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Challenges in modeling the emergence of novel pathogens

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ABSTRACT

The emergence of infectious agents with pandemic potential present scientific challenges from detection to data interpretation to understanding determinants of risk and forecasts. Mathematical models could play an essential role in how we prepare for future emergent pathogens. Here, we describe core directions for expansion of the existing tools and knowledge base, including: using mathematical models to identify critical directions and paths for strengthening data collection to detect and respond to outbreaks of novel pathogens; expanding basic theory to identify infectious agents and contexts that present the greatest risks, over both the short and longer term; by strengthening estimation tools that make the most use of the likely range and uncertainties in existing data; and by ensuring modelling applications are carefully communicated and developed within diverse and equitable collaborations for increased public health benefit.

1. Introduction

In 2020, the emergence of novel pathogens, or the successful spread of a pathogen into a new host environment, sprung to unwanted prominence. The previously unknown coronavirus, SARS-CoV-2 made the jump to humans from a zoonotic reservoir in China, and it rapidly achieved global reach (Kissler et al., 2020). Mathematical models were deployed at every stage of this trajectory and continue to be an important part of scientific and political conversations regarding how to best contain the spread of SARS-CoV-2 and other pathogens with pandemic potential. But with the zoonotic virome diverse and rich with both known and unknown pathogens, key challenges remain to effectively use models to understand and mitigate the emergence of future zoonotic epidemics. Although there have been striking advances in some of the challenges laid out in previous overviews (Lloyd-Smith et al., 2015), for example in viral genomic epidemiology (Grubaugh et al., 2019) and characterising host competence (Mollentze et al., 2020), other challenges remain relatively neglected, such as understanding the potential roles of intermediate hosts in pathogen emergence (a role further complicated in the case of SARS-CoV-2 by the prospect of "spillback" from people into intermediate hosts) (Fagre et al., 2021). Still further challenges, such as characterising the nature and distribution of spillover risks and developing mechanistic cross-species models, have been topics of sustained inquiry but remain areas of active debate (Becker et al., 2019). In addition to these familiar challenges in mathematical modeling for pathogen emergence, new ones have emerged in the wake of SARS-CoV-2. Here we provide an overview of some of the current landscape of major challenges.

For a pathogen to emerge within a new host population two steps are involved: introduction and establishment. Although these two steps can be further divided into ecologically distinct substeps (Plowright et al., 2017), these two stages are crucially driven by distinct underlying dynamic processes. First, the infectious agent must be introduced into the new host population. In the case of zoonotic pathogens, which have been estimated to represent the majority (approximately 60%) of human pathogens (Jones et al., 2008), introduction into people (i.e., spillover)

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may occur directly from a wildlife reservoir, from a livestock reservoir, or from a wildlife reservoir via an intermediate species such as a domesticated animal. The complex phenomenon of pathogen spillover occurs at the interface of people, animals, and environments and can be driven by changes in any of these realms, including human-wildlife contact patterns, climate and habitat composition, and human health and well-being. Introduction can also happen via movement of infected conspecifics from another population or via shifts in range caused by pathogenic evolution or environmental change (e.g., in the case of vector-borne pathogens, such as dengue, or those with an environmental reservoir, such as cholera). Second, the pathogen must become established within the new host population (requiring sustained local transmission between hosts, commonly summarised by a value of R_0, or the expected number of secondary infections per infected individual, greater than 1). While these two stages of emergence are dynamically distinct phenomena, in the practice of modelling the two become intertwined, with data from each stage commonly necessary to make inferences about the other. Models are useful for advancing understanding of both stages as well as the interactions between them, and critical challenges remain to effectively modelling both stages.

Here, we consider challenges in the ways in which models can contribute to strengthening data collection in the context of future pandemics; identify major challenges in predicting the emergence potential of novel and potentially zoonotic pathogens; detail important questions in estimation of critical pandemic related parameters; and discuss challenges related to the use of models to inform public health response to disease emergence events. While the emergence of a novel pathogen might occur with devastating impact in any host species (evidenced, for example, by devastation of the citrus industry by the virus *Citrus tristeza* (Lee et al., 1994)), our focus is predominantly on emergence of pathogens within human populations.

2. Data challenges of detecting emergence of future pandemics

Two of the major questions around data in the context of future pandemics are: What data need to be collected to detect pathogen emergence? And, what can we do with (and what are the limits of) data that already exist? Models may contribute to answering both questions.

