Original research

Epidemiological impact of prioritising SARS-CoV-2 vaccination by antibody status: mathematical modelling analyses

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ABSTRACT

Background Vaccines against SARS-CoV-2 have been developed, but their availability falls far short of global needs. This study aimed to investigate the impact of prioritising available doses on the basis of recipient antibody status, that is by exposure status, using Qatar as an example.

Methods Vaccination impact (defined as the reduction in infection incidence and the number of vaccinations needed to avert one infection or one adverse disease outcome) was assessed under different scale-up scenarios using a deterministic meta-population mathematical model describing SARS-CoV-2 transmission and disease progression in the presence of vaccination.

Results For a vaccine that protects against infection with an efficacy of 95%, half as many vaccinations were needed to avert one infection, disease outcome or death by prioritising antibody-negative individuals for vaccination. Prioritisation by antibody status reduced incidence at a faster rate and led to faster elimination of infection and return to normalcy. Further prioritisation by age group amplified the gains of prioritisation by antibody status. Gains from prioritisation by antibody status were largest in settings where the proportion of the population already infected at the commencement of vaccination was 30%–60%. For a vaccine that only protects against disease and not infection, vaccine impact was reduced by half, whether this impact was measured in terms of averted infections or disease outcomes, but the relative gains from using antibody status to prioritise vaccination recipients were similar.

Conclusions Major health and economic gains can be achieved more quickly by prioritizing those who are antibody-negative while doses of the vaccine remain in short supply.

Summary box

What are the new findings?

- This study showed that major health gains can be attained by prioritising available COVID-19 vaccine doses to individuals who are antibody-negative.
- Such prioritisation reduced infection incidence and COVID-19 hospitalisations at a faster rate and led to faster elimination of infection and return to normalcy.
- Gains from prioritisation by antibody status (reduction in the incidence of infection and disease) were largest in settings where the proportion of the population already infected at the start of vaccination is 30%–60%.
- For a vaccine that only protects against disease and not infection, vaccine impact was reduced by half, but the relative gains from using antibody status to prioritise vaccination recipients were similar.

How might it impact on healthcare in the future?

- Vaccine delivery systems need to prioritise available doses to those who are antibody-negative while vaccine doses remain in short supply.
- This prioritisation will substantially ease the burden of COVID-19 acute-care and ICU-care bed hospitalisations.

INTRODUCTION

The SARS-CoV-2 pandemic has been one of the most challenging global health emergencies in recent history.[1 2] It is widely believed that vaccination offers the most effective solution to this emergency.[3] More than a 100 vaccines are currently under development,[4] with 3 of them reporting efficacies as high as 95%,[5–7] but access to them remains a formidable challenge. Speed of production, logistics and costs act as barriers for many countries to benefit from vaccine development.[8–12] With supply limitations and high demand, it is foreseeable that a large proportion of the world's population may not have access to these vaccines before 2022.[13]

Prioritising vaccination for specific subpopulations that will benefit most from it is one potential approach to optimise vaccine impact while vaccine supply is being expanded. Vaccine prioritisation is not meant to deprive any specific subpopulation of vaccination, but to maximise the impact of limited available supplies, until doses are enough to vaccinate everyone. Evidence suggests that reinfection with SARS-CoV-2 is a rare phenomenon and that most infected persons develop protective immunity against reinfection that lasts for at least a few months postprimary infection.[14–16] Therefore, vaccination is conceivably more beneficial for those who are antibody-negative than those whose immune systems have already confronted this infection and cleared it.

Against this background, the objective of this study was to investigate the impact of vaccination with or without prioritization by antibody status (ie, exposure status), using Qatar as an example. With the exact vaccine mechanism of action still unclear, its impact was assessed assuming two possible mechanisms of action, acting against both infection and disease, or acting only against disease. The study was possible thanks to a synergistic application of innovations in public health systems: use of mathematical modelling to inform public health response, use of digital healthcare systems to link diverse health information systems, create and analyse databases and use of outputs for development of mathematical models to forecast the epidemic trajectory, healthcare needs and impact of interventions such as vaccination.

METHODS

Mathematical model

A deterministic meta-population mathematical model was constructed to assess the impact of SARS-CoV-2 vaccination in Qatar by extending and adapting our previously validated and published models.[3 17–19] The model description is summarised below, and further details can be found in the previous publications.[3 19]

The model consisted of a set of coupled, non-linear differential equations and was structured by age (0–9, 10–19, …, ≥80 years) and grouped by the major nationalities of the population of Qatar. Unvaccinated and vaccinated populations were further stratified based on infection status (uninfected, infected), infection stage (mild/asymptomatic, severe, critical) and disease stage (severe disease requiring acute-care bed hospitalisation, critical disease requiring ICU-care bed hospitalisation) (online supplemental figure S1).

