6

The Role of Research

Julie Jacobson

Abstract

Based on multiple global and regional programs that have attempted to eliminate or eradicate disease, this chapter reviews what has been learned to date, identifies gaps in knowledge, and highlights opportunities for learning and debate. The central and important role of research has clearly been demonstrated in historical attempts to eliminate or eradicate, and lack of research has been linked to program setbacks and failure. Recurring themes in research needs of eradication or elimination initiatives are identified and an approach is proposed to define, articulate, and meet these needs.

In addition to complete surveillance and rigorous administration, the International Task Force for Disease Eradication has identified operational research as a key element for the success of an eradication or elimination program, because "the standard of success in an eradication program is unambiguous and uncompromising" (CDC 1993b:3). Research needs to be both proactive and reactive; it must focus on the key areas where a program can fail and build on strong monitoring and evaluation—always looking with a critical mind toward additional work that needs to be done. Finally, it requires innovative problem solving from the bottom up as well as top down.

Introduction

Humankind is developing rapidly, achieving things that could not be imagined in the last century. This progress has changed our planet, leaving us with a wealth of experience and knowledge as well as new challenges. As our world becomes increasingly connected, awareness of diseases and how they affect the human population has increased. This has led to ambitious goals of eliminating select pathogens that have plagued humankind, limiting our health as a species and causing great suffering.

Our first successful eradication effort with smallpox resulted in many new targets being set. The list of diseases and conditions with targets for elimination or eradication is extensive and diverse. Definitions of what elimination and eradication actually mean for different disease states are a point of confusion. Regardless, many crucial lessons have been gleaned from the challenges

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that were faced and should be applied to the research needed to improve programs, so as to increase the likelihood of success with these ventures.

Research and information needs change as programs develop and mature over time. The key to the speed of this development and adaptation is related to the research conducted in support of the program or agenda. Data is used to set the initial targets and strategy; new data is then used to modify the program as issues and barriers to success arise. Only through effective monitoring and evaluation can we identify these issues and establish appropriate research to overcome the problems. Prior to the initiation of a program, patterns can be seen in the issues that have impeded past programs, and these patterns can be used to establish a proactive research agenda in support of activities and strategies. Other setbacks attributable to unexpected events require a more reactive response and innovative approaches to overcome them.

Barriers to Success: Learning from Failures

In striving to eliminate disease, our history of failure and setbacks is rich. All of the elimination and eradication programs to date have yielded great successes as well as lessons learned throughout the process; however, significant lessons exist in the ultimate reasons for failure. Patterns quickly emerge and are important to use when the research needs of an elimination or eradication program are defined (Table 6.1). The primary reasons for failure include (CDC 1993a; Henderson 1998):

1. lack of understanding of the transmission of the targeted disease,
2. ineffective or incomplete treatments that do not eliminate transmission,
3. development of resistance to interventions,
4. insufficient diagnostic tools,
5. lack of understanding of the diverse influences on transmission in different settings.

As we attempt to do something that has never before been accomplished, it is only natural that we will confront unforeseen challenges. However, by proactively looking for these challenges, we can anticipate setbacks and develop the necessary tools and strategies to overcome initial programmatic limitations. Essentially, in an elimination or eradication program, we must confront the extremes at the far ends of the bell curve, for this is where the ultimate success of a program lies. In reflecting on the progressive success of guinea worm eradication, Don Hopkins (pers. comm.), who has championed its eradication, states: “Don’t leave the hard places for last; get in there early, because they will take the longest” and potentially teach you the most.

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Table 6.1 Unsuccessful disease eradication programs and the reasons for their failure (based on data from CDC 1993a; Henderson 1998).

Disease, date	Reasons for failure:	Research needed:
Hookworm, 1907	Mass treatment does not cure; it only decreases infection intensity so reinfection occurs	To understand transmission dynamics and drivers of infection
Yellow fever, 1915	Animal reservoir in nonhuman primates in forested areas	To understand transmission dynamics and drivers of infection
Yaws, 1955	No treatment was given to inapparent cases	To be able to diagnose all stages of disease important to ongoing transmission
	Some patients with overt disease were only partially treated, leading to relapse and ongoing transmission	To understand transmission dynamics and drivers of infection
	Premature withdrawal of disease-specific programs caused reemergence	
Malaria, 1955	Development of resistance in vectors and parasite	Monitoring of resistance in vectors and parasite for early detection
	Complicated and challenging vector ecology to control approaches	Into new chemotherapeutic options and insecticides
	Administrative shortcomings and increasing costs of program	To understand transmission dynamics and drivers of infection in different ecological settings to modify plan accordingly

When Theory Meets Data: Changing Targets and Program Goals

Ideally, initial program targets are based on the best data available at the time an elimination or eradication program is established. Through program monitoring, the data informing these decisions will increase over time. Multiple examples, from almost every program, demonstrate that the data set at the beginning does not resemble the data at the end.

In 2000, the target was set to eliminate lymphatic filariasis (LF) as a public health problem by 2020. Currently, large-scale, community-based drug distribution programs are underway in an expanding number of endemic countries. The community drug distribution program for LF reached 546 million people in 2009 and is arguably the largest public health program that has ever been conducted (Chu et al. 2010; Ottesen et al. 2008). The initial World Health Organization (WHO) strategy for the elimination of LF was based on the expectation that four to six rounds of mass drug administration at a community level could eliminate LF from that community. The original targets set in 2000 were based on modeling with available data (Gambhir et al. 2010). The program is now at its midpoint, with ten years remaining to complete the

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task. New modeling, based on data from sites in Asia and Africa that exhibit different vectors, vector densities, population density and other factors, has shown significant variation between sites, depending on the local transmission dynamics. One of the greatest challenges to a global program is to prepare for and react to this immense local diversity (Gambhir et al. 2010). The main interplay takes place between the vector and control of disease transmission; by addressing the vector directly (i.e., vector control) and/or reducing the parasite in the infected host, transmission can be interrupted by eliminating the pool of microfilaria for the vector to transmit. Operational research is currently underway to assess vectors, coverage, compliance, drug dosage and frequency, and end points to verify the success of elimination. All of this work needs to result in appropriate program changes for implementation, or the success of the program will be jeopardized.

