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ANTI - TUBERCULOSIS TREATMENT APPROACHES

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ABSTRACT
Biological uncertainties persist and impede progress in tuberculosis research despite two decades of increased effort. However, the therapeutic candidate pipeline is optimistic as a result of collaborative activities including academics, the pharmaceutical sector, and non-profit organisations. This extraordinary achievement comes with the inherent issue of prioritising multiple regimens for clinical trials and rethinking trial methods to hasten regimen development and take advantage of new advances in drug discovery. Markers of development from latent infection to active pulmonary disease, markers of therapeutic response and relapse predictors, in vitro methods to find clinically relevant synergies, and animal models to accurately assess the treatment shortening potential of new regimens are the things that are most desired. In this Review, we compare individualised therapy based on disease severity and host and pathogen features to "one-size-fits-all" regimens and treatment length from both a scientific and practical standpoint.

INTRODUCTION

The discovery of streptomycin, which won the Nobel Prize, made it possible to cure a number of infectious diseases, including tuberculosis (TB). Since then, numerous more recent antibiotics have been added to anti-TB medication therapy regimens, saving millions of lives. Despite earlier improvements, TB remained the world's greatest cause of infectious disease mortality, accounting for more than 1 million fatalities annually, up to the introduction of SARS-CoV-2. The current conventional treatment for TB is efficient but cumbersome. Patients with drug-susceptible TB without complications must take many antibiotics for a period of six months. The WHO advises that this be directly supervised because compliance is patchy, adding a significant amount of infrastructure to an exceptionally lengthy treatment regimen. Treatment failure rates have increased along with more toxic, significantly more expensive medicines as a result of the rise in drug resistance. Since treating active TB is the primary method of avoiding transmission in the majority of the world, improved interventions could significantly impact our capacity to reduce the morbidity and mortality caused by the illness and to restrict its spread. In the development of TB regimens, we are at a fascinating point. At the 12-month follow-up, a 4-month regimen that included rifapentine and moxifloxacin was discovered to be non-inferior to the typical 6-month regimen in the treatment of drug-susceptible TB for the first time in four decades1. Bedaquiline, pretomanid, and linezolid are the only three medications in the initial 6-month regimen, which has been approved for the treatment of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB. For all patient categories, nevertheless, shorter, better tolerated, and more effective treatments are required. This will necessitate the development of novel antibiotics as well as novel medication and clinical candidate combinations. The anti-TB medication pipeline is in good form compared to a decade ago, including antibiotic classes that have been repurposed and repositioned as well as therapeutic candidates that act via novel modes of action (Working Group on New TB Drugs). Due to this achievement, the prioritisation of effective pharmacological regimens has emerged as the most crucial area of study. Although there is a lot of ongoing research and development in this field, one significant constraint is the absence of animal and in vitro models that are validated for predicting the efficacy of individual medications and pharmacological combinations.

Burden of TB and illness spectrum

Distribution of the burden and disparities

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Around the world, the TB epidemic is spreading asynchronously. Eight countries accounted for two-thirds of all cases and 30 countries with a high TB burden accounted for 87% of new cases in 2019 (WHO tuberculosis)6. illness burden has diverse trajectories around the world due to socioeconomic factors, which are closely correlated with illness burden7. Similar to amyotrophic lateral sclerosis in incidence, tuberculosis is a very uncommon disease in the USA. China and the Russian Federation once had high rates of tuberculosis, but despite still having a heavy load, they are doing better than most high-burden nations. The TB-diabetes syndemic has reversed the trend in other parts of the world where incidence was previously moderate, including South America, North Africa, and some regions of Asia8,9. Diabetes is a significant risk factor for developing TB and presents a more complicated disease with higher mortality and relapse rates9,10. Although a number of coexisting conditions can make people more susceptible to TB, HIV-1 is the main factor that determines the risk of reactivation, which increases the prevalence of TB in sub-Saharan Africa. The COVID-19 pandemic's long-term effects, coupled with wealth disparities, will exacerbate the gap even more. Largely speaking, various locations and subcontinents confront distinctive difficulties that necessitate specific improvements in diagnostic and therapeutic approaches. However, based on the incorporation of global information, treatment guidelines, diagnostics, and research needs are frequently specified globally.

