Modelling the impact of extending dose intervals for COVID-19 vaccines in Canada

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Abstract

Background: Dual dose SARS-CoV-2 vaccines demonstrate high efficacy and will be critical in public health efforts to mitigate the COVID-19 pandemic and its health consequences; however, many jurisdictions face very constrained vaccine supply. We examined the impacts of extending the interval between two doses of mRNA vaccines in Canada in order to inform deliberations of Canada's National Advisory Committee on Immunization.

Methods: We developed an age-stratified, deterministic, compartmental model of SARS-CoV-2 transmission and disease to reproduce the epidemiologic features of the epidemic in Canada. Simulated vaccination comprised mRNA vaccines with explicit examination of effectiveness against disease (67% [first dose], 94% [second dose]), hospitalization (80% [first dose], 96% [second dose]), and death (85% [first dose], 96% [second dose]) in adults aged 20 years and older. Effectiveness against infection was assumed to be 90% relative to the effectiveness against disease. We used a 6-week mRNA dose interval as our base case (consistent with early program rollout across Canadian and international jurisdictions) and compared extended intervals of 12 weeks, 16 weeks, and 24 weeks. We began vaccinations on January 1, 2021 and simulated a third wave beginning on April 1, 2021.

Results: Extending mRNA dose intervals were projected to result in 12.1-18.9% fewer symptomatic cases, 9.5-13.5% fewer hospitalizations, and 7.5-9.7% fewer deaths in the population over a 12-month time horizon. The largest reductions in hospitalizations and deaths were observed in the longest interval of 24 weeks, though benefits were diminishing as intervals extended. Benefits of extended intervals stemmed largely from the ability to accelerate coverage in individuals aged 20-74 years as older individuals were already prioritized for early vaccination. Conditions under which mRNA dose extensions led to worse outcomes included: first-dose effectiveness < 65% against death; or protection following first dose waning to 0% by month three before the scheduled 2nd dose at 24-weeks. Probabilistic

simulations from a range of likely vaccine effectiveness values did not result in worse outcomes with extended intervals.

Conclusion: Under real-world effectiveness conditions, our results support a strategy of extending mRNA dose intervals across all age groups to minimize symptomatic cases, hospitalizations, and deaths while vaccine supply is constrained.

Introduction

One year into the coronavirus disease 2019 (COVID-19) pandemic, several vaccines have been approved by regulatory bodies across the globe and recommended by national and international immunization technical advisory groups. Many countries face limited vaccine supplies as manufacturers ramp up capacity while periodically encountering lower production output and interrupted operations. With constrained supply in the early months of 2021, the government of Canada faced questions about how to best allocate available vaccines (which were all two-dose schedules) to meet the public health goal of minimizing serious illness and deaths while minimizing societal disruption as a result of the COVID-19 pandemic. Specifically, should faster vaccine coverage be pursued by extending the time to second dose in exchange for lower of protection with the first dose until the second dose is administered? The question reflects the need to balance individual protection and population impact, given that individuals also benefit from indirect protection when overall SARS-CoV-2 circulation is diminished. That is, an individual's probability of infection declines faster with higher coverage at a population-level. Canada's National Advisory Committee on Immunization (NACI) had previously recommended, for Pfizer, Moderna, and AstraZeneca vaccines, that "jurisdictions may consider delaying the second dose due to logistic or epidemiologic reasons until further supplies of the vaccine become available, preferably within 6 weeks of the first dose".[1] The Public Health Agency of Canada (PHAC) developed a mathematical model to explore COVID-19 vaccination strategies with longer extended intervals, which were notably being deployed in the province of Quebec and the United Kingdom.[2,3]

Benefits from different vaccination strategies (various extended interval or no delay) may be realized under different conditions such as different dosing intervals, epidemic scenarios, and assumptions about protection against disease, protection against infection and waning. Such data on vaccine performance continue to emerge with new trial data and real-world evidence. The objective of our study was to

examine the epidemiological impact of extending dose intervals for vaccination strategies that use mRNA vaccines in the context of constrained vaccine supply in Canada.

Methods

Model description

A deterministic compartment model was constructed to represent transmission of SARS-CoV-2 and effects of vaccination on symptomatic disease, hospitalizations, and deaths in the Canadian population excluding residents of long-term care homes. The modelled population was stratified into five-year age groups up to 75+ years, according to 2019 demographic estimates.[4] Upon acquisition of infection (Figure 1), individuals are initially in a non-infectious latent period after which they either develop asymptomatic infection (infectious) or symptomatic infection (an infectious period preceded by a pre-symptomatic infectious period). Symptomatic individuals may experience mild/moderate or severe disease with the latter receiving hospital care, where they ceased to be infectious.

Transmission occurred via contacts between susceptible and infectious individuals. Contacts and mixing among age groups were based on the projected daily contacts for Canada.[5] The impact of public health measures and physical distancing on transmission was modelled as a time-dependent parameter that modulated the force of infection. All asymptomatic and mild/moderate symptomatic infections were assumed to recover while a proportion of individuals with severe symptomatic infections died in hospital. We assumed that individuals with severe symptoms self-isolated until hospitalization and that severe cases did not die without being hospitalized. Transmission from severe symptomatic cases was modelled assuming contact rates in isolation were 25% of the projected home contacts. We assumed severe cases did not contribute to infection once in the hospital setting and did not distinguish between

critical cases in intensive care and those in in the hospital ward. We assumed there was no waning immunity following infection-acquired immunity.

Individuals were vaccinated if susceptible or recovered (no previous vaccination). Model assumptions for vaccine performance were established based on available effectiveness studies and consultation with PHAC vaccine experts. Vaccinations were modelled as two-dose regimens with vaccine effectiveness having a joint effect on the force of infection and probabilities of symptomatic disease, hospitalizations, and death. A schematic of the general model structure is shown in Figure 1. The full set of model equations and parameter values are listed in the Supplementary Materials. Model parameters for the transmission model were calibrated by Bayesian inference with prior beliefs and constraints in parameter space informed by literature sources (described in the Supplementary Materials). Key model parameters used in this analysis are listed in Table 1.

