

# Age-targeted dose allocation can halve COVID-19 vaccine requirements

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## ABSTRACT

In anticipation of COVID-19 vaccine deployment, we use an age-structured mathematical model to investigate the benefits of optimizing age-specific dose allocation to suppress SARS-CoV-2 transmission. Across 179 countries, we find that the highest priority individuals are typically those between 30 and 59 years of age because of their high contact rates and higher risk of infection and disease. We reaffirm that vaccination alone may be insufficient to achieve herd immunity in some settings, and that additional intervention measures may be required. Nevertheless, we show that optimizing the allocation of vaccine doses can more than double their effectiveness.

## Main

Assuming a safe and sufficiently effective vaccine is approved for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the infection that causes coronavirus disease 19 (COVID-19), it is critical that initial deployments are targeted not only at those at greatest risk of infection and disease, but those most responsible for ongoing transmission. At present, there are no treatments to protect against SARS-CoV-2 infection or symptomatic COVID-19 disease; however, there are at least 76 potential vaccine candidates under either clinical (five) or pre-clinical (71) investigation<sup>1,2</sup>.

SARS-CoV-2 is highly transmissible (basic reproduction number,  $R_0 = 2.68$ ; 95% credible interval: 2.47 - 2.86)<sup>4</sup> and notoriously difficult to contain. In contrast with SARS-CoV-1, transmission of SARS-CoV-2 is partly driven by asymptomatic and presymptomatic individuals<sup>5</sup>, with the former accounting for up to 30% of all infections by some estimates<sup>6</sup>. Such "silent transmission" severely complicates infection control as it limits both (i) the capacity of non-pharmaceutical interventions such as case isolation and contact tracing to identify carriers and contain the spread of infection; and (ii) the potential impact on transmission of vaccines that prevent symptomatic disease only, since asymptomatic individuals can remain highly infectious. Together, these highlight the need for a vaccine that disrupts transmission and helps reach the herd immunity threshold: where the immune fraction of the population yields an effective reproduction number,  $R_{\text{eff}} < 1$ .

In the absence of pre-existing immunity, the minimum population-level vaccination coverage required to achieve herd immunity (under the assumption of homogeneous mixing and susceptibility across the population) is  $(1 - 1/R_0)/e$ ; where the vaccine efficacy,  $e$ , is included because even the most effective vaccines only confer partial protection — particularly amongst the elderly. Given an  $R_0$  of 2.68, SARS-CoV-2 herd immunity thresholds can be estimated at between 60 and 70%, which equates to approximately 90% population-wide vaccination coverage for a vaccine that is 70% effective. However, recent studies incorporating population heterogeneity have suggested that SARS-CoV-2 herd immunity thresholds may be considerably lower than naïve estimates<sup>7-10</sup>. This is due to the fact that young-to-middle-age groups have high contact rates combined with high infectiousness and susceptibility to infection. Removing these persons from the susceptible pool would therefore have disproportionate effects on the transmission potential. These observations are crucial for vaccination strategies, as they imply that the age-specific characteristics of both social mixing and SARS-CoV-2 infection could be leveraged to increase the efficiency of vaccine campaigns.

In this study we use an age-stratified SARS-CoV-2 transmission model — which incorporates age-dependent susceptibility and disease severity calibrated to COVID-19 patient data<sup>11</sup> — to estimate the age-specific transmission rates among infected individuals in 179 countries. We then use the candidate vaccine profiles developed by the World Health Organization<sup>12</sup> to

41 identify the optimal age-specific allocation of vaccine doses to limit SARS-CoV-2 transmission by: 1) minimizing the effective  
42 reproduction number,  $R_{\text{eff}}$ , for a fixed number of available vaccine doses (categorized according to the fraction of the population  
43 that could receive a full vaccination course, i.e., the population-level coverage); and 2) minimizing the number of doses required  
44 to suppress transmission and achieve elimination ( $R_{\text{eff}} < 1$ ).

45 We also consider two separate modes of action for vaccine candidates: those that reduce the recipient's susceptibility to  
46 infection; and those that protect against symptomatic disease in persons who become infected. In each case vaccine doses are  
47 allocated independently among individuals divided into 10-year age bands from 0 – 9 up to 70+ years of age.

48 At baseline, we assume that the vaccine is 70% effective<sup>12</sup> across all age groups and that both individual susceptibility  
49 and risk of symptomatic disease are age dependent (see Methods). Variations to these assumptions are investigated through  
50 sensitivity analysis (Supplement).

51 To demonstrate the breadth of optimal solutions that can be obtained across different regions, we provide detailed results  
52 for India, China and the United Kingdom (UK), which span low- to high-income settings and exhibit diverse population  
53 demographic structures and contact networks — moreover, the latter two (China<sup>13</sup> and the UK<sup>14</sup>) have pre-COVID-19 contact  
54 survey data available. We also provide the global distribution of minimum vaccination coverage required to achieve herd  
55 immunity. Detailed, age-specific breakdowns for the remaining 176 countries appear in the Supplement.

## 56 Results

### 57 Age-specific transmission rates

58 The different age distributions (Fig. 1A-C) and contact patterns in different countries drive highly heterogeneous transmission  
59 rates (Fig. 1D-F) among age groups and settings. Transmission in low- (e.g., India) and middle-income countries, which  
60 typically have bottom-heavy age pyramids, is predominately driven by younger age groups (0-29 years of age), particularly  
61 between individuals of the same age and from younger to older ages. However, there is often some additional inter-generational  
62 transmission generated by those between 20 and 59 years of age (Fig. 1A,D). Conversely, in China where high numbers of  
63 daily contacts were recorded among those aged 60 and above<sup>13</sup>, transmission is much more intensely concentrated in the  
64 older age groups. In high-income settings (e.g., the UK), we see that in addition to the intense within-age-group transmission  
65 among those aged 19 years and below (which is similar to low-income settings), there is considerably more inter-generational  
66 transmission generated by those individuals aged between 20 and 69 years, which becomes even more intense for regions with  
67 top-heavy age distributions such as Japan and Hong Kong (see Supplement).

### 68 Minimizing transmission with a fixed number of doses

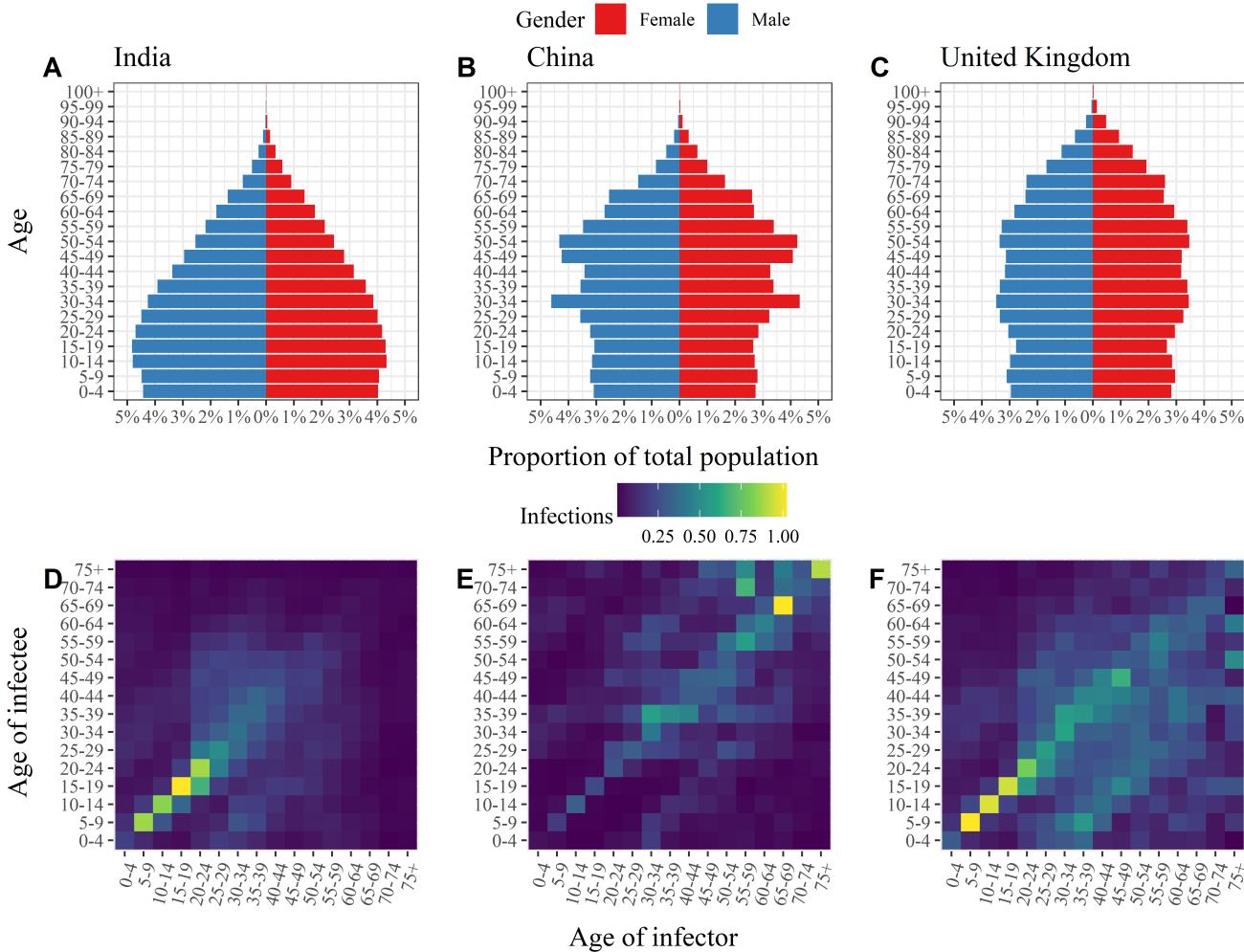
69 Targeted vaccination dramatically reduces the SARS-CoV-2 transmission rate relative to vaccination programs that uniformly  
70 distribute doses across the population (Fig. 2). Reductions are greatest at intermediate levels of population-level coverage (e.g.,  
71 60%) as results under the two strategies converge when coverage approaches 0 or 100%.

72 Countries with contacts concentrated among a limited number of age groups (e.g., China, Fig. 2B) exhibit greater reductions  
73 in transmission under targeted vaccine allocation, as do countries with higher median ages (e.g., the UK, Fig. 2C) because older  
74 populations with rectangular age distributions possess greater scope for targeted dose allocation.

75 Vaccines that reduce susceptibility to infection more effectively suppress transmission than those that prevent symptomatic  
76 disease among infected individuals (Fig. 2). The latter not only exhibit less improvement under targeted dose allocation, but  
77 they also fail to reach the herd immunity threshold in almost all settings considered (the exceptions being countries with  
78 baseline  $R_0$  values very close to one, e.g., Samoa).

