Epidemics 38 (2022) 100546

Contents lists available at ScienceDirect

Epidemics

journal homepage: www.elsevier.com/locate/epidemics

Challenges for modelling interventions for future pandemics

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ARTICLE INFO

Keywords:
Mathematical models
Pandemics
Pharmaceutical interventions
Non-pharmaceutical interventions
Policy support

ABSTRACT

Mathematical modelling and statistical inference provide a framework to evaluate different non-pharmaceutical and pharmaceutical interventions for the control of epidemics that has been widely used during the COVID-19 pandemic. In this paper, lessons learned from this and previous epidemics are used to highlight the challenges for future pandemic control. We consider the availability and use of data, as well as the need for correct parameterisation and calibration for different model frameworks. We discuss challenges that arise in describing and distinguishing between different interventions, within different modelling structures, and allowing both within and between host dynamics. We also highlight challenges in modelling the health economic and political aspects of interventions. Given the diversity of these challenges, a broad variety of interdisciplinary expertise is needed to address them, combining mathematical knowledge with biological and social insights, and including health economics and communication skills. Addressing these challenges for the future requires strong cross-disciplinary collaboration together with close communication between scientists and policy makers.

1. Introduction

In the first two decades of the 21st century, we have witnessed several outbreaks of infectious diseases that expanded across several continents (SARS, Zika, MERS), caused a large number of deaths (Ebola), or grew out to a pandemic (influenza 2009, SARS-CoV-2). By far the

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[1] www.gla.ac.uk/scrc.

https://doi.org/10.1016/j.epidem.2022.100546
Received 5 July 2021; Received in revised form 4 February 2022; Accepted 9 February 2022
Available online 11 February 2022
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largest impact on humanity can be attributed to the ongoing SARS-CoV-2 pandemic, that has affected almost all countries in the world in ways unimaginable before the year 2020. All these outbreaks required significant efforts in mitigation and control measures, since they caused millions of deaths worldwide and had enormous economic and social impacts.

From the start of the SARS-CoV-2 pandemic, mathematical modelling has played a key role in supporting policy makers in their decisions about control measures. Politicians and society alike have looked to modellers to provide them with predictions about the future course of the pandemic, with assessments of which interventions should work, and with guidance for how to interpret the developing numbers of cases, hospitalizations, and deaths (McBryde et al., 2020). This puts a large responsibility to those who develop mathematical models and analyse intervention strategies. Fortunately, there is a well-established toolbox for infectious disease modelling, based on the pioneering work of Kermack and McKendrick and many following generations of mathematical modellers (Diekmann et al., 2012). The theory of infectious disease dynamics described in terms of differential equations is grounded in dynamical systems theory, and has led to the development of key concepts such as the basic reproduction number. Nevertheless, there remain challenges for modelling of infectious diseases and interventions, many of which became clearly visible during the unfolding pandemic of SARS-CoV-2 (Thompson et al., 2020) and are discussed in detail in Marion et al. (2022).

Modelling can be useful in assessing impact of interventions, with three modelling approaches widely used: (i) compartmental models (deterministic or stochastic), in which the population is subdivided into a number of mutually exclusive groups and contacts are assumed to be instantaneous and random, (ii) network models, in which contacts are explicitly described between pairs of individuals and can be either static or dynamic, and (iii) individual (or agent) based micro-simulation models, in which individual agents and their interactions are simulated as a stochastic process with probability distributions describing population heterogeneity and transitions. Note that while network models are individual based models, this is not necessarily true vice versa. These approaches differ in the amount of information about individuals and their contacts that is included ranging from very explicit in individual based models to aggregated in compartmental models. In network models, details of the contact structure is taken into account, while individuals still may be alike with respect to other features. While individual based models seem to be most realistic, they require information on many more parameters and are mostly not amenable to mathematical analysis. Compartmental models on the other hand are more readily parameterised, but may lack the level of detail needed to answer policy related questions. Another important issue, that is especially relevant for assessing non-pharmaceutical interventions (NPI) relying on changes of contact networks and their transmissibility, is that all approaches have major drawbacks in addressing structural aspects on a level between the individual and population levels. We need to understand better the mesoscopic level, if we really want to assess the impact of interventions such as social distancing, closing of schools and workplaces, contact tracing, and travel restrictions on epidemic spread. While it is possible to describe the contact network in all details in an individual based model, it is time consuming to perform extensive model analysis including sensitivity analyses. For network models, some theoretical results are available, but mostly for networks with structure that does not properly reflect real contact patterns. Finally, with compartmental models it is hard to take correlations between connected individuals into account without generating an exploding number of equations.

Thus, the overriding challenge as with all modelling is to **find models that are complex enough to reflect sufficient details of the system, but simple enough not to get lost in the jungle of details.** Ideally, we need tools to describe exactly the structures of interest in a generic way, i.e., such that one can draw conclusions that are valid for a large range of parameter values and situations.

In application of modelling interventions for policy support, the main challenge is the **need to clearly define objectives and aims of modelling in interaction with policy makers**, who typically consult mathematical modellers to determine any intervention strategies that may need to be introduced in order to minimise the impact of an ongoing epidemic (Grimm et al., 2020). In such circumstances, it is vital that policy makers define what they consider the main aims of interventions, or more technically, the *objective function* that they are looking to minimise (e.g. Gösgens et al., 2021). For human pathogens, the objective may be simply to minimise the number of individuals getting sick or dying from infection, whilst for livestock or plant crop diseases, it may be important to minimise the direct cost of an outbreak to the agricultural industry. The aim of an intervention, which may also change over time, can often critically affect which control policy is deemed optimal. Also, there may be the question of transportability of interventions: an intervention that works in one country is not necessarily successful elsewhere, so policy makers have to take the specific circumstances into account that are important in their countries, but maybe cannot be included in models. Modellers and policy makers need to determine in interaction which questions can and should be answered by modelling and what the limitations of models are (Hadley et al., 2021).

In this paper, we reflect on what the above challenges mean for various aspects of mathematical modelling of interventions, e.g., for data collection and availability, for biological parameters that affect intervention effectiveness, for the social structure that may be targeted by interventions, and for the economic impact of intervention measures (Fig. 1). We limit our discussion to human-to-human transmission through direct contacts involving a pathogen such as virus or bacteria. We build on progress since publication of an earlier series of challenges paper (Lloyd-Smith et al., 2015), and delineate challenges that remain or have emerged since (see Table 1 for an overview of the key challenges). One of the main challenges that was addressed by Funk et al. (2015), namely incorporating behaviour into mathematical models, had proven to be crucial during the SARS-CoV-2 pandemic, but also challenges around vaccination (Metcalf et al., 2015) and around emergence of pathogens (Gog et al., 2015) are highly relevant. We hope to give inspiration to future generations of mathematical modellers who might be faced with dealing with a future pandemic and are struggling to give good advice to policy makers on which interventions may be effective in a given situation.

