Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Mini-symposium: COVID 19: The second year

Vaccines and variants: Modelling insights into emerging issues in COVID-19 epidemiology

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Educational Aims

The reader will come to appreciate that modellers have:

- Been central in understanding evolving COVID-19 epidemiology and guiding public health responses.
- Captured social interactions to project the consequences of reopening schools.
- Incorporated vaccine efficacy data with different vaccination strategies to predict the population level effectiveness.
- Used compartment models to estimate changes in transmissibility and lethality of COVID-19 Variants of Concern [VoC].

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ABSTRACT

Mathematical modelling has played a pivotal role in understanding the epidemiology of and guiding public health responses to the ongoing coronavirus disease of 2019 (COVID-19) pandemic. Here, we review the role of epidemiological models in understanding evolving epidemic characteristics, including the effects of vaccination and Variants of Concern (VoC). We highlight ways in which models continue to provide important insights, including (1) calculating the herd immunity threshold and evaluating its limitations; (2) verifying that nascent vaccines can prevent severe disease, infection, and transmission but may be less efficacious against VoC; (3) determining optimal vaccine allocation strategies under efficacy and supply constraints; and (4) determining that VoC are more transmissible and lethal than previously circulating strains, and that immune escape may jeopardize vaccine-induced herd immunity. Finally, we explore how models can help us anticipate and prepare for future stages of COVID-19 epidemiology (and that of other diseases) through forecasts and scenario projections, given current uncertainties and data limitations.

INTRODUCTION

In the continually changing epidemic landscape of COVID-19 (the disease caused by severe acute respiratory syndrome coronavirus-2; SARS-CoV-2), modelling has been central to understanding evolving COVID-19 epidemiology and guiding public health responses, particularly with respect to vaccines and Variants of Concern (VoC; viral strains hosting mutations that increase transmissibility, change immune response, or affect disease severity). In the eighteen months since COVID-19 emerged, multiple efficacious vaccines have become available, yet outbreaks continue, in part because of limited access to vaccines and emerging VoC. From early in the pandemic, modelling has characterised key epidemiological characteristics [1,2] and helped identify when and what type of restrictions should be used to gain epidemic control [3]. For example, models have explicitly captured social interactions to project the consequences of reopening schools [4–7], increasing the proportion of onsite workers [5,8], and reinstating international travel [9,10]. Analyses are now shifting to focus on

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understanding characteristics of mutating viruses [11] and optimising vaccine distribution [12–14]. Here, we update previous insights on the role of models in understanding COVID-19 epidemiology [15] with respect to vaccination and VoC.

INCORPORATING VACCINES AND VARIANTS INTO SIMPLE DISEASE MODELS

We can estimate important epidemiological characteristics and project meaningful future epidemic scenarios using disease transmission models, such as compartmental models. For infectious diseases with an incubation period (like COVID-19), compartmental models typically split the population into four compartments based on clinical status, SEIR: susceptible, exposed, infectious, recovered (Fig. 1; more detail described in [15]). From these dynamic models, we can estimate epidemiological characteristics such as the basic (or effective) reproduction number (R_0; the average number of secondary infections from each infectious individual in a fully [or partially] susceptible population) and predict epidemic outcomes, such as disease spread, epidemic duration, and attack rate. We can incorporate vaccination and VoC by adjusting infection, incubation, or mortality rates within the model (Fig. 1).

For COVID-19 vaccine analyses, modellers have incorporated vaccine efficacy data from clinical trials given different vaccination strategies to predict the population level effectiveness [14,16]. For VoC analyses, modellers have fit SEIR models to data to estimate changes in transmissibility and lethality [11].