79 Looking at the age-specific dose allocation under optimized vaccination (Fig. 3), we observe that vaccines that protect  
80 against symptomatic disease (Fig. 3A-C) prioritize slightly older age groups than those that reduce susceptibility to infection  
81 (Fig. 3D-F). In either case, we find that individuals between 30 and 49 years of age (i.e., those typically most responsible for  
82 inter-generational transmission) are often assigned the highest priority among all age groups. As more doses become available  
83 (e.g., as 60% population-level coverage is reached), the targeted age groups expand contiguously, either to include 10-19 and  
84 20-29 year olds or 50-59 year olds, depending on whether vaccination protects against infection or disease, respectively. For  
85 each level of vaccination coverage and protection mode, the lowest priority individuals are typically those 70 years of age and  
86 over. Notable exceptions include China (Fig. 3B,E) where the high number of contacts among individuals over the age of 60  
87 mean the elderly (i.e., 60+ year olds) should be the first group vaccinated.

88 In sensitivity analysis with reduced efficacy among 60+ year old individuals (i.e., 35% v. 70% in those <60 years old), we  
89 find similar results to those presented above, with changes in priority assigned to older individuals typically within the range of  
90 variation obtained from near-optimal solutions (grey bars) (Fig. S1). However, when we use an alternate model parameterization  
91 that only allows age-dependent variation in the clinical fraction (keeping individual susceptibility fixed across all age groups)  
92 we observe a shift in priority away from 50+ year old individuals to much younger age groups (particularly 10-19 year olds) in  
93 India and the UK; whilst the results in China are qualitatively similar under the different model parameterizations (Figs. S4-S9).



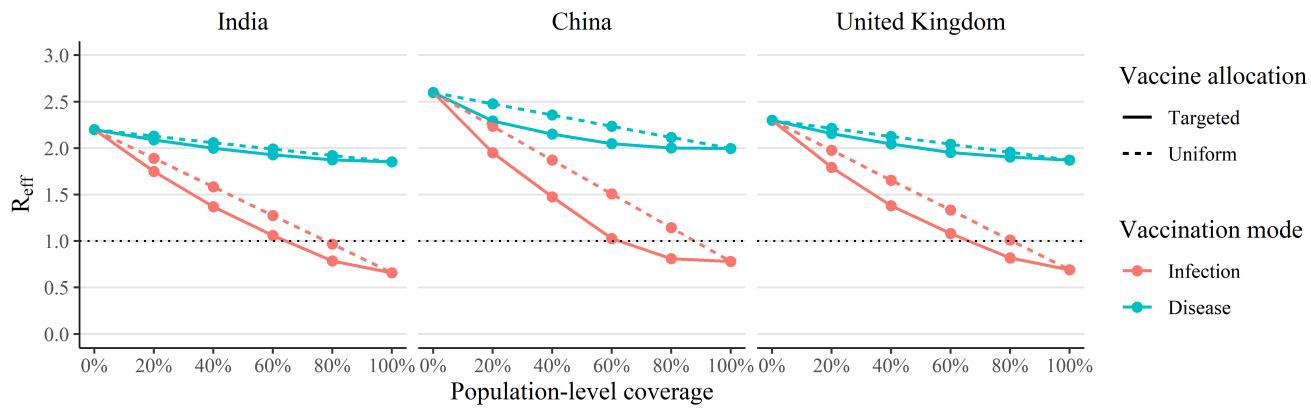
**Figure 1. Age distributions and age-specific transmission rates.** Population pyramids (Panels A-C) and transmission matrices (Panels D-F) for India (left), China (middle) and the United Kingdom (right). In Panels D-F the colouring of the  $i$ th row and  $j$ th column of the transmission matrices represents the average number of infections in age group  $i$  generated by an individual in age group  $j$  over the course of an infectious episode with COVID-19. The elements of each matrix have been rescaled such that the maximal eigenvalues of the respective transmission matrices match the basic reproduction numbers ( $R_0$ ) estimated by Abbott et al.<sup>15</sup>, namely India: 2.2; China: 2.6; and the United Kingdom: 2.3.

#### 94 Efficiently reaching the herd immunity threshold

95 Following our analysis of optimal age-specific vaccine allocation under the constraint of finite available doses, we next  
 96 investigated the inverse problem: calculating the minimum number of doses required to achieve herd immunity under targeted  
 97 vaccine allocation. Given the results of the previous section indicating that vaccines that protect against symptomatic disease  
 98 are often unable to achieve herd immunity, in this section we focused specifically on vaccines that reduce susceptibility to  
 99 infection, which were shown to be more effective.

100 Under uniform vaccine allocation programs we observe that with a vaccine that is 70% effective at reducing susceptibility  
 101 to infection most countries require population-level vaccination coverages in excess of 80% (Fig. 4). In particular, we find that  
 102 whilst vaccination appears to be a viable strategy to achieve herd immunity in some settings, more than 20% of the countries  
 103 considered would require substantial coverage levels (>85%) to reach this goal, whilst for several others (e.g., France) herd  
 104 immunity may be unachievable through vaccination alone.

105 In contrast, when dose allocation is optimized by targeting specific age groups, we observe dramatic reductions in the  
 106 minimum population-level coverage required to achieve herd immunity (Fig. 5) — with most countries requiring less than 65%  
 107 nationwide coverage under optimized, infection-preventing vaccination programs. As above, we find that countries with more  
 108 intensely concentrated contacts within particular age groups experience greater (relative) reductions in the minimum population



**Figure 2. Reduction in transmission under optimized vaccine allocation.** Effective reproduction number,  $R_{\text{eff}}$ , as a function of the population-level vaccination coverage when allocation is targeted towards priority age groups (solid lines) and the vaccine protects against infection (red) and disease (blue) for India (left), China (middle) and the United Kingdom (right). For comparison, we also plot the analogous reduction in  $R_{\text{eff}}$  when vaccine doses are allocated uniformly across age groups (dashed lines). The herd immunity threshold ( $R_{\text{eff}} < 1$ ) is indicated by the horizontal dotted black line.

109 coverage required to achieve herd immunity under targeted vaccination programs, which in some cases can exceed 50% (e.g.,  
110 Mozambique).

111 In both the uniform and targeted vaccination scenarios, the greatest variation in minimum coverage is observed across the  
112 African continent, which contains countries that require very low levels of vaccination (e.g., Angola, Mozambique), along with  
113 countries for which vaccination alone is insufficient to achieve herd immunity (e.g., Libya, Zimbabwe).

114 Results obtained through sensitivity analysis with reduced vaccine efficacy in the 60+ year age groups (i.e., 35% v. 70% in  
115 those less than 60 years of age) are in most cases within a few percent of those presented in Figs. 4 and 5 (see Figs. S2 and S3).  
116 One notable exception is China, which under constant vaccine efficacy required only 61% (88%) population-level coverage  
117 under a targeted (uniform) vaccination policy, but is unable to reach the herd immunity threshold when efficacy wanes in 60+  
118 year old individuals because of the high number of contacts amongst individuals in this age group.

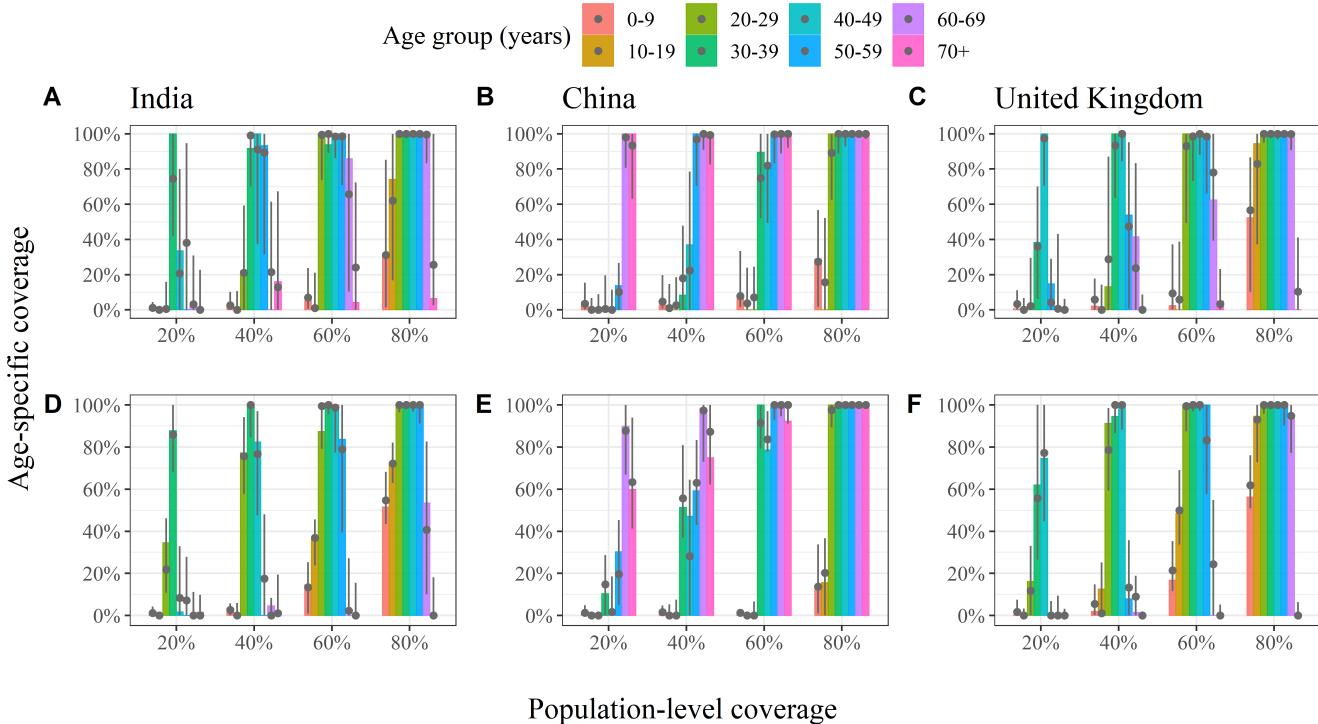
119 We note that the minimum target values presented in Figs. 4 and 5 are highly sensitive to: (i) case-count-derived estimates  
120 of the basic reproduction numbers provided by Abbott et al.<sup>15</sup> (and are therefore subject to biases introduced by variations in  
121 country-specific reporting rates); and (ii) the baseline vaccine efficacy (assumed here to be 70%). Nevertheless, our results can  
122 be readily rescaled without the need for re-optimization should updated estimates of  $R_0$  or vaccine efficacy become available.

## 123 Discussion

124 Targeting vaccination towards age groups that contribute more to the transmission of infection can dramatically enhance  
125 the effectiveness of COVID-19 vaccination. Whether the goal is to minimize transmission for a fixed number of doses or  
126 to minimize the number of doses required to achieve a certain reduction in transmission, our analysis indicates that dosage  
127 requirements or transmission rates can be halved under tailored age-specific vaccination strategies. Whilst the choice of which  
128 age groups to initially target for vaccination is dependent on setting, vaccinating middle-aged individuals (30–59 years of  
129 age) typically had the highest impact across the 179 countries considered (e.g., India and the UK). However, there were some  
130 settings (e.g., China) in which those aged 60 and above were the first to be selected for vaccination (in line with observed  
131 contact structures<sup>13</sup>).

