Epidemics 10 (2015) 35–39

Contents lists available at ScienceDirect

Epidemics

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

Nine challenges in modelling the emergence of novel pathogens

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ARTICLE INFO

Article history:
Received 12 March 2014
Received in revised form 19 August 2014
Accepted 8 September 2014
Available online 19 September 2014

Keywords:
Emerging infectious diseases
Zoonosis
Infectious disease dynamics
Host jump
Cross-species spillover transmission

ABSTRACT

Studying the emergence of novel infectious agents involves many processes spanning host species, spatial scales, and scientific disciplines. Mathematical models play an essential role in combining insights from these investigations and drawing robust inferences from field and experimental data. We describe nine challenges in modelling the emergence of novel pathogens, emphasizing the interface between models and data.

Introduction

While humankind continues to battle ancient adversaries such as tuberculosis and malaria, there is constant concern about the emergence of new human pathogens from sources in non-human animals (Jones et al., 2008). At the very least, this concern is justified by devastating pandemic emergences of HIV-1, HIV-2, and Spanish influenza. We have also seen the near-establishment of SARS-Coronavirus, and a relentless series of zoonotic threats competing for our attention and public health resources. At the time of writing, influenza A H7N9 in China (Centers for Disease Control and Prevention, 2013) and MERS-Coronavirus in the Saudi Arabian peninsula (Penttinen et al., 2013) are both causing substantial numbers of cases, and deaths, and health authorities are searching for effective responses.

This article focuses on challenges in modelling the emergence of pathogens that newly appear in human hosts, such as MERS-CoV or zoonotic influenza strains. We consider problems at the interface of models and data that pertain to interpreting patterns in observed outbreaks, and contributing to rational and robust assessment of risks posed by putative emerging pathogens. We assume that candidate zoonotic pathogens are circulating in some non-human reservoir population or populations, from which they can spill over to infect humans. Humans infected directly by animals are known as spillover or primary cases. If human-to-human transmission occurs, then subsequent cases infected by humans are termed non-primary.

In assessing pathogen emergence, it is useful to delineate what is known about a pathogen's ability to spread between humans. A crucial distinction exists between pathogens that are capable of sustained human-to-human transmission in some settings (i.e. $R_0 > 1$ in humans), and those that exhibit inefficient spread, with subcritical dynamics (i.e. $0 < R_0 < 1$). This latter group includes many pathogens viewed as significant future threats, such as influenza A H5N1, influenza A H7N9, MERS-CoV and monkeypox virus. Another group includes microbes detected by 'pathogen discovery' in various non-human animal populations (Lipkin and Firth, 2013), including many that are previously unknown to science (e.g. Anthony et al., 2013), the relevance of which is often unknown.

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http://dx.doi.org/10.1016/j.epidem.2014.09.002

1. Better capture the disease dynamics in proximal non-human species

One can imagine two extreme conceptual models for the dynamics of emergence from non-human hosts into humans. In 'static reservoir emergence', the dynamics of the pathogen in the reservoir do not change from their long-term pattern. Because of chance or some change in human behaviour, the pathogen spills over from this static reservoir system to cause human infection. In 'dynamic reservoir emergence', the ecology of the pathogen in its non-human hosts changes substantially prior to emergence in humans; changes could include transmission into domestic animals, or gains in transmissibility due to evolutionary changes in the pathogen. However, while the conceptual differentiation between static and dynamic reservoir emergence is attractive, key case studies point much more towards dynamic emergence. For example, Nipah virus caused outbreaks in pigs prior to infecting humans (Parashar et al., 2000) and outbreaks of Sin Nombre virus infection (including the first identified outbreak) have been linked to elevated rodent population densities following periods of increased rainfall (Hjelle and Glass, 2000).

Current assessments of emergence risks from novel pathogens focus heavily on the frequency of particular pathogen genotypes (Russell et al., 2012) or predicted (static) distributions of reservoir species (Fuller et al., 2013), and do not include dynamic factors in reservoir ecology. Therefore, an important, broad challenge is to use models in conjunction with available data to help detect and characterize potentially dangerous changes in the ecology of infectious diseases in key wildlife or livestock reservoirs.

