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Complete List of Authors:	Mandal, Sandip ; Indian Council of Medical Research Arinaminpathy, Nimalan; Imperial College London Bhargava, Balram; Indian Council of Medical Research Panda, Samiran; Indian Council of Medical Research, Epidemiology and Communicable Disease
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PRAGMATIC COVID-19 VACCINATION STRATEGY FOR INDIA: A MATHEMATICAL MODELLING BASED ANALYSIS

Sandip Mandal, Scientist- Indian Council of Medical Research (ICMR)[1],

Nimalan Arinaminpathy, Reader in Mathematical Epidemiology, Imperial College[2],

Balram Bhargava, Director General, ICMR and Secretary, Department of Health Research[1],

Samiran Panda, Head - Epidemiology and Communicable Disease (ECD) Division, ICMR and Director, ICMR - National AIDS Research Institute (0000-0002-5077-6275)[1*]

[1]Indian Council of Medical Research, New Delhi, India

[2]MRC Centre for Global Infectious Disease Analysis, School of Public Health, Imperial College London, London, UK

Correspondence to: pandasamiran@gmail.com /pandas.hq@icmr.gov.in / director@nariindia.org

Abstract

Objectives

To investigate the impact of targeted vaccination strategies on morbidity and mortality due to COVID-19 as well as on the incidence of SARS-CoV-2, in India.

Design

Mathematical modelling.

Settings

India's vulnerability to COVID-19.

Data sources

Country specific and age-segregated pattern of social contact, case fatality rate and demographic data.

Model

An age-structured dynamical model describing SARS-CoV-2 transmission in India incorporating uncertainty in natural history parameters.

Interventions

Comparison of different vaccine strategies by targeting priority groups such as key workers including health care professionals; individuals with comorbidities aged 24 – 50 years; and all those aged over 50.

Main outcome measures

Reduction in incidence and deaths averted in different vaccination scenarios, assuming that current restrictions are fully lifted at the same time as vaccination being implemented.

Results

The priority groups together account for about 25% of India's population. An infection preventing vaccine with 60% efficacy covering all these groups would reduce peak symptomatic incidence by 34.24% (95% credible intervals (CrI) 34.04 - 34.53), and cumulative mortality by 46.38% (95% CrI 46.13 - 46.63). A similar vaccine with ability to prevent symptoms (but not infection) will reduce peak incidence of symptomatic cases by 17.57% (95% CrI 14.41 - 21.16), and cumulative mortality by 52.05% (95% CrI 51.21 - 52.98). In the event of insufficient vaccine supply to cover all priority groups, model projections suggest that vaccine strategy should prioritise all who are above 50 years of age, and subsequently individuals with comorbidities. In settings with weakest transmission, such as sparsely-populated rural areas, all three target groups should have similar priority.

Conclusions

In the context of wide heterogeneity across India, an appropriately targeted vaccination strategy would witness substantial impact on burden due to COVID-19. Smart vaccination based on such considerations, rather than mass vaccination, is therefore the need of the hour.

Strengths and limitation of this study

- The model developed in this study is informed by age-dependent risk factors for SARS-CoV-2 infection among contacts, and is stratified by co-morbidities (diabetes and/or hypertension), and vaccination status.
- Data on mortality and large-scale contact tracing from within India, and the recent national sero-survey results have been used, which constitute a major strengths of this investigation.
- Distinguishing between 'infection-' and 'symptomatic disease –' preventing vaccines, the model has been simulated under a range of scenarios for the basic reproduction number (R0).
- Should they have been available, real life country-specific data on excess risks of deaths due to comorbidities would have added strength to the presented model.
- Key priority group-specific data on social mixing and potential transmission due to the same was not available and remained as a limitation.

INTRODUCTION

COVID-19 has caused substantial morbidity and mortality worldwide, at levels not witnessed since H1N1 influenza pandemic over a century ago.[1] Non-pharmaceutical measures for its prevention such as hand hygiene, use of masks and maintaining physical distance during

social interactions have played important roles in reducing the transmission of SARS-CoV-2, the causative agent. However, globally such measures, by themselves, are impractical for sustained suppression of viral transmission for long.[2–5] In the meantime, development of vaccines against COVID-19 has progressed at an unprecedented pace. Promising results from phase 3 clinical trials of some of these candidates have emerged within a year from the publication of the whole genome sequence of SARS-CoV-2.[6] Expectations on these vaccines range from prevention of infection and reduction of disease severity, to averting deaths among most at risk population groups.

Given that COVID-19 vaccines are already becoming available for distribution through public healthcare systems, many countries[7] are now critically reviewing their vaccination plans. A major concern is how to effectively reach and engage a far larger number of individuals, the majority of whom are adults, than those typically covered under universal immunization programmes for children. Other important considerations include central storage facilities, the need for a cold chain to be maintained till vaccines are transported to the intermediary storage stations, and administered at the remotest vaccine session sites, and resource mobilization. Ethics and equity have also remained integral to these discourses[8] where 'vaccine nationalism' has also been examined in depth.[9] The country of origin of a COVID-19 vaccine; production and procurement capacities of different countries; and concerns about inequitable global vaccine distribution all compound such challenges.[9–11]

Against this background, and with a robust countrywide childhood immunization program in place, India has come to the centre-stage of discussion related to COVID-19 vaccine. The second-most populous country in the world, India has accounted, at the time of writing, for 13% of COVID-19 cases reported worldwide, exceeded only by the United States. At the same time, India is also a major source of vaccine production worldwide, accounting in 2019 for more than 60% of vaccines provided to low- and middle-income countries.[12] In anticipation of mass vaccination against COVID-19, discussions are currently underway, on which population groups to be prioritised for vaccination first. While official discussions are ongoing, three clinical priority groups so far have been proposed as priority groups in India, (i) key workers, including healthcare professionals and other frontline workers, (ii) those over 50 years of age, and (iii) those aged between 24 to 50 years having comorbidities associated with increased risk of severe outcomes of COVID-19.[13]

In order to inform these ongoing discussions, we constructed a mechanistic mathematical model to estimate the potential epidemiological impact of vaccinating the aforementioned priority groups, as well as to explore the effects of different strategies for vaccination, amongst these groups. The model is informed by age-dependent risk factors for SARS-CoV-2 infection among contacts. Mortality and contact data generated by a large-scale contact tracing study in India, [14] and the recent national sero-survey results[15] have been used for this purpose. This modelling serves to illustrate some important considerations for vaccine planning, relevant to India as well as to other countries facing similar challenges.

METHODS

Reported cases of COVID-19 are currently in decline across India,[16] presumably reflecting the impact of early measures such as nationwide lockdown and ongoing control measures such as school closures, restrictions on large gatherings, and restrictions on incoming travel from abroad. However, the second round of national survey in August 2020 suggested seroprevalence of 7.1% (95% CI 6.2 – 8.2) at the country level, well under the theoretical herd immunity threshold for SARS-CoV-2, [17] suggesting that a full easing of restrictions would lead to a rebound in transmission. We modelled the potential impact of future vaccine rollout, in mitigating such a rebound. In particular, we examined which population groups should receive the vaccination first, under different scenarios for vaccine efficacy, and for the basic reproduction number, R0. We considered the three different population groups for prioritisation listed in figure 1, as outlined in ongoing discussion about COVID-19 vaccination strategy in India.[18]

Structure of the mathematical model

The model is a deterministic, compartmental framework, illustrated in figure 2 and shown in further detail in the supporting information. The model is stratified by different age groups (<24 year, 24 – 50 year, and >50 year); it is also stratified by comorbidities (diabetes and/or hypertension), and vaccination status. The model captures essential features in the natural history of SARS-CoV-2, including the role of asymptomatic infection, and the pronounced variations in disease severity, and mortality risk, by age. To capture age-specific patterns of

transmission (the 'age-mixing' matrix), we drew from recently published findings from a large contact tracing study in India.[14] For the prevalence of comorbidities in different age groups, we drew the most recent estimates from the Global Burden of Disease study.[19] As described below, we incorporated uncertainty in model parameters by defining plausible ranges for these parameters (see table S2), and then sampling from these ranges.

Vaccination scenarios

We first modelled the potential incidence and mortality impacts of vaccination in all of the population groups identified in figure 1. Next, to examine prioritisation amongst these groups, we assumed that there is a sufficient vaccine stock to cover a given proportion *p* of the population. We identified the priority group in whom this amount of vaccine would lead to the greatest reduction in overall deaths, relative to a scenario of no vaccine; for any unused vaccine stock, we then identified the second priority group in whom these remaining vaccines would again have the greatest reduction in overall deaths. In this way, we sought to identify a priority sequence for vaccine deployment. We repeated this analysis for a range of values for *p*, upto 25% of the population (the overall proportion of the population represented by the collective priority groups in figure 1). We repeated this analysis for a range of values for R0 from 1.25 to 2.5, to capture the variability of transmission intensity across different settings within India, ranging from urban to rural.[15]

In addition, interim efficacy estimates for the most advanced vaccine candidates rely on symptomatic illness as an endpoint; the extent to which these vaccines may reduce infectiousness is currently unknown. To address these uncertainties, we modelled two types of vaccine: one that reduces susceptibility to infection with no effect on severity (an 'infection-preventing' vaccine), and one that reduces severity of infection (including mortality) with no effect on susceptibility (a 'symptomatic disease preventing' vaccine). In practice, it is likely that vaccines would have a combination of these two effects. By dichotomising their effects in this way, our analysis incorporates the range of possible scenarios for vaccine-induced immunity.

Interim trial results from three separate vaccine candidates vary from 70% to 95%, [20,21] with other vaccine candidates also under consideration for use in India. As a conservative scenario for vaccine efficacy, given the complexity of implementation in a setting like India, we assumed a vaccine efficacy scenario of 60%. We also conducted sensitivity analysis while assuming 90% efficacy. Regarding duration of vaccine-induced immunity, again conservatively a range from 3 months to 1 year was considered.[22]

Uncertainty

For each model parameter relating to natural history of SARS-CoV-2, we defined a plausible range of parameter values (see table S2). After drawing 5,000 independent samples from these ranges using latin hypercube sampling, we performed model projections on each sample; we then estimated uncertainty on model projections, by designating the 2.5th and 97.5th percentiles as the 95% 'credible interval' (CrI).

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or plans of this research. However, dissemination plan of this investigation output will ensure availability of the results in the public domain and to inform public health discussions and debate.

Results

Figure 3 shows illustrative model projections for the impact of vaccination to cover all of the priority groups listed in figure 1, in the example of the basic reproduction number R0 = 2. These results suggest that an infection-preventing vaccine with 60% efficacy could reduce peak symptomatic incidence by 34.24% (95% CrI 34.04 – 34.53) and cumulative mortality by 46.38% (95% CrI 46.13 – 46.63). A symptomatic disease preventing vaccine would have similar impacts on mortality, but little impact on symptomatic incidence. Results suggest that such a vaccine could reduce peak symptomatic incidence by 17.57% (95% CrI 14.4 1– 21.16) and cumulative mortality by 52.05% (95% CrI 51.21 – 52.98). Table 1 summarises these overall impacts, illustrating, for example, that vaccinating those over 50 years old

would offer the greatest reductions in mortality per vaccinated individual, for both infection- and symptomatic disease preventing vaccines.

Even if there is ultimately sufficient vaccine production to cover all priority groups as shown in figure 1, in practice it is likely that supply would be staggered in the initial months of vaccine deployment, thus necessitating the identification of priority groups to target in these stages. Figure 4(A-C) shows illustrative results for an infection-preventing vaccine, for the optimal priority sequencing of priority groups. Most scenarios for R0 indicate prioritisation of those most at risk from severe outcomes of infection; first those over 50 years old, and then those with comorbidities. However, in settings with low transmission (R0 = 1.25), Fig.S3 shows that there is no clear efficiency gain from prioritising any single priority group. Figure 4(D-F) shows corresponding results for a symptomatic disease preventing vaccine; here again, priority groups are consistently those over 50 years old and then those with comorbidities, including in the low-R0 scenario (Fig.4D).

Discussion

Challenges that are particularly pressing in a country as large as India would persist even following the emergence of several vaccine candidates for COVID-19. The most contentions of them relate to rolling out of vaccines at population level. In this article, we have used a simple mathematical model of transmission dynamics, to show how vaccination efforts in the country might best be focused, in order to reduce mortality most effectively with a finite vaccine supply. Our results suggest that vaccinating all defined priority groups would have a substantial reduction in overall health burden, compared to a scenario of no vaccination, and complete lifting of restrictions. Such a strategy could reduce peak symptomatic incidence by 34%, and cumulative mortality by 46% .

In terms of prioritisation of population groups, our results show how the most efficient use of a given vaccine supply is shaped by both transmission intensity (R0) and infection- vs symptomatic disease preventing effect of the vaccine (figures 4). Conceptually, the fundamental dynamics underpinning these results arise from interactions between 'direct' effects of immunisation (i.e. the protection amongst those receiving the vaccine) and 'indirect' effects (i.e. the population-level benefits of general reductions in transmission). While in practice any vaccine is likely to exert a combination of both the effects, our work highlights that, for a vaccine supply sufficient to cover 25% of the population, direct effects would generally take precedence over indirect effects, in deciding prioritisation. Thus

vaccination rollout should generally prioritise those most at risk of severe outcomes of infection: the elderly, and those with co-morbidities. However, only in the lowest-transmission settings, and with an infection-preventing vaccine, keyworkers might have similar priority as with elderly (> 50 year) and those with comorbidities (figure 4A). It is in these scenarios that indirect effects would be as important as direct effects, in rational to vaccine impact.

Our results highlight the need for further data to help inform strategic priorities, both on transmission in real world settings (i.e. R0 in any given setting) and vaccine effect on transmission. On the first of these, although clinical trials so far have focused on symptomatic illness as an endpoint, interim findings for at least one vaccine candidate suggest the potential for reduced transmission as well.[20] However, further data are needed, for example through trial designs following up household cohorts to assess the risk of transmission amongst close contacts, and how this risk is affected by vaccination. Alternatively, a better understanding of how viral load correlates with SARS-CoV-2 transmission could allow better interpretation of available trial results, in terms of transmission risk. [23,24] On the latter point mentioned above, mathematical and statistical models – similar to those we have presented here - have been used to estimate R0 for SARS-CoV-2 in different settings, and may also be informative in the Indian context.[14] We note that in a country as large and complex as India, there will be a need for locally-tailored, locally-relevant estimates. As an indication of varying transmission intensity across the country, the second national serosurvey reported 16% seroprevalence of SARS-CoV-2 antibody among those living in urban slums; 8% among those living in urban non-slum setting; and 4% in rural settings.[15] Such variation is likely to be driven by factors such as population density, and indeed may call for different prioritisation strategies in different settings. For example, scenarios of R0 = 1.25 and 2.5 may be appropriate, respectively, in tribal and urban slum settings. In all of these considerations, robust surveillance data – including at the level of hospitalisations and mortality – could add fillip to refining model estimates.

As with any modelling study, our analysis has limitations to note, which should be regarded as illustrating the importance of different factors for policy decisions, and not as a predictive framework. It is subject to various uncertainties, for example, the increased risk of death as a result of comorbidities. Further data on these excess risks will be valuable in refining our findings. In considering the key worker population, although we incorporated vaccination

coverages consistent with the size of this population, we did not explicitly capture the broader societal impact of failing to vaccinate these individuals, again, an important area for future work.

In conclusion, models such as the one presented in this article can generate useful program insights. In practice the gains, as projected by the model due to vaccination of select population groups in real life settings, would gain enhancement from other prevention measures at the population level such as use of masks and maintenance of physical distance during social interactions. Such a synergy is expected to yield further dampening of SARS-CoV-2 transmission. We therefore conclude that rational and focused vaccination approaches, as outlined in this article, in the context of Indian COVID-19 epidemic makes for a smarter public health choice than mass vaccination.

	Infection preventing vaccine			Symptomatic disease preventing vaccine		
	Percentage reduction in peak symptomatic incidence	Percentage reduction in cumulative mortality	Number needed to vaccinate to avert one death	Percentage reduction in peak symptomatic incidence	Percentage reduction in cumulative mortality	Number needed to vaccinate to avert one death
(A) key workers (HCW + FW)	3.81 (3.76 – 3.87)	2.07 (2.06 – 2.07)	142 (95 - 232)	1.87 (1.53- 2.33)	2.01 (1.88 – 2.17)	146 (95 - 240)
(B) Key workers + Individuals with comorbidities (24 – 50 year)	13.52 (13.36 – 13.67)	5.93 (5.89- 5.96)	163 (106 – 285)	6.63 (5.33-8.13)	5.57 (5.11 – 6.12)	177 (111 - 303)

(C) Above two groups (A+B) + all individuals over 50 year of age	34.24 (34.04 – 34.53)	46.38 (46.13 – 46.63)	77 (49 – 125)	17.57 (14.41 – 21.16)	52.05 (51.21 – 52.98)	67 (44 - 106)

Table 1. Summary of epidemiological impacts for the different scenarios shown in figure 3. Numbers show median estimates, while parentheses show 95% credible intervals.

Author contributions

SP and BB conceptualised the study; SM, NA and SP developed the modelling approach and SM performed the modelling. All authors analysed and interpreted the results; SM and SP wrote a first draft of the manuscript, and all authors contributed to the final draft and approved the version for submission to the journal.

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Competing interests

The authors declare no competing interests.

Ethical approval

Not required.

Data sharing

The model code and dataset are available on request from the first author (SM) sandipccmb@gmail.com

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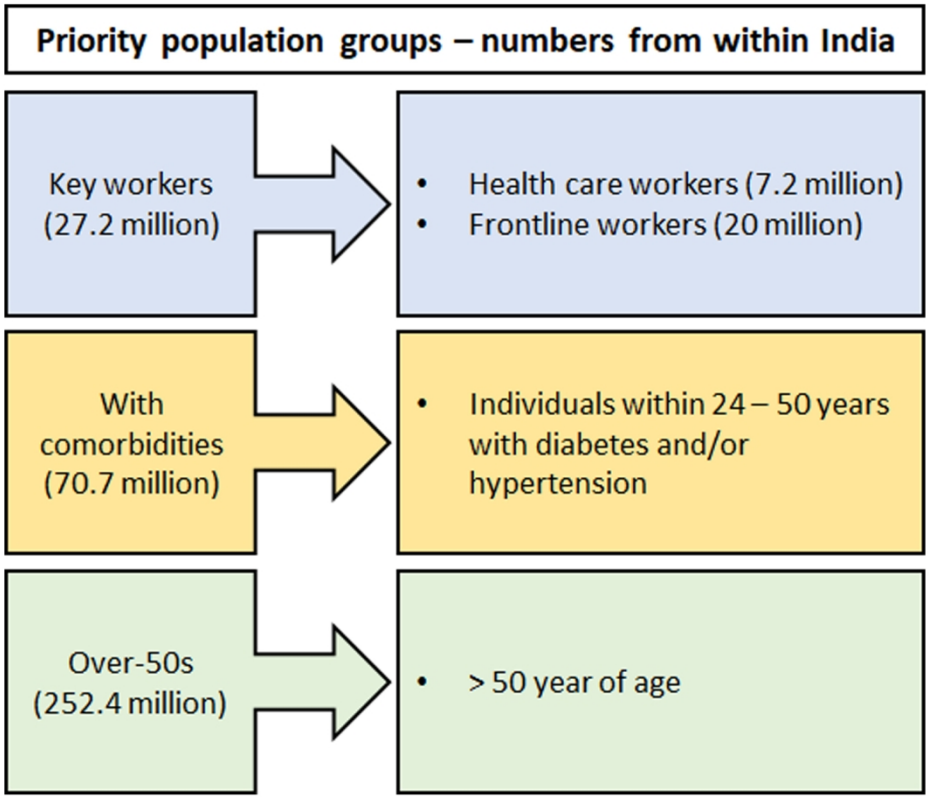
Figure Captions

Figure 1. Priority groups of people in three different scenarios. Sources: healthcare workers (HCW)[25], frontline workers (FW), those with diabetes and hypertension as co-morbidities[26], those over 50 years of age[27]. As described in the main text, when modelling vaccination coverage amongst essential workers, our focus is on the epidemiological impact of doing so (we do not address, for the example, the potential impacts for healthcare continuity, of vaccination coverage in HCWs).

Figure 2. Illustration of the compartmental model structure. The top and bottom halves of the figure show unvaccinated and vaccinated subpopulations, respectively. Boxes represent compartments, and arrows represent flows between different stages of the clinical course of infection. Compartments are as follows: Uninfected (U); Exposed (E); asymptomatic but infectious (A); presymptomatic (P); symptomatic (S); recovered and immune (R). The terms c_1,c_2 represent effectiveness of, respectively, an infection preventing and symptomatic disease preventing vaccine. The term μ represents the per-capita hazard of mortality; see table S2 for a list of all other model parameters. This model structure is further stratified by age groups, and by presence/absence of comorbidities.

Figure 3. Illustration of vaccine impact in each of the priority groups listed in Figure 1. Scenarios are shown in the example of R0 = 2, assuming that vaccine coverage is completed at the same time as current restrictions being fully lifted. Upper row shows results for an infection-preventing vaccine, while the lower row shows results from a symptomatic disease preventing vaccine. Scenarios show vaccination coverage in different combinations of priority groups: Keyworkers ('KeyW'); additionally including those with co-morbidities ('Co-M'); and additionally including those over 50 years of age ('>50').All horizontal axes show days after vaccination and restrictions being lifted. Solid lines show central (median) estimates, while shaded areas show 95% credible intervals as estimated by sampling uniformly from the ranges shown in table S2. The overall impact of vaccination in each of these scenarios is summarised in table 1, together with the amount of vaccines needed.

Figure 4. Prioritisation strategies for an infection-preventing vaccine (A, B, C) and for a symptomatic disease preventing vaccine (D, E, F). For the plots (A – C) we assume deployment of a vaccine having 60% efficacy in reducing susceptibility to infection, but no effect on development of symptoms following infection.The three priority groups listed in Fig.1 can be ordered in six distinct ways, for the priority sequence in which they would receive the vaccine (shown in Figs. S1 – S3, appendix). Here, we show optimal sequences for group prioritisation for minimising the overall mortality, under different levels of vaccine coverage, and for different values of R0. For example,in the case R0 = 2, if initial vaccine supply is only enough to cover 10% of the population, these vaccines should be deployed first amongst the over-50s (in green). If there is enough vaccine supply to cover 20% of the population, the optimal strategy would be to vaccinate the over-50s first, before spending the remaining vaccine supply amongst those with comorbidities. Similar priorities apply for R0 = 2.5. However, for low-transmission settings (R0 = 1.25), there is no clear prioritisation amongst the three priority groups. Fig.4A shows two example scenarios superimposed, illustrating their similarity; see Fig.S3 in the appendix for all 6 possible scenarios. For the plots (D – F) we assume deployment of a vaccine having 60% efficacy in reducing symptoms and mortality following infection, but no preventive effect on acquiring infection. For a symptomatic disease preventing vaccine, optimal prioritisation strategy is consistent across all R0 scenarios: first to cover those over 50 years old; then to cover those with comorbidities; and finally to cover keyworkers.



