Publishing TB research: The best science for better lives

Diana Stanley – Deputy Editor

March 20th 2024

Publishing TB research

- What we look for when assessing research
- Peer review process
- Submissions at The Lancet Respiratory Medicine
- Types of TB content we publish
- Where does the research come from?
- The Lancet Group
- Questions

- **Selecting content that will change or impact on research, clinical practice, and public health policies**
- **Novel and interesting to readership**
- **Ensure timely and robust content through a quality peer review process**
- **Assess the methodology:**
    - **Study design**
    - **Endpoints and follow up**
    - **Meets guidelines (CONSORT, STROBE, PRISMA)**
    - **Are data generalisable and limitations discussed?**

Publishing TB research – **An Editor's responsibility in peer review and publication**

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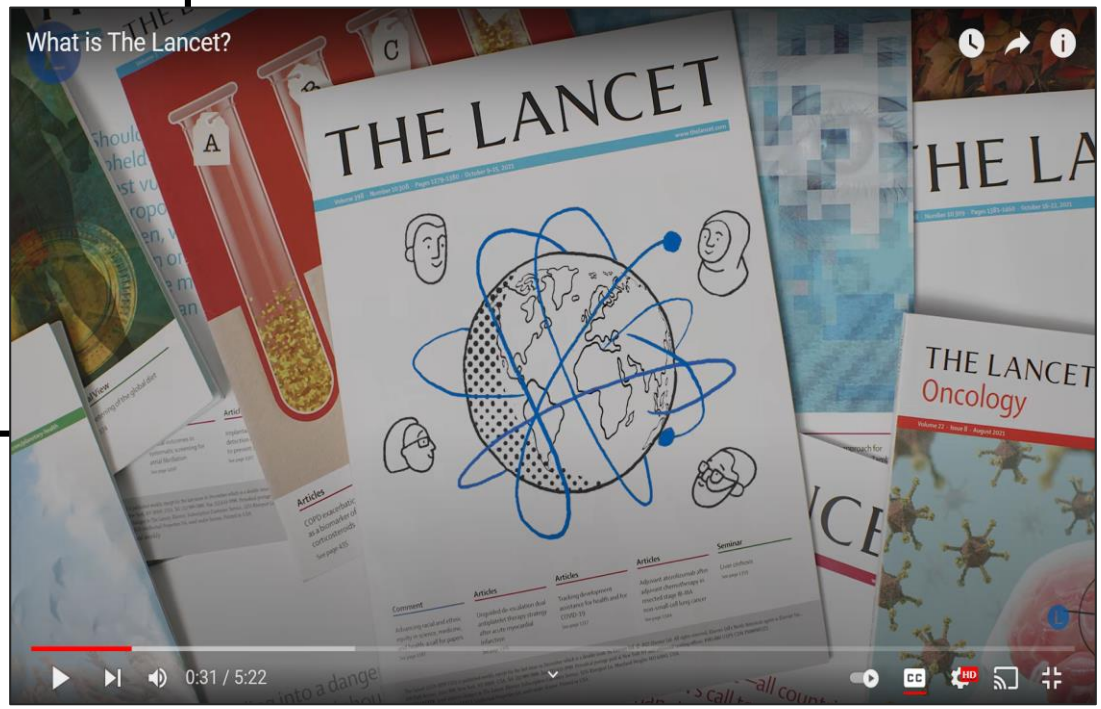
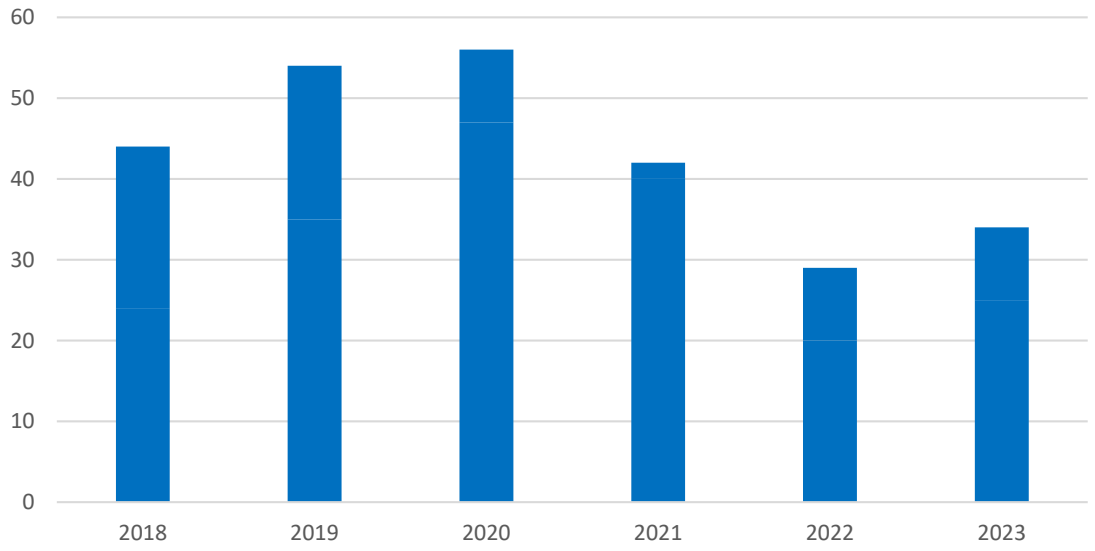


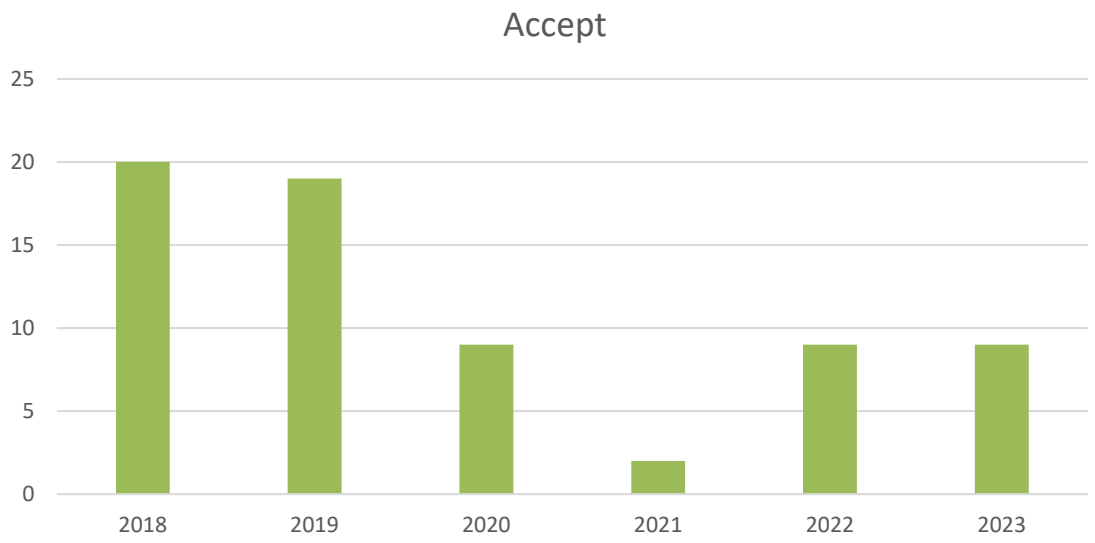
[The Lancet: journey of a paper]

TB submissions 2018-2023



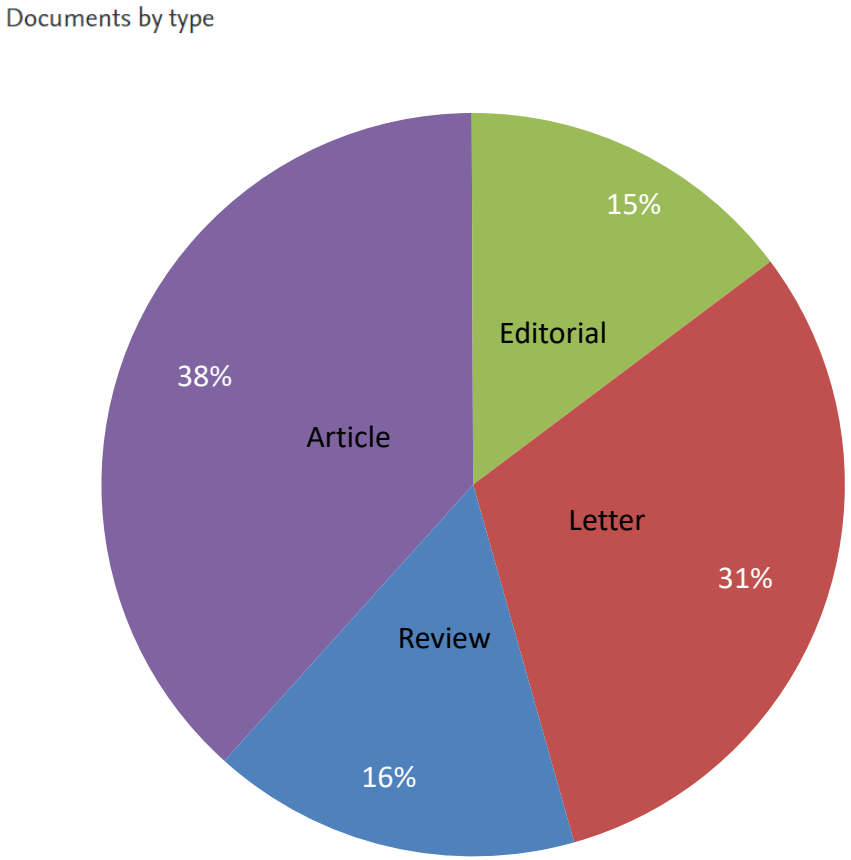
TB Submissions down about 30% post-pandemic

