

## Attachment F: Influential revisions to parameter assumptions used in Doherty Modelling

### Summary

Between the previous and current phases of our modelling work we have extensively reviewed available evidence regarding age-dependent mixing and susceptibility to the Delta variant, vaccine uptake, and vaccine effectiveness assumptions against acquisition, infectiousness and disease outcomes.

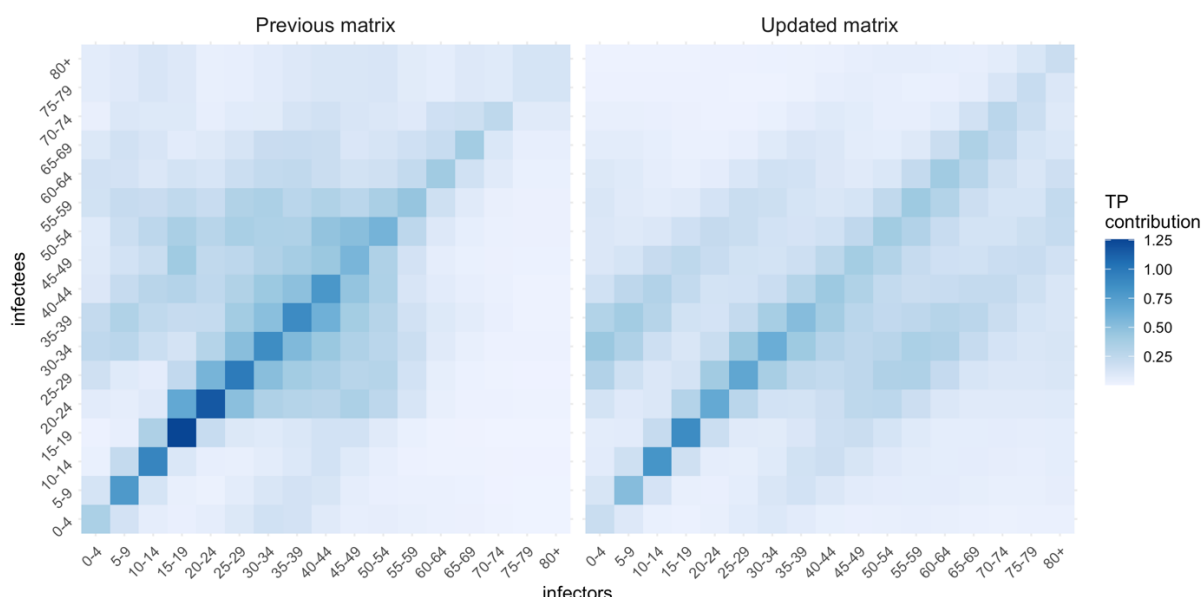
While values of individual parameters vary between phases of our work, we have assessed the consequences of these changes in aggregate and confirm that our previous recommendations of vaccine coverage thresholds of 70% and 80% for national plan transition phases remain robust.

### Social Mixing Assumptions

In the first phase of our National Plan modelling, we developed an age-structured transmission matrix characterising infection spread within and between age groups based on population mixing assumptions using widely accepted social contact matrices published by Prem et al [1]. The matrix (left panel, Figure 1) was extended to include an 80+ years cohort and weighted using age-specific susceptibility and transmissibility estimates from Davies et al [2].

For this phase of work we have updated the social mixing assumptions from the Prem paper to align more closely with reported observations in the Australian context. In this process we have identified errors in the original work by Prem, including an apparent overestimation of workplace contacts in Australia. The relative probability of transmission between household and non-household contact settings was also re-estimated and included in the transmission matrix resulting in an upweighting of household contacts.

