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Controlling the Seedbeds of Tuberculosis: Diagnosis and Treatment of Tuberculosis Infection

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Abstract

The billions of people with latent tuberculosis infection serve as the seedbeds for future cases of active tuberculosis. Virtually all episodes of tuberculosis disease are preceded by a period of asymptomatic *Mycobacterium tuberculosis* infection; therefore, identifying infected individuals most likely to progress to disease and treating such subclinical infections to prevent future disease provides a critical opportunity to interrupt tuberculosis transmission and reduce the global burden of tuberculosis disease. Programs focusing on single strategies rather than comprehensive programs that deliver an integrated arsenal for tuberculosis control may continue to struggle. Tuberculosis preventive therapy is a poorly utilized tool that is essential for controlling the reservoirs of disease that drive the current epidemic. Comprehensive control strategies that combine preventive therapy for the most high-risk populations and communities with improved case-finding and treatment, control of transmission and health systems strengthening could ultimately lead to worldwide tuberculosis elimination. This paper outlines challenges to

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Author contributions

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implementation of preventive therapy and provides pragmatic suggestions for overcoming them. It further advocates for tuberculosis preventive therapy as the core of a renewed global focus to implement a comprehensive epidemic control strategy that would reduce new tuberculosis cases to elimination targets. This strategy would be underpinned by accelerated research to further understand the biology of subclinical tuberculosis infections, develop novel diagnostics, and drug regimens specifically for subclinical tuberculosis infection, strengthen health systems, community engagement, and enhance sustainable large scale implementation of preventive therapy programs.

Current situation and rationale for change

The control of an infectious disease epidemic requires active case detection, treatment where possible, interruption of transmission, and enhancement of immunity for the susceptible. If elimination is desired, containment of the reservoirs, or seedbeds, of infection is essential. Tuberculosis is a disease whose pathogenesis is characterized by a period of asymptomatic subclinical infection that may last for weeks to decades; as a result, a large reservoir of infected human beings exists among whom new cases may arise at any time. While aggressive strategies to find and treat all cases of disease are necessary to turn the tide of the global tuberculosis epidemic, these strategies alone will not be sufficient to end tuberculosis by the 2035, the World Health Organization (WHO) target, because they do not address the large existing reservoir of infection. The WHO policy now recognizes that stopping the tuberculosis pandemic will require unprecedented efforts to address the human seedbeds of disease.[1]

Contemporary understanding of what has long been called “latent tuberculosis infection” has evolved. Rather than a binary distinction between “latent” and “active” states, tuberculosis infection is now understood as a dynamic multi-state gradient of latent subclinical infection to clinically active disease; a process that is imperfectly represented by the dichotomous classification.[2–4] The spectrum of tuberculosis infection ranges from individuals who mount effective immune responses that eradicate all viable bacilli, to those whose responses contain the infection but who continue to harbor populations of bacilli that intermittently replicate in macrophages, granulomata, and other tissues, engaged in an intricate *pas de deux* with the host immune system, to those with no effective immunity against tuberculosis who progress rapidly from tuberculosis infection to disease, such as young children, the chronically ill, and, HIV-infected individuals.[2,5] Differences in host immune responses influence the risk of tuberculosis infection progressing to active disease.

As shown in Figure 1, the population dynamics of tuberculosis begin with subclinical asymptomatic infections from which active cases arise; these then spread infection to contacts. Newly infected contacts may then progress to active tuberculosis disease, a process that may take weeks to more than a year, or enter the larger pool of the asymptomatically infected and remain at risk of future tuberculosis. Tuberculosis case-finding and treatment of disease prevents the spread of tuberculosis by reducing the number of secondary infections resulting from each new case but this strategy alone cannot lead to elimination.[6] The currently available vaccine mostly mitigates disease severity in infants and young children, and despite high levels of coverage in many countries, has not had an appreciable population-level impact on the incidence of pulmonary tuberculosis among adults

worldwide. The only strategy for preventing new cases from arising in individuals sufficiently exposed to tuberculosis is to administer treatment to those exposed to or infected by *M. tuberculosis*, which prevents progression to active disease in the newly or remotely infected.[4,7] Thus, treatment of latent tuberculosis infection – called preventive therapy to differentiate it from treatment of active disease, which requires multidrug therapy—is an essential component of the strategy for elimination of tuberculosis, yet it is the least exercised option of all of the proven tools for combatting the global epidemic.