2. Data challenges relating to interventions in a future epidemic

Biological characteristics and transmission routes strongly determine

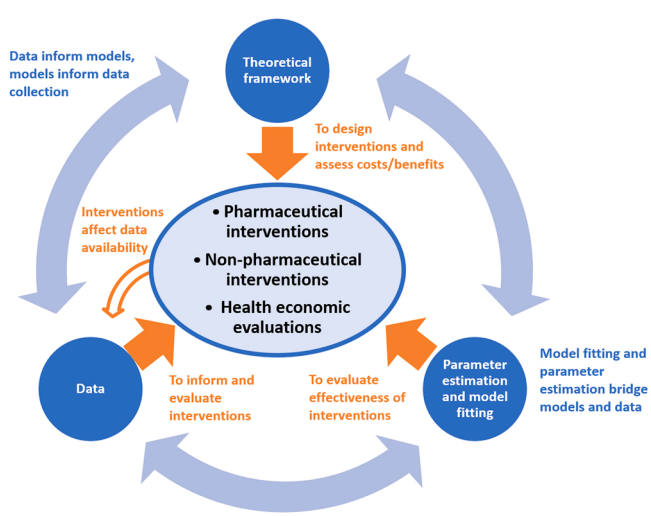

Fig. 1. Relationships between interventions and methodological aspects.

Table 1
Key challenges.

Topic	Key challenges
General Section 1	• Find models that are complex enough to reflect the system we want to describe in sufficient detail, but simple enough so that we do not get lost in the jungle of details. • Need to clearly define objectives and aims of modelling in interaction with policy makers
Data related to interventions Section 2	• Designing in advance data collection studies and statistical methods to overcome biases in biological data. • Developing methods to account and correct for lags and scarcity in surveillance data • Wider accessibility to mobility and behavioural data to quantify how interventions change contact patterns.
Mathematical framework Section 3	• Developing robust, flexible modelling tools that are readily available to plan interventions during epidemics • Designing public health measures that match the temporal and spatial scale of interventions with those of transmission • Translating modelling theory about pathogen evolution into epidemic-specific interventions that limit the risk of variants of concern emerging
Pharmaceutical interventions Section 4	• Modelling population heterogeneity (e.g., in vaccine efficacy, uptake, transmission) to investigate optimal vaccine prioritisation and allocation • Modelling vaccine strategies in a highly dynamic environment (including time-varying vaccine rollout, introduction of different vaccines with single or multiple doses, changes in NPIs) • Incorporating mechanisms to describe how treatment affects epidemic dynamics • Defining and modelling elimination
NPI Section 5	• Capturing adherence and take-up of NPIs across heterogeneous populations and contact networks • Modelling clustering in behaviour and its relation to clustering in e.g. geography or socioeconomic status • Incorporating the factors responsible for changing behaviour (uptake and adherence) over time.
Parameter estimation,Model fitting Section 6	• Parameterising multiple layers of interventions and their time-varying impacts • Statistical identification of different overlapping intervention impacts • Intervention impact detection across models
Economic modelling Section 7	• Including macroeconomic costs is critical to understand the full impact of infectious diseases and their control measures • Financial and non-financial constraints matter and need to be reflected in models • Different groups experience diseases and interventions differently, and models need to represent inequities better

which interventions could be effective, and on which time scale interventions should be rolled out. While data are unavoidably scarce for a new emerging disease, for various types of data challenges remain in later epidemic phases. Here we focus on data challenges related to modelling interventions, though other data challenges can emerge during an epidemic (Marion et al., 2022; Shadbolt et al., 2022). While most of these challenges are inherent to the nature of pathogen transmission, they also depend importantly on the availability of public resources, whereby data challenges are often enormously amplified in low- and middle-income countries (LMIC).

2.1. Biological and epidemiological data

Transmission models require key biological parameters, such as the duration of infectious period, infectivity of symptomatic and asymptomatic cases, hospitalisation probabilities, and infection fatality ratios. Intervention planning can then explore how changes to these model parameters influence future epidemic trajectories. A fundamental challenge is to link biological quantities (e.g., duration of viral shedding, antibody response) to epidemiologically relevant information (e.g., effective transmission probability, protection from infection), requiring the combination of biological and epidemiological studies. In the case of a newly emerging disease, however, not only are fundamental biological data scarce, but they are also affected by biases because of their dependence on uncertain information obtained from reported cases and surveillance data. Moreover, time interval distributions are sensitive to truncation and censoring biases when data are collected while the epidemic is expanding (Scalia Tomba et al., 2010; Park et al., 2021). In later phases, identified cases still depend heavily on the adopted surveillance strategy, and parameters like time interval distributions are potentially affected by intervention measures. **Designing data collection studies that overcome these biases, or statistical methods that account for them, remain fundamental issues for obtaining reliable parameter estimates.** We can define reliable to be either unbiased point estimates, uncertainty intervals that account for all potential aspects of uncertainty in the modelling process, or estimates that are unlikely to change drastically under realistic changes to the system. It will predominantly be case-specific as to which of these we need, if not all, but here we are specifically relating this to potential structural biases in data collection.

2.2. Surveillance data

Surveillance data (e.g., case notifications, hospitalisations, mortality but also excess mortality) represent the most direct monitoring tools of an ongoing epidemic. These data are used to estimate biological parameters, monitor the prevalence and severity of the disease, and calibrate transmission models that evaluate the impact of interventions. Regarding model calibration, special consideration should be given as to whether to use case notification, hospitalisation, or mortality data, or some combination of these. All empirical datasets may contain potential biases, depending on how they are assembled. Whilst case notification data may be sufficiently informative for pathogens with a low proportion of asymptomatic cases, such as the severe acute respiratory syndrome (SARS), they pose challenges for pathogens like SARS-CoV-2, characterised by a high proportion of unreported asymptomatic or mildly symptomatic cases. Testing protocols may change significantly during the epidemic, which can further disrupt fitting transmission models to cases data.

Hospital data tend to be more reliable because hospital-seeking behaviour is less likely to change over time, and are therefore used ubiquitously in modelling studies (Di Domenico et al., 2020; Rozhnova et al., 2021; Viana et al., 2021; Funk et al., 2021). However, the potential overwhelming of the healthcare system (with consequent shortage of medical and data-collection personnel) and an evolving understanding of when to seek medical attention might shift during a pandemic. Moreover, despite being routinely collected by hospitals, hospital data are rarely publicly available and, especially at the beginning of the epidemic, they are often not aggregated at a national scale. Especially in LMIC, high degree of inequities may impose a highly heterogeneous collection of data within the countries or data might not be collected at all. Also, there may be differing definitions in different countries, e.g. what constitutes an ICU bed, which makes country comparisons difficult. **Designing protocols of data collection and aggregation into publicly available datasets,** together with strategic margins of flexibility so that the protocols could be promptly adapted to the ongoing outbreak, could partially mitigate these biases. This would provide a framework that ensures consistency in data collection from the beginning of the outbreak (Shadbolt et al., 2022).

A further challenge when using surveillance data is that they are inevitably lagged relative to infections, upon which

interventions aim to act, due to the concatenation of incubation period and test- or care-seeking behaviour. Understanding these lags is vital when designing intervention timelines for two main reasons: first, to avoid severe consequences when the effect of an intervention manifests itself in the surveillance data only after a consistent delay (Pellis et al., 2021); second, to facilitate their later assessment. Gradual changes in policies can ensure windows of opportunity for disentangling the effect of different interventions and evaluating their effectiveness.

