Respiratory Research Review™

Making Education Easy

Issue 162 – 2019

In this issue:

Abbreviations used in this issue

BCG = Bacillus Calmette-Guérin
HIV = human immunodeficiency virus
MDR/XDR = multi-/extensively drug resistant
TB = tuberculosis

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Welcome to issue 162 of Respiratory Research Review.

Reading up on TB (tuberculosis) makes one feel like a world citizen, linked into the tragedy of the estimated 1.6 million people who die of this essentially treatable illness caused by a single organism. A lot more work is to be done; however, there is also plenty of good news about TB.

Many high-income countries have the lowest incidence of TB in years, with the incidence well under 10 per 100,000 people (Lancet Respir Med 2018). We include an article from Australia that broadly mirrors the NZ situation, noticing that many new immigrants contract active TB when visiting their family in their country of origin. Globally, the incidence is declining as well, however, a little slower than estimated by the WHO. Encouragingly, the mortality is declining more rapidly than expected. In April this year, Lancet Respir Med published an easy to read seminar on TB. It is a comprehensive review about the current state of the art and at the same time, new developments in risk factor management, diagnostic tools, emerging treatments, new preventions and how to modernise TB at a time with great political will to eliminate TB. Most fascinating in this article are the emerging tests for proteins and by-products TB bacteria are shedding during replication like lipoarabinomannan (LAM), which can be detected at the point of care in the urine. The family of Xpert tests is also developing by offering wider resistance testing, easier use, portability and battery-operated cartridges. The section on drug development is also fascinating with a number of drugs being repurposed for TB treatment, most surprisingly perhaps metformin (Respirology 2018).

A quick glance through the selection of articles in this review reveals that about half of all research is published in the N Engl J Med. That may be good news in itself attesting the high-quality research being undertaken. In case you are in need of some uplifting news following your long work hours in mid-winter, consider reading the 'free for all' commentary in Lancet Respir Med co-authored by the 'Initiative for Vaccine Research' at the WHO – 'The way forward for tuberculosis vaccines'. It starts with a stocktake of the current vaccines, covers candidate genes and reports on the effect of a recombinant attenuate cytomegalovirus vaccine expressing *Mycobacterium tuberculosis* antigens, which shows the best protection against an *M. tuberculosis* challenge ever reported.

Three more articles are recommended for people who wish to read a little more around TB. 'Pulmonary tuberculosis in Pope Clement XI' is a short editorial providing a historical account on the pope, his physician Giovanni Maria Lancisi and the management of TB in the pre-antibiotic area. Next, impressive by its clarity of thought and organisation, is the short, freely available editorial from a member of the Global TB Programme of the WHO covering 'Tuberculosis research questions identified through the WHO policy guideline development process'. My colleague, Dr Bronwen Rhodes, pointed out this open-access, thought-provoking review article to me: 'Revisiting the timetable of tuberculosis'. In a learned way, they review some of the older databases on TB, wonder whether 'late spikes' are actually re-infections and reflect on immunoreactivity. Based on their data, they wonder if classifying 2 billion people as having TB infection may divert funds from fundamental research and public health interventions. Newly infected people are who we ought to focus on, as they are at the highest risk of progression to active disease.

We hope you enjoy the selection, we value your feedback and we would like to finish with the title of an editorial by James Trauer from Monash suggesting it is all worth it: 'TB, you're a long time cured'.

Kind regards,

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KINDLY SUPPORTED BY

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. **FOR FULL BIO CLICK HERE**

Prevention of *M. tuberculosis* infection with H4:IC31 vaccine or BCG revaccination

