Review

Neglected and endemic zoonoses

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Endemic zoonoses are found throughout the developing world, wherever people live in close proximity to their animals, affecting not only the health of poor people but often also their livelihoods through the health of their livestock. Unlike newly emerging zoonoses that attract the attention of the developed world, these endemic zoonoses are by comparison neglected. This is, in part, a consequence of under-reporting, resulting in underestimation of their global burden, which in turn artificially downgrades their importance in the eyes of administrators and funding agencies. The development of cheap and effective vaccines is no guarantee that these endemic diseases will be eliminated in the near future. However, simply increasing awareness about their causes and how they may be prevented—often with very simple technologies—could reduce the incidence of many endemic zoonoses. Sustainable control of zoonoses is reliant on surveillance, but, as with other public-sector animal health services, this is rarely implemented in the developing world, not least because of the lack of sufficiently cheap diagnostics. Public–private partnerships have already provided advocacy for human disease control and could be equally effective in addressing endemic zoonoses.

Keywords: endemic zoonoses; poverty; burden of disease; under-reporting

1. INTRODUCTION

(a) The nature of neglect

The United Nations Millennium Summit agreed on the Millennium Development Goals (MDGs) in September 2000. The aim was to halve the proportion of people whose income is less than a dollar a day and halve the proportion of people suffering from hunger by 2015. This remains a formidable undertaking; more than a billion people in the developing world live on less than a dollar a day. There were eight such goals: to eradicate extreme poverty and hunger; achieve universal primary education; promote gender equality and empower women; reduce child mortality; improve maternal health; ensure environmental sustainability; develop a global partnership for development; and, of most relevance to the present review, goal number six: to 'combat HIV and AIDS, malaria *and other diseases*'. The Global Fund (http://www.theglobalfund.org) was created to finance the fight against AIDS, tuberculosis (TB) and malaria, diseases estimated to kill over six million people each year. To date US $11.3 billion has been committed for the fund to support interventions against these 'big three' diseases.

It is interesting to ask how the big three came to dominate the global health agenda. The answer lies in health economics, which has as its lodestar the DALY—the disability-adjusted life year; DALYs are a time-based measure that adds together years of life

lost owing to premature mortality with the equivalent number of years of life lived with disability or illness (Reithinger 2008). The WHO Global Burden of Disease (GBD) project 'draws on a wide range of data sources to quantify global and regional effects of diseases, injuries and risk factors on population health'; the overall burden of disease is assessed using the DALY (http://www.who.int/healthinfo/global_burden_disease/en/). A glance at the leading causes of burden of disease in the African region shows that the top disease is HIV/AIDS (46.7 million DALYs), with malaria fourth (30.9 million DALYs) and TB eighth (10.8 million DALYs); in all the big three cause 23.5 per cent of the disease burden as measured by DALYs in the region. It is easy to see why AIDS, TB and malaria have monopolized the global health agenda as it is a simple matter for those concerned with donor funding to consult the GBD tables and allocate resources accordingly.

However, one unintended consequence of providing such enormous sums to combat the big three has been to effectively erase the latter part of the pledge contained in MDG number six: to combat HIV and AIDS, malaria and other diseases. These 'other diseases' have come to be known as 'the neglected tropical diseases' (NTDs). This group includes such notorious tropical diseases as sleeping sickness, schistosomiasis, river blindness, hookworm, elephantiasis and trachoma. These diseases affect several hundred million people and kill at least half a million annually, yet nowadays they attract little attention from donors, policy makers or public health officials (Molyneux *et al.* 2005). The NTDs comprise 13 parasitic and bacterial infections, including three soil-transmitted

helminth infections (ascariasis, hookworm infection and trichuriasis), lymphatic filariasis, onchocerciasis, dracunculiasis, schistosomiasis, Chagas disease, human African trypanosomiasis (HAT), leishmaniasis, Buruli ulcer, leprosy and trachoma. This could be expanded to include dengue fever, the treponematoses, leptospirosis, strongyloidiasis, food-borne trematodiases, neurocysticercosis, echinococcosis, scabies and a number of other tropical infections. All lead to long-term disability, which, in turn, enhances or maintains poverty resulting from disfigurement or other sequelae of long-term illness, impaired childhood growth and development, adverse outcomes of pregnancy and reduced productive capacity (Hotez *et al.* 2007).

Given the very clear relationship between these diseases and poverty and that such poverty, as defined by the MDGs, is a feature almost exclusively of families living in the developing world, it is difficult to rationalize their 'neglect'. It becomes more puzzling because these diseases are some of the most common infections of people living on less than $2 per day. Molyneux (2008) has recently suggested that the other diseases referred to in the MDGs are ignored by policy makers and politicians who over-focus on targets around the big three diseases; targets which are in any case likely to prove unattainable.

Over-reliance on the burden of disease methodology and the DALY measure in setting health priorities has been criticized by health economists. Mathers *et al.* (2007) acknowledge that the GBD study faces a particular challenge in relation to NTDs given the comparative lack of information available. King & Bertino (2008) suggest that neglect stems in large part from the use of the DALY in policy planning. Where hospitals and clinics are not accessible, accurate measurements of morbidity and mortality from NTDs are difficult to obtain and, for most sub-Saharan African countries GBD almost certainly underestimates disease burden. They conclude that the present DALY framework needs to be revised if the GBD is to become a valid system for determining health priorities because the use of the DALY results in systematic undervaluation of NTDs. King & Bertino (2008) further suggest that the DALY is not value-free when dealing with workers in poor rural settings.

