7

DIAGNOSTIC CERTAINTY AND DISEASE CONTROL

Before attempting the heroic cure of disease, we seek first to ascertain its true nature.

—Ronald Ross, 1905

Despite media images that portray Africa as a disease-plagued continent and the concerns expressed, even by medical and public health experts, that in Africa health targets are often set but rarely achieved,[1] some well-planned and properly implemented programs have met with success. Smallpox was eradicated, guinea worm and polio have almost disappeared, and campaigns to control other vector-borne or vaccine-preventable diseases, notably measles and river blindness, are making impressive progress.[2] Many effective strategies for disease control are disarmingly simple: clean water, adequate nutrition, and depletion of the vectors, such as mosquitoes, that transmit infection. These interventions, which have been primarily responsible for infectious disease control in the West, can break the chain of transmission for many communicable diseases at once. Vaccines, insecticides, and medicines that target specific diseases augment these measures.[3] Laboratory science often plays an important behind-the-scenes role in disease control, particularly when it involves biomedical tools that are necessary components of today's ambitious disease eradication programs.

Globally, we have attempted to eradicate only a handful of human diseases and have not yet succeeded in eliminating most of them.[4] The social and economic benefits of eradication are so great, however, that the single success—smallpox—and the few near successes more than justify all failures. Eradication offers the supremely attractive prospect of never having to deal with a disease, or its causative organism, ever again. Premature deaths and disabling illnesses are prevented, and resources that would have been expended on preventing or treating the disease can be diverted to other causes. Eradication campaigns must be

built on a practical foundation. As experience has repeatedly demonstrated, the worst scourges are not always the easiest to eradicate.

Eradication Successes

Smallpox, which killed or disabled and disfigured countless people throughout most of recorded history, probably emerged around 10,000 BCE, when human societies shifted from the dispersion and seasonal migration required by hunting and gathering to more permanent and compact agricultural settlements. Because the virus infects each person only once and cannot survive for long outside the human body, it can maintain its existence only in settled and interconnected communities. According to the best estimates, a population of roughly two hundred thousand humans connected by not more than fourteen days of travel was needed to sustain smallpox. The dumbbell-shaped virus, which perhaps evolved from a rodent pathogen, seems to have been spread from Africa to India by Egyptian merchants in the last millennium BCE. Muslim clergy inadvertently carried smallpox across other parts of Africa and to Europe during the Middle Ages, and in 1519 Spaniards took the virus to the Americas. In Mexico City, then known as Tenochtitlan, a disastrous epidemic that both the immune *conquistadores* and the vulnerable Aztecs found shocking led to the fall of the fortified capital. Indeed, smallpox was the principal weapon that enabled the Spanish to subjugate the indigenous peoples. Within a single generation, it had wiped out a third of Mexico's native population. International trade in spices and other exotic items and the growing traffic in enslaved Africans ensured that by the eighteenth and nineteenth centuries smallpox had spread around the world. This single scourge accounted for one-tenth of all deaths and took a higher toll during epidemics. In the mid-twentieth century, just before the global smallpox eradication program began, the disease killed two or three million people and disfigured or disabled another ten to fifteen million every year.[5]

Interest in smallpox eradication emerged in the early nineteenth century, but it was not until 1967 that the WHO made its formal, landmark commitment to that goal. The program began just as an expensive malaria eradication effort was clearly failing, which raised doubts about the very idea of eradication. However, the proposal to eliminate smallpox was supported by substantial evidence of success: by the 1960s, smallpox had been eliminated from Europe, North America, East Asia, and North Africa. The elimination of the disease from the Soviet Union convinced the World Health Assembly to revisit the idea of eradicating smallpox from the thirty-three countries in Asia, South America, and sub-Saharan Africa that were its "last frontier."[6]

The major innovation that made smallpox eradicable was an effective vaccine. The first vaccinations, which were actually variolations, used material derived from smallpox and entailed significant risks. Those seeking to attain lifelong immunity inhaled dried powdered scabs or, more commonly, had their skin scarified and inoculated with fluid from active pustules. Variolation usually produced mild disease, but it could also cause full-blown and potentially fatal smallpox. The Vedas, the sacred Sanskrit texts of ancient India, contain the following passage: "put the fluid from the pustule onto the point of a needle, and introduce it into the arm, mixing the fluid with the blood; a fever will be produced but this illness will be very mild."[7] Although more is known about variolation in Asia and western Europe than in Africa, several African ethnic groups had developed vaccination protocols before extensive European contact, and the practice probably reached the Americas through the slave trade. Indeed, the feared Yoruba Ṣọpọnọ cult, banned by special ordinance in 1907, could deliberately spread the disease without becoming infected themselves, suggesting that variolation may have been part of initiation rites.[8]

In 1798, Edward Jenner, observing that people who got cowpox never seemed to catch smallpox,[9] developed a remarkably successful cowpox-based vaccine, which was the precursor of the vaccine used for smallpox eradication. Even in the unusual cases when protection was incomplete, only 3 percent of those vaccinated with Jenner's vaccine were likely to die of the disease when they became infected, as opposed to 30 percent of the unvaccinated. Vaccination is much safer than variolation; it does not leave pockmark scars and vaccinees do not need to be quarantined. Jenner's procedure was so safe and effective that, despite initial fears that it might be as risky as variolation, it had been widely accepted by 1840. Variolation was soon considered criminal, and political leaders were predicting that the vaccine could be used to eliminate the disease.[10]

