SUPPLEMENT ARTICLE

Perspectives on Advances in Tuberculosis Diagnostics, Drugs, and Vaccines

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Despite concerted efforts over the past 2 decades at developing new diagnostics, drugs, and vaccines with expanding pipelines, tuberculosis remains a global emergency. Several novel diagnostic technologies show promise of better point-of-care rapid tests for tuberculosis including nucleic acid–based amplification tests, imaging, and breath analysis of volatile organic compounds. Advances in new and repurposed drugs for use in multidrug-resistant (MDR) or extensively drug-resistant (XDR) tuberculosis have focused on development of several new drug regimens and their evaluation in clinical trials and now influence World Health Organization guidelines. Since the failure of the MVA85A vaccine 2 years ago, there have been no new tuberculosis vaccine candidates entering clinical testing. The current status quo of the lengthy treatment duration and poor treatment outcomes associated with MDR/XDR tuberculosis and with comorbidity of tuberculosis with human immunodeficiency virus and noncommunicable diseases is unacceptable. New innovations and political and funder commitment for early rapid diagnosis, shortening duration of therapy, improving treatment outcomes, and prevention are urgently required.

Keywords. tuberculosis; diagnostics; drugs; vaccines; management.

Tuberculosis remains a leading infectious disease cause of death globally, and an estimated 3 million cases of tuberculosis remained undiagnosed and untreated in 2013 [1, 2]. Early-stage disease, extrapulmonary tuberculosis, tuberculosis/human immunodeficiency virus (HIV) coinfection, childhood tuberculosis, and multidrug-resistant tuberculosis are particularly problematic to diagnose and treat. Autopsy studies from Africa confirm the large load of undiagnosed tuberculosis, subclinical tuberculosis, and tuberculosis comorbidity with HIV, pyogenic pneumonia, and other infectious and noncommunicable diseases [3–5]. This unacceptable status quo indicates that prevailing approaches to diagnosing, treating, managing, and preventing tuberculosis are inadequate and require critical appraisal. We discuss the current and developmental landscape of diagnostics, drugs, and vaccines.

TUBERCULOSIS DIAGNOSTICS

The definitive test for tuberculosis disease is detection of *Mycobacterium tuberculosis* complex bacilli (*Mtb*) in clinical specimens from a symptomatic patient [6].

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Sputum is the specimen of choice for diagnosing pulmonary disease, but the mucoid and viscous nature of the sample makes it difficult to manipulate and often interferes with test performance. Sample processing is usually necessary before diagnostic tests are applied, resulting in increasing complexity and cost. For extrapulmonary tuberculosis, sampling is dependent on the suspected site of disease and requires invasive procedures. Attempts to develop blood, urine, and breath-based tests have met with limited success, as they are lacking in sensitivity and specificity [7]. In 2010, the World Health Organization issued a recommendation against the use of serological tests [8]. Several novel diagnostic technologies are being explored with the aim of providing better point-of-care rapid tests for tuberculosis. They include nucleic acid amplification tests (NAATs), imaging, and the analysis of volatile organic compounds.

Nucleic Acid Amplification Tests

The most advanced of the new tests, and first to the market, were simple methods for amplifying and detecting nucleic acids that do not need laboratory facilities or specialist technical skills. They have the potential advantage of incorporating detection of mutations predictive of drug resistance. The Xpert MTB/RIF assay (Cepheid Inc) is an automated polymerase chain reaction–based test that can identify *Mtb* DNA in clinical specimens and detect rifampicin resistance. It has been widely rolled out globally and evaluated extensively at all points of healthcare [9–17]. The current assay might miss up to 15%–30% of rifampicin rpoB gene mutations that confer resistance. An optimized version of the Xpert MTB/RIF is being developed, and preliminary data suggest 10-fold higher sensitivity than the standard Xpert assay [18]. The optimized version has improved the performance both in terms of sensitivity for detection of *Mtb* and for the detection of rifampicin resistance mutations that are missed by the current assay. However, this optimized assay at this point has not been tested in any human clinical context. In addition, the GeneXpert technology is not really an optimized point-of-care assay and requires some technical training and equipment maintenance. When used at the point of care, it also cannot perform in settings requiring high throughput.

Two tuberculosis tests recently released to the market are described in Table 1. Evaluation of these devices is ongoing, and there is as yet little published data regarding their clinical performance.

Studies on the Truenat MTB test (Molbio Diagnostics, India) [19] undertaken in India found sensitivity and specificity to be similar to that of the Xpert MTB/RIF assay [20, 21], whereas a study using EasyNAT in Tanzania reported high specificity (100%) and a sensitivity compared with culture of 66.7%, with 10% of smear-negative cases found to be positive [22]. A study from China on the EasyNAT Diagnostic Kit (Ustar Biotechnologies, China) [23] using processed sputum reported sensitivity and specificity of 84% and 98%, respectively. The sensitivity in smear-negative cases was 60% [24]. There are several tests ready for evaluation, but not yet released into the market, and a fuller description of the tuberculosis NAAT product development pipeline may be found in the 2014 UNITAID Tuberculosis Diagnostics Technology and Market Landscape Report [25].

Imaging

A number of imaging techniques can be used to gauge the extent of disease and to monitor treatment, and imaging remains a first-line tool for investigating extrapulmonary manifestations of the disease [26]. Chest radiography played a major role in reducing the prevalence of tuberculosis in Europe and North America in the 1950s and 1960s, with mobile radiograph units used for mass screening of communities. The introduction of digital radiography has improved image quality and facilitates the storage and sharing of images and, if required, a second opinion may be sought by remote (electronic) access. Compared to film-based radiographs, running costs are reduced and reagent stockouts avoided, but the cost of buying/leasing and maintaining the equipment remains high. A further development

Table 1. Commercially Available Nucleic Acid Amplification Tests for Tuberculosis Intended for Use at the Point of Care

Device	Manufacturer	Technology	Target	Power Source	Drug Resistance	Sample Extraction	Time to Result
Expert MTB/RIF	Cepheid, USA	Real-time PCR	rpoB	Mains	Rifampicin	Automated	90 min
Truenat MTB	Molbio Diagnostics, India	Miniaturized chip-based real-time PCR	Ribonucleoside-diphosphate reductase gene	Mains or battery	None	Semiautomated using separate device	60 min
EasyNAT CPA diagnostic kit for *Mycobacterium tuberculosis* DNA	Ustar Biotechnologies, China	Isothermal cross-priming amplification	IS6110	Mains: Heating block or water bath and vortex required (not supplied)	None	Manual extraction	90 min, excluding sample extraction

Abbreviations: CPA, cross priming amplification; PCR, polymerase chain reaction.

is application of computer-aided image analysis to provide an automated imaging service. Studies suggest that sensitivities from automated readers can be similar to those obtained by eye but that specificity is reduced [27], a finding confirmed by studies in Africa [28, 29]. Alternative imaging technologies such as magnetic resonance imaging, computed tomography, and positron emission tomography–computed tomography (PET-CT) may eventually find utility in the investigation of extrapulmonary disease [26].

