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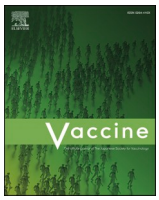

Short communication

Workshop report: One Health challenges and knowledge gaps in the control of intracellular infections with a focus on tuberculosis and leishmaniasis

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ABSTRACT

The VALIDATE Network brings together scientists addressing vaccine development for neglected infectious diseases caused by intracellular pathogens. In September 2023, the first workshop on One Health approaches to research and capacity building was held in Paarl, South Africa, with a focus on tuberculosis and leishmaniasis. Thirty-two scientists from 15 countries presented and discussed broad topics pertinent to zoonotic diseases, cross-species disease transmission, disease mitigation strategies, inequitable access to medicines and health technologies, and health system challenges in One Health. In this report, we summarize the gaps, challenges, and opportunities identified during the 2023 VALIDATE One Health workshop. We anticipate that the experiences and dialogues will be informative for animal, human, and environmental health investigators to guide the development of research projects and vaccine development with a One Health vision.

1. Introduction

"One Health is an integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals, and ecosystems. It recognizes that the health of humans, domestic and wild animals, plants, and the wider environment (including ecosystems) are closely linked and interdependent" (One Health High-Level Expert Panel) [1]. The interdependence of human, animal, and environmental health has been recognized for decades, especially in the context of zoonotic and vector-borne infectious diseases, and more recently antimicrobial resistance (AMR) [2–4]. One Health aims to remove the anthropocentric view of animal and environmental health management to improve human health. This creates the framework for a more holistic approach, under the philosophy of sustainable health approaches: "think globally, act locally" (Tripartite Guide to Addressing Zoonotic Diseases in Countries) [5].

The VALIDATE Network (www.validate-network.org) was established in 2017, aiming to accelerate vaccine development for neglected infectious diseases caused by *Mycobacterium* spp., *Leishmania* spp. and *Burkholderia* spp. [6,7]. These pathogens all cause a significant degree of human mortality and morbidity globally, particularly in low- and middle-income countries (LMIC). In addition, they can infect animal species. For example, *Mycobacterium bovis* associated tuberculosis (TB) is endemic in some wildlife populations and livestock, and leishmaniasis occurs in dogs and other domestic and wild mammals, both of which present a risk for zoonotic transmission [8,9]. The VALIDATE Network brings together individuals working on these complex intracellular pathogens to exploit their synergies, similarities and differences, aiming to expedite vaccine development for each pathogen. As of August 1st, 2024, VALIDATE had over 775 members from 76 countries, with 46.9 % of the membership identifying as female.

The network has attracted early career researchers and established investigators in veterinary and human health. This cross-disciplinary environment inspired VALIDATE's interest in applying a One Health approach to research and capacity building under the network's remit on vaccine development for intracellular and neglected pathogens. To this

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end, VALIDATE organized its first One Health Workshop in Paarl, South Africa, held on September 4th–6th, 2023. Thirty-two scientists, from a variety of human and animal research disciplines (ranging from basic sciences to social and implementation research), met to explore the application of a One Health model to TB and leishmaniasis research. Members from Argentina, Brazil, Colombia, Ethiopia, India, Ireland, Madagascar, Mexico, Saudi Arabia, Serbia, South Africa, Spain, Tunisia, United Kingdom, and the United States of America attended the workshop. Reflecting the membership composition of VALIDATE, 41 % of delegates were female. The research presented investigated TB and leishmaniasis across a range of species including (but not limited to) humans, cattle, dogs, and a broad range of African, South American, and European wildlife, as well as model species. This three-day workshop featured talks, panel discussions, and collaboration-building opportunities with the following objectives:

- To build on the One Health High-Level Expert Panel - Theory of Change [1] to identify the key challenges associated with employing a One Health approach to tackling TB and leishmaniasis, and what we, as a network, can do to address these;
- To provide an opportunity for each delegate to present their research, encourage collaboration, and the sharing of One Health experiences, to build knowledge within our community;
- To catalyze collaboration, including cross-pathogen and cross-discipline research.

Accordingly, the workshop was divided into four broad focus areas: 1) cross-species disease transmission, 2) disease mitigation strategies, 3) inequitable access to medicines and health technologies, and 4) health system challenges in One Health.

In this report, we summarize the gaps, challenges, and opportunities identified during the 2023 VALIDATE One Health Workshop. We anticipate that the experiences and dialogues will be informative for animal, human, and environmental health investigators to guide the development of research projects with a One Health vision. Recognizing the complexities associated with implementing the One Health approach, we also share this workshop experience as a catalytic mechanism to initiate cross-disciplinary exchanges and intersectoral interactions, which are at the center of successful One Health interventions.

