Memo

Decision to use the AstraZeneca COVID-19 vaccine: COVID-19 Vaccine Technical Advisory Group (CV TAG) recommendations

Date:	27th October 2021
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For your:	Information

Purpose of report

1. To summarise the COVID-19 Vaccine Technical Advisory Group's (CV TAG) recommendations on the decision to use the AstraZeneca COVID-19 vaccine ('the AstraZeneca vaccine').

Context

2. In February 2021, CV TAG advice was sought for use of the Pfizer COVID-19 vaccine for people who were 16 years and over, following Medsafe provisional approval. Cabinet agreed that the COVID-19 Vaccine Immunisation Programme proceed with the rollout of the Pfizer vaccine. It was noted that further advice would be provided to Cabinet on each vaccine candidate as they became available for use (following Medsafe approval), without knowing if a future vaccine was going to be more suitable or effective. In order to make decisions given the uncertainty, a Decision to Use framework was developed.
3. In July 2021, CV TAG advice was sought on the use of the Janssen COVID-19 vaccine for people aged 16 years and over, following Medsafe provisional approval. CV TAG advised that there was no current indication for wide use of the Janssen vaccine, however that it could be considered at an individual level where the Pfizer vaccine was not suitable e.g., anaphylaxis or other rare side effects following the first dose of the Pfizer vaccine. Cabinet considered the recommendations for the Decision to Use the Janssen vaccine and agreed to proceed with taking receipt of up to 500,000 doses in October 2021 for those individuals unable to receive the Pfizer vaccine (e.g., anaphylaxis), or for people who are hesitant to receive a messenger RNA (mRNA) vaccine.
4. At the time Cabinet made this decision, it was expected that Janssen's vaccine would be available in New Zealand in Q4 2021. However, as a result of subsequent regulatory issues relating to the manufacture of Janssen's vaccine, it is unlikely that Janssen will be able to provide supply any earlier than January 2022. Given the uncertainty around accessing

Janssen's vaccine in 2021, the Ministry's Policy team are looking to secure supply of the AstraZeneca vaccine in the coming weeks.

5. The Ministry's Policy team sought clinical and scientific advice from CV TAG on the use of the AstraZeneca vaccine in New Zealand.

6. The AstraZeneca vaccine was granted provisional approval by Medsafe for use in people aged 18 and over in New Zealand on 22 July 2021, under section 23 of the Medicines Act, with conditions.[1]

7. It is a two-dose non-replicating viral vector vaccine, and the second dose is administered between 4 and 12 weeks after the first dose. It can be stored at 2-8°C for up to 6 months. Multiple doses may be pre-drawn from one vial and used within one hour if stored at room temperature, or within six hours if stored at 2-8°C.[2]

8. The overall safety and efficacy of the AstraZeneca vaccine is based on analysis of pooled data from four phase III clinical trials (COV001, COV002, COV003, and COV005) conducted in the United Kingdom (UK), Brazil, and South Africa. At the time of analysis, 24,244 participants aged 18 and over had been randomised and received either the AstraZeneca vaccine or control. Additional safety of the AstraZeneca vaccine was established in a randomised phase III clinical trial conducted in the United States, Peru, and Chile.[3, 4]

9. The AstraZeneca vaccine provides efficacy against COVID-19 infection and severe disease. Vaccine efficacy against symptomatic, lab-confirmed, COVID-19 at least 14 days after two standard doses, with 4-to-12-week intervals, was 63.1% (95%CI: 51.8-71.1) in pooled data from the trials conducted in the UK, Brazil and South Africa.[3] In the US, Chile, and Peru trial, efficacy was 74% (95%CI: 65.3-80.5) from 15 days after the second dose when given four weeks apart.[4] Efficacy against severe disease or hospitalisation was found to be 100% (95% CI 72.2-100%) from >21 days after the second dose across clinical trials.[3, 4]

