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Mini-symposium: COVID 19: The second year

Vaccines for COVID-19: Where do we stand in 2021?

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Educational aims

The reader will come to appreciate:

- Which COVID-19 vaccines are currently in use globally, how they have been distributed, and what is known about their effectiveness.
- The barriers to achieving global herd immunity against SARS-CoV-2, including inequitable access to vaccines and the emergence of variant strains.
- Current priorities for COVID-19 vaccine development and research, including variant-specific vaccines, age extension trials and mixed schedules.

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ABSTRACT

As of July 2021, over 3 billion doses of a COVID-19 vaccines have been administered globally, and there are now 19 COVID-19 vaccines approved for use in at least one country. Several of these have been shown to be highly effective both in clinical trials and real-world observational studies, some of which have included special populations of interest. A small number of countries have approved a COVID-19 vaccine for use in adolescents or children. These are laudable achievements, but the global vaccination effort has been challenged by inequitable distribution of vaccines predominantly to high income countries, with only 0.9% of people in low-income countries having received at least one dose of a COVID-19 vaccine. Addressing this inequity is of critical importance and will result in better control of SARS-CoV-2 globally. Other challenges include: the reduced protection from COVID-19 vaccines against some strains of SARS-CoV-2, necessitating the development of variant specific vaccines; and uncertainties around the duration of protection from vaccine-induced immunity.

INTRODUCTION

As of early July 2021, over 181 million cases of COVID-19 and over 3.9 million deaths have been reported globally [1]. The impacts of the pandemic have been felt unequally around the world, with varying public health strategies leading to different epidemic trajectories [2]. Many countries are struggling with successive waves of COVID-19, and the goal of global elimination of SARS-CoV-2 has been abandoned and replaced with that of transition to endemicity.

A year ago, over 100 COVID-19 vaccines were under development, but none were approved for use [3]. Within 12 months several highly effective COVID-19 vaccines have achieved widespread use with over 3.04 billion doses administered, although unfortunately not equitably distributed. Of the global population, 23.4% have received at least one dose of a COVID-19 vaccine while only 0.9% of people in low-income countries have done so [4]).

Other factors that will influence the success of the global COVID-19 vaccination effort include the duration of immunity provided by vaccination, vaccine effectiveness against variant strains

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of SARS-CoV-2, and the impact of vaccines on transmission. Additionally, rare but serious adverse events associated with specific COVID-19 vaccines have been identified since their widespread use, in one case resulting in limitations to use in several countries.

VACCINE DEVELOPMENT

There are currently 105 COVID-19 vaccines in clinical trials, and 184 in pre-clinical development [5]. The majority of candidate vaccines target part or all of the SARS-CoV-2 spike protein. A variety of platform technologies are being studied, including protein subunit (32 candidates), viral vector (21 candidates), RNA (17 candidates), inactivated (16 candidates) and DNA (10 candidates). Only two live attenuated COVID-19 vaccines are in clinical trials, both in phase I.

mRNA nucleic acid vaccines and viral vector vaccines are newer technologies, and have been relatively fast to develop and manufacture, in part because developers required access only to the genome sequence of SARS-CoV-2 rather than physical samples of the virus. A programmatic limitation with mRNA vaccines has been their requirement for ultra-cold storage, making distribution logistically challenging. However, progress is being made; a phase I trial of a fridge-stable mRNA vaccine (mRNA-1283, Moderna) is now underway, and it is possible that lyophilised formulations will be available in the future [6,7].

VACCINES IN USE

As of June 2021, 19 unique COVID-19 vaccines have regulatory approval in at least one country, as shown in Table 1. Most of these have provisional or emergency authorisation only, often on the basis of interim phase III trial results, and in some cases without any available published clinical trial results.

Six unique vaccines have received Emergency Use Listing (EUL) by the World Health Organization (WHO), and several others are currently under review [8]. WHO Emergency Use Listing is a prerequisite for COVAX Facility vaccine supply, COVAX being an initiative of the Coalition of Epidemic Preparedness Innovations (CEPI), the Global Vaccine Alliance (Gavi) and the WHO, focussed on accelerating the development and manufacture of COVID-19 vaccines and ensuring equitable access globally through a shared procurement mechanism.

