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Review Article



Safety & effectiveness of COVID-19 vaccines: A narrative review

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There are currently eight vaccines against SARS-CoV-2 that have received Emergency Use Authorization by the WHO that can offer some protection to the world's population during the COVID-19 pandemic. Though research is being published all over the world, public health officials, policymakers and governments are collecting evidence-based information to establish the public health policies. Unfortunately, continued international travel, violations of lockdowns and social distancing, the lack of mask use, the emergence of mutant strains of the virus and lower adherence by a sector of the global population that remains sceptical of the protection offered by vaccines, or about any risks associated with vaccines, hamper these efforts. Here we examine the literature on the efficacy, effectiveness and safety of COVID-19 vaccines, with an emphasis on select categories of individuals and against new SARS-CoV-2 strains. The literature shows that these eight vaccines are highly effective in protecting the population from severe disease and death, but there are some issues concerning safety and adverse effects. Further, booster shots and variant-specific vaccines would also be required.

Key words Adverse effect - clinical trials - COVID-19 - efficacy - neutralization potential - risks - safety - SARS-CoV-2

The World Health Organization (WHO) list of Emergency Use Authorization (EUA)-qualified COVID-19 vaccines (as on 20 December, 2021) contains eight vaccines, namely the three adenoviralvectored vaccines ChAdOx1 nCoV-19 (University of Oxford/AstraZeneca), Ad26.CoV2.S (Janssen), Covishield, CrAdOxI, nCoV-19 (Serum Institute of India), two whole-inactivated coronavirus, which are the Covilo/BBIBP-CorV (SinoPharm/Beijing Institute of Biological Products), CoronaVac (Sinovac) and Covaxin, BBV152 (Bharat Biotech), and the messenger RNA (mRNA) vaccines mRNA-1273 (Moderna) and BNT162b2 (Pfizer-BioNTech)¹. mRNA vaccines work by injecting mRNA that encodes the SARS-CoV-2 spike protein directly into the host and have several advantages over conventional vaccine types, including improved safety, low potential for mutations, lower risk of antigen degradation *in vivo* and the potential for rapid mass production at a lower cost², although there are still challenges remaining regarding their pharmacological stability³.

Another mRNA vaccine, CureVac, was developed in the European Union (EU) by CureVac N.V. and the Coalition for Epidemic Preparedness Innovations, with the hope of being cheaper and lasting longer than other mRNA vaccines, but results on June 16, 2021 from a 40,000-person phase III two-dose trial found it 47 per cent effective at preventing the disease, which was lower than the ≥ 50 per cent requirement for approval by the WHO⁴. Other vaccines produced by Janssen, AstraZeneca, Sputnik-V and CanSino, use human and primate adenovirus vectors⁵. The vaccines manufactured by Novavax and GSK/Sanofi companies consist of purified pre-fusion stabilized SARS-CoV-2 spike protein, which is given in combination with an adjuvant to boost the immune response⁶. On June 1, 2021, the WHO validated the use of the Chinese Sinovac - CoronaVac COVID-19 vaccine for emergency use, although with interim policy recommendations7. CoronaVac is an inactivated vaccine with easy storage requirements⁸. It was only 51 per cent effective at preventing COVID-19 in latestage trials⁹. The vaccine's safety, immunogenicity and efficacy need to be tested across the three phases of clinical trials, although 'protection against severe disease and death is difficult to assess only in phase 3 clinical trials^{'10}

Vaccination against COVID-19 started in India on January 16, 2021¹¹. The Indian government and States launched an extensive vaccination campaign against COVID-19, targeting 300 million beneficiaries of priority groups such as healthcare and frontline workers and individuals older than 50¹². India's drug regulator (Central Drugs and Standards Committee - CDSCO) approved restricted emergency use of Covishield and Covaxin in India. Covishield (AstraZeneca vaccine ChAdOx1/AZD1222), approved for EUA by the WHO, is a two-dose version of the Oxford/AstraZeneca vaccine manufactured by the Serum Institute of India¹³. while Covaxin (BBV152 vaccine) is an inactivatedvirus vaccine^{11,14}. Phase I (safety and immunogenicity) and phase II trial (immune response and safety) data of Covaxin are published¹⁵. A phase 3 study confirmed the clinical efficacy of BBV152 against symptomatic COVID-19 disease and safety monitoring and assessment did not raise concerns about the vaccine¹⁶.

