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REVIEW ARTICLE

The best COVID-19 vaccine: understanding the conundrum behind comparing vaccines

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Abstract

Severe Acute Respiratory Syndrome-Corona Virus-2 (SARS-CoV-2) infection has created global devastation in the past three years. The Corona Virus Disease-19 (COVID-19) vaccine is the only available resource to fight SARS-CoV-2 infection and its associated complications. As world is trying to recover with the help of vaccines, the change in vaccine development strategy and allowing the usage of vaccines at an emergency level with small size clinical data has created a storm of confusion among many individuals concerning efficiency and efficacy of the vaccine. Though multiple pieces of literature are available regarding the different types and strategies of vaccine development, no paper gives an idea about which vaccine should be used in this emergency. More than 90 vaccine candidates are in the race showing 70-95% efficiency at clinical trials, and still, people are afraid to take vaccines due to lack of awareness. This review compares the available vaccines and evaluates their efficiency based on the available clinical trial results to answer the most frequently asked question of which vaccine is best to be taken at this time?

Keywords: Severe Acute Respiratory Syndrome-Corona Virus-2, Corona Virus Disease-19, Vaccine, Efficacy

Introduction

Severe Acute Respiratory Syndrome-Corona Virus-2 (SARS-CoV-2), a small virus, wreaked havoc and has impacted the entire world. This global pandemic's swift and massive shock has plunged the economy into a severe contraction [1]. The world economy has taken a powerful hit, thus affecting the livelihood of millions of people, including both large-scale and small-scale businesses.

Phase I of COVID-19 pandemic surprised everyone since there was no prior knowledge of treatment or any other preventive measures. Inaccessibility of a specific antiviral treatment costs people their lives to COVID-19. Nevertheless, in Phase II of the pandemic, various strategies were planned and implemented as people were more conscious, which eventually helped with the widespread. There was a significant response as a broad range of candidate COVID-19 vaccines were being analysed globally with the help of various technologies and platforms. Viral vector-based, protein subunit, nucleic acid (DNA, RNA) live attenuated and inactivated vaccines were prioritised despite the unspecified protection period.

Vaccines play an important role in maintaining global public health and lessening the impact of infectious diseases. Approximately 99 vaccines are at different clinical development stages [2]. Of these 99 vaccines, the final interim results completed clinical trials of four studies, i.e. Pfizer–BioNTech BNT162b2 mRNA vaccine [3-4], Moderna–U.S. National Institutes of Health (NIH) mRNA-1273 vaccine [5-6], the Astra Zeneca–Oxford ChAdOx1 nCov-19 vaccine [7-9], and the Gamaleya GamCOVIDVac (Sputnik V) vaccine [10-11] has been published so far. However, attention has focused on the most efficacious vaccine and comparing the reduction of the number of symptomatic cases. However, the efficacy and effectiveness of vaccines is the most debatable point [12]. The entire chaos is based on the variety of vaccine availability and their specific characteristics followed by their varied efficacy according to the types of vaccines. The main objective of this review is to create awareness of all the available vaccines and the one that best suits everyone.

Vaccines can be made using many different technologies [13]. The COVID-19 vaccines that are currently the most advanced are manufactured using four different approaches *viz.*:

a. Inactivated Vaccines - Inactivated vaccines contain non-living, non-replicating bacterium or virus that has been inactivated using either heat and/or chemicals. The fractional vaccines are produced by purifying only required additive compounds from inactivated bacteria/viruses (Figure 1A). The entire dose of antigen is administered in the injection. The Indian company Bharat Biotech partnered with the National Institute of Virology and the Indian Council of Medical Research (ICMR) to develop an inactivated coronavirus vaccine called Covaxin.

b. Messenger RNA (mRNA) vaccine - mRNA vaccines are nothing but genetically engineered mRNA that instruct cells to make the specific protein found on the surface of infecting bacteria/virus (S protein in case of COVID-19 virus). Post COVID mRNA vaccination, immune cells start manufacturing the S protein pieces and displaying them on cell surfaces. The immunological response will be triggered by cells in the same way as against spike protein of coronavirus by producing antibodies (Figure 1B). After vaccine administration, m-RNA is broken down immediately, preventing entry into the cellular nucleus. Both the Pfizer-BioNTech and the Moderna COVID-19 vaccines use this approach of mRNA vaccine.

c. Viral vector vaccine- In this type of vaccine, genetic material from the COVID-19 virus (mRNA coding for spike protein) is placed in a modified version of the different viruses that act as a genetic material carrier inside the cell (viral vector). Once cells translate the code into proteins (Spike protein) and display it on cell surfaces, the immune system develops the immunological response by producing antibodies against COVID-19 antigen, and if an individual gets infected with the COVID-19 virus later, the antibodies can be produced at a faster rate by cells due to memory generated by the vaccine. They will fight against the virus and neutralise, rendering the person free from infection. The Janssen/Johnson & Johnson (J&J) COVID-19 vaccine and Oxford-

