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COVID-19 vaccine strategies must focus on severe disease and global equity

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In September, 2020, the WHO Prioritisation Roadmap for COVID-19 vaccines gave priority to prevention of severe disease and the highest risk groups. In July, 2021, the revised Roadmap noted that despite the progressive emergence of SARS-CoV-2 variants of concern, defined as mutations conferring increased infectivity, virulence, or relative capacity for immunological escape, vaccine effectiveness against severe disease had been retained.[1] At the end of 2021, global differences in the inter-related variables of population seropositivity[2] and vaccine coverage[3] have widened, and omicron has been declared the fifth variant of concern.[4] Omicron was detected in Africa,[4] where successive waves of SARS-CoV-2 have resulted in prevalence of past infection higher than 80% in some regions[5] and despite greatly increased global vaccine supplies,[3] the average coverage that can be achieved there in 2021 is estimated to be only 17%.[6] In 2022, we argue that COVID-19 vaccine strategies must remain focused on severe disease, and that global equity in achieving high adult coverage (ie, for those aged 18 years and older) of at least one dose is key to minimising severe COVID-19.

The first four SARS-CoV-2 variants of concern were discovered in settings with high infection pressure before vaccines were available. The alpha variant of concern was detected in the UK, beta in South Africa, gamma in Brazil, and delta in India during the second half of 2020, but delta was not designated a variant of concern until May, 2021.[7] The delta variant of concern has infectivity around three-fold greater than the other variants of concern, which were all more infectious than the Wuhan strain[7] and by July, 2021, had attained global dominance.[3] By contrast, the omicron variant of concern was first brought to attention by an outbreak among adults (ie, those younger than 30 years) in the South African province of Gauteng, a setting of high infection-acquired immunity following a third delta wave but low vaccine coverage in this age group.[4,8] Omicron was declared a variant of concern on the basis of an unprecedented number of mutations, almost three-fold greater than for delta, previously associated with increases in infectivity and capacity for immune escape.[4] Based on the amount of detection in sewage and rapid increases in prevalence in South Africa of omicron, community prevalence could be higher than recognised.[8] As for previous variants of concern, disease severity can be anticipated to be greatest in infection-naive, unvaccinated people, with substantial preservation of protection against severe disease in the vaccinated.[1,4] According to in-vitro data from synthetic polymutant spike-protein pseudoviruses containing 20 or more mutations, vaccine boosting of infection-derived immunity might provide the strongest protection against strains like omicron.[4,9]

Indirect protection of at-risk older adults through vaccinating high-transmitting age groups (young adults and adolescents) against SARS-CoV-2 was influential in early modelling studies,[1,10] based on precedents for influenza.[11] However, although the effectiveness of COVID-19 vaccines against asymptomatic infection (a proxy for transmission) was high for the ancestral virus and alpha variant in the short term, it was reduced by around 20% against delta.[12] Studies from the Netherlands[13] and England[14] during delta dominance found similar secondary attack rates among household contacts of a fully vaccinated index case, irrespective of their vaccination status. Although vaccine effectiveness against transmission remained statistically significant in the Netherlands (63%; 95% CI 46–75),[13] in England, 39% of infections in fully vaccinated household contacts were proven by genomic analysis to have arisen from a fully vaccinated index case.[14] If omicron has similar characteristics to delta specifically of decreased vaccine effectiveness against infection and transmission,[12,13] which wanes over time,[14] this feature will similarly reduce the potential for indirect effects of vaccine strategies.

In contrast to viruses such as measles, with obligate viraemic spread, infection with seasonal coronaviruses or other common respiratory viruses is not associated with durable immunity to reinfection.[15] The increased infectivity of the delta variant has been posited to represent peak fitness of SARS-CoV-2;[16] to what extent this increased infectivity will be outcompeted by omicron is unclear. Much remains to be learned about the evolution of SARS-CoV-2; if it follows the pattern seen with the 2009 H1N1 influenza virus, capacity for immune escape from vaccine immunity will become more important as population immunity increases.[17] The speed of any such transition is also uncertain and could be much more rapid than for seasonal coronaviruses.[17] As omicron has shown, continued dominance of delta or any other variant of concern cannot be assumed. Careful monitoring in settings with differing forces of infection and vaccine coverage is crucial, recognising that as SARS-CoV-2 becomes endemic in a post-vaccine world, aggressive containment strategies including border controls will have much reduced benefits[18] and are likely to discourage global data sharing.[4]

Vaccine strategies prioritising delivery of first doses will have a maximal impact on severe disease in settings with

constrained vaccine supply and low coverage, where high seroprevalence often coexists with delivery constraints. This conclusion is based on three considerations.

