Neglected tropical diseases

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Introduction: The neglected tropical diseases (NTDs) are infectious diseases that principally impact the world's poorest people. They have been neglected for decades, initially as part of a general disregard for the developing world, and more recently due to the intensity of focus on HIV/AIDS, tuberculosis and malaria.

Sources of data: Primary research and review articles were selected for inclusion using searches of PubMed and our existing collections.

Results: There have been recent notable successes in NTD control. Dracunculiasis is approaching eradication. Leprosy and onchocerciasis are in decline. There are ambitious plans to eliminate trachoma and lymphatic filariasis. Investment in NTD control has high rates of economic return.

Conclusion: Although there are proven strategies to control several NTDs, these diseases continue to cause a massive burden of morbidity. There is urgent need for more basic and operational research, drug and vaccine development, and greater prioritization by governments and international agencies.

Introduction

The neglected tropical diseases (NTDs) are a subset of infectious diseases. The responsible pathogens are a biologically disparate group, including (1) vector-borne protozoa (such as *Trypanosoma cruzi*), bacteria (ocular serovars of *Chlamydia trachomatis*) and filarial worms (such as *Onchocerca volvulus*); (2) soil-transmitted helminths (STHs); and (3) the two species of non-tuberculosis mycobacteria that produce Buruli ulcer and leprosy, for which the mechanisms of acquiring infection are not yet fully understood. Clinical features, diagnostic algorithms and strategies for treatment, prevention and control are similarly

diverse. The collective term 'neglected tropical diseases' does, however, imply two important shared characteristics.

First, these diseases predominate in the tropics, but their predilection for hot places results principally from the fact that poverty is found in greatest concentration in the remote rural communities, urban slums and displaced populations near to the equator. Rather than thinking of them as tropical diseases, then, we should consider the NTDs as being primarily diseases of the 'bottom billion'—the poorest one-sixth of the world's population,[1,2] amongst whom they cause massive suffering through acute illness, long-term disability and early death. All low-income countries are affected by at least five NTDs simultaneously, and many individuals who live in those countries are concurrently infected by more than one pathogen.[3] Many of these infections are at least in part attributable to inadequate access to safe water, sanitation and appropriate housing. Many NTDs are therefore preventable or even eradicable with existing, safe and cost-effective tools, if only these could be made more widely available.[4]

Second, until very recently, they have all to a greater or lesser extent been neglected by funders, researchers and policy-makers. In September 2000, for example, the international community through the United Nations declared an ambitious worldwide commitment to reduce extreme poverty, with a deadline of 2015. This commitment was codified as the Millennium Development Goals.[5] Whilst these goals include broad targets to reduce child mortality and improve maternal health, a very specific commitment to combat HIV/AIDS and malaria led to greatly concentrated focus on these pathogens as well as on tuberculosis—the so-called 'big three'. As a consequence, attention to many other important causes of mortality and morbidity amongst poor populations, which had already been inadequate, declined still further.[6] In the last few years, this situation has begun to change. There is now a specific department within the World Health Organization (WHO) tasked with addressing the problem of NTDs, a new international alliance to raise the profile of and galvanize control efforts for NTDs, known as the Global Network for Neglected Tropical Diseases Control (www.GNNTDC.org), and a dedicated open-access journal, PLoS Neglected Tropical Diseases (www.plosntds .org), first published in 2007.

The diseases

Many diseases could be considered 'neglected' at the global or local level, and the increased interest in the burden and control of NTDs means that there are now clear advantages in being included under the

NTD rubric. A review of all candidates is beyond the scope of a single paper. Thirteen have been identified as being of particular importance in terms of their frequency amongst poor communities, and their clinical, social or economic impact[7] (Table 1); these diseases will be considered further below.

Seven of these diseases have both high prevalence and excellent prospects for successful control with existing technologies:[2] these are highlighted in Table 1. The diseases are grouped below by class of causative organism.

Diseases caused by protozoa

No genus better exemplifies how NTDs both cause and are caused by poverty than *Trypanosoma*, a group of unicellular protozoan parasites. Members of this genus include *Trypanosoma brucei* and *T. cruzi*, the causes of African sleeping sickness and Chagas disease, respectively. These conditions demonstrate the impact of NTDs, and also the recent progress made in NTD control.

