Recent Developments and Future Opportunities in the Treatment of Tuberculosis in Children

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Tuberculosis in children accounts for a significant proportion of the overall burden of disease, and yet for many years research into pediatric treatment has been neglected. Recently, there have been major developments in our understanding of pediatric tuberculosis, and a large number of studies are under way or planned. New drugs and regimens are being evaluated, and older drugs are being repurposed. Shorter regimens with potentially fewer side effects are being assessed for the treatment and prevention of both drug-susceptible and drug-resistant tuberculosis. It may be possible to tailor treatment so that children with less severe disease are given shorter regimens, and weekly dosing is under investigation for preventive therapy and for the continuation phase of treatment. The interaction with human immunodeficiency virus and the management of tuberculosis meningitis are also likely to be better understood. Exciting times lie ahead for pediatric tuberculosis, but much work remains to be done.

Keywords. tuberculosis; children; resistant; treatment; prevention.

Every year, millions of children are exposed to tuberculosis, and up to a million develop tuberculosis disease [1, 2]. If the infecting strain of Mycobacterium tuberculosis is resistant to isoniazid and rifampin, the 2 most effective first-line anti-tuberculosis drugs, then it is said to be multidrug resistant (MDR) [3]. It is estimated that hundreds of thousands of children are exposed to MDR tuberculosis each year and that >30,000 develop MDR tuberculosis disease [1]. Historically, childhood tuberculosis has been neglected [4], in terms of funding and research and development [5], as well as advocacy and public health prioritization. However, over the last few years there have been significant developments in our understanding of the treatment of children with tuberculosis infection and tuberculosis disease. In addition, there are promising new treatments and therapies under investigation.

When children are identified following exposure, drug prophylaxis can be given to prevent infection. If children are identified as having established tuberculosis infection (based on the results of host-directed tests that indicate immunological memory following prior sensitization to mycobacteria), sometimes called latent tuberculosis, they can also be given treatment to prevent the development of tuberculosis disease. Both prophylaxis and latent tuberculosis treatment can be termed preventive therapy.

Traditionally, once a child has developed symptoms and signs of tuberculosis, together with supportive evidence from microbiological, radiological, and immunological tests, they are said to have tuberculosis disease. However, tuberculosis disease in children is not a homogeneous entity. There is a wide spectrum of disease, from limited disease, confined to the intra- or extrathoracic lymph nodes, to severe disease such as disseminated, or adult-type, cavitary disease. Recently, investigators have suggested classifying children into 2 categories, severe and nonsevere disease [6], and potentially treating children with nonsevere disease with shorter and less intense regimens (Figure 1). When considering the challenges of treating children with tuberculosis, it is important to consider which drugs to give, in which
combination, at what dosage, in which formulation, and for how long (Figure 2). This review aims to provide an update on recent developments and future opportunities in the prevention and treatment of tuberculosis in children.

**DRUG-SUSCEPTIBLE TUBERCULOSIS DISEASE**

**Pharmacokinetics**

The World Health Organization (WHO) recommends that children with drug-susceptible tuberculosis are treated for 6 months: 2 months of rifampin, isoniazid, and pyrazinamide, followed by 4 months of rifampin and isoniazid. They advise that ethambutol should be added for the first 2 months in children with extensive disease or where rates of human immunodeficiency virus (HIV) infection and/or isoniazid resistance are high [7]. This regimen is highly effective and associated with few adverse events [8]. Ethambutol is not associated with ophthalmological adverse effects at the recommended dosages [9].

Following emerging pharmacokinetic evidence, the recommended dosages of these first-line medications were revised in 2010. Because children metabolize drugs more rapidly than adults, the same mg/kg dosage results in a comparatively lower serum concentration in children [10]. It is only by using the 2010 revised dosages that young children achieve the target serum concentrations associated with efficacy in adult studies [11]. There are potential concerns with this approach, however, as outcomes for children with tuberculosis prior to the revised dosages were good and there are few data to link drug concentrations with outcomes in children (Figure 3).