Susceptible populations were assumed at risk of acquiring the infection at a hazard rate that varies based on the infectious contact rate per day, nationality, age-specific exposure/susceptibility to the infection and subpopulation mixing and age group mixing matrices, parametrising mixing between individuals in different nationality and age groups. Infected individuals develop mild (or asymptomatic), severe or critical infections, following a latency period. The proportion of infected persons developing mild, severe or critical infections was age-dependent, based on relative risks that were based on the SARS-CoV-2 epidemic in France.[20] Severe and critical infections progress to severe and critical disease, respectively, prior to recovery. These are hospitalised in acute-care and ICU-care beds, respectively, based on existing standards of care. Critical disease cases have an additional risk of COVID-19 mortality.

The model assumes that infected individuals spend an average of 3.69 days in the latent infection stage, and 3.48 days in the infectiousness stage.[20] Duration of hospital stay in an acute-care bed and duration of hospital stay in an ICU-care bed were estimated through model fitting, at 7.4 days and 16.2 days, respectively.[19] The model assumes that infected persons are equally infectious regardless of symptoms.[19]

The model was coded, fitted and analysed using MATLAB R2019a.[21]

Model parametrisation and fitting

Model parameterisation was based on current data for SARS-CoV-2 natural history and epidemiology. The model was calibrated through fitting to the standardised and centralised databases of SARS-CoV-2 testing, infections, hospitalisations and mortality in Qatar (online supplemental figure S2),[22 23] as well as to findings of recently completed epidemiological studies.[22 24–26] Fitting to input data was performed using a non-linear least square fitting technique, based on the Nelder-Mead simplex algorithm.

Characteristics of the novel vaccine and its scale-up

Since the primary end point of vaccine randomized clinical trials was efficacy against laboratory-confirmed COVID-19 cases,[6 7 27] and not *any* infection documented or undocumented, it is unknown whether the vaccine acted by prophylactically reducing susceptibility to the infection (ie, VE_S efficacy, defined as the proportional reduction in susceptibility to infection among those vaccinated, compared with those

unvaccinated[3]), or whether it simply acted by reducing serious symptomatic COVID-19 cases with no effect on infection (ie, VE_P efficacy against disease progression, defined as a proportional reduction in the fraction of individuals with severe or critical infection among those vaccinated, but who still acquired the infection, compared with those unvaccinated[3]). These two mechanisms of action bracket the two extremes for the vaccine's biological effect and impact, with the reduction of both infection and disease being the most optimistic and the reduction of only severe disease forms being the most conservative.

Notwithstanding this uncertainty, considering the results of both the Pfizer-BioNTech and Moderna vaccines,[5 6] the impact of the vaccine was assessed assuming each of these mechanisms of action, VE_S = 95% and VE_P = 95%, and assuming that the vaccine will offer 1 year of protection. We further assumed that those vaccinated who still acquire the infection are equally infectious to those unvaccinated (no vaccine efficacy against infectiousness, ie, VE_I = 0%).

Vaccine programme scenarios

Several vaccination scenarios were considered and these were informed by the availability of the vaccine in Qatar and the tentative schedule of its incoming shipments over the coming months. The first shipment of the Pfizer-BioNTech COVID-19 vaccine arrived on 21 December 2020, and vaccination had just been launched.

The considered vaccination scenarios included administering the vaccine only to those who are antibody-negative, or irrespective of antibody status, administering a specific number of vaccinations or vaccinating to reach a specific coverage in a specific target population, and prioritising specific age brackets as opposed to others. While the impact of vaccination in Qatar was the focus of this study, the generic impact of vaccination was also assessed at *different* assumed levels of infection exposure in the population at time of onset of vaccination, to reflect generically the diversity of the epidemic situation in different countries.

It was assumed that the vaccine was introduced on 1 January 2021 and will be scaled up within 6 months. Vaccination was defined as completion of the full two-dose vaccine regimen. Since the purpose of vaccination is to alleviate the need for restrictions that affect social and economic activities, and since public perception of risk may change after the launch of vaccination towards more social contacts, it was assumed that social and physical distancing restrictions will be eased gradually during these 6 months, so that full 'normalcy' will be attained. Normalcy was defined as a contact rate in the population that is similar to that prior to the pandemic, leading to a basic reproduction number R_0 = 4 at the end of the 6 months duration for easing of restrictions. The value of R_0 = 4 is justified by the value reached in the very early phase of the epidemic in Qatar, right before the onset of interventions, existing estimates of R_0 for an epidemic in absence of interventions[28 29] and the recent emergence of variants of concern with higher infectiousness.[19 30–32]

Measures of vaccine impact

Direct and indirect public health benefits of vaccination were assessed. The direct impact results from direct effects of the vaccine (VE_S or VE_P). The indirect impact results from the reduction in onward transmission of the infection, applicable only in the case of VE_S.

