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Special issue: Invited review series: Tuberculosis update 2018

Tuberculosis updates 2018: Innovations and developments to end TB 2

Tuberculosis vaccines: Opportunities and challenges 3

Update on tuberculosis biomarkers: From correlates of risk, to correlates of active disease and of cure from disease 3

Epidemiological, clinical and mechanistic perspectives of tuberculosis in older people 4

Drug-resistant tuberculosis: An update on disease burden, diagnosis and treatment 5

Where is tuberculosis transmission happening? Insights from the literature, new tools to study transmission and implications for the elimination of tuberculosis 5

Implementing the End TB Strategy in the Western Pacific Region: Translating vision into reality 6

Latent tuberculosis infection: Opportunities and challenges 7

New drugs and regimens for tuberculosis 7

Drug resistance mechanisms and drug susceptibility testing for tuberculosis 8

Applying new tools to control tuberculosis 9

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World Tuberculosis day is on the 24th for March this year. To raise awareness and inform our members, we are publishing a special issue of the APSR Respiratory Updates on the *Respirology* review series "Tuberculosis Update 2018" edited by Chi Chiu Leung, Cynthia Chee and Ying Zhang and available at:

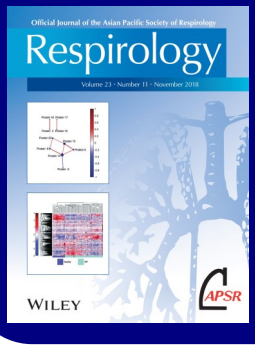
https://onlinelibrary.wiley.com/page/journal/14401843/tif_tuberculosis_updates_2018

TUBERCULOSIS UPDATES 2018
Series editors: Chi Chiu Leung, Cynthia Chee and Ying Zhang

Tuberculosis updates 2018: Innovations and developments to end TB

Leung CC, Chee C and Zhang Y.
Respirology 2017; 23: 356–358,
doi: 10.1111/resp.13244

The 2013 tuberculosis (TB) review series 'Tuberculosis: Current state of knowledge' highlighted important gaps in our existing knowledge on the complex interactions between the pathogen and the host. It also detailed major limitations in current control strategies. Since then, there have been major developments in new diagnostic tools and drugs/regimens for TB and latent TB infection (LTBI), some of which have modified clinical practice in both high- and low-burden countries. In 2014, the World Health Assembly approved the 'End TB Strategy', which set ambitious targets to achieve a 95% reduction in TB death and 90% reduction in TB incidence rate by 2035. To consolidate developments and to meet the upcoming challenges, we have invited a panel of international experts to critically re-examine the relevant issues in a new series of themed reviews focused on TB. **Read more…**



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Tuberculosis vaccines: Opportunities and challenges

Zhu B, Dockrell HM, Ottenhoff THM, Evans TG and Zhang Y.
Respirology 2018; 23: 359–368,

doi: 10.1111/resp.13245

Abstract: Tuberculosis (TB) is a serious disease around the world. Bacillus Calmette–Guérin (BCG) is the only TB vaccine licensed for use in human beings, and is effective in protecting infants and children against severe miliary and meningeal TB. However, BCG's protective efficacy is variable in adults. Novel TB vaccine candidates being developed include whole-cell vaccines (recombinant BCG (rBCG), attenuated *Mycobacterium tuberculosis*, killed *M. tuberculosis* or *Mycobacterium vaccae*), adjuvanted protein subunit vaccines, viral vector-delivered subunit vaccines, plasmid DNA vaccines, RNA-based vaccines etc. At least 12 novel TB vaccine candidates are now in clinical trials, including killed *M. vaccae*, rBCG *ΔureC::hly*, adjuvanted fusion proteins M72 and H56 and viral vectored MVA85A. Unfortunately, in TB, there are no correlates of vaccine-induced protection, although cell-mediated immune responses such as interferon-gamma (IFN-γ) production are widely used to assess vaccine's immunogenicity. Recent studies suggested that central memory T cells and local secreted IgA correlated with protection against TB disease. Clinical TB vaccine efficacy trials should invest in identifying correlates of protection, and evaluate new TB biomarkers emerging from human and animal studies. Accumulating new knowledge on *M. tuberculosis* antigens and immune profiles correlating with protection or disease risk will be of great help in designing next generation of TB vaccines.

