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.

Keywords: elimination; surveillance; modelling; dynamics

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 Figure 1 for a visualization of different control stages towards elimination).

[Figure 1 around here.]

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

Challenge 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 (Figure 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 [1]. 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 (Figure 1) increases the probability of emergence of anti-microbial 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 [2]. 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.

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

Cost-effectiveness of control methods is increasingly a deciding factor in their implementation [3,4]. 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 [5]. Second, control efforts are implemented within health systems very differently from eradication efforts. Control programs are usually integrated in horizontal programmes focused on strengthening primary care and providing 'health for all'[6]. 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 immunisation programmes (smallpox), or establishing a global laboratory network (polio) [7]. The impacts on health systems of such secondary or intangible benefits of elimination programs are particularly hard to measure [8], 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 Figure 1) can also lead to disengagement of communities with eradication efforts, complacency and 'individual fatigue' or even active refusal of vaccination [9]. In addition, a prolonged epidemic tail may contribute to seeding outbreaks elsewhere [10], escalating the costs and jeopardising chances of success.

For many diseases, the probability of severe complications and the costs of treatment vary with patient age. Population ageing will therefore also affect the costs of control and elimination programmes. The impacts of changing demography might be more costly for sustained, long-term control efforts than for intense, but time-limited eradication programmes which might be a new argument for eradication. Models that consider epidemic, economic and demographic detail on an appropriate time-scale will help answer these questions. Estimates of disease burden that incorporate dynamical effects of control efforts (e.g. [11]) provide a promising avenue for quantifying these costs and benefits.

Finally, in some circumstances, projected costs may suggest that eradication is not feasible. Given that some of the benefits of eradication are difficult or impossible to express in monetary terms (e.g. improving the vaccine supply chain may enable easier and cheaper distribution of future antigens; possible non-linear interactions with other pathogens),

financial reasoning and cost-effectiveness may not be the only reasoning to guide elimination efforts [12]. Can modelling approaches offer alternatives that take us beyond cost-effectiveness? Developing consistent metrics of health benefits would make it easier to measure total direct and indirect benefits of implemented efforts and improve economic evaluations used to inform public health decisions.

Challenge 3. Identify the most effective approaches to achieve eradication

The dynamics of infectious diseases close to elimination can be distinctly different from natural dynamics (Figure 1). The distribution of susceptibility is no longer governed by a combination of replenishment of the susceptible population through births, and immunity through past exposure but, instead, by vaccination coverage, the extent of mass drug administrations (in the case of many campaigns against NTDs [13]) or behavioural changes (e.g. guinea worm that is on track to be eliminated without the use of drug or vaccine [14,15]). These interventions introduce an element of heterogeneity, which can affect infection dynamics. If those susceptible (e.g., unvaccinated) are preferentially in contact with each other because of geographical and/or social proximity, there is a risk of large outbreaks, which can be hard to predict because introductions into those populations might be rare.

Models need to be designed to take into account these dynamical transitions and predict where and when outbreaks are at most risk of occurring, as well as suggest appropriate prevention and intervention strategies. Using outbreak data from England and Wales, Jansen and colleagues [16] showed that while measles transmission in the UK remained subcritical (locally eliminated with short-lived outbreaks from imported infections) the reproductive number, R, significantly increased in the wake of declining vaccination coverage, suggesting that continued low vaccine uptake could lead to re-establishment of endemic measles. Similar branching process models may have utility for identifying pivotal dynamics during the endgame. Additionally, endgame dynamics should be reconsidered in the light of a heterogeneous landscape of susceptibility and stochastic fade-outs to inform how much control is needed to drive an infection to extinction and, consequently, how to best allocate the resources in eradication efforts.

Approaches during the endgame often differ from sustained, less intense control during the 'middle game' (Figure 1). The smallpox effort switched from mass vaccination campaigns to repetitive active searches conducted by a massive army of health personnel going door-to-door to look for any last remaining cases. Modeling work and statistical inference from polio surveillance data identified the value of switching to a more immunologically effective monovalent vaccine [17] prompting a substantial investment in vaccine development. India was recently certified free from polio, resulting from this switch [18]. Using models to assess the limitations of conventional control measures in the face of shifting dynamics, and identifying strategies that increase the probability of eliminating infection, such as the optimal time to intensify efforts or switch strategies, could reduce the length of the epidemic tail (such as in polio).

