Challenges for modelling interventions for future pandemics

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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 collaborations 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 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 (Ch 06).

Modelling can be useful in assessing impact of interventions, with three modelling approaches widely used: compartmental models (deterministic or stochastic), network models (either static or dynamic), and individual (or agent) based micro-simulation models, in which individual agents and their interactions are simulated as a stochastic process. 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 parameterized, 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.

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 leading that may be targeted by interventions, and for the economic impact of intervention measures (Figure 1). 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. 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-CoV2

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.

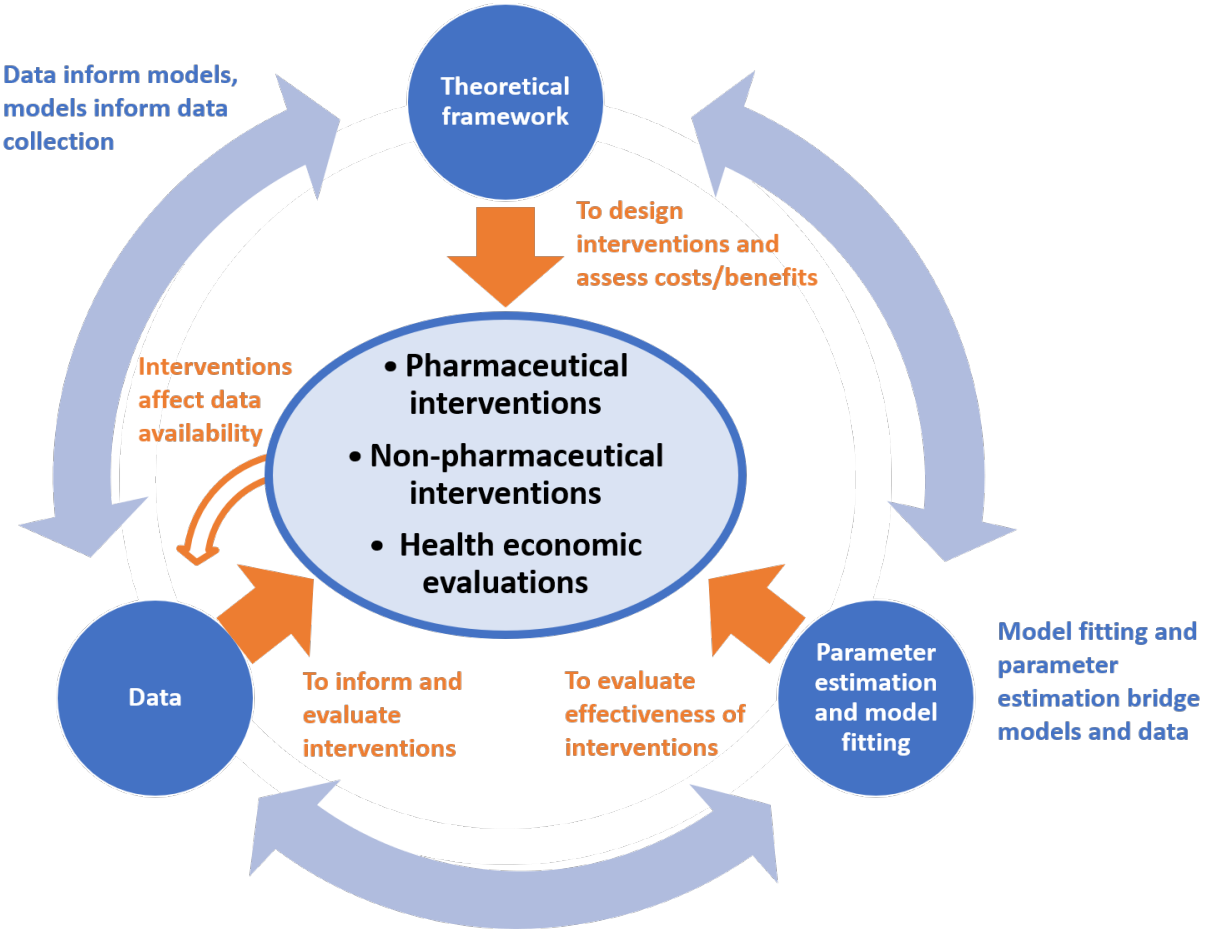

Figure 1: Relationships between interventions and methodological aspects.

