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Modeling waning and boosting of COVID-19 in Canada with vaccination

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ABSTRACT

SARS-CoV-2, the causative agent of COVID-19, has caused devastating health and economic impacts around the globe since its appearance in late 2019. The advent of effective vaccines leads to open questions on how best to vaccinate the population. To address such questions, we developed a model of COVID-19 infection by age that includes the waning and boosting of immunity against SARS-CoV-2 in the context of infection and vaccination. The model also accounts for changes to infectivity of the virus, such as public health mitigation protocols over time, increases in the transmissibility of variants of concern, changes in compliance to mask wearing and social distancing, and changes in testing rates. The model is employed to study public health mitigation and vaccination of the COVID-19 epidemic in Canada, including different vaccination programs (rollout by age), and delays between doses in a two-dose vaccine. We find that the decision to delay the second dose of vaccine is appropriate in the Canadian context. We also find that the benefits of a COVID-19 vaccination program in terms of reductions in infections is increased if vaccination of 15–19 year olds are included in the vaccine rollout.

1. Introduction

Several vaccination policy-making bodies, including the Government of Canada's National Advisory Committee on Immunization (NACI), have utilized transmission modeling studies to evaluate possible strategies for allocating vaccine against SARS-CoV-2. Some policy-making bodies have worked solely with in-house modelers, others with external ones, and still others a combination of both (Funk et al., 2020; Shea et al., 2020), while realizing that models are approximations of natural phenomena, given the quality of available information.

Most contemplated vaccination strategies are based on ethical or practical versus scientific considerations. Determining that healthcare workers (HCWs) should be vaccinated first, followed by other essential workers, institutionalized populations, especially elderly people, and others with chronic conditions that increase their risk of serious illness does not require modeling. Nor does identifying other essential workers. Those strategies involve directly protecting essential or vulnerable groups. Questions amenable to transmission modeling include the rate at which the vaccination program can be expanded to sub-populations not included in the aforementioned list, especially given a limitation in the number of doses available to the population at any given time. Additionally, modeling can assess indirect effects of vaccination. Might, for example, vaccinating some population groups have more impact on transmission than vaccinating others? Such questions are usually framed in terms of population immunity, considering single- and two-dose efficacies of available vaccines (Polack et al., 2020), as well as the number of doses available to the population. The apparent single-dose efficacy (Polack et al., 2020), together with our ability to produce and distribute doses, has led some to ask if we should adhere to the two-dose schedule or vaccinate twice as many people once, or vaccinate twice as many people once as soon as possible. Similarly, while the currently available vaccines seem efficacious in the short term for the age groups tested in the clinical trials, we have no idea how long such protection will last. We thus must consider the indirect effects of protecting certain population cohorts through vaccination in others, not just their caregivers, but other members of the general population as well.

Most models of the transmission of SARS-CoV-2 are modifications of a classic model in population biology in which the host population is partitioned into those who are susceptible to infection; infected, but not yet infectious; infectious; and removed from the process (e.g., Anderson

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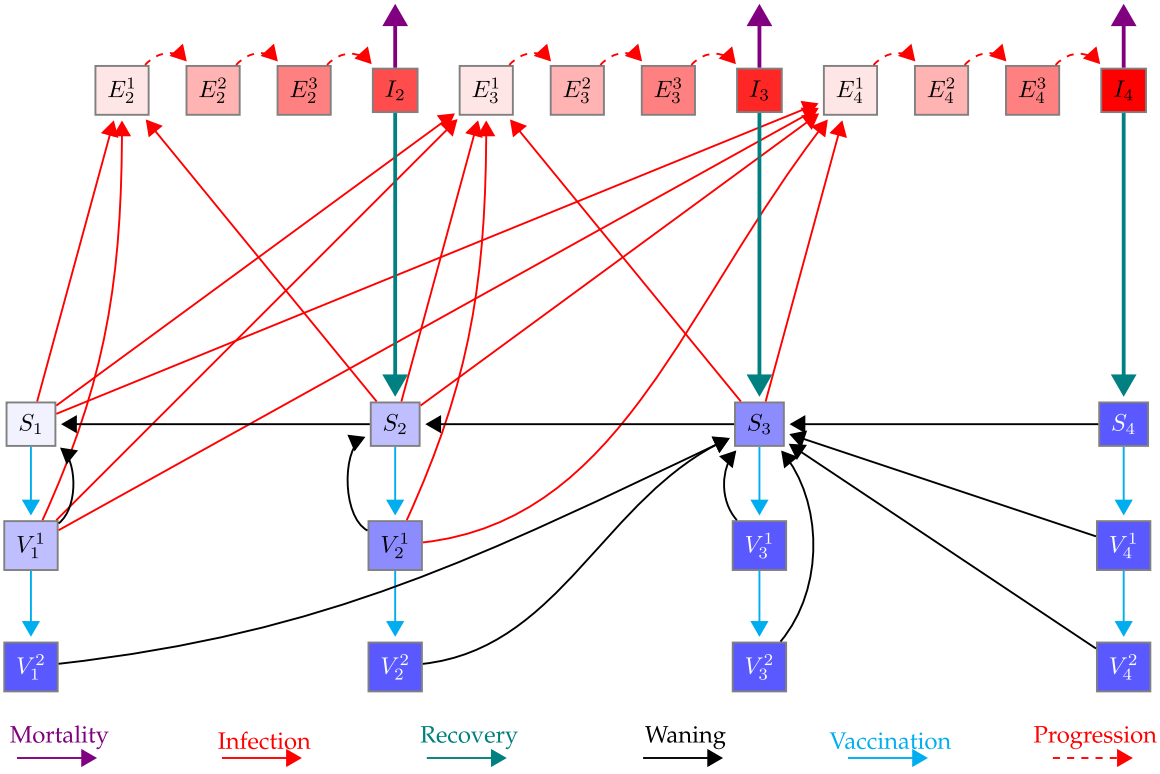