In April 2021, the Indian Government approved Sputnik V as a third vaccine¹². Sputnik V (Gam-COVID-Vac), which is a dual vector-based vaccine that combines type 26 and rAd5 recombinant adenovirus (rAd), exhibited 91.6 per cent efficacy against COVID-19¹⁷. Sinopharm's BBIBP-CorV (Covilo) showed 79 per cent efficacy against symptomatic SARS-CoV-2 infection and hospitalization in a large multi-country phase III trial after administering two doses 21 days apart, but efficacy could not be determined in people aged 60+ and with comorbidities, and there was an underrepresentation of women¹⁸.

In October 2021, India crossed the one billion vaccine doses milestone and by January 16, 2022, 70 per cent adult population was fully vaccinated¹⁹.

Efficacy/effectiveness of current COVID-19 vaccines

A systematic review on the efficacy of vaccines covering studies from January 1 to May 14, 2021 identified 30 studies, showed 80-90 per cent vaccine efficacy against symptomatic and asymptomatic infections in fully vaccinated people in nearly all studies²⁰. In clinical trials, three vaccines had higher (>90%) efficacy against COVID-19 infection [Pfizer-BioNTech (~95%), Moderna (~94%) and Sputnik V (~92%)] than the vaccines by Oxford-AstraZeneca (~70%) and Janssen (54-72%), against moderate and severe forms of COVID-19 infection¹⁰. The mRNA vaccines showed high efficacy against infection and a very high level of protection against severe disease, hospitalization and death while the risk of severe forms of COVID-19 infection and deaths was reduced by Moderna, Sputnik V, Janssen and Oxford-AstraZeneca vaccines. In contrast, this information was not available in the published trials for the Pfizer-BioNTech vaccine^{20,21}. Compared to the Pfizer vaccine, the Moderna vaccine can be kept at higher temperatures, making it easier to transport and store²². Other vaccines produced by other companies, and with positive efficacy results, received EUA status in some countries²³. The longitudinal assessment of vaccine participants is a necessary critical assessment because it provides information on whether vaccination can achieve long-lasting immunity²⁴.

Although most evidence suggests that 'immune responses elicited by SARS-CoV-2 infection are present and might protect against' reinfection, but the experience with seasonal coronaviruses and the present experience with SARS-CoV-2 suggest that immunity to natural infection might wane over time, as reinfection cases occur²⁵. For this reason, an extra booster dose can continue to offer protection²⁶.

Regarding the interchangeability of COVID-19 vaccines, the WHO recommends using the same COVID-19 vaccine for both doses of a two-dose schedule²⁷, but there is scientific evidence of the

effectiveness of heterologous vaccination with AstraZeneca or Covishield as the first dose and an mRNA vaccine as the second dose²⁸⁻³⁰.

Safety and adverse effects of current COVID-19 vaccines

As shown in Table I, current vaccines have demonstrated considerable efficacy in diminishing mild, moderate and severe cases with a low risk of adverse events²¹. For some of these vaccines [such as Convidicea (AD5-nCoV), Janssen (Ad26.COV2.S), Sinopharm (BBIBP-CorV), Covaxin (BBV152) and Sinovac (CoronaVac)], there is the information available on their immunogenicity and safety from phase I and II vaccine recipients, but evidence of their effectiveness is not clear²¹. Due to urgency, health regulatory agencies such as the EMA in the EU and the Food and Drug Administration (FDA) in the US evaluated only short-term adverse effects before their authorization. Records of adverse events in trial results on the BNT162b2 mRNA COVID-19 vaccine (Pfizer-BioNTech vaccine) continued up to six months from the second dose³⁹. Mild-to-moderate local responses such as discomfort, redness or inflammation at the injection site were the most commonly reported adverse effects in the clinical trials, while systemic events included fatigue, headache, body aches and fever³⁹. There were four serious issues among BNT162b2 participants in a clinical trial: shoulder injury from vaccine administration, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia and right leg paresthesia³⁹. Another adverse reaction in the Pfizer-BioNTech trial was lymphadenopathy with 64 vaccine recipients (0.3%) versus only six in the placebo group (<0.1%)³⁹. The clinical trial on the mRNA-1273 COVID-19 vaccine, manufactured by ModernaTX Inc., reported no serious adverse events, while moderate or mild adverse events included headache, fatigue, myalgia, chills and injection-site discomfort, but these were dose-dependent and more common after the second immunization⁴⁰.