Following the 2010 revision of pediatric tuberculosis dosing recommendations, the ratio of individual medications included in the fixed-dose combination (FDC) tablets similarly required updating. In 2013, the TB Alliance was awarded US$16.7 million from UNITAID to develop and introduce appropriately dosed, scored, dispersible, and palatable pediatric formulations in line with the revised recommendations [12]. New FDC tablets are finally expected to enter the market in 2016. Although developing new effective drugs and optimizing pharmacokinetic parameters are important, these efforts are irrelevant if the medications produced are not acceptable to children. Developing child-friendly FDC formulations is a central part of ensuring adherence to and completion of treatment. Although these developments for first-line tuberculosis drugs are encouraging,
understanding of the pharmacokinetics of many commonly used second-line drugs is still very rudimentary, and few child-friendly formulations exist.

**Treatment Shortening**

Six months is a long time to administer daily treatment to a child, and a number of recently completed adult studies have evaluated shortening treatment (Table 1). Although these studies were unsuccessful in their primary aim of shortening treatment to 4 months, each has provided important lessons for children. The RIFAQUIN trial suggests that it may be possible to treat patients with once-weekly rifapentine and moxifloxacin in the continuation phase of therapy [15]. This would have significant advantages for children, with reduced pill burden and likely improved adherence. The OFLOTUB study demonstrated that there was great variation in the efficacy of a fluoroquinolone-based 4-month regimen by country, by HIV status, and by body mass index [14]. This might suggest a potential future role for shortened treatment in certain groups of children, such as those with HIV or with less severe disease. The REMox study demonstrated more rapid culture conversion in the moxifloxacin-containing arms and provided further evidence for the safety of the fluoroquinolones [13].

Two planned phase 3 trials will further expand the evidence base for tuberculosis treatment shortening. The Tuberculosis Trials Consortium’s (TBTC) study 31 will evaluate whether rifapentine-containing regimens can shorten treatment in adults and children (as young as 12 years), and the TB Alliance’s NC-006 (STAND) trial in adults will evaluate whether a novel drug, PA-824, in combination with moxifloxacin and pyrazinamide can shorten treatment to 4 months.

In addition to these adult studies, a pediatric trial, the SHINE study, will evaluate whether children with nonsevere disease can be treated successfully with only 4 months of treatment [17]. It is due to start soon in Africa and India. More effective contact tracing following tuberculosis diagnosis in adults would likely result in the detection of more children with tuberculosis and at earlier stages of disease, with less severe forms. Earlier
detection of tuberculosis in children and resultant treatment with shorter regimens would ease the burden on healthcare providers, parents, and children, facilitating improved adherence and treatment outcomes.

**Drug Interactions**

Other problems with the current WHO-recommended regimen include interactions between rifampin and other medications. Rifampin is a potent inducer of the cytochrome P450 system and reduces the levels of many drugs, including antiretroviral medications [23]. The levels of nonnucleoside reverse transcriptase inhibitors are only partially affected by rifampin [24], but if the protease inhibitors (PIs) are given alone with rifampin, or if standard boosting with ritonavir (at a ratio of 4:1 lopinavir:ritonavir) is given, then increased rates of virological failure result [25, 26]. Although doubling the dose of lopinavir/ritonavir is insufficient [27], superboosting (to achieve a 1:1 ratio of lopinavir:ritonavir) is more successful [28]. Regimens that do not include rifampin would greatly simplify tuberculosis treatment in HIV-infected children requiring PIs.

**Tuberculous Meningitis**

Another area where there is potential to shorten and improve tuberculosis treatment in children is tuberculous meningitis (TBM), which disproportionately affects children. WHO recommends that children with TBM be treated for 2 months with isoniazid, rifampin, pyrazinamide, and ethambutol, followed by 10 months of isoniazid and rifampin at the standard dosages [7]. However, recent evidence suggests this may not be the optimal regimen for the treatment of TBM in children. Whereas isoniazid and pyrazinamide penetrate well into the cerebrospinal fluid (CSF), rifampin only achieves moderate CSF penetration and ethambutol, almost none [29–31]. A group in Cape Town, South Africa, treats TBM in children with a short, intensive regimen [32–34]. Their 6-month regimen consists of high-dose isoniazid, rifampin, pyrazinamide, and ethionamide. Treatment outcomes have been reasonable and the regimen is well tolerated. An exciting trial in adults with TBM in Indonesia has shown that high dosages of rifampin (given intravenously) combined with moxifloxacin improves treatment outcomes when given in addition to standard therapy [16]. Further studies in adults using high-dose rifampin and levofloxacin are also being conducted [18], and pediatric studies are soon to start [19].