Fig. 1. Schematic of the model for one age group. Here, S_1, S_2, S_3, and S_4 (purple shaded boxes) represent susceptible individuals who are immunologically naive, have some, moderate, and full immunity, respectively. I_2, I_3, and I_4 (red boxes) represent infected individuals with mild, moderate and severe symptoms, respectively, who will develop some, moderate, and full immunity once recovered (teal lines), respectively. V_i^j $(i = 1, 2, 3, 4, j = 1, 2)$ represent vaccinated individuals from the S_i classes $(i = 1, 2, 3, 4)$ after $j = 1, 2$ doses of vaccine given a two-dose schedule. E_i^k $(i = 2, 3, 4; k = 1, 2, 3)$ represent exposed individuals (infected, asymptomatic, not infectious) with progressive stages $k = 1, 2, 3$ that will experience mild I_2, moderate I_3, and severe I_4 symptoms. Susceptible and vaccinated individuals can be infected and move to the exposed classes (red lines). Susceptible and vaccinated classes at the same location on the immunity continuum have similar characteristics. Immunity gained from infection and vaccination can wane (black lines). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

and May (1992), Keeling and Rohani (2011), He et al. (2020) and Peak et al. (2020)). These modifications include features of the biology of COVID-19 that might affect transmission such as pre- and asymptomatic infections, hospitalization of some with symptomatic infections, vaccination, mortality, and waning of immunity (e.g., Nande et al., 2021; Bubar et al., 2021; Worby and Chang, 2020; Çenesiz and Guimarães, 2020; Anggriani et al., 2021; Lavine et al., 2021; Giannitsarou et al., 2020; Viana et al., 2021; Cheetham et al., 2021). To answer some of these questions in the context of pertussis (prior to the SARS-CoV-2 outbreak), we used a model with some of these features that emphasizes the waning and boosting of immunity and, furthermore, the relationship between immunity when infected and disease (Carlsson et al., 2020). We extend our model structure here to COVID-19.

We believe that economic calculations should be based on sound mathematical epidemiology, which we strove to provide, but are not economists, so have left economic questions for those with the requisite expertise. We also endeavored to make the case for vaccinating adolescents, relatively few of whom experience serious disease, but who – by virtue of their contacts – can be super-spreaders. Consequently, our answer to the question, "Might vaccinating some groups have more impact on transmission than vaccinating others?" is "Yes". The answer might differ for other policy goals (e.g., reducing deaths).

2. Model

We have implemented a model of COVID-19 infection with age structure (i.e., groups 0–4, 5–9, ..., 75+ years). A flow diagram of the model is shown in Fig. 1 for a single age group. The model is based on a Susceptible–Exposed–Infected–Vaccinated–Susceptible model structure (SEIVS). We use S_i, E_j^k, I_j, and V_i^ℓ to denote the number of susceptible, exposed, infectious and vaccinated individuals in each age group, where i $(1 \le i \le 4)$ denotes immune status, j $(1 \le j \le 3)$ denotes symptom severity, k $(1 \le k \le 3)$ represents stages in the exposed class (to obtain gamma-distributed exposed sojourns), and $\ell = 1, 2$ denotes the number of doses of vaccine that individuals have received.

The base model consists of an immune continuum along which we distinguish four states (fully susceptible (S_1), somewhat immune (S_2), moderately immune (S_3), and fully resistant to infection (S_4)), three infectious states with mild (I_2), moderate (I_3), and severe (I_4) symptoms, and three infected but non-yet-infectious states $(E_j^k,\ j = 2, 3, 4,\ k = 1, 2, 3)$. We assume that individuals of higher immune status are less susceptible to infection than those of lower status. As per (Knight and Mishra, 2020), we assume that co-morbidity determines the probability of mild, moderate, and severe symptoms for each age group. As probability of severe infection increases with comorbidity, and thus with age, in our model, severity of disease does not precisely reflect death and hospitalizations, which we do not track directly. Immunity develops after infection, and we assume that people with mild, moderate, and severe symptoms move to immune classes S_2, S_3 and S_4, respectively, upon recovery. This is tantamount to assuming that severity of symptoms is proportional to neutralizing immunity development (Robbiani et al., 2020; Piccoli et al., 2020; Dan et al., 2021). Finally, we assume that immunity wanes over time (Fig. 1, black lines), a characteristic common to other known coronaviruses (Sariol and Perlman, 2020).

We extend the base model to include two vaccinated states per immune state S_i, corresponding to one V_i^1 and two V_i^2 vaccine doses. We distinguish the susceptible and vaccinated states solely to facilitate calculating coverage. Here, we assume that two doses of vaccine provide the same level of immunity as S_4; i.e., people in V_i^2 have similar characteristics to those in S_4. Additionally, we assume that one dose of vaccine administered to individuals in immune states S_3 and

Table 1
Vaccination programs. Scenario 1, under two-dose coverage with 16 weeks between doses has been designed to resemble the actual COVID-19 vaccination program in Canada from January to April 2020.

Dosage	One-dose:	Full target coverage With neutralizing immunity moves individuals to V_i^2. Without neutralizing immunity moves individuals to V_i^1.
	Two doses:	[half, full] target coverage Doses separated by 4 weeks for half coverage, and 16 weeks for full coverage. First dose moves individuals to V_i^1. Second doses moves individuals to V_i^2.
Coverage	Target:	80% of the Canadian population
	Monthly coverage:	2.4%, 2.7%, 8.9%, 19.0%, 18.0%,18.0%, 10.2%, 1.0%
Scenario		
1	Vaccinate healthcare workers (HCWs)[a] (months 1–2) Vaccinate ages 65+ years (months 1–8) Vaccinate ages 60–64 years (months 3–8) Vaccinate ages 50–59 years (months 4–8 Vaccinate ages 45–49 years (months 5–8) Vaccinate ages 20–44 years (months 6–8)	
2	Vaccinate healthcare workers (HCWs)[a] (months 1–2) Vaccinate ages 65+ years (months 1–8) Vaccinate ages 55–64 years (months 3–8) Vaccinate ages 50–54 years (months 4–8) Vaccinate ages 45–49 years (months 5–8) Vaccinate ages 20–44 years (months 6–8)	
3	Vaccinate healthcare workers (HCWs)[a] (months 1–2) Vaccinate ages 65+ years (months 1–8) Vaccinate ages 50–64 years (months 3–8) Vaccinate ages 40–49 years (months 4–8) Vaccinate ages 25–39 years (months 5–8) Vaccinate ages 20–24 years (months 6–8)	
4	Vaccinate all adults 20+ years of age (months 1–8)	

[a]Assume that HCWs are aged 20–64 years and evenly distributed over each 5-year age group in this interval.