2.3. Seroprevalence data

For pathogens with high proportions of unascertained infections, models fitted only to surveillance data may not be sufficient to estimate the true incidence or prevalence. Here, seroprevalence data become fundamental to calibrate the models (Rozhnova et al., 2021; Viana et al., 2021) or, where available, community infection surveys. Moreover, longitudinal seroprevalence data, and individual data on the duration and extent to which prior infection confers protection against future infections, are required to investigate the impact of interventions on longer timescales. However, during initial stages of an epidemic **these data are usually available for either relatively short observation periods, small sample sizes, or selected populations**. Also, in LMIC, often there is capacity to conduct seroprevalence studies, but eventual low resource availability, lack of timely acquisition of supplies, and high inequities place barriers on gathering these data. A further challenge in using seroprevalence data can be due to the sensitivity of serology to identify individuals with prior infection. For example, there is growing evidence that SARS-CoV-2 antibodies may be below the level of detection for persons who experienced asymptomatic or mild infections (Burgess et al., 2020), and that antibody levels decline over time. Additionally, it is not clear to what extent a negative serological result denotes lack of immunity. Tackling these challenges is vital for modelling interventions in the long term.

When designing interventions, it is important to understand transmission within different settings. Genetic sequencing data can facilitate investigation of outbreaks by reconstructing potential transmission trees, e.g., to discriminate within-household transmission from between-household transmission (Marion et al., 2022; Swallow et al., 2022), or identify nosocomial transmission. Genetic sequencing is also important for monitoring the emergence of novel variants, which may adversely affect intervention policies, through, for example, increased transmission or vaccine escape mutations. **Genetic sequencing capacity is and will likely remain in the future highly heterogeneous across countries,** as manifested during the COVID-19 pandemic. Especially in LMIC the lack of sequencing capacities may severely hamper the timely sequencing of pathogens. This can skew the observation of any new variants of concern, leading to delays in identifying and adapting to novel variants.

2.4. Behavioural and adherence data

Scenario simulations exploring the impact of interventions require data on people';s behaviour and changes thereof as a response to interventions. For sexually transmitted pathogens, the relevant measure is the number of new sexual partnerships per unit of time; partnership duration, whether partnerships are overlapping in time or not, (Morris and Kretzschmar, 1997) and mixing between population subgroups with different sexual risk behaviour can be important quantities (Rozhnova et al., 2016, Erens et al.). For airborne diseases, an individual's behaviour is measured by the number of transmission-relevant contacts a person has per day in a specific setting. The baseline age-dependent mixing patterns of contacts relevant for airborne transmission are available for a few countries (Mossong et al., 2008) and have been projected for other countries for which social contact data are not available (Prem et al., 2017; Mistry et al., 2021). There are fewer contact data sources when it comes to evaluating the impact that different interventions might have on mixing. As part of the response to COVID-19, several countries have conducted contact surveys during different stages of the pandemic (Backer et al., 2021; Jarvis et al., 2020; Zhang et al., 2020), which have been used successfully in modelling studies (Rozhnova et al., 2021; Kucharski et al., 2020).

Understanding adherence to regulations is vital in evaluating past and designing future interventions. However, adherence data may be challenging to obtain. Partially to address this issue, the SARS-CoV-2 pandemic has showcased the importance of digital resources (such as contact tracing or health reporting apps). These tools allow the collection of large amounts of data while minimising delays in collection, and are widely accessible by many portions of society (Colizza et al., 2013). However, they have also revealed a strong hesitancy by many users mainly due to data privacy concerns (Blasimme and Vayena, 2020). Where government apps may struggle due to public confidence, private health apps could help to fill the void. Throughout the COVID-19 pandemic, various health apps have attempted to collect data, such as symptom profiles, and adherence data (Chidambaram et al., 2020). Reliance on digital apps, however, would further intensify the discrepancy of data availability between high- and low/middle-income countries, where digital tools are not widely available to the community.

Another challenge with adherence data is that high adherence might not correlate with contact reduction for some portions of society: for instance, essential workers might report high adherence to social distancing measures, while still performing most of their usual activities. Hence, surveys may be better focused on quantifying behaviour rather than adherence. Data collection apps and surveys strategically designed in collaboration between modellers, behavioural scientists, and statisticians may assume a fundamental role in planning behavioural data collection before, during, and after an epidemic, to optimise the available data both for prospective planning and retrospective assessment of the effect of interventions (Salathé et al., 2012). Mobile telephone data (Grantz et al., 2020; Oliver et al., 2020; Chang et al., 2021) and mobility data (Google, 2021) can also be leveraged to measure behavioural changes and adherence, and can be incorporated into transmission models. However, while the latter remain public, mobile telephone or airline data might not be accessible to all researchers. Wider accessibility to local and global mobility data might become a fundamental support to models for future pandemics, and may help to fill the lack of behavioural studies in countries with limited national resources. **Even with wider accessibility, a challenge still remains here pertaining to finding the acceptable level of aggregation that balances out privacy issues whilst accurately informing models of mobility patterns.** This is also discussed in Swallow et al. (2022).

2.5. Vaccination data

Vaccinations and treatments are key interventions for managing disease outbreaks. However, these are often not available at the start of a pandemic and need to be developed throughout its course (for example Ebola and COVID-19). When modelling the rollout of such interventions, their effectiveness has to be estimated as quickly as possible. The challenge is estimating effectiveness of interventions from noisy data, particularly when multiple interventions are implemented simultaneously (see also Section 4.1). In addition to the challenges involved in designing studies to estimate vaccine efficacy in the context of an evolving pandemic (Madewell et al., 2021), the way the data are collected and recorded also present challenges (Lipsitch and Dean, 2020). For example, vaccination data linked with other health care data or age-stratified vaccination data may not be readily available, thus limiting the opportunity to estimate the impact of the vaccine deployment on symptoms, transmission, risk of hospitalisation and death across different age groups. Finally, the uptake of vaccination is of utmost importance when assessing the impact of vaccination as increasing vaccine hesitancy has been shown to hamper the success of vaccination programmes in the past. Data quantifying vaccine hesitancy

would be vital for modelling vaccine impact (Shadbolt et al., 2022). Modelling the spread of vaccine hesitancy, such as through social media networks, may inform what type of data needs to be collected to parameterise models.

