

The neglected zoonoses—the case for integrated control and advocacy

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Abstract

The neglected zoonotic diseases (NZDs) have been all but eradicated in wealthier countries, but remain major causes of ill-health and mortality across Africa, Asia, and Latin America. This neglect is, in part, a consequence of under-reporting, resulting in an underestimation of their global burden that downgrades their relevance to policy-makers and funding agencies. Increasing awareness about the causes of NZDs and how they can be prevented could reduce the incidence of many endemic zoonoses. Addressing NZDs by targeting the animal reservoir can deliver a double benefit, as enhanced animal health means a reduced risk of infection for humans, as well as improved livelihoods through increased animal productivity. Advocacy for NZD control is increasing, but with it comes a growing awareness that NZD control demands activities both in the short term and over a long period of time. Moreover, despite the promise of cheap, effective vaccines or other control tools, these endemic diseases will not be sustainably controlled in the near future without long-term financial commitment, particularly as disease incidence decreases and other health priorities take hold. NZD intervention costs can seem high when compared with the public health benefits alone, but these costs are easily outweighed when a full cross-sector analysis is carried out and monetary/non-monetary benefits—particularly regarding the livestock sector—are taken into account. Public–private partnerships have recently provided advocacy for human disease control, and could prove equally effective in addressing endemic zoonoses through harnessing social impact investments. Evidence of the disease burdens imposed on communities by the NZDs and demonstration of the cost-effectiveness of integrated control can strengthen the case for a One Health approach to endemic zoonotic disease control.

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The origins of neglect

The Millennium Development Goals aimed, by 2015, to halve the proportion of people living on less than a dollar a day, and to halve the proportion of people suffering from hunger. Millennium Development Goal 6 aimed to 'combat Tuberculosis, HIV and AIDS, malaria (the 'big three') and other diseases';

the major focus of these 'other diseases' became known as the neglected tropical diseases (NTDs) [1]. In 2008, Molyneux [2] suggested that these 'other diseases' were being ignored by policy-makers and politicians, who over-focused on targets around the 'big three' diseases; targets that were likely to prove unattainable. The Global Fund (<http://www.theglobalfund.org>) was created to finance the fight against the 'big three', but only limited funding was mobilized to scale up NTD interventions.

The NTDs comprise 17 viral, parasitic and bacterial infections, and include dengue/severe dengue, rabies, Chagas disease, human African trypanosomiasis (HAT), leishmaniasis, three soil-transmitted helminth (STH) infections (ascariasis, hookworm infection, and trichuriasis), lymphatic filariasis, onchocerciasis (river blindness), dracunculiasis (guinea worm disease), schistosomiasis, cysticercosis/taeniasis, foodborne

trematodiasis, echinococcosis, lymphatic filariasis, Buruli ulcer, leprosy, trachoma, and Yaws. The NTDs affect several hundred million people (with a disease burden equivalent to malaria), killing at least half a million annually, but continue to attract relatively little attention from donors, policy-makers, and public health bodies [1]. NTDs are both drivers and manifestations of poverty and social inequality that often lead to long-term disability [2].

In 2005, the European Parliament adopted a resolution on 'Major and Neglected Diseases in Developing Countries', regretting 'the lack of R&D into diseases which almost exclusively affect poor people in developing countries' [3]. The resolution identified leishmaniasis, HAT, tuberculosis (TB), Chagas disease and neurocysticercosis as causes for concern, and called for the European Commission to broaden its approach to other NTDs (including, among others, anthrax, rabies and brucellosis, rabies, and echinococcosis (hydatid disease)). These neglected zoonotic diseases (NZDs) constitute a major burden for poor rural communities [4–6].

Since then, more than a decade of advocacy for NTDs has resulted in ambitious control and elimination targets being set by the WHO for 2020, and several successful partnerships have been formed to raise funds and provide advocacy for NTD control, including the Global Programme to Eliminate Lymphatic Filariasis (<http://www.filaria.org/>) and the Global Network for Neglected Tropical Diseases (<http://globalnetwork.org/>). Such advocacy resulted in the 2012 'London Declaration' (<http://unitingtocombatntds.org/resource/london-declaration>), followed by the World Health Assembly (WHA) Resolution WHA66.12 in May 2013. WHA66.12 targets all 17 NTDs and addresses diseases as co-endemic clusters rather than individually, marking a distinct change in our approach to dealing with these diseases of poverty.