One challenge to programs is that lessons from early successes can be misleading or not representative, as was observed in LF elimination initiatives in South Korea and Yemen. Although both countries provided early examples of successful elimination, and both countries had relatively limited disease in lower levels, only one used the WHO strategic approach in their programs. Due to the different epidemiology, South Korea relied on a screen-and-treat approach, which was feasible because of the localized disease distribution patterns in the country, instead of the WHO mass drug administration approach. Significant social and economic developments were also factors for success in South Korea, leading to improved housing and good vector control, which complemented the chemotherapeutic approach. From this example, two factors are significant. First, all models must be scrutinized in context of the local situation; disease transmission is always multifactorial, thus the approach will need to vary accordingly. Second, during a program, environmental and social changes can impact transmission; these changes should be sought and used to guide research questions during the lifetime of a program.

One Size Doesn't Fit All

A chief criticism of the early efforts in the 1950s in the malaria eradication initiative was the rigidity of the approach and the lack of accompanying research and learning. The malaria program had high levels of political commitment: the director of a national program reported directly to the head of the government in a fully vertical program that had its own staff and pay scales. This strength was offset, however, by a significant weakness: the programs did not generally involve any level of the community. Instead, they had detailed standardized operating procedures and worked under the assumption that all of the needed technology was available. Success relied solely on the strict application of the interventions according to plan, and research or learning was not

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incorporated into the plan. Ultimately, after significant investment of human and financial resources, this strategy failed.

The smallpox program learned from these mistakes and took a very different approach, working within the health system and engaging local communities as part of the program. Instead of having standard operating procedures, the smallpox project set broad goals and enabled flexibility and creativity in how these goals were achieved locally. Research was also included as part of the work, and during the program many new ideas were adopted: new tools were developed for vaccine delivery; field studies provided insight into epidemiology and transmission and were used to modify the approach; studies looked for animal reservoirs; and studies were conducted on the duration of vaccine efficacy (Henderson 1998). Ultimately, this flexible approach, which embraced research, led to the first successful eradication program.

Lack of a Baseline

One of the reasons cited for the failure of yaws elimination was the lack of pilot programs in critical geographic areas (Henderson 1998). This key feature is integral to the start and ongoing management of any elimination or eradication program. With yaws, excitement over a new tool prompted an effort to be initiated without a full plan or learning agenda in place. The new tool was injectable penicillin, which enabled yaws to be treated with a single injection (Henderson 1998; Narain et al. 2010). As encouraging as this was, there was no baseline data to form the basis of a plan for elimination. When a test was developed and serological surveys were conducted, a much larger number of subclinical infections were demonstrated; this led to the resurgence of disease in communities after the overt clinical cases were treated and reestablished transmission. Since there was no proof of cure diagnostic, some patients were insufficiently treated, which led to disease recurrence and reestablished transmission. This resurgence was exacerbated by the early withdrawal of disease-specific teams, which meant that early signs of reemerging infection went undetected. Henderson (1998) postulates that if this baseline work had been conducted, the elimination program might never have been attempted with the tools available at the time.

Monitoring and setting targets is difficult, if not impossible, without a solid or at least semisolid foundation. Prevalence of disease was used for the baseline to follow progress in leprosy and was defined as all people receiving treatment at a given moment over the total population. Leprosy is a disease that requires long-term treatment, and this means that as programs and treatment recommendations changed, the populations receiving treatment also changed. Consequently, prevalence was altered without actually providing a true indication of the program's success. Take, for example, the decrease in multibacillary multidrug therapy from 24 to 12 months. Although this effectively cut

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the number of patients by half and resulted in a significant decline in disease prevalence, it did not actually change the status of the disease. In addition, data on cases were collected and counted annually as of December 31. Thus data from patients on 6-month therapy with paucibacillary multidrug therapy or who received a single treatment for a single skin lesion were not included in the prevalence figures, resulting in data that did not truly reflect the progress or issues associated with the program. Incidence of new cases provides a better and more interesting measure. However, because of the long incubation period of leprosy, which ranges from 2–20 years, incidence is not an accurate measure of elimination; thus, some sort of screening is required. Interestingly, due to the definitions being used, many sites have eliminated leprosy even though new cases are still detected annually, as seen in South Africa (Lockwood and Suneetha 2005). A program needs to screen for relapse for up to five years after treatment, because of the slow-growing nature of the organism. This has not been fully addressed in global targets of the elimination program. Even today, debate continues and experts question whether leprosy should be targeted for elimination or more honestly tackled as an ongoing disease program (CDC 1993b; Lockwood and Suneetha 2005).

Lack of baseline data has also been cited in LF elimination and has limited the program's ability to learn. In an evaluation of the LF elimination programs from five country islands in the Pacific, only one country was able to provide useful data. All others used a convenience sample for their baseline data collection, which meant that this data could not be compared to the follow-up data after five rounds of mass drug administration. This information would have been very helpful in modeling and providing indicators for modifying programs that did not successfully meet the targets (Huppatz et al. 2009). Setting up sentinel sites for evaluation and research, particularly in early countries, could be very valuable, as early investment can prove extremely useful to later programming.

Elimination as a Public Health Problem

The phrase "elimination as a public health problem" is unclear in most, if not all, contexts. It has been a rallying tool to garner additional attention and resources to an area, but defining what a public health "problem" is and what indicators can be used to determine when something is no longer a "problem" is problematic. In addition, regardless of the programmatic target set, public health efforts must be maintained and sensitive surveillance and response must be continued if the target is anything less than complete elimination or eradication (Molyneux et al. 2004). In these cases, setting reasonable measurable targets that are subject to reevaluation and discussion through a carefully thought-out research agenda could help decrease the ambiguity and clarify reasonable end points.