2 Data challenges relating to interventions in a future epidemic

Biological characteristics and transmission routes strongly determine which interventions could be effective, and on which time scale interventions should be rolled out. Usually, data are scarce at the onset of the epidemic, but for various types of data the challenges remain in the later stages. Here we focus on data challenges related to modelling interventions, though other data challenges can emerge during an epidemic [cf Ch 06 and Ch 08].

153 **2.1 Biological data**

154 Transmission models require key biological parameters, such as the duration of infectious period,
155 infectivity of symptomatic and asymptomatic cases, and case fatality ratios. Intervention planning can
156 then explore how changes to these model parameters influence future epidemic trajectories. However,
157 not only are fundamental biological data scarce during the initial phase of an epidemic, but they are also
158 affected by biases because of their dependence on uncertain information obtained from reported cases
159 and surveillance data. Moreover, time interval distributions are sensitive to truncation and censoring
160 biases, since data are collected while the epidemic is expanding [Scalia Tomba 2010, Park et al. 2020]. In
161 later phases, identified cases still depend heavily on the adopted surveillance strategy, and parameters
162 like time interval distributions are potentially affected by the intervention measures. **Designing data**
163 **collection studies that overcome these biases, or statistical methods that account for them, remain**
164 **fundamental issues for obtaining reliable parameter estimates.**

165

166 **2.2 Surveillance data**

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

178

179 Hospital data tend to be more reliable because hospital-seeking behaviour is less likely to change over
180 time, and are therefore used ubiquitously in modelling studies [Di Domenico et al 2020, Rozhnova et al
181 2021, Viana et al 2021, Funk et al 2021]. However, the potential overwhelming of the healthcare system
182 and an evolving understanding of when to seek medical attention might shift during a pandemic.
183 Moreover, despite being routinely collected by hospitals, hospital data are rarely publicly available and,
184 especially at the beginning of the epidemic, they are often not aggregated at a national scale. **Designing**
185 **protocols of data collection and aggregation into publicly available datasets,** together with strategic
186 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 [cf Ch 08]

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 2020]; 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.

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**. 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 [cf Ch 06 and Ch 07], 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. This can skew the observation of any new variants of concern, leading to delays in identifying and adapting to novel variants**.

2.3 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 sexual partners per unit of time, but also partnership duration, concurrent partnerships [Morris 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 the impacts 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 2020, Jarvis et al 2020, Zhang et al 2020], which have been used successfully in modelling studies [Rozhnova et al 2021, Kucharski et al 2020]. However, in the absence of setting-specific contact matrices assessed at different time points during an ongoing epidemic, model simulations must involve assumptions that may influence model predictions.

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 2020]. However, they have also revealed a strong hesitancy by many users mainly due to data privacy concerns [Blasimme et al 2020]. Where government apps may struggle with 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, adherence data, and public insights [Chidanbaram et al 2020].

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 [Salathe 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. 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 Ch 07.

2.4 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. In addition to the challenges involved in designing studies to estimate vaccine efficacy in the context of an evolving pandemic [cf Ch 04a], the way the data are collected and recorded also present challenges [Lipsitch 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 (Ch 08). Modelling the spread of vaccine hesitancy, such as through social media networks, may inform what type of data needs to be collected to account for vaccine hesitancy in 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 [Keeling and Rohani 2011]. 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). 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 el 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 with 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.

For epidemics in human populations, the choice of interventions to introduce involves balancing the benefits in terms of disease reduction against the costs (see Introduction), 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 [Davies et al 2021; Viana 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].

Similarly, 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 above), 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 et al 2020b]. 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].

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 altering (typically decreasing) mutation supply. 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. An important challenge involves analysing evidence for evolutionary changes during epidemics [Day et al 2020] and **quantifying the net risk of emergence of 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 disease, but this may increase the likelihood of a vaccine-escape variant significantly [Saad-Roy 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.** Deciding between two candidate interventions may be possible without being able to assess their exact impacts in terms of precise numbers of future cases. Of course, a policy that is introduced at an early stage may not be truly 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 takes its course and reaches different strata of a population.

