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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Review

Modelling insights into the COVID-19 pandemic

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Educational aims

The reader will be able to appreciate that:

- Modellers use key disease parameters to estimate basic reproduction ratios.
- Knowing the reproduction ratio leads to important outcome estimates, such as the attack rate of an unmitigated epidemic and the herd immunity threshold.
- Reproduction ratios are setting specific and may change with interventions or increased immunity.
- The case fatality rate and infection fatality rate are distinct and should be interpreted differently when estimating disease severity.
- All models have limitations and early models may be more limited by data quality.

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is a newly emerged infectious disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that was declared a pandemic by the World Health Organization on 11th March, 2020. Response to this ongoing pandemic requires extensive collaboration across the scientific community in an attempt to contain its impact and limit further transmission. Mathematical modelling has been at the forefront of these response efforts by: (1) providing initial estimates of the SARS-CoV-2 reproduction rate, R_0 (of approximately 2–3); (2) updating these estimates following the implementation of various interventions (with significantly reduced, often sub-critical, transmission rates); (3) assessing the potential for global spread before significant case numbers had been reported internationally; and (4) quantifying the expected disease severity and burden of COVID-19, indicating that the likely true infection rate is often orders of magnitude greater than estimates based on confirmed case counts alone. In this review, we highlight the critical role played by mathematical modelling to understand COVID-19 thus far, the challenges posed by data availability and uncertainty, and the continuing utility of modelling-based approaches to guide decision making and inform the public health response.

†Unless otherwise stated, all bracketed error margins correspond to the 95% credible interval (CrI) for reported estimates.

INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a novel beta-coronavirus that first emerged in Wuhan in Hubei Province of China in late 2019 [1]. Whilst initial case reports were

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limited to Hubei Province, the virus quickly spread to neighbouring provinces and across mainland China before cases appeared internationally [2]. Since that time, coronavirus disease 2019 (COVID-19) – the disease associated with SARS-CoV-2 – has spread to over 188 countries around the globe with approximately 8 million confirmed cases, and more than 430,000 deaths (as of 16th June, 2020) [3].

Amongst the arsenal of public health response strategies, mathematical modelling has long played an important role in both characterising infectious disease transmission and evaluating intervention scenarios. Prominent examples include the Influenza AH1N1 pandemic in 2009 [4,5], the West-African Ebola outbreak 2013–2015 [6], and Zika emergence in Latin America in 2016–2017 [7]. Here we provide several examples of how mathematical modelling has been used throughout the COVID-19 pandemic to help understand the scale of transmission, disease severity, and the potential effectiveness of public health interventions. We also discuss the continuing importance of modelling to forecast the impact of easing restrictions and vaccination as many regions around the globe attempt to return to life as normal.

EARLY ASSESSMENT OF POTENTIAL GLOBAL SPREAD

Outside the initial Wuhan epicentre, air travel passenger volumes were a key metric used to evaluate the risk of exportation of COVID-19 to other regions. Using the significant positive correlation between reported case counts outside of mainland China and daily air travel volume from Wuhan, models identified outlier countries with low case numbers compared with travel-related expected counts, suggesting several regions had low detection rates [8].

Other groups used more complex fully integrated air-travel models to predict changes in the COVID-19 epicentre and assess averted cases due to travel restrictions. For instance, a meta-population disease transmission model indicated that Australia reduced imported cases by 79% as a result of the government-imposed travel ban, potentially preventing Australia from becoming the Asia-Pacific epicentre [9]. Similar assessments were performed for African and South American countries, which were initially found to be at much lower risk relative to Asian (e.g., Thailand, Cambodia, Malaysia), North American and European countries, due to their lower connectivity with China [10]. However, the risk to South America and Africa was predicted to increase considerably once a second epicentre was established in Italy [11].

ESTIMATES OF COVID-19 TRANSMISSIBILITY

An important first step in characterising the transmission potential of any novel infectious pathogen is to estimate the basic reproduction number (R_0), which quantifies the average number of secondary cases per infected individual in an infection-naïve population. This parameter provides an important threshold for infection control: when $R_0 > 1$ transmission is expected to be self-sustaining, whilst when $R_0 < 1$ transmission inevitably dies out [12].

