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In this issue:

Abbreviations used in this issue

CFU = colony-forming unit
HIV = human immunodeficiency virus
IGRA = interferon-γ release assay
MDR-TB = multidrug resistant TB
PCR = polymerase chain reaction
QFT = QantiFERON-TB Gold
TB = tuberculosis
TNF = tumour necrosis factor
UV = ultraviolet

Welcome to issue 126 of Respiratory Research Review, with the focus on TB (tuberculosis).

TB has existed since prehistoric times as paleopathologists can convincingly tell us. It currently affects more than 9 million people and causes 1.5 million deaths each year. Is our generation going to cause a change, or are we deluding ourselves in thinking we can eliminate TB by 2035 (defined as a 90% reduction in TB incidence)?

Since the WHO declared TB a global emergency in 1993, we have achieved the first goal in halting and reversing TB incidence. TB mortality has fallen by 47% since 1900 and an estimated 42 million lives have been saved. However, the last WHO report suggested a worrisome increase in TB estimates to 9 million new cases, up from 8.6 million in 2012 with the highest burden in southeast Asia and the western Pacific area, which harbour 56% of all TB seen in the world. I would challenge readers to explore the personal stories of TB through the medium of film to hear the untold stories of this devastating disease (cases TB Silent Killer and TB Unmasked) as suggested and reviewed by Jennifer Thorley.

Great academic overviews are published in the N Engl J Med, the BMJ, which summarise the updated TB NICE guidelines, and Eur Respir J, which published guidelines very relevant to the NZ situation: Management of latent *Mycobacterium tuberculosis* infection: WHO guidelines for low tuberculosis burden countries.

We have selected a few highlights, including the report of a human vaccination trial with live-attenuated *M. tuberculosis*, which may be just as effective as the BCG vaccination. With the production problems with BCG (Lancet), this may be an important alternative vaccine with significant future potential. We also review a few articles exploring the reduction of transmission, which includes the negative effect of smoking on TB immunity and the positive effect of UV dosing.

The most exciting new research may come from a group at Stanford in co-operation with Biomedical Information Research. By integrating gene expression data from several populations, the researchers came up with a three-gene whole blood test that could robustly and easily identify people with active TB. This has tremendous clinical implications for treatment and TB control.

With a strong political will from our political leaders to ensure that 'TB has no place in a future society', with about 20 new pipeline drugs coming on to the market and disruptive new genetic technologies changing our screening, testing and resistant testing landscape, we can be mildly optimistic that we can reduce the burden of TB over the next decade.

I hope you enjoy our selection and we are looking forward to any feedback and comments.

Kind regards

Professor Lutz Beckert
lutzbeckert@researchreview.co.nz

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Safety of human immunisation with a live-attenuated *Mycobacterium tuberculosis* vaccine

Authors: Spertini F et al.

Summary: This phase 1 trial randomised 36 clinically healthy adult volunteers to receive injections of a new live TB vaccine MTBVAC 5×10^3, 5×10^4 or 5×10^5 CFUs (colony-forming units) or BCG 5×10^5 CFUs. MTBVAC safety for all doses was similar to BCG safety, with no serious adverse events occurring. By day 210, all participants were IGRA-negative. MTBVAC was at least as immunogenic as BCG following whole blood stimulation with live MTBVAC or BCG. There was also a trend for more responders when MTBVAC was administered at the same dose as BCG (i.e. 5×10^5 CFUs), with more polyfunctional CD4+ central memory T-cells.

Comment: These researchers from Lausanne and Madrid report their successful first trial with live-attenuated *Mycobacterium* in 36 healthy volunteers. This study was founded by the Bill and Melinda Gates Foundation and although small in numbers, it is a major milestone. A live-attenuated vaccine contains more wild-type antigen and may hopefully become more effective and safer than the benchmark BCG vaccination as outlined in the accompanying editorial. None of this has reached clinical or statistical significance; however, this proof of concept joins successes in dengue and malaria vaccines. **Bottom line: live-attenuated *M. tuberculosis* vaccine seems as safe and at least as effective as BCG.**

Reference: Lancet Respir Med 2015;3(12):953–62
Abstract

Cigarette smoking impairs human pulmonary immunity to *Mycobacterium tuberculosis*

Authors: O'Leary SM et al.