Challenge 4. Quantify the landscape of susceptibility

For immunizing (or partially-immunizing) infections, the age, location and social grouping of individuals that remain susceptible as incidence declines to low levels, will be the key determinant of progress towards elimination. The main data-stream available for evaluating this landscape of susceptibility is often surveillance for cases or deaths - susceptibility itself

is generally a hidden variable. For completely immunizing infections, susceptible reconstruction can provide some insight into the dynamics of immunity – but inference is weakened specifically where the risk of infection is low (i.e., in an elimination context), since the assumption that everyone can acquire the infection no longer holds.

Expanding the statistical and modelling toolset available for inferring the temporal, geographic, or social patterns of susceptibility is a key challenge in using modelling to support elimination or eradication efforts. This effort will likely include development of models that can synthesise diverse sources of information encompassing serological surveys, coverage estimates, and demographic rates among others. Quantitative descriptions of past dynamics of the population via these variables will inform the likely current proportion of susceptible individuals, their ages, and geographic locations. The history of outbreaks will be an important piece in this puzzle – a large outbreak or campaign could deplete susceptibles such that a long interval without infection ('honey-moon period' [19]) results; and can be followed by a large, late age outbreak (observed during the recent measles outbreak in Swansea [20]).

Amongst these various data-streams, serological surveys supply perhaps the most direct measure of susceptibility. Nevertheless, there are considerable open challenges in the analyses of serological data. For many infections, vaccine and natural immunity cannot currently be distinguished. Ideally, clinical measures of serology could be improved to allow this, but in the absence of such progress, models that build around other known variables (past outbreak sizes, coverage estimates, etc.) may be able to generate inference to distinguish vaccine coverage from natural immunity. This will allow detection of whether the disease is still circulating in certain populations or spilling over from nearby reservoirs (crucial for diseases such as rinderpest and FMD where premature cessation of vaccination can lead to costly resurgence). More generally, much of the data collected as part of a serological survey is often jettisoned in analyses – in particular, continuous titres are translated into discrete positive / negative variables. Data on the continuum of titre values might be leveraged to infer levels, or recency of exposure via models that incorporate epidemiological data.

As we address increasingly complex pathogens, which may fluctuate in their characteristics over time, space and severity of infections (e.g. malaria, where low immunity is linked to more severe infections [21]) such modelling innovations that yield deeper insight into the biology may be key. Furthermore, they may contribute to identifying if and when pathogen escape from chemotherapy or vaccination is occurring. Finally, a challenge is developing models capable of forecasting the likely consequences if an elimination program were to fail (for example, [22]).

Challenge 5. Improve monitoring during and after the endgame

Once a disease is close to elimination locally, the few remaining cases may be concentrated in hard-to-reach groups, for social, logistical or geographic reasons; may be predominantly asymptomatic cases; and may be temporally very irregular. Following elimination, new outbreaks may develop rapidly and be detected through clusters of severe cases, or may develop more slowly and be detected though serological studies. As immunity shifts in the population following elimination, the age-distribution or characteristics of cases may also shift. The question of how to design the right surveillance strategy to assist the drive towards elimination, to confirm that elimination has been achieved and to assist in preventing re-emergence all require a detailed understanding of the characteristics of the

disease and its dynamics (see [23]). A classic problem in elimination and re-emergence is that passive surveillance may only capture the 'tip of the iceberg' - normally the symptomatic cases or those that are laboratory confirmed [24]. Responses based on only these cases may be delayed relative to the outbreak. Either new diagnostics are needed to identify and treat asymptomatic cases (e.g. visceral leishmaniasis [25]), or responses need to take into account the likely pool of infectives around an identified case (the ratio of infections to reported cases). If the dynamics of the disease are such that there are hotspots of infection, this may make a spatial response a very effective tool.

