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Short communication

# Thrombosis with Thrombocytopenia Syndrome (TTS) following AstraZeneca ChAdOx1 nCoV-19 (AZD1222) COVID-19 vaccination – A risk–benefit analysis for people < 60 years in Australia

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ABSTRACT

The AstraZeneca ChAdOx1 nCoV-19 (AZD1222) vaccine is associated with Thrombosis with Thrombocytopenia Syndrome (TTS) in 3/100,000 vaccinations with high fatality rates reported in many countries. We conducted a risk–benefit analysis for Australians aged 18–59 years, comparing the risk of vaccination versus infection, and rate of TTS to other vaccines which prompted policy change following rare adverse events – rotavirus, smallpox and oral polio vaccines. COVID-19 deaths over 12 months range from 0 to 417 in current and future worst case scenarios. In the past 15 months 20 COVID-19 deaths occurred in people < 60 years compared to 890 deaths over 60 years. The estimated possible number of TTS cases is 347, with vaccine-related deaths ranging from 17 to 153 if 80% of adults 18–59 years are vaccinated. The reported rate of TTS is in the same range as rare but serious adverse events associated with other vaccines that have been subject to policy change. In Australia, the potential risks of the AZD1222 vaccine in younger adults, who are at low risk of dying from COVID-19, may outweigh the benefits.



## 1. Introduction

Thrombosis with Thrombocytopenia Syndrome (TTS) is a complication of adenovirus vectored vaccines including the AstraZeneca ChAdOx1 nCoV-19 (AZD1222) COVID-19 vaccine with onset 4–42 days after vaccination [1]. The syndrome is similar to that induced by heparin and appears to be caused by the vaccine. It is associated with thrombosis in unusual sites such as cerebral venous sinus thrombosis (CVST) and splanchnic veins as well as arterial bed thrombosis. It appears to disproportionately severely affect younger adults although the data are evolving. Many patients have platelet factor 4 antibodies, suggesting the mechanism is similar to heparin-induced thrombocytopaenia [2]. Adenovirus vectors can bind to platelets, have been associated with thrombocytopaenia, and can trigger disseminated intravascular coagulation, so a plausible mechanism exists for causation [3]. The exact mechanism is unclear but several hypotheses have been proposed relating to the delivery of the DNA in the vaccine [4,5].

The benefits of the AZD1222 vaccine in preventing COVID-19 hospitalization and death, may outweigh the risks of rare side effects in countries experiencing high incidence of COVID-19. Australia, however, has had little community transmission of SARS-CoV-2, with 30,499 cases of COVID-19 and 910 deaths in total by June 27, 2021 [6]. Furthermore, the risk of death from COVID-19 is much lower for adults in the age group most at risk of TTS – those under 60 years – so the argument about vaccination preventing deaths in younger people needs to be tested against the risk of a rare but severe, potentially fatal side effect in the same age group [7].

Rare but significant adverse events may not be detected during clinical trials if those trials are not adequately powered for very rare events. A good example is the first rotavirus vaccine, Rotashield™, which caused an excess burden of intussusception requiring hospitalisation in one in 66,000–302,000 infants [8]. The safety signal and withdrawal of the vaccine occurred after almost 30% of eligible infants in the United States had been vaccinated [9].

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As such, we conducted a risk analysis to compare the potential risks of mass vaccination in adults aged 18–59 years in Australia with the AZD1222 vaccine versus the risk of morbidity and mortality from COVID-19 in the same age group in Australia under current and future plausible COVID-19 incidence scenarios.

The number of Australians aged 18–59 years is approximately 14,406,509 [10]. The community incidence of COVID-19 over a 12-month period was tested as a range, from 0 to 4% of the population from a range of population sero-surveys conducted in different countries in 2020, with zero (minimal transmission) being the predominant situation in Australia [11] during the pandemic, and 4% being a rate from areas that experienced severe first waves in parts of the United States [12]. We then assumed 60% of infections would be symptomatic and diagnosed [13]. The case fatality rate (CFR) by age was calculated from Australian government data on cases and deaths to June 27, 2021 [6] as shown in Table 1. CFRs for 20–29 years were applied to people aged 18 and 19 years for simplicity. Because data was provided in 10-year age bands, cases in persons aged 18–19 years were estimated at 20% of the cases in persons 20–29 years. The CFR was applied to symptomatic cases.