Vaccination, unlike variolation, was invented at one site (or possibly a very few sites) and distributed widely. It was difficult to maintain vaccine efficacy during long-distance transport because the live vaccine virus can only survive in living cells. As humans are the only host for smallpox, variola vaccines had to be maintained in people. In 1806, King Charles IV supported the transportation of variola vaccine from Spain to Latin America by the sequential inoculation of twenty-two orphans, who were brought on board ship specifically for this purpose. Jenner's cowpox vaccine could be transported as impregnated threads or in live cows, so it could be disseminated before other preservation methods were developed. Ultimately the eradication program was greatly served by the development of a heat-stable, freeze-dried portable vaccine. Additionally, the invention of the bifurcated needle produced an inexpensive inoculation device that could be used by relatively unskilled personnel to scratch the vaccine into the skin. The result of these developments was a safe smallpox vaccine that conferred

lifelong immunity and could be transported to any part of the world in a stable and deliverable form.

In addition to the technical advantages conferred by the vaccine and its delivery system, smallpox eradication was enabled by the convergence of pathogen, host, and political conditions that, in retrospect, offered a narrow window of opportunity. Whereas a proposal to eradicate smallpox had failed to garner unanimous support in 1953, every country committed itself to the eradication campaign at or immediately after the World Health Assembly of 1965.[11] Biologically, humans are the only hosts of the smallpox virus; it has no subclinical form and no hiding place in the environment. Transmission can be interrupted by vaccination, and both vaccination and infection provide lifelong immunity. An often overlooked but important fact is that people infected with the smallpox virus can easily be identified, even by laypeople, by the characteristic pustules, and individuals are infectious only when their condition is visibly identifiable. Smallpox was a disease of virtually complete diagnostic certainty, and the ease of diagnosis was a key factor that enabled its eradication.

The original strategy for smallpox eradication was to vaccinate the entire human population, or at least very close to it. This strategy was effective in eliminating the disease from Europe and North America, but it is unlikely that this plan would have achieved global eradication because too many at-risk people lived in remote areas. Because smallpox is transmitted only through close personal contact, it became obvious during the campaign that aggressively finding active cases and immunizing the people around them would suffice. A revised "identification, confinement and local immunization" strategy eventually achieved complete eradication.[12] Case-finding was easy: showing laypeople photographs of smallpox patients was sufficient to train them to find cases. The new "search and destroy" strategy was enormously effective in low-income regions: seventeen of the twenty-one West African countries eliminated smallpox in just two years.

In October 1975, three-year-old Rahima Banu of Bangladesh recovered from the last infection of the more severe form of smallpox, variola major. By 1977, the war-torn Horn of Africa was the last remaining focus of the disease. Early that year, the success of a concerted program to vaccinate Somali Muslims ahead of the Hajj (the annual pilgrimage to Mecca) ensured that the last natural viruses were contained within a limited geographic area. Aggressive case-finding turned up the penultimate case of naturally acquired smallpox. In October 1977, a Somali child with smallpox infected health worker Ali Maow Maalin. Maalin achieved international fame as the last case of smallpox on earth.[13] Thirty months later, WHO boldly declared smallpox gone for good.

Smallpox was vanquished just in time: within the next decade, the spread of HIV produced an immunocompromised subpopulation that cannot be vaccinated. In economic terms, eradication was highly cost effective. Countries that had

been plagued by the disease as recently as the 1970s gained from the productive lives that were saved. Where the disease had been eliminated, countries could save money by ending their vaccination programs. The value of smallpox eradication to people alive today is inestimable. Monetarily, almost US$1.4 billion is saved each year, fourteen times as much as was spent on the eleven-year campaign.[14]

One important lesson to be learned from the smallpox eradication campaign is that mass methods do not necessarily guarantee effective results.[15] Megan Vaughan (1991) has observed that during the colonial period Africans were unitized for the purpose of administration and health care delivery. Unitization is directly opposed to individualization, since it presumes that all individuals are identical for the purpose of the intervention. In the places where medicine and public health are most efficiently administered, arguably in Scandinavia, individualization of health care delivery is the norm. It is likely that the individualization that diagnostic development requires would improve the delivery of public health interventions. The shift from the campaign's original goal of immunizing everybody on earth to a strategy of case-finding and contact immunization changed the smallpox eradication campaign from a unitized to an individualized program: people were vaccinated only if they might have been exposed to the virus. In some places, less than 10 percent of the population needed to be vaccinated.

Among the many lessons from the smallpox eradication campaign that inform disease control today, the lesson most relevant to the problems facing Africa is the central role that diagnosis plays in public health and disease control. Smallpox, with its easily identifiable pustules that appear early in the infection and its lack of an infectious subclinical stage, is the diagnostician's ideal.

Dracunculiasis, or guinea worm, is another disease that can be diagnosed by the untrained eye. When the one-to-three-foot-long adult female worm is ready to lay her eggs, she bores her way out of the skin of the limbs of infected people, causing disabling inflammation and superinfection and announcing the diagnosis to the patient and anyone else who can bear to look. Guinea worm is not a killer, but the crippling "disease of the empty granary"[16] keeps workers away from their farms and children out of school. There is no vaccine or preventive treatment, but it is possible to interrupt the parasite's life cycle. People become infected by the worm when they drink water contaminated with cyclops, a type of plankton, which are infected with Guinea worm larvae. The larvae make their way from the intestine to the connective tissues of the infected person, usually in the legs, and mature there. If people in endemic areas do not drink water contaminated with larvae, if infected people do not shed eggs into public water supplies, and if freshwater cyclops that carry larvae are destroyed, the worm can be eliminated.

