Preventing and controlling zoonotic tuberculosis: a One Health approach

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Summary

The expression One Health refers to the unified human and veterinary approach to zoonoses, an approach that used to be identified with Medicine throughout the 20th Century. Zoonotic tuberculosis (TB), a disease due to bacteria of the *Mycobacterium tuberculosis* complex, is a recognized global public veterinary health problem. The significance of the health and economic threats posed by zoonotic TB has been recognized by several global health agencies, which have called for control and eradication programs for zoonotic TB. The interplay between humans, livestock, wildlife, and ecology in the epidemiology of zoonotic TB make arduous the control of the disease, as such zoonotic TB is the ideal target for the application of the One Health approach. This article argues that a successful One Health response to TB will consider the effects of disease on socio-economic well-being, and allow for addressing the social, cultural and economic conditions that facilitate spread and maintenance of this disease. The One Health approach will also enable the development of disease control programs involving both animal and human populations, fostering the participation of various stakeholders. One Health approach will also allow for expanding scientific knowledge, improve medical education and clinical care, and develop effective disease control programs for both human and animal populations.

L'approccio One Health *per la prevenzione e il controllo della tubercolosi*

Parole chiave
Animale selvatico,
Bestiame,
One Health,
Popolazione umana,
Programma di Controllo,
Programma di Sorveglianza,
Salute Pubblica,
Tubercolosi,
Zoonosi.

Riassunto

L'espressione *One Health* si riferisce a un approccio che coinvolge sia la medicina umana sia quella veterinaria nel controllo e nella cura delle zoonosi e di altre patologie. Approccio a lungo identificato con la "Medicina" nel corso del XX secolo. La tubercolosi è una zoonosi dovuta a batteri del complesso *Mycobacterium tuberculosis* ed è considerata un problema globale per la Salute Pubblica Veterinaria. Diverse organizzazioni mondiali per la Salute Pubblica hanno riconosciuto la rilevanza dei rischi e dei danni economici che essa può causare. Le stesse organizzazioni hanno sottolineato la necessità di definire programmi di eradicazione della malattia. Le interazioni tra esseri umani, bestiame e animali selvatici ne hanno reso difficile il controllo, queste stesse cause fanno della tubercolosi l'obiettivo ideale per implementare l'approccio *One Health*. L'articolo sostiene che l'approccio *One Health* alla tubercolosi si dimostrerà efficace se prenderà in considerazione gli effetti socio-economici della patologia e le condizioni socio-culturali ed economiche che ne facilitano la diffusione. L'approccio *One Health* sostiene lo sviluppo di programmi di controllo che includano sia la popolazione animale sia quella umana, favorendo in tal modo la partecipazione di rappresentanti di interessi diversi nella definizione dei programmi di cura e controllo della malattia.

Introduction

Zoonotic tuberculosis (TB), disease due to bacteria of the *Mycobacterium tuberculosis* (MTB) complex, is a recognized public veterinary health problem in developing countries (Ayele *et al.* 2004, Cleaveland *et al.* 2007, Cosivi *et al.* 1998, Kleeberg 1984, Nastasee 2009, Nawaz *et al.* 2012, Thoen *et al.* 2009). The disease is also recognized as a public health issue in such countries, although at lower levels due to the effectiveness of Bovine TB control (BTB) programs in livestock and mandated pasteurization of milk (Cosivi *et al.* 1998, Cotter *et al.* 1996, Kleeberg 1984, Lari *et al.* 2011). Disease caused by *Mycobacterium tuberculosis, Mycobacterium bovis* (BTB), and other spp of the MTB complex, including *Mycobacterium africanum* (Cadmus *et al.* 2006), *Mycobacterium caprae* (Bayraktar *et al.* 2011, Cunha *et al.* 2011, Cunha *et al.* 2012, Garcia-Jimenez *et al.* 2012, Gutierrez *et al.* 1997, Rodriguez *et al.* 2009) and *Mycobacterium orygis* (Dawson 2012), appear in humans, livestock and wildlife (Thoen *et al.* 2009). Other atypical mycobacteria (not members of the MTB complex) have been found in humans and small mammals from farms with BTB-infected cattle in Tanzania (Durnez *et al.* 2011).

The significance of the public health threats from zoonotic TB resulted in the adoption of a resolution by the World Organization for Animal Health (Office International des Epizooties; OIE) in 1983, calling for the eradication of *M. bovis* for public health and economic reasons, adoption of stringent meat inspection and pasteurization or boiling of milk for human consumption, and continued research into BTB, particularly in the improvement of diagnostic tests (Kleeberg 1984). Other forms of BTB include:

- recrudescent cases in the elderly, who acquired infection before BTB control was completed,
- cases in developed countries that were imported from other regions of the world where BTB control is absent or ineffective,
- cases associated with consumption of contaminated foods of animal origin, or exposure to tuberculous animals and their carcasses (Awah-Ndukum *et al.* 2011, Cosivi *et al.* 1998, Cotter *et al.* 1996, de la Rua-Domenech 2006, Doran *et al.* 2009, Kankya *et al.* 2010, Majoor *et al.* 2011, Rodriguez *et al.* 2009, Rodwell *et al.* 2008, Rodwell *et al.* 2010, Shrikirishna *et al.* 2009, Wilkins *et al.* 2008, Winthrop *et al.* 2005).

