Free, at last!

The progress of new disease eradication campaigns for Guinea worm disease and polio, and the prospect of tackling other diseases

Infectious diseases have moulded the development of the human species more than any other biological or abiological factor. They have influenced not only our biology, but also our history and political development; from the outcome of wars to the success of empires, and from the pace of technological advance to the structure of society itself. The introduction of smallpox to the Americas by European conquerors, for example, devastated the indigenous populations and destroyed mighty empires and advanced societies. In the 1400s, the Black Death killed between 30% and 60% of the European population, and continued to blight the continent intermittently until the eighteenth century with severe and lasting social, economic and political consequences. Similarly, the 1918–19 Spanish flu killed more people in less than one year than did the horrifying battlefields of the First World War. Even without causing major pandemics, persistent infectious diseases such as malaria, tuberculosis or measles have been imposing their burden on humanity with no less devastating effects.

The use of hygienic practices and the development of vaccines and antibiotics have given modern doctors and public health experts the edge over infectious diseases. Yet, many experts have long debated how to rid humanity of the worst diseases once and for all. So far, this has been a matter of rather academic and political debate, although global disease eradication—the complete elimination of a pathogen—became a reality in 1980 when smallpox was officially consigned to history (see Sidebar A; Figs 1,2). Despite this significant success, and despite the enormous advances made by the biomedical sciences during the last century, many infectious and potentially eradicable diseases continue to take their toll on humankind, particularly on the poorest of the world's people. However, some promising developments and successes during the past few years have rekindled the hope that further eradications can be achieved (Aylward & Birmingham, 2005). However, this does not necessarily imply that we will have to deal with fewer pathogens—we are 'discovering' new diseases much faster than we are eradicating old ones.

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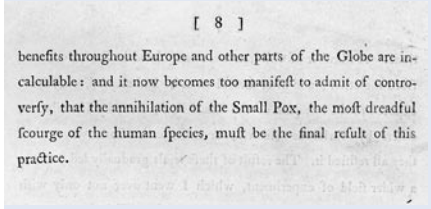
Before proceeding, it is worth defining the relative terms of victory in the war against infectious diseases. The ultimate goal, eradication, means the permanent global reduction of an infectious disease's prevalence to zero, as was achieved with smallpox. Once this goal has been reached, intervention measures are no longer needed. Conversely, elimination refers to the reduction of a disease's prevalence to zero in a defined geographical area; in this case, continued intervention measures are still required because the pathogen remains present elsewhere. Finally, disease control refers only to the reduction of a disease's incidence and prevalence—rather than a reduction to zero—either locally or globally.

In fact, smallpox was not the first bane to be tagged for oblivion. The story of disease eradication goes back further than 1980 and the field has grown to a point that it can now be considered a medical discipline in and of itself. Early in the twentieth century, for example, US Major General William Gorgas (1854–1920), Surgeon General of the US Army (1914–18), contributed to the successful elimination of yellow fever from Havana and Panama through control of the mosquito vector, which raised expectations that the disease could be completely eradicated. This hope eventually died after the discovery that yellow fever is a zoonose—a pathogen with an animal reservoir in which to reproduce;