The U.S. Centers for Diseases Control began a guinea worm eradication program in 1980. The Carter Center soon became the program's chief advocate and made a formal commitment to see eradication through in 1986. In the same year, the World Health Assembly put forward a resolution to eliminate the disease, upgrading the objective to eradication in 1991.[17] Thus the parasitic infestation guinea worm became the fifth disease that public health authorities and governments worldwide committed to eradicate, after yellow fever, yaws, malaria, and smallpox. With guinea worm, as with smallpox, diagnosis was no problem. In Cameroon, 19 percent of cases were detected within twenty-four hours in 1991. When cash prizes were offered to people who reported cases, 70 percent of cases were reported within one day.[18]

Once identified, guinea worm is eliminated by treating people with infestations and keeping their limbs away from communal water supplies, by providing safe water, or by supplying filtration devices that remove cyclops from the water. The eradication program is behind schedule but steadily advancing toward the goal of eradication. The tally was less than nine thousand cases in 2007, down from just over 150,000 in sixteen African countries in 1996 and almost one million in 1989. In 2008, only four countries—Ghana, Nigeria, Sudan, and Mali—reported cases of guinea worm. By 2009, there were only 513 cases worldwide and Nigeria, acknowledged as one of the most challenging countries at the last frontier, did not report a single case.[19] Problems have arisen with funding and in reaching affected populations, particularly those cordoned off by violent conflicts. But while the guinea worm eradication campaign does face challenges, the ease of diagnosis is a key reason for the program's success so far.

Eradication Challenges

In 1988, two years into the guinea worm eradication campaign, a bold step was made to begin the eradication of poliomyelitis, with a target completion date of 2000. In the first half of the twentieth century, amid a marked decline in the incidence of other infectious diseases in North America, thousands of middle-class children and a few adults were killed or crippled by the paralyzing disease—most notably, future president Franklin Delano Roosevelt. This epidemic spurred fund-raising for a concerted research effort to develop a vaccine, with American scientific heroes Albert Sabin, Jonas Salk, and Hilary Koprowski at the front lines.[20] These well-supported and largely political efforts resulted in several effective vaccines and the elimination of the disease in the United States by 1979. In 2001, 575 million polio immunizations were administered in ninety-four countries as part of the worldwide eradication effort.

Unlike smallpox and guinea worm disease, patients who can transmit polio can be reliably identified only by laboratory tests. Although a high prevalence of lameness in a population points to endemic poliomyelitis, less than half of seriously ill polio patients are paralyzed, so paralysis is not a sensitive enough diagnostic sign.[21] The virus is transmissible during the early stages of the illness, when symptoms often resemble those of other common conditions such as influenza. Recognizing this problem early in the campaign, WHO issued a statement explaining why it was essential to integrate laboratory and clinical approaches. High-burden countries, including many in Africa, would not necessarily need laboratory support to verify each infection, although local isolates should be preserved in order to track infections during the final mopping-up phase. Toward the end of the campaign, when most countries would be polio-free and some would have a few cases, laboratory support would be fundamental. In this strategy, polio eradication could begin even with diagnostic insufficiency in many endemic areas, but diagnostic development in the most troublesome spots would be essential to complete the campaign. A global laboratory network was an integral part of this plan.[22] As an editorial observed, "Progress achieved by the network has demonstrated that high-quality virology in support of public health activities can be made accessible to all areas of the world, including war-torn countries and countries without organized government or health infrastructure."[23] With sufficient support and motivation, laboratory diagnostics can be used anywhere, even for a viral disease such as polio. Polio surveillance has increased laboratory capacity for diagnosis and surveillance of other infections in many parts of Africa.

Polio eradication is now at a challenging last stage. Insufficient access and political will are the preeminent roadblocks, but there are biological challenges as well. The poor immune response of Indian children means that their vaccines must be carefully crafted and more frequently administered. The return of an eradicated polio subtype warrants reintroducing a discontinued vaccine in Nigeria. Viruses are periodically exported from the last four endemic nations (India, Nigeria, Afghanistan, and Pakistan) to other countries that have eliminated the disease.[24] All of these problems were identified, and are being addressed, using the results of laboratory tests that confirm infections, vaccine-derived immunity, and fingerprint poliovirus subtypes. Only with this real-time monitoring at the laboratory bench will we eradicate polio.

Measles, a virulent viral infection that is often fatal in very young children, is also high on the list of eradicable diseases. A population of two hundred thousand or more is needed to sustain the measles virus because it has no nonhuman reservoir. An effective vaccine was developed by researchers at Harvard University

in the 1950s, and infection or vaccination can produce lifelong immunity. Measles is highly contagious; it is caused by an airborne virus that infects up to 90 percent of exposed nonimmune people. Infected infants have a significant risk of dying from measles, and there is a severe risk to the unborn children of infected pregnant women. Individuals infected as adults often suffer long-term effects, including testicular damage in men and blindness. Not only is the disease itself debilitating, it precipitates a temporary immune deficiency during infection that makes patients susceptible to activation of latent infections such as tuberculosis or infections by other organisms. The historical impact from measles has been high and includes the depletion of isolated immune-naïve populations in Greenland and the Fiji islands.[25]