At the same time, workplace exposure to BTB can occur in veterinarians, livestock workers, and slaughterhouse workers (de la Rua-Domenech 2006, Rodriguez *et al.* 2009, Sunder *et al.* 2009, Winthrop *et al.* 2005). While the majority of BTB cases are zoonotic, there are documented cases of human-to-human transmission of pulmonary BTB (LoBue *et al.* 2004, Sunder *et al.* 2009). Rates of BTB in HIV-AIDS patients are higher than those in the general population, and the majority of BTB in developed countries are cases of BTB-HIV/AIDS co-infection (Cosivi *et al.* 1998, Humblet *et al.* 2009). Co-infections of BTB with HIV and other diseases are increasing across the globe, and many diseases involved in these complexes are at high risk for zoonosis in humans (Ayele *et al.* 2004, Cosivi *et al.* 1998, Hlavsa *et al.* 2008, Katale *et al.* 2012, Park *et al.* 2010).

In the developing world, non-pulmonary human TB is under-reported, and often is not a reportable disease (Katale *et al.* 2012). Rates of human *M. bovis* infection are higher in populations that own or live in areas with higher cattle populations (Katale *et al.* 2012). In this respect, it worthwhile noticing that living in close proximity to livestock with BTB has been associated with human BTB infection (Cosivi *et al.* 1998, Kankya *et al.* 2010). Studies have also found herds in households with human cases of TB were more likely to have BTB skin-test positive cattle than herds in households without TB, as it was the case in Ethiopia (Fetene *et al.* 2010, Regassa *et al.* 2008), Niger (Boukary *et al.* 2010), Zambia (Cook *et al.* 1966), Sweden (Sjögren I. and Sutherland 1974) and Denmark (Magnus 1966).

Traditional livestock management practices in developing countries, such as transhumance, communal grazing, or keeping livestock longer due to economic constraints, are associated with increasing risks for BTB in cattle (Katale *et al.* 2012, Mbugi *et al.* 2012b, Munyeme *et al.* 2008, Omer *et al.* 2001). Control of BTB in livestock can reduce risks for human infection by decreasing human exposure to *M. bovis* through livestock (Milian-Suazo *et al.* 2010, World Bank 2010a, World Bank 2010b), underlining the importance of controlling the disease from both veterinary and human medical perspectives.

The One Health Approach

History of the One Health approach

Associations between animal and human diseases have been observed from ancient civilizations to the present day (Steele 2008). Parallels in the progression of disease between humans and domestic animals as well as the historic use of animals as sentinels for human disease (Rabinowitz *et al.* 2009) support these associations. The evidence of 'shared risk' in humans and animals in recent history include:

- Minamata disease (mercury poisoning in humans and cats),
- anthrax in livestock and humans,

- West Nile virus in humans and animals (Rabinowitz *et al.* 2009).

Further, studies of human and animal ethnopharmacology have found commonality in the descriptions, symptoms, and treatments for humans and animals in traditional medicine, and that many remedies were used to treat both humans and animals (Nyamanga *et al.* 2006, Souto *et al.* 2011).

Some of the earliest applications of the concept of associations between human and animal disease were prompted by veterinarians in the United States, for example J. Law, a professor of veterinary medicine at Cornell University, advised the US Board of Health on the effects of zoonoses on public health in 1880 (Steele 2008). Early analyses of the impact of veterinary public health on human public health were developed in the second part of the 19th century and focused on hazards of milk obtained from unhealthy cows suffering from tuberculosis (TB), typhoid fever, diphtheria, and brucellosis. Actions to control milk-borne diseases included pasteurization after production, and control of bovine TB and brucellosis in cattle through Grade A milk requirements for cattle herd health status (Steele 2008). The success of this program resulted in the near eradication of these diseases as foodborne hazards in the United States.

Acceptance of the One Health approach

In the first decade of the 21st Century, the One Health concept was promoted by the veterinary medical community through the American Veterinary Medical Association (American Veterinary Medical Association 2008, King *et al.* 2008, Steele 2008), which established a unique One Health collaborative liaison with the American Medical Association (AMA) in 2006. In 2007, the AMA passed a landmark One Health resolution, and the AVMA officially established the One Health Initiative Task Force (OHITF) to develop strategies to enhance collaboration between human and veterinary medical professionals. The OHITF produced a strategic framework for reducing risks of infectious diseases at the human-animal-ecosystem interface, and developed the recommendations that formed the bases of the current One Health Initiative (Food and Animal Organisation *et al.* 2008). As a result, in 2009 the One Health Commission (OHC) was officially chartered for the wide spectrum purpose of promoting One Health both in the United States and worldwide (One Health Commission 2012).

The One Health concept has been subsequently supported by the AVMA, AMA, U.S. Centers for Disease Control and Prevention (CDC) and the American Society for Microbiology. The World Health Organization (WHO), the OIE, the United Nations (UN) Food and Agriculture Organization (FAO), UNICEF, the UN System Influenza Coordination, and the World Bank all embrace now the One Health approach. The World Bank has specifically recognized the importance of One Health and its economic benefits (World Bank 2010a and 2010b). Other major organizations promoting One Health include the U.S. Department of Agriculture (USDA), the U.S. National Environmental Health Association (NEHA), the European Union, the American Academy of Pediatrics, and many others (One Health Initiative 2012a). Recognition of the importance of One Health has also expanded beyond the medical and economic sciences, e.g. in the U.S., The National League of Cities has formally recognized and supported the work of the OHITF, and it has acknowledged how the success of the One Health Initiative will rely on leadership, communication skills and cooperation (Riedner 2012).