Myocarditis and pericarditis were reported in individuals receiving mRNA vaccines (Pfizer-BioNTech BNT162b2 and Moderna SpikeVax), especially in young males after the second dose, so the US Centres for Disease Control and Prevention (CDC) and FDA developed educational material for vaccine recipients and providers that described the possibility of myocarditis and its symptoms to be able to recognize and manage it⁴¹. There are insufficient data to describe the efficacy, safety and effectiveness of the BNT162b2 in children under 16 and the SpikeVax vaccine in individuals under 18⁴². Although the balance of benefits and risks varied by age and gender, but the benefits of preventing the COVID-19 disease and associated hospitalizations, intensive care unit admissions and deaths outweighed the risks such as expected myocarditis cases after vaccination in all populations for which vaccination was recommended⁴¹. There are currently no alternatives to mRNA COVID-19 vaccines for youths, so on May 10, 2021, the FDA expanded the EUA of the Pfizer-BioNTech COVID-19 vaccine to include adolescents 12 through 15 yr of age⁴¹.

Anaphylaxis has been the only life-threatening condition reported during the vaccination campaign with the Pfizer-BioNTech vaccine, so it has to be appropriately managed and prevented⁴³. Hypersensitivity-related adverse events for Pfizer-BioNTech and Moderna trial participants relative to the placebo groups were 0.12 and 0.4 per cent higher, respectively^{39,40}. In addition, the Pfizer-BioNTech trial reported one 'drug hypersensitivity reaction' and one case of anaphylaxis, while Moderna reported two cases of 'delayed hypersensitivity reactions'⁴⁴.

By December 23, 2020, among the 1,893,360 first doses of Pfizer-BioNTech vaccines administered in the US, only 0.2 per cent of adverse events were reported and submitted to the Vaccine Adverse Event Reporting System (VAERS)⁴⁵. As of January 10, 2021, a reported 4,041,396 first doses of Moderna COVID-19 vaccine had been administered in the United States, and reports of 1,266 (0.03%) adverse events after receipt of Moderna COVID-19 vaccine were submitted to VAERS⁴⁶.

Allergic reactions from the two available mRNA COVID-19 vaccines were due to polyethylene glycol (PEG)⁴⁷, also known as macrogol, while for the AstraZeneca and Johnson and Johnson COVID-19 vaccines, the filler polysorbate 80, also known as Tween 80, has been implicated in allergic reactions⁴⁸⁻⁵⁰. Allergic reactions are rare, but the CDC recommends avoiding mRNA vaccines in individuals who had anaphylaxis in the past^{42,51}. In addition, the CDC guidance indicates precaution for allergy due to 'a potential cross-reactive hypersensitivity between ingredients in mRNA and adenovirus vector COVID-19 vaccines'⁵².

The occurrence of thrombosis with thrombocytopenia syndrome was linked to adenovirus vector vaccines such as ChAdOx1 nCoV-19 (Oxford-

é é	efficacy, safety, pr	otection against variants an	d storage of COVID-19 vaccines listed by the World Health Organizat	ion: Findings from c	inical trials
Country; date of WHO's listing	`	Type of vaccine and regimen	Efficacy and safety profile against original virus and variants of concern	Storage	Cost per dose (US\$)
USA, January 31, 2020		m-RNA vaccine 2 doses regimen Three weeks apart Use for >12 yr old (for 12-15 yr children with comorbidities this vaccine is suggested)	 92-100% against infection 87% against hospitalization 92% against severe disease A possible causal relationship with very rare cases of myocarditis in young men (16-24) is reported and currently under investigation⁴¹ 75% reduction in neutralization activity against the Beta (B.1351), 88% reduction against Alpha (B.1.1.7) 	-70°C for shipping and six months storage 2-8°C for 30 days	20
USA; April 30, 2021		m-RNA-vaccine 2 doses regimen Four weeks apart Use for >18 yr old	94% against infection 100% against severe disease, hospitalization and death (<i>e.g.</i> , anaphylaxis) A possible causal relationship with very rare cases of myocarditis in young men is reported and currently under investigation Preliminary results indicate some reduction in neutralization activity against the Beta (B.1351) variant, and less marked decrease against Gamma (P1), Alpha (B.1.1.7), and Epsilon (B.1.429). The impact of delta (B.1617.2) is yet to be determined	-20°C for shipping and six months storage 2-8°C for 30 days	37
March 12, 2021		Viral vector Single dose regimen Use for >18 yr old	66% against infection 77% (after 14 days) to 86% (after 28 days) against severe disease 93% (after 14 days) to 100% (after 28 days) against hospitalization Efficacy was maintained against P2 and B1.351 variants Very rare severe allergic reactions reported in clinical trials Thrombosis with thrombocytopenia syndrome reported 3-15 days following vaccination	2-8°C for three months -20°C for two years	10
UK, February 15, 2021		Viral vector Two doses regimen Four weeks apart for two standard doses 12 wk apart for $\frac{1}{2}$ dose and full dose use for >18 yr old	92% protection against hospitalization with delta variant; 86% protection against hospitalization with Alfa variant No severe allergic reactions reported in clinical trials Thrombosis with thrombocytopenia syndrome reported 3-30 days following vaccination	2-8°C (pharmacy) for six months	4
China, June 1, 2021		Whole cell inactivated vaccine Two doses regime Two-four weeks apart Use for>18 yr old	 50-84% against infection 80-100% in preventing severe COVID-19 infections, hospitalization and deaths 51-83.5% in preventing symptomatic COVID-19 infection Safe and well tolerated in older adults 49.6% against infection (P. 1 variant) 50.7% (P. 2 variant) 	2-8°C pharmacy refrigerator	30
					Contd