Dye and colleagues estimated in the 1990s that one-third of the world population was infected with *M. tuberculosis*,[8] and a recent study from China found that one-quarter to one-third of adults in rural areas had tuberculosis infection,[9] highlighting the enormous reservoir that serves as the seedbed for new cases of active tuberculosis. Identification of high-risk epidemic locales (see “Data for action” paper in this series) as well as intensification of case-finding and improvements in treatment (see “Turning off the tap” paper in this series), while important, cannot alone achieve tuberculosis elimination because the reservoir of asymptomatically infected individuals will continue to produce millions of new cases of reactivation tuberculosis for decades to come. Even a highly effective new vaccine that prevents disease following new infection would not be sufficient for eliminating tuberculosis, as the current high prevalence of existing infections would not be affected. Thus, epidemiologically sound tuberculosis elimination strategies must include treatment of tuberculosis infection to be effective.[10]

Providing treatment to prevent the establishment of a productive infection or progression of infection to disease is an established strategy for controlling and eliminating major infectious diseases of public health relevance. For instance, eradication of smallpox was possible through a global multi-pronged strategy to limit transmission that included finding and offering vaccination to contacts of infected people residing in epidemic hotspots.[11] In addition, mass preventive therapy has been used to combat both *Chlamydia trachomatis* and *Onchocera volvulus*.[12] As the human reservoir of *M. tuberculosis* infection is enormous, overwhelmingly asymptomatic, and long-lived, a strategy of identifying individuals who are at highest risk of progression to disease, who would thus benefit the most from preventive therapy, is widely recommended.

Certain groups of people are known to be at elevated risk of progression to disease. These include close contacts of cases, young children, the elderly, and people with HIV infection or other immunodeficiencies. In addition, although currently available tuberculosis infection tests are imperfect proxies of risk, the Mantoux tuberculin skin test has been prospectively evaluated to predict benefit from preventive therapy in multiple settings and populations.[7] Less robust evidence exists for the newer interferon gamma release assays, though it is likely to be as predictive.

The benefits of tuberculosis preventive therapy have been known for more than 60 years. Pioneering studies in the 1950s–1960s provided overwhelming evidence of the efficacy of isoniazid preventive therapy in preventing active tuberculosis in children,[14] Alaskan Native populations, residents of congregate living facilities such as mental hospitals, and household contacts of tuberculosis patients.[7,14–16] Subsequent work has further documented benefits of

preventive therapy for individuals with evidence of recent infection, those with radiographic evidence of prior untreated tuberculosis, people with HIV infection, recipients of immunosuppressive therapy such as TNF-alpha inhibitors, and other immunocompromised individuals. Panel 1 summarizes the populations at risk for tuberculosis who should benefit from preventive therapy, tests for tuberculosis infection, and available options for treatment.

Despite abundance of evidence of its efficacy, use of preventive therapy outside North America has been limited over the past 40 years, as tuberculosis control programs have focused almost exclusively on detection and treatment of infectious tuberculosis cases. Preventive therapy has been patchily targeted at children ≤5 years old with household exposure to an infectious case. While most countries have formal policies recommending treatment of these individuals, implementation in countries with high tuberculosis burdens has been near absent. In addition, few of these countries have historically had policies addressing other higher-risk individuals. The World Health Organization first recommended isoniazid preventive therapy for people living with HIV "as a personal health measure" in 1998, and updated this to a public health recommendation in 2010.[17] However, of the 22 tuberculosis high burden countries, only South Africa and Brazil have ambitious national policies to provide preventive therapy to people infected with HIV.

The existence of obstacles to implementing preventive therapy is no justification for inaction in the face of the wealth of compelling evidence supportive of preventive therapy as an essential component of disease control. Large population-based studies of preventive therapy and mathematical models both suggest that preventive treatment of tuberculosis infection, as a component of a comprehensive approach that includes active case-finding and prompt effective treatment, can produce sufficient reduction in population-level transmission and rates of active disease to interrupt the cycle of infection, illness, and death.[18,19] This paper thus argues for an integrated approach intended to spur widespread implementation of preventive therapy in the context of comprehensive approach to addressing the tuberculosis epidemic. We summarize the successes of preventive therapy, provide a framework for understanding new and old challenges to implementation, and lay out a pragmatic roadmap to action.

Data and successes

Isoniazid preventive therapy, which is offered in conjunction with active screening to detect and treat cases of active tuberculosis disease, has long been recognized as an effective intervention for reducing the risk of tuberculosis at both the individual and population level. From the early 1950s and during two subsequent decades, numerous trials evaluated the efficacy of isoniazid in preventing tuberculosis in different populations and conditions.[7] By 1970, overwhelming evidence from multiple countries had demonstrated that isoniazid was effective for reducing the risk of TB disease, and was safe and well tolerated in both adults and children.[7] Declining TB incidence in rural Alaska following community-wide trials of isoniazid treatment and mass screening for disease suggested a reduced force of infection attributable to mass preventive therapy during the trials. In Alaska, where tuberculosis was endemic in the 1950s, a community-wide trial of isoniazid versus placebo found a 60%

decline in TB incidence for treated households that was sustained for more than two decades.[15]

The use of preventive therapy experienced a setback in the 1970s when case reports of isoniazid-associated hepatitis focused attention on the risks of preventive treatment and a large US Public Health Service Study reported eight deaths among 13,838 individuals enrolled in a trial of isoniazid,[20] although subsequent analysis suggested that an unrelated epidemic of hepatitis may have contributed to the deaths observed.[21] A series of papers using various models then argued that, for many individuals, the risks of preventive treatment outweighed the benefits.[22] Of note, none of these articles considered the public health gains of preventive therapy among the benefits.