The role of immune modulators in pediatric TBM is still unclear. A number of trials have demonstrated that the use of steroids offers a modest benefit on death and severe disability [35]. However, this may be restricted to only those with certain host genotypes [36], and the dosage to give children remains unclear [37]. Thalidomide has been used successfully in the treatment of optic neuritis and tuberculomas in children [38, 39], but a trial using high-dose thalidomide was stopped early due to worse outcomes in the intervention group [40]. The effect of aspirin is unclear. In one pediatric trial, aspirin demonstrated a benefit [41], whereas in another it did not [42]. It should be noted that pediatrics was included in a call for funding from the US National Institutes of Health in early 2015. It is hoped that this funding mechanism will generate additional information regarding the optimal host-directed therapy for children with tuberculosis, specifically TBM [43].

**Figure 3.** The relationship between the dosage of drug ingested, plasma serum concentration, and efficacy in adults and children with tuberculosis.
WHO recommends that child contacts of drug-susceptible tuberculosis source cases who are <5 years of age or who are HIV-infected receive daily isoniazid for 6 months [7]. However, providing daily therapy to a child who is clinically well can be challenging for many parents; adherence is frequently poor, particularly in high-burden settings [44, 45]. Shorter, simpler regimens, with lower pill burdens, are required.

Table 1. Recent and Planned Studies for the Treatment and Prevention of Drug-Susceptible Tuberculosis

<table>
<thead>
<tr>
<th>Indication</th>
<th>Completed or Planned</th>
<th>Study Name</th>
<th>Findings/Study Description</th>
</tr>
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<tbody>
<tr>
<td>Treatment Completed</td>
<td>REMox [13]</td>
<td>2HRZE/4HR vs 2HRZMfx/2HRMfx vs 2RMfxZE/2RMfx, n = 1931 participants</td>
<td>Confirmed the safety of moxifloxacin and, while more rapid culture conversion was observed in moxifloxacin-containing regimens, determined that substitution with moxifloxacin alone cannot shorten treatment from 6 mo to 4 mo.</td>
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<td></td>
<td>OFLOTUB [14]</td>
<td>2HRZE/4HR vs 2HRZGfx/2HRGfx; n = 1836 participants</td>
<td>Demonstrated inferiority of the 4-mo gatifloxacin-containing regimen and more unfavorable outcomes (death, failure, and recurrence). However, there was great variation by country and also by HIV status and body mass index (outcomes were similar between the 2 treatments for malnourished patients and those coinfected with HIV).</td>
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<td></td>
<td>RIFAQUIN [15]</td>
<td>2HRZE/4HR vs 2RMfxZE/2(BIW)P 900 mgMfx500 mg vs 2RMfxZE/4(QW)P1200 mgMfx500 mg; n = 827</td>
<td>Determined that, although the 4-mo regimen was inferior to the standard course of treatment (more patients relapsed), the alternative 6-mo experimental regimen, in which patients only had to take treatment once a week in the continuation phase, was noninferior.</td>
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<td></td>
<td>Indonesia [16]</td>
<td>Factorial design: R450 vs R600(IV) and Mfx400 vs Mfx800 vs E on background of HZ; n = 60 participants</td>
<td>Adults with TBM had reduced mortality when receiving the higher dosage of IV rifampin.</td>
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<tr>
<td></td>
<td>TBTC 31</td>
<td>2HRZE/4HR vs 2HPZE/2HP vs 2HPZMfx/2HPMfx</td>
<td>Will evaluate rifapentine-containing treatment shortening regimens in adults and children down to age 12 y.</td>
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<tr>
<td></td>
<td>NC-006 (STAND)</td>
<td>2HRZE/4HR vs 4Pa100 mgMfxZ vs 4Pa200 mgMfxZ. Includes open-label exploratory MDR-TB arm.</td>
<td>Will evaluate treatment-shortening regimen including PA-824, moxifloxacin, and pyrazinamide.</td>
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<tr>
<td></td>
<td>NC-005</td>
<td>2JPaZ for DS-TB; 2JPaZMfx for DR-TB</td>
<td>Will evaluate treatment-shortening bedaquiline- and PA-824–containing regimens for DS/DR-TB.</td>
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<tr>
<td></td>
<td>SHINE [17]</td>
<td>2HRZE/4HR vs 2HRZ(E)/2HR</td>
<td>Will evaluate shortened standard treatment in children with limited disease.</td>
</tr>
<tr>
<td></td>
<td>TBM-IT [18]</td>
<td>Will evaluate levofloxacin and rifampin (15 mg/kg) + OBT vs rifampin (10 mg/kg) + OBT for the first 2 mo in adults with TBM.</td>
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<td></td>
<td>PATCH [19]</td>
<td>Will evaluate safety and efficacy of levofloxacin and high-dose rifampin in TBM.</td>
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<tr>
<td>Prevention Completed</td>
<td>TBTC S26 (PREVENT TB) [20, 21]</td>
<td>Demonstrated that 3 mo of once-weekly treatment with rifapentine and isoniazid was as effective as 9 mo of daily isoniazid. Further pediatric data confirmed this regimen is safe in children down to age 2 y.</td>
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<tr>
<td>Planned</td>
<td>ACTG 5279</td>
<td>Will evaluate 4 wk of daily rifapentine and isoniazid in adults and children down to age 13 y.</td>
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<tr>
<td></td>
<td>P4v9</td>
<td>Will evaluate 4 mo of daily rifapamin in children aged 0–17 y.</td>
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<tr>
<td></td>
<td>TBTC S35</td>
<td>Will determine PK and safety of rifapentine/isoniazid fixed-dose combination in children and infants.</td>
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<td></td>
<td>ViDiKids [22]</td>
<td>Will evaluate whether monthly vitamin D, taken orally for 3 y, can reduce the risk of acquiring LTBI in schoolchildren in New Delhi.</td>
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</table>

