Impact of waning immunity against SARS-CoV-2 severity exacerbated by vaccine hesitancy

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Abstract

The SARS-CoV-2 pandemic has generated a considerable number of infections and associated morbidity and mor world. Recovery from these infections, combined with the onset of large-scale vaccination, have led to rapidly-char level immunological landscapes. In turn, these complexities have highlighted a number of important unknowns rela breadth and strength of immunity following recovery or vaccination. Using simple mathematical models, we investi term impacts of waning immunity against severe disease on immuno-epidemiological dynamics. We find that unce duration of severity-blocking immunity (imparted by either infection or vaccination) can lead to a large range of me population-level outcomes (*i.e.* infection characteristics and immune landscapes). Furthermore, we show that epid dynamics are sensitive to the strength and duration of underlying host immune responses; this implies that determ levels from hospitalizations requires accurate estimates of these immune parameters. More durable vaccines both uncertainties and alleviate the burden of SARS-CoV-2 in pessimistic outcomes. However, heterogeneity in vaccine drastically changes immune landscapes toward larger fractions of individuals with waned severity-blocking immuni hesitancy is substantial, more robust vaccines have almost no effects on population-level immuno-epidemiology, e rates are compensatorily high among vaccine-adopters. This pessimistic scenario for vaccination heterogeneity ari those few individuals that are vaccine-adopters are so readily re-vaccinated that the duration of vaccinal immunity appreciable consequences on their immune status. Furthermore, we find that this effect is heightened if vaccine-he increased transmissibility (*e.g.* due to riskier behavior). Overall, our results illustrate the necessity to characterize b transmission-blocking and severity-blocking immune time scales. Our findings also underline the importance of dev next-generation vaccines with equitable mass vaccine deployment.

Author summary

While the SARS-CoV-2 outbreak continues, the deployment of vaccines in many regions has blunted the severity o infections and decreased hospitalizations. However, the medium-term impacts of the duration of severity-blocking i potential interactions with heterogeneous vaccine uptake (*e.g.* from vaccine hesitancy) or more robust vaccines, re To titrate these effects, we use immuno-epidemiological models to examine potential future scenarios. We find that vaccine hesitancy (and correspondingly higher vaccination rates among adopters) can rapidly increase the fraction infected after waned severity-blocking immunity even when robust vaccines are deployed. This result underlines th pharmaceutical developments for broadly protective vaccines should be combined with campaigns to increase vac globally. We also show that this fraction is highly dependent on underlying immune uncertainties, which illustrates t accurately measuring immune parameters for proper prediction based on hospitalization data.

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic is a public health emergency that l dramatic impact across the world. In turn, it has generated a mass of epidemiological data and led to large modelli Initially, guided by data analyses, a number of jurisdictions successfully implemented a range of control measures transmission, prevent a surge in infections, and decrease the burden on healthcare systems (*e.g.* see [2] for a retr analysis). In parallel, research into pharmaceutical measures (such as vaccination or therapeutics) began, with ho control SARS-CoV-2 transmission via vaccination. Notably, with high enough coverage, transmission-blocking vac elicit immunity against infection) could lead to effective control and local elimination [3–6]. However, while the deve vaccines was successful (*e.g.* [7–9]), the susceptibility of vaccinated individuals to breakthrough infection relatively vaccination (*e.g.* even within weeks [10]) in conjunction with the emergence of immune-escape variants (*e.g.* [11]) local elimination is not possible with the current generation and partial uptake of vaccines. Since the deployment o many jurisdictions have changed their approach for SARS-CoV-2 management to focus on mitigation against seve vaccination.

Since the onset of the pandemic, a number of important gaps in our understanding of SARS-CoV-2 epidemiology h addressed by models [1]. For example, future transmission dynamics were illuminated in an early landmark paper [12]; the role of climate and susceptibility on pandemic dynamics was investigated by Baker et al. [13, 14]; Lavine the path to endemicity and the role of age structure; and others examined the role of novel variants [16–18]. In our we have investigated many SARS-CoV-2 immuno-epidemiological uncertainties from a qualitative perspective. Firs extended a simple SIR(S) model (see [19]) to show that the relative susceptibility to infection after waning of total t blocking immunity ε (so that $\varepsilon = 0$ and $\varepsilon = 1$ reduce to the SIR and SIRS models, respectively, and thus ε is a prox "strength of immunity") is a key determinant of post-pandemic trajectories [6]. We then extended this framework to dose vaccines [20], investigate the potential effects of vaccine nationalism [21], and examine the impact of accumu on the potential future burden of chronic disease [22].