2. EMERGING OR RE-EMERGING ZOONOTIC DISEASES

Nearly all of the infectious diseases that are household names have been transferred to us from domestic livestock diseases (e.g. influenza from pigs; May 2007); 58 per cent of the 1407 recognized species of human pathogen are zoonotic and, of these, 177 are regarded as emerging or re-emerging (Woolhouse & Gowtage-Sequeria 2005). An emerging disease as defined by WHO is one that has appeared in a population for the first time, while a re-emerging disease may have existed previously but is rapidly increasing in incidence or geographical range. Although zoonotic pathogens are the most likely source of emerging and re-emerging infectious disease, only a small minority have caused major epidemics in the human population (Woolhouse &

Gowtage-Sequeria 2005). The newly emerging (or re-emerging) diseases with which we have recently become familiar have all come from animals: bovine spongiform encephalopathy from cattle, severe acute respiratory syndrome from horseshoe bats, Nipah virus from fruit bats and H5N1 avian influenza from poultry. However, the health impact of some of these diseases has not been great in global terms; if we take the example of avian influenza, from 2003 to 2009 there were 413 cases reported globally and 256 deaths (http://www.who.int/csr/disease/avian_influenza/). Yet avian influenza is far from being a neglected disease in terms of funding; US $1.9 billion was pledged to control avian influenza in 2006. The FAO Global Programme for the Progressive Control of Avian Influenza had received (as of 25 July 2008) US $170.5 million (http://www.fao.org/avianflu/). These are large sums when set against the burden of disease data and similar funding scenarios surround the other emerging disease threats. Given the speed at which new viral diseases can emerge and spread, it is understandable that the global community should remain vigilant in terms of surveillance and ensuring trained personnel are on hand in an emergency (Weiss & McLean 2004). These diseases are headline grabbing simply because they pose a direct threat to the wellbeing of the rich, but clearly they are far from being included in the category of neglected.

3. ENDEMIC NEGLECTED ZOONOSES

'Endemic' zoonoses are found throughout the developing world where conditions for their maintenance and spread exist, and they may occasionally give rise to epidemics. Zoonoses have long been recognized and are associated with people living in close proximity to their animals. They affect not only the health of people in the poorest communities but also their livelihoods by lowering the productivity or even causing the death of their livestock. Unlike the emerging zoonoses, the endemic zoonoses fall very much into the category of neglected diseases and, as a result, some are now re-emerging health problems.

A number of recent reports from international organizations have focused on the problem of endemic zoonoses. The joint World Health Organisation and the Department for International Development (DFID) UK Animal Health Programme meeting held in Geneva in September 2005 (WHO 2006) drew attention to the relationship between poverty and the emergence or re-emergence of neglected zoonotic diseases particularly: anthrax, bovine TB, brucellosis, cysticercosis, cystic echinococcus, rabies and HAT. The European Technology Platform for Global Animal Health (http://www.ifaheurope.org/EUPlatform/) has also recognized the importance of neglected zoonoses. In 2005, the European Parliament adopted a resolution on 'Major and Neglected Diseases in Developing Countries', regretting 'the lack of R&D into diseases that almost exclusively affect poor people in developing countries' (European Parliament 2005). This resolution identified the following zoonotic diseases as being of particular concern: leishmaniasis, HAT, TB, Chagas disease, cysticercosis and neurocysticercosis, but

also called for the Commission to broaden its approach to include other neglected diseases. Such a list would include anthrax, rabies and brucellosis, generally regarded as neglected and also major causes of ill health in the poorest communities in developing countries in Africa, Latin America and Asia. Of the 27 infectious diseases listed in the WHO GDB table, 20 can be classified as zoonoses on the basis of documented natural transmission between animals and humans.

Food-borne diseases afflict almost half of the world's population at any given time, yet there is very little information in most countries on the spread of food-borne zoonotic infections among the human population. Brucellosis, bovine TB, some parasitic diseases and salmonellosis are of greatest importance. It is not the purpose of this review to cover all zoonotic diseases, but rather to discuss a number of endemic diseases and consider why they remain a constraint to the livelihoods of the poor in the developing world.

4. THE BURDEN OF ENDEMIC NEGLECTED ZOONOSES

The burden of the endemic zoonoses is usually greatly underestimated and, as with the non-zoonotic NTDs, this has serious consequences in terms of funding for both research and control initiatives. Diagnostics play a significant role in the problems of underestimation of disease. Many zoonotic diseases are notoriously difficult to diagnose as they are often confused with other diseases; for example, where malaria is present, fevers owing to brucellosis may be misdiagnosed. There may simply be no reliable and cheap diagnostic test available. In HAT, the screening test used for the chronic, non-zoonotic form of the disease (caused by *Trypanosoma gambiense*) does not work for zoonotic trypanosomiasis (caused by *Trypanosoma rhodesiense*). Few hospitals in the developing world have the capacity to distinguish between bovine TB and human TB. The result is that estimates of the incidence and burden imposed by the neglected endemic zoonoses seldom reflect their real importance in the communities in which they occur.