The emergence of the global HIV epidemic in the 1980's and 1990's led to renewed interest in preventing tuberculosis in high-risk individuals. Multiple observational and randomized trials showed that using isoniazid for 6–12 months reduced the risk of TB disease, particularly in those with positive tuberculin skin tests.[23] Guidelines developed in the US in 2000 emphasized the importance of targeting skin testing and preventive therapy at highest risk of developing disease, with careful clinical monitoring to reduce toxicity.[24] Yet isoniazid treatment was still little-used globally, including in populations with high rates of HIV infection.

The current consensus on the individual-level benefit of preventive therapy is incontrovertible. Compared to untreated individuals, the risk of clinically active tuberculosis disease is reduced by 60% in immunocompetent, HIV-uninfected individuals and by 32%–62% in HIV-infected adults who are treated with preventive therapy regimens of three to 12 months duration.[23,25] The benefit of isoniazid preventive therapy in HIV-infected individuals is additive to the benefit of antiretroviral therapy, which itself reduces tuberculosis risk of about 60%; the combination of the two can achieve dramatic reductions in rates of incident TB disease in people with HIV infection.[26–28] The risk of developing tuberculosis is reduced by about 60% among children aged 15 years or younger who receive preventive therapy.[29] Longer courses reduce subsequent disease among individuals at risk of exogenous re-infection.[30] Finally, evidence is accumulating that preventive therapy with an appropriate drug can offer protection to individuals exposed to drug-resistant tuberculosis.

At a population level, recent studies have built on the experience in Alaska and shown that the treatment of tuberculosis infection as part of a comprehensive tuberculosis control strategy that includes active case-finding, particularly among household contacts, can reduce tuberculosis incidence. In Rio de Janeiro, Brazil, a community-randomized trial involving eight urban neighborhoods with a baseline tuberculosis incidence ~340/100,000 compared the standard procedure of informing tuberculosis patients of the need for their household contacts to be evaluated, to active identification, evaluation, and appropriate treatment of tuberculosis infection and tuberculosis disease in household contacts. After five years, tuberculosis incidence in the intervention communities was 15% lower than in the standard procedure communities.[31]

The cluster-randomized THRio trial in Rio de Janeiro, Brazil, involving HIV-infected people enrolled in 29 clinics, demonstrated a benefit of isoniazid preventive treatment in a setting of moderate tuberculosis incidence, as part of an integrated care program for HIV care. In this study, strengthening the uptake of tuberculosis screening, tuberculin testing, and use of preventive therapy reduced the adjusted hazard of tuberculosis incidence and death in the study population by 25–30%.[32] Long-term follow up of individuals treated with isoniazid found that the benefit was durable over five years after treatment, and modeling based on the results of this intervention predicted that targeted treatment of just 20% of HIV-infected individuals with tuberculosis infection would produce a community-wide decline in HIV-related tuberculosis incidence and mortality of about 15%.[19,33]

Recent observational evidence from other settings also supports the effectiveness of preventive therapy as key component of achieving population-level reductions in tuberculosis incidence. To address a decade-long stagnation of tuberculosis incidence, Singapore started a new tuberculosis elimination initiative combining directly observed therapy, national surveillance, and treatment of latent infection in contacts. Tuberculosis incidence declined by 15–20% within five years, and treatment of latent infection was identified as a key contributor to this decline.[34] In a programmatic intervention targeting two neighborhoods with historically high TB incidence (40/100,000) in Texas, USA, a door-to-door mass screening was performed and isoniazid prescribed for all infected individuals. This community-based tuberculosis screening and preventive treatment appeared to have substantially decreased subsequent tuberculosis incidence since no tuberculosis cases were detected in the two intervention communities over the next ten years.[35]

Challenges

While more than a half-century of data support the use of preventive therapy as an important component of tuberculosis control, a number of challenges, both new and old, must be addressed to energize widespread implementation of current guidelines and respond to perceived and actual barriers to implementation, which include clinical, technical, health systems, and policy/advocacy dimensions (Panel 2).

On a clinical level, practitioners encounter the difficulty of screening HIV-infected adults for tuberculosis disease prior to initiating preventive therapy, limited access to tests for tuberculosis infection, the complexity of risk-factor driven algorithms to identify those at highest risk of disease, and the challenges of encouraging adherence to a treatment for an asymptomatic condition. These are accompanied by perceived problems such as fear of inducing drug resistance, even though there is evidence that this fear is unfounded,[36] and exaggerated perceptions of the risk of severe side effects.

