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Modelling challenges in context: Lessons from malaria, HIV, and tuberculosis

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ABSTRACT

Malaria, HIV, and tuberculosis (TB) collectively account for several million deaths each year, with all three ranking among the top ten killers in low-income countries. Despite being caused by very different organisms, malaria, HIV, and TB present a suite of challenges for mathematical modellers that are particularly pronounced in these infections, but represent general problems in infectious disease modelling, and highlight many of the challenges described throughout this issue. Here, we describe some of the unifying challenges that arise in modelling malaria, HIV, and TB, including variation in dynamics within the host, diversity in the pathogen, and heterogeneity in human contact networks and behaviour. Through the lens of these three pathogens, we provide specific examples of the other challenges in this issue and discuss their implications for informing public health efforts.

Introduction

Taken together, malaria, HIV, and tuberculosis (TB) infect more than a third of the global population and are responsible for almost three million deaths each year (WHO, 2013a,b,c). Substantial investments in the prevention and treatment of these three pathogens have led to significant reductions in morbidity and mortality worldwide over the past century (WHO, 2013a,b,c). Throughout this advancement, mathematical modelling has been a key tool in helping to understand transmission dynamics and in predicting the impact of control programmes (Anderson et al., 1991; Dye et al., 2013; Dye and Williams, 2010; Garnett et al., 2011; Macdonald, 1956; Mal, 2011; Stover, 2000). For example, vector control as a way to effectively reduce malaria was recognised through population-level compartmental modelling more than 100 years ago (Ross, 1910) and the importance of CD4+ lymphocytes as sites for HIV proliferation was predicted using simple models nearly two decades ago (Ho et al., 1995). Although these and other models have provided valuable insights, incomplete understanding of the biology and transmission of these three pathogens remains a significant hurdle to the development of useful mathematical frameworks; new theoretical approaches and improved integration of a variety of different kinds of data are needed. Here, we use malaria, HIV, and TB to examine unifying mathematical challenges across the field of infectious disease modelling, despite their biological differences, to provide concrete examples reflecting general problems in the field, and to consider the role that modelling can play to inform public health efforts. We focus our attention on relatively simple models, exposing the data gaps and uncertainties that create fundamental challenges in designing basic model structures and parameterisation, rather than on large-scale simulations, which often suffer from the same knowledge gaps as simpler frameworks but are less transparent and can be difficult to interpret. Indeed, we propose that, in general, while simple models often do not capture the biological complexities of these infections, more complex models may lack the data for parameterisation and validation, presenting a paradox for modellers. We identify challenges in the following main areas: variation in dynamics within

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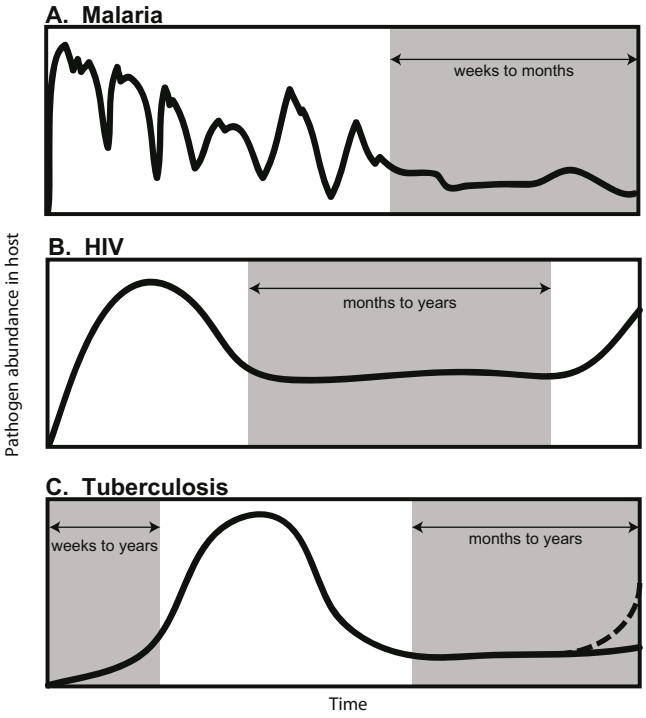

Fig. 1. Pathogen dynamics within individual infections. Grey shaded areas denote periods where the infection is asymptomatic, either due to chronicity in malaria (A) and HIV (B) or latency as in TB (C). Despite a lack of symptoms, particularly during chronic infections, individuals may still be infectious and contribute to spread of the pathogen.

the host, pathogen genetic diversity, and heterogeneity in human contact networks and behaviour. Throughout, we reference specific modelling challenges addressed in depth elsewhere in this issue (referred to by article and challenge number).