Priority groups of people in three different scenarios. Sources: healthcare workers (HCW) [Ref.25], frontline workers (FW), those with diabetes and hypertension as co-morbidities [Ref. 26], those over 50 years of age [Ref. 27]. As described in the main text, when modelling vaccination coverage amongst essential workers, our focus is on the epidemiological impact of doing so (we do not address, for the example, the potential impacts for healthcare continuity, of vaccination coverage in HCWs).

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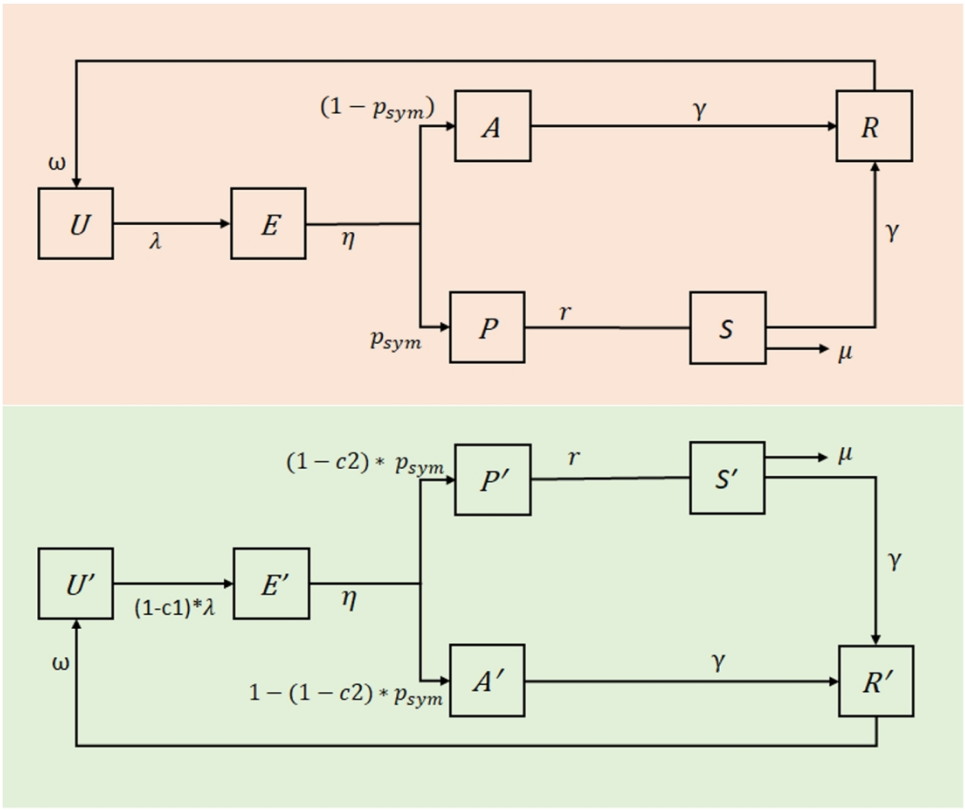

Illustration of the compartmental model structure. The top and bottom halves of the figure show unvaccinated and vaccinated subpopulations, respectively. Boxes represent compartments, and arrows represent flows between different stages of the clinical course of infection. Compartments are as follows: Uninfected (U); Exposed (E); asymptomatic but infectious (A); presymptomatic (P); symptomatic (S); recovered and immune (R). The terms c_1,c_2 represent effectiveness of, respectively, an infection preventing and symptomatic disease preventing vaccine. The term μ represents the per-capita hazard of mortality; see table S2 for a list of all other model parameters. This model structure is further stratified by age groups, and by presence/absence of comorbidities.

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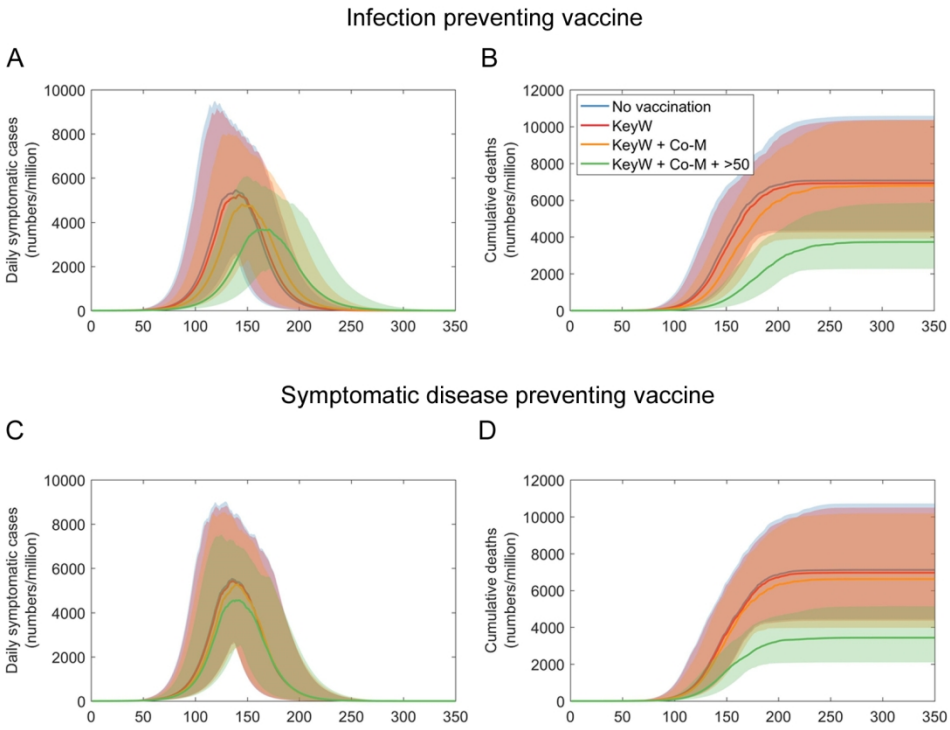
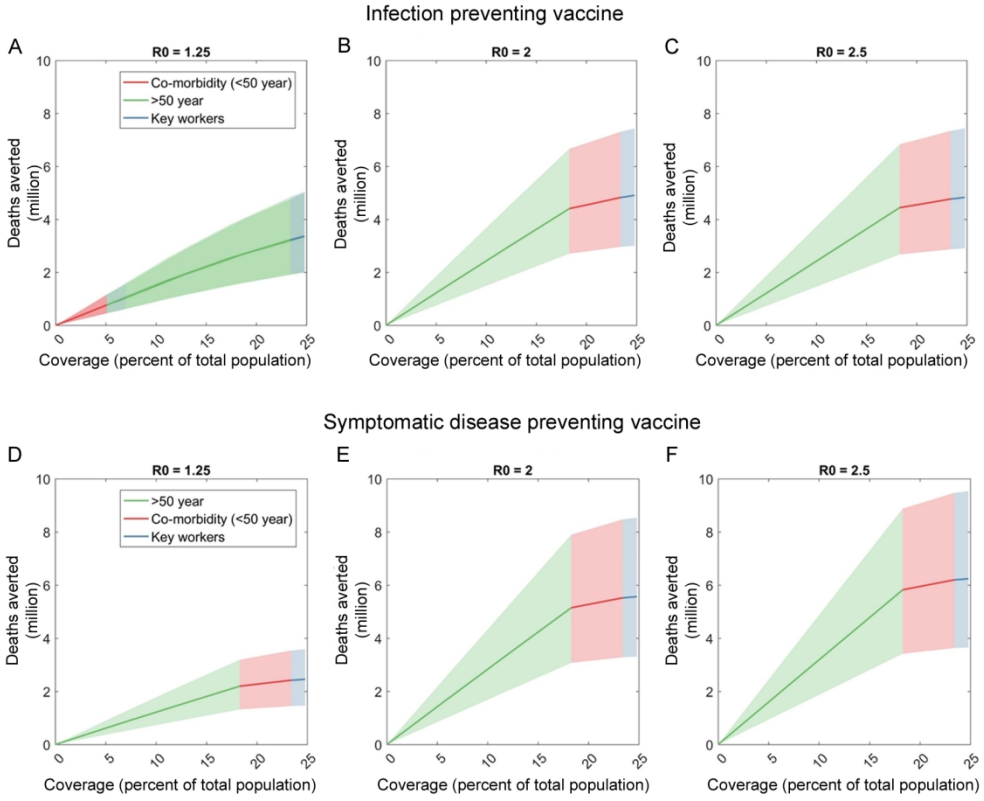


Illustration of vaccine impact in each of the priority groups listed in Figure 1. Scenarios are shown in the example of R0 = 2, assuming that vaccine coverage is completed at the same time as current restrictions being fully lifted. Upper row shows results for an infection-preventing vaccine, while the lower row shows results from a symptomatic disease preventing vaccine. Scenarios show vaccination coverage in different combinations of priority groups: Keyworkers ('KeyW'); additionally including those with co-morbidities ('Co-M'); and additionally including those over 50 years of age ('>50').All horizontal axes show days after vaccination and restrictions being lifted. Solid lines show central (median) estimates, while shaded areas show 95% credible intervals as estimated by sampling uniformly from the ranges shown in table S2. The overall impact of vaccination in each of these scenarios is summarised in table 1, together with the amount of vaccines needed.

147x120mm (300 x 300 DPI)



Prioritisation strategies for an infection-preventing vaccine (A, B, C) and for a symptomatic disease preventing vaccine (D, E, F). For the plots (A – C) we assume deployment of a vaccine having 60% efficacy in reducing susceptibility to infection, but no effect on development of symptoms following infection.The three priority groups listed in Fig.1 can be ordered in six distinct ways, for the priority sequence in which they would receive the vaccine (shown in Figs. S1 – S3, appendix). Here, we show optimal sequences for group prioritisation for minimising the overall mortality, under different levels of vaccine coverage, and for different values of R0. For example,in the case R0 = 2, if initial vaccine supply is only enough to cover 10% of the population, these vaccines should be deployed first amongst the over-50s (in green). If there is enough vaccine supply to cover 20% of the population, the optimal strategy would be to vaccinate the over-50s first, before spending the remaining vaccine supply amongst those with comorbidities. Similar priorities apply for R0 = 2.5. However, for low-transmission settings (R0 = 1.25), there is no clear prioritisation amongst the three priority groups. Fig.4A shows two example scenarios superimposed, illustrating their similarity; see Fig.S3 in the appendix for all 6 possible scenarios. For the plots (D – F) we assume deployment of a vaccine having 60% efficacy in reducing symptoms and mortality following infection, but no preventive effect on acquiring infection. For a symptomatic disease preventing vaccine, optimal prioritisation strategy is consistent across all R0 scenarios: first to cover those over 50 years old; then to cover those with comorbidities; and finally to cover keyworkers.

152x125mm (300 x 300 DPI)

PRAGMATIC COVID-19 VACCINATION STRATEGY FOR INDIA: A MATHEMATICAL MODELLING BASED ANALYSIS

Sandip Mandal[1], Nimalan Arinaminpathy[2], Balram Bhargava[1], Samiran Panda (0000-0002-5077-6275)[1*]

[1]Indian Council of Medical Research, New Delhi, India

[2]MRC Centre for Global Infectious Disease Analysis, School of Public Health, Imperial College London, London, UK

Correspondence to: pandasamiran@gmail.com /pandas.hq@icmr.gov.in/ director@nariindia.org

Supplementary materials

1. Model specification

We developed a deterministic, compartmental model of SARS-CoV-2 transmission and disease course with three different age groups: <24 year, 24 - 50 year and >50 year, and further stratified by the presence of comorbidities.

Governing equations

Model compartments are listed in Table S1, and model parameters listed in Table S2. Governing equations for the non-vaccinated population are as follows, where subscript i denotes age group, and subscript j denotes comorbidity group:

Uninfected (U):

$$\frac{dU_{ij}}{dt} = -\lambda_i U_{ij}$$

Exposed but not yet infectious (E):

$$\frac{dE_{ij}}{dt} = \lambda_i U_{ij} - \eta E_{ij}$$

Asymptomatic and infectious (A):

$$\frac{dA_{ij}}{dt} = \eta\left(1 - p^{(sym)}\right)E_{ij} - \gamma A_{ij}$$

Presymptomatic and infectious (P):

$$\frac{dP_{ij}}{dt} = \eta\, p^{(sym)}\, E_{ij} - r\, P_{ij}$$

Symptomatic and infectious (S):

$$\frac{dS_{ij}}{dt} = rP_{ij} - \mu_{ij}\, S_{ij}$$

Recovered and partially immune (R):

$$\frac{dR_{ij}}{dt} = \gamma(A_{ij} + S_{ij}) - \omega\, R_{ij}$$

A key parameter here is $p^{(sym)}$, the proportion of infected individuals developing symptoms.

Corresponding equations apply for the vaccinated compartments, but with primes distinguishing these compartments (e.g. U'). Additionally for this population, the term $p^{(sym)}$ is replaced by $(1 - c_2)p^{(sym)}$, where c_2 is vaccine efficacy in preventing disease.

For the force-of-infection experienced by non-vaccinated individuals, we have:

$$\lambda_i = \sum_{k,l} \beta\, m_{ik} \left\{ \left[S_{kl} + k\,(A_{kl} + P_{kl}) \right] + \left[S'_{kl} + k\,(A'_{kl} + P'_{kl}) \right] \right\}$$

And for vaccinated individuals:

$$\lambda'_i = (1 - c_1)\, \lambda_i,$$

where c_1 is the effect of the vaccine on reducing susceptibility to infection.

State symbol	Meaning
U_i	Uninfected (i = 1, 2, 3 indicating three age groups)
E_i	Exposed
A_i	Asymptomatic
P_i	Pre-symptomatic
S_i	Severe symptomatic
R_i	Recovered

Table S1 List of state variables

Parameter	Meaning	Values			Source/Remarks
β	Transmission rate	0.079 – 0.16			Calculated using next-generation matrix as described in ref[1]. Value shown here is to yield R0 = 1.25 – 2.5.
η	Incubation rate	(1/4 – 1/6) /day			Corresponds to an average incubation period of 4 to 6 days [2]
$p^{(sym)}$	Proportion developing symptoms	1/3 – 2/3			Wide variation noted in individual studies and meta-analysis [3–5]
k	Relative infectiousness of asymptomatic vs symptomatic infection	2/3 – 1			
r	Rate of developing symptoms	1 /day			Assumption, corresponds to mean pre-symptomatic duration of 1 day
γ	Recovery rate	0.2 /day			Assumption, corresponds to mean infectious period of 5 days[6]
ω	Per-capita rate at which post-infection immunity wanes	(1/365 – 1/90) /day			Assuming mean duration of immunity lasts for 3 months to 1 year.[7]
f	Fold-increase in case fatality rate as a result of comorbidities (diabetes and/or hypertension)	2.5			Drawn from recent systematic review [8]
	Age groups	<24 year	24-50 year	>50 year	

CFR_i	Case fatality rate in age group *i* in absence of comorbidities	0.1%	0.69%	6.42 %	Drawn from a recent study from two Indian States.[9]
μ_i	Mortality rate for severe cases	0.0002 /day	0.0014 /day	0.0137 /day	Hazard rates of μ_i are calculated to yield case fatality rates, using: $CFR_i = \mu_i/(\mu_i + \gamma)$
N_i	Population (India)	634.8 mn	492.7 mn	252.5 mn	Extrapolated from the Census of India 2011[10]
m_{ij}	Connectivity matrix between age group i with age group j	1.37 1.79 1.00	1.04 1.47 0.86	0.44 0.61 0.41	Drawn from ref.[9]

Table S2: Parameters used in the model simulation. There remains much uncertainty about parameters relating to SARS-CoV-2 natural history, e.g. infectiousness of asymptomatic people relative to symptomatic ones and, duration of pre-symptomatic period etc. In this study we adopted a range of parameter values to reflect this uncertainty in our model projections (figure 3-5, main text).

2. Priority population groups for vaccination – further information

Category	Numbers		Source
Number of healthcare workers (HCW)			
HCWs (qualified)	3827820		Karan et al (2019) [11]
Support workers	1245878		
HCW (without requisite qualifications)	2084185		
Total	7157883		
Frontline workers (FW)			
	Active	**Reserve**	
Armed forces	1443921	1155000	Information available in public domain [12,13]
Paramilitary forces	87000		
Central Armed Forces and Others	1403700	987800	
Municipal workers	15000000		
Total	20077421		
Co-morbidity (diabetes and/or hypertension)			
Population < 24 year of age with at-least one comorbidity	17801137 (2.8% population in this age group)		WHO SAGE report, 2013[14]
Population 24 – 50 year of age with at-least one comorbidity	70657970 (14.3% population in this age group)		
Population >50 year of age with at-least one comorbidity	73920897 (29.3% population in this age group)		
Elderly population			
Population > 50 year of age	252540802		Extrapolated from the Census of India 2011[10]

3. Additional model outputs

Figure 4 in the main text shows model results for how priority groups might be sequenced, to gain maximum impact (lives saved) from a limited vaccine supply. While the figure shows only the 'optimal' scenario, Figures S1 below shows all 6 possible scenarios for the order in which vaccination is deployed amongst the three priority groups, in the case of an infection-preventing vaccine. Of these, the optimally efficient scenario is selected as that with the greatest gradient (lives saved per person vaccinated) at each stage, i.e. the scenario having the most concave shape. These optimally efficient scenarios are shown highlighted in each set of figures with a red box.

Scenario definitions are as follows:
Scenario 1: Key workers → Co-morbidity → Elderly
Scenario 2: Key workers → Elderly → Co-morbidity
Scenario 3: Co-morbidity → Key workers → Elderly
Scenario 4: Co-morbidity → Elderly → Key workers
Scenario 5: Elderly → Key workers → Co-morbidity
Scenario 6: Elderly → Co-morbidity → Key workers

Figures S2 show corresponding results in the case of a disease-preventing vaccine.

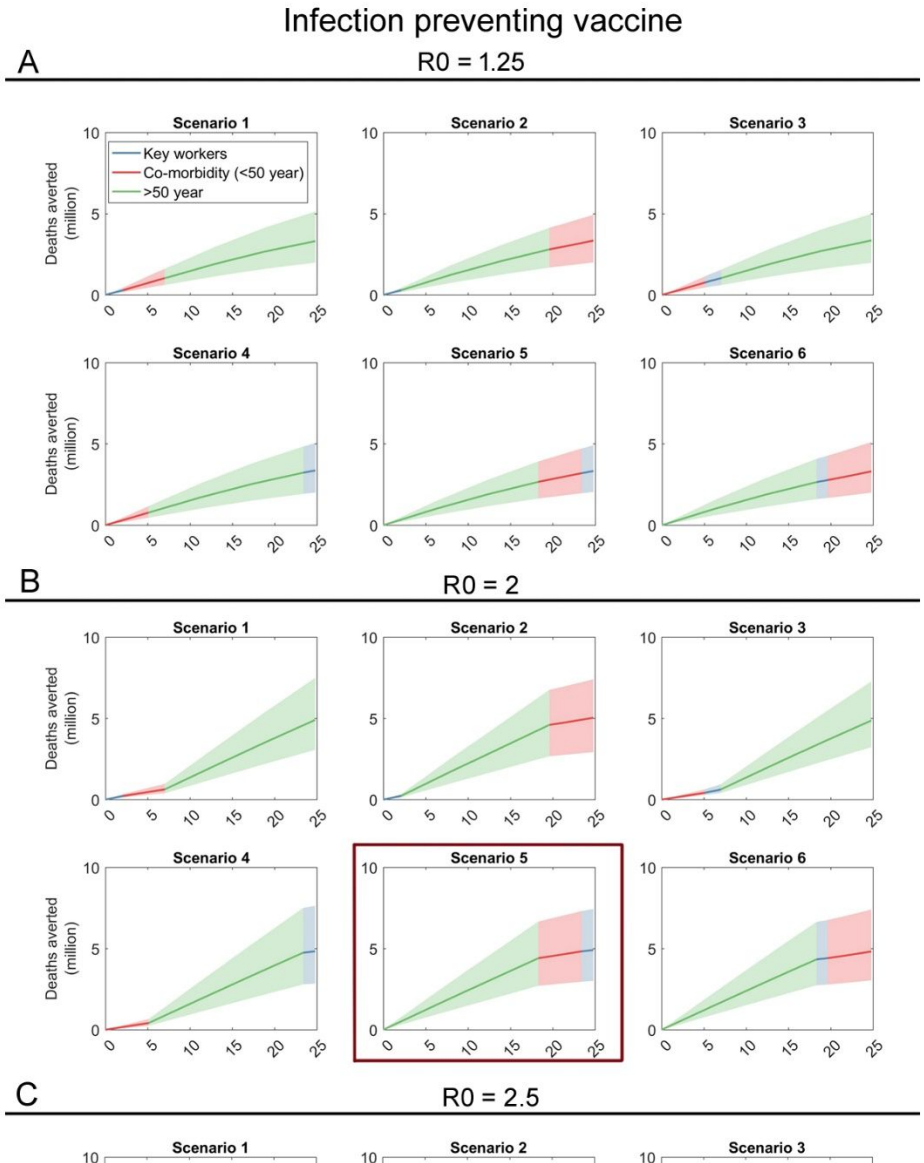


Figure S1. Scenarios for the order in which vaccination is deployed amongst the three priority groups, in the case of an infection-preventing vaccine of efficacy 60%. Optimally efficient scenarios are shown highlighted in each set of figures with a red box, with the exception of R0 =1.25, where no clear 'optimal' sequence is observed.