Update on tuberculosis biomarkers: From correlates of risk, to correlates of active disease and of cure from disease

Goletti D, Lee M-R, Wang J-Y, Walter N and Ottenhoff THM.
Respirology 2018; 23: 455–466,

doi: 10.1111/resp.13272

Abstract: Tuberculosis (TB) remains a devastating disease, yet despite its enormous toll on global health, tools to control TB are insufficient and often outdated. TB Biomarkers (TB-BM) would constitute extremely useful tools to measure infection status and predict outcome of infection, vaccination or therapy. There are several types of TB-BM: Correlate of Infection; Correlate of TB Disease; Correlate of Increased Risk of Developing Active TB Disease; Correlate of the Curative Response to Therapy; and Correlate of Protection (CoP). Most TB-BM currently studied are host-derived BM, and consist of transcriptomic, proteomic, metabolomic, cellular markers or marker combinations (‘signatures’). In particular,

vaccine-inducible CoP are expected to be transformative in developing new TB vaccines as they will de-risk vaccine research and development (R&D) as well as human testing at an early stage. In addition, CoP could also help minimizing the need for preclinical studies in experimental animals.

Of key importance is that TB-BM are tested and validated in different well-characterized human TB cohorts, preferably with complementary profiles and geographically diverse populations: genetic and environmental factors such as (viral) coinfections, exposure to non-tuberculous mycobacteria, nutritional status, metabolic status, age (infants vs children vs adolescents vs adults) and other factors impact host immune set points and host responses across different populations.

In this study, we review the most recent advances in research into TB-BM for the diagnosis of active TB, risk of TB development and treatment-induced TB cure.

Epidemiological, clinical and mechanistic perspectives of tuberculosis in older people

Yew WW, Yoshiyama T, Leung CC and Chan DP.
Respirology 2018; 23: 567–575,
doi: 10.1111/resp.13303

Abstract: With the ageing population globally, tuberculosis (TB) in older people becomes a major clinical and public health challenge. In many Asian countries, especially those located in the eastern and southeastern parts of the continent, geriatric TB is a significant problem. TB in the older patients is more difficult to diagnose in the early course of disease, and has poorer treatment outcomes, largely as increased failure and death. More drug-induced adverse reactions are also experienced by this population during TB therapy. Oxidative stress and mitochondrial dysfunction are now well recognized to be associated with the ageing process, and it is likely that the cellular and molecular perturbations interact inextricably with the immunological dysfunction biophysiologically inherent to ageing. These underlying mechanistic bases putatively contribute to the development of TB in the geriatric population and worsen the disease outcomes, especially when the TB is compounded by co-morbid conditions such as smoking and diabetes mellitus. Unravelling these mechanisms further would yield knowledge that might potentially help to prevent reactivated TB in older people, and also to better manage the established disease with drug regimens and other new therapeutic strategies. In addition, addressing the social elements associated with geriatric TB is also imperative in the relief of individual patient suffering and improvement of overall disease control.

Drug-resistant tuberculosis: An update on disease burden, diagnosis and treatment

Lange C, Chesov D, Heyckendorf J, Leung CC, Udwadia Z, Dheda K.
Respirology 2018; 23: 656–673,
doi: 10.1111/resp.13304

Abstract: The emergence of antimicrobial resistance against *Mycobacterium tuberculosis*, the leading cause of mortality due to a single microbial pathogen worldwide, represents a growing threat to public health and economic growth. The global burden of multidrug-resistant tuberculosis (MDR-TB) has recently increased by an annual rate of more than 20%. According to the World Health Organization approximately only half of all patients treated for MDR-TB achieved a successful outcome. For many years, patients with drug-resistant tuberculosis (TB) have received standardized treatment regimens, thereby accelerating the development of MDR-TB through drug-specific resistance amplification. Comprehensive drug susceptibility testing (phenotypic and/or genotypic) is necessary to inform physicians about the best drugs to treat individual patients with tailor-made treatment regimens. Phenotypic drug resistance can now often, but with variable sensitivity, be predicted by molecular drug susceptibility testing based on whole genome sequencing, which in the future could become an affordable method for the guidance of treatment decisions, especially in high-burden/resource-limited settings. More recently, MDR-TB treatment outcomes have dramatically improved with the use of bedaquiline-based regimens. Ongoing clinical trials with novel and repurposed drugs will potentially further improve cure-rates, and may substantially decrease the duration of MDR-TB treatment necessary to achieve relapse-free cure.

