Milroy Lecture: eradication of disease: hype, hope and reality

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ABSTRACT

The possibility for one generation to eradicate a disease is very motivating. It is also very difficult. The many failed eradication attempts outnumber the one current success (smallpox), although two eradication campaigns for polio and Guinea worm are tantalisingly close to their goals. The early stages of a well-planned eradication campaign generally go well; it is the last stage where technical, biological, social and political problems occur. This paper considers the opportunities and pitfalls in planning for eradication of a disease.

KEYWORDS: Eradication, elimination, infectious diseases

Introduction

The possibility of eradicating disease has been discussed for more than 100 years. A significant number of diseases have been targeted for eradication at various points, including hookworm (1907), yellow fever (1915), yaws (1954) and malaria (1955). So far, however, only one human disease, smallpox, has been eradicated,[1] with rinderpest, a major disease of cattle, eradicated more recently.[2] Both of these were viral infections that could be prevented with a highly effective, long-lasting vaccine. Polio and Guinea worm are now tantalisingly close to eradication, but polio eradication has been close to eradication for a decade and so shows how hard it is to achieve.

Eradication is highly attractive as a concept. The idea that one generation can, for all time, get rid of a disease for all successive generations is very motivating, including to people not usually involved in public health. Under some circumstances, eradication can be highly cost effective, because a time-limited surge in spend can save for all time, and this certainly was the case for smallpox.[3] Even doing the preparation for an eradication campaign can stimulate innovation and change mindsets; the fact that malaria eradication is currently being considered has led to a systematic search for new tools and approaches.[4]

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There are, therefore, many reasons to take eradication of disease seriously when it is technically and politically possible. A number of diseases that would not have been possible to eradicate in the past may become so in the future. This is, in part, because of the gradual reduction in transmission of many major infectious diseases as countries develop. In the UK, the incidence of several previously important diseases, including tuberculosis, diphtheria and typhoid, have dropped rapidly over the past 150 years as the country has become richer, sanitation improved and health services developed. Development is occurring and accelerating in many other countries, and a number of infectious diseases will become relatively much rarer with reduced force of transmission over the next 50 years, so diseases currently not realistic for eradication now might, in theory, become so. At the same time, science evolves rapidly, bringing better understanding of the epidemiology, drivers and possible preventive strategies for many current infectious diseases.

To understand eradication, it is important to understand a few concepts, including the epidemiological concept of the basic reproduction number R_0. If $R_0=1$, on average, one person passes on an infectious disease to another one person to another one person and the disease is stable in the population. If $R_0 > 1$, the disease is increasing in the population. If R_0 drops below 1, the disease is decreasing, and local elimination and eventually eradication become possible. Eradication means natural transmission of the disease has ceased completely in the world. Elimination, often (incorrectly) used interchangeably with eradication, is a geographically defined interruption of transmission, but infections may be imported (malaria in the UK, where it was once endemic, would be an example of this). Finally, there is the slippery concept of 'elimination as a public health problem', which can have many meanings.

Three factors have always been considered essential to any eradication effort. The first is effective interventions that alone or in combination can interrupt transmission of infection or at least take it well below $R_0=1$ in all epidemiological settings. The second is that the disease has to be easy to diagnose, preferably with minimal complex laboratory facilities, so that the final cases at the end of eradication are identifiable. Smallpox, for example, could be diagnosed just by looking at someone, so finding the last cases was relatively easy and, indeed, schoolchildren were good case finders in the final stages.[5] Finally, there must be no significant animal reservoir.

A number of important infectious diseases that are now rare in humans, such as plague, will never be eradicated, because there is always a wild animal reservoir for the disease. In addition, for any eradication to be successful, we will need relatively simple-to-use technology, considerable central organisation, and sustained political will and money.