Until recently, the association of measles with a characteristic rash was thought to be sufficient for diagnosis, but the accuracy of clinical diagnosis can vary substantially enough to make laboratory verification valuable. Laboratory support is also needed for other facets of a measles eradication program, such as calibrating the optimal timing of vaccination. Most babies are born with antibodies acquired from their mothers during gestation, which protect them against the measles virus until the antibody concentration declines, at about nine months of age. If measles vaccine is administered before this decline, the infant's maternal antibodies will inactivate the vaccine before the child can develop a protective immune response. Administer the vaccine too late, and a child could be left unprotected. For most children, vaccination at nine months works well, but infants born of HIV-positive mothers may be vulnerable before they reach their ninth month because they did not acquire sufficient passive antibody protection in utero. For this reason, WHO has advocated vaccinating these children at six months. However, laboratory tests performed in Zambia demonstrate that measles antibody concentrations in the children of HIV-positive mothers may be much less predictable. HIV infection status must be determined before vaccination, but often cannot be verified by six months. Vaccination of this growing subpopulation poses multiple diagnostic dilemmas that are becoming increasingly important as mother-to-child infection rates drop and survival of HIV-positive people improves.[26]

Determining the best way to deploy measles vaccines for underprotected babies is one of the most challenging problems that must be solved in order to eradicate the disease. Other more pedestrian challenges can, and will, be overcome. In 1999, 61 percent of the 871,000 measles deaths documented worldwide occurred in Africa. The WHO African region aimed to improve vaccination, case management, and surveillance, with the goal of halving deaths due to measles by 2005. Most countries that immediately began supplementary immunizations

increased vaccine coverage from between 30 percent and 50 percent to over 60 percent within five years, and improved surveillance allowed lab verification in up to 80 percent or 90 percent of cases.[27] The end result was an impressive reduction in the number of clinical measles cases in thirty-two African countries by 2005.[28] Overall, deaths from measles worldwide fell by 68 percent, with the greatest declines in Africa. The reduction was partly due to closing the disparity between suspected cases identified clinically and cases confirmed in the lab. Being able to differentiate measles from other maladies is a first and essential step toward implementing control and monitoring progress toward the 2020 eradication target.

Yaws is a contagious bacterial disease caused by a close relative of the etiologic agent of syphilis. An early attempt to eradicate yaws was unsuccessful because, although the disease itself produces clearly discernable lesions, symptomless or subclinical infections also occur, resulting in a hidden reservoir for the spiral bacteria that cause the disease. The energetic yaws eradication campaign lacked the targeted case-finding that enabled successful completion of the final, mopping up phase of smallpox eradication. The experts who planned that campaign were aware of the problem posed by subclinical infections, and the strategy applied in most areas where yaws was endemic included treating the contacts of infected people. Since there is no vaccine, the tool for eradication was procaine penicillin, an antibiotic that kills the Treponemal bacteria that cause the disease.[29] This plan was efficacious in areas of high endemicity, where everyone was presumed to be a contact, but as laboratory tests were not used, contacts had to come forward voluntarily. Unfortunately, in addition to failing to reach all those who were spreading the disease, it is likely that the campaign was instrumental in producing selective pressure for the development of penicillin-resistant bacteria in many parts of the world, as well as a preference for injectable medicines.

A control program that is implemented without precise diagnostic support can reduce disease prevalence only when a large proportion of the population is infected. In the final phase of an eradication campaign, when previously uncommon illnesses with similar symptoms become more prominent than the target disease, accurate diagnosis with laboratory support becomes essential. If the laboratory does not participate in case-finding at this crucial stage, the disease could rebound and the campaign could face a huge loss of financial investment and morale. Yaws was never eradicated. Although containment varies from place to place, it is largely a forgotten scourge that remains a threat to poor countries, including some that had almost completely eliminated it. For example, yaws was resurgent in Ghana in the 1980s, and over 1.6 million people had to be injected with procaine penicillin between 1981 and 1983 to contain the disease.[30]

Controlling the Ineradicable

The fortuitous diagnostic certainty of smallpox and guinea worm was a key factor in eradication campaigns for those diseases. One of the hard lessons from less successful eradication programs is that diagnostic precision is a prerequisite for eradication. Not every case of poliomyelitis or measles can be diagnosed clinically with certainty, so the campaigns against these diseases are developing diagnostic capability. Which diseases should we tackle next, and how? In theory, any infectious disease can be eradicated as long as human infection can be interrupted and there are effective and practical means to diagnose it. Some diseases are not presently eradicable but may become so when effective tools to interrupt transmission are developed. We cannot eradicate pathogens that have a nonhuman host from which the organism cannot be simultaneously eradicated, or if people can carry the organism undetected. Diseases that are transmitted too efficiently to permit a practicable intervention may also be ineradicable. Although public health advocates often refrain from mentioning matters of finance up front, cost-effectiveness is as paramount to sustaining eradication and elimination campaigns as are political and societal will.[31]

Infectious diseases that cannot presently be eradicated can often be eliminated within a restricted geographic area. This distinction is important: eradication is the "permanent reduction to zero of the worldwide incidence of infection caused by a specific agent as a result of deliberate efforts";[32] elimination refers to similar clearance in a specified geographical area. Control refers to reduction, but not to zero. Unlike eradication, continuing interventions are needed to maintain elimination or control.

Even when case-specific diagnosis is of limited benefit, population-level surveillance may be critical for disease control. This has been exemplarily illustrated following surveillance of bacteria that cause respiratory infections, which are among the most important causes of death among African babies. One way to reduce antimicrobial use and get around the mounting problem of resistance is to develop and apply effective vaccines against life-threatening bacterial infections. Among the most dangerous pathogens are *Streptococcus pneumoniae* and *Haemophilus influenzae* type B (Hib), which can cause bloodstream infections, meningitis, and pneumonia, as well as more innocuous ear infections, which are the most common manifestation in the West. Both bacterial species can be carried asymptomatically by some individuals, who unwittingly transmit the bacteria to susceptible children, but there are effective vaccines for both.