Where is tuberculosis transmission happening? Insights from the literature, new tools to study transmission and implications for the elimination of tuberculosis

Auld SC, Shah NS, Cohen T, Martinson NA, Gandhi NR.
Respirology 2018;
doi: 10.1111/resp.13333

Abstract: More than 10 million new cases of tuberculosis (TB) are diagnosed worldwide each year. The majority of these cases occur in low- and middle-income countries where the TB epidemic is predominantly driven by transmission. Efforts to 'end TB' will depend upon our ability to halt ongoing transmission. However, recent studies of new approaches to interrupt transmission have demonstrated inconsistent effects on reducing population-level TB incidence. TB transmission occurs across a wide range of settings, that include households and hospitals, but also community-based settings. While home-based contact investigations and infection control programmes in hospitals and clinics have a suc-

cessful track record as TB control activities, there is a gap in our knowledge of where, and between whom, community-based transmission of TB occurs. Novel tools, including molecular epidemiology, geospatial analyses and ventilation studies, provide hope for improving our understanding of transmission in countries where the burden of TB is greatest. By integrating these diverse and innovative tools, we can enhance our ability to identify transmission events by documenting the opportunity for transmission—through either an epidemiologic or geospatial connection—alongside genomic evidence for transmission, based upon genetically similar TB strains. A greater understanding of locations and patterns of transmission will translate into meaningful improvements in our current TB control activities by informing targeted, evidence□based public health interventions.

Implementing the End TB Strategy in the Western Pacific Region: Translating vision into reality

Rahevar K, Fujiwara PI, Ahmadova S, Morishita F, Reichman LB.
Respirology 2018;

doi: 10.1111/resp.13308

Abstract: The End TB Strategy aims to end the global tuberculosis (TB) epidemic by 2035 in line with the sustainable development goals targets and has been implemented in the World Health Organization (WHO) Western Pacific Region since 2015. Significant progress has been made in implementing this strategy. However, several challenges still remain. In 2016, an estimated 1.8 million people developed TB in the region, and of these about 20% were missed by national TB programmes. The gap in diagnosis and enrolment as well as treatment completion is greater with drug-resistant TB. Many TB-affected families face catastrophic costs due to the disease. Sustaining financing for TB care is a long-term challenge in many countries. This article emphasizes targeted interventions in high-risk populations, including systematic screening and patient-centred TB care. Several other approaches including improving TB diagnostic tools and algorithm, and engaging all care providers are suggested to find missing TB patients. Drug-resistant TB requires additional resourcing for laboratories, enrolment and patient support. Specific measures are required at different levels to mitigate financial burden due to TB including linking TB to overall social protection schemes. The Moscow Ministerial conference in 2017 and upcoming United Nations (UN) 2018 high-level meeting provide an opportunity to raise TB higher on the global agenda, forge partnerships and move towards universal health coverage.