HERD PROTECTION

An important theoretical concept for determining how to control an epidemic is herd protection: the indirect disease protection that occurs when a population is immune (from vaccination, prior infection, or both), slowing transmission as a pathogen encounters fewer susceptible individuals. As immunity builds in the population, some degree of herd protection can be expected [17]. To quantify the level of population immunity (e.g., vaccine coverage) needed to achieve herd protection, modellers calculate the herd immunity threshold (HIT; Fig. 2). The HIT is a useful modelling tool to guide vaccination campaigns, but in reality, there is unlikely to be a dichotomous threshold, beyond which transmission abruptly stops. The simplest calculation of HIT assumes homogeneous mixing (i.e., contact rates among all individuals in the population are uniform) and uses the following formula:

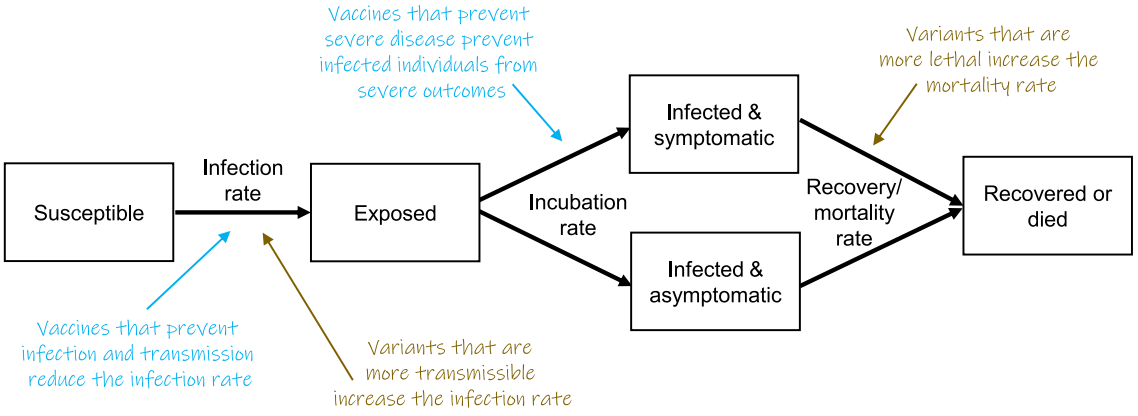

Fig. 1. Vaccination and VoC can be incorporated into mechanistic disease transmission models by modifying transition rates between states associated with infection, viral incubation, recovery, and mortality. In this conceptual figure, populations are split into susceptible, exposed, infected (split by clinical status), and recovered compartments and transition along the arrows at different rates corresponding to COVID-19 epidemiology. Vaccination (blue) and VoC (brown) can be modelled by adjusting different rates depending on how they function.

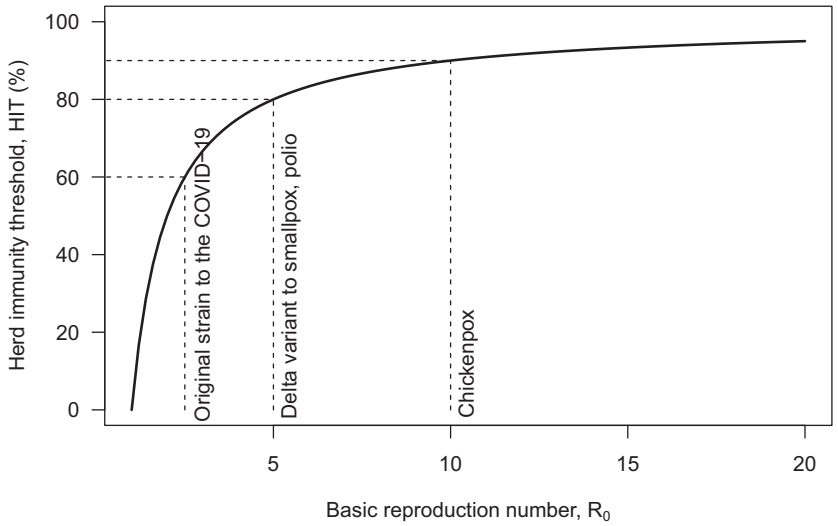

Fig. 2. The herd immunity threshold (HIT) is higher for diseases with higher transmissibility (basic reproduction numbers).

