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26 April 2017

**The Eradication of Infectious Diseases**

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When Gresham College was founded infectious diseases dominated medicine in Britain. Diseases such as plague, cholera, dysentery, malaria, polio, typhus, typhoid, tuberculosis and leprosy were widespread. Most remain major diseases of less wealthy countries, and can still be imported to industrialised countries. Controlling these diseases has been one of the great triumphs of public health and economic development and most of them are now in steady retreat. This lecture will consider the boldest method of control of any infectious disease; to eradicate it altogether.

The case for eradicating some of the world’s deadliest or most unpleasant infectious diseases is easily made. By the efforts of one generation, all subsequent generations are spared the disease. Wisely chosen, eradicating a disease can mean a short period of high investment followed by saving for all time because the costs associated with prevention and treatment of the disease are no longer needed. Eradication is a bold enough goal to excite interest and enthusiasm in parts of the public, press and political structures who are not usually engaged in public health.

This lecture will consider some of the diseases which have been eradicated (smallpox), are likely to be eradicated in the next few years (including polio), those where eradication is a technical possibility including many of the classical tropical diseases, and also those where although eradication is talked about it currently seems improbable including major diseases such as HIV and measles. There are formidable barriers to eradicating most infectious diseases; some of these are technical or biological, but many of the biggest hurdles are social or political. In 1979 my grandmother, who as a doctor in West Africa had seen the ravages of smallpox at first hand took me to pay homage at the statue of Dr Edward Jenner in Gloucester Cathedral in the year the World Health Organisation declared eradication of the disease. In public health we need the boldness of vision that allowed people to turn Jenner’s discovery of vaccination against smallpox into global eradication, but it must be tempered boldness. In a small church a few miles away from the statue of Jenner a prisoner of war from the English Civil War carved ruefully a (mis)quotation from Spencer’s *The Faerie Queene:* “Be bold, be bold, but not *too* bold”. This seems a good starting point when considering eradication.

Although it has a strict definition, for practical purposes *eradication* is the complete and permanent removal of an infection everywhere in the world. It will never occur again. Only one human disease has been eradicated to date- smallpox (although both the USA and Russia hold stocks of the virus). Additionally, one major cattle disease, Rinderpest, has been eradicated using vaccination. Part of the way towards eradication is *elimination* of a disease, usually in a defined geographical area. This is when transmission has ceased in that geographical area, although cases may be imported from elsewhere. For example in the UK plague, malaria, rabies and cholera, all of which used to be transmitted here, have been eliminated although malaria cases are imported into the UK every year.

The basic epidemiological concept to understand eradication is R0, or R. If R is 2 on average one person with a disease infects two people who give it to 4 people and so on, so the disease is expanding in the population. If R is 1, on average one person gives it one person who gives it to one person meaning the disease is stable. If R is less than one, say 0.5, then eight people transmit it to 4 people who transmit to 2 people and eventually the disease will die out. If R can be brought below one for long enough over a geographical area a disease will be eliminated; if it can be brought below one everywhere in the world for a sustained period it will be eradicated.

The tools we have available to reduce the transmission of infections vary by disease. For some diseases, especially viral diseases such as smallpox or polio, vaccination is highly effective. For insect borne diseases such as malaria or human African trypanosomiasis (sleeping sickness) attacking the vector or reducing biting will be important: insecticide treated bednets are an example. For many diseases finding cases and treating them with drugs, mass drug administration for the whole population can be used. Better housing, sanitation, clean water and diet can all play a role. Whatever method or combination of methods is used for eradication to be feasible they have to be able to get R under 1 everywhere.

In addition to an effective intervention there are a number of other preconditions for an eradication attempt. The disease must be relatively easy to diagnose or it will be impossible to find the final cases. Eradication is impossible if there is a significant animal reservoir, particularly if they are wild animals. For example it would not be possible to eradicate Ebola because it has reservoir in bats, or yellow fever because it has a reservoir in monkeys, or rabies because many animals can carry it. The intervention must be simple enough to be possible to use in some of the most basic health systems, since it likely the final cases will be in countries with weaker health systems, or in areas of conflict. There has to be extremely good organisation everywhere where the disease occurs, strong political will to succeed, and substantial resources. Every eradication attempt, whether successful or not, has taken much longer and cost more than those who planned it expected.

