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Editorial

World Tuberculosis Day March 24th 2019 Theme: “It’s TIME” – International Journal of Infectious Diseases Tuberculosis Theme Series



Tuberculosis today remains the world's number one cause of death from an infectious disease (WHO, 2018a). According to data from the World Health Organization Global Tuberculosis Report (WHO, 2018a), global efforts to control tuberculosis are not on target to achieve the goals of the WHO Strategy to end the global tuberculosis epidemic by 2030 (WHO, 2015). In 2017, an estimated 10 million people (5.8 million men, 3.2 million women, and 1 million children) developed tuberculosis and 4 million people with tuberculosis remained undiagnosed and untreated. There were 558,000 new cases of drug-resistant TB, 82% of which were multi-drug resistant tuberculosis (MDR-TB-resistance to isoniazid and rifampicin), and 8.5% has extensively drug resistant TB (XDR-TB -MDR-TB plus resistance to both a fluoroquinolone and an injectable) (WHO, 2018a).

Each year, World TB Day is commemorated on March 24, the day in 1882 when Professor Robert Koch first announced his discovery of *Mycobacterium tuberculosis*, the causative agent of tuberculosis (TB). It's a day when the world reflects on progress being made in achieving global TB control, the obstacles and what more can be done to facilitate global TB control activities. The theme for World TB Day on 24 March 2019 will be 'It's TIME' (STOP TB Partnership, 2019), and it has been kept simple and flexible, so World TB Day events can cover any aspect of work related to TB.

To commemorate World TB Day 2019, the International Journal of Infectious Diseases thematic issue contains 15 articles written by a distinguished global authorship covering a range of important epidemiological, clinical, management, prevention, research and funding issues. The articles provide a range of thought-provoking viewpoints on established dogma, current controversies, highlighting gaps and future challenges that need to be overcome to develop and achieve optimal interventions required for global TB control. These articles also illustrate vividly that 'It's Time' for governments and donors to keep the promises made in the political declaration at the UNGA-HLM-TB and to increase the much-needed resources to find, diagnose and treat 40 million adults and children who will be affected by TB by 2022, and to conduct research on new diagnostics, treatments and vaccines required to achieve global TB control (Tiberi S et al. 2018; Zumla & Petersen, 2018).

Pathogen *M. tuberculosis* versus host battleground

An estimated 1.7 billion people worldwide have latent *M. tuberculosis* infection (LTBI) (Houben and Dodd, 2016). Of these, up

to 10% are at risk of re-activating into active TB during their lifetime. Latent *M. tuberculosis* infection is defined by the World Health Organization (WHO) as 'a state of persistent immune response to *M. tuberculosis* antigens with no evidence of clinically active TB disease' (WHO, 2018b). The underlying host innate and acquired immune mechanisms underlying the state of LTBI remain undefined. Progress in understanding these through recent developments in understanding the granuloma as the host-pathogen battleground is reviewed by Rao et al. (2019a).

Tuberculin skin test and screening for LTBI

All countries signed up to the priority commitment in the political declaration arising from the historic United Nations High Level Meeting on TB held on September 28th 2018 (WHO, 2018c) for providing preventive treatment to 30 million individuals with LTBI by 2022. Screening for LTBI is also key to TB control and achieving the EndTB Strategy goals (WHO, 2015). The available LTBI screening tests include the interferon release assays (IGRAs) and the tuberculin skin test (TST), all of which are not accurate and cannot distinguish LTBI from active TB disease. Gualano et al. (2019) argue that TST is still a useful tool because it is well known, widely used and cheap. Clinical use of the TST as opposed to IGRAs should be prioritized according to availability of reagents, resources, national recommendations and specific clinical scenario. Clinical judgement remains fundamental in selecting the LTBI tests and interpreting the results of IGRA/TST tests. The ultimate test awaited is one that can more specifically distinguish active TB from LTBI. The use of IGRAs has increased in low TB endemic areas but TST will continue to be clinically useful in low and high TB endemic areas, until more predictive tests become available to allow for identification of individuals at the highest risk of progressing to developing active TB diseases.