3. Challenges in developing a theoretical framework for understanding intervention impact

3.1. Epidemiological distributions and within-host dynamics

One of the most common theoretical frameworks for understanding transmission is compartmental modelling, in which individuals are grouped according to their infection and/or symptom status or other determinants (Keeling and Rohani, 2011). A basic assumption in compartmental models is that all individuals within a compartment are the same. Deterministic or stochastic compartmental models can be used to represent epidemic dynamics, and the impacts of interventions can be assessed by making relevant adjustments to the model (e.g., altering the values of model parameters or including new compartments). Although a very versatile tool, compartmental models have their limitations and should be complemented by other approaches. Standard compartmental models are based on the assumption that individuals remain in compartments for exponentially distributed periods, while Gamma or Lognormal distributions often provide more accurate fits to data. Similarly, infectivity may be variable during the infectious period, which can be accounted for using age of infection models that assume continuous "infectivity curves" (Handel et al., 2013; Diekmann et al., 2021), sometimes approximated using multiple compartments of infectious individuals (Cunniffe et al., 2012; Hart et al., 2020). Although these elements of a framework for describing epidemics based on realistic biological distributions exist, and relationships between distributions of epidemiological time periods and key epidemiological parameters (e.g., reproduction numbers and epidemic growth rates) are well known, the challenge remains to integrate these components into **flexible and readily available epidemiological modelling tools that can be adapted for specific epidemics.**

Similar arguments hold for the task of incorporating waning immunity or partial immunity in compartmental models (Heffernan and Keeling, 2009). Boosting and waning of immunity is often included by distinguishing various levels of immunity and transitions between these levels. An alternative approach is to model waning immunity as an exponential decay process with boosting events as jumps in the immunity level (Diekmann et al., 2018). Combining within-host modelling of the immune system with between-host modelling of transmission dynamics to assess impact of interventions is an area for further research. A related challenge is to **develop a framework to allow interpretation of serological data collected in populations to assess the impacts of interventions** (Teunis et al., 2012; Hens et al., 2012).

3.2. Time scales and geographical scales

Another challenge is to **design interventions in which the scale of interventions is matched to the scale of transmission,** both geographically and temporally. Assessments of interventions sometimes rely on simple models that do not account explicitly for the geographical or spatial scale of transmission. For example, the level of vaccination required to achieve herd immunity is often stated, but standard approximations assume that the population is well-mixed. The time-dependent reproduction numbers can be tracked to assess the effectiveness of interventions and the level of interventions required to bring an epidemic under control (Wallinga and Teunis, 2004; Cori et al., 2013; Thompson et al., 2019), but are delayed by generation time intervals.

While the effects of some interventions may not depend on the spatial scale of transmission - for example, population-wide strategies such as nationwide social distancing measures - the effectiveness of many localised measures that seek to bring a newly invading pathogen under control depends critically on the relationship between the geographical and temporal scale of transmission and the equivalent geographical and temporal scale of the interventions. The importance of matching the spatial scale of interventions to the spatial scale of transmission has been demonstrated clearly using epidemiological models of foot and mouth disease epidemics, for which the scales over which to implement culling (Keeling et al., 2001; Ferguson et al., 2001; Tildesley et al., 2010) and reactive vaccination strategies (Tildesley et al., 2006) have been considered.

The introduction of interventions, as well as the duration over which interventions must be maintained, depends on the timescale of transmission. This in turn depends on the duration of epidemiological periods (see Section 3.1), and human behaviour plays a key role. When a pathogen first invades a new location, a timely response is critical to reduce the risk that initial cases of disease spark a large epidemic (Thompson, 2020). If interventions are instead introduced after several generations of infection have occurred, then containment may be impossible. At the opposite end of an epidemic, it is only possible to declare an epidemic over with confidence once a sufficient interval has passed since the "final case" (Nishiura et al., 2016). As an example, Ebola epidemics are declared over by the World Health Organization and interventions are relaxed once a period of 42 days has passed without any new probable or confirmed case, which is twice the length of an approximate maximal incubation period (World Health Organization, 2020) and should ensure a low probability that active cases are still present. As a result, matching both the spatial and temporal scales of interventions to the analogous epidemiological scales is a critical aspect of many disease control strategies (Gilligan et al., 2007; Filipe et al., 2012; Cunniffe et al., 2015).

For epidemics in human populations, the choice of interventions to introduce involves balancing the benefits in terms of disease reduction against the costs (see Section 1), including economic costs and health harms due to intense measures (Xue et al., 2012; Sandmann et al., 2021). As a result, localised interventions such as the introduction of tiers (risk levels which determine the intervention applied) (Davies et al., 2021; Viana et al., 2021) have the potential to lead to successful disease control without entire populations being placed under severe restrictions. When considering the optimal spatial extent of tiers, the spatial scale of transmission of the pathogen should be considered, accounting for the movement of individuals between tiers. Of particular importance is the insight that introducing restrictions along local authority borders may not provide the optimal balance between benefits and costs (Thompson et al., 2016).

3.3. Multiple strains and evolution

Interventions affect pathogen evolution in two key ways: by changing (typically increasing) the selection pressure on the pathogen, and by decreasing the number of infections, and hence the mutation supply upon which selection can act. When there is a plentiful supply of susceptible hosts, the selection pressure is relatively weak, and when there is a limited supply the selection pressure is relatively strong. Mutation supply is generally proportional to the number of infections. Interventions such as social distancing and vaccination can therefore increase the selection pressure for new variants, while simultaneously reducing mutation supply. Since the rate of pathogen adaptation depends on the balance between mutation supply and selection pressure, interventions may decrease cases in the short-term while increasing the likelihood that new variants will emerge (Ashby and Thompson, 2021). An important challenge involves analysing evidence for evolutionary changes during epidemics (Day et al., 2020) and **quantifying the net risk of emergence of future novel pathogen variants under interventions given these trade-offs** (Cobey et al., 2021).

Modelling of interventions typically focuses on epidemiological impacts on infections and mortality, without considering potential evolutionary consequences. This may lead to strategies, where short-term

reductions in infections or mortality may come at the cost of higher infections or mortality over the longer-term due to pathogen evolution. For example, from a short-term perspective it may be desirable to prioritise vaccinations for those who are most vulnerable to severe disease and death, but this may increase the likelihood of a vaccine-escape variant significantly (Saad-Roy et al., 2021). This may be the case if vaccines do not block transmission entirely and if vulnerable hosts are not the individuals who contribute most to transmission (Gog et al., 2021).

Some patterns are intuitive. For example, introducing a vaccine when prevalence (and hence mutation supply) is high is more likely to lead to a vaccine-escape variant emerging than when prevalence is low. However, the extent to which one must use NPIs to reduce cases while rolling out vaccinations to achieve substantial reductions in the risk of vaccine escape, or the order in which to vaccinate groups, requires more detailed modelling. Over the longer-term, if a pandemic pathogen transitions to an endemic state, then immune pressure from the host population may lead to diversification into a number of coexisting variants (Buckee et al., 2011), or successive variants emerging over time (Gupta et al., 1998). Modelling the transition to endemicity may therefore require a multi-strain framework.

Multi-strain frameworks can help to quantify both the likelihood and timescales over which new variants may emerge, and hence how interventions should be designed to limit opportunities for pathogen adaptation. Given that newly emergent strains are by definition rare, stochasticity is likely to play an important role in the probability that a new variant will go extinct even if it has above average fitness. While general theory exists to understand the effects of stochasticity on rates of adaptation, a key challenge is to **translate modelling theories about pathogen evolution under interventions to policies for specific epidemics**.

3.4. Interventions in different epidemic phases

Interventions have the potential for significant impact early in an outbreak and decision-makers may not be able to wait for uncertainties to be resolved before introducing control measures. A challenge is to **make models that are simple and robust, so that quick decisions can be supported even if precise predictions are not possible** (see also Swallow et al., 2022). Of course, a policy that is introduced at an early stage may not turn out to be optimal, so it is important to adopt adaptive approaches to decision-making and fine tune any response as more information becomes available (Shea et al., 2014; Atkins et al., 2020). Also, characteristics of people most affected by an epidemic may change as the epidemic reaches different strata of a population.