However, a number of key immuno-epidemiological questions remain. At the heart of these are uncertainties in wa against severe disease (*i.e.* 'severity-blocking immunity'), and the ensuing potential outcomes in the medium term. from a public health standpoint, determining the likelihood, timing, and magnitude of the next surge in severe disea Furthermore, many regions now rely on hospitalizations to monitor infection levels (especially with the pause of the infection survey study in the UK); waning severity-blocking immunity could have an important effect on these dyna variations in the fraction of infections that require hospitalization at a given time, and thus crucially affect subseque Additionally, since we have determined that the strength of immunity is a central parameter that shapes medium-te epidemiological dynamics [6], another outstanding unknown is the potential interplay between this parameter and t severity-blocking immunity. Finally, given important developments toward mucosal vaccines [23–25], a major ques determine the impacts that such vaccines with long-lasting transmission-blocking protection could have on potentia their uncertainties. For example, reducing these uncertainties may be important for robust estimates of infection le epidemic dynamics.

In this paper, we extend previous modelling efforts [6] to include a timescale of waning immunity against severe dis We begin with a characterization of the interplay between the strength of immunity, average duration of severity-blo and vaccination rate, and their respective (and combined) impacts on infection levels in individuals with waned sev immunity. We then investigate the impact of vaccine characteristics on these dynamics, and we examine potential immuno-epidemiological landscapes. Finally, we extend our model to include heterogeneities in vaccination that ar unequal access or hesitancy. While we cast our results in terms of vaccine hesitancy for simplicity, our findings are applicable for any setting with heterogeneous uptake in vaccination.

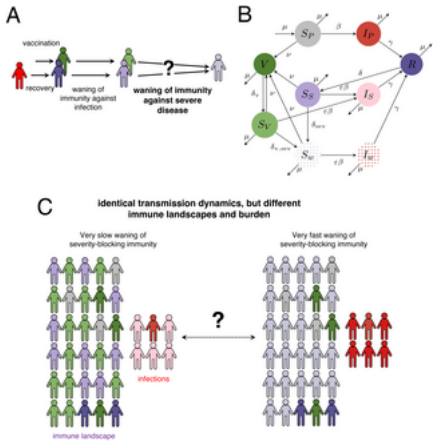

Fig 1. Model formulation.

(*A*) Schematic of individual immunity progression after infection or vaccination. (*B*) Model flow diagram, extende
of [6]. Each colour denotes an infection or immunity class. (*C*) Schematic of the range of population-level outcor
severity-blocking immunity.
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Model framework

We extend the model of [6]. As in [6], S_P denotes the fraction of fully susceptible individuals, I_P and I_S denotes the individuals with primary and secondary infections (the latter which have relative transmissibility α), respectively, R fraction of individuals that have recovered and are fully immune, S_S denotes the fraction of individuals with waned blocking immunity and who have relative susceptibility ε to infection, and V denotes the fraction of individuals that vaccinated and are fully immune. Furthermore, again as in [6] μ is the birth/death rate, γ is the recovery rate, δ and of waning of natural and vaccinal transmission-blocking immunity, respectively, and β is the transmission rate (assu dependent [13] as in previous work [6]). We additionally denote S_w as the fraction of individuals with waned severit immunity, and I_w as the fraction of individuals with infection after waned severity-blocking immunity. We denote δ_{se} the rates of waning from S_S to S_w and from S_V to S_w, respectively. The equations are as follows:

Note that we set $\alpha = 1$ throughout and focus on ε (see [6, 20–22]).

