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World TB Day 2017: Advances, Challenges and Opportunities in the "End-TB" Era

1. Introduction

To commemorate World TB Day March 24th, 2017 The International Journal of Infectious Diseases highlights the Advances, Challenges and Opportunities in the "End-TB" Era through publishing 42 articles by a distinguished global authorship. The series of articles review progress being made in achieving TB control, reviews innovations in drugs, diagnostics, vaccines and operational issues, and highlight remaining gaps and future challenges that need to be overcome to achieve the 'End TB' targets. There is little doubt from current WHO morbidity and mortality statistics,[1] that TB is the most common infectious cause of death worldwide; far surpassing both HIV and malaria.[2] The huge investments into HIV/AIDS and malaria have successfully reduced morbidity and mortality rates from these infections.

2. Why is TB different from HIV and Malaria?

TB has specific features that complicate control efforts, requiring unique and innovative approaches. These include the poorly understood complex biology and pathogenesis of *Mycobacterium tuberculosis* infection, potential long latency periods, unrecognized primary and re-infections, relatively asymptomatic disease onset leading to transmission months before most patients present for clinical care, a huge unrecognized reservoir of latent TB infections compounded by a limited repertoire of cheap and safe TB drugs, lengthy treatment with multiple drugs leading to poor adherence. The growing and widespread problem of drug resistance and major shortfalls in the available resources are other important factors that distinguish TB from malaria and HIV.

3. Resources for TB control

The WHO's "End TB" strategy aims to reduce TB deaths by 95%, reduce new cases by 90% between 2015 and 2035, and ensure that no family is burdened with catastrophic expenses due to TB.[3] However, this seems unrealistic to achieve in a situation where over half a million cases of MDR TB occur every year, only 20% are able to access appropriate care and treatment outcomes remain sub-optimal.[1,4] The mathematical model described by McBryde et al. (2017),[5] shows that MDR TB may sustain epidemic spread,[6] even in the presence of some fitness cost, and over time potentially replace drug susceptible strains in the absence of effective MDR TB control programs.[5,6]

Better utilization of resources, new diagnostics and affordable drugs all need research to provide an informed platform for rational use of available resources. However, research on TB is underfunded; over 60 percent of available money for TB R&D comes from public sources, and 65% of public money comes from a single country, the United States.[7] This is further emphasized by a study from Cambodia showing that TB receives less funding there compared to HIV and malaria, despite having a far bigger population health impact.[8]

A critical review of the WHO's "End-TB" strategy concludes that "if the End TB Strategy is to be successful in achieving TB elimination,[9] a more concerted action by funders and governments will be required for further investments into TB prevention, detection and treatment".[9] The proportion of HIV-infected patients with TB influences the predictions and demonstrates the need for close collaboration between TB and HIV programs.[10] A limited resource is negative-pressure isolation rooms. Present guidelines are equivocal regarding when to de-isolate TB patients leading to some patients being unnecessarily isolated for months, which is associated with patient harm and occupies a scarce and expensive resource.[11]

4. Tackling TB Co-morbidities with infectious and non-communicable diseases

Co-infection with HIV greatly increases mortality and risk of treatment failure,[12] and diabetes mellitus also increases morbidity and mortality of TB.[13] These important co-morbidities clearly demonstrate that TB management needs an integrated approach and that every TB patient should be investigated for HIV and diabetes, and every patient with HIV and diabetes should be screened for active TB diseases and LTBI.

Following a cohort of 1696 TB patients in Tanzania, Nagu and colleagues found that ART-näive TB/HIV patients had a seven-fold mortality risk (RR = 7.42; 95% CI: 3.87, 14.22; $p < 0.0001$), whereas TB/HIV patients on ART had a five-fold mortality risk (RR = 4.78; 95% CI: 2.41, 9.49; $p < 0.0001$).[12] The median time to death was shortest among ART-näive TB/HIV patients (thirty-six days). A thirty-day increase on ART duration associated with a 3% mortality reduction (RR = 0.97; 95% CI: 0.95, 0.99; $p < 0.02$), independent of CD4+ T lymphocyte count and ART regimen.[12]

Diabetes mellitus, DM, increases the risk of developing TB by two to three fold and increases the risk of TB treatment failure, relapse and death.[13] Hypertension is an increasing problem

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worldwide but this review of the literature found no evidence in previously published studies of an association between TB and hypertension.[14]

A study from The Republic of Congo,[15] highlights the importance of coordinating diagnostics and treatment of HIV and TB/HIV and describes how TB control programs there operate as distinct entities with separate case management plans and protocols. For instance, HIV testing is not systematically performed among TB patients and the actual prevalence of TB/HIV co-infection remains unknown.

