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REVIEW ARTICLE

Rethinking disease eradication: putting countries first

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There have been various infectious disease eradication programs implemented in various parts of the world with varying degrees of success since the early 1900s. Of all those programs, the one that achieved monumental success was the Smallpox Eradication Program (SEP). Most of the global health leaders and authorities that came up with the new idea of disease eradication in the 1980s tried to design and shape the new programs based on their experience in the SEP. The SEP had a very effective tool, vaccine, that did not require a cold chain system, and a relatively simple way of administration. The total cost of the eradication program was about US$300 million and the entire campaign took about 10 y. However, the Guinea worm and polio eradication programs that followed in the footsteps of SEP attained varying levels of success, consuming a huge amount of resources and taking a much longer time (>30 y each). This paper reviews the factors that played major roles in hindering the attainment of eradication goals and outlines possible recommendations for the way forward. Among other things, this paper strongly emphasizes that endemic countries should take the lead in all matters pertaining to making decisions for disease elimination and/or eradication initiatives and that 'elimination as a public health problem' is the preferred option rather than going for complete eradication at the expense of other health programs and thereby contributing to weakening of already fragile health systems, mainly in Africa.

Keywords: disease eradication, elimination, Guinea worm disease, polio, smallpox, yaws.

Introduction

Since the 1950s, there have been seven eradication programs: hookworm, yellow fever, yaws, malaria, smallpox, dracunculiasis and poliomyelitis.[1] The programmatic lessons learned from the earlier attempts of hookworm (1909) and yellow fever (1918), as well as the malaria and yaws eradication programs of the 1950s and 1960s, have been a great resource for several disease elimination and eradication initiatives that came into being over the last 4 decades. There is no doubt that history will repeat itself if we fail to learn from our past mistakes.

The term 'eradication' is defined as the permanent reduction to zero of the worldwide incidence of infection caused by a specific agent as a result of deliberate efforts while 'elimination' refers to reduction to zero of the incidence of a specified disease in a defined geographical area as a result of deliberate efforts. For disease eradication, intervention measures are no longer needed, while for elimination, continued intervention measures are required to a limited extent. At this juncture, it is worth noting that there are three principal indicators of disease eradicability: (i) the availability of an effective intervention to interrupt transmission of the infectious agent; (ii) the availability of practical diagnostic tools with sufficient sensitivity and specificity to detect levels of infection; and (iii) whether humans are essential for the lifecycle of the agent, which has no other vertebrate reservoir and does not amplify in the environment.[2] A fourth eradicability criteria was added later by Cochi and Dowdle, namely that the success of the eradication strategy must be demonstrated in a large geographic area or region.[3] The criteria developed by the International Task Force for Disease Eradication in 1993 and modified by the Dahlem conference in 1998 divides the criteria for targeting a disease for eradication into three broad categories: (i) biological and technical feasibility; (ii) costs and benefits; and (iii) societal and political considerations.[4]

Of all the regions of the world, Africa is the most devastated by a number of infectious diseases. Therefore, the idea of infectious disease elimination or eradication should be welcome news for Africans more than anyone else. The big question is, however, have these initiatives been coming up with sound plans, effective tools and the required resources to successfully accomplish the intended task in the shortest timeframe possible? Most of all, have national political commitments been secured for these eradication initiatives from each of the affected countries? This paper explores the strengths and limitations of some disease eradication programs with an attempt to provide recommendations for similar initiatives in the future.

