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Booster Doses and Prioritizing Lives Saved

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Globally, more than 5 million people have died from Covid-19 since the start of the pandemic.¹ This is certainly a grim number, but we are starting to see the lifesaving effect of vaccines.² From the global public health perspective, the initial primary objective of Covid-19 vaccination is to decrease the severe consequences of Covid-19, allowing for the earliest possible stabilization of health care systems, communities, and economies. The vaccines studied to date are highly effective against severe disease and death.³ Although vaccine effectiveness against infection appears to decline with increasing time since vaccination, it is reassuring that vaccines continue to perform well against severe disease and death.⁴ However, continued follow-up is needed to determine whether the effectiveness against severe disease and death will decline substantially in the future.

On the basis of this decline in vaccine effectiveness against infection and the growing number of hospitalizations among vaccinated persons, Israel recommended booster doses of the BNT162b2 vaccine (Pfizer–BioNTech) in July 2021, starting with persons 60 years of age or older and then quickly expanding to all persons 12 years of age or older. At the time, no data regarding the effectiveness of booster doses had been published. However, studies by Arbel et al.⁵ and Bar-On et al.,⁶ now published in the *Journal*, provide much-needed evidence of the effectiveness of the booster dose.

Booster vaccine effectiveness can be calculated as 1 minus the adjusted rate or hazard ratio among persons who received a booster, as compared with persons who did not receive a booster or with unvaccinated persons. Whereas the absolute effectiveness can be calculated by comparing the risk among persons who received two vaccine doses plus a booster with the risk among unvaccinated persons, the investigators in these two studies evaluated the effect of the booster by comparing the risk among those who received two doses plus a booster with the risk among those who received two doses. Although neither study showed a formal calculation of booster vaccine effectiveness, data from both studies indicated relative effectiveness against severe disease or death of 90 to 95%. This means that if the absolute effectiveness of two vaccine doses is 90%, the absolute effectiveness of two doses plus a booster is 99 to 100%.

In a setting such as Israel, where vaccination coverage is high and vaccine supply is sufficient, the analytic approach taken in these studies is reasonable. The few

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remaining unvaccinated people are probably different from vaccinated people in terms of characteristics beyond vaccination status that affect the risk of infection — for example, they may have different behaviors — and such differences could lead to bias. In the analysis by Bar-On and colleagues, persons who received the booster were different from those who did not receive the booster in terms of age group, which affects the risk of infection. Their secondary analysis, which compared the rates among persons who had received the booster at least 12 days earlier with the rates among persons who had received the booster 3 to 7 days earlier, is useful in supporting their findings, because it decreases some of the bias that arises in comparing the rates with those among two-dose recipients. Data provided by these two studies, along with other data regarding booster effectiveness and safety that are being generated, will provide valuable guidance for decision making in other countries, as the risk–benefit balance of introducing a booster dose is assessed.

As of November 23, 2021, a total of 107 countries are providing additional or booster doses to at least some segment of the population (World Health Organization: personal communication). However, while some countries are offering booster doses, many countries are still struggling to vaccinate their population with the primary series. Population coverage with a full primary series is less than 10% in 45 countries and less than 40% in 105 countries.⁷ The low current vaccination rates are largely due to limited vaccine supply in low-income countries, which is forecasted to be resolved by early 2022, although challenges will remain in ensuring that everyone is vaccinated.⁸

Many factors must be considered in a decision to offer a booster. A country might choose to introduce a booster dose in certain segments of the population, depending on the epidemiologic situation, vaccination coverage, population immunity due to infection-induced immunity, and other factors, such as the need to maintain an essential workforce. However, many countries need to determine the best use of their limited vaccine supply in the near future. In most settings, more is still to be gained by focusing on vaccinating the unvaccinated. One U.S. analysis of direct benefits showed that, among those 65 years of age or older, 481 persons needed to be vaccinated with a booster dose to prevent one hospitalization, whereas 50 persons needed to be vaccinated with the primary series to prevent one hospitalization; among those 18 to 29 years of age, 8738 persons needed to be vaccinated with a booster dose to prevent one hospitalization, whereas 396 persons needed to be vaccinated with the primary series.⁹ Thus, it is important that vaccination with the primary series, especially in high-risk populations, remain a top priority everywhere, because this will ultimately lead to a greater reduction in severe disease and death.

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