Summary: These researchers compared functional impairment of human alveolar macrophages obtained from nonsmokers, smokers and former smokers who had prior *M. tuberculosis* infection. Smokers had significantly more alveolar macrophages than nonsmokers or former smokers ($p<0.01$), and the alveolar macrophages from smokers were unable to control intracellular *M. tuberculosis* growth on *in vitro* challenge. Compared with uninfected alveolar macrophages in the corresponding group, significantly greater generation of TNF-α, interferon-γ and interleukin-1β was seen in *M. tuberculosis*-infected alveolar macrophages from nonsmokers ($p<0.05$), but not those from smokers or former smokers. Alveolar macrophages from smokers and nonsmokers induced FoxP3+ T-regulatory cell phenotype responses in allogeneic admixed T-cells (>4.8 fold [$p<0.05$]), and this regulatory phenotype continued to be driven by the alveolar macrophages after *M. tuberculosis* infection.

Comment: These Irish researchers explore a molecular link as to why smokers are more easily infected with *M. tuberculosis* and why they tend to have worse treatment outcomes. They obtained human alveolar macrophages via bronchoscopy in smokers, ex-smokers and never-smokers. Smokers had a higher number of macrophages in the mucosa; however, macrophages from smokers produced lower levels of TNF-α, interferon-γ and interleukin-1β after stimulation with mycobacteria. **Bottom line: the pulmonary macrophages in smokers seem to be impaired, which seems to make patients more susceptible to TB infection and disease.**

Reference: Am J Respir Crit Care Med 2014;190(12):1430–6
Abstract

Institutional tuberculosis transmission. Controlled trial of upper room ultraviolet air disinfection: a basis for new dosing guidelines

Authors: Mphaphlele M et al.

Summary: In this research, 90 guinea pigs breathed untreated exhaust hospital ward air over a 7-month exposure period and another 90 guinea pigs breathed only air from the same six-bed TB ward on alternate days, when upper room germicidal air disinfection by UV radiation was switched on. Compared with the guinea pigs exposed to the disinfected air, those exposed only to the untreated air were significantly more likely to exhibit tuberculin skin test conversion (>6 mm; hazard ratio 4.9 [95% CI 2.8, 8.6]).

Comment: Part of infection control is 6–12 air changes per hour, but this is often not feasible in countries with a high disease burden and limited resources. UV irradiation has long been the standard method for water disinfection, but research about air disinfection is limited. Using a classic experimental setup utilising groups of guinea pigs, the researchers reported that guinea pigs exposed to UV light-treated air had 15 infections and guinea pigs exposed to standard air had 49 infections over a 4-month period. **Bottom line: upper room UV light germicidal radiation can be highly effective, commercially viable and safe for patients.**

Reference: Am J Respir Crit Care Med 2015; 192(4):477–84
Abstract

For more information, please go to www.medsafe.govt.nz

Genome-wide expression for diagnosis of pulmonary tuberculosis

Authors: Sweeney TE et al.

Summary: These authors sought to derive a diagnostic gene set in the peripheral blood of patients with active TB using data from two public gene expression microarray repositories. Gene expression was compared in patients with latent TB or other diseases versus those with active TB using a validated multicohort analysis framework. Using meta-analytical methods on three datasets (n=1023), three genes (*GBP5*, *DUSP3* and *KLF2*) were identified that were highly diagnostic for active TB. The diagnostic power of this set of genes was validated in eight more datasets including adults and children from ten countries to separate active TB from healthy controls (global area under the receiver operating characteristic curve 0.90 [95% CI 0.85, 0.95]), latent TB (0.88 [0.84, 0.92]) and other diseases (0.84 [0.80, 0.95]), with no evidence of confounding by HIV infection status, bacterial drug resistance or BCG vaccination. In addition, data from another four cohorts showed declines in TB score during treatment of active TB.