94

Cost per dose (US\$)			15-20	our-insights/ candidates/. 219-vaccine- he injection) er.in/science/ d document ed/bitstream/ of Covaxin:
Storage	2-8°C (pharmacy) for six months	2-8°C (pharmacy)	2-8°C (pharmacy)	md-medical-products. $p_f-COVID-19-vaccine$ r:com/2020/08/COVIJ ness, or swelling at t acss, or swelling at t s://www.businessinsid ers.who.int/ris/restrict =y; For the cost =y; For the cost
Efficacy and safety profile against original virus and variants of concern	72-85% against infection 92% protection against hospitalization with delta variant; 86% protection against hospitalization with Alfa variant No severe allergic reactions reported in clinical trials Thrombosis with thrombocytopenia syndrome reported 3-30 days following vaccination	79% against infection and hospitalization No severe allergic reactions reported in clinical trials	78% efficacy against infection, hospitalization and deaths	lidated from: https://www.mckinsey.com/industries/pharmaceuticals- nd https://www.statista.com/chart/23510/estimated-effectiveness- 58/reported-cost-per-dose-of-COVID-19-vaccines/and https://observe All vaccines report mild-to-moderate local reactions (e.g., pain, red and fever), For information on protection against variants see: http ine-3-most-worrisome-coronavirus-variants/articleshow/81472174.cm -19. Released on November 3, 2021. Available from: https://extran dation-BBV152-background-2021.1-eng.pdf?sequence=1&isAllowea nice-of-Covaxin-rs-600-for-states-rs-1200-for-private-hospitals-2887
Type of vaccine and regimen	Viral vector Two doses regimen Four weeks apart for two standard doses 12 wk apart for $\frac{1}{2}$ dose and full dose use for >18 yr old	Whole cell inactivated vaccine Two doses regime Three-four weeks apart Use for >18 yr old	Whole virion inactivated vaccine Two doses regimen Four weeks apart Use for >18 yr	s sources can be also va cines-save-the-world ww.statista.com/chart/236 wy.statista.com/chart/236 wr-johnson-astrazenecal. headache, body aches, vaccines-work-against-th vaccines-SAGE-recommen varcines-SAGE-recommen iarat-biotech-announces-j iarat-biotech-announces-j
Country; date of WHO's listing	India, February 15, 2021	China, May 7, 2021	India, November 3, 2021	l above from variou will-COVID-19-vac. ned from: https://wn derna-pfizer-novava events (e.g., fatigue events (e.g., fatigue s:-how-well-covid-15 fn BBV152 Covaxir 4/WHO-2019-nCoV-
COVID-19 vaccine	Covishield TM (Serum Institute of India Pvt. Ltd) (ChAdOx1-S) ³⁶	BIBP/Sinopharma (Beijing BioInstitute of Biological Products Co. Ltd) ³⁷	Covaxin (Bharat Biotech BBV152) ³⁸	Information gatherec on-pins-and-needles- Cost per dose obtai price-comparison-mc and a few systemic news/one-chart-show on the Bharat Biotec handle/10665/34704. https://www.dnaindia

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AstraZeneca) and AD26.CoV2 \cdot S (Johnson and Johnson), raising concerns⁴³. For example, a populationbased cohort study in Denmark and Norway showed 'increased rates of venous thromboembolic events, including cerebral venous thrombosis' in recipients of ChAdOx1, more venous thromboembolic events were observed in the vaccinated cohort than expected in the general population, and the standardized morbidity ratio was significantly greater than unity⁵³.

