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

The expected outcome of COVID-19 vaccination strategies

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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.

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.

1 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.

1.1 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.

1.1.1 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.

1.1.2 *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).

1.2 Burden stratified by occupation category

1.2.1 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).

1.2.2 *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.

1.3 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 Groenvoorziening Afvalverwerking Schoonmaakbranche Buitenland	*Denominator calculated as [age-group-specific] 'totale werkzame beroepsbevolking' minus sum of above categories*
Not applicable	N.v.t. (kinderen, gepensioneerden, werkzoekenden)	*Denominator calculated as [age-group-specific] national population size minus sum of all above categories*

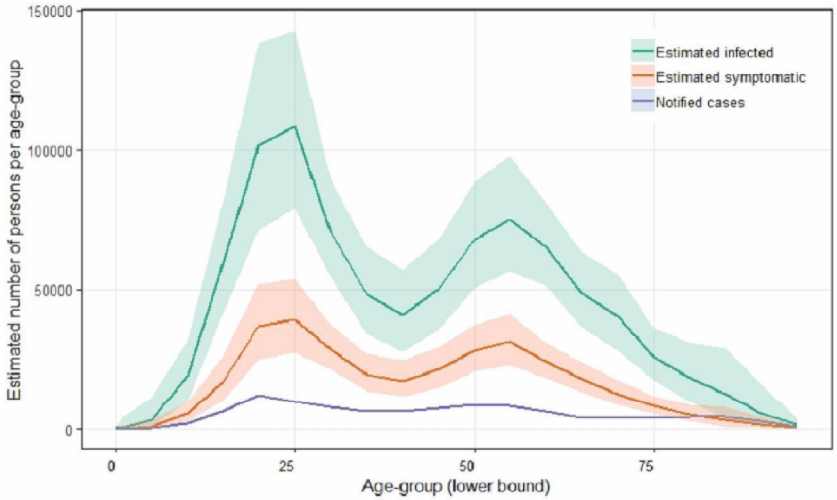

Figure 1. Estimated cumulative number of patients (as of 24th Sept 2020) with symptomatic and asymptomatic infection per age-group (lower bound indicated). This is based on smoothed seroprevalence – adjusted for survey representativeness and seroreversion – from PICO3, and the estimated proportion of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

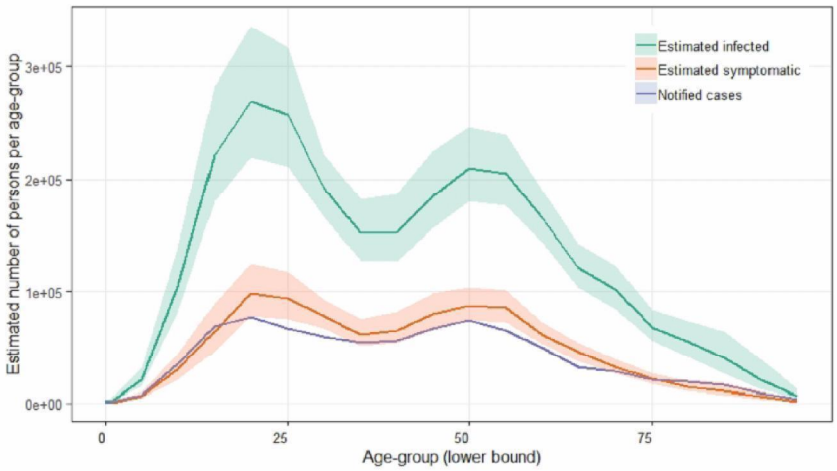

Figure 2. Estimated cumulative number of patients (as of 31 Dec 2020) with symptomatic and asymptomatic infection per age-group (lower bound indicated). This is based on smoothed seroprevalence from PICO2 until 24 Sept, and OSIRIS cases adjusted for estimated ascertainment from 25 Sept through 31 Dec.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

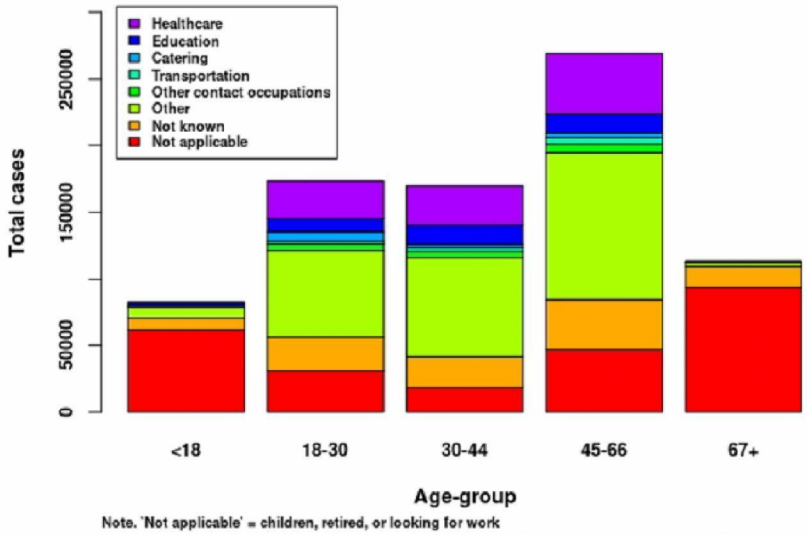

Figure 3. Distribution over occupation categories (from OSIRIS) stratified by broad age-group, using the 'full' analysis period definition (i.e., 27 Feb 2020 through 31 Dec 2020).

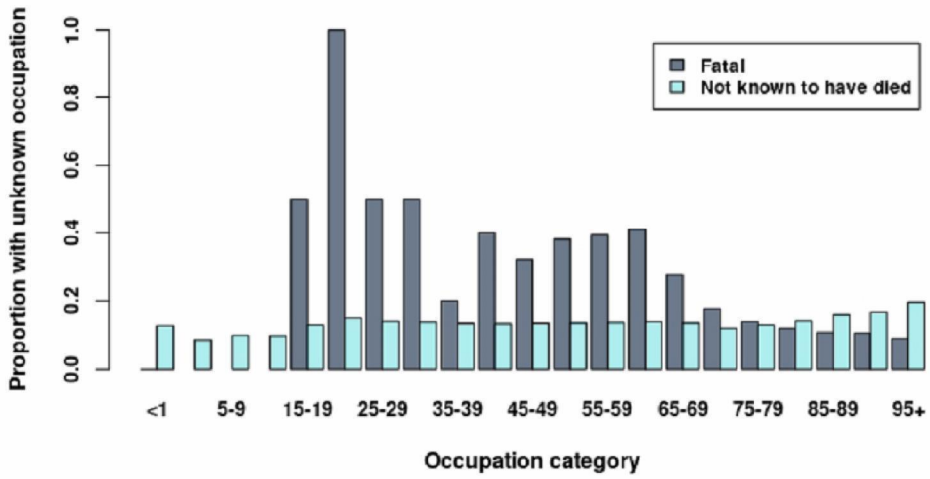

Figure 4. Proportion of OSIRIS notifications with occupation 'not known' per age-group, comparing (notified) fatal cases with (notified) cases who are not known to have died, 27 Feb through 31 Dec 2020. Note that for age-groups below 45-49 years, the denominators for the 'fatal' series are very small.

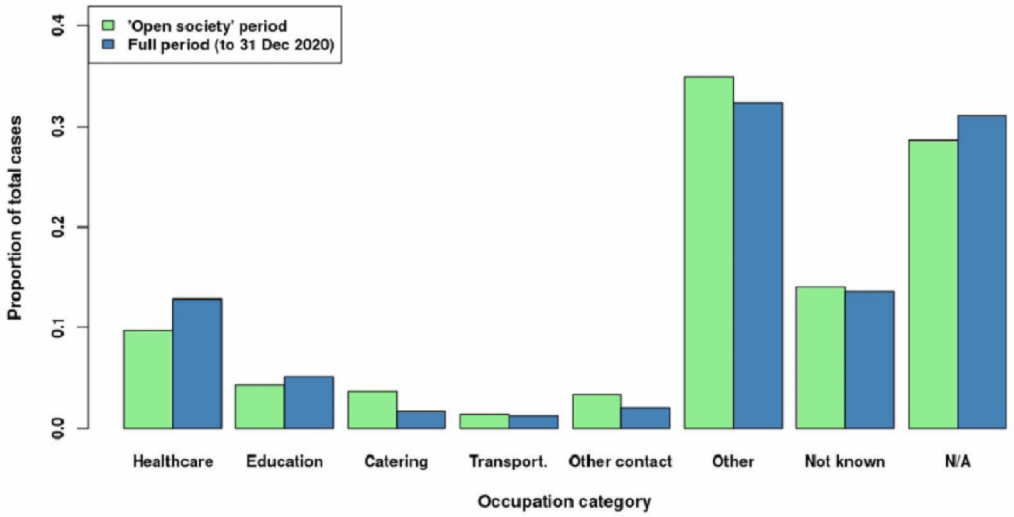

Figure 5. Distribution over occupation categories (from OSIRIS notifications, all ages), comparing two analysis period definitions ('full period' = 27 Feb through 31 Dec 2020; 'open society' = 1 June through 20 Sept 2020).

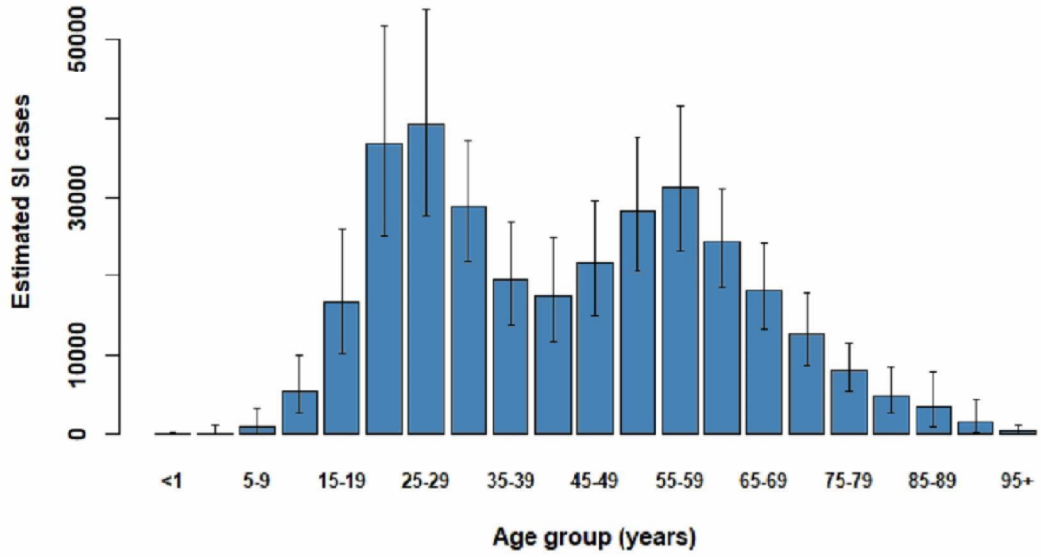

Figure 6. Estimated cumulative symptomatic (SI) incidence per 5-year age-group with 95% CIs, up to 24 Sept 2020.

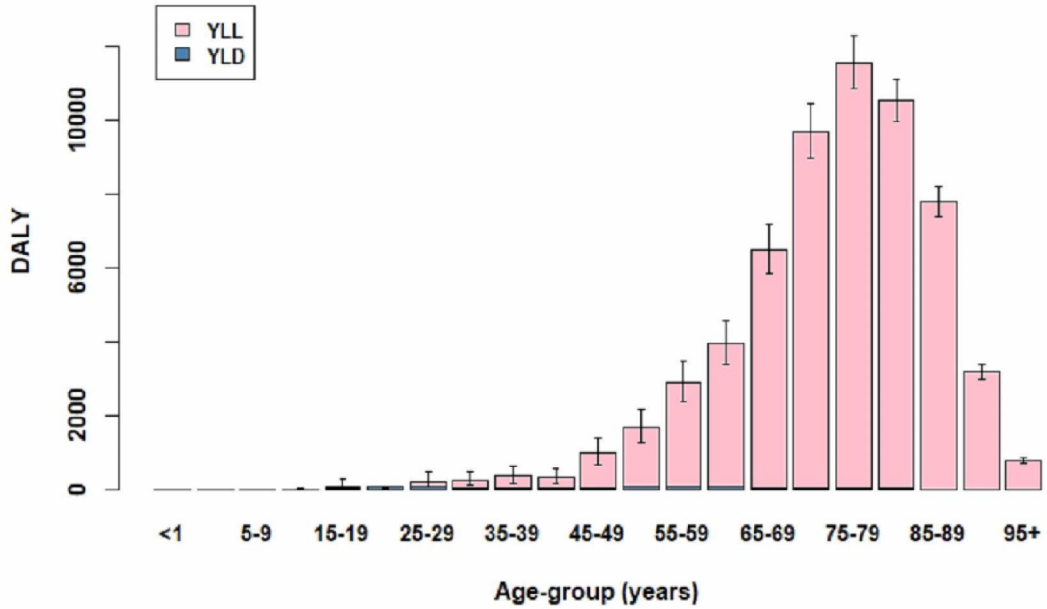

Figure 7. Estimated DALY (split into YLD and YLL) per 5-year age-group with 95% CIs, up to 24 Sept 2020.

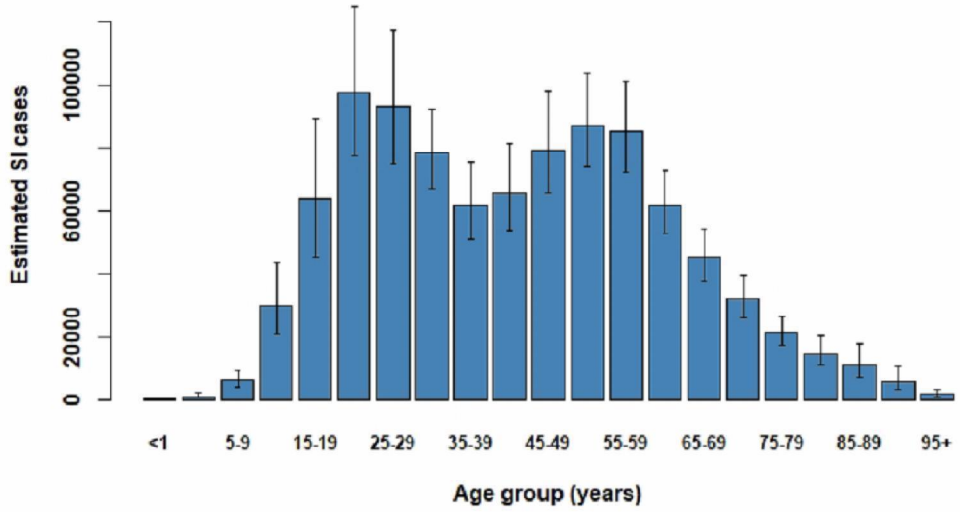

Figure 8. Estimated SI cases per 5-year age-group with 95% CIs, up to 31 Dec 2020.

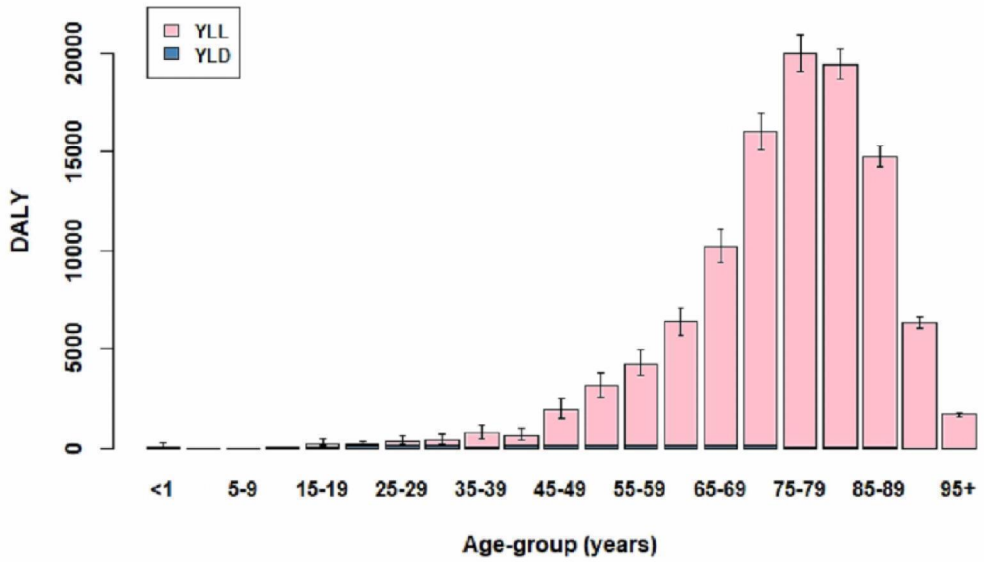

Figure 9. Estimated DALY (split into YLD and YLL) per 5-year age-group with 95% CIs, up to 31 Dec 2020.

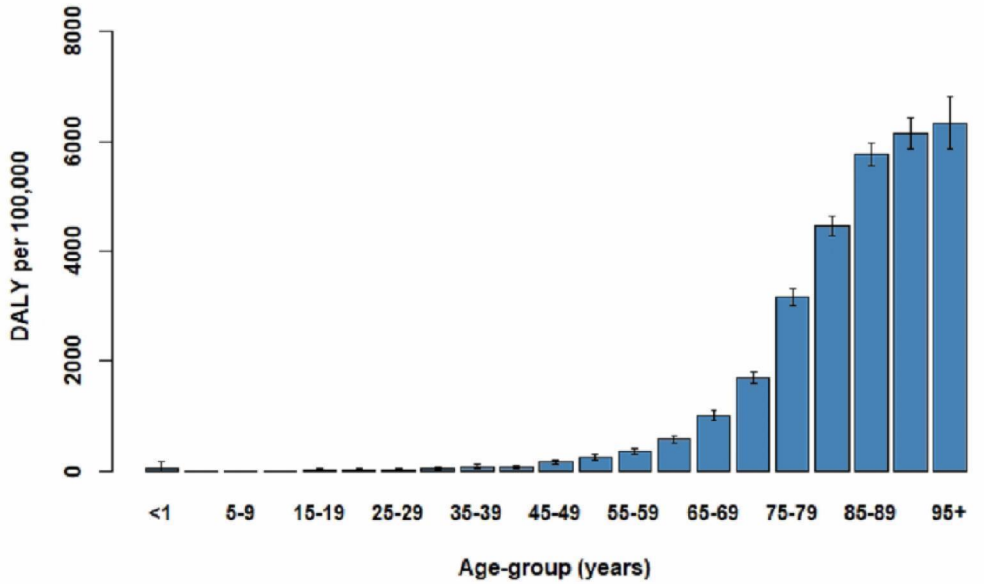

Figure 10. Estimated disease burden per 5-year age-group as DALYs per 100,000 persons, up to 31 Dec 2020.

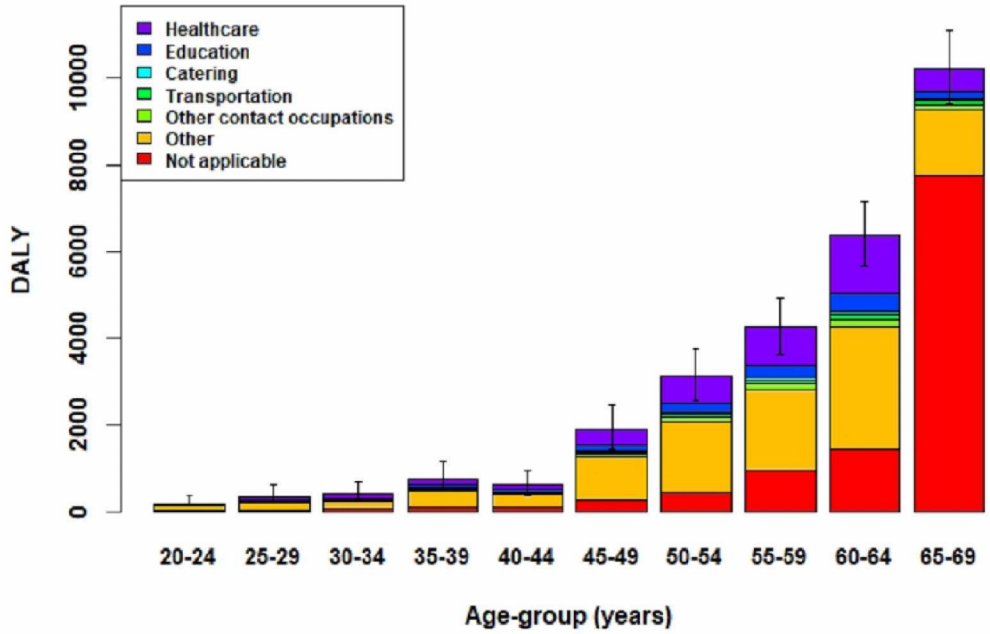

Figure 11. Estimated absolute disease burden (in DALYs) per occupation category (with occupation 'Not known' imputed) and 5-year age-group, up to 31 Dec 2020.