WHA66.12 was a turning point for advocacy for the NTDs; however, although a number of NZDs were included (rabies, echinococcosis (hydatid disease), leishmaniasis, *Trypanosoma brucei rhodesiense* sleeping sickness, and *Taenia solium* cysticercosis), three major bacterial NZDs (anthrax, brucellosis, and bovine TB) were omitted. Examination of all resolutions arising from the 66 WHAs (from 1948 to 2013) indicated that only 21 resolutions targeted one or more NZDs (<4% of the total resolutions passed to date on infectious diseases) [7]. A WHA resolution for all NZDs is an essential prerequisite for advocacy [7].

Costs and burden of NZDs

The impact of NZDs falls most heavily on the poor, impacting on the health systems in which they live. Affected populations

often live in close contact with their animals, and are at risk for infection (directly or indirectly from the animal reservoir). Once infected, poor people have less access to the required health information that would lead to appropriate diagnosis and treatment. Primary healthcare facilities are often not readily accessible in remote rural areas or in slums, and patients can ill afford the time and money for repeated visits to a health centre. The burden of caring for a sick family member can push households further into poverty, and the death of a breadwinner can devastate a rural household.

Livestock are central to survival strategies in poor households, and may be sold to meet emergency expenditures—such as school fees, treatment and hospitalization of family members, or food in times of shortage. Poorer people keep fewer animals and suffer disproportionately from any illness or death of their livestock, so that intervening to control NZDs improves both the health of livestock and livelihoods, while at the same time protecting human health [4–6].

'Neglect' is, in part, an unintended consequence of the adoption of a system of disease prioritization, which impacts directly on investment and funding. Calculating a global burden of human disease (GBD), although logical, does not offer an equitable strategy on which to base investments to control neglected diseases. Where hospitals and clinics are not accessible, accurate measurements of morbidity and mortality resulting from NTDs are difficult to obtain, and, for most sub-Saharan African countries, use of the disability-adjusted life-year (DALY) can result in systematic undervaluation of NTDs [8]. Over-reliance by policy-makers on GBD methodology in setting health priorities tends to devalue diseases for which reliable metrics are not available [9]. King and Bertino [8] concluded that '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' [9]. Efforts have been made to improve on GDB estimates for three endemic zoonoses (rabies, echinococcosis, and HAT) by the use of mathematical modelling to estimate under-reporting, but, for most NZDs, data are scant. Whereas the socio-economic burden has been considered for several parasitic zoonoses [10], the NZDs are largely under-reported, which contributes to underestimation of the disease burden. In humans, NZDs may be confused with other diseases; for example, where malaria is present, fevers due to brucellosis [11] or HAT [12] are often misdiagnosed. Although diagnostic tests are available for screening NZDs in animal populations, many are not standardized for routine surveillance in the community in developing world settings, and the absence of a reference standard is problematic [13,14].

Canning [15] argues that the overall burden of disease should not be the criterion for priority-setting, but rather that the cost-effectiveness of interventions should be used. Cost-benefit approaches that combine health and economic benefits allow the health sector to present arguments to policy-makers that are based on the rate of return on investment rather than tables of DALYs; interventions against NTDs should be viewed as investments in human capital, and form an integral part of global poverty reduction [15]. The cost benefits of interventions against the NZDs in low-income countries can have exceptionally high rankings—targeting the animal population as the source of the disease in people can be highly cost-effective, as interventions to control zoonoses are often best applied in their animal hosts. The costs of such interventions, together with animal health benefits, will drive the cost-effectiveness of intervention strategies. The impact of intervention may be estimated in terms of DALYs prevented (notwithstanding the caveats surrounding the DALY) or improved livestock productivity [16].

NZDs are endemic throughout the developing world, and can give rise to outbreaks and epidemics, with poly-infection being common. NZDs predominantly affect individuals living in close proximity to their animals who are exposed to disease vectors or poorly regulated animal products.

Anthrax

The role of *Bacillus anthracis* in causing illness in poor livestock-keeping communities and the impact of sudden deaths in their herds and flocks are largely ignored by policy-makers in developing countries [4–6]. Anthrax is transmitted by spores in contaminated soil, infecting humans via contact or consumption of dead animals or animal products. Contamination of pasture is the source of most animal cases in endemic countries. In animals, the disease is almost always fatal, and vaccination forms the only basis for effective control. Global estimates of disease burden are not provided for anthrax, as the WHO considers that anthrax 'is not a major public-health problem in the world today, although occasional epidemics do occur' [4–6]. Investment in anthrax research is maintained largely because of its bio-terrorist potential, and remains the focus of research for improved vaccines.

