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Vaccination against COVID-19 and society's return to normality in England: a modelling study of impacts of different types of naturally acquired and vaccine induced immunity

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ABSTRACT

Objectives: To project impacts of mass vaccination against COVID-19, and investigate possible impacts of different types of naturally acquired and vaccine-induced immunity on future dynamics of SARS-CoV-2 transmission from 2021 to 2029 in England.

Design: deterministic, discrete-time population dynamic modelling.

Participants: Population in England.

Interventions: mass vaccination programmes.

Outcome measures: daily and cumulative number of deaths from COVID-19.

Results: If vaccine efficacy is ≥70%, the vaccine-induced sterilising immunity lasts ≥182 days, and the reinfectivity is greatly reduced (by ≥40%), mass vaccination programmes can prevent further COVID-19 outbreaks in England. Under such optimistic scenarios, the cumulative number of COVID-19 deaths is estimated to be from 113,000 to 115,000 by the end of 2029 in England. However, under plausible scenarios with lower vaccine efficacy, shorter durability of immunity, and smaller reduction in reinfectivity, repeated vaccination programmes could not prevent further COVID-19 outbreaks.

Conclusions: Under optimistic scenarios, mass immunisation using efficacious vaccines may enable society safely to return to normality. However, under plausible scenarios with low vaccine efficacy and short durability of immunity, COVID-19 could continue to cause recurrent waves of severe morbidity and mortality despite frequent vaccinations. It is crucial to monitor the vaccination effects in the real world, and to better understand characteristics of naturally acquired and vaccine induced immunity against SARS-CoV-2.

ARTICLE SUMMARY:

Strengths and limitations of this study

- We used a population dynamic model to assess impacts of vaccination programmes on future dynamics of SARS-CoV-2 transmission dynamics, and to explicitly investigate the impacts of different types of immune responses to SARS-CoV-2 infection and vaccines on the COVID-19 epidemic in England.
- The model has been verified based on historically observed outcome data in England, and a large number of projection scenarios are explored.
- Findings from our study improves the understanding of key immunological parameters relevant to future SARS-CoV-2 transmission dynamics and vaccination strategies.
- This is a deterministic simulation model, and uncertainty in estimated parameters may have not been fully accommodated. There remain many uncertainties regarding durability and types of naturally acquired and vaccine-induced immunity.

INTRODUCTION

The COVID-19 pandemic caused by the spread of SARD-CoV-2 virus has resulted in a huge number of deaths and severe disruptions of economies and social activities around the world. The spread of the SARS-CoV-2 virus can be suppressed by non-pharmaceutical interventions (NPIs) and lockdown measures.[1] Because of their disruptive socioeconomic consequences, lockdown restrictions cannot last indefinitely.

Only a few months after the initial identification of SARS-CoV-2 pathogen, there were more than 200 vaccine candidates in development globally.[2] Since December 2020, three vaccines against COVID-19 have been approved for use in the UK, and a vaccination programme has been started to rollout, prioritised primarily by age and comorbidity, with older people being vaccinated first.[3] Although mass vaccination is a promising strategy to enable society to safely return to normality, there is great uncertainty about COVID-19 vaccines, including their safety and efficacy, and durability of different types of protection after vaccination.

The protection of naturally acquired or vaccine-induced immune responses may be attributable to infection protection, disease reduction, and reinfectivity reduction.[4] Studies of diseases caused by other human coronaviruses (HCoVs) indicated that infection protection immunity is likely to be short-lived, while disease reduction and reinfectivity reduction are likely long lasting.[5] Therefore, we conducted a modelling study to investigate possible impacts of different types of naturally acquired and vaccine-induced immunity on future dynamics of SARS-CoV-2 transmission in England.

METHODS

Model structure

This is a deterministic discrete-time (day) population dynamic model, implemented with computational language R.[6] The population are classified into categories by sex, age (5-year age bands for age <10 years, and 10-year age bands for age ≥10 years), and COVID-19 infection status (figure 1). The main infection compartments include susceptible, exposed, infectious, recovered, and vaccinated. Here “exposed” refers to a pre-infectious status of infected individuals. Infected individuals are classified as asymptomatic or symptomatic, and symptomatic individuals are classified as not being isolated, self-isolated, and hospitalised. We assume that hospitalised patients are effectively isolated and no longer able to transmit the virus to the general population, but patients who self-isolate at home may transmit virus to household contacts. The recovered and vaccinated are protected from reinfection, but they may be reinfected if the immunity is short-lived.

Parameters and data sources

Details on the model's structure (appendix figure 1), parameters (appendix table 1), source of data, and mathematical equations are available in Supplementary files. Initial parameter values were estimated based on a review of relevant literature, and key parameter estimates were adjusted so that the simulated numbers of COVID-19 deaths, hospitalised patients, and recovered individuals were as similar as possible to the data historically reported from March 2020 to January 2021 in England.[7]

We obtained population demographic statistics in England from the Office for National Statistics,[8] and the whole population is assumed to be susceptible to SARS-CoV-2 infection at the beginning of 2020. We assume incubation periods, infectious periods, days of hospital stay, and days of deaths after being infected, to be gamma distributed.[9-11] Age specific case fatality rates and hospitalisation rates of symptomatic cases were based on a study by Verity et al.[11] Average sex-and-age-specific rates of all-cause deaths in England during 2015-2019[8] are applied to people who are not infected with or recovered from COVID-19. We assumed that the number of births equals to the number of deaths each day, and did not consider the influence of population migration. We adjusted the number of individuals belonging to each age group at the beginning of a year since 2021, by shifting a proportion of them to the adjacent higher age group.

For simplicity, effects of NPI measures, including restrictions on social activities, contact tracing and testing, were materialised by changes in transmission risk per contact between a susceptible and an infectious individual,[12] and average numbers of contacts of the general population (appendix table 2 in supplementary files). We estimate that the transmission risk per contact between infectious and susceptible individuals was reduced by 32%, from 0·068 before the implementation of any NPIs to 0·046 by March 15, 2020 after implementing basic NPI measures. Because of the new virus variant (B.1.1.7),[13] the average transmission risk per contact was increased to 0·056 by the end of 2020. We assume that the transmission risk per contact from April to September is 20% lower than that from October to February, to incorporate the impact of seasonality on future projections since April 2021. We do not use the reproduction number as an input parameter, but derived the basic and effective reproduction numbers based on model's transmission parameters (equation 79 in Supplementary files).[12 14]

The sex-and-age-specific numbers of daily contacts per person were based on the UK data from a study of European countries.[15] We consider only the daily contacts of the general population and household contacts of individuals self-isolated at home. We estimated that the lockdown measures from March 24, 2020 reduced general population contacts by 60-85%, although household contacts were unchanged. The NPI measures were relaxed or strengthened over time, which were reflected in

the assumed social contacts and transmission risk (Supplementary files). After rolling out vaccination, we assume that, since June 2021, social contracts are return to normal as before the pandemic in England, although basic hygienic measures would be maintained.

Vaccination and projection scenarios

Results of randomised controlled trials shown that vaccines were efficacious in reducing symptomatic diseases, compared with placebo.[16 17] Vaccination of prioritised individuals began from 8 December 2020 in England and around 2 million individuals were vaccinated (mostly with a single dose) by January 10, 2021.[18] For simplicity, we assume that the mass vaccination starts from January 1, 2021 with a 80% coverage of eligible individuals, and the maximum number of individuals vaccinated daily is 300,000. The mass vaccination is modelled as an age-based phase approach, starting from people aged ≥70, followed by individuals aged 60-69, 50-59, 20-49, and then those aged 16-19. Although both Pfizer-BioNTec and AstraZeneca vaccines are 2-dose regimens, the policy in the UK has been to initially provide the first dose to as many adults as possible. Data from clinical trials indicated that the short-term vaccine efficacy after the first dose of the Pfizer-BioNTech and the AstraZeneca vaccine is, respectively, about 90% and 70%.[16] For simplicity, we do not separate single or double dose vaccination, and assume a range of the overall vaccine efficacy (90%, 70% or 50%) and the protection effects start 14 days after vaccination.

The reduction in symptomatic cases in vaccinated individuals may be due to induced antibodies in susceptible individuals (infection protection), or a lower proportion of infected individuals being symptomatic (i.e., disease reduction), or a combination of both. There are many different possible combinations of infection protection and disease reduction for a given overall vaccine efficacy in reducing symptomatic cases (appendix figure 2 in supplementary files). We assume that vaccine efficacy for reducing symptomatic cases is equally attributable to infection reduction and disease reduction in the main projections. For vaccines with 90%, 70% and 50% overall efficacy, the equal partial efficacy for the infection protection and for disease reduction is around 69%, 45%, and 29%, respectively (see Supplementary files for details).

Immune responses against COVID-19 infection, either naturally acquired from past infection or vaccine-induced, may reduce individuals' susceptibility to infection (sterilising or infection protection immunity), reduce pathology so that disease is less severe after being infected (disease reduction immunity), and reduce infectivity of those who are reinfected after the waning of immunity (reinfectivity reduction immunity).[4] According to immunological characteristics of other HCoVs, infection protection immunity may wane after a short period, while disease protection and reinfectivity reduction immunity are likely longer lasting.[5] For example, antibodies against SARS-CoV-1 virus in recovered patients was no longer detectable after 2-3 years, while specific memory T cells

remained detected after 11 years.[19] Therefore, we assume that the disease reduction and reinfectivity reduction immunity are long lasting (>10 years).[5] We assume that naturally acquired sterilising immunity lasts for 365 or 730 days, and vaccine-induced sterilising immunity lasts for 182, 365 or 730 days. Available evidence indicated that the viral loads and the duration of virus shedding in the infected individuals after vaccination were considerably reduced, compared with unvaccinated individuals.[20 21] Therefore, we assume that reinfectivity after waning of sterilising immunity is reduced by 20%, 40% or 60%. In this study, we assume that the infectivity of ineffectively vaccinated individuals is the same as individuals after waning of sterilising immunity, and vaccination of individuals recovered from natural infection prevents or delays the waning of their sterilising immunity.

We run the model and calibrate key transmission parameters by visually comparing estimated numbers of daily COVID-19 deaths, and hospitalised patients, with official records from January 1, 2020 to January 31, 2021 in England. We used estimates of transmission parameters by the end of January 2021 to project COVID-19 deaths from 2021 to 2029, under various scenarios of vaccine efficacy, durability and protection characteristics of naturally acquired and vaccine-induced immunity. The number of deaths from SARS-CoV-2 infections is the main endpoint in this study.

Patient and public involvement

No patients and the public were involved in this literature and secondary data based, computational modelling study.

RESULTS

Our derived basic reproduction number (R0) was 3·68 at the initial stage of the COVID-19 epidemic in England (appendix figure 3 in supplementary files). After implementing NPI and lockdown measures, the effective reproduction value (Rt) was reduced to 0·66 from March 24, 2020. Thereafter, the Rt values fluctuated along with changing NPI policies, and our estimated R values during March 2020 and January 2021 were within the ranges reported in England (Appendix figure 3 in Supplementary files).[22] The estimated prevalence of SARS-CoV-2 infection (appendix figure 4), the number of hospitalised COVID-19 patients (appendix figure 5), and the estimated daily deaths from COVID-19 (appendix figure 6) are well matched with the reported data from March 2020 to January 2021 in England (Supplementary files).

Vaccine efficacy, immunity durability, and reinfectivity

Figure 2 shows the impacts of partial vaccine efficacy regarding disease reduction relative to infection protection, durability of immunity, and reinfectivity, given the same overall vaccine efficacy (70%) in reducing symptomatic cases. There are three general inferences. As expected, the number of COVID-19 deaths is smaller following a greater reduction in reinfectivity (figure 2A, 2B, 2C). Second, a greater reduction in reinfectivity makes the durability of immunity less influential, if a vaccine is efficacious for infection protection (figure 2c). Third, the greater the infection protection by a vaccine, the smaller the number of COVID-19 deaths, although there are exceptions (figure 2A). A combination of a shorter duration of immunity and smaller reduction in the reinfectivity makes the disease reduction efficacy more important.

Population susceptibility and COVID-19 outbreaks

Changes in the prevalence of susceptible individuals and daily peaks of COVID-19 deaths in England during 2020 and 2029 are shown in figure 3 (additional details in supplementary table 1), under assumptions of 90% vaccine efficacy, 40% reduction in reinfectivity after waning of sterilising immunity, and different durations of naturally acquired and vaccine-induced sterilising immunity.

The prevalence of susceptible individuals is reduced to <30% after a single wave of mass vaccination starting from January 2021, but starts to increase from January 2022, if the duration of vaccine immunity is 365 days (figure 3A). The raised prevalence of susceptible individuals leads to an outbreak with a high peak (n=1,394) of daily COVID-19 deaths in November 2023. The prevalence of the susceptible is reduced to about 47% by the natural infection during the outbreak, then increases to >90% by the end of 2025 due to waning of immunity, which is followed with a new outbreak from December 2029. Clearly, a single wave of mass vaccination is insufficient if the immune response is short-lived. Three waves of repeated annual revaccination programmes delay the new outbreak, with a peak (n=632) of daily COVID-19 deaths in March 2027 (figure 3B). Five repeated waves of annual revaccination programmes almost prevent any new outbreaks before the end of 2029 (figure 3C).

If the vaccine immunity lasts only 182 days, the prevalence of susceptible individuals starts to increase six months after vaccination (figure 3D, 3E, 3F). A single wave of mass vaccination is followed with two new peaks of daily COVID-19 deaths (figure 3D), and the three and five repeated waves of annual vaccination programmes result in corresponding changes in the prevalence of susceptible individuals, each with a single peak of daily COVID-19 deaths (figure 3E, 3F). If the vaccine immunity lasts only 182 days, the annual mass vaccination programmes are insufficient to sustain a constantly low prevalence of the susceptible, and the prevalence of the susceptible fluctuates up and down biannually (figure 3E, 3F). Notably, the COVID-19 outbreaks start about two years after

stopping the annual mass vaccination programmes, due to the assumed duration of natural immunity (730 days).

Total COVID-19 deaths under various scenarios

The projected total numbers of COVID-19 deaths during 2020-2029, under various scenarios, are shown in table 1 (more details in Supplementary table 2). If there no waning of immunity, a single mass vaccination programme prevents COVID-19 outbreaks after returning to normality. If there is waning of sterilising immunity, mass vaccination programmes may prevent further COVID-19 outbreaks under scenarios with high vaccine efficacy, longer lasting immunity, and large reduction in reinfectivity after waning of sterilising immunity. Under optimistic scenarios, the cumulative number of COVID-19 deaths is estimated to be from 113,000 to 115,000 by the end of 2029 in England. However, the total number of COVID-19 deaths may be up to 754,000 by the end of 2029, under the scenario with low vaccine efficacy (50%), short duration of sterilising immunity, and high reinfectivity (table 1).

If the overall vaccine efficacy is 90%, the natural immunity lasts 730 days on average and the reinfectivity after immunity waning is reduced by 60%, two repeated annual vaccination programmes are able to prevent further outbreaks, even if the duration of the vaccine immunity is only 180 days. However, if the reinfectivity is reduced by 40%, five to nine annual revaccination programmes are required, depending on durability of immunity. If both the natural and vaccine immunity are short-lived (365 day and 180 days, respectively), and the reduction in reinfectivity is smaller (e.g., by 40% or 20%), further COVID-19 outbreaks cannot be prevented by repeated annual vaccination programmes (table 1).

If vaccine efficacy is 70%, the duration of natural immunity lasts 730 days and the reinfectivity is reduced by 60%, two to three annual vaccination programmes can prevent further COVID-19 outbreaks (table 1). If the sterilising immunity is short-lived (for 365 or 182 days only) and the reduction in reinfectivity is low (e.g., by only 20%), the annual mass vaccination programmes are not able to prevent further COVID-19 outbreaks. Similarly, when the vaccine efficacy is 50%, annual mass vaccination programmes prevent further COVID-19 outbreaks, only if the sterilising immunity is long lasting and the reduction in reinfectivity is large.

Intervals between immunisation programmes

Results of sensitivity analyses based on vaccination programmes every two years or twice a year are shown in supplementary table 3. Programmes every two years can prevent COVID-19 outbreaks in scenarios with longer duration of sterilising immunity and larger reduction in reinfectivity. In addition, biannual vaccination programmes (twice a year) are more effective in reducing COVID-19

deaths, compared with annual programmes, in scenarios with low vaccine efficacy, short duration of sterilising immunity, and small reduction in reinfectivity. For example, in the scenario of 70% vaccine efficacy, 365 and 182 days of natural and vaccine immunity respectively, and 20% reduction in reinfectivity, the total number of COVID-19 deaths is estimated to be around 524,000 by annual vaccination programmes (table 1), which is reduced to around 228,000 by biannual vaccination programmes (Supplementary table-3). However, because a wave of mass vaccination of 80% individuals aged ≥16 years takes more than five months to complete, repeated vaccination every six months may not be practically feasible.

DISCUSSIONS

Mass immunisation using efficacious vaccines may enable society safely to return to normality. Repeated vaccination programmes may be required to prevent further COVID-19 outbreaks, depending on vaccine efficacy, the durability and characteristics of different types of immune response to naturally acquired and vaccine-induced immune responses. Evidence on diseases caused by other common HCoVs indicated that the infection protection immunity may be short-lived, but the disease reduction and the reinfectivity reduction immunity are likely to be longer lasting.[5] We found that, if reinfectivity is greatly reduced (e.g., by 60%), two or three repeated annual mass vaccination programmes prevent further COVID-19 outbreaks, even if the vaccine induced sterilising immunity lasts only 182 days. Under such optimistic scenarios, the cumulative number of COVID-19 deaths during 2020-2029 in England is estimated to be around 113,000. If both the natural and vaccine immunity are short-lived (365 and 180 days, respectively), and reinfectivity is reduced only by 40% or 20%, further COVID-19 outbreaks cannot be prevented by annual vaccination programmes. The total number of COVID-19 deaths is estimated to be around 754,000 by the end of 2029, under a pessimistic scenario with low vaccine efficacy (50%), short duration of sterilising immunity, and high reinfectivity.

There were several published modelling studies of vaccination again COVID-19 in the UK.[23-26] Two studies assessed impacts of the relaxation of social restriction after vaccination,[24 25] and one study assessed impacts of vaccination on hospital admissions,[26] but covered a shorter time horizon and did not consider waning of immunity. Another study of SARS-CoV-2 vaccination in the UK focused on economic evaluations.[26] Compared with previous studies, our study has separately considered the durability of naturally acquired and vaccine induced immunity, over a 10 year period from 2020 to 2029, and compared a wider range of plausible scenarios. We explicitly investigated the impacts of different types of immune responses to SARS-CoV-2 infection and vaccines on the COVID-19 epidemic in a country. Findings from our study will improve the understanding of key immunological

parameters relevant to future changes in SARS-CoV-2 transmission dynamics and vaccination strategies.

Evidence from randomised controlled trials showed that vaccines against SARS-CoV-2 are efficacious in reducing symptomatic COVID-19 cases, compared with placebo.[17] The reduction in symptomatic cases in the vaccine group may be attributable to infection protection or disease reduction. Available evidence showed that vaccines reduced the risk of SARS-CoV-2 virus infection in vaccinated individuals,[27] and household members of vaccinated healthcare workers has a lower risk of COVID-19 infection than those of unvaccinated.[28] In this study, we explored the impacts of different proportions of a vaccine's infection protection efficacy and disease reduction efficacy. Different combinations of the two efficacy components have impacts on the transmission dynamics, depending on the duration of immune response and reinfectivity after waning of sterilising immunity. Because of lack of data, we assumed that vaccine efficacy is equally attributable to the infection and disease reduction immunity.

We assumed a range of overall vaccine efficacy, including 50%, 70% and 90%, without considering doses of vaccines. As most vaccinated individuals will eventually receive the second dose of vaccine, we might have under-estimated vaccine efficacy. On the other hand, vaccines that are efficacious against current SARS-CoV-2 virus may become less efficacious against new virus variants. Although the impact of new virus variants on the vaccine efficacy was not explicitly considered, the analysis included scenarios with a low vaccine efficacy (50%). In addition, we assume that there will be no important safety issues for vaccines licensed to use. We focused on the impacts and interactions of vaccine efficacy, different types of immune response to SARS-CoV-2, and assumed no more restrictions by NPI measures after return to normality in England from June 2021. Therefore, the pessimistic scenarios in our analyses may not be allowed to happen in the real world, as NPI (including lockdown) measures may be introduced again if the vaccination programmes are insufficient to avoid the new outbreaks of COVID-19.

This is a deterministic simulation model, and uncertainty in estimated parameters may have not been fully accommodated. For simplicity, stochastic uncertainty, to quantify confidence intervals around the model's outputs, was not modelled. However, the model has been verified based on historically observed outcome data in England,[7] and a large number of projection scenarios are explored. Although many uncertainties remain, including durability and types of naturally acquired and vaccine-induced immunity, our model can be updated to assess vaccination strategies, as new evidence emerges.

Conclusions

Under optimistic scenarios, mass immunisation using efficacious vaccines may enable society safely to return to normality. However, under plausible scenarios with low vaccine efficacy and short durability of immunity, COVID-19 could continue to cause recurrent waves of severe morbidity and mortality despite frequent vaccinations, and necessitate stringent NPI restrictions. It is crucial to monitor the vaccination effects in the real world, and to better understand characteristics of naturally acquired and vaccine induced immunity against SARS-CoV-2.

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Contributors: FS designed, developed the model, retrieved data for estimating parameters, conducted computational calculations, and prepared the draft manuscript. MOB provided methodological support, helped interpret results and critically revised the draft manuscript. FS accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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FIGURE LEGENDS:

Figure 1: Modelling COVID-19 epidemics in England - main compartments and transitions across status

Figure 2: Projected numbers of COVID-19 deaths with different combinations of infection and disease protection vaccine efficacy, durability of immune response, and reduction in reinfectivity. The cumulative number of COVID-19 deaths in England by the end of 2029, after nine repeated annual vaccinations of 80% individuals aged ≥16 during 2021-2029. The overall vaccine efficacy was 70%; "0·00/0·70" refers to all vaccine efficacy attributable to disease protection, "0·45/0·45" refers to equal infection and disease protection, "0·70/0·00" refers to all efficacy attributable to infection protection. Duration of immunity: "365/182" refers to 365 days of natural immunity and 182 days vaccine immunity, "365/365" refers to 365 days natural and vaccine immunity, "730/365" refers to 730 and 365 days, respectively, natural and vaccine immunity. Figure 2A, 2B and 2C show results under the assumption of 20%, 40% and 60% reduction in reinfectivity.

Figure 3 Projected peaks of daily COVID-19 deaths and the prevalence of susceptible individuals (%) during 2020-2029 under scenarios with different immunity durability and vaccine strategies. We assume 90% vaccine efficacy; 80% coverage of individuals aged ≥16; 40% reduction in reinfectivity and 730 days natural immunity for all scenarios in Figure 3. We assume 365 days (Figure 3A, 3B, 3C) or 182 days (Figure 3D, 3E, 3F) vaccine immunity, and single vaccination (Figure 3A, 3D), three annual vaccination (Figure 3B, 3E), or five annual vaccination programmes (Figure 3C, 3F).

ONLINE SUPPLEMENTARY MATERIALS

Supplementary Files: Model structure, data sources, model parameters, and mathematical equations

Supplementary Tables: Additional results of relevant scenarios

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Table 1. Projected total COVID-19 deaths by the end of 2029 in England under various scenarios

Notes to Table 1: We assume annual vaccination covers 80% of individuals aged ≥16 years, and the overall vaccine efficacy is equally attributable to the infection and disease protection. The maximum number of waves of annual mass vaccination is nine during 2021-2029. Results in the table are from scenarios with the possibly minimum numbers of waves of annual vaccination that prevent any further COVID-19 outbreaks during 2022-2029 under a given scenario, or those in which further COVID-19 outbreaks cannot be prevented by the maximum number of annual mass vaccination programmes.

Scenario	Waves of annual vaccination	Overall vaccine efficacy	Reduction in reinfectivity	Immunity duration (days)		Total COVID-19 deaths (2020-2029)
				Natural	Vaccine	
st1-01	1	90%	60%	>10 years	>10 years	112,815
st1-02	2	90%	60%	730	730	112,815
st1-03	2	90%	60%	730	365	112,815
st1-04	2	90%	60%	730	182	112,815
st1-05	3	90%	60%	365	365	112,870
st1-06	3	90%	60%	365	182	112,870
st1-07	1	90%	40%	>10 years	>10 years	112,878
st1-08	5	90%	40%	730	730	112,878
st1-09	6	90%	40%	730	365	112,878
st1-10	9	90%	40%	730	182	112,878
st1-11	7	90%	40%	365	365	112,986
st1-12	9	90%	40%	365	182	112,986
st1-13	1	90%	20%	>10 years	>10 years	112,942
st1-14	7	90%	20%	730	730	112,942
st1-15	9	90%	20%	730	365	114,351
st1-16	9	90%	20%	730	182	137,484
st1-17	9	90%	20%	365	365	133,713
st1-18	9	90%	20%	365	182	237,701
st1-19	1	70%	60%	>10 years	>10 years	114,065
st1-20	2	70%	60%	730	730	114,065
st1-21	3	70%	60%	730	365	114,065
st1-22	3	70%	60%	730	182	114,065
st1-23	3	70%	60%	365	365	114,223
st1-24	5	70%	60%	365	182	115,782
st1-25	1	70%	40%	>10 years	>10 years	114,271
st1-26	6	70%	40%	730	730	114,271
st1-27	8	70%	40%	730	365	114,271
st1-28	9	70%	40%	730	182	129,197
st1-29	9	70%	40%	365	365	139,064
st1-30	9	70%	40%	365	182	208,516
st1-31	1	70%	20%	>10 years	>10 years	115,004
st1-32	9	70%	20%	730	730	128,318
st1-33	9	70%	20%	730	365	163,962
st1-34	9	70%	20%	730	182	200,252
st1-35	9	70%	20%	365	365	316,166
st1-36	9	70%	20%	365	182	524,396
st1-37	1	50%	60%	>10 years	>10 years	115,414
st1-38	3	50%	60%	730	730	115,414
st1-39	3	50%	60%	730	365	115,414
st1-40	3	50%	60%	730	182	115,419
st1-41	9	50%	60%	365	365	117,163

st1-42	9	50%	60%	365	182	125,400
st1-43	1	50%	40%	>10 years	>10 years	116,605
st1-44	9	50%	40%	730	730	116,693
st1-45	9	50%	40%	730	365	135,263
st1-46	9	50%	40%	730	182	165,916
st1-47	9	50%	40%	365	365	236,326
st1-48	9	50%	40%	365	182	316,759
st1-49	1	50%	20%	>10 years	>10 years	139,385
st1-50	9	50%	20%	730	730	213,589
st1-51	9	50%	20%	730	365	239,474
st1-52	9	50%	20%	730	182	275,955
st1-53	9	50%	20%	365	365	578,710
st1-54	9	50%	20%	365	182	754,019

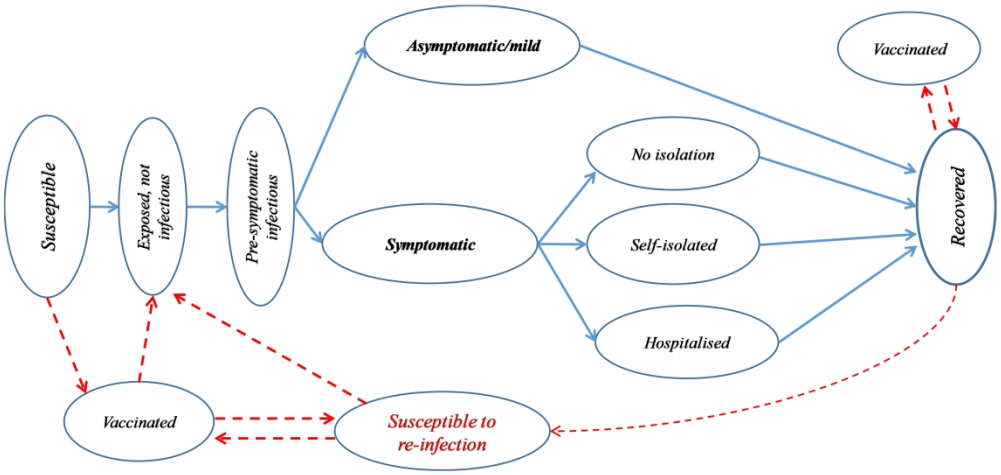


Figure 1: Modelling COVID-19 epidemics in England - main compartments and transitions across status

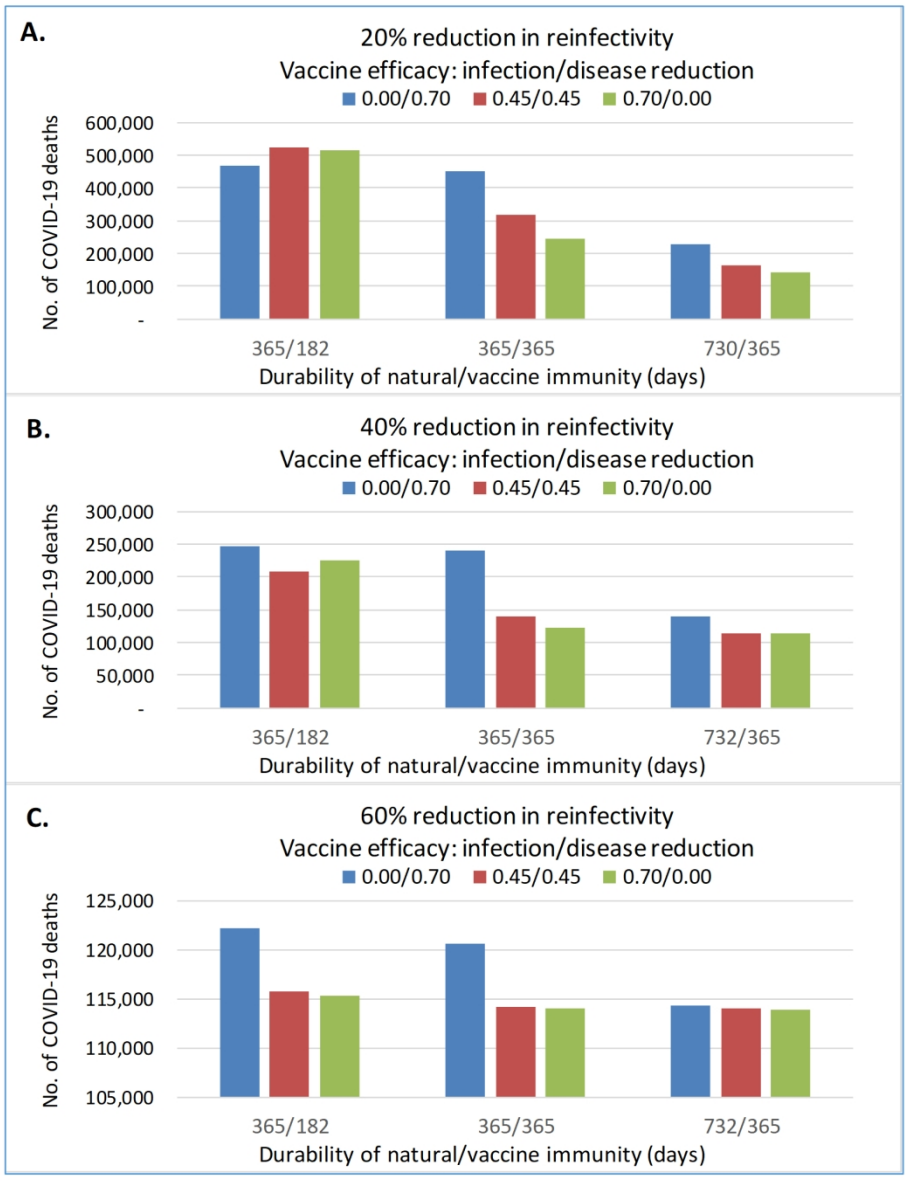


Figure 2: Projected numbers of COVID-19 deaths with different combinations of infection and disease protection vaccine efficacy, durability of immune response, and reduction in reinfectivity. The cumulative number of COVID-19 deaths in England by the end of 2029, after nine repeated annual vaccinations of 80% individuals aged ≥16 during 2021-2029. The overall vaccine efficacy was 70%; "0·00/0·70" refers to all vaccine efficacy attributable to disease protection, "0·45/0·45" refers to equal infection and disease protection, "0·70/0·00" refers to all efficacy attributable to infection protection. Duration of immunity: "365/182" refers to 365 days of natural immunity and 182 days vaccine immunity, "365/365" refers to 365 days natural and vaccine immunity, "730/365" refers to 730 and 365 days, respectively, natural and vaccine immunity. Figure 2A, 2B and 2C show results under the assumption of 20%, 40% and 60% reduction in reinfectivity.

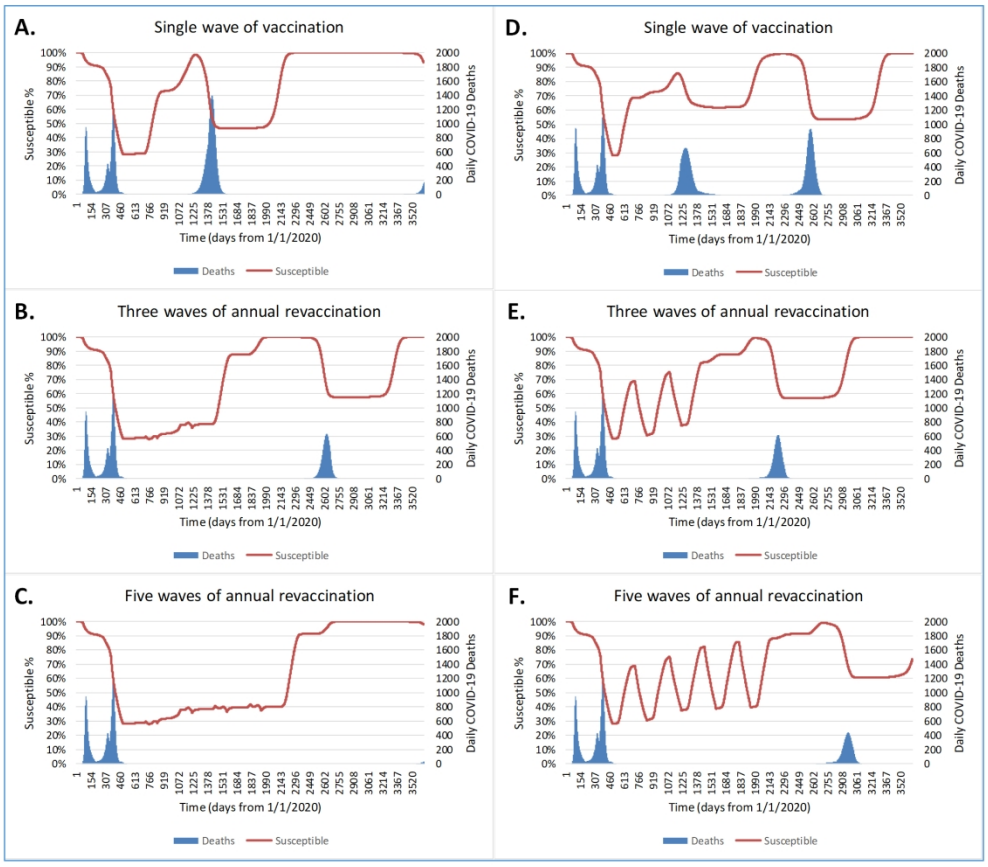


Figure 3 Projected peaks of daily COVID-19 deaths and the prevalence of susceptible individuals (%) during 2020-2029 under scenarios with different immunity durability and vaccine strategies. We assume 90% vaccine efficacy; 80% coverage of individuals aged ≥16; 40% reduction in reinfectivity and 730 days natural immunity for all scenarios in Figure 3. We assume 365 days (Figure 3A, 3B, 3C) or 182 days (Figure 3D, 3E, 3F) vaccine immunity, and single vaccination (Figure 3A, 3D), three annual vaccination (Figure 3B, 3E), or five annual vaccination programmes (Figure 3C, 3F).

Supplementary Tables to:

Vaccination against COVID-19 and society's return to normality in England: a modelling investigation of different types of naturally acquired and vaccine induced immunity

Supplementary Table 1:

Additional outcomes for scenarios in Figure 3. Estimated numbers of deaths from COVID-19

Scenario	Vaccination: waves (interval)	Overall vaccine efficacy	Reduction in reinfectivity	Immunity duration (days)		COVID-19 deaths			
				Natural	Vaccine	2020-2021	2022-2025	2026-2029	Total: 2020-2029
Fig.3A	1	0.9	0.6	730	365	112,878	140,312	4,871	258,061
Fig.3B	3(365)	0.9	0.6	730	365	112,878	-	60,448	173,326
Fig.3C	5(365)	0.9	0.6	730	365	112,878	-	752	113,630
Fig.3D	1	0.9	0.6	730	182	112,878	95,441	98,177	306,496
Fig.3E	3(365)	0.9	0.6	730	182	112,878	12,372	52,244	177,494
Fig.3F	5(365)	0.9	0.6	730	182	112,878	-	51,946	164,824

Supplementary Table 2:

The projected numbers of COVID-19 deaths under various simulation scenarios

Scenario	Vaccination: waves (interval)	Overall vaccine efficacy	Reduction in reinfectivity	Immunity duration (days)		COVID-19 deaths			
				Natural	Vaccine	2020-2021	2022-2025	2026-2029	Total: 2020-2029
st1-01	2(365)	90%	60%	730	730	112,815	-	-	112,815
st1-02	2(365)	90%	60%	730	365	112,815	-	-	112,815
st1-03	2(365)	90%	60%	730	182	112,815	-	-	112,815
st1-04	3(365)	90%	60%	365	365	112,870	-	-	112,870
st1-05	3(365)	90%	60%	365	182	112,870	-	-	112,870
st1-06	5(365)	90%	40%	730	730	112,878	-	-	112,878
st1-07	6(365)	90%	40%	730	365	112,878	-	-	112,878
st1-08	9(365)	90%	40%	730	182	112,878	-	-	112,878
st1-09	7(365)	90%	40%	365	365	112,986	-	-	112,986
st1-10	9(365)	90%	40%	365	182	112,986	-	-	112,986
st1-11	7(365)	90%	20%	730	730	112,942	-	-	112,942
st1-12	9(365)	90%	20%	730	365	112,942	-	1,409	114,351
st1-13	9(365)	90%	20%	730	182	112,942	24,542	-	137,484
st1-14	9(365)	90%	20%	365	365	113,147	17,147	3,419	133,713
st1-15	9(365)	90%	20%	365	182	113,616	75,130	48,955	237,701
st1-16	2(365)	70%	60%	730	730	114,065	-	-	114,065
st1-17	3(365)	70%	60%	730	365	114,065	-	-	114,065
st1-18	3(365)	70%	60%	730	182	114,065	-	-	114,065
st1-19	3(365)	70%	60%	365	365	114,223	-	-	114,223
st1-20	3(365)	70%	60%	365	182	114,228	1,554	-	115,782
st1-21	6(365)	70%	40%	730	730	114,271	-	-	114,271
st1-22	8(365)	70%	40%	730	365	114,271	-	-	114,271
st1-23	9(365)	70%	40%	730	182	114,275	3,740	11,182	129,197
st1-24	9(365)	70%	40%	365	365	114,814	24,220	30	139,064
st1-25	9(365)	70%	40%	365	182	115,419	60,365	32,732	208,516
st1-26	9(365)	70%	20%	730	730	114,594	4,879	8,845	128,318
st1-27	9(365)	70%	20%	730	365	114,594	24,982	24,386	163,962
st1-28	9(365)	70%	20%	730	182	115,076	55,193	29,983	200,252
st1-29	9(365)	70%	20%	365	365	116,681	133,875	65,610	316,166
st1-30	9(365)	70%	20%	365	182	119,965	280,585	123,846	524,396
st1-31	3(365)	50%	60%	730	730	115,414	-	-	115,414
st1-32	3(365)	50%	60%	730	365	115,414	-	-	115,414
st1-33	3(365)	50%	60%	730	182	115,419	-	-	115,419
st1-34	9(365)	50%	60%	365	365	115,723	1,440	-	117,163
st1-35	9(365)	50%	60%	365	182	115,836	9,564	-	125,400
st1-36	9(365)	50%	40%	730	730	115,965	435	293	116,693
st1-37	9(365)	50%	40%	730	365	115,965	1,500	17,798	135,263
st1-38	9(365)	50%	40%	730	182	116,276	31,849	17,791	165,916
st1-39	9(365)	50%	40%	365	365	117,753	83,968	34,605	236,326
st1-40	9(365)	50%	40%	365	182	118,845	118,689	79,225	316,759
st1-41	9(365)	50%	20%	730	730	117,545	56,380	39,664	213,589
st1-42	9(365)	50%	20%	730	365	117,545	66,524	55,405	239,474
st1-43	9(365)	50%	20%	730	182	118,740	153,640	3,575	275,955
st1-44	9(365)	50%	20%	365	365	126,982	267,930	183,798	578,710
st1-45	9(365)	50%	20%	365	182	137,272	396,172	220,575	754,019

Notes to supplementary Table 2.

1. Assumptions: vaccine efficacy equally attributable to infection and disease protection; mass vaccination with 80% coverage of individuals aged 16+.
2. Vaccination waves (interval): number of waves and days between the starting dates of the two adjacent waves. This appendix table shows results of repeated annual mass vaccination programms. There are maximally nine waves of annual mass vaccination programmes during 2021-2029. Under some scenarios, COVID-19 outbreaks before the end of 2029 can be prevented with 2-7 waves of annual vaccination programmes.

Supplementary Table 3:
Results of sensitivity analyses. Estimated numbers of deaths from COVID-19

Scenario	Vaccination: waves (interval)	Overall vaccine efficacy	Reduction in reinfectivity	Immunity duration (days)		COVID-19 deaths			
				Natural	Vaccine	2020-2021	2022-2025	2026-2029	Total: 2020-2029
Different frequency and days between vaccination programmes									
L92c1	2(730)	0.9	60%	730	730	112,815	-	-	112,815
Lm92c1	2(730)	0.9	60%	730	365	112,815	-	-	112,815
L94c2	4(730)	0.9	40%	730	730	112,878	-	-	112,878
Ls916s3	16(182)	0.9	40%	730	182	112,942	-	-	112,942
Ms93s1	3(182)	0.9	60%	365	182	112,870	-	-	112,870
Ms913s2	13(182)	0.9	40%	365	182	112,878	-	-	112,878
M916s3	16(182)	0.9	20%	365	365	113,145	-	-	113,145
Ms918s3	18(182)	0.9	20%	365	182	113,153	5,724	4,569	123,446
L73c1	3(730)	0.7	60%	730	730	114,065	-	-	114,065
Lm73c1	3(730)	0.7	60%	730	365	114,065	-	-	114,065
Ls710s2	10(182)	0.7	40%	730	182	114,275	-	-	114,275
L718s3	18(182)	0.7	20%	730	730	114,576	-	-	114,576
Ls718s3	18(182)	0.7	20%	730	182	114,600	-	13,802	128,402
Lm718s3	18(182)	0.7	20%	730	365	114,576	-	-	114,576
Ms73s1	3(182)	0.7	60%	365	182	114,228	-	-	114,228
M718s2	18(182)	0.7	40%	365	365	114,642	-	-	114,642
Ms718s2	18(182)	0.7	40%	365	182	114,674	650	5,067	120,391
M718s3	18(182)	0.7	20%	365	365	115,808	24,794	19,794	160,396
Ms718s3	18(182)	0.7	20%	365	182	116,168	64,685	47,241	228,094
No reduction in reinfectivity after immunity waning									
L99m0	9(365)	0.9	0%	730	730	113,012	-	1,255	114,267
Lm99m0	9(365)	0.9	0%	730	365	113,012	17,702	7,512	138,226
Ls99m0	9(365)	0.9	0%	730	182	113,070	30,619	47,229	190,918
M99m0	9(365)	0.9	0%	365	365	113,684	52,806	35,665	202,155
Ms99m0	9(365)	0.9	0%	365	182	115,880	261,365	29,700	406,945
L79m0	9(365)	0.7	0%	730	730	115,522	49,095	28,213	192,830
Lm79m0	9(365)	0.7	0%	730	365	115,522	51,428	56,044	222,994
Ls79m0	9(365)	0.7	0%	730	182	117,170	167,268	499	284,937
M79m0	9(365)	0.7	0%	365	365	123,398	250,649	159,941	533,988
Ms79m0	9(365)	0.7	0%	365	182	143,421	381,311	350,640	875,372

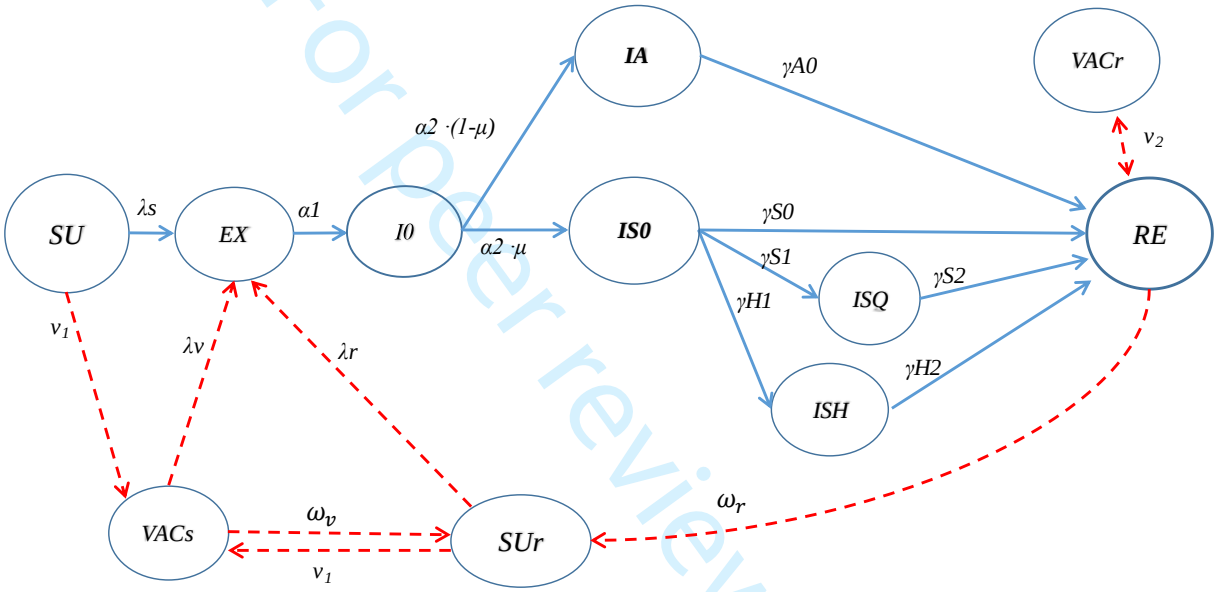
Supplementary files to:

Vaccination against COVID-19 and society's return to normality in England: a modelling investigation of different types of naturally acquired and vaccine induced immunity

1. Model structure and status

This is a discrete-time population dynamic simulation model. Population in England are partitioned into discrete categories by sex (male or female), age (0-4, 5-9, then by 10 year age bands, and 80+), and Covid-19 infection categories. The main infection categories include: susceptible (SU), exposed (EX), infected (IN), and recovered (RE) (appendix figure 1). The infected individuals are further categorised as asymptomatic, symptomatic, self-isolated, and hospitalised.

Appendix figure 1: Model structure and transmission across status



Definitions of compartmental variables in appendix figure 1

- SU: susceptible individuals
- SUr: Individuals susceptible to reinfection after immunity waning
- EX: exposed individuals, not infectious
- I0: infectious, before symptom onset
- IA: infectious individuals with no or very mild symptoms
- IS0: symptomatic patients who are not quarantined
- ISQ: symptomatic patients self-isolated
- ISH: symptomatic patients who are hospitalised
- RE: recovered from covid-19 infection
- VACs: vaccinated susceptible individuals
- VACr: vaccinated individuals who recovered from infection

Transition parameters in appendix figure 1:

- λ_s: Force of infection (λ) measures the risk (probability) of infection transmission, which is a function of transmission rate (β) and the prevalence of infectious individuals (I) among the population (N): $\lambda=\beta \cdot I/N$. [1]
- β: The transmission rate β in this discrete-time model is defined as the average number of individuals infected daily by an infectious person. It is a function of the number of daily close contacts per person (c), and the transmission risk per contact between a susceptible and an infectious individual (η): i.e., $\beta=c \cdot \eta$. [2]
- α1: rate of progressing from being exposed to being infectious.
- α2: rate of progressing from being asymptomatic infectious to symptomatic.
- μ: proportion of infected individuals who will be symptomatic; age-specific
- *infA*: The fraction of infection force for infected individuals with no or mild symptoms. It was assumed that infA=0.5 in this study.
- fS0: fraction of symptomatic patients who will not be quarantined.
- fSq: fraction of symptomatic patients who will be quarantined (self-isolation).
- fSh: fraction of symptomatic patients who will be hospitalised (including ICU admission).
- γA0: rate of recovering for asymptomatic individuals
- γS0 rate of recovering for symptomatic, not isolated/hospitalised patients
- γS1: rate of being isolated in symptomatic patients
- γS2: rate of recovering in isolated patients
- γH1: rate of being hospitalised for symptomatic patients
- γH2: rate of recovering in hospitalised patients
- ν_1: rate of vaccinating susceptible individuals
- ν_2: rate of vaccinating recovered individuals
- ω_v: rate of immunity waning in vaccinated individuals
- ω_r: rate of immunity waning in recovered individuals

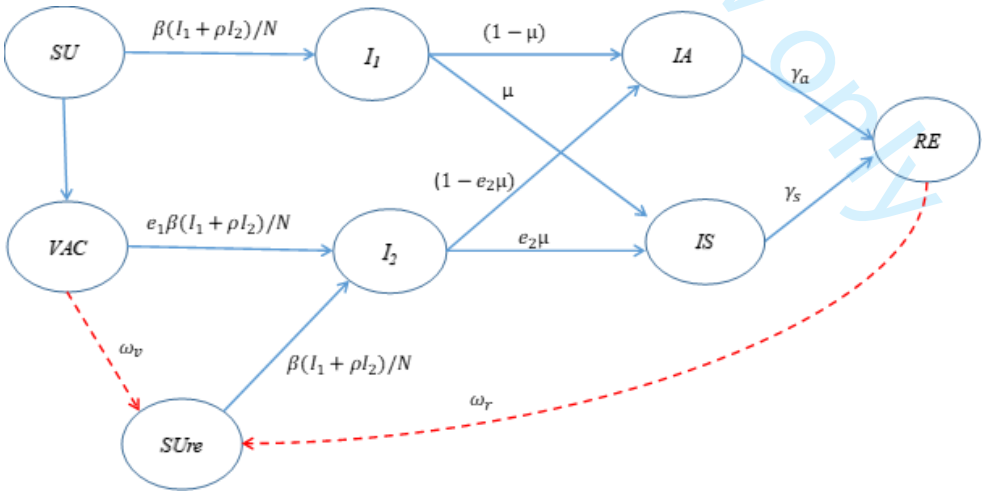
All individuals in England are assumed to be susceptible to SARS-CoV-2 infection at the beginning of 2020. Susceptible individuals may be infected by contacting infectious individuals, and the infection status is changed from "susceptible" (SU) to "exposed" (EX). The exposed individuals are not infectious during the early incubation period, but start to be infectious before the onset of symptoms. Individuals infected with SARS-CoV-2 virus may have no or very mild symptoms (IA), and palpable symptoms (symptomatic or clinical infections). Asymptomatic individuals can spread SARS-CoV-2 virus before recovery, although the transmission risk may be lower than symptomatic patients. Symptomatic patients are further classified into three categories: symptomatic patients who are neither isolated nor hospitalised (IS0), those who self-isolate at home (ISQ), and those who are hospitalised (including those being admitted to intensive care units) (ISH). Symptomatic patients are infectious and can transmit the

virus to susceptible people before being isolated, hospitalised or recovered. We assume that hospitalised patients (ISH) are well isolated and no longer able to spread the virus to the susceptible population, although infectious patients who are self-isolated at home (ISQ) may transmit virus to household contacts.

Individuals may recover from previous infection of SARS-CoV-2 (RE), and the susceptible and recovered individuals may be vaccinated with vaccines again SARS-CoV-2 virus (VAC1 and VAC2). Individuals recovered or effectively vaccinated may develop immune responses against infection with SARS-CoV-2. However, if the protective immunity is not long lasting, individuals who have recovered or vaccinated may become susceptible again after the waning of the immunity (SUr).

The immune response against COVID-19, either by naturally acquired from past SARSE-CoV-2 infection or vaccine-induced, may be long lasting or short-lived. Immune response may reduce susceptibility of individuals to infection (infection protection, or sterilising, immunity), reduce disease severity after being infected (disease reduction immunity), and reduce infectivity of those who are reinfected after recovery or being vaccinated (reinfectivity reduction immunity).[3] According to existing evidence on immunological characteristics for other human coronaviruses, immunity against reinfection (sterilising immunity) may be waning in several months, while disease and reinfectivity reduction responses are likely long lasting.[3] According to these basic concepts specified by Lavine et al,[3] we incorporate the three types of immune responses into the model, to explicitly evaluate their impacts on future transmission dynamics (appendix figure 2).

Appendix figure 2: Types of immune responses by natural infection or vaccination



Notes to appendix figure 2:

- Appendix figure2 is a simplified version of appendix figure 1, not showing isolation and hospitalisation for symptomatic patients.
- N: The number of the population
- β: The transmission rate, i.e., the average number of individuals infected daily by an infectious person. It is a function of the number of daily close contacts per person (c), and the transmission risk per contact between a susceptible and an infectious individual (η): i.e., $\beta=c\cdot\eta$.
- I_1: Infectious individuals with primary infection
- I_2: Infectious individuals with secondary infection (infected after being vaccinated or recovered)
- ρ: Relative infectivity of the secondary infection (I_2) compared with the primary infection (I_1). For example, if ρ=0.6, the infectivity of I_2 is 40% lower than the infectivity of I_1
- μ: proportion of infected individuals who will be symptomatic; age-specific
- e_1: Relative efficacy of vaccine for sterilising immunity, reducing risk of virus transmission
- e_2: Relative efficacy of vaccine for pathology reduction, reducing the proportion of symptomatic cases after being infected
- IA: Asymptomatic individuals
- IS: Symptomatic patients
- γ_a : Average rate of recovering of asymptomatic individuals
- γ_s : Average rate of recovering of asymptomatic individuals
- ω_v: rate of immunity waning in vaccinated individuals
- ω_r: rate of immunity waning in recovered individuals

Overall and partial vaccine efficacy

Results of randomised controlled trials shown that vaccines may be >90% efficacious (e.g., Pfizer mRNA vaccine) in reducing severe symptomatic diseases, compared with the placebo group.[4] In appendix figure 2, e_1 and e_2 are parameters of vaccine's efficacy in blocking virus transmission and reducing symptomatic cases in the infected, respectively. The reduction in symptomatic cases in the vaccine group may be due to the prevention of infection in susceptible individuals (related to e_1), or a lower proportion of infected individuals being symptomatic in the vaccine group (related to e_2), or due to a combination of both. Let λ is the transmission risk and μ is the proportion of symptomatic cases in the infected without vaccination. After being vaccinated, the transmission risk is reduced to $\lambda\cdot e_1$, and the proportion of symptomatic cases reduced to $\mu\cdot e_2$. For a vaccine with 90% efficacy in reducing the number of symptomatic cases (compared with the control group), it should be true that $e_1\cdot e_2=(1-0.90)$, or $e_1=0.10/\ e_2$. There are many different possible combinations of e_1 and e_2 for a given overall efficacy in reducing symptomatic cases. For example, $e_1=e_2=SQRT(0.30)=0.548$ corresponds to a 70% efficacy of vaccine with equal sterilising immunity and pathology reduction. If e_1=1 (i.e., zero efficacy in sterilising immunity), all vaccine efficacy will be attributable to the pathology reduction, with e_2=0.30, for a vaccine with 70% efficacy. The partial efficacy is calculated using: $Ei = 1-(1-Eo)/Ed$, where Ei is the partial efficacy for infection protection, Ed is the partial efficacy for disease reduction, and Eo

is the overall vaccine efficacy. The equal partial efficacy is calculated by: $Ei = Ed = 1 - \sqrt{(1 - Eo)}$. For vaccines with 90%, 70% and 50% overall efficacy, the equal partial efficacy for the infection protection and disease reduction is 69.4%, 45.2%, and 29.3%, respectively.

2. Parameterisation, data sources, and simulation scenarios

2.1 Transition parameters and distribution of infectious period

In appendix figure 1, force of infection (λ) measures the risk of infection,[1] which is a function of transmission rate (η) and the prevalence of existing infectious individuals (I) among the population (N): $\lambda=\eta \cdot I/N$. The transmission rate η in the discrete-time model can be defined as the average number of new infected individuals generated daily by an infected person. That is, $\eta=Rt/T$, in which Rt is effective reproduction number and T is the average infectious period for infected individuals. We calculated η as a function of the number of daily contacts per person (c), and the risk of transmission per contact between a susceptible and an infected individual (β): η=c*β.[2]

The transition rate between model's compartments in infectious models is often assumed to be constant, calculated by 1/x, in which "x" is the average period that subjects remain before the transition to the model's next compartments.[1] Therefore, the infectious period in standard SIR or SEIR models is usually assumed to be exponentially distributed, with some limitations of the use of exponentially distributed infectious period.[5 6] In this study, we assumed that the transition probability between model's compartments are based on gamma distributed period that individuals remain in a compartment.[7] The transition probability (y) at t is: $y_t = (cg_t - cg_{t-1})/(1 - cg_t)$, where cg_t is the gamma cumulative probability by the end of t. Given mean and shape (k) parameters, the gamma distribution based transition probability is used as a deterministic value to estimate the number of individuals moving between two status in this study.