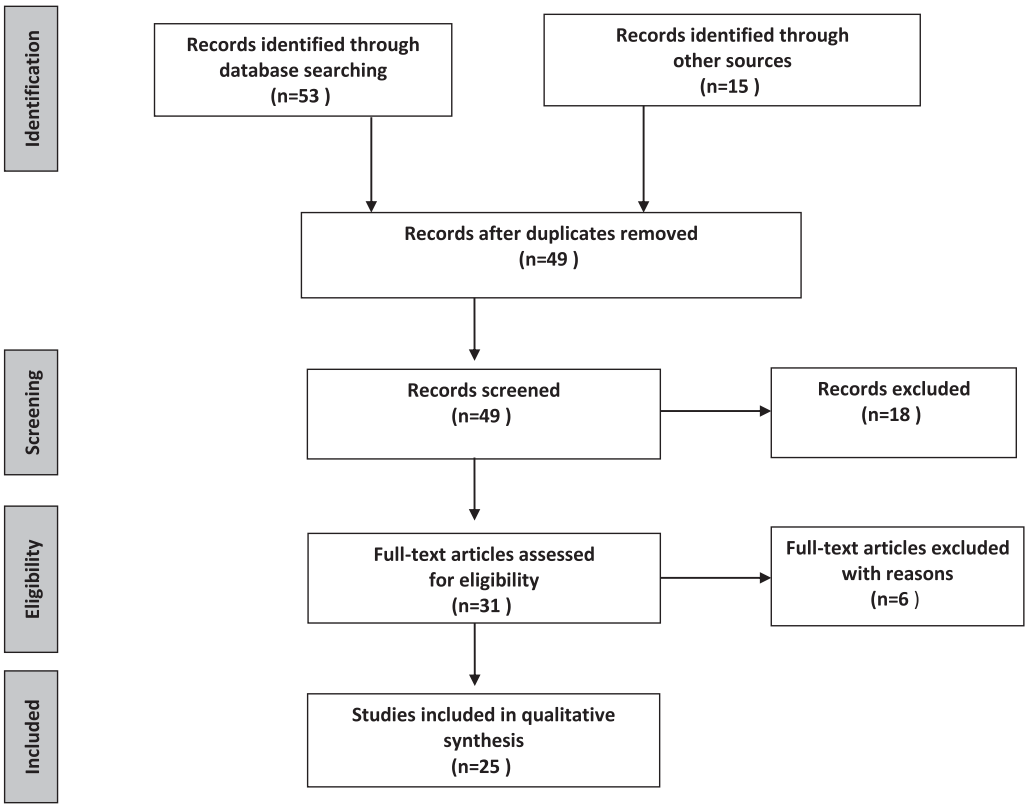

Figure 1. Flow diagram of search results from the PubMed Central website (PMC) database, 1 September 2020 using the PRISMA method.

Methods

A systematic review of the available literature on selected disease eradication programs was conducted from the National Center for Biotechnology Information website, PubMed Central database on 1 September 2020 using search items related to disease eradication, smallpox, polio, Guinea worm and yaws. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) method was employed to identify and screen relevant literature.[5] A total of 53 records were found, plus 15 from other sources, out of which 25 full text articles and book chapters were included in the review (Figure 1). Additional consultations were made to collect programmatic updates from experts in the field by means of personal communication.

The timeless legacy of smallpox eradication

First of all, it would be most instructive to look at the most successful campaign of the global Smallpox Eradication Program (SEP). Smallpox is a viral disease caused by three different species of *Variola* categorized by their severity levels as *V. major*, *V. minor* and *V. intermediate*. A person ill with smallpox sheds millions of infective viruses into their immediate environment from the rash on their skin and open sores in the throat. Each victim remains infectious from just before the rash appears until the last scab drops off about 3 wk later, but is most highly contagious during the first few days of that period. Smallpox is known as the greatest killer in history. Overall, one out of every four victims died.[6] In many ways, the perils of smallpox are similar to those we are currently experiencing with COVID-19. As previously documented, smallpox eradication achieved that kind of phenomenal success in a relatively short period of time and reasonable amount of resources. A disease that plagued humankind for thousands of years and killed millions of people all over the world took exactly 10 y, 9 mo and 26 d to eliminate after the world decided upon its eradication. This was a remarkable and unprecedented human achievement.[7] The key to this groundbreaking achievement was the availability of a very effective (freeze-dried) vaccine that was stable in any environment without any need for a cold chain system. Thanks to the cutting-edge discovery of Edward Jenner, the vaccination (which was a matter of inoculating the vaccine with multiple punctures by a bifurcated needle) was easily administered by field workers with minimal qualifications after short-term training and modest supervision. Skilled professionals and epidemiologists were only required at national coordination and supervisory levels. On 8 December 1979, the official certificate was signed by the members of the Global Commission certifying the global eradication of smallpox. A US$300 million effort succeeded in completely eradicating smallpox in less than 10 y.[8] The eradication of smallpox remains an iconic achievement of the twentieth century.[9] Thus far, smallpox is the first and only human disease known to have been eradicated from the world.[10]