The burden of endemic zoonoses falls particularly heavily on the poor as they are often forced to live in close contact with their animals and so are more likely to become infected from these disease reservoirs. Once infected, the poor are less likely to have access to and receive proper treatment. The poor are particularly affected by failure to diagnose their problems; livestock keepers often live in remote rural areas and may not be able to afford the time and money for repeated visits to a health centre. The burden of looking after a seriously ill family member may push the household further into poverty and illness or death of a breadwinner can be devastating for rural households. Moreover, the impact of these diseases is compounded in poor households where zoonoses affect both people and animals; because poor people keep fewer animals, they will suffer disproportionally from the illness or death of their livestock. Livestock are often central to survival strategies in poor

households as they may be sold to meet emergency expenditures—such as school fees, treatment and hospitalization of family members or food in times of shortage (WHO 2006).

As with other neglected diseases, attempts to calculate a global burden for the neglected zoonoses are likely to result in underestimates. As King & Bertino (2008) concluded: 'for most sub-Saharan African countries, GDB burden has been extrapolated from scant data taken from other locations, meaning estimates will be only approximate with a strong tendency towards underestimation of disease burden'—in other words, these estimates are simply, in their opinion, wrong. However, efforts have been made recently to improve on the global estimates of disease burden for three of the endemic zoonoses, HAT, echinoccocosis and rabies, using mathematical modelling to estimate the extent of under-reporting (table 1).

(a) *Sleeping sickness*

The problems of under-reporting of diseases endemic among the rural poor are well illustrated by attempts to calculate the burden of disease for sleeping sickness. There are two forms of sleeping sickness: the chronic *gambiense* and acute *rhodesiense* forms; only the acute form is a strictly zoonotic disease. The causal agent of zoonotic sleeping sickness, *Trypanosoma brucei rhodesiense*, infects humans and wild animals, but in recent years cattle have been found to be the most important reservoir in east and southern Africa (Fèvre *et al.* 2001). Untreated, the disease is always fatal in humans, but has little or no effect on the productivity of indigenous cattle. A study in Uganda found that an astonishing 92 per cent of sleeping sickness deaths are not reported (Odiit *et al.* 2005). When considering relative costs to the local health system, sleeping sickness cases occupy more patient admission time than all other infectious diseases other than malaria; severe malaria accounting for approximately 40 per cent of hospital days and HAT 30 per cent. The true burden of HAT is poorly reflected in many existing assessments (Fèvre *et al.* 2008).

(b) *Cystic echinococcosis*

Cystic echinococcosis (CE) is an emerging zoonotic parasitic disease throughout the world. Hydatid disease is a condition of livestock and humans that arises from eating infective eggs of the cestode *Echinococcus granulosus*. Dogs are the primary definitive hosts of the parasite, with livestock acting as intermediate hosts and humans as aberrant intermediate hosts.

CE not only causes severe disease and possible death in humans, but, unlike sleeping sickness, also causes production losses in livestock. Recently, Budke *et al.* (2006), in a groundbreaking study, estimated the global burden of CE in both humans and livestock, taking into account under-reporting. Human-associated annual economic losses adjusted for under-reporting (including medical costs, wage losses and post-operative deaths) are estimated at US $1.9 billion and livestock losses US $2.1 billion.

Table 1. Ten leading causes of burden of disease (DALYs) in the African region (from WHO 2004) compared with the three endemic zoonotic diseases for which detailed global burdens have been calculated to allow for under-reporting.

		DALYs (millions)
	disease or injury	
1[a]	HIV/AIDS	46.7
2	lower respiratory infections	42.2
3	diarrhoeal diseases	32.2
4[a]	malaria	30.9
5	neonatal infections	13.4
6	birth asphyxia and birth trauma	13.4
7	prematurity and low birth weight	11.3
8[a]	tuberculosis	10.8
9	road traffic accidents	7.2
10	protein-energy malnutrition	7.1
	selected endemic zoonoses	
	rabies (Africa and Asia)	1.7
	HAT	1.3
	cystic echinococcus (global)	0.3

[a]The big three diseases.

(c) *Rabies*

Despite its notoriety as a fatal zoonotic disease and that effective and economical control measures are available, rabies remains a neglected disease in the developing world. Hard data on incidence of rabies are difficult to obtain and under-reporting is a significant factor. To quantify the burden of rabies in Africa and Asia and to allow for under-reporting, Knobel et al. (2005) developed an elegant predictive model based on the numbers of dog bites—bites are reported more frequently than human cases of rabies; the dog bite data were then used to infer numbers of human deaths. The model assumed that the human population at risk from canine rabies was the number of people living in areas where the dog population was sufficient to maintain the disease endemically. The threshold density for rabies persistence was calculated to be 4.5 dogs km^{-2}. Using this model, it was calculated that there were over 55 000 human deaths from rabies per year in Africa and Asia, leading to a total DALY score of 1.7 million, and it was calculated that the total global cost of rabies was US $583 million. These costs are borne almost entirely by people in the developing world where more than 99 per cent of all fatalities from this disease occur (WHO 1998).

Apart from the three diseases for which detailed global burdens have been calculated to allow for under-reporting, attempts to assess the impact of other neglected zoonoses have been proved difficult for a variety of reasons, best illustrated by the following examples.