An eradication campaign traditionally has four phases: the preparation phase; an attack phase during which widespread use of effective interventions leads to the incidence of the disease dropping rapidly; a consolidation phase; and the eradication phase, when R_0 is reliably ≤1 almost everywhere, eradication becomes a possibility and the final push to eradicate is attempted. The first three phases are exactly the same as for a good control programme. It is the final push that makes eradication different from good control, and it is this that causes the greatest difficulties – both technically and politically – and causes the costs to build up. It is possible to be highly ambitious in reducing the impact of a disease globally or eliminating it in a few defined areas without going for the final step of eradication, and this will be the right approach for the great majority of diseases.

Some of the problems that occur when we try to eradicate diseases

Attempting eradication comes with trade offs that need to be addressed honestly. Trying and failing to achieve eradication comes at a very high cost financially, with consequently negative impacts on other diseases but often also for control efforts for the disease involved. Two examples are instructive. The massive campaign to eradicate malaria in the 1950s and 1960s was a remarkable global effort and led to a substantial reduction in malaria almost everywhere and local elimination of malaria from North America, Europe and parts of Australasia, Central Asia and Latin America. In public health terms, it was undoubtedly a success, but it was deemed to be a failure because the goal was eradication and this was not achieved. The result was a collapse in morale and funding for malaria, which lead to rapid rebound of the disease in many places and much-reduced investment in malaria control and research for almost 30 years.[6] Leprosy is another disease that had a global eradication effort. By effective case finding and treatment, the number of prevalent cases of active leprosy dropped rapidly, giving the appearance of success. However, the incidence of new cases has remained largely stable in Latin America and parts of South Asia.[7] The result of giving the appearance of getting towards eradication was very bad for leprosy control; Paul Fine asked the question 'what has been eliminated?' in leprosy and concluded that it was probably funding and expertise rather than disease.[8]

In deciding whether to attempt eradication, at least five issues can cause the attempt to fail. The first is that the technology and methods we currently have are insufficient to achieve the goal. This should be an obvious point, but, for example, the 1950s global malaria eradication campaign began despite the fact that some of those planning it knew from mathematical models that we did not have the tools to interrupt transmission in high-incidence settings in Africa. In addition, some people seriously promote human immunodeficiency virus (HIV) as an eradication target despite no evidence that we can interrupt transmission in all at-risk groups.

The second issue is the biological inevitability that exerting extreme selection pressure, which eradication inevitably does, significantly increases the risk of resistance evolving around the biological pressure put on the organisms that we are trying to eliminate. This may be drug resistance, insecticide resistance (eg to vectors), shifts in antigens for vaccine targets or behavioural changes. Smallpox had relatively little scope to evolve around vaccination, while complex organisms such as malaria parasites and mosquitoes, and organisms with substantial genetic or antigentic variability such as influenza, are much more able to do so. Anopheles mosquito resistance to dichlorodiphenyltrichloroethane (DDT) developed during the malaria eradication campaign in part due to this evolutionary pressure.

The third is organisation. With anything less than outstanding organisation everywhere that a disease exists, eradication will be impossible. However, equally important are social and political factors, which usually dominate in the terminal phases. These are not easy to predict reliably at the start. As incidence of a disease drops to much lower levels, it is increasingly unlikely to be seen as a problem by people in endemic countries, and all of the eradication campaigns to date, including the successful smallpox campaign, have found that some social groups object strongly to the very heavy control efforts needed toward the end of the programme to achieve the eradication of a disease they no longer see as a problem for them.[5] Polio, which has been very close to eradication for more than a decade, suffered in part from imperfect organisation[9] but more from social concerns from social and religious groups in Nigeria and Pakistan, who see no reason to collaborate on a disease they seldom now see.[10]

The final issue is one of political will, which is important to address social concerns, manage the major organisational challenges (in endemic countries) and maintain funding (in donor countries). It is a political reality that eradication is most attractive when a disease is very common and the voting public can clearly see that the benefits of getting rid of it are enormous. However, diseases are common because their incidence is high (R_0 is usually well above 1), so the chances of eradication are small. When the disease is very uncommon, the political advantage of investing a lot of resource into getting rid of the very final cases is low, as other public health problems become relatively more important to the population. For this reason, there is a political paradox for eradication in both space and time; it is most popular in the places where it is least technically possible and is also most popular early on in a campaign when the disease is furthest away from eradication. For example, many ministers in West Africa are very enthusiastic about malaria eradication because it is a major problem for their populations, but this, by definition, is because the incidence is high, and so elimination is a very long way off (R_0 >100 in many places). In Latin America, where malaria probably could technically be eliminated, it is not, because people now see bigger problems.

