FORGING THE CHAIN

SCENES FROM THE BATTLE AGAINST NEGLECTED TROPICAL DISEASES

WITH THE SUPPORT OF INNOVATIVE PARTNERS

World Health Organization

IDM
INNOVATIVE
AND
INTENSIFIED
DISEASE
MANAGEMENT

“RESULTS BUILD TRUST, AND WITH TRUST, COMMITMENT ESCALATES.”

Dr Margaret Chan, WHO Director-General

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CIRDES
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DDT
↓
DICHLORODIPHENYL-TRICHLOROETHANE

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DRUGS FOR NEGLECTED DISEASES INITIATIVE

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PARTNERING IN THE BATTLE AGAINST NEGLECTED TROPICAL DISEASES

"Man and his species are in perpetual struggle with microbes, with incompatible mothers-in-law, with drunken car-drivers and with cosmic rays from Outer Space."

Gordon, 1958

Battling neglected tropical diseases (NTDs) is not easy for a number of reasons. The microbial world is mobile and the targets keep changing.

This book reflects on a 15-year battle – one that is still continuing – against five tropical diseases that have been long neglected yet take a heavy toll in death and human suffering today.

It introduces some of the protagonists involved – patients in remote villages, health workers, community leaders, district and health ministry officials, researchers, donors and agency staff under the leadership of the World Health Organization (WHO). Its goal is to situate NTDs historically, culturally, and scientifically, and to illustrate the efforts taken over the years to end suffering and bring hope to the thousands of people who have been afflicted by these deadly diseases.

Helping the WHO in this endeavour goes beyond fighting pathogens. It involves vigilance over a dangerous world and dedication to public health and well-being in a number of respects – from supporting human rights to creating a better environment for all.

NEGLECT: A BROKEN CHAIN

Neglect: The Latin words negligere mean "detached" or "disrupted". The opposite is religere, or re-linking – as one would do with a broken chain – or "bringing all together," a good definition of teamwork.

Over the years, tropical diseases have caused hundreds of thousands of deaths, immense suffering and permanent disability.

It is surprising that they have not received as much attention from the international and medical communities until now.

The term neglected tropical disease was not coined out of thin air. It is linked to a group of specific diseases characterized by poverty and remote inaccessible areas. These features lend themselves to neglect and breaks in the links of the chain providing access to health care.

For the chain to function a number of crucial links have to be created.

For a medicine to be provided to a patient in such a situation at an affordable cost – or at no cost, in most cases – a great deal must be done beforehand. And no link in this chain of access is forged easily. For example, the medicine has to be produced, shipped, imported, distributed and delivered. The location concerned can make "the middle of nowhere" sound like a euphemism.

A doctor or, at least, a qualified nurse, must be available to administer the treatment correctly.

Generally, some kind of supporting structure is necessary, such as a refrigerator to keep the medication at a suitable temperature, a generator to power the refrigerator, and equipment and chemicals to ensure sterile conditions.

Before that, a diagnosis must be made. In many cases, that means a diagnostic test has to be transported, used and the results interpreted, often in a laboratory.

Earlier still, the patient must decide that whatever is wrong is worth medical attention. That is a significant factor. Seeking treatment may mean losing a day's work at subsistence farming. Or spending (or borrowing) money needed for other things to travel to the nearest health clinic. Because many tropical diseases are best treated early, but may have benign or ambiguous symptoms, people in rural, isolated communities frequently must be educated about what to look for. Often even this is not enough, and mobile medical teams must pass through the area, actively screening for infections.

Of course, medicines and diagnostic tests have to be developed to begin with. For tropical diseases that largely affect the poor, that means the wider world has to notice there is a problem in the first place and must donate funding to deal with it.

Several of these tropical diseases have caused hundreds of thousands of deaths over the years, enormous suffering and permanent disability. There have always been breaks in this chain of access.

THE TERM "TROPICAL": LEGENDS, MYTHS AND FEARS

"Some will allow no diseases to be new, others think that many old ones are ceased: and that such which are esteemed new, will have but their time: however, the mercy of God hath scattered the great heap of diseases, and not loaded any one country with all: some may be new in one country which have been old in another. New discoveries of the earth discover new diseases: for besides the common swarm, there are endemial and local infirmities proper unto certain regions, which in the whole earth make no small number: and if Asia, Africa, and America should bring in their list, Pandora's box would swell, and there must be a strange pathology."

Sir Thomas Browne, 1657

For centuries, the tropics were more than a geographical zone to European travellers. They were a psychological maze filled with miasma, danger and magic. Getting to the tropics was no small feat, and those who did so in the 18th and 19th centuries frequently returned with stories of the remoteness of these regions, the vast impenetrable forests, the epic colours and exotic wild animals, which only added to the mystery. But there were also horrific diseases that were more likely to be attributed to the atmosphere or literally to "vapours" than to scientifically proven causes.

This impression remains into the 21st century, but it has to be tempered with a realistic perspective. The tropics are no longer far off; they are a short flight away. So are the diseases. While "tropical" in an endemic sense, these diseases have no borders in an era of rapid global travel.

Tourists rightly fear contracting malaria when they visit tropical areas, but less well-known diseases pose their own threats and have their own forms of mobility. Europe, for example, now has a large reservoir of Latin American immigrants who silently carry Chagas disease. If these infections continue undiscovered, the disease will kill many of them – in a region where no one expects to see it. Those infected also may pass the disease on through blood transfusions and organ transplants. Buruli ulcer is no longer confined to Africa as once thought but has appeared in Australia, China and Japan. As people move and climates change, tropical diseases can no longer be contained in far-off exotic countries.

NEGLECTED TROPICAL DISEASES

"As long as poverty, injustice and gross inequality exist in our world, none of us can truly rest."

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Nelson Mandela, 2005

The following diseases are grouped under the term NTDs. They have a number of common characteristics:

- → They currently infect more than 1 billion people.
- → They cause significant death and suffering.
- → They affect populations mired in poverty, with low visibility and little political influence.
- → They do not "travel" to temperate regions – persons who are infected might travel, but the diseases themselves do not spread in a standard fashion beyond endemic tropical areas.
- → They often cause stigma and lead to discrimination, especially of girls and women.
- → Until recently, they attracted insufficient research attention, especially into potential treatments.
- → They can be controlled, prevented and possibly eliminated.

- → *Helminth infections*
  Soil-transmitted helminthiasis: ascariasis, trichuriasis and hookworm infections
  Lymphatic filariasis
  Onchocerciasis
  Schistosomiasis
  Dracunculiasis (guinea-worm disease)
  Cysticercosis
  Echinococcosis
  Foodborne trematodiases
- → *Viral infections*
  Dengue
  Rabies
- → *Protozoan infections*
  Leishmaniasis (visceral and cutaneous)
  Sleeping sickness (human African trypanosomiasis)
  Chagas disease
- → *Bacterial infections*
  Leprosy
  Trachoma
  Buruli ulcer
  Endemic treponematoses

FIVE OR SIX UNIQUE DISEASES?

When something is a complicated mess – a catastrophe that affects others – the temptation is to look away. But for WHO, this is unethical and inhumane.

It so happens that of the group of NTDs, five (or six) are notoriously difficult and complicated to detect, treat and prevent. Even the number is confusing, for example, it is as yet undecided whether visceral leishmaniasis and cutaneous leishmaniasis are one or two diseases.

WHO has placed five – or six – diseases in a unique group. They are said to require innovative and intensive disease management (IDM). In practical terms, they are a continuing challenge to both medical and international communities.

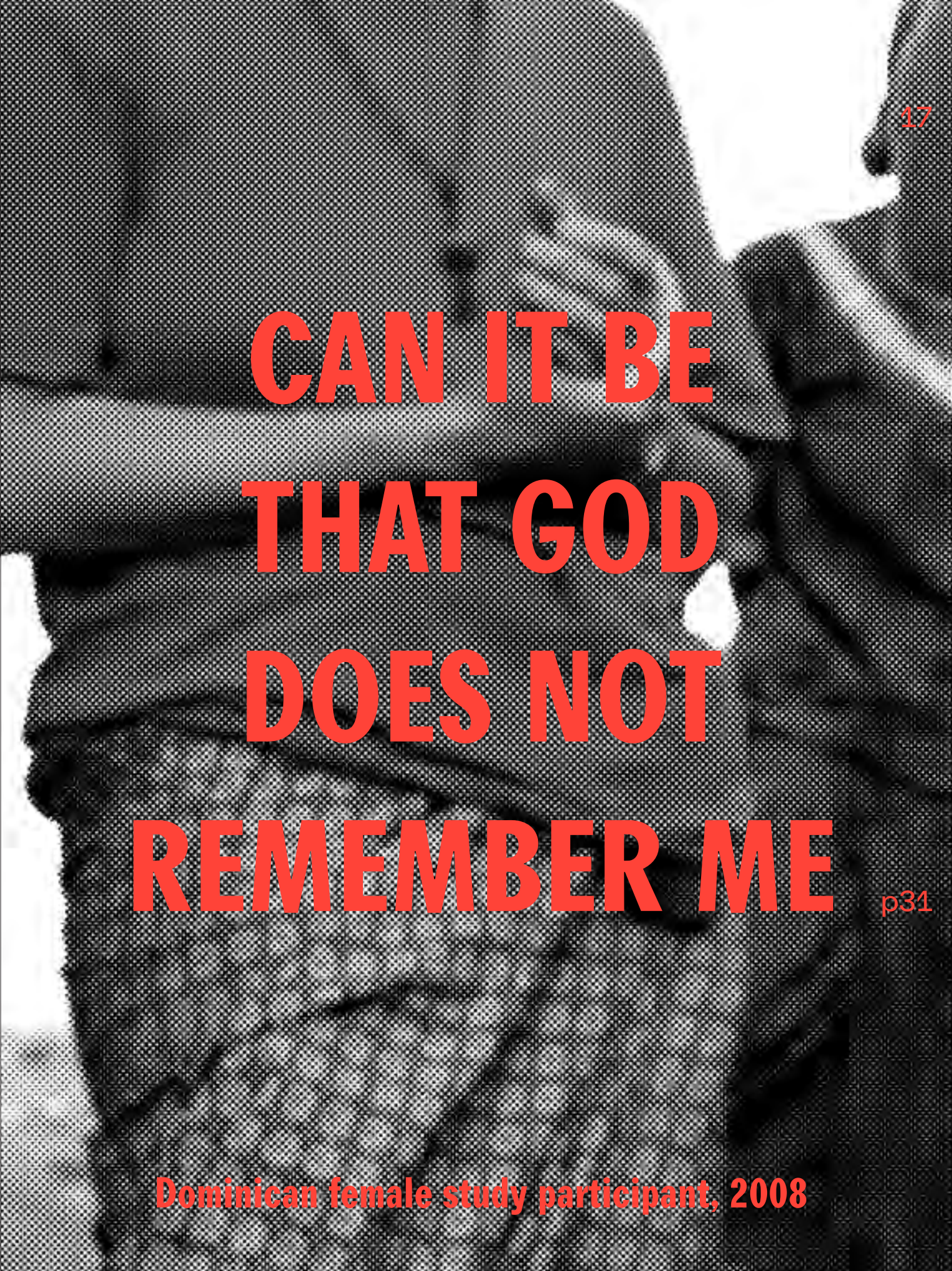
They affect hundreds of thousands of humans, most of whom are desperately poor. Human African trypanosomiasis or HAT (informally known as sleeping sickness), Chagas disease, visceral and cutaneous leishmaniasis, Buruli ulcer and yaws can appear in many different forms. Medications that work for some do not work for others. The diseases are best treated early, yet the symptoms of early infection are frequently non-existent or mild. If symptoms are present, they may be – and often are – mistaken for something else, such as an insignificant skin rash or a headache.

More severe symptoms may sometimes be misinterpreted later. Rural health workers are often unable to obtain the sophisticated medical advice required to identify the illness. They may diagnose brain cancer rather than HAT, or ulcers rather than visceral leishmaniasis, or heart problems rather than Chagas disease. Arriving at a correct diagnosis can require sophisticated medical testing not easily carried out in remote locations.

The poor, meanwhile, often suffer from “minor” health problems. Struggling to survive, they prefer not to visit the doctor or nearest health clinic for a seemingly insignificant illness. They may go only when it is serious. But by then, treatment is more complicated and difficult, and permanent damage may have been done. In many cases, it is too late to save the patient’s life or to prevent crippling damage.

Treating these diseases – let alone diagnosing them – requires specialized health care, including extended stays in hospitals. Health workers with specific skills are needed to provide this care.

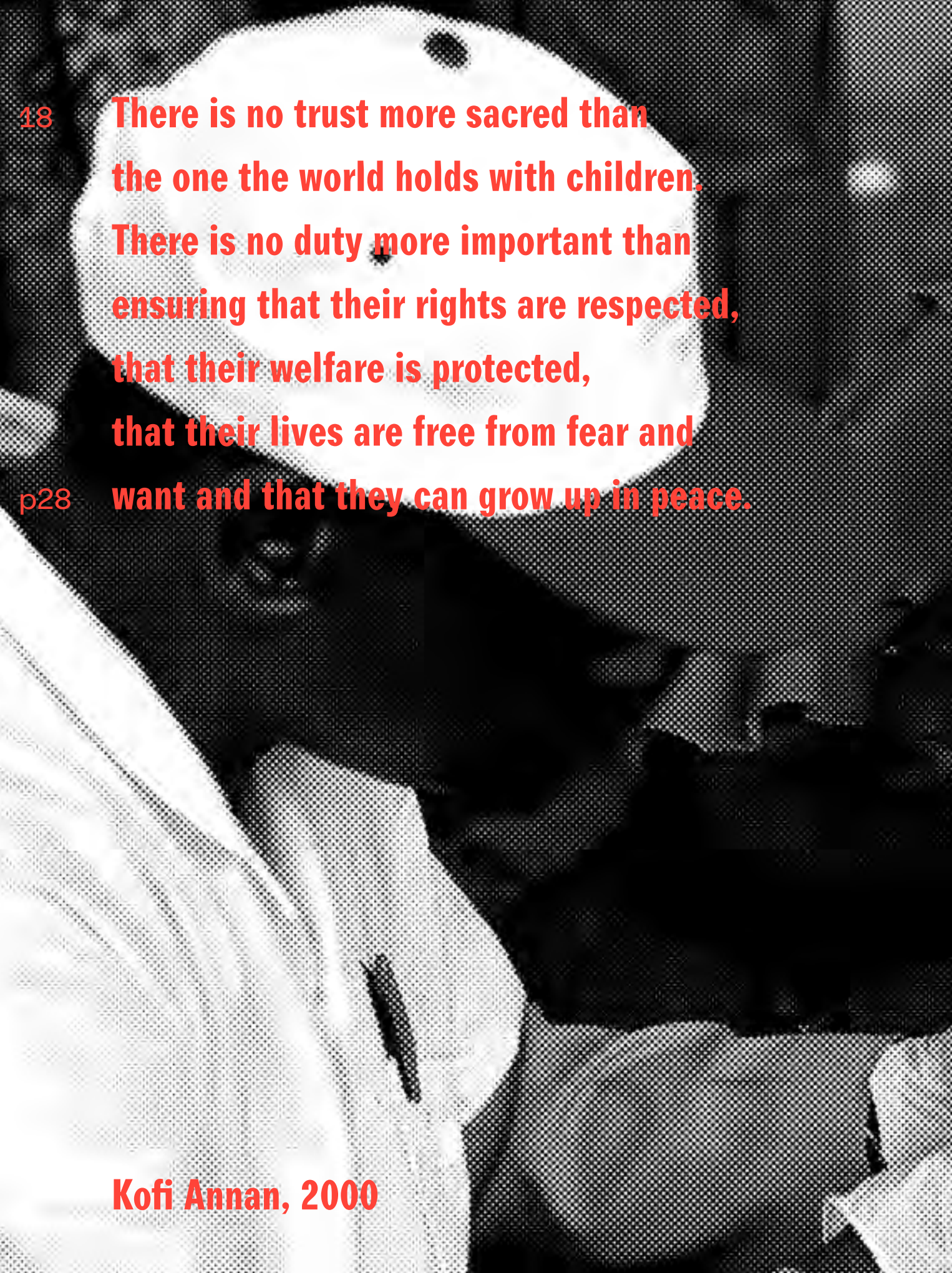
Also more or less complex – but never easy – are methods for attacking the vectors, the pathways by which these diseases emerge from their tropical environments to infect humans.



CAN IT BE THAT GOD DOES NOT REMEMBER ME

p31

Dominican female study participant, 2008



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There is no trust more sacred than
the one the world holds with children.
There is no duty more important than
ensuring that their rights are respected,
that their welfare is protected,
that their lives are free from fear and
want and that they can grow up in peace.

p28

Kofi Annan, 2000


ACCESS
TO HEALTH SYSTEMS
ACCESS
TO DIAGNOSIS
ACCESS
TO TREATMENT

THERE HAVE ALWAYS BEEN BREAKS IN THIS CHAIN OF ACCESS

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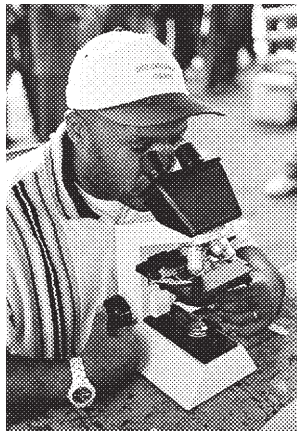
ACCESS TO DIAGNOSIS

From a public health standpoint, diagnosis occur within a continuum: if they are inappropriate to a given situation, they may not be affordable or workable.



Among the different tools used for managing the control and elimination of NTDs, the role of diagnostic tools has not been as well conceptualized as for drugs. This shortcoming is in part a reflection of the large range of definitions and uses for diagnostics.

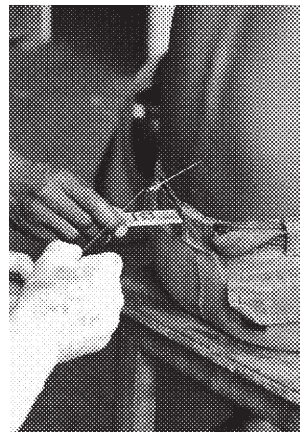
The classical definition is that a diagnostic is used to identify a disease. But even in that case, it depends on whether the diagnosis is applied to an individual or to a population. For example, when screening populations, a first test is applied to determine the part of the population where the disease prevalence is highest. For this, a very sensitive test is used, even if it is not very specific – that is, it may report falsepositive results. Afterwards, a more specific test is used to identify individual patients.

Diagnostics also can be used for assessing epidemiological situations or for monitoring the progress of disease-control or disease-elimination processes.

In addition, varying diagnostics can apply to active screening, routine passive identification, tests of cures and decision-making by public health authorities.

Finally, access and application are critical issues. Different tests are frequently necessary depending on whether patients are sought in the field or can come to health clinics, on whether more or less highly trained health workers are administering the tests, and on whether the tests can be stored properly under the conditions encountered – in tropical heat, for example, rather than in temperature-controlled laboratories.

p20



AWARENESS

Diagnosing and treating patients through health facilities and mobile teams is only part of the process of saving lives.

Simple actions such as plastering the walls of houses can dramatically decrease the incidence of Chagas disease. Sanitation and environmental improvements can greatly reduce the spread of visceral leishmaniasis.

Moreover, to be treated under the best conditions, patients must be identified early. That means such people must be conscious that they are ill; must know that effective treatment is available if the doctor is visited quickly; and must know that the disease, if left untreated, can have irreversible and even fatal consequences.

Informing and educating populations at risk is crucial for reducing the toll of tropical diseases. In poor and remote areas, carrying out this task is a challenge. On the other hand, major payoffs can come from creating awareness, changing attitudes, and persuading potential victims to alter disease-spreading forms of behaviour and to adopt recent innovations.

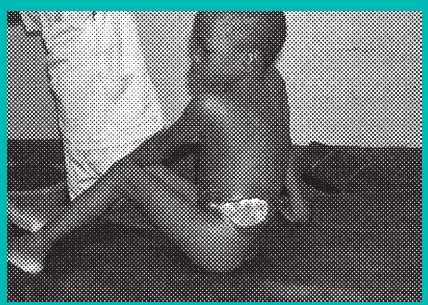
So-called "sensitization campaigns" have, therefore, been organized in endemic regions. Much educational material has been developed, including comics that can be understood by children and illiterate adults. On the WHO website, information, education, and communication activities are assigned the same importance as disease-control strategies.

On a larger scale, mass media can help to create an agenda for public debate that can produce greater global attention and resources for combating these diseases. For example, a website – beatchagas.org – is dedicated to Chagas disease. It provides information and educational material and has even enlisted, for publicity purposes, the world's most famous football player, Lionel Messi, to help create awareness of the damage caused by this largely silent disease.

BURULI ULCER

Buruli ulcer occurs in tropical and subtropical regions of Africa, the Americas and the Pacific. It is also found in temperate countries such as Australia, China and Japan.

In 1897, Sir Albert Cook, a British missionary doctor working in Uganda discovered the disease. He described the characteristic skin ulcers but did not publish his findings in the medical literature. In 1948, MacCallum and colleagues published the first article describing cases of the disease in Bairnsdale, Australia. The causative bacterium (germ) was identified, and the scientists named the new disease "Bairnsdale ulcer". Today, the disease is popularly called Buruli ulcer because of the large number of cases reported in Buruli County, Uganda, in the 1960s.



The bacterium – *Mycobacterium ulcerans* – belongs to the same family of organisms as the "famous" bacteria that cause leprosy and tuberculosis. However, *M. ulcerans* produces a unique toxin that damages the skin, inhibits the local immune response and enables the disease to progress dramatically without pain and fever. So people who are infected often do not seek care until it is too late. Without treatment, the disease can spread to the bones. Often it causes deformities and long-term functional disabilities. Most patients are children.

Initially the diagnosis is (as for other diseases) clinical. It is then confirmed by laboratory tests. Confirmation is complex, requires costly materials and is available only in well-equipped laboratories, which are usually far from where most patients live. A simple new test to detect the toxin could provide faster diagnosis in the field.

Current treatments are safe and well known; roughly the same antibiotics are used as for the treatment of tuberculosis but for a shorter duration (two rather than six months). Despite advances in science and technology, the origin of the bacterium in the environment remains a mystery. How the disease is transmitted from the environment to people is still not understood. Recently, scientists found the bacterium in some aquatic plants and insects but it is not clear how or if these might contribute to transmission of the disease.

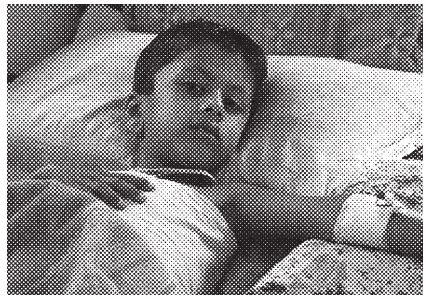
International awareness grew following WHO's involvement in 1998, when it organized the first International Conference on Buruli Ulcer Control and Research in Yamoussoukro, Côte d'Ivoire, from 6 to 8 July. Since then, surveillance, diagnosis and treatment of the disease have advanced.

IT CAN BE DONE

It is not easy but if a country wants to attack a disease with determination and persistence, using existing medications and methods, it can be controlled.

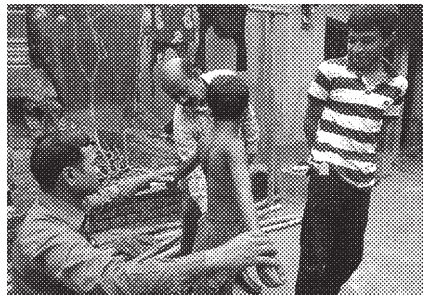
India contacted WHO in the mid-1990s about the possibility of eliminating yaws, which had been a domestic public health curse for centuries. Health officials were told it was entirely possible – that it was simply a matter of organization, funding and commitment. Wherever a case was identified, they should treat all in the surrounding community with intramuscular injections of penicillin. Then they should return and carry out a second round of treatments to make sure that there were no new cases. Beginning in 1996, Indian health workers did just that, fanning out over the country, ensuring cases were reported, responding without exception to all of them, travelling in mobile teams to isolated communities, administering millions of doses of antibiotics, and keeping careful and thorough records. It took seven years, but in the second most-populous country in the world, the last confirmed infection of yaws was treated and cured in 2003. Active surveillance based on clinical symptoms and serological tests – necessary for sustaining the victory – has not identified a single case since.

Visceral leishmaniasis, a tougher challenge because the disease has numerous non-human reservoirs, was considered a near-insurmountable problem in Bangladesh a decade ago. But the country was determined to face it. WHO, working in cooperation with Bangladesh's Ministry of Health and Family Welfare, introduced the use of a single dose of AmBisome in major endemic areas of the country. WHO has continued to provide technical and financial support, including drug donation, which has helped to cover the costs of a focused, persistent campaign.



As a result of these efforts, the burden of the disease has declined to less than one case per 10 000 people in endemic areas.

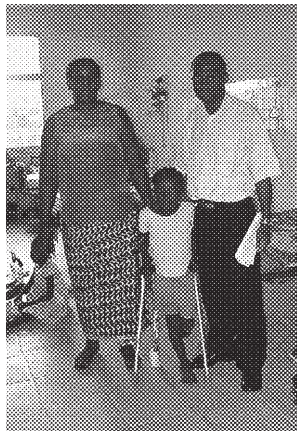
Throughout Africa, the noose is tightening around sleeping sickness. Attacked on numerous fronts based on its vulnerabilities in different regions, the disease now infects well below 10 000 people annually, a steep drop from the estimated 400 000 cases that was estimated to have occurred annually in the 1990s.