Vaccination

As of March 12, 2021, three COVID-19 vaccines had been approved for use in Canada: two mRNA vaccines that have demonstrated high efficacy against symptomatic disease and a viral vector vaccine with lower efficacy against symptomatic disease.[6–8] We considered vaccination programs consisting of an mRNA vaccine, which is the major vaccine in Canada, using different dose intervals (Table 2). In the base case, mRNA vaccines were modelled as a two-dose regimen with a 6-week interval between doses. We then examined the potential impact on symptomatic disease, hospitalizations, and deaths from extending the interval between doses for mRNA vaccines to 12, 16, and 24 weeks. In all scenarios, extended intervals for mRNA vaccines did not begin until March 1, 2021, prior to which a 6-week interval was maintained. Table 2 lists the definitions of the vaccination strategies in this analysis. mRNA vaccines were administered to all adults aged 20 years and older in descending order of age group until age 55 years and then administered proportionally to all individuals aged 20-54 years. We assumed first

vaccine coverage of 65% in individuals aged 20-64 years and 80% in ages 65 and older.[9] Once the vaccine coverage for first dose administration was reached in the age group (65% or 80%), the next prioritized age group would receive their first doses until coverage was reached. All susceptible and recovered individuals were eligible to be vaccinated, but individuals with active infections were not vaccinated. For simplicity, individuals who were infected between the first and second dose did not receive a second dose.

The vaccine effectiveness assumptions used in the model are listed in Table 3. We represented vaccine effectiveness as "leaky" protection in which all vaccinated individuals were subject to some residual risk of infection and symptomatic disease. This is in contrast to an "all-or-none" vaccine which confers complete protection to a proportion of vaccinated individuals. We used the same concept of vaccine effectiveness as Swan et al., in which the overall effectiveness against symptomatic disease (VE_{dis}) is a function of the risk of infection and risk of symptomatic disease conditional on infection.[10] Formally, this is represented as, $VE_{dis} = 1 - (1 - VE_{inf})(1 - VE_{symp})$, where VE_{inf} represents effectiveness against infection and VE_{symp} represents the effectiveness against symptomatic disease, conditional on infection. In addition, vaccine effectiveness against hospitalizations was modelled conditional on symptomatic disease ($VE_{hosp} = 1 - (1 - VE_{dis})(1 - VE_{hosp|disease})$ and vaccine effectiveness against deaths was modelled conditional on hospitalizations ($VE_{death} = 1 - (1 - VE_{hosp})(1 - VE_{death|hosp})$. We assumed that vaccine effectiveness against infections was 90% of the effectiveness against symptomatic disease. Recent real-world effectiveness estimates suggest that mRNA vaccines may be almost as effective at preventing infections as they are at preventing symptomatic disease.[11–16] First-dose effectiveness values (Table 3) were based on estimates from the United Kingdom, where an extended dose interval strategy was employed.[13,16–19] Second-dose effectiveness values (Table 3) were based on estimates from Israel, where >50% of the population had received two doses by early March.[20,21] For both vaccines, protection began 14 and 7 days after administrating the first and second doses, respectively.[6,7] We used a mild waning

effect in our base case analysis with an average duration of protection of two years under a single dose (protection dropped to 0% in 2 years or protected individuals became susceptible at a rate of 1% per week) and interrogated the impact of waning protection by examining durations of protection of 3-6 months in sensitivity analysis. We did not examine waning protection after the second dose due to the short time horizon used for this analysis (12 months). We also tested sensitivity of our results to first dose VE_{hosp} and VE_{death} values between 50% and 85% while holding second dose effectiveness at their base case values.

We examined the joint uncertainty in our vaccine effectiveness assumptions by running probabilistic simulations using 2,000 samples. The distributions used to draw random values represented our current belief about the range and distribution of likely effectiveness values (Table 3). We also ran probabilistic simulations to examine a conservative scenario of low effectiveness against infection.

Vaccine uptake was constrained by the available vaccine supply and the capacity to administer doses. The explicit supply schedule used in this analysis is provided in the Supplementary Materials and was based on public announcements.[22,23] We assumed that half the weekly supply would be reserved for the second dose with a 6-week interval[24] but extended intervals would allow for the entire weekly supply to be used. The maximum daily rate of administration was assumed to be 150,000 doses in January-March 2021 and increased to 350,000 in April 2021, 450,000 in May 2021, and 525,000 in June-December 2021. The rate of vaccination was explicitly constrained to be the lesser of the total number of doses available and the maximum daily rate of vaccination. We assumed that individuals eligible for their second dose would take priority over those waiting to receive their first dose.

Model scenarios

We calibrated our model to four calibration targets using data from Ontario, Canada, up to December 18, 2020: daily hospital admissions, daily deaths (excluding long-term care), cumulative hospitalizations

by age, and cumulative deaths by age (excluding long-term care). We defined an epidemic trajectory (in the absence of vaccinations) of decreasing infections (R_{eff} = 0.9) starting December 18, 2020 and simulated a third wave beginning on April 1, 2021 (R_{eff} = 1.2), using a time-dependent parameter representing the aggregate effect of different levels of public health measures and physical and social distancing on the force of infection. We did not simulate any additional interventions after the simulated third wave (i.e. modulate the time-dependent parameter) to change the epidemic trajectory (other than vaccinations). We then simulated vaccinations beginning on January 1, 2021 until January 1, 2022 and examined the impact of extending dose intervals for mRNA vaccines starting on March 1, 2021. We also simulated third waves of varying severity (R_{eff} = 1.1, R_{eff} = 1.3) to examine the role of different epidemic scenarios on our assumptions.

Results

Vaccine uptake

Figure 2 shows the progression of cumulative vaccinations with the first and second dose for the different vaccination strategies. Extension of the dose interval for mRNA vaccines resulted in accelerated coverage with the first dose in individuals aged 20-74 years with longer intervals having greater impact on younger individuals due to prioritization by age (Figure 3). Under the supply and rollout scenarios used in this model, extending the interval for mRNA vaccines from 6 weeks to 24 weeks advanced the time to coverage for all individuals aged 20 years and older by 33 days, from August 4, 2021 to July 2, 2021.

