National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

The expected outcome of COVID-19 vaccination strategies

Colophon

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Contents

Samenvatting

De verwachte uitkomsten van COVID-19 vaccinatie strategieën

COVID-19 is een ziekte die wordt veroorzaakt door een infectie met het SARS-CoV-2-virus. Dit coronavirus verspreidt zich sinds 2020 in Nederland. Er zijn vaccins ingekocht om iedereen in Nederland die in aanmerking komt te vaccineren tegen COVID-19. Het ministerie van Volksgezondheid, Welzijn en Sport (VWS) heeft de Gezondheidsraad gevraagd adviezen te geven over de COVID-19-vaccinatie. Om de Gezondheidsraad en VWS hierbij te ondersteunen heeft het RIVM-berekeningen gedaan over de ziektelast door COVID-19 en de verwachte impact van vaccinatie tegen COVID-19 op deze ziektelast. In deze publicatie staan de uitkomsten van deze berekeningen. Deze publicatie is een aanvulling op een eerder briefrapport van het RIVM (rapportnummer 2020-0151).

De ziektelast per persoon door COVID-19 neemt scherp toe met hogere leeftijd. Het RIVM heeft berekend wanneer het voor de volksgezondheid voordelig kan zijn om een tweede dosis van een COVID-19 vaccin uit te stellen. Zodat meer mensen eerder hun eerste dosis kunnen krijgen. De berekening laten zien dat vaccinatie van oudere leeftijdsgroepen (60 jaar en ouder) veel ziektelast voorkomt. Diverse mogelijkheden voor leeftijdsvolgorde bij het vaccineren van de gezonde 18 tot 60-jarigen voorkomen een vergelijkbare ziektelast, bij het huidige leveringsschema. Het RIVM bekijkt de vaccinatie in context van andere maatregelen tegen COVID-19, zoals grootschalig testen.

Omdat de beschikbare informatie over de werkzaamheid en de beschikbaarheid van vaccins tegen COVID-19 snel kan veranderen is bij elke analyse de datum aangegeven. Als er nieuwe informatie is, kunnen de analyses aangepast worden en verschijnen er mogelijk nieuwe, geactualiseerde versies van dit overzicht.

Abstract

COVID-19 is a disease caused by infection with the SARS-CoV-2 virus. This new coronavirus has been spreading in the Netherlands since 2020. Vaccines have been purchased to vaccinate everyone in the Netherlands who is eligible to be vaccinated against COVID-19. The Ministry of Health, Welfare and Sport (VWS) has asked the Health Council of the Netherlands to advise on COVID-19 vaccination. To support the Health Council and VWS in this regard, RIVM has calculated the disease burden due to COVID-19 and assessed the expected impact of vaccination against COVID-19. This publication contains the results of these calculations. This publication is an addition to an earlier RIVM report (report number 2020-2015).

The disease burden per capita due to COVID-19 increases sharply with higher age. The RIVM calculated when it pays off to defer a second dose of a COVID-19 vaccine such that more persons can receive their first dose earlier, when adopting a public health point of view. The RIVM shows that vaccination in the older age groups (60 years and older) prevents a high burden of disease. Vaccination programs with various possible ordering of age groups of healthy 18 to 60 year olds prevent a comparable disease burden. The RIVM evaluates vaccination in the context of other control measures such as large-scale testing.

Because of a rapid change in information on the efficacy and availability of vaccines against COVID-19, each analysis is indicated with a date. When new information becomes available, the analyses could be adjusted and new, updated versions of this report might appear.

1 Introduction

In this report we present the expected outcome of COVID-19 vaccination strategies in The Netherlands. The outcome will typically include the number of infections, cases, hospitalizations, or ICU-admissions. Other outcomes, relating to number of deaths, life years lost, or disability-adjusted life years (DALY's), are also reported for some analyses. We assume, unless stated otherwise, that an objective of vaccination is to minimize the burden of disease (measured in DALY's). We realize that for the cabinet other outcomes relating to the burden on the health care system (length of stay, number of beds occupied) are also relevant, and that outcomes relating to people with a profession in critical sectors might be weighed differently. The outcome of a COVID-19 vaccination strategy will depend crucially on the use of non-pharmaceutical control measures and testing. Available information changes rapidly, whether it is information on the COVID-19 epidemic, the effectiveness of the vaccines, or the availability of the vaccines. We will indicate for each part of our report when it has last been updated.

2 What is the disease burden of COVID-19 by age-group and occupation category?

Analysis updated, as of 15 Feb 2021

Disease burden in disability-adjusted life-years (DALYs) is already routinely calculated, based on notified cases and deaths in OSIRIS and hospital admission and ICU admission data provided by NICE. In this report we extend these previous estimates [1, 2] to account for under ascertainment in notifications, and we estimate disease burden as of 31 Dec 2020. We stratify disease burden estimates by age-group and by occupation category, and present both absolute DALYs and DALYs/100,000 persons (a measure of relative burden, that adjusts for denominator population size). For the per-capita DALY estimates stratified by occupation category, estimates of the denominator – the total number of persons in each category (from CBS), stratified by age-group – are required. As the available information from CBS [3] contains the number of persons in each occupation per 10-year age-group (15-25, ... 65-75) only, assumptions were required to map the 10-year denominator age-groups to 5-year age-groups (see below). In a supplementary analysis, we explore the impact on DALYs when the expected morbidity contributed by post-acute COVID-19 health outcomes is included. This is preliminary work based on very limited data sources, and so results should be considered as approximate only.

2.1 Burden stratified by age-group

For the methodology used for disease burden estimation, see [1, 2]. Briefly, the clinical pathway progression is as follows: confirmed SARS-CoV-2 positive cases who develop mild symptomatic COVID-19 can progress to moderate disease (requiring hospital admission), and then to severe disease (requiring ICU admission). Death due to COVID-19 is assumed possible following any of these three disease states (see Table 1). We carry out two sets of analyses: for the period from the start of the epidemic until 24 Sept 2020 (representing the period covered by the PICO3 serosurvey, and coincidentally before the second wave fully took off: 2145 positive cases were notified – and more relevant for disease burden, 7 COVID-19 deaths – on 24 Sept), and for the period from the start of the epidemic until 31 Dec 2020.

2.1.1 Analysis period until 24 September 2020

The cumulative incidence of Mild infections was based on age-group specific seroprevalence from the PICO3 study conducted between 22 Sept and 23 Nov 2020 (the 'index' date of 25 Sept was selected as 90% of participants responded by 9 Oct, with 14 days assumed for development of an IgG response), weighted to adjust for survey representativeness and seroreversion (Figure 1) and the estimated age-group specific symptomatic proportion. The latter was derived using PICO2 study data (collected in June/July 2020), where 'symptomatic' is defined according to the ECDC case definition (fever and/or cough and/or shortness of breath and/or loss of smell/taste), and where the observed proportion of seropositive persons reporting symptoms is

adjusted for reported symptom occurrence among seronegative persons; for further details see [4]. The age-aggregated symptomatic proportion using this approach and PICO2 data was estimated at 63%.

The cumulative incidence of infection, and of symptomatic infection (SI), with SARS-CoV-2 was estimated at 872,700 and 323,900, respectively (Figure 6). This entails that overall ascertainment of estimated cumulative SI incidence by the total number of OSIRIS notifications in this period (n=107,662) was 33%. DALY estimates, as calculated using the approach detailed in [1, 2], are shown in Figure 7. Very little of the total COVID-19 disease burden (60,900 DALYs; 95% CI: 59,100–62,700) was contributed by morbidity (i.e., YLD accounted for approximately 1.0% of the total DALYs). The highest absolute burden in a given age-group was observed for 75-79 years.

2.1.2 Analysis period until 31 Dec 2020

For this period, as no seroprevalence data an alternative (provisional) approach to estimating cumulative SI incidence for the period 25 Sept through 31 Dec 2020 was required. We pooled nine estimates of the ascertainment of all infected persons by notified cases based on population-level survey data from England (nine occasions when members of a community cohort underwent virological testing, conducted by the ONS between 18-24 Sept and 22-28 Nov 2020). Using these data entailed making two strong assumptions: (i) testing policy, availability of tests, and willingness to be tested in England is broadly similar to the Netherlands over this period, and (ii) ascertainment does not vary with age. The pooled age-independent ascertainment estimate is 38.7% (95% CI: 36.1–41.4%). We then estimated cumulative infection incidence for the period 25 Sept through 31 Dec 2020 by synthesising estimates using this approach (while adjusting precision of estimated ascertainment for multiple age-groups) with those from a second approach (for age-groups 30-34 and older only): multiplying age-group specific cumulative hospital admission ratios by the cumulative incidence as of 24 Sept 2020. The second approach is the same general method used in for estimating the prevalent number of infectious persons that is presented on the coronavirus dashboard. After integration of the estimated symptomatic proportion, we estimated a cumulative SI incidence of 950,600 (95% CI: 897,100–1,009,600) between 27 Feb and 31 Dec (Figure 2, Figure 8). The cumulative infection incidence over this full analysis period was estimated at 2,571,400 (95% CI: 2,444,900–2,710,700), or 14.8% (95% CI: 14.0-15.6%) of the total population.

The estimated age-aggregated ascertainment of cumulative SI incidence and cumulative infection incidence by the cumulative number of OSIRIS notified cases (n=808,791) over this period was 85% (95% CI: 80-90%) and 31% (95% CI: 30-33%), respectively. The SI case ascertainment figure of 85% appears unrealistically high; however, there are two factors that should be considered. First, the proportion of all infections that are symptomatic was estimated with respect to the ECDC case definition, which is stricter than the criterion for testing by the GGD (any of a list of symptoms, which includes very mild and non-specific respiratory symptoms). Second, from 1 Dec 2020 testing was expanded to include asymptomatic persons who had travelled abroad or

were identified via contact tracing; an unknown, though likely small, percentage of positive results were recorded among asymptomatic testees. Total DALYs in this period were estimated at 106,900 (95% CI: 104,600–109,300), of which 1.6% were contributed by YLD (Figure 9).

The age-specific burden estimates for the full period (27 Feb through 31 Dec 2020) are quite similar to those for the pre-second wave period (27 Feb through 24 Sept), except for a much higher estimated cumulative SI incidence and a correspondingly higher YLD in the full period. However, the estimated total disease burden in the full period did not increase in proportion to the increase in cumulative incidence of infection (2,571,000 vs 873,000 persons; i.e., 2.9 times the estimated total number of infections but only 1.75 times the total burden), because the YLL contribution to disease burden was lower since the first wave (in part because of the somewhat younger age-distribution of infections and in part because of improvements in patient management and care).

2.2 Burden stratified by occupation category

2.2.1 Methods

We first defined occupation categories according to notified case data in OSIRIS (Table 2), and then plotted the distribution over occupation category, also stratified by (fairly broad) age-group (Figure 3). Estimation of the occupation category denominators required the set of occupation categories in OSIRIS to be mapped to the '4-digit code' categories used by CBS. A perfect match was not possible; in particular for the category 'Other contact professions' (see Table 2 for the adopted mapping).

Two definitions of the period for defining the distribution of notified over occupation category are relevant: (i) the period from 27 Feb 2020 (the date of the first notified case) through 31 Dec 2020 , and (ii) the period with 'open society' and non-priority testing policy (1 Jun to 20 Sep 2020). Note that the 'full period' definition contains periods in which there was restricted testing (i.e., before 1 June priority was given to severe/hospitalised cases) and/or priority testing for certain occupations, such as healthcare workers and the education sector, and so the distribution of occupation categories among notified cases is influenced by access to testing.

The distribution over occupation category during periods of 'open society' and non-priority testing policy will reflect the burden due to potentially higher transmission risks for certain categories, e.g., catering (restaurant/cafe/bar) occupations. The same distribution if calculated from only those cases notified only during those periods of time in which practicing of certain occupations was drastically limited through lockdown measures, such as catering and contact professions, will reflect potentially lower transmission risks for the affected occupations (see Figure 5, which suggests a higher proportion of cases for the Catering category when restaurants were generally open compared to the 'full period').

In the main analysis, we apply the occupation category distribution based on notification data (from OSIRIS) during the full period (thus this

also reflects the impacts of testing policy, closure of certain parts of the economy, various (sector-specific) preventative measures in place, and the periods in which lockdown was imposed) (Figure 3) to estimate the disease burden stratified occupation category. A limitation of this analysis is the assumption that the occupation provided in a notified case's OSIRIS record applied throughout the analysis period (i.e., person was not (temporarily) inactive in their occupation and did not become unemployed). Because a substantial proportion of notifications had occupation 'Not known'; we apply simple univariate imputation to re-distribute the Not known category among the observed occupation categories.

As an additional analysis, we also apply the occupation category distribution based on notifications (OSIRIS) made during the 'open society' period (Figure 5) to estimate the disease burden per occupation category. Note that by applying the occupation distribution derived from the 'open society' period to periods in which strict measures were in place (some occupations could not be practiced; for others, contact patterns and ensuing transmission risk might be quite different), we effectively attempt to estimate the distribution of disease burden over occupation category that would have been observed, assuming that the measures were not in place. This is an imperfect counterfactual; we recognise that the proportion in category 'education' will not be fully representative of the term-time situation with in-person teaching, due to the (partial) continuation of online teaching after 1st June 2020, and the school vacation period. As well, the proportions in all categories will reflect the effect of ongoing safety measures in place since 1 June 2020 (e.g., Catering: spacing of restaurant tables; Transportation: no contact with bus drivers).

To estimate DALYs stratified by occupation category, we simply apply the occupation category distribution that had been determined on the basis of 10-year age-groups to the narrower, 5-year age-groups used to assign OSIRIS cases to occupation category; e.g. the distribution inferred for 25-34 years is applied to both 25-29 and 30-34 years, and the assumed denominator population for these two 5-year age-groups is the 10-year denominator population weighted according the national population sizes of the 25-29 and 30-34 years age-groups. Importantly, the occupation distribution is calculated separately within each age-group and applied to the DALYs within each age-group.
All burden estimates are restricted to the 'work-eligible' age range (defined as age 20 through 69 years).

2.2.2 Summary of results (analysis period to 31 Dec 2020)

While the absolute burden is greatest for the 'non-working' occupation category (consisting of retired persons, employment seekers and presumably students), largely because of the much higher mortality burden among older aged retirees (Figure 11, Figure 14), when the size of the occupation denominator is taken into account (i.e. the DALY/100,000 measure, aggregating over age), the category Healthcare appear to bear a disproportionally high relative burden (Figure 15). The higher relative burden for this category holds true also when calculated separately per age-group, as the relative disease burden is notably higher than seen for other occupations starting from age-group 45-49

(Figure 13). The higher relative burden among healthcare workers is attributable to the relatively high cumulative incidence of symptomatic infection seen across all age-groups for this category (Figure 12), which presumably reflects a combination of increased workplace exposure and a higher likelihood of being tested (at least during part of the year).
Note that the relative disease burden for a given occupation category, as estimated for the full analysis period, is not necessarily indicative of the recent burden; for instance, widespread availability of PPE and other risk-reducing measures may mean that the proportion of burden experienced by healthcare workers over the last half of the year is now much reduced.
In addition, this approach does not take into account possible variation in the risk of severe disease and/or mortality by occupation, because the occupation distribution (per age-group) is applied to the total burden (for that age-group). For instance, if healthcare workers have better underlying health and therefore better prognosis compared with other occupations, then both the absolute and relative disease burden will have been overestimated for this group. Unfortunately, applying a separate occupation category distribution as observed among fatal cases for the calculation of YLL (which could address this issue) is not viable, due to relatively high level of missingness of occupation information among working age fatal cases (Figure 4).
The supplementary analysis, in which the distribution of positive cases over occupation category was determined during the 'open society' period, showed similar patterns of absolute and relative burden (Figure 16,Figure 17), except that Other contact professions now indicated the second higher relative burden of all occupation categories.

2.3 Overall summary

The total disease burden for the period until 31 Dec 2020 presented here is known to underestimate the true burden, mainly because of the under ascertainment of mortality due to COVID-19 in OSIRIS, but also because post-acute health outcomes are not yet included. Nevertheless, we can draw several useful conclusions from this exercise. COVID-19 disease burden is overwhelmingly determined by premature mortality (>98% of DALYs). The absolute disease burden (in DALYs) grew more slowly between the first and second SARS-CoV-2 waves in proportion to the estimate cumulative incidence of infection. This is due to improvements in COVID-19 patient prognosis, but also to changes in the age-distribution of infected persons, with consequence impact on risk of severe or fatal outcomes. Using the relative disease burden measure (DALYs per 100,000 population), we can compare the per-capita burden between different strata of the population. Thus the (age-aggregated) burden experienced by healthcare workers (approximately 660 DALYs per 100,000; Figure 15) is an order of magnitude lower than the burden experienced by the oldest segment of the population (e.g., approximately 6000 DALYs per 100,000 for the age-groups 85-89 years and older; Figure 10).

Table 1. Summary of data sources, DALY parameters, and other decisions, for analysis period 27 Feb through 31 Dec 2020 (note that the cumulative incidence of Mild cases in the period 25 Sep through 31 Dec 2020 was estimated differently, text).

Parameter	**Value/Source**
Analysis period	27 Feb 2020 t/m 31 Dec 2020
Life expectancy	5-year bins, determined based on 1-year CBS values for 2019[a]. The interpolated 1-year LE for the exact midpoint of each age-category is used (e.g. LE(82.5) for LE(80-84); LE(97.5) for LE(95+))
Incidence Mild **cases**	Estimated symptomatic infection cases derived from seroprevalence data (from PICO3) and symptomatic proportion (derived using PICO2), with estimated 95% uncertainty interval [Beta distribution].
Underreporting adjustment Mild	N/A
Disability duration Mild	10 days
Incidence Moderate **cases**	Cumulative NICE non-ICU hospital admissions, per 5-year age-group. Assumed Poisson distributed.
Underreporting adjustment Moderate	1.10 (1.06-1.18) [Uniform distribution]
Disability duration Moderate	8 days
Incidence Severe **cases**	Cumulative NICE ICU admissions, per 5-year age-group. Assumed Poisson distributed.
Underreporting adjustment Severe	1.0
Disability duration Severe	19 days (NB. a preceding Moderate phase of 10 days duration is assumed)
Deaths	Cumulative deaths in OSIRIS (per 5-year age-group). Assumed Poisson distributed.
Underreporting adjustment Deaths	1.0
Age-groups	<1, 1-4, 5-9, ... 80-84, 85-89, 90-94, 95+
Disability weights	Mild: 0.051; Moderate: 0.133; Severe: 0.655
Notes	Occupation category distribution for all OSIRIS notified cases (including those admitted to hospital and/or ICU and/or deceased) is determined from the full analysis period, with the distribution derived from the 'open society' period (1 June 2020 t/m 20 Sept 2020) applied in supplementary analysis.

[a] URL: https://opendata.cbs.nl/statline/#/CBS/nl/dataset/37360ned/table?fromstatweb

Table 2. Definition of occupation categories and proposed set of denominator occupations from CBS.

Occupation category	Occupation label(s) in OSIRIS	CBS occupation category(s) for population denominator
Healthcare	(Gezondheids)zorg	1011 Artsen 1012 Gespecialiseerd verpleegkundigen 1033 Verpleegkundigen (mbo) 1034 Medisch praktijkassistenten 1051 Verzorgenden
Education	Onderwijs en kinderopvang	0111 Docenten hoger onderwijs en hoogleraren 0112 Docenten beroepsgerichte vakken 0113 Docenten algemene vakken secundair onderwijs 0114 Leerkrachten basisonderwijs 0115 Onderwijskundigen en overige docenten 0121 Beroepsgroep sportinstructeurs 0131 Leidsters kinderopvang en onderwijsassistenten
Catering	Horecamedewerker	1112 Koks 1113 Kelners en barpersoneel 1122 Keukenhulpen
Transportation	Transport	1211 Dekofficieren en piloten 1212 Chauffeurs auto's, taxi's en bestelwagens 1213 Buschauffeurs en trambestuurders 1214 Vrachtwagenchauffeurs
Other contact professions	Overige contactberoepen Seksindustrie	1013 Fysiotherapeuten 1035 Medisch vakspecialisten 1114 Kappers en schoonheidsspecialisten 1116 Verleners van overige persoonlijke diensten (o.a. rijinstructeurs, prostituees)
Other	Klinisch laboratorium Landbouw Andere sector Werk met dieren of dierlijke producten	*Denominator calculated as [age-group-specific] 'totale werkzame beroepsbevolking' minus sum of above categories*

Occupation category	Occupation label(s) in OSIRIS	CBS occupation category(s) for population denominator
	Groenvoorziening Afvalverwerking Schoonmaakbranche Buitenland	
Not applicable	N.v.t. (kinderen, gepensioneerden, werkzoekenden)	*Denominator calculated as [age-group-specific] national population size minus sum of all above categories*

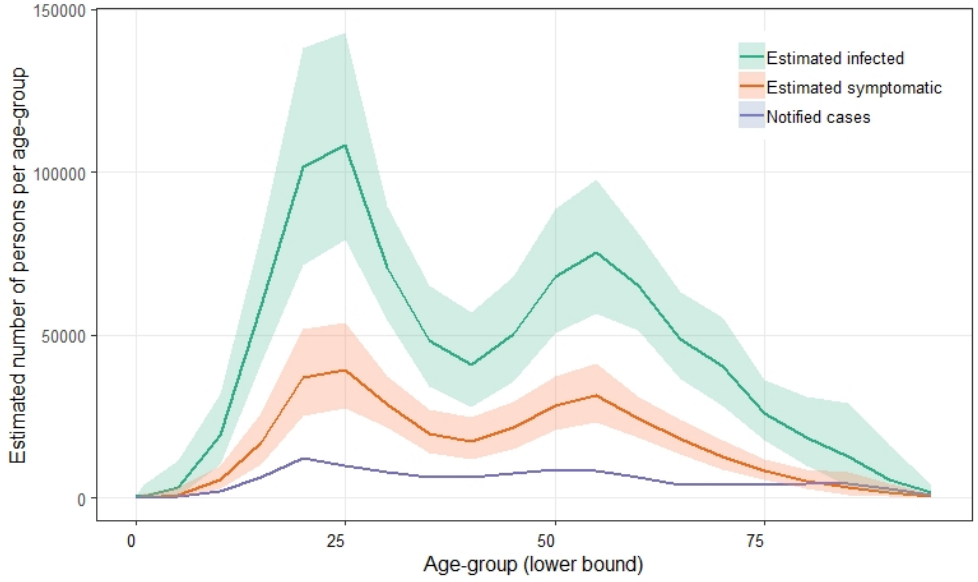

Figure 1. Estimated cumulative number of patients (as of 24th Sept 2020) with symptomatic and asymptomatic infection per age-group (lower bound indicated). This is based on smoothed seroprevalence – adjusted for survey representativeness and seroreversion – from PICO3, and the estimated proportion of symptomatic infection, derived using PICO2 data. Plot also shows the cumulative notified cases from OSIRIS.