Several countries now endorse the One Health approach to address different zoonotic diseases (Komba *et al.* 2012, Marcotić *et al.* 2009, One Health Initiative 2012b), and these days One Health principles are an important part of global health training for medical professionals and development programs (Conrad *et al.* 2009, One Health Global Network 2012).

It is noteworthy that a trend to foster integrated human-animal surveillance systems was observed in surveillance programs for emerging zoonoses (Vrbova *et al.* 2010). However, despite the diffused awareness of the advantages of the One Health paradigm, barriers to its implementation in some industrialized countries include absence of evidence, governmental structures, and "relatively low degree of suffering" (Meisser *et al.* 2011).

As the One Health concept has emerged as an approach to deal with public and veterinary health, the scope of One Health has been expanding to encompass other concepts. Ecosystem Health is an approach that links ecosystem change with human health (Rapport *et al.* 1999), and Ecohealth expands on Ecosystem Health to include sociology (Leung *et al.* 2012), all of which can be viewed as logical extensions of One Health. The One Health-One Medicine concept, while historically incorporating conservation medicine under its umbrella (Kahn *et al.* 2012), has also been viewed as an expansion of conservation medicine, whose goal is the pursuit of the health of ecosystems and the species that live within them (Osofsky *et al.* 2005).

Advantages of the One Health approach

The report provided by the American Veterinary Medical Association (AVMA) on One Health Task Force offers a comprehensive outline of the following advantages to be gained through a One Health approach (American Veterinary Medical Association 2008, King *et al.* 2008). By coupling human health, animal health, ecology, sociology, and economics, the One Health approach can:

a. Improve animal and human health globally through collaboration among all the health sciences, especially between the veterinary and human medical professions, to address critical needs:
b. Meet new global challenges head-on through collaboration among multiple professions – veterinary medicine, human medicine, environmental, wildlife and public health;
c. Develop centers of excellence for education and training in specific areas through enhanced collaboration among colleges and schools of veterinary medicine, human medicine, and public health;
d. Expand the body of scientific knowledge to create innovative programs to improve health.

The One Health approach is considered by many professionals to be a critical necessity to address zoonotic diseases, would they be existing, emerging, or re-emerging diseases. One Health does so by addressing the very nature of zoonoses - the transmission of disease between human and animal species must be addressed at multiple levels, rather than focusing solely on humans or animals for disease prevention and control (Holveck *et al.* 2007, Khan *et al.* 2012, Mbugi *et al.* 2012a, Nara *et al.* 2008, Siembieda *et al.* 2011). Recognizing synergistic relationships in human and animal populations can be used for prevention-oriented planning and research will support One Health goals (Rock *et al.* 2009, Singer 2009). The emergence of new or old diseases have been linked to changing ecological conditions: deforestation, urbanization, population growth, and climate change create situations where humans are exposed to new ecosystems with novel pathogens, creating opportunities for zoonotic disease transmission (Coker *et al.* 2011, Siembieda *et al.* 2011). The One Health approach includes consideration of environmental and ecological factors in the development of effective disease control programs (Beasley 2009, Coker *et al.* 2011, Leung *et al.* 2012, Rweyemamu *et al.* 2012, Zinnstag *et al.* 2011).

Coordinating human and veterinary medical professionals and institutions through One Health is critical in regions where resources are scarce. Surveillance programs for humans and livestock are often absent or lacking, making it difficult to identify zoonotic disease outbreaks and conduct the risk assessments necessary to formulate effective control programs (Merianos 2007). In areas where human health services are poor, there has been recognition that zoonoses typically affect populations where veterinary medical services are poor and animals harbor more zoonotic diseases (rural livestock-keeping communities, urban slums) (World Health Organisation 2006), and regional disease surveillance may be more advanced in animals than humans due to efforts by the FAO and OIE (Shears 2000).

Combined public health and veterinary ministries and integrated surveillance programs under a One Health approach will result in efficiency gains that will help reduce costs, improve access to health services, and allow for more cost-effective disease control in regions with limited resources and where diagnostic and surveillance programs are scanty (Coker *et al.* 2011, Mbugi *et al.* 2012b, Rass 2006, Schelling et. al 2005, Shears 2000, World Bank 2010b). As it was highlighted by the World Bank include, examples of efficiency gains followed from the endorsement of the One Health approach can be found in the joint animal-human vaccination campaigns in Chad (Shears 2000, Zinsstag *et al.* 2005); dog vaccination and sterilization reducing human rabies in India; joint public health and veterinary worker farm visits to reduce costs in Kyrgyzstan; and integration of human and animal health facilities lowering operation costs in Canada (World Bank 2010b). At the same time, it is noteworthy that wildlife conservation and ecosystem preservation also benefit from a One Health approach. By including these components in more 'holistic' approaches to disease control and prevention, stakeholders will be more aware of the negative impacts of potential interventions and, consequently, more favorable approaches may be used (Osofsky *et al.* 2005).

The One Health approach can have a positive impact on the economic costs related to the management of zoonotic diseases. These economic burdens fall more heavily on emerging countries than on the developed world (Merianos 2007). Epizootics of disease that can be controlled by vaccination have serious consequences for livestock industries, both upstream (inputs, genetic resources) and downstream (slaughter, processing, marketing), jobs, income, or market access, and also have serious consequences for food security and food safety (Nara *et al.* 2008). Zoonotic diseases also have negative consequences for livestock production:

- decreased milk production;
- reduced fertility, slower growth
- animal mortality,
- losses when the presence of disease restricts the markets for animal products (Lamy *et al.* 2012, Zinsstag *et al.* 2008).