At the health-systems level, ambiguous or ambivalent guidelines for diagnosing and treating tuberculosis infection undermine clinician confidence. Inadequate health training and insufficient numbers of health care workers, compounded by drug stock-outs, limit utilization of preventive therapy. In addition, the lack of effective monitoring and evaluation surveillance systems to oversee uptake, side effects, adherence, resistance, and program impact make assessment of country-level efforts difficult. Further hampering use of

preventive therapy is a very low level of community engagement and demand, in contrast to the demand for antiretroviral therapy and, increasingly, for treatment of hepatitis C virus infection. Finally, the poor prioritization of research funding for new tools for tuberculosis control, which could include new vaccines to prevent infection and new diagnostics to predict risk of progression to disease, stifles innovation and restricts progress.

A further challenge in preventing tuberculosis is the high incidence of re-infection in HIV-infected individuals and other high-risk populations in sub-Saharan Africa, as well as other identified hotspots of uncontrolled transmission. The benefit of preventive therapy in these settings is less durable, as the treatment effect appears to wane soon after discontinuation. This suggests that people treated for tuberculosis infection are either rapidly re-infected, or persistent bacilli are not sterilized by isoniazid.[29,37] A cluster-randomized trial conducted in the high-burden setting of gold mines in South Africa, showed that mass screening and isoniazid preventive therapy was successful in preventing tuberculosis while individuals were on therapy, but had no durable effect in reducing overall tuberculosis incidence.[38] Similar limitation of benefit to the time during which individuals were taking preventive therapy was observed in studies in HIV-infected individuals in Botswana and Soweto, South Africa.[30,39] Thus, while short courses of preventive therapy can provide short- to medium-term protection even in high-burden settings, long-term protection may only be conferred where transmission is better controlled through active case-finding and treatment. Further research is required to understand population-level effects of preventive therapy in transmission hotspots and to inform efforts to control re-infection and subsequent disease.

Solutions to most of the technical challenges mentioned above are available and can be implemented now. For example, if tests for infection are not available or affordable, epidemiologically targeted preventive therapy can be offered as post-exposure treatment to the highest risk individuals without evidence of current active tuberculosis, such as those with HIV, child contacts an infectious case[40,41] or individuals with medical conditions that increase tuberculosis risk. A symptom screening algorithm with 80% sensitivity and a negative predictive value of 97% for diagnosing active TB in HIV-infected adults has been promulgated by the World Health Organization.[42] In children, World Health Organization guidance encourages simple symptom-based screening, since asymptomatic children are unlikely to have active tuberculosis, or to acquire drug resistance if minimal disease is missed.[43,44] The availability of cheap, rapid, and sensitive microbiological screening tools, or screening algorithms based on new tuberculosis infection diagnostics would complement efforts to scale up.

Adherence may be improved and hepatotoxicity reduced through the use of shorter rifamycin-based preventive therapy regimens rather than the use isoniazid over long durations (i.e., 6, 9, 12 or 36 months). For individuals taking isoniazid, rates of drug-related liver injury can be kept low (<1–3%) with appropriate screening and monitoring, though isoniazid-induced hepatoxicity may still result in one death for every 25,000–40,000 patients treated.[39] In contrast, liver toxicity rates with rifamycin-based regimens are significantly lower, and adherence to these shorter course regimens is generally much better. Rifamycin-based regimen options include a weekly regimen of rifapentine plus isoniazid for three months, and daily regimens of isoniazid plus rifampicin or rifampicin alone for three to four

months.[25,39,45–47] These are all considered options in developed countries, and are likely to have a considerable impact on uptake as well as the workload and health workforce required to administer and monitor preventive treatment. Further improvements in the ease of administering and taking preventive therapy are anticipated, as a new fixed-dose combination tablet of rifapentine and isoniazid is expected to be marketed later this year, and a bold four-week regimen of daily rifapentine and isoniazid is currently being evaluated.[48,49] Unfortunately, in resource-constrained high tuberculosis burden countries, preventive therapy with 6–36 months of isoniazid is uninspiringly presented as the only option. This is perceived as a pragmatic choice probably because most of the historical evidence for preventive therapy is with isoniazid, which is cheap and widely available. However, the adoption of shorter, easier to complete regimens would be particularly advantageous in settings of high tuberculosis burden and limited resources, as this would enable many more people to complete preventive therapy given a limited number of healthcare staff to administer treatment and monitor adverse events. While offering real hope in addressing the adherence challenge, to be successful these biomedical advances will have to be supported by ongoing qualitative work to explore individual and community understanding of latency, its relationship to disease and the need for treating infections with an antibiotic to prevent active disease. There is a further need to understand how to structure tuberculosis preventive therapy programs from the perspective of the patient in order to design relevant interventions to promote adherence and thus a more responsive preventive therapy program.

