Modelling direct and herd protection effects of vaccination against the SARS-CoV-2 Delta variant in Australia

Emma McBryde
Professor of Infectious Diseases Modelling and Epidemiology
James Cook University
Australian Institute of Tropical Health and Medicine
Townsville, Queensland, Australia

Michael Meehan
Research Fellow
James Cook University
Australian Institute of Tropical Health and Medicine
Townsville, Queensland, Australia

Jamie Caldwell
James Cook University
Australian Institute of Tropical Health and Medicine
Infectious Diseases Modelling and Epidemiology
Townsville, Queensland, Australia

Adeshina Adekunle
Research Fellow
James Cook University
Australian Institute of Tropical Health and Medicine
Townsville, Queensland, Australia

Samson Ogunlade
James Cook University
Australian Institute of Tropical Health and Medicine
Townsville, Queensland, Australia

Abdul Kuddus
James Cook University
Australian Institute of Tropical Health and Medicine
Townsville, Queensland, Australia

Romain Ragonnet
Research Fellow
Monash University
School of Public Health and Preventive Medicine
Melbourne, Victoria, Australia

Pavithra Jayasundara
Monash University
Department of Epidemiology and Preventive Medicine
Melbourne, Victoria, Australia
James M Trauer  
Head, Epidemiological Modelling Unit  
Monash University  
School of Public Health and Preventive Medicine  
Melbourne, Victoria, Australia

Robert C Cope  
Australian National University  
Biological Data Sciences Institute ANU College of Science  
Canberra, Australian Capital Territory, Australia

Corresponding author:  
Professor Emma McBryde  
emma.mcbryde@jcu.edu.au

Competing interests: No relevant disclosures

Funding:  
ESM would like to acknowledge funding from an NHMRC investigator grant #1195102  
JMT would like to acknowledge an NHMRC early Career Fellowship #1142638  
and funding from MRFF Rapid Response Digital Health Covid RRDHI000027  
PJ would like to acknowledge salary support from MRFF Rapid Response Digital Health Covid RRDHI000027  
MM would like to acknowledge ARC support for a Discovery Early Career Fellowship

This article has been accepted for publication and has undergone full peer review but has not been through the full structural and scientific editing, typesetting, pagination and proofreading processes which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.5694/mja2.51263
Abstract

Objectives: To analyse the direct and indirect effects of vaccination by vaccine type, age-strategy, and coverage on Australia’s Coronavirus Disease 2019 epidemic.

Design: Our model incorporates age-specific mixing, infectiousness, susceptibility and severity to assess the final size of the epidemic under different public health intervention scenarios in Australia.

Main Outcome measures: The model predicts the final infected population, cumulative hospitalizations, deaths and years of life lost following an epidemic wave, taking into account vaccination and additional mitigation measures.

Results: Assuming a pre-vaccination effective reproduction number for the Delta variant of 5, we show that the current “Mixed” program (vaccinating over 60s with AstraZeneca and under 60s with Pfizer) would not achieve herd immunity, unless 85% of the population is covered (including many 5-16 year-olds).

At a lower effective reproduction number of 3, the Mixed program can achieve herd immunity at 60-70% coverage without vaccinating 5-15 year-olds. An effective reproduction number of 7 precludes achieving herd immunity with existing vaccines, however vaccination still prevents over 85% of deaths compared with no vaccination.

Conclusion: Vaccinating the vulnerable first is the optimal policy at low coverage, but vaccinating high transmitters becomes more important in settings where reproduction numbers are lower and coverage is higher. Vaccinating over 85% of the population including children would likely be needed to achieve herd immunity at the most plausible effective reproduction number of 5. Even without herd immunity, vaccines are highly beneficial at reducing deaths.

Summary box

The known: Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2) variants are known to be more transmissible than the original Wuhan strain, making herd immunity challenging.

The new: We find that prioritising the older-vulnerable leads to fewer deaths and is the optimal strategy when vaccine coverage is under 70%. Herd immunity is unlikely unless children 5-15 are vaccinated, but current vaccine targets are expected to prevent substantial numbers of deaths.

The implications: Australia is unlikely to achieve herd protection unless vaccination is extended to younger ages or combined with other measures. Australia should now prioritise delivering Pfizer vaccine to 12-40 year-olds.
On 2nd July 2021, the Australian National Cabinet announced a four-step plan to transition from a strategy for Corona Virus disease 2019 (COVID-19) control to a re-opening and return to normal life (1). To move to a more liberal setting (increasing international arrivals, reduced lockdowns and simplified quarantine for vaccinated people (1)) requires vaccinating a 70% of adult Australians to limit hospitalisations and deaths from COVID-19 – by either direct protection or herd protection. However, herd immunity has become more difficult to achieve with the more infectious Delta variant raising the immunity threshold (2). Further, currently available vaccines are slightly less effective at reducing symptomatic infection from the Delta variant (3-5).

We previously investigated herd immunity thresholds and estimated optimised vaccine distribution around the world for the original Wuhan strain (6), and here update this analysis for the Delta variant in Australia.

The Delta variant is approximately twice as infectious as the original Wuhan strain (7); however, given the pervasive implementation of mitigation measures, the exact value of its pre-vaccination reproduction number (expected number of new cases caused by a typical infected case in the absence of vaccination), which we denote $R_{eff}$, remains unclear.

For our primary analysis, we assume $R_{eff}$ equals 5, which is at the lower end of estimates used by Blakely et al. (8), the central value used by the Grattan report (9) and higher than that used by the Doherty report (10).