LTBI and drug-resistant TB exposure

The treatment of suspected latent multidrug resistant TB (MDR-TB) is discussed by Moore et al. where they highlight important issues and unknowns about the management of individuals who have been exposed to infectious MDR-TB within the household. They vividly illustrate the complexities of management with patient case histories and the shortcomings of current recommendations by international agencies, due to a lack of an evidence base. Current guidelines from the

WHO and ECDC recommend close follow up of contacts to MDR-TB cases for 2 years but stop short of recommending treatment for all. The viewpoint suggests that until the three ongoing randomised controlled trials of preventive therapy (V-QUIN trial, TB CHAMP and PHOENIX trial) are completed, there will remain large knowledge gaps about how individuals known to have been exposed to patients with MDR-TB should be managed. In the interim, there exists an important opportunity to systematically gather large-scale observational data on exposed contacts under surveillance.

E-DETECT TB—a new surveillance database

Surveillance of populations at risk is a key to identify latent TB before it become active TB and the migration from high prevalence countries to low prevalence countries is an opportunity to identify people with latent TB as described in the paper by [Ohd et al. \(2019\)](#). Overcoming considerable administrative, practical and legal challenges, they describe development of a newly developed European database E-DETECT TB on latent and active TB in migrants arriving in Europe. E-DETECT TB has started inviting other EU member countries to contribute data to the database. E-DETECT TB aims to address the present lack of evidence concerning coverage, impact and cost-effectiveness in migrant TB screening. Through collaborative efforts, country-level screening is collated by using agreed key variables in a joint database.

LTBI and risk of tuberculosis in transplant recipients

Tuberculosis is an important infectious disease cause of morbidity and death in transplant recipients worldwide and this is often a neglected clinical issue. Tuberculosis can also cause loss of kidney allograft. [Krishnamoorthy et al. \(2019\)](#) highlight the issues related to prevention, diagnosis and treatment of tuberculosis in renal transplant recipients. Most of the TB cases in renal transplant recipients are due to re-activation of LTBI in the recipient or from the donor kidney. TB can also occur due to increased susceptibility to acquiring new *M. tuberculosis* infection which rapidly progresses to miliary TB because of immunosuppressive therapy. They emphasise that all donors and recipients are routinely screened for LTBI and active TB disease prior to transplant ([Krishnamoorthy et al., 2019](#)), maintaining a high degree of clinical awareness of the possibility of TB.

Non-communicable diseases and LTBI

The association between chronic non-communicable diseases diabetes mellitus type 2, chronic kidney disease and rheumatoid arthritis and LTBI has been a subject of much discussion and debate. Any medical condition which impairs the immune system will lead to an increase risk of LTBI developing into active TB. [Ugarte-Gil et al. \(2019\)](#) review the increasing evidence that people with non-communicable diseases constitute a high-risk group for both acquiring LTBI and developing active TB. They remind us that with the global pandemic of type 2 diabetes, diabetes has become an important risk factor for developing active TB disease. Although the potential pathophysiological and immunological pathways between several noncommunicable diseases and LTBI and/or active TB disease are better known, further studies evaluating better screening tools for LTBI, safe prophylaxis, and treatments for TB in this specific population are much needed ([Ugarte-Gil et al., 2019](#)).

Treatment landscape for MDR/XDR-TB

The relentless spread of MDR-TB and the high mortality rates are fuelled by intermittent access to drugs, significant drug

adverse effects and poor adherence to medication. Only about 55% of MDR-TB cases who receive treatment are successfully treated. The most important issues in TB treatment are related to what are the optimal regimens for MDR/XDR-TB, drug toxicity, availability of drugs and patient adherence and follow-up. [Honeyborne et al. \(2019\)](#) review the current the changing treatment landscape for MDR/XDR-TB and discuss whether results from current ongoing clinical trials will revolutionise and inform a brave new world of MDR-XDR-TB treatment? Newly-approved TB drugs such as bedaquiline and delamanid provide new treatment options for MDR/XDR-TB and several ongoing trials are described, which if successful, will reduce treatment for MDR/XDR-TB to 6–9 months.

Regulating and defining antibiotic resistance breakpoints

Using the famous saying of the philosopher George Santayana, ‘Those who cannot remember the past are condemned to repeat it’ [Köser et al. \(2019\)](#) remind us that despite the consensus that antibiotic resistance represents a key driver for poor treatment outcomes, the standards to define resistance that apply to all other major bacterial pathogens have not been followed for traditional anti-TB drugs. The classification of *M. tuberculosis* as susceptible or resistant to a drug depend on reliable laboratory support for the clinician, no matter whether molecular or culture methods are used. They highlight that six years after the approval of bedaquiline and delamanid, neither Janssen or Otsuka have generated the necessary data to define robust breakpoints to these agents. They call upon EMA and FDA to ensure that history does not repeat itself when they approve novel anti-TB agents. They also suggest that since WHO effectively controls the market size for novel drugs, it should adopt a more muscular approach to ensure that pure, quality-controlled compounds are available immediately to all laboratories wishing to implement phenotypic DST.

