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Seven challenges for modelling indirect transmission: Vector-borne diseases, macroparasites and neglected tropical diseases

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ABSTRACT

Many of the challenges which face modellers of directly transmitted pathogens also arise when modelling the epidemiology of pathogens with indirect transmission – whether through environmental stages, vectors, intermediate hosts or multiple hosts. In particular, understanding the roles of different hosts, how to measure contact and infection patterns, heterogeneities in contact rates, and the dynamics close to elimination are all relevant challenges, regardless of the mode of transmission. However, there remain a number of challenges that are specific and unique to modelling vector-borne diseases and macroparasites. Moreover, many of the neglected tropical diseases which are currently targeted for control and elimination are vector-borne, macroparasitic, or both, and so this article includes challenges which will assist in accelerating the control of these high-burden diseases. Here, we discuss the challenges of indirect measures of infection in humans, whether through vectors or transmission life stages and in estimating the contribution of different host groups to transmission. We also discuss the issues of "evolution-proof" interventions against vector-borne disease.

Introduction

The majority of core insights on the dynamics of infectious diseases are based on models of directly or sexually transmitted viruses or bacterial pathogens, as reflected in the other challenge papers in this issue. However, there are a huge number of pathogens which have multi-component transmission cycles, involving either vectors or complex pathogen life cycles. These pathogens present challenges in terms of the basic modelling structures and the extrapolation of insights from simpler systems to these complex systems and in more policy-related questions, as previously reviewed by other authors (Basáñez et al., 2012; Reiner et al., 2013; Smith et al., 2014).

Vector-borne diseases (VBDs), in which vectors, usually insects, take infection from one host to the next, are responsible for approximately 17% of the global infectious disease burden (World Health Organization, 2014). The most commonly modelled VBDs are malaria and dengue (Reiner et al., 2013), but many others cause a notable burden of disease in humans and other animals. There are a number of novel strategies being considered for VBDs, particularly for mosquito-borne infections, including biological controls (e.g. *Wolbachia*) and genetically modified vectors (McGraw and O'Neill, 2013; Sinkins and Gould, 2006), the success of which depend on our understanding of both the population

Abbreviations: EIP, extrinsic incubation period; EIR, entomological inoculation rate; FOI, force of infection; M&E, monitoring and evaluation; NTD, neglected tropical disease; VBD, vector-borne disease; VC, vectorial capacity.

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dynamics of the vector and the transmission dynamics of the disease.

Macroparasites reproduce via infective stages outside the host, which generates different challenges for modelling their transmission. Despite a long history of macroparasite modelling (e.g. Anderson and May, 1991), the number of publications in this area is much lower than for directly transmitted pathogens, so there are many opportunities to apply recent advances in epidemiological modelling and statistical analyses in this area.

Neglected tropical diseases (NTDs) are a group of diseases that predominantly affect low-income populations in tropical countries. They include a wide range of infections, causative agents and routes of transmission, including macroparasites and VBDs, grouped for advocacy rather than epidemiological reasons. A number of NTDs lack well-defined models, and a diversity of approaches by multiple research groups is urgently needed (Kealey, 2010; The Lancet, 2014). Following several years of advocacy, these infections are now the subject of intense control efforts with many targeted for elimination over the next decades (WHO, 2012). As such, there are opportunities for novel mathematical modelling to inform the design of these programmes with immediate implementation and feedback, and a potentially large impact on human health.

Given the diverse nature of the infections covered here, we cannot hope to cover all the challenges in modelling for the future. We have therefore selected only 7 challenges within the groupings of (a) improvements in basic model structure, (b) contact processes and reservoirs of infection, (c) indirect measures of infection and (d) "evolution-proof" control. These challenges range from more technical modelling questions to clear biological or policy questions. They could arguably also have been grouped into those in which the structure of available models is not satisfactory or the modelling technique is not optimum (challenges 1, 4, 5 and 7) and those where the data have not been collected but the technical conditions to do so are present (challenges 2, 3 and 6).