Model outcomes (and resulting conclusions) are especially sensitive to $R_{eff}$. This value is highly uncertain as it incorporates ever changing mitigation strategies including contact tracing, mask use and mobility changes, along with viral evolution. We therefore consider outcomes ranging from $R_{eff} = 3$ to $R_{eff} = 7$. Additionally, we developed a flexible online tool, which allows the user to vary model parameters as new evidence emerges, including: $R_{eff}$; the choice of vaccine; and the extent of pre-existing population immunity due to natural infection, reflected by seroprevalence.

Age-specific vaccine strategies have been a large part of the COVID response in Australia (11). Published age-specific contact matrices show that young adults are more sociable than other groups in Australia, with a marked decline in contacts above age 55 (12), whereas estimated COVID-19 infection fatality rates show that older people make up the most vulnerable group. Hence, we investigate two alternative strategies for vaccine distribution given fixed, limited supply: the first focuses on vaccinating the vulnerable (≥55), and the second prioritizes vaccinating the most infectious (<55). We also present results for AstraZeneca only, Pfizer only, or the current Mixed program recommended by the Australian Technical Advisory Group on Immunisation (ATAGI) of vaccinating under 60 year-olds with Pfizer and 60 year-olds and older with AstraZeneca (11). Other vaccine types are also available in our online tool.

**Methods**

Vaccine programs
Following the vaccine availability in Australia, we consider three vaccine program possibilities:

1. All vaccinations being Pfizer
2. All vaccinations being AstraZeneca
3. Mixed: Pfizer for <60 and AstraZeneca for ≥60s (the current ATAGI policy)

Eligibility

We consider two age cut-offs for vaccine eligibility:

1. 15+ years
2. 5+ years

Age-specific coverage priority strategies

We also consider three different age-specific coverage strategies including all of the population over the age cut-off:

1. the vulnerable first strategy: Vaccinate the older, more vulnerable population (55+ year-olds) first, followed by <55 year-olds
2. the transmitters first strategy: Vaccinate the more sociable (<55 year-olds) first followed by the older
3. the untargeted strategy: even distribution of vaccine across all eligible age groups.

Uptake

We consider different uptake proportions, indicative of the maximum vaccine acceptance of the target groups. The results presented in the main analysis assume a maximum uptake of 90% across all eligible age groups.

Vaccine efficacy, mechanisms and model assumptions

We model the impact of vaccination through: \( V_a \), defined as the efficacy of the vaccine on susceptibility to acquiring infection; \( V_s \), the efficacy of vaccine on the proportion of people developing symptomatic disease given an infection takes place (which leads to both reduced severity and reduced infectiousness of the vaccinated infected person); \( V_m \), the efficacy of vaccine in preventing case morbidity and mortality (i.e., hospitalization and death); and \( V_t \), the reduced probability of transmitting disease, given infection. The reduction in symptomatic COVID-19 risk, as measured by the overall vaccine efficacy (\( V_e \)), is derived from literature, which is specific to the Delta strain. The parameters \( V_e \), and \( V_a \) relate to it through the formula, \( 1 - V_e = (1-V_a)(1-V_s) \). Values for \( V_s \) and \( V_m \) are derived from data on earlier variants (13). Values are given in Table 1.

Mathematical methods

The full mathematical methodology is elaborated in the Appendix and has been published elsewhere (6). Briefly, we combine inferred daily rates of age-specific contacts (12) with differences in susceptibility and infection by age (18), to build a table of expected transmission events over each individual’s infectious lifetime (the so-called next-generation matrix, \( R_{ij} \)). This table allows us to calculate the total number of infected individuals in
each age and vaccination group over the course of an epidemic wave, using the final-size equation (20):

\[ 1 - \tilde{z}_i = \exp[-\tilde{N}_i^{-1} \sum_j \tilde{K}_{ij} \tilde{N}_j \tilde{z}_j], \]

where \( \tilde{z}_i \) is the fraction of individuals in group \( i \) (where \( i \) indexes both age and vaccination status) that become infected throughout the course of the epidemic, and \( \tilde{N}_i \) is the total number of individuals in this group.

Next, we combine age-specific estimates for infection-fatality rate (21, 22) and life-expectancy with estimates for vaccine efficacy from Table 1. This allows us to calculate the cumulative number of infections, deaths and years of life lost under each strategy.

Our online tool is available at: https://covid-19-aithm.shinyapps.io/vaccine_coverage_analysis

Our code is publicly available here: https://github.com/michaeltmeehan/covid19/tree/main/immunization_australia

Our default assumption for the effective reproduction number before vaccination (\( R_{\text{eff} v} \)) for the Delta strain is 5.0, but we explore values from 3 to 7 in Figure 1. We define coverage as the number of vaccine courses (2 doses) available divided by the total Australian population (independent of the minimum vaccination age or the uptake proportion).

**Results**

Infections and herd protection

For all effective reproduction numbers and vaccination programs, prioritizing transmitters leads to fewer (or, at worst, an equal number of) infections (Figure 1, panel a). Extending vaccine recipients to 5+ (from 15+) improves the outcomes for infections in the Pfizer and Mixed programs (Figure 1, panel a) if \( R_{\text{eff} v} = 5 \) and \( R_{\text{eff} v} = 7 \) but not for \( R_{\text{eff} v} = 3 \).

Notably, if \( R_{\text{eff} v} = 7 \) (Figure 1, bottom row), then no program or strategy achieves herd immunity, regardless of age of eligibility. For \( R_{\text{eff} v} = 5 \) (Figure 1, middle row) herd immunity can be achieved only if the minimum vaccination age is extended down to 5+. If \( R_{\text{eff} v} = 3 \) (Figure 1, top row), we estimate that we can achieve herd immunity at 60% coverage using a Pfizer or Mixed program and transmitter strategy, regardless of age of eligibility. This threshold increases to 70% coverage when using the untargeted or vulnerable strategies. AstraZeneca program does not achieve herd immunity under any model assumptions.