2.2 Parameterisation and data sources

We estimated initial parameters based on relevant literature and data from the UK government websites (appendix table 1). Key parameters were calibrated according to the reported numbers of covid-19 deaths, hospitalised patients, and the prevalence of infected individuals in England from January 2020 to January 2021.[8]

Appendix table 1: Summary of key model parameters

Parameter	Value			Source
Proportion of asymptomatic cases in infected individuals (%)				
Age: 0-9	0.71			Davis et al. [9]
10-19	0.79			
20-29	0.73			
30-39	0.67			
40-49	0.60			
50-59	0.51			
60-69	0.37			
70+	0.31			
Proportion of self-isolated symptomatic cases who are not hospitalised				
Age:	**0-49**	**50-69**	**70+**	Assumed by authors, and calibrated according to reported COVID-19 deaths.
Before 13/03/2021	0.10	0.10	0.10	
13/03-23/03/2020	0.40	0.60	0.80	
After 24/03/2020	0.80-0.90	0.80-0.95	0.90-0.95	
Estimated values of gamma distributed parameters (mean, shape k)				
	Before 12/03/20	**13/03-23/03/20**	**After 23/03/20**	
Duration from exposed to preclinical infectious (day)	4.0 (4)	4.0 (4)	4.0 (4)	Zhang et al. [10] Davies et al. [7] Ferguson et al. [11]
Duration of preclinical infectious (day)	1.5 (2)	1.5 (2)	1.5 (2)	
Infectious period before recovery (day)	5.0 (5)	5.0 (5)	5.0 (5)	
Infectious period before being isolated (day)	4.0 (4)	3.0 (3)	2.0 (2)	
Infectious period during isolation at home (day)	2.0 (2)	3.0 (3)	4.0 (4)	
Infectious period before being hospitalised (day)	4.0 (4)	3.0 (3)	2.0 (2)	
Duration of hospitalisation (day)	10.0 (10)	10.0 (10)	10.0 (10)	
Delay from being infected to deaths from Covid-19 (day)	23.0 (23)	23.0 (23)	23.0 (23)	Verity et al. [12]
Case fatality rates (%)				
Age: 0-9	0.0026			Verity et al. [12]; Chinese CDC [13]
10-19	0.0148			
20-29	0.0600			
30-39	0.1460			
40-49	0.2950			
50-59	1.2500			
60-69	3.9900			
70-79	8.6100			
80+	13.400			
Transmission risk by asymptomatic individuals	50% of the transmission risk by symptomatic cases			Ferguson et al. [11].
Age specific rates of hospitalisation among infected individuals				
0-9	0.010%			Verity et al. [12]
10-19	0.041%			

20-29	1.04%	
30-39	3.43%	
40-49	4.25%	
50-59	8.16%	
60-69	11.8%	
70-79	16.6%	
80+	18.4%	

We obtained population statistics in England (estimates of mid-year 2020) from Office for National Statistics. It was assumed that all individuals in England were susceptible to SARS-CoV-2 infection at the beginning of 2020. By contacting with infectious individuals, susceptible individuals may be infected, and their infection category is changed from "susceptible" (SU) to "exposed" (EX). "Exposed" refers to the pre-infectious status of infected individuals. According to data from previous studies, the period of incubation before symptom onset was on average 5.5 days,[10] and the exposed individuals start to be infectious about 1.5 days before the onset of symptoms.[7 11] Therefore, we assumed a gamma distribution of incubation period, with a mean non-infectious period of 4 days (k=4.0) after being exposed, and a mean infectious period of 1.5 days (k=2) before symptom onset.

Individuals infected with SARS-CoV-2 virus may have no or very mild symptoms (asymptomatic infected), and palpable symptoms (symptomatic patients). As in previous modelling studies [7 11], it was assumed that asymptomatic individuals can spread SARS-CoV-2 virus before recovery, although the infectious risk was assumed to be half of symptomatic patients.[11] We used age-specific rates of asymptomatic cases in the infected individuals, reported in a study based on data from 6 countries[9] (appendix table 1).

Symptomatic patients are further classified into three categories: symptomatic patients who are neither isolated nor hospitalised (mainly at the initial phase of the epidemic), those who are self-isolated at home, those who are hospitalised (see appendix figure 1). We assume that asymptomatic individuals were not isolated, although the average number of daily contacts could be reduced by non-pharmaceutical interventions (NPIs), including social distancing, testing, contact tracing, and lockdown. Assumed proportions of self-isolation of symptomatic cases who are not hospitalised, depending on age and NPI measures are shown in appendix table 1.

We assume that only symptomatic patients are hospitalised, and age specific rates of hospitalisation among symptomatic individuals were from Verity et al.[12] The hospitalisation rates were calibrated according to reported numbers of hospitalised patients with covid-19 in England.[14] Based on the reported number of hospitalised patients and estimated number of symptomatic cases, the hospitalisation rate was estimated to be 70% lower than the estimated by Verity et al.[12] Symptomatic patients are infectious and can transmit the virus to susceptible people before being hospitalised or isolated. We assume that

hospitalised patients are no longer able to spread the virus to susceptible individuals in the community. However, infected individuals who are self-isolated at home may transmit virus to household contacts. The infectious period before recovery was assumed to be gamma distributed, with a mean value of 5 days. Before implementing any NPIs, the infectious period of symptomatic cases was of a mean value of 4 days (k=4) before being quarantined or hospitalised. After implementing NPI measures, the infectious period for isolated and hospitalised patients was reduced, having a mean value of 2 days (k=2). The mean hospital stay was assumed to be 10 days (k=10) (including ICU admitted patients) (appendix table 1). Verity et al estimated that the average duration from symptom onset to death was 17.8 days.[12] Therefore, we assume that covid-19 related deaths occur on average 23 days (k=23) after being exposed/infected.

The simulation starts from 1 January 2020, over a period of 10 years until the end of 2029. We assume that the first exposed case was imported to England on January 15th 2020, and the daily number of infectious cases imported was increased by one until 9 February 2020, with a total number of 351 cases imported in 25 days. The sex-and-age-specific numbers of household and community daily contacts per person in the UK were obtained from a study in 8 European countries.[15 16] For the purpose of simplicity, we considered only household contacts (relevant to self-isolation at home) and general daily contacts (for all types of contacts). The risk of positive transmission per contact between susceptible and infectious individuals (β) was estimated by calibrating estimated and reported numbers of covid-19 deaths in England, household and general daily contacts per person, and other model parameters. The transmission risk by asymptomatic individuals was assumed to be 50% by symptomatic patients.[11]

In this study, all COVID-19 related deaths are assumed to be from symptomatic cases, and age specific case fatality rates were based on a study by Verity et al.[12] We assume that individuals infected with Covid-19 will not die from other causes before recovery. Average sex and age specific rates of all-cause deaths in England during 2015-2019 [17] were applied to people who are not infected with or recovered from covid-19. For simplicity and maintaining a stable population, we assumed that the number of births at day t equals to the number of all deaths at day t-1. Furthermore, for simplicity, we did not consider the influence of migration on the population. We adjusted the number of individuals belong to an age group (all <80+) at the beginning of the year since 2021 by shifting 20% (for age group 0-4 and 5-9) or 10% (for age group 10-19, … 70-79) of them to the adjacent higher age group.

NPI and seasonal impacts on transmission parameters

Since March 2020, NPI measures were recommended and gradually tightened in England, including hand washing, mouth covering when coughing in public places, home isolation of individuals with COVID-19 like symptoms, shielding of vulnerable individuals, avoiding non-essential contacts, and maintaining social distancing. These measures reduced contacts and transmission risk, and shortened

the period of transmission by symptomatic individuals. We assumed that the general population's contact rates were reduced by 10% to 40%, depending on age and co-morbidity (appendix table 2). Based on the reported number of COVID-19 deaths, we estimate that the transmission risk per contact between infectious and susceptible individuals was reduced by 32%, from β=0.068 before the implementation of any NPIs to 0.046 by 15 March 2020. The UK government put lockdown measures in place from 24 March 2020, including working from home if possible, closure of schools and non-essential shops, pubs and restaurants, avoiding non-essential travelling, and cancelling gathering activities. We assume that numbers of general population contacts were reduced by 60-85%. We assume that the household contacts were not influenced by the NPI measures.

Appendix table 2: Assumed impacts of NPIs on general contacts in England. Notes: Values are scaling fractions to reduce the normal contacts. For example, a fraction of 0.80 means the contacts are reduced by 20%.

Time	Age group			
	0-19	**20-59**	**60-69**	**70+**
Before 13/3/2020	1.00	1.00	1.00	1.00
13/03/2020-	0.90	0.80	0.70	0.60
17/03/2020-	0.80	0.70	0.60	0.50
24/03/2020-	0.40	0.30	0.20	0.15
05/07/2020-	0.60	0.55	0.40	0.20
01/09/2020-	0.80	0.60	0.50	0.30
05/11/2020-	0.60	0.30	0.20	0.15
02/12/2020-	0.70	0.60	0.50	0.30
05/01/2021-	0.40	0.30	0.20	0.15
08/03/2021-	0.80	0.60	0.50	0.30
01/06/2021-	1.00	1.00	1.00	1.00

The lockdown measures in England started to be relaxed from 13 May 2020 by allowing partial returning to work. Further relaxing of control measures followed, including reopening of some shops and allowing outdoor meetings up to six people from 1 June, re-opening of more non-essential shops from 5 June, and further relaxing of restrictions (such as re-opening of pubs and restaurants) from 5 July 2020. However, social distancing measures was maintained and face covering was required where social distancing could not be implemented. From 1 September 2020, schools in England were re-opening. Consequently, the transmission risk per contact between susceptible and infectious individuals was increased to 0.052 since September. The impacts of these changes in NPIs were reflected in the assumed social contacts and transmission risk. Because of the new virus variant in the UK,[18] the average transmission risk per contact was increased to β=0.052 by November 2020, and β=0.056 by the end of 2020.

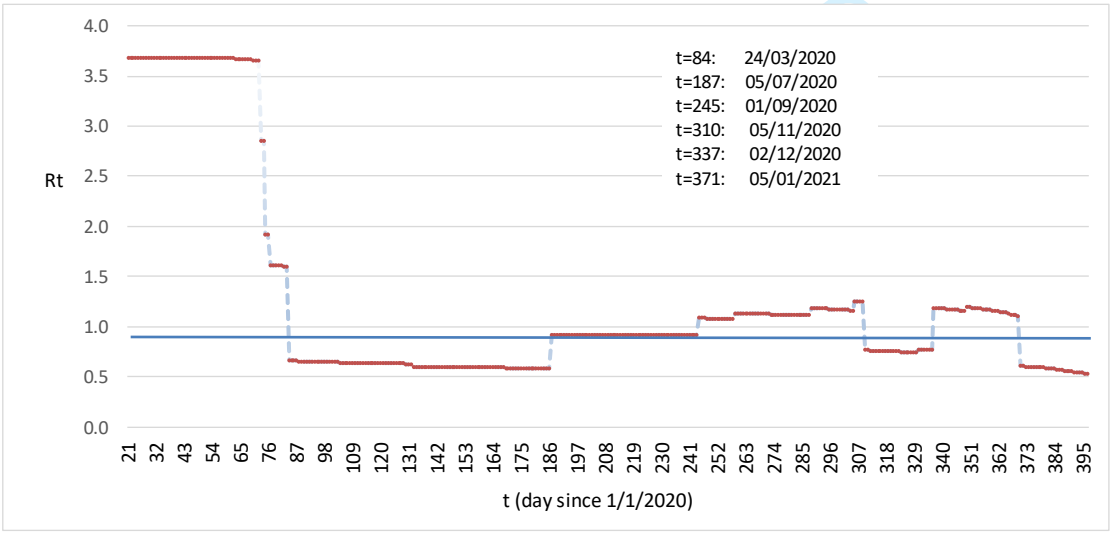
To incorporate the impact of seasonality on future projections since 2021, we assumed that the transmission risk from April to September is 20% lower than that from October to February, according to observed changes in transmission dynamics during March 2020 to January 2021 in England.

Model validation

We used the developed model and initially estimated parameters to simulate the covid-19 epidemic in England from January 2020 to January 2021. Key parameters were calibrated based on reported covid-19 related deaths, hospitalised patients, and infection rates in England.

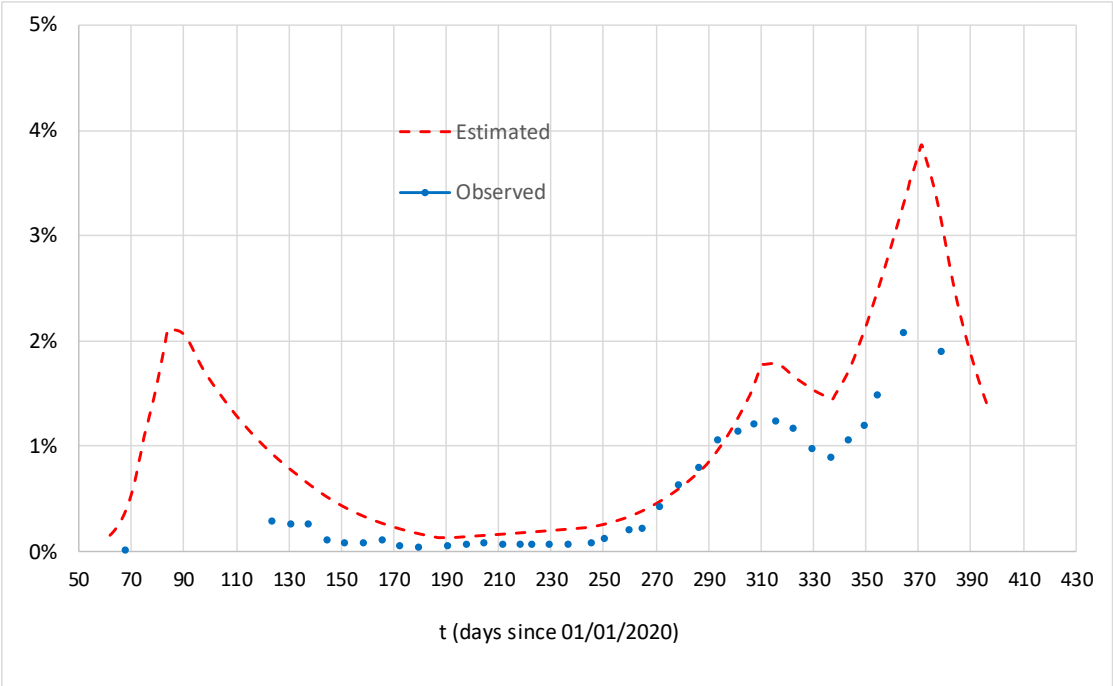
We assume that the first exposed case was imported to England on 15 January 2020, and the number of cases imported each day increased by one more case than the previous day until 9 February 2020 (the total number of cases imported in 25 days was therefore 351). We don't use the reproduction number (R0 or Rt) as an input parameter, but derived the reproduction numbers based on a method used by Giordano and colleagues (see equation 55 in Mathematical equations) [1 19]. We estimated that the basic reproduction number (R0) was 3.68 at the initial stage of the COVID-19 epidemic before any control measures were taken in England, which is similar to findings from previous studies.[7 11] Following the implementation of NPI measures, the estimated reproduction value (Rt) was reduced to 0.66 by 24 March. The Rt value was increased to 0.92 by 5 July 2020 after the NPI measures were relaxed, and Rt was about 1.13 after school reopening since September 2020. The Rt was reduced to 0.75 since 5 November 2020 after reintroducing NPI measures, increased to about 1.19 after relaxing NPIs since 2 December 2020, and reduced again to about 0.60 since 5 January 2021 after reintroducing lockdown measures (plus rolling out of vaccination) (appendix figure 3). The estimated R values were within the range of the reported in England (https://coronavirus.data.gov.uk/).

Appendix figure 3 Estimated reproduction numbers, between 01/2020 – 01/2021, in England



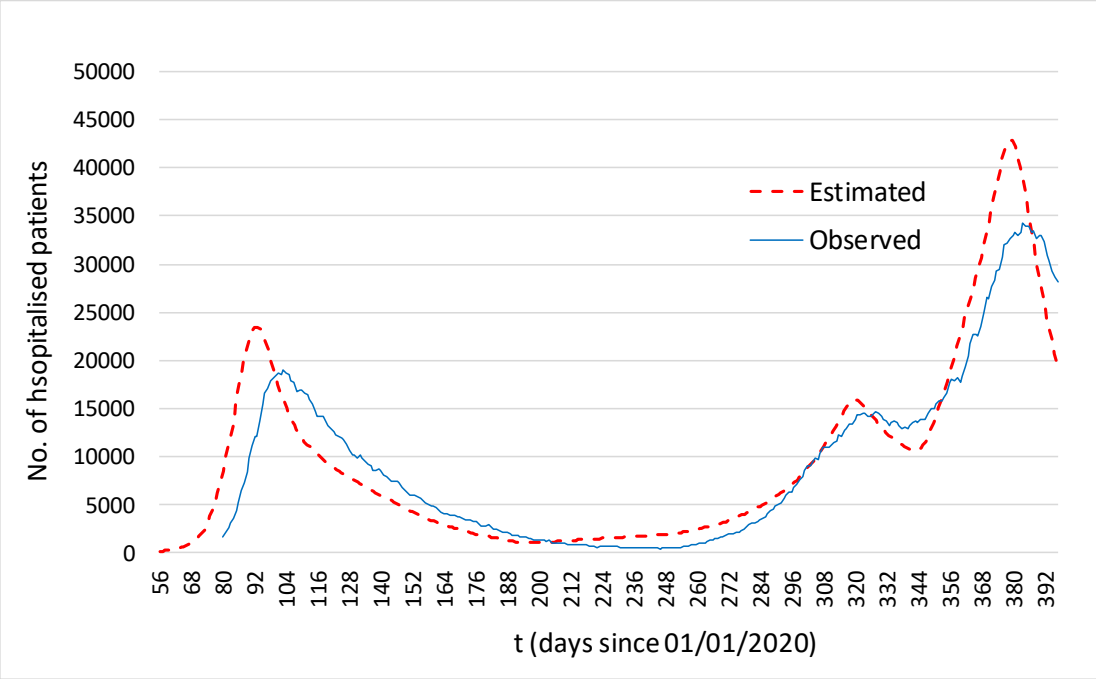
The model estimated that the prevalence of the recovered was 5.5 by 26 April, 7.6% by 24 May, and 8.5% by 24 June 2020, which were similar to the estimated rates of positive antibodies to Covid-19 in the UK (i.e., 7.1% in May-June 2020).[20] Data on the prevalence of infected individuals in the community was available from May 2020. The model estimated prevalence of infected individuals from January 2020 to January 2021, which had a similar trend as the reported prevalence in England (appendix figure 4).

Appendix figure 4: Estimated and reported prevalence of infection, from January 2020 to January 2021, in England



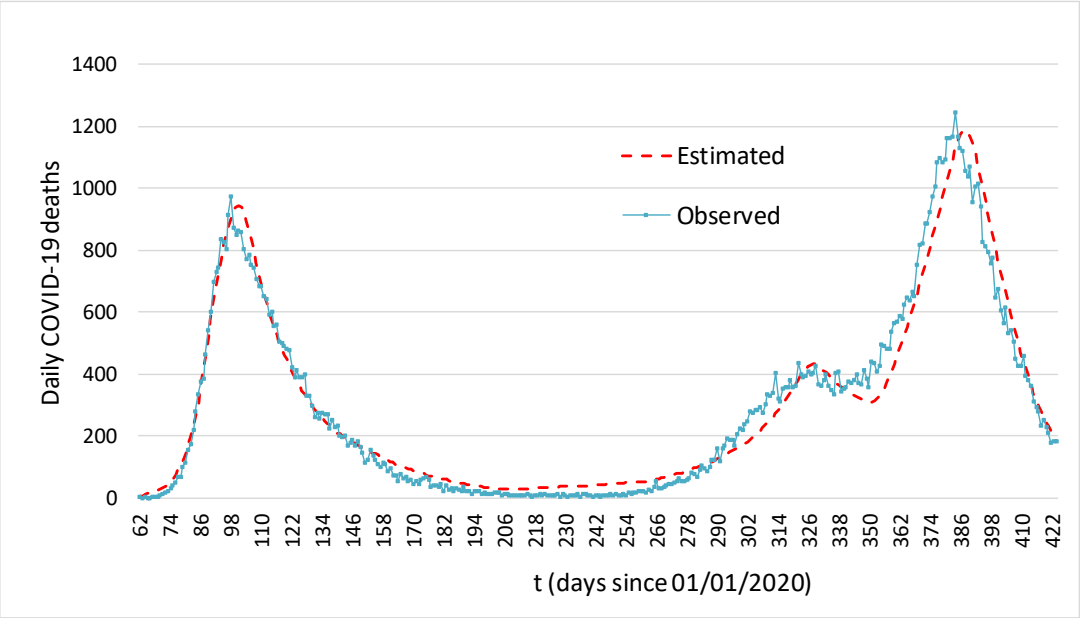
Changes in the estimated numbers of hospitalised COVID-19 patients were of similar trends as the reported numbers of hospitalised patients during 01/2020-01/2021. However, there were considerable differences at peak time points (appendix figure 5), which may be explained by reduced hospitalisation rates during peak period.

Appendix figure 5: Reported and estimated numbers of hospitalised Covid-19 patients, during 01/2020-01/2021, in England



Appendix figure 6 shows that the estimated daily deaths well matched the observed daily deaths from Covid-19, from January 2020 to January 2021, in England.

Appendix figure 6: Reported and estimated daily deaths from Covid-19, during 01/2020-01/2021, in England



3. Vaccination and projection scenarios

We used estimates of transmission parameters, age-specific hospitalisation rates and case fatality rates in January 2021 to project COVID-19 deaths from 2021-2029, under various scenarios of vaccine efficacy, durability of both naturally acquired and vaccine induced immunity, and reduction in reinfectivity. We assume that, since June 2021, there are no more restrictions on social activities, and social contracts are return to normal as before the pandemic, although basic hygienic measures would be maintained. Projection scenarios are defined from the following aspects: vaccine efficacy, durability of natural and vaccine induced sterilising immunity, and reduction in reinfectivity after the waning of infection protection immunity. In this study, we assume that the disease reduction and reinfectivity reduction immunity are long lasting, according to immunological characteristics of other endemic HCoVs.[3]

Results of randomised controlled trials shown that vaccines may be >90% efficacious (e.g., Pfizer mRNA vaccine) in reducing severe symptomatic diseases, compared with the placebo group. Assume that e_1 and e_2 are parameters of vaccine's efficacy in blocking virus transmission and reducing symptomatic cases in the infected, respectively. The reduction in symptomatic cases in the vaccine group may be due to the prevention of infection in susceptible individuals (i.e., infection protection, related to e_1), or a lower proportion of infected individuals being symptomatic in the vaccine group (i.e., disease reduction, related to e_2), or due to a combination of both. For a vaccine with 90% efficacy in reducing the number of symptomatic cases (compared with the control group), it is true that $e_1 \cdot e_2 = (1-0.90)$, or $e_1 = (1-0.90)/ e_2$. There are many different possible combinations of e_1 and e_2 for a 90% efficacy in reducing symptomatic cases. Because of lack of empirical data, we assume that vaccine efficacy is equally attributable to infection and disease reduction in the main projections. The sterilising immunity after vaccination has been demonstrated. For example, an observational study in the UK (SIREN) found that the risk of being infected was reduced by 70% in health workers after one dose of the Pfizer-BioNTech vaccine.[21 22]

Vaccination of prioritised individuals began from 8 December 2020 in the UK and around 2 million individuals were vaccinated (mostly with a single dose of Pfizer vaccine) by 10 January 2021.[23] For simplicity, we assume that the mass vaccination starts from 1 January 2021 with a 80% coverage of eligible individuals. We assume that the maximum number of individuals vaccinated per day is 300,000 in England, which matched well with the actual number of vaccinated individuals (mostly with a single dose) in England according to the official statistics. The mass vaccination is modelled as an age-based phase approach, starting from people aged ≥70, followed by individuals aged 60-69, 50-59, 20-49, and then those aged 16-19. Although both Pfizer-BioNTec and AstraZeneca vaccines are 2-dose regimens, the policy in the UK has been to initially provide the first dose to as many individuals as possible to

maximise the public health impact. Exploratory assessment of data from clinical trials found that the short-term vaccine efficacy from the first dose of the Pfizer-BioNTech vaccine and the AstraZeneca vaccine is, respectively, about 90% and 70%.[24] For simplicity, we did not separate single or double dose vaccination, and assume that the overall vaccine efficacy is 70% or 90%, and the protection effects start 14 days after vaccination.

Available evidence has indicated that the duration of sterilising (infection protection) immunity after coronavirus infection ranges from 0.5 to two years.[3] Serum neutralizing antibodies were detected in all participants at four months follow up after SAR-CoV-2 mRNA vaccination.[25] Therefore, we assume that naturally acquired sterilising immunity lasts for 365 or 730 days, and vaccine-induced sterilising immunity lasts for 182, 365 or 730 days. After waning of sterilising immunity, individuals may be susceptible again to infection with SARS-CoV-2 virus, but the disease reduction immunity is likely longer lasting.[3] Due to the existence of disease reduction immunity, the reinfectivity of individuals who are reinfected after waning of sterilising immunity may be reduced. Lavine and colleagues estimated that the secondary transmissibility was 0.35 of the primary transmissibility (i.e., the reinfectivity was reduced by 65%).[3] Evidence from clinical trials and vaccination in the real world indicated that the viral loads and the duration of virus shedding in the infected individuals after vaccination were considerably reduced, compared with unvaccinated individuals.[26 27] Therefore, we assume that reinfectivity after waning of sterilising immunity is reduced by 20%, 40% or 60%. We also assume that the infectivity of ineffectively vaccinated individuals is the same as recovered individuals after the waning of sterilising immunity. In addition, we assume that vaccination of individuals recovered from natural infection boosts their naturally acquired immunity, which prevents or delays the waning of their sterilising immunity.

In this study, we focus on deaths in people infected with COVID-19, although our model also produces estimates of changes in effective reproduction values (Rt), numbers of infected and vaccinated individuals, and hospitalised patients. We performed multiple simulations under various scenarios. For clarity, we focus on results of selected scenarios in the main text, but report more data on simulation results in Supplementary Tables.

4. Model's mathematical equations

Notations:

- subscript used: "s" refers to sex, 1: male, 2: female, 3: both male and female; "a" refers to age group, 1: 0-4 years, 2: 5-9 years, 3: 10-19, …, 10: ≥ 80; 11: all age groups. "t" refers to time (day).
- N: The number of the population
- λ_s: Force of infection (λ) measures the risk (probability) of infection transmission, which is a function of transmission rate (β) and the prevalence of infectious individuals (I) among the population (N): $\lambda=\beta \cdot I/N$. [1]
- β: The transmission rate β in this discrete-time model is defined as the average number of individuals infected daily by an infectious person. It is a function of the number of daily close contacts per person (c), and the transmission risk per contact between a susceptible and an infectious individual (η): i.e., $\beta=c \cdot \eta$. [2]
- α1: rate of progressing from being exposed to being infectious.
- α2: rate of progressing from being asymptomatic infectious to symptomatic.
- μ: proportion of infected individuals who will be symptomatic; age-specific
- *infA*: The fraction of infection force for infected individuals with no or mild symptoms. It was assumed that infA=0.5 in this study.
- fS0: fraction of symptomatic patients who will not be quarantined.
- fSq: fraction of symptomatic patients who will be quarantined (self-isolation).
- fSh: fraction of symptomatic patients who will be hospitalised (including ICU admission).
- γA0: rate of recovering for asymptomatic individuals
- γS0 rate of recovering for symptomatic, not isolated/hospitalised patients
- γS1: rate of being isolated in symptomatic patients
- γS2: rate of recovering in isolated patients
- γH1: rate of being hospitalised for symptomatic patients

  γ*YH2*: rate of recovering in hospitalised patients
- ν_1: rate of vaccinating susceptible individuals
- ν_2: rate of vaccinating recovered individuals
- ρ: Relative infectivity of the secondary infection (I_2) compared with the primary infection (I_1). For example, if ρ=0.6, the infectivity of I_2 is 40% lower than the infectivity of I_1
- e_1: Relative efficacy of vaccine for sterilising immunity, reducing risk of virus transmission
- e_2: Relative efficacy of vaccine for pathology reduction, reducing the proportion of symptomatic cases after being infected
- *IA*: Asymptomatic individuals
- *IS*: Symptomatic patients

- γ_a : Average rate of recovering of asymptomatic individuals
- γ_s : Average rate of recovering of asymptomatic individuals
- ω_v: rate of immunity waning in vaccinated individuals
- ω_r: rate of immunity waning in recovered individuals
- $drOth_{s,a,t}$: sex, age-specific risk of deaths from causes other than covid-19, specific by week of the year.
- $drCov_{s,a,d}$: death risk from infected individuals before recovery, specific according to days since being infected.
- ds0, dsq, and dhos are the proportion of covid-19 deaths among symptomatic patients who are not quarantined, those who are isolated, or hospitalised, respectively. 1=ds0+dsq+dhos

Sex and age specific population:

$$\boldsymbol{N_{s,a,t}} = SU_{s,a,t} + SUr_{s,a,t} + VAC1_{s,a,t} + EX1_{s,a,t} + I01_{s,a,t} + EX2_{s,a,t} + I02_{s,a,t} + IA_{s,a,t} + IS0_{s,a,t} + ISQ_{s,a,t} + ISH_{s,a,t} + RE_{s,a,m,t} \quad (1)$$

Total number of the primary infection with no symptoms (age-specific):

$$aIA1_{a,t} = \sum_s (IA1_{s,a,t} + I01_{s,a,t} \cdot (1 - \mu_a)) \quad (2)$$

Total number of the primary infections with symptoms, isolated (age-specific):

$$aISQ1_{a,t} = \sum_s (ISQ1_{s,a,,t}) \quad (3)$$

Total number of the primary infections with symptoms, not isolated (age-specific):

$$aIS01_{a,t} = \sum_{s,} (IS01_{s,a,t} + I01_{s,a,t} \cdot \mu_a) \quad (4)$$

Total number of the secondary infection with no symptoms (age-specific):

$$aIA2_{a,t} = \sum_s (IA2_{s,a,t} + I02_{s,a,t} \cdot (1 - \mu_a \cdot e_2)) \quad (5)$$

Total number of the secondary infections with symptoms, isolated (age-specific):

$$aISQ2_{a,t} = \sum_s (ISQ2_{s,a,,t}) \quad (6)$$

Total number of the secondary infections with symptoms, not isolated (age-specific):

$$aIS02_{a,t} = \sum_{s,} (IS02_{s,a,t} + I02_{s,a,t} \cdot \mu_a \cdot e_2) \quad (7)$$

Sex and age specific susceptible population:

$$\boldsymbol{SU_{s,a,t+1}} = \left(SU_{s,a,t} - su\mathrm{Exp}_{s,a,t} - VAC1_{s,a,t}\right) \cdot (1 - drOth_{s,a,t}) + NewBirth_{s,t} \quad (8)$$

Note: $drOth_{s,a,,t}$ is sex, age-specific death rates for non-covid causes, specific by week of the year.

Newly exposed/infected with SARS-CoV-2 in susceptible individuals:

$$suExp_{s,a,t} = \sum_{j=1}^{10} SU_{s,a,t} \cdot \eta_t \left(\left(\left(Ca_{a,j,t} \cdot \frac{infA \cdot aIA1_{j,t} + aIS1_{j,t}}{N_{3,j,t}} + Cb_{a,j,t} \cdot \frac{aISQ1_{j,t}}{N_{3,j,t}} \right) \right) + \rho \cdot \left(Ca_{a,j,t} \cdot \frac{infA \cdot aIA2_{j,t} + aIS2_{j,t}}{N_{3,j,t}} + Cb_{a,j,t} \cdot \frac{aISQ2_{j,t}}{N_{3,j,t}} \right) \right) \quad (9)$$

Notes: $Ca_{a,j,t}$ is the average number of general contacts between people aged a and j; and $Cb_{a,j,t}$ is the average number of household contacts between people age a and j.

Newly exposed/infected in vaccinated individuals:

$$vacExp_{s,a,t} = \sum_{j=1}^{10} VAC1_{s,a,t} \cdot \eta_t \cdot e_1 \left(\left(\left(Ca_{a,j,t} \cdot \frac{infA \cdot aIA1_{j,t} + aIS1_{j,t}}{N_{3,j,t}} + Cb_{a,j,t} \cdot \frac{aISQ1_{j,t}}{N_{3,j,t}} \right) \right) + \rho \cdot \left(Ca_{a,j,t} \cdot \frac{infA \cdot aIA2_{j,t} + aIS2_{j,t}}{N_{3,j,t}} + Cb_{a,j,t} \cdot \frac{aISQ2_{j,t}}{N_{3,j,t}} \right) \right) \quad (10)$$

Newly exposed/infected in the recovered or vaccinated after waning of immunity:

$$sureExp_{s,a,t} = \sum_{j=1}^{10} SUre_{s,a,t} \cdot \eta_t \left(\left(\left(Ca_{a,j,t} \cdot \frac{infA \cdot aIA1_{j,t} + aIS1_{j,t}}{N_{3,j,t}} + Cb_{a,j,t} \cdot \frac{aISQ1_{j,t}}{N_{3,j,t}} \right) \right) + \rho \cdot \left(Ca_{a,j,t} \cdot \frac{infA \cdot aIA2_{j,t} + aIS2_{j,t}}{N_{3,j,t}} + Cb_{a,j,t} \cdot \frac{aISQ2_{j,t}}{N_{3,j,t}} \right) \right) \quad (11)$$

The number of the recovered or vaccinated who lose sterilising immunity (d from 1 to tt):

$$SUre_{s,a,t+1} = (SUre_{s,a,t} - sureEXP_{s,a,t}) \cdot (1 - drOth_{s,a,t}) + \sum_{d=1}^{tt} \left(iRE_{s,a,d,t} \cdot \omega_{r,d} + iVAC1_{s,a,d,t} \cdot \omega_{v,d} \right) \quad (12)$$

Notes: "*tt*" is the total number of days simulated. $\omega_{r,d}$ and $\omega_{v,d}$ are gamma distributed rate of immunity waning, respectively, a function of days since the recovery and vaccination. $iRE_{s,a,d,t}$ is the number of recovered since d days from recovery; and $eVAC1_{s,a,d,t}$ is the number of vaccinated since d days after vaccination.

The number of new (d=1) primary infections in susceptible individuals:

$$iEX1_{s,a,1,t} = suEXP_{s,a,t} \quad (13)$$

The number of new (d=1) secondary infections in recovered or vaccinated individuals:

$$iEX2_{s,a,1,t} = sureEXP_{s,a,t} + vacExp_{s,a,t} \quad (14)$$

For d=1,2,3…60 (assuming all will be dead or recovered by day 60 after being infected):

$$iEX1_{s,a,d+1,t+1} = iEX1_{s,a,d,t} \cdot (1 - \alpha 1_d) \quad (15)$$

$$iEX2_{s,a,d+1,t+1} = iEX2_{s,a,d,t} \cdot (1 - \alpha 1_d) \quad (16)$$

Assumed that covid-19 deaths were from symptomatic patients only. Overall deaths from covid-19 were calculated using the case fatality rates, and timing of covid-19 related deaths were assumed to have a gamma distribution according to days since being infected. Therefore a variable was introduced to record number of symptomatic individuals by days since being exposed/infected to calculate number of covid-19 deaths:

$$iSY_{s,a,1,t} = \mu_a\left(suExp_{s,a,t} + e_2 \cdot (surExp_{s,a,t} + vacExp_{s,a,,t})\right) \quad (17)$$

For d=1,2,3…60 (the transmission completed by day 60):

$$iSY_{s,a,d+1,t+1} = iSY_{s,a,d,t} \cdot (1 - drCov_{s,a,d}) \quad (18)$$

The number of covid-19 deaths at time t:

$$dthCov_{s,a,t} = \sum_{d=1}^{60} iSY_{s,a,d,t} \cdot drCov_{s,a,d} \quad (19)$$

The number of new (d=1) primary infections individuals before onset of symptoms:

$$iI01_{s,a,1,t+1} = \sum_{d=1}^{60} iEX1_{s,a,d,t} \cdot \alpha 1_d \quad (20)$$

The number of new (d=1) secondary infectious individuals before onset of symptoms:

$$iI02_{s,a,1,t+1} = \sum_{d=1}^{60} iEX2_{s,a,d,t} \cdot \alpha 1_d \quad (21)$$

For d=1,2,3…60 (the transmission completed by day 60):

$$iI01_{s,a,d+1,t+1} = iI01_{s,a,d,t} \cdot (1 - \alpha 2_d) \quad (22)$$

$$iI02_{s,a,d+1,t+1} = iI02_{s,a,d,t} \cdot (1 - \alpha 2_d) \quad (23)$$

The number of all infectious individuals before onset of symptoms:

$$\boldsymbol{I0_{s,a,t}} = \sum_{d=1}^{60} iI0_{s,a,d,t} \quad (24)$$

The number of new (d=1) infected individuals with no or very mild symptoms:

$$iIA_{s,a,1,t+1} = \sum_{d=1}^{60}\left(iI01_{s,a,d,t} \cdot \alpha 2_d \cdot (1 - \mu_a) + iI02_{s,a,d,t} \cdot \alpha 2_d \cdot (1 - e_2\mu_a)\right) \quad (25)$$

For d=1,2,3…60 (the transmission completed by day 60):

$$iIA_{s,a,d+1,t+1} = iIA_{s,a,d,t} \cdot (1 - \gamma A_d) \quad (26)$$

The number of all infectious individuals with no or mild symptoms:

$$IA\_(s,a,t) = \sum_{d=1}^{60} iIA_{s,a,d,t} \quad (27)$$

The number of all new (d=1) symptomatic patients:

$$SYM_{s,a,t+1} = \sum_{d=1}^{60}(iI01_{s,a,d,t} + e_2 \cdot iI02_{s,a,d,t}) \cdot \alpha 2_d \cdot \mu_a \quad (28)$$

The number of new (d=1) symptomatic patients who are not self-isolated:

$$iIS0_{s,a,1,t} = SYM_{s,a,t} \cdot fS0_t \quad (29)$$

Symptomatic patients (before being isolated or hospitalised:

$$iIS0_{s,a,,d+1,t+1} = (iIS0_{s,a,,d,t} - dthCov_{s,a,t} \cdot ds0_d) \cdot (1 - \Upsilon S0_d) \quad (30)$$

The number of new (d=1) symptomatic patients being isolated/quarantined:

$$iSQ_{s,a,1,t} = SYM_{s,a,t} \cdot fSq_{a,t} \quad (31)$$

Isolated symptomatic patients:

$$iSQ_{s,a,d+1,t+1} = \sum_{d=1}^{60}(iSQ_{s,a,d,t} - dthCov_{s,a,t} \cdot dsq_d) \cdot (1 - \Upsilon S1_d) \quad (32)$$

The number of new (d=1) symptomatic patients being hospitalised:

$$iSH_{s,a,1,t} = SYM_{s,a,t} \cdot fSh_{a,t} \quad (33)$$

Hospitalised symptomatic patients:

$$iSH_{s,a,d+1,t+1} = \sum_{d=1}^{60}(iSH_{s,a,d,t} - dthCov_{s,a,t} \cdot dsh_d) \cdot (1 - \Upsilon H1_d) \quad (34)$$

The number newly recovered people (d=1):

$$iRE_{s,a,1,t+1} = \sum_{d=1}^{60}\left(iIA_{s,a,d,t} \cdot \Upsilon A0_d + iIS0_{s,a,d,t} \cdot \Upsilon S0_d + iISQ_{s,a,d,t} \cdot \Upsilon S2_d + iISH_{s,a,d,t} \cdot \Upsilon H2_d + VAC2_t\right) \quad (35)$$

Note: $VAC2_t$ is the number of newly vaccinated individuals who recovered from previous infections.

All recovered for d=1,2,3…tt:

$$iRE_{s,a,d+1,t+1} = (iRE_{s,a,d,t} - VAC2_t) \cdot (1 - \mu r_d) \cdot (1 - drOth_{s,a,t}) \quad (36)$$

All recovered individuals:

$$\boldsymbol{RE_{s,a,t}} = \sum_{d=1}^{tt} iRE_{s,a,d,t} \quad (37)$$

Derived reproduction values (R0, Rt)

The basic reproduction ratio (R0) is defined as the average number of individuals infected by a typical infectious individual in a total susceptible population, and effective reproduction ratio (Rt) is the number of individuals infected by an infectious individual when only a proportion of the population are susceptible and the disease transmission dynamic may be influenced by control measures.[28] R values depend on the risk of infection per contact between an infectious and susceptible person, person-to-person contacts between individuals, the rate of transition from exposed to infectious, infectious period, and the prevalence of susceptible individuals in the population.[1] In this study, we don't use the reproduction ratio directly in simulating the spread of SARS-CoV-2 virus. To facilitate the understanding of effects of different intervention strategies, we estimated R0 and Rt during the simulation period, based on average values of relevant parameters and the calculation method used in a modelling study by Giordano et al.[19]

Average values of relevant parameters for estimating R values:

Weighted average fraction of symptomatic individuals in all infected individuals:

$$fS_t = \sum_a (\mu_a \cdot N_{3,a,t}/N_{3,11,t}) \quad (38)$$

Weighted average fraction of hospitalised symptomatic patients:

$$fH_t = \sum_a (fSH_{a,t} \cdot N_{3,a,t}/N_{3,11,t}) \quad (39)$$

Weighted average fraction of symptomatic patients self-isolated:

$$fQ_t = \sum_a (fSQq_{a,t} \cdot N_{3,a,t}/N_{3,11,t}) \quad (40)$$

Risk of daily transmission per infectious individual, depending on asymptomatic or symptomatic, household isolated or not:

$$\beta I0_t = \sum_{a,j=1}^{10} \mu_t \cdot Ca_{a,j,t} \cdot \frac{N_{j,t}}{N_{3,11,t}} \cdot (infA \cdot (1 - fS_t) + fS_t) \quad (41)$$

$$\beta IA_t = \sum_{a,j=1}^{10} \mu_t \cdot Ca_{a,j,t} \cdot \frac{N_{j,t}}{N_{3,11,t}} \cdot infA \cdot (1 - fS_t) \quad (42)$$

$$\beta SQ_t = \sum_{a,j=1}^{10} \mu_t \cdot Cb_{a,j,t} \cdot \frac{N_{j,t}}{N_{3,11,t}} \cdot (infA \cdot (1 - fS_t) + fS_t) \quad (43)$$

$$\beta S0_t = \sum_{a,j=1}^{10} \mu_t \cdot Ca_{a,j,t} \cdot \frac{N_{j,t}}{N_{3,11,t}} \quad (44)$$

The following transition variables are calculated for estimating R values:

$$d1_t = \alpha 2_t \cdot (1 - fS_t) \quad (45)$$

$$d2_t = \alpha 2_t \cdot fS_t \cdot fS0_t \quad (46)$$

$$d3_t = \alpha 2_t \cdot fS_t \cdot fSQ_t \quad (47)$$

$$d4_t = \alpha 2_t \cdot fS_t \cdot fSH_t \quad (48)$$

$$dA1_t = d1_t + d2_t + d3_t + d4_t \quad (49)$$

$$d5_t = \alpha 2_t \cdot (1 - fS_t \cdot e_2) \quad (50)$$

$$d6_t = \alpha 2_t \cdot fS_t \cdot fS0_t \cdot e_2 \quad (51)$$

$$d7_t = \alpha 2_t \cdot fS_t \cdot fSQ_t \cdot e_2 \quad (52)$$

$$d8_t = \alpha 2_t \cdot fS_t \cdot fSH_t \cdot e_2 \quad (53)$$

$$dA2_t = d5_t + d6_t + d7_t + d8_t \quad (54)$$

Effective reproductive value (Rt):

$$Rt = \frac{SU_{3,11,t}}{N_{3,11,t}} \left(\beta I0_t \cdot \frac{1}{dA1_t} + \beta IA_t \cdot \frac{d1_t}{dA1_t \cdot YA0_t} + \beta S0_t \cdot \frac{d2_t}{dA1_t \cdot YS0_t} + \beta SQ_t \cdot \frac{d3_t}{dA1_t \cdot YS1_t} + \beta SH_t \cdot \frac{d4_t}{dA1_t \cdot YH1_t}\right) + \left(\frac{SUre_{3,11,t}}{N_{3,11,t}} + \frac{VAC1_{3,11,t}}{N_{3,11,t}} \cdot e_1\right) \cdot \rho \cdot \left(\beta I0_t \cdot \frac{1}{dA2_t} + \beta IA_t \cdot \frac{d5_t}{dA2_t \cdot YA0_t} + \beta S0_t \cdot \frac{d6_t}{dA2_t \cdot YS0_t} + \beta SQ_t \cdot \frac{d7_t}{dA2_t \cdot YS1_t} + \beta SH_t \cdot \frac{d8_t}{dA2_t \cdot YH1_t}\right) \quad (55)$$

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Vaccination against COVID-19 and society's return to normality in England: a modelling study of impacts of different types of naturally acquired and vaccine induced immunity

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ABSTRACT

Objectives: To project impacts of mass vaccination against COVID-19, and investigate possible impacts of different types of naturally acquired and vaccine-induced immunity on future dynamics of SARS-CoV-2 transmission from 2021 to 2024 in England.

Design: Deterministic, compartmental, discrete-time SEIR modelling.

Participants: Population in England.

Interventions: mass vaccination programmes.

Outcome measures: daily and cumulative number of deaths from COVID-19.

Results: If vaccine efficacy remains high (85%), the vaccine-induced sterilising immunity lasts ≥182 days, and the reinfectivity is greatly reduced (by ≥60%), annual mass vaccination programmes can prevent further COVID-19 outbreaks in England. Under optimistic scenarios, with annual revaccination programmes, the cumulative number of COVID-19 deaths is estimated to be from 130,000 to 150,000 by the end of 2024. However, the total number of COVID-19 deaths may be up to 431,000 by the end of 2024, under scenarios with compromised vaccine efficacy (62.5%), short duration of natural and vaccine immunity (365/182 days), and small reduction in reinfectivity (30%).

Conclusions: Under optimistic scenarios, mass immunisation using efficacious vaccines may enable society safely to return to normality. However, under plausible scenarios with low vaccine efficacy and short durability of immunity, COVID-19 could continue to cause recurrent waves of severe morbidity and mortality despite frequent vaccinations. It is crucial to monitor the vaccination effects in the real world, and to better understand characteristics of naturally acquired and vaccine induced immunity against SARS-CoV-2.

ARTICLE SUMMARY:

Strengths and limitations of this study

- This is the first modelling study to explicitly investigate the impacts of different types of immune responses to SARS-CoV-2 infection and vaccines on the COVID-19 epidemic in England.
- The model has been verified based on historically observed data in England, and a large number of projection scenarios are explored.
- This is a deterministic model to answer "what-if" questions, and uncertainty in estimated parameters may have not been fully accommodated.
- There remain many uncertainties regarding durability and types of naturally acquired and vaccine-induced immunity against SARS-CoV-2 virus.

INTRODUCTION

The COVID-19 pandemic caused by the spread of SARD-CoV-2 virus has resulted in a huge number of deaths and severe disruptions of economies and social activities around the world. The spread of the SARS-CoV-2 virus can be suppressed by non-pharmaceutical interventions (NPIs) and lockdown measures.[1] Because of their disruptive socioeconomic consequences, lockdown restrictions cannot last indefinitely.

Only a few months after the initial identification of SARS-CoV-2 pathogen, there were more than 200 vaccine candidates in development globally.[2] Results of randomised controlled trials shown that vaccines were efficacious in reducing symptomatic diseases, compared with placebo.[3 4] Between 3 December 2020 and 31 July 2021, four vaccines against COVID-19 were approved for emergency use in the UK, and a vaccination programme has been started to rollout since 8 December 2020, prioritised primarily by age and comorbidity, with older people being vaccinated first.[5] By 30 July 2021, the coverage rate of vaccination in adults aged ≥18 in the UK was 88.5% for dose-1 and 72.1% for dose-2 of COVID-19 vaccines.[6] Although the number of people infected with SARS-CoV-2 virus in the UK was large during June-July 2021, numbers of hospitalised COVID-19 patients and related deaths had remained relative low, partly due to the protection of vaccines.[6] Therefore, lockdown restrictions in England have been mostly lifted since 19 July 2021.[7] Although mass vaccination is a promising strategy to enable society to safely return to normality, without mandatory NPIs, there is great uncertainty about the effects of COVID-19 vaccines and society's return to normality, including vaccines' long-term efficacy and emerging new variants of SARS-CoV-2 virus.[8 9]

There have been many mathematical modelling studies to investigate COVID-19 dynamics and the impacts of control measures (for example [10-13]). Several modelling studies evaluated impacts of vaccines on the dynamics and consequences of COVID-19 epidemics in the UK.[14-17] Two of these studies assessed impacts of the relaxation of social restriction after vaccination in the UK,[15 16] and one study assessed impacts of vaccination on hospital admissions,[17] but covered a shorter time horizon and did not consider waning of immunity. Another study of SARS-CoV-2 vaccination in the UK focused on economic evaluations.[17] There have been some published modelling studies of vaccination against COVID-19 in other countries. For example, a modelling study examined the nation-wide vaccination and returning to normal life in the United States of America (USA), finding that vaccination alone was insufficient and NPI measures were still required.[18]

The protection of naturally acquired or vaccine-induced immune responses may be attributable to infection protection, disease reduction, and reinfectivity reduction.[19] Studies of diseases caused by other human coronaviruses (HCoVs) indicated that infection protection immunity is likely to be short-lived, while disease reduction and reinfectivity reduction are likely long lasting.[20] We are not aware of

modelling studies that considered these important immunity characteristics in the evaluation of national mass vaccination programmes against COVID-19 epidemics. Therefore, we conducted a modelling study to investigate possible impacts of different types of naturally acquired and vaccine-induced immunity on future dynamics of SARS-CoV-2 transmission in England.

METHODS

Model structure

This is a deterministic, compartmental, discrete-time (day) population dynamic model, implemented with computational language R.[21] The population are classified into categories by sex, age (5-year age bands for age <10 years, and 10-year age bands for age ≥10 years), and COVID-19 infection status (figure 1). The main infection compartments include susceptible, exposed, infectious, recovered, and vaccinated. Here "exposed" refers to a pre-infectious status of infected individuals. Infected individuals are classified as asymptomatic or symptomatic, and symptomatic individuals are classified as not being isolated, self-isolated, and hospitalised. We assume that hospitalised patients are effectively isolated and no longer able to transmit the virus to the general population, but patients who self-isolate at home may transmit virus to household contacts. The recovered and effectively vaccinated are protected from reinfection, but they may be reinfected if the immunity is short-lived.

Parameters and data sources

Details on the model's structure (appendix figure 1), parameters, data sources (appendix table 1), and mathematical equations are available in Supplementary files. Initial parameter values were estimated based on a review of relevant literature, and key parameter estimates were calibrated so that the simulated numbers of COVID-19 deaths, hospitalised patients, and infected individuals were as similar as possible to historically reported data from March 2020 to June 2021 in England.[6]

We obtained population demographic statistics in England from the Office for National Statistics,[22] and the whole population is assumed to be susceptible to SARS-CoV-2 infection at the beginning of 2020. We assume incubation periods, infectious periods, days of hospital stay, and days of deaths after being infected, to be gamma distributed (appendix table 1 in supplementary files).[10 23 24] Age specific case fatality rates and hospitalisation rates of symptomatic cases were based on a study by Verity et al.[24] Average sex-and-age-specific rates of all-cause deaths from 2015 to 2019 in England[22] are applied to people who are not infected with or recovered from COVID-19. We assumed that the number of births equals to the number of deaths each day, and did not consider the influence of population migration. We adjusted the number of individuals belonging to each age group at the beginning of a year since 2021, by shifting a proportion of them to the adjacent higher age group.

Effects of NPI measures, including restrictions on social activities, contact tracing and testing, were materialised by changes in transmission risk per contact between a susceptible and an infectious individual,[25] and average numbers of contacts of the general population (appendix table 2 in supplementary files). We estimate that the transmission risk per contact between infectious and susceptible individuals was reduced by 30%, from 0·094 before the implementation of any NPIs to 0·066 by March 15, 2020 after implementing basic NPI measures. Because of the new virus variants,[26] the average transmission risk per contact was increased to 0·077 by the end of 2020, and 0.081 since June 2021. We assume that, since September 2021, the transmission risk per contact is 10% higher in September, October, March and April, and 20% higher in the winter months of November, December, January and February, compared with the risk in summer months from May to August. We do not use the reproduction number as an input parameter, but derived the basic and effective reproduction numbers based on model's transmission parameters (equation 55 in Supplementary files).[12 25]

The sex-and-age-specific numbers of daily contacts per person were based on the UK data from a study of European countries.[27] We consider only the daily contacts of the general population and household contacts of individuals self-isolated at home. We estimated that the lockdown measures from 24 March 2020 reduced general population contacts by 60-85%, although household contacts were unchanged. The NPI measures were relaxed or strengthened over time, which were reflected in the assumed social contacts and transmission risk (Supplementary files). Social contacts in England since 19 July 2021 are return to normal as before the pandemic in England, although some basic hygienic measures would be maintained.

Vaccination and projection scenarios

Vaccination of prioritised individuals began from 8 December 2020 in England.[28] The Joint Committee on Vaccination and Immunisation (JCVI) in the UK previously recommended COVID-19 vaccination of individuals aged ≥18, and also recommended vaccination of young people aged 16-17 years old on 4 August 2021.[29] The vaccine uptake rate in adults aged ≥18 was 88.5% for dose-1 and 72.1% for dose-2 by 30 July 2021,[6] and the coverage with two does was >90% in adults aged ≥65, 80-90% in those aged 50-64, and around 60% in those aged 40-49.[30] In this study, the mass vaccination is modelled as an age-based phase approach, starting from people aged ≥70, followed by individuals aged 60-69, 50-59, 30-49, and then those aged 16-29 years old. We assume that the mass vaccination starts from 1 January 2021, and the maximum number of individuals vaccinated daily is 180,000, to matched with numbers of vaccinated individuals according to the official statistics. In the main analysis, we assume that the uptake rate is 75%, 80%, 85% and 90%, respectively, in adults aged 16-29, 30-39, 40-49, and ≥50 years old. Because of uncertain coverage of vaccination in younger people, we conducted

sensitivity analyses under scenarios with lower (60%, 70%, and 80%) and higher (80%, 85%, and 90%) coverage of vaccination in people aged 16-29, 30-39, and 40-49 years old, respectively.

Both Pfizer-BioNTec and AstraZeneca vaccines are 2-dose regimens, and the policy in the UK has been to initially provide the first dose to as many adults as possible. Data from clinical trials indicated that the short-term vaccine efficacy after the first dose of the Pfizer-BioNTech and the AstraZeneca vaccine is about 90% and 70%, rerspectively.[3] Public Health England (PHE) in July 2021 estimated that the efficacy was 55-70% after the first dose, and 70-85% or 85-95% after the second dose.[30] In this study, we assume that the overall vaccine efficacy is 62.5% after the first dose and 85% after the second dose. The protection effects start 14 days after the first dose vaccination, and the interval between the first and second dose is nine weeks. The overall vaccine efficacy after the second dose may be lower than 85.0% due to new variants of SARS-CoV-2 virus. Therefore, we assume a scenario in which the vaccine efficacy is reduced by new viral variants, to be 44.0% after the first dose and 62.5% after the second dose, during 2022-2024.

The reduction in symptomatic cases in vaccinated individuals may be due to induced antibodies in susceptible individuals (infection protection), or a reduction in symptomatic cases among infected individuals (disease reduction), or a combination of both. There are many different possible combinations of infection protection and disease reduction for a given overall vaccine efficacy in reducing symptomatic cases (appendix figure 2 in supplementary files). We assume that vaccine efficacy for reducing symptomatic cases is equally attributable to infection reduction and disease reduction in the main projections. For vaccines with 62.5% and 85.0% overall efficacy, the equal partial efficacy for the infection protection and for disease reduction is 38.8% and 61.3%, respectively (see Supplementary files for details).

Immune responses against COVID-19 infection, either naturally acquired from prior infection or vaccine-induced, may reduce individuals' susceptibility to infection (infection protection or sterilising immunity), reduce pathology so that disease is less severe after being infected (disease reduction immunity), and reduce infectivity of those who are reinfected after the waning of immunity (reinfectivity reduction immunity).[19] According to immunological characteristics of other HCoVs, infection protection immunity may wane after a short period, while disease protection and reinfectivity reduction immunity are likely longer lasting.[20] For example, antibodies against SARS-CoV-1 virus in recovered patients was no longer detectable after 2-3 years, while specific memory T cells remained detected after 11 years.[31] Therefore, we assume that the disease reduction and reinfectivity reduction immunity are long lasting (>4 years).[20] We assume that naturally acquired sterilising immunity lasts for 365 or 730 days, and vaccine-induced sterilising immunity lasts for 182 or 365 days. Available evidence indicated that the viral loads and the duration of virus shedding in the infected individuals after vaccination were considerably reduced, compared with unvaccinated

individuals.[32 33] Public Health England in July 2021 estimated that the reinfectivity was reduced by 35-50% after the first dose of vaccines,[30] although it is possible that the reduction in reinfectivity may be larger than 35-50% after the second dose of vaccines. More recent studies reported that fully vaccinated individuals who were infected were between 41% and 78% less likely to transmit the virus to unvaccinated individuals.[34] In this study, we assume that reinfectivity after waning of sterilising immunity is reduced by 30%, 45% or 60%. We also assume that the infectivity of ineffectively vaccinated individuals is the same as recovered individuals whose sterilising immunity has waned, and vaccination of individuals recovered from natural infection boosts their naturally acquired immunity.

We considered scenarios with different frequency of revaccination programmes, including a single vaccination programme, multiple (2-4) annual revaccinations, and revaccination programmes with different frequency and time intervals. The main characteristics of the simulated scenarios are summarised in appendix table 3 in supplementary files.

We run the model and calibrate key transmission parameters by visually comparing estimated numbers of daily COVID-19 deaths, and hospitalised patients, with official records from 1 January 2020 to 30 June 2021 in England.[6] We used estimates of transmission parameters by the end of June 2021 to project COVID-19 deaths from 2021 to 2024, under various scenarios of vaccine efficacy, durability and protection characteristics of naturally acquired and vaccine-induced immunity. The number of deaths from SARS-CoV-2 infections is the main endpoint in this study.