In the footsteps of smallpox eradication

Enthused by the astounding success of SEP, a number of disease elimination and eradication programs were conceived, received endorsement by the World Health Assembly (WHA) and became operational at various time points. In 1974, the WHO launched a new initiative, the Expanded Program on Immunization (EPI). The success and relatively low cost of smallpox eradication inspired a global effort to dramatically expand the use of safe and effective vaccines. The Pan American Health Organization launched the EPI in 1977, its polio eradication in 1985 and recorded its last polio cases in 1991. Encouraged by progress in the Americas, the 41st WHA in 1988 adopted a resolution for the worldwide eradication of polio. This marked the launch of the Global Polio Eradication Initiative, spearheaded by national governments, the WHO, Rotary International, the US Centers for Disease Control and Prevention and UNICEF, and was later joined by additional key partners, including the Bill & Melinda Gates Foundation and Gavi, the Vaccine Alliance.[11]

According to the WHO, progress to date has been remarkable. In 1994, the WHO Region of the Americas was certified polio-free, followed by the WHO Western Pacific Region in 2000 and the WHO European Region in June 2002. On 27 March 2014, the WHO South-East Asia Region was certified polio-free, indicating that the transmission of wild poliovirus was interrupted in a bloc of 11 countries stretching from Indonesia to India. This achievement marks a significant leap forward in the global eradication initiative, with 80% of the world's population now living in certified polio-free regions. This notable progress claimed an overall investment of US$17 billion over a period of 32 y. 'But perhaps the biggest bump in the road has been the emergence of circulating vaccine-derived polioviruses (cVDPVs), genetically unstable Sabin-strain viruses that revert toward the genotypic and phenotypic profile of the virulent parent strain as they circulate for extended periods in a population with low immunity levels. Critics challenge the feasibility of eradication and the wisdom of devoting hundreds of millions of dollars to a single disease, arguing for a more integrated approach to control of serious global health problems.'[12] From the perspective of strengthening health systems, much more could have been achieved with the same amount of investment if the polio vaccination had remained an integral part of the EPI and primary healthcare platform rather than making it a vertical, single-disease focused eradication program. Concerning major child-killer diseases like measles, this approach could have provided huge benefits by saving millions of lives as well as building sustainable health delivery systems, especially in Africa.

The long march for Guinea worm eradication

Guinea worm disease (GWD), also known as dracunculiasis, a nematode infection transmitted to humans exclusively through ingestion of infected copepods while drinking contaminated water, is one of those diseases that was slated for eradication as per 1986 WHA resolution 39.21. The eradication of GWD was considered as 'a uniquely visible and measurable indicator of progress' to attaining the objectives of the International Drinking Water Supply and Sanitation Decade (IDWSSD). Because the global Guinea worm eradication program (GWEP) had still to undergo expansion to more affected countries in Africa, the 45th WHA in 1991 resolved to eradicate GWD by 31 December 1995.[13]

From 1981 to 2011, there were seven WHA resolutions passed to accomplish the Guinea worm eradication effort successfully. A huge amount of resources have been invested, both by international donors and program countries over the last 35 y, but the work is far from being over yet. It should be acknowledged, of course, that the global GWEP has achieved remarkable milestones in eliminating the disease from several endemic countries in Asia and Africa. The drastic reduction in the number of reported cases has been exceptional. Although significant work was done during the first decade of the GWEP (1980–1990), the program was initially supposed to achieve eradication by 1995. The big question is: What is causing the undue delay in attaining this long-awaited goal?

