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Improving specific disease outcomes through a One Health approach – tuberculosis

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Summary
Early discoveries in the field of tuberculosis more than a century ago indicated that the success of disease control in human populations would depend on the success of control measures in animals, and vice versa. Recognising the zoonotic importance of a cattle-derived pathogen was the beginning of the eradication of bovine tuberculosis from most of the cattle population in Europe. It was a costly and resource-intensive process, but a successful one. The resulting near disappearance of zoonotic tuberculosis from the human population exemplifies probably one of the largest One Health successes in medical history. Since that time many advances in tuberculosis diagnosis, vaccinology, molecular epidemiology and immunopathogenetic studies have been made within the disciplinary divides of human and animal health research. More recently, the discovery of similarities in the interactions between the natural hosts and the causative agents of tuberculosis, as well as similarities in the resulting disease consequences, have led to a renewed appraisal of the benefits of collaborative approaches. It is to be hoped that, in the future, the combined body of scientific knowledge will also provide the basis for practical One Health initiatives at community level.

Keywords
Mycobacterium bovis – *Mycobacterium tuberculosis* – One Health – Zoonotic tuberculosis.

Introduction

Despite considerable regional progress in reducing the number of human tuberculosis cases and associated deaths, the global burden of human tuberculosis remains enormous. In 2011, there were an estimated 8.7 million new cases of the disease and 1.4 million people died. Geographically, the tuberculosis burden is highest in Asia and Africa and the latter has the highest number of cases and deaths relative to population (1).

Bovine tuberculosis (BTB) is a disease of livestock and wildlife and causes global economic losses of US$3 billion annually despite widespread control efforts (2). Before the implementation of compulsory milk pasteurisation to prevent the transmission of *Mycobacterium bovis*, the causative agent of BTB, to humans via the food chain, a significant number of tuberculosis cases in humans in Europe were caused by *M. bovis* (3). Owing to its continued occurrence in developing countries where no or only limited control measures are applied, the World Health Organization (WHO) listed BTB amongst seven endemic neglected zoonoses (4). This was not solely based on economic livestock losses but on an integrated assessment of the disease impact on human livelihoods, especially in marginalised communities. This is in line with the underlying principle of One Health, which is to increase the benefits of health interventions by directing them towards more than one sector alone.

In large parts of the world, namely in developing countries, human and bovine tuberculosis co-exist with only limited control measures in place (5) (Fig. 1 and Fig. 2).

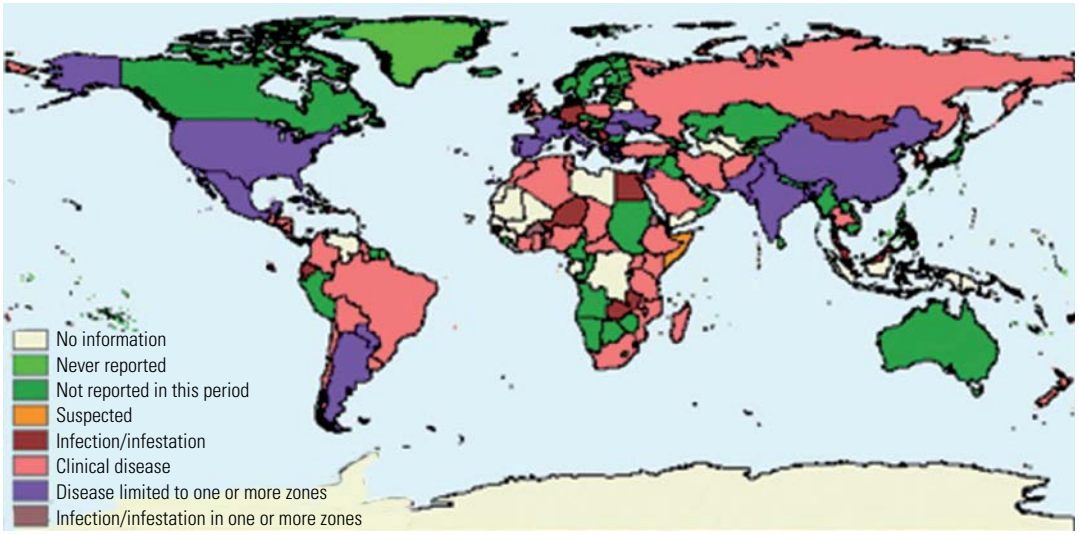

Fig. 1
Global distribution of bovine tuberculosis in domestic animals between January and June 2013
Source: World Animal Health Information System (WAHIS)

Tuberculosis in mammals, including humans, can be caused by any of the members of the *Mycobacterium tuberculosis* complex (MTBC), which currently comprises *M. tuberculosis, M. bovis* (including the attenuated *M. bovis* Bacille Calmette-Guerin [BCG] vaccine strain), *M. microti, M. africanum*, *M. cannettii*, *M. caprae, M. pinnipedii, M. orygis, M. mungi* and dassie bacillus.