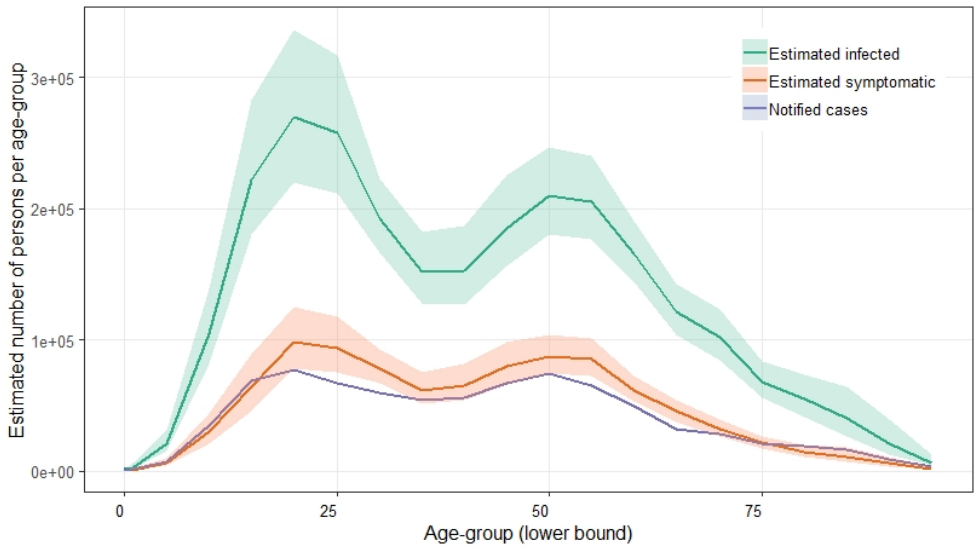

Figure 2. Estimated cumulative number of patients (as of 31 Dec 2020) with symptomatic and asymptomatic infection per age-group (lower bound indicated). This is based on smoothed seroprevalence from PICO2 until 24 Sept, and OSIRIS cases adjusted for estimated ascertainment from 25 Sept through 31 Dec. Plot also shows cumulative notified cases from OSIRIS.

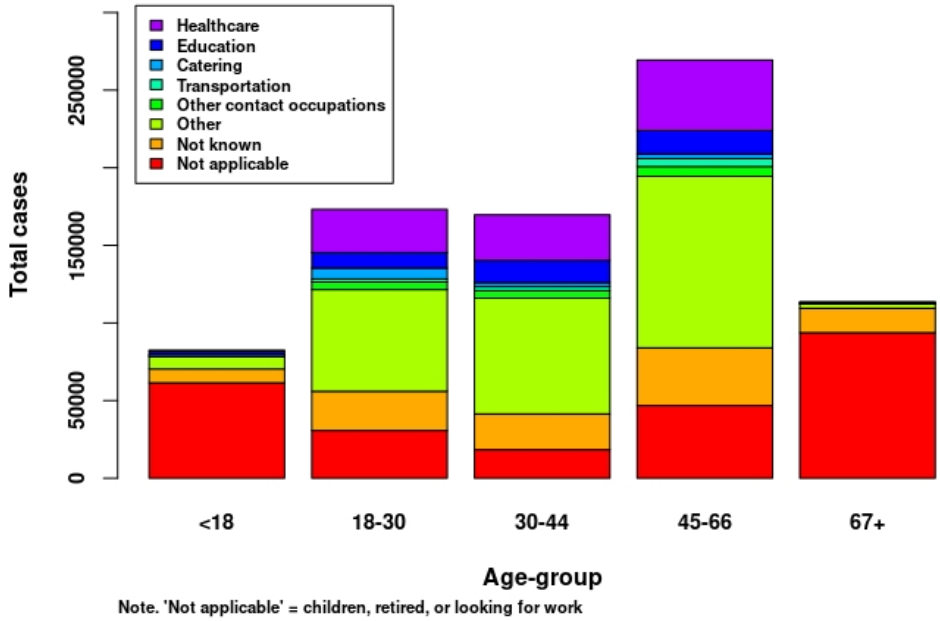

Figure 3. Distribution over occupation categories (from OSIRIS) stratified by broad age-group, using the 'full' analysis period definition (i.e., 27 Feb 2020 through 31 Dec 2020).

Figure 4. Proportion of OSIRIS notifications with occupation 'not known' per age-group, comparing (notified) fatal cases with (notified) cases who are not known to have died, 27 Feb through 31 Dec 2020. Note that for age-groups below 45-49 years, the denominators for the 'fatal' series are very small.

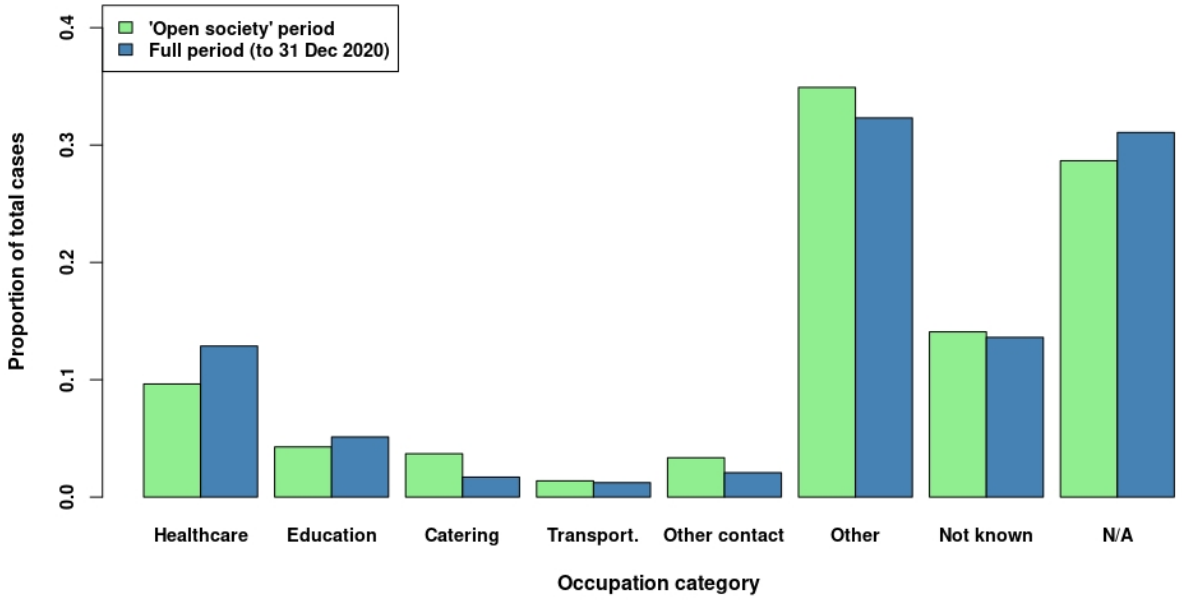

Figure 5. Distribution over occupation categories (from OSIRIS notifications, all ages), comparing two analysis period definitions ('full period' = 27 Feb through 31 Dec 2020; 'open society' = 1 June through 20 Sept 2020).

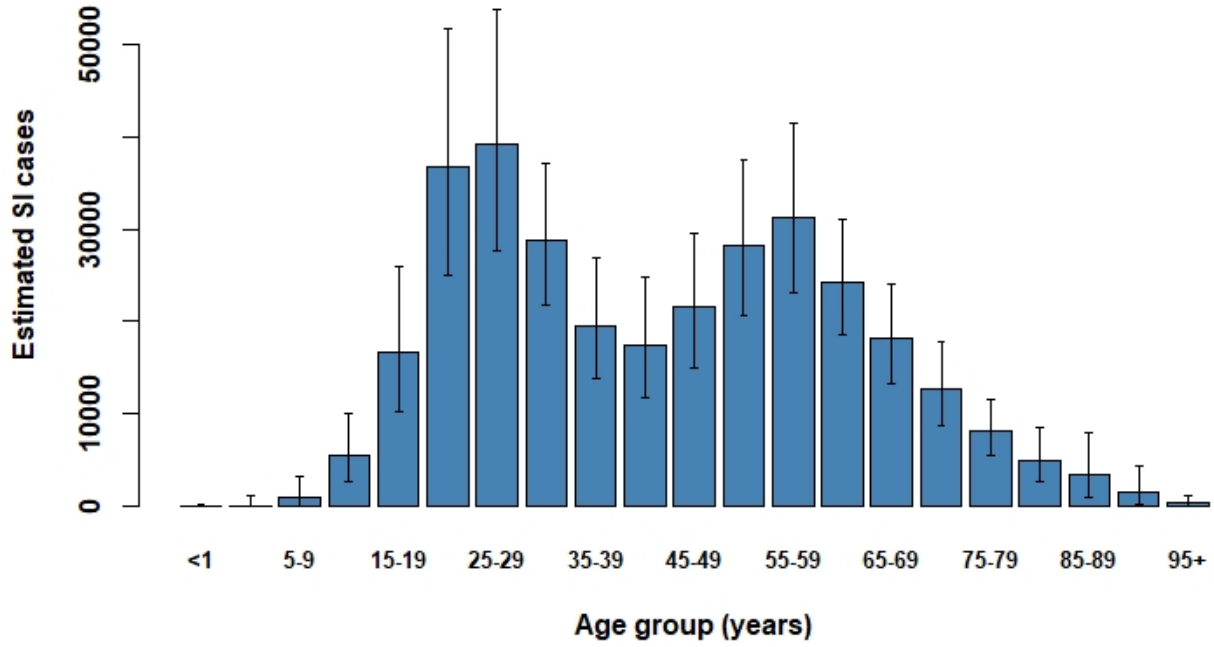

Figure 6. Estimated cumulative symptomatic (SI) incidence per 5-year age-group with 95% CIs, up to 24 Sept 2020.

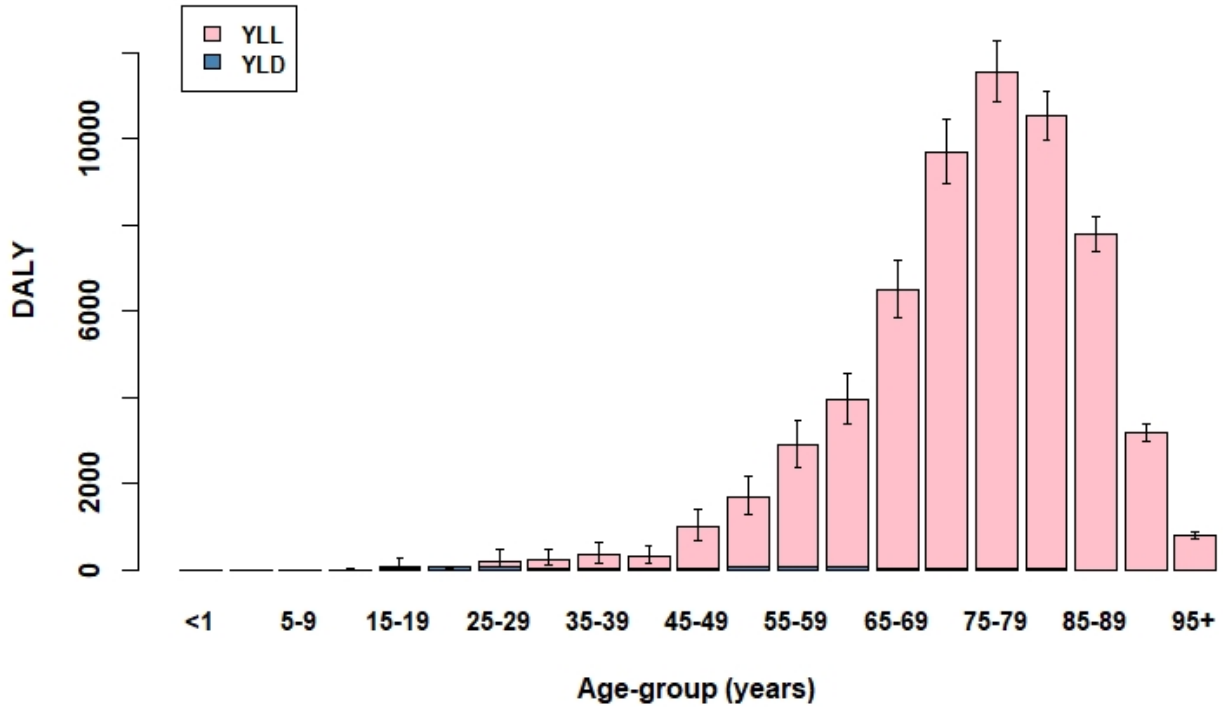

Figure 7. Estimated DALY (split into YLD and YLL) per 5-year age-group with 95% CIs, up to 24 Sept 2020.

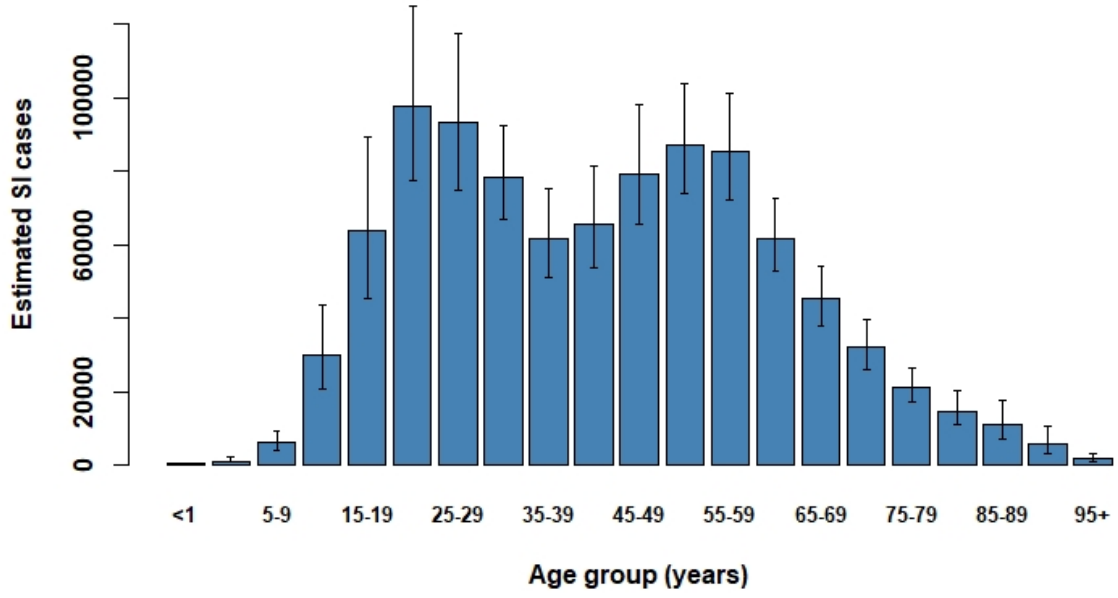

Figure 8. Estimated SI cases per 5-year age-group with 95% CIs, up to 31 Dec 2020.

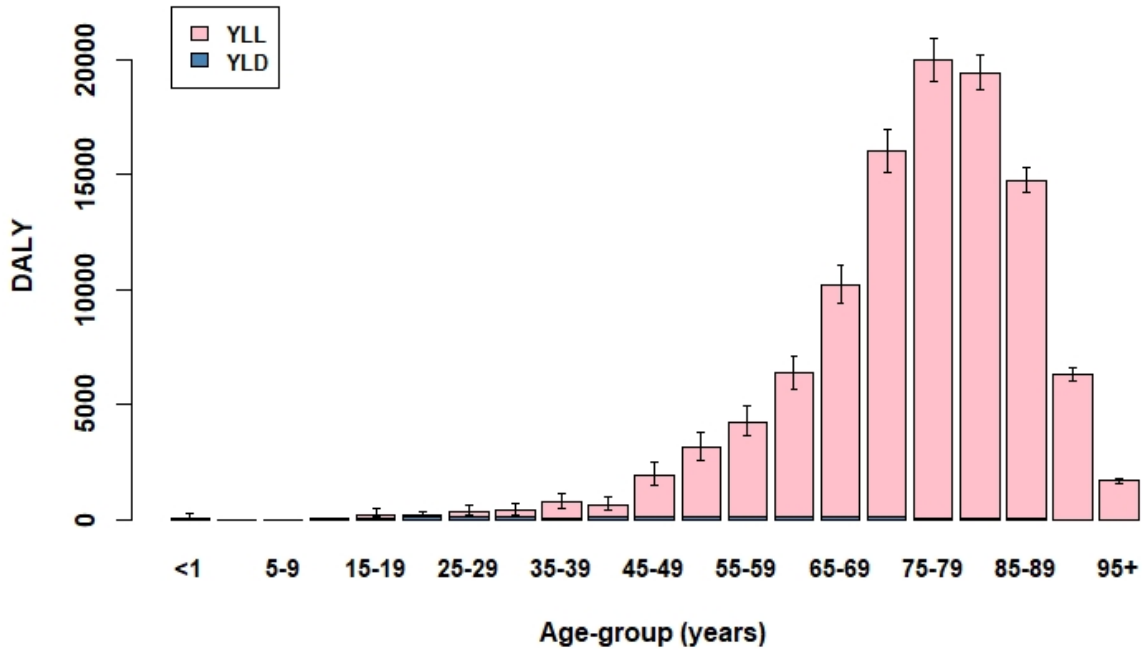

Figure 9. Estimated DALY (split into YLD and YLL) per 5-year age-group with 95% CIs, up to 31 Dec 2020.

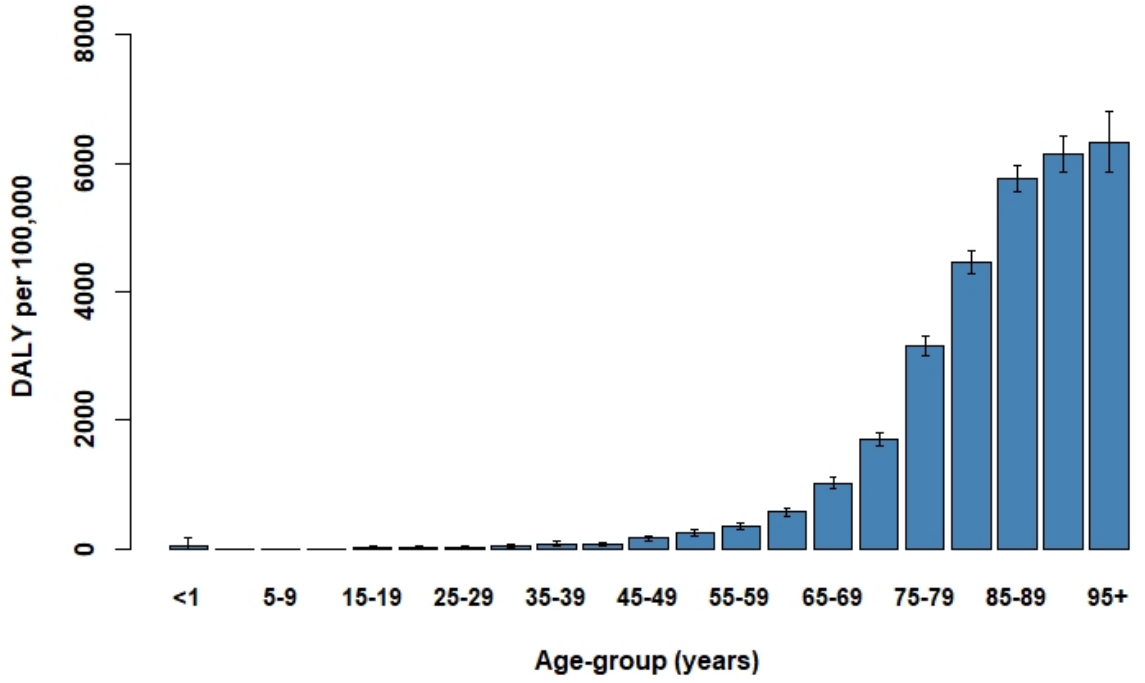

Figure 10. Estimated disease burden per 5-year age-group as DALYs per 100,000 persons, up to 31 Dec 2020.

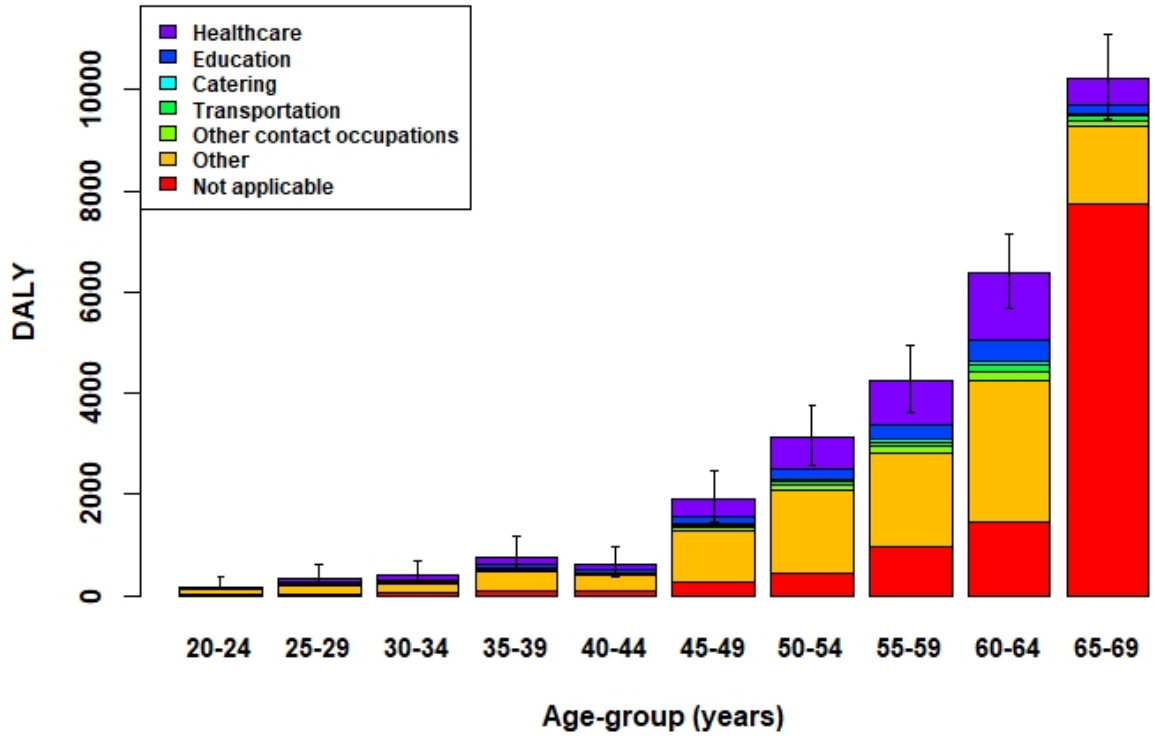

Figure 11. Estimated absolute disease burden (in DALYs) per occupation category (with occupation 'Not known' imputed) and 5-year age-group, up to 31 Dec 2020.

