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Adverse effects of oral second-line antituberculosis drugs in children

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ABSTRACT

Introduction: Increasing numbers of children with drug-resistant tuberculosis are accessing second-line antituberculosis drugs; these are more toxic than first-line drugs. Little is known about the safety of new antituberculosis drugs in children. Knowledge of adverse effects, and how to assess and manage these, is important to ensure good adherence and treatment outcomes.

Areas covered: A PubMed search was performed to identify articles addressing adverse effects of second-line antituberculosis drugs; a general search was done for the new drugs delamanid and bedaquiline. This review discusses adverse effects associated with oral second-line antituberculosis drugs. The spectrum of adverse effects caused by antituberculosis drugs is wide; the majority are mild or moderate, but these are important to manage as it could lead to non-adherence to treatment. Adverse effects may be more common in HIV-infected than in HIV-uninfected children.

Expert opinion: Although children may experience fewer adverse effects from oral second-line antituberculosis drugs than adults, evidence from prospective studies of the incidence of adverse events in children is limited. Higher doses of second-line drugs, new antituberculosis drugs, and new drug regimens are being evaluated in children: these call for strict pharmacovigilance in children treated in the near future, as adverse effect profiles may change.

1. Introduction

Children with drug-resistant tuberculosis (DR-TB) are increasingly accessing care. An estimated 850,000 children develop tuberculosis (TB) every year; of these, approximately 25,000 will have multidrug-resistant tuberculosis (MDR-TB; i.e., resistance to at least isoniazid and rifampicin) \cite{1}. Although the proportion of children accessing appropriate second-line antituberculosis treatment for mainly MDR-TB is still relatively small, the number of children treated is increasing due to changes in global guidelines for diagnosis and treatment. MDR-TB is treated with combinations of the second-line antituberculosis drugs, which the World Health Organization (WHO) recently reorganized into four groups (Table 1) \cite{2}. Two novel TB drugs, bedaquiline and delamanid, now included in WHO Group D2, have recently received conditional approval for use in adults with MDR-TB and will become more frequently used components of MDR-TB treatment in the near future. Currently recommended MDR-TB treatment regimens in children typically include five to seven medications for as long as 18 months. Second-line antituberculosis drugs have more adverse effects than the first-line drugs. This, combined with the large number of medications used for long duration, lead to frequently observed adverse effects in children on MDR-TB treatment. However, there is a paucity of high-quality prospective data on the safety and tolerability of these drugs in children.

There are a number of reasons why the safety of the second-line antituberculosis drugs should be reviewed in children. First, children may experience a different spectrum, frequency, or severity of adverse effects compared to adults, and although efficacy trials of antituberculosis drugs or regimens are usually not required in children with tuberculosis, dose finding, safety, and tolerability studies of these drugs remain critically important in children \cite{3}. However, few such studies have been done to date. Adverse antituberculosis drug effects are often reported to be less common in children compared to adults; possible reasons may be lower concentrations of drugs at the same mg/kg body weight doses in children compared to adults and the difficulty in assessing adverse effects in children.

Second, health-care providers caring for children with MDR-TB should have a detailed knowledge of the possible adverse effects of the second-line antituberculosis drugs in order to safely and successfully manage children’s treatment. Antituberculosis treatment includes a number of drugs, which all have potential adverse effects, which may be more severe if certain drugs are combined, and children with MDR-TB may have comorbid conditions, such as HIV coinfection, requiring medications which could have similar adverse effects to the antituberculosis drugs. In current complicated multidrug regimens, it can be difficult to determine the culprit drug(s). It is also important to do baseline testing (before starting treatment), as abnormalities from other causes may already be present.
Severe adverse effects, such as severe hepatotoxicity or severe cutaneous adverse effects, should lead to immediate discontinuation of the likely drug(s) responsible, as there is a high risk of mortality. Even so, with some severe adverse effects (e.g., hepatotoxicity), patients can be rechallenged with the likely responsible drug(s), while in others, a rechallenge with the responsible drug may be fatal. Some adverse effects are not fatal but could cause irreversible morbidity. Although many adverse events are mild or moderate and do not require stopping or changing of drugs, if these are not addressed by the health-care workers, adverse events may lead to non-adherence because they are unpleasant or unacceptable to the patient or their family [4,5]. Health-care workers managing patients with MDR-TB should also be aware of possible rare but severe adverse effects, which can occur with anti-tuberculosis drugs. In some cases, there may be no alternative drug options to those drugs causing adverse effects, and it may be necessary to weigh the risks of tolerating potentially serious adverse effects versus poor or failed response to treatment.

Finally, MDR-TB treatment outcomes in children are usually better than that in adults, with more than 80% successfully treated [6,7]. However, improving the safety and tolerability of treatment while maintaining the efficacy is an important priority in children. In designing novel MDR-TB regimens for children, the safety of component drugs will be a key consideration. An in-depth understanding of individual drugs and any potential overlapping or synergistic adverse effects will be important for constructing future safe and well-tolerated MDR-TB regimens in children.

In this review, we provide a brief description of the more important adverse effects of the currently available oral second-line antituberculosis drugs (injectable agents are reviewed separately in this journal). We also include the new antituberculosis drugs soon to be available in children: delamanid and bedaquiline.

### 2. Methods

We searched PubMed without date or language restrictions, using the following search terms: ‘tuberculosis, second-line drugs, adverse effects or side-effects, child*’; ‘tuberculosis, multidrug-resistant, treatment, adverse effects or side-effects, child*’; and ‘tuberculosis, drug-resistant, treatment, toxicity, child*’; many abstracts were not applicable to the review, and there was a great overlap between search results. We also searched adverse effects or toxicity for each individual drug in children and used a general search where no published data were available in children, such as with the new drugs. Abstracts were reviewed and full-text articles retrieved for studies with relevant information. The reference lists of identified articles were searched for additional relevant reports.

### 3. Definitions

Published literature on toxicity of drugs often uses different terms inconsistently. Therefore, we clarify our use of terms for this review as follows: an adverse (drug) effect (adverse drug reaction) is an unintended symptom, sign, condition, or abnormal laboratory test finding caused by taking a specific drug (or in some cases, a combination of two or more drugs). An adverse event refers to any unfavorable and unintended symptom, sign, condition, abnormal laboratory finding, or disease temporally associated with the use of a drug regardless of whether it is considered related to the drug [8]. An adverse effect is a special type of adverse event in which a causative relationship can be shown [8].