Sidebar A | Benchmarking on smallpox

"Having considered the development and results of the global programme on smallpox eradication initiated by WHO in 1958 and intensified since 1967 [The World Health Assembly] declares solemnly that the world and its peoples have won freedom from smallpox, which was a most devastating disease sweeping in epidemic form through many countries since earliest time, leaving death, blindness and disfigurement in its wake and which only a decade ago was rampant in Africa, Asia and South America"; these words, in a resolution of the 33rd World Health Assembly in 1980, officially declared smallpox to be eradicated (Pennington, 2003). Although the virus was already disappearing from developed countries owing to mass vaccination campaigns—smallpox, at least its *Variola major* form, was eliminated from the USA in the 1940s—global eradication still required an extraordinary concerted action. It was mainly orchestrated by the WHO and based on mass vaccination, and detecting and containing smallpox patients and their contacts down to the last case in the most remote areas, which involved tens of thousands of health workers and volunteers for years (Figs 1,2). But it was not only human ingenuity and efforts that won this battle. "It has long been recognized that smallpox is unusually vulnerable to control measures: there are predictable seasonal declines in prevalence; its geographic distribution is often focal, even in highly endemic countries; survivors are immune for life; almost all victims are easily recognized; smallpox is not as contagious as measles or chickenpox; and each victim is only infectious for up to 3 weeks. Moreover, the 12-day incubation period of smallpox is long enough to permit health workers to trace and prevent disease in contacts. There is no animal reservoir," wrote Donald Hopkins in 1976, on the verge of smallpox eradication (Hopkins, 1976). Whilst the new eradication campaigns are built on and inspired by this successful experience, and although they can take advantage of more advanced technologies, the diseases they fight are not necessarily as prone to be defeated, and industrialized countries not so willing to cooperate.



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benefits throughout Europe and other parts of the Globe are incalculable: and it now becomes too manifeft to admit of controverfy, that the annihilation of the Small Pox, the moft dreadful fcourge of the human fpecies, muft be the final refult of this practice.

Prophecy of eradication of smallpox, from *The Origin of the Vaccine Inoculation* by Edward Jenner (1801). Jenner is usually credited as the first to have induced immunization against smallpox by inoculating with cowpox vaccine. However, many have pointed out that vaccination with cowpox matter is documented in England and probably elsewhere well before Jenner's work. Credit: Wellcome Library, London.

Fig 1 | Smallpox eradication in Bangladesh. Rewards were given to those residents who had reported suspected cases of smallpox that were confirmed by an epidemiologist. This sign, photographed in 1975, was displaying the message announcing a 250 Taka (the official currency of Bangladesh) reward for reporting such a case. All rewards were handed out in a public place. Early on during the eradication campaign, the reward was 50 Taka, but as the campaign turned up fewer and fewer cases, the reward grew to 250 Taka. Credit: CDC/WHO; Stanley O. Foster.

in this case, non-human primates (Staples & Monath, 2008).

The second disease to be targeted for eradication was yaws, a non-venereal infection caused by the spirochaete *Treponema pallidum pertenue,* that can lead to bone, joint and soft tissue destruction in the worst cases. The World Health Organization (WHO; Geneva, Switzerland) launched the Global Yaws Control Programme in 1952, which treated 300 million people in 46 countries over 12 years, reducing the global levels of the disease by 95% (Rinaldi, 2008). After this encouraging achievement, however, attention shifted to other health emergencies and yaws resurged in many areas, particularly south-east Asia and Africa. Another failure was the malaria eradication programme that the WHO conducted during the 1950s, '60s and '70s. Despite substantial financial and material resources, the programme ultimately failed, mainly because of technical challenges, especially in Africa (Aylward & Birmingham, 2005). Malaria now accounts for the deaths of between one and three million people in Sub-Saharan Africa each year.

Lessons have been learned from both the failures and successes; it is now clear that no eradication programme stands a chance of success if not backed by careful evaluation and analysis. The International Task Force for Disease Eradication (ITFDE; The Carter Center, Atlanta, GA, USA)—an international group of experts founded in 1988—has highlighted seven diseases that it considers to be practically eradicable: Guinea worm disease, poliomyelitis, mumps, measles, rubella, lymphatic filariasis and cysticercosis (www.cartercenter.org). In addition, the WHO has stated that neonatal tetanus, leprosy, onchocerciasis and trachoma could be eliminated 'as public health problems' within a few years.