VACCINE EFFICACY AND EFFECTIVENESS

Vaccine efficacy measures the proportionate reduction (relative risk reduction) of specific outcomes of interest among vaccinated persons compared to unvaccinated persons in "ideal" conditions, as in a phase III randomised controlled clinical trial. Vaccine effectiveness refers to the relative risk reduction of the same outcomes but in populations under real-world conditions, as in observational studies ('phase IV' studies). For several currently used COVID-19 vaccines, efficacy or effectiveness data are only available from interim analyses of phase III trials, or preprint publications.

Phase III results have been published or announced for 13 of the COVID-19 vaccines currently in use, with reported efficacy ranging from 50% to 95% for those with published data. Table 1 presents a summary of efficacy and effectiveness for the vaccines currently in use, including preprint or announced results, where published data are not available. Many COVID-19 vaccines show excellent efficacy against severe illness, even if efficacy against symptomatic illness is less impressive. Emerging evidence suggests that some COVID-19 vaccines also reduce the risk of asymptomatic illness, and therefore may reduce transmission of SARS-CoV-2.

The available phase IV effectiveness data generally correlate well with clinical trial findings, as shown in Table 1. This is reassuring since many countries are prioritising vaccinating population groups who are excluded or under-represented in clinical trials, such as older adults and people with medical co-morbidities, who may have reduced immune responses to vaccines.

In the absence of direct head-to-head studies, efficacy cannot yet be directly compared between different COVID-19 vaccines for a multitude of reasons, including differing settings, inclusion criteria and outcome definitions within the trials, and varying rates and dominant strains of SARS-CoV-2 in the countries where the trials were undertaken.

It is too early to know the duration of protection afforded by the currently available vaccines (or indeed by natural immunity). A correlate of protection (CoP) would facilitate more rapid evaluation of newer vaccines (including those focussed on variants, and in special populations), and of the need for and timing of vaccine booster doses. No CoP has yet been established, although neutralising antibody titres appear to be highly predictive of vaccine efficacy [9].

COVID-19 VACCINES IN CHILDREN

The majority of children with COVID-19 have mild or asymptomatic illness, though severe illness has been described, and is more likely in children with co-morbidities or in infants aged under 3 months [10]. COVID-19 is also associated with a rare post-infectious syndrome called multisystem inflammatory syndrome (MIS-C) or Paediatric Multisystem Inflammatory Syndrome – Temporally Associated with SARS-CoV-2 (PIM-TS), which exclusively affects children and leads to intensive care admission in the majority of cases [11]. In addition to protection against these severe outcomes, vaccination of children will be a critical step in achieving herd immunity against SARS-CoV-2.

BNT162b2 (Pfizer; BioNTech) was the first COVID-19 to be approved in children (aged 12–15), initially in Canada and now in several other countries [12]. In an ongoing phase III trial of 2260 adolescents aged 12 to 15 years, BNT162b2 was shown to be safe and high effective (efficacy 100% (95% CI, 75.3 to 100)) [13]. A trial of this vaccine in children aged 6 months to 11 years has commenced [14]. More recently, Sinovac's mRNA vaccine CoronaVac has been approved for use in children aged $\geq$ 3 years in China, on the basis of a phase I/II trial showing acceptable safety and strong immune responses in 100% of participants in the higher dose group [15,16].

Vaccine efficacy of 100% has been announced for Moderna's mRNA-1273 in adolescents aged 12–17 years, and its approval in this age group is anticipated [17]. Moderna have also announced a trial in children aged 6 months to 12 years is planned [17].

VARIANTS

Multiple mutant strains of SARS-CoV-2 are circulating globally, some of which have been designated by the World Health Organization as 'variants of interest' or 'variants of concern' [18]. The latter (currently 4 identified) are associated with significant features such as increased transmissibility, increased virulence or decrease in effectiveness of public health measures or vaccines [18].

Table 2 summarises available data on the immunogenicity, efficacy or effectiveness of COVID-19 vaccines against the four variants of concern of SARS-CoV-2. Protection may be lower against some strains e.g. Beta, or B.1.351, first identified in South Africa. Few studies have reported on protection against severe illness or hospitalisation, however it is promising to note that AZD1222 (University of Oxford; AstraZeneca) and BNT162b2 both appear to provide excellent protection against hospitalisation due to the delta strain [19].

