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
Recently, the National Advisory Committee on Immunization (NACI) recommended against using the AstraZeneca COVID-19 vaccine pending further review of the risk for Vaccine-Induced Prothrombotic Immune Thrombocytopenia (VIPIT). Using straightforward calculations and based on current evidence, we propose that even if the risk is found to be causally related to the AstraZeneca vaccine, the benefits of continuing immunization of essential workers with AstraZeneca by far outweigh the risk. We consider the case of British Columbia as an example. The province is expected to received an addtional 246700 doses of AstraZeneca vaccine through US and COVAX until April 11th, enough to provide the first dose of vaccine to all unvacinated front-line workers. We estimate that if British Columbia continues the front-line worker vaccination program with the AstraZeneca vaccine, we expect to see 2 VIPIT-related deaths, 40,000 fewer cases of COVID-19, 500 fewer hospitalizations, 100 fewer deaths, and 1,800 fewer cases of Long COVID even if all essential workers were under 55 and assuming the highest estimated rate of 1 in 100,000 currently reported for VIPIT.

KEYWORDS
COVID19; astrazeneca; vaccination; essentialworkers; clots; thrombocytopenia; harm-benefit; BC

1. Background

Recently, NACI recommended against using AstraZeneca COVID-19 Vaccine for Canadians under the age of 55, due to concerns about the incidence of Vaccine-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 AstraZeneca 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). BC had initially slated the AstraZeneca vaccine for outbreak control and front-line workers vaccination program. on

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

On April 1st, the UK Medicines & Healthcare Products Regulatory Agency 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 AstraZeneca vaccine (total incidence rate 1 in 600,000) (MHRA 2021).

Canadian provinces are expected to receive 1.5 million doses of the AstraZeneca 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 AstraZeneca 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 AstraZeneca vaccine was initially slated for essential workers due to its easier handling and storage requirements. If it is logistically possible to switch the vaccine allocation for above 55 years old age groups to the AstraZeneca vaccine and use either Pfizer-BioNTech or Moderna vaccines for younger front-line workers without delay, that might be the preferred approach. However, if that is not logistically feasible, one might ask whether the benefits of deploying the AstraZeneca vaccine for front-line workers outweigh the rate but serious risk for VIPIT.

Harm-benefit of the administering the AZ doses to younger front-line workers can be analyzed from either a societal or a personal perspective. From a societal perspective and assuming a utilitarian framework, we can estimate compare outcomes such as deaths, life years lost, or Quality-Adjusted Life Years (QALYs) under different scenarios. However, a net-beneficial intervention at the societal level does not necessary translate to a net-benefit at the personal level, as the those who carry the burden of risk may be different from those who are likely to benefit from the intervention.

Whether explicitly stated or not, the choice of the outcome is affected by value judgments as well. Choosing life-years lost as an outcome, for instance, favours younger people. To make things more complex, roll-out decisions can get tangled in all sorts of societal issues, including public trust in not only COVID-19 vaccines but vaccine hesitancy in general.

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

2. Methods

We estimated benefits of the AstraZeneca 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 1.05 from January 1, 2021