Further barriers to implementation concern health systems and policies. Available guidelines do not provide sufficient guidance for national preventive therapy programs to proceed. Firstly, leadership and the responsibility for prescribing and providing preventive therapy is unclear. Ownership could rest with tuberculosis programs, HIV programs, primary care clinics, the private sector, or some combination of these, but a plan that outlines responsibilities and a process for coordination of efforts is necessary no matter what the arrangement. In addition, tuberculosis programs would need to consider further devolution of responsibilities to procure and distribute drugs for preventive therapy.

Secondly, preventive therapy has to be implemented in clinical settings with heavy workloads and program-specific delivery targets. While tuberculosis programs naturally have access to high-risk groups such as household contacts, the workload of dealing with active cases often overwhelms staff, who thus deprioritize preventive therapy. Within HIV programs, clinicians have competing priorities, such as initiating antiretroviral therapy and managing infectious and non-infectious HIV-associated co-morbidities. As a result, treatment of tuberculosis infection is often de-emphasized. Training and motivating health care workers and building systems that can undertake the additional task of providing tuberculosis preventive therapy is an important but difficult challenge. Much innovation and evidence of successful strategies is required to address this challenge. Answers may lie in some well-known but underutilized approaches, such as task shifting to the lay cadres of the health work force, decentralization of centres of LTBI testing, delivery of treatment and monitoring of individuals on preventive therapy, as well as some least explored options, such as innovative approaches for simplifying LTBI testing which could include tools for self-testing.

Thirdly, international consensus process and outcome indicators for preventive therapy programs are not yet available, making it difficult to assess the successes and limitations of programs. For example, accurate country-level assessments of uptake of preventive therapy among HIV-infected people who newly presented for care have proven elusive due to concerns with the quality of monitoring and evaluation. An analysis of the uptake of preventive therapy in 150 clinical sites in South Africa suggested an increase in the absolute numbers of individuals prescribed preventive therapy (from 3,309 in 2010 to 49,130 in 2011) but a decrease in the proportion of patients receiving it (from 19% in 2010 to 11% in 2011).[50] Although encouraging, a reported surge in recipients is an insufficient indicator of successful implementation.[51] Indicators such as increases in coverage, completion rates, rates of adverse events, and active tuberculosis among those receiving preventive therapy are needed to demonstrate intervention fidelity. Monitoring downward trends in the incidence of new infections and subsequent cases would provide evidence for interruption of transmission. The “Data for action” paper in this series argues for an approach where existing data collection systems are augmented with such new information and increasingly utilized to inform success of local tuberculosis control interventions such as a preventive therapy program.

There is also a challenging lack of advocacy and leadership to promote preventive therapy. Within Global Fund programs and grants, tuberculosis is enormously under-emphasized, reflecting country-level and community-level lack of advocacy and demand. In contrast, widespread availability of antiretroviral therapy has been promoted by the powerful voice of affected communities coupled with visionary leaders who devised programs like the President’s Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund for AIDS, TB & Malaria. Building this support for tuberculosis preventive therapy will require education and engagement of both populations at risk and clinical and public health leaders.[54]

Proposed action plan

The abundance of existing evidence and knowledge about tuberculosis infection and preventive therapy provides a solid base for concerted global action to incorporate treatment of tuberculosis infection into a comprehensive and epidemiologically sound strategy for tuberculosis elimination. While the magnitude of the challenges involved and the corresponding level of ambition required are substantial, these efforts are necessary because case-finding and treatment approaches alone will not be sufficient, and both novel diagnostics to accurately identify incipient disease and effective vaccines to prevent infection or disease remain distant goals. In addition to biomedical interventions, political leadership and will are required to modify the risk environment by addressing the social determinants of tuberculosis that perpetuate inequalities in health (see “Tuberculosis control – a biosocial approach” in this series).[53] Finally, we need a global interdisciplinary approach to accelerate research that furthers our understanding of the biology of tuberculosis infection, develops novel diagnostics and drug regimens for tuberculosis infection, strengthens health systems, and enhances sustainable large scale implementation of preventive therapy programs. In this section we provide a roadmap to address identified key implementation barriers and immediately enhance implementation.

i) The clinical and technical approach

Tuberculosis preventive therapy should be implemented alongside tracing of case-contacts and other high-risk individuals, targeted active case-finding, and effective treatment of active disease (see “Turning off the tap” paper in this series) as a routine component of tuberculosis control programs world-wide. Commitment to preventive therapy as a core element of control is needed at the global, national, provincial, and local levels. In addition, preventive treatment for tuberculosis should be incorporated into other health programs that provide treatment to populations at risk, such as HIV care, substance use treatment, and occupational health clinics. We propose a single-bundle strategy of routine active case finding to identify people with active disease who should be promptly initiated on effective multidrug chemotherapeutic regimens and those without disease for risk-stratified treatment of *M. tuberculosis* infection (Panel 3). Recognizing the importance of expanding preventive interventions, in 2014 the World Health Organization revised guidelines for the diagnosis and treatment of tuberculosis infection.[55] The guidelines are primarily targeted at high-income or upper middle-income countries with an estimated TB incidence rate of less than 100 per 100 000 population and have broadened the definitions of at risk groups. Our proposed risk-stratified strategy aims to support these efforts and will ensure that preventive therapy is safely and efficiently provided to individuals at increased risk of disease in all settings, including high-burden countries.