Table 1
Summary of COVID-19 vaccines approved or in use globally.

Vaccine	Use/Access*	Vaccine efficacy (95% CI)	Vaccine effectiveness (95% CI)	Special populations (95% CI)
mRNA VACCINES				
BNT162b2 *Nucleoside modified mRNA encoding full length spike protein (stabilised in prefusion conformation)* Other names: Comirnaty, Tozinameran Developers: Pfizer, BioNTech, Fosun Pharma	WHO EUL ✓ COVAX ✓ Approved in 90 countries	Symptomatic illness: 95% (90.3–97.6) [35] Severe illness: 100% (non-estimable) [35]	Symptomatic illness: Israel – 94% (87–98) [36] Israel – 97·0% (96·7–97·2) – [37] Israel – 93.0% (95%CI 92.6–93.4) [38] UK – 80% (95% CI 73 to 85%) [39] Severe illness: Qatar – 97.4% (92.2–99.5) [40] Israel – 92% (55–100) [36] Hospitalisation: Scotland – 91% (85–94) [41] Israel: 93.4% (95%CI 91.9–94.7) [38] Severe/critical illness: Israel – 97·2% (96·8–97·5) [37] Asymptomatic illness: 91·5% (90·7–92·2) [37]	Adults ≥ 65 years: effectiveness 96·4% (95·9–97·0) [37] Children 12–15 years: efficacy 100% (75.3–100) [13] Effectiveness in people with immunocompromise: Israel – 84% (19–100) [42] Israel – 71% (95%CI 37–87) [43] Immunogenicity similar in pregnant vs non-pregnant women [44]
mRNA-1273 *mRNA* Other names: Spikevax, Elasomeran, COVID-19 Vaccine Moderna; TAK-919 Developer: Moderna	WHO EUL✓ COVAX ✓ Approved in 54 countries	Symptomatic illness: 94.1% (89.3–96.8) [45] Severe illness: 100% (non-estimable) [45]	Symptomatic illness: USA (healthcare workers) – 90% (68–97) [46]	Adults ≥ 65 years: efficacy 86.4% (95% CI: 61.4–95.2%) [45] Children 12–17 years: efficacy 100% (press release) [17]
VIRAL VECTOR VACCINES				
AZD1222 *Recombinant replication deficient ChAdOx1 adenoviral vector vaccine encoding full length spike protein* Other names: ChAdOx1_nCoV-19, COVID-19 Vaccine AstraZeneca, Vaxzevria, Covishield Developers: University of Oxford, AstraZeneca Serum Institute of India (for Covishield)	WHO EUL✓ Approved in 161 countries	Symptomatic illness: 70.4% (54.8–80.6) [47]; Symptomatic illness, with dose interval ≥ 12 weeks: 81.3% (60.3–91.2) [48] Severe illness: 100% (press release) [49] Asymptomatic infection: 69.7% (95%CI: 33.0–86.3) [50]	Symptomatic illness: 79% (95% CI 65 to 88%) [39] Hospitalisation: 85% (75–94) [41]	Adults ≥ 65 years: efficacy against symptomatic infection 100% (press release) [49] Adults ≥ 80 years: effectiveness against symptomatic infection after a single dose 80·4% (95% CI 36·4–94·5) [51]
Ad26.COV2.S *Recombinant replication deficient adenovirus type 26 vector encoding the full length spike protein* Other names: Ad26COVS1, JNJ-78435735 Developer: Janssen Pharmaceutical Companies	WHO EUL✓ COVAX ✓ Approved in 52 countries	Symptomatic illness: 66.9% (59.1–73.4) at ≥ 14 days and 66.5 (55.5–75.1) at ≥ 28 days after single dose [52] Severe-critical illness: 85.4% (54.2 to 96.9) [52] Asymptomatic infection: 74.2 (47.13–88.57) (not published) [53]	Symptomatic illness ≥ 14 days after single dose: 76.7% (30.3–95.3) [54]	Adults ≥ 65 years: efficacy against moderate-severe infection 68.6% (38.6–85.1) [55]