A mixture of biological, medical, economic and technical factors can contribute to making a disease potentially eradicable (Dowdle, 1999). The biological factors include that the disease should be restricted to humans—or humans should at least be essential to the pathogen's life cycle; that the disease be epidemiologically vulnerable—it should not spread easily and should have a natural seasonal decline in prevalence; and that no reservoir should exist either in another organism or in the environment. Neonatal tetanus, for example, can be eliminated

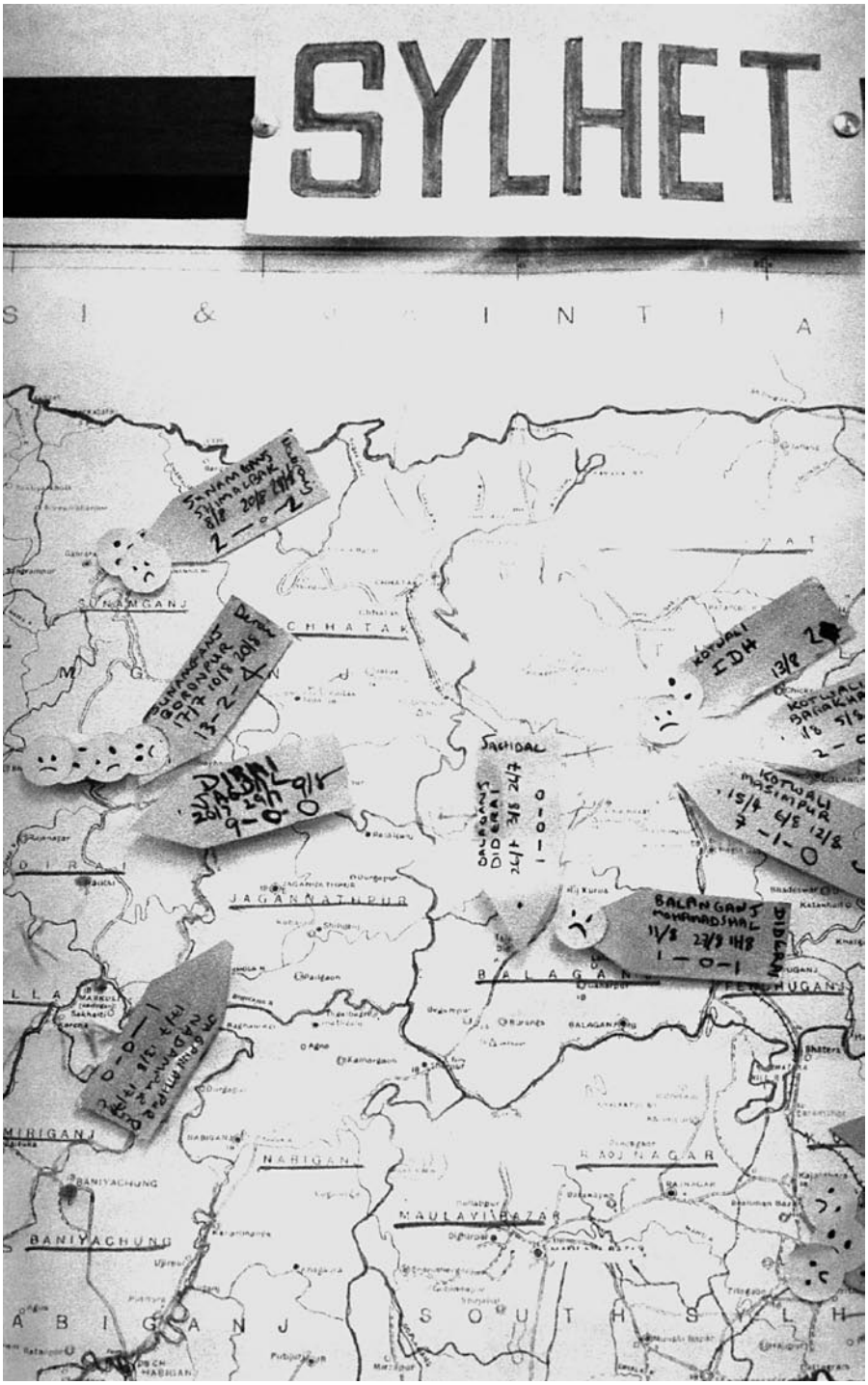

Fig 2 | Smallpox eradication in Bangladesh continued. Sylhet is a district region in Bangladesh, and this map depicted the 'thana' and villages throughout the district in 1975. The flagged areas represented the villages in which smallpox cases had been uncovered. During the house to house searches, each one of the 12 million homes had to be visited, in order to show residents the smallpox case photograph, as well as to announce the money reward for anyone reporting a case, and to ask if they had seen or knew of any cases resembling the one pictured. When eradication efforts began, there was one surveillance team for each of the five regions. With increasing volunteerism this grew to one team for each of the 55 districts and, in some regions, one team was assigned to each thana. A thana is analogous to a county in the United States; there were 415 thana to patrol. Some local residents became resident vaccinators and played a profound role in achieving a successful outcome to the eradication programme. As locals, they were viewed as familiar and trusted, and spoke the local dialect, thereby facilitating enhanced communication with fellow inhabitants. Credit: CDC/WHO; Stanley O. Foster.