As an epidemic progresses, and more data become available, a policy that may have seemed optimal when data were scarce, may no longer prove to be most effective. The ability to resolve uncertainty itself may also depend upon the initial interventions that are chosen. An intense policy of suppression in the early stages may appear optimal to minimise the short-term impact of an outbreak, but this may also lead to a protracted period in which model parameters cannot be resolved, given the resultant small number of initial cases. Meanwhile a less intense initial policy, whilst not optimal in the short term, may lead to faster parameter resolution and the ability to switch to a preferred policy sooner, once uncertainty is resolved. While policy considerations determine which interventions are actually implemented, there is a need to develop approaches for **estimating impacts of interventions that are in place and at the same time resolving uncertainty to establish the optimal long-term control policy**.

4. Challenges in modelling pharmaceutical interventions and prevention

4.1. Vaccination

Vaccination (see also Madewell et al., 2021) is a pharmaceutical intervention of primary importance, as it allows conferring protection against infection and/or disease to individuals in a safe and controlled way. Mathematical models can be used to evaluate the effectiveness of vaccination and inform the design of optimal vaccination strategies in terms of feasibility, costs, and disease burden (Matrajt et al., 2021; Bubar et al., 2021). Questions that have been particularly acute during the SARS-CoV-2 pandemic include how to inform optimal vaccination policies under a dynamic and quickly evolving vaccine landscape, involving: (i) uncertain or unknown efficacy of vaccine against infection and disease (e.g. reduction in risk of infection, hospitalisation or death, as well as in the chance of onward transmission); (ii) delivery of multiple recommended doses or boosters, raising questions on whether a broader distribution of less-protective single-dose vaccination is better than delivery of multiple doses to fewer individuals and, if so, how far apart from each other (Hill and Keeling, 2021; Saad-Roy et al., 2021); (iii) simultaneous use of multiple vaccines with different properties, which, on the one hand, might shape the evolutionary landscape, and, on the other hand, opens up questions about the consequences of mixing and matching doses from different vaccines; (iv) possible evolution of vaccine escapes that become dominant and potentially shape other simultaneous interventions (Saad-Roy et al., 2021, and Section 3.4); (v) timing from inoculation to protection, which substantially affects the effectiveness of reactive vaccination strategies.

A fundamental modelling challenge is informing vaccine prioritisation and allocation when vaccine effectiveness and contact structure are highly heterogeneous. Possible allocation strategies may differ substantially in their target such as prioritisation by age or risk group (Wallinga et al., 2010; Viana et al., 2021; Bubar et al., 2021), and specific strategies like ring immunisation may be considered for specific diseases (Kucharski et al., 2016; Kretzschmar et al., 2004). Mathematical models should ideally be able to compare different allocation strategies targeting different strata of the population. However, models encapsulating all the required complexities are often too detailed to parameterise robustly, and rather multiple simpler models are used that capture only a part of the desired heterogeneities.

If a vaccine is available before an outbreak starts, the epidemic dynamics can be described by a model with constant parameters, more amenable to mathematical tractability. However, with newly emerging pathogens, vaccines are typically developed and distributed while an outbreak is ongoing, raising further challenges during the transient vaccination phase. Indeed, **mathematical models should capture dynamic vaccine deployment and distribution, which is often spread over a long time period, and untangle the effects of vaccination compared to the effects of NPIs or lockdowns** (Moore et al., 2021; Jentsch et al., 2021; Viana et al., 2021). These challenges come on top of the inevitable aforementioned uncertainty in vaccine efficacy, which might improve over time, as well as the specific distribution policy, and uncertainties concerning changes in contact patterns and transmission. Issues related to vaccination are not confined to mass-vaccination campaigns during the outbreak itself, but extend also to later phases, when long-term vaccination strategies must be investigated in order to face a potential endemic phase of the disease.

4.2. Treatment as prevention

Treatment of an infectious disease firstly benefits the patient, who gets the treatment, but often also impacts transmission by reducing the duration of an infection, infectiousness (Cohen et al. 2011) or both. Therefore, in modelling interventions, we are interested in how application of a treatment in a large part of the infected population influences

the epidemic dynamics. An example of major public health relevance is HIV, where the strategy of "treatment as prevention" has been declared the major strategy that may lead to elimination of HIV transmission in the long run. Strategic goals like the 90–90–90 goal formulated by UNAIDS (UNAIDS, 2017), which aims at 90% of infected persons knowing their HIV status, 90% of those starting antiretroviral treatment, and 90% of those being virally suppressed, is viewed as a step towards eradicating HIV globally. More recently, the UNAIDS strategy has been updated to the 95–95–95 goal, with elimination of HIV transmission as a target on the horizon. The rationale is that treatment reduces the viral load to undetectable levels and with that stops further transmission. Mathematical modelling has been used to assess whether this strategy is sufficient to achieve elimination of HIV transmission in the foreseeable future (Granich et al., 2009; Eaton et al., 2012). Apart from treatment of infected persons, also pre-exposure prophylaxis (PrEP) is used to prevent transmission to susceptible persons and influences the epidemic dynamics of HIV.

For other infectious diseases for which no vaccine is available, mass treatment is sometimes an intervention option. Mass drug administration has been tested as an intervention for vector-borne diseases like schistosomiasis (Mutapi et al., 2017), sexually transmitted diseases like gonorrhoea and chlamydia (Korenromp et al., 2000), and hepatitis C infection (Hill et al., 2017). However, these intervention programmes have not always been successful, some of them because of development of resistance to antibiotics and antivirals, some of them because of lack of adherence to treatment regimens and difficulties in rolling out treatment in large parts of a population, or because of reinfection after treatment, as in the case of hepatitis C infection (Lambers et al., 2011).

A challenge for mathematical modelling of treatment impact is to incorporate the mechanism with which treatment affects epidemic dynamics in an appropriate way into the model. How do treated people differ from untreated infected persons? What is the effect of treatment in different phases of the infectious period, and by how much is infectiousness lowered? Do treated persons have different contact patterns than untreated persons? Furthermore, if elimination is the goal, we are confronted with **the challenges of defining what we mean by elimination and how to model an infection at the point of elimination**. It is clear that stochastic models are required, that can describe extinction properly, but which stochastic processes will govern the dynamics near extinction? When do we know that extinction has actually taken place? This question has been addressed in the context of polio (Eichner & Dietz, 1996).

An emerging challenge is **how mathematical models can inform the design of pharmaceutical products in view of potential health crises.** Mathematical models could explore the effect of pharmaceutical products on the disease dynamics at the population level, and help investigate to what extent sub-optimal but generic drugs could contribute to the response to pandemics, or to virus elimination (Slater et al., 2017). Also, they could help to assess when during an emerging outbreak vaccines should best be used, and what are the trade-offs between fast production, effectiveness, and broadness/specificity of vaccines or drugs (Hollingsworth et al., 2011).