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There are many examples of where this has not been done and programs have suffered as a result. In leprosy, the target for elimination is 1 case in a population of 10,000. This is a figure that can be easily manipulated by choosing a different denominator. In 2001 the WHO, despite data to the contrary, declared that leprosy had been eliminated as a public health problem by including in the denominator the total population of all the countries who had reported at least one case. What does this target truly indicate? Leprosy transmission still occurs, and incidence of new cases has not decreased in many settings despite the progress in decreased prevalence (Lockwood and Suneetha 2005). The importance of 1 case per 10,000 population for disease transmission or program planning is not clear; thus the significance of reaching or not reaching this target seems to have little meaning programmatically, outside of declaring that it has been met.

Proving Zero to Define Success

Starting a program is frequently straightforward: to eliminate a disease, you detect cases and intervene to block transmission. Of course, this becomes much more complicated, as discussed above, when you need to ensure that you can detect all cases and all stages of infection, and either treat completely or prevent further transmission. The final challenge is to prove success: How do you prove a zero? How do you address confidence intervals? These questions quickly become important, and early sites where successful elimination has been achieved will likely differ (e.g., in terms of lower transmission, different socioeconomic or cultural considerations) from areas that enter later in a program. How do these factors affect indicators and measures of success?

All elimination or eradication programs struggle with these issues. The fact that we cannot prove a zero means that we need to find another way. This challenge needs to be addressed early in a program so that the tools are available to measure success. Models frequently can play a role in this stage, and new diagnostic tools may be needed (CDC 1993b; Gambhir et al. 2010; Hall and Fauci 2009; Marais and Pai 2007). Specificity becomes increasingly important as false positives are a huge distraction to a program in the final stages. Algorithms for diagnostic procedures need to be defined.

In the onchocerciasis elimination initiative in the Americas, the program has been challenged to meet their elimination criteria, which rely on capturing a sufficient number of black flies (the vector) to look for transmission. In some areas, the required number of flies has not been met despite extraordinary efforts. Although it is obvious that a lack of vectors is a good thing, from a disease transmission perspective, this poses a problem in terms of ensuring that elimination criteria have been met.

Another example derives from the LF initiative. To start a program, a community must demonstrate that 1% of the population is infected to initiate mass

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treatment. When it comes to stopping the program, they have to prove that less than 1% of people are infected. In the early protocols that were developed, this meant that 3,000 school-aged children needed to be sampled. This is a huge sample. It is programmatically very challenging, expensive, and has resulted in huge backups in the laboratory. In an effort to simplify this process, modeling based on data from well-defined populations is being used to identify new sampling protocols currently under development.

Understanding Transmission and R_0

Insufficient knowledge of transmission, and what is required to break transmission, has led to disappointment in many programs (Table 6.1). To block transmission and eliminate disease, an understanding of transmission is a basic prerequisite. For many current programs, however, understanding is insufficient, thus posing one of the greatest challenges to many ongoing initiatives today.

Leprosy is one of the oldest scourges affecting humankind, yet it is also one of the most poorly understood. Despite all of our technical advances, transmission of leprosy remains a mystery. Although the prevalence rates of leprosy have decreased—some even meet the targets of < 1 case per 10,000 population—the incidence of cases has not decreased in many areas of the world. We do not understand how or why multidrug treatment has been unable to stop transmission. This simple fact has not been embraced by the program. Consequently, there has been limited debate and insufficient research to be able to modify and expand the program beyond the current approach (Broekmans et al. 2002; Lockwood and Suneetha 2005; Vashishtha 2009). This is a major limitation and poses a threat to the program's success.

In both LF and onchocerciasis, understanding R_0 is a significant discussion point, involving a complex combination of factors (Gambhir et al. 2010) related to:

- the infection level in the community prior to the start of the control program and mass drug administration;
- the vector efficiency, density, and annual biting rate;
- the years of high-level coverage at the community level; and
- the rates of systematic noncompliance.

Modeling is helpful, but new data indicate that models need to be modified for local situations and frequently use variables that are not easily measured in the field. For onchocerciasis, we may only be able to determine R_0 after the successful elimination in the Americas, once data is collected on the vectors and indicators of infection in humans after the programs are successful and no recurrence has been observed. Even when the R_0 may be known for the Americas, the usefulness of this information in Africa remains questionable, because of the different vectors and transmission dynamics (WHO/APOC

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2009). Ultimately it is this elusive figure that we would like to know and measure to prove that the job is done. Work is continuing in both the LF and onchocerciasis programs to define and refine the elimination criteria and measures of success as new data becomes available.

In Chagas disease, new transmission risks have been identified over the course of the project, causing adjustment to be made in ongoing elimination efforts. The transmission of Chagas comes from the bite of infected triatomines, primarily *Triatoma infestan.* These insects live in the walls of poor-quality huts, which are generally associated with people living in poverty. The approach to the disease has relied on improved housing, as treatment has been inadequate, particularly for the chronic stage of the disease, and good insecticides for the vector do not exist. Progress has been made in vector control, but treatment still lags; thus the focus of the program remains on improved housing. Due to transmission, the distribution of cases is almost exclusively in the rural poor parts of the Americas. However, the detection of cases in more urban centers led to the discovery of a new mechanism for transmission: one that is linked to blood transfusions. Advances in the control of the blood supply, spurred by HIV, were used to improve screening for Chagas in endemic settings. Finally, as programs have had success with these approaches, the remaining transmission mode which now dominates is congenital infection. Unfortunately, little is being done to counteract this. The current strategy involves waiting until infected women are out of their childbearing years (Dias 2009; Schmunis et al. 1996). However, attention should be given to the early detection of infected infants to facilitate treatment. In addition, recent case investigations have implicated oral transmission in some settings. Thus, the program will thus have to work to understand the implications of this on their elimination plans.