Human African trypanosomiasis

Human African trypanosomiasis (HAT), or sleeping sickness, is caused by two parasites (*T. brucei gambiense* and *T. brucei rhodesiense*) transmitted by tsetse flies (*Glossina* sp.). It is endemic in parts of 36 African countries, putting a total of about 60 million people at risk.[8] The use of mobile screening and treatment teams together with vector control measures led to almost complete interruption of transmission by the mid-1960s. These efforts were not sustained, however, and the disease re-emerged during the 1980s; by 1997, around 450 000 people were estimated to be infected, the vast majority with *T. b. gambiense*.[8] Subsequent resumption of active case finding activities, a reduction in civil strife in endemic areas and improved availability of drugs have been accompanied by apparent reductions in the annual incidence from more than 37 500 per year in 1998 to less than 12 000 in 2006.[9,10] However, mathematical models based on outbreak data[11] suggest that under-detection of sleeping sickness is considerable.

The clinical syndromes of gambiense and rhodesiense HAT are different. The more human-adapted *T. b. gambiense* causes a slowly progressive disease that tends to present late, while the zoonotic parasite *T. b. rhodesiense* causes much more aggressive acute illness. Initial symptoms of both include fever, headache and lymphadenopathy; grossly enlarged posterior cervical lymph nodes in HAT are known as Winterbottom's sign. Later, daytime somnolence and nocturnal insomnia give rise to the 'sleeping sickness' label, although overall sleep time

Table 1: The 13 core NTDs

Disease	Name of causative agent	Class of causative agent	Usual mechanism of acquisition	Site of infection with mature agent	Clinical features	Estimated number infected (millions)	Estimated DALYs lost (millions), 2002	Control strategy	Aim of control strategy	References
Ascariasis*	*A. lumbricoides*	Helminth	Ingestion of eggs	Small intestine	Abdominal distension, pain malabsorption, intestinal obstruction, impaired growth, reduced school performance	807–1221	1.8	Periodic mass deworming of children using benzimidazole antihelminthics	Prevention of morbidity in children living in endemic areas	39,109
Dracunculiasis	*D. medinensis*	Helminth	Ingestion of water containing copepods infected with larval stage	Subcutaneous tissues	Painful skin bulla that progresses to an ulcer, from which a worm protrudes	0.002	Not known	Provision of protected water sources, education, filtration of drinking water, case detection and containment, cyclopicides	Eradication	79
Hookworm infection*	*A. duodenale, N. americanus*	Helminth	Skin penetration by soil-dwelling infective (third-stage) larvae	Upper part of small intestine	Intestinal blood loss, iron deficiency, protein malnutrition, impaired growth, reduced school performance	576–740	0.06	Periodic mass deworming of children using benzimidazole antihelminthics	Prevention of morbidity in children living in endemic areas	39,109
Lymphatic filariasis*	*W. bancrofti, B. malayi, B. timori*	Helminth	Skin penetration by infective (third-stage) larvae at the site of the bite from the mosquito vector (*Anopheles, Aedes, Culex, Mansonia*, or *Ochlerotatus*), after escaping from the mosquito's proboscis	Lymphatic vessels	Hydrocoele, lymphoedema and elephantiasis	120	5.8	Annual mass drug administration of albendazole plus either diethylcarbamazine or (where co-endemic with onchocerciasis) ivermectin	Elimination as a public health problem by 2020	109,110
Onchocerciasis*	*O. volvulus*	Helminth	Injection of infective (third-stage) larvae in the saliva of a biting, parasitized female blackfly (*Simulium sp.*)	Subcutaneous tissues	Subcutaneous nodules, pruritus, skin atrophy, skin pigmentation, blindness	37	0.5	Annual mass drug administration of ivermectin	Elimination as a cause of blindness by 2020	109