Gatekeeper Consilia for new TB drugs

MDR-TB is a growing challenge worldwide and 2 million cases of MDR-TB are anticipated within the next two decades. One of the potential causes of MDR-TB is iatrogenic and we risk losing our new drugs through inexperience and repetition of basic errors of adding single active drugs to failing regimens. [Tiberi et al. \(2019\)](#) justify the formation of TB Consilia act as gatekeepers to the new drugs, monitor guideline adherence and mandate active drug safety monitoring. TB consilia are now recommended by funding bodies, the WHO and manufacturers of drugs available for compassionate use in the hope that these drugs will be protected and will continue to be useful in the future. They discuss Consilia, their origin and evolution and give some examples of how they operate. The Consilia concept may ensure that the advice of experts in TB management is available to health care staff throughout a country and is seen as an important guarantee that new TB drugs are used appropriately thus increasing the argument that they should be made available for compassionate use ([Tiberi et al., 2019](#)).

Clustering and spatial distribution of smear positive pulmonary tuberculosis cases in China

The annual incidence of notified smear positive pulmonary TB cases in China is 30 per 100 000 population. [Mao et al. \(2019\)](#) investigated the spatio-temporal variations of 4,711,571 smear positive pulmonary TB cases. The clustering and spatial distribution is discussed the gradual decrease in the number reported smear-positive PTB case was because of intensive measures on TB including implemented DOTS and national TB prevention and control plans, improved case notifications, increased TB budget

and financial aid, improved public health system and strengthened government dominance (Mao et al., 2019). The most likely spatio-temporal cluster was detected in four periods and located areas in the central region, covering the Hubei, Hunan, Jiangxi, Anhui, as well as Guizhou and Guangdong. They conclude that their results indicated that the capability and utility of the spatio-temporal approach in epidemiology characteristics and suggested that the high-risk periods and areas should be paid more attention for monitoring and early warning.

Reducing mortality in Brazilian TB patients

A study from the State of Paraná, Brazil, from 2008 to 2015 of 944 deaths of adult TB patients showed that three quarters of deaths occurred within 60 days of diagnosis. The authors highlight that the prime problem is late diagnosis and adherence to treatment. Adequate monitoring of comorbidities and multisectoral support may prevent early and late death (Oliveira et al., 2019). They suggest that communication between health services at the different levels such as primary, secondary, laboratory and hospital is fundamental to promote integrated care. The presence of comorbidities and individual behaviours that cause vulnerabilities associated with early death reinforces the need for more frequent contact between patients and health professionals, individualised therapeutic regimens and multisectoral support to ensure better adherence to treatment and thus prevent death caused by TB.

Holistic family-centred multisectoral care for children with TB

TB affects children's health and development in multiple ways, directly through disease and its sequelae and indirectly through the health and survival of their primary care givers according to Detjen et al. (2019). Responses to reduce TB-related disease and death in children therefore need to be family-centered and multi-sectoral, addressing TB within the context of the broader determinants of health. They state that Primary health care (PHC) as envisaged by the Alma Ata and Astana declarations calls for health services to be improved through the lens of equity and community vulnerability, highlighting that implementing integrated packages of interventions specifically at the community and primary health facility level will avert 77% of preventable maternal, newborn and child deaths. Renewed focus on holistic PHC will enhance countries' efforts to reach maternal, newborn and child health targets contained in the Sustainable Development Goals (SDGs).

Prevention, BCG efficacy and new boosters

Whilst there is consensus that BCG vaccination of infants provides protection against disseminated TB disease, TB meningitis and death, the efficacy of BCG in preventing adult pulmonary TB is not as widely accepted by the global TB community. de Gijzel and von Reyn. (2019) review the protective efficacy of BCG vaccination against pulmonary TB in adults. They summarize an increasing body of good quality evidence to conclude that BCG provides up to 80% efficacy against pulmonary TB for 10 years and 50% efficacy for 50 years. Their conclusion is based on both prospective trials that now include recently updated follow-up data, as well as new retrospective reviews from Norway and the UK. These studies refute the myth that BCG is not effective against pulmonary TB. They suggest that development of new priming vaccines to replace BCG and new boosters to extend efficacy should be based on this current body of data.