**Figure 1: Age based transmission matrices used in previous work (left) based on assumptions of the Prem [1] and Davies [2] papers, and updated (right) to incorporate emerging evidence on age-based mixing (Australia) and the relative susceptibility of individuals aged <16 years (England)**



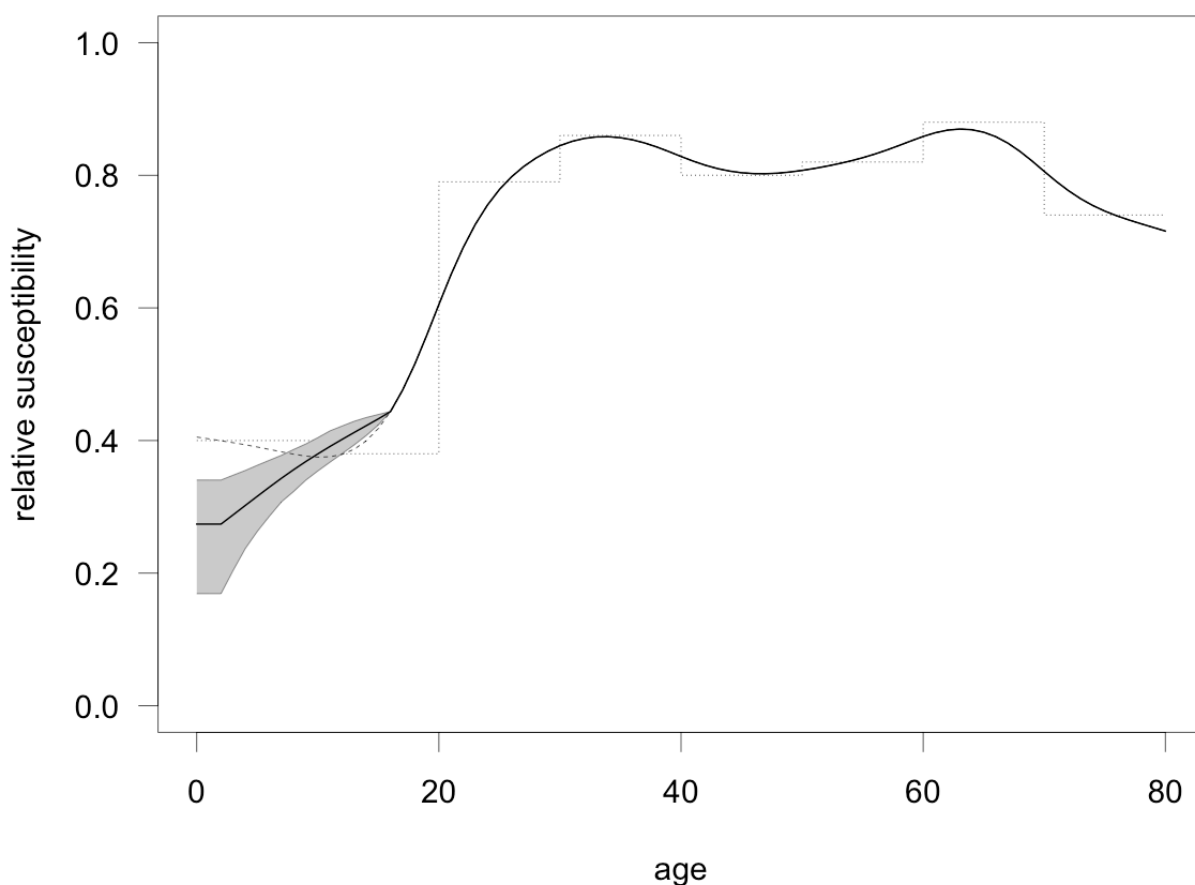
We have re-estimated transmission parameters to fit infection age distributions from the UK post-reopening and with full school attendance since the beginning of September. There has been very limited vaccination of the 12-15 years cohort in the UK, with current first dose coverage approximately 15%

compared with ~60% in Australia. The UK also has a nationwide infection survey that randomly screens 150,000 people each fortnight (approximately 0.2% of the population).