S_4 also results in resistance to infection; i.e., V_3^1 and V_4^1 have similar characteristics to S_4. Finally, we assume that one dose of vaccine given to individuals in S_1 and S_2 provides immunity similar to states S_2 and S_3, respectively. In other words, V_1^1 has similar characteristics to S_2 and V_2^1 to S_3. Concurrently, we assume that immunity can wane from the vaccinated classes as from their corresponding S classes (Fig. 1, black lines).

A detailed model description is provided in the Supplementary Material, including parameter values and references. Briefly, we track mild, moderate and severe symptoms by age given age-specific model parameters defining the population contact structure during successive public health mitigation phases throughout the COVID-19 pandemic. We then add a vaccination program and track vaccine doses by age under specific scenarios of interest. We quantify vaccination program outcomes by calculating the number of infections averted and percent reduction in the number of infections with mild, moderate, and severe symptoms by age. We consider parameters specific to the Canadian population and public health mitigation strategies, including distributions of comorbidities by age (Clark et al., 2020) and variations in contacts between age groups, in school, work and other settings (Prem et al., 2017), to reflect school closures, social distancing measures and work-from-home orders. We further reduce the contact matrix by a factor reflecting the use of personal protective equipment (PPE), hand-washing, and other non-pharmaceutical interventions (NPIs).

We consider vaccination programs as described by current vaccination coverage data (Berry et al., 2020) and the National Advisory Committee on Immunization vaccination program description (National Advisory Council on Immunization Canada, 2020). We also consider vaccination programs including the prioritization of certain age groups and other sub-populations (e.g., HCWs). To quantify the outcomes of the current vaccination program under way in Canada (a two-dose program with 16 weeks separating the first and second doses), we compare this program to one-dose scenarios, including a one-dose vaccine that provides neutralizing immunity (vaccination moves individuals to V_i^2 classes whereby they are resistant to infection), a one-dose vaccine that provides some non-neutralizing immunity (vaccination moves individuals to V_i^1 classes, whereby those in classes V_1^1 and V_2^1 have some susceptibility to infection), and a two-dose vaccine program that covers only half of the target population, but separates the doses using the vaccine-developed-recommended interval of 28 days. In the two-dose program, individuals move to V_i^1 classes first, and then to V_i^2 classes after the prescribed period (28 days or 16 weeks). We note that, to compare one-versus two-dose programs with the same amount of vaccine (i.e., when supply is limited), it is sufficient to compare one-dose delivery with full target coverage to two-dose delivery with half target coverage. We also note that results of a program with a delayed (beyond the interval recommended by the manufacturer, or the government chosen time frame) second dose will lie between those of the one-dose program with non-neutralizing immunity and the two-dose program with full target coverage with no delay between doses (not considered here). The vaccination programs are described in Table 1.

Vaccination programs are implemented on a week-by-week basis until a target coverage level is achieved. The target coverage level takes into account the age groups that have been approved to receive a COVID-19 vaccine (see Table 1). Given the desired coverage, we determine the requisite vaccination rate (σ_i^1, where i represents the immune state) for each age group. To model a two-dose program, we determine the rate for the first dose as for a single dose and the rate for second dose given the recommended interval between doses (provided by the vaccine manufacturer, or the government chosen time frame). We note that, when we calculate vaccination rates for the first dose, we remove individuals who were already vaccinated or have known infection (e.g., I_4). Consequently, we allow people unaware that they have been or are currently infected to be vaccinated; for example, those in the exposed classes, or who are asymptomatic or have mild symptoms (some fraction of the mild and moderate states). In these cases, we assume that vaccination does not alter the level of immunity acquired; that is, we assume that ensuing immunity depends solely on the severity of symptoms currently experienced (i.e., those vaccinated