(d) *Bovine tuberculosis*

Mycobacterium tuberculosis is the most common form of human TB and is one of the big three killer diseases worldwide. Bovine TB, in contrast, is now a very rare disease in the West; for example, in the UK since 1990, there has been only one case of indigenous human *Mycobacterium bovis* infection recently acquired from an animal source. Most cases of zoonotic TB are attributed in the UK, to either (i) reactivation of long-standing latent infections acquired before adoption of milk pasteurization, or (ii) infections contracted abroad (de la Rua-Domenech 2006). However, in the developing world where it is transmitted zoonotically by drinking un-boiled milk and from the close contact of humans with their livestock, *M. bovis* may contribute significantly to the human epidemic (Cosivi et al. 1995). In a study of a district of Tanzania, *M. bovis* was isolated from 4 per cent of cases of pulmonary TB (Cleaveland et al. 2007); this compares with between 0.5 and 1.5 per cent of all the culture-confirmed TB cases in industrialized countries (de la Rua-Domenech 2006).

(e) *Chagas disease*

Chagas disease is the most important parasitic disease of the Americas and, like other NTDs, is associated with poverty. Caused by *Trypanosoma cruzi*, with reservoirs in dogs and a range of wild animal hosts, Chagas disease is mainly transmitted by triatomine bugs, but can also be transmitted congenitally, through blood transfusion or organ transplantation, and through the ingestion of contaminated food or fluids. Most infected people do not know that they have become infected, as the symptoms are benign in the initial acute stage, after which the disease may be asymptomatic for many years (Tarleton et al. 2007). Because of this long asymptomatic phase, Chagas disease is considered a 'silent killer' (Maguire 2006), and it is difficult to estimate the true burden of disease. It is estimated that there are up to 15 million existing cases of Chagas disease, with 50 000–200 000 new infections occurring each year.

(f) *Leishmaniasis*

Leishmaniasis is considered the third most important vector-borne disease globally, with an estimated 350 million people at risk in 88 countries, 12 million cases worldwide and around 50 000 deaths every year (WHO 2004). Leishmaniasis is not a single disease but rather a complex of vector-borne diseases caused by over 20 species of *Leishmania*. The leishmaniases can be roughly divided into two groups of diseases: visceral (a chronic systemic disease that can be fatal if left untreated) and cutaneous (causing non-fatal but often extensive skin ulceration). However, when it comes to assessing the burden imposed by these diseases, the picture is not so clear. WHO data indicate that the leishmaniases contribute an estimated 2.4 million DALYs (WHO 2004) and while these figures are regularly quoted, there are questions over their validity. Bern et al. (2008) suggest that current methods of assessing disease burden fail to account for the variation in clinical presentation and distribution of the disease, demanding intense medical interventions within small foci. As with other neglected diseases, reliable data (on incidence, duration and impact of the various syndromes associated with leishmaniasis) are lacking, and it is generally agreed that the disease burden widely quoted for leishmaniasis is inaccurate and out of date (Bern et al. 2008; Reithinger 2008).

(g) Anthrax

Human cases of anthrax, caused by *Bacillus anthracis*, are associated with infections in sheep, goats or cattle or exposure to contaminated animal products including wool, hides or carcasses. Pasture contamination is the source of most animal cases in endemic countries. Global estimates of disease burden are not given for anthrax as WHO considers that anthrax 'is not a major public-health problem in the world today, although occasional epidemics do occur'. However, because of its potential for use as a biological weapon, anthrax is now the focus of much research to develop improved vaccines. In contrast to the fear that mention of this disease in the developed world provokes because of its bio-terrorist potential, its role in causing illness in poor livestock-keeping communities and sudden deaths in their herds and flocks is largely ignored (WHO 2006).

(h) Cysticercosis

Cysticercosis is caused by ingestion of *Taenia solium* eggs dispersed by a human carrier, the primary intermediate host being the pig. Human cysticercosis is associated with poverty and is endemic in South and Central America, China, the Indian subcontinent and southeast Asia and sub-Saharan Africa. Neurocysticercosis is the most important neurological disease of parasitic origin in humans and the leading cause of late-onset epilepsy in areas where *T. solium* is endemic. When cysticercosis is associated with epilepsy, the burden of disease will dramatically increase owing to the social stigmatization and discrimination which can follow and which may be a barrier to diagnosis and treatment. As neurocysticercosis cases tend to be found in clusters, the epilepsy related to it can result in a particularly high socio-economic burden for poor families in the endemic areas (WHO 2003).

It has been estimated that worldwide around 2.5 million people are infected with *T. solium* and that every year 50 000 deaths are caused by neurocysticercosis (Mafojane *et al.* 2003). The global burden of symptomatic cysticercosis in the 75 million people living in the endemic zone in Latin America was estimated to amount to 400 000 cases (Bern *et al.* 1999). Prevalence of cysticercosis in pigs in Latin America varies from less than 2 per cent to more than 75 per cent, with an average of 17 per cent (Pawlowski *et al.* 2005). Following an increase in pig production in smallholder farms, neurocysticercosis is an emerging public health problem in eastern Africa, with up to 45 per cent of pigs infected in some villages in Uganda; in many other countries, cysticercosis rates in pigs are around 10 per cent (Phiri *et al.* 2003). In most Asian countries, accurate data on *T. solium* is scarce (Singh *et al.* 2002), but the disease is known to occur frequently in parts of Indonesia, China, India and Vietnam (Pawlowski *et al.* 2005).