The number and nomenclature of MTBC members have been subject to changes as new variants have been discovered and specifics of the phylogenetic branching within the complex have been revealed (6). New members of the complex were generally named after the animal species in which they were first diagnosed, implying a certain host specificity (7, 8, 9, 10). However, this concept has gradually lost its significance, as the organisms are detected in an increasing range of hosts, including humans (11, 12, 13). This has far-reaching implications in the context of One Health, as all members of the MTBC can be transmitted between animals and humans (with the potential for spillback) and therefore warrant an interdisciplinary approach.

Mycobacterium bovis is by far the most important causative agent of tuberculosis in livestock and wildlife and is commonly referred to as bovine tuberculosis. However, *M. tuberculosis,* which is primarily associated with tuberculosis in humans, has also been identified as an emerging threat to wildlife and domestic animal health, especially in countries where human tuberculosis is highly prevalent. *Mycobacterium tuberculosis* is the cause of a rising infection pressure at the interface between humans and animals, including captive and free-ranging wildlife (14, 15, 16).

Mycobacterium bovis and *M. tuberculosis* can be transmitted between humans and animals in both directions and they have the ability to cause chronic progressive devastating disease in both populations. For these reasons, tuberculosis is best researched and managed using a One Health approach.

This paper reviews the linkages between animals, humans and the environments which give rise to inter-species transmission of *M. bovis* and other MTBC members. Furthermore, it highlights the benefits of the close relatedness of MTBC members, especially *M. bovis* and *M. tuberculosis*, for interdisciplinary approaches to the control of these pathogens.

Milestones in tuberculosis research with relevance to One Health

During the century following the discovery of the tubercle bacillus by Robert Koch in 1882, the control of human tuberculosis benefited from discoveries in the veterinary field, including tuberculin (an *in vitro* diagnostic reagent) and the attenuated *M. bovis* Bacille Calmette-Guerin (BCG) vaccine. These discoveries therefore rank among the early milestones in One Health as far as tuberculosis is concerned.

The introduction of tuberculin skin-testing marked the beginning of systematic BTB control by detecting and eliminating *M. bovis*-infected cattle herds. This BTB test-and-slaughter control strategy, in combination with the

implementation of compulsory milk pasteurisation, probably constituted the biggest and most effective One Health approach in the history of zoonotic tuberculosis control. Pasteurisation was particularly effective at reducing the number of extrapulmonary tuberculosis cases in children, which had been largely attributed to the consumption of unpasteurised, infected milk (3, 17, 18). The implementation of BTB eradication programmes was accompanied by a sharp decline in the incidence of human tuberculosis due to *M. bovis* (3). These campaigns benefited from considerable scientific, technical and financial commitment, but it should not be forgotten that they could not have succeeded without public awareness campaigns ensuring farmer cooperation (19).

The BCG vaccine, which is the safest vaccine known to humankind, was derived from *M. bovis* of bovine origin and its protective effect was first demonstrated in a cattle challenge experiment (20). Increasing international collaboration and intensified global efforts to improve BCG and to produce new next-generation vaccine candidates promise to advance knowledge and skills in both the medical and the veterinary sector. The calf tuberculosis model, for example, affords a unique opportunity to evaluate neonatal immune responses to vaccination and infection. The safety and efficacy of promising tuberculosis vaccines may also be evaluated in calves prior to testing in costly non-human primates. A dozen novel tuberculosis vaccine candidates are currently being evaluated in human clinical trials and are available for evaluation in animals (21, 22).