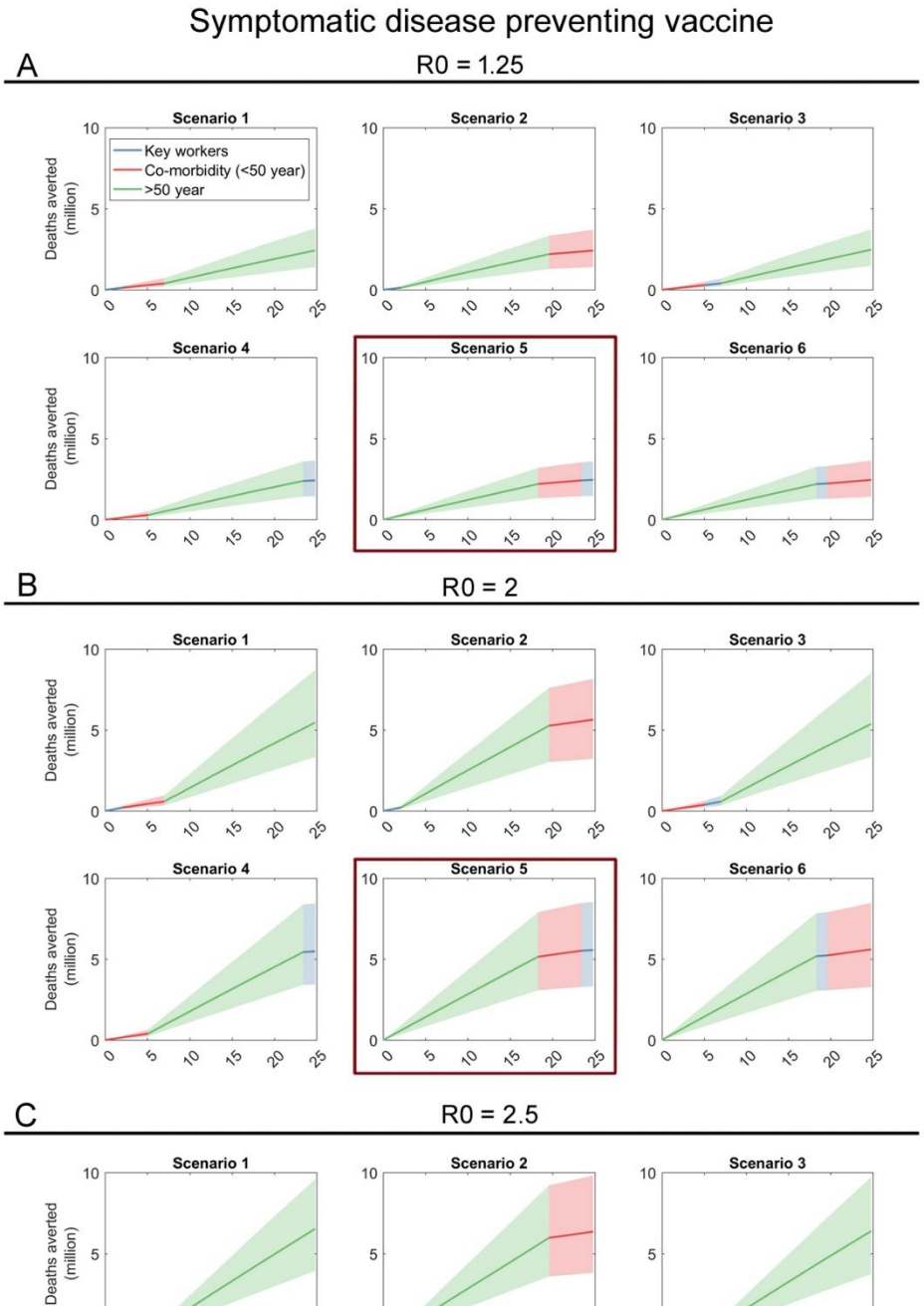


Figure S2. Scenarios as in figure S1, in the case of a disease-preventing vaccine of efficacy 60%. Optimally efficient scenarios are shown highlighted in each set of figures with a red box.

4. Sensitivity analysis to vaccine efficacy

While results in the main text assumed (conservatively) a vaccine efficacy of 60%, below we present alternative results for 90%, showing that Figures 4 and 5 in the main text remain qualitatively unchanged.

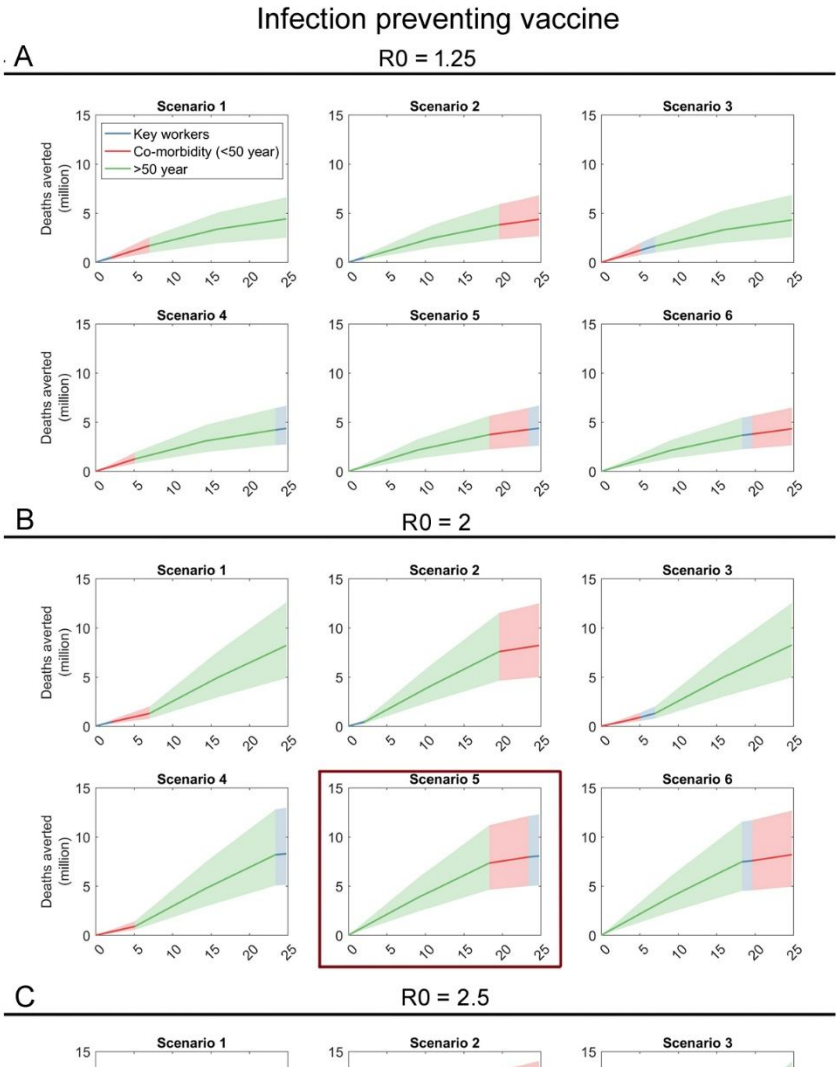


Figure S3. Scenarios for the order in which vaccination is deployed amongst the three priority groups, in the case of an infection-preventing vaccine of efficacy 90%. Optimally

efficient scenarios are shown highlighted in each set of figures with a red box. No clear 'optimal' sequence is observed for R0 =1.25.

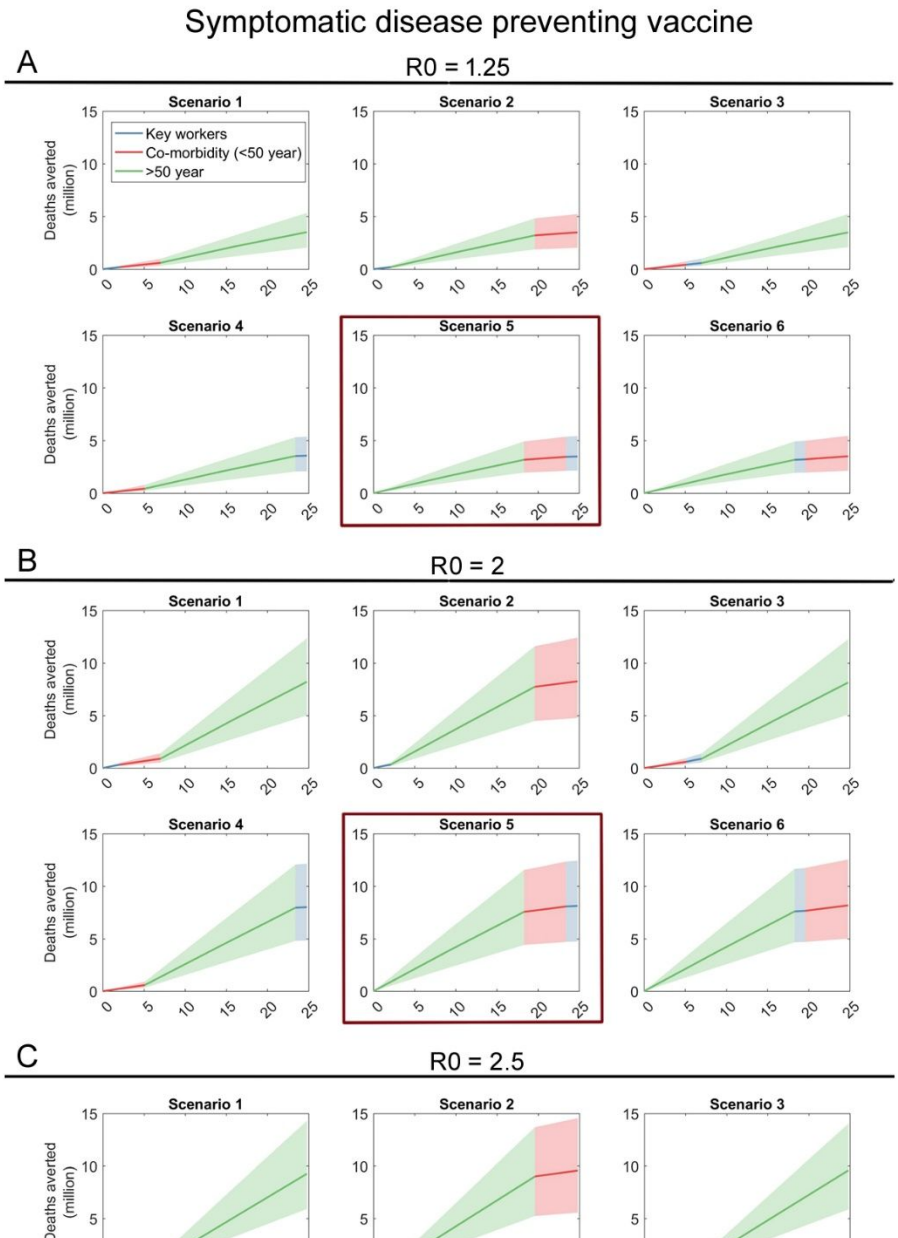


Figure S4. Scenarios as in figure S3, in the case of a disease-preventing vaccine of efficacy 90%. Optimally efficient scenarios are shown highlighted in each set of figures with a red box.

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TRIPOD Checklist: Prediction Model Development

Section/Topic	Item	Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	3,4
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	4,5
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	5,6
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	N/A
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	N/A
	5b	Describe eligibility criteria for participants.	N/A
	5c	Give details of treatments received, if relevant.	N/A
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	7,8
	6b	Report any actions to blind assessment of the outcome to be predicted.	N/A
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	Table S2
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	N/A
Sample size	8	Explain how the study size was arrived at.	N/A
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	N/A
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	5,6
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	5,6, SI ps 1-2
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	Figs. S1-S4
Risk groups	11	Provide details on how risk groups were created, if done.	N/A
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	Fig. 1
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	SI ps 5
Model development	14a	Specify the number of participants and outcome events in each analysis.	N/A
	14b	If done, report the unadjusted association between each candidate predictor and outcome.	7
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	5, Fig 3-4.
	15b	Explain how to the use the prediction model.	8
Model performance	16	Report performance measures (with CIs) for the prediction model.	Table 1
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	9,10
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	8-10
Implications	20	Discuss the potential clinical use of the model and implications for future research.	10
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	SI ps 1-5
Funding	22	Give the source of funding and the role of the funders for the present study.	11

We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

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INDIA'S PRAGMATIC VACCINATION STRATEGY AGAINST COVID-19: A MATHEMATICAL MODELLING BASED ANALYSIS

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INDIA'S PRAGMATIC VACCINATION STRATEGY AGAINST COVID-19: A MATHEMATICAL MODELLING BASED ANALYSIS

Sandip Mandal, Scientist- Indian Council of Medical Research (ICMR)[1],

Nimalan Arinaminpathy, Reader in Mathematical Epidemiology, Imperial College[2],

Balram Bhargava, Director General, ICMR and Secretary, Department of Health Research[1],

Samiran Panda, Head - Epidemiology and Communicable Disease (ECD) Division, ICMR and Director, ICMR - National AIDS Research Institute (0000-0002-5077-6275)[1*]

[1]Indian Council of Medical Research, New Delhi, India

[2]MRC Centre for Global Infectious Disease Analysis, School of Public Health, Imperial College London, London, UK

Correspondence to: pandasamiran@gmail.com /pandas.hq@icmr.gov.in / director@nariindia.org

Abstract

Objectives

To investigate the impact of targeted vaccination strategies on morbidity and mortality due to COVID-19, as well as on the incidence of SARS-CoV-2, in India.

Design

Mathematical modelling.

Settings

Indian epidemic of COVID-19 and vulnerable population.

Data sources

Country specific and age-segregated pattern of social contact, case fatality rate and demographic data obtained from peer-reviewed literature and public domain.

Model

An age-structured dynamical model describing SARS-CoV-2 transmission in India incorporating uncertainty in natural history parameters was constructed.

Interventions

Comparison of different vaccine strategies by targeting priority groups such as key workers including health care professionals, individuals with comorbidities (24 – 60 year), and all above 60.

Main outcome measures

Incidence reduction and averted deaths in different scenarios, assuming that the current restrictions are fully lifted as vaccination is implemented.

Results

The priority groups together account for about 18% of India's population. An infection preventing vaccine with 60% efficacy covering all these groups would reduce peak symptomatic incidence by 20.6% (95% uncertainty intervals (CrI) 16.7 - 25.4), and cumulative mortality by 29.7% (95% CrI 25.8- 33.8). A similar vaccine with ability to prevent symptoms (but not infection) will reduce peak incidence of symptomatic cases by 10.4% (95% CrI 8.4 – 13.0), and cumulative mortality by 32.9% (95% CrI 28.6 - 37.3). In the event of insufficient vaccine supply to cover all priority groups, model projections suggest that after keyworkers, vaccine strategy should prioritise all who are > 60, and subsequently individuals with comorbidities. In settings with weakest transmission, such as sparsely-populated rural areas, those with comorbidities should be prioritised after keyworkers.

Conclusions

An appropriately targeted vaccination strategy would witness substantial mitigation of impact of COVID-19 in a country like India with wide heterogenity. 'Smart vaccination', based on public health considerations, rather than mass vaccination, appears prudent.

Strengths and limitation of this study

- The model in this study is informed by age-dependent risk factors for SARS-CoV-2 infection among contacts, and is stratified by co-morbidities (diabetes and/or hypertension), and vaccination status.
- Data on mortality and large-scale contact tracing from within India, and the recent national sero-survey results were used, which constituted a major strength of this investigation.
- Distinguishing between 'infection' and 'symptomatic disease ' preventing vaccines, the model was simulated under a range of scenarios for the basic reproduction number (R0).
- Should they have been available, real life country-specific data on excess risks of deaths due to comorbidities would have added strength to the presented model.
- Key priority group-specific data on social mixing and potential associated transmission was not available, and remained as a limitation.

INTRODUCTION

COVID-19 has caused substantial morbidity and mortality worldwide, at levels not witnessed since the H1N1 influenza pandemic over a century ago.[1] Non-pharmaceutical measures for its prevention such as hand hygiene, use of masks and maintaining physical distance during social interactions have played important roles in reducing the transmission of SARS-CoV-2, the causative agent. However, such measures, by themselves, are impractical for sustained

suppression of viral transmission for long.[2–5] In the meantime, development of vaccines against COVID-19 has progressed at an unprecedented pace. Promising results from phase 3 clinical trials of some of these candidates have emerged within a year from the publication of the whole genome sequence of SARS-CoV-2.[6] Expectations on these vaccines range from prevention of infection and reduction of disease severity, to averting deaths among most at risk population groups.

Given that COVID-19 vaccines are already becoming available for distribution through public healthcare systems, many countries[7] are now critically reviewing their vaccination plans. A major concern is how to effectively reach and engage a far larger number of individuals, the majority of whom are adults, than those typically covered under universal immunization programmes for children. Other important considerations include central storage facilities, the need for a cold chain to be maintained till vaccines are transported to the intermediary storage stations, and administered at the remotest vaccine session sites, and resource mobilization. Ethics and equity have also remained integral to these discourses[8] where 'vaccine nationalism' has been examined in depth.[9] The country of origin of a COVID-19 vaccine, production and procurement capacities of different countries, and concerns about inequitable global vaccine distribution; all compound such challenges.[9–11]

Against this background, and with a robust countrywide immunization program for children in place, India has come to the centre-stage of discussion related to COVID-19 vaccine. The second-most populous country in the world, India has accounted, at the time of writing, for 9% of COVID-19 cases reported worldwide, exceeded only by the United States and Brazil. Worth noting in this context is that India serves as a major source of vaccine production worldwide, accounting in 2019 for more than 60% of vaccines provided to low- and middle-income countries.[12] In anticipation of mass vaccination against COVID-19, discussions were held on which population groups to be prioritised for vaccination. Three priority groups so far have been proposed based on public health considerations in India, (i) key workers, including healthcare professionals and other frontline workers, (ii) those over 60 years of age, and (iii) those aged between 24 to 60 years having comorbidities, as they are at increased risk of severe COVID-19 disease.[13]

In order to inform these discussions, we constructed a mechanistic mathematical model to estimate potential epidemiological impact of vaccinating the aforementioned priority

groups, as well as to explore the effects of different strategies for vaccination, amongst these groups. The model is informed by age-dependent risk factors for SARS-CoV-2 infection among contacts. Mortality and contact data generated by a large-scale contact tracing study in India, [14] and the recent national sero-survey results[15] have been used for this purpose. This modelling serves to illustrate some important considerations for vaccine planning, relevant to India as well as to other countries facing similar challenges.

METHODS

India's national serological survey completed its second round in August 2020, and estimated a seroprevalence of 7.1% (95% CI 6.2 – 8.2) at the country level, well under the theoretical herd immunity threshold for SARS-CoV-2. [16] The third round, completed in January 2021, estimated the seroprevalence to be 25%, underlining again the existence of a considerable proportion of vulnerable population in the country. Such findings suggested that a full easing of restrictions would lead to a rebound in transmission. (Indeed, several parts of the country are already seeing an increase in infections at the time of writing.) We modelled the potential impact of future vaccine rollout, in mitigating such a rebound. In particular, we examined which population groups should receive the vaccination first, under different scenarios for vaccine efficacy, and for the basic reproduction number, R0 (the latter, as estimated in the absence of any infection- or vaccine-induced immunity). We considered three different population groups for discussion as listed in figure 1, and in line with the ground reality in India.[17] Consistent with ongoing practice, we assumed that key workers would receive vaccine first due to obvious ethical consideration (i.e. we excluded alternative scenarios where other groups might be prioritised over key workers). Holding this as a given, we examined the conditions under which those over 60 years of age should subsequently be prioritised over those with comorbidities, and vice versa.

Structure of the mathematical model

The model is a deterministic, compartmental framework, illustrated in figure 2 and shown in further detail in the supporting information. The model is stratified by different age groups

(<24 year, 24 – 60 year, and >60 year); it is also stratified by comorbidities (diabetes and/or hypertension), and vaccination status. The model captures essential features in the natural history of SARS-CoV-2, including the role of asymptomatic infection, and the pronounced variations in disease severity, and mortality risk, by age (see table S1). To capture age-specific patterns of transmission (the 'age-mixing' matrix), we drew from recently published findings from a large contact tracing study in India.[14] For the prevalence of comorbidities in different age groups, we drew the most recent estimates from the Global Burden of Disease study.[18] As described below, we incorporated uncertainty in model parameters by defining plausible ranges for these parameters (see table S2), and then sampling from these ranges.

Vaccination scenarios

We first modelled the potential impact of vaccination on incidence and mortality in all of the population groups identified in figure 1 (see table S3). Next, to examine prioritisation amongst these groups, we assumed that there is a sufficient vaccine stock to cover a given proportion *p* of the overall population. Assuming that key workers would receive first priority, we identified the second priority group in whom this amount of vaccine would lead to the greatest reduction in overall deaths, relative to a scenario of no vaccine; for any unused vaccine stock, we then identified how much of the remaining priority group would be covered with the remaining vaccine supply. We note that this analysis does not address temporal sequencing (i.e. which groups to vaccinate first in time). For instance, if model results suggest that the greatest mortality reductions could be achieved through vaccinating 100% of a given group and using remaining vaccine to immunise 25% of the remaining priority group, in practice the implementation of this coverage could proceed in both groups simultaneously. For simplicity in the modelling, for a given vaccine supply, we assumed that vaccination coverage is completed in advance of the epidemic (and can thus be modelled through initial conditions for the dynamical equations). We simulated deaths averted by vaccination, relative to a scenario of no vaccination. However, for comparison, we also modelled a 'uniform' strategy where vaccine supply is allocated proportionately amongst the two risk groups (those above 60 year of age and those between 24-60 year and with co-morbidity), rather than prioritising one over the other.

We repeated this analysis for a range of values for *p*, up to 18% of the population (the overall proportion of the population represented by the collective priority groups in figure 1). We also repeated this analysis for a range of values for R0 from 1.25 to 2.5, to capture the variability of transmission intensity across different settings within India, ranging from urban to rural.[15]

In addition, efficacy estimates for currently licensed vaccines – whether obtained through interim analyses or through bridging studies or trials in other countries - rely on symptomatic illness as an endpoint. The extent to which these vaccines may reduce infectiousness is currently unknown. In order to address these uncertainties, we modelled two types of vaccine: one that reduces susceptibility to infection with no effect on severity (an 'infection-preventing' vaccine), and one that reduces severity of infection (including mortality) with no effect on susceptibility (a 'symptomatic disease preventing/modifying' vaccine). In practice, it is likely that vaccines would have a combination of these two effects. By dichotomising their effects in this way, our analysis incorporates a range of possible scenarios for vaccine-induced protection.