Bovine TB

The non-zoonotic *Mycobacterium tuberculosis* TB is the most common form of human TB, and is one of the 'big three' killer diseases worldwide. Although less is known about the zoonotic *Mycobacterium bovis* TB, most cases in the developed world are attributed to either reactivation of long-standing latent infections acquired before the adoption of milk pasteurization, or infections contracted abroad. In the developing world, where

M. bovis is acquired mainly through the consumption of unpasteurized dairy products and from close contact with livestock, the contribution of *M. bovis* to TB epidemics of humans is unknown. *M. bovis* TB is frequently found outside the lungs, and it is almost impossible in impoverished settings to distinguish between regular TB, which responds to common drugs (notwithstanding the complexities arising from drug-resistant strains), and *M. bovis* TB, which requires more expensive drug therapy. In a study of a district of Tanzania, *M. bovis* was isolated from 4% of cases of pulmonary TB [17]; this compares with between 0.5% and 1.5% of all culture-confirmed TB cases in industrialized countries [18].

Brucellosis

The world's most widespread zoonosis affects cattle, sheep, goats, pigs, and other animals, leading to abortion, infertility, and low milk yields. Humans acquire brucellosis from direct contact with livestock or from drinking unpasteurized milk. Brucellosis is a chronic disease with a risk of disabling consequences, but is rarely fatal in affected humans. Brucellosis is frequently misdiagnosed as malaria, typhoid, or venereal disease [11]. Misdiagnosis is expensive; individuals incur significant expense in failing to acquire diagnosis and treatment, and fail to conduct their daily activities, through being unwell. Across the developing world, brucellosis is still a very common but often neglected disease, and constitutes a major under-reported problem. Brucellosis is the most common bacterial zoonosis globally, with over 0.5 million new cases annually and with prevalence rates in some countries exceeding ten cases per 100 000 population [19]. Industrialized countries have largely controlled or eradicated brucellosis and bovine TB by using vaccination with S19/Rev1 (for brucellosis) and test and slaughter (T&S) plus financial compensation (for both zoonoses) [20]. Dealing with the problem in livestock alleviates the problem for humans, but countries in the developing world may not have the requisite level of organization of veterinary services or the financial resources to fund a vaccination campaign, or be willing to compensate farmers for culling livestock, without which vaccination and T&S policies cannot be implemented.

T. solium neurocysticercosis

The helminth parasite *T. solium* is associated with poverty, particularly poor sanitation, and is endemic to South and Central America, China, the Indian subcontinent, Southeast Asia, and sub-Saharan Africa. An estimated 2.5 million people are infected with *T. solium*, and there are 50 000 deaths annually due to neurocysticercosis [21]. The global burden of cysticercosis (symptomatic) in the endemic zone of Latin America was estimated to be 400 000 cases in 75 million people [22]. When

the disease is associated with epilepsy, the burden is greater, owing to social stigmatization and discrimination, which are barriers to diagnosis and treatment. In most Asian countries, accurate data on *T. solium* are scarce, but it is common in parts of Indonesia, China, India, Vietnam, and Laos [22,23]. The prevalence of cysticercosis in pigs in Latin America varies from <2% to >75%, with an average of 17% [24]. Up to 45% of pigs are infected in some villages in Uganda, and in many countries cysticercosis rates in pigs are 10% [25]. Neurocysticercosis is considered to be the most common preventable cause of acquired epilepsy in the developing world, and the most important neurological disease of parasitic origin in humans. With the rise in pig production in smallholder farms across the developing world, neurocysticercosis is increasingly becoming an emerging public health problem. Cases tend to be clustered, and late-onset epilepsy generates a high socio-economic burden for poor families in the endemic areas [26].

