Respiratory RESEARCH REVIEW™

Making Education Easy

Issue 175 – 2020

In this issue:

Abbreviations used in this issue

BCG = bacillus Calmette-Guérin
CFU = colony-forming unit
HIV = human immunodeficiency virus
HR = hazard ratio
IGRA = interferon-γ release assay
MDR = multidrug resistant
NTM = nontuberculous mycobacterial
TB = tuberculosis

Welcome to issue 175 of Respiratory Research Review.

"We are facing an unprecedented pandemic. A quarter of the world's population is infected and, between 2020 and 2021, it is predicted that 10 million people will have fallen ill, 3 million will not have been diagnosed or received care, and more than 1 million – mainly the most vulnerable – will have died." That is how our colleagues have cited the WHO TB report 2019 in their editorial 'Tackling two pandemics: a plea on World Tuberculosis Day'. We adopted their framing for this issue of Respiratory Research Review. Maybe we can learn to treat COVID-19 by reflection on lessons learned treating TB. After all, both illnesses frequently present with respiratory symptoms. Both illnesses are more likely to affect the elderly, patients with comorbidities and healthcare workers. Both illnesses have considerable social impacts, including stigma, discrimination, economic impacts and catastrophic costs to individuals/whānau.

Over the last few months, we have collectively brushed up on our epidemiology and public health knowledge. (NZ can be very grateful for a strong public health response). Over the coming months, we may have to refresh our learning on intracellular signalling pathways, including opportunities of biochemical interruptions. It is also likely that we will learn a lot more about possible vaccines: antibody binding sites, RNA vaccines, attenuated vaccines, live vaccines, phases of vaccine development and therapeutic targets. Progress for developing vaccines for TB has been slow and it may help to explore the reasons behind this a bit deeper. The only licensed vaccine against TB is the live strain of a related pathogen, *Mycobacterium bovis*, a strain known as BCG (bacillus Calmette-Guérin), which was developed between 1908 and 1921. This vaccine has been administered to about 2 billion people, has an efficacy of about 15% (Nature 2020) and is not without its problems. In this selection, we cover three reports on vaccine development: a proof-of-concept study using BCG intravenously, a 3-year follow-up of using a TB protein and adjuvant, and a new live-attenuated *Mycobacterium tuberculosis* vaccine in adults. Lancet Respir Med has comprehensively summarised in its TB series 'Insights and challenges in tuberculosis vaccine development'.

In this rather divisive world, it is encouraging to see how progress is being made via co-operation. The American Thoracic Society, the European Respiratory Society, the Infectious Diseases Society of America and the US Centers for Disease Control and Prevention have published a new practice guideline on the 'Treatment of drug-resistant tuberculosis'. The 21 key recommendations are too many to summarise here; however, their first recommendation is that the treatment of drug-resistant TB should be guided by a TB expert. Key findings for me were a fresh classification of second-line drugs, the suggestion that at least five drugs should be used in the intensive phase, that the total treatment duration should be 15–21 months, and that most of the treatment can now be based on oral therapy. The document is freely available for the interested reader, with clear graphics, precise summaries and a strong selection of the key literature.

Three recommendations for the interested reader are: i) 'The Lancet Respiratory Medicine Commission: 2019 update: epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant and incurable tuberculosis'; ii) a stimulating and challenging discussion paper in the BMJ asking just because a QuantiFERON test is positive, does this mean that the *M. tuberculosis* infection is life long; and iii) the excellent TB 2019 series in Lancet Respir Med.

We hope you enjoy the selection; we appreciate comments and feedback. We hope you are keeping well through these winter months.

Kind regards,

Professor Lutz Beckert
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The global prevalence of latent tuberculosis

Authors: Cohen A et al.

Summary: This systematic review and meta-analysis included 88 studies from 36 countries reporting latent TB infection estimates. Based on 41 IGRA (n=67,167) and 67 tuberculin skin test with 10mm cutoff (n=284,644) results, the global prevalences of latent TB infection were 24.8% and 21.2%, respectively. These estimated prevalences correlate well with incidence rates reported by the WHO (Rs=0.70 [p<0.001]).