### Table 1. World Health Organization drug groups for second-line drugs recommended for the treatment of rifampicin resistant and multidrug resistant TB.

<table>
<thead>
<tr>
<th>Drug groups</th>
<th>Drug names</th>
<th>Abbreviations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A.</td>
<td>Levofloxacin</td>
<td>Lfx</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Moxifloxacin</td>
<td>Mfx</td>
</tr>
<tr>
<td></td>
<td>Gatifloxacin</td>
<td>Gfx</td>
</tr>
<tr>
<td>Group B.</td>
<td>Amikacin</td>
<td>Am</td>
</tr>
<tr>
<td>Second-line injectable agents</td>
<td>Capreomycin</td>
<td>Cm</td>
</tr>
<tr>
<td></td>
<td>Kanamycin</td>
<td>Km (S)</td>
</tr>
<tr>
<td></td>
<td>(Streptomycin – only if susceptible in special cases)</td>
<td></td>
</tr>
<tr>
<td>Group C.</td>
<td>Ethionamide/prothionamide</td>
<td>Eto/Pto</td>
</tr>
<tr>
<td>Other core second-line agents</td>
<td>Cycloserine/terizidone</td>
<td>Cs/Trd</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>Lzd</td>
</tr>
<tr>
<td></td>
<td>Clofazimine</td>
<td>Cfz</td>
</tr>
<tr>
<td></td>
<td>Z</td>
<td></td>
</tr>
<tr>
<td>Group D.</td>
<td>D1 Pyrazinamide</td>
<td>E</td>
</tr>
<tr>
<td>Add-on agents (not part of the core multidrug-resistant TB regimen)</td>
<td>Ethambutol</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>D2 Bedaquiline</td>
<td>Dlm</td>
</tr>
<tr>
<td></td>
<td>Delamanid</td>
<td>PAS</td>
</tr>
<tr>
<td></td>
<td>D3 p-Aminosalicylic acid</td>
<td>Impenem–clavulanate</td>
</tr>
<tr>
<td></td>
<td>Imipenem–clavulanate</td>
<td>Mpm</td>
</tr>
<tr>
<td></td>
<td>Meropenem</td>
<td>Amx–Clv</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin–clavulanate (only used with imipenem or meropenem)</td>
<td>(T)</td>
</tr>
<tr>
<td></td>
<td>(Thiocetazone – only for HIV-negative cases)</td>
<td></td>
</tr>
</tbody>
</table>

TB: tuberculosis.

Data taken from Ref. [2].
Standard grading of many adverse events is available, such as in the Division of AIDS table of adverse events, and can assist in decisions of whether to discontinue treatment or not and for safety monitoring purposes in clinical research [8].

4. Prevalence of adverse events from second-line antituberculosis drugs in children

Children, especially those younger than 10 years of age, seem to tolerate second-line combination antituberculosis therapy better than adults [9,10]. There are few studies of MDR-TB in children which have monitored adverse events closely [7,9]. In a systematic review and meta-analysis, adverse events were documented in 39.1% (95% confidence interval [CI]: 28.7–49.4) of HIV-infected and HIV-uninfected children treated for DR-TB [6]. However, in a small cohort of adolescents coinfected with HIV, adverse effects were documented in 8/11 (72%) cases, and in a systematic review and meta-analysis of MDR-TB in HIV-infected adults and children, adverse events were documented in 92.5% (95% CI: 83.7–100) of HIV-coinfected children [11,12]. Our own experience in children is also that HIV-infected patients have higher rates of adverse events compared to HIV-uninfected children [13,14]. However, the majority of adverse events in children are mild to moderate, not necessitating interruption or complete cessation of treatment, and even with the few severe adverse events, permanent discontinuation of drugs is rarely necessary [7,9].

5. Adverse effects associated with the second-line antituberculosis drugs

Table 2 summarizes the most common adverse effects with the drugs that could be responsible and how to monitor for these adverse effects. Table 3 summarizes adverse effects by antituberculosis drug, including rare adverse effects.

5.1. Fluoroquinolones (WHO Group A)

The fluoroquinolones used for antituberculosis therapy are ofloxacin (Ofx) and, more frequently, its L-isomer levofloxacin (Lfx) and moxifloxacin (Mfx). The fluoroquinolones inhibit the mycobacterial DNA gyrase (topoisomerase II) leading to disruption of bacterial DNA synthesis, resulting in cell death [15]. The fluoroquinolones have bactericidal activity against metabolizing bacilli, with a relative potency against Mycobacterium tuberculosis of Mfx>Lfx>Ofx [16]. They are also active against dormant mycobacteria [17]. Fluoroquinolones are well absorbed after oral administration and distribute widely in the body including in cerebrospinal fluid (CSF).

The most frequent adverse effects of fluoroquinolones are gastrointestinal disturbances (0.9–4.7%) including loss of appetite, nausea and vomiting, abdominal discomfort, and anorexia [18,19]. In rare cases, fluoroquinolones have been associated with Clostridium difficile infections causing mild diarrhea to life-threatening pseudomembranous colitis [20].

Central nervous system (CNS) adverse effects occur in up to 5% of patients, although less than 0.5% are serious [21,22]. These are often dose dependent and generally reversible after cessation of the fluoroquinolone [18,19]. Dizziness, headache, and drowsiness are the most common complaints, while more severe effects such as hallucinations, agitation, anxiety, restlessness, paranoia, depression, suicidal ideation, psychosis, and convulsions are rare [18,19,23]. Cases of peripheral neuropathy, Guillain–Barré syndrome, and secondary intracranial hypertension associated with fluoroquinolone use have been reported [19,24,25]. In children receiving Ofx, mood/sleep disturbances have been reported and may be underrecognized [18].