Having used laboratory-based surveillance to demonstrate that Hib was a major cause of childhood deaths in The Gambia, the Medical Research Council research center in Fagara was able to show that, within seven years of deploying

an Hib vaccine, the disease all but disappeared. Two years later, researchers found that a new hypervirulent strain of Hib had appeared.[33] This surveillance brought to light the need for long-term assurance of vaccine programs, and perhaps for booster doses of the vaccine. Without surveillance, elimination would be ultimately unsuccessful and the investment in vaccines wasted. In Mali, Hib surveillance found that, between 2002 and 2005, 12 percent of hospital admissions and 19.3 percent of deaths could be attributed to the bacteria. This alarming data was taken from the lab to the clinic and, ultimately, to the country's presidential suite and prompted the introduction of Hib vaccination, so that by 2007 there was a 68 percent reduction in the disease.[34] African countries that had some surveillance data introduced life-saving Hib vaccines first, with impressive results. Overall, vaccines were introduced last in countries that were furthest from those nations that had data before 1995.[35] Costly but life-saving interventions are harder to justify and implement without local surveillance data, which can only be collected with laboratories.

S. pneumoniae, otherwise known as pneumococcus, presents a much more complicated problem. There are several different serotypes of pneumococcus. Each serotype is enveloped in a different sugary capsule, its cloaklike disguise from the immune system. Immune systems can be educated to recognize specific capsule types by preexposure through infection or vaccination but immunization against one serotype does not protect against others. Fortunately, less than a dozen serotypes are responsible for most pneumococcal disease, and these also include the types that are more likely to be resistant to antibiotics. When a multivalent vaccine protecting against seven types was deployed in the United States, *S. pneumoniae* infections declined substantially and, when infections did occur, they were less likely to be drug resistant.[36] Both the reduction in resistance and the "herd effect" were unanticipated. A herd effect is seen when individuals who have not been vaccinated, but who live in the vicinity of vaccinated individuals, are protected from the disease. With pneumococcal vaccines, this phenomenon is best illustrated by the protection of unvaccinated children attending day care centers where a large number of children have been vaccinated. When pneumococcal bacteria lost their niche in those centers, even unvaccinated children were protected.

In Africa, where pneumococcal infection often manifests as life-threatening respiratory or bloodstream infections and where complete vaccine coverage is often hard to achieve, the herd effect would be valuable. There is one major caveat: there are several dozen types of *S. pneumoniae,* each of which has a different, slippery, carbohydrate capsule. Each vaccine protects only against a limited number of capsular types, which must be carefully selected. Pneumococcal vaccines have been most successful when extensive surveillance precedes their deployment to ensure that the vaccine targets locally relevant types. Such studies

have been done in some parts of Africa, but most are not extensive enough to adequately inform vaccine deployment.[37] Moreover, prevaccination surveillance alone is insufficient. Today's most virulent and antimicrobial-resistant types are the focus of current vaccines. When these vaccines are used intensively, new types will replace the old. This process is already beginning in the United States.[38] We must monitor disease-causing serotypes constantly in order to keep the vaccines up to date.

Tuberculosis is a disease of contemporary as well as historical significance. Contrary to nineteenth-century myths that the hectic fevers and heightened awareness of mortality that accompanied "consumption" spurred creative genius, the disease cut short the lives of many novelists, poets, and composers.[39] The 1943 discovery of the antibiotic streptomycin by Selman Waksman's graduate student Albert Schatz was the first step in turning the "white plague" into a condition that could be managed and even cured.[40] The problem of recrudescence because of resistance that emerges during treatment was conquered by the introduction of combination therapy, which followed the development of other antituberculosis drugs such as isoniazid, para-amino salicylic acid, and rifampicin. Many thought that over time TB would become less common and eventually cease to be a significant health threat. Experts in global health were startled by the emergence of multidrug-resistant tuberculosis (MDR-TB), which was entirely predictable but had been overlooked.

A third of the world's population today is latently infected with *Mycobacterium tuberculosis.* The immune systems of most of these people keep active infection at bay. The immunocompromised are not so fortunate; they will likely experience TB activation or acquire active disease after exposure. The combined emergence of drug-resistant bacteria and HIV in the last quarter of the twentieth century has made TB one of the greatest threats to public health. Adherence to prescribed TB therapy is important because even a short course of treatment takes at least six months and drug-resistant bacteria can be selected in the patient during this time. WHO declared a global emergency in 1993 and, to stop the spread of the disease and the emergence of resistant strains, proposed directly observed short course therapy (DOTS) for all TB patients. As the name of the strategy implies, patients on DOTS are observed by another person each time they take their medicine so that they do not forget doses or willfully decide to stop therapy prematurely. A regular and sufficient drug supply is essential for the DOTS program to succeed, as is the capacity to diagnose new cases and verify cures. All this requires considerable investment in support, evaluation, and reporting, as well as a national-level political commitment.[41]