Interim trial results from three separate vaccine candidates vary from 70% to 95%, [19,20] with other vaccine candidates also under consideration for use in India. As a conservative scenario for vaccine efficacy, given the complexity of implementation in a setting like India, we assumed a vaccine efficacy scenario of 60%. As a sensitivity analysis, we also simulated an alternative vaccine efficacy of 90% (Figs. S3 – S4). Regarding duration of vaccine-induced immunity, again conservatively a range from 3 months to 1 year was considered.[21]

Uncertainty

For each model parameter relating to natural history of SARS-CoV-2 infection, we defined a plausible range of parameter values (see table S2). After drawing 5,000 independent samples from these ranges using latin hypercube sampling, we performed model projections on each sample and then estimated uncertainty on model projections, by designating the 2.5th and 97.5th percentiles as the 95% 'uncertainty interval' (CrI).

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or plans of this research. However, dissemination plan of this investigation output will ensure availability of the results in the public domain and to inform public health discussions and debate.

Results

Figure 3 shows illustrative model projections for the impact of vaccination to cover all of the priority groups listed in figure 1, in the example of the basic reproduction number R0 = 2. These results suggest that an infection-preventing vaccine with 60% efficacy could reduce peak symptomatic incidence by 20.6% (95% CrI 16.7 – 25.4) and cumulative mortality by 29.7% (95% CrI 25.8 – 33.8), relative to a scenario of no vaccination. A symptomatic disease preventing vaccine would have similar impacts on mortality, but little impact on symptomatic incidence. Results suggest that such a vaccine could reduce peak symptomatic incidence by 10.4% (95% CrI 8.4– 13.0) and cumulative mortality by 32.9% (95% CrI 28.6 – 37.3). Table 1 summarises these overall impacts, illustrating, for example, that vaccinating those over 60 year old would offer the greatest reductions in mortality per vaccinated individual, for both infection and symptomatic disease preventing vaccines.

Even if there is ultimately sufficient vaccine production to cover all priority groups as shown in figure 1, in practice it is likely that supply would be staggered in the initial months of vaccine deployment, thus necessitating the identification of priority groups to target in these stages. Figure 4(A-C) shows illustrative results for an infection-preventing vaccine, for the optimal sequencing of priority groups. Most scenarios for R0, indicate prioritisation of those over 60 year old (those most at risk from severe outcomes of infection), before covering those with comorbidities (Figs. 4B,C). However, in settings with low transmission (R0 = 1.25), those with comorbidities should be prioritised over those older than 60 year (Fig. 4A). Figure 4(D-F) shows corresponding results for a symptomatic disease preventing vaccine; here again, the priority group after keyworkers is generally those over 60 year old (Figs. 4E,F) except in the low-R0 scenario (Fig. 4D), where those with comorbidities would instead be prioritised. In all cases, prioritising risk groups in this way would avert more

deaths, or have comparable impact to, a 'uniform' strategy of allocating vaccines proportionally amongst risk groups (dotted grey line).

Discussion

Challenges that are particularly pressing in a country as large as India would persist even following the emergence of several vaccine candidates for COVID-19. The most contentions of them relate to rolling out of vaccines at population level. In this study, we have used a simple mathematical model of transmission dynamics, to show how vaccination efforts in the country might best be focused, in order to reduce mortality most effectively with a finite vaccine supply. Our results suggest that vaccinating all defined priority groups would have a substantial reduction in overall health burden, compared to a scenario of no vaccination, and complete lifting of restrictions. Such a strategy could reduce peak symptomatic incidence by about 21%, and cumulative mortality by about 30% .

In terms of prioritisation of population groups, our results show how the most efficient use of a given vaccine supply is shaped by transmission intensity (R0), whether for infection- or symptomatic-disease-preventing effects of the vaccine (figures 4). Conceptually, the fundamental dynamics underpinning these results arise from interactions between 'direct' effects of immunisation (i.e. the protection amongst those receiving the vaccine) and 'indirect' effects (i.e. the population-level benefits of general reductions in transmission). While in practice any vaccine is likely to exert a combination of both the effects, our work highlights that, for a vaccine supply sufficient to cover 18% of the population, direct effects would generally take precedence over indirect effects, in deciding prioritisation. Thus vaccination rollout should generally prioritise those most at risk of severe outcomes of infection; in the present case, the elderly. However, only in the lowest-transmission settings would those with comorbidities be prioritised over the elderly. As those with comorbidities include young adults, who have greater contact rates than the elderly, vaccinating this group would raise stronger indirect effects; it is in low-R0 scenarios that such effects would be as important as direct effects.

Our results highlight the need for further data to help inform strategic priorities, both on transmission in real world settings (i.e. R0 in any given setting) and vaccine effect on

transmission. On the first of these, although clinical trials so far have focused on symptomatic illness as an endpoint, interim findings for at least one vaccine candidate suggest the potential for reduced transmission as well.[19] However, further data are needed, for example through trial designs following up household cohorts to assess the risk of transmission amongst close contacts, and how this risk is affected by vaccination. Alternatively, a better understanding of how viral load correlates with SARS-CoV-2 transmission could allow better interpretation of available trial results, in terms of transmission risk. [22,23] On the latter point mentioned above, mathematical and statistical models – similar to those we have presented here - have been used to estimate R0 for SARS-CoV-2 in different settings, and may also be informative in the Indian context.[14] We note that in a country as large and complex as India, there will be a need for locally-tailored, locally-relevant estimates. As an indication of varying transmission intensity across the country, the second national serosurvey reported 16% seroprevalence of SARS-CoV-2 antibody among those living in urban slums; 8% among those living in urban non-slum setting; and 4% in rural settings.[15] Such variation is likely to be driven by factors such as population density, and indeed may call for different prioritisation strategies in different settings. For example, scenarios of R0 = 1.25 and 2.5 may be appropriate, respectively, in rural and urban slum settings. In all of these considerations, robust surveillance data – including at the level of hospitalisations and mortality – would be invaluable in refining model estimates.

As described above, our analysis does not explicitly address temporal sequencing, i.e. which groups to cover first: for simplicity, we modelled vaccination coverage as being completed in advance of the epidemic, concentrating on identifying the groups who would have the most impact on mortality if receiving the vaccine. Nonetheless, our results can be interpreted in terms of temporal sequencing as well; in particular, even in the scenario where there is sufficient vaccine to cover 100% of the identified risk groups, critical challenges of prioritisation will arise in the event that an epidemic begins during the course of vaccine rollout. In such an event, the 'effective' coverage is simply the number of individuals who have been successfully immunised before being exposed to infection. Framed in this way, our results can therefore also be interpreted as the sequence of prioritisation that should be implemented, in order to maximise vaccine impact under a given amount of effective coverage.

As with any modelling study, our analysis has limitations to note, which should be regarded as illustrating the importance of different factors for policy decisions, and not as a predictive framework. It is subject to various uncertainties, for example, the increased risk of death as a result of comorbidities. Further data on these excess risks will be valuable in refining our findings. In considering the key worker population, although we incorporated vaccination coverages consistent with the size of this population, we did not explicitly capture the broader societal impact of failing to vaccinate these individuals, another important area for future work. Finally, an important uncertainty relevant to our current work is the dynamics of immunity, whether induced by vaccination or by infection. For example, there is evidence that memory B-cells and neutralising antibodies persist at detectable levels in blood for months post-infection [24–26]. Despite important recent advances in understanding implications for disease outcome upon reinfection [27], there remains much uncertainty, including on the role of the cellular immune response [28]. A recent modelling study showed how immune mechanisms could mediate a decline in the severity of COVID-19 as it becomes endemic in the coming years [29], but it remains unclear how current licensed vaccines, in India and elsewhere, might shape these dynamics. Addressing these issues are beyond the scope of our current work, which focuses on the implications of vaccination for immediate mitigation of health burden: nonetheless, these again represent important areas for future work to address.

In conclusion, models such as the one presented in this article can generate useful program insights. In practice the gains, as projected by the model due to vaccination of select population groups in real life settings, would enhance from other prevention measures at the population level such as use of masks and maintenance of physical distance during social interactions. Such a synergy is expected to yield further dampening of SARS-CoV-2 transmission. We therefore conclude that rational and focused vaccination approaches, as outlined in this article, in the context of Indian COVID-19 epidemic makes for a smarter public health choice than mass vaccination.

Author contributions

SP and BB conceptualised the study; SM, NA and SP developed the modelling approach and SM performed the modelling. All authors analysed and interpreted the results; SM and SP wrote a first draft of the manuscript, and all authors contributed to the final draft and approved the version for submission to the journal.

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Competing interests

The authors declare no competing interests.

Ethical approval

Not required.

Data sharing

The model code and dataset are publicly available at https://github.com/sandipccmb/COVID-19-vaccination-strategy.

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	Infection preventing vaccine			Symptomatic disease preventing vaccine		
	Percentage reduction in peak symptomatic incidence	Percentage reduction in cumulative mortality	Number needed to vaccinate to avert one death	Percentage reduction in peak symptomatic incidence	Percentage reduction in cumulative mortality	Number needed to vaccinate to avert one death
(A) key workers (HCW + FW)	4.8 (3.8 – 6.3)	2.0 (1.4 – 2.8)	1872 (1292 - 3031)	2.3 (1.8- 3.1)	2.0 (1.7 – 2.4)	1877 (1226 - 3034)
(B) Key workers + Individuals with comorbidities (24 – 60 years)	18.8 (14.9 – 23.6)	11.8 (8.2– 15.7)	320 (213 – 528)	8.9 (7.1–11.9)	13.6 (10.8 – 16.4)	273 (179 - 460)
(C) Above two groups (A+B) + all individuals over 60 years of age	20.6 (16.7 – 25.4)	29.7 (25.8 – 33.8)	127 (87 – 196)	10.4 (8.4 – 13.0)	32.9 (28.6 – 37.3)	114 (76 - 184)

Table 1. Summary of epidemiological impacts for the different scenarios shown in figure 3. Numbers show median estimates, while parentheses show 95% uncertainty intervals.

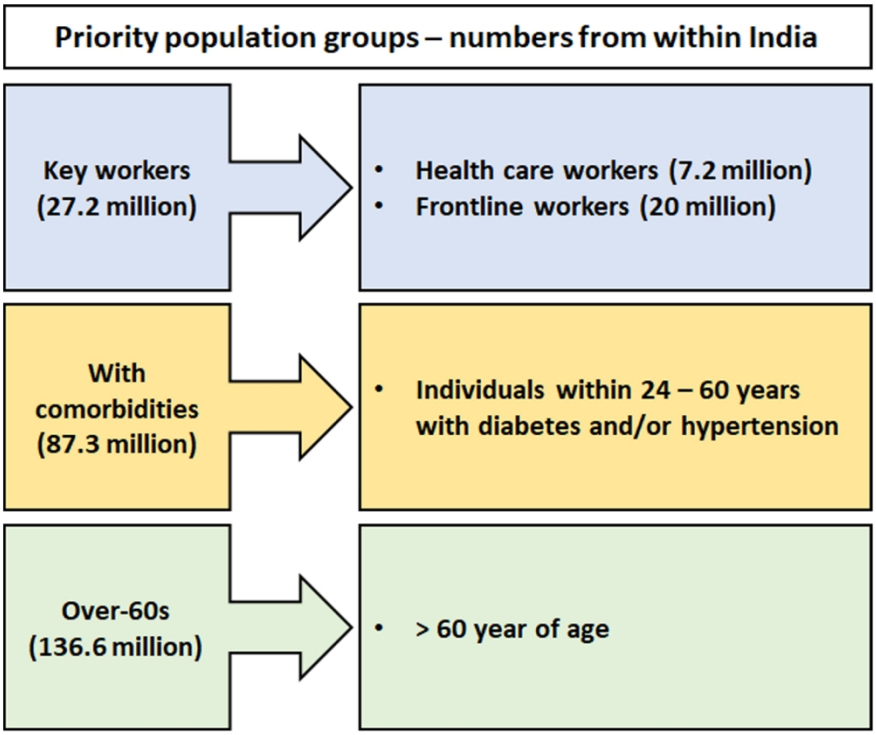
Figure captions

Figure 1. Priority groups of people in three different scenarios. Sources: healthcare workers (HCW)[30], frontline workers (FW), those with diabetes and hypertension as co-morbidities[31], those over 60 years of age[32]. As described in the main text, when modelling vaccination coverage amongst essential workers, our focus is on the epidemiological impact of doing so (we do not address, for the example, the potential impacts for healthcare continuity, of vaccination coverage in HCWs).

Figure 2. Illustration of the compartmental model structure. The top and bottom halves of the figure show unvaccinated and vaccinated subpopulations, respectively. Boxes represent compartments, and arrows represent flows between different stages of the clinical course of infection. Compartments are as follows: Uninfected (U); Exposed (E); asymptomatic but infectious (A); presymptomatic (P); symptomatic (S); recovered and immune (R). The terms c_1,c_2 represent effectiveness of, respectively, an infection preventing and symptomatic disease preventing vaccine. The term μ represents the per-capita hazard of mortality; see table S2 for a list of all other model parameters. This model structure is further stratified by age groups, and by presence/absence of comorbidities.

Figure 3. Illustration of vaccine impact in each of the priority groups listed in Figure 1. Scenarios are shown in the example of R0 = 2, assuming that vaccine coverage is completed at the same time as current restrictions being fully lifted. Upper row shows results for an infection-preventing vaccine, while the lower row shows results from a symptomatic disease preventing vaccine. Scenarios show vaccination coverage in different combinations of priority groups: Keyworkers ('KeyW'); additionally including those with co-morbidities ('Co-M'); and additionally including those over 60 years of age ('>60').All horizontal axes show days after vaccination and restrictions being lifted. Solid lines show central (median) estimates, while shaded areas show 95% uncertainty intervals as estimated by sampling uniformly from the ranges shown in table S2. The overall impact of vaccination in each of these scenarios is summarised in table 1, together with the amount of vaccines needed.

Figure 4. Optimal prioritisation strategies for an infection-preventing vaccine (A, B, C) and for a symptomatic disease preventing vaccine (D, E, F). For reference, dotted black lines in all plots show a 'uniform' strategy where available vaccines are allocated proportionately amongst the two risk groups, rather than prioritising one over the other (for clarity, uncertainty intervals not shown for this scenario). For the plots (A – C) we assume deployment of a vaccine having 60% efficacy in reducing susceptibility to infection, but no effect on development of symptoms following infection. Assuming keyworkers receive first priority, Figs.S1 – S2 in the supporting information show different strategies for subsequently prioritising those over 60 years old, vs those with comorbidities. Here, we show those strategies that are optimal for minimising the overall mortality, under different levels of vaccine coverage, and for different values of R0. For example,in the case R0 = 2, if initial vaccine supply is only enough to cover 10% of the population, then after covering keyworkers, these vaccines should be deployed preferentially amongst the over-60s (in green). If there is enough vaccine supply to cover 20% of the population, the optimal strategy would be to vaccinate the over-60s after keyworkers, and spending any remaining vaccine supply amongst those with comorbidities. Similar priorities apply for R0 = 2.5. However, for low-transmission settings (R0 = 1.25), those with comorbidities would be prioritised over the elderly. For the plots (D – F) we assume deployment of a vaccine having 60% efficacy in reducing symptoms and mortality following infection, but no preventive effect on acquiring infection. For such a vaccine, optimal prioritisation strategies are similar to those shown in plots (A-C).



Priority groups of people in three different scenarios. Sources: healthcare workers (HCW) [ref. 30], frontline workers (FW), those with diabetes and hypertension as co-morbidities [ref. 31], those over 60 years of age [ref. 32]. As described in the main text, when modelling vaccination coverage amongst essential workers, our focus is on the epidemiological impact of doing so (we do not address, for the example, the potential impacts for healthcare continuity, of vaccination coverage in HCWs).

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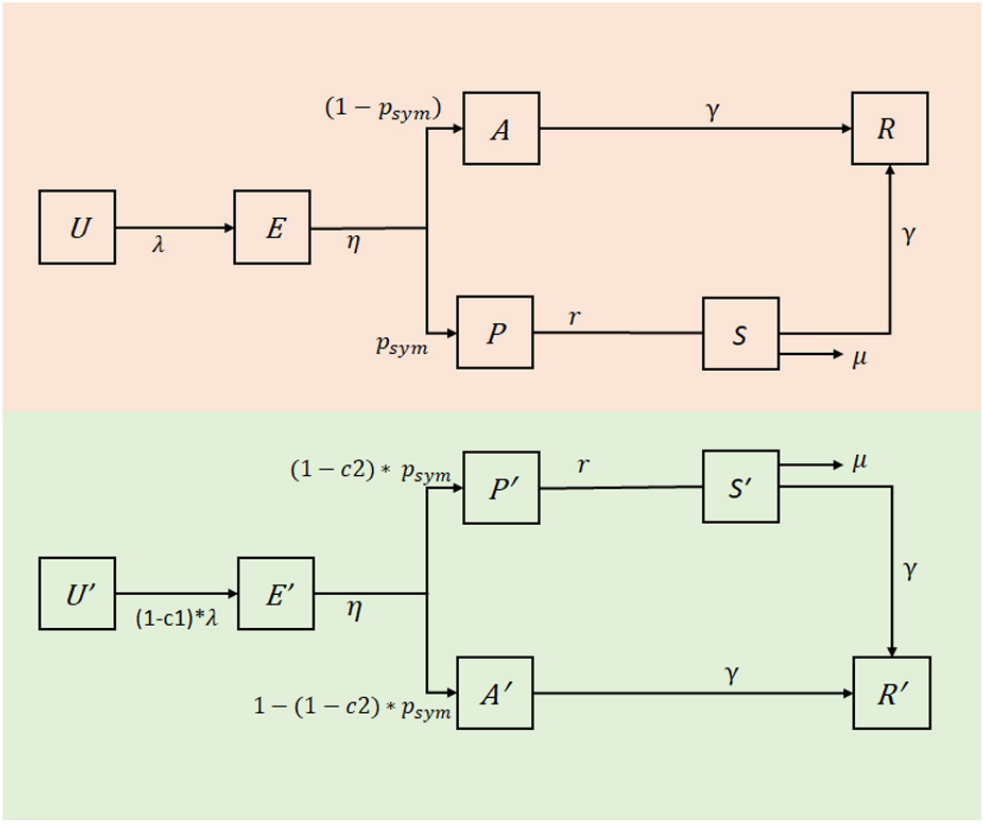

Illustration of the compartmental model structure. The top and bottom halves of the figure show unvaccinated and vaccinated subpopulations, respectively. Boxes represent compartments, and arrows represent flows between different stages of the clinical course of infection. Compartments are as follows: Uninfected (U); Exposed (E); asymptomatic but infectious (A); presymptomatic (P); symptomatic (S); recovered and immune (R). The terms c_1,c_2 represent effectiveness of, respectively, an infection preventing and symptomatic disease preventing vaccine. The term μ represents the per-capita hazard of mortality; see table S2 for a list of all other model parameters. This model structure is further stratified by age groups, and by presence/absence of comorbidities.

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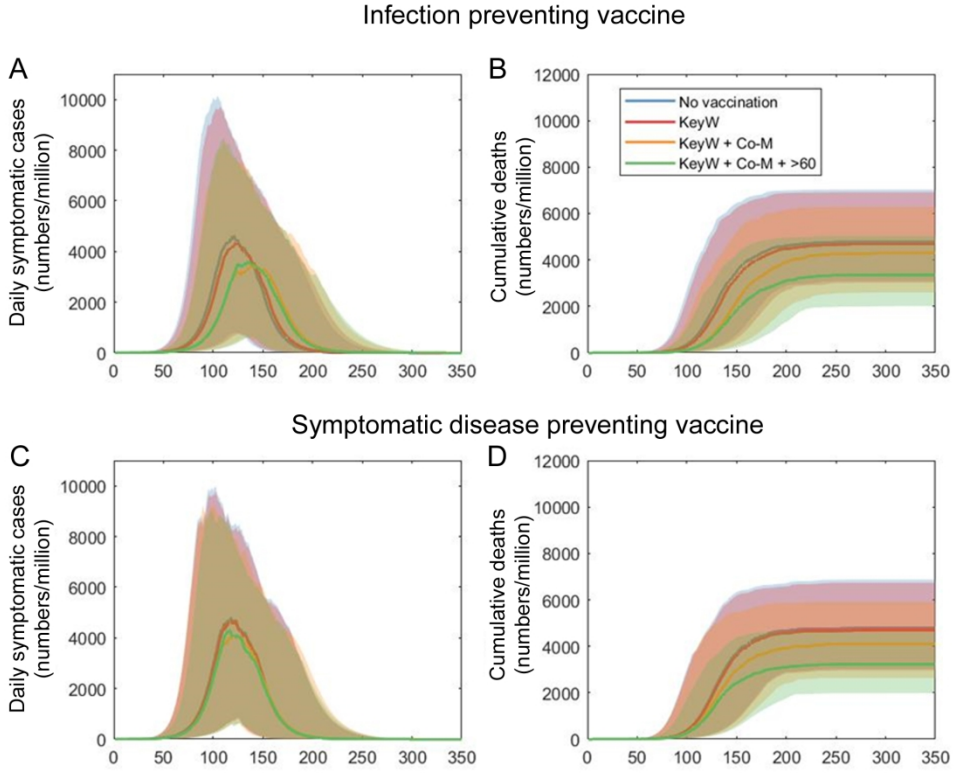

Illustration of vaccine impact in each of the priority groups listed in Figure 1. Scenarios are shown in the example of R0 = 2, assuming that vaccine coverage is completed at the same time as current restrictions being fully lifted. Upper row shows results for an infection-preventing vaccine, while the lower row shows results from a symptomatic disease preventing vaccine. Scenarios show vaccination coverage in different combinations of priority groups: Keyworkers ('KeyW'); additionally including those with co-morbidities ('Co-M'); and additionally including those over 60 years of age ('>60').All horizontal axes show days after vaccination and restrictions being lifted. Solid lines show central (median) estimates, while shaded areas show 95% uncertainty intervals as estimated by sampling uniformly from the ranges shown in table S2. The overall impact of vaccination in each of these scenarios is summarised in table 1, together with the amount of vaccines needed.