We assumed 100% efficacy of the AZD1222 vaccine against death as a best-case scenario, [14] and that 80% of people in this age group will eventually be vaccinated (11,525,207/14,406,509 people), as it was being offered to all adults in Australia until April 2021, [15] with enough vaccine doses planned for the whole population. We assume that a small proportion of people, up to 20% will either receive a different vaccine or remain unvaccinated.

The incidence of possible TTS in vaccinated people was estimated to be 3.1/100,000 for people < 50 years and 2.7/100,000 for 50–59 years based on Australian data [16]. The case fatality rate of TTS was estimated to be 44% in Germany, [17] but 18% in the UK [18]. In Australia, a much lower case fatality rate which fluctuated between 3 and 5%, based on two deaths which have been attributed to the vaccine (of over 300 reported deaths following vaccination) [16]. We therefore tested a range of case fatality rates from 5 to 44%.

We also compared the rate of reported TTS with the rate of adverse events caused by other vaccines which have prompted policy changes because of the risk of rare, serious adverse events. These have a range of incidence estimates. For comparison with other vaccines with rare adverse effects, we also used a range of high and low estimates for TTS. We used 1/100,000 as a low estimate and 11/100,000 as a high estimate based on a study from Denmark and Norway [19]. High and low estimates of the incidence of adverse events were obtained from published literature for the rotavirus vaccine Rotashield™ [8] and variola (smallpox) vaccine (used to vaccinate United States armed forces after 9/11, but later restricted to selected groups because of myopericarditis.) [20,21]. We also reviewed rates of vaccine-associated paralytic poliomyelitis (VAPP) following oral, live viral polio vaccine (OPV), [22] which prompted most high-income countries (who have achieved elimination of polio) to switch to the more expensive inactivated polio vaccine (IPV). In Australia, IPV was adopted in 2006, despite its much higher price, because VAPP was considered an unacceptable risk given polio had been eliminated [23].

**Table 1**
Case fatality rate (CFR) observed in Australia to June 27, 2021.

| Age group | Cases | Deaths | CFR |
|---|---|---|---|
| 18–29 | 8020 | 1 | 0.000125 |
| 30–39 | 5477 | 2 | 0.000365 |
| 40–49 | 3909 | 2 | 0.000512 |
| 50–59 | 3536 | 15 | 0.004242 |
| >=60 | 6232 | 890 | 0.142811 |

Table 2 shows the comparisons of deaths due to COVID-19 and possible TTS over 12 months for people 18–59 years by varying hypothetical incidences of infection, including the current scenario of 0 cases and a worst-case scenario of 4% infection rate. Table 2 also shows the actual reported deaths from COVID-19 in 2020 in Australia.

For comparison, the reported deaths in people 60 years and over from COVID-19 in 2020–21 in Australia was 890 (compare to 20 in people < 60 years).

The worst case estimates above reflect hypothetical, severe scenarios with infection rates orders of magnitude higher than experienced in Australia to date (0.15% for this demographic based on diagnosed cases). The estimated 1–4% rate of COVID-19 is unlikely to eventuate given the measures used in Australia to contain COVID-19, including border closure, hotel quarantine, extensive testing and contact tracing and isolation. Further, we overestimated the benefit of the AZD1222 vaccine, given it has very low efficacy against the Beta variant, which has already been detected in hotel quarantine in Australia [24].

Fig. 1 shows that the rate of reported TTS following the AZD1222 vaccine is in the range of that for three other vaccines which have previously been withdrawn or subject to a change in policy due to adverse events: smallpox, rotavirus and OPV [20–22].