Determination to finish the job and finish it definitively will be vital this time. It is an issue that has arisen in the past with tropical diseases. Sleeping sickness and yaws were nearly eliminated in the 1960s, but when attention and efforts waned, the diseases resurged and the "penalty of success" took its toll.

LONG-TERM CARE IS A LINK IN THE CHAIN, NOT A LUXURY

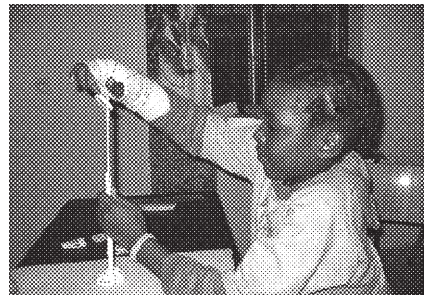
It is good to diagnose people. It is good to treat them. It is even better to cure them. But it is bad to stop there. The ethical care of people with NTDs requires follow-up and monitoring of complications and sequelae, because often the job is not finished. The long-term consequences must be faced.



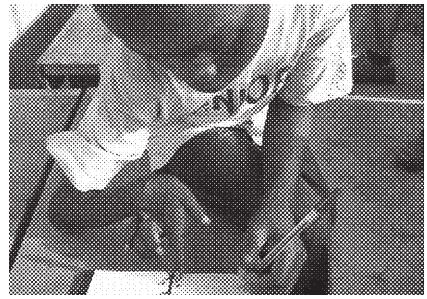
Surgery for Buruli ulcer – where muscle and even bone may be removed – frequently causes disability. Physiotherapy and reconstructive surgery are essential. Patients cured of advanced sleeping sickness often have permanent neurological damage. Special education may be necessary for children, and patients of all ages may require psychiatric help. Late clinical manifestations of Chagas disease can mean further medical procedures are called for, such as digestive surgery, organ transplants, implantation of cardiac equipment such as pacemakers and long-term management of heart problems. Lengthy dermatological treatments and plastic surgery are often required following cases of leishmaniasis.

These are all links in the chain of care. All must be forged if the diseases are to be conquered.

With such treatment, many patients can recover and live largely normal lives. Without it, they may be serious economic and psychological burdens to their families. As many of those affected by NTDs are children, the cost can be especially high.

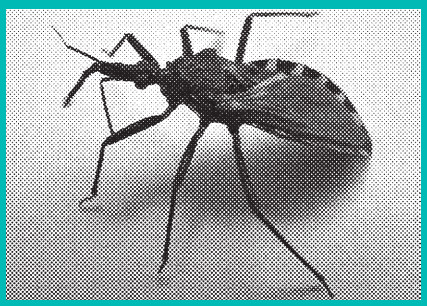


Taking charge of such follow-up and monitoring is a process which calls for different medical skills and techniques to those used in the initial treatment: plastic surgeons, physiotherapists, digestive specialists, dermatologists and cardiologists enter the picture. It is important that such personnel are available in endemic countries – and that funding be provided to cover expenses – so that patients can recover to the fullest extent possible.



CHAGAS DISEASE

Chagas disease, also known as American trypanosomiasis, is a life-threatening illness caused by a protozoan parasite *Trypanosoma cruzi*. It is spread among humans and other mammals by an insect vector, the triatomine bugs, in the Latin American endemic area.



The parasite is transmitted to humans through the faeces/urine of infected triatomine bugs. Typically, during the day, the insects hide in the cracks of poorly constructed houses in rural or suburban areas. At night, they bite humans and animals on exposed areas of skin, and the bugs defecate close to the bite. The parasites enter the body when the person instinctively smears the bug faeces into the bites, the eyes, the mouth, or into any break in the skin. The infection can also be acquired through consumption of food contaminated with triatomine bug faeces, through blood transfusion from infected donors, from an infected mother to her foetus during pregnancy or at childbirth (congenital transmission), through organ transplants using organs from infected donors, and even through laboratory accidents.

Today an estimated 7 million people are infected with *T. cruzi*, mostly in 21 Latin American countries (excluding the Caribbean). Chagas disease was once entirely confined to Central and South America. However, in recent decades it has increasingly been detected in Canada, the United States of America, and many European and some western Pacific countries. This is due mainly to population mobility between Latin America and the rest of the world.

Chagas disease presents itself in two phases. An initial acute phase lasts about two months and, if diagnosed, can be treated and cured with any of two antiparasitic medicines: benznidazole or nifurtimox. Detection, however, is not easy, since symptoms usually vary from non-existent to mild and unspecific. In other cases, there are skin lesions or purplish swellings of the eyelids or unspecific general symptoms often misidentified by health workers, particularly in non-endemic areas.

In its subsequent chronic phase, Chagas disease may also go undetected since most patients do not become ill. Nevertheless, up to 30% of those infected gradually suffer from cardiac disorders and another 10% from digestive problems (typically, enlargement of the oesophagus or colon) or neurological damage. In later years, the infection can lead to sudden death caused by progressive destruction of the heart muscle, and the nervous system.

Antiparasitic treatment works less well the longer a person has been infected. The treatment has a long duration (up two months) and adverse reactions are frequent (in up to 40% of patients). While antiphrastic treatment at this stage cannot reverse damage already done, it can prevent or reduce progression of the disease and, typically, is combined with specific treatments for cardiac or digestive problems caused by long-term infection.

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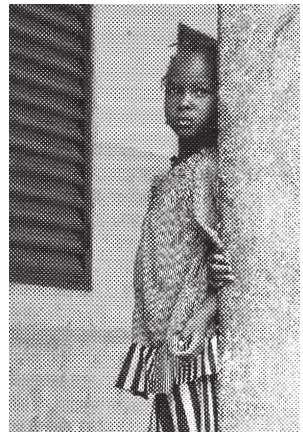
THE CRUEL TOLL ON CHILDREN

"There is no trust more sacred than the one the world holds with children. There is no duty more important than ensuring that their rights are respected, that their welfare is protected, that their lives are free from fear and want and that they can grow up in peace."

p18

Kofi Annan, 2000



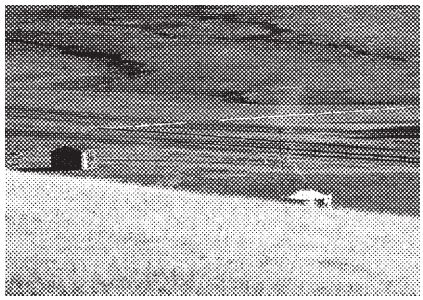
Children are most vulnerable to tropical diseases because of their immature immune systems, active lifestyles and the high rates of malnutrition in rural developing regions where these diseases prevail.

Their exposure frequently predates birth, as infections during pregnancy produce infants who have birth defects or low birth weights.

If untreated, children, like adults, die of sleeping sickness and visceral leishmaniasis. If Chagas disease starts early on in their lives, they die or are disabled as early as middle age. Buruli ulcer and yaws mostly strike the young, and the consequences – chronic pain, stunting, disfigurement, cognitive impairments, and loss of muscle and bone to surgery – last a lifetime, hampering growth and development in many other ways.

The secondary consequences of NTDs are also devastating. Susceptibility to other health risks such as malaria and HIV/AIDS may be heightened. Illnesses prevent children from attending school. As a result they are denied a good start in life. The effects combine to feed new generations into the vicious cycle of extreme poverty – lack of education, lack of land ownership, lack of social power and political voice, and continued gender inequality.

CLIMATE CHANGE (WEREN'T THINGS COMPLICATED ENOUGH?)



Rising global temperatures and the expansion of the world's tropical regions may be bad news for the millions of people newly exposed to Chagas disease, leishmaniasis and other warm-weather diseases.

Or perhaps not. Given that tropical diseases and their interplay with ecosystems and micro-climates are hard to understand in their current state, scientists and epidemiologists are unable to predict with any degree of precision what effects climate change will have on the complicated links between parasites, bacteria, animals, humans, and vectors such as flies and bugs. They do know, however, that they will have to watch closely and react effectively as patterns of infection and disease distribution are altered, perhaps drastically.

It is also possible that disease ranges will be reduced by climate change, although currently the track record is not convincing. Disrupted landscapes in the past have meant that parasites have jumped increasingly from animal hosts to human beings, as occurred in Latin America when human populations partially cleared tropical forests. The triatomine bugs and *T. cruzi* parasites they carried adjusted easily to domestic life, and human Chagas infections climbed steeply.

There are three main areas that must be watched as environmental conditions alter over the coming years.

→ *Increased poverty*
Climate shifts in rural tropical areas may damage subsistence agriculture, leaving farming populations more poor, more malnourished and more vulnerable to disease.

→ *Migration*
If landscapes are significantly altered by, for example droughts, people may be forced to move, bringing endemic diseases with them.

→ *Increased ranges for vectors*
Warmer temperatures may expand territories favouring tsetse flies, sandflies, triatomine bugs and other disease-transmitting pests.

ARMED CONFLICTS: DRIVERS OF EPIDEMICS

p32

"War is not an adventure. It is a disease."

Antoine de Saint-Exupéry, 1942

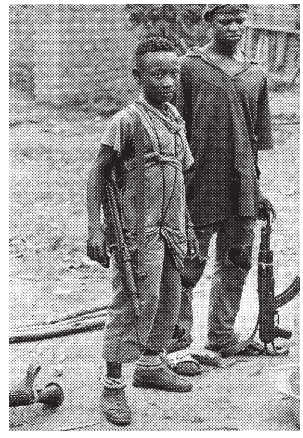
Conflict helped spread the bubonic plague in the 14th century. Soldiers returning home at the end of the First World War took the swine flu with them, spawning a pandemic that killed some 20 million people. The old story is now being acted out in Aleppo, the Syrian Arab Republic, where bombing and artillery fire have destroyed the city's sanitation system. Sandflies, responsible for transmitting cutaneous leishmaniasis, are flourishing in the waste and sewage that flood the streets and buildings, and the flesheating disease has infected so many inhabitants that it has been nicknamed "Aleppo boil."

The civil war is sending the disease elsewhere too, as refugees flee the fighting and seek shelter in camps that often have poor hygiene. Lebanon had had no reported cases of cutaneous leishmaniasis before 2008, and only sporadic infections were discovered after that ... until the conflict in the neighbouring Syrian Arab Republic began.

Now the disease is common. Almost all of the confirmed cases are among refugees who have flooded across the border. The average age of those infected is 17, and many have disfiguring lesions. More disturbing is that 80% have contracted the illness after being in Lebanon for more than eight weeks, which is the known incubation period for the disease. For that to occur sandflies must be present and reproducing – and spreading the disease – in a region that previously was free of it.

There is great concern that the flies will establish a permanent habitat in Lebanon, especially in rural areas with high densities of refugees, such as the Bekaa Valley.

Similarly, major epidemics of visceral leishmaniasis occurred during conflicts and population displacements in Sudan's Upper Nile province in 1994 and more recently in South Sudan in 2014. Thousands have died as a result. In other areas where conflicts have prevailed over the past 30 years, there have been similar flare-ups, for example, of sleeping sickness and Buruli ulcer in the Democratic Republic of the Congo, and sleeping sickness in Angola.



CONFLICTS, CAMPS AND CRIPPLING VULNERABILITY

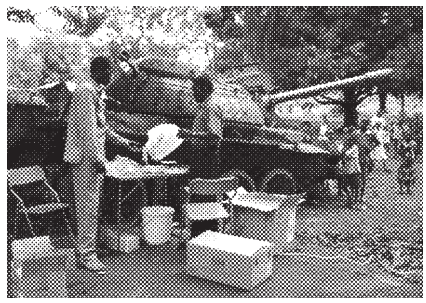
"Can it be that God does not remember me."

p17

Dominican female study participant, 2008

Conflicts, political strife and other situations that strip people of their human rights cause sudden increases in poverty and cripple health systems. Levels of hygiene also decline. For impoverished and otherwise vulnerable populations, the results can be tragic.

Wars and other violent situations displace populations. For the extreme poor, living conditions deteriorate to abysmal levels. Displaced groups of tens or hundreds of thousands resettle under chaotic circumstances in areas that are ill prepared and ill equipped to host them. The resulting overcrowded camps have little or no sanitation, as has been the case recently in Sudan's Darfur region. Or camps are established in locations that increase exposure to disease vectors – for example, forest encampments in the Democratic Republic of the Congo have exposed displaced groups to tsetse fly habitats. Cases of sleeping sickness surged accordingly.



The negative effects on health care are obvious. Developing countries are already strained to provide basic health services while facing shortages of money, roads, electricity and trained personnel. War destroys these fragile structures. Access to health workers becomes difficult, medicines are not available, diagnostic tests are not conducted, and diseases start spreading. Programmes targeting specific diseases are among the first to collapse, as limited resources are directed towards general health care, and as violence makes travelling, surveying for cases, and tracking and treating clusters of infection impossible. Years of painstaking progress against a particular tropical disease can be unravelled in a matter of months, as occurred with sleeping sickness during civil conflicts in Angola and the Democratic Republic of the Congo.


WAR
IS NOT
AN

ADVENTURE

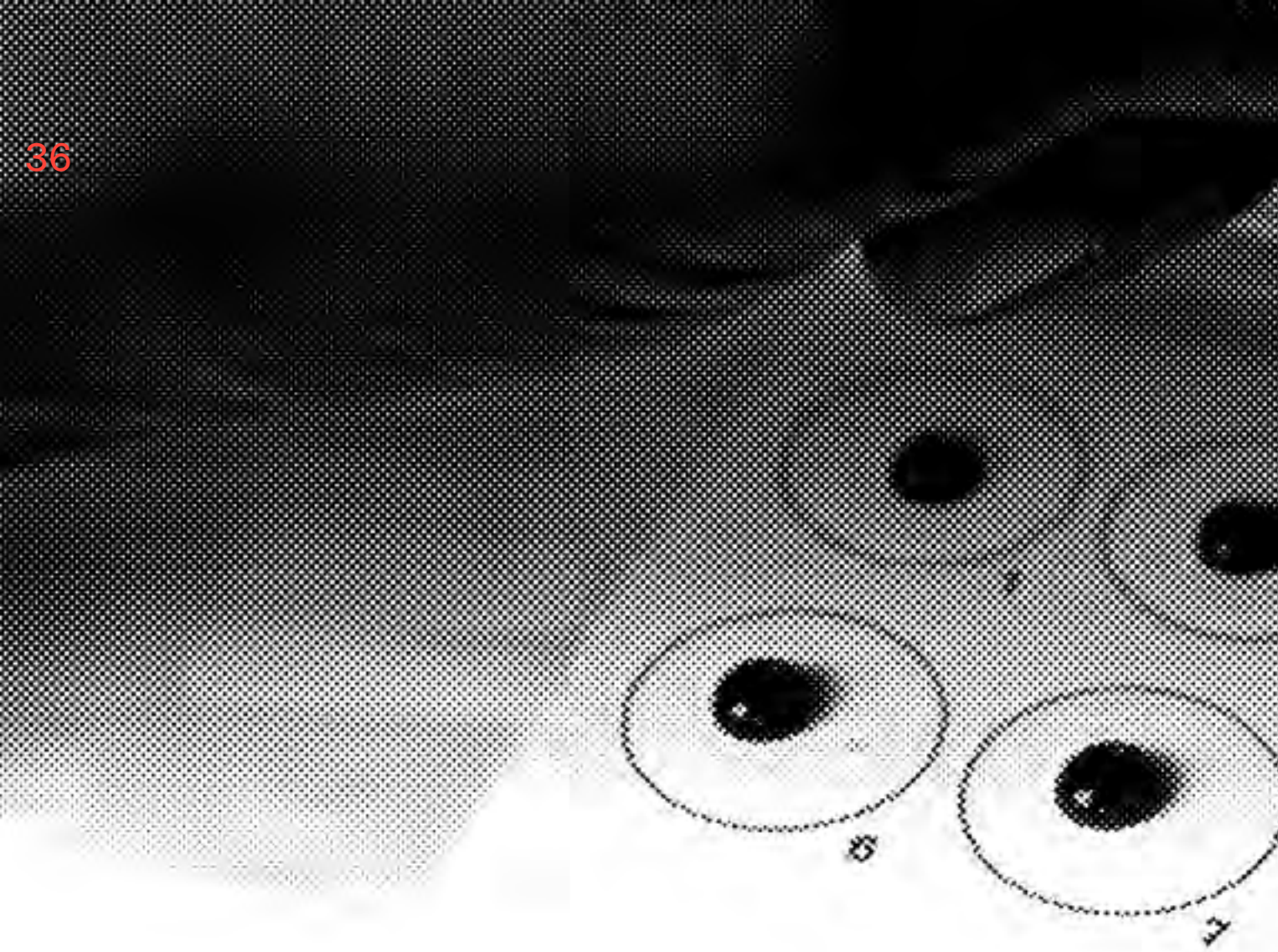

IT
IS
A

35

DISEASE

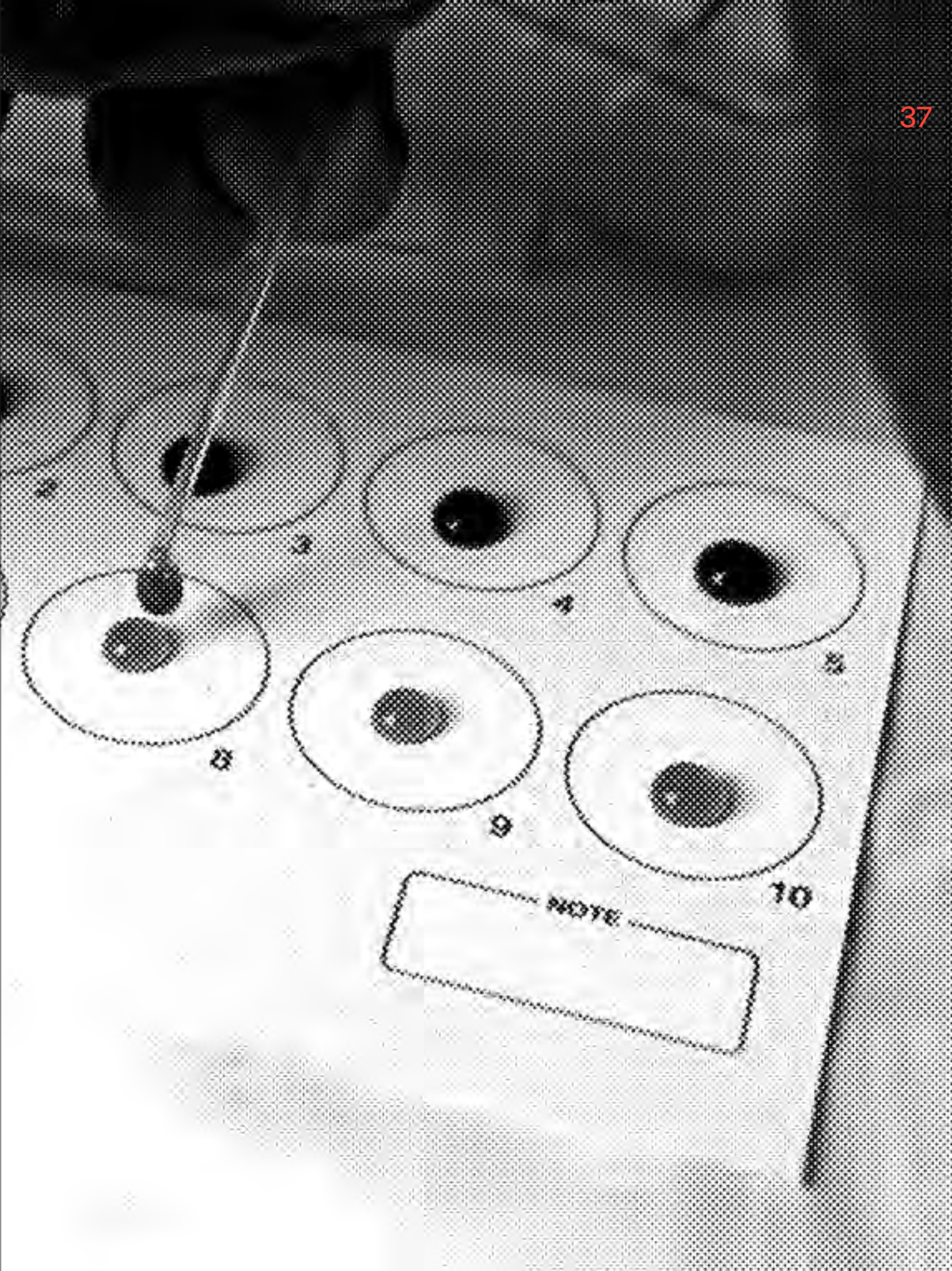
p30

Antoine de Saint-Exupéry, 1942



Added to the dilemma of diagnosing NTDs is the fact that early treatment yields the best results, and is most often safe.

p42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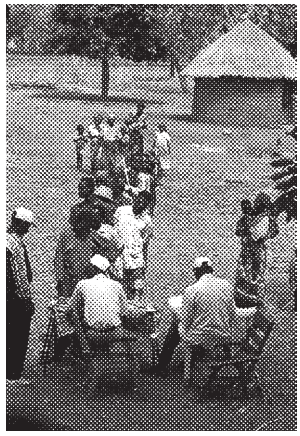
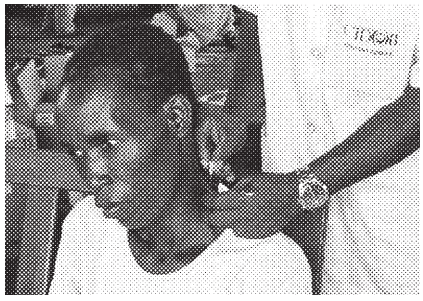
DETECTION RATES

Eliminating a disease means finding and treating all infected cases. But case detection is a numbers game where the cases that slip through the net can quickly add up. That is why strategies for case detection are important.



For a population of 30 000 with a disease prevalence of 5%, for example, some 1500 people will be ill. To systematically screen the population to find those cases and treat them, health authorities will request the entire population to attend screenings. But in practice, it is rare for more than 60% to come, meaning 40% of those infected will go unidentified (and may well go on to infect others). That comes to 600 unidentified cases.



Among those who attend the screenings, some who are ill will be missed by the shortcomings of the diagnostic test applied. For example, a test with 95% sensitivity will miss 5% of patients – in this case a total of 30.

If a direct diagnostic test is used, in which health workers must physically see the causative parasite, the sensitivity of the test drops to 60-70%, meaning that among the 855 remaining patients, around 350 who are infected will go unidentified.

In sum, under quite routine and normal conditions, only 350 patients out of a total of 1500 will be identified. The detection rate is thus only 23%.

These gaps in detection are why multiple screening sessions must normally be used to catch sufficient numbers of patients to bring a disease under control. In the past, low detection rates were tackled “upstream” by raising attendance at screenings – in fact, in the colonial era health teams used coercive measures. Currently, low attendance can only be addressed through the use of more frequent and betterdesigned disease-information campaigns.

Practical problems related to detection rates are a factor of great significance. Increasing attendance at screenings (at the very beginning of the process) is largely more effective than trying to improve the sensitivity of a screening test by 1-2%. If people do not come to be tested, such a 1-2% improvement is of little use when surveying large populations.

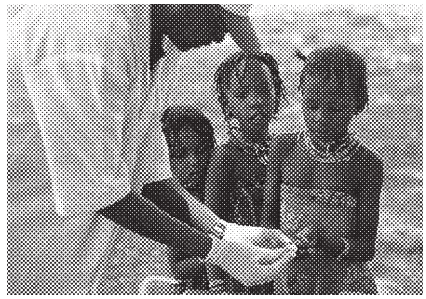
DIAGNOSIS AND ITS DIFFICULTIES

Delivering effective treatment against NTDs is often less of a challenge than determining what – or if – treatment is needed. Diagnosis can be a complex process that hampers control and elimination efforts.

Various factors contribute to this complexity. The first is the absolute importance of being certain of a correct diagnosis before beginning to administer dangerous drugs.

Medications with inherent risks are required for several NTDs, including sleeping sickness, Chagas disease and leishmaniasis. The more dangerous the treatment required, the more specific and accurate the diagnostic procedure must be. This often means that several tests must be carried out to eliminate uncertainty. Clinical observation, the least expensive and most easily available form of diagnosis in poor, rural regions, is far from sufficient. Skin lesions, for example, may be early signs of Buruli ulcer, cutaneous leishmaniasis or a number of other illnesses.

Parasites that have different strains, such as those that cause leishmaniasis, are another complicating factor. Diagnostic tests must be developed to detect all such strains, especially if mobile medical teams only see a patient once and only have one chance to determine if more attention is needed.



At the opposite end of the spectrum, a diagnostic procedure also has to be as sensitive as possible, again, because a patient may have only one opportunity to be tested. A false-negative result in such a situation can be fatal.

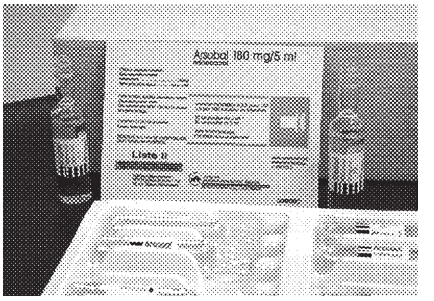
The upshot of these difficulties is that diagnostics for NTDs must have a very high “positive predictive value” (PPV), that is, a high rate of yielding correct results. Because PPV tests are not available for some of these diseases, the certainty arises instead from thorough investigation of various kinds of biological material – blood, plasma, glandular tissue, bone marrow, cerebrospinal fluid – and involves combining different techniques, such as serological tests, microscopy, blood centrifuging and DNA amplification. These processes are complex to carry out in what is often primitive conditions prevailing during field visits, and typically require highly trained personnel using advanced equipment and reagents.