132 Additionally, the ability of vaccination to reduce transmission is highly dependent on the type of protection conferred<sup>16</sup>.  
133 Since asymptomatic individuals contribute substantially to SARS-CoV-2 transmission, vaccines that prevent symptomatic  
134 disease but allow transmissible asymptomatic infection failed to achieve herd immunity in the overwhelming majority of  
135 settings considered; whereas vaccines that prevent initial infection by reducing the recipient's susceptibility were far more  
136 likely to achieve elimination (and concomitantly possess greater scope for optimization). In either case, we emphasize that a  
137 vaccine with less than 100% efficacy may require substantial population-level coverage in order to achieve herd immunity<sup>17</sup>,  
138 although this threshold can be considerably reduced through targeted vaccination — as suggested by studies that account for  
139 heterogeneities in population susceptibility and mixing<sup>10</sup>.

140 In settings for which vaccination alone proves insufficient, supplementary measures may need to be invoked to achieve  
141 elimination; this may include a reliance on pre-existing immunity generated by initial COVID-19 epidemic waves — which

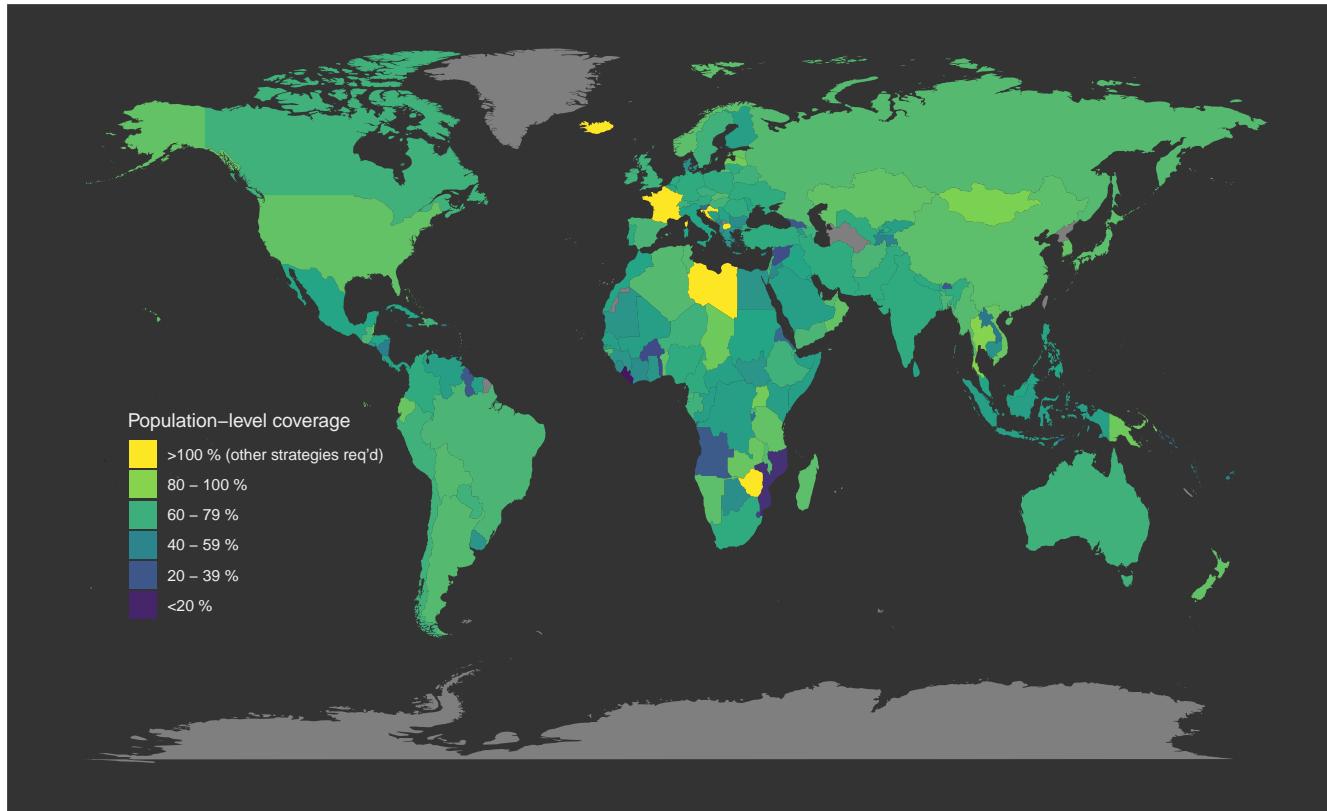


**Figure 3. Optimal age-specific vaccination policy.** The optimum coverage level for each age group (coloured bars) for varying population coverage levels for India (left), China (middle) and the United Kingdom (right). Alongside the global optimal solution (coloured bars) we provide the 2.5–97.5 percentile ranges (vertical grey lines) and median values (grey dots) of age-specific coverage levels for all locally optimal solutions whose  $R_{\text{eff}}$  is within 1% of the global optimal value. **Panels A-C** show the results for vaccines that prevent symptomatic disease. **Panels D-F** give the analogous results for vaccines that prevent infection. Here we have assumed that the vaccine is 70% effective across all age groups (remaining model parameters assume their baseline values which can be found in Table S1).

several serological surveys reveal may have already reached a sizeable fraction of the optimal targets identified in our analysis<sup>18</sup>. We have chosen not to account for pre-existing immunity as a result of past infection in our analysis because of the difficulties in quantifying its contribution relative to that of vaccination.

Throughout our analysis we have attempted to account for parameter uncertainty by exploring a range of alternatives suggested by the World Health Organization's recent vaccination modelling call<sup>12</sup>. Nevertheless, several limitations and possible extensions to the existing analysis remain. To begin, no vaccine provides perfect protection — and certainly not across all age groups. The results presented herein assume a vaccine efficacy of 70% that is sustained across all age groups at baseline; however, results assuming reduced efficacy (35%) in individuals over 60 years of age are presented in the Supplementary Materials. We found that reduced efficacy in individuals over 60 years of age had a negligible impact on the predicted minimum vaccination coverage targets and the level of priority assigned to particular age groups for most countries — China being a notable exception. Moreover, since the former estimates scale linearly with baseline efficacy, it is straightforward to update these values for vaccine efficacies other than 70%; nonetheless, the priority assigned to each age group should remain invariant.

Next, we chose optimization targets designed to reduce transmission, which we defined through the reduction in the effective reproduction number,  $R_{\text{eff}}$ . Whilst such targets may be suitable for settings in which transmission is currently suppressed by existing (non-pharmaceutical) control measures (e.g., New Zealand), countries with ongoing epidemics may choose to prioritize more severe outcomes such as COVID-19-related mortality. Although dynamic outputs such as cumulative morbidity (e.g., Disability-Adjusted-Life-Years; DALYs) and mortality are beyond the scope of the present analysis, we anticipate that such targets will bias optimal vaccine allocation towards older age groups who typically suffer worse disease-related outcomes. This was demonstrated in the recent analyses aiming to minimize deaths through vaccination by Hogan et al.<sup>16</sup> and Matrajt et al.<sup>19</sup>. These authors found that when doses are limited, older age groups should be the first to receive vaccination. Ultimately however, we expect that the best way to limit deaths is to limit transmission, such that the priority age-groups identified by these alternate optimization targets will not deviate significantly from the results obtained here when population-level coverage is sufficient to limit transmission; this view is supported by<sup>16, 19</sup> and the recent analysis by Ragonnet et al.<sup>20</sup> which optimized



**Figure 4. Global target vaccination coverage under uniform vaccination policy.** Map of the minimum target vaccination coverage required to achieve herd immunity under uniform vaccine allocation programs. Countries coloured bright yellow are incapable of achieving herd immunity through vaccination alone (i.e., their minimum coverage thresholds exceed 100%).

age-specific mixing to achieve herd immunity whilst minimizing deaths and years of life lost.

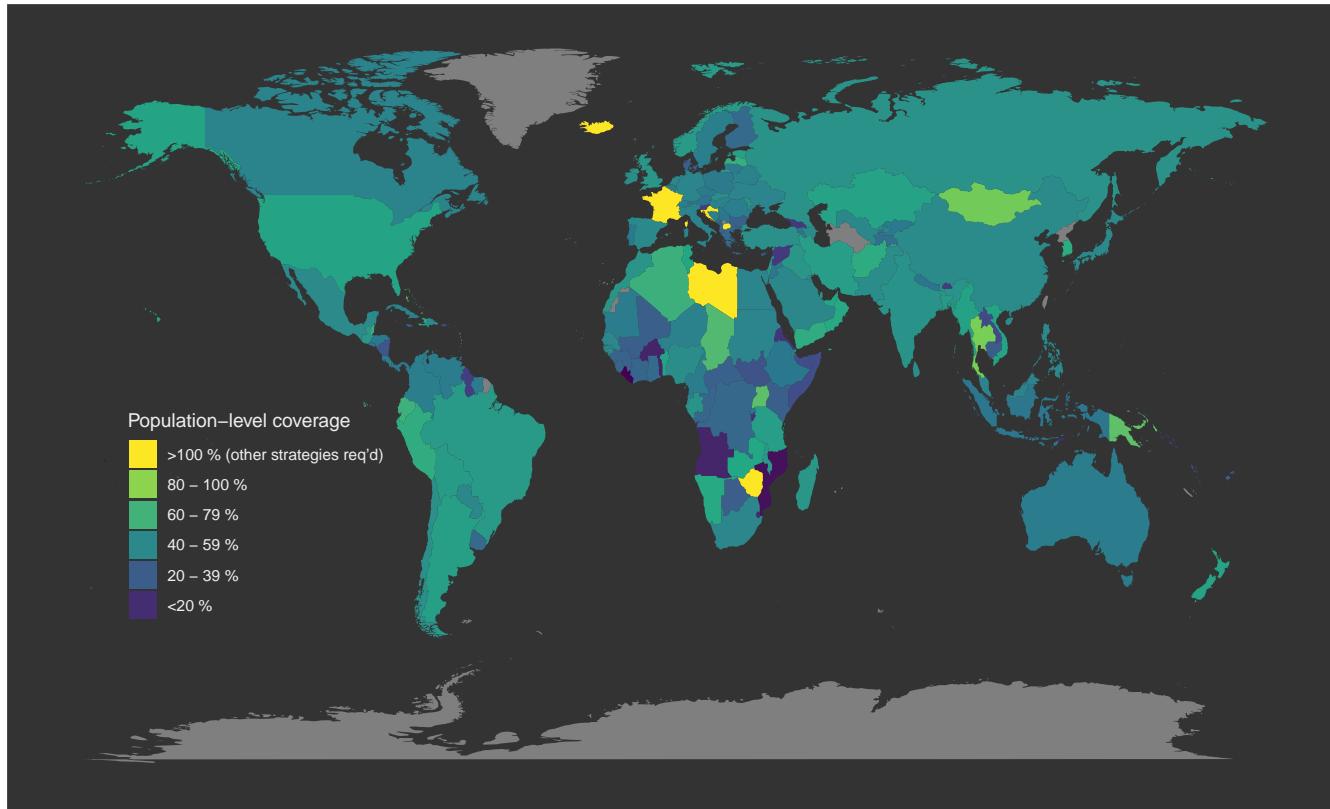
Furthermore, to avoid excessive speculation, we have not factored in the costs and feasibility of age-specific vaccine roll-out as part of our optimization search. However, alongside the global optimal solutions identified for each age group and setting, we have also indicated a range of possible age-specific coverage levels that have near-equivalent (within 1%) transmission reduction potential that may be selected if proven more cost-effective in practice.