There are in practice four stages to an elimination or eradication attempt. Initially there is a preparation stage in which the scale of the problem, the possible tools are tested, mathematical modelling and political analysis is undertaken. Once there is a technically feasible plan there is then the attack phase in which the intervention to interrupt transmission is rolled out everywhere the disease occurs. Unless the disease for eradication has been very badly chosen, this will invariably be successful in the sense that disease numbers will initially drop rapidly. Then follows a consolidation phase in which the health systems are adjusted to the new reality. Finally is the push to true elimination and then eradication. This final stage is what differentiates eradication attempt from good disease control. It is also the stage which is most difficult both technically and politically, and where most eradication attempts have foundered.

Smallpox is to date the only disease that has been eradicated, so it is worth considering in detail. A terrible disease, which killed between 300 and 500 million people in the 20th century, and left many others scarred and disabled, the WHO declared eradication as the goal in 1959. With the benefit of hindsight smallpox was a good choice: it had a highly effective vaccine, which was easy to administer and long lasting; it was very easy to identify cases since you could simply see them; it was widely feared so political and social support for eradication was strong; there was no animal reservoir; it had limited ability to evolve around the vaccine (unlike for example influenza, the common cold or HIV). Despite this politics and organisational problems almost derailed the eradication attempt on several occasions.

The smallpox eradication attempt, which involved vaccination using a simple bifurcated needle, was extremely well organised even in some of the most difficult environments either because of remoteness or political problems such as war. By the mid-1960s it was in full swing, and the last continuous case, in Somalia, occurred in 1977. There was one case due to laboratory error in Birmingham a year later. The cost effectiveness of this eradication campaign which is estimated to have cost $300 million was very high with savings about 160 times that. There is no doubt, even with the benefit of hindsight, the decision to attempt eradication was the right one.

One of the key operational lessons from the smallpox campaign was that in the initial attack phase it was essential to have complete tactical rigidity with everybody doing the same thing. In the final stages, when smallpox was fragmented into lots of small local epidemics there needed to be great tactical flexibility to adapt the local campaign to the local environment. This for example included recruiting schoolchildren to find the final cases.

Two other diseases are now very close to eradication, although victory cannot be assured at this stage. The first is polio. A crippling disease, highly effective oral and injected vaccines for polio have been available for many years. Polio cases which are symptomatic (most are not) are relatively easy to diagnose because of the characteristic paralysis they cause. There is no known animal reservoir. Rapid progress was made in shrinking the map of polio from the mid-1980s to the early 2000s. At that point progress slowed. Some of the problems were technical, including vaccine efficacy, and very rare cases of polio caused by the live vaccine itself. The main barrier to eliminating polio was however political. Polio cases continue to be transmitted in areas of instability where it was difficult to access such as Waziristan (in Pakistan near Afghanistan), Somalia and for different political reasons northern Nigeria. Cases got re-exported from these places setting off new mini epidemics in for example Syria. Gradually over the last 15 years the numbers have crept down, and in the last 12 months cases have been reported. Tragically, social and political opposition to the polio eradication attempt has led to many polio workers being killed.

The second disease where we are probably down to the last few cases is Guinea worm. Once very common, this very painful worm which comes out through the skin has had transmission interrupted by improving access to clean water and the simple method of teaching people to drink water from open sources through a pipe with a cloth filter. The filter stops the water fleas which pass on the worm from being ingested. The end stage of this eradication attempt has however been complicated by finding that occasionally dogs can act as a reservoir of infection.

Alongside these actual and probable successes, there have however been many failed or relatively ineffective eradication attempts. These include attempts to eradicate hookworm, yellow fever (which has an animal reservoir), Yaws which is a close relative of syphilis, malaria and leprosy.