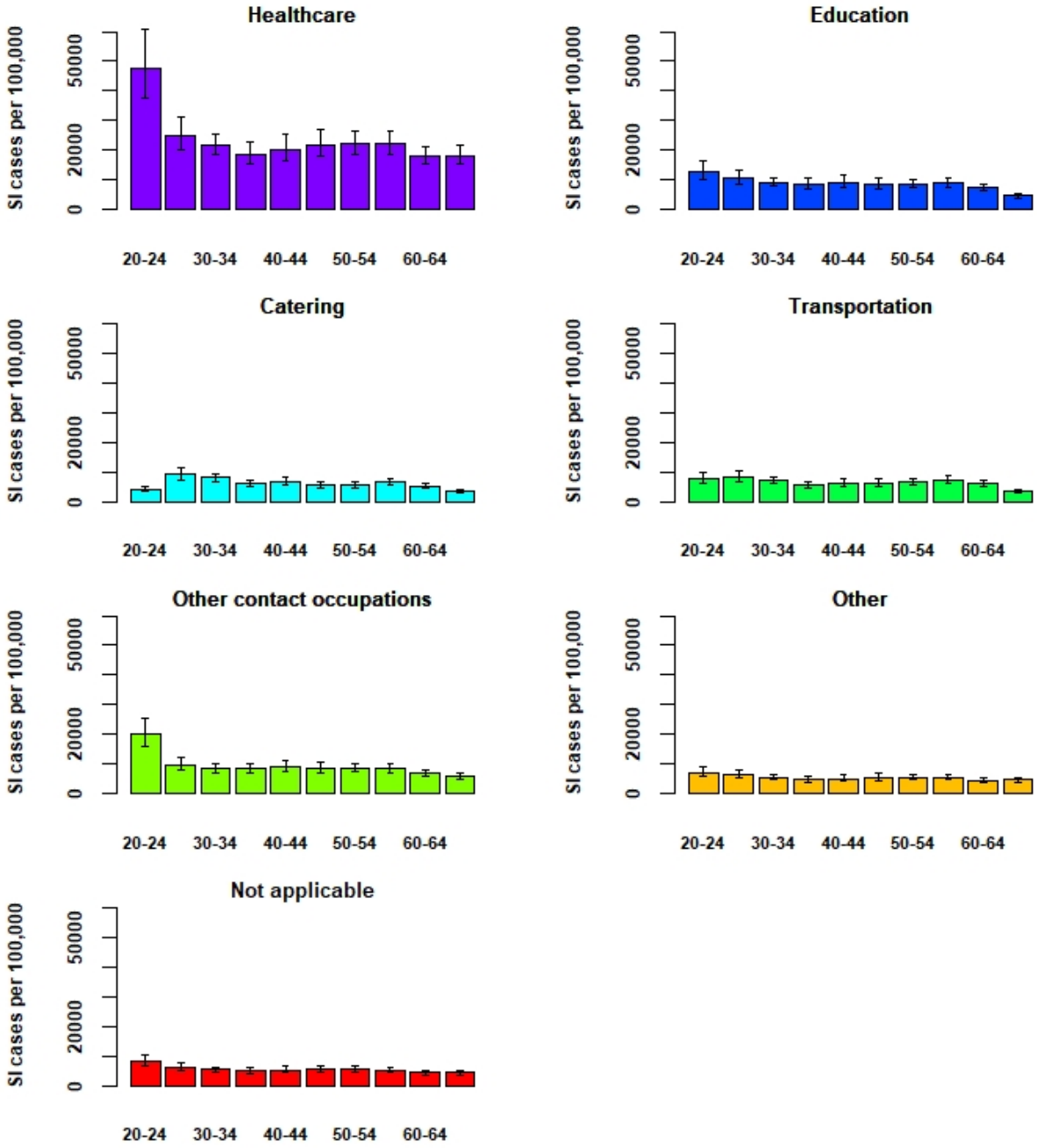

Figure 12. Estimated cumulative incidence (per 100,000) of symptomatic infection per occupation category and 5-year age-group (as the estimated total number of patients per 100,0000 persons in each category within each age-group), up to 31 Dec 2020 and shown for the age range 20-69 years only. 'Not known' occupation imputed.

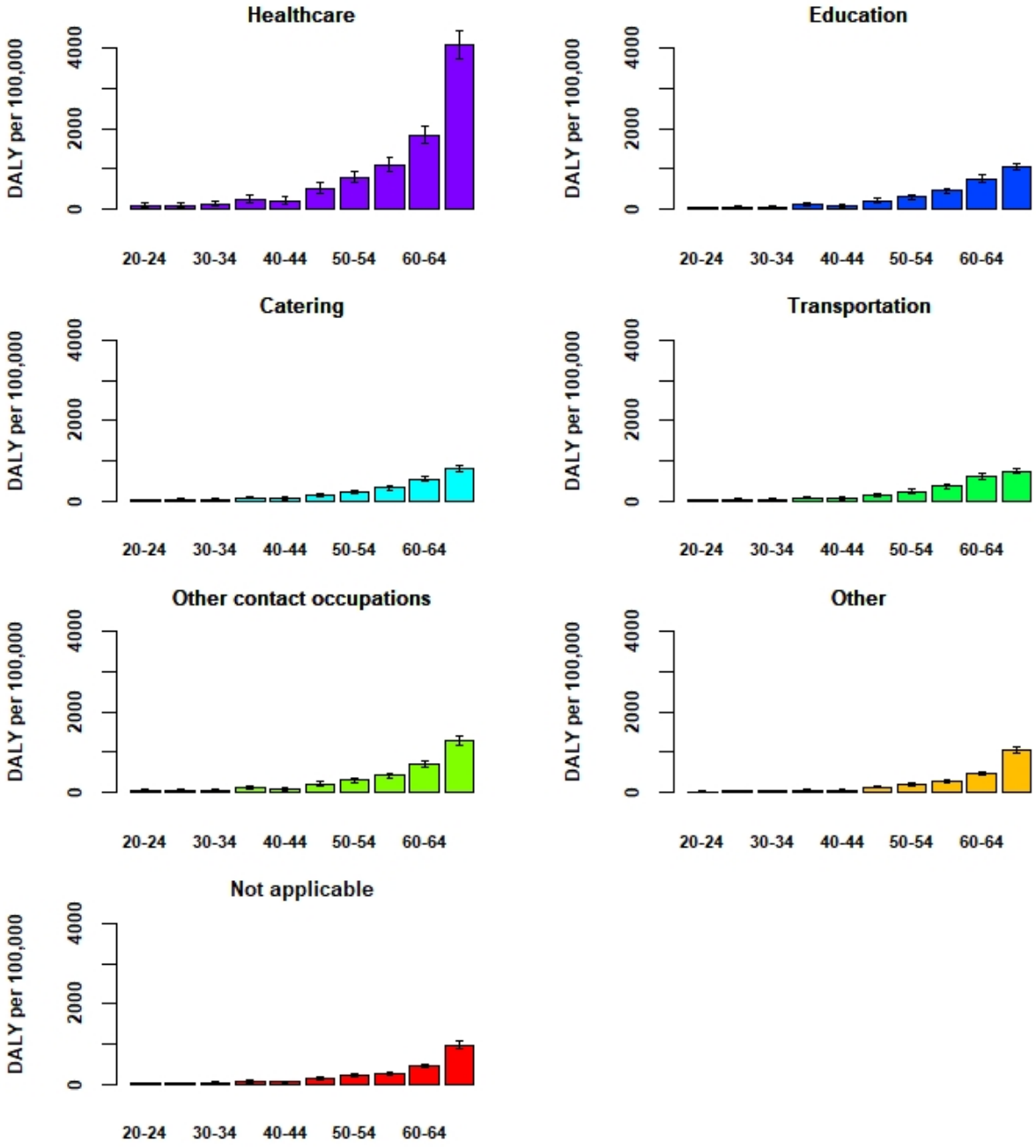

Figure 13. Estimated disease burden per occupation category and 5-year age-group (as DALYs per 100,0000 persons in each category within each age-group), up to 31 Dec 2020, and shown for the age range 20-69 years only. 'Not known' occupation imputed.

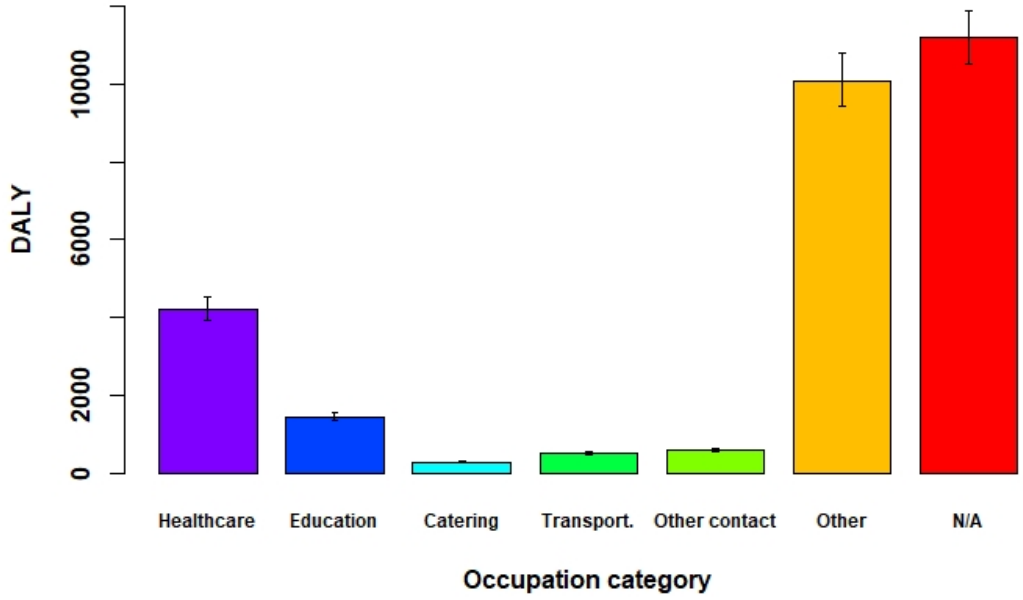

Figure 14. Estimated absolute disease burden per occupation category (as DALYs), up to 31 Dec 2020 and within the age range 20-69 years only. 'Not known' occupation imputed.

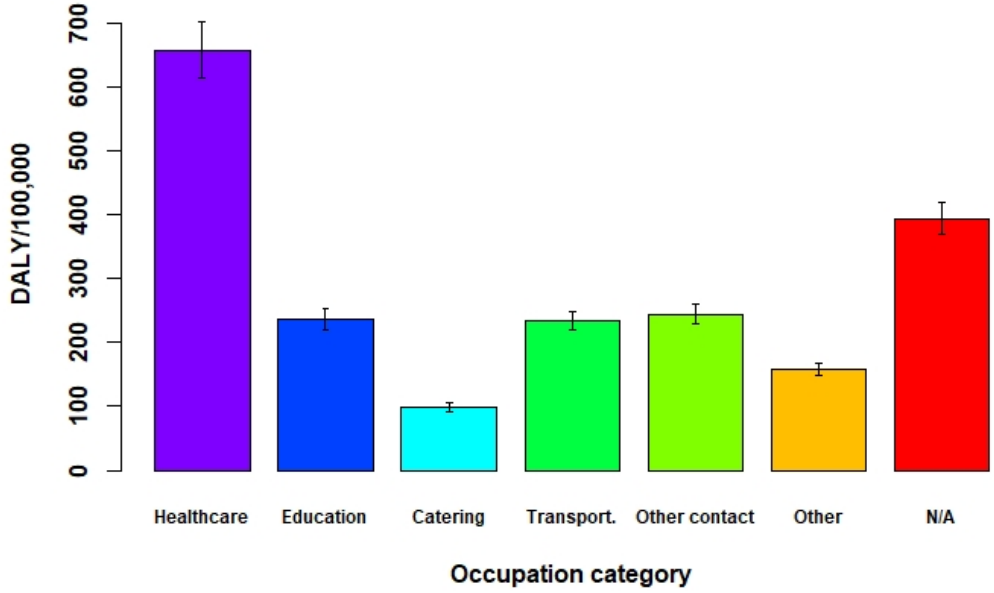

Figure 15. Estimated disease burden per occupation category (as DALYs per 100,0000 persons in each category, aggregating over age), up to 31 Dec 2020 and within the age range 20-69 years only. 'Not known' occupation imputed

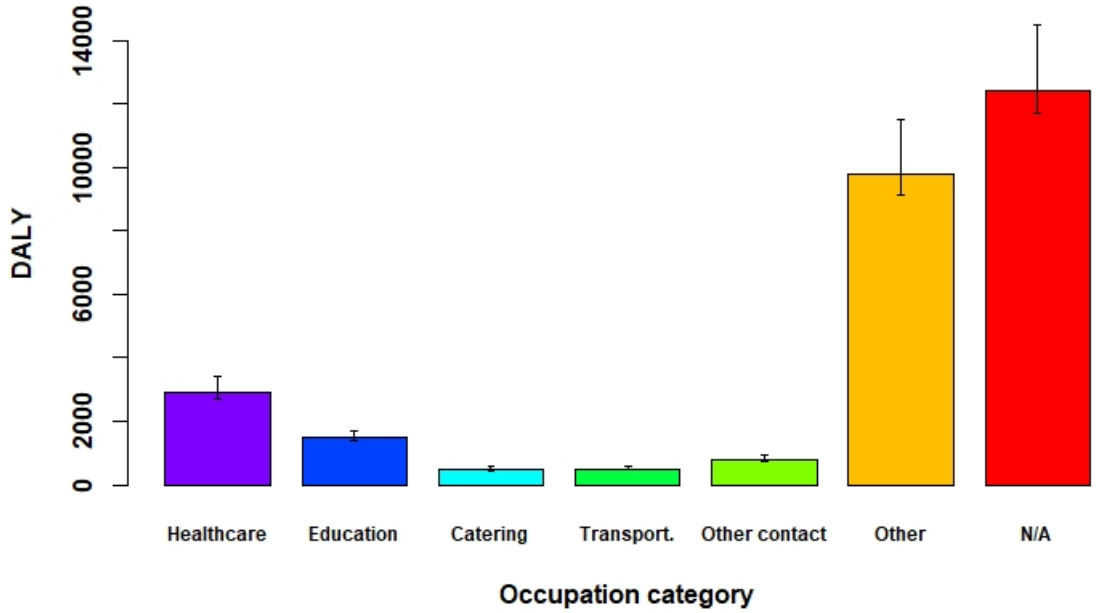

Figure 16. Expected absolute disease burden per occupation category (as DALYs), up to 31 Dec 2020 and within the age range 20-69 years only. 'Open society' occupation category distribution used. 'Not known' occupation imputed.

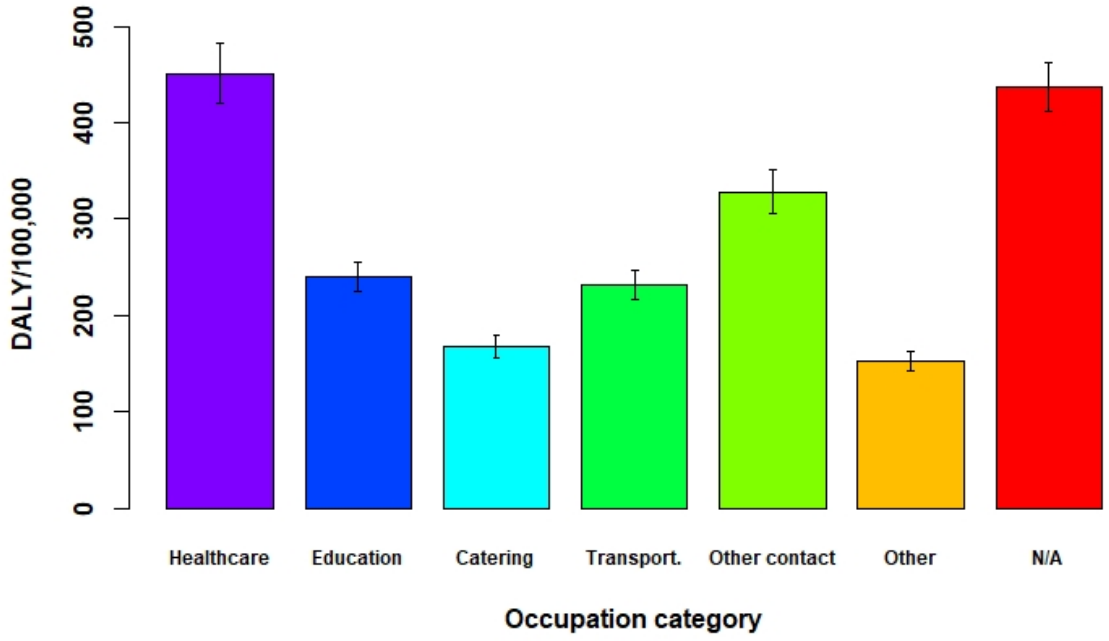

Figure 17. Expected relative disease burden per occupation category (as DALYs per 100,0000 persons in each category, aggregating over age), up to 31 Dec 2020 and within the age range 20-69 years only. 'Open society' occupation category distribution used. 'Not known' occupation imputed.

3 Can we use the AstraZeneca vaccine for 60-70 year olds living at home, rather than Pfizer-BioNTech/Moderna vaccines?

Analysis of 29 Jan 2021.

Here we report on modelling results to answer the question of whether the AstraZeneca vaccine should be used for 60-69 years old living at home rather than the Pfizer-BioNTech/Moderna vaccines due to delays in the latter's availability. The results presented here are intended to provide a roadmap of possible outcomes of different vaccination scenarios and should not be interpreted as predictions of exact incidence or hospital admission numbers.

3.1 Context

To date (Jan 29th, 2021) there is little available information on the efficacy against disease for the AstraZeneca vaccine in 60-69 year olds. There is little available information on when the vaccination of 60-69 year olds can start with the AstraZeneca vaccine or when it can start with the Pfizer-BioNTech vaccine. The uptake of the vaccine in this age group is unknown. The epidemiological situation around the time that vaccination may start is highly uncertain, as the new variant of the SARS-CoV-2 virus might have become the most common variant of the virus. The non-pharmaceutical interventions that are in place around the time of vaccination may differ from those that are in place now.

3.2 A qualitative exploration

As a consequence, our analysis focuses on exploring potential outcomes rather than predicting the actual numbers of infections and hospital admissions. We discern three possible situations around the time of vaccination: the risk of infection will be declining at the time that the 60-69 year olds will be vaccinated; the risk of infection will be more or less stable at the time that the 60-69 year olds will be vaccinated; the risk of infection will be increasing at the time that the 60-69 year olds will be vaccinated.

- First, the risk of infection might continue to decline. In that case the differences in health benefit between the options remain limited.
- Second, the risk of infection might become stable. In that case, the differences in health benefit between the options are determined by the time difference between vaccinating early with AstraZeneca and later with Pfizer, and by the difference in efficacy of the AstraZeneca and Pfizer vaccines.
- Third, the risk of infection might increase. This is plausible when the control measures do not suffice to control the spread of the new variant. A proportion of 60-69 year olds will have been infected earlier and these individuals are immune to reinfection. The largest differences in health benefits occur when most infections among the 60-69 year olds are due to infectors in the same age category.

In all cases, over a short time horizon there is a benefit of vaccinating earlier over vaccinating later. Over a longer time horizon, when the epidemic continues, the most health benefits are obtained by vaccinating with the vaccine with the higher efficacy. We present simulations to explore the second and third options further.

3.3 Main Results

Below we present several sets of simulation results under two main assumptions: 1) a non-constant force of infection, 2) constant force of infection. The results of these two sets of simulations can be viewed as a lower and upper bound of potential impacts of different vaccination scenarios, where assumption (1) represents an optimistic scenario where force of infection drops quickly and (2) represents a pessimistic scenario in which the force of infection in this group remains constant despite non-pharmaceutical interventions and vaccination efforts.

3.3.1 Non-constant force of infection

Delaying vaccination in all 60-69 year olds until the Pfizer-BioNTech vaccine is available results in a higher peak in incidence of infections and hospital admissions compared to scenarios in which vaccination of 60-64 year olds with the AstraZeneca vaccine begins sooner, even if the AstraZeneca has very low efficacy (Figure 18). The scenario in which 60-64 year olds receive the AstraZeneca vaccine with ~60% efficacy and the 65-69 year olds receive the Pfizer-BioNTech vaccine results in the lowest cumulative incidence and hospitalisations. To assess how a reduction in the efficacy of the AstraZeneca vaccine impacts our results, we evaluated the relative difference in cumulative infections and hospital admissions assuming the AstraZeneca has an efficacy of 10% and 30%. Vaccinating 60-64 year olds with the AstraZeneca vaccine with a sub-optimal efficacy of 30% results in 10.2% more cumulative infections and 10.2% more cumulative hospital admissions compared to vaccinating this group with an AstraZeneca vaccine with 62% efficacy (Table 4). If the AstraZeneca vaccine has a further reduced efficacy of 10%, the cumulative infections increase by 33.5% and the cumulative hospital admission increase by 33.3%. Delaying vaccination in 60-64 year olds until the Pfizer-BioNTech vaccine is available will result in an increase of 19.4% cumulative infections and hospital admissions. However, vaccinating all individuals 60-69 with the Pfizer-BioNTech vaccine reduces incidence faster than in the scenarios in which 60-64 year olds receive an AstraZeneca vaccine with sub-optimal efficacy due to the high efficacy of the Pfizer-BioNTech vaccine.