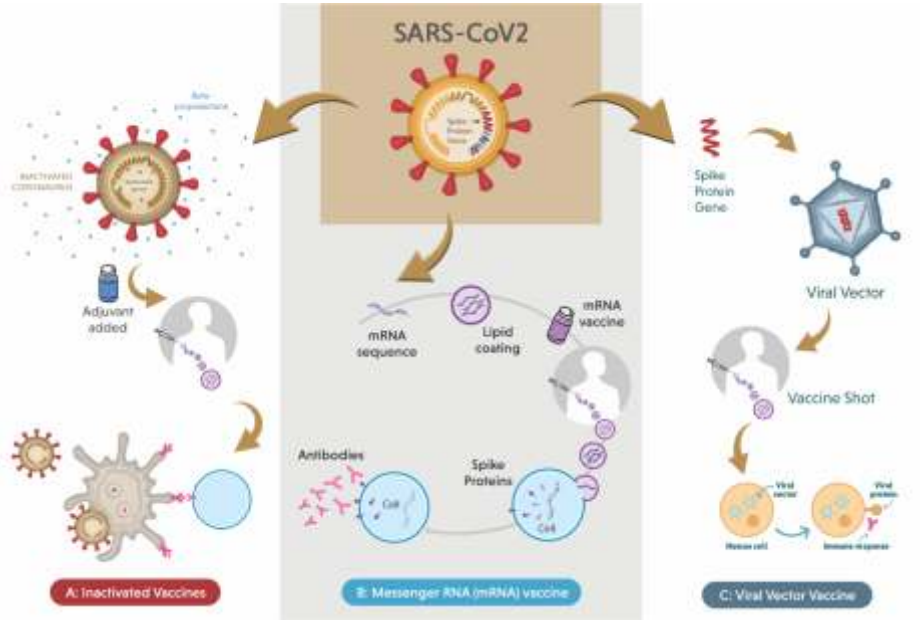

Figure 1: Techniques employed for COVID -19 vaccine development - 1A) inactivated vaccine – is manufactured using live virus inactivation 1B) mRNA vaccine – is uses genetically engineered mRNA to develop an immune response. In contrast, 1C) viral vector vaccine uses vector carrier to transport the genetic material to cells to generate an immune response against it.

AstraZeneca COVID-19 vaccine is vector vaccine. Sputnik V is also an adenovirus viral vector vaccine for COVID-19 developed by the Gamaleya Research Institute of Epidemiology and Microbiology in Russia.

d. Protein Subunit Vaccine- When only the part of a virus subunit is used to stimulate the immune system, the vaccine is called protein subunit vaccine. As mentioned above, this type of COVID-19 vaccine contains harmless S proteins and generates an immunological response. Novavax is working on a protein subunit COVID-19 vaccine.

All vaccines, irrespective of their type, work by teaching our bodies to recognise and fight the pathogen safely. They encourage our immune system to produce antibodies, T-cells, or both so that if we encounter the infection later, the immune system knows how to defend against it [14].

Average, best and superior… Fueling the perception with a vaccine efficacy rate

Debates intensify over the efficacy of the vaccine. The Food and Drug Administration(FDA) has defined efficacy by a primary endpoint of reduction in COVID-19 cases, reduction in COVID-19 severity (from severe to mild disease), or Relative Risk Reduction (RRR) in SARS-CoV-2 infections [15]. The effectiveness of the vaccine is directly proportional to its efficacy. It is influenced by vaccine coverage, access to healthcare centres, costs associated and other factors that are not related to the vaccine [16].

Compared to other treatment strategies and drug usage, only vaccines can prove unequalled against SARS-CoV-2 infections. The clinical trials of phase III were required for all vaccine candidates to demonstrate that they are effective and secure to cater for a larger population [17]. However, considering the severity of the situation, vaccines showing early signs of promise and are in the later phases of clinical testing are approved for emergency use (Table 1).