Focusing on the first question, what surveillance tools could most effectively be leveraged to detect that pathogen emergence is (or was) occurring? Models could be used to probe what scope (temporal, spatial), types of data (individual measurements, clinical convenience samples, designed cohort studies), and types of measurements (symptoms, antibody responses, sequencing), and samping intensity are needed to reliably detect anomalies indicative of a pathogen emergence event. For example, a sudden uptick in cross-reactive antibodies to coronaviruses relative to baseline in a convenience sample (e.g., from a blood bank) might have provided a useful early warning of an emergent coronavirus (Mina et al., 2020), but the scale and scope of sampling required for a relevant anomaly to be reliably detected remains an open question, especially in light of recent evidence for cross-reactivity against SARS-CoV-2 in pre-pandemic sera in Southern Sudan, for example (Wiens et al., 2021). Similarly, genetic sequencing clearly has the potential to identify pathogen emergence events, via sampling in human populations, or in animal reservoirs. However, whether the required frequency of sampling, or range of reservoir or spillover host individuals sampled, is likely to be tractable is unknown, and should not be oversold (Carlson, 2020). Models could be designed to explore this issue, for example exploring the degree to which pathogen life histories might require different sampling designs, or whether existing convenience samples (e.g., blood banks) or unexpected clusters of large case reports might be adequate.

For pathogens that are already circulating within a focal population, emergence could take the form of the appearance and establishment of novel variants (e.g., greater transmission, or immune escape, or greater virulence, as for SARS-CoV-2 (McCormick et al., 2021); or features such as artemisinin resistance for malaria (Miotto et al. 2013)). Curtailing the spread of such variants has clear public health benefits. Characterising the degree of surveillance required to detect novel sequences at a fast enough rate to enable containment could be addressed via modeling. For example, detection of a potentially problematic novel sequence, and thus the full pipeline from sampling to analysis must occur at speeds and scope such that the emergent pathogen has not had a sufficient window of time to spread widely in the population, and will thus require models that encompass both the logistics of detection but also the life history of the pathogen, and magnitude of human connectivity. For poorly characterised or unknown pathogens, predicting potential geographical 'emergence hotspots' could facilitate more efficient and targeted surveillance and model building (Lessler et al., 2017). Overall, a first challenge for models in addressing the data around emergence events is thus in informing the utility and best designs for curation of wide-scale, regularly collected data on pathogen (or variant) presence via direct detection or immune measurement.

Moving to the question of the uses and limitations of existing pathogen emergence data, a major set of issues is the variation in data quality and completeness that emerges from global resource inequalities. Ebola outbreaks, for example, can easily evade detection in places where access to care or availability of confirmatory diagnostics are limited (Jephcott et al., 2017; Glennon et al., 2019). Data on emerging outbreaks inherently reflect those outbreaks which have successfully been detected and pathogens conclusively identified. Available data therefore reflects extensive but difficult-to-quantify biases toward larger, more syndromically distinct outbreaks in places with well-resourced health systems and effective disease surveillance programs (Glennon et al., 2020). Furthermore, as much pathogen prevalence data is collected in clinical settings, surveillance represents a low priority relative to providing direct care in many situations (Kim et al., 2013). Models that characterise relevant data biases and feedback loops, as well as models that identify approaches to correct or account for such challenges, will be of value for planning exercises. Awareness of these limitations will be key to effective and just prioritisation of disease prediction and prevention efforts. A second challenge for modeling is therefore in appropriately addressing these imbalances in the data, e.g., via integration of data collected by different systems (including qualitative study), ethical collaboration with diverse public health practitioners and other experts, and quantitative estimation of underreporting and other observation biases.

Relatedly, beyond direct or indirect measures of pathogen presence and abundance, modeling might also be used to ask the question of whether existing non-traditional data-streams (such as contact patterns from mobile devices (Chang et al., 2021; Wesolowski et al., 2016), global connectivity from integrated global data sources (Tatem et al., 2006), population heterogeneity by integrating satellite images to census data (Worldpop, 2021), digital trend data) could contribute to anticipating the trajectory that will follow pathogen emergence. Suggestive use cases exist. For example, mobility data from mobile devices contributed to understanding the early phases of spread (and effects of containment) of SARS-CoV-2 (Lai et al., 2020). However, such data do not directly measure transmission events, and, for example, only limited predictability could be obtained from mobile phone data for the spatial spread of a measles outbreak in Pakistan (Wesolowski et al., 2018). In the context of future pandemics, models could evaluate the characteristics of data that would most powerfully refine inference into future pandemic trajectories (temporal scale? spatial scale? demographic features?) to identify a critical set of extensions that could be requested of technology companies and should be included in data use agreements (bearing in mind ethical and privacy constraints). Navigating such questions of scale, building responsive relationships between those collecting and modelling data, and developing empirically-grounded models to build, test, and refine hypotheses are long-term challenges in infectious disease dynamics (Lessler et al., 2015) that require special consideration and creativity in the case of novel pathogens for which