Based on this writer's personal experience with the program since 1992 and reviewing the available literature, the following possible factors hindered the progress of the GWEP: (i) the initial planning was not thorough enough in scrutinizing and addressing the potential programmatic challenges. The target date of December 1995 was set even before completing the national case searches in various endemic countries. Ethiopia completed its national case search in 1994. Some of the endemic countries like Sudan were waging civil wars until South Sudan's independence in 2011. Country-specific situations were not thoroughly assessed. The number of reported GWD cases in 1995 was 152 814[14]; (ii) as per the original WHA resolution, safe water provision should have been the primary intervention for a lasting solution. In fact, Guinea worm elimination in a community was considered 'as a uniquely visible and measurable indicator of progress' for the IDWSSD. However, the program gradually shifted its focus to other software interventions like cloth filter distribution, chemical treatment of ponds with temephos®, case containment, etc. In the early 1990s, there were two opposing viewpoints reflected in various forums and program review meetings. As a result, there were intensive debates between those arguing for a quick-win and those that were against it. Those who were opposed to the quick-win approaches argued that the GWEP was not delivering appropriate interventions that could protect endemic communities from contracting other waterborne diseases. Cloth filters and chemical treatment of ponds would not render drinking water safe from most disease-causing pathogens. Consequently, in 2011, 80% (388/483) of endemic villages did not have one single source of a safe water supply point.[13] Had the program measured its progress in terms of the numbers of safe water points built each year and benefitting the communities served, as originally advocated by IDWSSD, instead of counting the number of people with Guinea worms, then it would have had a greater impact and been a source of encouragement to all the stakeholders involved in the program, regardless of the delay in achieving the eradication goal; (iii) behavioral change activities needed more time and resources. Most of the endemic communities were located in remote areas at the end of the road. Literacy rates were low and the inhabitants were mostly pastoralists and nomadic or seminomadic with limited infrastructure. It was not easy to design appropriate health education materials addressing the norms and taboos hindering progress in those settings. Successive sociocultural and anthropological studies were needed to understand the knowledge, attitudes, practices and behavioral patterns

prevailing in those communities. It was not easy, if almost impossible, to conduct longitudinal studies in such hard-pressed, short-deadline programmatic settings; (iv) civil unrest was commonplace in most of the known endemic areas. Again, more time was needed to implement appropriate control interventions in these conflict-ridden communities; (v) zoonotic transmission emerged as a formidable challenge. The re-emergence of GWD in some countries like Ethiopia, Chad and South Sudan (after interruption of transmission) was mainly associated with zoonotic transmission. Eberhard et al. described the new transmission dynamic in Chad as different from what was already known in the GWEP. 'The current epidemiologic pattern of the disease in Chad is unlike that seen previously in Chad or other endemic countries, i.e. no clustering of cases by village or association with a common water source, the average number of worms per person was small, and a large number of dogs were found to be infected. Molecular sequencing suggests these infections were all caused by *Dracunculus medinensis*. It appears that the infection in dogs is serving as the major driving force sustaining transmission in Chad, that an aberrant life cycle involving a paratenic host common to people and dogs is occurring, and that the cases in humans are sporadic and incidental.'[16] In addition to this, on 14 March 2019, on its website, the WHO officially announced new reports of GWD cases in Angola; (vi) there was inadequate focus on research and innovative approaches. There were no reliable point of care diagnostic tools. The program had to rely on the travel histories of infected individuals. The endemic communities mostly had low literacy levels and therefore it was very difficult for them to recall where they have been about 1 y earlier (due to the year-long incubation period). This recall bias caused lots of problems in contact-tracing and identifying sources of infection; and (vii) there was a lack of flexibility in making adjustments based on changing circumstances. No significant effort was made to address the issue of zoonotic transmission that was reported (by personal communication) in Ethiopia in 2003 until the global program was caught by surprise in Chad in 2010 (10 y since reporting the interruption of GWD transmission in that country). Molyneux cautions that 'the question of the use of the term "eradication" following the findings in dogs infected with *D. medinensis* in Chad, and the possibility that the infection can be transmitted without the human host involvement, poses significant problems in confirming global eradication. In addition, post-intervention surveillance periods are necessary prior to any final assessment by an independent body to verify absence of transmission. The assessments required to provide sufficient evidence that transmission has been arrested are potentially expensive when needed at scale and in all previously endemic countries'.[17] Hopkins et al. expressed their optimism in 2017, when they wrote, 'In Ethiopia the few known infections in baboons are also being researched but current indications are that infected baboons are handicapped and hence more likely to be killed by dogs and that the small numbers of dogs, baboons, and residual endemic human cases are associated with forest activities in a very small area where assiduous application of Abate should stop transmission to all.'[18] However, contrary to expectation, there were confirmed animal GWD infections among cats, dogs and baboons reported in July/August 2020 in Ethiopia (unpublished report, Ethiopia Public Health Institute). Still, progress has been remarkable using simple but effective public health methods. The employment of these measures must continue. Eradication of GWD is a noble goal, but the added challenges and complexities now facing the program suggest that this aim is, at best, many years away. At worst, it is simply a pipe dream.[19]