As an epidemic progresses, and more data become available, interventions may have a more limited effect since containment is then impossible. Additionally, 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 ethical considerations such as an individual's right to treatment must be prioritised over allowing a pathogen to spread without interventions, there is a need to develop approaches for **estimating impacts of interventions that are in place and resolving uncertainty to establish the optimal long-term control policy**. As described in the Introduction, identifying the optimal policy requires the objective function for the ongoing epidemic to be defined clearly.

4 Challenges in modelling pharmaceutical interventions and prevention

4.1 Vaccination

Vaccination [see also Ch 4a] 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 2020, 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, 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].

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 based on the different stratification 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 certain amount of vaccine is available before the outbreak starts, the following spread can still be described by an epidemic model with constant parameters, more amenable to mathematical tractability. However, with new emerging pathogens, vaccines are typically developed and distributed while the outbreak is ongoing, raising further challenges during the transient vaccination phase. Indeed, mathematical models should capture the dynamic vaccine deployment and distribution, which is often spread over a long time period, and untangle the effect stemming from vaccination compared to the effect from 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 the uncertainty in underlying changes in contact patterns and transmission. The issues related to vaccination are not confined to the mass-vaccination campaign during the outbreak itself, but extend also in the later phase, when long-term vaccination strategies must be investigated in order to face a potential endemic phase of the disease. Booster

458 vaccination sometime after the second dose, or indeed the need for a yearly vaccination analogous to
459 the seasonal vaccination are possible options for the future.
460
461 **4.2 Treatment as prevention**
462 Treatment of an infectious disease firstly benefits the patient, who gets the treatment, but often also
463 impacts transmission by reducing the duration of an infection, infectiousness [Cohen et al 2011] or
464 both. Therefore, in modelling interventions, we are interested in how application of a treatment in a
465 large part of the infected population influences the epidemic dynamics. An example of major public
466 health relevance is HIV, where the strategy of "treatment as prevention" has been declared the major
467 strategy that may lead to elimination of HIV in the long run. Strategic goals like the 90-90-90 goal
468 formulated by WHO [UNAIDS 2017], which aims at 90 percent of infected persons knowing their HIV
469 status, 90 percent of those starting antiretroviral treatment, and 90 percent of those being virally
470 suppressed, is viewed as a step towards eradicating HIV globally. More recently, the WHO strategy has
471 been updated to the 95-95-95 goal, with HIV elimination as a target on the horizon. The rationale is that
472 treatment reduces the viral load to undetectable levels and with that stops further transmission.
473 Mathematical modelling has been used to assess whether this strategy is sufficient to achieve
474 elimination of HIV in the foreseeable future [Granich et al 2009; Eaton et al 2012]. Apart from treatment
475 of infected persons, also pre-exposure prophylaxis (PrEP) is used to prevent transmission to susceptible
476 persons and influences the epidemic dynamics of HIV.
477
478 For other infectious diseases for which no vaccine is available, mass treatment is sometimes an
479 intervention option. Mass drug administration has been tested as an intervention for vector-borne
480 diseases [Mutapi et al 2017], sexually transmitted diseases like gonorrhoea and chlamydia [Korenromp
481 et al 2000], and hepatitis C infection [Hill et al 2017]. However, these intervention programmes have not
482 always been very successful, some of them because of development of resistance to antibiotics and
483 antivirals, some of them because of lack of adherence to treatment regimens and difficulties in rolling
484 out treatment in large parts of a population, or because of reinfection after treatment, as in the case for
485 instance of hepatitis C infection [Lambers et al 2011].
486
487 **A challenge for mathematical modelling of treatment impact is to incorporate the mechanism with**
488 **which treatment affects epidemic dynamics** in an appropriate way into the model. How do treated
489 people differ from untreated infected persons? What is the effect of treatment in different phases of
490 the infectious period, and by how much is infectiousness lowered? Do treated persons have different
491 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 or 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 2012].