Cystic echinococcosis (CE)

CE is an emerging zoonotic parasitic disease where small ruminants and dogs are reared together, and is responsible for debilitating, potentially life-threatening human disease. Budke et al. estimated the global burden of CE in both humans and livestock, taking into account under-reporting [27]. Globally, human-associated annual economic losses (including medical costs, wage losses, and postoperative deaths) were estimated at US\$1.9 billion, with livestock losses—largely in countries with functional meat hygiene systems, owing to the economic impact of organ condemnation—being US\$2.19 billion. Although several species of *Echinococcus* exist, *Echinococcus granulosus* tapeworm infection is spread between dogs and small ruminants, with people becoming infected through eating tapeworm eggs. Human transmission occurs through the consumption of contaminated raw vegetables or from handling infected dogs. Untreated cysts in humans (often in the liver or kidneys) can grow to be very large, requiring expensive—and often high-risk—surgery for their removal. The ongoing human impact is substantial, manifesting as missed working days, and the risk of relapse or death, particularly if large cysts burst before surgery can be performed. There have been improvements in the diagnosis and treatment of human and animal cystic echinococcosis, and the diagnosis of canine echinococcosis, and trials of vaccines against *E. granulosus* in animals are underway [28,29].

Leishmaniasis

This vector-borne, protozoan parasitic disease is considered to be the third most important vector-borne disease globally, with an estimated 350 million people being at risk in 88 countries, 12 million cases worldwide, and approximately 50 000 deaths every year [30]. Transmission is mostly zoonotic (via dogs and

small rodents), but the disease can be spread between humans. Cutaneous leishmaniasis, the most common form, is non-fatal, but can cause extensive skin ulceration, leading to terrible facial disfigurement and stigmatization. Visceral leishmaniasis is a chronic systemic disease that affects the internal organs and can be fatal if left untreated. WHO data estimate the leishmaniasis to contribute 2.4 million DALYs [31], but current methods of assessing disease burden fail to account for variations in clinical presentation, which often demand intense medical interventions within small foci. Reliable data on the incidence, duration and impact of the various syndromes associated with leishmaniasis are not available [32].

Rabies

Rabies is a notoriously fatal zoonotic disease; it is caused by a virus that enters the body following the bite of an infected animal, and migrates to the brain. 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, a model was developed that used dog-bite data to infer numbers of human deaths [33]. The threshold density for rabies persistence was calculated to be 4.5 dogs/km². Fifty-five thousand human deaths from rabies per year in Africa and Asia produce a total DALY score of 1.7 million and a cost of US\$583 million. Costs are borne almost entirely by people in the developing world, where >99% of all fatalities occur [5]. Dog vaccination is a proven, simple, low-cost intervention for effective control in many rabies-endemic countries.

Zoonotic sleeping sickness

Trypanosoma brucei rhodesiense causes acute sleeping sickness (Rhodesian HAT (rHAT)), and infects a range of wildlife [34] and domestic animals [35]. Cattle constitute the most important reservoir in East Africa and southern Africa [36], and are responsible for the spread of rHAT in Uganda [37,38]. Untreated, the disease is always fatal in humans, but has little or no effect on the productivity of indigenous cattle. Under-reporting is common; a study in Uganda found that 92% of sleeping sickness deaths are not reported [12]. Sleeping sickness cases in Uganda are responsible for more patient admission time than all other infectious diseases other than malaria, severe malaria accounting for approximately 40% of hospital days and HAT 30%. The burden of HAT is poorly reflected in many existing assessments [39].

Integrated control of the NZDs

Sustainable health improvements in resource-poor countries require cross-sectoral, integrated, participatory or One Health

approaches. The effectiveness of a zoonosis intervention can be measured as the proportion of the human and/or animal population covered and cured or protected against a disease. For any drug/vaccine intervention, a range of biological, cultural, sociological, political and ecological factors are involved, including availability, accessibility, affordability, efficacy, acceptability, diagnostic accuracy, and provider and consumer compliance. Determinants of effectiveness of surveillance and interventions at different scales, from the household to the government level, can be assessed through a combination of quantitative and qualitative epidemiological, social and anthropological methods to produce a quantifiable framework of effectiveness [40,41]. The synergistic benefits of close interplay between human and animal health have been demonstrated in a number of settings. Integrated study designs for simultaneous investigation of health status in humans and animals, for rapid identification of the source of a zoonotic disease, have been developed (for example, in Kyrgyzstan, the seroprevalence of human brucellosis is closely related to keeping sheep [42], and frameworks developed to assess societal costs [43] have shown that it is possible to eliminate human brucellosis through effective interventions in animals).

The NZDs can be tackled in an integrated manner by focusing on a point of epidemiological or practical interaction that can benefit human and animal health. The European Commission-funded project Integrated Control of Neglected Zoonoses in Africa (ICONZ) has been evaluating the cost-effectiveness of a range of strategies based on clustering diseases and targeting interventions for bacterial (anthrax, bovine TB, and brucellosis), dog/small ruminant-associated (rabies, leishmaniasis and hydatid disease, and pig-associated disease—cysticercosis and neurocysticercosis) and vector-borne (zoonotic rHAT) (<http://www.iconzafrica.org>) diseases.