Thus, after recovery or vaccination, individuals have a period of "complete" immunity (R or V, respectively), after w into partially susceptible classes (S_S and S_V, respectively), where their relative susceptibility to infection is ε. Beyo individuals eventually wane to S_w (at rates δ_{sev} and $\delta_{V,sev}$, respectively), which denotes individuals with waned se immunity. In this class, the relative susceptibility to infection is still ε, but individuals enter a different infectious clas infected after such waning (see Fig 1B for flow diagram). Thus, individuals have severity-blocking immunity while t S_S, or in V and S_V (with average durations and , respectively).

To focus on clinical severity-blocking immunity, note that we assume that the relative susceptibility of individuals in same (and that the relative transmissibility $\alpha = 1$ in I_w and I_S is also identical). Because of this assumption, our mo between a range of immune landscapes and population-level burden, while having identical transmission dynamics scenarios (schematically depicted in Fig 1C). In one extreme case, if there is no (or very slow) waning of severity-b immunity, no individuals enter the compartments with waned severity-blocking immunity. On the other hand, if there waning of severity-blocking immunity, all individuals enter S_w almost immediately after complete transmission-bloc wanes. Additionally, since hospitalizations (in the longer term) are likely to reflect the dynamics of I_w, we also calcu of individuals that are in this class over time (*i.e.*). Note that the incorporation of vaccine hesitancy in our model is S1 Text, *electronic supplementary materials*. Finally, we have produced an online interactive application (at https://grenfelllab.shinyapps.io/covid19immunity/), which can be used to examine a broad set of model scenarios.

Results and discussion

Vaccination, duration of severity-blocking immunity, and dynamics of waned infections

In Fig 2, we examine the potential epidemiological dynamics that result in changes of both severity-blocking immun vaccination coverage. We use seasonal transmission rates as in previous work [6, 22], and assume the same simp nonpharmaceutical intervention settings as in [22]. (For a specific expression for $\beta(t)$ in the absence of nonpharma intervention, see [6], which uses values derived by [13].) For each vaccination rate (*i.e.* each panel of Fig 2), we pl individuals that are infected with waned severity-blocking immunity (*i.e.* I_w) (*top row*), the fraction of all infections th (*i.e.*) (*middle row*), and the relative change in this latter fraction compared to complete susceptibility to reinfection transmission-blocking immunity wanes (*i.e.* $\varepsilon = 1$ giving the SIRS model, see the caption of Fig 2 for mathematical

row). For all panels of Fig 2, we assume the same average duration of transmission-blocking vaccinal (0.33 years) (0.25 years) immunity. Note that while we take these to be relatively short (as in [22]) since infection can happen re after recovery or vaccination (*e.g.* for infection after vaccination see [10]), the effects of longer durations can be ex thoroughly with our companion interactive online application (at https://grenfelllab.shinyapps.io/covid19immunity/). each panel of Fig 2, we assume that the durations of vaccinal and natural severity-blocking immunity are the same (identified by the columnar label). Additionally, note that since the vaccination rate is fixed within each panel, the tra dynamics across columns of each panel for a fixed value of ε are identical. However, because of the additional imr the underlying immunity landscapes change, leading to differences in infection characteristics and potential burder