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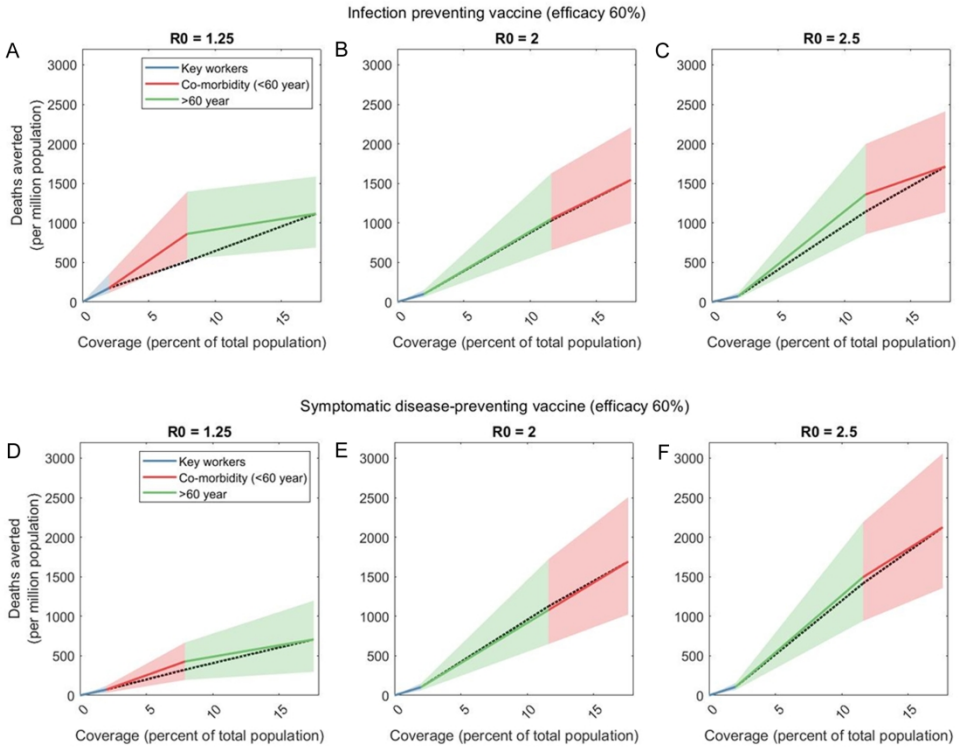

Optimal prioritisation strategies for an infection-preventing vaccine (A, B, C) and for a symptomatic disease preventing vaccine (D, E, F). For reference, dotted black lines in all plots show a 'uniform' strategy where available vaccines are allocated proportionately amongst the two risk groups, rather than prioritising one over the other (for clarity, uncertainty intervals not shown for this scenario). For the plots (A – C) we assume deployment of a vaccine having 60% efficacy in reducing susceptibility to infection, but no effect on development of symptoms following infection. Assuming keyworkers receive first priority, Figs.S1 – S2 in the supporting information show different strategies for subsequently prioritising those over 60 years old, vs those with comorbidities. Here, we show those strategies that are optimal for minimising the overall mortality, under different levels of vaccine coverage, and for different values of R0. For example,in the case R0 = 2, if initial vaccine supply is only enough to cover 10% of the population, then after covering keyworkers, these vaccines should be deployed preferentially amongst the over-60s (in green). If there is enough vaccine supply to cover 20% of the population, the optimal strategy would be to vaccinate the over-60s after keyworkers, and spending any remaining vaccine supply amongst those with comorbidities. Similar priorities apply for R0 = 2.5. However, for low-transmission settings (R0 = 1.25), those with comorbidities would be prioritised over the elderly. For the plots (D – F) we assume deployment of a vaccine having 60% efficacy in reducing symptoms and mortality following infection, but no preventive effect on acquiring infection. For such a vaccine, optimal prioritisation strategies are similar to those shown in plots (A-C).

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INDIA'S PRAGMATIC VACCINATION STRATEGY AGAINST COVID-19: A MATHEMATICAL MODELLING BASED ANALYSIS

Sandip Mandal[1], Nimalan Arinaminpathy[2], Balram Bhargava[1], Samiran Panda (0000-0002-5077-6275)[1*]

[1]Indian Council of Medical Research, New Delhi, India

[2]MRC Centre for Global Infectious Disease Analysis, School of Public Health, Imperial College London, London, UK

Correspondence to: pandasamiran@gmail.com /pandas.hq@icmr.gov.in/ director@nariindia.org

Supplementary materials

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1. Model specification

We developed a deterministic, compartmental model of SARS-CoV-2 transmission and disease course with three different age groups: <24 year, 24 - 60 year and >60 year, and further stratified by the presence of comorbidities. In all equations that follow, state variables (e.g. *U*, *E* etc) denote the respective *proportions* of the total population in the corresponding states. Thus at time zero (prior to the epidemic), all state variables sum to 1. In this way, the model results can be applied to different administrative scales within India (e.g. districts), regardless of the actual population size involved. Accordingly, all model results are shown as population rates, e.g. deaths per million population (Figure 3, main text).

Governing equations

Model compartments are listed in Table S1, and model parameters listed in Table S2. Governing equations for the non-vaccinated population are as follows, where subscript i denotes age group, and subscript j denotes comorbidity group:

Uninfected (U):

$$\frac{dU_{ij}}{dt} = -\lambda_i U_{ij}$$

Exposed but not yet infectious (E):

$$\frac{dE_{ij}}{dt} = \lambda_i U_{ij} - \eta E_{ij}$$

Asymptomatic and infectious (A):

$$\frac{dA_{ij}}{dt} = \eta \left(1 - p^{(sym)}\right) E_{ij} - \gamma A_{ij}$$

Presymptomatic and infectious (P):

$$\frac{dP_{ij}}{dt} = \eta\, p^{(sym)}\, E_{ij} - r\, P_{ij}$$

Symptomatic and infectious (S):

$$\frac{dS_{ij}}{dt} = rP_{ij} - \mu_{ij}\, S_{ij}$$

Recovered and partially immune (R):

$$\frac{dR_{ij}}{dt} = \gamma(A_{ij} + S_{ij})$$

A key parameter here is $p^{(sym)}$, the proportion of infected individuals developing symptoms.

Corresponding equations apply for the vaccinated compartments, but with primes distinguishing these compartments (e.g. U'). Additionally for this population, the term $p^{(sym)}$ is replaced by $(1 - c_2)p^{(sym)}$, where c_2 is vaccine efficacy in preventing disease.

For the force-of-infection experienced by non-vaccinated individuals, we have:

$$\lambda_i = \sum_{k,l} \beta \, m_{ik} \{[S_{kl} + k \, (A_{kl} + P_{kl})] + [S'_{kl} + k \, (A'_{kl} + P'_{kl})]\}$$

And for vaccinated individuals:

$$\lambda'_i = (1 - c_1) \, \lambda_i,$$

where c_1 is the effect of the vaccine on reducing susceptibility to infection.

Overall, the value of the basic reproduction number (R_0) for this model is proportional to the value of β, the rate-of-infection attributable to symptomatic individuals (noting that k acts as an adjustment for a/pre-symptomatic individuals). As described below, we controlled for R_0 by adjusting the value of β accordingly.

State symbol	Meaning
U_i	Uninfected (i = 1, 2, 3 indicating three age groups)
E_i	Exposed
A_i	Asymptomatic
P_i	Pre-symptomatic
S_i	Severe symptomatic
R_i	Recovered

Table S1 List of state variables

Parameter	Meaning	Values			Source/Remarks
β	Transmission rate	0.079 – 0.16			Calculated using next-generation matrix as described in ref[1]. Value shown here is to yield R0 = 1.25 – 2.5.
η	Amongst those exposed, rate of developing infectiousness	(1/3 – 1/5) /day			Corresponds to an average latent period of 3-5 days: together with the period of presymptomatic transmission (see r below), corresponds to an overall average incubation period of 4-6 days [2]
$p^{(sym)}$	Proportion developing symptoms	1/3 – 2/3			Wide variation noted in individual studies and meta-analysis [3–5]
k	Relative infectiousness of asymptomatic vs symptomatic infection	2/3 – 1			
r	Rate of developing symptoms	1 /day			Assumption, corresponds to mean pre-symptomatic duration of 1 day
γ	Recovery rate	0.2 /day			Assumption, corresponds to mean infectious period of 5 days[6]
f	Fold-increase in case fatality rate as a result of comorbidities (diabetes and/or hypertension)	2.5			Drawn from recent systematic review [8]
	Age groups	<24 year	24-60 year	>60 year	

CFR_i	Case fatality rate in age group *i* in absence of comorbidities	0.1%	1.45%	10.9 %	Drawn from a recent study from two Indian States.[9]
μ_i	Mortality rate for severe cases	0.0002 /day	0.0029 /day	0.02 45 /day	Hazard rates of μ_i are calculated to yield case fatality rates, using: $CFR_i = \mu_i/(\mu_i + \gamma)$. Uncertainty in the mortality hazards are considered +/-25%.
N_i	Population (India)	634 mn	614 mn	131 mn	Extrapolated from the Census of India 2011[10]
m_{ij}	Connectivity matrix between age group i with age group j	1.37 2.52 0.28	1.43 2.90 0.34	0.05 0.01 0.02	Drawn from ref.[9] Uncertainty in the each element of the contact matrix is considered +/-25%.

Table S2: Parameters used in the model simulation. There remains much uncertainty about parameters relating to SARS-CoV-2 natural history, e.g. infectiousness of asymptomatic people relative to symptomatic ones and, duration of pre-symptomatic period etc. In this study we adopted a range of parameter values to reflect this uncertainty in our model projections (figure 3-5, main text).

2. Model execution

Using latin hypercube sampling, we drew 5,000 independent samples from the parameter ranges listed in Table S2. For each sample, and under given scenarios for R_0 and vaccine coverage, we then performed the following steps:

1. Control for the basic reproduction number (R_0), as follows:
    a. In the absence of any vaccination coverage or prior immunity, use analytical methods described in (ref[1]) to calculate the value ρ of the reproduction number when $\beta = 1$.
    b. Set $\beta = R_0/\rho$, thus yielding the scenario-specified value of R_0 for the basic reproduction number.
2. Construct initial conditions for the dynamical system, as follows:
    a. Construct a disease-free population with no prior immunity except for those who have been vaccinated (the latter, in line with the specified scenario for vaccination coverage).
    b. Introduce infection by displacing 1 individual from the susceptible, unvaccinated adult population, to the symptomatic, unvaccinated adult compartment (the specific choice of characteristics for this seeding infection are not important for the model outcomes we analyse).
3. Simulate the system of equations listed in section 1, until there are no further new infections.
4. Record the cumulative deaths that occurred over the simulation period.

We repeated these steps for each of the 5,000 samples, to obtain a corresponding number of estimates for cumulative deaths. We then estimated uncertainty by taking 2.5th, 50th and 97.5th percentiles over these samples.

3. Priority population groups for vaccination – further information

Category	Numbers		Source
Number of healthcare workers (HCW)			
HCWs (qualified)	3827820		Karan et al (2019) [11]
Support workers	1245878		
HCW (without requisite qualifications)	2084185		
Total	7157883		
Frontline workers (FW)			
	Active	**Reserve**	
Armed forces	1443921	1155000	Information available in public domain [12,13]
Paramilitary forces	87000		
Central Armed Forces and Others	1403700	987800	
Municipal workers	15000000		
Total	20077421		
Co-morbidity (diabetes and/or hypertension)			
Population < 24 year of age with at-least one comorbidity	17801137 (2.8% population in this age group)		WHO SAGE report, 2013[14]
Population 24 – 60 year of age with at-least one comorbidity	87283375 (14.3% population in this age group)		
Population >60 year of age with at-least one comorbidity	58726385 (43.0% population in this age group)		
Elderly population			
Population > 60 year of age	136620434		Extrapolated from the Census of India 2011[10]

Table S3: Priority population groups for vaccination.

4. Additional model outputs

Figure 4 in the main text shows model results for how priority groups might be sequenced, to gain maximum impact (lives saved) from a limited vaccine supply. While the figure shows only the 'optimal' scenario, Figures S1 below shows all 2 possible scenarios for the order in which vaccination is deployed amongst the priority groups, in the case of an infection-preventing vaccine, and assuming that keyworkers receive first priority. Of these, the optimally efficient scenario is selected as that with the greatest gradient (lives saved per person vaccinated) at each stage, i.e. the scenario having the most concave shape. Figures S2 show corresponding results in the case of a disease-preventing vaccine.

Scenario definitions are as follows:

Scenario 1: Key workers → Co-morbidity → Elderly

Scenario 2: Key workers → Elderly → Co-morbidity

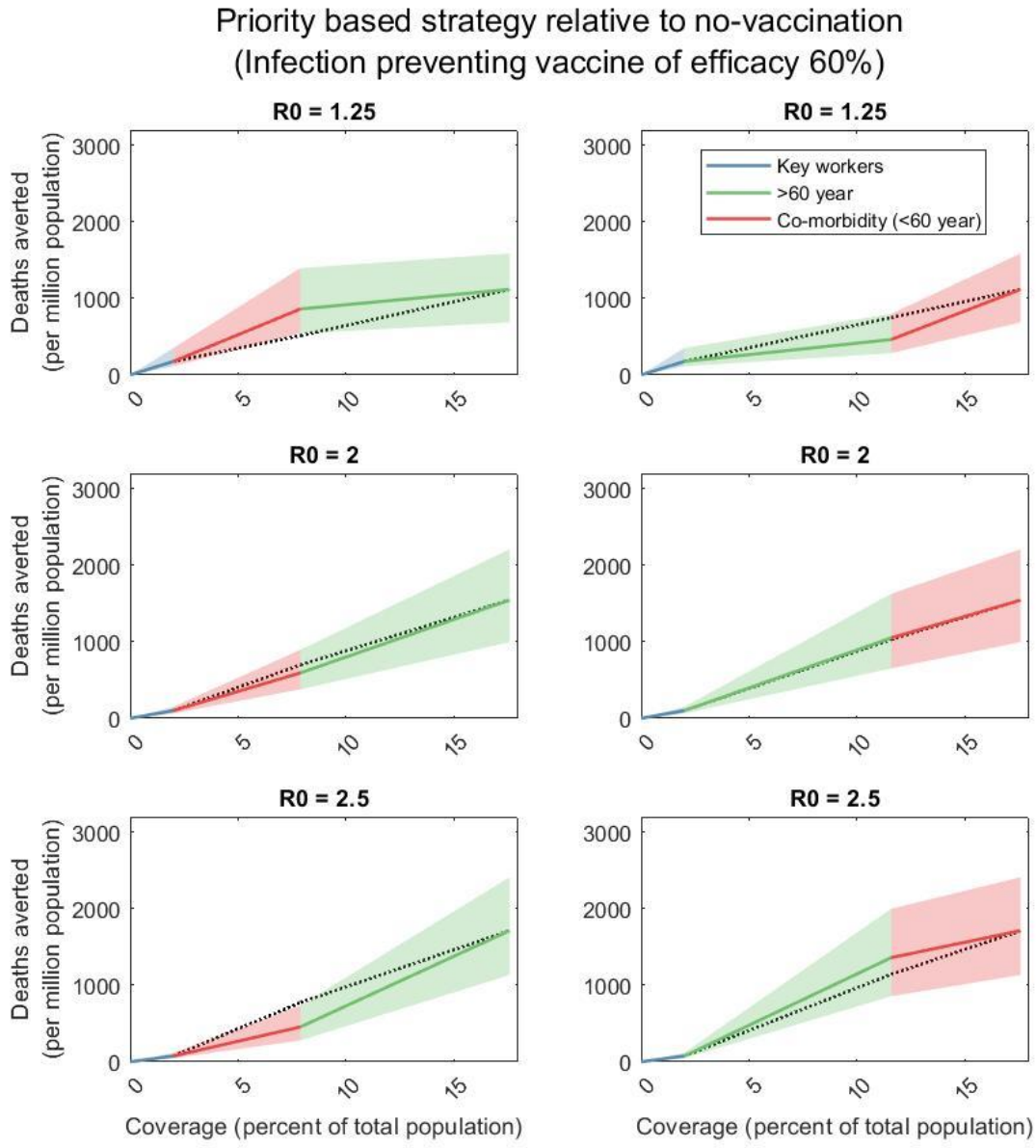

Figure S1. Scenarios for the order in which vaccination is deployed amongst the priority groups, in the case of an infection-preventing vaccine of efficacy 60%. We assume that keyworkers always receive first priority, and present scenarios for the prioritisation of the remaining two groups. As in the main text, dotted black lines show a 'uniform' strat R0 = 2.5 where available vaccines are allocated proportionately amongst the two risk groups, rather than prioritising one over the other.

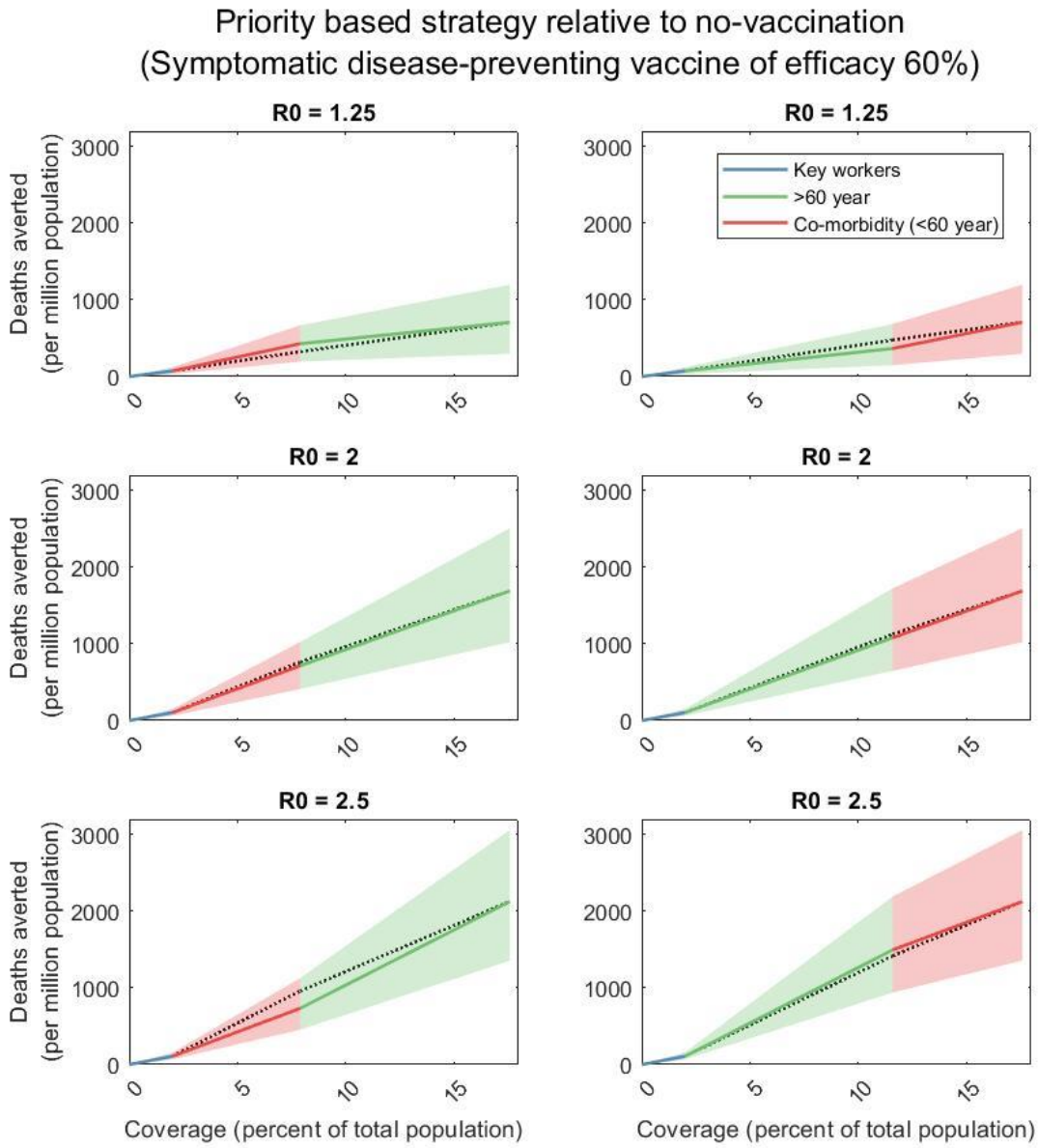

Figure S2. Scenarios as in figure S1, in the case of a disease-preventing vaccine of efficacy 60%.

5. Sensitivity analysis to vaccine efficacy

While results in the main text assumed (conservatively) a vaccine efficacy of 60%, below we present alternative results for 90%, showing that Figures 4 and 5 in the main text remain qualitatively unchanged.

