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Commentary

Which are the best coronavirus disease 2019 vaccines?

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More than 300 different coronavirus disease 2019 (COVID-19) vaccine candidates are in different stages of development. Twenty-one vaccines are currently in clinical use, but peer-reviewed phase III results are only available for the mRNA vaccines BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna), the adenovirus-vectored vaccines ChAdOx1 (AstraZeneca-Oxford), Sputnik V (Gamaleya) and Ad26.COV2.S (Janssen), the inactivated vaccines BBIBP-CorV (Beijing Institute-Sinopharm), WIBP-CorV (Wuhan Institute-Sinopharm) and CoronaVac (Sinovac), and the adjuvanted NVX-CoV2373 (Novavax) vaccine [1]. In their respective registrational, randomized clinical trials (RCTs), these vaccines were shown to have a range of efficacies using similar, but not identical, end points (Table 1). Individual RCTs had considerably different trial protocols, end-point definitions, triggers for RT-PCR testing, ascertainment procedures and follow-up durations [1,2]. Moreover, the backdrop to the different RCTs differed widely in terms of risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and transmission dynamics, circulating SARS-CoV-2 variants of concern and adherence to non-pharmacological control interventions [1–3].

COVID-19 vaccines are often compared based on their reported efficacy results. However, without careful consideration and textualization, such direct comparisons can be misleading. Randomization may ensure comparability of groups within individual trials, but it does not permit comparisons between trials. The potential incomparability of COVID-19 vaccine trial results was not unforeseen. In their blueprint for the development of COVID-19 vaccines, the World Health Organization recommended an adaptive trial design with multiple candidates being evaluated in parallel against a single placebo and under a common protocol [3]. Importantly, stringent regulatory oversight and transparent trial reporting are crucial elements for the informed assessment of benefits and risks associated with COVID-19 vaccines. Unfortunately, such elements have not always been forthcoming [4].

By definition, vaccine RCTs are executed under idealized conditions to enable robust evaluations and support regulatory marketing authorization. Vaccine efficacy represents the relative risk reduction achieved in vaccinated versus unvaccinated populations in RCT settings. Once deployed in a wider population, vaccine effectiveness describes the relative risk reduction attributable to the vaccine in real-world settings. Vaccine efficacy does not necessarily predict vaccine effectiveness in specific settings [3]. For example, vaccine effectiveness achieved with BNT162b2 (Pfizer-BioNTech) or ChAdOx1 (AstraZeneca-Oxford) vaccines in national rollouts matched or exceeded the efficacies reported in their respective randomized trials [1,5]. On the other hand, BBIBP-CorV (Beijing Institute-Sinopharm) and WIBP-CorV (Wuhan Institute-Sinopharm) were associated with efficacies of 64% to 78.1% in their phase III RCT, but their effectiveness in the real-world appear to be considerably below such rates [1,6].

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Table 1
Selected characteristics of COVID-19 vaccines with peer-reviewed phase III clinical trial data