The total impact of the vaccine, the sum of its direct and indirect impacts, was estimated by comparing incidence at a given time in presence of vaccination, with that in the no-vaccination counterfactual scenario. Impact was also estimated by quantifying *effectiveness*, the number of vaccinations needed to avert one infection or one adverse disease outcome during a specific period. This metric is closely related to cost-effectiveness, but with no costs included. Impact of the vaccine was further assessed by estimating the number of days needed to eliminate the infection after initiating vaccination, with infection elimination being defined as an incidence rate ≤1 infection per 100 000 person-days.

Uncertainty and sensitivity analyses

Ranges of outcome uncertainty predicted by the model were calculated using 500 simulation runs that applied Latin Hypercube sampling[33 34] from a multidimensional distribution of model parameters, assuming each set of parameters is equally likely. These parameters include the duration of the latent infection stage and the duration of the infectiousness stage. At each run, input parameter values were selected from ranges specified by assuming ±30% uncertainty around parameter point estimates. The resulting distribution for each outcome predicted by the model was then used to derive the means and associated 95% uncertainty intervals for vaccine effectiveness at each time point. Further details about this type of uncertainty analysis can be found in the study by Ayoub *et al*.[19]

Given that the variants of concern may reduce the efficacy of the vaccines,[35] impact of the vaccine was assessed in a sensitivity analysis in which both VE_S and VE_P were reduced and varied between 50% and 95%. In addition, the impact of the vaccine was assessed in another sensitivity analysis in which the vaccine duration of protection varied between 6 and 12 months.

RESULTS

For 500 000 vaccinations administered (regardless of age) in the first 6 months of the year (VE_S = 95%), vaccination of only antibody-negative persons would yield, by 30 June 2021, a reduction of 98% in the daily number of new infections, 83 200 averted infections, 5.9 vaccinations to avert one infection and 155 days to eliminate the infection (figure 1). Meanwhile, vaccination irrespective of antibody status would yield, by 30