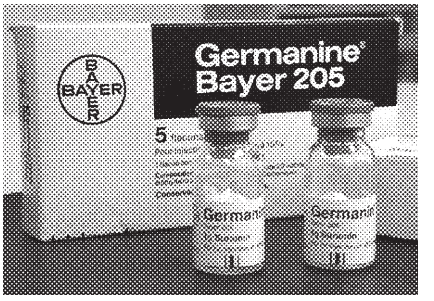
DRUG DONATIONS VERSUS PREFERENTIAL PRICING

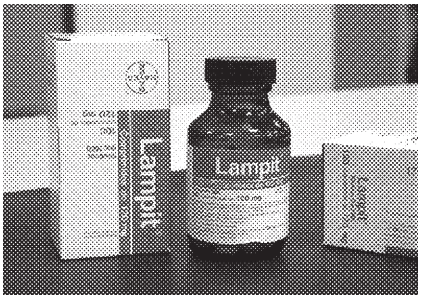
Existing medications – already manufactured and distributed for sale on international markets – are effective against several NTDs. Offering these medications at a discount, rather than providing them free of charge, is sometimes proposed. However, when no nongovernmental organizations (NGO), or only a few, are managing the delivery and administration of these drugs to the extreme poor in remote locations, the absence of an effective national distribution system through which the medications can reach their targeted locations renders preferential pricing ineffective.

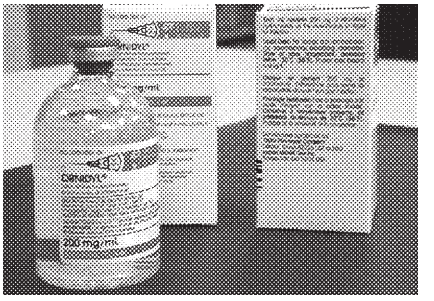
For the most deadly NTDs, the medications are quite expensive. Even if a preferential price is offered, there may be no market, e.g. no nearby pharmacy and no paying arrangement by which the cost of the medication can be covered. In that case, the drug must be ordered by an individual or by an agency, shipped to the country concerned and distributed in the appropriate locations. This is a costly and inefficient approach, compared with donating the medication to a national programme and supporting that programme to identify and treat patients as part of a carefully designed strategy to tackle the disease in question.

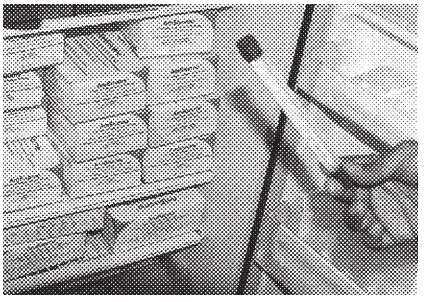
It is often said that donations are not a sustainable solution to combating these diseases. But, given the typical poverty of those infected, their far-flung locations and the need for efficient public health strategies to address the overall burden of these diseases, donations are the most helpful and most viable solution.

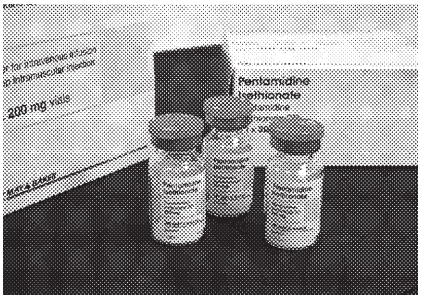












DRUGS: THE QUEST GOES ON

Developing new medications has always been a major challenge in the battle against NTDs. For human African trypanosomiasis (sleeping sickness), leishmaniasis and Chagas disease, creating and administering better medications is of central concern.

The list of requirements effective drugs must satisfy is long. As the majority of medications used against NTDs are dangerous for patients and complex to administer in remote facilities, introducing new ones means overall strategies must be modified, because drug requirements largely guide existing strategies.

Meanwhile, the roster of existing drugs is limited, and the development of new ones has proven to be a lengthy process. The major questions are:

→ How to reduce severe side-effects (including, in some cases, death)?

→ How to reduce the amount of hospitalization required, so that treatment is more practical and less burdensome?

→ How to avoid resistance to the old drugs?

In other words, is it possible to develop effective, safe, and easy-to-administer drugs for these diseases?

There are three possibilities – testing combinations of existing drugs, improving existing ones, or developing new ones. An initiative launched in 2002, the Drugs for Neglected Diseases *initiative*, or DND*i*, has revolutionized the way drugs are developed. Efforts now are shared by pharmaceutical firms and research institutes, and clinical trials are organized with the collaboration of national control programmes for the targeted diseases. Compound libraries also are shared.

The joint efforts of different partners (DND*i*, Institute of Tropical Medicine (ITM)-Antwerp, Epicentre, Médecins sans Frontières (MSF), Swiss Tropical Institute (STI), etc.) have allowed the successful testing of different drug combinations, such as nifurtimox–eflornithine combination therapy (NECT) for treating sleeping sickness. In addition, new drugs are being developed in close collaboration with DND*i* and the pharmaceutical industry. The promising drug, fexinidazole for sleeping sickness, for example, is now being developed in collaboration with DND*i* and Sanofi.

Improvements are being made to several existing medications thanks to the new collaborative landscape. Amphotericin B had been used to treat leishmaniasis, but was not very effective. A liposomal form was developed by Gilead Sciences, but it was expensive and required lengthy hospitalization. Following further research, the medication has been improved. It is now available as a one-shot treatment, and a generous donation from Gilead has solved the problem of cost.

The new approach shows that effective organization and partnerships can help to solve the scientific/technical challenges posed by these diseases, and that dramatic improvements in treatment can be achieved.

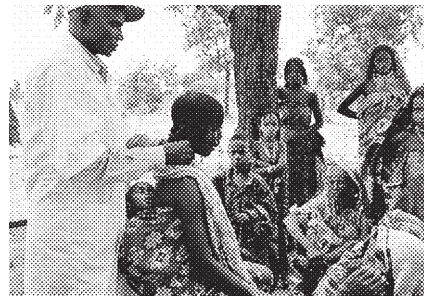
THE IMPORTANCE OF EARLY DIAGNOSIS AND TREATMENT

Added to the dilemma of diagnosing NTDs is the fact that early treatment yields the best results, and is most often safe.

Unfortunately, the early symptoms of these diseases can be ambiguous, mild or lacking altogether. When the illness becomes obvious, it is often too late to avoid permanent disfigurement, disability or death. For Chagas disease, if treatment is not given during the early “acute” phase – although the term “acute” is misleading, since the symptoms can be hard to detect – the progression is hidden, lasts for decades and is ultimately irreversible.

It is a characteristic of these health threats that those infected often do not consider themselves “sick” enough to visit the doctor. Impoverished people in remote regions of developing countries are rarely in perfect health. Usually they just get on with life. An additional problem is that health workers in such areas often make errors in diagnosis. They misinterpret the unspecific symptoms that are present and go on to prescribe incorrect treatments. If a diagnosis is incorrect or not made, individuals harbouring infection are vulnerable in the future to a serious or even fatal illness. They can also spread the disease to others. When a number of people are in this situation, the rate of transmission in communities and surrounding regions can be very high.

The maximum number of infected people must be identified as early as possible if the aim is to: diagnose and cure as many patients as possible; avoid the use of dangerous drugs wherever feasible; limit the complications that occur with advanced cases; and reduce and finally end transmission of these diseases.



Over the years, public health campaigns have approached this challenge in different ways, notably by dispatching medical teams to the field to carry out mass screening and testing of everyone in a community whether or not they have symptoms. Such work is labour intensive, tiring, costly and hard to sustain over time. However, early detection is still worth the effort.

Meanwhile, research continues to find better diagnostics to make the reduction of cases more feasible and efficient.

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"THE EATER OF MEN"

"The British are claiming that for administering countries, three Governors are required, the first Governor in the ship (in his coffin), the second Governor on the spot (in place), and the third Governor on the ship (in order to replace the one who will become sick.")

Anonymous

European missionaries and physicians reported extraordinary fatality rates from sleeping sickness in the late 19th and early 20th centuries. Newspaper accounts, employing the melodramatic language of the time, called the disease "the eater of men."

Belgian priests operating the educational colony of Berghes Sainte Marie, opened in the Congo in 1890, said they had begun the undertaking with 1143 children and adolescents. By the time the colony was abandoned in 1898, almost all had died. Only 250 children remained, most of them very young and born after the institution had been founded.

Not long after, investigating physicians reported that an epidemic in the Busoga region of southern Uganda beginning in 1901 had killed 30 000 over three years. (Decades later, observing from a longer perspective, health officials determined that the epidemic had, in fact, waxed and waned until 1920, and had taken more than 250 000 lives.)

The reports from Busoga were followed by the findings of Cuthbert Christy, a member of a British scientific expedition sent to Africa to study the alarming spread of the disease. Dr Christy determined in 1903 that two thirds of the population of Buvuma Island, in Lake Victoria, had recently died from sleeping sickness.

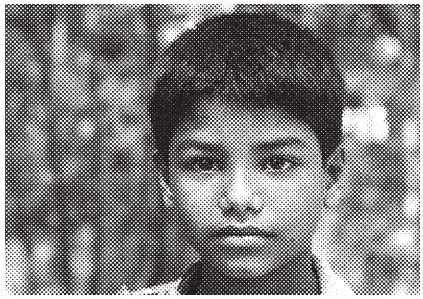
The press accounts reinforced the fearful, mystical image of the tropics in the northern public imagination, while the heavy toll taken by the outbreaks raised serious concern among European governments about the future of their African colonies.

ELIMINATION AND ERADICATION

Eradication has a wonderful appeal – it is what people want after they have solved a problem. They want to think that they can relax, and not worry any more. An eradicated disease cannot return.

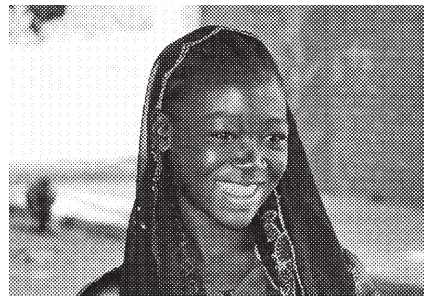
Unfortunately, reaching such a point is extremely difficult. To date, among diseases affecting humans, only smallpox has been eradicated.

Because sleeping sickness, Chagas disease and leishmaniasis have non-human reservoirs, there is no realistic chance that they will ever be eradicated. It is necessary to plan for a future of committed surveillance and response. There is some hope for yaws, which spreads only from person to person. Even in that case, however, the subtle and ambiguous early symptoms make the disease a difficult target.



In comparison with eradication, elimination of NTDs is an achievable objective – although "elimination" can have varying definitions. If the process of fighting them is thought of as a continuum, one starts with epidemics, which are characterized by a very high level of prevalence requiring emergency measures in response. Prevalence that is somewhat less high can still present a heavy burden for populations, and can require serious and sustained efforts to reduce the number of cases. In some situations, low numbers of cases can be regarded as satisfactory, but if the diseases are well embedded in local environments, relaxing or reducing control measures is often a serious mistake. They can rebound quickly. In fact, it is at the low rate of prevalence where the issue of elimination arises and must be carefully considered.

The first step is to define what amounts to "elimination of a disease as a public health problem". It is a political and social decision: what number of cases is acceptable to governments? Whatever the decision, resources and a strategy must then be dedicated to maintaining that level. Simply stopping efforts at case detection and care does not maintain the requisite low level of infection – it invites resurgence.



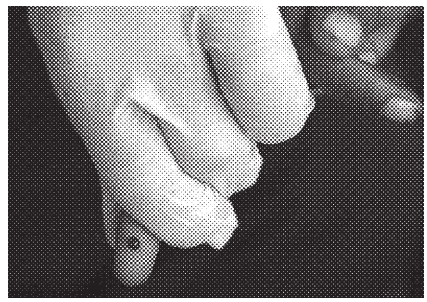
A more intensive response to a very low level of cases is to aim for reducing the number of infections to zero within a given country or area. That is a more difficult goal to reach but, as illustrated by India in the case of yaws, it can be done. The status of zero cases needs to be verified, which is not an easy task. But once that point has been reached, maintaining cases at zero is easier than maintaining cases at a stipulated low level. However, effective surveillance mechanisms must still be established and maintained.

IS ELIMINATION DIFFERENT FROM ZERO CASES?

Use of the term “elimination” rather than “eradication” is a question of a sensible choice. Indeed, eradication means extinction of the disease worldwide and it is achieved only when the disease infects no one else and when no other hosts or reservoirs are infected. Once that point has been reached, natural risk of reintroduction is impossible. But “elimination” means reduction to zero of the incidence of infection only in a defined geographical area, Continued actions to prevent re-establishment of transmission may or may not be required.

The 2020 target for some NTDs is to achieve “elimination as a public health problem”, which means that effective control had led to a reduction of transmission and burden of the disease such that it ceases to be of public health importance.

If the term “elimination as a public health problem” rather than “elimination” is used, it is probably because the exact number of cases is not the most important matter; what matters is the level of acceptability. Just as people agree to some reductions in their freedom in exchange for security following the social contract theory, people may accept a low number of cases. That is why the definition and achievement of this level are important. But then, when this level is reached, or when the elimination is close, sufficient political will is required to sustain this reasonable level. If eradication of a disease is impossible, sustaining a low level of cases can be very complicated because of the link between the number of cases, and the level of international interest and commitment.

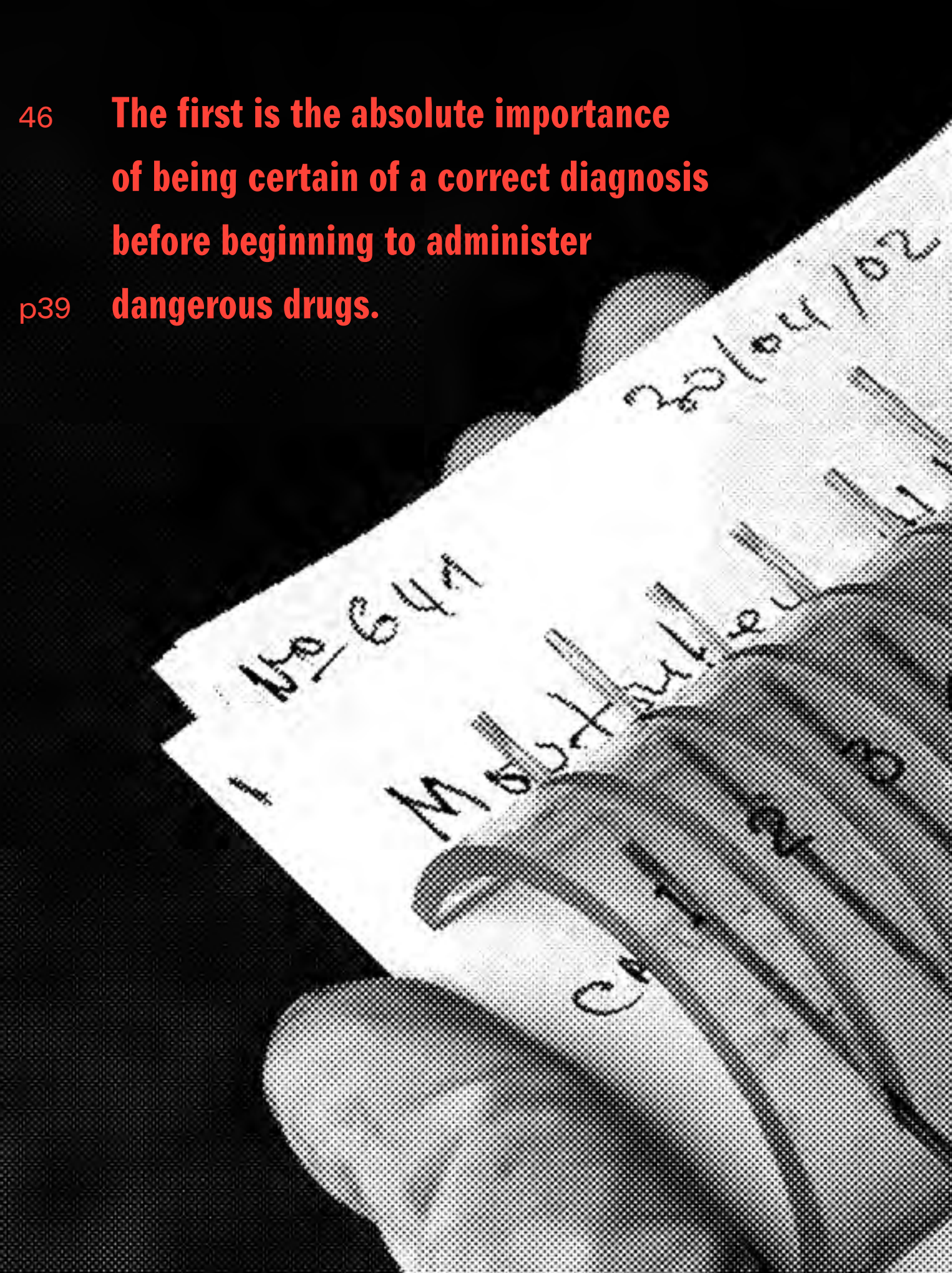


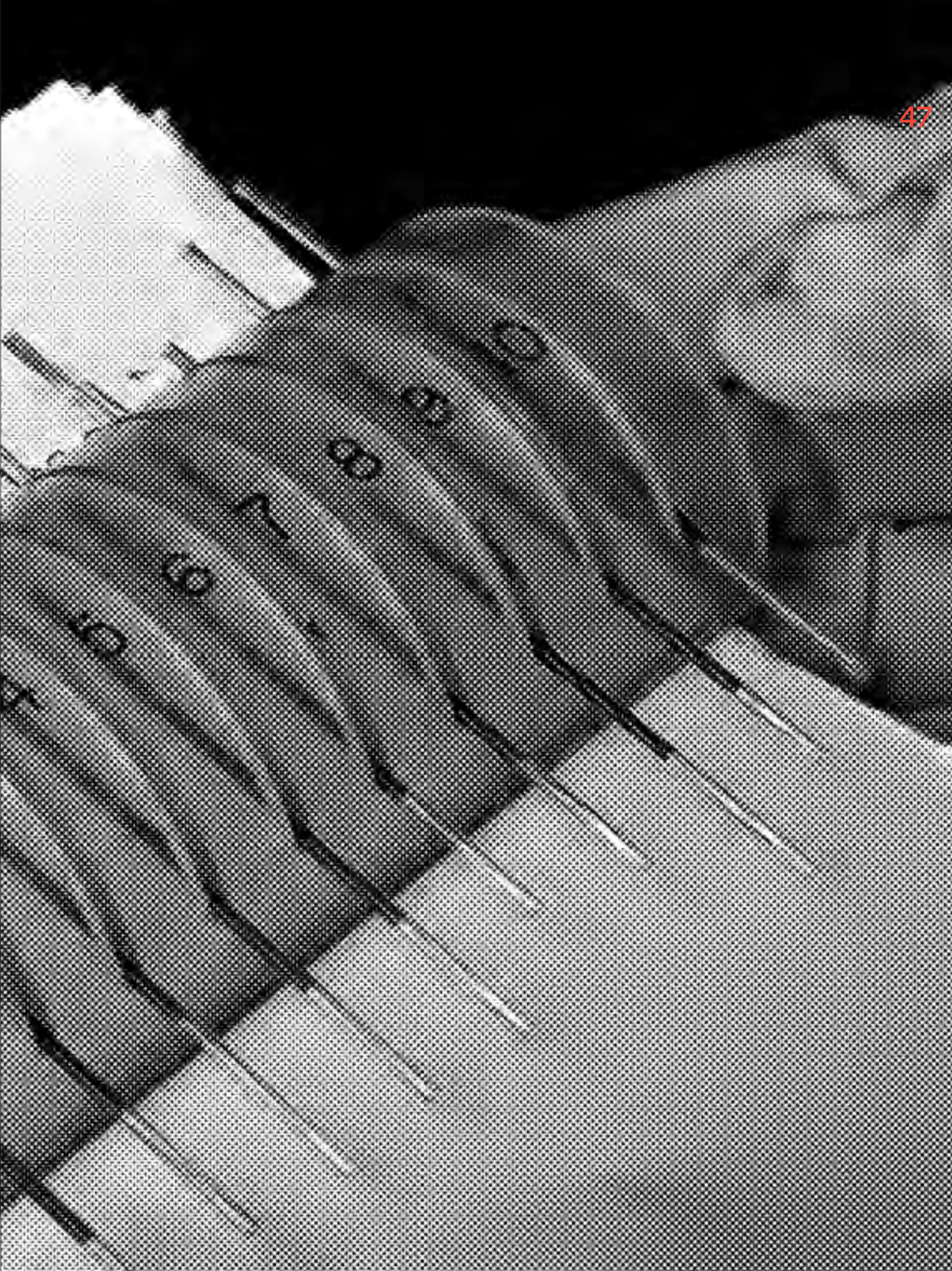
This is why many diseases have the same dismal history. When there is an epidemic, interest is high and strategies are implemented. International interest wanes when the number of cases decreases and the elimination of the disease as a public health problem is achieved.

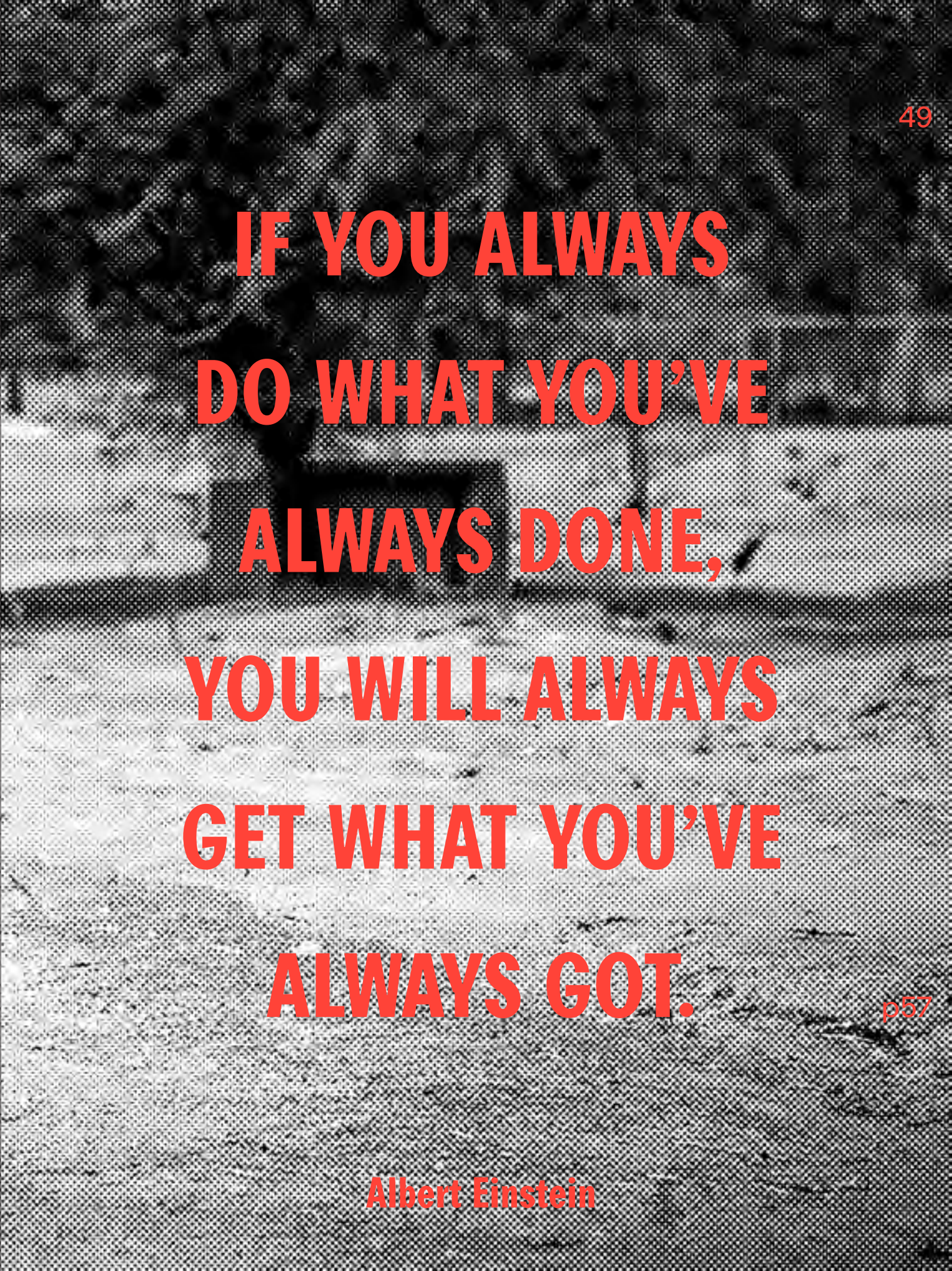
If health actors are still sensitized and interested in the fight, the number of cases will continue to decrease and a reasonable and acceptable low level of cases will be maintained. If the fight is abandoned, resurgence and a new cycle of crisis and response will begin.

46 **The first is the absolute importance of being certain of a correct diagnosis before beginning to administer**

p39 **dangerous drugs.**







IF YOU ALWAYS DO WHAT YOU'VE ALWAYS DONE, YOU WILL ALWAYS GET WHAT YOU'VE ALWAYS GOT.

p57

Albert Einstein

It also means that calculating average prevalence based on the entire population of a country provides very little useful information for policy decisions.