2. Cross-species disease transmission

Professor Bernardo Villarreal-Ramos (Aberystwyth University, UK) spoke on bovine TB risks at multi-species interfaces. There are at least 11 *Mycobacterium* species which cause TB in humans and other animal species. *Mycobacterium tuberculosis* (*M. tb*) is the main aetiologic agent of human TB worldwide; however, geographical variations exist, whereby other species that cause TB in humans are highly prevalent, such as *M. africanum* in West Africa [10]. *M. bovis* is considered the main cause of TB in bovids and is known to cause TB in other animal species, such as badgers and white tail deer [11]. It is also the leading cause of zoonotic TB. More recently, *M. orygis* has been identified as a significant cause of TB in both humans and cattle [12].

TB appears to be a two-way street in which there is a constant co-evolutionary arms race between host and pathogen, with antibiotic use representing a major selective pressure. While *M. tb* is developing resistance to antibiotics at a rapid rate due to their imperfect use, this is not the case for *M. bovis,* since animals are less frequently prescribed antibiotics as treatment due to animal health regulations. However, resistant *M. bovis* isolates, especially to fluoroquinolones, have been reported globally in recent years due to increasing usage of antimicrobials in the treatment of bovine pneumonia [13], representing an unforeseen challenge from an off-target effect. To an extent, host specificity has acted as a barrier to the infection of domestic animals with drug resistant *M. tb* [14]. However, a major concern regarding management of pulmonary TB is the potential induction of antibiotic resistance in human *M. orygis* infections, which can lead to drug resistant *M. orygis* capable of developing in animal reservoirs.

Reinforcing this challenge, Professor Robert J. Wilkinson (The Francis Crick Institute, UK) spoke on the One Health aspects of drug-resistant TB in humans. Antitubercular drug resistance is largely believed to arise in vivo but is often subsequently transmitted [15]. It is of significant global importance but variably distributed, with under-ascertainment contributing to the failure of effective treatment. Recent advances have established that drug-resistant TB can be inferred accurately from whole genome sequencing [16]. However, wide implementation of these technologies represents a current roadblock. As previously mentioned, although antibiotic treatment of *M. bovis* is rare, this mycobacterial species is constitutively resistant to pyrazinamide, and misdiagnosis of zoonotic TB could lead to the development of further drug resistance in human patients.

Professor Christian Gortazar (Universidad de Castilla, Spain) spoke on the epidemiology of animal TB. Due to the multi-host nature of *M. bovis* and its ability to survive in the environment, controlling animal TB requires targeting of complex maintenance communities, such as wild boar and red deer in Spain, and the integration of all available control tools, including vaccination [17,18]. Research by Gortazar and his team suggests that animal vaccination with heat-inactivated *M. bovis* could overcome some of the barriers to BCG vaccination such as logistical and safety constraints [18,19], and vaccinated individuals might benefit from additional non-specific trained-immunity effects.

It is of interest that heat inactivated vaccines appear sufficient to control TB in wild boar [18]. While heat-inactivated vaccines typically induce Th2-type immunity [20], which could limit their applicability to TB given the importance of the cell-mediated response in protection, vaccines using either the entire inactivated or fragmented, lysed forms of *M. tb* have been shown to induce both Th1 cell-mediated and humoral immune responses against a variety of antigens [21]. It is also thought that that live vaccines confer greater protection through the induction of responses to antigens synthesized in vivo and potentially influence the type of immune response. This underscores the need to better understand the nature of the protective response in different species conferred by vaccination with BCG against TB and whether this translates to other species, underscoring the requirement to better understand comparative immunology for pathogen control.

Subsequent discussion among delegates centered around the key challenges that remain for control of TB in wildlife [22]. Professor Michele Miller (Stellenbosch University, South Africa) provided an overview of TB in South African wildlife and how reported cases represent only the ‘tip of the iceberg’. She noted that animal TB has routinely been researched, diagnosed, and managed separately from human TB, despite similarities in causative pathogen characteristics, as well as certain aspects of TB epidemiology and pathogenesis [23]. The significant knowledge gaps, especially in countries with high human and animal TB burdens, regarding the risk of transmission and disease in multi-host systems were highlighted. Closer collaborations and incorporation of multi-disciplinary approaches are needed to determine the relative contributions of the environment, domestic and wild animals, and humans in maintaining and spreading mycobacterial infections.

