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Global implication of booster doses of COVID-19 vaccine

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To the Editor

The emergence of highly transmissible novel COVID-19 variants such as the delta (B.1.617.2) has sparked worldwide fear leading to the consideration for booster doses of COVID-19 vaccines in previously vaccinated individuals. COVID-19 booster doses refer to the extra doses of the vaccine needed to increase the immunity of healthy individuals who have completed their primary vaccination series.

The rationale: Administration of the booster dosage can either be homologous with the same vaccine used as in primary series or heterologous wherein a completely different vaccine platform is used for boost immunizations and prevent development of immune escape [1]. Additionally, emergence of newer variant(s) of concern (VOCs) such as the delta poses further challenges owing to immune escape. Such had been the case with the ChAdOx1 nCoV-19 (AstraZeneca) vaccine which was developed against the original strain of COVID-19 and had lower neutralization efficacy against the delta variant [2, 3]. Moreover, additional doses of COVID-19 vaccine are also warranted in specific population groups such as elderly population. Data from a retrospective study in Israel revealed that nearly 40% of the breakthrough infections occurred in immunocompromised individuals [4]. Similarly, estimates from the Centers for Disease Control and Prevention (CDC) suggest that 66% of hospitalization and 85% of deaths following breakthrough infections in fully vaccinated individuals occurred in people aged ≥ 65 years [5]. Lastly, a heterologous booster dose of a m-RNA vaccine with a high protective efficacy against novel variants such as delta might be needed for countries which have initially utilized an inactivated-virus vaccine for primary vaccination. United Arab Emirates (UAE), Bahrain and Philippines advocate a booster dose with m-RNA vaccine as Sinopharm vaccine with a low protective efficacy against Delta was administered during the early phases of vaccination [6].

The flip-side: There is evidence regarding the waning of protective efficacy, but that does not necessarily mean increased predisposition to infection as cell mediated immune response and the memory B and T-cells have a critical role in developing a long-lasting immunity. Vaccines which were developed in the initial phases of the pandemic might not be equally efficacious against all the COVID-19 variants. This was reflected in data from the Unites States (US) as well as Israel wherein vaccines had a lower efficacy in preventing breakthrough or reinfections [4, 7]. Estimates from the CDC report that among 189 million people vaccinated against COVID-19, only 41,127 patients (0.02%) had breakthrough COVID-19 infection leading to hospitalization or deaths [5]. Additionally, during the recent surge of the Delta variant of COVID-19 in the US as compared to vaccinated individuals, unvaccinated ones had six times higher risk of infection and

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Table 1 - Recommendations for COVID-19 booster dose by various public health agencies

