PREPRINT

Continuing COVID-19 Vaccination of Front-Line Workers in BC with the AstraZeneca Vaccine: Benefits in the Face of Increased Risk for Prothrombotic Thrombocytopenia

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ABSTRACT

Background: Recently, Canada's National Advisory Committee on Immunization (NACI) recommended against using the AstraZeneca COVID-19 vaccine in younger adults pending further review of the risk for Vaccine-Induced Prothrombotic Immune Thrombocytopenia (VIPIT). As a result, the province of British Columbia halted its front-line workers vaccination program which used the AstraZeneca vaccine. The province is expected to receive an additional 246,700 doses of AstraZeneca vaccine through US and COVAX until April 11th, enough to provide the first dose of vaccine to all unvaccinated front-line workers. It is unclear whether mRNA vaccines can be immediately made available to front-line workers. We evaluated the harms and benefits of delaying vaccination of front-line workers in BC.

Methods: We reviewed the latest available evidence and used compartmental modelling to *a)* compare the expected number of mortality due to COVID-19 and VIPIT under the scenarios of immediately continuing vaccination of front-line workers with the AstraZeneca vaccine or delaying it in favour of mRNA vaccines, and *b)* compare the mortality risk of immediately receiving the AstraZeneca vaccine and delaying vaccination at a personal level for different age groups.

Results: We estimate that if British Columbia immediately continues the front-line worker vaccination program with the AstraZeneca vaccine, we expect to see no VIPIT-related deaths, about 40,000 fewer cases of COVID-19, 750 fewer hospitalizations, 180 fewer COVID-related deaths, and 2,150 fewer cases of Long COVID.

Conclusions: The benefits of immediately continuing immunization of front-line workers with AstraZeneca far outweigh the risk both at a societal level and at a personal level for recipients over 30 years old.

KEYWORDS
COVID19; vaccination; front-line workers; blood clots; vaccine-induced prothrombotic immune thrombocytopenia; harm-benefit; BC

1. Background

Recently, NACI recommended against using AstraZeneca (AZ) COVID-19 Vaccine for Canadians under the age of 55, due to concerns about the incidence of Vaccine-

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Induced Prothrombotic Immune Thrombocytopenia (VIPIT) based on European reports (NACI 2021). On Match 18, 2021, the European Medicines Agency estimated the incidence of VIPIT at approximately 1 per 1,000,000 people vaccinated with the AZ vaccine (EMA 2021). A higher estimated rate of 1 per 100,000 by the Paul-Ehrlich Institut in Germany was published on March 19th (PEI 2021). It was this higher rate reported by the Paul-Ehrlich Institut that led NACI to recommend against using this vaccine in adults under 55 years old (NACI 2021).

On April 1st, the UK Medicines & Healthcare Products Regulatory Agency (MHRA) updated its own previously reported data to report a total of 22 cerebral venous sinus thrombosis (CVST) and 8 other clot-related events from 18.1 million doses of the AZ vaccine (total incidence rate 1 in 600,000) (MHRA 2021a). On April 7th, MHRA concluded a possible link between the AZ vaccine and extremely rare clotting events and updated its data to report 79 UK cases of VIPIT (51 in women and 28 in men between 18 to 79 years old), including 44 cases of CVST and 35 cases of thrombosis in other major veins (incidence rate 1 in 250,000)(MHRA 2021b).

On the same day, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) concluded that VIPIT should be listed as a very rate side effect of the AZ vaccine. PRAC noted that as of 22 March, a total of 86 cases of VIPIT (62 cases of CVST and 24 cases of splanchnic vein thrombosis) and 18 fatalities out of about 25 million vaccine doses were reported in EudraVigilance, the EU drug safety database (EMA 2021). As of April 4th, 2021, 222 cases of VIPIT (169 cases of CVST and 53 cases of splanchnic vein thrombosis) had been reported to EudraVigilance out of around 34 million people who had received the AZ vaccine (EMA 2021).

BC had initially slated the AZ vaccine for outbreak control and front-line workers vaccination program. on March 29th and following NACI's recommendation, BC paused using the AZ vaccine for those under 60 and put the front-line workers vaccination program on hold.