It should be underscored that, in any disease eradication program, the last few cases are always very difficult to detect and contain. The Ethiopia GWEP has been grappling with a handful of GWD cases per year for the past 20 y (Figure 2). A similar trend can also be observed in the global annual GWD incidence graphic summary (Figure 3). If the target was 'elimination as a public health problem', then the job would have been finished much earlier. In addition, the pre- and post-elimination surveillance activities are resource-intensive and highly demanding. Annual precertification costs range from about US$343 000 in Cote d'Ivoire to more than US$1.6 million in Nigeria. Total spending is influenced by population size and land mass.[20] Usually, this huge burden is imposed on the implementing countries with limited resource support from donors. As one writer summarized it, 'The idea of eradication was openly challenged. The scientist and writer Rene Debos asserted that it was untenable to believe that a single organism could be extracted from the complex ecological world in which it had evolved. Health officials openly condemned the program that required so many resources and which contributed little to providing basic health services, as they saw it'.[8]

The Indian Yaws Eradication Program: a good example

Technical feasibility alone should not be the major driving force to embarking on global disease eradication programs. Multidimensional assessments, a series of consultations including pilot testing of interventions, should be thoroughly considered. Epidemiological relevance (burden of disease), economic affordability, social acceptability and, above all, government commitment for long-term engagement should guide decision-making in tandem with technical feasibility. A good example in this regard is the Indian Yaws Eradication Program (YEP). Earlier on, there were a number of attempts to eradicate yaws since the establishment of the WHO in 1948. Later, in 1986, the National Institute of Communicable Diseases, encouraged by the success of smallpox eradication and the progress being made in Guinea worm eradication in the country, convened a meeting to develop a strategy for yaws eradication. The country's strategy consisted of an active search for and treatment of infectious cases, as well as health education and social mobilization in the community. Cases were to be treated with long-acting benzathine penicillin, thereby rendering them non-infectious; simultaneously, family contacts were given penicillin shots as prophylaxis. For cases that were sensitive to penicillin, tetracycline or erythromycin was recommended for a period of 15 d.

A case in point from the Indian YEP was that before implementing their nationwide program, the strategy was first piloted in one district during 1996–1997 and, subsequently, based on positive feedback from the pilot studies, the program was rolled out to an additional four states. By 1999, the program was further expanded to all 51 endemic districts in 10 states. The program then made a progressive move from elimination to eradication, defined by the program as 'the absence of new cases for a continuous period of three years as validated through serological

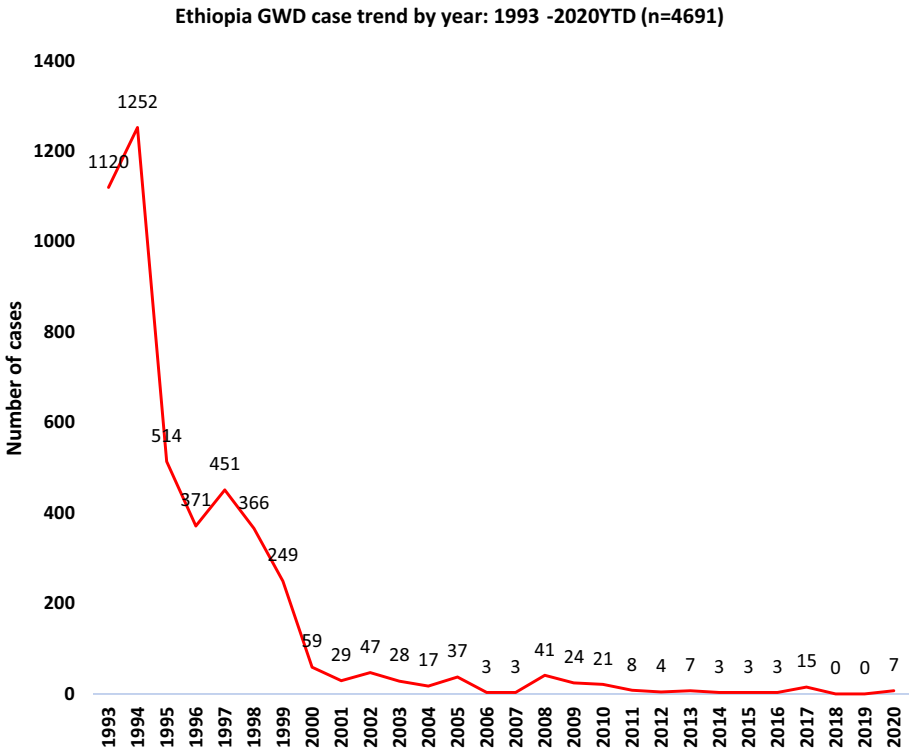

Figure 2. Guinea worm disease cases reported during 1993–2020 (YTD) (unpublished report, MOH Ethiopia).