$$HIT = 1 - \frac{1}{R_0}$$

In practice, HIT varies by context because contact and infection rates are not homogenous within populations: HIT is modified by factors like biological characteristics (e.g., age), behaviors (e.g., occupation), connectedness (e.g., contact patterns), mitigation efforts (e.g., physical distancing), vaccine coverage, and natural immunity. Therefore, for COVID-19 there should be less emphasis on reaching one specific HIT and more focus on achieving substantial levels of herd protection to slow spread. Early COVID-19 studies estimated a HIT of ~60–70% based on initial R_0 estimates of ~2.5–3.5 (Fig. 2; [18–20]). However, heterogeneous mixing and changing epidemiology make HIT a moving target. For example, the Alpha variant (B.1.1.7) has been estimated to be ~60% more transmissible than the wild-type SARS-CoV-2 strain [21], implying a HIT of ≥80%. If significant levels of herd protection are achieved, the focus can shift to keeping $R_{effectiive}$ below one, allowing low levels of sustained transmission without causing large epidemics.

IMPACT OF VACCINATION ON COVID-19 INFECTION AND TRANSMISSION

A major challenge for using models to predict the impacts of vaccination (and thus guide vaccination strategies) is the mismatch between some model parameters (e.g., infection rates) and data generated from vaccination studies. Vaccines can help alleviate disease burden through multiple pathways, by: (1) preventing infection, (2) rendering infected persons less infectious, or (3) preventing severe outcomes in those infected (Fig. 1), which consequently reduces the total number of infected individuals and/or the proportion of symptomatic infections. Typical clinical trial endpoints relate only to symptomatic disease and certain specified adverse clinical outcomes (e.g. hospitalisation and death) [22], and so do not distinguish whether these outcomes are attributable to reduced transmission or reduced disease given transmission (Fig. 3). If vaccines do not markedly reduce transmission, exponential growth may still occur, with the potential to overwhelm health services [23]. Therefore, incorporating realistic estimates for key model parameters is extremely important.

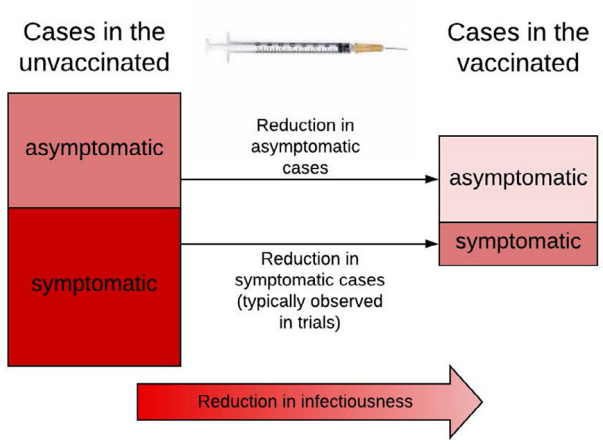

Fig. 3. Multiple observed and unobserved mechanisms may influence the effect of vaccination on the COVID-19 epidemic. Comparing cases in an unvaccinated population (left) with cases in a vaccinated population (right) with two infected categories, vaccination could (1) reduce the infectiousness of asymptomatic and/or symptomatic cases, (2) reduce the number of symptomatic cases arising in the population, and/or (3) reduce the number of asymptomatic cases arising. Note that pathway 2) is often the primary outcome reported by clinical trials, whereas pathways 1) and 3) are often not observed.

To better predict the real-world impact of vaccines on the COVID-19 epidemic, we present early evidence for key epidemiological characteristics that are important for disease modelling (Table 1), although this evidence base has already advanced considerably since the search was performed. Recent studies indicate that many currently available vaccines (BioNTech-Pfizer, Moderna, Sputnik V, Oxford-AstraZeneca, Janssen, Novavax, Sinovac, and Sinopharm) are 51–95% effective at reducing clinical COVID-19 and 85–100% effective at preventing severe disease based on clinical trial data [24]. To estimate other important model parameters from clinical trial data, we undertook a systematic review and determined that several COVID-19 vaccines are effective at preventing infection and onward transmission (Table 1; see Supplementary Material for methods and full results). Some vaccines show evidence of preventing infection based on the comparison of the proportion of asymptomatic infected individuals in vaccine and placebo groups [25]. Some vaccines show evidence of reduced infectiousness of COVID-19 cases, based on proxies of infectiousness (such as estimating the viral load through PCR cycle thresholds, or Ct) that appear lower in vaccinated patients [26].