Population impact of extended dose intervals

Figure 4 and Table 4 show the cumulative incidence of symptomatic disease, hospitalizations, and deaths projected under different vaccination strategies. Under a base case mRNA dose interval of 6 weeks, the model projected cumulative incidence of symptomatic disease, hospitalizations, and deaths in the population of 5,387, 76.09, and 15.53 per 100,000 12 months after the start of the vaccination campaign. Compared to a 6 week interval for mRNA vaccines, dose intervals of 12 to 24 weeks resulted in 12.1-18.9% fewer cases of symptomatic disease (651-1,020 per 100,000), 9.5-13.5% (7.23-10.27 per 100,000) fewer hospitalizations, and 7.5-9.7% (1.16-1.51 per 100,000) fewer deaths. Figure 5 shows the reductions in symptomatic disease, hospitalizations, and deaths of extended intervals at 12 months compared to a 6-week interval from probabilistic simulations. Over the range of sampled values, symptomatic disease, hospitalizations, and deaths decreased in the population with longer intervals. None of the sampled scenarios resulted in worse outcomes compared to a 6-week interval.

In a scenario where the vaccines offered lower protection against infection (VE_{inf} = 50% VE_{dis}), a 6-week mRNA dose interval was projected to result in cumulative incidence of symptomatic disease, hospitalizations, and deaths in the population of 6,931, 94.39, and 18.68 per 100,000 at 12 months. Extending the mRNA dose interval resulted in 9.2-14.9% (639-1,030 per 100,000) fewer cases of symptomatic disease, 7.6-10.8% (7.17-10.2 per 100,000) fewer hospitalizations, and 6.3-8.1% (1.18-1.51 per 100,000) fewer deaths (Table 5). Probabilistic simulations of vaccine effectiveness values assuming a lower VE_{inf} (40-60% of VE_{dis}) showed extended intervals reduced symptomatic disease, hospitalizations, and deaths at 12 months compared to a 6-week interval (Supplementary Materials). None of the sampled values resulted in worse outcomes.

Subgroup analysis

Tables 6 and 7 show the cumulative incidence of symptomatic disease, hospitalizations, and deaths per 100,000 at 12 months by age group. The model projected the largest reductions in hospitalizations and deaths with a 24-week interval for individuals aged 20-74 and with a 16-week interval for individuals aged 75+ years. Longer intervals (16 or 24 weeks) were not optimal in reducing the less critical outcome of symptomatic disease, and a 24-week interval resulted in an increase in symptomatic disease in individuals aged 75+ years compared to a 6-week interval. A scenario of lower effectiveness against infection (VE_{inf} = 50% VE_{dis}) projected similar benefits of extended intervals but showed an increase in symptomatic disease in individuals aged 65-74 years compared to a 6-week interval. As all intervals reduced hospitalizations (i.e. severe infections) in the model, increases in symptomatic disease were mild/moderate cases.

Role of dose 1 effectiveness

Figure 6 shows the cumulative incidence of hospitalizations and deaths over a range of dose 1 VE_{hosp} and VE_{death} values, while VE_{dis} was held at 50% and dose 2 VE_{hosp} and VE_{death} were held at their base case values. Extending the dose interval was projected to reduce hospitalizations at VE_{hosp} values as low as 50% though benefits between a 12-week and 24-week interval became imperceptible at dose 1 VE_{hosp} of 50%. At dose 1 VE_{death} of 65% and 70%, extending the dose interval to 12-24 weeks was projected to increase deaths in the period up until approximately October 2021. However, all extended intervals decreased overall deaths by January 2022 at dose 1 VE_{death} of at least 65%. At a dose 1 VE_{hosp} less than 65%, 16-week and 24-week intervals resulted in an increase in overall deaths. Examination of additional third wave scenarios showed that extended intervals would reduce deaths at lower VE_{death} values if the

third wave was more severe than the base case (Supplementary Materials). Conversely, if the third wave was less severe than the base case higher VE_{death} values were needed to reduce deaths.

Role of dose 1 duration of protection

Figure 7 shows the cumulative incidence of symptomatic disease, hospitalizations, and deaths over a range of dose 1 durations of protection (three to six months). In all scenarios, extension of the dose interval reduced overall symptomatic disease and hospitalizations. In a scenario where the average duration of protection after dose 1 was three months, the model projected a small increase in deaths with a 24-week interval.

Discussion

Our model projected that longer mRNA dose intervals (between 12 and 24 weeks) would increase public health benefits in terms of fewer symptomatic cases, hospitalizations, and deaths while vaccine supply is constrained. Overall, our findings show that extending the dose interval conferred benefits to the population by accelerating coverage in individuals lower in the prioritization sequence (Figure 3). Concordant with this, our model also projected a diminishing rate of return in preventing serious outcomes as the dose interval became longer but higher risk age groups were already vaccinated with shorter intervals. It is important to note that these findings are presented in the context of an assumed third wave beginning in April 2021. If a third wave can be avoided or delayed, then the benefits of extending the dose interval would likely diminish.

Two conditions led to worse outcomes (increased deaths) with extending the mRNA dose interval. The first resulted from an average dose 1 duration of protection of three months (i.e. protection dropped to 0% in three months). At the time of this study, we were unaware of any indications that protection from

the first dose is waning at a rapid rate. The second resulted from a dose 1 effectiveness against death was less than 65% (that is, more than 32% less effective than dose 2). Recently, effectiveness estimates from the United Kingdom have reported dose 1 effectiveness against death of approximately 80% in adults ≥80 years of age and.[17,18] In addition, dose 1 effectiveness against hospitalizations, which were a condition for deaths in our model, have been reported at 70-80%, largely in elderly individuals.[17,19] Examination of additional third wave scenarios showed that, as the severity of our simulated third wave increased, extended intervals could confer benefits at lower effectiveness values as individuals with longer wait times for vaccines faced increasing cumulative risks of infection and onward transmission as well as severe outcomes. Conversely, as the severity of the simulated third wave decreased, extended intervals required higher effectiveness against death after the first dose to reduce deaths as there are fewer deaths to be prevented in a milder resurgence (Supplementary Materials). While the third wave scenarios are not forecasts of how the epidemic will necessarily unfold in Canada, they illustrate how extended intervals provide a strategy to reduce morbidity and mortality when there is an expectation of increasing risks of infection and severe outcomes in the short term. Our model findings can also be extended to other dual dose vaccines such as viral vector vaccines, which have shown early indications of similar performance against severe outcomes.[17,19] Although our findings reflect population-level effects, it is important to consider the impact of extending the dose interval in subgroups for whom the vaccine may be less effective, such as immunosuppressed individuals.[25,26]