Comparative studies of human tuberculosis have traditionally relied on the mouse and guinea-pig animal models. The main advantages of using these infection models in conjunction with human studies is that one can control the strain, dose and timing of infection in the animals, whereas in humans those are very difficult, or impossible, to determine or control. The disadvantages of these models are that the pathology induced is different, the protection mechanisms against the tubercle bacilli are not the same, and they only focus on single factors in the disease process. The latter, also referred to as the reductionist approach, does not make provision for the investigation of natural host–pathogen interactions at the molecular, cellular, and tissue level, including the effects of interventions such as vaccination (23). Since the outcome of infection with *M. tuberculosis* or *M. bovis* depends on the innate resistance and susceptibility of the host and on the balance between pro- and anti-inflammatory responses, which are influenced by factors intrinsic to the bacterium (i.e. virulence), it is more desirable to study a pathogen in its natural reservoir. The use of non-human primates, such as macaques, can only partially bridge the gap between human and animal studies as, although these monkeys are susceptible to *M. tuberculosis*, they are not a natural reservoir and the stress experienced by wild animals in captivity may lead to immune responses outside the immunopathogenetic pathway for tuberculosis (24).

A much more mutually beneficial approach has been identified following recent advances in the characterisation

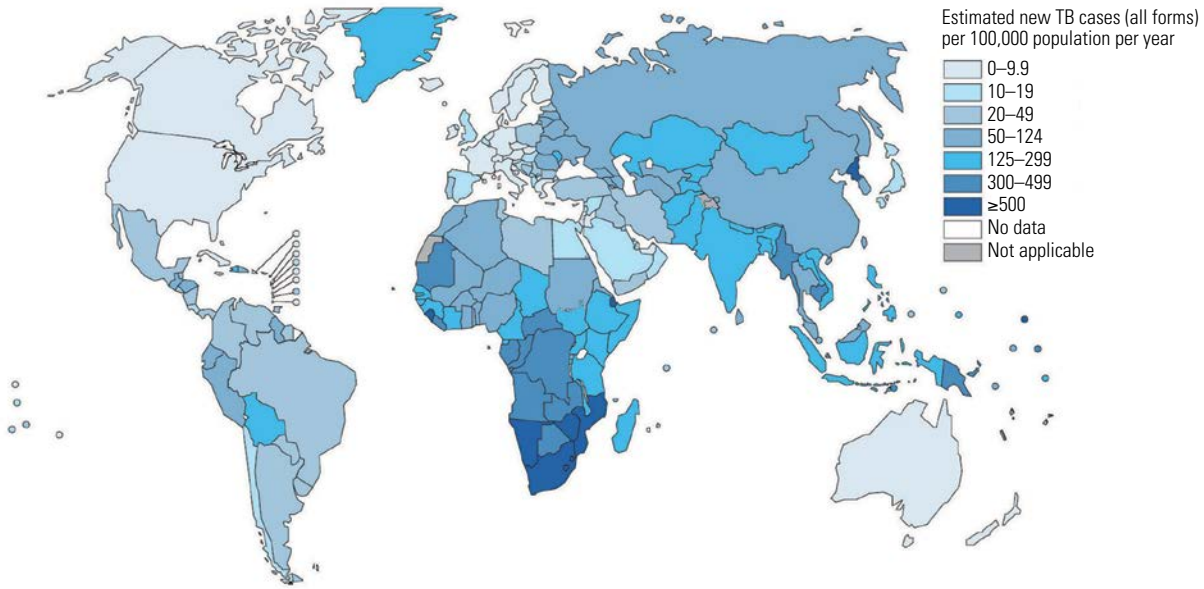

Fig. 2
Estimated human tuberculosis incidence rates
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of the immune response of cattle to *M. bovis*. This affords a new opportunity to gain further insight into the mechanisms of immunopathogenesis and also to identify immune correlates of protection, utilising the natural host–pathogen relationship. This approach seems well justified since *M. tuberculosis* and *M. bovis* are >99% identical at DNA level and induce similar host responses, disease profiles and pathology. New insights in the similitude in the disease profiles may help to overcome the perceived disadvantage of using *M. bovis* instead of *M. tuberculosis* (25). While there may be some species differences between the immune response of humans and cattle to mycobacterial infections, there are fewer significant differences between cattle and humans than between mice and humans (26). These developments also promise to render the bovine model more accessible to medical scientists than in the past, when it was much more expensive and when research groups in the veterinary and medical fields were generally not integrated and did not often collaborate with each other (27).