5. Challenges in modelling non-pharmaceutical interventions, human behaviour

NPIs (also termed "public health and social measures") are used to control transmission where vaccine or treatment is absent or not sufficient for keeping disease at bay. For respiratory viruses like SARS-CoV-2, these have included e.g. stay-at-home orders, closure of non-essential public spaces, limits on gatherings, border controls and travel restrictions, and use of face masks. For a sexually transmitted infection, these may be condom use, having fewer sexual partners, or voluntary male circumcision. NPIs which reduce social mixing can be relatively untargeted, such as widespread stay-at-home orders. More targeted measures aim to reduce contacts among those most likely to be infectious, such as Test, Trace and Isolate policies (TTI). Others, like face mask or condom use, work by reducing the risk of transmission per contact. Border controls and travel restrictions aim to limit the seeding of new infections internationally or across regions. Establishing baselines for comparison and defining the levels at which human behaviour should be included in models have previously been discussed (Eames et al., 2015; Funk et al., 2015). However, recent advances in data availability have highlighted the complex interplay of variability in human behaviour across socioeconomic and demographic scales.

5.1. *Heterogeneity of populations and contact networks*

Behavioural responses and engagement with NPIs and TTI will likely not be uniform across populations, time and different combinations of interventions. To assess possible effectiveness in practice, models of interventions should therefore capture uptake and adherence. Analyses should consider interactions with other interventions (e.g. relationship between isolation take-up and work-at-home orders) and with operational parameters (e.g. testing uptake and test booking delays), potential trade-offs and compensatory behaviours, uptake and degree of adherence (e.g. a partial but incomplete reduction in non-essential contacts), and sustainability of adherence over time.

There are important heterogeneities in the capability across population groups to engage with interventions, which likely correlate with other risks of infection. These heterogeneities present challenges in the interpretation of the relevant data, and in selecting the salient features for each model. Many settings have observed stark correlations between socioeconomic and ethnic inequalities, and COVID-19 infection and mortality. Some correlations reflect discrepancies in vulnerability to severe disease, and some reflect inequalities in exposure, including the extent to which they are protected by NPIs to NPIs and participate in TTI measures (SPI-B, 2020). For instance, the ability to work from home is related to measures of socioeconomic deprivation and probability of infection with SARS-CoV-2 (Pouwels et al., 2021; EMG Transmission Group, 2021). Individuals working outside of the home and making out-of-household contacts during 'lockdown' differ from those who are able to reduce their contacts, as are their respective contact networks. They are likely to have larger household sizes or to work in high-contact roles or within non-policy adherent workplaces, with implications for how the contact network scales with implementation of NPIs and for what can be assumed about adherence to other interventions such as TTI (Public Health England, 2020).

To understand the effectiveness of interventions, we need ways to model clustering of intervention uptake and adherence among individuals who might also cluster on the network of contacts, the potential transmission network. We can model these clusters by including particular settings within the model, such as schools or workplaces with their own contact patterns, or via particular classes of individuals. The modelling required will vary significantly depending on the degree of integration between the cluster and the wider community, e.g., an outbreak on a mostly closed campus (such as a university or factory with employee dormitories) will have a different impact than an outbreak in a high-risk work setting where employees return to their own homes daily.

Despite the need for models which embed clusters into the community (beyond the addition of age stratification), descriptions of social contacts by other population heterogeneities are often limited by the availability of data (Section 2.3). Modelled effects of an NPI on contacts often do not account for compensatory/altered contact patterns, such as those deriving from informal childcare provision when schools are closed.

Shared structural influences on uptake and adherence to interventions by neighbourhood or local area could lead to 'pockets' of high transmission and disease (Victora et al., 2018; Todd and Bambra, 2021). Including indices of social deprivation in a structured

population model, or levels of deprivation in a spatial model, can reflect socioeconomic influences on behavioural engagement with interventions (Section 2.3). Household models might instead assume a higher probability of introduction of infection into the household, while accounting for the variable household sizes as they correlate with income. Agent-based models could explore the impacts of TTI or other such interventions according to the number of infectious contacts of each person, their personal adherence to interventions, and changes to adherence based on the adherence of those around them. All of these models would further benefit from knowing what proportion of contacts from a person within a cluster are also a part of the same cluster (Centola, 2010; Sprague and House, 2017). Generalised modelling approaches to population heterogeneities have previously considered contact networks where the degree distribution of contacts captures this variability, though time-varying components in modified homogeneously mixing compartmental models can achieve similar effects (Bansal et al., 2007).

Clustering in behaviours may result from a shared local environment, e.g. where there are many individuals in insecure jobs without sick pay, or arise via direct behavioural influences over a network of social relationships. The resultant clustering and the effects on transmission of infections will depend on the extent to which these social relationships and the potential transmission network overlap. Increasingly, 'virtual' network ties via social media are becoming important for influencing uptake and adherence to interventions and vaccination (Wilson and Wiysonge, 2020). Some interventions utilise social networks for their recruitment (Nikolopoulos et al., 2016) or distribution (Lippman et al., 2018), adding another consideration to dependencies between different network types in influencing the effectiveness of interventions against future pandemics.

Uptake and adherence to interventions, and their impact on the characteristics of the contact network, could also change as a function of the epidemic itself. It is feasible to model population behavioural responses, and uptake and adherence to interventions, as dynamic and as dependent on characteristics of the epidemic (Funk et al., 2015), but it remains challenging in practice to specify the relationship, especially for a new infection and in the context of an emergency (Teslya et al., 2020). In practice, the public does not have perfect information about the course of the epidemic and is in some cases actively misinformed. This lack of information is enhanced by asymptomaticity and delays between infection, symptoms, hospitalisations and death (Pellis et al., 2021; da Silva et al., 2019). Furthermore, there may be strong barriers to adherence which are independent of individuals' willingness or intentions. Under imperfect adherence to multiple NPIs, quantifying which interventions are most impactful is essential for managing an outbreak.

5.2. *Contact tracing, quarantine, and isolation*

One of the main advantages of contact tracing and cluster investigation is that they are directed specifically to individuals who are more likely to have been exposed to the infection. However, capturing the specific contact network and the TTI process over such a network constitutes a key modelling challenge for mathematical epidemiology (Müller and Kretzschmar, 2021), particularly because realistic networks and clustering due to social settings (e.g., households and workplaces) are difficult to measure and describe mathematically (see also Marion et al., 2022), but strongly affect the effectiveness of TTI (House and Keeling, 2010). Different tracing policies (e.g., forward tracing of the secondary cases or backward tracing of the potential infector of a confirmed case) require different modelling considerations (Müller et al., 2000; Kojaku et al., 2021), although in practice it is often impossible to identify the direction of the infection between two confirmed cases. Backward/forward tracing often becomes indistinguishable from outbreak investigation, which focuses on transmission in particular environments rather than between specific individuals, bringing in additional complexities in terms of modelling possibly overlapping clustered networks and superspreading events. TTI serves a dual role as a transmission surveillance and control tool, finding cases among harder-to-reach groups, and informing interventions which break transmission chains. The balance between these roles can vary greatly.