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Schistosomiasis*	S. mansoni, S. haematobium, S. japonicum, S. intercalatum, S. mekongi	Helminth	Penetration of skin by cercariae that have emerged from water-dwelling snail intermediate hosts	Perivesical venous plexus or mesenteric veins	Haematuria, bladder obstruction, renal failure, bladder cancer (S. haematobium); periportal fibrosis, portal hypertension, ascites and varices (mesenteric schistosomes).	200	1.7	Annual mass drug administration of praziquantel, improved access to safe water and sanitation, and health education	Prevention of morbidity in children living in endemic areas	48,109
Trichuriasis*	Trichuris trichiuria	Helminth	Ingestion of eggs	Large intestine, especially caecum	Colitis, chronic dysentery, rectal prolapsed, impaired growth, reduced school performance	604–795	1.0	Periodic mass deworming of children using benzimidazole antihelminthics	Prevention of morbidity in children living in endemic areas	39,109
Chagas disease	T. cruzi	Protozoon	Inoculation by host's fingers into conjunctival sac or site of bite following excretion of mature parasite in faeces of biting triatomine bug	Intracellularly in tissues throughout the body	Cardiomyopathy, cardiac dysrhythmia, mega-oesophagus, mega-colon	15	0.7	Vector control, insecticide-treated bed nets, dog collars, adequate housing	Varies by region	109
Human African trypanosomiasis	T. brucei	Protozoon	Injection by parasitized tsetse fly	Blood, lymph, cerebrospinal fluid	Fever, headache lymphadenopathy, neurological decline, daytime somnolence, coma, death	<0.1	1.5	Vector control, rapid diagnosis and prompt treatment	Not yet defined	109
Leishmaniasis	More than 20 species of Leishmania	Protozoon	Injection by parasitized sandfly	CL skin MCL: skin plus oropharnyx VL: disseminated disease	CL: skin ulcer MCL: skin ulcer plus oropharyngeal destruction VL: fevers, night sweats, weight loss, anaemia, immuno-suppression	12	2.1	Vector control, rapid diagnosis and prompt treatment	VL: elimination as a public health problem in Bangladesh, India and Nepal by 2015	109
Buruli ulcer	M. ulcerans	Bacterium	Unknown	Skin	Skin ulcer with an undermined edge	Unknown	Unknown	Rapid diagnosis and prompt treatment	Reduction in morbidity and socio-economic burden	
Leprosy	M. leprae	Bacterium	Unknown	Skin and nerves	Skin changes, anaesthesia	0.4	0.2	Rapid diagnosis and prompt treatment with life-long follow-up	Microbiological cure, prevention of disability	109
Trachoma*	C. trachomatis	Bacterium	Mechanical transfer of elementary bodies by flies, fomites or fingers	Conjunctiva	Conjunctivitis, trachomatous scarring, trichiasis, corneal opacity, blindness	84	2.3	SAFE strategy: surgery for trichiasis, antibiotics (by MDA) to treat infection, face washing and environmenal improvement to reduce transmission	Elimination as a public health problem by 2020	81,109,111

*Diseases have both high prevalence and excellent prospects for control.

is unaltered. Personality change, deterioration in higher mental function and Parkinsonian movement disorders are noted. Progressive neurological decline culminates in coma then death.[12] Serology, using the card agglutination test for trypanosomiasis, detects antibodies to *T. b. gambiense*. It is relatively expensive, but is widely used as a screening test. It is less than 100% specific, though specificity can be improved by using a higher titre cut off.[13] Since treatment is difficult to administer, and potentially toxic, the diagnosis needs to be confirmed by microscopic identification of the organism in lymph node aspirates or samples of blood, bone marrow or cerebrospinal fluid (CSF).[10,12]

Optimal treatment of sleeping sickness is governed by disease stage at diagnosis, which can only be determined following examination of the CSF. In early disease, treatment options include pentamidine and suramin. Later, when drug penetration to the central nervous system is required, the only agents available are melarsoprol (an arsenical with 10% mortality) or—for *T. b. gambiense* only—eflornithine. Originally developed for use in cancer chemotherapy, eflornithine is highly active against *T. b. gambiense*,[14] but production was abandoned in 1995 on grounds of cost. The drug then re-surfaced as a hair growth retardant, and only a subsequent international advocacy campaign finally guaranteed its supply (along with that of melarsoprol and pentamidine) in landmark deals between WHO and the drugs' manufacturers.[15] A recent multicentre trial has shown that combination treatment with oral nifurtimox and low-dose intravenous eflornithine is at least as effective as (and safer and easier to administer than) standard dose eflornithine given alone.[16] As a result, this drug combination has been placed on WHO's essential drugs list.[17] The development of better diagnostic tools and wholly orally administered regimens are current priorities.[15,18]

Chagas disease

Trypanosoma cruzi infects approximately 200 000 new people per year in the Americas; the estimated prevalence is 15 million. This makes Chagas disease the most important human parasitic condition in the New World.[19] International migration now exports Chagas to developed countries, too.[20,21] Night-biting triatomine ('kissing') bugs living on livestock or in cracks in walls are the vectors. Mature parasites are excreted in the faeces of the bugs whilst they feed, and inoculated directly through broken skin or via transfer on fingers into the conjunctival sac.

Acute infection tends to be a mild self-limiting febrile illness. Approximately 30% of infected individuals develop chronic Chagas disease, which most commonly affects the heart (causing cardiomyopathy and dysrhythmias) or the gut (causing mega-oesophagus or mega-colon). Immune suppression from any cause may result in

reactivation of latent infection, causing severe cardiac and neurological sequelae.[22]

The mainstays of diagnosis are somewhat unreliable serological tests, though direct identification of the parasite in blood smears and xeno-diagnosis are sometimes successful in acute and chronic infection, respectively.[23] Available treatments (benznidazole and nifurtimox) are of questionable efficacy against chronic disease, require long courses and have severe side-effects.