Table 1: Details of COVID-19 vaccines with their efficacy data

Name of vaccine	Type of vaccine	Primary Developers	Number of doses required	Efficacy of vaccine after complete dosage	Country of origin
Comirnaty (BNT162b2) [41-42]	mRNA-based vaccine	Pfizer, BioNTech; Fosun Pharma	2	94.8 to 95%	Multi-national
Moderna COVID-19 Vaccine (mRNA-1273) [43]	mRNA-based vaccine	Moderna, BARDA, NIAID	2	94.1%	US
COVID-19 Vaccine AstraZeneca (AZD1222); also known as Vaxzevria and Covishield [44]	Adenovirus vaccine	BARDA, OWS	2	70.4%	UK
Sputnik V [45]	Recombinant adenovirus vaccine [rAd26/ rAd5]	Gamaleya Research Institute, Acellena Contract Drug Research and Development	2	91.6%	Russia
COVID-19 Vaccine Janssen (JNJ-78436735; Ad26.COV2.S) [46]	Non-replicating viral vector	Janssen Vaccines [Johnson & Johnson]	1	66.9%	The Netherlands, U.S.
CoronaVac [47]	Inactivated vaccine (formalin with alum adjuvant)	Sinovac	2	50.39	China
BBIBP-CorV, also known as Sinopharm COVID-19 vaccine [48] (no interim report available while writing the paper)	Inactivated vaccine	Beijing Institute of Biological Products; China National Pharma-ceutical Group [Sinopharm]	2	79% based on news	China

Continued...

Name of vaccine	Type of vaccine	Primary Developers	Number of doses required	Efficacy of vaccine after complete dosage	Country of origin
EpiVacCorona [49]	Peptide vaccine	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology	2	Phase III ongoing	Russia
Convidicea (Ad5-nCoV) [50]	Recombinant vaccine [adenovirus type 5 vector]	CanSino Biologics	1	Phase III is ongoing	China
Covaxin (BBV152) [51]	Inactivated vaccine	Bharat Biotech, ICMR; Ocugen	2	80.6	India
WIBP-CorV [52]	Inactivated vaccine	Wuhan Institute of Biological Products; China National Pharmaceutical Group [Sinopharm]	No	72.8	China
CoviVac [53]	Inactivated vaccine	Chumakov Federal Scientific Center for Research and Development of Immune and Biological Products	2	In Phase I trial	Russia
ZF2001[54]	Recombinant vaccine	Anhui Zhifei Longcom Biopharmaceutical, Institute of Microbiology of the Chinese Academy of Sciences	2 to 3	In Phase III	ZF2001
QazVac (QazCOVID-in) [55]	Inactivated vaccine	Research Institute for Biological Safety Problems	2	In Phase III	QazVac (QazCOVID-in)

BNT 162, commonly known as the Pfizer vaccine developed by Pfizer and BioNTech, is the first and only COVID-19 vaccine approved by the U.S. FDA. The first Emergency Use Authorization (EUA) was issued on 11th December2020 for the Pfizer-BioNTech COVID-19 Vaccine by US FDA for individuals aged16 years and older, based on its safety and efficacy data from a randomised, controlled, blinded ongoing clinical trial of thousands of individuals. BNT162 was the first vaccine candidate approved by WHO on 31st December 2020 for emergency use [17]. These lipid-based, nucleoside-modified mRNA vaccines have demonstrated 95% efficacy based on phase III clinical trial results in preventing diseases.

The second vaccine approved by FDA under EUA was ModernamRNA-1273. Based on the availability of data on coronaviruses causing Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS) [17]. mRNA-1273, a novel Lipid Nanoparticle [LNP]-the encapsulated mRNA-based vaccine was authorised for distribution and use under a EUA on 18th December 2020 by the FDA in people 18 years or older [18]. Estimated vaccine efficacy of 94.1 % [95% CI, 89.3 to 96.8%] was observed on 196 COVID-19 cases for primary analysis for Moderna mRNA-1273.

After BNT 162 approval for emergency use, United Kingdom (UK). approved its second vaccine AZ D1222 COVID-19 in December 2020, developed by AstraZeneca and the Oxford Vaccine Group of the University of Oxford. AZD1222 (formerly ChadOx1 nCoV-19) mainly consists of replication-deficient simian adenovirus vector ChAdOx1, containing the structural surface glycoprotein(S) of SARS-CoV-2 and tissue plasminogen activator (tPA) signal sequence. It expresses codon-optimized S protein sequences [19]. The clinical trials study result signified an acceptable safety, reactogenicity, and immunogenicity of a viral vectored coronavirus vaccine profile for ChAdOx1 nCoV19 and showed increased antibody response by homologous boosting [19]. Although two standard doses participants showed 62.1% [95% CI 41.0–75.7] vaccine efficacy, surprisingly, for the first low dose and second standard dose (LD/SD), it was 90.0% [95% CI 67.4–97.0] [7].

On 27th February 2021, US FDA rolled out EUA for a single-dose Janssen/Ad26.COV2.S COVID-19 vaccine, developed by the Janssen Pharmaceutical Companies of J&J, in the 18 years and above age group. Based on the information provided by the manufacturer, this viral vector-based J&J vaccine, or Ad26.COV2.S has shown to be 66.3% effective in an ongoing, large-scale clinical trial [20]. Compared to all existing two-dose COVID-19 Vaccine J&Js single dose of Ad26.COV2.S demonstrated to elicit a robust humoral response post-vaccination. Interestingly all Phase 3 clinical trials of vaccines showed the presence of S-binding and neutralising antibodies in more than 90% of the vaccine recipients, regardless of age group or vaccine dose [21].

