



Elimination and Eradication of disease: what have we learned from past successes and failures and how that can guide us in future efforts

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ABSTRACT

Elimination and eradication (E&E) are the most ambitious public health goals for a program to achieve. In fact, historically, the world has seen many failures in the attempt to eliminate and eradicate diseases. Individual, disease-specific elimination goals have been achieved in some regions (e.g. wild polio in the Americas in 1994 and South-East Asia a full 20 years later and then in Africa in 2020) but there is only one successful human disease eradication program: the Global Smallpox Eradication Program. The World Health Organization's new 2030 NTD Roadmap titled '*Ending the Neglect to Attain the Sustainable Development Goals*' which was launched in 2021, targets twelve diverse diseases for elimination or eradication in the years and decades ahead.(1)

Traditionally, E&E programs are implemented as extremely vertical programs. Some argue that this verticality is essential to the success of the program and a laser-like focus is required to achieve the goal. Others argue that we need a more integrated, health systems approach. The reality is that we probably need both, applied sensibly into the context in which the program fits. This vertical approach however, has hindered the ability to learn across programs to either benefit from successes or to avoid the same mistakes. For the world to most rapidly eliminate or eradicate its next disease, we will need to learn from previous successes and failures in E&E programs and apply their lessons to other disease efforts including the twelve NTDs targeted for elimination or eradication.

To help ensure the best chance of success in current programs, we have reviewed past and ongoing E&E programs, summarized lessons learned, and identified common elements contributing to success and failure. Building on these elements, we created an approach for evaluating E&E programs, proposing a set of review questions designed to identify areas that may require strengthening or adaptation within a program. A proactive independent review of programs based on historic lessons could help avoid unnecessary setbacks and delays, saving time and resources, and building stronger and more resilient programs that adapt to our changing global environment.

METHODS

We explored disease elimination and eradication program efforts to learn from their experiences, successes, and challenges. To do this we reviewed data from publications and program reports, as well as expert interviews. For literature review we searched for papers, books, presentations, and reports from elimination and eradication programs with an emphasis on reviews, lessons learned, and cross program comparisons, which were few. We reviewed most thoroughly works looking at the successes of both smallpox and rinderpest. With the experts we conducted a series of semi-structured interviews with pioneers who have been part of successful elimination or eradication programs ('the Eradicationists') at the global, regional, and country-level across several disease areas: smallpox, Guinea worm, lymphatic filariasis, schistosomiasis, and rinderpest. Interviews were conducted with Eric Ottesen (The Task Force for Global Health, May 5, 2020), Gautam Biswas (World Health Organization, May 6, 2020), Dieudonne Sankara (World Health Organization, May 11, 2020), Joel Breman (Chair International Certification Committee for Disease Eradication May 15, 2020), Donald Hopkins (Special Advisor for Guinea Work Eradication at the Carter Center, May 18, 2020), William Foege (Professor Emeritus at Emory University, May 27, 2020), Yao Sodohlan (Director Mectizan Donation Program, May 29, 2020), Samuel Makoy Yibi (National Director for the Guinea Worm Eradication Program in South Sudan, June 17, 2020), David Morens (Senior Scientific Advisor at the United States National Institute of Allergy and Infectious Diseases, February 2, 2021), and Juergen Richt (Kansas State University College of Veterinary Medicine, February 11, 2021).

From this review, an initial analysis was presented and further discussed at the Coalition for Operational Research on Neglected Tropical Diseases (COR-NTD) Annual Meeting (2020). Input from this workshop was used to further refine the analysis and proposed independent review questions.

Critical Failure Points and Drivers of Success

From a review of the literature, we found a well-documented pattern of where E&E programs have failed, highlighting several common underlying areas of risk. These areas of risk can be grouped into three categories around the building blocks of the program; 1) strategy, 2) the context in which the program exists, and 3) tools. In addition, three broader, cross-cutting risks which can impact a program's chance of success; 1) a failure of a program to adapt; 2) a failure of program management or leadership; and 3) failure of a program to detect outliers and the unexpected. These risks are seen through the analysis of the program experience described in more detail below.

Understanding why programs have failed naturally leads us to try to understand how to mitigate these risks. To do that, it is necessary to understand how successful E&E programs have overcome these risks. Lessons on success came primarily from the expert interviews and, at a high level, revolved around two broad elements: people and programs. People matter; individuals' commitment, motivation, honesty, and integrity as well as deep community engagement will drive programs to success. If communities are meaningfully and respectfully engaged, they will be the strongest and most effective tool to ensure goals are met. The second element is a technically strong program with well-defined goal & objectives, reliable funding, clear indicators, continuous evaluation, and programmatic adaptation that embraces new information.

We have distilled and summarized a set of lessons learned from both failed and successful programs which can serve as guidance for future elimination or eradication efforts. The seven key lessons that emerged from the analysis are listed in the box below.