In Uruguay, Chile and Brazil, as well as in large areas of Argentina and Paraguay, the use of residual insecticides in and around houses has led to elimination of domestic triatomines, sustained interruption of transmission by the principal vector, *Triatoma infestans*,[24,25] and a 40% reduction in the estimated global burden of disease since 1990, when up to 18 million were thought to be infected.[24] Unfortunately, there are no proven tools for detecting the return of low-intensity vector populations,[26] and control has proven more difficult elsewhere in northern South America and in Central America, where there are significant peridomestic and silvatic populations of triatomine bugs.

Adequate housing is the definitive solution to Chagas disease, but at $200–$2000 per house, is difficult to fund. Encouragingly, however, there is now increasing academic and private sector interest in the disease.[26] An increasing understanding of the eco-epidemiology via geo-spatial analysis may help refine future control strategies.[27]

Leishmaniasis

About 20 species of obligate intracellular protozoan parasites of the genus *Leishmania* cause a spectrum of disease ranging from self-healing cutaneous ulcers to fatal visceral disease. The group causes more morbidity and mortality than any human parasite other than malaria and lymphatic filariasis (LF).[28] Infection occurs via the bite of an infected female sandfly, infected blood or organs, or transplacentally.[29]

Cutaneous leishmaniasis (CL) is the most common leishmaniasis syndrome and is one of the most important causes of chronic ulcerating skin lesions worldwide. Some weeks after infection, a papule develops and evolves into a nodule, then an ulcer with a depressed centre and raised border. This ulcer may spontaneously heal. In other instances the lesion may disseminate to remote skin sites (diffuse CL), or, in the case of New World CL, spread to the nasal mucosa causing destruction of the nasal septum and palate (mucocutaneous leishmaniasis). The latter may cause significant facial disfiguring or even death through airway compromise.

In visceral leishmaniasis (VL, 'kala-azar'), disease commences with a low-grade fever and anorexia, and may progress to feature pancytopenia, immunosuppression, massive splenomegaly, haemorrhage and

death. Leishmaniasis is complicated by HIV co-infection: more severe disease occurs at unusual anatomical sites in those with HIV, and virtually 100% of cases relapse after treatment in the absence of effective HIV management.[29]

Leishmaniasis occurs on all continents save Australia and Antarctica. CL predominates in Latin America, Central Asia and south-western Asia,[28] while 90% of the world's VL occurs in India, Bangladesh, Nepal, Sudan and Brazil.[29] During the long civil war in Sudan, population displacement exposed the hitherto naive Upper Nile region to infection, causing the deaths of about 100 000 people: 30–60% of the population in the region and more than 90% of residents of the hardest-hit communities.[30] *Leishmania* transmission cycles vary from sylvatic (in Central American rain forests, for example, where transmission can occur between animals without intervening human infection) to domestic (in which the predominant reservoirs are humans and dogs).

Gold standard diagnosis is by demonstration of parasites in tissue aspirates. This is difficult in endemic areas, where serological tests are generally relied upon.[31] In resource-rich countries, culture or PCR can identify the infecting organism to species level.

Treatment is complex and tailored to the clinical syndrome, severity of infection, the infecting species and susceptibility patterns in the region of probable acquisition.[29,32] It may also depend on local drug availability. Most old world CL lesions heal spontaneously in months and may not require treatment. When actively managed, regimens for CL include topical paromomycin, pentavalent antimonials and intravenous liposomal amphotericin B.[29] For VL, parenteral paromomycin, antimonials and amphotericin B have been the mainstays of therapy, but the recent introduction of the oral agent miltefosine[33,34] has augmented the range of therapies available. Nearly all untreated VL patients die.

Control programmes aim to reduce the incidence of infection through early diagnosis and prompt treatment, and control of exposure to vectors using bed nets and residual insecticides. There is an ambitious project to eliminate VL as a public health problem from Bangladesh, India and Nepal by 2015 using a combination of these tools.[35] In areas where canines are important reservoirs, treated dog collars have been shown to reduce both human and canine infections.[36] No reliable vaccine has yet been produced; work continues.[36,37]

Diseases caused by helminths

The term 'helminth' is derived from the Greek for worm and there is evidence that mankind has been aware of these organisms throughout

recorded history. The phylum Nematoda (roundworms) includes the STHs (*Ascaris*, hookworms, whipworm and *Strongyloides*) and the filarial worms that cause LF, river blindness and dracunculiasis. The other helminth groupings are both classes of the phylum Platyhelminthes: the Cestoda (parasitic flatworms) including *Taenia solium* and *Taenia saginata*), and Trematoda (flukes), which includes the genus *Schistosoma*. Currently, neither *Strongyloides* nor *Taenia* is classed as a 'core' NTD.[7,38]