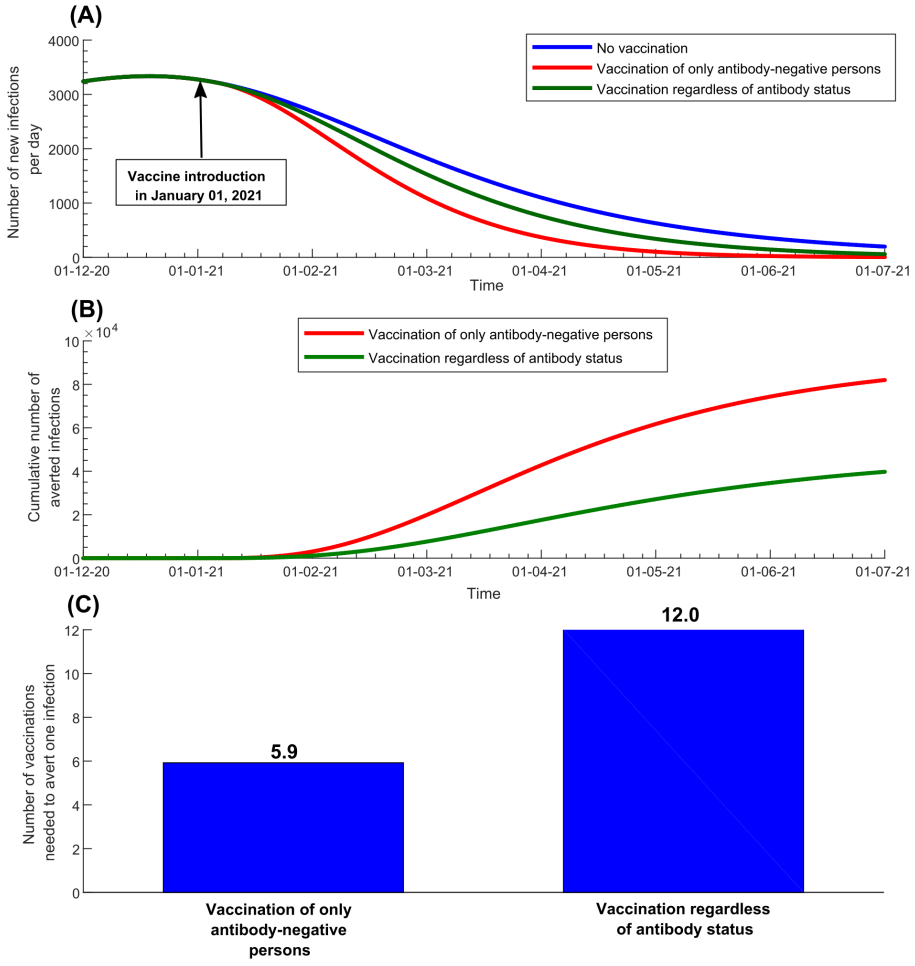

Figure 1 Impact of 500 000 SARS-CoV-2 vaccinations with or without prioritisation by antibody status. Impact was assessed based on (A) the number of new infections, (B) the cumulative number of averted infections and (C) the number of vaccinations needed to prevent one infection. Vaccination is introduced on 1 January 2021 and is scaled up until 30 June 2021, with concurrent gradual easing of social and physical distancing restrictions to reach an R_0 of 4 by 30 June 2021. The vaccine is assumed to have an efficacy of 95% against infection: $VE_S = 95\%$. Duration of vaccine-induced protection is 1 year.

June 2021, a reduction of 73% in the daily number of new infections, 40 600 averted infections, 12.0 vaccinations to avert one infection and 228 days to eliminate the infection.

For $VE_S = 95\%$, figure 2 shows the impact of achieving vaccine coverage of 80% only among those who are antibody-negative, or of reaching 80% coverage in the whole population, by 30 June 2021. As expected, the impact of the vaccine on infection is the same in both scenarios, as the number of people who benefited from the vaccine (only those antibody-negative) is the same in both scenarios. Seventy-seven days are needed to reach elimination, but elimination is reached with far fewer vaccinations if only those who are antibody-negative are prioritised. This is reflected in effectiveness, as only 8.6 vaccinations would be needed to avert one infection by prioritising antibody-negative persons, but 20.6 vaccinations would be needed by vaccinating irrespective of antibody status. Similar results are found for gains (reduction in incidence of infection and disease) attained by prioritising according to antibody status in the case of a vaccine that only reduces disease with $VE_P = 95\%$ (online supplemental figure S3).

Figure 3 shows the impact of SARS-CoV-2 vaccination to reach 80% coverage among those antibody-negative for a vaccine that reduces both infection and disease ($VE_S = 95\%$) compared with a vaccine that reduces only disease ($VE_P = 95\%$). Figure 4 shows the corresponding effectiveness in terms of the number of vaccinations needed to avert one severe disease case, one critical disease case or one COVID-19 death. A vaccine with $VE_S = 95\%$ has a twofold higher impact than a vaccine with $VE_P = 95\%$, whether this impact is measured in terms of averted infections or disease outcomes (figure 3), or effectiveness in terms of the number of vaccinations needed to avert one disease outcome (figure 4).

Online supplemental figure S4 shows, for $VE_S = 95\%$, the effectiveness of age-group prioritisation in administering the vaccine only to those who are antibody-negative. Fewer vaccinations would be needed to avert