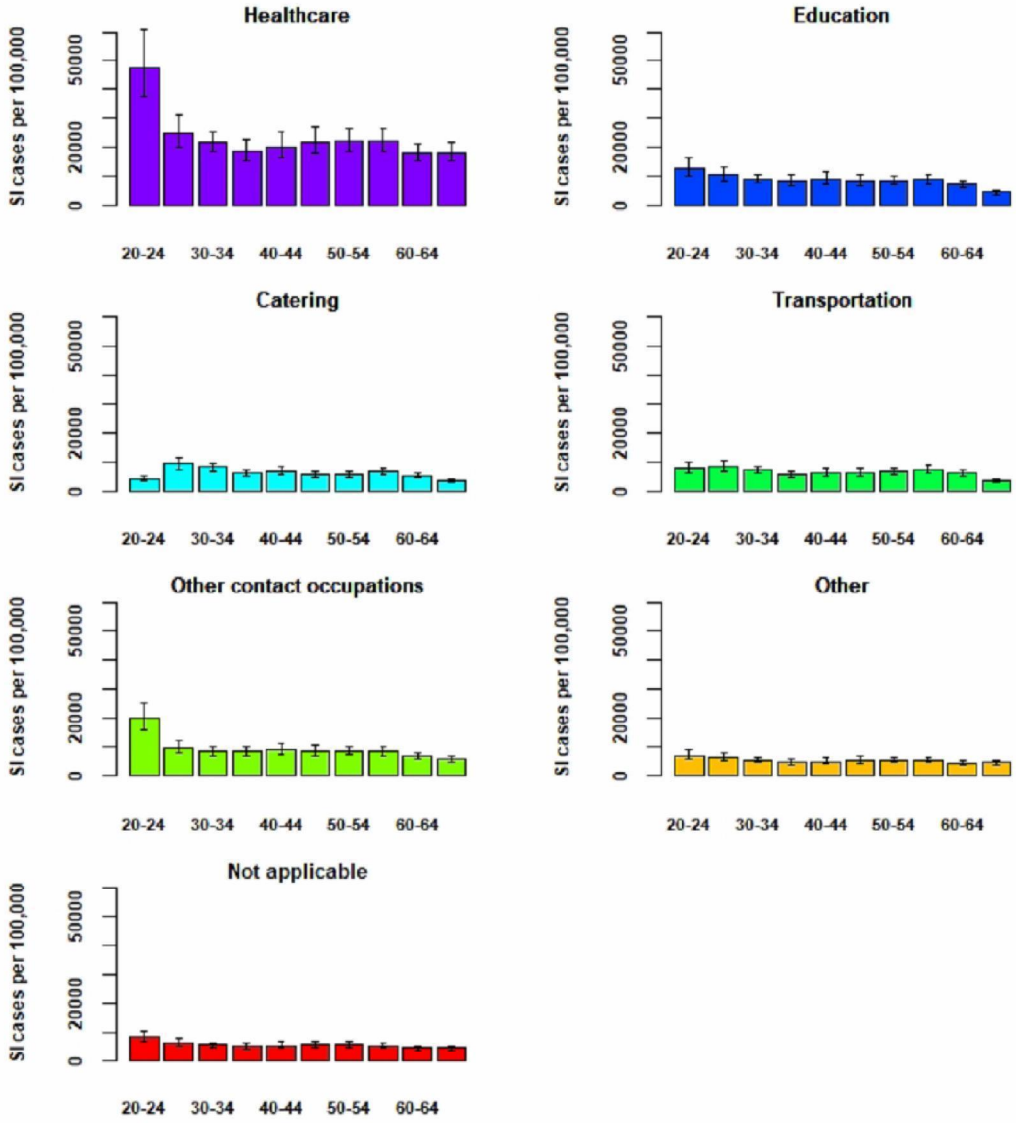

Figure 12. Estimated cumulative incidence (per 100,000) of symptomatic infection per occupation category and 5-year age-group (as the estimated total number of patients per 100,0000 persons in each category within each age-group), up to 31 Dec 2020 and shown for the age range 20-69 years only. 'Not known'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

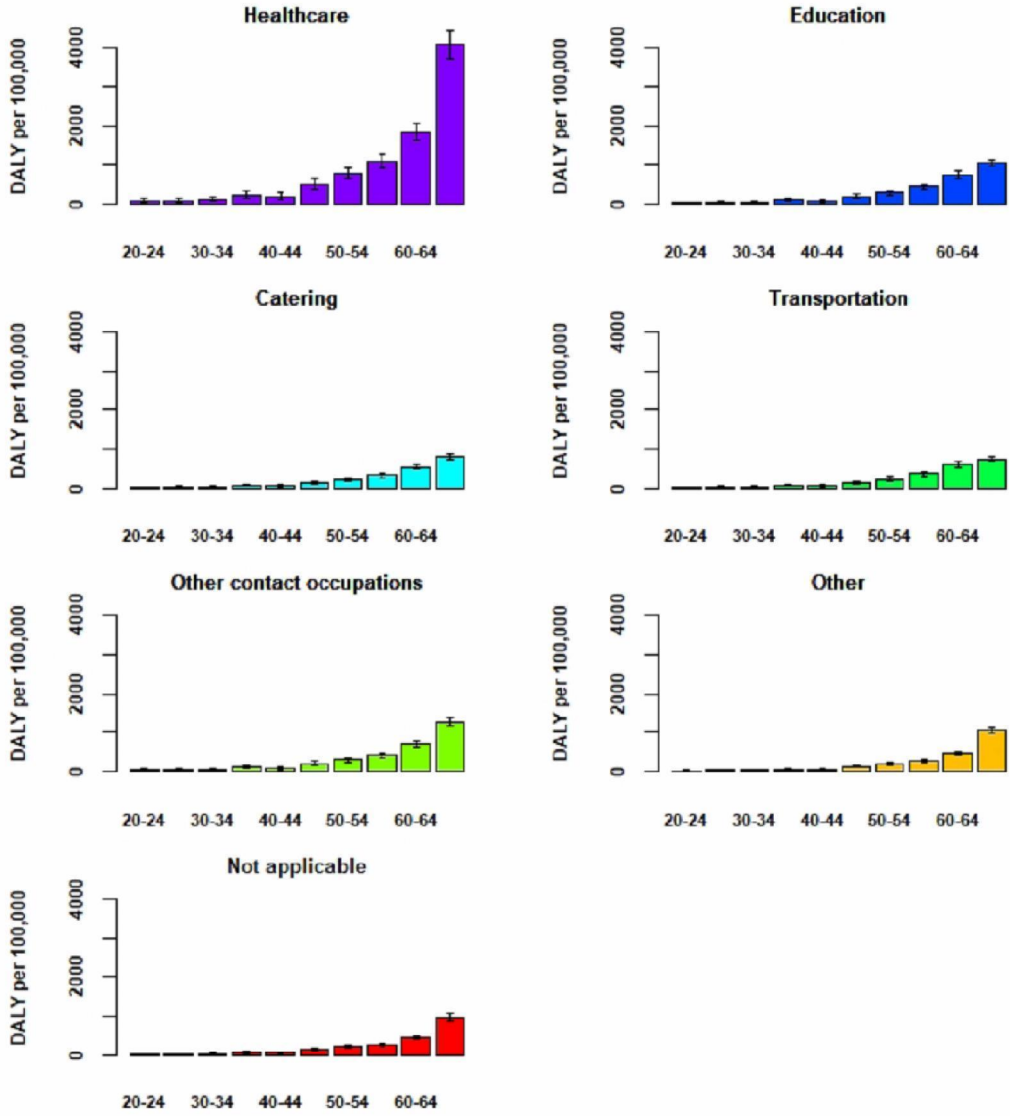

Figure 13. Estimated disease burden per occupation category and 5-year age-group (as DALYs per 100,0000 persons in each category within each age-group), up to 31 Dec 2020, and shown for the age range 20-69 years only. 'Not known' occupation imputed.

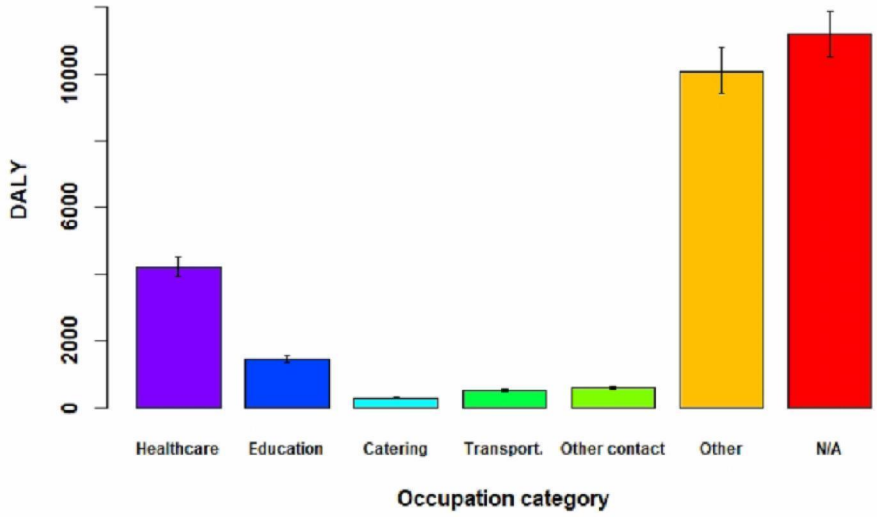

Figure 14. Estimated absolute disease burden per occupation category (as DALYs), up to 31 Dec 2020 and within the age range 20-69 years only. 'Not known' occupation imputed.

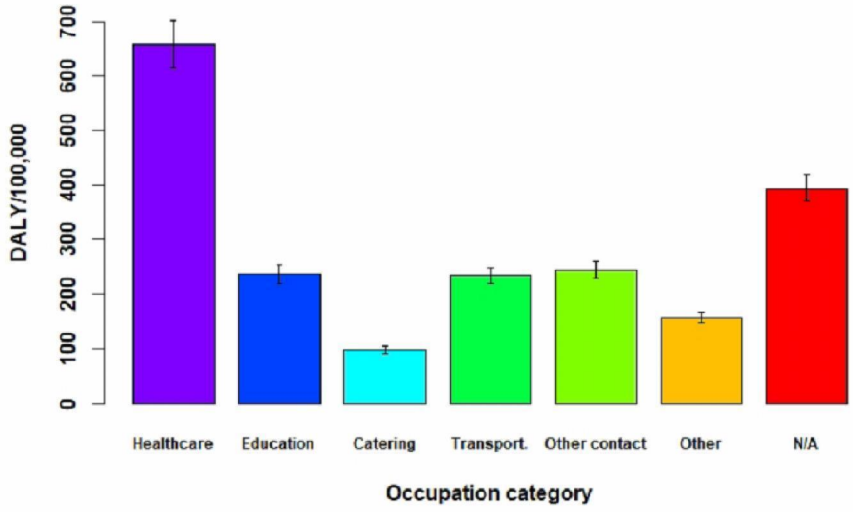

Figure 15. Estimated disease burden per occupation category (as DALYs per 100,0000 persons in each category, aggregating over age), up to 31 Dec 2020 and within the age range 20-69 years only. 'Not known' occupation imputed

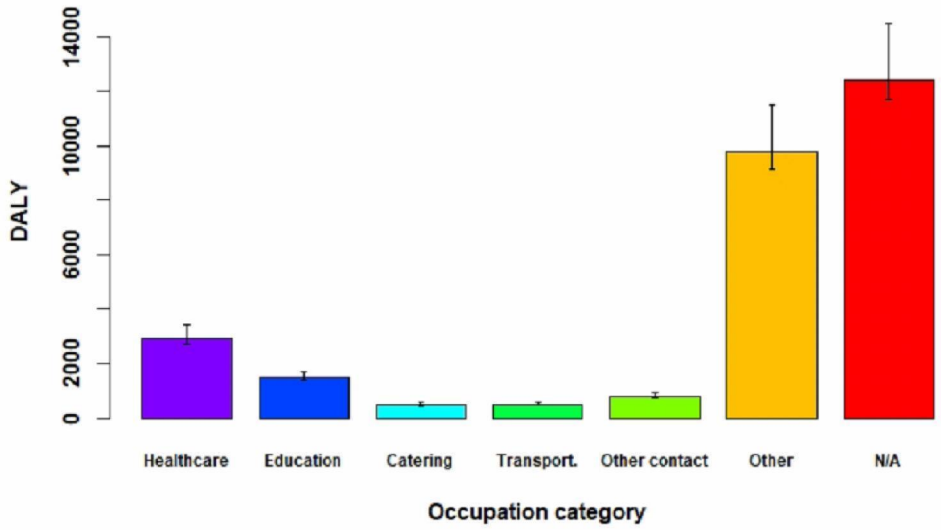

Figure 16. Expected absolute disease burden per occupation category (as DALYs), up to 31 Dec 2020 and within the age range 20-69 years only. 'Open society' occupation category distribution used. 'Not known' occupation imputed.

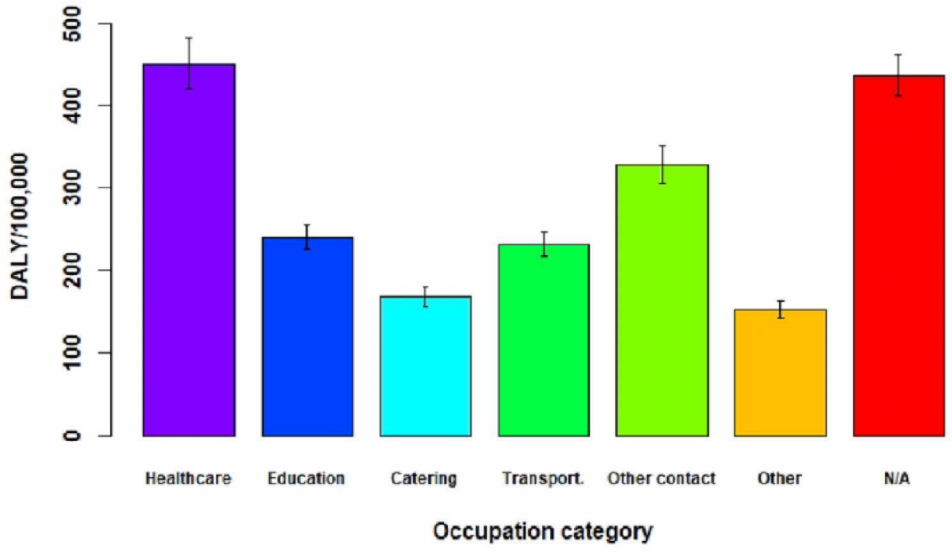

Figure 17. Expected relative disease burden per occupation category (as DALYs per 100,0000 persons in each category, aggregating over age), up to 31 Dec 2020 and within the age range 20-69 years only. 'Open society' occupation category distribution used. 'Not known' occupation imputed.

2 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.

2.1 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.

2.2 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.

2.3 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.

2.3.1 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.

2.3.2 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.

-

2.3.3 *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%).

-

2.4 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].
4.
5. 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.

6.

2.5 Potential limitations

7. 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.

8.

9. 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.

10.

2.6 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]

11.

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%

12.

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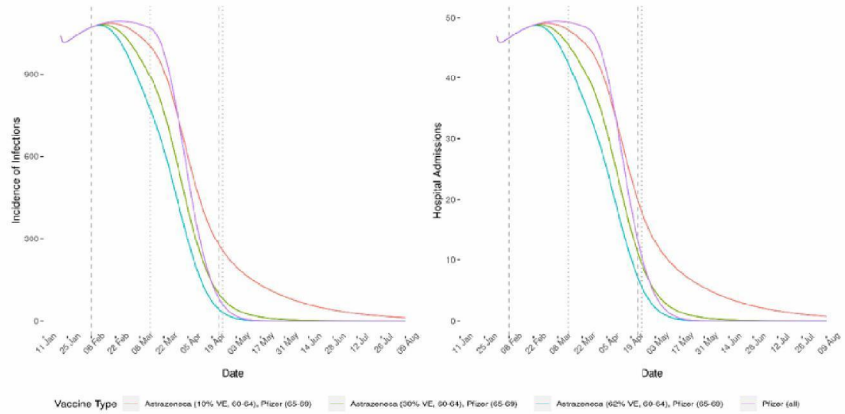

Figure 18. Modelled daily incidence of infections (left) and daily hospital admissions (right) in 60-69 year olds under different vaccination scenarios. In all scenarios, people aged 65-69 receive the Pfizer vaccine, and the vaccine is

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%

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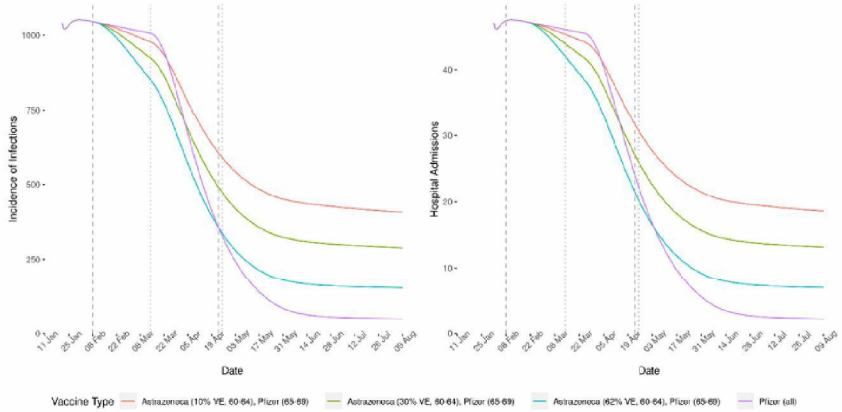

Figure 19. Modelled daily incidence of infections (left) and daily hospital admissions (right) in 60-69 year olds under different vaccination scenarios under the assumption of a constant force of infection. In all scenarios, people aged 65-69 receive the Pfizer vaccine, and the vaccine is varied among 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%

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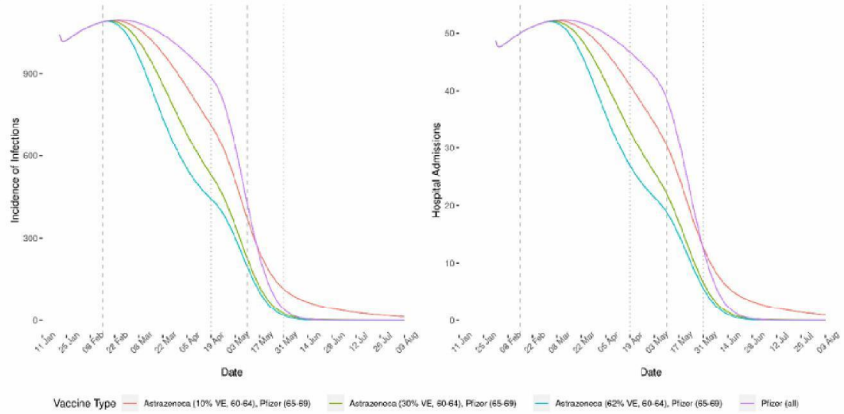

Figure 20. Modelled daily incidence of infections (left) and daily hospital admissions (right) in 60-69 year olds under different vaccination scenarios. In all scenarios, people aged 65-69 receive the Pfizer vaccine, and the vaccine is varied among individuals aged 60-64. The vertical grey dashed lines 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%

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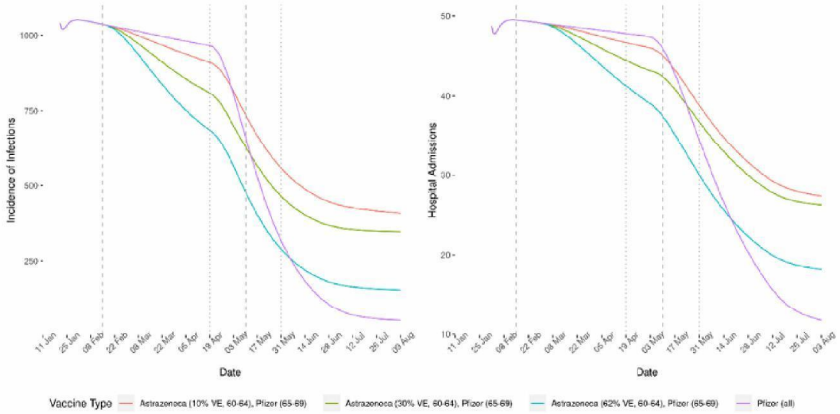

Figure 21. Modelled daily incidence of infections (left) and daily hospital admissions (right) in 60-69 year olds under different vaccination scenarios under the assumption of constant force of infection. In all scenarios, people aged 65-69 receive the Pfizer vaccine, and the vaccine is varied among 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.

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

20. Analysis of 3 Feb 2021, updated 31 March 2021
21.
22. 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.
23.
24. 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?
25.
26. 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.
27.
28. 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.
29.
30. 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.

31.

32. 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.

33.

34. 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.

35.

36. For the AstraZeneca 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 AstraZeneca vaccine.

37.

3.1 Modelling Results

38. To further investigate the impact of deferring the second dose on hospital admissions we model the number of hospital admissions under two vaccination scenarios: a scenario where the duration between doses remains as it is now (5 weeks between Pfizer doses, 4 weeks between Moderna doses, and 12 weeks between AstraZeneca doses) (we will refer to this as "basis") and a scenario where second doses of the Pfizer BioNTech, Moderna and AstraZeneca vaccines are delayed (we will refer to this as "deferral of the second dose"). See Simulation Model section and Table 8 below for details. We adhere to vaccination schedules for both scenarios that have been provided by the group responsible for planning the vaccination schemes (RIVM/LCC). We observe that both scenarios require the same amount of additional control measures, and that there is a 17.35% reduction in hospital admissions between 1 April 2021 and 31 August 2021 when the second dose is deferred compared to the basis scenario (Figure 22, Table 9). The differences only arise in the summer months

when, due to the seasonality of SARS-CoV-2, transmission may be lower. Our model does not account for seasonality, thus the actual difference between these two scenarios may be smaller.

39.

40. We performed a sensitivity analysis using the vaccine effectiveness estimates for the Pfizer vaccine from Vasileiou et al. [9] which are lower than those from Hall et al. [10] (Table 8). We did not assume different vaccine effectiveness estimates for the other vaccines. When using this estimate we observe that the deferral of the second dose scenario requires less additional control measures compared to the basis scenario. We observe a 4.2% increase in hospital admissions between 1 April 2021 and 31 August 2021 when the second dose is deferred compared to the basis scenario (Figure 23 (left), Table 9). For each of the different estimates for vaccine effectiveness we find that deferring the second dose minimises hospitalisations while not requiring additional, stricter control measures.

41.

42. The large difference in percentage increase or decrease in hospital admissions arises because in our simulations additional control measures are implemented whenever a threshold for new cases per day is surpassed to avoid exceeding the available healthcare capacity. In the basis scenario, with vaccine effectiveness estimates based on Vasileiou et al., cases surpass the threshold to re-impose stricter measures in the third week of June due to a sharp rise following the relaxation of measures (Figure 23 (right)). The strict measures then causes cases to drop quickly. When the second dose is deferred, cases rise more slowly throughout June and into July, but do not pass the threshold requiring stricter measures be re-imposed. Fewer hospitalisations occur under the basis scenario because more strict interventions are required at the end of June to contain the epidemic; without such additional control measures the number of hospitalisations in the basis scenario would have been substantially larger than the number of hospitalisations in the scenario where the second dose is deferred.

43.

44. We also investigated how these two vaccination scenarios compare when we assume measures are only relaxed and strict measures are not re-imposed regardless of whether daily cases rise above the threshold. We found that deferring the second dose resulted a 9% reduction in hospitalisations when we assumed the vaccine effectiveness estimates for Pfizer from Hall et al. (Table 9, Figure 24). Similarly we found a 7.5% reduction in hospitalisations when we assumed the vaccine effectiveness estimate of the first dose of the Pfizer vaccine from Vasileiou et al. (Table 9, Figure 25). These reductions are smaller than those observed in the main analysis where we assume strict control measures are re-imposed due to an uncontrolled epidemic that occurs when strict control measures are relaxed in mid-April before sufficient vaccination coverage is achieved.

45.

46. We stress that the vaccination schemes provided to us for the basis scenario and the deferral of the second dose differ in

several aspects, due to increased availability of vaccines over time, and requirement to meet the target coverages. These differences are highlighted in Figure 24.

47.

Table 4.1. Vaccine effectiveness estimates and delay to protection assumed for the Pfizer vaccine in the main and sensitivity analyses.

Analysis	Vaccine Effectiveness (1st dose)	Vaccine Effectiveness (2nd dose)	Delay to protection (1st dose)	Delay to protection (2nd dose)	Reference
Main	70%	85%	21 days	7 days	Hall et al. [10]
Sensitivity	64.5%*	85%	7 days	7 days	Vasileiou et al. [9]

* this estimate represents the average vaccine effectiveness over 6 weeks.

Table 4.2. Cumulative daily hospital admissions and percent difference (relative to basis scenario) for the main analysis and sensitivity analysis when we assume strict measures are re-imposed if cases rise above 37.5 per 100,000 people per day (Y) and when we assume no strict measures are re-imposed (N).