Soil-transmitted helminths

The STHs are a group of infections acquired through ingestion of, or contact with, soil containing worm eggs or larvae. More than a billion people are infected by one or more of these parasites.[39] Children are most affected, as they tend to both harbour the greatest number of worms and be most susceptible to their effects, which include anaemia, growth stunting, and reduced physical fitness, educational performance and school attendance.[40] Though death is an uncommon outcome, this group of infections has enormous poverty-promoting impact.[41]

The most important STHs are the common roundworm (*Ascaris lumbricoides*), the whipworm (*Trichuris trichiura*) and the hookworms (*Necator americanus* and *Ancylostoma duodenale*). The greatest burden of disease is found in the Americas, China and Sub-Saharan Africa. These worms have similar lifecycles in that adults infect the gastro-intestinal tract, reproduce sexually and release eggs which are passed in faeces into the environment. Hookworms differ from *Ascaris* and *Trichuris* in that, rather than being acquired through ingestion of eggs larvae develop to the infective stage in the soil then penetrate intact skin to initiate the parasitic phase.

Helminth epidemiology is distinct from that of many other infections. With the exception of *Strongyloides*, they cannot replicate in the human host or be transmitted from person to person, adult worms have a finite lifespan, and in addition to whether or not an individual is infected, the intensity of infection (usually measured by the number of eggs per gram of faeces[42]) is important. Some members of populations in which STHs are endemic are more 'wormy' than others: commonly 70% of the community worm burden is concentrated in 15–30% of the population.[43] The role of protective immunity in creating this 'aggregated' or 'overdispersed' distribution remains poorly understood. At the community level, WHO use both prevalence and intensity of infection to categorize communities into high-, medium- and low-transmission intensity environments, in order to inform mass treatment strategies.[44] The benzimidazole antihelminthics, albendazole and mebendazole, are the treatments of choice.[42] Nematodes in livestock develop resistance to these drugs when they are used repeatedly,

and there is concern that this may account for the decreased efficacy of human mass treatment noted in some settings.[45] Work to identify markers of drug resistance is ongoing.[46]

Schistosomiasis

Five species of parasitic trematodes of the family Schistosomatidae infect humans. They have a complex life cycle involving snails as intermediate hosts. Infected snails shed cercariae into the water, which can penetrate intact human skin and locate and enter post-capillary venules. Further development takes place in the lungs and liver before migration to the perivesical venous plexus (*Schistosoma haematobium*) or the mesenteric veins (*S. mansoni*, *S. japonicum*, *S. intercalatum* and *S. mekongi*). Adult pairs remain *in copulo* at these intravascular sites for the remainder of their lives.

Acute illness ('Katayama fever') is characterized by fever, lethargy and eosinophilia, occurring a few weeks after first infection.[47] Most of the disease burden from schistosomiasis (bilharzias), however, is caused by passage of eggs through the walls of blood vessels and intestine, ureters or bladder, or by lodgement in liver or lungs of eggs washed away by the portal venous system. Over time, the resulting granulomatous inflammation can lead to haematuria, bladder obstruction, renal failure or bladder cancer (in *S. haematobium* infection), or, in infection with mesenteric schistosomes, periportal fibrosis, portal hypertension, ascites and varices. Eggs that reach the lumen of bladder or bowel are expelled in urine or faeces. Contained miracidia are released when the egg is immersed in water, and actively seek out and penetrate the snail intermediate host.[48]

Diagnosis of chronic disease is by the detection of eggs in urine or faeces, usually after concentration methods have been applied. Serological diagnosis is sensitive but non-specific.[48]

Approximately 200 million people are infected worldwide, with an overdispersed distribution of infection intensity within geographically focal endemic areas.[48] Snail control with molluscides is complicated, poorly cost-effective and potentially toxic to other water life.[48] Recommended methods of control include mass distribution of praziquantel, improved access to safe water and sanitation and health education.[49,50] In its first 5 years of operation from 2003 to 2008, Schistosomiasis Control Initiative-supported programmes have administered praziquantel to more than 44 million people in six countries in Africa.

Lymphatic filariasis

LF is classically associated with endemic elephantiasis, lymphoedema and hydrocele. Twenty per cent of the world's population lives in

endemic areas.[51] More than 120 million people in 83 countries are infected, over 40 million of whom are disfigured by the disease.[52] Microfilariae of the causative worms, *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori*, are transmitted by mosquitoes. Adult worms lodge in the lymphatic system where they live for years, viviparously producing millions of microfilariae that circulate in blood. Infection is predominantly acquired in childhood and remains asymptomatic for many years. Enlargement of the limbs, genitals or breasts has massive psychological, social and economic impact on the sufferer.[53] Damaged skin is predisposed to secondary bacterial infection, which may be an important cofactor in progression of elephantiasis.