	BNT162b2 (Pfizer-BioNTech)	mRNA-1273 (Moderna)	ChAdOx1 (AstraZeneca-Oxford)	Sputnik V (Gamaleya)	Ad26.COV2.S (Janssen)	NVX-CoV2373 (Novavax)	CoronaVac (Sinovac)	BBIBP-CorV (Beijing Sinopharm)	WIBP-CorV (Wuhan-Sinopharm)
Primary efficacy end point in phase III registration trials	Symptomatic COVID-19 with onset ≥7 days after second dose among participants without serological or virological evidence of SARS-CoV-2 infection up to 7 days after second dose	Symptomatic COVID-19 with onset ≥14 days after second dose among participants who were seronegative at baseline	Symptomatic COVID-19 confirmed via a nucleic acid test >14 days after second dose in seronegative participants	PCR-confirmed COVID-19 from day 21 days after dose 1 among participants who received 2 doses	Moderate to severe or critical, centrally confirmed COVID-19 with onset ≥14 days after vaccination among seronegative and SARS-CoV-2 negative participants	Virologically confirmed, symptomatic COVID-19 > 7 days after the second dose among participants who were seronegative at baseline	Symptomatic, RT-PCR-confirmed COVID-19 ≥ 14 days after the second dose of vaccination	Symptomatic COVID-19 with onset ≥14 days after second dose among participants who received both doses, contributed at least one efficacy follow-up visit, and had negative PCR tests at enrolment	
Primary vaccine efficacy in phase III registration trials	95%, based on 170 events in 36 523 participants	94.1%, based on 196 events in 28 207 participants	66.7%, based on 332 events in 17 178 participants	91.6%, based on 78 events in 19 866 participants	67%, based on 464 events in 39 058 participants	89.7%, based on 106 events in 14 039 participants	83.5%, based on 41 events in 10 029 participants	78.1%, based on 116 events in 25 463 participants	72.8%, based on 121 events in 25 480 participants
Prevention of severe COVID-19 as a secondary vaccine efficacy end point	88.9%, based on 10 events in 42 573 participants	100%, based on 30 events in 28 207 participants	100%, based on 15 events in 23 570 participants	100%, based on 20 events in 19 866 participants	76.7%, based on 74 events in 39 058 participants	100%, based on 5 events in 14 039 participants	100%, based on 6 events in in 10 029 participants	100%, based on 2 events in 25 463 participants	100%, based on 2 events in 25 480 participants
Published real-world safety data	Yes	Yes	Yes	No	Yes	No	Yes	No	No
Published real-world effectiveness data	Yes, multiple settings	Yes, multiple settings	Yes, multiple settings	No	Yes, limited	No	Yes, limited	No	No
Published clinical and/or *in vitro* data against VOC	Clinical and *in vitro*	*In vitro*	Clinical and *in vitro*	None	Clinical and *in vitro*	Clinical	No	Very limited, *in vitro*	None
Administration schedule	2 doses, 21 days apart	2 doses, 28 days apart	2 doses, 28 days apart	2 doses, 21 days apart	1 dose	2 doses, 21 days apart	2 doses, 14 days apart	2 doses, 21 days apart	2 doses, 21 days apart
Storage temperatures	−60°C to −80°C	−15°C to −25°C	2°C to 8°C	2°C to 8°C (lyophilized), and −18°C (frozen)	2°C to 8°C	2°C to 8°C	2°C to 8°C	2°C to 8°C	2°C to 8°C
Approximate cost per dose[a]	€€€	€€€ to €€€€	€	€€	€€	€€€	€€€€	€€€ to €€€€	not available
Number of countries reporting current use	112	65	181	49	38	0	38	64	2
Authorized by EMA	Yes	Yes	Yes	No	Yes	No	No	No	No
Authorized by FDA	Yes	Yes	No	No	No	No	No	No	No
Authorized by WHO	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No

Abbreviations: COVID-19, coronavirus disease 2019; EMA, European Medicines Agency; FDA, US Food and Drug Administration; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VOC, SARS-CoV-2 variants of concern; WHO, World Health Organization.

[a] € = <5 Euro; €€ = 5 to <10 Euro; €€€ = 10 to 20 Euro; €€€€ = >20 Euro.

The ultimate aim of COVID-19 vaccines is to mitigate severe health outcomes, including death, and to reduce the impact of COVID-19 on health-care services. However, adequately powered RCTs to evaluate severe COVID-19 are not feasible, especially among younger age groups and in those without co-existing medical co-morbidities [3]. Furthermore, the interpretation of vaccine effect on disease severity may be confounded by differences in risk mitigation practices among high-risk populations, as well as variable access to high-quality medical care and to therapeutics that may reduce the risk of disease progression (e.g. monoclonal antibodies) or mortality (e.g. systemic corticosteroids, tocilizumab), and the locally circulating SARS-CoV-2 variants. Although severe COVID-19 outcomes are often evaluated in RCTs as secondary outcomes, the comparisons across different vaccines remain subject to the same trial-to-trial incomparability discussed above. On the other hand, useful differential clinical effectiveness may be observed in some real-world vaccine effectiveness studies [5,7]. However, the non-randomized nature of these studies may limit their internal validity.