PET-CT is another modality that is being explored for tuberculosis [19]. Fluorodeoxyglucose (FDG) accumulates in metabolically active immune system cells and can serve as a marker of tuberculosis-associated inflammation. FDG PET-CT at 2 months has been shown in pilot studies to correlate with outcome in patients with confirmed MDR tuberculosis [30]. However, as FDG accumulates in all metabolically active cells, it has low specificity as a diagnostic and is unable to distinguish between tuberculosis and other metabolically active lung processes such as malignancy. New radioprobes for PET and single-proton emission computed tomography are being developed that target not glucose metabolism but markers of tuberculosis-specific pathology including tissue pH, hypoxia, tissue calcification [31], and inflammation [32, 33].

Breath Tests

Volatile organic compounds (VOC) and gases are produced by *Mtb* as byproducts of their metabolic processes, and their detection by analysis of breath or volatile compounds [34] emanating from clinical specimens is being exploited for development of breath-based tests. The most sensitive detectors and those best suited to differentiating complex mixtures are olfactory systems of mammals and insects [35]. Giant African pouched rats (*Cricetomys gambianus*) have been trained to recognize the smell of *Mtb*-infected sputum [36]. When samples were exposed to ten different rats, 91% of *Mtb* smear-positive samples were detected [37]. Attempts to mimic the rats using electronic and chromatographic methods have so far been disappointing. E-nose technologies that showed early promise were found to be unreliable [38]. Developers of a chromatographic-based breath test have reported sensitivities and specificities of 71% and 72%, respectively, when comparing untreated tuberculosis patients against nonsymptomatic individuals [38].

E-health

A feature shared by many of the new diagnostic devices is the capacity to transmit data via wireless or cell phone technology to an external database. The ability to store, retrieve, and share data in a central repository offers considerable logistic advantages for health providers and may facilitate an improved service for patients. However, as presented in Table 2, there are a number of concerns to be addressed about this new and currently unregulated technology. It is as yet unclear who shall own the data, and for what purposes it would be used. A second, and pressing issue, is compatibility and standardization of data handling storage and systems, because if manufacturers choose to adopt different systems, the potential benefits of e-health to the patient and the health provider will be diluted.

NEW TUBERCULOSIS DRUGS, REPURPOSED DRUGS, AND TREATMENT REGIMENS

Advances in new and repurposed drugs continuously update World Health Organization (WHO) guidelines for use in designing treatment regimens for MDR and XDR tuberculosis. Figure 1 illustrates tuberculosis drug development over time. Recent attention has focused on development of the new

Table 2. Potential Advantage and Pitfalls of eHealth and Transfer of Information From In Vitro Diagnostics Devices to External Data Handling and Storage Facilities

Advantages	Beneficiaries	Risks	Victims
1. Access to online expert opinion	Patients, health professionals	1. Breaches of confidentiality	Patients
2. Improved record keeping	Health providers, patients	2. Exclusion of patients with poor access to the technology	Patients
3. Improved stock management	Health providers, manufacturers, distributors	3. Exclusion of sites/communities with poor access to the technology	Patients and health providers
4. Improved quality control data	Health providers	4. Lack of access to information during equipment failure or power outages	Health providers, patients
5. Improved epidemiological data collection	Control program, policy makers	5. Data used for inappropriate purposes (eg, unsolicited marketing of products, insurance policies)	Health providers, patients
6. Monitoring device performance	Manufacturers, distributors	6. Failure to integrate leading to multiple systems, resulting in chaos	Health providers, patients
7. Improved market intelligence	Manufacturers, distributors, private health providers	7. Increased suspicion and mistrust of health providers promotes delayed health seeking	Patients

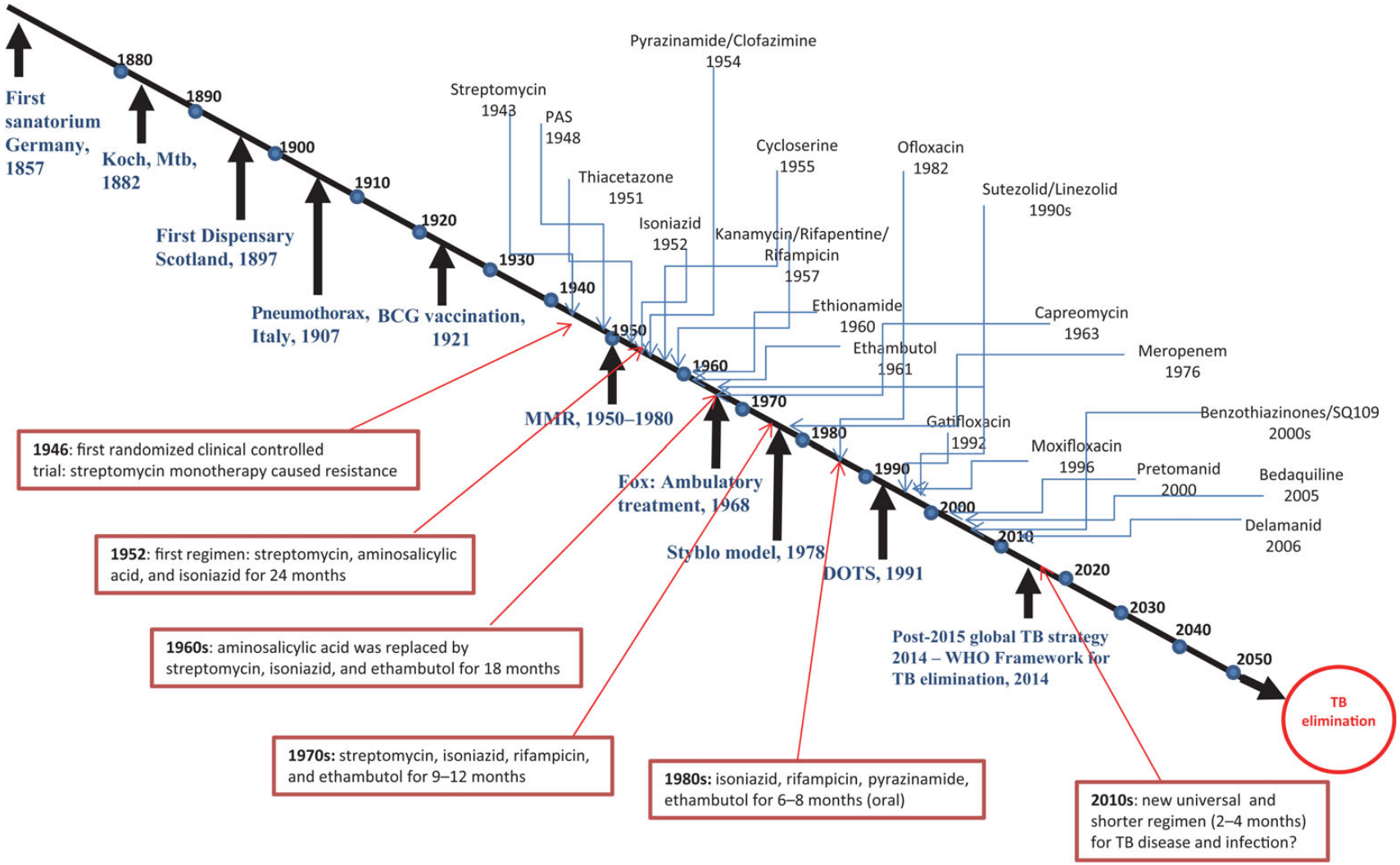

Figure 1. Historical timelines of discovery of tuberculosis drugs and introduction of tuberculosis treatment regimens used at programmatic level. Abbreviations: DOTS, directly observed treatment, short-course; MMR, mass miniature radiograph; Mtb, *Mycobacterium tuberculosis*; PAS, para-aminosalicylic acid; TB, tuberculosis; WHO, World Health Organization.

drugs bedaquiline, delamanid, pretomanid (PA-824), sutezolid, and SQ109 and their evaluation in clinical trials (Table 3).

