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# Supporting Information

## Supplementary results

**This appendix was part of the submitted manuscript and has been peer reviewed. It is posted as supplied by the authors.**

Appendix to: McBryde ES, Meehan MT, Caldwell JM, et al. Modelling direct and herd protection effects of vaccination against the SARS-CoV-2 Delta variant in Australia. *Med J Aust* 2021; doi: 10.5694/mja2.51263.

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

## 1 Non-technical explanation of methods

We build a 16 x 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 16 x 16 and based on 5-year age groups, Figure 1, 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 1, right panel. It can be seen that the highest transmitters are in the 15 to 50 year old groups.

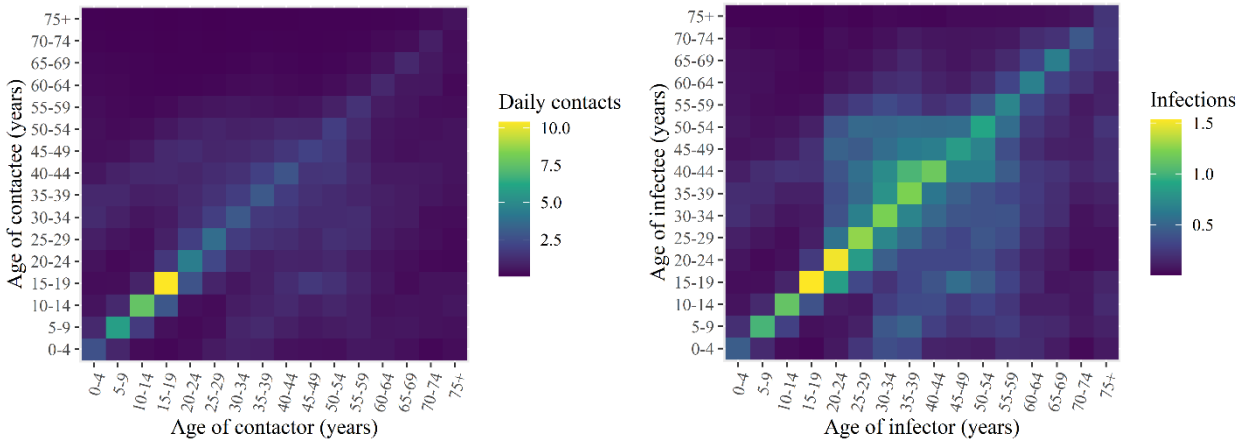



Figure 1. Left panel provides the age specific contact matrix for Australia, based on data from Prem *et al.* (2021). Right panel provides the next generation matrix further modified for infectiousness susceptibility, duration of infection and scaling constant.

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 $a \in \{0-4, 5-9, 10-14, \ldots, 70-74, 75+\}$ and assume that individuals in age group $a$ possess a relative susceptibility to infection $u_a$. Once infected, an age-dependent fraction $y_a$ go on to develop symptomatic (i.e., clinical) disease whilst the remaining $1-y_a$ 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 $a$ makes $c_{aa'}$ contacts with individuals in age group $a'$ leading to the following expression for the (unscaled) next-generation matrix (NGM) (Diekmann et al. 2010 (8)):

$$\overline{K}^u{}_{aa'} = \frac{u_a S_a c_{aa'}}{N_{a'}}[y_{a'} + (1-y_{a'})f]\tau$$

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

The $(a, a')$th entry of the 16 × 16 NGM $\overline{K}^u$ is proportional to the average number of new infections in age group $a$ generated by an individual in age group $a'$ 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, $R_{\mathrm{eff}_{\bar{v}}}$, which is proportional to the maximal eigenvalue, or spectral radius of $\overline{K}^u$ (or $\rho(\overline{K}^u)$), can be expressed as

$$R_{\mathrm{eff}_{\bar{v}}} = \eta\rho(\overline{K}^u) \quad \Rightarrow \quad \eta = \frac{R_{\mathrm{eff}_{\bar{v}}}}{\rho(\overline{K}^u)}$$

Incorporating this definition of $\eta$ along with the possibility of pre-existing immunity $p_a$ the next-generation matrix $K^u$ is given by

$$K^u{}_{aa'} = \eta \cdot \frac{u_a S_a c_{aa'}}{N_{a'}}[y_{a'} + (1-y_{a'})f]\tau.$$