3.3.2 Constant force of infection

Delaying vaccination in all 60-69 year olds until the Pfizer-BioNTech vaccine is available results in a slightly higher peak in incidence of infections and hospital admissions compared to scenarios in which vaccination of 60-64 year olds with the AstraZeneca vaccine begins sooner, even if the AstraZeneca has very low efficacy (Figure 19). However, vaccinating all 60-69 year olds with the Pfizer-BioNTech results in a reduction of 3.46% cumulative infections and a reduction of 2.32% of cumulative hospital admissions (Table 5). This is due to the high efficacy of the Pfizer-BioNTech vaccine, which will reduce incidence faster than vaccines with lower efficacy. The scenario in which 60-64

year olds receive the AstraZeneca vaccine with ~60% efficacy and the 65-69 year olds receive the Pfizer-BioNTech vaccine results in the next lowest cumulative incidence and hospitalisations. If the AstraZeneca vaccine is assumed to have an efficacy of 30%, then 21.3% more cumulative infections and 20.1% more cumulative hospital admissions occur compared to vaccinating this group with an AstraZeneca vaccine with 62% efficacy. If the AstraZeneca vaccine is assumed to have a further reduced efficacy of 10%, then increases of cumulative infections by 39.6% and cumulative hospital admissions by 37.4% occur.

3.3.3 Delayed vaccination distribution

If vaccination distribution is delayed until mid-February (AstraZeneca) and mid-April (Pfizer-BioNTech) and we do not assume a constant force of infection, our results show a similar pattern of incidence and hospital admissions (Figure 20) compared to the original vaccination schedule. However, unlike with the original vaccination schedule (in which AstraZeneca begins 8 February 2021 and Pfizer-BioNTech begins 14 March 2021) vaccinating all individuals aged 60-69 with the Pfizer-BioNTech results in the highest cumulative infections and hospital admissions (Table 6). If we assume both a delayed vaccine schedule and a constant force of infections our results show a similar pattern of incidence and hospital admissions (Figure 21) as in the original vaccine schedule. However, when the vaccination schedule is delayed vaccinating 60-64 year olds with the AstraZeneca vaccine with 62% efficacy results in the lowest cumulative infections and hospital admissions (Table 7). Vaccinating all individuals aged 60-69 with the Pfizer-BioNTech vaccine results in an increase in cumulative infections (9.59%) and hospital admissions (3.97%).

3.4 Methods

We used a compartmental Susceptible-Exposed-Infectious-Recovered (SEIR) model determine the incidence and hospital admissions over time under three different vaccination scenarios:

1. 60-64 year olds receive the AstraZeneca vaccine with vaccine efficacy as reported in [5], while 65-69 year olds receive the Pfizer-BioNTech vaccine with vaccine efficacy as reported in [6].
2. All 60-69 year olds receive the Pfizer-BioNTech vaccine with vaccine efficacy as reported in [6].
3. 60-64 year olds receive the AstraZeneca vaccine with vaccine efficacy of 10% after both doses 1 and 2 (this scenario was explored due to recent evidence that the AstraZeneca has low efficacy in this age group), while 65-69 year olds receive the Pfizer-BioNTech vaccine with vaccine efficacy as reported in [6].

Within our modelling approach we make several important assumptions. Specifically, we assume R = 1.22 (estimated for the UK coronavirus variant VOC202012/01 in the Netherlands for January 7th), vaccine uptake is 85%, the distribution of the AstraZeneca vaccine begins on 8 February 2021 with 12 weeks between administration of the first and second doses, and distribution of the Pfizer-BioNTech vaccine begins on 14 March 2021 with 6 weeks between administration of the first and second doses. In the event of vaccine distribution delays, we also modelled the scenario when AstraZeneca distribution begins on 15

February 2021 and the Pfizer-BioNTech vaccine distribution begins on 19 April 2021. We assume 25,000 vaccines are administered to each 5-year age group daily. For example, in the Pfizer only case, 25,000 vaccines are administered to 60-64 year olds and 25,000 are administered to 65-69 year olds. The assumed vaccine efficacies and times to protection (i.e., the time from receipt of the vaccine to protection being conferred) are shown in Table 1. For the scenario in which we assume a low vaccine efficacy for the AstraZeneca vaccine, we assume an efficacy of 10% after both the first and second doses. Hospital admissions are calculated as incidence * rate from infection to hospital. The rate from infection to hospital was assumed to be 2.51%. A delay from infection to hospitalisation of 11 days was assumed. The initial conditions of our simulations were chosen so that concur with current COVID-19 surveillance streams (OSIRIS and NICE), such that the number of hospitalisation admissions begins at ~50 per day. We count infections and hospital admissions over the period 21 January to 9 August 2021.

3.5 Potential limitations

We have made several assumptions. One of these is that people who refuse vaccines do so at random, and that these are not clustered. It is highly likely that vaccine refusers cluster together. This will lead to a reduced impact of vaccination, but it will affect the alternative vaccination scenarios in similar ways, such that the relative differences in health benefits is likely to be maintained. Another is that we assume that the epidemic is similar in all regions of the Netherlands. Even though regions do differ in the incidence of infection, a long and sustained period where the epidemic grows in one region but declines in another has not occurred. We have modelled the mode of action of all vaccines as "leaky", i.e. the model assumes that at a vaccine efficacy of 50% vaccinated individuals have half the risk of being infected during each exposure as unvaccinated individuals. Since the number of exposures for each susceptible individual in this simulation study is very limited, we expect the results to generalize to other modes of action.

We simulated the 60-69 year age group in isolation, using two extremes: all infections are due to infectors within this age group (figure 1, table 2) and all infections are due to infectors outside this age group (figure 2, table 3). We do not include the additional benefits that vaccination of 60-69 year olds may have by reducing infections in other age groups, and we do not account for the benefits of redistributing vaccines to other age groups. To test how sensitive the outcomes are to such an approach we used a simulation model that includes all age groups, for a situation where the curfew and severest measures of the lockdown are lifted. We find an ordering of vaccine options consistent with the results reported here: AstraZeneca with 62% efficacy gives the least hospital admissions up to August 9th, 2021, followed by AstraZeneca with 30% efficacy, then Pfizer-BioNTech, then AstraZeneca with 10% efficacy. The relative differences are smaller than presented here; the absolute differences are similar: the order of magnitude is a few hundred hospital admissions among the 60-69 year olds.

3.6 Tables and Figures

Table 3. Vaccine efficacies against infection and times to protection by vaccine manufacturer. The values in this table were obtained from the references listed in the "Reference" column. Time to protection indicates the length of time (in days) from vaccine receipt to when protection from the vaccine is conferred.

Vaccine	Efficacy (dose 1)	Time to protection (Dose 1)	Efficacy (dose 2)	Time to protection (dose 2)	Reference
Pfizer/BioNTech	0.926	14 days	0.948	7 days	[6]
Moderna	0.896	14 days	0.941	14 days	[7]
AstraZeneca	0.583	21 days	0.621	14 days	[5]

Table 4. Percent change in cumulative infections and hospital admissions under the different vaccination scenarios. In all scenarios, people aged 65-69 receive the Pfizer vaccine, so the vaccine type only varies among individuals aged 60-64. The reference scenario is where the AstraZeneca vaccine has an efficacy of 62% in individuals aged 60-64. AstraZeneca vaccination was assumed to start on 8 February 2021 and Pfizer vaccination was assumed to start on 14 March 2021

Vaccine	Change in Cumulative Incidence (%)	Change in Cumulative hospital admissions (%)
AstraZeneca (10% VE)	33.5%	33.3%
AstraZeneca (30% VE)	10.2%	10.2%
AstraZeneca (62% VE)	reference	reference
Pfizer/BioNTech	19.4%	19.4%

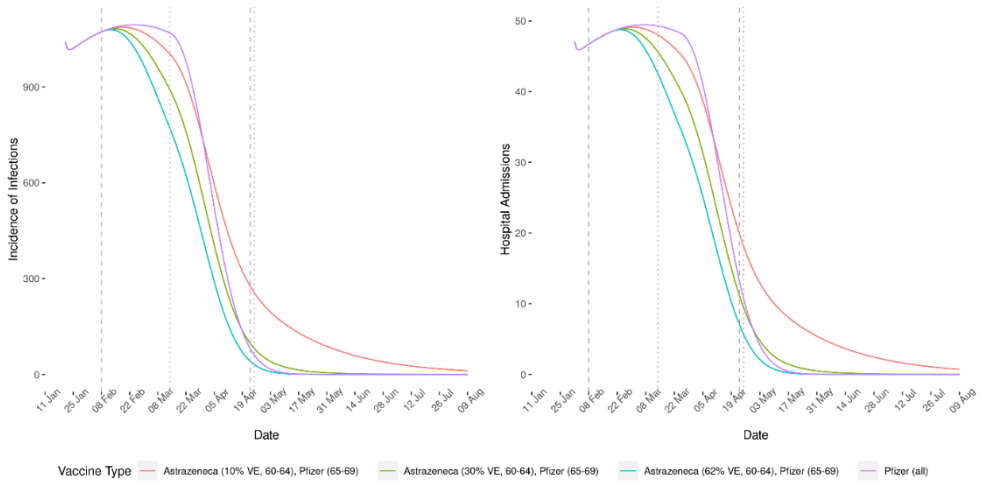

Figure 18. Modelled daily incidence of infections (left) and daily hospital admissions (right) in 60-69 year olds under different vaccination scenarios. In all scenarios, people aged 65-69 receive the Pfizer vaccine, and the vaccine is varied among individuals aged 60-64. The vertical grey dashed lines indicate the start of AstraZeneca vaccination for doses 1 and 2. Dose 1 is assumed to start being administered on 8 February 2021 with dose 2 following 12-weeks later. The dotted grey vertical lines indicate the start of Pfizer vaccination (in this age group) for doses 1 and 2. Dose 1 is assumed to start being administered on 14 March 2021 with dose 2 following 6-weeks later. Date refers to either time of infection or time of hospital admission.

Table 5. Percent change in cumulative infections and hospital admissions under the different vaccination scenarios under the assumption of a constant force of infection. In all scenarios, people aged 65-69 receive the Pfizer vaccine, so the vaccine type only varies among individuals aged 60-64. The reference scenario is where the AstraZeneca vaccine has an efficacy of 62% in individuals aged 60-64. AstraZeneca vaccination was assumed to start on 8 February 2021 and Pfizer vaccination was assumed to start on 14 March 2021.

Vaccine	Change in Cumulative Incidence (%)	Change in Cumulative Hospital Admissions (%)
AstraZeneca (10% VE)	39.6%	37.4%
AstraZeneca (30% VE)	21.3%	20.1%
AstraZeneca (62% VE)	reference	reference
Pfizer/BioNTech	-3.46%	-2.32%

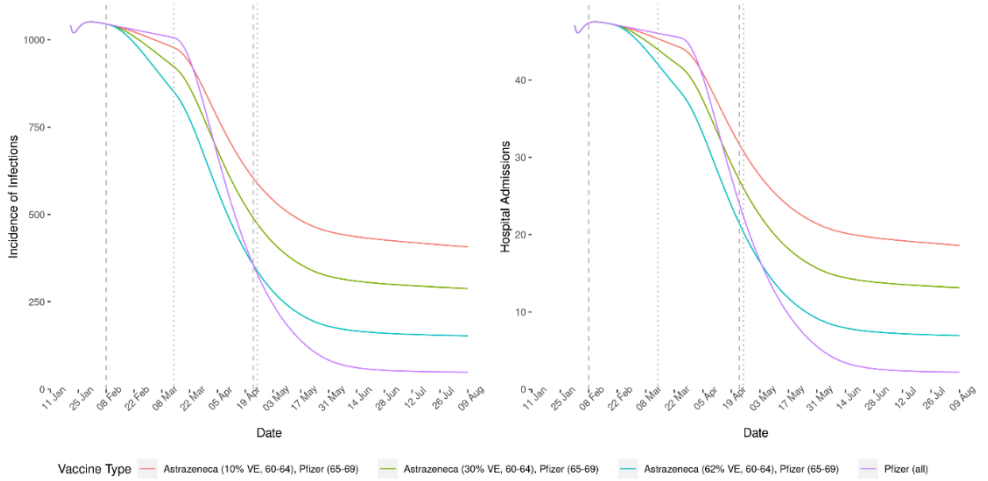

Figure 19. Modelled daily incidence of infections (left) and daily hospital admissions (right) in 60-69 year olds under different vaccination scenarios under the assumption of a constant force of infection. In all scenarios, people aged 65-69 receive the Pfizer vaccine, and the vaccine is varied among individuals aged 60-64. The vertical grey dashed lines indicate the start of AstraZeneca vaccination for doses 1 and 2. Dose 1 is assumed to start being administered on 8 February 2021 with dose 2 following 12-weeks later. The dotted grey vertical lines indicate the start of Pfizer vaccination (in this age group) for doses 1 and 2. Dose 1 is assumed to start being administered on 14 March 2021 with dose 2 following 6-weeks later. Date refers to either time of infection or time of hospital admission.

Table 6. Percent change in cumulative infections and hospital admissions under the different vaccination scenarios. In all scenarios, people aged 65-69 receive the Pfizer vaccine, so the vaccine type only varies among individuals aged 60-64. The reference scenario is where the AstraZeneca vaccine has an efficacy of 62% in individuals aged 60-64. AstraZeneca vaccination was assumed to start on 15 February 2021 and Pfizer vaccination was assumed to start on 19 April 2021.

Vaccine	**Change in Cumulative Incidence (%)**	**Change in Cumulative Hospital Admissions (%)**
AstraZeneca (10% VE)	24.9%	23.6%
AstraZeneca (30% VE)	7.75%	7.42%
AstraZeneca (62% VE)	reference	reference
Pfizer/BioNTech	29.3%	28.0%

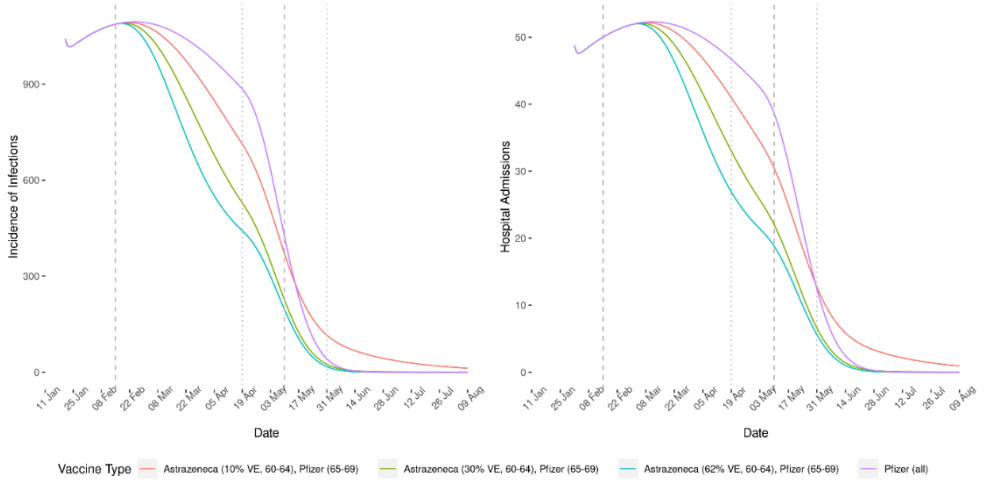

Figure 20. Modelled daily incidence of infections (left) and daily hospital admissions (right) in 60-69 year olds under different vaccination scenarios. In all scenarios, people aged 65-69 receive the Pfizer vaccine, and the vaccine is varied among individuals aged 60-64. The vertical grey dashed lines indicate the start of AstraZeneca vaccination for doses 1 and 2. Dose 1 is assumed to start being administered on 15 February 2021 with dose 2 following 12-weeks later. The dotted grey vertical lines indicate the start of Pfizer vaccination (in this age group) for doses 1 and 2. Dose 1 is assumed to start being administered on 19 April 2021 with dose 2 following 6-weeks later. Date refers to either time of infection or time of hospital admission.

Table 7. Percent change in cumulative infections and hospital admissions under the different vaccination scenarios under the assumption of a constant force of infection. In all scenarios, people aged 65-69 receive the Pfizer vaccine, so the vaccine type only varies among individuals aged 60-64. The reference scenario is where the AstraZeneca vaccine has an efficacy of 62% in individuals aged 60-64. AstraZeneca vaccination was assumed to start on 15 February 2021 and Pfizer vaccination was assumed to start on 19 April 2021.

Vaccine	**% change in Cumulative Incidence**	**% change Cumulative hospital admissions**
AstraZeneca (10% VE)	31.6%	16.0%
AstraZeneca (30% VE)	20.4%	12.1%
AstraZeneca (62% VE)	reference	reference
Pfizer/BioNTech	9.59%	3.97%

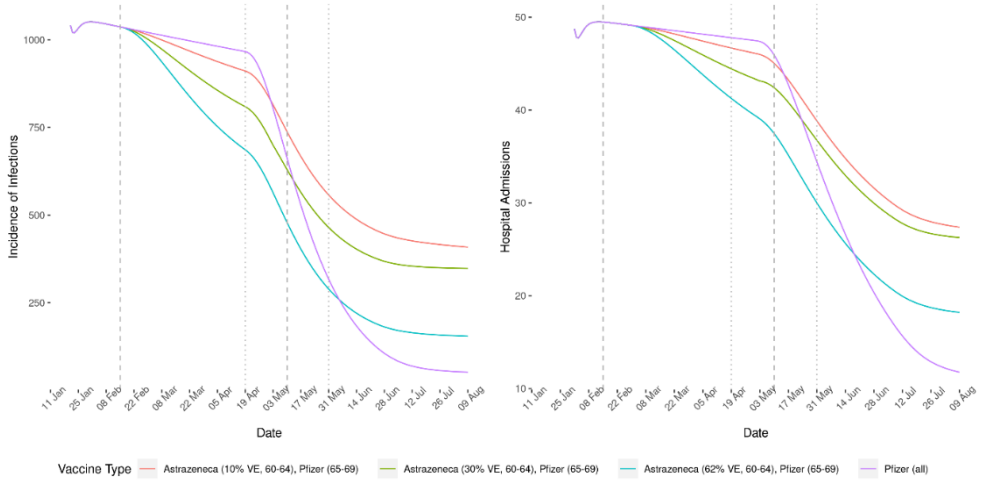

Figure 21. Modelled daily incidence of infections (left) and daily hospital admissions (right) in 60-69 year olds under different vaccination scenarios under the assumption of constant force of infection. In all scenarios, people aged 65-69 receive the Pfizer vaccine, and the vaccine is varied among individuals aged 60-64. The vertical grey dashed lines indicate the start of AstraZeneca vaccination for doses 1 and 2. Dose 1 is assumed to start being administered on 15 February 2021 with dose 2 following 12-weeks later. The dotted grey vertical lines indicate the start of Pfizer vaccination (in this age group) for doses 1 and 2. Dose 1 is assumed to start being administered on 19 April 2021 with dose 2 following 6-weeks later. Date refers to either time of infection or time of hospital admission.

4 What are the effects of deferral of the second dose for the AstraZeneca, Pfizer, Moderna vaccines?

Analysis of 3 Feb 2021

The registration of the vaccines from Pfizer-BioNTech, Moderna and Astra Zeneca are based on administering two doses. The vaccine trials allow for estimating the efficacy after a single dose and after a second dose. Typically, the vaccine efficacy after a single dose is measured from two weeks after receiving the single dose up to receiving the second dose, and the vaccine efficacy after two doses is measured from one week after receiving the second dose. In these vaccine trials the objective is to measure protection at the individual level.

When we focus on protection of a group of individuals rather than the individual protection, the question arises what the best use of scarce vaccines would be: if we have 100 doses of vaccine for 100 individuals, would it be better to vaccinate the entire population with a single dose or half of the population with two doses?

Whenever the efficacy after a single dose is higher than the increase of efficacy from one to two doses, it is better to give everyone a single dose. Whenever the increase of efficacy from one to two doses is higher than the efficacy after a single dose it is better to give half the population two doses. For example, when efficacy after the first dose is 70% and efficacy after the second dose is 90%, it would be better to give a dose as a first, single dose to someone who is unvaccinated (increase in protection with 70%) rather than as a second dose to someone who already had a single dose (increase in protection with 20%). This provides a statistical criterion: if the efficacy after a single dose is more than half the efficacy after two doses, it is worthwhile to defer the second dose.

After considering the results from the vaccine trials, as summarized in Table 3, we find that the efficacy after a single dose is more than half the efficacy after two doses for all three vaccines (Pfizer-BioNTech, Moderna and Astra Zeneca); therefore it is worthwhile to defer the second dose because, in the longer term, a sufficient number of doses will be available. Thus, everyone will receive a second dose. There is no argument for leaving individuals protected with only a single dose and deny them a second dose in the future.

Quantifying the health benefits of deferring a second dose for a vaccine can be done by assuming a future risk of disease (number of new COVID-19 cases per susceptible per day) and calculate for how long individuals are subjected to this risk without vaccination, with a single dose, and with two doses. By comparing the two options of giving two doses with a recommended short interval or a longer interval we can calculate the number of cases prevented by deferring the second dose.

Another approach to quantify the health benefit of deferring a second dose for a vaccine is to take a time horizon, say 200 days into the future, and calculate what the expected proportion of time each individual on average is protected by the vaccine. This will be a proportion that is a bit lower than the stated vaccine efficacy. By comparing the two options of giving two doses with a recommended short interval or a longer interval we can calculate the additional proportion of the population protected until the time horizon by deferring the second dose.

An example for the Pfizer-BioNTech vaccine. The vaccines are scarce, we get one batch of vaccine doses sufficient to vaccinate everyone once right now, and another batch of the same size in six weeks. If we take a time horizon of 200 days, and we would take the recommended three weeks between the first and second dose, we could protect a proportion of 0.829 of the population during the 200 days. If we would defer the second dose and take six weeks between the first and second dose, we could protect a proportion of 0.88 of the population during the 200 days.