Better use of combination of existing tools

The search for new tools to end the TB epidemic has also focussed attention on the use of existing tools and ensuring

maximal benefit. Gosce et al. (2019) in their viewpoint discuss the hypothesis of BCG vaccination following latent TB treatment and its potential impact across different settings. They point out several studies which have shown the importance of implementing different preventive strategies alongside treatment of TB disease, including BCG vaccination and treatment of LTBI. Large-scale population level LTBI treatment is not currently part of WHO guidelines which recommend LTBI treatment only to high-risk populations. Moreover, BCG is known to be highly efficacious if given to individuals who are not already infected with *M. tuberculosis*. Thus, a combined LTBI treatment followed by BCG vaccination could be tried in trials in countries with a high prevalence of drug-resistant TB (Gosce et al., 2019).

Future therapies—precision medicine and MDR-TB

Multidrug-resistant TB (MDR-TB) is a major threat to global health. In 2017, only 55% of patients with MDR-TB who received WHO recommended treatment were cured (WHO, 2018a). Many patients with MDR-TB patients who recover after receiving WHO-approved MDR-TB treatment regimens continue to suffer from functional disability due to lung damage. Thus, conventional TB drug therapy needs to be complemented with host-directed therapies (HDTs) to reduce tissue damage and improve functional treatment outcomes. Rao et al. (2019b) viewpoint focusses on the expanding pipeline of new and repurposed drugs and cell-based therapies which have potential for use as host-directed therapies for adjunct treatment of MDR-TB. They also review recent data on biomarkers, immune cells, circulating effector molecules and genetics which could be utilised for developing personalised HDTs in light of experiences in cancer therapy. New concepts are always difficult for funding agencies and reviewers to understand and take forward but with time these will see the light of day and make an important contribution to 'holistic' management of MDR/XDR-TB.

Conclusions

Fulfilling the WHO EndTB strategy goals and achieving global TB control remains a daunting and seemingly unachievable task at the current slow pace of progress. The papers in this World TB Day 2019 theme series present examples of the numerous challenges that face global control efforts, as well as potential solutions. The historic UN-General Assembly High-Level Meeting on TB held in New York in September 2018 (Petersen et al., 2017) focused global attention on the world's deadliest infectious disease and generated high expectations of a major 'step-up' in political will to bring the devastating global TB epidemic under control. World TB Day 2019 events worldwide should ensure that political and donor commitments made at the UNGA-HLM-TB are delivered in a timely fashion, including increased funding for research and innovation for new and improved diagnostic, treatment and prevention tools. Meanwhile tuberculosis health services globally should receive adequate funding to reach out to all communities and high-risk groups, proactively diagnose, and treat all adults and children with tuberculosis in all of its clinical forms, and make bedaquiline and delamanid available universally for effective treatment of MDR-TB.

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Eskild Petersen^{a,b,c,*}

^aInstitute of Clinical Medicine, University of Aarhus, Denmark

^bThe Royal Hospital, Muscat, Oman

^cESCMID Emerging Infections Task Force, Basel, Switzerland

Martin Rao
Champalimaud Centre for the Unknown, Lisbon, Portugal

Giuseppe Ippolito
Gina Gualano

National Institute for Infectious Diseases Lazzaro Spallanzani-IRCCS,
Rome, Italy

Jeremiah Chakaya^{a,b}

^aInternational Union Against TB and Lung Diseases, Paris, France

^bDepartment of Medicine, Kenyatta University, Nairobi, Kenya

Francine Ntoumi
Fondation Congolaise pour la Recherche Médicale (FCRM), Brazzaville, Congo

David Moore
TB Centre, London School of Hygiene and Tropical Medicine, London, UK

Rhiannon Allen
Public Health England National Mycobacteriology Laboratory North and Central, Heartlands Hospital, Birmingham, United Kingdom

Katherine Gaskell
TB Centre, London School of Hygiene and Tropical Medicine, London, UK

Joanna Nederby Öhd^{a,b}

Maria-Pia Hergens^{a,b}

^aDepartment of Public Health Science, Karolinska Institutet, 171 77 Stockholm, Sweden

^bDepartment of Communicable Disease Control and Prevention, Stockholm County Council, Stockholm, Sweden

Sriram Krishnamoorthy
Department of Urology & Renal transplantation, Sri Ramachandra Medical College & Research Institute, Chennai, Tamil Nadu, India

Cesar Ugarte-Gil^{a,b}

^aInstituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima 15102 Lima, Peru