Comment: It was a Russian mathematician who had crucial input in working out our highly effective, time-honoured, multidrug regimen for TB. It is not surprising then that another group of biostatisticians, with cosponsorship from the Bill and Melinda Gates Foundation, may have come up with a game changing blood test to robustly identify active TB infection. This three-gene peripheral blood test performs very well in children and is unaffected by HIV status. This test still needs to go through clinical validation studies; however, the **bottom line is: it may be possible to create solar-powered PCR instruments to deliver point-of-care TB diagnosis.**

Reference: Lancet Respir Med 2016;4(3):213–24
Abstract

Screening for TB by sputum culture in high-risk groups in Copenhagen, Denmark: a novel and promising approach

Authors: Jensen SG et al.

Summary: The results were reported for a community-based programme that offered TB screening on seven occasions with smear microscopy and culture examination of spot sputum samples to all individuals present at 11 locations where socially marginalised people gather in Copenhagen, Denmark. If TB was found, the individual underwent genotyping, nucleic acid amplification testing and chest radiography. There were 36 cases of TB identified among 1075 individuals screened, two-thirds of which were identified at the first screening; the prevalence was 2233 per 100,000. All but one of the identified TB cases had a positive culture, seven had a positive smear and 28 had TB-suggestive chest radiographs. Of the 21 individuals who underwent nucleic acid amplification testing, 12 were positive. All identified patients with TB received treatment, with a success rate of 83.3%.

Comment: This study is less futuristic than solar-powered PCR point-of-care TB diagnosis based on gene expression; this study is based in our real world, with disappearing mobile x-ray units and difficult contact tracing of high-risk, socially marginalised people like the homeless and alcoholics. These Danish authors present a 2-year study of more than 1000 participants, proving that direct sputum samples of high-risk people can identify more people with active TB than chest x-ray screening would have been able to. Most patients with acid-fast bacillus were smear negative. **Bottom line: screening a high-risk group with spot sputum culture is feasible and promising.**

Reference: Thorax 2015;70(10):979–83
Abstract

Prognostic value of interferon-γ release assays, a population-based study from a TB low-incidence country

Authors: Hermansen TS et al.

Summary: These authors analysed QFT (QantiFERON-TB Gold) results from 15,980 Danish individuals and data on all TB cases in Denmark during 2005–2012 to determine the predictive value of QFT for coprevalent TB (0–90 days after testing) and incident TB (>90 days). Of 1703 positive and 13,463 negative QFT cases, coprevalent TB was diagnosed in 10.7% and 0.3%, respectively. Among QFT-positive cases, those aged <35 years were more likely to have coprevalent TB than older cases (19.3% vs. 7.2% [p<0.001]). Over follow-up of 52,807 person-years (median 3.36 years), the respective positive and negative predictive values for incident TB were 1.32% and 99.85%, and the respective incidence rates of incident TB for QFT-positive and -negative cases were 383 and 45 per 100,000 person-years. Among QFT-positive cases, the incidence rate for incident TB was associated with <2-year duration since QFT (p<0.001) but not age <35 years (p=0.087).

Comment: The next two articles explore the IGRA in populations with low TB incidence. These Danish authors investigated the positive predictive value of QFT in about 15,000 individuals. QFT is an excellent test to exclude TB; a finding confirmed by this study. Approximately 10% of the screened population had a positive QFT and 183 (10%) developed TB. Wei Shen Lim provides an excellent editorial overview of this and related studies. **Bottom line: a negative QFT test excludes TB with 99.5% certainty; a positive QFT suggests the risk of developing active TB is 1.3–4%.**

Reference: Thorax 2016;71(7):652–8
Abstract

T-SPOT.TB interferon-γ release assay performance in healthcare worker screening at nineteen U.S. hospitals

Authors: King TC et al.