For a given $R_{\mathrm{eff}_{\bar{v}}}$ we use the expression given above to calculate the scaling factor $\eta$ in terms of $R_{\mathrm{eff}_{\bar{v}}}$ and $\rho(\overline{K}^u)$. Daily, age-specific contact rates $c_{aa'}$ 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 $1-Va$), a reduced risk of symptomatic disease (by a factor $1-Vs$), a reduced risk of hospitalisation or death (by a factor $1-Vm$) and are potentially less infectious (by a factor $1-Vt$). Each of these factors is dependent on the combination of SARS-CoV-2 strain and vaccine. If a proportion $v_a$ of individuals in age group $a$ are vaccinated, then the modified 16 × 16 next-generation matrix in the presence of vaccination is given by

$$K^{\mathrm{vac}}{}_{aa'} = \eta \cdot \frac{u_a S_a c_{aa'}}{N_{a'}} \{[y_{a'} + (1 - y_{a'})f](1 - v_{a'}) + [(1 - Vs)y_{a'} + (1 - (1 - Vs)y_{a'})f](1 - Vt)(1 - Va)v_{a'}\}\tau.$$

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 × 32) next-generation matrix $\widetilde{K}$, which can be expressed as the matrix product:

$$\widetilde{K} = \begin{bmatrix} 1 - v \\ (1 - Va)v \end{bmatrix} [K^u \quad K^v]$$

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

$$K^v_{ij} = \eta \cdot \frac{u_i S_i c_{ij}}{N_j} \left[\left(1 - Vs \cdot v_j\right)y_j + \left(1 - \left(1 - Vs \cdot v_j\right)y_j\right)f\right]\left(1 - Vt \cdot v_j\right)\tau.$$

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)):

$$1 - \tilde{z}_i = \exp\left[-\widetilde{N}_i^{-1} \sum_j \widetilde{K}_{ij} \widetilde{N}_j \tilde{z}_j\right]$$

where $\tilde{z}_i$ is the fraction of individuals in group $i$ that become infected throughout the epidemic, $\widetilde{N}_i$ is the population size of group $i$ and $\widetilde{K}_{ij}$ is the extended next-generation matrix defined in the previous section. Note that here we use the extended (32 × 32) next-generation matrix $\widetilde{K}_{ij}$ 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 $\widetilde{N} = ((1 - v_a)N_a, v_a N_a)$ 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:

$$\begin{aligned} D &= \text{Unvaccinated deaths} + \text{Vaccinated deaths} \\ &= \sum_{a \in \{0-4,\ldots,75+\}} d_a z_a^u (1 - v_a)(1 - p_a)S_a + \sum_{a \in \{0-4,\ldots,75+\}} d_a z_a^v (1 - Vm)(1 - Vs)v_a(1 - p_a)S_a \\ &= \sum_{a \in \{0-4,\ldots,75+\}} d_a [z_a^u (1 - v_a) + z_a^v (1 - Vm)(1 - Vs)v_a](1 - p_a)S_a \end{aligned}$$

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

$$\begin{aligned} H &= \text{Unvaccinated hospitalisations} + \text{Vaccinated hospitalisations} \\ &= \sum_{a\in\{0-4,\ldots,75+\}} h_a[z_a^u(1-v_a) + z_a^v(1-Vm)(1-Vs)v_a](1-p_a)S_a \end{aligned}$$

where $h_a$ is the age-specific hospitalisation rate.

## 3. Parameter values

Table 1. Model parameters.

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

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.

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

*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)).