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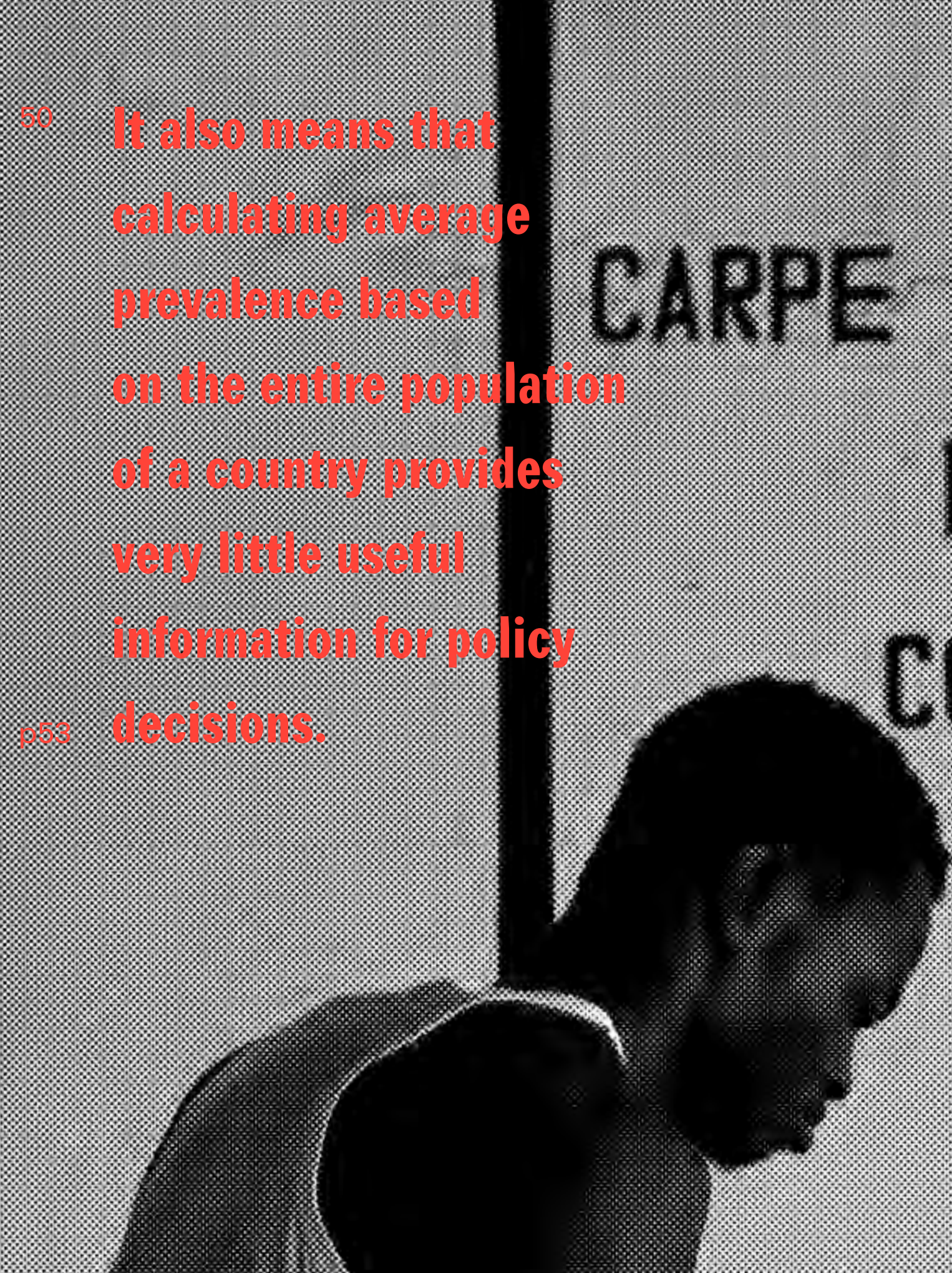


MENUS

FRITE ET BRAISEE

MAQUEREAU BRAISE

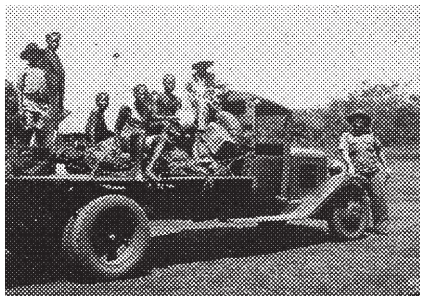
OTTELETTE DE BŒUF

1/4 DE POULET

SOUPE VIANDE

SOUPE POISSON

ANOTHER FRANCO-ANGLO SPAT



The French and British colonial administrations were confronted by the same health disaster in the early 20th century but tackled it with different approaches. The French principle of the systematic screening of populations for sleeping sickness – based on rigorous organization and standardized treatment carried out by mobile teams – was almost completely the opposite of the British approach, which was based on district hospitals.

The British approach had the disadvantage of granting only nearby populations the chance for early diagnosis and care. The results were alarming. The worsening situation in Ghana led the administration to create a Committee on Human Trypanosomiasis in 1934. The Committee concluded that the threat of future epidemics was serious enough to warrant an immediate survey to map the infected areas, followed by a mass treatment campaign to care for those infected. The entomologist, K.R.S. Morris, and the physician, G.F. Saunders, were sent to the Gold Coast, and the administration established a formal Trypanosomiasis Campaign led by Morris, Saunders and the epidemiologist B.B. Waddy of the London-based Royal Society of Tropical Medicine and Hygiene.

In 1937, the campaign reported sleeping sickness-induced depopulation in the Lawra District, and in 1938, Morris concluded that there was a major sleeping sickness epidemic in the valleys of the Kamba and Kulpawn rivers, tributaries of the Black Volta. In the 1940s, local officials confirmed Morris's findings, citing examples of widespread depopulation in the northwest. Between 1949 and 1959, colonial officials discovered additional outbreaks in the northwest and northeast.

These continuing crises stimulated internal debate over the effectiveness of the district hospital approach, and, as early as 1932, Jamot was asked to organize a control service in Nigeria. A trial was subsequently made in the Gold Coast using a few mobile teams based on the French model, but the effort was undermined by poor resource allocation and by a lack of conviction – intrusion into indigenous populations was opposed by British philosophy, and officials were not in favour of the coercion the French used to ensure that screening campaigns were thoroughly conducted.

As the outbreaks continued, Waddy attempted the mobile-team approach again in 1951, but internal resistance once again hindered the programme. Discouraged, Waddy resigned in 1955, and British efforts over the years focused mainly on vector control.

In a later article in The Times, Waddy confessed his admiration for *homo medicus colonicus gallicus* (French military doctors), referring to them as "a battalion of eccentrics".

WIDESPREAD, YET FOCAL

Sleeping sickness, Chagas disease, leishmaniasis, Buruli ulcer and yaws have broad endemic ranges but are not spread evenly. Cases typically occur in clusters, explaining many of the complexities involved in dealing with them.

To begin with, there is the matter of perspective. If the health minister of an African country looks at the figures and sees that only a few hundred domestic cases of a disease have been reported, they may decide the disease is not much of a problem. On the other hand, 40% of the inhabitants of a particular village may be infected. For them, it's a huge problem. Is it worth a more intensive response, when resources are limited? What is the correct choice?

The focal nature of these diseases also means that active detection and screening methods are justified in some areas, whereas passive detection and general surveillance methods more logically apply to the illnesses' more widespread. Decisions must be made about which methods should be used in which locations. Such choices must be made carefully, because small outbreaks can erupt into epidemics if they are not properly managed.

Each disease focus has its own specificity and its own prevalence level. The consequence is that control measures must be adapted to each of them, and cannot be applied uniformly over a vast territory. For example, there are over 650 sleeping sickness foci.

The occurrence of cases in clusters also means that different disease strains may be present or may develop. That can affect the choices to be made about preventive measures, diagnostic testing and treatment. Leishmaniasis and Chagas disease, with their many varieties, are a special illustration of this challenge. Surveillance and research have to take variations into account, and public health officials have to make astute decisions on which public education programmes to use, and where. Populations in remote places need to be aware of the dangers these diseases pose, but they also need appropriate information, as symptoms and response measures may vary.

When campaigns are developed to eliminate NTDs, all foci must be taken into account, one by one, and prevalence figures must be measured separately.

The focal characteristics of these diseases imply that elimination processes must include convincing governments and donors that the burden of a disease is linked to a particular district or community. It means that, in the same country, a disease can be the most frequent cause of death in a specific location and anecdotal in another. It also means that calculating average prevalence based on the entire population of a country provides very little useful information for policy decisions.

For advocacy and fundraising campaigns, the focal nature of these diseases also makes it difficult or misleading to use a single figure in describing their burden.

"EVEN FREE OF CHARGE IS TOO EXPENSIVE FOR US"

"Drugs are donated for treatment, but what good do they do if cases are detected too late? Understanding this, the company donating the drugs also gives WHO the funds needed to support active screening …

Industry commitment continues because my staff took the company's CEO and senior executives on a field trip to Africa last month. These executives saw the people, the illness, the lumbar punctures under the mango trees, the cases detected, and the medicines given. Seeing the people, being eye-to-eye with their misery, has great power to motivate the right kind of public-private partnership …

Results build trust, and with trust, commitment escalates."

p66

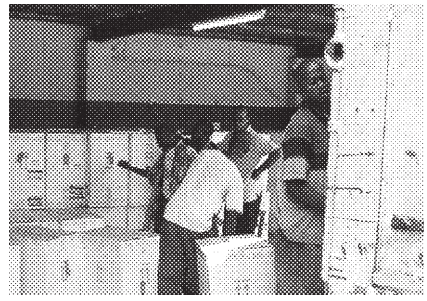
Dr Margaret Chan, 2012

A few years ago, a representative of WHO enthusiastically told an African minister of health that the pharmaceutical firm Aventis had agreed to provide drugs against sleeping sickness for free.

The minister responded that, "Even free of charge is too expensive for us."

He was proved right and the phrase "free of charge is too expensive" subsequently became a motto for campaigns against NTDs.

The reality is that a drug, free of charge, does not get the job done. It does not guarantee delivery to remote populations, as someone has to pay for it to be shipped and distributed. It also has to be correctly administered, which means that health staff must be trained.



After training, money must be found to send those staff members into the field. A free drug, moreover, is of no use if the people who need it are not diagnosed. Active disease-screening programmes are costly, especially if performed in remote locations. Passive screening, where patients seek diagnosis, requires that health centres be constructed and staffed in locations where people can reach them.

Discussions of donations to the campaign against NTDs now routinely include consideration of the costs of access, training, diagnosis and related expenses. Participating pharmaceutical firms, including Sanofi, Bayer HealthCare and Gilead Sciences, regularly contribute to the costs of delivery as well as providing medications free of charge.

GLOBAL PATHOGEN STEW OF HUMAN, ANIMALS AND VECTORS

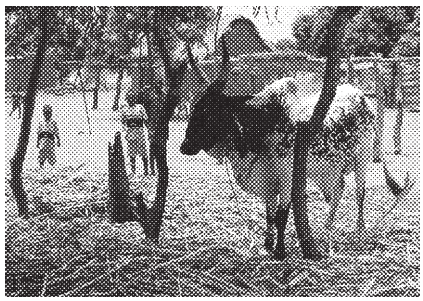
«Rien comme la forêt tropicale ne peut donner la mesure de la faiblesse de l'homme».

(A tropical forest, more than anywhere else, exposes the frailness of man.)

p100 *Anonymous*

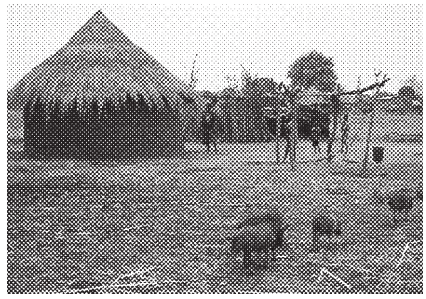
So many billions, and we all must live together. Seven billion people, 1.3 billion cattle, 1 billion pigs, 2 billion smaller ruminants, 500 million dogs and cats, 50 billion poultry reared annually, vast unknown numbers of wild animals, over 200 million insects for every human on earth, all deeply connected and interdependent. Living together and unable to live alone…

In direct and indirect ways, we need each other. We also make each other sick.



Animals, humans and NTDs are strongly connected. Controlling the diseases is immensely complicated. The parasites and bacteria that cause the diseases – with the exception of the bacterium that causes yaws, which spreads only from human to human – infect animals as well as humans. Flies, bugs and, in some cases, rodents and other creatures serve as vectors that take tropical-disease pathogens from one host to another. Opportunistic and adaptable, the pathogens shelter and reproduce in these various homes. In addition, they evolve and diversify – there are now some 20 *Leishmania* species. They turn the world into a vast biology experiment. The more closely people interact with animals in endemic regions – which happens extensively among impoverished populations living in tropical forests and savannah – the more they suffer the consequences.

The ability of these diseases to survive in more than one host adds to the complexity of tracing, isolating and eliminating the diseases. Killing off farm animals is not an option because people need to eat. Treating animals as well as humans to end or prevent infection has been tried, but in developing countries, where resources are limited, providing direct health care to animals is most often not a priority.



The vectors – tsetse flies for sleeping sickness, triatomine bugs for Chagas disease, sandflies for leishmaniasis – can and have been attacked over the years, but the task is daunting. It is hard to rid the world of billions upon billions of insects. And the methods that might be used against them, such as pesticides, increasingly have to be considered for their impact on human health and the environment. (Dichlorodiphenyltrichloroethane (DDT) was once considered a miracle method for eradicating tsetse flies and malarial mosquitoes until its cancer-causing properties and wide natural damage were better understood.)

Human-animal-vector complexities teach the hard truth that there is no miracle way to defeat these diseases. The difficulties are probably one reason why, in the past, certain tropical diseases have been neglected. The current approach is to accept the difficulty, to face the complexities, to attack on as many fronts as possible and to do what can be done with the tools available. Strategies are developed based on a thorough understanding of hosts, vectors and disease behaviour.

HUMAN AFRICAN TRYPANOSOMIASIS

Human African trypanosomiasis or HAT, but also known as sleeping sickness, is a deadly disease caused by infection with the protozoan parasites *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*. The parasites are transmitted to humans through the bites of infected tsetse flies. This disease has been endemic in Africa since prehistoric times, with occasional large epidemics. It has had a major impact on the development of African populations. The first written description compatible with a HAT case appeared in 1374.

Tsetse flies are found in sub-Saharan Africa, but there are regions where tsetse flies are found but sleeping sickness does not occur. Rural populations whose livelihoods depend on agriculture, fishing, animal husbandry, or hunting in endemic regions are most exposed to the flies. The disease is found in 36 African countries and threatens the lives of millions of people. The *T.b. gambiense* parasite (98% of reported cases) is found in 24 countries in West and Central Africa. The *T.b. rhodesiense* strain (under 2% of reported cases) occurs in 13 counties in eastern and southern Africa. If diagnosed, HAT is curable; if untreated, it is fatal. People may be infected for months and even years without noticeable symptoms. In the first stage after infection, the trypanosomes multiply in the blood and lymph systems, causing unspecific symptoms such as bouts of fever and headaches. The second stage is reached when the parasites cross the blood-brain barrier and infect the central nervous system. It is marked by more significant and progressive symptoms. These include disruption of the sleep cycle – hence "sleeping sickness" – confusion, behavioural changes, sensory disturbances, poor coordination, coma and, ultimately, death. Treatment differs for each stage and is more complex for the second stage. Determining if a case has reached the second stage is important but can be a delicate matter. Lumbar punctures have to be performed, sometimes under difficult conditions, to determine if the parasite is present in the cerebrospinal fluid.

Sleeping sickness is controlled mainly by mobile teams – which screen entire village populations – and by patient diagnosis at health facilities. Detecting and treating all infected individuals reduces the reservoirs of the parasite, and fewer flies are infected as a result. That can halt the spread of the disease. There are also methods for reducing tsetse fly populations. This can be effective, as the fly is the only vector for transmitting HAT to humans.

Surveillance of the disease, and the diagnosis and treatment of cases, is complicated because most of those affected live in remote areas with limited access to adequate health services. In addition, population displacement, war and poverty contribute to the spread of HAT. Occasionally, the disease is diagnosed outside of Africa in travellers or migrants who have visited or lived in endemic areas.

In a context of upheavals resulting from armed conflicts, which led to the collapse of national health systems, HAT cases surged in the 1990s. Estimated cases climbed as high as 300 000 annually. National responses lacked resources and coordination. A major breakthrough was negotiated by WHO in 2000 when pharmaceutical firms manufacturing antitrypanosomal medicines agreed to resume production of the necessary medications in sufficient quantities, and to donate them. The firms also agreed to support other costs to ensure access to treatment – a significant charitable act. The five medicines currently used against the disease are donated by manufacturers to WHO and distributed free of charge to endemic countries. Under the direction of WHO, and with the help of national control programmes, NGOs and bilateral cooperation, the number of cases was reduced by 90% between 2000 and 2014.

I

THE CONCEPT OF INNOVATION

"If you always do what you've always done, you will always get what you've always got."

Albert Einstein

p48

Innovation is not research. Innovation can reassemble things or concepts in a different way so that a solution is found or a process is improved.

Innovation means conceptualizing and doing things differently. It implies adapting methods and tools, mixing new and old, and testing novel ideas in search of better results. It is the concept Pascal illustrated when he said, "Words differently arranged have a different meaning, and meanings differently arranged have different effects."

Innovation also can be illustrated by the enlightenment phrase *sapere aude*, or dare to think.

The process of innovation is critical to eliminating NTDs. They have been around for hundreds and even thousands of years. Ending their long-term neglect is itself an innovation, and new ideas, approaches, methods, and combinations of tools are crucial if they are to be defeated.

Among numerous other definitions, one of the most simple is that innovation is a combination of creativity and risk taking.

THE PATH OF INSTITUTIONAL CHANGE

"Whatever you do, or dream you can, begin it.

Boldness has genius and power and magic in it."

Goethe

Something had to be done in the 1990s. By then it was clear that many tropical diseases had been so severely neglected that tens of thousands of people were dying from them every year. Lives that could have been saved. Moreover, the trends were not looking good. WHO had long focused on tropical diseases, but had tackled them separately, seeking bilateral funding for separate programmes and struggling against the technical complexities in separate efforts. The neglected diseases fell into an awkward category: they were too "small" for major campaigns and were largely ignored by funders – and often by the health systems of countries in which they were endemic. Many of those countries invested their limited resources into fighting "bigger" diseases such as malaria and HIV/AIDS. Still, the toll of death and disability was significant and continued to rise. At the same time, bilateral funding for separate efforts against the "smaller" diseases began to decrease. When a major pharmaceutical firm ceased production of the lone remaining medication available for treating sleeping sickness, WHO, various NGOs and several philanthropic foundations raised the alarm. The pharmaceutical firm agreed to resume production altruistically: the medicine would no longer be for sale but for distribution only by WHO, and it would be used to provide treatment free of charge. An idea took hold: WHO would innovate a strategy to package these diseases together rather than tackling them separately. Considered as a group, the diseases were not too small to capture attention.

A "think tank" convened in Berlin in 2003 explored these and other ideas with major stakeholders, and the concepts were further developed during a second meeting held in Berlin in 2005. Strategies focused on: linking NTDs and human rights; the importance of sustaining progress, rather than relaxing attention when the diseases were almost eliminated; bridging gaps between research and disease control; developing more effective treatment tools and approaches; creating frameworks for new partnerships; securing access to drugs; and ensuring external financing.

These renewed efforts – and some encouraging results from the revitalized campaign against sleeping sickness – led the Director-General of WHO to establish the Organization's Department of Control of Neglected Tropical Diseases in 2005. Significant funding and cooperative commitments were obtained from a broad range of partners, including foundations, WHO Member States, pharmaceutical companies and various health organizations. As efforts and advocacy intensified, WHO formulated a "roadmap" to drive the international community forward in tackling the neglected diseases, with specific targets set for 2015 and 2020. The World Health Assembly (WHA) adopted resolution WHA66.12 on NTDs in 2013, and countries throughout the world pledged the necessary support for the programme.

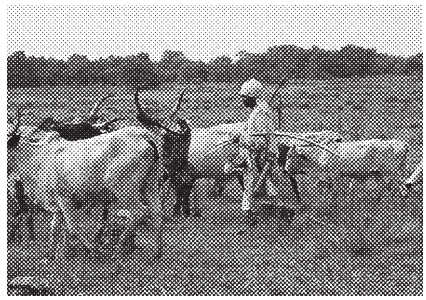
HUMANS, ANIMALS AND INTERDEPENDENCE

In vast regions where NTDs persist, animals – especially cattle – are the only wealth families have. They provide income, food, power for pulling ploughs, transportation, clothing, companionship and security. They are also deeply rooted in local cultures and traditions. The fact that humans and animals are linked in such vital ways makes the negative link in which both serve as reservoirs for disease a problem with no easy solution. Should people rid themselves of animals and starve?

Combating diseases such as sleeping sickness thus involves facing the antagonism between possible actions for public health purposes – such as stopping cattle breeding and slaughtering wild animals – and economic realities: animals have a central role in most African societies and provide milk, meat, manure and other critical products. There is the additional irony that humans unwittingly host parasites that do great harm to animals. Nagana (animal African trypanosomiasis), for example, reduces growth, diminishes milk productivity and eventually kills several species of farm animal.

Trypanosomiasis, meanwhile, is lethal for both human and animal hosts, and its economic cost to poor families is evident in the way vast regions with considerable agricultural potential are undeveloped in Africa. The heavy presence of tsetse flies in these territories makes them impractical for cattle.

Controlling infection in domestic animals may help to control tropical diseases that infect humans; in some cases, cattle have been sprayed with insecticides to deflect tsetse flies. Elsewhere in the world, dogs have been vaccinated to protect humans against rabies. Such strategies boil down to effectiveness and money.



In reality, the dilemma illustrates why it is so difficult to defeat tropical diseases. It also explains why efforts to reduce transmission have concentrated on vectors. In rural regions of Africa, families do not suffer when flies die but, if a cow dies of trypanosomiasis, it can be a devastating loss, leading to malnutrition and economic damage that means when a family member falls ill health-care costs are out of the question.

UNDER- AND OVER-INVESTING

A balance must be struck with campaigns against tropical diseases. The diseases generally occur in contexts of severe scarcity among the extreme poor. With no money, nothing can be done. But too much money injected too rapidly can cause more damage than benefit, rather like drowning a flower in water.

The application of disease-fighting resources at the local level must be carefully adapted to community capacities. If people are hired to clear brush and spray insecticide to reduce populations of tsetse flies, the rate of pay may lure so many people from farming that food shortages result, increasing malnutrition and raising food prices to a level where many inhabitants will be unable to cope.

Is investment in screening and treatment programmes matched by the availability of doctors, nurses and laboratory technicians? If they leave their usual jobs to join mobile health teams, who will care for the patients they leave behind? If they are paid too little, how will they feed their families?

The lesson that money must be carefully invested, at levels countries and communities can absorb has repeatedly been learned the hard way. In one case, millions of dollars were budgeted for a vector-control programme in a major African country. This significant investment was hampered by the fact that the country had only one qualified entomologist to oversee the effort. How could it have been done effectively?

It is vital to have enough money to battle NTDs. It is also vital to understand local conditions thoroughly so as not to waste the resources invested or, in the worst case, cause more harm than good.

JAMOT: THE DISCIPLINED ECCENTRIC

The brutal toll taken by sleeping sickness a century ago led a French military physician named Eugène Jamot to devise a revolutionary approach. Jamot, who served with the French Colonial Army Health Corps, first in the region of the former colony of Oubangi-Chari and later in Cameroon, spent 22 years battling sleeping sickness. His philosophy was simple and innovative: "if patients can't go to the hospital, the hospital must go to them". His tactic – the use of mobile medical teams – is still employed today.

Beginning in 1926, Jamot ran his programme as if it were a military campaign. It was vertically organized, disciplined, and imperative in character. Vigorous, systematic screening was carried out to detect early cases of sleeping sickness, and any cases discovered were treated immediately. The mobile teams used gland palpitation and gland puncture for diagnosis, and treated each positive case with injections of an arsenic derivative, a drug found to be effective and often used in combination with one of several other drugs.

Jamot operated under three basic principles. The first was that everyone in a village or targeted region should be there the day a team visited – that is, case detection and treatment should cover the highest possible percentage of the population at risk. Second, the teams must be self-contained, independent, and all encompassing – they should include all the skilled personnel needed and all the equipment needed to do whatever was required. His third requirement was absolute autonomy of the sleeping-sickness service in technical, administrative and budgetary matters. Jamot had zero tolerance to interference and he made many enemies.

His approach, however, was effective. The prevalence of the disease, that is, the percentage of people infected within a defined population, fell in Cameroon from 60% in 1919 to under 4% by 1930.

Other colonial administrations took note. By the late 1960s, through work by mobile teams and aggressive vector-control campaigns, the reported percentage of sleeping sickness cases caused by the parasite *T.b. gambiense* in Africa had fallen to below 0.1% of the continent's population.

KEY ACHIEVEMENTS

"Learning and innovation go hand in hand. The arrogance of success is to think that what you did yesterday will be sufficient for tomorrow."

p71

William Pollard

BURULI ULCER

The past 10 years have seen major advances in the control and treatment of Buruli ulcer. Antibiotic therapy has revolutionized management of the disease. WHO, together with its partners, has guaranteed an uninterrupted supply of antibiotics to affected countries to ensure that all patients receive treatment free of charge.

Diagnosis using polymerase chain reaction (PCR) has improved laboratory confirmation of cases. WHO has established a network of 17 laboratories in 14 countries to assist affected countries in confirming cases.

