Preventing and controlling zoonotic tuberculosis:
a One Health approach

John B. Kaneene1, RoseAnn Miller1, Bruce Kaplan2, James H. Steele3 & Charles O. Thoen4

1 Center for Comparative Epidemiology, 736 Wilson Road, Room A-109, Michigan State University, East Lansing, MI 48824, United States of America.
2 Specializes in Internal Medicine, 4748 Hamlets Grove Drive, Sarasota, FL 34235, United States of America.
3 Veterinarian Practitioner, 153 Edgehill Circle, Kaysville, UT 84037, United States of America.
4 Department of Veterinary Microbiology and Preventive Medicine, College of Veterinary Medicine, Iowa State University, Ames, IA 50011, United States of America.

* Corresponding author at: Center for Comparative Epidemiology, 736 Wilson Road, Room A-109, Michigan State University, East Lansing, MI 48824, United States of America. Tel.: +1 517 355-2269, e-mail: kaneene@cvm.msu.edu

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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.

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


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:

- recrudescents 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,

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 (Ayale 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 ethnomedical knowledge 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, Marcotic 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, Zinsstag 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 (Gortazar 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, Kanka 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


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, Fatene 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 (Allepz 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 (Allepz 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 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).


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 has 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, Leselier 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 Mycobacterium 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, Leselier 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, Leselier 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 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.

References


