Welcome to this issue of Respiratory Research Review with the focus on TB (tuberculosis). TB is one of the biggest global challenges of our time, and we are making small incremental gains like achieving the lowest ever rate of TB in the US and a global decline in TB incidence by 1.5% between 2014 and 2015. Sometimes it takes a ‘glossy magazine’ to focus on what is important, like the article by Nicole Davis in Harvard Public Health on ‘How TB is breaking the rules of biology’. TB is killing 1.5 million people each year and infecting 9.6 million; however, our fundamental understanding of TB is still based on observations made in the 18th and 19th centuries. Not all TB cells are homogenous; some cells have special tasks, like securing long-term survival or creating a ‘molecular bomb shelter’. It is a great overview with a great sense of optimism.

The WHO is leading the fight against TB, although the reduction in the incidence by 1.5% is not a reason for celebration, as it falls short of the reduction needed to cut TB death by 90% and TB disease by 80% between 2015 and 2030. TB and poverty continue to go hand in hand with poor housing, poor nutrition and poor education. And it certainly didn’t help the status of TB that it was left off the list of 12 families of antibiotic-resistant bacteria for which new drugs are urgently needed. Maybe Sanjay Tanday is right to doubt that we can ever eliminate TB, the voiceless disease (Lancet Respir Med). We can, however, give it our voice and be mindful of the challenges and also success of TB treatment.

Lancet Respir Med has dedicated its April 2017 edition largely to TB, with some visionary articles of original research, commissioned work and editorials. The most pragmatic and sobering article is by Keertan Dheda and colleagues on the outcomes of patients with XDR (extensively drug-resistant)-TB who are discharged home. These patients are perceived to be terminally ill; however, 21% survive more than 12 months, posing a significant public health challenge for their communities. I strongly recommend browsing the April edition of Lancet Respir Med. The interested reader should also consider the European Union standards on TB care, the ERS-endorsed clinical practice guidelines on treatment of drug-susceptible TB, and the WHO update on the treatment of drug-resistant TB.

The selection of articles for this issue will focus on two aspects of TB care: firstly, the importance of diagnosis and treating the individual patient in order to prevent new cases, and secondly, diagnosing and treating patients with latent TB to reduce the likelihood of disease progression; without treatment, about 5–10% of patients with latent TB will develop active disease.

We hope you enjoy the selection and appreciate comments and feedback.

Kind regards
Professor Lutz Beckert
lutzbeckert@researchreview.co.nz

Abbreviations used in this issue
BMI = body mass index
MDR = multidrug-resistant
NF = nuclear factor
TB = tuberculosis
TNF = tumour necrosis factor
XDR = extensively drug-resistant
TB in healthcare workers in the UK

Authors: Davidson JA et al.
Summary: This was an analysis of 2009–2013 TB surveillance and genotyping data from a retrospective cohort of 2320 notified cases of TB among UK healthcare workers, with comparisons made using data from non-healthcare workers; 85% of affected healthcare workers were born in other countries. The healthcare workers had a higher TB rate than the non-healthcare workers (23.4 vs. 16.2 per 100,000), but there was no difference after stratification by country of birth for most countries of birth, including the UK. There were only ten cases of confirmed nosocomial transmission among healthcare workers during 2010–2012, and of these only two involved transmission to patients.

Comment: In London alone, around six people per day develop active TB; it has been dubbed the TB capital of Europe. This study explores the 2320 cases of TB in healthcare workers; about a quarter had symptoms for 4 months prior to diagnosis. The incidence of TB in healthcare workers was higher than in non-healthcare workers; however, after stratifying for country of birth, the incidence of TB in healthcare workers was not higher than the background risk. Bottom line: the majority of TB occurred in healthcare workers from high TB burden countries and was likely reactivation of latent TB rather than nosocomial transmission.