in humans through vaccination, but the bacterium *Clostridium tetani* itself cannot be eradicated as its spores are ubiquitous in the environment. Important technical and medical factors include the availability of effective, affordable diagnostic tools and the means to interrupt transmission through the use of a vaccine or an efficient drug; while non-scientific considerations include the cost of eradication, and the expected level of social and political commitment to support the initiative. Failing to consider these aspects carefully in advance can ultimately ruin an otherwise promising eradication programme.

To save time, money and organizational resources, several campaigns that target different diseases are being conducted contemporaneously on a global or local scale, often integrating one effort into another. "Poor understanding of technical/operational feasibility, poor strategy, insecurity, inadequate funding and over-confidence are all major threats to completing the task," commented Donald Hopkins, Vice-President of the Health Programs at The Carter Center and a leading expert in eradication science. "One important strategic consideration is the need, in my view, to always start in the presumed most difficult geographic areas first, because such areas will require the most time."

At present, two major global efforts are under way to eradicate Guinea worm disease and poliomyelitis. The project closest to reaching its goal might be the one targeting Guinea worm disease, or dracunculiasis, which may even achieve success this year—meaning that zero cases of the disease would be reported during 2010. Guinea worm disease is a parasitic infection by the nematode *Dracunculus medinensis*, the larvae of which enter the human body when a person drinks contaminated water. Once inside the body, the larvae develop, and the female and male