Seven Strategic Lessons from Elimination and Eradication Programs

- 1. Know and test your assumptions*
- 2. Understand the context-specific infrastructure*
- 3. Engage/include communities and adapt locally*
- 4. Continuously test and adapt your tools*
- 5. Expect the unexpected*
- 6. People and partnership matter*
- 7. Think about and plan for the last mile early on*

In the following section, we will systematically review these lessons and discuss areas at risk of failure and more detailed reflections on the drivers for success. Figure 1 highlights a few reflections on risks of failure and drivers of success documented during our interviews with 'the Eradicationists'.

Finally, we propose a set of new independent program review questions which can be used to assess a program's risks related to the key failure points and elements for success so that they can be proactively and systematically addressed.

Figure 1: Quotes taken from interviews with 'the Eradicationists'

<p>People</p> <ul style="list-style-type: none">• <i>Eradication is an optimist's sport - Bill Foegel</i>• <i>'Certainty is the Achilles heel of science' [attributed to Richard Feynman]...and that is why we are still fighting polio - Bill Foegel</i>• <i>Integrity and honesty are the most essential characteristics in the country team – Joel Bremen</i> <p>Bremen</p> <ul style="list-style-type: none">• <i>Sit with the communities.. they know much more about their community than you will ever know and you need to tap into that knowledge - Don Hopkins</i> <p>Program</p> <ul style="list-style-type: none">• <i>The best decisions are based on the best science. The best results are based on the best management – Bill Foegel</i>• <i>Scientists are great at understanding disease, not necessarily elimination – Joel Bremen</i>• <i>Start with the hardest place first- Don Hopkins</i>• <i>Define the last mile first - Bill Foegel</i>• <i>Be prepared and expect to have to adapt – Don Hopkins</i>
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Know and test your assumptions

All programs are, or should be, built on a series of assumptions that are based on the best knowledge and evidence available at the time the program strategy is established. One of the most fundamental assumptions which will impact the success of a program is that transmission is understood. In our review, the lack of understanding of transmission dynamics was identified as the main reason for program strategy failure starting with hookworm in 1907, yellow fever in 1915, yaws in 1955, and malaria in 1955.(2–4)). Despite these programs ultimately not achieving their goals due to these blind spots, they taught us a great deal about potential risks to E&E strategies. As such, changes in

transmission dynamics are now expected as E&E efforts progress. This has been seen in, has challenged and continues to challenge programs from polio to Guinea worm.

In more recent NTD elimination and eradication efforts, the most common assumption is that treatment will break transmission. Those familiar with the successful rinderpest eradication program noted that the single most critical reason for its success was the existence of an effective and deployable tool, a single-dose, inactivated, thermostable vaccine which conferred life-long immunity to vaccinated cattle.(5,6) In fact the tissue culture rinderpest vaccine (TCRV) was described as “one of the finest vaccines ever developed in human or veterinary medicine. It protected against all clades of rinderpest virus, provided lifelong immunity to cattle, was never associated with any adverse reactions, and a single tissue culture infectious dose was immunogenic.”(7) This is similar to smallpox; the key attribute was a powerful vaccine that provided high level durable immunity with a single inoculation and led to the only human disease eradicated. The NTDs do not have a vaccine and eradication has yet to ever be successful on the global scale with treatment as the main intervention. There are several examples of where this approach is being used, has resulted in impressive public health impact, and has broken transmission in some settings, even at scale, but all programs are still struggling to break transmission at the global level.

For example, in onchocerciasis programs, the initial hypothesis was if you treat the heavily infected (meso- and hyper-endemic) areas, that transmission in the lesser infected (hypo-endemic) areas would not be sustained and infection would disappear.(8) This hypothesis did not prove to be true. With the new program goal of elimination, many historically untreated hypo-endemic sites will subsequently require years of interventions to catch up.

In leprosy, improved access to effective multidrug treatment resulted in a significant decrease in prevalence and cases worldwide. It was believed that, as active cases were treated, the incidence of new cases would decrease; however, the treatment of current cases did not decrease the incidence of newly detected cases. Sustained incidence and the presence of cases in children has demonstrated the continued persistence of transmission, highlighting key gaps in understanding of leprosy transmission and underscoring that the strategy was not sufficient to reach elimination of transmission. Now, leprosy programs are adapting and moving towards incorporating post-exposure prophylaxis (PEP) for close contacts of confirmed cases to stop transmission. This new strategy has been shown to decrease the incidence of new cases by 57% in the 2 years following the treatment.(9) New cases trigger active case finding in contacts and targets distribution of a single dose of rifampicin to all contacts, called a focal mass drug administration (fMDA) (10,11) This new approach is enabling progress towards decreasing incidence and hence towards the newly adopted goals of zero leprosy. These examples show the importance of testing assumptions that to mitigate against strategy-related risks. E&E programs need to be willing and able to challenge their assumptions and adapt their strategies in response to changes in or increased understanding of transmission dynamics.