Anthrax, bovine TB, and brucellosis

Although they are controlled across most of Europe, these bacterial zoonoses, which infect livestock and humans, coexist in many communities, and still present a significant global challenge. Integrated surveillance and control for these zoonoses could be implemented and offer significant value, particularly in the developing world, considering the similar risk factors between these diseases. Brucellosis, bovine TB and anthrax are transmitted via direct contact with infected animals. Unpasteurized milk/milk products and abortion materials present major risks for the acquisition of brucellosis and bovine TB in poor communities. These bacterial NZDs impose a dual burden in affected communities, in terms of animal productivity losses and impact on human health (although the human burden is often poorly characterized, owing to underdiagnosis and under-reporting) [44]. Bacterial zoonoses are re-emerging

across sub-Saharan Africa, owing to the coexistence of pastoralist movements and an increase in intensive management arising from intensification of livestock production systems, with far-reaching social and political implications [45]. A recent study found that most cases of brucellosis in Kampala, Uganda resulted from consumption of raw milk transported from peri-urban areas of Kampala and/or dairy production areas outside Kampala [46].

Brucellosis and bovine TB screening could be integrated by use of the Rose Bengal test in parallel with bovine TB skin testing. The Rose Bengal test is a cheap, simple, agglutination test, with high sensitivity. The intradermal bovine TB skin test is read after 48 h, when the results of the brucellosis test would also be available, and farmers and communities could be informed of both. Testing of at-risk humans could also save the costs of multiple community visits, but the logistical difficulties of this approach still present problems, particularly in extensive systems.

There is no vaccine for bovine TB, and T&S is not usually applied in Africa, where, without compensation, communities are not willing to give up an animal for slaughter. There are effective vaccines for brucellosis—S19 for cattle, and Rev1 for small ruminants—and communities are willing to pay for vaccination. Vaccination can be implemented in intensive and commercial farms, but delivery across much of Africa remains challenging. The development of a conjunctival form of S19 would increase adoption in pastoralist communities [44].

In the absence of T&S policies, integrated community participatory approaches may prove useful for the control of brucellosis and bovine TB. Participatory and trans-disciplinary approaches for the development of locally adapted interventions against brucellosis and bovine TB have been used to develop health interventions in mobile pastoralist communities in Chad and Mongolia [46–48].

Zoonotic trypanosomiasis and tick-borne animal diseases

rHAT, caused by *Trypanosoma brucei rhodesiense*, is endemic in several foci across East Africa [49,50]. Sleeping sickness can be cured if diagnosed and treated early, but most of those affected live in remote areas with poor access to healthcare services [51]. A range of wildlife can act as reservoirs of rHAT [34], but in Uganda the reservoir of infection comprises domestic cattle [35,36]. The northwards migration of infected cattle from the endemic sleeping sickness foci has resulted in a large expansion of the rHAT focus, which now borders the *Trypanosoma brucei gambiense* (chronic) HAT focus [38,51]. Convergence of two forms of HAT will have major implications for the management of human sleeping sickness in Uganda [52,53].

The importance of the animal reservoir in controlling Rhodesian sleeping sickness has long been recognized but largely ignored. Identification of human infective parasites in livestock is performed with a molecular marker, the *SRA* gene [35]. Studies of endemic foci in Uganda have shown up to 40% of cattle carrying *Trypanosoma brucei rhodesiense* [36]. Given the contribution of the animal reservoir to transmission of rHAT, treatment of livestock to remove the parasites followed by vector control to prevent re-infection is the preferred option [37,54]. The removal of all trypanosomes from cattle requires injection of a low-cost (US\$0.5) trypanocidal drug. Animals can be kept free from re-infection with human-infective and animal-infective trypanosomes by treatment with long-lasting formulations of synthetic pyrethroids. Restricted application of insecticide to only the legs and belly of the bovine host, where most tsetse flies feed [55], has brought trypanosomiasis control within the reach of poor farmers in Africa. Furthermore, insecticidal treatment of only 20% of a cattle population is sufficient to control both rHAT and animal trypanosomes in that population [56,57]. If insecticide is also applied to the ears, then restricted application of insecticide also removes ticks, reducing the challenge from East Coast fever, *Babesia*, and anaplasmosis, and this is the main driver for farmers to maintain monthly application of insecticides [58].