The indirect costs of zoonoses are often overlooked (Narrod *et al.* 2012). The impact of zoonoses in terms of disability-adjusted life-years (DALYs) can be quantified by using a One Health approach (Grace *et al.* 2012): a cost-benefit analysis of vaccinating livestock in Mongolia for brucellosis found that the estimated costs for vaccination (US$ 8.3 million) were exceeded by the overall benefit (US$ 26.6 million), with an average benefit-cost ratio of 3.2 (Roth *et al.* 2003). Economic losses from outbreaks of Nipah virus, West Nile Fever, SARS, HPAI, BSE, and RVF from 1997–2009 were at least of $80 billion: prevention would have avoided losses of $6.7 B/year (World Bank 2010b). Cost-benefit analyses have determined that interventions in animal populations to reduce levels of zoonotic diseases were cost effective: control of the animal diseases was less expensive than the costs of disease in humans (World Bank 2010b, Zinsstag *et al.* 2008).

Interdisciplinary One Health research efforts can be directed to enhance and address gaps in existing information for use in the development of control programs to promote the health and well-being of humans, animals, and ecosystems. In addition to advances in laboratory sciences, a common 'toolbox' of protocols for integrated disease surveillance, joint animal/human epidemiological studies, and health services should be developed, using expertise from human and veterinary medicine, social sciences, ecology, economics, and other fields (Zinsstag et al 2009). Systems theory can be used to study these complex systems and identify properties and determinants of health from micro- to macro-scales (Zinsstag *et al.* 2011). Examples of systems biology models include one of persistent tuberculosis in humans (Young *et al.* 2008), which could be expanded to include livestock, wildlife, and ecological and sociological drivers as part of a TB control (Zinsstag *et al.* 2011).

Using a One Health approach for the control of zoonotic tuberculosis

The interplay between humans, livestock, wildlife, and ecology in the epidemiology of zoonotic diseases, including TB, makes control of the diseases complex (Nishi *et al.* 2006, Palmer *et al.* 2012a, Siembieda *et al.* 2011) and an ideal target for the application of the One Health approach.

The Wildlife Conservation Society includes tuberculosis among its 'deadly dozen' – potentially lethal zoonoses that could spread around the world due to behavioral changes to compensate for the effects of global warming (Singer 2009). Overall reductions in health (and immune systems) in humans and livestock due to water and food insecurity can contribute to the spread of zoonotic disease (Lamy *et al.* 2012, Singer 2009). The geographic distribution of different clonal complexes of BTB (e.g. Africa2, Af2) that infect both livestock and humans suggests that geographically distributed factors (e.g. wildlife habitats, climate, water availability) are integral to the transmission of these clones (Berg *et al.* 2011). Environmental/ecological conditions can promote contact between wildlife and livestock, which can increase transmission of TB at livestock – wildlife interfaces (Gortázar *et al.* 2012, Miller *et al.* 2007, Munyeme *et al.* 2008, Palmer *et al.* 2012a, Siembieda *et al.* 2011). Ecological change, both natural and anthropogenic, can increase or concentrate wildlife populations, which can promote the spread of BTB or increase competition between wildlife and livestock for water and food (Cunha *et al.* 2011, Miller *et al.* 2007, Okafor *et al.* 2011, Siembieda *et al.* 2011, Singer 2009). Finally, associations may exist between climate/weather and the ability of mycobacteria to survive outside the host, which would make indirect transmission of tuberculosis between species possible (Fine *et al.* 2011, Humblet *et al.* 2010, Young *et al.* 2008).

Control of livestock BTB in developed countries relies on test-and-cull policies for affected animals. The socio-economic costs of this approach can be economically impossible for livestock owners in developing countries, and result in refusals to participate in BTB control programs (Cosivi *et al.* 1998, Katale *et al.* 2012). In addition, this approach is not effective when wildlife reservoirs of disease are present and capable of re-infecting livestock (Coleman *et al.* 2011, Cosivi *et al.* 1998, Cunha *et al.* 2012, Mbugi *et al.* 2012b, Munyeme *et al.* 2008, Okafor *et al.* 2011, Palmere *et al.* 2012a). However, when levels of BTB in wildlife reservoirs are reduced, or the wildlife reservoir populations are decreased, levels of BTB in livestock (Coleman *et al.* 2011) or wildlife spillover species (Nugent *et al.* 2012) are also seen to decline.

Control of BTB in wildlife reservoirs has relied on population reduction through increased hunting, trapping, or poisoning (Nugent *et al.* 2012, O'Brien *et al.* 2006) and vaccination (Buddle *et al.* 2011b, Chambers *et al.* 2011, Lesellier *et al.* 2006, Palmer *et al.* 2012b, Wedlock *et al.* 2005), and these strategies have met with mixed success. Efforts to reduce wildlife populations for disease control can be difficult and are often met with public criticism (Carstensen *et al.* 2011, Corner 2006, de la Rua-Domenech *et al.* 2006, Nishi *et al.* 2006, O'Brien *et al.* 2006, Okafor *et al.* 2011). Vaccination of either the wildlife reservoir or the livestock population is an anticipated alternative to culling (Buddle *et al.* 2011b, Chambers *et al.* 2011, Lesellier *et al.* 2006, Palmer 2007, Wedlock *et al.* 2005). Development of novel approaches to control diseases in livestock and wildlife, including BTB, which are both biologically relevant and acceptable to livestock owners is an important goal of One Health (Zinsstag *et al.* 2005). Ultimately, successful control of BTB in wildlife and livestock will reduce human infection, reduce losses to productivity and reduce market restrictions from countries where eradication programs are in place (Ayele *et al.* 2004).

