Covid-19 vaccination: evidence of waning immunity is overstated

The case for universal boosters is weak, and the benefits are unclear

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The resurgence of covid-19 in high income countries with advanced vaccine programmes has raised concerns about the durability of vaccine effectiveness, especially against the more transmissible delta variant. This has led some to argue in favour of booster doses for the general population before clear evidence of benefit, which we believe is misguided.

Since the initial randomised trials showed high efficacy of vaccines against a primary endpoint of symptomatic covid-19,¹⁻⁴ observational studies continue to evaluate and report real world performance of vaccines in different contexts and over time.^{5,6} In addition to providing direct protection against covid-19 disease, available vaccines also substantially reduce transmission, partly by protecting against both symptomatic and asymptomatic infection.⁷ Despite concerns about the immune escape potential of the delta variant, studies consistently indicate that vaccines provide high levels of protection against symptomatic and severe disease as well as death caused by this variant.^{5,6}

With this context in mind, studies with systematic sampling do seem to suggest a modest waning in protection against infection over time.^{5,6} However, the primary objective of covid-19 vaccines is to protect against severe illness rather than infection, and multiple well designed studies have found sustained vaccine effectiveness against severe covid-19 for most adults. One large UK study, published as a preprint, using a case-control design based on PCR results showed that very high levels of protection against severe disease continued beyond five months after vaccination, especially among people who have no serious underlying conditions.⁸

On the other hand, estimated reductions in vaccine protection against infection vary widely and are more difficult to interpret. These dynamic estimates across studies and countries are heavily influenced by prevalence, behaviour, and circulating variants, and comparing them is not reliable for determining changes in immune protection over time. For instance, while one study from Israel found that the relative rate of infection increased over time after vaccination, several potential biases arise because the timing of vaccination was not random and factors such as risk of exposure to covid-19 and tendency to seek testing confound any association between time since vaccination and infection.⁹ Similarly, while infections among immunised healthcare workers in San Diego, California, increased from June to July, these changes could be explained by increased community prevalence rather than an abrupt waning of immunity.¹⁰ The effect of behaviour change on measured vaccine effectiveness is also suggested in

another US study that found a drop in effectiveness over time only among people under 65.¹¹ These examples show the fundamental challenges of assessing effectiveness against infection using routine surveillance data and highlight the need for systematic sampling, consideration of a comprehensive range of measured and unmeasured confounders, and careful interpretation.⁵

Long term immune response

From an immunological standpoint, plasma neutralising antibody titres are expected to decay eventually following vaccination, but robust and long lived plasmablast and germinal B cell responses have been shown after mRNA vaccination, and memory B cells have been shown to increase over at least six months, improve functionally, and provide cross-variant protection.^{12,13} Plasma neutralising antibody titres may predict some level of protection from symptomatic infection. However, understanding of the strength of this relation over longer periods remains limited.^{14,15} Given reported differences in sustained effectiveness against severe disease versus infection, neutralising antibodies are unlikely to be the only mechanism of protection; cellular immunity is more important in long term protection against severe disease.⁶

Most importantly, the long term effect of boosters on reducing infection, transmission, and hospital admissions remains unknown. Although boosters increase plasma antibody levels and may temporarily extend antibody mediated protection, they have not been shown to augment the memory B and T cell responses expected to provide long term protection against severe disease for most immunocompetent people.¹⁶ In an observational study from Israel reporting benefit associated with a third dose of the Pfizer-BioNTech vaccine (BNT162b2),¹⁷ the follow-up period in the boosted group was just seven person days for severe disease and 12 person days for infection—too short to assess long term effectiveness. The findings were also highly vulnerable to confounding.¹⁷ Any potential benefit of additional doses, particularly against symptomatic and severe disease, should be assessed on long term data, ideally from randomised control trials.¹⁸

Additional vaccine doses are reasonable for people who might not achieve an adequate response to the primary vaccination because of immunosuppression or advanced age,¹⁹ but overstating evidence of waning immunity for the general population has already had important ramifications, including affecting vaccine confidence. In addition, a focus on waning immunity in high income countries diverts attention and limited vaccine supplies away from the urgent need for primary vaccination of people with

no immunity, particularly in low and middle income countries. This will worsen unacceptable vaccine inequities, prolong the pandemic and its devastating public health and socioeconomic impacts, and increase the risk of new variants.²⁰

The large epidemic waves now occurring for the first time during the vaccine era show the ability of more transmissible variants to challenge covid-19 control even in countries with high coverage. This currently poses a greater threat than waning immunity. Demonstration that antibody levels can be boosted in the general population should not be considered evidence of long term effectiveness, and robust clinical data are required to assess the need for additional doses. The risks of remaining unvaccinated are clear and far outweigh the unknown benefits of re-vaccinating the general population. Rapid scale-up of vaccination coverage globally remains the most urgent public health priority.

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