Interventions targeted at dogs and small ruminants

Three NZDs (rabies, leishmaniasis, and hydatid disease) can be addressed by targeting dogs. Vaccination for rabies is a tried and tested intervention, with high cost/benefit ratios. Although there is an increasing commitment to eliminate rabies from developing countries with annual rounds of mass dog vaccination, this target is challenging. The Global Alliance for Rabies Control, established in 2005, has raised awareness, supported control programmes, and promoted educational initiatives (<http://www.rabiescontrol.net/>). Community rabies vaccination campaigns could be combined with interventions for hydatidosis or leishmaniasis, offering added value. There is now some activity ongoing in most countries, but even countries with the resources do not often meet and sustain these rates, and a permanent plan of action is needed to organize rabies vaccinations as part of the annual calendar. KwaZulu province in South Africa recently completed its first year without a single case of human rabies, thanks to a dog rabies control programme supported by the Bill and Melinda Gates Foundation. Tanzania embarked on an ambitious programme to repeatedly vaccinate dogs in 28 districts, but willingness to participate in vaccination was negated by fear of rabies, high medical treatment costs, and the threat of dog-culling. Problems with campaign mobilization, timing, the location of central points, equipment and staff and project organization created barriers

to community compliance [59]. 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 [60], and such campaigns could be extended to other dog zoonoses in these regions.

Leishmaniasis

The sand fly transmits *Leishmania infantum* from dogs to humans, and deltamethrin-impregnated dog collars for control have proved successful. Modelling has indicated that community-wide use of treated dog collars could be more effective than a dog-culling strategy, especially where transmission rates are high, although the impact of collaring is dependent on collar coverage and the rate of loss of collars [32]. An over 80% reduction in canine incidence was shown in trials of treated dog collars in Italy [61,62]. Monthly application of pour-on insecticides was also effective in reducing canine incidence in Italy [62] and Brazil [63].

E. granulosus

CE transmission can be prevented by deworming dogs, stray dog population control, and preventing dogs from eating cyst-infected livestock viscera. A number of low-cost approaches could be used for CE control, including preventing dogs from eating openly discarded cysts during the process of backyard slaughter and in established government slaughterhouses [64].

Dog interventions for this group of NZDs demand a clear understanding of the role of the dog in the community, which, in turn, will influence the mode of delivery and practicality of achieving a high level of vaccination coverage. During annual rabies vaccination campaigns, it would be straightforward to use this single community visit to also de-worm the dogs and apply insecticidal collars in areas where hydatid and leishmaniasis prevail. This offers a practical and economical way of interrupting disease transmission, reducing risk, and delivering messages about overall dog management, health, and welfare. Owned dogs can easily be vaccinated, wormed, and collared, but the village dogs (belonging to everyone) are more difficult to catch and treat [59]. For stray animals, interventions may include dog population control/culling, oral vaccination in baits to prevent rabies, and slaughterhouse legislation for destruction of cyst-infected livestock viscera to prevent stray dogs having access to cysts.

Pig-associated zoonoses

T. solium cysticercosis was declared to be eradicable by the International Task Force for Disease Eradication in 1993, but, despite a relatively uncomplicated epidemiology and progress in operational research, global eradication of *T. solium* is considered to be unlikely in the near future [21]. It is clear that

effective control of *T. solium* will require multiple interventions implemented simultaneously in both pigs and humans. Where open defecation is the norm, pigs and people are caught in a vicious cycle of *T. solium* cysticercosis/taeniasis. The most sustainable solution is to stop *T. solium* transmission from human to pigs with the provision of clean water and sanitation combined with veterinary sanitary measures, such as meat inspection and treatment of infected animals. Repeated mass drug administration (MDA) of antihelminthic drugs such as praziquantel, niclosamide and albendazole to human *T. solium* carriers has been applied in mass treatment programmes in China and Latin America [21]. Integration of *T. solium* control with existing MDA programmes for STHs or other parasitic NTD-causing organisms such as foodborne trematodes or those causing schistosomiasis offers the opportunity to capitalize on existing frameworks for control under larger NTD programmes. Diagnosis of the presence of adult tapeworms relies on the detection of parasite antigens in faeces (coproantigens), and tests have good specificity and sensitivity [65]. There have been advances in the diagnosis of *T. solium* infections with immunodiagnosics [21]; serological tests indicate whether the cysts carried in people or animals are alive or dead (treatment is appropriate for live cysts). Recombinant parasite antigen vaccines have been developed that could prevent *T. solium* transmission [30], but these are not yet commercially available. Pig vaccines may prove useful in commercial settings, but adequate take-up of such vaccines by poor farmers in rural areas where pigs are left free to run and feed on waste seems unlikely.