Summary: The performance characteristics of 42,155 T-SPOT.TB IGRA tests were assessed during serial screening programmes of 16,076 healthcare workers from 19 geographically diverse US hospitals; 19,630 serial pairs were evaluated. The respective mean positivity, conversion and reversion rates were 2.3%, 0.8% and 17.6%. Correlations were seen between positivity and conversion rates and known TB risk factors, including age and sex. The T-SPOT.TB test had an observed specificity of ≥98.6%.

Comment: In this US-based article the researchers report on 40,000 T-SPOT.TB tests performed on 16,000 healthcare workers in 19 US hospitals. At baseline 2.3% of the population were positive. The conversion rate was 0.8% over the study period; it varied from 0% to 1.9% depending on the clinical setting. Also, 18% of samples that tested positive at baseline became negative and 80% of samples initially borderline became clearly positive or negative on the next testing. These findings are likely to be relevant to the NZ situation. **Bottom line: screening with IGRAs is reproducible, specific and clinically meaningful.**

Reference: Am J Respir Crit Care Med 2015;192(3):367–73
Abstract

Benefit of treatment of latent tuberculosis infection in individual patients

Authors: Dobler CC et al.

Summary: With the use of a Markov model, a decision aid to gauge the likelihood of a hypothetical individual's net gain in quality-adjusted life-years associated with latent TB infection treatment was developed. The model incorporated personalised risk estimates of TB reactivation, TB death, quality of life impairment and side effects. It was estimated the treatment of latent TB infection would be beneficial when the annual risk of TB reactivation exceeded 13–93 and 15–119 per 100,000 for females and males aged 10–75 years, respectively; these threshold levels were associated with respective numbers needed to treat to avoid one TB case of 93, 77, 85 and 72.

Comment: This is a great article from our colleagues in Australia addressing the issue that the WHO identified in the treatment of latent TB as a key strategy to achieve TB elimination. In clinical practice, the physician needs to weigh up benefits and risks for TB treatment with the individual patients. This article is focussed on the science of developing a prediction model using available prevalence and risk data. For the clinician, the twenty online case studies may be of greatest clinical utility. **Bottom line: the benefit of treating latent TB outweighs the risk in the majority, but not all patients.**

Reference: Eur Respir J 2015;46(5):1397–406
Abstract

Rapid, comprehensive, and affordable mycobacterial diagnosis with whole-genome sequencing

Authors: Pankhurst LJ et al., for the COMPASS-TB Study Group

Summary: Whole-genome sequencing of mycobacteria in newly positive liquid cultures was prospectively compared with routine laboratory diagnostic workflows for diagnostic accuracy, processing times and cost in eight European and North American laboratories. Compared with routine laboratory workflows, a single whole-genome sequencing attempt was associated with 93% accuracy for both predicting species (322/345 specimens; 356 mycobacteria specimens submitted) and drug susceptibility (628/672 specimens; 168 *M. tuberculosis* complex specimens identified). Whole-genome sequencing linked 16% of 91 patients in the UK to an outbreak, diagnosed one case of MDR-TB prior to completion of routine diagnosis and identified a new MDR-TB cluster. Full whole-genome sequencing diagnostics were able to be generated quicker than the final reference laboratory reports (median 98 vs. 31 days) and at a lower cost (£481 vs. £518 per culture-positive specimen).

Comment: This is another article that demonstrates how new molecular techniques may revolutionise our management of TB. These international researchers compared the accuracy, processing time and cost of routine results with results from whole-genome sequencing using data from eight TB laboratories. Performing whole-genome sequencing only once, the authors report that it is 93% accurate in identifying the species, 93% accurate in predicting drug susceptibility and faster and cheaper than routine testing. The editorial by a mathematician and epidemiologist elaborates on its future potential. **Bottom line: whole-genome sequencing will become a fast, accurate and affordable clinical method to improve our understanding of TB control.**

Reference: Lancet Respir Med 2016;4(1):49-58
Abstract

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Intensified antituberculosis therapy in adults with tuberculous meningitis