Abbreviations: ACTG, AIDS Clinical Trials Group; BIW, twice a week; DR, drug-resistant; DS, drug-susceptible; E, ethambutol; Gfx, gatifloxacin; H, isoniazid; HIV, human immunodeficiency virus; IV, intravenous; J, bedaquiline; LTBI, latent tuberculosis; MDR, multidrug-resistant; Mfx, moxifloxacin; OBT, optimized background therapy; P, rifapentine; Pa, PA-824; PK, pharmacokinetics; QW, once a week; R, rifampin; TB, tuberculosis; TBM, tuberculous meningitis; TBTC, Tuberculosis Trials Consortium; Z, pyrazinamide.

**PREVENTIVE THERAPY FOR DRUG-SUSCEPTIBLE TUBERCULOSIS**

WHO recommends that child contacts of drug-susceptible tuberculosis source cases who are <5 years of age or who are HIV-infected receive daily isoniazid for 6 months [7]. However,
as effective in preventing tuberculosis disease and was also associated with better adherence than 9 months of daily isoniazid [20]. The group continued to recruit children for an additional 2 years until >1000 children had been enrolled; the 3-month regimen was associated with limited toxicity [21]. Detailed pharmacokinetic studies and extensive modeling provide good evidence for the best dosage to give children when using either whole tablets or crushed tablets [46]. Rifapentine was approved by the US Food and Drug Administration in late 2014 for treatment of latent tuberculosis in people aged ≥2 years. A further study is now under way to evaluate ultra-short-course preventive therapy for adults with HIV consisting of only 4 weeks of daily rifapentine and isoniazid [47]. Although these options are exciting, longer-term follow-up is required. Other preventive therapies under consideration, including vitamin D supplementation [22], are shown in Table 1.

**DRUG-RESISTANT TUBERCULOSIS DISEASE**

A systematic review and meta-analysis, published in 2012, identified only 8 studies reporting the treatment of MDR tuberculosis in children; 315 children were included in the meta-analysis [48]. Successful outcomes were seen in 82% of children, compared with 62% in adults [49]. Although successful, these individualized approaches require high levels of expertise from clinicians, the treatment is long and is associated with significant adverse events. One-quarter of children treated with injectable drugs experience some degree of permanent hearing loss [50], and >50% of children given ethionamide develop thyroid dysfunction [51, 52].

Since 2012, a large number of case series and studies that describe the treatment of MDR tuberculosis in children have been published, and a WHO-commissioned individual-patient meta-analysis is under way to inform policy. Several pharmacokinetic investigations of second-line tuberculosis drugs in children have been completed [53–55], a novel delivery system has been developed [56], and a consensus statement suggesting common definitions for pediatric MDR tuberculosis research has been written [57], as have treatment guidelines [58–60] and a practical field guide [61]. One recent study of confirmed and presumed MDR tuberculosis classified children as having had severe and nonsevere disease [62]. The children with nonsevere disease were more commonly treated as outpatients, were less likely to receive an injectable medication, and were given shorter total durations of medication. Although not a trial, these study findings suggest that for more limited disease, it may be possible to give shorter durations of therapy and even omit the injectable medication altogether. Many trials of new MDR tuberculosis treatment regimens are under way in adults [63]; findings will likely inform pediatric practice (Table 2).