Deaths, years of life lost, hospitalisations

For preventing years of life lost, the optimal strategy depends on \( R_{\text{eff} v} \). When \( R_{\text{eff} v} \geq 5 \) (Figure 1, middle and bottom rows), we find that the vulnerable strategy is either superior, or equivalent to both the untargeted and transmitter strategies (Figure 1, panel b). The only exception is a small window between 75 and 82% coverage where the transmitter strategy marginally outperforms the other two strategies, provided the minimum vaccination age is five years old and Pfizer is included in the vaccination program.
When $R_{eff} = 3$ we find that within the coverage range of 50-70% for the Mixed and Pfizer programs, the transmitter strategy is superior to the vulnerable strategy at reducing years of life lost (YLL). For coverages less than 50%, the vulnerable strategy is always superior. Similar results are found for both hospitalizations and deaths (see Figure A2, Appendix). Outcomes for each of the three strategies converge when the entire eligible population is fully vaccinated.

Lowering the age of vaccine eligibility to include 5 year-olds typically worsens the outcome for YLL for a given coverage (Figure 1, panel b) until adult coverage is saturated. At this point, vaccinating those aged 5-15 years reduces YLL.

In all cases the Pfizer and Mixed vaccination programs outperform the AstraZeneca only program. The difference is most pronounced for infections (Figure 1, panel a) but much less so for hospitalizations (Figure A2, panel a), deaths (Figure A2, panel b) and years of life lost (Figure 1, panel b).

Figure 2 examines deaths given the current Mixed vaccination program in more detail and compares the expected deaths from COVID-19 to that of a completed outbreak in an unvaccinated population. It compares vaccinating 15+ in the lower panel with over 5+ in the upper panel. It divides deaths into those occurring amongst the vaccinated (red) and unvaccinated (maroon) populations. The plots also show the deaths averted (blue) which are divided into deaths averted in infected people who survive because of the vaccine effect on severity / mortality (light blue), and those who do not die because they never acquire infection (dark blue). The figures show the importance of expanding vaccine eligibility to 5+ in order to achieve herd immunity at over 80% coverage. They also show that at high level of vaccination, a substantial minority of deaths will be in the vaccinated population.

**Sensitivity analysis**

The results depend crucially on the assumed input parameter values. If $R_{eff}$ is as high as 7, as shown in Figure 1, then herd immunity is not possible. On the other hand, if the effective reproduction ratio could be constrained to below 2.7, through non-vaccination means, then herd immunity is achievable using AstraZeneca, Pfizer or mixed programs.

We provide an online tool in which the user can explore a range of assumptions and determine the sensitivity of the model outputs to these.

Further, in the appendix, we present a thorough sensitivity analysis that considers variations in additional key input parameters not presented above (the infectiousness of asymptomatic relative to symptomatic cases, the overall vaccine efficacy $V_e$ against symptomatic infection, and the odds ratio of death for Delta v. original SARS-CoV-2 strains). We also examine a second synthetic contact matrix, more directly matched to empirical matrices. In all cases we find that our general conclusions regarding the ability of vaccination to achieve herd immunity, and the ranked performance of each vaccination strategy are robust.

**Discussion**

We show that the current decision in Australia to vaccinate the vulnerable older age groups first is the optimal strategy for reducing hospitalizations, deaths and years of life lost from
COVID-19 for a highly infectious COVID-19 variant like Delta. The use of AstraZeneca for the elderly and Pfizer for the younger population allows for the possibility of herd immunity. However, if the effective reproduction number of the Delta strain is as high as five, at least 85% of total Australian population -including children- would need to be vaccinated to achieve herd immunity. Hence the current plan to vaccinate 80% of the adult population -or about 65% of the total population- falls far short of herd immunity. Even without herd immunity, vaccination averts many deaths and years of life lost, by both reducing infection (in vaccinated and unvaccinated individuals) and directly reducing severity of disease in the vaccinee.

For lower reproduction numbers – reflective of typical Australian city undergoing partial lockdown measures or an alternative form of mitigation – we show that targeting transmitters first could provide a shortcut to herd immunity at lower vaccine coverage rates, compared with untargeted strategies, or strategies targeting the vulnerable older age-groups.

The Doherty model predictions (10) (pp 1-12) for a given reproduction number are based on similar methods (see Meehan, 2020 (6)) and are in overall alignment with this work. Differences arise in considering plausible effective reproduction numbers in the setting of multiple public health interventions. In particular, the need to vaccinate teenagers and even younger children to achieve herd immunity and avoid substantial loss of life is evident when the reproduction number is slightly higher than the Doherty input of 3.6.

This work considers pre-vaccination effective reproduction number, encompassing all public health and individual mitigations strategies excluding vaccination ($R_{eff_v}$). This value changes with public health response; under partial lockdown conditions we may expect it to be under three, and favour targeting vaccination to high transmitters. Our baseline $R_{eff_v}$ was five, to simulate relaxation of all general mitigation measures and reliance on a specific public health response. We also investigated a fully unmitigated epidemic in which we assume $R_{eff_v}=7$, which would preclude herd immunity with currently available vaccines. To accommodate uncertainty in $R_{eff_v}$, we have produced a flexible tool and open-source code to which these emerging values can be input.