The essential lesson is that we need to follow the pattern of cases to detect new transmission patterns. As a program progresses, nondominant transmission mechanisms gain importance. Research into the mode of transmission and how to approach it early on will help a program counteract bottlenecks later.

Monitoring and Evaluation: Learning while Doing versus Formal Operational Research

The neonatal tetanus (NNT) elimination program in Egypt demonstrates the importance of using surveillance data to adapt programs and the essential element of flexibility in programming. The NNT program initiated what was felt to be an aggressive plan in 1988, based on the globally accepted approach that used annual nationwide tetanus toxoid vaccination and targeted pregnant women from 1988–1993. The campaigns were held in two rounds: one month apart in November and December each year with the participation of multiple partners, nongovernmental organizations (NGOs), and advocacy activities. Although this increased coverage immediately from 7% to 85%, and

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subsequently brought down NNT incidence from 3.7 per 1000 live births to 1.6 per 1000 live births, it was still above the elimination target. In looking deeper into the data, a few areas (governorates) were found to be responsible for a disproportionate number of cases: 66% of the cases were reported in areas with only 32% of the population. This led to a learning-while-doing approach, which targeted the high-incidence areas to improve routine coverage and expanded the target population of the campaign to cover all married women of childbearing age, regardless of pregnancy. Although this improved indicators, the highest risk areas still posed a problem. Thus a high-risk strategy was implemented: the governorates were subdivided into their districts, all women of childbearing age were targeted regardless of marital status, and there was significant involvement of the local communities. This was accompanied by work to improve reporting and surveillance data. With these investments as well as improved surveillance, which should increase the reporting of cases, incidence of NNT was brought for the first time down to 0.6 per 1000 live births, below the 1 per 1000 target (CDC 1996). This example illustrates the importance of data to drive programs.

The line distinguishing formal research versus dynamic programming from monitoring and learning can be blurred when a program incorporates a test-and-adapt approach. Here, a frequent weakness is the lack of in-depth monitoring as well as a lack of publication of the experience, from which other programs could learn. Planning for this type of learning should be factored into the research plan, and appropriate data should be collected to assist decision making. In addition, information should be disseminated so that programs can adopt new practices if needed.

The guinea worm eradication program in India lobbied for all program managers to be trained in basic operational research techniques to support the program. They outlined a basic framework that included considerations of the health system resources, service delivery, and the beneficiary or consumer (Kumar 1990). Empowerment of the program managers to be critical thinkers and problem solvers likely played a role in the program's success.

Case Reports

All monitoring plans should include some level of case investigation and reporting. Because reporting and intensity of investigation may increase over the lifetime of the project as cases decrease, the need to understand why a case occurs increases in a reciprocal fashion. Case investigation can be a key part of setting research priorities. Case reports have informed programs related to tuberculosis, *Haemophilus influenzae* type b (Hib), Chagas, guinea worm, and polio and have resulted in changes to the program or new research. Case reports are crucial for identifying resistance or programmatic failures (CDC 1993b; Broekmans et al. 2002; Dias 2009; Donnelly et al. 2003; Howie et al.

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2007; Kumar 1990; Lemon and Robertson 1991). Case reports are also where you identify the outliers and detect the unexpected.

The Ends of the Bell Curve: When Outliers Matter

In trying to eliminate and eradicate a disease, a large proportion of the population and their communities will be addressed through minor modifications of the program. Unfortunately, in disease eradication, this is not enough. Success relies on reaching the critical proportion of the population to stop all disease transmission, and this involves not just the center of the bell curve but the outliers as well.

The current barriers within the polio program reflect the ends of the bell curve beautifully. In India, the barrier is technical: the challenge is the failure of a successfully delivered intervention. The failure is the lack of immunity conferred from the oral vaccine in Indian children from some areas. This is believed to be related to the local ecology of both the gut flora and the environment, resulting in intense exposure to intestinal pathogens early in life which alter the ability to respond effectively to the oral vaccine. In Nigeria, the problem is just the opposite: failure is due to a lack of understanding of the sociobehavioral axis of acceptance of the intervention, resulting in failure to deliver the vaccine. This difference was detected by monitoring the number of doses of vaccine given to acute flaccid paralysis and polio cases, which were identified through surveillance. In India, children have received many doses of vaccine, and the vaccine itself is not conferring immunity; in Nigeria cases have never been immunized, so the delivery system was broken. The key to overcoming both of these barriers lies in the program's ability to detect cases, understand why there are setbacks, and having a dynamic approach to address the challenges based on the underlying cause. Local site-specific problem solving and monitoring should be reviewed to set new research priorities.

The Unexpected

Expecting the unexpected may be too much to ask; however, it is important to be receptive to the unexpected so that programs can detect changes in patterns and respond. There are many examples that get even more interesting as programs approach the finish line.

In southern Mali, a poor farmer infected with guinea worm walked 400 km by foot when his fields were struck by drought. He contaminated a watering hole in an area that had never had a case of guinea worm, and this resulted in an outbreak among the nomadic warring tribes in northern Mali.

The Yanomami, who inhabit the Amazon rainforest across the border of Brazil and Venezuela, pose a challenge for the elimination of onchocerciasis in the Americas. This group is comprised of several tribes, mostly nomadic and some xenophobic, that kill any non-Yanomami on sight. This poses a challenge

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for community-based drug distribution. Helicopters are used for drug distribution, but migration patterns are not stable so flights have been made to a location only to find a community gone. In such a case, community engagement can help, taking advantage of local knowledge, good surveillance, good communication, case reports, and creative problem solving early on to address hard to reach populations and approaches to gain trust. New communication tools (e.g., cell phones, Twitter, Google Earth) could potentially be applied to address these issues. Operational research focused on using these tools in new initiatives would be valuable.