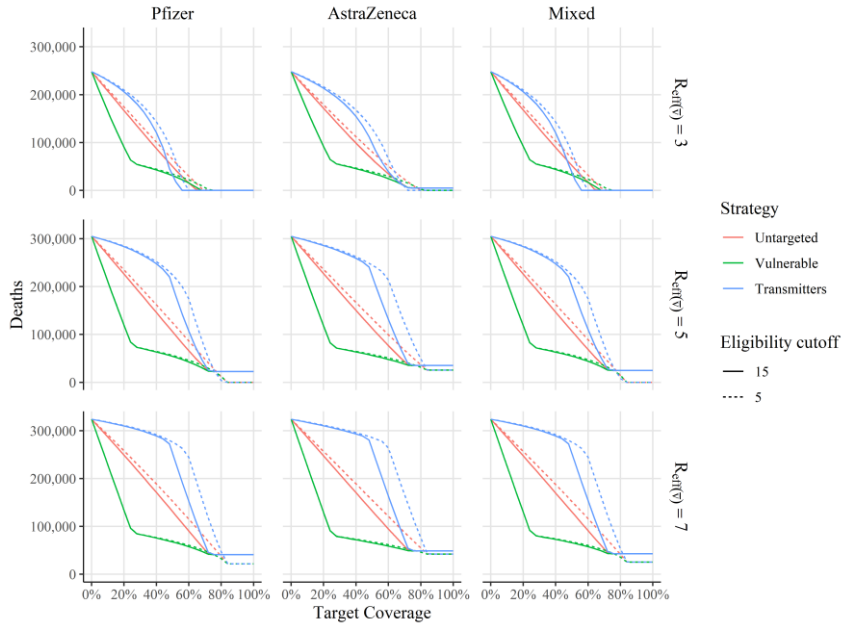
| Outcome | Odds ratio (95% CI) |
|---|---|
| Hospitalisation | 2.08 (1.80, 2.38) |
| Death | 2.32 (1.47, 3.30) |

Table 4. Vaccine efficacy.

| Vaccine | Clinical trial efficacy ($Ve$) (95% CI) | Efficacy against acquisition ($Va$) | Efficacy against symptomatic disease ($Vs$) | Efficacy against transmission ($Vt$) | Efficacy against severe disease given symptomatic disease ($Vm$) |
|---|---|---|---|---|---|
| BNT162b2 (Pfizer) | 0.880 (0.853, 0.901) | 0.76 | 0.5 | 0.5 | 0.5 |
| ChAdOx1 (AstraZeneca) | 0.670 (0.613, 0.718) | 0.48 | 0.37 | 0.5 | 0.8 |

# 4. Hospitalisation and deaths

## *a. Coverage versus hospitalisations*




## *b. Coverage versus deaths*

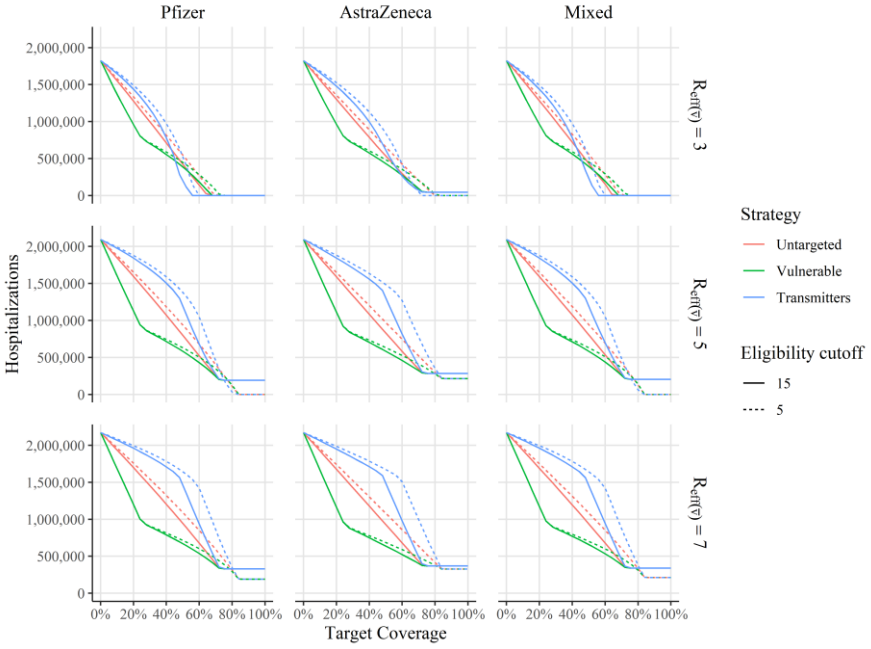



*Figure 2.* Model predictions for the impact of different vaccine programs: Pfizer, AstraZeneca or Mixed, indicated by column. Each is considered for values of $R_{\text{eff}_{\bar{v}}}$ of 3, 5 and 7, indicated by rows. Vaccine uptake is fixed at 90%. For each subgraph there are three strategies (vulnerable, 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 ($R_{\text{eff}_{\bar{v}}}$), 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 3. Note, for clarity, we also reproduce the first panel of Figure 3 (infections v. coverage) in Figure 4 using a discrete x-axis.