1. Understanding infection dynamics in the host

The majority of models designed to inform policy on malaria, HIV, and TB are based upon population-level compartmental models, which generally assume single categories of infected and immune people, a fixed rate of recovery, and simple estimates for the duration of infectiousness (Dowdy et al., 2013; Johnson and White, 2011; Reiner et al., 2013). The most commonly used Susceptible-Infected-Recovered (SIR) compartmental models were developed to study outbreaks of acute immunising infections among immunologically naïve populations, often describing the potential for an epidemic through summary statistics such as the reproductive number, R_0. These assumptions must be modified for endemic pathogens exhibiting variable infection dynamics in the host (Article 15, Gog et al., 2015) Challenge #2), heterogeneous immunological states between hosts (Article 11, Wikramartna et al., 2015, Challenge #4), and significant spatial and temporal variation in risk (Article 20, Riley et al., 2015, Challenge #1). At the level of an individual, all three of these pathogens cause a wide range of clinical and infection outcomes related to host genetic heterogeneity, coinfection, or previous exposure (Article 11, Wikramartna et al., 2015, Challenge #5), and this creates extensive variability in both the infection length and the dynamics of infectiousness of an individual (Fig. 1). Therefore, assumptions of a constant rate of loss of infectiousness and a uniform recovery rate may not adequately represent the infectious population underlying transmission.

In malaria, sustained parasite proliferation in the blood by the most virulent species *Plasmodium falciparum* may lead to a chronic phase of highly variable intensity and duration (Bull et al., 1998; Newbold et al., 1997) (Fig. 1A). Repeated and simultaneous infections with different antigenically diverse parasites lead to a "semi-immune" status in older children and adults in endemic regions that is protective against severe disease (Bull et al., 2005); however, little is known about how patterns of exposure alter the distribution of chronic periods and the extent of the infectious population (Hansen and Buckee, 2013; Churcher et al., 2013; Killeen et al., 2006; Lin et al., 2014; Lindblade et al., 2013) (Article 8, Cunniffe et al., 2015, Challenge #6). Most infected individuals in endemic regions harbour multiple clones and have a complex history of exposure (Article 15, Gog et al., 2015, Challenge #5), and although compartments can be added to SIR frameworks to account for the accumulation of multiple exposures, basic parameters are lacking to describe these individuals including relative infectiousness to mosquitoes, susceptibility to new infections, and rates of clearance of infection (Article 11, Wikramartna et al., 2015, Challenge #5; Article 18, Pellis et al., 2015, Challenge #1). Ultimately, this means that the probability of a mosquito bite leading to infection is poorly defined, so feedback between human and mosquito components of the model may be mis-specified, complicating estimates of the impact of different interventions (Hansen and Buckee, 2013).

Infection with HIV is incurable, which removes the need to estimate heterogeneous parameters of recovery and immunity, but complex within-host dynamics lead to variable infectious periods (Fig. 1B). An HIV infection is characterised by an initial acute phase with rapid pathogen growth, followed by stabilisation at a set point viral load that plays a critical role in determining the duration of the chronic period (Fraser et al., 2007) but is highly heterogeneous among individuals, likely the result of complex and poorly understood interplay between the host immune system and the virus (Perreau et al., 2013) (Article 13, Metcalf et al., 2015a, Challenge #3). As a result, the progression from chronic, low-density infections to full-blown AIDS and the variable length of chronic infections remain difficult to incorporate within epidemiological models (Fig. 1B). In particular, including individual heterogeneity in the rate of transition through these different states of disease and infectiousness will require a better understanding of the complex mechanisms determining the dynamics of HIV within an individual.

The dominant source of variability in the within-host dynamics of tuberculosis infections results from heterogeneity in the timing of active disease. Most new infections result in an asymptomatic "latent" infection, with innate immunity controlling bacillary growth in the lung (Ernst, 2012) (see Orme, 2014 for a novel view on latent infections). Although latent infection confers immunity to active disease arising from reinfection (Andrews et al., 2012), a small proportion of those who are latently infected progress to active disease (Ernst, 2012). The lack of data on the distribution of times between becoming infectious to self-cure, disease or diagnosis, with indirect estimates suggesting that this period can range from a few months to several years (Tiemersma et al., 2011), makes realistic incorporation of the initiation of active disease into models difficult (Article 22, Lessler et al., 2015, Challenge #3) (Fig. 1C). It is clear that TB progresses much more rapidly in HIV-positive than in HIV-negative individuals (Lawn and Churchyard, 2009), emphasising the important and understudied dynamics that may result from co-infection (Article 13, Metcalf et al., 2015a, Challenge #2).