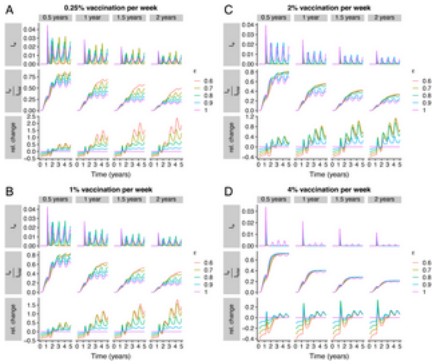

Fig 2. Dynamics of different durations of natural and vaccinal severity protection, with variable vaccination rates, for different strengths of immunity.
(*A*), (*B*), (*C*), and (*D*) have vaccination rates $v = 0.0025$ per week, $v = 0.01$ per week, $v = 0.02$ per week, and v = week, respectively. In all panels, we assume that years and that years. For each column, we assume that the d severity-blocking immunity imparted from vaccination or infection is the same and is equal to the columnar label Thus, years and years. In each panel, the *top*, *middle*, and *bottom* rows depict the fraction of individuals in I_W, infections that are in I_W (*i.e.* , where), and the relative change in for each ε compared to $\varepsilon = 1$, *i.e.* , respectivel when $f_1(t) > 0$). Other parameters are week^{-1} and $\mu = 0.02$ years^{-1}, as in previous work [6, 20–22]. The initial c and throughout are a fraction 10^{-9} of individuals with primary infection (I_P) and the remainder fully susceptible (as in previous work with the simpler model [6].
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Intuitively, as the duration of severity-blocking immunity increases, the fraction of individuals with infections after se immunity has waned decreases (compare left to right plots of the top rows of Fig 2A–2D). Similarly, driven by more boosting of immunity, higher vaccination rates result in further decreases (compare top rows of Fig 2A–2D). Furthe relative susceptibility to reinfection (*i.e.* stronger immunity) initially leads to a smaller fraction of infections with wan (*middle rows*, Fig 2A–2D). However, especially for lower vaccination rates, an increase in the strength of immunity potentially lead to larger fractions of infections that are in I_W (*middle* and *bottom rows*, Fig 2A). Additionally, interme can lead to larger peaks (and deeper troughs) in I_W (*top row*, Fig 2A). Interestingly, these results are partially remin findings of [6], where, in some scenarios, stronger immunity can lead to a bigger (and delayed) second peak in infe very high vaccination coverage (Fig 2) dampens these effects because of more frequent gains in immunity.

Overall, these results illustrate an additional potential complication associated with predicting the number of total ir on hospitalizations alone, in addition to a wide variety of known difficulties. To reduce this particular complexity, suc would likely necessitate robust parameter estimates for the strength of immunity and the duration of severity-blocki These could be obtained from large immuno-epidemiological cohort studies, echoing previous calls for such monit

Future vaccine refinements

So far, we have assumed that the period of complete immunity imparted by vaccination is transient, with relatively susceptibility after waning. While this reflects current settings with existing vaccines (*e.g.* in part due to circulating i variants), pan-coronavirus and pan-sarbecovirus vaccines [30] are in development. Additionally, there have been r advances in the development of mucosal vaccines [23, 24], which would likely be able to more successfully block t Furthermore, it seems that such a mucosal vaccine could generate immunity across sarbecoviruses [23], and thus generate broad immune responses to novel SARS-CoV-2 variants. In Fig 3, we examine the impact of a more dura transmission-blocking vaccine on severity dynamics, for intermediate (1% per week) and high (2% per week) vacci (panels *A* and *B*, respectively). To allow for appropriate comparisons within and across panels, we assume that the vaccinal severity-blocking immunity is conserved within a column (indicated by the columnar label) within each par we assume that for 90% of that duration, vaccinal immunity also fully blocks transmission. (Note that this contrasts where the average complete vaccinal immunity was assumed to be 0.33 years.) Finally, we take a moderately opti assumption and assume that severity-blocking immunity after infection lasts on average 1.5 years (in Fig 2, this va concurrently with that imparted following vaccination). Finally, in each panel, the top row denotes the total infection the bottom three rows are as in those of each panel of Fig 2.