Another vector-based popular vaccine developed by the Gamaleya Research Institute in Russia and the Health Ministry of the Russian Federation, Sputnik V, isused in nearly 70 nations. However, the administration of Sputnik V has been slowed down due to controversy of the Russian government authorising its usage much before early-stage trial results were even published [22]. Sputnik V also known as Gam-COVID-Vac is a non-replicating viral vector vaccine with two

different adenoviral vectors (recombinant Ad26 [rAd26] and recombinant Ad5 [rAd5]), both carrying the SARS-CoV-2 spike glycoprotein gene in a prime-boost regimen rationalised to overcome boosting of viral vector-specific antibodies. The interim study of the Gam-COVID-Vac against COVID-19 at phase 3 trial showed 91.6% [95% CI 85·6–95·2] efficacy. This vaccine was well tolerated in a large cohort [23].

The 2 to 8 °C storage and shipping temperature for inactivated COVID 19 vaccines, namely Covaxin, Sinopharm and the Sinovac-CoronaVac, make them more suitable for low-income countries with limited cold storage [24-25]. Of these three, the Sinopharm COVID-19 vaccine was listed for EUL on 7th May 2021 [26]. Beijing Bio-Institute of Biological Products Co Ltdhas produced the Sinopharm vaccine subsidiary of China National Biotec Group (CNBG). The Sinovac-CoronaVac (previously known as PiCoVacc) was listed for EUL on 1st June 2021 [27]. However, Covaxin, the COVID-19 vaccine developed by Indian pharmaceutical company Bharat Biotech in collaboration with the Indian Council of Medical Research, a government-funded biomedical research institute, and its subsidiary, the National Institute of Virology, got WHO EUA nod in November 2021 [28]. According to Sinopharm's press release, their vaccine was 79.34% effective at preventing new cases of COVID-19. While for Sinovac- CoronaVac, the efficacy rate was 62% at Hong Kong trials and 50.4% at Brazil's Butantan Institute, preventing severe and mild disease in healthcare workers. Smaller trials in Turkey were 91.25% effective, whereas it was only 65.3% effective in Indonesia [18]. Considering the variation in results of Sinopharm or Sinovac clinical trials conducted at different geographical locations and immerging new COVID-19 waves in places with a high per capita level have raised concerns about low real-world effectiveness of Sinopharm or Sinovac vaccine than expected [29].The Indian COVID-19 vaccine - Covaxin, which recently completed the third stage of trials, shows an efficacy rate of 78%, providing 100% protection against severity and mortality.

Thus, considering the varied efficacy data of all the rolled out COVID-19 vaccines, the most important question is regarding the efficacy required for a vaccine to be considered efficient for an immunogenic response. Even though the research is limited, preliminary research studies have declared desired effectiveness of>70% to eradicate the infection [30]. Given the norms about social distancing measures that are followed, the preventative vaccines may add to obliterating the virus and will have a significant effect even with less than 70% efficacy. Similarly, the decrease in infection length can be seen in the vaccines with an efficacy below 70%. A study with simulation experiments stated that to prevent a pandemic, the effectiveness of the vaccination must be 60% along with 100% vaccination coverage. It has been observed that the threshold of the vaccine efficacy rises to 70% when coverage drops to 75% [30].

As for any vaccine, we must also perceive the effectiveness of these vaccines in the geriatric population, adolescents, pregnant women and immunocompromised groups, and long-term protection from these vaccines. As efficacy can depict only participants who could benefit from the vaccine, the Absolute Risk Reduction (ARR), which is expressed as the difference between

strike rates with and without a vaccine, considers the whole population, tend to be ignored as they give a much less impressive effect size than RRRs [12]. Efficacy parameters are variables; thus, the efficacy percentage is not solely a good predictor of any impact that these vaccines might have. It depends on how soon and how well they work in the real world, in high-risk people receiving them and most importantly, the mode of delivery.

With different efficacy associated with every individual vaccine, the idea of a mix-and-match regimen of different COVID-19 vaccines came into the picture. Surprisingly, the study revealed that recipients of two different COVID-19 vaccines developed strong immune responses, including immunosuppressed individuals against the virus [31]. The side effects after administration of mix-and-match regimen were no worse than those caused by standard regimens [32-34], proving the safety and the effectiveness of mix-and-match vaccine regimens. These studies were conducted on different populations at different time points including the hyper-infectious Delta variant period, unanimously confirming that mix-and-match or heterologous vaccination is highly protective. The mix-and-match regimen data also highlight the usefulness of mixed immunisation programmes in third-world/lower-income countries, where shortages of certain vaccines are the main issue [35].