Comment: The WHO estimate of the burden of TB infection is based mainly on calculations based on the incidence of smear-positive cases, assumptions of durations of infectiousness and average transmissions per year. Documentation of immune responses has improved significantly with the introduction of commercial IGRAs. We don't know whether a TB infection is lifelong or whether a positive test only reflects an appropriate immune response (BMJ 2019). About 10% develop active disease and we have no method to identify the people at highest risk. We still have a relevant **bottom line: about a quarter of the world population has latent TB.**

Reference: Eur Respir J 2019;54:1900655
Abstract

Independent commentary by Professor Lutz Beckert

Professor Lutz Beckert is the Associate Dean Medical Education with 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 with the view of future collaborations.

Unmasking the hidden tuberculosis mortality burden in a large *post mortem* study in Maputo Central Hospital, Mozambique

Authors: Garcia-Basteiro AL et al.

Summary: TB burden was evaluated for 223 patients who died in a sub-Saharan African tertiary referral hospital. The decedents included 54 children, 57 maternal deaths and 112 other adults, and 56.5% were HIV-positive. In-house real-time PCR-positive lung samples (all patients) and CSF and CNS samples (HIV-positive patients) as well as samples that showed histological findings suggestive of TB were analysed with the Xpert MTB/RIF Ultra assay. TB was the cause of death in 31 patients, including 6% of the children, 9% of the maternal deaths and 21% of the other adults. The respective sensitivity and specificity values of the main clinical diagnosis to detect TB as the cause of death were 19.4% and 97.4% compared with autopsy findings. An additional 31 decedents who died of non-TB causes were found to have TB, the identification of which was facilitated by Xpert Ultra in 15 cases. *M. tuberculosis* DNA was detected by TB-PCR and Xpert Ultra in the absence of histological TB lesions for 18 patients. The overall respective rates of TB at death and TB findings were 27.8% and 35.9%.

Comment: The authors summarise the key findings in their crucial figure. Essentially, it is an autopsy study of 223 deaths. Overall, 14% of adults and children died of TB, but alarmingly 80% of these were not diagnosed prior to death. The accompanying editorial is titled 'Still dying in plain sight: missed and misclassified death due to tuberculosis in hospitals'. It places the data in context and points out that many patients don't present with a cough or fever, making a clinical or sputum-based diagnosis, like Xpert, difficult. **Bottom line: clinical diagnosis of TB is poor; diagnostic algorithms should improve the diagnostic accuracy.**

Reference: Eur Respir J 2019;54:1900312
Abstract

Extensive global movement of multidrug-resistant *M. tuberculosis* strains revealed by whole-genome analysis

Authors: Cohen KA et al.

Summary: These researchers undertook a phylogenetic analysis of 5310 *M. tuberculosis* whole-genome sequences obtained from five continents to examine the geographical distribution of MDR-TB. Their analysis revealed extensive international dissemination of MDR-TB: there were 32 migrant MDR-TB clades with descendants isolated in 17 countries. Global spread of varied genetic backgrounds was indicated by relatively recent movement of strains from Beijing and non-Beijing lineages. There was shared relatively recent common ancestry among migrant MDR-TB clade members (median divergence estimates, 13–27 years). Regarding extensively drug-resistant TB, there was no evidence of migrant clades, but its development was common within migratory MDR-TB clades.

Comment: MDR-TB is a significant threat to global TB control with nearly 500,000 new cases and about 250,000 deaths each year. MDR-TB is due to both *de novo* acquisitions of resistance during (suboptimal) treatment and person-to-person transmission in countries with low TB prevalence. The authors utilised a dataset of about 5000 TB cases and applied molecular fingerprinting to characterise clades of MDR-TB with respect to geographical dispersion. **Bottom line: whole-genome sequencing suggested that MDR strains move more widely internationally than previously recognised, and this technique can assist public health efforts to contain resistant TB.**

Reference: Thorax 2019;74:882–9
Abstract

Transmissibility and potential for disease progression of drug resistant *Mycobacterium tuberculosis*

Authors: Becerra MC et al.

Summary: Associations between phenotypical drug resistance and TB infection (positive tuberculin skin test) and TB disease (confirmed by sputum smear or chest x-ray) were prospectively explored for a cohort of 10,160 household contacts of 3339 index patients with pulmonary TB in Peru; 6189 of the household contacts had been exposed to drug-susceptible *M. tuberculosis* strains, 1659 to isoniazid- or rifampicin-resistant strains, and 1541 to isoniazid- and rifampicin-resistant strains (MDR). Compared with household contacts of patients with drug-sensitive TB, those of patients with MDR-TB had an 8% higher risk of TB infection after 12 months of follow-up. There was no significant increase in the risk of incident TB disease between household contacts of patients with MDR-TB versus those of patients with drug-sensitive TB (adjusted HR 1.28 [95% CI 0.9, 1.83]).