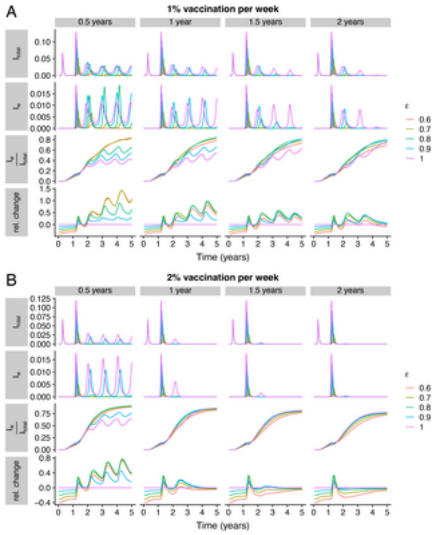

Fig 3. Impacts of longer transmission-blocking vaccines on severity dynamics.
In (*A*) and (*B*), the vaccination rates are 0.01 per week and 0.02 per week, respectively. In both panels, the top r
the total fraction $I_{\text{total}} = I_P + I_S + I_W$ of individuals that are infected. The second to fourth rows are as in the rows
of Fig 2 (see caption of Fig 2 for definitions). Across both panels, we assume that the duration of vaccinal transr
blocking immunity is 90% of the duration of severity-blocking immunity (the columnar label), and that transmissi
and severity-blocking immunity after infection last 0.25 years and 1.5 years, respectively (*i.e.* years and years)
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Even for an intermediate vaccination rate, a more durable vaccine leads to fewer total infections (Fig 3, *top row*, cc
right plots) and fewer infections after severity-blocking immunity has waned (*second row*). Furthermore, with increa
the fraction depends increasingly less on the strength of immunity (*third and bottom rows*, Fig 3, compare left to ri
different setting, this decrease in dependence on ε is akin to that observed in Fig 2 for very high vaccination rates.
more durable vaccine is analogous to very high vaccination rates (*i.e.* more frequent boosting) with a less durable
a high vaccination rate further accentuates the effects of a durable vaccine on epidemiological dynamics (compare
Thus, the development and deployment of a durable vaccine, combined with a high vaccination rate, can substanti
uncertainties in outcomes.

Immuno-epidemiological outlooks

So far, we have examined changes in severity dynamics via total and relative infection levels across a range of set
strength of immunity and durations of both severity-blocking and transmission-blocking immunity. In Fig 4, we sum
medium-term immuno-epidemiological scenarios based on optimistic or pessimistic assumptions on severity-block
different vaccination rates, and changes in durability of vaccines. For each scenario, we present time series of infe
severity-blocking immunity has waned and of the fraction of infections that these consist of. Below, we illustrate im
infection phenotypes over time. Note that at the bottom of each such area plot are the three infection types (I_P, I_S,
the total fraction of individuals infected is immediately seen visually. While we had previously assumed in Fig 2 (for
vaccines) that the durations of vaccinal and natural severity-blocking immunity were equal, we now relax this assu
optimistic scenarios for waning of severity-blocking immunity (*i.e.* second column of Fig 4) and assume in those se
average duration of vaccinal severity-blocking immunity is (optimistically) slightly longer than that of natural severit
immunity (2 years instead of 1.5 years). For a more durable vaccine, we assume that transmission-blocking immur
average 1.33 years, and that severity-blocking immunity lasts on average either 1.5 years (in the more pessimistic
faster waning) or 3 years (if waning is optimistically slower).

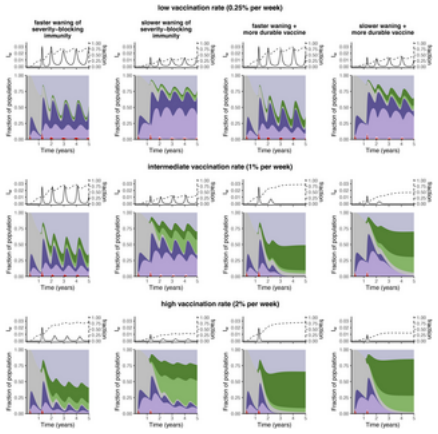

Fig 4. Synoptic landscapes of severity-blocking immunity.
The *top*, *middle* and *bottom* rows have vaccination rates 0.0025, 0.01, and 0.02 per week, respectively. The *left* columns illustrate scenarios with a less durable vaccine, *i.e.* years, whereas the *rightmost* two columns represe with a more durable vaccine, *i.e.* years. The *first* and *third* columns assume faster waning of severity-blocking i the *first* column having years and the *third* column having years (since the vaccine is more durable) and years hand, the *second* and *fourth* columns assume slower waning of severity-blocking immunity, with the *second* col years and years, and the *fourth* column having years and years. In each panel, the left and right axes of the t and the fraction , respectively, and the area plot colours correspond to the compartments in Fig 1B. In all panels other parameters are as in Figs 2 and 3, and the colours in the area plots are as in Fig 1B.
https://doi.org/10.1371/journal.pcbi.1012211.g004

With a low vaccination rate, vaccinal characteristics have limited impact on immuno-epidemiological dynamics (co plots and right two plots, *top row*, Fig 4). However, the relative time scale of waning severity-blocking immunity dra immune landscape (*top row*, Fig 4). With an intermediate vaccination rate, a durable vaccine has important dynam also seen in [20, 22]) (*middle row*, Fig 4). Intermediate vaccination rates also partially modulate pessimistic outcom wanes rapidly; this is further emphasized if vaccination is increased further (Fig 4). However, if severity-blocking im rapidly and a vaccine does not provide long-lasting transmission-blocking protection, then the buildup of susceptib severity-blocking immunity remains substantial irrespective of vaccination rates (compare leftmost plots of each ro to decrease this accumulation, a high vaccination rate with a more durable vaccine is necessary.