Table 1 (*continued*)

Vaccine	Use/Access*	Vaccine efficacy (95% CI)	Vaccine effectiveness (95% CI)	Special populations (95% CI)
(Johnson & Johnson)	Africa Regulatory Taskforce Endorsed			
Ad5-nCoV *Replication deficient adenovirus type 5 vector encoding full length spike protein* Trade names: Convidecia Developer: CanSinoBIO	Approved in 8 countries In use in 3 countries Production goal 100 million doses in 2021	Symptomatic illness 65–69% (press release) [56] Severe illness: 90–95% (press release) [56]	Not published or announced	
Sputnik V *Non-replicating adenovirus types 5 and 26 vectors (heterologous)* Other names: Gam-COVID-Vac, rAd26-S + rAd5-S Developer: The Gamaleya National Center	Approved in 69 countries	Symptomatic illness: 91·6% (85·6–95.2) [57] Severe illness: 100% (94.4–100) [57]	Symptomatic illness: Russia – 97.6% (press release) [58] UAE – 97.8% (press release) [59] Bahrain – 94.3% (press release) [60] Severe illness: UAE – 100% (press release) [58]	Adults > 60 years: efficacy 91.8% (67.1–98.3) [57]
Sputnik Light *Non-replicating adenovirus vector type 26* Other names: Gam-COVID-Vac Developer: The Gamaleya National Center	Approved in 10 countries		Symptomatic illness: 78.6–83.7% (press release – Argentina) [61]	
INACTIVATED VACCINES				
BBIBP-CorV *Inactivated whole virus with aluminium hydroxide adjuvant* Other names: SARS-CoV-2 Vaccine (Vero Cell) Developers/Manufacturers Sinopharm, Beijing Institute of Biological Products	WHO EUL ✓ COVAX ✓ Approved in 55 countries	Symptomatic illness: 78.1% (64.8% −86.3%) [62] Severe illness: 100% (non-estimable)	Not published or announced	
COVIV *Inactivated whole virus with aluminium hydroxide adjuvant* Other names: Inactivated (Vero cell) Developer: Sinopharm, Wuhan Institute of Biological Products	Approved in 1 country, in use in 2 countries	Symptomatic illness: 72.8% (95%CI: 58.1–82.4) Severe illness: 100% (non-estimable) [62]	Not published or announced	
CoronaVac *Inactivated whole virus* Developer: Sinovac Biotech	WHO EUL✓ Approved in 33 countries	Symptomatic illness: Brazil – 50·7% (36·0–62·0) [63] Indonesia – 65.3% (20.0–85.1) [64] Turkey – 83.5% (65.4–92.1) [64] Severe illness: 100% (16.9–100.0) [63]	Symptomatic infection: 50.7% (95% CI: 33.3–62.5%) [65] Symptomatic infection (not published): 67% (65–69) [64] Hospitalisation (not published): 85% (83–87) [64]	Adults ≥ 60 years (Chile): Effectiveness against symptomatic illness: 67.4% (64.6–69; effectiveness against hospitalisation: 83.3% (80.4–85.8) [64]

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Table 1 (*continued*)