Table 5. Monte Carlo parameter distributions

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

Note that overall vaccine efficacy $Ve$ is not a direct model input. Instead, we decompose this value into a component responsible for conferring protection against acquisition of infection ($Va$), and the remainder into conferring protection against developing symptomatic disease given infection ($Vs$).

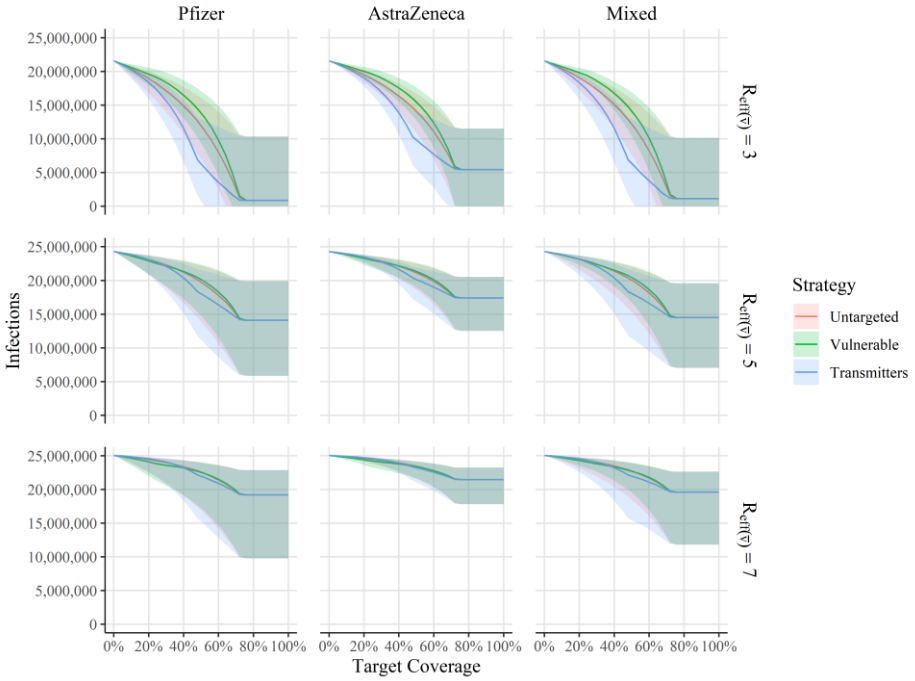
The decomposition is conducted randomly using a uniform distribution to first assign the value of $Va$ (which ranges from 0.25 times the overall vaccine efficacy up to the overall vaccine efficacy):

$$Va \sim U(0.25 \times Ve, Ve)$$

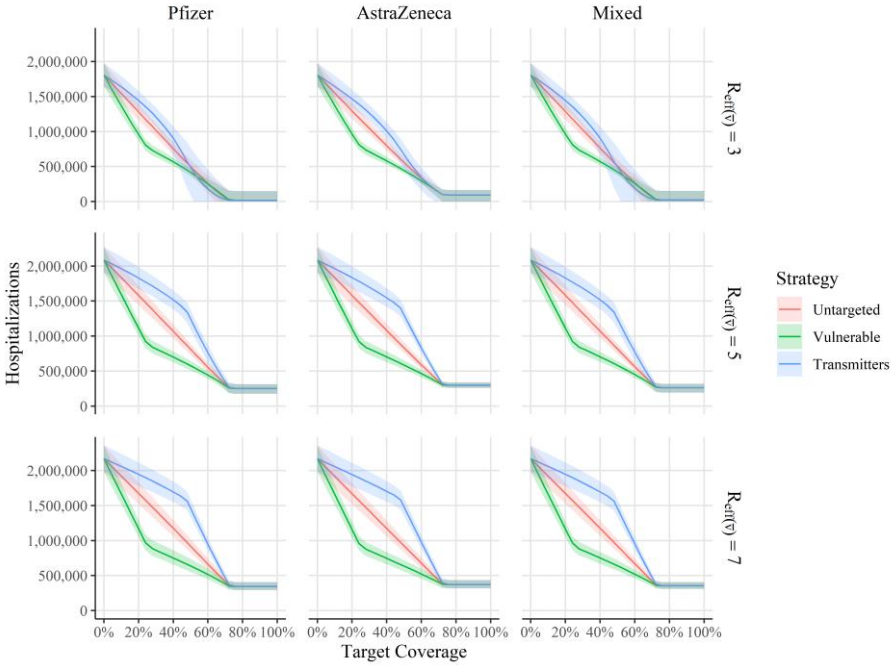
and then back-calculating $Vs$ to preserve the overall vaccine efficacy $Ve$:

$$Vs = 1 - \frac{1 - Ve}{1 - Va}.$$

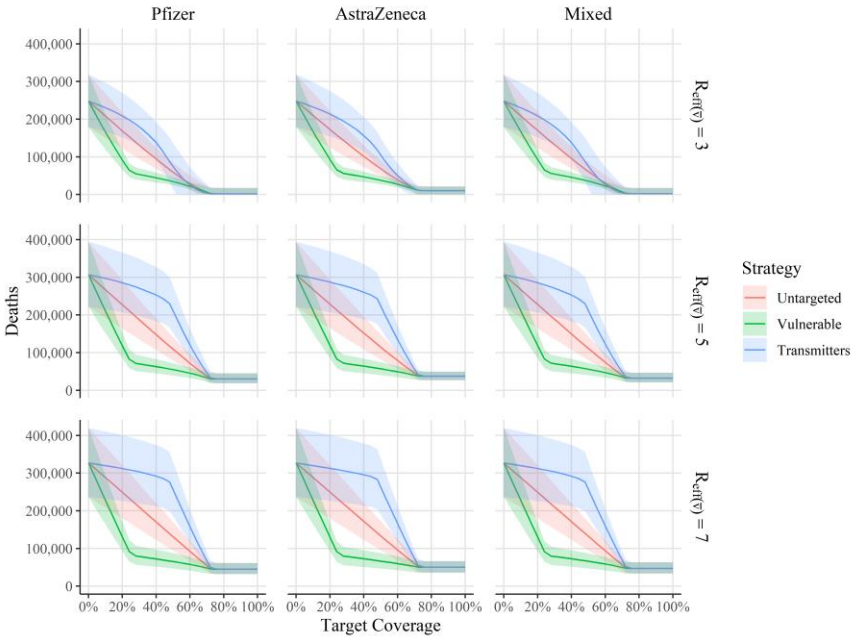
### *a. Coverage versus infections*




### *b. Coverage versus hospitalisations*



### c. *Coverage versus deaths*




### d. *Coverage versus years of life lost*

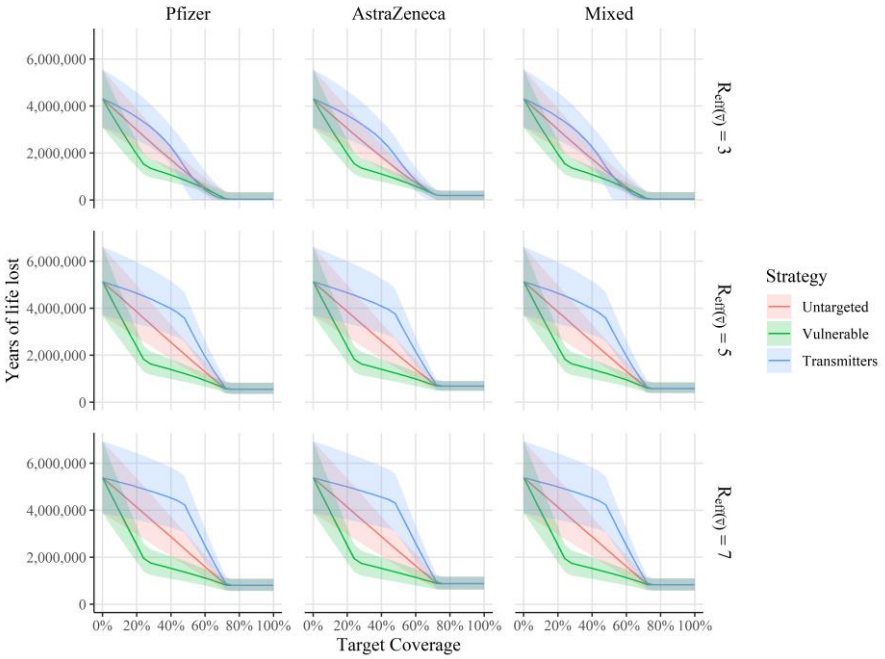



*Figure 3.* Sensitivity analysis for model predictions for the impact of different vaccine programs: Pfizer, AstraZeneca or Mixed, indicated by column. Each is considered for values of $R_{\text{eff}_{\overline{\nu}}}$ of 3, 5 and 7, indicated by rows. Vaccine uptake is fixed at 90% and eligibility age 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.