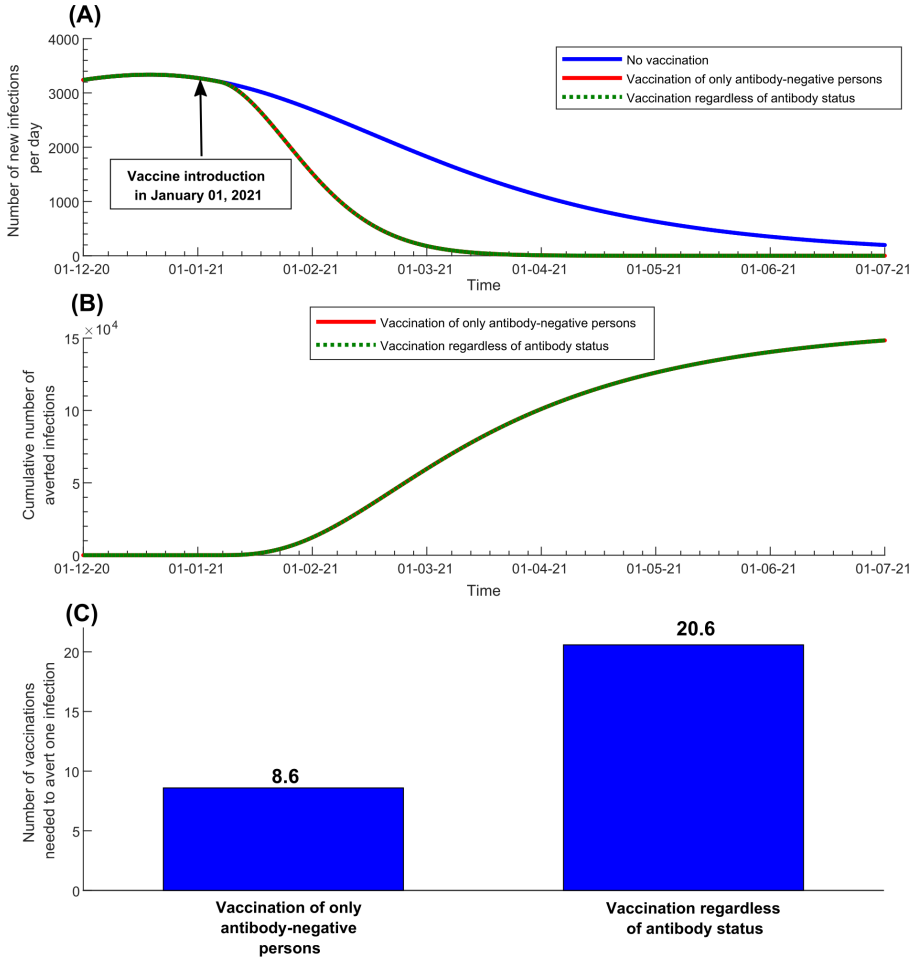

Figure 2 Impact of SARS-CoV-2 vaccination to reach 80% coverage among only the antibody-negative, or to reach 80% coverage of the whole population. Impact was assessed based on (A) the number of new infections, (B) the cumulative number of averted infections and (C) the number of vaccinations needed to prevent one infection. Vaccination is introduced on 1 January 2021 and is scaled up until 30 June 2021, with concurrent gradual easing of social and physical distancing restrictions to reach an R_0 of 4 by 30 June 2021. The vaccine is assumed to have an efficacy of 95% against infection: $VE_S = 95\%$. Duration of vaccine-induced protection is 1 year.

one infection or one disease outcome by prioritising the vaccine for those 20–49 years of age and older, as expected given the lower susceptibility to infection for children as opposed to adults. Online supplemental figure S5 shows the same results, but by administering the vaccine irrespective of antibody status. While vaccinating those 20–49 years of age and older irrespective of antibody status is also more effective, the differential gains are reduced and the effectiveness has a more complex pattern. This complexity arises from the fact that seroprevalence varies considerably by age in Qatar with the lowest levels among children, followed by those >50 years of age and is highest among those 20–49 years of age.[22 25 26 36]

The above results show the impact of vaccination in Qatar, a country where 56.2% of the population is estimated, through serological surveys and mathematical modelling,[19 22 25 26 36] to have been infected by 1 January 2021, at the onset of vaccination. Meanwhile, figure 5 shows the impact of vaccination at *different* assumed levels of infection exposure in the population at the onset of vaccination with the assumption that easing of restrictions will begin following the onset of vaccination. The figure specifically compares the number of days needed to eliminate the infection in a scenario in which vaccination is administered only to people antibody-negative at a coverage of 80%, with a scenario in which an *equal number* of vaccinations was administered, but irrespective of antibody status. In the scenario in which only those antibody-negative are being vaccinated, the higher the infection exposure is at onset of vaccination, the less time is needed to reach elimination, as expected, as the vaccine is provided *only* to those who will directly benefit from it.

However, the situation is more nuanced for the scenario in which individuals are vaccinated irrespective of antibody status. If infection exposure is very low at the onset of vaccination, less time would be needed to reach elimination, as the vast majority of those vaccinated are antibody-negative and will directly