A recent innovation – thin-layer chromatography to detect mycolactone – holds great promise for diagnosis in the field. The equipment is simple and inexpensive, and yields results within one hour.

Surgical and rehabilitation skills have been enhanced in affected countries to ensure that those with complications receive adequate, high-quality care.

Standard recording and reporting forms used in all endemic countries have improved surveillance of the disease. Finally, information, education and communication materials have been developed for use in all endemic countries for training and to raise awareness.

CHAGAS DISEASE

Since the 1990s, great advances have been made in Latin America in interrupting vectorial transmission by the main domiciliary insect species, such as Rhodnius prolixus in Central America and Triatoma infestans in South America. This progress has been made through spraying homes with residual insecticides, improving dwellings (for example. by plastering cracks) and enhancing domestic hygiene to prevent vectorial infection.

Universal blood screening to prevent transfusional transmission has been implemented in the 21 endemic Latin American countries, and in several disease non-endemic countries in Europe and the western Pacific.

The launch by WHO in 2007 of the Non-Endemic Countries Initiative (NECI) continued to stimulate political impetus for the control and elimination of the disease and marked a historic signal for action in both disease-endemic and non-endemic countries.

The adoption of a new WHA resolution, in 2010, updated strategy control taking into account all transmission routes and the need for care of millions of affected people, starting at primary health care level. It also promoted sustained control actions made possible thanks to the commitment of Member States, the strength of their research and control organizations, and support from many international partners.

Implementing and monitoring blood screening to prevent infection through organ transplantation and diagnosis of infection in pregnant women, their newborns and siblings has been promoted and is being progressively implemented in disease endemic and non-endemic countries.

The "tricycle strategy", launched at the 2013 NECI meeting, stressed the need for programmes to be run with two "power wheels" (interrupting transmission and providing care in affected populations) and a "steering wheel" (an information and surveillance system). It also promoted an active strategy of diagnosis, treatment and interruption of transmission, and set up mechanisms to increase the visibility of the disease and of the people affected by it. The production of several information and training materials, the launch of the BeatChagas page and the design of courses to train health officials in the control of Chagas, in collaboration with new WHO collaborating centres, are examples of that the strategy.

Access to anti-parasitic medications has been improved by: updating the essential list of anti-parasitic medications; organizing a drug distribution system in Latin America and rest of the world for both nifurtimox and benznidazole; and linking the system to the information and surveillance of patients, and transmission routes worldwide.

HUMAN AFRICAN TRYPANOSOMIASIS

Reinforced control and surveillance activities in endemic countries through support to Sleeping Sickness National Control Programmes (SSNCPs) have markedly decreased the number of cases reported to WHO annually, from more than 37 000 in 1999 to 3762 new cases in 2014 (around 90% reduction). This is the lowest figure achieved since reliable global records of reported HAT cases became available.

To ensure access to the best treatment available, WHO supplies the medicines and the treatment kits. Most patients are treated with less toxic (arsenic-free) medicines and less than 1% with melarsoprol, a more toxic treatment. A pharmacovigilance system has been implemented to monitor the efficacy and safety of novel combination therapy, or NECT.

The WHO Atlas of HAT – an initiative to map cases at village level and control activities – is an invaluable tool for planning, executing and monitoring the process of HAT elimination. Currently, the 195 098 cases declared since 2000 are included in the database, of which 94% are geo-referenced at village level. WHO has started to build capacity at country level by providing SSNCPs with equipment, software and training on data management to facilitate ownership and use of the Atlas at local level.

A WHO Expert Committee on HAT control and surveillance was convened in 2013 to update knowledge of the disease and a new technical report was published.

The WHO HAT specimen bank supports research in new diagnostic tools by coordinating research institutions' work and helping to supply the biological material necessary to develop new prototypes or diagnostic tests.

The HAT elimination network ensures coordinated, strengthened and sustained efforts to battle the disease. This functional network includes SSNCPs, groups developing new tools to fight HAT, international agencies, NGOs and donors.

Two collaborating centres provide technical support for HAT control and surveillance: the Department of Parasitology at the ITM in Antwerp (Belgium) and Research Unit 177 of the Institut de Recherche pour le Développement (IRD), based in the Centre International de Recherche-Développement sur l'Elevage en zones Subhumides (CIRDES) in Bobo-Dioulasso (Burkina Faso).

VISCERAL AND CUTANEOUS LEISHMANIASIS

In May 2007, the Sixtieth World Health Assembly adopted the first ever resolution on control of leishmaniasis (WHA60.13).

In 2010, WHO convened a Leishmaniasis Expert Committee that led to the development of the technical report series on control of the leishmaniasis.

In order to provide policy guidance, WHO has developed a regional strategic framework and case management manuals for the control of both visceral and cutaneous leishmaniasis in the WHO Americas, Eastern Mediterranean and European regions.

WHO has also supported surveillance and provided medicines for the treatment of cutaneous leishmaniasis in crisis-affected countries such as Afghanistan, the Syrian Arab Republic and other Asian countries.

As part of strengthening health systems in areas where leishmaniasis is endemic, capacity building activities including training of health workers and provision of diagnostic and medical supplies have helped to improve access to treatment. Online courses, with a tutored, self-learning methodology, have benefited more than 5000 students during the past two years in Africa, the Americas and the Middle East.

A leishmaniasis surveillance system has been established in all six endemic countries, namely Bangladesh, Brazil, Ethiopia, India, Nepal, South Sudan and Sudan, which contribute to over 90% of the global burden of visceral leishmaniasis. Epidemiological information on leishmaniasis is now regularly updated and available at the WHO Leishmaniasis, Global and Regional Health Observatories websites.

Emergency outbreak response has improved. For example, in South Sudan more than 36 000 cases were treated with a low case-fatality rate (less than 5%) from 2009 to 2014. In the Syrian Arab Republic, more than 200 000 cases have been treated over the past three years.

In South-East Asia, major reductions have been achieved in the number of cases, from some 182 000 cases during 2005-2008 to 85 469 cases in 2011-2014 (-53%); 10 209 cases were reported in 2014. Furthermore in 2014, the target for elimination of visceral leishmaniasis in endemic areas of South-East Asia (that is, less than 1 case per 10 000 inhabitants) was achieved in 82% of sub-districts in India, in 97% of sub-districts in Bangladesh and in 100% of districts in Nepal. Those countries have adopted single-dose AmBisome as first-line treatment; WHO provides the medicine.

YAWS

Advances in yaws eradication accelerated in 2012 when researchers in Papua New Guinea discovered that a single dose of a well known and safe antibiotic – azithromycin – cures yaws in the same way as injectable benzathine penicillin.

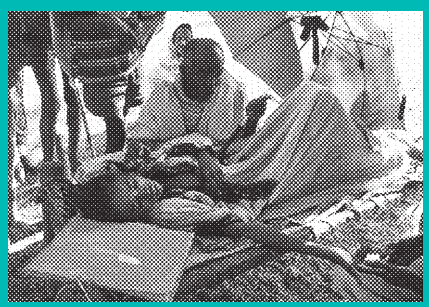
This finding marked a turning point in the treatment of yaws over the past 60 years and paved the way for WHO's Morges Strategy on yaws eradication by 2020.

The validation of a new rapid dual syphilis test allows simultaneous screening and confirmation of yaws in the field, avoiding the need to draw blood from patients for laboratory analysis using traditional methods.

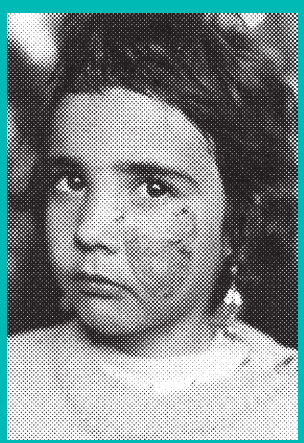
A novel PCR test can confirm yaws from samples taken from ulcers. PCR is key for monitoring resistance to azithromycin and confirming suspected cases, especially during the "last mile" of yaws eradication efforts. Finally, information, education and communication materials have been developed for use in all endemic countries to inform communities and train health workers about the disease.

LEISHMANIASIS (VISCERAL AND CUTANEOUS)

Leishmaniasis occurs in diverse forms in the tropics, the subtropics and in some temperate regions. It is caused by infections by protozoan parasites from more than 20 *Leishmania* species. Leishmaniasis is endemic in some 100 countries worldwide but it sometimes occurs in other localities when travellers are diagnosed with the disease after returning home. The parasites are transmitted to humans through the bite of infected female phlebotomine sandflies. There are three main forms of the disease: cutaneous, visceral and mucocutaneous.



Visceral leishmaniasis or kala-azar, the most severe form of the disease, is fatal if left untreated. It affects the vital organs and causes fever, weight loss, enlargement of the spleen and liver, and anaemia. Over 90% of reported cases occur in six countries: Bangladesh, Brazil, Ethiopia, India, South Sudan, and Sudan. The disease infects an estimated 300 000 people and causes around 20 000 deaths per year. Children and young adults are most often infected.



Cutaneous leishmaniasis, the most common form of the disease, causes ulcers on exposed parts of the body, leading to disfigurement, permanent scars, stigmatization and, in some cases, disability. About 95% of cutaneous cases are reported from the Americas, Central Asia, the Mediterranean basin, and the Middle East. An estimated 700 000-1 300 000 new cases occur worldwide annually.

Mucocutaneous leishmaniasis, the most destructive form of the disease, causes partial or total mutilation of mucous membranes in the nose, mouth and throat.

Control of leishmaniasis involves early detection and adequate treatment of cases, control of sandfly vectors and reservoir hosts, surveillance, behavioural change, effective communication about the dangers of the disease, and social mobilization. It is diagnosed by combining clinical signs with parasitological or serological tests. Treatment is challenging because the medicines can be toxic, are not always effective, and can be difficult to procure and store. (Often there is need for a “cold chain”). Treatment may also require long hospitalization and specialized health care.

Leishmaniasis is a poverty-related disease aggravated by many factors, including poor socioeconomic conditions, malnutrition, unregulated population movements or migrations, and environmental and climatic changes. Epidemics of leishmaniasis can be overwhelming and protracted, with high mortality rates. Epidemics are frequent in regions where there are wars, conflicts, mass population displacements, and food insecurity, as well as in difficult-toaccess areas.

Co-infection with HIV intensifies the burden of visceral and cutaneous leishmaniasis by causing severe forms that are more difficult to manage. This poses major challenges for control. HIV significantly increases the progression of visceral leishmaniasis, and visceral disease accelerates HIV disease progression.

Post kala-dermal leishmaniasis, a skin complication of visceral leishmaniasis, appears as a macular, papular or nodular rash on the face, upper arms, trunk and other parts of the body usually within six months to one or more years after the apparent cure of the visceral disease. But it can occur earlier. People affected by post-kala-azar dermal leishmaniasis pose a risk of infecting others with kala-azar.


EVEN
FREE OF

CHARGE

IS TOO EXPENSIVE

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FOR US

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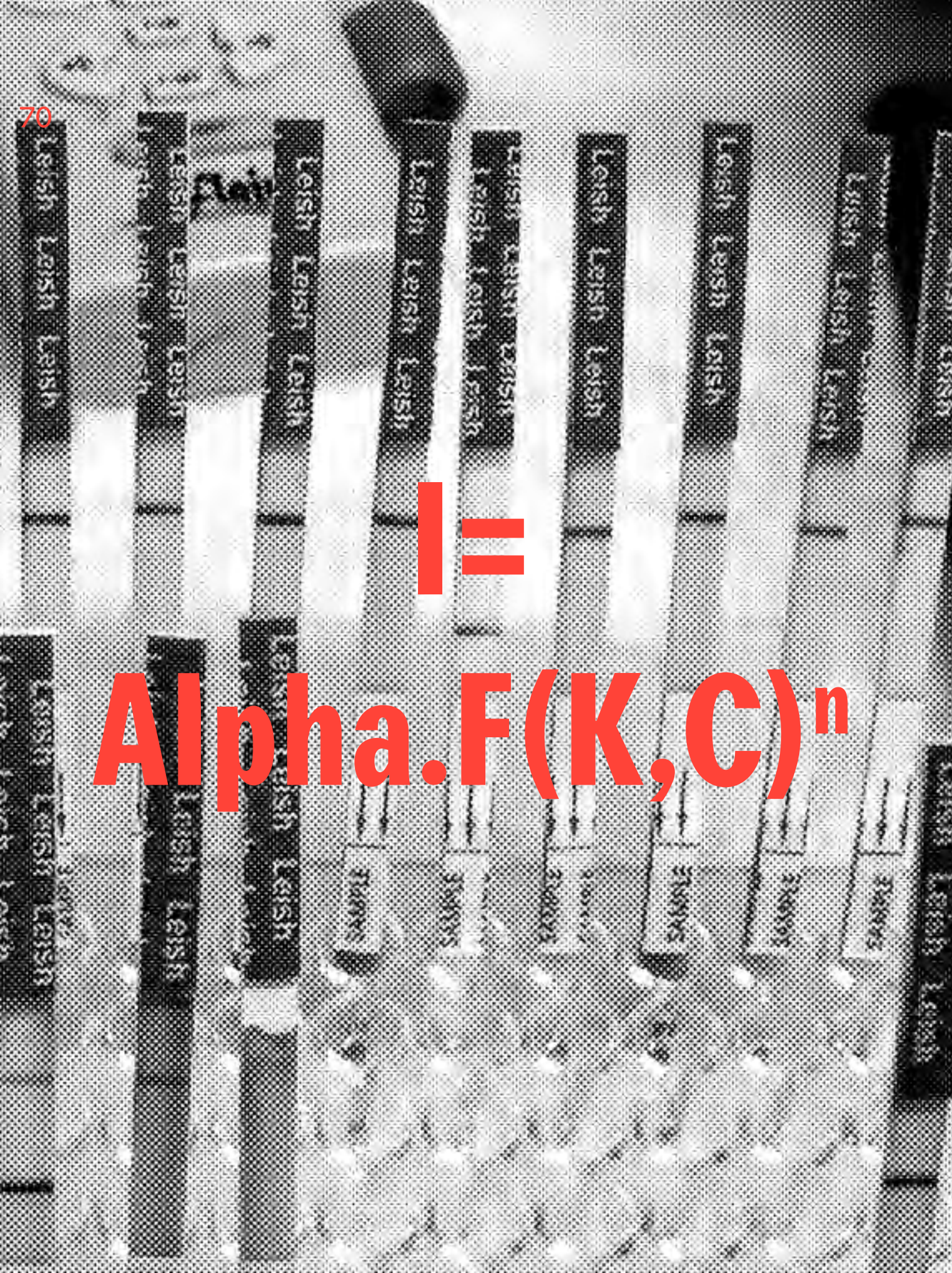

I=
Alpha.F(K,C)n

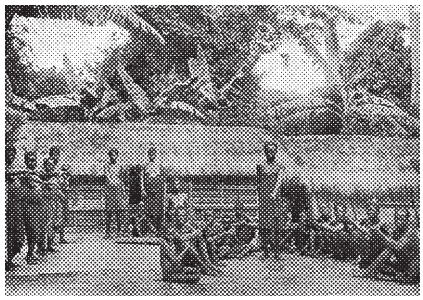
Innovation is a function of Know-how and Creativity which is multiplied by a constant Alpha (A) and raised to a power N where: Creativity is simply the methods and frameworks that we use to create new ideas and knowledge.

Know-how is the things that we already know, e.g. company history, libraries, employees skills Alpha (A) is composed of two components, a desire or need to innovate and resistance. This can make the results negative!

The power N is a representation of the maturity level of the frameworks that have been put in place to exploit innovation.

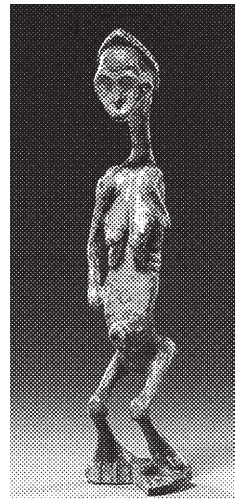
MAGIC AND DAMNED DISEASES: WHY IS IT SO DIFFICULT TO GET PATIENTS TO COME FOR TREATMENT?

One reason that it is difficult to get patients to come for treatment is obvious: if people are feeling bad already, why should they want to feel worse? News travels, and it is well known that treatment for tropical diseases can be far from pleasant. Advanced infections of Buruli ulcer require carving out the necrotic tissue with a scalpel. Lumbar punctures are needed to diagnose second-stage sleeping sickness and if the results of procedure are positive, the medications that follow have toxic and sometimes fatal side-effects.



For centuries, tropical diseases have been attributed to evil spirits. Considering the pain dealt out by the medical profession, it is no surprise that many people still prefer that view of things. Instead of visiting doctors, many go to faith healers. This longstanding custom, coupled with the tendency of rural tropical communities to isolate people who are ill, often dispatching them to traditional practitioners who carry out exorcisms, seriously complicates efforts to screen populations for disease, to identify infections early, allowing treatments to be carried out when it is safest and most effective.

At the opposite end of the spectrum, other diseases, such as post-kala-azar dermal leishmaniasis, are not considered to be as severe as they should be. People cured of potentially fatal visceral leishmaniasis prefer to think their illnesses are over; having sought treatment, they sometimes do not think they need additional medical care because a few skin lesions have appeared. But post-kala-azar dermal leishmaniasis poses a high threat of disseminating visceral disease to others. It contributes greatly to expanding epidemics.



The terse phrase used by medical field workers for such situations is “needs education”. That is a brief way of saying that with NTDs, information often has been neglected along with everything else. In campaigns against these diseases, community education to overcome counterproductive local traditions and attitudes can be as important as research, medications and money.

MIGRATION AND TRAVEL

Migration has always been a major factor in the dissemination of diseases. Through population movements, pathogens can be transported and transmitted. This is the case with Chagas disease. Millions of people have emigrated in recent decades – have settled all over the world – and many, before leaving, were unknowingly infected with the *T. cruzi* parasite that causes the illness.

A large proportion of those infected will never develop Chagas disease, but the majority are able to transmit it through blood donations. Many of the younger women among them have the potential to transmit it during pregnancy and childbirth, with potentially severe consequences for their children. It is important to take measures to prevent the risk to themselves and to their progeny. Although there is no risk of dissemination of the pathogen endemically in these cases because the insect vector is lacking, the individual risk for those infected is significant.

More and more people travel with every passing year. Most are ignorant of the risk posed by tropical diseases, and the cost can be high. Tourists have been infected with sleeping sickness, for example, while visiting game parks in East Africa. If they return home to temperate regions and fall ill, it can be difficult for their physicians to diagnose a disease they do not expect to see. Leishmaniasis also frequently infects travellers. The main danger in such cases is misdiagnosis and the consequent lack of appropriate treatment, or treatment that arrives too late to save patients' lives.

DON'T WAIT: OR THE MIRAGE OF THE MAGIC TOOL

Why treat patients with an arsenic-based drug knowing that they have a 40% chance of enduring excruciating side-effects, and a 10% chance that the medication will kill them? Why perform emergency lumbar punctures of children in non-antiseptic locations?

The answer is that the battle against NTDs is not being carried out in the realm of theory. If 10% of patients die, the other 90% will survive, and while many suffer terribly, that is better than dying.

There is a recurring debate about whether funding and time are better spent on research to develop new and more effective treatments for these diseases. This argument posits that treatment should wait until better tools are available, and that focusing overwhelmingly on developing these tools will yield better results in the long run.

The philosophy behind public health campaigns is important and current efforts against NTDs do include a significant emphasis on research. But research takes time, and the guiding principle behind the current campaigns is that patients must be treated immediately with the tools at hand and not wait for a better drug. Compared to the current situation, Eugène Jamot coped with much more primitive medications and equipment when his mobile screening and treatment teams combed the African countryside in the 1920s and 1930s. By not waiting, he saved hundreds of thousands of lives.

Under the current approach, called innovative and intensified disease management (IDM), the term *intensive* comes first. That philosophy is based in part on proven experience – since at least the mid-19th century, tropical diseases, always difficult, always complicated, have thwarted the medical profession's long-awaited desire for tools to combat NTDs that never appear. But the approach is based for the most part on the conviction that when people are dying, you do what you can with what you have.

ANATOMY OF MOBILE TEAMS

Long a symbol of the challenges and drama of treating tropical diseases, mobile teams now usually travel in convoys of all-terrain vehicles. Logic continues to support the concept developed by Eugène Jamot that infections still occur in rural locations far from clinics and hospitals, and that the tropical diseases targeted are best treated if diagnosed early in the course of infection. The prerequisite for this idea is the mass screening of populations at risk, as symptoms of early infection may be ambiguous or go unnoticed altogether.

The mobile teams take with them all necessary equipment: microscopes, registries, syringes for sampling lymph nodes and blood, special syringes for lumbar punctures, tubes for centrifuges, the centrifuges themselves, reagents and equipment for serological testing, cotton wool, alcohol, disinfectants, medicines, examination tables and generators to power electrical equipment. The personnel include doctors, nurses, specialized technicians, laboratory technicians familiar with specific procedures, cooks and drivers. All the equipment that the staff needs for an extended trip is also packed, such as tents, mattresses, food, clothing and spare petrol.

Screening patrols are carefully prepared. Populations are alerted several weeks in advance to ensure their attendance when the teams arrive. Anyone who misses an opportunity to be diagnosed – and, if necessary, treated – will not have a second chance for a considerable time, as teams generally spend only one day at each scheduled location. Infected people who miss a screening may well pay with their lives.

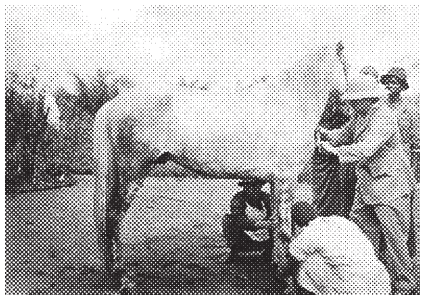
The highly organized process examines from 500 to 700 people per day. During the course of a single trip, up to 20 000 people may be screened. Current tours generally last three weeks – an impressive logistical feat, but one that pales in comparison with the marathon efforts of the past.

During the 1950s, mobile teams consisting of more than 300 doctors, nurses and technicians periodically left Brazzaville and travelled from village to village for 11 months, finally arriving at Lake Chad.

MIRACLE OR NIGHTMARE?

Medical treatments derived from arsenic have been known since 1863, when Antoine Béchamp synthesized the first treatment, which was coupled with aniline.

In 1904, this drug was introduced to treat sleeping sickness. In 1904, Paul Ehrlich proposed Salvarsan 606, which was considered the first effective medication against the disease and named the "magic bullet". With this discovery, Ehrlich developed a form of chemotherapy for which he won the Nobel Prize. In 1910, the drug was used for treating syphilis and again was considered a "miracle drug".



It is true that arsenic can be effective in treating some diseases. It is also a poison. In the case of sleeping sickness, the side-effects can be severe – almost always extremely painful, and in 10% of cases fatal. There can be a fine line between a miracle and a nightmare. Gruesome and often darkly humorous accounts have given arsenic treatment legendary status among tropical-disease specialists. One apocryphal tale has the explorer David Livingstone trekking through the east African tsetse-fly belt. His horse falls ill and is cured with a solution of 1% potassium arsenite (AsO2).

Then there is a relapse. Livingstone offers his horse another dose, but the animal turns its head and says, "Dear Dr Livingstone, I don't want your medicine. Let me die in peace." (Friedheim and Distefeanco, 1989).

In 1990, when eflornithine was approved as a replacement for melarsoprol (the descendant of Salvarsan), newspapers spoke again about a "miracle drug". But the side-effects of eflornithine are also far from pleasant.

The term "miracle drug" has since been applied many times to highly dangerous and painful drugs, including the antimonials and nifurtimox, which are currently used in combination with eflornithine for treating advanced sleeping sickness.

Of note is a pattern, over the decades, in which researchers and physicians continue to run after "miracles", and then, later, advocate for the development of newer drugs, because the previous "miracles" turned out to be a nightmares…

WHO SAYS OLD DISEASES CAN'T FIND NEW TERRITORIES? AND WHO SAYS YOU CAN'T HAVE A NEW DISEASE?

One of the common features of NTDs is that they do not spread endemically from South to North, but from South to South.

There is a serious potential threat involving Chagas disease because the triatomine bugs that transmit the *T. cruzi* parasite have a vast range, which includes tropical Asia. In fact, the triatomine bug was first identified and described in 1773 by a Swedish scientist gathering insects from that part of the world. There may be nothing keeping Chagas disease from spreading there but the introduction of the parasite.

With the exchange of populations from Latin America, including millions of migrants, many people unknowingly carry the disease with them. If such individuals were to visit or settle in Asia and be bitten by one of the insects, it could start a whole new chain of infection in the world's most populous region – a nightmarish development.

As HIV/AIDS and Ebola virus disease have demonstrated recently, it is also possible for tropical diseases long present in animals to mutate slightly – or simply to find an opportunity – and jump to humans. Growing human populations inevitably increase the chance of coming into contact with such pathogens. And environmental changes, such as the razing of tropical forests, can upset old equilibria and send parasites, bacteria and viruses looking for new hosts.

Recently, the parasites *T. lewisi* and *T. evansi*, known for infecting camels and cattle in the Middle East and Asia, have been found to infect humans. So far these cases are termed "atypical". (In fact, it is uncertain that this development is "new." It may be that this is an existing tropical disease so infrequent and so neglected that it has been causing illness in humans for years without being recognized.) But deaths have been reported and epidemiologists are worried, especially because these two parasites have macabre family connections. They are related to the trypanosome that causes Chagas disease and to the two forms of trypanosome that cause sleeping sickness. The prospect that they might mutate and move easily from camels and cattle to human hosts is of great concern. These regions of the world are volatile and complex, and human beings, whilst fighting old diseases, must always be vigilant for new ones.