Given biases in acquisition of childhood infections due to the low symptomatic fraction, data on the age distribution of infections among under-16s in the UK is probably the best source of information on the relative susceptibility/infectiousness of the 5-11 cohort versus the 12-15 cohort, and therefore of the likely effectiveness of our 12+ (and hopefully imminent 5+) vaccination program on transmission with minimal restrictions. After a delay since schools reopened, prevalence in the 12-15 cohort in England has increased markedly to more than 8%, while in the 2-11 years group it has only increased from 2% to 3%<sup>1</sup>.

Figure 2 compares previous and revised estimates of relative susceptibility by age, based on these most recent observations.

**Figure 2: Relative susceptibility by age. New mean estimates are shown by the black line (grey region reflects 95% CIs), with previous estimates represented by dotted/dashed lines for comparison.**



As shown in the right panel of Figure 1, the net consequence of this reanalysis has been an overall reduction in the proportional contribution of children aged 5-11 years to transmission, and some increase in attribution to individuals aged 16-24 years.

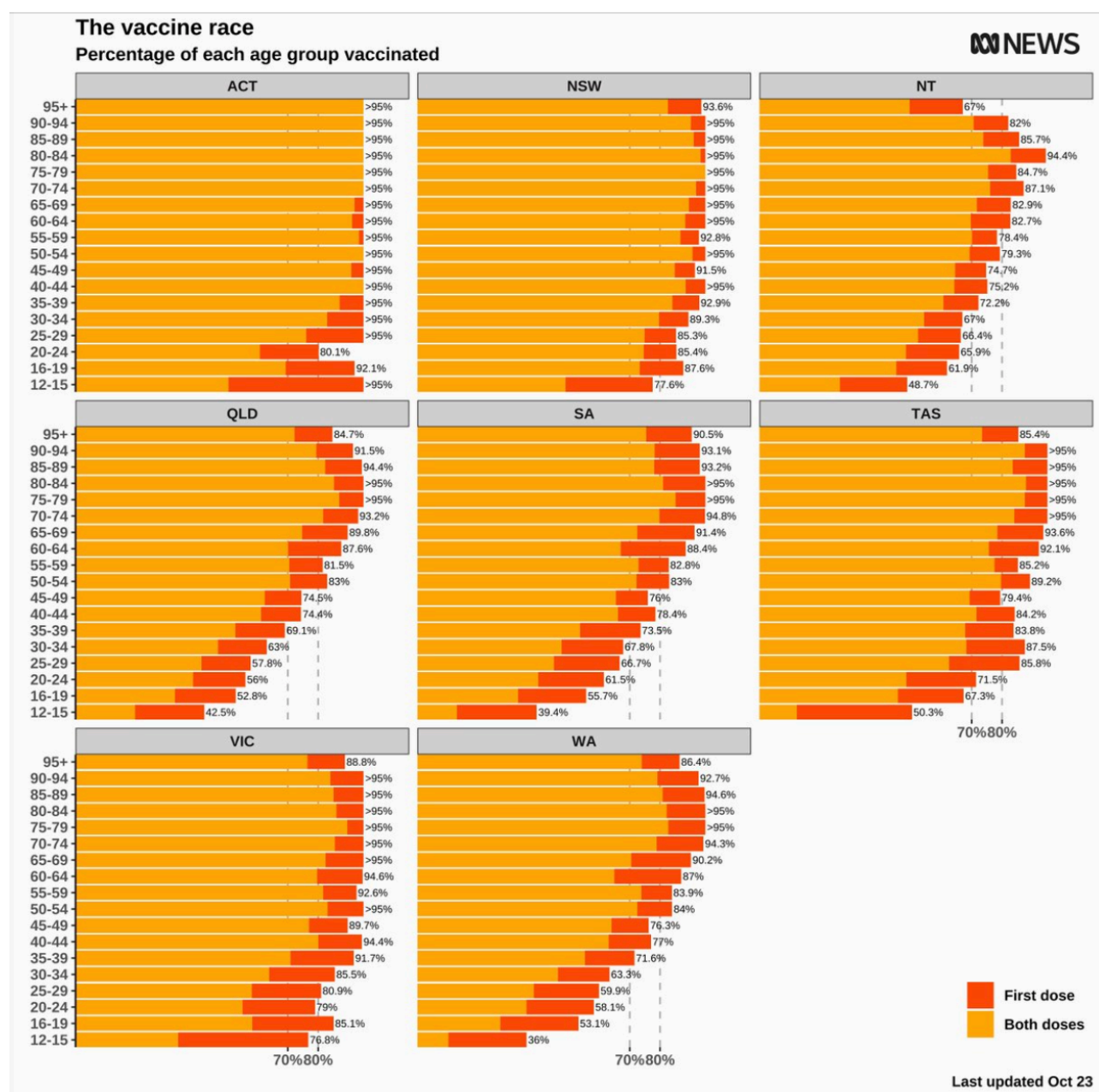
The new model enables extrapolation to any population within Australia. The main consequence of this change has been a more optimistic expectation of overall vaccine impact on transmission potential (TP) in populations with a high proportion of children than previously anticipated (countered in some populations by large household size), and a boost in TP reduction associated with vaccination of the 16-24 years group.