Analysis	Scenario	Strict Measures re-imposed?	Cumulative Hospital Admissions	Percent Difference
Main	Basis	Y	7159	Reference
	Defer 2nd dose	Y	5917	-17.34%
	Basis	N	14861	Reference
	Defer 2nd dose	N	13532	-8.95%
Sensitivity	Basis	Y	5730*	Reference
	Defer 2nd dose	Y	5970	4.2%
	Basis	N	15084	Reference
	Defer 2nd dose	N	13946	-7.54%

* stricter measures were imposed in this basis scenario for a longer period of time than in the scenario where the second dose was deferred

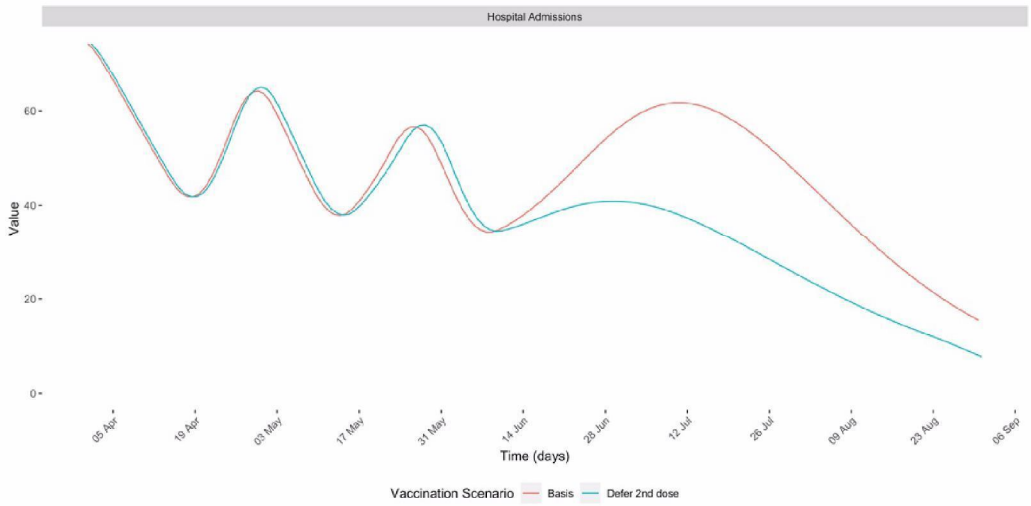

Figure 4.1. Modelled hospital admissions per day from 1 April 2021 to 31 August 2021 under the basis vaccination scenario (red line) and under the scenario in which the second dose is deferred (blue line). We assume the first dose vaccine effectiveness for the Pfizer vaccine after a single dose as reported in Hall et al. and that protection is conferred 21 days after vaccine receipt. These results do not represent a prediction, but instead should be used as a relative comparison of potential outcomes under these two vaccination scenarios.

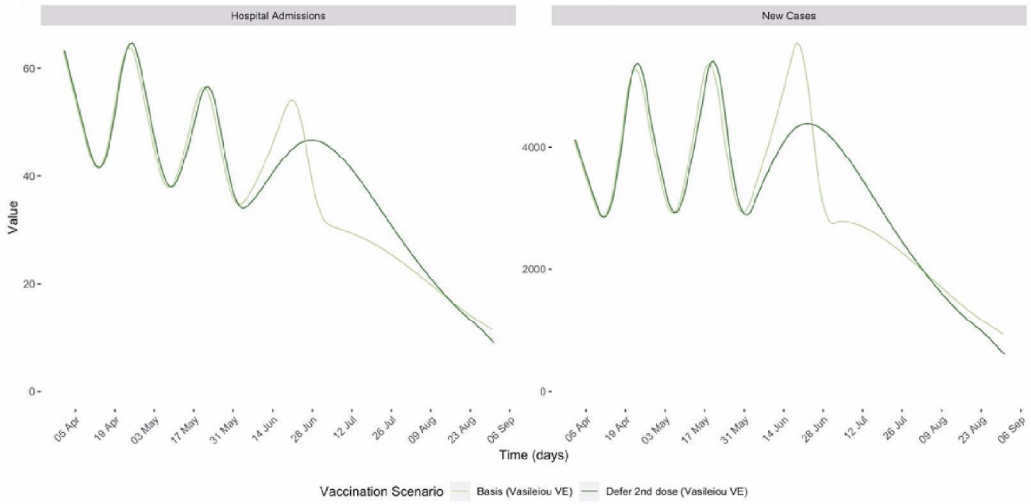

Figure 4.2. Modelled hospital admissions per day (left) and new daily cases (right) from 1 April 2021 to 31 August 2021 under the basis vaccination scenario (light green line) and under the scenario in which the second dose is deferred (dark blue line). We assume the average vaccine effectiveness for the Pfizer vaccine after a single dose as reported in Vasileiou et al. and that protection is conferred 7 days after the receipt of the vaccine. These results do not represent a prediction, but instead should be used as a relative comparison of potential outcomes under these two vaccination scenarios.

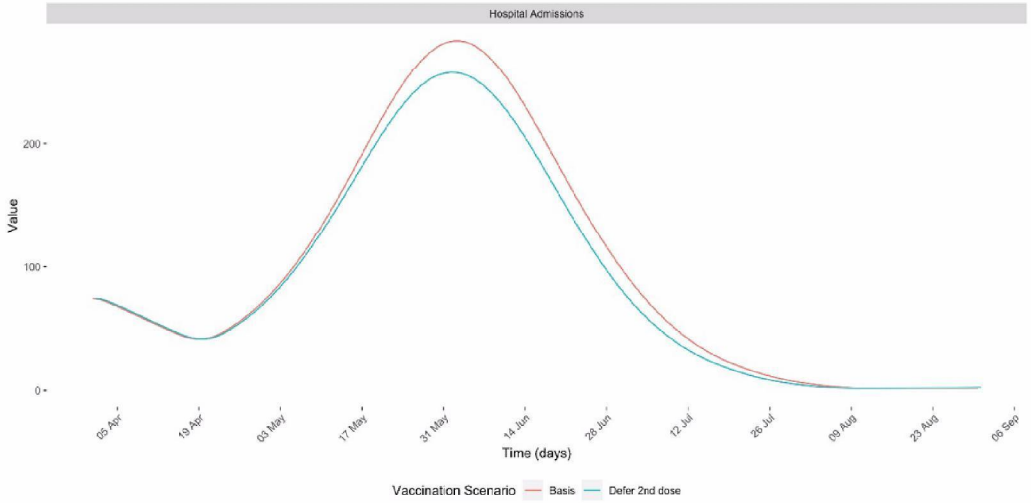

Figure 4.3. Modelled hospital admissions per day from 1 April 2021 to 31 August 2021 under the basis vaccination scenario (red line) and under the scenario in which the second dose is deferred (blue line) assuming no strict measures are re-imposed. We assume the first dose vaccine effectiveness for the Pfizer vaccine after a single dose as reported in Hall et al. and that protection is conferred 21 days after vaccine receipt. These results do not represent a prediction, but instead should be used as a relative comparison of potential outcomes under these two vaccination scenarios.

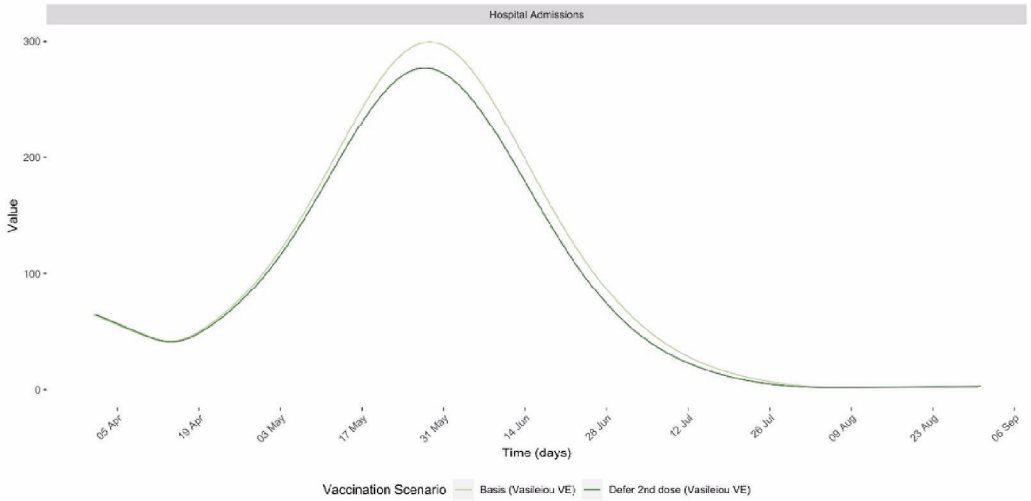

Figure 4.4. Modelled hospital admissions per day from 1 April 2021 to 31 August 2021 under the basis vaccination scenario (light green line) and under the scenario in which the second dose is deferred (dark blue line) under the assumption that no strict measures are re-imposed. We assume the average vaccine effectiveness for the Pfizer vaccine after a single dose as reported in Vasileiou et al. and that protection is conferred 7 days after the receipt of the vaccine. These results do not represent a prediction, but instead should be used

as a relative comparison of potential outcomes under these two vaccination scenarios.

3.2 Simulation model

48. 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 similar to a situation in February 2021 are used to begin the simulation and are relaxed if cases fall below a threshold. Measures similar to those of 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. The model assumes that vaccination protects against infection. We use updated vaccine effectiveness estimates for the Pfizer vaccine based on a recent pre-print [10]. Specifically, we assume the Pfizer vaccine effectiveness against infection 21 days after the first dose is 70% and the vaccine effectiveness against infection 7 days after the second dose is 85%.
49.
50. We also looked at the reported vaccine effectiveness of the Pfizer and AstraZeneca vaccines against hospitalization in a study by Vasileiou et al. (preprint, not peer-reviewed) [9]. Their reported vaccine effectiveness against hospitalization for the Pfizer vaccine (mean VE = 64.5%) after a single dose is lower than vaccine effectiveness against infection in other reports [10], which suggests that these estimates might serve as lower bound on vaccine effectiveness against infection (we do not investigate the alternative explanation that the hospitalisation rate of vaccinated cases is higher than the hospitalisation rate of unvaccinated cases). The lower vaccine effectiveness here might be caused by the declining trend in vaccine effectiveness after the first dose. Our model does not take into account vaccine effectiveness over time, so we used the mean single dose vaccine effectiveness from Vasileiou et al. and assumed protection began 7 days after vaccination [9]. For the vaccine effectiveness after the second dose we used the estimate from Hall et al. [10]. The estimates of vaccine effectiveness of the AstraZeneca vaccine against hospitalisation (mean VE = 80.5%) is reported to be higher than estimates of vaccine effectiveness against infection. To account for this, the rate at which hospitalisation admissions occur is reduced so that the VE against hospitalisations is 80.5%.
51.
52. The objective of this specific model is to capture the dynamic aspects of vaccine allocation when comparing the alternative vaccination schemes, specifically the basis scheme compared to

deferring the second dose. The distribution of vaccine doses by scenario is shown in Figure 24. Due to differences in number of first dose allocations and timing of those vaccinations between the two scenarios, there are differences in the number of vaccines allocated. Additionally, in the deferral scenario, no future second doses are allocated (historic second doses are included). Therefore, the total number of vaccines allocated is less than in the basis scenario. Because the time window for this simulation study is 1 April to 31 August, a duration of 12 weeks between the first and second dose for the Pfizer vaccine would mean that most second doses would be administered outside this time window or in August when the risk of infection is low in all simulations. Therefore the difference in results between not allocating second doses and deferring by a period of 12 weeks is expected to be very small.

53. 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.

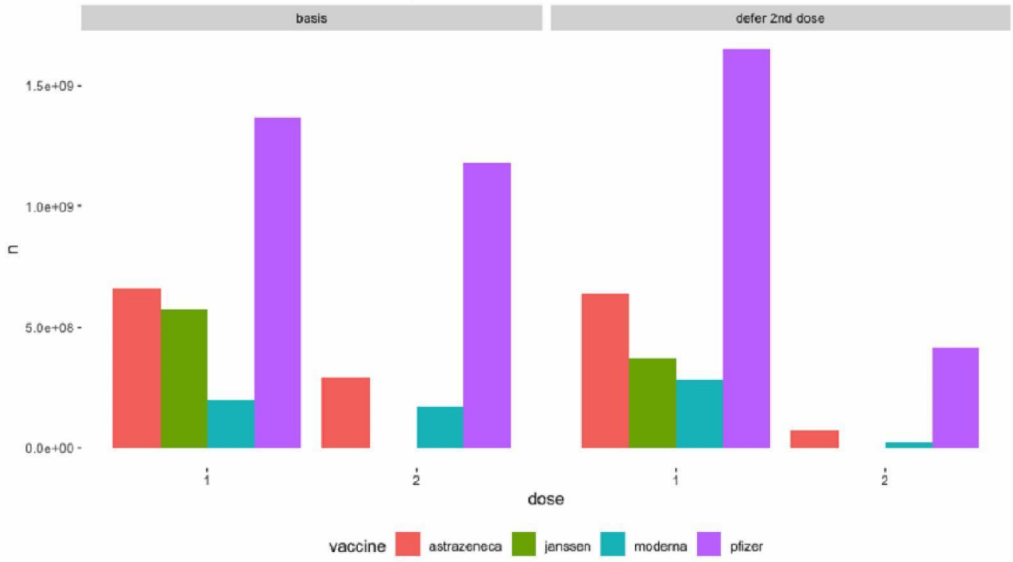

Figure 4.5. Number of vaccines distributed by dose for the basis scenario and when the second dose is deferred.

54.

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

55. Analysis of 3 Feb 2021
56.

4.1 Context

57. 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.
58.

4.2 Direct protection

59. 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.
60.
61. 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.
62.

4.3 Data

63. 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.

64.

65. 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.

66. ICU data from: https://stichting-nice.nl/covid-19-op-de-ic.jsp

67.

4.4 Vaccination programme

68. 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.

69.

4.5 Results

70. 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.

71.

72. 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.

73.

4.6 Limitations

74. 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.
75.
76. 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.
77.
78. 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.
79.
80. 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.

81.

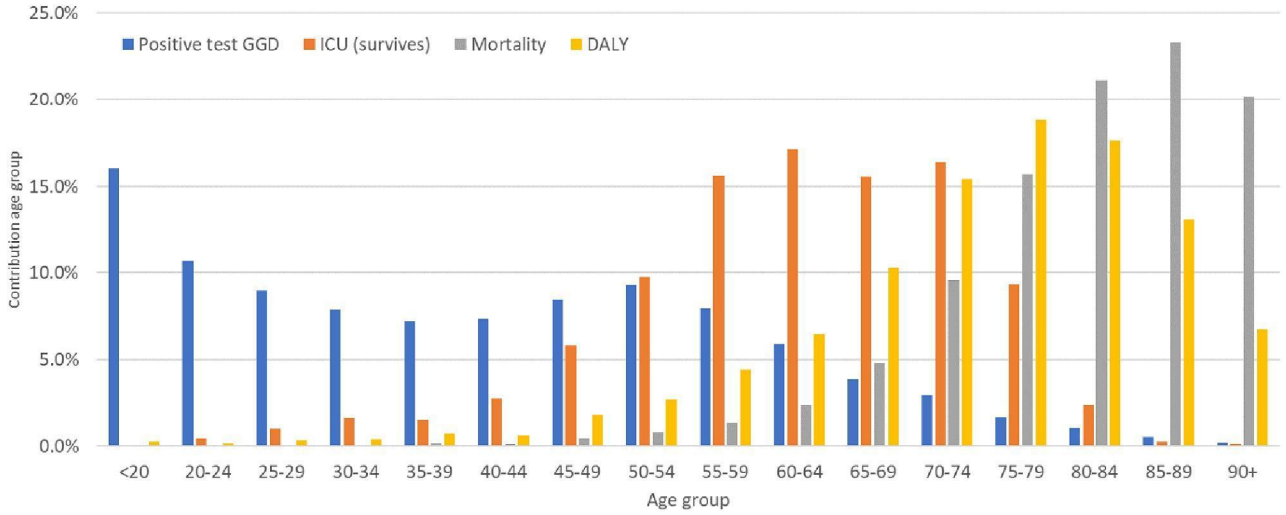

Figure 22. The contribution of age groups towards the overall reported disease burden by age. DALYs in yellow, mortality in grey, ICU admission in orange and positive tests in blue bars.

82.

83.

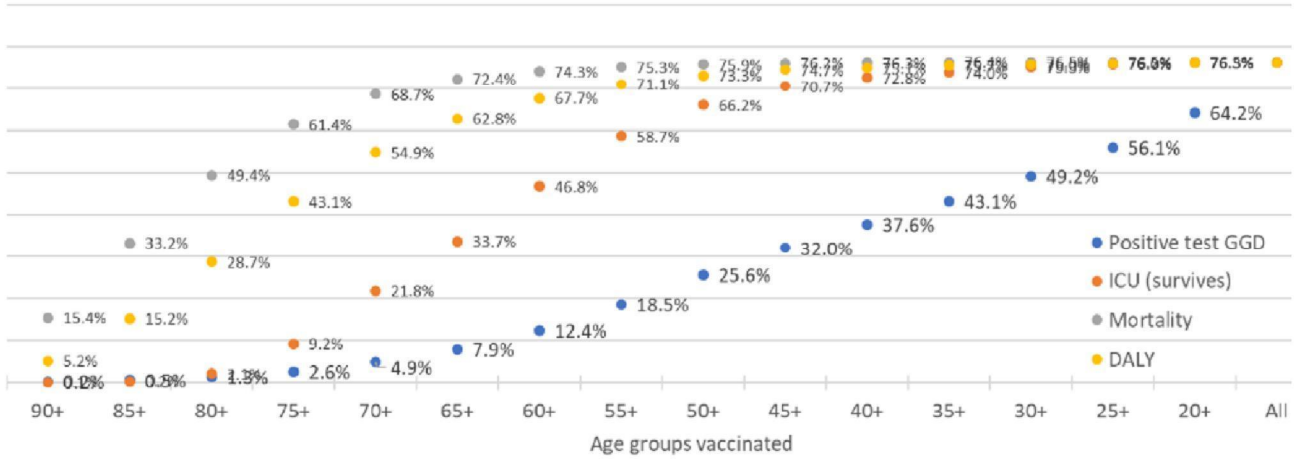

Figure 23. Incremental level of prevented disease burden (DALY, mortality, ICU admission and positive test) for vaccination programmes targeting more age groups, starting with only vaccinating those aged 90+.

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

Analysis of 10 Feb 2021, text updated 15 March 2021

5.1 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.

5.2 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.

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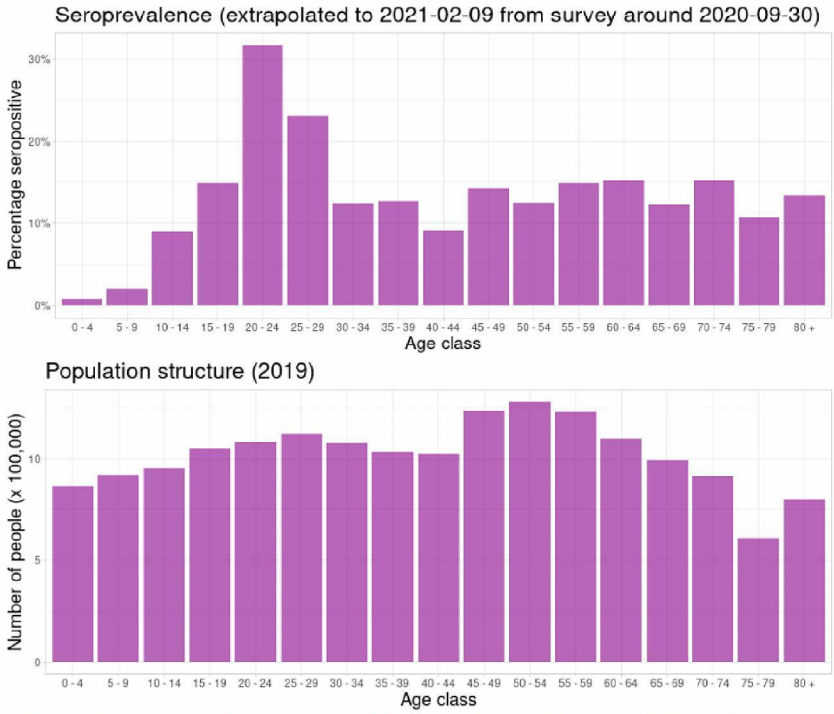

Figure 24. Current estimate of the age-specific percentage of the population with detectable antibodies against SARS-CoV-2 in the Netherlands after natural infection, as of February 10th, 2021. (a) estimated percentage seropositive. The estimates are based on the Pienter-Corona study among a representative 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.

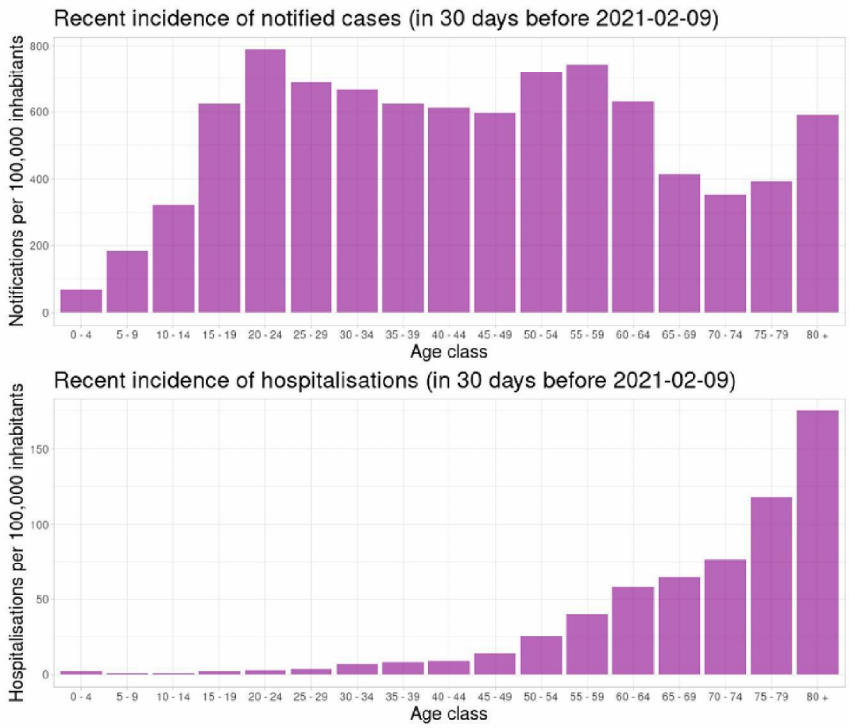

Figure 25. Incidence of notified COVID-19 cases in the Netherlands, by age, over the interval 10 January – 9 February 2021. (a) Cases with a positive test as notified to the GGD and recorded in the OSIRIS system. (b) severe cases with a positive test and admitted to the hospital as recorded in the NICE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

5.3 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.

5.4 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).

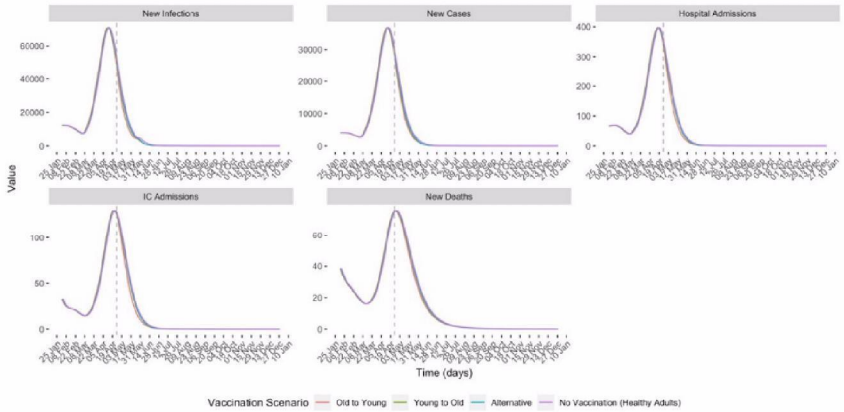

Figure 26. New infections, new cases, hospital admissions, IC admissions, and new deaths under different AstraZeneca and Janssen vaccine allocation schemes: 1) old to young, 2) young to old, 3) alternative, 4) no vaccination (in healthy adults). Lines for the vaccine schemes have been jittered for increased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

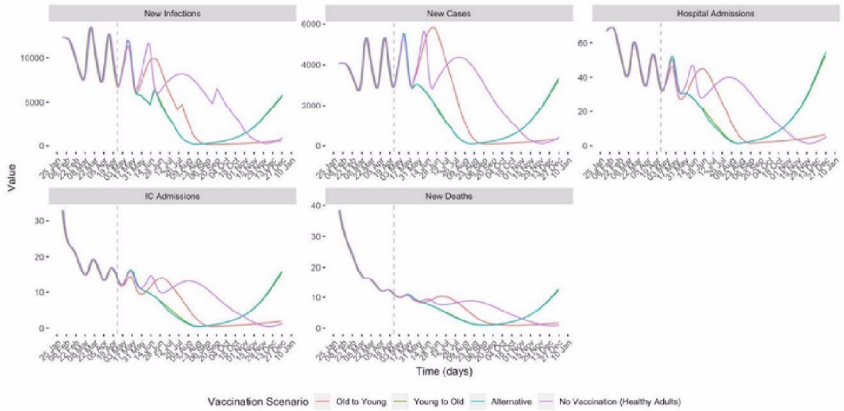

Figure 27. Sensitivity analysis of expected outcomes when strict measures are re-imposed after new daily cases rise above threshold of 35.7 new cases per 100,000 people per day. New infections, new cases, hospital admissions, IC admissions, and new deaths under different AstraZeneca and Janssen vaccine 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

5.4.1 *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.