The biggest eradication attempt so far was the WHO malaria eradication campaign. Malaria was, and is, one of the great killers of children and adults; there is no doubt eradicating it would be a huge boon to humanity. The first global attempt to eradicate it starting in the 1940s was organised on a massive scale, and remains an extraordinary technical and logistical operation. It was partially successful as it led to malaria being pushed out of Europe, the USA, and several areas of Asia. Eradication is however something where partial success is still perceived as failure. The malaria eradication campaign collapsed in the early 1970s, and there were multiple reasons for its failure. Probably the most important was we simply did not have technical tools sufficient to take R below one everywhere in the world. In many areas, particularly of Africa, R for malaria is over 100. Getting that below 1 for a sustained period would be difficult even with highly effective interventions. The tools we had, spraying DDT insecticides for mosquito control and drug treatment, were sufficient to overwhelm the relatively low R in most of Europe and the USA but not in Africa. The second set of reasons were that the very strong evolutionary selection pressure imposed on mosquitoes and the parasite by the campaign meant that insecticide and drug resistance started to evolve. There were compounding organisational problems, and on top of them significant political difficulties. Because the natural force of transmission of malaria is high in many countries, as soon as the pressure of the (very expensive) eradication campaign stopped malaria roared back. The point about malaria eradication is that unless it is eliminated everywhere (true eradication) it will rapidly re-establish itself by re-invading from places it has not been eliminated and where its natural transmission is high. It took three decades before malaria control lost the stigma associated with what was seen as a major failure, and during this period there was limited investment relative to the need. Over the last 15 years thanks to renewed investment malaria rates have dropped in most cost the world making elimination substantially more realistic in several geographical areas then it was in the 1970s, and new tools have been developed. Whether, or when, we are ready for another attempt at global eradication is a central question for international public health, although a major drive to develop the technical tools necessary for success in eradication is underway.

The most damaging starting point for many eradication attempts has been a strong optimism bias. Without optimism we would never even try eradication attempts, however technically feasible; with irrational optimism we will always fail. Two other eradication attempts which were relative failures are worth examining. In both cases overpromising eradication led to subsequent underinvestment and damage to existing effective control programs when this did not happen. The first is leprosy, a major stigmatising disease that causes substantial disability. A decision was taken to eradicate it as a public health problem in 1991. Success, defined as prevalent cases, was redefined several times and in theory the goal was reached in 2000. Despite this, the number of new cases (incidence) remain stable in the key affected countries. The promise of eradication however led to disinvestment from leprosy, to the point where the question was recently asked: what was being eliminated? Leprosy or the science and expertise to control it? Arguably the eradication attempt, by failing, damaged leprosy control.

Another eradication target was Yaws, a close relative of syphilis but not passed on sexually. After initial success number of cases was so small that attention switched away from it; the control programs collapsed and the disease rebounded almost to the same levels it had been before the eradication attempt in many parts of the world.

If trying to eradicate one disease is difficult, trying to eliminate and eradicate multiple diseases simultaneously in the same place is even harder as a result of the risk of cannibalism between the programs. Whilst program staff, organised vertically, may concentrate only on their disease, the governments and donors who have to pay for eradication attempts and even more importantly the staff on the ground delivering them are all the same people: it has therefore proved very difficult to maintain more than one major eradication attempt simultaneously. This point is important because the world committed to eradicate or eliminate multiple neglected tropical diseases by 2020, including Yaws, Guinea worm, human African trypanosomiasis (sleeping sickness), onchocerciasis (river blindness), trachoma another major blinding disease and several others. For each of the neglected tropical diseases listed above eradication is probably technically possible with existing tools, and elimination in many countries is realistic, but the timelines for eradication are overly optimistic and undertaking them all simultaneously is going to be a serious challenge once we get to the end game which is always the most difficult and expensive part.