Canadian provinces are expected to receive 1.5 million doses of the AZ vaccine from the US and another 316,800 doses from the COVAX program between now and April 11th (Government of Canada 2021). British Columbia expects to receive 246,700 doses from these two AZ deliveries, enough to finish providing the first dose to all remaining front-line workers.

The 300,690 doses of Pfizer-BioNTech and 105,900 doses of Moderna vaccines expected within the same time frame are currently allocated for the priority groups, indigenous population, and age-based vaccination campaign currently vaccinating those in their 70s. The AZ vaccine was initially slated for front-line workers due to its easier handling and storage requirements. If it is not logistically possible to switch the vaccine allocation for above 55 years old age groups to the AZ vaccine and use either Pfizer-BioNTech or Moderna vaccines for younger front-line workers without delay, one might ask whether the benefits of immediately deploying the AZ vaccine for front-line workers outweigh the rare but serious risk for VIPIT.

Here, we provide a preliminary harm-benefit analysis of immediate vaccination of all front-line workers with the AZ COVID-19 vaccine. We based our analysis on mortality alone, and explore the risk both from a societal and personal perspective.

Table 1. Harm-benefit parameters and their distribution

	Estimates		
Variable	EMA Base Value	EMA Probability Distribution	NACI Base Value[a]
Rate of VIPIT	1 in 153,000	$\beta(222, 3.4 \times 10^7)$	1 in 100,000
VIPIT Mortality Risk	20%	$\beta(18, 86)$	40%

[a]A probability distribution could not be calculated as numerators and denominators were not reported.

2. Methods

We estimated benefits of the AZ COVID-19 matrix using a BC-specific age-structured COVID-19 compartmental model by Mulberry and colleagues that takes into account transmission, age-based contact structure, front-line worker status, and rising R_0 due to variants of concern (Mulberry et al. 2021). The model included susceptible, exposed, infectious and recovered (SEIR) status and was based on the transmission model by Bubar et al (Bubar et al. 2021).

We ran the model from January 2021 to September 2021, which is when expect the vaccination campaign to conclude. To follow BC vaccination strategy and case counts in the first three months of 2021, we held R_0 at 1.00 from January 1, 2021 for 60 days during which people over 80 years old eligible for vaccination. Age groups that were offered vaccination were considered to be vaccinated at a steady pace until everyone who is not vaccine-hesitant is vaccinated. Around the end of March, we raised R_0 to either 1.15 or 1.3 to account for variants of concern gaining a foothold in BC.

We assumed the first dose of the vaccine, regardless of the manufacturer, to offer a 80% efficacy against serious illness. We further assume that all British Columbians will be offered a first dose before July 1st, 2021, and a second dose before the end of September 2021. We assumed that each dose of the AZ vaccine to be independently associated with the highest reported risk for VIPIT. We did not consider the risk for anaphylaxis, as all vaccines seem to have a similar risk in that regard and the risk can be mitigated in the vaccination clinic.

For harm-benefit analysis from a societal perspective, we compared expected number of deaths under each vaccination strategy. We did a probabilistic analysis where enough data was available. For harm-benefit analysis from a personal perspective, we compared the mortality risk due to VIPIT with mortality risk from COVID-19 due to delayed vaccination in each age group. We assumed the risk from VIPIT to be constant across all age groups under 60.

All the analysis was performed using publicly-available data and code. This manuscript is produced by a reproducible R Markdown script, which is available on Github.

3. Results

3.1. *Harm-Benefit From A Societal Perspective*

Assuming that BC allocates all 246,700 doses to front-line workers, we can estimate the expected number of deaths due to VIPIT, $E(death)_{VIPIT}$, as shown below. To err on the side of caution, we assume that each dose of the vaccine is independently associated with the risk for VIPIT and that the risk of VIPIT is uniform across all age groups. We also assume that there is enough uptake that BC is able to administer

all these doses.

$$E(death)_{VIPIT} = d \times P(VIPIT|AZ) \times P(death|VIPIT, AZ)$$

where d is the number of doses administered, $P(VIPIT|AZ)$ is the risk of VIPIT after receiving each dose, and $P(death|VIPIT, AZ)$ is the case fatality for VIPIT.