5 Challenges in modelling non-pharmaceutical interventions, human behaviour

NPIs are measures used to control transmission of infection in the absence of vaccination or treatment. For a respiratory virus like SARS-CoV-2, these have included stay-at-home orders, closure of non-essential workplaces, schools, hospitality and leisure facilities, limits on sizes of gatherings, border controls and travel restrictions, curfews and personal protective equipment (PPE) requirements (e.g., use of face masks). For a sexually transmitted infection, these may be condom use, having fewer sexual partners, or voluntary male circumcision. Some NPIs which reduce social mixing can be relatively untargeted, such as stay-at-home orders applied to the majority of the population. More targeted measures aim to reduce contacts among those most likely to be infectious, such as Test, Trace and Isolate policies (TTI). Others, like the use of PPE 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, over time and across different combinations of interventions. Models of NPIs, TTI and other

interventions should therefore capture uptake and adherence in order to assess possible effectiveness in practice. 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 booking delays), the potential for threshold effects, uptake along multiple steps in an intervention, potential trade-offs and compensatory behaviours, scales of adherence (e.g. a partial but incomplete reduction in non-essential contacts) and sustainability of adherence over time.

There are important heterogeneities in capabilities across population groups to engage with interventions, which likely correlate with other risks of infection. These heterogeneities present challenges both in the interpretation of the relevant data, and in selecting the salient features for each model. Many settings have observed stark socioeconomic and ethnic inequalities across the population with respect to COVID-19 infection and mortality, some of which reflect long standing societal effects on vulnerability to severe disease and some of which reflect inequalities in exposure including the ability to physically distance (adhere to NPIs) and take up and adhere to isolation or quarantine notifications (SPI-B, 2020). For instance, the ability to work from home is related to measures of socioeconomic deprivation and associated with probability of infection with SARS-CoV-2 [Pouwels et al., 2021, EMG Transmission Group, 2021]. The individuals, and the characteristics of their social contact networks, who are still working outside of the home and making out-of-household contacts during 'lockdown', are different from those who are able to reduce their contacts. 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 attempt to model these clusters either by including particular settings within the model, such as schools or workplaces with their own contact patterns, or via including particular classes of individuals. The modelling required to capture the transmission patterns 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 key modelling role in correctly embedding clusters into the community, beyond age classification, descriptions of social contacts by other population heterogeneities are often limited by

559 the availability of data, or pertain to a specific outbreak investigation that does not easily generalise
560 [Section 2, behaviour]. These often do not account for compensatory/altered contact patterns as a
561 result of an NPI seeking to limit infectious contacts, such as those deriving from informal childcare
562 provision when schools are closed.
563
564 **Shared structural influences on uptake and adherence to interventions by neighbourhood or local**
565 **area could lead to 'pockets' of high transmission and disease** [Vitora et al., 2018, Todd et al., 2021].
566 Including indices of social deprivation in a structured population model, or levels of deprivation in a
567 spatial model, can reflect socioeconomic influences on behavioural engagement with interventions
568 [Section 2, adherence]. Household models might instead assume a higher probability of introduction of
569 infection into the household, while accounting for the variable household sizes as they correlate with
570 income. Agent-based models could explore the impacts of TTI or other such interventions according to
571 the number of infectious contacts of each person, their personal adherence to interventions, and any
572 changes to adherence based on the adherence of those around them. All of these models would
573 further benefit from knowing what proportion of contacts from a person within a cluster are also a part
574 of the same cluster [Centola et al., 2010, Sprague et al., 2017]. Generalised modelling approaches to
575 population heterogeneities have previously considered contact networks where the degree distribution
576 of contacts captures this variability, though time-varying components in modified homogeneously
577 mixing compartmental models can achieve similar effects [Bansal et al., 2007].
578
579 Clustering in behaviours may result from a shared local environment, such as in areas where there are
580 many individuals in insecure jobs without sick pay or arise via direct behavioural influences over a
581 network of social relationships. The resultant patterns of clustering that this might produce and the
582 effects on transmission of infections will depend upon the extent to which these social relationships and
583 the potential transmission network ties overlay each other. Increasingly, the 'virtual' network ties via
584 social media are becoming important for influencing uptake and adherence to interventions and
585 vaccination, though the extent to which these overlap with potential transmission networks, and
586 therefore the effects on epidemic dynamics might differ [Wilson et al., 2020]. Some interventions utilise
587 social networks for their recruitment [Nikolopoulos et al., 2016] or distribution [Lippman et al., 2019],
588 adding another consideration to dependencies between different network types in influencing the
589 effectiveness of interventions against future pandemics.
590
591 **Uptake and adherence to interventions, and their impact on the characteristics of the contact**
592 **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 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 delays between infection, symptoms, hospitalisations and death [Pellis et al., 2020, 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 & 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 Ch 06), but strongly affect the effectiveness of contact tracing [House & 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. Contact tracing 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.