Patient and public involvement

No patients and the public were involved in this literature and secondary data based, computational modelling study.

RESULTS

Our derived basic reproduction number (R0) was 3·68 at the initial stage of the COVID-19 epidemic in England. After implementing NPI and lockdown measures, the effective reproduction value (Rt) was reduced to 0·66 after 24 March 2020. Thereafter, the Rt values fluctuated along with changing NPI policies, and our estimated R values were within the ranges reported in England (Appendix figure 3 in Supplementary files).[35] The estimated prevalence of SARS-CoV-2 infection (appendix figure 4), the number of hospitalised COVID-19 patients (appendix figure 5), and the estimated daily deaths from COVID-19 (appendix figure 6) are well matched with the reported data from March 2020 to June 2021 in England (Supplementary files).

Vaccine efficacy, immunity durability, and reinfectivity

Figure 2 shows the impacts of partial vaccine efficacy regarding disease reduction relative to infection protection, durability of immunity, and reinfectivity, given the same overall vaccine efficacy in reducing symptomatic cases. There are three general inferences. As expected, the number of COVID-19 deaths is smaller following a greater reduction in reinfectivity (figure 2A, 2B, 2C). Second, a greater reduction in reinfectivity makes the durability of immunity less influential, if a vaccine is efficacious for infection protection (figure 2c). Third, the impacts of partial efficacy of infection protection relative to disease reduction by a vaccine is substantial when the duration of immunity is short-lasting. A combination of a shorter duration of immunity and smaller reduction in the reinfectivity makes the disease reduction efficacy more beneficial (figure 2A, 2B).

Population susceptibility and COVID-19 outbreaks

Changes in the prevalence of susceptible individuals and daily peaks of COVID-19 deaths in England during 2020 and 2024 are shown in figure 3, under assumptions of 85% vaccine efficacy after the second dose, 45% reduction in reinfectivity after waning of sterilising immunity, and different durations of sterilising immunity.

The overall prevalence of susceptible individuals is reduced to around 25% by August 2021, after a single wave of mass vaccination starting from January 2021. It starts to increase to above 70% by December 2022, if the duration of natural and vaccine-induced immunity is 730 and 365 days, respectively (figure 3A). The raised prevalence of susceptible individuals leads to an outbreak with a high peak (n=627) of daily COVID-19 deaths in May 2023. The prevalence of the susceptible is slightly reduced by the natural infection during the outbreak, then increases again due to waning of immunity. Two waves of repeated annual revaccination programmes delay the new outbreak, with a peak of daily COVID-19 deaths (n=731) in May 2024 (figure 3B). Four repeated waves of annual revaccination programmes almost prevent any new outbreaks before the end of 2024, with no more than 50 daily COVID-19 deaths during 2022-2024 (figure 3C).

If the natural and vaccine immunity lasts only 365 and 182 days, respectively, the annual mass vaccination programmes are insufficient to sustain a constantly low prevalence of the susceptible, and the prevalence of the susceptible fluctuates up and down biannually (figure 3D-F). A single wave of mass vaccination is followed with multiple high peaks of daily COVID-19 deaths (figure 3D), and annual revaccination programmes result in corresponding changes in the prevalence of susceptible individuals and daily COVID-19 deaths (figure 3E, 3F). With four annual revaccination programmes, there are two flattened peaks of daily deaths from COVID-19 in March 2022 (n=151) and April 2024 (n=168), respectively (figure 3E).

Projected COVID-19 deaths under various scenarios

The projected total numbers and daily peaks of COVID-19 deaths during 2020-2024, under all assumed scenarios, are available in supplementary table 1 and supplementary table 2. If there is no waning of immunity (i.e., immunity duration >4 years) and high vaccine efficacy, a single vaccination programme may prevent COVID-19 outbreaks during 2022-2024, after returning to normality (supplementary table 1). Otherwise, repeated vaccination programmes are required to prevent further large outbreaks with high peaks of daily deaths from COVID-19.

Table 1 shows results of annual vaccination programmes under selected scenarios. With annual revaccinations under optimistic scenarios, the cumulative number of COVID-19 deaths is estimated to be from 130,000 to 150,000 by the end of 2024. However, the total number of COVID-19 deaths may be up to 431,000 by the end of 2024, under scenarios with compromised long-term vaccine efficacy (62.5%), short duration of natural and vaccine immunity (365/182 days), and small reduction in reinfectivity (30%) (table 1).

Results of revaccination programmes with different frequency (from two to six revaccinations during 2021-2024) are shown in figure 4 and supplementary table 2. Revaccination programmes every two years can prevent outbreaks during 2022-2024 in a scenario with high vaccine efficacy (85%), large reduction in reinfectivity (60%), and long duration of immunity (730/365 days). Under assumed scenarios, more frequent revaccinations are associated with smaller total numbers and lower peaks of daily deaths from COVID-19 (supplementary table 2). As expected, frequent revaccinations are particularly important when the immunity response is short-lived (figure 4).

Results of scenarios with lower or higher vaccination coverage in younger adults are presented in supplementary table 3. As expected, lower coverage of vaccination programmes is associated with larger number of total COVID-19 deaths. For example, the projected cumulative number of COVID-19 deaths by the end of 2024 is around 195,000, under a scenario (labelled as 'A2c4' in supplementary table 3) of annual revaccination, 85% vaccine efficacy, short duration of immunity (365/182 days), and 75-90% vaccination coverage. The number of COVID-19 deaths is reduced to around 183,000 in scenario (A2c4y) with 80-90% coverage, and increased to around 210,000 in scenario (A2c4x) with 60-90% coverage (supplementary table 3).

DISCUSSIONS

Mass immunisation using efficacious vaccines may enable society safely to return to normality. Repeated vaccination programmes are very likely to be required to prevent further COVID-19 outbreaks, depending on vaccine efficacy, the durability and characteristics of different types of

immune response to naturally acquired and vaccine-induced immune responses. Evidence on diseases caused by other common HCoVs indicated that the infection protection immunity may be short-lived, but the disease reduction and the reinfectivity reduction immunity are likely to be longer lasting.[20] We found that, if vaccine efficacy is high (85%) and reinfectivity is greatly reduced (e.g., by 60%), repeated annual mass vaccination programmes prevent further COVID-19 large outbreaks, even if the vaccine induced sterilising immunity lasts only 182 days. Under optimistic scenarios, the cumulative number of COVID-19 deaths during 2020-2024 in England is estimated to be from 130,000 to 150,000. If both the natural and vaccine immunity are short-lived (365 and 180 days, respectively), and reinfectivity is reduced only by 45% or 30%, further COVID-19 outbreaks cannot be prevented by annual vaccination programmes. The total number of COVID-19 deaths is estimated to be around 431,000 by the end of 2024, under a pessimistic scenario with low long-term vaccine efficacy (62.5%), short duration of vaccine immunity (365/182 days), and small reduction in reinfectivity (30%) (Table 1).

When natural and vaccine-induced immune response against SARS-CoV-2 infection is short-lived, more frequent revaccinations (e.g., every 8-10 months) can reduce deaths from COVID-19, compared with less frequent or annual revaccination programmes. However, frequent revaccination may not always be feasible, due to the availability of vaccine doses, resource restrictions, organisational complexity, and possibly decreased compliance by the public.

Compared with previous modelling studies,[14-17] our study has considered the durability of naturally acquired and vaccine induced immunity, over a five year period from 2020 to 2024, and compared a wider range of plausible scenarios. We explicitly investigated the impacts of different types of immune responses to SARS-CoV-2 infection and vaccines on the COVID-19 epidemic in a country. Findings from our study will improve the understanding of key immunological parameters relevant to future changes in SARS-CoV-2 transmission dynamics and vaccination strategies.

Evidence from randomised controlled trials showed that vaccines against SARS-CoV-2 are efficacious in reducing symptomatic COVID-19 cases.[4] The reduction in symptomatic cases in the vaccine group may be attributable to infection protection or disease reduction. Available evidence showed that vaccines reduced the risk of SARS-CoV-2 virus infection in vaccinated individuals,[36] and household members of vaccinated healthcare workers has a lower risk of COVID-19 infection than those of unvaccinated.[37] In this study, we explored the impacts of different proportions of a vaccine's infection protection efficacy and disease reduction efficacy. Different combinations of the two efficacy components have impacts on the transmission dynamics, depending on the duration of immune response and reinfectivity after waning of sterilising immunity. Because of lack of data, we assumed that vaccine efficacy is equally attributable to the infection and disease reduction immunity.

Vaccines that are efficacious against current SARS-CoV-2 virus may become less efficacious against new emerging variants.[8] Therefore, we modelled a range of overall long-term vaccine efficacy (62.5% vs. 85.0%). Although the vaccine efficacy might be reduced by new viral variants, it is also possible that repeated vaccinations may boost immune responses. We assume that there will be no important safety issues for vaccines licensed to use. We focused on the impacts and interactions of vaccine efficacy, different types of immune response to SARS-CoV-2, and assumed no more restrictions by NPI measures after return to normality in England from 19 July 2021. However, the pessimistic scenarios in our analyses may not be allowed to happen in the real world, as NPI (including lockdown) measures may have to be introduced again if the vaccination programmes are insufficient to avoid the new outbreaks of COVID-19.

This is a deterministic simulation model, and uncertainty in estimated parameters may have not been fully accommodated. For simplicity, stochastic uncertainty, to quantify confidence intervals around the model's outputs, was not modelled. However, the model has been verified based on historically observed outcome data in England, and a large number of projection scenarios are explored to explicitly answer "what-if" questions. Although many uncertainties remain, including durability and types of naturally acquired and vaccine-induced immunity, our model can be updated to assess vaccination strategies, as new evidence emerges.

Conclusions

Under optimistic scenarios, mass immunisation using efficacious vaccines may enable society safely to return to normality. However, under plausible scenarios with low vaccine efficacy and short durability of immunity, COVID-19 could continue to cause recurrent waves of severe morbidity and mortality despite frequent vaccinations, and necessitate stringent NPI restrictions. It is crucial to monitor the vaccination effects in the real world, and to better understand characteristics of naturally acquired and vaccine induced immunity against SARS-CoV-2.

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Contributors: FS designed, developed the model, retrieved data for estimating parameters, conducted computational calculations, and prepared the draft manuscript. MOB provided methodological support, helped interpret results and critically revised the draft manuscript. FS

accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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FIGURE LEGENDS:

Figure 1: Modelling COVID-19 epidemics in England - main compartments and transitions across status. See supplementary files for details on definitions of transition parameters

Figure 2. Projected numbers of COVID-19 deaths with different combinations of partial efficacy of infection and disease protection, immunity duration, and reduction in reinfectivity.

The cumulative number of COVID-19 deaths by the end of 2024, after four repeated annual vaccinations of 90% individuals aged ≥18 during 2021-2024. The overall vaccine efficacy was 85%; "0·00/0·85" refers to all vaccine efficacy attributable to disease protection, "0·61/0·61" refers to equal infection and disease protection, "0·85/0·00" refers to all efficacy attributable to infection protection. Immunity duration: "365/182" refers to 365 days and 182 days, "and "730/365" refers to 730 and 365 days, respectively, natural and vaccine immunity. Figure 2A, 2B and 2C shows results under the assumption of 30%, 45% and 60% reduction in reinfectivity.

Figure 3. Projected peaks of daily COVID-19 deaths and the prevalence of susceptible individuals during 2020-2024 under scenarios with different immunity durability and vaccine strategies. We assume 85% long-term vaccine efficacy; 75-90% coverage of individuals aged ≥16; 45% reduction in reinfectivity, longer (730/365 days, fig 3A-C) or shorter lasting (365/182 days, fig 3D-F) natural/vaccine immunity. Results were after a single vaccination (fig 3A and 3D), two annual vaccination programmes (fig 3B and 3E), and four annual vaccination programmes (Figure 3C and 3F).

Figure 4. Results of revaccination programmes with different frequency. Vaccine efficacy is 85.0% in fig 4A/C and 62.5% in fig 4B/D, respectively. Duration of immunity lasts 730/365 in fig 4A/B and 365/182 days in fig 4C/D, respectively.

ONLINE SUPPLEMENTARY MATERIALS

Supplementary Files: Model structure, data sources, model parameters, and mathematical equations

Supplementary Tables: Additional results of relevant scenarios

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Table 1. Projected total and daily peak COVID-19 deaths after annual vaccination programmes by 2024 in England

Scenario	Long-term vaccine efficacy	Reduction in reinfectivity	Immunity duration (day): Natural /vaccine	Total COVID-19 deaths (2020-2024)	Daily peaks of COVID-19 deaths		
					2022	2023	2024
A1b4	85.0%	60%	730/365	127,550	28	0	0
A2b4	85.0%	45%	730/365	134,421	42	0	36
A3b4	85.0%	30%	730/365	152,926	64	4	131
A1c4	85.0%	60%	365/182	148,093	89	2	7
A2c4	85.0%	45%	365/182	194,661	151	55	168
A3c4	85.0%	30%	365/182	229,664	208	145	96
B1b4	62.5%	60%	730/365	143,233	104	0	0
B2b4	62.5%	45%	730/365	179,002	209	0	224
B3b4	62.5%	30%	730/365	233,075	366	3	384
B1c4	62.5%	60%	365/182	198,684	351	2	47
B2c4	62.5%	45%	365/182	350,016	615	537	886
B3c4	62.5%	30%	365/182	430,219	888	616	1362

Notes to Table 1: Scenario labels are corresponding to those used in supplementary table 1. We assume annual vaccination covers 75-90% of individuals aged ≥16 years; the short-term vaccine efficacy is 62.5% after the first dose and 85% after the second dose, and the overall vaccine efficacy is equally attributable to the infection and disease protection. “Long-term vaccine efficacy” refers to vaccine efficacy in fully vaccinated after January 2022.

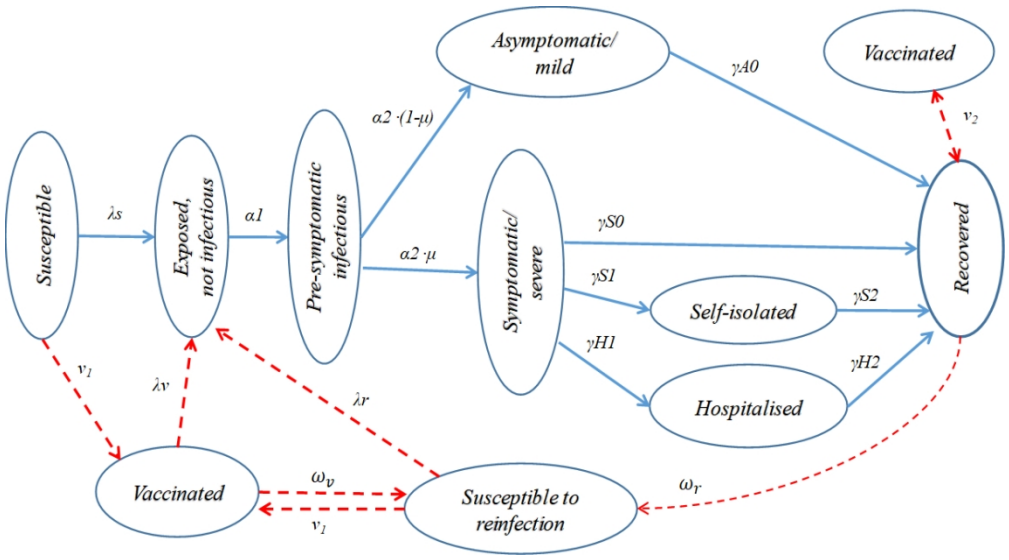


Figure 1: Modelling COVID-19 epidemics in England - main compartments and transitions across status. See supplementary files for details on definitions of transition parameters

324x177mm (96 x 96 DPI)

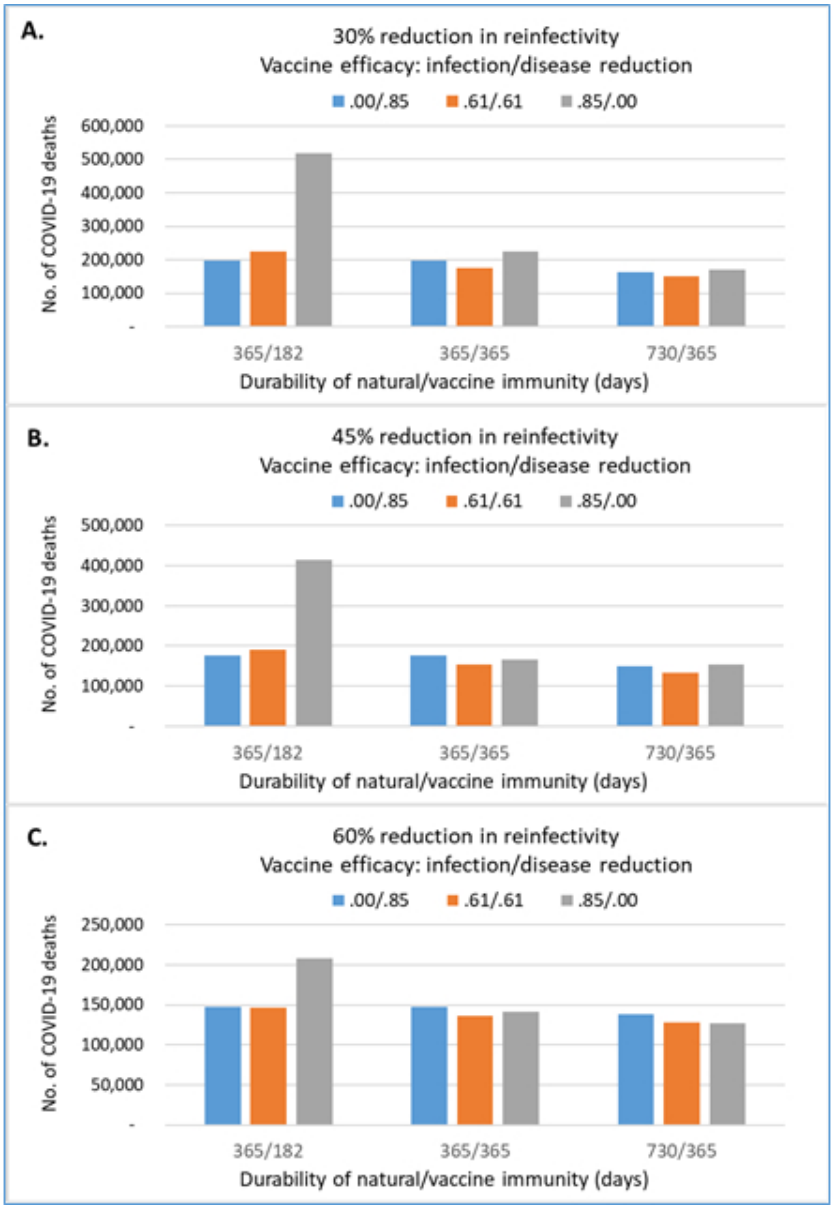


Figure 2. Projected numbers of COVID-19 deaths with different combinations of partial efficacy of infection and disease protection, immunity duration, and reduction in reinfectivity. The cumulative number of COVID-19 deaths by the end of 2024, after four repeated annual vaccinations of 90% individuals aged ≥18 during 2021-2024. The overall vaccine efficacy was 85%; "0·00/0·85" refers to all vaccine efficacy attributable to disease protection, "0·61/0·61" refers to equal infection and disease protection, "0·85/0·00" refers to all efficacy attributable to infection protection. Immunity duration: "365/182" refers to 365 days and 182 days, "and "730/365" refers to 730 and 365 days, respectively, natural and vaccine immunity. Figure 2A, 2B and 2C shows results under the assumption of 30%, 45% and 60% reduction in reinfectivity.

118x169mm (96 x 96 DPI)

Figure 3. Projected peaks of daily COVID-19 deaths and the prevalence of susceptible individuals during 2020-2024 under scenarios with different immunity durability and vaccine strategies. We assume 85% long-term vaccine efficacy; 75-90% coverage of individuals aged ≥16; 45% reduction in reinfectivity, longer (730/365 days, fig 3A-C) or shorter lasting (365/182 days, fig 3D-F) natural/vaccine immunity. Results were after a single vaccination (fig 3A and 3D), two annual vaccination programmes (fig 3B and 3E), and four annual vaccination programmes (Figure 3C and 3F).

314x271mm (96 x 96 DPI)

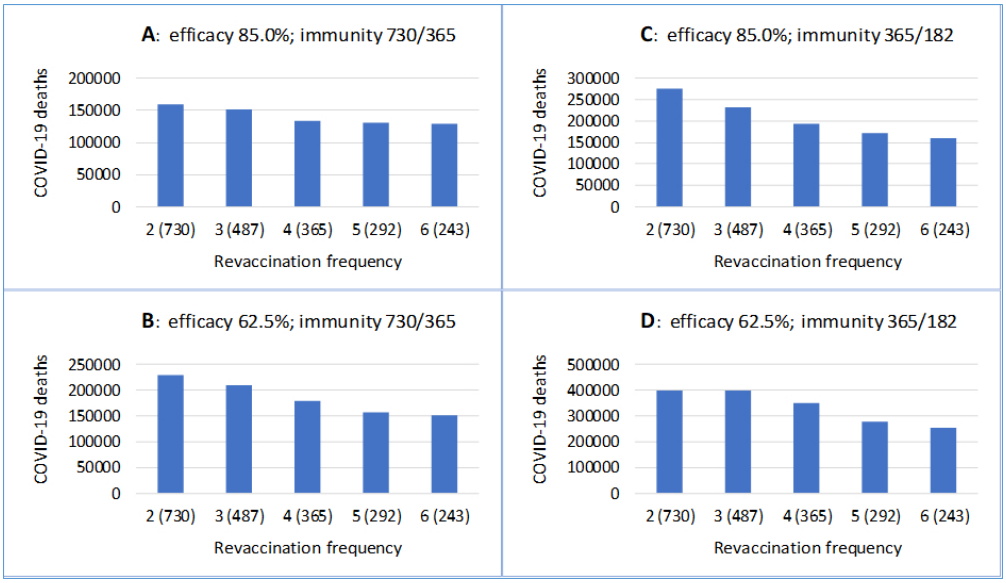


Figure 4. Results of revaccination programmes with different frequency. Vaccine efficacy is 85.0% in fig 4A/C and 62.5% in fig 4B/D, respectively. Duration of immunity lasts 730/365 in fig 4A/B and 365/182 days in fig 4C/D, respectively.

248x142mm (96 x 96 DPI)

Supplementary tables for:

Vaccination against COVID-19 and society's return to normality in England: a modelling investigation of different types of naturally acquired and vaccine induced immunity

1. Projected total and daily peaks of COVID-19 deaths by the end of 2024 in England, under different scenarios of annual vaccination programmes Data sources and model verification
2. Projected total and daily peaks of COVID-19 deaths by the end of 2024 in England by revaccination frequency.
3. Projected total and daily peaks of COVID-19 deaths by the end of 2024 in England, under different scenarios of uptake rate of vaccination in younger adults

Supplementary table: 1

Projected total and daily peaks of COVID-19 deaths by the end of 2024 in England under different scenarios of annual vaccination programmes

Assumptions and notes:

75-90% vaccination coverage of individuals aged >=16 years old.
Initial overall vaccine efficacy: 62.5% after dose-1 and 85% after dose-2.
The overall vaccine efficacy is equally attributable to the infection and disease protection.

Scenario	Vaccination waves (interval days)	Long-term vaccine efficacy	Reduction in reinfectivity	Immunity duration (day): Natural /vaccine	Total COVID-19 deaths (2020-2024)	Daily peaks of COVID-19 deaths		
						2022	2023	2024
A1a1	1	85.0%	60%	No waning	128,039	28	0	0
A1a2	2 (365)	85.0%	60%	No waning	127,464	28	0	0
A1a3	3 (365)	85.0%	60%	No waning	127,464	28	0	0
A1a4	4 (365)	85.0%	60%	No waning	127,464	28	0	0
A1b1	1	85.0%	60%	730/365	242,691	28	592	582
A1b2	2 (365)	85.0%	60%	730/365	154,956	28	0	592
A1b3	3 (365)	85.0%	60%	730/365	127,550	28	0	0
A1b4	4 (365)	85.0%	60%	730/365	127,550	28	0	0
A1c1	1	85.0%	60%	365/182	239,044	281	452	56
A1c2	2 (365)	85.0%	60%	365/182	196,149	89	78	392
A1c3	3 (365)	85.0%	60%	365/182	155,320	89	2	109
A1c4	4 (365)	85.0%	60%	365/182	148,093	89	2	7
B1a1	1	62.5%	60%	No waning	144,586	105	0	0
B1a2	2 (365)	62.5%	60%	No waning	142,720	104	0	0
B1a3	3 (365)	62.5%	60%	No waning	142,720	104	0	0
B1a4	4 (365)	62.5%	60%	No waning	142,720	104	0	0
B1b1	1	62.5%	60%	730/365	320,789	105	952	950
B1b2	2 (365)	62.5%	60%	730/365	230,198	104	0	1066
B1b3	3 (365)	62.5%	60%	730/365	143,670	104	0	16
B1b4	4 (365)	62.5%	60%	730/365	143,233	104	0	0
B1c1	1	62.5%	60%	365/182	353,663	528	536	407

B1c2	2 (365)	62.5%	60%	365/182	292,109	351	103	915
B1c3	3 (365)	62.5%	60%	365/182	225,230	351	2	412
B1c4	4 (365)	62.5%	60%	365/182	198,684	351	2	47
A2a1	1	85.0%	45%	No waning	132,749	42	0	0
A2a2	2 (365)	85.0%	45%	No waning	131,963	42	0	0
A2a3	3 (365)	85.0%	45%	No waning	131,963	42	0	0
A2a4	4 (365)	85.0%	45%	No waning	131,963	42	0	0
A2b1	1	85.0%	45%	730/365	265,799	42	627	243
A2b2	2 (365)	85.0%	45%	730/365	206,600	42	9	731
A2b3	3 (365)	85.0%	45%	730/365	159,912	42	0	582
A2b4	4 (365)	85.0%	45%	730/365	134,421	42	0	36
A2c1	1	85.0%	45%	365/182	373,907	479	588	435
A2c2	2 (365)	85.0%	45%	365/182	266,690	151	675	628
A2c3	3 (365)	85.0%	45%	365/182	222,944	151	55	363
A2c4	4 (365)	85.0%	45%	365/182	194,661	151	55	168
B2a1	1	62.5%	45%	No waning	163,679	209	0	0
B2a2	2 (365)	62.5%	45%	No waning	161,055	209	0	0
B2a3	3 (365)	62.5%	45%	No waning	161,055	209	0	0
B2a4	4 (365)	62.5%	45%	No waning	161,055	209	0	0
B2b1	1	62.5%	45%	730/365	383,433	209	916	801
B2b2	2 (365)	62.5%	45%	730/365	304,138	209	13	1301
B2b3	3 (365)	62.5%	45%	730/365	236,662	209	0	952
B2b4	4 (365)	62.5%	45%	730/365	179,002	209	0	224
B2c1	1	62.5%	45%	365/182	611,929	867	1542	2437
B2c2	2 (365)	62.5%	45%	365/182	443,176	615	1860	1096
B2c3	3 (365)	62.5%	45%	365/182	376,242	615	537	1092
B2c4	4 (365)	62.5%	45%	365/182	350,016	615	537	886
A3a1	1	85.0%	30%	No waning	138,595	64	0	0
A3a2	2 (365)	85.0%	30%	No waning	137,672	64	0	0
A3a3	3 (365)	85.0%	30%	No waning	137,672	64	0	0
A3a4	4 (365)	85.0%	30%	No waning	137,672	64	0	0

A3b1	1	85.0%	30%	730/365	301,437	64	1235	218
A3b2	2 (365)	85.0%	30%	730/365	259,144	64	297	1645
A3b3	3 (365)	85.0%	30%	730/365	187,753	64	4	324
A3b4	4 (365)	85.0%	30%	730/365	152,926	64	4	131
A3c1	1	85.0%	30%	365/182	498,043	743	764	1933
A3c2	2 (365)	85.0%	30%	365/182	321,779	208	537	599
A3c3	3 (365)	85.0%	30%	365/182	317,223	208	145	618
A3c4	4 (365)	85.0%	30%	365/182	229,664	208	145	96
B3a1	1	62.5%	30%	No waning	188,227	366	0	0
B3a2	2 (365)	62.5%	30%	No waning	185,384	366	0	0
B3a3	3 (365)	62.5%	30%	No waning	185,384	366	0	0
B3a4	4 (365)	62.5%	30%	No waning	185,384	366	0	0
B3b1	1	62.5%	30%	730/365	448,904	366	1093	649
B3b2	2 (365)	62.5%	30%	730/365	392,651	366	98	2877
B3b3	3 (365)	62.5%	30%	730/365	291,181	366	3	720
B3b4	4 (365)	62.5%	30%	730/365	233,075	366	3	384
B3c1	1	62.5%	30%	365/182	822,318	1095	2571	3202
B3c2	2 (365)	62.5%	30%	365/182	682,299	888	1714	5055
B3c3	3 (365)	62.5%	30%	365/182	627,017	888	616	3165
B3c4	4 (365)	62.5%	30%	365/182	430,219	888	616	1362

Supplementary table: 2

Projected total and daily peaks of COVID-19 deaths by the end of 2024 in England by revaccination frequency

Assumptions and notes:

Age-based 75-90% vaccination coverage of individuals aged 16+.
Initial overall vaccine efficacy: 62.5% after dose-1 and 85% after dose-2.
The overall vaccine efficacy is equally attributable to the infection and disease protection.

Scenario	Vaccination waves (interval days)	Long-term vaccine efficacy	Reduction in reinfectivity	Immunity duration (day): Natural /vaccine	Total COVID-19 deaths (2020-2024)	Daily peaks of COVID-19 deaths		
						2022	2023	2024
FAa2	2 (730)	85.0%	60%	730/365	140,596	28	42	22
FAa3	3 (487)	85.0%	60%	730/365	129,991	28	0	14
FAa4	4 (365)	85.0%	60%	730/365	127,550	28	0	0
FAa5	5 (292)	85.0%	60%	730/365	126,529	22	0	0
FAa6	6 (243)	85.0%	60%	730/365	125,523	18	0	0
FAb2	2 (730)	62.5%	60%	730/365	179,155	105	89	79
FAb3	3 (487)	62.5%	60%	730/365	154,959	105	1	56
FAb4	4 (365)	62.5%	60%	730/365	143,233	104	0	0
FAb5	5 (292)	62.5%	60%	730/365	139,718	86	0	0
FAb6	6 (243)	62.5%	60%	730/365	136,348	71	0	0
FAc2	2 (730)	85.0%	60%	365/182	217,980	281	385	0
FAc3	3 (487)	85.0%	60%	365/182	169,204	196	21	14
FAc4	4 (365)	85.0%	60%	365/182	148,093	89	2	7
FAc5	5 (292)	85.0%	60%	365/182	138,246	48	1	5
FAc6	6 (243)	85.0%	60%	365/182	133,413	32	0	1
FAd2	2 (730)	62.5%	60%	365/182	276,596	528	334	8
FAd3	3 (487)	62.5%	60%	365/182	253,667	528	46	212
FAd4	4 (365)	62.5%	60%	365/182	198,684	351	2	47
FAd5	5 (292)	62.5%	60%	365/182	173,428	235	0	26
FAd6	6 (243)	62.5%	60%	365/182	162,428	156	0	30
FBa2	2 (730)	85.0%	45%	730/365	158,901	42	207	2
FBa3	3 (487)	85.0%	45%	730/365	150,943	42	23	185
FBa4	4 (365)	85.0%	45%	730/365	134,421	42	0	36
FBa5	5 (292)	85.0%	45%	730/365	130,614	34	0	0
FBa6	6 (243)	85.0%	45%	730/365	129,085	24	0	0

FBb2	2 (730)	62.5%	45%	730/365	230,119	209	181	175
FBb3	3 (487)	62.5%	45%	730/365	210,446	209	32	426
FBb4	4 (365)	62.5%	45%	730/365	179,002	209	0	224
FBb5	5 (292)	62.5%	45%	730/365	158,367	172	0	53
FBb6	6 (243)	62.5%	45%	730/365	150,833	148	0	10
FBc2	2 (730)	85.0%	45%	365/182	275,028	479	565	14
FBc3	3 (487)	85.0%	45%	365/182	231,322	377	87	231
FBc4	4 (365)	85.0%	45%	365/182	194,661	151	55	168
FBc5	5 (292)	85.0%	45%	365/182	170,881	80	49	102
FBc6	6 (243)	85.0%	45%	365/182	158,864	50	24	80
FBd2	2 (730)	62.5%	45%	365/182	400,280	867	1052	73
FBd3	3 (487)	62.5%	45%	365/182	397,725	867	507	522
FBd4	4 (365)	62.5%	45%	365/182	350,016	615	537	886
FBd5	5 (292)	62.5%	45%	365/182	278,879	390	314	540
FBd6	6 (243)	62.5%	45%	365/182	255,266	282	238	470

FCa2	2 (730)	85.0%	30%	730/365	187,710	64	461	0
FCa3	3 (487)	85.0%	30%	730/365	181,301	64	286	455
FCa4	4 (365)	85.0%	30%	730/365	152,926	64	4	131
FCa5	5 (292)	85.0%	30%	730/365	144,263	48	0	58
FCa6	6 (243)	85.0%	30%	730/365	135,771	38	0	50
FCb2	2 (730)	62.5%	30%	730/365	289,900	366	251	349
FCb3	3 (487)	62.5%	30%	730/365	283,517	366	215	1173
FCb4	4 (365)	62.5%	30%	730/365	233,075	366	3	384
FCb5	5 (292)	62.5%	30%	730/365	215,885	318	0	228
FCb6	6 (243)	62.5%	30%	730/365	196,552	275	0	368
FCc2	2 (730)	85.0%	30%	365/182	460,413	743	764	1973
FCc3	3 (487)	85.0%	30%	365/182	306,941	564	488	550
FCc4	4 (365)	85.0%	30%	365/182	229,664	208	145	96
FCc5	5 (292)	85.0%	30%	365/182	207,684	106	189	130
FCc6	6 (243)	85.0%	30%	365/182	181,143	65	159	88
FCd2	2 (730)	62.5%	30%	365/182	674,854	1095	2328	5638
FCd3	3 (487)	62.5%	30%	365/182	548,250	1019	737	613
FCd4	4 (365)	62.5%	30%	365/182	430,219	888	616	1362
FCd5	5 (292)	62.5%	30%	365/182	336,705	543	527	255
FCd6	6 (243)	62.5%	30%	365/182	306,706	428	506	659

Supplementary table: 3

Projected total and daily peaks of COVID-19 deaths by the end of 2024 in England under different scenarios of uptake rate of vaccination in younger adults

Assumptions and notes:

Initial overall vaccine efficacy: 62.5% after dose-1 and 85% after dose-2.

The overall vaccine efficacy is equally attributable to the infection and disease protection.

Reinfectivity is reduced by 45%.

Scenario	Uptake rate	Vaccination waves (interval days)	Long-term vaccine efficacy	Immunity duration (day): Natural /vaccine	Total COVID-19 deaths (2020-2024)	Daily peaks of COVID-19 deaths		
						2022	2023	2024
Higher coverage in younger adults: age 16-29: 80%; age 30-39: 85%; age 40-49%: 90; age 50+: 90%								
A2b1y	0.80-0.90	1	85.0%	730/365	269147	33	544	328
A2b2y	0.80-0.90	2 (365)	85.0%	730/365	203065	33	5	646
A2b3y	0.80-0.90	3 (365)	85.0%	730/365	149709	33	0	516
A2b4y	0.80-0.90	4 (365)	85.0%	730/365	131794	33	0	23
A2c1y	0.80-0.90	1	85.0%	365/182	374300	652	681	597
A2c2y	0.80-0.90	2 (365)	85.0%	365/182	253530	114	454	438
A2c3y	0.80-0.90	3 (365)	85.0%	365/182	214420	114	41	215
A2c4y	0.80-0.90	4 (365)	85.0%	365/182	182710	114	41	82
B2b1y	0.80-0.90	1	62.5%	730/365	380068	171	852	787
B2b2y	0.80-0.90	2 (365)	62.5%	730/365	294212	171	17	1339
B2b3y	0.80-0.90	3 (365)	62.5%	730/365	230951	171	0	813
B2b4y	0.80-0.90	4 (365)	62.5%	730/365	175249	171	0	187
B2c1y	0.80-0.90	1	62.5%	365/182	618489	764	1506	1842
B2c2y	0.80-0.90	2 (365)	62.5%	365/182	425932	515	1578	875
B2c3y	0.80-0.90	3 (365)	62.5%	365/182	356424	515	465	877
B2c4y	0.80-0.90	4 (365)	62.5%	365/182	331865	515	465	695
Moderate coverage in younger adults: age 16-29: 75%; age 30-39: 80%; age 40-49: 85%; age 50+: 90%								
A2b1	0.75-0.90	1	85.0%	730/365	265799	42	627	243
A2b2	0.75-0.90	2 (365)	85.0%	730/365	206600	42	9	731
A2b3	0.75-0.90	3 (365)	85.0%	730/365	159912	42	0	582
A2b4	0.75-0.90	4 (365)	85.0%	730/365	134421	42	0	36
A2c1	0.75-0.90	1	85.0%	365/182	373907	479	588	435
A2c2	0.75-0.90	2 (365)	85.0%	365/182	266690	151	675	628

A2c3	0.75-0.90	3 (365)	85.0%	365/182	222944	151	55	363
A2c4	0.75-0.90	4 (365)	85.0%	365/182	194661	151	55	168
B2b1	0.75-0.90	1	62.5%	730/365	383433	209	916	801
B2b2	0.75-0.90	2 (365)	62.5%	730/365	304138	209	13	1301
B2b3	0.75-0.90	3 (365)	62.5%	730/365	236662	209	0	952
B2b4	0.75-0.90	4 (365)	62.5%	730/365	179002	209	0	224
B2c1	0.75-0.90	1	62.5%	365/182	611929	867	1542	2437
B2c2	0.75-0.90	2 (365)	62.5%	365/182	443176	615	1860	1096
B2c3	0.75-0.90	3 (365)	62.5%	365/182	376242	615	537	1092
B2c4	0.75-0.90	4 (365)	62.5%	365/182	350016	615	537	886

Lower vaccination coverage in younger adults: age 16-29: 60%; age 30-39: 70%; age 40-49: 80%; age 50+: 90%

A2b1x	0.60-0.90	1	85.0%	730/365	266219	67	638	209
A2b2x	0.60-0.90	2 (365)	85.0%	730/365	214159	67	14	761
A2b3x	0.60-0.90	3 (365)	85.0%	730/365	171971	67	0	562
A2b4x	0.60-0.90	4 (365)	85.0%	730/365	140179	67	0	46
A2c1x	0.60-0.90	1	85.0%	365/182	379362	477	550	353
A2c2x	0.60-0.90	2 (365)	85.0%	365/182	290730	243	1064	1066
A2c3x	0.60-0.90	3 (365)	85.0%	365/182	243384	243	46	548
A2c4x	0.60-0.90	4 (365)	85.0%	365/182	209857	243	46	255
B2b1x	0.60-0.90	1	62.5%	730/365	398443	306	1376	1052
B2b2x	0.60-0.90	2 (365)	62.5%	730/365	333844	306	3	1150
B2b3x	0.60-0.90	3 (365)	62.5%	730/365	237005	306	0	1250
B2b4x	0.60-0.90	4 (365)	62.5%	730/365	185126	306	0	240
B2c1x	0.60-0.90	1	62.5%	365/182	520700	977	1747	1732
B2c2x	0.60-0.90	2 (365)	62.5%	365/182	470214	814	2238	1526
B2c3x	0.60-0.90	3 (365)	62.5%	365/182	406564	814	563	1408
B2c4x	0.60-0.90	4 (365)	62.5%	365/182	377531	814	563	1140

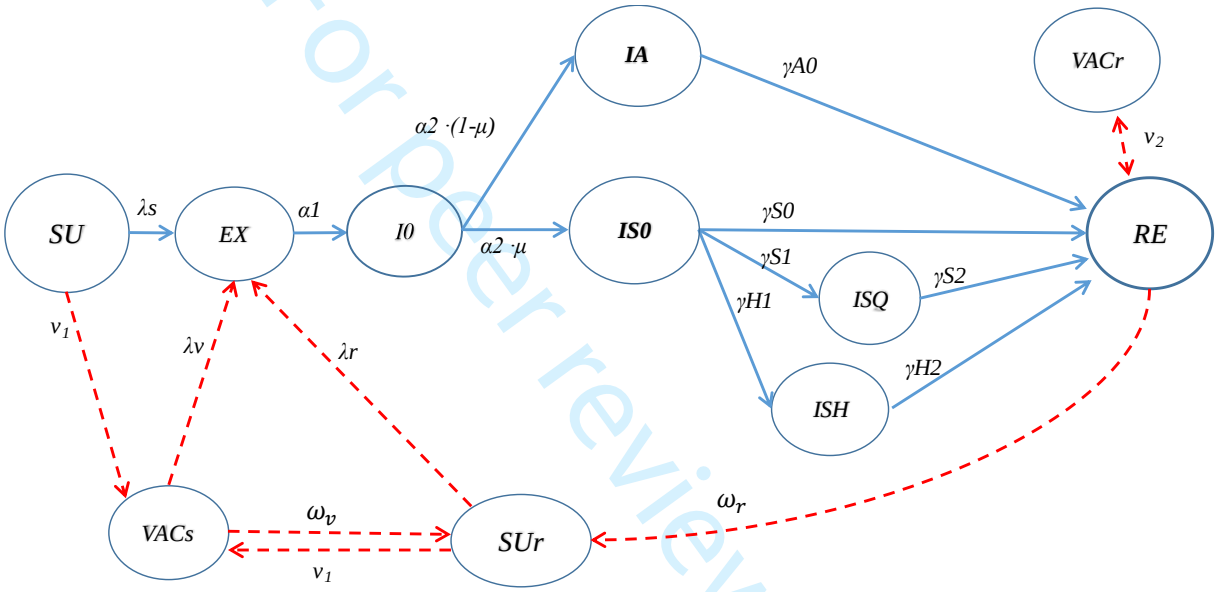
Supplementary files for:

Vaccination against COVID-19 and society's return to normality in England: a modelling investigation of different types of naturally acquired and vaccine induced immunity

1. Model structure and status

This is a discrete-time population dynamic simulation model. Population in England are partitioned into discrete categories by sex (male or female), age (0-4, 5-9, then by 10 year age bands, and 80+), and Covid-19 infection categories. The main infection categories include: susceptible (SU), exposed (EX), infected (IN), and recovered (RE) (appendix figure 1). The infected individuals are further categorised as asymptomatic, symptomatic, self-isolated, and hospitalised.

Appendix figure 1: Model structure and transmission across status



Definitions of compartmental variables in appendix figure 1

- SU: susceptible individuals
- SUr: Individuals susceptible to reinfection after immunity waning
- EX: exposed individuals, not infectious
- I0: infectious, before symptom onset
- IA: infectious individuals with no or very mild symptoms
- IS0: symptomatic patients who are not quarantined
- ISQ: symptomatic patients self-isolated
- ISH: symptomatic patients who are hospitalised
- RE: recovered from covid-19 infection
- VACs: vaccinated susceptible individuals
- VACr: vaccinated individuals who recovered from infection

Transition parameters in appendix figure 1:

- λ_s: Force of infection (λ) measures the risk (probability) of infection transmission.
- $\alpha 1$: rate of progressing from being exposed to being infectious.

- $\alpha 2$: rate of progressing from being asymptomatic infectious to symptomatic.
- μ: proportion of infected individuals who will be symptomatic; age-specific
- $\gamma A0$: rate of recovering for asymptomatic individuals
- $\gamma S0$ rate of recovering for symptomatic, not isolated/hospitalised patients
- $\gamma S1$: rate of being isolated in symptomatic patients
- $\gamma S2$: rate of recovering in isolated patients
- $\gamma H1$: rate of being hospitalised for symptomatic patients
- $\gamma H2$: rate of recovering in hospitalised patients
- ν_1: rate of vaccinating susceptible individuals
- ν_2: rate of vaccinating recovered individuals
- ω_v: rate of immunity waning in vaccinated individuals
- ω_r: rate of immunity waning in recovered individuals

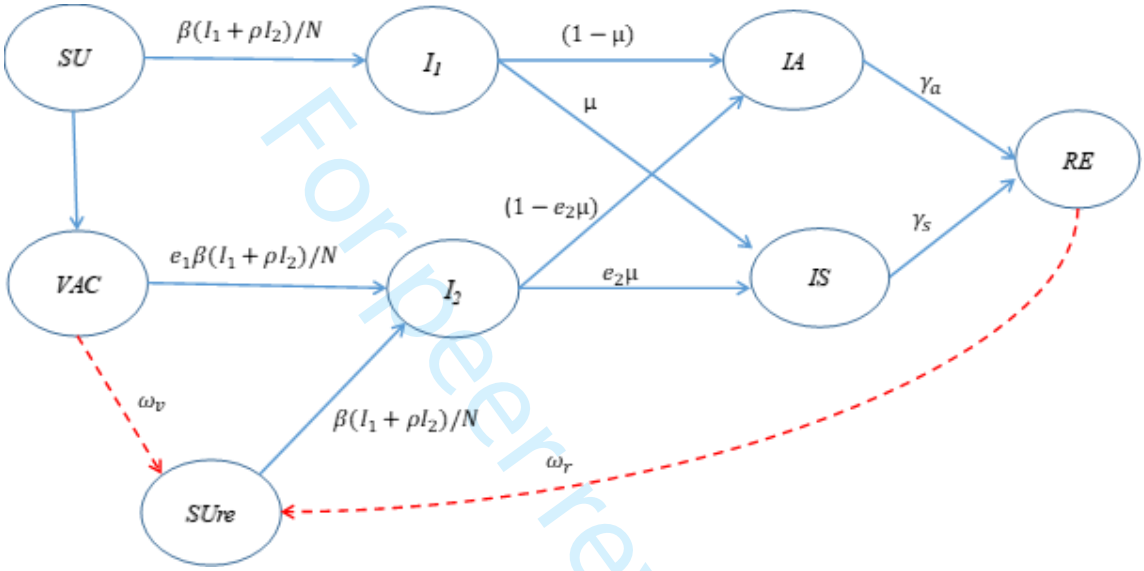
All individuals in England are assumed to be susceptible to SARS-CoV-2 infection at the beginning of 2020. Susceptible individuals may be infected by contacting infectious individuals, and the infection status is changed from "susceptible" (SU) to "exposed" (EX). The exposed individuals are not infectious during the early incubation period, but start to be infectious before the onset of symptoms. Individuals infected with SARS-CoV-2 virus may have no or very mild symptoms (IA), and palpable symptoms (symptomatic or clinical infections). Asymptomatic individuals can spread SARS-CoV-2 virus before recovery, although the transmission risk may be lower than symptomatic patients. Symptomatic patients are further classified into three categories: symptomatic patients who are neither isolated nor hospitalised (IS0), those who self-isolate at home (ISQ), and those who are hospitalised (including those being admitted to intensive care units) (ISH). Symptomatic patients are infectious and can transmit the virus to susceptible people before being isolated, hospitalised or recovered. We assume that hospitalised patients (ISH) are well isolated and no longer able to spread the virus to the susceptible population, although infectious patients who are self-isolated at home (ISQ) may transmit virus to household contacts.

Individuals may recover from previous infection of SARS-CoV-2 (RE), and the susceptible and recovered individuals may be vaccinated with vaccines again SARS-CoV-2 virus (VAC1 and VAC2). Individuals recovered or effectively vaccinated may develop immune responses against infection with SARS-CoV-2. However, if the protective immunity is not long lasting, individuals who have recovered or vaccinated may become susceptible again after the waning of the immunity (SUr).

The immune response against COVID-19, either by naturally acquired from past SARSE-CoV-2 infection or vaccine-induced, may be long lasting or short-lived. Immune response may reduce susceptibility of individuals to infection (infection protection, or sterilising, immunity), reduce disease severity after being infected (disease reduction immunity), and reduce infectivity of those who are reinfected after recovery or being vaccinated (reinfectivity reduction immunity).[1] According to existing

evidence on immunological characteristics for other human coronaviruses, immunity against reinfection (sterilising immunity) may be waning in several months, while disease and reinfectivity reduction responses are likely long lasting.[1] According to these basic concepts specified by Lavine et al,[1] we incorporate the three types of immune responses into the model, to explicitly evaluate their impacts on future transmission dynamics (appendix figure 2).

Appendix figure 2: Types of immune responses by natural infection or vaccination



Notes to appendix figure 2:

- Appendix figure2 is a simplified version of appendix figure 1, not showing isolation and hospitalisation for symptomatic patients.
- *N*: The number of the population
- β: The transmission rate, i.e., the average number of individuals infected daily by an infectious person. It is a function of the number of daily close contacts per person (c), and the transmission risk per contact between a susceptible and an infectious individual (η): i.e., $\beta=c\cdot\eta$.
- I_1: Infectious individuals with primary infection
- I_2: Infectious individuals with secondary infection (infected after being vaccinated or recovered)
- ρ: Relative infectivity of the secondary infection (I_2) compared with the primary infection (I_1). For example, if ρ=0.6, the infectivity of I_2 is 40% lower than the infectivity of I_1
- μ: proportion of infected individuals who will be symptomatic; age-specific
- e_1: Relative efficacy of vaccine for sterilising immunity, reducing risk of virus transmission
- e_2: Relative efficacy of vaccine for pathology reduction, reducing the proportion of symptomatic cases after being infected
- *IA*: Asymptomatic individuals
- *IS*: Symptomatic patients
- γ_a : Average rate of recovering of asymptomatic individuals
- γ_s : Average rate of recovering of asymptomatic individuals

- ω_v: rate of immunity waning in vaccinated individuals
- ω_r: rate of immunity waning in recovered individuals

Overall and partial vaccine efficacy

Results of randomised controlled trials shown that vaccines may be >90% efficacious (e.g., Pfizer mRNA vaccine) in reducing severe symptomatic diseases, compared with the placebo group.[2] In appendix figure 2, e_1 and e_2 are parameters of vaccine's efficacy in blocking virus transmission and reducing symptomatic cases in the infected, respectively. The reduction in symptomatic cases in the vaccine group may be due to the prevention of infection in susceptible individuals (related to e_1), or a lower proportion of infected individuals being symptomatic in the vaccine group (related to e_2), or due to a combination of both (note: e_1 and $e_2 \geq 1$ - overall VE, and ≤ 1). Let λ is the transmission risk and μ is the proportion of symptomatic cases in the infected without vaccination. After being vaccinated, the transmission risk is reduced to $\lambda \cdot e_1$, and the proportion of symptomatic cases reduced to $\mu \cdot e_2$. For a vaccine with 90% efficacy in reducing the number of symptomatic cases (compared with the control group), it should be true that $e_1 \cdot e_2 = (1-0.90)$, or $e_1 = 0.10 / e_2$. There are many different possible combinations of e_1 and e_2 for a given overall efficacy in reducing symptomatic cases. For example, $e_1 = e_2 = SQRT(0.30) = 0.548$ corresponds to a 70% efficacy of vaccine with equal sterilising immunity and pathology reduction. If e_1=1 (i.e., zero efficacy in sterilising immunity), all vaccine efficacy will be attributable to the pathology reduction, with e_2=0.30, for a vaccine with 70% efficacy. The partial efficacy is calculated using: $Ei = 1 - (1 - Eo)/Ed$, where Ei is the partial efficacy for infection protection, Ed is the partial efficacy for disease reduction, and Eo is the overall vaccine efficacy. The equal partial efficacy is calculated by: $Ei = Ed = 1 - \sqrt{(1 - Eo)}$. For vaccines with 90%, 70% and 50% overall efficacy, the equal partial efficacy for the infection protection and disease reduction is 69.4%, 45.2%, and 29.3%, respectively.

2. Parameterisation, data sources, and simulation scenarios

2.1 Transition parameters and distribution of infectious period

In appendix figure 1, force of infection (λ) measures the risk of infection,[3] which is a function of transmission rate (η) and the prevalence of existing infectious individuals (I) among the population (N): $\lambda=\eta \cdot I/N$. The transmission rate η in the discrete-time model can be defined as the average number of new infected individuals generated daily by an infected person. That is, $\eta=Rt/T$, in which Rt is effective reproduction number and T is the average infectious period for infected individuals. We calculated η as a function of the number of daily contacts per person (c), and the risk of transmission per contact between a susceptible and an infected individual (β): η=c*β.[4]

The transition rate between model's compartments in infectious models is often assumed to be constant, calculated by 1/x, in which "x" is the average period that subjects remain before the transition to the model's next compartments.[3] Therefore, the infectious period in standard SIR or SEIR models is usually assumed to be exponentially distributed, with some limitations of the use of exponentially distributed infectious period.[5 6] In this study, we assumed that the transition probability between model's compartments are based on gamma distributed periods that individuals remain in a compartment.[7] The transition probability (y) at t is: $y_t = (cg_t - cg_{t-1})/(1 - cg_t)$, where cg_t is the gamma cumulative probability by the end of t. Given mean and shape (k) parameters, the gamma distribution based transition probability is used as a deterministic value to estimate the number of individuals moving between two status in this study.

2.2 Parameterisation and data sources

We estimated initial parameters based on relevant literature and data from the UK government websites (appendix table 1). Key parameters were calibrated according to the reported numbers of covid-19 deaths, hospitalised patients, and the prevalence of infected individuals in England from January 2020 to June 2021.[8]

Appendix table 1: Summary of key model parameters and data sources

Parameter	Value			Source
Proportion of asymptomatic cases in infected individuals (%)				
Age: 0-9	0.71			Davis et al. [9]
10-19	0.79			
20-29	0.73			
30-39	0.67			
40-49	0.60			
50-59	0.51			
60-69	0.37			
70+	0.31			
Proportion of self-isolated symptomatic cases who are not hospitalised				
Age:	**0-49**	**50-69**	**70+**	Assumed by authors, and calibrated according to reported COVID-19 deaths.
Before 13/03/2021	0.10	0.10	0.10	
13/03-23/03/2020	0.40	0.60	0.80	
After 24/03/2020	0.80-0.90	0.80-0.95	0.90-0.95	
Estimated values of gamma distributed parameters (mean, shape k)				
	Before 12/03/20	**13/03-23/03/20**	**After 23/03/20**	
Duration from exposed to being preclinical infectious (day)	4.0 (4)	4.0 (4)	4.0 (4)	Zhang et al. [10] Davies et al. [7] Ferguson et al. [11]
Duration of preclinical infectious (day)	1.5 (2)	1.5 (2)	1.5 (2)	
Infectious period before recovery (day)	5.0 (5)	5.0 (5)	5.0 (5)	
Infectious period before being isolated (day)	4.0 (4)	3.0 (3)	2.0 (2)	
Infectious period during isolation at home (day)	2.0 (2)	3.0 (3)	4.0 (4)	
Infectious period before being hospitalised (day)	4.0 (4)	3.0 (3)	2.0 (2)	
Duration of hospitalisation (day)	10.0 (10)	10.0 (10)	10.0 (10)	
Delay from being infected to deaths from Covid-19 (day)	23.0 (23)	23.0 (23)	23.0 (23)	Verity et al. [12]
Case fatality rates (%)				
Age: 0-9	0.0026			Verity et al. [12]; Chinese CDC [13]
10-19	0.0148			
20-29	0.0600			
30-39	0.1460			
40-49	0.2950			
50-59	1.2500			
60-69	3.9900			
70-79	8.6100			
80+	13.400			
Transmission risk by asymptomatic individuals	21% of the transmission risk by symptomatic cases			Li et al.[14]
Age specific rates of hospitalisation among infected individuals				
0-9	0.010%			Verity et al. [12]
10-19	0.041%			

20-29	1.04%	
30-39	3.43%	
40-49	4.25%	
50-59	8.16%	
60-69	11.8%	
70-79	16.6%	
80+	18.4%	

We obtained population statistics in England (estimates of mid-year 2020) from Office for National Statistics. It was assumed that all individuals in England were susceptible to SARS-CoV-2 infection at the beginning of 2020. By contacting with infectious individuals, susceptible individuals may be infected, and their infection category is changed from "susceptible" (SU) to "exposed" (EX). "Exposed" refers to the pre-infectious status of infected individuals. According to data from previous studies, the period of incubation before symptom onset was on average 5.5 days,[10] and the exposed individuals start to be infectious about 1.5 days before the onset of symptoms.[7 11] Therefore, we assumed a gamma distribution of incubation period, with a mean non-infectious period of 4 days (k=4.0) after being exposed, and a mean infectious period of 1.5 days (k=2) before symptom onset.

Individuals infected with SARS-CoV-2 virus may have no or very mild symptoms (asymptomatic infected), and palpable symptoms (symptomatic patients). As in previous modelling studies [7 11], it was assumed that asymptomatic individuals can spread SARS-CoV-2 virus before recovery, although the infectious risk was assumed to be 21% of symptomatic patients.[14] We used age-specific rates of asymptomatic cases in the infected individuals, reported in a study based on data from 6 countries[9] (appendix table 1).

Symptomatic patients are further classified into three categories: symptomatic patients who are neither isolated nor hospitalised (mainly at the initial phase of the epidemic), those who are self-isolated at home, those who are hospitalised (see appendix figure 1). We assume that asymptomatic individuals were not isolated, although the average number of daily contacts could be reduced by non-pharmaceutical interventions (NPIs), including social distancing, testing, contact tracing, and lockdown. Assumed proportions of self-isolation of symptomatic cases who are not hospitalised, depending on age and NPI measures are shown in appendix table 1.

We assume that only symptomatic patients are hospitalised, and age specific rates of hospitalisation among symptomatic individuals were from Verity et al.[12] The hospitalisation rates were calibrated according to reported numbers of hospitalised patients with covid-19 in England.[15] Based on the reported number of hospitalised patients and estimated number of symptomatic cases, the hospitalisation rate was estimated to be 70% lower than the estimated by Verity et al.[12] Symptomatic patients are infectious and can transmit the virus to susceptible people before being hospitalised or isolated. We assume that hospitalised patients are no longer able to spread the virus to susceptible individuals in the community. However, infected individuals who are self-isolated at home may transmit virus to household contacts.