In countries with uncontrolled *M. tuberculosis* transmission, re-infection may limit the long-term benefit of short courses of preventive therapy, particularly within transmission hotspots. In particularly vulnerable groups, such as people living with HIV, miners, and prisoners in areas with high transmission rates of tuberculosis, and other groups with a high risk of developing disease due to occupational (e.g. healthcare workers) or behavioral exposures (e.g. drug-users), extended or periodic schedules of preventive therapy should be implemented. It should be noted that *M. tuberculosis* transmission rates were astonishingly high in Alaska in the 1950s — >90% of children were infected by age 15 — when the Bethel household isoniazid study was undertaken, and rates of infection fell precipitously as a concerted program of case finding, treatment, and preventive therapy was implemented.[55] This is strong evidence that preventive therapy plays an important role even in high-burden areas.

ii) Health-systems, policy, and leadership

To more broadly deliver tuberculosis preventive therapy, engagement of other health programs that provide care to high risk populations is essential. HIV programs can easily provide preventive therapy to HIV-infected individuals, while maternal and child health programs could actively support preventive therapy provision in young and vulnerable children. As the link between diabetes and tuberculosis becomes better understood, diabetes clinics and primary health programs caring for people with diabetes could consider tuberculosis prevention, diagnosis, and treatment. Occupational health programs are responsible for providing treatment to workers at increased risk of tuberculosis, such as miners and healthcare workers, but too often neglect prevention. In many settings, primary health centers and private practitioners can deliver preventive therapy to others who would benefit, such as contacts of cases, people with diabetes or immunosuppression, and refugees

or immigrants from high-burden areas. It is essential to identify and standardize functional monitoring and reporting pathways to support preventive therapy implementation across providers, such as latent tuberculosis registries, since this is a key driver and the only proof of actual implementation.[56] In 2011 the World Health Organization launched a handbook for the programmatic management and implementation of drug-resistant tuberculosis activities and surveillance[57] A similar tool-kit is urgently required to decode existing preventive therapy guidelines and offer practical guidance to National HIV, tuberculosis, and other program managers, monitoring and evaluation coordinators, and clinicians to accelerate preventive therapy implementation in partner countries.

iii) Advocacy approach

Wider uptake of tuberculosis preventive therapy will require leadership and evidence-based advocacy by clinicians, public health officials, and communities at risk. These stakeholders should demand that preventive therapy be provided at every opportunity and contact with the health-system, as it is an essential part of the tuberculosis control package. For example, for certain individuals, preventive therapy will be easier to administer in antiretroviral therapy clinics and in antenatal programs than through tuberculosis clinics. In addition, the lack of understanding of tuberculosis infection and the role of preventive therapy needs to be addressed among affected individuals, their health-providers, and their communities. This education may be the key to triggering bottom-up advocacy as is seen for HIV prevention and may increase the acceptability of treatment for an asymptomatic condition.

Projected population impact and cost

There is good evidence of the population-level impact and cost-effectiveness of preventive therapy on tuberculosis dynamics in both low and higher income countries. One projection for India suggests that by increasing use of preventive therapy gradually by 2050, tuberculosis incidence could be reduced to one case per million, and deaths could be reduced to fewer than ten per million by 2035 (compared to a current estimated incidence of 1,710 per million and estimated mortality of 190 per million population.[58] Another projection for the Republic of Kirabati (population ~100,000, tuberculosis incidence 487/100,000) suggested that a combination of active case finding and mass treatment with a full course of anti-tuberculosis drugs given to the entire population from 2015 intermittently at five-yearly rounds could eliminate TB from this Pacific island by 2030.[59] A systematic review by Chavan et al. provides robust evidence of the effectiveness and cost effectiveness of preventive therapy in high-income countries. Remarkably, the analysis concluded that tuberculosis preventive therapy would be effective and cost effective even for adults up to 80 years old.[60]

Conclusions

After more than three decades of policy that focused only on the detection and treatment of active cases of tuberculosis, a better understanding of the epidemiology and population dynamics of the disease has emerged, and the essential role of controlling the seedbeds of disease — asymptomatic tuberculosis infections — is now understood. Evidence of the effectiveness of preventive therapy in high-risk individuals is abundant, and proof of the

population-level impact of preventive therapy exists in multiple settings across the globe. Implementation of tuberculosis preventive therapy will require addressing clinical, administrative, structural, and economic barriers, and the engagement of multiple sectors, not just national tuberculosis programs. With the advent of new therapies that shorten and simplify preventive therapy, the ability of health systems to reach and treat more high-risk individuals will be enhanced. As with malaria, HIV, and other infectious diseases of public health consequence, the key role of preventive therapy as part of a comprehensive control strategy for tuberculosis must be recognized and executed.