10. Intervals between doses varied in clinical trials, and post hoc analysis indicated that longer intervals were associated with a stronger immune response. When the dose interval was stratified in the initial phase III trial, an interval of <6 weeks was associated with 55.1% (95%CI 33.0-69·9%) efficacy, at 6-8 weeks it was 59·9% (95%CI 32.0–6.4%), at 8-11 weeks it was 63.7% (95%CI 28.0-81.7%) and ≥12 weeks it was 81.3% (95%CI 60.3 – 91.2%).[5]

11. Estimates for effectiveness against viral infection ranged from 73% to 94.9% pre-Delta,[6-9] and against severe disease were 72.8% (95%CI: 71.8-73.8).[10] Real world effectiveness has seen a modest decline, however it is unclear if this is due to Delta or waning efficacy of the vaccine. Results from a UK study demonstrated high vaccine effectiveness against hospitalisation, however it declined from 93.9% (95% CI: 91.3%-95.7%) at 1 week after the second dose to 77% (95% CI: 70.3%-82.3%) at 20+ weeks. Effectiveness against symptomatic COVID-19 also declined from 62.7% (95% CI: 61.7%-63.8%) at 1 week after the second dose to 47.3% (95% CI: 45%-49.6%) at 20+ weeks.[11] Effectiveness against death was 94.1% (95%CI: 91.8-95.8) at 2-9 weeks after the second dose and then fell to 78.7% (95%CI: 52.7-90.4) by 20+ weeks.[11]

12. Data about effects on transmission remain limited. Unvaccinated members of a household, in which the primary infection is someone vaccinated with one dose of AstraZeneca, were (for respectively AstraZeneca, and AstraZeneca and Pfizer together) around 40-50%,[12] and 30%,[13] less likely to become a secondary infection compared to those in unvaccinated healthcare worker households.

13. Continued safety monitoring is essential to understand the long-term safety profile of this platform.

    a. Severe occurrences of various systemic reactions after the first dose were reported in <10% 18-55 year olds in the phase I/II trial, which were reduced with the use of prophylactic paracetamol.[14] The most frequent solicited adverse events (reported in more than 1 in 10 people) were injection-site tenderness and pain, feeling feverish (pyrexia), chills, myalgia, headache, malaise, arthralgia, and nausea.[14, 15] Systemic adverse events of all severities were less common in those over 55 years compared to younger adults, and also less common after a second dose.[16] Overall, reactogenicity rates appear higher among ≤ 50 than > 50 year-olds, women and those with prior symptomatic/confirmed COVID-19.[17]

14. *Thrombosis with thrombocytopaenia syndrome (TTS):* A very rare and serious syndrome called thrombosis with thrombocytopaenia syndrome (TTS) has been observed following vaccination with the AstraZeneca vaccine during post-marketing use. This includes cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis (CVST), splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia.[18]

    a. The European Medicines Agency (EMA) concluded on 8 April 2021 that there was a strong relationship between TTS coagulation disorders and administration of the vaccine, such as disseminated intravascular coagulation, CVST, as well as arterial thromboembolic and haemorrhagic stroke. According to the EMA, a total of 1,503 cases had been reported worldwide as of 31 July 2021, while around 592 million doses of the AstraZeneca vaccine had been administered by 25 July 2021. The majority of the events occurred within the first 21 days following vaccination but have also been reported after this period.[19-21]
    b. Whilst specific risk factors for thromboembolism in combination with thrombocytopenia have not been identified, cases have occurred in patients with a previous history of thrombosis, as well as in patients with autoimmune disorders, including immune thrombocytopenia.[18]
    c. Up to 6 October 2021, there were 424 cases of TTS reported to the UK's MHRA following vaccination with AstraZeneca, of which 46 were following the second dose. Of the 424 reports, 213 occurred in women, and 207 occurred in men aged from 18 to 93 years. The overall case fatality rate was 17% with 72 deaths, six of which occurred after the second dose. This equates to 15.2 cases reported per million first doses.[22]
    d. In Australia, the risk of developing TTS after a first dose of AstraZeneca was estimated to be 20 in a million.[23] As of 17 October, there have been 156 cases of TTS assessed as related to the AstraZeneca vaccine in Australia from approximately 12.6 million vaccine doses. These cases most often occurred about 2-3 weeks after vaccination. The risk of TTS after a second dose appears to be much lower than after the first dose. The risk of dying from TTS after vaccination is reported to be approximately 1 in a million (for people receiving a first dose), and somewhat less than this when both doses are taken into consideration.[24]
    e. The incidence rate is higher in the younger adult age groups following the first dose compared to older age groups. According to data from the UK's MHRA, the incidence