Reference: Thorax 2017;72(7):654–9

An evaluation of automated chest radiography reading software for tuberculosis screening among public- and private-sector patients

Authors: Rahman MT et al.
Summary: The utility of computer-aided reading for chest radiography as a triage tool prior to Xpert MTB/RIF TB screening was evaluated in 18,036 consecutive adults from Bangladesh presenting with TB symptoms. The TB prevalence according to Xpert was 15%, and 49% of chest x-rays were graded as abnormal by the radiologist, resulting in 91% sensitivity and 58% specificity. At a similar sensitivity, computer-aided reading had 41% specificity, with a 36% reduction in Xpert tests. Computer-aided reading had an AUC (area under the receiver operating characteristic curve) of 0.74, but its performance declined as patient age increased. The radiologist grading was better in all subanalyses.

Comment: Trials on shortened treatment of MDR (multidrug resistant)-TB in Bangladesh have informed the WHO guidelines. This Bangladesh article on screening for TB has the potential to cause change as well. In many Asian countries people access private healthcare because of convenience and perceived higher quality. Private providers are excluded from the WHO-subsidised Xpert MTB/RIF test. So, the general screening tool is a chest x-ray; a suspicious chest x-ray leads to Xpert testing. This study explores if a computer-aided reading could reduce the cost to the patient. Bottom line: at this stage the radiologist is superior to computer-assisted reading.

Reference: Eur Respir J 2017;49(5):1602159

Risk of developing tuberculosis disease among persons diagnosed with latent tuberculosis infection in the Netherlands

Authors: Erkens CGM et al.
Summary: TB incidence rates and associated risk factors were investigated for patients notified with latent TB infection in the Netherlands during 2005–2013, stratified by target group for screening, and by initiation and completion of preventive treatment. The respective incidences of TB for patients completing, stopping and not receiving preventive treatment were 187, 436 and 355 per 100,000 person-years for contacts of TB patients, respectively, and they were 63, 96 and 110 per 100,000 person-years for other target groups; the highest incidences were seen during the first year postdiagnosis for both groups. Compared with other target groups, contacts of TB patients had a higher rate of developing TB (rate ratio 3.1 [95% CI 2.0, 4.9]). Independent factors associated with progression to TB among contacts of TB patients were age <5 years and stopping preventive treatment within 28 days versus those not receiving preventive treatment, and among other target groups, the only independent associated factor was birth in a foreign country.

Comment: One of the ways the WHO is aiming to reduce the burden of TB is to reduce latent TB in countries with an incidence of less than 5 per 100,000 population. These Dutch authors report on the effect of treatment for latent TB using data from the Netherland surveillance system for TB. Of about 15,000 patients with latent TB, 134 developed active TB, 76 (58%) of these were within a year of diagnosing latent TB. The risk of disease activation was particularly high in children under the age of 5 years, immunocompromised patients and patients with high-risk exposure. Bottom line: taking treatment for latent TB reduced the risk of progression to active disease to 0.6%.


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The prevalence of latent tuberculosis infection in the United States

Authors: Mancuso JD et al.

Summary: Using the tuberculin skin test and an interferon-γ release assay, latent TB prevalences were estimated for 6083 individuals aged ≥6 years enrolled in the US NHANES (National Health and Nutrition Examination Survey) during 2011–2012. Tuberculin skin test and QuantIFERON-TB Gold in-tube test results provided respective estimated latent TB infection prevalences in 2011–2012 of 4.4% and 4.8%, corresponding to 12,398,000 and 13,628,000 individuals, respectively. There has been a slight decline in prevalence since 2000 among patients born in the US, but not for those born in other countries, and the prevalence has consistently been higher in earlier birth cohorts than in more recent ones. Individuals born outside the US, close contacts of TB patients and certain racial/ethnic groups comprise the higher risk groups.

Comment: The incidence of active TB in the US is at the lowest rate ever; however, it is still well short of the WHO aim of eliminated TB. In the US, genotyping confirmed that 80% of TB cases are due to progression of latent TB. As Christopher Whalen explains in his accompanying editorial, in order to make progress in eliminating TB, one needs to shrink the pool of latent infection. This article is using data from the 1999–2000 and 2011–2012 NHANES. Bottom line: over the last decade, the pool of latent TB infection is unchanged in the US at about 12.4 million people.


Abstract

Safety and immunogenicity of adenovirus 35 tuberculosis vaccine candidate in adults with active or previous tuberculosis

Authors: van Zyl-Smit RN et al.