<sup>1</sup><https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/coronaviruscovid19infectionsurveys/pilot/15october2021#age-analysis-of-the-number-of-people-who-had-covid-19>.

## Vaccine coverage assumptions

Our initial coverage scenarios considered optimal age-based vaccine distribution strategies to minimise transmission and disease. The Quantum team in Health advise that the actual rollout in the Australian population has most closely approximated the ‘all ages’ strategy, which resulted in high uptake in the peak transmitting age groups identified above, maximising population wide benefits of the program. Extension of vaccine eligibility to the 12+ years group has further increased whole of population coverage (Figure 3). In addition, the pace of rollout has exceeded expectations, particularly in states with community transmission, enabling threshold targets of 70 and 80% to be reached earlier in some states than the dates anticipated in our earlier work, which were 1<sup>st</sup> and 22<sup>nd</sup> November respectively.

**Figure 3: Visualisation of one and two dose vaccine coverage by age and state, as of 23 October 2021**  
(source: <https://twitter.com/CaseyBriggs/status/1451771648412045315>)



Of note, it is anticipated that ‘final’ vaccine coverage in the order of 90% will be achieved within weeks of the 80% target, which is much faster than in the original simulations provided by Quantum. Should these expectations be realised, we anticipate greater constraint of transmission in the initial weeks following the transition to Phase C than was estimated by our model.

### *Vaccine effectiveness assumptions*

We have updated our assumptions of vaccine effectiveness (VE) against infection and onwards transmission, based on new evidence from the UK specific to the Delta variant. On balance, these changes have resulted in some reduction in overall effectiveness of the Astra Zeneca vaccine, but none for Pfizer which has been the predominant vaccine delivered through the program.

**Table 1A:** Vaccine effectiveness estimates (%) against overall (asymptomatic and symptomatic) infection of SARS-CoV-2 Delta variant based on **Shiek et al 2021** [3] (as per ATAGI July 2021 advice document).

Vaccine	Dose 1*			Dose 2†		
	Lower limit	Point estimate	Upper limit	Lower limit	Point estimate	Upper limit
AstraZeneca	9	<b>18</b>	25	53	<b>60</b>	66
Pfizer BNT	17	<b>30</b>	41	75	<b>79</b>	82

\*estimates in study for  $\geq 28$  days post dose 1 and pre dose 2

†estimates in study for  $\geq 14$  days post dose 2

**Table 1B:** Vaccine effectiveness estimates (%) against overall (asymptomatic and symptomatic) infection of SARS-CoV-2 Delta variant based on **Pouwels et al 2021** [4].