Empowering the Field

No one knows the field better than those who live within and are part of the culture. External observations and learning can help provide perspective and objectivity, but some of the most amazing things can happen from the field innovating for themselves. As an example, during the recent 2006 introduction of Japanese encephalitis (JE) vaccine into India, the successful introduction was thought to be impossible by most international experts with good reason: India had not introduced a new vaccine, they had never conducted an injectable vaccine campaign, there was no external financing available, the only available supply of vaccine came from China, and JE was not an international priority. JE was, however, a national and local priority. All of these barriers were overcome in an 8-month period of time to prevent further JE outbreaks triggered when a seasonal outbreak drew international attention, and the background work had been done to provide the supportive data for decision making. During this dynamic process, much innovation happened at the field level to prepare for introduction. At the national level, immunization safety and waste disposal had been discussed and debated for several years. Among the hotly debated issues were needle cutters to remove the sharp (needle) from the syringe and decrease the volume of the medical sharps waste for disposal. The JE campaigns targeted over 9 million children in their first year. There was concern over what would be done about the volume of sharp medical waste. Safety boxes were to be provided, but in the state of West Bengal they asked for needle cutters, which they were told were not available by the central level due to the ongoing debate. So, they developed their own for use in the campaigns by constructing a plastic container with a wire cutter attached (Figure 6.1). This way the needles could be disposed of as sharps, decreasing the sharps waste by over 90%. This innovation was very effective and had significant ownership at the local level.

The lesson here is twofold: What may look impossible from the global or national level may be possible when affected communities are motivated. In addition, innovations from the field can identify solutions, frequently very cost effective, that would not have otherwise been considered at central levels.

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Figure 6.1 Needle cutter that was locally produced in West Bengal, India, for the Japanese encephalitis immunization campaign (picture by Julie Jacobson).

Elimination, Eradication, and the Treatment of the Patient

Technically, almost no elimination or eradication program depends on the treatment of ill or infected patients and their sequelae. The importance of a patient lies in their ability to *transmit* disease. This is evident in the focus of different programs that exclude some or all patient treatment as elements of the interventions for elimination or eradication. The following are a few examples that all represent different challenges in this paradox and the program's approach: human African trypanosomiasis (HAT), LF, and tuberculosis.

The Pan African Tsetse and Trypanosomiasis Eradication Campaign (PATTEC) approach to HAT eradication is based completely on the elimination of the vector and not the pathogen or the disease. Technically, no treatment needs to occur for this program to be successful. What does this mean from a public health perspective? Can you call it a success if you eliminate the tsetse fly while allowing all infected patients from this 100% fatal illness to die? The dynamic tension between treatment of the individual and the prevention of disease are felt most when there are limited human and financial resources with which to work. I would postulate that both need to be addressed to meet the public health needs and should therefore be included in the program for success. To complement the PATTEC approach, a screen-and-treat program with donated drugs is being conducted through separate funding by WHO and NGOs like Medicine Sans Frontiers to assist affected countries (Ahmad 2003; Kabayo 2002; Rogers and Randolph 2002).

The focus of the tuberculosis elimination initiative is treatment of smear-positive adults (Broekmans et al. 2002; CDC 1998; Vashishtha 2009). This, however, leaves other forms of tuberculosis unattended programmatically and stands in stark contrast to a clinician's duty to treat all disease and prevent suffering and death. Most programs have addressed this issue, and treatment is

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available for all patients clinically ill with tuberculosis regardless of the location of the pathogen, although technically it would only be necessary from the elimination perspective to treat those patients able to transmit disease. With the focus on smear-positive patients, the biggest challenge to the program is a diagnostic gap for pediatric diagnosis, detection of latent disease, and resistance. From an elimination perspective, undetected cases, latent disease, and resistance are the primary risks to ongoing transmission (CDC 1998; Dye and Williams 2008; Marais and Pai 2007). Pediatric populations present a unique challenge as they frequently have lower numbers of bacteria and do not give good sputum specimens for diagnosis, thus greatly decreasing the sensitivity of the test. This is similar to the challenge seen with the latent cases: latent disease can progress to an active state and reestablish transmission. In low-transmission countries, detecting and treating these cases based on screening of high-risk populations (e.g., immigrants from high-incidence countries, people held in institutions or prisons, and HIV-positive populations) constitute a vital component of the elimination plan (Broekmans et al. 2002; CDC 1998). In high-risk countries, these people remain mostly untreated. Diagnostic tests that can quickly detect resistance are needed to guide the appropriate selection of therapies and isolation of drug-resistant patients to stop the spread of resistance; this process is slow and cumbersome from cultured sputum specimens. All of this work depends on good surveillance data with sufficient detail to detect new trends. For example, when the association with HIV was discovered in the United States, a program began in 1993 to collect data on HIV with the newly reported tuberculosis cases (CDC 1998). This observation uncovered a new prominent driver of infection that was important to address.

Debate on this topic continues in the LF and trachoma programs, where surgery and other preventative tools are required but are frequently not funded (Perera et al. 2007). For Chagas, an approach is used that focuses on the vector, both through indoor residual spraying and improved housing in the lower resource rural areas where the disease is endemic. Interestingly, disease patterns did shift and this allowed urban transmission to be detected, which was subsequently traced back to blood transfusion. This, in turn, increased attention to the problem and initiated a program to improve the safety and screening of donated blood in affected countries. Effective treatment for patients in the chronic phase of Chagas is controversial; thus all focus is on prevention (Broekmans et al. 2002; Dias 2007, 2009). Although, in this case, there is no moral dilemma, research into new tools is needed to address the clinical pathology, prevent disease progression, and eliminate the human reservoir of infection. Even if the treatment does not eliminate disease, the treatment of patients must be considered as part of a program to increase acceptance by the community and health professionals, increase uptake of preventative measures, leverage funding to expand programs, and to relieve suffering.