Table 1 summarises data from the following studies: [26,27,36,28–35].

OPTIMISING VACCINE DISTRIBUTION

Mathematical modelling is an ideal tool to determine optimal vaccine allocation policies that balance individual and population benefits. The primary way models can help guide vaccine distribution strategies is by generating multiple plausible future scenarios (i.e., simulating disease spread given different conditions). For example, for vaccines with limited supply, models can compare different distribution approaches (e.g., targeting those most vulnerable, targeting superspreaders) to determine their effect on various optimisation targets (e.g., reducing mortality, outbreak duration) to help answer the critical question of who should receive vaccines first. Similarly, models can project possible outcomes for a suite of decisions associated with vaccine distribution, such as identifying the optimal timing of distribution and whether fractional doses could better curtail an epidemic.

For COVID-19, modelling studies have focused on how to optimally allocate vaccines given limited supply, showing that optimal strategies vary depending on total supply, program goals, and context. Given low vaccine efficacy, low coverage, or sustained transmission, prioritizing individuals >60 years of age should lead to the greatest reductions in hospitalisations and mortality [37], while targeting younger individuals should lead to the greatest reduction in incidence [14]. However, clear thresholds for vaccine efficacy and population-level coverage were identified, beyond which (e.g., when vaccine supply increases) a suppression strategy that targets middle-aged [30–59] transmitters becomes optimal across all optimisation targets (e.g., incidence, hospitalisations, and deaths) [13,38]. Because human contact patterns are heterogeneous but broadly understood, targeted strategies are likely to be far more effective at reducing disease burden than indiscriminate vaccination campaigns, whether targeting is directed according to age [14], occupation (e.g. essential-workers; [29]), or those with higher degrees of social connectivity [40]. Similarly, at the global level, several modelling studies have found that allocating available doses in proportion to each country's population size (compared to the current practices favouring high-income countries) is close to the optimal strategy [13] and could double the global number of deaths averted [41]. Further, initially distributing single doses (for two dose vaccines) should avert more deaths than providing fewer people with two doses, provided that protection con-

Table 1
Brief overview of vaccine efficacy studies against different SARS-CoV-2 strains, focusing on clinical outcomes (i.e., reduction in symptomatic disease) and reduction in asymptomatic covid or changes to infectiousness of breakthrough infections deduced from viral load (inferred from cycle threshold, Ct). SD is standard dose, LD is low dose.