S. No.	Organization, Country	Recommendations for booster dose
1.	CDC, US	*Pfizer-BioNTech or Moderna (6 months after last dose):* - Age ≥65 years - Age ≥18 years living in long-term care settings - Age ≥18 years with underlying medical conditions* - Age ≥18 years and working/living in high-risk settings** *Johnson & Johnson's Janssen (2 months after last dose):* - Age ≥18 years
2.	NHS, UK	*Individuals most at risk of COVID-19 who received 2nd dose at least 6 months back and meeting the following criteria:* - Age > 50 years - Care home workers, frontline health and social care workers - Age ≥16 years with underlying medical conditions leading to high risk of serious COVID-19 infection - Age ≥16 years and immunocompromised or is the main carer/ co-habitant of an immunocompromised person at risk of COVID-19 - Pregnant and in one of the eligible groups
3.	ATAGI, Australia	*Pfizer mRNA vaccine recommended as single booster dose and is preferred to Vaxzevria (AstraZeneca) for booster dose in following cases:* - Individuals ≥50 years and at greater risk of severe COVID-19 infection - Individuals at an increased occupational risk of COVID-19 *Vaxzevria (AstraZeneca): booster dose in the following situations:* - Vaxzevria (AstraZeneca) used in first two doses and no contraindications or precautions for use - Significant adverse reaction following previous mRNA vaccine dose contraindicating further doses of mRNA vaccine
4.	Malaysian Health Ministry	- Conditional approval for the Pfizer-BioNTech mRNA vaccine as booster shot in adults aged ≥18 years and at least six months after receiving the second dose
5.	NACI, Canada	- Moderately to severely immunocompromised individuals*** in authorized age groups: primary series of three doses of an authorized mRNA vaccine - Booster (third) dose in moderately to severely immunocompromised individuals*** following 1- or 2- dose primary series - Booster dose at least 6 months after completing their primary series *should* be offered in: - Adults in long-term care or other congregate settings caring for seniors - Adults ≥80 years of age Booster dose at least 6 months after completing their primary series *may* be offered in: - Adults 70-79 years of age - Individuals post 2 dose of AstraZeneca vaccine or 1 dose of Janssen vaccine - Adults in or from First Nations, Inuit and Métis communities - Frontline healthcare workers with direct in-person contact with patients * Moderna Spikevax or Pfizer-BioNTech Comirnaty vaccines: booster dose
6.	EMA, Europe	- Booster dose of Comirnaty (BioNTech/Pfizer) and Spikevax (Moderna) vaccine may be given to immunocompromised people at least 28 days after 2nd dose
7.	Ministry of Health, Israel	- Booster dose in all individuals ≥12 years of age and previously vaccinated with two doses and at least five months elapsed following the second dose
8.	STIKO, Germany	*Booster vaccination with an mRNA vaccine in:* - People ≥70 years of age - Age <70 years and residents and cared for in facilities for care for the elderly - Nursing staff and other workers in direct contact with the caregivers - Personnel in medical facilities with direct patient contact

*Includes chronic kidney disease, chronic lung disease, chronic liver disease, Diabetes (type 1 or type 2), Dementia, stroke, immunocompromised including HIV infection, cardiac diseases (heart failure, coronary artery disease, cardiomyopathies, hypertension), Down's syndrome, obesity

**Includes first responders (healthcare workers, firefighters, police, congregate care staff), education staff (teachers, support staff, daycare workers), food and agriculture workers, manufacturing workers, corrections workers, U.S. Postal Service workers, public transit workers, grocery store workers

***Moderately to severely immunosuppressed includes: active treatment for solid tumor/hematologic malignancies, solid-organ transplant on immunosuppressants, chimeric antigen receptor (CAR)-T-cell therapy/hematopoietic stem cell transplant (within 2 years or on immunosuppressants), moderate to severe primary immunodeficiency, Stage 3 or advanced untreated HIV infection and AIDS, active treatment with anti-B cell therapies, high-dose systemic corticosteroids, alkylating agents, antimetabolites, or tumor-necrosis factor (TNF) inhibitors

Abbreviations: ATAGI: Australian Technical Advisory Group on Immunization; CDC: Centers for Disease Control and Prevention; EMA: European Medicines Agency; mRNA: messenger RNA; NACI: National Advisory Committee on Immunization; NHS: National Health Service; STIKO: Standing Committee on Vaccination; UK: United Kingdom; US: United States

eleven times greater risk of death [7]. Lastly, we cannot unsee the possibility of increased immunological adverse effects of COVID-19 vaccines such as myocarditis (mRNA-based vaccines) or Guillain-Barre syndrome (adenovirus-vectored vaccines) [8, 9].

The Evidence: Currently, there is limited data regarding the real-world effectiveness of administration of booster doses. Much of this is derived from a study from Israel where booster (third) doses of the BNT162b2 mRNA vaccine (Pfizer-BioNTech) have been approved for individuals ≥60 years of age in July 2021. This study evaluated 11,37,804 fully vaccinated individuals over a period of one month and reported lower rates of confirmed COVID-19 infection (reduced by a factor of 11.3 [95% CI: 10.4 to 12.3]) and severe illness (reduced by a factor of 19.5 [95% CI: 12.9 to 29.5]) in the booster group as compared to the non-booster group after at least 12 days of vaccination [10]. However, observation studies such as these might be limited by multiple biases such as those of confounding variables or due to behavioral changes adopted following booster vaccination. In addition, the follow-up was short and little is known about the duration of the protective response of the booster doses. Recently, Pfizer and BioNTech SE reported the results of the first phase 3 RCT evaluating efficacy and safety of booster dose of the Pfizer-BioNTech m-RNA based COVID-19 vaccine in over 10,000 individuals aged 16 years and above. In this trial, the relative vaccine efficacy among patients receiving the booster dose was 95.6% (95% CI: 89.3-98.6%) as compared to those receiving a placebo with similar adverse event profile as previous trials on the same vaccine [11].