Culturally appropriate education and active participation of livestock owners and other stakeholders is critical for the success of zoonotic disease control programs (Munyeme *et al.* 2010, Nastasee 2008, Nishi *et al.* 2006, Shirima *et al.* 2003, Zinsstag *et al.* 2005). Studies in sub-Saharan Africa found that knowledge about BTB in cattle owners was low: few were aware of the disease and how it was spread, fewer were aware of wildlife reservoirs in the area, and awareness was associated with personal history with BTB and geographic regions (Amenu *et al.* 2010, Kankya *et al.* 2010, Munyeme *et al.* 2010). In these instances, the One Health multidisciplinary/interdisciplinary approach, incorporating veterinary medical, ecological, public health, and sociological expertise, can provide useful disease control strategies.

Control programs for zoonotic TB require action at all levels of its epidemiology

The epidemiology of zoonotic TB varies throughout the world, depending on the human, livestock, and wildlife populations, and on existing TB control programs, environmental conditions, and the socio-economic status of countries or regions (developing versus industrial countries) (Humblet *et al.* 2009). Isolation of both *M. bovis* and *M. tuberculosis* from livestock (Awah-Ndukum *et al.* 2011, Cadmus *et al.* 2006, Cadmus *et al.* 2011, Chen *et al.* 2009, Fatene *et al.* 2010, Gumi *et al.* 2012, Jenkins *et al.* 2011, Kassa *et al.* 2012, Kazwala *et al.* 2001, Romero *et al.* 2011, Thakur *et al.* 2012) and humans (Awah-Ndukum *et al.* 2011, Cadmus *et al.* 2006, Chen *et al.* 2009, Fetene *et al.* 2010, Gumi *et al.* 2012, Milian-Suazo *et al.* 2010, Romero *et al.* 2011), *M. caprae* (García-Jiménez *et al.* 2012, Gutiérrez *et al.* 1997, Rodríguez *et al.* 2009) and *M. orygis* (Dawson *et al.* 2012) in livestock and humans indicates cycling of *M. tuberculosis*-complex organisms between livestock and humans. In addition, finding cattle and goats with *M. tuberculosis* infection (Awah-Ndukum *et al.* 2011, Cadmus *et al.* 2006, Chet *et al.* 2009, Fetene *et al.* 2010, Gumi *et al.* 2012, Jenkins *et al.* 2011, Kassa *et al.* 2012, Romero *et al.* 2011) demonstrates that the traditional paradigm of MTB being strictly transmitted from human-to-human is incorrect, and animal reservoirs must also be included in MTB control and prevention programs.

Milk from infected cattle is one of the most common sources of BTB infection for humans, and many regional cultures and customs (consumption of undercooked animal products, direct contact) support transmission of BTB from animals to humans (Ayele *et al.* 2004, Ben Kahla *et al.* 2011, Cosivi *et al.* 1998, Fetene *et al.* 2010, Hlavsa *et al.* 2008, Katale *et al.* 2012, Kazwala *et al.* 2001, Park *et al.* 2010, Regassa *et al.* 2008, Shirima *et al.* 2003). In abattoirs in Tanzania, the most common cause for carcass condemnation was BTB (1.2% of all carcasses in one year), highlighting the public health risks to consumers of foods from these animals and to abattoir workers (Komba *et al.* 2012). Other atypical mycobacteria (mycobacteria not in the MTB complex) have been recovered from milk, which poses a significant danger to immunocompromised consumers of raw or unprocessed milk (e.g., HIV sufferers) (Durnez *et al.* 2009, Katale *et al.* 2012).

The ability of BTB, and other MTB, to infect a wide diversity of animals beyond cattle indicates that more than one host species should be taken into consideration when developing BTB control programs (Allepuz *et al.* 2011, Corner 2006, Cunha *et al.* 2012, García-Bocanegra *et al.* 2012, Humblet *et al.* 2009). Outbreaks of BTB have been reported in different livestock species when BTB was transmitted from cattle to small ruminants and swine (Di Marco *et al.* 2012, Kassa *et al.* 2012). Once infection is present, it may become self-sustaining in some cases (Di Marco *et al.* 2012). Presence of wildlife reservoirs has made BTB eradication difficult in countries where conventional BTB control programs had effectively eliminated the disease from livestock (Allepuz *et al.* 2011, Coleman *et al.* 2011, Cunha *et al.* 2011, Doran *et al.* 2009, Palmer *et al.*2012a, Palmer *et al.*2012b, Santos *et al.* 2012), and makes control of BTB in livestock difficult when complete segregation of livestock and wildlife is difficult (Cunha *et al.* 2012, Gortázar *et al.* 2012, Katale *et al.* 2012, Mbugi *et al.* 2012).