Contact tracing 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]. Modelling the real impact of these limitations is often extremely challenging, but at the same time fundamental to

627 evaluate the effectiveness of TTI and identify what aspects can be improved. The effectiveness of TTI
628 needs to be balanced with the societal impact of quarantine, which depends on its duration and
629 effectiveness in preventing onward transmission [Ashcroft et al 2021]. Recently smartphone apps for
630 digital contact tracing have been developed, which are aimed at mitigating these limitations, while
631 introducing further challenges connected with a realistic modelling of the app uptake and mechanisms
632 [Ferretti et al 2020].
633
634 One of the main objectives of modelling interventions is to analyse their cost-effectiveness. Depending
635 on the particular contact tracing policy, not only infected individuals, but all (possibly healthy) known
636 contacts of a confirmed case may be required to quarantine. This introduces further complexities, as an
637 effective mathematical model should keep track not only of the infector-infectee pairs, but also of the
638 infectious contacts where transmission was unsuccessful, in order to quantify the potential disruption to
639 healthy individuals and society in general [Kucharski et al 2020] (see also Section 7).
640

641 ## 6 Challenges in parameter estimation and model fitting

642 Fitting a model to data can have two main goals: one goal is to estimate parameters that have not been
643 measured by fitting to those that have been measured; the second goal is to fit a model to observations
644 up to the present in order to predict what will happen in the future. The nature of challenges to
645 modelling and inferring impacts of interventions will vary at different stages of an epidemic. For
646 prediction of intervention impact, much work is done using scenario simulation using mathematical
647 models of transmission [Davies et al 2020; Teslya 2020]. Expert elicitation may be an option, but that
648 also comes with its own challenges [Section 5 of Ch 07].
649
650 Interventions have the potential to impact numbers in all compartments of a compartmental model, as
651 well as a large proportion of/all individuals in IBMs, but many of those impacts are unobservable
652 directly and must be inferred indirectly from changes in positive test rates or numbers of deaths and/or
653 hospitalisations [Section 2, surveillance data]. Observation models are required in this case, using latent
654 states or other statistical approaches to account for delays on impacts. Exactly what aspect(s) of the
655 model the intervention is impacting and the exact form in which the intervention is introduced to the
656 model will change the level of interpretation that can be made, such as whether the impact is directly
657 on specific outputs of the model, or forcing introduced on specific model parameters. Interventions can
658 also be introduced at different strengths and levels, and measuring that level of severity and how it
659 changes through time is challenging from both a modelling and a statistical perspective. Non-linear
660 effects are potential issues, as are qualitative interventions.

Political and national boundaries are usually the domain on which interventions are introduced [Section 2 of Ch 02], 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 [Soltecz 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, 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, adherence/behavioural data; Section 5]. These uncertainties, coupled with underreporting 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.

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 health 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 above 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 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, Bozzani et al. 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. This approach ignores that the total costs of programmes may be very high, such as when entire populations require vaccinating against newly emerged pathogens. It is therefore important that economic evaluations of interventions that are delivered to a substantial fraction of the population incorporate full budget impact analyses [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 provides a readily applicable analytical framework. 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 add decision making value compared to models which do not disaggregate outcomes by equity strata, yet these 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. In reality, data to parameterize these assumptions is 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.

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 (take-up 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

Table 1: Key challenges

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 strata 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, and the fast increase in computing power and communication speed. 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), Brooks-Pollock et al (2015), Lloyd-Smith et al (2015), and are explored further in [Roberts et al (Ch 02); Metcalf et al (Ch 03)].

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.

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Authors contributions

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.

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