Some important considerations before embarking on eradication

The risk of trying but failing to eradicate is much smaller when elimination is 'sticky', ie when early gains are maintained even if elimination efforts stop, for example, because of a war, funding crisis or resistance evolving to a key tool. Sometimes this is because geographical isolation (eg an island or isolated

ecological niche) means that reintroduction is unlikely if an area is cleared of a disease or vector. In other places, if the disease has an R_0 of about 1 (ie is broadly stable) and is halved during an eradication attempt (even if it fails), the new 'normal' will be half the number of cases as before the campaign. Some of the neglected tropical diseases, such as lymphatic filariasis and trachoma, are probably in this group in certain geographical areas. However, this is not the case for some of the candidates for elimination, such as measles and polio:[11] as their R_0 is naturally well above 1, if a campaign fails in an area, or transmission continues at a low level in some high-risk groups, the incidence bounces back as soon as vaccine coverage drops, as has repeatedly been seen with polio. The recent mini-epidemics of measles in several communities in the UK where uptake of the measles, mumps and rubella (MMR) vaccine was low show how easily this can happen.[12]

One situation has repeatedly been shown to be unhelpful – when multiple diseases are being targeted for eradication simultaneously. The World Health Organization (WHO)'s smallpox eradication campaign was almost derailed on several occasions by the simultaneous (larger) WHO malaria eradication campaign.[5] Although the diseases themselves are very different, those who are expected to fund, organise and deliver elimination or eradication efforts in the field are often the same people. This eradication 'cannibalism' is a real risk at present, with multiple neglected tropical diseases setting highly ambitious 'elimination' targets at the same time as we are struggling to complete polio eradication.[13] Only if a disease is sufficiently small (in funding terms) and geographically distinct that it will not materially interfere with either resource or organisation is this not a risk; positive examples are the highly successful and focussed Guinea worm eradication campaign in Africa[14] and onchocerciasis elimination in the Americas.[15]

Finally, it is worth pointing out the difficulties of mathematically modelling the final stages of eradication. In the final stages of successful eradication campaigns, we end up with multiple islands of ongoing transmission with very different transmission intensities, of unknown size and, sometimes, with new routes of transmission and reservoirs. Even more importantly, social and organisational factors become increasingly dominant as eradication continues, and these are almost impossible to model reliably.

Conclusions

The energy, innovation and resources involved in eradication campaigns have helped inspire radical advances in controlling infectious diseases and continue to do so. By definition, eradication attracts bold thinkers. Smallpox and rinderpest show that it can be done – and that, under some circumstances, it is the right thing to do. However, unless we are very selective, eradication can distort public health priorities. A failed eradication campaign at best is a colossal waste of resources and at worst can set back control by many years. DA Henderson, the leader of the successful smallpox eradication campaign, said, 'I believe it is critical we should not be blinded to a range of new public health paradigms by staring too fixedly at the blinding beacon of a few eradication dreams'.[16]

To achieve eradication you need good technology, the maths must be right and, above all, the social, economic and political science for the endgame must be there before we start. Calling for eradication is easy, achieving it is not, and it will take a long time – always longer than planned and with most efforts in the 'final mile' when political support begins to evaporate. When eradication works, it leads to large investments producing indefinite gains. Trying and failing eradication is costly,[17] pulls resources from other priorities, breeds cynicism and may destroy good control programmes. The key, therefore, is not to call for it where we cannot achieve it, and, for most diseases, we cannot. Once committed to a few sensible and achievable targets for eradication, determination, organisation, stoicism, deep pockets for a very long haul, innovation and flexibility are essential. ■

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