The influence of first-dose effectiveness and duration of protection have similarly been highlighted by other vaccine models that compared extended dosing intervals to no delay for mRNA-vaccination strategies,[27,28] as well as vaccine models that compared the use of different proportions of the vaccine supply for extended dosing strategies.[29] Extended intervals up to 24 weeks were preferred given high first dose effectiveness against disease (Moghadas et al: 80%[28]; Jurgens and Lackner: 46.5%[27]), or given limited waning (greater than 18-week duration of protection when first dose effectiveness was low[28]; up

to ~10% waning per month[27]). Using a greater proportion of the supply for extended dosing strategies was preferred even with extreme waning assumptions (e.g., protection drops to zero within 6 weeks of not receiving second dose).[29] However, we note that these models focused on effectiveness against infection and/or disease as data on effectiveness against other outcomes were limited at the time of those studies.

There are some limitations to the present study. First, our model stratified risk by age and was used to inform broad population-based vaccination strategies but was not designed to examine other high-risk groups such as immunocompromised individuals for whom extended intervals may not be an optimal strategy. Second, we did not consider long-term implications of immune responses, vaccine escape, and variants of concern. However, the third wave simulated in our model and our sensitivity analyses could be considered as a proxy for variant of concern scenarios with higher transmission rates, variable vaccine effectiveness or waning protection. Our sensitivity analyses can inform ongoing evaluation of extended intervals if effectiveness begins to diminish or waning protection accelerates. In addition, we used a simplistic epidemic scenario and did not simulate scenarios of dynamic public health measures that may be deployed to confront a third wave or any subsequent resurgences following implementation of additional public health measures.

Our model adds to the current literature examining different mRNA dose interval strategies with explicit consideration of real-world effectiveness against symptomatic disease, hospitalizations and death. Strategies of extended intervals were examined in the context of the early COVID-19 vaccination campaign in Canada. Further, our model findings can be used to inform ongoing monitoring of extended interval strategies as effectiveness data continue to unfold.

Conclusion

In conclusion, our modelling is generally consistent with other models, supporting the extension of dose intervals across all age groups for population benefit during a period of constrained supply with a largely un-vaccinated population. Under our base-case scenario and in most sensitivity analyses, extended intervals will reduce symptomatic disease, hospitalizations, and deaths while vaccine supply is constrained.

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Tables

Table 1. Key model parameters and vaccine characteristics

Parameter	**Value**	**Source/Rationale**
Transmission coefficient (β)	0.0225	Calibrated
Latent period (1/ρ), days	3.96	Calibrated, informed by Zhao et al.[30]
Pre-symptomatic period ($1/\delta_p$), days	2.48	Calibrated, informed by He et al.[31]
Mild/moderate symptom onset to recovery (1/γ), days	5.11	Calibrated
Severe symptom onset to hospitalization ($1/\delta_x$), days	5.70	Calibrated, informed by PHAC Weekly Epidemiological Report 17 January to 23 January 2021[32]
Length of hospital stay, non-survivors ($losd_h$)	19.84	Calibrated, informed by CIHI[33]
Probability of severe/hospitalization | infected (κ)	0-19: 0.0013 20-29: 0.0042 30-39: 0.0079 40-49: 0.0108 50-59: 0.0194 60-69: 0.0602 70-74: 0.1093 75+: 0.5298	Calibrated
Probability of death | hospitalized	0-19: 0.0064 20-29: 0.0180 30-39: 0.0614 40-49: 0.0767 50-59: 0.1880 60-69: 0.2273 70-74: 0.4055 75+: 0.5268	Calibrated
Time to effect, first dose (days)	14	Baden et al.[6] Polack et al.[7]
Time to effect, second dose (days)	7	Baden et al.[6] Polack et al.[7]
Duration of vaccine protection after first dose (years)	2	Assumption

Table 2. Vaccination strategies using different mRNA dose intervals

Strategy	**Dose interval** Sequence: 75+, 70-74, 65-69, 60-64, 55-59, 20-54
mRNA6	6-week interval
mRNA12	12-week interval
mRNA16	16-week interval
mRNA24	24-week interval

Table 3. Vaccine effectiveness assumptions

Vaccine effectiveness	**Base case value (range for probabilistic analysis)**	**Distribution (for probabilistic analysis)**
VE Infection	90% x VE Disease (80-95%)	Uniform (0.8, 0.95)
VE Infection (conservative)	50% x VE Disease (40-60%)	Uniform (0.4, 0.6)
VE Disease Dose 1, <65 years	67% (48-79%)[13]	Beta (22.18, 11.56)
VE Disease Dose 1, 65+ years	58% (36-71%)[17]	Beta (16.28, 12.79)
VE Disease Dose 2, 20+ years	94% (87-98%)[20,21]	Beta (63.27, 4.13)
VE Hospitalization Dose 1, 20+ years	80% (70-85%)[16,17,19]	Beta (84.85, 22.52)
VE Hospitalization Dose 2, 20+ years	96% (95-97%)[20]	Beta (2888.52, 121.46)
VE Death Dose 1, 20+ years	85% (75-92%)[17,18]	Beta (55.59, 9.99)
VE Death Dose 2, 20+ years	Assumed same value as Dose 2 VE Hospitalization	

Table 4. Cumulative incidence of symptomatic disease, hospitalizations, and deaths per 100,000 at 12 months when VE_{inf} = 90% VE_{dis}. Relative reductions in parentheses.

Program Name	Symptomatic disease	Hospitalizations	Deaths
mRNA6	5,387 (Ref)	76.09 (Ref)	15.53 (Ref)
mRNA12	4,736 (12.1%)	68.86 (9.5%)	14.37 (7.5%)
mRNA16	4,571 (15.2%)	67.34 (11.5%)	14.15 (8.9%)
mRNA24	4,368 (18.9%)	65.82 (13.5%)	14.02 (9.7%)

Table 5. Cumulative incidence of symptomatic disease, hospitalizations, and deaths per 100,000 at 12 months when VE_{inf}=50% VE_{dis}. Relative reductions in parentheses.