Vaccine	Progenitor or mixed strains	B.1.1.7	B.1.351	P1,2	B.1.617	Reference, time period, study description
Pfizer BioNTech-Pfizer (BNT162b2)	^^Asymptomatic COVID 95.0% efficacy (90.3–97.6) ^Any COVID efficacy 94.6% (89.9–97.3)	*Reduced infection 89.5% (85.9–92.3) reduced severe/critical/fatal disease 100.0% (81.7–100.0)	+Infectiousness of breakthrough infections compared with unvaccinated: reduced viral load: 2.8–4.5 fold decrease in viral load 12–37 days after first dose #1.64-fold decrease in viral load in those >60 years *Efficacy against infection 75.0% (70.5–78.9) Severe disease 100% (73.7–100)		++Reduced symptomatic covid 87.9% (95% CI: 78.2–93.2) after two doses	^^Multi-National (Polack 2020) 27/07/2020–14/11/2020 ^UK (Lumley 2021) 01/09/2020–28/02/2021) *QATAR 01/02/2021–31/03/2021 (Abu-Raddad) +Israel (Levine-Tiefenbrun 2021) 21/12/2020 - 11/02/2021 #Israel (Petter 2021) 01/12/2020–30/01/2021 ++UK (Bernal JL 2021) 26 October 2020–16 May 2021
Oxford AstraZeneca (ChAdOx1 nCOV-19)	^Asymotomatic covid reduced by 27.3% (−17.2 to 54.9) 14 days after second dose (3.8% in the two standard doses SD/SD and 58.9% in the one low dose followed by a standard dose LD/SD) ^Reduction in severe disease: efficacy 70.4% (54.8–80.6%) across two regimens. For the subgroup SD/SD, efficacy was 62.1% (41.0–75.7) and for LD/SD it was 90.0% (67.4–97.0%) #Mild to moderate COVID efficacy 21.9% for the whole study group	^Breakthrough infections in vaccinated had lower viral loads compared with unvaccinated (Ct 18.3 vs 19.7)	#Sub-group analysis for the B.1.315 variant efficacy against mild-moderate COVID was 10.4% (−54.8% to 76.8) '		++Efficacy for reduced symptomatic covid 59.8% (95% CI: 28.9–77.3)	^U.K. and Brazil (Voysey2021) 23/04/2020–04/11/2020 #South Africa (Madhi2021) 24/06/2020–09/11/2020 ++UK (Bernal JL 2021) 26 October 2020–16 May 2021
Janssen (Ad26.CoV2.S)	^reduction in COVID of any severity 66.5% (55.5–75.1) moderate to severe/critical COVID 66.9% (95% CI 59.0, 73.4) >14 days after single dose 66.1% (95% CI 55.0, 74.8) measured >28 days post single vaccination reduction in severe/critical COVID 76.7% at >14 days post single vaccination 85.4%(54.2–96.9) >=28 days after vaccination		*Reduced risk of infection 64.0% (41.2–78.7% effective) Symptomatic disease 81.7% (46.2–95.4%) ^Moderate to severe–critical Covid-19 52.0% and 64.0% for >14 days and >28 days after administration, respectively, efficacy against severe–critical Covid-19 was 73.1% and 81.7%, for >14 and >28 days respectively	*Reduction in asymptomatic infection 20% at 1–29 days post vaccination		*Jansen 2021 ^Latin America, U.S., South Africa (Sadof 2021) 21/09/2021-22/01/2021
Novavax (NVX-CoV2373)	*Reduction in symptomatic disease 96.4% (73.8–99.5)	*reduction in symptomatic disease 86.3% (71.3–93.5)	^reduction in symptomatic disease efficacy 51% (−0.6 to 76.2%).			*UK (Heath 2021) 28/09/2020–28/11/2020

(*continued on next page*)

Table 1 (*continued*)

Vaccine	Progenitor or mixed strains	B.1.1.7	B.1.351	P1.2	B.1.617	Reference, time period, study description
Natural immunity	^if both anti-nucleocapsid IgG and anti-spike antibody titres positive, 94% 54–99) protection against any COVID infection	*anti-spike protein signal of prior infection reduced viral load in breakthrough infection (Ct 27.2 vs Ct 18.3) anti-spike protein signal of prior infection conferred 98% protection (82–99%) against any PCR positivity: 85% reduction (74–92)				^South Africa (Shinde, 2021) 17/08/2020–25/11/2020 ^UK (Iumley, 2020) 23/04/2020–30/11/2020 *UK(Lumley 2021) 23/04/2020–28/02/2021
Evidence for reduced infectiousness in breakthrough infections						
Evidence for reduced susceptibility to any infection						

ferred by a single dose is sufficiently high [12,42]. Given sustained transmission, rapidly gaining population immunity is paramount.