A caveat to this study is that we afforded the most favourable possible benefit of the AstraZeneca vaccine, attributing 100% efficacy against death. However, the trials were not powered for this outcome and the estimate is based on a single death in the control group. The emergence of variants of concern with substantial vaccine escape could change the balance for the vaccine to be less favourable. The limitations of this risk analysis include the use of TTS rate estimates based on incidence following the first dose only, uncertainty over the rate of TTS, for which data are still emerging, and which may underestimate the risk in younger adults, especially when older adults are vaccinated first. Case ascertainment may differ in different countries. Further, our worst-case estimates of COVID-19 incidence rates are unlikely to occur in Australia based on incidence in the past year. Should a severe COVID-19 epidemic occur in Australia in the future, and if no other vaccines were available, the benefits of using the AZD1222 vaccine would outweigh the risks. However, even in countries experiencing high rates of COVID-19 such as Canada and The Netherlands, the AZD1222 vaccine has been restricted to older adults over 55 or 60 years [25]. Finally, the case fatality rates reported from Australia are much lower than rates reported elsewhere, possibly reflecting differences in ascertainment compared to other countries. The postulated reason is better case management, but there is no supporting evidence for Australia having vastly different diagnostic or treatment approaches to any other country.

For the current situation of low incidence of COVID-19, the risk of fatality from possible TTS or serious morbidity such as stroke in healthy younger adults, is unacceptable in Australia, when there is a choice of other vaccines. Given the majority of deaths have been in people over 60 years, risk–benefit calculation will be much more favourable for the vaccine in this older age group. This analysis was done after the death of a 48-year-old woman, and shared with senior health officials in Australia on April 8, 2021. Later on the same date, an age cut-off of 50 years was announced along with a separate risk-analysis. This age restriction was revised on June 17, 2021 to 60 years following the death of a 52-year-old woman [16]. The rate of TTS estimated by the Australian government for the age group < 50 years and 50–59 years was similar (3.1 vs 2.7 per 100,000), with rates dropping to 1.4–1.9 per 100,000 at 60 years [16] and over, so 60 years may have been a more appropriate age cut-off initially. In scenarios where there is low community transmission, the number of deaths from COVID-19 in older people 60 years and over would likely be higher than deaths from the vac-

**Table 2**
Risk analysis of vaccination with ChAdOx1-S (AZD1222) versus COVID-19 in Australians aged 18–59 years by varying 12 month incidences of COVID-19 and observed deaths in 2020–21.*

| SARS-CoV-2 infection rate over 12 months | Fatalities from COVID-19 over 12 months in 18–59 years (persons) | Fatalities prevented by AZD1222 vaccine (80% vaccinated) | Possible TTS incidence | Possible fatalities from TTS |
|---|---|---|---|---|
| Current COVID-19 scenario | | | | |
| Negligible | 0 | 0 | 347 | 17–153 |
| Observed rate of diagnosed COVID-19 January 2020 to June 27, 2021, Australians aged 18–59 years and possible TTS | | | | |
| 0.15% | 20 | N/A | 347 | 17–153 |
| Worst case hypothetical COVID-19 incidence scenarios | | | | |
| 1% | 102 | 81 | 347 | 17–153 |
| 4% | 406 | 325 | 347 | 17–153 |

* Calculation for TTS was done on 11,525,207 vaccinated, being 80% of the total age group (14,406,509). TTS incidence 3.1 per 100,000 doses of vaccine. (16) Fatality of TTS ranging from 5 to 44%.