Program Name	Symptomatic disease	Hospitalizations	Deaths
mRNA6	6,931 (Ref)	162.01 (Ref)	33.93 (Ref)
mRNA12	6,292 (9.2%)	87.22 (7.6%)	17.50 (6.3%)
mRNA16	6,095 (12.1%)	85.27 (9.7%)	17.23 (7.8%)
mRNA24	5,902 (14.9%)	84.19 (10.8%)	17.17 (8.1%)

Table 6. Cumulative incidence of symptomatic disease, hospitalizations, and deaths per 100,000 by age group at 12 months when VE_{inf}=90% VE_{dis}. Relative reductions in parentheses. Bolded cells indicate the strategy with the largest reductions in outcomes for each age group.

Age group	Strategy	Symptomatic disease	Hospitalizations	Deaths
75+	mRNA6	543.25 (Ref)	276.97 (Ref)	117.05 (Ref)
	mRNA12	**538.32 (9.1%)**	263.79 (4.8%)	110.30 (5.8%)
	mRNA16	546.46 (5.9%)	**262.72 (5.1%)**	**109.05 (6.8%)**
	mRNA24	559.11 (-2.9%)*	265.42 (4.2%)	109.44 (6.5%)
65-74	mRNA6	1,476.92 (Ref)	115.24 (Ref)	26.90 (Ref)
	mRNA12	**1,438.94 (2.6%)**	107.16 (7.0%)	24.73 (8.1%)
	mRNA16	1,447.70 (2.0%)	106.86 (7.3%)	24.71 (8.1%)
	mRNA24	1,446.46 (2.1%)	**105.26 (8.7%)**	**24.19 (10.1%)**
55-64	mRNA6	2,961.92 (Ref)	99.33 (Ref)	13.54 (Ref)
	mRNA12	2,693.64 (9.1%)	89.37 (10.0%)	12.17 (10.1%)
	mRNA16	2,617.86 (11.6%)	86.36 (13.1%)	11.75 (13.2%)
	mRNA24	**2,541.40 (14.2%)**	**83.76 (15.7%)**	**11.40 (15.8%)**
40-54	mRNA6	6,030.52 (Ref)	82.99 (Ref)	6.69 (Ref)
	mRNA12	5,180.47 (14.1%)	71.12 (14.3%)	5.76 (13.9%)
	mRNA16	4,981.75 (17.4%)	68.30 (17.7%)	5.54 (17.2%)
	mRNA24	**4,712.7 (21.9%)**	**64.69 (22.1%)**	**5.26 (21.4%)**
20-39	mRNA6	5,839.58 (Ref)	34.52 (Ref)	0.91 (Ref)
	mRNA12	5,030.73 (13.9%)	29.61 (14.2%)	0.78 (14.3%)
	mRNA16	4,817.54 (17.5%)	28.34 (17.9%)	0.75 (17.6%)
	mRNA24	**4,568.67 (21.8%)**	**26.87 (22.2%)**	**0.71 (22.0%)**

*Increase in cumulative incidence at 12 months compared to mRNA6.

Table 7. Cumulative incidence of symptomatic disease, hospitalizations, and deaths per 100,000 by age group at 12 months when VE_{inf}=50% VE_{dis}. Relative reductions in parentheses. Bolded cells indicate the strategy with the largest reductions in outcomes for each age group.

Age group	Strategy	Symptomatic disease	Hospitalizations	Deaths
75+	mRNA6	682.81 (Ref)	341.68 (Ref)	140.62 (Ref)
	mRNA12	**673.43 (1.4%)**	325.55 (4.7%)	132.68 (5.6%)
	mRNA16	680.13 (0.4%)	**323.23 (5.4%)**	**130.87 (6.9%)**
	mRNA24	702.46 (-2.9%)*	330.22 (3.4%)	132.33 (5.9%)
65-74	mRNA6	1,804.03 (Ref)	137.27 (Ref)	31.19 (Ref)
	mRNA12	1,819.96 (-0.9%)*	133.80 (2.5%)	30.03 (3.7%)
	mRNA16	**1,815.42 (-0.6%)***	132.91 (3.2%)	30.09 (3.5%)
	mRNA24	1,844.66 (-2.2%)*	**132.33 (3.6%)**	**29.47 (5.5%)**
55-64	mRNA6	3,833.59 (Ref)	127.87 (Ref)	17.08 (Ref)
	mRNA12	3,568.23 (6.9%)	117.44 (8.2%)	15.64 (8.4%)
	mRNA16	3,483.86 (9.1%)	114.02 (10.8%)	15.15 (11.3%)
	mRNA24	**3,421.87 (10.7%)**	**111.64 (12.7%)**	**14.82 (13.2%)**
40-54	mRNA6	7,532.01 (Ref)	102.25 (Ref)	8.11 (Ref)
	mRNA12	6,667.78 (11.5%)	90.05 (11.9%)	7.15 (11.8%)
	mRNA16	6,417.77 (14.8%)	86.59 (15.3%)	6.88 (15.2%)
	mRNA24	**6,130.28 (18.6%)**	**82.75 (19.1%)**	**6.60 (18.6%)**
20-39	mRNA6	7,338.11 (Ref)	42.81 (Ref)	1.11 (Ref)
	mRNA12	6,492.86 (11.5%)	37.65 (12.1%)	0.98 (11.7%)
	mRNA16	6,226.69 (15.1%)	36.10 (15.7%)	0.94 (15.3%)
	mRNA24	**5,983.07 (18.5%)**	**34.60 (19.2%)**	**0.90 (18.9%)**

*Increase in cumulative incidence at 12 months compared to mRNA6.