Our model has simplifications and limitations. We combine all non-vaccination public health interventions into a single value, reflected in $R_{eff_v}$, rather than modelling them separately. This value is fixed for each simulation, and our model examines the final size of an epidemic not dynamic timesteps. Hence our model is not designed to predict the unfolding epidemic curve, sequential interventions or the effects of waning immunity – the last of which remains poorly understood. We examine outcomes of years of life lost, deaths, hospitalisations and infections. Long-COVID is another outcome currently being quantified, which can be estimated from our model outputs using the age-specific infections when precise data are available but is currently not considered. Contact pattern heterogeneity is incorporated but only to the level of 5-year age groups and uses synthetic matrices, not empirical data (12). We do not model the impact of different occupations, or subgroups. This may lead to over-estimation of vaccine effect if subgroups remain unvaccinated or under-estimation of the effect of targeting high-transmitter subgroups.
At the time of writing, the highest risk groups, including all Australians over 70, have had the opportunity to be fully vaccinated, with vaccination rates (first or second dose) over 80% in this age group (23). Australia’s current focus is vaccinating 60+ with AstraZeneca and 40-59 year-olds with Pfizer, although this is changing rapidly, particularly in hotspots. Our results suggest that short-term future priorities should be to expand vaccination access to all ages who are approved for Pfizer; namely, 12-39 year-olds. Supply of mRNA vaccines – Pfizer and Moderna – is the current rate-limiting step.

As a nation, we need to start considering what level of vaccination is acceptable before opening Australia to international travellers and transitioning away from our aggressive control strategy. With existing intentions of the Australian population regarding vaccination, current vaccine efficacy and the infectiousness of the Delta variant, herd immunity through vaccination alone seems improbable. If children are vaccinated and new vaccines with long lasting sterilising immunity become available this could change. However, even without herd immunity, we can expect to achieve substantial reductions in deaths, hospitalisations and years of life lost from COVID-19 provided we strategically vaccinate the majority of the elderly and vulnerable population, then also vaccinate the highest transmitters. Therefore, reaching herd immunity should be our aim but not be the arbiter of transition to Phase B in the National Plan (1). Substantial levels of herd protection still occur at coverage levels lower than that required to reach true herd immunity.

References


Table 1. Inputs into the model for vaccine efficacy against the Delta variant of SARS-CoV-2.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>$V_a$</th>
<th>$V_s$</th>
<th>Reduction in symptomatic COVID (Ve)</th>
<th>References</th>
<th>$V_i$</th>
<th>References</th>
<th>$V_m$</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer</td>
<td>0.76</td>
<td>0.50</td>
<td>0.88</td>
<td>(5, 13, 14)</td>
<td>0.5</td>
<td>(15)</td>
<td>0.5</td>
<td>(16)</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>0.48</td>
<td>0.37</td>
<td>0.67</td>
<td>(5, 13, 17)</td>
<td>0.5</td>
<td>(15)</td>
<td>0.8</td>
<td>(16)</td>
</tr>
</tbody>
</table>
Figure 1. Model predictions for the impact of different vaccine programs: Pfizer, AstraZeneca or Mixed, indicated by column. Each is considered for values of $R_{eff}$ of 3, 5 and 7, indicated by rows. Vaccine uptake ceiling is fixed at 90%. For each subgraph there are three strategies (vulnerable, transmitters and untargeted), indicated by colours, and two age of vaccine cut-offs (5 years and 15 years), indicated by line type. Panel a shows coverage versus infections and panel b shows coverage versus years of life lost.

a. Coverage versus infections

![Coverage versus infections diagram]

b. Coverage versus years of life lost

![Coverage versus years of life lost diagram]
Figure 2 Total deaths for the three different strategies of age-specific vaccine coverage for the Mixed program, $R_{eff} = 5$ and uptake =90%. Panel a) presents estimates for an age cut-off for vaccination of 5 years and panel b) shows results for vaccination age cut-off of 15. The expected number of deaths (in a completed outbreak in a fully unvaccinated population) is the height of the stacked bar of both red and blue colours. We have divided the averted deaths into those who became infected but did not die as a result of being vaccinated (light blue) and those who did not become infected, as a result of personal or herd immunity (dark blue).

a. Vaccine eligibility age: over 5 years  

b. Vaccine eligibility age: over 15 years
Modelling direct and herd protection effects of vaccination against the SARS-CoV-2 Delta variant in Australia: Technical appendix

1 Non-technical explanation of methods

We build a 16 by 16 next generation matrix which provides the class-specific reproduction number for each of 16 age-classes \{0 – 4, 5 – 9, 10 – 14, ..., 70 – 74, 75+\}. For example, the value in row 0-4 column 0-4 is the expected number of 0-4 year olds infected by a typical 0-4 year old case throughout their infectious period.

To build this matrix, we start with the age-based contact matrix for Australia, published by Prem et al. (2021) (1) which is also 16x16 and based on 5-year age groups, Figure A, left panel. We modify this by changing the risk of transmission per contact according to the age of the transmitter and the age of the susceptible receiver of contacts (Davies et al. 2020, (2)). Each cell is then multiplied through by the duration of infection and scaled to ensure that it calibrates to the effective reproduction number under investigation, shown in Figure A1 right panel. It can be seen that the highest transmitters are in the 15 to 50 year old groups.

Figure A1. Left panel provides the age specific contact matrix for Australia, taken from Prem et al. (2021). Right panel provides the next generation matrix based on Prem and modified for infectiousness susceptibility, duration of infection and scaling constant.

We then expand the matrix further to account for vaccinated and unvaccinated in each age group (yielding a 32 x 32 element matrix) and apply the effects of vaccine on both susceptibility and infectiousness to the next generation matrix.