Incorporating tools and knowledge from the human and animal TB fields has facilitated progress in understanding TB at a systems level, which provides a more holistic view, rather than one that is species-specific. This approach addresses the priorities outlined in the WHO/FAO/OIE “Roadmap for Zoonotic Tuberculosis”, while using resources more productively to fill knowledge gaps [24]. This will further add to our understanding and provide information for strategies to address future influences, such as climate change, on infectious diseases. For example, as tools were developed to detect mycobacterial infections in wildlife, there was a rapid increase in the number of wildlife species reported with *M. bovis* infection in South Africa [25]. Similarly, the role of environmental contamination and indirect transmission of

M. tuberculosis complex (MTBC) species has been previously overlooked, although more recent studies have shown this to be an important component of TB epidemiology in multi-host systems [26]. One Health TB research, which includes interfaces between domestic and wild animals, environmental sources, and human communities will contribute to improved TB management and control strategies.

Dr. Sara Savić from the Scientific Veterinary Institute "Novi Sad", Serbia, spoke on the importance of vectors in managing pathogen spread within and between animals and humans, using *Leishmania* as an illustrative example. The *Phlebotominae* (sandfly) vector that transmits *Leishmania* can now be found as far north as central Europe, including the Balkans region, due to climate change [27]. Consequently, the pathogen is spreading in a similar way, and leishmaniasis is re-emerging in central and eastern Europe for the first time in several decades. Dogs are the main animal reservoir for leishmaniasis in Europe. Free movement of people and pets within the European Union has allowed the spread of disease, in part due to the lack of infection surveillance [28].

These presentations highlighted the complexities associated with multi-host infections. The threat of drug resistance, pathogen spillover to new hosts, and impacts of climate change, especially on vector-borne pathogens, requires novel approaches to disease control. Critically, development of effective vaccination programs that consider multiple hosts demands a greater understanding of comparative immunology and epidemiology of these diseases across species.

3. Disease mitigation strategies

The primary goal of vaccination is to elicit protective or therapeutic immune responses, which are intrinsically complex processes that have been impossible to reproduce in vitro to date. Therefore, the progression of promising vaccine candidates into the clinical pipeline still ultimately requires the use of higher organisms, making the use of animals an unavoidable requisite. Profesor Rogelio Hernandez Pando (Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico) presented the use of models for animal and human TB vaccines. Three main species are widely used for the evaluation of new TB vaccines: mice, guinea pigs, and non-human primates; in sequential order [29]. The "go/no-go" criterion for progression is based on the achievement of superior protection than that obtained with BCG, the current gold-standard, or similar protection to BCG but with improved safety. However, such models have intrinsic complexities due to the slow growth of the pathogen, the duration of experiments (usually 6–9 months), and the requirement for costly biosafety level 3 facilities. Although mice (*Mus musculus)* remain the most widely used model for pre-clinical evaluation of vaccine efficacy and safety [30], this species does not fully recapitulate the features of human TB, posing a pressing challenge for expedited vaccine research.

Addressing this issue, Dr. Rachel Tanner (University of Oxford, UK) shared research on cross-species antigen discovery and ex vivo screening tools for TB vaccine development. While immunological assessment of TB and bovine TB vaccines has focused on the induction of cell-mediated immunity, a growing body of literature indicates a role for antibodies in protection [31–33]. Dr. Tanner and collaborators have taken an unbiased approach to antigen discovery for the design of novel vaccine candidates, using whole-protein microarrays spanning the entire proteome of *M. tb* to identify targets recognized by BCG-induced antibodies in serum from humans, non-human primates and cattle. Inclusion of preclinical animal samples allowed array results to be related to levels of protection from *M. tb* or *M. bovis* challenge in matched animals [34]. Other emerging antigen discovery strategies such as immunopeptidomics and ex vivo screening tools for the evaluation of TB vaccine candidates were also discussed, including immune organoids. Future work aims to combine these approaches to develop and screen TB vaccine candidates, which may benefit from targeting humoral as well as cell-mediated immunity.

Professor Eamonn Gormley (University College Dublin, Ireland) continued the discussion of TB vaccination, presenting his experience of developing and adapting the BCG vaccine for use in wildlife reservoirs, specifically European badgers. Vaccination of badgers is now a key policy element of the national program to eradicate TB from cattle herds in Ireland [35]. The successful translation of laboratory studies to field implementation of vaccine delivery required buy-in and ongoing engagement with key stakeholders, including policy makers in the Department of Agriculture, Food and the Marine, veterinarians, and farming organizations. Such a cooperative approach is essential for the successful delivery of a vaccination strategy for wildlife.