ChAdOx1 nCoV-19 vaccine induced immune thrombotic thrombocytopenia and cerebral venous sinus thrombosis with fatal intracerebral haemorrhaging⁵³⁻⁵⁵. Following administration of the Johnson & Johnson vaccine, a case of thrombocytopenia, elevated D-dimers and pulmonary emboli was found⁵⁶. EMA reported other blood clots associated with thrombocytopenia, including arterial thromboses and splanchnic vein thrombosis, after administration of the AstraZeneca vaccine⁵⁷. All patients in each series had high levels of antibodies against antigenic complexes of platelet factor 4. as seen in heparin-induced thrombocytopenia. Therefore, this condition was defined as 'vaccineinduced immune thrombotic thrombocytopenia', requiring high-dose immunoglobulins and certain non-heparin anticoagulants for treatment^{57,58}. A case report of Guillain-Barre syndrome followed the administration of the first dose of the ChAdOx1 vaccine⁵⁹, and two cases of autoimmune hepatitis were triggered by Covishield vaccination⁶⁰.

The Coalition of Epidemic Preparedness Innovations (CEPI) questioned the use of alum and other adjuvants that might promote T-helper2 (Th2) responses⁶¹. Moreover, T-helper17 (Th17) inflammatory responses, which play a role in the pathogenesis of COVID-19-related pneumonia and oedema by promoting eosinophilic activation and infiltration, could also explain coronavirus-vaccine immune enhancement⁶². Therefore, an understanding of Th17 responses is critical for the successful clinical development and production of COVID-19 vaccines and plays a potential role in selecting vaccine dose, adjuvants and route⁶².

Do COVID-19 vaccines sensitize humans to antibody-dependent enhanced (ADE) breakthrough infection? ADE is a complex phenomenon that includes vaccine hypersensitivity (VAH), delayedtype hypersensitivity and/or an Arthus reaction⁶³. VAH has a complex and poorly defined immunopathology post-vaccination outcome that may be associated with non-protective antibodies⁶⁴. ADE in SARS-CoV and MERS-CoV infection showed the development of poorly or non-neutralizing antibodies after vaccination or infection enhance subsequent infections⁶⁵. Several SARS-CoV and MERS-CoV vaccines have elicited a post-challenge VAH in laboratory animals. For example, in the 1960s, the formalin-inactivated measles vaccine in children caused VAH 8-12 months after the vaccination, leading to lung lesions, revealing damage to parenchymal tissue, pulmonary neutrophilia with abundant macrophages and lymphocytes and excess eosinophils⁶⁶. Lessons learned from adverse effects caused by SARS-CoV and MERS-CoV vaccines may help to develop better immunotherapeutics and vaccines against SARS-CoV-2⁶⁵.

Overvaccination in patients predisposed to autoimmune disease may enhance the possibility of developing an autoimmune response⁶³. Since the mRNA vaccines against COVID-19 are the first mRNA vaccines authorized for the market, there is a possibility that these may generate strong type 1 interferon responses that could lead to inflammation and autoimmune conditions⁶⁷.

A vaccine in the market requires safety monitoring surveillance to detect and evaluate rare adverse events not identified in prelicensure clinical trials. In the US, the CDC has three long-standing vaccine safety programmes: VAERS, the Vaccine Safety Datalink and the Clinical Immunization Safety Assessment⁶⁸.

Efficacy of the vaccines against new viral strains

Considering that the SARS-CoV-2 virus, like other viruses, mutates^{69,70}, why are some RNA vaccines effective against the new strains of the SARS-CoV-2 virus, while others are less, or not at all? These new variants result from mutations in the viral genomes, occurring due to the consequences of viral replication, which are advantageous to the survival of the virus. Among these variants, WHO, US CDC, and the EU's European Centre for Disease Prevention identified some variants as being significant variants, referring to them as variants of concern (VOCs) and variants of interest (VOIs) (Table II). VOCs emerged as a more significant threat to public health due to their enhanced transmissibility and infectivity71. Global concern is the continued spread of the highly transmissible Delta variant, which has become predominant worldwide72,73 and has better transmission potential (60%) than the alpha variant⁷⁴. Currently, omicron variant is becoming the predominant strain resulting from a combination