Latent TB infection remains a difficult clinical and public health issue and the risk factors for progressing from latent TB to symptomatic disease are not fully understood except when the patient is obviously immunocompromised by HIV-infection, by immunosuppressive drugs including anti-TNF therapy, or by regimens required post-transplant. Also strategies for treating latent MDR TB are urgently needed.[16]

5. Public Health, Social and Operational Issues

An important challenge is how to reach marginalized groups with increased risk of TB like residents of refugee camps and migrants especially in low incidence countries, where infection control is very difficult.[17] Co-morbidities like HIV, diabetes mellitus, viral hepatitis and alcohol, drug and cigarette use, psychological care are important components for optimal patient management to ensure compliance.[17]

Informed approaches to surveillance and control require reliable, quality controlled diagnostics especially on drug susceptibility. The report by Alabi et al. describes the establishment of a TB reference laboratory in Gabon offering diagnostics, culture, susceptibility testing and molecular diagnostics.[18]

The challenge of MDR TB is highlighted by Migliori et al., reviewing the situation among migrants entering Europe.[19] Over a quarter of TB cases in the European Union and European Economic Area (EU/EEA) are reported among foreign-born individuals and about 25% of the global multidrug-resistant TB (MDR-TB) cases are reported in the European Region, particularly from the former Soviet Union countries.[19] One aspect of this is the importance of the stigma from receiving a diagnosis of TB, which must be addressed to encourage contact with the health care service.[20]

The Ebola virus disease, EVD, epidemic had profound impact on the health care systems of the affected countries in West Africa.[21] The study reviewed the impact on BCG immunizations, TB diagnosis and management in the affected countries.[21] The EVD epidemic no doubt increased TB morbidity and mortality, and the likely impact will not be known for several years to come. Under-five vaccinations for TB with BCG, were affected adversely by the EVD epidemic. The EVD outbreak was a result of global failure and represents yet another 'wake-up call' to the international community and particularly to African governments.[21]

Development of qualified, knowledgeable health care staff is important to assure quality and rational utilization of resources, but few studies have addressed the impact of training in TB management on the behavior of health care staff.[22] Another review addresses the quality of care that is routinely provided in both public and private sectors. Quality TB care is patient-centric care that is consistent with international standards, delivered in an accessible, timely, safe, effective, efficient and equitable manner.[23]

It is well known that prisons are hot-spots for TB transmission. A study from India shows that the OR of being diagnosed with TB was 6 in district prisons compared to central facilities; the OR was 5.2 in facilities with more than 500 inmates compared to facilities with fewer than 500 inmates, and diagnostic facilities reduced the risk of TB with an OR of 0.5 compared to facilities without.[24] Lack of TB screening at admission to the prison increased the OR of diagnosing TB to 2.7.[24]

Children are an important target group to reduce under-5 mortality and morbidity, as well as the pool of latent infection, in TB endemic areas.[25] Barriers to the provision of preventive therapy in resource-limited settings include: 1) the perceived inability to rule out active disease, 2) fear of creating drug resistance, 3) non-implementation of existing guidelines in the absence of adequate monitoring and 4) poor adherence with long preventive therapy courses. Barriers to TB treatment include: 1) perceived diagnostic difficulties, 2) non-availability of chest radiography, 3) young children presenting to unprepared maternal and child health (MCH) services and 4) the absence of child friendly drug formulations.[26]

6. Molecular studies

A review by Yeboah-Manu and colleagues highlights that *Mycobacterium africanum* is found primarily in West Africa and seems to progress less frequently to clinical disease and may even show lower transmissibility.[27] This presents an opportunity to improve current understanding of host-pathogen interactions, and for the development and evaluation of diagnostics, host-directed therapies, and vaccines for tuberculosis . *M. africanum* may also have important differences in transmission, pathogenesis, and host-pathogen interactions, which could affect the evaluation of TB intervention tools (diagnostics and vaccines).[27]

The unequal geographical distribution and spread of *Mycobacterium tuberculosis* complex (MTBC) species means that individual research findings from one country or region cannot be generalized across the continent. Thus, generalizing data from previous and ongoing research studies on MTBC may be inaccurate and inappropriate. A major rethink is required regarding the design and structure of future clinical trials of new interventions.

The potential challenges for using whole genome sequencing, WGS, for studies of MDR and XDR are discussed by McNerney R (2017),[28] and studies of standardized protocols for DNA extraction and sequencing are urgently needed. This would be the first step for the development of harmonized methods to analyze, report and interpret molecular sequencing technologies to guide the development of personalized therapeutic regimens leading to improved patient outcomes.