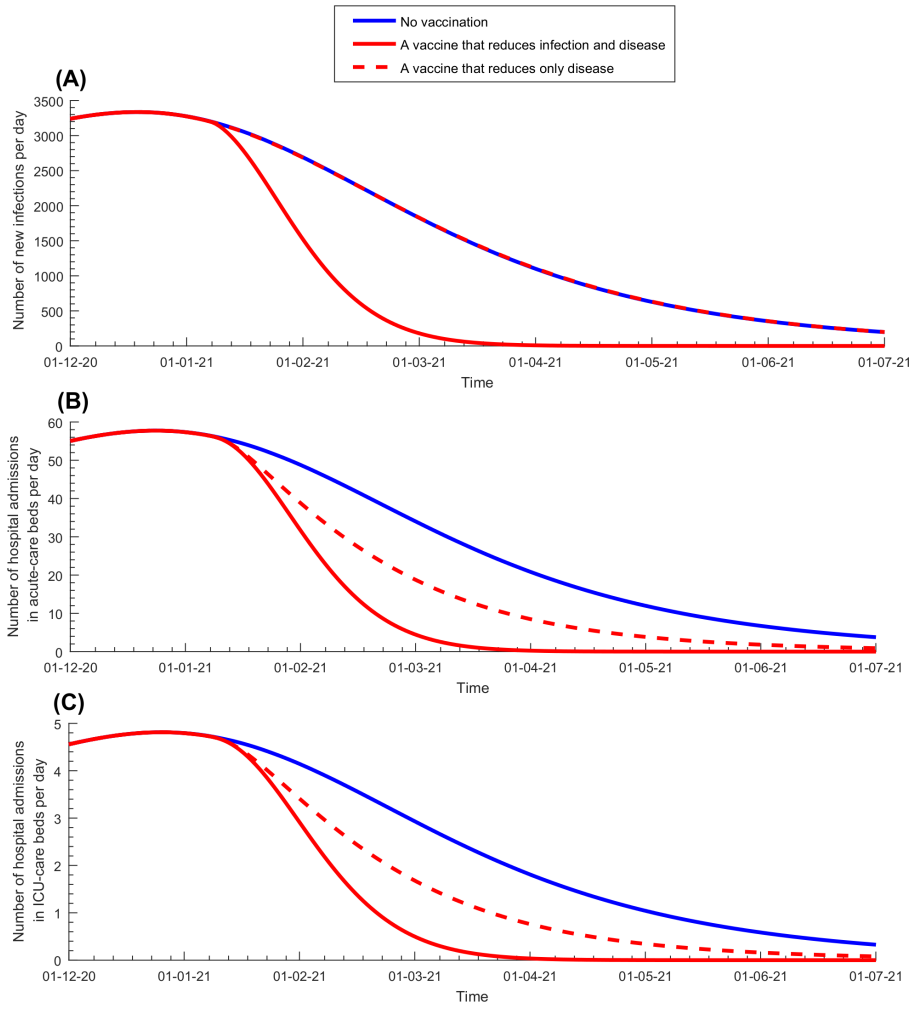

Figure 3 Impact of SARS-CoV-2 vaccination to reach 80% coverage for a vaccine that reduces infection and disease ($VE_S = 95\%$) compared with a vaccine that reduces only disease ($VE_P = 95\%$). Impact was assessed based on (A) the number of new infections per day, (B) the number of new hospital admissions in acute-care beds per day and (C) the number of new hospital admissions in ICU beds per day. Only those who are antibody-negative are being vaccinated. Vaccination is introduced on 1 January 2021 and is scaled up until 30 June 2021, with concurrent gradual easing of social and physical distancing restrictions to reach an R_0 of 4 by 30 June 2021. Duration of vaccine-induced protection is 1 year.

benefit from the vaccine. If infection exposure is very high at onset of vaccination (>60%), less time would also be needed to reach elimination, as the population is already close to the herd immunity threshold (at 80% infection exposure for R_0 of 4), and will attain it quickly, even though most of those vaccinated are already antibody-positive and will not directly benefit from vaccination. The longest time to elimination is seen when infection exposure at onset of vaccination is in the intermediate range, between 30% and 60%, as the population is not close to the herd immunity threshold, but at the same time, many of those vaccinated have already been exposed to the infection and will not directly benefit from the vaccine.

Online supplemental figure S6 shows the results of the uncertainty analysis for vaccine effectiveness. The results demonstrate relatively narrow uncertainty intervals, thereby affirming the results. Online supplemental figures S7 and S8 show the impact of varying VE_S and VE_P between 50% and 95%, and the impact of varying the vaccine duration of protection between 6 and 12 months, respectively. The results affirmed the gains from prioritisation by antibody status, even for broad ranges of vaccine efficacy or vaccine duration of protection.

DISCUSSION

The first finding of this study is that there are major gains by prioritising available vaccines to persons who are antibody-negative, regardless of whether the vaccine reduces infection and disease, or just disease. With vaccine availability falling far short of global needs, such prioritisation will reduce the incidence rate of the infection more quickly, thereby eliminating the infection and returning to normalcy sooner. Vaccination would thus avert more disease cases and deaths and would be more cost-effective, with fewer vaccinations needed to avert one infection or disease outcome.