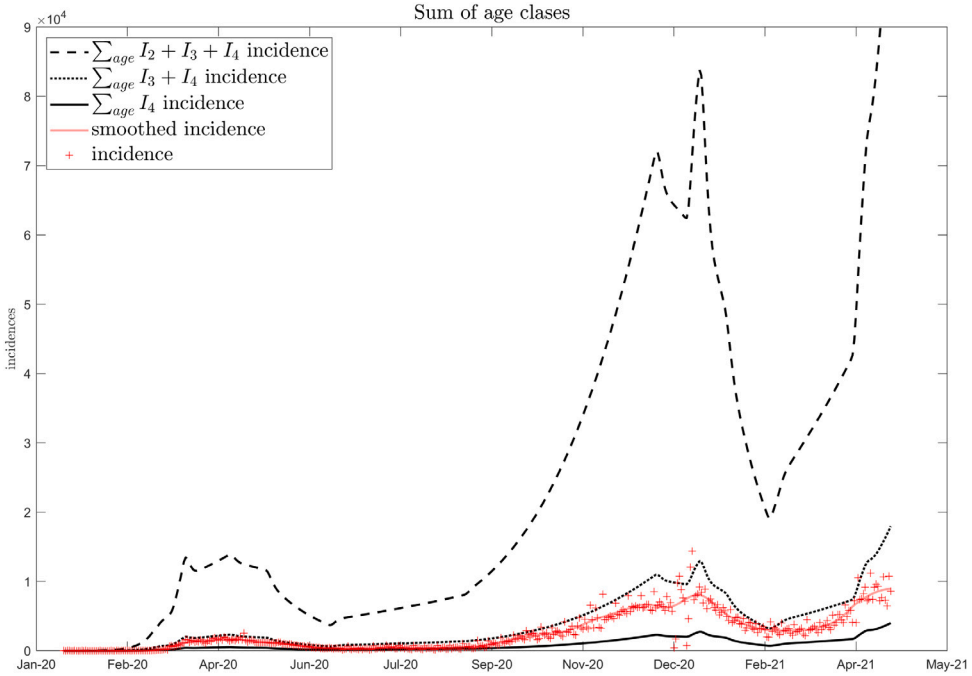

Fig. 2. Daily incidence. Predicted incidence of severe (I_4, solid line), moderate + severe infections ($I_3 + I_4$, dotted line), and mild + moderate + severe infections ($I_2 + I_3 + I_4$, dashed line) are shown. Daily COVID-19 reports from Berry et al. (2020) are shown (red crosses), and loess smoothed in Matlab (red line). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

from E_2^j, I_2 and E_3^j, I_3 follow their disease course and recover to S_2 and S_3, respectively). This is a reasonable assumption insofar that an infected individual's immune system would be primed at the time of vaccination.

While HCWs represent priority groups for vaccination, we do not explicitly model these sub-populations. Age distribution information for these groups, however, is available (Canadian Institute for Health Information, 2020; Mattison and Lavis, 2016; Ministry of Long-Term Care, 2020; Lum et al., 2010). Herewith, we assume a uniform distribution of HCWs over each 5-year age group from 20 to 64 years (see Supplementary Material for details).

The model incorporates public health mitigation strategies as adapted by the Canadian population, on average (since mitigation can vary between different jurisdictions). Specific modifications to the contact matrices are provided in the Supplementary Material. In the past, the choice of mitigation matrix is informed by the mitigation strategies adapted by different provinces and territories. However, as we cannot predict the future, we must adapt specific contact matrix structures projecting forward in time. Given the time frame under consideration, Summer and Fall 2021, we have chosen to adopt the same matrices implemented over Summer and early Fall 2020.

2.1. Temporal changes in testing rate and contact tracing

While temporal changes in contact structure, as affected by different public health mitigation strategies over time, and temporal changes in vaccine availability to different age groups have been addressed explicitly in our modeling structure, using modified contact matrices and calculation of different vaccination rates (see above), we have not explicitly incorporated changes in the testing rate, or in contact tracing activities. Both these, however, affect the transmission of the virus. We therefore assume that temporal variation in testing and contact tracing can be captured in the parameter κ in our model, which also is used to reflect variation in PPE and social distancing compliance. Parameter κ is the only model parameter that is fit to COVID-19 data; therefore, it can capture changes in behavior and pubic health mitigation over time.

2.2. Variants of concern

In recent months, different variants of the SARS-COV-2 virus have emerged (Mahase, 2021b). It has been reported that these variants may be up to 1.5 times more transmissible than the original wild type strain (Rees-Spear et al., 2021; Horby et al., 2021; Volz et al., 2021; Grabowski et al., 2021; Davies et al., 2021). Our mathematical model can incorporate the difference in transmission, again, using parameter κ, the only model parameter that is fit to COVID-19 data. As transmissibility increases in the population, the value of κ will naturally increase to reflect this effect in the COVID-19 data.

It is believed that the effectiveness of currently approved vaccines will be minimally altered by the variants of concern (Callaway and Mallapaty, 2021; Wise, 2021; Mahase, 2021a). We therefore choose to keep parameters reflecting vaccine efficacy to be constant even when the variants of concern exist in the circulation of the virus in the population.

2.3. Sensitivity analysis

Outcomes of a vaccination program may be sensitive to assumed model parameters. We consider variations in the waning rate between consecutive susceptible and vaccine classes (ω), susceptibility by immune status (α), and vaccine characteristics (ρ, ϵ, q). We also consider changes in the assumed fitting proportion for κ. Details of our sensitivity analysis are found in the Supplemental material and the results are in Figure S9.

3. Results

3.1. Model fitting

Fig. 2 plots the model fit from January 2020 to April 15, 2021. The daily reported infections (crosses) from Berry et al. (2020) and simulated daily incidence of I_4 severe (solid line), $I_3 + I_4$ moderate + severe (dotted line), and $I_2 + I_3 + I_4$ mild + moderate + severe (dashed line) infections for the entire population are shown. The model