TB submissions accepted 2018-2023



2018 and 2019 slightly higher than normal due to a TB themed issue in 2018 and the update on TB commission in 2019

TB Published Content –2013 – 2024



Source: Scopus (14/3/24)

TB Content – Articles

Peer reviewed reports of original research that are likely to change clinical practice, policy or substantially change thinking about a disease. These include interventional clinical trials, observational studies, modelling studies, and meta-analyses. **Original research** papers are always externally peer reviewed.

Articles

Xpert MTB/RIF Ultra and Xpert MTB/RIF for diagnosis of tuberculosis in an HIV-endemic setting with a high burden of previous tuberculosis: a two-cohort diagnostic accuracy study

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Summary

Background Xpert MTB/RIF Ultra (Ultra) is a new test for tuberculosis undergoing global roll-out. We assessed the performance of Ultra compared with Xpert MTB/RIF (Xpert) in an HIV-endemic setting where previous tuberculosis is frequent and current test performance is suboptimal.

Methods In this two-cohort diagnostic accuracy study, we used sputum samples from patients in South Africa to evaluate the accuracy of Ultra and Xpert against a single culture reference standard. For the first cohort (cohort A), we recruited adults (aged ≥18 years) with symptoms of presumptive tuberculosis at Scottsdene clinic in Cape Town, South Africa. We collected three sputum samples from each patient in cohort A, two at the first visit of which one was tested using Xpert and the other was tested using culture, and one sample the next morning which was tested using Ultra. In a separate cohort of patients with presumptive tuberculosis and recent previous tuberculosis (≤2 years) who had submitted sputum samples to the National Health Laboratory Services (cohort B), decontaminated sediments were, after processing, randomly allocated (1:1) for testing with Ultra or Xpert. For both cohorts we calculated the sensitivity and specificity of Ultra and Xpert and evaluated the effects of different methods of interpreting Ultra trace results.

Findings Between Feb 6, 2016, and Feb 2, 2018, we recruited 302 people into cohort A, all of whom provided sputum samples and 239 were included in the head-to-head analyses of Ultra and Xpert. For cohort B, we collected sputum samples from eligible patients who had submitted samples between Dec 6, 2016, and Dec 21, 2017, to give a cohort of 831 samples, of which 352 were eligible for inclusion in analyses and randomly assigned to Ultra (n=173) or Xpert (n=179). In cohort A, Ultra gave more non-actionable results (not positive or negative) than did Xpert (28 [10%] 275 *vs* 14 [5%] 301; p=0·011). In the head-to-head analysis, in smear-negative patients, sensitivity of Ultra was 80% (95% CI 64–90) and of Xpert was 73% (57–85; p=0·45). Overall, specificity of Ultra was lower than that of Xpert (90% [84–94] *vs* 99% [95–100]; p=0·001). In cohort B, overall sensitivity was 92% (81–98) for Xpert versus 86% (73–95; p=0·36) for Ultra and overall specificity was 69% (60–77) for Ultra versus 84% (78–91; p=0·005) for Xpert. Ultra specificity estimates improved after reclassification of results with the lowest Ultra-positive semiquantitation category (trace) to negative (15% [8–22]). In cohort A, the positive predictive value (PPV) for Ultra was 78% (67–87) and for Xpert was 96% (87–99; p=0·004); in cohort B, the PPV for Ultra was 50% (43–57) and for Xpert was 70% (61–78; p=0·014). Ultra PPV estimates in previously treated patients were low: at 15% tuberculosis prevalence, half of Ultra-positive patients with presumptive tuberculosis would be culture negative, increasing to approximately 70% in patients with recent previous tuberculosis. In cohort B, 21 (28%) of 76 samples that were Ultra positive were rifampicin indeterminate (all trace) and, like cohort A, most were culture negative (19 [90%] of 21).

Interpretation In a setting with a high burden of previous tuberculosis, Ultra generated more non-actionable results and had diminished specificity compared with Xpert. In patients with recent previous tuberculosis, a quarter of Ultra-positive samples were indeterminate for rifampicin resistance and culture negative, suggesting that additional drug-resistance testing will probably be unsuccessful. Our data have implications for the handling of Ultra-positive results in patients with previous tuberculosis in high burden settings.

Funding South African Medical Research Council, the EDCTP2 program, and the Faculty of Medicine and Health Sciences, Stellenbosch University.

Introduction

Xpert MTB/RIF (Xpert) has been scaled-up for the diagnosis of tuberculosis and rifampicin resistance; however, Xpert performs suboptimally, especially in smear-negative sputum samples, which are frequently obtained from patients who are HIV positive.[1–3]

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TB Content – Reviews

Review - A definitive overview of a major topic or an update of knowledge in a narrower field of current interest. These can be disease-orientated, clinically focused overviews or reviews of health systems or health policy. These **evidence reviews** are always externally peer reviewed.

Personal View - These are opinion pieces that reflect an individual perception, involvement, or contribution to the field, and should be prepared in a similar way to a Review.

Personal View

Clinical trials of tuberculosis vaccines in the era of increased access to preventive antibiotic treatment

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Approximately 10·6 million people worldwide develop tuberculosis each year, representing a failure in epidemic control that is accentuated by the absence of effective vaccines to prevent infection or disease in adolescents and adults. Without effective vaccines, tuberculosis prevention has relied on testing for *Mycobacterium tuberculosis* infection and treating with antibiotics to prevent progression to tuberculosis disease, known as tuberculosis preventive treatment (TPT). Novel tuberculosis vaccines are in development and phase 3 efficacy trials are imminent. The development of effective, shorter, and safer TPT regimens has broadened the groups eligible for TPT beyond people with HIV and child contacts of people with tuberculosis; future vaccine trials will be undertaken in an era of increased TPT access. Changes in the prevention standard will have implications for tuberculosis vaccine trials of disease prevention, for which safety and sufficient accrual of cases are crucial. In this paper, we examine the urgent need for trials that allow the evaluation of new vaccines and fulfil the ethical duty of researchers to provide TPT. We observe how HIV vaccine trials have incorporated preventive treatment in the form of pre-exposure prophylaxis, propose trial designs that integrate TPT, and summarise considerations for each design in terms of trial validity, efficiency, participant safety, and ethics.

Introduction

An estimated 10·6 million people worldwide develop active tuberculosis disease each year, pointing to a serious unmet need for prevention.[1] Once infected with *Mycobacterium tuberculosis*, around 5–15% of people are estimated to develop active disease,[2] which requires 4–6 months of treatment with a multidrug regimen. Treatment of infection, also known as tuberculosis preventive treatment (TPT), reduces the risk of progression to active disease. For decades, prevention of tuberculosis disease has largely been limited to daily isoniazid monotherapy given for 6 months or more to people at highest risk of progressing from infection to disease: people living with HIV and children younger than 5 years of age who are contacts of people with tuberculosis.[3] First introduced in 1921[4] and still the only licensed vaccine against *M tuberculosis*, the Bacille Calmette-Guérin (BCG) vaccine given at birth protects infants and young children against severe forms of tuberculosis, but vaccination offers inconsistent protection against pulmonary tuberculosis in adolescents and adults, who account for most *M tuberculosis* transmission. Thus, BCG at birth has not resulted in long-term protection and reductions in tuberculosis incidence at a population level. Moreover, our understanding of the correlates of protection required to advance vaccine development remains incomplete. Eliminating tuberculosis in line with the WHO End TB Strategy 2035 target—to reduce the incidence rate of tuberculosis by 90% compared with 2015 levels—will involve developing and introducing safe, effective, and affordable new tuberculosis vaccines.[5]