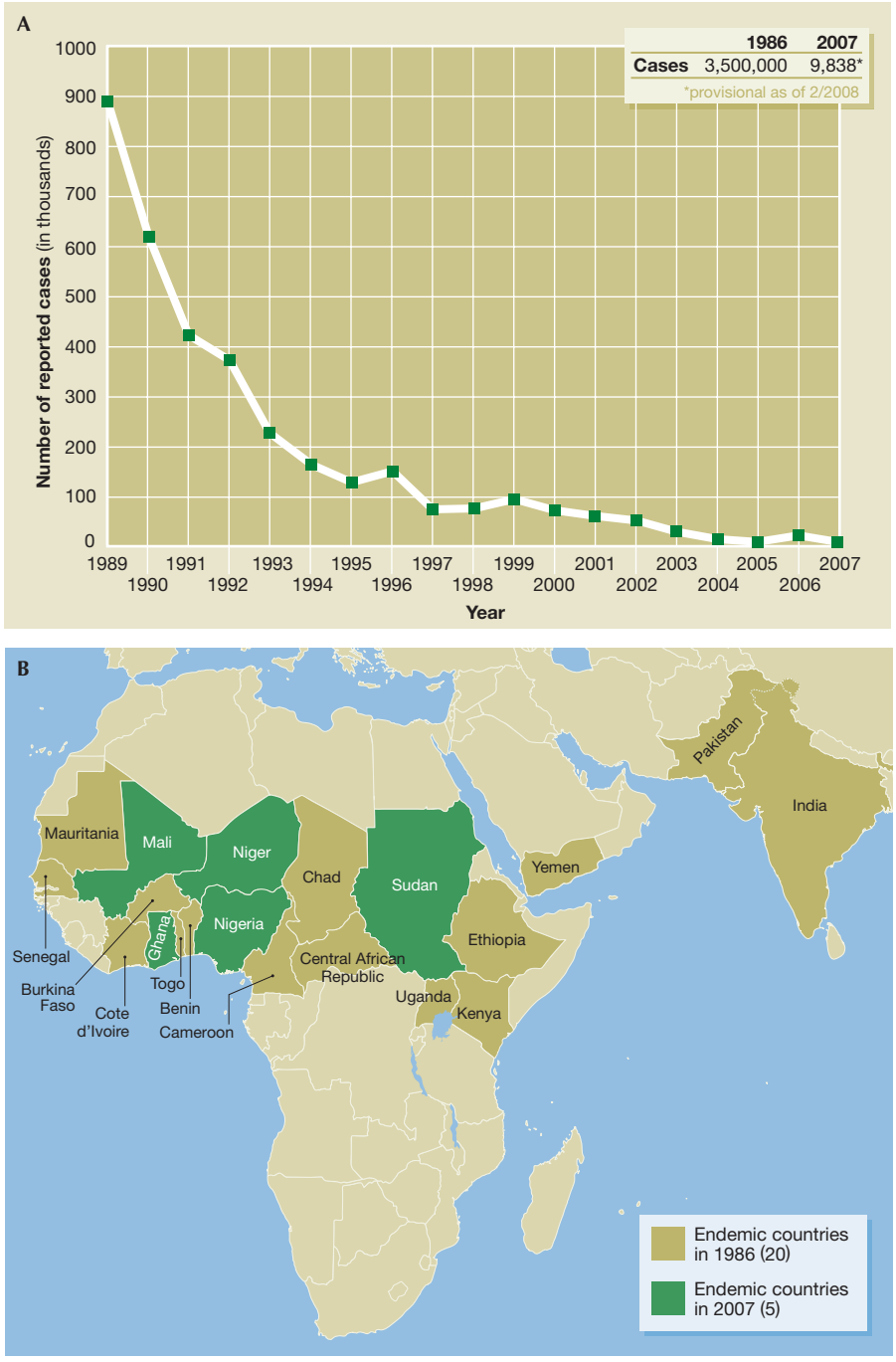

Fig 3 | Number and map of distribution of reported indigenous cases of Guinea worm by country up to 2007. As of December 2008, 4,643 new cases have been reported, and Ethiopia, where 39 cases were reported, was added to the list of countries where the disease is still endemic. Source: The Carter Center.

worms mate. Larvae-carrying female worms then move through the subcutaneous tissues and cause a painful sore in the skin, usually on the lower limbs, which stimulates the afflicted to seek relief by immersing the limb into water. On contact with the water, each female worm releases its larvae (Barry, 2007; WHO 2008a) and the cycle starts again.

Although not usually a fatal disease, Guinea worm disease causes prolonged suffering and disability, and adds an extra burden of torment and deprivation on poor, rural communities. "Villagers of all ages were too weak to walk or permanently scarred and crippled. As a result, a community would go hungry because its farmers were too sick to work the fields," wrote Jimmy Carter, former US President and founder of The Carter Center, about his first encounter with Guinea worm disease in a village in Ghana in 1988 (Carter, 2008).