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Looking for Patterns

Different tools lead to different failures. For example, with a vaccine you do not have resistance; however, there are limitations in the host's ability to respond to the vaccine. This cannot be screened for by culturing pathogens and can only be followed through ongoing sensitive surveillance. Vaccines are extremely powerful tools but are frequently limited by their precision. Pneumococcal vaccine, for example, is limited since it covers only a subset of pneumococcal serotypes in the conjugated vaccine. These serotypes vary according to geographic areas and times of life. This means that the effectiveness of the pneumo vaccine depends on the pathogenic serotypes in a community and the age of the population.

The second limitation of a vaccine is the host response. No vaccine is 100% efficacious. Depending on the type of vaccine, different parts of the immune system are activated and multiple doses may be required to seroconvert or to obtain sufficient sustainable levels of antibodies and cellular immunity. Examples of limited seroconversion and inadequate immune response in polio have led to the development of monovalent vaccines to improve strain-specific immunity. The initial polio vaccine that was used as the basis for eradication is an oral vaccine, which contains the three types of polio. The trade-off for having all three types in one vaccine is having lower levels of antibodies for each and needing more doses to get an adequate immune response to all three types. This fact combined with a much deeper understanding of transmission patterns—recognizing which strains were coming from where—allows a more focused vaccine to be used to stop transmission. At the beginning of the program, knowing if an acute flaccid paralysis patient was polio positive or negative sufficed; as the program progressed, however, the need for more detailed and accurate data, including the type of polio and where the infection originated, was required.

Measles provides another example. The measles vaccine is a single dose with high seroconversion (greater than 90%). However, a second opportunity is necessary to have high enough immunity at the population level to stop transmission and outbreaks. For drugs, failure comes with increasing resistance due to selective pressure on the pathogen allowing resistant organisms to flourish, and in some cases replace, the original circulating pathogen. This can be monitored through treatment failures and culturing of the pathogen if possible (for viruses and bacteria) to determine how common these strains are and by what mechanism the resistance has developed. Early malaria eradication and tuberculosis elimination programs have confronted issues of drug resistance that have required new approaches and strategies to be developed (CDC 1993b; Hall and Fauci 2009). With both vaccine and drug approaches, monitoring the program impact is necessary to detect hypo-responsiveness and allows issues to be addressed as they arise. Part of the operational research

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agenda should look for such possibilities as well as what response would be required and implications for new tools that may need to be developed.

Observing programs to detect patterns can reveal synergies and new opportunities. This has led to the integration of seven of the programs for neglected tropical diseases that are now approached through an integrated platform, with community-based mass drug administration as the focal point of the programs. In addition, this has allowed the strengths of the platforms built for a specific disease, such as LF or schistosomiasis, to be utilized for seven diseases, thus expanding the scope and impact of the projects. This has been an important element in enhancing efforts for schistosomiasis, trachoma, and LF elimination. However, questions remain: Have we exploited common strategies enough? What could LF learn from the malaria experience or onchocerciasis share with efforts to eliminate HAT?

What is considered a minor part in one strategy may significantly impact another. For example, the deployment of long-lasting bed nets for malaria may have a large impact on the transmission of LF in co-endemic areas. How can we build on these opportunities? The SAFE strategy for trachoma elimination is an acronym for surgery, antibiotics, face washing, and environmental improvement. The last two points rely on provision of water and sanitation where it does not exist. When looking at the other neglected diseases, schistosomiasis and soil-transmitted helminthes could greatly benefit from water and sanitation. Could the case be made for further support by building a stronger evidence base to support these activities with additional funds as part of the plan for successful elimination and sustainability of impact? Programs will continue to struggle for funding, and this kind of integrated thinking could help us accomplish more with less by working together.

New Era of Embracing Research as Part of the Program

Currently, the best example of truly embracing research is the MalERA project, which is being developed in support of the renewed efforts to achieve malaria eradication. This call for eradication was made knowing that the necessary tools were not yet available to finish the task, but with hope that they will be in the near future and that they will be able to be introduced into programs to achieve the goal. From the beginning of the effort, this has set a tone of receptivity to new approaches and the desire to know. Hence there is regular debate and discussion on the creation of the plan for eradication, which includes a full research agenda. The MalERA project is a new community-based initiative that supports the development of a Malaria Eradication Research Agenda (MalERA) (Hall and Fauci 2009). The project encourages participation from the broader malaria community as well as creative, critical, and innovative thinking and is addressing the full spectrum of tools, strategies, and implementation. Thus far seven themes have been identified and are currently

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being explored through scientific and technical workshops, dialog with lead research agencies, and solicited input through the internet including: drugs, vaccines, vector control, modeling, monitoring/evaluation/surveillance, integration strategies, and health systems/operations. The key considerations and research approaches are summarized in the case study below. This project is to be praised not only for its inclusive process but also for the publication of the research agenda in several formats for comment and debate.

For successful malaria eradication, the essential goal of the strategy is to stop transmission and break the parasite life cycle. The challenges are many and focus around the complex life cycle of the pathogen and the diversity of settings in which malaria is transmitted as well as the adaptability of the parasite and the vector, interactions with the human host and the control program. The current strategy for control is combined drug therapy to treat patients and combat resistance, vector control with indoor residual spraying and insecticide-treated bed nets to prevent transmission, and strategies to identify and treat cases early. Social, economic, and behavioral factors all influence the human interaction with the parasite life cycle. Challenges in this area relate to compliance with prevention efforts and treatment as well as willingness to buy only combination therapy to decrease the emergence of resistance. In areas where interventions are currently successful and disease levels fall, two types of new challenges arise: (a) programmatic and political, keeping attention on sustaining the efforts and the investment for control, and (b) technical, detection and accurate diagnosis of cases as prevalence decreases. This demonstrates the importance of approaching problems and issues from both a programmatic perspective as well as a biomedical perspective. To stop transmission, the strategy will need to expand from treatment of sick patients to include detection and treatment of asymptomatic cases that can sustain transmission. This will require new and different diagnostics with the ability to have appropriate sensitivity and specificity with lower population prevalence and parasite density.