In this modelling study, we have exclusively chosen to optimize vaccine allocation by age. This choice is motivated by the most readily available patient and contact data (which regularly provide breakdowns by age) and the subsequent analyses that have firmly established that infection and disease risk vary substantially by age. Subsequent studies could also consider alternative demographic strata with known correlations with infection risk and disease severity, including occupation (e.g., health- and aged-care workers) and socio-economic status, as well as the presence of comorbidities.

Another important limitation of our analysis is the reliance on case-based estimates for the basic reproduction number,  $R_0$ , in each country. To be conservative, we have taken the upper limit of the 90% credible interval provided by the analysis in Abbott et al.<sup>15</sup>. Whilst variations in reporting rates within different host countries will likely bias these estimates, our predictions for the minimum vaccination coverage for each country can be re-scaled to account for any updated values. Regardless, we point out that it is only the total reduction in  $R_{\text{eff}}$  (in the fixed doses case) or minimum target coverage (in the unlimited doses case) that is sensitive to  $R_0$ , while the optimal age-specific allocation of available doses should remain unaltered.

We also note that the limited efficacy of disease-preventing vaccines stems from the prominence of sub-clinical transmitters, which, following Davies et al.<sup>11</sup>, we have assumed are 50% as infectious as clinical cases. If the contribution of asymptomatic transmission (either in the natural infection case or post-vaccination) is found to be lower, the estimated effectiveness of vaccines that prevent symptomatic disease would correspondingly increase.

Another important consideration is the impact of waning vaccine-induced immunity, and the potentially harmful consequences of delaying an individual's age-at-first-infection. This issue is known to influence the course of vaccination for several other communicable diseases (e.g., varicella<sup>21</sup> and rubella) and may have important ramifications for COVID-19 that should be explored as more data become available — particularly given the significantly poorer outcomes observed among older



**Figure 5. Global target vaccination coverage under optimized vaccination policy.** Map of the minimum target vaccination coverage required to achieve herd immunity under country-specific optimized vaccine allocation programs. Countries coloured yellow are incapable of achieving herd immunity through vaccination alone (i.e., their minimum coverage threshold exceeds 100%).

189 individuals.

190 Finally, if and when a COVID-19 vaccine is approved and made available globally, it is critical that doses are allocated in  
191 a manner that most efficiently curtails transmission — as initial supplies will undoubtedly be limited. Our study shows that  
192 setting- and age-specific optimization of vaccine allocation can provide substantial improvements in efficiency over uniform  
193 vaccination programs, saving up to half of the available doses to achieve the same reduction in transmission in some settings.  
194 Moreover, in deriving the minimum coverage thresholds required to achieve herd immunity in 179 countries, this analysis has  
195 also underscored the often overlooked and unsavory outcome that vaccination alone may not be enough to completely suppress  
196 COVID-19 (particularly if the vaccine fails to prevent initial infection). In this case, permanent control measures — which may  
197 include social distancing or improved hygiene — may be required alongside vaccination.

## 198 Methods

### 199 Calibrating transmission and the next-generation matrix

200 To model the transmission of SARS-CoV-2 we stratify the population into 16 5-year age bands  $i \in \{0 - 4, 5 - 9, 10 - 14, \dots, 70 -\}$   
201 74, 75+\} and assume that individuals in age group  $i$  possess a relative susceptibility to infection  $u_i$ . Once infected, an age-  
202 dependent fraction  $y_i$  go on to develop symptomatic (i.e., clinical) disease whilst the remaining  $(1 - y_i)$  develop asymptomatic  
203 (i.e., sub-clinical) disease. We assume that individuals in the sub-clinical class are less infectious than those in the clinical class  
204 by a relative factor  $f$  (set at 0.5<sup>11</sup>) and that the total time spent infectious for both classes is  $\tau = 5.0$  days<sup>11</sup>.

Each day, each individual in age group  $j$  makes  $c_{ij}$  contacts with individuals in age group  $i$  leading to the following expression for the (unscaled) next-generation matrix (NGM)<sup>11,22</sup>:

$$\bar{K}_{ij} = \frac{u_i S_i c_{ij}}{N_j} [y_j + (1 - y_j)f] \tau \quad (1)$$

205 where  $S_i$  is the number of susceptible individuals in age group  $i$  and  $N_j$  is total number of individuals in age group  $j$ .

The  $(i, j)$ th entry of the NGM  $\bar{K}$  is proportional to the average number of new infections in age group  $i$  generated by an individual in age group  $j$  over their entire 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 by  $\eta$ . In particular, the basic reproduction number,  $R_0$ , which is proportional to the maximal eigenvalue of  $\bar{K}$ , can be expressed as

$$R_0 = \eta \rho(\bar{K}) \Rightarrow \eta = \frac{R_0}{\rho(\bar{K})} \quad (2)$$

where we use  $\rho(\bar{K})$  to denote the spectral radius of the matrix  $\bar{K}$ .

For each of the 179 countries considered in our analysis we used estimates of  $R_0$  based on observed case counts<sup>15</sup> to calibrate country-specific values for the scaling factor  $\eta$ . In particular, we assume  $R_0$  in each country is equal to the maximum value of the 90% credible interval upper limit of the time-varying reproduction number estimates generated by Abbott et al.<sup>15</sup>. Where these values are unrealistically high (e.g., North Macedonia returned an  $R_0$  greater than 30) we used estimates provided by the Centres for Disease Control and Prevention (CDC).

We assume that the age-dependent susceptibility ( $u_i$ ) and clinical fraction ( $y_i$ ) are universal across all countries and allow only the age-specific contact rates ( $c_{ij}$ ), initial population sizes ( $S_i$  and  $N_j$ ) and transmission scaling factor  $\eta$  to vary among settings, i.e., all other parameters remain fixed among countries (see Table S1).

We consider three separate models for age-dependent susceptibility and clinical fraction: M1 — allowing both age-dependent susceptibility and clinical fraction; M2 — allowing age-dependent susceptibility only; and M3 — allowing age-dependent clinical fraction only. The results for model M1 are those presented in the main article, whilst results for models M2 and M3 appear in the Supplement. Parameter values under each model have been calibrated to patient data in Davies et al.<sup>11</sup> and can be found in Table S2.

Where available, the daily, age-dependent contact rates,  $c_{ij}$ , between individuals in each country were taken from previously conducted nationwide contact surveys. This was the case for China<sup>13</sup> and the UK<sup>14</sup>, as well Italy, Germany, Luxembourg, the Netherlands, Poland, Finland and Belgium<sup>23</sup> and Zimbabwe<sup>24</sup>. In the absence of such survey data, synthetic contact matrices extrapolated from existing contact surveys across multiple settings were used<sup>25,26</sup>.

## Modelling vaccination

To incorporate vaccination of otherwise susceptible individuals, we let  $v_i$  denote the fraction of individuals in age group  $i$  that are vaccinated (i.e., the coverage of age-group  $i$ ),  $e$  denote the baseline efficacy of the vaccine, and  $r_i$  its age-dependent relative efficacy. For tractability, here we divide the population into 10-year age bands such that the vector  $v_i$  has eight free parameters that are repeated pairwise to cover the 16 5-year age bands defined above.

We investigate two distinct modes of action for potential vaccines, those that protect against initial infection and those that protect against symptomatic disease following infection. The former equates to a removal of susceptible individuals from the total population whilst the latter influences the fraction of individuals that go on to develop symptomatic disease. The unscaled NGM in each instance transforms, respectively, to:

$$\bar{K}_{ij}^{\text{vac,inf}} = \frac{u_i(1 - er_i v_i)S_i c_{ij}}{N_j} [y_j + (1 - y_j)f] \tau. \quad (3)$$

and

$$\bar{K}_{ij}^{\text{vac,dis}} = \frac{u_i S_i c_{ij}}{N_j} [(1 - er_j v_j)y_j + (1 - (1 - er_j v_j)y_j)f] \tau. \quad (4)$$

In the presence of vaccination, the effective reproduction number,  $R_{\text{eff}}$ , can be calculated via

$$R_{\text{eff}}^k = \eta \rho(\bar{K}^{\text{vac},k}) \quad (5)$$

where the index  $k \in \{\text{inf}, \text{dis}\}$  denotes the type of protection conferred by vaccination, and the scaling factor  $\eta$  is calibrated according the procedure described in the previous section.

## Optimizing vaccination

Using expression (5) for the effective reproduction number as a function of the age-specific vaccination proportions  $\mathbf{v} = (v_{0-9}, v_{10-19}, \dots, v_{70+})$ , we pursue two optimization targets: 1) minimizing the effective reproduction number ( $R_{\text{eff}}$ ) for a given (fixed) number of doses; and 2) minimizing the total number of doses (i.e., population-level coverage) required to achieve herd immunity, which we define as obtaining an effective reproduction number less than one. These optimization problems can respectively be stated as

## 1. Minimizing transmission with a fixed number of doses.

$$\text{Minimize } R_{\text{eff}}(\mathbf{v}) \text{ subject to } \sum_i v_i N_i = \text{constant.} \quad (6)$$

## 2. Efficiently reaching the herd immunity threshold.

$$\text{Minimize } \sum_i v_i N_i \text{ subject to } R_{\text{eff}}(\mathbf{v}) < 1. \quad (7)$$

237 Since the surface  $R_{\text{eff}}(\mathbf{v}) = \text{const.}$  is highly complex, we expect that there may be multiple solutions to the optimization  
238 problems 1. and 2. Therefore, we used a stochastic simulated annealing algorithm to search the parameter space and re-ran it  
239 multiple times to uncover multiple solutions of roughly equivalent quality (i.e., similar objective values). Hence, in addition to  
240 storing the global optimum value (i.e., the solution with the minimum objective value among all solutions obtained) we also  
241 retained the values obtained from each of the remaining runs whose objective value was within 1% of the global optimum (the  
242 range of these values is indicated by the grey bars in Fig. 3).

## 243 Data and code availability

244 All input data and model source code has been deposited in a recognized public source repository GitHub, <https://github.com/michaeltmeehan/covid19>.

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## 304 Author contributions statement

305 M.M., R.R and E.M. conceived the project, M.M. and D.C. conducted the simulations, M.M., J.C., D.C., A.A., J.T., R.R. and  
306 E.M. analysed the results. All authors reviewed the manuscript.

## 307 Additional information

308 **Competing interests** The authors do not have any competing interests to declare.