Another important aim of COVID-19 vaccines is to prevent or reduce asymptomatic SARS-CoV-2 infections and transmission. If such benefits are demonstrated, mass COVID-19 vaccination could facilitate the removal of various COVID-19-related restrictions and hasten economic recovery. However, to capture such outcomes, COVID-19 clinical trial protocols need to incorporate regular RT-PCR testing for the trial participants. In the majority of the reported COVID-19 vaccine RCTs, these assessments were either absent, or were limited to small subgroups [1]. So far, the evidence that COVID-19 reduces asymptomatic SARS-CoV-2 infections is derived from subgroup analyses from registrational mRNA-1273 (Moderna) and ChAdOx1 (AstraZeneca-Oxford) trials, and observational studies of care-home residents and health-care workers. The evidence for reduced transmission in association with COVID-19 vaccination is based on epidemiological studies [8]. Although some of these observational studies adjusted their analyses for potential confounders, unmeasured bias cannot be excluded. The reports of reduced asymptomatic SARS-CoV-2 infection and transmissibility are certainly encouraging. However, they are not alone sufficient to prefer particular COVID-19 vaccines over others.

Beyond vaccine efficacy, safety is an important differential consideration. Rigorous post-marketing surveillance is essential to identify rare adverse events that may not be detected in registrational RCTs. Post-vaccination thrombosis with thrombocytopenia syndrome (TTS), characterized by acute arterial or venous thrombotic events with low platelet count and detectable platelet factor-4-heparin antibodies, was reported in association with ChAdOx1 (AstraZeneca-Oxford) and Ad26.COV2.S (Janssen) vaccines [9]. The estimated incidence of TTS is 1–10 and 1–7 per million in ChAdOx1 (AstraZeneca-Oxford) and Ad26.COV2.S (Janssen) recipients, respectively [10,11]. After meticulous risk–benefit assessments, the European Medicines Agency concluded that the risk of severe COVID-19 outcomes outweighs the rare risk of ChAdOx1 (AstraZeneca-Oxford) -associated TTS [10]. Similarly, the US Advisory Committee on Immunization Practices advised that the benefits of Ad26.COV2.S (Janssen) outweigh the exceedingly small risk of TTS [11]. Neither the European Medicines Agency nor the US Advisory Committee on Immunization Practices consider ChAdOx1 (AstraZeneca-Oxford) or Ad26.COV2.S (Janssen) contraindicated for any sex or age group [10,11]. There have also been rare reports of myocarditis and pericarditis in association with BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) [12]. However, the relatedness of myocarditis and pericarditis to COVID-19 vaccines has not been confirmed.

It is noteworthy that of the 21 COVID-19 vaccines in current use, potentially serious adverse events have so far only been identified in association with COVID-19 vaccines that are authorized in countries with robust pharmacovigilance procedures and regulatory monitoring [10,12]. Though intended to evaluate, quantify and contextualize any potential vaccine-related adverse events, the reporting of serious adverse events potentially linked to COVID-19 vaccines resulted in negative publicity and inconsistent public health messaging. In turn, this contributed to lower public acceptance of certain COVID-19 vaccine brands, while elevating others. Perhaps unwittingly, some ended up preferring COVID-19 vaccines with no publicly available post-marketing effectiveness or safety data over those with comprehensive and carefully calibrated benefit–risk assessments [13]. To make informed decisions regarding COVID-19 vaccination, policy-makers, health-care professionals and the general public need to understand how vaccine effects are reported. Once deployed, real-world effectiveness and safety studies are required to assess the relative and absolute benefits and risks in the settings of interest [2,3].

Clinical, epidemiological and neutralizing antibody data have demonstrated that some COVID-19 vaccines are less effective against certain SARS-CoV-2 variants. For example, in clinical trials, ChAdOx1 (AstraZeneca-Oxford) and Ad26.COV2.S (Janssen) demonstrated reduced efficacy against the beta SARS-CoV-2 variant (B.1.351 lineage), whereas BNT162b2 (Pfizer-BioNTech) was highly effective against the same variant in a real-world study from Qatar [14,15]. Moreover, neutralizing activity of sera from BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) recipients was reduced by 4.5- to 6.7-fold against the gamma SARS-CoV-2 variant (P.1 lineage), though this reduction does not necessarily imply reduced clinical effectiveness [14]. More recently, it has been shown that single doses of BNT162b2 (Pfizer-BioNTech) or ChAdOx1 (AstraZeneca-Oxford) vaccines are associated with reduced effectiveness against the delta SARS-CoV-2 variant (B.1.617 lineage), and to a lesser extent in recipients of two doses of either vaccine [7]. Local and regional genomic surveillance are therefore imperative when considering COVID-19 vaccines for specific settings.