Range of diseases

Latent tuberculosis infection (LTBI), according to the World Health Organisation, is characterised by a prolonged immune response to Mycobacterium tuberculosis antigen stimulation without signs of clinically manifested active TB and with bacillary replication absent or below an unknown threshold as a result of immunological control. In 2014 (ref. 13), 1.7 billion people worldwide—just under one-fourth of the population—were impacted with LTBI. The rate and risk of LTBI reactivation increase within the first two years after infection and subsequently decrease between two and five years and after14. The difficulty in confirming initial hypotheses16, such as the assumption that an asymptomatic infection lasts a lifetime17, as well as reinfection in high-incidence areas, make it difficult to quantify the rates of late reactivation vs early progression. The large gaps that exist in our understanding of reactivation hamper our efforts towards TB eradication as the burden of LTBI provides an enormous reservoir from which active TB cases can develop. Our prospects of achieving the global goals of 90% reduction in TB incidence by 2035 and elimination of TB (less than 1 incident case per 1,000,000 per year) by 2050 (ref. 18) will be greatly increased by identifying and prioritising this demographic. In around 5–15% of infected people during the course of their lifetime19, active pulmonary TB illness either manifests after 1-2 years of infection or when latent infection is reactivated. Progressive bacterial replication, pulmonary necrosis, and cavitary lesions that facilitate bacterial transmission are the hallmarks of TB disease20. Despite the fact that the outcome of M. tuberculosis infection has typically been depicted as a bimodal distribution between active and latent TB based on the presence or absence of clinical symptoms, it is now more and more commonly seen as a continuous spectrum produced by a varied immunopathology that supports bacterial replication, persistence, or killing21,22,23,24, extending to within-host heterogeneity25. The current pharmacological regimen for the treatment of drug-susceptible, uncomplicated TB is the result of decades' worth of clinical trials26. Since its implementation forty years ago, this short-course therapy with isoniazid, rifampicin, pyrazinamide, and ethambutol for two months, followed by four months of isoniazid and rifampicin, has not changed. Contrarily, several drug-resistant TB clinical studies have just ended or are still recruiting participants, creating a dynamic environment and offering chances to increase cure rates and shorten the length of treatment from 24 to 6 months2,27. The goal of major drug development programmes is to find medicines that, when taken together, result in shorter, safer, and easier treatment regimens that can cure all TB28 patients. Soon after isoniazid was launched in 1952, it was thought that it might be utilised to stop the reactivation of LTBI. Later clinical trials conducted in the 1950s and 1960s showed a significant decrease in active TB and long-lasting protection in patients receiving isoniazid29,30. Based on these findings, preventing TB infection by administering isoniazid for 6 or 9 months became a popular TB control strategy and is still practised today. More recently, rifamycin was swapped for or combined to isoniazid, successfully reducing the length of the treatment31,32. Although they have not been explicitly evaluated in clinical trials32,33,34, five regimens of varying lengths that include isoniazid and/or a rifamycin are recommended globally and thought to be equal by measures of efficacy and hepatotoxicity. Delamanid (PHOENIx MDR-TB) (ClinicalTrials.gov, NCT03568383) and levofloxacin in children36 and adults37,38 are now being studied as preventative therapy in household contacts of patients with MDR-TB, in