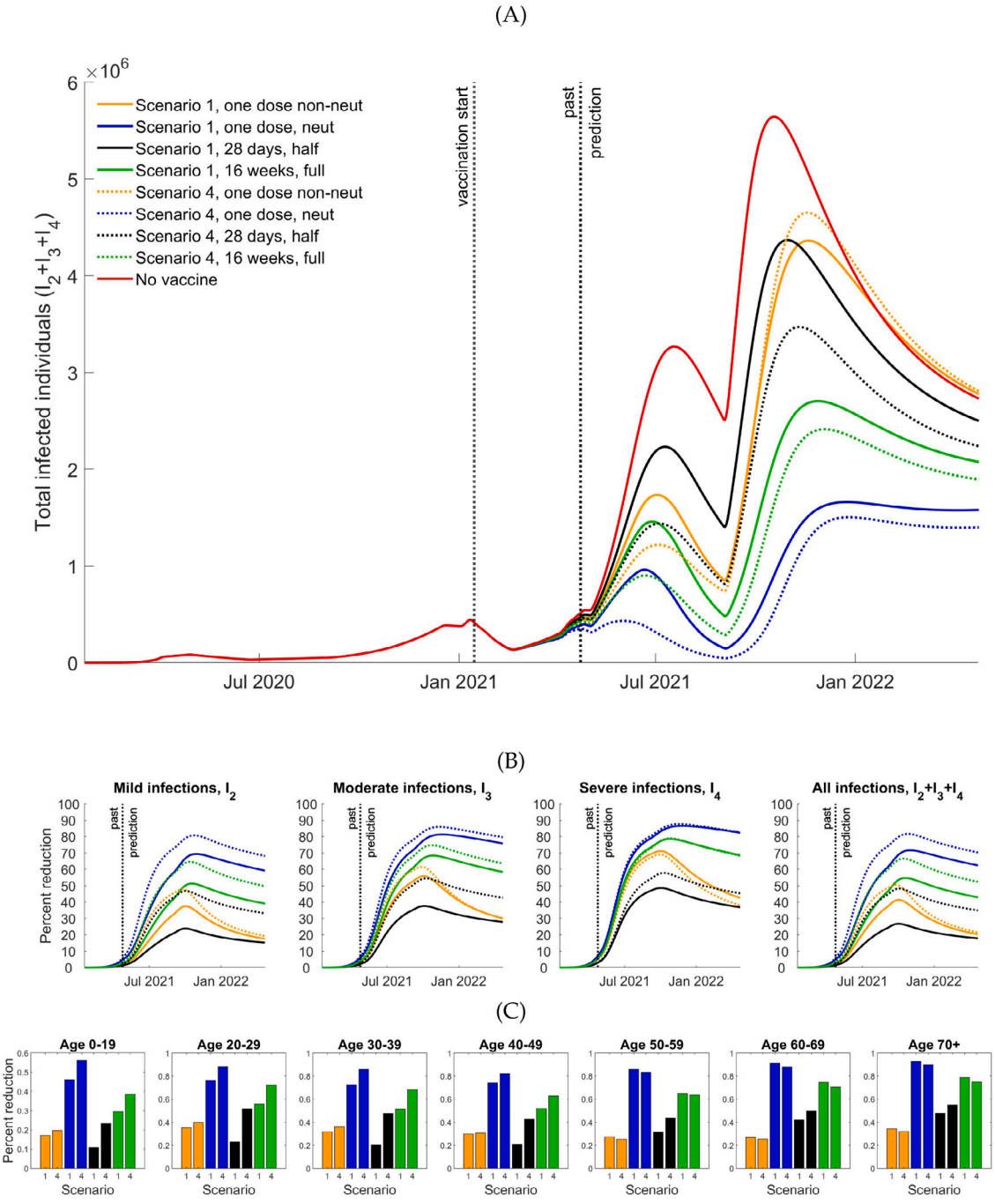

Fig. 3. Effect of vaccination, Scenarios 1 and 4. (A) Infected populations without (red line) and with one dose that is non-neutralizing (blue), one dose that is neutralizing (orange), two doses at half target coverage with 28 days between doses (black) and two doses at full target coverage with 16 weeks between doses (green). (B) Percent reduction in I_2, I_3, I_4, and $I_2 + I_3 + I_4$ infections over time. (C) Percent reduction on day 365 for each age group given one-dose non-neutralizing (orange), one-dose neutralizing (blue), two-dose half target coverage (black) and two-dose full target coverage (green) vaccines. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

is fit using parameter κ, which reflects the population compliance to public health mitigation factors, and incorporates temporal variations in testing, contact tracing and transmissibility of the virus (as variants of concern infiltrate the population). Parameter κ is determined so that daily reported incidence lies between the severe (solid line) and moderate + severe (dotted line) curves. The model fitting also incorporates the different public health mitigation periods of various strengths, that are reflected using modified contact matrices for work-from-home, school closure, business closures, etc (see Table S3), and the Canadian vaccine roll-out program (see Table 1) starting on January 15, 2021. Additionally, parameters were determined so that the basic reproduction number R_0 corresponds to the median value reported for the Canadian COVID-19 epidemic, $R_0 = 2.6$ (Knight and Mishra, 2020). Given the correspondence illustrated, we plot age-specific predictions in Supplementary Figure S1. Additionally, in the Supplementary Figure S2, we plot the reduction in the average number of contacts for the entire population over time, given modifications in the contact matrices (x) and the combined effect of the modifications in the contact matrices and the fitted value of parameter κ (+).

3.2. Vaccination

Vaccination, no matter the type of one- or two-dose vaccine considered here (see Table 1) always reduces the number of infections in every age group (Figs. 3 and S3). Intuitively, a one-dose neutralizing vaccine (blue lines) has the best outcome. A two-dose vaccine at half target coverage with 28 days between doses (black lines) performs the worst in the short-term, and a one-dose non-neutralizing vaccine performs the worst in the long-term. For all one- and two-dose vaccines, the best outcome for the entire population is realized when all adults 20+ years of age are vaccinated over the entire vaccination program (Scenario 4, dotted lines), except when considering a one-dose non-neutralizing vaccine, when the Scenario 1 vaccine program slightly outperforms all others.

To compare the epidemic outcome with no vaccine (red line) to each vaccination program, we plot the percent reduction in the number of I_2, I_3, I_4, and $I_2 + I_3 + I_4$ cases over time, projected for a year after initiation of the vaccination program. These are plotted in Fig. 3 panels (B), and for specified age groups, in panel (C). Panel (B) shows that the best overall reduction in all infections (right) occurs under Scenario 4, when adults aged 20+ years are vaccinated every month. In panel (C), however, we observe that reductions in severe infections in age groups 50+ years are greatest under Scenario 1, except for the two-dose vaccine with half coverage and 28 days between doses (black). We only present results for Scenarios 1 and 4 in the main text, but results for Scenarios 2 and 3 are provided in the Supplementary Material. In addition, Fig. 3 shows that the relative ordering of effectiveness of strategies is consistent over time, despite differing by the specific group considered, e.g. young versus older adults. This indicates that measurements of reduction at any time point should give a comparative ordering of strategies.

The I_4, and total ($I_2 + I_3 + I_4$) infections averted given a two-dose, full target coverage vaccination program (with 16 weeks between doses) under Scenarios 1 and 4 are shown in Figure S4 (see Supplementary Figure S4 for all scenarios under a two-dose, full target coverage, vaccination program). We observe that the number of I_4 and total infections averted due to vaccination continue to increase beyond the vaccination program (July 2021). Once again, it is also evident that Scenario 4 results in the maximum total cases averted, but Scenario 1 results in the greatest number averted among those aged 60+ years (see Fig. 4, last column).

