50 within 14 days of receiving the vaccine could have been predicted by 16 March, whereas 5 cases had been reported. Similarly, 1.35 cases of CVST were predicted on average in this age group, but there had been 12 by the same cut-off date. There was no evidence of a similar imbalance in the older population that had received the vaccine.

The Committee decided that the vaccines demonstrated effectiveness in avoiding COVID-19 hospitalization and death outweighed the extraordinarily low risk of developing DIC or CVST. Patients should be mindful of the remote likelihood of such syndromes, and if signs indicative of clotting complications arise, they should seek medical treatment immediately and notify healthcare providers of their recent vaccination. Already, steps are being taken to update the vaccine's product details to provide more information on these risks.

The PRAC will look at these threats further, including the risks associated with other forms of COVID-19 vaccines (although no signal has been identified from monitoring so far). Close safety analysis of cases of blood clotting disorders will continue, and new research will be launched to include more laboratory data and real-world facts. The EMA will inform you of the situation [10].

3. Conclusion

This review article presents the status of COVID-19 vaccines evaluated by the WHO Emergency Use Listing (EUL) assessment process and those liberated as well. Data was obtained from the WHO, Gavi – The Vaccine Alliance from Bill & Melinda Gates Foundation, Oxford Vaccine Group, Serum Institute of India, AstraZeneca, European Medicines Agency EMA among others. As can be seen, there is still no totally effective vaccine, and many clinical trials are still needed, and even immunized citizens are still at risk of recontagion. Virus mutation is a recurring problem and different vaccine production methodologies are still being studied.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors state that they have no conflict of interest to disclose.

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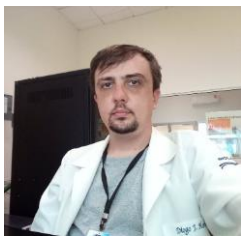	**Dr. Diogo José Horst** has Post-doctorate in Chemical Engineering, Federal University of São Paulo, UNIFESP, and Centro de Investigación en Materiales Avanzados, CIMAV, Mexico (2020-2021). Post-Doctorate in Engineering and Mechanical Sciences, Federal University of Santa Catarina, UFSC (2018-2020). D.Eng of Production Engineering from Federal University of Technology Paraná, UTFPR (2016). M.Eng of Production Engineering from Federal University of Technology Paraná (2013). Bachelor's at Biology from Leonardo da Vinci Universitary Center (2009). Bachelor's at Mechanical Technology from Santa Catarina State University, UDESC (2010). Profissional Technician in Electromechanics from National Service of Industrial Apprenticeship, SENAI (2005). Research lines: Nanotechnology, Biotechnology, Graphene, Niobium, Ceramic Materials, Carbon Nanostructures, Polymers, Metals, Rare Earths, Plasma Transformation, and Renewable Energy Development.
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