rate is 20.9 per million doses in those aged 18-49 years, compared to 10.9 per million doses in those aged 50 years and over.[22] According to data from Australia's COVID-19 vaccine weekly safety report up to 21 October 2021, the reporting rate of TTS remains higher in people aged under 60 years (2.5 per 100,000 doses) compared to those aged 60 and over (1.8 per 100,000 doses). Women in younger age groups seem to be slightly more likely to develop clots in unusual locations, such as the brain or abdomen, which have more serious outcomes. Eight people have died as a result of TTS, and of those six were women.[24]

15. *Guillian-Barré syndrome (GBS).* GBS has been reported very rarely following vaccination with the AstraZeneca vaccine.[18] At the EMA Pharmacovigilance Risk Assessment Committee (PRAC) meeting from 05-08 July 2021, it was recommended that a warning for GBS following vaccination be added to the data sheet. They did not ascribe causality but concluded that it is possible that GBS is a side effect of the vaccine.[25] On 08 September, the EMA added GBS following vaccination as a very rare side effect to the AstraZeneca product information sheet.[26]
16. *Capillary leak syndrome (CLS).* Very rare cases of CLS have been reported in the first days after vaccination with the AstraZeneca vaccine. A history of CLS was apparent in some of these cases. Fatal outcome has been reported.[18] Both the UK's MHRA and the EMA's PRAC recommend that people with a history of CLS should not receive the vaccine.[27, 28] On 10 June 2021, PRAC recommended that CLS be added as an adverse reaction for the AstraZeneca vaccine.
17. Several countries have restricted the use of the AstraZeneca vaccine in different age groups, including Australia, Canada, Germany and the UK.[29-32]
    a. In Australia, the Australian Technical Advisory Group on Immunisation (ATAGI) has provided guidance about the risk-benefit for the AstraZeneca vaccine by age group. In a large outbreak, ATAGI advises that the benefits of the AstraZeneca vaccine are greater than the risk of rare side effects for all age groups. Where background risk of COVID-19 exposure and disease is low, AstraZeneca vaccine is recommended only for people aged 60 and over. However, anyone aged 18 to 59 years can choose to receive the AstraZeneca vaccine either following discussion with a qualified health professional, or if they provide verbal or written consent. Most people have their second dose 12 weeks after their first, but ATAGI recommends 4 to 8 weeks between the first and second doses in an outbreak so maximal protection against COVID-19 can be achieved earlier.[23]
    b. In Canada, the National Advisory Committee on Immunisation recommends the AstraZeneca vaccine for individuals 30 years of age and older who do not wish to wait for an mRNA vaccine, expanded from its previous guidance of a higher age limit of 55 years because of concerns over TTS.[31]
    c. In the UK, MHRA recommend adults aged 18-39 years with no underlying health conditions are offered an alternative to the Oxford-AstraZeneca vaccine, if this does not cause delays in having the vaccine.
18. This advice should be considered as part of the Decision to Use Framework and alongside policy considerations on the sequencing of the COVID-19 Vaccine and Immunisation Programme.

Recommendations

19. CV TAG met on 19 October to discuss use of the AstraZeneca COVID-19 vaccine, noting the information provided in the Pfizer vaccine Data Sheet.

