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Covid-19 vaccines, immunity, and boosters

Many people still lack essential (and enduring) protection from primary vaccination

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Since our previous editorial in September 2021,[1] a growing body of evidence about covid-19 vaccine effectiveness, including that of third and booster doses, has been published, and several countries have authorized boosters for general adult populations.[2]

Well conducted real world studies of vaccine effectiveness are an important complement to randomized controlled trials. For example, two linked studies use test negative designs to analyze rich datasets from large health systems. Firstly, Israel and colleagues (doi:10.1136/bmj-2021-067873) estimated changes over time in the effectiveness of the Pfizer-BioNTech BNT162b2 vaccine against SARS-CoV-2 infection among members of a nationwide healthcare system in Israel during a period dominated by the delta variant.[3] They found an increased risk of infection associated with intervals longer than three months since full vaccination. Adjusted odds ratios were 2.37 at three to four months after vaccination but increased only slightly to 2.82 at six months or more.

The second study, by Bruxvoort and colleagues (doi:10.1136/bmj-2021-068848), evaluated the effectiveness of Moderna's mRNA-1273 vaccine against SARS-CoV-2 variants including delta, alpha, mu, and others among 8153 cases and matched controls in an integrated healthcare system in California.[4] Vaccine effectiveness against infection with the delta variant was 94.1% (95% confidence interval 90.5% to 96.3%) at two months or less after vaccination, declining to 80.0% (70.2% to 86.6%) at five to six months. For non-delta variants, vaccine effectiveness was higher and more stable over time, declining from 98.6% at two months or less to 88.7% at five to six months. Importantly, vaccine effectiveness against admission to hospital with the delta variant remained at 97.5% (92.7% to 99.2%).

Although these studies provide valuable insights, all observational studies are vulnerable to biases related to underlying differences between the studied populations, which can lead to differences between the estimated and true effectiveness. For context, consider the initial randomized trial evaluating the BNT162b2 vaccine, conducted before the emergence of the delta variant, which reported an estimated efficacy against symptomatic infection by pre-delta variants of 96.2% (93.3% to 98.1%) at two months or less, 90.1% (86.6% to 92.9%) at two to four months, and 83.7% (74.7% to 89.9%) at four to six months after vaccination.[5] These changes over time are consistent with Israel and colleagues' findings, indicating that residual bias in that study is likely small. We can have confidence in their observation that effectiveness remains relatively stable beyond six months, even in the context of delta. Supporting this, in a post hoc analysis during a period dominated by delta, differences in infection rates between participants originally randomized to the vaccine and those who received the vaccine after unblinding six months later suggest a minimal and more gradual decline in efficacy from 83.7% at four to six months to 78% at 10-12 months.[6] Together, the observational and randomized data to date suggest that after an initial decline, protection may become more stable, even in the context of delta.

We previously argued that studies showing modest waning of immunity do not support indiscriminate use of booster doses outside of older and medically vulnerable populations.[7] A randomized controlled trial (not yet peer reviewed) has since found that a third dose of BNT162b2, about 11 months after the primary course, gave 95.3% (88.5% to 97.9%) relative efficacy against symptomatic infection during 2.5 months of follow-up, compared with two doses alone.[8] This is consistent with observational data of booster effectiveness,[9-11] including a rigorously conducted matched cohort study showing that these benefits extend to severe outcomes, primarily among older people.[12] Booster doses may also have a role in helping to reduce transmission in well vaccinated populations during periods of substantial community transmission.[13]

Research still in preprint suggests that the new omicron variant is associated with reduced neutralizing antibody responses following two doses of vaccine, which is reversed by a booster dose or hybrid immunity from a combination of vaccination and infection.[14,15] A reduction in vaccine effectiveness and improved protection afforded by booster doses is also supported by preliminary clinical data from the UK.[16] That broader and increased antibody titers generated by a third or booster dose may be able to overcome the reduced neutralization associated with the omicron variant is therefore plausible. Further research evaluating the effectiveness of primary and additional vaccine doses against omicron is clearly a priority.

Although a third or booster dose clearly provides additional protection on top of simply reversing previous waning, the greatest protection from the worst clinical outcomes remains heavily concentrated in the first two doses.[17] The long term durability of protection against hospital admission afforded by two dose vaccine regimens is clear, particularly with an extended interval between the two doses (and even in the face of new variants).[18] Given the importance of reducing disease burden globally, vaccinations in low income settings, where the vast majority of people are yet to receive even a first dose,

should be prioritized over additional doses in high income settings. Policies that preferentially stockpile vaccine doses in high income settings remain indefensible. Although we do not know the precise circumstances that led to the emergence of omicron, that the extreme disparities in access to vaccines between high income and low income settings create the ideal conditions for the ongoing evolution of SARS-CoV-2 is clear.

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