To move the malaria research and development effort forward, the National Institute of Allergy and Infectious Diseases (NIAID) is playing a central role and has committed to the pursuit of the following goals (NIAID and NIH 2008a):

1. Increase fundamental understanding of the complex interactions among malaria parasites, the mosquito vectors responsible for their transmission, and the human host.
2. Strengthen the ability to identify, develop, validate, and evaluate new tools and strategies for treatment, prevention, and control of malaria.
3. Enhance both national and international research and the research training infrastructure to meet malaria research needs, particularly for community-based and community-supported clinical trials in malaria endemic countries.

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4. Advance research to develop tools to support and sustain global efforts to control, eliminate, and eventually eradicate malaria.

In the research agenda, work is ongoing to identify weak spots in the life cycle or ecology of transmission. The life cycle of the parasite has key biological bottlenecks that are the focus of interventions: the initial point of infection, when there are few parasites and uptake of the sexual stage of the parasite by the mosquito. Research is now focused on taking advantage of these weak points. *Plasmodium falciparum* has dominated the thinking in malaria globally due to severity of disease and resistance. If malaria eradication is to be successful, all malaria parasites will need to be addressed. Each parasite presents a different challenge and will require a different research investment (Hall and Fauci 2009; NIAID and NIH 2008a, b).

The discussion and plan to address these issues is ongoing. Table 6.2 shows some of the research needs identified. Only time will tell how effective these efforts are and how this research will support and guide the program. However, they provide a new paradigm for embracing research as a part of an eradication program.

From the work done on malaria we can devise some generalizations and reflections for other diseases:

- Focus on the weak points in transmission that could be the focal points for interventions.
- Social and behavioral issues at the individual, community and global level need to be studied and interventions found.
- Inclusive proactive process, from the beginning of the project, can establish a culture that is receptive to change.
- Innate epidemiology will shift as the program progresses, and assumptions will need to be retested as transmission dynamics change.
- Tool requirements will vary at different stages of a program and thus need to be thought about early to be ready in time.

Yin and Yang

Elimination and eradication efforts are an optimist's sport. If you are not an optimist, the reasons why any program can or will fail can be overwhelming. However, unbridled or ignorant optimism constitutes an important reason why programs fail. Keys to success are critical thinking, innovative problem solving, persistence, and high levels of energy. To encourage critical thinking and problem solving, a program should invite the critics to the table and the pessimists into the debate. They can help point out weaknesses in the program and potential barriers to success that can help to guide the research agenda.

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Developing the Research Plan

Research is an essential component to an elimination or eradication program. In developing a research strategy in support of a program, it is important to learn from our history as demonstrated above. One approach is to look at the criteria that determined that the pathogen was able to be eliminated (Table 6.3) (Molyneux et al. 2004) and determine how to monitor these characteristics, where the weak spots are in the plan and what backup strategies would need to be developed.

Look at all areas of potential failure: the tool, the delivery system, the strategy, and detection and response to the unexpected. This framework can be used to design the crucial elements of the research plan (Figure 6.2). The research agenda should consider how it responds to new data from monitoring and evaluation programs as well as how new data generated through research is used to guide programming. Early deliberation should define what success would look like and how it would be measured. Criteria to start programs are frequently easier and more straightforward than criteria to stop an intervention. Thus, early attention should be paid to stopping criteria and the additional tools that may be required. The plan should allow for innovation from the field and early communication, discussion, and dissemination of results.

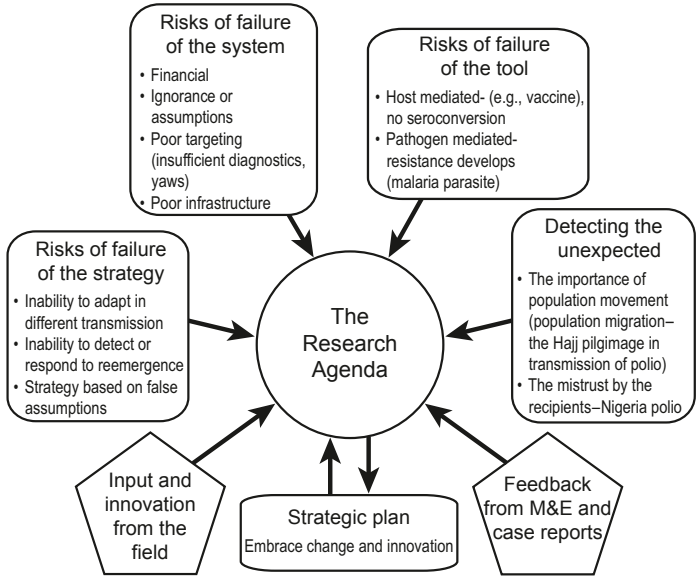

Figure 6.2 Framework for establishing research priorities in elimination or eradication programs. M&E: monitoring and evaluation.

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Table 6.2 Epidemiologic states and examples of priority research requirements.