An important route of infection, particularly between wildlife and domestic animals, is the indirect transmission of mycobacteria by environmental substrates. Studies have demonstrated that wildlife reservoirs are capable of excreting *M. bovis* capable of serving as a source of infection for other animals (Courtenay *et al.* 2006, Palmer *et al.* 2004), and *M. bovis* can exist in environmental samples for an extended period of time (Fine *et al.* 2011, Humblet *et al.* 2010, Young *et al.* 2008). Experimental studies have showed that *M. bovis* can be transmitted between white-tailed deer (Palmer *et al.* 2001), from white-tailed deer to dairy calves (Palmer *et al.* 2004), and studies have found evidence for environmental contamination as a source of infection for cattle (Green *et al.* 2012, Okafor *et al.* 2011).

Wildlife disease detection and surveillance programs are rare (Siembieda *et al.* 2011) due to difficulties in enumerating and testing free-ranging wildlife populations. In instances where wildlife reservoirs are commonly hunted, surveillance programs have relied on post-mortem testing of hunter-harvested wildlife (O'Brien *et al.* 2006). However, when harvesting wildlife for surveillance is not feasible (e.g. rare or endangered species) programs involve trapping, sampling, and releasing animals to collect samples for immunological tests (Chambers 2009). Once detected, control programs for wildlife disease, including BTB, can be difficult to implement and maintain, and are often unpopular (O'Brien *et al.* 2010, Santos *et al.* 2012). While culling infected wildlife is a useful strategy for reducing BTB risk for livestock in many situations (O'Brien *et al.* 2010), there have been instances where culling has had mixed impacts on livestock BTB (Chambers *et al.* 2011, Griffin *et al.* 2005). In fact, some critics have suggested that, given the economic costs and unpopularity of BTB control in wildlife reservoirs and the successes of pasteurization and food hygiene, the costs far outweigh the benefits of control programs, and BTB should not be considered a public health issue (Torgerson and Torgerson 2009).

Sharing human and veterinary resources

Sharing resources between public health and veterinary medical scientists takes advantage of existing infrastructure and reduces unnecessary duplication. It also has the shared benefit of increasing interaction between professionals in these disciplines (Kazwala *et al.* 2006, Young *et al.* 2008). These interactions will raise awareness in all areas, from medical professionals, to governmental agencies, and other stakeholders. Combined public health and veterinary laboratory resources will result in efficiency gains that will help reduce costs and improve access to health services, particularly in developing countries where zoonotic TB is an important issue and resources are limited (Coker *et al.* 2011, World Bank 2010b).

Training for current and future health sciences workers requires a paradigm shift to the perspective of 'shared risk' between humans and animals (Zinsstag *et al.* 2005, Zinsstag *et al.* 2009). Communications between medical and veterinary medical students are critical and must include crossover education and opportunities for communication and exploration of local priorities and perceived needs (Nara *et al.* 2008, Schelling *et al.* 2005, Tibbo *et al.* 2008). An example of one training program designed to meet these needs is the analytical epidemiology curricula being developed under a One Health approach to address regional zoonoses, including BTB, in Zambia (Monath *et al.* 2010). Educational efforts should also be expanded to span different disciplines (e.g., ecology, sociology, etc.) to create a cadre of multidisciplinary professionals for One Health programs (Merianos 2007), and curricula at academic institutions should be designed with the One Health approach in mind (Zinsstag *et al.* 2005).

In addition to formal education programs, development of virtual Centers of Expertise for One Health approaches to TB control and research have been proposed (Brownlie *et al.* 2012, Dockrell 2012). Using these resources, new researchers will be able to contribute to trans-disciplinary research on zoonotic TB in a holistic approach, where these researchers will work jointly, using shared conceptual frameworks that integrate the disciplinary-specific concepts, theories, and approaches from their areas of expertise (Zinsstag *et al.*2008).

Sharing research between disciplines

Research that integrates human and animal health across different disciplines is critical for the success of One Health approaches to disease control (Tibbo *et al.* 2008).

Several programs that can provide important information to One Health-based TB control are being conducted in sub-Saharan Africa. The Health for Animals and Livelihood Improvement (HALI) program in Tanzania (Conrad *et al.* 2009) is currently involved in detection of *M. bovis* in cattle that provide milk for human consumption, and from wildlife sharing water and habitat with infected cattle; sampling water for the presence of *M. bovis* and other waterborne pathogens and parasites; and identifying possible animal sentinel species for human TB (rats). Another program is the Federation of American Scientists' Animal Health Emerging Animal Diseases (AHEAD) International Lookout for Infectious Animal Disease (ILIAD) program in South Africa (102). ILIAD has been designed to develop regional programs to detect and document the extent of infectious diseases shared by wildlife and livestock, and provide disease treatment, prevention and control programs to increase livestock production, protect the health of wildlife, develop physical and professional resources to sustain the programs, and bring communications and epidemiology information technologies to rural areas. Additionally, the Southern Center for Infectious Disease Surveillance (SACIDS) is conducting research using a One Health approach in the Serengeti National Park, to describe interactions at the human-livestock-wildlife interface to determine how TB is transmitted between these groups (Mbugi *et al.* 2012b, Rweyemamu *et al.* 2012).