From the next generation matrix, we can derive the effective reproduction number (as the dominant eigenvalue) and the final size (total number of infections at the end of a completed epidemic) using an adaptation of well-known final size methods, described in detail in section 2. This latter value is age-specific and vaccine status-specific, allowing the following further estimates to be made: death and hospitalisation rates modified by age and vaccination status, years of life lost, and relative proportions of vaccinated and unvaccinated populations infected or dying.
2 Mathematical methods
To model the transmission of SARS-CoV-2 we stratify the population into 16 5-year age bands \( \alpha \in \{0 − 4, 5 − 9, 10 − 14, \ldots, 70 − 74, 75+\} \) and assume that individuals in age group \( \alpha \) possess a relative susceptibility to infection \( u_\alpha \). Once infected, an age-dependent fraction \( y_\alpha \) go on to develop symptomatic (i.e., clinical) disease whilst the remaining \( 1 − y_\alpha \) develop asymptomatic (i.e., sub-clinical) disease. We assume that individuals in the sub-clinical class are less infectious than those in the clinical class by a relative factor \( f \) (baseline value 0.25 (2-7)) and that the total time spent infectious for both classes is \( \tau \) days.

Each day, each individual in age group \( \alpha \) makes \( c_{\alpha \alpha'} \) contacts with individuals in age group \( \alpha' \) leading to the following expression for the (unscaled) next-generation matrix (NGM) (Diekmann et al. 2010 (8)):

\[
\bar{K}_{\alpha \alpha'}^u = \frac{u_\alpha S_\alpha c_{\alpha \alpha'}}{N_{\alpha'}}[y_{\alpha'} + (1 − y_{\alpha'})f] \tau
\]

where \( S_\alpha \) is the number of susceptible individuals in age group \( \alpha \) and \( N_{\alpha'} \) is the total number of individuals in age group \( \alpha' \). We allow that prior to vaccination an age-specific fraction \( p_\alpha \) of individuals have immunity as a result of previous infection, such that \( S_\alpha = (1 − p_\alpha)N_\alpha \).

The \((\alpha, \alpha')\)th entry of the \( 16 \times 16 \) NGM \( \bar{K}_u \) is proportional to the average number of new infections in age group \( \alpha \) generated by an individual in age group \( \alpha' \) over their infectious lifetime. To calculate the actual number of infections generated by each individual these entries must be scaled by the (pseudo-)probability of transmission given contact, which we denote \( \eta \). In particular, the effective reproduction number in the absence of vaccination, \( R_{\text{eff}}^v \), which is proportional to the maximal eigenvalue, or spectral radius of \( \bar{K}_u \) (or \( \rho(\bar{K}_u) \)), can be expressed as

\[
R_{\text{eff}}^v = \eta \rho(\bar{K}_u) \quad \Rightarrow \quad \eta = \frac{R_{\text{eff}}^v}{\rho(\bar{K}_u)}
\]

Incorporating this definition of \( \eta \) along with the possibility of pre-existing immunity \( p_\alpha \) the next-generation matrix \( K_u \) is given by

\[
K_{\alpha \alpha'}^u = \eta \cdot \frac{u_\alpha S_\alpha c_{\alpha \alpha'}}{N_{\alpha'}}[y_{\alpha'} + (1 − y_{\alpha'})f] \tau.
\]

For a given \( R_{\text{eff}}^v \) we use the expression given above to calculate the scaling factor \( \eta \) in terms of \( R_{\text{eff}}^v \) and \( \rho(\bar{K}_u) \). Daily, age-specific contact rates \( c_{\alpha \alpha'} \) are provided by the synthetic matrices presented in (Prem et al. 2021).

2.1 Incorporating vaccination
In the presence of vaccination we further subdivide the population into those who are vaccinated and those who are unvaccinated. Individuals who are vaccinated experience a reduced risk of acquiring infection (by a factor \( 1 − V_\alpha \)), a reduced risk of symptomatic disease (by a factor \( 1 − V_s \)), a reduced risk of hospitalisation or death (by a factor \( 1 − V_m \)) and are potentially less infectious (by a factor \( 1 − V_t \)). Each of these factors is dependent on the combination of SARS-CoV-2 strain and vaccine. If a proportion \( v_\alpha \) of individuals in age group \( \alpha \) are vaccinated, then the modified \( 16 \times 16 \) next-generation matrix in the presence of vaccination is given by
$$K_{aa'}^{\text{vac}} = \eta \cdot \frac{u_a S_a c_{aa'}}{N_{a'}} \left( [y_{a'} + (1 - y_{a'})f](1 - v_{a'}) + [(1 - Vs)y_{a'} + (1 - (1 - Vs)y_{a'})f](1 - Vt)(1 - Va)v_{a'} \right).$$

Note that this expression does not include the reduced risk of hospitalisation or death $(1 - Vm)$ as this is assumed to impact patient outcome only, and have no effect on transmission.

Further, this expression only stratifies the population according to age (i.e., the indices $a, a'$ only index the 16 age groups introduced above). If we wish to additionally track the transmission rates between individuals of different ages and different vaccination status, then we can use the expanded $(32 \times 32)$ next-generation matrix $\tilde{R}$, which can be expressed as the matrix product:

$$\tilde{R} = \begin{bmatrix} 1 - v \\ (1 - V_a)v \end{bmatrix} \left[ K^u \quad K^v \right]$$

where the terms $1 - v$ and $(1 - V_a)v$ in the first factor are $16 \times 16$ diagonal matrices, the matrix $K^u$ is defined above and

$$K_{ij}^v = \eta \cdot \frac{u_j S_i c_{ij}}{N_j} \left( [1 - V_s \cdot v_j]y_j + (1 - (1 - V_s \cdot v_j)y_j)f \right)(1 - Vt \cdot v_j)\tau.$$

The indices $i, j$ in the expression above span the full set of 32 possible age-group x vaccination categories.