Society must assume the responsibility of ensuring that TB patients recover because their highly transmissible and deadly illness poses a threat to public

health. DOTS programs are therefore national endeavors that are monitored internationally. In 1992, twenty countries were implementing DOTS. By 2002, it was so obvious that DOTS was successful and cost effective that the number had jumped to 180. Although 2002 targets—to detect 85 percent of cases and successfully treat 70 percent of them—were not met in many developing countries, one Indian study showed that two hundred thousand lives and $400 million were saved when DOTS was properly implemented. The sum of lives saved from premature death and illness-related disabilities averted, called a disability-adjusted life year (DALY), is used by the World Bank as a currency for health in order to evaluate the cost-effectiveness of specific health interventions. The DALY is a unit invented by Christopher J. Murray and Alan D. Lopez (1997), who recognized that monetary estimates failed to reasonably catalog the losses from illness at the population level. Simply put, DALYs for a disease are computed by adding years of life lost and years lived with disability. By this measure, the value of DOTS was amply demonstrated by the TB control program in Beijing where the cost of saving a DALY could be reduced by 90 percent simply by applying DOTS.[42] A much understated component of DOTS is diagnosis and cure verification by sputum smear microscopy. DOTS made these successes because drugs are provided with a delivery system that includes diagnostics.

It is difficult and time consuming to grow *M. tuberculosis* in the laboratory, and therefore culturing every clinical specimen is impractical. On the other hand, because of their waxy cell coat, Mycobacteria can be distinguished by their resistance to acid decolorization after staining. Virtually all other bacteria are decolorized by acid, so the presence of acid-fast, rod-shaped bacteria in sputum is indicative of active pulmonary tuberculosis. A lab technician can smear sputum on a slide, fix it, stain it, attempt to decolorize it with acid, and then observe bacteria under the microscope. Other than a short list of inexpensive materials, the other requirements are that the setup is suitable to avoid infection of lab workers and that the slides are properly read and reported. Test sensitivity is not high, but because patients with active infection cough up high numbers of bacteria, this simple, cheap, and practicable diagnostic test will pick up most cases of the disease. Sputum smear microscopy also aids in verifying cure. By the WHO definition, only patients who are smear-negative close to and at the end of the short course of treatment are said to be cured. Those for whom this verification was negative or impossible are said to have "completed treatment."[43]

The successes of DOTS are inextricably linked to ease of laboratory-based diagnosis for TB. The effectiveness and simplicity of sputum smear staining for *M. tuberculosis* has made it possible to mount lifesaving interventions in the most unlikely places, including remote villages and refugee camps. However, in some parts of the world, including locations in Africa, access to DOTS remains difficult.

According to a 2005 report, it took more than a month to place 91 percent of tuberculosis patients from the Amhara region of Ethiopia in treatment.[44] Patients who had the foresight to go straight to the general hospital, which implemented a DOTS program including sputum smear microscopy (and lived close enough to do so), managed to avoid delay. Patients who visited local health clinics or private doctors waited from weeks to months for a diagnosis, just like the patients who visited indigenous practitioners or unsanctioned providers. In Ethiopia, the lack of diagnostic facilities at the primary health care level delays treatment for patients and facilitates the spread of disease. Similar reports have come from Ghana, The Gambia, Zambia, and Botswana.[45] The further afield testing moves from the patient, the longer the delay in diagnosis and the greater the chance that other individuals with similar difficulties in accessing DOTS programs will be infected. TB is a deadly disease, but undiagnosed or underdiagnosed TB is a public health disaster, which is amplified by each delay.

In areas where DOTS is inadequately implemented, multidrug-resistant tuberculosis (MDR-TB) emerges and spreads, with potentially devastating consequences. Patients with MDR-TB are commonly discovered only when first-line treatment does not cure them, by which time the disease has often inflicted permanent damage and has spread to other individuals. Second-line TB drugs needed to deal with resistant infections are more expensive, more toxic, more difficult to administer, and less effective. Crucially, although sputum smear microscopy is an effective diagnostic test for TB, it cannot distinguish MDR-TB from more easily treatable forms of the disease. Therefore, when MDR-TB emerges, even institutions that have good DOTS programs can lose diagnostic sufficiency.

According to British researcher Ruth McNerney, there was no routine testing for MDR-TB when drug-resistant *M. tuberculosis* emerged in Uganda. The consequent crisis is aptly described by project coordinator Edward Jones, who observed that individuals infected with MDR-TB were transmitting it in their communities and to health workers.[46] Recently, "exceedingly drug-resistant" strains, called XDR-TB, have emerged. XDR-TB strains are resistant to the first-line drugs rifampicin and isoniazid, a second-line fluoroquinolone, and at least one of the three commonly used second-line injectable drugs: capreomycin, kanamycin, and amikacin. The infections they cause are, in essence, untreatable. One of the most publicized examples of the devastation this deadly form of TB can cause was an outbreak in rural Kwazulu Natal, South Africa, where XDR-TB resulted in the rapid demise of fifty-three individuals, including six health workers who caught the infection from their patients.[47] Mathematical models have identified the slow time to diagnosis as the principal factor that precipitated that epidemic.[48]

A clear picture of the difficulties of dealing with resistant tuberculosis has been generated in many of the nation-states of the former Soviet Union, where

misuse of antituberculosis drugs, with other factors, has resulted in widespread resistance. When there are no facilities for susceptibility testing, resistant infections are treated with the same drug cocktail as susceptible ones, fostering the resistance problem.[49] In an Uzbekistani study,[50] patients infected with multidrug-resistant strains were less likely to recover after completing a DOTS course, and if they survived, they were likely to experience a recurrence of TB within twenty-two months of completing treatment. Overall, infection with multidrug-resistant TB was the factor most associated with death in treated TB patients.