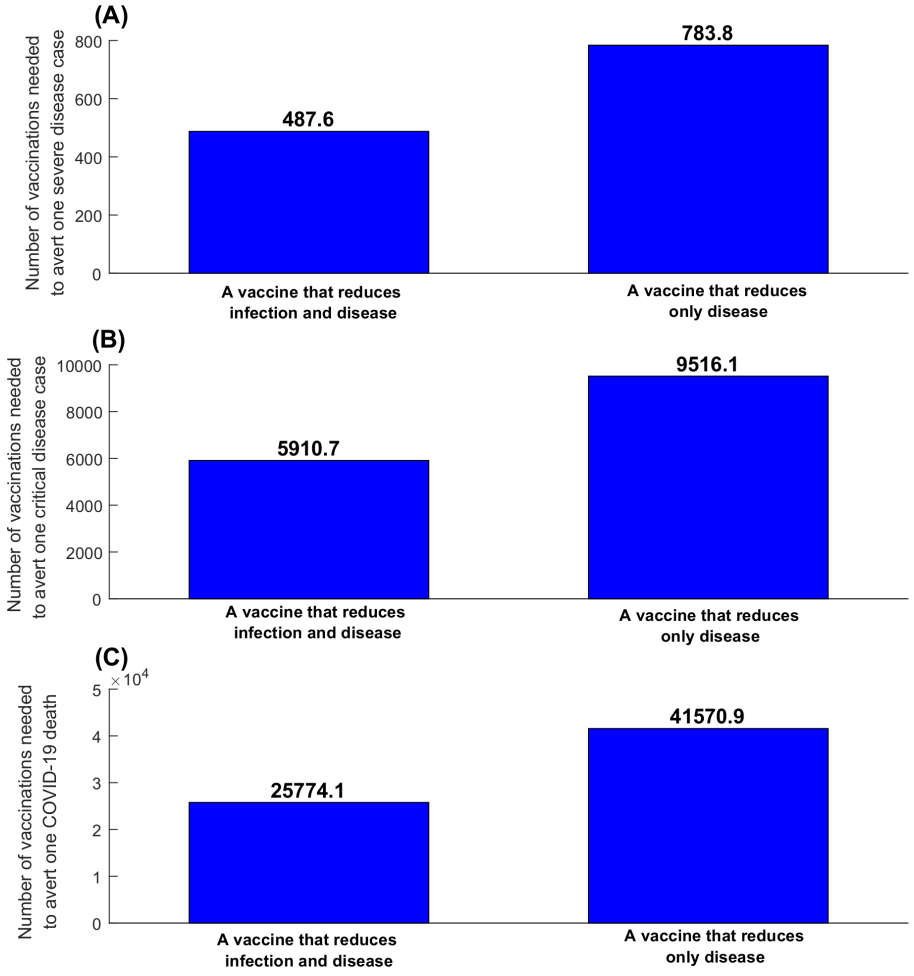

Figure 4 Effectiveness of SARS-CoV-2 vaccination for a vaccine that reduces infection and disease ($VE_S = 95\%$) compared with a vaccine that reduces only disease ($VE_P = 95\%$). The number of vaccinations needed to prevent (A) one severe disease case, (B) one critical disease case and (C) one COVID-19 death. Only those antibody-negative are being vaccinated with a coverage of 80%. Vaccination is introduced on 1 January 2021 and is scaled up until 30 June 2021, with concurrent gradual easing of social and physical distancing restrictions to reach an R_0 of 4 by 30 June 2021. Duration of vaccine-induced protection is 1 year.

As much as our results point toward substantial health and economic gains for vaccine prioritisation by exposure status, actual implementation of such an approach is still contingent on the feasibility and cost of wide-scale antibody testing, as a component of vaccination programmes in various countries, as well as equity in prioritising the vaccine for some as opposed to others.

The second finding of this study is that the gains of prioritising vaccination by antibody status are largest in settings where the proportion of the population previously infected (at time of launch of vaccination) is between 30% and 60%. For countries that are still at limited infection exposure, prioritisation by antibody status will not yield such significant gains, as very few vaccinations are given to those previously infected, irrespective of whether prioritisation is implemented.

A third finding of this study is that the impact of the vaccine depends on whether the vaccine reduces infection and disease, or reduces only disease. The impact of the former was twofold higher than the impact of the latter, regardless of whether this impact is measured in terms of averted disease cases, or in terms of the number of vaccinations needed to avert one disease outcome. This finding is explained by the fact that for a vaccine that reduces susceptibility to infection (a 'VE_S' vaccine), half of the beneficial impact is *indirect*, by reducing the onward transmission of the infection in the population, in addition to the *direct* impact of preventing infection among those vaccinated.

This study has some limitations. The study is specific only to the country of Qatar. However, the impact of prioritising vaccination by antibody status is undoubtfully more general, as it is driven by the same concept of providing the vaccine to those who will immediately benefit from it. Model estimates are contingent on the validity and generalisability of input data and assumptions. Our results are based on current understanding of SARS-CoV-2 natural history and disease progression, but our understanding of this infection is still evolving. A key assumption is that those infected acquire protective immunity against reinfection that lasts for at least a year. This assumption is supported