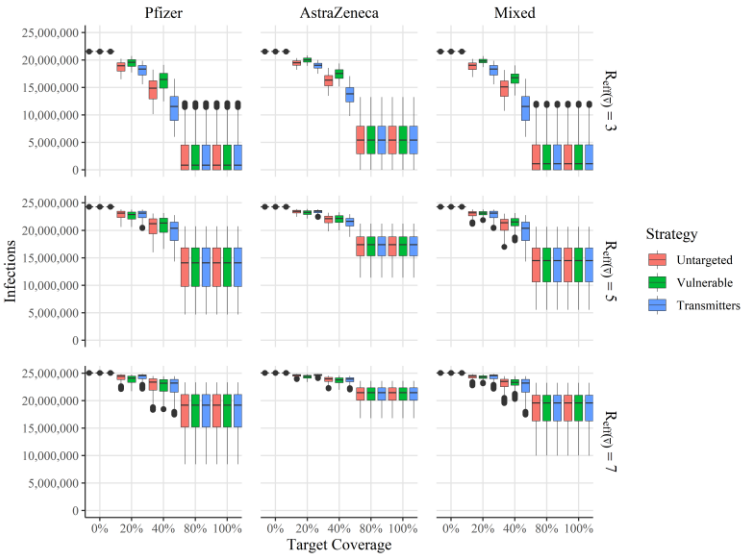



*Figure 4.* Reproduction of Figure 3, panel a using a discrete coverage lattice. Sensitivity analysis for model predictions for the impact of different vaccine programs: Pfizer, AstraZeneca or Mixed, indicated by column. Each is considered for values of $R_{\text{eff}_{\bar{\nu}}}$ of 3, 5 and 7, indicated 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 $R_{\text{eff}_{\bar{\nu}}} \geq 5$ whilst vaccine eligibility is constrained to those over 15 years of age (which is the case for all panels in Figure 3.)

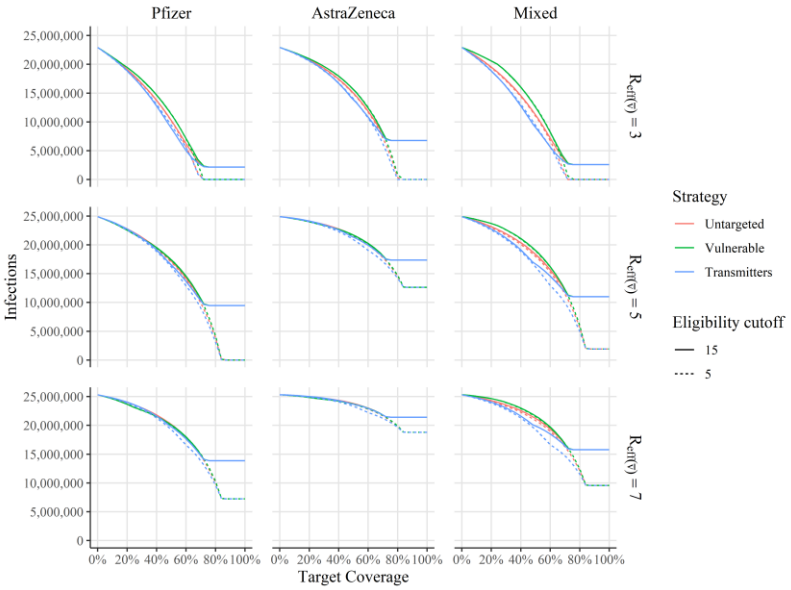
## 5.1 Contact matrix

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 ($c_{ij}^{\mathrm{POLYMOD}}$) emerging from the contact survey. We then applied age-specific adjustments to account for age distribution differences between Australia and the UK, such that