**PREVENTIVE THERAPY FOR DRUG-RESISTANT TUBERCULOSIS**

Few studies have assessed preventive therapy in MDR tuberculosis child contacts [68–70], and there is limited evidence to support policy and variable guidelines [7, 71–75]. A recent prospective study from Cape Town recruited 186 children who had been exposed to adult source cases with MDR tuberculosis. All were offered 3-drug preventive therapy with ofloxacin, ethambutol, and high-dose isoniazid. Six children developed tuberculosis, and 1 infant died. Factors associated with poor outcome were age <12 months, HIV infection, and poor adherence [67]. There was no control group, however. A number of randomized, double-blind, placebo-controlled trials are planned to evaluate levofloxacin for the prevention of tuberculosis in MDR tuberculosis contacts (Table 2).

**NEW AND RETOOLED ANTITUBERCULOSIS DRUGS IN CHILDREN**

**Inclusion of Children Into Trials**

Until recently, there had not been a new class of tuberculosis drug developed in >40 years [76]. However, in the last decade the pipeline has grown [77]. Not only have a number of new chemical entities been discovered and advanced to later stages of evaluation, a number of older drugs, used off-label to treat MDR tuberculosis, are being repurposed (Table 3). Of concern, however, is the lack of inclusion of children in these efforts. Most experts agree that if a drug or drug regimen has been proven effective in adult studies in the treatment of mainly multidrug-resistant tuberculosis, then there is no need to carry out efficacy studies in children. However, issues specific to children do need to be addressed. First, child-friendly formulations are needed. Second, safety data must be produced as children experience side effects in different ways and at different frequencies than adults. Third, pharmacokinetics must be explored to determine appropriate dosing as children metabolize medications more rapidly than adults, leading to lower serum concentrations following comparable mg/kg dosing. A number of commentators have proposed a pragmatic approach for when studies should commence in children and adolescents (Figure 4) [78, 79].

**New Drugs**

Two new drugs, bedaquiline and delamanid, recently conditionally approved for the treatment of MDR tuberculosis, are undergoing phase 3 trials in adults. Bedaquiline is a diarylquinoline that acts by inhibiting intracellular ATP synthase. It has a very long half-life and is effective against actively replicating as well as dormant bacilli. It has been shown to reduce the time to culture conversion in adults with pulmonary tuberculosis, as well as to increase the proportion who culture-convert [80].
Bedaquiline was approved by the FDA in late 2012 and has since been given an interim recommendation by WHO [81]. Although it has not been licensed for use in children, bioequivalence studies of 2 pediatric formulations (granules and water-dispersible tablets) have been conducted [82], and pharmacokinetic studies are planned. The Centers for Disease Control and Prevention advises that on a case-by-case basis, bedaquiline might be considered in children with MDR tuberculosis [83]. Delamanid is a nitroimidazole and acts predominantly on mycolic acid synthesis to stop cell wall production. It has been shown to increase culture conversion and also to improve outcomes in adult studies [84, 85]. It was approved by the European Medicines Agency in early 2014 and received a WHO recommendation in late 2014. Pediatric formulations have been developed, and pharmacokinetic and safety studies are under way in children [86]. A single case report describes the successful use of delamanid in a 12-year-old boy who was infected with a highly resistant organism and failing treatment [87]. In addition to these 2 drugs, a number of novel chemical entities are being evaluated, including PA-824 [63].