Open defecation is a key indicator of socio-economic marginalization [66,67], with global inequalities being reflected in how and where a person defecates. Today, 2.6 billion people lack improved sanitation, and 1.1 billion of these practise open defecation, which is believed to be responsible for the death of one-and-a-half million children annually [68]. Community-led total sanitation (CLTS) aims to mobilize a community to a point where open defecation is no longer practised and the village can be declared 'open defecation free' [69]. CLTS is premised on the idea that 'once people are convinced about the need for sanitation, they construct their own toilets according to resources available' [70]. Facilitators drive 'self-realization' by using 'local and crude words for "shit" and "shitting" ... rather than polite terms' [70]; disgust, shame and fear drive the community towards collective action [71]. If open defecation free status can be maintained, CLTS should impact on cysticercosis, STH diseases, and other diseases arising from poor sanitation, e.g. dysentery and cholera.

Changing human behaviour is difficult to achieve, especially for zoonotic infections, in which years may pass between infection and clinical symptoms. Communities are unaware that

white nodules in pigs and epilepsy in humans are linked, and may relate epilepsy to witchcraft, and white nodules in pigs to bad practice in farming. Village slaughter and the absence of meat inspection mean that infected pigs enter the food chain. The economic benefit of selling 'clean' meat is non-existent, and farmers and communities need to be able to recognize uninfected meat. Pig management practices (confinement and treating with oxfendazol) can contribute to breaking the *T. solium* cycle, and also impact on African swine fever and gastrointestinal parasites; however, the broader socio-economic and welfare impacts of pig confinement must be considered before this control method is promoted. Health education can contribute to behaviour change. 'Vicious Worm' (<http://www.theviciousworm.org>) is an interactive education tool with three layers of health information: the city—aimed at decision-makers; the town—aimed at health practitioners; and the village—aimed at local communities [72].

Advocacy

The WHO Neglected Zoonotic Disease conference series has significantly raised the profile of NZDs, drawing attention to the relationship between poverty and the emergence or re-emergence of neglected zoonotic diseases, particularly: anthrax; bovine TB; brucellosis; cysticercosis; CE; rabies; and HAT [4–6]. Participants of the most recent meeting 'From Advocacy to Action', held at the WHO headquarters in November 2014 (http://www.who.int/neglected_diseases/zoonoses/fourth_international_nzd_meeting/en/) agreed that, although 'challenges undoubtedly remain' regarding the currently available toolbox for NZD control, the time is right to move forwards with the implementation of large-scale control programmes. Large European Commission investments for the NZDs now include: ICONZ (<http://iconz.africa.org/>); Advocacy for the Neglected Zoonoses (ADVANZ; <http://www.advanz.org/>); and the European Technology Platform for Global Animal Health (<http://www.ifaheurope.org/EUPlatform/>) [73].

There is a perception that, if NZDs achieve a higher profile with government and donors and if we can show that it is feasible and cost-effective to intervene, funds will flow and control will follow. Several NZDs have achieved such a high profile, but remain neglected. From an economic standpoint, the costs and benefits of controlling NZDs support the implementation of a control programme—not to mention the ethical responsibility of the state in ensuring optimal human health for its citizens. However, to take action, policy-makers need to know the cost and burden of the disease, the best method of controlling it, how long this will take, the full economic cost of control, and options for apportioning costs.

Rabies has achieved considerable advocacy through the Global Alliance for Rabies Control, but still kills an estimated 55 000 people every year, mainly in Africa and Asia, despite cheap and effective vaccines being available for humans, dogs, and even for wildlife. Among all of the neglected NZDs, dog rabies elimination is the lowest hanging fruit. However, even with these excellent, cheap and effective dog vaccines available, and with burdens and costs well understood, there is no guarantee that elimination will be easily achieved [59]. The costs of intervention in an animal reservoir may seem high as compared with the public health benefits alone, and profitability may not be obvious from a single-sector perspective. For rabies, from a human health perspective, a dog bite wound requires cleaning, and a post-exposure treatment (PET) vaccination is essential, but expensive. As dog-to-dog transmission drives rabies epidemics, PET alone will not eliminate rabies. From an animal health perspective, rabies in cattle, and not dogs, is important, so national rabies vaccination programmes are not prioritized. For rabies, the cost benefit of vaccinating dogs may take many years to be realized, and requires universal high coverage to be achieved annually. In N'Djamena in Chad, the cumulative cost of dog rabies mass vaccination and human PET was equal to the cumulative cost of PET alone after 6 years, and only became more cost-effective after 7 years [74].