Authors: Nemes E et al., for the C-040-404 Study Team

Summary: High-risk adolescents who had received neonatal BCG vaccine were randomised to receive H4:IC31 (a candidate subunit vaccine against TB disease; n=308), BCG revaccination (n=312) or placebo (n=310) in this phase 2 trial. Immunogenicity was seen with both the BCG and H4:IC31 vaccines. Compared with placebo, H4:IC31 and BCG vaccine recipients had lower QFT (QuantiFERON-TB Gold In-tube) conversion rates (14.3% and 13.1%, respectively, vs. 15.8%) with lower sustained conversion rates (8.1% and 6.7% vs. 11.6%). Initial QFT conversion was not prevented by either vaccine, with efficacy point estimates of 9.4% (p=0.63) and 20.1% (p=0.29) for the H4:IC31 and BCG vaccines, respectively. BCG vaccine significantly reduced the rate of sustained QFT conversion (efficacy 45.4% [p=0.03]), whereas H4:IC31 vaccine did not (30.5% [p=0.16]). Serious adverse event rates did not differ significantly for the two vaccines, except for more mild-to-moderate injection-site reactions with BCG revaccination.

Comment: An effective vaccine will be an important tool to prevent TB infection. This is becoming more relevant with the emergence of MDR (multidrug resistant) strains. These South African authors need to be congratulated for their trial design. They included seroconversion as a surrogate outcome marker, which allowed them to complete their trial within 3 years. They also compared their candidate vaccine of a recombinant fusion protein (H4) and adjuvant (IC31), with revaccination with BCG in adolescents. **Bottom line: both vaccines were safe, and neither reduced the seroconversion of the QFT test. Both reduced sustained seroconversion, which may translate into reduced active disease.**

Reference: N Engl J Med 2018;379:138–49
Abstract

Prediction of susceptibility to first-line tuberculosis drugs by DNA sequencing

Authors: The CRyPTIC Consortium and the 100,000 Genomes Project

Summary: These researchers tested DNA sequencing for accurately predicting susceptibility profiles to the first-line anti-TB drugs isoniazid, rifampicin, ethambutol and pyrazinamide. Using whole-genome sequencing, they tested 10,209 isolates obtained from 16 countries for mutations associated with drug resistance and drug susceptibility across nine genes, and individual phenotypes were predicted if mutations of unknown association were not present. They then predicted complete susceptibility profiles to identify how first-line drug therapy might be directed. The largest proportion of phenotypes was predicted for rifampicin (95.4%) and the smallest was predicted for ethambutol (89.8%). The respective sensitivity values for correctly predicting resistance to isoniazid, rifampicin, ethambutol and pyrazinamide were 97.1%, 97.5%, 94.6% and 91.3%, and the respective specificity values for susceptibility were 99.0%, 98.8%, 93.6% and 96.8%. Among isolates with complete phenotypic drug-susceptibility profiles (n=7516), 78.0% had complete genotypic predictions, among which 89.5% were correctly predicted. Among the 4037 phenotypic profiles that were predicted to be susceptible to all four anti-TB agents, 97.9% were correctly predicted.

Comment: This is essentially a proof-of-concept study demonstrating that 'whole-gene sequencing' is coming of age and showing promise in detecting all drug resistance mutations in a single test. The authors managed to access data from more than 10,000 *M. tuberculosis* isolates from 16 countries. They performed whole-genome sequencing to predict susceptibility to all first-line drugs, which has a better specificity over PCR-based assays and can reduce workload and turnaround time. **Bottom line: the technology is promising although not perfect; the biggest hurdle will be to make whole-gene sequencing available for the countries with the highest burden of drug-resistant TB.**

Reference: N Engl J Med 2018;379:1403–15
Abstract

Estimating the prevalence of latent tuberculosis in a low-incidence setting: Australia

Authors: Dale KD et al.

Summary: The prevalence and distribution of latent TB infection were estimated for individuals born in Australia and those born in other countries according to 2006, 2011 and 2016 Australian census data. The proportion of Australian residents with latent TB infection increased from 4.6% in 2006 to 5.1% in 2016 due to an increase in the proportion of the population born in other countries from 23.8% to 28.3%. Among residents estimated to have latent TB infection in 2016, 93.2% were born in other countries, 21.6% were aged <35 years and 34.4% had migrated to Australia since 2007.