### Table 2. Recent and Planned Studies for the Treatment and Prevention of Drug-Resistant Tuberculosis

<table>
<thead>
<tr>
<th>Indication</th>
<th>Completed or Planned</th>
<th>Study Name</th>
<th>Findings/Study Description</th>
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<tbody>
<tr>
<td>Treatment</td>
<td>Planned</td>
<td>STREAM I [64]</td>
<td>OBT vs 4MfxCfzEZKmHPto/6MfxCfzEZ Will evaluate standardized shortened 9-mo regimen for MDR-TB.</td>
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<td></td>
<td>STREAM II</td>
<td>9-mo all-oral regimen including bedaquiline vs 6-mo regimen including both an injectable and bedaquiline Will evaluate the addition/substitution of bedaquiline to the experimental regimen from STREAM I.</td>
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<tr>
<td></td>
<td></td>
<td>PRACTECAL (MSF)</td>
<td>JPaLzdMfx vs JPaLzdCfz vs JPaLzd          Will evaluate 3 experimental regimens</td>
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<td></td>
<td></td>
<td>NiX-TB (GATB)</td>
<td>6–9 mo all-oral regimen: PaLzdJ(Z) Will evaluate shortened regimens with novel drugs for XDR-TB in adults and adolescents down to age 14 y.</td>
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<td></td>
<td>End-TB (UNITAID)</td>
<td>Various 9-mo combinations of bedaquiline/delamanid, levofloxacin/moxifloxacin, pyrazinamide, clofazimine Will evaluate whether novel and repurposed drugs can improve outcomes for people with MDR/XDR-TB.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NeXT (MRC-SA)</td>
<td>Bedaquiline, linezolid, levofloxacin, pyrazinamide, ethionamide/high-dose isoniazid Will evaluate whether 6–9-mo regimen with novel drugs can improve outcomes for people with MDR/XDR-TB.</td>
</tr>
<tr>
<td>Prevention</td>
<td>Completed</td>
<td>USA [65]</td>
<td>After exposure to a teacher with MDR-TB in a school, 31 children developed latent infection. Twenty-six were treated with levofloxacin and pyrazinamide. Twelve required a change in therapy secondary to adverse effects. None developed TB. Observational study.</td>
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<td>Micronesia [66]</td>
<td>Of 232 contacts identified, 119 were offered preventive therapy, of whom 104 initiated a fluoroquinolone-based regimen. None of those who started preventive therapy developed TB disease, whereas 3 of the 15 (20%) who did not take treatment did. Observational outbreak investigation.</td>
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<td>Cape Town [67]</td>
<td>186 children who had been exposed to adult source cases with MDR-TB. All were offered 3-drug preventive therapy with ofloxacin, ethambutol, and high-dose isoniazid. Six children developed TB and 1 infant died. Factors associated with poor outcome were age &lt;12 mo, HIV infection, and poor adherence. Prospective observational study.</td>
</tr>
<tr>
<td></td>
<td>Planned</td>
<td>TB-CHAMP</td>
<td>Double-blind RCT to evaluate levofloxacin vs placebo in children aged &lt;5 y following contact with an adult MDR-TB source case. Due to start recruiting in South Africa in 2015.</td>
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<td></td>
<td></td>
<td>ACTG 5300 (Phoenix)</td>
<td>Double-blind RCT to evaluate levofloxacin and isoniazid vs isoniazid in all contacts (adults and children) following contact with an MDR-TB source case. Due to start recruiting in 2015.</td>
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<tr>
<td></td>
<td></td>
<td>V-QUIN</td>
<td>Double-blind RCT to evaluate levofloxacin vs placebo in all contacts (adults and children) following contact with an MDR-TB source case. Due to start recruiting in 2015 in Vietnam.</td>
</tr>
</tbody>
</table>

Abbreviations: ACTG, AIDS Clinical Trials Group; Cfz, clofazimine; E, ethambutol; GATB, Global Alliance for Tuberculosis Drug Development; H, isoniazid; J, bedaquiline; Km, kanamycin; Lzd, linezolid; MDR, multidrug-resistant; Mfx, moxifloxacin; MRC-SA, Medical Research Council of South Africa; MSF, Médecins Sans Frontières; OBT, optimized background therapy; Pa, PA-824; Pto, prothionamide; RCT, randomized controlled trial; TB, tuberculosis; XDR, extensively drug-resistant; Z, pyrazinamide.