direct detection and measurement are especially difficult.

3. Challenges in predicting emergence potential of wildlife and novel zoonotic pathogens

Promptly detecting pathogen emergence is clearly, in itself, ambitious. An even more ambitious goal would be to identify pathogens within their zoonotic reservoir before they have had the opportunity to spill over into people, as well as to understand and mitigate the risk of emergence after spillover. There are many possible threads by which models could contribute to this.

Sequencing important pathogen reservoirs, such as the 'virome' is increasingly tractable on large scales, and has certainly deepened our understanding of the community ecology of viruses (Wille et al., 2019). Nevertheless, vast numbers of species remain undescribed. Estimates of richness in the global zoonotic virome vary widely, from approximately 10,000 viruses with zoonotic potential (Carlson et al., 2019) to over 600, 000 (Carroll et al., 2018). As the vast majority of sequenced viruses will be irrelevant to human health, identifying ways to target sampling to more relevant parts of the biome is an important question, for viruses, but also beyond (bacteria, protozoa), and with potential to contribute to monitoring of zoonotic reservoirs (Lloyd-Smith et al., 2015). This question links to the important theoretical challenge of pinpointing characteristics of pathogens with spillover potential.

A series of theoretical approaches have evaluated the degree to which very general characteristics (e.g., mutation rate, degree of clustering in host contacts, pathogen related mortality) shape risks of pathogen emergence (reviewed in Gandon et al., 2013). Another way to tackle this question is to use a comparative approach: models are used to leverage knowledge and trait characteristics of hosts and pathogens that have historically spilled over to identify features of future pandemic pathogens (Olival et al., 2017; Wells et al., 2020; Shaw et al., 2020). Remaining key challenges in this area are to more realistically link species-level predictions to real-world landscapes by accounting for fine-scale species distributions and exposure risk. This area of study may prove particularly important for the interdisciplinary challenge of understanding the effects of ecological and climatic change on disease emergence. A related approach, and which echoes a perennial and persisting challenge in biology is in generating a genotype to phenotype map (Visscher et al., 2017). This might require possibly unfeasible (at this stage) mechanistic understanding of features from cellular tropism to pathogen replication to interactions with existing immunity in animal reservoirs and human populations. Such understanding would enable characterization of host range and zoonotic potential, but also the trajectory of adaptation to human to human transmission that could occur subsequent to introduction of pathogens into human populations. Better calibrated and detailed models capturing within-host to between-host dynamics (Ke et al., n.d.) will be important to the latter. Further, arguably, a critical and as yet unresolved component will be a larger understanding of the landscape of immunity for the focal species and across the pathogen community (Rice et al., 2021), as cross-reactivity among different pathogen species might constrain pathogen emergence (an effect that has been proposed, for example, for influenza; Gostic et al., 2016). Engaging with this in turn requires engaging with the important modeling challenge of moving beyond a single pathogen perspective to encompass multiple species, a well recognised and persisting challenge in the study of infectious pathogens (Lipsitch et al., 2009; Wikramaratna et al., 2015; Kucharski et al., 2016).

As the focal pathogen spreads, growing immunity within the population will elicit selection pressures on within-human replication and human to human transmission. For SARS-CoV-2, in early 2021, variants of concern feature plasticity in combinations of traits encompassing receptor avidity, immune escape, transmissibility and virulence (Martin et al., 2021). Knowledge of correlations between these traits and trade-offs (implying a genotype to phenotype map) would open the way to better anticipating everything from immune escape to shifts in virulence, as well as a better understanding of how these evolutionary events might be driven by acquired immunity, therapeutics, or vaccination regimes (Saad-Roy et al., 2021). While the potential for such mechanistic details to refine the predictions of evolutionary models is clear, adequate characterisation of mechanism remains an important frontier, to which more nuanced knowledge of molecular mechanisms, through to better models of within-host spread could be brought to bear.