Although there is neither a vaccine nor a specific drug for the prevention or treatment of Guinea worm disease, it is nonetheless a vulnerable target: simply teaching people about the origin of the infection, and filtering contaminated water and protecting water sources from being entered by people with emerging Guinea worms can short circuit the life cycle of the parasite. However, effective implementation of these 'simple' interventions in remote, rural areas of Africa remains a major task, which requires a lot of attention and dedication, and cooperation from residents in affected communities. These inexpensive interventions have already had a huge economic and social impact: in the early 1980s, Guinea worm disease was endemic in 20 countries in Asia and Africa, with some 3.5 million cases occurring annually. A large-scale campaign by national eradication programmes, the US Centers for Disease Control and Prevention (CDC; Atlanta, GA, USA), the WHO, The Carter Center, UNICEF and others have reduced the global prevalence to slightly more than 4,600 new cases reported as of December 2008 in just six African countries where the disease remains endemic: Sudan, Ghana, Mali, Niger, Nigeria and Ethiopia (Fig 3).

Sudan, which accounts for more than 80% of all current cases, is the most problematic area owing to its vast size, poor infrastructure, and the armed conflicts that have continually taken place in the southern and western regions during the past 25 years. "The biggest concern about the eventual success of the Guinea worm eradication campaign is insecurity. Armed conflicts of any type can immediately halt the implementation of interventions against transmission of Guinea worm disease," said Ernesto Ruiz-Tiben, Director of the Guinea Worm Eradication Program at The Carter Center. "All remaining endemic countries are at risk of insecurity. During 2008, insecurity in parts of southern Sudan and Mali [had] already interfered with eradication activities."

Guinea worm could be eradicated by simple health education and behavioural changes, which could provide public health officials with a potentially high-profile success. But is the date set for eradication feasible? "Target dates are just that," commented Ruiz-Tiben. "It is unlikely that transmission of

Guinea worm disease in southern Sudan will be stopped during 2009, but more likely that other remaining endemic countries will do so and report zero cases of the disease throughout 2010." Indeed, running the 'last mile' is the most difficult, Ruiz-Tiben explained, particularly with Guinea worm disease for which there is no immunity, no medical treatment and no vaccine. The programme also requires that a public health worker identifies patients on the exact day that the worms emerge through the skin to prevent transmission of their infection through the contamination of water sources. "Stopping transmission requires total attention to details, the right diligence, discipline and correct disposition from all volunteer workers and supervisory staff," Ruiz-Tiben noted.

Next in line for eradication is poliomyelitis, a viral infectious disease caused by poliovirus. Although mass vaccination campaigns using the trivalent oral poliovirus vaccine (OPV; Fig 4), developed by the medical researcher Albert Sabin (1906–1993), reduced the global incidence of polio by more than 99%, the situation here is more complex and disease strongholds remain in Pakistan, Afghanistan and India, as well as in several countries in Africa (Fig 5). At present, some 1,500 total cases are known, more than 90% of which are in endemic countries. "Although overall case numbers have not fallen substantially since 2007, the programme passed some key milestones this year [2008]," commented Bruce Aylward, Director of the Global Polio Eradication Initiative of the WHO (www.polioeradication.org). "Most importantly, western Uttar Pradesh [a state in northern India], the most entrenched poliovirus reservoir in the world, finally stopped transmission of its indigenous type 1 poliovirus (the most dangerous of the two remaining types) by the aggressive application of new tools (monovalent OPV type 1) and tactics (shortened interval between polio campaigns). This feat demonstrates that 'technically' polio can now be eradicated anywhere in the world." The other important milestones, Aylward continued, include the new political commitments by the Heads of Government in both Nigeria and Pakistan to personally ensure that their countries achieve eradication.

No new official target date has been set for polio eradication after the original 2000 target expired. "There is no reason that all of the remaining infected countries could not be finished by 2010 if they fully applied the strategies over the next 24 months," Aylward commented. In support of his optimistic view are two recent studies that confirm the greater effectiveness of monovalent OPV type 1 compared with the older trivalent OPV, showing the real potential of this new vaccine to eradicate polio (El-Sayed *et al*, 2008; Jenkins *et al*, 2008).