Bedaquiline was approved by the FDA in late 2012 and has since been given an interim recommendation by WHO [81]. Although it has not been licensed for use in children, bioequivalence studies of 2 pediatric formulations (granules and water-dispersible tablets) have been conducted [82], and pharmacokinetic studies are planned. The Centers for Disease Control and Prevention advises that on a case-by-case basis, bedaquiline might be considered in children with MDR tuberculosis [83]. Delamanid is a nitroimidazole and acts predominantly on mycolic acid synthesis to stop cell wall production. It has been shown to increase culture conversion and also to improve outcomes in adult studies [84, 85]. It was approved by the European Medicines Agency in early 2014 and received a WHO recommendation in late 2014. Pediatric formulations have been developed, and pharmacokinetic and safety studies are under way in children [86]. A single case report describes the successful use of delamanid in a 12-year-old boy who was infected with a highly resistant organism and failing treatment [87]. In addition to these 2 drugs, a number of novel chemical entities are being evaluated, including PA-824 [63].
Repurposed Drugs

The role of the fluoroquinolones in the treatment of tuberculosis has expanded. As discussed, a number of studies are investigating whether fluoroquinolones might have a role in treatment shortening, improving treatment outcomes in TBM, as well as in MDR tuberculosis preventive therapy. Later-generation fluoroquinolones (moxifloxacin and levofloxacin) seem to be more efficacious [88] and have a higher barrier to development of resistance [89] than earlier-generation drugs (ofloxacin). They are likely to play an important role in the treatment of both drug-resistant and drug-susceptible disease in the future. The traditional concerns that this drug class causes arthropathy (based on early studies in juvenile beagles) [90] have not been substantiated [91–93]. The rifamycins have also gained renewed attention. The potential use of rifapentine to provide weekly therapy in either the continuation phase of tuberculosis disease treatment or preventive therapy has been discussed. In addition, investigators are assessing whether higher doses of rifampin (up to 35 mg/kg) are tolerable and can improve efficacy or shorten treatment in adults [94–96]. It will be important to explore these higher dosages in children to elucidate pharmacokinetics and safety.

A number of antibiotics indicated for other infections are also under investigation for tuberculosis [63, 97–99]. Linezolid has gained much attention following a trial published in 2012 that showed the drug to be highly effective in treating adults with extensively drug-resistant tuberculosis (ie, MDR tuberculosis with additional resistance to a second-line injectable drug and a fluoroquinolone) who were failing therapy [100]. However, almost all of the adults experienced significant side effects. Data on the use of linezolid in children treated for drug-resistant tuberculosis are extremely limited; a recent review identified only 18 treated children [101]. Although caution should be exercised when prescribing this potentially toxic medication, adverse events appear to be less common in children than in adults. Clofazimine, traditionally an antileprosy drug, has also gained interest mainly due to its central role in the “Bangladesh regimen” discussed below [102]. Although there are few descriptions

### Table 3. Individual Drug Developments for the Treatment and Prevention of Tuberculosis in Children Over the Last 10 Years

<table>
<thead>
<tr>
<th>WHO Category</th>
<th>Drug Name</th>
<th>Developments</th>
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<tbody>
<tr>
<td>First-line drugs</td>
<td>Isoniazid</td>
<td>Dosage revised in 2010 for DS-TB</td>
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<tr>
<td></td>
<td>Rifampin</td>
<td>Dosage revised in 2010 for DS-TB Higher dosages being evaluated</td>
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<tr>
<td></td>
<td>Rifapentine</td>
<td>Advised for weekly use in combination with isoniazid for preventive therapy</td>
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<tr>
<td></td>
<td>Pyrazinamide</td>
<td>Dosage revised in 2010 for DS-TB Increasingly recognized as an important</td>
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<tr>
<td></td>
<td>Ethambutol</td>
<td>Drug Name Developments</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Extensive review found to be safe at dosages used in children</td>
</tr>
<tr>
<td>Second-line drugs</td>
<td>Injectables</td>
<td>Pediatric PK data: potential to reduce dose of amikacin (and, hopefully,</td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolones</td>
<td>Use in shortened regimens; use in DR-TB regimens; use in TBM</td>
</tr>
<tr>
<td></td>
<td>Ethionamide</td>
<td>Clearer understanding of PK</td>
</tr>
<tr>
<td></td>
<td>PAS</td>
<td>Clearer understanding of PK; dosing spoon</td>
</tr>
<tr>
<td></td>
<td>Cycloserine</td>
<td>Clearer understanding of PK</td>
</tr>
<tr>
<td>Repurposed drugs</td>
<td>Clofazimine</td>
<td>PK studies ongoing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Used in MDR-TB when no sufficient other drugs available</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Large existing safety database for use in children with leprosy</td>
</tr>
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<td></td>
<td></td>
<td>Key component of “Bangladesh regimen”</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>Multiple studies showing good efficacy in MDR-TB regimens in both in vivo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and in vitro studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Extensive adverse events in adults, much better safety profile in children</td>
</tr>
<tr>
<td>New drugs</td>
<td>Bedaquiline</td>
<td>Licensed in adults with FDA and EMA and endorsed by WHO</td>
</tr>
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<td></td>
<td></td>
<td>Pediatric formulation under development</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose-finding and safety studies planned in MDR-TB (HIV infected and</td>
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<td></td>
<td>Delamanid</td>
<td>Licensed in adults with EMA and endorsed by WHO</td>
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<td></td>
<td></td>
<td>Pediatric formulation under development</td>
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<tr>
<td></td>
<td>PA-824</td>
<td>Adult PK and safety data developed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No data yet in children</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Key component in NC-006 regimen</td>
</tr>
</tbody>
</table>