Comment: The prevalence of MDR-TB is up to 36% in some countries. The WHO predicts that by 2050, MDR-TB could kill 10 million people annually. Most cases acquire an infection with an MDR-TB strain, rather than acquiring resistance. These researchers followed about 10,000 household contacts of patients with susceptible and MDR-TB strains. They found that MDR-TB is just as infective as susceptible TB; however, because it is harder to treat, it ensures a 'fitness cost'. **Bottom line: household contacts of patients with MDR-TB are at higher risk of TB infections than household contacts of drug-susceptible TB.**

Reference: BMJ 2019;367:l5894
Abstract

CONGRATULATIONS TO

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Drug-associated adverse events in the treatment of multidrug-resistant tuberculosis

Authors: Lan Z et al., the Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment 2017

Summary: A meta-analysis was undertaken on data from 9178 individual patients enrolled in 35 studies reporting adverse events that led to permanent discontinuation of anti-TB medications; the included studies had low risk of bias, and variability between studies was significant for most outcomes analysed. Drugs associated with low adverse event risks leading to permanent anti-TB medication discontinuation included levofloxacin (1.3%), moxifloxacin (2.9%), bedaquiline (1.7%) and clofazimine (1.6%), whereas those with high risks included three second-line injectable drugs (amikacin [10.2%], kanamycin [7.5%] and capreomycin [8.2%]), aminosalicylic acid (11.6%) and linezolid (14.1%).

Comment: We have already alluded to the clinical practice guidelines of drug-resistant TB, the increased complexity of treatment, considerable cost and poorer prognosis. This meta-analysis of 50 studies, including almost 10,000 patients, reports on the side effects, about a quarter of which were patient-reported. Visual disturbances, ototoxicity, nephrotoxicity, peripheral neuropathy, myelosuppression, hepatotoxicity, cardiovascular and musculoskeletal side effects are the most common reasons to discontinue treatment. Second-line injectable drugs, aminosalicylic acid and linezolid have the highest incidence of side effects. **Bottom line: fluoroquinolones, clofazimine and bedaquiline had the lowest incidence of adverse effects leading to permanent drug discontinuation.**

Reference: Lancet Respir Med 2020;8:383–94
Abstract

Willingness to take multidrug-resistant tuberculosis (MDR-TB) preventive therapy among adult and adolescent household contacts of MDR-TB index cases

Authors: Suryavanshi N et al., for the A5300/I2003 Study Team

Summary: This cross-sectional study interviewed 743 household contacts of 278 index patients with MDR-TB or rifampicin-resistant TB regarding their willingness to take a hypothetical, newly developed MDR-TB preventive therapy. Seventy-nine percent of the household contacts indicated they would be willing to take a hypothetical MDR-TB preventive therapy, and this percentage decreased to 70% with the potential for mild side effects. Factors significantly associated with a greater likelihood of willingness to take the hypothetical MDR-TB preventive therapy included current employment or schooling (adjusted odds ratio 1.83 [95% CI 1.07, 3.13]), appropriate TB-related knowledge (2.22 [1.23, 3.99]), confidence in taking MDR-TB preventive therapy (7.16 [3.33, 15.42]) and being comfortable about disclosing their decision to do so to others (2.29 [1.29, 4.06]).

Comment: Household contacts of patients with MDR-TB are at increased risk of infection due to the prolonged exposure in a shared environment. Treatment of MDR-TB is costly, lengthy and toxic. However, treating household contacts of MDR-TB is a key public health tool to stop the spread of MDR-TB. In this study from South Africa and eight other countries, household members of about 300 patients with MDR-TB were asked about their willingness to take MDR-TB treatment if clinically indicated. It led to a rather reassuring **bottom line: most household contacts would be willing to take MDR-TB treatment, even if they were to have mild side effects.**

Reference: Clin Infect Dis 2020;70:436–45
Abstract

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Analysis of loss to follow-up in 4099 multidrug-resistant pulmonary tuberculosis patients

Authors: Walker IF et al.