Latent tuberculosis infection: Opportunities and challenges

Chee CBE, Reves R, Zhang Y, Belknap R.
Respirology 2018;
doi: 10.1111/resp.13346

Abstract: Diagnosing and treating latent tuberculosis (TB) infection (LTBI) is recognized by the World Health Organization as an important strategy to accelerate the decline in global TB and achieve TB elimination. Even among low-TB burden countries that have achieved high rates of detection and successful treatment for active TB, a number of barriers have prevented implementing or expanding LTBI treatment programmes. Of those infected with TB, relatively few will develop active disease and the current diagnostic tests have a low predictive value. LTBI treatment using isoniazid (INH) has low completion rates due to the long duration of therapy and poor tolerability. Both patients and physicians often perceive the risk of toxicity to be greater than the risk of reactivation TB. As a result, LTBI treatment has had a limited or negligible role outside of countries with high resources and low burden of disease. New tools have emerged including the interferon-gamma release assays that more accurately diagnose LTBI, particularly in people vaccinated with Bacillus Calmette–Guerin (BCG). Shorter, better tolerated treatment using rifamycins are proving safe and effective alternatives to INH. While still imperfect, TB prevention using these new diagnostic and treatment tools appear cost effective in modelling studies in the United States and have the potential to improve TB prevention efforts globally. Continued research to understand the host–organism interactions within the spectrum of LTBI is needed to develop better tools. Until then, overcoming the barriers and optimizing our current tools is essential for progressing toward TB elimination.

New drugs and regimens for tuberculosis

Chang K-C, Nuermberger E, Sotgiu G, Leung C-C.
Respirology 2018;
doi: 10.1111/resp.13345

Abstract: Since standardized rifampin-based first-line regimens and fluoroquinolone-based second-line regimens were used to treat tuberculosis (TB), unfortunately without timely modification according to the drug resistance profile, TB and drug-resistant disease are still important public health threats worldwide. Although the last decade has witnessed advances in rapid diagnostic tools and use of repurposed and novel drugs for better managing drug-resistant TB, we need an appropriate TB control strategy and a well-functioning health infrastructure to ensure optimal operational use of rapid tests, judicious use of effective treatment regimens that can be rapidly tailored according to the drug resistance profile and

timely management of risk factors and co-morbidities that promote infection and its progression to disease. We searched the published literature to discuss (i) standardized versus individualized therapies, including the choice between a single one-size-fit-all regimen versus different options with different key drugs determined mainly by rapid drug susceptibility testing, (ii) alternative regimens for managing drug-susceptible TB, (iii) evidence for using the World Health Organization (WHO) longer and shorter regimens for multidrug-resistant TB and (iv) evidence for using repurposed and novel drugs. We hope an easily applicable combination of biomarkers that accurately predict individual treatment outcome will soon be available to ultimately guide individualized therapy.

Drug resistance mechanisms and drug susceptibility testing for tuberculosis

Miotto P, Zhang Y, Cirillo DM, Yam WC.
Respirology 2018;
doi: 10.1111/resp.13393

Abstract: Tuberculosis (TB) caused by *Mycobacterium tuberculosis* (MTB) is the deadliest infectious disease and the associated global threat has worsened with the emergence of drug resistance, in particular multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB). Although the World Health Organization (WHO) End-TB Strategy advocates for universal access to antimicrobial susceptibility testing, this is not widely available and/or it is still underused.

The majority of drug resistance in clinical MTB strains is attributed to chromosomal mutations. Resistance-related mutations could also exert certain fitness cost to the drug-resistant MTB strains and growth fitness could be restored by the presence of compensatory mutations. Understanding these underlying mechanisms could provide an important insight into TB pathogenesis and predict the future trend of MDR-TB global pandemic. This review covers the mechanisms of resistance in MTB and provides a comprehensive overview of current phenotypic and molecular approaches for drug susceptibility testing, with particular attention to the methods endorsed and recommended by the WHO.

Applying new tools to control tuberculosis

Leung, CC, Chee, CBE, Zhang, Y.
Respirology. 2018;

doi: 10.1111/resp.13429

In this Tuberculosis Updates 2018 series, experts from various parts of the world review important innovations and developments in a global effort to end the tuberculosis (TB) epidemic. Major gaps remain in reaching, diagnosing and effectively managing TB patients in many parts of the world. Social inequities continue to hamper TB control, especially in resource-limited settings. Universal health coverage and social protection are necessary to remove the barriers to the access to quality TB care. **Read more...**

The 24th Congress of the APSR will be held at the National Convention Center (NCC), Hanoi, Vietnam, 14–17 November 2019, hosted by the VietNam Respiratory Society (VNRS) hoihohapvietnam.org

The organizers are gathering a panel of internationally-renowned experts who will be leading discussions in their respected areas.

See the congress website for the latest updates:
apsr2019.com

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