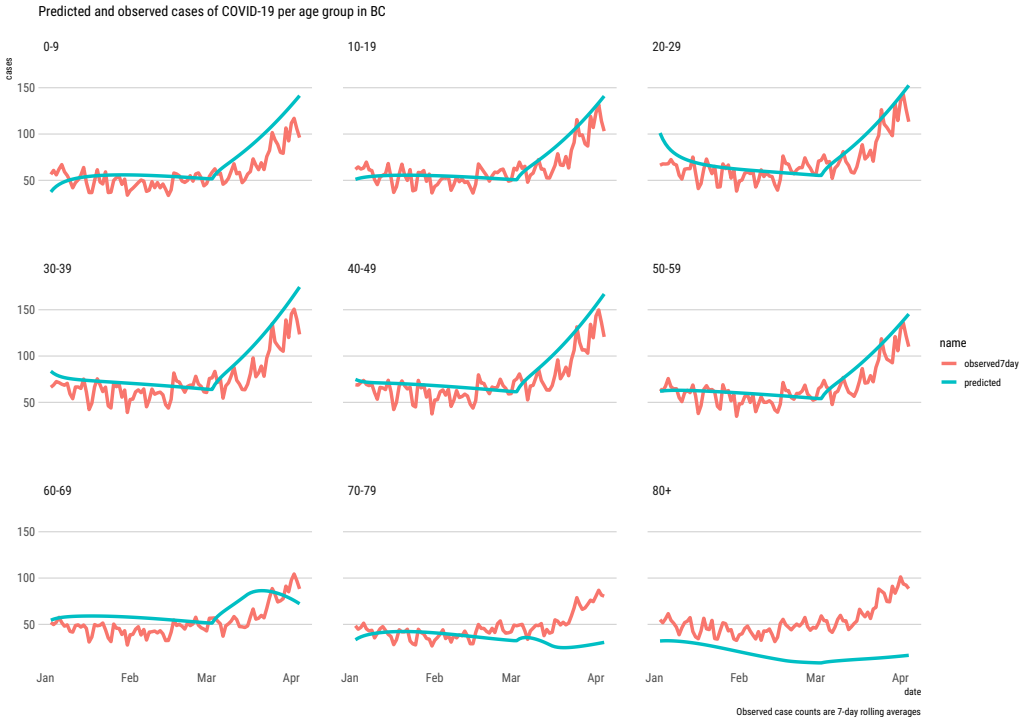

Figure 1. Face validity of model case counts

for 90 days during which people over 80 years old followed by those between 70-79 years old became 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 90% 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 AstraZeneca 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. 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

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

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 all recipients are under 55 and as such at higher risk for VIPIT. We also assume that there is enough uptake that BC is able to administer all these doses.

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

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

To err on the side of caution, we will follow NACI's lead and assume the highest reported rate of VIPIT, which is 1 in 100,000 recipients, so $P(VIPIT|AZ) = \frac{1}{100,000}$. On the other hand, as reported by NACI, case fatality due to VIPIT is currently estimated at 40% but is likely to decrease as there will be more awareness and better early treatment. Again to err on the side of caution, we'll keep the estimate at 40%: $P(death|VIPIT, AZ) = 40\%$

$$\begin{aligned} E(death)_{VIPIT} &= n \times 2 \times \frac{1}{100,000} \times \frac{40}{100} \\ &= 246,700 \times \frac{8}{1,000,000} \\ &\approx 2 \end{aligned}$$

The expected number of mortality under the scenario of immediately offering the AstraZeneca vaccine to all front-line workers is 2 persons in BC.

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 AstraZeneca vaccine.

We compared immediately prioritizing essential workers for a vaccine (Scenario A) and delaying it until after those over 70 are fully vaccinated (Scenario B).

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.