## 309 Supplementary Information

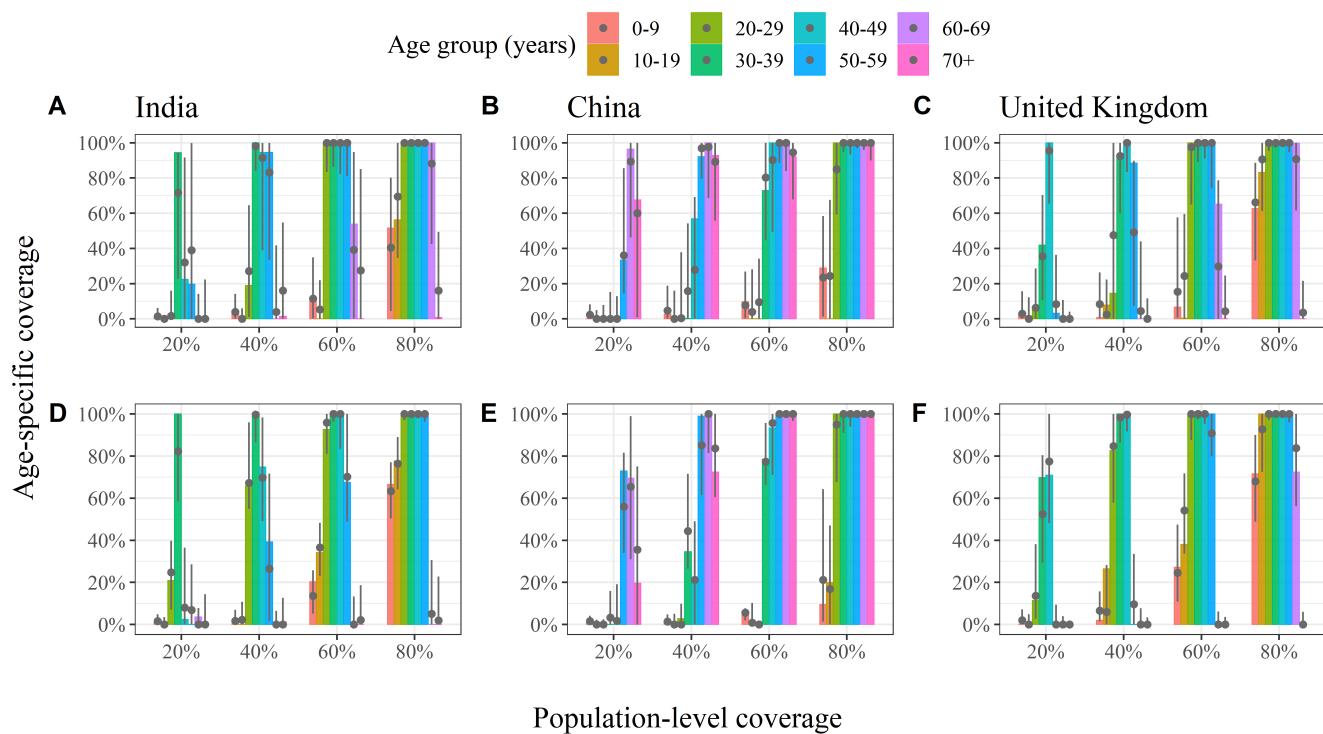
310 In addition to the data provided below, further model inputs and results — including optimization results for all 179 countries  
311 — can be found in the public GitHub repository: [https://github.com/michaeltmeehan/covid19/optimize\\_vaccination](https://github.com/michaeltmeehan/covid19/optimize_vaccination).

Parameter	Description	Baseline value (range)
$u_i$	Relative susceptibility of age group $i$	See table S2
$y_i$	Fraction of infected individuals that develop clinical infection	See table S2
$\tau$	Infectious period	5.0 days
$f$	Relative infectiousness of asymptomatic individuals	0.5
$\eta$	Probability of transmission given contact	Fitted
$v_i$	Proportion of vaccinated individuals in age group $i$	Optimized
$e$	Overall vaccine efficacy	0.7
$r_i$	Relative vaccine efficacy in individuals over the age of 60	1.0 (0.5-1.0)

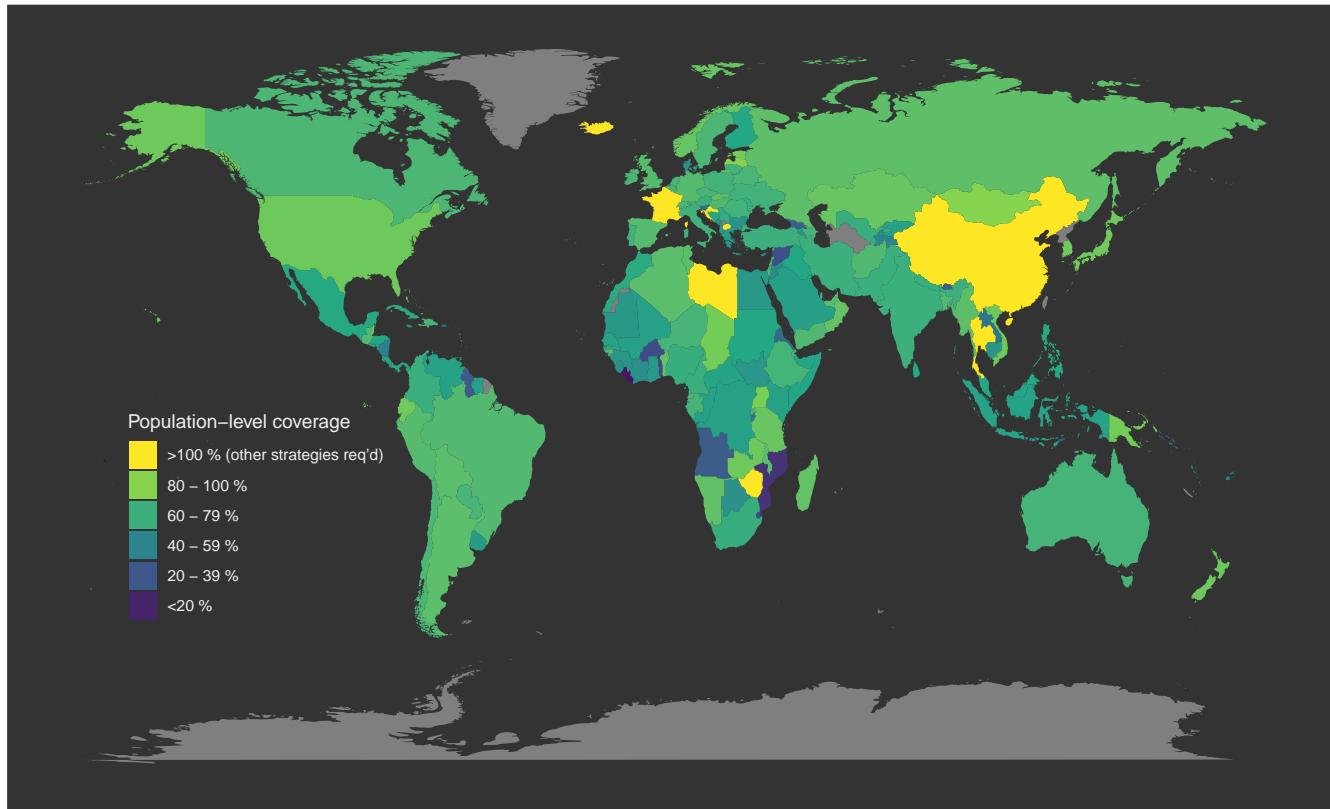
**Table S1.** Transmission model parameters adapted from<sup>11</sup>.

Age-group (years)	Relative susceptibility ( $u_i$ )		Clinical fraction ( $y_i$ )	
	M1	(M2, M3)	M1	(M2, M3)
0 – 4	0.39	(0.018, 1.0)	0.28	(0.50, 0.14)
5 – 9	0.39	(0.018, 1.0)	0.28	(0.50, 0.14)
10 – 14	0.38	(0.018, 1.0)	0.20	(0.50, 0.14)
15 – 19	0.38	(0.018, 1.0)	0.20	(0.50, 0.15)
20 – 24	0.79	(0.022, 1.0)	0.26	(0.50, 0.18)
25 – 29	0.79	(0.028, 1.0)	0.26	(0.50, 0.23)
30 – 34	0.87	(0.036, 1.0)	0.33	(0.50, 0.29)
35 – 39	0.87	(0.042, 1.0)	0.33	(0.50, 0.34)
40 – 44	0.80	(0.046, 1.0)	0.40	(0.50, 0.38)
45 – 49	0.80	(0.049, 1.0)	0.40	(0.50, 0.40)
50 – 54	0.82	(0.053, 1.0)	0.49	(0.50, 0.44)
55 – 59	0.82	(0.060, 1.0)	0.49	(0.50, 0.50)
60 – 64	0.89	(0.067, 1.0)	0.63	(0.50, 0.55)
65 – 69	0.89	(0.070, 1.0)	0.63	(0.50, 0.57)
70 – 74	0.74	(0.071, 1.0)	0.69	(0.50, 0.58)
75+	0.74	(0.071, 1.0)	0.69	(0.50, 0.58)

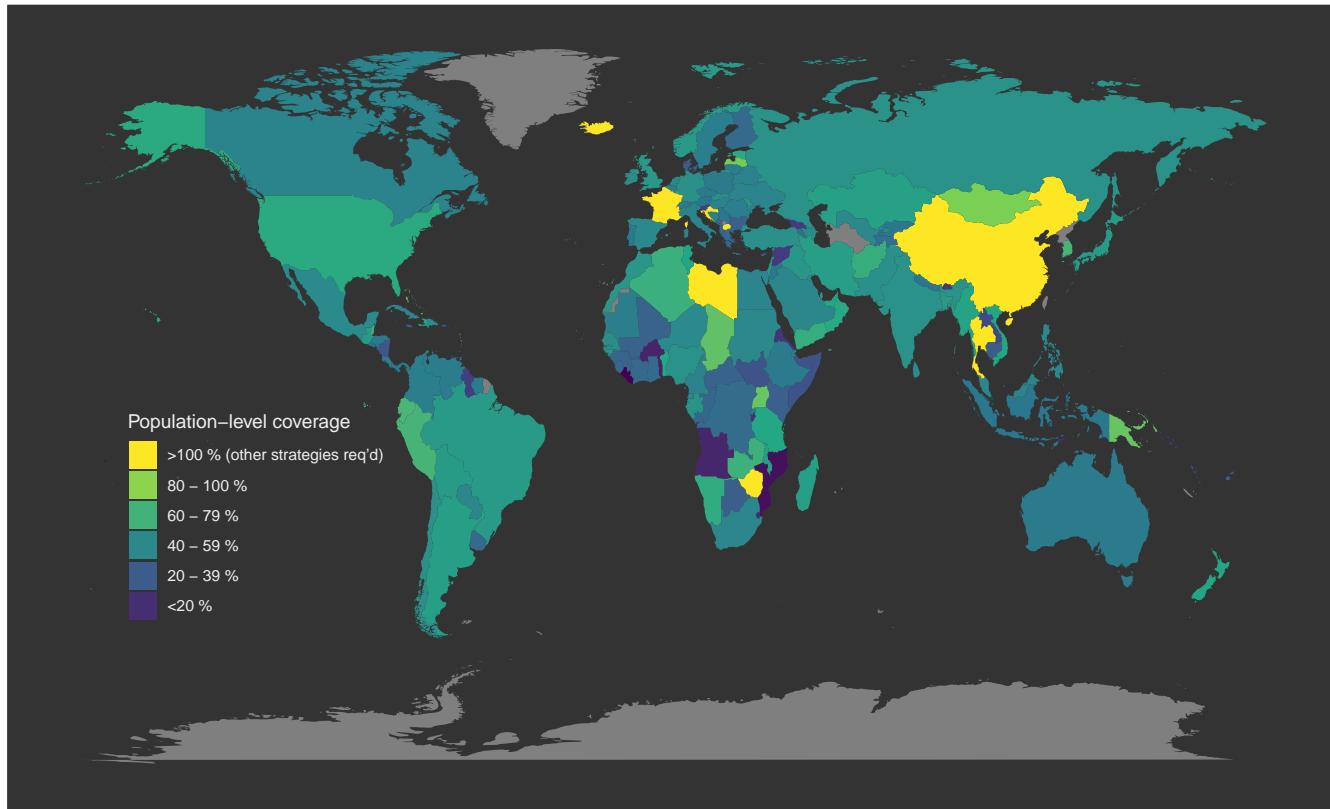
**Table S2.** Fitted values of age-dependent susceptibility and clinical fraction generated by Davies et al.<sup>11</sup> allowing for both age-dependent susceptibility and clinical fraction (M1); age-dependent susceptibility only (M2); and age-dependent clinical fraction only (M3).