Interventions for NZD in the animal reservoir (mass vaccination, drug treatment, and education) must be supported and operationalized across health and agriculture ministries. Long-term national and regional plans for elimination demand significant buy-in from both human and animal health sectors. When a full cross-sector analysis is undertaken and all stakeholder benefits (monetary/non-monetary) are taken into account, interventions for NZDs can become highly cost-effective. For example, when the costs of brucellosis mass vaccination are shared between the health and livestock sectors in proportion to their benefits, brucellosis control becomes cost-effective [75].

Communicating information to governments, donor bodies and communities is key to control. Provider and/or commercial interest add a political dimension to disease prioritization or neglect, and there is now concern about the public health threat of new, re-emerging and neglected zoonoses in the industrialized world [76,77]. Identification of gaps can help in targeting funds to the areas of greatest need. The Neglected Zoonoses Research Database <http://www.zoonosis.ac.uk/ICONZ/> provides a global picture of funding and research for eight NZDs, and includes a publications database, a research projects database, and a funders database.

Interventions for NZD control require long-term commitments to realize the economic benefits. For example, elimination of human CE requires a long-term, multi-sector plan that

builds on strong political mobilization and an integrated infrastructure, and behaviour change interventions, which, even in the most favourable environments, may take up to 20 years [29]. Programmes may require significant front-loading (establishment of vaccine banks; drugs and logistics for mass treatments; and educational campaigns). These long-term and often front-loaded programmes can be difficult to support within government or donor funding cycles. Often, once the number of cases begins to decrease, systems for surveillance and control become difficult to sustain.

Stamp Out Sleeping Sickness in Uganda (<http://www.stampoutsleepingsickness.org>) has shown that it is possible to keep districts affected by zoonotic HAT clear of infection by removing the reservoir of infection with mass treatments of cattle with trypanocides, and by preventing re-infection by the use of insecticides. This has large cost benefits, and an investment of \$US40 million could tackle the whole at-risk area and remove the risk of zoonotic HAT—funds that Uganda does not have. An innovative funding mechanism provides hope for sustainable sleeping sickness control; use of a Development Impact Bonds (DIB) private investment could raise the funds needed for large-scale, long-term delivery <http://www.cgdev.org/working-group/development-impact-bond-working-group>. Private investors provide up-front funding for the DIB and, as with other investments, take on the risk of reward or loss. Funds are directed to implement the programme, and outcomes are assessed independently. If objectives are not met, investors absorb the loss, but if they are achieved, international donors repay the private investors with interest. Investors have a strong incentive to manage their risk by bringing rigour and discipline to the DIB process. This increases the probabilities of both achieving the development outcome and of generating a financial return. This novel funding mechanism is also being explored for other NZDs, such as rabies.

Conclusion

There is widespread acknowledgement of the value of an integrated approach to tackling the NZDs, but agreement is now needed on the politics and finance. Policy-makers need to know the current cost and burden of the disease, the best method of controlling it, the full economic cost of control, and the impacts on their communities. However, in many poorer countries, putting resources into the surveillance and treatment of animal populations rarely meets with much support, despite that fact that improved human and animal health can play a major role in promoting food security and eradicating poverty [77,78]. Given the institutional limitations in the veterinary and human public

health sectors in Africa, interventions for NZDs could benefit from adopting a One Health approach that supports inter-sector working practices [78,79].

More often than not, the cheapest and most effective strategy for dealing with zoonotic diseases is to control infection in the animal population, and for those NZDs for which the human disease cannot be maintained in the absence of an animal reservoir, for which effective tools are available, and for which significant advocacy has been raised, elimination may be possible, e.g. zoonotic HAT and rabies [16]. The solution may be a top-down approach—such as a vaccination programme or MDA—but sustained control is about working within the community to change behaviour and practice. New funding models offer the potential for raising the resources required, enabling greater attention to be paid to navigating the local realities in planning and implementation that are essential for ensuring that these neglected diseases are controlled sustainably.

Transparency declaration

The funders had no role in conceiving or writing this article, and the authors declare that they have no competing interests.

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