The infectious period before recovery was assumed to be gamma distributed, with a mean value of 5 days. Before implementing any NPIs, the infectious period of symptomatic cases was of a mean value of 4 days (k=4) before being quarantined or hospitalised. After implementing NPI measures, the infectious period for isolated and hospitalised patients was reduced, having a mean value of 2 days (k=2). The mean hospital stay was assumed to be 10 days (k=10) (including ICU admitted patients) (appendix table 1). Verity et al estimated that the average duration from symptom onset to death was 17.8 days.[12] Therefore, we assume that covid-19 related deaths occur on average 23 days (k=23) after being exposed/infected.

The simulation starts from 1 January 2020, over a period of five years until the end of 2024. We assume that the first exposed case was imported to England on January 15th 2020, and the daily number of infectious cases imported was increased by one until 9 February 2020, with a total number of 351 cases imported in 25 days. The sex-and-age-specific numbers of household and community daily contacts per person in the UK were obtained from a study in 8 European countries.[16 17] For the purpose of simplicity, we considered only household contacts (relevant to self-isolation at home) and general daily contacts (for all types of contacts). The risk of positive transmission per contact between susceptible and infectious individuals (β) was estimated by calibrating estimated and reported numbers of covid-19 deaths in England, household and general daily contacts per person, and other model parameters.

In this study, all COVID-19 related deaths are assumed to be from symptomatic cases, and age specific case fatality rates were based on a study by Verity et al.[12] We assume that individuals infected with Covid-19 will not die from other causes before recovery. Average sex and age specific rates of all-cause deaths in England during 2015-2019 [18] were applied to people who are not infected with or recovered from covid-19. For simplicity and maintaining a stable population, we assumed that the number of births at day t equals to the number of all deaths at day t-1. Furthermore, we did not consider the influence of migration on the population. We adjusted the number of individuals belong to an age group (all <80+) at the beginning of the year since 2021 by shifting 20% (for age group 0-4 and 5-9) or 10% (for age group 10-19, … 70-79) of them to the adjacent higher age group.

NPI and seasonal impacts on transmission parameters

Since March 2020, NPI measures were recommended and gradually tightened in England, including hand washing, mouth covering when coughing in public places, home isolation of individuals with COVID-19 like symptoms, shielding of vulnerable individuals, avoiding non-essential contacts, and maintaining social distancing. These measures reduced contacts and transmission risk, and shortened the period of transmission by symptomatic individuals. We assumed that the general population's contact rates were reduced by 10% to 40%, depending on age and co-morbidity (appendix table 2). Based on the reported number of COVID-19 deaths, we estimate that the transmission risk per contact between infectious and susceptible individuals was reduced from β=0.094 before the implementation of any NPIs to 0.069 by 15 March 2020 and 0.062 since May 2020. The UK government put lockdown

measures in place from 24 March 2020, including working from home if possible, closure of schools and non-essential shops, pubs and restaurants, avoiding non-essential travelling, and cancelling gathering activities. We assume that numbers of general population contacts were reduced by 60-85% (appendix table 2). We assume that the household contacts were not influenced by the NPI measures.

Appendix table 2: Assumed impacts of NPIs on general contacts in England. Notes: Values are scaling fractions to reduce the normal contacts. For example, a fraction of 0.80 means the contacts are reduced by 20%.

Time	Age group			
	0-19	**20-59**	**60-69**	**70+**
Before 13/3/2020	1.00	1.00	1.00	1.00
13/03/2020-	0.90	0.80	0.70	0.60
17/03/2020-	0.80	0.70	0.60	0.50
24/03/2020-	0.40	0.30	0.20	0.15
05/07/2020-	0.60	0.55	0.40	0.20
01/09/2020-	0.80	0.60	0.50	0.30
05/11/2020-	0.60	0.30	0.20	0.15
02/12/2020-	0.70	0.60	0.50	0.30
05/01/2021-	0.40	0.30	0.20	0.15
08/03/2021-	0.80	0.60	0.50	0.30
01/05/2021	0.90	0.80	0.70	0.60
19/07/2021-	1.00	1.00	1.00	1.00

The lockdown measures in England started to be relaxed from 13 May 2020 by allowing partial returning to work. Further relaxing of control measures followed, including reopening of some shops and allowing outdoor meetings up to six people from 1 June, re-opening of more non-essential shops from 5 June, and further relaxing of restrictions (such as re-opening of pubs and restaurants) from 5 July 2020. However, social distancing measures was maintained and face covering was required where social distancing could not be implemented. From 1 September 2020, schools in England were re-opening. Consequently, the transmission risk per contact between susceptible and infectious individuals was increased since September. The impacts of these changes in NPIs were reflected in the assumed social contacts and transmission risk. Because of the new virus variants,[19] the average transmission risk per contact was increased β=0.077 since October 2020, and β=0.081 since June 2021.

To incorporate the impact of seasonality on future projections, we assumed that the transmission risk is increased by 10% in September, October, March and April, and increased by 20% in November, December, January and February.

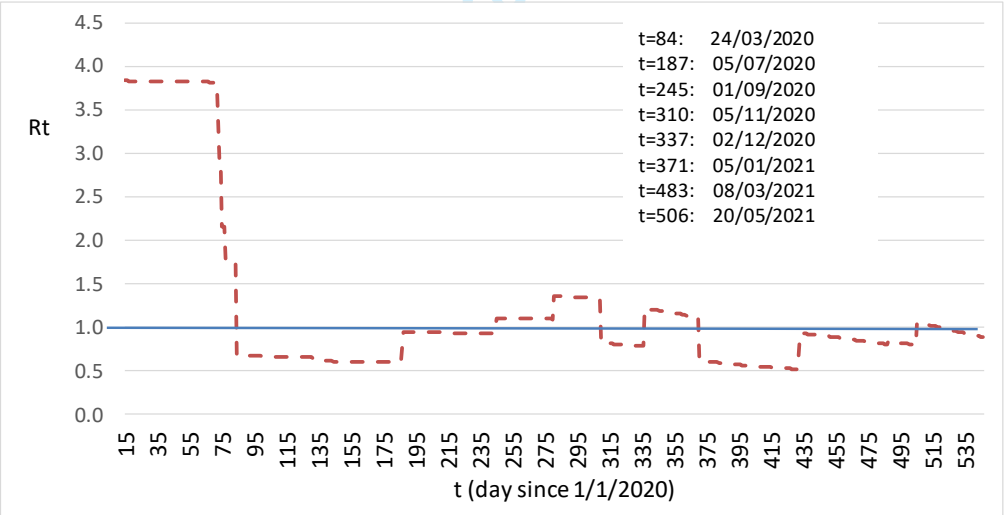
Model verification

We used the developed model and initially estimated parameters to simulate the covid-19 epidemic in England from January 2020 to June 2021. Key parameters were calibrated based mainly on reported

covid-19 related deaths, although numbers of hospitalised patients and infection rates in England were also considered.

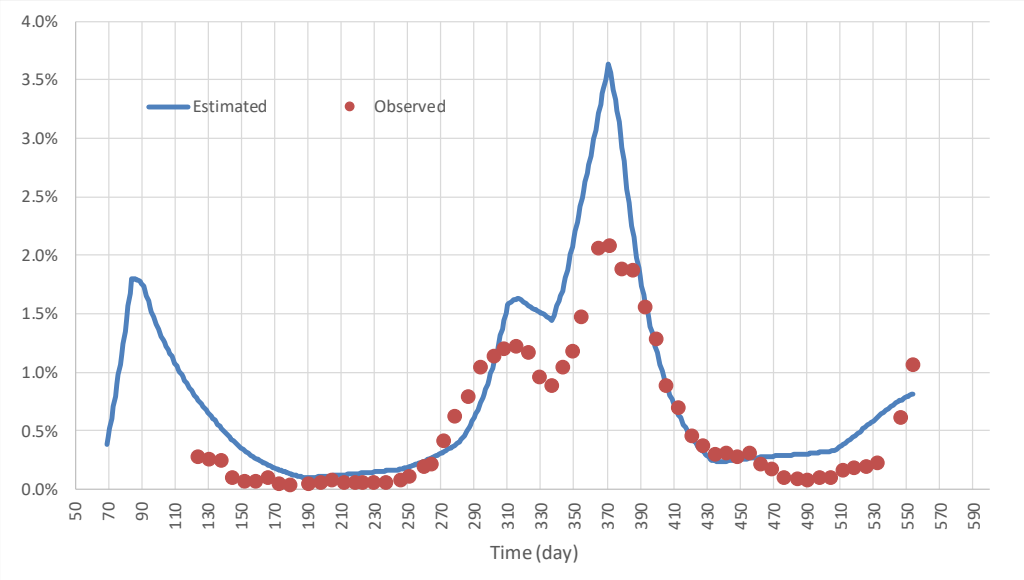
We assume that the first exposed case was imported to England on 15 January 2020, and the number of cases imported each day increased by one more case than the previous day until 9 February 2020 (the total number of cases imported in 25 days was therefore 351). We don't use the reproduction number (R0 or Rt) as an input parameter, but derived the reproduction numbers based on a method used by Giordano and colleagues (see equation 55 in Mathematical equations) [3 20]. We estimated that the basic reproduction number (R0) was 3.63 at the initial stage of the COVID-19 epidemic before any control measures were taken in England, which is similar to findings from previous studies.[7 11] Following the implementation of NPI measures, the estimated reproduction value (Rt) was reduced to 0.65 by 24 March. The Rt value was increased to 0.93 by 5 July 2020 after the NPI measures were relaxed, and Rt was about 1.09 after school reopening in September and 1.31 by October 2020. The Rt was reduced to 0.79 since 5 November 2020 after reintroducing NPI measures, increased to about 1.17 after relaxing NPIs since 2 December 2020, and reduced again to about 0.57 since 5 January 2021 after reintroducing lockdown measures (plus rolling out of vaccination) (appendix figure 3). The estimated R values were within the range of the reported in England (https://coronavirus.data.gov.uk/).

Appendix figure 3: Estimated reproduction numbers, between 01/2020 – 06/2021, in England



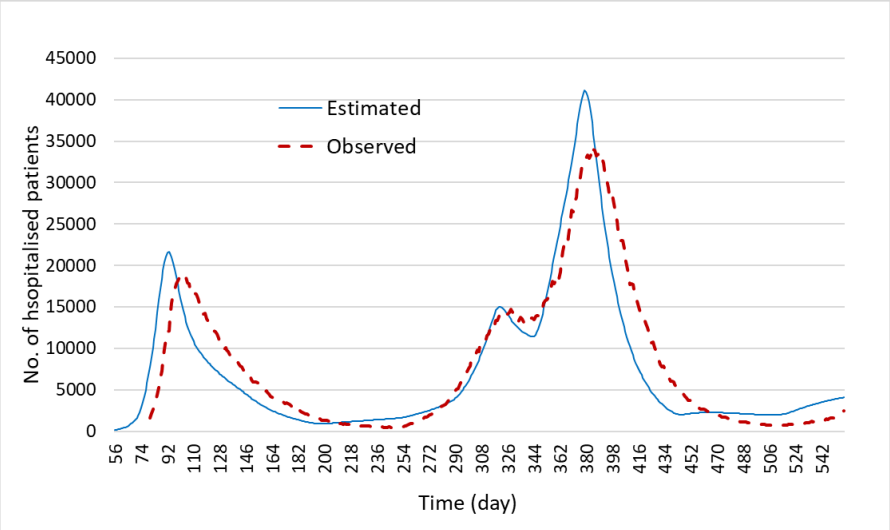
The model estimated that the prevalence of the recovered was 5.5 by 26 April, 7.6% by 24 May, and 8.5% by 24 June 2020, which were similar to the estimated rates of positive antibodies to Covid-19 in the UK (i.e., 7.1% in May-June 2020).[21] Data on the prevalence of infected individuals in the community was available from May 2020. The model estimated prevalence of infected individuals from January 2020 to January 2021, which had a similar trend as the reported prevalence in England (appendix figure 4).

Appendix figure 4: Estimated and reported prevalence of infection, from January 2020 to June 2021, in England



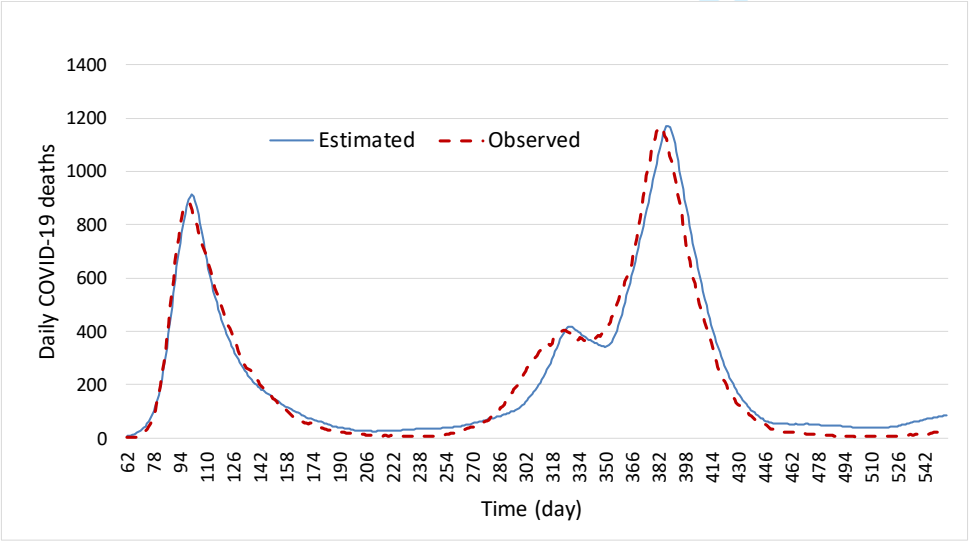
Changes in the estimated numbers of hospitalised COVID-19 patients were of similar trends as the reported numbers of hospitalised patients during 01/2020-01/2021. However, there were considerable differences at peak time points (appendix figure 5), which may be explained by reduced hospitalisation rates during peak period.

Appendix figure 5: Reported and estimated numbers of hospitalised Covid-19 patients, during 01/2020-01/2021, in England



Appendix figure 6 shows that the estimated daily deaths well matched the observed daily deaths from Covid-19, from January 2020 to June 2021, in England.

Appendix figure 6: Reported and estimated daily deaths from Covid-19, during 01/2020-06/2021, in England



3. Vaccination and projection scenarios

We used estimates of transmission parameters, age-specific hospitalisation rates and case fatality rates in June 2021 to project COVID-19 deaths from 2021 to 2024, under various scenarios of vaccine efficacy, durability of both naturally acquired and vaccine induced immunity, and reduction in reinfectivity. There are no more restrictions on social activities since 19 July 2021 in England, and social contacts are return to normal as before the pandemic, but basic hygienic measures would be maintained.

The UK Government's Vaccination Taskforce has recommended rollout of vaccines against COVID-19 to be prioritised primarily by age and comorbidity, with older people being vaccinated first.[22] The Joint Committee on Vaccination and Immunisation (JCVI) in the UK previously recommended COVID-19 vaccination of individuals aged ≥18, and also recommended vaccination of young people aged 16-17 years old on 4 August 2021.[23] Vaccination of prioritised individuals began from 8 December 2020 in the UK and around 2 million individuals were vaccinated (mostly with a single dose of Pfizer vaccine) by 10 January 2021.[24] By July 2021, the coverage of individuals who were fully vaccinated (with two does) was >90% in adults aged ≥65, 80-90% in those aged 50-64, 60% in adults aged 40-49.[25] For young adults aged 18-39, about 36% have received the first dose of vaccines by July 2021. Therefore, the vaccination coverage in England has been high in older adults, but it remains uncertain whether such high coverage could be achieved in younger adults. In this study, the mass vaccination is modelled as an age-based phase approach, starting from people aged ≥70, followed by individuals aged 60-69, 50-59, 30-49, and then those aged 16-29. We assume that the mass vaccination starts from 1 January 2021, and the maximum number of individuals vaccinated per day is 180,000 in England, to matched with numbers of vaccinated individuals according to the official statistics. In the main analysis, we assume that the uptake rate is 75%, 80%, 85% and 90%, respectively, in adults aged 16-29, 30-39, 40-49, and ≥50 years old. Because of uncertain coverage of vaccination in younger people, we conducted sensitivity analyses under scenarios with lower (60%, 70%, and 80%) and higher (80%, 85%, and 90%) coverage of vaccination in people aged 16-29, 30-39, and 40-49 years old, respectively.

Results of randomised controlled trials shown that vaccines may be >90% efficacious (e.g., Pfizer mRNA vaccine) in reducing severe symptomatic diseases, compared with the placebo group. Assume that e_1 and e_2 are parameters of vaccine's efficacy in blocking virus transmission and reducing symptomatic cases in the infected, respectively (as in appendix figure 2). The reduction in symptomatic cases in the vaccine group may be due to the prevention of infection in susceptible individuals (i.e., infection protection, related to e_1), or a lower proportion of infected individuals being symptomatic in the vaccine group (i.e., disease reduction, related to e_2), or due to a combination of both. For a vaccine with 90% efficacy in reducing the number of symptomatic cases (compared with the control group), it is true that $e_1 \cdot e_2 = (1-0.90)$, or $e_1 = (1-0.90)/e_2$ (note: e_1 and e_2 ≥1-overall VE, ≤1). There are many different possible combinations of e_1 and e_2 for an overall efficacy in reducing symptomatic cases. We assume that vaccine efficacy is equally attributable to infection and disease reduction in the main

projections. The infection protection (sterilising immunity) after vaccination has been demonstrated. For example, an observational study in the UK (SIREN) found that the risk of being infected was reduced by 70% in health workers after a single dose of the Pfizer-BioNTech vaccine.[26 27]

Both Pfizer-BioNTec and AstraZeneca vaccines are 2-dose regimens, the policy in the UK has been to initially provide the first dose to as many individuals as possible to maximise the public health impact.[28] Exploratory assessment of data from clinical trials found that the short-term vaccine efficacy from the first dose of the Pfizer-BioNTech vaccine and the AstraZeneca vaccine is about 90% and 70%, respectively.[28] Public Health England (PHE) in July 2021 estimated that the efficacy was 55-70% after the first dose, and 70-85% or 85-95% after the second dose.[25] Therefore, we assume that the overall vaccine efficacy is 62.5% after the first dose and 85% after the second dose. The protection effects start 14 days after the first dose vaccination, and the interval between the first and second dose is 9 weeks. For vaccines with 62.5% and 85.0% overall efficacy, the equal partial efficacy for the infection protection and for disease reduction is 38.8% and 61.3%, respectively. The overall vaccine efficacy after the second dose may be lower than 85.0% due to new variants of SARS-CoV-2 virus. Therefore, we evaluated two overall vaccine efficacy rates, 62.5% or 85.0%, after the second dose of vaccine.

Available evidence has indicated that the duration of sterilising (infection protection) immunity after coronavirus infection ranges from 0.5 to two years.[1] Serum neutralizing antibodies were detected in all participants at four months follow up after SAR-CoV-2 mRNA vaccination.[29] Therefore, we assume that naturally acquired sterilising immunity lasts for 365 or 730 days, and vaccine-induced sterilising immunity lasts for 182 or 365 days. After waning of sterilising immunity, individuals may be susceptible again to infection with SARS-CoV-2 virus, but the disease reduction immunity is likely longer lasting.[1] Due to the existence of disease reduction immunity, the reinfectivity of individuals who are reinfected after waning of sterilising immunity may be reduced. Lavine and colleagues estimated that the secondary transmissibility (i.e., reinfectivity) was 35% of the primary transmissibility (i.e., the reinfectivity was reduced by 65%).[1] Evidence from clinical trials and vaccination in the real world indicated that the viral loads and the duration of virus shedding in the infected individuals after vaccination were considerably reduced, compared with unvaccinated individuals.[30 31] Based on preliminary data, PHE estimated that the reinfectivity was reduced by 35-50% after the first dose of vaccines.[25] The reduction in reinfectivity is likely to be larger after the second dose of vaccines. More recent studies reported that fully vaccinated individuals who were infected were up to 78% less likely to transmit the virus to unvaccinated individuals.[32] Therefore, we assume a range of the risk of reinfectivity after waning of sterilising immunity; the reinfectivity is reduced by 30%, 45% or 60%. We also assume that the infectivity of ineffectively vaccinated individuals is the same as recovered individuals whose sterilising immunity has waned, and that vaccination of individuals recovered from natural infection boosts their naturally acquired immunity.

We considered different frequent scenarios of revaccination programmes. First, we evaluated a single vaccination programme and multiple (2-4) annual vaccination programmes during 2021-2024. In addition, simulation projections were conducted by revaccination programmes with different intervals, including 2-6 revaccination programme and corresponding intervals between them.

In summary, projection scenarios are defined from the following aspects: vaccine efficacy, frequency of revaccination programmes, durability of natural and vaccine induced sterilising immunity, reduction in reinfectivity after the waning of natural and vaccine-induced immunity against reinfection. The main characteristics of the simulated scenarios are available in supplementary table 1, supplementary table 2 and supplementary table 3.

In this study, we focus on deaths in people infected with COVID-19, although our model also produces estimates of changes in effective reproduction values (Rt), numbers of infected and vaccinated individuals, and hospitalised patients. We performed multiple simulations under various scenarios. For clarity, we focus on results of selected scenarios in the main text, but report more data on simulation results in supplementary tables.

4. Model's mathematical equations

Notations:

- subscript used: "s" refers to sex, 1: male, 2: female, 3: both male and female; "a" refers to age group, 1: 0-4 years, 2: 5-9 years, 3: 10-19, …, 10: ≥ 80; 11: all age groups. "t" refers to time (day).
- N: The number of the population
- λ_s: Force of infection (λ) measures the risk (probability) of infection transmission, which is a function of transmission rate (β) and the prevalence of infectious individuals (I) among the population (N): $\lambda=\beta \cdot I/N$. [3]
- β: The transmission rate β in this discrete-time model is defined as the average number of individuals infected daily by an infectious person. It is a function of the number of daily close contacts per person (c), and the transmission risk per contact between a susceptible and an infectious individual (η): i.e., $\beta=c \cdot \eta$. [4]
- α1: rate of progressing from being exposed to being infectious.
- α2: rate of progressing from being asymptomatic infectious to symptomatic.
- μ: proportion of infected individuals who will be symptomatic; age-specific
- *infA*: The fraction of infection force for infected individuals with no or mild symptoms. It was assumed that infA=0.5 in this study.
- fS0: fraction of symptomatic patients who will not be quarantined.
- fSq: fraction of symptomatic patients who will be quarantined (self-isolation).
- fSh: fraction of symptomatic patients who will be hospitalised (including ICU admission).
- γA0: rate of recovering for asymptomatic individuals
- γS0 rate of recovering for symptomatic, not isolated/hospitalised patients
- γS1: rate of being isolated in symptomatic patients
- γS2: rate of recovering in isolated patients
- γH1: rate of being hospitalised for symptomatic patients

  γ*YH2*: rate of recovering in hospitalised patients
- ν_1: rate of vaccinating susceptible individuals
- ν_2: rate of vaccinating recovered individuals
- ρ: Relative infectivity of the secondary infection (I_2) compared with the primary infection (I_1). For example, if ρ=0.6, the infectivity of I_2 is 40% lower than the infectivity of I_1
- e_1: Relative efficacy of vaccine for sterilising immunity, reducing risk of virus transmission
- e_2: Relative efficacy of vaccine for pathology reduction, reducing the proportion of symptomatic cases after being infected
- IA: Asymptomatic individuals
- IS: Symptomatic patients
- γ_a : Average rate of recovering of asymptomatic individuals
- γ_s : Average rate of recovering of asymptomatic individuals

- ω_v: rate of immunity waning in vaccinated individuals
- ω_r: rate of immunity waning in recovered individuals
- $drOth_{s,a,t}$: sex, age-specific risk of deaths from causes other than covid-19, specific by week of the year.
- $drCov_{s,a,d}$: death risk from infected individuals before recovery, specific according to days since being infected.
- ds0, dsq, and dhos are the proportion of covid-19 deaths among symptomatic patients who are not quarantined, those who are isolated, or hospitalised, respectively. 1=ds0+dsq+dhos

Sex and age specific population:

$$\boldsymbol{N_{s,a,t}} = SU_{s,a,t} + SUr_{s,a,t} + VAC1_{s,a,t} + EX1_{s,a,t} + I01_{s,a,t} + EX2_{s,a,t} + I02_{s,a,t} + IA_{s,a,t} + IS0_{s,a,t} + ISQ_{s,a,t} + ISH_{s,a,t} + RE_{s,a,m,t} \quad (1)$$

Total number of the primary infection with no symptoms (age-specific):

$$aIA1_{a,t} = \sum_s (IA1_{s,a,t} + I01_{s,a,t} \cdot (1 - \mu_a)) \quad (2)$$

Total number of the primary infections with symptoms, isolated (age-specific):

$$aISQ1_{a,t} = \sum_s (ISQ1_{s,a,,t}) \quad (3)$$

Total number of the primary infections with symptoms, not isolated (age-specific):

$$aIS01_{a,t} = \sum_{s,} (IS01_{s,a,t} + I01_{s,a,t} \cdot \mu_a) \quad (4)$$

Total number of the secondary infection with no symptoms (age-specific):

$$aIA2_{a,t} = \sum_s (IA2_{s,a,t} + I02_{s,a,t} \cdot (1 - \mu_a \cdot e_2)) \quad (5)$$

Total number of the secondary infections with symptoms, isolated (age-specific):

$$aISQ2_{a,t} = \sum_s (ISQ2_{s,a,,t}) \quad (6)$$

Total number of the secondary infections with symptoms, not isolated (age-specific):

$$aIS02_{a,t} = \sum_{s,} (IS02_{s,a,t} + I02_{s,a,t} \cdot \mu_a \cdot e_2) \quad (7)$$

Sex and age specific susceptible population:

$$\boldsymbol{SU_{s,a,t+1}} = (SU_{s,a,t} - su\mathrm{Exp}_{s,a,t} - VAC1_{s,a,t}) \cdot (1 - drOth_{s,a,t}) + NewBirth_{s,t} \quad (8)$$

Note: $drOth_{s,a,,t}$ is sex, age-specific death rates for non-covid causes, specific by week of the year.

Newly exposed/infected with SARS-CoV-2 in susceptible individuals:

$$suExp_{s,a,t} = \sum_{j=1}^{10} SU_{s,a,t} \cdot \eta_t \left(\left((Ca_{a,j,t} \cdot \frac{infA \cdot aIA1_{j,t} + aIS1_{j,t}}{N_{3,j,t}} + Cb_{a,j,t} \cdot \frac{aISQ1_{j,t}}{N_{3,j,t}}) \right) + \rho \cdot \left(Ca_{a,j,t} \cdot \frac{infA \cdot aIA2_{j,t} + aIS2_{j,t}}{N_{3,j,t}} + Cb_{a,j,t} \cdot \frac{aISQ2_{j,t}}{N_{3,j,t}} \right) \right) \quad (9)$$

Notes: $Ca_{a,j,t}$ is the average number of general contacts between people aged a and j; and $Cb_{a,j,t}$ is the average number of household contacts between people age a and j.

Newly exposed/infected in vaccinated individuals:

$$vacExp_{s,a,t} = \sum_{j=1}^{10} VAC1_{s,a,t} \cdot \eta_t \cdot e_1 \left(\left((Ca_{a,j,t} \cdot \frac{infA \cdot aIA1_{j,t} + aIS1_{j,t}}{N_{3,j,t}} + Cb_{a,j,t} \cdot \frac{aISQ1_{j,t}}{N_{3,j,t}}) \right) + \rho \cdot \left(Ca_{a,j,t} \cdot \frac{infA \cdot aIA2_{j,t} + aIS2_{j,t}}{N_{3,j,t}} + Cb_{a,j,t} \cdot \frac{aISQ2_{j,t}}{N_{3,j,t}} \right) \right) \quad (10)$$

Newly exposed/infected in the recovered or vaccinated after waning of immunity:

$$sureExp_{s,a,t} = \sum_{j=1}^{10} SUre_{s,a,t} \cdot \eta_t \left(\left((Ca_{a,j,t} \cdot \frac{infA \cdot aIA1_{j,t} + aIS1_{j,t}}{N_{3,j,t}} + Cb_{a,j,t} \cdot \frac{aISQ1_{j,t}}{N_{3,j,t}}) \right) + \rho \cdot \left(Ca_{a,j,t} \cdot \frac{infA \cdot aIA2_{j,t} + aIS2_{j,t}}{N_{3,j,t}} + Cb_{a,j,t} \cdot \frac{aISQ2_{j,t}}{N_{3,j,t}} \right) \right) \quad (11)$$

The number of the recovered or vaccinated who lose sterilising immunity (d from 1 to tt):

$$SUre_{s,a,t+1} = (SUre_{s,a,t} - sureEXP_{s,a,t}) \cdot (1 - drOth_{s,a,t}) + \sum_{d=1}^{tt} (iRE_{s,a,d,t} \cdot \omega_{r,d} + iVAC1_{s,a,d,t} \cdot \omega_{v,d}) \quad (12)$$

Notes: "*tt*" is the total number of days simulated. $\omega_{r,d}$ and $\omega_{v,d}$ are gamma distributed rate of immunity waning, respectively, a function of days since the recovery and vaccination. $iRE_{s,a,d,t}$ is the number of recovered since d days from recovery; and $eVAC1_{s,a,d,t}$ is the number of vaccinated since d days after vaccination.

The number of new (d=1) primary infections in susceptible individuals:

$$iEX1_{s,a,1,t} = suEXP_{s,a,t} \quad (13)$$

The number of new (d=1) secondary infections in recovered or vaccinated individuals:

$$iEX2_{s,a,1,t} = sureEXP_{s,a,t} + vacExp_{s,a,t} \quad (14)$$

For d=1,2,3…60 (assuming all will be dead or recovered by day 60 after being infected):

$$iEX1_{s,a,d+1,t+1} = iEX1_{s,a,d,t} \cdot (1 - \alpha 1_d) \quad (15)$$

$$iEX2_{s,a,d+1,t+1} = iEX2_{s,a,d,t} \cdot (1 - \alpha 1_d) \quad (16)$$

Assumed that covid-19 deaths were from symptomatic patients only. Overall deaths from covid-19 were calculated using the case fatality rates, and timing of covid-19 related deaths were assumed to have a gamma distribution according to days since being infected. Therefore a variable was introduced to record number of symptomatic individuals by days since being exposed/infected to calculate number of covid-19 deaths:

$$iSY_{s,a,1,t} = \mu_a\left(suExp_{s,a,t} + e_2 \cdot (surExp_{s,a,t} + vacExp_{s,a,,t})\right) \quad (17)$$

For d=1,2,3…60 (the transmission completed by day 60):

$$iSY_{s,a,d+1,t+1} = iSY_{s,a,d,t} \cdot (1 - drCov_{s,a,d}) \quad (18)$$

The number of covid-19 deaths at time t:

$$dthCov_{s,a,t} = \sum_{d=1}^{60} iSY_{s,a,d,t} \cdot drCov_{s,a,d} \quad (19)$$

The number of new (d=1) primary infections individuals before onset of symptoms:

$$iI01_{s,a,1,t+1} = \sum_{d=1}^{60} iEX1_{s,a,d,t} \cdot \alpha 1_d \quad (20)$$

The number of new (d=1) secondary infectious individuals before onset of symptoms:

$$iI02_{s,a,1,t+1} = \sum_{d=1}^{60} iEX2_{s,a,d,t} \cdot \alpha 1_d \quad (21)$$

For d=1,2,3…60 (the transmission completed by day 60):

$$iI01_{s,a,d+1,t+1} = iI01_{s,a,d,t} \cdot (1 - \alpha 2_d) \quad (22)$$

$$iI02_{s,a,d+1,t+1} = iI02_{s,a,d,t} \cdot (1 - \alpha 2_d) \quad (23)$$

The number of all infectious individuals before onset of symptoms:

$$\boldsymbol{I0_{s,a,t}} = \sum_{d=1}^{60} iI0_{s,a,d,t} \quad (24)$$

The number of new (d=1) infected individuals with no or very mild symptoms:

$$iIA_{s,a,1,t+1} = \sum_{d=1}^{60}\left(iI01_{s,a,d,t} \cdot \alpha 2_d \cdot (1 - \mu_a) + iI02_{s,a,d,t} \cdot \alpha 2_d \cdot (1 - e_2\mu_a)\right) \quad (25)$$

For d=1,2,3…60 (the transmission completed by day 60):

$$iIA_{s,a,d+1,t+1} = iIA_{s,a,d,t} \cdot (1 - \gamma A_d) \quad (26)$$

The number of all infectious individuals with no or mild symptoms:

$$IA\_(s,a,t) = \sum_{d=1}^{60} iIA_{s,a,d,t} \quad (27)$$

The number of all new (d=1) symptomatic patients:

$$SYM_{s,a,t+1} = \sum_{d=1}^{60}(iI01_{s,a,d,t} + e_2 \cdot iI02_{s,a,d,t}) \cdot \alpha 2_d \cdot \mu_a \quad (28)$$

The number of new (d=1) symptomatic patients who are not self-isolated:

$$iIS0_{s,a,1,t} = SYM_{s,a,t} \cdot fS0_t \quad (29)$$

Symptomatic patients (before being isolated or hospitalised:

$$iIS0_{s,a,,d+1,t+1} = (iIS0_{s,a,,d,t} - dthCov_{s,a,t} \cdot ds0_d) \cdot (1 - YS0_d) \quad (30)$$

The number of new (d=1) symptomatic patients being isolated/quarantined:

$$iSQ_{s,a,1,t} = SYM_{s,a,t} \cdot fSq_{a,t} \quad (31)$$

Isolated symptomatic patients:

$$iSQ_{s,a,d+1,t+1} = \sum_{d=1}^{60}(iSQ_{s,a,d,t} - dthCov_{s,a,t} \cdot dsq_d) \cdot (1 - YS1_d) \quad (32)$$

The number of new (d=1) symptomatic patients being hospitalised:

$$iSH_{s,a,1,t} = SYM_{s,a,t} \cdot fSh_{a,t} \quad (33)$$

Hospitalised symptomatic patients:

$$iSH_{s,a,d+1,t+1} = \sum_{d=1}^{60}(iSH_{s,a,d,t} - dthCov_{s,a,t} \cdot dsh_d) \cdot (1 - YH1_d) \quad (34)$$

The number newly recovered people (d=1):

$$iRE_{s,a,1,t+1} = \sum_{d=1}^{60}(iIA_{s,a,d,t} \cdot YA0_d + iIS0_{s,a,d,t} \cdot YS0_d + iISQ_{s,a,d,t} \cdot YS2_d + iISH_{s,a,d,t} \cdot YH2_d + VAC2_t) \quad (35)$$

Note: $VAC2_t$ is the number of newly vaccinated individuals who recovered from previous infections.

All recovered for d=1,2,3…tt:

$$iRE_{s,a,d+1,t+1} = (iRE_{s,a,d,t} - VAC2_t) \cdot (1 - \mu r_d) \cdot (1 - drOth_{s,a,t}) \quad (36)$$

All recovered individuals:

$$\boldsymbol{RE_{s,a,t}} = \sum_{d=1}^{tt} iRE_{s,a,d,t} \quad (37)$$

Derived reproduction values (R0, Rt)

The basic reproduction ratio (R0) is defined as the average number of individuals infected by a typical infectious individual in a total susceptible population, and effective reproduction ratio (Rt) is the number

of individuals infected by an infectious individual when only a proportion of the population are susceptible and the disease transmission dynamic may be influenced by control measures.[33] R values depend on the risk of infection per contact between an infectious and susceptible person, person-to-person contacts between individuals, the rate of transition from exposed to infectious, infectious period, and the prevalence of susceptible individuals in the population.[3] In this study, we don't use the reproduction ratio directly in simulating the spread of SARS-CoV-2 virus. To facilitate the understanding of effects of different intervention strategies, we estimated R0 and Rt during the simulation period, based on average values of relevant parameters and the calculation method used in a modelling study by Giordano et al.[20]

Average values of relevant parameters for estimating R values:

Weighted average fraction of symptomatic individuals in all infected individuals:

$$fS_t = \sum_a (\mu_a \cdot N_{3,a,t}/N_{3,11,t}) \quad (38)$$

Weighted average fraction of hospitalised symptomatic patients:

$$fH_t = \sum_a (fSH_{a,t} \cdot N_{3,a,t}/N_{3,11,t}) \quad (39)$$

Weighted average fraction of symptomatic patients self-isolated:

$$fQ_t = \sum_a (fSQ_{a,t} \cdot N_{3,a,t}/N_{3,11,t}) \quad (40)$$

Risk of daily transmission per infectious individual, depending on asymptomatic or symptomatic, household isolated or not:

$$\beta I0_t = \sum_{a,j=1}^{10} \mu_t \cdot Ca_{a,j,t} \cdot \frac{N_{j,t}}{N_{3,11,t}} \cdot (infA \cdot (1 - fS_t) + fS_t) \quad (41)$$

$$\beta IA_t = \sum_{a,j=1}^{10} \mu_t \cdot Ca_{a,j,t} \cdot \frac{N_{j,t}}{N_{3,11,t}} \cdot infA \cdot (1 - fS_t) \quad (42)$$

$$\beta SQ_t = \sum_{a,j=1}^{10} \mu_t \cdot Cb_{a,j,t} \cdot \frac{N_{j,t}}{N_{3,11,t}} \cdot (infA \cdot (1 - fS_t) + fS_t) \quad (43)$$

$$\beta S0_t = \sum_{a,j=1}^{10} \mu_t \cdot Ca_{a,j,t} \cdot \frac{N_{j,t}}{N_{3,11,t}} \quad (44)$$

The following transition variables are calculated for estimating R values:

$$d1_t = \alpha 2_t \cdot (1 - fS_t) \quad (45)$$

$$d2_t = \alpha 2_t \cdot fS_t \cdot fS0_t \quad (46)$$

$$d3_t = \alpha 2_t \cdot fS_t \cdot fSQ_t \quad (47)$$

$$d4_t = \alpha 2_t \cdot fS_t \cdot fSH_t \quad (48)$$

$$dA1_t = d1_t + d2_t + d3_t + d4_t \quad (49)$$

$$d5_t = \alpha 2_t \cdot (1 - fS_t \cdot e_2) \quad (50)$$

$$d6_t = \alpha 2_t \cdot fS_t \cdot fS0_t \cdot e_2 \quad (51)$$

$$d7_t = \alpha 2_t \cdot fS_t \cdot fSQ_t \cdot e_2 \quad (52)$$

$$d8_t = \alpha 2_t \cdot fS_t \cdot fSH_t \cdot e_2 \quad (53)$$

$$dA2_t = d5_t + d6_t + d7_t + d8_t \quad (54)$$

Effective reproductive value (Rt):

$$Rt = \frac{SU_{3,11,t}}{N_{3,11,t}} \left(\beta I0_t \cdot \frac{1}{dA1_t} + \beta IA_t \cdot \frac{d1_t}{dA1_t \cdot YA0_t} + \beta S0_t \cdot \frac{d2_t}{dA1_t \cdot YS0_t} + \beta SQ_t \cdot \frac{d3_t}{dA1_t \cdot YS1_t} + \beta SH_t \cdot \frac{d4_t}{dA1_t \cdot YH1_t}\right) + \left(\frac{SUre_{3,11,t}}{N_{3,11,t}} + \frac{VAC1_{3,11,t}}{N_{3,11,t}} \cdot e_1\right) \cdot \rho \cdot \left(\beta I0_t \cdot \frac{1}{dA2_t} + \beta IA_t \cdot \frac{d5_t}{dA2_t \cdot YA0_t} + \beta S0_t \cdot \frac{d6_t}{dA2_t \cdot YS0_t} + \beta SQ_t \cdot \frac{d7_t}{dA2_t \cdot YS1_t} + \beta SH_t \cdot \frac{d8_t}{dA2_t \cdot YH1_t}\right) \quad (55)$$

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Vaccination against COVID-19 and society's return to normality in England: a modelling study of impacts of different types of naturally acquired and vaccine induced immunity

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Vaccination against COVID-19 and society's return to normality in England: a modelling study of impacts of different types of naturally acquired and vaccine induced immunity

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ABSTRACT

Objectives: To project impacts of mass vaccination against COVID-19, and investigate possible impacts of different types of naturally acquired and vaccine-induced immunity on future dynamics of SARS-CoV-2 transmission from 2021 to 2024 in England.

Design: Deterministic, compartmental, discrete-time SEIR modelling.

Participants: Population in England.

Interventions: mass vaccination programmes.

Outcome measures: daily and cumulative number of deaths from COVID-19.

Results: If vaccine efficacy remains high (85%), the vaccine-induced sterilising immunity lasts ≥182 days, and the reinfectivity is greatly reduced (by ≥60%), annual mass vaccination programmes can prevent further COVID-19 outbreaks in England. Under optimistic scenarios, with annual revaccination programmes, the cumulative number of COVID-19 deaths is estimated to be from 130,000 to 150,000 by the end of 2024. However, the total number of COVID-19 deaths may be up to 431,000 by the end of 2024, under scenarios with compromised vaccine efficacy (62.5%), short duration of natural and vaccine immunity (365/182 days), and small reduction in reinfectivity (30%). Under the assumed scenarios, more frequent revaccinations are associated with smaller total numbers and lower peaks of daily deaths from COVID-19.

Conclusions: Under optimistic scenarios, mass immunisation using efficacious vaccines may enable society safely to return to normality. However, under plausible scenarios with low vaccine efficacy and short durability of immunity, COVID-19 could continue to cause recurrent waves of severe morbidity and mortality despite frequent vaccinations. It is crucial to monitor the vaccination effects in the real world, and to better understand characteristics of naturally acquired and vaccine induced immunity against SARS-CoV-2.

ARTICLE SUMMARY:

Strengths and limitations of this study

- This is the first modelling study to explicitly investigate the impacts of different types of immune responses to SARS-CoV-2 infection and vaccines on the COVID-19 epidemic in England.
- The model has been calibrated based on historically observed data in England, and plausible futures are explored via a large number of projection scenarios.
- This is a deterministic model to answer "what-if" questions, and uncertainty in estimated parameters may have not been fully accommodated.
- There remain many uncertainties regarding durability and types of naturally acquired and vaccine-induced immunity against SARS-CoV-2 virus.

INTRODUCTION

The COVID-19 pandemic caused by the spread of SARD-CoV-2 virus has resulted in more than 4.2 million deaths globally by the end of July 2021,[1] and severe disruptions of economies and social activities around the world. The spread of the SARS-CoV-2 virus can be suppressed by non-pharmaceutical interventions (NPIs) and lockdown measures.[2] Because of their disruptive socioeconomic consequences, lockdown restrictions cannot last indefinitely.

Only a few months after the initial identification of SARS-CoV-2 pathogen, there were more than 200 vaccine candidates in development globally.[3] Results of randomised controlled trials shown that vaccines were efficacious in reducing symptomatic diseases, compared with placebo.[4 5] Between 3 December 2020 and 31 July 2021, four vaccines against COVID-19 were approved for emergency use in the UK, and a vaccination programme has been started to rollout since 8 December 2020, prioritised primarily by age and comorbidity, with older people being vaccinated first.[6] By 30 July 2021, the coverage rate of vaccination in adults aged ≥18 in the UK was 88.5% for dose-1 and 72.1% for dose-2 of COVID-19 vaccines.[7] Although the number of people infected with SARS-CoV-2 virus in the UK was large during June-July 2021, numbers of hospitalised COVID-19 patients and related deaths had remained relatively low, partly due to the protection of vaccines. For example, there were more than 56,000 cases tested positive reported on 15 July 2021, while daily hospital admissions of patients with COVID-19 ranged from 593 to 836 during 15-31 July 2021, and the reported daily deaths due to COVID-19 ranged from 39 to 92 during the same period in England.[7] Therefore, lockdown restrictions in England have been mostly lifted since 19 July 2021.[8] Although mass vaccination is a promising strategy to enable society to safely return to normality, without mandatory NPIs, there is great uncertainty about the effects of COVID-19 vaccines and society's return to normality, including vaccines' long-term efficacy and emerging new variants of SARS-CoV-2 virus.[9 10]

There have been many mathematical modelling studies to investigate COVID-19 dynamics and the impacts of control measures (for example [11-13]). Several modelling studies evaluated impacts of vaccines on the dynamics and consequences of COVID-19 epidemics in the UK.[14-17] Two of these studies assessed impacts of the relaxation of social restriction after vaccination in the UK,[15 16] and one study assessed impacts of vaccination on hospital admissions,[17] but covered a shorter time horizon and did not consider waning of immunity. Another study of SARS-CoV-2 vaccination in the UK focused on economic evaluations.[17] There have been some published modelling studies of vaccination against COVID-19 in other countries. For example, a modelling study examined the nation-wide vaccination and returning to normal life in the United States of America (USA), finding that vaccination alone was insufficient and NPI measures were still required.[18]

The protection of naturally acquired or vaccine-induced immune responses may be attributable to infection protection, disease reduction, and reinfectivity reduction.[19] Studies of diseases caused by other human coronaviruses (HCoVs) indicated that infection protection immunity is likely to be short-lived, while disease reduction and reinfectivity reduction are likely long lasting.[20] We are not aware of modelling studies that considered these important immunity characteristics in the evaluation of national mass vaccination programmes against COVID-19 epidemics. Therefore, we conducted a modelling study to investigate possible impacts of different types of naturally acquired and vaccine-induced immunity on future dynamics of SARS-CoV-2 transmission in England.

METHODS

Model structure

This is a deterministic, compartmental, discrete-time (day) population dynamic model, implemented with computational language R.[21] The population are classified into categories by sex, age (5-year age bands for age <10 years, and 10-year age bands for age ≥10 years), and COVID-19 infection status (figure 1). The main infection compartments include susceptible, exposed, infectious, recovered, and vaccinated. Here "exposed" refers to a pre-infectious status of infected individuals. Infected individuals are classified as asymptomatic or symptomatic, and symptomatic individuals are classified as not being isolated, self-isolated, and hospitalised. We assume that hospitalised patients are effectively isolated and no longer able to transmit the virus to the general population, but patients who self-isolate at home may transmit virus to household contacts. The recovered and effectively vaccinated are protected from reinfection, but they may be reinfected if the immunity is short-lived.

Parameters and data sources

Details on the model's structure (appendix figure 1), parameters, data sources (appendix table 1), and mathematical equations are available in Supplementary files. Initial parameter values were estimated based on a review of relevant literature, and key parameter estimates were calibrated so that the simulated numbers of COVID-19 deaths, hospitalised patients, and infected individuals were as similar as possible to historically reported data from March 2020 to June 2021 in England.[22]

We obtained population demographic statistics in England from the Office for National Statistics,[23] and the whole population is assumed to be susceptible to SARS-CoV-2 infection at the beginning of 2020. We assume incubation periods, infectious periods, days of hospital stay, and days of deaths after being infected, to be gamma distributed (appendix table 1 in supplementary files).[11 24 25] Age specific case fatality rates and hospitalisation rates of symptomatic cases were based on a study by Verity et al.[25] Average sex-and-age-specific rates of all-cause deaths from 2015 to 2019 in England[23]

are applied to people who are not infected with or recovered from COVID-19. We assumed that the number of births equals to the number of deaths each day, and did not consider the influence of population migration. We adjusted the number of individuals belonging to each age group at the beginning of a year since 2021, by shifting a proportion of them to the adjacent higher age group.

Effects of NPI measures, including restrictions on social activities, contact tracing and testing, were materialised by changes in transmission risk per contact between a susceptible and an infectious individual,[26] and average numbers of contacts of the general population (appendix table 1 in supplementary files). We estimate that the transmission risk per contact between infectious and susceptible individuals was reduced by 30%, from 0·094 before the implementation of any NPIs to 0·066 by March 15, 2020 after implementing basic NPI measures. Because of the new virus variants,[27] the average transmission risk per contact was increased to 0·077 by the end of 2020, and 0.081 since June 2021. We assume that, since September 2021, the transmission risk per contact is 10% higher in September, October, March and April, and 20% higher in the winter months of November, December, January and February, compared with the risk in summer months from May to August.[28] We do not use the reproduction number as an input parameter, but derived the basic and effective reproduction numbers based on model's transmission parameters (equation 55 in Supplementary files).[13 26]

The sex-and-age-specific numbers of daily contacts per person were based on the UK data from a study of European countries.[29] We consider only the daily contacts of the general population and household contacts of individuals self-isolated at home. We estimated that the lockdown measures from 24 March 2020 reduced general population contacts by 60-85%, although household contacts were unchanged. The NPI measures were relaxed or strengthened over time, which were reflected in the assumed social contacts and transmission risk (Supplementary files). Social contacts in England since 19 July 2021 are return to normal as before the pandemic in England, although some basic hygienic measures would be maintained.

Vaccination and projection scenarios

Vaccination of prioritised individuals began from 8 December 2020 in England.[30] The Joint Committee on Vaccination and Immunisation (JCVI) in the UK previously recommended COVID-19 vaccination of individuals aged ≥18, and also recommended vaccination of young people aged 16-17 years old on 4 August 2021.[31] The vaccine uptake rate in adults aged ≥18 was 88.5% for dose-1 and 72.1% for dose-2 by 30 July 2021,[22] and the coverage with two does was >90% in adults aged ≥65, 80-90% in those aged 50-64, and around 60% in those aged 40-49.[32] In this study, the mass vaccination is modelled as an age-based phase approach, starting from people aged ≥70, followed by individuals aged 60-69, 50-59, 30-49, and then those aged 16-29 years old. We assume that the mass vaccination starts from 1

January 2021, and the maximum number of individuals vaccinated daily is 180,000, to matched with numbers of vaccinated individuals according to the official statistics. In the main analysis, we assume that the uptake rate is 75%, 80%, 85% and 90%, respectively, in adults aged 16-29, 30-39, 40-49, and ≥50 years old. Because of uncertain coverage of vaccination in younger people, we conducted sensitivity analyses under scenarios with lower (60%, 70%, and 80%) and higher (80%, 85%, and 90%) coverage of vaccination in people aged 16-29, 30-39, and 40-49 years old, respectively.

Both Pfizer-BioNTec and AstraZeneca vaccines are 2-dose regimens, and the policy in the UK has been to initially provide the first dose to as many adults as possible. Data from clinical trials indicated that the short-term vaccine efficacy after the first dose of the Pfizer-BioNTech and the AstraZeneca vaccine is about 90% and 70%, rerspectively.[4] Public Health England (PHE) in July 2021 estimated that the efficacy was 55-70% after the first dose, and 70-85% or 85-95% after the second dose.[32] In this study, we assume that the overall vaccine efficacy is 62.5% after the first dose and 85% after the second dose. The protection effects start 14 days after the first dose vaccination, and the interval between the first and second dose is nine weeks. The overall vaccine efficacy after the second dose may be lower than 85.0% due to new variants of SARS-CoV-2 virus. Therefore, we assume a scenario in which the vaccine efficacy is reduced by new viral variants, to be 44.0% after the first dose and 62.5% after the second dose, during 2022-2024.

The reduction in symptomatic cases in vaccinated individuals may be due to induced antibodies in susceptible individuals (infection protection), or a reduction in symptomatic cases among infected individuals (disease reduction), or a combination of both. There are many different possible combinations of infection protection and disease reduction for a given overall vaccine efficacy in reducing symptomatic cases (appendix figure 2 in supplementary files). We assume that vaccine efficacy for reducing symptomatic cases is equally attributable to infection reduction and disease reduction in the main projections. For vaccines with 62.5% and 85.0% overall efficacy, the equal partial efficacy for the infection protection and for disease reduction is 38.8% and 61.3%, respectively (see Supplementary files for details).

Immune responses against COVID-19 infection, either naturally acquired from prior infection or vaccine-induced, may reduce individuals' susceptibility to infection (infection protection or sterilising immunity), reduce pathology so that disease is less severe after being infected (disease reduction immunity), and reduce infectivity of those who are reinfected after the waning of immunity (reinfectivity reduction immunity).[19] According to immunological characteristics of other HCoVs, infection protection immunity may wane after a short period, while disease protection and reinfectivity reduction immunity are likely longer lasting.[20] For example, antibodies against SARS-CoV-1 virus in recovered patients was no longer detectable after 2-3 years, while specific memory T cells remained detected after 11 years.[33] Therefore, we assume that the disease reduction and

reinfectivity reduction immunity are long lasting (>4 years).[20] We assume that naturally acquired sterilising immunity lasts for 365 or 730 days, and vaccine-induced sterilising immunity lasts for 182 or 365 days. Available evidence indicated that the viral loads and the duration of virus shedding in the infected individuals after vaccination were considerably reduced, compared with unvaccinated individuals.[34 35] Public Health England in July 2021 estimated that the reinfectivity was reduced by 35-50% after the first dose of vaccines,[32] although it is possible that the reduction in reinfectivity may be larger than 35-50% after the second dose of vaccines. More recent studies reported that fully vaccinated individuals who were infected were between 41% and 78% less likely to transmit the virus to unvaccinated individuals.[36] In this study, we assume that reinfectivity after waning of sterilising immunity is reduced by 30%, 45% or 60%. We also assume that the infectivity of ineffectively vaccinated individuals is the same as recovered individuals whose sterilising immunity has waned, and vaccination of individuals recovered from natural infection boosts their naturally acquired immunity.

We considered scenarios with different frequency of revaccination programmes, including a single vaccination programme, multiple (2-4) annual revaccinations, and revaccination programmes with different frequency and time intervals. The main characteristics of the simulated scenarios are summarised in supplementary table 1, supplementary table 2 and supplementary table 3.

We run the model and calibrate key transmission parameters by visually comparing estimated numbers of daily COVID-19 deaths, and hospitalised patients, with official records from 1 January 2020 to 30 June 2021 in England.[22] We used estimates of transmission parameters by the end of June 2021 to project COVID-19 deaths from 2021 to 2024, under various scenarios of vaccine efficacy, durability and protection characteristics of naturally acquired and vaccine-induced immunity. The number of deaths from SARS-CoV-2 infections is the main endpoint in this study.

Patient and public involvement

No patients and the public were involved in this literature and secondary data based, computational modelling study.

RESULTS

Our derived basic reproduction number (R0) was 3·68 at the initial stage of the COVID-19 epidemic in England. After implementing NPI and lockdown measures, the effective reproduction value (Rt) was reduced to 0·66 after 24 March 2020. Thereafter, the Rt values fluctuated along with changing NPI policies, and our estimated R values were within the ranges reported in England (Appendix figure 3 in Supplementary files).[37] The estimated prevalence of SARS-CoV-2 infection (appendix figure 4), the

number of hospitalised COVID-19 patients (appendix figure 5), and the estimated daily deaths from COVID-19 (appendix figure 6) are well matched with the reported data from March 2020 to June 2021 in England (Supplementary files).

Vaccine efficacy, immunity durability, and reinfectivity

Figure 2 shows the impacts of partial vaccine efficacy regarding disease reduction relative to infection protection, durability of immunity, and reinfectivity, given the same overall vaccine efficacy in reducing symptomatic cases. There are three general inferences. As expected, the number of COVID-19 deaths is smaller following a greater reduction in reinfectivity (figure 2A, 2B, 2C). Second, a greater reduction in reinfectivity makes the durability of immunity less influential, if a vaccine is efficacious for infection protection (figure 2c). Third, the impacts of partial efficacy of infection protection relative to disease reduction by a vaccine is substantial when the duration of immunity is short-lasting. A combination of a shorter duration of immunity and smaller reduction in the reinfectivity makes the disease reduction efficacy more beneficial (figure 2A, 2B).

Population susceptibility and COVID-19 outbreaks

Changes in the prevalence of susceptible individuals and daily peaks of COVID-19 deaths in England during 2020 and 2024 are shown in figure 3, under assumptions of 85% vaccine efficacy after the second dose, 45% reduction in reinfectivity after waning of sterilising immunity, and different durations of sterilising immunity.

The overall prevalence of susceptible individuals is reduced to around 25% by August 2021, after a single wave of mass vaccination starting from January 2021. It starts to increase to above 70% by December 2022, if the duration of natural and vaccine-induced immunity is 730 and 365 days, respectively (figure 3A). The raised prevalence of susceptible individuals leads to an outbreak with a high peak (n=627) of daily COVID-19 deaths in May 2023. The prevalence of the susceptible is reduced from 74% to 68% by the natural infection during the outbreak, then slightly increases again (69%) due to waning of immunity. After the outbreak wave in January 2024, the prevalence of the susceptible is reduced to around 60% (figure 3A). Two waves of repeated annual revaccination programmes delay the new outbreak, with a peak of daily COVID-19 deaths (n=731) in May 2024 (figure 3B). Four repeated waves of annual revaccination programmes almost prevent any new outbreaks before the end of 2024, with no more than 50 daily COVID-19 deaths during 2022-2024 (figure 3C).

If the natural and vaccine immunity lasts only 365 and 182 days, respectively, the annual mass vaccination programmes are insufficient to sustain a constantly low prevalence of the susceptible, and the prevalence of the susceptible fluctuates up and down biannually (figure 3D-F). A single wave

of mass vaccination is followed with multiple high peaks of daily COVID-19 deaths (figure 3D), and annual revaccination programmes result in corresponding changes in the prevalence of susceptible individuals and daily COVID-19 deaths (figure 3E, 3F). With four annual revaccination programmes, there are two flattened peaks of daily deaths from COVID-19 in March 2022 (n=151) and April 2024 (n=168), respectively (figure 3E).

Projected COVID-19 deaths under various scenarios

The projected total numbers and daily peaks of COVID-19 deaths during 2020-2024, under all assumed scenarios, are available in supplementary table 1 and supplementary table 2. If there is no waning of immunity (i.e., immunity duration >4 years) and high vaccine efficacy, a single vaccination programme may prevent COVID-19 outbreaks during 2022-2024, after returning to normality (supplementary table 1). Otherwise, repeated vaccination programmes are required to prevent further large outbreaks with high peaks of daily deaths from COVID-19.