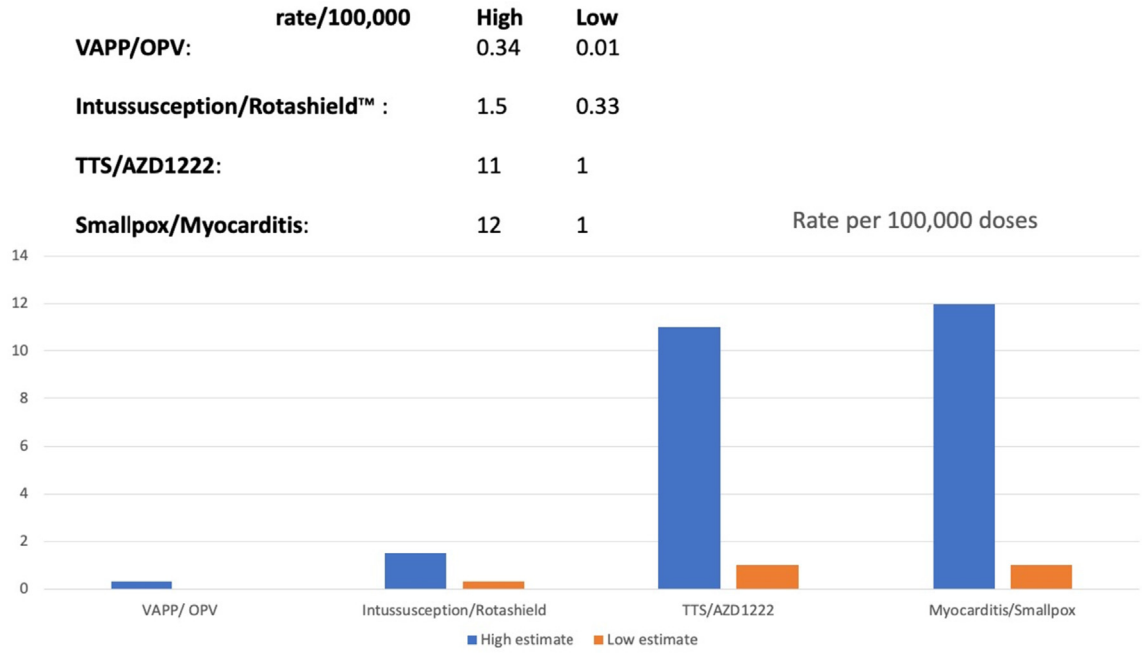


**Fig. 1.** Comparative rate of rare adverse events of the AZD1222 ChAdOx1 nCoV-19 (AZD1222) COVID-19 vaccine compared to other vaccines subject to policy change*. *Oral Polio Vaccine (OPV) remains in use in low-income countries, but has been replaced by Inactivated Polio Vaccine (IPV) in high-income countries such as Australia, which have achieved elimination of poliomyelitis. Smallpox vaccine remains in use for selected laboratory and military personnel. Rotashield™ was ceased in 1999.

cine over a period of a year or more (based on 890 deaths from COVID-19 in people 60 years and over in Australia), but a risk-analysis of age subgroups over 60 years would also be useful. Other vaccines may still be preferable in all age groups if available, especially if they have other advantages such as higher efficacy, shorter dosing interval, better coverage of variants of concern and fewer side-effects. The additional consideration of vector-induced immunity for adenovirus vector vaccines if annual or repeated boosters are needed, further shifts the balance toward other alternatives in the longer term. The latest policy decision to avoid use of this vaccine in adults < 60 years in Australia is entirely consistent with past vaccine risk–benefit policy decisions when rare but serious adverse events were identified. In addition to risk analysis, an ethical framework can helpfully inform population level risk benefit determinations [26].

Whilst many have argued that pausing or ceasing vaccine programs to investigate safety signals will damage vaccine confidence, the damage to vaccine confidence may be greater if avoidable severe morbidity and mortality occurs in healthy young people as a result of vaccination. Faltering vaccine confidence has been seen in Australia, a country with historically high vaccination rates and low conscientious objection, following the change in age restriction for the AstraZeneca vaccine and highly publicised deaths. There has been reported hesitancy in people aged 50–59 years who received a first dose but are reluctant to get the second. The impact on vaccine confidence, including for people 60 years and over is yet to be fully understood. However, achieving high vaccination rates is the only proposition for societal and economic recovery [27,28].

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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