Vaccine	Use/Access*	Vaccine efficacy (95% CI)	Vaccine effectiveness (95% CI)	Special populations (95% CI)
			COVID-19 related death: 80% (95%CI: 73–86) (not published) [64]	
Covaxin Other names: BBV152 Developer: Bharat Biotech	Approved in 9 countries	Symptomatic illness: 78% (95%CI: 61–88%) (press release) [66,67] Severe illness:100% (95%CI: 60–100%) (press release) Asymptomatic infection: 70% (no confidence intervals provided) (press release)	Not published or announced	
QazVac Other names: QazCovid-in Developer: Kazakhstan RIBSP	Approved in 1 country	Not published or announced	Not published or announced	
KoviVac Developer: Chumakov Center	Approved in 1 country	Not published or announced	Not published or announced	
SARS-CoV-2 Vaccine (Vero Cells) Other names: Keweike Developer: Minhai Biotechnology CO	Approved in 1 country	Not published or announced	Not published or announced	
COVIran Barakat Developer: Shifa Pharmed Industrial Co.	Approved in 1 country	Not published or announced	Not published or announced	
PROTEIN SUBUNIT				
Zifivax Other names: RBD-Dimer/ ZF2001 Developer: Anhui Zhifei Longcom	Approved in 2 countries	Not published or announced	Not published or announced	
EpiVacCorona Developer: FBRI	Approved in 2 countries	Not published or announced	Not published or announced	
Soberana 02/Soberana Plus *Protein subunit of SARS-CoV-2 spike RBD chemically conjugated to tetanus toxoid* Other names: FINLAY-FR-2 Developer: Instituto Finlay de Vacunas	In use in 1 country	Symptomatic illness after 2 of 3 doses: 62% (press release) [68]	Not published or announced	
Abdala *Protein subunit adjuvanted with aluminium hydroxide* Other names: CIGB-66 Developer: Center for Genetic Engineering and Biotechnology	In use in 1 country	Symptomatic illness: 92.28% (press release) [69]	Not published or announced	

*Source: Nicole E. Basta & Erica E.M. Moodie on behalf of the McGill University COVID19 Vaccine Tracker Team. Available at covid19.trackvaccines.org.

The next phase of COVID-19 vaccine development involves variant-specific and multi-valent COVID-19 vaccines, which may be utilised as booster doses to those already vaccinated or for primary vaccination courses. Candidate vaccines targeting the Beta (B.1.351) strain include BNT162b2s01 (Pfizer; BioNTech), currently in phase III trial, mRNA-1273.351 (Moderna) and the bivalent mRNA-1273.211 (Moderna), both registered to enter phase III trials this year.

HETEROLOGOUS (MIXED) SCHEDULES

Heterologous schedules involving different vaccines for the initial and booster doses have been required for a variety of reasons, including global supply constraints and safety issues relating to the vaccine used for the first dose.

Early safety and immunogenicity data of such schedules are emerging. A study involving 363 participants aged $\geq$ 50 years in the UK showed an increase in systemic reactogenicity (i.e. fever, chills, fatigue, headache, joint pain, malaise, and muscle ache) after the second dose in participants receiving a dose each of AZD1222 and BNT162b2 4 weeks' apart, compared to homologous schedules, and regardless of which vaccine was given first. Reassuringly, these symptoms were short lived [20]. In a follow up preprint paper, the authors reported that regardless of which vaccine was given first, a mixed schedule resulted in a higher geometric mean concentration (GMC) of anti-spike IgG at 28 days post-boost, compared to a homologous schedule of AZD1222 [21]. A German preprint study reported no difference in reactogenicity and equal/improved immunogenicity in 26 individuals aged 25–46 given AZD1222 followed by BNT162b2 8 weeks apart compared to two doses of BNT162b2 [22]. These early data suggest that mixed schedules

Table 2
COVID-19 vaccine immunogenicity, efficacy and effectiveness against variant strains of SARS-CoV-2.