Diarylquinolones

Bedaquiline selectively targets the proton pump of adenosine triphosphate (ATP) synthesis, leading to inadequate ATP [48]. Bedaquiline's bactericidal activity is superior to that of isoniazid and rifampicin [48]. The results of phase 2 trials suggest that a standard 2-month treatment regimen with bedaquiline can have high culture conversion rates, rapid sputum culture conversion, and low acquired resistance to companion drugs in newly diagnosed MDR tuberculosis cases [39, 49]. Both WHO [50] and the US Centers for Disease Control and Prevention [51] issued recommendations that support the use of bedaquiline, at the dose of 400 mg daily for 2 weeks, then 200 mg 3 times a week for 22 weeks, added to an optimized background regimen to treat MDR tuberculosis in adults when the following conditions are met: pharmacovigilance is in place, informed consent is ensured and QT monitoring is possible [50, 51]. Due to an increased risk of QT prolongation and death, simultaneous use of bedaquiline and delamanid is not recommended [50, 51]. Phase 3 trials of the use of bedaquiline for shortening duration of therapy are under way.

Nitroimidazoles

Delamanid (OPC-67683) and pretomanid (PA-824) inhibit the synthesis of mycolic acids and are active against both replicating and anaerobic, nonreplicating *Mtb* persisters and have shown potential for improving treatment outcomes for MDR tuberculosis [40–44, 52–56]. They are currently in phase 2 and phase 3 clinical trials (Table 3) [40–44]. Based on the available evidence, WHO [54] recommends the use of delamanid at the dose of 100 mg twice daily for 6 months, added to optimized background regimen in adults, when pharmacovigilance is in place and informed consent ensured. Although anecdotal evidence suggests that delamanid is effective and safe in children [55], 2 clinical trials (NCT01859923 and NCT01856634) are studying delamanid in the treatment of pediatric MDR tuberculosis.

Diacon et al assessed the 14-day early bactericidal activity of a regimen composed of pretomanid, moxifloxacin, and pyrazinamide, which proved to be significantly higher than that of bedaquiline alone, bedaquiline plus pyrazinamide, and bedaquiline plus pretomanid (but not to pretomanid plus pyrazinamide), and comparable to that of the standard treatment regimen (isoniazid, rifampicin, and pyrazinamide with streptomycin or ethambutol). Interestingly, the addition of pyrazinamide increased the activity of both bedaquiline and pretomanid [39, 42, 44, 56]. Pharmacokinetic/pharmacodynamic and safety studies are under way combining bedaquiline and delamanid and, although the combination of these is not currently recommended, outcomes from these studies may change that.

In a recent phase 2b trial, the bactericidal activity of a new 8-week regimen including moxifloxacin, pretomanid, and pyrazinamide was compared to that of the standard antituberculosis regimen for drug-susceptible and drug-resistant tuberculosis. The new regimen yielded higher bactericidal activity in liquid culture than the current WHO-recommended regimen after 2 months of treatment [43].

Tuberculosis-354 is a second-generation nitroimidazole and the first tuberculosis drug to enter phase 1 trials since 2009 [57].

Oxazolidinones

Sutezolid (PNU-100480) has potent anti-*Mtb* activity and acts by binding to 23S RNA and 50S ribosomal subunits [58], preventing the initiation of protein synthesis. It is safe and well tolerated [59, 60]. Recent phase 2 clinical trials of sutezolid (NCT01225640) assessing safety and efficacy using early bactericidal activity (EBA) and whole-blood bactericidal activity were completed [45] (Table 3). Tedizolid, recently approved by the US Food and Drug Administration for skin and skin structure infections, has shown activity in vitro against *Mtb* [61], but no studies in *Mtb*-infected humans has been performed. AZD5847, another new oxazolidinone, has been shown to have activity in mice [62], and human studies are ongoing.

Ethylenediamines

SQ109 is an analogue of ethambutol active against both drug-susceptible and drug-resistant *Mtb* by targeting MmpL3 and inhibiting the protein synthesis [63]. In a 2-week phase 2 EBA trial, SQ109, although safe, did not appear to be active alone or to enhance the activity of rifampicin [46]. Similarly, in a recent trial that compared ethambutol with SQ109 for drug-susceptible tuberculosis in a 12-week intensive phase regimen including rifampicin, isoniazid, and pyrazinamide, no difference was seen in 12-week culture conversion [64].

Benzothiazinones

These new classes of antituberculosis drugs, in preclinical development phase, are able to inhibit the synthesis of decaprenylphospho-arabinose, the precursor of the arabinans in the mycobacterial cell wall [23]. Preliminary evidence suggests the BTZ043 is potent, with activity against 240 clinical isolates of *Mtb*, including drug-susceptible, MDR, and XDR tuberculosis. Additive interactions and no antagonism were found between BTZ043 and rifampicin, isoniazid, ethambutol, pretomanid, moxifloxacin, meropenem with or without clavulanate, and SQ109, whereas synergic effects were found combining BTZ043 and bedaquiline (Table 3) [47].

In addition, some repurposed drugs for treatment of MDR/XDR tuberculosis (linezolid, clofazimine, moxifloxacin and levofloxacin, meropenem, rifapentine) are summarized in Table 4 [65–83].

REMOX, OFLOTUB, AND RIFAQUIN FLUOROQUINOLONE TRIALS

Recently, 3 trials failed to demonstrate noninferiority of 4-month fluoroquinolone-containing regimens compared with standard 6-month therapy. The Rapid Evaluation of Moxifloxacin in Tuberculosis (REMoxTB) study was a randomized, double-blind, placebo-controlled trial evaluating 2 regimens in which either ethambutol or isoniazid was substituted by moxifloxacin in a single 4-month combination therapy [84]. The Ofloxacine-Containing, Short-Course Regimen for the Treatment of Pulmonary Tuberculosis trial [85, 86] evaluated a standard 6-month regimen that included ethambutol during the 2-month intensive phase against a 4-month regimen in which ethambutol was substituted with gatifloxacin during the intensive phase and continued, along with rifampicin and isoniazid, during the continuation phase. The High-Dose Rifapentine with Moxifloxacin for Pulmonary Tuberculosis trial [87] evaluated 2 regimens in which moxifloxacin replaced isoniazid in an intensive phase. Although these results have been disappointing, ongoing combination regimens in phase 3 clinical trials using existing, repurposed, and new drugs, together with developments in adjunct host-directed therapies, provide hope for increasing therapeutic efficacy; shortening treatment duration and improving treatment outcomes for drug-susceptible and drug-resistant tuberculosis remain global priorities. Rifapentine and clofazimine and high-dose rifampicin are under investigation for treatment-shortening regimens of drug-susceptible tuberculosis, not just for MDR and XDR tuberculosis.