Vaccination programs targeting specific age groups will change the age distribution of new infections. In turn, changes in the age distribution of reported cases will occur. It is therefore important to determine what changes in the age distribution should be expected, so that such changes are not misinterpreted as vaccination program failure, or shifts in infection target by the pathogen. Fig. 5 plots the age distribution of daily I_4 (left column) and $I_2 + I_3 + I_4$ infections (right column) for Scenarios 1 (panel A) and 4 (panel B) given a two-dose, full target coverage vaccination program with 16 weeks between doses. We see that the age distribution of I_4 and $I_2 + I_3 + I_4$ infections varies for both scenarios during and after the vaccination program, including a shift to a higher fraction of severe cases reported in younger age groups. This, however, does not mean that there is a shift of COVID-19 targets of infection. This merely reflects the distribution of the vaccine to older ages. Supplementary Figure S5 provides the same information for the other vaccines and vaccination programs listed in Table 1.

3.2.1. Indirect vaccine effects

Vaccination not only protects vaccinated individuals, it also protects others. In Fig. 6, we plot the percent reduction in I_4 infections during the year after initiation of a vaccine program assuming that only one group is vaccinated at a time. To quantify the indirect effect, we vaccinate individuals in a single age group to a maximum 0.5% of the Canadian population each month for six months. That is, we determine the fraction of the population in each age group that needs to be vaccinated so that 0.5% of the entire Canadian population is vaccinated in one month, and up to 3% over 6 months. Fig. 6 (left panel, and Supplementary Figure S6, which plots the percent reduction in I_2, I_3 and I_4 infections 90, 180 and 365 days after vaccination program initiation) clearly shows the direct effect of vaccination within a single age group (the diagonal elements). We also observe that vaccination of any age group benefits others (off-diagonal elements). These indirect effects are most pronounced for the 15–19 year age group. Vaccination coverage of 3% of this population reduces infections in other age groups by approximately 10% (light blue shading) during the year that vaccination begins.

Until very recently, COVID-19 vaccines in Canada were not approved for use in children under the age of 16 (Health Canada, 2021). To maximize benefit of a vaccination program in the younger age groups, vaccination of 16–19 year olds (in age group 15–19) should be considered. It is important to ensure, however, that vaccination of 16–19 year olds would not decrease the benefit of vaccination among the elderly. To quantify the benefit of vaccinating 16–19 year olds, we added this age group to those to which vaccines are distributed in the final two months of the vaccination programs (see Table 1). Overall, we find that redistribution to include vaccination of 16–19 year-olds benefits the entire population. All age groups experience increments in percent reduction of COVID-19, from 10 to 65 percentage points (Fig. 6, right panel).

3.2.2. Restrictions in vaccine supply

Given restrictions in supply, and wanting to maximize the benefit of a vaccination program, it is necessary to quantify differences in outcome of programs that administer one dose to twice as many people as could be fully vaccinated (with 2 doses each). We now compare and contrast the two-dose, half target coverage (doses 28 days apart), and one-dose non-neutralizing programs studied here. Fig. 3 demonstrates that under the vaccine parameters assumed, which are representative of the Moderna, Pfizer and AstraZeneca vaccines, a one-dose non-neutralizing vaccine (orange) will outperform a two-dose vaccine half-coverage (black) program in the short-term, and even some months after the vaccination program has ended (July 2021). We observe, thus, that given anticipation of limitations in vaccine procurement (i.e., shipment or production delays) to accomplish a two-dose full target coverage vaccination program with 28 days between doses, it seems appropriate to administer one dose of vaccine, and allow for a delay in the second dose until shipments can be procured. Early into the vaccination program, Canadian officials opted to modify the program to allow for a delayed second dose. These results justify this early choice.

3.3. COVID-19 resurgence in fall 2021

Figs. 3 and 5 (and Supplementary Figures S3 and S5) show that a resurgence of COVID-19 infection may occur in Fall 2021. We note that the magnitude of a resurgence will depend on many parameters, including, vaccine uptake (in all age groups), public health mitigation and relaxation during and beyond Summer 2021, population compliance to PPE wearing and social distancing, testing rates, contact tracing levels, the transmissibility of the prevalent variant strains at the time, and the waning rate of immunity. Therefore, the forecasting for Fall 2021 is very complex. We leave such considerations for future work.

3.4. Robustness of results

We consider the effects of variations in the waning rate, susceptibility, fitting proportion for I_3, and vaccine characteristics on the overall vaccine program outcome in the Supplementary Material. Again, we find that delivery of a first dose to a larger number of people (which will be followed by a delayed second dose) can provide a better outcome than delivering a two-dose regimen with standard timing between doses to half as many people. We also find that Scenario 1 benefits older age groups, and thus this scenario provides the greatest reduction in severe infection.