R_0 is often estimated using time series of confirmed case counts coupled with additional information on the disease epidemiology, including the time lag between symptom onset in primary and secondary cases, i.e., the serial interval. These data can be used as inputs for statistical models to generate estimates of R_0 directly; or can be used to estimate the parameters of compartmental models of disease transmission from which R_0 is subsequently inferred. Initially, modellers used data on the number of internationally exported cases from Wuhan to estimate the basic reproduction number in Wuhan as 2.68 (95% credible interval 2.47–2.86), corresponding to an epidemic doubling time of 6·4 days (5·8–7·1 days) [13,14].

Subsequent estimates of R_0 in Wuhan from several modelling studies, including both statistical and compartmental-based approaches, have ranged from 1.40 to 6.49 with a median value of 2.79 (IQR: 1.16) [15]. Limited data forced early authors to assume median serial intervals similar to those observed for SARS-CoV-1 (8.6 days) and MERS (7.6 days); however, later analyses have suggested a shorter median serial interval of 4.0 days (3.1–4.9 days) for SARS-CoV-2 [16] implying that some original estimates of R_0 may need to be revised down (since R_0 estimates are positively correlated with the serial interval for a given epidemic curve) [8,9,11].

SIMPLE MODELS OF DISEASE TRANSMISSION

In the absence of detailed epidemiological data, modellers often begin with simple models of disease transmission which only differentiate individuals according to disease status. For the case of COVID-19, which has an appreciable incubation period prior to the onset of active infection, the most appropriate model of this type is the Susceptible-Expose-Infected-Recovered (SEIR) model [12] shown in Fig. 1 below.

The main strength of these simple constructions is that they allow straightforward computation of important results, including the eventual proportion of the population infected in an unmitigated epidemic (i.e., the final size) and the proportion immune required to extinguish ongoing transmission (i.e., the herd immunity threshold). As an example of the utility of these simple constructions, in Fig. 2 we plot both the final size and herd immunity threshold as a function of the reproduction number to determine the reduced reproduction number capable of achieving the desired level of herd immunity (i.e., that corresponding to the original reproduction number 2.5).

These simple models can also guide long-term disease control. For example, they show the vaccine protection target should be at least 60%, provided the vaccine prevents infection, not just severe disease. They can also be used to assess whether the first wave has led to herd immunity and hence the risk of reintroduction in countries with local elimination [17]. More complex models add nuance to these estimates, for example elimination is more likely in the presence of transmission heterogeneity [18]. This is because in a highly heterogeneous infection most people infect few others, and when numbers become small, fade-out of the epidemic is more probable. Similarly establishing infection in naïve populations requires a greater number of introductions of people with infection.

Fig. 2 also illustrates the concept of 'epidemic overshoot', represented by the difference between the red and blue lines. For example, if an infection with $R_0 = 2.5$ (similar to COVID-19) spreads rapidly in an immunologically naïve population, it will infect up to 90% of the population. However, if its spread is sufficiently restrained by public health measures for natural immunity to slowly accrue, then only 60% of the population will become infected even if these restraints are subsequently lifted.

ESTIMATING THE IMPACT ON TRANSMISSION AND DISEASE OF SPECIFIC INTERVENTIONS

Throughout the global outbreak, many different public health interventions and government-imposed restrictions on human movement have been initiated to curtail transmission. To quantify the effect of these different interventions on the spread of disease, modellers estimate the time-varying effective reproduction number, R_t [19,20]. This quantity is analogous to R_0, but also accounts

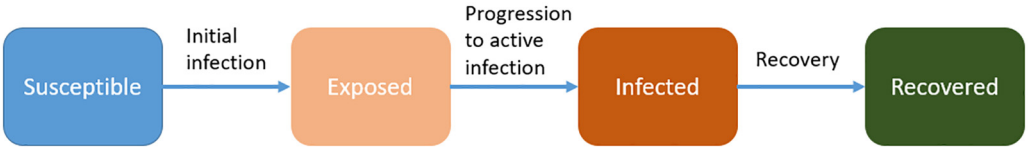

Fig. 1. In the SEIR model individuals are stratified into four broad categories according to their infection status: individuals susceptible to infection (S); exposed individuals that have been infected but have not yet developed active infection (E); infectious individuals (who may be pre-symptomatic, asymptomatic or symptomatic) (I); and individuals who have recovered from infection and are immune, or removed from the population through death (R).