Dermatological problems occur in less than 0.5% of patients. Photosensitivity, usually mild but which may be severe, is a fluoroquinolone class effect, but the phototoxic potential of Ofx, Lfx, and Mfx seems to be minimal [22,26]. Cutaneous hypersensitivity reactions can present as rash, pruritus, urticaria, erythema, and angioedema [22,27]. Although rare, severe reactions such as toxic epidermal necrolysis or Stevens–Johnson syndrome have been reported in adults and children following fluoroquinolone therapy [28–30].

Concern about musculoskeletal adverse effects, particularly chondrotoxicity, has historically limited the widespread fluoroquinolone use in children. In studies on juvenile animals, fluoroquinolones as a class exhibit a potential to induce irreversible cartilage damage on weight-bearing joints [31]. Nevertheless, data from multiple observational studies concluded that there is no documentation of sustained injury on bone or joint growth or severe or irreversible arthropathy in children although there may be some association between fluoroquinolones and reversible arthralgia [19,32,33].

Data on the risk of arthropathy in children on long-term fluoroquinolone therapy, as for antituberculosis treatment, are limited. In children receiving Ofx for between 6 and 18 months, Grade 1 to 2 musculoskeletal disorders [8] occurred in 3–9% of patients with no signs of severe arthropathy [7,18,34]. In a small case series on five children on Lfx-containing antituberculosis regimens, two children experienced joint pain necessitating discontinuation of Lfx in one [35]. The arthropathic potential of long-term Mfx therapy in children is difficult to assess due to limited reports; of 23 children 7–15 years of age in one study, five reported arthralgia, which resolved spontaneously without discontinuation of Mfx [36]. Tendonitis and Achilles tendon rupture are extremely rare in children. We could not find a single case report of tendon rupture in children; this agrees with our clinical experience, having treated hundreds of children with fluoroquinolones for long durations (6–24 months).

Fluoroquinolones, especially Mfx, may cause QT-interval prolongation [19]. Studies in children receiving Mfx (n = 32) and Lfx (n = 23) for DR-TB treatment found no evidence of QT prolongation >450 ms [36–38]. We did not identify any report on arrhythmia or sudden death associated with fluoroquinolone use in children. Nevertheless, clinicians should be aware of this possible adverse effect especially when
fluoroquinolones are used with other drugs with QT-prolonging potential (e.g. delamanid, bedaquiline, clarithromycin, or clofazimine).

Disordered glucose regulation associated with fluoroquinolones, especially gatifloxacin, has been reported in adults (not in children) with differences between the fluoroquinolones and very low risk for Lfx and Mfx [19]. Further rare adverse effects of the fluoroquinolones include hemolytic anemia, hepatotoxicity, pancreatitis, interstitial nephritis, and ophthalmological problems [19]. None of these adverse events have been reported in children. However, ongoing surveillance is critically important as more children will receive long-term fluoroquinolone therapy as part of MDR-TB regimens in future.

### 5.2. Thioamides (WHO Group C)

The thioamides, ethionamide (Eto), and its propyl analog prothionamide (Pto) form important components in the treatment of MDR-TB and drug-susceptible disseminated TB (e.g. TB meningitis). Eto and Pto are produgs that, following enzymatic activation by mycobacterial EthA, inhibit InhA, a target shared with isoniazid [39], resulting in inhibition of mycolic acid biosynthesis and cell lysis [40]. Eto and Pto are bacteriostatic drugs but can be bactericidal at higher doses [41].

The main adverse effects of thioamide are gastrointestinal disturbances, resulting in nausea, abdominal discomfort, vomiting, diarrhea, and, as a result of these symptoms, weight loss [42]. Pto was developed to improve tolerability, but gastrointestinal adverse effects still occur in the majority of patients. Gastrointestinal intolerance is dose dependent, generally improves after the first weeks of therapy, and can often be reduced by dose ramping (increasing the dose over a few days) or giving divided daily doses at the beginning of therapy [43]. In children, we do not recommend antiemetics, although in adolescents this may be an option.

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Table 2. An alphabetical list of more common adverse effects due to drugs used in multidrug-resistant tuberculosis treatment, likely drugs that could be responsible, and how to monitor for these adverse effects.