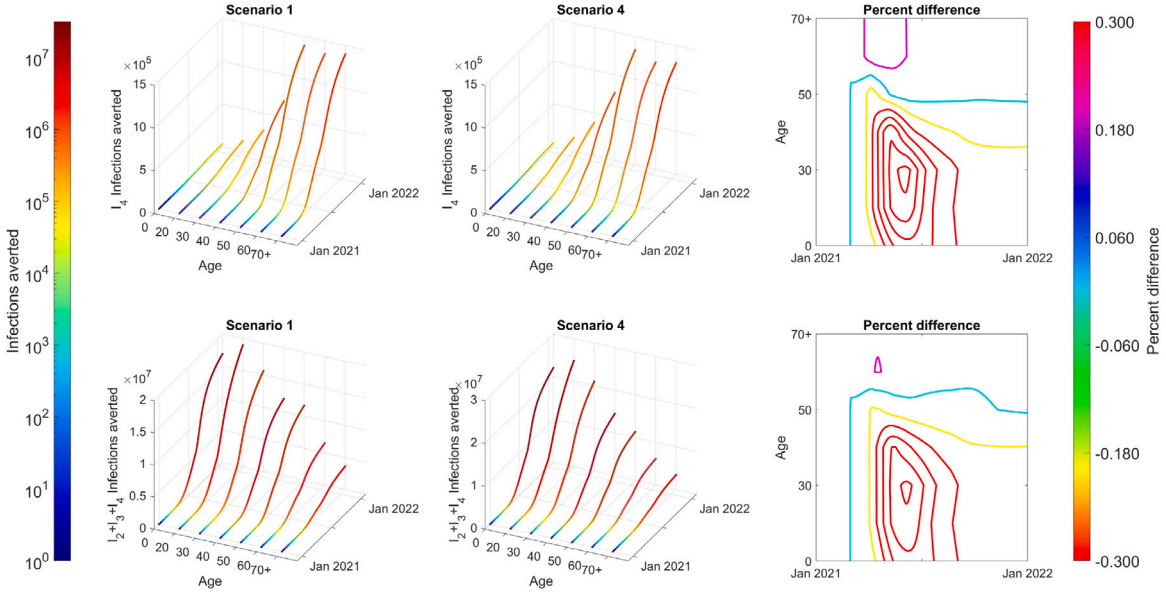

Fig. 4. Infections averted: Scenarios 1 and 4, two-dose, full target coverage, with 16 weeks between doses. Infections averted in I_4 (top row) and $I_2 + I_3 + I_4$ (bottom row) given Scenarios 1 (left column) and 4 (middle column). The percent difference between Scenarios 1 and 4, calculated as ([Scenario 1 infections averted] - [Scenario 4 infections averted])/[Scenario 1 infections averted] is shown (last column). Here, infections averted are determined by the difference between cumulative incidence with no vaccine and under the vaccination program considered. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

We developed a model of COVID-19 infection by age that includes the waning and boosting of immunity against SARS-CoV-2 due to infection or vaccination. The model, which is first evaluated over different mitigation and vaccination phases (from January 2020 to April 2021) of the COVID-19 epidemic in Canada, is used to study various COVID-19 vaccination programs (National Advisory Council on Immunization Canada, 2020), including administration of one and two doses and different scenarios that involve prioritization of certain groups. As per 2020–2021 public health programming, we implement the vaccination programs using the assumed mitigation matrix Phase 3 that involves moderate relaxation of restrictions on school, work and other contacts (see Supplementary Material, Demographic Parameters), but additional changes in contact transmission using a linear factor reflecting the use of masks and other PPE, hand-washing, testing rate, contact tracing, and the increased transmissibility of variants of concern. Intuitively, we find that a one-dose neutralizing vaccine has the best outcome under each coverage program, Scenarios 1–4. Model results, however, can also be used to assess outcomes of programs that (1) provide one dose to twice as many people versus two doses to half as many, and (2) delays in providing the second dose of two-dose vaccines. Ultimately, given the parameters assumed here, representative of two-dose vaccines currently approved for use in Canada, we find that, if needed, delivery of one dose to a larger number of people can provide a slightly better outcome than delivering a two-dose program to half as many people, at least into the Fall of 2021. A sensitivity analysis considering different waning rates (ω), susceptibility (α), fitting proportion for κ, and vaccine parameters (see Table S4) show that our conclusions are robust. However, we recommend that delays in delivery of a second dose, when it comes available, should be minimized to realize the maximum benefit from a two-dose vaccination program. Ultimately, we find that the early decision of the Canadian government to allow 16 weeks between vaccine doses will achieve better outcomes than a one-dose non-neutralizing scenario, and a two-dose half coverage scenario with 28 days between vaccine doses.

During a vaccination program, compliance with physical/social distancing, use of masks and other PPE and other NPIs may wane. In current work, we are developing relaxation scenarios that will allow (a) certain economic sectors to be re-opened in stages, and (b) some relaxation in public health programming or PPE and/or other NPI compliance. Preliminary simulations show that mild relaxation too early can erode the gains from a vaccination program. Additionally, the existence and magnitude of a Fall 2021 resurgence depends on these factors. A study of relaxation and COVID-19 resurgence remains a course for immediate work.

Some models of the COVID-19 pandemic have incorporated the effects of waning immunity (Çenesiz and Guimarães, 2020; Anggriani et al., 2021; Lavine et al., 2021; Giannitsarou et al., 2020). To our knowledge, no other model of COVID-19 infection or vaccination considers differential immunity development after infection or vaccination with waning immunity and age structure. Our model can provide distributions of immunity by age before, during, and after a vaccination program. An added benefit thus lies in the utility of our model structure to permit studying vaccination programming that maximizes immunity generation and boosting in the population while minimizing severe COVID-19 illnesses and deaths. Additionally, it allows for better-informed estimates of the reproduction number. Studies of optimal vaccination programs and immunity distribution-informed reproduction numbers are planned.

CRediT authorship contribution statement

Lauren Childs: Developed the model, Conducted numerical simulations, Model analysis, Interpretation of results, Writing manuscript. **David W. Dick:** Conducted numerical simulations, Model analysis, Interpretation of results, Writing manuscript. **Zhilan Feng:** Developed the model, Model analysis, Interpretation of results, Writing manuscript. **Jane M. Heffernan:** Developed the model, Conducted numerical simulations, Model analysis, Interpretation of results, Writing manuscript. **Jing Li:** Developed the model, Conducted numerical simulations, Model analysis, Interpretation of results, Writing manuscript. **Gergely Röst:** Developed the model, Model analysis, Interpretation of results, Writing manuscript.