According to the most recent data from UK and EU submitted to EudraVigilance (as of April 4th, 2021):

$$\begin{aligned} E(death)_{VIPIT} &= d \times \frac{1}{153,000} \times \frac{20}{100} \\ &= 246,700 \times \frac{2}{1,530,000} \\ &\approx 0.32 \end{aligned}$$

Deterministic analysis leads to an expected number of death of 0.32 if we immediately offer a first dose of the AZ vaccine to all eligible front-line workers in BC. Probabilistic analysis according to respective beta distributions (Table 1) leads to an expected number of death of 0.28 [95% CI 0.17-0.41], which means the probability of observing at least one death is almost zero.

NACI had based its analysis on the more pessimistic estimates of a chance of 1 in 100,000 for VIPIT, and a mortality probability of 40%. In this worst-case scenario analysis, the expected number of deaths in BC would be 1:

$$\begin{aligned} E(death)_{VIPIT-WorstCase} &= d \times \frac{1}{100,000} \times \frac{40}{100} \\ &= 246,700 \times \frac{4}{1,000,000} \\ &\approx 1 \end{aligned}$$

We used a compartmental model of transmission and vaccination of COVID-19 in BC to estimate benefits of immediately continuing the front-line workers vaccination program using the AZ vaccine.

Predicted epidemiological curve and age-stratified case counts showed good agreement with observed counts reported by BC CDC, as shown in Figure 1.

We compared immediately prioritizing of front-line workers for the AZ vaccine (Scenario A) and delaying it until after those over 70 are fully vaccinated (Scenario B). Figure 2 shows the progression of the vaccination campaign, as well as projections for COVID-19 cases, hospitalizations, and deaths under the two scenarios.

In our analysis, Scenario A led to 38471 fewer cases of COVID-19, 754 fewer hospitalizations, 183 fewer deaths, and 2149 fewer cases of Long COVID, assuming $R_0 = 1.3$ and that vaccine effeteness in preventing transmission is on average 60%. Figure 3 shows results for a wider range of R_0 and efficacy against infection values.