Table 1 shows results of annual vaccination programmes under selected scenarios. With annual revaccinations under optimistic scenarios, the cumulative number of COVID-19 deaths is estimated to be from 130,000 to 150,000 by the end of 2024. However, the total number of COVID-19 deaths may be up to 431,000 by the end of 2024, and the number of daily peak deaths may be as high as around 900 in 2022, 600 in 2023 and 1,400 in 2024, under scenarios with compromised long-term vaccine efficacy (62.5%), short duration of natural and vaccine immunity (365/182 days), and small reduction in reinfectivity (30%) (table 1).

Results of revaccination programmes with different frequency (from two to six revaccinations during 2021-2024) are shown in figure 4 and supplementary table 2. Revaccination programmes every two years can prevent outbreaks during 2022-2024 in a scenario with high vaccine efficacy (85%), large reduction in reinfectivity (60%), and long duration of immunity (730/365 days). Under assumed scenarios, more frequent revaccinations are associated with smaller total numbers and lower peaks of daily deaths from COVID-19 (supplementary table 2). As expected, frequent revaccinations are particularly important when the immunity response is short-lived (figure 4A, 4B, 4C, 4D). For example, under scenarios of lower long-term vaccine efficacy (62.5%), lower reduction in reinfectivity (30%), and shorter duration of immunity (365/182), the projected number of total COVID-19 deaths by the end of 2024 is reduced from around 430,000 by annual revaccination programmes to around 310,000 by more frequent revaccinations every 8 months (supplementary table 2).

Results of scenarios with lower or higher vaccination coverage in younger adults are presented in supplementary table 3. As expected, lower coverage of vaccination programmes is associated with larger number of total COVID-19 deaths. For example, the projected cumulative number of COVID-19 deaths by the end of 2024 is around 195,000, under a scenario (labelled as ‘A2c4’ in supplementary

table 3) of annual revaccination, 85% vaccine efficacy, short duration of immunity (365/182 days), and 75-90% vaccination coverage. The number of COVID-19 deaths is reduced to around 183,000 in scenario (A2c4y) with 80-90% coverage, and increased to around 210,000 in scenario (A2c4x) with 60-90% coverage (supplementary table 3).

DISCUSSIONS

Mass immunisation using efficacious vaccines may enable society safely to return to normality. Repeated vaccination programmes are very likely to be required to prevent further COVID-19 outbreaks, depending on vaccine efficacy, the durability and characteristics of different types of immune response to naturally acquired and vaccine-induced immune responses. Evidence on diseases caused by other common HCoVs indicated that the infection protection immunity may be short-lived, but the disease reduction and the reinfectivity reduction immunity are likely to be longer lasting.[20] We found that, if vaccine efficacy is high (85%) and reinfectivity is greatly reduced (e.g., by 60%), repeated annual mass vaccination programmes prevent further COVID-19 large outbreaks, even if the vaccine induced sterilising immunity lasts only 182 days. Under optimistic scenarios, the cumulative number of COVID-19 deaths during 2020-2024 in England is estimated to be from 130,000 to 150,000. If both the natural and vaccine immunity are short-lived (365 and 180 days, respectively), and reinfectivity is reduced only by 45% or 30%, further COVID-19 outbreaks cannot be prevented by annual vaccination programmes. The total number of COVID-19 deaths is estimated to be around 431,000 by the end of 2024, under a pessimistic scenario with low long-term vaccine efficacy (62.5%), short duration of vaccine immunity (365/182 days), and small reduction in reinfectivity (30%) (Table 1).

When natural and vaccine-induced immune response against SARS-CoV-2 infection is short-lived, more frequent revaccinations (e.g., every 8-10 months) can reduce deaths from COVID-19, compared with less frequent or annual revaccination programmes. However, frequent revaccination may not always be feasible, due to the availability of vaccine doses, resource restrictions, organisational complexity, and possibly decreased compliance by the public.

Compared with previous modelling studies,[14-17] our study has considered the durability of naturally acquired and vaccine induced immunity, over a five year period from 2020 to 2024, and compared a wider range of plausible scenarios. We explicitly investigated the impacts of different types of immune responses to SARS-CoV-2 infection and vaccines on the COVID-19 epidemic in a country. Findings from our study will improve the understanding of key immunological parameters relevant to future changes in SARS-CoV-2 transmission dynamics and vaccination strategies.

Evidence from randomised controlled trials showed that vaccines against SARS-CoV-2 are efficacious in reducing symptomatic COVID-19 cases.[5] The reduction in symptomatic cases in the vaccine group may be attributable to infection protection or disease reduction. Available evidence showed that vaccines reduced the risk of SARS-CoV-2 virus infection in vaccinated individuals,[38] and household members of vaccinated healthcare workers has a lower risk of COVID-19 infection than those of unvaccinated.[39] In this study, we explored the impacts of different proportions of a vaccine's infection protection efficacy and disease reduction efficacy. Different combinations of the two efficacy components have impacts on the transmission dynamics, depending on the duration of immune response and reinfectivity after waning of sterilising immunity. Because of lack of data, we assumed that vaccine efficacy is equally attributable to the infection and disease reduction immunity.

Vaccines that are efficacious against current SARS-CoV-2 virus may become less efficacious against new emerging variants.[9] Therefore, we modelled a range of overall long-term vaccine efficacy (62.5% vs. 85.0%). Although the vaccine efficacy might be reduced by new viral variants, it is also possible that repeated vaccinations may boost immune responses.[40] We assume that there will be no important safety issues for vaccines licensed to use. We focused on the impacts and interactions of vaccine efficacy, different types of immune response to SARS-CoV-2, and assumed no more restrictions by NPI measures after return to normality in England from 19 July 2021. However, the pessimistic scenarios in our analyses may not be allowed to happen in the real world, as NPI (including lockdown) measures may have to be introduced again if the vaccination programmes are insufficient to avoid the new outbreaks of COVID-19.

This is a deterministic simulation model, and uncertainty in estimated parameters may have not been fully accommodated. For simplicity, stochastic uncertainty, to quantify confidence intervals around the model's outputs, was not modelled. However, the model has been calibrated based on historically observed outcome data in England, and a large number of projection scenarios are explored to explicitly answer "what-if" questions. Although many uncertainties remain, including durability and types of naturally acquired and vaccine-induced immunity, our model can be updated to assess vaccination strategies, as new evidence emerges.

Conclusions

Under optimistic scenarios, mass immunisation using efficacious vaccines may enable society safely to return to normality. However, under plausible scenarios with low vaccine efficacy and short durability of immunity, COVID-19 could continue to cause recurrent waves of severe morbidity and mortality despite frequent vaccinations, and necessitate stringent NPI restrictions. It is crucial to monitor the vaccination effects in the real world, and to better understand characteristics of naturally acquired and vaccine induced immunity against SARS-CoV-2.

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Contributors: FS designed, developed the model, retrieved data for estimating parameters, conducted computational calculations, and prepared the draft manuscript. MOB provided methodological support, helped interpret results and critically revised the draft manuscript. FS accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Patient consent for publication: Not applicable.

Ethics approval statement: Not applicable. No human participants involved in this modelling study using data from published or openly accessible sources.

FIGURE LEGENDS:

Figure 1: Modelling COVID-19 epidemics in England - main compartments and transitions across status. See supplementary files for details on definitions of transition parameters

Figure 2. Projected numbers of COVID-19 deaths with different combinations of partial efficacy of infection and disease protection, immunity duration, and reduction in reinfectivity.

The cumulative number of COVID-19 deaths by the end of 2024, after four repeated annual vaccinations of 90% individuals aged ≥18 during 2021-2024. The overall vaccine efficacy was 85%; "0·00/0·85" refers to all vaccine efficacy attributable to disease protection, "0·61/0·61" refers to equal infection and disease protection, "0·85/0·00" refers to all efficacy attributable to infection protection. Immunity duration: "365/182" refers to 365 days and 182 days, "and "730/365" refers to 730 and 365 days, respectively, natural and vaccine immunity. Figure 2A, 2B and 2C shows results under the assumption of 30%, 45% and 60% reduction in reinfectivity.

Figure 3. Projected peaks of daily COVID-19 deaths and the prevalence of susceptible individuals during 2020-2024 under scenarios with different immunity durability and vaccine strategies. We assume 85% long-term vaccine efficacy; 75-90% coverage of individuals aged ≥16; 45% reduction in reinfectivity, longer (730/365 days, fig 3A-C) or shorter lasting (365/182 days, fig 3D-F) natural/vaccine immunity. Results were after a single vaccination (fig 3A and 3D), two annual vaccination programmes (fig 3B and 3E), and four annual vaccination programmes (Figure 3C and 3F).

Figure 4. Results of revaccination programmes with different frequency. Vaccine efficacy is 85.0% in fig 4A/C and 62.5% in fig 4B/D, respectively. Duration of immunity lasts 730/365 in fig 4A/B and 365/182 days in fig 4C/D, respectively.

ONLINE SUPPLEMENTARY MATERIALS

Supplementary Files: Model structure, data sources, model parameters, mathematical equations, and R code used.

Supplementary Table 1: Projected total and daily peaks of COVID-19 deaths by the end of 2024 in England, under different scenarios of annual vaccination programmes

Supplementary Table 2: Projected total and daily peaks of COVID-19 deaths by the end of 2024 in England by revaccination frequency.

Supplementary Table 3: Projected total and daily peaks of COVID-19 deaths by the end of 2024 in England, under different scenarios of uptake rate of vaccination in younger adults

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Table 1. Projected total and daily peak COVID-19 deaths after annual vaccination programmes by 2024 in England

Scenario	Long-term vaccine efficacy	Reduction in reinfectivity	Immunity duration (day): Natural /vaccine	Total COVID-19 deaths (2020-2024)	Daily peaks of COVID-19 deaths		
					2022	2023	2024
A1b4	85.0%	60%	730/365	127,550	28	0	0
A2b4	85.0%	45%	730/365	134,421	42	0	36
A3b4	85.0%	30%	730/365	152,926	64	4	131
A1c4	85.0%	60%	365/182	148,093	89	2	7
A2c4	85.0%	45%	365/182	194,661	151	55	168
A3c4	85.0%	30%	365/182	229,664	208	145	96
B1b4	62.5%	60%	730/365	143,233	104	0	0
B2b4	62.5%	45%	730/365	179,002	209	0	224
B3b4	62.5%	30%	730/365	233,075	366	3	384
B1c4	62.5%	60%	365/182	198,684	351	2	47
B2c4	62.5%	45%	365/182	350,016	615	537	886
B3c4	62.5%	30%	365/182	430,219	888	616	1362

Notes to Table 1: Scenario labels are corresponding to those used in supplementary table 1. We assume annual vaccination covers 75-90% of individuals aged ≥16 years; the short-term vaccine efficacy is 62.5% after the first dose and 85% after the second dose, and the overall vaccine efficacy is equally attributable to the infection and disease protection. "Long-term vaccine efficacy" refers to vaccine efficacy in fully vaccinated after January 2022.

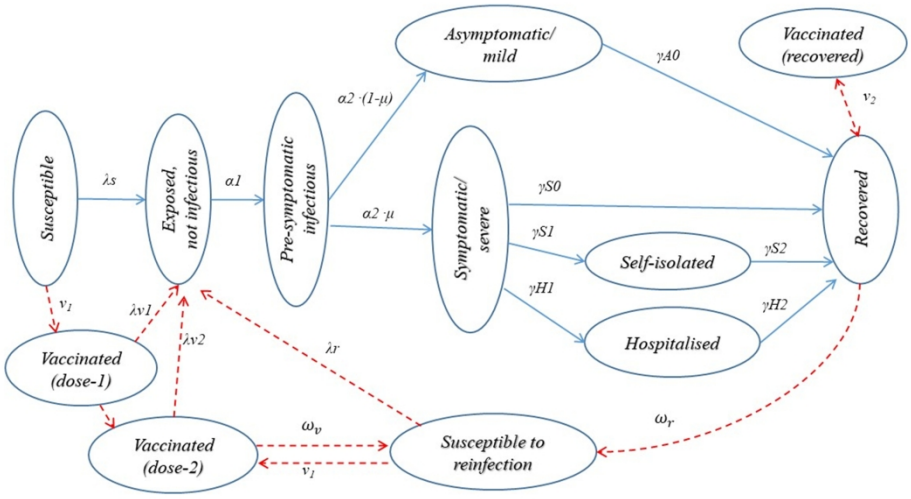

Figure 1: Modelling COVID-19 epidemics in England - main compartments and transitions across status. See supplementary files for details on definitions of transition parameters

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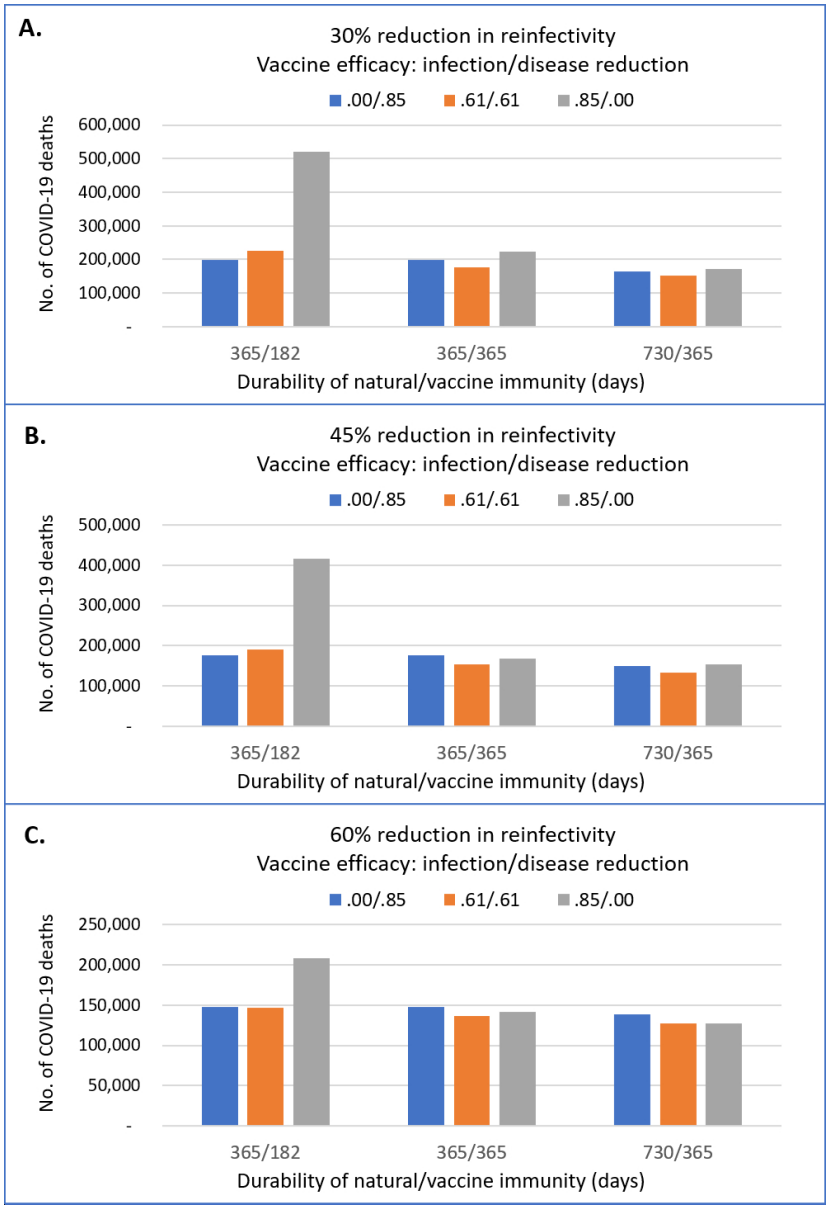

Figure 2. Projected numbers of COVID-19 deaths with different combinations of partial efficacy of infection and disease protection, immunity duration, and reduction in reinfectivity. The cumulative number of COVID-19 deaths by the end of 2024, after four repeated annual vaccinations of 90% individuals aged ≥18 during 2021-2024. The overall vaccine efficacy was 85%; "0·00/0·85" refers to all vaccine efficacy attributable to disease protection, "0·61/0·61" refers to equal infection and disease protection, "0·85/0·00" refers to all efficacy attributable to infection protection. Immunity duration: "365/182" refers to 365 days and 182 days, "and "730/365" refers to 730 and 365 days, respectively, natural and vaccine immunity. Figure 2A, 2B and 2C shows results under the assumption of 30%, 45% and 60% reduction in reinfectivity.

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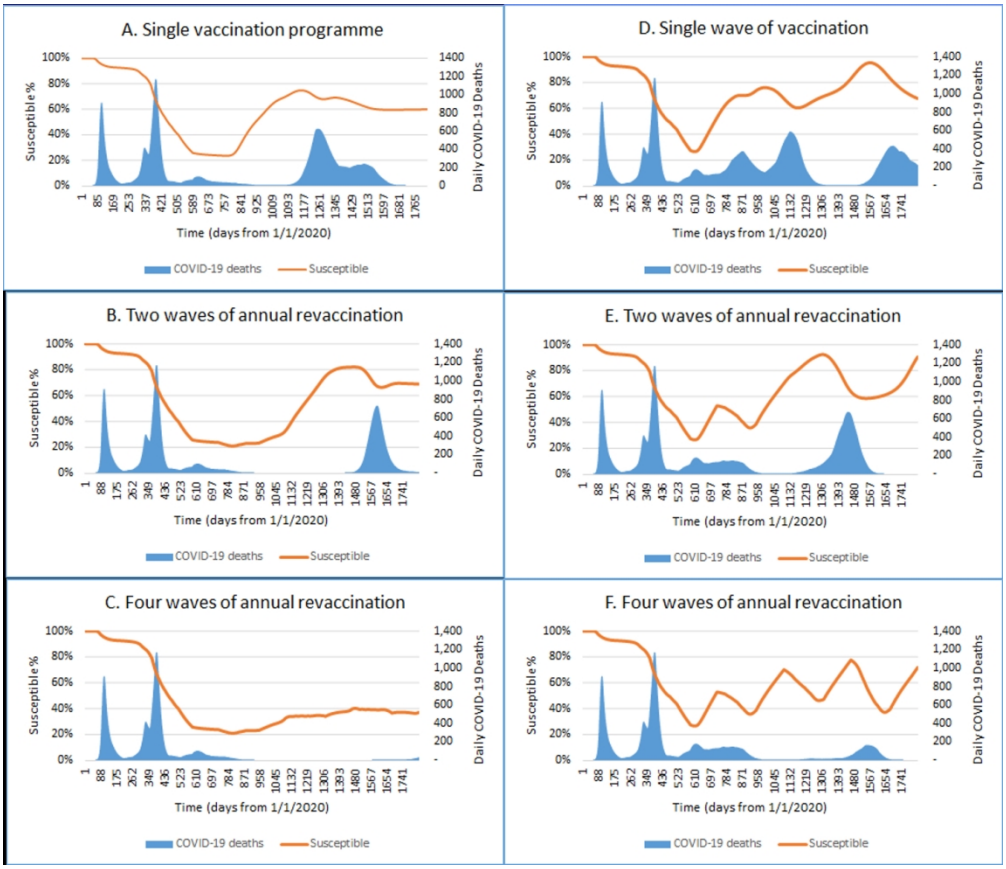


Figure 3. Projected peaks of daily COVID-19 deaths and the prevalence of susceptible individuals during 2020-2024 under scenarios with different immunity durability and vaccine strategies. We assume 85% long-term vaccine efficacy; 75-90% coverage of individuals aged ≥16; 45% reduction in reinfectivity, longer (730/365 days, fig 3A-C) or shorter lasting (365/182 days, fig 3D-F) natural/vaccine immunity. Results were after a single vaccination (fig 3A and 3D), two annual vaccination programmes (fig 3B and 3E), and four annual vaccination programmes (Figure 3C and 3F).

252x217mm (150 x 150 DPI)

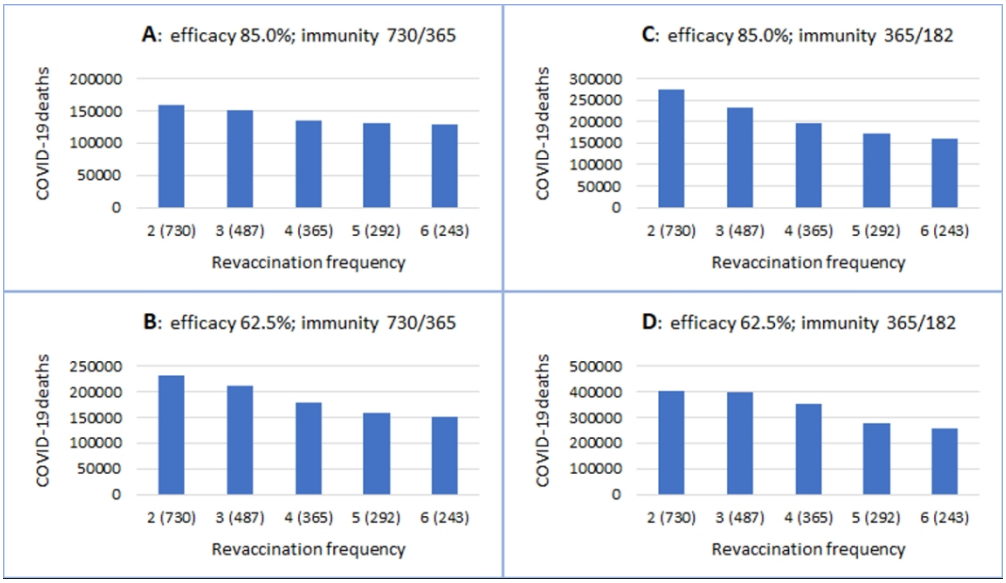


Figure 4. Results of revaccination programmes with different frequency. Vaccine efficacy is 85.0% in fig 4A/C and 62.5% in fig 4B/D, respectively. Duration of immunity lasts 730/365 in fig 4A/B and 365/182 days in fig 4C/D, respectively.

204x117mm (150 x 150 DPI)

Supplementary table 1:

Projected total and daily peaks of COVID-19 deaths by the end of 2024 in England under different scenarios of annual vaccination programmes

Assumptions and notes:

- 75-90% vaccination coverage of individuals aged >=16 years old.
- Initial overall vaccine efficacy: 62.5% after dose-1 and 85% after dose-2.
- The overall vaccine efficacy is equally attributable to the infection and disease protection.

Scenario	Vaccination waves (interval days)	Long-term vaccine efficacy	Reduction in reinfectivity	Immunity duration (day): Natural /vaccine	Total COVID-19 deaths (2020-2024)	Daily peaks of COVID-19 deaths		
						2022	2023	2024
A1a1	1	85.0%	60%	No waning	128,039	28	0	0
A1a2	2 (365)	85.0%	60%	No waning	127,464	28	0	0
A1a3	3 (365)	85.0%	60%	No waning	127,464	28	0	0
A1a4	4 (365)	85.0%	60%	No waning	127,464	28	0	0
A1b1	1	85.0%	60%	730/365	242,691	28	592	582
A1b2	2 (365)	85.0%	60%	730/365	154,956	28	0	592
A1b3	3 (365)	85.0%	60%	730/365	127,550	28	0	0
A1b4	4 (365)	85.0%	60%	730/365	127,550	28	0	0
A1c1	1	85.0%	60%	365/182	239,044	281	452	56
A1c2	2 (365)	85.0%	60%	365/182	196,149	89	78	392
A1c3	3 (365)	85.0%	60%	365/182	155,320	89	2	109
A1c4	4 (365)	85.0%	60%	365/182	148,093	89	2	7
B1a1	1	62.5%	60%	No waning	144,586	105	0	0
B1a2	2 (365)	62.5%	60%	No waning	142,720	104	0	0
B1a3	3 (365)	62.5%	60%	No waning	142,720	104	0	0
B1a4	4 (365)	62.5%	60%	No waning	142,720	104	0	0
B1b1	1	62.5%	60%	730/365	320,789	105	952	950
B1b2	2 (365)	62.5%	60%	730/365	230,198	104	0	1066
B1b3	3 (365)	62.5%	60%	730/365	143,670	104	0	16
B1b4	4 (365)	62.5%	60%	730/365	143,233	104	0	0
B1c1	1	62.5%	60%	365/182	353,663	528	536	407
B1c2	2 (365)	62.5%	60%	365/182	292,109	351	103	915
B1c3	3 (365)	62.5%	60%	365/182	225,230	351	2	412
B1c4	4 (365)	62.5%	60%	365/182	198,684	351	2	47
A2a1	1	85.0%	45%	No waning	132,749	42	0	0

A2a2	2 (365)	85.0%	45%	No waning	131,963	42	0	0
A2a3	3 (365)	85.0%	45%	No waning	131,963	42	0	0
A2a4	4 (365)	85.0%	45%	No waning	131,963	42	0	0
A2b1	1	85.0%	45%	730/365	265,799	42	627	243
A2b2	2 (365)	85.0%	45%	730/365	206,600	42	9	731
A2b3	3 (365)	85.0%	45%	730/365	159,912	42	0	582
A2b4	4 (365)	85.0%	45%	730/365	134,421	42	0	36
A2c1	1	85.0%	45%	365/182	373,907	479	588	435
A2c2	2 (365)	85.0%	45%	365/182	266,690	151	675	628
A2c3	3 (365)	85.0%	45%	365/182	222,944	151	55	363
A2c4	4 (365)	85.0%	45%	365/182	194,661	151	55	168
B2a1	1	62.5%	45%	No waning	163,679	209	0	0
B2a2	2 (365)	62.5%	45%	No waning	161,055	209	0	0
B2a3	3 (365)	62.5%	45%	No waning	161,055	209	0	0
B2a4	4 (365)	62.5%	45%	No waning	161,055	209	0	0
B2b1	1	62.5%	45%	730/365	383,433	209	916	801
B2b2	2 (365)	62.5%	45%	730/365	304,138	209	13	1301
B2b3	3 (365)	62.5%	45%	730/365	236,662	209	0	952
B2b4	4 (365)	62.5%	45%	730/365	179,002	209	0	224
B2c1	1	62.5%	45%	365/182	611,929	867	1542	2437
B2c2	2 (365)	62.5%	45%	365/182	443,176	615	1860	1096
B2c3	3 (365)	62.5%	45%	365/182	376,242	615	537	1092
B2c4	4 (365)	62.5%	45%	365/182	,016	615	537	886

A3a1	1	85.0%	30%	No waning	138,595	64	0	0
A3a2	2 (365)	85.0%	30%	No waning	137,672	64	0	0
A3a3	3 (365)	85.0%	30%	No waning	137,672	64	0	0
A3a4	4 (365)	85.0%	30%	No waning	137,672	64	0	0
A3b1	1	85.0%	30%	730/365	301,437	64	1235	218
A3b2	2 (365)	85.0%	30%	730/365	259,144	64	297	1645
A3b3	3 (365)	85.0%	30%	730/365	187,753	64	4	324
A3b4	4 (365)	85.0%	30%	730/365	152,926	64	4	131
A3c1	1	85.0%	30%	365/182	498,043	743	764	1933
A3c2	2 (365)	85.0%	30%	365/182	321,779	208	537	599
A3c3	3 (365)	85.0%	30%	365/182	317,223	208	145	618
A3c4	4 (365)	85.0%	30%	365/182	229,664	208	145	96
B3a1	1	62.5%	30%	No waning	188,227	366	0	0
B3a2	2 (365)	62.5%	30%	No waning	185,384	366	0	0
B3a3	3 (365)	62.5%	30%	No waning	185,384	366	0	0
B3a4	4 (365)	62.5%	30%	No waning	185,384	366	0	0
B3b1	1	62.5%	30%	730/365	448,904	366	1093	649

B3b2	2 (365)	62.5%	30%	730/365	392,651	366	98	2877
B3b3	3 (365)	62.5%	30%	730/365	291,181	366	3	720
B3b4	4 (365)	62.5%	30%	730/365	233,075	366	3	384
B3c1	1	62.5%	30%	365/182	822,318	1095	2571	3202
B3c2	2 (365)	62.5%	30%	365/182	682,299	888	1714	5055
B3c3	3 (365)	62.5%	30%	365/182	627,017	888	616	3165
B3c4	4 (365)	62.5%	30%	365/182	430,219	888	616	1362

Supplementary table 2:

Projected total and daily peaks of COVID-19 deaths by the end of 2024 in England by revaccination frequency

Assumptions and notes:

- Age-based 75-90% vaccination coverage of individuals aged 16+.
- Initial overall vaccine efficacy: 62.5% after dose-1 and 85% after dose-2.
- The overall vaccine efficacy is equally attributable to the infection and disease protection.

Scenario	Vaccination waves (interval days)	Long-term vaccine efficacy	Reduction in reinfectivity	Immunity duration (day): Natural /vaccine	Total COVID-19 deaths (2020-2024)	Daily peaks of COVID-19 deaths		
						2022	2023	2024
FAa2	2 (730)	85.0%	60%	730/365	140,596	28	42	22
FAa3	3 (487)	85.0%	60%	730/365	129,991	28	0	14
FAa4	4 (365)	85.0%	60%	730/365	127,550	28	0	0
FAa5	5 (292)	85.0%	60%	730/365	126,529	22	0	0
FAa6	6 (243)	85.0%	60%	730/365	125,523	18	0	0
FAb2	2 (730)	62.5%	60%	730/365	179,155	105	89	79
FAb3	3 (487)	62.5%	60%	730/365	154,959	105	1	56
FAb4	4 (365)	62.5%	60%	730/365	143,233	104	0	0
FAb5	5 (292)	62.5%	60%	730/365	139,718	86	0	0
FAb6	6 (243)	62.5%	60%	730/365	136,348	71	0	0
FAc2	2 (730)	85.0%	60%	365/182	217,980	281	385	0
FAc3	3 (487)	85.0%	60%	365/182	169,204	196	21	14
FAc4	4 (365)	85.0%	60%	365/182	148,093	89	2	7
FAc5	5 (292)	85.0%	60%	365/182	138,246	48	1	5
FAc6	6 (243)	85.0%	60%	365/182	133,413	32	0	1
FAd2	2 (730)	62.5%	60%	365/182	276,596	528	334	8
FAd3	3 (487)	62.5%	60%	365/182	253,667	528	46	212
FAd4	4 (365)	62.5%	60%	365/182	198,684	351	2	47
FAd5	5 (292)	62.5%	60%	365/182	173,428	235	0	26
FAd6	6 (243)	62.5%	60%	365/182	162,428	156	0	30
FBa2	2 (730)	85.0%	45%	730/365	158,901	42	207	2
FBa3	3 (487)	85.0%	45%	730/365	150,943	42	23	185
FBa4	4 (365)	85.0%	45%	730/365	134,421	42	0	36
FBa5	5 (292)	85.0%	45%	730/365	130,614	34	0	0
FBa6	6 (243)	85.0%	45%	730/365	129,085	24	0	0

FBb2	2 (730)	62.5%	45%	730/365	230,119	209	181	175
FBb3	3 (487)	62.5%	45%	730/365	210,446	209	32	426
FBb4	4 (365)	62.5%	45%	730/365	179,002	209	0	224
FBb5	5 (292)	62.5%	45%	730/365	158,367	172	0	53
FBb6	6 (243)	62.5%	45%	730/365	150,833	148	0	10
FBc2	2 (730)	85.0%	45%	365/182	275,028	479	565	14
FBc3	3 (487)	85.0%	45%	365/182	231,322	377	87	231
FBc4	4 (365)	85.0%	45%	365/182	194,661	151	55	168
FBc5	5 (292)	85.0%	45%	365/182	170,881	80	49	102
FBc6	6 (243)	85.0%	45%	365/182	158,864	50	24	80
FBd2	2 (730)	62.5%	45%	365/182	400,280	867	1052	73
FBd3	3 (487)	62.5%	45%	365/182	397,725	867	507	522
FBd4	4 (365)	62.5%	45%	365/182	350,016	615	537	886
FBd5	5 (292)	62.5%	45%	365/182	278,879	390	314	540
FBd6	6 (243)	62.5%	45%	365/182	255,266	282	238	470

FCa2	2 (730)	85.0%	30%	730/365	187,710	64	461	0
FCa3	3 (487)	85.0%	30%	730/365	181,301	64	286	455
FCa4	4 (365)	85.0%	30%	730/365	152,926	64	4	131
FCa5	5 (292)	85.0%	30%	730/365	144,263	48	0	58
FCa6	6 (243)	85.0%	30%	730/365	135,771	38	0	50
FCb2	2 (730)	62.5%	30%	730/365	289,900	366	251	349
FCb3	3 (487)	62.5%	30%	730/365	283,517	366	215	1173
FCb4	4 (365)	62.5%	30%	730/365	233,075	366	3	384
FCb5	5 (292)	62.5%	30%	730/365	215,885	318	0	228
FCb6	6 (243)	62.5%	30%	730/365	196,552	275	0	368
FCc2	2 (730)	85.0%	30%	365/182	460,413	743	764	1973
FCc3	3 (487)	85.0%	30%	365/182	306,941	564	488	550
FCc4	4 (365)	85.0%	30%	365/182	229,664	208	145	96
FCc5	5 (292)	85.0%	30%	365/182	207,684	106	189	130
FCc6	6 (243)	85.0%	30%	365/182	181,143	65	159	88
FCd2	2 (730)	62.5%	30%	365/182	674,854	1095	2328	5638
FCd3	3 (487)	62.5%	30%	365/182	548,250	1019	737	613
FCd4	4 (365)	62.5%	30%	365/182	430,219	888	616	1362
FCd5	5 (292)	62.5%	30%	365/182	336,705	543	527	255
FCd6	6 (243)	62.5%	30%	365/182	306,706	428	506	659

Supplementary table 3:

Projected total and daily peaks of COVID-19 deaths by the end of 2024 in England under different scenarios of uptake rate of vaccination in younger adults

Assumptions and notes:

- Initial overall vaccine efficacy: 62.5% after dose-1 and 85% after dose-2.
- The overall vaccine efficacy is equally attributable to the infection and disease protection.
- Reinfectivity is reduced by 45%.

Scenario	Uptake rate	Vaccination waves (interval days)	Long-term vaccine efficacy	Immunity duration (day): Natural /vaccine	Total COVID-19 deaths (2020-2024)	Daily peaks of COVID-19 deaths		
						2022	2023	2024
Higher coverage in younger adults: age 16-29: 80%; age 30-39: 85%; age 40-49%: 90; age 50+: 90%								
A2b1y	0.80-0.90	1	85.0%	730/365	269147	33	544	328
A2b2y	0.80-0.90	2 (365)	85.0%	730/365	203065	33	5	646
A2b3y	0.80-0.90	3 (365)	85.0%	730/365	149709	33	0	516
A2b4y	0.80-0.90	4 (365)	85.0%	730/365	131794	33	0	23
A2c1y	0.80-0.90	1	85.0%	365/182	374300	652	681	597
A2c2y	0.80-0.90	2 (365)	85.0%	365/182	253530	114	454	438
A2c3y	0.80-0.90	3 (365)	85.0%	365/182	214420	114	41	215
A2c4y	0.80-0.90	4 (365)	85.0%	365/182	182710	114	41	82
B2b1y	0.80-0.90	1	62.5%	730/365	380068	171	852	787
B2b2y	0.80-0.90	2 (365)	62.5%	730/365	294212	171	17	1339
B2b3y	0.80-0.90	3 (365)	62.5%	730/365	230951	171	0	813
B2b4y	0.80-0.90	4 (365)	62.5%	730/365	175249	171	0	187
B2c1y	0.80-0.90	1	62.5%	365/182	618489	764	1506	1842
B2c2y	0.80-0.90	2 (365)	62.5%	365/182	425932	515	1578	875
B2c3y	0.80-0.90	3 (365)	62.5%	365/182	356424	515	465	877
B2c4y	0.80-0.90	4 (365)	62.5%	365/182	331865	515	465	695
Moderate coverage in younger adults: age 16-29: 75%; age 30-39: 80%; age 40-49: 85%; age 50+: 90%								
A2b1	0.75-0.90	1	85.0%	730/365	265799	42	627	243
A2b2	0.75-0.90	2 (365)	85.0%	730/365	206600	42	9	731
A2b3	0.75-0.90	3 (365)	85.0%	730/365	159912	42	0	582
A2b4	0.75-0.90	4 (365)	85.0%	730/365	134421	42	0	36
A2c1	0.75-0.90	1	85.0%	365/182	373907	479	588	435
A2c2	0.75-0.90	2 (365)	85.0%	365/182	266690	151	675	628
A2c3	0.75-0.90	3 (365)	85.0%	365/182	222944	151	55	363
A2c4	0.75-0.90	4 (365)	85.0%	365/182	194661	151	55	168

B2b1	0.75-0.90	1	62.5%	730/365	383433	209	916	801
B2b2	0.75-0.90	2 (365)	62.5%	730/365	304138	209	13	1301
B2b3	0.75-0.90	3 (365)	62.5%	730/365	236662	209	0	952
B2b4	0.75-0.90	4 (365)	62.5%	730/365	179002	209	0	224
B2c1	0.75-0.90	1	62.5%	365/182	611929	867	1542	2437
B2c2	0.75-0.90	2 (365)	62.5%	365/182	443176	615	1860	1096
B2c3	0.75-0.90	3 (365)	62.5%	365/182	376242	615	537	1092
B2c4	0.75-0.90	4 (365)	62.5%	365/182	350016	615	537	886

Lower vaccination coverage in younger adults: age 16-29: 60%; age 30-39: 70%; age 40-49: 80%; age 50+: 90%

A2b1x	0.60-0.90	1	85.0%	730/365	266219	67	638	209
A2b2x	0.60-0.90	2 (365)	85.0%	730/365	214159	67	14	761
A2b3x	0.60-0.90	3 (365)	85.0%	730/365	171971	67	0	562
A2b4x	0.60-0.90	4 (365)	85.0%	730/365	140179	67	0	46
A2c1x	0.60-0.90	1	85.0%	365/182	379362	477	550	353
A2c2x	0.60-0.90	2 (365)	85.0%	365/182	290730	243	1064	1066
A2c3x	0.60-0.90	3 (365)	85.0%	365/182	243384	243	46	548
A2c4x	0.60-0.90	4 (365)	85.0%	365/182	209857	243	46	255
B2b1x	0.60-0.90	1	62.5%	730/365	398443	306	1376	1052
B2b2x	0.60-0.90	2 (365)	62.5%	730/365	333844	306	3	1150
B2b3x	0.60-0.90	3 (365)	62.5%	730/365	237005	306	0	1250
B2b4x	0.60-0.90	4 (365)	62.5%	730/365	185126	306	0	240
B2c1x	0.60-0.90	1	62.5%	365/182	520700	977	1747	1732
B2c2x	0.60-0.90	2 (365)	62.5%	365/182	470214	814	2238	1526
B2c3x	0.60-0.90	3 (365)	62.5%	365/182	406564	814	563	1408
B2c4x	0.60-0.90	4 (365)	62.5%	365/182	377531	814	563	1140

Supplementary files for:

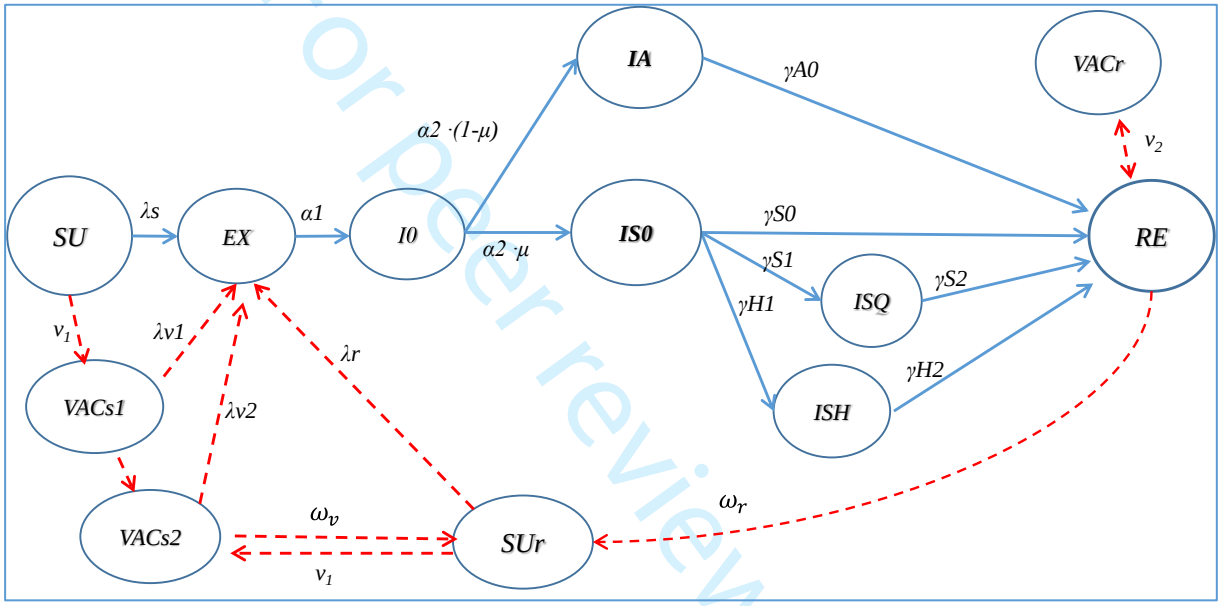
Vaccination against COVID-19 and society's return to normality in England: a modelling investigation of different types of naturally acquired and vaccine induced immunity

1. **Model structure and status**
2. **Data sources and model verification**
3. **Projection scenarios**
4. **Mathematical equations**
5. **R-code used and related input data files**
6. **References**

1. Model structure and status

This is a discrete-time population dynamic simulation model. Population in England are partitioned into discrete categories by sex (male or female), age (0-4, 5-9, then by 10 year age bands, and 80+), and Covid-19 infection categories. The main infection categories include: susceptible (SU), exposed (EX), infected (IN), and recovered (RE) (appendix figure 1). The infected individuals are further categorised as asymptomatic, symptomatic, self-isolated, and hospitalised.

Appendix figure 1: Model structure and transmission across states



Definitions of compartmental states in appendix figure 1

- SU: susceptible individuals
- SUr: Individuals susceptible to reinfection after immunity waning
- EX: exposed individuals, not infectious
- I0: infectious, before symptom onset
- IA: infectious individuals with no or very mild symptoms
- IS0: symptomatic patients who are not quarantined
- ISQ: symptomatic patients self-isolated
- ISH: symptomatic patients who are hospitalised
- RE: recovered from covid-19 infection
- VACs1: vaccinated (dose-1) susceptible individuals
- VACs2: vaccinated (dose-1) susceptible individuals
- VACr: vaccinated individuals who recovered from infection

Transition parameters in appendix figure 1:

- λ_s: Force of infection (λ) measures the risk (probability) of infection transmission.

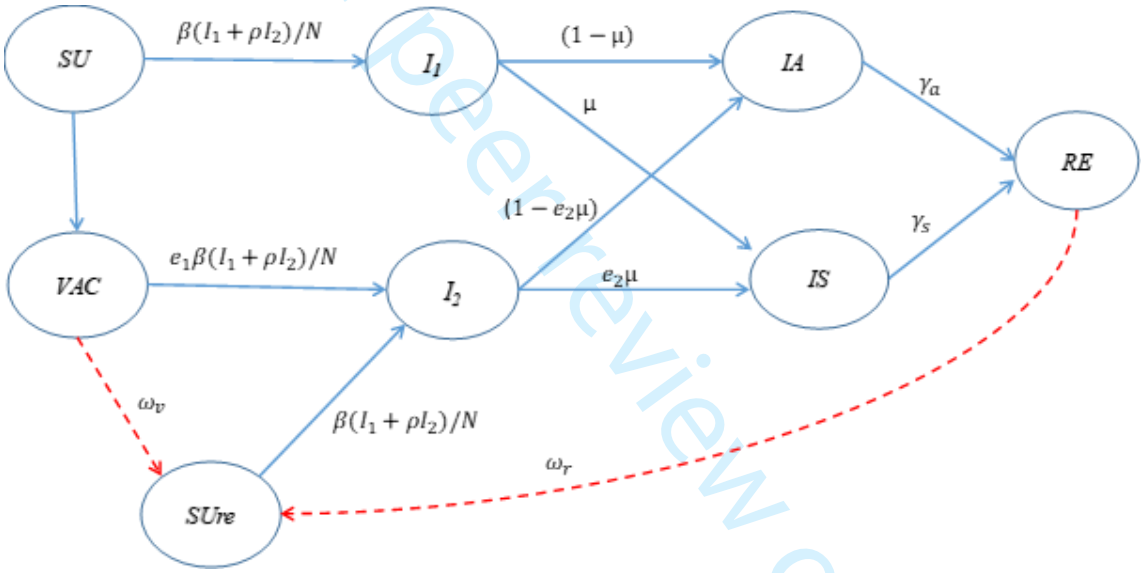
- λ_{v1}: Force of infection (λ) after the first dose vaccine.
- λ_{v2}: Force of infection (λ) after the second dose vaccine.
- λ_r: Force of infection (λ) after waning of vaccine-induced or naturally acquired immunity.
- $\alpha 1$: rate of progressing from being exposed to being infectious.
- $\alpha 2$: rate of progressing from being asymptomatic infectious to symptomatic.
- μ: proportion of infected individuals who will be symptomatic; age-specific
- $\gamma A0$: rate of recovering for asymptomatic individuals
- $\gamma S0$ rate of recovering for symptomatic, not isolated/hospitalised patients
- $\gamma S1$: rate of being isolated in symptomatic patients
- $\gamma S2$: rate of recovering in isolated patients
- $\gamma H1$: rate of being hospitalised for symptomatic patients
- $\gamma H2$: rate of recovering in hospitalised patients
- ν_1: rate of vaccinating susceptible individuals
- ν_2: rate of vaccinating recovered individuals
- ω_v: rate of immunity waning in vaccinated individuals
- ω_r: rate of immunity waning in recovered individuals

All individuals in England are assumed to be susceptible to SARS-CoV-2 infection at the beginning of 2020. Susceptible individuals may be infected by contacting infectious individuals, and the infection status is changed from "susceptible" (SU) to "exposed" (EX). The exposed individuals are not infectious during the early incubation period, but start to be infectious before the onset of symptoms. Individuals infected with SARS-CoV-2 virus may have no or very mild symptoms (IA), and palpable symptoms (symptomatic or clinical infections). Asymptomatic individuals can spread SARS-CoV-2 virus before recovery, although the transmission risk may be lower than symptomatic patients. Symptomatic patients are further classified into three categories: symptomatic patients who are neither isolated nor hospitalised (IS0), those who self-isolate at home (ISQ), and those who are hospitalised (including those being admitted to intensive care units) (ISH). Symptomatic patients are infectious and can transmit the virus to susceptible people before being isolated, hospitalised or recovered. We assume that hospitalised patients (ISH) are well isolated and no longer able to spread the virus to the susceptible population, although infectious patients who are self-isolated at home (ISQ) may transmit virus to household contacts.

Individuals may recover from previous infection of SARS-CoV-2 (RE), and the susceptible and recovered individuals may be vaccinated with vaccines again SARS-CoV-2 virus (VAC1 and VAC2). Individuals recovered or effectively vaccinated may develop immune responses against infection with SARS-CoV-2. However, if the protective immunity is not long lasting, individuals who have recovered or vaccinated may become susceptible again after the waning of the immunity (SUr).

The immune response against COVID-19, either by naturally acquired from past SARSE-CoV-2 infection or vaccine-induced, may be long lasting or short-lived. Immune response may reduce susceptibility of individuals to infection (infection protection, or sterilising, immunity), reduce disease severity after being infected (disease reduction immunity), and reduce infectivity of those who are reinfected after recovery or being vaccinated (reinfectivity reduction immunity).[1] According to existing evidence on immunological characteristics for other human coronaviruses, immunity against reinfection (sterilising immunity) may be waning in several months, while disease and reinfectivity reduction responses are likely long lasting.[1] According to these basic concepts specified by Lavine et al,[1] we incorporate the three types of immune responses into the model, to explicitly evaluate their impacts on future transmission dynamics (appendix figure 2).

Appendix figure 2: Illustration of immune responses by natural infection or vaccination



Notes to appendix figure 2:

- Appendix figure2 is a simplified version of appendix figure 1, not showing isolation and hospitalisation for symptomatic patients.
- *N*: The number of the population
- β: The transmission rate, i.e., the average number of individuals infected daily by an infectious person. It is a function of the number of daily close contacts per person (c), and the transmission risk per contact between a susceptible and an infectious individual (η): i.e., $\beta=c\cdot\eta$.
- I_1: Infectious individuals with primary infection
- I_2: Infectious individuals with secondary infection (infected after being vaccinated or recovered)
- ρ: Relative infectivity of the secondary infection (I_2) compared with the primary infection (I_1). For example, if ρ=0.6, the infectivity of I_2 is 40% lower than the infectivity of I_1
- μ: proportion of infected individuals who will be symptomatic; age-specific
- e_1: Relative efficacy of vaccine for sterilising immunity, reducing risk of virus transmission

- e_2: Relative efficacy of vaccine for pathology reduction, reducing the proportion of symptomatic cases after being infected
- IA: Asymptomatic individuals
- IS: Symptomatic patients
- γ_a : Average rate of recovering of asymptomatic individuals
- γ_s : Average rate of recovering of asymptomatic individuals
- ω_v: rate of immunity waning in vaccinated individuals
- ω_r: rate of immunity waning in recovered individuals

Overall and partial vaccine efficacy

Results of randomised controlled trials shown that vaccines may be >90% efficacious (e.g., Pfizer mRNA vaccine) in reducing severe symptomatic diseases, compared with the placebo group.[2] In appendix figure 2, e_1 and e_2 are parameters of vaccine's efficacy in blocking virus transmission and reducing symptomatic cases in the infected, respectively. The reduction in symptomatic cases in the vaccine group may be due to the prevention of infection in susceptible individuals (related to e_1), or a lower proportion of infected individuals being symptomatic in the vaccine group (related to e_2), or due to a combination of both (note: e_1 and $e_2 \geq 1$ - overall VE, and ≤ 1). Let λ is the transmission risk and μ is the proportion of symptomatic cases in the infected without vaccination. After being vaccinated, the transmission risk is reduced to $\lambda \cdot e_1$, and the proportion of symptomatic cases reduced to $\mu \cdot e_2$. For a vaccine with 90% efficacy in reducing the number of symptomatic cases (compared with the control group), it should be true that $e_1 \cdot e_2 = (1-0.90)$, or $e_1 = 0.10 / e_2$. There are many different possible combinations of e_1 and e_2 for a given overall efficacy in reducing symptomatic cases. For example, $e_1 = e_2 = SQRT(0.30) = 0.548$ corresponds to a 70% efficacy of vaccine with equal sterilising immunity and pathology reduction. If e_1=1 (i.e., zero efficacy in sterilising immunity), all vaccine efficacy will be attributable to the pathology reduction, with e_2=0.30, for a vaccine with 70% efficacy. The partial efficacy is calculated using: $Ei = 1 - (1 - Eo)/Ed$, where Ei is the partial efficacy for infection protection, Ed is the partial efficacy for disease reduction, and Eo is the overall vaccine efficacy. The equal partial efficacy is calculated by: $Ei = Ed = 1 - \sqrt{(1 - Eo)}$. For vaccines with 90%, 70% and 50% overall efficacy, the equal partial efficacy for the infection protection and disease reduction is 69.4%, 45.2%, and 29.3%, respectively.

2. Parameterisation, data sources, and simulation scenarios

2.1 Transition parameters and distribution of infectious period

In appendix figure 1, force of infection (λ) measures the risk of infection,[3] which is a function of transmission rate (η) and the prevalence of existing infectious individuals (I) among the population (N): $\lambda=\eta \cdot I/N$. The transmission rate η in the discrete-time model can be defined as the average number of new infected individuals generated daily by an infected person. That is, $\eta=Rt/T$, in which Rt is effective reproduction number and T is the average infectious period for infected individuals. We calculated η as a function of the number of daily contacts per person (c), and the risk of transmission per contact between a susceptible and an infected individual (β): η=c*β.[4]

The transition rate between model's compartments in infectious models is often assumed to be constant, calculated by 1/x, in which "x" is the average period that subjects remain before the transition to the model's next compartments.[3] Therefore, the infectious period in standard SIR or SEIR models is usually assumed to be exponentially distributed, with some limitations of the use of exponentially distributed infectious period.[5 6] In this study, we assumed that the transition probability between model's compartments are based on gamma distributed periods that individuals remain in a compartment.[7] The transition probability (y) at t is: $y_t = (cg_t - cg_{t-1})/(1 - cg_t)$, where cg_t is the gamma cumulative probability by the end of t. Given mean and shape (k) parameters, the gamma distribution based transition probability is used as a deterministic value to estimate the number of individuals moving between two status in this study.

2.2 Parameterisation and data sources

We estimated initial parameters based on relevant literature and data from the UK government websites (appendix table 1). Key parameters were calibrated according to the reported numbers of covid-19 deaths, hospitalised patients, and the prevalence of infected individuals in England from January 2020 to June 2021.[8]

Appendix table 1: Summary of key model parameters and data sources

Parameter	Value			Source and notes
Proportion of asymptomatic cases in infected individuals (%)				
Age: 0-9	0.71			Davis et al. [9]
10-19	0.79			
20-29	0.73			
30-39	0.67			
40-49	0.60			
50-59	0.51			
60-69	0.37			
70+	0.31			
Proportion of self-isolated symptomatic cases who are not hospitalised				
Age:	**0-49**	**50-69**	**70+**	Assumed by authors, and calibrated according to reported COVID-19 deaths.
Before 13/03/2021	0.10	0.10	0.10	
13/03-23/03/2020	0.40	0.60	0.80	
After 24/03/2020	0.80-0.90	0.80-0.95	0.90-0.95	
Estimated values of gamma distributed parameters (mean, shape k)				
	Before 12/03/20	**13/03-23/03/20**	**After 23/03/20**	Zhang et al. [10] Davies et al. [7] Ferguson et al. [11]
Duration from exposed to being preclinical infectious (day)	4.0 (4)	4.0 (4)	4.0 (4)	
Duration of preclinical infectious (day)	1.5 (2)	1.5 (2)	1.5 (2)	
Infectious period before recovery (day)	5.0 (5)	5.0 (5)	5.0 (5)	
Infectious period before being isolated (day)	4.0 (4)	3.0 (3)	2.0 (2)	
Infectious period during isolation at home (day)	2.0 (2)	3.0 (3)	4.0 (4)	
Infectious period before being hospitalised (day)	4.0 (4)	3.0 (3)	2.0 (2)	
Duration of hospitalisation (day)	10.0 (10)	10.0 (10)	10.0 (10)	
Delay from being infected to deaths from Covid-19 (day)	23.0 (23)	23.0 (23)	23.0 (23)	Verity et al. [12]
Case fatality rates (%)				
Age: 0-9	0.0026			Verity et al. [12]; Chinese CDC [13]
10-19	0.0148			
20-29	0.0600			
30-39	0.1460			
40-49	0.2950			
50-59	1.2500			
60-69	3.9900			
70-79	8.6100			
80+	13.400			
Age specific rates of hospitalisation among infected individuals				
0-9	0.010%			Verity et al. [12]
10-19	0.041%			
20-29	1.04%			
30-39	3.43%			
40-49	4.25%			
50-59	8.16%			
60-69	11.8%			

70-79	16.6%	
80+	18.4%	
SARS-CoV-2 transmission related parameters		
Initial importing of infected cases	The first exposed case was imported to England on 15 January, and the daily number of infectious cases imported was increased by one until 9 February 2020, with a total number of 351 cases imported in 25 days.	Assumed by authors and calibrated with the observed number of covid-19 deaths in England.
the risk of transmission per contact between a susceptible and an infected individual (β)	Before any NPI measures: 0.094 NPI measures (03/2020): 0.066 Alpha variant (10/2020-): 0.077 Delta variant (06/2021-): 0.081	Calibrated according to changes in reported R values,[14] NPI policies[15] and reported covid-19 deaths.[8]
Seasonal changes in transmission risk (09/2021-12/2024)	10% higher in September, October, March and April, and 20% higher in November, December, January and February, compared with the risk in summer months from May to August.	Literature (e.g.,[16]) and authors' assumptions.
Transmission risk by asymptomatic individuals	21% of the transmission risk by symptomatic cases	Li et al.[17]

Assumed impacts of NPIs on general contacts in England. Notes:
Notes: Values are scaling fractions to reduce the normal contacts. For example, a fraction of 0.80 means the contacts are reduced by 20%.

Age group	**0-19**	**20-59**	**60-69**	**70+**	
Before 13/3/2020	1.00	1.00	1.00	1.00	The sex-and-age-specific numbers of daily contacts per person from Mossong et al.[18] Calibrated according to covid-19 control restrictions[15] and reported covid-19 deaths in England.[8]
13/03/2020-	0.90	0.80	0.70	0.60	
17/03/2020-	0.80	0.70	0.60	0.50	
24/03/2020-	0.40	0.30	0.20	0.15	
05/07/2020-	0.60	0.55	0.40	0.20	
01/09/2020-	0.80	0.60	0.50	0.30	
05/11/2020-	0.60	0.30	0.20	0.15	
02/12/2020-	0.70	0.60	0.50	0.30	
05/01/2021-	0.40	0.30	0.20	0.15	
08/03/2021-	0.80	0.60	0.50	0.30	
01/05/2021	0.90	0.80	0.70	0.60	
19/07/2021-	1.00	1.00	1.00	1.00	

Vaccine relative efficacy in reducing symptomatic cases
Notes: We assume that vaccine efficacy for reducing symptomatic cases is equally attributable to infection reduction and disease reduction in the main projections.