Table	e II. Charact	eristics of SA	RS-CoV-2 vari	iants of concern (VOC, Alpha,	Beta, Gamma, Del	ta and omicron) ai	nd variants of interest (VOI, Lambda and Mu)
	Variant	Next strain	Lineages	First detected	Country	Date designated	Spread number of nations	Attributes
Variants of concern	Alpha	201/501Y. V1	B.1.1.7	September 2020	UK	December 18, 2020	173	Evidence of increased transmissibility (\sim 50% increase) and disease severity based on case fatality and hospitalizations rates
	Beta	20H/501. V2	B.1.351 B.1.351.2 B.1.351.3	May 2020	South Africa	December 18, 2020	122	Evidence of increased transmissibility (~50% increase) and has an impact on therapeutics (bamlanivimab and etesevimab) and vaccines (reduced neutralization by post-vaccination serum)
	Gamma	20J/501Y. V3	P. 1 P. 1.1 P. 1.2	November 2020	Brazil	January 11, 2021	74	Evidence of impact on monoclonal antibody treatments (bamlanivimab and etesevimab) and vaccines (reduced neutralization by post-vaccination serum)
	Delta	21A/S: 478K	B.1.617.2 AY.1 AY.2 AY.3	October 2020	India	May 11, 2021 (VOI: 4 April 2021)	100	Evidence of increased transmissibility and has an impact on monoclonal antibody treatments and vaccines (reduced neutralization by post-vaccination serum)
	Omicron	21K	B.1.1.529	November 2021	Multiple countries	November 26, 2021	Not reported yet	Not fully investigated yet
Variants of interest	Lambda	N/A	C.37	December 2020	Peru	June 14, 2021	N/A	N/A
	Mu		B.1.621	January 2021	Columbia			
Last updat variants tha coronavirus https://www map-trackii, N/A, not av	ed: 20 Dec it are being : %2019-ncov/ ?businessins, ng-the-COVI ailable	sember 2021. monitored cur variants/varia ider.com/COV D-19-delta-va	Information rently and car <i>mi-info.html</i>); <i>TD-19-vaccine</i> <i>riant.</i> WHO, N	obtained from 1 be found at the CDC has no VO -efficacy-variants World Health Org	WHO (<i>http</i> WHO as we I listed and c <i>-india-south</i> - (anization; CI	s://www.who.int/en s as at the USA Co only two VOCs: D africa-brazil-uk-20, OC, Centres for Di	/activities/tracking enter of Disease C elta and Omicron 221-5; for transmis isease Control; VC	<i>z</i> -SARS-CoV-2-variants/) there are a number of Control and Prevention found (<i>https://www.cdc.gov/</i> i. There is also information in the magazine about: ssion see: <i>https://www.aljazeera.com/news/2021/7/7/</i> DI, variants of interest; VOCs, variants of concerns;

of increased transmissibility and the ability to evade natural and artificial immunization⁷⁵. WHO monitors the global spread and epidemiology of VOCs and VOIs and coordinates laboratory investigations⁷⁶.

Several SARS-CoV-2 VOCs have emerged and were originally identified in the UK (variant B.1.1.7 or alpha), South Africa (B.1.351 or beta), Brazil (P.1 or gamma), India (B.1.617.2 or delta) and South Africa (B.1.1.529 or omicron)⁷⁷. These VOCs are considered severe public health threats because of their association with higher transmissibility, morbidity, mortality and potential immune escape⁷⁸ by infection or vaccine-induced antibodies resulting from the accumulation of mutations in the spike protein⁷⁹. In other words, these may alter the clinical manifestation of the disease and efficacy of available vaccines and therapeutics, as well as the ability of reverse transcription-polymerase chain reaction (RT-PCR) assays to detect the virus⁸⁰.

Though the efficacy of the ChAdOx1 nCoV-19 vaccine against the alpha variant was similar to that reported in previous studies⁸¹, the vaccine conferred only minimal protection against COVID-19 infection caused by the Beta variant⁸². The NVX-CoV2373 vaccine (Novavax) also demonstrated efficacy against the Alpha and Beta variants of SARS-CoV-2⁸³. The Novavax vaccine is 86 per cent efficacious against the Alpha variant and 60 per cent efficacious against the Beta variant⁸⁴. Although the neutralization capacity of several COVID-19 vaccines (mRNA-1273, NVX-CoV2373, BNT162b2 and ChAdOx1 nCoV-19) was reduced against the Beta (B.1.351) variant⁸⁵, but Covaxin conferred significant protection against both Beta (B.1.351) and Delta (B.1.617.2) variants⁷⁰.