7. Immunological studies

Intact immune responses to cytomegalovirus (CMV) and Epstein-Barr virus (EBV) represent a biologically and clinically relevant correlate of 'immunological fitness' in humans. The study reported by Nagu et al., [29] found that Increased cellular immune responses to CMV and EBV antigens at the time of diagnosis of pulmonary tuberculosis were associated with increased survival after a standard six months anti-TB therapy.[29] Thus an intact immune responses to cytomegalovirus (CMV) and Epstein-Barr virus (EBV) may be a predictors for treatment outcome.[29] The study by Valentini et al. showed that BCG immunization induced antibodies against host proteins.[30] How this aberrant immune response modifies the immune response to BCG needs further study, but BCG is also used as immunotherapy in selected cases of bladder cancer, indicating a positive but unspecific effect on the immune response. The second study by Valentini et al. used peptide arrays to dissect the epitope specific humoral immune responses across the entire *M. tuberculosis* protein molecules.[31] An interesting finding was that patients from South America recognized more peptides compared to patients from South Africa (both groups HIV-negative).[31] A study using peptide microarrays

found that sera from patients with sarcoidosis and Löfgren's syndrome recognised 68 - 78% *M. tuberculosis* peptides once again suggesting mycobacterial involvement in sarcoidosis.[32]

Using paleomicrobiology it is possible to study the evolution of MTBC over the past ten millennia and its association with human migration, providing new insight into the probable origin of the different MTBC bacterial lineages.[33]

8. TB Treatment

Tiberi et al. describe the evolution in WHO TB classifications (taking into account an independently proposed new classification) and recent changes in WHO guidance, while discussing the differences among them, including the latest evidence on the ex-group five drugs.[34]

Despite the large investment made in treating patients with rifampin-resistant TB, the majority of these patients still receive suboptimal therapy and achieve poor outcomes. A study that reviewed data regarding the expected return on investment in performing second-line DST for all patients with rifampicin-resistant TB concluded that "incorporating second-line DST into the routine care of all patients diagnosed with rifampin-resistant TB on Xpert® seems a justifiable investment to make".[35]

Sotgiu et al. reviewed studies describing a 9 to 12-month regimen for MDR-TB cases, known as the Bangladesh regimen.[36] The protocol includes an initial phase of 4 to 6 months of kanamycin, moxifloxacin, prothionamide, clofazimine, pyrazinamide, high dose isoniazid and ethambutol followed by 5 months of moxifloxacin, clofazimine, pyrazinamide and ethambutol.[36]

There is an unmet need for TB treatment trials recruiting children and adolescents.[37] Urgent questions address efficacy, toxicity and prophylactic treatment of contacts to MDR TB.[37]

A study from Tblisi, Georgia, described pulmonary surgery in 137 patients half with MDR/XDR TB.[38] Whereas it was too early to describe outcomes in terms of mortality, the study found that "from the 98% of DS-TB cases presenting cavities or tuberculomas and considered bacteriology cured according to WHO definitions, 56% were AFB positive from samples from the surgical specimens". Thus surgery need to be revisited in patients with extensive pulmonary lesions even those with bacterial cure or patients where bacterial cure is not possible.[38]

The study by Hanna et al. reviewed seven project teams developing first-in-class translational and quantitative methodologies that aim to inform drug development decision-making dose selection, trial design and safety assessments, to achieve shorter and safer therapies for patients in need.[39] These tools offer the opportunity to evaluate multiple hypotheses and provide a means to identify, quantify, and understand relevant sources of variability, to optimize translation and clinical trial design.[39]

In recent years there has been renewed interest in the use of natural products, due to the wide range of pharmacophores and a high degree of stereochemistry, and therefore three-dimensionality that natural products possess.[40] Compound groups like the phenazines (which include clofazimine), piperidines, mycins (which include the rifampicins), quinolones (including the fluoquinolones and bedaquiline) and antimicrobial peptides (teixobactin, sansanmycins, Cyclomarin A, ecumicin, griselimycin, lariatins and trichoderins).[40]

A review of the literature on anti-PD-1/PD-L1 therapy based on the use in cancer therapy, indicate that anti-PD-1/PD-L1 therapy[41] may be of potential benefit in chronic lung infections thus adding another potential intervention to the growing portfolio of host-directed therapies.[41]