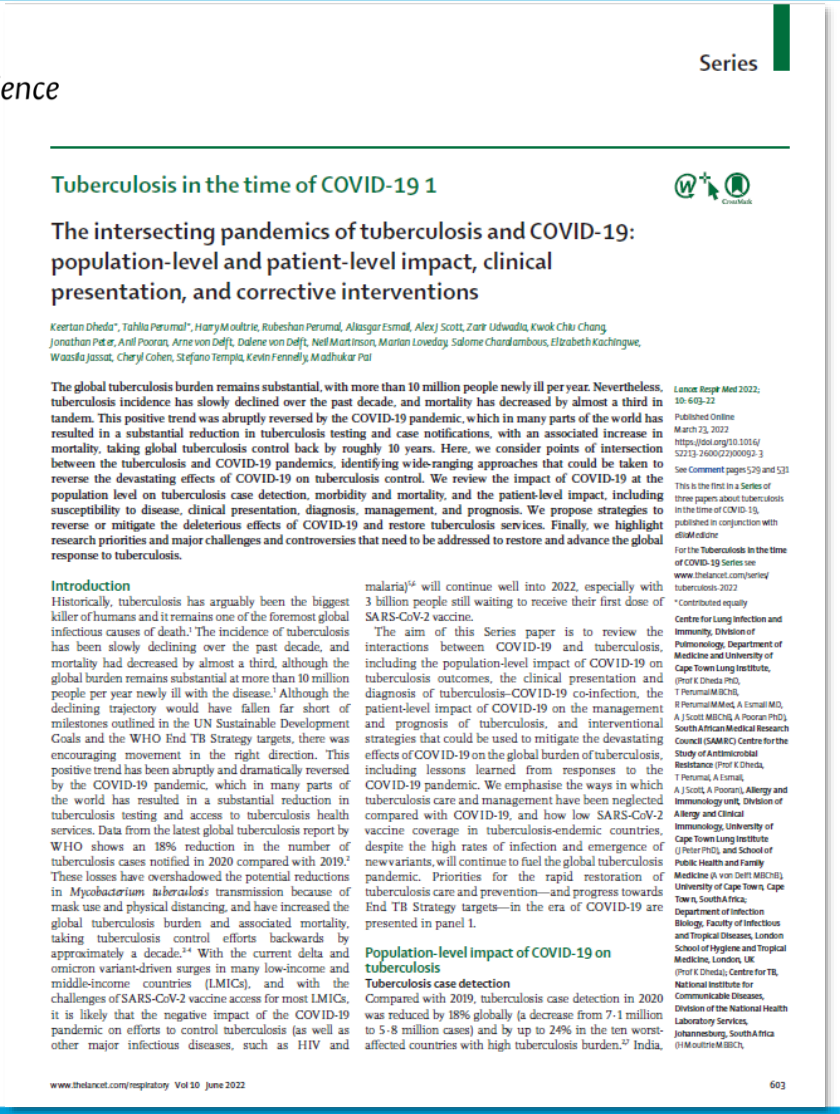
In the past 5 years, advances have been made in preclinical and clinical tuberculosis vaccine development; candidates, approaches, and bottlenecks in tuberculosis vaccine development have been reviewed extensively elsewhere.[6–8] A phase 2b trial[9] in South Africa showed that revaccination with BCG in adolescents who had not been exposed to *M tuberculosis* and were not infected with HIV had an estimated efficacy of about 45% (95% CI 6·4–68·1) against sustained *M tuberculosis* infection, indicated by serial positive interferon-γ release assays (IGRA) suggesting infection with *M tuberculosis*. In addition, the subunit tuberculosis vaccine candidate M72/AS01$_E$ conferred 49·7% (95% CI 2·1–74·2) protection against the development of bacteriologically confirmed pulmonary tuberculosis disease for 3 years after vaccination in a phase 2b trial among adults in Kenya, South Africa, and Zambia who were infected with *M tuberculosis* but not HIV.[10] These trials were done during the time in which national and WHO guidelines recommended TPT for limited high-risk groups. As such, tuberculosis vaccine trials that enrolled adolescents and adults without HIV infection did not provide TPT to participants who entered trials with reactive IGRA results suggestive of *M tuberculosis* infection, people who recorded IGRA conversion during the study, or people with recent exposure to tuberculosis. However, since 2018, WHO has expanded TPT recommendations to include adults and adolescents without HIV infection at highest risk of disease progression from recent exposure to *M tuberculosis*, and endorsed a wider array of TPT regimens, including several shorter and simpler regimens as an alternative to at least 6 months of isoniazid monotherapy, with improved safety, tolerability, and adherence.[3] National programmes are increasingly adopting the new guidance, in addition to considering TPT for individuals in congregate settings, health-care workers, and individuals with clinical risk factors that heighten the risk of tuberculosis disease, such as people with diabetes. Developers, sponsors, and trialists of new tuberculosis vaccines will need to consider this changed but still evolving standard of prevention in the design

TB Content – series

eBioMedicine
Part of THE LANCET *Discovery Science*

THE LANCET
Respiratory Medicine

Commissioned by our editors, or in partnership with academic institutions, *The Lancet Respiratory Medicine*'s Series include two or more Reviews that take an in-depth look at a topic of special interest, explore new research, and advance the fields of respiratory medicine, critical care and health policy.



Series

Tuberculosis in the time of COVID-19 1

The intersecting pandemics of tuberculosis and COVID-19: population-level and patient-level impact, clinical presentation, and corrective interventions

Keertan Dheda*, Tahlia Perumal*, Harry Moultrie, Rubeshan Perumal, Aliasgar Esmail, Alex J Scott, Zarir Udwadia, Kwok Chiu Chang, Jonathan Peter, Anil Pooran, Arne von Delft, Dalene von Delft, Neil Martinson, Marian Loveday, Salome Charalambous, Elizabeth Kachingwe, Waasila Jassat, Cheryl Cohen, Stefano Tempia, Kevin Fennelly, Madhukar Pai

The global tuberculosis burden remains substantial, with more than 10 million people newly ill per year. Nevertheless, tuberculosis incidence has slowly declined over the past decade, and mortality has decreased by almost a third in tandem. This positive trend was abruptly reversed by the COVID-19 pandemic, which in many parts of the world has resulted in a substantial reduction in tuberculosis testing and case notifications, with an associated increase in mortality, taking global tuberculosis control back by roughly 10 years. Here, we consider points of intersection between the tuberculosis and COVID-19 pandemics, identifying wide-ranging approaches that could be taken to reverse the devastating effects of COVID-19 on tuberculosis control. We review the impact of COVID-19 at the population level on tuberculosis case detection, morbidity and mortality, and the patient-level impact, including susceptibility to disease, clinical presentation, diagnosis, management, and prognosis. We propose strategies to reverse or mitigate the deleterious effects of COVID-19 and restore tuberculosis services. Finally, we highlight research priorities and major challenges and controversies that need to be addressed to restore and advance the global response to tuberculosis.

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See Comment pages 529 and 531
This is the first in a Series of three papers about tuberculosis in the time of COVID-19, published in conjunction with eBioMedicine
For the Tuberculosis in the time of COVID-19 Series see www.thelancet.com/series/tuberculosis-2022

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Introduction

Historically, tuberculosis has arguably been the biggest killer of humans and it remains one of the foremost global infectious causes of death.[1] The incidence of tuberculosis has been slowly declining over the past decade, and mortality had decreased by almost a third, although the global burden remains substantial at more than 10 million people per year newly ill with the disease.[1] Although the declining trajectory would have fallen far short of milestones outlined in the UN Sustainable Development Goals and the WHO End TB Strategy targets, there was encouraging movement in the right direction. This positive trend has been abruptly and dramatically reversed by the COVID-19 pandemic, which in many parts of the world has resulted in a substantial reduction in tuberculosis testing and access to tuberculosis health services. Data from the latest global tuberculosis report by WHO shows an 18% reduction in the number of tuberculosis cases notified in 2020 compared with 2019.[2] These losses have overshadowed the potential reductions in *Mycobacterium tuberculosis* transmission because of mask use and physical distancing, and have increased the global tuberculosis burden and associated mortality, taking tuberculosis control efforts backwards by approximately a decade.[3,4] With the current delta and omicron variant-driven surges in many low-income and middle-income countries (LMICs), and with the challenges of SARS-CoV-2 vaccine access for most LMICs, it is likely that the negative impact of the COVID-19 pandemic on efforts to control tuberculosis (as well as other major infectious diseases, such as HIV and malaria)[5,6] will continue well into 2022, especially with 3 billion people still waiting to receive their first dose of SARS-CoV-2 vaccine.