Figures

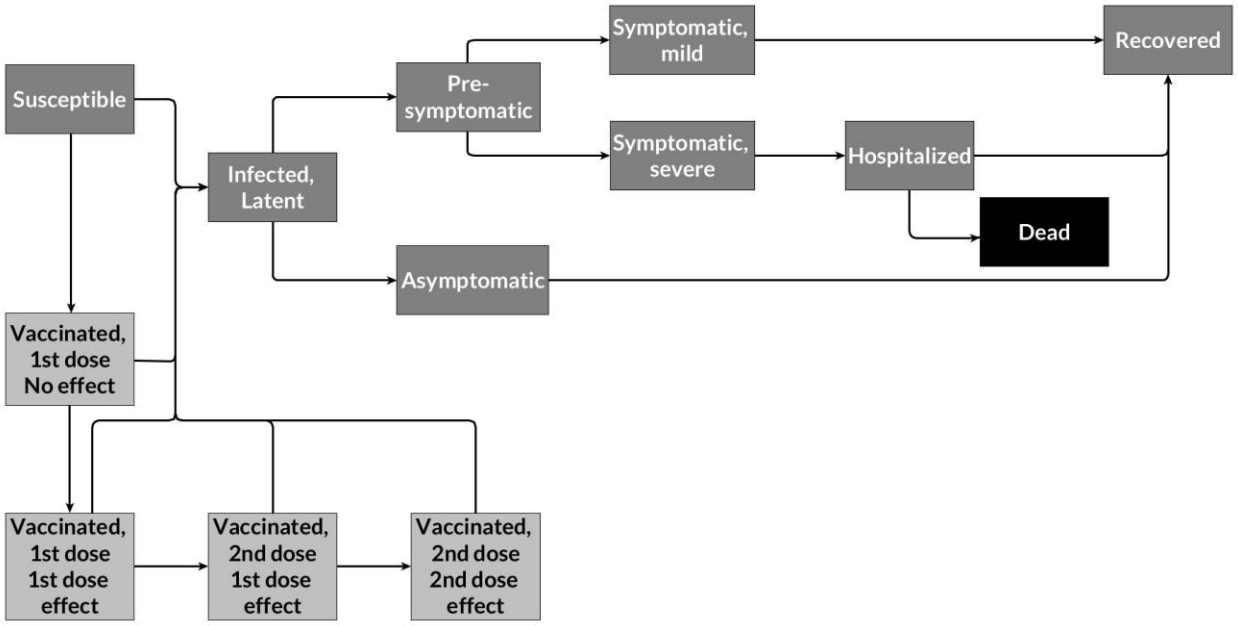

Figure 1. Schematic of general model structure.

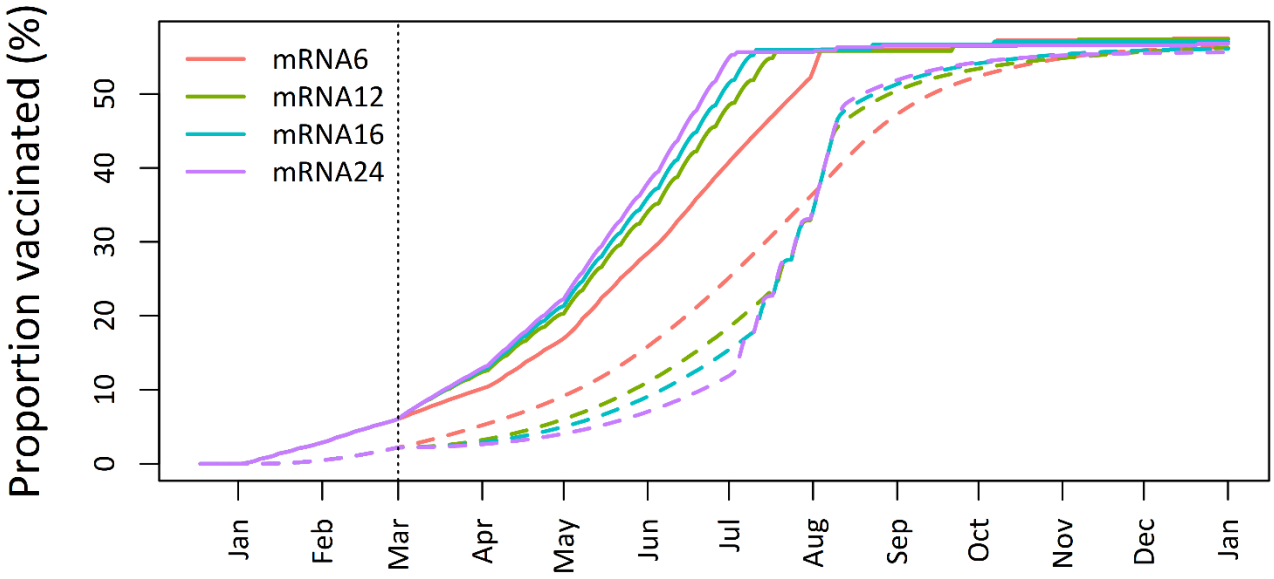

Figure 2. Cumulative vaccinations. Dashed lines represent second dose. Vertical dotted line represents beginning of extended intervals for mRNA vaccines.

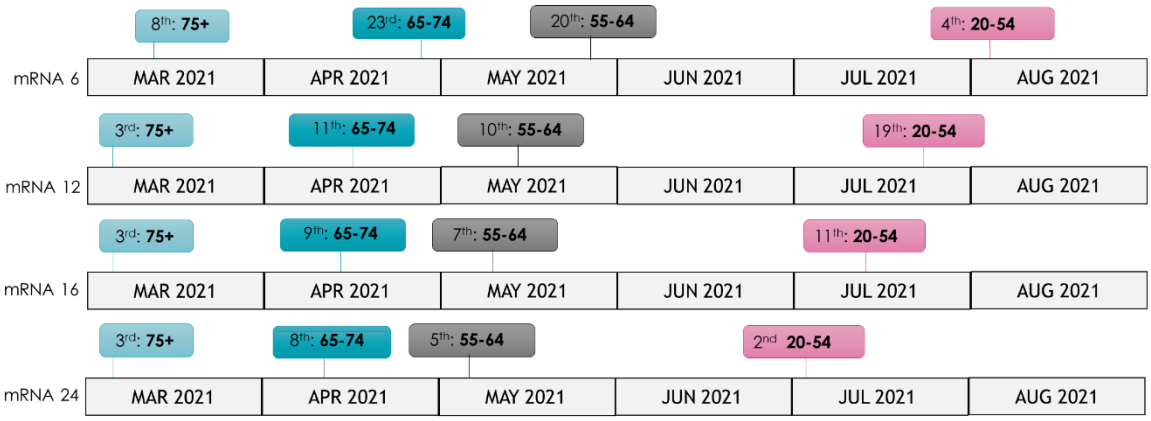

Figure 3. Time to coverage (65% in 20-64 years and 80% in 65+ years) with first dose.