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Key Messages

- Latent tuberculosis infection serves as the seedbed for virtually all new tuberculosis cases and must be addressed as an essential part of tuberculosis elimination.
- The efficacy and effectiveness of treating latent tuberculosis infection have been known for more than 50 years, but policies have not emphasized the epidemiologic impact of treating these infections.
- A number of clinical, administrative, and policy constraints have limited use of preventive therapy.
- Populations at highest risk of progression from latent to active tuberculosis can be identified, and diagnostic tests and risk stratification can be used to select those individuals most likely to benefit from preventive therapy.
- Newer regimens for treating latent tuberculosis can simplify, shorten, and improve adherence to preventive therapy.

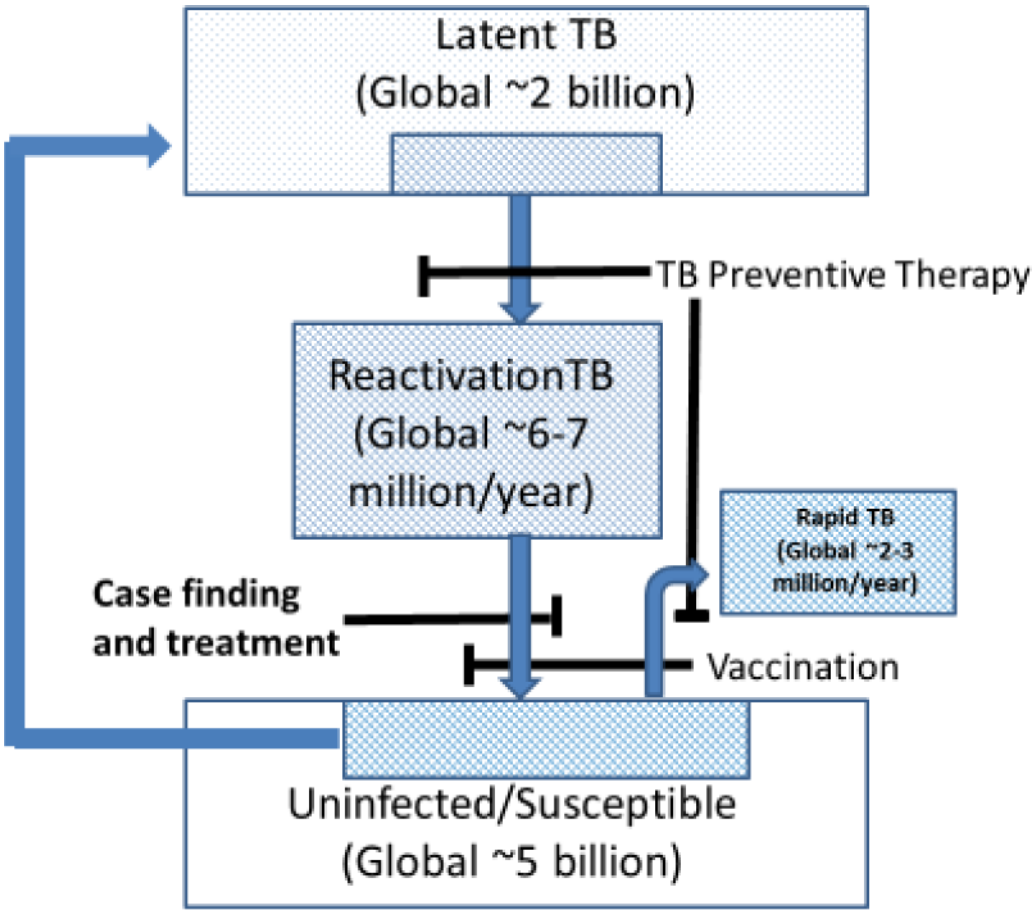

Figure 1.

Population-level Control Strategies for TB Elimination. Arrows indicate the dynamics of *M. tuberculosis* in the world's population, with flow from latent infection to active disease, transmission to new hosts, followed by either rapid progression to disease and ongoing transmission, or entry into the pool of latent infections. Bars show how different control measures affect these dynamics, interrupting the chain of events. Even if diagnosis and treatment of active TB is maximized and a new effective vaccine is developed, reactivation from the billions of latently infected will result in new cases for decades to come.

Panel 1

Populations and individuals who benefit from tuberculosis preventive therapy, testing strategies and treatment regimens.