Design and selection of future experimental regimens will need to incorporate a triage process so that accelerated evaluation of treatment-shortening regimens can be achieved. Whereas the recent phase 3 fluoroquinolone trials have pointed to the difficulty of predicting successful 4-month regimens using existing biomarkers, an alternative strategy uses novel trial designs looking at clinically relevant outcomes as an alternative to biomarkers for screening new drugs or drug combinations. Viable approaches include the multiarm, multistage trial design and other adaptive trial designs [88]. While optimal drug treatment regimens are developed, even if they are made up of fewer drugs and are for a shorter duration, it will be critical that adherence to full-course chemotherapy is monitored to minimize the generation of drug resistance.

TUBERCULOSIS VACCINE DEVELOPMENT

The universal hope that by 2015 a candidate vaccine that would be able, at least partially, to boost protection induced by BCG alone would become available from the existing pipeline [89] has not materialized. The failure of the MVA85A vaccine to demonstrate any improvement over BCG in an infant efficacy trial [90] has led to reluctance by funders to invest in further tuberculosis vaccine efficacy trials, and the effectiveness of other vaccines in clinical development has been brought under close scrutiny [91, 92]. The post-2015 strategy of the Stop TB Partnership is more ambitious, aiming for a 90% reduction in tuberculosis incidence by 2035 [1]. Mathematical modeling highlights the contribution that an effective vaccine could make toward achievement of this goal [93]. Given the current uncertainty in the field, there is a high risk of failure in the development and testing of a new tuberculosis vaccine; however, as the potential gains in terms of reduced global mortality and morbidity are also high, clinical development of tuberculosis vaccine candidates must continue.

Following the failure of MVA85A, there has been no new, high-profile tuberculosis vaccine candidate entering clinical testing in the last 2 years. The number of candidates in clinical testing remains at 16 and can be divided into priming vaccines (VPM1002, MTBVAC), prime-boost vaccines (M72 + AS0, MVA85A, Crucell Ad35, Hybrid 1 + IC31, Hybrid 4 + IC31, Hybrid 56 + IC31, Ad5Ag85A, ChAdOx1 85A + MVA85A, Combination Crucell Ad35 + MVA85A, DAR-901, ID93 + GLA-SE), and immunotherapeutic vaccines (*Mycobacterium indicus pranii*, *Mycobacterium vaccae*, RUTI) [89]. As BCG confers some protection in childhood, the optimum strategy is believed to be a prime-boost strategy in adolescents or young adults that would prevent progression to pulmonary tuberculosis disease. However, the incidence of disease in adolescents is lower than that of infants, and efficacy trials in adolescents would be substantially larger than the MVA85A infant efficacy trial, which recruited 2797 infants and had follow-up for a median of 24.6 months. In addition, with a large proportion of the population in tuberculosis-endemic countries already latently infected with tuberculosis, the vaccine candidate likely to have the greatest impact on transmission would be one that worked both before and following latent tuberculosis infection [91].

Since 2013, attention has been focused on strategies for reducing the risk of failure in tuberculosis vaccine efficacy trials with a disease endpoint. Such strategies include improving animal models, human challenge models, and prevention of infection trials. Identifying vaccine failure in preclinical development or early clinical development is critical if scarce resources available for clinical vaccine testing are to be used most effectively. However, uncertainty in how to identify early success or failure of a tuberculosis vaccine candidate and lack of a correlate of protection has led to a situation of status quo in the field.

Future Tuberculosis Vaccine Prospects

Following the recent launch of 2 major tuberculosis vaccine consortiums funded through the Horizon 2020 European Union Framework Programme for Research and Innovation, reinvigoration of tuberculosis vaccine development programs is anticipated. The Tuberculosis Vaccine Initiative Consortium (TBVI) was

Table 3. Summary of the Main New Antituberculosis Drugs With the Most Relevant Studies and Related Findings

Drug	Class	Study ID Number	Clinical Trial Phase	Registration Number	Main Findings	Reference
Bedaquiline (TMC207)	Diarylquinoline	TMC207-TIDP13-C208	Phase 2	NCT00449644	The addition of delamanid (TMC207) to OBR reduced the time to C conversion, compared with OBR (HR, 11.8; 95% CI, 2.3–61.3; $P = .003$) and increased the proportion of C converters (48% vs 9%). The mean log(10) count of CFU in SS declined more rapidly in the TMC207 group than in OBR group. No significant differences in average plasma TMC207 concentrations were noted between patients with and those without C conversion. Most AE were mild to moderate.	[39]
Delamanid Trial 204 (OPC 67 683)	Nitroimidazole	242–07-204	Phase 2	NCT00685360	Among patients who received OBR plus 100 mg of delamanid BID, 45.4% had C conversion at 2 mo, as compared with 29.6% of patients receiving OBR ($P = .008$). As compared with OBR, the group receiving OBR plus delamanid 200 mg BID had a higher proportion of SS and C conversion (41.9%, $P = .04$. Most AEs were mild to moderate and evenly distributed across groups. Although no clinical events due to QT prolongation on ECG were observed, QT prolongation was reported significantly more frequently in the delamanid groups.	[40]
Delamanid Trial 208 (OPC 67 683)	Nitroimidazole	242-09-213	Phase 3	NCT01424670	Patients who participated in the previously reported controlled trial of delamanid and the subsequent open-label extension trial were eligible to participate in a 24-month observational study designed to capture treatment outcomes. Favorable outcomes were observed in 143/192 (74.5%) patients receiving delamanid for ≥6 mo, vs 126/229 (55%) patients who received delamanid for ≤2 mo. Mortality was reduced to 1.0% among those receiving long-term delamanid vs short-term/no delamanid (8.3%; $P < .001$). Treatment benefit was also seen among XDR-TB patients.	[41]
Pretomanid Trial NC-001 (PA-824)	Nitroimidazole	NC-001-(J-M-Pa-Z)	Phase 2	NCT01215851	The mean 14-d EBA of pretomanid (PA-824) -moxifloxacin-pyrazinamide (n = 13; 0.233 [SD, 0.128]) was significantly higher than that of bedaquiline (n = 14; 0.061 [SD, 0.068]), bedaquiline-pyrazinamide (n = 15; 0.131 [SD, 0.102]), bedaquiline-PA-824 (n = 14; 0.114 [SD, 0.050]), but not PA-824-pyrazinamide (n = 14; 0.154 [SD, 0.040]), and comparable with that of standard treatment (n = 10; 0.140 [SD, 0.094]). Treatments were well tolerated and appeared safe. One patient on PA-824-moxifloxacin-pyrazinamide was withdrawn because of corrected QT interval changes exceeding prespecified criteria.	[42]

Table 3 continued.