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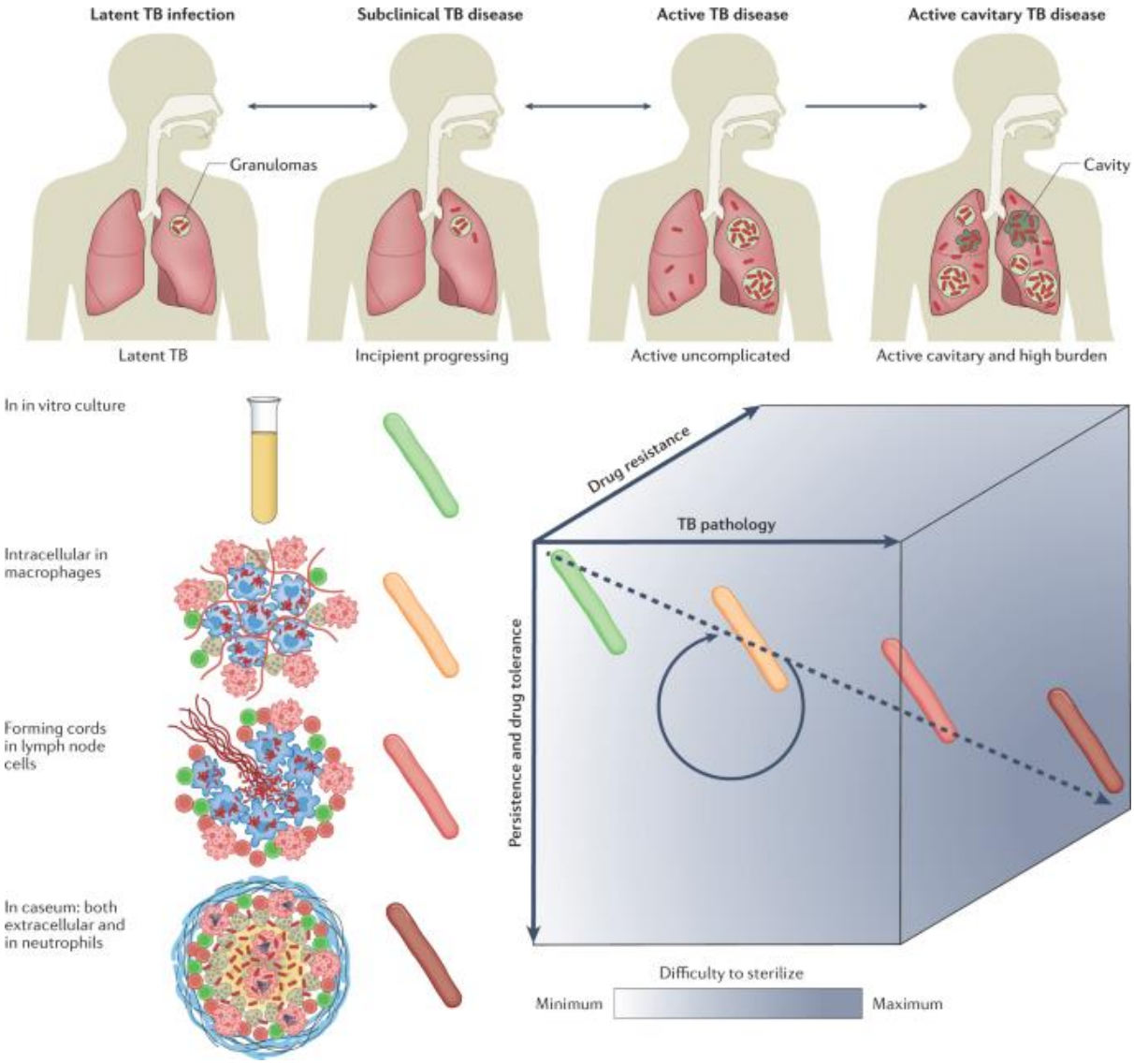
addition to historical trials with pyrazinamide35. A three-dimensional representation of the spectrum of TB infection and disease is shown in Figure 2. There are significant treatment hurdles as a result of the wide variety of symptoms and microbial diversity (see below). LTBI is now understood to be a dynamic continuum of infection response21,23. People at the "active" end of the latency spectrum (also known as "progressors") are at a high risk of becoming ill actively and would benefit from reactivation risk assessment and therapy. To achieve the worldwide goals for TB control and elimination by 2050 (ref. 18), it is essential to identify and treat this group. There have been in-depth reviews of the entire LTBI spectrum, from genuine latency to developing disease20,23. LTBI is only operationally defined as a state of persistent immune response to stimulation by M. tuberculosis antigens without evidence of clinically manifested active TB, which makes it difficult to prioritise those who are most at risk for developing TB disease39. This is due to the lack of validated immune and bacteriological markers. Overall, LTBI has more basic knowledge gaps than active illness.

Figure 1 depicts TB infection, the disease spectrum, and the difficulties it brings.



Three axes, including disease pathophysiology and severity, bacterial persistence and treatment tolerance, and genetic resistance, are present in the spectrum of tuberculosis (TB). The pathology of TB disease is a dynamic