However, several problems might still threaten the initiative's success. "The key ones are now 'operational', which means fully implementing the proven strategies in each infected area. In India, the challenge is to mount a very aggressive response to the new type 1 importation in west Uttar Pradesh, despite the fatigue of the population and disappointment of health workers," said Aylward. "In Pakistan and Afghanistan, the new security challenges require reworking how the polio campaigns are run to ensure sufficient children can be reached in those areas." Furthermore, the availability of financial resources for polio eradication remains a cause for concern: for 2008–2009, the Initiative estimates a funding gap of US$355 million, and a further US$490 million are needed for 2010–2012, as well as the resources for a 3-year' follow up and subsequent post-eradication efforts.

Even after eradication, various health challenges will remain. The OPV used in the immunization campaigns in many poorer countries contains live virus, which can result in vaccine-associated paralytic polio in rare cases. OPV viruses might also spread among local populations—several such outbreaks have been documented since 2000—and might also revert to the wild-type phenotype (Aylward *et al*, 2005). Most developed countries have turned to using the inactivated poliovirus vaccine, but this is considerably more expensive than OPV and is not available in comparable quantities. Although fighting polio in poor countries still depends on the massive use of OPV, OPV itself will ultimately have to be discontinued if poliomyelitis is to be truly eradicated. An 'exit strategy' to halt vaccination with the live virus is therefore needed (Aylward *et al*, 2005).

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Fig 4 | This 1963 poster featured the US Centers for Disease Control and Prevention (CDC) national symbol of public health, the 'Wellbee', who was depicted here encouraging the public to receive an oral polio vaccine. CDC used the Wellbee in its comprehensive marketing campaign that used newspapers, posters, leaflets, radio and television, as well as personal appearances at public health events. Wellbee's first assignment was to sponsor the Sabin type II oral polio vaccine campaigns across the United States. Later, Wellbee's character was incorporated into other health promotion campaigns, including diphtheria and tetanus immunizations, hand-washing, physical fitness and injury prevention. Credit: CDC/Mary Hilpertshauser.

In 2006, Isao Arita of the Agency for Cooperation in International Health (Kumamoto, Japan) and colleagues identified four crucial issues that hamper polio eradication: the high proportion of sub-clinical cases, vaccine-caused cases, population and/or political changes, and the prolonged duration of the global programme with its associated costs; incomplete polio eradication has already cost around US$4 billion, compared with smallpox eradication that cost a mere US$300 million. The authors concluded that polio might never be wiped out and that the WHO ought to shift its efforts from eradication to disease control (Arita *et al*, 2006).

Needless to say, the article ignited harsh debate. In a subsequent analysis of

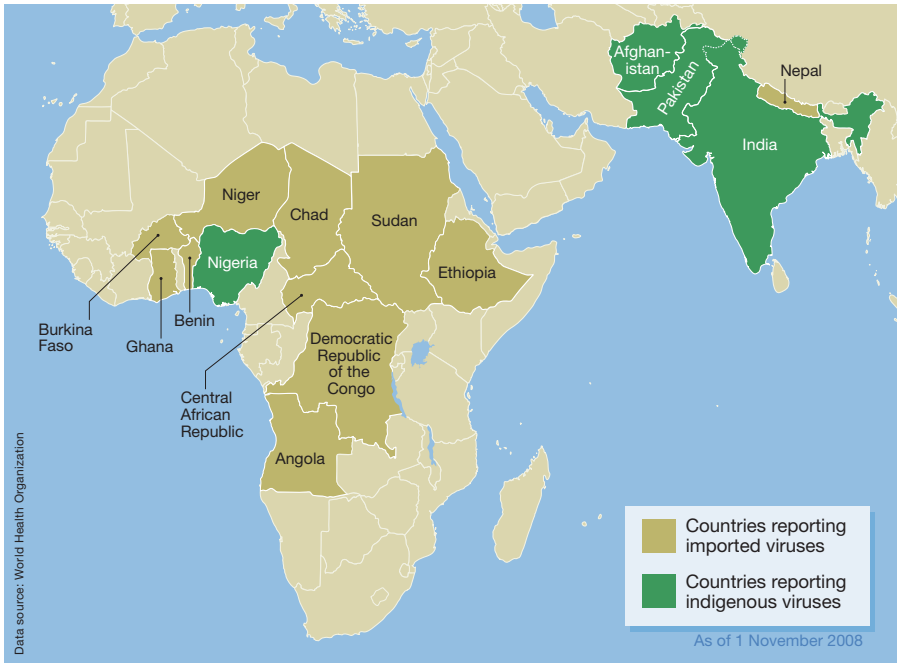

Fig 5 | Map of polio cases worldwide, as reported in 2008. Source: WHO.