The aim of this Series paper is to review the interactions between COVID-19 and tuberculosis, including the population-level impact of COVID-19 on tuberculosis outcomes, the clinical presentation and diagnosis of tuberculosis–COVID-19 co-infection, the patient-level impact of COVID-19 on the management and prognosis of tuberculosis, and interventional strategies that could be used to mitigate the devastating effects of COVID-19 on the global burden of tuberculosis, including lessons learned from responses to the COVID-19 pandemic. We emphasise the ways in which tuberculosis care and management have been neglected compared with COVID-19, and how low SARS-CoV-2 vaccine coverage in tuberculosis-endemic countries, despite the high rates of infection and emergence of new variants, will continue to fuel the global tuberculosis pandemic. Priorities for the rapid restoration of tuberculosis care and prevention—and progress towards End TB Strategy targets—in the era of COVID-19 are presented in panel 1.

Population-level impact of COVID-19 on tuberculosis

Tuberculosis case detection

Compared with 2019, tuberculosis case detection in 2020 was reduced by 18% globally (a decrease from 7·1 million to 5·8 million cases) and by up to 24% in the ten worst-affected countries with high tuberculosis burden.[2,7] India,

TB Content – Editorials

Editorials are the voice of each Lancet journal, raising awareness on clinical and global health topics and health-related matters. These are written in-house by the journal's editorial team and are signed by the journal. **Editorials** are not externally peer reviewed.

Editorial

Editorial

Editorial

Tackling tuberculosis: what lies beneath the surface?

World TB Day on March 24, 2022, provided an opportunity to raise awareness of the devastating health, social, and economic impacts of tuberculosis—the world's second leading infectious killer after COVID-19—and to consider what is needed to strengthen care and control efforts to end tuberculosis. The COVID-19 pandemic has reversed years of progress in reducing the global burden of tuberculosis, with case notifications falling substantially and mortality increasing for the first time in over a decade. A renewed commitment is needed to understand the scale of the problem, to identify priorities and provide resources for the rapid restoration of tuberculosis services, and to support new efforts to reach many more individuals with tuberculosis disease.

In a Series paper in this issue of *The Lancet Respiratory Medicine*, Keertan Dheda and colleagues identify points of intersection between the COVID-19 and tuberculosis pandemics, and propose strategies to address the deleterious effects of COVID-19 and advance tuberculosis care and prevention. In many parts of the world, COVID-19 has resulted in a substantial reduction in tuberculosis testing and access to health services, but new opportunities to tackle tuberculosis have also emerged. On April 20, 2022, the WHO Global TB Programme published its second, consolidated report of country successes in mitigating the impact of the COVID-19 pandemic on tuberculosis services. The report describes steps taken to maintain and improve tuberculosis service provision, including examples of dual testing for tuberculosis and SARS-CoV-2 infection, screening for tuberculosis as part of SARS-CoV-2 vaccination programmes, and use of digital technologies to support treatment adherence and reduce health facility visits. Substantial investment will be needed to scale up tuberculosis case finding, prevention, and treatment in the time of COVID-19, especially in lower-income settings where SARS-CoV-2 vaccines have yet to make their mark.

Armed conflicts, natural disasters, and the pervasive effects of poverty are among the many other challenges that threaten progress towards tuberculosis elimination. Tuberculosis control requires a tailored, flexible, multi-pronged approach and understanding of the local setting to reduce the individual and population impact of disease and mitigate the risk of drug resistance. However, as Rein Houben and colleagues emphasise in a Comment in this issue, we are currently missing not only millions of people who would reach the standard threshold of sputum-positive clinical or subclinical tuberculosis, but potentially millions more who have crossed the threshold of *Mycobacterium tuberculosis* transmission and could be detected by other methods (eg, induced sputum or bioaerosol sampling). In addition, millions of individuals with non-infectious disease (eg, detectable on chest x-ray) who already have disease pathology and who could progress to classic infectious disease are currently unmeasured and therefore unserved. To reach beyond the tip of iceberg and make major advances in the fight against tuberculosis, comprehensive and feasible approaches to case finding, prevention, and treatment are needed that consider the full spectrum of disease—applicable in the local context with steps to understand and address local barriers to progress.

An important part of the solution will be the wider implementation of available, evidence-based methods to manage infection and halt *M tuberculosis* transmission. For example, a new publication from WHO highlights the potential value of programmes for infection prevention and control. Another key component will be research advances to develop and deliver new approaches to tuberculosis prevention, diagnosis, and treatment across the disease spectrum. We welcome the announcement from the US National Institute of Allergy and Infectious Diseases of four new grant awards—with total funding in the first year of approximately US$4·3 million—to establish Tuberculosis Research Advancement Centers, which will support the development of a new generation of tuberculosis researchers. Investment in research, including initiatives to provide high-quality training to researchers from countries with a high tuberculosis burden—who could subsequently apply and share their skills where they are needed most—will help to secure meaningful progress towards tuberculosis elimination.

Ultimately, new knowledge and a growing range of evidence-based tools will make a substantial difference only if they are backed by the political will, advocacy, and investment required to allow their application. Global leaders must honour their commitment to end tuberculosis with a strong, unified global response that matches the huge scale of the devastation currently wrought by tuberculosis. ■ *The Lancet Respiratory Medicine*

For the **paper by Dheda and colleagues** see Series page 603
For the **WHO report of country successes stories** see https://www.who.int/publications/i/item/9789240048232
For more on the **effects of armed conflict** see Comment page 533
For more on the **social determinants of tuberculosis** see Comment *Lancet* 2018; **391**: 1129–32
For more on the **missing millions** see Comment page 537
For the **WHO summary on infection prevention and control** see https://www.who.int/publications/m/item/global-report-on-infection-prevention-and-control
For more on **sputum-free diagnostics** see *eBioMedicine* 2022; **78**: 103939
For more on **treatment across the disease spectrum** see *eBioMedicine* 2022; **78**: 103928
For the **NIAID announcement** see https://www.nih.gov/news-events/news-releases/nih-funds-new-tuberculosis-research-advancement-centers

TB Content – comments

Most Comments are commissioned by journal editors, but spontaneous Comments are considered on topics relevant to a general medical audience, including events within the past month, or in the near future. These **expert opinion** pieces are not normally externally peer reviewed.

Advances in tuberculosis control during the past decade

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Tuberculosis, the leading cause of death from a curable infectious disease, is a major threat to human health globally. WHO estimated that 10·6 million new cases of tuberculosis and 1·6 million tuberculosis-associated deaths occurred in 2021. The COVID-19 pandemic disrupted health systems and exposed prevailing deficiencies in tuberculosis-control programmes globally, reversing the hard-won reduction of global tuberculosis incidence observed until 2020. Nevertheless, the past decade has celebrated several major scientific breakthroughs that could advance the achievement of a tuberculosis-free world.

Mathematical models suggest that to achieve a substantial reduction in tuberculosis incidence and mortality, widescale implementation of multiple strategies is required. These strategies include effective tuberculosis prevention to reduce latent infection; augmented case-finding and improved linkage to tuberculosis care to shorten the period of infectiousness; and context-specific infection control measures that consider population mobility, trust in health-care providers and health institutions, force of tuberculosis transmission, and prevalence of HIV.

The period between the onset of tuberculosis disease and a tuberculosis diagnosis is characterised by increased infectiousness and risk of tuberculosis transmission, with greater transmission generated by index cases that are smear positive. Although the excess risk of tuberculosis transmission within households has been well characterised, tuberculosis transmission in high tuberculosis-burden or HIV-burden settings is also likely to occur in other congregate settings, including health-care facilities, recreational hubs, and transportation nodal points where individuals might cluster in space and over time. Current and planned research seeks to evaluate tuberculosis-transmission risk through breath aerosols for the detection of infectiousness among clinical and subclinical patients with tuberculosis and through geospatial mapping to identify tuberculosis hotspots, which might offer opportunities for targeted interventions to halt transmission.[1]

Achieving tuberculosis eradication requires sensitive sputum-based and non-sputum-based diagnostic tools capable of diagnosing latent tuberculosis, predicting the risk of progression to active disease, and identifying *Mycobacterium tuberculosis* in individuals who are infectious. The widescale implementation of highly sensitive next-generation molecular tools for *M tuberculosis* detection, such as the Xpert MTB/RIF Ultra, provides the potential to identify subclinical and clinical tuberculosis, making it suitable for both active and passive case finding.[2,3] However, improved case detection without linkage to care limits the effects of passive tuberculosis case finding on tuberculosis morbidity and mortality.[4] Preventive tuberculosis therapy shows incontrovertible individual-level benefit, but epidemiological and context-specific health system factors substantially moderate its effect at the population level.[5] Any future tuberculosis prevention and treatment strategies should use the contemporary, although still incomplete, understanding of tuberculosis pathogenesis that has focused away from the dichotomy of latent and active disease to a more detailed perspective of the dynamic, multistate, bidirectional spectrum of latent, incipient, subclinical, and clinically active tuberculosis.[6]