Until very recently, diagnosis was technically difficult, requiring preparation of blood films. The development of card-based antigen detection assays[54] has been a massive advance. Chemotherapy (see below) is a cornerstone to control efforts, but for the individual sufferer the use of techniques that improve the lymphatic flow and rigorous hygiene for affected parts is as important, resulting in reduced frequency of acute episodes of inflammation ('filarial fevers') and in considerable improvement of the elephantiasis itself.

WHO aims to eliminate LF as a public health problem by 2020.[55] To reduce microfilaraemia and thereby reduce transmission, annual mass treatment with albendazole plus either diethylcarbamezine or (in areas co-endemic for onchocerciasis) ivermectin is recommended.[56] Distribution has been made possible by donations of product and money by the drugs' manufacturers. In its first 8 years of operation, the global programme to eliminate LF prevented an estimated 11 million cases of LF disease[57]—an intervention that, according to the Disease Control Priorities Project—is amongst the most cost-effective of all health-improving strategies.[58,59] In 2007, treatment programmes were active in 48 of 81 endemic countries, distributing drugs to some 546 million people.[60] Preliminary studies of antibiotics active against *Wolbachia*, an essential endosymbiont bacterial infection of adult filariae, have shown promise.[61]

Onchocerciasis

Onchocerciasis (river blindness) is caused by infection with *O. volvulus*. Adult worms live in subcutaneous nodules, from which their progeny (microfilariae) emerge to migrate throughout the body, predominantly within the skin. This produces an intense pruritus and a chronic dermatitis that leads ultimately to skin atrophy and depigmentation, and also creates opportunities for uptake by biting blackflies of the genus *Simulium*. Transmission to other hosts can occur at the vector's next meal. Migration of microfilariae through the anterior and posterior

segments of the eye precipitates inflammatory reactions that may lead to blindness through sclerosing keratitis, cataract or optic atrophy.[62,63]

Simulium breeds along fast-flowing rivers and streams, so onchocerciasis-endemic areas tend to include the most agriculturally fertile land available.

Three international programmes—two in Africa and one in the Americas[64–66]—have achieved dramatic success in reducing onchocerciasis transmission, using a combination of larvicide spraying at blackfly breeding sites,[67,68] and periodic mass drug administration of ivermectin to affected human populations. There is good recent evidence of interruption of transmission in two of the four endemic foci in Guatemala[69,70] and in several hyperendemic foci of Mali and Senegal[71] using yearly or twice-yearly ivermectin distribution alone. There is, however, new and worrying evidence that ivermectin's ability to inhibit production of microfilariae by adult female worms diminishes after several rounds of treatment.[72] Though there are as yet no data suggesting that the drug's immediate microfilaricidal activity will be lost, elimination of onchocerciasis may ultimately require the use of complementary strategies, such as antibiotics aimed at *Wolbachia* (as for lymphatic filariasis),[66,73] macrofilaricidal agents[74] or an effective vaccine.[75]

Dracunculiasis

Dracunculiasis is infection with the Guinea worm, *Dracunculus medinensis*. Larval stages of this organism are ingested by several genera of pond- and well-dwelling predatory microcrustaceans (copepods), in which they develop to the infective stage. Water-containing copepods is swallowed by human hosts, whereupon *D. medinensis* is released to invade, mature, mate and reproduce. Fertilized females migrate to the subcutaneous tissues, stimulating formation of a painful cutaneous bulla (Fig. 1A). This bursts, allowing the body of the worm to protrude (Fig. 1B). When the affected part is immersed in water (either incidentally or to soothe the pain), larvae are disgorged from the worm's ruptured uterus.[76]

Individual cases of dracunculiasis are managed by carefully winding the protruding end of the worm around a small stick, rotating it a little each day to extract the worm intact; the ulcer should be monitored for the development of secondary bacterial infection. Prevention of transmission is technically straightforward, however, and international commitment for global eradication was secured in 1991.[77] By provision of protected water sources, education of the community about not swimming or wading in supplies of drinking water, filtration of drinking water through finely woven cloth, case detection and containment, and

Fig. 1 Dracunculiasis. (A) An itchy blister appears following release of fluid from adult female worm located in the subcutaneous tissue. (B) A 60-cm long worm then gradually emerges over a week or two. Photographs generously supplied by Dr Ahmed Tayeh.

the use of cyclopicides,[76] the annual total worldwide incidence has dropped from 892 055 in 1989 to 2619 in 2008.[78,79] Only six countries, all in Sub-Saharan Africa, are still considered to have endemic transmission,[79] and all six have individually committed to the goal of eradication.[80]