WHO AND PRIVATE SECTOR: A UNIQUE APPROACH TO PARTNERING

Agreements between pharmaceutical companies and WHO's Innovative and Intensive Disease Management Unit are specific and set out clear parameters:

→ drugs are produced exclusively for WHO;

→ drugs are distributed exclusively by WHO in cooperation with recipient governments;

→ distribution is rarely done through NGOs, but generally carried out in collaboration with the national control programmes, which have the expertise to administer such medications;

→ the drugs distributed are often quite toxic; at a minimum, they must be carefully and properly administered by well-trained health workers;

→ pharmaceutical firms do not participate in the distribution and administration of the drugs;

→ three of WHO's main pharmaceutical partners in the campaign against IDM diseases contribute financially to the costs of distribution and to the costs of national programmes to screen populations for infection;

→ all agreements are designed to support WHO's overall strategy for fighting NTDs.

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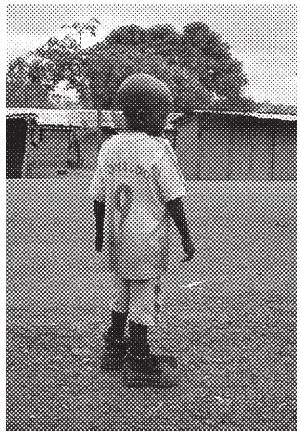
POVERTY, DISEASE, POVERTY

"The people's misery: mother of diseases."

p80

Johann Peter Franck, 1790



Governments in many regions of Africa, Asia and Latin America have scant resources available to fight tropical diseases, the victims of which are often the poorest of the poor.

The relationship between a patient and NTDs creates a double bind: both the sufferer and the disease are neglected. Living mainly in remote rural areas, with no political voice and no funds to pay for health care, these populations are trapped in a cycle of poverty and disease. Lack of proper hygiene – no clean drinking water, no proper sanitation, and no proper waste disposal – exposes them to a high risk of infection. If this were not enough, chronic malnutrition leaves them vulnerable because it weakens their immune systems. Flies and other vectors of disease thrive in these situations.

A vicious cycle develops. Poverty leads to disease, which leads to more poverty. That is especially true when coupled with other factors – armed conflict, forced population movements, illiteracy, lack of education, lack of land ownership and gender inequality. Women and children are most vulnerable and are those most often infected. The result is that new generations get off to a bad start.

For poor families, the economic impact of a serious illness is not just confined to the price of essential medicines but to the loss of income from not being able to work. Debts escalate – including time lost through not being able to carry on subsistence agriculture – with negative effects not only on the individual but also on spouses, children, elderly parents and other relatives.

In addition, even after treatment, Chagas disease, Buruli ulcer, cutaneous leishmaniasis and yaws can permanently disfigure or disable. In many cases patients are shunned socially or left physically unable to work. They become burdens on their relatives and their families are further mired in poverty.

THE PRICE OF DEVELOPMENT

"... in the evening the mosquitoes, and in the day the tsetse flies with wings raked back like tiny jet-fighters (a board above the bank at the last village had warned them in three languages: 'Zone of sleeping sickness. Be careful of the tsetse flies'). The captain read his breviary with a fly-whisk in his hand, and whenever he made a kill he held up the tiny corpse for the passenger's inspection, saying 'tsetse' – it was nearly the limit of their communication, for neither spoke the other's language with ease or accuracy."

Graham Greene, 1960

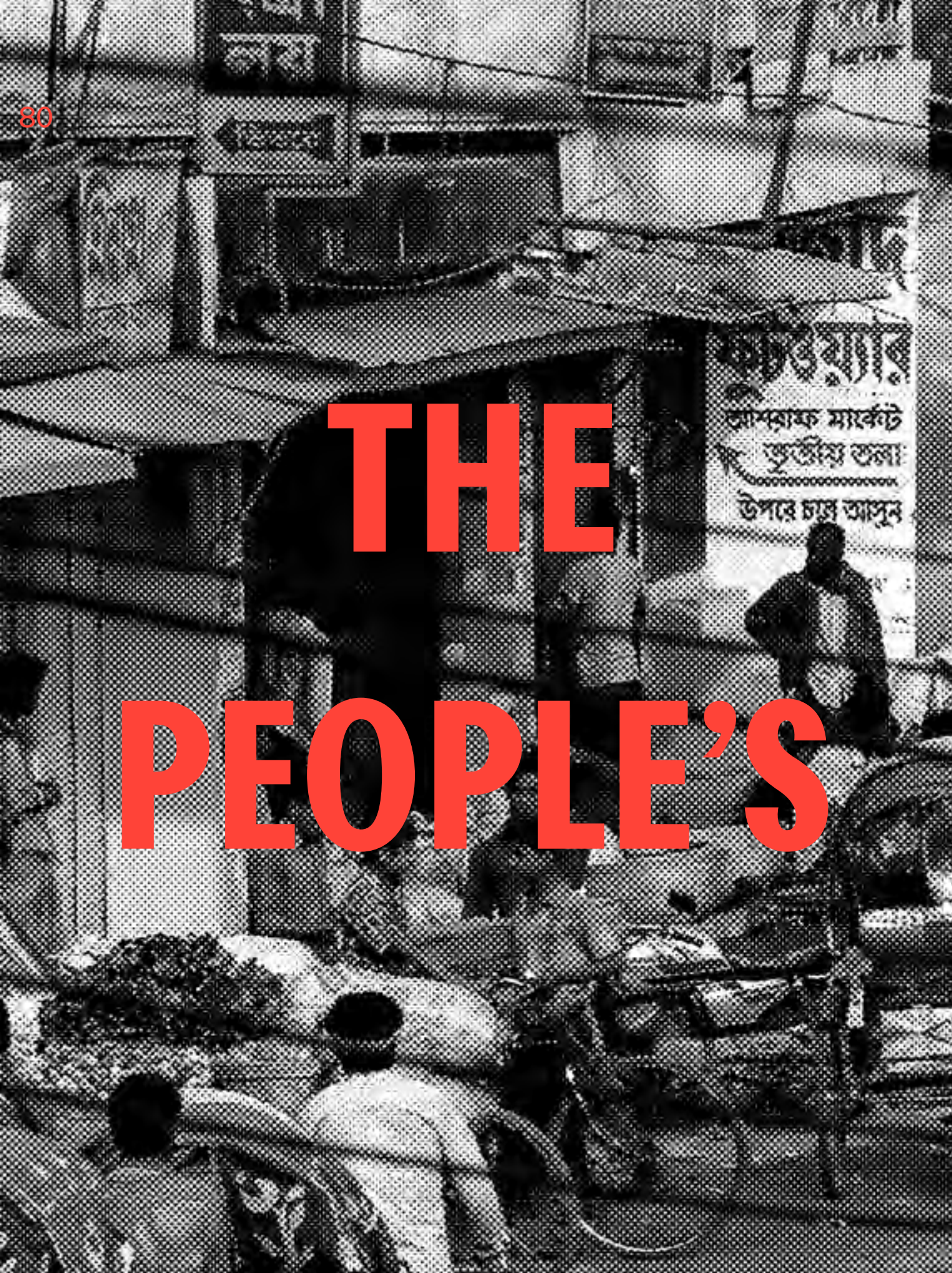
Railroads, roads and expanded travel and commerce were the aims of colonial activity in much of Africa at the turn of 20th century. The catastrophic epidemics of sleeping sickness that erupted – and the mounting caseloads of other tropical diseases – were not part of the plan. Medical and scientific research missions were dispatched repeatedly to investigate the causes and to determine what could be done.

Much was discovered about tsetse flies, trypanosome parasites, host animals, infection cycles and pathologies. Only later did it become clear that "progress" itself was a major factor. The disturbances caused by colonial settlement and expansion – mandatory population shifts, forced labour to build roads and railways, the increased travel made possible by these roads and railways – had broken down sanitary barriers maintained in the past by long distances between villages. Colonial pacification efforts also brought an end to tribal wars that had kept communities and micro-ecosystems isolated. The overall effect was to disrupt the fragile equilibrium that had been established between man and disease.

As a result, sleeping sickness and other diseases spread to new locations where human resistance was low and where there was little knowledge of how to avoid infection. In other cases, unprepared populations were installed in endemic regions.

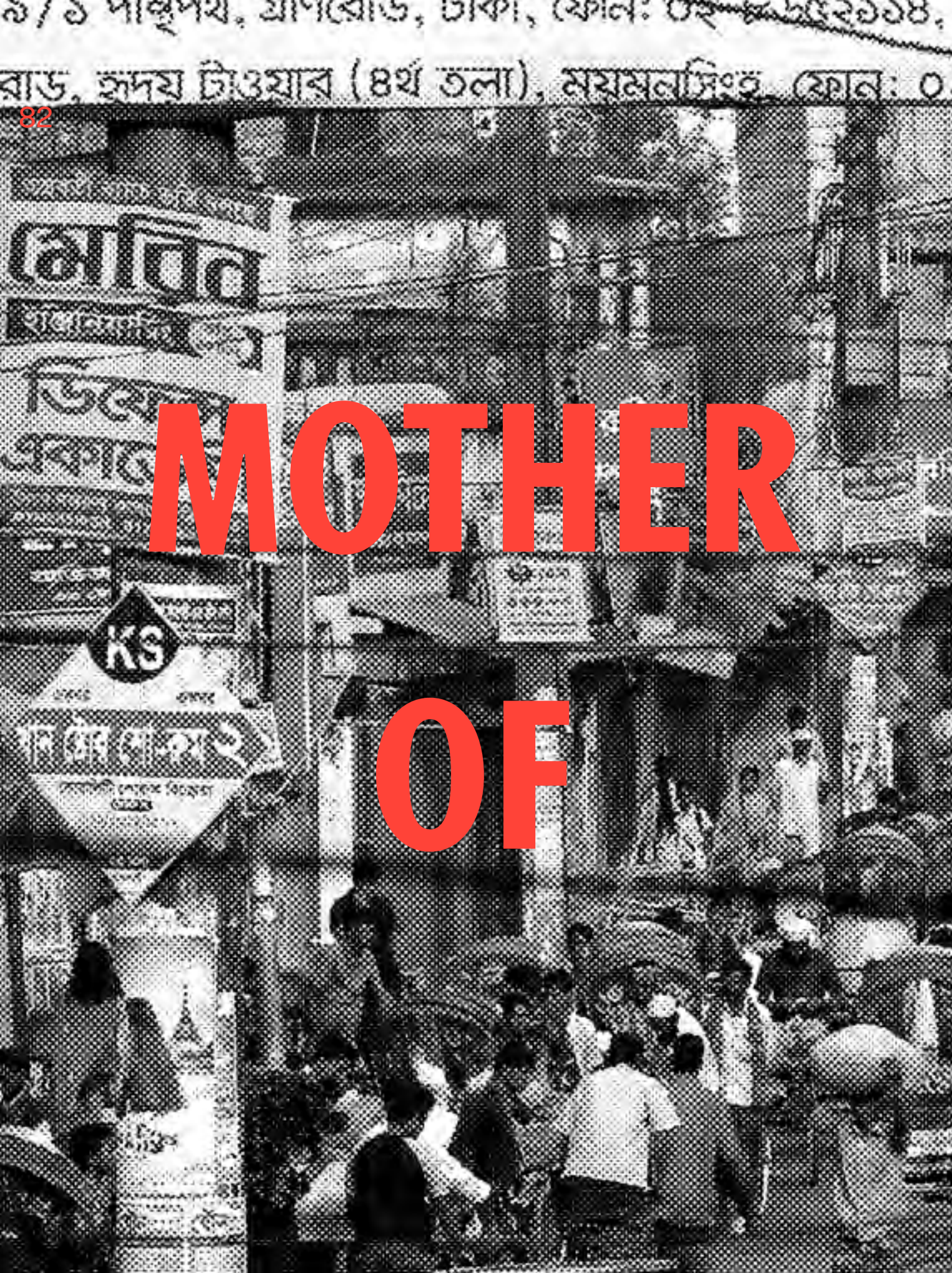
A famous example is the railway project linking Brazzaville with the Atlantic Ocean at Pointe Noire, Congo. Some 137 000 men were requisitioned to carry out construction, many from the Sara tribe in Chad. These new arrivals had little immunity to diseases prevalent in the tropical forests traversed by the railroad. More than 20 000 workers died during construction. The causes were accidents, malaria, intestinal diseases, and, in many cases, sleeping sickness. The later dispersion of the surviving workers further extended the range of the disease. The debacle led the journalist Albert Londres to write, "Every tie of this railroad should be strewn with dried flower seeds. Each seed would be a way of honouring, with each crossing, the memory of a Negro fallen for civilization."

The mixed effects of "progress" continued well into the 20th century. The Aswan dam, opened in 1967, was built to generate electricity, control flooding of the Nile and provide water for irrigation. But it also extended the range of the snails that serve as hosts for urinary and intestinal schistosomiasis, and rates of those diseases climbed in Egypt.



THE PEOPLE'S

MISERY



MOTHER OF

DISEASES

83

p78

Johann Peter Franck, 1790

84 **The more closely people interact with animals in endemic regions—which happens extensively among impoverished populations living in tropical forests and savannah—the more they suffer**

p55 **the consequences.**

FROM THEORY TO REALITY

It is interesting how often a promising new medical tool, as efficient as it may appear, turns out to be less effective than expected.

Before 2004, the only way to treat Buruli ulcer was to work on the consequences – to use radical surgery to carve out the flesh that had been infected and damaged.

After many trials, it was demonstrated that a combination of known antibiotics, when administered early in the course of infection, could cure patients. This alternative to surgery was enthusiastically embraced. WHO and its partners convened an international meeting in March 2009 in Cotonou, Benin, and issued the Cotonou Declaration on Buruli Ulcer calling for a new treatment strategy based on early diagnosis and rapid treatment with antibiotics.

But then the question arose of how to diagnose cases early? The lesions of the disease just after infection are too ambiguous to be identified with certainty by health workers, and there is no accurate biochemical test.

A possibility for such a test was identified and supported by WHO based on detecting the toxin (mycolactone) produced by the invading bacteria. The concept was shown to be workable and preliminary efforts to develop it yielded promising results.

But it may take significant efforts to go from a preliminary diagnostic tool to one that can be manufactured efficiently and used effectively in the field. Financial support for concluding the process has yet to be found.

Antibiotics are now used to treat Buruli ulcer, but the promise of the therapy is not fully realized because of continuing problems with diagnosis. As has been the case before, resources are found and committed to developing a new and better treatment with the result that additional resources are required to truly take advantage of it. The actual investment needed proves to be greater than originally anticipated and the funding (not surprisingly) dries up, stalling the achievement of the full potential of a breakthrough.

A ROADMAP OF TARGETS

To better coordinate the involvement of partners and to strengthen links between the private sector and governments, a meeting on Partners for NTDs was organized by WHO in 2010.

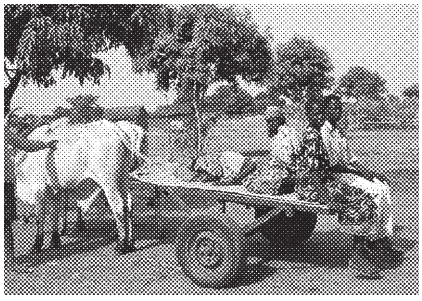
One of the main achievements of the meeting was that all partners and countries requested WHO's Director-General to prepare a roadmap marking targets to be achieved against the diseases. The roadmap involves WHO and all participating stakeholders, governments, pharmaceutical firms, foundations and NGOs.

The WHO roadmap on NTDs was presented in London in January 2012 and represents the basis on which all partners are committed. The stakeholders endorsed it at a series of events.

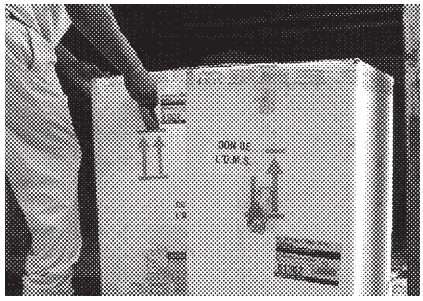
NTD	2015	2020
BURULI ULCER	Study completed and oral antibiotic therapy incorporated into control and treatment	70% of all cases detected early and cured with antibiotics in all endemic countries
CHAGAS DISEASE	Transmission through blood transfusion interrupted in the Americas, Europe and Western Pacific	Intra-domiciliary transmission interrupted in the Region of the Americas
CUTANEOUS LEISHMANIASIS	70% of all cases detected and at least 90% of all detected cases treated in the Eastern Mediterranean Region	Not Determined
ENDEMIC TREPONEMATOSES (YAWS)	Not Determined	Eradication
HUMAN AFRICAN TRYPANOSOMIASIS	Elimination of the disease in 80% of foci	Global elimination
VISCERAL LEISHMANIASIS	Not Determined	Elimination from the Indian subcontinent

REACHING THE PATIENT: THE LONG VOYAGE

The transport of drugs from where they are manufactured to where they are used is a significant expense. If for some diseases a simple pill is required, a container can bring millions of doses which then can be transferred in large quantities in a truck or in a single 4x4 vehicle. This makes the cost per unit low.



But for these unique IDM diseases, each treatment for a single patient may involve a kilo or more of medication and related equipment, such as infusion pipes, water for dilution of the drug and liquid for infusion of the medication. In addition, drugs may require transport and storage by cold chain. (This is the case with AmBisome, which is widely used to treat leishmaniasis in Africa and Asia.) Such refrigeration and temperature monitoring pose challenges in warm tropical regions. And they add significantly to delivery costs.



One treatment for sleeping sickness with eflornithine costs more than US$ 550 when transport expenses are included. There are additional expenses involved in delivering the equipment and solvents for correct administration of the drug. In total, an eflornithine kit for treating two patients weighs 40 kg and costs over US$ 1212. For treatment of late-stage sleeping sickness, distribution of a 38 kg treatment kit for NECT drug combination – enough for four patients – costs over US$ 330 per patient.

CHASING RAINBOWS VERSUS SLOGGING THROUGH REALITY

The high-tech breakthrough and the miracle drug may well become a reality. Who knows? There have already been encouraging improvements in treatments for Buruli ulcer, yaws and sleeping sickness.

If there is one lesson campaigns against NTDs has taught us dating back to Eugène Jamot's no-frills but highly disciplined assault on sleeping sickness in the 1920s and 1930s, it is that commitment, effective coordination and persistence in applying the tools already available eliminates these diseases and saves lives.

India eliminated yaws before oral antibiotic medication was introduced. It reached its goal by using the older, more costly, and more complicated method of intramuscular injections of penicillin, and by doggedly tracking down every case and giving medications to surrounding populations, year after year, for seven years. Yaws could be eliminated everywhere in the world if all endemic countries took the same approach with the same level of commitment.

Research into new treatments and methods is important, but it is also important to balance resources and efforts towards these goals to avoid interfering with or reducing effective efforts that are already under way.

There is always the danger that the search for "perfect" tools will divert capacities and attention from unglamorous ongoing daily work. But the reality is that hard and repetitive, and often discouraging work, saves lives, and will ultimately defeat these diseases if enough determination and resources are marshalled.

SAFETY AND EFFECTIVENESS TRUMP COST

The principle that NTDs must be fought in the present with the tools available has a corollary: when a new and better tool comes along, it is used, regardless of cost. It is commonplace in the business and government worlds to choose cost-effective approaches to problems but, in matters of health, the operating principles are different. Early in the campaign against NTDs, WHO and its partners established a set of non-negotiable priorities:

→ use of quality-assured drugs

→ it would use the most effective drugs

→ it would use the safest drugs

→ treatment would be administered by highly skilled personnel.

Melarsoprol was a brutal medication that for years offered the best results in treating advanced sleeping sickness. Eflornithine, a less toxic and more effective drug, has now replaced it. It is more expensive, but it is the best treatment available. The pharmaceutical firm donating the drug has agreed to this approach for ethical reasons and because it offers the greatest chance of eliminating the disease.

Similarly, better and sometimes more costly treatments – such as AmBisome – are progressively replacing the drugs formerly employed against various strains of leishmaniasis. Also, combinations of medications – such as NECT, against sleeping sickness – that have shown the best results are now routinely administered. In addition, benznidazole is now guaranteed to be available as an alternative to nifurtimox in geographical areas where it best serves to treat Chagas disease.

In some cases, money can be saved at the same time as treatment is improved. Rifampicin and streptomycin were major breakthroughs in the early cure of Buruli ulcer infections (and halted damage during later stages of the disease). These antibiotics have become the much-preferred alternative to invasive surgery and lengthy hospital stays. Ease of use in the field is another area of improvement.

A DANGEROUS SILENCE

It estimated that 7 million people have Chagas disease. Most are unaware that they are infected, and health officials consequently have no idea of the exact number of cases. Half the time, the causative parasite elicits no symptoms during early infection. In other cases, the symptoms are mild and ignored. In still others, the clues offered are ambiguous and misdiagnosed.

Largely silent to begin with, Chagas disease then falls silent for decades. Eventually, 20 or 30, or even 40 years later, a third to a half of patients suffer serious and even fatal complications caused by the slow and progressive destruction of heart muscle, digestive tracts and nervous systems.

Chagas disease is a silent killer. This characteristic makes it a huge public health challenge. Less than 10% of those infected are discovered. Treatment during the two months immediately following infection is most easily done and is almost always successful, but such treatment is given to a very small percentage of those who have the disease because the others are not diagnosed.

The challenge of finding cases early is thus the major barrier to reducing the heavy toll of suffering and death. Because it is endemic in much of Latin America, and because the *T. cruzi* parasite has numerous animal hosts, it is an unlikely candidate for elimination. Chagas disease requires massive screening programmes and extensive public-education campaigns.

Insecticide spraying and housing improvements can reduce populations of the triatomine bugs that spread the disease, but quick, broad-based detection of those infected is necessary to control it and reduce its impact. Immense commitment and resources will be required to break through the silence behind which Chagas disease wreaks its damage.

THE NEED TO REVISIT STRATEGIES

Any strategy for fighting a disease has to be reconsidered on a regular basis. Among the reasons:

→ societal changes and concepts need to be adjusted;

→ health responses should be altered as the number of cases declines or increases;

→ the health systems delivering care are themselves subject to change, sometimes improving, sometimes collapsing;

→ actions must be adjusted for varying environments and for the differing locations of patients;

→ and new tools are often introduced requiring alterations in strategy to be used efficiently.

When cases of sleeping sickness have been reduced to low levels in an endemic country, strategies must switch from the use of mobile teams to processes of “integrated passive detection” where local health workers keep a close and persistent watch for the appearance of new cases. The same changeover is necessary when the prevalence of leishmaniasis has been greatly diminished.

Another example of a strategic shift occurred in 2007, when approaches to Chagas disease were reviewed and updated. WHO and its partners recognized that the illness was not only a regional problem but also a global one, as millions of Latin American emigrants who had settled elsewhere were unknowingly infected.

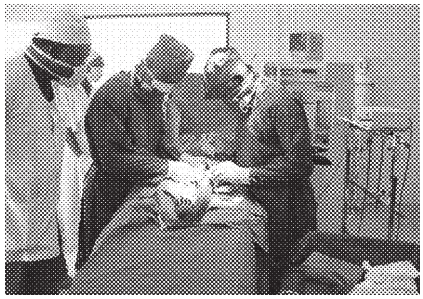
Before 2007, efforts against Chagas disease had focused on vector control and on reducing transmission through blood transfusion. The new strategy directed more attention on patients, increasing the treatment rate of acute (that is, early) cases as a way of preventing more serious complications later.

The strategy was scaled up: donated drugs were obtained; the screening of populations at risk was improved; transmission through organ transplants was systematically prevented; and new diagnostic tools were developed. Health authorities in Asia, Europe and North America participated in reducing the burden of the disease by increasing their diagnosis and treatment of Latin Americans who had settled in their countries. This enlargement of the response against Chagas disease also led to an increase in research into new diagnostic and treatment tools.

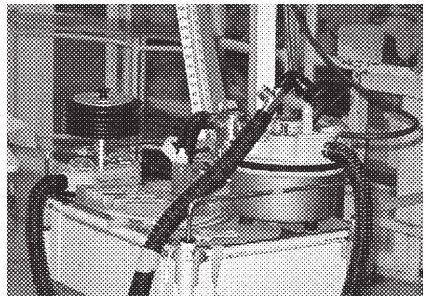
HIGHLY SKILLED STAFF 1-0: REMOTE AND DANGEROUS AREAS

Chagas disease, leishmaniasis, Buruli ulcer and sleeping sickness all require treatment by highly skilled health staff, such as surgeons, cardiologists, neurologists and dermatologists. Such specialists need to be trained on the specifics of these diseases. For example, Buruli ulcer and cutaneous leishmaniasis can be misdiagnosed as dozens of other conditions and, in its early phase, sleeping sickness is frequently mistaken for malaria.

How do you train health staff when they work in remote places? How do you reach them during wars and other armed conflicts, when epidemics of these diseases often occur?



WHO has always facilitated the training of health staff and community health workers. Among other activities, the Organization develops training materials and provides support in organizing technical training sessions and workshops.



In recent years, WHO has offered high-quality courses online, an approach that enables information to reach medical workers isolated by war or geography. Such Internet-based learning has made valuable contributions in situations where no other kinds of training can take place. For example, WHO's 12-week interactive online course on cutaneous leishmaniasis, launched in 2014, and taught in both English and French, has helped physicians in Aleppo, the Syrian Arab Republic, familiarize themselves with diagnosis and treatment of the disease, which has become widespread as civil war has destroyed that city's sanitation and public health systems. Similar online training has assisted health officials in conflict-torn areas of Afghanistan and Yemen.