For the Astra Zeneca vaccine, a recent pre-print (not yet peer reviewed) indicates that a longer time interval between the first and second doses improves vaccine efficacy. The study found that efficacy was highest in individuals who received two standard doses if the second dose was given 12 or more weeks after the first dose (82.4%) compared to less than 6 weeks after the first dose (54.9%). These efficacy estimates were supported by immunogenicity data showing a 2-fold higher antibody binding response after an interval of 12 or more weeks compared to less than 6 weeks [8]. This study provides evidence to support recommending a longer interval between doses for the Astra Zeneca vaccine.

5 What would have been the direct protection offered by targeting different age groups with a vaccine, had it been available before September 2020?

Analysis of 3 Feb 2021

5.1 Context

In this analysis we explore the direct impact of a COVID vaccination programme targeting specific age groups in a retrospective analysis, using data on reported COVID-19 cases, ICU admissions, morality and Disability Adjusted Life Years (DALYs) in the Netherlands over the period since September 1st , as available on December 14th 2020.

5.2 Direct protection

The impact of a vaccination programme is the sum of two effects, direct protection and indirect protection. When vaccination programmes are implemented two things happen: 1) vaccines prevent disease in those vaccinated called direct protection and 2) when the vaccine (partially) prevents transmission of infection, transmission will slow down, reducing the risk of infection in all, which results in indirect protection. The overall impact of a vaccination programme is the sum of these two processes. To date (February 3rd, 2021) there is no strong evidence for the vaccines against COVID-19 to be effective in reducing transmission of the SARS-CoV-2 virus. Given the uncertainties around the vaccine efficacy against transmission we look only at the direct protection.

The projected direct protection can be quantified in several ways. For example, you could look at the number of prevented hospitalizations or deaths, using different time horizons (coming days, weeks, or years), or you could look at a relative reduction, for example a percentage reduction of cases. For each of these ways there are pros and cons. For this analysis we choose to look at the percentage reduction of disease burden. We use the age distribution of cases rather than the absolute number and take it as indicative for the age distribution we will observe in the coming months.

5.3 Data

In this analysis we look at three levels of disease: mortality, ICU admissions and positive tests at the GGD. Mortality are those reported at the GGD and therefore do not include deaths which might be due to COVID but are not reported as such, it does therefore not include the so called excess mortality. The ICU admissions are those admission of which the patients survive, to circumvent double counting with mortality. The positive tests at the GGD are used as a proxy for infections. It is known that the propensity to test given symptoms is different between age groups, and it is therefore not perfect, but it is a good start. For the age distribution of tests and ICU we looked at the data from the 1st of September, as testing and ICU admission was different in the first wave. As these first three items are counts of cases and does not include a relative weight for severity for example the

number of life years foregone due to death, or that ICU admissions is more severe compared to an asymptomatic infection we also included DALYs as an end-point. DALYs stand for Disability Adjusted Life Year and includes the life expectancy as well as a different severity for different disease outcomes. In case the vaccination programme aims to reduce disease burden it is theoretically better to look at DALYs.

Cases and mortality from: https://www.rivm.nl/sites/default/files/2020-12/COVID-19_WebSite_rapport_wekelijks_20201215_1259.pdf; Table 14 and 21. ICU data from: https://stichting-nice.nl/covid-19-op-de-ic.jsp

5.4 Vaccination programme

For this analysis we look at the percentage reduction of disease burden of a programme in which 85% of the population receives the vaccine, and of which 90% is protected against any included disease end-point. Therefore, the overall impact of the programme in this analysis is a 76.5% reduction of disease (85% coverage * 90% efficacy). Though these values are not unlike the efficacy and coverage of the Pfizer-BioNTech vaccine in the elderly, the purpose of using these values is comparing the order of magnitude of the direct protection offered by targeting vaccination at specific age groups.

5.5 Results

There is a very distinct age pattern between mortality, DALY, ICU admissions and positive tests at the GGD. In Figure 22 we show the age distribution for the three end-points. Mortality is concentrated in the oldest age groups, ICU admissions of which the patients survive are in the those who are between 50 and 75, and positive tests are in those younger. DALYs peak at age 75 to 80, a younger age compared to mortality due to a longer life expectancy at this age.

The difference in age pattern has a clear implication for the expected direct impact of a vaccination programme. In Figure 23 we show the incremental direct impact of targeting vaccination at an increasing group of people, starting with only vaccinating those aged 90+, then vaccinating those aged 85+, and so on. The maximum impact by direct protection (which is 76.5%) is achieved when all age groups are vaccinated. However, a substantial impact can already be achieved by vaccinating selected age groups. If we are interested in reducing mortality by 50% via direct protection, it suffices to vaccinate the 75+ year olds. If we are interested in reducing DALYs by 50% via direct protection, it suffices to vaccinate the 70+ year olds. If we are interested in reducing ICU admissions by 50%, it suffices to vaccinate the 55+ year olds.

5.6 Limitations

We focus only on the direct protection offered by vaccination against COVID-19, in temporary absence of strong evidence supporting efficacy of vaccinates in reducing transmission of SARS-CoV-2. Such evidence might surface in the coming weeks. The indirect protection offered by vaccination can be substantial and should be included at a later stage.

For the moment, these estimates provide a tentative lower bound of the total protection offered by vaccination.

We have used data recorded in a part of the "second wave" of the pandemic in the Netherlands. The distribution of reported cases, ICU admissions and deaths over age groups might not necessarily be representative of the distribution of cases, admissions and deaths in a future wave of the pandemic, but we don't have reasons to expect large differences in the distribution.

We use hypothetical values for the vaccine uptake and the vaccine efficacy. The values might be close to what we expect for the uptake and efficacy of the Pfizer-BioNTech vaccine in the elderly, they will be too high for the uptake and efficacy of the AstraZeneca vaccine.

We calculate the percentage reduction in the disease burden by direct protection, using the age distribution of cases, ICU admissions and deaths as recorded from September 1st to December 15th, 2020. The non-pharmaceutical control measures that were in place in that period have been adapted to the incidence of reported cases and hospital admission and ICU admissions at that time. Control measures or vaccination might have some effect on the age distribution of cases, and it is important to realize that the finding is conditional on the particular control measures that were in place from September 1 to December 15, 2020.

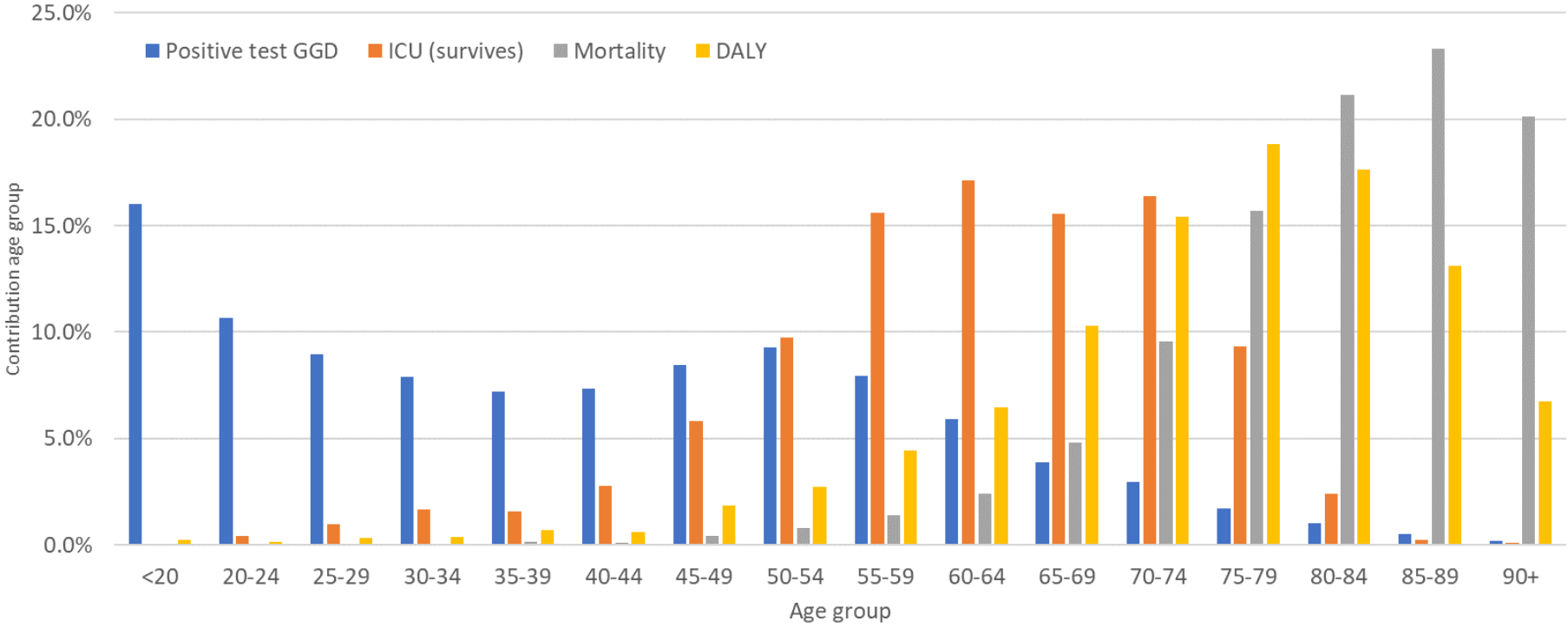

Figure 22. The contribution of age groups towards the overall reported disease burden by age. DALYs in yellow, mortality in grey, ICU admission in orange and positive tests in blue bars.

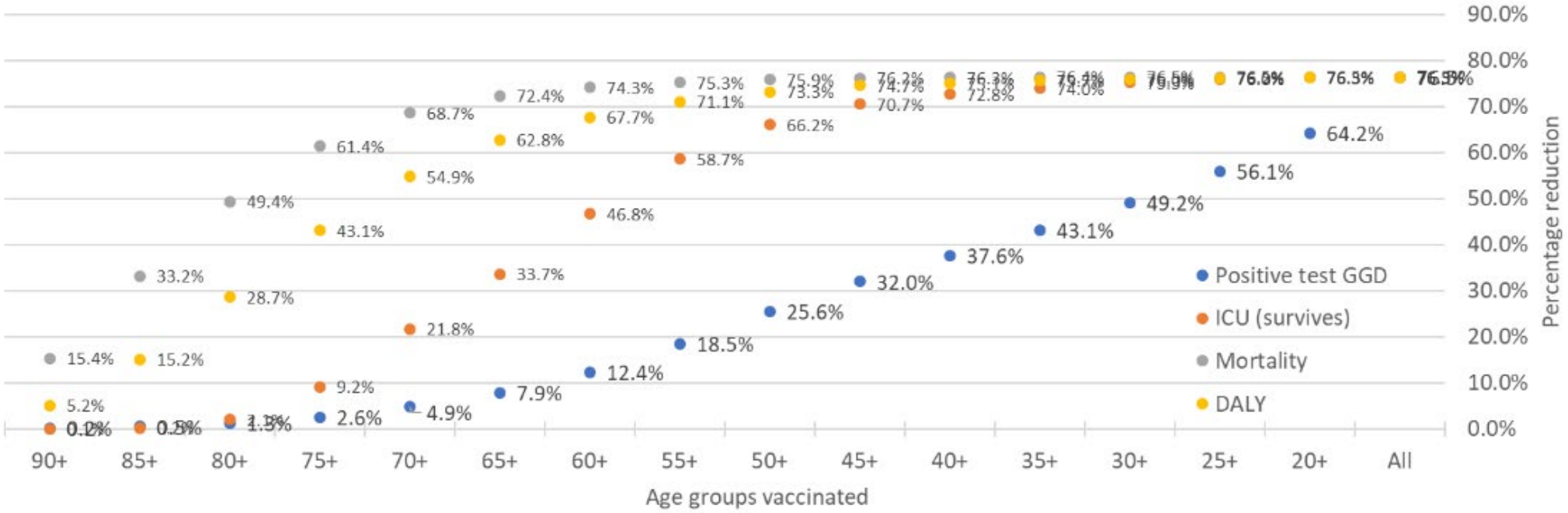

Figure 23. Incremental level of prevented disease burden (DALY, mortality, ICU admission and positive test) for vaccination programmes targeting more age groups, starting with only vaccinating those aged 90+.

6 Which groups within the 18-59 year old should be vaccinated first?

Analysis of 10 Feb 2021, text updated 15 March 2021

6.1 Context

The individuals at highest risk of severe COVID-19 are scheduled to be vaccinated first. These include all individuals aged 60 and older and individuals with underlying health conditions. In addition to those, some professional groups including health workers have been selected for vaccination. The AstraZeneca Moderna, and Janssen vaccines have been approved by the EMA for ages 18 and older, the BioNTech-Pfizer vaccine has been approved for ages 16 and older. This leaves the question how to vaccinate the healthy adult population under 60 years of age.

There are various ways to categorize the healthy adult population: for example, by age or by profession. For professional categories, there is little evidence for a substantial difference in burden of disease. Comparisons between professions are complicated by differences in testing behavior between different professions. There is no evidence for vaccine efficacy against absence from work, which makes it difficult to make a case for vaccinating professions that are considered critical infrastructure. There is a limited role for gender or geographical location. In contrast, age is the most relevant indicator for both the risk of contracting infection (as measured by the number of close contacts that are made) and the burden of COVID-19 disease. Here we categorize the population by age, taking broad 10-year age groups and including the 18-19 with the 20-29 year old.

6.2 Current state of the pandemic in the Netherlands

We estimate that the overall percentage of the population that has detectable levels of antibodies against SARS-CoV-2 in the Netherlands after natural infection, as of February 10th, 2021, is in the order of 15% to 20%. We can estimate the cumulative number of infected with SARS-CoV-2 in the Netherlands based on the number of hospitalisations and the ratio of seroconversions per hospitalization. This estimation procedure uses the age-specific ratio of individuals seropositive according to the Pienter-Corona 2 study in June 2020 and number of hospitalizations up to July 2020. The resulting estimate is: 3,085,611 (95% interval 2619491 – 3575860). This corresponds to a percentage of the total population of 17.7% (95% interval 15.0% - 20.6%), where the 95% interval is taken too broad by construction. These values are also in line with an extrapolation of the approach to calculate the proportion immunes by age shown in Figure 24.

The overall percentage of the population with detectable levels of antibodies hides marked differences by age, the 18-29 year old has the highest percentage (Figure 24). The incidence of notified cases over the past 30 days was highest in the 18-29 year old group, followed by the 50-59 year old group (Figure 25). Combining the incidence of notified

cases with the percentage seropositive reveals that the hazard rate of becoming a notified case is highest in the 20-29 year old group, followed by the 50-59 year old group.

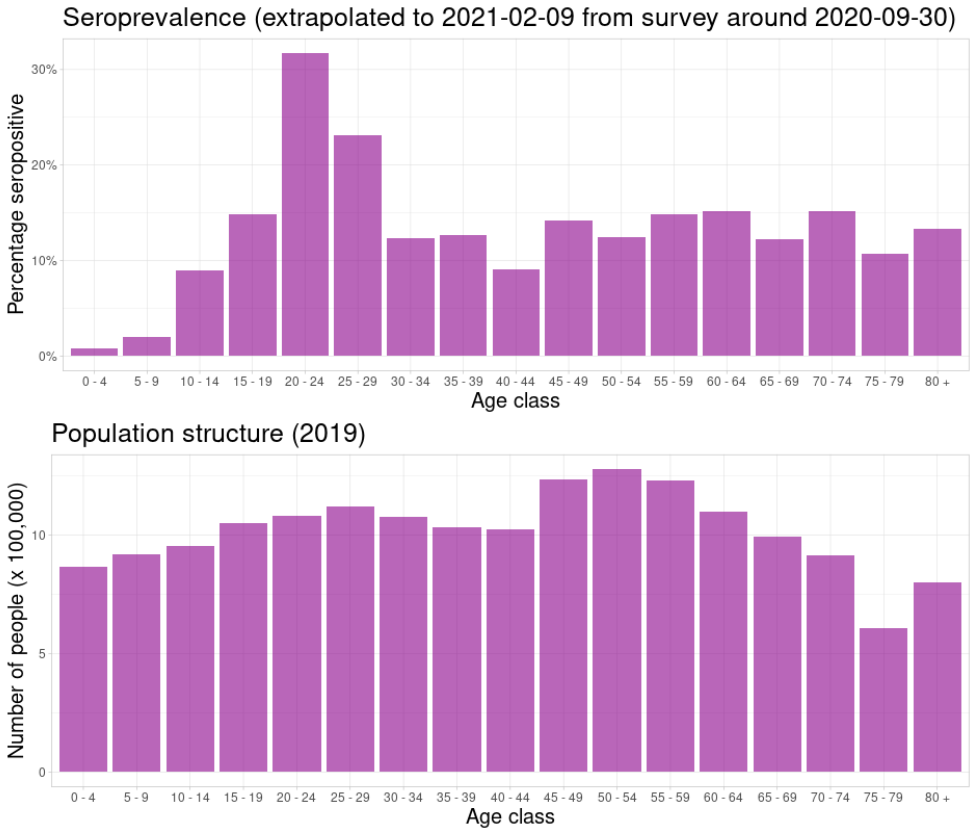

Figure 24. Current estimate of the age-specific percentage of the population with detectable antibodies against SARS-CoV-2 in the Netherlands after natural infection, as of February 10th, 2021. (a) estimated percentage seropositive. The estimates are based on the Pienter-Corona study among a representative sample of the Dutch population (https://www.rivm.nl/pienter-corona-studie). Blood samples were collected late September, and antibody levels become detectable around two weeks after infection. Extrapolation from October September 2020 is based on reported COVID-19 cases hospitalisations. (b) The number of people in each age group in the Dutch population, shown here for 2019, is shown as a reference.

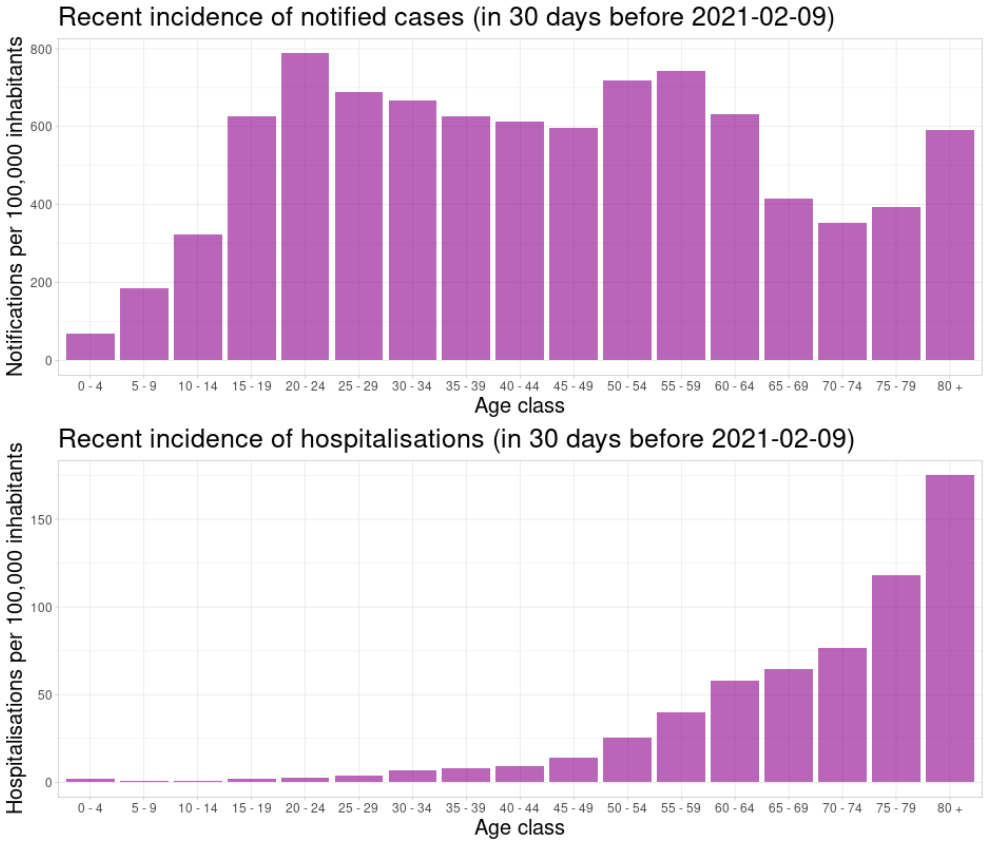

Figure 25. Incidence of notified COVID-19 cases in the Netherlands, by age, over the interval 10 January – 9 February 2021. (a) Cases with a positive test as notified to the GGD and recorded in the OSIRIS system. (b) severe cases with a positive test and admitted to the hospital as recorded in the NICE database, which includes cases who tested positive but were admitted for other causes than COVID-19.

6.3 Exploring vaccination schemes

We look at a few vaccination schemes where healthy adult individuals are ranked according to their age-specific risk. First, we focus on the risk of severe COVID-19 disease, where we take hospitalization as a proxy of severe disease; second, we focus on the risk of becoming a COVID-19 case.

- Ranking by age-specific risk of severe outcome. In an earlier section we have reported on the burden of COVID-19 disease by age, most of the burden is due to mortality. We have also shown the number of hospitalizations with a positive test (Figure 2b). Ranking age groups by risk of severe outcomes would result in ranking the oldest first. The order would be: 50-59, 40-49, 30-39, 18-29.
- Ranking by age-specific risk of becoming a case. Here we might distinguish between the risk per capita (incidence rate) or the risk per susceptible (hazard rate). Both measures result in similar ranking of age groups. The order would be: 18-29, 50-59, 40-49, 30-39, the last two age groups hardly differ.
- Ranking by age-specific risk of becoming a case, with stronger focus on the general trend. The general trend is here that within

the adult population the risk declines with age. The order would be: 18-29, 30-39, 40-49, 50-59.
- A natural reference point for evaluating the impact of these vaccination schemes is no vaccination for the healthy adult population.