If one looks at the possible side effects of these vaccines, irrespective of the type of vaccine, their side effects are common. These temporary side effects include pain, redness, or swelling at the vaccine administration site, tiredness, headache, muscle pain, chills, fever, or nausea throughout the rest of the body. In very few rare cases, side effects are serious [36-37].

Numbers can be misleading

Until now, over 200 million coronavirus vaccines doses have been delivered successfully. The clinical trial data has been rolling in from several countries. The top-line findings from those studies suggest a range of protection up to 95% efficacy for vaccines made by Pfizer and BioNTech. Correspondingly, it showed about 70% efficacy based on initial results on vaccines produced by the University of Oxford and AstraZeneca. According to David Kennedy, who studies the ecology and evolution of infectious diseases at Pennsylvania State University in University Park, the effectiveness of vaccines should not be compared based on those results alone. Every efficacy measure has a degree of uncertainty. Also, the definitions of essential criteria, such as what constitutes a 'severe' about COVID-19 compared to a 'moderate' one, changes with every clinical trial.

Each COVID-19 vaccine trial involves different people from different demographics. In the case of the Oxford-AstraZeneca vaccine, for example, the J&J one-dose vaccine from 28 days post-vaccination gives 66% protection against moderate to severe COVID infections. However, the variability is based on geographic locations, *e.g.* in the United States, the vaccine was 72% protective while in South America,66% and 57% in South Africa. Also, Oxford and AstraZeneca collected the vaccine's efficacy data in people over 65 years. Novavax and Janssen conducted more extensive trials in South Africa than Oxford and AstraZeneca. However, both vaccines had lower efficacy rates in South Africa than in other countries. The Janssen vaccine participants who received the vaccine were less likely to require hospitalisation for COVID-19 than those who

received placebo shots. As the number of people receiving vaccines is dynamically changing with some new findings every day, it is essential to understand that the efficiency of vaccines is estimated on parameters that will change as more clinical trial results will be out. Conclusion on the best vaccine is still under investigation and requires more in-depth clinical trials with different population sizes and backgrounds.

Unfortunately, comparing vaccines based on currently available trial (interim) data is made even more difficult by disparate study protocols, including primary endpoints (such as what is considered a COVID-19 case, and when is this assessed), types of a placebo, study populations, background risks of COVID-19 during the study, duration of exposure, and different definitions of populations for analyses both within and between studies, as well as definitions of endpoints and statistical methods for efficacy.

Is the new variant a concern for COVID vaccine development?

During the second and third waves of the pandemic, when a virus was widely circulating in a population causing infections, the likelihood of the virus mutating increased. SARS-CoV-2 is throwing out variants and will continue because relatively few people globally have been vaccinated. As the virus gets more opportunities to spread and replicate - it gets more opportunities to undergo mutation. It is essential to understand that viral mutations have little to no impact on the virulence of the virus. However, the site of mutation in a virus generally affects a virus's properties, like speed transmission or infection severity, as seen in the omicron variant of COVID-19.

However, for COVID-19, the emerging "variants of concern" arising due to mutation in the S protein appear to be more transmissible (*e.g.* Omicron) or deadlier (*e.g.* Delta) or a combination of two (*e.g.* Deltacron) than the wild-type SARS-CoV-2spurring vaccine efficacy concerns. Current COVID-19 vaccines are based on the original Wuhan-hu-1SARS-CoV-2 surface binding spike protein (exception, Covaxin). The Novavax, Janssen/J&J, and AstraZeneca vaccines trials in South Africa, where the B.1.351 variant of concern represents virtually all the circulating SARS-CoV-2, seemed to justify those concerns with lower vaccine efficacy when compared with trials in B.1.351 non-dominant countries.

The considerable data on the mRNA vaccines' efficacy against SARS-CoV-2 variants were collected by measuring the neutralising antibody titers in serum samples from immunised individuals exposed to genetically engineered versions of concerning variants. Such studies have shown lower levels of neutralising antibodies elicited by a vaccine against SARS-CoV-2 variants than against older, more common isolates. Fortunately, vaccine-induced neutralisation titers are so high that serum can still effectively neutralise the virus even with a six-fold decrease in titer. In addition to neutralising antibodies, mRNA vaccines induce virus-specific cytotoxic T cells and T helper cells that may also protect against infection [38].

Modifying vaccines to target variants is relatively simple. For example, with Pfizer-BioNTech's and Moderna's mRNA vaccines, a slight change in a computer program and the synthetic for the synthesising portion of mRNA can change the vaccine. The most satisfying way of dealing with

SARS-CoV-2 variants would be Modifying COVID-19 vaccines.