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continuum that progresses from a wholly latent, asymptomatic infection to an active disease with a large bacterial burden in open cavities, which promotes transmission and more frequent treatment failure. People who have latent TB infection and are developing incipient TB are at a high risk of becoming active and would benefit from therapy and risk assessment for reactivation. The variety of microenvironments produced by the spectrum of immunopathology allow the pathogen to respond with metabolic and physiological changes that result in drug tolerance or phenotypic drug resistance and persistent disease. In terms of the number of medications a bacterium is resistant to as well as the degree of resistance to each drug, drug tolerance as well as additional patient and pathogen characteristics cause a spectrum of genetic resistance. Such variation along three dimensions hampers clinical trials and generates a gradient of diminished treatment efficacy and lesion sterilisation both within and across patients. It also presents a multifaceted challenge for healthcare programmes. The severity of active symptomatic TB can vary, however it is typically categorised as either cavitary illness or moderate non-cavitary disease. Clinical research conducted over many years have repeatedly shown that cavitary illness has a worse prognosis and worse treatment outcomes.40,41,42. According to recent retrospective investigations, patients with cavities and a high bacterial burden in their sputum may need treatment for more than 6 months, whereas in patients with non-cavitary mild illness, 4-month therapy was not superior to 6-month therapy43. Therefore, sputum smear and chest X-ray radiography, which are both widely accessible, could be used to identify patients who would benefit from shorter treatment durations. A minimum of three to four antibiotics must be used in combination to treat drug-susceptible and drug-resistant M. tuberculosis strains, which results in intricate patterns of drug susceptibility and resistance. The M. tuberculosis strain that is causing the infection is categorised as totally drug sensitive, mono-resistant, MDR, or XDR. Individual drug susceptibility profiles within the latter two categories direct the creation of patient-tailored treatment regimens, which are governed by institutional regulations and national recommendations.44,45. Host immunity creates a variety of microenvironmental niches in both LTBI and active disease that allow M. tuberculosis to grow unfavourably or completely stop growing. In a single sick person, several lesions of various types and immunological reactions coexist. Drug resistance or drug tolerance in bacteria is related to the physiological condition of non-replication. In fact, the response to medication therapy is biphasic, requiring a longer phase in order to completely sterilise surviving populations after an initial phase of rapid but imperfect clearance of the majority of infecting bacilli46. A persister subpopulation is created in a specified bacterial population when drug tolerance is either imparted by physiological heterogeneity that already exists or is produced by a range of stresses47,48,49. Even in the presence of uniform conditions, cell-to-cell variability generates an almost infinite range of phenotypically heterogeneous subpopulations50,51,52,53,54,55, which is thought to ensure survival because at least a small percentage of cells are predisposed to react to potential threats like antibiotics, a tactic known as "bet-hedging"56. Cell-to-cell heterogeneity is thought to be the result of stochastic noise as well as particular regulatory systems that relate bacterial metabolism and cell cycle development with shifting host-associated environmental stress. The term "phenomic potential"57 refers to the addition of adaptive regulatory components to the stochastic noise process for the production of phenotypically different bacteria within a population. Due to long-standing host-pathogen co-evolution58 and the ensuing adaptations of M. tuberculosis in response to host immunity, the phenomenon of drug tolerance is particularly acute at the sites of TB disease and is a hallmark of the disease as well as a significant factor contributing to prolonged therapy duration. There is considerable agreement that individual diversity in TB disease persistence, relapse, and reactivation is influenced by phenotypic treatment resistance. To know how in vitro observations of these processes might be used to forecast clinical result, however, there are still significant knowledge gaps. We examine the difficulties in treating complex diseases in the part that follows.

Treatment difficulties

All active TB disease forms must be treated with numerous antibiotics given over a long period of time60. In Supplementary Table 1, a list of approved first-line, second-line, and third-line medications is provided for the treatment of drug-susceptible, MDR, and XDR TB, respectively. Drug development and therapy are made more difficult by the heterogeneity of illness progression, host response, and drug resistance characteristics, but it also offers opportunity to stratify patient populations and improve preventive and therapeutic approaches. Due to the fact that TB is primarily a disease of resource-poor nations, current infrastructure barely allows for relatively sophisticated interventions. This increases the already challenging research mandate's operational and implementation issues significantly.

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Identifying LTBI patients who are very susceptible to reactivation