This results in four vaccination schemes:
1) Old to young: vaccination begins with 50-59 year olds and then progresses through 10-year age bands in decreasing order (50-59, 40-49, etc.)
2) Young to old: vaccination begins in 18-19 year olds and then progress through 10-year age bands in increasing order (18-19, 20-29, 30-39, etc.)
3) Alternative: vaccination begins in 18-30 years olds followed by 50-59 year olds and then progresses to 40-49 year olds and then 30-39 year olds.
4) No vaccination: there is no vaccination in the healthy adult population.

We assess the relative performance of these vaccination schemes with different simulation models.

6.4 Modelling results, part 1: relative performance of the vaccination schemes

There are only moderate differences between the different vaccine allocation schemes (Figure 26, Table 8). Old to young results in the fewest cumulative outcomes. All vaccination strategies in healthy adults result in fewer outcomes than the situation in which there is no vaccination in the healthy adult population. Because the epidemic is declining when vaccination of healthy people begins (grey line in Figure 26) there is only a decrease in outcomes when vaccinating healthy adults versus not vaccinating healthy adults. This analysis assumes a one way relaxation of non-pharmaceutical interventions (i.e., interventions are not re-imposed if cases rise after measures are relaxed). This results in a resurgence in infections following the relaxation of measures. These results underscore the importance of keeping non-pharmaceutical interventions in place during vaccine roll-out and the potential for resurgence if measures are relaxed too soon.

We performed a sensitivity analysis where we assume strict measures, similar to a situation in February 2021, are re-imposed if cases rise above 35.7 per 100,000 people per day (Figure 27, Table 8). Overall, re-imposing strict measures reduces outcomes substantially; however, it requires measures to be relaxed and then made stricter several times, resulting in the jagged shape seen in Figure 27. When strict measures are re-imposed, the alternative vaccination scheme results in the fewest new infections, the young to old scheme results in the fewest cases, and the old to young approach results in the fewest hospital admissions, IC admissions, and deaths (Table 8).

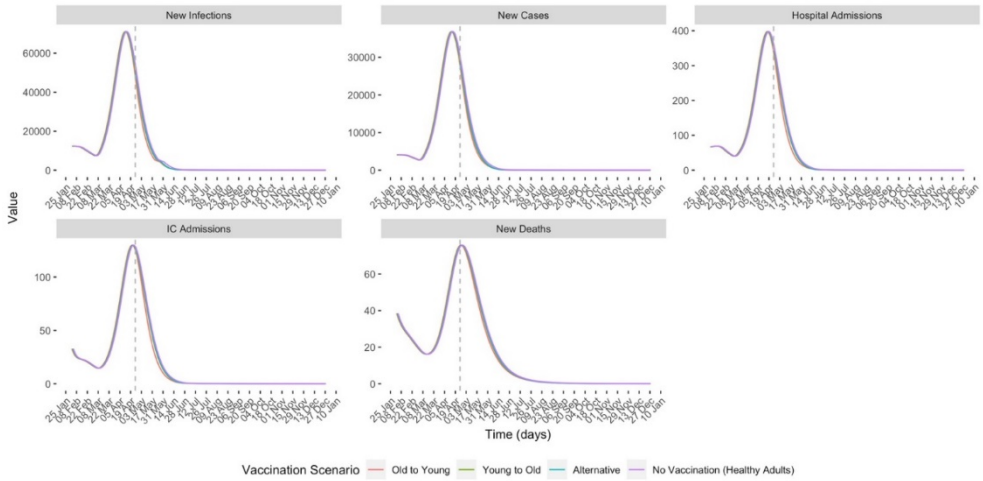

Figure 26. New infections, new cases, hospital admissions, IC admissions, and new deaths under different AstraZeneca and Janssen vaccine allocation schemes: 1) old to young, 2) young to old, 3) alternative, 4) no vaccination (in healthy adults). Lines for the vaccine schemes have been jittered for increased visibility. The grey vertical dashed line represents the start of vaccination in healthy adults.

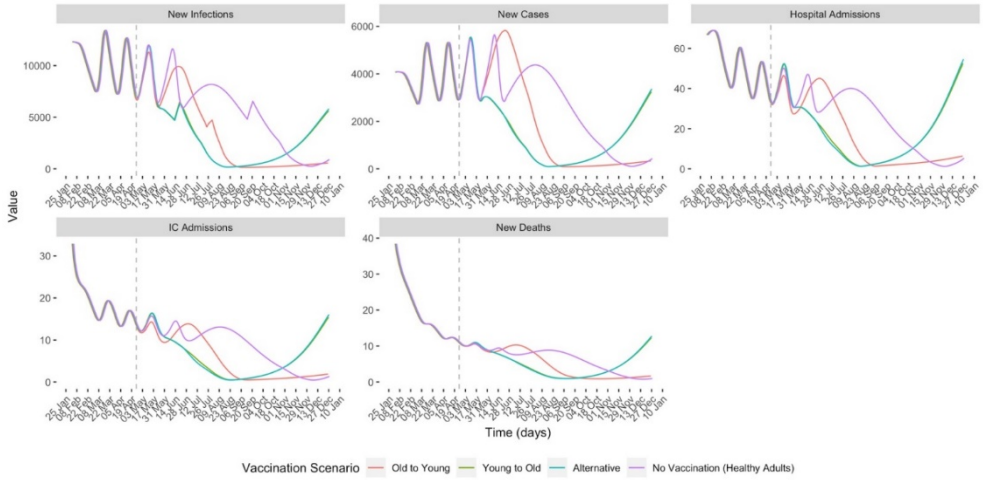

Figure 27. Sensitivity analysis of expected outcomes when strict measures are re-imposed after new daily cases rise above threshold of 35.7 new cases per 100,000 people per day. New infections, new cases, hospital admissions, IC admissions, and new deaths under different AstraZeneca and Janssen vaccine allocation schemes are shown. Vaccine allocation schemes: 1) old to young, 2) young to old, 3) alternative, 4) no vaccination (in healthy adults). The grey vertical dashed line represents the start of vaccination in healthy adults.

Table 8. Cumulative new infections, new cases, hospital admissions, IC admissions, and new deaths under different vaccine allocation schemes over the period 1 February – 31 December 2021. Since vaccination of healthy adults starts on 25 April 2021, differences between vaccination schemes are moderate. Vaccination schemes with the best performance are highlighted in bold. The main analysis assumes a one-way relaxation of measures. The sensitivity analysis assumes lockdown measures are re-imposed if new daily cases reach the upper threshold 35.7 per 100,000 per day.

Analysis	Scenario	New Infections	New Cases	Hospital Admissions	IC Admissions	Deaths
Main	Old to young	**3,152,724**	**1,583,983**	**18,088**	**6,306**	**5,307**
	Young to old	3,210,120	1,604,006	18,571	6,493	5,387
	Alternative	3,209,656	1,603,808	18,566	6,491	5,386
	No Vaccination (Healthy adults)	3,260,150	1,628,193	18,756	6,553	5,429
Sensitivity Analysis	Old to young	1,712,100	792,657	**8,605**	**3,009**	**2,909**
	Young to old	1,667,260	**717,194**	9,278	3,189	2,981
	Alternative	**1,666,294**	718,383	9,280	3,183	2,982
	No Vaccination (Healthy adults)	2,215,366	970,967	10,503	3,687	3,249

6.4.1 Simulation model

A full description of the simulation model can be found in the Appendix. Briefly, we use an age-structured compartmental susceptible-exposed-infected-recovered model (SEIR) that is extended to include compartments for vaccinated individuals, hospitalisations, intensive care admissions, and deaths. The population is partitioned into 10-year age bands. The contacts within and between age groups is based on contacts as monitored in the Pienter Corona 3 & 4 studies with contact changes according to non-pharmaceutical control measures at different periods in 2020 and 2021. Measures are only relaxed and not re-imposed if cases rise, so these results indicate a pessimistic scenario. We conduct a sensitivity analysis in which measures similar to a situation in February 2021 are re-imposed if cases rise above 35.7 per 100,000 per day. To account for the increasing proportion of cases due to the UK variant of concern, we assume an effective reproduction that is the midpoint between the wildtype (0.94) and the UK variant (1.13) for an effective reproduction number of 1.04.

All healthy adults are vaccinated by a vaccine with properties similar to that of AstraZeneca or Janssen (Table A3). Vaccination of healthy adults is assumed to begin on 25 April with approximately 1,425,000 doses allocated to 50-59 year olds, 1,165,000 doses allocated to 40-49 year olds, and 3,325,000 doses allocated to 18-39 years olds. Vaccine efficacy is assumed to be against infection (and therefore against symptoms and transmission).

The objective of this specific model is to capture the dynamic aspects of vaccine allocation when comparing the alternative vaccination schemes. As this model is not explicitly calibrated, fitted or tested against actual observations, the outcome will not be a quantitative prediction; rather, the objective is to detect the ordering of the vaccination schemes with respect to alternative outcomes.

6.5 Modelling results, part 2: relative performance of the vaccination schemes with alternative sets of non-pharmaceutical control measures

Having established that there are small differences between the vaccination schemes for healthy adults, we explore these differences with alternative sets of non-pharmaceutical control measures. We establish that the relative order for cumulative hospital admission as outcome appears robust to such changes, the vaccination scheme "old to young" results in the least hospital admissions (Table 9) regardless of the non-pharmaceutical control measures.

Table 9. Cumulative hospital admissions under different vaccine allocation schemes and different sets of non-pharmaceutical control measures over the period 1 May – 1 August 2021. Since vaccination of healthy adults starts on 25 April 2021, differences between vaccination schemes are very small. The presented numbers reflect the median with a 95% interval for simulation outcomes. Vaccination schemes with the best performance are highlighted in bold.

Vaccine Allocation Scheme	Continue with current control measures	Schools open, lift evening curfew and allow more than 1 visitor per household per 1 March 2021	Schools and non-essential retail open lift evening curfew and allow more than 1 visitor per household per 1 March 2021
Old to young	**314** (25-1449)	**2274** (268-3906)	**4109** (803-5515)
Young to old	**314** (25-1452)	2282 (269-3919)	4122 (802-5532)
Alternative	**314** (25-1450)	2278 (269-3916)	4114 (802-5529)
No Vaccination	316 (25-1458)	2311 (274-3962)	4162 (832-5565)

6.5.1 *Simulation model*

We use an age-structured compartmental model (SEIR). The population is partitioned into 10-year age bands. The contacts within and between age groups is based on contacts are monitored in the Pienter 3 study with changes according to alternative sets of non-pharmaceutical control measures (https://www.rivm.nl/coronavirus-covid-19/hoe-berekeningen-bijdragen-aan-bestrijding-van-virus/rekenmodellen). The vaccine efficacy is assumed to be against infection (and therefore against symptoms and transmission). The objective of this specific model is to make short-term prognoses for number of ICU admissions and hospital admissions. This model is fitted to actual observations of ICU admission per day in the Netherlands and produces a distribution of outcomes. More background on this model can be found on the RIVM webpages (https://www.rivm.nl/coronavirus-covid-19/rekenmodellen). The objective is to here to detect an effect of non-pharmaceutical control measures on the relative performance of the vaccination schemes.

6.5.2 *Assumptions*

a. Transmission rates are estimated from the daily rates of ICU admissions in the Netherlands
b. Vaccination in healthy individuals starts on 25 April 2021
c. Vaccines are adapted from the current vaccination scheme

d. The same contact matrix is assumed for the entire period of the simulation

6.6 Limitations

In proposing the three vaccination schemes we have not explicitly accounted for several factors. Of these factors, transmission stands out. In the simulation models we assume that vaccination has an effect on transmission, even though at the time of writing there is no clear evidence available for a protective effect of vaccines against transmission; we expect that such evidence might become available in the near future. This effect of vaccination on transmission would provide an argument for targeting those age groups that contribute most to transmission. A useful measure to quantify the contribution of a group to transmission is the product of incidence of infection and force of infection, a measure that is proportional to the relative decrease in the reproduction number after a vaccinating a single person in that group whenever at-risk events for transmission are reciprocal, such as is the case for COVID-19 [9]. If case ascertainment varies little by age within the healthy adult population, this measure coincides with the incidence rate of cases and hazard rate of cases. The vaccination schemes that target transmitters will then coincide with the vaccination schemes based on the risk of becoming a notified case.

We have assumed that a proportion of healthy individuals in each age group receive the AstraZeneca vaccine and the remaining (who are willing to be vaccinated) receive the Janssen vaccine (based on the projected availability of both vaccines). However, we have made no additional choice regarding which group receives which vaccine and how many doses. The choice of vaccines might become relevant if the objective of vaccination includes blocking transmission of infection to the vulnerable population that is not vaccinated (an estimated 15% of each age groups is not vaccinated). In that case the vaccine efficacy against transmission will be relevant, and the vaccine with the highest efficacy against transmission should be allocated to the age group that contributes most to further transmission. As explained above, this is the age group with the highest incidence rate of infection and the highest hazard rate of infection. In the current state of the pandemic in the Netherlands, this is the 18-29 year old age group.

A change of control measures affects the age-distribution of cases and could potentially affect the ranking of age groups. However, during the entire pandemic in the Netherlands, the ranking of age groups with respect to incidence of infection has been rather robust to changes in the control measures, with the 18-29 year old age group having the highest incidence and hazard rate of cases. The additional simulations in Table 2 confirm that the performance of the vaccination schemes is robust over a range of different non-pharmaceutical control measures, in case the vaccination of healthy adults starts in the descending phase of an epidemic wave.

There are several variants of concern that have a different reproduction number and could also vary in regard to vaccine efficacy. As long as the ordering of the age groups are not differentially affected, this does not

change the order in the vaccination scheme. A decreased vaccine efficacy for transmission against a new variant of concern could have consequences for which vaccines should be allocated to the groups that contribute most to further transmission.

Vaccination of the 15-17 year olds is not considered here, but the incidence of reported cases and the seroprevalence in this age group is, on average, of a similar magnitude as the 40-49 year olds. When vaccines are approved for the younger ages, it would be natural to consider this age group as well. Following the order of age groups as discussed here, the age group will be the last in line for all three schemes.

We have not accounted for the socio-geographical clustering of vaccine refusers. The clustering of vaccine refusers in low coverage areas may result in local outbreaks of COVID-19, even at a high national vaccine coverage. This underlines the need to vaccinate the vulnerable individuals that are willing to be vaccinated in low coverage areas.

The estimated impact of vaccination schemes is highly dependent on the non-pharmaceutical control measures, the advent of new variants, the precise choice of vaccines and the rate of vaccination. Therefore, the estimates should be considered with great care. The relative ordering of the impact of the vaccination schemes is more relevant to decisions making and more robust to future changes in non-pharmaceutical control measures.

7 Vaccine efficacy against infection and transmission

Analysis of 18 Feb 2021, text updated 23 March 2021

Vaccination against COVID-19 is currently being implemented worldwide to curb the ongoing pandemic. However, there are still questions about the exact nature of protection offered by the various vaccines currently in use and those still in development. Two of those important questions are whether the vaccines 1) prevent infection and 2) block transmission. Preventing infection refers to a vaccine preventing a vaccinated individual from getting infected even if they are exposed to the virus. Blocking transmission refers to the vaccine preventing a vaccinated individual who gets infected with the virus from infecting other people. Few studies have been published that provide answers to these two questions, however those available as of March 23rd, 2021 are summarised in this report. We anticipate more results addressing these questions will be available in the coming months.

7.1 Pfizer/BioNTech

A recent preprint found that the Pfizer/BioNTech vaccine had an effectiveness of 51% against infection 13-24 days after the first dose [10]. A re-analysis of this data by Hunter et al. found that by 24 days after vaccination vaccine effectiveness reached 90% [11] (note: vaccine effectiveness is measured in the general population whereas vaccine efficacy is measured in a trial, these two quantities can differ). Two recent studies in Israel released pre-prints in early February which evaluated viral load in vaccinated individuals. The first study found that vaccination reduced viral load by 1.6 to 20 times in vaccinated individuals who tested positive for SARS-CoV-2 [12]. The second study found that infections occurring 12-28 days after vaccination had a 4-fold reduction in viral load [13]. These results suggest that vaccination may reduce viral shedding and contagiousness, which may prevent onward transmission. A study of health care workers found that 1 dose of the Pfizer/BioNTech vaccine resulted in a reduction of the rate of SARS-CoV-2 infection by 75% 15-28 days after the first dose of vaccination. Estimates of the reduction in infection after the second dose were not included [14]. A recent study from the UK estimated vaccine effectiveness against symptomatic COVID-19 to be approximately 60-70% in individuals aged 70 and older after the first dose. Vaccine effectiveness increased to approximately 85-90% after the second dose. However, one drawback of this study is that they only include symptomatic cases of COVID-19. Therefore, the results do not generalise to vaccine effectiveness against all cases of COVID-19 (both symptomatic and asymptomatic) [15]. Finally, a study in health care workers in the UK found vaccine effectiveness against symptomatic and asymptomatic infection to be 70% (95% CI: 53%, 87%) 21 days after the first dose and 85% (95% CI: 74% - 96%) 7 days after the second dose. This study was conducted when the UK variant (B.1.1.7) predominated SARS-CoV-2 infections in the UK and provides evidence that the Pfizer/BioNTech vaccine protects against the UK variant [16].

7.2 Moderna

The original clinical trial to assess vaccine efficacy was not designed to determine efficacy against infection and transmission. The data were not sufficient to assess asymptomatic infection; however, the results from a preliminary exploratory analysis suggested some degree of protection against asymptomatic infection after the first dose. Studies to assess asymptomatic or subclinical infections and viral shedding as well as to assess how vaccination affects infectiousness are underway [7].

7.3 AstraZeneca

In a study in the UK in which study participants self-administered a nose and throat swab weekly, efficacy against asymptomatic COVID-19 (or unknown symptom status) was shown to be small and in most cases not statistically significant from zero. Efficacy was estimated in all participants as 27.3% (95% CI: -17.2%, 54.9%), in low dose/standard dose (LD/SD) recipients as 58.9% (1.0, 82.9), and standard/standard dose (SD/SD) recipients as 3.8% (-72.4%, 46.3%). LD/SD participants only included those 18-55 years old [5]. It is unclear whether this may explain at least part of the differences observed between the LD/SD and SD/SD recipients. Results from a more recent study in the UK with the same design (weekly self-administered nose and throat swabs) were similar. VE against asymptomatic COVID-19 occurring more than 14 days after a booster dose are as follows: 49.3% (7.4%, 72.2%) in LD/SD recipients and 2.0% (-50.7%, 36.2%) in SD/SD recipients. This study further uses PCR positivity after vaccination as a measure to assess reduction in the burden of infection. They found that after a single standard dose of the vaccine, the vaccine reduced PCR positivity by 67.6% (49.5%, 78.7%) and after a second standard dose PCR positivity was reduced by 49.5% (37.7%, 59.0%). These results indicate that the vaccine may have a substantial impact on transmission by reducing infections in the population [8]. A recent study from the UK estimated vaccine effectiveness against symptomatic COVID-19 to be approximately 60-75% in individuals aged 70 and older after the first dose. The study did not include estimates of vaccine effectiveness after the second dose. As this study only included symptomatic cases of COVID-19, the results do not generalise to vaccine effectiveness against all cases of COVID-19 (both symptomatic and asymptomatic) [15]. There was no data available about the AstraZeneca vaccine's ability to prevent transmission.

7.4 Vaccine efficacy and variants of the SARS-CoV-2 virus

7.4.1 Epidemiology in the Netherlands

The 20I/501.V1 /VOC 202012/01 (B.1.1.7) has spread rapidly to become the dominant variant in the Netherlands. Surveillance for variant SARS-CoV-2 viruses is based on a random sample from persons who tested positive for SARS-CoV-2 infection. Up to week 4 of 2021 (up to 31 Jan 2021), the percentage of the samples obtained each week were calculated for the variant 20I/501.V1 /VOC 202012/01 (B.1.1.7) (UK variant) and for the 20H/501.V2 variant (SA variant) (Figure 28).

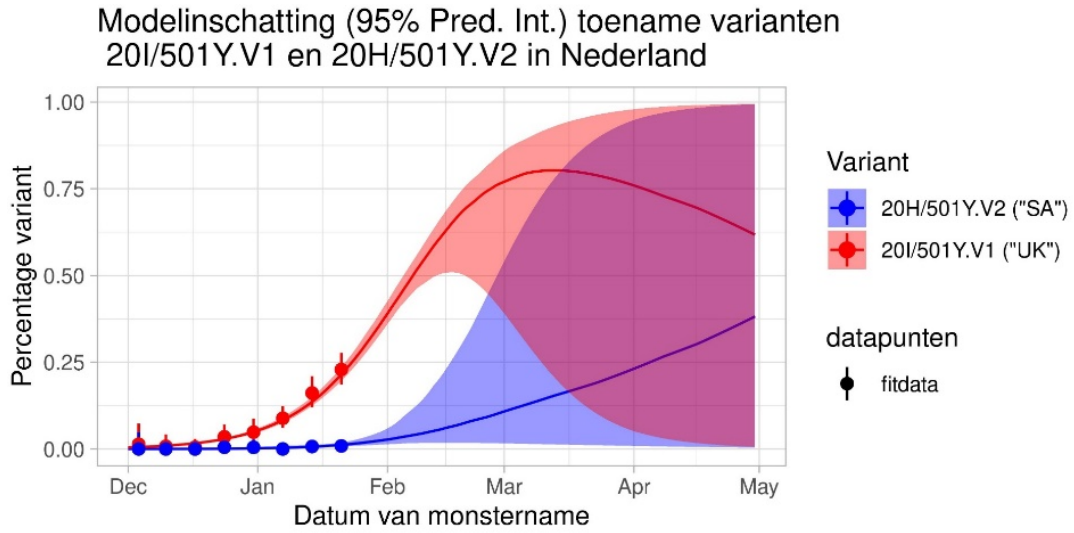

Figure 28. Observed percentage of variants by date of sampling in the Netherlands, 2021. Lines indicate median, shaded area indicates the 95% confidence interval, of logistic growth curves that are fitted to the observations.

7.4.2 *Transmissibility*

The variants appear to have increased transmissibility compared to previously circulating variants. We fitted the increase of the variants using logistic regression, and converted the estimated growth rates to estimates for the reproduction number R. The resulting estimates reveal that the 20I/501.V1 /VOC 202012/01 (B.1.1.7) (UK variant) has a reproduction number that is 36% higher (95% CI: 34% , 38%) as compared to the existing variant; the 20H/501.V2 variant (SA variant) has a reproduction number that is 47% higher (95% CI: 22% , 78%) as compared to the existing variant.