14 days after the first dose	62.5%	Public Health England [19]
After the second dose	85.0%	
Long-term efficacy after revaccination	62.5%, 85.0%	Public Health England,[19] and authors' assumption.
Durability of naturally acquired sterilising immunity	365 or 730 days	Lavine et al,[1] Le Bert et al,[20] Widge et al.[21]
Durability of vaccine-induced sterilising immunity	182 or 365 days	
Durability of immunity against severe disease after re-infection	>4 years	
Reduction in reinfectivity (transmission risk) in vaccinated or recovered individuals	30%, 45% or 60%	Mallapaty et al,[22] PHE.[19]

Vaccination programme related parameters Notes: The mass vaccination is modelled as an age-based phase approach, starting from people aged ⩾70, followed by individuals aged 60-69, 50-59, 30-49, and then those aged 16-29 years old.		
Maximum number of vaccinated individuals per day in England	180,000	According to data on numbers of vaccinated individuals[8]
Interval between the first and second vaccine dose	9 weeks	PHE[19]
Vaccination coverage	75%, 80%, 85% and 90%, respectively, in adults aged 16-29, 30-39, 40-49, and ⩾50 years old.	Reported vaccination data[8 19] and authors' assumption.
Vaccination coverage sensitivity analyses	Lower (60%, 70%, and 80%) and higher (80%, 85%, and 90%) in people aged 16-29, 30-39, and 40-49 years old, respectively.	Authors' assumptions.
Frequency of revaccination programmes	Number of (days between) repeated vaccination programmes during 2021-2024: 1 (…), 2 (365), 3 (365); 2 (730), 3 (487), 4 (365), 5 (292), 6 (243)	Authors' assumption

We obtained population statistics in England (estimates of mid-year 2020) from Office for National Statistics. It was assumed that all individuals in England were susceptible to SARS-CoV-2 infection at the beginning of 2020. By contacting with infectious individuals, susceptible individuals may be infected, and their infection category is changed from "susceptible" (SU) to "exposed" (EX). "Exposed" refers to the pre-infectious status of infected individuals. According to data from previous studies, the period of incubation before symptom onset was on average 5.5 days,[10] and the exposed individuals start to be infectious about 1.5 days before the onset of symptoms.[7 11] Therefore, we assumed a gamma distribution of incubation period, with a mean non-infectious period of 4 days (k=4.0) after being exposed, and a mean infectious period of 1.5 days (k=2) before symptom onset (appendix table 1).

Individuals infected with SARS-CoV-2 virus may have no or very mild symptoms (asymptomatic infected), and palpable symptoms (symptomatic patients). As in previous modelling studies [7 11], it was assumed that asymptomatic individuals can spread SARS-CoV-2 virus before recovery, although the infectious risk was assumed to be 21% of symptomatic patients.[17] We used age-specific rates of asymptomatic cases in the infected individuals, reported in a study based on data from 6 countries (appendix table 1).[9]

Symptomatic patients are further classified into three categories: symptomatic patients who are neither isolated nor hospitalised (mainly at the initial phase of the epidemic), those who are self-isolated at home, those who are hospitalised (see appendix figure 1). We assume that asymptomatic individuals were not isolated, although the average number of daily contacts could be reduced by non-pharmaceutical interventions (NPIs), including social distancing, testing, contact tracing, and lockdown. Assumed proportions of self-isolation of symptomatic cases who are not hospitalised, depending on age and NPI measures are shown in appendix table 1.

We assume that only symptomatic patients are hospitalised, and age specific rates of hospitalisation among symptomatic individuals were from Verity et al.[12] The hospitalisation rates were calibrated according to reported numbers of hospitalised patients with covid-19 in England.[23] Based on the reported number of hospitalised patients and estimated number of symptomatic cases, the hospitalisation rate was estimated to be 70% lower than the estimated by Verity et al.[12] Symptomatic patients are infectious and can transmit the virus to susceptible people before being hospitalised or isolated. We assume that hospitalised patients are no longer able to spread the virus to susceptible individuals in the community. However, infected individuals who are self-isolated at home may transmit virus to household contacts. The infectious period before recovery was assumed to be gamma distributed, with a mean value of 5 days. Before implementing any NPIs, the infectious period of symptomatic cases was of a mean value of 4 days (k=4) before being quarantined or hospitalised. After implementing NPI measures, the infectious period for isolated and hospitalised patients was reduced, having a mean value of 2 days (k=2). The mean hospital stay was assumed to be 10 days (k=10) (including ICU admitted patients) (appendix table 1). Verity et al estimated that the average duration from symptom onset to death was 17.8 days.[12] Therefore, we assume that covid-19 related deaths occur on average 23 days (k=23) after being exposed/infected.

The simulation starts from 1 January 2020, over a period of five years until the end of 2024. We assume that the first exposed case was imported to England on January 15th 2020, and the daily number of infectious cases imported was increased by one until 9 February 2020, with a total number of 351 cases imported in 25 days. The sex-and-age-specific numbers of household and community daily contacts per person in the UK were obtained from a study in 8 European countries.[18 24] For the purpose of simplicity, we considered only household contacts (relevant to self-isolation at home) and general daily contacts (for all types of contacts). The risk of positive transmission per contact between susceptible and infectious individuals (β) was estimated by calibrating estimated and reported numbers of covid-19 deaths in England, household and general daily contacts per person, and other model parameters.

In this study, all COVID-19 related deaths are assumed to be from symptomatic cases, and age specific case fatality rates were based on a study by Verity et al.[12] We assume that individuals infected with Covid-19 will not die from other causes before recovery. Average sex and age specific rates of all-cause deaths in England during 2015-2019 [25] were applied to people who are not infected with or recovered from covid-19. For simplicity and maintaining a stable population, we assumed that the number of births at day t equals to the number of all deaths at day t-1. Furthermore, we did not consider the influence of migration on the population. We adjusted the number of individuals belong to an age group (all <80+) at the beginning of the year since 2021 by shifting 20% (for age group 0-4 and 5-9) or 10% (for age group 10-19, … 70-79) of them to the adjacent higher age group.

NPI and seasonal impacts on transmission parameters

Since March 2020, NPI measures were recommended and gradually tightened in England, including hand washing, mouth covering when coughing in public places, home isolation of individuals with COVID-19 like symptoms, shielding of vulnerable individuals, avoiding non-essential contacts, and maintaining social distancing. These measures reduced contacts and transmission risk, and shortened the period of transmission by symptomatic individuals. We assumed that the general population's contact rates were reduced by 10% to 40%, depending on age and co-morbidity. Based on the reported number of COVID-19 deaths, we estimate that the transmission risk per contact between infectious and susceptible individuals was reduced from β=0.094 before the implementation of any NPIs to 0.069 by 15 March 2020 and 0.062 since May 2020. The UK government put lockdown measures in place from 24 March 2020, including working from home if possible, closure of schools and non-essential shops, pubs and restaurants, avoiding non-essential travelling, and cancelling gathering activities. We assume that numbers of general population contacts were reduced by 60-85% (appendix table 1). We assume that the household contacts were not influenced by the NPI measures.

The lockdown measures in England started to be relaxed from 13 May 2020 by allowing partial returning to work. Further relaxing of control measures followed, including reopening of some shops and allowing outdoor meetings up to six people from 1 June, re-opening of more non-essential shops from 5 June, and further relaxing of restrictions (such as re-opening of pubs and restaurants) from 5 July 2020. However, social distancing measures was maintained and face covering was required where social distancing could not be implemented. From 1 September 2020, schools in England were re-opening. Consequently, the transmission risk per contact between susceptible and infectious individuals was increased since September. The impacts of these changes in NPIs were reflected in the assumed social contacts and transmission risk. Because of the new virus variants,[26] the average transmission risk per contact was increased β=0.077 since October 2020, and β=0.081 since June 2021.

To incorporate the impact of seasonality on future projections, we assumed that the transmission risk is increased by 10% in September, October, March and April, and increased by 20% in November, December, January and February.

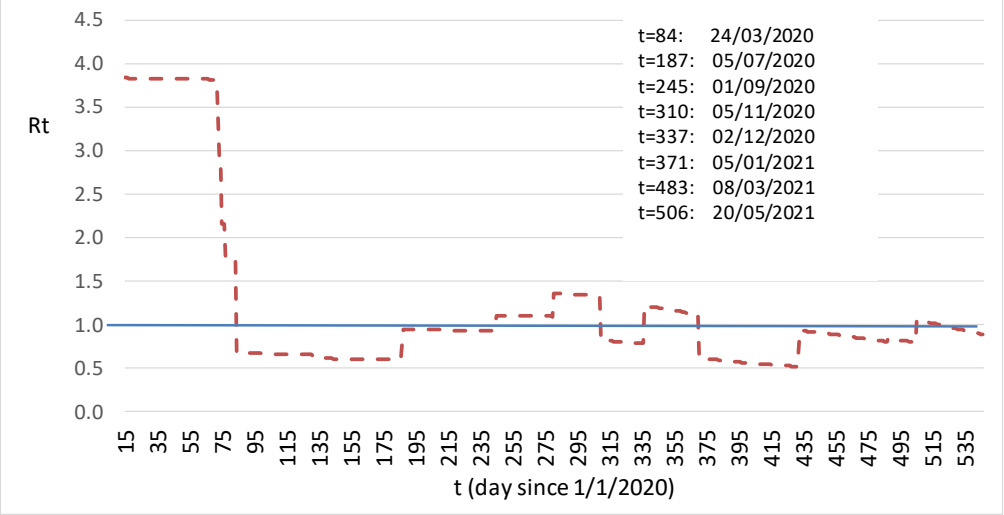
Model verification/calibration

We used the developed model and initially estimated parameters to simulate the covid-19 epidemic in England from January 2020 to June 2021. Key parameters were calibrated based mainly on reported covid-19 related deaths, although numbers of hospitalised patients and infection rates in England were also considered.

We assume that the first exposed case was imported to England on 15 January 2020, and the number of cases imported each day increased by one more case than the previous day until 9 February 2020 (the total number of cases imported in 25 days was therefore 351). We don't use the reproduction number

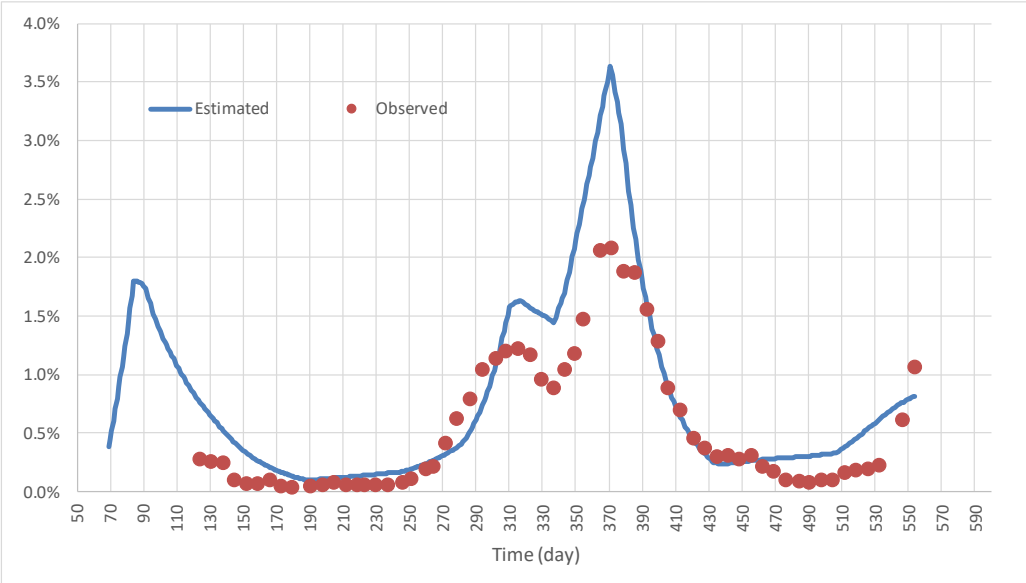
(R0 or Rt) as an input parameter, but derived the reproduction numbers based on a method used by Giordano and colleagues (see equation 55 in Mathematical equations) [3 27]. We estimated that the basic reproduction number (R0) was 3.63 at the initial stage of the COVID-19 epidemic before any control measures were taken in England, which is similar to findings from previous studies.[7 11] Following the implementation of NPI measures, the estimated reproduction value (Rt) was reduced to 0.65 by 24 March. The Rt value was increased to 0.93 by 5 July 2020 after the NPI measures were relaxed, and Rt was about 1.09 after school reopening in September and 1.31 by October 2020. The Rt was reduced to 0.79 since 5 November 2020 after reintroducing NPI measures, increased to about 1.17 after relaxing NPIs since 2 December 2020, and reduced again to about 0.57 since 5 January 2021 after reintroducing lockdown measures (plus rolling out of vaccination) (appendix figure 3). The estimated R values were within the range of the reported in England (https://coronavirus.data.gov.uk/).

Appendix figure 3: Estimated reproduction numbers, between 01/2020 – 06/2021, in England



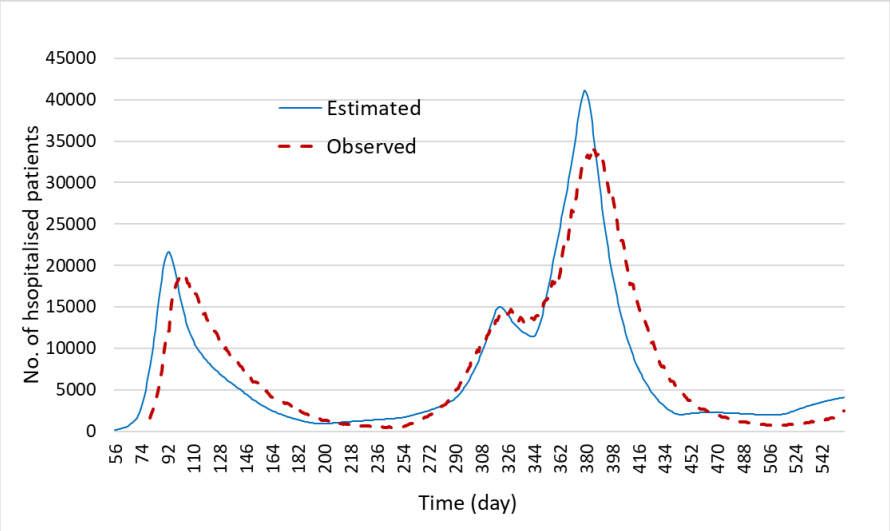
The model estimated that the prevalence of the recovered was 5.5 by 26 April, 7.6% by 24 May, and 8.5% by 24 June 2020, which were similar to the estimated rates of positive antibodies to Covid-19 in the UK (i.e., 7.1% in May-June 2020).[28] Data on the prevalence of infected individuals in the community was available from May 2020. The model estimated prevalence of infected individuals from January 2020 to January 2021, which had a similar trend as the reported prevalence in England (appendix figure 4).

Appendix figure 4: Estimated and reported prevalence of infection, from January 2020 to June 2021, in England



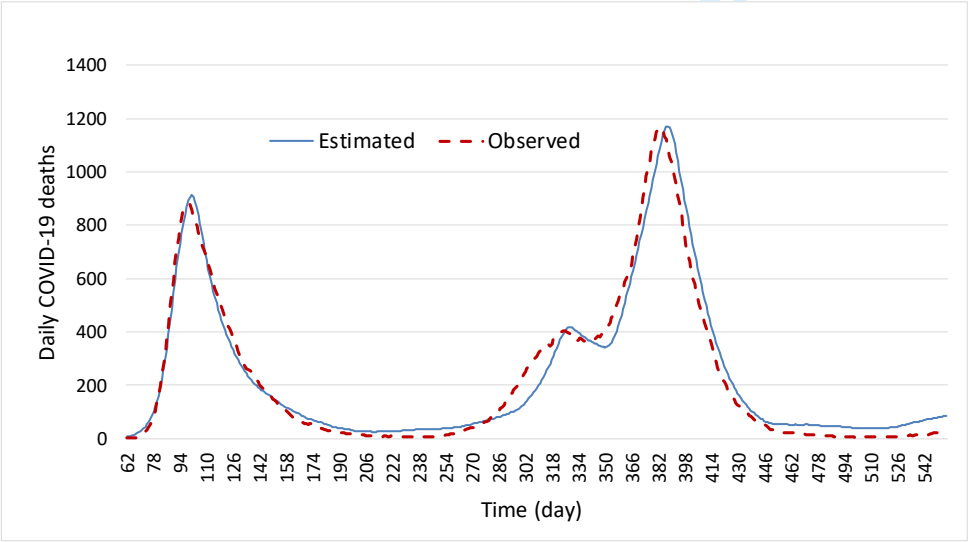
Changes in the estimated numbers of hospitalised COVID-19 patients were of similar trends as the reported numbers of hospitalised patients during 01/2020-01/2021. However, there were considerable differences at peak time points (appendix figure 5), which may be explained by reduced hospitalisation rates during peak period.

Appendix figure 5: Reported and estimated numbers of hospitalised Covid-19 patients, during 01/2020-01/2021, in England



Appendix figure 6 shows that the estimated daily deaths well matched the observed daily deaths from Covid-19, from January 2020 to June 2021, in England.

Appendix figure 6: Reported and estimated daily deaths from Covid-19, during 01/2020-06/2021, in England



3. Vaccination and projection scenarios

We used estimates of transmission parameters, age-specific hospitalisation rates and case fatality rates in June 2021 to project COVID-19 deaths from 2021 to 2024, under various scenarios of vaccine efficacy, durability of both naturally acquired and vaccine induced immunity, and reduction in reinfectivity. There are no more restrictions on social activities since 19 July 2021 in England, and social contacts are return to normal as before the pandemic, but basic hygienic measures would be maintained.

The UK Government's Vaccination Taskforce has recommended rollout of vaccines against COVID-19 to be prioritised primarily by age and comorbidity, with older people being vaccinated first.[29] The Joint Committee on Vaccination and Immunisation (JCVI) in the UK previously recommended COVID-19 vaccination of individuals aged ≥18, and also recommended vaccination of young people aged 16-17 years old on 4 August 2021.[30] Vaccination of prioritised individuals began from 8 December 2020 in the UK and around 2 million individuals were vaccinated (mostly with a single dose of Pfizer vaccine) by 10 January 2021.[31] By July 2021, the coverage of individuals who were fully vaccinated (with two does) was >90% in adults aged ≥65, 80-90% in those aged 50-64, 60% in adults aged 40-49.[32] For young adults aged 18-39, about 36% have received the first dose of vaccines by July 2021. Therefore, the vaccination coverage in England has been high in older adults, but it remains uncertain whether such high coverage could be achieved in younger adults. In this study, the mass vaccination is modelled as an age-based phase approach, starting from people aged ≥70, followed by individuals aged 60-69, 50-59, 30-49, and then those aged 16-29. We assume that the mass vaccination starts from 1 January 2021, and the maximum number of individuals vaccinated per day is 180,000 in England, to matched with numbers of vaccinated individuals according to the official statistics. In the main analysis, we assume that the uptake rate is 75%, 80%, 85% and 90%, respectively, in adults aged 16-29, 30-39, 40-49, and ≥50 years old. Because of uncertain coverage of vaccination in younger people, we conducted sensitivity analyses under scenarios with lower (60%, 70%, and 80%) and higher (80%, 85%, and 90%) coverage of vaccination in people aged 16-29, 30-39, and 40-49 years old, respectively.

Results of randomised controlled trials shown that vaccines may be >90% efficacious (e.g., Pfizer mRNA vaccine) in reducing severe symptomatic diseases, compared with the placebo group. Assume that e_1 and e_2 are parameters of vaccine's efficacy in blocking virus transmission and reducing symptomatic cases in the infected, respectively (as in appendix figure 2). The reduction in symptomatic cases in the vaccine group may be due to the prevention of infection in susceptible individuals (i.e., infection protection, related to e_1), or a lower proportion of infected individuals being symptomatic in the vaccine group (i.e., disease reduction, related to e_2), or due to a combination of both. For a vaccine with 90% efficacy in reducing the number of symptomatic cases (compared with the control group), it is true that $e_1 \cdot e_2 = (1-0.90)$, or $e_1 = (1-0.90)/e_2$ (note: e_1 and e_2 ≥1-overall VE, ≤1). There are many different possible combinations of e_1 and e_2 for an overall efficacy in reducing symptomatic cases. We assume that vaccine efficacy is equally attributable to infection and disease reduction in the main

projections. The infection protection (sterilising immunity) after vaccination has been demonstrated. For example, an observational study in the UK (SIREN) found that the risk of being infected was reduced by 70% in health workers after a single dose of the Pfizer-BioNTech vaccine.[33 34]

Both Pfizer-BioNTec and AstraZeneca vaccines are 2-dose regimens, the policy in the UK has been to initially provide the first dose to as many individuals as possible to maximise the public health impact.[35] Exploratory assessment of data from clinical trials found that the short-term vaccine efficacy from the first dose of the Pfizer-BioNTech vaccine and the AstraZeneca vaccine is about 90% and 70%, respectively.[35] Public Health England (PHE) in July 2021 estimated that the efficacy was 55-70% after the first dose, and 70-85% or 85-95% after the second dose.[32] Therefore, we assume that the overall vaccine efficacy is 62.5% after the first dose and 85% after the second dose. The protection effects start 14 days after the first dose vaccination, and the interval between the first and second dose is 9 weeks. For vaccines with 62.5% and 85.0% overall efficacy, the equal partial efficacy for the infection protection and for disease reduction is 38.8% and 61.3%, respectively. The overall vaccine efficacy after the second dose may be lower than 85.0% due to new variants of SARS-CoV-2 virus. Therefore, we evaluated two overall vaccine efficacy rates, 62.5% or 85.0%, after the second dose of vaccine.

Available evidence has indicated that the duration of sterilising (infection protection) immunity after coronavirus infection ranges from 0.5 to two years.[1] Serum neutralizing antibodies were detected in all participants at four months follow up after SAR-CoV-2 mRNA vaccination.[21] Therefore, we assume that naturally acquired sterilising immunity lasts for 365 or 730 days, and vaccine-induced sterilising immunity lasts for 182 or 365 days. After waning of sterilising immunity, individuals may be susceptible again to infection with SARS-CoV-2 virus, but the disease reduction immunity is likely longer lasting.[1] Due to the existence of disease reduction immunity, the reinfectivity of individuals who are reinfected after waning of sterilising immunity may be reduced. Lavine and colleagues estimated that the secondary transmissibility (i.e., reinfectivity) was 35% of the primary transmissibility (i.e., the reinfectivity was reduced by 65%).[1] Evidence from clinical trials and vaccination in the real world indicated that the viral loads and the duration of virus shedding in the infected individuals after vaccination were considerably reduced, compared with unvaccinated individuals.[36 37] Based on preliminary data, PHE estimated that the reinfectivity was reduced by 35-50% after the first dose of vaccines.[32] The reduction in reinfectivity is likely to be larger after the second dose of vaccines. More recent studies reported that fully vaccinated individuals who were infected were up to 78% less likely to transmit the virus to unvaccinated individuals.[22] Therefore, we assume a range of the risk of reinfectivity after waning of sterilising immunity; the reinfectivity is reduced by 30%, 45% or 60%. We also assume that the infectivity of ineffectively vaccinated individuals is the same as recovered individuals whose sterilising immunity has waned, and that vaccination of individuals recovered from natural infection boosts their naturally acquired immunity.

We considered different frequent scenarios of revaccination programmes. First, we evaluated a single vaccination programme and multiple (2-4) annual vaccination programmes during 2021-2024. In addition, simulation projections were conducted by revaccination programmes with different intervals, including 2-6 revaccination programme and corresponding intervals between them.

In summary, projection scenarios are defined from the following aspects: vaccine efficacy, frequency of revaccination programmes, durability of natural and vaccine induced sterilising immunity, reduction in reinfectivity after the waning of natural and vaccine-induced immunity against reinfection. The main characteristics of the simulated scenarios are available in supplementary table 1, supplementary table 2 and supplementary table 3.

In this study, we focus on deaths in people infected with COVID-19, although our model also produces estimates of changes in effective reproduction values (Rt), numbers of infected and vaccinated individuals, and hospitalised patients. We performed multiple simulations under various scenarios. For clarity, we focus on results of selected scenarios in the main text, but report more data on simulation results in supplementary tables.

4. Model's mathematical equations

Notations:

- subscript used: "s" refers to sex, 1: male, 2: female, 3: both male and female; "a" refers to age group, 1: 0-4 years, 2: 5-9 years, 3: 10-19, …, 10: ≥ 80; 11: all age groups. "t" refers to time (day).
- N: The number of the population
- λ_s: Force of infection (λ) measures the risk (probability) of infection transmission, which is a function of transmission rate (β) and the prevalence of infectious individuals (I) among the population (N): $\lambda=\beta \cdot I/N$. [3]
- β: The transmission rate β in this discrete-time model is defined as the average number of individuals infected daily by an infectious person. It is a function of the number of daily close contacts per person (c), and the transmission risk per contact between a susceptible and an infectious individual (η): i.e., $\beta=c \cdot \eta$. [4]
- α1: rate of progressing from being exposed to being infectious.
- α2: rate of progressing from being asymptomatic infectious to symptomatic.
- μ: proportion of infected individuals who will be symptomatic; age-specific
- *infA*: The fraction of infection force for infected individuals with no or mild symptoms. It was assumed that infA=0.5 in this study.
- fS0: fraction of symptomatic patients who will not be quarantined.
- fSq: fraction of symptomatic patients who will be quarantined (self-isolation).
- fSh: fraction of symptomatic patients who will be hospitalised (including ICU admission).
- γA0: rate of recovering for asymptomatic individuals
- γS0 rate of recovering for symptomatic, not isolated/hospitalised patients
- γS1: rate of being isolated in symptomatic patients
- γS2: rate of recovering in isolated patients
- γH1: rate of being hospitalised for symptomatic patients

  γ*YH2*: rate of recovering in hospitalised patients
- ν_1: rate of vaccinating susceptible individuals
- ν_2: rate of vaccinating recovered individuals
- ρ: Relative infectivity of the secondary infection (I_2) compared with the primary infection (I_1). For example, if ρ=0.6, the infectivity of I_2 is 40% lower than the infectivity of I_1
- e_1: Relative efficacy of vaccine for sterilising immunity, reducing risk of virus transmission
- e_2: Relative efficacy of vaccine for pathology reduction, reducing the proportion of symptomatic cases after being infected
- IA: Asymptomatic individuals
- IS: Symptomatic patients
- γ_a : Average rate of recovering of asymptomatic individuals
- γ_s : Average rate of recovering of asymptomatic individuals

- ω_v: rate of immunity waning in vaccinated individuals
- ω_r: rate of immunity waning in recovered individuals
- $drOth_{s,a,t}$: sex, age-specific risk of deaths from causes other than covid-19, specific by week of the year.
- $drCov_{s,a,d}$: death risk from infected individuals before recovery, specific according to days since being infected.
- ds0, dsq, and dhos are the proportion of covid-19 deaths among symptomatic patients who are not quarantined, those who are isolated, or hospitalised, respectively. 1=ds0+dsq+dhos

Sex and age specific population:

$$\boldsymbol{N_{s,a,t}} = SU_{s,a,t} + SUr_{s,a,t} + VAC1_{s,a,t} + EX1_{s,a,t} + I01_{s,a,t} + EX2_{s,a,t} + I02_{s,a,t} + IA_{s,a,t} + IS0_{s,a,t} + ISQ_{s,a,t} + ISH_{s,a,t} + RE_{s,a,m,t} \quad (1)$$

Total number of the primary infection with no symptoms (age-specific):

$$aIA1_{a,t} = \sum_s (IA1_{s,a,t} + I01_{s,a,t} \cdot (1 - \mu_a)) \quad (2)$$

Total number of the primary infections with symptoms, isolated (age-specific):

$$aISQ1_{a,t} = \sum_s (ISQ1_{s,a,,t}) \quad (3)$$

Total number of the primary infections with symptoms, not isolated (age-specific):

$$aIS01_{a,t} = \sum_{s,} (IS01_{s,a,t} + I01_{s,a,t} \cdot \mu_a) \quad (4)$$

Total number of the secondary infection with no symptoms (age-specific):

$$aIA2_{a,t} = \sum_s (IA2_{s,a,t} + I02_{s,a,t} \cdot (1 - \mu_a \cdot e_2)) \quad (5)$$

Total number of the secondary infections with symptoms, isolated (age-specific):

$$aISQ2_{a,t} = \sum_s (ISQ2_{s,a,,t}) \quad (6)$$

Total number of the secondary infections with symptoms, not isolated (age-specific):

$$aIS02_{a,t} = \sum_{s,} (IS02_{s,a,t} + I02_{s,a,t} \cdot \mu_a \cdot e_2) \quad (7)$$

Sex and age specific susceptible population:

$$\boldsymbol{SU_{s,a,t+1}} = (SU_{s,a,t} - su\mathrm{Exp}_{s,a,t} - VAC1_{s,a,t}) \cdot (1 - drOth_{s,a,t}) + NewBirth_{s,t} \quad (8)$$

Note: $drOth_{s,a,,t}$ is sex, age-specific death rates for non-covid causes, specific by week of the year.

Newly exposed/infected with SARS-CoV-2 in susceptible individuals:

$$suExp_{s,a,t} = \sum_{j=1}^{10} SU_{s,a,t} \cdot \eta_t \left(\left((Ca_{a,j,t} \cdot \frac{infA \cdot aIA1_{j,t} + aIS1_{j,t}}{N_{3,j,t}} + Cb_{a,j,t} \cdot \frac{aISQ1_{j,t}}{N_{3,j,t}}) \right) + \rho \cdot \left(Ca_{a,j,t} \cdot \frac{infA \cdot aIA2_{j,t} + aIS2_{j,t}}{N_{3,j,t}} + Cb_{a,j,t} \cdot \frac{aISQ2_{j,t}}{N_{3,j,t}} \right) \right) \quad (9)$$

Notes: $Ca_{a,j,t}$ is the average number of general contacts between people aged a and j; and $Cb_{a,j,t}$ is the average number of household contacts between people age a and j.

Newly exposed/infected in vaccinated individuals:

$$vacExp_{s,a,t} = \sum_{j=1}^{10} VAC1_{s,a,t} \cdot \eta_t \cdot e_1 \left(\left((Ca_{a,j,t} \cdot \frac{infA \cdot aIA1_{j,t} + aIS1_{j,t}}{N_{3,j,t}} + Cb_{a,j,t} \cdot \frac{aISQ1_{j,t}}{N_{3,j,t}}) \right) + \rho \cdot \left(Ca_{a,j,t} \cdot \frac{infA \cdot aIA2_{j,t} + aIS2_{j,t}}{N_{3,j,t}} + Cb_{a,j,t} \cdot \frac{aISQ2_{j,t}}{N_{3,j,t}} \right) \right) \quad (10)$$

Newly exposed/infected in the recovered or vaccinated after waning of immunity:

$$sureExp_{s,a,t} = \sum_{j=1}^{10} SUre_{s,a,t} \cdot \eta_t \left(\left((Ca_{a,j,t} \cdot \frac{infA \cdot aIA1_{j,t} + aIS1_{j,t}}{N_{3,j,t}} + Cb_{a,j,t} \cdot \frac{aISQ1_{j,t}}{N_{3,j,t}}) \right) + \rho \cdot \left(Ca_{a,j,t} \cdot \frac{infA \cdot aIA2_{j,t} + aIS2_{j,t}}{N_{3,j,t}} + Cb_{a,j,t} \cdot \frac{aISQ2_{j,t}}{N_{3,j,t}} \right) \right) \quad (11)$$

The number of the recovered or vaccinated who lose sterilising immunity (d from 1 to tt):

$$SUre_{s,a,t+1} = (SUre_{s,a,t} - sureEXP_{s,a,t}) \cdot (1 - drOth_{s,a,t}) + \sum_{d=1}^{tt} (iRE_{s,a,d,t} \cdot \omega_{r,d} + iVAC1_{s,a,d,t} \cdot \omega_{v,d}) \quad (12)$$

Notes: "*tt*" is the total number of days simulated. $\omega_{r,d}$ and $\omega_{v,d}$ are gamma distributed rate of immunity waning, respectively, a function of days since the recovery and vaccination. $iRE_{s,a,d,t}$ is the number of recovered since d days from recovery; and $eVAC1_{s,a,d,t}$ is the number of vaccinated since d days after vaccination.

The number of new (d=1) primary infections in susceptible individuals:

$$iEX1_{s,a,1,t} = suEXP_{s,a,t} \quad (13)$$

The number of new (d=1) secondary infections in recovered or vaccinated individuals:

$$iEX2_{s,a,1,t} = sureEXP_{s,a,t} + vacExp_{s,a,t} \quad (14)$$

For d=1,2,3…60 (assuming all will be dead or recovered by day 60 after being infected):

$$iEX1_{s,a,d+1,t+1} = iEX1_{s,a,d,t} \cdot (1 - \alpha 1_d) \quad (15)$$

$$iEX2_{s,a,d+1,t+1} = iEX2_{s,a,d,t} \cdot (1 - \alpha 1_d) \quad (16)$$

Assumed that covid-19 deaths were from symptomatic patients only. Overall deaths from covid-19 were calculated using the case fatality rates, and timing of covid-19 related deaths were assumed to have a gamma distribution according to days since being infected. Therefore a variable was introduced to record number of symptomatic individuals by days since being exposed/infected to calculate number of covid-19 deaths:

$$iSY_{s,a,1,t} = \mu_a\left(suExp_{s,a,t} + e_2 \cdot (surExp_{s,a,t} + vacExp_{s,a,,t})\right) \quad (17)$$

For d=1,2,3…60 (the transmission completed by day 60):

$$iSY_{s,a,d+1,t+1} = iSY_{s,a,d,t} \cdot (1 - drCov_{s,a,d}) \quad (18)$$

The number of covid-19 deaths at time t:

$$dthCov_{s,a,t} = \sum_{d=1}^{60} iSY_{s,a,d,t} \cdot drCov_{s,a,d} \quad (19)$$

The number of new (d=1) primary infections individuals before onset of symptoms:

$$iI01_{s,a,1,t+1} = \sum_{d=1}^{60} iEX1_{s,a,d,t} \cdot \alpha 1_d \quad (20)$$

The number of new (d=1) secondary infectious individuals before onset of symptoms:

$$iI02_{s,a,1,t+1} = \sum_{d=1}^{60} iEX2_{s,a,d,t} \cdot \alpha 1_d \quad (21)$$

For d=1,2,3…60 (the transmission completed by day 60):

$$iI01_{s,a,d+1,t+1} = iI01_{s,a,d,t} \cdot (1 - \alpha 2_d) \quad (22)$$

$$iI02_{s,a,d+1,t+1} = iI02_{s,a,d,t} \cdot (1 - \alpha 2_d) \quad (23)$$

The number of all infectious individuals before onset of symptoms:

$$\boldsymbol{I0_{s,a,t}} = \sum_{d=1}^{60} iI0_{s,a,d,t} \quad (24)$$

The number of new (d=1) infected individuals with no or very mild symptoms:

$$iIA_{s,a,1,t+1} = \sum_{d=1}^{60}\left(iI01_{s,a,d,t} \cdot \alpha 2_d \cdot (1 - \mu_a) + iI02_{s,a,d,t} \cdot \alpha 2_d \cdot (1 - e_2\mu_a)\right) \quad (25)$$

For d=1,2,3…60 (the transmission completed by day 60):

$$iIA_{s,a,d+1,t+1} = iIA_{s,a,d,t} \cdot (1 - \gamma A_d) \quad (26)$$

The number of all infectious individuals with no or mild symptoms:

$$IA\_(s,a,t) = \sum_{d=1}^{60} iIA_{s,a,d,t} \quad (27)$$

The number of all new (d=1) symptomatic patients:

$$SYM_{s,a,t+1} = \sum_{d=1}^{60}(iI01_{s,a,d,t} + e_2 \cdot iI02_{s,a,d,t}) \cdot \alpha 2_d \cdot \mu_a \quad (28)$$

The number of new (d=1) symptomatic patients who are not self-isolated:

$$iIS0_{s,a,1,t} = SYM_{s,a,t} \cdot fS0_t \quad (29)$$

Symptomatic patients (before being isolated or hospitalised:

$$iIS0_{s,a,,d+1,t+1} = (iIS0_{s,a,,d,t} - dthCov_{s,a,t} \cdot ds0_d) \cdot (1 - YS0_d) \quad (30)$$

The number of new (d=1) symptomatic patients being isolated/quarantined:

$$iSQ_{s,a,1,t} = SYM_{s,a,t} \cdot fSq_{a,t} \quad (31)$$

Isolated symptomatic patients:

$$iSQ_{s,a,d+1,t+1} = \sum_{d=1}^{60}(iSQ_{s,a,d,t} - dthCov_{s,a,t} \cdot dsq_d) \cdot (1 - YS1_d) \quad (32)$$

The number of new (d=1) symptomatic patients being hospitalised:

$$iSH_{s,a,1,t} = SYM_{s,a,t} \cdot fSh_{a,t} \quad (33)$$

Hospitalised symptomatic patients:

$$iSH_{s,a,d+1,t+1} = \sum_{d=1}^{60}(iSH_{s,a,d,t} - dthCov_{s,a,t} \cdot dsh_d) \cdot (1 - YH1_d) \quad (34)$$

The number newly recovered people (d=1):

$$iRE_{s,a,1,t+1} = \sum_{d=1}^{60}(iIA_{s,a,d,t} \cdot YA0_d + iIS0_{s,a,d,t} \cdot YS0_d + iISQ_{s,a,d,t} \cdot YS2_d + iISH_{s,a,d,t} \cdot YH2_d + VAC2_t) \quad (35)$$

Note: $VAC2_t$ is the number of newly vaccinated individuals who recovered from previous infections.

All recovered for d=1,2,3…tt:

$$iRE_{s,a,d+1,t+1} = (iRE_{s,a,d,t} - VAC2_t) \cdot (1 - \mu r_d) \cdot (1 - drOth_{s,a,t}) \quad (36)$$

All recovered individuals:

$$\boldsymbol{RE_{s,a,t}} = \sum_{d=1}^{tt} iRE_{s,a,d,t} \quad (37)$$

Derived reproduction values (R0, Rt)

The basic reproduction ratio (R0) is defined as the average number of individuals infected by a typical infectious individual in a total susceptible population, and effective reproduction ratio (Rt) is the number

of individuals infected by an infectious individual when only a proportion of the population are susceptible and the disease transmission dynamic may be influenced by control measures.[38] R values depend on the risk of infection per contact between an infectious and susceptible person, person-to-person contacts between individuals, the rate of transition from exposed to infectious, infectious period, and the prevalence of susceptible individuals in the population.[3] In this study, we don't use the reproduction ratio directly in simulating the spread of SARS-CoV-2 virus. To facilitate the understanding of effects of different intervention strategies, we estimated R0 and Rt during the simulation period, based on average values of relevant parameters and the calculation method used in a modelling study by Giordano et al.[27]

Average values of relevant parameters for estimating R values:

Weighted average fraction of symptomatic individuals in all infected individuals:

$$fS_t = \sum_a \left(\mu_a \cdot N_{3,a,t}/N_{3,11,t}\right) \quad (38)$$

Weighted average fraction of hospitalised symptomatic patients:

$$fH_t = \sum_a \left(fSH_{a,t} \cdot N_{3,a,t}/N_{3,11,t}\right) \quad (39)$$

Weighted average fraction of symptomatic patients self-isolated:

$$fQ_t = \sum_a \left(fSQq_{a,t} \cdot N_{3,a,t}/N_{3,11,t}\right) \quad (40)$$

Risk of daily transmission per infectious individual, depending on asymptomatic or symptomatic, household isolated or not:

$$\beta I0_t = \sum_{a,j=1}^{10} \mu_t \cdot Ca_{a,j,t} \cdot \frac{N_{j,t}}{N_{3,11,t}} \cdot (infA \cdot (1 - fS_t) + fS_t) \quad (41)$$

$$\beta IA_t = \sum_{a,j=1}^{10} \mu_t \cdot Ca_{a,j,t} \cdot \frac{N_{j,t}}{N_{3,11,t}} \cdot infA \cdot (1 - fS_t) \quad (42)$$

$$\beta SQ_t = \sum_{a,j=1}^{10} \mu_t \cdot Cb_{a,j,t} \cdot \frac{N_{j,t}}{N_{3,11,t}} \cdot (infA \cdot (1 - fS_t) + fS_t) \quad (43)$$

$$\beta S0_t = \sum_{a,j=1}^{10} \mu_t \cdot Ca_{a,j,t} \cdot \frac{N_{j,t}}{N_{3,11,t}} \quad (44)$$

The following transition variables are calculated for estimating R values:

$$d1_t = \alpha 2_t \cdot (1 - fS_t) \quad (45)$$

$$d2_t = \alpha 2_t \cdot fS_t \cdot fS0_t \quad (46)$$

$$d3_t = \alpha 2_t \cdot fS_t \cdot fSQ_t \quad (47)$$

$$d4_t = \alpha 2_t \cdot fS_t \cdot fSH_t \quad (48)$$

$$dA1_t = d1_t + d2_t + d3_t + d4_t \quad (49)$$

$$d5_t = \alpha 2_t \cdot (1 - fS_t \cdot e_2) \quad (50)$$

$$d6_t = \alpha 2_t \cdot fS_t \cdot fS0_t \cdot e_2 \quad (51)$$

$$d7_t = \alpha 2_t \cdot fS_t \cdot fSQ_t \cdot e_2 \quad (52)$$

$$d8_t = \alpha 2_t \cdot fS_t \cdot fSH_t \cdot e_2 \quad (53)$$

$$dA2_t = d5_t + d6_t + d7_t + d8_t \quad (54)$$

Effective reproductive value (Rt):

$$Rt = \frac{SU_{3,11,t}}{N_{3,11,t}} \left(\beta I0_t \cdot \frac{1}{dA1_t} + \beta IA_t \cdot \frac{d1_t}{dA1_t \cdot YA0_t} + \beta S0_t \cdot \frac{d2_t}{dA1_t \cdot YS0_t} + \beta SQ_t \cdot \frac{d3_t}{dA1_t \cdot YS1_t} + \beta SH_t \cdot \frac{d4_t}{dA1_t \cdot YH1_t}\right) + \left(\frac{SUre_{3,11,t}}{N_{3,11,t}} + \frac{VAC1_{3,11,t}}{N_{3,11,t}} \cdot e_1\right) \cdot \rho \cdot \left(\beta I0_t \cdot \frac{1}{dA2_t} + \beta IA_t \cdot \frac{d5_t}{dA2_t \cdot YA0_t} + \beta S0_t \cdot \frac{d6_t}{dA2_t \cdot YS0_t} + \beta SQ_t \cdot \frac{d7_t}{dA2_t \cdot YS1_t} + \beta SH_t \cdot \frac{d8_t}{dA2_t \cdot YH1_t}\right) \quad (55)$$

5. Modelling R code and input data files

R code used in this modelling study is provided below. Input data and parameters shown in the code is from a scenario with the following assumptions: annual revaccination during 2021-2024, long-term vaccine efficacy 62.5%, reduction in reinfectivity after waning of immunity 45%. Input data files required for running the R code are provided at the end of this section.