Understand the Context-Specific Infrastructure

A global E&E program for any disease has to work in all endemic settings to succeed in its goals. It is important to understand the context the program is functioning within to see if all elements of the strategy are possible in the local context. Limitations in the necessary infrastructure and supporting systems may not be sufficient to put into action all aspects of the strategy.

This brings in some of the adages from the Eradicationists- namely, Don Hopkins who, in an oral interview on May 18, 2020, recommended to “start in the hardest places first” with the idea that this will take you the longest and you will learn the most. For example, areas suffering from conflict and civil

disruption from disease or disaster represent the most difficult places to effectively deliver health services. This is demonstrated by the geographies where polio and Guinea worm are still a challenge. However, more broadly, chronic issues with staffing in hard-to-reach settings and limited technical staff can be equally crippling. To mitigate against such system-related risks, E&E programs should look for ways that their program or activities can help bolster or strengthen the unique and varied systems in which they work that vary greatly depending on the local context.

For example, the reintroduction or reemergence of Guinea worm in the Gambella Region of Ethiopia demonstrated this kind of system-level failure. Ethiopia is recognized to have one of the best primary health care systems with reach down to the very local level. At the time of the reemergence, the Community Health Worker and Health Development Army system, the first line of defense for Guinea worm, was weak with many unfilled positions leaving the region vulnerable and introducing delays in detection, diagnosis, and response. To address the challenges in Ethiopia, additional partner support including a high level field visit by the WHO, primary donor, and the Minister of Health, was required to understand and overcome limitations, bolster staffing, and build national commitment. (12) (personal experience)

In South Sudan, infrastructure is arguably amongst the most limited globally. Despite this, the Guinea worm eradication program needed to reach down to the village level to be successful. As a result, it was one of the first programs with an active presence in villages. Furthermore, the program's need to find a way to carry out its work in the face of severely limited health infrastructure created an opportunity to strengthen the new country's health system. The Guinea worm program's staff and volunteers demonstrated their importance to the health of the South Sudanese beyond GW by being the first to detect and report outbreaks such as measles to the central level. Through this they were acknowledged and became the community level health workers for the newly developing health system in the country and compensated for their efforts. In this way, Guinea worm volunteers became the first building blocks of the new health care system with field presence in the communities (from an oral interview with M. S. Yibi, June 17, 2020). This example demonstrates that if programs understand the limitations in infrastructure or systems, creative solutions can be developed that, in this case, both strengthened the E&E program and the health system more generally.

In Rinderpest eradication, the strategy relied on working with veterinarians and doing mass vaccination. This strategy was not working in conflict affected regions. The development of a thermostable vaccine allowed a new delivery strategy to be deployed that was adapted to the context including remote pastoralist communities and utilized community-based animal health workers (CAHW). This allowed the vaccine to reach populations that had been unreachable or overlooked in the past. (6,7)

Engage and include communities and adapt locally

Our next theme is inspired by an old false assumption: one strategy will work in all settings and if it isn't working you aren't doing it well enough. Success is actually not driven by a top-down command and control, siloed process, even though has been for decades. E&E is a disbursed, decentralized, community dependent public health initiative. Success is driven by the empowerment of an effective, innovative, and forthright, local management. This premise was well laid out in an article by Teshome Gebre, where he argues for local ownership and national level decision making as the most essential elements in a program including learnings from yaws elimination in India. (13)

It is true that quality control of your program is essential and ensuring that the program is being done appropriately and with sufficient rigor is important, so centralized monitoring of progress and

process is essential; however, it is also important to question if the strategy itself is the issue. If you are doing the same thing in all settings and if your strategy has not evolved over the lifecycle of the program, you are at risk of failure. Adaptation in tools and strategies will be required.

A key failure of the previous Global Malaria Eradication Program was its unwillingness to adapt the strategy to different contexts. Early efforts on malaria eradication had strong political commitment and buy-in but a poor understanding of the need for the program to learn from communities and adapt to the local context. Ultimately, the program's response to these challenges was to abandon the elimination goal.(14,15) The Global Smallpox Eradication Program embraced the lessons from the failed malaria eradication efforts; one of the most important being the need to adapt to different settings. It was ultimately that ability to learn and adapt from communities that was a pillar of success in the smallpox program (House of Fire, oral interview with Bill Foege, May 27, 2020) (2)

The Guinea worm eradication program has several examples of local innovations and adaptation that were embraced by the program. For example, convincing communities that the water they have been drinking all their lives was contaminated was not easy. During our interview (May 11, 2020), Dr. Sankara reflected on how he adapted his communication approach to better resonate with the local populations. During a community discussion, he used a piece of cloth to filter the local, contaminated water to catch the tiny, swimming cylopods which carry the Guinea worm parasite. Then, releasing the filtrate into a clean glass of water and holding it up to the light, he was able to clearly show the cylopods swimming in the water to the community. This demonstration was very effective and soon was replicated in other areas to help communicate the risk to communities.