Heterogeneous within-host dynamics for all three infections make it difficult to establish the timing and duration of latent or chronic infection periods, where transmission potential may differ significantly from acute infection. As a result, modelling the impact of individual-level interventions on population-level transmission is challenging. Given the paucity of data on the dynamics of natural infections in endemic regions (Article 22, Lessler et al., 2015, Challenge #3), standard model frameworks frequently assume that varying previous exposure does not alter distributions of infectious

periods in malaria, that infectiousness is not related to within-host infection dynamics for HIV, and that TB progression rates are randomly distributed. Note that we have focused here on simple models, but the same uncertain parameters governing within-host dynamics must also be estimated in more complex frameworks (Article 15, Gog et al., 2015, Challenge #7; Article 23, De Angelis, 2015). A more thorough understanding of within host infection dynamics of malaria, HIV, and TB will lead to a more accurate assessment of the infectious populations responsible for transmission, a crucial quantity when evaluating interventions to inform policy decisions.

2. Incorporating pathogen genetic variation

Although very different organisms cause malaria, HIV, and TB, pathogen genetic diversity is a major obstacle to the design and use of vaccines and therapeutics for all three, hindering control and elimination prospects. Any model incorporating multiple pathogen strains faces the challenge of keeping track of people infected with, and immune to, different strains (Article 11, Wikramartna et al., 2015), as well as defining the antigenic relationships between strains, their rate of genetic change (Articles 13, Metcalf et al., 2015a, and 14, Frost, 2015), genetic bottlenecks resulting from transmission (Article 15, Gog et al., 2015, Challenge #1), and the consequences and frequency of superinfection (Article 15, Gog et al., 2015, Challenge #5; Article 16, Roberts, 2015, Challenge #6).

The malaria parasite exhibits remarkable genetic diversity, especially among gene families such as the *var* genes, which are involved in phenotypic variation within the host and associated with disease outcome (Johnston et al., 2013). Diversity among these gene families is continually generated through frequent recombination, a mode of diversification that is difficult to accommodate within modelling frameworks (Article 14, Frost, 2015, Challenge #5). Indeed, malaria parasite genomic diversity is so great in endemic regions that we still lack adequate genotype markers, making it nearly impossible to track genotypes in a population or to sensitively establish the multiplicity of infection (Manske et al., 2012). Model complexities arising from frequent superinfection include a rapid increase in the number of categories necessary to account for individuals harbouring varying numbers of genotypes and insufficient data to accurately assign immunological relationships against parasite genotypes. Most models incorporating superinfection assume independence of strains with a fixed time since infection for each genotype, neglecting the impact of superinfection on duration of infection and relative infectiousness to mosquitoes (Article 15, Gog et al., 2015, Challenge #5; Article 16, Roberts, 2015, Challenge #6). In particular, parameterising the outcome of competition between strains within a single host plays an important role for understanding how variation created in a single infection carries over to the next human host, as the mosquito vector acts as a critical genetic bottleneck (Conway et al., 1999) (Article 15, Gog et al., 2015).

Rapid diversification within and between hosts poses significant challenges for HIV, where every possible point mutation may arise in a single day during HIV proliferation (Perelson et al., 1997), and this complex within-host diversity is subsequently shaped through pressure from the host's immune system and drug treatment (Article 15, Gog et al., 2015, Challenge #2). On a population level, the antigenic *Env* glycoprotein exhibits extensive diversity, which increases by 1–2% every year (Novitsky et al., 2009). Modellers must decide whether to include both within-host and population-level models of viral diversification. In the absence of an explicit within-host component, assumptions must be made about how diversity generated during an individual infection relates to the subset of viral genomes that are successfully transmitted (Article 14, Frost, 2015, Challenge #7). Despite a recent rise in interest, there remains insufficient data about the relationship between within host diversification and transmission for HIV, so current theoretical frameworks make strong assumptions about the bottleneck imposed by transmission (Article 15, Gog et al., 2015, Challenge #1) and the impact of superinfection (Article 15, Gog et al., 2015, Challenges #5 and #6).