5. PROSPECTS FOR CONTROL OF NEGLECTED ZOONOSES

It is not our intention in this review to cover all the efforts that have been or are being made to control the neglected zoonoses but rather to consider some examples of control programmes and note the lessons learned from them. There is a temptation when considering control of diseases affecting the poor to opt for the 'big push'—global solutions that, while desirable, have little chance of effective implementation given the socio-economic conditions surrounding their epidemiology. The current tendency among aid agencies is to talk of the 'eradication' of diseases; for example, the eradication of malaria is now considered by some to be an achievable goal.[1] There is of course the well-documented example of eradication, in the proper sense of the term, of smallpox (declared eradicated 1980), and polio has been eliminated in high-income and middle-income countries. The Global Rinderpest Eradication Programme is of more relevance to the present review; the whole of Asia is thought to have been disease-free since 2000 and most of Africa is also now free from the disease. According to the FAO 'There is no known technical reason why eradication of rinderpest should not now be achieved' (http://www.fao.org/Ag/againfo/programmes/en/grep/home.html). What these rare examples of eradication have in common is that the diseases are caused by viruses, for which technically superb vaccines have been developed. Eradication of rinderpest was made possible by the development of a most effective vaccine by Walter Plowright in the 1950s; this vaccine was subsequently modified to deal with the problem of maintaining a cold chain in the tropics (House & Mariner 1996). This potential for global eradication is a feature that sets some vaccines apart and attracts the attention of economists as on-going costs are eliminated (Beutels *et al.* 2008). However, even when excellent vaccines are available, this is no guarantee that elimination or eradication is easily achieved. For example, rabies kills 55 000 people every year mainly in Africa and Asia, despite there being very effective vaccines available for humans, dogs and even for wildlife. Vaccines for foxes have been proved very effective in eliminating rabies from the wildlife reservoir in western Europe (Smith *et al.* 2008), but extending this scheme to the whole of the current EU member states would prove costly (€10M to €16M; Freuling *et al.* 2008). Dog-transmitted rabies is the greatest threat, and in order to prevent the transmission of rabies in a dog population, it is thought necessary to vaccinate a minimum of 60–70% of dogs. Even countries with sufficient resources do not often meet and sustain these rates. One reason for such failure might be that dog owners feel that it is too expensive to vaccinate their pets. It was estimated in 1998 that the cost of vaccinating dogs in developing countries, where more than 99 per cent of all human deaths from rabies occur, ranged from US $1.19 in the Philippines to US $2.70 in Malawi (Meltzer & Rupprecht 1998); in communities living on $1 per day, dog vaccination would not be lightly undertaken. To address this problem, the Alliance for Rabies Control (http://www.rabiescontrol.net/) was established in 2005 to raise awareness about the continued presence of this neglected disease, support rabies control programmes and promote educational initiatives.

Control and eradication programmes for brucellosis have been successfully implemented within the European Union (Godfroid & Käsbohrer 2002), but brucellosis remains an important disease in sub-Saharan Africa. The incidence is the highest in pastoral production systems and decreases as herd size and size of landholding decrease (McDermott & Arimib 2002). A recent study has shown that most cases in Kampala, Uganda, resulted from consumption of raw milk transported from peri-urban and rural areas of Kampala and/or dairy production areas outside Kampala (Makita *et al.* 2008). The most rational approach for preventing human brucellosis is to control infection in animals. Although there are effective vaccines for use in cattle and goats, control efforts in poor endemic areas have failed mainly because of inadequate infrastructure and funding. To be effective, control measures should continue over a prolonged period, complemented with a monitoring system; such systems are difficult to sustain once the number of cases begins to decrease (Franco *et al.* 2007).

For many neglected diseases, there are no effective vaccines available, making elimination a formidable task. This has its origins in the biology of the causative organisms; beyond the viruses (and some bacteria) producing effective and safe vaccines has not proved easy. The vaccines effective against protozoal diseases in animals, such as theilerosis and avian coccidiosis, involve exposure to virulent or attenuated parasites so that immunity to natural infection is established early in life (Jenkins 2001). Among the zoonotic protozoa, the trypanosomes offer a particularly salutary tale of the fruitless search for vaccines. Expert opinion is now agreed that a vaccine for sleeping sickness is highly unlikely because these parasites make many thousands of antigenic variants, allowing them to evade the host immune response (Stuart *et al.* 2008). Public–private partnerships (PPPs) have been set up to improve the diagnosis (Foundation for Innovative Diagnostics: http://www.finddiagnostics.org) and treatment of neglected diseases, including sleeping sickness (Drugs for Neglected Diseases initiative: http://www.dndi.org).