surveys among children aged 1–5 years'. An effective surveillance system with cash rewards for reporting cases was put in place during the 3-y period. Finally, and most importantly, the success of the Indian YEP could be attributed to strong government commitment. 'The program was primarily funded by the government out of its own resources and as part of its national 5-year Plan, with additional technical and financial support from the WHO.'[20] In relation to the correct use of the term 'eradication', it is important to note that eradication as a concept is specifically defined as a reduction to zero global incidence of a specific pathogen, not a disease, which results from such an infection. This represents a crucial distinction: the words disease and infection are used interchangeably but incorrectly. Even the WHO, reporting recently on the yaws program in India, entitled their publication 'Eradication of yaws in India'. Thus even the WHO is unable to consistently use the correct terminology.[4] In this connection, it is worth mentioning that a new global yaws eradication movement, using azithromycin (an orally administered antibiotic), is in progress under the auspices of the WHO.

More eradication programs under consideration

At the moment, there are some diseases under consideration for eradication. Malaria is one of the most contemplated with a much higher approval rating by prominent donors as well as by distinguished global health authorities. 'From roughly 1980 to 2007, speaking of elimination and eradication in connection with malaria was regarded as naive and overambitious. However, speeches by Bill and Melinda Gates on Oct 17, 2007 calling for nothing less than global malaria eradication, radically changed this dynamic. Since then, there has been an upsurge of commitment to elimination and eventual eradication, and these concepts are now mainstream in the international malaria community and embraced by the Roll Back Malaria Partnership and by WHO.'[21] When talking of malaria eradication, it is important once again to take note of the concept of eradication, which is defined as the removal from the planet of a specific infection, not disease, raising the question regarding which of the five human species of *Plasmodium* is to be targeted. This has yet to be specified.[17]

There is also a recent call, put forward by some prominent global health experts, for trachoma eradication. The experts boldly claimed that 'Why not more enthusiasm for trachoma eradication? As infection is eliminated in more countries, the argument that eradication is impossible becomes more difficult to make.'[22] In both cases, apart from expressing enthusiasm for malaria and trachoma eradication, the authors did not provide plausible evidence regarding any groundbreaking discovery in the area of diagnostics, therapeutics or vaccines for the proposed eradication initiatives. This would undoubtedly place participating endemic countries into the same vicious cycle of endless conundrum. A group of trachoma experts attending a research conference were interviewed as to whether trachoma could be eradicated and most respondents suggested that 'continued investment in trachoma control efforts, coupled with identification of new ways to assess transmission and development of more effective interventions, could strengthen support for adopting a formal eradication goal'.[23]