Global perspective: On 30th July, 2021, Israel became the first country in the world to announce the administration of a third dose of the BNT162b2 vaccine to all individuals ≥60 years of age who have completed the primary vaccination series at least five months earlier with the aim to reduce the burden on the health care systems. Subsequent recommendations by the CDC, National Health Service (NHS) and Australian Technical Advisory Group on Immunization (ATAGI) allowed administration of the third (booster) dose (Table 1) [12-14].

Recommendations for a booster dose by developed countries can have a boomerang effect on other countries leading to a demand supply imbalance and further hampering the global vaccination rates. This situation becomes worse in Sub-Saharan countries with extremely poor rates of vaccination attributed to limited vaccine availability in these resource limited countries (Figure 1A and 1B). This is in stark contrast to the situation in developed countries such as the US and UK where 56.8% and 66.9% of the population is fully vaccinated respectively [15]. Advocation of booster doses in these developed countries would further hamper vaccination in resource poor countries (Figure 1C and 1D). There is a great disparity among the vaccine statistics in developed and developing nations. This calls for vaccine equity among WHO member states with a need to prioritize vaccinations among the marginalized sections of the society as unvaccinated individuals contribute to the further spread of infection and triggering emergence of newer variants. The recommendations of WHO in order to stop this ravaging pandemic is to vaccinate 40% of individuals in every country by the end of 2021 and to achieve a vaccination target of at least 70% by the first half of 2022 (Figure 1E) [16]. This would require around six billion doses just to vaccinate low-and-middle income countries, the same number of doses administered globally up till now. In order to ensure equitable access to the vaccines across the globe and to prevent vaccine hoarding, a joint endeavor between WHO, GAVI, the Vaccine Alliance, and the Coalition for Epidemic Preparedness Innovations termed COVAX was launched. However, this initiative has not yet helped in achieving its aim of vaccination of the people in poor countries which do not have resources for vaccine manufacture or its purchase from the global market (Figure 1F).

Conclusion: The current evidence and need for booster doses of COVID-19 is still unclear with the current vaccines offering considerable protection against severe disease, hospitalization and death even with newer variants such as the delta. It is reasonable and likely that booster doses of COVID-19 akin to that of influenza vaccines would be needed in future. However, the current focus should be on ramping up the global vaccine supply for greater coverage in the marginalized population groups who have yet not received the first dose of any vaccine.