Another example of local innovation which has contributed to the success of the Guinea worm eradication program is an adaptation of one of the main tools of the program, the water filter. As described in interviews with Gautam Biswas (May 6, 2020), Don Hopkin (May 18, 2020), and Dieudonne Sankara (May 11, 2020), Nomadic herdsman would not be at home during the day where there was filtered water to drink so they remained at risk by using unfiltered sources. With local innovation however, herdsman took small pieces of the filter cloth and tied it to the end of a reed that they would then use as a straw to drink from the same water as their cattle but avoiding infection with the Guinea worm parasite. After observing this, Health & Development International (HDI) championed the efforts to replicate this adaptation and make the Guinea worm straw available in multiple program settings where people's work took them away from home and safe water sources.(16,17)

Again, turning to Rinderpest, local adaptation was essential in the final pushes to eradicate. This included as mentioned above the CAHW that could reach communities locally with the thermostable vaccine. It also included increased community involvement to get vaccines accepted and into at-risk animals by integrating Rinderpest vaccine with other interventions aligned with local priorities. They also moved away from large and expensive serosurveillance and utilized local community members to alert that there was rinderpest seen especially in the pastoralist communities that were well attuned to the disease transmission in their herds. This allowed quicker response and more targeted interventions that then could block transmission and then follow with the more expensive serosurveillance for confirmation of transmission being blocked.(6,7)

These examples demonstrate the power of engaging with and listening to local communities as local insights and innovation can help signal when current strategies are not working and provide innovations and adaptations to overcome challenges.

Continue to test and adapt your tools

For programs to be successful, the tools and interventions need to be effective, accessible, and deployable in all contexts and evolve with the program needs over time. Programs need to be able to monitor the effectiveness of the tools to detect early any loss of effectiveness that could put the program at risk and adopt and deploy effectively new tools that are developed. As mentioned above, the innovation of a thermostable rinderpest vaccine was a turning point in the success of the program allowing a new delivery strategy to be developed more aligned with the program needs.(5–7) The need for diagnostic tools to evolve over the lifetime of an E&E effort is well documented in evaluation of the early rinderpest eradication efforts and in a recent publication looking at diagnostics in context of the LF elimination program.(7,18) Drug resistance and insecticide resistance are also well recognized challenges that emerge and evolve over the lifecycle of elimination and eradication programs. Are your tools doing what you think they are and how can you tell if they are not?

For example, drug and insecticide resistance are well-demonstrated and documented issues in malaria control and elimination programs. But the emergence of chloroquine resistance was largely dismissed as an issue early on and was only later, ultimately seen as a significant threat to the success of the program. *‘Nevertheless, as more and more countries joined the campaign and reported the achievement of total coverage with attack measures, often after strenuous efforts to reach remote areas, emerging problems were overlooked. Even the confirmation of chloroquine resistance in 1960, after treatment failures had been reported since the late 1950s from Venezuela and Thailand, was not given its full epidemiological importance because the campaign still hoped to interrupt transmission by spraying.’*(2)

As part of the new malaria eradication efforts through Malaria Eradication Research Agenda (malERA) Initiative, the issues of insecticide and drug resistance have been responded to in the new malaria eradication planning and research agenda. Renewed efforts for malaria eradication have also learned from the past and now are focusing on parasitemia and not just clinical disease to break transmission. This change in focus has required significant work in new diagnostics.(19,20)

The initial yaws elimination effort reduced clinical cases by 95% worldwide. However, the last remaining cases were not actively sought and sub-clinical cases were missed due to limitations in the diagnostics which contributed to ongoing transmission. Without an effective tool to identify everyone who required treatment and effectively respond to resurgence, the program ultimately failed to reach its eradication goal.(15)

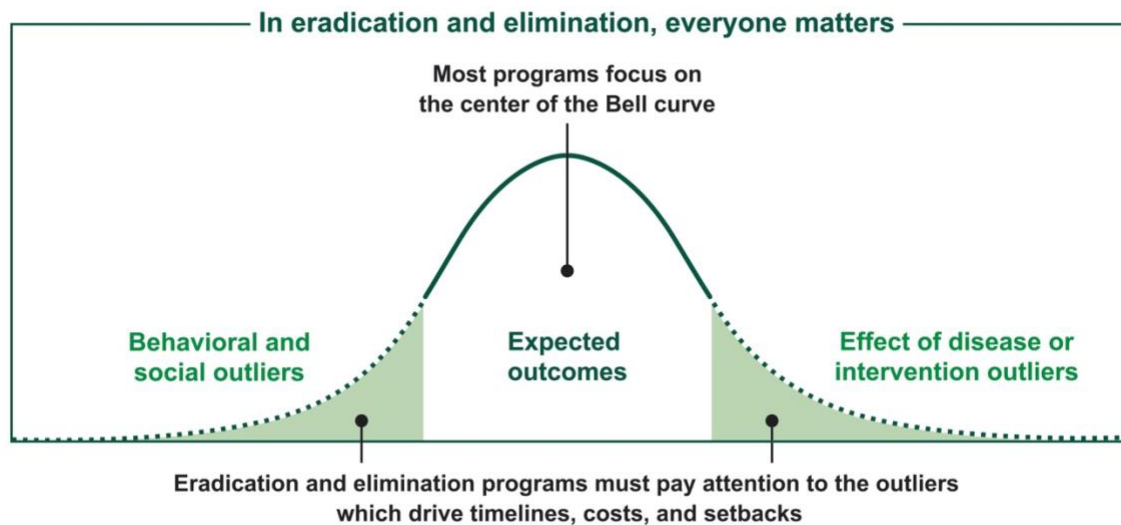
Yaws eradication efforts have been revitalized with improved diagnostic options and data showing oral azithromycin is effective treatment which inspired a new drug donation from EMS in Brazil. However, this advance is tempered by an early acknowledgement and understanding that azithromycin resistance can emerge after even just one round of MDA.(21) This is now pro-actively being built into the evolving strategy for yaws eradication. Screening for resistance is being included in the M&E strategy along with immediate treatment with injectable penicillin in remaining and resistant cases to stop the spread of resistant strains that could threaten the eradication efforts.(22)