^bTB Centre and Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK

Daniela E. Kirwan
Infection & Immunity Research Institute, St. George's, University of London, UK

Isobella Honeyborne
Timothy D. McHugh
Division of Infection and Immunity, Center for Clinical Microbiology, University College London, London, UK

Claudio U. Köser
Department of Genetics, University of Cambridge, Cambridge, UK

Katharina Kranzer
Clinical Research Department, London School of Hygiene and Tropical Medicine & Biomedical Research and Training Institute, Harare, Zimbabwe

Simon Tiberi^{a,b}
^aDivision of Infection, Royal London Hospital, Barts Health NHS Trust, London, UK

^bBlizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK

Giovanni Battista Migliori
Istituti Clinici Scientifici Maugeri IRCCS, Tradate, Italy

Qiang Mao
Department of Infection Management, Gansu Provincial People's Hospital, China

Yahong Yang
Department of Medical Records Statistics, The First People's Hospital of Jingmen, China

Simoni P. Oliveira
Health Secretariat of Paraná State, Postgraduate Program in Health
Sciences, Maringá State University, Paraná, Brazil

Rosilene F. Cardoso
Maringá State University, Paraná, Brazil

Anne Detjen
United Nations Children's Fund (UNICEF), New York, USA

Ben Marais
Centre for Research Excellence in Tuberculosis and the Marie Bashir
Institute for Infectious Diseases and Biosecurity, University of Sydney,
Sydney, Australia

David de Gijssel^{a,b}
C. Fordham von Reyn^{a,b}
^aInfectious Disease and International Health, Dartmouth-Hitchcock
Medical Center, Lebanon, NH, USA

^bGeisel School of Medicine at Dartmouth, Hanover, NH, USA

Lara Goscé
Institute for Global Health, University College London, London, UK

Ibrahim Abubakar
Institute for Global Health, University College London, London, UK

Markus Maeurer^{a,b}
^aChampalimaud Centre for the Unknown, Lisbon, Portugal

^bDepartment of Haematology and Oncology, Krankenhaus Nordwest,
Frankfurt, Germany

Alimuddin Zumla^{a,b}
^aDivision of Infection and Immunity, Center for Clinical Microbiology,
University College London, UK

^bThe National Institute of Health Research Biomedical Research
Centre at UCL Hospitals, London, UK

* Corresponding author at: Institute of Clinical Medicine, Uni-
versity of Aarhus, Denmark.

E-mail addresses: eskild.petersen@gmail.com (E. Petersen),
martin.rao@research.fchampalimaud.org (M. Rao),
giuseppe.ippolito@inmi.it (G. Ippolito),
gina.gualano@inmi.it (G. Gualano),
chakaya.jm@gmail.com (J. Chakaya),
ffntoumi@hotmail.com (F. Ntoumi),
david.moore@lshtm.ac.uk (D. Moore),
kate.gaskell@lshtm.ac.uk (K. Gaskell),
joanna.nederby-ohd@sll.se (J. Öhd),
maria-pia.hergens@sll.se (M. Hergens),
sriramuro@gmail.com (S. Krishnamoorthy),
cesar.ugarte@upch.pe (C. Ugarte-Gil),
dkirwan@sgul.ac.uk (D. Kirwan),
i.honeyborne@ucl.ac.uk (I. Honeyborne),
t.mchugh@ucl.ac.uk (T. McHugh),
katharina.kranzer@lshtm.ac.uk (K. Kranzer),
simon.tiberi@bartshealth.nhs.uk (S. Tiberi),
giovannibattista.migliori@icsmaugeri.it (G. Migliori),
yangyhgssrmyy@163.com (Q. Mao),
yangyhgssrmyy@163.com (Y. Yang),
simonipimenta@gmail.com (S. Oliveira),
rfressatticardoso@gmail.com (R. Cardoso),
adetjen@unicef.org (A. Detjen),
ben.marais@health.nsw.gov.au (B. Marais),
david.degijssel@dartmouth.edu (D. de Gijssel),
c.fordham.von.reyn@dartmouth.edu (C. von Reyn),
l.gosce@ucl.ac.uk (L. Goscé),
i.abubakar@ucl.ac.uk (I. Abubakar),
markus.maeurer@fundacaochampalimaud.pt (M. Maeurer),
a.zumla@ucl.ac.uk (A. Zumla).

Corresponding Editor: Eskild Petersen, Aarhus, Denmark