 In addition to these diseases where at least the technical outlook for elimination and possibly eradication is reasonable, there is excitable talk about eradicating diseases such as HIV and measles. The likelihood of either of these in the foreseeable future is slim. In the case of HIV whilst death rates are falling rapidly due to wider availability of effective treatment, the incidence of new cases of is not dropping at an appreciable rate in the most highly affected countries. To achieve this would require either or all of a vaccine, a full cure, or a major behavioural intervention: all have proved elusive. Measles has recently (2000) been eliminated from the USA, but it is highly infectious and in any relaxation of control efforts will lead to its reintroduction. Measles elimination in most developing countries is a very long way off. The MMR scare that followed the unscientific claims of Andrew Wakefield, amplified in parts of the media, led to mini-outbreaks in parts of the UK demonstrating both that no country is immune from vaccine scares, and that measles can rebound very rapidly.

Eradication or elimination is least risky where any advances are ‘sticky’. This means than an advance, once achieved, will be maintained. For example, if the disease is reduced by half, and R is around 1, even if there is then an interruption (e.g. a stockout, a war, a vaccine scare) the gains achieved so far will be maintained.

The major stumbling blocks to eradication are as often political or social as they are technical. There is a political paradox for eradication. It is most popular in the places it is least achievable: for example in parts of West Africa where we are a long way from having tool strong enough to eliminate the disease malaria eradication is exceptionally attractive to politicians because their constituents or have family members affected by it. The fact it has such high transmission rates is what makes it important politically; that is exactly what makes it difficult technically. In Latin America, where many countries could technically eliminate malaria, the political enthusiasm for doing so is low because so few people are affected by it and most of those are in marginalised groups. There is also a temporal paradox: eradication is most popular at the time we are furthest away from it (at the beginning of a campaign), but becomes less popular as the importance of the disease relative to other conditions decreases due to successful campaigns. Maintaining political support in the early attack phase when everything is going well and people can see an important local problem disappearing is straightforward but maintaining it when for many years large resources have to be ploughed into a campaign for a disease which because it is close to eradication so very few people see is much harder.

Linked to this is the social problem that the last cases will often be in places which are either highly fragile or in frank conflict (polio and smallpox are both examples). It is also easy to weave a conspiracy theory around the fact that foreign groups and the government are putting huge resources into a disease which almost nobody sees any more. The violent opposition to polio vaccination for eradication was also seen at a lower level in the terminal stages of smallpox eradication and the first global malaria eradication campaign. Perfectly rationally, people prioritise the diseases and social issues they see a lot of rather than ones that used to be a problem in the past. In the case of polio several political groups and actors in various conflicts additionally used the campaign for their own ends. The biomedical model of disease is also not universally accepted.

Each eradication campaign will have its own specific technical problems but some are general to all attempts. If the infection under attack is able to evolve resistance to a drug or around a vaccine it will do so due to the extreme evolutionary pressure and eradication campaign exerts. As the infection becomes less and less common it does not subside equally everywhere but turns into multiple small islands of high transmission in a sea of very low transmission. Each one of these has to be found and tackled individually: many will be in very difficult to reach areas. It is likely that new modes of transmission or new reservoirs of infection will be found towards the end of eradication campaigns as happened with Guinea worm.

These political, social and technical difficulties should not put us off eradication attempts but should make us clear eyed about the probability of success before we start. Eliminating specific diseases from specific geographical areas has occurred many times and will occur many times into the future; wherever this can be achieved and maintained it should be considered. For many of the classical tropical diseases this is already occurring. Full-blown global eradication is a much tougher proposition and only a small number of diseases combine both technical feasibility and the potential for durable political support for the long haul. We have some absolute and relative successes already: Smallpox is gone, Guinea worm eradication in humans will succeed, polio will if we can sustain support. Excitement about (and money for) malaria eradication has triggered widespread innovation. Many of the neglected tropical diseases are technically realistic prospects for eradication, although it will take a long time even if a serious attempt is made. Trying and failing eradication is however costly, pulls resources from other priorities, breeds cynicism and may destroy good control programmes for decades. Don’t call for it when we can’t do it, and for most diseases we can’t. Once committed determination, excellent science, organisation, stoicism, deep pockets, innovation and flexibility are essential.

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