<table>
<thead>
<tr>
<th>Adverse drug effect</th>
<th>Possible causative drugs</th>
<th>How to monitor</th>
<th>Frequency of tests*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia/arthritis</td>
<td>FQNs, Z (especially in combination), Rfb</td>
<td>Painful joints, watch gait, examine joints</td>
<td>Routine follow-up*</td>
</tr>
<tr>
<td>Blood dyscrasias</td>
<td>H, Eto/Pto, Rfb, Z, E, FQNs, PAS, Cs, Cla</td>
<td>Clinically – anemia, petechiae</td>
<td>Routine follow-up</td>
</tr>
<tr>
<td>Central nervous system toxicity: headache, drowsiness, seizures, weakness, insomnia, and hallucinations</td>
<td>FQNs (insomnia and hallucinations), H, Eto/Pto, Cs/Trd, Cla</td>
<td>Full blood count when suspected</td>
<td>Routine follow-up</td>
</tr>
<tr>
<td>Depression/psychosis</td>
<td>H, Eto, Cs/Trd</td>
<td>History and observation</td>
<td>Routine follow-up</td>
</tr>
<tr>
<td>Endocrine effects</td>
<td>- hypothyroidism - gynecomastia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flu-like symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GIT disturbances: nausea, vomiting, abdominal pain, and diarrhea</td>
<td>Very common, mainly Eto/Pto, E, PAS, FQNs, Cs, Lzd, Bdq</td>
<td>Mainly history of abdominal complaints. With new-onset vomiting or abdominal pain, consider hepatitis</td>
<td>Routine follow-up</td>
</tr>
<tr>
<td>Hearing impair/toxicity</td>
<td>Am, Km, Cs, S</td>
<td>Audiology</td>
<td>Monthly after completion of SLID</td>
</tr>
<tr>
<td>Hair loss</td>
<td>H, Eto/Pto</td>
<td>History/clinical examination</td>
<td>Routine follow-up</td>
</tr>
<tr>
<td>Intracranial hypertension</td>
<td>FQNs</td>
<td>History/ophtalmoscopy and CT scan/LP when suspected</td>
<td>Routine follow-up</td>
</tr>
<tr>
<td>Jaundice/hepatotoxicity</td>
<td>H, Z, Eto/Pto, PAS, FQNs (Mfx more likely)</td>
<td>New-onset vomiting, abdominal pain, and jaundice</td>
<td>Alamine transference and bilirubin – usually as clinically indicated but can do 2-monthly</td>
</tr>
<tr>
<td>K⁺ (potassium) loss</td>
<td>Cm, PAS</td>
<td>K⁺ levels</td>
<td>2-monthly Routine follow-up</td>
</tr>
<tr>
<td>Lactic acidosis</td>
<td>Lzd</td>
<td>Clinical examination and lactate levels if suspected</td>
<td>Routine follow-up</td>
</tr>
<tr>
<td>Myelosuppression</td>
<td>Lzd</td>
<td>Full blood count</td>
<td>Monthly Routine follow-up</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>Cm, Am, Km, S</td>
<td>Serum creatinine</td>
<td>2-monthly Routine follow-up</td>
</tr>
<tr>
<td>Optic neuritis: vision acuity/color blindness</td>
<td>E, Lzd, H, Eto, PAS, Cs/Pas</td>
<td>Vision and color blindness testing</td>
<td>Routine follow-up</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Lzd, H, Eto/Pto, Cs/Pas</td>
<td>History of pain in hands/feet, watch mobility and gait, test sensation, position</td>
<td>Routine follow-up</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Lzd</td>
<td>Abdominal pain/clinically, serum amylase if suspected</td>
<td>Routine follow-up</td>
</tr>
<tr>
<td>QTc-interval prolongation</td>
<td>Bdq, Dlb, FQN (Mfx), Cfx, Cla</td>
<td>ECG</td>
<td>Currently not routinely done except with Dlb and Bdq</td>
</tr>
<tr>
<td>Rashes/cutaneous adverse drug effects including pruritus</td>
<td>Z, FQNs, Cs/Trd, PAS, and many other</td>
<td>History and clinical examination</td>
<td>Routine follow-up</td>
</tr>
<tr>
<td>Skin discolouration – red skin</td>
<td>Cfx</td>
<td>Clinical examination</td>
<td>Routine follow-up</td>
</tr>
<tr>
<td>Tendinitis/tendinopathy</td>
<td>FQNs</td>
<td>Clinical examination</td>
<td>Routine follow-up</td>
</tr>
<tr>
<td>Uveitis</td>
<td>Rfb</td>
<td>Examination of eyes</td>
<td>Routine follow-up</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>H, FQNs</td>
<td>Clinical examination</td>
<td>Routine follow-up</td>
</tr>
<tr>
<td>Vestibular toxicity</td>
<td>S, Am, Km, Cs</td>
<td>History, clinical observation</td>
<td>Routine follow-up</td>
</tr>
</tbody>
</table>

Am: amikacin; Bdq: bedaquiline; Cfx: clofazimine; Cla: clarithromycin; Cm: capreomycin; Cs: cycloserine; Dlb: delamanid; E: ethambutol; Eto: ethionamide; Eto/Pto: ethionamide/prothionamide; FQNs: fluoroquinolones; H: isoniazid; Km: kanamycin; Lzd: linezolid; Mfx: moxifloxacin; PAS: para-aminosalicylic acid; Pto: prothionamide; Rfb: rifabutin; S: streptomycin; Trd: terizidone; Z: pyrazinamide; CT: computed tomography; ECG: electrocardiogram; GIT: gastrointestinal; LP: lumbar puncture; QTc: corrected QT; SLID: second-line injectable drug; TSH: thyroid-stimulating hormone.

*Routine follow-up would be at least monthly initially and then 2-monthly.
Table 3. Adverse effects (AEs) associated with second-line antituberculosis drugs in children.

<table>
<thead>
<tr>
<th>Antituberculosis drugs</th>
<th>Adverse effects (AEs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolones</td>
<td>Common: Gastrointestinal disturbance; central nervous system (CNS) AEs (e.g. dizziness, headache, drowsiness, and hallucinations); arthralgia; cutaneous AEs (usually mild, e.g., pruritus, rash, and photosensitivity)</td>
</tr>
<tr>
<td>- Moxifloxacin</td>
<td>Rare: Arthritis; tendonitis; QT prolongation (Mfx&gt;Lfx/Ofx); severe cutaneous AEs; hemolytic anemia; hepatotoxicity; pancreatitis; secondary intracranial hypertension; and ophthalmologic problems</td>
</tr>
<tr>
<td>- Levofloxacin</td>
<td>Common: Gastrointestinal disturbances; hepatotoxicity; and hypothyroidism</td>
</tr>
<tr>
<td>- Ofloxacin</td>
<td>Common: CNS AEs (peripheral neuritis, seizures, and psychosis); gynecomastia; alopecia; hypoglycemia; pellagra-like rash; and blood dyscrasias</td>
</tr>
<tr>
<td>Thioamides</td>
<td>Common: Gastrointestinal disturbances; hepatotoxicity; and hypothyroidism</td>
</tr>
<tr>
<td>- Ethionamide</td>
<td>Rare: CNS AEs (peripheral neuritis, seizures, and psychosis); gynecomastia; alopecia; hypoglycemia; pellagra-like rash; and blood dyscrasias</td>
</tr>
<tr>
<td>- Prothionamide</td>
<td>Common: Gastrointestinal disturbances; hepatotoxicity; and hypothyroidism</td>
</tr>
<tr>
<td>Cycloserine/terizidone</td>
<td>Common: CNS AEs (dizziness, headache, tremor, insomnia, anxiety, lethargy, inability to concentrate, and depression)</td>
</tr>
<tr>
<td>- Para-aminosalicylic acid</td>
<td>Rare: Hepatotoxicity; hypokalemia; hypersensitivity reactions (fever and maculopapular rash); severe cutaneous AEs; and blood dyscrasias</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Common: Myelosuppression (anemia, thrombocytopenia, and leucopenia); peripheral neuropathy</td>
</tr>
<tr>
<td>Clofazime</td>
<td>Rare: Pancreatitis; vision loss (optic neuritis); hyperlactatemia and lactic acidosis, and rhabdomyolysis</td>
</tr>
<tr>
<td>Delamanid</td>
<td>Common: Gastrointestinal disturbances; red–brown discoloration of the skin</td>
</tr>
<tr>
<td>Bedaquiline</td>
<td>Rare: QT prolongation; hepatotoxicity in adults</td>
</tr>
</tbody>
</table>

During therapy with Eto and Pto, asymptomatic elevation of liver transaminases frequently occurs in adults and children, and hepatotoxicity has been reported in about 2% of adult patients [44]. Following cessation of thioamide therapy, liver transaminases generally normalize, and it has been shown that thioamides can be restarted without recurrence of hepatotoxicity in children [45].