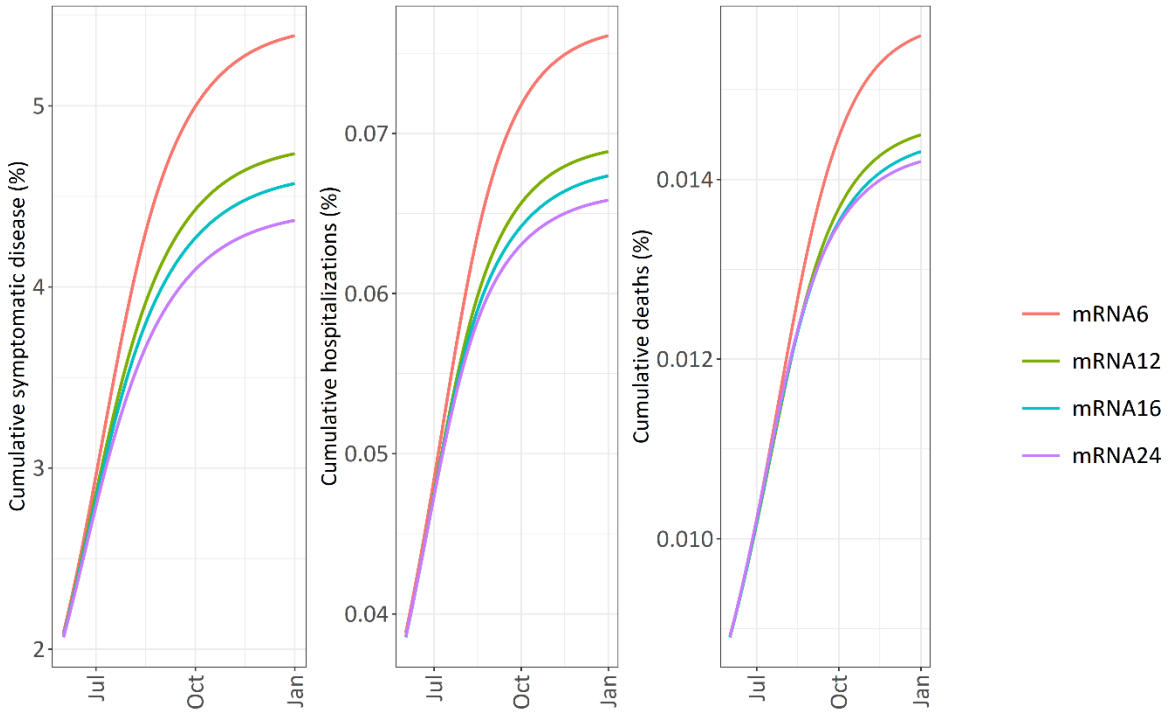

Figure 4. Cumulative incidence of symptomatic disease, hospitalizations, and deaths starting six months after beginning of vaccination campaign.

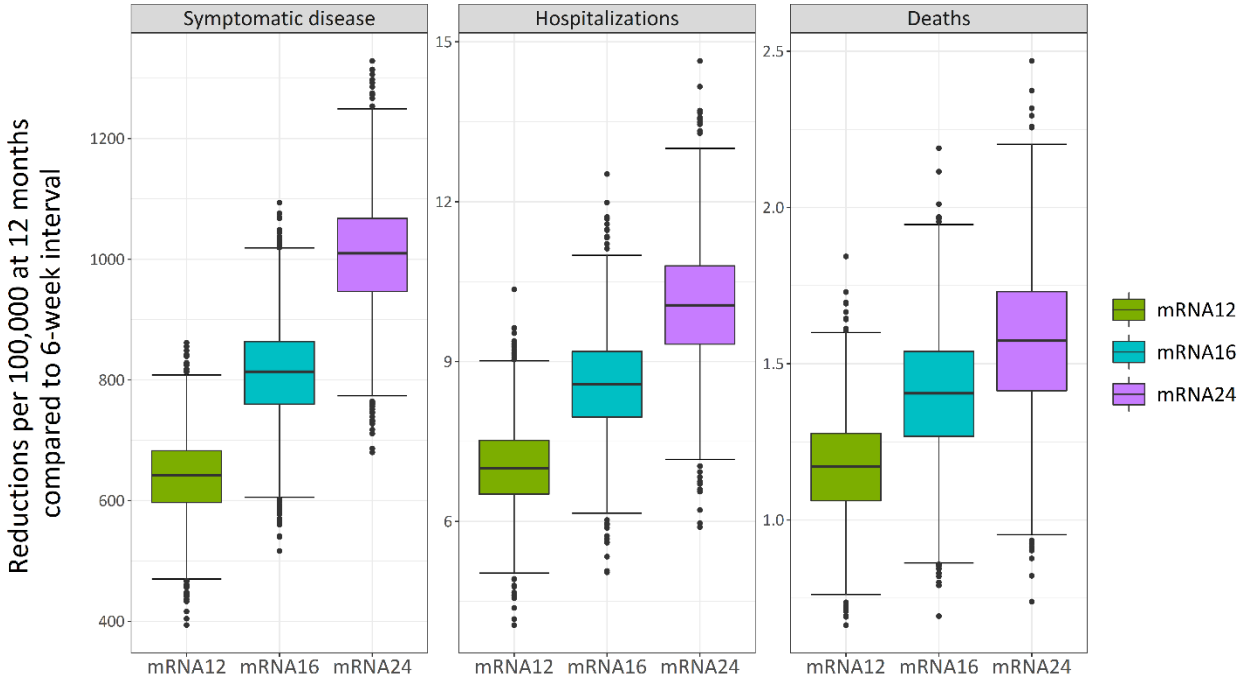

Figure 5. Reductions in symptomatic disease, hospitalizations, and deaths at 12 months compared to a 6-week interval (mRNA6) from probabilistic simulations of 2,000 samples. VE_{inf} = 80-95% VE_{dis}.