2. Expand models for cross-species spillover transmission from general principles to specific, mechanistic frameworks integrating all relevant data types

Characterization of the spillover force of infection is crucial to emergence dynamics. Very general frameworks have been advanced, for instance to decompose the spillover force of infection into (Lloyd-Smith et al., 2009):

$$\begin{aligned}\text{Spillover FOI} = {} & \text{prevalence in reservoir} \\ & \times \text{reservoir-human contact rate} \\ & \times \text{P(infection|contact)}.\end{aligned}$$

We need a new generation of approaches that take advantage of broader developments in infectious disease dynamics and epidemiology. For instance, ecologic, economic or environmental factors giving rise to interactions among the three terms should be considered, and their dynamical consequences explored. Constructing more mechanistic models of spillover transmission will raise specific challenges, but may also present new solutions. For instance, when human infection occurs via environmental reservoirs, or through food, it may be possible to integrate many complexities of reservoir ecology into their impact on environmental burden, then use dose–response relationships to understand risk to humans. Otherwise, there can be many challenges associated with finding a relevant characterization of prevalence in the reservoir, particularly when the system involves multiple host species and multiple pathogen strains, each possibly posing different risks to humans. Transmission dynamic models that incorporate data from sequence-based or niche modelling approaches may help to predict spillover risk more generally.

Epidemiology has well-developed frameworks for risk factor analysis, which can be applied to spillover because primary cases can be viewed as independent outcomes (at least approximately). Thus there are opportunities to integrate a biostatistical approach to primary cases with a stochastic model of subsequent transmission, creating a joint inference framework. For example, primary infection with Nipah virus in Bangladesh is associated with drinking date-palm sap, while on-going transmission is associated with close contacts among humans (Gurley et al., 2007). A joint framework that links these co-factors using a mechanistic model may aid in distinguishing between primary and non-primary cases (see Challenge 4). Studies of age-based mixing patterns have shed light on transmission dynamics of endemic pathogens (Mossong et al., 2008); there could be similar benefits to linking spillover risk factor information to data on mixing patterns in relevant human populations. Analogously, the coupling between spatial distribution of spillover risk and spatial factors influencing human-to-human transmission may govern the risk of a major outbreak (for instance, risk will be lower if spillover occurs chiefly in remote settlements than if it happens in crowded urban areas).

3. Harness pathogen genetic data across the human–animal interface to map transmission and detect adaptation

Pathogen sequence data could shed light on central questions in zoonotic emergence, by reconstructing transmission connections or looking for adaptation in a new host. However, numerous challenges persist. Because of historic interdisciplinary divisions, isolates from animals and humans have often been grown, detected or analyzed using different approaches, which effectively precludes useful inference. Pathogen isolates are often rare, particularly in difficult-to-culture genera, so isolates from linked cases are unusual. Animal sources of human spillover cases are often gone (dead, eaten, or moved away) by the time the human cases are detected and investigated, so that sequences come from other animal individuals that may not be closely linked. Any inferences about pathogen evolution must include uncertainty arising from (typically poorly known) transmission and evolutionary processes in animal hosts. This situation is particularly challenging if multiple species are involved in circulation of the pathogen, as for avian influenza. Many current examples are based on coarse sampling and use appropriately coarse analyses, such as phylogenies, but higher-resolution methods (preferably not sensitive to missing samples) will be needed as isolate detection improves. These methods will need to explicitly link transmission mechanisms to sequence evolution.

Challenges also arise when trying to assess whether evolutionary adaptation played a role in a past emergence event, and when any adaptive mutations occurred (Pepin et al., 2010). Often, there is no baseline surveillance prior to emergence, so ancestral genotypes cannot be assessed, or available samples are separated by substantial gaps. There is typically poor information about pathogen diversity in animal hosts, let alone in individual animals.

4. Improve methods to analyze stochastic dynamics after pathogen introduction, accounting for heterogeneities and imperfect observation

Substantial progress has been made on modelling the stochastic dynamics of early generations of transmission after a novel pathogen is introduced to a population, yet major challenges remain.

Particular challenges arise from heterogeneities (typically uncharacterized) in host contact patterns, host susceptibility and infectiousness, environmental factors, and possibly pathogen phenotypes. Which of these matter for a given outbreak, and how can this be determined? Further challenges arise from host population structure at scales from households to cities, and the resulting possibility that local pools of susceptibles will be depleted. These