### 2.2 Calculating the final size and disease-related mortality

To calculate the total number of infections and deaths throughout the course of an epidemic wave we use the vectorised form of the final size equation given by (Andreasen 2011(9)):

$$1 - \tilde{z}_i = \exp \left( -\tilde{N}_i^{-1} \sum_j \tilde{R}_{ij} \tilde{N}_j \tilde{z}_j \right)$$

where $\tilde{z}_i$ is the fraction of individuals in group $i$ that become infected throughout the epidemic, $\tilde{N}_i$ is the population size of group $i$ and $\tilde{R}_{ij}$ is the extended next-generation matrix defined in the previous section. Note that here we use the extended $(32 \times 32)$ next-generation matrix $\tilde{R}_{ij}$ that stratifies by both age and vaccination status because the infection-fatality rate for vaccinated individuals is reduced by a factor $(1 - Vs) \times (1 - Vm)$ relative to those that are unvaccinated. Moreover, the population size $\tilde{N} = ((1 - v_a)N_a, v_a N_a)$ is a combined vector of the number of vaccinated and unvaccinated individuals in each age group.

Solving the final size equation numerically, we can determine the total number of deaths $D$ using the following expression:

$$D = \text{Unvaccinated deaths} + \text{Vaccinated deaths}$$

$$= \sum_{a \in \{0-4, 75+\}} d_a z_a^u (1 - v_a)(1 - p_a) S_a + \sum_{a \in \{0-4, 75+\}} d_a z_a^v (1 - Vm)(1 - Vs)v_a(1 - p_a) S_a$$

$$= \sum_{a \in \{0-4, 75+\}} d_a [z_a^u (1 - v_a) + z_a^v (1 - Vm)(1 - Vs)v_a](1 - p_a) S_a$$

where $d_a$ is the age-specific infection-fatality rate (O’Driscoll et al. 2020(10), Fisman et al. 2021(11)), and $z_a^u$ and $z_a^v$ are the fractions of the unvaccinated and vaccinated populations in each age group.
that become infected, respectively. The values $d_a$ are listed in Table 2. Using the total numbers of deaths in each group and the life expectancy we also estimate the years of life lost (see Table 2).

Similarly, the total number of hospitalisation is calculated as

$$H = \text{Unvaccinated hospitalisations} + \text{Vaccinated hospitalisations}$$

$$= \sum_{a \in \{0-4,\ldots,75+\}} h_a [z_a^u (1 - v_a) + z_a^v (1 - Vm) (1 - Vs) v_a] (1 - p_a) S_a$$

where $h_a$ is the age-specific hospitalisation rate.
3. Parameter values

Table 1. Model parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$u_a$</td>
<td>Relative susceptibility of age group $a$</td>
<td>See Table 2</td>
</tr>
<tr>
<td>$y_a$</td>
<td>Fraction of infected individuals in age group $a$ that develop clinical symptoms</td>
<td>See Table 2</td>
</tr>
<tr>
<td>$\tau$</td>
<td>Infectious period</td>
<td>5.0 days</td>
</tr>
<tr>
<td>$f$</td>
<td>Relative infectiousness of asymptomatic individuals</td>
<td>0.25</td>
</tr>
<tr>
<td>$p_a$</td>
<td>Fraction of individuals in age group $a$ with pre-existing immunity</td>
<td>0.016</td>
</tr>
<tr>
<td>$\eta$</td>
<td>(Pseudo-)Probability of transmission given contact</td>
<td>Fitted</td>
</tr>
<tr>
<td>$v_a$</td>
<td>Proportion of vaccinated individuals in age group $a$</td>
<td>Variable</td>
</tr>
</tbody>
</table>

Table 2. Age-specific epidemiological parameters. Data for age-specific relative susceptibility and clinical fraction taken from (Davies et al. 2020 (2)); data for hospitalisation and infection-fatality rate taken from (Walker et al. 2020) and (O’Driscoll et al. 2020 (10)), respectively; life expectancy table interpolated from Australian Bureau of Statistics (12). **Note that the age-specific hospitalisation and infection-fatality rates provided below are specific to the wild-type SARS-CoV-2 strain. In our analysis, these values are scaled by the odds ratios given in Table 3.

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Relative susceptibility $(u_a)$*</th>
<th>Clinical fraction $(y_a)$</th>
<th>Hospitalisation rate** $(h_a)$</th>
<th>Infection-fatality rate** $(d_a)$</th>
<th>Life expectancy (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>0.39</td>
<td>0.28</td>
<td>0.001</td>
<td>2.98E-05</td>
<td>81.1</td>
</tr>
<tr>
<td>5-9</td>
<td>0.39</td>
<td>0.28</td>
<td>0.001</td>
<td>6.9E-06</td>
<td>81.2</td>
</tr>
<tr>
<td>10-14</td>
<td>0.38</td>
<td>0.2</td>
<td>0.001</td>
<td>1.1E-05</td>
<td>81.3</td>
</tr>
<tr>
<td>15-19</td>
<td>0.38</td>
<td>0.2</td>
<td>0.002</td>
<td>2.57E-05</td>
<td>81.4</td>
</tr>
<tr>
<td>20-24</td>
<td>0.79</td>
<td>0.26</td>
<td>0.005</td>
<td>7.88E-05</td>
<td>81.5</td>
</tr>
<tr>
<td>25-29</td>
<td>0.79</td>
<td>0.26</td>
<td>0.01</td>
<td>0.000171</td>
<td>81.7</td>
</tr>
<tr>
<td>30-34</td>
<td>0.87</td>
<td>0.33</td>
<td>0.016</td>
<td>0.00033</td>
<td>81.9</td>
</tr>
<tr>
<td>35-39</td>
<td>0.87</td>
<td>0.33</td>
<td>0.023</td>
<td>0.000545</td>
<td>82.2</td>
</tr>
<tr>
<td>40-44</td>
<td>0.80</td>
<td>0.4</td>
<td>0.029</td>
<td>0.001052</td>
<td>82.4</td>
</tr>
<tr>
<td>45-49</td>
<td>0.80</td>
<td>0.4</td>
<td>0.039</td>
<td>0.001675</td>
<td>82.8</td>
</tr>
<tr>
<td>50-54</td>
<td>0.82</td>
<td>0.49</td>
<td>0.058</td>
<td>0.002992</td>
<td>83.4</td>
</tr>
<tr>
<td>55-59</td>
<td>0.82</td>
<td>0.49</td>
<td>0.072</td>
<td>0.004583</td>
<td>84.1</td>
</tr>
<tr>
<td>60-64</td>
<td>0.89</td>
<td>0.63</td>
<td>0.102</td>
<td>0.006017</td>
<td>84.7</td>
</tr>
<tr>
<td>65-69</td>
<td>0.89</td>
<td>0.63</td>
<td>0.117</td>
<td>0.015209</td>
<td>85.8</td>
</tr>
<tr>
<td>70-74</td>
<td>0.74</td>
<td>0.69</td>
<td>0.146</td>
<td>0.024209</td>
<td>87.4</td>
</tr>
<tr>
<td>75+</td>
<td>0.74</td>
<td>0.69</td>
<td>0.177</td>
<td>0.043257</td>
<td>89.0</td>
</tr>
</tbody>
</table>