Thioamides inhibit thyroid hormone synthesis by blocking organization and uptake of iodine into thyroid cells. During long-term therapy, hypothyroidism occurs frequently (20–70%) in adults and in children [13,46,47]. HIV infection and concomitant treatment with para-aminosalicylic acid (PAS) is associated with an increased risk for hypothyroidism [13,48]. Although the clinical significance of hypothyroidism due to thioamide therapy has not yet been evaluated, our practice is to supplement thyroxine in children with elevated thyroid-stimulating hormone (TSH) and low free thyroxine levels, given the potential impact of hypothyroidism on neurodevelopment in young children [7,13].

Thioamide use has also been associated with CNS toxicity including peripheral neuropathy, psychosis, behavioral disorders, seizures, or pellagra-like encephalopathy in adults, but there are no reports in children [42]. Niacin or pyridoxine supplementation might be beneficial in case of nervous system toxicity [49].

Other rare adverse effects of thioamides include gynecomastia, alopecia, hypoglycemia, pellagra-like rash, and blood count alterations [42].

5.3. Cycloserine/terizidone (WHO Group C)

Cycloserine is an analog of the amino acid D-alanine and inhibits enzymes needed for synthesis of peptidoglycan, a key component of the M. tuberculosis cell wall [50]. Terizidone is a molecule formed by the combination of two molecules of D-cycloserine [51]. Cycloserine and terizidone are bacteriostatic drugs with relatively weak antimycobacterial activity at currently recommended doses, yet are still currently routinely used for MDR-TB treatment in adults and in children. They do have the advantage of good CSF penetration, which is important for the treatment of tuberculous meningitis.

Cycloserine is known to exert CNS effects as an agonist of N-methyl-D-aspartate receptors and at low doses is being explored as a potential treatment for a number of neuropsychiatric conditions [52]. At the much higher doses used in TB treatment, cycloserine has well-known CNS adverse effects. These are highly variable, ranging from relatively mild effects including dizziness, headache, tremor, insomnia, anxiety, lethargy, inability to concentrate, to more serious effects including severe depression, suicidal ideation, psychosis, seizures, and encephalopathy [53,54]. In a small study, when cycloserine dosing was targeted to maintain peak concentrations between 20 and 40 µg/ml, only 4 of 60 participants experienced CNS adverse effects; all four had concentrations >40 µg/ml [55]. This suggests that these effects are dose related and concentration related, and symptoms are reversible upon cycloserine discontinuation or dose reduction.

Cycloserine may lead to peripheral neuropathy via direct antagonistic effects on pyridoxine and by increasing its renal elimination; pyridoxine should be coadministered to reduce this risk [56]. Other more rare adverse effects, including Stevens–Johnson syndrome have been reported [57]. There is limited published information on terizidone. It has been suggested that terizidone has fewer adverse effects than cycloserine; however, there are no published data to our knowledge to support this assumption.

A recent systematic review and meta-analysis attempted to describe the frequency of cycloserine- and terizidone-associated adverse effects in adults treated for MDR-TB [58]. This review included 27 studies reporting cycloserine safety data, which included 2164 patients, and 10 studies reporting terizidone safety data, which included 707 patients. The pooled frequency of any adverse effect due to cycloserine was 9.1% (95% CI: 6.4–11.7), with the majority of these being psychiatric adverse effects. Reporting of terizidone safety was highly variable, with serious adverse effects described in 0–31% of participants in these studies. In adults, there is a large burden of preexisting and incident mental illness during MDR-TB.
treatment, which complicates attribution of these psychiatric events; aggressive management with psychiatric medications appears to be very effective and may limit the need for cycloserine or terizidone dose adjustment [59]. There are limited published safety data for either cycloserine or terizidone in children with MDR-TB. A systematic review of children treated for MDR-TB reported 6 of 182 children had cycloserine-associated adverse effects, which included depression, anxiety, hallucinations, psychosis, and blurred vision [6]. Neurologic and psychiatric symptoms may be more difficult to elicit especially in young children, and a high index of suspicion is required. In our experience in children younger than 14 years of age, severe adverse effects with terizidone are rare.

5.4. Linezolid (WHO Group C)

Linezolid, an oxazolidinone class antibiotic, selectively inhibits bacterial protein synthesis. Its high durable efficacy against extensively drug-resistant (XDR)-TB (i.e. MDR-TB plus resistance to a fluoroquinolone and a second-line injectable agent) [60,61] and good CSF penetration have made it an increasingly important antituberculosis drug [62]. It is being evaluated as a component of multiple novel TB regimens, including treatment shortening regimens, currently under evaluation; however, severe toxicity remains a concern, and it is currently often reserved for the difficult-to-treat MDR-TB and XDR-TB cases in children.

Overall, adverse effects with linezolid are reported to be less frequent in children than in adults [63]. The mechanisms of most adverse effects are thought to be due to the inhibition of mitochondrial protein synthesis [64]. Gastrointestinal disturbances, such as vomiting and diarrhea, are the most common. These are usually mild, occurring before 1 month, and rarely require treatment modification [61].

Neurologic adverse effects are well described with linezolid in adults and children and are an important concern [65]. Peripheral neuropathy is the most frequent, occurring among patients on prolonged durations of linezolid therapy. It presents as paresthesia and numbness of the distal extremities in a ‘stocking and glove’ distribution and is not responsive to pyridoxine; although reversible, the improvement may be slow [66,67]. Optic neuropathy presents as painless, progressive loss of color vision and visual acuity, with onset generally after 3–12 months of linezolid treatment; it may improve after linezolid discontinuation but can result in permanent visual deficits [66].