Natural SARS-CoV-2 infection is associated with a reduced risk of re-infection [16], and a single COVID-19 vaccine dose elicits intense neutralizing antibody responses in COVID-19 survivors [17]. Furthermore, in individuals with previous SARS-CoV-2 infection, a single dose of BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) boosted neutralizing titres against beta SARS-CoV-2 variants (B.1.351 lineage) by up to 1000-fold [18]. These data may influence the choice of COVID-19 vaccines. For example, a setting with high SARS-CoV-2 seropositivity rates may choose a COVID-19 vaccination policy based on single-dose regimens. Those with circulating SARS-CoV-2 variants and limited resources may consider a single dose of an mRNA vaccine for individuals with documented previous natural SARS-CoV-2 infections.

Regardless of how effective and safe a COVID-19 vaccine is, major production and distribution scale up are required to meet the global demand. Almost all existing COVID-19 vaccines experienced periods of short supply and delayed deliveries [19]. In the case of Sputnik V (Gamaleya), which consists of an adenovirus 26-vectored first dose and an adenovirus 5-vectored second dose, delays in the delivery of the second dose forced some national programmes to cancel their orders or to use alternative vaccines as second doses [20]. Heterologous ChAdOx1 nCoV-19 and mRNA vaccine use was shown to result in potent induction of SARS-CoV-2 S-specific antibodies [21]. However, there are no peer-reviewed clinical data to guide heterologous COVID-19 vaccination.

Last, but not least, COVID-19 vaccine procurement costs and logistic requirements have obvious implications for policy-makers (Table 1). Many countries do not have the resources for the storage temperatures required for BNT162b2 (Pfizer-BioNTech) (−60°C to −80°C), or for mRNA-1273 (Moderna) (−15°C to −25°C) [22]. On the other hand, the existing cold-chain procedures and infrastructure for routine childhood vaccination could be used for COVID-19 vaccines that require storage at 2°C to 8°C (Table 1). Moreover, a single-dose schedule, such as that of Ad26.COV2.S (Janssen), may be appealing in settings where resources cannot accommodate two-dose vaccine schedules. Decision-makers will need to balance vaccine efficacy and safety data against the available resources. These can be complex considerations and may lead to pragmatic decisions driven by accessibility, feasibility and prioritization. In some settings, a moderately efficacious but affordable vaccine with relatively simple logistics may yield superior public health benefits compared with highly efficacious but unfeasible alternatives. Realistically, the ability to choose certain COVID-19 vaccines over others is a privilege that is not enjoyed by a majority of the human population. Based on predicted 12-week mortality modelling, Latin America, central and eastern Europe, central Asia and southern Africa are the regions with the highest COVID-19 vaccine needs to avert the worst clinical outcomes [23]. The same are regions where COVID-19 vaccine coverage has so far been disappointingly low [1].

In conclusion, rather than by direct comparison of vaccine efficacy data, differentiation of the available COVID-19 vaccines requires careful evaluation of the available evidence in its totality. Based on the completeness and accessibility of the data derived from phase III clinical trials, the breadth and depth of real-world data on safety and effectiveness, including against SARS-CoV-2 variants, and the complexity of the required logistics for mass deployment, we consider BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) to be the preferred COVID-19 vaccines where the required economic and organizational means are available. Otherwise, ChAdOx1 (AstraZeneca-Oxford) and Ad26.COV2.S (Janssen) could be reasonable alternatives. The remaining COVID-19 vaccines in current use have considerable gaps in their peer-reviewed published evidence base, including limited or absent corroboration from real-world data to elucidate their effectiveness or safety.

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