5.5 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)

5.5.1 *Simulation model*

85. 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.

86.

5.5.2 *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

e.

5.6 Limitations

f. 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.

g.

h. 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.

i.

j. 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.

k.

l. 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.

m.

n. 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.

o.

p. 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.

q.

r. 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.

s.

6 Vaccine efficacy against infection and transmission

Analysis of 18 Feb 2021, text updated 29 April 2021

t.

u. 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 (transmitting to) other people. With the roll-out of vaccination programs across the globe, more and more studies are being published that characterize the protection conferred by vaccination. Most of these studies are observational studies and estimate vaccine *effectiveness* (VE) in real world settings. Vaccine *effectiveness* is measured in the general population using an observational study design whereas vaccine *efficacy* is measured in a randomized clinical trial. These two quantities can differ. The available information as of April 22rd, 2021 are summarized in this report. We anticipate more results addressing these questions will be available in the coming months.

v.

6.1 Vaccine effectiveness against infection

6.1.1 Pfizer/BioNTech and Moderna

w. Many observational studies have provided information about the performance of the Pfizer/BioNTech vaccine. Few studies have been published which look specifically at the Moderna vaccine. However, however, as both the Pfizer/BioNTech and Moderna are mRNA vaccines, it is reasonable to assume they perform similarly in real world settings.

x.

y. A study from Israel found that the Pfizer/BioNTech vaccine had an effectiveness of 51% against infection 13-24 days after the first dose [11]. A re-analysis of this data by Hunter et al. found that by 24 days after vaccination vaccine effectiveness reached 90% [12]. A more recent study from Israel found that the Pfizer/BioNTech had a VE against infection of 13% (-23%, 38%) 4 – 10 days after the first dose, 75% (66%, 82%) when partially vaccinated (defined as >10 days after the first dose to 1 – 10 days after the second dose), and 88% (83%, 92%) when fully vaccinated (defined as > 10 days after the second dose) [13]. 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 generalize to vaccine effectiveness against all cases of COVID-19 (both symptomatic and asymptomatic) [15]. 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 [10]. On March 29, 2021 the United States Centers for Disease Control and Prevention (CDC) published results from a study in healthcare and frontline workers. They found that the currently available mRNA vaccines (Pfizer/BioNTech and Moderna) are 80% (57%, 90%) effective against infection 14 or more days after the first dose. The VE against infection rises to 90% (68%, 97%) 14 or more days after the second dose [16]. The study did not stratify VE estimates by vaccine. A Swedish cohort study found that the estimated VE against infection was 86% (72%, 94%) ≥7 days after second dose with the Pfizer/BioNTech vaccine, but only 42% (14%, 63%) ≥14 days after a single dose [17].

z.

6.1.2 *AstraZeneca*

aa. In a clinical trial 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 used 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 generalize to vaccine effectiveness against all cases of COVID-19 (both symptomatic and asymptomatic) [15].

bb.

6.2 Vaccine effectiveness against transmission

cc. Only one study, to date, has been designed to specifically assess whether the COVID-19 vaccines block onward transmission. Shah et al. used a household study to determine if household members of vaccinated health care workers had a reduced risk of infection compared to household members of unvaccinated health care workers. The study found a 30% reduction in infections 14 or more days after the first dose with either the Pfizer/BioNTech or AstraZeneca vaccines. This reduction rose to 54% 14 or more days after the second dose. The study investigators suggest that these may be underestimates of the true effect of either the Pfizer/BioNTech or AstraZeneca vaccines on transmission because they may have been exposed to SARS-CoV-2 outside the household [18].

dd.

ee. A study by Harris et al. [19] used surveillance data of laboratory confirmed cases of COVID-19 in England that is linked to individuals who share the same address. This data was further linked to vaccination information, so the study investigators could investigate the number of secondary infections occurring in households where the index case was vaccinated or not. Individuals included in the study were vaccinated with either the AstraZeneca or Pfizer/BioNTech vaccines. The study found that the likelihood of transmission from a vaccinated (with a single dose) index case to a household member is 40-50% lower than if the index case is unvaccinated. The study found similar effects for both the AstraZeneca and Pfizer/BioNTech vaccines. Reduction in likelihood of transmission occurred 14 or more days after vaccination. The study found little difference in the effects of the vaccines on transmission when stratifying by age of index case and/or contact suggesting that the effects of vaccine on transmission are robust across age groups.

ff.

gg. Some studies have used proxies to estimate the effect of COVID-19 vaccines on transmission, such as cycle

threshold (CT) value and viral load. CT value is inversely proportional to viral load, therefore a higher CT value indicates a lower viral load and a lower potential for transmitting to other individuals. Two studies in Israel released as pre-prints in early February which evaluated viral load in vaccinated individuals found that vaccination with the Pfizer/BioNTech vaccine reduced viral load [20, 21]. Specifically, Petter et al. found that viral load was reduced by 1.6 to 20 times in vaccinated individuals who tested positive for SARS-CoV-2 [20]. Levine-Tiefenbrun et al. found that infections occurring 12-28 days after vaccination had a 4-fold reduction in viral load [21]. A third study from Israel found increasing CT values at different time points after the first dose of the Pfizer/BioNTech vaccine with the highest average CT value occurring >10 days after the second dose [13]. A prospective study in care home residents in the UK found higher CT values (which corresponds to lower viral load) in vaccinated individuals 28 or more days after vaccination (mean = 31.1). Mean CT value 0-27 days (mean = 26.9) after vaccination was similar to unvaccinated. Study participants were vaccinated with either the Pfizer/BioNTech or AstraZeneca vaccines. These results indicate that these two vaccines may impact transmission in the elderly population [22]. Similar impacts of the Pfizer/BioNTech vaccine in nursing home residents were observed by McEllistrem et al. [23]. In a phase II/II clinical trial, Emary et al. found that CT values in those vaccinated with the AstraZeneca vaccine were higher than controls regardless of whether individuals were infected with the UK variant (B.1.1.7) or not. Additionally the study found that AstraZeneca vaccination reduced the median length of time individuals tested positive by one week [24]. All of these results suggest that vaccination may reduce viral shedding and contagiousness, which may prevent onward transmission.

hh.

ii. There have been no studies, to date, that have specifically investigated the impact of the Moderna or Janssen vaccines on transmission. However, studies are under way to assess how the Moderna vaccine affects infectiousness [7].

jj.

kk. Overall, these results are a promising indication that vaccination does provide some level of protection against onward transmission.

ll.

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

6.3.1 *Epidemiology in the Netherlands*

mm. Since January 2021, the variant 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 15 of 2021

(up to 18 April 2021), the percentage of the samples obtained each week were calculated for the variants B.1.1.7 (UK variant), B.1.351 (South Africa variant), and P.1 (Brazil variant) (Figure 28).

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oo.

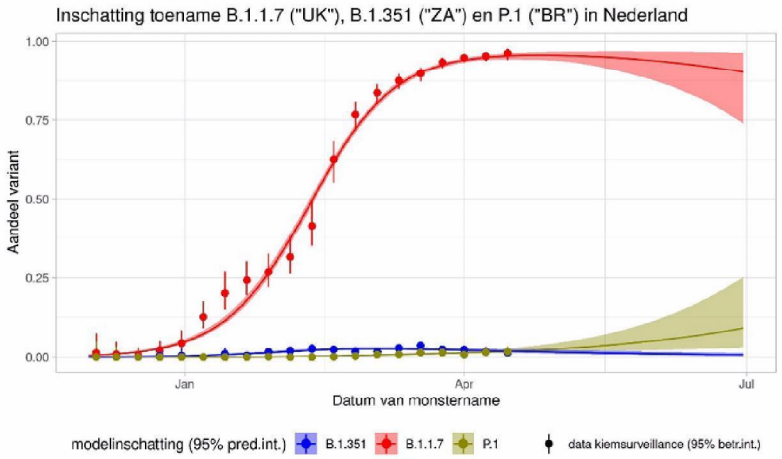

Figure 28. Observed percentage of variants by date of sampling in the Netherlands, 2021. Lines indicate median, shaded area indicates the 95% confidence interval, of logistic growth curves that are fitted to the observations. Projections are based on the assumption that vaccination does not affect the estimated differences in transmissibility.

pp.

6.3.2 *Transmissibility*

qq. 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 B.1.1.7 variant has a reproduction number that is 33% higher (95% CI: 32% , 34%) as compared to the previous variants; the B.1.351 variant has a reproduction number that is 26% higher (95% CI: 24% , 30%) as compared to the previous variants; the P.1 variant has a reproduction number that is 44% higher than the previous variants (95% CI: 38% , 51%).

rr.

6.3.3 *Severity of disease*

ss. There is evidence from analysis of multiple different datasets in the UK and Denmark (https://dx.doi.org/10.2139/ssrn.3792894) 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 [25].

tt.

6.3.4 *Vaccine efficacy*

uu. There are indications that the vaccine efficacy might be lower for some variants as compared to the wild type

variant. However, there are 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 [26]. One possible interpretation is that the vaccine efficacy of the AstraZeneca vaccine is lowered against this variant. However, other plausible explanations cannot be excluded. A recent clinical trial found that the efficacy of the AstraZeneca vaccine against symptomatic infection was lower for infections with the UK variant (B.1.1.7). Specifically, the vaccine efficacy was 70.4% (43.6%, 84.5%) for the B.1.1.7 lineage and 81.5% (67.9, 89.4%) for non-B.1.1.7 lineages [24].

vv.

6.1.5 *Conclusion*

ww. 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.

xx.

yy.

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

zz. Analysis of 25 Feb 2021, text updated 15 March 2021
aaa.
bbb. 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
5)
6) 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.
7)

7.1 Summary

8) 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.
9)

7.2 Methods

10) 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.

11)

12) 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.

13)

14) 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).

15)

16) 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.

17)

7.3 Results

18) 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.

19)

20) 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).

21)

7.4 Discussion

22) The conclusions drawn here, namely 1) vaccination reduces disease outcomes and 2) different prioritization 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.

23)

24) 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.

25)

26) 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.

7.5 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

28)

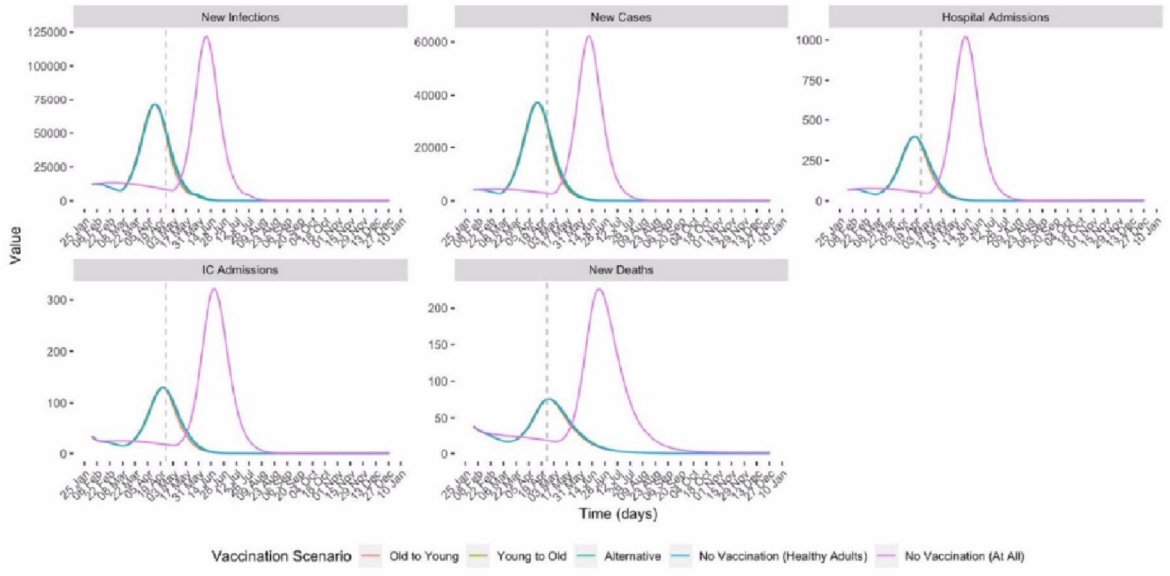

Figure 29. 7-day rolling average of new infections, new cases, hospital admissions, IC admissions, and new deaths under different AstraZeneca and Janssen vaccine allocation scenarios: 1) old to young, 2) young to old, 3) alternative, 4) no vaccination (in healthy adults), 5) no vaccination (at all). 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.

29)

30)

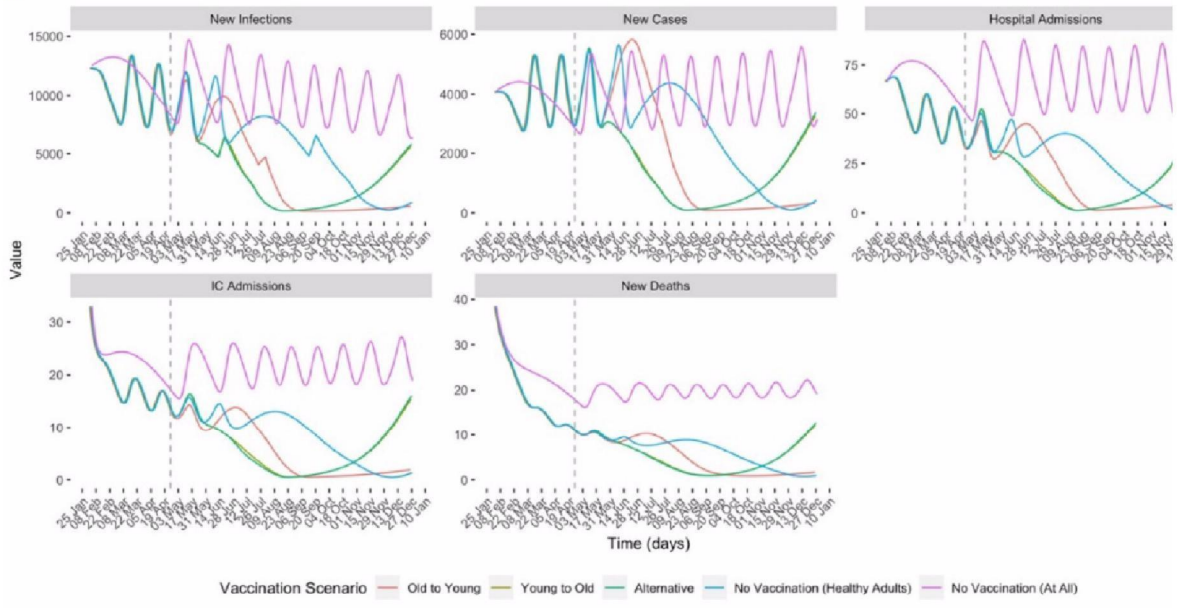

Figure 30. 7-day rolling average of new infections, new cases, hospital admissions, IC admissions, and new deaths under different AstraZeneca and Janssen vaccine allocation scenarios: 1) old to young, 2) young to old, 3) alternative, 4) no vaccination (in healthy adults), 5) no vaccination (at all). 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.

8 Large-scale testing

31) Analysis of 5 March 2021

32)

33) 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 [27] and recent modelling papers on the impact of testing, we provide an overview to illustrate the generic features in these papers.

34)

8.1 Mass testing in a single campaign

35) 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 [28].

36)

37) 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 [29].

38)

8.2 Repeated testing

39) Several modelling studies have investigated the expected impact of repeated testing, including Bootsma et al. [30], Paltiel et al. [31], and Bosetti et al. [28]. 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.

40)

41) 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).

42)

8.3 Testing before participating in an event

43) 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 [32]. 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 [33].

44)

8.4 The health benefits of testing and time scales

45) 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.

46)

47) 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.

48)

8.5 Conclusion

49) 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.

50)
51)

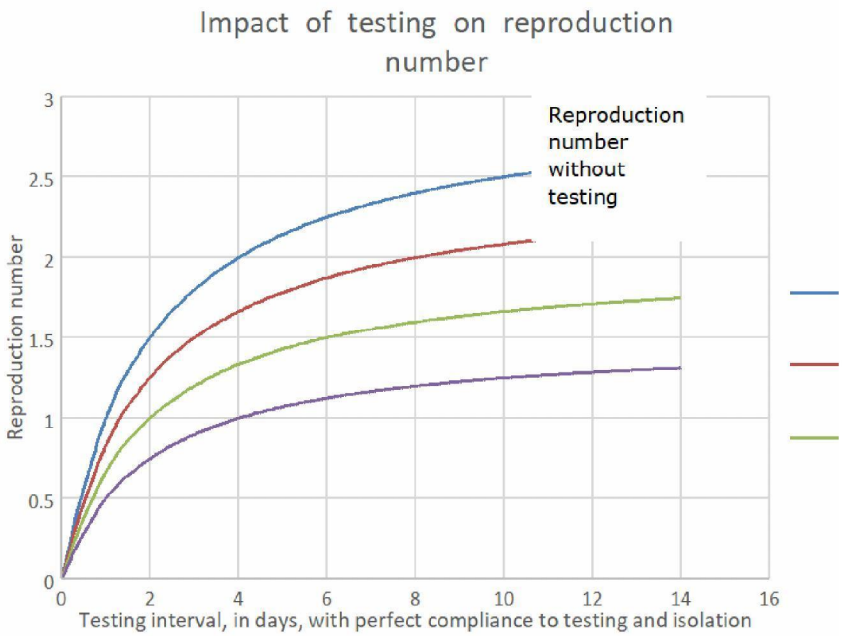

Figure 31. The impact of repeated universal testing at different intervals on transmission of infection, as measured by the reproduction number. We assume here that everyone participates in testing, that the test is perfect, and that everyone who tests positive goes into isolation and does not transmit 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.

9 When we have different types of vaccines, which should be allocated to which group?

52) Analysis of 15 March 2021
53)

9.1 Context

The Current vaccination programme in the Netherlands is focusing on high-risk individuals such as the elderly, and now several types of vaccines (BioNTech-Pfizer, Moderna, AstraZeneca, and Janssen) are available. These vaccines have different efficacies of preventing infection or symptomatic illness. The question here is that, given the limited amount of vaccine stocks, which vaccine should be allocated to which subgroups?

In this analysis, we simulate the expected impact of vaccinations by vaccine type. Optimal allocation strategies can differ, depending on the endpoint that we wish to minimize. Here we show the allocation scheme for the minimization with respect to:

A. the number of new infections
B. the number of hospitalizations
C. the number of deaths

54) Here we categorize the population by age. While other stratifications such as by sex or by profession might be informative, there is little evidence for the contribution of those factors to the transmission process. By contrast, in terms of both contact patterns and the burden of COVID-19 diseases, age is reported as one of the most influential determinants.
55)

9.2 Overview of the allocation scheme

The allocation scheme is an expanded methodology based on Wallinga et al. [34]. To decide the target group, we calculate the "importance weight" per age-group per vaccine type. The interpretation of this quantity is the expected decrease in the number of new infections/hospitalizations/deaths due to a single unit of vaccination. We here describe this concept with a brief algorithm below:

- Step-1: Decide the target index that you wish to minimize (e.g., hospitalization)
- Step-2: Calculate importance weights per age-group per vaccine type
- Step-3: Find a combination of age-group and vaccine type that has the largest importance weight
- Step-4: Allocate a single unit of the selected vaccine to the selected age-group
- Step-5: Re-calculate importance weights by decreasing the weights in the targeted age-group. Others remain the same.
- Step-6: Repeat above until the end of vaccine stocks

In this scheme, we have set three large assumptions to approximate the reproduction matrix (i.e., a matrix that indicates the average number of new infections by a single infected individual in each stratum) and relate it to the observed data; (i) transmission occurs according to mass-action type dynamics, (ii) at-risk contacts are reciprocal (e.g., if person-X can infect person-Y, person-Y can infect person-X as well), and (iii) there is no major change in the age distribution of the risk of infection during the allocation. With these assumptions, we can calculate the expected change in transmissions, without detailed information about contacts between groups [34].

9.3 Input data

All data are age-specific, and the population is stratified into [<20, 21-30, 31-40, 41-50, 51-60, 60+]. As input data, we used below observational data:

- Population structure
- Seroprevalence data
- Incidence of notified cases per stratum
- Maximum vaccine uptake (willingness to be vaccinated)
- Infection hospitalization rate
- Infection mortality rate
- Vaccine efficacy against infection and symptomatic illness

All the data are visualized in Figure 32. The nature of these input data should be noted. The seroprevalence data is from the Pienter-Corona study among a representative sample of the Dutch population, collected in June 2020 (https://www.rivm.nl/pienter-corona-studie). We used this data to calculate the number of susceptible individuals per stratum, that is, 1 – seropositive rate. We used infection hospitalization rate and infection mortality rate that were estimated by published studies [35, 36], and thus these are not Dutch specific estimates.

Several inputs are not based on the observed data but on assumptions. First, for the maximum vaccine uptake, we assumed 80% for all age groups. Second, we assumed that vaccine efficacy is constant over age-groups (Table 11). These two are visualized in colored bars in Figure 32, to emphasize that they are assumed.

9.4 Simulation setting

Now we can calculate the expected decrease in each minimization index (i.e., the number of new infections, hospitalizations, and deaths) as a function of the number of allocated vaccines. To quantify those effects, a natural reference point is no vaccination for the population. Thus, in the following sections we show the impact of vaccinations as the percentage reduction of each index. The starting point of effective reproduction number (i.e., the reference point of new infections without any vaccination) was set as 1.25.

The simulation scenario is set as follows. We have a vaccine stock that covers 80% of the total population. The breakdown of the stock is Pfizer-

BioNTech (46%), AstraZeneca (22%), Moderna (8%), and Janssen (24%). Note that we consider the unit of vaccines as a set of full doses; for example, Pfizer vaccine needs to be administered twice, and the set of those two doses is defined as a single unit here. Besides, we assume that one person can receive only one type of vaccines. Thus, 80% of the population is vaccinated at the end of the allocation.

9.5 **Result-1: Simulated vaccine allocations**

In general, higher efficacious vaccines are allocated firstly, and then lower efficacious are distributed later on (Figure 33 (A), (C), and (E)). If available, it is natural to prioritize the allocation of high efficacy vaccines. However, depending on the target minimization index, the type of vaccines which each age group receives would differ. If a specific age group is significantly contributing to the target index, it is better to distribute higher efficacious vaccines to that group. For example, there is a large contribution of age 21-30 for the number of infections, and thus higher efficacious vaccines (Pfizer) are distributed to that group (Figure S1 (B)). If we wish to minimize the number of hospitalizations or deaths, Pfizer vaccines would be distributed to the eldery. (Figure S2 and S3 (F)). Figure S1 – S3 shows the detailed breakdown of allocated vaccines by age group and vaccine type.