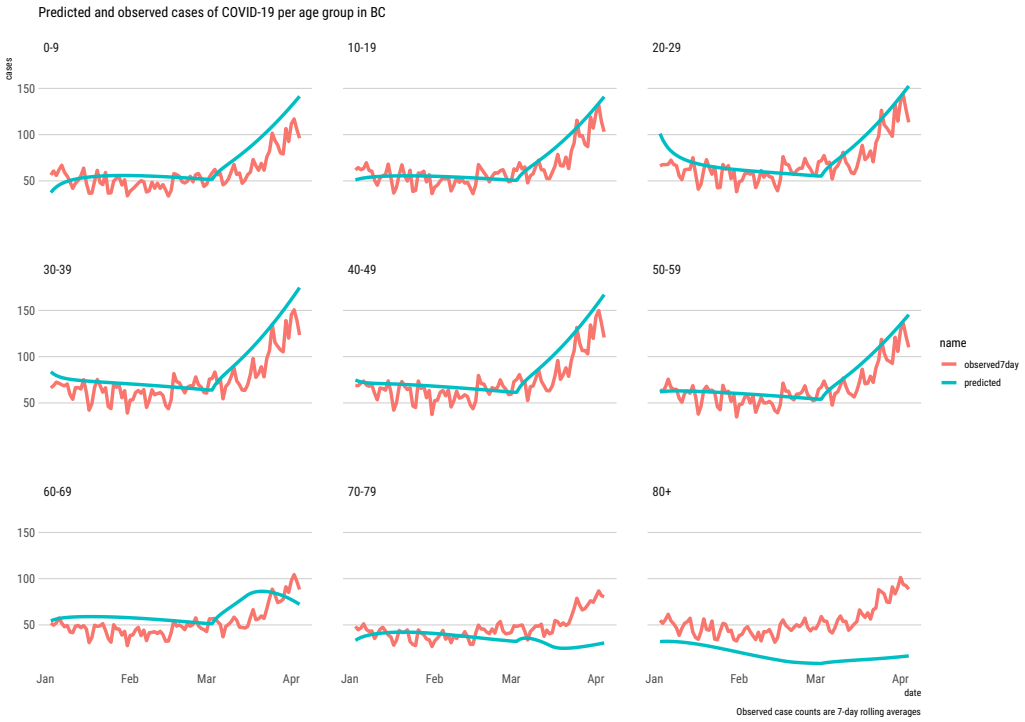

Figure 1. Face validity of model case counts

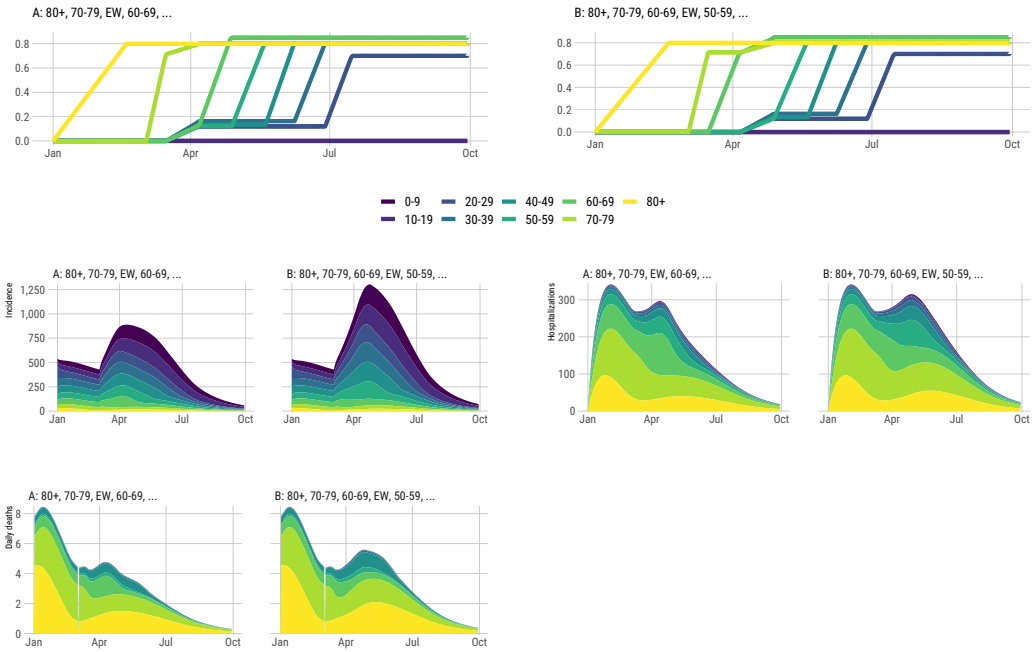

Figure 2. Projection of the progression of the vaccination for different age groups and front-line workers (EW) as well as COVID-19 cases and outcomes