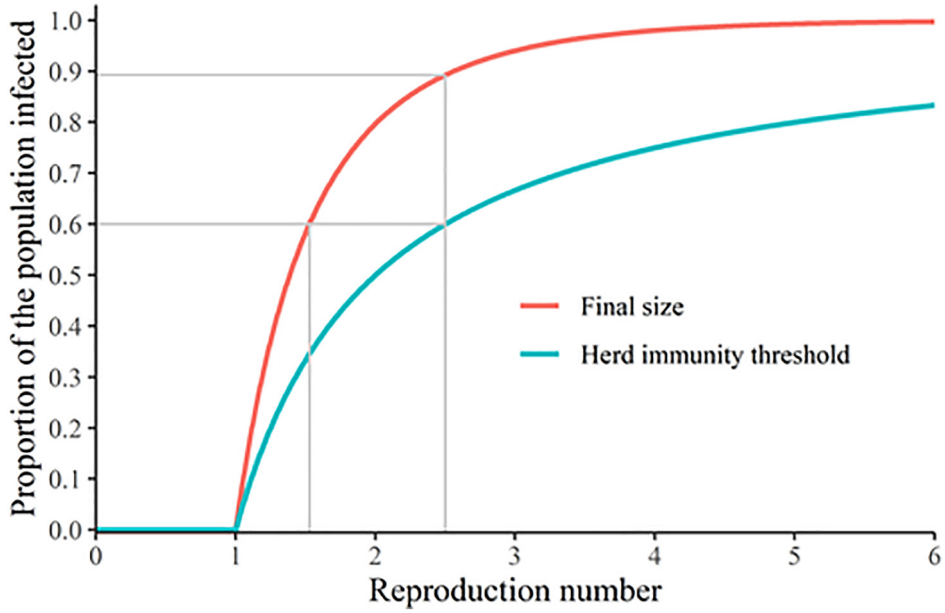

Fig. 2. Final size of an epidemic (red) and the herd immunity threshold (blue) as a function of the reproduction number. An R_0 of 2.5 under homogeneous mixing assumptions leads to a population attack rate of nearly 90%. However, an immunity rate of 60% is sufficient to prevent an epidemic. One strategy, called mitigation, is to reduce the reproduction number sufficiently to achieve herd immunity. In the simplified illustration above, this would be achieved by reducing the effective reproduction number to 1.53 throughout the course of the epidemic's first wave.

for (1) any appreciable depletion of the susceptible population and (2) behavioural changes or public health interventions that inhibit person-to-person contact or individual infectivity (see Fig. 3).

The effective reproduction number (R_t) in Wuhan – estimated using a stochastic (i.e., random) transmission model [21] – fell from a median baseline value of 2.35 (1.15–4.77) one week before travel restrictions were introduced on Jan 23, to 1.05 (0.41–2.39) one week after, representing a 55% reduction in transmissibility. Elsewhere, the initial reproduction numbers R_0 across 11 European countries were estimated at 3.87 (3.01–4.66) [13]. Following the implementation of various interventions, the time-varying reproduction numbers fell by more than 60% to a mean value of $R_t = 1.43$, ranging from 0.97 (0.14–2.14) for Norway to 2.64 (1.40–4.18) for Sweden [13].

The rapid implementation of public health responses obscured the separate contributions of each intervention measure on overall transmission levels. As a result, alternative data sources on human movement and mixing have been useful for delineating prominent sources of transmission in the community and ascertaining which restrictions can be safely relaxed without compromising control.

One rational approach is to estimate different sources of community transmission from contact matrices [22,23]. Changes in contact patterns (both number and intensity) are a fundamental driver of changes in the reproduction number. Measuring contact-induced changes in the reproduction number can be used to predict changes in response to relaxing restrictions, which is critical for determining policy on exiting lockdown. An early analysis of the Wuhan outbreak used synthetic contact matrices to show that workplace closure is likely to have a much greater impact on cases averted than school closures [24]. Davies et al. showed that contact patterns were insufficient to account for age-based case differences and inferred that a lower clinical fraction or lower susceptibility or both are at play. Models examining public health action in Australia also suggest that the majority of transmission is occurring in the 30–50 year age groups [25].