The order of allocations and the timing of switching from one age group to another are dependent on the target minimization index. When we set the target minimization index as the number of infections or hospitalizations, these two schemes allow us to distribute vaccines to several age-groups parallelly (Figure 33 (B) and (D)). By contrast, if we set the target minimization index as the number of deaths, the allocation scheme would focus on one age group, from old to young, and would not switch to the next age group until one age group is finished (Figure 33 (F)).

9.6 **Result-2: There is a trade-off amongst different allocation strategies**

If we choose to minimize the number of infections, that allocation scheme is not efficient for the minimization of deaths (Figure 34 (A)). In contrast, if we try to minimize the number of hospitalizations or deaths (Figure 34 (B) and (C)), those strategies are not efficient for preventing infections. Especially, those trade-off effects occur at the early phase of allocations; this is because mainly younger age groups became drivers of transmissions, compared to older groups such as 60+, while younger individuals are not in high-risk groups in terms of hospitalization or death.

9.7 **Potential limitations**

a. We do not consider the time-course of acquiring immunity. That is, our model assumes that the vaccinated individuals are protected immediately after receiving vaccines. In reality, it takes

10-14 days after vaccination. Besides, if the immunity is short-lived, our results are valid only for that time frame.

b. We also assumed that vaccinating previously infected individuals would have not affected their immunity. However, it is possible that previous infections might act as the first dose of vaccine and that vaccinating those individuals might result in a boost of their immunity.
c. The assumption on vaccine efficacy is strong, age-specific efficacy is still unclear. In addition, our simulation assumes that vaccines can protect a certain proportion of vaccinees completely from infection, but more concrete evidence about the probability of protecting individuals from infections or symptomatic illness is needed.
d. We assume that individuals are randomly mixing in each stratum. If there were a specific group that refuses vaccinations, and if its proportion became significantly large in a certain age group, that kind of clustering effect might change the result of simulations.

Tables and Figures

Table 10.11. Vaccine efficacies by vaccine manufacturer. Note that these vaccine efficacies are measured as overall efficacy in the original studies (not age-dependent), and thus the uniform distribution over age is an assumption in this analysis.

Age	Pfizer [37]	Moderna [7]	AstraZeneca [5]	Janssen [38]
0-20y	0.946	0.941	0.621	0.663
21-30y	0.946	0.941	0.621	0.663
31-40y	0.946	0.941	0.621	0.663
41-50y	0.946	0.941	0.621	0.663
51-60y	0.946	0.941	0.621	0.663
61y+	0.946	0.941	0.621	0.663

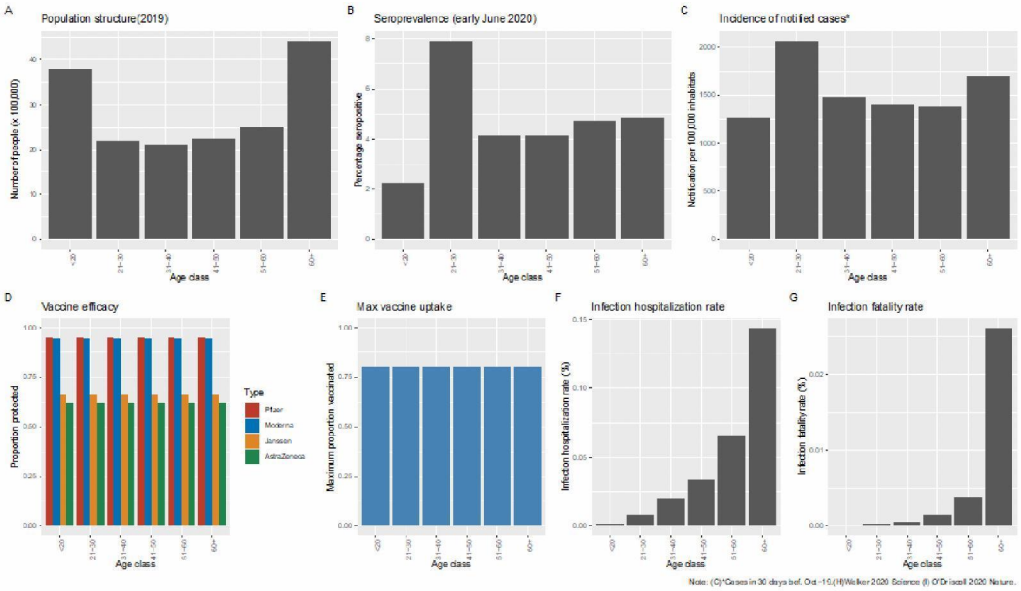

Figure 32. Age-specific Input data. (A) Population structure in the Netherlands in 2019 (B) Seroprevalence observed in the Pienter-Corona study among a representative sample of the Dutch population in June (https://www.rivm.nl/pienter-corona-studie). (C) Incidence of notified cases, in 30 days before Oct-19 (D) Vaccine Efficacy by vaccine type. Red bars indicate Pfizer, blue indicates Moderna, orange indicates Janssen, and green indicates AstraZeneca. Note that the constant age distribution here is an assumption, based on reported over all vaccine efficacies (Table-1). (E) Maximum vaccine uptake per age group. 80% for all groups is assumed here. (F) Infection hepatization rate. These values are based on the study by Walker (2020) Science. Their estimates are reported as 5-year age bins, and thus we took average to aggregate their estimates into [20<,21-30,31-40,41-50,51-60,60+] in this analysis. (G) Infection mortality rate. These values are based on the study by O'Driscoll (2020) Nature [36]. Aggregations of estimates were conducted in the same manner as (F). Note that (F) and (G) are not Dutch-specific data.

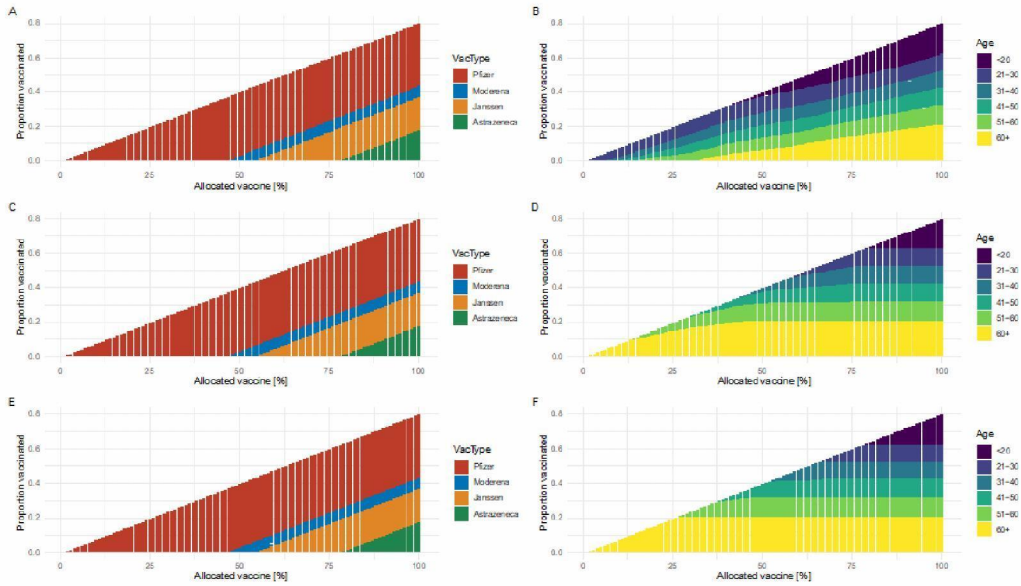

Figure 33. Simulated timeline of vaccine allocations when the minimizing target is the number of infections ((A) and (B), hospitalizations ((C) and (D)), and deaths ((E)and (F)). X-axis is the percentage of allocated vaccines, and "100%" (end of x-axis) means that all the stocks were distributed (80% total population coverage). In left three panels, red bars show Pfizer, blue bars show Moderna, orange indicates Janssen, and green indicates AstraZeneca. In right three panels, the darker color shows the younger age groups, and age bins are [20<,21-30,31-40,41-50,51-60,60+].

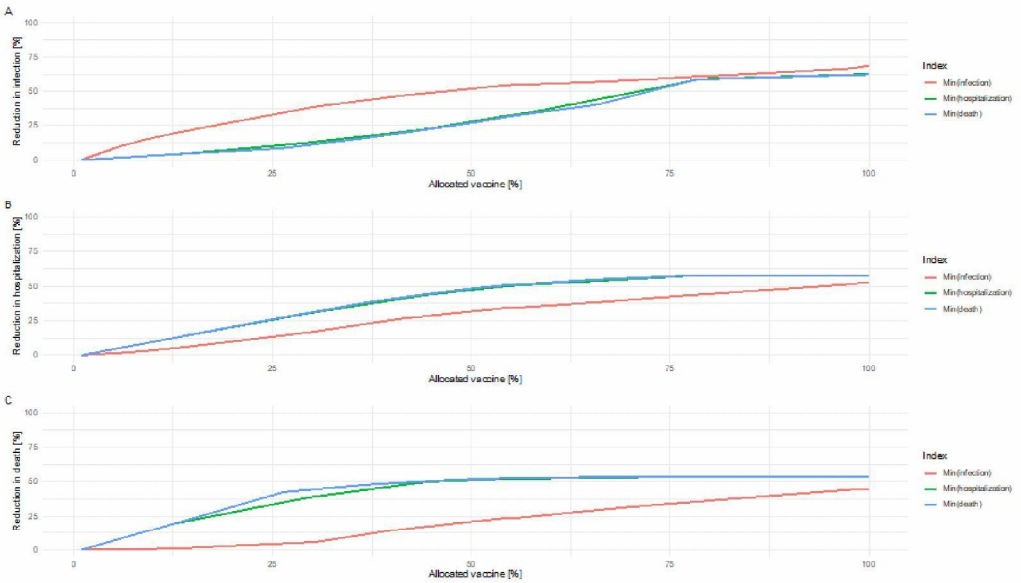

Figure 34. Simulated impact of vaccinations on target indexes. Y-axis shows the percentage reduction in the number of infections (A), hospitalizations (B), and

deaths (C). "0 %" stands for reference points (no vaccination). X-axis is the percentage of allocated vaccines, and "100%" (end of x-axis) means that all the stocks were distributed (80% total population coverage). percentage of allocated vaccines, and "100%" (end of x-axis) means that all the stocks were distributed (80% total population coverage). Red, green, and blue plots indicate the allocation strategies to minimize the number of infections, hospitalizations, and deaths respectively.

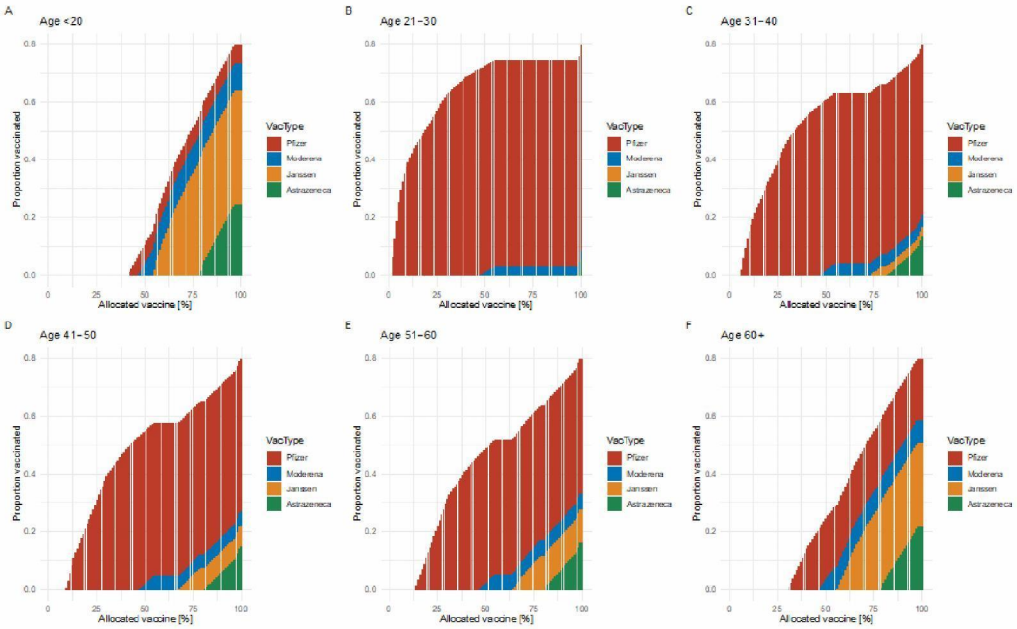

Figure S1. Simulated timeline of vaccine allocations when the minimizing target is the number of infections. Red bars show Pfizer, blue bars show Moderna, orange indicates Janssen, and green indicates AstraZeneca. X-axis is the percentage of allocated vaccines, and "100%" (end of x-axis) means that all the stocks were distributed (80% total population coverage). Y-axis means the proportion of vaccinated individuals in each age-group. From the top-left figure, results of (A) Age < 20, (B) Age 21-30, (C) Age 31-40, (D) Age 41-50, (E) Age 51-60, and (F) Age 61+ are shown.

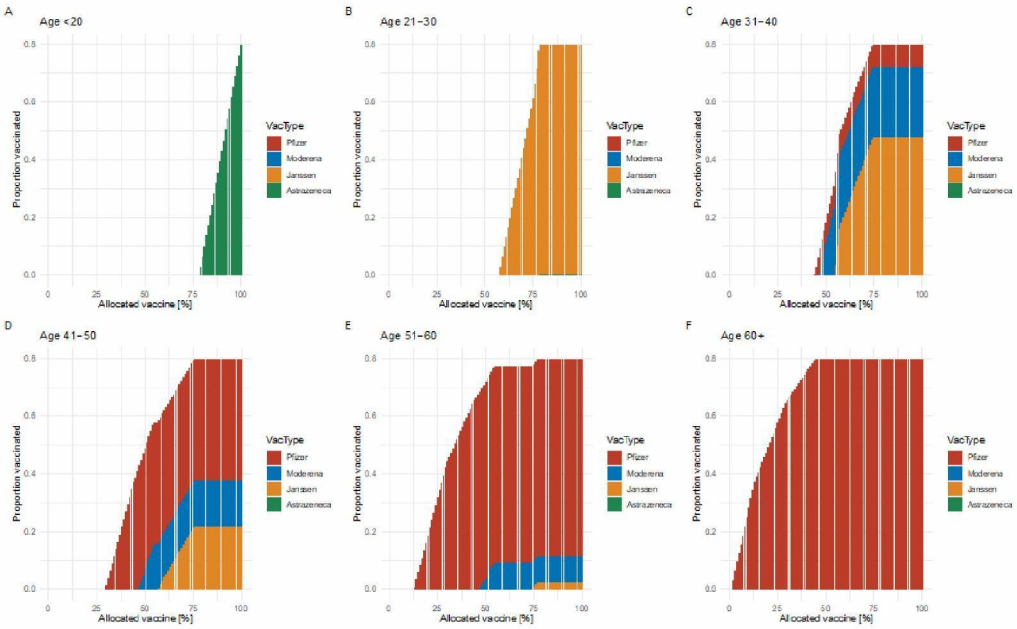

Figure S2. Simulated timeline of vaccine allocations when the minimizing target is the number of hospitalizations. Red bars show Pfizer, blue bars show Moderna, orange indicates Janssen, and green indicates AstraZeneca. X-axis is the percentage of allocated vaccines, and "100%" (end of x-axis) means that all the stocks were distributed (80% total population coverage). Y-axis means the proportion of vaccinated individuals in each age-group. From the top-left figure, results of (A) Age < 20, (B) Age 21-30, (C) Age 31-40, (D) Age 41-50, (E) Age 51-60, and (F) Age 61+ are shown.

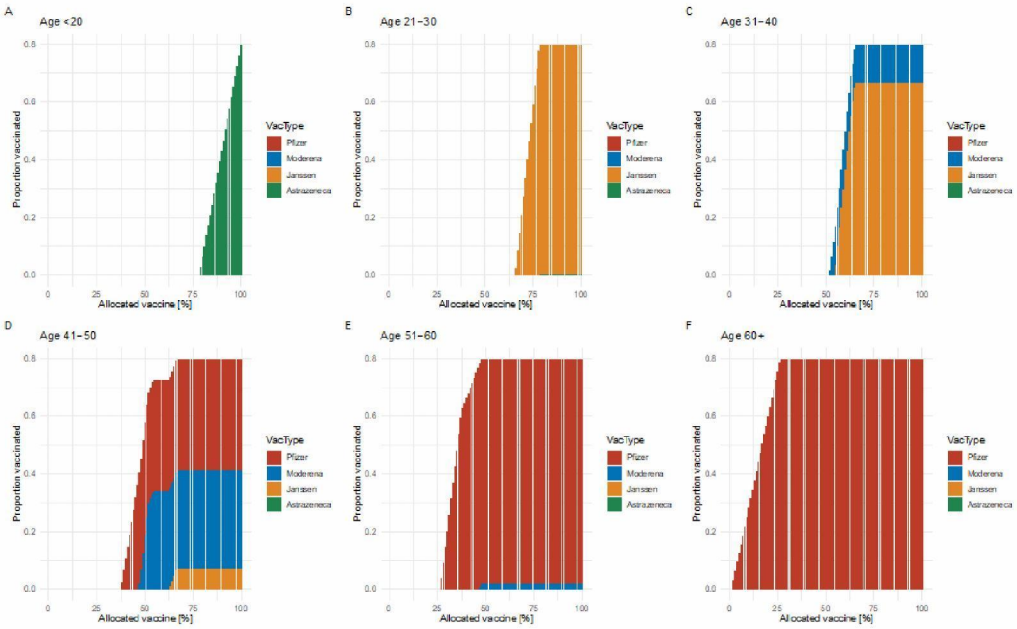

Figure S3. Simulated timeline of vaccine allocations when the minimizing target is the number of deaths. Red bars show Pfizer, blue bars show Moderna, orange indicates Janssen, and green indicates AstraZeneca. X-axis is the percentage of allocated vaccines, and "100%" (end of x-axis) means that all the stocks were distributed (80% total population coverage). Y-axis means the proportion of vaccinated individuals in each age-group. From the top-left figure, results of (A) Age < 20, (B) Age 21-30, (C) Age 31-40, (D) Age 41-50, (E) Age 51-60, and (F) Age 61+ are shown.

10 Modelling alternative vaccination strategies for adenovirus vaccines

56) Text updated 2 June 2021, Analysis of 10 May 2021

57)

10.1 Context

58) Several vaccines (Pfizer/BioNTech, Moderna, AstraZeneca, Janssen) against SARS-CoV-2 have been approved for emergency use by the European Medicines Agency to combat the COVID-19 pandemic. All of the approved vaccines are currently in use as part of the vaccination program in The Netherlands. However, due to evidence of adverse events, specifically thrombosis and thrombocytopenia syndrome (TTS), after vaccination with adenovirus vaccines (AstraZeneca and Janssen) [39-41] there is concern about the risk-benefit relationship of these vaccines. Vaccination strategies that limit the administration of AstraZeneca and/or Janssen vaccines also limit the adverse events caused by these vaccines; however, may cause delays in the vaccination program while replacement mRNA vaccines (Pfizer/BioNTech and Moderna) are procured. In this section, we investigate different vaccination strategies with respect to the number of daily cases, daily hospital admissions, and daily deaths and the total number of expected TTS events. The strategies investigated are detailed in table 32.

59)

Table 32. Vaccination strategie descriptions. The description for all strategies under the basis strategy indicate how these strategies differ from the basis scenario. The mRNA strategy can be viewed as the "no AstraZeneca" strategy, while the Janssen60 strategy can be viewed as the "no Janssen" strategy.

60) Strategy	61) **Description**
62) Basis	63) Scenario in which vaccine supplies are like planned. The target group size with medical indication (MI) is assumed to be 1.5 million and vaccine coverage is assumed to be 85% for group MI and 75% for groups without MI.
64) A	The AstraZeneca vaccine is allocated to people 50 years and

Z	above. The target group size with MI is assumed to be 1 million.
67) mRNA	68) Second doses of AstraZeneca are replaced with an mRNA vaccine.
69) Janssen60	70) The Janssen vaccine is not administered to people aged below 60 years.
71) Janssen50	72) The Janssen vaccine is not administered to people aged below 50 years.
73) Janssen40	74) The Janssen vaccine is not administered to people aged below 40 years.

75)

76) The abbreviations for each strategy will be used throughout this section. A summary of the total number of each type of vaccine allocated within each vaccination strategy is shown in figure 35.

77)

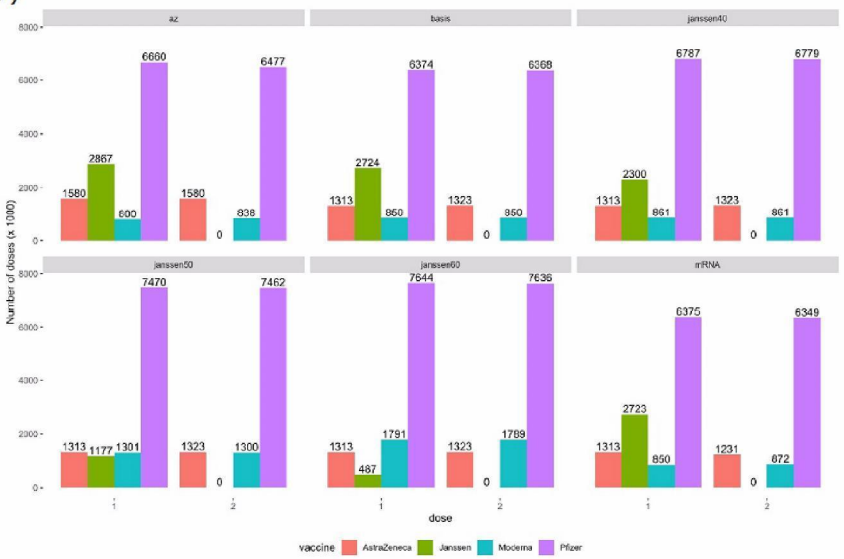

Figure 35. Total number of vaccine doses allocated (x 1,000) in each vaccination strategy by vaccine type.

78)

79)

10.2 Summary

80) We modelled cases, hospital admission, and deaths as well as the expected number of TTS events for several different vaccination strategies to determine the possible effects of discontinuing or restricting the use of adenovirus vaccines (AstraZeneca and Janssen). We found that there were very small differences in cumulative numbers of cases, hospital admissions, and deaths by vaccination strategy, however vaccination strategies that included the vaccination of healthy adults with Janssen resulted in the fewest cases, hospital admissions, and deaths.

81)

82) The vaccination strategies in which the fewest number of AstraZeneca and Janssen vaccines were administered (Janssen60 followed by Janssen50 and then Janssen40) resulted in the fewest expected TTS events, while the strategy with the greatest number of AstraZeneca and Janssen vaccines administered (AZ) resulted in the most expected TTS events. However, due to the rare occurrence of TTS events, there were not large differences in the expected number of events between vaccination strategies.

83)

84) The results presented here represent the expected outcomes under specific model assumptions. The optimal vaccination strategy may

change depending on the timing of the relaxation of measures or if the epidemiological situation changes. Regardless of the epidemiological situation, the expected number of adverse events will remain stable as they only depend on the number of vaccines administered.