Similarly, the single-dose Janssen COVID-19 vaccine candidate demonstrated efficacy against the Beta variant⁸⁶. The Moderna vaccine candidate (mRNA-1273) also demonstrated efficacy against the Alpha and Beta SARS-CoV-2 variants, findings that were based on *in vitro* neutralization studies conducted using serum collected from individuals vaccinated with the mRNA-1273 vaccine⁸⁷. Therefore, South Africa adjourned campaigns to vaccinate its front-line health care workers (HCWs) with the Oxford-AstraZeneca vaccine after a small clinical trial suggested that it ineffectively prevented mild to moderate illness from the dominant variant in the country⁸⁸. The results of a clinical trial confirmed that a two-dose regimen of the ChAdOx1 nCoV-19 (AstraZeneca) vaccine did

not protect individuals against the mild-to-moderate B.1.351 variant⁸⁹.

Mutations observed in the SARS-CoV-2 variants identified in the UK and South Africa had small effects on the effectiveness of the Pfizer-BioNTech vaccine⁹⁰. A two-strain mathematical framework using Ontario (Canada) as a case study found that, given the levels of under-reporting and case levels at that time, 'a variant strain was unlikely to dominate' until the first quarter of 2021, and high vaccine efficacy was required across strains to make it possible to have an immune population in Ontario by the end of 2021⁹¹. The UK research showed that the Pfizer-BioNTech vaccine was 92 per cent effective against symptomatic cases of the alpha variant and offered 83 per cent protection against the Delta variant⁹². A study in Qatar found similar results: the Pfizer-BioNTech vaccine offered 90 per cent protection against the Alpha variant and 75 per cent protection against the Beta variant⁹³. In a US-based study carried out during July 2021, 346 of the 469 COVID-19 cases (74%) among Massachusetts residents occurred in fully vaccinated people with two doses of Pfizer-BioNTech, Moderna, or a single dose of Janssen vaccine ≥ 14 days before exposure⁹⁴. Genomic sequencing of testing identified the new Delta variant in 90 per cent of cases⁸⁶. Even vaccinated people may get infected with COVID-19 due to the Delta variant, and on July 27, 2021, the US CDC released a recommendation to invite citizens to wear masks in indoor public environments where the risk of COVID-19 transmission is high⁸⁴.

The neutralization potential of BBV152/Covaxin, the inactivated SARS-CoV-2 vaccine rolled out in India, was also effective against Beta and Delta variants, but since reduced neutralization activity may result in reduced vaccine effectiveness, further studies are needed for Covaxin against these two variants⁷⁸. A single dose of Pfizer or AstraZeneca offered little protection against the Beta and Delta variants and a neutralizing response was generated against the Delta variant only after the administration of the second dose⁷⁴. Despite being lower, the remaining neutralization capacity conferred by the Pfizer vaccine against Delta and other VOCs was protective⁹⁵.

Until February 6, 2022, the WHO described eight variants of interest (VOIs), namely Epsilon (B.1.427 and B.1.429); Zeta (P.2); Eta (B.1.525); Theta (P.3); Iota (B.1.526); Kappa (B.1.617.1); Lambda (C.37) and Mu (B.1.621)⁹⁶. However, there is still a lack

of detailed knowledge about their transmissibility, infectivity, re-infectivity, immune escape and vaccine activity⁶¹. A preprint highlighted that the lambda variant (lineage C.37), which spread from Peru in December 2020, displayed increased infectivity and immune escape against the Coronovac vaccine⁹⁷. Table II summarizes the profiles of the VOCs and VOIs. The most recent data on the variants reported in India are available at the Indian SARS-CoV-2 Genomic Consortia (INSACOG) website. The predominant SARS-CoV-2 variant currently circulating in India is Delta (B.1.617.2 and AY.4)⁹⁸. Covaxin (BBV152) exhibited good protection (65.2%) against the Delta variant, and although a minor reduction in the neutralizing antibody titre was observed, the sera of vaccinated individuals still effectively neutralized the Delta, Delta AY.1 and B.1.617.3 variants⁹⁹. In contrast, breakthrough infections were reported due to the Delta variant in individuals fully vaccinated with Covishield¹⁰⁰.