Drug	Class	Study ID Number	Clinical Trial Phase	Registration Number	Main Findings	Reference
Pretomanid Trial NC-002 (PA-824)	Nitroimidazole	NC-002-(M-Pa-Z)	Phase 2	NCT01498419	The study evaluated a novel regimen for efficacy and safety in DS and MDR-TB during the first 8 wk of treatment. Smear-positive DS, treatment-naive PTB patients randomized were enrolled to receive 8 wk of moxifloxacin, pretomanid (100 mg) and pyrazinamide (MPa100Z – regimen 1) or moxifloxacin, pretomanid (200 mg), and pyrazinamide (MPa200Z- regimen 2) or the current standard regimen for DS-PTB, (isoniazid, rifampicin, PZA, and ethambutol, HRZE) as positive control]). A group of MDR participants received moxifloxacin 400 mg, pretomanid 200 mg, and pyrazinamide 1500 mg (DRMPa200Z). The regimen 1 BA days 0–56 (n = 54; 0.155 [95% BCI, .133–.178]) in DS patients was significantly greater than for standard regimen (n = 54; 0.112 [95% BCI, .093–.131]). Regimen 2 had similar BA to regimen standard. The BA days 7–14 was well correlated with BA days 7–56. AEs were equally distributed among group and control subjects. The most common AE was hyperuricemia in 59 (28.5%) patients spread similarly across treatment groups. Other common AEs were nausea in 37 (17.9%) and vomiting in 25 (12.1%) patients. No patient had corrected QT interval exceeding 500 msec. No phenotypic resistance developed . The MPaZ combination, previously found to have promising activity over 14 d in DS-TB, was safe, well tolerated, and demonstrated superior BA in DS-TB during 8 wk of treatment. Results were consistent between DS-TB and MDR-TB.	[43]
Pretomanid Trial NC-003 (PA-824)	Nitroimidazole	NC-003-(C-J-Pa-Z)	Phase 2	NCT01691534	Experimental and clinical evidence suggests that the new drugs bedaquiline (Bdq) and pretomanid (Pto), combined with an existing drug, pyrazinamide (Z), and a repurposed drug, clofazimine (Cfz), may assist treatment shortening of both DS-TB and DR-TB. The study evaluated the 14-d early BA of Cfz and Z in monotherapy and in combinations with Pto and Bdq. Groups of 15 treatment-naive, SS-positive pulmonary TB patients were randomized to receive combinations of Bdq with Z-Cfz, Pto-Z, Pto-Z-Cfz and Pto-Cfz, or Cfz or Z alone, or standard combination treatment for 14 d. The primary endpoint was the mean daily fall in $\log_{10}$ *M. tuberculosis* CFU/mL SS estimated by joint nonlinear mixed effects Bayesian regression modeling. Results: estimated activities were 0.167 (95% CI, .075–.257) for Bdq-Pto-Z, 0.151 (95% CI, .071–.232) for standard treatment, 0.124 (95% CI, .035–.214) for Bdq-Z-Cfz, 0.115 (95% CI, .039–.189) for Bdq-Pto-Z-Cfz, and 0.076 (95% CI, .005–.145) for Bdq-Pto-Cfz. Z alone had modest activity (0.036; 95% CI, −.026–.099). Cfz had no activity alone (−.017; 95% CI, −.085 to .053) or in combinations. Treatments were well tolerated and safe. Bdq-Pto-Z, including 2 novel agents without resistance in prevalent *M. tuberculosis* strains, is a potential new TB treatment regimen. Cfz had no measurable activity in the first 14 d of treatment.	[44]

Table 3 continued.

Drug	Class	Study ID Number	Clinical Trial Phase	Registration Number	Main Findings	Reference
Sutezolid Trial Sutezolid EBA and WBA (PNU-100480)	Oxazolidinone	B1171003	Phase 2	NCT01225640	All patients completed assigned treatments and began subsequent standard TB treatment according to protocol. The 90% CI for BA in sputum over the 14-d interval excluded zero for all treatments and both monitoring methods, as did those for cumulative WBA. There were no treatment-related serious AEs, premature discontinuations, or dose reductions due to laboratory abnormalities. There was no effect on the QT interval. Seven sutezolid-treated patients (14%) had transient, asymptomatic ALT elevations to 173 ± 34 U/L on day 14 that subsequently normalized promptly; none met Hy's criteria for serious liver injury. The BA of sutezolid 600 mg BID or 1200 mg OB was readily detected in sputum and blood. Both schedules were generally safe and well tolerated.	[45]
SQ109 Trial SQ109-01	Ethylenediamine	LMU-IMPH-SQ109-01	Phase 2	NCT01218217	This first study in patients was done to determine safety, tolerability, pharmacokinetics, and bacteriological effect of different doses of SQ109 alone and in combination with rifampicin when administered over 14 d. SQ109 was safe and generally well tolerated. Mild to moderate dose-dependent gastrointestinal complaints were the most frequent adverse events. No relevant QT prolongation was noted. Maximum SQ109 plasma concentrations were lower than MICs. Exposure to SQ109 (AUC0-24) increased by drug accumulation upon repeated administration in the SQ109 monotherapy groups. Coadministration of SQ109 150 mg with rifampicin resulted in decreasing SQ109 exposures from day 1 to day 14. A higher (300 mg) dose of SQ109 largely outweighed the evolving inductive effect of rifampicin. The daily fall in log CFU/mL of sputum was 0.093 (95% CI, .126–.059) with rifampicin, 0.133 (95% CI, .166–.100) with rifampicin plus 150 mg of SQ109 and 0.089 (95% CI, .121–.057) with rifampicin plus 300 mg of SQ109. Treatments with SQ109 alone showed no significant activity. SQ109 alone or with rifampicin was safe over 14 d. Upon coadministration with rifampicin, 300 mg of SQ109 yielded a higher exposure than the 150-mg dose. SQ109 did not appear to be active alone or to enhance the activity of rifampicin during the 14 d of treatment.	[46]

Table 3 continued.

Drug	Class	Study ID Number	Clinical Trial Phase	Registration Number	Main Findings	Reference
Benzothiazinones (BTZ043)	2-[(2S)-2-methyl-1,4-dioxa-8-azaspiro [4.5]dec-8-yl]-8-nitro-6-trifluoromethyl-4H-1,3-benzothiazin-4-one/Rv3790 -		Preclinical development phases		The authors studied the interaction profiles of BTZ043, the current lead compound, with several anti-TB drugs or drug candidates against *M. tuberculosis* strain H37Rv, namely, rifampicin, isoniazid, ethambutol, delamanid, pretomanid (PA-824), moxifloxacin, meropenem with or without clavulanate, and SQ-109. No antagonism was found between BTZ043 and the tested compounds, and most of the interactions were purely additive. BTZ043 acts synergistically with delamanid, with a fractional inhibitory concentration index of 0.5. TMC207 at a quarter of the MIC (20 ng/mL) used in combination with BTZ043 (1/4 MIC, 0.375 ng/mL) had a stronger bactericidal effect on *M. tuberculosis* than delamanid alone at a concentration of 80 ng/mL. This synergy was not observed when the combination was tested on a BTZ-resistant *M. tuberculosis* mutant, suggesting that DprE1 inhibition is the basis for the interaction. This finding excludes the possibility of synergy occurring through an off-target mechanism. The authors hypothesize that sub-MICs of BTZ043 weaken the bacterial cell wall and allow improved penetration of delamanid to its target. Synergy between 2 new antimycobacterial compounds, (delamanid and BTZ043), with novel targets, offers an attractive foundation for a new anti-TB regimen.	[47]