85)

10.3 Methods

86) 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, hospitalizations, 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. In the main analysis, the contact matrices changed based on criteria as indicated in the Dutch government roadmap (see Appendix). Based on this criterium, measures were relaxed in late June 2021. However, we performed a sensitivity analysis whereby we relaxed measures on 1 June 2021.

87)

88) The objective of this specific model is to capture the dynamic aspects of vaccine allocation when comparing alternative vaccination strategies. The model is initialized by fitting Osiris case data from 31 January 2021 to April 20, 2021 (Figure 36). The outcomes of the model should not be considered a quantitative prediction; rather, one realization of possible outcomes given a set of assumptions. The objective is to determine the relative performance of different vaccination strategies with respect to new cases, hospital admissions, and new deaths.

89)

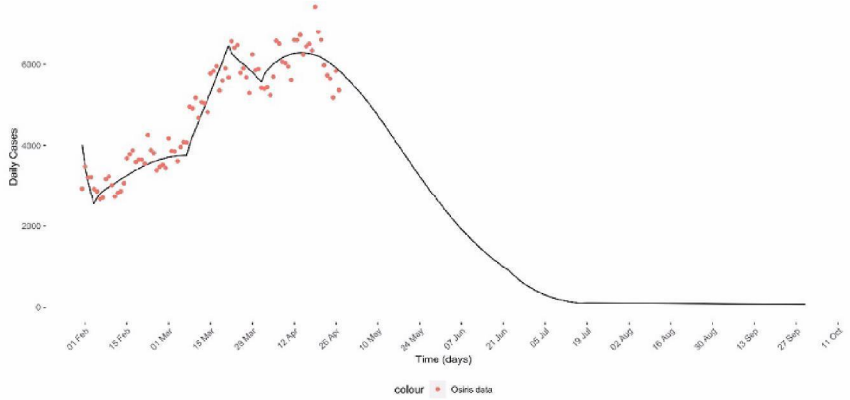

Figure 311.1. Model fit to Osiris daily cases from 31 Jan 2021 to 20 April 2021. Red dots indicated Osiris daily cases. Black line indicates model fit.

90) To determine the number of expected TTS events, the total number of AstraZeneca and Janssen vaccines were multiplied by the rates reported in [39-41]. To calculate the rate of TTS events due to the Janssen vaccine, we divided the rates reported by the FDA [39] by 1.7 to account for incidence in total population. The FDA only reported the rates of TTS events in women, thus the multiplier was calculated by dividing the number of female vaccine recipients (3.99 million) by the total amount of Janssen vaccines given as of April 21, 2021 (6.8 million).

91)

92) The vaccine effectiveness (VE) of each vaccine *against infection* were assumed to be those shown in table 33. Additionally, a VE against transmission of 30% after dose 1 and 54% is assumed for Pfizer and Moderna as well as a VE of 80.5% against hospitalization is assumed for AstraZeneca.

93)

Table 33. Vaccine effectiveness after dose 1 and dose 2 assumed in the model for each vaccine type.

94) Vaccine	95) VE* (dose 1)
97)	

	Pfizer	70%
	101) Moderna	102) 89.6%
	104) AstraZeneca	105) 58.3%
	107) Janssen	108) 66.1%

110) *VE indicates vaccine effectiveness against infection. A VE of 80.5% against hospitalizations is assumed for AstraZeneca. Additionally, a VE against transmission of 30% after dose 1 and 54% is assumed for Pfizer and Moderna.

111)

112)

10.4 Results

10.4.1 Main analysis

There were very small differences observed in cumulative numbers of cases, hospital admissions, and deaths by vaccination strategy (Figure 37, Table 34). The strategy in which the Janssen vaccine was not administered to individuals aged below 60 (Janssen60) resulted in the fewest cumulative hospitalizations. The Janssen60 and Janssen50 strategies resulted in the fewest cumulative deaths, while Janssen50 resulted in the fewest cumulative cases (by a small margin). The cumulative totals presented in table 34 should not be considered a prediction for the exact number of cases, hospitalizations, and deaths. Rather, they should be used to determine relative ordering of the vaccination strategies with respect to each outcome.

113)

114) The number of expected TTS events due to AstraZeneca and Janssen vaccination are shown in table 35. The values are calculated from the beginning of the vaccination program and thus include historic vaccinations and TTS events. The vaccination strategies in which the fewest number of AstraZeneca and Janssen vaccines were administered (Janssen60 followed by Janssen50 and then Janssen40) resulted in the fewest expected TTS events, while the strategy with the greatest number of AstraZeneca and Janssen vaccines administered (AZ) resulted in the most expected TTS events. However, due to the rare occurrence of TTS events, there were not large differences in the expected number of events between vaccination strategies.

115)

116)

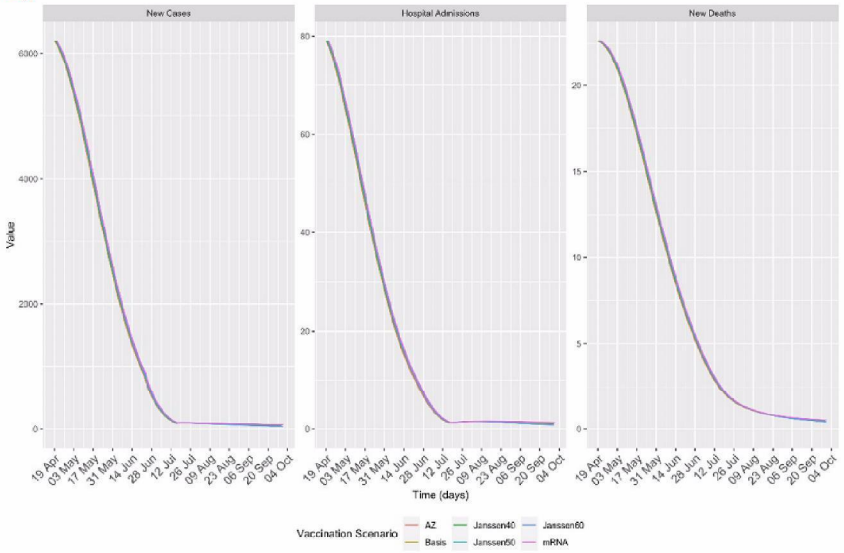

Figure 11.2. Modelled new cases, hospital admissions, and deaths under different vaccination strategies in the main analysis.

Table 34. Cumulative sum and percent difference of modelled outcomes from the main analysis. Percent difference is relative to the basis scenario.

117) Scenario	118) Value*	119) NewCases^	120) HospitalAd

				m i s s i o n s
	122) B a s i s	123) C u m u l a t i v e s u m	124) 2 4 2 , 8 2 1	125) 2 9 5 6
127)	128) P e r c e n t d i f f e r e n c e	129) R e f e r e n c e	130) R e f e r e n c e	
132) A Z +	133) C u m u l a t i v e s u m	134) 2 4 2 , 1 4 7	135) 2 9 4 2	

137)	138) Percentdifference	139) 0.28%	-	140) 0.47%	-	
142) mRNA	143) Cumulativesum	144) 242,747		145) 29555		
147)	148) Percentdifference	149) 0.03%	-	150) 0.03%	-	
152) Jan	Cum	241		**293**		

	s s e n 6 0	u l a t i v e s u m	2 3 8	,		
157)	158) P e r c e n t d i f f e r e n c e	159) 0 . 6 5 %	-	160) **0** **.** **7** **8** **%**	-	
162) J a n s s e n 5 0	163) C u m u l a t i v e s u m	164) **2** **4** **1** **,** **2** **3** **3**		165) 2 9 3 7		
167)	168) P e r c e n t d i f f	**0** **.** **6** **5** **%**	-	170) 0 . 6 4 %	-	

		e r e n c e			
172) J a n s s e n 4 0	173) C u m u l a t i v e s u m	174) 2 4 2 , 2 3 6		175) 2 9 5 2	
177)	178) P e r c e n t d i f f e r e n c e	179) 0 . 2 4 %	-	180) 0 . 1 4 %	-

182) *Cumulative from 20 April 2021 to 30 September 2021

183) + Size of medical indication target group is 1 million

184) ^ An ascertainment rate of 33% is assumed

185)

Table 35. Expected number of TTS events resulting from AstraZeneca and Janssen vaccination using rates from different sources.

186) Scenario	187) TTS Events (AstraZeneca, raw	TTS Events (AstraZeneca, corr	Fatal TTS Events (AstraZeneca	193) TTS Events from AstraZeneca[b]

	e	(
)	c t e d f o r u n d e r r e p o r t i n g)	T h r o m b o c y t o p e n i a & c o a g u l a t i o n d


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)

195) Basis	196) 15.1	197) 19.6	198) 4.32	199) 39.38/55.13
201) AZd	202) 17.9	203) 23.1	204) 4.83	205) 47.40/66.36
207) mRNA	208) 15.2	209) 19.6	210) 4.32	211) 39.38

				/ 55.13
213) Jansse n60	214) 15.1	215) 19.6	216) 4.32	217) 39.38/ 55.13
219) Jansse n50	220) 15.1	221) 19.6	222) 4.32	223) 39.38/ 55.13

225) Jan sse n40	226) 15.1	227) 19.6	228) 4.32	229) 39.38/55.13

231) [a] Source: EMA [40]
232) [b] Source: Pottegard et al. 2021 [41]
233) [c] Source: FDA [39]
[d] Size of medical indication target group is 1 million, instead of 1.5 million

234)
235)

10.4.2 *Sensitivity analysis*

We performed a sensitivity analysis where measures are relaxed three weeks earlier around 1 June 2021. In this situation, more hospitalizations and deaths occurred compared with the main analysis where measures were not relaxed until late June. The vaccination strategy in which people below aged 50 are not vaccinated with Janssen (Janssen50) resulted in the fewest cumulative cases, hospitalizations, and deaths (Table 36). Compared to the Basis scenario, vaccinating people 50 and above with Janssen results in approximately 5% fewer cases, 5% fewer hospitalizations, 3% fewer deaths. The cumulative totals presented in table 36 should not be considered a prediction for the exact number of cases, hospitalizations, and deaths. Rather, they should be used to determine relative ordering of the vaccination strategies with respect to each outcome.

236)
237)
238)

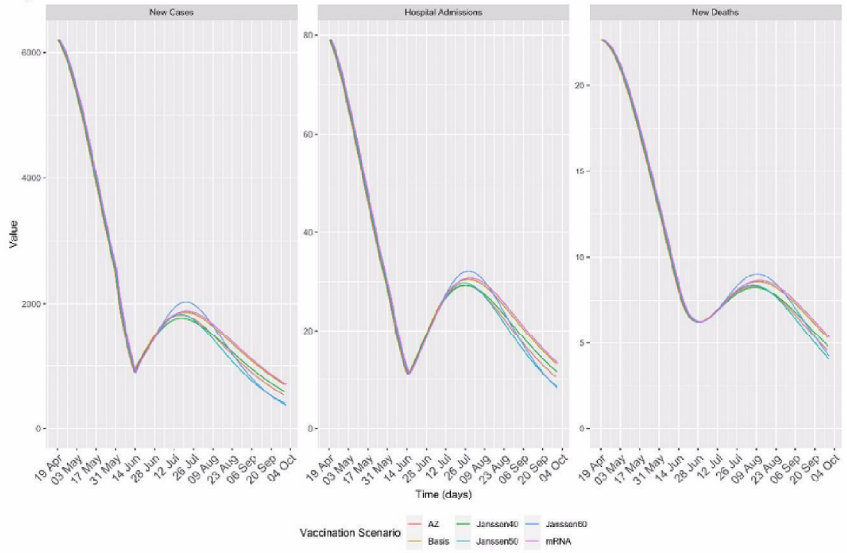

Figure 11.3. Modelled new cases, hospital admissions, and deaths under different vaccination strategies in the sensitivity analysis.

239)

Table 36. Cumulative sum and percent difference of modelled outcomes from the sensitivity analysis. Percent difference is relative to the basis scenario.

240) Scenario	241) Value*	242) NewCases	Hospital

			^	A
				dmissions
	245) Basis	246) Cumulativesum	247) 3633,748	248) 50600
	250)	251) Percentdifference	252) Reference	253) Reference
	255) AZ+	256) Cumulatives		

		um			
	260)	261) Percentdifference	262) 3.07%	-	263) 3.56% -
	265) mRNA	266) Cumulativesum	267) 364,758		268) 50078
	270)	271) Percentdifference	272) 0.28%		273) 0.36%
	275) J				

	ansseen60				
	280)	281) Percentdifference	282) 2.54%	-	283) 2.45% -
	285) Janseen50	286) Cumulativesum	287) **344,462**		288) **4813**
	290)	**291)** Percentdiffer	-		

		e n c e			
	295) Janssen 40	296) Cumulative sum	297) 352,638		298) 49288
	300)	301) Percent difference	302) 2.50%	-	303) 2.61% -

305) *Cumulative from 20 April 2021 to 30 September 2021 (percent difference

306) + Size of medical indication target group is 1 million

307) ^An ascertainment rate of 33% is assumed

308)

10.5 Discussion

309) In both the main and sensitivity analysis, vaccination strategies involving vaccinating healthy adults with Janssen resulted in the lowest numbers of cases, hospitalizations, and deaths. However, the differences were not large in both analyses. The optimal vaccination strategy may change depending on the timing of the relaxation of measures or if the epidemiological situation changes. Regardless of the epidemiological situation, the expected number of adverse events

will remain stable as they only depend on the number of vaccines administered.

11 Impact of vaccinating 12 – 17 year olds

310) Analysis of 16 June 2021, text updated 22 June 2021

311)

11.1 Context

As the national vaccination program progresses, all adults will soon be vaccinated with their first dose of a COVID-19 vaccine. There is potential for increased transmission in winter months due to seasonality of transmission, possible waning of vaccine protection, and the emergence of new variants. To prevent an increase in infections in the winter months, additional vaccinations may be necessary, such as a booster vaccination for those who are at high risk of severe disease or including more age cohorts (12-17 year olds) in the vaccination program. If we don't vaccinate more, we might require more non-pharmaceutical infection control during winter. From a health economics perspective, the additional costs for vaccination are small as the investment in vaccines and vaccination infrastructure have already been made.

There is considerable debate about whether to vaccinate 12 – 17 year olds as they are much less likely to experience severe disease [42-44] and may experience adverse events from vaccination [45]. However, 15 – 17 year olds are likely to be contributors to transmission in the very possible event of large outbreaks or epidemic this winter. Potential for transmission is particularly strong in secondary schools where school children live in a household with unvaccinated household members (in groups with low vaccine coverage). Additionally, while disease burden in 12 – 17 is lower than in other age groups, there is a substantial disease burden among adolescents, with an order of magnitude that is similar to seasonal influenza.

312)

313) Here, we consider the direct and indirect impacts of vaccinating 12 -17 years on disease outcomes (cases, hospitalization admissions, IC admissions, and deaths)

314)

11.2 Methods

315) A full description of the simulation model can be found in the Appendix. In this analysis we incorporate additional features into our age-stratified SEIR model, namely seasonality of transmission rate and waning vaccine protection. Seasonal cycles are a well-known feature of many respiratory viral infections, such as influenza and respiratory syncytial virus (RSV) [46-49]. Studies have shown that meteorological factors, such as temperature and specific humidity affect transmission of SARS-Cov-2 in temperate climates; however the amount of seasonal variability varies [50-52]. To account for the seasonal pattern of SARS-CoV-2 whereby, transmission is lower in

summer and higher in winter, we define the

transmission rate as a function of seasonality [52]:

316)

317)

318) where *is the baseline (non-seasonal) transmission*

*rate, is the a*mplitude of seasonal forcing, and *t* is the

day of the year. We assume [52] in the main analysis and [53] in a sensitivity analysis. These values of the amplitude of seasonal forcing result in estimates of R_0 shown in Figure 12.1.

319)

320) In addition to seasonal variation in transmission, transmission of SARS-CoV-2 might be higher in winter 2021/2022 compared to winter 2020/2021 due to the emergence of the alpha variant. This variant has been shown to increase R_0 by 40-100% [54, 55] compared to wildtype.

321)

322) The transmission rate is estimated by fitting the model to OSIRIS case data from 31 January 2021 to 25 May 2021. The data is fit piecewise to correspond with the correct contact patterns of each time window. Contact matrices are obtained from the Pienter Corona Study [56, 57] to approximate different contact patterns under different levels of non-pharmaceutical interventions across age groups. Forward simulations are performed from 25 May 2021 to 31 March 2022. We assume no control measures are in place after summer 2021 for the remainder of the simulated time frame (until 31 March 2022). Thus, contact patterns are assumed to be similar to those in April 2017 (pre-COVID-19).

323)

324) It is still unknown whether, and how much, vaccine efficacy for vaccines against SARS-Cov-2

wanes over time. We look at two extremes. First, we include waning vaccine efficacy as a logistic function, parameterized so that 50% waning occurs after 6 months and complete waning occurs after 1 year (Figure 12.2). Second, we perform sensitivity analyses where we assume no waning. All vaccine types wane at the same rate. We do not assume waning of immunity from infection.

325)

326) The objective of this specific model is to capture the dynamic aspects of vaccine allocation when comparing alternative vaccination strategies in children aged 12 – 17 years. Specifically, we compare the direct and indirect effects of vaccination in 12 - 17 year olds compared to no vaccination in this age group. In the scenario in which 12 – 17 year olds are vaccinated we assume that they receive the Pfizer/BioNTech vaccine beginning 15 July 2021. We assume 50,000 doses are administered per day and a vaccine coverage of 70% in this age group.

327)

328) We simulate new cases, hospital admissions, IC admissions, and new deaths for each vaccination strategy. We calculate the cumulative sum of each outcome for the entire simulation period. We also calculate the percent difference in each disease outcome for the scenario in which 12 – 17 year olds are vaccinated compared to no vaccination in this age group. The outcomes of the model should not be considered a quantitative prediction; rather, one realization of possible outcomes given a set of assumptions.

329)

11.3 Results

11.3.1 Main Analysis

Our main finding is that there may be a very large epidemic in winter if no control measures are implemented, regardless of whether 12 – 17 year olds are vaccinated (Figure 12.3, Figure 12.4). In the main analysis, we assume vaccine efficacy wanes completely after 1 year. Under this model assumption, we found that vaccination of 12 – 17 year olds results in a 23.9% - 24.5% decrease in all disease outcomes in the 10 - 19 age group (Table 12.1). Due to the stratification of the model population in 10-year age bands, we cannot separate 12 – 17 year olds from the 10 – 19 year age group, therefore we report the effects of vaccinating 12 – 17 year olds on the entire 10 – 19 year age group, which includes the direct effects of vaccination on 12 – 17 year olds and the indirect effects on the 10 – 11 and 18 – 19 year olds. In the remainder of the population (individuals aged 20 years and above), the effect of vaccinating 12 -17 year olds averts thousands of cases, hundreds of hospital admissions, and tens of IC admissions and deaths (Table 12.2). However, due to the size of the outbreak percent differences are small (between -1.5% -to -0.1%, Table 12.2).

330)

11.3.2 *Sensitivity Analyses*

We performed several sensitivity analyses to assess the impact of vaccinating 12 – 17 year olds under different model assumptions. First, we relaxed the assumption of waning vaccine efficacy and assumed that vaccine efficacy does not wane. This scenario is similar to providing booster doses to the adult population, so immunity to infection remains high. Even when we assumed vaccine efficacy did not wane, we still observed a considerable winter epidemic. However, the winter epidemic had a smaller amplitude and was delayed compared to a scenario in which vaccine efficacy wanes (Figure 12.5, Figure 12.6). We found a 31.1% – 31.7% decrease in all disease outcomes in the 10 – 19 year age group when 12 – 17 year olds were vaccinated (Table 12.3). We also found that vaccination of 12 – 17 year olds averts tens of thousands of cases and hundreds of hospital admissions, IC admissions, and deaths in individuals aged 20 and above, resulting in a decrease of 2.0% to 4.1% in percent difference compared to not vaccinating 12 – 17 year olds (Table 12.4).

331)

332) Our main analysis also assumes all control measures are relaxed after summer 2021 and are not reimplemented in the fall or winter. When we assumed that contact patterns, and thus control measures, were similar to the situation in June 2020 in The Netherlands we observed no winter epidemic (Figure 12.7). The epidemic died out in summer 2021 and did not have a resurgence in winter. Therefore, there was no additional benefit of vaccinating 12 – 17 year olds (Table 12.5).

333)

334) Finally, we assumed that the amplitude of seasonal forcing of the transmission rate of 0.5, similar to that estimated by Liu et al. [52], in the main analysis. Using this amplitude of seasonal forcing results in a maximum R_0 greater than 5 in the winter months of 2021/2022. To determine the robustness of our results based on our assumption of the amplitude of seasonal forcing, we used a value of 0.14, as estimated by the RIVM model to project IC admissions [53]. We still observed a winter epidemic, albeit smaller, using a lower value of seasonal variation and larger effects, both direct and indirect, of vaccinating 12 – 17 year olds (Figure 12.8, Figure 12.9). There was a 35.8% to 38.9% reduction in disease outcomes in the 10 – 19 age group (Table 12.6) and a 3.2% to 7.3% reduction in ages 20 and above (Table 12.7) when 12 -17 year olds were vaccinated compared to when 12 -17 year olds were not vaccinated.

335)

336)

11.4 Discussion

337) We show that there are direct benefits of vaccinating 12 – 17 year olds on the 10 – 19 year age group regardless of assumptions about waning

vaccine effectiveness. Indirect benefits of vaccinating 12 – 17 year olds are more modest, but still results in large numbers of averted disease outcomes. Indirect benefits are smaller if vaccine protection is assumed to wane completely after a year due to the high number of susceptibles re-introduced into the population. Regardless, vaccinating 12 – 17 year olds reduced disease burden in the population and reduce the effective reproduction number in winter by 20 - 35% [58].

338)

339) If the 12 – 17 year olds are not vaccinated, they will have the highest incidence and contribute most to future infection. Physical distancing measures will be most effective if they are targeted at age groups that contribute most to further spread, and these correspond to the groups with the highest incidence of infection for infections where at-risk events are reciprocal (such as SARS-CoV-2 infections) [34]. That implies that closure of secondary schools, which reduces contacts among the age group with the highest incidence of infection, will be a very effective non-pharmaceutical control measure. If 12 – 17 year olds are vaccinated, they are less likely to be the age group with the highest incidence, and there is no obvious need for school closure.

340)

341) The results presented here represent extreme situations, such that the results can be considered an upper bound of disease outcome (or a lower bound of the impact of vaccinating 12 -17 year olds) when vaccine protection wanes completely. When no waning of vaccine protection is assumed, the results can be considered as a lower bound of disease outcomes (or an upper bound of the impact of vaccinating 12 - 17 year olds).

342)

343) The size of the epidemic this winter is very uncertain and sensitive to our model assumptions about waning immunity and reproduction number, however these results show that a rise in infections is very likely in the winter months. Given the possibility of new variants and uncertain duration of immune protection after vaccination, there is an argument to vaccinate beyond current campaign targeting individuals 18 and above. If the 12-17 year olds are vaccinated, they will not have a high incidence of infection and there will be no obvious need for school closures as a control measure. Which other control measures will be in place, besides case finding and contract tracing, depends on the required control effort to avoid a large

epidemic in winter that exceeds the available healthcare capacity.