Vaccine	Dose 1*			Dose 2†		
	Lower limit	Point estimate	Upper limit	Lower limit	Point estimate	Upper limit
AstraZeneca	35	<b>46</b>	55	62	<b>67</b>	71
Pfizer BNT	50	<b>57</b>	63	77	<b>80</b>	83

\*estimates in study for  $\geq 21$  days post dose 1 and pre dose 2

†estimates in study for  $\geq 14$  days post dose 2

Pouwels et al's second dose estimates for the Delta variant broadly agree with Shiek et al's estimates. However, Pouwels et al's estimates are less likely to be biased by differential test-seeking behaviour according to vaccination status. They used data from the Office for National Statistics COVID-19 Infection Survey, a large community-based survey of individuals living in randomly selected households across the UK, where testing was performed according to a pre-determined schedule, irrespective of symptoms, vaccination status or prior infection.

Note that Eyre et al [6] also provide delta-specific estimates of VE against acquisition but caution against using these as overall estimates of VE since the study mostly captured symptomatic infections. Thus, the reduction in infection of vaccinated contacts in the study cannot account for the increased chance of asymptomatic infection in the vaccinated contacts (who are less likely to be detected based on the study design).

**ACTION TAKEN:** for acquisition VE parameters use values in Table 1B rather than Table 1A.

**Table 2A:** Vaccine effectiveness estimates (%) reasonable to use as against onward transmission to **household members (i.e., 100% household contacts)** in case of breakthrough infections in vaccine recipients for the **Alpha variant** based on **Harris et al 2021** [5] (as per ATAGI 2021 advice document).

Vaccine	Dose 1			Dose 2
	Lower limit	Point estimate	Upper limit	Point estimate
AstraZeneca	38	<b>48</b>	57	<b>65*</b>
Pfizer BNT	38	<b>46</b>	53	<b>65*</b>

*\*These estimates are an ATAGI expert view 3 May and 7 July 2021.*

**Table 2B:** Vaccine effectiveness estimates (%) against onward transmission to **contacts (70% household contacts)** in case of breakthrough infections in vaccine recipients for the **Alpha variant** based on **Eyre et al 2021** [6].

Vaccine	Dose 1*			Dose 2†		
	Lower limit	Point estimate	Upper limit	Lower limit	Point estimate	Upper limit
AstraZeneca	12	<b>18</b>	24	37	<b>63</b>	78
Pfizer BNT	20	<b>26</b>	30	71	<b>82</b>	88

*†estimates in study for ≥14 days post dose 2*

**Table 2C:** Vaccine effectiveness estimates (%) against onward transmission to **contacts (70% household contacts)** in case of breakthrough infections in vaccine recipients for the **Delta variant** based on **Eyre et al 2021** [6].

Vaccine	Dose 1*			Dose 2†		
	Lower limit	Point estimate	Upper limit	Lower limit	Point estimate	Upper limit
AstraZeneca	0	<b>2</b>	10	28	<b>36</b>	43
Pfizer BNT	6	<b>13</b>	19	52	<b>65</b>	74

*†estimates in study for ≥14 days post dose 2*

Both Harris et al and Eyre et al primarily capture symptomatic infections. For the values in Table 2C to be considered a VE against onward transmission, we need to assume that the fraction of infections in contacts that are symptomatic is independent of the vaccination status of the source case. This would seem reasonable from a virological and immunological perspective.

**ACTION TAKEN:** for breakthrough transmission VE parameters use values in Table 2C rather than Table 2A.

**Table 3A:** Combined vaccine effectiveness assumptions on transmission for the Delta variant based on **Sheik [3] and Harris [5]** (as per ATAGI July 2021 advice document).

Vaccine	Reduction in infection ( $E_i$ )	Reduction in onward transmission ( $E_t$ )	Calculated overall reduction in transmission*
AstraZeneca Dose 1	18%	48%	57%
AstraZeneca Dose 2	60%	65%	86%
Pfizer BNT Dose 1	30%	46%	62%
Pfizer BNT Dose 2	79%	65%	93%

\*Calculated overall reduction in transmission =  $1-(1-E_i)*(1-E_t)$

**Table 3B:** Combined vaccine effectiveness assumptions on transmission for the Delta variant based on **Pouwels [4] and Eyre [6]**.