Heterogeneities in vaccination coverage

Current vaccination rates are very variable globally and at local scales, both due to inequity in supply and hesitanc uptake of bivalent booster doses in the United States has been low, even among those who received the initial vac specific region, inequity in supply can arise from a number of issues, including due to vaccine nationalism by other vaccine hesitancy can emerge from underlying behavioural drivers [32, 33]. As shown and discussed in previous w heterogeneities in vaccination can have important immuno-epidemiological impacts on the medium- and long-term SARS-CoV-2 (e.g. [6, 34]).

To investigate the potential consequences of vaccination heterogeneity on medium-term immune landscapes and i infections after waning of severity-blocking immunity, we consider a simple extension of our basic framework with t group whose individuals never receive vaccinations, but otherwise mix homogeneously with individuals that are in adopter group (see S1 Text, *electronic supplementary materials*, for model equations). In Fig 5, we illustrate the m outcomes for a range of vaccine-hesitant group sizes (*rows*), for different scenarios of severity-blocking immunity a characteristics (*columns*). In all these panels, we assume that the average vaccination rate is 2% per week (*i.e.* vN $N_1 = 1 - N_2$ is the fraction of individuals that are vaccine-adopters and N_2 is the fraction of individuals that are nev which corresponds to a 'high' vaccination scenario in the homogeneous setting of Fig 4.

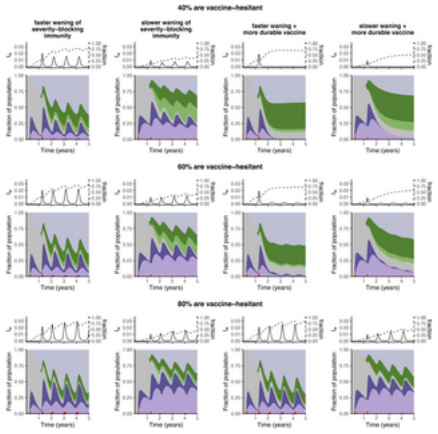

Fig 5. Synoptic landscapes with vaccine heterogeneities, caused by either unequal access or hesitancy.
We assume a 2% weekly vaccination rate (*c.f.bottom row*, Fig 4), and keep the average vaccination rate consta row so that the vaccination rate among vaccine-adopters is v, where $vN_1 = 0.02$ ($N_1 = 1 - N_2$ is the fraction of v adopters, and N_2 is the fraction of individuals that are vaccine-hesitant). The columnar scenarios are as in those
https://doi.org/10.1371/journal.pcbi.1012211.g005

Direct comparisons between Fig 4 (*bottom row*) and the rows of Fig 5 reveal that the homogeneous vaccination as optimistic upper bound. In particular, vaccination heterogeneity increases the fraction of infections after severity-blo has waned, and can even lead to recurrent outbreaks if there are very few individuals that are receiving vaccinatio these observations emerge because vaccine-adopters are a heavily vaccinated group of individuals who are re-va On the other hand, individuals with waned immunity that are never vaccinated can only regain immunity via infectio an optimistic scenario where there is slower waning of severity-blocking immunity, a large fraction of these never-v individuals have waned severity-blocking immunity. Furthermore, if there is a substantial fraction of individuals that vaccination, a more durable vaccine has almost no immuno-epidemiological effect on the population-level dynamic two columns with right two columns, respectively, of Fig 5, *bottom row*). Finally, if the average vaccination rate dec impact of the resulting vaccine heterogeneity on immuno-epidemiological outcomes is slightly attenuated (*e.g.*, see *electronic supplementary materials* where the average rate is 0.01 per week).