344)

11.5 Tables and Figures

Table 12.1. Cumulative sum and percent difference of modelled outcomes in 10 – 19 year old age group with and without vaccination in 12 – 17 year olds. No vaccination is used as the reference for percent difference. ***We assume vaccine effectiveness wanes completely after 1 year.*** *We also assume normal contact patterns with no non-pharmaceutical interventions beyond summer 2021. Simulations were run from 25 May 2021 until 31 March 2022.*

345) **Scenario**	346) **Outcome**	347) **Value**
349) Novaccination of 12–17 year olds	350) Cases	351) 318,978
353)	354) Hospital Admissions	355) 131
357)	358) I	2

		C Admissions	.4
	362)	363) Deaths	364) 3.3
	366) Vaccination of 12–17 year olds 370)	367) Cases	368) 240,710
		371) Hospital Admissions	372) 99.2
	374)	375) IC	17

		A d m i s s i o n s	8
	379)	380) D e a t h s	381) 2 . 5

383)
384)

Table 12.2. Cumulative sum and percent difference of modelled outcomes in all age groups except 10 - 19 with and without vaccination in 12 – 17 year olds. No vaccination is used as the reference for percent difference. ***We assume vaccine effectiveness wanes completely after 1 year.*** *We also assume normal contact patterns (pre-COVID-19) with no non-pharmaceutical interventions beyond summer 2021. Simulations were run from 25 May 2021 until 31 March 2022.*

	385) **S** **c** **e** **n** **a** **r** **i** **o**	386) **O** **u** **t** **c** **o** **m** **e**	387) **V** **a** **l** **u** **e**
	389) N o v a c c i n a t i	C a s e s	391) 2 , 2 4 5 , 5 8 1
	393) n	394) H o	5 1

	of 12–17 year olds	s pital Admissions	, 592
	398)	399) ICAdmissions	400) 16,672
	402)	403) Deaths	404) 16,140
	406) Vaccinatio	Cases	408) 2,212,022
	410) o	411) H	5

	f 1 2 – 1 7 y e a r o l d s	o s p i t a l A d m i s s i o n s	1 , 2 7 9
	415)	416) I C A d m i s s i o n s	417) 1 6 , 5 8 1
	419)	420) D e a t h s	421) 1 6 , 1 1 7

Table 12.3. Cumulative sum and percent difference of modelled outcomes in the 10 – 19 year old age group with and without vaccination in 12 – 17 year olds. No vaccination is used as the reference for percent difference. ***We assume vaccine effectiveness does not wane.*** *We also assume normal contact patterns with no non-pharmaceutical interventions beyond summer 2021. Simulations were run from 25 May 2021 until 31 March 2022.*

423) **Scenario**	424) **Outcome**	425) **Value**
427) Novaccination of 12–17 year olds	428) Cases	429) 305,562
431)	432) Hospital Admissions	433) 126
435)	436) ICA	22.4

		d m i s s i o n s	
	440)	441) D e a t h s	442) 3 . 2
	444) V a c c i n a t i o n o f 1 2 – 1 7 448) y e a r o l d s	445) C a s e s	446) 2 0 8 , 8 1 2
		449) H o s p i t a l A d m i s s i o n s	450) 8 6 . 1
	452)	453) I C A d	1 5 . 5

		m i s s i o n s	
456)	457) D e a t h s	458) 2 . 2	

460)
461)

Table 12.4. Cumulative sum and percent difference of modelled outcomes in all age groups with and without vaccination in 12 – 17 year olds. No vaccination is used as the reference for percent difference. ***We assume vaccine effectiveness does not wane.*** *We also assume normal contact patterns with no non-pharmaceutical interventions beyond summer 2021. Simulations were run from 25 May 2021 until 31 March 2022.*

462) **S c e n a r i o**	463) **O u t c o m e**	464) **V a l u e**
466) N o v a c c i n a t i o n	C a s e s	468) 1 , 6 9 9 , 2 9 3
470) o f 1	471) H o s p i	3 5 , 3 5 1

	2–17 years olds		t	
	475)	476) ICAdmissions		477) 11,450
	479)	480) Deaths		481) 10,769
	483) Vaccination of 12		Cases	485) 1,630,256
	487)	488) Hosp		34,4

	–17 years old	i tal Admissions	5 0
491)	492)	ICAdmissions	493) 11,165
495)	496)	Deaths	497) 10,552
499) 500)			

Table 12.5. Cumulative sum and percent difference of modelled outcomes in the total population with and without vaccination in 12 – 17 year olds. No vaccination is used as the reference for percent difference. We assume vaccine effectiveness does not wane. We assume contact patterns similar to the situation in June 2020 continue through March 2022. Simulations were run from 25 May 2021 until 31 March 2022.

501) **Scenario**	502) **Outcome**	503) **Value**
505) No vaccination of 12–17 year olds	506) Cases	507) 15,088
509)	510) Hospital Admissions	511) 219
513)	514) ICA	129

		d m i s s i o n s	
518)	519) D e a t h s		520) 3 2 2
522) V a c c i n	523) C a s e s		524) 1 5 , 0 8 8
526)	527) H o s p i t a l A d m i s s i o n s		528) 2 1 9
530)	531) I C A d m		1 2 9

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	535)		536)
	D		3
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538)
539)

Table 12.6. Cumulative sum and percent difference of modelled outcomes in the 10 – 19 year old age group with and without vaccination in 12 – 17 year olds. No vaccination is used as the reference for percent difference. We assume vaccine effectiveness does not wane and a lower amplitude of seasonal forcing (0.15). We also assume normal contact patterns with no non-pharmaceutical interventions beyond summer 2021. Simulations were run from 25 May 2021 until 31 March 2022.

540) **Scenario**	541) **Outcome**	542) **Value**
544) No vaccination	Cases	546) 188,741
548)	549) Hospi	77.8

	2–17 years olds	t		
		554) ICAdmissions	555) 14.0	
553)				
		558) Deaths	559) 2.01	
557)				
	561) Vaccination of 12	Cases	563) 115,239	
565)		566) Hospit	47.7	

	–17 years old	a Admissions	
569)		570) ICAdmissions	571) 8.69
573)		574) Deaths	575) 1.29
577)			

Table 12.7. Cumulative sum and percent difference of modelled outcomes in 20+ year olds with and without vaccination in 12 – 17 year olds. No vaccination is used as the reference for percent difference. We assume vaccine effectiveness does not wane and a lower amplitude of seasonal forcing (0.15). We also assume normal contact patterns with no non-pharmaceutical interventions beyond summer 2021. Simulations were run from 25 May 2021 until 31 March 2022.

578) **Scenario**	579) **Outcome**	580) **Value**
582) Novaccination of 12–17 year olds	583) Cases	584) 1,018,730
586)	587) Hospital Admissions	588) 21,857
590)	591) IC	7,

		A	0
		dmissions	48
	595)	596) Deaths	597) 6,927
	599) Vaccination of 12–17 year olds	600) Cases	601) 944,769
	603)	604) Hospital Admissions	605) 20,810
	607)	608) ICA	6,7

		d m i s s i o n s	0 4
611)	612)	D e a t h s	613) 6 , 6 5 9

615)
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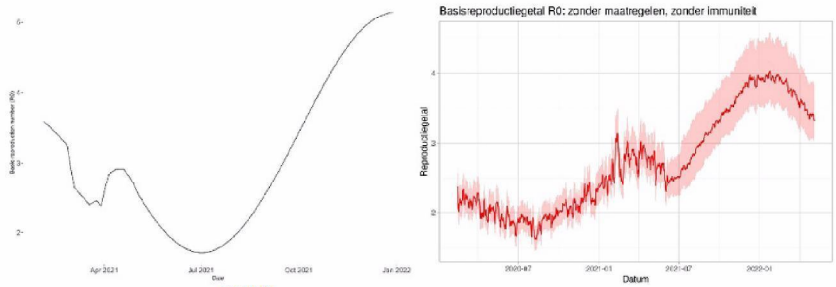

628)

[redacted]

632)

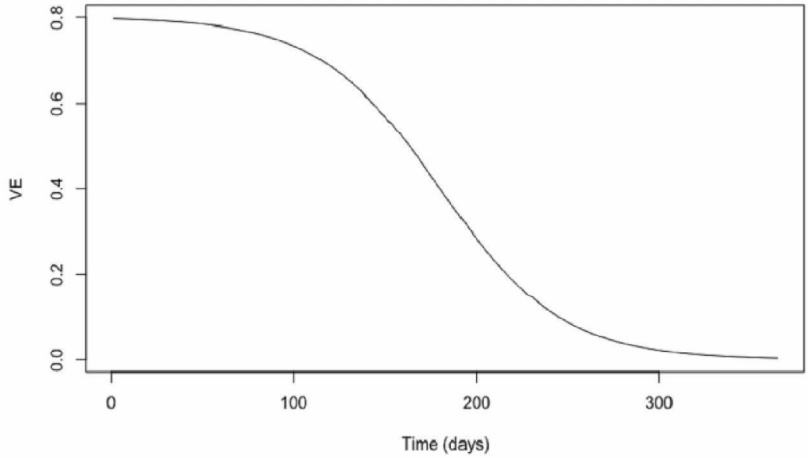

Figure 12.2. Example of vaccine effectiveness waning. We assume a logistic curve in which 50% waning occurs at 6 months since vaccination.

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634)

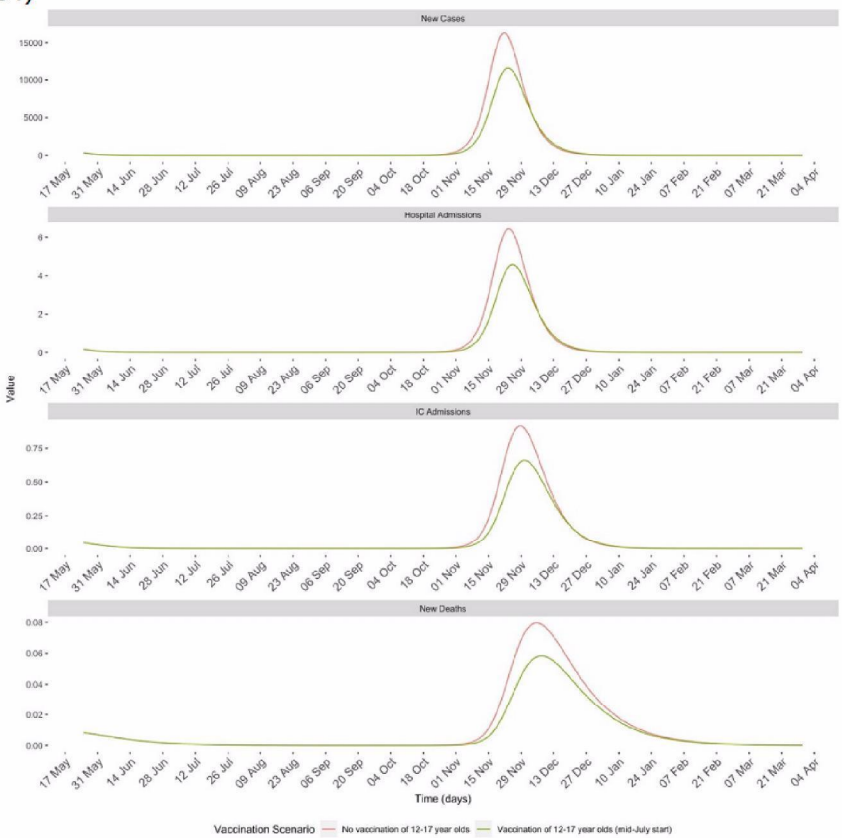

Figure 12.3. Figure 5. Modelled outcomes in 10 – 19 year olds with (red) and without (green) vaccination in 12 – 17 year olds. ***We assume vaccine effectiveness wanes completely after 1 year.*** *Simulations were run from 25 May 2021 until 31 March 2022.*

635)
636)

637)

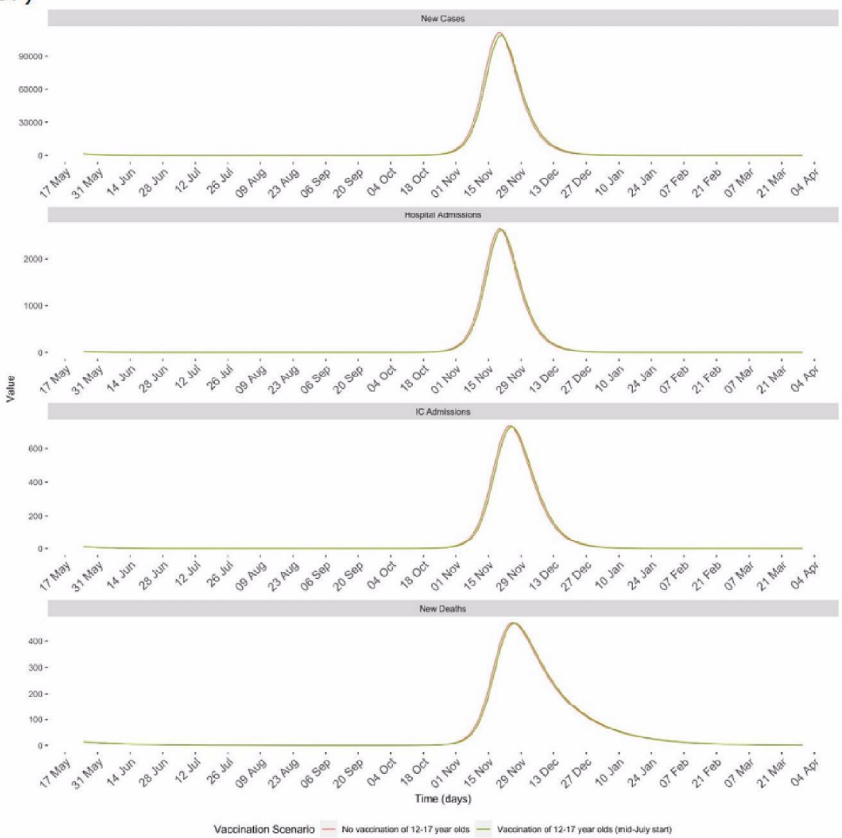

Figure 12.4. Modelled outcomes in all age groups except 10 – 19 year olds with (blue) and without (red) vaccination in 12 – 17 year olds. ***We assume vaccine effectiveness wanes completely after 1 year.*** *Simulations were run from 25 May 2021 until 31 March 2022.*

638)

639)

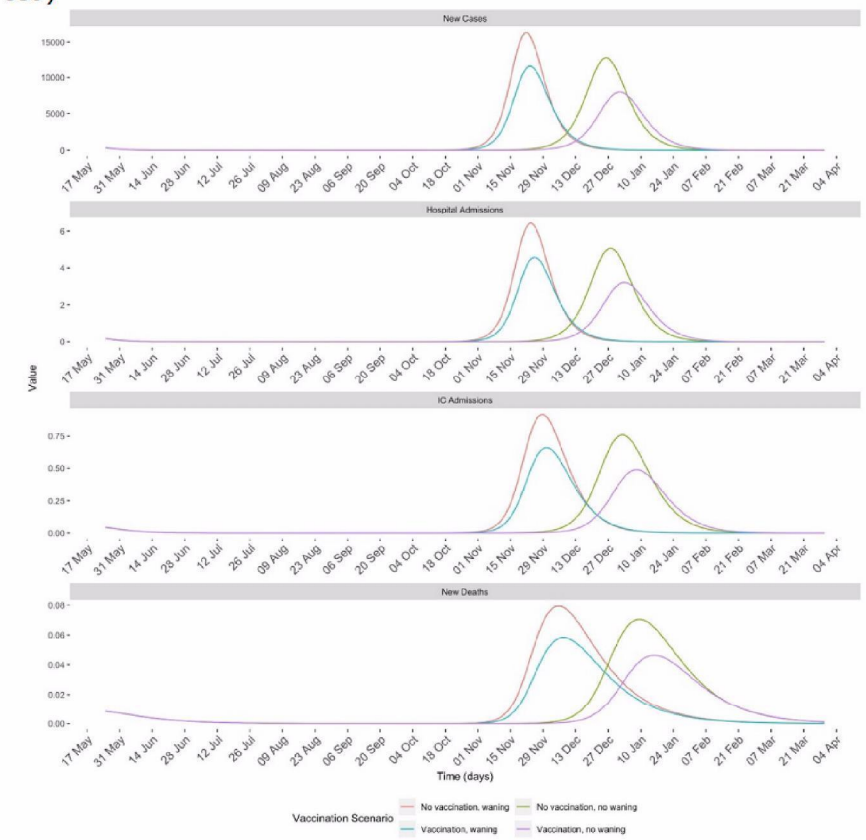

Figure 12.5. Modelled outcomes in all 10 – 19 year olds under different assumptions about waning vaccine effectiveness and vaccination of 12 – 17 year olds. Red and green lines assume complete waning of vaccine protection after 1 year. Blue and purple lines assume vaccine effectiveness does not wane. Simulations were run from 25 May 2021 until 31 March 2022.

640)

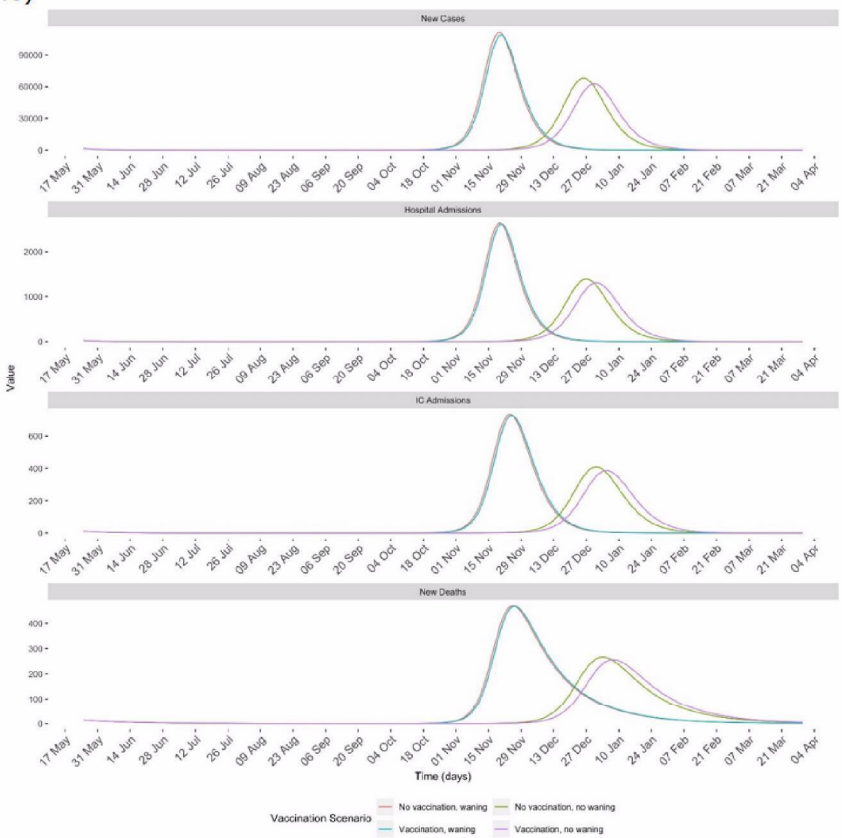

Figure 12.6. Modelled outcomes in all age groups except 10 – 19 year olds under different assumptions about waning vaccine effectiveness and vaccination of 12 – 17 year olds. Red and green lines assume complete waning of vaccine protection after 1 year. Blue and purple lines assume vaccine effectiveness does not wane. Simulations were run from 25 May 2021 until 31 March 2022.

641)

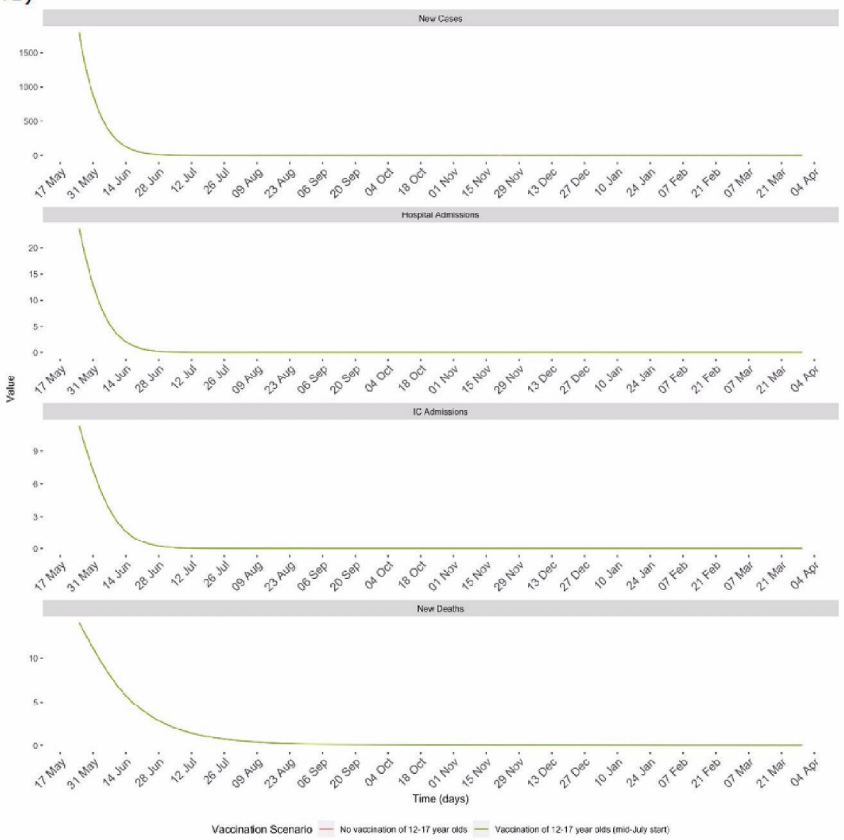

Figure 12.7. Modelled outcomes in the entire population under the assumption that vaccine protection does not wane. We assume contact patterns similar to the situation in June 2020 continue through March 2022. Simulations were run from 25 May 2021 until 31 March 2022.

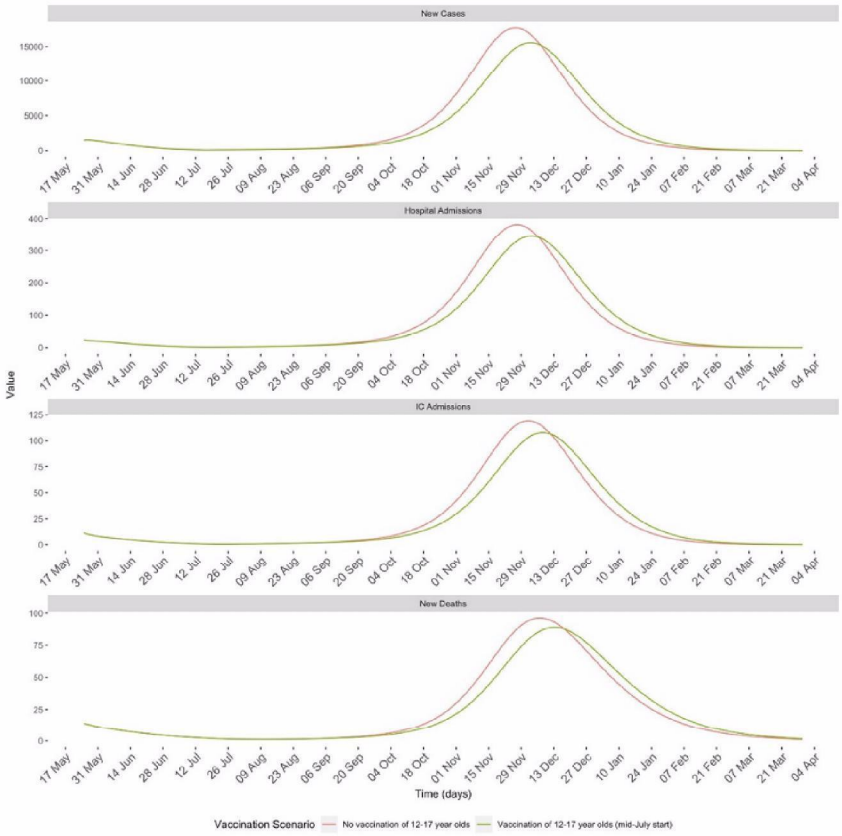

Figure 12.8. Modelled outcomes in all 10 – 19 year olds with and without vaccination of 12 – 17 year olds. We assume vaccine effectiveness does not wane and a lower amplitude of seasonal forcing (0.15). We also assume normal contact patterns with no non-pharmaceutical interventions beyond summer 2021. Simulations were run from 25 May 2021 until 31 March 2022.