Best COVID-19 vaccine: The winner

The COVID-19 pandemic can end only if a large share of the world population gets immune to achieve herd immunity against the SARS-CoV-2 virus [39]. As the COVID-19 pandemic enters its third year, only 63.9% of the world population has received at least one dose of a COVID-19 vaccine. The same number in low-income countries is as low as 14.1% [40]. We need as many vaccines as possible to tackle the pandemic in such unprecedented times. But since these vaccines are in widespread use and will be further distributed by COVAX, a global alliance that provides vaccine doses to low-and middle-income nations, it's of utmost importance that the safety and effectiveness of all these vaccines be closely monitored. In the given situation when the third wave caused much damage where vaccine supply is limited, any effort to rank the vaccines based on the reported effectiveness should not be considered. Other factors such as the vaccine supplies, costs, deployment logistics, protection duration, and ability to defend off emerging viral variants should also be contemplated. All these available vaccines were studied at different time zone in various countries. Hence, each trial can only offer a snapshot of protection against the dominant viral variants in that particular time or place. Pfizer and Moderna's vaccines were tested before the emergence of troubling new variants in Britain, South Africa, and Brazil. At the same time, the J&J vaccine was still being tested when the variants were making the rounds. That might translate into protection over one to two years is not the same. Also, comparing different vaccines becomes challenging due to the differences in their designs. Similarly, In Phase 3 clinical trials, they tested vaccines for different outcomes; for example, both Pfizer's and Moderna's trials tested for any symptomatic COVID infection. However, Pfizer started counting cases seven days after receiving the second dose of vaccine, while Moderna waited until day 14 to begin counting cases.

Today, all the EUA COVID-19 vaccines differ in many aspects, including the clinical trials they undergo. Thus, making direct comparisons between these COVID-19 vaccines is like comparing apples to oranges. Head-to-head comparison can only be done using two vaccine usage in trial for an accurate judgment but is rarely made. Considering the data and the availability of vaccines, the best-suited vaccine is the one available to you. It is crucial to note that vaccines do not save lives; vaccination does. Delaying vaccination right now can be a risky choice while we are uncertain about the emergence of a potentially scary third wave.

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References

1. Sannathimmappa MB, Nambiar V, Patil R. Emerging and re-emerging viral infections in the 21st century: Microbiological and public health perspectives. *J Krishna Inst Med Sci Univ* 2021;10(2):1-20.
2. Zimmer C, Corum J WS-L. Covid-19 Vaccine Tracker. Accessed 5th Jul 2021: https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html
3. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, *et al*. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* 2020; 383(27):2603-2615.
4. Pfizer PC go. CC. Study to describe the safety, tolerability, immunogenicity, and efficacy of RNA vaccine candidates against COVID-19 in healthy individuals 2020: https://clinicaltrials.gov/ct2/show/NCT04368728.
5. Promising Interim Results from Clinical Trial of NIH-Moderna COVID-19 Vaccine 2020. Accessed 5th Jul 2021: https://www.nih.gov/news-events/news-releases/promising-interim-results-clinical-trial-nih-moderna-covid-19-vaccine
6. Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, *et al*. An mRNA Vaccine against SARS-CoV-2 – Preliminary Report. *N Engl J Med* 2020; 383(20):1920-1931.
7. AstraZeneca. Phase III double-blind, placebo-controlled study of AZD1222 for the prevention of COVID-19 in adults. Accessed 5th Jul 2021: https://clinicaltrials.gov/ct2/show/NCT04516746
8. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, *et al*. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021; 397(10269):99-111.
9. Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, *et al*. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet* 2020; 396(10249):467-478.
10. Gamaleya Research Institute of Epidemiology and Microbiology HM of the RF. Clinical trial of efficacy, safety, and immunogenicity of Gam-COVID-Vac vaccine against COVID-19. Accessed 6th Jul 2021: https://clinicaltrials.gov/ct2/show/NCT04530396
11. Logunov DY, Dolzhikova IV, Shcheblyakov DV, Tukhvatulin AI, Zubkova OV, Dzharullaeva AS, *et al*. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. *Lancet* 2021;397(10275): 671-681.
12. Olliaro P, Torreele E, Vaillant M. COVID-19 vaccine efficacy and effectiveness–the elephant (not) in the room. *The Lancet Microbe* 2021;2(7):e279-280.
13. Kyriakidis NC, López-Cortés A, González EV, Grimaldos AB, Prado EO. SARS-CoV-2 vaccines strategies: a comprehensive review of phase 3 candidates. *NPJ Vaccines* 2021;6(1).
14. Center for Disease control. Understanding how vaccines work: The immune system—the body's defense against infection. Accessed 10th Aug 2021: https://www.cdc.gov/vaccines/hcp/conversations/understanding-vacc-work.html
15. USFDA. COVID-19: Developing Drugs and Biological Products for Treatment or Prevention, Guidance for Industry. *US Dep Heal Hum Serv Food Drug Adm* 2021. Available from: https://www.fda.gov/media/137926/download
16. Hodgson SH, Mansatta K, Mallett G, Harris V, Emary KRW, Pollard AJ. What defines an efficacious COVID-19 vaccine? A review of the challenges assessing the clinical efficacy of vaccines against SARS-CoV-2. *Lancet Infect Dis* 2021;21(2):e26–35.
17. Kashte S, Gulbake A, El-Amin SF, Gupta A. COVID-19 vaccines: rapid development, implications, challenges and future prospects. *Hum Cell*. 2021; 34(3):711-733.
18. Chakraborty S, Mallajosyula V, Tato CM, Tan GS, Wang TT. SARS-CoV-2 vaccines in advanced clinical trials: Where do we stand? *Adv Drug Deliv Rev* 2021;172:314–338.
19. Yan Z, Yang M, Lai CL. Covid-19 vaccines: A review of the safety and efficacy of current clinical trials. *Pharmaceuticals* 2021;14(5).
20. Johnson & Johnson's Janssen COVID-19 Vaccine Overview and Safety. CDC.gov. 2021. Accessed 12th Aug 2021: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/janssen.html
21. Sadoff J, Le Gars M, Shukarev G, Heerwegh D, Truyers C, de Groot AM, *et al*. Interim Results of a Phase 1–2a Trial of Ad26.COV2.S Covid-19 Vaccine. *N Engl J Med* 2021;384(19):1824–35.