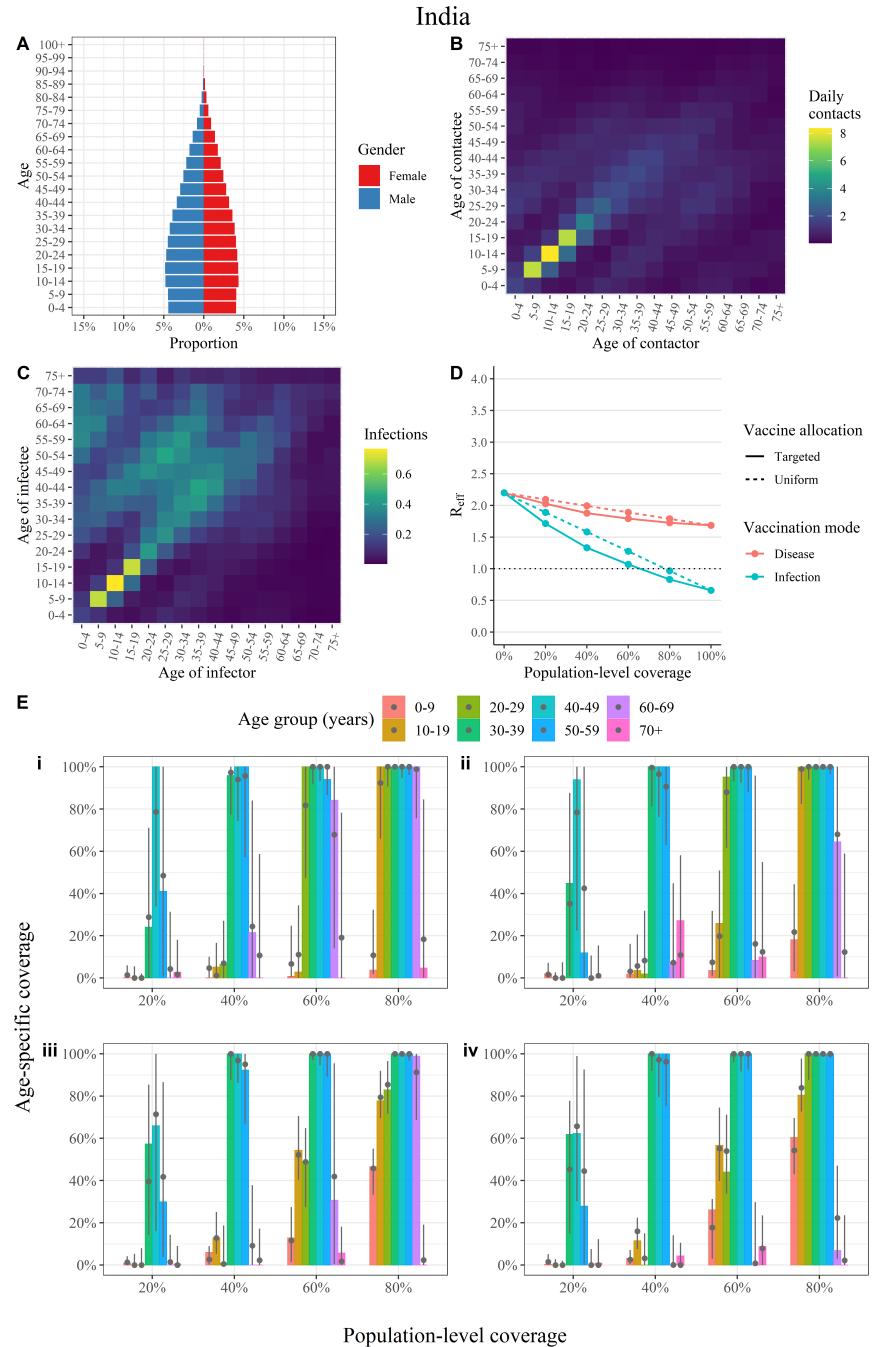
**Figure S1. Optimal age-specific vaccination policy (with reduced efficacy in 60+ year olds).** The optimum coverage level for each age group (coloured bars) for varying levels of population-level coverage for India (left), China (middle) and the United Kingdom (right). Alongside the global optimal solution (coloured bars) we provide the 2.5–97.5 percentile ranges (vertical grey lines) and median values (grey dots) of age-specific coverage levels for all locally optimal solutions whose  $R_{\text{eff}}$  is within 1% of the global optimal value. **Panels A-C** show the results for vaccines that prevent symptomatic disease and **Panels D-F** give the analogous results for vaccines that prevent infection. Here we have assumed that the vaccine is 70% effective for individuals aged 60 years and less and is 35% effective in those over the age of 60 (remaining model parameters assume their baseline values, which can be found in Tables S1 and S2).



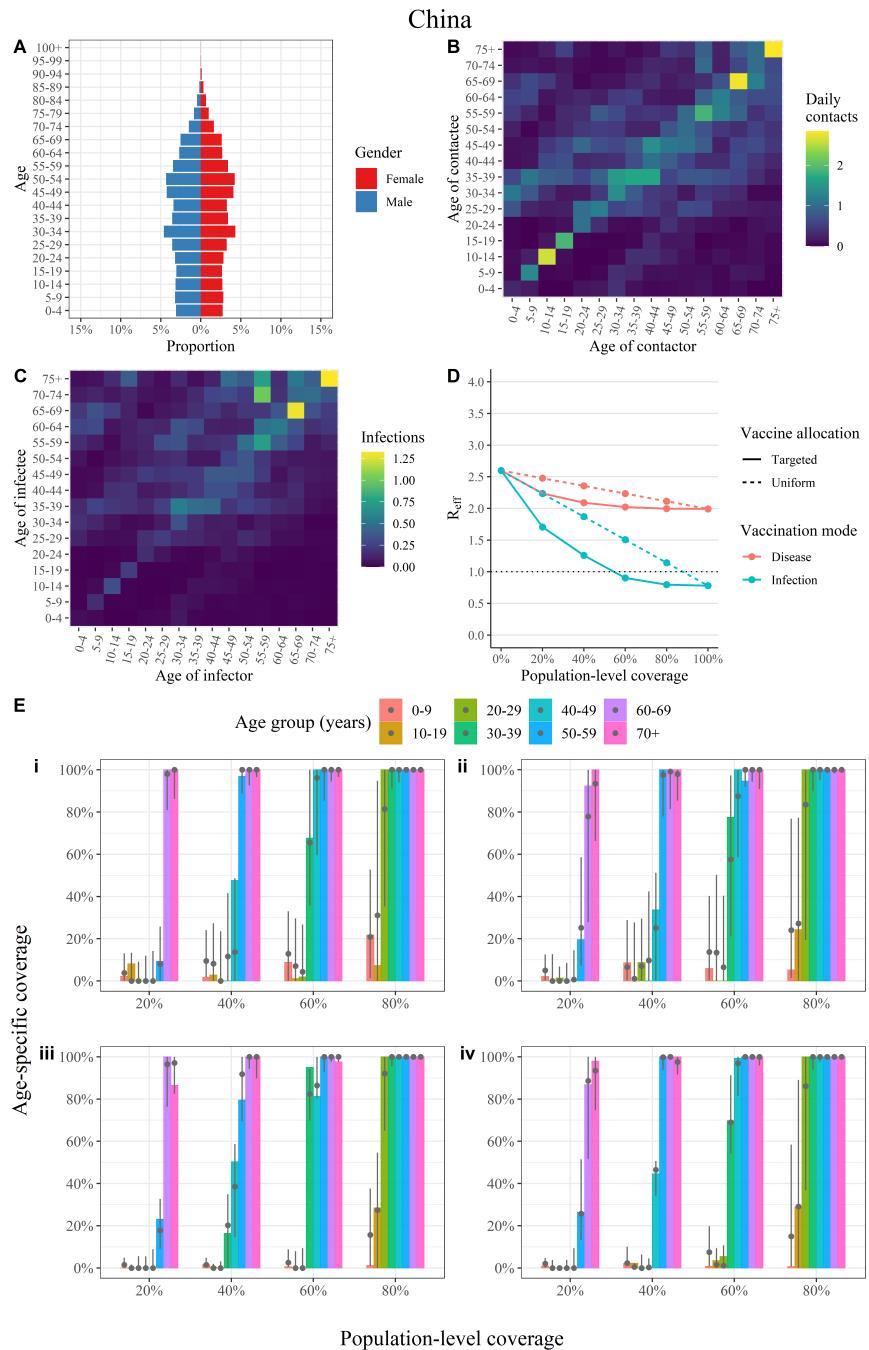
**Figure S2. Global target vaccination coverage under uniform vaccination policy (with reduced efficacy in 60+ year olds).** Map of the minimum target vaccination coverage required to achieve herd immunity under uniform vaccine allocation programs. Countries coloured bright yellow are incapable of achieving herd immunity through vaccination alone (i.e., their minimum coverage thresholds exceed 100%). Here we have assumed that the vaccine is 70% effective for individuals aged 60 years and less and is 35% effective in those over the age of 60 (remaining model parameters assume their baseline values, which can be found in Tables S1 and S2).