THE SUSTAINABILITY PUZZLE

Sustainable is a fashionable word. Lately it has been applied to almost everything: sustainable development, sustainable energy, and sustainable climate. Ironically, it is most often used when a situation is anything but sustainable.

Sustainability is only important when a problem is under control and when a good state of affairs needs to be maintained. At which point the initial problem is often forgotten until it recurs. Sustainable control of tropical diseases is most often mentioned during outbreaks.

The most important consideration when a disease has not been eliminated is dedicating all efforts and resources to doing so. When public health programmes are efficiently and effectively conducted – and when sufficient will and resources are available – it is possible to reduce human cases of a particular disease in a particular region or country to zero. But the problem is not solved. For many tropical diseases, the causative organisms will persist in animal hosts and will still pose a threat to humans.

The challenge with sustainability is that maintaining control over an eliminated disease requires a different approach and falls into a different category of behaviour, which has not been particularly successful with individuals or with humans. Attention, motivation and funding are easier to maintain when there is a crisis. Being perpetually on guard against something that may occur loses impetus after a while.

Targeted disease-elimination programmes must eventually give way to surveillance programmes that are less costly but harder to justify as developing countries' budgets are renewed year after year with no new cases being reported, and as they mull over how best to spend their limited resources. Experience has shown the importance of preparing in advance for when NTDs are brought under control. Health systems have to be adapted and different strategies adopted to cope with the new situation. Otherwise, sooner or later, the diseases will be neglected once again and, when that happens, they will resurge. Tropical disease specialists refer to these instances of repeated history as "the penalty of success".

Sleeping sickness and yaws are prominent examples. Both diseases were virtually eliminated in the 1960s and re-emerged two decades later. Failure to maintain control over them was a tragic shortcoming of human psychology and organizational behaviour that cost hundreds of thousands of lives.

DECIDING WHEN TREATMENT STOPS

Because NTDs are complex, they cannot be avoided or eliminated only by giving drugs to patients. The fight against them needs short- and long-term actions.

→ Before treatment, by sensitizing populations at risk to increase the number of cases discovered, especially in their early stages, and by raising international awareness so that funding can be obtained an strategies developed to carry out screening missions in the field.

→ During treatment, by diagnosing patients accurately and quickly, and by treating them efficiently and thoroughly.

→ After the initial crisis, by dealing with disabilities and helping with any other long-term consequences, such as the debts run up during treatment, patients' inability to work, and psychological care, when needed.

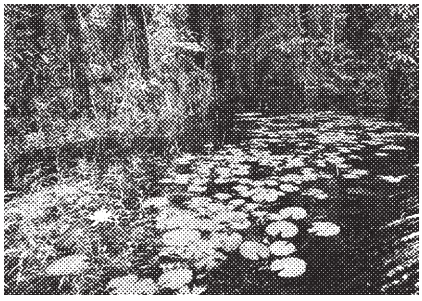
This holistic approach is the best route to defeating these highly damaging diseases. But the longer term aspects of care are often not taken into account, probably because of the costs involved.

The term used by WHO and its partners is *intensive and innovative disease management*. The diseases must be addressed immediately and intensively, and managed over the longer term. Partnerships are thus crucial to the campaigns waged against them. Help is not only needed in medical terms, it is also needed to provide human, economic and technical resources for the broader issues involved, with different partners contributing resources and effort according to their competencies. Through partnerships, it becomes possible to "cure" patients beyond the act of providing drugs. Indeed, an "infection cure" means that no more germs remain in the patient's body. But a "disease cure" may require secondary care after "infection cure" to deal with the after effects of the diseases.

This approach marks a new way of combating NTDs, and is one that promises to deliver better and more sustainable results. It is why current strategies give the same level of importance to interrupting disease transmission as they give to treating patients.

BURULI ULCER TRANSMISSION MYSTERY

In the 21st century, we have discovered the Higgs boson and the chemical composition of comets, but we still do not know how the bacterium that causes Buruli ulcer is transmitted from nature to human beings. Tropical ecosystems are so complex – and some locations are still so effectively remote – that this puzzle has yet to be solved.



For efforts to conquer the disease, and to protect people in Africa, Latin America and South-East Asia, that missing information is no small thing. Because early diagnosis of the disease remains difficult, and effective treatment with antibiotics relies on rapid diagnosis, it may be that the best way to reduce the burden of Buruli ulcer is to attempt to reduce transmission.

If people are not infected to begin with, they will not have to be diagnosed and cured. In any case, other tropical diseases are routinely attacked on several fronts: patients are treated; cases isolated and vectors reduced. This combined approach is usually effective.

Such a strategy might well be feasible with Buruli ulcer if the missing link were discovered. But the disease does not occur in massive waves of infection. It crops up in small clusters of cases, usually in remote locations. It also appears to shift from its natural host or hosts to humans in or around water. It is not easy for researchers to trace and observe this critical step. The causative *M. ulcerans* pathogen has been found in some aquatic plants and insects. There also appear to be links with polluted water. But there may or may not be connections between those findings and the infection of human beings. The specifics are still missing.

The problem vexes epidemiologists. It also is an indication that the traditional conception of the tropics as a place of magic, mystery and danger hasn't been entirely dispelled after centuries of exploration and scientific inquiry. Mysteries still remain.

A DANGEROUS AND WELL-TRAVELLED SILENCE

Some years ago, WHO received a phone inquiry from a well-known European hospital. Referred to the Department of Control of Neglected Tropical Diseases, the physician making the call asked for a specific medicine against Chagas disease. He had a patient who had recently received a heart-lung transplant. She had briefly improved after the operation, but then developed complications.

A mysterious infection was making her seriously ill, and numerous efforts to identify the cause had finally revealed Chagas disease. The medication was dispatched, but the patient died several days later.

It turned out that she had emigrated from Latin America 40 years before.

The case prompted WHO to alert non-endemic countries to the dangers posed by Chagas disease. The countries were told that diseases that could be a hidden – in some cases for a long time – could cause serious heart diseases, especially in individuals from Latin America. In addition, WHO established a network of services to help national blood banks and organ-transplant programmes around the world screen for the causative *T. cruzi* parasite, explaining that it could be spread through transfusions and transplants. Neonatal services worldwide were also warned that the illness could be passed from mothers to foetuses and infants.

As similar cases were discovered and reported far from Latin America, it became clear that Chagas disease is now a global problem. It only spreads endemically in its traditional region, where triatomine bugs serve as the vector. But with its vast estimated caseload of some 7 million people, the long and largely symptom-free duration of infection, and the propensity of Latin Americans to travel and settle in other countries, it can now re-emerge anywhere. Tourist, immigrants, expatriates are also at risk of infection, due to their high mobility. It arrives silently in people infected long ago, disabling and killing in places where doctors least expect to see or recognize it.

The vast Latin American diaspora, which grows every year, means it is likely that hundreds of thousands and perhaps millions of people have the disease and are living undetected outside endemic areas. Since the 1990s, intergovernmental initiatives have included attempts to interrupt transmission through blood transfusion – a step that applies equally to countries inside and outside Latin America – and to spread news of the disease far beyond its traditional boundaries.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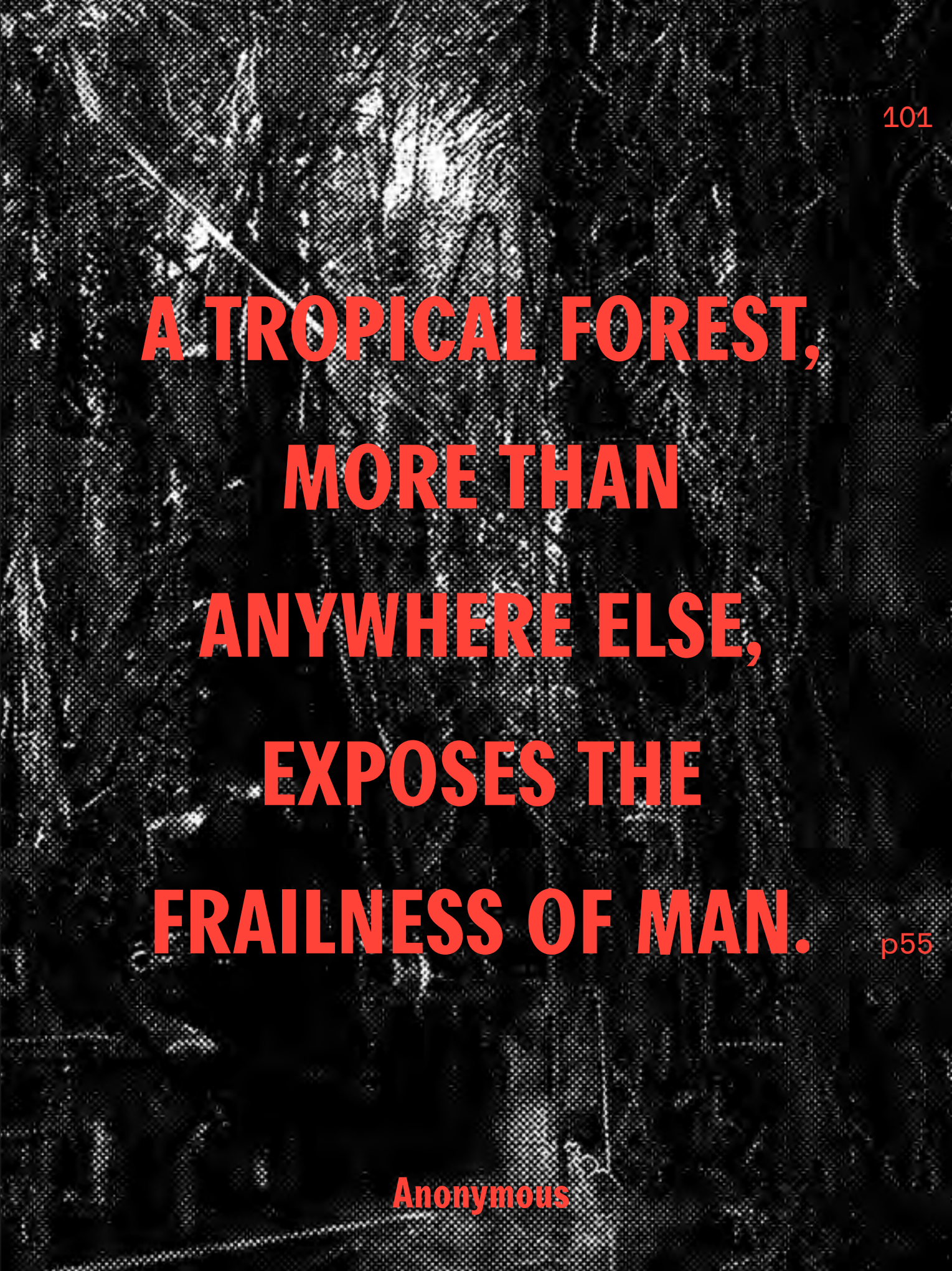
As long as poverty, injustice
and gross inequality exist
in our world, none of us
p13
can truly rest.
Nelson Mandela, 2005



A TROPICAL FOREST, MORE THAN ANYWHERE ELSE, EXPOSES THE FRAILNESS OF MAN.

p55

Anonymous

IMPROVE WOMEN'S HEALTH, IMPROVE THE WORLD.

p109

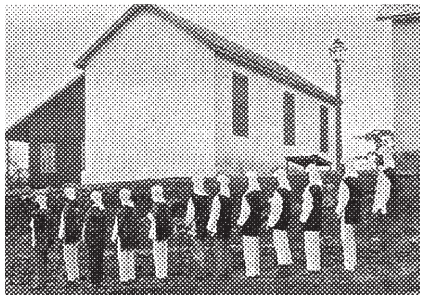
WHO, 2009

EARLY SWIPES AT VECTOR CONTROL, OR A BRIEF HISTORY OF FLY KILLING

One of the first innovations for combating sleeping sickness was the tsetse broom – which was just that: a broom. The flies, when spotted, were swept away and, one hoped, killed.

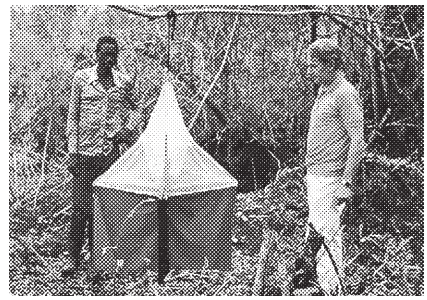
A long tradition among livestock herders in the Sudan was to use gourds filled with blood as bait to attract the flies and keep them from feeding on cattle.

The first systematic effort to trap tsetse by a colonial administration was under the Portuguese in 1911 on the island of Principe (Sao Tome and Principe) where, after several years, the flies were eliminated by some 300 field workers who wore vests of black cloth with the backs covered with birdlime. The flies were attracted by the sticky substance and were unable to escape once they had landed.



Over the years, a huge variety of methods has been tried to reduce the population of NTD vectors involving traps, screens, bush clearing, insecticides, impregnated nets, the sterile-insect technique (irradiation of male flies to stop reproduction), impregnated fences, and blankets soaked with insecticide and placed on cattle. Removing waste around houses has been found to decrease transmission of leishmaniasis by rodents. The ploughing of nearby fields has the same effect, by disrupting shelters for the vectors. Coating the walls of houses in partially settled areas of Latin America keeps triatomine bugs from hiding in the cracks between wooden boards, and lessens the chance that they will transmit Chagas disease to humans.

The breadth and imagination of these measures indicates the desperation these diseases have caused in communities and among public health authorities. Furthermore, repeated attempts (and frequent failures) to raise money for them is indicative of the competition that is rife between research efforts aimed at high-tech solutions and less “sexy” methods that still get the job done, but does not attract donor funding.



Hard decisions have to be made, and veterans of the campaign against these diseases sometimes express frustration when simple methods turn out to be more effective than complicated approaches, yet receive less attention and resources. Coating vests with birdlime was a desperate, low-tech response to a devastating epidemic of sleeping sickness, and no one is suggesting that it be repeated. But the simple method did show that the simplest of ideas could work.

A VIRTUOUS CIRCLE: WHO'S PARTNERSHIPS AND COLLABORATION

Before 1999, there was a tragic lack of access to the drugs needed for treating most NTDs. In most cases, work on new drugs had stopped. An even greater concern was that many pharmaceutical firms were threatening to halt production of existing drugs because disease-control activities were minimal and the market for the medications was limited.

The relationship between drug companies, governments, and NGOs was dramatically modified by the "Pretoria lawsuit" on access to drugs for HIV – a trial begun in 1998 and won by South Africa in April 2001. Discussion during the trial about access to drugs and the social responsibilities of pharmaceutical firms opened a new era in the treatment of diseases afflicting the poor.

Since then, for most NTDs, many partnerships and collaborative agreements have been concluded. Most drugs are now donated, and their availability is guaranteed.

Many of the companies manage the donations themselves. Others are funded by alliances and NGOs. The particularity of these arrangements is that the donations are made to WHO, and WHO is in charge of distributing the medications.

In 2001, when the first five-year agreement was signed by WHO and Sanofi (then known as Aventis) to combat sleeping sickness, it reflected a long discussion that had taken place the year before. The intent was to find the best possible way to: ensure that WHO could help countries better organize their control programmes; enable WHO to ensure the best use of the drugs against neglected diseases; and enable it to coordinate control activities worldwide. A principle was established whereby a cash contribution to WHO was added to the in-kind donation of drugs. Sanofi accepted this principle of supporting the WHO strategy, and was followed by Bayer a few months later.

This original bilateral collaboration between WHO and Sanofi has been renewed three times. It has also been extended to other NTDs. The two partners will mark 20 years of cooperation in 2020.

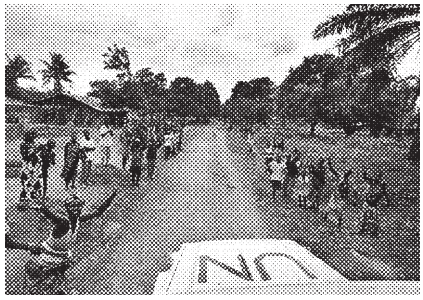
Along with supporting WHO strategies, pharmaceutical firms are contributing to the development of new drugs in collaboration with partners. They are also ensuring the future availability of these drugs by preparing upcoming donations to WHO.

These are long-term collaborations allowing WHO to provide stability for other stakeholders and enabling it to coordinate its disease-control programmes with various partners. Thus, pharmaceutical firms and NGOs are sharing and accompanying the Organization's efforts towards the elimination of these diseases.

PREYING ON VULNERABILITY

While armed conflicts and other upheavals spread many forms of misery, they play an especially prominent role in the transmission of NTDs.

Visceral and cutaneous leishmaniasis thrive in situations where systems for diagnosis and treatment break down. Refugee camps are frequent sites for outbreaks, as they tend to combine poor sanitation – which provides fertile conditions for the breeding of sandflies – with incoming populations who are malnourished and lack immunity. Recent outbreaks in camps in South Sudan and in Lebanon (where refugees have fled fighting in the Syrian Arab Republic) are among the latest in a long list of epidemics in refugee camps.

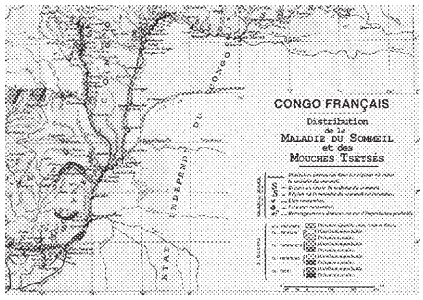


Environmental changes and alterations in landscape are another risk factor. Poor populations carrying out deforestation to establish subsistence farms often move into sandfly habitats at the same time as they remove other animal species and become themselves a food source for the flies, and a host for *Leishmania* parasites. This can lead – and has led – to rapid increases in cases.

It is apparent that global warming and other significant environmental events such as drought, famine and flooding can cause population migrations into endemic areas – or cause shifts in the location of the disease, creating new endemic areas and increasing its prevalence in human beings.

For public health authorities, leishmaniasis – and the rapid pace at which it can expand – poses special challenges. Prevention, control and treatment frequently require providing and even increasing health care under conditions that make doing so especially difficult. Often that requires finding international support, funding and personnel to stand-in for national health systems that have largely ceased to function.

WHERE ARE THE PATIENTS? AND HOW MANY ARE THERE?

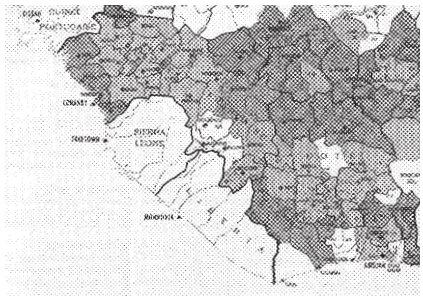


The minimum requirement for monitoring any disease control or elimination programme is to be able to respond to the question: where are the patients and how many are there?

This information is vital for monitoring progress and for understanding the epidemiology of a disease.

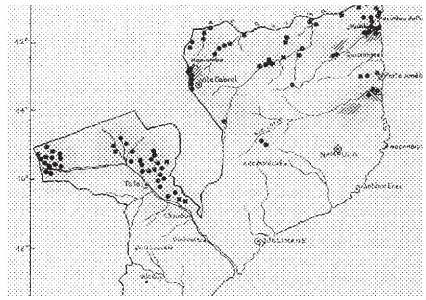
Since the beginning of the 20th century, physicians have devoted time and energy to creating and maintaining maps showing the distribution of diseases. (Regrettably, the tactic has often been abandoned once the situation has improved.)

Regardless of the tool adopted – pencil, global positioning system (GPS) or geographic software – the mapping of diseases is essential. Atlases of the different NTDs are effective tools, and are increasingly being used for decision-making and for monitoring control activities. They also are being used to test different hypotheses on how to proceed with disease-elimination campaigns.



One of the key elements of such mapping is that data need to be centralized before being released, which ensures the quality of the information and allows it to be appropriately collated.

One new tool available when the fight against sleeping sickness was resumed in 2000 was the Internet. Tropical disease specialists at WHO, working in collaboration with the Food and Agriculture Organization of the United Nations (FAO), used it to develop and disseminate a comprehensive atlas of sleeping sickness. Information on cases sent by endemic countries is entered into a database that maps its location to village level and summarizes the activities carried out in response. The database and related atlases are updated regularly. For the period 2000-2012, some 93% of reported cases were mapped. Health officials in endemic countries who need recent information consult the Atlas online. Starting with the most affected countries, WHO is building capacity to exploit the Atlas locally.



THE PILL AND THE WILL

Yaws is ripe for global elimination. This is because the causative bacterium spreads from person to person and there is no animal reservoir in which it can hide – it is vulnerable to thoroughly conducted public health campaigns.

Furthermore, because yaws causes significant suffering and overwhelmingly affects children – some 75% of infections occur in people under age 15 – there is a strong moral and practical imperative to eliminate the disease. Some 10% of those infected, if untreated, are left disfigured and disabled within five years.

In addition, it is now easier and less expensive to carry out campaigns against yaws. Since 2012, a single oral dose of the antibiotic azithromycin has replaced the previous standard treatment of a single intramuscular injection of benzathine penicillin. This latest advance means that health workers no longer have to deal with hypodermic needles, with their accompanying transport requirements, sterility and proper disposal. This is a major advantage when care often must be administered in rural, underdeveloped locations.

The term “simple” does not often come up in relation to tropical diseases, but now that a single pill can cure yaws, the best approach is a simple one: to batter it into submission by skipping the diagnostic tests and giving one 30 mg antibiotic pill to every person in every endemic region. The problem in conquering the disease is not medical or technical, it is in finding sufficient money and commitment. The new international strategy for yaws – the “Morges Strategy” – focuses on mass treatment because such an approach is logical. In fact, it worked during a trial run on the island of Vanuatu in July 2013.

At least 88 tropical countries and territories were once endemic for yaws. The eradication campaigns of the 1950s and 1960s targeted 46 countries. Currently, there are 13 endemic countries.

The dream is to eliminate a disease that has caused suffering and disability for millions of people for hundreds of years. Why not do it? India eliminated yaws in 2003 before the antibiotic pills were available – public health workers there accomplished the feat using the old treatment of intramuscular injection.

Now that a cheaper, easier method is available, it is not a question of whether the world can afford to eradicate yaws, but more a question of how it can afford not to?

W

THE CRUEL TOLL ON WOMEN

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“Improve women's health, improve the world.”

WHO, 2009

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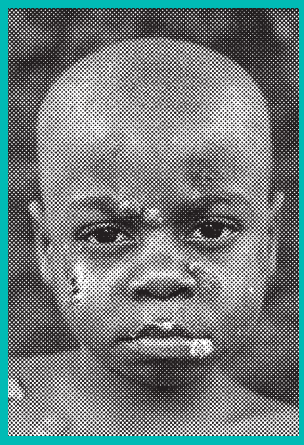
The physical suffering is severe enough. But for those who survive diseases such as leishmaniasis the psychological suffering can last a lifetime. A frequent consequence of cutaneous leishmaniasis is scarring, including of the face. Scarring often leads to social rejection, especially for women. Yaws and Buruli ulcer also disfigure, maim, stigmatize and shame. Added to the emotional pain of being an outcast is the economic suffering, as women who are shunned by their communities usually are unable to find work.

NTDs infect women more often than men, and this difference increases with poverty. These diseases can reduce fertility and, if infections set in during pregnancy, they can cause miscarriages and neonatal deaths. A further consequence is increased susceptibility to sexually transmitted infections, including HIV.

Recent conflicts in the Middle East have led to explosive outbreaks of cutaneous leishmaniasis among the desperate populations thronging refugee and resettlement camps. Women already struggling to survive and care for their children are increasingly exposed to this dangerous and demoralizing illness. Reducing the global burden of the disease would have far-reaching positive effects.

YAWS



Yaws is a chronic bacterial infection affecting the skin and bones. It occurs most often in children. If untreated, it can lead to disfigurement and disability. Yaws is found in humid tropical countries in Africa, Asia, Latin America and the Pacific. It is spread from person to person through skin contact, usually in conditions of poverty and poor hygiene.

The bacterium, *Treponema pallidum*, subspecies *pertenue*, is closely related to the bacterium that causes syphilis. However, yaws is transmitted non-sexually. The first symptoms of infection are usually painless bumps on the skin.

In the years after the identification of the causative agent in 1905, treatment often involved the use of toxic drugs, but following the discovery of penicillin it was found that a single injection of that antibiotic could produce a cure. Under the leadership of WHO, mass screening and mass treatment campaigns were deployed between 1950 and 1964; some 300 million people were screened and 50 million treated, reducing the incidence of yaws to 2.5 million, or by 95%. In one of the world's sadder public health stories, eradication of the disease was considered achieved, structures were prematurely dismantled, international attention waned, and the disease resurged, with explosive epidemics in the 1970s and 1990s.

Yaws, with no reservoir outside of human hosts, is vulnerable to efficiently conducted screening-and-treatment programmes. The strategy of mass screening with mobile teams is still implemented, and recent campaigns have seen a rapid decline in cases.

India reported its last case of yaws in 2003, and continued surveillance has confirmed that the disease has not recurred there. Because yaws is not a lethal affliction, passive detection – that is, depending on patients to come to health clinics – is not effective, and active screening, education and sensitization of vulnerable populations, along with improvements in hygiene, are important to stop transmission. Diagnosis may be based on different and complementary methods of clinical and blood tests, and more recently on PCR tests carried out in reference laboratories.

A clinical trial in Papua New Guinea in 2012 demonstrated that a single oral dose of the antibiotic azithromycin can effect a cure. That breakthrough should accelerate eradication of the disease – based on WHO's Morges strategy – in the 13 countries currently affected.