After two decades of reliance on a multidrug, 6-month, drug-sensitive tuberculosis regimen, compelling evidence of a new regimen for tuberculosis treatment shortening has emerged.[7] However, despite a WHO recommendation, restricted and inequitable access to component drugs, unknown safety and efficacy during antiretroviral therapy coadministration, and the lack of a safety and tolerability advantage over previous regimens have delayed the implementation and scale-up of this novel 4-month regimen for drug-sensitive tuberculosis. Diagnostic and treatment gaps are even larger for drug-resistant tuberculosis, despite increasing incidence rates globally. Rapid resistance profiling and access to safe, effective, and shortened treatment regimens are key to reducing drug-resistant tuberculosis incidence rates, prevalence rates, morbidity, and mortality. Rapid molecular diagnostics suitable for implementation in low-resource settings with high tuberculosis burden or HIV burden are emerging and could produce treatment-informing results within 90 min.[8] WHO-endorsed, all-oral, shorter, highly effective drug-resistant tuberculosis regimens represent substantial progress in the treatment of drug-resistant tuberculosis, in which previous

TB Content – Correspondence

Our readers' reflections on content published in the Lancet journals or on other topics of general interest to our readers. These **letters** are not normally externally peer reviewed.

Correspondence

Outbreak of multidrug-resistant tuberculosis on Daru Island: an update

The unprecedented outbreak of drug-resistant tuberculosis (DR-TB) on Daru Island, highlighted by Jennifer Furin and Helen Cox in their commentary,[1] is a major priority for the Government of Papua New Guinea.[2] We wish to highlight the substantial progress made since the emergency response team for drug-resistant tuberculosis was formed.

The incidence of tuberculosis in Papua New Guinea is very high, the highest in the western Pacific region and tenth highest globally.[3] Western Province is the largest, most geographically diverse, arguably the most remote, and one of the poorest provinces in Papua New Guinea. Daru is the provincial capital, located on a small island. The health system in the province and in Daru specifically is characteristic of a low-resource environment with limited financial and human resources, able to undertake little more than basic preventive and curative health services. Addressing the multidrug-resistant tuberculosis (MDR-TB) epidemic, therefore, not only requires immediate and effective tuberculosis control interventions, but equally strong efforts to strengthen the health system.

Furin and Cox mentioned that "the national and international response to Daru has been inadequate".[1] This statement does not do justice to response efforts so far by the Government of Papua New Guinea and its partners: Department of Foreign Affairs and Trade of Australia, Burnet Institute, World Vision International, and WHO. The coordinated approach includes a multidrug and extensively DR-TB response taskforce established in September 2014, led by the Deputy Secretary of the National Department of Health; a National Strategic Plan for tuberculosis 2015–2020 endorsed by the National Economic Council of the Government of Papua New Guinea; Government funding for all tuberculosis drugs including those that are MDR-TB secured; and a technically sound provincial MDR-TB response plan is being implemented, led by the province with assistance of all partners.

The Government of Papua New Guinea and WHO jointly organised an international meeting on Nov 25, 2015, to reach out to the global community for their support.[2] Additional funds from the Government of Papua New Guinea were released in January, 2016, to address the outbreak in Daru, with more Government funding committed later in 2016. The joint Government of Papua New Guinea and partner efforts have resulted in substantial progress with improvements in diagnosis, treatment, and care for patients with drug-resistant tuberculosis in Daru.[4] The case detection of drug-resistant tuberculosis has increased (61 cases in 2013 and 120 cases in 2015), all diagnosed patients are treated in accordance with international standards, and the strengthening of case management systems for all tuberculosis (including drug resistant tuberculosis) has markedly improved retention in care. Five community treatment sites run by local health workers and treatment supporters were recently established and are showing increased treatment adherence and minimal loss to follow-up. These sites put patients at the centre of care and contribute to breaking stigma in the community.

Addressing the MDR-TB outbreak in Daru requires long-term support and further investment that will also strengthen health services. The Government of Papua New Guinea welcomes further international funding to support its ongoing response.

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PK is the Secretary of Health (National Department of Health) in Papua New Guinea. PD is the Deputy Secretary of Health and Chair of emergency response team for drug resistant tuberculosis in Papua New Guinea. SB is the executive manager of Public Health of the National Department of Health in Papua New Guinea. We declare no competing interests.

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1 Furin J, Cox H. Outbreak of multidrug-resistant tuberculosis on Daru Island. *Lancet Respir Med* 2016; **4**: 347–49.
2 Papua New Guinea Department of Health, WHO. Drug resistant TB: an extraordinary situation requires extraordinary measure. https://www.burnet.edu.au/system/asset/file/2033/Joint_Statement_TB-Mtg_25Nov2015_1_.pdf (accessed March 7, 2016).
3 WHO. Global Tuberculosis Report 2015. Geneva: World Health Organization, 2015
4 Updates on situation of drug-resistant tuberculosis in Papua New Guinea, with special emphasis on Daru Island. http://www.wpro.who.int/papuanewguinea/areas/tb_leprosy/daru_update/en/ (accessed on March 6, 2016).

TB Content – News and Spotlight

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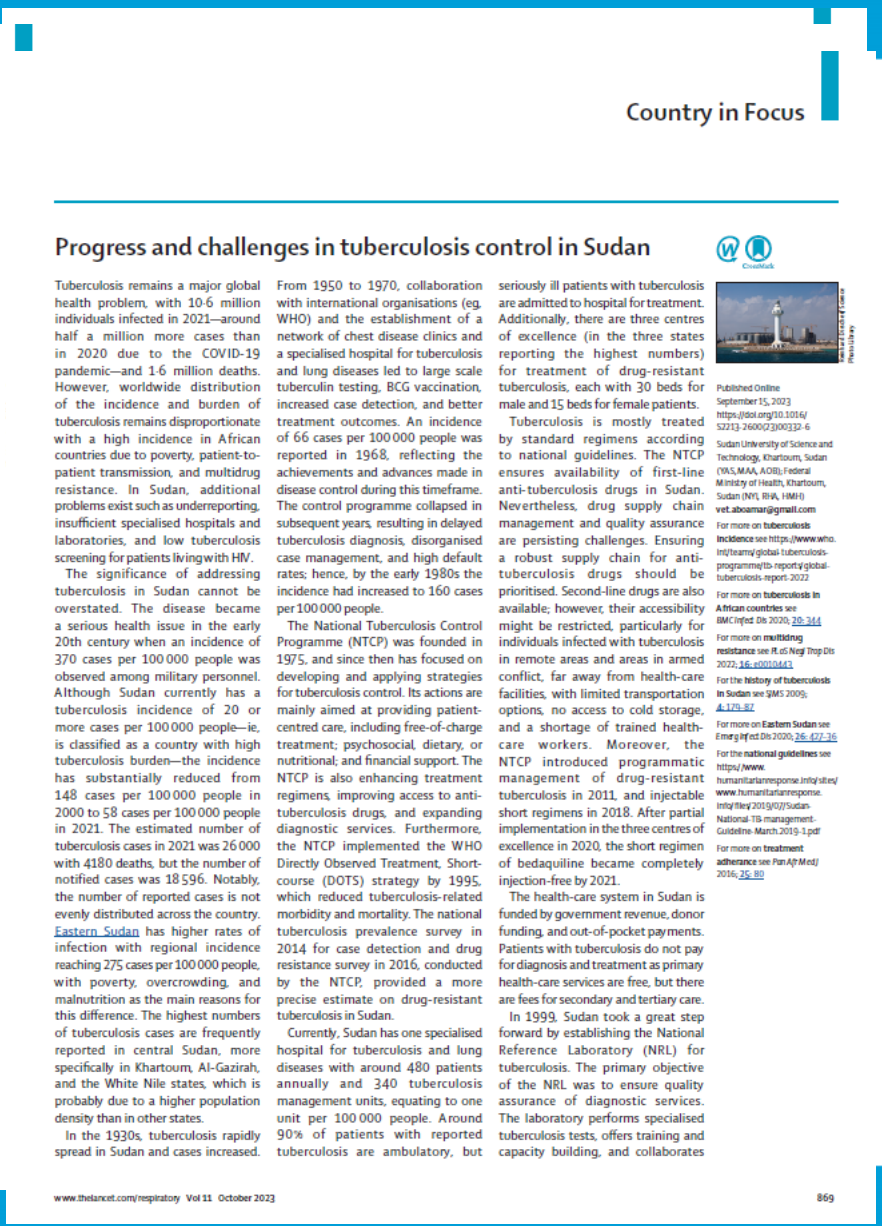
Spotlight pieces look at health and medicine within society, including book, film, play, and exhibit reviews, as well as pieces written by individuals with lived experience. These pieces are commissioned by journal editors. These **opinion pieces** are not externally peer reviewed.