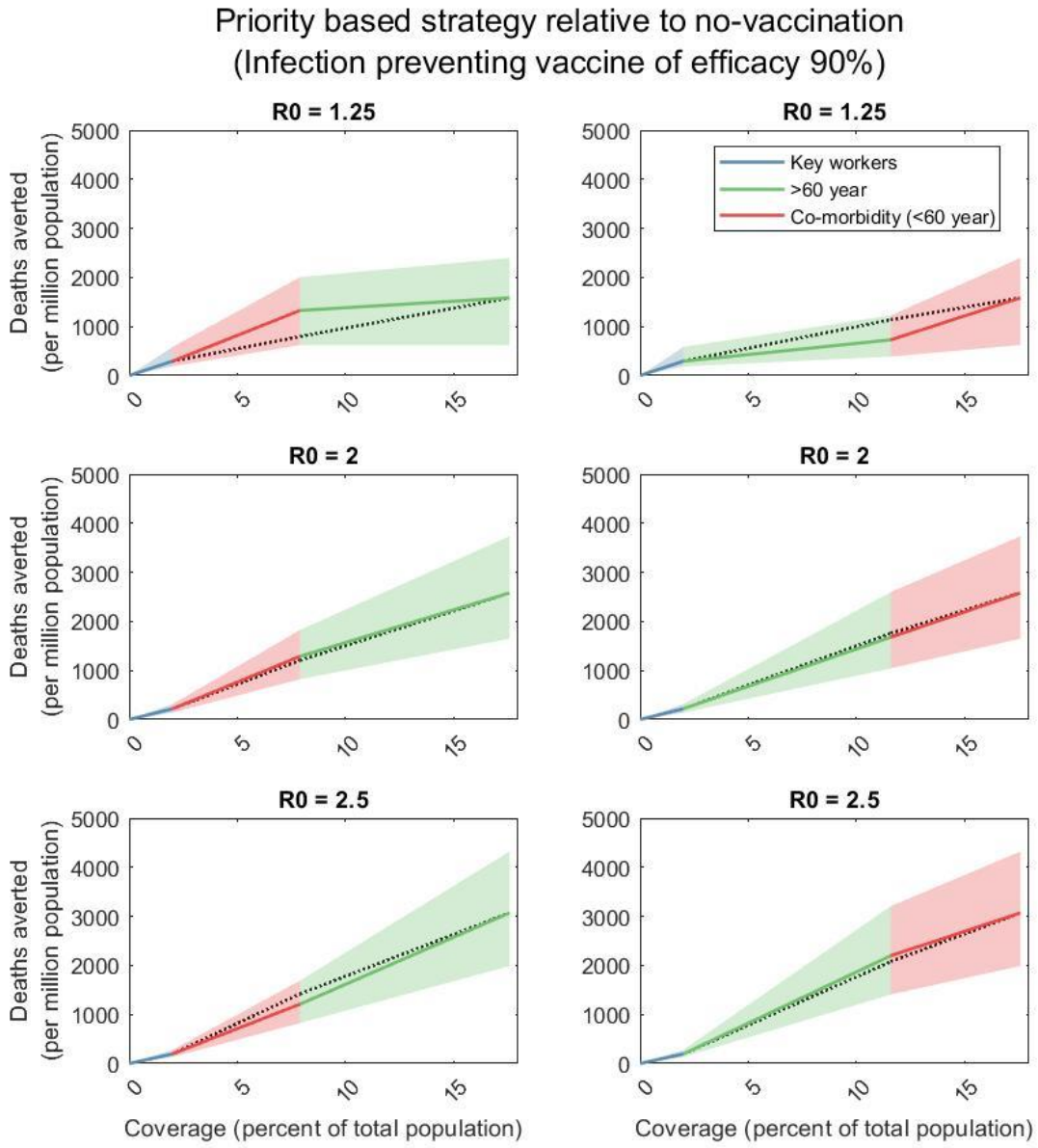

Figure S3. Scenarios for the order in which vaccination is deployed amongst the three priority groups, in the case of an infection-preventing vaccine of efficacy 90%.

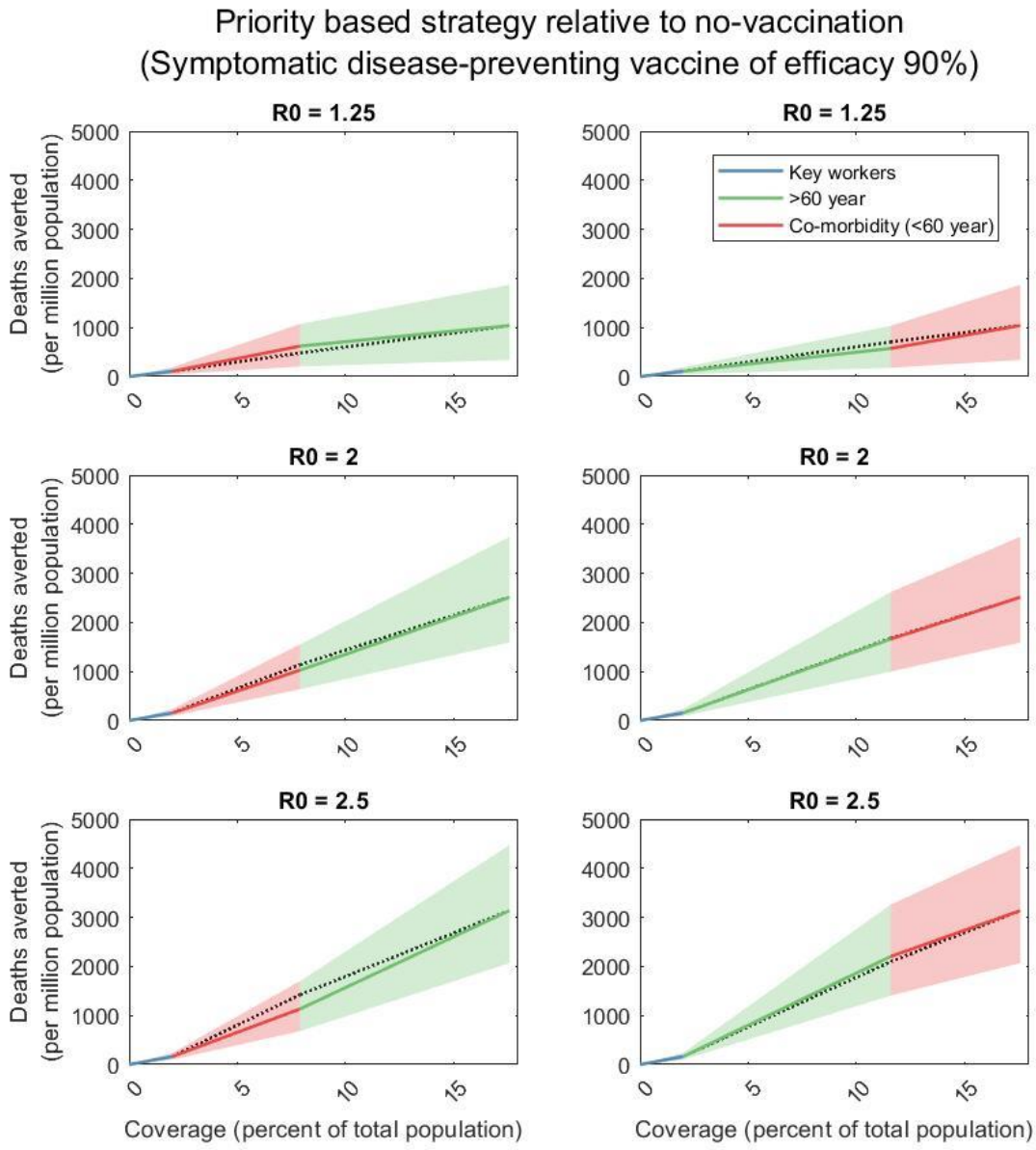

Figure S4. Scenarios as in figure S3, in the case of a disease-preventing vaccine of efficacy 90%.

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INDIA'S PRAGMATIC VACCINATION STRATEGY AGAINST COVID-19: A MATHEMATICAL MODELLING BASED ANALYSIS

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INDIA'S PRAGMATIC VACCINATION STRATEGY AGAINST COVID-19: A MATHEMATICAL MODELLING BASED ANALYSIS

Sandip Mandal, Scientist- Indian Council of Medical Research (ICMR)[1],

Nimalan Arinaminpathy, Reader in Mathematical Epidemiology, Imperial College[2],

Balram Bhargava, Director General, ICMR and Secretary, Department of Health Research[1],

Samiran Panda, Head - Epidemiology and Communicable Disease (ECD) Division, ICMR and Director, ICMR - National AIDS Research Institute (0000-0002-5077-6275)[1*]

[1]Indian Council of Medical Research, New Delhi, India

[2]MRC Centre for Global Infectious Disease Analysis, School of Public Health, Imperial College London, London, UK

Correspondence to: pandasamiran@gmail.com /pandas.hq@icmr.gov.in / director@nariindia.org

Abstract

Objectives

To investigate the impact of targeted vaccination strategies on morbidity and mortality due to COVID-19, as well as on the incidence of SARS-CoV-2, in India.

Design

Mathematical modelling.

Settings

Indian epidemic of COVID-19 and vulnerable population.

Data sources

Country specific and age-segregated pattern of social contact, case fatality rate and demographic data obtained from peer-reviewed literature and public domain.

Model

An age-structured dynamical model describing SARS-CoV-2 transmission in India incorporating uncertainty in natural history parameters was constructed.

Interventions

Comparison of different vaccine strategies by targeting priority groups such as key workers including health care professionals, individuals with comorbidities (24 – 60 year), and all above 60.

Main outcome measures

Incidence reduction and averted deaths in different scenarios, assuming that the current restrictions are fully lifted as vaccination is implemented.

Results

The priority groups together account for about 18% of India's population. An infection preventing vaccine with 60% efficacy covering all these groups would reduce peak symptomatic incidence by 20.6% (95% uncertainty intervals (CrI) 16.7 - 25.4), and cumulative mortality by 29.7% (95% CrI 25.8- 33.8). A similar vaccine with ability to prevent symptoms (but not infection) will reduce peak incidence of symptomatic cases by 10.4% (95% CrI 8.4 – 13.0), and cumulative mortality by 32.9% (95% CrI 28.6 - 37.3). In the event of insufficient vaccine supply to cover all priority groups, model projections suggest that after keyworkers, vaccine strategy should prioritise all who are > 60, and subsequently individuals with comorbidities. In settings with weakest transmission, such as sparsely-populated rural areas, those with comorbidities should be prioritised after keyworkers.

Conclusions

An appropriately targeted vaccination strategy would witness substantial mitigation of impact of COVID-19 in a country like India with wide heterogenity. 'Smart vaccination', based on public health considerations, rather than mass vaccination, appears prudent.

Strengths and limitation of this study

- The model in this study is informed by age-dependent risk factors for SARS-CoV-2 infection among contacts, and is stratified by co-morbidities (diabetes and/or hypertension), and vaccination status.
- Data on mortality and large-scale contact tracing from within India, and the recent national sero-survey results were used, which constituted a major strength of this investigation.
- Distinguishing between 'infection' and 'symptomatic disease ' preventing vaccines, the model was simulated under a range of scenarios for the basic reproduction number (R0).
- Should they have been available, real life country-specific data on excess risks of deaths due to comorbidities would have added strength to the presented model.
- Key priority group-specific data on social mixing and potential associated transmission was not available, and remained as a limitation.

INTRODUCTION

COVID-19 has caused substantial morbidity and mortality worldwide, at levels not witnessed since the H1N1 influenza pandemic over a century ago.[1] Non-pharmaceutical measures for its prevention such as hand hygiene, use of masks and maintaining physical distance during social interactions have played important roles in reducing the transmission of SARS-CoV-2, the causative agent. However, such measures, by themselves, are impractical for sustained

suppression of viral transmission for long.[2–5] In the meantime, development of vaccines against COVID-19 has progressed at an unprecedented pace. Promising results from phase 3 clinical trials of some of these candidates have emerged within a year from the publication of the whole genome sequence of SARS-CoV-2.[6] Expectations on these vaccines range from prevention of infection and reduction of disease severity, to averting deaths among most at risk population groups.

Given that COVID-19 vaccines are already becoming available for distribution through public healthcare systems, many countries[7] are now critically reviewing their vaccination plans. A major concern is how to effectively reach and engage a far larger number of individuals, the majority of whom are adults, than those typically covered under universal immunization programmes for children. Other important considerations include central storage facilities, the need for a cold chain to be maintained till vaccines are transported to the intermediary storage stations, and administered at the remotest vaccine session sites, and resource mobilization. Ethics and equity have also remained integral to these discourses[8] where 'vaccine nationalism' has been examined in depth.[9] The country of origin of a COVID-19 vaccine, production and procurement capacities of different countries, and concerns about inequitable global vaccine distribution; all compound such challenges.[9–11]

Against this background, and with a robust countrywide immunization program for children in place, India has come to the centre-stage of discussion related to COVID-19 vaccine. The second-most populous country in the world, India has accounted, at the time of writing, for 9% of COVID-19 cases reported worldwide, exceeded only by the United States and Brazil. Worth noting in this context is that India serves as a major source of vaccine production worldwide, accounting in 2019 for more than 60% of vaccines provided to low- and middle-income countries.[12] In anticipation of mass vaccination against COVID-19, discussions were held on which population groups to be prioritised for vaccination. Three priority groups so far have been proposed based on public health considerations in India, (i) key workers, including healthcare professionals and other frontline workers, (ii) those over 60 years of age, and (iii) those aged between 24 to 60 years having comorbidities, as they are at increased risk of severe COVID-19 disease.[13]

In order to inform these discussions, we constructed a mechanistic mathematical model to estimate potential epidemiological impact of vaccinating the aforementioned priority

groups, as well as to explore the effects of different strategies for vaccination, amongst these groups. The model is informed by age-dependent risk factors for SARS-CoV-2 infection among contacts. Mortality and contact data generated by a large-scale contact tracing study in India, [14] and the recent national sero-survey results[15] have been used for this purpose. This modelling serves to illustrate some important considerations for vaccine planning, relevant to India as well as to other countries facing similar challenges.

METHODS

India's national serological survey completed its second round in August 2020, and estimated a seroprevalence of 7.1% (95% CI 6.2 – 8.2) at the country level, well under the theoretical herd immunity threshold for SARS-CoV-2. [16] The third round, completed in January 2021, estimated the seroprevalence to be 25%, underlining again the existence of a considerable proportion of vulnerable population in the country. Such findings suggested that a full easing of restrictions would lead to a rebound in transmission. (Indeed, several parts of the country are already seeing an increase in infections at the time of writing.) We modelled the potential impact of future vaccine rollout, in mitigating such a rebound. In particular, we examined which population groups should receive the vaccination first, under different scenarios for vaccine efficacy, and for the basic reproduction number, R0 (the latter, as estimated in the absence of any infection- or vaccine-induced immunity). We considered three different population groups for discussion as listed in figure 1, and in line with the ground reality in India.[17] Consistent with ongoing practice, we assumed that key workers would receive vaccine first due to obvious ethical consideration (i.e. we excluded alternative scenarios where other groups might be prioritised over key workers). Holding this as a given, we examined the conditions under which those over 60 years of age should subsequently be prioritised over those with comorbidities, and vice versa.

Structure of the mathematical model

The model is a deterministic, compartmental framework, illustrated in figure 2 and shown in further detail in the supporting information. The model is stratified by different age groups

(<24 year, 24 – 60 year, and >60 year); it is also stratified by comorbidities (diabetes and/or hypertension), and vaccination status. The model captures essential features in the natural history of SARS-CoV-2, including the role of asymptomatic infection, and the pronounced variations in disease severity, and mortality risk, by age (see table S1). To capture age-specific patterns of transmission (the 'age-mixing' matrix), we drew from recently published findings from a large contact tracing study in India.[14] For the prevalence of comorbidities in different age groups, we drew the most recent estimates from the Global Burden of Disease study.[18] As described below, we incorporated uncertainty in model parameters by defining plausible ranges for these parameters (see table S2), and then sampling from these ranges.

Vaccination scenarios

Since R_0 can be a strong driver for the epidemiological outcomes of vaccination, we held the value of R_0 fixed at a value of 2, and also performed sensitivity analyses with alternative scenarios of 1.5 and 2.5. We first modelled the potential impact of vaccination on incidence and mortality in all of the population groups identified in figure 1 (see table S3). Next, to examine prioritisation amongst these groups, we assumed that there is a sufficient vaccine stock to cover a given proportion *p* of the overall population. Assuming that key workers would receive first priority, we identified the second priority group in whom this amount of vaccine would lead to the greatest reduction in overall deaths, relative to a scenario of no vaccine; for any unused vaccine stock, we then identified how much of the remaining priority group would be covered with the remaining vaccine supply. We note that this analysis does not address temporal sequencing (i.e. which groups to vaccinate first in time). For instance, if model results suggest that the greatest mortality reductions could be achieved through vaccinating 100% of a given group and using remaining vaccine to immunise 25% of the remaining priority group, in practice the implementation of this coverage could proceed in both groups simultaneously. For simplicity in the modelling, for a given vaccine supply, we assumed that vaccination coverage is completed in advance of the epidemic (and can thus be modelled through initial conditions for the dynamical equations). We simulated deaths averted by vaccination, relative to a scenario of no vaccination. However, for comparison, we also modelled a 'uniform' strategy where vaccine supply is allocated proportionately amongst the two risk groups (those above 60 year of age and

those between 24-60 year and with co-morbidity), rather than prioritising one over the other.

We repeated this analysis for a range of values for *p*, up to 18% of the population (the overall proportion of the population represented by the collective priority groups in figure 1). We also repeated this analysis for a range of values for R0 from 1.25 to 2.5, to capture the variability of transmission intensity across different settings within India, ranging from urban to rural.[15]

In addition, efficacy estimates for currently licensed vaccines – whether obtained through interim analyses or through bridging studies or trials in other countries - rely on symptomatic illness as an endpoint. The extent to which these vaccines may reduce infectiousness is currently unknown. In order to address these uncertainties, we modelled two types of vaccine: one that reduces susceptibility to infection with no effect on severity (an 'infection-preventing' vaccine), and one that reduces severity of infection (including mortality) with no effect on susceptibility (a 'symptomatic disease preventing/modifying' vaccine). In practice, it is likely that vaccines would have a combination of these two effects. By dichotomising their effects in this way, our analysis incorporates a range of possible scenarios for vaccine-induced protection.

Interim trial results from three separate vaccine candidates vary from 70% to 95%, [19,20] with other vaccine candidates also under consideration for use in India. As a conservative scenario for vaccine efficacy, given the complexity of implementation in a setting like India, we assumed a vaccine efficacy scenario of 60%. As a sensitivity analysis, we also simulated an alternative vaccine efficacy of 90% (Figs. S3 – S4). Regarding duration of vaccine-induced immunity, again conservatively a range from 3 months to 1 year was considered.[21]

Uncertainty

For each model parameter relating to natural history of SARS-CoV-2 infection, we defined a plausible range of parameter values (see table S2). After drawing 5,000 independent samples from these ranges using latin hypercube sampling, we performed model projections on each sample and then estimated uncertainty on model projections, by designating the 2.5th and 97.5th percentiles as the 95% 'uncertainty interval' (CrI).

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or plans of this research. However, dissemination plan of this investigation output will ensure availability of the results in the public domain and to inform public health discussions and debate.

Results

Figure 3 shows illustrative model projections for the impact of vaccination to cover all of the priority groups listed in figure 1, in the example of the basic reproduction number R0 = 2. These results suggest that an infection-preventing vaccine with 60% efficacy could reduce peak symptomatic incidence by 20.6% (95% CrI 16.7 – 25.4) and cumulative mortality by 29.7% (95% CrI 25.8 – 33.8), relative to a scenario of no vaccination. A symptomatic disease preventing vaccine would have similar impacts on mortality, but little impact on symptomatic incidence. Results suggest that such a vaccine could reduce peak symptomatic incidence by 10.4% (95% CrI 8.4– 13.0) and cumulative mortality by 32.9% (95% CrI 28.6 – 37.3). Table 1 summarises these overall impacts, illustrating, for example, that vaccinating those over 60 year old would offer the greatest reductions in mortality per vaccinated individual, for both infection and symptomatic disease preventing vaccines.

Even if there is ultimately sufficient vaccine production to cover all priority groups as shown in figure 1, in practice it is likely that supply would be staggered in the initial months of vaccine deployment, thus necessitating the identification of priority groups to target in these stages. Figure 4(A-C) shows illustrative results for an infection-preventing vaccine, for the optimal sequencing of priority groups. Most scenarios for R0, indicate prioritisation of those over 60 year old (those most at risk from severe outcomes of infection), before

covering those with comorbidities (Figs. 4B,C). However, in settings with low transmission (R0 = 1.25), those with comorbidities should be prioritised over those older than 60 year (Fig. 4A). Figure 4(D-F) shows corresponding results for a symptomatic disease preventing vaccine; here again, the priority group after keyworkers is generally those over 60 year old (Figs. 4E,F) except in the low-R0 scenario (Fig. 4D), where those with comorbidities would instead be prioritised. In all cases, prioritising risk groups in this way would avert more deaths, or have comparable impact to, a 'uniform' strategy of allocating vaccines proportionally amongst risk groups (dotted grey line).

Discussion

Challenges that are particularly pressing in a country as large as India would persist even following the emergence of several vaccine candidates for COVID-19. The most contentions of them relate to rolling out of vaccines at population level. In this study, we have used a simple mathematical model of transmission dynamics, to show how vaccination efforts in the country might best be focused, in order to reduce mortality most effectively with a finite vaccine supply. Our results suggest that vaccinating all defined priority groups would have a substantial reduction in overall health burden, compared to a scenario of no vaccination, and complete lifting of restrictions. Such a strategy could reduce peak symptomatic incidence by about 21%, and cumulative mortality by about 30% .

In terms of prioritisation of population groups, our results show how the most efficient use of a given vaccine supply is shaped by transmission intensity (R0), whether for infection- or symptomatic-disease-preventing effects of the vaccine (figures 4). Conceptually, the fundamental dynamics underpinning these results arise from interactions between 'direct' effects of immunisation (i.e. the protection amongst those receiving the vaccine) and 'indirect' effects (i.e. the population-level benefits of general reductions in transmission). While in practice any vaccine is likely to exert a combination of both the effects, our work highlights that, for a vaccine supply sufficient to cover 18% of the population, direct effects would generally take precedence over indirect effects, in deciding prioritisation. Thus vaccination rollout should generally prioritise those most at risk of severe outcomes of infection; in the present case, the elderly. However, only in the lowest-transmission settings would those with comorbidities be prioritised over the elderly. As those with comorbidities include young adults, who have greater contact rates than the elderly, vaccinating this

group would raise stronger indirect effects; it is in low-R0 scenarios that such effects would be as important as direct effects.

Our results highlight the need for further data to help inform strategic priorities. First, there is a need to understand transmission in real world settings (i.e. R0 in any given setting). In particular, mathematical and statistical models – similar to those we have presented here - have been used to estimate R0 for SARS-CoV-2 in different settings, and may also be informative in the Indian context.[14] We note that in a country as large and complex as India, there will be a need for locally-tailored, locally-relevant estimates. As an indication of varying transmission intensity across the country, the second national serosurvey reported 16% seroprevalence of SARS-CoV-2 antibody among those living in urban slums; 8% among those living in urban non-slum setting; and 4% in rural settings.[15] Such variation is likely to be driven by factors such as population density, and indeed may call for different prioritisation strategies in different settings. For example, scenarios of R0 = 1.25 and 2.5 may be appropriate, respectively, in rural and urban slum settings. Further work should also address how these populations influence each other in transmission, as a result of population mobility, as well as the contribution of different population subgroups, such as schoolchildren, on transmission. Second, our work highlights the need to better understand the effect of vaccination on transmission. Although clinical trials so far have focused on symptomatic illness as an endpoint, interim findings for at least one vaccine candidate suggest the potential for reduced transmission as well.[19] However, further data are needed, for example through trial designs following up household cohorts to assess the risk of transmission amongst close contacts, and how this risk is affected by vaccination. Alternatively, a better understanding of how viral load correlates with SARS-CoV-2 transmission could allow better interpretation of available trial results, in terms of transmission risk. [22,23] On the latter point mentioned above, In all of these considerations, robust surveillance data – including at the level of hospitalisations and mortality – would be invaluable in refining model estimates.