Hematological adverse effects of linezolid are not uncommon and include reversible anemia, thrombocytopenia, and leukopenia [66,68]. These should be screened for routinely and usually respond to dose reduction. Other adverse effects are less common, but potentially serious and important to be aware of. Linezolid-associated hyperlactatemia and lactic acidosis have been described, which usually resolve over 1 to 2 weeks after linezolid discontinuation [66]. This has been reported in children, most frequently in association with liver disease or other serious comorbidities [69–71]. Rhabdomyolysis [72] and serotonin syndrome in patients receiving a serotonin agonist drug have rarely been reported with linezolid [66,73]. The majority of these adverse effects appear to be dose and time dependent, with higher doses and longer treatment durations greatly increasing the risk; however, the specific risks have not been well described.

In a systematic review including 107 adults treated with linezolid for MDR-TB/XDR-TB, 59% experienced an adverse effect, of which 69% required linezolid discontinuation or dose adjustment. The most common adverse effects were peripheral neuropathy (47%), anemia (38%), gastrointestinal disorders (17%), optic neuritis (13%), and thrombocytopenia (12%) [74]. Subsequent studies confirmed these findings [75]. There is a significant increase in risk of experiencing an adverse effect when using a dose >600 mg daily [74].

A 2014 literature review identified 18 children from eight different reports treated with linezolid for MDR-TB [76]. Fifty percent experienced an adverse effect, with peripheral neuropathy the most common (4/18, 22%); 2 (11%) had linezolid permanently discontinued, and 5 (28%) had a dose reduction. Gastrointestinal disturbances, hepatotoxicity, anemia, and thrombocytopenia were also reported. Subsequent reports have shown similar findings [77,78]. The single life-threatening adverse event was a case of severe pancreatitis and lactic acidosis [71]. Other antituberculosis drugs have overlapping toxicities and may have contributed to some of these adverse events. Peripheral neuropathy may be caused by high-dose isoniazid, ethionamide, and cycloserine/terizidone; therefore, close monitoring of these patients is especially important. HIV-infected children appear to be at higher risk for adverse events, possibly due to overlapping toxicities with the nucleoside reverse transcriptase inhibitor class of antiretrovirals which also inhibit mitochondrial DNA synthesis [79]. A recent study in 86 HIV-uninfected children with TB meningitis found no significant increase in frequency of adverse events when receiving additional linezolid for 1–4 months (linezolid group 33.3% [n = 36] versus control group 32%) [62].

Substantial inter-patient variability in linezolid clearance occurs, which could justify the role of therapeutic drug monitoring (TDM) in future. A center conducting TDM for linezolid in adults has reported a 0% adverse event rate [75].

5.5. Clofazimine (WHO Group C)

Clofazimine is a riminophenazine compound that has been used for the treatment of leprosy but is only now being explored for use in antituberculosis treatment. To date, its mechanism of action remains unclear. Clofazimine is a produg, which is reduced by type 2 NADH-quinone oxidoreductase (NDH-2), which then releases reactive oxygen species upon spontaneous reoxidation by O2 [80]. It competes with menaquinone, the only quinone present in mycobacteria, and a key electron acceptor, for its reduction by NDH-2 [80].

To date, clofazimine has been used mostly in salvage antituberculosis treatment regimens, but the success of a shortened clofazimine-containing regimen for MDR-TB has generated interest in its more widespread use [81]. Clofazimine is now included in the WHO–recommended 9–12-month shortened treatment regimen for MDR-TB [2] and is
isolates may benefit four were M. tuberculosis – gene (usually intermediate) or orange discoloration of the skin, eyes, and body fluids [84]. This resolves slowly over the course of months, but can persist for longer [85]. Ichthyosis, a skin disorder with thickened, dry, scaly skin which can be quite distressing to patients, may occur in up to a quarter of patients treated with clofazimine [82]. Clofazimine is known to prolong the QT-interval; however, this has been poorly characterized. This is of particular concern if clofazimine is to be combined with Mfx and the novel TB drugs bedaquiline, delamanid, or pretomanid, all of which also cause QT-interval prolongation.

Most clofazimine safety data are from leprosy patients, and there is relatively little experience with clofazimine in the treatment of MDR-TB or in children. In a systematic review of the safety of clofazimine in MDR-TB and XDR-TB treatment, including five studies with 602 clofazimine-treated patients, the proportion experiencing a clofazimine-attributed adverse effect ranged from 0 to 11%; however, only 0.1% overall discontinued clofazimine [86]. Data from more recent studies have been somewhat variable. In a randomized controlled trial in 105 adults with MDR-TB who received an optimized background regimen (OBR) with or without clofazimine, in clofazimine-treated patients skin discoloration was reported in 94.3% and ichthyosis in 47.2%; there was no difference in gastrointestinal adverse effects between the two groups [87]. However, in a South African cohort, dermatologic adverse effects were reported less frequently, with a dermatologic reaction reported in only 6 of 42 (14%); only three participants in this cohort discontinued clofazimine [88]. There are limited data on children with MDR-TB treated with clofazimine. In a recently reported case series, seven children with MDR-TB were treated with clofazimine for a median of 20-month duration [78]. Clofazimine-attributed adverse effects were reported in four children, including one with transient gastritis, one with ichthyosis, one with red skin discoloration, and one with ichthyosis and red skin discoloration; clofazimine was not interrupted or discontinued in any case. Additional data in children are important, given the potentially increased use of clofazimine for MDR-TB treatment.

5.6. High-dose isoniazid (WHO Group D1)

Isoniazid is a bactericidal drug in drug-susceptible M. tuberculosis. It is a prodrug that is converted by a mycobacterial catalase-peroxidase to an active metabolite. Following activation, isoniazid inhibits the biosynthesis of mycolic acids in the mycobacterial cell wall [89]. Resistance to isoniazid is conferred mainly by mutations in either katG gene (usually intermediate- to high-level resistance) or InhA promoter region (usually low-level resistance) [90]. Patients infected with low-level isoniazid-resistant M. tuberculosis isolates may benefit from treatment with high-dose isoniazid [91].