In Fig 6, we examine the cumulative number of infections in I_W that occur after the onset of vaccination up to year 5 population size), as a function of the fraction of individuals that are vaccine-hesitant. As in Fig 5, we assume that th vaccination rate is 2% per week. Across scenarios, an increase in vaccine hesitancy leads to a greater number of i This effect is further magnified if severity-blocking immunity wanes rapidly (compare *left* with *right* panels of Fig 6, hesitants have a higher transmissibility. As illustrated in Fig 5, vaccine hesitancy counters the deployment of a mor vaccine (*bottom* panels, Fig 6). In particular, sufficient vaccine hesitancy can lead to a sharp increase in the cumul infections in I_W (*bottom left* panel, Fig 6). Thus, if the fraction of individuals that are vaccine-hesitant is below this th are very few infections with waned severity-blocking immunity. However, if the fraction of individuals that are vacci increases further beyond this threshold, the cumulative number is substantially increased. If vaccine-hesitants hav transmissibility, we find that this threshold occurs for a much smaller level of vaccine hesitancy (*bottom left panel*, I impact immuno-epidemiological dynamics (see S2 Fig, *electronic supplementary materials* for an example). Overa illustrate that, even with corresponding adjustments to vaccination rates among adopters, vaccine hesitancy can su hinder the epidemiological benefits of more durable vaccines.

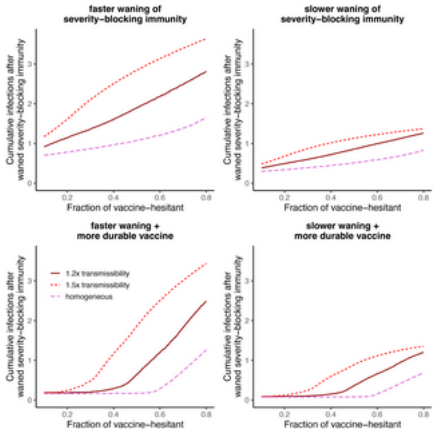

Fig 6. Cumulative infections with waned severity-blocking immunity after the onset of vaccination up to year 5 as a function of the fraction of individuals that ar

The *top left*, *top right*, *bottom left*, and *bottom right* panel depict the same scenarios as the first, second, third, a columns of Figs 4 and 5, respectively. As in Fig 5, the average vaccination rate is constant. In each panel, the d denote different relative transmissibility values for vaccine hesitants.
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Caveats and future directions

To distill the impacts of severity-blocking immunity on potential medium-term outcomes, we have made a number c assumptions in our modelling framework that should be relaxed in future work. First, we have ignored vaccine dosi *e.g.* [20]) and assumed that individuals get vaccinated at some rate, with each subsequent vaccine they obtain givi vaccinal immunity. In reality, multiple doses can lead to more robust immunity, and incorporating explicit vaccine do could reveal subsequent impacts. Relatedly, we have ignored the potential accumulation of immunity (whether tran blocking or against severity) after multiple exposures. Combining this refined model with that of [22] could elucidate that may emerge due to the interaction between accumulating immunity and waning severity-blocking immunity. W ignored the impact of time-dependent variable vaccination rates, and incorporating this with specific vaccination da regions would be valuable. Notwithstanding these complexities, we have shown that the qualitative impact of hesit performance is robust to underlying assumptions. This underlines the importance of more refined and granular mo of hesitancy in future work.

While we have examined heterogeneities in vaccination, we have ignored various other heterogeneities, *e.g.* in tra 36], or due to age [15] or vulnerabilities [37]. Exploring these further, and their confluence with vaccination heterog severity-blocking immunity, is an important future direction. In particular, we have assumed that interactions betwe that are vaccine-hesitant and those that adopt vaccines are homogeneous. In reality, however, interactions within a more likely than between groups. These features could enhance transmission potential and reduce the likelihood o vaccination (see *e.g.* [6] for a simple consideration of this), and examining the interplay between these effects and blocking immunity is an important are of future research.

Relatedly, we have ignored the dynamics of human behavior [38], especially regarding adherence to nonpharmace interventions (*e.g.* [39, 40]) or vaccination [41, 42]. However, the potential feedbacks between these social and epi dynamics could shape immuno-epidemiological trajectories. Thus, incorporating these features into an epidemiolo model with severity-blocking immunity would be particularly fruitful.