642)

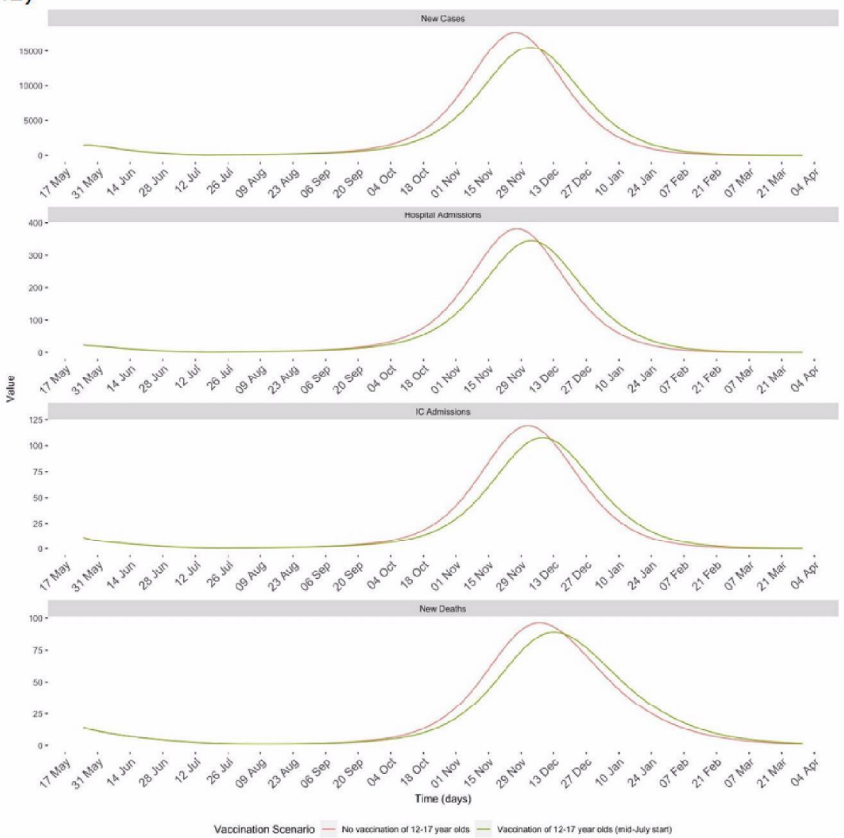

Figure 12.9. Modelled outcomes in all 20+ year olds with and without vaccination of 12 – 17 year olds. We assume vaccine effectiveness does not wane and a lower amplitude of seasonal forcing (0.15). We also assume normal contact patterns with no non-pharmaceutical interventions beyond summer 2021. Simulations were run from 25 May 2021 until 31 March 2022.

12 Appendix

643) Text updated 15 March 2021
644)

12.1 Model Description

12.1.1 Overview

645) 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 [59]. 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 is shown in Table A1 and Table A2.
646)

12.1.2 Initial conditions

647) 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 [60] 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.

648)

12.1.3 *Transmission matrices*

649) The model uses different contact matrices from the Pienter Corona Study [56, 57] 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.

650)

651) 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.

652)

653) 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 [61]. 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).

654)

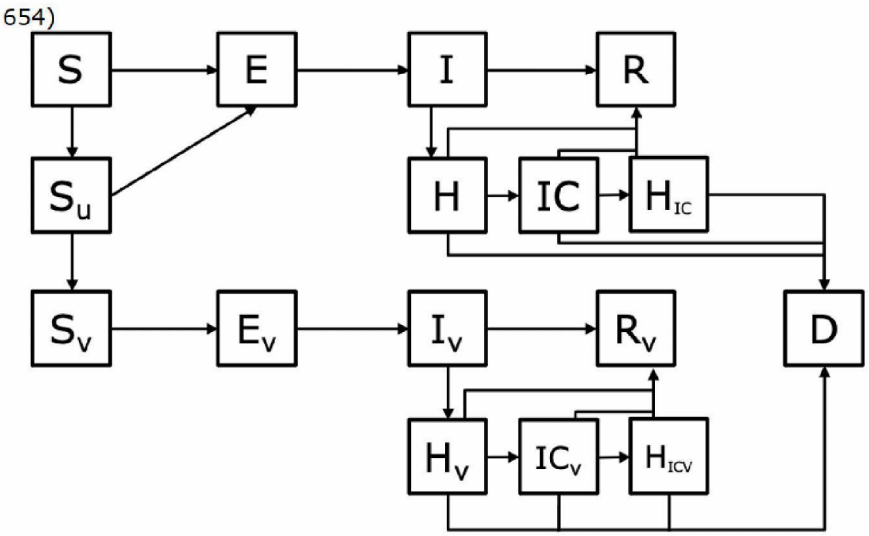

Figure A1. Basic conceptual model diagram. This diagram does not include the additional states after the second dose of vaccination or the age structure in the model. S = susceptible, E = exposed, I = Infectious, R = Recovered, H = hospitalized, IC = In intensive care, HIC = return to the hospital ward 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.

655)

12.1.4 *Vaccination*

656) 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.

657)

12.1.5 *Limitations*

658) 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).

659)

660) The model is coded in R [62] as a system of ordinary differential equations that are numerically solved using the lsoda function in the desolve package [63]. 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

12.2 Equations

661)

$$\frac{dS}{dt} = -\lambda * S - \alpha * S$$

$$\frac{dS_{hold_{1d}}}{dt} = \alpha * S - (1/\delta) * S_{hold_{1d}} - \lambda * S_{hold_{1d}}$$

$$\frac{dS_{v_{1d}}}{dt} = (1/\delta) * S_{hold_{1d}} - \eta * \lambda * S_{v_{1d}} - \alpha_2 * S_{v_{1d}}$$

$$\frac{dS_{hold_{2d}}}{dt} = \alpha_2 * S_{v_{1d}} - (1/\delta_2) * S_{hold_{2d}} - \eta * \lambda * S_{hold_{2d}}$$

$$\frac{dS_{v_{2d}}}{dt} = (1/\delta_2) * S_{hold_{2d}} - \eta_2 * \lambda * S_{v_{2d}}$$

$$\frac{dE}{dt} = \lambda * (S + S_{hold_{1d}}) - \sigma * E$$

$$\frac{dE_{v_{1d}}}{dt} = \eta * \lambda * (S_{v_{1d}} + S_{hold_{2d}}) - \sigma * E_{v_{1d}}$$

$$\frac{dE_{v_{2d}}}{dt} = \eta_2 * \lambda * S_{v_{2d}} - \sigma * E_{v_{2d}}$$

$$\frac{dI}{dt} = \sigma * E - (\gamma + h) * I$$

$$\frac{dI_{v_{1d}}}{dt} = \sigma * E_{v_{1d}} - (\gamma + h) * I_{v_{1d}}$$

$$\frac{dI_{v_{2d}}}{dt} = \sigma * E_{v_{2d}} - (\gamma + h) * I_{v_{2d}}$$

$$\frac{dH}{dt} = h * I - (i_1 + d + r) * H$$

$$\frac{dH_{v_{1d}}}{dt} = h * I_{v_{1d}} - (i_1 + d + r) * H_{v_{1d}}$$

$$\frac{dH_{v_{2d}}}{dt} = h * I_{v_{2d}} - (i_1 + d + r) * H_{v_{2d}}$$

$$\frac{dIC}{dt} = i_1 * H - (i_2 + d_{ic}) * IC$$

$$\frac{dIC_{v_{1d}}}{dt} = i_1 * Hv_1d - (i_2 + d_ic) * IC_{v_{1d}}$$

$$\frac{dIC_{v_{2d}}}{dt} = i_1 * Hv_2d - (i_2 + d_ic) * IC_{v_{2d}}$$

$$\frac{dH_{IC}}{dt} = i_2 * IC - (r_{ic} + d_{hic}) * H_{IC}$$

$$\frac{dH_{IC_{v_{1d}}}}{dt} = i_2 * IC_{v_{1d}} - (r_{ic} + d_{hic}) * H_{IC_{v_{1d}}}$$

$$\frac{dH_{IC_{v_{2d}}}}{dt} = i_2 * IC_{v_{2d}} - (r_ic + d_hic) * H_{IC_{v_{2d}}}$$

$$\frac{dD}{dt} = d * (H + H_{v_{1d}} + H_{v_{2d}}) + d_{ic} * (IC + IC_{v_{1d}} + IC_{v_{2d}}) + d_{hic} * (H_{IC} + H_{IC_{v_{1d}}} + H_{IC_{v_{2d}}})$$

$$\frac{dR}{dt} = \gamma * I + r * H + r_{ic} * H_{IC}$$

$$\frac{dR_{v_{1d}}}{dt} = \gamma * I_{v_{1d}} + r * H_{v_{1d}} + r_{ic} * H_{IC_{v_{1d}}}$$

$$\frac{dR_{v_{2d}}}{dt} = \gamma * I_{v_{2d}} + r * H_{v_{2d}} + r_{ic} * H_{IC_{v_{2d}}}$$

12.3 Outcomes

662) 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.

663)

Daily infections =
Daily cases =
Hospital admissions =
IC admissions =

Daily deaths =
Life years lost = deaths * life expectancy

12.4 Input Parameters

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

Parameter	Description	Value	Details
	Basic reproduction number	2.3	Based on model fit to IC admissions
	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
	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
	Delay to protection of first dose	See Table 2	With multiple vaccines, the weighted average is used
	Delay to protection of second dose	See Table 2	With multiple vaccines, the weighted average is used
*	1 – vaccine efficacy of first dose	See Table 2	With multiple vaccines, the weighted average is used
	1 – vaccine efficacy of second dose	See Table 2	With multiple vaccines, the weighted average is used

664)

Table A2. Age-dependent model parameters.

Parameter	Description	Age group	Value	Details
	Rate from infectious to hospital	0-9	0.0015	Calculated as the probability of infection to hospital divided by time from symptoms to hospital:
		10-19	0.0001	
		20-29	0.0002	
		30-39	0.0007	
		40-49	0.0013	
		50-59	0.0028	
		60-69	0.0044	
		70-79	0.0097	
		80+	0.0107	

	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	
	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	
	Rate from hospital (before IC) to death	0-9	0.0003	Calculated as the probability of death from hospital admission divided by average length of time in hospital before death (7 days)
		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	
		80+	0.0444	
	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	
	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	
	Rate of recovery from hospital (before IC)	0-9	0.1263	Calculated as 1 – the probability of death from hospital admissions divided by the
		10-19	0.1260	
		20-29	0.1254	
		30-39	0.1238	
		40-49	0.1234	
		50-59	0.1215	

		60-69	0.1132	average time from hospital admission to discharge (7.9 days)
		70-79	0.0976	
		80+	0.0872	
	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 discharge (10.1 days)
		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	
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%	[37]
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%	[64]

13 References

665)
666)
1. *Verder kijken dan corona, over de toekomst van onze gezondheid.* Volksgezondheid Toekomst Verkenning (VTV), 2020.
2. Lagerweij, G., et al., *Staat van Infectieziekten in Nederland, 2019*, in *State of Infectious Diseases in the Netherlands, 2019*. 2021, Rijksinstituut voor Volksgezondheid en Milieu RIVM.
3. Central Bureau for Statistics (CBS). *Werkzame beroepsbevolking; beroep.* . Statline 2020 [cited 2020 16 Nov 2020]; Available from: https://opendata.cbs.nl/statline/#/CBS/nl/dataset/82808NED/table.
4. McDonald, S., et al., *Estimating the asymptomatic proportion of SARS-CoV-2 infection in the general population: Analysis of a nationwide serosurvey in the Netherlands.* Submitted, 2021.
5. Voysey, M., et al., *Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK.* The Lancet, 2021. **397**(10269): p. 99-111.
6. Skowronski, D. and G. De Serres, *Efficacy of the Pfizer vaccine by interval from specified dose (all-available efficacy population)*, P.O.D. Efficacy, Editor. 2020.
7. Baden, L.R., et al., *Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine.* New England Journal of Medicine, 2020.
8. Voysey, M., et al., *Single Dose Administration, And The Influence Of The Timing Of The Booster Dose On Immunogenicity and Efficacy Of ChAdOx1 nCoV-19 (AZD1222) Vaccine*. 2021.
9. Vasileiou, E., et al., *Effectiveness of First Dose of COVID-19 Vaccines Against Hospital Admissions in Scotland: National Prospective Cohort Study of 5.4 Million People.* Available at SSRN: https://ssrn.com/abstract=3789264 or http://dx.doi.org/10.2139/ssrn.3789264, 2021.
10. Hall, V.J., et al., *Effectiveness of BNT162b2 mRNA Vaccine Against Infection and COVID-19 Vaccine Coverage in Healthcare Workers in England, Multicentre Prospective Cohort Study (the SIREN Study).* Available at SSRN: https://ssrn.com/abstract=3790399, 2021.
11. Chodick, G., et al., *The effectiveness of the first dose of BNT162b2 vaccine in reducing SARS-CoV-2 infection 13-24 days after immunization: real-world evidence.* medRxiv, 2021: p. 2021.01.27.21250612.
12. Hunter, P.R. and J. Brainard, *Estimating the effectiveness of the Pfizer COVID-19 BNT162b2 vaccine after a single dose. A reanalysis of a study of 'real-world' vaccination outcomes from Israel.* medRxiv, 2021: p. 2021.02.01.21250957.
13. Regev-Yochay, G., et al., *Decreased Infectivity Following BNT162b2 Vaccination.* Available at SSRN: https://ssrn.com/abstract=3815668, 2021.

14. Amit, S., et al., *Early rate reductions of SARS-CoV-2 infection and COVID-19 in BNT162b2 vaccine recipients.* The Lancet, 2021. **397**(10277): p. 875-877.
15. Bernal, J.L., et al., *Early effectiveness of COVID-19 vaccination with BNT162b2 mRNA vaccine and ChAdOx1 adenovirus vector vaccine on symptomatic disease, hospitalisations and mortality in older adults in England.* medRxiv, 2021: p. 2021.03.01.21252652.
16. Thompson, M.G., et al., *Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers — Eight U.S. Locations, December 2020–March 2021.* Morbidity and Mortality Weekly Report (MMWR), 2021. **70**(March 29, 2021).
17. Björk, J., et al., *Effectiveness of the BNT162b2 vaccine in preventing COVID-19 in the working age population – first results from a cohort study in Southern Sweden.* medRxiv, 2021: p. 2021.04.20.21254636.
18. V Shah, A.S., et al., *Effect of vaccination on transmission of COVID-19: an observational study in healthcare workers and their households.* medRxiv, 2021: p. 2021.03.11.21253275.
19. Harris, R.J., et al., *Impact of vaccination on household transmission of SARS-CoV-2 in England.* pre-print, 2021.
20. Petter, E., et al., *Initial real world evidence for lower viral load of individuals who have been vaccinated by BNT162b2.* medRxiv, 2021: p. 2021.02.08.21251329.
21. Levine-Tiefenbrun, M., et al., *Decreased SARS-CoV-2 viral load following vaccination.* medRxiv, 2021: p. 2021.02.06.21251283.
22. Shrotri, M., et al., *Vaccine effectiveness of the first dose of ChAdOx1 nCoV-19 and BNT162b2 against SARS-CoV-2 infection in residents of Long-Term Care Facilities (VIVALDI study).* medRxiv, 2021: p. 2021.03.26.21254391.
23. McEllistrem, M.C., et al., *Single dose of a mRNA SARS-CoV-2 vaccine is associated with lower nasopharyngeal viral load among nursing home residents with asymptomatic COVID-19.* Clinical Infectious Diseases, 2021.
24. Emary, K.R.W., et al., *Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): an exploratory analysis of a randomised controlled trial.* The Lancet, 2021. **397**(10282): p. 1351-1362.
25. Scientific Advisory Group for Emergencies, *NERVTAG: Update note on B.1.1.7 severity, 11 February 2021*, New and Emerging Respiratory Virus Threats Advisory Group, Editor. 2021: London.
26. Madhi, S.A., et al., *Safety and efficacy of the ChAdOx1 nCoV-19 (AZD1222) Covid-19 vaccine against the B.1.351 variant in South Africa.* medRxiv, 2021: p. 2021.02.10.21251247.
27. Rijksinstituut voor Volksgezondheid en Milieu (RIVM), *Grootschalig testen van personen zonder klachten*. 2020: Bilthoven.
28. Bosetti, P., et al., *Impact of mass testing during an epidemic rebound of SARS-CoV-2: a modelling study using the example of France.* Eurosurveillance, 2021. **26**(1): p. 2001978.

29. Pavelka, M., et al., *The effectiveness of population-wide, rapid antigen test based screening in reducing SARS-CoV-2 infection prevalence in Slovakia.* medRxiv, 2020: p. 2020.12.02.20240648.
30. Bootsma, M., et al., *Regular universal screening for SARS-CoV-2 infection may not allow reopening of society after controlling a pandemic wave.* medRxiv, 2020: p. 2020.11.18.20233122.
31. Paltiel, A.D., A. Zheng, and R.P. Walensky, *Assessment of SARS-CoV-2 Screening Strategies to Permit the Safe Reopening of College Campuses in the United States.* JAMA Network Open, 2020. **3**(7): p. e2016818-e2016818.
32. Hellewell, J., et al., *Estimating the effectiveness of routine asymptomatic PCR testing at different frequencies for the detection of SARS-CoV-2 infections.* medRxiv, 2020: p. 2020.11.24.20229948.
33. van Dissel, J., *Advies n.a.v. 100e OMT*, Centrum Infectieziektebestrijding, Editor. 2021, RIVM: Bilthoven.
34. Wallinga, J., M. van Boven, and M. Lipsitch, *Optimizing infectious disease interventions during an emerging epidemic.* Proceedings of the National Academy of Sciences, 2010. **107**(2): p. 923-928.
35. Walker, P.G.T., et al., *The impact of COVID-19 and strategies for mitigation and suppression in low- and middle-income countries.* Science, 2020. **369**(6502): p. 413-422.
36. O'Driscoll, M., et al., *Age-specific mortality and immunity patterns of SARS-CoV-2.* Nature, 2021. **590**(7844): p. 140-145.
37. Polack, F.P., et al., *Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine.* New England Journal of Medicine, 2020. **383**(27): p. 2603-2615.
38. Oliver, S., et al., *The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Janssen COVID-19 Vaccine — United States, February 2021. .* Morbidity and Mortality Weekly Report (MMWR), 2021. **70**: p. 329–332.
39. Center for Preparedness and Response, *Johnson & Johnson/Janssen COVID-19 Vaccine and Thrombosis with Thrombocytopenia Syndrome (TTS): Update for Clinicians*. 2021.
40. Committee for Medicinal Products for Human Use (CHMP), *Assessment Report*. 2021.
41. Pottegård, A., et al., *Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study.* BMJ, 2021. **373**: p. n1114.
42. Zimmermann, P. and N. Curtis, *Coronavirus Infections in Children Including COVID-19: An Overview of the Epidemiology, Clinical Features, Diagnosis, Treatment and Prevention Options in Children.* Pediatr Infect Dis J, 2020. **39**(5): p. 355-368.
43. Castagnoli, R., et al., *Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents: A Systematic Review.* JAMA Pediatrics, 2020. **174**(9): p. 882-889.
44. Ludvigsson, J.F., *Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults.* Acta Paediatr, 2020. **109**(6): p. 1088-1095.

45. Marshall, M., et al., *Symptomatic Acute Myocarditis in Seven Adolescents Following Pfizer-BioNTech COVID-19 Vaccination.* Pediatrics, 2021: p. e2021052478.
46. Martinez, M.E., *The calendar of epidemics: Seasonal cycles of infectious diseases.* PLOS Pathogens, 2018. **14**(11): p. e1007327.
47. Shaman, J. and M. Kohn, *Absolute humidity modulates influenza survival, transmission, and seasonality.* Proceedings of the National Academy of Sciences, 2009. **106**(9): p. 3243-3248.
48. Shaman, J., et al., *Absolute Humidity and the Seasonal Onset of Influenza in the Continental United States.* PLOS Biology, 2010. **8**(2): p. e1000316.
49. Pitzer, V.E., et al., *Environmental Drivers of the Spatiotemporal Dynamics of Respiratory Syncytial Virus in the United States.* PLOS Pathogens, 2015. **11**(1): p. e1004591.
50. Ma, Y., et al., *Role of air temperature and humidity in the transmission of SARS-CoV-2 in the United States.* medRxiv, 2020.
51. Gavenčiak, T., et al., *Seasonal variation in SARS-CoV-2 transmission in temperate climates.* medRxiv, 2021: p. 2021.06.10.21258647.
52. Liu, X., et al., *The role of seasonality in the spread of COVID-19 pandemic.* Environmental research, 2021. **195**: p. 110874.
53. Rijksinstituut voor Volksgezondheid en Milieu (RIVM), *Beschrijving transmissiemodel berekening zorgbelasting*. 2021: Bilthoven.
54. Volz, E., et al., *Assessing transmissibility of SARS-CoV-2 lineage B.1.1.7 in England.* Nature, 2021. **593**(7858): p. 266-269.
55. Davies, N.G., et al., *Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England.* Science, 2021. **372**(6538): p. eabg3055.
56. Backer, J.A., et al., *Impact of physical distancing measures against COVID-19 on contacts and mixing patterns: repeated cross-sectional surveys, the Netherlands, 2016–17, April 2020 and June 2020.* Eurosurveillance, 2021. **26**(8): p. 2000994.
57. Verberk, J.D.M., et al., *Third national biobank for population-based seroprevalence studies in the Netherlands, including the Caribbean Netherlands.* BMC Infectious Diseases, 2019. **19**(1): p. 470.
58. van Dissel, J. and Cib-RIVM, *COVID-19: Tweede Kamer-briefing 22 juni 2021*, R.v.V.e.M. (RIVM), Editor. 2021: Bilthoven.
59. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). *Rekenmodellen openbaar en toegankelijk*. 2021 [cited 2021 4 March 2021]; Available from: https://www.rivm.nl/coronavirus-covid-19/hoe-berekeningen-bijdragen-aan-bestrijding-van-virus/rekenmodellen.
60. Rijksinstituut voor Volksgezondheid en Milieu (RIVM), *Epidemiologische situatie van SARS-CoV-2 in Nederland*. 2021, RIVM: Bilthoven.
61. Rijksoverheid, *Routekaart coronamaatregelen bestuurdersversie*. 2021.
62. R Core Team, *R: A Language and Environment for Statistical Computing*. 2020, R Foundation for Statistical Computing: Vienna, Austria.

63. Soetaert, K., T. Petzoldt, and R.W. Setzer, *Solving Differential Equations in R: Package deSolve.* 2010, 2010. **33**(9): p. 25.
64. Federal Drug Administration, *Vaccines and Related Biological Products Advisory Committee Meeting February 26, 2021: Janssen Ad26.COV2.S Vaccine for the Prevention of COVID-19*, Vaccines and Related Biological Products Advisory Committee, Editor. 2021.

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