Status:	Epidemiologic features:	Priority research requirements:
Current situation	1.3 M deaths/yr (mostly children)	Expand research on non-falciparum malaria
	300–500 M clinical cases/yr	Expand research on combination drug therapy
	Children and young pregnant women are primary at-risk populations	Expand research and development for malaria vaccines
	4–5 species infecting humans, including *Plasmodium falciparum, P. vivax*, and *P. knowlesi*	Expand research on vector biology and ecology on non-gambiae Anopheline mosquitoes
	Some areas with very high entomological inoculation rates (EIRs)	
	Widespread drug resistance	
1. Control*	Ongoing surveillance documents:	Assure and expand pipeline of available interventions (drugs, vaccines, insecticides/repellents, diagnostics)
	Decrease incidence and prevalence of disease in areas where control has been implemented	Assess degree of parasite population diversity to discover, identify, validate, evaluate, and optimize interventional tools and strategies
		Develop mathematical models based on emerging field data to help guide product development and optimize combinations of interventions
2. Elimination of disease*	Ongoing surveillance documents:	Assess changing epidemiology of malaria, including shifts in burden of disease and source of gametocytes
	No deaths directly attributed to malaria	Adapt tools and interventions to situation of decreasing incidence and prevalence
	Incidence and prevalence of uncomplicated malaria is falling and/or low	
	EIRs can still sustain infection	

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Table 6.2 (continued)

Status	Epidemiologic features:	Priority research requirements:
3. Elimination of infection*	Ongoing surveillance documents: No deaths directly attributed to malaria Low and falling prevalence of parasitemia Low incidence, mainly due to short epidemics that are rapidly identified, treated, and contained Low EIRs, whether due to low rates of infection in mosquitoes, decreased vectorial capacity or reduced biting behavior Drug and insecticide resistance is identified prospectively and managed	Assess changing epidemiology of malaria, including shifts in burden of disease and source of gametocytes Adapt tools and interventions to situation of low incidence and prevalence (e.g., improved diagnostics for surveillance in mosquito populations) Evaluate utility of transmission reduction strategies (e.g., transmission-blocking vaccines, transgenic mosquitoes)
4. Eradication*	No malaria deaths Prevalence = 0 Incidence = 0 EIR = 0	Develop validated, rapid, highly sensitive diagnostics for detection of human and mosquito infections during surveillance period

*According to International Task Force on Disease Eradication in order of progression (earlier to later).

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Table 6.3 Criteria for targeting a disease for eradication and the subsequent research and program needs.

Biological and technical feasibility:	Research questions and program considerations:
Natural history of biological agent	Understand transmission including latent and subclinical infection, duration of pathogen in the environment
Non-human reservoirs	Define reservoirs both human and nonhuman, risks of exposure, and transmission from the reservoir
Effective intervention tool	Follow efficacy, cure, and relapse rate Detect resistance early
Effective delivery strategy	Differentiate resistance from poor delivery Define appropriate programmatic monitors that are relevant to modify the program
Simple and practical diagnostic	Can you detect latent or subclinical cases? Will you be able to detect recurrence versus reinfection? How will sensitivity vs. specificity needs of the diagnostic tool adapt as prevalence changes? What additional tests or algorithms will be needed?
Sensitive surveillance	Can you detect cases early? Where will cases present? Who will need to be sensitized to identify cases? Could cases be confused with something else? If so, what? Who are providers in the community (public, private, traditional) that will need to be included in surveillance and treatment protocols? How will you encourage reporting?
Field-proven strategies	How will strategies need to be modified in different settings? How will you detect failure of the system?

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Table 6.3 (continued)

Costs and benefits:	Research questions and program considerations:
Cases averted per year	How will you measure and how often? How will this data be used? How will it be presented and in what format to influence decision making at what level? How will you fund collection of this data?
Coincident benefits	
Intangible benefits	
Estimated annual direct global savings	
Estimated total external financing	
Societal and political considerations:	**Research questions and program considerations:**
Political commitment (endemic and/or industrialized)	What is the measure and how will you follow? What action will be taken if indicators shift?
Social support (endemic and/or industrialized)	
Disease burden in politically unstable areas	How will you address delivery in unstable settings? Identify the different partners working in this setting.
Core partnerships and advocates	How will this be organized and monitored for effectiveness? Define roles?
Technical consensus	How will new data be discussed and deliberated? How will program/strategy updates be incorporated?
Donor base (number of donors 1M or more)	How will new donors be brought on board? How will historic donors be kept invested? How will new funding needs be met when new challenges arise? How will research and advocacy be funded?

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Funding Programs and Research

In all assessments of all programs, the issue of funding will be brought up as one of the reasons for setbacks and failure. Elimination programs are greatly aided by support through selected institutions and foundations. The Nippon Foundation, for example, made a generous donation and supported the worldwide costs of leprosy elimination between 1994 and 1999, which treated more that 13 million people (Lockwood and Suneetha 2005). Rotary International and their network continue to provide significant support to the polio efforts. Lions Club has provided important funding for the Onchocerciasis Elimination Program in the Americas (OEPA). Drug donation programs for LF and onchocerciasis have been the cornerstone for elimination efforts. Ensuring funding sufficient to achieve the final goal is always a challenge. Providing supportive data on cost-effectiveness or cost-benefit can help programs generate program funds; however, research needs are not usually addressed through such analyses. Establishing the case for how research can support a program and result in cost or time savings in the long run would help in defining the value and getting the funds to support research. Flexibility in funding also helps a program be responsive to challenges as they arrive and is essential for elimination or eradication.

Conclusion: Guiding Principles for Research

- Criteria that establish whether a disease is able to be eliminated or eradicated can also guide the research agenda.
- Know that program targets and strategies will change over the lifetime of a program and be prepared to provide the data necessary to inform the decision-making process and enable mechanisms for modifying the strategy.
- Include adaptive programming with appropriate monitoring and evaluation as part of the research agenda.
- Think through the stages of the program and the tools that will be required to anticipate needs so they don't become barriers.
- Pay attention to the ends of the Bell curve. Outliers matter in elimination and eradication programs. Case reports and investigations should feed into research needs.
- The research agenda should be proactive, interactive, and incorporate innovation from the outside as well as from the bottom up, with a critical eye focused on the success of the program.
- Sufficient and flexible funding is required to address program barriers and the research agenda to support decision making.

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