Abbreviations: DS, drug-susceptible; DR, drug-resistant; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HIV, human immunodeficiency virus; MDR, multidrug-resistant; PAS, para-Aminosalicylic acid; PK, pharmacokinetics; TB, tuberculosis; WHO, World Health Organization.
of children treated for tuberculosis using clofazimine, there is significant experience with the drug in children for the treatment of leprosy. Apart from reversible skin discoloration, clofazimine appears to be well tolerated [103]. Thioridazine (an antipsychotic), paromomycin (an aminoglycoside), clarithromycin, meropenem, and doxycycline have all been recently reevaluated and used when other drugs are unavailable or intolerable, yet their respective roles in future tuberculosis treatment regimens for children remain unclear.

**NEW REGIMENS**

The development of regimens, in addition to individual drugs, is especially important given the need to effectively treat both rapidly replicating and metabolically inactive bacilli and to prevent the development of resistance [104].

In 2010, a seminal article was published describing an observational study conducted in Bangladesh [102]. Sequential cohorts of adults with MDR tuberculosis were given different treatment regimens, each differing from the previous one by the substitution or addition of 1 drug. The final cohort was given a 9-month regimen, including a later-generation fluoroquinolone and clofazimine. Eighty-eight percent of these patients had a favorable outcome, compared with substantially poorer outcomes for the 5 previous cohorts. This study has led to a number of further studies, one of which, STREAM, is a randomized noninferiority trial that compares a similar 9-month regimen to the standard WHO-recommended regimen. It should be completed by the end of 2016 [64], and a further study, STREAM II, is planned to follow that will include bedaquiline with the aim of evaluating a 9-month, all-oral regimen as well as a 6-month regimen. Although the individual drugs that make up the "Bangladesh regimen" are available for children, and are already being used to treat tuberculosis or other indications in children, few children have been given this shortened regimen, and neither STREAM nor STREAM II has included or plans to include children. More work needs to be done to determine the optimal use of novel and repurposed drugs and to evaluate their ability to shorten treatment and eliminate the use of injectables, especially in children.

The previously mentioned TB Alliance NC-006 (STAND) study will evaluate the novel drug PA-824, in combination with bedaquiline (QUIN-HCR). The study aims to compare the efficacy of this regimen to the standard chemotherapy regimen in children with multidrug-resistant or extensively drug-resistant tuberculosis.
with pyrazinamide and moxifloxacin, to shorten treatment for both drug-susceptible as well as drug-resistant tuberculosis in adults. Plans to evaluate the potential for delamanid to replace the injectable have also been discussed. Although children may not be included in these initial studies, if a regimen demonstrates efficacy, and appropriate formulations are available together with pediatric pharmacokinetic and safety data for the individual drugs, then it should be considered for use in children.

CONCLUSIONS

More research has been carried out in pediatric tuberculosis in the last 10 years than in prior decades combined, and drug dosages have been revised. However, no new regimes have yet been evaluated or introduced for treatment of childhood tuberculosis. New drugs and new regimes should be available to treat children within the next few years, and “older” drugs are likely to find new tuberculosis indications. It may become possible to treat tuberculosis with longer-acting drugs, given on a weekly basis for both drug-susceptible preventive therapy and also for the continuation phase of drug-susceptible tuberculosis treatment. A movement to categorize children based on disease severity for both drug-resistant and drug-susceptible disease, and to provide differing regimes based on severity, may lead to shortened treatment duration for large numbers of children. Research to evaluate these treatments in children will require significant investment and the collaboration of large consortia of investigators.

Notes

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