Booster and third doses of Comirnaty mRNA vaccine – a brief literature review

Background

In many countries that have achieved high two-dose coverage, attention has turned to breakthrough infections in the vaccinated, and to the need for boosters. A number of countries have indicated their intention to implement a booster programme. (1) The largest number of booster doses have been administered in Israel (40% of population), Uruguay and Chile (more than 20%). (2) Israel has the most extensive eligibility, including anyone over the age of 12 years, while most countries have restricted boosters to older age groups. (1)

It is important to distinguish booster programmes, aimed at increasing immune responses which have waned since administering two vaccine doses, from the additional dose recommended for people with compromised immunity who are less likely to have had an adequate immune response from two doses.

A third (additional) dose was recently recommended for people with severe immunocompromise in New Zealand and has also been endorsed by the World Health Organization. (3) It is also important to be clear about the rationale for booster doses. Are they being given to boost protection against severe disease or aimed at reducing breakthrough infection and transmission?

What is the aim of booster doses and who would benefit?

Breakthrough infections in vaccinated people have been reported more commonly since the much more infectious delta variant became dominant, and with increasing time since vaccination in countries which commenced programmes from early in 2021. However, as those most at-risk of severe COVID-19 due to advanced age or multiple pre-existing conditions were typically vaccinated first, it has been difficult to tease out the relative contributions of delta dominance, time since vaccination and frailty to occurrence of breakthrough infections. Importantly, the great majority of breakthrough delta infections cause mild symptoms. (4)

Breakthrough infection causing severe disease

The largest study included almost 7 million adults in England more than 14 days post receipt of either BNT162b2 (Pfizer) or ChAdOx1 (Astra Zeneca) during a 6-month period to mid-June 2021. This study identified 2,031 deaths and 1,929 hospital admissions with confirmed COVID-19 infection within the previous 28 days. (5) More than 93% of deaths and 75% of admissions occurred in people more than 70 years of age, compared with 0.4% and 7% for people less than 50 years of age. Dose 2 recipients had an 83% lower chance of death (OR 0.17; 95% CI 0.13-0.22) and almost 80% of deaths occurred in the 5% of people at highest risk of severe COVID-19 pre-vaccination. The greatest increases in risk were seen in people with Down's syndrome, people with organ transplants, those receiving chemotherapy and in the elderly

living in residential care. (5) Similarly, in Scotland amongst delta infections in the fully vaccinated, people with 3 or more co-morbidities accounted for less than 5% of the total infections, yet had a 5-10 fold higher chance of death than those without co-morbidities. (6) No deaths were seen in those <40 years fully vaccinated with Pfizer.

What about declining antibodies – isn't that a problem for everyone?

There are two important issues to be aware of about antibody. First, immunity to SARS-CoV-2 infection is due to more than just antibody – immunity could be shown in less than 14 days after receiving vaccines in the early trials, when antibody was at a very low level. Second, protection persists against severe disease despite low antibody level. Cellular immunity – T cells and memory B cells – is also important.

A number of studies have examined cohorts of health care workers (HCWs). The SIREN cohort in the UK found that HCWs who had recovered from SARS-CoV-2 infection had around 85% protection against subsequent infection. (7) Cohorts based in Israel and the US and have looked at antibody levels and protection after vaccination. (8,9) The Israeli study, with 4,808 HCWs who had received 2 doses of Pfizer vaccine, showed that neutralising antibody levels decreased rapidly in the first 3 months then more slowly to 6 months, with more rapid declines in with increasing age (> 45 years vs <45 years and especially >65 years), in males than in females and in people with immune suppression. However, it did not provide data on COVID-19 infections. (8) The US study prospectively followed 227 HCWs who had two doses of Pfizer vaccine and compared them with 17 unvaccinated HCWs working in a large veteran's affairs hospital, showing similar antibody declines to the Israeli study. However, while 59/227 (26%) of vaccinated HCWs developed serological evidence of infection only 2 were symptomatic - unimmunised HCWs had similar rates of PCR-proven infection (4/17;24%) but all were symptomatic and one required ICU admission. (9)

Finally regarding measurable cellular immunity, broad T-cell responses against SARS-CoV-2 variants can be shown to be persisting to 8 months after COVID-19 vaccination.(10)

In summary, although there is convincing evidence of declining antibody over time post dose 2 of Pfizer vaccine, risk of severe COVID-19 seems to be largely limited to those with advanced age and/or multiple co-morbidities whereas severe COVID-19 can occur due to delta variant in much younger unimmunised people. Nevertheless, for workers in health or aged care, minimising even mild or asymptomatic infection is important to minimise transmission risk to vulnerable people in their care, although personal protective measures are also key.

Do booster doses work in boosting immunity and protection against COVID-19?

Two recent studies from Israel have demonstrated high short-term effectiveness of booster (third) doses of Pfizer vaccine. (9,11) The first focused on those more than 60 years of age who received their last dose more than 5 months previously, (9) while the second included persons from 16 years of age (11). Substantial reductions were shown in SARS-CoV-2

infections in people of all ages, but severe disease was rare under 40 years of age and significant reductions in death from COVID-19 were only seen in people over 60 years of age. (9,11). Antibody responses are robust following the third dose (12) and reactogenicity appears comparable to post the second dose, (13) but data are limited.

Key points:

- Additional (third) doses of COVID-19 vaccine are warranted as part of an *extended primary series* for people who may not have generated a response after two doses due to severe immunocompromise.
- At least a single booster dose – making COVID-19 vaccination a 3-dose series - is likely to be needed for adults older than 65 years who are currently included in annual influenza programmes. This is most urgent for those over 70 years, with significant co-morbidities or requiring residential care
- Booster doses merit consideration for people who have continued occupational exposure to SARS-CoV-2 and are caring for people with COVID-19 disease, such as workers in health and aged care. However, personal protective measures will remain key for the health workforce.

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