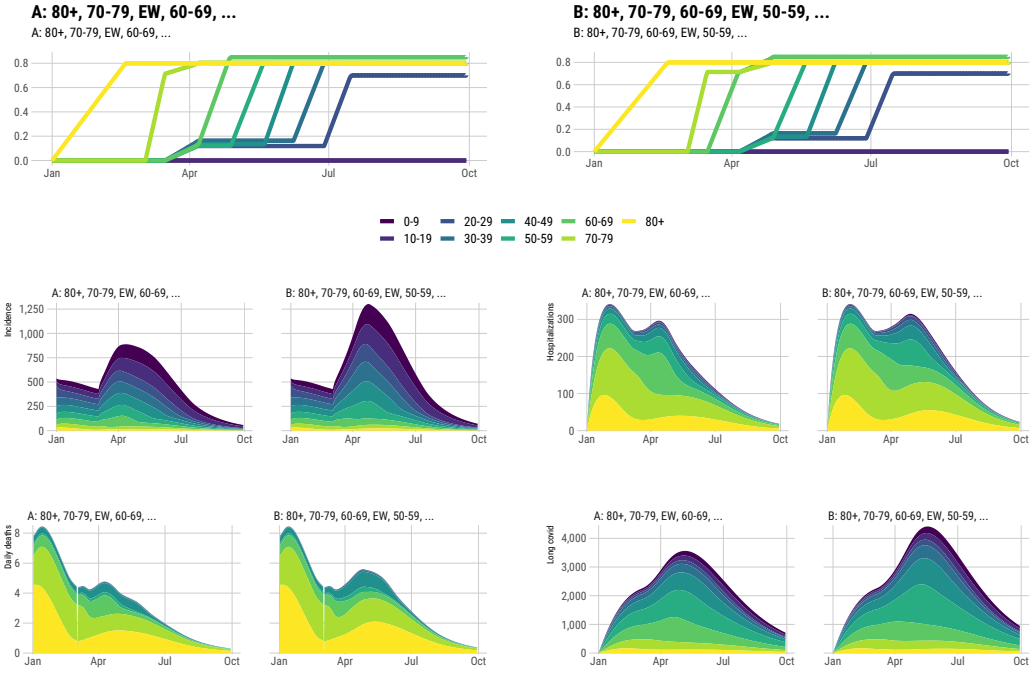

Figure 2. Projection of the Progression of the Vaccination Program and COVID-19

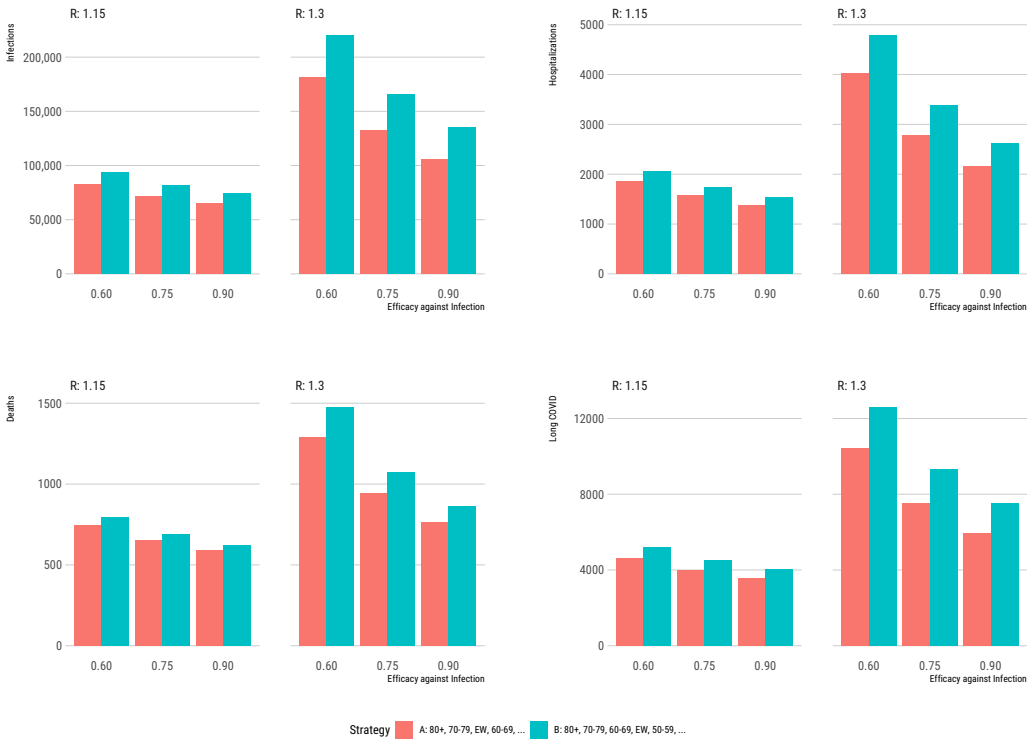

Figure 3. COVID-19 outcomes under different vaccination scenarios

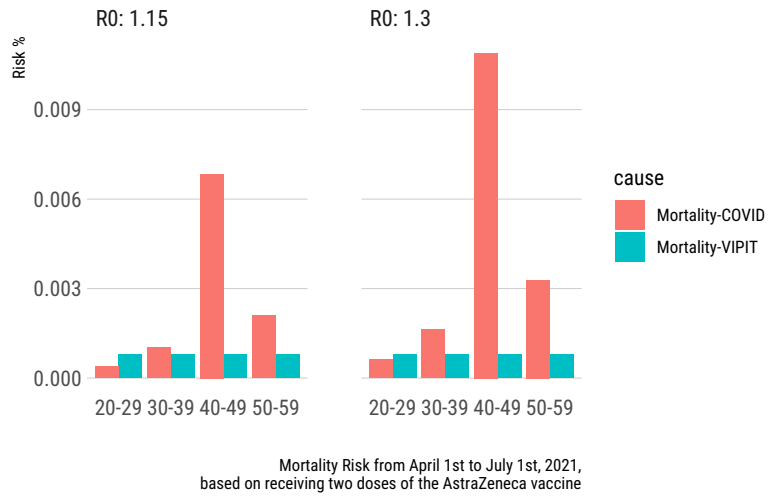

Figure 4. Mortality risk comparison for different age groups

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 AstraZeneca 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 3 compares the risk of VIPIT-related mortality from 2 doses of the AstraZeneca vaccine with the mortality risk from COVID-19 due to delayed vaccination. 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 found that under both scenarios, the mortality risk due to COVID-19 to be much higher than the highest estimate of the mortality associated with the risk for VIPIT in 40-49 and 50-59 age groups. 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 risk of vaccination with the AstraZeneca vaccine was higher than that of COVID-19 from April 1st to July 1st, 2021.

4. Discussion

In its analysis of AstraZeneca 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 AstraZeneca 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 AstraZeneca 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 AstraZeneca 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 essential workers had per capita COVID-19 case and death rates that were 2.5-3 folds higher than that of neighborhoods with the lowest share of essential workers (Chagla et al. 2021, Rao et al. (2021)).

Based on our analysis from a societal perspective and assuming a consequentialist framework, immediately making the AstraZeneca vaccine available to essential workers is, assuming optimal uptake, net-beneficial by a wide margin. Our analysis from a personal perspective shows that the risk of contracting COVID-19 and dying from it due to delayed vaccination is at least two times higher than the risk of dying from VIPIT in those over 40, and also in those who are over 30 in large outbreak areas.

4.1. *Doing vs. Allowing Harm*

For a public health intervention to be deemed ethically acceptable, being net-beneficial at a societal level is not enough in and of itself. As tragic as COVID-19 related mortality is, some hold that such events are not comparable to causing death of otherwise healthy people because of known even if rare side effect of a vaccine. as famously demonstrated in the Trolley Problem, some people intuitively hold that causing harm in worse than allowing harm, while others believe that at the end of the day the consequences matter providing that the intention is benevolent.