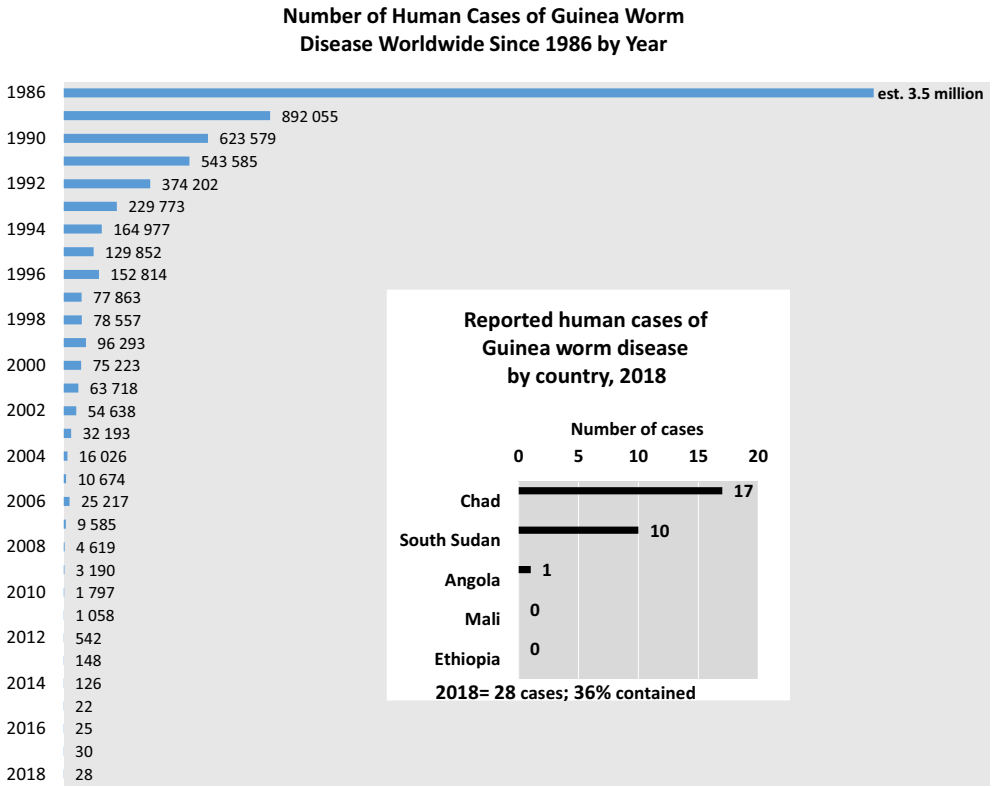

Figure 3. Global Guinea worm disease cases by year, 1986–2018. (Source: www.cartercenter.org).

Cochi and Dowdle remind us that the previous failures of eradication programs have been largely attributable to the failure of the interventions or strategies, providing a cautionary note for the need to understand the natural history and biology of the disease thoroughly as a fundamental precept when considering an eradication or elimination program. For example, non-human primates were found to harbor yellow fever virus in 1915 and malaria mosquito vectors eventually became resistant to the insecticides. In the case of yaws, the prevalence and importance of inapparent infections were underestimated. In 1998, Hinman and Hopkins provided a list of the 10 main lessons from these collective experiences, of which the following are highly relevant for this paper: (i) understand the natural history of the disease thoroughly; (ii) consult widely before embarking on eradication; (iii) remain open-minded and flexible; expect the unexpected; (iv) some countries may need more help than others; and (v) political commitment at all levels is essential.[3]

Concluding remarks

In most instances, the idea of initiating disease eradication programs with short deadlines is meant to enthuse donors and secure funding, mainly for global and country-level operations. As clearly witnessed and evidenced with the Guinea worm and polio eradication programs, it would have been more sensible if the programs opted for 'elimination as a public health problem'. This would have been a more realistic and attainable goal with modest investment. The incident cases that may be reported after achieving the elimination threshold could be taken care of by the health system. This writer is of the opinion that the current modus operandi, in which countries are requested to vote and pass resolutions at the WHA without thorough consultations among their in-country policymakers and experts, should not be the way to go for disease eradication initiatives in the future. Each and every endemic country should be the centerpiece at all stages of conceiving the initiative, designing and piloting the project and developing the strategy for full-scale implementation, as was the case with the Indian YEP. Setting target dates for elimination should also be left to the respective program countries themselves (along with their regional or subregional counterparts, where applicable). The idea of targeting a single disease for global eradication by lobbying with some influential personalities, donors and global health authorities should be discouraged. This single-disease vertical approach would not help much endemic countries but would rather rob them off of their meager resources and by so doing contribute to further weakening of the fragile health systems.

The possibility for one generation to eradicate a disease is highly 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 tantalizingly close to their goals. The early stages of a well-planned eradication campaign generally go well; it is during the final stage when technical, biological, social and political problems occur.[24,25] As a way forward, it would

be prudent to take note of the three programmatic shifts outlined in the new WHO/neglected tropical disease (NTD) roadmap 2021–2030: (i) moving from process orientation to impact orientation; (ii) leaping from siloed disease-specific programs that have limited interfaces with national healthcare systems and adjacent sectors to platform-based approaches in the context of Universal Health Coverage (UHC); and (iii) shifting from externally driven agenda reliant on partner support and donor funding to country ownership and financing with NTDs integrated in national health plans and budgets, and supported by partners and donors to overcome outstanding challenges.[26] The bottom line is that the top-down approach of imposing global vertical disease eradication initiatives should be avoided.

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