Current diagnostics for human TB are focused on pulmonary disease associated with *M. tuberculosis* (sputum smears, very few extrapulmonary lesions tested) and requirements for mycobacterial culture for diagnostics are often skipped, resulting in missed diagnosis of *M. bovis* (Cotter *et al.* 1996). Differentiation of mycobacterial species responsible for pulmonary TB is often not pursued. Use of inappropriate diagnostic protocols or laboratory techniques (e.g. using culture media that inhibits *M. bovis*) or lack of additional testing to identify the species MTB, contributes to under-reporting of human BTB (Bayraktar *et al.* 2011, De Kantor *et al.* 2008). Such a shortcoming has significant implications for the treatment of zoonotic TB: *M. bovis* is resistant to pyrazinamide, a drug often used for the treatment of *M. tuberculosis* infection (Bilal *et al.* 2010, Cosivi *et al.* 1998, de la Rua-Domenech 2006), and the proportion of deaths amongst BTB patients is higher than among patients with MTB (Majoor *et al.* 2011, Rodwell *et al.* 2008). Determination of species also adds important information needed by epidemiological studies to identify sources of infection and routes of transmission (Bayraktar *et al.* 2011, Cadmus *et al.* 2011, Cunha *et al.* 2012, Duarte *et al.* 2010, García-Jiménez *et al.* 2012, Jenkins *et al.* 2011, Rodríguez *et al.* 2009).

Using One Health approaches, particularly in sharing resources, training, and knowledge of laboratory and health care workers, should decrease this form of misdiagnosis. Refinement of currently-used tests for BTB to improve sensitivity and specificity, particularly those that can be readily used in the field in developing countries and the development of new tests, are goals for TB research. Serological diagnostic tests for human and animal tuberculosis, which measure cell-mediated and humoral immune responses [gamma-interferon assay, ELISA, Multi-Antigen Print Immuno-Assay (MAPIA), immunochromatographic rapid test (ICT or RT), lab-on-a-chip (LOC) devices] are being developed, refined, and tested under field conditions (Buddle *et al.* 2011a, Chambers 2009, Chambers *et al.* 2011, de la Rua-Domenech 2006, García-Bocanegra *et al.* 2012, Lyaschenko *et al.* 2008, Wadhwa *et al.* 2012, Zinsstag *et al.* 2008). Microarray analysis to identify specific genetic markers that identify cattle more likely to be false positives on screening tests is being conducted to improve the effectiveness of the screening protocol (Lim *et al.* 2012). Researchers also continue to make improvements to traditional TB tests, including skin testing in cattle (Buddle *et al.* 2011a).

Improving diagnostic tools for MTB infections is an ongoing goal for research in both human and veterinary medical sciences. For example, molecular techniques (spoligotyping, MIRU-VNTR, IS*6110* RFLP, deletion typing, nested PCR) are being developed and refined for use with isolates from both humans and animals. Molecular approaches for detection of mycobacteria are more sensitive, specific, and rapid than traditional mycobacterial culture (Allix *et al.* 2006, Awah-Ndukum *et al.* 2011, Berg *et al.* 2011, Cadmus *et al.* 2006, Duarte *et al.* 2010, Durnez *et al.* 2009, Grant *et al.* 2012, Gumi *et al.* 2012, Gutiérrez *et al.* 1997, Hlavsa *et al.* 2008, Nawaz *et al.* 2012, Van Soolingen *et al.* 1994). These tools are being used to identify circulating strains and species of mycobacteria in given regions and populations, which is needed to describe the transmission and molecular diversity of mycobacteria and are gaining acceptance as tools for use in outbreak investigations (Allix *et al.* 2006, Awah-Ndukum *et al.* 2011, Bayraktar *et al.* 2011, Berg *et al.* 2011, Cadmus *et al.* 2006, Cadmus *et al.* 2011, Cunha *et al.* 2011, Cunha *et al.* 2012, Di Marco *et al.* 2012, Duarte *et al.* 2010, García-Bocanegra *et al.* 2012, García-Jiménez *et al.* 2012, Humblet *et al.* 2010, Jenkins *et al.* 2011, Kazwala *et al.* 2006, Lari *et al.* 2011, Mbugi 2012b, Rodríguez *et al.* 2009, Rodwell *et al.* 2010, Romero *et al.* 2011, Shrikirishna *et al.* 2009, Van Soolingen *et al.* 1994).

Research into novel approaches to the prevention of tuberculosis can be used not only for animal but human disease control and prevention. Current studies into the immunology, diagnostics, and treatment (Dooley *et al.* 2012) of TB involve research using information gleaned from both humans and animals. For example, experimental trials to determine if drug-assisted protective immunity against *M. bovis* infection is present in calves (Dean *et al.* 2008) may have applications for human BTB control.

The development of effective TB vaccines has been identified as an important goal by the STOP TB partnership and other international TB control agencies (Gutiérrez *et al.* 2012, Kaufmann *et al.* 2010). Even though the bulk of vaccine research is directed towards the development of human MTB vaccines, discoveries in human vaccine research can be applied to the development of novel animal vaccines (Waters *et al.* 2012). The TBVAC Consortium has been funded by the EU (Dockrell 2012), with the goal of development of new vaccines against TB. These efforts include interdisciplinary research involving identification of new antigens, testing in animal models, new delivery systems and adjuvants. Recently, efforts to develop DNA vaccines for TB that induce cellular immunity against TB have been successfully tested in animal models (Okada and Kita 2010). The Gates Foundation has funded a study of biomarkers for TB in Africa through their Grand Challenges (Dockrell 2012): the goal of this study is to longitudinally follow cohorts at seven different sites to identify biomarkers for the development of TB or protection from TB. To date, investigators have detected differences in human immune responses in different populations (Malawi *vs.* UK), demonstrating the impact of environment on immune response, and are currently studying the effects of helminthes co-infection on immunity against TB and other diseases.