In onchocerciasis, the program’s early mapping efforts relied on nodule palpation as a non-sensitive and non-specific sign of disease. This method was very helpful to target areas that were heavily infected and could most benefit from interventions; however, proved to be insufficient as the program shifted its goal to elimination. Now, the program is still struggling with inadequate surveillance tools to support elimination efforts now underway.(23) A similar analysis has looked at the needs for new diagnostics for onchocerciasis where gaps remain to efficiently guide programmatic decision making for elimination.(23)

Expect the unexpected

Outliers matter, they are important because they challenge the assumptions built into the program. Outliers and unexpected findings are opportunities to learn, and course correct, if warranted. Frequently outliers can reveal transmission knowledge gaps, as such, outliers are the key to eradication. Normal control programs focus on the center of the bell curve. While this can decrease disease and relieve suffering, it is not sufficient to stop transmission and eradicate disease (figure 2).(24) In order to eradicate, deliberate attention needs to go to the tails of the bell curve to understand what is driving and potentially sustaining transmission in these settings.

Figure 2: Control programs typically focus on the center of the bell curve. Elimination and eradication programs need to also consider the outliers, or the tails to understand the potential drivers of sustained transmission.



Outliers can come from unexpected human behaviors. For example, distrust in the polio eradication program flourished in northern Nigeria after rumors circulated that the vaccine was harmful and being used to sterilize the population. Consequently, households began to hide children, even passing babies over the fence, when vaccinators would visit to hide them from the team. This unexpected experience hampered eradication efforts until the issue was uncovered and addressed by the program.(25) This experience also emphasizes the importance of considering the socio-political environment when determining the potential effectiveness of an intervention.(26) Understanding community dynamics, motivations, interests and incentives lie at the heart of effective programs.

Outliers can also come from unanticipated changes in the pathogen or its transmission as seen with the continued emergence of Guinea worm infections in dogs in Chad. Chad had a 10-year period where no cases were reported, but weakness in the reporting system led to the country never being certified as Guinea worm free. When a human case was confirmed in 2010, the pattern of cases was not a classic outbreak pattern but instead sporadic. Subsequently, in 2012, cases in dogs were found and recognized as a potential source of human infection.(27,28) Based on these findings in Chad, infections in dogs are now a recognized threat to success of the program and pose a risk of spreading to the neighboring countries of Cameroon and Central African Republic (5). The recognition of dog cases has

led to significant investigation in all remaining endemic countries and resulted in the detection of cases at much lower levels in dogs, cats and wildlife such as baboons.(27,29)

Rumors and case investigations are important tools to understand where transmission patterns are deviating from known patterns. Investigation of an unexpected case may uncover a weakness in the program indicating the need to adapt or establish a new research priority to learn more. For example, in our interview, Don Hopkins (May 18, 2020) described the situation when rumors led to the detection of cases in northern Mali which was thought to not be endemic for Guinea worm. Upon investigation it was discovered that the source of the outbreak was a farmer fleeing failed crops due to drought in the south of the country. The farmer walked over 400 km north to Algeria during which time his Guinea worm emerged, and he contaminated a water source infecting the northern nomadic Tuareg. This unexpected activity required starting a new program in a challenging newly endemic area.(30) (Don Hopkins interview)

People and partnership matter

Successful E&E programs require comprehensive coalitions or partnerships, and it is an investment to make them strong and flexible by building on partners' strengths with open communication. Coalitions or partnerships should include a clear plan with measurable goals and partner roles adapted to strengths which embrace and respect the diversity of what is required for success. It is also essential to have a source of flexible adaptive funding to support the partnership, prospective investment in upcoming needs, and program adaptation over time.(7,7,24,31) The establishment of a global partnership was the turning point that resulted in the eradication of rinderpest.(31,32)

Everyone can be replaced but that does not mean they are replaceable. People and strong partnerships are essential to elimination and eradication. Talent and commitment should be rewarded and nurtured at all levels. The contributions of all partners need to be acknowledged and when one partner suffers a setback others will need to step in.(24,32) An example of this is when the END Fund stepped in and was able to generate interest and funding from philanthropists and local companies to fill a funding gap when a coup in Mali meant that USAID could not transmit funds for the NTD program due to US government regulations.(33) Close communication and partnership through the Uniting to Combat NTDs Stakeholders Working Group and Donors Working group allowed peer to peer conversations and problem solving to overcome potential program interruptions.