In addition to the challenge of designing the right surveillance method epidemiologically, there are challenges around interpreting existing surveillance data, or designing new surveillance strategies that are logistically feasible. This includes not only monitoring of disease, but also of control processes, such as drug distribution, bed net usage (rather than distribution) and systematic uptake or refusal of vaccines (e.g. [26]).

A further complication in designing surveillance is accounting for spatial coupling (e.g. [27]) and interconnectedness of areas at different stages of elimination. For example, as part of a feasibility study of malaria elimination in Zanzibar, mobile phone movement data suggested that travel from mainland Tanzania was so intense that local controls alone would be unlikely to eliminate malaria due to high rates of importation [28].

Challenge 6. Identify post-eradication opportunities and threats

Finally, in the event of successful elimination/eradication how long do we need to hold the line? Should one invest in maintaining herd immunity, or implement low-level indefinite control, or stop with the efforts altogether (as with smallpox)? If we were to scale down or stop control efforts, when would it be safe to do so (see [24])? Should we switch to a different strategy and, if so, when? What are the spatial strategies for maintaining freedom from disease? What defines the width of a protective *cordon sanitaire* and how should elimination efforts be coordinated across international boundaries?

Models that estimate or account for spatial coupling could guide spatial strategies, to minimize re-introductions from endemic areas (through coordinated efforts) and maintain disease freedom (through for example the design of *cordon sanitaires*). Finally, models should be able to provide guidance on whether eradication has been achieved, by informing estimates of the proportion of cases detected for a given surveillance program [24].

Detection of low-level infection requires ever more sensitive and more accurate detection methods, so surveillance abilities are crucial in post-eradication strategies. Measuring loss of herd immunity or finding asymptomatic carriers might require new surveillance and monitoring techniques and better statistical tools in analysis of the relevant data. All of these need to be considered in a dynamical framework to predict possible shifts in dynamical regimes or potential tipping points for re-emergence of eliminated pathogens or emergence of related ones through competitive release in vacated niches [2].

Conclusions

Eradication initiatives require sustained public health, political, financial and individual efforts. It is a dynamical challenge that requires vast data integration over temporal, geographical and socioeconomic scales. Yet the inherently dynamic nature of infectious diseases can also have unexpected advantages. Even though the malaria eradication

programme in the 1950s failed, a number of successful countries have remained malaria free [29]. Models demonstrated malaria elimination to be a surprisingly stable state [29], indicating that elimination could be incrementally achieved without needing the simultaneous and correspondingly expensive effort as required for say polio. The eradication endgame poses a diverse set of challenges that can be addressed in a modelling framework leading to improved surveillance and control.

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Figures

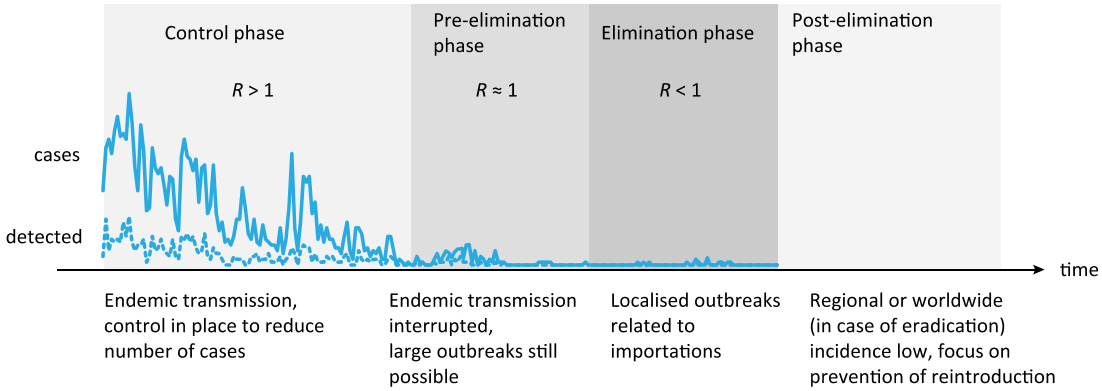

Figure 1. Stages towards and after elimination in a given location and milestones on the path to elimination. Adapted from [24,30]. Shading illustrates control intensity (darker gray for heightened efforts).