The first cosideration is that even in infection-naive people, efficacy and effectiveness of a single dose against severe disease is high in the short-term. A systematic review including studies up to mid-August, 2021, identified 21 efficacy trials and 58 vaccine effectiveness studies of COVID-19 vaccines, most from high-income countries.[19] Despite the short time window of 21 days between first and second doses used in vaccine trials and by many countries, single-dose efficacy and effectiveness against severe disease for mRNA (60–90% for BNT162b2; 75–80% for mRNA1273) and adenoviral vector vaccines (75–100% for ChAdOx1; 85% for Ad26.COV2) was high, but lower for inactivated viral vaccines (37–46% for CoronaVac).[19] In Canada, where longer intervals to the second dose were routine, first dose vaccine effectiveness of mRNA vaccines was highest more than 35 days after receipt in all age groups.[20] Another Canadian study found high vaccine effectiveness was maintained up to 4 months after a single dose of an mRNA vaccine.[21] For BNT162b2, the geometric mean titre of spike antibody was six-fold higher when the second dose was given more than 60 days after the first, compared with a 21-day dose interval.[22] For Ad26.COV2, humoral and cellular immunity matured over 8 months after a single dose.[23] Most vaccine effectiveness studies, and all but one efficacy trial, were during periods when variants of concern other than delta predominated.[19] Observational studies from Ontario, Canada,[24] and England[25] found high single-dose vaccine effectiveness against severe disease due to delta, but whether this will be applicable to omicron is unknown.

The second consideration is that in people with previous documented SARS-CoV-2 infection, accumulating evidence shows protection against reinfection, which is substantially augmented after a single dose of a range of COVID-19 vaccines. A systematic review of studies of reinfection after previous documented SARS-CoV-2 infection estimated protection of around 90% for up to 10 months, independent of whether antibodies were present postinfection.[26] However, this finding might be age-dependent, as a Danish population-based study found protection among people older than 65 years of only 45%.[27] An Israeli study examined protection against delta following previous SARS-CoV-2 infection, with or without subsequent vaccination.[28] Infection-naive recipients of two doses of BNT162b2 in Israel were seven times more likely (95% CI 5·5–9·2) to develop delta infection than individuals with previous infection, among whom a single BNT162b2 dose gave an additional 50% reduction in infection risk (odds ratio [OR] 0·5; 95% CI 0·3–0·9). This increment in protection among previously infected people after one vaccine dose is similar to a study done in Scotland during dominance of the alpha variant of concern (0·4; 0·3–0·54).[29] Most recently, analysis of confirmed SARS-CoV-2 infections during August and September, 2021, from the Israeli Ministry of Health database found similar age-adjusted incidence per 100 000 days at risk in people with past infection who were vaccinated with BNT162b2 between 4 months and 6 months previously (10·3; 95% CI 9·4–11·4) and those who received a booster dose in the previous 2 months (8·2; 8·0–8·5). By contrast, those who had their second dose of BNT162b2 between 4 months and 6 months previously had an incidence of 69·2 (68·8–69·8).[30] Immunogenicity studies support the findings from these observational studies of the importance of the first dose. People with previous infection have immune responses to one vaccine dose, which are at least equivalent to two doses in the infection-naive for mRNA,[31–33] adenoviral vector,[34,35] and inactivated whole virus vaccines,[36] even up to 11 months after infection.[34] There was no additive response to a second dose[31–35] and immune responses were broader, incorporating T-cell and B-memory responses, with greater affinity and persistence than in infection-naive people and improved neutralisation activity against the delta variant of concern.[37] High prevalence of HIV in Africa, and possible higher COVID-19 mortality among people living with HIV than in the general population, makes comparative data important.[38] In a randomised trial done in South Africa, people living with HIV with well controlled HIV suppression had equivalent blocking antibodies but had two-fold lower neutralising antibodies after two doses of ChAdOx1 than HIV-negative individuals who were SARS-CoV-2 negative at baseline. Notably, people living with HIV who were SARS-CoV-2 seropositive at baseline had substantially higher blocking and neutralising antibody responses than people who were seronegative, with little change in titre after the second dose compared with the first dose of ChAdOx1.[39]

The third consideration is that seroprevalence is now high in countries with substantial community transmission and low vaccine coverage due to supply constraints. For example in Kenya, seroprevalence increased from 4% in June, 2020, to 49% by March, 2021, when vaccine coverage was 2%,[40] and in the Central African Republic was recently estimated to have reached 80%.[5] On June 30, 2021, before delta resurgence, modelled global seroprevalence by region ranged from 70% in southeast Asia and 50% in Africa to around 1% in the western Pacific.[41] Estimates of seroprevalence should be considered minimum estimates,[42] but nevertheless indicate underascertainment of cases ranging from ten-fold in Europe and North America to 50-fold in southeast Asia.[43] In July, 2021, after the delta wave, mean seroprevalence across India was 68% (95% CI 66–69), varying from 87% in Bihar to 41% in Kerala.[44] In September, 2021, Kerala accounted for 65% of cases in India, whereas cases decreased ten-fold in other Indian states, consistent with their higher prevalence of infection-acquired immunity.[45] In the Amazonas region

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of Brazil, with a very high prevalence of hybrid (vaccine and infection-acquired) immunity, despite delta emergence case numbers have remained low and variant of interest mu has not increased in prevalence despite immune escape characteristics,[46] consistent with neutralisation data suggesting that hybrid immunity was more protective against highly mutated SARS-CoV-2 strains.[9]