Country in Focus

Progress and challenges in tuberculosis control in Sudan

Tuberculosis remains a major global health problem, with 10·6 million individuals infected in 2021—around half a million more cases than in 2020 due to the COVID-19 pandemic—and 1·6 million deaths. However, worldwide distribution of the incidence and burden of tuberculosis remains disproportionate with a high incidence in African countries due to poverty, patient-to-patient transmission, and multidrug resistance. In Sudan, additional problems exist such as underreporting, insufficient specialised hospitals and laboratories, and low tuberculosis screening for patients living with HIV.

The significance of addressing tuberculosis in Sudan cannot be overstated. The disease became a serious health issue in the early 20th century when an incidence of 370 cases per 100 000 people was observed among military personnel. Although Sudan currently has a tuberculosis incidence of 20 or more cases per 100 000 people—ie, is classified as a country with high tuberculosis burden—the incidence has substantially reduced from 148 cases per 100 000 people in 2000 to 58 cases per 100 000 people in 2021. The estimated number of tuberculosis cases in 2021 was 26 000 with 4180 deaths, but the number of notified cases was 18 596. Notably, the number of reported cases is not evenly distributed across the country. Eastern Sudan has higher rates of infection with regional incidence reaching 275 cases per 100 000 people, with poverty, overcrowding, and malnutrition as the main reasons for this difference. The highest numbers of tuberculosis cases are frequently reported in central Sudan, more specifically in Khartoum, Al-Gazirah, and the White Nile states, which is probably due to a higher population density than in other states.

In the 1930s, tuberculosis rapidly spread in Sudan and cases increased. From 1950 to 1970, collaboration with international organisations (eg, WHO) and the establishment of a network of chest disease clinics and a specialised hospital for tuberculosis and lung diseases led to large scale tuberculin testing, BCG vaccination, increased case detection, and better treatment outcomes. An incidence of 66 cases per 100 000 people was reported in 1968, reflecting the achievements and advances made in disease control during this timeframe. The control programme collapsed in subsequent years, resulting in delayed tuberculosis diagnosis, disorganised case management, and high default rates; hence, by the early 1980s the incidence had increased to 160 cases per 100 000 people.

The National Tuberculosis Control Programme (NTCP) was founded in 1975, and since then has focused on developing and applying strategies for tuberculosis control. Its actions are mainly aimed at providing patient-centred care, including free-of-charge treatment; psychosocial, dietary, or nutritional; and financial support. The NTCP is also enhancing treatment regimens, improving access to anti-tuberculosis drugs, and expanding diagnostic services. Furthermore, the NTCP implemented the WHO Directly Observed Treatment, Short-course (DOTS) strategy by 1995, which reduced tuberculosis-related morbidity and mortality. The national tuberculosis prevalence survey in 2014 for case detection and drug resistance survey in 2016, conducted by the NTCP, provided a more precise estimate on drug-resistant tuberculosis in Sudan.

Currently, Sudan has one specialised hospital for tuberculosis and lung diseases with around 480 patients annually and 340 tuberculosis management units, equating to one unit per 100 000 people. Around 90% of patients with reported tuberculosis are ambulatory, but seriously ill patients with tuberculosis are admitted to hospital for treatment. Additionally, there are three centres of excellence (in the three states reporting the highest numbers) for treatment of drug-resistant tuberculosis, each with 30 beds for male and 15 beds for female patients.

Tuberculosis is mostly treated by standard regimens according to national guidelines. The NTCP ensures availability of first-line anti-tuberculosis drugs in Sudan. Nevertheless, drug supply chain management and quality assurance are persisting challenges. Ensuring a robust supply chain for anti-tuberculosis drugs should be prioritised. Second-line drugs are also available; however, their accessibility might be restricted, particularly for individuals infected with tuberculosis in remote areas and areas in armed conflict, far away from health-care facilities, with limited transportation options, no access to cold storage, and a shortage of trained health-care workers. Moreover, the NTCP introduced programmatic management of drug-resistant tuberculosis in 2011, and injectable short regimens in 2018. After partial implementation in the three centres of excellence in 2020, the short regimen of bedaquiline became completely injection-free by 2021.

The health-care system in Sudan is funded by government revenue, donor funding, and out-of-pocket payments. Patients with tuberculosis do not pay for diagnosis and treatment as primary health-care services are free, but there are fees for secondary and tertiary care.

In 1999, Sudan took a great step forward by establishing the National Reference Laboratory (NRL) for tuberculosis. The primary objective of the NRL was to ensure quality assurance of diagnostic services. The laboratory performs specialised tuberculosis tests, offers training and capacity building, and collaborates

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For more on **tuberculosis incidence** see https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022

For more on **tuberculosis in African countries** see *BMC Infect Dis* 2020; 20: 344

For more on **multidrug resistance** see *PLoS Negl Trop Dis* 2022; 16: e0010443

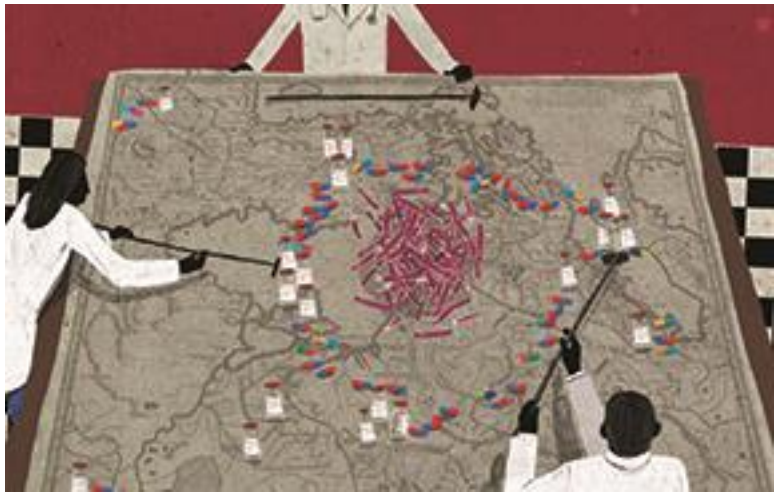
For the **history of tuberculosis in Sudan** see *SJMS* 2009; 4: 179–87

For more on **Eastern Sudan** see *Emerg Infect Dis* 2020; 26: 427–36

For the **national guidelines** see https://www.humanitarianresponse.info/sites/www.humanitarianresponse.info/files/2019/07/Sudan-National-TB-management-Guideline-March-2019-1.pdf

For more on **treatment adherance** see *Pan Afr Med J* 2016; 25: 80

TB content - Commissions



Topics for Commissions are selected by our editors, who work with academic partners to identify the most pressing issues in medicine and global health, with the aim of producing recommendations to change public policy or improve practice. Author groups are formed in collaboration between the lead Commissioners and editor representing a broad range of international expertise. These **in-depth reports** are usually conducted over 2-3 years and are always externally peer reviewed.

Commission Update

The Lancet Respiratory Medicine Commission: 2019 update: epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant and incurable tuberculosis

Keertan Dheda, Tawanda Gumbo, Gary Maartens, Kelly E Dooley, Megan Murray, Jennifer Furin, Edward A Nardell, Robin M Warren, on behalf of *The Lancet Respiratory Medicine* drug-resistant tuberculosis Commission group*

Lancet Respir Med 2019; 7: 820–26

*Members listed at end of report
Centre for Lung Infection and Immunity, Division of Pulmonology, Department of Medicine and UCT Lung Institute & South African Medical Research Council/University of Cape Town Centre for the Study of Antimicrobial Resistance, University of Cape Town, Cape Town, South Africa (Prof K Dheda PhD); Faculty of Infectious and Tropical Diseases, Department of Infection Biology, London School of Hygiene and Tropical Medicine, London, UK (Prof K Dheda); Center for Infectious Diseases Research and Experimental Therapeutics, Baylor Research Institute, Baylor University