20. **CV TAG noted that**:

    a. The contraindications for the AstraZeneca vaccine are:[18]

        i. Hypersensitivity to the active substance or to any of the excipients.
        ii. Patients who have experienced major venous and/or arterial thrombosis with thrombocytopenia following vaccination with any COVID-19 vaccine.
        iii. Individuals who have previously experienced episodes of capillary leak syndrome.

    b. COVID-19 disease is associated with many complications including the development of blood clots. Administration of the AstraZeneca vaccine is rarely associated with thrombosis and thrombosis with thrombocytopaenia syndrome (TTS). TTS has a higher incidence among younger populations which is important to be aware of, however the risk is much less common than thrombotic complications from the COVID-19 disease itself.
    c. In general, the Pfizer vaccine offers a higher level of protection than the AstraZeneca vaccine. The efficacy of the AstraZeneca vaccine against symptomatic, laboratory confirmed COVID-19 at least 14 days after two standard doses, with 4-to-12-week intervals, was 63.1% (95%CI: 51.8-71.1)[3], compared to 95% (95%CI: 90.3-97.6) for the Pfizer vaccine.[33] However the AstraZeneca vaccine still provides high protection and efficacy against infection, disease, and death.
    d. Data are still emerging on the safety and efficacy of heterologous ("mixed dose") vaccine schedules from approved vaccines in New Zealand. Initial results show that mixed schedules of the Pfizer vaccine with the AstraZeneca vaccine (for example, one dose of AstraZeneca followed some weeks later by one dose of Pfizer) is associated with an acceptable reactogenicity profile and generates levels of anti-spike neutralising antibody equivalent or greater than those associated with high levels of protection in primary efficacy trials.[34-36] In the UK COM-COV study, participants were randomised to a first dose of Pfizer with a second dose of AstraZeneca 4-weeks later. Antibody responses were inferior to two doses of Pfizer/BioNTech (homologous).[36] The relevance of this to clinical effectiveness is unknown, though the vaccine schedule was still considered to provide protection.
    e. Data on safety and efficacy of the AstraZeneca vaccine in people aged less than 18 years and old and in pregnant women, or women who became pregnant after receiving the vaccine, are limited. Medsafe consider available data insufficient to assess risk-benefit in people aged less than 18 years old or pregnant women.[18]
    f. The AstraZeneca vaccine is included as part of the ComFluCOV study looking at the safety and immunogenicity of concomitant administration of AstraZeneca or Pfizer COVID-19 vaccines with three different seasonal influenza vaccines in adults. Most reactions were mild to moderate, with local and unsolicited systemic reactions similar between randomised groups. No significant difference was observed regardless of whether the shots were given on the same day or 3-4 weeks apart.[37]

21. **CV TAG recommends that:**

a. The COVID-19 Vaccine Immunisation Programme use the AstraZeneca vaccine as a second-line vaccine, with Pfizer remaining the first-line and preferred vaccine.

b. Use of the AstraZeneca vaccine be restricted to people who have a contraindication to the Pfizer vaccine, or people who would prefer to get the AstraZeneca vaccine and are currently under a Vaccination Order, or who are unvaccinated or incompletely vaccinated and hesitant about getting the Pfizer vaccine.

c. Within the groups outlined in 21)b, the AstraZeneca vaccine be made available to the following eligible groups:

   i. People aged 60 years and over without contraindications.

   ii. People aged 18 to 59 without contraindications and who prefer to receive the AstraZeneca vaccine after discussion with a qualified health professional.

d. There is currently insufficient data on the AstraZeneca COVID-19 vaccine to recommended it during pregnancy. Use in pregnancy should be based on an assessment of benefits and risks by the consumer and their healthcare professional.

e. With regard to timing:

   i. two doses of the AstraZeneca vaccine, given 4 to 12 weeks apart, are necessary to be considered fully vaccinated.

   ii. a shorter interval of more than 4 to less than 8 weeks between the first and second doses is recommended in an outbreak to provide earlier protection.

   iii. administration of the AstraZeneca vaccine as a second dose should occur at least 28 days after the most recent dose of another COVID-19 vaccine.

   iv. there be no upper limit on time since the last dose.

   v. the AstraZeneca vaccine may be administered before, after, or at the same time as the influenza, MMR, HPV, diphtheria/tetanus/pertussis combination vaccine (Boostrix), and other vaccines. The only exception to this advice is for the live-attenuated shingles vaccine (Zostavax) where a 7-day interval, before or after administering the AstraZeneca vaccine is advised.

22. CV TAG will continue to monitor the evidence and will update their recommendations as data become available.

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