The WHO currently advises preventive treatment for people with LTBI who are at a high risk of TB reactivation, such as those who are HIV-1 positive, infants and young children who live with pulmonary TB patients, and patients who are receiving immunosuppressive therapy32,33,34,39. Recent scientific advancements have made it possible to identify patients who are at risk of LTBI reactivation based on immunobiology rather than the primarily operational factors mentioned above61. These include non-invasive positron emission tomography-computed tomography (PET-CT) and PET-magnetic resonance imaging (PET-MRI), immune response markers discovered by transcriptomics62 and other omics approaches, genome-wide association studies of host and pathogen, epigenetics, and the discovery of differentially expressed genes in people with LTBI and progressors in both patients and animal models. However, to ascertain the usefulness of biomarkers in evaluating the magnitude of the mycobacterial load and markers of protective immunity as surrogates of incipient TB63, validation studies are required. Although some of these methods are incompatible with the capabilities in countries with limited resources, they nonetheless make a significant contribution to our understanding of reactivation and can serve as the foundation for the creation of surrogate markers that are tailored to the global health conditions where TB burdens are greatest. Implementation challenges will persist in converting 'high risk' classification into useful treatment of probable progressors64 once predictive markers have been proven in prospective clinical research. The limitations of current preventive therapy further exacerbate this: there is no universal regimen effective against drug-resistant M. tuberculosis32, isoniazid has limited sterilising activity and hepatotoxicity65, there are drug interactions between rifamycins and anti-retroviral therapy, and there are low acceptance and completion rates globally68. Moreover, it will be logistically difficult to incorporate LTBI therapy into the present TB treatment protocols. Regardless of the possibility of reactivation, the CDC presently advises therapy for every infected person. Unless the infecting M. tuberculosis strain is presumptively resistant to both isoniazid and rifampin33, the preferable regimens are same to those advised by the WHO: three rifamycin-based regimens and two alternative monotherapy regimens with daily isoniazid. The USA and possibly other nations with a low or moderate prevalence of LTBI can manage this treatment strategy.

determining the extent of a patient's active TB disease

As predictors of illness outcome, cavitation status and bacterial burden in sputum are consistently emerging42,43. The current American Thoracic Society/CDC/Infectious Diseases Society of America Clinical Practise Guidelines69 state that therapy for individuals with severe cavitary TB and positive sputum cultures persisting at 2 months should last for 9 months. Patients with low body mass indices, smokers, diabetics, and HIV-1 positive individuals are also given consideration for longer treatment durations. Patients with non-cavitary TB, drug-susceptible M. tuberculosis infection, and low sputum load could successfully finish therapy within 4 instead of 6 months, according to a recent study of clinical trial data. As an alternative to the conventional 6-month treatment period, this raises the prospect of a stratified approach that would customise treatment duration based on the severity of the initial disease (high bacterial burden in sputum and cavitary disease)43. When necessary, shortening the course of therapy would increase completion rates and bring much-needed respite to healthcare systems. In settings with limited resources, markers like the presence of cavities and the amount of bacteria in the sputum can be detected. If their link with the length of the treatment course were systematically included in clinical trials, however, they could be promptly validated70. The application of new flexible treatment guidelines on a global scale is the remaining problem, pending formal validation, given burden disparities and specific treatment challenges in various countries and subcontinents.

knowledge of drug tolerance

The secret to attaining a quicker, more lasting cure is to target persisters and drug-tolerant bacterial populations71. These populations are responsible for the LTBI's and active disease's drug resistance. Although the clinical importance of each one and how they affect treatment outcomes are still unknowns, the research community has a fair understanding of the microenvironments and stress conditions that exist at the site of disease. We know how

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M. tuberculosis adapts to these circumstances and how this translates to decreased drug susceptibility in these animals because we have created assays that replicate immunological pressure, environmental stress, and drug-induced stress in vitro and ex vivo. Ex vivo models, which most closely mimic in vivo conditions, include those that use rabbit explanted cavity caseum (72), and M. tuberculosis (53, 73) that can be selectively cultured from patient sputum. However, these models are resource-intensive by nature and are typically used to profile clinical development compounds and approved drugs. There is still a significant knowledge gap regarding intracellular M. tuberculosis drug tolerance for two reasons. First, M. tuberculosis infection experiments use a variety of immortal cell lines and, rarely, macrophages generated from primary blood or bone marrow monocytes, which results in inconsistent potency levels. For instance, macrophage-like immortalised cell lines are frequently utilised despite the fact that M. tuberculosis is 100 times less vulnerable to rifampicin in hypoxic lipid-loaded macrophages than in normoxic THP-1-derived macrophages74,75. This is due to the cell lines' low cost and simplicity of maintenance. There is a lack of a comparison of anti-TB drug efficacy in infected primary macrophages and common cell lines. Second, it is now widely acknowledged that polymorphonuclear leukocytes represent a vital and hospitable environment for bacterial survival and reproduction76,77,78,79. Instead of killing mycobacteria, neutrophils appear to offer a sanctuary and transfer them to macrophages where they can continue to pose a threat to host tissue80. A test to determine the drug tolerance of M. tuberculosis found inside and surrounding neutrophils and other granulocytes has not yet been created, neither in vivo nor ex vivo. A recent study found that granulocytes are retained in M. tuberculosis-infected mouse lungs for at least as long as monocytes and macrophages, which is consistent with a model in which M. tuberculosis uses granulocytes as a replicative niche for intracellular growth81. However, the short lifespan of neutrophils may present a challenge.