Vaccine	Reduction in infection ( $E_i$ )	Reduction in onward transmission ( $E_t$ )	Calculated overall reduction in transmission*
AstraZeneca Dose 1	46%	2%	46%
AstraZeneca Dose 2	67%	36%	79%
Pfizer BNT Dose 1	57%	13%	63%
Pfizer BNT Dose 2	80%	65%	93%

\*Calculated overall reduction in transmission =  $1-(1-E_i)*(1-E_t)$

**ACTION TAKEN:** for combined VE parameters on transmission for the Delta variant use values in Table 3B rather than Table 3A.

Since completion of the first phase of the National Plan modelling, further evidence has emerged regarding vaccine effectiveness (VE) against clinical outcomes for the Delta variant.

**Table 4A:** Vaccine effectiveness estimates (% reduction) against symptomatic disease, hospitalisation, ICU admission and death for the Delta variant used in National Plan Modelling.

Vaccine	Symptomatic infection <sup>a</sup>	Hospitalisation <sup>b</sup>	ICU admission <sup>c</sup>	Mortality <sup>b</sup>
AstraZeneca Dose 1	33%	69%	69%	69%
AstraZeneca Dose 2	61%	86%	86%	90%
Pfizer BNT Dose 1	33%	71%	71%	71%
Pfizer BNT Dose 2	83%	87%	87%	92%

<sup>a</sup> Sheik et al [3]. Study reports VE against asymptomatic and symptomatic infection. We use their estimates of VE against *symptomatic* infection.

<sup>b</sup> London School of Hygiene and Tropical Medicine central estimates used for UK roadmap modelling on 9 June 2021 for Delta, see Table 3 [7]. These Delta VE assumptions are scaled from VE estimates for pre-existing and Alpha variants. The starting Alpha assumptions for *hospitalisation* and *second dose mortality* are based on a range of studies and are in line with Public Health England's (PHE) COVID-19 vaccine surveillance report for pre-Alpha and Alpha (week 22) [8]. The starting Alpha assumptions for *first dose mortality* are informed by findings from Dagan et al [9] and Lopez Bernal et al [10]. Note that these assumptions are consistent with PHE's week 31 report (5 August 2021). To obtain estimates for Delta, the Alpha VE assumptions for both hospitalisation and mortality were reduced by half of the relative reductions by dose and product estimated by Lopez Bernal et al for symptomatic infection [11] (see Table 2). See LSHTM roadmap report from 9 June for further details [7].

<sup>c</sup> Few studies report VE against ICU admission for either ancestral or Delta variants. One study conducted in India (Victor et al [12]) reports 95% and 94% reductions in ICU admission after dose 1 and dose 2 of AstraZeneca, respectively. The findings from this study are unlikely to be directly transferable to the Australian setting due to health system differences. In the absence of relevant data for our setting, we assume the same reductions in ICU admission given vaccination as for hospitalisation.

**Table 4B:** Vaccine effectiveness estimates (% reduction) against symptomatic disease, hospitalisation, ICU admission and death for the Delta variant updated according to studies published since National Plan Modelling work.

Vaccine	Time post dose	Symptomatic infection <sup>a</sup>	Hospitalisation <sup>b</sup>	ICU admission <sup>c</sup>	Mortality <sup>b</sup>
AstraZeneca Dose 1	≥28 days	40%	81%	81%	88%
AstraZeneca Dose 2	≥14 days	71%	93%	93%	93%
AstraZeneca Dose 2	≥20 weeks	-	77%	77%	79%
Pfizer BNT Dose 1	≥28 days	58%	92%	92%	89%
Pfizer BNT Dose 2	≥14 days	84%	97%	97%	95%
Pfizer BNT Dose 2	≥20 weeks	-	93%	93%	90%

<sup>a</sup> Pouwels et al [4]. Study reports VE against asymptomatic and symptomatic infection. We use their estimates of VE against *symptomatic* infection.