Vaccination of livestock and wildlife for BTB control is been investigated in developing countries and in countries with wildlife reservoirs of BTB (Chambers *et al.* 2011, Cosivi *et al.* 1998, Gortázar *et al.* 2008, Katale *et al.* 2012, Lesellier *et al.* 2006, Mbugi *et al.* 2012b, Palmer *et al.* 2012b, Wedlock *et al.* 2005, Zinsstag *et al.* 2008). In some instances, vaccination does not prevent infection, but reduces the burden of disease in the vaccinated wildlife (Chambers *et al.* 2011). With ongoing research to develop better vaccines and delivery methods, vaccination has been recognized as a future option for control of BTB transmission between wildlife and livestock (Palmer *et al.* 2012a). In addition to efficacy studies, there are concerns that vaccination may confound screening tests for BTB. Cattle exposed to BCG (Bacillus Calmette-Guérin, an attenuated strain of *M. tuberculosis* used for vaccination), will give false positives through skin testing. Concerns have been raised that vaccinated wildlife may transmit BCG to livestock (Palmer *et al.* 2010), and hunters may be exposed to BCG from vaccinated deer (Palmer *et al.* 2012b). However, current studies have demonstrated that, while BCG is shed from vaccinated wildlife (Chambers *et al.* 2011, Lesellier *et al.* 2006, Palmer *et al.* 2010, Wedlock *et al.* 2005), the risk of transmitting BCG from wildlife to livestock or humans is considered to be low (Chambers *et al.* 2011, Palmer *et al.* 2012b).

Research is also ongoing in the development of vaccines and vaccine delivery systems for use in cattle and wildlife reservoirs of BTB, which will be critical in situations where conventional test-and-slaughter control programs are not practical, and where it is impossible to segregate wildlife reservoirs from livestock or when slaughter of infected wildlife is socially controversial (Buddle *et al.* 2001b, Carstensen *et al.* 2011, Gortázar *et al.* 2012, O'Brien *et al.* 2006, Waters *et al.* 2012). Vaccination can reduce the impact of BTB on wildlife populations, particularly where threatened or endangered species [e.g., lions and cheetahs in South Africa (de Vos *et al.* 2001); Iberian lynx in Spain (Gortázar *et al.* 2012)] are threatened (Buddle *et al.* 2011b, Lesellier *et al.* 2006, Waters *et al.* 2012).

Improved efficiency of TB surveillance, diagnosis, and control programs

The following have all proved to be necessary to develop comprehensive zoonotic TB control programs:

- improved diagnostic tests,
- better wildlife,
- transboundary surveillance programs,
- application of control measures to livestock and wildlife,
- additional research into the role of different wildlife species,
- the role of ecosystem environments on the transmission of BTB (García-Bocanegra *et al.* 2012, Humblet *et al.* 2009, Mbugi *et al.* 2012a).

The transboundary nature of zoonotic TB automatically expands the scope of surveillance and control programs: in sub-Saharan Africa, wildlife reservoirs, livestock, and pastoralists constantly traverse large geographic areas, providing opportunities to both acquire and transport zoonotic diseases as they move across borders (Capobianco Dondona *et al.* 2010, Rass 2006, Schwabe 1984).

Early detection of BTB in both human and animal populations, a cornerstone of the One Health approach to zoonoses control, is critical to control the disease in all populations (Meisser *et al.* 2011). Simultaneous surveillance of human and animal populations, which would reduce detection time (Narrod *et al.* 2012, Schelling *et al.* 2003, Zinsstag *et al.* 2005, Zinsstag *et al.* 2009), is an emerging strategy in zoonotic disease surveillance (Vrbova *et al.* 2010) and the integration of human and animal surveillance and prevention programs has been strongly recommended for BTB (Ayele *et al.* 2004, Boukary *et al.* 2010, Chen *et al.* 2009, Cleaveland *et al.* 2007, Cosivi *et al.* 1998).

Collaborative efforts between public health, agriculture, and wildlife professionals, with support from the public, are critical to the control of BTB (Cunha *et al.* 2012, Okafor *et al.* 2011). Lack of stakeholder support can seriously reduce the effectiveness of BTB control programs, as seen in the control of BTB in wild white tailed-deer in Michigan and Minnesota (Carstensen *et al.* 2011). Control programs have successfully reduced BTB levels in wild deer in Minnesota with public acceptance and support (Carstensen *et al.* 2011), while lack of cooperation with farmers and hunters in Michigan have made control programs more difficult to maintain (Carstensen *et al.* 2011, O'Brien *et al.* 2006).

Conclusions

The One Health approach offers many advantages in controlling disease. These include: 1) efficiency as a result of shared surveillance programs, laboratory facilities, training of personnel, and research; 2) potentially positive impacts on the disease in livestock, wildlife, and humans; 3) opportunity to involve trans-disciplinary teams of professionals in biomedical sciences, social sciences, and ecological sciences. Given the complex nature of the epidemiology of zoonotic TB, and the influences of sociological, economic, and ecological factors, One Health provides an excellent economical approach for conducting research, and the development of effective disease control and prevention programs for zoonotic tuberculosis.

Conflict of interest/Competing interests

Dr Kaneene is the most recent former chairperson of the Zoonotic TB Sub-Section of the International Union Against Tuberculosis and Lung Disease (IUATLD). Dr Kaplan is a member of the One Health Initiative Team (http://www.onehealthinitiative.com/index.php). Dr Steele is a current member of the One Health Initiative Website Advisory Board.

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