Summary: This phase 2 trial randomised adults from South Africa with active pulmonary TB (on treatment for 1–4 months) or pulmonary TB regarded as cured following ≥12 months of treatment to receive AERAS-402 (a live, replication-deficient adenovirus 35-vectored TB candidate vaccine; three doses; n=61) or placebo (n=11). Vaccine recipients showed no evidence of temporal or dose-related changes in clinical status, lung function or radiology, and injection-site reactions were mild or moderate. Dipstick haematuria occurred in 41% and 27% of AERAS-402 and placebo recipients, respectively; no gross haematuria occurred. AERAS-402 administration was associated with robust CD8+ and moderate CD4+ T-cell responses, mainly to Ag85B.

Comment: We have previously reflected on the challenges of developing a vaccine against TB (Respiratory Research Review, issue 90). This group of researchers report on a new vaccine, an adenovirus containing three TB antigens, which has been effective in animal studies and volunteers. This study explores possible safety issues in case this vaccine to prevent TB infection was inadvertently administered to patients with active or recently treated TB. The nonprimary outcome of a significant immune response following the vaccination is exciting. Bottom line: the study shows that the new vaccine can be safely administered to patients with current or recent TB treatment without significant immunological complications.

Reference: Am J Respir Crit Care Med 2017;195(9):1171–80

Abstract

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SP110b controls host immunity and susceptibility to tuberculosis

**Authors:** Leu J-S et al.

**Summary:** This research studied the role of SP110b in controlling host immunity and susceptibility to TB and identified the fundamental immunological and molecular mechanisms affected by SP110b. Cell-based approaches, mouse models of *Mycobacterium tuberculosis* infection and genetic characterisation of patients with TB were used to achieve these objectives. It was found that SP110b modulated NF-κB (nuclear factor κB) activity, which led to downregulation of TNF-α production and, at the same time, upregulation of NF-κB-induced antiapoptotic gene expression. Thus, interferon-γ-mediated monocyte and/or macrophage cell death were suppressed. TNF-α was also downregulated in Ipr1-expressing mice infected with *M. tuberculosis*, resulting in alleviated cell death, less severe necrotic lung lesions, more efficient control of *M. tuberculosis* growth in the lungs and longer survival. The genetic studies in patients with TB suggested a key role of the SP110 gene in the modulation of TB susceptibility, along with *NFKB1* and *TNFα* genes.

**Comment:** One of the unsolved puzzles of TB is why in some people the immune system seems to clear the disease, yet in others it causes an active disease. In this article, Taiwanese researchers present a number of elegant experiments arguing the case that the nuclear protein SP110 may well have a physiological role of SP110 may be to reduce the innate immune system, to clear TB. The physiological role of SP110 may be to reduce excess host immunity and cell death. **Bottom line:** SP110 may become a therapeutic target; a reduction in this nuclear protein may become a host-directed therapy against TB.

**Reference:** Am J Respir Crit Care Med 2017; 195(3):389–92

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**Expected effects of adopting a 9 month regimen for multidrug-resistant tuberculosis**

**Authors:** Kendall EA et al.

**Summary:** These researchers performed population modelling to investigate the impact of introducing the 9-month regimen for MDR-TB endorsed by the WHO in 2016. Under optimistic assumptions, the short-course and the previous longer regimen would result in respective MDR-TB incidences of 3.3 and 4.3 per 100,000 population by 2024; i.e., a reduction of 23%. The reductions in incidence with the short-course regimen would be 14% and 11% if only treatment effectiveness and treatment availability was affected, respectively. With pessimistic assumptions, introducing the short-course regimen would have minimal impact and even potential for harm. The effect of the shorter regimen was greater in settings with more ongoing MDR-TB transmission, but the results were otherwise similar across settings with different levels of TB incidence and prevalences of MDR.