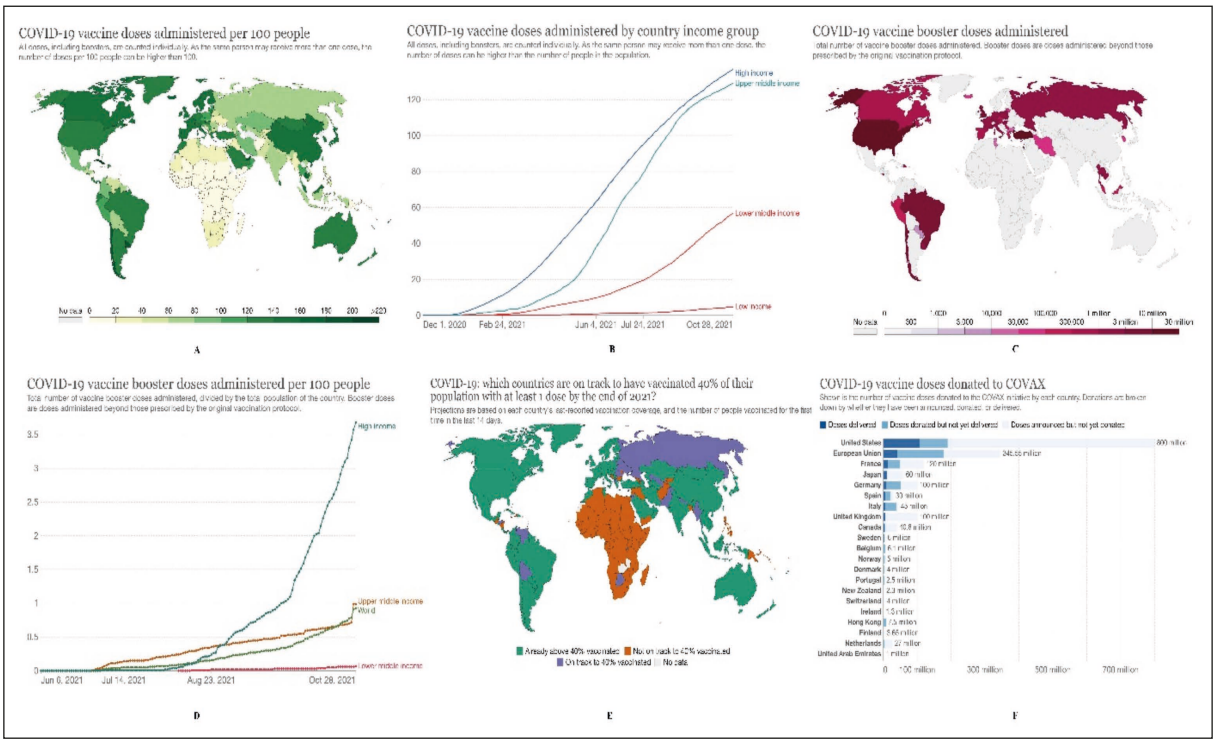

Figure 1A: Graphical representation showing the COVID-19 vaccine doses administered per 100 people worldwide. Countries marked in dark green with good vaccination coverage are predominantly developed ones such as UK, Canada, US while developing countries mostly in sub-Saharan region have poor vaccination rates as revealed by the pale-yellow color in the world map.

Figure 1B: Graphical representation showing the COVID-19 vaccine doses administered based on the country income group. High income countries occupy the highest position in the graph showing good vaccine coverage while low-income countries are in the bottom portion of the curve revealing a poor vaccine coverage.

Figure 1C: Graphical representation showing the COVID-19 vaccine booster doses administered worldwide. Most of the countries marked in the map are the developed nations where booster doses have begun to be administered.

Figure 1D: Graphical representation showing the COVID-19 vaccine doses administered per 100 people based on the country income group. High income countries occupy the highest position in the graph showing good booster coverage while lower middle-income countries are in the bottom portion of the curve revealing a poor booster coverage.

Figure 1E: Graphical representation showing the country wise projections in terms of achieving the WHO's target of vaccinating 40% of the population with at least 1 dose by the end of 2021.The map shows which countries have already surpassed this 40% target (green color), those that are on track to meet it by the end of 2021 based on recent vaccination rates (purple color) and those that are not on track (orange). Most of the developed countries have already surpassed the target while most of the developing nations in sub-Saharan Africa are not on track to achieve at least 40% vaccination rates.

Figure 1F: Bar diagram showing the COVID-19 vaccine doses donated to the COVAX initiative. The dark blue shade represents the doses delivered; the sky-blue shade represents the doses donated but not yet delivered while the light-blue shade represents the doses announced to be donated but yet not donated.

Source: Our World in Data. Available at: https://ourworldindata.org/ coronavirus19 (Accessed on 29th October, 2021).

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Conflict of interest

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Ethical approval
The submitted work does not contain human subjects research and is composed of review of the available literature and suggestions to improve clinical practice. The authors certify that there are no ethical conflicts that would preclude its publication.

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