22. Nogrady B. Mounting evidence suggests Sputnik COVID vaccine is safe and effective. *Nature* 2021; 595(7867):339-340.
23. Logunov DY, Dolzhikova I V, Shcheblyakov D V, Tukhvatulin AI, Zubkova O V, Dzharullaeva AS, *et al*. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. *Lancet* 2021;397(10275):671-681.
24. Al Kaabi N, Zhang Y, Xia S, Yang Y, Al Qahtani MM, Abdulrazzaq N, *et al*. Effect of 2 Inactivated SARS-CoV-2 Vaccines on Symptomatic COVID-19 Infection in Adults. *JAMA* 2021;326(1):35.
25. Thiagarajan K. What do we know about India's Covaxin vaccine? *BMJ* 2021;373:1–2.
26. WHO. WHO lists additional COVID-19 vaccine for emergency use and issues interim policy recommendations. 2021. Accessed 12th Aug 2021: https://www.who.int/news/item/07-05-2021-who-lists-additional-covid-19-vaccine-for-emergency-use-and-issues-interim-policy-recommendations
27. WHO. WHO validates Sinovac COVID-19 vaccine for emergency use and issues interim policy recommendations 2021. Accessed 12th Aug 2021: https://www.who.int/news/item/01-06-2021-who-validates-sinovac-covid-19-vaccine-for-emergency-use-and-issues-interim-policy-recommendations
28. PTI. WHO decision on Covaxin EUA in September. 2021. Accessed 12th Aug 2021: https://www.thehindu.com/sci-tech/health/who-decision-on-covaxin-eua-in-september/article35865147.ece
29. Li TL& J. What we now know about the efficacy of China's Covid-19 vaccines. *Quartz* 2021. Accessed 12th Aug 2021: qz.com/2018838/what-we-know-about-efficacy-of-sinopharm-sinovac-vaccines/
30. Bartsch SM, O'Shea KJ, Ferguson MC, Bottazzi ME, Wedlock PT, Strych U, *et al*. vaccine efficacy needed for a COVID-19 coronavirus vaccine to prevent or stop an epidemic as the sole intervention. *Am J Prev Med* 2020; 59(4):493-503.
31. Schmidt T, Klemis V, Schub D, Schneitler S, Reichert MC, Wilkens H, *et al*. Cellular immunity predominates over humoral immunity after homologous and heterologous mRNA and vector based COVID 19 vaccine regimens in solid organ transplant recipients. *Am J Transplant* 2021;21(12): 3990-4002.
32. Schmidt T, Klemis V, Schub D, Mihm J, Hielscher F, Marx S, *et al*. Immunogenicity and reactogenicity of heterologous ChAdOx1 nCoV-19/mRNA vaccination. *Nat Med* 2021;27(9):1530-1535.
33. Borobia AM, Carcas AJ, Pérez-Olmeda M, Castaño L, Bertran MJ, García-Pérez J, *et al*. Immunogenicity and reactogenicity of BNT162b2 booster in ChAdOx1-S-primed participants (CombiVacS): a multicentre, open-label, randomised, controlled, phase 2 trial. *Lancet* 2021;398(10295):121-130.
34. Shaw RH, Stuart A, Greenland M, Liu X, Nguyen Van-Tam JS, Snape MD. Heterologous prime-boost COVID-19 vaccination: initial reactogenicity data. *Lancet* 2021; 397(10289): 2043-2036.
35. Callaway E. Mix-and-match COVID vaccines ace the effectiveness test. *Nature* 2021. Accessed 12th Aug 2021: https://www.nature.com/articles/d41586-021-02853-4
36. Ministry of Health and Family Welfare. Common Side Effects (AEFI): Some common ailments that can be expected after vaccination. 2022. Available from: https://www.mohfw.gov.in/covid_vaccination/vaccination/common-side-effects-aefi.html
37. Center for Disease Control. Possible side effects after getting a COVID-19 vaccine 2022. Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/expect/after.html
38. Moore JP, Offit PA. SARS-CoV-2 vaccines and the growing threat of viral variants. *JAMA* 2021; 325(9):821.
39. Mathieu E, Ritchie H, Ortiz-Ospina E, Roser M, Hasell J, Appel C, *et al*. A global database of COVID-19 vaccinations. *Nat Hum Behav* 2021;5(7):947-953.
40. Coronavirus (COVID-19) Vaccinations. 2022. Accessed 18th Mar 2022: https://ourworldindata.org/covid-vaccinations
41. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, *et al*. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* 2020;383(27):2603-2615.
42. Wang X. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* 2021;384(16): 1577–1578.
43. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, *et al*. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2021; 384(5): 403-416.
44. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, *et al*. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet (London, England)* 2021;397(10269):99–111.