In the context of therapeutic interventions, Dr. Rajiv Kumar's (Banaras Hindu University, India) presentation, "Translating Discoveries into Better Outcomes for Parasitic Diseases in India", addressed the concept of host-targeted therapies to treat human visceral leishmaniasis (similarly proposed for human cutaneous leishmaniasis and TB [36]). Results from his research suggest that drugs targeting regulatory/immune check point molecules from the human host, in combination with conventional anti-parasitic drugs, enhance anti-parasitic immune responses. Whether these approaches are useful for the control of canine leishmaniasis remains unknown.

Mitigation of infectious diseases such as TB and leishmaniasis may be improved by enhancing host immune responses through vaccination and/or host-directed therapies. However, further research is required into the mechanisms associated with such responses. Animal models and improved molecular techniques are being used to advance preventive and therapeutic strategies, but this pipeline could be expedited by applying a One Health approach for application to animal and human health in parallel. The importance of including stakeholders and policymakers early in the development of new programs was highlighted by the success of badger vaccination in the Irish TB campaign.

4. Inequitable access to medicine and health technologies in a One Health context

The World Health Organization has identified 11 neglected tropical diseases (NTD) as the focus of elimination efforts. In addition, the United Nations Sustainable Development Goal 3 includes a call to "end the epidemics of AIDS, TB, malaria and NTD", including leishmaniasis, by 2030 [37]. The affected patients are disproportionately concentrated in under-resourced settings in tropical and subtropical areas of the world [38]. Unfortunately, inequities in access to healthcare, including diagnostics, drugs, medical interventions, and vaccines, are often related to stigma, discrimination, geographic and socioeconomic barriers in marginalized populations [39,40]. Consequently, researchers aiming to address these diseases experience challenges associated with access and participation of affected groups, who thus continue to suffer from underrepresentation.

Effective chemotherapeutics are an essential component in the fight against infectious diseases. However, these drugs are often susceptible to loss of efficacy due to misuse in animal and human health, and due to environmental perturbations. In the presentation by Dr. Maria Adelaida Gómez (CIDEIM, Colombia), "Unexpected Consequences of Antimicrobial Usage, the Example of Antimony", AMR was once again highlighted as a global health problem, and one that is exacerbated due to limited access to drugs, diagnostics and education, especially in highly endemic LMIC countries. Lack of access to opportune diagnosis and treatment was also considered as a challenge for control of leishmaniasis globally. In addition, Dr. Gómez discussed the unanticipated impacts of water pollution (a reflection of limited access to resources and infrastructure) and cultural practices, that contribute to treatment failure with anti-leishmanial drugs. For example, the effects of arsenic contamination of water sources due to anthropogenic practices such as uncontrolled mining has been shown to contribute to selection of cross-resistance to antimony in *Leishmania* [41]. This can result in increased numbers of unresponsive cases and relapses due to persistent infections, as evidenced in cases of post kala-azar dermal leishmaniasis.

Dr. Fred Quinn (University of Georgia Veterinary School, USA) presented research on understanding TB transmission within and outside of human social networks. He showed how current epidemiological tools only permit the identification of approximately 20 % of transmission sources in human TB, which indicates that our understanding of the transmission of infection is, at best, partial [42]. Potential asymptomatic carriage and subclinical stages were also discussed and could include individuals (humans and animals) that carry the pathogen in the upper airways without the induction of immune responses, but still have potential to transmit to others. Whilst it is known that TB-causing organisms, including *M. tb,* can infect other domestic and wild animal species, the potential of these reservoirs is only uncovered following outbreaks of TB in humans in a retrospective manner, instigating reactive rather than preventive control strategies. The underappreciated relevance of asymptomatic infections in animals, despite the better characterized effect of subclinical, or latent infections in humans, illustrates potential gaps in infrastructure such as tools to differentiate persistent asymptomatic infections versus vaccination induced immunity, especially for animals of economic relevance. This can create reluctance among farmers to test or vaccinate their livestock, impacting control efforts. There is a clear need to improve our understanding of the dynamics of infection with *M. tb* and other TB-causing pathogens in asymptomatic humans, as well as in domestic and wildlife populations.