MODELLING ESTIMATES OF INFECTION SEVERITY AND AGE DEPENDENCY

Calculating mortality rates among reported cases (case fatality ratio, CFR) is particularly difficult during the early stages of an epidemic, and these inaccuracies and biases flow through to estimates of the impact of the public health measures to contain COVID-19 [26]. To-date, estimates of the burden of COVID-19 – infection rates, case rates, hospitalisation and fatality rates – have primarily used clinical and laboratory-confirmed case definitions in a variety of surveillance settings (Fig. 4) [27]. Biases introduced by delayed patient outcomes and case under-ascertainment can lead to under- and over-estimates of these rates, respectively. For instance, case fatality rates based on patient outcomes recorded from the Wuhan epicentre in early January were as high as 15%, owing to under-ascertainment of cases. Modelling strategies to reduce bias have since been used – accounting for data censoring

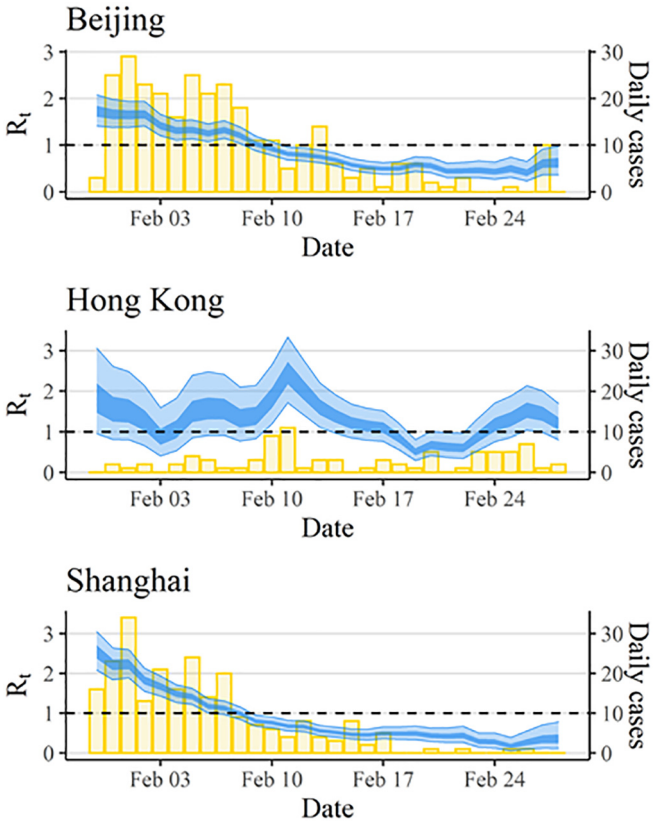

Fig. 3. Estimates of R_t in Beijing, Hong Kong and Shanghai Provinces throughout February 2020. The dark (light) blue shaded band corresponds to the 50 (95)% credible interval covering the 25–75th (2.5–97.5th) percentiles of the posterior estimates. Also shown in gold are the number of new daily cases as provided by the Johns Hopkins University public database [3]. Note, these R_t estimates are based on crude confirmed case counts and do not account for reporting delays, imported cases or variations in case ascertainment.

and estimating undetected cases – with recent CFR estimates converging on much lower values around 1–2% [28,29].

Mortality as a fraction of all infected individuals (infection fatality ratio, IFR) is in many ways more important than the case fatality ratio, as IFR provides accurate estimates of the expected total attack rate/mortality rate/severe infection rate in the whole population. IFR also provides estimates of the underlying cumulative infected population (therefore immune fraction) over time (assuming mortality is accurately reported – which is not always the case [30]). IFR estimates are challenging as they need to incorporate both unreported cases and asymptomatic infections in their denominator. To achieve this, Verity et al. used international travellers tested for COVID-19 regardless of their symptom status, finding an overall IFR of 0.66% [31]. Similarly, estimates from France found an IFR of 0.7% [32].

A striking feature of these two studies [31,32] and indeed all COVID-19 analyses is the very low number of children diagnosed as cases [33]. IFR ranged from 0.00260% in 0–9 year olds to 13.4% in those aged 80 years and over in Verity et al. [31] and from 0.001% in individuals less than 20 years of age to 10.1% in those over the age of 80 in Salje et al. [32] – a 10,000-fold relative risk ratio.

So for a given infection, children are much less likely to have severe disease, but are they less infectious or less susceptible to infection or both? Here studies differ. Population screening studies in Iceland and Italy have found lower rates of infection in children, including when asymptomatic populations were tested and likely equivalent rates of exposure between adults and children [34,35]. By contrast, a study on household contacts suggested that child contacts are as likely to become infected as adult contacts [36]. Similarly, there is a lack of consensus about the infectiousness of children with disease relative to adults, although there have been very few reported instances of children infecting others globally.