7.4.3 *Severity of disease*

There is evidence from analysis of multiple different datasets in the UK that infection with VOC B.1.1.7 is associated with an increased risk of hospitalisation and death compared to infection with non-VOC viruses [17].

7.4.4 *Vaccine efficacy*

There are indications that the vaccine efficacy might be lower for some variants as compared to the old variant. Very few data. One manuscript (not peer reviewed) reports a low vaccine efficacy of the AstraZeneca vaccine in South Africa where the B.1.351 (501Y.V2) variant is dominant [18]. One possible interpretation is that the vaccine efficacy of the AstraZeneca vaccine is lowered against this variant. However, other plausible explanations cannot be excluded.

7.4.5 *Conclusion*

The vaccine trials that included a test for PCR positivity, as a proxy for SARS-CoV-2 infection, suggest that there is a substantial reduction in infection after receiving one or two doses of vaccine. An open question is what number of infections will be caused by a typical infected individual that is vaccinated. As a decreased viral load can lead to absence of typical symptoms, it is possible that individuals will expose

others over a longer time period. But a decreased viral load could lead to lowered contagiousness, such that vaccinated but infected individuals could infect fewer others per unit of time. The number of infections caused by an infected individual that is vaccinated might therefore be smaller or larger than the number of infections caused by an infected individual that is not vaccinated.

8 What is the expected impact of vaccination on disease outcomes?

Analysis of 25 Feb 2021, text updated 15 March 2021

The impact of a vaccination program is defined as the proportion of events (e.g., cases, hospitalisations, deaths) prevented in a population with vaccination compared to a population without vaccination. Using modelling we can assess the expected impact of a vaccination program by comparing simulated populations with and without vaccination under the same conditions. In this section, we report the estimated impact of several vaccination strategies in The Netherlands with respect to new infections, new cases, hospital admissions, intensive care admissions, deaths, life years lost, and disability adjusted life years (DALYs). The vaccination strategies assessed are:

1) Old to young: vaccination begins with 50-59 year olds and then progresses through 10-year age bands in decreasing order (50-59, 40-49, etc.)
2) Young to old: vaccination begins in 18-19 year olds and then progress through 10-year age bands in increasing order (18-19, 20-29, 30-39, etc.)
3) Alternative: vaccination begins in 18-29 years olds followed by 50-59 year olds and then progresses to 40-49 year olds and then 30-39 year olds.
4) No vaccination: there is no vaccination in the healthy adult population

We focus on the order of age groups and, therefore, present simulations where everyone in the 18-59 year age group would receive a similar vaccine. These vaccination strategies are compared to no vaccination in the population at all.

8.1 Summary

Regardless of the vaccination strategy, implementing a COVID-19 vaccination program results in fewer cumulative new infections, new cases, hospital admissions, IC admissions, new deaths, life years lost, and DALYs compared to no vaccination (Table 1). Overall, there was very little difference between the different vaccination programs (Figure 1), but the old to young vaccination program resulted in the smallest number of infections, cases, hospital admissions, IC admissions, deaths, life years lost and DALYs.

8.2 Methods

A full description of the simulation model can be found in the Appendix. Briefly, we use an age-structured compartmental susceptible-exposed-infected-recovered model (SEIR) that is extended to include compartments for vaccinated individuals, hospitalisations, intensive care admissions, and deaths. The population is partitioned into 10-year age bands. The contacts within and between age groups is based on contacts as monitored in the Pienter Corona 3 & 4 studies with contact changes

according to non-pharmaceutical control measures at different periods in 2020 and 2021.

The objective of this specific model is to capture the dynamic aspects of vaccine allocation when comparing the alternative vaccination schemes. As this model is not explicitly calibrated, fitted or tested against actual observations, the outcome will not be a quantitative prediction; rather, the objective is to detect the ordering of the vaccination schemes with respect to alternative outcomes.

In the model, all individuals vaccinated before 1 February 2021 are assumed to be vaccinated on 31 January. We include vaccination with all currently approved vaccines (Pfizer/BioNTech, Moderna, AstraZeneca, Janssen). All healthy adults are vaccinated by a vaccine with properties similar to that of AstraZeneca or Janssen (Table A3). Vaccination of healthy adults is assumed to begin on 25 April with approximately 1,425,000 doses allocated to 50-59 year olds, 1,165,000 doses allocated to 40-49 year olds, and 3,325,000 doses allocated to 18-39 years olds. Vaccine efficacy is assumed to be against infection (and therefore against symptoms and transmission).

In the simulations we also include the indirect protection offered by the reduction in risk of infection assuming the vaccine protects at least partially against infection. We report the numbers for each outcome of interest, for the various vaccination strategies and the numbers that would have resulted without vaccination. The difference in number of outcomes between the vaccination strategies and no vaccination is the result of both direct and indirect protection.

8.3 Results

Regardless of the vaccination strategy, implementing a COVID-19 vaccination program results in fewer cumulative new infections, new cases, hospital admissions, IC admissions, new deaths, life years lost, and DALYs compared to no vaccination (Table 10). There are only moderate differences between the different vaccine allocation schemes (Figure 29, Table 10). Old to young results in the fewest cumulative outcomes. All vaccination strategies in healthy adults result in fewer outcomes than the situation in which there is no vaccination in the healthy adult population. Because the epidemic is declining when vaccination of healthy people begins (grey line in Figure 29) there is only a decrease in outcomes when vaccinating healthy adults versus not vaccinating healthy adults. This analysis assumes a one way relaxation of non-pharmaceutical interventions (i.e., interventions are not re-imposed if cases rise after measures are relaxed). This results in a resurgence in infections following the relaxation of measures. These results underscore the importance of keeping non-pharmaceutical interventions in place during vaccine roll-out and the potential for resurgence if measures are relaxed too soon.

We performed a sensitivity analysis where we assume strict measures, similar to a situation in February 2021, are re-imposed if cases rise above 35.7 per 100,000 people per day (Figure 30, Table 10). Overall, re-imposing strict measures reduces outcomes substantially compared

to the situation modelled in the main analysis. When strict measures are re-imposed, the alternative vaccination scheme results in the fewest new infections, the young to old scheme results in the fewest cases, and the old to young approach results in the fewest hospital admissions, IC admissions, and deaths (Table 10).

8.4 Discussion

The conclusions drawn here, namely 1) vaccination reduces disease outcomes and 2) different prioritisation of healthy persons aged 18-59 results in similar cumulative disease outcomes (e.g., infections, cases, hospital admissions), are robust to different model assumptions and parameter values. In earlier sections of this report we used different model assumptions and parameter values, but reached the same conclusions stated above. However, the specific values of the disease outcomes according to this model are not robust to different parameter values as we do observe different values when different parameter values are used. Regardless, the trend and overall conclusions remained the same.

A limitation of our approach is that the model is deterministic and therefore, does not take into account uncertainty due to inherent chance events in the infection process, and does not take into account uncertainty in parameter value inputs or estimated outputs. Therefore, these results should not be interpreted as projections, but rather as an indication of the trends in disease outcomes under different vaccination strategies and model assumptions.

We have not included the vaccination of the 16-17 year olds in this discussion, even though the Pfizer/BioNTech vaccine is registered for use in this age group. We have not discussed the choice of vaccine for each age group and focused on the allocation of vaccines with properties similar to the AstraZeneca and Janssen vaccines.

8.5 Tables and Figures

Table 10. Cumulative totals of each outcome under the four vaccination scenarios: old to young, young to old, alternative, and no vaccination (in healthy adults) with a reference of no vaccination at all. The values of these totals are sensitive to the precise choice of parameter values and are not intended as predictions; these values might change in future versions of this report. The main analysis assumes a one-way relaxation of measures. The sensitivity analysis assumes lockdown measures are re-imposed if new daily cases reach the upper threshold 35.7 per 100,000 people per day.

Analysis	Scenario	New Infections	New Cases	Hospital Admissions	IC Admissions	Deaths	Life Years Lost	DALYs
Main	Old to young	**3,152,724**	**1,583,983**	**18,088**	**6,306**	**5,307**	**82,557**	**82,557**
	Young to old	3,210,120	1,604,006	18,571	6,493	5,387	84,126	84,126
	Alternative	3,209,656	1,603,808	18,566	6,491	5,386	84,108	84,108
	No Vaccination (Healthy adults)	3,260,150	1,628,193	18,756	6,553	5,429	84,826	84,826
	No Vaccination (at all)	5,324,327	2,553,812	43,172	14,437	13,687	194,729	194,729
Sensitivity Analysis	Old to young	1,712,100	792,657	**8,605**	**3,009**	**2,909**	**44,177**	**44,177**
	Young to old	1,667,260	**717,194**	9,278	3,189	2,981	44,427	44,427
	Alternative	**1,666,294**	718,383	9,280	3,183	2,982	44,369	44,369
	No Vaccination (Healthy adults)	2,215,366	970,967	10,503	3,687	3,249	50,716	50,716
	No Vaccination (at all)	3,456,088	1,328,815	22,395	7,364	7,020	98,262	98,262

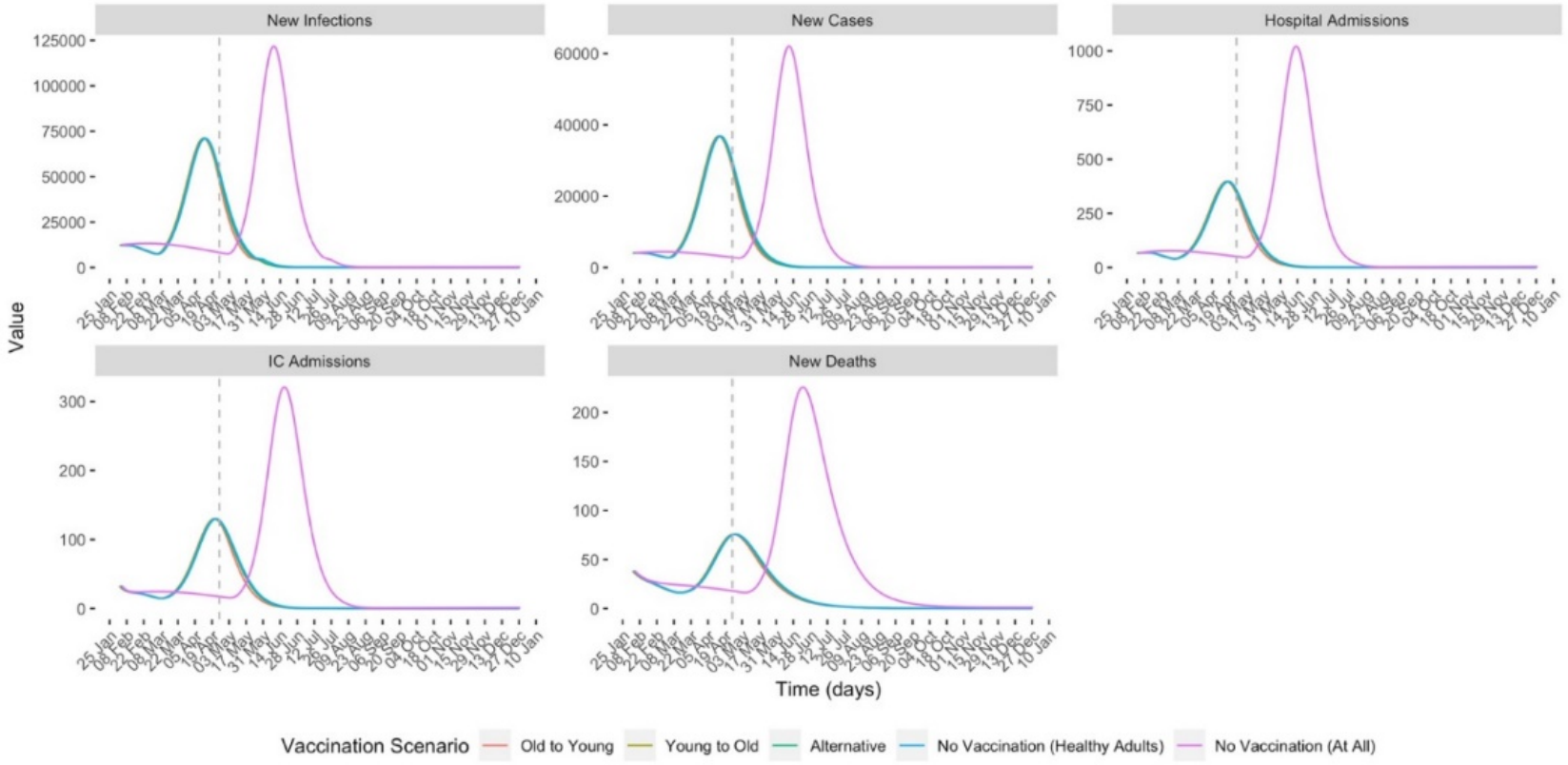

Figure 29. 7-day rolling average of new infections, new cases, hospital admissions, IC admissions, and new deaths under different AstraZeneca and Janssen vaccine allocation scenarios: 1) old to young, 2) young to old, 3) alternative, 4) no vaccination (in healthy adults), 5) no vaccination (at all). Note: lines for the vaccine strategies have been jittered for increased visibility because the simulation outcomes of the alternative strategies 'old to young', 'young to old' and 'alternative' are very similar. The grey vertical dashed line indicates when vaccination in healthy adults begins.

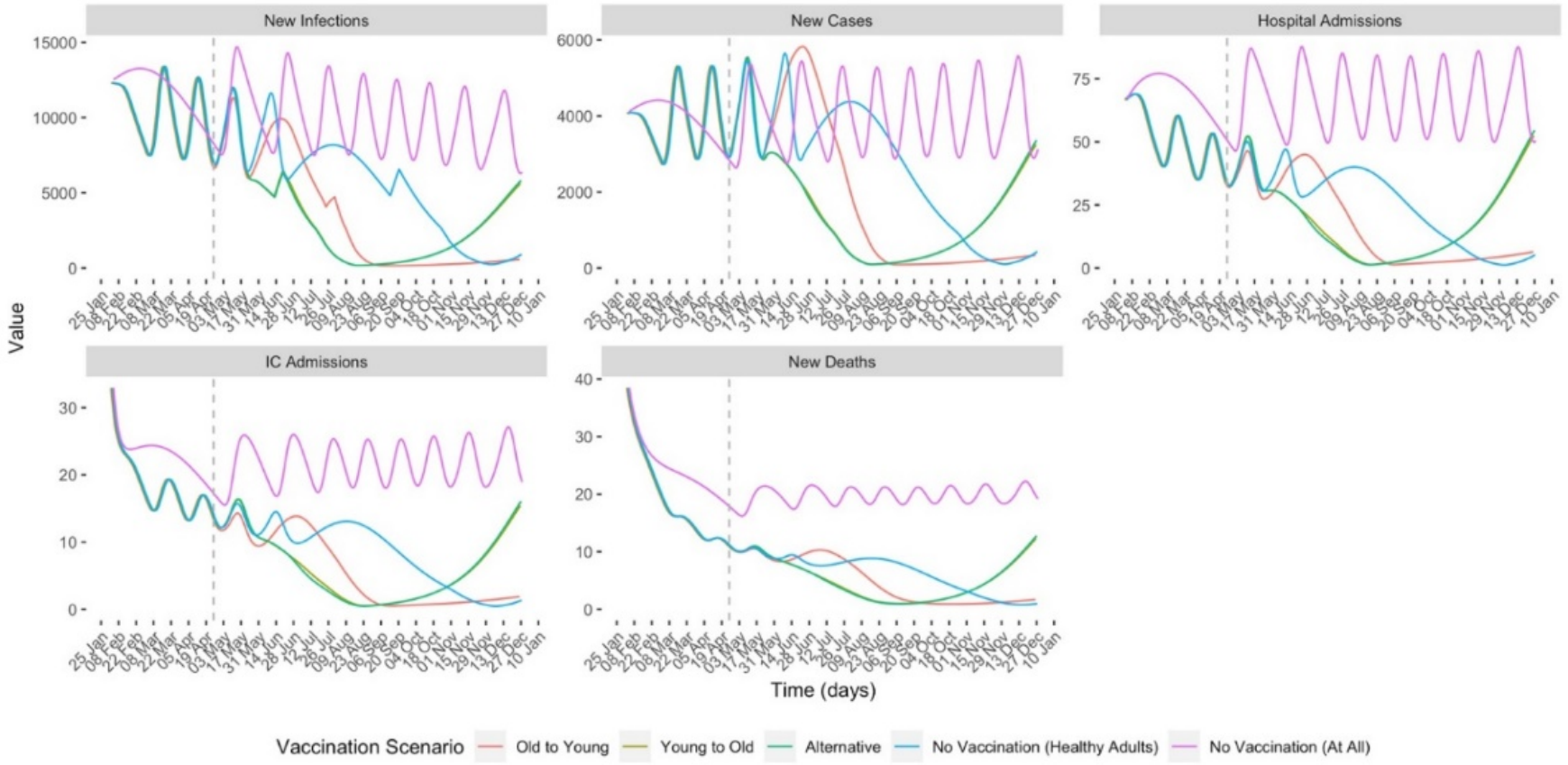

Figure 30. 7-day rolling average of new infections, new cases, hospital admissions, IC admissions, and new deaths under different AstraZeneca and Janssen vaccine allocation scenarios: 1) old to young, 2) young to old, 3) alternative, 4) no vaccination (in healthy adults), 5) no vaccination (at all). Measures similar to a situation in February 2021 are re-imposed if cases rise above 35.7 per 100.000 per day. The grey vertical dashed line indicates when vaccination in healthy adults begins.

9 Large-scale testing

Analysis of 5 March 2021

Mass testing has been suggested as an approach to limit the spread of SARS-CoV-2. The idea is to test as many people as possible in a specified population and isolate those who test positive. The approach has been applied at different scales: the municipality of Lansingerland in the Netherlands (and is now being piloted in three different places in the Netherlands), the city of Liverpool in the UK, and the entire country of Slovakia. Several modelling papers have appeared on the impact of mass testing. In addition to the background document provided by the Outbreak Management Team on November 30 2020 [19] and recent modelling papers on the impact of testing, we provide an overview to illustrate the generic features in these papers.

9.1 Mass testing in a single campaign

An example of a modelling study that investigates the impact of a single testing campaign is provided by Bosetti et al. This study shows that if 75% of the population would participate in a single testing campaign, the number of daily infections would be reduced by 21% when measured 10 days after mass testing. The precise percentage will depend on participation rate and sensitivity of the test. If the epidemic grows with a doubling time of 21 days, it would take another 10 days for the epidemic to get back to the number of daily infections observed before the mass testing. The precise gain in time will depend on the participation rate, the sensitivity of the test, and the doubling time. In a sensitivity analysis the study shows that the number of days to return to the pre-mass testing epidemiological situation ('time gain') ranges from 6 to 13 days when participation rate is 90% and doubling time ranges from 10 to 21 days [20].

Pavelka et al. provide an analysis of mass testing in Slovakia. Since mass testing was accompanied by concurrent implementation of other stringent control measures it is difficult to separate the impact of testing from these other control measures [21].

9.2 Repeated testing

Several modelling studies have investigated the expected impact of repeated testing, including Bootsma et al.[22], Paltiel et al. [23], and Bosetti et al. [20]. Even though the modelling approaches differ, these studies reach a similar conclusion: a high frequency of testing combined with epidemic control measures, such as isolation of infected individuals and quarantine for their close contacts, is required to control the spread of SARS-CoV-2 infections, with a time interval between successive tests that is in the order of a few days.

The required short testing interval is determined by the generation time of the SARS-CoV-2 infection. The generation time is defined as the typical duration between successive infections in a transmission chain. For SARS-CoV-2 the average generation time is estimated to be around

4 days. We use a standard epidemic transmission model to show the relation between generation time and the impact of testing. In this standard model we partition the population into those who are susceptible to infection, those who are infected but not yet infectious, those who are infectious, and those who are immune (known as an SEIR model). We assume that the rapid antigen test provides a positive result for the persons who are infectious, and a negative test result for the persons who are not infectious with perfect sensitivity and specificity. Testing and case isolation shorten the time that infectious individuals ('infectives') will be in the general population and infect others. The typical duration of the interval during which infectives can infect others is determined by the average generation time of the SARS-CoV-2 infection. The duration can range between 0 days and the average generation time, and is typically half the average generation time, for SARS-CoV-2 at around 2 days. When we would introduce repeated testing with a testing interval that is also half the average generation time, we can expect a halving of the number of secondary infections per infective, see Figure 1. We assume that the test is perfect in detecting infectious persons, we assume that persons who test positive adhere perfectly to isolation guidelines and will not infect others. We know that the rapid tests are not perfect and that a substantial proportion of the population does not comply with isolation measures, and therefore the actual impact will be less. The results show that even with these overoptimistic assumptions, the reduction in the reproduction number is modest and requires frequent testing with an interval shorter than the generation time of the infection (Figure 31).

9.3 Testing before participating in an event

Another approach to testing involves requiring a certificate of a recent negative test result to be admitted to an event where many persons meet in close physical proximity, for example a conference, a concert or air travel. The idea is that infectious individuals will give a positive test result and cannot participate in the event, and that persons who are not infectious will give a negative test result and are allowed to participate in the event. A relevant study is Hellewell et al. The study analyses how the probability of a positive PCR test changes since time of infection for a group of care workers who eventually reported symptoms. The results show that the probability of a positive PCR test increases fast in the four days after infection to a peak value. This implies that a negative test result will indicate absence of infectiousness for only a short period of time [24]. The OMT advised that the validity of a certificate for a negative PCR should expire within 48 hours and for a rapid antigen test within 24 hours [25].

9.4 The health benefits of testing and time scales

Testing is essential to monitor the epidemic. We expect a limited impact of testing and case isolation on the reproduction number. When combined with other control measures in a control strategy they may add to control of the pandemic.

The benefits of testing are tied to short time scales. A single campaign with mass testing will result in a time gain of days up to two weeks before the number of daily infections is back at the original level.

Repeated testing requires a testing interval of a few days, shorter than the generation time of the infection, in order to expect any effect on the effective reproduction number. The expiration time for negative test results is one or two days. The short time scales are tied to time scales of the infection cycle. Therefore, we expect these results to hold in general.