Summary: Using data from 4099 patients with MDR-TB, these researchers evaluated when loss to follow-up occured according to month of MDR-TB treatment, and identified risk factors associated with loss to follow-up. Overall, 702 of the patients were lost to follow-up, which occurred in a median of 7 months. Loss to follow-up occurred mostly during the initial phase of treatment (75% within the first 11 months). Factors associated with loss to follow-up were age 36–50 vs. 0–25 years (HR 1.3 [95% CI 1.0, 1.6]), HIV positivity (1.8 [1.2, 2.7]), receipt of an individualised versus a standard treatment regimen (0.7 [0.6, 1.0]) and a recorded serious adverse event (0.5 [0.4, 0.6]).

Comment: Patients on treatment for MDR-TB who are lost to follow-up are at increased risk of death and pose a public health risk of ongoing MDR-TB transmission. These authors report on the characteristics of patients treated for MDR-TB who were lost to follow-up. Most patients were lost within the first 7 months of treatment, many of whom were HIV-positive, received standardised treatment and reported fewer (!) side effects. The authors speculate that the lack of reporting of side effects may actually be a sign of noncompliance. **Bottom line: TB programmes should offer targeted support for patients of working age and with HIV infection.**

Reference: Eur Respir J 2019;54:1800353
Abstract

Live-attenuated *Mycobacterium tuberculosis* vaccine MTBVAC versus BCG in adults and neonates

Authors: Tameris M et al., the MTBVAC Clinical Trial Team

Summary: Healthy adults were randomised to receive intradermal injections of MTBVAC (a live-attenuated *M. tuberculosis* candidate vaccine; n=9) or BCG vaccine (n=9), and after favourable review of 28-day reactogenicity and safety data in this cohort, infants were randomised to receive MTBVAC 2.5×10^3 (n=9), 2.5×10^4 (n=9) or 2.5×10^5 (n=10) CFUs (colony-forming units) or BCG vaccine (n=8). Only BCG and the MTBVAC 2.5×10^5 CFU recipients experienced injection-site reactions, which were mild with no local or regional injection-site complications. The groups had similar rates of systemic adverse events with most being mild. There were eight serious adverse events reported in seven participants overall, including one infant who received MTBVAC 2.5×10^3 CFUs treated for unconfirmed TB and one who received 2.5×10^5 CFUs treated for unlikely TB. All MTBVAC vaccine doses induced durable immunological responses that peaked 70 days after vaccination and remained detectable out to day 360; responses to MTBVAC 2.5×10^5 CFUs exceeded those induced by an equivalent BCG vaccine dose out to day 360. There was also evidence of dose-related IGRA conversion.

Comment: We have reported on this proof-of-concept trial of a live attenuated *M. tuberculosis* vaccine in normal volunteers before (Respiratory Research Review, issue 126). This is the first randomised controlled field trial in 18 healthy volunteers who had a previous BCG vaccination, and 17 infants, who were randomised to the BCG vaccination or the live-attenuated TB vaccination. Jacqueline Achkar interprets the findings and puts them in context in her accompanying editorial. **Bottom line: the novel live-attenuated TB vaccination induces an acceptable immune response, including a positive IGRA test, and should move forward to be tested for its potential to prevent active disease.**

Reference: Lancet Respir Med 2019;7:757–70
Abstract

Final analysis of a trial of M72/AS01E vaccine to prevent tuberculosis

Authors: Tait DR et al.

Summary: Adults with *M. tuberculosis* infection but no evidence of active disease were randomised to receive monthly doses for 2 months of M72/AS01E (evaluable n=1626) or placebo (evaluable n=1663). The respective incidences of M72/AS01E (a candidate vaccine against *M. tuberculosis*) and placebo recipients who met the first case definition of bacteriologically confirmed pulmonary TB not associated with HIV infection were 0.3 and 0.6 cases per 100 person-years, and M72/AS01E vaccine efficacy at 36 months was 49.7%. Among M72/AS01E recipients, there were increases in M72-specific antibody levels and M72-specific CD4+ T cell counts after the first dose, and these persisted during follow-up. No significant between-group differences were seen for serious adverse events, potential immune-mediated diseases or deaths.

Comment: We have summarised the proof-of-concept study for this new vaccine before (Respiratory Research Review, issue 114). It is a novel fusion protein of two TB antigens combined with the adjuvant system AS01. This randomised trial involved more than 3000 volunteers who had a positive IGRA test and no signs of active TB. The vaccine was well tolerated. A total of 13 in the vaccinated group and 26 participants in the placebo group developed active TB, which translates to a vaccine efficiency of 50% at 3 months. **Bottom line: the vaccine elicited an immune response and had an efficacy of 54% protection against active TB.**

Reference: N Engl J Med 2019;381:2429–39
Abstract

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

Prevention of tuberculosis in macaques after intravenous BCG immunization

Authors: Darrah PA et al.

