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Six challenges in the eradication of infectious diseases

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ABSTRACT

Eradication and elimination are increasingly a part of the global health agenda. Once control measures have driven infection to low levels, the ecology of disease may change posing challenges for eradication efforts. These challenges vary from identifying pockets of susceptibles, improving monitoring during and after the endgame, to quantifying the economics of disease eradication versus sustained control, all of which are shaped and influenced by processes of loss of immunity, susceptible build-up, emergence of resistance, population heterogeneities and non-compliance with control measures. Here we discuss how modelling can be used to address these challenges.

Introduction

Only two diseases, smallpox and rinderpest, have been eradicated. Yet eradication is increasingly part of the language of the global health community. Calls have been made for the eradication of diseases as diverse as guinea worm and malaria. While each disease poses a unique set of issues, there are a number of recurring challenges that emerge during the endgame, or the phase during which control efforts are intensified and targeted towards achieving elimination locally and eradication globally (see Fig. 1 for a visualization of different control stages towards elimination).

In order to be successful, eradication effort has to permanently eliminate a pathogen everywhere in the world; pathogen prevalence is globally reduced to zero, thereby removing the risk of re-introduction and re-establishment. Elimination, on the other hand, is a more localized effort that focuses on reduction to zero incidence of a certain pathogen in a given area, with active measures to prevent pathogen re-establishment from other areas after elimination. Since eradication is elimination on global scale, there are many similarities between those two efforts, particularly in dynamical transitions from endemic transmission to elimination and post-elimination period of enhanced vigilance (see Fig. 1). Once infection is driven to very low levels, the ecology of pathogens may change requiring different surveillance and control strategies. Susceptible build-up, waning of immunity, increase in the age of infection, non-compliance of individuals with control measures, pathogen change and emergence of resistance as a result of intensified efforts all become increasingly important during the final stages of eradication programmes. This calls for the development of a research agenda for epidemiological modellers that directly addresses these challenges, from the design of models to target control strategies, to the optimization of surveillance and determining data needs to address, amongst others, the questions we outline below.

In addition to visualizing stages of elimination and corresponding reduction in disease prevalence and change in dynamical regime, Fig. 1 also serves as a timeline of eradication efforts that we use to structure the rest of this manuscript. Before eradication efforts are attempted, is there a way to estimate how likely are they to succeed and how much they are going to cost compared to sustained control? Is there a way to quantify the susceptible landscape

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that will improve targeting of efforts and monitoring strategies in the pre-elimination and elimination phase?

1. Provide a systematic framework for when we should try to eradicate

Eradication of infectious diseases is a vast public health, political and economic commitment and the intensity of efforts needed to eliminate a disease cannot be sustained indefinitely. The costs and risks are high, as are the potential benefits. During the dynamic transition from endemic transmission to local elimination (Fig. 1) potential shifts in age at first infection, waning of immunity, susceptible build-up, emergence of resistance, etc. can lead to dynamical feedbacks and logistical challenges that can cause unanticipated difficulties for eradication. For emerging infections, modelling pathogen properties demonstrated how timing of infectiousness and appearance of symptoms determines the likely success of isolating infectious individuals and their contacts in controlling an outbreak (Fraser et al., 2004). An analogous framework that can identify what makes a disease "easy" vs. "hard" to eradicate would be a first step in providing a mechanism of prioritizing efforts and strategies.

Such a framework needs to include processes that shape infectious disease dynamics but that operate on very different time scales. For example, intensive efforts exert strong selective pressures on the pathogen and prolonging the elimination phase (Fig. 1) increases the probability of emergence of antimicrobial or insecticide resistance, vaccine escape or antigenic divergence, potentially creating novel problems. While the evolutionary timescales over which drugs fail due to resistance are affected by application strategies or drug regimens, replenishment of susceptible populations and ageing of "naturally immunised" cohorts occur on demographic time-scales determined by turnover, which varies drastically across populations. Models can help identify key-time scales for eradication, how they vary for different pathogens, and how long can intensified elimination efforts be sustained, without detrimental consequences.