The importance of the animal reservoir in controlling Rhodesian sleeping sickness has long been recognized, and the simplistic response to this insight—destroying wild animal hosts—was neither a successful nor an acceptable solution. We have only recently been able to assess the importance of the domestic animal reservoir in sleeping sickness with the validation of a molecular marker (SRA gene) for the identification of human infective parasites (Welburn *et al.* 2001). Studies of endemic foci in Uganda have revealed just how important the domestic reservoir can be, with up to 40 per cent of cattle carrying *T. brucei rhodesiense* (Fèvre *et al.* 2001). Given the importance of the animal reservoir in Rhodesian sleeping sickness, vector control is easily the best control option (Welburn *et al.* 2006). The enormous cost of tsetse control programmes meant they became unsustainable if the goal of elimination was not reached. There are recent examples of effective elimination of geographically isolated tsetse populations or populations on the ecological limits of tsetse distribution, such as the sterile insect project on Unguja Island, Zanzibar (Vreysen *et al.* 2000), and the aerial spraying of the Okavango Delta in Botswana (Kgori *et al.* 2006). The Pan African Tsetse and Trypanosomosis Eradication Campaign (http://www.who.int/trypanosomiasis_african/partners/pattec/en/index.html) was established in 2000 with support from the African Development Bank to deal with trypanosomiasis in general in Africa rather than to tackle human sleeping sickness. However, if isolation of a tsetse population is not feasible, then reinvasion is a constant threat raising questions of economic sustainability, let alone the desirability of adopting tsetse elimination as a goal (Hargrove 2003; Enserink 2007).

The development of innovative tools to trap and kill tsetse flies has moved the focus of tsetse control from grandiose elimination schemes to local control interventions involving communities and the efforts of farmers themselves. Treating host animals directly with insecticide became a practical proposition with the introduction of long-lasting formulations of synthetic pyrethroids to be poured on or sprayed on cattle. Recent research has shown that it is not necessary to treat the whole animal but only the parts of cattle on which tsetse preferentially feed—the legs and the belly (Torr *et al.* 2007); this restricted application technology (RAP) has brought trypanosomiasis control within the reach of poor farmers in Africa at a cost of around US 2 cents/animal/treatment. A PPP—The Stamp Out Sleeping Sickness campaign: http://www.sleepingsickness.org/—aims to control the northward spread of Rhodesian sleeping sickness in Uganda (Picozzi *et al.* 2005) using RAP combined with trypanocidal drugs.

The 'Southern Cone' initiative to eliminate Chagas disease also employed a very simple technique to eliminate the insect vector of disease; spraying houses with insecticide had a dramatic effect on transmission rates in the southern part of South America (Dias *et al.* 2002) because the only vector, *Triatoma infestans*, is an obligate human feeder and is restricted to human habitation. However, this approach may prove difficult to replicate elsewhere in Latin America where there are many different vector species, each with distinct feeding, infestation behaviour patterns and wild reservoirs (Tarleton *et al.* 2007).

Despite substantial efforts, no effective vaccine is available for leishmaniasis (Kedzierski *et al.* 2006). First-generation candidate vaccines against leishmaniasis, prepared using inactivated whole parasites, have recently undergone clinical trials. Although these studies gave some indication of protection, the trials were an overall failure (Noazin *et al.* 2008). The *Leishmania donovani* 'complex' is now thought to comprise only two species, *Leishmania infantum* and *L. donovani*, which are responsible for visceral leishmaniasis (VL; Lukes *et al.* 2007). Dogs are the major reservoir of *L. infantum* in Brazil, but direct treatment of the canine reservoir is seldom effective; consequently the Ministry of Health and the Ministry of Agriculture, Livestock and Food Supply have recently prohibited the treatment of canine VL in Brazil (Dantas-Torres 2008). Control of VL in Brazil has instead focused

on control of the sandfly vector by residual insecticide spraying and culling of positive dogs. Although effective in urban areas with high concentrations of sandflies, residual spraying of insecticides is no longer tenable in most situations. Effectiveness of culling may be limited by the long interval between diagnosis and dog removal, the sensitivity of diagnostic tests and the natural objection of the dog owner to the cull (Moreira *et al.* 2004). Moreover, there is a very high turnover of dogs by replacement in Brazil, and dog culling as a control strategy for VL is no longer considered effective (Nunes *et al.* 2008).

The introduction of deltamethrin-impregnated dog collars in several countries is a novel method of leishmaniasis control that has met with varying levels of success. A very significant reduction in canine incidence (over 80%) has been demonstrated in trials of treated dog collars in Italy (Foglia Manzillo *et al.* 2006; Ferroglio *et al.* 2008). Following a field trial in Brazil, mathematical modelling suggested that community-wide use of treated dog collars should be more effective than the currently practised dog culling strategy especially where transmission rates are high; impact of collaring is dependent on collar coverage and also the rate of loss of collars (Reithinger *et al.* 2004). Monthly application of pour-on insecticides has also been shown to be effective in reducing canine incidence in Italy (Ferroglio *et al.* 2008) and Brazil (Giffoni *et al.* 2002). Interestingly, it has been shown in Nepal that increased bed-net usage could also decrease the incidence of VL (Bern *et al.* 2000). Dogs are thought to act as disease reservoir for VL in the Horn of Africa but, as with other neglected diseases in Africa, poverty, poor housing, crowded conditions, lack of bed nets and collapse of healthcare systems all intensify the spread of VL (Bern *et al.* 2008). Elimination of VL remains a formidable undertaking in the developing world, requiring integrated control and treatment programmes (Joshi *et al.* 2008) and may well be a pipe dream at present (Joshi *et al.* 2006).