Summary: Macaque monkeys were administered intravenous, intradermal or aerosolised BCG vaccine in this research. Compared with intradermal or aerosol administration, intravenous administration was associated with substantially greater antigen-responsive CD4 and CD8 T-cell responses in blood, spleen, bronchoalveolar lavage and lung lymph nodes, as well as greater antigen-responsive T-cell counts across all lung parenchymal tissues. The animals were challenged with virulent *M. tuberculosis* 6 months after vaccination. Of the ten macaques that received intravenous vaccination, nine were highly protected and six showed no detectable levels of infection.

Comment: This article is a little dense to read and reports trial results from nonhuman primates. We have included it because of its important proof-of-concept design, relevance to the vaccine discussion, and its scholarly editorial. In this editorial, Behar and Sassetti review the development of the BCG vaccination, its strengths, its weaknesses (like the efficacy of 15% and the Lübeck disaster) and preparing the ground for the expected immune response. The immune response and protection against TB after intravenous BCG vaccination was profound in the macaques. **Bottom line: BCG vaccination may be substantially more protective against TB if given intravenously.**

Reference: Nature 2020;577:95–102
Abstract

Community-wide screening for tuberculosis in a high-prevalence setting

Authors: Marks GB et al.

Summary: Individuals aged ≥15 years were cluster-randomised by subcommune in a Vietnamese province to screening for pulmonary TB, regardless of symptoms, annually for 3 years starting in 2014 (n=42,150) or not (n=41,680). Nucleic acid amplification tests for *M. tuberculosis* conducted at 4 years revealed pulmonary TB in 126 and 226 per 100,000 population in the active screening and control groups, respectively (primary outcome; prevalence ratio, 0.56 [95% CI 0.40, 0.78]), but there was no significant difference between the two groups for the secondary outcome of TB infection prevalence among children born in 2012 (3.3% vs. 2.6%; 1.29 [0.70, 2.36]).

Comment: Part of the WHO END TB strategy is improving access to diagnosis, treatment and supportive care. However, 3.6 million people didn't receive a TB diagnosis or treatment in 2017. Colleagues from the Woolcock Institute, in collaboration with researchers from Vietnam, report on the efficacy of active screening versus standard case finding in the Vietnamese province of Ca Mau. The cluster randomised controlled trial included more than 40,000 participants in each arm. The incidence of TB in the active intervention group reduced from 389 to 126 per 100,000 over 4 years. **Bottom line: active screening reduced the incidence of TB by 41% over 4 years.**

Reference: N Engl J Med 2019;381:1347–57
Abstract

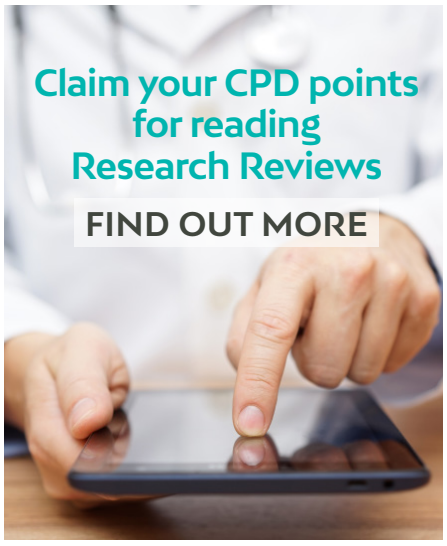
Systematic or test-guided treatment for tuberculosis in HIV-infected adults

Authors: Blanc F-X et al., for the STATIS ANRS 12290 Trial Team

Summary: Antiretroviral therapy-naïve adults with HIV infection (CD4+ T-cell count <100 cells/mm^3) were randomised to screening (Xpert MTB/RIF test, urinary lipoarabinomannan test and chest x-ray) to determine if TB treatment should be initiated (n=525) or systematic empirical treatment with rifampicin, isoniazid, ethambutol and pyrazinamide daily for 2 months, followed by rifampicin and isoniazid daily for 4 months (n=522). There was no significant difference between the systematic treatment and guided treatment groups for death from any cause or invasive bacterial disease (primary endpoint) at week 24 (19.4 vs. 20.3 per 100 person-years; adjusted HR 0.95 [95% CI 0.63, 1.44]) or at week 48 (12.8 vs. 13.3 per 100 person-years; 0.97 [0.67, 1.40]). Compared with guided treatment, systematic treatment was associated with a lower likelihood of TB at week 24 (3.0% vs. 17.9%; adjusted HR 0.15 [95% CI 0.09, 0.26]), but more grade 3–4 drug-related adverse events (17.4% vs. 7.2%; 2.57 [1.75, 3.78]) and serious adverse events.