VACCINE	Alpha (B.1.1.7) First identified in UK	Beta (B.1.351) First identified in South Africa	Gamma (P.1) First identified in Brazil	Delta (B.1.617.2) First identified in India
mRNA VACCINES				
BNT162b2 Developer: Pfizer/BioNTech	Effectiveness against symptomatic infection 89.5%(95% CI 85.9–92.3) [40] Effectiveness 93.4% (95% CI 90.4–95.5) [70] In ≥ 70 years old single dose: Effectiveness against symptomatic illness: 67% (95% CI 57–75) [71] Effectiveness against symptomatic infection (Israel): 95.3% (95% CI 94.9–95.7) [37]Neutralising antibody 2.6-fold reduced vs wild-type (95% CI 2.2–3.1) [72]	Effectiveness against symptomatic infection 75% (95% CI 70.5–78.9) [40] Neutralising antibody 4.9 fold reduced vs wild-type (95% CI 4.2–5.7) [72] in one study, 7.6-fold lower than for an early strain ($p < 0.0001$) in another [73]	In ≥ 70 years old single dose: Effectiveness against symptomatic illness: 61% (95% CI 45–72) [study included both BNT162b2 and mRNA-1273; 85% received BNT162b2][71]Neutralising antibody reduced 2.6-fold vs an early isolate ($p < 0.0001$) [74] Neutralising antibody reduced 3.8-fold compared to early strain [75]	Effectiveness against symptomatic infection 87.9% (95% CI 78.2–93.2) [70]Effectiveness against PCR-confirmed infection: 79% (95%CI 75–82) [76] Effectiveness against hospitalisation: 96% (86–99) [77]Neutralising antibody 5.8 fold reduced vs wild-type (95% CI 5.0–6.9) [72] Neutralising antibody titres reduced 2.5-fold compared to early strain [78]
mRNA-1273 Developer: Moderna	Neutralising antibody reduced 1.2-fold vs wild-type [79]	Neutralising antibody reduced 6.4-fold vs wild-type [79]	Neutralising antibody reduced 3.5-fold vs wild type [79] Neutralising antibody reduced 4.8-fold compared to early strain [75]	
VIRAL VECTOR VACCINES				
AZD1222 Developers: University of Oxford, AstraZeneca	Efficacy against symptomatic infection with B.1.1.7: 70.4% (95% CI 43.6–84.5) [50] Efficacy asymptomatic infection: 28.9% (95%CI: −77.1–71.4) [50] Effectiveness 66.1% (95% CI 54.0–75.0) [70]	Efficacy against symptomatic infection 10.4% (95% CI, −76.8 to 54.8) [80] Neutralising antibody reduced 9-fold vs an early isolate ($p < 0.0001$) [73]	Neutralising antibody reduced 2.9-fold vs an early isolate ($p < 0.0001$) [74]	Effectiveness against symptomatic infection 59.8% (95% CI 28.9–77.3) [70] Effectiveness against PCR-confirmed infection: 60% (95%CI 53–66) [76] Effectiveness against hospitalisation: 92% (75–97) [77] Neutralising antibody titres reduced 4.3-fold compared to early strain [78]
Ad26.COV2.S Developer: Janssen Pharmaceutical Companies (Johnson & Johnson)		Efficacy against moderate-to-severe infection: 64.0% (41.2–78.7) [52] Efficacy against severe infection: 81.7 (46.2–95.4) [52] Neutralising antibody 5-fold reduced vs wild-type [81]	Neutralising antibody 3.3-fold reduced vs wild-type [81]	
Ad5-nCoV Developer: CanSino				
Sputnik V Developer: The Gamaleya National Center	No significant difference in neutralising activity compared to wild-type strain [82]	Neutralising activity reduced by median 6.8-fold compared to wild-type [82]	99.65% of participants induced IgG antibodies after second dose (press release) [83]	
INACTIVATED VACCINES				
SARS-CoV-2 Vaccine (Vero Cell) Developer: Sinopharm/BIBP	No significant difference in neutralising activity compared to wild-type [84]	Neutralising antibodies decreased 1.6-fold compared to wild-type strain [85]		
CoronaVac Developer: Sinovac	Neutralising activity decreased 1.21-fold compared to wild-type [86] Neutralising activity decreased by a factor of 0.5 [84]	Neutralising activity decreased 5.27-fold compared to wild-type [86] Neutralising activity decreased by a factor of 0.3 [84]	Neutralising activity decreased 3.92-fold compared to wild-type [86] Effectiveness against symptomatic illness 49.6% (95% CI 11.3–71.4) and [87] In ≥ 70 years old: Effectiveness against symptomatic illness: 41.6% (26.9–53.3) [88]	

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Table 2 (*continued*)

VACCINE	Alpha (B.1.1.7) First identified in UK	Beta (B.1.351) First identified in South Africa	Gamma (P.1) First identified in Brazil	Delta (B.1.617.2) First identified in India
BBV152/Covaxin Developer: Bharat Biotech	Neutralising activity was comparable to a heterologous (unclassified) strain [89]	Neutralisation activity was reduced 3.0-fold compared to early B.1 strain [90]		Neutralisation activity was reduced 2.7-fold compared to early B.1 strain [90]
PROTEIN SUBUNIT Trade name: Zifivax		Neutralising antibodies decreased 1.6-fold compared to wild-type strain [85]		
Developer: Anhui Zhifei Longcom				

are likely to be acceptable, and may even be superior, compared to homologous schedules.