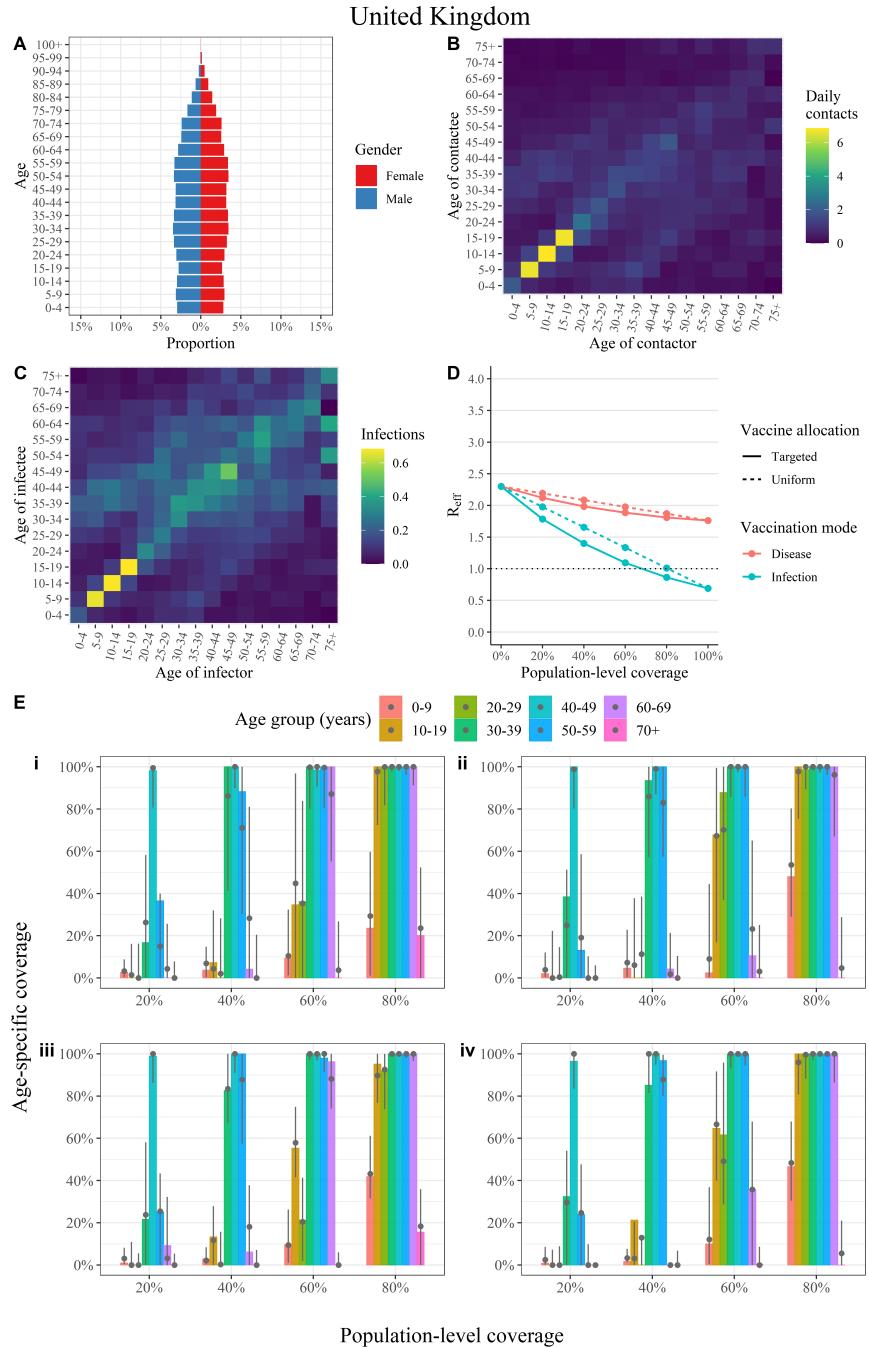
**Figure S3. Global target vaccination coverage under optimized vaccination policy (with reduced efficacy in 60+ year olds).** Map of the minimum target vaccination coverage required to achieve herd immunity under country-specific optimized vaccine allocation programs. Countries coloured yellow are incapable of achieving herd immunity through vaccination alone (i.e., their minimum coverage threshold exceeds 100%). Here we have assumed that the vaccine is 70% effective for individuals aged 60 years and less and is 35% effective in those over the age of 60 (remaining model parameters assume their baseline values, which can be found in Tables S1 and S2).



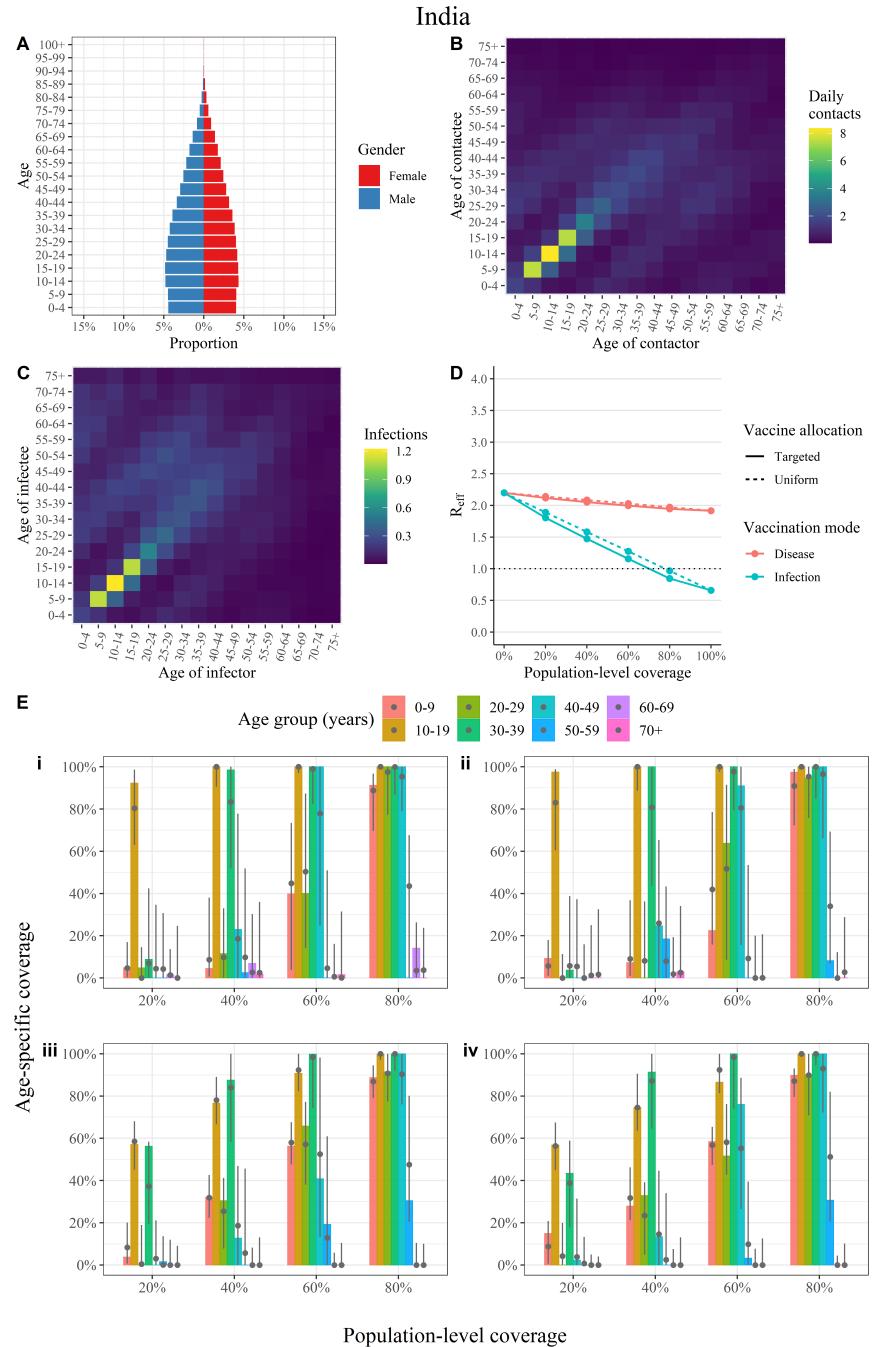
**Figure S4. Full country results for India, allowing age-dependent susceptibility only (M2).** **Panel A:** Population pyramid. **Panel B:** Age-specific daily contact rates. **Panel C:** Age-specific infection rates over the lifetime of infection. **Panel D:** Reduction in transmission ( $R_{eff}$ ) as a function of population-level vaccination coverage for vaccines that prevent infection (blue) and disease (red) under targeted (solid) and uniform (dashed) vaccination programs. **Panel E:** Optimal age-specific vaccination coverage for varying levels of population-level coverage. Coloured bars represent the global optimum value whilst the grey vertical lines (dots) indicate the 2.5-97.5 percentile range (median) of near-optimal solutions (i.e., solutions with an  $R_{eff}$  within 1% of the global optimum). The top row (**i, ii**) give the results for disease-preventing vaccines and the bottom row (**iii, iv**) give the results for infection-preventing vaccines. The windows on the left (**i, iii**) give the results for vaccines with constant efficacy (70%) across all age groups and the windows on the right (**ii, iv**) give the results for vaccines with variable efficacy amongst 60+ year olds (35% v. 70% in <60 year olds).