9. Diagnostics and Biomarkers

The study by Heller et al describes a cross-sectional study including 100 Malawian patients with a clinical indication for ultrasound and reviewed the literature on point-of-care ultrasound (POCUS) in Sub-Saharan Africa.[42] The study concludes that "Ultrasonography has evolved as a highly sensitive and specific imaging tool for diagnosing relevant conditions at the point of care in immune-competent and immune- compromised patients".[42] Gambhir and colleagues review the different imaging modalities available including, MRI, CT, ultrasonography and ^{18}F-fluorodeoxyglucose (FDG) PET-CT for the diagnosis of extrapulmonary TB.[43]

A review of molecular diagnostics and typing of mycobacteria using DNS extracted from slides suggests that the method may have potential.[44] New rapid diagnostics remain a priority, and Yerlikaya et al.,[45] describe the database curated by FIND and partners on the development of a well-curated and user-friendly TB biomarker database.[45]

Host biomarkers may provide a sensitive and specific approach to detect subclinical manifestations of clinical or subclinical TB, and transcriptomics allows inspection of tens of thousands of variables (such as gene expression, protein or metabolite levels) in one step.[46] The first attempts to reduce the number of transcripts in transcriptomic profiling of TB shows that the information contained in such large biosignatures is redundant, but more specific signatures can be derived by a more selective approach.[46]

A suitable approach for new markers for early diagnosis is the paper by Valentini et al.,[30] describing the use of peptide arrays to find *Mycobacterium* specific antibodies. Serology has so far not been regarded as a useful tool for TB diagnosis, but given that no early diagnostic tool is available (quantiferon-release assays cannot distinguish latent and active TB) this should be explored further.

10. Vaccines

The age old Bacille Calmette–Guérin (BCG) vaccine offers only limited protection against TB and a healthy pipeline of new TB vaccines are under various stages of development and evaluation. Kaufmann et al. reviewed new vaccine candidates for TB including subunit, inactivated whole-cell and live mycobacterial vaccines.[47] Current testing procedures evaluate the potency of new candidates in animal models by measuring the reduction of the bacillary load in the lungs during the acute phase of the infection. However, so far none of the candidates has been able to prevent the establishment of infection. The main characteristics of several laboratory animal models are reviewed, reflecting that none are able to simulate all the characteristics of human tuberculosis. Therefore, it is important to test new candidates in several models in order to generate convincing evidence of efficacy, including better efficacy than BCG in humans. It is also important to use "in silico" and "ex vivo" models to better understand experimental data and to replace or refine experimental animal models.[48] Using a mouse model, one study showed that immunizing with proteins involved in cell wall biosynthesis induced a better protection against aerosol challenge compared to BCG even without an adjuvant.[49]

11. Tuberculosis and world literature

The historic literature overview provides an important reminder of the devastation that TB caused before effective treatment became available.[50] Mortality was high in all age groups, and often patients were sick for many years with low quality of life. The review warns us what the situation will look like if MDR and XDR-TB are not brought under control.[50]

12. Conclusions

Even though new drugs and treatment regimens are becoming available, the cost remains prohibitive and responsible and optimal introduction of these is required. The investments in TB are insufficient to reach the "End TB" goal, and the situation regarding MDR and XDR TB is worsening. Bold political and funder commitments, analogous to the ivermectin donation program that helped to control onchocerciasis in West Africa in the 1980s, are required. New, more effective drugs and innovations for improving TB treatment outcomes are needed as well. A wide range of host-directed therapies (HDT) require evaluation as adjuncts to current TB drug treatment. Funders must take the bold step of investing in novel concepts that challenge conventional approaches and invest in evaluation of the efficacy of the wide range of HDTs available in randomized, placebo-controlled clinical trials as adjuncts to current TB treatment regimens.

The need for recruiting, educating, and retaining health care staff is highlighted, and the reviews also underline the importance of integrating HIV and TB management programs[15] and the importance of diabetes mellitus as a TB co-morbidity.[13] The report that patients with apparent cure still had live *Mycobacteria* in surgically removed tissue, underlines that better markers for cure are badly needed and that surgery may be considered in patients with persistent lesions after treatment for drug resistant TB, even after apparent bacterial cure.

The current status quo is unacceptable. Among the many problems include: no effective TB vaccine, the lengthy treatment duration of TB, the high death rates associated with MDR/XDR TB, the long term functional disability suffered by TB patients due to permanent lung damage and the associated drug toxicities, the neglect of childhood TB, the large burden of comorbidity with TB and HIV or NCDs, and sparse affordable TB drug pipeline

The prospects of controlling TB and achieving the WHO 'End TB targets' are daunting. It is clear that research funding allocated to TB is substantially less than what is available for HIV and malaria. This must change, given that TB remains the largest infectious disease killer on the planet. Progress in HIV and malaria prevention and management over the past three decades has demonstrated that huge investments in research and control programs do pay dividends.

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