VACCINE SAFETY

Given the speed and scale of the COVID-19 vaccine rollout, vaccine safety has been closely monitored by regulators and has been the subject of intense media scrutiny. Although safety outcomes are a major focus of clinical trials, these trials are underpowered to detect extremely rare adverse events, which instead are typically detected in post-licensure safety surveillance. It is therefore unsurprising that some COVID-19 vaccines have been found to be associated with very rare but in some cases serious adverse events, some of which have had programmatic implications.

A rare, newly identified syndrome now called thrombosis with thrombocytopenia syndrome (TTS) has been reported in association with two viral vector vaccines, AZD1222 and Ad26.COV2.S (Janssen; Johnson & Johnson), suggesting a potential class effect [23–25]. This rare immune-mediated disorder involves thrombosis in varying locations, accompanied by thrombocytopenia. To date TTS has not been reported in association with any other viral vector vaccine. TTS appears to be more common in younger adults, leading several countries to restrict its use to older age groups with varying age cut-offs, and in some cases leading to the use of heterologous schedules to complete vaccination courses following a first dose of AZD1222 [26].

More recently, myocarditis has been reported at higher than expected rates in adults and adolescents who have received an

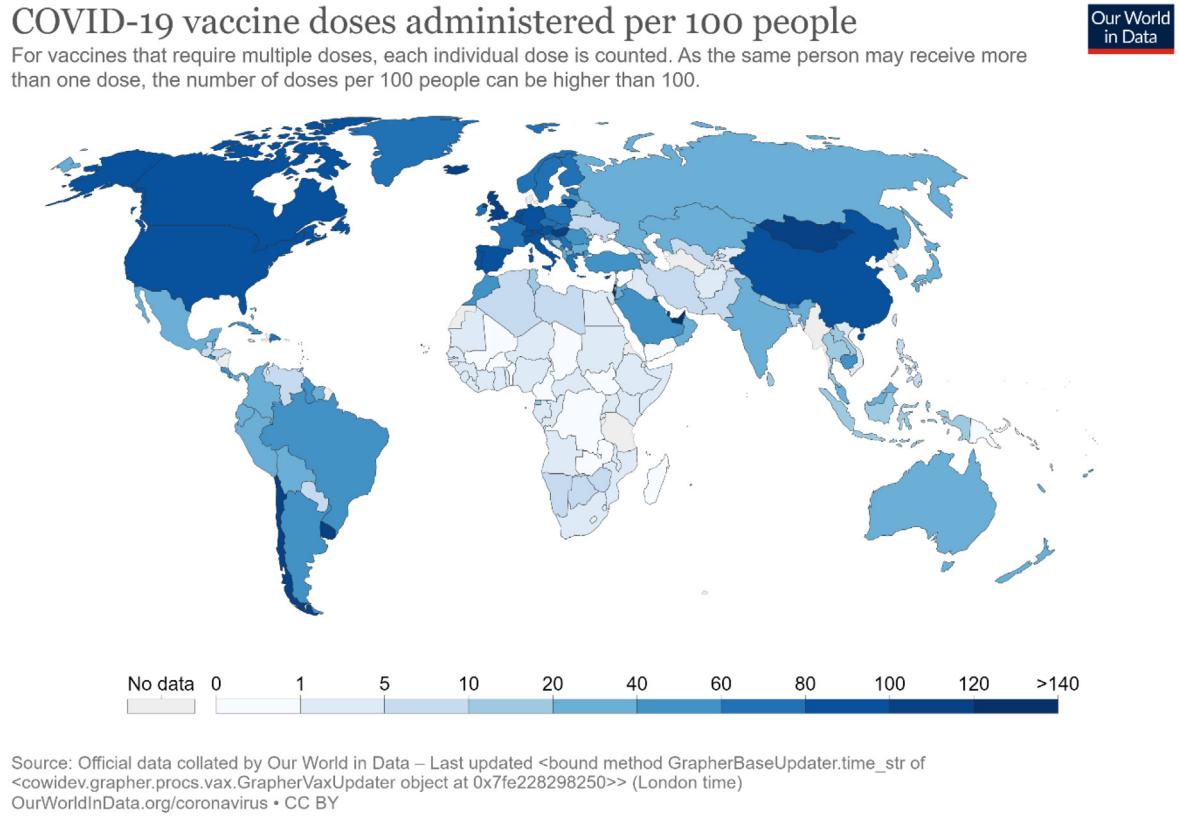

Fig. 1. COVID-19 vaccine doses administered per 100 people, June 29, 2021 [31].