<sup>b</sup> Andrews et al [13]. Estimates in study are for ≥28 days post dose 1 and ≥14 days post dose 2 with ≥20 weeks post dose 2 in parentheses following the primary immunisation course.

<sup>c</sup> Few studies report VE against ICU admission for either ancestral or Delta variants. One study conducted in India (Victor et al [12]) reports 95% and 94% reductions in ICU admission after dose 1 and dose 2 of AstraZeneca, respectively. The findings from this study are unlikely to be directly transferable to the Australian setting due to health system differences. In the absence of relevant data for our setting, we assume the same reductions in ICU admission given vaccination as for hospitalisation.

**ACTION TAKEN:** for clinical outcomes VE parameters use values in Table 4B rather than Table 4A and ≥ 20 weeks post dose 2 estimates for VEs against hospitalisation, ICU admission and mortality.

**Table 5. Disease severity assumptions for *unvaccinated individuals***

Parameter	Description	Source	Value(s)	
Wildtype severity parameters				
Pr(symptoms   wt)	Probability of symptomatic disease given wildtype infection	Davies et al. Nature Medicine (2020) [2]  Clinical fractions estimated for 10-year age groups.	Age group	Symptomatic fraction
			0-9	0.28
			10-19	0.20
			20-29	0.26
			30-39	0.33
			40-49	0.40
			50-59	0.49
			60-69	0.63
			70+	0.69
Pr(hosp   symptoms)	Probability of hospital admission given symptomatic wildtype infection	Knock et al. Pre-print [14]. Prepared for UK roadmap modelling by Imperial group. UK data first wave.	Age-specific.  See Tables S6 and S8 of Knock et al.	
Pr(ICU   hosp)	Probability of ICU admission given hospital admission	Same as above.	Same as above.	
Pr(death   ward)	Probability of death for ward patients (no ICU stay)	Same as above.	Same as above.	
Pr(death   ICU)	Probability of death for ICU patients	Same as above.	Same as above.	
Pr(death   post-ICU ward)	Probability of death for post-ICU patients	Same as above.	Same as above.	

Alpha severity parameters (versus wildtype)			
Pr(symptoms   alpha)	Probability of symptomatic disease given Alpha infection	A number of studies using UK data suggest that the probability of reporting symptoms is consistent for wildtype and Alpha  Walker et al. Pre-print [15].  Graham et al. Lancet Public Health (2021) [16].	RR=1
Pr(hosp   alpha)	Probability of hospitalisation given Alpha infection	Bager et al. Lancet Infect Dis (2021) [17]. Denmark data.	OR=1.42
Pr(ICU   alpha)	Probability of ICU admission given Alpha infection	Patone et al. Lancet ID [18]. UK data.	HR=2.15
Pr(death   alpha)	Probability of death given Alpha infection	Davies et al. Nature (2021) [19]. UK data.	HR=1.61
Delta severity parameters (versus Alpha)			
Pr(hosp   delta)	Probability of hospitalisation given Delta infection	Bager et al. Lancet ID (2021) [20]. Denmark data.	RR = 3.01
Delta severity parameters (versus wildtype)			
Pr(hosp   delta)		Fisman & Tuite. Pre-print [21]. Canada data.	*OR = 2.08
Pr(ICU   delta)	Probability of ICU admission given Delta infection	Fisman & Tuite. Pre-print [21]. Canada data.	*OR = 3.35
Pr(death   delta)	Probability of death given Delta infection	Fisman & Tuite. Pre-print [21]. Canada data.	*OR = 2.33

\*Note that for Pr(hosp | delta), Pr(ICU | delta) and Pr(death | delta) is direct estimate of Delta versus wildtype (rather than Alpha).

**ACTION TAKEN:** Incorporate delta severity parameters into overall estimates of disease severity.

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