The Lancet Respiratory Medicine **Commission on drug-resistant tuberculosis was published in 2017, which comprehensively reviewed and provided recommendations on various aspects of the disease. Several key new developments regarding drug-resistant tuberculosis are outlined in this Commission Update. The WHO guidelines on treating drug-resistant tuberculosis were updated in 2019 with a reclassification of second line anti-tuberculosis drugs. An injection-free MDR tuberculosis treatment regimen is now recommended. Over the past 3 years, advances in treatment include the recognition of the safety and mortality benefit of bedaquiline, the finding that the 9–11 month injectable-based 'Bangladesh' regimen was non-inferior to longer regimens, and promising interim results of a novel 6 month 3-drug regimen (bedaquiline, pretomanid, and linezolid). Studies of explanted lungs from patients with drug-resistant tuberculosis have shown substantial drug-specific gradients across pulmonary cavities, suggesting that alternative dosing and drug delivery strategies are needed to reduce functional monotherapy at the site of disease. Several controversies are discussed including the optimal route of drug administration, optimal number of drugs constituting a regimen, selection of individual drugs for a regimen, duration of the regimen, and minimal desirable standards of antibiotic stewardship. Newer rapid nucleic acid amplification test platforms, including point-of-care systems that facilitate active case-finding, are discussed. The rapid diagnosis of resistance to other drugs, (notably fluoroquinolones), and detection of resistance by targeted or whole genome sequencing will probably change the diagnostic landscape in the near future.**

Introduction

Addressing the drug-resistant tuberculosis epidemic is crucial to reduce morbidity, mortality, and economic and health-care related costs. Multidrug-resistant (MDR) tuberculosis, and resistance beyond MDR tuberculosis, poses a severe threat to global health security and is the only major airborne drug-resistant epidemic. The number of confirmed MDR cases over the past 5 years has almost doubled globally. Drug-resistant tuberculosis has a high mortality and is responsible for about one third of deaths related to antimicrobial resistance globally. Thus, it underpins the global antimicrobial resistance threat and the disease should be prioritised as a key component of the global antimicrobial resistance response. Drug-resistant tuberculosis is associated with devastating economic consequences and could cost the global economy about US$16·7 trillion between 2015 and 2050.

With the introduction of new drugs and molecular diagnostic technologies in the past 5 years, the field of drug-resistant tuberculosis has become an exciting and rapidly changing landscape. Results from clinical trials and systematic reviews,[1] updated guidance from the WHO,[2] and information about newer technologies prompted us to update *The Lancet Respiratory Medicine* Commission[3] on drug-resistant tuberculosis (appendix pp 2–6).

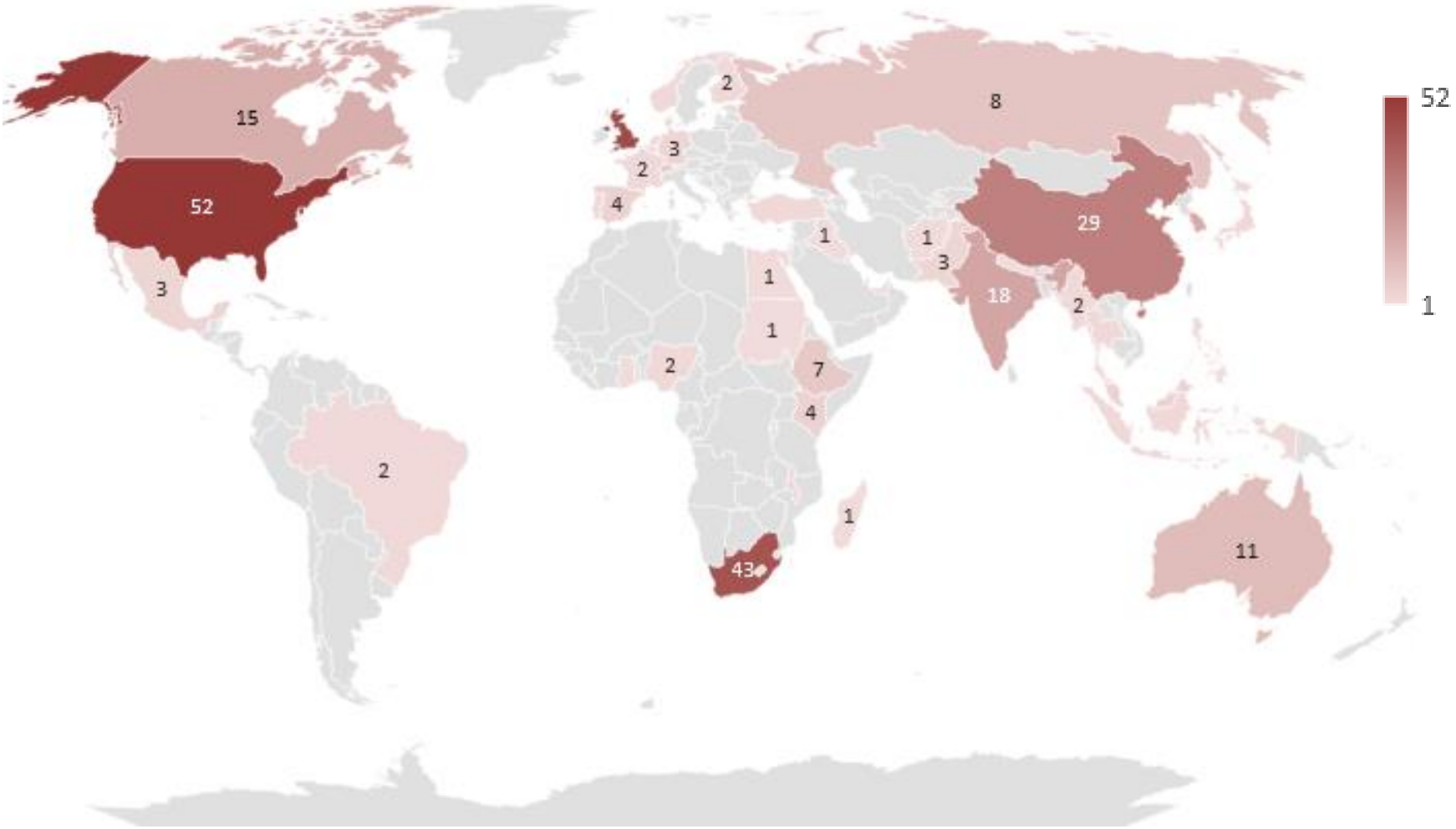
Key messages

- The WHO has published a new hierarchical classification of second-line anti-tuberculosis drugs broadly based on treatment-related outcomes
- An all-oral treatment regimen for multidrug-resistant (MDR) tuberculosis is now recommended
- Several observational studies have indicated that bedaquiline is relatively safe and associated with a reduction in mortality in patients with drug-resistant tuberculosis
- The optimal treatment duration and number of drugs in a regimen remains to be clarified
- Over the past 2 years, data indicate that a successful all-oral 6–9 month treatment regimen for MDR tuberculosis is a feasible and promising prospect
- Newer genomic approaches including the automated Xpert drug-resistant tuberculosis cartridge, whole genome sequencing, and targeted sequencing are likely to accelerate the time to diagnosis and selection of individualised regimens (impact studies are needed)
- Point-of-care portable battery-operated genomic tools (eg, Xpert Edge and Xpert Omni) will facilitate community-based active case finding of drug-resistant tuberculosis
- Emerging data about pharmacokinetic mismatch due to transcavitary and intralesional drug gradients suggest that optimal dosing and alternative drug delivery methods are needed to prevent resistance amplification and improve outcomes
- Several new approaches, including the evaluation of repurposed drugs and new compounds, hold promise to further improve drug-resistant tuberculosis outcomes in patients

Medical management of MDR tuberculosis

Given that second line injectable drugs are no longer recommended as part of a first-line multidrug-resistant (MDR) tuberculosis regimen for most patients, the current definition of extensively drug-resistant (XDR) tuberculosis has become less clinically relevant.[4] In the future, XDR tuberculosis will probably be defined on the

TB Submitted Content – Geographical Representation



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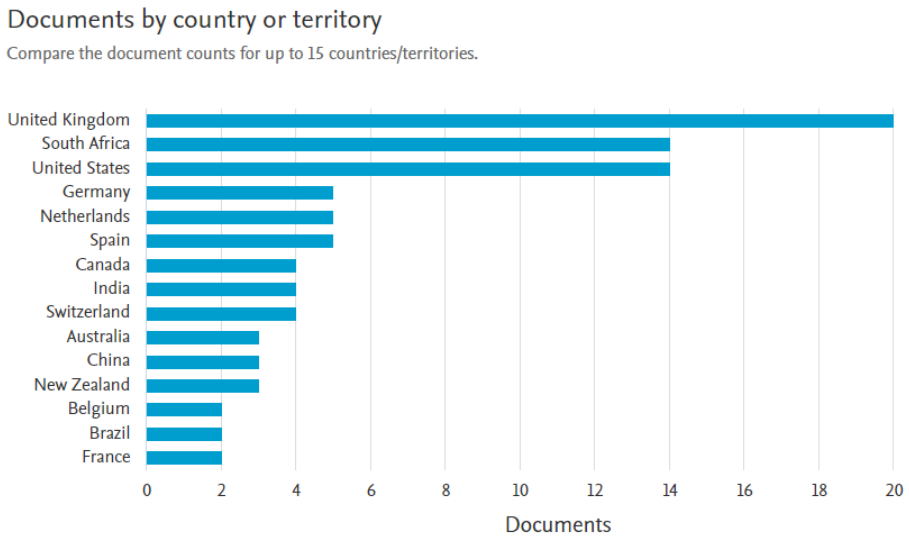