Comment: It is estimated that about 250,000 patients annually die with the combined infections of TB and HIV. Many patients die of disseminated TB after initiation of antiviral therapy. TB is not easy to diagnose in HIV-infected patients with atypical chest x-ray changes and not many symptoms. Many physicians use empirical TB treatment when starting antiretroviral therapy. These international authors recruited more than 1000 patients into this trial to test whether patients do better on treatment after diagnosis or empirical treatment. **Bottom line: empirical treatment for TB was not superior to a strategy of TB screening and targeted treatment.**

Reference: N Engl J Med 2020;382:2397–410
Abstract



Accuracy of Xpert MTB/RIF Ultra for the diagnosis of pleural TB in a multicenter cohort study

Authors: Wang G et al.

Summary: This study evaluated the performance of the Xpert MTB/RIF Ultra for pleural TB diagnosis. In total, 317 individuals with suspected pleural TB were recruited; 208 of them were diagnosed with pleural TB. Comparisons for *M. tuberculosis* detection showed that Xpert Ultra (44.23%) was more sensitive than culture (26.44% [p<0.001]), Xpert (19.23% [p<0.001]) and smear (1.44% [p<0.001]). When Xpert Ultra outcomes were integrated, the percentage of definite pleural TB cases increased from 56.25% to 64.90%. The respective specificity values for smear, culture, Xpert and Xpert Ultra were 100%, 100%, 98.67% and 98.67%.

Comment: On a world scale, pleural TB remains one of the most common causes for a pleural effusion; however, the diagnosis is often difficult because of the paucibacillary nature of the disease. These Chinese researchers report on the performance of the enhanced Xpert Ultra unit, which results in detecting TB in a paucibacillary setting like spinal fluid, pleural fluid or paediatric sputum samples. The researchers used a multimodal diagnostic algorithm as the gold standard and compared the performance of Xpert Ultra. **Bottom line: Xpert Ultra outperforms culture and standard Xpert in diagnosing pleural TB and could speed up clinical treatment in practice.**

Reference: Chest 2020;157:268–75
Abstract

Prognostic factors associated with long-term mortality in 1445 patients with nontuberculous mycobacterial pulmonary disease

Authors: Jhun BW et al.

Summary: Prognostic factors associated with long-term mortality were examined in 1445 patients with NTM (nontuberculous mycobacterial) pulmonary disease in this 15-year follow-up study. The respective overall 5-, 10- and 15-year cumulative mortality rates were 12.4%, 24.0% and 36.4%. Factors significantly associated with mortality were older age, male sex, low body mass index, chronic pulmonary aspergillosis, pulmonary or extrapulmonary malignancy, chronic heart or liver disease, erythrocyte sedimentation rate and the following aetiological organisms when compared with *M. avium*: *M. intracellulare* (adjusted HR 1.40 [95% CI 1.03, 1.91]) and *M. abscessus* (2.19 [1.36, 3.51]), but not *M. massiliense* (0.99 [0.61, 1.64]). There were also significant associations between the cavitary nodular bronchiectatic and fibrocavitary forms of NTM pulmonary disease, versus the noncavitary nodular bronchiectatic form, and mortality (respective adjusted HRs 1.70 [95% CI 1.12, 2.59] and 2.12 [1.57, 3.08]).

Comment: The burden of NTM pulmonary disease is increasing. The organisms vary regionally; the most frequent are *M. avium*, *M. intracellulare*, *M. abscessus* and *M. massiliense*. Ideally, NTM treatment should eradicate the organism, leading to cure; however, the current treatment is not well tolerated and has limited efficacy. These Korean researchers followed almost 1500 patients with NTM over 15 years to elucidate some biomarkers of adverse outcome. The accompanying editorial gives us the **bottom line: mortality was associated with cavitating disease, the NTM organism and demographic characteristics like old age, male sex, low body mass index and coexisting morbidity.**

Reference: Eur Respir J 2020;55:1900798
Abstract

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