*these values are as published, and are later scaled, so the relative values are more important than the absolute values
Table 3. (Adjusted) Odds ratios for hospitalisation and infection for Delta variant relative to non-VOC strains (Fisman et al. 2021 (11)).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalisation</td>
<td>2.08 (1.80, 2.38)</td>
</tr>
<tr>
<td>Death</td>
<td>2.32 (1.47, 3.30)</td>
</tr>
</tbody>
</table>

Table 4. Vaccine efficacy.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Clinical trial efficacy (Ve) (95% CI)</th>
<th>Efficacy against acquisition (Va)</th>
<th>Efficacy against symptomatic disease (Vs)</th>
<th>Efficacy against transmission (Vt)</th>
<th>Efficacy against severe disease given symptomatic disease (Vm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNT162b2 (Pfizer)</td>
<td>0.880 (0.853, 0.901)</td>
<td>0.76</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>ChAdOx1 (AstraZeneca)</td>
<td>0.670 (0.613, 0.718)</td>
<td>0.48</td>
<td>0.37</td>
<td>0.5</td>
<td>0.8</td>
</tr>
</tbody>
</table>
4. Hospitalisation and deaths

a. **Coverage versus hospitalisations**

![Graph showing hospitalisations for different vaccine programs and coverage levels.]

b. **Coverage versus deaths**

![Graph showing deaths for different vaccine programs and coverage levels.]

**Figure A2.** Model predictions for the impact of different vaccine programs: Pfizer, AstraZeneca or Mixed, indicated by column. Each is considered for values of $R_{effv}$ of 3, 5 and 7, indicated by rows. Vaccine uptake is fixed at 90%. For each subgraph there are three strategies (vulnerable, transmitters and untargeted), indicated by colours, and two age of vaccine cut-offs (5 years and 15 years), indicated by line type. Panel a shows coverage versus hospitalisations and panel b shows coverage versus deaths.
5. Sensitivity analysis

Owing to the relatively recent emergence and dominance of the Delta variant of SARS-CoV-2, several of the parameters used in our primary analysis remain considerably uncertain. Outcome sensitivity to the most central of these, the effective reproduction number in the absence of vaccination ($R_{eff_0}$), is explored in the main article; however, uncertainty in the remaining model parameters may still have significant impacts on our results.

To encapsulate this uncertainty and explore their effect on each of our measured outcomes, we conducted a Monte-Carlo-type sensitivity analysis where 1,000 parameter combinations were drawn from the probability distributions described in Table 5 using Latin-Hypercube-Sampling. Given these parameter combinations, we then forward-simulated our model (i.e., solved the generalised final size equation) to calculate the cumulative number of infections, hospitalisations, deaths and years of life lost. The results of this analysis are presented in Figure A3. Note, for clarity, we also reproduce the first panel of Figure A3 (infections v. coverage) in Figure A4 using a discrete x-axis.

Table 5. Monte Carlo parameter distributions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Central estimate (95% CI) or (Range)</th>
<th>Monte Carlo distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>$f$</td>
<td>Relative infectiousness of asymptomatic individuals</td>
<td>0.25 (Range: 0.15, 1)</td>
<td>Triangular( Min = 0.15, Mode = 0.25, Max = 1 )</td>
</tr>
<tr>
<td>$V_e_{Pfizer}$</td>
<td>Clinical efficacy of Pfizer at preventing symptomatic COVID-19</td>
<td>0.880 (95% CI: 0.853, 0.901)</td>
<td>Triangular( Min = 0.853, Mode = 0.880, Max = 0.901 )</td>
</tr>
<tr>
<td>$V_e_{AstraZeneca}$</td>
<td>Clinical efficacy of AstraZeneca at preventing symptomatic COVID-19</td>
<td>0.670 (95% CI: 0.613, 0.718)</td>
<td>Triangular( Min = 0.613, Mode = 0.670, Max = 0.718 )</td>
</tr>
<tr>
<td>$O_R_{hospitalisation}$</td>
<td>Odds ratio of hospitalisation for Delta variant (relative non-VOCs)</td>
<td>2.08 (95% CI: 1.80, 2.38)</td>
<td>Triangular( Min = 1.80, Mode = 2.08, Max = 2.38 )</td>
</tr>
<tr>
<td>$O_R_{death}$</td>
<td>Odds ratio of death for Delta variant (relative non-VOCs)</td>
<td>2.32 (95% CI: 1.47, 3.30)</td>
<td>Triangular( Min = 1.47, Mode = 2.32, Max = 3.30 )</td>
</tr>
</tbody>
</table>