Given the relatively uncomplicated epidemiology of *T. solium*, elimination or even eradication might seem a reasonable and even feasible goal. However, as the simplest solution to this problem is the provision of clean water and sanitation combined with veterinary sanitary measures, such as enforced meat inspection and treatment of infected animals, the reality is formidable. The size of the task becomes clear when we examine global data on water and sanitation; WHO estimated in 2002 (http://www.who.int/water_sanitation_health/publications/facts2004/en/index.html) that 1.1 billion people (17% of the global population) lacked access to improved water sources, and in sub-Saharan Africa, 42 per cent of the population was without improved water. At the same time, 2.6 billion people lacked access to improved sanitation; this represented 42 per cent of the world's population, and in sub-Saharan Africa, sanitation coverage is a mere 36 per cent. Of more relevance to cysticercosis transmission, only 31 per cent of the rural inhabitants in developing countries had access to improved sanitation, as opposed to 73 per cent of urban dwellers.

There have been advances in the laboratory diagnosis of *T. solium* infections using immunodiagnostics (Garcia *et al.* 2000; Pawlowski *et al.* 2005). Detection of the presence of tapeworms is useful for control interventions as removal of the adult tapeworm breaks the transmission cycle. Diagnosis of adult tapeworms relies on the detection of parasite antigens in faeces (coproantigens), and such tests have been shown to have good specificity and sensitivity (Allan *et al.* 2003). Vaccines based on recombinant parasite antigens have been developed recently for use in pigs to prevent *T. solium* transmission (Lightowlers *et al.* 2003). While pig vaccines may prove useful in commercial settings, take-up of such vaccines by poor farmers in rural areas where pigs are left free to run and feed on waste seems unlikely. Treatment of human *T. solium* carriers with praziquantel would be the simplest and most effective method of control and has been used in mass treatment programmes in China and Latin America (Pawlowski *et al.* 2005). Despite progress in operational research, global eradication of *T. solium* is thought to be unlikely in the near future (Pawlowski *et al.* 2005).

As with cysticercosis, there have been improvements in the diagnosis and treatment of human and animal CE, the diagnosis of canine echinococcosis and vaccination against *E. granulosus* in animals. Control programmes against hydatidosis have been implemented in several endemic countries (Craig & Larrieu 2006). Despite some success in island states (e.g. Iceland), it is acknowledged that elimination of human CE is a formidable task and achieving such a goal, even in the most favourable environments, may take up to 20 years (Craig *et al.* 2007).

6. DISCUSSION

We have seen that neglect, in terms of disease control, has come about in part as an unintended consequence of adoption of a system of prioritization and hence funding that, while logical, is not universally accepted as being either fair or sensible. When we turn to the endemic zoonoses of the developing world, they are best described as the 'more neglected diseases'. This has come about largely owing to the difficulty in defining the burden of these diseases, which are subject to gross under-reporting. The frequent division of responsibility for the control of zoonotic infections between medical and veterinary authorities provides a further barrier to sustainable control.

There is also a political dimension to prioritization, in that provider interest may also play a part. Shiffman (2006) suggests that when a disease is perceived to be a threat to the people of rich countries or when pharmaceutical companies see the disease as a source of potential sales, donors are more likely to pay attention. Trade and industrial interests may increasingly influence the tackling of global health problems (Ollila 2005) so that NTDs are given a low priority simply because they offer negligible marketable opportunities (Boutayeb 2007). Neglect of tropical diseases may be connected to the fact that these diseases do not pose any major threat to rich countries and no powerful interest groups have mobilized around them.

Canning (2006) argues that the overall burden of disease should not be the criterion for priority setting, but that cost-effective interventions should be prioritized. Such a cost-benefit approach, combining health and economic benefits, would allow the health sector to present arguments to policy makers based on the rate of return on investment rather than tables of DALYs. While many people find objectionable the assignment of a monetary value to health, many health interventions in low-income countries have exceptionally high rankings in terms of cost-benefit ratios. Canning (2006) suggests that interventions against 'neglected' tropical diseases should be viewed as investments in human capital and form an integral part of global poverty reduction.

There is also a very powerful utilitarian argument put forward by Molyneux (2008) in suggesting that many of the neglected diseases represent 'low-hanging fruit' for control and elimination, yet donors ignore such opportunities despite the availability of cheap or donated drugs and ample evidence that such interventions are effective. There is support from King & Bertino (2008) for this view, calculating that the application of the DALY in policy estimates in effect discounts the utility of comprehensively treating NTDs. Molyneux (2008) backs up his utilitarian argument by considering the biology of neglected diseases; the reproductive lifespan of the causative organisms of some neglected diseases or their vectors is long: *Wuchereria bancrofti* (4–6 years); *Onchocerca volvulus* (12–14 years); triatomine bugs (vectors of *T. cruzi*; approx. 2 years); Guinea worm (*Dracunculus medinensis*; 1 year to reach maturity). These organisms are either macro-parasites, have long-lived vectors, or are slow growing as in leprosy. Molyneux (2008) contrasts successes in controlling chronic biologically stable infections with the difficulty of controlling malaria, TB and HIV/AIDS. The big three, with their inherently different biology, incur problems caused by the rapid evolution of drug resistance and the relatively high cost both of existing drugs and of the development of affordable alternative products. Moreover, the likelihood that drug resistance and insecticide resistance will develop in diseases caused by macro-parasites or macro-vectors is small by comparison with that in malaria, TB and HIV/AIDS. As the organisms responsible for NTDs have little capacity to change, controlling them is often within the capacity of local health systems as constant revision of control strategies is unnecessary. Some of the neglected endemic zoonoses we have considered meet Molyneux's (2008) utilitarian criteria. For example, *T. brucei rhodesiense* is transmitted by the tsetse fly—a macro-vector reproducing very slowly, particularly susceptible to insecticides with no sign of insecticide resistance emerging (Maudlin 2006). It is no surprise that a simple and cheap insecticide-based methodology has been shown to be effective in controlling sleeping sickness in Uganda (http://www.sleepingsickness.org/).