Improvements in basic model structure

1. How can complex macroparasite processes best be modelled?

Macroparasitic infections (e.g. helminths and filarial nematodes) are characterized by relatively complex lifecycles and long time spans in the human host (from a few months to many years). Part of the parasite lifecycle is external to the host and there is no direct reproduction within the host, and therefore the burden of infection (e.g. number of helminths) can only increase through re-infection. The parasite load determines both transmission and morbidity of such infections. Importantly, this load can vary enormously between individuals, often well described by a highly overdispersed negative binomial distribution (Adler and Kretzschmar, 1992; Kretzschmar, 1993; Kretzschmar and Adler, 1993), an idea that goes back to Anderson and May (Anderson and May, 1978; May and Anderson, 1978). Thus, for macroparasites, a mathematical model needs to include the actual parasite load of each host, rather than simply tracking the total number of infectives. It may also be necessary to represent the various stages of the parasite lifecycle, in which there may be density-dependent effects, and to allow for parasite gender and mating. Furthermore, it is often desirable to incorporate immune responses to infection, and thus to include aspects of the infection history of each host. Multispecies infections are common, presenting additional complexity. While adding extra variables for each host is in principle straightforward, the increased complexity of additional state variables and nonlinearities inevitably means that exact results are difficult to obtain. Various approaches have been taken, including the use of hybrid models (Nasell, 1985) where stochastic variation of one or more variables is ignored. This can be a useful simplifying strategy when different aspects of the process are happening on very different timescales. For example, in a recent study of competition and coexistence of multispecies helminth infections (Bottomley et al., 2007), it was assumed that the free-living stage of the parasite is short relative to that of the adult worm and that their number is deterministic and in equilibrium.

Alternative, fully stochastic macroparasite models focus on particular aspects of the process, thus enabling analytic results. Often the aim is to eliminate some non-linear effects or to approximate them by linear ones. In early work (Tallis and Leyton, 1966, 1969), no interaction between the host and its parasites was allowed. Where appropriate, a useful simplification is to eliminate feedback in the infection cycle (Grenfell et al., 1995) or to assume there is direct infection of one host by another (Barbour and Kafetzaki, 1993). Analytic results can be obtained for models in which parasite-induced host mortality is the only source of nonlinearity and branching process approximations are a valuable tool (Herbert and Isham, 2000; Isham, 1995). Moment closure techniques can give helpful insight when the nonlinearities have suitably simple product forms (Grenfell et al., 1995).

Guidelines are needed on how best to approximate a complex system by a simpler one, clarifying those features that can reasonably be ignored while retaining those most responsible for determining its dynamics. There is a need for generic classes of fully stochastic and hybrid models to be identified that are applicable to groups of macroparasite infections.

Contact patterns and reservoirs of infection

2. Quantifying contributions of host and vector species for vector-borne infections with complex reservoirs

For any pathogen with multiple host species, the risk of cross-species transmission in a "target" host is determined by the spillover force of infection (spillover FOI). For zoonotic infections, where humans are the target host, this is the instantaneous hazard of animal-derived infection experienced by a susceptible human. For a directly transmitted zoonosis maintained in a single "reservoir" (non-human host) species, the spillover FOI can be calculated as the product of the prevalence in reservoir, the reservoir-human contact rate, and the probability of infection given contact (Lloyd-Smith et al., 2009). For zoonoses with complex reservoirs – i.e., those with multiple host species (and potentially multiple vector species) contributing to transmission – the spillover FOI is still a useful concept for quantifying human risk; however, an understanding of how transmission is maintained within and between the multiple reservoir species becomes essential for identifying both indirect and direct determinants of human risk and, therefore, for predicting the potential impact of proposed interventions.

Work on the ecology of tick-borne pathogens, such as *Borrelia burgdorferi* (the cause of Lyme disease) and Louping-ill virus, has emphasized that the ecology of the vector species – particularly the effects of different host species on vector abundance – must be taken into account to understand the contributions of specific wildlife species to pathogen maintenance, and that the role of a host species in determining risk to a target host may depend on the community composition of hosts and vectors (Gilbert et al., 2001; LoGiudice et al., 2003; Ostfeld and Keesing, 2000). For zoonoses with complex reservoirs, reduction of human risk via interventions targeted at animal hosts may be more effective, and will often be more cost-effective, than interventions targeted at humans; however, a formal framework for quantifying the contributions of hosts and vectors to pathogen invasion and persistence in specific