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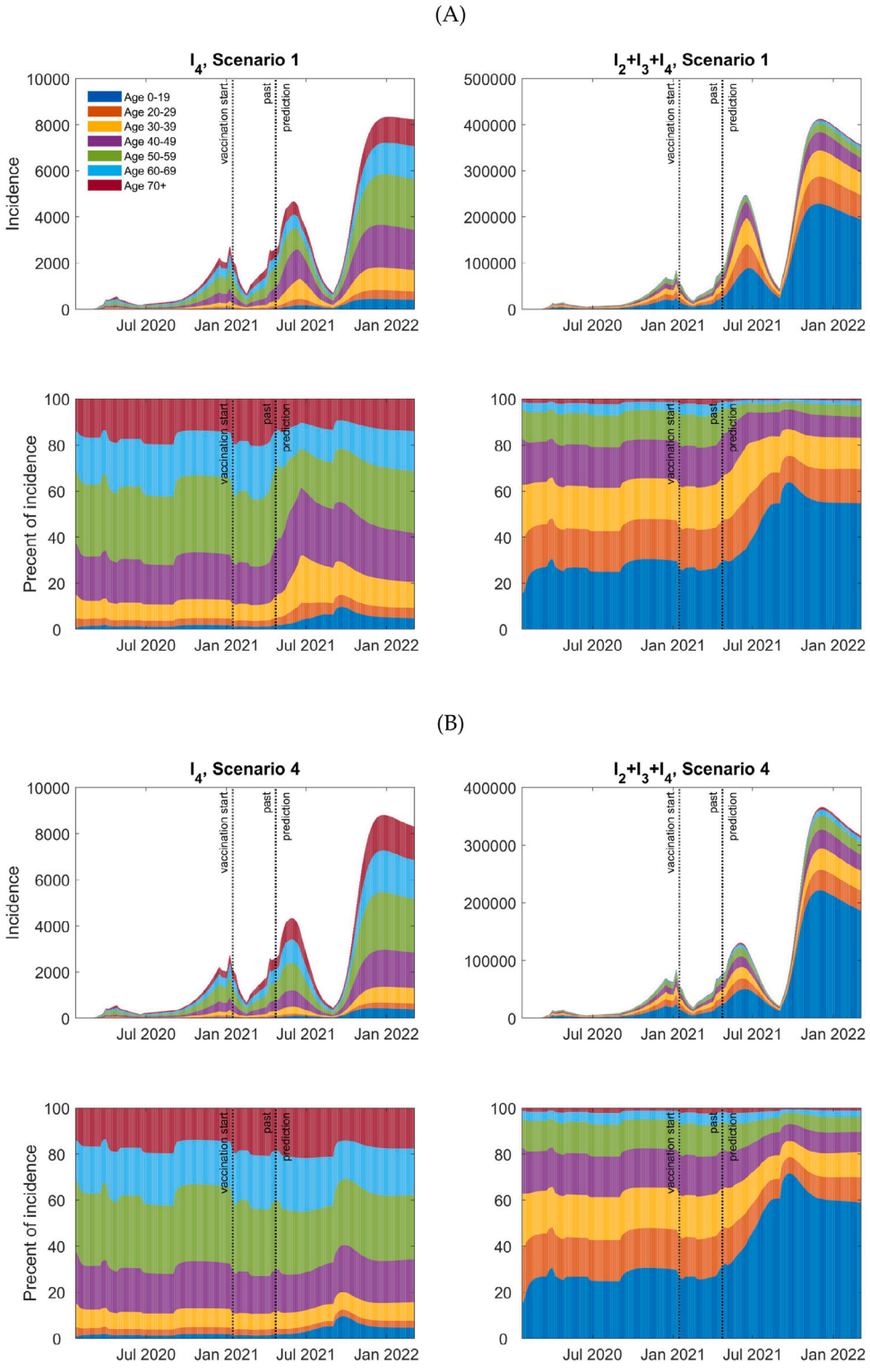

Fig. 5. Age distribution of daily incidence: two-dose, full target coverage with 16 weeks between doses. (panel A) Scenario 1. (panel B) Scenario 4. In both panels, we plot the daily incidence of I_4 and $I_2 + I_3 + I_4$ infections by age (top row), and by the percent in each group (bottom row).

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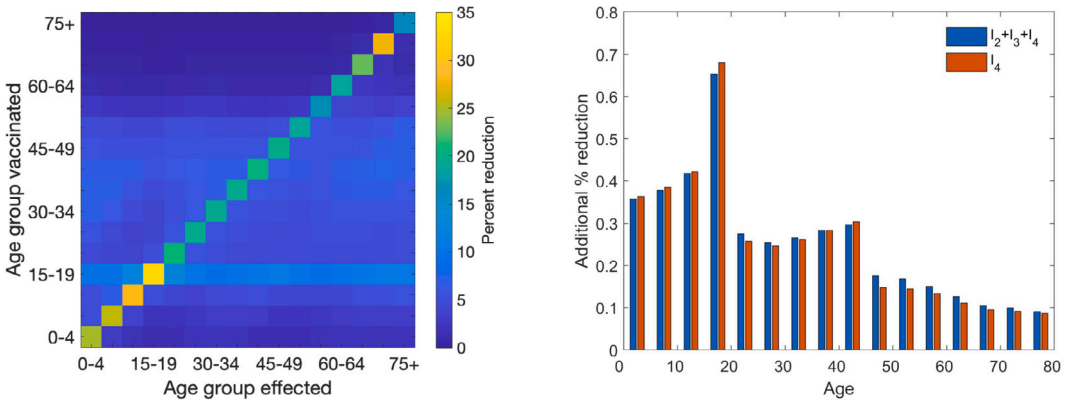

Fig. 6. Indirect effects of vaccination. (left) The percent reduction (color) in the number of severe infections for each age group (x-axis), given two-dose vaccination with 28 days separating doses, and two weeks until full realization of neutralizing immunity of one age group (y-axis). Vaccination rates are calculated so that roughly 0.5% of the Canadian population is vaccinated each month for six months (up to 3% coverage over 6 months) whereby all vaccinated individuals are taken from a single age group (y-axis). (right) The further reduction in infections of $I_2 + I_3 + I_4$ (blue bars) and I_4 (red bars) when including vaccination of 16–19 year-olds in the final two months of a two-dose full target coverage vaccination program with 16 weeks between doses. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Appendix A. Supplementary data

Supplementary material related to this article can be found online at https://doi.org/10.1016/j.epidem.2022.100583.

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