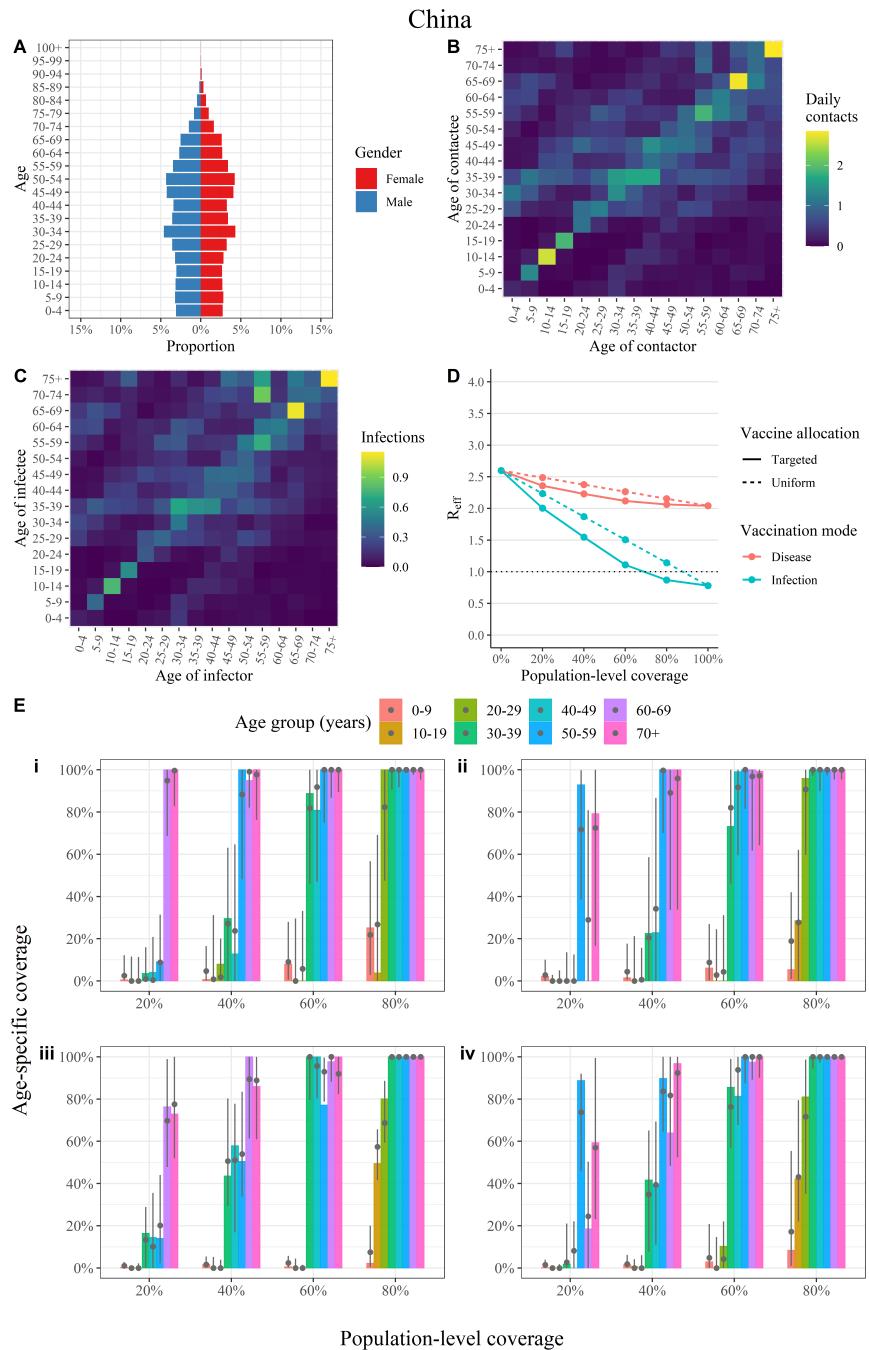
**Figure S5. Full country results for China, allowing age-dependent susceptibility only (M2).** **Panel A:** Population pyramid. **Panel B:** Age-specific daily contact rates. **Panel C:** Age-specific infection rates over the lifetime of infection. **Panel D:** Reduction in transmission ( $R_{eff}$ ) as a function of population-level vaccination coverage for vaccines that prevent infection (blue) and disease (red) under targeted (solid) and uniform (dashed) vaccination programs. **Panel E:** Optimal age-specific vaccination coverage for varying levels of population-level coverage. Coloured bars represent the global optimum value whilst the grey vertical lines (dots) indicate the 2.5-97.5 percentile range (median) of near-optimal solutions (i.e., solutions with an  $R_{eff}$  within 1% of the global optimum). The top row (i, ii) give the results for disease-preventing vaccines and the bottom row (iii, iv) give the results for infection-preventing vaccines. The windows on the left (i, iii) give the results for vaccines with constant efficacy (70%) across all age groups and the windows on the right (ii, iv) give the results for vaccines with variable efficacy amongst 60+ year olds (35% v. 70% in <60 year olds).



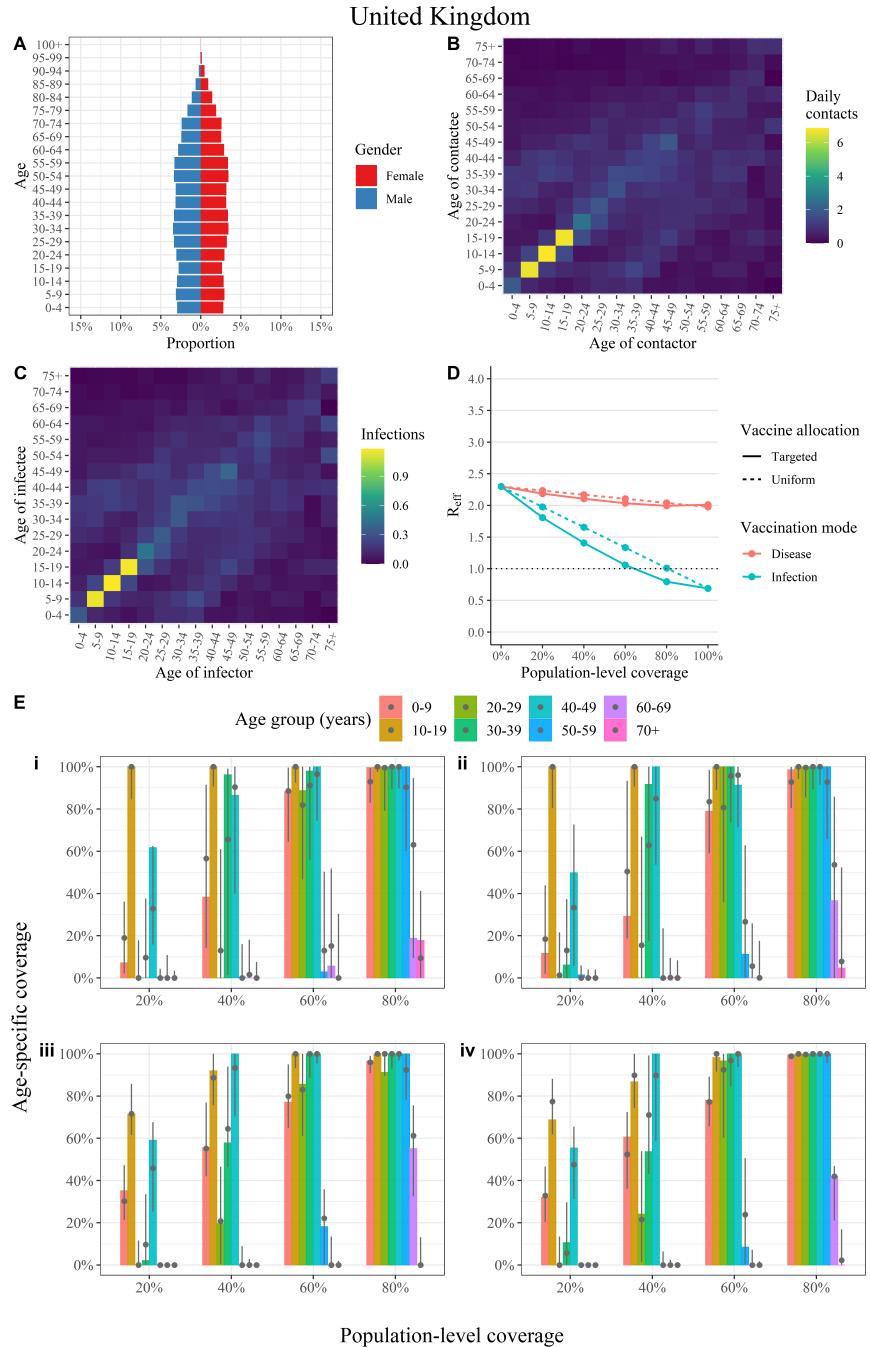
**Figure S6. Full country results for the United Kingdom, allowing age-dependent susceptibility only (M2). Panel A:** Population pyramid. **Panel B:** Age-specific daily contact rates. **Panel C:** Age-specific infection rates over the lifetime of infection. **Panel D:** Reduction in transmission ( $R_{eff}$ ) as a function of population-level vaccination coverage for vaccines that prevent infection (blue) and disease (red) under targeted (solid) and uniform (dashed) vaccination programs. **Panel E:** Optimal age-specific vaccination coverage for varying levels of population-level coverage. Coloured bars represent the global optimum value whilst the grey vertical lines (dots) indicate the 2.5-97.5 percentile range (median) of near-optimal solutions (i.e., solutions with an  $R_{eff}$  within 1% of the global optimum). The top row (i, ii) give the results for disease-preventing vaccines and the bottom row (iii, iv) give the results for infection-preventing vaccines. The windows on the left (i, iii) give the results for vaccines with constant efficacy (70%) across all age groups and the windows on the right (ii, iv) give the results for vaccines with variable efficacy amongst 60+ year olds (35% v. 70% in <60 year olds).



**Figure S7. Full country results for India, allowing age-dependent clinical fraction only (M3).** **Panel A:** Population pyramid. **Panel B:** Age-specific daily contact rates. **Panel C:** Age-specific infection rates over the lifetime of infection. **Panel D:** Reduction in transmission ( $R_{eff}$ ) as a function of population-level vaccination coverage for vaccines that prevent infection (blue) and disease (red) under targeted (solid) and uniform (dashed) vaccination programs. **Panel E:** Optimal age-specific vaccination coverage for varying levels of population-level coverage. Coloured bars represent the global optimum value whilst the grey vertical lines (dots) indicate the 2.5-97.5 percentile range (median) of near-optimal solutions (i.e., solutions with an  $R_{eff}$  within 1% of the global optimum). The top row (**i, ii**) give the results for disease-preventing vaccines and the bottom row (**iii, iv**) give the results for infection-preventing vaccines. The windows on the left (**i, iii**) give the results for vaccines with constant efficacy (70%) across all age groups and the windows on the right (**ii, iv**) give the results for vaccines with variable efficacy amongst 60+ year olds (35% v. 70% in <60 year olds).



**Figure S8. Full country results for China, allowing age-dependent clinical fraction only (M3).** **Panel A:** Population pyramid. **Panel B:** Age-specific daily contact rates. **Panel C:** Age-specific infection rates over the lifetime of infection. **Panel D:** Reduction in transmission ( $R_{\text{eff}}$ ) as a function of population-level vaccination coverage for vaccines that prevent infection (blue) and disease (red) under targeted (solid) and uniform (dashed) vaccination programs. **Panel E:** Optimal age-specific vaccination coverage for varying levels of population-level coverage. Coloured bars represent the global optimum value whilst the grey vertical lines (dots) indicate the 2.5-97.5 percentile range (median) of near-optimal solutions (i.e., solutions with an  $R_{\text{eff}}$  within 1% of the global optimum). The top row (i, ii) give the results for disease-preventing vaccines and the bottom row (iii, iv) give the results for infection-preventing vaccines. The windows on the left (i, iii) give the results for vaccines with constant efficacy (70%) across all age groups and the windows on the right (ii, iv) give the results for vaccines with variable efficacy amongst 60+ year olds (35% v. 70% in <60 year olds).



**Figure S9. Full country results for the United Kingdom, allowing age-dependent clinical fraction only (M3). Panel A:** Population pyramid. **Panel B:** Age-specific daily contact rates. **Panel C:** Age-specific infection rates over the lifetime of infection. **Panel D:** Reduction in transmission ( $R_{eff}$ ) as a function of population-level vaccination coverage for vaccines that prevent infection (blue) and disease (red) under targeted (solid) and uniform (dashed) vaccination programs. **Panel E:** Optimal age-specific vaccination coverage for varying levels of population-level coverage. Coloured bars represent the global optimum value whilst the grey vertical lines (dots) indicate the 2.5-97.5 percentile range (median) of near-optimal solutions (i.e., solutions with an  $R_{eff}$  within 1% of the global optimum). The top row (i, ii) give the results for disease-preventing vaccines and the bottom row (iii, iv) give the results for infection-preventing vaccines. The windows on the left (i, iii) give the results for vaccines with constant efficacy (70%) across all age groups and the windows on the right (ii, iv) give the results for vaccines with variable efficacy amongst 60+ year olds (35% v. 70% in <60 year olds).