5.1 R code used

```
#############################################################################
## R code for simulating outbreak of covid-19 in England
#############################################################################

        tt <-1827           # 1827, from 1/1/20 to 31/12/24

#-----------------------------------------------------------------------------------------
                VAC <- 1        # Vaccination: 1- yes; 0-no
                VACtime <-367   # relevant if VAC=1
                back.nom <-1    # re-normality from 'back.tim', 1-Yes, 0-No
                back.tim <-566  # t=566:19/7/2021
                ASYinf <-0.21   # Relative infectivity of asymptomatic cases

                dGap <-365      # Interval between vac waves (day)

        #  VAC coverage for age groups
                vac.crg1 <-0.75             # 0.60    VAC coverage age 16-29
                vac.crg2 <-0.80             # 0.70    VAC coverage age 30-39
                vac.crg3 <-0.85             # 0.80    VAC coverage age 40-49
                vac.crg4 <-0.90             # 0.90    VAC coverage age 50+

                bta.nom <- 0.081    # from back.tim
   #++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++

                 nRvac <-4                  # revaccination waves
                InfI2   <-0.45              # Relative infectivity after immunity loss
                rVEinf1  <-0.3876           # Efficacy of vaccine dose-1 on transmission risk
                rVEsym1  <-0.3876           # Efficacy of vaccine dose-1 on reduced symptomatic cases
                rVEinf2  <-0.6127           # Efficacy of vaccine dose-2 on transmission risk
                rVEsym2  <-0.6127           # Efficacy of vaccine dose-2 on reduced symptomatic cases
                rVEinf3  <-0.3876           # Long-term VE on infection
                rVEsym3  <-0.3876           # Long-term VE on symptoms
                rWinter1 <- 1.10            # Winter transmissibility: Sep-Oct, Mar-Apr
                rWinter2 <- 1.20            # Winter transmissibility: Nov-Feb
                pIM <-1                     # Natural immunity: 1-long-lived; 0-short-lived
                gwan.m <-730                # mean durability (days) of immunity
                gwan.s <-27.019             # gamma shape k
                pIMv <-1                    # Vaccine immunity 1:long-lived; 0:short-lived
                gwanv.m <-365               # mean durability (days) of vaccine immunity
                gwanv.s <-19.105            # gamma shape k


##++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
##  Vaccination timing, waves and age groups
##============================================================================
        vac.AGP  <- array(0, dim=c(7))              # no. of agegroups to be vaccinated phase 1-6
        vac.tim <- array(0, dim=c(18))              # starting time of each vaccination wave
        vagp        <- array(0, dim=c(18,7))    # agegroup (Vp:1-6, age 1,2)
#-----------------------------------------------------------------------------------------
        vac.tim[1] <-VACtime
        if(nRvac>1)                 {
        for(rev in 2:nRvac) {
          vac.tim[rev] <- vac.tim[rev-1] +dGap           # time of re-vaccination
                                    }
                                    }
```

```
        vac.dmaxi <- 180000         # Maximum no. of individuals vaccinated
   #------------------------------------------------------------------------
                      vac.AGP[1] <-6          # 1: 70+;   2: 60-69;  3: 50-59;
                                              # 4: 40-49; 5: 20-39;  6: 16(10)-19
        if(nRvac>1)               {
        for(rev in 2:nRvac) {
                      vac.AGP[rev] <-6
                                  }
                                  }
   #------------------------------------------------------------------------
   # Age ranges for vaccination from age phase 1 to 4
   #----------------------------------------------------------------------------
        vagp[1,1] <- 9             # age grp 9:       70+
        vagp[1,2] <- 10            # age grp 10:      85+
        vagp[2,1] <- 8             # age grp 8:       60-69
        vagp[2,2] <- 8             # age grp 8:
        vagp[3,1] <- 7             # age grp 7:       50-59
        vagp[3,2] <- 7             # age grp 7:
        vagp[4,1] <- 6             # age grp 6:       40-49
        vagp[4,2] <- 6             # age grp 6:
        vagp[5,1] <- 4             # age grp 4:       20-29
        vagp[5,2] <- 5             # age grp 5:       30-39
        vagp[6,1] <- 3             # age grp 3:       10-19
        vagp[6,2] <- 3             # age grp 3:       (40% for 16-19)
  #==============================================================================
        ts    <- 15           # Epidemic simulation start from 01/02/2020
        seeds <-1                  # Inital no. of exposed/infected
        dv0   <-14                 # Days required for developing immunity after vaccination
        tv0   <-63            # duration between dose-1 and dose-2: 9 weeks on average
        tw0   <-tt            # longest duration before immunity loss in recovered
        dd    <-60            # maximum days from exposed to recover or death.
        tm0   <-tt            # only used for defining death risk by days when tt<1096
        tage  <-367                # t starting to shift age up

##$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$
        beta     <- array(0, dim=c(tt))        # Infection risk per contact between susceptible and infected
        adjHsp   <- array(0, dim=c(tt))        # Adjust ratio for hospitalisation rate
        adjDth   <- array(0, dim=c(tt))        # Adjust case fatality to hospital fatality
###=============================================================================
##  Calibrate beta[t], adjHsp, adjDth
##==============================================================================
   for(t in 1:tt)        {        # No covid epidemdic before ts
          beta[t] <-0.094
   #--------------------------------------------
        if(NPI==1)          {
   #--------------------------------------------
        if(t>74)   {               # t> 15/03/2020
               beta[t] <- 0.069    # social distancing
                    }                       #

        if(t>83)   {               # t> 23/03/2020
               beta[t] <-0.066     # Lockdown date
                    }                       #

        if(t>132) {                # t=132:11/05/2020
               beta[t] <-0.062     # Advised wearing face covering
                    }                       #

        if(t>280) {                # t=291: 17/10/2020:
               beta[t] <-0.077     # Increased transmissibility by new variant
                    }                       #

        if(t>487) {                # t>= 01/05/2021
               beta[t] <-0.081              # new delta variant
                    }                       #

        if(back.nom==1)           {         # Returning to normal life
        if(t>(back.tim-1))  {
                      beta[t] <-bta.nom
                                  }
```

```
                                        }

                                }   # end if NPI==1

                        } # for t in ts:tt

#=============================================================================
#  Ratio for adjusting case fatality rate
#=============================================================================
        for(t in 1:tt)                  {
                                adjDth[t] <- 2.00               # higher death rate initially
        if(t>91)   {            adjDth[t] <- 1.80    }         # t=92:  1/4/20:
        if(t>100)  {            adjDth[t] <- 1.60    }
        if(t>110)  {            adjDth[t] <- 1.40    }
                                }   # end t in ts:tt
#=============================================================================
#  Ratio for calibrating hospitalisation rate
#=============================================================================
        for(t in 1:tt) {  adjHsp[t] <-0.30  }

##============================================================================================
## output files for simulation results
##--------------------------------------------------------------------------------------------
  Header.scen <-cbind("Time", "Rt", "POP_N", "SUS", "SUS.rec","SUS.vac", "RE", "VAef1", "VAef2", "New.VAC",
                      "New_Exp", "New_Sym","New_HS", "HS_pts", "Infect_sum", "DthCov-day", "DthCov_cum",
                      "DthAll_day" )   # End Header.out
    OFileName <- paste("...\\ResOut".out", sep="")
     write.table(Header.scen, file=OFileName, sep="\t", quote=FALSE,
                                        append=FALSE, row.names=FALSE, col.names=FALSE)
##============================================================================================
## Definition of Population and other key variables
##--------------------------------------------------------------------------------
        N    <- array(0, dim=c(tt,3,11))   # Total population[t,sex,age,cmb]
        SU   <- array(0, dim=c(tt,3,11))   # Suceptable[t,sex,age,cmb]
        EX   <- array(0, dim=c(tt,3,11))   # Exposed[t,sex,age,cmb]
        EXv1   <- array(0, dim=c(tt,3,11))   # Exposed in vaccinated
        EXv2   <- array(0, dim=c(tt,3,11))
        I0   <- array(0, dim=c(tt,3,11))   # Infected -presymptomatic
        I0v1   <- array(0, dim=c(tt,3,11))   # Infected -presymptomatic in vaccinated
        I0v2   <- array(0, dim=c(tt,3,11))
        IM0  <- array(0, dim=c(tt,3,11))   # Infected no quarantine -mild
        IM0v  <- array(0, dim=c(tt,3,11))   # Infection after vaccination or reinfection
        IS0  <- array(0, dim=c(tt,3,11))   # Infected no quarantine/no hospital -severe
        IS0v  <- array(0, dim=c(tt,3,11))   # Infection after vaccination or reinfection
        ISq  <- array(0, dim=c(tt,3,11))   # To be quarantined -severe
        ISqv  <- array(0, dim=c(tt,3,11))   # Infection after vaccination or reinfection
        ISh  <- array(0, dim=c(tt,3,11))   # To be hospitalised
        IShv  <- array(0, dim=c(tt,3,11))  # Infection after vaccination or reinfection
        QS  <- array(0, dim=c(tt,3,11))    # Quarantined -severe
        QSv  <- array(0, dim=c(tt,3,11))
        HS  <- array(0, dim=c(tt,3,11))   # Hospitalised -severe
        HSv  <- array(0, dim=c(tt,3,11))
        RE   <- array(0, dim=c(tt,3,11))   # Recovered

        eRE  <- array(0, dim=c(tt,tw0,3,11)) # By days since recovered/vacciated for waning immunity

        SU.vac   <- array(0, dim=c(tt,3,11))   # Suceptable from vaccinated
        SU.rec   <- array(0, dim=c(tt,3,11))   # Suceptable from recovered clinical
        vac.SU   <- array(0, dim=c(tt,3,11))   # Vaccinated suceptable[t,sex,age,cmb]
        vac.SUvac   <- array(0, dim=c(tt,3,11)) # vaccinated in loss of vaccine immunity
        vac.SUrec   <- array(0, dim=c(tt,3,11))  # vaccination of loss immunity in clinical recovered

        eEX   <- array(0, dim=c(tt,dd,3,11))   # Exposed[t,sex,age,cmb]
        eEXv1   <- array(0, dim=c(tt,dd,3,11))   # Exposed in vaccinated
        eEXv2   <- array(0, dim=c(tt,dd,3,11))
        eI0   <- array(0, dim=c(tt,dd,3,11))   # Infected -presymptomatic
        eI0v1   <- array(0, dim=c(tt,dd,3,11))   # Infected -presymptomatic in vaccinated
        eI0v2   <- array(0, dim=c(tt,dd,3,11))
        eIM0  <- array(0, dim=c(tt,dd,3,11))   # Infected no quarantine -mild
        eIM0v  <- array(0, dim=c(tt,dd,3,11))
```

```
eIS0  <- array(0, dim=c(tt,dd,3,11))   # Infected no quarantine/no hospital -severe
eIS0v  <- array(0, dim=c(tt,dd,3,11))
eISq  <- array(0, dim=c(tt,dd,3,11))   # To be quarantined -severe
eISqv  <- array(0, dim=c(tt,dd,3,11))
eISh  <- array(0, dim=c(tt,dd,3,11))   # To be hospitalised
eIShv  <- array(0, dim=c(tt,dd,3,11))
eQS  <- array(0, dim=c(tt,dd,3,11))   # Quarantined -severe
eQSv  <- array(0, dim=c(tt,dd,3,11))
eHS  <- array(0, dim=c(tt,dd,3,11))   # Hospitalised -severe
eHSv  <- array(0, dim=c(tt,dd,3,11))

 VA0   <- array(0, dim=c(tt,3,11))         # Vaccinated before immunity developed
 VAef1   <- array(0, dim=c(tt,3,11))      # Successful partial immunised
 VAef2   <- array(0, dim=c(tt,3,11))
eVA0    <- array(0, dim=c(tt,dv0,3,11)) # Specify days since vacciation 1-14 days
eVAef1   <- array(0, dim=c(tt,tv0,3,11))  # by days since vaccinated dose-1
eVAef2   <- array(0, dim=c(tt,tw0,3,11))  #  by days since vaccinated dose-2

eInf  <- array(0, dim=c(tt,dd,3,11))  #  Tracing with days since exposed/infected
eInfv  <- array(0, dim=c(tt,dd,3,11))  #  Tracing with days since exposed/infected in reinfected
Infect.sum <- array(0, dim=c(tt))          # Total no. of infected at t

#---------------------------------
# Temproary variable for up shifting ages

jN <- array(0, dim=c(10)); jSU <- array(0, dim=c(10)); jSU.vac <- array(0, dim=c(10))
jSU.rec <- array(0, dim=c(10)); jRE <- array(0, dim=c(10)); jEX <- array(0, dim=c(10))
jI0 <- array(0, dim=c(10)); jIM0 <- array(0, dim=c(10)); jIS0 <- array(0, dim=c(10))
jISq <- array(0, dim=c(10)); jISh <- array(0, dim=c(10)); jQS <- array(0, dim=c(10))
jHS <- array(0, dim=c(10))

jEXv1 <- array(0, dim=c(10)); jI0v1 <- array(0, dim=c(10))
jEXv2 <- array(0, dim=c(10)); jI0v2 <- array(0, dim=c(10)); jIM0v <- array(0, dim=c(10))
jIS0v <- array(0, dim=c(10)); jISqv <- array(0, dim=c(10)); jIShv <- array(0, dim=c(10))
jQSv <- array(0, dim=c(10)); jHSv <- array(0, dim=c(10)); jVA0 <- array(0, dim=c(10))
jVAef1 <- array(0, dim=c(10)); jVAef2 <- array(0, dim=c(10))

jeEX <- array(0, dim=c(dd,10)); jeI0 <- array(0, dim=c(dd,10)); jeIM0 <- array(0, dim=c(dd,10))
jeIS0 <- array(0, dim=c(dd,10)); jeISq <- array(0, dim=c(dd,10)); jeISh <- array(0, dim=c(dd,10))
jeQS <- array(0, dim=c(dd,10)); jeHS <- array(0, dim=c(dd,10))

jeEXv1 <- array(0, dim=c(dd,10)); jeI0v1 <- array(0, dim=c(dd,10)); jeEXv2 <- array(0, dim=c(dd,10))
jeI0v2 <- array(0, dim=c(dd,10))

jeIM0v <- array(0, dim=c(dd,10)); jeIS0v <- array(0, dim=c(dd,10)); jeISqv <- array(0, dim=c(dd,10))
jeIShv <- array(0, dim=c(dd,10)); jeQSv <- array(0, dim=c(dd,10)); jeHSv <- array(0, dim=c(dd,10))
jeInf  <- array(0, dim=c(dd,10)); jeInfv  <- array(0, dim=c(dd,10))

jeVA0    <- array(0, dim=c(dv0,10)); jeVAef1   <- array(0, dim=c(tv0,10)); jeVAef2   <- array(0, dim=c(tw0,10))
jeRE  <- array(0, dim=c(tw0,10))

#----------------------------------

HS.new  <- array(0, dim=c(tt,3,11)) ; allHS  <- array(0, dim=c(tt))

Bsex   <- array(0, dim=c(2))  # % sex ratio for births
dBth   <- array(0, dim=c(11))          # No. of births/day, note: dBth[>1] <-0

I.i0  <- array(0, dim=c(tt,11))          # total no. of pre-clin infectious
I.m0  <- array(0, dim=c(tt,11))          # total no. of mild cases - not quarantined
I.m  <- array(0, dim=c(tt,11))
I.s0  <- array(0, dim=c(tt,11))          # total no. of severe cases - not quarantined
I.s  <- array(0, dim=c(tt,11))
I.sq  <- array(0, dim=c(tt,11))          # total no. of severe cases - quarantined
I.i0v  <- array(0, dim=c(tt,11))         # total no. of pre-clin infectious
I.m0v  <- array(0, dim=c(tt,11))         # total no. of mild cases - not quarantined
I.mv  <- array(0, dim=c(tt,11))
I.s0v  <- array(0, dim=c(tt,11))         # total no. of severe cases - not quarantined
I.sv  <- array(0, dim=c(tt,11))
I.sqv  <- array(0, dim=c(tt,11))         # total no. of severe cases - quarantined
```

```
IAl   <- array(0, dim=c(tt))

Rt  <- array(0, dim=c(tt))
exposed.n  <- array(0, dim=c(tt))

drisk.inf  <- array(0, dim=c(2,11))  # death risk in symptomatic cases
rHosp <- array(0, dim=c(11))       # Case hospitalisation rate

rADth0  <- array(0, dim=c(366,3,11))  # 5yr average death rate/1000/day without comordity

 nDth.inf <- array(0, dim=c(tt,3,11))  # Covid related deaths -all
nDth.s0 <- array(0, dim=c(tt,dd,3,11))  # Covid related deaths -infected
nDth.sq <- array(0, dim=c(tt,dd,3,11))  # Covid related deaths -infected
nDth.ss <- array(0, dim=c(tt,3,11))  # Covid related deaths -outside hospital
nDth.hos <- array(0, dim=c(tt,dd,3,11))  # Covid related deaths-hospital

 nDth.infv <- array(0, dim=c(tt,3,11))  # Covid related deaths -all
nDth.s0v <- array(0, dim=c(tt,dd,3,11))  # Covid related deaths -infected
nDth.sqv <- array(0, dim=c(tt,dd,3,11))  # Covid related deaths -infected
nDth.ssv <- array(0, dim=c(tt,3,11))  # Covid related deaths -outside hospital
nDth.hosv <- array(0, dim=c(tt,dd,3,11))  # Covid related deaths-hospital

nDth.cov <- array(0, dim=c(tt,3,11))  # Covid related deaths
nDth.oth  <- array(0, dim=c(tt,3,11))  # no. of other deaths in SU, RE and VAC

nDth.all <- array(0, dim=c(tt,3,11))  # All cause deaths including covid & non-covid deaths
nDthHos.all <- array(0, dim=c(tt,3,11))  # All cause deaths including covid & non-covid deaths
nDthHos.allv <- array(0, dim=c(tt,3,11))

nDthcum.cov <- array(0, dim=c(tt))      # Covid related deaths -Cumulative

beta2.i0 <- array(0, dim=c(tt)); beta2.m0 <- array(0, dim=c(tt)); beta2.mq <- array(0, dim=c(tt))
beta2.s0 <- array(0, dim=c(tt)); beta2.sq <- array(0, dim=c(tt)); beta2.al <- array(0, dim=c(tt))

dk <- array(0, dim=c(tt,18)); dA  <- array(0, dim=c(tt)); dAv1 <- array(0, dim=c(tt))
dAv2 <- array(0, dim=c(tt))

gdth.inf <- array(0, dim=c(dd))          # gamma distribution of deaths by days since infected
gdth.hos <- array(0, dim=c(dd))          # gamma distribution of deaths by days since hos admin
alp1     <- array(0, dim=c(dd))          # Transition rate from exposed to I0
alp2     <- array(0, dim=c(dd))          # Transition rate from I0 to I_clinical
gm0.m    <- array(0, dim=c(tt))          # gamma mean from IM0 to RE
gm0.s    <- array(0, dim=c(tt))          # gamma sd
gs0.m    <- array(0, dim=c(tt))          # gamma mean from IS0 to RE
gs0.s    <- array(0, dim=c(tt))          # gamma sd
gs1.m    <- array(0, dim=c(tt))          # gamma mean from ISq to QS
gs1.s    <- array(0, dim=c(tt))          # gamma sd
gs2.m    <- array(0, dim=c(tt))          # gamma mean from QS to RE
gs2.s    <- array(0, dim=c(tt))          # gamma sd
gh1.m    <- array(0, dim=c(tt))          # gamma mean from ISh to HS
gh1.s    <- array(0, dim=c(tt))          # gamma sd
gh2.m    <- array(0, dim=c(tt))          # gamma mean from HS to RE
gh2.s    <- array(0, dim=c(tt))          # gamma sd

# Day since infection specific transition rates:
gam.m0   <- array(0, dim=c(tt,dd))       # duration from IM0 to RE
gam.s0   <- array(0, dim=c(tt,dd))       # duration from IS0 to RE
gam.s1   <- array(0, dim=c(tt,dd))       # duration from ISq to QS
gam.s2   <- array(0, dim=c(tt,dd))       # duration from QS to RE
gam.h1   <- array(0, dim=c(tt,dd))       # duration from ISh to HS
gam.h2   <- array(0, dim=c(tt,dd))       # duration from HS to RE

# Average transition rates for estimating Rt
gam.m0a <- array(0, dim=c(tt))           # duration from IM0 to RE
gam.s0a  <- array(0, dim=c(tt))          # duration from IS0 to RE
gam.s1a  <- array(0, dim=c(tt))          # duration from ISq to QS
gam.s2a  <- array(0, dim=c(tt))          # duration from QS to RE
gam.h1a  <- array(0, dim=c(tt))          # duration from ISh to HS
gam.h2a  <- array(0, dim=c(tt))          # duration from HS to RE
```

```
gimm.wan <- array(0, dim=c(tw0))  # Distribution of immunity waning
gimmv.wan <- array(0, dim=c(tw0))  # Distribution of vaccine immunity waning

cum_gdth.inf <- array(0, dim=c(dd))    # gamma distribution of deaths by days since infected
cum_gdth.hos <- array(0, dim=c(dd))    # gamma distribution of deaths by days since hos admin
cum_alp1<- array(0, dim=c(dd))         # Transition rate from exposed to I0
cum_alp2<- array(0, dim=c(dd))         # Transition rate from I0 to I_clinical
cum_gm0.m       <- array(0, dim=c(tt))          # gamma mean from IM0 to RE
cum_gm0.s       <- array(0, dim=c(tt))          # gamma sd
cum_gs0.m       <- array(0, dim=c(tt))          # gamma mean from IS0 to RE
cum_gs0.s       <- array(0, dim=c(tt))          # gamma sd
cum_gs1.m       <- array(0, dim=c(tt))          # gamma mean from ISq to QS
cum_gs1.s       <- array(0, dim=c(tt))          # gamma sd
cum_gs2.m       <- array(0, dim=c(tt))          # gamma mean from QS to RE
cum_gs2.s       <- array(0, dim=c(tt))          # gamma sd
cum_gh1.m       <- array(0, dim=c(tt))          # gamma mean from ISh to HS
cum_gh1.s       <- array(0, dim=c(tt))          # gamma sd
cum_gh2.m       <- array(0, dim=c(tt))          # gamma mean from HS to RE
cum_gh2.s       <- array(0, dim=c(tt))          # gamma sd

# Day since infection specific transition rates:
cum_gam.m0      <- array(0, dim=c(tt,dd))       # duration from IM0 to RE
cum_gam.s0      <- array(0, dim=c(tt,dd))       # duration from IS0 to RE
cum_gam.s1      <- array(0, dim=c(tt,dd))       # duration from ISq to QS
cum_gam.s2      <- array(0, dim=c(tt,dd))       # duration from QS to RE
cum_gam.h1      <- array(0, dim=c(tt,dd))       # duration from ISh to HS
cum_gam.h2      <- array(0, dim=c(tt,dd))       # duration from HS to RE

# Average transition rates for estimating Rt
cum_gam.m0a     <- array(0, dim=c(tt))          # duration from IM0 to RE
cum_gam.s0a     <- array(0, dim=c(tt))          # duration from IS0 to RE
cum_gam.s1a     <- array(0, dim=c(tt))          # duration from ISq to QS
cum_gam.s2a     <- array(0, dim=c(tt))          # duration from QS to RE
cum_gam.h1a     <- array(0, dim=c(tt))          # duration from ISh to HS
cum_gam.h2a     <- array(0, dim=c(tt))          # duration from HS to RE

cum_gimm.wan <- array(0, dim=c(tw0))  # Distribution of immunity waning
cum_gimmv.wan <- array(0, dim=c(tw0))  # Distribution of vaccine immunity waning

rFm     <- array(0, dim=c(11))                  # % from I0 to Mild -age-specific
rFsq    <- array(0, dim=c(tt,11))       # % from I0 to QS
rFhos   <- array(0, dim=c(tt,11))       # % from I0 to HS

rFhos.al  <- array(0, dim=c(tt)); rFm.al  <- array(0, dim=c(tt)); rFsq.al  <- array(0, dim=c(tt))

New.expsu   <- array(0, dim=c(tt,3,11))# Newly exposed in SU
New.expv0  <- array(0, dim=c(tt,3,11)) # Newly exposed in VA0
New.expv1  <- array(0, dim=c(tt,3,11)) # Newly exposed in VAef1
New.expv2  <- array(0, dim=c(tt,3,11)) # Newly exposed in VAef2
New.expal  <- array(0, dim=c(tt,3,11))  # Newly exposed -all

Expv0       <- array(0, dim=c(tt,dv0,3,11))         # Newly exposed in VA0 by day
Expv1       <- array(0, dim=c(tt,tv0,3,11))         # Newly exposed in VAef by day
Expv2       <- array(0, dim=c(tt,tt,3,11))

New.explosv1  <- array(0, dim=c(tt,3,11))         # Newly exposed due to loss immunity in vaccinated
New.explosrec <- array(0, dim=c(tt,3,11))         # Newly exposed due to loss immunity in recovered

New.vac   <- array(0, dim=c(tt,3,11))    # Newly vaccinated

New.sym   <- array(0, dim=c(tt,3,11))   # New symptomatic

eSeed <- array(0, dim=c(tt,dd,3,11))   # Seeds of exposed
Seed.all <- array(0, dim=c(tt,3,11))   # Seeds of exposed

CMTa <- array(0, dim=c(11,11))     # Contact matrix by age for all contacts symmetric
CMTh <- array(0, dim=c(11,11))     # Contact matrix by age for home contacts symmetric

adjCNTa <- array(0, dim=c(tt,11))     # adjust no. of Contacts at home by age & m
```

```
V.day     <- array(0, dim=c(18,7))          # no. of days for vaccination (age grp 1-6)
V.dmax    <- array(0, dim=c(18,7))          # maximum vaccinated per day by age grp (1-6)
T.vac     <- array(0, dim=c(18,7))          # maximum vaccinated per day by age grpe (1-6)
vacend    <- array(0, dim=c(18,7))          # End date for vaccinating group Vp

## READ: data on initial population 01-01-2020

 inPOP <-read.table(file="...\\inPOPEng20.csv", header=TRUE, sep=",")

# Obtain data on initial population in England 2020 (start of the year)

          for(a in 1:10) {    # Input UK population

           N[1,1,a] <-inPOP[a,3]*1000          #   male all
           N[1,2,a] <-inPOP[a,4]*1000          # female all

          drisk.inf[1,a] <-inPOP[a,5]          # case fatality   male
          drisk.inf[2,a] <-inPOP[a,6]          # case fatality female

          rHosp[a] <- inPOP[a,7]  # Hospitalisation rate (cases)

                                }   # End input POP data

  #-------------------------------------------------
          for(s in 1:2)          {
          for(a in 1:10)         {
            N[1,3,11] <- N[1,3,11] + N[1,s,a];  N[1,s,11] <- N[1,s,11] + N[1,s,a];  N[1,3,a] <- N[1,3,a] + N[1,s,a]
           SU[1,s,a] <-  N[1,s,a];  SU[1,3,11] <-SU[1,3,11] +SU[1,s,a]

                                }
                                }

##=============================================
##   Birth related parameters, note: CMB[s,a]
##=============================================
          dBth[1] <-1800                # No. of births per day; for day-1 only
                                        # dBth =no. of deaths/day for other days
          Bsex[1] <-0.512               # male %
          Bsex[2] <-0.488               # female %

## READ: data on 5 year (2015-2019) average death rate/1000/day

 inAllDth <-read.table(file="...\\inDTH1519Eng10.csv", header=TRUE, sep=",")
                    d<- 1               # day from 1 to 364=7x52
          for(w in 1:52) {      # Input death rate for male week 1-52
          for(dw in 1:7) {
           for(a in 1:10) {
                    cc<-a+1
           rADth0[d,1,a] <-inAllDth[w,cc]/1000
                                 }          # end a in 1:10
                      d <- d+1
                                }   # end for dw in 1:7
                                }   # end for w  in 1:52
                    d<- 1               # day from 1 to 364=7x52
          for(w in 53:104) {            # Input death rate for female week 1-52
          for(dw in 1:7) {
           for(a in 1:10)  {
                    cc<-a+1
           rADth0[d,2,a] <-inAllDth[w,cc]/1000
                                  }     # end a in 1:10
                      d <- d+1
                                }
                                }

          for(s in 1:2)          {
          for(a in 1:10)         {
          rADth0[365,s,a] <- rADth0[364,s,a]   # 366 days in 2020
          rADth0[366,s,a] <- rADth0[364,s,a]   # 366 days in 2020
                                }
```

```
                                    }

## READ: contact matrix all and at home
                inCM <-read.table(file="…\\inCMATRIX10.csv", header=TRUE, sep=",")

      for(a in 1:10)    {    # Input Contact matrix data
      for(j in 1:10)    {
       # All contacts (for community transmission)
                                    ca <-j+1
                          CMTa[a,j] <-inCM[a,ca]
       # Contacts at home (for home isolation)
                                    ch <-j+11
                          CMTh[a,j] <-inCM[a,ch]
                                    }
                                    }

##-----------------------------------------------------
## Key input parameters
##-----------------------------------------------------
     # % of mild illness among infected - age-specific, constant overtime
     # Data source: Davies et al Nature Med: Age-dependent effects in transmission
               for(a in 1:2)          { rFm[a] <- 0.71 }       # age 0-9
                                       rFm[3] <- 0.79         # age 10-19
                                       rFm[4] <- 0.73         # age 20-29
                                       rFm[5] <- 0.67         # age 30-39
                                       rFm[6] <- 0.60         # age 40-49
                                       rFm[7] <- 0.51         # age 50-59
                                       rFm[8] <- 0.37         # age 60-69
               for(a in 9:10)  { rFm[a] <- 0.31 }       # age 70+

   #-----------------------------------------------
   #          Verity et al:
   #          17.8 days from onset to deaths

               gdth.m <-23.0        # mean days from exposed to deaths
               gdth.s <-4.796       # sd

#              READ: data on other input parameters

  inParam <-read.table(file="...\\inParamet20.csv", header=TRUE, sep=",")

    for(t in ts:tt)       {      # Epidemic simulation starts from ts
               if(t>(ts-1))           {           ### t>ts
                          c <-2                  # data column
                                    }

    #=================================================================
    #  Effects of NPI control measures
    #-----------------------------------------------------------------
    # Control-1: case based self-isolation mandated on 12/03/2020
    #  Reduced infectious periods for symptomatic patients since 13/03/2020
    #-----------------------------------------------------------------
               if(t>72)  {    #  after date: 12/03/2020 -self isolation of symptomatic individuals
                          c <-3
                            }
    #-----------------------------------------------------------------
    # Control-2:  Social distance encouraged in the UK 16/03/2020
    #  shielding of vulnerable people
    #-----------------------------------------------------------------
               if(t>76)  {     # After date 16/03/2020 -social distance
                          c <-4
                            }
    #=================================================================
    # Control-3: lockdown from 24/03/2020 in the UK; stay at home and other restrictions
    #-----------------------------------------------------------------
               if(t>83)  {            # lockdown initial
                          c <-5
                            }
    #=================================================================
    # On 4 July 2020: third step in easing national restrictions
```

```
  #  including 2m => 2m or 1m social distancing, restaurants/pubs
  #   reopening, holiday accommodations, museum, place of worships, ...
  #=================================================================
          if(t>186) {           # date: 04/07/2020 more shops/pubs open
                        c <-6
                              }
   #=====================================================
   # Reopening of schools from September 2020
   #=====================================================
          if(t>244) {           # date: 01/09/2020 more shops/pubs re-opening
                        c <-7
                              }
  #=====================================================
  # 2nd national restrictions
  #-----------------------------------------------------
          if(t>309) {           # Date: 05/11/2020 localised control measures
                        c <-8
                               }
  #=====================================================
  # Lifting national restrictions
  #-----------------------------------------------------
          if(t>336) {           # Date: 02/12/2020 Lifing national restrictions
                        c <-9
                               }
  #=====================================================
  # National lockdown restrictions
  #-----------------------------------------------------
          if(t>370) {           # Date: 05/01/2021 National restrictions
                        c <-10
                               }
  #=====================================================
  # Partial lifting national lockdown restrictions
  #-----------------------------------------------------
          if(t>432) {           #  t=440: 15/03/2021; partially lifting national restrictions
                        c <-11
                               }
          if(t>505) {           #  t=506: 20/05/2021
                        c <-12
                               }
  #=====================================================
  # Return to normal from back.tim
  #-----------------------------------------------------
          if(back.nom==1)    {
          if(t>(back.tim-1))   {
                        c <-13
                               }
                               }

# ### Get data from dataframe "inPar"
          # % home quarantine among symptomatic cases

          for(a in 1:6)         {  # age 0-49
                    rFsq[t,a] <- inPar[1,c]
                               }
          for(a in 7:8)   {  # age 50-69
                    rFsq[t,a] <- inPar[2,c]
                               }
          for(a in 9:10)  {  # age 70+
                    rFsq[t,a] <- inPar[3,c]
                               }

   #-----------------------------------------------------------
   # Transition parameters for E-I0-TM/S-QM/S-RE
   #  gamma distribution mean and shape
   #-----------------------------------------------------------

          alp1.m <- inPar[4,c]        # gamma mean -days incupation non-infectious period
          alp1.s <- inPar[5,c]        # gamma sd
          alp2.m <- inPar[6,c]        # gamma mean -infectiou duration before symptomatic
          alp2.s <- inPar[7,c]        # gamma sd
```

```
            gm0.m[t] <-inParam[8,c]     # mean days infectious period- no quarantine -mild
            gm0.s[t] <-inParam[9,c]     # gamma sd

            gs0.m[t] <-inParam[10,c]    # mean duration of infectious no quarantine -severe
            gs0.s[t] <-inParam[11,c]    # gamma sd

            gs1.m[t] <-inParam[12,c]    # mean days of infectious before quarantine -severe
            gs1.s[t] <-inParam[13,c]    # gamma sd
            gs2.m[t] <-inParam[14,c]    # mean duration from quarantine to recovery -severe
            gs2.s[t] <-inParam[15,c]    # gamma sd

            gh1.m[t] <-inParam[16,c]    # mean days before hospitalisation -severe
            gh1.s[t] <-inParam[17,c]    # gamma sd
            gh2.m[t] <-inParam[18,c]    # mean days of non-ICU hospitalisation -severe
            gh2.s[t] <-inParam[19,c]    # gamma sd

    #-------------------------------------------------
    #  adjCNT=1, no change; adjCNT<1, reduced contacts
    #-------------------------------------------------
            for(a in 1:3)               {       # Age 0-19 children
                adjCNTa[t,a] <- inParam[20,c]
                                        }
            for(a in 4:7)               {       # Age 20-59
                adjCNTa[t,a] <- inParam[21,c]
                                        }
            for(a in 8:8)               {       # Age 60-69
                adjCNTa[t,a] <- inParam[22,c]
                                        }
            for(a in 9:10)      {       # Age 70+
                adjCNTa[t,a] <- inParam[23,c]
                                        }

                                }       ## End tt for input parameters

#-----------------------------------------------------------------------
    # Hospitalisation rate by age grp based on Verity et al.
            for(t in 1:tt)      {
            for(a in 1:10)      {
             rFhos[t,a] <-(rHosp[a]/(1-rFm[a])) *adjHsp[t]
                                }
                                }
#=======================================================================
 #  Calculating transition rate by days since exposed, infected, ...
 #   cumulative (pgamma) from 1 to dd: eventually all will be transfered to next status ....
 #=================================================================== ====
            for(d in 1:dd)      {
                cum_alp1[d] <- pgamma(d, (alp1.m/alp1.s)^2, scale=(alp1.s^2)/alp1.m, log=FALSE)
                cum_alp2[d] <- pgamma(d, (alp2.m/alp2.s)^2, scale=(alp2.s^2)/alp2.m, log=FALSE)
             cum_gdth.inf[d] <- pgamma(d, (gdth.m/gdth.s)^2, scale=(gdth.s^2)/gdth.m, log=FALSE)
                                }

            # Translating cumulative probability to transition rate by d
                        alp1[1] <- cum_alp1[1]
                       alp2[1] <- cum_alp2[1]
                    gdth.inf[1] <- cum_gdth.inf[1
            for(d in 2:dd)      {
                    if(cum_alp1[d-1]<1) {
                alp1[d] <- (cum_alp1[d]-cum_alp1[d-1])/(1-cum_alp1[d-1])
                                        } else {    alp1[d] <-1             }

                    if(cum_alp2[d-1]<1) {
                alp2[d] <- (cum_alp2[d]-cum_alp2[d-1])/(1-cum_alp2[d-1])
                                        } else {    alp2[d] <-1             }

                    if(cum_gdth.inf[d-1]<1)     {
              gdth.inf[d] <- (cum_gdth.inf[d]-cum_gdth.inf[d-1])/(1-cum_gdth.inf[d-1])
                                        } else {    gdth.inf[d]<-1      }

                                }
```

```
        for(t in ts:tt)         {       # start t in 1:tt

        for(d in 1:dd)          {       # start d in 1:dd
        cum_gam.m0[t,d] <- pgamma(d, (gm0.m[t]/gm0.s[t])^2, scale=gm0.s[t]^2/gm0.m[t], log=FALSE)

        cum_gam.s0[t,d] <- pgamma(d, (gs0.m[t]/gs0.s[t])^2, scale=gs0.s[t]^2/gs0.m[t], log=FALSE)
        cum_gam.s1[t,d] <- pgamma(d, (gs1.m[t]/gs1.s[t])^2, scale=gs1.s[t]^2/gs1.m[t], log=FALSE)
        cum_gam.s2[t,d] <- pgamma(d, (gs2.m[t]/gs2.s[t])^2, scale=gs2.s[t]^2/gs2.m[t], log=FALSE)

        cum_gam.h1[t,d] <- pgamma(d, (gh1.m[t]/gh1.s[t])^2, scale=gh1.s[t]^2/gh1.m[t], log=FALSE)
        cum_gam.h2[t,d] <- pgamma(d, (gh2.m[t]/gh2.s[t])^2, scale=gh2.s[t]^2/gh2.m[t], log=FALSE)
                        }   # end d in 1:dd

        gam.m0[t,1] <- cum_gam.m0[t,1]; gam.s0[t,1] <- cum_gam.s0[t,1]; gam.s1[t,1] <- cum_gam.s1[t,1]
        gam.s2[t,1] <- cum_gam.s2[t,1]; gam.h1[t,1] <- cum_gam.h1[t,1]; gam.h2[t,1] <- cum_gam.h2[t,1]

        for(d in 2:dd)          {       # start d in 2:dd

                if(cum_gam.m0[t,d-1]<1)     {
        gam.m0[t,d] <- (cum_gam.m0[t,d]-cum_gam.m0[t,d-1])/(1-cum_gam.m0[t,d-1])
                                } else {    gam.m0[t,d]<-1      }
                if(cum_gam.s0[t,d-1]<1)      {
        gam.s0[t,d] <- (cum_gam.s0[t,d]-cum_gam.s0[t,d-1])/(1-cum_gam.s0[t,d-1])
                                } else {    gam.s0[t,d]<-1      }
                if(cum_gam.s1[t,d-1]<1)      {
        gam.s1[t,d] <- (cum_gam.s1[t,d]-cum_gam.s1[t,d-1])/(1-cum_gam.s1[t,d-1])
                                } else {    gam.s1[t,d]<-1      }
                if(cum_gam.s2[t,d-1]<1)      {
        gam.s2[t,d] <- (cum_gam.s2[t,d]-cum_gam.s2[t,d-1])/(1-cum_gam.s2[t,d-1])
                                } else {    gam.s2[t,d]<-1      }
                if(cum_gam.h1[t,d-1]<1)      {
        gam.h1[t,d] <- (cum_gam.h1[t,d]-cum_gam.h1[t,d-1])/(1-cum_gam.h1[t,d-1])
                                } else {    gam.h1[t,d]<-1      }
                if(cum_gam.h2[t,d-1]<1)      {
        gam.h2[t,d] <- (cum_gam.h2[t,d]-cum_gam.h2[t,d-1])/(1-cum_gam.h2[t,d-1])
                                } else {    gam.h2[t,d]<-1      }
                                }   # end d in 2:dd

        #---------------------------------------------------------------------------
        #  Average transition rates for estimating Rt.
        #   Average transition rates were estimated by exponential distribution,
        #---------------------------------------------------------------------------
                alp2.a    <-(1/alp2.m)/1.337            # gamma m=1.5
                gam.m0a[t] <-(1/gm0.m[t])/1.11                  # gamma m=5
                gam.s0a[t] <-(1/gs0.m[t])/1.11                  # gamma m=5
                gam.s1a[t] <-(1/gs1.m[t])/1.25                  # gamma m=2
                gam.s2a[t] <-(1/gs2.m[t])/1.125                 # gamma m=4
                gam.h1a[t] <-(1/gh1.m[t])/1.25                  # gamma m=2
                        }       # end t in 1:tt

#-------------------------------------------------------------------------------
# Distribution of immunity duration:
        for(w in 1:tw0)         {       # start w in 1:tw
        cum_gimm.wan[w] <- pgamma(w, (gwan.m/gwan.s)^2, scale=gwan.s^2/gwan.m, log=FALSE)
                        }       # end w in 1:tw

                gimm.wan[1] <- cum_gimm.wan[1]

        for(w in 2:tw0)         {
                if(cum_gimm.wan[w-1]<1) {
        gimm.wan[w] <- (cum_gimm.wan[w]-cum_gimm.wan[w-1])/(1-cum_gimm.wan[w-1])
                          } else { gimm.wan[w]<-1    }
                        }

  if(pIM==1)    {   # If permanent immunity -gimm.wan=0
        for(w in 1:tw0)         {
                gimm.wan[w] <- 0.0
                        }
                        }   # end if pIM=1
```

```
  # Distribution of vaccine immunity duration:

        for(w in 1:tw0)     {       # start w in 1:tw
        cum_gimmv.wan[w] <- pgamma(w, (gwanv.m/gwanv.s)^2, scale=gwanv.s^2/gwanv.m, log=FALSE)
                            }       # end w in 1:tw

                gimmv.wan[1] <- cum_gimmv.wan[1]

        for(w in 2:tw0)     {
                if(cum_gimmv.wan[w-1]<1) {
        gimmv.wan[w] <- (cum_gimmv.wan[w]-cum_gimmv.wan[w-1])/(1-cum_gimmv.wan[w-1])
                          }     else    {       gimmv.wan[w] <-1 }
                            }

    if(pIMv==1)     {   # If permanent vaccine immunity -gimm.wan=0
        for(w in 1:tw0)     {
                gimmv.wan[w] <- 0.0
                            }
                            }   # end if pIMv=1


##============================================================
##  Simulation of covid-19 epidemic
##============================================================
   for(t in 2:tt)       {       ############ Start simulation
#=====================================================================
# Seasonality adjustment of beta[t]

        if(t>639) {     # From Sept 2021
                beta[t]<- bta.nom
        if(t.dr >240)       {               # from about Sept
        if(t.dr <301)       {               # to about Oct
        beta[t]<- bta.nom *rWinter1  # beta increased by rWinter
                            }
                            }
        if(t.dr >300)       {               # from Nov to Dec
        beta[t]<- bta.nom *rWinter2  # beta increased by rWinter
                            }
        if(t.dr <60)        {               # From Jan to Feb
        beta[t]<- bta.nom *rWinter2  # beta increased by rWinter
                            }
        if(t.dr >59)        {               # from Mar
        if(t.dr <120)       {               # to about Apr
        beta[t]<- bta.nom *rWinter1  # beta increased by rWinter
                            }
                            }
                            }   # end t>639

#=====================================================
#  Days of the year for non-covid death rate
#=====================================================
        if(t==2)    {   t.dr <-1        }       # start year 1
        if(t==368)      {   t.dr <-1        }       # start year 2
        if(t==733)      {   t.dr <-1        }       # start year 3
        if(t==1098)     {   t.dr <-1        }       # start year 4
        if(t==1463)     {   t.dr <-1        }       # start year 5
        if(t==1828)     {   t.dr <-1        }       # start year 6
        if(t==2193)     {   t.dr <-1        }       # start year 7
        if(t==2558)     {   t.dr <-1        }       # start year 8
        if(t==2923)     {   t.dr <-1        }       # start year 9
        if(t==3288)     {   t.dr <-1        }       # start year 10

#=====================================================================
#  First running through t from 1 to ts a period of no covid epidemic

    if(t<ts)            {    #####  The susceptile from t=1 to t=ts
        for(a in 1:10)      {
        for(s in 1:2)       {
          N[t,s,a] <- N[t-1,s,a]*(1-rADth0[t.dr,s,a]) +dBth[a]*Bsex[s];  SU[t,s,a] <- N[t,s,a]
```

```
                                } }
                                }   #### end if t<ts

#=====================================================================
#  Simulating from ts to tt for covid epidemic
#---------------------------------------------------------------------------------------
            if(t==ts)  {
                        eSeed[ts,3,1,5] <- seeds
            for(a in 1:10)          {
            for(s in 1:2)           {
            for(m in 1:2)           {
              N[t,s,a] <-N[t-1,s,a]*(1-rADth0[t.dr,s,a]) +dBth[a]*Bsex[s];  SU[t,s,a] <-N[t,s,a]
                        for(d in 1:10)          {
             Seed.all[t,s,a] <-Seed.all[t,s,a] +eSeed[t,d,s,a]
                                        }
                                } } }
                                }  # end if t==ts

#=====================================================================
            if(t>ts)    {    #### start simulating covid epidemic

#  Seeding exposed per day from 15/01/2020 to 29/02/2020 (t=60)
             if(t<40) {  eSeed[t,3,1,5] <- eSeed[t-1,3,1,5] +1    }

            for(a in 1:10)          {
            for(s in 1:2)           {
            for(d in 1:10)          {
             Seed.all[t,s,a] <-Seed.all[t,s,a] +eSeed[t,d,s,a]
                                }
                                }
                                }

  #=======================================================
  # Average rFm & rFhos for estimating R0/Rt: weighted by age specific proportion of relevant cases

             for(a in 1:10)          {
                        rFsq.al[t-1] <- rFsq.al[t-1]+  rFsq[t-1,a]*N[t-1,3,a]/N[t-1,3,11]
                         rFm.al[t-1] <-  rFm.al[t-1] +      rFm[a]*N[t-1,3,a]/N[t-1,3,11]
                       rFhos.al[t-1] <-rFhos.al[t-1] +rFhos[t-1,a]*N[t-1,3,a]/N[t-1,3,11]
                                }  # end a in 1:10

#=============================================================================
# Overall infectious individuals in the population

             for(a in 1:10)          {
             for(s in 1:2)           {
            I.i0[t-1,a] <-I.i0[t-1,a] +I0[t-1,s,a]                                  # pre-clinical infectious
            I.i0v[t-1,a] <-I.i0v[t-1,a] +I0v1[t-1,s,a] +I0v2[t-1,s,a]
             I.m0[t-1,a] <- I.m0[t-1,a] +IM0[t-1,s,a]
              I.m[t-1,a] <-  I.m[t-1,a] +IM0[t-1,s,a] +I0[t-1,s,a]*rFm[a]  # All asymptomatic/mild cases
            I.m0v[t-1,a] <-I.m0v[t-1,a] + IM0v[t-1,s,a]
             I.mv[t-1,a] <- I.mv[t-1,a] + IM0v[t-1,s,a] +
                                I0v1[t-1,s,a]*(1-(1-rVEsym1)*(1-rFm[a])) +
                                I0v2[t-1,s,a]*(1-(1-rVEsym2)*(1-rFm[a]))        # Among asym/mild: vaccinated and
                                                                                # after immunity waning in the recovered
             I.sq[t-1,a] <-I.sq[t-1,a] +QS[t-1,s,a]
            I.sqv[t-1,a] <-I.sqv[t-1,a] +QSv[t-1,s,a]
             I.s0[t-1,a] <-I.s0[t-1,a] +IS0[t-1,s,a]+ISq[t-1,s,a]+ISh[t-1,s,a]
              I.s[t-1,a] <- I.s[t-1,a] +IS0[t-1,s,a]+ISq[t-1,s,a]+ISh[t-1,s,a] +I0[t-1,s,a]*(1-rFm[a])

            I.s0v[t-1,a] <-I.s0v[t-1,a] +IS0v[t-1,s,a]+ISqv[t-1,s,a]+IShv[t-1,s,a]
             I.sv[t-1,a] <- I.sv[t-1,a] +IS0v[t-1,s,a]+ISqv[t-1,s,a]+IShv[t-1,s,a] +
                                                I0v1[t-1,s,a] *(1-rVEsym1)*(1-rFm[a]) +
                                                I0v2[t-1,s,a] *(1-rVEsym2)*(1-rFm[a])
                                }
                                }

#=============================================================================
# Estimating average no. of daily transmission per infectious individuals for estimating R0/Rt
```

```
        for(a in 1:10)        {
        for(j in 1:10)        {
        #-------------------------------------------------------------------------
                Ii0 <-(I.i0[t-1,j]+I.i0v[t-1,j])
                        if(Ii0>0)  {
                rIi0 <-(I.i0[t-1,j]+I.i0v[t-1,j]*InfI2)/(I.i0[t-1,j]+I.i0v[t-1,j])
                                        } else { rIi0 <-1 }
        beta2.i0[t-1] <-beta2.i0[t-1] +(beta[t-1]*CMTa[a,j]*adjCNTa[t-1,a]*
                        N[t-1,3,j]/N[t-1,3,11]) *(rFm[a]*ASYinf +(1-rFm[a])) *rIi0
        #-------------------------------------------------------------------------
                Im0 <-(I.m0[t-1,j]+I.m0v[t-1,j])
                        if(Im0>0){
                rIm0 <-(I.m0[t-1,j]+I.m0v[t-1,j]*InfI2)/(I.m0[t-1,j]+I.m0v[t-1,j])
                                        } else { rIm0 <-1 }
        beta2.m0[t-1] <-beta2.m0[t-1] +(beta[t-1]*CMTa[a,j]*adjCNTa[t-1,a]*
                        N[t-1,3,j]/N[t-1,3,11]) *ASYinf          * rIm0
        #-------------------------------------------------------------------------
                Is0 <-(I.s0[t-1,j]+I.s0v[t-1,j])
                        if(Is0>0)  {
                rIs0 <-(I.s0[t-1,j]+I.s0v[t-1,j]*InfI2)/(I.s0[t-1,j]+I.s0v[t-1,j])
                                        } else { rIs0 <-1 }
        beta2.s0[t-1] <-beta2.s0[t-1] +(beta[t-1]*CMTa[a,j]*adjCNTa[t-1,a]*
                        N[t-1,3,j]/N[t-1,3,11]) * rIs0
        #-------------------------------------------------------------------------
                Isq <-(I.sq[t-1,j]+I.sqv[t-1,j])
                        if(Isq>0)  {
                rIsq <-(I.sq[t-1,j]+I.sqv[t-1,j]*InfI2)/(I.sq[t-1,j]+I.sqv[t-1,j])
                                } else { rIsq <-1 }
        beta2.sq[t-1] <-beta2.sq[t-1] +(beta[t-1]*CMTh[a,j]*
                        N[t-1,3,j]/N[t-1,3,11]) * rIsq
                        }
                        }

  #-------------------------------------------------------------------------------
  # transition rate from I0 to IM0, etc.
  #-------------------------------------------------------------------------------
        dk[t-1,1] <-alp2.a*   rFm.al[t-1]                                  # To IM0
        dk[t-1,2] <-alp2.a*(1-rFm.al[t-1])*(1-rFhos.al[t-1])*(1-rFsq.al[t-1])   # To IS0
        dk[t-1,3] <-alp2.a*(1-rFm.al[t-1])*(1-rFhos.al[t-1])*   rFsq.al[t-1]    # To ISq
        dk[t-1,4] <-alp2.a*(1-rFm.al[t-1])*   rFhos.al[t-1]                # To ISh

        for(k in 1:4) { dA[t-1] <-dA[t-1] +dk[t-1,k]  }

        dk[t-1,5] <-alp2.a*(1-(1-rVEsym1)*(1-rFm.al[t-1]))                                  # To IM0v
        dk[t-1,6] <-alp2.a*   (1-rVEsym1)*(1-rFm.al[t-1])*(1-rFhos.al[t-1])*(1-rFsq.al[t-1])    # To IS0v
        dk[t-1,7] <-alp2.a*   (1-rVEsym1)*(1-rFm.al[t-1])*(1-rFhos.al[t-1])*   rFsq.al[t-1]     # To ISqv
        dk[t-1,8] <-alp2.a*   (1-rVEsym1)*(1-rFm.al[t-1])*   rFhos.al[t-1]                 # To IShv

        for(k in 5:8) { dAv1[t-1] <-dAv1[t-1] +dk[t-1,k]  }

        dk[t-1,9] <-alp2.a*(1-(1-rVEsym2)*(1-rFm.al[t-1]))                                  # To IM0v
        dk[t-1,10] <-alp2.a*   (1-rVEsym2)*(1-rFm.al[t-1])*(1-rFhos.al[t-1])*(1-rFsq.al[t-1])    # To IS0v
        dk[t-1,11] <-alp2.a*   (1-rVEsym2)*(1-rFm.al[t-1])*(1-rFhos.al[t-1])*   rFsq.al[t-1]     # To ISqv
        dk[t-1,12] <-alp2.a*   (1-rVEsym2)*(1-rFm.al[t-1])*   rFhos.al[t-1]                 # To IShv

        for(k in 9:12) { dAv2[t-1] <-dAv2[t-1] +dk[t-1,k]  }

#=============================================================
#  Estimating R0 and effective Rt
#-------------------------------------------------------------

        Rt[t-1] <- ((SU[t-1,3,11]+VA0[t-1,3,11])/N[t-1,3,11]) *
                (beta2.i0[t-1]                  /(dA[t-1])                  +
                 beta2.m0[t-1]*dk[t-1,1]        /(dA[t-1]*gam.m0a[t-1])     +
                 beta2.s0[t-1]*dk[t-1,2]        /(dA[t-1]*gam.s0a[t-1])     +
                 beta2.s0[t-1]*dk[t-1,3]        /(dA[t-1]*gam.s1a[t-1])     +
                 beta2.sq[t-1]*dk[t-1,3]*gam.s1a[t-1] /(dA[t-1]*gam.s2a[t-1])          +
                 beta2.s0[t-1]*dk[t-1,4]        /(dA[t-1]*gam.h1a[t-1]))    +
                   (VAef1[t-1,3,11]/N[t-1,3,11])*(1-rVEinf1) *
                (beta2.i0[t-1]                  /(dAv1[t-1])                +
```

```
                    beta2.m0[t-1]*dk[t-1,5]              /(dAv1[t-1]*gam.m0a[t-1]) +
                    beta2.s0[t-1]*dk[t-1,6]             /(dAv1[t-1]*gam.s0a[t-1]) +
                    beta2.s0[t-1]*dk[t-1,7]             /(dAv1[t-1]*gam.s1a[t-1]) +
                    beta2.sq[t-1]*dk[t-1,7]*gam.s1a[t-1] /(dAv1[t-1]*gam.s2a[t-1]) +
                    beta2.s0[t-1]*dk[t-1,8]             /(dAv1[t-1]*gam.h1a[t-1])) +
                      (VAef2[t-1,3,11]/N[t-1,3,11])*(1-rVEinf2) *
                    (beta2.i0[t-1]                       /(dAv2[t-1])                 +
                    beta2.m0[t-1]*dk[t-1,9]              /(dAv2[t-1]*gam.m0a[t-1]) +
                    beta2.s0[t-1]*dk[t-1,10]            /(dAv2[t-1]*gam.s0a[t-1]) +
                    beta2.s0[t-1]*dk[t-1,11]            /(dAv2[t-1]*gam.s1a[t-1]) +
                    beta2.sq[t-1]*dk[t-1,11]*gam.s1a[t-1] /(dAv2[t-1]*gam.s2a[t-1]) +
                    beta2.s0[t-1]*dk[t-1,12]            /(dAv2[t-1]*gam.h1a[t-1])) +
                      ((SU.vac[t-1,3,11] +SU.rec[t-1,3,11])/N[t-1,3,11]) *
                    (beta2.i0[t-1]                       /(dAv2[t-1])                 +
                    beta2.m0[t-1]*dk[t-1,9]              /(dAv2[t-1]*gam.m0a[t-1]) +
                    beta2.s0[t-1]*dk[t-1,10]            /(dAv2[t-1]*gam.s0a[t-1]) +
                    beta2.s0[t-1]*dk[t-1,11]            /(dAv2[t-1]*gam.s1a[t-1]) +
                    beta2.sq[t-1]*dk[t-1,11]*gam.s1a[t-1] /(dAv2[t-1]*gam.s2a[t-1]) +
                    beta2.s0[t-1]*dk[t-1,12]            /(dAv2[t-1]*gam.h1a[t-1]))

#=============================================================================
#  Susceptable infected by contacting infectious individuals with any age-sex
#   not quarantined or household isolated in the whole population
#-----------------------------------------------------------------------------

          for(s in 1:2)          {
          for(a in 1:10)         {
          for(j in 1:10)         {

  # Temporary variable:
          ConInf <-  CMTa[a,j]*adjCNTa[t-1,a] *
            (ASYinf *(I.m[t-1,j] +InfI2 *I.mv[t-1,j]) +I.s[t-1,j] +InfI2 *I.sv[t-1,j])/N[t-1,3,j] +
                CMTh[a,j]* (I.sq[t-1,j] +InfI2 *I.sqv[t-1,j])/N[t-1,3,j]

  # Exposed from susceptible
          New.expsu[t-1,s,a] <-New.expsu[t-1,s,a] + beta[t-1] *SU[t-1,s,a] *ConInf
                                 }            # end age j
           SU[t-1,s,a] <-  SU[t-1,s,a] -New.expsu[t-1,s,a]
                                 }
                                 }

 #-------------------------------------------------
          for(s in 1:2)          {
          for(v in 1:dv0)        {
          for(a in 1:10)         {
          for(j in 1:10)         {

  # Temporary variable:
          ConInf <-  CMTa[a,j]*adjCNTa[t-1,a] *
            (ASYinf *(I.m[t-1,j] +InfI2 *I.mv[t-1,j]) +I.s[t-1,j] +InfI2 *I.sv[t-1,j])/N[t-1,3,j] +
                CMTh[a,j]* (I.sq[t-1,j] +InfI2 *I.sqv[t-1,j])/N[t-1,3,j]

  # Exposed in early vaccinated (<14 days):
              Expv0.temp <- beta[t-1] *eVA0[t-1,v,s,a] *ConInf
          Expv0[t-1,v,s,a] <- Expv0[t-1,v,s,a] +Expv0.temp
           eVA0[t-1,v,s,a] <-  eVA0[t-1,v,s,a] -Expv0.temp
                                 }
          New.expv0[t-1,s,a] <-New.expv0[t-1,s,a] +Expv0[t-1,v,s,a]
                                 }
                                 }
                                 }


  #-------------------------------------------------
          for(s in 1:2)          {
          for(w in 1:tv0)        {
          for(a in 1:10)         {
          for(j in 1:10)         {

  # Temporary variable:
```

```
            ConInf <-  CMTa[a,j]*adjCNTa[t-1,a] *
              (ASYinf *(I.m[t-1,j] +InfI2 *I.mv[t-1,j]) +I.s[t-1,j] +InfI2 *I.sv[t-1,j])/N[t-1,3,j] +
                    CMTh[a,j]* (I.sq[t-1,j] +InfI2 *I.sqv[t-1,j])/N[t-1,3,j]

  # Exposed in vaccinated dose-1 (risk reduced by "1-rVEinf1"):
            Expv1.temp <- beta[t-1] *eVAef1[t-1,w,s,a] *ConInf *(1-rVEinf1)
            Expv1[t-1,w,s,a] <-Expv1[t-1,w,s,a] + Expv1.temp
             eVAef1[t-1,w,s,a] <- eVAef1[t-1,w,s,a] -Expv1.temp
                                  }
            New.expv1[t-1,s,a] <-New.expv1[t-1,s,a] +Expv1[t-1,w,s,a]
                                  }
                                  }
                                  }

  #-------------------------------------------------------
            for(s in 1:2)         {
               tv1<-(t-vac.tim[1]); if(tv1<2) { tv1<-2  }
            for(w in 1:tv1)       {
            for(a in 1:10)        {
            for(j in 1:10)        {

  # Temporary variable:
            ConInf <-  CMTa[a,j]*adjCNTa[t-1,a] *
              (ASYinf *(I.m[t-1,j] +InfI2 *I.mv[t-1,j]) +I.s[t-1,j] +InfI2 *I.sv[t-1,j])/N[t-1,3,j] +
                    CMTh[a,j]* (I.sq[t-1,j] +InfI2 *I.sqv[t-1,j])/N[t-1,3,j]

  # Exposed in vaccinated dose-2 (risk reduced by "1-rVEinf2"):
            Expv2.temp <- beta[t-1] *eVAef2[t-1,w,s,a] *ConInf *(1-rVEinf2)
            Expv2[t-1,w,s,a] <-Expv2[t-1,w,s,a] + Expv2.temp
             eVAef2[t-1,w,s,a] <- eVAef2[t-1,w,s,a] -Expv2.temp
                                  }
            New.expv2[t-1,s,a] <-New.expv2[t-1,s,a] +Expv2[t-1,w,s,a]
                                  }
                                  }
                                  }

   #-------------------------------------------------------

            for(s in 1:2)         {
            for(a in 1:10)        {
            for(j in 1:10)        {

  # Temporary variable:
            ConInf <-  CMTa[a,j]*adjCNTa[t-1,a] *
              (ASYinf *(I.m[t-1,j] +InfI2 *I.mv[t-1,j]) +I.s[t-1,j] +InfI2 *I.sv[t-1,j])/N[t-1,3,j] +
                    CMTh[a,j]* (I.sq[t-1,j] +InfI2 *I.sqv[t-1,j])/N[t-1,3,j]

  # Exposed due to loss of immunity in vaccinated/recovered (risk fraction: "rLOSinf"):
             New.explosv1[t-1,s,a]  <- New.explosv1[t-1,s,a] + beta[t-1] *(SU.vac[t-1,s,a]) *ConInf
            New.explosrec[t-1,s,a] <- New.explosrec[t-1,s,a] + beta[t-1] *(SU.rec[t-1,s,a]) *ConInf
                                  }

            SU.vac[t-1,s,a] <-SU.vac[t-1,s,a] - New.explosv1[t-1,s,a]
            SU.rec[t-1,s,a] <-SU.rec[t-1,s,a] -New.explosrec[t-1,s,a]
                                  }
                                  }


##########################################################

            if(VAC==1)                    {           ### Vaccination yes=1 or no=0

#=========================================================================
#  Total vaccinated and days required to complete vaccination
            if(t <vac.tim[1]+1 )  { Vtru<-0; Vp<-7; Rv<-0 }   # Vtru: vaccination true-1 or false-0
              for(rev in 1:nRvac)                 {           # from 1 to nRvac -no. of vac programs
            if(t== (vac.tim[rev]+1) )       {
                                  Vtru <-1;   Vp <-1;   Rv <-rev
                        T.vac[Rv,1] <- vac.tim[rev] +1          # T.vac starting time for age Vp==1
                                                }
```

```
                                                }           # end for rev in 1:nRvac
#=============================================================================

          if( Vtru==1)          {

  #-------------------------------------------------------------
          for(nVp in 2:6)                 {
           if(t==T.vac[Rv,nVp]) {  Vp <-nVp  }
                                                }
  #-------------------------------------------------------------
                    Totalvac <-0
  #-----------------------------------------------------------------------------

             vaccrg <-vac.crg4                  # if Vp<4: age 50+

          if(Vp==6)             {
          if(Rv==1) { vaccrg <-vac.crg1*0.4 }  # 16-19  in 10-19
          if(Rv >1) { vaccrg <-vac.crg1*0.1 }  # new 16 in 10-19
                                }           # end if Vp=6

          if(Vp==5)             {
                vaccrg <-vac.crg2   # age 20-39
                                }           # end if Vp=5

          if(Vp==4)             {
                vaccrg <-vac.crg3   # age 40-49
                                }           # end if Vp=4

          #-----------------------------------------------------------------------------

          for(a in vagp[Vp,1]:vagp[Vp,2])       {           # a from low to high age limit
          for(s in 1:2)                         {           # s in 1:2

   # Vaccinated among SU, RE, and lost immunity:
   # In not-exposed only

          Totalvac <-Totalvac + (SU[t-1,s,a] +    RE[t-1,s,a] +SU.vac[t-1,s,a] +SU.rec[t-1,s,a] ) *vaccrg


   # vaccination of people vaccinated for at leas 91 days (3 months)

          vcrg <- vaccrg
          if(Vp==6) { vcrg <- vac.crg1 }
          if(Rv>1) {
                    for(w in 91:t)          {
             Totalvac <- Totalvac + eVAef2[t-1,w,s,a] *vcrg
                                                }
                                                }  # end Rv>1
                                                }           # end s
                                                }           # end a

  #-------------------------------------------------------------------------------------------
          if( t==T.vac[Rv,Vp] )                 {           # Fixing V.day, V.dmax, vacend estimates at T.vac[Rv,Vp]
           V.day[Rv,Vp] <- round(Totalvac/vac.dmaxi) +1 # V.day: no. of days required for Vp phase
          V.dmax[Rv,Vp] <-Totalvac/V.day[Rv,Vp]                   # Totalvac at the 1st day of a vac phase
          vacend[Rv,Vp] <- T.vac[Rv,Vp] +V.day[Rv,Vp] -1
          if(Vp<6)  {  T.vac[Rv,Vp+1] <-vacend[Rv,Vp] +1  }
                                                }           # end if t==T.vac
    #-------------------------------------------------------------------------------------------------

                                                }           # end if Vtru==1
                                                }           # end if VAC==1

#=============================================================
# Estimating VA, SU, EX, I, and RE, hospitalised, ICU, and no. of tests required

  for(s in 1:2)         {           ### sex male-1, female-2
  for(a in 1:10)        {           ### age group 1-10

          if(VAC==1)                    {           # Vaccination: 1-yes or 0-no
```

```
            if(Vtru==1)                     {
            if(Vp<(vac.AGP[Rv]+1) )     {           # only apply to Vp 1-6
#-------------------------------------------------------------------------
               vaccrg <-vac.crg4                    # if Vp<4: age 50+

            if(Vp==6)           {
            if(Rv==1) { vaccrg <-vac.crg1*0.4 }  # 18-19 in 10-19
            if(Rv >1) { vaccrg <-vac.crg1*0.1 }  # new 16 in 10-19
                                }           # end if Vp=6
            if(Vp==5)           {
                  vaccrg <-vac.crg2   # age 20-39
                                }           # end if Vp=5
            if(Vp==4)           {
                  vaccrg <-vac.crg3   # age 40-49
                                }           # end if Vp=4
#-------------------------------------------------------------------------
            if(a>vagp[Vp,1]-1) {
            if(a<vagp[Vp,2]+1){

  # Vaccinating susceptible
  #-----------------------------------------------------------------
               vac.SU[t-1,s,a] <- V.dmax[Rv,Vp] *(SU[t-1,s,a]*vaccrg)/Totalvac
            if(vac.SU[t-1,s,a]>SU[t-1,s,a]) {   vac.SU[t-1,s,a] <-SU[t-1,s,a]*vaccrg }
                  SU[t-1,s,a] <-SU[t-1,s,a] -vac.SU[t-1,s,a]
               New.vac[t-1,s,a] <- vac.SU[t-1,s,a]

    # Vaccinating loss of immunity in vaccinated
    #-----------------------------------------------------------------
               vac.SUvac[t-1,s,a] <- V.dmax[Rv,Vp] *(SU.vac[t-1,s,a]*vaccrg)/Totalvac
            if(vac.SUvac[t-1,s,a]>SU.vac[t-1,s,a]) { vac.SUvac[t-1,s,a] <-SU.vac[t-1,s,a]*vaccrg }
                  SU.vac[t-1,s,a] <- SU.vac[t-1,s,a] -vac.SUvac[t-1,s,a]

               New.vac[t-1,s,a] <-New.vac[t-1,s,a] +vac.SUvac[t-1,s,a]

    # Vaccinating loss of immunity in recovered
    #-----------------------------------------------------------------
               vac.SUrec[t-1,s,a] <- V.dmax[Rv,Vp] *(SU.rec[t-1,s,a]*vaccrg)/Totalvac
            if(vac.SUrec[t-1,s,a]>SU.rec[t-1,s,a]) { vac.SUrec[t-1,s,a] <-SU.rec[t-1,s,a]*vaccrg }
                  SU.rec[t-1,s,a] <- SU.rec[t-1,s,a] -vac.SUrec[t-1,s,a]
               New.vac[t-1,s,a] <-New.vac[t-1,s,a] +vac.SUrec[t-1,s,a]

    # Vaccinating all recovered
                  vac.RE<-0
               for(w in 1:t)       {
                  vac.RE <-V.dmax[Rv,Vp] *(eRE[t-1,w,s,a]*vaccrg)/Totalvac
               if(vac.RE>eRE[t-1,w,s,a]) { vac.RE <-eRE[t-1,w,s,a]*vaccrg  }
                   eRE[t-1,w,s,a] <- eRE[t-1,w,s,a] -vac.RE
                   eRE[t,1,s,a] <- eRE[t,1,s,a] +vac.RE *(1-rADth0[t.dr,s,a])   # Boost RE status after vaccination
             New.vac[t-1,s,a] <- New.vac[t-1,s,a] +vac.RE
                                  } # end w in 1:t

    # Re-vaccinating previous vaccinated, if Rv>1
    #-----------------------------------------------------------
            if(Rv>1) {
            vcrg <- vaccrg
            if(Vp==6) { vcrg <- vac.crg1 }          # for age 16-19
                  vac.VAef <-0
               for(w in 91:t)     {
                  vac.VAef <-V.dmax[Rv,Vp] *(eVAef2[t-1,w,s,a]*vcrg)/Totalvac
               if(vac.VAef>eVAef2[t-1,w,s,a]) { vac.VAef <-eVAef2[t-1,w,s,a]*vcrg  }
                   eVAef2[t-1,w,s,a] <- eVAef2[t-1,w,s,a] -vac.VAef
                     eVAef2[t,1,s,a] <- eVAef2[t,1,s,a] +vac.VAef *(1-rADth0[t.dr,s,a])
             New.vac[t-1,s,a] <- New.vac[t-1,s,a] +vac.VAef
                                  } # end w in 91:t
                  }  # End if Rv>1

    #-----------------------------------------------------------
                                }           # end a>a1-1
                                }           # end a<a2+1
```

```
        if( Vp==vac.AGP[Rv] )       {
            if(t==vacend[Rv,Vp]+1)  {  Vtru <-0  }
                                    }
                                    }           # end if Vp<7
                                    }           # end if Vtru==1

#=============================================================================
#  Calculating no. of VA status at time t

        eVA0[t,1,s,a] <- vac.SU[t-1,s,a] *(1-rADth0[t.dr,s,a])
        VA0[t,s,a] <-eVA0[t,1,s,a]
        for(v in 2:14)          {
          eVA0[t,v,s,a] <-eVA0[t-1,v-1,s,a] *(1-rADth0[t.dr,s,a])
            VA0[t,s,a] <-VA0[t,s,a] +eVA0[t,v,s,a]
                        }           # end for v in 2:14

        #-------------------------------------------------------------
          eVAef1[t,1,s,a] <-eVA0[t-1,14,s,a]*(1-rADth0[t.dr,s,a])
        VAef1[t,s,a] <- eVAef1[t,1,s,a]
        for(w in 2:63)      {
          eVAef1[t,w,s,a] <-eVAef1[t-1,w-1,s,a]*(1-rADth0[t.dr,s,a])
            VAef1[t,s,a] <-VAef1[t,s,a] +eVAef1[t,w,s,a]
                        }

        #-------------------------------------------------------------
        #  eVAef2 include renewed vaccination of previously vaccinated
        #-------------------------------------------------------------
          eVAef2[t,1,s,a] <- eVAef2[t,1,s,a] +(eVAef1[t-1,63,s,a] +
                        vac.SUvac[t-1,s,a] +vac.SUrec[t-1,s,a])*(1-rADth0[t.dr,s,a])
                tv1<-(t-vac.tim[1]); if(tv1<3) { tv1<-3  }
        for(w in 2:tv1)     {
          eVAef2[t,w,s,a] <- eVAef2[t-1,w-1,s,a] *(1-gimmv.wan[w-1])*(1-rADth0[t.dr,s,a])
                        }
        for(w in 1:tv1)     {
                VAef2[t,s,a] <-VAef2[t,s,a] +eVAef2[t,w,s,a]
                        }

                        }   ###  end if VAC==1

 #=============================================================================
 # Estimating return to susceptible in the recovered/vaccinated, minus newly infected due to loss of immunity
 #-----------------------------------------------------------------------------

                SUvac <-0
            tv1 <-(t-vac.tim[1]); if(tv1<2) { tv1<-2  }      # Loss of vaccine immunity
          for(w in 1:tv1)     {
            SUvac <- SUvac +eVAef2[t-1,w,s,a] *gimmv.wan[w]
                                    }
            SU.vac[t,s,a] <-(SU.vac[t-1,s,a] +SUvac) *(1-rADth0[t.dr,s,a])

                SUrec  <-0
            tw1 <-(t-ts); if(tw1<2) { tw1<-2  }              # Loss of natural immunity
          for(w in 1:tw1)     {
            SUrec <- SUrec  +eRE[t-1,w,s,a] *gimm.wan[w]
                                    }
            SU.rec[t,s,a]<- (SU.rec[t-1,s,a] +SUrec) *(1-rADth0[t.dr,s,a])

#=============================================================================
# Estimating SU, EX, I, and RE
#   New exposed and vaccinated already removed from SU[t-1, ...]
#=============================================================================
        SU[t,s,a] <-(SU[t-1,s,a])*(1-rADth0[t.dr,s,a]) +
                                        dBth[a]*Bsex[s] -Seed.all[t,s,a]

         New.expal[t-1,s,a] <-  New.expsu[t-1,s,a]    +New.expv0[t-1,s,a] +
                                New.expv1[t-1,s,a]    +New.expv2[t-1,s,a] +
                                New.explosv1[t-1,s,a] +New.explosrec[t-1,s,a]

 #=============================================================================
 # All newsymptomatic cases at t. rVEsym: efficacy of vaccine on symptomatic cases
```

```
#-------------------------------------------------------------------
        for(d in 2:dd)          {
    New.sym[t,s,a] <- New.sym[t,s,a] + (eI0[t-1,d-1,s,a] +
                                        eI0v1[t-1,d-1,s,a]*(1-rVEsym1) +
                                        eI0v2[t-1,d-1,s,a]*(1-rVEsym2) ) *alp2[d-1]*(1-rFm[a])
                            }   # end for d in 2:dd

         eEX[t,1,s,a] <-(New.expsu[t-1,s,a] +New.expv0[t-1,s,a]) +eSeed[t,1,s,a]

        eEXv1[t,1,s,a] <-New.expv1[t-1,s,a]

        eEXv2[t,1,s,a] <-(New.expv2[t-1,s,a] +New.explosv1[t-1,s,a] +New.explosrec[t-1,s,a])

        # All covid deaths from symptomatic cases, ie, (1-rFm)
        #-------------------------------------------------------------------------------
          eInf[t,1,s,a] <- eEX[t,1,s,a] *(1-rFm[a]) *drisk.inf[s,a]*adjDth[t]
          eInfv[t,1,s,a] <- (eEXv1[t,1,s,a] *(1-rVEsym1)*(1-rFm[a]) +
                                eEXv2[t,1,s,a] *(1-rVEsym2)*(1-rFm[a]) ) *drisk.inf[s,a]*adjDth[t]
        #-------------------------------------------------------------------------------
                    I0.1   <-0; I0v1.1 <-0; I0v2.1 <-0

        for(d in 2:dd)          {  # d in 2:dd=60
          I0.1  <- I0.1   +  eI0[t-1,d-1,s,a]*alp2[d-1]
          I0v1.1 <-I0v1.1 +eI0v1[t-1,d-1,s,a]*alp2[d-1]
          I0v2.1 <-I0v2.1 +eI0v2[t-1,d-1,s,a]*alp2[d-1]

           eI0[t,1,s,a] <-   eI0[t,1,s,a] +   eEX[t-1,d-1,s,a]*alp1[d-1]              # From Exp to I0
          eI0v1[t,1,s,a] <-eI0v1[t,1,s,a] + eEXv1[t-1,d-1,s,a]*alp1[d-1]          # Exposed in vaccinated dose-1
          eI0v2[t,1,s,a] <-eI0v2[t,1,s,a] + eEXv2[t-1,d-1,s,a]*alp1[d-1]          # Exposed in vaccinated dose-2

           eQS[t,1,s,a] <- eQS[t,1,s,a] + eISq[t-1,d-1,s,a]*gam.s1[t-1,d-1]
          eQSv[t,1,s,a] <-eQSv[t,1,s,a] +eISqv[t-1,d-1,s,a]*gam.s1[t-1,d-1]
           eHS[t,1,s,a] <- eHS[t,1,s,a] + eISh[t-1,d-1,s,a]*gam.h1[t-1,d-1]
          eHSv[t,1,s,a] <-eHSv[t,1,s,a] +eIShv[t-1,d-1,s,a]*gam.h1[t-1,d-1]

                            }   # end d in 2:dd

        #-------------------------------------------------------------------------------------
        # Allocate I0.all to IM, IS, etc
        #-------------------------------------------------------------------------------------
          eIM0[t,1,s,a] <- I0.1 *rFm[a]
          eIS0[t,1,s,a] <- I0.1 *(1-rFm[a]) *(1-rFhos[t-1,a])*(1-rFsq[t-1,a])
          eISq[t,1,s,a] <- I0.1 *(1-rFm[a]) *(1-rFhos[t-1,a])*   rFsq[t-1,a]
          eISh[t,1,s,a] <- I0.1 *(1-rFm[a]) *   rFhos[t-1,a]

          eIM0v[t,1,s,a] <- I0v1.1* (1-(1-rVEsym1)*(1-rFm[a])) +I0v2.1*(1-(1-rVEsym2)*(1-rFm[a]))
          eIS0v[t,1,s,a] <-(I0v1.1* (1-rVEsym1)+I0v2.1*(1-rVEsym2))*(1-rFm[a])*(1-rFhos[t-1,a])*(1-rFsq[t-1,a])
          eISqv[t,1,s,a] <-(I0v1.1* (1-rVEsym1)+I0v2.1*(1-rVEsym2))*(1-rFm[a])*(1-rFhos[t-1,a])*   rFsq[t-1,a]
          eIShv[t,1,s,a] <-(I0v1.1* (1-rVEsym1)+I0v2.1*(1-rVEsym2))*(1-rFm[a])*   rFhos[t-1,a]

        #=====================================================================================
        # Estimate covid related deaths by days since exposed/infected
        # ------------------------------------------------------------------
        for(d in 2:dd+1)      {
           nDth.inf[t-1,s,a] <- nDth.inf[t-1,s,a]+ eInf[t-1,d-1,s,a]*gdth.inf[d-1]
          nDth.infv[t-1,s,a] <-nDth.infv[t-1,s,a]+eInfv[t-1,d-1,s,a]*gdth.inf[d-1]
                                    }

        #=====================================================================================
        # UK data: 64% covid-19 deaths in hospital, 36% in other settings
        if(HS[t-1,s,a]>0) { r.dhos<-nDth.inf[t-1,s,a] *0.64/HS[t-1,s,a] } else { r.dhos<-0 }
        if(r.dhos>0.9)          { r.dhos<-0.9 }

        for(d in 1:dd)                  {
          nDth.hos[t-1,d,s,a] <- eHS[t-1,d,s,a]*r.dhos
                    if(nDth.hos[t-1,d,s,a]<0) { nDth.hos[t-1,d,s,a]<-0  }
                                    }

        for(d in 1:dd)          {                       # All hospital deaths
         nDthHos.all[t-1,s,a] <-nDthHos.all[t-1,s,a] +nDth.hos[t-1,d,s,a]
```

```
                                }

        nDth.cov[t-1,s,a] <-nDth.cov[t-1,s,a] +nDthHos.all[t-1,s,a]  # sum up covid deaths

  # Deaths outside hospitals in IS0 and QS:
        nDth.ss[t-1,s,a] <- nDth.inf[t-1,s,a] -nDthHos.all[t-1,s,a]
                if(nDth.ss[t-1,s,a]<0) { nDth.ss[t-1,s,a]<-0  }

          nS0Sq <- IS0[t-1,s,a] +QS[t-1,s,a]                  # Temporary variable

        if(nS0Sq>0) { r.dss<-nDth.ss[t-1,s,a]/nS0Sq } else { r.dss<-0             }
        if(r.dss>1) { r.dss<-0.99 }

         for(d in 1:dd)                 {
          nDth.s0[t-1,d,s,a] <-eIS0[t-1,d,s,a] *r.dss
                if(nDth.s0[t-1,d,s,a]<0) { nDth.s0[t-1,d,s,a]<-0  }
          nDth.sq[t-1,d,s,a] <- eQS[t-1,d,s,a] *r.dss
                if(nDth.sq[t-1,d,s,a]<0) { nDth.sq[t-1,d,s,a]<-0  }

        nDth.cov[t-1,s,a] <-nDth.cov[t-1,s,a] +nDth.s0[t-1,d,s,a] +nDth.sq[t-1,d,s,a]      ## sum up covid deaths


                                }

        #-------------------------------------------------
        # Repeat the above for covid deaths in reinfected
        #-------------------------------------------------

        if(HSv[t-1,s,a]>0) { r.dhosv<-nDth.infv[t-1,s,a] *0.64/HSv[t-1,s,a] } else { r.dhosv<-0 }
        if(r.dhosv>0.9)       { r.dhosv<-0.9 }

        for(d in 1:dd)                  {
          nDth.hosv[t-1,d,s,a] <- eHSv[t-1,d,s,a]*r.dhosv
                if(nDth.hosv[t-1,d,s,a]<0) { nDth.hosv[t-1,d,s,a]<-0  }
                                }

        for(d in 1:dd)          {
         nDthHos.allv[t-1,s,a] <-nDthHos.allv[t-1,s,a] +nDth.hosv[t-1,d,s,a]
                                }

        nDth.cov[t-1,s,a] <-nDth.cov[t-1,s,a] +nDthHos.allv[t-1,s,a]            # sum up covid deaths

  # Deaths outside hospitals in IS0 and QS:
        nDth.ssv[t-1,s,a] <- nDth.infv[t-1,s,a] -nDthHos.allv[t-1,s,a]
                if(nDth.ssv[t-1,s,a]<0) { nDth.ssv[t-1,s,a]<-0  }

          nS0Sqv <- IS0v[t-1,s,a] +QSv[t-1,s,a]                         # Temporary variable

        if(nS0Sqv>0) { r.dssv<-nDth.ssv[t-1,s,a]/nS0Sqv } else { r.dssv<-0    }
        if(r.dssv>1) { r.dssv<-0.99 }

         for(d in 1:dd)                 {
          nDth.s0v[t-1,d,s,a] <-eIS0v[t-1,d,s,a] *r.dssv
                if(nDth.s0v[t-1,d,s,a]<0) { nDth.s0v[t-1,d,s,a]<-0  }
          nDth.sqv[t-1,d,s,a] <- eQSv[t-1,d,s,a] *r.dssv
                if(nDth.sqv[t-1,d,s,a]<0) { nDth.sqv[t-1,d,s,a]<-0  }

        nDth.cov[t-1,s,a] <-nDth.cov[t-1,s,a] +nDth.s0v[t-1,d,s,a] +nDth.sqv[t-1,d,s,a]   ## sum up covid deaths

                                }

#=============================================================================================-

        for(d in 2:dd)          {

          eEX[t,d,s,a] <-  eEX[t-1,d-1,s,a]*(1-alp1[d-1]) +eSeed[t,d,s,a]
         eEXv1[t,d,s,a] <-eEXv1[t-1,d-1,s,a]*(1-alp1[d-1])
         eEXv2[t,d,s,a] <-eEXv2[t-1,d-1,s,a]*(1-alp1[d-1])

          eI0[t,d,s,a] <-  eI0[t-1,d-1,s,a]*(1-alp2[d-1])
         eI0v1[t,d,s,a] <-eI0v1[t-1,d-1,s,a]*(1-alp2[d-1])
```

```
                eI0v2[t,d,s,a] <-eI0v2[t-1,d-1,s,a]*(1-alp2[d-1])

               eIM0[t,d,s,a] <- eIM0[t-1,d-1,s,a]*(1-gam.m0[t-1,d-1])
               eISq[t,d,s,a] <- eISq[t-1,d-1,s,a]*(1-gam.s1[t-1,d-1])
               eISh[t,d,s,a] <- eISh[t-1,d-1,s,a]*(1-gam.h1[t-1,d-1])

               eIS0[t,d,s,a] <-(eIS0[t-1,d-1,s,a]- nDth.s0[t-1,d-1,s,a])*(1-gam.s0[t-1,d-1])
                eQS[t,d,s,a] <- (eQS[t-1,d-1,s,a]- nDth.sq[t-1,d-1,s,a])*(1-gam.s2[t-1,d-1])
                eHS[t,d,s,a] <- (eHS[t-1,d-1,s,a]-nDth.hos[t-1,d-1,s,a])*(1-gam.h2[t-1,d-1])

               eIM0v[t,d,s,a] <- eIM0v[t-1,d-1,s,a]*(1-gam.m0[t-1,d-1])
               eISqv[t,d,s,a] <- eISqv[t-1,d-1,s,a]*(1-gam.s1[t-1,d-1])
               eIShv[t,d,s,a] <- eIShv[t-1,d-1,s,a]*(1-gam.h1[t-1,d-1])

               eIS0v[t,d,s,a] <-(eIS0v[t-1,d-1,s,a]- nDth.s0v[t-1,d-1,s,a])*(1-gam.s0[t-1,d-1])
                eQSv[t,d,s,a] <- (eQSv[t-1,d-1,s,a]- nDth.sqv[t-1,d-1,s,a])*(1-gam.s2[t-1,d-1])
                eHSv[t,d,s,a] <- (eHSv[t-1,d-1,s,a]-nDth.hosv[t-1,d-1,s,a])*(1-gam.h2[t-1,d-1])

               eInf[t,d,s,a] <- eInf[t-1,d-1,s,a]*(1-gdth.inf[d-1])

               eInfv[t,d,s,a] <- eInfv[t-1,d-1,s,a]*(1-gdth.inf[d-1])

                                        } # End d in 2:dd

#=============================================================================
#  Overall EX, I0, IM, IS, etc
#=============================================================================
               for(d in 1:dd)          {   # d in 1:dd

                EX[t,s,a] <-  EX[t,s,a] + eEX[t,d,s,a]
                I0[t,s,a] <-  I0[t,s,a] + eI0[t,d,s,a]
               IM0[t,s,a] <- IM0[t,s,a] +eIM0[t,d,s,a]
               IS0[t,s,a] <- IS0[t,s,a] +eIS0[t,d,s,a]
               ISq[t,s,a] <- ISq[t,s,a] +eISq[t,d,s,a]
                QS[t,s,a] <-  QS[t,s,a] + eQS[t,d,s,a]
               ISh[t,s,a] <- ISh[t,s,a] +eISh[t,d,s,a]
                HS[t,s,a] <-  HS[t,s,a] + eHS[t,d,s,a]

               EXv1[t,s,a] <- EXv1[t,s,a] +eEXv1[t,d,s,a]
               I0v1[t,s,a] <- I0v1[t,s,a] +eI0v1[t,d,s,a]

               EXv2[t,s,a] <- EXv2[t,s,a] +eEXv2[t,d,s,a]
               I0v2[t,s,a] <- I0v2[t,s,a] +eI0v2[t,d,s,a]

               IM0v[t,s,a] <- IM0v[t,s,a] +eIM0v[t,d,s,a]
               IS0v[t,s,a] <- IS0v[t,s,a] +eIS0v[t,d,s,a]
               ISqv[t,s,a] <- ISqv[t,s,a] +eISqv[t,d,s,a]
                QSv[t,s,a] <-  QSv[t,s,a] + eQSv[t,d,s,a]
               IShv[t,s,a] <- IShv[t,s,a] +eIShv[t,d,s,a]
                HSv[t,s,a] <-  HSv[t,s,a] + eHSv[t,d,s,a]

                                        }   # end for d in 1:dd

                HS.new[t,s,a] <-eHS[t,1,s,a]  +eHSv[t,1,s,a]       # New hospital admission

#=============================================================================
#  Recovered from infected
#-------------------------------------------------------
               for(d in 1:dd)                       {
                 eRE[t,1,s,a] <-eRE[t,1,s,a] +
                          (eQS[t-1,d,s,a]-  nDth.sq[t-1,d,s,a])*gam.s2[t-1,d] +
                     (eIS0[t-1,d,s,a]-  nDth.s0[t-1,d,s,a])*gam.s0[t-1,d] +
                          (eHS[t-1,d,s,a]- nDth.hos[t-1,d,s,a])*gam.h2[t-1,d] +
                          eIM0[t-1,d,s,a]                    *gam.m0[t-1,d] +
                          (eQSv[t-1,d,s,a]-  nDth.sqv[t-1,d,s,a])*gam.s2[t-1,d] +
                     (eIS0v[t-1,d,s,a]-  nDth.s0v[t-1,d,s,a])*gam.s0[t-1,d] +
                          (eHSv[t-1,d,s,a]- nDth.hosv[t-1,d,s,a])*gam.h2[t-1,d] +
                          eIM0v[t-1,d,s,a]                    *gam.m0[t-1,d]

                                                  }  # end for d in 1:dd
```

```
            RE[t,s,a] <-eRE[t,1,s,a]

                        tw1 <-(t-ts); if(tw1<3) { tw1<-3  }
             for(w in 2:tw1)      {
              eRE[t,w,s,a] <- eRE[t-1,w-1,s,a]*(1-rADth0[t.dr,s,a]) *(1-gimm.wan[w-1])

                 if(w==tw1)   {
              eRE[t,w,s,a] <-(eRE[t,w-1,s,a]+eRE[t-1,w,s,a]) *(1-rADth0[t.dr,s,a]) *(1-gimm.wan[tw1])
                                  }

            RE[t,s,a] <-RE[t,s,a] +eRE[t,w,s,a]

                                          }            # end w in 2:tw1

#-------------------------------------------------------------------------
             N[t,s,a] <-    SU[t,s,a] + SU.vac[t,s,a] + SU.rec[t,s,a] +
                                  EX[t,s,a] +   EXv1[t,s,a] + EXv2[t,s,a] +
                                  I0[t,s,a] +   I0v1[t,s,a] + I0v2[t,s,a] +
                                 IM0[t,s,a] +          IS0[t,s,a] +
                                 ISq[t,s,a] +    QS[t,s,a] +
                                 ISh[t,s,a] +           HS[t,s,a] +
                                IM0v[t,s,a] +  IS0v[t,s,a] +
                                ISqv[t,s,a] +   QSv[t,s,a] +
                                IShv[t,s,a] +          HSv[t,s,a] +
                              VA0[t,s,a] +  VAef1[t,s,a] + VAef2[t,s,a] +
                                 RE[t,s,a]

#-------------------------------------------------------------------------
                                } #---------End for age in 1:18    ######
                                } #---------End for sex in 1:2     ######

                     }    ###### end if t>ts ########

#=========================================================================================
#  Upgrading age at the beginning of a year (t1)
#    jN[a], etc, are used to record N[a], etc, before their adjustments, because
#     unchanged N[a] is required for the adjustment of N[a+1], etc.
#-----------------------------------------------------------------------------------
            if(t==tage)            {
            for(s in 1:2)          {
            for(a in 1:10)         {
            if(a>1)   { Ag1<-1; Ag2<-1; Ag3<-10; Ag4<-10; a1<-(a-1) }          # for age 10 to 79
            if(a==1)  { Ag1<-1; Ag2<-0; Ag3<-5;  Ag4<-5;  a1<-1     }          # for age 0-4
            if(a==2)  { Ag1<-1; Ag2<-1; Ag3<-5;  Ag4<-5;  a1<-1     }          # for age 5-9
            if(a==3)  { Ag1<-1; Ag2<-1; Ag3<-10; Ag4<-5;  a1<-2     }          # for age 10-19
            if(a==10) { Ag1<-0; Ag2<-1; Ag3<-10; Ag4<-10; a1<-9     }          # for age 80+
                        jN[a] <- N[t,s,a]
                       N[t,s,a] <-   N[t,s,a] - Ag1*  N[t,s,a]/(Ag3)  + Ag2* jN[a1]/(Ag4)
                        jSU[a] <- SU[t,s,a]
                      SU[t,s,a] <-  SU[t,s,a] - Ag1* SU[t,s,a]/(Ag3)  +Ag2* jSU[a1]/(Ag4)
                        jRE[a] <- RE[t,s,a]
                      RE[t,s,a] <-  RE[t,s,a] - Ag1* RE[t,s,a]/(Ag3)  +Ag2* jRE[a1]/(Ag4)
                        jEX[a] <- EX[t,s,a]
                      EX[t,s,a] <-  EX[t,s,a] - Ag1* EX[t,s,a]/(Ag3)  +Ag2* jEX[a1]/(Ag4)
                        jI0[a] <- I0[t,s,a]
                      I0[t,s,a] <-  I0[t,s,a] - Ag1* I0[t,s,a]/(Ag3)  +Ag2* jI0[a1]/(Ag4)
                        jIM0[a] <- IM0[t,s,a]
                     IM0[t,s,a] <- IM0[t,s,a] -Ag1* IM0[t,s,a]/(Ag3)  +Ag2*jIM0[a1]/(Ag4)
                        jIS0[a] <- IS0[t,s,a]
                     IS0[t,s,a] <- IS0[t,s,a] -Ag1* IS0[t,s,a]/(Ag3)  +Ag2*jIS0[a1]/(Ag4)
                        jISq[a] <- ISq[t,s,a]
                     ISq[t,s,a] <- ISq[t,s,a] -Ag1* ISq[t,s,a]/(Ag3)  +Ag2*jISq[a1]/(Ag4)
                        jISh[a] <- ISh[t,s,a]
                     ISh[t,s,a] <- ISh[t,s,a] -Ag1* ISh[t,s,a]/(Ag3)  +Ag2*jISh[a1]/(Ag4)
                        jQS[a] <- QS[t,s,a]
                      QS[t,s,a] <-  QS[t,s,a] -Ag1*  QS[t,s,a]/(Ag3)  +Ag2* jQS[a1]/(Ag4)
                        jHS[a] <- HS[t,s,a]
                      HS[t,s,a] <-  HS[t,s,a] -Ag1*  HS[t,s,a]/(Ag3)  +Ag2* jHS[a1]/(Ag4)
```

```
  jEXv1[a] <- EXv1[t,s,a]
EXv1[t,s,a] <- EXv1[t,s,a] -  Ag1*  EXv1[t,s,a]/(Ag3)  +Ag2* jEXv1[a1]/(Ag4)
  jI0v1[a] <- I0v1[t,s,a]
I0v1[t,s,a] <- I0v1[t,s,a] -  Ag1*  I0v1[t,s,a]/(Ag3)  +Ag2* jI0v1[a1]/(Ag4)
  jEXv2[a] <- EXv2[t,s,a]
EXv2[t,s,a] <- EXv2[t,s,a] -  Ag1*  EXv2[t,s,a]/(Ag3)  +Ag2* jEXv2[a1]/(Ag4)
  jI0v2[a] <- I0v2[t,s,a]
I0v2[t,s,a] <- I0v2[t,s,a] -  Ag1*  I0v2[t,s,a]/(Ag3)  +Ag2* jI0v2[a1]/(Ag4)

  jIM0v[a] <- IM0v[t,s,a]
IM0v[t,s,a] <- IM0v[t,s,a] -Ag1* IM0v[t,s,a]/(Ag3)  +Ag2*jIM0v[a1]/(Ag4)
  jIS0v[a] <- IS0v[t,s,a]
IS0v[t,s,a] <- IS0v[t,s,a] -Ag1* IS0v[t,s,a]/(Ag3)  +Ag2*jIS0v[a1]/(Ag4)
  jISqv[a] <- ISq[t,s,a]
ISqv[t,s,a] <- ISqv[t,s,a] -Ag1* ISqv[t,s,a]/(Ag3)  +Ag2*jISqv[a1]/(Ag4)
  jIShv[a] <- IShv[t,s,a]
IShv[t,s,a] <- IShv[t,s,a] -Ag1* IShv[t,s,a]/(Ag3)  +Ag2*jIShv[a1]/(Ag4)
  jQSv[a] <- QSv[t,s,a]
 QSv[t,s,a] <-  QSv[t,s,a] -Ag1*  QSv[t,s,a]/(Ag3)  +Ag2* jQSv[a1]/(Ag4)
  jHSv[a] <- HSv[t,s,a]
 HSv[t,s,a] <-  HSv[t,s,a] -Ag1*  HSv[t,s,a]/(Ag3)  +Ag2* jHSv[a1]/(Ag4)
  jSU.vac[a] <- SU.vac[t,s,a]
 SU.vac[t,s,a] <-  SU.vac[t,s,a] -Ag1* SU.vac[t,s,a]/(Ag3)  +Ag2* jSU.vac[a1]/(Ag4)
  jSU.rec[a] <- SU.rec[t,s,a]
 SU.rec[t,s,a] <-  SU.rec[t,s,a] -Ag1* SU.rec[t,s,a]/(Ag3)  +Ag2* jSU.rec[a1]/(Ag4)
  jVA0[a] <- VA0[t,s,a]
 VA0[t,s,a] <-  VA0[t,s,a] -Ag1*  VA0[t,s,a]/(Ag3) +Ag2* jVA0[a1]/(Ag4)

  jVAef1[a] <- VAef1[t,s,a]
VAef1[t,s,a] <- VAef1[t,s,a] -Ag1* VAef1[t,s,a]/(Ag3) +Ag2*jVAef1[a1]/(Ag4)
  jVAef2[a] <- VAef2[t,s,a]
VAef2[t,s,a] <- VAef2[t,s,a] -Ag1* VAef2[t,s,a]/(Ag3) +Ag2*jVAef2[a1]/(Ag4)

            for(d in 1:dd)          {
   jeEX[d,a] <- eEX[t,d,s,a]
 eEX[t,d,s,a] <-   eEX[t,d,s,a] -Ag1*  eEX[t,d,s,a]/(Ag3)  +Ag2*  jeEX[d,a1]/(Ag4)
   jeI0[d,a] <- eI0[t,d,s,a]
 eI0[t,d,s,a] <-   eI0[t,d,s,a] -Ag1*  eI0[t,d,s,a]/(Ag3)  +Ag2*  jeI0[d,a1]/(Ag4)
   jeIM0[d,a] <- eIM0[t,d,s,a]
eIM0[t,d,s,a] <-  eIM0[t,d,s,a] -Ag1* eIM0[t,d,s,a]/(Ag3)  +Ag2* jeIM0[d,a1]/(Ag4)
   jeIS0[d,a] <- eIS0[t,d,s,a]
eIS0[t,d,s,a] <-  eIS0[t,d,s,a] -Ag1* eIS0[t,d,s,a]/(Ag3)  +Ag2* jeIS0[d,a1]/(Ag4)
   jeISq[d,a] <- eISq[t,d,s,a]
eISq[t,d,s,a] <-  eISq[t,d,s,a] -Ag1* eISq[t,d,s,a]/(Ag3)  +Ag2* jeISq[d,a1]/(Ag4)
   jeISh[d,a] <- eISh[t,d,s,a]
eISh[t,d,s,a] <-  eISh[t,d,s,a] -Ag1* eISh[t,d,s,a]/(Ag3)  +Ag2* jeISh[d,a1]/(Ag4)
   jeQS[d,a] <- eQS[t,d,s,a]
 eQS[t,d,s,a] <-   eQS[t,d,s,a] -Ag1*  eQS[t,d,s,a]/(Ag3)  +Ag2*  jeQS[d,a1]/(Ag4)
   jeHS[d,a] <- eHS[t,d,s,a]
 eHS[t,d,s,a] <-   eHS[t,d,s,a] -Ag1*  eHS[t,d,s,a]/(Ag3)  +Ag2*  jeHS[d,a1]/(Ag4)

   jeEXv1[d,a] <- eEXv1[t,d,s,a]
 eEXv1[t,d,s,a] <-   eEXv1[t,d,s,a] -Ag1*  eEXv1[t,d,s,a]/(Ag3)  +Ag2*  jeEXv1[d,a1]/(Ag4)
   jeI0v1[d,a] <- eI0v1[t,d,s,a]
 eI0v1[t,d,s,a] <-   eI0v1[t,d,s,a] -Ag1*  eI0v1[t,d,s,a]/(Ag3)  +Ag2*  jeI0v1[d,a1]/(Ag4)
   jeEXv2[d,a] <- eEXv2[t,d,s,a]
 eEXv2[t,d,s,a] <-   eEXv2[t,d,s,a] -Ag1*  eEXv2[t,d,s,a]/(Ag3)  +Ag2*  jeEXv2[d,a1]/(Ag4)
   jeI0v2[d,a] <- eI0v2[t,d,s,a]
 eI0v2[t,d,s,a] <-   eI0v2[t,d,s,a] -Ag1*  eI0v2[t,d,s,a]/(Ag3)  +Ag2*  jeI0v2[d,a1]/(Ag4)

   jeIM0v[d,a] <- eIM0v[t,d,s,a]
eIM0v[t,d,s,a] <-  eIM0v[t,d,s,a] -Ag1* eIM0v[t,d,s,a]/(Ag3)  +Ag2* jeIM0v[d,a1]/(Ag4)
   jeIS0v[d,a] <- eIS0v[t,d,s,a]
eIS0v[t,d,s,a] <-  eIS0v[t,d,s,a] -Ag1* eIS0v[t,d,s,a]/(Ag3)  +Ag2* jeIS0v[d,a1]/(Ag4)
   jeISqv[d,a] <- eISqv[t,d,s,a]
eISqv[t,d,s,a] <-  eISqv[t,d,s,a] -Ag1* eISqv[t,d,s,a]/(Ag3)  +Ag2* jeISqv[d,a1]/(Ag4)
   jeIShv[d,a] <- eIShv[t,d,s,a]
eIShv[t,d,s,a] <-  eIShv[t,d,s,a] -Ag1* eIShv[t,d,s,a]/(Ag3)  +Ag2* jeIShv[d,a1]/(Ag4)
   jeQSv[d,a] <- eQSv[t,d,s,a]
 eQSv[t,d,s,a] <-   eQSv[t,d,s,a] -Ag1*  eQSv[t,d,s,a]/(Ag3)  +Ag2*  jeQSv[d,a1]/(Ag4)
```

```
                    jeHSv[d,a] <- eHSv[t,d,s,a]
                   eHSv[t,d,s,a] <-  eHSv[t,d,s,a] -Ag1*  eHSv[t,d,s,a]/(Ag3)  +Ag2*  jeHSv[d,a1]/(Ag4)
                    jeInf[d,a] <- eInf[t,d,s,a]
                   eInf[t,d,s,a] <-  eInf[t,d,s,a] -Ag1*  eInf[t,d,s,a]/(Ag3)  +Ag2*  jeInf[d,a1]/(Ag4)
                    jeInfv[d,a] <- eInfv[t,d,s,a]
                   eInfv[t,d,s,a] <-  eInfv[t,d,s,a] -Ag1* eInfv[t,d,s,a]/(Ag3)  +Ag2* jeInfv[d,a1]/(Ag4)
                                      }   # end d in 1:dd

                        for(v in 1:dv0)       {
                    jeVA0[v,a] <- eVA0[t,v,s,a]
                   eVA0[t,v,s,a] <- eVA0[t,v,s,a] -Ag1* eVA0[t,v,s,a]/(Ag3) +Ag2*jeVA0[v,a1]/(Ag4)
                                      }  # end dt in 1:14

                        for(w in 1:tv0)       {
                    jeVAef1[w,a] <- eVAef1[t,w,s,a]
                   eVAef1[t,w,s,a] <-eVAef1[t,w,s,a] -Ag1* eVAef1[t,w,s,a]/(Ag3) +Ag2* jeVAef1[w,a1]/(Ag4)
                                      }

                                   tv1<-(t-vac.tim[1]); if(tv1<1) { tv1<-2  }
                        for(w in 1:tv1)       {
                    jeVAef2[w,a] <- eVAef2[t,w,s,a]
                   eVAef2[t,w,s,a] <-eVAef2[t,w,s,a] -Ag1* eVAef2[t,w,s,a]/(Ag3) +Ag2* jeVAef2[w,a1]/(Ag4)
                                      }

                                    tw1 <-(t-ts); if(tw1<2) { tw1<-2  }
                        for(w in 1:tw1)       {
                    jeRE[w,a] <- eRE[t,w,s,a]
                eRE[t,w,s,a] <-   eRE[t,w,s,a] -Ag1* eRE[t,w,s,a]/(Ag3) +Ag2* jeRE[w,a1]/(Ag4)
                                      }

                        }             # end a
                        }             # end s

                        tage <- tage+365     # t for next age shifting up

                                  }           # end if t==tage

#=============================================================================
#  Population estimates and all cause deaths
#   add births and minus all cause deaths according to 5yr average death rates
#=============================================================================

            for(s in 1:2)           {
            for(a in 1:10)          {

  # Monitoring deaths in SU, RE and Effectively vaccinated (non-covid deaths)
            nDth.oth[t-1,s,a] <-(SU[t-1,s,a] +RE[t-1,s,a] +SU.vac[t-1,s,a] +SU.rec[t-1,s,a] +
                                 VA0[t-1,s,a] +VAef1[t-1,s,a] +VAef2[t-1,s,a]) *(rADth0[t.dr,s,a])

  # All deaths:
              nDth.all[t-1,s,a] <-nDth.oth[t-1,s,a] +nDth.cov[t-1,s,a]

#=============================================================================
            # Total numbers of S, E, I and R:
 #---------------------------------------------

               SU[t,3,11] <-  SU[t,3,11]  +  SU[t,s,a]
               EX[t,3,11] <-  EX[t,3,11]  +  EX[t,s,a]
              EXv1[t,3,11] <- EXv1[t,3,11]  + EXv1[t,s,a]
              EXv2[t,3,11] <- EXv2[t,3,11]  + EXv2[t,s,a]
               I0[t,3,11] <-  I0[t,3,11]  +  I0[t,s,a]
              I0v1[t,3,11] <- I0v1[t,3,11]  + I0v1[t,s,a]
              I0v2[t,3,11] <- I0v2[t,3,11]  + I0v2[t,s,a]
              IM0[t,3,11] <- IM0[t,3,11]  + IM0[t,s,a]
              IS0[t,3,11] <- IS0[t,3,11]  + IS0[t,s,a]
              ISq[t,3,11] <- ISq[t,3,11]  + ISq[t,s,a]
              ISh[t,3,11] <- ISh[t,3,11]  + ISh[t,s,a]
               QS[t,3,11] <-  QS[t,3,11]  +  QS[t,s,a]
               HS[t,3,11] <-  HS[t,3,11]  +  HS[t,s,a]
              IM0v[t,3,11] <- IM0v[t,3,11]  + IM0v[t,s,a]
```

```
                IS0v[t,3,11] <-  IS0v[t,3,11]  + IS0v[t,s,a]
                ISqv[t,3,11] <-  ISqv[t,3,11]  + ISqv[t,s,a]
                IShv[t,3,11] <-  IShv[t,3,11]  + IShv[t,s,a]
                 QSv[t,3,11] <-   QSv[t,3,11]  +  QSv[t,s,a]
                 HSv[t,3,11] <-   HSv[t,3,11]  +  HSv[t,s,a]

                  SU.vac[t,3,11] <-   SU.vac[t,3,11]  +  SU.vac[t,s,a]
                  SU.rec[t,3,11] <-   SU.rec[t,3,11]  +  SU.rec[t,s,a]

                 RE[t,3,11]  <- RE[t,3,11]  + RE[t,s,a]

                  N[t,3,11]  <-  N[t,3,11]  +  N[t,s,a]

                 HS.new[t,3,11] <-HS.new[t,3,11] +  HS.new[t,s,a]

               allHS[t] <- allHS[t] +  HS[t,s,a] + HSv[t,s,a]

                nDth.cov[t-1,3,11] <-round( nDth.cov[t-1,3,11] + nDth.cov[t-1,s,a] )

                nDthHos.all[t-1,3,11] <- nDthHos.all[t-1,3,11] +
                                nDthHos.all[t-1,s,a] +nDthHos.allv[t-1,s,a]

                nDth.ss[t-1,3,11] <- nDth.ss[t-1,3,11] +
                                nDth.ss[t-1,s,a] + nDth.ssv[t-1,s,a]

               nDth.oth[t-1,3,11] <- nDth.oth[t-1,3,11] +nDth.oth[t-1,s,a]

               nDth.all[t-1,3,11] <- nDth.all[t-1,3,11] +nDth.all[t-1,s,a]

               #------------------------------------------------
               # Assume the births = normal deaths to maintain the total N unchanged over time:
                        dBth[1] <- nDth.all[t-1,3,11]

               New.expal[t-1,3,11] <-New.expal[t-1,3,11] +New.expal[t-1,s,a]

               New.expsu[t-1,3,11] <-New.expsu[t-1,3,11] +New.expsu[t-1,s,a]
               New.expv0[t-1,3,11] <-New.expv0[t-1,3,11] +New.expv0[t-1,s,a]
               New.expv1[t-1,3,11] <-New.expv1[t-1,3,11] +New.expv1[t-1,s,a]
               New.expv2[t-1,3,11] <-New.expv2[t-1,3,11] +New.expv2[t-1,s,a]
               New.explosrec[t-1,3,11] <-New.explosrec[t-1,3,11] +New.explosrec[t-1,s,a]

               New.vac[t-1,3,11] <-New.vac[t-1,3,11] +New.vac[t-1,s,a]

               New.sym[t,3,11] <-round( New.sym[t,3,11] +New.sym[t,s,a] )

                 VA0[t,3,11] <-   VA0[t,3,11]  +  VA0[t,s,a]
                VAef1[t,3,11] <-  VAef1[t,3,11]  + VAef1[t,s,a]
                VAef2[t,3,11] <-  VAef2[t,3,11]  + VAef2[t,s,a]

                                } # end a
                                } # end s

               # Avoiding extremely small scientic notation for these variables

                  SU.vac[t,3,11] <-  round(SU.vac[t,3,11], digits=0)
                  SU.rec[t,3,11] <-  round(SU.rec[t,3,11], digits=0)
                    VAef1[t,3,11] <-  round(  VAef1[t,3,11], digits=0)
                    VAef2[t,3,11] <-  round(  VAef2[t,3,11], digits=0)

##############################################################
##   Cumulative number of deaths
##------------------------------------------------------------
        nDthcum.cov[t] <- nDthcum.cov[t-1] +nDth.cov[t-1,3,11]

 # Sum of all infected at t:
        Infect.sum[t] <-EX[t,3,11]  +EXv1[t,3,11] +EXv2[t,3,11] +
                                I0[t,3,11]  +I0v1[t,3,11] +I0v2[t,3,11] +
                                IM0[t,3,11] +
                                IS0[t,3,11] +
                                ISq[t,3,11] +  QS[t,3,11] +
```

```
                                ISh[t,3,11] +  HS[t,3,11] +
                                IM0v[t,3,11] +
                                IS0v[t,3,11] +
                                ISqv[t,3,11] +  QSv[t,3,11] +
                                ISshv[t,3,11] +  HSv[t,3,11]

    ##=====================================================================
    # Obtaining N[t,3,11], and so on:
    #=====================================================================
            for(a in 1:10)          {
            for(s in 1:2)           {
              N[t,s,11] <-  N[t,s,11] +   N[t,s,a]
              N[t,3,a] <-   N[t,3,a] +   N[t,s,a]
                                }
                                }

            t.dr <- t.dr +1                     # incremental by one day for daily death rate

            }           # end for   t in 2:tt

#-----------------------------------------------------
# Output scenario specific results
#-----------------------------------------------------

              Result.mul <-data.frame(Rt[], N[,3,11], SU[,3,11], SU.rec[,3,11], SU.vac[,3,11], RE[,3,11], VAef1[,3,11],
                      VAef2[,3,11], New.vac[,3,11],  New.expal[,3,11], New.sym[,3,11], HS.new[,3,11], allHS[],
                      Infect.sum[], nDth.cov[,3,11], nDthcum.cov[], nDth.all[,3,11] )
             OutFileName <- paste("...\\ResOut".out", sep="")
              write.table(Result.mul,file=OutFileName, sep="\t",quote=FALSE,append=TRUE,col.names=FALSE)
```