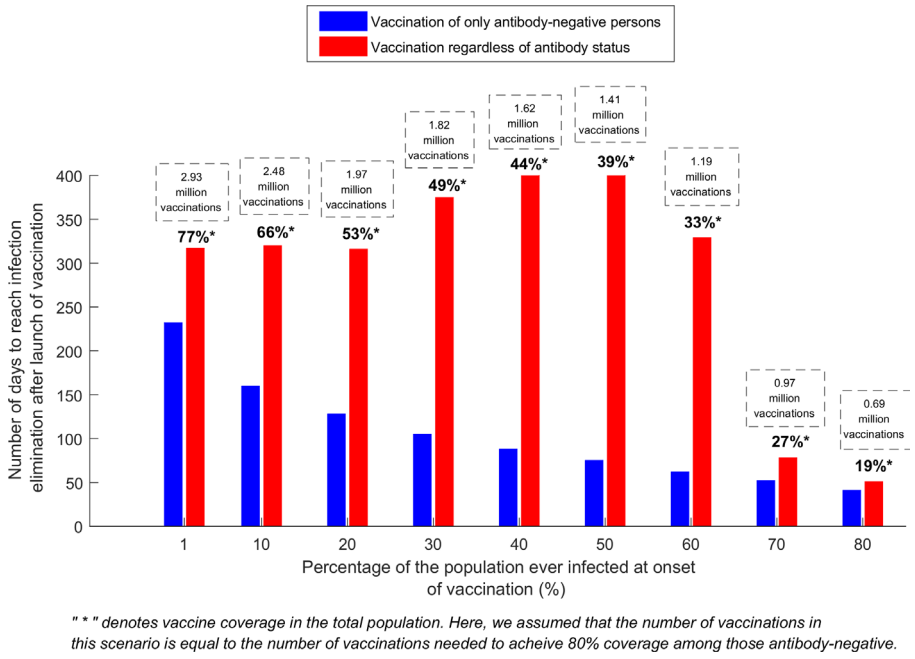

Figure 5 The number of days needed to eliminate the infection after launching vaccination at different assumed levels of infection exposure (attack rate) in the population at time of vaccination onset. The number of days needed to eliminate the infection in a scenario in which vaccination is administered only to those who are antibody-negative at 80% coverage, is compared with a scenario in which an *equal* number of vaccinations was administered, but irrespective of antibody status. Vaccination is introduced on 1 January 2021 and is scaled up until 30 June 2021, with concurrent gradual easing of social and physical distancing restrictions to reach an R_0 of 4 by 30 June 2021. The vaccine is assumed to have an efficacy of 95% against infection: $VE_S = 95\%$. Duration of vaccine-induced protection is 1 year.

by epidemiological and basic science studies of reinfection and immune response,[14 37–39] including two studies in Qatar that demonstrated very low incidence rate of reinfection (<1 per 10 000 person-weeks), no evidence of waning of immunity for over 7 months of follow-up and an efficacy of natural infection against reinfection of 95.2%.[14 37] Further studies with long-term follow-up are still needed to assess the exact duration of natural immunity.

Vaccine-induced immunity is assumed to last for 1 year, but the duration of this immunity is also unknown. Therefore, model predictions may not be valid if either duration of natural immunity or vaccine-induced immunity lasts less than a year, whether because of waning immunity or appearance of mutant virus variants that circumvent immunity to earlier variants. The recent emergence of variants of concern may affect the potential impact of vaccination, as vaccines may be less efficacious against these variants.[32 35] Therefore, the above analyses need to be updated with the evolution of the epidemiological situation, and especially the introduction or emergence of new variants of concern.

The model assumes that vaccinated persons are protected once vaccinated, but vaccine protection builds up gradually over the course of few weeks following inoculation, and peaks only after the second dose.[6] A vaccine that converts a symptomatic infection into an asymptomatic infection could, in theory, increase infection transmission, as asymptomatic infections are difficult to diagnose and isolate.[40] However, growing evidence, including just-published, real-world vaccine effectiveness data from Israel,[41] demonstrate that the vaccine was equally efficacious regardless of symptoms. Uncertainty and sensitivity analyses were conducted for a broader assessment of vaccination impact under different assumptions, and these analyses confirmed the findings (online supplemental figures S6–S8).

In conclusion, major health and economic gains can be attained by prioritising vaccination for those who are antibody-negative, as long as doses of the vaccine remain in short supply.

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Contributors HHA co-designed the study, constructed and parameterised the mathematical model, conducted the mathematical modelling analyses and co-wrote the first draft of the manuscript. HC conducted the statistical analyses and contributed to the parameterisation of the mathematical model. LJA-R conceived and co-designed the study, led the conduct of the analyses and co-wrote the first draft of the manuscript. All authors contributed to conceptualisation of the analyses, discussion and interpretation of the results and writing of the manuscript. All authors have read and approved the final manuscript.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplemental information.

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