Populations at increased risk
Residents of or immigrants from high-burden areas
People with HIV infection
Contacts of infectious cases
Recent TST or IGRA converters
Recipients of TNF-alpha blockers
Recipients of immunosuppressive therapy and/or transplantation
Residents of congregate living facilities including prisons
Homeless people
People with diabetes
Cigarette smokers
Miners and people with silicosis
Residents of congregate living facilities
Health care workers and people who visit health care facilities (in high tuberculosis burden areas)
Tests for tuberculosis infection
Tuberculin skin test (TST)
≥5 mm induration at 2–3 days considered positive for HIV-infected individuals, close contacts of cases, and young children
≥10 mm induration at 2–3 days considered positive for other risk categories
≥15 mm induration at 2–3 days for those with no identifiable risk factors.
Interferon Gamma Release Assays (IGRA):
Quantiferon-Gold In Tube Assay (QGIT): >0·35 IU/ml considered positivie
T-SPOT Test: >8 spot-forming cells considered positive.
Proxy measures of tuberculosis infection when testing unavailable
Household contact with a pulmonary tuberculosis case
Resident of areas with high-burden of latent tuberculosis
Treatment regimens for tuberculosis infection
Isoniazid daily or twice weekly for 6, 9, 12, or 36 months
Rifampin daily for 3–4 months
Rifampin and isoniazid daily or two to three times per week for 3 months
Rifapentine and isoniazid once weekly for 12 weeks

Panel 2

Barriers to implementation of tuberculosis preventive therapy and proposed responses

Category	Barriers	Proposed responses
Clinical	Excluding active tuberculosis, especially in HIV+ patients	Use of clinical algorithms, more use of chest x-rays
	Need for tuberculin or other testing (IGRA)	Develop new simpler tests that are more predictive of subsequent active TB, improve global production of tuberculin, treat high-risk patients without testing
	Poor adherence and completion of preventive therapy	Use of short-course regimens Supervision of therapy
	Drug toxicity	Encourage monthly monitoring, patient education
	Perceived risk of acquiring drug resistance	Available evidence suggests this is not a problem
Health System	Lack of consistent guidelines	Harmonized global and national guidelines Development of preventive therapy toolkit
	Inadequately trained staff	Enhanced training for doctors, nurses and other health workers
	Stock-outs of drugs and diagnostics (TST and IGRAs)	Strengthened supply chain
	Poor surveillance and reporting	Better health information systems, increased monitoring and evaluation
	Inadequate funding	**a.** Expansion of vertical health programs to address TB prevention (e.g., HIV PMTCT), with benchmarks for disease control **b.** More integration of tuberculosis control into primary health care
Policy/Advocacy	Lack of priority for prevention, with emphasis on proportion of active cases treated	Realignment of TB Control Programs to incorporate prevention, with performance evaluation linked to incidence
	Inadequate investment in basic, clinical and implementation research and training	Increased funding for research
	Lack of advocacy and demand from groups most at risk	Education and empowerment of at-risk group, including people with HIV, families

Panel 3

Treatment of *M. tuberculosis* infection as part of a comprehensive approach to improve global tuberculosis control

Reduce tuberculosis at the individual level		
Risk-stratified preventive therapy	Provide preventive therapy to non-diseased individuals at risk of tuberculosis, or those who may transmit future disease to vulnerable people	
	Proven M. tuberculosis infection (*tuberculin skin test or interferon gamma release assay positive**)	Always treat in: - People with HIV infection - other immune compromised individuals - young children (<5yrs of age) - recent skin test converters - individuals with abnormal chest x-rays consistent with untreated prior tuberculosis Consider treating in: - cigarette smokers or people with chronic lung disease - people with diabetes - malnourished individuals - recent immigrants from high-burden countries - health care workers - prisoners or residents of congregate living facilities, e.g., long-term care
	Likely M. tuberculosis infection/re-infection (close contact with an infectious source case)	Always treat in: - immune compromised individuals (including people living with HIV in a tuberculosis endemic setting) - young children (<5yrs of age) - household contact with extensive exposure (all ages)
Early diagnosis and prompt treatment	Early disease identification and adequate treatment (also of drug-resistant TB)	
	Passive case-finding	Enhanced community awareness; universal access to care; well-functioning systems; better diagnostic tools
	Active case-finding	Focus on high-risk groups eg. routine screening of close contacts to tuberculosis patients, mine workers, prisoners, and people living with HIV or diabetes.
Reduce tuberculosis at the population level		
Limit transmission	In addition to the individual approaches listed above consider creative measures to identify transmission “hot-spots” and improve infection control	
Increase disease resilience	Ensure optimal HIV care and reduced HIV transmission, reduce cigarette smoking, indoor and outdoor air pollution, malnutrition, diabetes, alcohol, and substance abuse	

* Acknowledging sensitivity and specificity limitations, not mandatory in people living with HIV in a tuberculosis endemic setting