Currently, many laboratories that are capable of sputum smear microscopy find it difficult to extend their services to include drug susceptibility testing. The unfortunate paradox is that even though DOTS is based on a cheap and robust diagnostic protocol, a poorly managed DOTS program leads to resistance and makes it necessary to augment affordable laboratory technologies with more expensive ones. MDR-TB and XDR-TB require considerably more sophisticated diagnostics for detection and management because the susceptibility of the tubercule bacteria to different drugs must be determined when a diagnosis is made and monitored throughout treatment. Conventionally, this protocol requires expensive and time-consuming culture and sensitivity testing. Unlike fast-growing bacteria such as *Salmonella* and *Streptococcus,* which produce colonies after overnight culture, plate culture of *M. tuberculosis* on special complex media takes forty-two days to grow and requires sophisticated and expensive safety measures. When traditional methods are used, return of susceptibility testing results can take four to eight weeks.

Multidrug-resistant TB is presently uncommon in Africa. Unfortunately, commitment to the standard DOTS protocol is not common enough, and HIV prevalence is high so that resistant strains have begun to emerge and spread. Recent drug-resistant epidemics in South Africa and Botswana demonstrate that when resistant strains become commonplace, sputum smear microscopy is inadequate to support TB care.[51] It is only because these epidemics occurred in areas with some access to diagnostic facilities that they were identified at all. DOTS aims to treat 85 percent of diagnosed cases successfully; if many infections are resistant, there must be means to detect them and send them right to second-tier therapy.

Like bacterial culture and susceptibility testing methods, as well as the tests used to diagnose malaria before the advent of rapid diagnostic tests, the cardinal test for tuberculosis—sputum smear microscopy—is about a century old. Age old tests do not require expensive or labile materials; however, they are often tedious, require some specialist training, and do not always identify exceptional cases of the disease that are commonplace today but were rare when the test was developed. For example, sputum smear microscopy, a simple and informative

technique, is incapable of identifying drug-resistant strains of TB. It is also inadequate today for another important reason: it fails to diagnose tuberculosis in many HIV-positive patients, who in modern times are among those most likely to have active TB. HIV-infected TB patients deteriorate quickly and are often in-patients. Therefore, if not treated rapidly and successfully, they place health workers at risk of infection. These factors, as much as multidrug resistance, contributed to the much-publicized deadly outbreak of XDR-TB in Tugela Ferry, KwaZulu Natal, South Africa. Diagnostics that are more sensitive than sputum smear microscopy, more rapid than culture, and less expensive than PCR are urgently needed to contain tuberculosis in parts of Africa where HIV infection is common.[52]

Eventually drug sensitivity testing, as well as diagnosis, will be required at the point of care in most places. Simply monitoring trends from sentinel sites will be inadequate, and the international health community will have to face the prospect of making *M. tuberculosis* culture and drug susceptibility testing available throughout Africa. BACTEC instrumentation, an automated specimen culture system devised and marketed by U.S. diagnostics manufacturer Becton Dickinson, has made TB culture faster and safer and is already in use in some African laboratories. Molecular testing also offers some promise and this capacity may need to be built in places where molecular diagnostics are not commonly used today.[53] The most promise comes from newer line-probe assays—molecular assays that don't use cumbersome and finicky equipment—and point-of-care tests that are in development.[54] Like malaria diagnostics, their quality and performance in resource-poor laboratories needs to be assured, but this cannot be done too quickly. The evolutionary innovation by *Mycobacterium tuberculosis* has far outpaced our ability to diagnose and treat the infection these bacteria cause.

Can TB, in particular MDR-TB, be rapidly and effectively detected in African laboratories using today's technology? A two-year capacity building project in Lesotho illustrates that it can.[55] Before the effort began, only seventeen clinics performed sputum smear microscopy and patients in Lesotho with MDR-TB were typically diagnosed, when they were at all, in South Africa and the United States. In 2006, new culture facilities and line-probe assays were installed in the national reference laboratory, staff members were trained, and quality control mechanisms were put in place. By 2008 the laboratory was reliably processing almost eight thousand specimens a year. It was also providing quality assurance for sputum smear microscopy performed in district health centers, and training laboratory technicians from other African countries. The entire capacity-building project cost about half a million U.S. dollars, much less than the projected expenses for out-of-control MDR-TB epidemics.

The Ultimate Challenge of Malaria

All successful or nearly successful control and eradication campaigns have been associated with diagnostic certainty. The failure of the worldwide 1955–69 malaria eradication campaign placed malaria squarely in the category of ineradicable diseases. Transmission rates in parts of sub-Saharan Africa were so high that the interventions barely dented its incidence. This campaign relied entirely on chemical agents for which resistance rapidly emerged and spread.[56] Within five years of its commencement, mosquitoes resistant to the insecticide DDT were widespread, and *Plasmodium* parasites resistant to the drug of choice, chloroquine, had become a menace.[57] The failure to reevaluate the program's strategy, coupled with the insistence that it not extend beyond the original date for completion, left many countries to battle resurgent malaria alone. Sadly, some of these places had long suffered from endemic disease but had made real progress toward control, if not elimination.