The scope of this manuscript and our lack of expertise in this area prevents us from doing justice to this important dilemma, and we refer the interested reader to the appropriate literature (Woollard and Howard-Snyder 2016).

However, we believe that our conclusions hold regardless of the position we take with respect to this ethical dilemma, 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.

Either way, all potential risks and latest evidence should be clearly communicated with recipients before an informed consent is sought.

4.2. *Communications and Vaccine Hesitancy*

Each time a recommendation for vaccine safety is reversed, there might be a penalty in public trust, which could fuel vaccine hesitancy. Even if a vaccination program is net beneficial from both a societal and a personal perspective, vaccine side effects are likely to attract more news coverage and attention on social media. Potential impacts of COVID-19 vaccine roll-out on vaccine hesitancy, regardless of them being positive or negative, might spill over into public perception of the routine vaccination programs for the years to come.

5. Limitations

We did not consider ethical aspects of vaccine roll-out, and factors such as uptake and vaccine hesitancy, as they were beyond our expertise. 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 AstraZeneca vaccine or due to an intrinsic difference in risk.

6. Conclusions

Immediate prioritization of front-line workers save lives. The optimum strategy is, if logistically feasible, is to make Pfizer-BioNTech or Moderna vaccine immediately available to essential workers and reallocate the AstraZeneca vaccine for older individuals. If that is not possible, continuing vaccination of front-line workers using AstraZeneca vaccine is net-beneficial at a societal level. At a personal level, current evidence suggests mortality risk posed by VIPIT is significantly lower that mortality risk of contracting COVID-19 due to delayed vaccination for 40-59 years old adults and for 30-39 adults who live in an areas with larger outbreaks.

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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