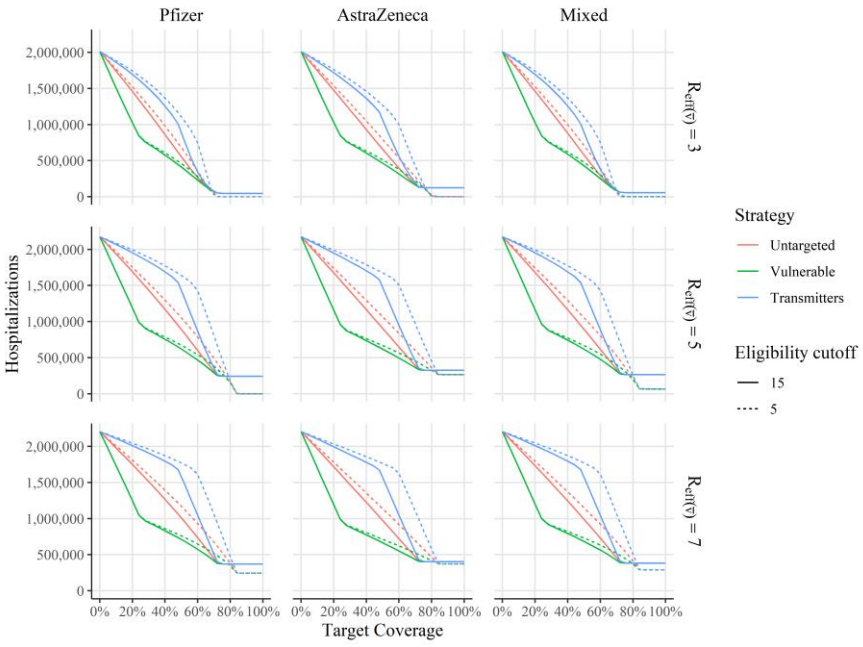
$$c_{ij} = c_{ij}^{\mathrm{POLYMOD}} \times \frac{\pi_j^{\mathrm{AUS}}}{\pi_j^{\mathrm{UK}}},$$

where $\pi_j^{\mathrm{AUS}}$ and $\pi_j^{\mathrm{UK}}$ are the proportion of the population aged $j$ in Australia and the UK, respectively. The results are shown in Figure 5.

