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Modelling vaccination strategies for COVID-19

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Despite the rapid development of safe and highly effective vaccines against coronavirus disease 2019 (COVID-19), the strategy for their distribution has been and remains contentious. Mathematical models can be used to guide and inform these strategies; however, uncertainties in critical immunological and evolutionary parameters of SARS-CoV-2 can limit the predictive power of models. Notwithstanding these ongoing uncertainties, we discuss how models have been applied to guide health policy decisions related to vaccination against COVID-19, and how they may be applied in the future in the context of booster doses under different scenarios related to disease-specific factors and global distribution.

Mathematical modelling of the epidemiological impact of vaccination has a long and productive history[1]. The dynamics of disease transmission and immunity in a population in the context of vaccination are typically modelled using either network or compartmental approaches. In network models, interactions between individuals (or nodes) within a population are modelled as networks with specific structures[2]. The location of individuals within these networks, as well as their degree of connectivity to other individuals, influences their infection or immune type (for example, susceptible, infectious or recovered) as the simulated disease spreads. By contrast, compartmental models assume that the infection process is 'well-mixed' at some or all scales of interest. Individuals typically transition between these same infection or immune types at rates governed by parameters related to transmission, disease life history and immune characteristics. For SARS-CoV-2 infection, it is increasingly apparent that the strength, breadth and duration of immunity may depend on whether the individual's particular history includes infection by the virus or one (or more) vaccine doses. Network models may be better suited for capturing individual-based variations in life histories than compartmental models; however, network models come at a higher computational cost and are much more demanding in terms of the numbers of parameters that require estimation from often limited data. All models can be coupled with assumptions related to the adoption of non-pharmaceutical interventions as well as specific rates of vaccine administration to simulate 'realistic' scenarios for vaccine rollout. Both compartmental and network models have been extensively used by government public health agencies throughout the COVID-19 pandemic to guide policy response.

Although it is possible to estimate clinical parameters related to disease life history (such as the duration of the infectious period), for SARS-CoV-2 in particular, many immunological and evolutionary parameters remain largely unknown. Notably, SARS-CoV-2 is a virus with high evolutionary potential, as evidenced by the emergence of novel strains, including some with increased transmissibility and a greater ability to evade host immune responses (such as the Omicron variant, which rapidly became the dominant strain globally at the end of 2021). It is currently unclear in which populations the selection of new variants is predominantly occurring, and understanding this will be crucial to accurately model future variant emergence and dynamics. With these modelling concepts in mind, we discuss how vaccine strategies at different scales have been examined with modelling during the COVID-19 pandemic.

Vaccine distribution strategies

Within country. Supply limitations during the initial stages of COVID-19 vaccine rollout prompted the establishment of specific distribution strategies within countries who secured early access to vaccines. By incorporating disease-specific factors such as age-based mortality and transmission rates, mathematical models proved to be useful tools for exploring how distribution strategies could be optimized to minimize specific outcomes, such as disease burden or mortality. Ultimately, the strong correlation of severe COVID-19 with age led to models supporting age-based vaccine distribution strategies for minimizing mortality[3,4], and countries around the world largely adopted this recommendation, prioritizing shots for older individuals and health-care workers early on. This differs from modelling results for the distribution of influenza virus vaccines[5], which recommend vaccination be prioritized for school-age children and young adults owing to the large role of children in the transmission of this disease.

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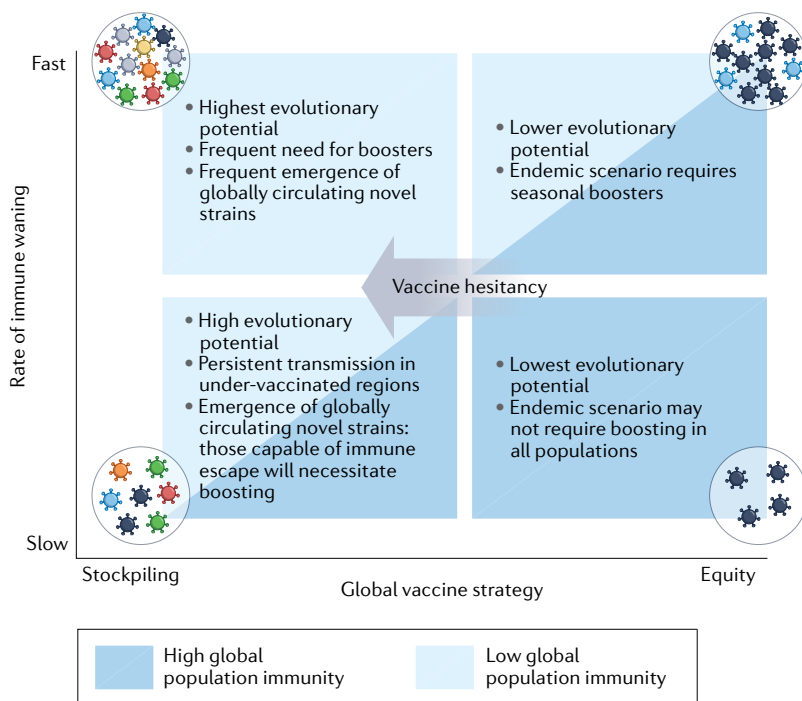
Fig. 1 | **Summary of potential future scenarios for global SARS-CoV-2 transmission depending on the chosen global vaccine strategies and rate of immune waning following infection or vaccination.** Vaccine stockpiling and rapidly waning immunity result in low global population immunity towards SARS-CoV-2, and may prompt frequent variant emergence and booster administration. High global population immunity is achieved under scenarios characterized by equitable vaccine allocation and more durable immunity. Under these scenarios, variant emergence may be less frequent, and the need for boosters may also be reduced. Vaccine hesitancy acts similarly to vaccine inequity in leaving large portions of the population unvaccinated, lowering overall global population immunity.