5.2 Input data files for running the R code

5.2-1 Age-sex-specific population, case-fatality rates, and hospitalisation rates "inParamet20.csv"

agrp	age	n_m	n_f	cft_m	cft_f	hosp_r
1	0	1679.281	1596.919	3.22E-05	1.95E-05	0.000141
2	5	1815.031	1728.698	3.22E-05	1.95E-05	0.000141
3	10	3334.701	3166.337	0.000183	0.000111	0.000516
4	20	3722.353	3549.491	0.000742	0.00045	0.014247
5	30	3776.43	3800.291	0.001806	0.001094	0.051194
6	40	3541.015	3593.888	0.003649	0.002211	0.070833
7	50	3753.483	3861.581	0.01546	0.00937	0.16
8	60	2904.167	3053.137	0.049348	0.029908	0.318919
9	70	2258.713	2521.105	0.106488	0.064538	0.535484
10	80	1163.586	1690.569	0.16573	0.100442	0.593548

5.2-2 General and household contacts per person day "inCMATRIX10.csv"

agegrp	a01	a02	a03	a04	a05	a06	a07	a08	a09	a10	h01	h02	h03	h04	h05	h06	h07	h08	h09	h10
1	1.7112	0.8034	0.6746	0.9657	1.644	0.6343	0.3257	0.1181	0.0446	0.0144	0.4788	0.5519	0.4667	0.4201	0.9003	0.188	0.06	0.0069	0.0005	0.001
2	0.6816	4.0343	0.9241	0.527	1.5545	0.9406	0.3	0.1504	0.053	0.027	0.2633	0.9183	0.6405	0.195	1.0256	0.3971	0.0324	0.0024	0.0003	0
3	0.24695	1.2525	7.7556	1.1873	1.3592	1.5294	0.5501	0.12925	0.05445	0.0531	0.13135	0.34485	1.43255	0.106	0.56165	0.624	0.0924	0.022	0.0019	0.0002
4	0.58115	0.35205	1.5978	3.92775	2.21165	1.94385	0.9814	0.1812	0.04545	0.0513	0.3288	0.1887	0.2676	0.8976	0.1759	0.25075	0.2221	0.0292	0.00135	0.0016
5	0.51325	0.91745	1.0955	1.8358	3.2517	2.0502	1.05485	0.27515	0.09215	0.0632	0.3491	0.5867	0.5529	0.0839	0.73455	0.0971	0.04185	0.019	0	0
6	0.1894	0.51185	1.8394	1.72385	2.3032	3.32855	1.1846	0.2469	0.09625	0.068	0.14665	0.3314	1.09355	0.2537	0.18465	0.5841	0.07945	0.02515	0.00905	0.0082
7	0.16105	0.16875	0.8093	1.867	1.7188	2.0792	1.86615	0.56305	0.18725	0.122	0.0701	0.05255	0.41045	0.3961	0.09315	0.10955	0.4917	0.05785	0.0032	0.0024
8	0.0431	0.23415	0.30125	0.7199	0.9967	0.9832	0.9769	0.9971	0.22895	0.1383	0.03365	0.03505	0.1736	0.1045	0.1491	0.17185	0.11215	0.5643	0.03465	0
9	0.0467	0.02455	0.4952	0.54	0.38355	0.9781	0.63465	0.8508	0.88915	1.0773	0.0103	0.0112	0.2227	0.0135	0.0207	0.25315	0.0555	0.1004	0.31395	0.3604
10	0.0206	0.0007	0.2481	0.1256	0.386	0.7299	0.4298	0.4669	1.0408	1.4766	0.0206	0	0.0362	0.0186	0.0414	0.1252	0.0766	0	0.3811	0.5412

5.2-3 Transmission related input parameters "inParamet20.csv"

paramet	t_ts	t_73	t_77	t_84	t_187	t_254	t_310	t_337	t_371	t_433	t_506	re_norm
rFSQ1	0.1	0.1	0.4	0.8	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
rFSQ2	0.1	0.2	0.6	0.8	0.95	0.95	0.95	0.95	0.95	0.95	0.95	0.95
rFSQ3	0.1	0.4	0.8	0.9	0.95	0.95	0.95	0.95	0.95	0.95	0.95	0.95
a1m	4	4	4	4	4	4	4	4	4	4	4	4
a1s	2	2	2	2	2	2	2	2	2	2	2	2
a2m	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
a2s	1.061	1.061	1.061	1.061	1.061	1.061	1.061	1.061	1.061	1.061	1.061	1.061
gm0m	5	5	5	5	5	5	5	5	5	5	5	5
gm0s	2.236	2.236	2.236	2.236	2.236	2.236	2.236	2.236	2.236	2.236	2.236	2.236
gs0m	5	5	5	5	5	5	5	5	5	5	5	5
gs0s	2.236	2.236	2.236	2.236	2.236	2.236	2.236	2.236	2.236	2.236	2.236	2.236
gs1m	4	3	3	2	2	2	2	2	2	2	2	2
gs1s	2	1.732	1.732	1.414	1.414	1.414	1.414	1.414	1.414	1.414	1.414	1.414
gs2m	2	3	3	4	4	4	4	4	4	4	4	4
gs2s	1.414	1.732	1.732	2	2	2	2	2	2	2	2	2
gh1m	4	3	3	2	2	2	2	2	2	2	2	2
gh1s	2	1.732	1.732	1.414	1.414	1.414	1.414	1.414	1.414	1.414	1.414	1.414
gh2m	10	10	10	10	10	10	10	10	10	10	10	10
gn2s	3.162	3.162	3.162	3.162	3.162	3.162	3.162	3.162	3.162	3.162	3.162	3.162
ac1a	1	0.9	0.8	0.4	0.6	0.8	0.6	0.7	0.4	0.7	0.9	1
ac3a	1	0.8	0.7	0.3	0.55	0.6	0.3	0.6	0.3	0.6	0.8	1
ac4a	1	0.7	0.6	0.2	0.4	0.5	0.2	0.5	0.2	0.5	0.7	1
ac5a	1	0.6	0.5	0.15	0.2	0.3	0.15	0.3	0.15	0.3	0.6	1

5.2-4 Population age-sex-specific death risk by week "inDTH1519Eng10.csv"

agrp	a01	a02	a03	a04	a05	a06	a07	a08	a09	a10
m01	0.002671	0.000229	0.000669	0.001443	0.002844	0.007457	0.01506	0.038052	0.097395	0.372278
m02	0.002593	0.000153	0.000627	0.00166	0.002807	0.00697	0.014316	0.038425	0.098107	0.383425
m03	0.002907	0.000229	0.00046	0.001479	0.002696	0.006708	0.01387	0.036699	0.094224	0.37748
m04	0.002593	0.000229	0.000544	0.001479	0.002881	0.006445	0.014019	0.034694	0.093447	0.368439
m05	0.002907	0.000229	0.000544	0.001407	0.00277	0.006745	0.014316	0.036233	0.091376	0.359646
m06	0.002593	0.000229	0.00046	0.001299	0.002918	0.00652	0.013647	0.035487	0.091247	0.347509
m07	0.002593	0.000229	0.000585	0.001515	0.002474	0.006033	0.013684	0.0353	0.090276	0.35333
m08	0.002593	0.000153	0.000544	0.001696	0.002511	0.005808	0.013833	0.034694	0.088529	0.338221
m09	0.002436	0.000229	0.000585	0.001515	0.002696	0.006558	0.013721	0.034648	0.088141	0.3324
m10	0.00275	0.000153	0.000544	0.001227	0.00277	0.005996	0.013498	0.034974	0.086393	0.336487
m11	0.002671	0.000153	0.000585	0.001443	0.002548	0.006258	0.013498	0.033622	0.085099	0.315062
m12	0.002907	0.000153	0.00046	0.001407	0.002474	0.00652	0.013238	0.032689	0.082899	0.313328
m13	0.002279	0.000153	0.000585	0.001588	0.002696	0.006183	0.012792	0.032736	0.083352	0.30404
m14	0.002514	0.000153	0.000544	0.001299	0.002733	0.005696	0.012494	0.033015	0.082964	0.307879
m15	0.002514	0.000229	0.000585	0.001588	0.002696	0.006183	0.013163	0.032736	0.081087	0.297724
m16	0.002671	0.000229	0.000502	0.001299	0.002622	0.005808	0.01294	0.032176	0.080116	0.294132
m17	0.002436	0.000153	0.000544	0.001588	0.002548	0.005546	0.012754	0.032036	0.078887	0.285463
m18	0.002593	0.000153	0.000585	0.001407	0.002881	0.005771	0.012717	0.031943	0.07811	0.285339
m19	0.002436	0.000153	0.000502	0.001515	0.002659	0.005883	0.012308	0.031523	0.078692	0.283977
m20	0.002514	0.000153	0.000418	0.001335	0.002585	0.005808	0.012606	0.031104	0.076686	0.276794
m21	0.002671	7.64E-05	0.000502	0.001479	0.002659	0.005733	0.012643	0.03129	0.075198	0.276051
m22	0.0022	0.000306	0.000627	0.001696	0.002474	0.005321	0.012271	0.030451	0.074162	0.265029
m23	0.002514	0.000306	0.000418	0.001515	0.002511	0.005471	0.012159	0.030264	0.076686	0.264286
m24	0.002593	0.000306	0.000544	0.001299	0.002659	0.005996	0.012234	0.029705	0.074551	0.262552
m25	0.002279	0.000153	0.000544	0.001371	0.002437	0.005621	0.012457	0.030217	0.076104	0.266886
m26	0.002514	0.000229	0.000502	0.001263	0.002585	0.005471	0.011862	0.030264	0.07468	0.25896
m27	0.002279	0.000153	0.000418	0.001551	0.002696	0.005359	0.012568	0.030684	0.075716	0.266639
m28	0.002357	0.000153	0.000544	0.001479	0.002327	0.005584	0.011899	0.029891	0.072415	0.255988
m29	0.002671	0.000229	0.000418	0.001371	0.002511	0.005659	0.012978	0.029984	0.073127	0.262799
m30	0.002436	0.000229	0.000418	0.001263	0.002548	0.005771	0.01149	0.029098	0.07578	0.262056
m31	0.002279	0.000153	0.000544	0.001551	0.002511	0.005584	0.011936	0.028958	0.071703	0.25252
m32	0.002436	0.000306	0.000544	0.001371	0.002659	0.005846	0.012085	0.030404	0.073062	0.262304
m33	0.00275	0.000229	0.000502	0.001299	0.002548	0.005621	0.011862	0.029425	0.074227	0.261313
m34	0.002121	7.64E-05	0.000376	0.001299	0.002511	0.004797	0.012011	0.029378	0.073127	0.260322
m35	0.002907	0.000153	0.000502	0.001588	0.002401	0.005021	0.012383	0.030404	0.071833	0.257226
m36	0.001964	0.000153	0.000585	0.001371	0.002179	0.005434	0.011564	0.028539	0.07481	0.256359
m37	0.002279	0.000153	0.000376	0.001335	0.002401	0.005171	0.011713	0.030031	0.07591	0.268992
m38	0.002043	0.000229	0.000335	0.001335	0.002548	0.005359	0.012494	0.029425	0.073515	0.270354
m39	0.002671	0.000153	0.000418	0.001191	0.002511	0.005246	0.011974	0.029891	0.076427	0.276546
m40	0.002436	0.000229	0.000585	0.001515	0.002437	0.005471	0.012234	0.030031	0.079534	0.278528
m41	0.002436	0.000153	0.000585	0.001371	0.002437	0.005509	0.012606	0.030357	0.079598	0.288435
m42	0.002514	0.000153	0.000585	0.001407	0.00229	0.005621	0.011788	0.03087	0.078239	0.294008
m43	0.002671	0.000229	0.000502	0.001299	0.00229	0.005359	0.012457	0.030964	0.078175	0.290417
m44	0.002514	0.000229	0.000585	0.001227	0.002364	0.005509	0.012271	0.031803	0.081475	0.296609
m45	0.002357	0.000229	0.000502	0.001118	0.002364	0.005284	0.012234	0.032502	0.081669	0.303421
m46	0.002514	0.000229	0.00046	0.001443	0.002401	0.005584	0.012643	0.031383	0.082058	0.305402
m47	0.00275	0.000153	0.000627	0.001227	0.002364	0.005621	0.012606	0.03171	0.082511	0.306145
m48	0.002671	7.64E-05	0.00046	0.001443	0.002327	0.005434	0.013387	0.031756	0.080699	0.313824
m49	0.002357	0.000306	0.000502	0.001335	0.002548	0.005434	0.013238	0.032782	0.085293	0.322369
m50	0.002121	0.000306	0.000585	0.001371	0.002511	0.005471	0.013163	0.033388	0.086005	0.327199
m51	0.002671	0.000306	0.000418	0.001299	0.002511	0.005584	0.013387	0.034135	0.088723	0.336859
m52	0.002593	0.000382	0.00046	0.001299	0.002474	0.006108	0.013535	0.034508	0.089694	0.347509

f01	0.002314	0.00024	0.000308	0.000713	0.001725	0.004231	0.010467	0.026299	0.068384	0.358013
f02	0.002562	0.000401	0.000308	0.000638	0.001652	0.003936	0.009381	0.025145	0.069481	0.368451
f03	0.001901	0.00024	0.000352	0.000713	0.001725	0.0039	0.009344	0.024303	0.06821	0.364013
f04	0.002396	0.00016	0.00022	0.000676	0.001432	0.003863	0.00891	0.023771	0.063301	0.347739
f05	0.002149	0.00024	0.000352	0.000638	0.001578	0.003863	0.009417	0.023904	0.063994	0.342151
f06	0.002644	0.00016	0.000352	0.000751	0.001578	0.003863	0.00891	0.023061	0.062897	0.322343
f07	0.002066	0.00016	0.000308	0.000826	0.001468	0.004047	0.009018	0.02346	0.062261	0.320864
f08	0.001983	0.00016	0.000352	0.000788	0.001578	0.00401	0.009018	0.022706	0.061626	0.315768
f09	0.002231	0.00016	0.000308	0.000788	0.001615	0.00401	0.008801	0.023194	0.061453	0.311412
f10	0.002066	0.00024	0.000396	0.000638	0.001432	0.00401	0.009091	0.022041	0.060818	0.308618
f11	0.001901	8.02E-05	0.000308	0.000713	0.001542	0.003789	0.008729	0.022041	0.06024	0.301221
f12	0.002149	0.00016	0.000352	0.000826	0.001395	0.003716	0.008366	0.02142	0.058681	0.286345
f13	0.001983	0.00024	0.000264	0.000751	0.001615	0.003458	0.008692	0.022085	0.057872	0.280427
f14	0.001901	0.00016	0.000308	0.000638	0.001468	0.003789	0.00862	0.021287	0.056024	0.275907
f15	0.001983	0.00024	0.000352	0.000713	0.001468	0.003826	0.008475	0.021198	0.056428	0.273194
f16	0.002066	0.00016	0.000352	0.000676	0.001505	0.003605	0.008765	0.02111	0.055331	0.267195
f17	0.002066	0.00016	0.000308	0.000676	0.001468	0.003789	0.00804	0.02142	0.053771	0.257414
f18	0.001735	0.00024	0.000264	0.000638	0.001395	0.003532	0.008149	0.020888	0.053078	0.253798
f19	0.002066	0.00016	0.000308	0.000601	0.001395	0.003752	0.008547	0.020445	0.052963	0.254291
f20	0.001983	0.00016	0.000352	0.000751	0.001578	0.003679	0.007968	0.020445	0.051865	0.248209
f21	0.001901	0.00016	0.000264	0.000751	0.001505	0.003642	0.00804	0.020134	0.051923	0.246976
f22	0.002149	0.00016	0.000264	0.000676	0.001468	0.003421	0.007932	0.019602	0.051403	0.237689
f23	0.001901	8.02E-05	0.000308	0.000488	0.001468	0.003421	0.007968	0.020622	0.051634	0.234319
f24	0.002314	0.00016	0.000396	0.000563	0.001358	0.003495	0.008258	0.019292	0.050883	0.237032
f25	0.001983	0.00016	0.000176	0.000676	0.001505	0.003679	0.007714	0.019602	0.050826	0.238429
f26	0.001653	8.02E-05	0.000396	0.000676	0.001468	0.003752	0.008185	0.019691	0.049266	0.231114
f27	0.002066	0.00024	0.00044	0.000638	0.001395	0.003458	0.008511	0.019025	0.051865	0.237114
f28	0.002149	0.00016	0.000352	0.000563	0.001432	0.003605	0.007896	0.018493	0.049959	0.225854
f29	0.001735	8.02E-05	0.000264	0.000638	0.001432	0.003458	0.007859	0.019114	0.050017	0.235059
f30	0.002066	0.00024	0.000308	0.000525	0.001725	0.003495	0.007751	0.019513	0.050537	0.235059
f31	0.002231	0.00016	0.000264	0.000638	0.001505	0.003532	0.008004	0.018538	0.048689	0.223553
f32	0.002149	8.02E-05	0.000352	0.000525	0.001432	0.003348	0.008113	0.019513	0.049035	0.23136
f33	0.002066	8.02E-05	0.000308	0.000563	0.001395	0.003458	0.007896	0.018892	0.050306	0.230867
f34	0.001735	0.00016	0.000352	0.000713	0.001358	0.003201	0.007533	0.020045	0.049959	0.231278
f35	0.002231	8.02E-05	0.00022	0.000751	0.001395	0.003532	0.007896	0.018937	0.050364	0.226758
f36	0.001818	0.00024	0.000264	0.000563	0.001285	0.003421	0.007751	0.018759	0.050537	0.22947
f37	0.002066	0.00016	0.000308	0.000638	0.001358	0.003348	0.008222	0.019779	0.050999	0.229635
f38	0.001901	0.00024	0.00022	0.000601	0.001285	0.003348	0.008294	0.019646	0.051519	0.236621
f39	0.002314	0.00016	0.000264	0.000601	0.001468	0.003458	0.008403	0.019558	0.053194	0.245004
f40	0.002231	0.00024	0.000352	0.000525	0.001321	0.003642	0.007896	0.020001	0.052327	0.245743
f41	0.002396	8.02E-05	0.000352	0.000601	0.001248	0.003495	0.008222	0.019957	0.053713	0.259222
f42	0.001901	0.00024	0.000264	0.000638	0.001395	0.003421	0.008004	0.02009	0.054176	0.259962
f43	0.002231	0.00024	0.00022	0.000563	0.001358	0.003458	0.00833	0.020533	0.05406	0.25725
f44	0.002231	0.00016	0.00022	0.000488	0.001615	0.003458	0.008801	0.020533	0.054233	0.267852
f45	0.002231	0.00024	0.000396	0.000488	0.001432	0.003532	0.008801	0.020489	0.055619	0.270236
f46	0.002149	0.000321	0.000396	0.000525	0.001395	0.003495	0.008801	0.020711	0.0551	0.270153
f47	0.001818	0.00016	0.000308	0.000563	0.001468	0.003789	0.008366	0.021553	0.057525	0.269332
f48	0.002066	0.00024	0.00022	0.000638	0.001505	0.0039	0.008403	0.021198	0.057352	0.279359
f49	0.001983	0.00016	0.000264	0.000563	0.001432	0.003789	0.00891	0.021598	0.061511	0.290536
f50	0.001901	0.00024	0.000352	0.000563	0.001468	0.004047	0.008366	0.022751	0.061164	0.298262
f51	0.002314	0.00024	0.000352	0.000563	0.001505	0.003495	0.009091	0.023416	0.062435	0.311823
f52	0.001901	0.00016	0.000352	0.000638	0.001615	0.003789	0.009055	0.023061	0.064687	0.316097

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