The Eradicationist interviews identified a number of important points related to people and partnerships. Numerous examples of strongly committed individuals that drove programs to success or avoided setbacks were given through these interviews. This element of human level commitment and perseverance is hard to find documented in the peer reviewed literature but is too important to overlook. It is well documented in some of the books about the experience of eradicating smallpox which detail the perspectives and commitment of the people involved.(34) As Joel Bremen, Bill Foegel, and Don Hopkins all emphasized in our interviews, find the right people and invest in them.

Eric Ottesen brought out another aspect of this in his interview (May 5, 2020), "value each partner and understand their needs, especially donors." If you are not meeting your partners' needs or understanding what motivates them, your partnership will suffer and you may lose partners all together.

Think about the last mile

Consistently, the challenges of the last mile emerge as the most difficult to overcome. The last mile is the longest mile. The epidemiological curves of polio and Guinea worm depict the challenges of the end game well. The fight is not over but it has changed. We still have not fully embraced the advice “planning for the end at the beginning” given by Bill Foege. It is hard to predict the ending in specifics but we know that the end will take longer than expected and be expensive. Investments in work that can decrease the long tail of elimination or eradication should pay back to the program and justify expenses. Some work has been done to model this through the consideration of eradication investment cases that show some of the trade-offs in cost and equity of sustaining elimination as opposed to full eradication.(35,36)

One piece of advice to shorten the timeline shared by the Eradicationists, recommends tackling the hardest places first and planning for the last mile at the beginning. As second lesson notes that the end is hard, and it is not over until it is all gone. As mentioned above, Yaws decreased cases by 95% in 1964 and then stopped the vertical program to be integrated into primary health care which resulted in the eventual failure of the effort and resurgence of disease.(15) Human African trypanosomiasis (HAT) shares a similar tale with cases down to ~4,000 in 1960 and a slow and steady resurgence at the beginning of the 21st century to almost 300,000 estimated cases. It has now taken decades to regain progress with millions of dollars spent on test and treat campaigns and new diagnostic and drug development to improve treatment and outcomes to again bring levels down. Now HAT is again looking at integration with the health system with new diagnostics and treatments appropriate for use in the periphery of the health system but this integration is being heavily debated to avoid past mistakes. (37,38)

A path forward: Tools to Mitigate the Risk of Failure

E&E programs must constantly challenge accepted/established approaches because disease epidemiology changes in extremely surprising and unpredictable ways as they progress towards the end. The seven critical lessons learned in our review of existing and historical E&E programs have given a useful insight into how to create or rework programs to mitigate the risk of failure. In response to this we propose two critical tools to mitigate risk and plan for success. The first is a rigorous and responsive research agenda embedded into the program and informing the strategic plan. The second tool is a newly proposed independent review process to identify areas of risk or weaknesses to be proactively addressed.

Research Agenda

An embedded research plan is a critical element to an E&E program.(24) The research plan should address all potential areas of risk including testing assumptions, looking at processes for weaknesses, investigating unexpected findings and outliers, and questioning all the tools at use in the program. In addition, proactive investments in research for tools appropriate at different stages of the program need to be considered from the early stages of the program.(23,39–42)

One of the best considered and evaluated eradication efforts is the new malaria eradication program.(2,43) When the target of eradication was adopted again, there was an extensive pro-active process of reviewing past efforts and what worked and what didn't through the Malaria Eradication Research Agenda (malERA) Initiative. As part of this work a comprehensive research agenda accompanies the malaria eradication efforts that includes a drive for deeper understanding of

transmission and reservoirs and well as the need to continue to learn and re-evaluate assumptions and tools during the effort using approaches like modeling.(20,43–45)

Independent Review Framework

E&E programs are unlike any other public health program. The international community needs a method to assess E&E programs with a systematic approach built on past experience and to reinforce continuous learning. We should consider a regular maintenance plan similar to what you do with your car. Every so often the program needs to be strategically looked at- check the fluid levels, kick the tires and see if the program is performing optimally. Part of this maintenance system should include a major overhaul when you have decreased cases 90% and are entering the end game. We can call it the 90% rule. At that point the whole program should be critically evaluated with all program elements and assumptions reviewed. Considering tactics better suited to the last 10% could save time and money by focusing on what has been learned from the outliers at the ends of the bell curve.