Further to barriers in accessing human health resources, investigations into access to medicines and technologies for animal health are lacking, yet critical for prevention and control of zoonotic infections. Dr. Ana Marcia Guimarães (Universidade de São Paulo, Brazil) discussed the challenges around the use of genomics for the control of bovine and human TB. The disparity in investment between animal and human TB genomics research, fueled by an underappreciated role of One Health in disease control, was highlighted. Public data repositories hold nearly 20 times the number of sequenced genomes of the human pathogen *M. tb* compared to the predominantly animal pathogen *M. bovis*. While the extensive sequencing of *M. tb* isolates is justified by the need to detect antibiotic resistance, the control of animal TB could greatly benefit from wider genome sequencing to detect pathogen transmission patterns, and better understand the *M. bovis* population structure. These benefits were illustrated using phylogenomics to study *M. bovis* lineages distributed globally [43–45] and to evaluate the transmission and introduction of animal TB in multi-host species settings [46].

To narrow the gap in investment and enhance animal TB genomics, Dr. Guimarães emphasized the importance of strengthening public health policies, improving laboratory infrastructure, and providing personnel training. Importantly, the significance of recognizing the impact of animal TB on the global burden of human disease and its effects on livelihoods, dependent on livestock and wildlife conservation, was highlighted. In addition to being strengthened worldwide, national programs of animal TB control need to incorporate specific guidelines for actively searching, diagnosing, and caring for individuals with zoonotic TB, as well as providing socioeconomic support for those affected by animal TB outbreaks.

Dr. Richard Burchmore (University of Glasgow, UK) shared his experience in the implementation of "-omics" approaches to identify prognostic markers and drug targets for human cutaneous and visceral leishmaniasis [47]. His presentation "How to Win at Hide and Seek - Using Omics Approaches to Find and Target Neglected Pathogens", exemplified the imbalance in the use of genomic, transcriptomic, proteomic, and metabolomic techniques for informing diagnostic and therapeutic interventions for human versus animal leishmaniasis.

Together, these talks reflected on critical differences in investment, prioritization, awareness, and knowledge of medicines and technologies to prevent, diagnose and treat human and animal infections. Speakers illustrated the disparity in access to resources to research TB and leishmaniasis in humans and animals and emphasized the benefit of taking a One Health approach to understanding the epidemiology and pathogenesis of these diseases.

5. Health system challenges in One Health

A major concern in public health is the potential for transmission of pathogens to humans from animals, such as domestic animals, including pets or livestock, or through contact or consumption of wildlife-derived products [48,49]. A first step in the prevention of infection is an understanding of the transmission dynamics of the pathogen in different groups of individuals (humans and animals), and the potential cross-interactions between members of those groups. To this end, appropriate infrastructure (for research and healthcare), as well as access to health systems, should be equally sought for animals as for humans. Despite this, unarticulated research priorities, policies, and an imbalanced distribution of resources limits the efficacy of interventions, sustains the cycles of transmission and perpetuates endemicity of disease (both for humans and animals).

Dr. Lin-Mari de Klerk-Lorist (South African Department of Agriculture, Land Reform and Rural Development, DALRRD) provided an overview of animal disease control programs and associated challenges in South Africa. The main function of DALRRD in South Africa is to manage the risks associated with animal health, which include zoonoses. Several acts and regulations have been formulated over the past 60 years to aid in this vision, but some barriers and constraints remain [50]. The impact of illegal activities (such as poaching), budget constraints, unavailability of accredited laboratories, and lack of diagnostic tests were highlighted as some of the challenges being faced by state veterinarians in South Africa [50]. However, the One Health concept is gaining momentum and therein lies hope for positive change.

Dr. Juan Dib (Fundación Salud Para el Trópico, Santa Marta, Colombia) presented on strategies for tackling infectious diseases in indigenous populations and the intercultural challenges of using a One Health approach. The importance of the societal and political aspects of implementation of One Health recommendations were highlighted, considering experience gained over 30 years of research and participation in healthcare assistance in indigenous communities of the Sierra Nevada de Santa Marta in Northern Colombia. These communities experience high endemicity of TB and leishmaniasis, as well as other NTD [51]. Research undertaken by Dr. Dib and his team included discussions and comparisons of the traditional occidental views of One Health systems, which are based predominantly on western scientific and medical methodologies, with the indigenous communities' views of One Health, according to their cosmovision and holistic understanding of life. Importantly, it is a commonly held view that indigenous communities are part of the natural environment, and that the health of that environment is central for the preservation of the health of the community, and the individual within the community.