45. Logunov DY, Dolzhikova I V, Shcheblyakov D V, Tukhvatulin AI, Zubkova O V, Dzharullaeva AS, *et al*. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. *Lancet (London, England)* 2021; 397(10275):671-681.
46. Sadoff J, Gray G, Vandebosch A, Cárdenas V, Shukarev G, Grinsztejn B, *et al*. Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. *N Engl J Med* 2021; 384(23):2187-2201.
47. Hitchings MDT, Ranzani OT, Torres MSS, de Oliveira SB, Almiron M, Said R, *et al*. Effectiveness of CoronaVac among healthcare workers in the setting of high SARS-CoV-2 gamma variant transmission in Manaus, Brazil: A test-negative case-control study. *Lancet Reg Heal-Am* 2021;100025.
48. Wee S, Qin A. China approves Covid-19 vaccine as it moves to inoculate millions. Accessed 12thDec 2020: https://www.nytimes.com/2020/12/30/business/china-vaccine.html
49. Federal Budgetary Research Institution State Research Center of Virology and Biotechnology "Vector." Study of the Tolerability, Safety, Immunogenicity and Preventive Efficacy of the EpiVacCorona Vaccine for the Prevention of COVID-19. ClinicalTrials.gov. 2021. Accessed 11th Aug 2021: https://clinicaltrials.gov/ct2/show/NCT04780035
50. Inc. CB and BI of B. Phase III trial of a COVID-19 vaccine of adenovirus vector in adults 18 years old and above. ClinicalTrials.gov. 2020 Accessed 11th Aug 2021: https://clinicaltrials.gov/ct2/show/NCT04526990
51. Sapkal GN, Yadav PD, Ella R, Deshpande GR, Sahay RR, Gupta N, *et al*. Neutralization of UK-variant VUI-202012/01 with COVAXIN vaccinated human serum. *bioRxiv* 2021;91:2021.01.26.426986.
52. Al Kaabi N, Zhang Y, Xia S, Yang Y, Al Qahtani MM, Abdulrazzaq N, et al. Effect of 2 Inactivated SARS-CoV-2 Vaccines on Symptomatic COVID-19 Infection in Adults: A Randomized Clinical Trial". *JAMA* 2021; 326 (1): 35–45.
53. Codagenix I. Safety and immunogenicity of COVI-VAC, a live attenuated vaccine against COVID-19. ClinicalTrials.gov. 2020 Accessed 11th Aug 2021: https://clinicaltrials.gov/ct2/show/NCT04619628
54. Anhui Zhifei Longcom Biologic Pharmacy Co. L. A phase III clinical trial to determine the safety and efficacy of ZF2001 for prevention of COVID-19 [Internet]. ClinicalTrials.gov. 2020.Accessed 11th Aug 2021: https://clinicaltrials.gov/ct2/show/NCT04646590
55. Research institute for biological safety problems. immunogenicity, efficacy and safety of QazCovid-in® COVID-19 vaccine. ClinicalTrials.gov. 2020. Accessed 11th Aug 2021: https://clinicaltrials.gov/ct2/show/NCT04691908

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