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; BA, bactericidal activity; BCI, Bayesian credibility interval; BID, twice daily; BTZ, benzothiazinone; C, culture; CFU, colony-forming unit; CI, confidence interval; DR-TB, drug-resistant tuberculosis; DS-TB, drug-susceptible tuberculosis; EBA, early bactericidal activity; ECG, electrocardiogram; HR, hazard ratio; HRZE, isoniazid rifampin pyrazinamide ethambutol; MDR-TB, multidrug-resistant tuberculosis; MIC, minimum inhibitory concentration; MPaZ, moxifloxacin Pa824 pyrazinamide; OB, once daily; OBR, optimized background regimen; PTB, pulmonary tuberculosis; PZA, pyrazinamide; QT, QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle; SS, sputum smear; TB, tuberculosis; WBA, whole-blood bactericidal activity; XDR-TB, extensively drug-resistant tuberculosis.

Table 4. Summary of the Main Reproposed Antituberculosis Drugs With the Most Relevant Studies and Related Findings

Drug	Class	Main Findings	Reference
Linezolid	Oxazolidinone	Systematic review and meta-analysis on efficacy, safety and tolerability of linezolid-containing regimes based on individual data analysis based on 12 studies (11 countries from 3 continents) reporting complete information on safety, tolerability, efficacy of linezolid-containing regimes in treating MDR-TB cases. Most MDR-TB cases achieved SS (86/93 [92.5%]) and C (100/107 [93.5%]) conversion after treatment with individualized regimens containing linezolid (median [interquartile range] times for SS and C conversions were 43.5 [21–90] and 61 [29–119] days, respectively), and 99/121 (81.8%) patients were successfully treated. No significant differences were detected in the subgroup efficacy analysis (daily linezolid dosage ≤600 mg vs >600 mg). AEs were observed in 63/107 (58.9%) patients, of which 54/79 (68.4%) were major AEs that included anemia (38.1%), peripheral neuropathy (47.1%), gastrointestinal disorders (16.7%), optic neuritis (13.2%), and thrombocytopenia (11.8%). The proportion of adverse events was significantly higher when the linezolid daily dosage exceeded 600 mg. The study results suggest an excellent efficacy but also the necessity of caution in the prescription of linezolid.	[65]
		Retrospective, nonrandomized, unblinded observational study evaluating safety and tolerability of linezolid (600 mg OD or BID). in MDR/XDR-TB treatment in 4 European countries. Out of 195 MDR/XDR-TB patients, 85 were treated with linezolid for a mean of 221 d. Of these, 35/85 (41.2%) experienced major AEs attributed to linezolid (anaemia, thrombocytopenia and/or polyneuropathy), requiring discontinuation in 27 (77%) cases. Most AEs occurred after 60 d of treatment. Twice-daily administration produced more major AE than once-daily dosing ($P = .0004$), with no difference in efficacy found. Outcomes were similar in patients treated with/without linezolid ($P = .8$), although linezolid-treated cases had more first-line ($P = .002$) and second-line ($P = .02$) drug resistance and a higher number of previous treatment regimens (4.5 vs 2.3; $P = .07$). Linezolid 600 mg OD added to an individualized multidrug regimen may improve the chance of bacteriological conversion, providing a better chance of treatment success in only the most complicated MDR/XDR-TB cases. Its safety profile does not warrant use in cases for which there are other, safer, alternatives.	[66]
		Forty-one patients were enrolled, who had C-positive XDR-TB and who had not had a response to any available chemotherapeutic option during the previous 6 mo. Patients were randomly assigned to linezolid therapy that started immediately or after 2 mo, at a dose of 600 mg per day, without a change in their OBR. The primary endpoint was the time to SS/C conversion on solid medium, with data censored 4 mo after study entry. By 4 mo, 15/19 patients (79%) in the immediate-start group and 7/20 (35%) in the delayed-start group had C conversion ($P = .001$). In addition, 34/39 patients (87%) had a negative C within 6 mo after linezolid had been added to their drug regimen. Of the 38 patients with exposure to linezolid, 31 (82%) had clinically significant AEs that were possibly or probably related to linezolid, including 3 patients who discontinued therapy. Patients who received 300 mg per day after the second randomization had fewer AEs than those who continued taking 600 mg per day. 13 patients completed therapy and have not had a relapse. 4 cases of acquired resistance to linezolid have been observed. Linezolid is effective at achieving C conversion among patients with treatment-refractory pulmonary XDR-TB, but patients must be monitored carefully for AEs.	[67]
		The authors evaluated treatment with linezolid (800 mg once daily for 1 to 4 mo as guided by SS/C status and tolerance and then at 1200 mg thrice weekly until ≥1 y after C conversion), in addition to OBD among 10 consecutive patients with XDR-TB or fluoroquinolone-resistant MDR-TB. All achieved stable cure, with anemia corrected and neuropathy stabilized, ameliorated, or avoided after switching to intermittent dosing. Serum linezolid profiles appeared better optimized.	[68]
		Prospective pharmacokinetic study aimed at quantifying the effect of clarithromycin on the exposure of linezolid. All subjects received 300 mg linezolid twice daily during the entire study, consecutively coadministered with 250 mg and 500 mg clarithromycin once daily. Linezolid exposure increased by a median of 44% (interquartile range, 23%–102%, $P = .043$) after coadministration of 500 mg clarithromycin (n = 5) vs baseline, whereas 250 mg clarithromycin had no statistically significant effect. Coadministration was well tolerated by most patients; none experienced severe AE. One patient reported common toxicity criteria grade 2 gastrointestinal AE. Clarithromycin significantly increased linezolid serum exposure after combining clarithromycin with linezolid in MDR-TB patients. The drug–drug interaction is possibly P-glycoprotein-mediated. Due to large interpatient variability, TDM is advisable to determine individual effect size.	[69]

Table 4 continued.