Note that overall vaccine efficacy $V_e$ is not a direct model input. Instead, we decompose this value into a component responsible for conferring protection against acquisition of infection ($V_a$), and the remainder into conferring protection against developing symptomatic disease given infection ($V_s$). The decomposition is conducted randomly using a uniform distribution to first assign the value of $V_a$ (which ranges from 0.25 times the overall vaccine efficacy up to the overall vaccine efficacy):
\[ V_a \sim U(0.25 \times V_e, V_e) \]

and then back-calculating \( V_s \) to preserve the overall vaccine efficacy \( V_e \): \[
V_s = 1 - \frac{1 - V_e}{1 - V_a}
\]

**a. Coverage versus infections**

![Graph showing coverage versus infections for Pfizer, AstraZeneca, and Mixed vaccination strategies with different target coverages.]

**b. Coverage versus hospitalisations**

![Graph showing coverage versus hospitalisations for Pfizer, AstraZeneca, and Mixed vaccination strategies with different target coverages.]

- Strategy: Unvaccinated, Vulnerable, Transmitters.
c. **Coverage versus deaths**

![Figure A3](image)

**Figure A3.** Sensitivity analysis for model predictions for the impact of different vaccine programs: Pfizer, AstraZeneca or Mixed, indicated by column. Each is considered for values of $R_{eff}$ of 3, 5 and 7, indicated by rows. Vaccine uptake is fixed at 90% and eligibility age at 15. For each subgraph there are three strategies (vulnerable, transmitters and untargeted), indicated by colours. Panel a shows coverage versus infections; panel b shows coverage versus hospitalisations; panel c shows coverage versus deaths; and panel d shows coverage versus years of life lost. The central line in each subpanel for each vaccination strategy gives the median outcome estimate across the range of sampled parameters, whilst the upper and lower limits of each ribbon give the 95% central confidence interval.
Figure A4. Reproduction of Figure A3, panel a using a discrete coverage lattice. Sensitivity analysis for model predictions for the impact of different vaccine programs: Pfizer, AstraZeneca or Mixed, indicated by column. Each is considered for values of $R_{eff}$ of 3, 5 and 7, indicated by rows. Vaccine uptake is fixed at 90% and eligibility age at 15. For each subgraph there are three strategies (vulnerable, transmitters and untargeted), indicated by colours.

Incorporating uncertainty into the parameters described in Table 5, we find an apparent increase in the overlap between the performance of each of the three vaccination strategies (untargeted, vulnerable and transmitters) across the different outcomes; however, we emphasise that the ranking described in the main article is largely preserved for fixed parameter values (e.g., equal vaccine efficacy, relative infectiousness). Notably, the range of predicted values can vary considerably for certain outcomes when parameter uncertainty is included; however, our conclusions regarding the predicted capacity for vaccination to achieve herd immunity remain robust. That is, across the parameter ranges considered, herd immunity remains unachievable for $R_{eff} \geq 5$ whilst vaccine eligibility is constrained to those over 15 years of age (which is the case for all panels in Figure A3.)
5.1 Contact matrix

In a sensitivity analysis, we used an alternative approach to generate the age-specific contact rates $c_{ij}$. These rates were obtained by extrapolating the contact rates estimated for the United Kingdom (UK), where a contact survey was conducted in 2005-2006 (13). We used the R package socialmixr (v 0.1.8) to extract the UK age-specific contact rates ($c_{ij}^{POLYMOD}$) emerging from the contact survey. We then applied age-specific adjustments to account for age distribution differences between Australia and the UK, such that

$$c_{ij} = c_{ij}^{POLYMOD} \times \frac{\pi_j^{AUS}}{\pi_j^{UK}},$$

where $\pi_j^{AUS}$ and $\pi_j^{UK}$ are the proportion of the population aged $j$ in Australia and the UK, respectively. The results are shown in Figure A5.

---

**a. Coverage versus infections**

---

**b. Coverage versus hospitalisations**
c. **Coverage versus deaths**

![Figure A5](image)

Contact sensitivity analysis for model predictions for the impact of different vaccine programs: Pfizer, AstraZeneca or Mixed, indicated by column. Each is considered for values of $R_{eff}v$ of 3, 5 and 7, indicated by rows. Vaccine uptake is fixed at 90% and eligibility age at 15. For each subgraph there are three strategies (vulnerable, transmitters and untargeted), indicated by colours.

Panel a shows coverage versus infections; panel b shows coverage versus hospitalisations; panel c shows coverage versus deaths; and panel d shows coverage versus years of life lost. The central line in each subpanel for each vaccination strategy gives the median outcome estimate across the range of sampled parameters, whilst the upper and lower limits of each ribbon give the 95% central confidence interval.

**Figure A5.** Contact sensitivity analysis for model predictions for the impact of different vaccine programs: Pfizer, AstraZeneca or Mixed, indicated by column. Each is considered for values of $R_{eff}v$ of 3, 5 and 7, indicated by rows. Vaccine uptake is fixed at 90% and eligibility age at 15. For each subgraph there are three strategies (vulnerable, transmitters and untargeted), indicated by colours. Panel a shows coverage versus infections; panel b shows coverage versus hospitalisations; panel c shows coverage versus deaths; and panel d shows coverage versus years of life lost. The central line in each subpanel for each vaccination strategy gives the median outcome estimate across the range of sampled parameters, whilst the upper and lower limits of each ribbon give the 95% central confidence interval.
References