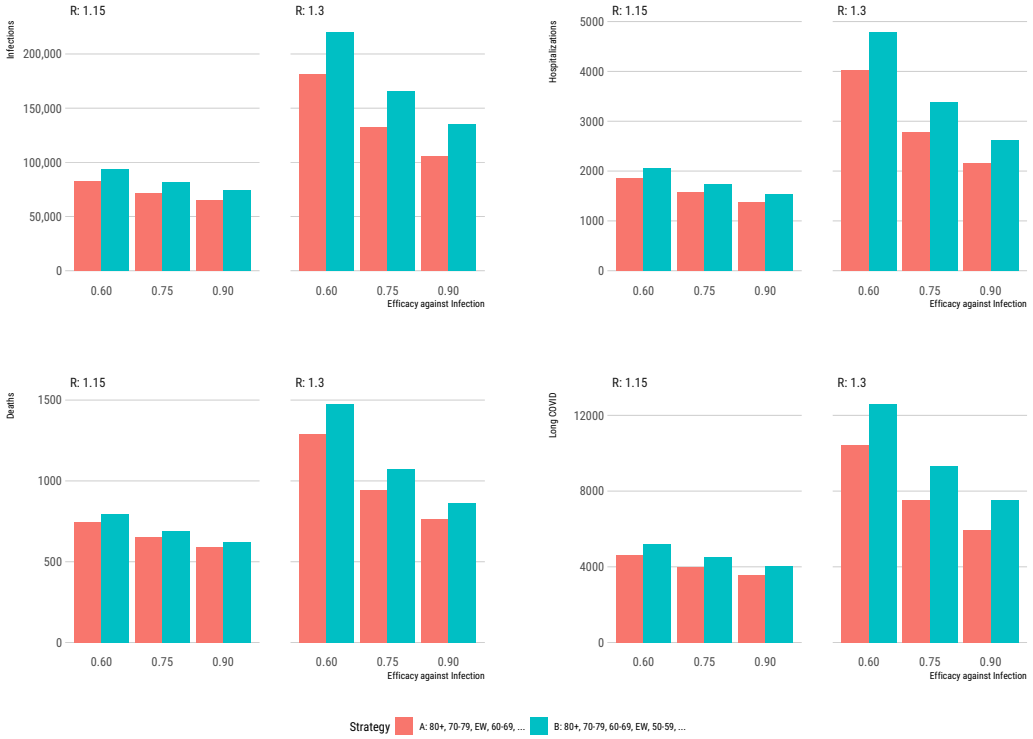

Figure 3. COVID-19 outcomes under different vaccination scenarios for different age group and front line workers (EW)

3.2. *Harm-Benefit From a Personal Perspective*

Not all interventions that are net-beneficial at a societal level are net-beneficial for each member of the society, as those who carry the burden of the risk of adverse events may not be the same people who benefit from mitigation of the risk from contracting COVID19.

In mathematical terms, we compared

$$P(death)_{VIPIT} = P(AZ) \times P(VIPIT|AZ) \times P(death|VIPIT, AZ)$$
$$P(death)_{delayedVaccination} = P(COVID-19) \times P(death|COVID-19)$$

where $P(AZ)$ is the probability of getting the AZ vaccine (assumed to be 1 here), and $P(COVID-19)$ is the probability of contracting COVID-19 due to delayed vaccination.

We used results from our compartmental model to project mortality risk from COVID-19 due to delayed vaccination.

Figure 4 compares the risk of VIPIT-related mortality from 2 doses of the AZ vaccine with the mortality risk from COVID-19 due to delayed vaccination from April 1st to July 1st, 2021. We did the comparison under two scenarios of R_0 of either 1.15 or 1.30, to represent different intensities for the third wave, or alternatively to represent different geographical parts of the province during the third wave. We calculated the mortality risk associated with VIPIT using both the latest and most comprehensive evidence by EMA, and the worst-case scenario considered by NACI. Using EMA estimates, we found that under both R_0 scenarios, the mortality risk due to COVID-

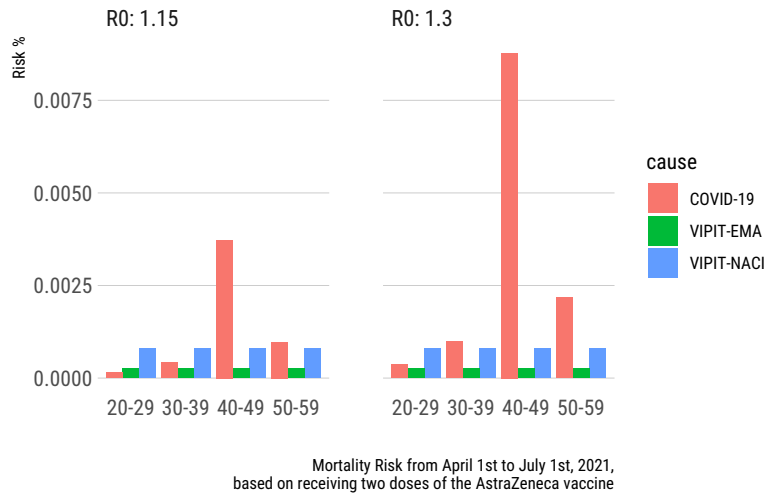

Figure 4. Mortality risk comparison for different age groups based on the estimated risk for VIPIT by the EMA and NACI

19 to be much higher than the mortality risk associated with VIPIT in those over 40. Mortality risk from COVID-19 was also higher for 30-39 age group, although the difference was negligible under R_0 of 1.15 scenario. For the 20-29 age group, the estimated mortality risk of vaccination with the AZ vaccine was comparable to that of COVID-19. Using the worst-case VIPIT estimates considered by NACI, mortality risk from COVID-19 was higher than that of VIPIT for those over 40 and those over 30 in high-risk areas.