Modelling studies have found that if protection against severe disease in infection-naive people is high after the first dose, vaccine strategies maximising supply of first doses are favoured across a range of settings.[47,48] This preference is strengthened when increased single-dose protection with previous infection and improved efficiency of vaccine supply and delivery are considered. Importantly, this approach might be appropriate irrespective of HIV prevalence[38] and to all vaccine platforms except inactivated viral vaccines, which have relatively low first dose effectiveness in people who are SARS-CoV-2 infection-naive.[19,48]

In countries where vaccine coverage is not constrained by supply, high two-dose coverage is important to minimise severe disease, particularly in groups at highest risk from breakthrough infection because of older age (ie, those older than 60 years) or underlying conditions, who require supplementary or booster doses to be adequately protected.

In high-income and high-middle-income countries, where vaccination programmes began in early 2021, and high two-dose coverage has been reached, attention has turned to breakthrough infections and waning immunity. The largest study included almost 7 million adults in England to investigate severe breakthrough infection more than 14 days after receipt of BNT162b2 or ChAdOx1 during a 6-month period to mid-June, 2021.[49] Among 2031 deaths and 1929 hospital admissions, more than 93% of deaths and 75% of admissions occurred in people older than 70 years, compared with 0·4% of deaths and 7% of admissions that occurred in people younger than 50 years. The greatest increases in risk were in people with Down syndrome, people who were severely immunosuppressed (eg, organ transplant or current chemotherapy patients), or whose frailty required residential care. After the second dose, the risk of death was reduced by 83% (OR 0·17; 95% CI 0·13–0·22), with almost 80% of deaths occurring in the 5% of people at highest risk.[49] This finding highlights the importance of older at-risk adults receiving at least two doses. Among recipients of two doses of BNT162b2 or ChAdOx1, another study in England found the strongest evidence of waning vaccine effectiveness against severe COVID-19 in people over 65 years with high frailty.[25]

In Israel, third doses of BNT162b2 were made available to people who had received their second dose more than 5 months before, first to those older than 60 years and subsequently down to those 16 years of age starting in July, 2021. In a cohort study, incidence of severe disease among two-dose recipients was highest among people 70 years and older (448 per 100 000) or with three or more comorbidities (503 per 100 000), decreasing ten-fold in those aged 40–69 years (to 58 per 100 000) or with one or two comorbidities (to 50 per 100 000). Estimated vaccine effectiveness of a third (booster) dose against hospitalisation was more than 90% in all these categories of age and comorbidity.[50] Data for comorbidity status stratified by age were not given, but incidence of severe disease after two doses was very low for people aged 16–39 years (2·5 per 100 000) or with no comorbidities (3·1 per 100 000).[50] Notably, during booster introduction in Israel, incidence of severe disease was about five-fold higher in unvaccinated adults than in two-dose recipients of any age.[51]

Even in countries with large populations at high risk of severe disease due to age and comorbidities, increasing two-dose coverage in the unvaccinated has a substantially greater effect than booster doses in fully vaccinated populations at low risk of severe breakthrough disease.[52] Implementation of booster doses beyond those at highest risk by countries with abundant vaccine supplies could compromise vaccine availability at the global level into 2022. Outside high-risk groups, fully vaccinated people who develop SARS-CoV-2 infection are more likely to be asymptomatic or mildly symptomatic than incompletely vaccinated or unvaccinated people,[53] and could acquire broader protective immunity, including against variants.[54] Fully vaccinated people at low risk of severe disease could possibly develop more effective strengthening of immunity after subsequent infection with SARS-CoV-2 than from booster doses—assessment of overall risk–benefit will require data on the severity and duration of symptoms after infection by age and

***Panel*: Global COVID-19 vaccine strategies in 2022**

- COVID-19 vaccine strategies should continue to prioritise prevention of severe disease
- Variants of concern such as delta and potentially omicron render strategies aimed at SARS-CoV-2 transmission unlikely to have more than a short-term effect on preventing severe COVID-19
- In countries with a high prevalence of previous infection and a low proportion of the population being older than 60 years prioritising delivery of the first dose will have the greatest effect on preventing severe COVID-19
- In countries with a low prevalence of previous infection and a high proportion of the population being older than 60 years, protection against severe disease in adults requires at least two doses
- In people who are severely immunocompromised or older than 60 years, evidence supports booster doses of mRNA or adenoviral vector vaccines to prevent severe disease; booster doses for all adults could compromise timely global availability of first doses

comorbidity status in people younger than 50 years who have received two or three doses.

In the panel, we summarise our conclusions and recommendations for global COVID-19 vaccine strategies in 2022. The emergence of delta and now omicron further reinforces the importance of access to COVID-19 vaccines globally and equitably for the health of all. Constrained vaccine supply has driven opportunities for SARS-CoV-2 to mutate to be more infectious. The emergence of omicron has emphasised that further delay in widely delivering at least first doses is fraught with peril for all.

Contributors

PBM wrote the original draft. All other authors contributed to reviewing and editing the manuscript.

Declaration of interests

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