**Comment:** MDR-TB continues to be a major challenge, and we have already alluded to the immense humanitarian burden. **Lancet Respir Med** Amanda McNaughton and colleagues have published the cost of treating a single case of MDR-TB in Wellington; approximately $327,000 instead of $17,000 for a patient with fully susceptible TB. In some countries, treating MDR-TB consumes half of the budget available for TB control. These authors from Johns Hopkins modelled the possible impact of **WHO endorsed** short-course treatment of drug-resistant TB, which costs less than US$1000 per patient. **Bottom line:** with some risk, this short regimen has the potential to substantially lessen the MDR-TB epidemic.

**Reference:** Lancet Respir Med 2017;5(3):191–9

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**Independent commentary by Professor Lutz Beckert.**

Professor Lutz Beckert is the Head of Department of Medicine of the University of Otago, Christchurch. He is also a Respiratory Physician at Canterbury District Health Board with particular clinical interests in interstitial lung disease, pulmonary vascular disease, respiratory physiology and COPD (chronic obstructive pulmonary disease). Lutz is happy to be contacted to discuss research ideas either as a sounding board or considering future collaborations.

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Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR- and XDR-TB

Authors: Borisov SE et al.

Summary: In this study enrolling participants from five continents, 428 culture-confirmed MDR- and XDR-TB cases were hospitalised for a median of 179 days, during which the patients were exposed to bedaquiline for a median of 168 days; treatment regimens included linezolid, moxifloxacin, clofazimine and carbapenems. The respective 30-day sputum smear and culture conversion rates were 63.6% and 30.1%, the respective 60-day rates were 81.1% and 56.7%, the respective 90-day rates were 85.5% and 80.5%, and the respective end-of-treatment rates were 88.7% and 91.2%. The respective median times to smear and culture conversion were 34 days and 60 days. Among participants who completed treatment (n=247), the success rate was 71.3%, the mortality rate was 13.4% and the failure rate was 7.7%. Bedaquiline was interrupted in 5.9% of participants because of adverse events.

Comment: This is arguably the most remarkable study in this review. Firstly, this study uses real-world data from 25 MDR-TB reference centres in 15 countries to assess the safety, tolerability and effectiveness of bedaquiline in patients with MDR- and XDR-TB. Second, they reported an even better efficacy of bedaquiline-treated patients than the randomised trial; with a cure rate of 62%. Thirdly, Lorenzo Guglielmetti in his editorial gives us the bottom line: bedaquiline is a huge step forward, and its usage needs to be monitored and scaled up to avoid being remembered as a missed opportunity in the history of TB control.

Reference: Eur Respir J 2017;49(5):1700387

Randomized trial of liposomal amikacin for inhalation in nontuberculous mycobacterial lung disease

Authors: Olivier KN et al.

Summary: This phase 2 study randomised patients with treatment-refractory pulmonary nontuberculous mycobacterial infection to receive inhalaed liposomal amikacin 550mg (n=64) or placebo (n=45) once daily added to their multidrug regimen for 84 days; open-label inhalaed liposomal amikacin was permitted for a further 84 days in both groups. Eighty participants completed the randomised phase and 59 completed open-label treatment. There was no significant difference between the liposomal amikacin and placebo arms for the primary endpoint of change from baseline to day 84 on a semiquantitative mycobacterial growth scale (p=0.072), but liposomal amikacin was associated with a significantly greater proportion of participants with ≥1 negative sputum culture (32% vs. 9% [p=0.000]) and significantly greater 6-minute walk distance (+20.6 vs. −25.0m [p=0.017]) at day 84. A treatment effect was seen mainly in participants without cystic fibrosis with M. avium complex, and persisted 1 year after receiving liposomal amikacin. Most adverse events were respiratory events, with some affected participants discontinuing treatment as a result.

Comment: Treatment options for nontuberculous mycobacteria are limited and we have very few clinical trials to guide our management. These American authors report an efficacy and safety study of inhaled liposomal amikacin. In this small study, efficacy and improvement in quality of life weren’t demonstrated; however, participants treated with inhalaed liposomal amikacin had a greater sputum conversion rate and an improved 6-minute walk distance. Jason Stout and Kirsten Dicks warn us in the accompanying editorial not to rush towards this new therapy, but to enrol patients into further studies. Bottom line: Inhaled liposomal amikacin for nontuberculous mycobacteria is promising.