Safety and efficacy of the vaccines in select categories of people

Another issue is that clinical trials are studies conducted on select categories of individuals, generally healthy people. Thus, concerns exist about safety and effectiveness in specific categories of people. For instance, there are doubts that all COVID-19 vaccines can stimulate an immune response in older individuals $(\geq 65 \text{ yr})$, especially those with co-morbidities, such as hypertension, obesity and diabetes mellitus¹⁰¹. Older patients, especially those older than 65 and with co-morbidities, are more susceptible to a severe form of COVID-19 that can progress rapidly, often leading to death¹⁰². In general, the efficacy of vaccines in older people is not well studied. The impact of immunosenescence on vaccine safety is even more uncertain². The presence of chronic diseases (e.g., diabetes) and fragility, including immunodepression, may be better forecasters of weak immunologic responses than age^{103} .

Even though the safety and efficacy of COVID-19 vaccines in older people are critical to their health², no studies have been done to examine the response of this category of individuals to all COVID-19 vaccines. Vaccines developed by the University of Oxford/ AstraZeneca (ChAdOx1) and Janssen (Ad26.COV2) depend on the genetic alteration of adenoviruses that are inactivated, due to the replacement of the *E1* gene with the spike gene². The ChAdOx1 nCoV-19

(AZD1222) vaccine is better tolerated by older than younger people, and after the second dose, it has similar immunogenicity across all ages¹⁰⁴. However, additional assessment of AZD1222 is planned¹⁰⁵. A second trial on the Moderna vaccine showed binding- and neutralizing-antibody responses in older people (>55 yr), similar to previously reported vaccine recipients between 18 and 55 yr of age⁴⁰.

Pregnant and lactating women are excluded from vaccine research because they are not recognized as a high-priority group, despite the risk of complications and poor perinatal outcomes¹⁰⁶, and because of previous experience of pregnancies complicated by infection with other coronaviruses, such as SARS-CoV and MERS-CoV, making pregnant women vulnerable to severe SARS-CoV-2 disease¹⁰⁷. A retrospective study based on the clinical criteria confirmed that pregnancy significantly increased the risk of severe COVID-19¹⁰⁸. Based on a review of maternal and neonatal COVID-19 morbidity and mortality data, the COVID-19 vaccines should be administered to those at the highest risk of severe infection until the safety and efficacy of vaccines are thoroughly validated¹⁰⁹. Therefore, in consultation with their obstetricians, pregnant women will need to consider the benefits and risks of COVID-19 vaccines. The US CDC, the American College of Obstetricians and Gynaecologists and the Society for Maternal-Foetal Medicine each issued guidance supporting vaccination in pregnant individuals¹¹⁰.

Another critical issue concerns COVID-19 vaccination in children. Children of any age are susceptible to SARS-CoV-2 infection, including severe disease manifestations. Previously healthy children are also at risk of severe COVID-19 and multisystem inflammatory syndrome in children (MIS-C)⁶⁸. Children might differ from adults in terms of the safety, reactogenicity and immunogenicity of vaccines⁶⁸. Paediatric clinical trials can offer direct and indirect benefits from COVID-19 vaccination¹¹¹.

Updates on COVID-19 and vaccines

On November 26, 2021, the WHO designated B.1.1.529 (Omicron) as a new VoC, although its pathogenicity as well as its potential to evade immune response from vaccines and natural immunity is relatively unknown¹¹². Since other variants could emerge in the future, coordinated global responses that address vaccines and lockdown measures against SARS-CoV-2, surveillance systems that monitor viral mutations and the effectiveness of vaccines, as well

as overcoming vaccine and economic inequalities, are needed.

A third dose of the Pfizer-BioNTech vaccine is effective in protecting individuals against severe COVID-19-related outcomes, compared with receiving only two doses at least five months prior¹¹³. A booster of Moderna or Pfizer-BioNTech may produce antibodies against SARS-CoV-2 in organ transplant patients with an immunodepression state^{114,115}. On August 13, 2021, the US FDA authorized a third dose of the Pfizer-BioNTech or Moderna vaccines for immunocompromised people, who are particularly at risk for severe disease¹¹⁶, and the EMA concluded that an extra dose of these COVID-19 vaccines may be given to these patients at least 28 days after their second dose¹¹⁷.

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