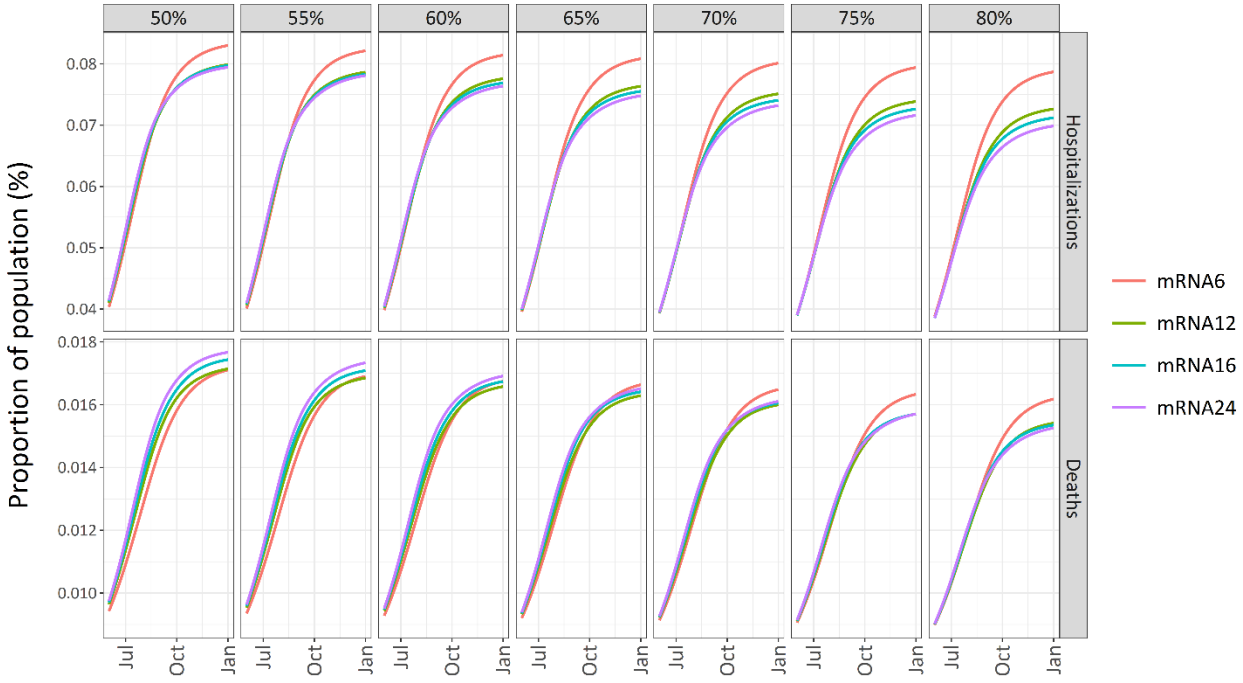

Figure 6. Sensitivity analysis: cumulative incidence of hospitalizations and deaths over different dose 1 VE_{hosp} and VE_{death} values starting six months after the beginning of the vaccination campaign. VE_{inf} = 90% VE_{dis} and VE_{dis} = 50%.

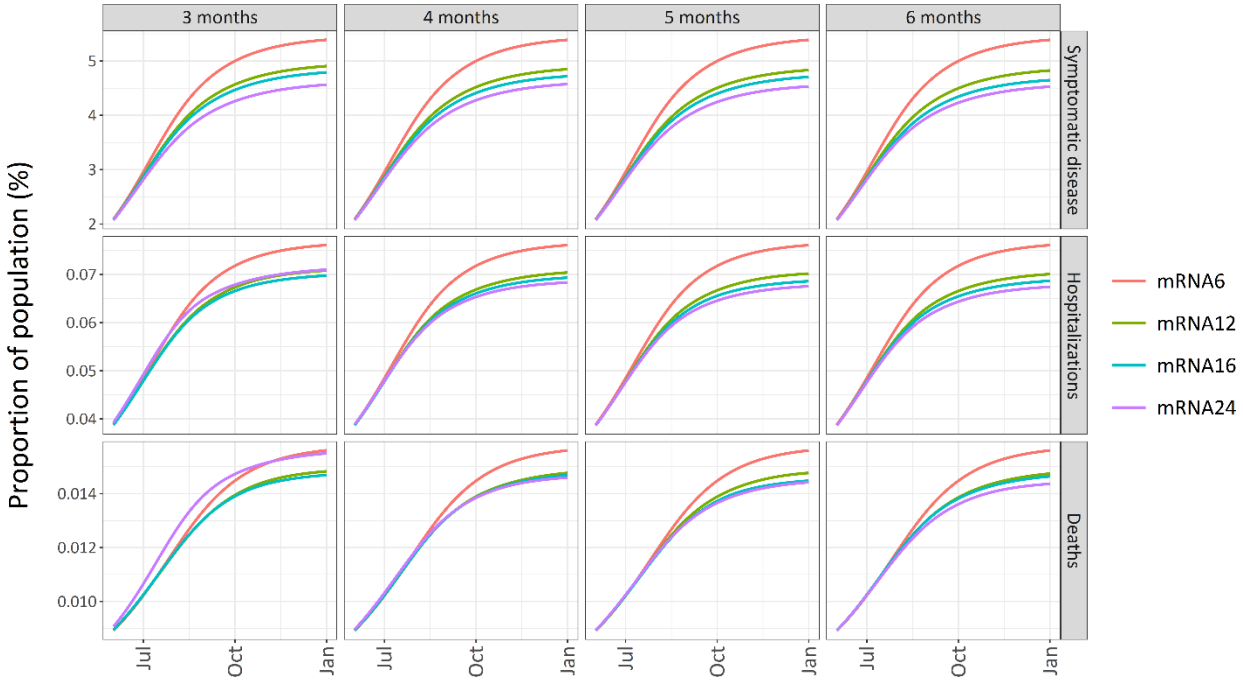

Figure 7. Sensitivity analysis: cumulative incidence of symptomatic disease, hospitalizations, and deaths over different durations of protection after dose 1.