Diagnosis

The difficulty of obtaining a correct diagnosis of tuberculosis remains a serious stumbling block in the fight against the world's largest treatable infectious cause of death in humans. It is estimated that merely 30% of all people suffering from tuberculosis are correctly diagnosed (28). In addition, fewer than 10% of those infected will develop clinical signs, while the majority will develop latent tuberculosis infection with a 5% to 10% lifetime risk of post-primary disease. According to estimates by the WHO, 1.5 billion people worldwide suffer from latent tuberculosis. Despite this obvious disease burden there is no gold standard assay to diagnose this condition.

While it has remained unclear for a long time whether different stages of infection exist in *M. bovis*-infected cattle (i.e. active versus latent infection), recent studies have suggested that latent disease and reactivation may indeed occur in cattle. It can be expected that this will prompt new joint approaches for the development of a test able to differentiate between active and latent tuberculosis infections in humans and livestock (29, 30).

In the 1980s, a blood-based interferon gamma (IFN-γ) assay was developed as an *in vitro* biomarker for *M. bovis* infection to detect cellular immunity in cattle infected with *M. bovis* (31). In human medicine, a similar version of the IFN-γ test (QuantiFERON) has subsequently been developed and recently approved in a number of countries to support the diagnosis of latent tuberculosis infection in humans (32). The recombinant MTBC-specific antigens ESAT-6 and CFP-10 are used in both test systems for optimised diagnostic performance and vaccine studies (33).

It seems paradoxical that accurate data concerning the occurrence of *M. bovis* in humans are still lacking, despite extensive efforts by governments and the WHO to improve the diagnostic rate. The question is whether those data are truly difficult to collect (technically) or whether they may be ignored for financial reasons. Inherent differences in the microbiological growth characteristics of *M. bovis* and *M. tuberculosis* mean that they do not grow equally well in the same growth medium. The growth medium usually used for human samples primarily supports the growth of *M. tuberculosis*, so in a diagnostic laboratory dedicated to the isolation of *M. tuberculosis* from human patients, *M. bovis* can therefore be easily missed. This is aggravated by the fact that patients co-infected with *M. bovis* and *M. tuberculosis* have only a negligible chance of being correctly diagnosed (34).

It is probably fair to state that most health practitioners consider *M. bovis* to be an unlikely cause of tuberculosis in humans, either due to its near disappearance in developed countries or due to an overwhelming high burden of human tuberculosis in developing countries. Recent efforts to determine the minimum test specifications for a new tuberculosis point-of-care diagnostic test in resource-poor settings, based on medical and patient needs, identified the speed of diagnosis, ease of application and affordability as the main criteria, while detectability and differentiation of all tuberculosis-causing mycobacteria were not mentioned (35).

Molecular epidemiology as a One Health tool

The past two decades have witnessed the development and implementation of molecular tools which have enabled medical and veterinary scientists to study the transmission of *M. bovis* and *M. tuberculosis* within and between host species. Owing to the close genetic relationship of the two *Mycobacterium* species it is now possible to apply essentially the same typing techniques and markers (e.g. restriction fragment length polymorphism probes IS*6110*, variable-number tandem-repeat loci) for both species, with small modifications. This has promoted the generation of international databanks of genotypes as well as trace-back and trace-forward investigations in human and animal, including wildlife, populations across countries and continents (12, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46).

The causative role of *M. bovis* in zoonotic tuberculosis in humans has long been recognised. However, it was not until the advent of molecular *M. bovis* typing that it became possible to confirm this link beyond doubt. Genetic strain characterisation made it possible to compare *M. bovis* strains isolated from humans with those from

domestic or wild animals. Scientifically driven collaborative molecular epidemiology investigations across the medical and veterinary sectors demonstrate the beginning of a One Health approach (41, 47, 48). To date, the scientific reporting in the vast majority of cases does not include information on how the molecular data were translated into effective risk reduction measures for humans.