VARIANTS OF CONCERN (VOC): EPIDEMIOLOGY AND INTERACTION WITH VACCINES

Mathematical models can help us understand how viral evolution is shaped by selective pressure and competition among strains over limited resources (i.e., susceptible hosts), and how this affects epidemic trajectories. As viruses replicate and spread, genetic mutations accrue. Viruses become more transmissible and less pathogenic over time, often evolving into endemic diseases [43,44] and similar mutations can arise in different regions given exposure to similar selective pressures. This process can lead to multiple co-circulating strains with varying transmissibility, severity, and susceptibility to interventions. When co-circulating strains provide cross-immunity (i.e., infection from either strain confers high levels of immunity to both strains), disease models show that competition favours variants with higher R_0, leading to strain replacement [45]; when strains have similar R_0 values, epidemic cycles can emerge, which may mimic seasonal epidemics [45–47]. Fitting models with time series of incidence data can allow for the estimation of strain-specific growth rates, R_0, and the extent of cross-immunity conferred to other strains [21]. Infectious disease models can further capture the impact of variants and provide practical assistance for vaccine distribution given new strains, provided there is robust evidence regarding the impact of mutations on transmissibility, degree of immune escape to specific vaccines, and waning immunity.

SARS-CoV-2 is likely to continue evolving and circulating around the globe as an endemic disease, possibly with epidemic cycles. Through natural evolution, SARS-CoV-2 would likely continue spreading and shift to primary infection in younger age groups [44], and VoC make global eradication even more unlikely. Several mutated SARS-CoV-2 viruses have emerged independently and are considered VoC based on increased transmissibility, change in clinical severity, reduced immunity following infection/-vaccination, or a combination of these (Table 1). Although these VoC arose separately, they have commonalities (e.g., changes in specific sites of the spike protein), likely because of similar selective pressures (e.g., increasing immunity). Early evidence suggests that natural and vaccine immunity are not complete or robust to new variants (e.g., Table 1). For instance, a simulation study from Manaus (Brazil) indicated that prior natural infection from the previously circulating strain generated only 54–79% protection against the Gamma variant [11]. Using a simple disease model that assumes long-term immunity and homogeneous mixing, we show that vaccination coverage can become unattainable with VoC with increased transmissibility and/or immune evasion (Fig. 4). For instance, a vaccine that is 90% effective at reducing transmission (e.g., Moderna against the wild-type strain) would require at least 62% coverage to achieve herd immunity, but if vaccine escape mutants lead to vaccine efficacy less than 60% (some evidence shown in Table 1), herd immunity cannot be achieved through vaccination alone (Fig. 4).

LOOKING INTO THE FUTURE

Modelling can provide unique insights into COVID-19 in the future. The ability of some variants to escape pre-existing immunity (infection- or vaccine-induced) guarantees that the world has many more years of COVID-19 decision making ahead. As more evidence arises regarding the extent, duration, and nature of post-infection immunity [48,49], models could predict the size and severity of future COVID-19 epidemics in places with a history of