An important component in developing models to project the impacts of such pathogen traits and trade-offs (or the genotype to phenotype map) is that they may differ from host to host. Sex differences in immune function, for example, are ubiquitous (Klein and Katie, 2016); and older individuals generally have less efficient immunity as a result of immunosenescence (Simon et al., 2015). The feedback driven nature of immunity may also mean that very small differences may escalate into highly variable outcomes (e.g., along the lines described in ecological terms by 'alternative stable states' (Metcalf et al., 2020)). Such population heterogeneities may have important consequences for both the prospects for pathogen spillover, initial pathogen spread (i.e., the effective reproductive number (Lloyd-Smith et al., 2005; Metcalf et al., 2015a, 2015b)), and selection on pathogen traits, such as virulence (Miller and Metcalf, 2019). However, such heterogeneities remain relatively rarely modeled, in part as they are generally extremely hard to quantify in practice (see next section), especially when one considers that individual variation in important traits such as immunity, behavior, and mobility may all compound to produce highly complex patterns. Nevertheless, efforts to evaluate the purely theoretical impact of such heterogeneities, rooted in broadly known differences (by sex, age) could significantly advance understanding of variation in transmission dynamics and disease outcomes within and between host populations.

4. Challenges in estimation around novel pathogen establishment and early-stage epidemics

While many spillover events may rapidly go extinct in human populations, sometimes primary infections (i.e., people infected directly from the reservoir or entering the local population from elsewhere) will go on to infect other people. Branching process models are commonly used to estimate the risk that initial cases of disease will establish sustained chains of transmission (Althaus et al., 2015.; Guzzetta et al., 2016; Abdullah et al., 2018; Thompson et al., 2016, 2019, 2020). These models were applied early in the COVID-19 pandemic, when cases had only been observed in China, to assess the risk the cases exported to other countries would establish local epidemics and to investigate how control measures affect this risk (Hellewell et al., 2020; Thompson, 2020). Modeling approaches have also been developed to extract key epidemiological measures such as R_0 from observations of early 'stuttering chains' of transmission (Blumberg and James, 2013). Although several methods have been developed to estimate R0 from such early observational data, these estimates are highly uncertain–especially for diseases characterised by high heterogeneity in secondary infections–and can be misleading when generalised. Stuttering chains can be recurrent but not necessarily transition to a larger threat (as is the case for MERS-CoV, for example) or can appear subcritical in many settings while retaining epidemic potential (as in the case of Ebola). Further methods development is needed to help estimate (and contextualise estimates of) core parameters such as R0, the incubation period, and the asymptomatic ratio of a disease in the earliest and most epidemiologically uncertain phases of outbreaks. Furthermore, combining such methods with an understanding of local context is important for making early estimates more reliable, actionable, and generalisable. Working with public health authorities attuned to the particular circumstances of localised outbreaks as well as integrating novel epidemiological data with pre-existing, geographically varying data (e.g., mobility data, serological data to estimate potential cross-immunity) could help clarify uncertainty and generalisability when estimating risk of a novel pathogen establishing ongoing transmission.

For events that follow this phase, the classical modeling toolkit was perhaps first defined during the emergence of HIV (May and Anderson, 1987). This work established a roadmap for estimating the range of core parameters required to delineate the trajectory that an emerging pathogen will take from the early growth in cases (R_0, generation time, incubation period, overdispersion, infection fatality ratio (Metcalf et al., 2017)). This toolkit has been expanded by use of genetic data-streams to infer incidence or pathogen population growth (Vaughan et al., 2019), or innovative use of cross-sectional data on viral copy numbers across individual populations to capture whether pathogen populations are growing or shrinking (Hay et al., 2020). There are presumably an array of further innovations in this space that might further enhance this set of approaches; building around elements listed in previous sections, and grappling with key features such as how to address variability (e.g., presence of superspreading) but also uncertainty in critical transmission parameters (e.g., incubation time, quantities such as R_0 in human populations once spillover has occurred) and grounding them mechanistically (e.g., in heterogeneity in contact patterns or distributions of co-morbidities).