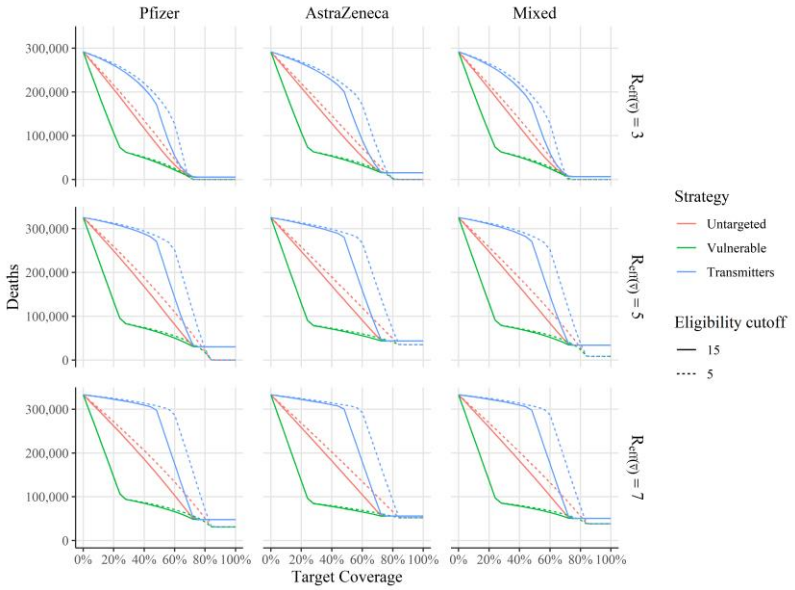
### *a. Coverage versus infections*




### *b. Coverage versus hospitalisations*



### c. *Coverage versus deaths*




### d. *Coverage versus years of life lost*

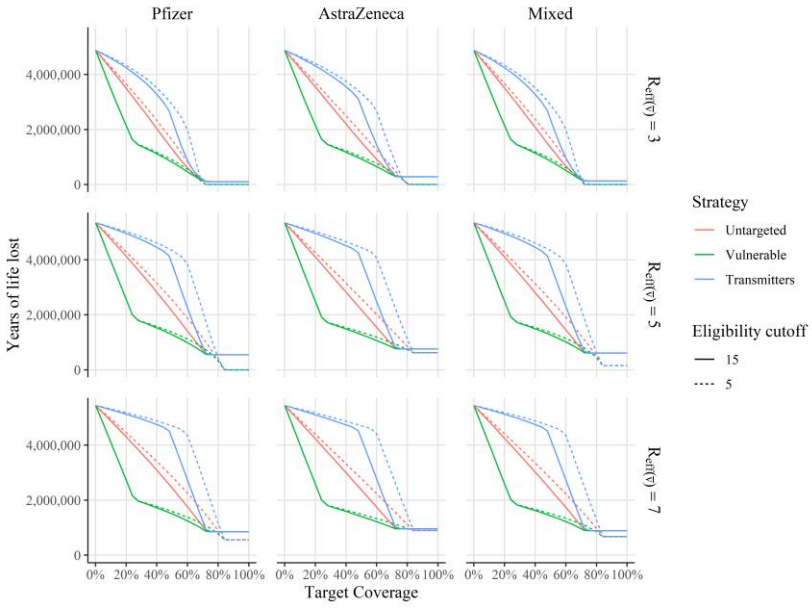



*Figure 5.* Contact sensitivity analysis for model predictions for the impact of different vaccine programs: Pfizer, AstraZeneca or Mixed, indicated by column. Each is considered for values of $R_{\text{eff}_{\bar{v}}}$ of 3, 5 and 7, indicated by rows. Vaccine uptake is fixed at 90% and eligibility 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


1. Prem K, Zandvoort KV, Klepac P, et al; Centre for the Mathematical Modelling of Infectious Diseases COVID-19 Working Group. Projecting contact matrices in 177 geographical regions: an update and comparison with empirical data for the COVID-19 era. PLoS Comput Biol 2021; 17: e1009098.

2. Davies NG, Klepac P, Liu Y, et al. Age-dependent effects in the transmission and control of COVID-19 epidemics. Nat Med 2020; 26: 1205-1211.

3. Buitrago-Garcia D, Egli-Gany D, Counotte MJ, et al. Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: a living systematic review and meta-analysis. PLoS Med 2020; 17: e1003346.

4. Nakajo K, Nishiura H. Transmissibility of asymptomatic COVID-19: data from Japanese clusters. Int J Infect Dis 2021; 105: 236-238.

5. Qiu X, Nergiz AI, Maraolo AE, et al. Defining the role of asymptomatic and pre-symptomatic SARS-CoV-2 transmission: a living systematic review. Clin Microbiol Infect 2021; 27: 511-519.

6. Sayampanathan AA, Heng CS, Pin PH, et al. Infectivity of asymptomatic versus symptomatic COVID-19. Lancet 2021; 397: 93-94.

7. Yan D, Zhang X, Chen C, et al. Characteristics of viral shedding time in SARS-CoV-2 infections: a systematic review and meta-analysis. Front Public Health 2021; 9: 209.

8. Diekmann O, Heesterbeek JA, Roberts MG. The construction of next-generation matrices for compartmental epidemic models. J R Soc Interface 2010; 7: 873-885.

9. Andreasen V. The final size of an epidemic and its relation to the basic reproduction number. Bull Math Biol 2011; 73: 2305-2321.

10. O'Driscoll M, Ribeiro Dos Santos G, Wang L, et al. Age-specific mortality and immunity patterns of SARS-CoV-2. Nature 2021; 590: 140-145.

11. Fisman DN, Tuite AR. Progressive increase in virulence of novel SARS-CoV-2 variants in Ontario, Canada [preprint], version 3. medRxiv 2021.07.05.21260050; 4 Aug 2021. doi: https://doi.org/10.1101/2021.07.05.21260050 (viewed Aug 2021).

12. Australian Bureau of Statistics. Deaths in Australia. Updated 25 June 2021. https://www.aihw.gov.au/reports/life-expectancy-death/deaths-in-australia/contents/life-expectancy (viewed Aug 2021).

13. Mossong J, Hens N, Jit M, Beutels P, Auranen K, Mikolajczyk R, et al. Social contacts and mixing patterns relevant to the spread of infectious diseases. PLoS Med 2008; 5: e74.