Drug	Class	Main Findings	Reference
Clofazimine	Riminophenazine	A systematic review of studies reporting on the efficacy and safety of clofazimine as part of combination therapy for DR-TB (12 studies, comprising 3489 patients across 10 countries). Treatment success ranged from 16.5% (95% CI, 2.7%–38.7%) to 87.8% (95% CI, 76.8%–95.6%), with an overall pooled proportion of 61.96% achieving treatment success (95% CI, 52.79%–71.12%) (τ^2 0.07). Mortality, treatment interruptions, defaulting, and AEs were all in line with DR-TB treatment outcomes overall. The most commonly reported AEs were gastrointestinal disturbances and skin pigmentation. Clofazimine could be considered as an additional therapeutic option in the treatment of DR-TB. The optimal dose of clofazimine and duration of use require further investigation.	[70]
		The authors searched multiple databases for studies published through February 2012 that reported use of Clofazimine in MDR- and XDR-TB treatment regimens. They identified 9 observational studies (6 MDR-TB and 3 XDR-TB) including patients with MDR-TB treated with clofazimine. Overall, 65% (95% CI, 54–76) of the patients experienced favorable outcomes (cure or treatment completion). Using random-effects meta-analysis, 65% (95% CI, 52–79) of those with MDR-TB and 66% (95% CI, 42–89) of those with XDR-TB experienced favorable treatment outcomes.	[71]
		The authors reported the treatment outcome of all patients with MDR-TB enrolled from May 1997 to December 2007. The most effective treatment regimen (among 6 standardized treatment regimens) required a minimum of 9 mo of treatment with gatifloxacin, clofazimine, ethambutol, and pyrazinamide throughout the treatment period supplemented by prothionamide, kanamycin, and high-dose isoniazid during an intensive phase of a minimum of 4 mo, giving a relapse-free cure of 87.9% (95% CI, 82.7–91.6) among 206 patients. Major AEs were infrequent and manageable. Compared with the 221 patients treated with regimens based on ofloxacin and commonly prothionamide throughout, the HR of any adverse outcome was 0.39 (95% CI, .26–.59). Serial regimen formulation guided by overall treatment effectiveness resulted in treatment outcomes comparable to those obtained with first-line treatment.	[72]
		The study was aimed to directly compare the activity of a standard second-line drug regimen with or without the addition of clofazimine in a mouse model of MDR-TB. Our comparative outcomes included time to C conversion in the mouse lungs and the percentage of relapses after treatment cessation. After 2 mo, the bacillary load in lungs was reduced from 9.74 $\log_{10}$ at baseline to 3.61 and 4.68 in mice treated with or without clofazimine, respectively ($P < .001$). Mice treated with clofazimine were C-negative after 5 mo, whereas all mice treated without clofazimine remained heavily C-positive for the entire 9 mo of the study. The relapse rate was 7% among mice treated with clofazimine for 8–9 mo. The clofazimine contribution was substantial in these experimental conditions	[73]
Moxifloxacin	Fluoroquinolone	The study compared the efficacy of moxifloxacin (M) and high-dose levofloxacin (L) alone or in combination with ethionamide (Et), amikacin (A), and pyrazinamide (Z) given for 2 or 7 mo. After 2 mo of treatment, lung CFU counts were similar in mice receiving either FQ alone, but, after 4 and 5 mo, CFU counts were 2 $\log_{10}$ lower in mice receiving moxifloxacin. Mice receiving 2MEtZA/3MEt and 2LEtZA/3LEt had 1.0 and 2.7 $\log_{10}$ lung CFUs, respectively. When Z was given throughout, both regimens rendered mice culture negative by 5 mo, and most mice did not relapse after 7 mo of treatment, with fewer relapses observed in the M group after 6 and 7 mo of treatment. In murine TB, M had superior efficacy compared with L despite lower serum drug exposures and may remain the fluoroquinolone of choice for second-line regimens. Z contributed substantial sterilizing activity beyond 2 mo in FQ-containing second-line regimens, largely compensating for L's weaker activity.	[74]
		The study was aimed to compare the antimicrobial activity and safety of MXF vs isoniazid during the first 8 wk of combination therapy for pulmonary TB. Of 433 participants enrolled, 328 were eligible for the primary efficacy analysis. Of these, 35 (11%) were HIV positive, 248 (76%) had cavitation on baseline chest radiograph, and 213 (65%) were enrolled at African sites. Negative C at week 8 were observed in 90/164 (54.9%) participants in the isoniazid arm, and 99/164 (60.4%) in the MXF arm ($P = .37$). In multivariate analysis, cavitation and enrollment at an African site were associated with lower likelihood of week 8 C negativity. The proportion of participants who discontinued assigned treatment was 31/214 (14.5%) for the MXF group vs 22/205 (10.7%) for the isoniazid group (RR, 1.35; 95% CI, .81–2.25). Substitution of MXF for isoniazid resulted in a small but statistically nonsignificant increase in week 8 C negativity.	[75]

Table 4 continued.

Drug	Class	Main Findings	Reference
Levofloxacin	Fluoroquinolone	The study was aimed to compare the effectiveness of LFX and MXF in terms of C conversion after 3 mo of treatment for MDR-TB (182 patients with MDR-TB, sensitive to LFX and MXF). At 3 mo of treatment, 68 (88.3%) of the 77 patients in the LFX group and 67 (90.5%) of the 74 in the MXF group showed conversion to negative C (OR for LFX compared with MXF, 0.78; 95%, CI, .27–2.20). AEs were reported in 6 patients (7.7%) in the LFX group and 4 (5.2%) in the MXF group ($P = .75$). The choice of LFX or MXF for treatment of patients with MDR-TB may not affect sputum C conversion at 3 mo of treatment.	[76]
		The use of FQs to treat lower LTRIs other than TB allows selection of FQ-resistant TB when TB is misdiagnosed. This study maps national guidelines on the use of FQs for LRTIs in Europe and determines the risk of FQ-resistant TB upon FQ treatment before TB diagnosis. A questionnaire was developed to map existing national LRTI and CAP guidelines. A systematic review and meta-analysis were performed to determine the risk of FQ-resistant TB if prescribed FQs prior to TB diagnosis. 15 of 24 (80%) responding European Respiratory Society national delegates reported having national LRTI management guidelines, 7 including recommendations on FQ use and 1 recommending FQs as the first-choice drug. 18/24 countries had national CAP management guidelines, 2 recommending FQ as the drug of choice. 6 studies investigating FQ exposure and the risk of FQ-resistant TB were analyzed. TB patients had a 3-fold higher risk of having FQ-resistant TB when prescribed FQs before TB diagnosis, compared to non-FQ-exposed patients (OR, 2.81, 95% CI, 1.47–5.39). Although the majority of European countries hold national LRTI/CAP guidelines, the results suggest that a risk of developing FQ resistance exists.	[77]
Meropenem-clavulanate	Carbapenem- Clavulanic acid	The study was aimed to evaluate the contribution of meropenem-clavulanate when added to linezolid-containing regimens in terms of efficacy and safety/tolerability in treating MDR- and XDR- TB cases after 3 mo of second-line treatment. The clinical severity of cases was worse than that of controls (drug susceptibility profile, proportion of SS positive and of re-treatment cases). The group of cases yielded a higher proportion of SS converters (28/32 [87.5%] vs 9/16 [56.3%]; $P = .02$) and C converters (31/37 [83.8%] vs 15 /24 [62.5%]; $P = .06$). Excluding XDR-TB patients (11/98 [11.2%]), cases scored a significantly higher proportion of C converters than controls ($P = .03$). One case had to withdraw from meropenem-clavulanate due to increased transaminase levels. The results of our study provide: (1) preliminary evidence on effectiveness and safety/tolerability of meropenem-clavulanate; (2) reference to design further trials; and (3) a guide to clinicians for its rationale use within salvage/compassionate regimens.	[78]
Rifapentine	Rifamycins	The study aimed to compare rifapentine and isoniazid once a week with rifampicin and isoniazid twice a week. 1004 patients were enrolled (502 per treatment group); 928 successfully completed treatment, and 803 completed the 28-mo study. Crude rates of failure/relapse were 46/502 (9.2%) in those on rifapentine once a week, and 28/502 (5.6%) in those given rifampicin twice a week (relative risk 1.64, 95% CI, 1.04–2.58, $P = .04$). By proportional hazards regression, 5 characteristics were independently associated with increased risk of failure/relapse: C-positive at 2 mo (HR, 2.8; 95% CI, 1.7–4.6); cavitation on chest radiography (HR, 3.0; 95% CI, 1.6–5.9); being underweight (HR, 3.0; 95% CI, 1.8–4.9); bilateral pulmonary involvement (HR, 1.8; 95% CI, 1.0–3.1); and being a non-Hispanic white person (HR, 1.8; 95% CI, 1.1–3.0). Adjustment for imbalances in 2-month C and cavitation diminished the association of treatment group with outcome (HR, 1.34; 95% CI, .83–2.18; $P = .23$). Of participants without cavitation, rates of failure/relapse were 6/210 (2.9%) in the once a week group and 6/241 (2.5%) in the twice a week group (RR, 1.15; 95% CI, .38–3.50; $P = .81$). Rates of AEs and death were similar in the 2 treatment groups. Rifapentine once a week is safe and effective for treatment of pulmonary TB in HIV-negative people without cavitation on chest radiography. Clinical, radiographic, and microbiological data help to identify TB patients at increased risk of failure or relapse when treated with either regimen	[79]
		The study compared the antimicrobial activity and safety of rifapentine vs rifampicin during the first 8 wks of pulmonary TB treatment (intensive phase), with isoniazid, pyrazinamide, and ethambutol. Negative C on solid media occurred in 145/174 participants (83.3%) in the rifampicin group and 171 of 198 participants (86.4%) in the rifapentine group (difference, 3.0%; 95% CI, −4.3 to 10.5); negative C in liquid media occurred in 110/169 (65.1%) in the rifampicin group and 133/196 (67.9%) in the rifapentine group (difference, 2.8%; 95% CI, −6.9 to 12.4). Among 529 participants who received study therapy, 40/254 participants (15.7%) in the rifampicin group and 40/275 participants (14.5%) in the rifapentine group prematurely discontinued treatment ($P = .79$). The rifapentine regimen was safe but not significantly more active than a standard rifampicin regimen, by the surrogate endpoint of C status at completion of intensive phase.	[80]