Priorities for drug development

The shortcomings of TB treatment can be attributed to four main problems: treating TB takes much longer than treating other bacterial lung infections because of a combination of drug, pathogen, and host factors; drug tolerance fuels and synergizes with drug resistance; single drug and regimen development tested in sequence is naturally slow while tools are emerging to rationally prioritise regimens early in the cascade; and a surprisingly small number of drugs have been proven effective. Although the separation into such broad categories could seem unduly simplistic, it offers a helpful starting point to highlight potential topics for future study and indicate top priorities for drug development.Addressing biological knowledge gaps to optimize treatment.

The ability of M. tuberculosis to persist and multiply within host cells intended to eradicate bacterial pathogens93,94, suboptimal drug penetration at disease sites, and extreme drug tolerance of certain subpopulations, some of which are found in necrotic granulomas and cavity caseum, are all factors that contribute to persistent TB disease. To assure the best possible medication administration to bacilli in dynamic physical locations and metabolic states, it can be difficult to use such niche-specific pharmacokinetics and pharmacodynamics. Enhancing immune and memory response effectiveness, increasing the effectiveness of macrophage and neutrophil bactericidal mechanisms to counter the immune evasion mechanisms of M. tuberculosis, and disrupting granuloma structure to improve lung function and integrity are the four main concepts that underpin host-directed approaches that support antibacterial therapy to accelerate cure. These methods and the accompanying medicines that are being developed in clinical trials are outside the purview of this analysis and have recently undergone thorough reviews3.

Our understanding will undoubtedly improve as a result of a multifaceted approach that focuses on the pathogen, its metabolic and physiological adaptations, its precise location in relation to immune cells and lesion structures, and its susceptibility to drugs and drug combinations in these niches. This information may also contribute to the knowledge needed to create shorter regimens. Sputum, infected mouse lungs, ex vivo and in vitro macrophages, and other pertinent habitats have been the focus of recent research to identify mycobacterial targets that are crucial and vulnerable in persistence niches (reviewed in ref.95). The extremely low concentration of pathogen transcripts relative to host transcripts in biological samples represents a tremendous barrier and a constraint of currently available methods, despite the fact that host transcriptome investigations are common and produce more robust data. Given the continuously growing performance of sequencing technologies and big data analysis, this obstacle,

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however, is likely to be overcame shortly. Multi-omics profiling of M. tuberculosis in caseum, foamy hypoxic macrophages, neutrophils, and other persister populations in particular lesion compartments will identify pathways and functions that are essential for mycobacterial survival and may represent new antibiotic targets, potentially allowing for a reduction in treatment time. Similarly, persistence habitats including ex vivo caseum, macrophages, and mice infections could be subjected to a functional genomics screen based on validated CRISPR interference to uncover susceptible targets as well as targets that support or oppose drug therapy.

A rapidly developing area integrates experimental, systems biology, and computational approaches in potent platforms like INDIGO and DiaMOND to successfully harness the potential of synergistic drug interactions in multiple therapy regimens to speed lasting cure. They provide a living database of drug interactions that researchers can draw from to hone their predicting abilities. Because TB is a polymicrobial disease spread across multiple sites of infection, understanding which model systems and in vitro assays predict synergies that might translate into the clinic is complex. This is because in vitro synergies are measured in a homogeneous environment using constant drug concentrations, whereas TB is a polymicrobial disease spread across multiple sites of infectionIt is likely that synergy and antagonism are influenced by stochastic and adaptive cell-to-cell betting that results in a selective benefit for the entire bacterial population in ways that may be challenging to replicate in vitro. A promising example is the activation of a regulatory network by bedaquiline treatment in vitro, which coordinates many mechanisms to force M. tuberculosis into a tolerant state. This regulatory network can be disrupted by deleting the anticipated transcription factors Rv0324 and Rv0880, which increases bedaquiline lethality. This discovery made it possible to predict that pretomanid could work in concert with bedaquiline by blocking the Rv0880-response regulon and enhancing bedaquiline's capacity for population-level death. The critical next step for bedaquiline-pretomanid, the cornerstone of the incredibly effective NIX-TB regimen2, and for all predicted drug-drug synergies in general is identifying bacterial populations to which this applies in animal models and in patients with TB. This is true even though the authors experimentally confirmed the predictions in vitro. Pathway-based in vitro models, like INDIGO, make it possible to create hypotheses to test underlying biological pathways and modify in vitro growth settings to enhance predictions. The DiaMOND platform's ability to predict outcomes was recently tested utilising drug combination dose responses recorded under eight settings that mimic lesion microenvironments. To create classifiers that predicted the result of a multi-drug treatment in a mouse model of illness relapse, machine learning was applied to all two-drug and three-drug combinations of ten antibiotics. The variable medication concentrations observed by bacilli at the sites of infection make it more difficult to identify favourable pharmacodynamic interactions in vitro that translate into the clinic since potency interactions fundamentally depend on the relative concentration of each drug in the combination.