As with any modelling study, our analysis has limitations to note, which should be regarded as illustrating the importance of different factors for policy decisions, and not as a predictive framework. As described above, our analysis does not explicitly address temporal sequencing, i.e. which groups to cover first: for simplicity, we modelled vaccination coverage as being completed in advance of the epidemic, concentrating on identifying the groups who would have the most impact on mortality if receiving the vaccine. Our analysis is

subject to various uncertainties, for example, the increased risk of death as a result of comorbidities. Further data on these excess risks will be valuable in refining our findings. In considering the key worker population, although we incorporated vaccination coverages consistent with the size of this population, we did not explicitly capture the broader societal impact of failing to vaccinate these individuals, another important area for future work. Finally, an important uncertainty relevant to our current work is the dynamics of immunity, whether induced by vaccination or by infection. For example, there is evidence that memory B-cells and neutralising antibodies persist at detectable levels in blood for months post-infection [24–26]. Despite important recent advances in understanding implications for disease outcome upon reinfection [27], there remains much uncertainty, including on the role of the cellular immune response [28]. A recent modelling study showed how immune mechanisms could mediate a decline in the severity of COVID-19 as it becomes endemic in the coming years [29], but it remains unclear how current licensed vaccines, in India and elsewhere, might shape these dynamics. Addressing these issues are beyond the scope of our current work, which focuses on the implications of vaccination for immediate mitigation of health burden: nonetheless, these again represent important areas for future work to address.

In conclusion, models such as the one presented in this article can generate useful program insights. In practice the gains, as projected by the model due to vaccination of select population groups in real life settings, would enhance from other prevention measures at the population level such as use of masks and maintenance of physical distance during social interactions. Such a synergy is expected to yield further dampening of SARS-CoV-2 transmission. We therefore conclude that rational and focused vaccination approaches, as outlined in this article, in the context of Indian COVID-19 epidemic makes for a smarter public health choice than mass vaccination.

Author contributions

SP and BB conceptualised the study; SM, NA and SP developed the modelling approach and SM performed the modelling. All authors analysed and interpreted the results; SM and SP wrote a first draft of the manuscript, and all authors contributed to the final draft and approved the version for submission to the journal.

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Competing interests

The authors declare no competing interests.

Ethical approval

Not required.

Data sharing

The model code and dataset are publicly available at https://github.com/sandipccmb/COVID-19-vaccination-strategy.

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	Infection preventing vaccine			Symptomatic disease preventing vaccine		
	Percentage reduction in peak	Percentage reduction in	Number needed to vaccinate	Percentage reduction in peak	Percentage reduction in	Number needed to vaccinate

	symptomatic incidence	cumulative mortality	to avert one death	symptomatic incidence	cumulative mortality	to avert one death
(A) key workers (HCW + FW)	4.8 (3.8 – 6.3)	2.0 (1.4 – 2.8)	1872 (1292 - 3031)	2.3 (1.8- 3.1)	2.0 (1.7 – 2.4)	1877 (1226 - 3034)
(B) Key workers + Individuals with comorbidities (24 – 60 years)	18.8 (14.9 – 23.6)	11.8 (8.2– 15.7)	320 (213 – 528)	8.9 (7.1–11.9)	13.6 (10.8 – 16.4)	273 (179 - 460)
(C) Above two groups (A+B) + all individuals over 60 years of age	20.6 (16.7 – 25.4)	29.7 (25.8 – 33.8)	127 (87 – 196)	10.4 (8.4 – 13.0)	32.9 (28.6 – 37.3)	114 (76 - 184)

Table 1. Summary of epidemiological impacts for the different scenarios shown in figure 3. Numbers show median estimates, while parentheses show 95% uncertainty intervals.

Figure captions

Figure 1. Priority groups of people in three different scenarios. Sources: healthcare workers (HCW)[30], frontline workers (FW), those with diabetes and hypertension as co-morbidities[31], those over 60 years of age[32]. As described in the main text, when modelling vaccination coverage amongst essential workers, our focus is on the epidemiological impact

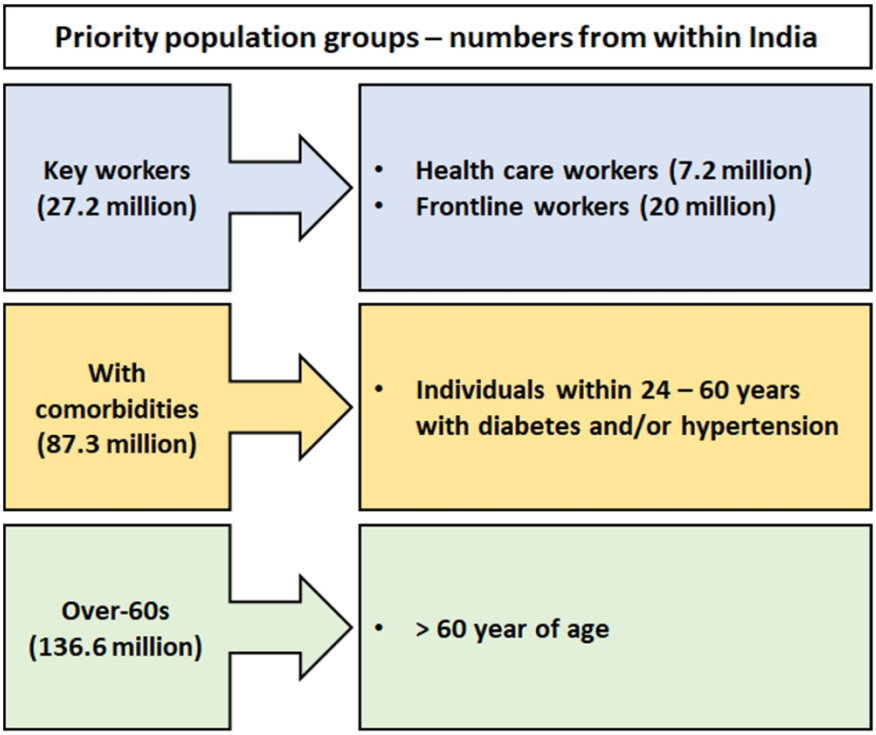
of doing so (we do not address, for the example, the potential impacts for healthcare continuity, of vaccination coverage in HCWs).

Figure 2. Illustration of the compartmental model structure. The top and bottom halves of the figure show unvaccinated and vaccinated subpopulations, respectively. Boxes represent compartments, and arrows represent flows between different stages of the clinical course of infection. Compartments are as follows: Uninfected (U); Exposed (E); asymptomatic but infectious (A); presymptomatic (P); symptomatic (S); recovered and immune (R). The terms c_1,c_2 represent effectiveness of, respectively, an infection preventing and symptomatic disease preventing vaccine. The term μ represents the per-capita hazard of mortality; see table S2 for a list of all other model parameters. This model structure is further stratified by age groups, and by presence/absence of comorbidities.

Figure 3. Illustration of vaccine impact in each of the priority groups listed in Figure 1. Scenarios are shown in the example of R0 = 2, assuming that vaccine coverage is completed at the same time as current restrictions being fully lifted. Upper row shows results for an infection-preventing vaccine, while the lower row shows results from a symptomatic disease preventing vaccine. Scenarios show vaccination coverage in different combinations of priority groups: Keyworkers ('KeyW'); additionally including those with co-morbidities ('Co-M'); and additionally including those over 60 years of age ('>60').All horizontal axes show days after vaccination and restrictions being lifted. Solid lines show central (median) estimates, while shaded areas show 95% uncertainty intervals as estimated by sampling uniformly from the ranges shown in table S2. The overall impact of vaccination in each of these scenarios is summarised in table 1, together with the amount of vaccines needed.

Figure 4. Optimal prioritisation strategies for an infection-preventing vaccine (A, B, C) and for a symptomatic disease preventing vaccine (D, E, F). For reference, dotted black lines in all plots show a 'uniform' strategy where available vaccines are allocated proportionately amongst the two risk groups, rather than prioritising one over the other (for clarity, uncertainty intervals not shown for this scenario). For the plots (A – C) we assume

deployment of a vaccine having 60% efficacy in reducing susceptibility to infection, but no effect on development of symptoms following infection. Assuming keyworkers receive first priority, Figs.S1 – S2 in the supporting information show different strategies for subsequently prioritising those over 60 years old, vs those with comorbidities. Here, we show those strategies that are optimal for minimising the overall mortality, under different levels of vaccine coverage, and for different values of R0. For example,in the case R0 = 2, if initial vaccine supply is only enough to cover 10% of the population, then after covering keyworkers, these vaccines should be deployed preferentially amongst the over-60s (in green). If there is enough vaccine supply to cover 20% of the population, the optimal strategy would be to vaccinate the over-60s after keyworkers, and spending any remaining vaccine supply amongst those with comorbidities. Similar priorities apply for R0 = 2.5. However, for low-transmission settings (R0 = 1.25), those with comorbidities would be prioritised over the elderly. For the plots (D – F) we assume deployment of a vaccine having 60% efficacy in reducing symptoms and mortality following infection, but no preventive effect on acquiring infection. For such a vaccine, optimal prioritisation strategies are similar to those shown in plots (A-C).



Priority groups of people in three different scenarios. Sources: healthcare workers (HCW) [ref. 30], frontline workers (FW), those with diabetes and hypertension as co-morbidities [ref. 31], those over 60 years of age [ref. 32]. As described in the main text, when modelling vaccination coverage amongst essential workers, our focus is on the epidemiological impact of doing so (we do not address, for the example, the potential impacts for healthcare continuity, of vaccination coverage in HCWs).

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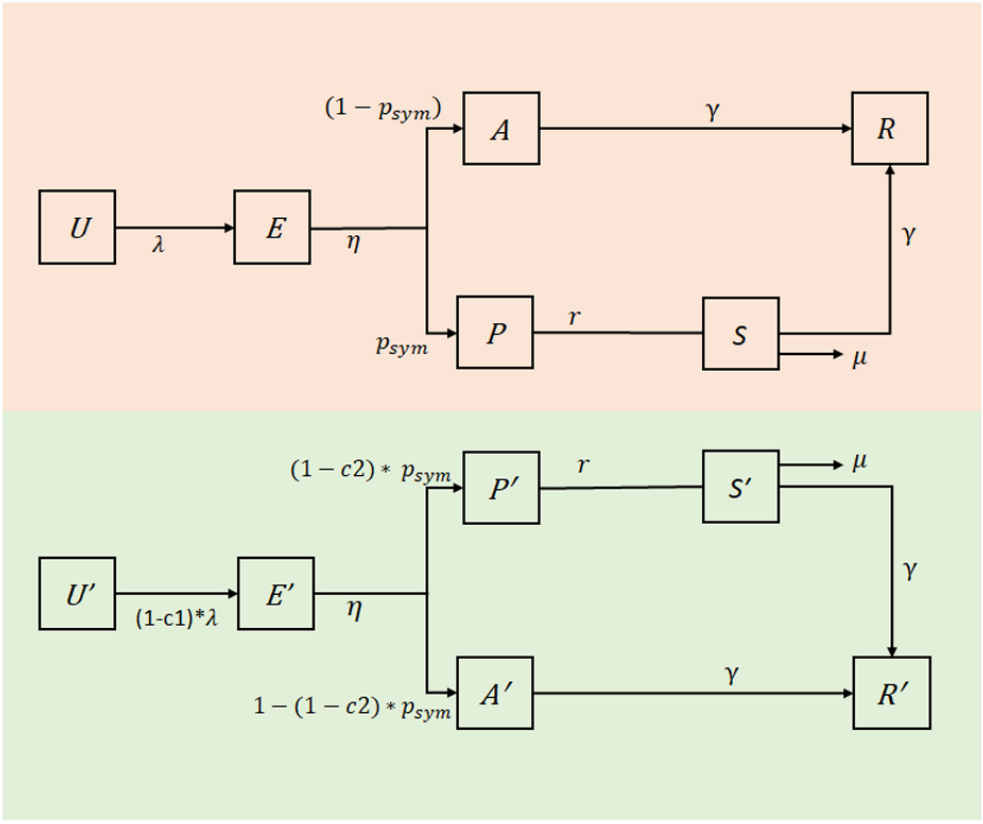

Illustration of the compartmental model structure. The top and bottom halves of the figure show unvaccinated and vaccinated subpopulations, respectively. Boxes represent compartments, and arrows represent flows between different stages of the clinical course of infection. Compartments are as follows: Uninfected (U); Exposed (E); asymptomatic but infectious (A); presymptomatic (P); symptomatic (S); recovered and immune (R). The terms c_1,c_2 represent effectiveness of, respectively, an infection preventing and symptomatic disease preventing vaccine. The term μ represents the per-capita hazard of mortality; see table S2 for a list of all other model parameters. This model structure is further stratified by age groups, and by presence/absence of comorbidities.

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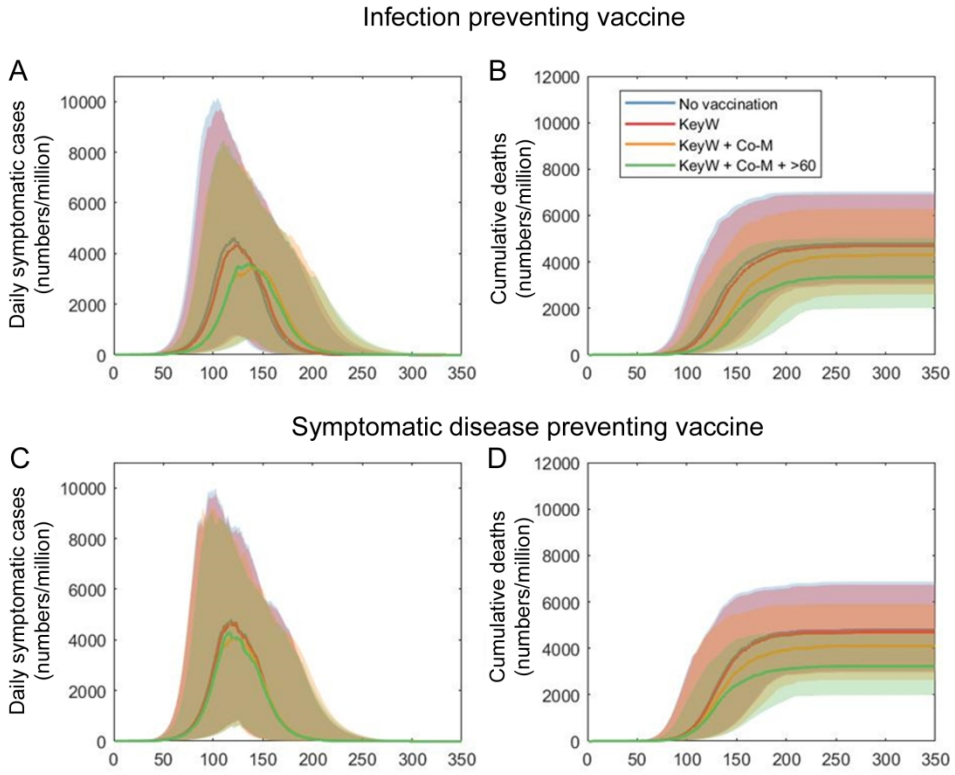

Illustration of vaccine impact in each of the priority groups listed in Figure 1. Scenarios are shown in the example of R0 = 2, assuming that vaccine coverage is completed at the same time as current restrictions being fully lifted. Upper row shows results for an infection-preventing vaccine, while the lower row shows results from a symptomatic disease preventing vaccine. Scenarios show vaccination coverage in different combinations of priority groups: Keyworkers ('KeyW'); additionally including those with co-morbidities ('Co-M'); and additionally including those over 60 years of age ('>60').All horizontal axes show days after vaccination and restrictions being lifted. Solid lines show central (median) estimates, while shaded areas show 95% uncertainty intervals as estimated by sampling uniformly from the ranges shown in table S2. The overall impact of vaccination in each of these scenarios is summarised in table 1, together with the amount of vaccines needed.

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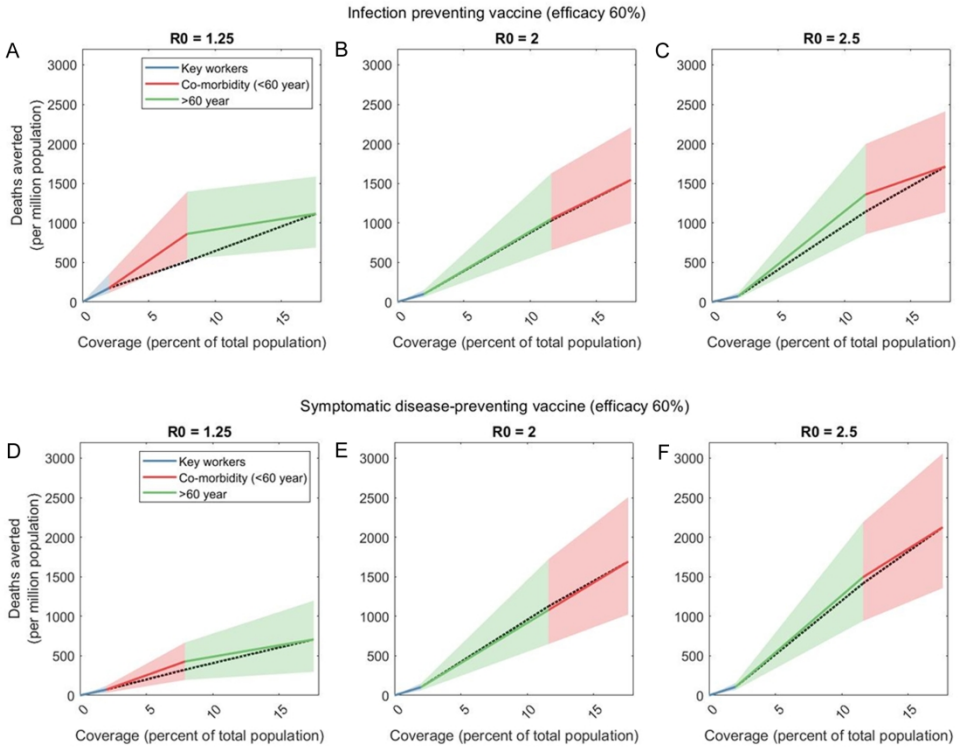

Optimal prioritisation strategies for an infection-preventing vaccine (A, B, C) and for a symptomatic disease preventing vaccine (D, E, F). For reference, dotted black lines in all plots show a 'uniform' strategy where available vaccines are allocated proportionately amongst the two risk groups, rather than prioritising one over the other (for clarity, uncertainty intervals not shown for this scenario). For the plots (A – C) we assume deployment of a vaccine having 60% efficacy in reducing susceptibility to infection, but no effect on development of symptoms following infection. Assuming keyworkers receive first priority, Figs.S1 – S2 in the supporting information show different strategies for subsequently prioritising those over 60 years old, vs those with comorbidities. Here, we show those strategies that are optimal for minimising the overall mortality, under different levels of vaccine coverage, and for different values of R0. For example,in the case R0 = 2, if initial vaccine supply is only enough to cover 10% of the population, then after covering keyworkers, these vaccines should be deployed preferentially amongst the over-60s (in green). If there is enough vaccine supply to cover 20% of the population, the optimal strategy would be to vaccinate the over-60s after keyworkers, and spending any remaining vaccine supply amongst those with comorbidities. Similar priorities apply for R0 = 2.5. However, for low-transmission settings (R0 = 1.25), those with comorbidities would be prioritised over the elderly. For the plots (D – F) we assume deployment of a vaccine having 60% efficacy in reducing symptoms and mortality following infection, but no preventive effect on acquiring infection. For such a vaccine, optimal prioritisation strategies are similar to those shown in plots (A-C).

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INDIA'S PRAGMATIC VACCINATION STRATEGY AGAINST COVID-19: A MATHEMATICAL MODELLING BASED ANALYSIS

Sandip Mandal[1], Nimalan Arinaminpathy[2], Balram Bhargava[1], Samiran Panda (0000-0002-5077-6275)[1*]

[1]Indian Council of Medical Research, New Delhi, India

[2]MRC Centre for Global Infectious Disease Analysis, School of Public Health, Imperial College London, London, UK

Correspondence to: pandasamiran@gmail.com /pandas.hq@icmr.gov.in/ director@nariindia.org

Supplementary materials

Table of Contents

1. Model specification

We developed a deterministic, compartmental model of SARS-CoV-2 transmission and disease course with three different age groups: <24 year, 24 - 60 year and >60 year, and further stratified by the presence of comorbidities. In all equations that follow, state variables (e.g. *U*, *E* etc) denote the respective *proportions* of the total population in the corresponding states. Thus at time zero (prior to the epidemic), all state variables sum to 1. In this way, the model results can be applied to different administrative scales within India (e.g. districts), regardless of the actual population size involved. Accordingly, all model results are shown as population rates, e.g. deaths per million population (Figure 3, main text).

Governing equations

Model compartments are listed in Table S1, and model parameters listed in Table S2. Governing equations for the non-vaccinated population are as follows, where subscript i denotes age group, and subscript j denotes comorbidity group:

Uninfected (U):

$$\frac{dU_{ij}}{dt} = -\lambda_i U_{ij}$$

Exposed but not yet infectious (E):

$$\frac{dE_{ij}}{dt} = \lambda_i U_{ij} - \eta E_{ij}$$

Asymptomatic and infectious (A):

$$\frac{dA_{ij}}{dt} = \eta \left(1 - p^{(sym)}\right) E_{ij} - \gamma A_{ij}$$

Presymptomatic and infectious (P):

$$\frac{dP_{ij}}{dt} = \eta\, p^{(sym)}\, E_{ij} - r\, P_{ij}$$

Symptomatic and infectious (S):

$$\frac{dS_{ij}}{dt} = r P_{ij} - \mu_{ij}\, S_{ij}$$

Recovered and partially immune (R):

$$\frac{dR_{ij}}{dt} = \gamma (A_{ij} + S_{ij})$$

A key parameter here is $p^{(sym)}$, the proportion of infected individuals developing symptoms.

Corresponding equations apply for the vaccinated compartments, but with primes distinguishing these compartments (e.g. U'). Additionally for this population, the term $p^{(sym)}$ is replaced by $(1 - c_2)p^{(sym)}$, where c_2 is vaccine efficacy in preventing disease.