granted €24.6 million from the European Commission and other government sources for TBVAC2020, which aims to discover and develop new tuberculosis vaccines (www.TBVI.eu). The EMI-TB Consortium (Eliciting Mucosal Immunity in Tuberculosis), led by the Institute for Infection and Immunity, St George's University, London, was awarded €8 million to establish effective mucosal immunity against *Mtb* (http://www.emi-tb.org/). Both consortiums will be generating vaccine candidates for clinical testing, and with renewed activity in preclinical development, there is a need to prepare for future screening and testing of these candidates.

In addition, the Global Tuberculosis Vaccine Partnership (GTBVP), a global initiative working on tuberculosis vaccines, is now being established. The GTBVP includes the European Commission, the European Investment Bank, the Bill & Melinda Gates Foundation, and the Department of Science and Technology South Africa in collaboration with Aeras, TBVI, the South African Medical Research Council, and the European and Developing Countries Clinical Trials Partnership. The aim of the GTBVP is to mobilize and optimize use of globally available funds to manage the global vaccine pipeline efficiently and effectively, to provide a rational process for selecting the best candidates and help them to move forward into the clinical development, while ensuring they comply with established and consensed criteria at the global level.

Preparation for clinical testing of a vaccine can substantially accelerate the progression of a candidate. Recent studies have shown that a subunit vaccine can be delivered safely to the lung using an aerosol delivery device in both nonhuman primates and humans Although these studies were performed with MVA85A, the proof-of-concept safety and immunogenicity data generated from this study [94, 95] will accelerate the clinical testing of aerosol vaccines emerging from the TBVAC2020 and EMI-TB consortiums.

CONCLUSIONS

The current status quo of the lengthy treatment duration and poor treatment outcomes associated with MDR/XDR tuberculosis, and with comorbidity of tuberculosis with HIV and noncommunicable diseases, is unacceptable. New innovations for shortening duration of therapy and improving treatment outcomes are urgently required. The tuberculosis drug pipeline remains sparse. The tuberculosis drug pipeline remains thin [57]. A range of host-directed therapies, including cellular therapy, repurposed drugs, and immune-based therapies, are emerging [96–101] and provide hope for reducing duration of therapy and improving treatment of MDR tuberculosis. These require evaluation in randomized, placebo-controlled clinical trials as adjuncts to current tuberculosis treatment regimens. Meanwhile, proactive screening for tuberculosis using best available diagnostics, making

Table 4 continued.

Drug	Class	Main Findings	Reference
		Using a mouse model with a high bacterial burden and human-equivalent drug dosing, the study compared the efficacy of rifapentine- and MXF-containing regimens with that of the standard daily short-course regimen based on rifampicin, isoniazid, and pyrazinamide. Bactericidal activity was assessed by lung CFU counts, and sterilizing activity was assessed by the proportion of mice with C-positive relapse after 2, 3, 4, and 6 mo of treatment. The results demonstrate that replacing rifampicin with rifapentine and isoniazid with MXF dramatically increased the activity of the standard daily regimen. After just 2 mo of treatment, mice receiving rifapentine- and MXF-containing regimens were found to have negative lung C, while those given the standard regimen still harbored 3.17 $\log_{10}$ CFU in the lungs ($P < .01$). No relapse was observed after just 3 mo of treatment with daily and thrice-weekly administered rifapentine- and MXF-containing regimens, whereas the standard daily regimen required 6 mo to prevent relapse in all mice. Rifapentine should no longer be viewed solely as a rifamycin for once-weekly administration. The results suggest that treatment regimens based on daily and thrice-weekly administration of rifapentine and MXF may permit shortening the current 6 mo duration of treatment to 3 mo or less.	[81]

Abbreviations: τ^2, tau-squared statistic; AE, adverse events; BID, twice daily; C, culture; CAP, community-acquired pneumonia; CFU, colony-forming unit; CI, confidence interval; DR-TB, drug- resistant tuberculosis; FQ, fluoroquinolone; HIV, human immunodeficiency virus; HR, hazard ratio; LFX, levofloxacin; LTRI, respiratory tract infections; MDR-TB, multidrug-resistant tuberculosis; MXF, moxifloxacin; OB, once daily; OBR, optimized background regimen; OR, odds ratio; RR, relative risk; SS, sputum smear; SS/C, sputum smear and culture; TB, tuberculosis; TDM, therapeutic drug monitoring; XDR-TB, extensively drug-resistant tuberculosis.

an accurate, early diagnosis of drug-sensitive or drug-resistant tuberculosis, and initiating the most appropriate tuberculosis treatment regimen is crucial in detecting missed cases of tuberculosis and reducing morbidity, mortality, and further transmission within the community. New innovations for early, rapid diagnosis at points of care, for shortening duration of therapy and improving treatment outcomes of MDR tuberculosis, and for prevention are urgently required.

Notes

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