Comment: This prevalence study from colleagues in Melbourne is very similar to observations in NZ. The overall prevalence of TB is low. If one separates the population into Australian born and overseas born, it becomes apparent the incidence of overseas born residents reflects closely the prevalence of their country of origin. The authors suggest that in lieu of national prevalence surveys, attention and support should be offered to all migrants. They point out that refugees only make up 2–3% of migrants to Australia. **Bottom line: people not born in Australia or NZ carry the highest burden of latent TB.**

Reference: Eur Respir J 2018;52:1801218
Abstract

A trial of a shorter regimen for rifampin-resistant tuberculosis

Authors: Nunn AJ et al., for the STREAM Study Collaborators

Summary: Patients with rifampicin-resistant TB susceptible to fluoroquinolones and aminoglycosides (evaluable n=383) were randomised in a 2:1 ratio to receive a 9- to 11-month regimen that included high-dose moxifloxacin or a 20-month regimen as per the 2011 WHO guidelines, in this phase 3 noninferiority trial. The proportion of participants with a favourable status at 132 weeks (primary efficacy outcome) did not differ significantly between the short and long regimens (78.8% vs. 79.8% [p=0.02 for noninferiority]), with similar findings seen in a per-protocol analysis. The respective grade ≥3 adverse event rates in the short and long regimen groups were 48.2% and 45.4%, the QT interval/corrected QT interval prolongation rates were 11.0% and 6.4% (p=0.14), the mortality rates were 8.5% and 6.4% and the acquired fluoroquinolone or aminoglycoside resistance rates were 3.3% and 2.3%.

Comment: In 2011, the WHO issued guidelines for the treatment of rifampicin-resistant TB suggesting treatment for 18–24 months. The so-called Bangladesh regimen used a seven-drug cocktail including high-dose isoniazid, a potent fluoroquinolone, clofazimine and an injectable agent for 9 months. In this paper, patients with rifampicin-resistant TB from Ethiopia, Mongolia, South Africa and Vietnam were randomised to receive the standard 18- to 24-month regimen, or the modified 9-month treatment. **Bottom line: the 9-month regimen was not inferior to treat rifampicin-resistant TB. However, death occurred between 8.5% and 6.4%; in addition, almost half of the participants suffered severe adverse events.**

Reference: N Engl J Med 2019;380:1201–13
Abstract

Under-reporting of diagnosed tuberculosis to the national surveillance system in China

Authors: Li T et al.

Summary: This retrospective inventory study sought to determine under-reporting and delayed treatment of TB in nine counties in China in 2015. There were 5606 patients in whom TB was identified from project health and social insurance data records, for whom 19.3% had not been reported to the TB Information Management System. Among the 4524 patients with TB who were reported, 31.3% were not registered for treatment within 7 days of diagnosis. Under-reporting was more likely for children, patients with TB pleurisy, those diagnosed in eastern and central regions and those with a TB diagnosis recorded in either health facilities or social insurance systems, but not both. Patients previously treated for TB, those with negative or unknown sputum results and those diagnosed in the eastern region were less likely to start treatment without delay.

Comment: The WHO estimates that almost 40% of all patients with TB are not reported. Under-reporting can delay treatment, prolonging the illness and increasing the risk of transmission. China has a functional public health system and a falling incidence of TB. The authors of this paper reviewed more than 60,000 records from 259 health facilities to calculate the percentage diagnosed but not referred to the TB Information Management System. The WHO estimates nonreporting of 15% in Europe, 20% in Africa, 30% in the Eastern Mediterranean and 50% in Asian countries with a large private sector. **Bottom line: the nonreporting in China was 22%.**