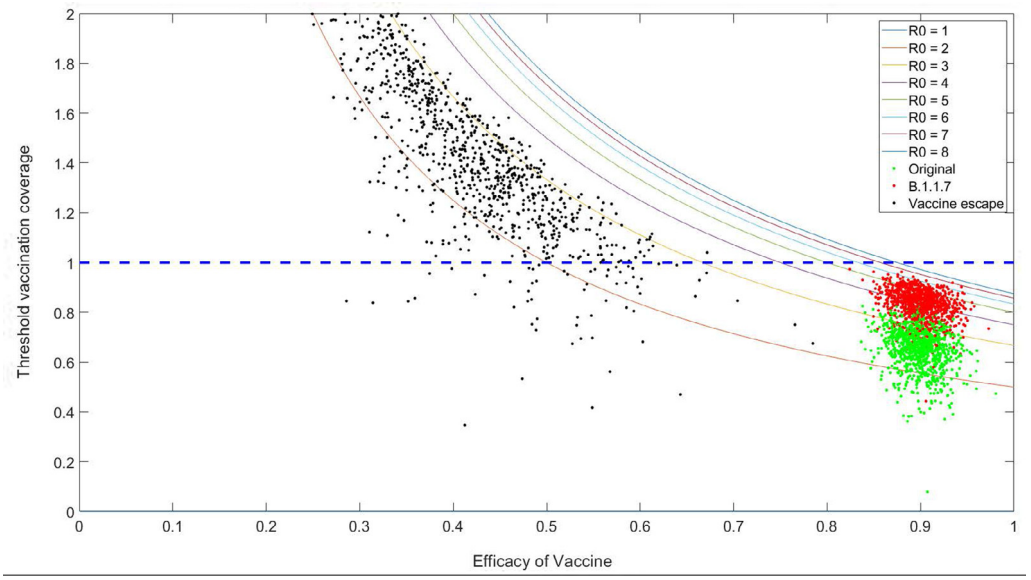

Fig. 4. Low vaccine efficacy and/or high transmissibility indicate herd immunity cannot be achieved through vaccination alone, based on a simple disease model. The plot shows vaccine coverage (vertical axis) versus vaccine efficacy (horizontal axis) for diseases with differing levels of transmissibility (colored solid lines). The solid lines show the herd immunity threshold for these differing parameters. The red, green and black dots demonstrate plausible ranges of values for R_0 and vaccine efficacy for three different vaccine-variant pairings. Values are drawn from these ranges using Monte-Carlo sampling for the R_0 and the vaccine efficacy was performed and the required coverage to achieve herd immunity was calculated as HIT=$(1-1/R_0)$/VE which was plotted as a dot for each of 1000 draws from each vaccine/variant pairing.

prior infection. Further, modelling will continue to play a critical role in guiding pandemic responses, whether it is used to identify key characteristics of emerging variants or to project disease spread under various scenarios in the short-, medium-, or long-term. Model uncertainty, which arises due to simplifying model assumptions and observation error in data inputs, will dissipate as evidence emerges, and does not preclude scenario comparisons with appropriate communication of uncertainty. These types of models provide invaluable knowledge that can be used to design future epidemic control planning, including for pathogens other than SARS-CoV-2.

While we know that COVID-19 control will rely significantly on vaccination, it remains unclear what population-level impact it will have: elimination, regular strain replacement, age-shift in infection, or different outcomes in different regions. We can use models to estimate the population-level impact of vaccination using trial-based vaccine efficacy estimates to consider different coverage levels and roll-out strategies. Using the ever-increasing knowledge of waning vaccine immunity profiles, modelling will also help determine whether vaccination will need to be repeated at regular intervals and how this should be targeted. Based on early evidence, the main barrier to effective control through vaccination could be the emergence of new viral variants escaping vaccine immunity [11]. As vaccination coverage increases, reduced transmission will reduce opportunities for emergence and population immunity will act as a selective pressure, increasing the rate of vaccine escape mutants; however, it is unclear which process will predominate. Two causes for optimism are that (1) to date, VoC have few genotypic changes with convergent phenotypic mutations, and (2) new vaccine technologies are rapidly emerging. Thus, the world's ability to control future outbreaks will likely depend on how the virus evolves and the capacity to rapidly access and distribute adapted vaccines.

CONCLUSION

As the COVID-19 pandemic continues to unfold, models can help us understand emerging issues with COVID-19 epidemiology, vaccination, and VoC. In this review, we discuss the role of models in understanding: herd protection and its limitations; the role of vaccines in preventing severe disease, infection, and transmission and their lowered efficaciousness against VoC; how optimal vaccine allocation strategies vary depending on vaccine supply and efficacy; the extent to which VoC are more transmissible and lethal compared with previously circulating strains; immune escape may undermine vaccine efforts to reach herd immunity; and how we can anticipate future stages of COVID-19 (and other emerging infectious diseases) through forecasts and scenario projections.

DIRECTIONS FOR FUTURE RESEARCH

- What population-level impact will vaccination have: elimination, regular strain replacement, age-shift in infection, or different outcomes in different regions?
- The extent to which VoC are more transmissible and lethal compared with previously circulating strains.
- How we can anticipate future stages of COVID-19 through forecasts and scenario projections?

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prrv.2021.07.002.

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