TTI typically requires an extensive infrastructure able to identify infected cases and swiftly search and isolate as many of their contacts as possible. In the case of fast epidemics, this translates into important limitations, for instance in terms of the maximal number of individuals that can be reached and isolated every day and unavoidable delays along the process, which strongly influence the effectiveness of the intervention (Kretzschmar et al., 2020; Contreras et al., 2021; Scarabel et al., 2021). Modelling the real impact of these limitations is often extremely challenging, but at the same time fundamental to evaluate the effectiveness of TTI and identify what aspects can be improved. In LMIC, the lack of resources such as diagnostic tests and isolation facilities adds additional limitations to the effectiveness of TTI. Recently smartphone apps for digital contact tracing have been developed, which are aimed at mitigating these limitations, while introducing further challenges connected with a realistic modelling of the app uptake and mechanisms (Ferretti et al., 2020). The effectiveness of TTI needs to be balanced with the societal impact of quarantine, which depends on its duration and effectiveness in preventing onward transmission, hence models should not only quantify the transmission potential prevented by isolation, but also the expected isolation burden of both infected and healthy individuals (Ashcroft et al., 2021; Kucharski et al., 2020).

6. Challenges in parameter estimation and model fitting

Fitting a model to data can have two main goals: one goal is to estimate parameters that have not been measured by fitting to those that have been measured; the second goal is to fit a model to observations up to the present in order to predict what will happen in the future. The nature of challenges to modelling and inferring impacts of interventions will vary at different stages of an epidemic. For prediction of intervention impact, much work is done via scenario simulation using mathematical models of transmission (Davies et al., 2020; Teslya et al., 2020). Expert elicitation may be an option, but that also comes with its own challenges (Swallow et al., 2022).

Interventions have the potential to impact numbers in all compartments of a compartmental model, as well as a large proportion of/all individuals in individual-baseds models, but many of those impacts are unobservable directly and must be inferred indirectly from changes in positive test rates or numbers of deaths and/or hospitalisations (Section 2.2). Observation models are required in this case, using latent states or other statistical approaches to account for delays on impacts. Exactly what aspect(s) of the model the intervention is impacting and the exact form in which the intervention is introduced to the model will change the level of interpretation that can be made, such as whether the impact is directly on specific outputs of the model, or forcing introduced on specific model parameters. Interventions can also be introduced at different strengths and levels, and measuring that level of severity and how it changes through time is challenging from both a modelling and a statistical perspective. Non-linear effects are potential issues, as are qualitative interventions.

Political and national boundaries are usually the domain on which interventions are introduced (Glennon et al., 2021), but there are many other geographical, political and behavioural boundaries that will impact the efficacy of intervention measures, that may or may not be known or observable. The fact that there has been little attempt to introduce global interventions- combined with the fact that a variety of measures is often introduced even within countries and nations- has made tracking interventions and measuring their impact particularly challenging (Flaxman et al., 2020; Brauner et al., 2021). The introduction of multiple interventions simultaneously, such as closing borders,

schools, pubs, shopping centres, etc. can make extracting the success of any single measure difficult (Soltesz et al., 2020). **Statistical identification of parameters measuring individual impacts will likely be impossible,** as structural and practical non-identifiability will be at play without careful experimental design and model sensitivity analysis (Browning et al., 2020). **Multiple layers of interventions such as NPIs make the evaluation of these layers individually incredibly difficult as the epidemics evolve**, especially as the introduction of subsequent NPIs can impact the efficacy of or adherence to existing interventions. More transmissible variants, vaccine escape variants and associated increased/decreased mortality may also necessitate the re-evaluation of model estimates or flexibility within the model for those estimates to be temporally indexed. **There is a challenge in measuring if an intervention is inherently unsuccessful, or whether it is unsuccessful due to a lack of public adherence** (Gelfand et al., 2021) (Section 2.3; Section 5). These uncertainties, coupled with under-reporting of case incidence and asymptomatic individuals, also make estimation and communication of intervention impacts challenging. Experimental design of interventions in pandemic scenarios, which otherwise may be the most appropriate approach in other domains, inevitably has significant challenges for ethical reasons, as well as associated political and logistical difficulties.

Between-country comparisons often receive significant backlash from politicians and the media and can easily be open to criticism for not accounting for some underlying process that has not been considered (demographic or environmental differences, for example) (Pearce et al., 2020; Xiang and Swallow, 2021; Komarova et al., 2020). Data collection procedures also vary drastically between nations and privacy constraints make large-scale analyses challenging to complete. In particular, in LMIC data may be scarce due to limited resources, which leads to severe heterogeneity between countries in data quality and difficulties for cross-country comparisons in dealing with skewed and missing data.

There is a large range of different models used to study epidemic outcomes, all with their own assumptions, mechanisms and uncertainties. Measuring impacts of interventions will subsequently vary according to which model is used or which data are used to estimate it. **Combining the impact of interventions observed across models adds an additional dimension to the challenges.** There is also a significant difference between models used for explanation or estimation and those used for prediction or forecasting, both structurally and from a philosophical perspective (Hanna, 1969; Shmueli, 2010). This will be particularly challenging when choosing between models for estimating impacts of interventions as opposed to models developed for scenario exploration or forecasting. It is therefore important not to assume automatically that these models can be used interchangeably.

7. Challenges in modelling economic and political aspects of interventions

NPIs seek to reduce transmission through reducing the number, length, and/or intensity of contacts between people where transmission could occur. Some of the NPIs mentioned in Section 5 are relatively cost-free – for example, mask wearing is considered a moderately effective NPI, requiring minimal upfront cost from mask users, and having minimal impact on day-to-day activities for most users (Greenhalgh, 2020; Czypionka et al., 2020). Other NPIs can be highly costly in micro- and macroeconomic terms – for example, the closure of non-essential shops and/or hospitality sectors. For respiratory pathogens, these more restrictive NPIs are likely to be both more effective at reducing transmission and much more costly to individuals and the broader economy than less restrictive NPIs. In addition, the imposition of NPIs that affect the extent to which people are able to work productively will have a direct impact on household finances, and are likely to cause a proportion of households to fall below the poverty line.

To allow decision makers to make these trade-offs in a consistent and data-driven way, there is **a challenge for transmission modellers and health economists assessing the impact and cost-effectiveness of NPIs to quantify and include broader household costs and macroeconomic impacts**. The measurement of household costs is comparatively simple, and a range of validated and tested tools exist to measure an exhaustive list of medical and non-medical expenditures (World Health Organization, 2017), though it is critical that comparable data are collected before and after the imposition of NPIs. The estimation of the broader macroeconomic impact of NPIs is more challenging, and generally requires the combining of epidemiological transmission models and complex macroeconomic models (Keogh-Brown et al., 2020, Smith et al., 2020). Ideally models would be fully combined, allowing two-way feedback between epidemiological and macroeconomic factors – for example, if the closure of a sector's workplaces reduces social mixing but leads to a fall in productivity resulting in redundancies, workers' movements between sectors with different levels of mixing would also change transmission. However, in practice, it is very complex to stratify epidemiological and macroeconomic models in a sufficiently detailed and consistent way to reflect these feedback loops, and the current state-of-the-art is for transmission model outputs to inform macroeconomic models.