When the program collapsed at the end of the 1960s, neither the parasite nor its mosquito vectors had been vanquished. What was closest to eradication was the community of public health officials and biomedical scientists with malaria expertise. Malaria imposed an increasing disease burden on Africa between the 1980s and 2000, but overcoming the discouraging legacy of the failed campaign and rebuilding a community of experts to address the mounting crisis took time. In the 1990s, researchers and private funders expressed renewed interest in malaria, which had become synonymous with poverty and suffering. The new impetus to attack the disease was evident at the 56th annual meeting of the American Society of Tropical Medicine and Hygiene, held in Philadelphia in November 2007. In contrast to the previous campaign's kickoff gathering three decades before, malaria researchers were in the majority and malaria was the unofficial theme of the meeting. Conference attendees included researchers from malaria-endemic countries, including Africa, who were able to participate as a result of recent improvements in research funding. The meeting rooms buzzed with reports of new developments in understanding the malaria parasite, the mosquito vector, and the course of the disease, as well as new directions for therapies, vaccines, and diagnostics.

I had browsed the schedule of the meeting ahead of time and looked forward to a veritable feast of new scientific information about tropical infections in general and malaria in particular. However, like many in the audience, I was unprepared for what we heard at the keynote lecture. Keynote lectures at large biomedical science meetings are typically well presented, even flamboyant—or, at least, as colorful as research scientists can make them. A ballroom is converted into an auditorium, and the speaker's image and Powerpoint presentation are

projected on a large screen. Keynote lectures are often comprehensive and synthetic and sometimes insightful, but they rarely impart new information to insiders in the field. Many scientists attend the keynote lecture because they know everyone else will be there; it is the perfect place to catch up with old friends and former collaborators. For students, new researchers, or guests, a keynote lecture usually serves as a succinct introduction to the field.

In 2007, the society invited Tadataka Yamada, the president of the Bill and Melinda Gates Foundation's Global Health Program, to give the address. The Gates Foundation had been instrumental in the revival of malaria research as well as in delivering effective interventions, such as insecticide-impregnated bed nets and potent artemisinin combination therapies. Although conference-goers often chat quietly during a keynote lecture, Yamada's quiet but insistent voice, and his evident pain at the ravages of malaria, compelled silence. After recounting the dire statistics associated with the global burden of malaria, Yamada made a startling announcement: in spite of the failure of the 1955–69 campaign, the Gates Foundation was making a commitment to support the eradication of malaria.

Yamada's announcement followed an invitation to a select group of malariologists, who had been forewarned six weeks before in Seattle. There, the Gateses, in back-to-back presentations, challenged malariologists to eradicate malaria within their lifetimes.[58] In response, WHO's director general, Margaret Chan, announced that this global organization would share in this commitment. Considering the gravity of the announcement, which stunned some into silence, the attendees' response was either subdued or skeptical. Some gave this rich and famous couple indulgent smiles and acknowledged that their wealth and philanthropy entitled them to have pie-in-the-sky dreams. Even Chan was later quoted as saying, "It is elimination-slash-eradication, depending on the availability of tools."[59] Given the broken promises that litter the history of malaria control, scientists have been wary of making any real commitments without hard evidence of effective measures for eradication. At best, some malariologists have suggested, an eradication plan might help bolster control. But there are no models for malaria control. In Europe and North America, the disease was eliminated. In the parts of the world where malaria still plagues people, it remains uncontrolled. Perhaps, as Stephen Hoffman presciently observed, "Common use of the word [control] … represents our recognition of our inability to eradicate malaria."[60] Dr. Hoffman has complained that malaria control is a visionless goal with origins in the failed eradication effort of the 1960s.

As Dr. Yamada reiterated the Gates Foundation's determination to see eradication through and outlined a scientific framework for doing so, it was impossible not to take this proposition seriously. Yamada was able to justify the need for a new program in less than ten minutes of his hour-long presentation. The

human and financial cost of the disease was great, as was the moral imperative. Quietly but firmly, he asked: "Can we sit in a world in which the vast majority of us never worry about this problem while there are people who worry about losing their children, especially as we can contemplate eradication?"

Most scientists and heath policy advocates had not contemplated eradicating malaria for forty years. At its peak, the earlier campaign had eliminated the disease from two-thirds of the globe. The recent surge in malaria research, the new disease control tools that had come to the fore, and the impressive progress from African countries such as Zambia suggested that it was time to reconsider eradication.

The technical literature describes malaria as a disease that is ineradicable for biological reasons.[61] In making a commitment to see an eradication program through before its feasibility had been certified, the Gates Foundation banked its faith on technological development. Essentially, the commitment is built on the assumption that scientific research can and will overcome all existing biological roadblocks to malaria eradication. The initial challenge will be identifying precisely what these roadblocks are. Key reasons for the failure of the older campaign include pathogen and vector resistance, secondary vectors, and a terminal loss of will and financial support. A less commonly discussed factor that must be addressed in any future malaria eradication campaign is the difficulty of diagnosing people and mosquitoes carrying malaria parasites. The difficulty of diagnosis directed the failed campaign at all individuals instead of only those who have the parasite. The smallpox campaign, by contrast, succeeded by targeting infected people and their contacts.

For malaria, mass treatment with today's tools could spell failure because intensive use of any biocide creates needless selective pressure for the development of resistance to drugs and insecticides. Biocidal agents are much more effective against specific targets. It is possible that had the application of chloroquine and DDT been more focused, their effective life spans could have been extended. Whether careful targeting would have altered the course of the malaria eradication campaign remains an open question. At a minimum, diagnostic precision would have made it clear right away that the strategy was not working in Africa and perhaps prompted a shift in approach before donor fatigue set in. Developing and deploying the tools required to monitor progress is essential to any control or eradication effort. In describing the ultimate goal for malaria, eradication, Yamada suggested an analogy between disease control and playing tennis: "If you don't keep score, you are just practicing." The score, he insisted, must be lives saved. Only with diagnostic precision can we keep score.