Invariably, the utility of any distribution scheme depends highly on the degree of vaccine uptake, and countries around the world have seen population-level COVID-19 vaccination rates saturate due to vaccine hesitancy.

Between countries. At the start of 2022, we face the challenge of global vaccine distribution with a now abundant vaccine supply. In the absence of supply constraints, models indicate that sharing doses with nations with low vaccine access is necessarily beneficial from a global perspective, as gains in immunity in these regions come at no cost to immunity in high access regions[6]. The drive to vaccinate countries globally is proceeding concurrently with the roll-out of 'booster' vaccine doses, particularly in high-income countries. Initially, this was due to evidence of waning vaccine-induced and infection-induced immunity against circulating SARS-CoV-2 strains over approximately 6 months to 1 year (see for instance REF.[7]). However, preliminary evidence that three mRNA vaccine doses provide neutralization of the Omicron variant[8] has led to an acceleration of these booster programmes. Future models will thus need to encompass the immune life history of individuals (that is, the timing, number, and type or strain of previous vaccines or infections) to accurately model population-level immunity to circulating and emerging SARS-CoV-2 strains. In this sense, network models may prove to be increasingly useful.

From the perspective of a single country in isolation, booster administration in the short term will indeed likely increase population-level immunity against SARS-CoV-2, and particularly the Omicron variant, thus lowering the burden of COVID-19. However, when the situation is evaluated globally, the value of booster doses in the absence of large-scale vaccination campaigns in low-income and middle-income countries is less clear. When infection-induced and vaccine-induced immunity wane rapidly (thus allowing for more rapid reinfection and transmission among vaccinated individuals), models show that the benefits of vaccine sharing with supply constraints in terms of lowering the global infection burden are reduced, as a state of herd immunity cannot be achieved in any region[6]. However, if subsequent infections are milder, the impact of reducing the pressure on health-care systems by vaccination, particularly in lower income countries where these systems may be more fragile, cannot be overlooked. Indeed, if vaccines provide protection against severe disease following infection with emerging strains (although do not necessarily prevent infection and transmission), the 'endemic' state of SARS-CoV-2 transmission may be more rapidly achievable, as modelled by Lavine et al.[9], and may mimic milder infections first obtained in childhood.

In general, persistent viral transmission in under-vaccinated populations presents a scenario for the potential evolution of variants. Indeed, although its geographic origin remains uncertain, this may reflect the situation for the Omicron variant. Critically, the emergence of Omicron reinforces modelling predictions[6] that only strategies that suppress viral transmission and evolution globally will be effective (and equitable) for minimizing the long-term burden of COVID-19 worldwide.

Ultimately, the frequency with which booster doses will need to be administered will depend on both immunological parameters (that is, the rate of waning immunity against a single variant) and the durability of immunity in the face of antigenic evolution (that is, the emergence of novel strains). Vaccine distribution strategies that generate large regions of under-vaccinated individuals, either through vaccine hesitancy or national vaccine stockpiling, will increase the possibility for antigenic evolution, thus lowering average population-level immunity. These concepts are illustrated schematically in FIG. 1.

Conclusion

Important aspects of the dynamics of SARS-CoV-2 immunity and antigenic evolution remain uncertain, which may ultimately impact chosen vaccine administration schemes in the longer-term and the value of modelling approaches. The timing of the administration of boosters is likely to depend on factors related to antigenic evolution and immunological waning, yet models support the need to prioritize rapid and equitable vaccination of individuals in all countries. With increasing data available, our ability to estimate parameters related to adaptive immune responses and pathogen evolution, as well as to accurately incorporate effects of human behaviour, will continue to improve. Ultimately, combining sets of compartmental and

network models (with common data but different structural assumptions) has the potential to increase the power and robustness of epidemiological predictions[10]. We argue that this is the way forwards, and that modelling following this approach will provide a powerful predictive tool for guiding vaccination strategies against SARS-CoV-2 and other endemic or future emerging pathogens.

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Competing interests
The authors declare no competing interests.