Reference: BMJ Open 2019;9:e021529
Abstract

One month of rifapentine plus isoniazid to prevent HIV-related tuberculosis

Authors: Swindells S et al., for the BRIEF TB/A5279 Study Team

Summary: This phase 3 noninferiority trial compared the efficacy and safety of the standard-of-care 9-month regimen of isoniazid alone (9-month group; n=1498) with that of rifapentine plus isoniazid (1-month group; n=1488) in HIV-infected patients who were living in areas of high TB prevalence or who had evidence of latent TB infection. The study completion rate was significantly greater in the 1-month group than in the 9-month group (97% vs. 90% [p<0.001]). Over a median of 3.3 years of follow-up, the primary endpoint (diagnosis of active TB or death from TB or an unknown cause) occurred in 2% of both the 1-month and 9-month groups (respective incidence rates, 0.65 and 0.67 per 100 person-years); the predefined noninferiority criterion was met. The serious adverse event rates were 6% and 7% in the 1-month and 9-month groups, respectively (p=0.07).

Comment: Worldwide, TB is the leading cause of death in patients with HIV infection, with approximately 1000 patients infected with HIV dying from TB each day. If an HIV-positive patient is exposed to TB, she or he should take 6–9 months of prophylactic treatment with isoniazid. These authors randomised more than 3000 HIV-positive patients to receive isoniazid for 9 months or rifapentine plus isoniazid for 1 month. As the accompanying editorial points out, improving brevity, acceptability, safety and cost of preventive therapy will have major benefits. **Bottom line: the 1-month regimen was not inferior, had similar side effects and a better completion rate.**

Reference: N Engl J Med 2019;380:1001–11
Abstract

Each month we highlight a particularly excellent paper with our butterfly symbol.

Platelets regulate pulmonary inflammation and tissue destruction in tuberculosis

Authors: Fox KA et al.

Summary: These researchers sought to determine the functional role of platelets in the innate inflammatory and matrix-degrading response in TB by examining markers of platelet activation in plasma obtained from 50 patients with TB before treatment and 50 controls; 25 patients were also followed longitudinally. Additional experiments were also performed in murine models and in 15 patients with TB and matched controls. Compared with controls, patients with TB exhibited upregulation of five of six platelet-associated mediators, although the levels normalised by treatment day 60. Patients with *M. tuberculosis* infection were found to have upregulated monocyte collagenase MMP-1 (matrix metalloproteinase-1) gene expression, and their platelets exhibited enhanced *M. tuberculosis*-induced secretion of MMP-1 and -10, which drove degradation of type I collagen. Consistent with an M2 monocyte phenotype, the platelets increased monocyte IL-1 and IL-10 secretion and decreased IL-12 and macrophage-derived chemokine secretion. There was also decreased intracellular *M. tuberculosis* destruction by monocytes. Platelets were detected in the lungs of mice, and there was upregulation of secreted platelet mediators in human bronchoalveolar fluid, which correlated with MMP and IL-1β levels.

Comment: This article is challenging our thinking that platelets only participate in the coagulation cascade. In a number of elegant and complicated experiments, these British authors demonstrated that platelets can support the host defence with their preloaded chemokines, cytokines, growth factors and enzymes. Donal Cox and Joseph Keane cite their role in defending against *Staphylococcus aureus*, *Neisseria gonorrhoea* and *Helicobacter pylori*. The authors present evidence that platelets could also enable TB, by secreting collagenase which causes cavitation, influences monocyte maturation and inhibits macrophages. **Bottom line: platelets drive proinflammatory tissue degradation and may become a therapeutic target of anti-TB treatments.**

Reference: Am J Respir Crit Care Med 2018;198:245–55
Abstract

Adjunctive vitamin D in tuberculosis treatment

Authors: Jolliffe DA et al.

Summary: This was a meta-analysis of individual participant data from eight randomised controlled trials (n=1850) investigating adjunctive vitamin D during antimicrobial therapy for pulmonary TB. Adjunctive vitamin D had no significant impact on sputum culture conversion overall (adjusted hazard ratio 1.06 [95% CI 0.91, 1.23]), but was associated with accelerated sputum culture conversion in participants with MDR pulmonary TB (13.44 [2.96, 60.90]), although not in participants whose isolates were sensitive to rifampicin and/or isoniazid (1.02 [0.88, 1.19]; p=0.02 for interaction). Adjunctive vitamin D was also associated with accelerated sputum smear conversion overall (adjusted hazard ratio 1.15 [95% CI 1.01, 1.31]), but had no significant effect on the other secondary outcomes of mean weight at 8 weeks and adverse events.