Integrating diverse data sources is likely to prove important both in the very early phases when stuttering chains are occurring, and once sustained spread has occurred. For example, phylodynamic approaches can provide another window onto how a virus moves through space (Bedford et al., 2020; Deng et al., 2020). Such integration can also provide a means to triangulate on core measures such as R_0 (Vaughan et al., 2020.) using a different source of data (noting that this approach may have limited power to resolve the issue of pinning down transmission for a pathogen like SARS-CoV-2 where the genome evolves relatively slowly, time to onset of symptoms, as well as incubation and infection periods are variable, and the asymptomatic ratio is high). Expanding models to estimate critical aspects of within-host dynamics (using data on viral load, immune parameters, etc) but also to translate these estimates into parameters relevant to population scale transmission remains very much in its early phases.

There are also very important required modelling extensions of the classical toolkit to use new data sources. There is arguably more data than ever before on aspects of human contact and risk. Since every model of pathogen emergence arguably involves a contact rate, such data have clear potential. However, there are still gaps in thinking about how best to harness these data. Transmission events remain frustratingly unspecified; they are only 'observed' (and even then, indirectly) in extraordinarily detailed data such as those obtained by contact tracing (e.g., Bi et al. 2020)). Thus, we do not know whether the 'medium' or 'big' data sources we have access to at the population scale, be they diary studies of contacts, or mobile phone call data records (Grantz et al., 2020) actually capture transmission relevant contacts. Sampling bias in these and other less traditional datasets, from mobile phone records viral sequence data, is pervasive and difficult to assess systematically; such bias may lead to mis-specification when these samples are used to inform population-level models. A challenge is finding a principled way to grapple with these issues of model mis-specification that remains tractable, and also sensibly reflects uncertainty. Multi-model comparisons (Reich et al., 2019) may make important contributions here.

Models of early pathogen spread that better account for logistics and health systems are relevant to understanding and adjusting for heterogeneous surveillance and reporting, but also to understanding and improving potential for intervention and containment at early phases. Spatial mechanistic models that include population connectivity networks, socioeconomic factors and distribution of potential reservoir species as recently employed to model Ebola emergence (Redding et al., 2019) may provide crucial insights into spatial aspects of disease emergence. Such mechanistic models can be also used to explore a wide range of possible scenarios in order to explore the model behaviour across a large array of combinations of transmission parameters or narrow down intractable parameter values through likelihood-free approximation methods such as Approximate Bayesian Computation (Minter and Retkute, 2019, Wells et al., 2019). Such likelihood-free methods rely on narrowing down unknown parameters by matching the output of computer simulations to available empirical evidence and may be also used as means for generating forecasts or evaluating the outcomes of a range of possible scenarios of how epidemics may unfold after the initial emergence process. They may therefore prove useful for addressing the technical challenges of multi-scale models. Challenges to be tackled in this area—in which models integrate many layers and scales to account for realistic social-spatial aspects of disease—include balancing inclusion of these critical aspects with sensible model complexity, efficient sampling of large unknown parameter spaces, integrating social and systemic information appropriately (e.g., grounding modelled relationships in social scientific theories of disease), and accurately validating models (Oberpriller et al., 2021) amid the generally sparse empirical evidence available for emerging diseases. Many of these challenges are common across multi-scale modelling approaches (Gog et al., 2015), but are additionally complicated by the unique data limitations and complex social aspects of disease emergence.

5. Challenges in harnessing models for public health benefit

Beyond developing methods and theory, there are important challenges in implementing models to effectively contribute to outbreak prevention and response. Such challenges are cross-cutting, affecting every stage and scale of emergence and of model development. Broadly, these challenges include assessment and communication of uncertainty; clear contextualisation of short- and long-term disease prevention and control strategies; development of infrastructure for effective and responsive modelling in cooperation with public health bodies; and equitable access to epidemiological tools and insights provided by modelling.