A major aspect of Dr. Dib's experience was the observation that societal views of individuals in culturally distinct communities are not necessarily the same as those of western societies, but in indigenous communities a One Health angle has often been organically incorporated. It is important to bear in mind that indigenous communities have developed their own health research methodologies, which have allowed them to survive in their environment. It was proposed that One Health research (as defined by WHO) in indigenous communities should incorporate indigenous researchers employing indigenous methodologies. Ideally, such research should be led by community members, allowing the effective communication of outcomes to indigenous leaders and facilitating adaptation of research recommendations. In turn, this could translate into greater effectiveness and sustainability of such outcomes, not only for indigenous communities but more broadly across heterogenous populations.

Dr. Niaina Rakotosamimanana (Institut Pasteur, Madagascar) presented examples of the impact and solutions to inequitable healthcare infrastructure on TB in Madagascar. Access to healthcare resources in remote communities is a major source of inequality. Dr.

Rakotosamimanana shared his experiences on the implementation of measures to bridge this gap, describing the use of novel technologies for improving TB detection and obtaining epidemiological information from remote communities in Madagascar. Measures being evaluated included the use of educational videos, electronic medication reminders, remote monitoring and even drones for sample and treatment transportation [52].

The examples presented by Drs. Dib and Rakotosamimanana highlight contrasting views of the One Health approaches adopted by different indigenous communities around the world. On the one hand, some indigenous communities consider themselves autonomous and independent and would prefer to preserve their own healthcare strategies which have allowed them to thrive in their environment. Such communities may fear the introduction of practices different to those traditionally employed, and the possibility of raising individuals unable to withstand subsequent environmental challenges or unable to contribute to the maintenance and survival of the community. On the other hand, there are rural communities who are more willing to accept novel health strategies, including the use of technological developments such as drones and videos to ensure access to required resources intended to improve community health. These two contrasting approaches highlight the need for involvement of the communities in the implementation and maintenance of One Health approaches [53,54].

María Isabel Echavarría (Centro Internacional de Entrenamiento e Investigaciones Médicas, CIDEIM in Cali, Colombia) addressed the challenges associated with implementing interventions to manage infectious diseases of poverty. Despite the intense study and development of multiple health technologies and innovations in recent decades, putting these solutions into practice was one of the main bottlenecks in diminishing the impact of NTD. Implementation research (IR) and social innovation in health (SIH) play a fundamental role in the identification of the context in which measures will be implemented and the potential barriers that may arise. This requires the participation of multiple stakeholders that will contribute to the definition of the problem and the co-creation of solutions, as well as monitoring and evaluation of the implementation processes [55].

Implementation research has been defined as the systematic approach to understanding and addressing barriers to the effective implementation of health interventions, strategies, and policies in clinical and community settings [56]. In this context, effective implementation of health solutions requires the active participation of stakeholders, which include communities affected by health problems being addressed, policy makers, academic institutions, and industrial sectors. It is at this point that social innovation in health is expected to contribute, by empowering communities to have greater control over decisions that affect their own health.

The One Health approach recognizes interconnection between human, animal, and environmental health. To this end, IR in One Health should promote collaboration and coordination of efforts across multiple disciplines and sectors to address health challenges comprehensively. A new vision of interdisciplinarity and intersectionality should arise, involving, for example, interaction between human, animal and environmental health policy makers, funding bodies, and affected communities. However, for these solutions to be carried out in real contexts, they will also need effective and inclusive implementation processes. It is at this point that IR and SIH provide the theoretical and practical framework for implantation of those integrative health solutions.

Speakers in this section of the workshop highlighted the importance of affected communities and their environment, as the effectors and beneficiaries of any potential strategies that could contribute to solving health issues in a comprehensive manner. As with modern efforts to develop personalized medicine in a biological sense, it is important to consider that communities are different in a cultural sense, and that the environments from which they derive their livelihoods will dictate the formation and stratification of social interactions and interventions. Thus, the environment in which communities live and develop is an essential component to the successful delivery of strategies that will contribute to the implementation of health solutions for individual communities.

6. Conclusion

One Health, IR, and SIH are vital to addressing contemporary global health challenges. One Health reminds us of the interconnectedness of humans, animals, and the environment, while IR and SIH ensure that innovative and inclusive solutions are developed and documented, and that evidence-based practices are effectively put into practice. The first VALIDATE One Health Workshop brought together human and veterinary health experts in TB and leishmaniasis research to discuss experiences, challenges, and opportunities in implementing the One Health approach for management of these infectious diseases across the globe. Endorsing the guidance of “think globally, act locally”, representatives from a range of high-, low- and middle-income countries participated, allowing comparison of experiences from environmentally, geographically, and culturally diverse regions. Workshop themes were centered on dissecting the determinants of cross-species disease transmission, contrasting disease mitigation strategies and discussing the barriers to effective implementation of One Health actions across human and animal TB and leishmaniasis. This offered a unique opportunity to identify critical gaps and propose possible solutions and approaches to promote a One Health approach for two diseases that exemplify the complexities of vector borne and airborne infections (Table 1).