the economic and health effects of polio eradication and control strategies, Kimberly Thompson and Radboud Duintjer Tebbens, from the Harvard School of Public Health in Boston (MA, USA), highlighted that "eradication offers both lower cumulative costs and cases than control", despite the fact that implementing an eradication and post-eradication strategy would involve investing a total of US$8 billion over 20 years (Thompson & Tebbens, 2007). "She [Thompson] clearly demonstrated that the 'best buy' for the world was very much to finish the job of eradication and that the concept of control was in fact a false premise, i.e. the world would again suffer hundreds of thousands of polio cases a year if it did not finish eradication", said Aylward.

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"At this stage, to revert to polio control would be a huge setback and mistake, in my opinion. The world must figure out a way to conclude the polio eradication campaign successfully. Polio eradication will be cheaper than indefinite continuation of polio control," confirmed Hopkins.

In the future, eradication programmes could even tackle more diseases than those highlighted by the ITFDE. "The list will eventually be increased modestly, mostly dependent on new tools for diagnosis and/or treatment," Hopkins said. "Yaws is an example of a potential new addition to the list based on new political and financial conditions." Indeed, yaws looks to be a beatable enemy given the appropriate political will, which was demonstrated by its elimination from India in 2006. The WHO has therefore set a target of 2012 to eliminate yaws in the remaining two endemic countries in Asia: Indonesia and Timor-Leste (Asiedu *et al*, 2008; WHO 2008b). "The technical reasons for yaws eradication were presented in such a way by technocrats that it got the approval of bureaucrats—decision makers—and hence the budget for the same," said Akshay Dhariwal of the National Institute of Communicable Diseases in Delhi, India. "I recall when a photograph of a yaws case with 'gangosa' [the destructive ulceration of the palate and nose] was shown to the Secretary of the Government of India and he was told that it is eradicable: his comment written on file was, 'If it is eradicable, do it.'"

Looking to the future of disease eradication and control causes mixed feelings. Various landmark projects are nearing completion with enormous support from the public and private sectors, and scientists have learned a lot about the technical and political requirements for success on a case-by-case basis. "I believe that the environment for neglected tropical diseases is favourable, provided over-zealous advocates don't ruin it by making unwise claims, such as for eradication, where only control is possible," said Hopkins. "Where there are tools to enable effective control, grouping selected ones of these diseases together can help mobilize resources for disease control, but not for disease eradication."

Similarly, Ahmed Tayeh, of the WHO, and Sandy Cairncross, an epidemiologist at the London School of Hygiene and Tropical Medicine, UK, wrote of Guinea worm disease: "[A] target date can help to boost the advocacy effort at the international level and in the endemic countries, but setting a target which is not achievable devalues the currency and diminishes its impact on stakeholders" (Tayeh & Cairncross, 2007); an observation that is valid for any eradication programme.

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Conversely, the commitment to ongoing programmes and to starting new ones tends to extinguish rapidly and therefore needs continual revitalization. A lack of financial and human resources translates directly into prolonged eradication programmes and frustration, both of which can have a negative impact on future commitment. Such a vicious circle might potentially hamper even the most advanced of public health programmes and, as Tayeh commented, the "[g]oal to achieve eradication is always over optimistic […] because it is based on political decisions". The financial and economic crisis the world is experiencing will not help in this sense; at least, the world might capitalize on the investment in eradication it has already sustained.

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