Effectively assessing and communicating the uncertainty involved in model predictions is crucial to meeting the needs of public health decision makers and policy makers, as well as facilitating informed decision-making by the general public in the face of misinformation (Metcalf et al., 2015a, 2015b). Clear communication is especially difficult in the early stages of an epidemic, when basic data such as infection rates, infection fatality ratios, and risk factors may be unavailable or strongly skewed by the chance circumstances of early cases. While this difficulty is common across most disease emergence events including evolution and range expansion of known human pathogens, it is especially critical in the case of novel pathogens, for which the most basic physiological and epidemiological aspects of disease are typically unknown at the point of initial case detection. Strong observation biases common in early outbreak data (shaped, for example, by inequities in access to diagnostic testing) further limit the efficacy and accuracy of modelling in early-stage epidemics. Limitations of data and modelling tools are especially salient in attempts to forecast the absolute course of an epidemic (e.g., as opposed to modelling relative impacts of interventions); forecasts are subject to the same pervasive limitations as other models, as well as inevitable feedback loops between model production, public health decision-making, individual risk perceptions and tolerances, and the impacts of behavioural and political choices (Funk et al., 2015). Careless or overconfident communication of modelling predictions during this stage risks losing the trust and cooperation of public health decision makers and the general public (Kupferschmidt, 2020). Nonetheless, the early stages of an outbreak, while case counts are still low, offer the best opportunity for effective intervention to minimise direct and indirect costs. Waiting for more accurate data risks foregoing the chance to intervene while an outbreak is still manageable. There is therefore an urgent need to develop strategies to balance communication of urgency and uncertainty in presenting modelling results as a disease begins to emerge, as well as to effectively communicate changes in strategy as modelling approaches evolve with new data (Becker et al., 2021).

Similarly, there is an urgent need to improve communication of model assumptions and limitations, including contextualisation of short-term and narrowly disease-centered strategies (e.g., vaccination and behavior changes such as masking and social distancing) within local context and long-term or holistic strategies (e.g., broad improvements in sanitation, access to safe housing and work environments, and universalisation of care). Models have been used to disentangle the influences of such factors on the dynamics of endemic and historical emerging diseases (e.g., Phillips et al., 2020), and recent efforts have retrospectively estimated the consequences of such fundamental causes of disease as structural racism on the emergence of COVID-19 in the United States (Richardson et al., 2021). Prospectively estimating the impacts of strengthened health infrastructure, public health policies of critical but indirect benefit for transmission (e.g., eviction moratoria and decarceration), and broad social change, however, represents a major challenge. As modellers work to advance our understanding of the ecological and social environment (e.g., climate, health infrastructure, structural inequality, and interactions with other diseases) on disease spread, it remains important to highlight the limitations of acting only on the proximate mechanisms and easily measured parameters most commonly captured by quantitative modelling. In particular, modellers can support systemic public health efforts by emphasising that parameters such as R_0 and infection fatality ratios are emergent and changeable properties of a disease within a human social context, rather than inherent properties of pathogens themselves. Relatedly, heterogeneities in such values are not fully biological or neutral, but often reflect social and political injustices that modellers should not be afraid to identify as causes of disease or targets for intervention (Bhala et al., 2020).

Finally, additional efforts are needed to define and shape the role of modelling within broader public health efforts in disease prevention and outbreak response. More work is needed to strengthen collaborations between modellers, public health decision makers, and the public. Support is also needed for data sharing infrastructure and for the development of accessible tools based on modelling to enable insights from modelling to be distributed more equitably. In response to COVID-19, national and international authorities have committed to new modelling-focused public health centres such as the US Center for Forecasting and Outbreak Analytics and the new WHO Hub for Pandemic and Epidemic Intelligence (Centers for Disease Control and Prevention, 2021, Balakrishnan and Shankar, 2021). Such bodies aim to address clear needs regarding international coordination and data sharing, but it remains to be seen whether they will further isolate and privilege quantitative knowledge (contributing to the epistemic injustice that pervades global health; Bhakuni et al., 2021) or be able to make room for the truly diverse collaboration needed to address the complex, global, interdisciplinary challenge of disease emergence. Aligning incentives away from profit-driven and nationalist solutions (Katz et al., 2021) as well as academic reward systems that prioritise novelty (Metcalf et al., 2015a, 2015b), and instead building networks of global, equitable, diverse, and transparent collaboration is one of the central challenges of pandemic prevention and one in which modellers ought to be active participants.

6. Conclusions

Detection, and even more ambitiously, anticipation of the emergence of an infectious agent into a new host population could importantly contribute to efforts to assess, prevent, control, and contain future pandemic risks. We have outlined here an array of ways that models have the potential to inform these questions, and important challenges ahead. A global health perspective underscores the enormous advantages in terms of speed and transparency for early reporting of potentially important spillover events. Both better fundamental understanding and expectations, alongside global data standards, transparency and sharing, informed by model framing, could contribute to this while also guarding against over-selling the potential of this research agenda.

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