7. Future plans and actions

We intend these experiences and reflections to serve as a starting point for addressing common challenges posed by policy, cultural and industrial practices, civil unrest, incomplete understanding of disease eco-epidemiology, among other issues, which together halt advances in reducing the multi-species burden of these and other similar infectious diseases of global health importance. While compiling this report, an imbalance in the amount of content devoted to TB compared with leishmaniasis became evident. This is likely a reflection of imbalance in the relative magnitude of research (and funding) devoted to these diseases, further highlighting the need for investment in R&D to tackle leishmaniasis and other NTDs of global importance. In addition, the short duration of the workshop (3 days) did not permit in depth discussions of many topics relevant to these diseases, including immunological mechanisms, host genetics, or novel vaccine development. However, it is recommended that these are included in future workshops.

As demonstrable outcomes of the benefits of the VALIDATE Network, actions to date resulting from this workshop have included discussions of new collaborations between workshop members, such as a joint funding award, grant proposal, and a scientific manuscript, including:

- The workshop facilitated the development of a collaborative project between researchers in Colombia and Brazil entitled “Factors determining interruption of treatment and death in the homeless population with tuberculosis in the city of São Paulo”, that has since been funded by The Department of Science and Technology, of the Secretariat of Science, Technology, Innovation and Health Complex, of the Ministry of Health, Brazil. This project will study the determinants of treatment abandonment or loss to follow-up, as well as the high TB mortality rate in the homeless population.
- A collaborative grant application between researchers in Madagascar, South Africa, and Switzerland, is underway. This project entitled “Diagnosis and speciation of the *Mycobacterium tuberculosis* complex in animals and humans”, will focus on developing a high-throughput innovative DNA-based assay for detecting and genotyping animal MTBC, using multiple sample types to enhance

Table 1
Knowledge gaps identified and possible solutions to challenges in implementing a One Health approach to the control of tuberculosis and leishmaniasis discussed during the first VALIDATE One Health Workshop in 2023.