For the force-of-infection experienced by non-vaccinated individuals, we have:

$$\lambda_i = \sum_{k,l} \beta\, m_{ik} \{[S_{kl} + k\,(A_{kl} + P_{kl})] + [S'_{kl} + k\,(A'_{kl} + P'_{kl})]\}$$

And for vaccinated individuals:

$$\lambda'_i = (1 - c_1)\,\lambda_i,$$

where c_1 is the effect of the vaccine on reducing susceptibility to infection.

Overall, the value of the basic reproduction number (R_0) for this model is proportional to the value of β, the rate-of-infection attributable to symptomatic individuals (noting that k acts as an adjustment for a/pre-symptomatic individuals). As described below, we controlled for R_0 by adjusting the value of β accordingly.

State symbol	Meaning
U_i	Uninfected (i = 1, 2, 3 indicating three age groups)
E_i	Exposed
A_i	Asymptomatic
P_i	Pre-symptomatic
S_i	Severe symptomatic
R_i	Recovered

Table S1 List of state variables

Parameter	Meaning	Values			Source/Remarks
β	Transmission rate	0.079 – 0.16			Calculated using next-generation matrix as described in ref[1]. Value shown here is to yield R0 = 1.25 – 2.5.
η	Amongst those exposed, rate of developing infectiousness	(1/3 – 1/5) /day			Corresponds to an average latent period of 3-5 days: together with the period of presymptomatic transmission (see r below), corresponds to an overall average incubation period of 4-6 days [2]
$p^{(sym)}$	Proportion developing symptoms	1/3 – 2/3			Wide variation noted in individual studies and meta-analysis [3–5]
k	Relative infectiousness of asymptomatic vs symptomatic infection	2/3 – 1			
r	Rate of developing symptoms	1 /day			Assumption, corresponds to mean pre-symptomatic duration of 1 day
γ	Recovery rate	0.2 /day			Assumption, corresponds to mean infectious period of 5 days[6]
f	Fold-increase in case fatality rate as a result of comorbidities (diabetes and/or hypertension)	2.5			Drawn from recent systematic review [8]
	Age groups	<24 year	24-60 year	>60 year	

CFR_i	Case fatality rate in age group *i* in absence of comorbidities	0.1%	1.45%	10.9 %	Drawn from a recent study from two Indian States.[9]
μ_i	Mortality rate for severe cases	0.0002 /day	0.0029 /day	0.02 45 /day	Hazard rates of μ_i are calculated to yield case fatality rates, using: $CFR_i = \mu_i/(\mu_i + \gamma)$. Uncertainty in the mortality hazards are considered +/-25%.
N_i	Population (India)	634 mn	614 mn	131 mn	Extrapolated from the Census of India 2011[10]
m_{ij}	Connectivity matrix between age group i with age group j	1.37 2.52 0.28	1.43 2.90 0.34	0.05 0.01 0.02	Drawn from ref.[9] Uncertainty in the each element of the contact matrix is considered +/-25%.

Table S2: Parameters used in the model simulation. There remains much uncertainty about parameters relating to SARS-CoV-2 natural history, e.g. infectiousness of asymptomatic people relative to symptomatic ones and, duration of pre-symptomatic period etc. In this study we adopted a range of parameter values to reflect this uncertainty in our model projections (figure 3-5, main text).

2. Model execution

Using latin hypercube sampling, we drew 5,000 independent samples from the parameter ranges listed in Table S2. For each sample, and under given scenarios for R_0 and vaccine coverage, we then performed the following steps:

1. Control for the basic reproduction number (R_0), as follows:
    a. In the absence of any vaccination coverage or prior immunity, use analytical methods described in (ref[1]) to calculate the value ρ of the reproduction number when $\beta = 1$.
    b. Set $\beta = R_0/\rho$, thus yielding the scenario-specified value of R_0 for the basic reproduction number.
2. Construct initial conditions for the dynamical system, as follows:
    a. Construct a disease-free population with no prior immunity except for those who have been vaccinated (the latter, in line with the specified scenario for vaccination coverage).
    b. Introduce infection by displacing 1 individual from the susceptible, unvaccinated adult population, to the symptomatic, unvaccinated adult compartment (the specific choice of characteristics for this seeding infection are not important for the model outcomes we analyse).
3. Simulate the system of equations listed in section 1, until there are no further new infections.
4. Record the cumulative deaths that occurred over the simulation period.

We repeated these steps for each of the 5,000 samples, to obtain a corresponding number of estimates for cumulative deaths. We then estimated uncertainty by taking 2.5th, 50th and 97.5th percentiles over these samples.

3. Priority population groups for vaccination – further information

Category	Numbers		Source
Number of healthcare workers (HCW)			
HCWs (qualified)	3827820		Karan et al (2019) [11]
Support workers	1245878		
HCW (without requisite qualifications)	2084185		
Total	7157883		
Frontline workers (FW)			
	Active	**Reserve**	
Armed forces	1443921	1155000	Information available in public domain [12,13]
Paramilitary forces	87000		
Central Armed Forces and Others	1403700	987800	
Municipal workers	15000000		
Total	20077421		
Co-morbidity (diabetes and/or hypertension)			
Population < 24 year of age with at-least one comorbidity	17801137 (2.8% population in this age group)		WHO SAGE report, 2013[14]
Population 24 – 60 year of age with at-least one comorbidity	87283375 (14.3% population in this age group)		
Population >60 year of age with at-least one comorbidity	58726385 (43.0% population in this age group)		
Elderly population			
Population > 60 year of age	136620434		Extrapolated from the Census of India 2011[10]

Table S3: Priority population groups for vaccination.

4. Additional model outputs

Figure 4 in the main text shows model results for how priority groups might be sequenced, to gain maximum impact (lives saved) from a limited vaccine supply. While the figure shows only the 'optimal' scenario, Figures S1 below shows all 2 possible scenarios for the order in which vaccination is deployed amongst the priority groups, in the case of an infection-preventing vaccine, and assuming that keyworkers receive first priority. Of these, the optimally efficient scenario is selected as that with the greatest gradient (lives saved per person vaccinated) at each stage, i.e. the scenario having the most concave shape. Figures S2 show corresponding results in the case of a disease-preventing vaccine.

Scenario definitions are as follows:

Scenario 1: Key workers → Co-morbidity → Elderly

Scenario 2: Key workers → Elderly → Co-morbidity

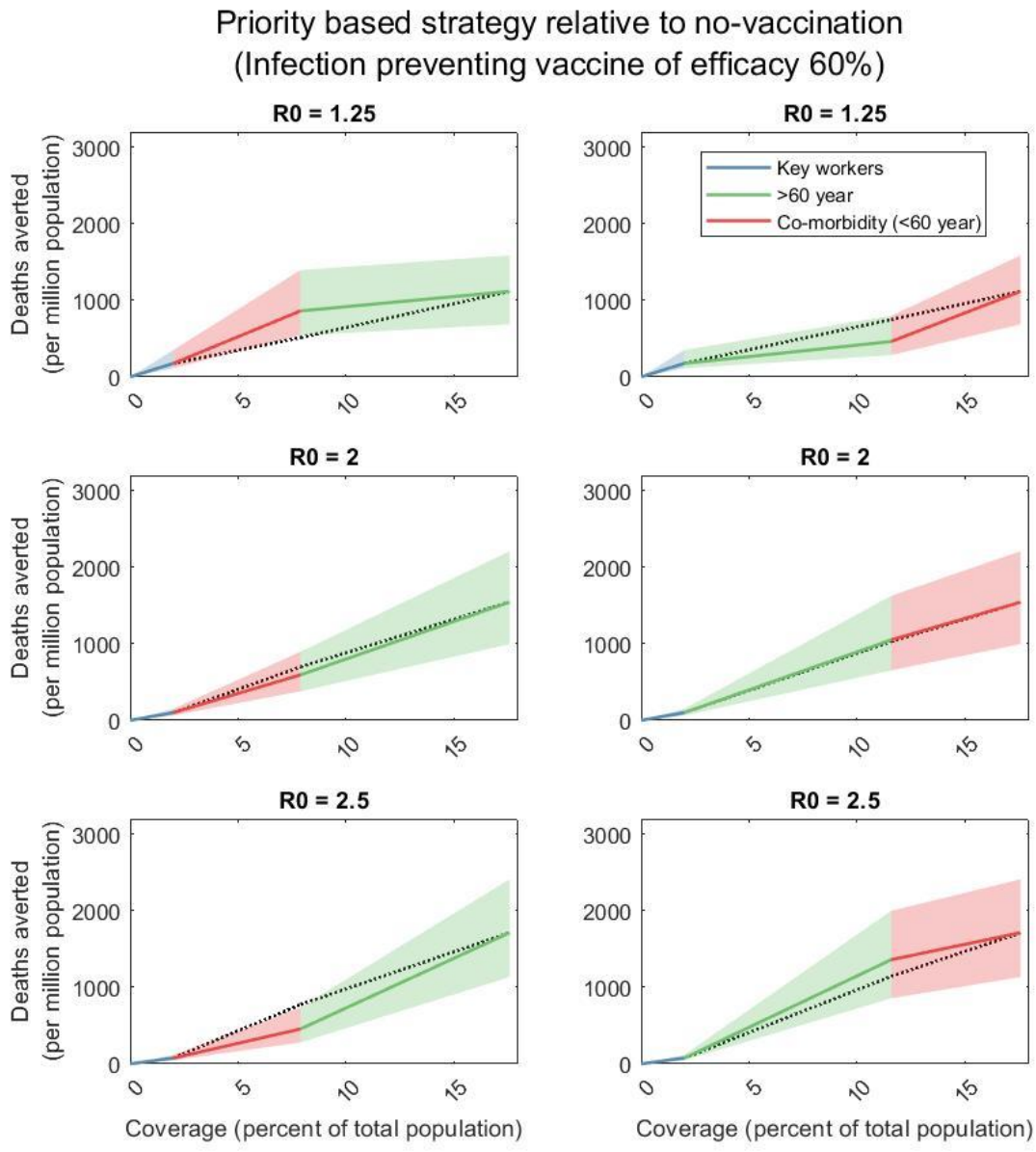

Figure S1. Scenarios for the order in which vaccination is deployed amongst the priority groups, in the case of an infection-preventing vaccine of efficacy 60%. We assume R0 = 2.5 keyworkers always receive first priority, and present scenarios for the prioritisation of the remaining two groups. As in the main text, dotted black lines show a 'uniform' strategy where available vaccines are allocated proportionately amongst the two risk groups, rather than prioritising one over the other.

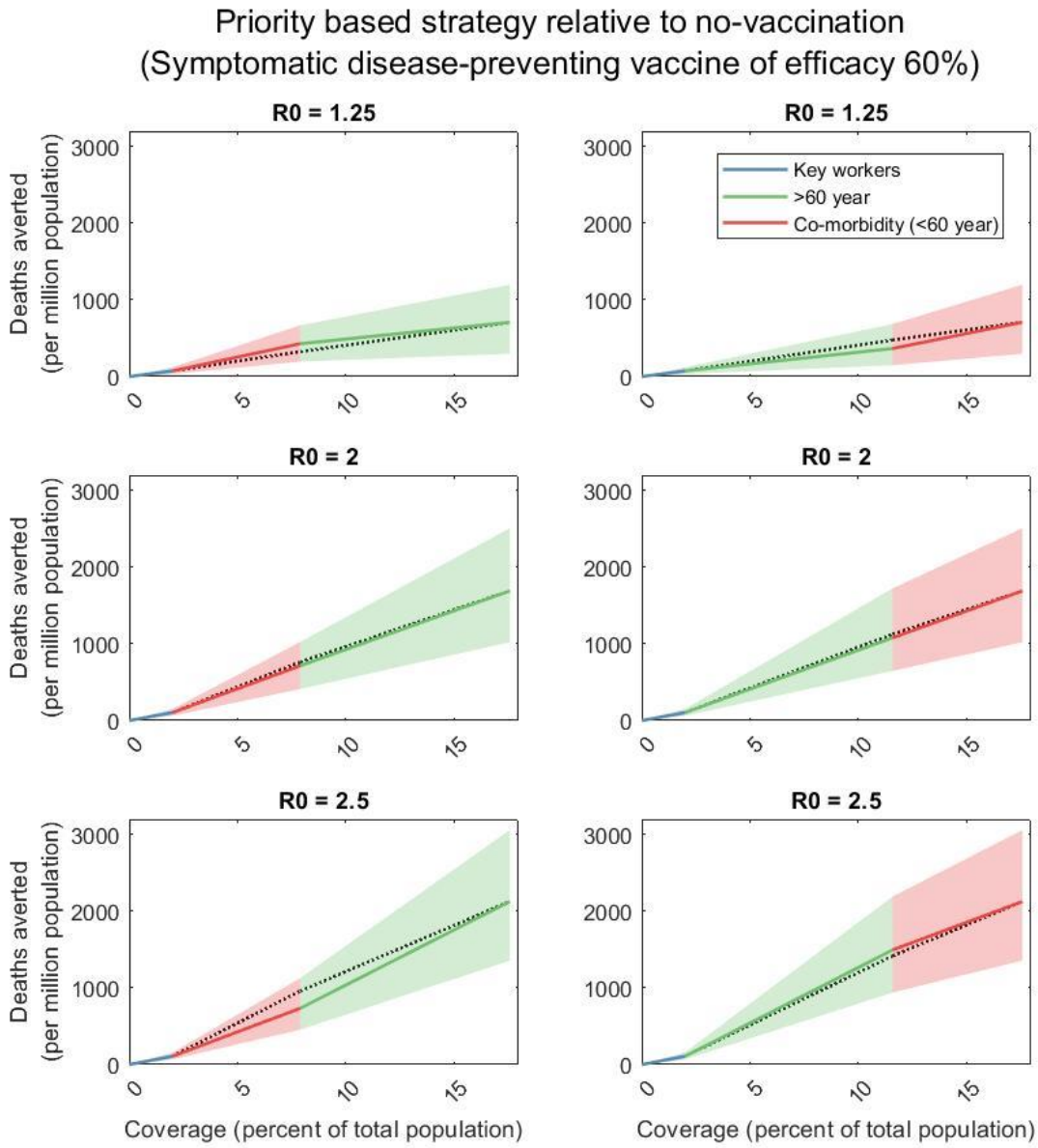

Figure S2. Scenarios as in figure S1, in the case of a disease-preventing vaccine of efficacy 60%.

5. Sensitivity analysis to vaccine efficacy

While results in the main text assumed (conservatively) a vaccine efficacy of 60%, below we present alternative results for 90%, showing that Figures 4 and 5 in the main text remain qualitatively unchanged.

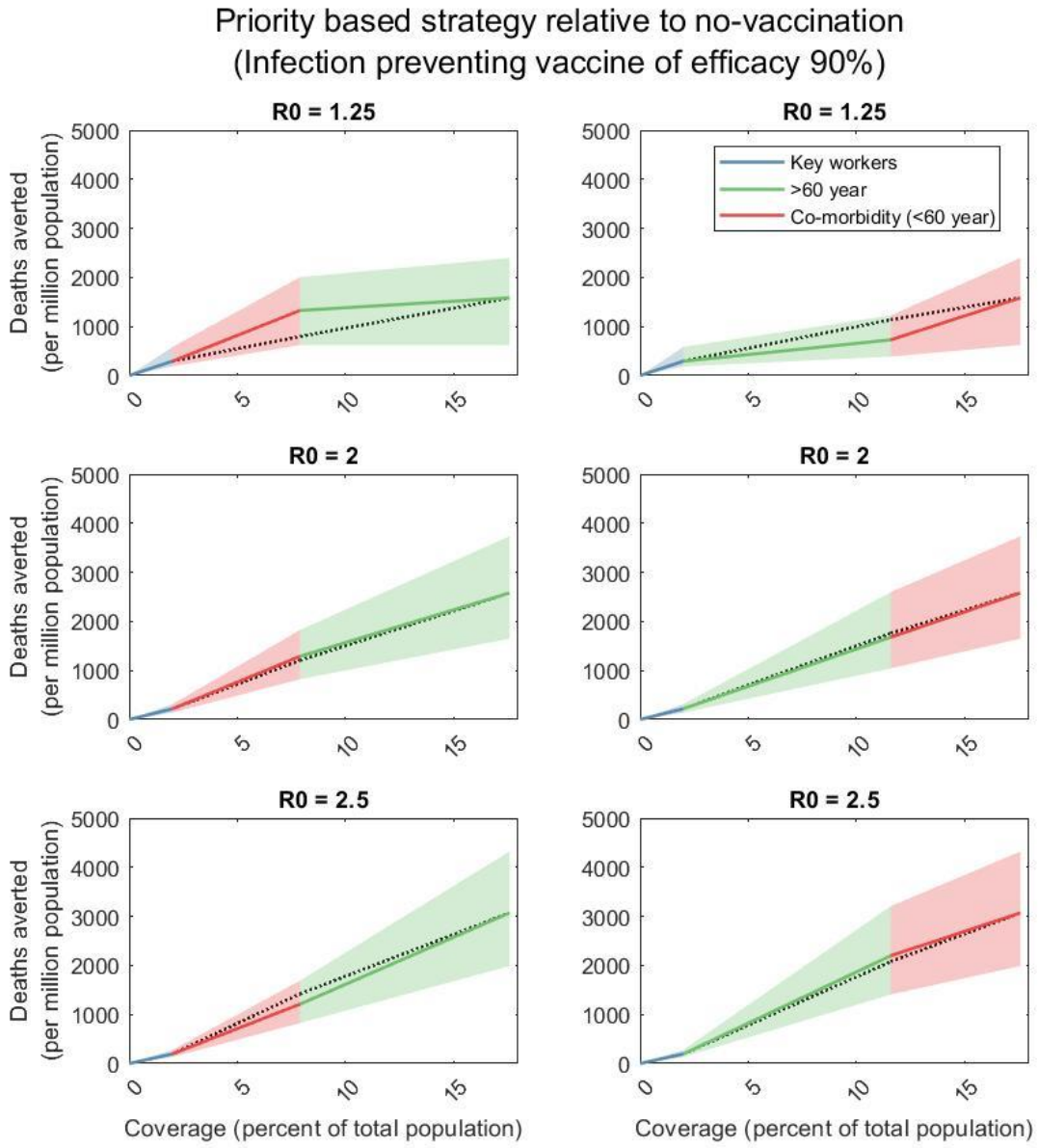

Figure S3. Scenarios for the order in which vaccination is deployed amongst the three priority groups, in the case of an infection-preventing vaccine of efficacy 90%.

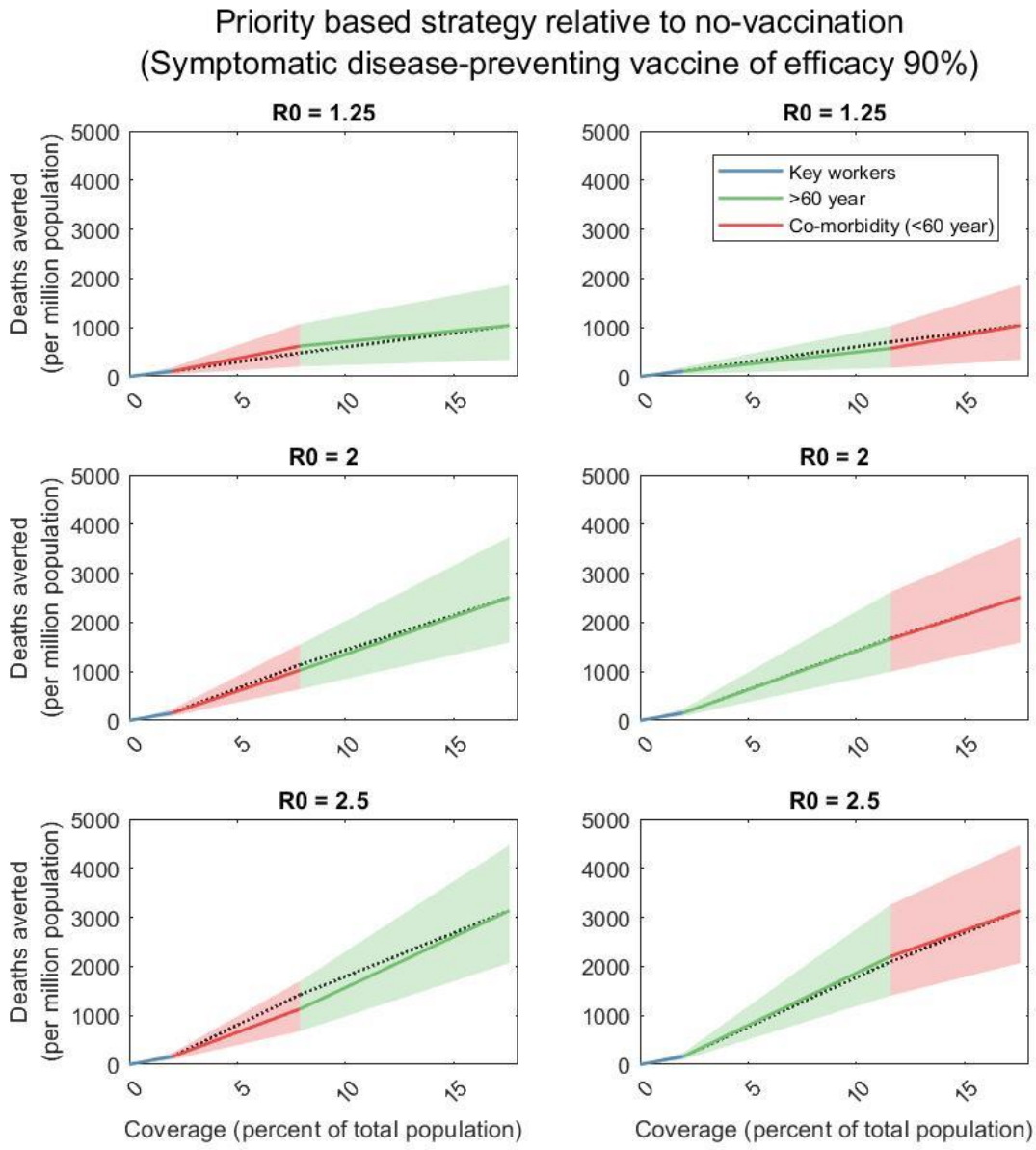

Figure S4. Scenarios as in figure S3, in the case of a disease-preventing vaccine of efficacy 90%.

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