

## In brief

### COVID-19 vaccine booster shots

12 October 2021

#### Summary

- The effect of waning immunity is still emerging internationally. Some jurisdictions such as Israel, have seen high rates of hospitalisation concurrent with waning immunity, while others such as the United Kingdom (UK), have seen a decline in hospitalisations and deaths despite decreasing antibody levels.<sup>1,2</sup>
- This has raised questions about the need for booster doses of vaccine.
- The European Centre for Disease Prevention and Control suggests that vaccine effectiveness against severe disease should be chosen as the primary outcome of interest for assessing whether there is a clear need for a booster dose.<sup>3</sup>
- Most studies on boosters provide data on protection against the rate of infection. In these studies, booster shots were given five to six months following the initial vaccine schedule, with some up to nine months later.<sup>4-6</sup>
- While booster shots reduce the odds of testing positive for SARS-CoV-2 infection, promote neutralising antibody potency and increase antibody levels, their long-term effect on reducing infection, transmission and hospital admissions remains unknown.
- Evidence available for different population groups includes:
  - Support for third vaccine doses for people with weakened immune systems such as kidney transplant recipients and patients receiving maintenance haemodialysis or peritoneal dialysis who may not develop a fulsome response with two doses of the vaccine.<sup>7-10</sup>
  - Support for individuals who are at increased risk for COVID-19 exposure and transmission because of occupational or institutional setting receiving a booster shot, based on their individual benefits and risks.<sup>11</sup>
  - Limited and inconclusive data on any widespread need for booster doses in the general population, following a primary vaccination series.<sup>12</sup>
- Large-scale booster vaccination campaigns amplify the degree of inequality in vaccine access and the World Health Organization has called for a moratorium on COVID-19 boosters with the aim to ensure at least 10% of people in all countries are vaccinated before booster doses are given.<sup>13, 14</sup>
- The ECDC in Europe and ATAGI in Australia recommend maximising the first and second dose vaccine uptake across the community. ATAGI recommends a third dose of the COVID-19 vaccine as part of the primary course in individuals who are severely immunocompromised.<sup>3, 15, 16</sup>
- Booster doses are authorised in the United States (US), the UK, Israel, France, Germany and Singapore when certain criteria such as age and risk of severe disease are met. Canada has recommended a third dose for people who are moderately to severely immunocompromised.<sup>17-22</sup>

- In countries with much lower vaccination rates, there is an increased likelihood that new vaccine-resistant variants will emerge and subsequently spread in a new outbreak wave.<sup>23</sup>
- There are some suggestions that a third dose of vaccine may provide lifelong immunity, however this is yet to be demonstrated.<sup>24</sup>

### Background

- [Waning serum antibodies](#) against SARS-CoV-2, and increasing case numbers caused by the [highly contagious Delta variant](#), have initiated discussions about long-term immunity and the need for vaccine boosters.<sup>25, 26</sup>
- If boosters are used, there will be a need to [identify the specific circumstances](#) in which the benefits of doing so are clearly valuable.<sup>23</sup>
- [Additional doses](#) can be defined as:
  - third doses given as part of the primary course, to reach a comparable (optimal) level of protection
  - booster doses, which are additional COVID-19 doses required at a broader population level, to optimise protection due to waning of immunity over time.<sup>15</sup>

### Waning immunity

- Questions remain on the longevity of immune responses induced by mRNA vaccines, with emerging evidence of a [decline in humoral response](#) six months after receipt of the second dose of the Comirnaty vaccine. However, [protection against hospitalization](#) and death persisted at a [robust level for six months](#) after the second dose.<sup>27-29</sup>
- Virus [specific antibodies were maintained](#) at ≥16 weeks after receiving a single dose of Vaxzervia, however evidence suggests a waning of [spike protein \(S-antibody\) levels](#) in individuals over a 3 to 10 weeks period after a second dose of either Vaxzervia or Comirnaty.<sup>30, 31</sup>
- Antibodies elicited by Moderna have been shown to [persist 6 months](#) after the second dose.<sup>32</sup>
- Johnson & Johnson elicited durable [humoral and cellular immune responses](#) with minimal decreases for at least eight months after immunisation.<sup>33</sup>

### Evidence booster doses

- [Local and systemic reactions](#) reported following the third (booster) dose administration are similar to those reported following the second dose and considerably greater than those reported following the first dose.<sup>34</sup>
- Booster shots protect against both the rate of infection and the rate of severe illness. In most studies, booster shots were given five to six months following the initial vaccine schedule, with some up to nine months later.