Despite the efforts of analyses to overcome biases in clinical cohorts, the accuracy of estimates will be markedly improved when sero-epidemiological data become available. Such studies measure the presence/absence of SARS-CoV-2-specific antibodies in random samples of the population, to infer the extent of cumulative infection with the virus and (by extension) population immunity against COVID-19. Because sero-epidemiological data are broad-based, random and do not require current infection, they provide critical insights into COVID-19 transmission – allowing models to significantly reduce the uncertainty in the parameter estimates of clinical severity, asymptomatic infection and infection fatality risk [23]. For example, measuring sero-prevalence by age will confirm whether children are less susceptible to infection, or just less likely to get symptomatic disease.

Several serological tests for COVID-19 are currently available with differing accuracy and a significant number of sero-prevalence studies have been completed in several countries. In

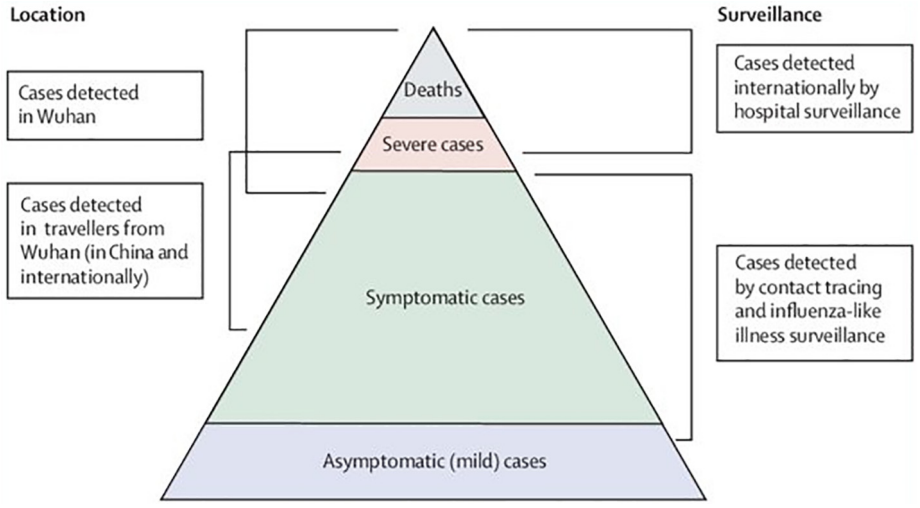

Fig. 4. Adapted from Verity et al. [27] CC BY 4.0, shows the pyramid of case severity and the different surveillance activities that capture these levels of severity.

Europe, estimated sero-prevalences have ranged from approximately 4 to 9% (including 4.4% in France [24] and 8.7% in Switzerland [25]) even in the hardest-hit countries [37]. Whilst these estimates are high relative to reported case counts, they remain very low compared with the goal of reaching 'herd immunity', which would allow restrictions to be lifted and a return to normal life. Hence all countries need to be alert to second waves of infection as soon as lockdown measures ease to the extent that the reproduction number exceeds one.

Testing, both for active disease and past infection through sero-surveys will continue to be crucial over the coming years. There is a need to assess the proportion of recovered individuals over time, the duration of the immunity and probability of reinfection. Long-term and large-scale longitudinal serological follow-ups need to be conducted so that models can make inferences about the burden of COVID-19 in different populations, age groups and the potential risk of the different waves of this pandemic.

ESTIMATING THE IMPACT ON LOW- AND MIDDLE-INCOME COUNTRIES (LMIC) AND OTHER VULNERABLE GROUPS

Demographic, epidemiological, and socioeconomic factors will likely result in differential impacts of COVID-19 on low- and middle-income countries (LMIC) and other vulnerable groups compared with high resource settings. Using standard compartmental models (e.g., Fig. 1), we can use population age structures, mixing matrices, and case fatality ratios to capture dynamics in low resource settings. For example, transmission models for LMIC typically employ younger age distributions than high-income countries, which could mitigate disease burden if children are less susceptible to COVID-19 disease and/or less infectious [38].

In contrast, social mixing patterns and altered infection fatality rates in LMIC and other vulnerable groups (e.g., prisoners, refugees, migrant workers, and indigenous communities) may lead to greater epidemic impact. In such settings, people often live in close quarters and there may be high intergenerational mixing, while inadequate sanitation may further intensify the likelihood of transmission given contact. For low income settings, higher case fatality ratios may better reflect the elevated risk of death among infected individuals, due to limited availability of healthcare resources and personal protective equipment, poverty and the high prevalence of comorbidities. A further challenge for modellers arises from the often poorer quality of input data supplied by weak surveillance systems, which limit the ability to calibrate and validate models in such settings.