Knowledge gap identified	Possible solutions discussed
Imbalance in research on intracellular pathogens (TB, leishmaniasis)	• Improve funding/resources that can be used for neglected intracellular pathogens • Increase collaboration and transdisciplinary research/knowledge to exploit similarities in diseases and pathogens.
Cross-species disease transmission	
Unknown epidemiology deriving primarily from gaps in animal testing and reactive/ passive diagnosis	• Deploy molecular typing techniques to monitor potential spread of infections. Typing technology could involve whole genome sequencing (WGS), spoligotyping and/or specific PCR products • Ensure active surveillance for rapid identification of foci re-emergence of infection in areas with low incidence • Incorporate animal and human surveillance for specific zoonotic diseases
Poor knowledge of host genetic basis of resistance	• Expand research on genetic/epigenetic differences between resistant and susceptible hosts • Identify genomic basis for resistance within and across species (e.g., resistance to bovine TB in different cattle breeds)
Intersectoral differences in the foreseen need for development and use of vaccines in wildlife and domestic animal populations	• Promote intersectoral discussion on the feasibility and usefulness of vaccine deployment • Strengthen research on correlates of vaccine protection in animals, and establish their difference from markers of infection/disease • Harness knowledge and tools developed for human and livestock TB for wildlife TB • Generate knowledge and incorporate species differences in immune responses into vaccine development
Disease mitigation strategies	
Absence of multiplex diagnostic tools in veterinary health	• Establish sample biobanks to allow retrospective analysis of novel diagnostic tools as they are developed in different species. Besides the inherent benefit in widening deployment of novel diagnostic tools for different species, the storage of historical samples will allow for greater collaboration between researchers working across different species, including humans
Potential consequences of interventions on the target host species, surrounding habitat and other surrounding species	• Continue monitoring of the environment, and animal and human populations within habitats in which interventions have been deployed. Monitoring should include the appearance of novel, potentially invasive, host species or the decline of endemic species as a result of improved survival of target host species for intervention
Lack of specific markers for infection vs. disease, potentially including the "carrier", subclinical or latent states	• Develop tools that would allow differentiation between carrier and infected/diseased state, such as those that allow detection of the pathogen compared to the induction of immune responses against specific antigens
Development of markers that allow distinction of vaccinated from infected hosts and correlates of protection	• Support of comparative research that would investigate markers of protection, infection, and disease across animal and human hosts • Promote in-depth exploration of immunological aspects of diseases associated with intracellular pathogens, including understanding function of immune cell populations across species; this includes ensuring availability and sharing of immunological tools such as monoclonal antibodies for non-model species • Improve understanding of protective immunity across species • Develop novel vaccines that allow vaccinated individuals to be distinguished from infected individuals • Develop diagnostic tools that allow accurate identification of infected animals; ideally, tests that allow detection of the pathogen itself • Alternatively, immune response-based tests that differentiate vaccinated versus infected individuals (DIVA) • Expand use of "omics" for novel vaccine development strategies
Inequitable access to medicines and health technologies	
Lack of systematic diagnosis and management of co-infections (symptomatic and asymptomatic) in both humans and animals	• Increase research into the influence of co-infections in humans and animals on disease susceptibility and progression • Develop tools that allow distinction of disease-causing pathogens such as *M. tb* and *M. bovis* as treatment may be affected by the species • Evaluate the effects of persistent subclinical co-infections and the effects of antimicrobial usage (and misuse) on the emergence of drug resistance and cross-resistance
Health system challenges in One Health	
Limited implementation research for animal and human vaccines and related research (particularly applying lessons learned in humans to animal health)	• Increase funding for IR in human and animal health • Develop a pool of facilitators to enable the flow of research information from human to animal, and from animal to human versus animal research • Real life implementation of outcomes should be considered early in the research process of basic and applied sciences • Provide evidence to policy makers on potential solutions to actual and perceived problems
Minimal social science and social innovation in veterinary research	• Research on efficacy of communication and interaction between stakeholders in human and animal care, and effects on patient outcomes • Identify societal issues preventing the deployment of tools that would contribute to the control of infectious disease • Circumvent negative perceptions of tools that would contribute to the deployment of measures for the control of infectious diseases in different settings • Develop tools that allow accurate evaluation of the cost/benefit analysis of the implementation of tools that allow the control of infectious diseases

(*continued on next page*)

Table 1 (*continued*)

Knowledge gap identified	Possible solutions discussed
Limited cross-communication between human and animal researchers	• Stimulate the formation of multidisciplinary teams for research on infectious diseases and the development of control measures for such diseases • Promote transitioning from the anthroponotic and zoonotic view of animal and human health to an integrated One Health view • Facilitate interaction between human and animal researchers in the study of infectious diseases • Expand research on climate change from transmission patterns to biological effects on hosts and pathogens • Improve connections between researchers in different disciplines including climate, environmental, social, and animal and human health scientists
Government and funder engagement in One Health challenges; public buy-in for One Health	• Publicize and acknowledge successful deployment of tools for the prevention of infectious diseases • Promote environments that allow researchers to engage with funders and government/policy makers to incorporate animal health research • Engage and invite government, funders and communities to One Health discussions • Improve public engagement and education in One Health to promote the message that healthy animals are the product of a healthy society • Develop tools to inform the public on the impact of zoonoses on economic and societal living conditions • Develop tools that allow social acceptance and promotion of the benefits of One Health research • Promote dialogue between organizations responsible for the delivery of human and animal health through cooperation on zoonoses surveillance and management policies • Continue education and identification of benefits of One Health approach for governmental agencies and policy-makers responsible for animal and human health
Training the next generation of researchers for One Health	• Promote North-South and South-South One Health training through the VALIDATE Network, including laboratory collaborations and exchanges • Senior scientists should involve early career researchers when interacting with funders and policy makers for exposure and networking
Ethical considerations of implementing "Western" views on indigenous communities	• Involve indigenous communities in the development of research programs and implementation of research outcomes

real-time diagnosis at a global scale. This will facilitate surveillance for MTBC in humans, animals and the environment and provide insights into interface transmission.

- The One Health Workshop provided an important opportunity to network with scientists of differing expertise. A partnership between researchers in Brazil and South Africa has provided important training for an African post-doctoral fellow in *M. bovis* bioinformatic analyses. This has resulted in a manuscript analyzing *M. bovis* whole genome sequences from South African wildlife.

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Declaration of competing interest

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Data availability

No data was used for the research described in the article.

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