Diseases caused by bacteria

Trachoma

Ocular serovars of C. *trachomatis*, the causative organism of trachoma, are passed from eye to eye in endemic communities by eye-seeking flies, fomites and direct finger–eye contact. Infection often leads to the inflammatory changes of active trachoma in the conjunctiva and subconjunctival tissues; these changes resolve by organization (with deposition of collagen) as the episode of infection is cleared. In trachoma-endemic communities, residents experience repeated cycles of infection and resolution over many years, leading, in some individuals, to scarring and contracture of the upper lid, pulling the upper lashes posteriorly so that they rub on the surface of the globe (a condition known as trichiasis, Fig. 2). This damages the cornea, ultimately leading to blindness.[81] Current estimates suggest that 40.6 million people have active trachoma in 57 endemic countries.[82] It is the commonest infectious cause of blindness,[83] affecting most heavily the poorest and most remote communities of the poorest and driest countries of the world.[84]

The four-part strategy developed to interrupt the pathophysiological cascade of trachoma comprises *s*urgery to reposition in-turned lashes, *a*ntibiotics to clear infection, and *f*acial cleanliness and *e*nvironmental improvement to reduce transmission. Together, this package of interventions is known as the 'SAFE' strategy. Using it, the WHO and
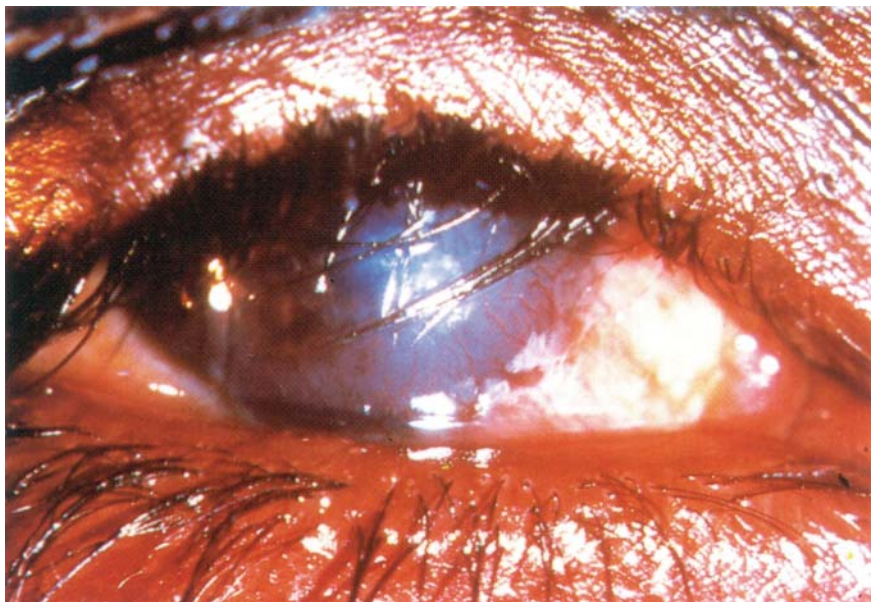
Fig. 2 *Trachomatous trichiasis*. Picture © World Health Organization. Reproduced with permission.

partners aim to eliminate trachoma as a cause of blindness by the year 2020.[85] Several endemic countries have already made considerable progress towards this goal.[86–89]

The antibiotic of choice for the A component of SAFE is azithromycin, as it can be given as a single oral dose.[81] Though available data are limited, there is as yet no evidence that significant macrolide resistance develops in *C. trachomatis* following mass treatment with this drug.[90]

Buruli ulcer

Buruli ulcer is caused by *Mycobacterium ulcerans*. Uniquely amongst the mycobacteria, this organism produces a plasmid-encoded toxin (mycolactone[91]) which diffuses into the adjacent subcutaneous fat, causing progressive necrosis and inhibiting inflammation. This results in characteristic undermining of the edge of the ulcer so that a large area of non-viable skin surrounds the ulcer.[92] Lesions usually begin as a single subcutaneous nodule or a more diffuse firm plaque before ulcerating days to weeks later (Fig. 3); a rapidly progressive oedematous form also occurs. Ulcers persist for many months. Lesions are most common on the limbs and when they heal in proximity to a joint, scarring may result in a fixed flexion deformity. Lesions of the hands impair function, and genital or facial ulcers are highly disfiguring. Disseminated infection has been observed in HIV infected patients.[93]

Children aged 5–15 years are most at risk, but no age group is spared, and a second peak in the elderly has been observed in Benin.[94] Most cases occur towards the end of the rainy season in the humid

Fig. 3 Buruli ulcer. Due to undermining at the edge a large area of non-viable skin surrounds the ulcer.

wetland areas of West Africa. Cases have been reported from highly focal areas with similar climates in more than 30 countries. Southeast Australia is unusual in that, despite its temperate climate, clusters of cases continue to emerge in small coastal communities near Melbourne. The exact mode of transmission remains elusive but various fresh water bugs and small fish have been found to harbour the organism in West Africa,[92,95] while *M. ulcerans* DNA has been detected in mosquitoes in Australia.[96]

Medical treatment with an 8 week course of rifampicin and streptomycin is a recent development.[97] This regimen is successful in the majority of cases and is associated with a relapse rate of less than 3%. Large ulcers may need skin grafting after antibiotic treatment. Lesions close to joints require physiotherapy to prevent the development of fixed deformities.