9.5 Conclusion

Large-scale repeated testing has little impact on the reproduction number unless it is done every other day, combined with a high level of compliance to isolation for those who tested positive.

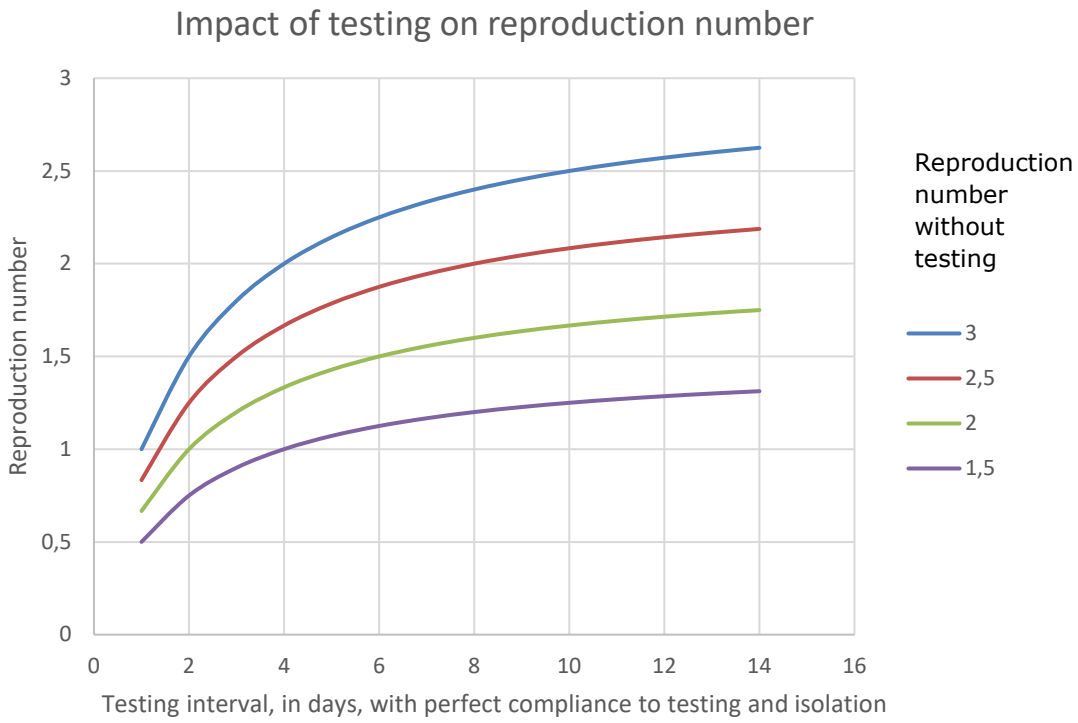

Figure 31. The impact of repeated universal testing at different intervals on transmission of infection, as measured by the reproduction number. We assume here that everyone participates in testing, that the test is perfect, and that everyone who tests positive goes into isolation and does not transmit infection. We assume here that the generation time of the infection is about 4 days. The equation we use to calculate the reproduction number with large-scale testing is R c/(c+2), with R the reproduction number of the dominant variant is 1.5, 2, or 3 secondary infections per infective in absence of any control measures and immunity, c is the duration of the interval between successive tests in days, 2 days is half the duration of the mean generation time.

10 Appendix

Text updated 15 March 2021

10.1 Model Description

10.1.1 Overview

Here we describe an age-structured compartmental susceptible-exposed-infectious-recovered model. The population is partitioned into 10-year age bands (0-9, 10-19, …, 70-79, 80+). The contacts within and between age groups are based on contacts as monitored in the Pienter 3 study with changes according to non-pharmaceutical control measures that reflect April 2020, June 2020, and September 2020 [26]. In each age group we partition the population into those who are susceptible (S), infected but not yet infectious (E), infectious (I) and recovered and immune (R). The population is further divided into those who are hospitalized, in intensive care (IC), and dead (Figure A1). We include additional states for those individuals who are vaccinated with 1 dose vaccinated with 2 doses. When a person is vaccinated, they first enter a hold state where they are vaccinated, but not yet protected. After a delay period, they enter the protected state for the dose they have received. Differences in susceptibility and infectiousness by age group are accounted for by multiplying the relative susceptibility/infectiousness by the contact matrix and using this transmission matrix in place of the contact matrix when calculating the force of infection. A full list of model input parameters are shown in Table A1 and Table A2.

10.1.2 Initial conditions

The model begins on 1 February 2021 and simulates forward in time until 30 September 2021. The initial conditions, the numbers of individuals in each compartment of the model, are based on Dutch data sources. The initial number of recovered individuals is based on the total cumulative incidence in The Netherlands up to 31 December 2020 (approximately 14.8% of the Dutch population) and then including an additional 176,400 positives recorded between 1 January 2021 and 2 February 2021 assuming an ascertainment of 32%. This results in 3.13 million total people (approximately 18% of the Dutch population) who have been infected previously with SARS-CoV-2 and are included in the recovered (R) compartment. Using the number of cases by age group between 26 January 2021 and 2 February 2021 from the RIVM sitrep published on 2 February 2021 [27] we can determine the number of infections in that week by multiplying the number of cases in each age group by 3 (because we assume an ascertainment of 32%). To determine the number of individuals in the exposed (E) and infectious (I) compartments on the first day of the simulation, we divide by seven to get the number of infections per day and then multiply the latent period and infectious period, respectively. The initial number of individuals in the hospital (H), intensive care (IC), and hospital after IC (HIC) were based on hospital and IC occupancy data from NICE on 1 February 2021. Finally, the number of individuals in the susceptible (S)

compartment is the total size of each age group minus the E, I, H, IC, HIC, and R compartments.

10.1.3 Transmission matrices

The model uses different contact matrices from the Pienter Corona Study [28, 29] to approximate different contact patterns under different levels of non-pharmaceutical interventions across age groups. These contact matrices are converted to transmission matrices to incorporate differences in susceptibility and infectiousness by age group. The contact matrices are converted to transmission matrices by multiplying rows and columns by estimates of the relative susceptibility and infectiousness by age group.

At the beginning of the simulation, an age-specific transmission matrix is used to reflect a situation in February 2021 (we refer to this matrix as February 2021). This transmission matrix is calibrated to the age distribution of cases used in the initial conditions.

The February 2021 matrix is used until new daily cases reach the threshold whereby measures can be relaxed. This threshold is based on the Dutch government's corona road map [30]. Specifically, if new daily cases fall below 14.3 cases per 100000 people, non-pharmaceutical interventions are relaxed, and an age-specific transmission matrix is used that reflects a situation as in the end of summer 2020 (we refer to this matrix as September 2020). If new daily cases fall further to below 5 cases per 100000 people non-pharmaceutical interventions are relaxed further and an age-specific transmission matrix is used that reflects a situation in the beginning of summer 2020 (we refer to this matrix as June 2020). Finally, if new daily cases fall further to below 0.5 cases per 100000 people non-pharmaceutical interventions are removed entirely and an age-specific transmission matrix is used that reflects a situation prior to the COVID-19 pandemic (we refer to this matrix as 2017).

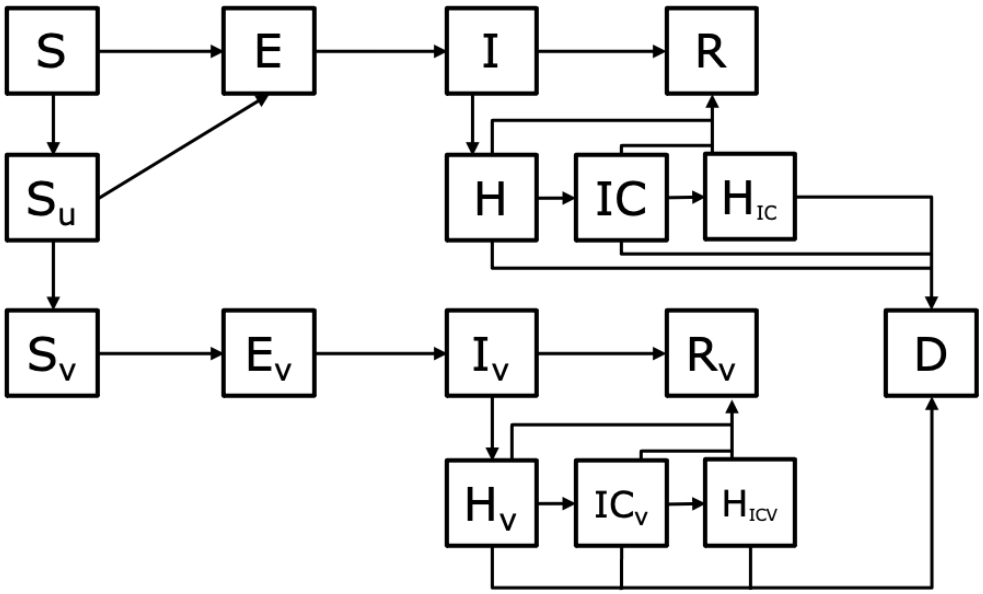

Figure A1. Basic conceptual model diagram. This diagram does not include the additional states after the second dose of vaccination or the age structure in the model. S = susceptible, E = exposed, I = Infectious, R = Recovered, H = hospitalized, IC = In intensive care, HIC = return to the hospital ward following treatment in IC, Su = vaccinated, but not yet protected, D = dead. States with subscript V indicate individuals who are vaccinated and protected by vaccination. This model assumes the "leaky" vaccine protection, so vaccinated and protected individuals can still be infected, hospitalized, etc. but at a reduced rate.

10.1.4 Vaccination

The vaccine is assumed to provide "leaky" protection, which means that the vaccine reduces the probability of infection but does not render a person completely immune. We assume the vaccine reduces susceptibility to infection and thus indirectly reduces transmission. The model is designed to incorporate a single 2-dose vaccine, so to incorporate multiple vaccines, the weighted average of vaccination rate, delay to protection, and vaccine efficacy (Table A3) are used.

10.1.5 Limitations

We have made several assumptions. One of these is that people who refuse vaccines do so at random, and that these are not clustered. It is highly likely that vaccine refusers cluster together. This will lead to a reduced impact of vaccination, but it will affect the alternative vaccination scenarios in similar ways, such that the relative differences in health benefits is likely to be maintained. Another is that we assume that the epidemic is similar in all regions of the Netherlands. Even though regions do differ in the incidence of infection, a long and sustained period where the epidemic grows in one region but declines in another has not occurred. We have modelled the mode of action of all vaccines as "leaky", i.e. the model assumes that at a vaccine efficacy of 50% vaccinated individuals have half the risk of being infected during each exposure as unvaccinated individuals. Since the number of exposures for each susceptible individual in this simulation study is very limited, we expect the results to generalize to other modes of action. We do not incorporate waning of vaccine protection in this model. Thus, vaccine efficacies are fixed over time. The effects of a vaccination

program may be overestimated if significant waning of vaccine-related protection occurs during the time frame of these simulations. Additionally, we do not explicitly include variants in the model, so we assume the transmission rate is fixed over time. However, we chose an effective reproduction number that was the mid-point between the wild type strain and that of the UK variant of concern (Table A1).

The model is coded in R [31] as a system of ordinary differential equations that are numerically solved using the lsoda function in the desolve package [32]. For the full set of model equations see the Equations section. The objective of this specific model is to capture the dynamic aspects of vaccine allocation when comparing the alternative vaccination schemes. The parameter values are obtained by calibrating to the number of observed cases by age group in early February 2021. As this model is not explicitly fitted or tested against actual observations, the outcome will not be a quantitative prediction; rather, the objective is to detect the ordering of the vaccination schemes with respect to alternative outcomes

10.2 Equations

$$\lambda = \beta * \left(C * \frac{I + I_{v1d} + I_{v2d}}{N}\right)$$

$$\begin{aligned}
\frac{dS}{dt} &= -\lambda * S - \alpha * S \\
\frac{dS_{hold_{1d}}}{dt} &= \alpha * S - (1/\delta) * S_{hold_{1d}} - \lambda * S_{hold_{1d}} \\
\frac{dS_{v_{1d}}}{dt} &= (1/\delta) * S_{hold_{1d}} - \eta * \lambda * S_{v_{1d}} - \alpha_2 * S_{v_{1d}} \\
\frac{dS_{hold_{2d}}}{dt} &= \alpha_2 * S_{v_{1d}} - (1/\delta_2) * S_{hold_{2d}} - \eta * \lambda * S_{hold_{2d}} \\
\frac{dS_{v_{2d}}}{dt} &= (1/\delta_2) * S_{hold_{2d}} - \eta_2 * \lambda * S_{v_{2d}} \\
\frac{dE}{dt} &= \lambda * (S + S_{hold_{1d}}) - \sigma * E \\
\frac{dE_{v_{1d}}}{dt} &= \eta * \lambda * (S_{v_{1d}} + S_{hold_{2d}}) - \sigma * E_{v_{1d}} \\
\frac{dE_{v_{2d}}}{dt} &= \eta_2 * \lambda * S_{v_{2d}} - \sigma * E_{v_{2d}} \\
\frac{dI}{dt} &= \sigma * E - (\gamma + h) * I \\
\frac{dI_{v_{1d}}}{dt} &= \sigma * E_{v_{1d}} - (\gamma + h) * I_{v_{1d}} \\
\frac{dI_{v_{2d}}}{dt} &= \sigma * E_{v_{2d}} - (\gamma + h) * I_{v_{2d}} \\
\frac{dH}{dt} &= h * I - (i_1 + d + r) * H \\
\frac{dH_{v_{1d}}}{dt} &= h * I_{v_{1d}} - (i_1 + d + r) * H_{v_{1d}} \\
\frac{dH_{v_{2d}}}{dt} &= h * I_{v_{2d}} - (i_1 + d + r) * H_{v_{2d}} \\
\frac{dIC}{dt} &= i_1 * H - (i_2 + d_{ic}) * IC \\
\frac{dIC_{v_{1d}}}{dt} &= i_1 * Hv_1d - (i_2 + d_ic) * IC_{v_{1d}} \\
\frac{dIC_{v_{2d}}}{dt} &= i_1 * Hv_2d - (i_2 + d_ic) * IC_{v_{2d}} \\
\frac{dH_{IC}}{dt} &= i_2 * IC - (r_{ic} + d_{hic}) * H_{IC} \\
\frac{dH_{IC_{v_{1d}}}}{dt} &= i_2 * IC_{v_{1d}} - (r_{ic} + d_{hic}) * H_{IC_{v_{1d}}} \\
\frac{dH_{IC_{v_{2d}}}}{dt} &= i_2 * IC_{v_{2d}} - (r_ic + d_hic) * H_{IC_{v_{2d}}} \\
\frac{dD}{dt} &= d * (H + H_{v_{1d}} + H_{v_{2d}}) + d_{ic} * (IC + IC_{v_{1d}} + IC_{v_{2d}}) \\
&\quad + d_{hic} * (H_{IC} + H_{IC_{v_{1d}}} + H_{IC_{v_{2d}}}) \\
\frac{dR}{dt} &= \gamma * I + r * H + r_{ic} * H_{IC} \\
\frac{dR_{v_{1d}}}{dt} &= \gamma * I_{v_{1d}} + r * H_{v_{1d}} + r_{ic} * H_{IC_{v_{1d}}} \\
\frac{dR_{v_{2d}}}{dt} &= \gamma * I_{v_{2d}} + r * H_{v_{2d}} + r_{ic} * H_{IC_{v_{2d}}}
\end{aligned}$$

10.3 Outcomes

We use the model to determine the number of daily infections, daily cases, hospital admissions, IC admissions, life years lost, DALYs, and deaths under different vaccination scenarios. The mathematical equations for determining each outcome are shown below. Due to the high percentage (~98%) of DALYs attributable to life years lost, we approximate DALYs by life years lost. Parameter definitions and values are shown in Table A1 and Table A2.

Daily infections = $S + S_{hold_{1d}} + (\eta * (S_{v_{1d}} + S_{hold_{2d}})) + (\eta_2 * S_{v_{2d}})) * \lambda$
Daily cases = $\sigma * (E + E_{v_{1d}} + E_{v_{2d}}) * P(\text{ascertainment})$
Hospital admissions = $(I + I_{v_{1d}} + I_{v_{2d}}) * h$
IC admissions = $(H + H_{v_{1d}} + H_{v_{2d}}) * i_1$

Daily deaths = $(H + H_{v_{1d}} + H_{v_{2d}}) * d + (IC + IC_{v_{1d}} + IC_{v_{2d}}) * d_{IC} + (H_{IC} + H_{IC_{v_{1d}}} + H_{IC_{v_{2d}}}) * h_{IC}$
Life years lost = deaths * life expectancy

10.4 Input Parameters

Table A1. Model parameters that do not vary with age.

Parameter	Description	Value	Details
R_0	Basic reproduction number	2.3	Based on model fit to IC admissions
R_{eff}	Effective reproduction number	1.04	Chosen to be the mid-point of the effective reproduction number of the wild type strain (0.94) and the UK variant of concern (1.13)
β	Transmission rate	0.00061	
σ	Inverse of the latent period	0.5	This results in a latent period of 2 days
γ	Inverse of the infectious period	0.5	This results in an infectious period of 2 days
λ	Force of infection	Varies over time	
α	Rate of vaccination with the first dose	This depends on the vaccine allocation schedule and varies over time	Calculated as a composite rate of multiple vaccines
α_2	Rate of vaccination with the second dose	This depends on the vaccine allocation schedule and varies over time	Calculated as a composite rate of multiple vaccines
δ	Delay to protection of first dose	See Table 2	With multiple vaccines, the weighted average is used
δ_2	Delay to protection of second dose	See Table 2	With multiple vaccines, the weighted average is used
η	1 – vaccine efficacy of first dose	See Table 2	With multiple vaccines, the weighted average is used
η_2	1 – vaccine efficacy of second dose	See Table 2	With multiple vaccines, the weighted average is used

Table A2. Age-dependent model parameters.

Parameter	Description	Age group	Value	Details
h	Rate from infectious to hospital	0-9	0.0015	Calculated as the probability of infection to hospital divided by time from symptoms to hospital: $0.00347/2.29$
		10-19	0.0001	$0.000377/5.51$
		20-29	0.0002	$0.000949/5.05$
		30-39	0.0007	$0.00388/5.66$
		40-49	0.0013	$0.00842/6.55$
		50-59	0.0028	$0.0165/5.88$
		60-69	0.0044	$0.0251/5.69$
		70-79	0.0097	$0.0494/5.09$
		80+	0.0107	$0.0463/4.33$
i_1	Rate from hospital ward to IC	0-9	0.0000	Calculated as the probability of IC admission from hospital divided by average time from hospital admission to IC admission (2.28 days)
		10-19	0.0271	
		20-29	0.0422	
		30-39	0.0482	
		40-49	0.0719	
		50-59	0.0886	
		60-69	0.1070	
		70-79	0.0860	
		80+	0.0154	
i_2	Rate from IC back to hospital ward	0-9	0.0555	Calculated as the probability of admission back to hospital ward from IC divided by average length of stay in IC (15.6 days)
		10-19	0.0555	
		20-29	0.0555	
		30-39	0.0555	
		40-49	0.0555	
		50-59	0.0531	
		60-69	0.0080	
		70-79	0.0367	
		80+	0.0356	
d	Rate from hospital (before IC) to death	0-9	0.0003	Calculated as the probability of death from hospital admission divided by average
		10-19	0.0006	
		20-29	0.0014	
		30-39	0.0031	
		40-49	0.0036	
		50-59	0.0057	
		60-69	0.0151	
		70-79	0.0327	

Parameter	Description	Age group	Value	Details
		80+	0.0444	length of time in hospital before death (7 days)
d_{ic}	Rate from IC to death	0-9	0.0071	Calculated as the probability of death from IC divided by average length of time in IC before death (19 days)
		10-19	0.0071	
		20-29	0.0071	
		30-39	0.0071	
		40-49	0.0071	
		50-59	0.0090	
		60-69	0.0463	
		70-79	0.0225	
		80+	0.0234	
d_{hic}	Rate from hospital (after IC) to death	0-9	0.0000	Calculated as the probability of death from hospital ward (after IC) divided by average length of time in hospital ward (after IC) before death (10 days)
		10-19	0.0000	
		20-29	0.0000	
		30-39	0.0000	
		40-49	0.0000	
		50-59	0.0010	
		60-69	0.0040	
		70-79	0.0120	
		80+	0.0290	
r	Rate of recovery from hospital (before IC)	0-9	0.1263	Calculated as 1 – the probability of death from hospital admissions divided by the average time from hospital admission to discharge (7.9 days)
		10-19	0.1260	
		20-29	0.1254	
		30-39	0.1238	
		40-49	0.1234	
		50-59	0.1215	
		60-69	0.1132	
		70-79	0.0976	
		80+	0.0872	
r_{ic}	Rate of recovery from hospital (after IC)	0-9	0.0857	Calculated as 1 – the probability of death from hospital ward after IC divided by the average time from hospital ward (after IC) to
		10-19	0.0857	
		20-29	0.0857	
		30-39	0.0857	
		40-49	0.0857	
		50-59	0.0821	
		60-69	0.0119	
		70-79	0.0567	
		80+	0.0550	

Parameter	Description	Age group	Value	Details
				discharge (10.1 days)
Life Expectancy		0-9	77.89	Additional years of life expectancy
		10-19	67.93	
		20-29	58.08	
		30-39	48.28	
		40-49	38.6	
		50-59	29.22	
		60-69	20.52	
		70-79	12.76	
		80+	4.35	
Relative Susceptibility/ Infectiousness		0-9	1.000	
		10-19	3.051	
		20-29	5.751	
		30-39	3.538	
		40-49	3.705	
		50-59	4.365	
		60-69	5.688	
		70-79	5.324	
		80+	7.211	

Table A3. Vaccine efficacy and delay to protection for each vaccine by dose based on clinical trial data.

Vaccine	Dose	Delay to Protection	Vaccine Efficacy	Reference
Pfizer	1	14	92.6%	[6]
	2	7	94.8%	[33]
Moderna	1	14	89.6%	[7]
	2	14	94.1%	
AstraZeneca	1	21	58.3%	[5]
	2	14	62.1%	
Janssen	1	14	66.1%	[34]

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