There are sophisticated techniques available, and many more are being developed, to examine the metabolic condition of bacteria and follow them during treatment in animal models and inpatient bioaerosols. The identification and mapping of M. tuberculosis persisters that endure drug therapy is a crucial pragmatic result of these activities that will help prioritise future research. Although resected lung tissues from individuals undergoing elective surgery for drug-resistant illness may be an underutilised resource, validating the results from samples of the human lung is difficult. As previously stated, the involvement of macrophages, which is considerably more accessible to in vitro and ex vivo research, has eclipsed the contribution of M. tuberculosis bacilli that survive and grow in and surrounding neutrophils to chronic disease76,77,81. The majority of M. tuberculosis bacilli in sputum and cavity caseum, however, are extracellular or found inside neutrophils, with a minor percentage reproducing in macrophages79. Consistent with these discoveries, a signature of active TB is dominated by a neutrophil-driven interferon-inducible gene profile112 and cavity caseum is typically infiltrated with infected neutrophils in both animal models and people.

putting emphasis on effective medication combinations

Over the past 5–10 years, a new paradigm of pan-TB regimen development has gained traction as a result of an expanding pipeline of anti-TB medication candidates (Fig. 2a). A significant number of drug candidates and recently licenced medications with unique modes of action have made it possible to develop new regimens to treat

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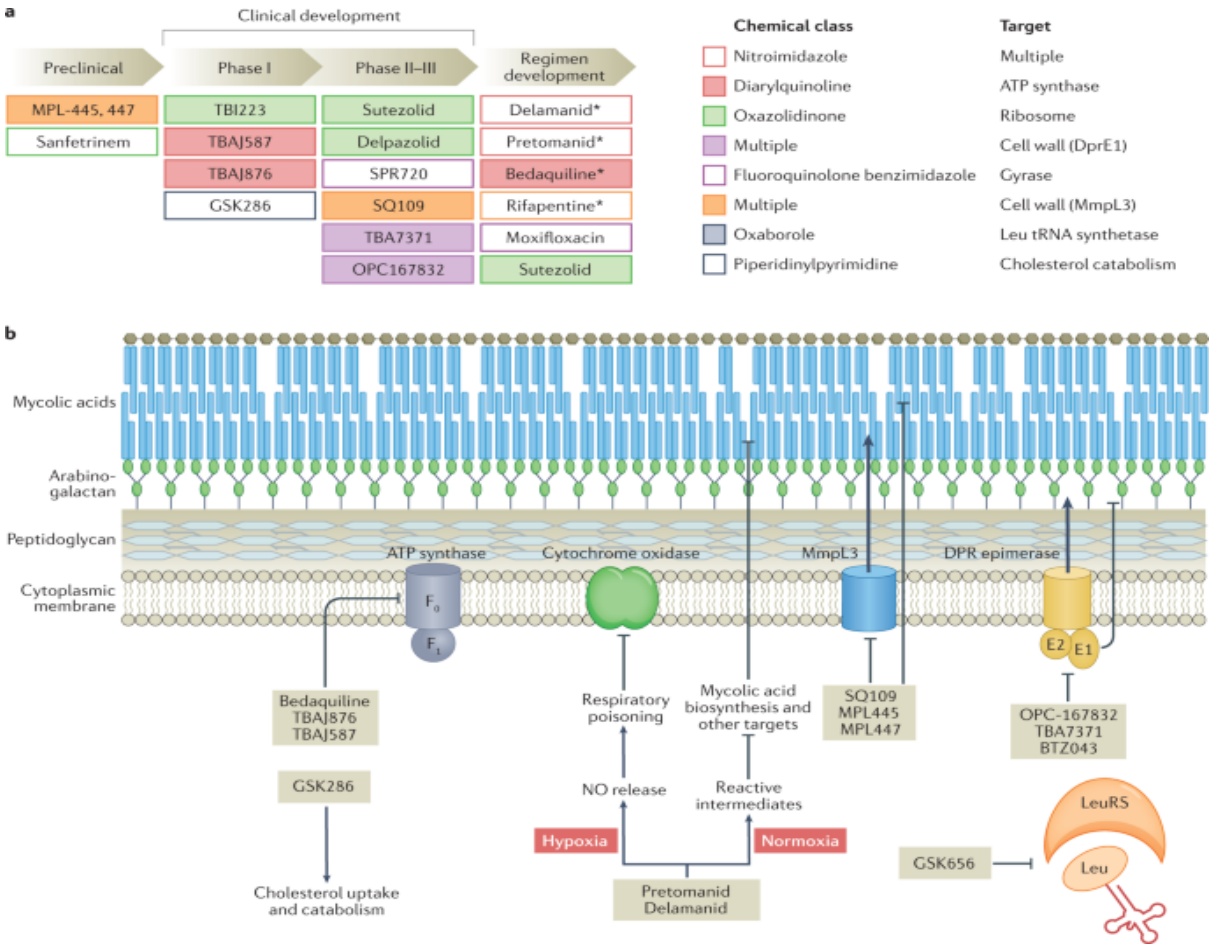
drug-susceptible, MDR, and XDR M. tuberculosis infections (Fig. 2b). Universal regimens would significantly speed up global TB control efforts.