Impacts of other infectious diseases historically and current models of COVID-19 in LMIC suggest there will be a considerable difference in mortality between high-income and low-income countries. For instance, mortality rates from the 1918–1920 Spanish flu pandemic were significantly higher in Asia, Sub-Saharan Africa, and Latin America compared with North America and Europe [39]. To date, there are no models for COVID-19 in Latin America despite the shift in the epicentre to South America [2]. However, there have been a limited number of modelling studies for Africa that provide a framework for modelling COVID-19 more broadly for LMIC. For example, one study used synthetic contact matrices, shifted the age-specific probability of becoming severely infected (compared with estimates from high-income countries), and simulated community led interventions such as neighbourhood house swaps. The results indicated that an unmitigated epidemic would lead to millions of clinical cases (e.g., 4.1 million during the first year of the epidemic in Niger) and that interventions would only confer partial protection [40].

LIMITATIONS OF COVID-19 MODELLING

Whilst models can be very useful tools in the COVID-19 response, there are limitations to the information they can provide and how they can be used. Early in the epidemic, many critical features of the disease are highly uncertain, and this uncertainty may propagate through important model results. Presently, we still lack a complete understanding of the factors that influence transmissibility and disease severity, how these features vary across populations and settings, and the prevalence and epidemiological significance of asymptomatic infections.

Estimates of the incubation period are highly prioritized, as so much of the public health response hinges on this characteristic. Furthermore, inferred reproduction numbers are highly correlated with the serial interval (which is dominated by the incubation period). As an illustration of the challenges in estimating fundamental disease parameters, we reviewed the estimates for the incubation period (Textbox 1) showing the range of results arising from different settings and surveillance methods (see supplementary material).

We conducted a systematic review of the incubation period of COVID-19, a key epidemiological parameter for understanding its transmission dynamics. Our findings were as follows:

- 20 eligible studies were identified that reported the incubation period of COVID-19.
- 17 of these 20 studies were based on data from China.
- 13 of these 20 studies reported on fewer than 100 patients.
  - o 12 of these 20 studies reported the mean incubation period.
- These 12 studies estimated a mean incubation period of 3.6–7.4 days.
  - o 12 of these 20 studies reported the median incubation period.
- These 12 studies estimated a median incubation period of 3–12 days.

These findings highlight that:

- There are considerable methodological issues in estimating even apparently simple epidemiological quantities.
- Estimates of key epidemiological parameters are often derived from well-described groups of patients who are very small in number compared to the total number of global cases
- Epidemiological parameters of COVID-19 cannot be accurately inferred from other related viruses (e.g., SARS-CoV-1).

CONCLUSIONS

Epidemiologists and modellers around the world have worked at an impressive pace and amid enormous uncertainty to provide important insights into SARS-CoV-2 transmission to guide public health action, although many important knowledge gaps remain. The duration of infectiousness, the duration of protective immunity after infection and/or disease, the effect of "superspreading" in transmission and the true burden of COVID-19 in different populations remains poorly quantified. Several epidemiological studies collecting COVID-19 data are underway and will help to understand these quantities better.

Since the COVID-19 epidemic began nearly six months ago, models have shaped our understanding of how the disease spreads, who is most vulnerable and who presents the greatest risk, and the impact of interventions on curtailing transmission. This information has likely helped avert millions of cases and thousands of deaths globally. Despite this enormous accomplishment, there are still many issues that create uncertainty in model estimates and projections. These issues do not discount the value of models, but emphasise the importance of acknowledging the uncertainty of modelling forecasts.

In epidemiological modelling, the "no model fits all" approach needs to be taken into account. The majority of the current COVID-19 models have been developed and fitted in high income countries that were affected early in the course of the pandemic and where there is infrastructure for modelling. Most of the unique cultural and social conditions that exist in LMIC and other vulnerable populations have not been taken into account, adding further limitations to current model projections. The more we know about the transmission dynamics of SARS-CoV-2 in different settings, the better our models will be able to explore and estimate potential long-term epidemiologic outcomes.

Whilst models will always be imperfect simulations of reality, limited by our understanding of the disease and the unique factors shaping transmission dynamics in different settings, they will continue to play an important role in guiding policies through this pandemic.

DIRECTIONS FOR FUTURE RESEARCH

- Improving quality of parameter inputs for models.
- Adapting models to different contexts, particularly for low- and middle- income countries.
- Incorporating a better understanding of the extent of asymptomatic spread and the duration of protective immunity into models.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prrv.2020.06.014.

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