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

Panel: **Examples of ongoing studies that aim to address outstanding research questions**

Tuberculosis transmission

Protecting Households On Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Patients (PHOENIx MDR-TB; NCT03568383)

Tuberculosis diagnostics

Mycobacterium tuberculosis detection

Validating the Use of Blood Transcriptomic Signatures for the Diagnosis of Active Pulmonary Tuberculosis (ISIT-TB; NCT04995406)

Early Risk Assessment in Household Contacts (≥10 Years) of TB Patients by New Diagnostic Tests in 3 African Countries (ERASE-TB; NCT04781257)

Xpert Active Case-finding Trial 3 (XACT-3; NCT04303104)

Resistance profiling

Triage Test for All Oral DR-TB Regimen (TRiAD Study; NCT05175794)

Treatment of tuberculosis or drug-resistant tuberculosis

Clofazimine- and Rifapentine-Containing Treatment Shortening Regimens in Drug-Susceptible Tuberculosis: The CLO-FAST Study (NCT04311502)

Safety and Efficacy Evaluation of 4-month Regimen of OPC-167832, Delamanid and Bedaquiline in Participants With Drug-Susceptible Pulmonary TB (NCT05221502)

Vaccines

Clinical Trial to Investigate Therapeutic Vaccine (RUTI) Against Tuberculosis (TB; NCT04919239)

Study to Check the Efficacy and Safety of Recombinant BCG Vaccine in Prevention of TB Recurrence (NCT03152903)

Efficacy, Safety and Immunogenicity Evaluation of MTBVAC in Newborns in Sub-Saharan Africa (MTBVACN3; NCT04975178)

BCG Revaccination in Children and Adolescents (BRiC; NCT05330884)

Safety and Immune Responses After Vaccination With Two Investigational RNA-based Vaccines Against Tuberculosis in Healthy Volunteers (NCT05537038)

M72/AS01E vaccine candidates are planned for phase 3 clinical trials

ID93/GLA-SE vaccine candidates are planned for 2b/3 clinical trials

pharmacotherapy was prohibitively long, toxic, and of suboptimal efficacy.[9] However, the introduction of novel treatment regimens incorporating drugs with incompletely characterised genotypic–phenotypic concordance might be a threat to the durability of these regimens. For newer drugs, such as bedaquiline and pretomanid, the absence of high genotypic–phenotypic concordance limits the development of molecular assays for drug susceptibility testing. The availability of rapid phenotypic drug-susceptibility profiling to support the roll-out of new drugs would substantially change the future of drug-resistant tuberculosis care.

Despite several issues, BCG, which was first introduced in the 1920s, remains the only licensed tuberculosis vaccine. However, the past decade has seen substantial advances in tuberculosis vaccine development. Currently, ten vaccine candidates are undergoing clinical trial evaluation, including live-attenuated, viral-vector, protein subunit, and whole-cell inactivated vaccines.[10] These vaccine candidates seek to prevent tuberculosis infection and progression to tuberculosis disease, as well as to be an adjunct to drug therapy for accelerating cure, shortening treatment, and preventing relapse. Furthermore, clinical trials of mRNA-based tuberculosis vaccine candidates are currently in development. A persistent challenge impeding tuberculosis vaccine development has been the lack of clearly defined immune correlates of protection as a surrogate for vaccine efficacy. Although cross-reactive, immunogenic tuberculosis antigens have been identified, characterising cell-mediated and humoral immunity signalling protection against tuberculosis infection and progression to tuberculosis disease remains elusive. Efficacy signals for preventing tuberculosis infection, progression to tuberculosis disease, and preventing relapse have been detected in early-phase vaccine studies, with confirmation underway in larger trials.

There is optimism around several major advances in the scientific understanding of tuberculosis transmission and pathogenesis, improved diagnostic assays for *M tuberculosis* detection and resistance profiling, and the implementation of shorter, safer, and more effective regimens for the treatment of tuberculosis. To achieve a tuberculosis-free world, however, more progress is needed in developing an effective tuberculosis vaccine, implementing coordinated tuberculosis control interventions with multiple aspects, mitigating the socioeconomic drivers of tuberculosis, and sustaining high levels of political support to bring new scientific advances to the field.

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