Authors: Heemskerk AD et al

Summary: Hospitalised patients with tuberculous meningitis were randomised to receive a standard 9-month anti-TB regimen of rifampicin 10 mg/kg/day (n=409) or an intensified regimen of rifampicin 15 mg/kg/day and levofloxacin 20 mg/kg/day for the first 8 weeks of treatment (n=408); 349 participants also had HIV infection. No significant difference was seen between the intensified and standard treatment arms for death after 9 months (primary outcome; hazard ratio 0.94 [95% CI 0.73, 1.22]), and there was also no significant between-group difference for any of the subgroups assessed (with the possible exception of participants with isoniazid-resistant *M. tuberculosis* infection), the secondary outcomes assessed or adverse events leading to interruption of treatment.

Comment: This study serves as a reminder of the current toll of TB. This randomised controlled trial of intensified therapy with an increased rifampicin dose and added levofloxacin was performed in Vietnam with support from the UK. In just over 3 years, the researchers recruited 817 patients with TB meningitis, where the overall mortality rate was above 25%, although only one organism was rifampicin-resistant. The number of adverse events to treatment was around 10% and was a little higher in the intensified treatment group. Peter Donald from South Africa wrote this sobering editorial. **Bottom line: intensified treatment of TB meningitis was not associated with increased survival.**

Reference: N Engl J Med 2016;374(2):124–34
Abstract

Fluoroquinolone therapy for the prevention of multidrug-resistant tuberculosis in contacts

Authors: Fox GJ et al.

Summary: These researchers investigated the cost-effectiveness, potential benefits and risks of a 6-month daily fluoroquinolone course for latent TB in contacts of patients with MDR-TB. A decision analysis found that compared with no treatment, fluoroquinolone therapy led to health system savings, a lower incidence of MDR-TB and reduced mortality. It was also determined that the incidence of MDR-TB with acquired fluoroquinolone resistance would be lower in infected contacts who received fluoroquinolone therapy.

Comment: These Canadian authors provide only a theoretical model; however, any strategy to reduce the burden of MDR-TB will be of great interest, as 500,000 individuals develop this disease each year. MDR-TB has a poor prognosis, is complex and expensive to treat and the treatment is often toxic. Prophylactic treatment with isoniazid and/or rifampicin does not add any value. The authors present some mathematical modelling of an exposed person receiving 6 months of a fluoroquinolone or surveillance only, not treatment. **Bottom line: fluoroquinolone after MDR-TB exposure would save costs and reduce the incidence of, and mortality related to, MDR-TB.**

Reference: Am J Respir Crit Care Med 2015;192(2):229–37
Abstract

Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis

Authors: Pym AS et al.

Summary: These researchers investigated the efficacy and safety of 24 weeks of bedaquiline on a background regimen of anti-TB drugs according to guidelines in this phase 2 trial of 233 participants, among whom 63.5% had MDR-TB and 18.9% and 16.3% had pre-extensively and extensively drug-resistant TB, respectively; 87.1% had received second-line treatment before enrolment. Follow-up was 120 weeks. The mortality rate was 6.9% and the discontinuation rate within the first 24 weeks was 8.6%, mostly due to adverse or MDR-TB-related events. Adverse events were typical of those associated with MDR-TB treatment. Among 205 participants evaluable for efficacy, the 120-week culture conversion rate was 72.2%, with respective rates of 73.1%, 70.5% and 62.2% in participants with MDR-TB and pre-extensively and extensively drug-resistant TB.

Comment: This open-label, single-arm study explored the safety, tolerability and efficacy of the new TB medication bedaquiline. A total of 233 patients were enrolled. In all participants the organism was at least resistant to isoniazid/rifampicin and about a quarter had more extensive drug resistance. Addition of bedaquiline led to an 80% sputum conversion rate at 24 weeks and was well tolerated; 6.4% reported hepatic side effects. The mortality rate of this MDR-TB group was 6.9%. **Bottom line: while a control group drug trial is currently recruiting, we can be carefully optimistic that bedaquiline is safe and effective in the treatment of MDR-TB.**

Reference: Eur Respir J 2016;47(2):564–74
Abstract

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.