If I could catch a rainbow,
I would do it, just for you,
And, share with you, its beauty,
on the days you're feeling blue.
If I could, I would build a mountain,
you could call your very own.
A place to find serenity,
a place just to be alone.
If I could, I would take your troubles,
and toss them into the sea.
But, all these things, I'm finding,
are impossible for me.
I cannot build a mountain,
or catch a rainbow fair;
but, let me be, what I know best,
A Friend, who's always there.

Sandra Lewis Pringle

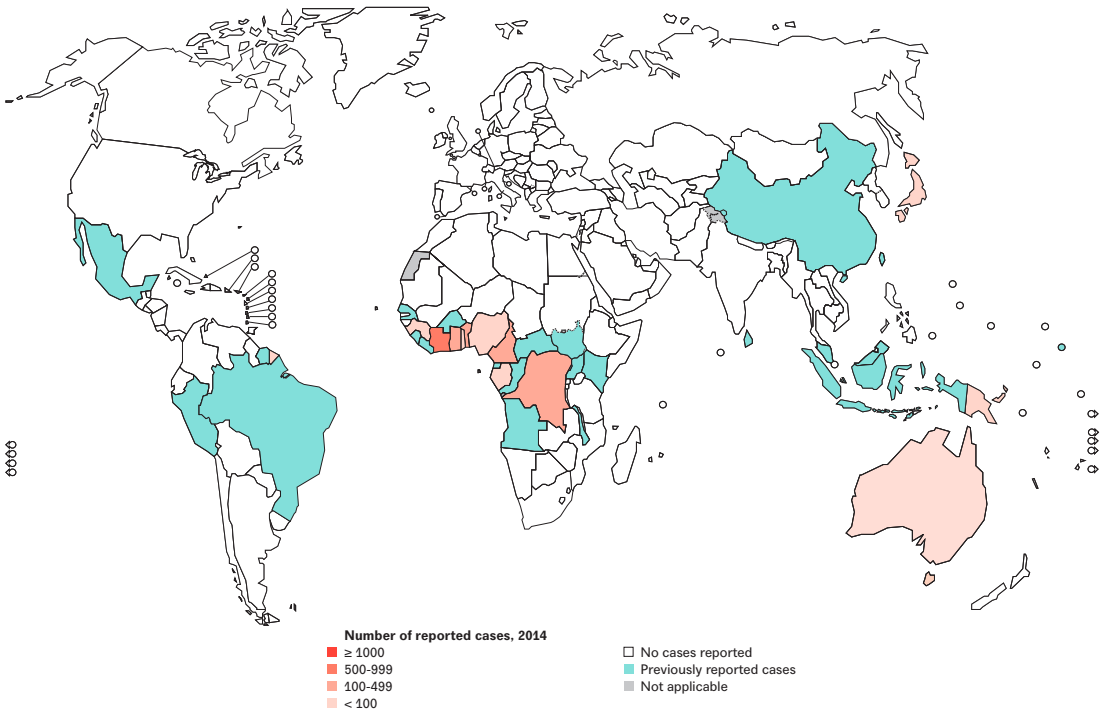
Industry is present. Your donations of drugs and other support opened an opportunity which public health has seized.

p77

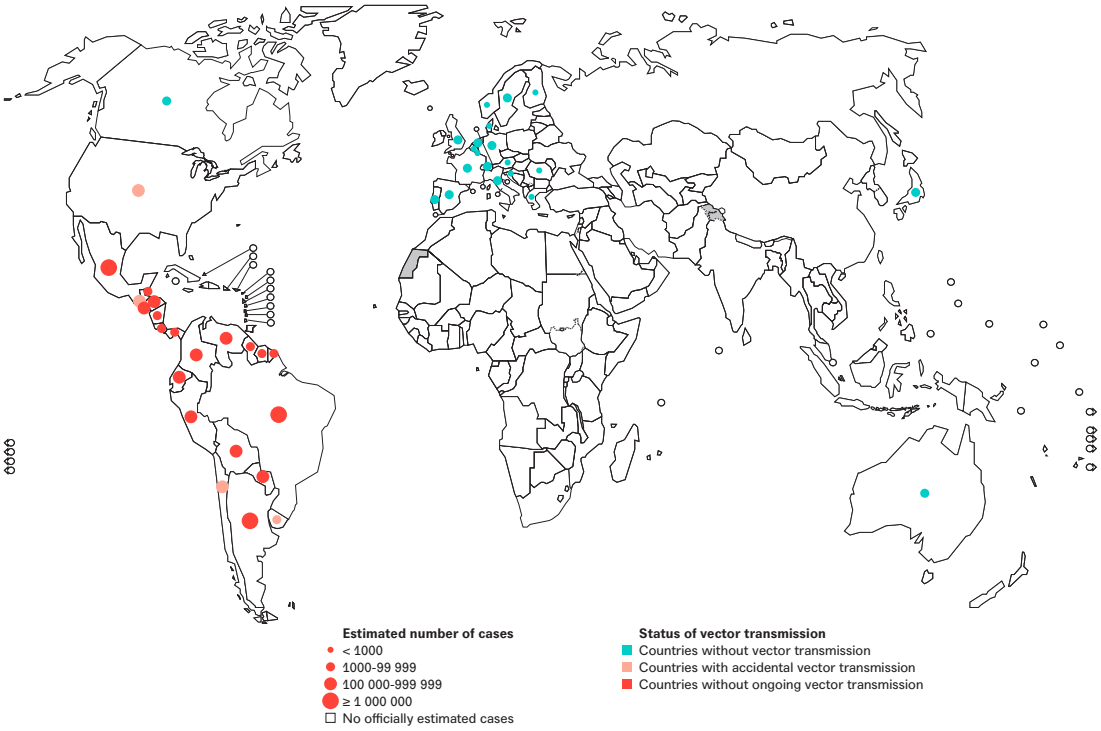
Dr Margaret Chan, 2007

FACES FROM THE BATTLE AGAINST NEGLECTED TROPICAL DISEASES

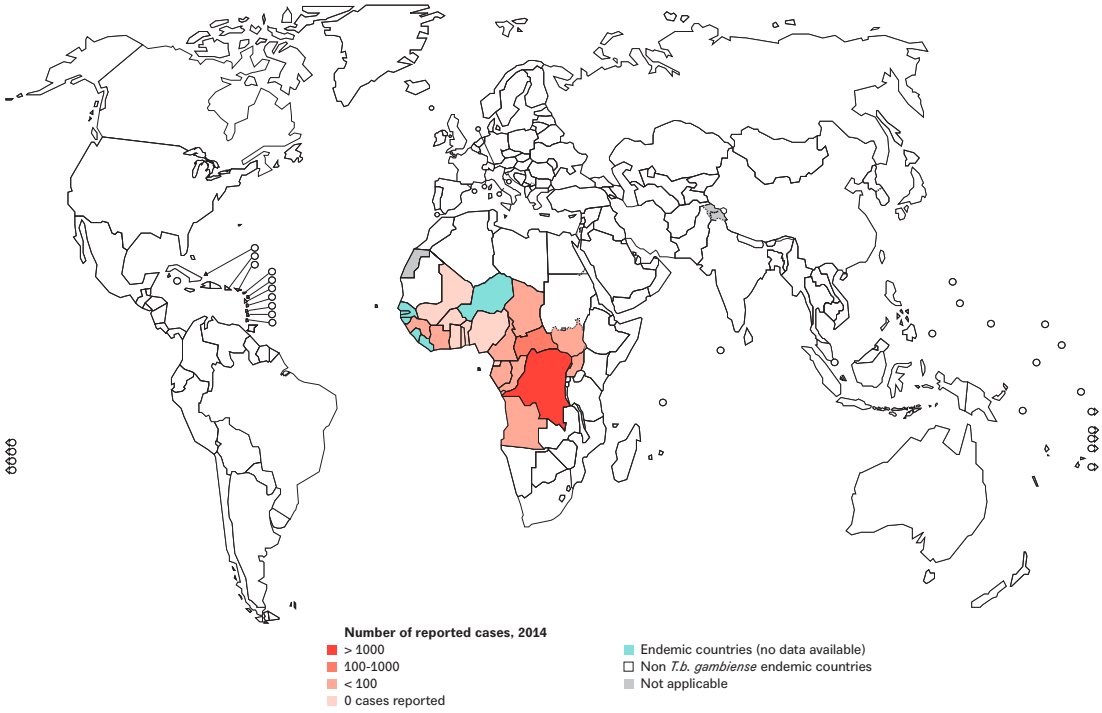
DISTRIBUTION OF BURULI ULCER, WORLDWIDE, 2014



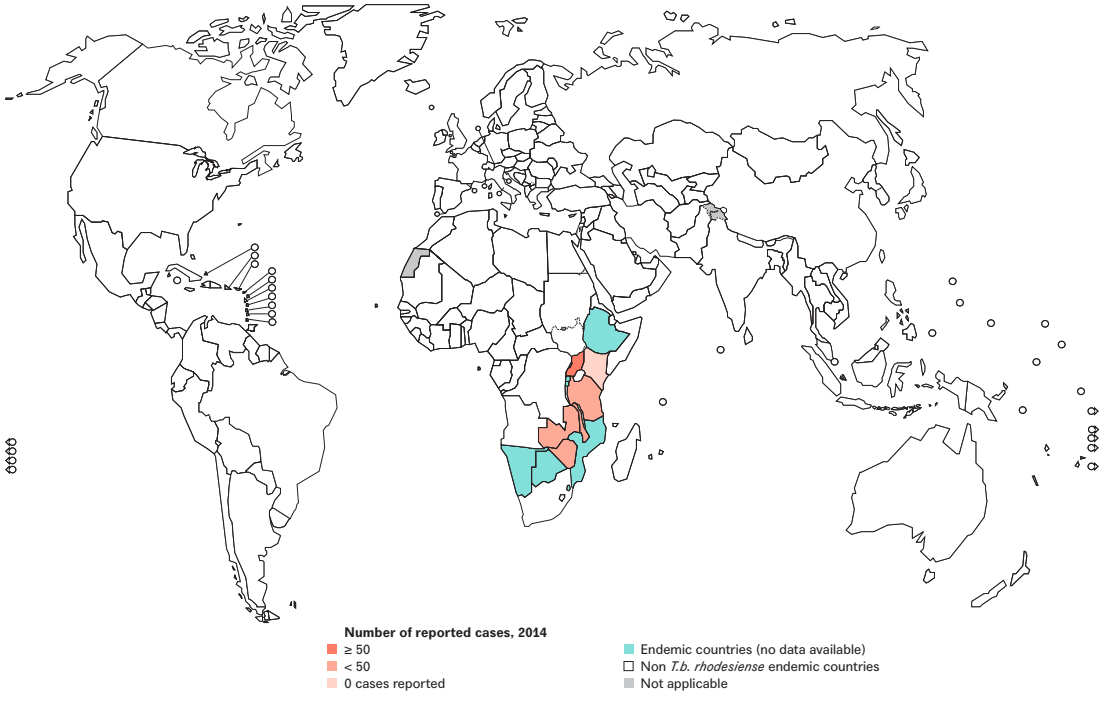
ESTIMATED NUMBER OF CASES OF CHAGAS DISEASE, WORLDWIDE, 2015



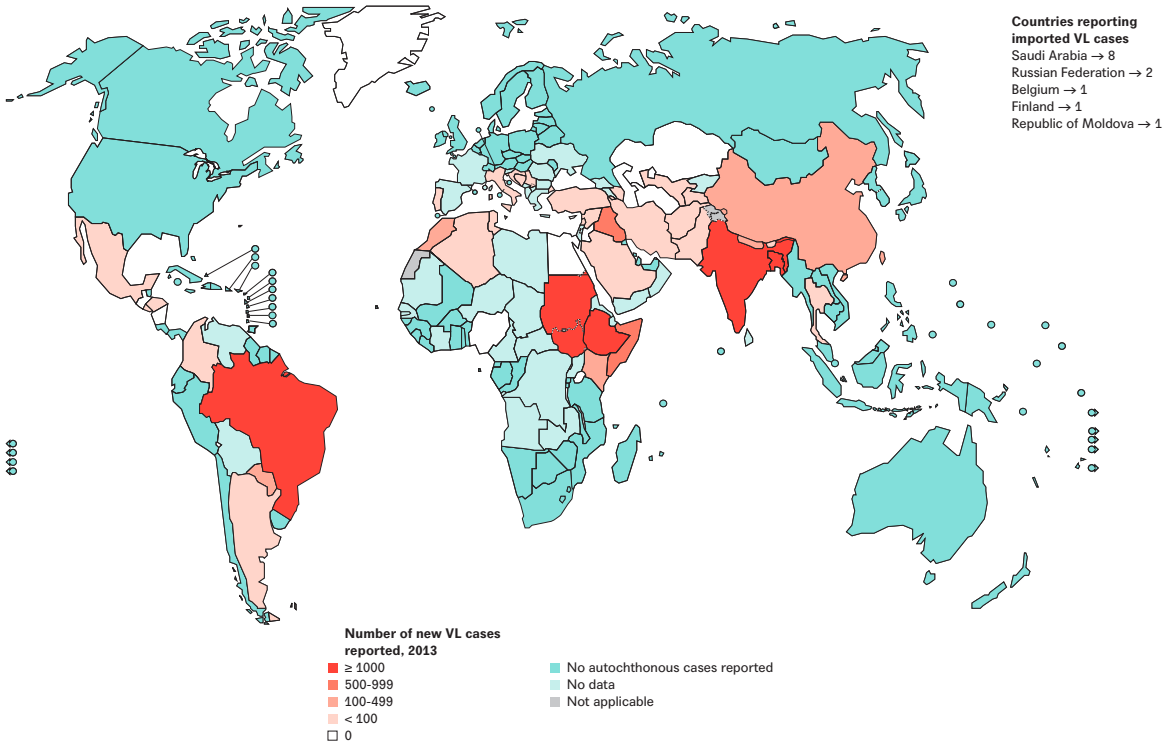
DISTRIBUTION OF HUMAN AFRICAN TRYPANOSOMIASIS *(T.B. GAMBIENSE)*, WORLDWIDE, 2014



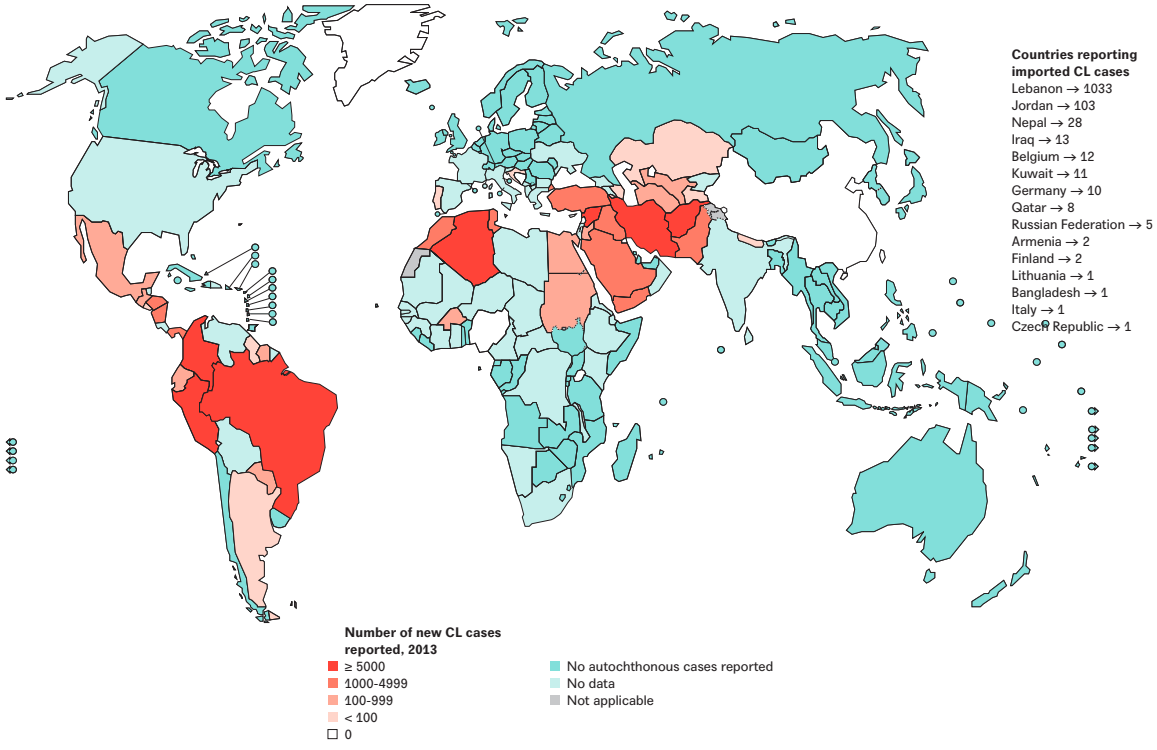
DISTRIBUTION OF HUMAN AFRICAN TRYPANOSOMIASIS *(T.B. RHODESIENSE)*, WORLDWIDE, 2014



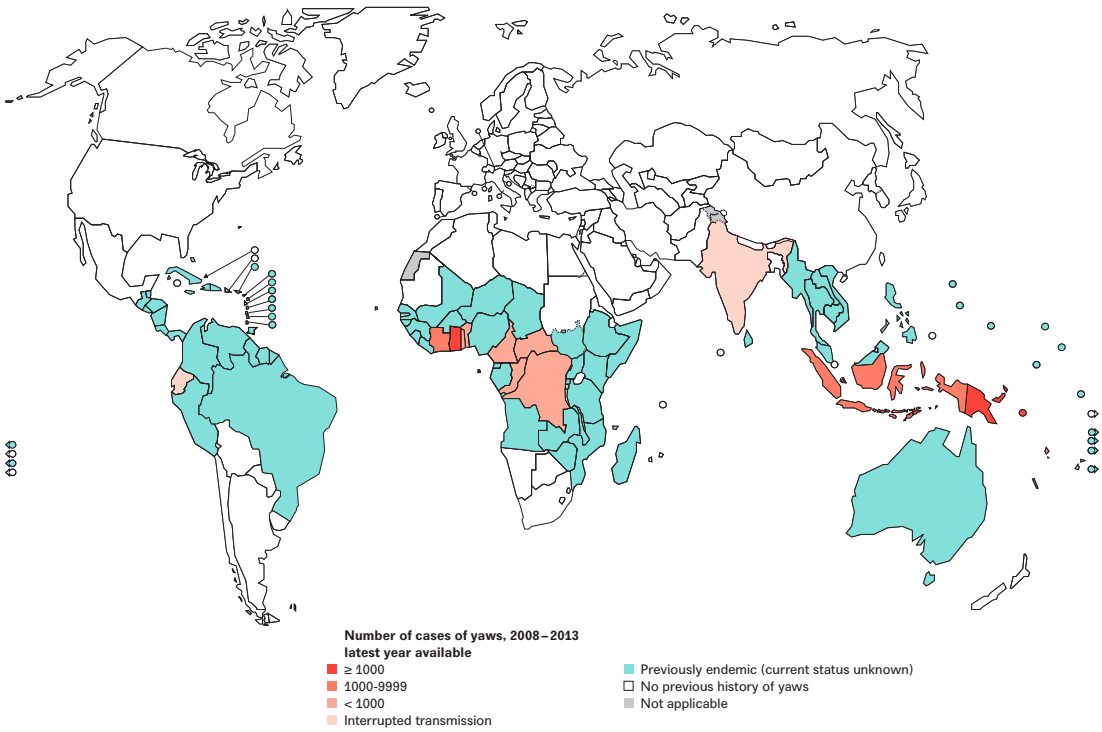
DISTRIBUTION OF VISCERAL LEISHMANIASIS (VL), WORLDWIDE, 2013



DISTRIBUTION OF CUTANEOUS LEISHMANIASIS (CL), WORLDWIDE, 2013



DISTRIBUTION OF YAWS, WORLDWIDE, 2008-2013



OFFICIAL AGREEMENTS SIGNED BETWEEN WHO AND DONORS FOR IMPLEMENTATION OF IDM ACTIVITIES

PERIOD	DONOR	DESCRIPTION OF AGREEMENT	CASH	IN-KIND
2001–2006	SANOFI	Donated eflornithine, melarsoprol and pentamidine, with additional financial support for implementing WHO HAT activities	US$ 25 million	Unlimited
2002–2007	BAYER	Donated suramin for treatment of HAT patients in endemic countries		10 000 vials per year
2008–2009	GOV. OF FRANCE	Support to engaging a medical officer for the HAT programme	US$ 437 000	
2008–2011	GOV. OF SPAIN	Support to leishmaniasis control (in Ethiopia and Sudan)	US$ 2 150 897	
2010	GOV. OF SPAIN	Support to implementing leishmaniasis control activities	€750 000	
2006–2011	SANOFI	Donated eflornithine, melarsoprol and pentamidine, with additional financial support to implementing WHO/IDM activities	US$ 25 million	Unlimited
2006–2011	FIND	Agreement to support the WHO HAT specimen bank	US$ 375 000 per year	
2010–2011	ANESVAD	Support to developing information, education and communication materials for the diagnosis, management and/or control of Buruli ulcer	€471 876	
2011–2016	FIND	Agreement for collaboration in development and implementation of diagnostic tests for HAT	US$ 500 000	
2007–2012	BAYER	Donated nifurtimox (120 mg) for treatment of Chagas disease		2.5 million tablets

2007–2012	BAYER	Support to implementing Chagas disease control and elimination activities	US$ 1.5 million	
2012–2017	BAYER	Donated suramin for treatment of HAT patients in endemic countries		10 000 vials per year
2012–2017	BAYER	Support to implementing Chagas disease control and elimination activities	US$ 1.5 million	
2012–2017	BAYER	Donated nifurtimox (120 mg) for treatment of Chagas disease		5 million tablets
2013–2015	BAYER	Support to reinforce access to health care for HAT patients in the Democratic Republic of the Congo	€300 000	
2014–2019	BAYER	Donated nifurtimox (120 mg) and (30 mg) for treatment of human African trypanosomiasis		300 000 (120 mg) and 20 000 (30 mg)
2012	ANESVAD	Support to procuring streptomycin for countries where Buruli ulcer is endemic	€208 152	
2013	ALM	Support to supplying rifampicin and streptomycin for WHO Global Buruli Ulcer Initiative programme	US$ 150 000	
2013	ALM	Support to implementing WHO Buruli ulcer clinical trials	US$ 150 000	
2014	ALM	Support to implementing WHO Buruli ulcer clinical trials	US$ 150 000	
2014	ALM	Support to supplying rifampicin and streptomycin for WHO Global Buruli Ulcer Initiative programme	US$ 75 000	
2011–2015	SANOFI	Donated eflornithine, melarsoprol and pentamidine, with additional financial support to implementing WHO/IDM activities	US$ 25 million	

2011–2016	GILEAD	Donated quantities of liposomal amphotericin B (lyophilized 50 mg formulation) free of charge to WHO for use in treating human visceral leishmaniasis in targeted treatment populations in eligible endemic countries		445 000 vials
2012–2016	DFID	Support to WHO/NTD for capacity strengthening and visceral leishmaniasis programme coordination and elimination programmes (East Africa and South Asia)	£2.7 million	
2013–2015	Bill & Melinda Gates Foundation	Support to implementing innovative approaches for case detection and management for sustainable elimination of *T.b. gambiense* HAT	US$ 2.9 million	
2014	FIND	Support to studies evaluating the sensitivity and specificity of fluorescent thin-layer chromatography and PCR for diagnosis of Buruli ulcer	US$ 80 000	
2015–2016	TFGH	Support to implementing randomized controlled trials comparing the efficacy of single-dose treatment against yaws (azithromycin 20mg/kg versus 30 mg/kg)	US$ 428 518	
2015	GE Healthcare Bio-Sciences AB	Donated DE52 Cellulose and Cytopore 2 for use in the manufacture of mAECT for the detection of HAT parasite		50 kg of DE52 Cellulose and 6 kg of Cytopore 2
2016–2018	DFID	Support to visceral leishmaniasis control programmes in East Africa	£1 224 830	

Notes: ALM, American Leprosy Missions; DFID, United Kingdom Department for International Development; FIND, Foundation for Innovative New Diagnostics; GE, General Electric – Healthcare Bio-Sciences AB) GOV., Government; HAT, human African trypanosomiasis; TFGH, Task Force for Global Health; WHO/IDM, WHO Innovative and Intensified Disease Management; WHO/NTD WHO Department of Control of Neglected Tropical Diseases.
All the financial figures are from the annual WHO financial reports 2001-2015.

RESOLUTIONS OF THE WHA CONCERNING SIX IDM NTDS 1948–2013

SUBJECT AREA	RESOLUTION	TITLE	YEAR
Neglected tropical diseases	WHA66.12	Neglected tropical diseases	2013
Chagas disease	WHA63.20	Chagas disease: control and elimination	2010
Buruli ulcer	WHA57.1	Surveillance and control of *Mycobacterium ulcerans* disease (Buruli ulcer)	2004
Human African trypanosomiasis	WHA57.2	Control of human African trypanosomiasis	2004
Human African trypanosomiasis	WHA56.7	Pan African tsetse and trypanosomiasis eradication campaign	2003
Chagas disease	WHA51.14	Elimination of transmission of Chagas disease	1998
Human African trypanosomiasis	WHA50.36	African trypanosomiasis	1997
Endemic treponematoses	WHA31.58	Control of endemic treponematoses	1978
Endemic treponematoses	WHA2.36	Bejel and other treponematoses	1949

IDM, innovative and intensified disease management; NTD, neglected tropical disease; WHA, World Health Assembly

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