To systematically assess a program for the risks seen in figure 3 and to identify weaknesses that can be addressed, we have defined a set of questions that can be the basis for an independent review. Figure 4, lists the questions that have emerged, refined by peer input at COR-NTD. With these elements we can begin to build a framework for a resilient program.

Figure 3: Summary of key areas for elimination and eradication programs to assess as identified during case reviews and interviews with experts.

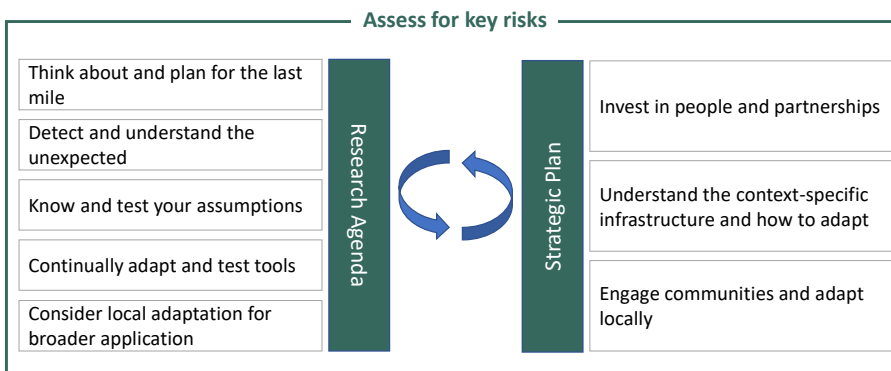


Figure 4: Questions to help elimination and eradication programs assess key risks, weaknesses, and areas where research or adaptation may be required for success.

Independent Review Questions

Know and test your assumptions

What are the program assumptions with regards to transmission? Effectiveness of interventions?

- Is the current strategy aligned to the latest understanding of the disease?
- Have the assumptions been reviewed and revisited to see if they are still relevant?
- Are there gaps in understanding of transmission dynamics? Are gaps part of the research agenda?
- Are all aspects of the transmission cycle exploited for weaknesses to improve the program's ability to eliminate transmission?
- Is the program designed to detect or adapt to changing transmission patterns?
- Is there a strategy to detect or respond to reemergence?

Understand the context-specific infrastructure

What are the assumptions about the ability of countries and communities to successfully put in place all aspects of the strategy?

- Does the program have a way to understand the infrastructure or settings that the program is running in to anticipate needs for support?
- Are there sufficient financial and human resources to put the strategy in action at all levels?
- Are poor infrastructure or conflict issues accounted for in planning?
- Is there sufficient political and local buy-in to the program?
- Are there resources to address gaps where system gaps may limit the ability to implement program elements?

Role of Communities: Engage and adapt locally

What adjustments are needed to ensure that the program is relevant to local context?

- Are communities and community members engaged in the implementation of the program and problem solving of local challenges?
- Are they empowered to provide frank and open feedback and suggestions to the program team?
- Is the program able to adapt with input and innovation from the field? Is this adaptation reviewed for further implications in the local and other settings?
- Are local innovations included or reviewed to be included in the research agenda?

Continuously test and adapt your tools

What are the program assumptions with regards to the ability to measure endpoints? Effectiveness of tools?

- Are there host-mediated limitations to the tools being used in the program (e.g., vaccine or diagnostic- no seroconversion)? Are the limitations accounted for in the plan?
- Are there populations where interventions cannot be used or are contraindicated? Does the program have a strategy to overcome these limitations?
- Is the program designed to be able to detect if pathogen-mediated resistance develops to the interventions?
- Is the targeting of the interventions using the available tools and strategies appropriate (e.g., insufficient diagnostics, sampling strategies)?
- Is there a strategy to detect or respond to lack of response to prevention/treatment?
- Is innovation introduction and uptake slowed by delays in regulatory, guidelines, or funding?
- Are there investments in tools (diagnostics, treatments, and any environmental control) for all stages of the program?
- Is there an independent review process in support of elimination or eradication?

Outliers: Expect the unexpected

What are the unexpected findings telling you about the program?

- Does the program conduct case investigations? Are these investigations used to adapt the program and/or create research questions?
- Is the program able to account for the importance of population movement (seasonal, conflict, weather, holiday/cultural events)?
- Is there trust in the program? Are there areas where mistrust by the recipients limits access?
- Does the program investigate outliers, unusual cases by presentation, geography, or demographics?
- Is there a way to detect cases from areas that are not thought to be endemic?

People and Partnership

Does the strategic plan measure and monitor the health of the partnership and reward strong management?

- Are there sufficient systems to ensure effective leadership?
- Are there sufficient systems to ensure effective supervision?
- Are there sufficient systems to ensure effective delivery of interventions?
- Are there sufficient systems to reliably measure impact endpoints?
- Is there a regular review of M&E data at all levels that is linked to decision making?
- Does data drive decisions?
- Is there a robust and inclusive partnership with open communication and clear roles?
- Are there processes in place to measure and support a strong partnership?
- Are there clear measurable goals that are understood by all program partners?
- Is there a regular review of programs at all levels?
- Is there a way to reward/acknowledge critical staff at all levels?