Isoniazid is arguably the most used antituberculosis drug, and adverse effects are well-characterized. Hepatotoxicity is most serious: slight elevation of liver enzymes (less than three times upper limit of normal [ULN]) occurs in up to 40% with preventive therapy [92]; in this study, 16/227 (7%) had transaminase levels greater than three times ULN – four were switched to rifampicin preventive therapy. In an extensive review, Donald [93] showed that there is no significant influence of dose regarding those with increased serum transaminases; increased transaminase levels were reported in 141/1762 (8%) children receiving isoniazid at 10 mg/kg compared to 139/1406 (9.8%) children receiving doses of 10–20 mg/kg. However, persons with increased isoniazid concentrations or its metabolites, as found in slow acetylators of isoniazid, seemed more likely to experience rise of transaminase levels above normal [93]. New-onset vomiting and abdominal pain are early warning signs of significant hepatotoxicity; jaundice is a late sign, in which case all hepatotoxic drugs should immediately be discontinued, as continuation of these drugs, including isoniazid, could lead to rapidly fatal hepatic failure. Once transaminases and bilirubin levels have returned to normal, isoniazid can be reintroduced, but with high-dose isoniazid in an isoniazid-resistant case, the benefit of this should be weighed against the risk.

Dose-related neurotoxicity, such as peripheral neuropathy, seizures, psychosis, ataxia, and optic neuritis, is rare in children and can be prevented in high-dose isoniazid by adding pyridoxine to the regimen. Very rare hematological adverse effects, also responsive to pyridoxine, are sideroblastic anemia, hemolytic anemia, thrombocytopenia, and aplastic anemia. Skin rashes are common; in adolescents, acneiform eruptions are common [94].

5.7. Delamanid (WHO Group D2)

Delamanid (Deltyba®), previously OPC-67683, is a new antituberculosis drug derived from the nitro-dihydro-imidazooxazole class of compounds that inhibits mycolic acid synthesis [95]. The drug has been approved by the European Medicines Agency (EMA) and several other countries for treatment of MDR-TB in adults and is now also available through the Global Drug Facility. It is not yet approved by the United States Food and Drug Administration (FDA). It has been available through compassionate use from the manufacturer to children older than 12 years of age and more recently for children down to 6 years of age and more than 20 kg body weight [96].

Delamanid is likely a prodrug activated by mycobacterial F420-dependent Ddn coenzymes and is eliminated directly from plasma. It is not excreted in the urine but metabolized largely by plasma albumin. It is largely converted to its primary metabolite, DM-6705, which is thought to be mainly responsible for its effect of QTC prolongation [97].

Adverse events were similar in a study comparing delamanid 100 mg twice-daily, 200 mg twice-daily, and placebo group in patients on background MDR-TB treatment except for QTC prolongation, which differed significantly between the
three groups in pairwise comparisons (highest in the delamanid 200-mg twice-daily group). No patients with prolonged QTc interval were symptomatic, and no patient stopped delamanid due to QTc prolongation [95]. Administration of concomitant drugs with QT prolongation effect or CYP3A4 inhibitors (as the delamanid metabolite DM-6705 is metabolized by CYP3A4) and hypoalbuminemia may be associated with an increased risk of QTc prolongation [95,97].

Hepatotoxicity was found at a rate of 3% across all three adult MDR-TB groups in the study by Gler et al. [95]. However, a single report of severe hepatotoxicity in a 25-year-old male was reported to the EMA [98]. The EMA therefore advises to avoid delamanid in patients with moderate-to-severe hepatic impairment [97].

Two studies, a Phase 1, open-label, multiple-dose, age-dec and a Phase 2 open-label, multiple-dose trial to assess the safety, tolerability, pharmacokinetics, and efficacy of delamanid in children with MDR-TB, are ongoing [99]. Provisional results have been presented in older children: of 13 HIV-uninfected children 6–17 years of age (six children <12 years of age), none experienced any serious adverse events, and no child had an absolute corrected QT by Fridericia’s formula (QTcf) of >500 ms or an increase in QTcf from baseline >60 ms [100]. Although delamanid therefore seems safe and well tolerated in children, more data on dose and safety in children are required, especially in HIV-infected and in younger children; younger children are currently being enrolled.

5.8. Bedaquiline (WHO Group D2)

Bedaquiline (TMC 207) is a diarylquinoline, a new class of antituberculosis drug and the first new drug to be approved for tuberculosis treatment since rifampin in 1971 [101]. It is an adenosine triphosphate synthase inhibitor specific for M. tuberculosis and some nontuberculous mycobacteria; it kills both dormant and actively replicating mycobacteria [101]. Bedaquiline received accelerated approval by the FDA in 2012 for adults >18 years of age with MDR-TB [102], WHO does not recommend using bedaquiline in children since there are no pediatric data available [103]; however, the Centers for Disease Control and Prevention has allowed for bedaquiline to be used off-label on a case-by-case basis in children [104]. No reports of bedaquiline use in children have yet been published. Two studies on dose finding, safety, and tolerability in children with MDR-TB and with and without HIV coinfection are planned – Janssen Therapeutics C211 (in HIV-uninfected children) has recently started enrolling children >11 years of age, and IMPAACT P1108 (HIV-infected and uninfected children) is scheduled to open late 2016 [105].

Nausea was the only adverse effect more common in the bedaquiline plus OBR MDR-TB treatment group compared to the control OBR MDR-TB treatment group in adults [106]. Other frequent adverse effects noted were headache and arthralgia [107]. QTc-interval prolongation is a known adverse effect, which usually is minimal, but in one study, 7/35 (20%) experienced a ≥60-ms increase in QT interval, leading to bedaquiline discontinuation in 2/35 (6%) cases [108]. Caution is therefore advised in using bedaquiline with other antituberculosis drugs with the potential of QT prolongation.

A higher mortality rate was found in the bedaquiline group in one randomized controlled trial comparing placebo plus OBR with bedaquiline plus OBR for treatment of MDR-TB. In this adult Phase 2 study (C208), 10 of 79 in the bedaquiline group vs. 2 of 81 in the placebo group died; only one death occurred within the 24-week trial period while receiving bedaquiline. No specific association with bedaquiline was identified in any of the other deaths, which occurred long after stopping bedaquiline [109]. This led to a black box warning and was included in the adverse effects section of the bedaquiline (Sirturo) product insert [102,110]. However, subsequent studies in adults under more programmatic conditions have not found increased mortality with bedaquiline [106].