Another important challenge is **how to represent financial and non-financial constraints in models** (Bozzani et al., 2018, 2020). The majority of health economic evaluations, including in infectious diseases, take a marginal approach and assess the incremental costs and benefits of interventions and policies. These compare the ratio of incremental costs and benefits to willingness-to-pay thresholds which, generally, represent the marginal opportunity cost of additional health spending, or the benefits that will be foregone in place of new spending. Although many infectious disease interventions may be highly cost-effective, the marginal approach ignores that total costs of programmes may be very high, such as when entire populations require vaccinating against newly emerged pathogens, and may require a substantial proportion of health system budgets. It is therefore important that economic evaluations of interventions that are delivered to a substantial fraction of the population incorporate full budget impact analyses to assess affordability alongside cost-effectiveness (Weerasuriya et al., 2021).

In practice, non-financial constraints are arguably more critical and much less visible than financial constraints. For example, patients in intensive care may require ventilators, but also – critically – one-to-one nursing care and attention from specialist intensive care clinicians. These human resource inputs cannot be quickly scaled up in pandemic response. Therefore, models estimating the number of people with care needs reliant on human resources and other non-financial factors for their delivery – for example, critical care staff, oxygen, needles, and treatment drug doses – should consider these operational needs. It is generally possible to include constraints and optimisation functions in models without requiring significant structural changes and doing so could help to inform real-world prioritisation of scarce resources.

Finally, people experience health and economic impacts of infectious diseases differently. Socioeconomic status is a key stratum across which health and economic indicators vary and ensuring equitable benefits from health interventions and programmes, but **incorporating equity aspects into infectious disease models is a key challenge**. For example, recent methodological advances in equity-informative cost-effectiveness analysis provide a readily applicable analytical framework (Cookson et al., 2020; Asaria et al., 2015). The key contribution of these methods is the disaggregation of health impacts and economic consequences across equity strata, for example distribution across people of different socioeconomic status.

Recent applications of extended cost-effectiveness analyses using infectious disease models improve on models which do not disaggregate outcomes by equity strata, yet are subject to a number of highly restrictive assumptions such as perfectly assortative mixing within strata, uniform underlying distribution of susceptibility, transmission conditional on exposure, and severity and death conditional on infection

(Verguet et al., 2013; Verguet et al., 2015; Rheingans et al., 2012). In reality, data to parameterise these assumptions are hard to obtain – for example the extent to which people of different strata contact – or do not contact – each other. Where data are available, they are likely to be confounded by other factors; for example, observing a greater rate of deaths due to an infectious pathogen could be due to differential and potentially unquantifiable mixing, susceptibility, or severity in each group.

In practice, models have been informative with relatively simple distributional assumptions across these factors, and where data are unknown or highly confounded, sensitivity analyses can show whether plausible differences by socioeconomic stratum between, for example, mixing and severity, explain the differential outcomes observed (Munday et al., 2018).

8. Discussion and conclusions

Use of mathematical modelling to assess the impact of interventions has taken enormous strides since the turn of the century, fuelled by an increasing number of emergence events of new pathogens, large outbreaks of infectious diseases spanning several countries or continents, the fast increase in computing power and communication speed, and fruitful international collaboration of the modelling community. Nevertheless, many challenges remain for the modelling community in developing fast, precise, and flexible tools for supporting public health responses to future pandemics.

We discussed different types of interventions, each posing various challenges in terms of data availability and modelling requirements (Table 1). We did not address the possibilities of synergy or interference of different interventions, when rolled out simultaneously. If there are interactions, one also needs to ask in which order interventions should best be rolled out, or which combinations of interventions are most effective. These are extremely complex questions for mathematical modelling.

While this document focuses on the impact of human-to-human transmission, zoonotic spill over and vector-borne diseases (e.g., dengue fever and malaria) remain key areas of concern for future pandemics. Where animals can act as an infection reservoir and continue to seed infection among humans, targeted interventions are required, with a corresponding new set of behavioural interventions and structural pressures on uptake and adherence. The challenges of those transmission routes have been discussed a.o. by Hollingsworth et al. (2015) and Brooks-Pollock et al. (2015), and are explored further in Roberts et al. (2021) and Metcalf et al. (2021).

The challenges for modelling interventions identified and discussed here are diverse. Finding solutions will require a broad variety of skills and expertise, ranging from mathematical creativity and precision over biological insight to social sciences and communication skills. It is clear that addressing these challenges will require the strong collaboration of researchers from different disciplines, and close communication between scientists and policy makers. Only if knowledge and ideas from different fields can be combined, will it be possible to find solutions to the broad questions sketched in this document. We have witnessed a continuous development of the research field loosely termed "infectious disease dynamics" in the last decades, in which various strands of research including applied mathematics, pathogen biology, human behaviour, economics, and policy science have grown together and merged to create a fascinating and rapidly expanding research field.

While scientists have established closer and closer international collaborations over the last decades, and research in mathematical modelling of infectious diseases has developed into a truly international activity, there is much less international collaboration in the actual response to a pandemic (Priesemann et al., 2021). Policy making and pandemic response is limited by country borders, and which leads to asynchronous waves of an epidemic between countries and out of phase epidemics just across a border. Hopefully, good collaboration among scientists can eventually also inspire more cross-country collaboration in fighting a pandemic.

CRediT authorship contribution statement

All authors took part in discussions and wrote sections of the manuscript. MEK coordinated discussions throughout and compiled the final version of the manuscript. All authors edited the manuscript and approved the final version for publication.

Funding information

This work was supported by the Isaac Newton Institute (EPSRC grant no. EP/R014604/1). MEK was supported by grants from The Netherlands Organisation for Health Research and Development (ZonMw), grant number 10430022010001, and grant number 91216062, and by the H2020 Project 101003480 (CORESMA). RNT was supported by the UKRI, grant number EP/V053507/1. GR was supported by Fundação para a Ciência e a Tecnologia (FCT) project reference 131_596787873. and by the VERDI project 101045989 funded by the European Union. LP and CO are funded by the Wellcome Trust and the Royal Society (grant 202562/Z/16/Z). LP is also supported by the UKRI through the JUNIPER modelling consortium (grant number MR/V038613/1) and by The Alan Turing Institute for Data Science and Artificial Intelligence. HBS is funded by the Wellcome Trust and Royal Society (202562/Z/16/Z), and the Alexander von Humboldt Foundation. DV had support from the National Council for Scientific and Technological Development of Brazil (CNPq - Refs. 441057/2020-9, 424141/2018-3, 309569/2019-2). FS is supported by the UKRI through the JUNIPER modelling consortium (grant number MR/V038613/1). EF is supported by UKRI (Medical Research Council)/Department of Health and Social Care (National Insitute of Health Research) MR/V028618/1. JPG's work was supported by funding from the UK Health Security Agency and the UK Department of Health and Social Care. This funder had no role in the study design, data analysis, data interpretation, or writing of the report. The views expressed in this article are those of the authors and not necessarily those of the UK Health Security Agency or the UK Department of Health and Social Care.

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.

Acknowledgements

We thank Valerie Isham and Denis Mollison for valuable contributions and support during our weekly discussion meetings. We thank Hans Heesterbeek and Viola Priesemann for comments on earlier versions of the manuscript. The authors would like to thank the Isaac Newton Institute for Mathematical Sciences, Cambridge, for support during the Infectious Dynamics of Pandemics programme where work on this paper was undertaken. This work was supported by EPSRC grant no. EP/R014604/1.

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