4. Discussion

In its analysis of AZ vaccine, NACI weighed the risk of adverse events against the age-stratified risk of mortality due to COVID-19, pending an overall risk-assessment. However, the benefits of the AZ vaccine go beyond preventing COVID-related mortality and include protection against more common COVID complications in younger adults including severe disease, hospitalizations, and Long COVID. The recent sharp decline of COVID-19 cases in the UK suggests that the AZ vaccine might also prevent onward transmission of the virus (Our World in Data 2021).

The number of confirmed daily COVID-19 cases in the UK has plummeted from about 60,000 cases a day in early January 2021 when a national lockdown was imposed and about 3% of the population had received at least one vaccine dose, to about 11,000 cases per day on February 22, 2021 when a roadmap to easing lockdowns was announced to about 6000 cases per day on March 8, 2021 when the first phase of easing public health restrictions was commenced (BBC 2021) and has continuously declined since then to just above 4500 cases as of April 2, 2021 (47% of the UK population have so far received one dose of a COVID-19 vaccine). As about half of all vaccine doses administered in the UK have been AZ vaccines, and based on the estimated AZ vaccine efficacy of about 76% against symptomatic COVID-19 and 64% against any NAAT-positive COVID-19 infection between 22 and 90 days after the first dose (Voysey et al. 2021), and real-world single-dose AZ vaccine effectiveness of about 60% against symptomatic COVID-19 and 80% against COVID-19 hospitalization (Public Health England 2021), it is suggested that the AZ vaccine is effective in reducing the

overall burden of COVID-19.

Potential prevention of onward transmission with the AZ vaccine could be especially critical for front-line workers during the current wave of COVID cases. Of note, two recent studies from Toronto, Ontario have shown that neighbourhoods with the highest proportion of front-line workers had per capita COVID-19 case and death rates that were 2.5-3 folds higher than that of neighbourhoods with the lowest share of front-line workers (Chagla et al. 2021, Rao et al. (2021)).

Based on our analysis, immediately making the AZ vaccine available to front-line workers is, assuming optimal uptake, net-beneficial by a wide margin from a societal perspective. Our analysis from a personal perspective shows that the risk of contracting COVID-19 and dying from it due to delayed vaccination is considerably higher than the risk of dying from VIPIT in those over 40, and also in those over 30 in high-risk areas.

For a public health intervention to be deemed ethically acceptable, being net-beneficial at a societal level is not enough in and of itself. We recognize that many intuitively consider mortality due a public health intervention in an otherwise healthy person to be ethically worse than failing to protect someone from mortality due to COVID-19. We believe that our conclusions hold regardless of the position we take with respect to the *doing vs. allowing harm* problem(Woollard and Howard-Snyder 2016), as long as the expected benefit outweighs the harm at a personal level, as seems to be the case for most age groups in our study.

Our findings confirm the recent recommendation by the UK Joint Committee on Vaccination and Immunisation (JCVI) that the benefits of the AZ vaccine far outweigh the risk in 30 years old or older recipients (JCVI 2021).

5. Limitations

Our analysis does not consider ethical aspects of vaccine roll-out and factors such as uptake and vaccine hesitancy, as they were beyond our expertise. However, we recognize that each time a recommendation for vaccine safety is reversed, there might be a penalty in public trust, which could fuel vaccine hesitancy. Potential for these effects should be weighed carefully by policy makers.

Our analysis is based on currently available estimated rates of 1 in million to 1 in 100,000 for VIPIT and might need correction should higher rates of this complication be reported.

We have not considered potential sex differences in the risk for VIPIT. Although cases identified to date have been predominantly female, it remains unclear whether this was due to more females receiving the AZ vaccine or due to an intrinsic difference in risk.

6. Conclusions

Current evidence suggests that benefits of immediate prioritization of front-line workers for vaccination with the AZ vaccine far outweigh the risk, both at a societal and at a personal level for those over 40, and those over 30 in high-risk areas. Ultimately, in dynamic situations like this where the evidence is uncertain and evolving, vaccine roll-out decision are judgment calls that need to take a complex network of medical, epidemiological, ethical, logistics, and societal considerations into account.

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