Although *Mycobacterium tuberculosis* is one of the least diverse bacterial pathogens, among the few of its loci that vary are genes that harbour mutations coding for drug resistance (McGrath et al., 2014). Evidence that different drug resistant strains and lineages have different mutation rates, different fitness costs and elicit different levels of immunity suggests the epidemiological dynamics of drug resistant TB will require a better understanding of the biology of strain differences and the inclusion of multiple strains in models (Ford et al., 2013) (Article 14, Frost, 2015, Challenge #6). Selection within the host and resulting emergence of drug resistance at a population level is not well understood although the relationship between pathogen diversity and the immune system is known to be critical. Models must be adapted to include evolution and dynamics of pathogen genotypes across scales in order to understand the emergence and maintenance of diverse populations of *Mycobactrium tuberculosis* (Article 13, Metcalf et al., 2015a, Challenge #4). Consequences for TB epidemiology depend on measuring and understanding fitness across pathogen generations, for which little conclusive data exists (Dye and Williams, 2009). Characterising the impact of genetic diversity on the fitness of drug resistant TB strains will allow for incorporation into strain models.

Pathogen genetic diversity is often ignored within prevailing models of malaria, HIV, and TB despite the variety of strains and genotypes known to circulate at the population level. As antigenic variation among, and competition between, strains will alter their frequency in the population and transmission overall, the inclusion of multiple genetic variants will be important for many policy questions, particularly in relation to drug resistance.

3. Accounting for heterogeneous contact rates and changes in behaviour

The inclusion of realistic human behaviours relating to the spread of disease and the efficacy of interventions remains a challenge for many infectious disease models (Articles 18, Pellis et al., 2015, and 20, Riley et al., 2015), but represents a particular problem for malaria, HIV, and TB. Heterogeneities from dynamic contact networks, such as sexual contacts in HIV and indirect contacts in vector-borne infections like malaria, as well as a wide range of behaviours that influence exposure and effectiveness of treatment, are challenging to accurately parameterise (Kato et al., 2013; Miller, 2009) (Article 18, Pellis et al., 2015; Article 19, Ball, 2015, Challenges #3 and #4). Travel of infected individuals, which is often difficult to measure, spreads infections within and between countries and regions (Article 4, Funk, 2015, Challenge #6; Article 20, Riley et al., 2015, Challenge #3), jeopardising the sustainability of control programmes and prospects for elimination (Buckee et al., 2013) (Article 3, Klepac, 2015). In all three cases, vulnerable groups may exhibit fundamentally different epidemiological dynamics than the general population, and must be modelled and parameterised separately.

Malaria requires a vector for transmission, in contrast to many pathogens including HIV and TB, so contacts between people are by definition indirect (Fig. 2A). The variability of vector habitats and hosts means that malaria prevalence shows strong geographical heterogeneity (Article 6, Hollingsworth, 2015, Challenge #2), with transmission being focused in so-called "hotspots" or in mobile populations that are exposed to infection through forestry or

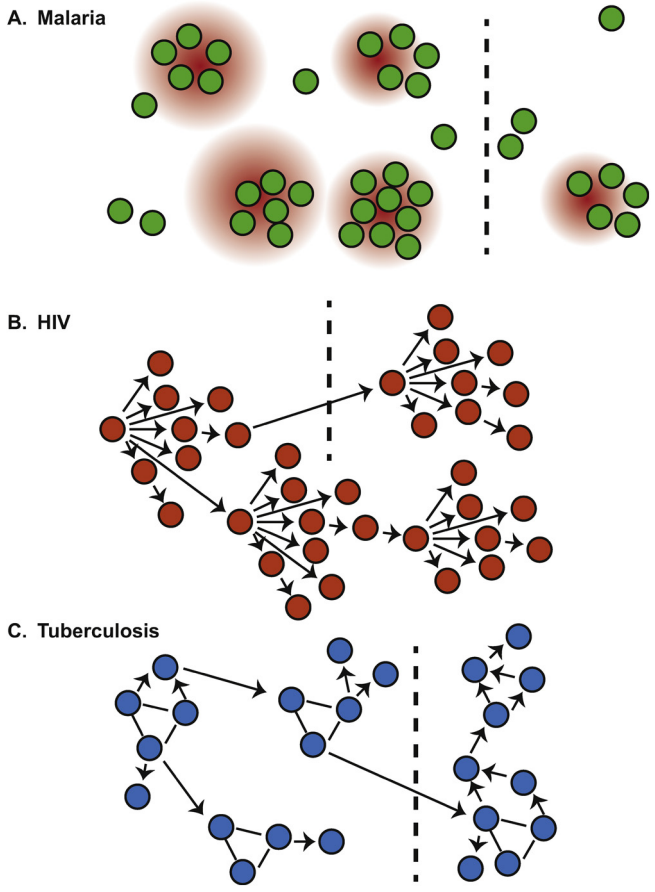

Fig. 2. Networks for spread of infection. Malaria (A) transmission between individuals (circles) requires the mosquito vector, resulting in "hotspots" for transmission driven by heightened exposure to malaria-infected mosquitoes in certain regions (red shaded circles). For HIV (B) and TB (C) transmission occurs between individuals in a directed fashion indicated by arrows. Dotted black lines indicate spatially separated populations. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