Comirnaty (Pfizer)

- Multiple studies have shown that a booster shot reduces the odds of testing positive for SARS-CoV-2 infection. Individual studies show booster shots:
  - [lower the rate of infection](#) by a factor of 11.3 and lower the rate of severe illness by a factor of 19.5<sup>35</sup>
  - [reduce the odds of testing positive](#) for SARS-CoV-2 infection by 46-68%<sup>4</sup>
  - could [prolong protection and further increase the breadth of protection](#)<sup>5</sup>
  - is associated with an [increase of 2.2 in the Ct](#), corresponding to more than a 4-fold reduction in viral load.<sup>6</sup>

### Vaxzevria (AstraZeneca)

- A [third dose in the UK](#) induced antibodies to a level that correlates with high efficacy after second dose and boosts T-cell responses.<sup>36</sup>

### Coronavac

- A third booster dose of inactivated vaccine produces a [highly sifted humoral immune response](#) via a sustained evolution of antibodies, capable of effectively neutralizing SARS-CoV-2 variants of concern.<sup>37</sup>

### Heterologous dosing

- A third booster dose of Vaxzevria (after receiving an initial two doses of Comirnaty), promoted not just neutralizing antibody potency, but also [induced breadth against dominant SARS-CoV-2 variants](#).<sup>38</sup>
- A third CoronaVac or Comirnaty vaccine, following two-dose CoronaVac vaccine regimen, found that CoronaVac inoculations yield 1.7 and 1.8 times [increases in median values of IgG-S and IgG-N titers](#), respectively.<sup>39</sup>

### Modified vaccines

- A preprint preliminary analysis on [modified COVID-19 mRNA](#) vaccines as boosters found titers against the wild-type original strain of COVID-19, Beta and Gamma variants, increased to levels similar to or higher than peak titers, after the primary series vaccinations.<sup>40</sup>
- A single booster dose of mRNA-1273 or variant-modified mRNAs, including multivalent mRNA-1273.211, following Spikevax (Moderna) vaccine regimen. Interim analysis showed all boosters increased neutralisation titers against key variants of concern (VOC) and variants of interest (VOIs), including Beta, Gamma and Delta, that were statistically equivalent to peak titers measured after the primary vaccine series.<sup>41</sup>

## Patient groups

- There is evidence to support a third dose in patient groups including:
  - kidney transplant recipients, where a [third mRNA injection](#) improved the humoral response to vaccination<sup>7, 8</sup>
  - patients receiving maintenance hemodialysis or peritoneal dialysis, where a third dose of the BNT162b2 vaccine [substantially increased antibody levels](#)<sup>9</sup>
  - a case report of a patient with rheumatoid arthritis received four doses of Comirnaty which led to IgA and IgG seroconversion and [development of neutralising antibodies](#).<sup>10</sup>

## Ethics

- Large-scale booster vaccination campaigns [amplify the degree of inequality in vaccine access](#). There are many calls to focus attention on [prioritising first dose vaccinations](#) across the world [rather than planning third doses](#) for people in high-income settings.<sup>14, 42, 43</sup>
- The World Health Organization has called for a moratorium on COVID-19 boosters, with the [aim of ensuring that at least 10% of people in all countries are vaccinated](#) before extra doses are provided to some people.<sup>13</sup>
- The case for COVID-19 vaccine boosters at this point is weak. They might not be necessary for most people, and [could divert much-needed doses away from others](#).<sup>26</sup>
- Even if boosting were eventually shown to decrease the medium-term risk of serious disease, [current vaccine supplies could save more lives](#) if [used in previously unvaccinated populations](#) than if used as boosters in vaccinated populations.<sup>19, 23</sup>
- By constraining the scarce supply of vaccines that could be sent to countries with much [lower vaccination rates](#), these campaigns also [increase the likelihood that vaccine-resistant variants will develop](#).<sup>14, 23</sup>

### Grey literature and Jurisdictional policy

#### Australia

- In the Australian Technical Advisory Group on Immunisation (ATAGI) [statement about the need for additional doses of COVID-19 vaccines](#), the group strongly recommend maximising the first and second dose vaccine uptake across the community.<sup>15</sup>
- At this time, the Therapeutic Goods Administration has not yet received a registration application for the administration of additional doses of any COVID-19 vaccines.

#### United States

- [U.S. Food and Drug Administration \(FDA\)](#): On 22 September 2021, FDA authorised a single booster dose of Pfizer-BioNTech vaccine, to be administered at least six months after completion of the primary series, for certain populations, including:
  - individuals 65 years of age and older
  - individuals 18 through 64 years of age at high risk of severe COVID-19
  - individuals 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19, including severe COVID-19.<sup>17</sup>

#### United Kingdom

- [National Health Service \(NHS\)](#): Booster vaccine doses will be available for people most at risk from COVID-19 who have already had two doses of a vaccine. Boosters will be available at least 6 months after the second dose. Eligible groups include:
  - people aged 50 and over
  - people who live and work in care homes
  - frontline health and social care workers
  - people aged 16 and over with a health condition that puts them at high risk of getting seriously ill from COVID-19