mRNA COVID-19 vaccine (BNT162b2 or mRNA-1273) in the United States and Israel [27,28]. This safety signal continues to be investigated by regulators and to date has not led to any restrictions on the use of mRNA vaccines.

GLOBAL VACCINE DISTRIBUTION

Investments by several high-income countries accelerated the vaccine development process, and enabled these countries to secure their own vaccine supply. The largest of these is Operation Warp Speed, a US public–private partnership which invested US $18 billion in into a portfolio of 8 vaccine candidates, all obliged to enter into product delivery commitments with the USA [29].

Equitable global vaccine distribution would provide the best chance of suppressing new variants, generating herd immunity, and eventually bringing the pandemic to an end. COVAX aimed to provide a central negotiating system between countries and vaccine developers, and to distribute the vaccines globally in an equitable manner, starting with enough doses for 20% of each participating country's population. Further distribution would be based on measures of need (burden of disease, universal health coverage service index, health system saturation, high risk groups for COVID-19).

High income countries invested in COVAX while maintaining their direct bilateral deals, often securing enough doses to vaccinate their population several times over. This parallel investment and acquisition process has enabled vaccine access and roll-out to occur most rapidly in the USA and European countries, but with the consequence of making fewer doses available for COVAX and for low middle income countries (LMIC) [30]. This has demonstrably reinforced global inequalities, as demonstrated in Fig. 1.

So far 10 countries have administered 75% of all COVID-19 vaccines and COVAX has been responsible for less than 4% [30]. The People's Vaccine Alliance has estimated that, at the current rate, low-income countries could take 57 years to fully vaccinate their populations, whereas G7 countries might reach that milestone in the next 6 months [30]. Promisingly, G7 countries have recently pledged the donation of 870 million doses of COVID-19 vaccines and reaffirmed their support for COVAX as "the primary route for providing vaccines to the poorest countries", though these donations are yet to be enacted [32].

LMIC countries have consequently entered their own unilateral contracts with countries such as India, China or Russia. Serum Institute of India (SII), India's largest vaccine manufacturer has provided vaccines to 95 countries, while China is now the largest global exporter of COVID-19 vaccines to countries across Asia, Africa and Latin America [33]. Interestingly, Cuba decided against joining COVAX, and independently developed their vaccine candidates, two of which are now in Phase 3 clinical trials [34].

CONCLUSION

The past 18 months have seen extraordinary scientific achievements that have yielded a growing global portfolio of effective vaccines against COVID-19. Several vaccines are confirmed to be safe and effective both in healthy individuals and in special populations (such as older adults or adolescents), particularly against severe illness. These findings have been replicated in real-world studies in various countries. Protection appears to be reduced against some variant strains, and variant-specific vaccines are already under development.

Unfortunately, despite the proactive efforts of the COVAX facility and other bodies to ensure equitable vaccine distribution, the supply of COVID-19 vaccines has been predominantly to high income countries, resulting in very low vaccination rates in low- and middle-income countries Addressing this inequity will benefit all by eventually leading to better control of SARS-CoV-2. All countries should be reminded that COVID-19 anywhere is a risk of COVID-19 everywhere.

DIRECTIONS FOR FUTURE RESEARCH

- Phase IV effectiveness studies of COVID-19 vaccine performance in low and middle income countries.
- Further clinical trials in special populations of interest including children.
- Determination of standardised immune correlates of protection against SARS-CoV-2 to be used in future clinical trials of new and re-designed COVID-19 vaccines.
- Continued, integrated international surveillance of SARS-CoV-2 molecular epidemiology to monitor and detect variants.

CONFLICTS OF INTEREST

None of the authors have any conflicts of interest to declare.

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