agricultural work (Bousema et al., 2010; Ahmed et al., 2013; Carrara et al., 2013). These heterogeneities are obscured by prevalence estimates that are generally derived on large spatial scales, and decrease the predictive power of mathematical models of transmission (Hasibeder and Dye, 1988) (Article 20, Riley et al., 2015, Challenges #1 and #5). Complex dynamics may emerge from the interaction of seasonal travel for agricultural work and seasonal changes in the environmental drivers of mosquito populations, and are difficult to accommodate in current model frameworks. Additional variation arises as many individuals do not seek treatment or use preventive measures like bed nets despite widespread availability, which makes it difficult to predict the impact of interventions and the timelines required for control and elimination.

HIV spreads unevenly through communities defined by distinct behaviours (Fig. 2B), such as sex workers, men who have sex with men, and injecting drug users (Gupta et al., 1989; Eaton et al., 2011; Garnett and Anderson, 1994; Tanser et al., 2011; Zuma et al., 2005). Measuring and quantifying the heterogeneities in these networks remains challenging (Article 21, Eames, 2015); for example, partnership acquisition rates are needed to generate realistic contact networks in models, but generally only cross-sectional data is available on the total number of partners each individual has over a specified time period (Abuelezam et al., 2013). These different social groups may also exhibit systematic variations in behaviours affecting treatment-seeking, adherence to treatment, and exposure, such as the use of condoms or the dropout of people over the so-called treatment cascade (Losina et al., 2010), which can further alter the risk and course of infection. Even when detailed data is available, the incorporation of temporally changing interactions is challenging to include and nearly impossible to accurately parameterise. Static and highly simplified contact patterns are often used in the absence of data on the complex and dynamic network structures that actually underlie HIV transmission.

For the spread of TB (Fig. 2C), many occupational and behavioural risk factors that enhance transmission have been clearly identified, focusing attention on the homeless and substance users in low burden settings in the US and Europe (Lonnroth et al., 2009), and on health care workers, drivers of crowded vehicles, prisoners, migrants, those working in mines and residents of overcrowded slums in high burden countries (Bates et al., 2004). Collecting reliable data on patterns of movement and migration is difficult, particularly across borders among refugee and migrant communities, who are at high risk of infection (Article 22, Lessler et al., 2015). Among those infected, behaviour strongly influences the duration of infectiousness because treatment seeking depends on access to care and recognition of symptoms, which overlap with other chronic lung conditions including smoking (Storla et al., 2008). All of these factors lead to difficulty identifying the infectious population, while the lack of granularity in incidence and prevalence data and the inability to directly capture values for behavioural parameters make valid parameterisation of models challenging (Article 23, De Angelis, 2015, Challenge #4).

Despite the known importance of behaviour on disease prevalence, the extent of the infectious population, and the emergence of drug resistance, the social factors that drive individual behaviours are poorly understood. What level of behaviour change is necessary to alter an epidemic (Article 4, Funk, 2015, Challenge #1) and the level of detailed data required to measure this change (Article 4 Challenges #2 and #4) remain open questions. Social and spatial aspects are often not accounted for in traditional model frameworks, which generalise behaviour on a population level, and this not only distorts epidemic dynamics but also underestimates re-exposure and reinfection among groups most at risk (Perkins et al., 2013) (Articles 16, Roberts, 2015, and 19, Ball, 2015). Furthermore, most models treat behaviour as static, although modifications of behaviour are likely to change as perception of risk shifts along with transmission. Incorporating variation in behaviour over the course of an intervention or in the case of multiple interventions is essential if models are to reliably predict the impact of the interventions or calculate their cost-effectiveness (Dye and Williams, 2008; Long and Stavert, 2013) (Article 2, Klepac, 2015, Challenge #5).

Conclusion

As we move towards control and potentially elimination for malaria, HIV, and TB, mathematical models provide a powerful framework to consider the possible impact of interventions, identify areas where further empirical work is needed, and focus on the important policy and research questions. Critical knowledge gaps for the effective application of models for policy include spatial and temporal variations in disease prevalence and transmission intensity, host–pathogen interactions and infection outcome, and human behaviour. Most importantly, better communication between modellers and experimentalists or field workers will be needed to refine the questions, determine which data are most important and must urgently needed, and to ensure that the analytical work leads to better policy and better control of all three infections (Article 2, Cunniffe et al., 2015; Metcalf et al., 2015b, Challenges #4 and #6).

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