- carers aged 16 and over
- people aged 16 and over who live with someone who is more likely to get infections (such as someone who has HIV, has had a transplant or is having certain treatments for cancer, lupus or rheumatoid arthritis)
- people who are pregnant and in one of the eligible groups can also get a booster dose.<sup>18</sup>
- [BMJ News](#): Booster vaccines are being rolled out in autumn as the UK secures 60 million more Pfizer doses.<sup>44</sup>
- [NHS News](#): The NHS is encouraging people to get a COVID booster jab, with bookings open from 21 September 2021. People will receive either one dose of Pfizer or half a dose of Moderna.<sup>45</sup>

### Israel

- [Nature news](#): Israel has started administering booster shots to people over the age of 60. The latest study involving 1.1 million people, found that booster shots reduces the risk of severe disease by almost 20-fold.<sup>19</sup>
- [Reuters News](#): In late August 2021, Israel began offering a COVID-19 booster to all vaccinated people for whom at least five months have passed since their second dose.<sup>46</sup>

### Canada

- [Government of Canada](#): The recommendations on the use of COVID-19 vaccines states that:
  - There is currently no evidence on the need for booster doses of COVID-19 vaccine after the vaccine series is complete.
  - Given the emergence of VOC against which vaccine effectiveness may be decreased, additional vaccine doses may be necessary.<sup>47</sup>
- [National Advisory Committee on Immunization \(NACI\) rapid response](#): The latest recommendations made on 10 September 2021 include the following:
  - For those who have not yet been immunised, NACI recommends that moderately to severely immunocompromised individuals in the authorised age groups should be immunised with a primary series of three doses of an authorised mRNA vaccine (strong NACI recommendation).
  - For moderately to severely immunocompromised individuals in the authorised age groups, who have previously received a one- or two-dose complete primary COVID-19 vaccine series (with a homologous or heterologous schedule using mRNA or viral vector vaccines), NACI recommends that an additional dose of an authorised mRNA COVID-19 vaccine should be offered (strong NACI recommendation).
  - An additional dose of a viral vector vaccine should only be considered when other authorised COVID-19 vaccines are contraindicated or inaccessible. Informed consent for an additional dose of viral vector vaccine should include discussion about the lack of evidence on the use of an additional dose of viral vector COVID-19 vaccine in this population (discretionary NACI recommendation).<sup>20</sup>

### European Union/European Economic Area (EU/EAA)

- [European Centre for Disease Prevention and Control \(ECDC\) and European Medicines Agency \(EMA\)](#): The latest press release states that there is no urgent need for the administration of booster doses of vaccines to fully vaccinated individuals in the general population. Additional doses should already be considered for people with severely weakened immune systems as part of their primary vaccination.<sup>48</sup>
- The ECDC [Interim public health considerations for the provision of additional COVID-19 vaccine doses](#) states:
  - Providing all eligible individuals with the recommended dose regimen should remain the current priority for COVID-19 vaccination programmes.
  - It is important to distinguish between 'booster' doses for people who responded adequately to primary vaccination and additional doses for those with weakened immune systems who did not.
  - Vaccine effectiveness against severe disease should be chosen as the primary outcome for assessing whether there is a clear need for a booster dose in specific groups.<sup>3</sup>
- [European Medicines Agency News](#): The EMA are evaluating data on booster doses of COVID-19 vaccine Comirnaty (Pfizer).<sup>49</sup>

### Germany

- [The Local News, Germany](#): Several states across Germany have now started issuing top-up vaccination doses to certain groups of the population.<sup>21</sup>

### France

- [euronews](#): France has started giving COVID booster vaccines to its elderly (over the age of 65) and people with underlying health conditions. To be eligible a minimum of six months must have passed since they got fully vaccinated with the Pfizer or Moderna vaccine.<sup>50</sup>

### Singapore

- [Ministry of Health](#): On 3 September 2021, the Ministry of Health announced that they were commencing a booster programme for two subgroups:
  - Persons who are moderately to severely immunocompromised. They will be encouraged to receive a booster dose two months after their second dose.
  - Persons aged 60 years and above, as well as residents of aged care facilities. From 14 September, they will be progressively invited to receive a booster dose at least six months after receiving two doses of vaccines.<sup>22</sup>

### Other countries

- [Reuters News](#): Reuters compiled a list of countries and regions that are considering booster vaccinations (updated on 14 September 2021).<sup>51</sup>

To inform this brief, PubMed and Google searches were conducted using terms COVID-19 vaccines AND (Boost\* OR third) AND (ethics OR equity) on 23 September 2021. The daily evidence digest was checked on the 12 October for any additional studies before publication. The Critical Intelligence Unit [living evidence table on COVID-19 vaccines](#) was also used to source information.

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