Biological feasibility of eradication depends, among other factors, on the pathogen lifecycle, its reservoirs, persistence in the environment, clinical manifestations of disease, sensitivity and specificity of laboratory tests to confirm the disease as well as safe and effective control measures. A related biological factor is the presence of related pathogens that might take advantage of a niche vacated by eradication (Lloyd-Smith, 2013). Although crucial, biological factors are not the only prerequisites – logistic, operational, political and socioeconomic factors are all critical in determining whether or not eradication can be achieved and should be incorporated into models.

2. Develop quantitative models of the economics of control versus eradication

Cost-effectiveness of control methods is increasingly a deciding factor in their implementation (Jit et al., 2008; Baguelin et al., 2012). The reasons for this are fairly intuitive, as it is rational not to attempt something unless the benefits of that action exceed the costs. Yet it can be difficult to accurately estimate costs of control efforts and their benefits when eradication is one of several options. Should we aim for long-term control, tolerating a certain level of infection, or should we push for eradication? When is one option preferable and what kind of models do we need to help distinguish between the two?

Analysis of costs is hard even retrospectively, but estimating these costs in advance is even more challenging. There are several reasons for this. First, costs of expanding control efforts increase; for example, the last foci of infection, or pockets of susceptibility will be those that are hardest to reach, either geographically or socially (e.g. vaccine refusers). The challenge for modelling is to accurately tie the economics of scaling up control programmes with the epidemiology and changing ecology of the disease (Klepac et al., 2011). Second, control efforts are implemented within health systems very differently from eradication efforts. Control programmes are usually integrated in horizontal programmes focused on strengthening primary care and providing 'health for all' (Aylward et al., 1998). Elimination and eradication efforts on the other hand often require a targeted 'vertical approach,' sometimes at the expense of other public health issues. But elimination efforts can also strengthen primary healthcare by providing basic services and improving surveillance (yaws), training personnel and expanding immunization programmes (smallpox), or establishing a global laboratory network (polio) (Klepac et al., 2013). The impacts on health systems of such secondary or intangible benefits of elimination programmes are particularly hard to measure (Closser et al., 2012), posing a challenge of how to integrate them into models.

Expansion of efforts is very costly and prolonging the endgame leads to donor fatigue risking re-emergence if efforts are scaled-down prematurely. Prolonged low incidence levels during the epidemic tail (as illustrated by the low number of cases in the elimination phase in Fig. 1) can also lead to disengagement of communities with eradication efforts, complacency and 'individual fatigue' or even active refusal of vaccination (Saint-Victor and Omer, 2013). In addition, a prolonged epidemic tail may contribute

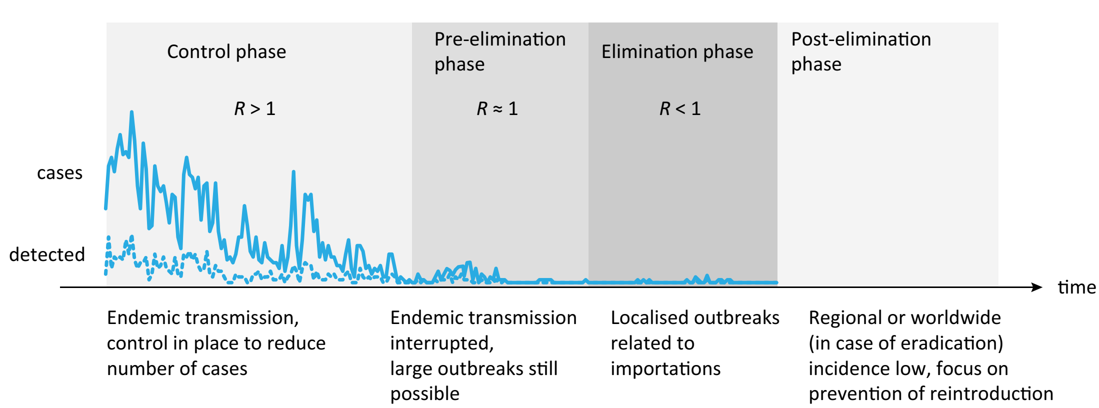

Fig. 1. Stages towards and after elimination in a given location and milestones on the path to elimination. Adapted from (Townsend et al., 2013b; World Health Organization, 2007). Shading illustrates control intensity (darker grey for heightened efforts).