The most positive and effective response to neglect of the diseases affecting poor people in the developing world have been for interested parties to form partnerships, fundraise and provide advocacy for the control of these diseases. Successful public–private partnerships have been formed for the control of 'worms' (e.g. The Global Programme to Eliminate Lymphatic Filariasis—http://www.filariasis.org/—and The Global Network for NTDs—http://globalnetwork.org/). Advocacy for neglected diseases has been improved by the foundation of PLoS NTDs (http://www.plosntds.org/). The key to the success of the global chemotherapy-based control programmes has been the availability of simple and effective drugs such as praziquantel (Lammie *et al.* 2006), which could also be used effectively for control of zoonotic cysticercosis regionally (Pawlowski *et al.* 2005). However, as with schistosomiasis (Fenwick 2006), a sustainable reduction in transmission of cysticercosis will be achieved only by improving health education, training, hygiene behaviour, water supply and sanitation.

The availability of cheap and effective vaccines is no guarantee that a disease is in danger of extinction, as we have seen in the case of rabies. Even in poor regions where canine rabies continues to be highly endemic, simply increasing awareness about the cause of the disease and how it may be prevented could reduce its incidence (Briggs & Hanlon 2007). Health education has also proved effective in controlling *T. solium* transmission in Mexico and, most importantly, independently of direct treatment interventions (Sarti *et al.* 1997).

What cysticercosis and sleeping sickness have in common is the prerequisite that human and animal health interventions are integrated, underlining the need for a 'one medicine' approach to human and animal health (Zinsstag *et al.* 2005) and particularly the need to integrate data on human and animal health (Singer & Ryff 2007).

Control of endemic zoonotic diseases is reliant on surveillance but, as with other public-sector animal health services, surveillance in sub-Saharan Africa is rarely implemented outside southern Africa. Brucellosis, for example, is often ignored in humans, and most cases go undiagnosed and untreated (McDermott & Arimib 2002). This is a serious constraint shared with other endemic zoonoses such as sleeping sickness, which could be met by more effective monitoring systems; this in turn is predicated on the development of easy to use diagnostics that must be made available very cheaply if they are ever to be more than research tools.

Finally we should consider whether elimination is always the best option when considering how to deal with endemic diseases in the developing world. Feachem & Sabot (2008) have suggested that this strategy of disease elimination might have the unintended consequence of encouraging donors to invest in elimination programmes at the expense of under-resourced control efforts. Feachem & Sabot (2008) question what interventions should be used in areas with weak health systems, particularly in sub-Saharan Africa, and how much elimination will actually cost. This dilemma is perhaps best illustrated by efforts to deal with sleeping sickness over the last century: whether tsetse should be controlled or eradicated and if so, how this should be achieved. Hargrove (2003) gets to the heart of the matter when he suggests

that this may come down simply to the power of the different interest groups involved; the perceived benefit of eradicating tsetse depends on the extent to which the flies either upset, or appear to protect, the distinctive type of land use beloved by each lobby, and because the people and institutions that recommend attacking the fly often prefer the particular control technique that they themselves have developed or refined, or are best able to afford. We may note that the poor farmer, at risk from disease and loss of livelihood, is rarely involved in this debate.

This tension, between the respective merits of control and elimination strategies, is reflected more generally in differences at a macro-level aired by development economists. For example, Sachs (2005) has argued that if the developed countries increased their foreign aid substantially, the world could eliminate extreme poverty by 2025. By contrast, Easterly (2006) suggests the developed world should free itself from such Panglossian goals and concentrate on simple things that can be done well: modest interventions, small-scale programmes with built-in feedback. Given this logic, it is encouraging from the viewpoint of controlling endemic diseases that Easterly (2006) notes that foreign aid successes are found more frequently in public health than in other sectors and suggests that this is due to the immediate feedback that health programme beneficiaries give to programme workers.

Development experts are agreed that every child has a right to a life free from hunger disease and suffering and that, in the case of the world's poor, this is clearly not happening. However, as Easterly (2001) concludes, 'it is much easier to describe the problems facing poor countries than it is to come up with workable solutions to their poverty'; dealing with the neglected diseases is no exception. One thing is clear—setting health priorities by fashion is best avoided (May 2007).

ENDNOTE

[1]We should note here that eradication and elimination are often confused. Elimination is the reduction to zero of the incidence of a disease in a defined geographical area as a result of deliberate efforts. Eradication is the permanent reduction to zero of the worldwide incidence of infection as a result of deliberate efforts. Importantly, elimination demands continued efforts to prevent re-establishment while intervention efforts are no longer needed if eradication is achieved (Molyneux *et al.* 2004).

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