Leprosy

Mycobacterium leprae is a slow-growing organism that produces chronic granulomatous inflammatory changes in infected skin and peripheral nerves. Initial clinical manifestations of infection depend on the exuberance of the host's cell-mediated immune response. A vigorous response results in paucibacillary disease, defined as five or fewer visible skin lesions. Minimal response is associated with multibacillary disease, with six or more symmetrically distributed skin lesions; acid-fast bacilli may be visible on stained slit skin smears. Damage to nerves results in long-term disfigurement and disability.[98,99] The risk of impaired nerve function is much greater in those with multibacillary disease.[100]

WHO recommends multi-drug therapy (with combinations of dapsone, rifampicin and clofazimine) including monthly supervision, though questions remain about the optimal length of the treatment course for multibacillary disease. Patient education, prevention of disability and rehabilitation should accompany drug treatment and continue for the rest of the patient's life.[99,101]

In 1991, leprosy was scheduled for global 'elimination as a public health problem'—defined as reduction in prevalence to less than one case per 10 000 persons—by the year 2000. The increased focus that this resolution demanded had some positive impact, and 'global elimination' was later certified by WHO as having been achieved.[102] Given leprosy's long incubation period and the potential for sequelae decades after successful completion of MDT, however, a decline in the number of patients currently registered as receiving MDT per unit population may not be the most useful index of disease control;[101,103] and certifying elimination had unfortunate consequences for both clinical services and research programmes. About 254 525 new leprosy cases were

registered worldwide in 2007, a decline in global incidence of 4% on the figures for 2006.[104]

Discussion

In recent years there have been concerted efforts to quantify the worldwide impact of various types of disease. The first global burden of disease survey began in 1990, classifying human afflictions into 'communicable', 'non-communicable' and 'trauma' categories; 'infectious and parasitic diseases' are a sub-group of the communicable diseases. In the developing world, communicable diseases remain the leading cause of morbidity and mortality. In Africa, for example, they account for 73% of the total disease burden and 71% of deaths.[105] A fifth of this is attributable to the neglected tropical disease group, although it is likely that this represents a substantial underestimate of their true burden, for a number of reasons. The 'infectious and parasitic' group currently excludes several important NTDs; case definitions are not always clear-cut; data, especially from the poorest countries, are almost certainly incomplete; and the level of disability wrought by NTDs is frequently under-appreciated.[11,48,105,106]

In addition to the importance of the NTDs as causes of morbidity and mortality amongst the poorest peoples, the existence of proven and highly cost-effective treatments provides another imperative to make their control a public health priority. Although the causative organisms are biologically diverse, a characteristic they tend to share is relative reproductive stability. Concerns about the possible decreasing efficacy of ivermectin against *O. volvulus*, benzimidazoles against soil-transmitted helminths, and pentavalent antimony against VL in India[32] notwithstanding, these organisms and their vectors tend not to easily acquire resistance to chemotherapy or insecticides.[4] This simplifies intervention strategies. In comparison, treatment and control programmes associated with the 'big three' diseases are much more medically complex, and therefore more expensive.

NTD control benefits more than just the individuals spared of the effects of illness. It has also been shown to provide impressive rates of economic return and to strengthen public health services for relatively modest levels of investment.[4] Integration of control efforts for co-endemic NTDs has the potential to enhance the impact of interventions whilst saving scarce resources.[107] Co-administration of praziquantel for schistosomiasis and benzimidazole antihelminthics for STHs, for example, is already routine in schistomiasis control initiative-supported programmes.[108]

NTDs remain a cause of massive suffering. The rationale and the tools to control them are at hand. Progress is now being made in reducing the attributable burden of disease, with reduction in the incidence of Guinea worm to a point at which global eradication is in sight,[79] striking declines in the burdens of Chagas disease,[24] leprosy[104] and onchocerciasis[64] and successful elimination of trachoma from Morocco[86] and Ghana[87] and of LF from China and the Republic of Korea.[60] If sufficient resources and political can be harnessed, sustained reductions in the burden of NTDs might transform the lives of some of the most disadvantaged peoples on Earth.

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