Fig. 2 shows the pipeline for potential anti-tuberculosis drugs as well as their modes of action.



a. Promising therapeutic candidates that are now undergoing preclinical and clinical testing are displayed. This includes the creation of regimens that mix existing, novel, and repurposed medication classes. Asterisks are used to denote approved medications (the FDA allowed pretomanid for use in the bedaquiline-pretomanid-linezolid regimen, but the EMA only approved delamanid). According to chemical type and target pathway, drugs are colour coded. See Working Group on New TB Drugs for a comprehensive list of published candidates that are now in the pipeline, from early preclinical development to regulatory approval, as well as an analysis of their mode of action.

b. Schematized versions of the targets of recently licenced medications and clinical candidates, with unique mechanisms of action, are listed in part, along with a simplified form of the cell envelope and cytoplasmic membrane of Mycobacterium TB. The vast majority of new targets are connected to membranes. The ATP synthase is the target of the diarylquinolines bedaquiline, TBAJ-876, and TBAJ-587. Pretomanid and Delamanid, two nitroimidazoles, have a dual mode of action under low and normal oxygen tension, block numerous vital pathways, and are bactericidal to both replicating and non-replicating

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mycobacteria.Among a wide range of compounds that target MmpL3, which is involved in the export of trehalose monomycolate, a component of mycolic acid, SQ109 and the MPL series are the most advanced. The three chemically different series OPC167832, TBA7371, and BTZ043 all aim for DprE1. The mycobacteria are the only ones with MmpL3 and DprE1. GSK286 is a novel chemical with a novel mechanism of action related to cholesterol catabolism, while GSK656 is the first oxaborole in clinical development targeting a mycobacterial tRNA synthetase. From Springer Nature Limited, with permission.

Conclusion

The COVID-19 outbreak's effects have already shown that we are unlikely to meet the WHO's "end TB strategy" goals of an 80% decline in TB incidence and a 90% decline in TB-related fatalities by 2030. These objectives are frequently viewed as an optimistic scenario, even under more favourable conditions, due to the logistical challenges of a 6-month multidrug regimen and the worse treatment outcomes in the presence of an infection that is resistant to antibiotics. If we rely on the conventional strategy of repeated huge clinical trials with minor incremental adjustments in medication regimens, this will take decades. Shorter and more effective medicines, however, could help us achieve our millennium goals much more quickly. Innovative trial designs and regimens with unique mechanisms of action will result in breakthroughs. One encouraging step in that approach is the success of bedaquiline-pretomanid-linezolid for MDR and XDR M. tuberculosis, which has given rise to an almost infinite number of potential variations. We are optimistic that the preclinical and clinical methods we discussed in this Review would enable early selection and evaluation of medication combinations and significantly speed up the licencing of more compact treatment regimens. Sociological shifts support collaborative efforts that accelerate the search for ground-breaking drug candidates28, such as the removal of barriers between groups of academic institutions, non-governmental organisations, donors, and drug sponsors. However, in order to truly speed up drug development, all processes must alter, from modernised clinical trials to sustained funding of basic and applied research. Additionally, we may eventually develop more individualised treatments, which would necessitate significant modifications to the way most of the world currently provides healthcare. Although there are still significant obstacles to overcome, change has already occurred, so there is reason for hope with a good dosage of realism.

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