Comment: Vitamin D has long been an attractive adjuvant treatment against TB. Historically TB has been associated with vitamin D deficiency. Vitamin D has a recognised role in immune regulation and it has been investigated in several studies, which have not been conclusive. In this study, a group of international authors performed a meta-analysis of individual participant data from randomised controlled trials of patients receiving vitamin D as adjuvant treatment. They are carefully positive in their **bottom line: adjunctive vitamin D did not influence the time to sputum conversion in drug-sensitive TB; however, it may accelerate sputum conversion in patients with MDR TB.**

Reference: Eur Respir J 2019;53:1802003
Abstract

High treatment success rate for multidrug-resistant and extensively drug-resistant tuberculosis using a bedaquiline-containing treatment regimen

Authors: Ndjeka N et al.

Summary: This research reported on 200 South African patients with pre-XDR (extensively drug resistant) TB or XDR TB (67% with HIV infection) who were treated with 24 weeks of bedaquiline on an optimised, individualised background regimen that could include levofloxacin, linezolid and clofazimine as needed. Sixteen patients did not complete 6 months of bedaquiline, and 146 (73.0%) had favourable outcomes, with a cure rate of 69.5%. The mortality rate was 12.5%, 10.0% were lost from treatment and 4.5% failed treatment. There were 22 adverse events recorded that were attributed to bedaquiline, including five cases of corrected QT intervals >500 msec, 11 increases in corrected QT intervals of >50 msec from baseline and one case of paroxysmal atrial flutter.

Comment: Treatment of MDR TB has a poor treatment success, is lengthy and is associated with significant side effects. The reader may wish to explore the chilling commentary on the 'Management of adverse reactions to high-dose moxifloxacin used in multidrug-resistant tuberculosis treatment programmes'. These South African authors report on the successful treatment of MDR TB and XDR TB adding the first new TB drug in decades to the regimen, bedaquiline. In the 200 patients, treatment failure was only reported in nine; however, 25 patients died and 20 were lost to follow-up. **Bottom line: bedaquiline was associated with a high rate of successful treatment for this pre-XDR TB and XDR TB cohort.**

Reference: Eur Respir J 2018;52:1801528
Abstract

Bidirectional association between tuberculosis and sarcoidosis

Authors: Wang S-H et al.

Summary: The relationship between TB and sarcoidosis was explored using Taiwanese insurance data from retrospective, longitudinal cohorts of 31,221 patients with TB and 62,442 matched controls, and 2442 patients with sarcoidosis and 9688 controls. Compared with the respective control groups, patients with TB had an 8.09-fold (95% CI 3.66, 17.90) increased risk of developing sarcoidosis and patients with sarcoidosis had a 1.85-fold (1.36, 2.50) increased risk of developing TB. The highest risk of developing sarcoidosis was seen in patients with extrapulmonary TB, while the highest risk of developing extrapulmonary TB was seen in patients with sarcoidosis compared with the controls without sarcoidosis. The increased risk of developing sarcoidosis with TB was seen throughout the follow-up period, but the risk of developing TB with sarcoidosis was only elevated during the first year.

Comment: The relationship between sarcoidosis and TB has been a longstanding conundrum, plagued by misdiagnoses and poor diagnostic tools. A transmissive aetiology on the background of genetic susceptibility has been hypothesised. This study from Taiwan is probably not the final word in this matter; however, the numbers enrolled in this study are impressive. Using their national database, the authors used 30,000 patients with TB and compared their likelihood of developing sarcoidosis with 60,000 controls. **Bottom line: patients with a history of TB had an 8-fold higher risk of developing sarcoidosis compared with non-TB patients.**

Reference: Respirology 2019;24:467–74
Abstract