Outbreak investigations using molecular markers have also revealed that *M. tuberculosis* can be transmitted from humans to cattle, and that there is the possibility of co-infection of cattle herds with *M. bovis* and *M. tuberculosis* (49, 50, 51). This poses a new challenge for animal health and veterinary public health interventions, as the role of cattle in the transmission of *M. tuberculosis* is currently poorly understood. *Mycobacterium tuberculosis* was found to be avirulent for cattle in a number of studies, while others reported lesions in cattle that were indistinguishable from those caused by *M. bovis*. It would seem that the ecology of the human tuberculosis bacillus at the human–livestock interface is far more complex than currently known. The virulence and outcome of *M. tuberculosis* infections in cattle may be determined by a combination of the genotype of the *M. tuberculosis* strain, the immune status and response of the animals, and the disease burden in the human population (50, 52). Di Pietrantonio and Schurr have speculated that this could indicate a new host-mycobacterial co-adaptation resulting in host-pathogen specificity for tuberculosis; if this is the case, the earlier discussed bovine animal model for human tuberculosis has even further mutual benefit for veterinary and medical tuberculosis research than previously thought (53).

One Health in practice

A literature search of tuberculosis in the One Health context typically yields publications reporting on knowledge gaps and threats of, and risk factors for, human tuberculosis of animal origin (14, 54, 55, 56, 57). Despite a fair degree of interdisciplinary collaboration one can notice a strong tendency towards veterinary-led investigations in these papers.

In developed countries, human tuberculosis cases caused by *M. bovis* or other MTBC members occur sporadically and often attract the scientific interest of veterinary and medical investigators alike. The isolated nature of these cases, however, generally precludes the establishment of longer-term collaborative programmes at institutional level (12, 58).

Overall, examples of One Health in practice driven at non-academic, governmental level currently appear to be either lacking or remain unpublished. One possible reason may be that a sustainable One Health strategy needs to reach beyond the collection of scientific data; it should be able to implement cross-disciplinary initiatives which can add value and result in long-term health and societal benefits for communities at the interface with zoonotic diseases.

South Africa has one of the highest human tuberculosis burdens and HIV/tuberculosis co-infection rates in the world and BTB occurs sporadically in cattle herds but is also endemic in African buffaloes (*Syncerus caffer*) in the Kruger National Park and the Hluhluwe-iMfolozi Park (HiP) (1, 59). The persisting risk of BTB spillover to or from the communal livestock of neighbouring communities has raised increasing public health concern (60). Geoghan and co-workers conducted testing for BTB in communal cattle at the interface with wildlife in HiP, resulting in several test-positive, unconfirmed cases. These and other findings prompted a ten-month multidisciplinary study in the same area to document health issues and disease awareness regarding animal, human and environmental health. Household visits were conducted to gather information on dairy production, use and consumption in view of risk factors for milk-borne zoonoses as well as to collect dairy samples for laboratory analyses. Households were subsequently informed of the outcome and given instant practical advice to reduce pathogen introduction via feedback meetings, videos and public health brochures in the local language. All the latter have since been integrated as part of regular extension work in the district. Monitoring of the public health uptake demonstrated the acceptance of at least three basic hygiene measures in 97% of the households (Geoghan, personal communication). These basic measures are considered to be effective in reducing the risk of zoonotic disease transmission via milk.

Training One Health practitioners within the veterinary, medical and associated professions has been recognised as being instrumental in educating a new generation of health professionals who will practise One Health free from professional prejudice and disciplinary silos. An increasing number of postgraduate courses are offered by tertiary training institutions internationally, some of which are aiming to be regionally relevant, while others provide students with a global perspective of One Health issues. For details on these courses the reader is referred to the World Wide Web. It should also be mentioned that the ultimate goal should be to integrate One Health training into the undergraduate curriculum of the health professions to make One Health part of a problem-solving approach for health issues at the human–animal and human–environment interfaces (61).

The control of BTB in cattle by means of test-and-slaughter programmes is expensive and requires a long-term financial commitment from governments, which is often not

affordable for developing countries. On the other hand, in countries with a wildlife reservoir, eradication of BTB in cattle is considered impossible due to the constant risk of re-infection. In infected free-ranging wildlife populations in Africa the potential for spillover to endangered and rare species poses a threat to conservation and species diversity (62). Under these different circumstances, vaccination against tuberculosis is regarded as the most feasible or the only effective control measure (63, 64, 65, 66). Vaccine efficacy trials involving experimental challenge and field studies in cattle and wildlife reservoirs are initiatives with outcomes relevant for both veterinary and medical applications (64). During vaccine trials in the United States a dose-related recovery of BCG from vaccinated white-tailed deer *(Odocoileus virginianus)* suggested that human consumption of hunter-harvested deer may expose humans to BCG. The consequences of resulting positive skin-test reactivity could compromise public health surveillance for human tuberculosis in countries where BCG vaccination in humans is no longer applied (67). Furthermore, the consequences of BCG exposure from animal-derived foods on human health, especially in countries with a high HIV/AIDS burden, is largely unknown and constitutes an area where One Health research is indicated (68).