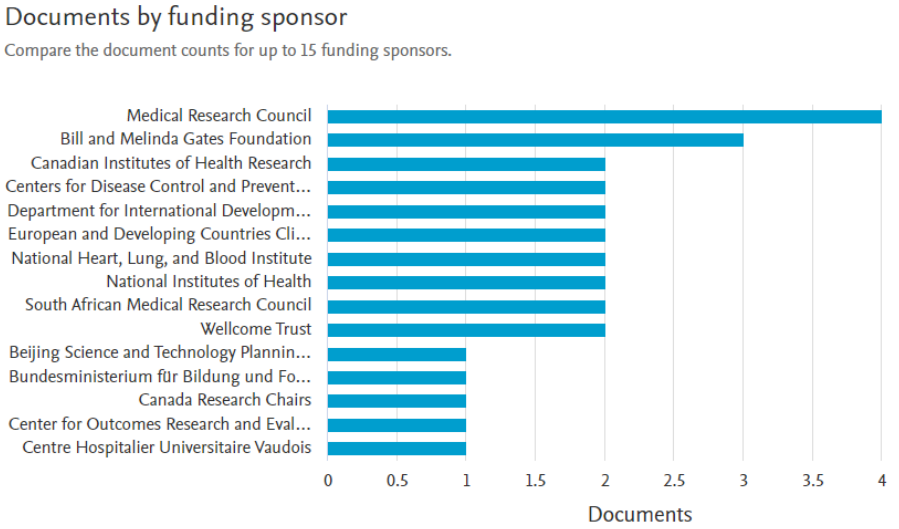

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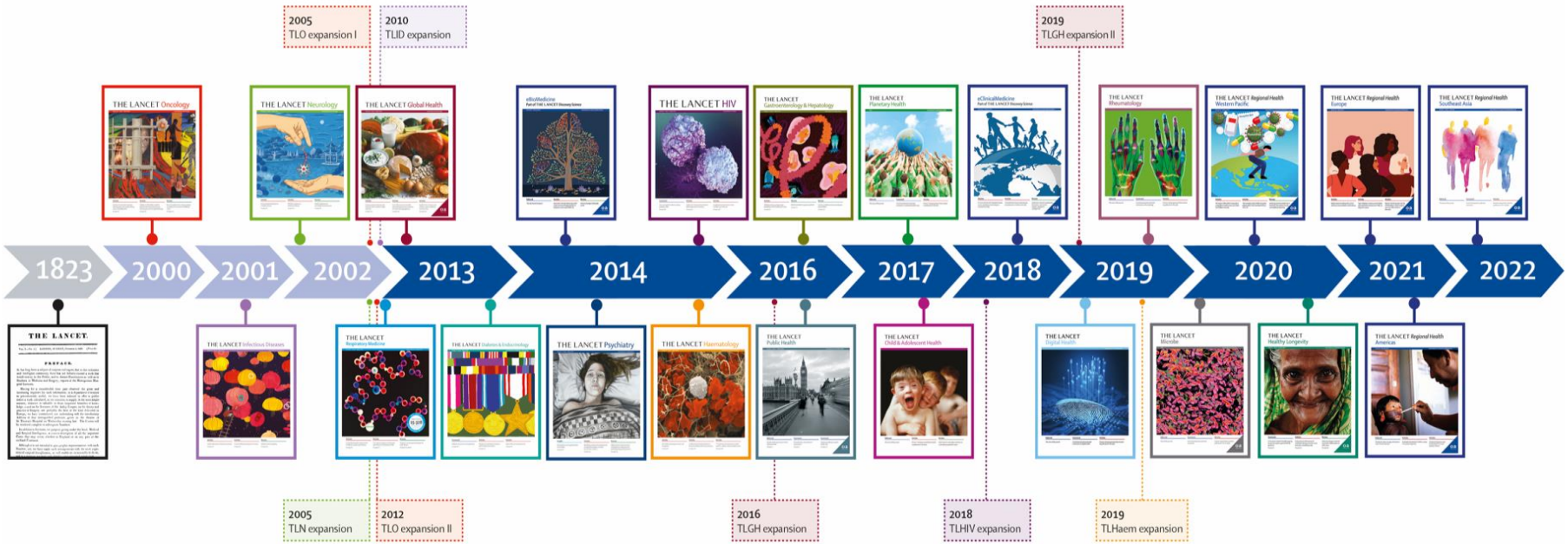

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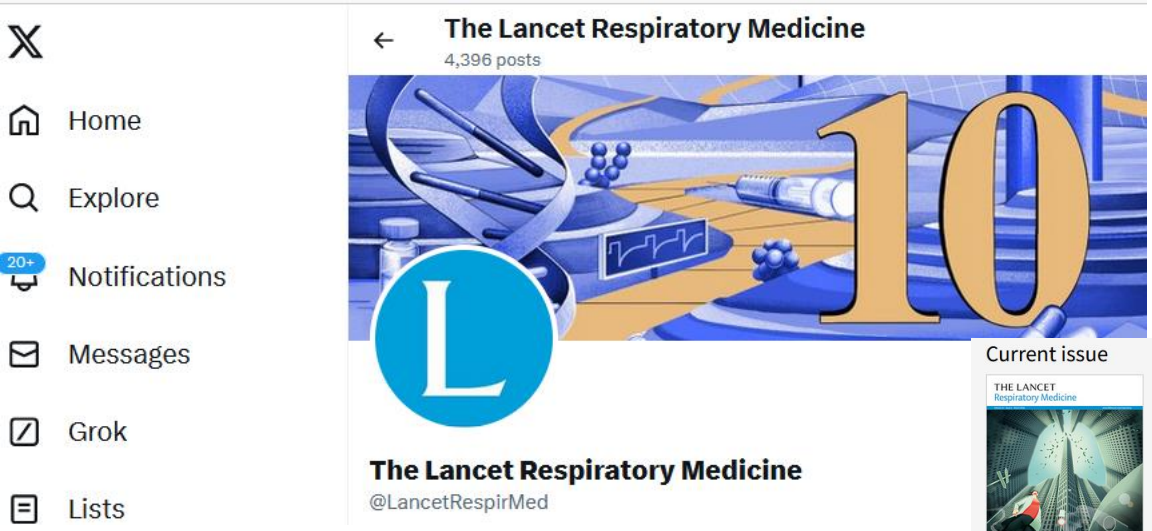
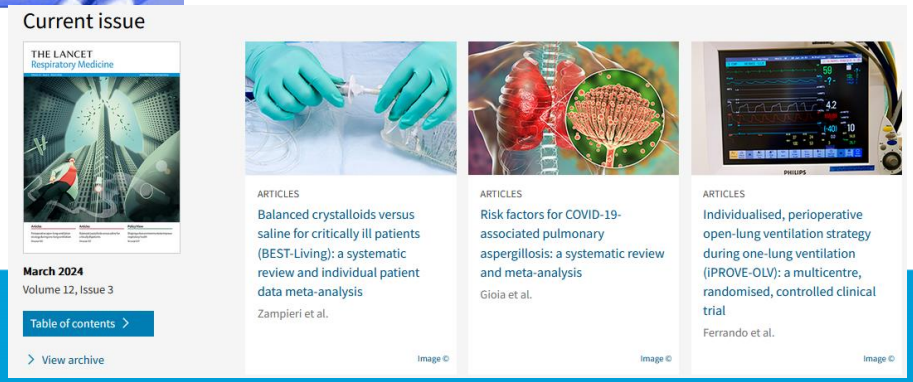
Publishing TB research – Global Reach and Impact

Trial finds adequate food can reduce deaths in TB patients, spread within their families

The Reducing Activation of Tuberculosis Through Improvement of Nutritional Status (RATIONS) trial is the largest trial to produce evidence on the difference nutritional support makes to TB treatment and prevention.

THE LANCET Respiratory Medicine pod cast





Questions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"I have no recollection of the rest of that day. His loss was felt on so many levels, a great loss to me, to the Trust, and to medicine. It demonstrated to me how cruel and unforgiving the virus could be."
Essay: COVID-19: the lessons learned amongst the losses
TLRM tea and chat with US and Germany teams!
zoom
We forget that covid-19 is a new disease, never having been seen until late 2019, w/ different features than any prior illness. A truly outstanding review today on its pathophysiology thelancet.com/journals/lanre... @LancetRespirMed @osuchm and colleagues
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