Think about and plan for the last mile

Does the program think ahead and invest in future needs?

- Is the program tackling the hardest areas?
- Is the program anticipating and investing in tools and strategies for the end game?
- Does the program review the lessons from success at district, province, or country level to look at changes made to the program at the end and what it may mean for the program end game overall?
- Is there partner and political commitment being generated for the sustained effort required for the last mile?

Research Agenda

Does the research agenda address all areas where programs can be at risk?

- Does the strategy include a robust research agenda?
- Does the research respond to issues or innovations identified in the field in a dynamic fashion?
- Are research findings rapidly accounted for in the program?
- Does the research agenda cover all necessary elements of the program including tools, social science, ecological elements, transmission dynamics, and program processes?
- Are unexpected programmatic findings investigated and used to inform additional research needs?
- Does the research agenda challenge the strategic plans assumptions?
- Are research investments made in anticipation of upcoming program needs, especially with regard to diagnostics?
- Does the research address the potential needs of the end game learning from early successes?
- Is the program able to quickly absorb new interventions or tools? What is the process? What are the barriers?

Notable papers

1. Henderson DA. Eradication: lessons from the past. Bull World Health Organ. 1998;76 Suppl 2:17–21. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2305698/>
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4. Nájera JA, González-Silva M, Alonso PL. Some lessons for the future from the Global Malaria Eradication Programme (1955-1969). PLoS Med. 2011 Jan 25;8(1):e1000412. DOI: [10.1371/journal.pmed.1000412](https://doi.org/10.1371/journal.pmed.1000412)
5. Cochi SL, Dowdle WR, editors. The Role of Research. In: Disease eradication in the 21st century: implications for global health. Cambridge, Mass: MIT Press; 2011. p. 63–86. (Strüngmann Forum reports). Available from: <https://assets.pubpub.org/stjmfst0/21587654686498.pdf>
6. Roeder P, Mariner J, Kock R. Rinderpest: the veterinary perspective on eradication. Philos Trans R Soc Lond B Biol Sci [Internet]. 2013 Aug 5 [cited 2021 May 26];368(1623). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3720037/>

DISCUSSION

To be successful in elimination and eradication efforts, we need to learn from the past to effectively plan for the future, strive to learn what we don't know, and think creatively about solutions. Undertaking a program with the goal of elimination of transmission or eradication should not be taken lightly. Many new approaches are available now to consider the investments required and the work necessary to achieve the goal. The extensive multi-year and multi-million-dollar process undertaken through MalERA in support of malaria eradication will not be possible to replicate for all other programs,

particularly in the historically underfunded area of NTDs. We can, however, learn from this effort and try to take essential elements and use them to help ensure a higher likelihood of success. The world is significantly different than when smallpox was eradicated. We do not have a vaccine, like smallpox and rinderpest, for the NTDs identified for eradication and elimination so we will need to use all the tools at our disposal to ensure that we are able to achieve eradication for a second time. We hope that the questions that have come through this analysis can be the building blocks of helping to establish an effective evaluation tool to objectively strengthen and improve programs.

The NTDs in many cases may prove “easier” to eliminate and eradicate as their complex and somewhat fragile lifecycles offer many areas where interventions can be targeted to put pressure and ultimately block transmission. This does however, mean that all areas where interventions can be used to prevent transmission should be considered by the programs. There is potential for many of these efforts overlap with the interventions needed by other disease areas to achieve their health targets. Working with these programs in a supportive, collaborative, and more integrated way can help to strengthen both programs (cite integration paper if ready in time). This theme of integration into health systems and cross sector collaboration including water, sanitation and hygiene, education, and One Health are clearly, and appropriately, highlighted in the WHO’s NTD 2030 Roadmap titled ‘*Ending the Neglect to Attain the Sustainable Development Goals*’ launched in January 2021.

In the new WHO NTD 2030 roadmap, the need for quantitative and qualitative monitoring and evaluation of programs is highlighted. The monitoring tools and gap assessment tools are further discussed in the M&E framework entitled ‘*Ending the neglect to attain the Sustainable Development Goals A framework for monitoring and evaluating progress of the road map for neglected tropical diseases 2021–2030*’ that accompanies the Roadmap. In this document, it is clear that there is still significant remaining work to define and target an evaluation tool and process that will build on the current disease specific and program monitoring tools. In reviewing past programs, evidence shows that there are predictable areas of weakness that are risks to E&E efforts that we can learn from and use to assess and strengthen programs. The independent review concept proposed in this paper strives to create a tool which can be used to assess E&E programs against these known areas of weakness in an effort to proactively identify and address them. The use of such a tool can help identify risks early and prevent today’s E&E programs from suffering from the same mistakes of the past.

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