We have also omitted individual variations in viral loads and immune kinetics. In particular, it would be particularly i formulate cross-scale models that couple our framework with within-host dynamics. Coupled with a model for viral framework could potentially aid in understanding viral phylodynamics of SARS-CoV-2 (see [29, 43, 44]). Relatedly, the dynamics of Long COVID, and exploring the connections between this, severity-blocking immunity, and potenti chronic burden is a salient avenue for future work. Overall, understanding the impacts of these various heterogene complex models with comprehensive data (*e.g.* from large cohort studies [29]).

In line with previous work (see *e.g.* [6, 20–22, 45]) we have assumed that NPIs decrease transmission by a fixed v periods of time. However, NPIs are often implemented dynamically. Furthermore, in the absence of mandated NPIs still choose to adhere to certain interventions (*e.g.* mask-wearing, social distancing). Incorporating the underlying s that then determine NPI adherence in such a setting may be important [39]. Thus, a potentially fruitful future avenu couple our simple immuno-epidemiological models with more realistic formulations of NPI adherence, calibrated to regions of interest.

The impacts of vaccination, transmission-blocking and severity-blocking immunity, vaccine hesitancy, varying perio climatic effects on transmission can be further explored using the interactive online application at https://grenfelllab.shinyapps.io/covid19immunity/.

Conclusion

As the SARS-CoV-2 outbreak continues to progress, testing and monitoring of infections has been widely relaxed a health emergency of international concern (PHEIC) has ended, but transmission remains high. In parallel, while the accumulated so far has improved our understanding of host immune responses following infection or vaccination, a uncertainties remain, especially in the duration of immunity against severe disease and in the relative susceptibility after waning of transmission-blocking immunity.

Our simple models reveal that a large range of outcomes can emerge from uncertainties in both the duration of sev immunity and the strength of immunity, and from the confluence of these two parameters. In particular, our findings the strength of immunity shapes immuno-epidemiological dynamics at multiple resolutions, and that the duration of blocking immunity has a major effect on population-level immune landscapes and potential burdens. Thus, to prop dynamics from hospitalization data, accurate estimates of both these parameters are needed, which could be acco future cohort studies monitoring immuno-epidemiology [29] and a Global Immunological Observatory [26–28].

Finally, we have also shown that high vaccination rates, in combination with a more durable vaccine, can alleviate outcomes for both the buildup of susceptible individuals with waned severity-blocking immunity and for the level of waned severity-blocking immunity. Our results also illustrate the importance of broad vaccination coverage, echoin findings that argued for equities in vaccination access [20–22, 34]. In particular, we find that ignoring the specter of hesitancy in regions awash with vaccines can, at the population-level, essentially counteract important pharmaceu developments to improve vaccine breadth and strength. Since we have shown that this result is generally robust to assumptions on underlying uncertainties of severity-blocking immunity, our work underlines the need to identify and behavioural drivers of vaccine hesitancy [33]. In tandem, since the impact of hesitancy is especially amplified if vac

have higher transmissibility, our results further stress the importance of nonpharmaceutical interventions in regions levels of hesitancy. Overall, to prevent pessimistic outcomes from waning severity-blocking immunity, increases in vaccination rates in conjunction with the development of more robust vaccines are necessary.

Supporting information

S1 Fig. Vaccine hesitancy with a lower baseline vaccination rate.
This figure is as in Fig 5, but with an average vaccination rate of 1% per week (instead of the 2% per week in Fig 5
https://doi.org/10.1371/journal.pcbi.1012211.s001
(PDF)

S2 Fig. The impacts of increased transmissibility of vaccine hesitants on immuno-epidemiological dynamics.
This figure is as in Fig 5, but with $\alpha_V = 1.2$.
https://doi.org/10.1371/journal.pcbi.1012211.s002
(PDF)

S1 Text. Supplementary information text.
https://doi.org/10.1371/journal.pcbi.1012211.s003
(PDF)

S1 File. Zip file with R code.
https://doi.org/10.1371/journal.pcbi.1012211.s004
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