Conclusions

There was an early period during which tuberculosis research was almost exclusively driven by a One Health approach, which led to breakthroughs in control and diagnosis of the disease. However, for decades thereafter, the disciplinary divide between veterinary and medical sectors led to diverging strategies that prevented further common approaches. More recently, the advantages of One Health approaches to tuberculosis research have not only been re-discovered, but financial constraints make discipline-locked approaches less affordable and acceptable. The translation of interdisciplinary knowledge into implemented One Health in practice, however, remains to be seen.

De meilleurs résultats spécifiques en prophylaxie grâce à l'approche « Une seule santé » : l'exemple de la tuberculose

A.L. Michel

Résumé

Dès les premières investigations en matière de tuberculose, qui remontent à la fin du XIXe siècle, il est apparu que le succès de la lutte contre cette maladie chez l'homme dépendait du succès des mesures de lutte appliquées chez les animaux, et réciproquement. Le constat de la nature zoonotique de l'agent pathogène originellement présent chez les bovins s'est traduit à terme par l'éradication de la tuberculose bovine dans la quasi-intégralité de la population bovine européenne. Ce processus a certes mobilisé des sommes et des ressources considérables mais il a été couronné de succès. La conséquence en a été la disparition presque totale de la tuberculose zoonotique chez l'homme, qui constitue l'une des plus grandes réussites « Une seule santé » de l'histoire de la médecine. Depuis lors, la recherche sur la tuberculose a fait des progrès remarquables au carrefour de la médecine humaine et vétérinaire, notamment sur le diagnostic, la vaccinologie, l'épidémiologie moléculaire et l'immunopathogénie de cette maladie. Plus récemment, la découverte des similitudes à l'œuvre tant au niveau des interactions

entre les hôtes naturels et les agents responsables de la tuberculose que des manifestations pathologiques qui en résultent a permis de valoriser encore plus les apports des méthodes de collaboration intersectorielle. On peut espérer qu'à l'avenir, la mise en commun de corpus de connaissances scientifiques permettra de mener à bien des initiatives concrètes « Une seule santé » au niveau des populations locales.

Mots-clés
Mycobacterium bovis – *Mycobacterium tuberculosis* – Tuberculose zoonotique – Une seule santé.

Obtención de mejores resultados en determinadas enfermedades abordándolas desde el ángulo de «Una sola salud»: el caso de la tuberculosis

A.L. Michel

Resumen
Los primeros descubrimientos relativos a la tuberculosis, hace más de un siglo, dejaban presagiar que el éxito de la lucha contra la enfermedad en poblaciones humanas dependería de la eficacia de las medidas de lucha en los animales, y viceversa. El hecho de entender la importancia zoonótica de un patógeno aislado en el ganado fue el punto de partida que llevó a erradicar la tuberculosis bovina en buena parte de la población vacuna de Europa. Fue un proceso caro en dinero y recursos, pero fructífero. Sus resultados, concretados en la virtual desaparición de la tuberculosis zoonótica de las poblaciones humanas, ejemplifican probablemente uno de los mayores éxitos obtenidos en la historia de la medicina trabajando desde los presupuestos de «Una sola salud». Desde entonces ha habido muchos avances en los estudios sobre diagnóstico, vacunología, epidemiología molecular e inmunopatogenética de la tuberculosis dentro de las respectivas fronteras disciplinares de la investigación sobre salud humana y sanidad animal. En fechas más recientes, el descubrimiento de semejanzas en la interacción entre anfitriones naturales y agentes causales de la tuberculosis, y también en las consiguientes enfermedades, ha llevado a valorar de nuevo los beneficios de la labor de colaboración. Es de esperar que, en el futuro, el acervo combinado de conocimientos científicos siente también las bases de iniciativas prácticas en clave de «Una sola salud» a escala comunitaria.

Palabras clave
Mycobacterium bovis – *Mycobacterium tuberculosis* – Tuberculosis zoonótica – Una sola salud.

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