5.9. PAS (WHO Group D3)

PAS was the first effective antituberculosis drug to be used in 1944; however, its mechanism of action remains unclear. Mutations in the thymidylate synthase gene, found in PAS-resistant M. tuberculosis strains, imply that PAS may inhibit thymidylate synthesis, and it could also interfere with the organism’s acquisition of iron [111]. PAS is primarily considered a bacteriostatic drug, but a single high daily dose PAS might have bactericidal activity [112]. PAS is now mainly used as an enterically coated granular formulation.

PAS is often poorly tolerated mainly because of its gastrointestinal adverse effects. The granular PAS formulation seems to be better tolerated than older formulations; nevertheless, half of 12 patients reported mild nausea, vomiting, diarrhea, or bloating [113]. A recent study of once-daily compared to twice-daily dose of PAS granules showed little difference in tolerance in adult MDR-TB patients [114]. Gastrointestinal intolerance led to withdrawal of PAS in 5–7% of patients in two studies in adults [115,116]. No specific data are available in children, but in our experience, gastrointestinal disturbances, in particular diarrhea, are common, but usually resolve after 1 to 2 weeks.

Hypothyroidism, a common adverse effect associated with PAS, is caused by inhibition of thyroid peroxidase [13]. It is more frequent when PAS is used together with the thioamides and in HIV-infected children. In one small study, 15 of 19 (79%) children with a high rate of HIV infection developed hypothyroidism while on both PAS and ethionamide [117]. Our practice is to do thyroid function tests at baseline to exclude disease-related thyroid dysfunction and thereafter every 2 to 3 months. If both the TSH is raised and the free T4 is low, we supplement children with levothyroxine until the end of antituberculosis treatment [13]. Symptomatic hypothyroidism and goiter in children are rare.

Although hypokalemia is not specifically associated with PAS, it may occur in children who are severely malnourished and have diarrhea, especially in HIV-infected children [117]. Hepatotoxicity may occur in 0.3–0.5% of patients on PAS [94]. Although PAS and its metabolite are eliminated mainly in the urine, PAS is acetylated in the liver and intestines to N-acetyl-PAS; the latter is an inactive but hepatotoxic
metabolite [118]. If discontinuation of hepatotoxic drugs is required, as is the case with moderate or severe hepatotoxicity, PAS may be rechallenged once hepatic enzymes have normalized.

Hypersensitivity reactions, mainly fever and maculopapular rash and a case of drug reaction with eosinophilia and systemic symptoms syndrome, have been described with PAS, but these are rare [119,120].

The specific role of PAS as the cause of adverse effects in MDR-TB regimens has not often been studied. In a study from Korea, PAS was associated with adverse effects in 47/192 (24%) patients, the majority of which were gastrointestinal [121]. No such studies are available in children.

5.10. Amoxicillin/clavulanate (WHO Group D3; to be used with meropenem or imipenem)

The combination of a beta-lactam and a beta-lactamase inhibitor (clavulanate) has its effect on the mycobacterial cell wall [122]. M. tuberculosis produces a chromosomally encoded beta-lactamase enzyme, and therefore, the use of clavulanate is essential for killing M. tuberculosis. The efficacy of these combinations against M. tuberculosis is controversial, especially in cases where this is most needed, such as XDR-TB [122–125]. However, a few clinical studies have shown some positive effect [126].

Common adverse effects are gastrointestinal disturbances, including diarrhea, and skin rashes. Hypersensitivity reactions are known with amoxicillin, but can also be associated with clavulanate [127]. Severe hypersensitivity reactions or anaphylaxis should lead to discontinuation of the drug. Hepatotoxicity has been associated with amoxicillin/clavulanate, although a recent systematic review and meta-analysis has shown a low incidence of drug-induced liver injury with amoxicillin/clavulanate [128]. A number of cases have been described in children [129].

6. Conclusion

An increasing number of children with drug-resistant TB are being treated with second-line antituberculosis drugs, and new drugs are starting to be introduced. The second-line drugs are generally seen as more toxic, and they have many additional adverse effects compared to first-line drugs, which the health-care worker managing children with drug-resistant TB should be aware of. As children often cannot effectively communicate drug adverse effects, caregivers and health-care workers have a special responsibility to evaluate for these effects. Fortunately, the majority of currently known adverse effects are mild to moderate, but some adverse effects may be severe and irreversible and thus important to diagnose and to act upon early.

7. Expert opinion

The spectrum of adverse events due to second-line antituberculosis drugs in children is wide. It is often difficult to tease out the role of individual drugs as cause of specific adverse events, since antituberculosis drugs have overlapping toxicities and they are always used in combination regimens. Identifying the culprit drug is even more difficult if TB treatment is used with other medications, such as antiretroviral drugs. In this review, we have not addressed drug–drug interactions in depth, which could complicate matters even further.

Although it is frequently anecdotally reported that children experience fewer adverse events than adults on antituberculosis treatment, there is limited evidence from rigorous prospective clinical studies. Retrospective studies rely on health-care workers accurately documenting adverse events, which are frequently omitted. Furthermore, adverse events are difficult to monitor in children: a history of symptoms may be difficult to obtain in children; clinical examination for adverse events such as peripheral neuritis, hearing or vision loss, and depression or other CNS features is complicated and often not possible in young children; and special investigations such as laboratory tests and age-appropriate ophthalmological or hearing evaluation are rarely available in resource-limited settings where the majority of children with MDR-TB are treated. High-quality prospective studies in children of the safety of second-line containing MDR-TB treatment regimens are needed; such data are important for informing safety monitoring recommendations and for informing future regimen design.

There are currently few widely available child-friendly formulations of the second-line drugs, which results in children receiving split or crushed adult tablets or capsules. There is a potential for inaccurate dosing, which may increase the risk of adverse effects if this results in higher than recommended doses being given. Additionally, crushing or splitting adult tablets can worsen palatability and can contribute to drug-associated vomiting. The development of child-friendly formulations that are more palatable and allow more accurate dosing may improve the safety and tolerability of MDR-TB treatment in children.

The observed lower rate of adverse events in children may also be due to lower drug exposure in children than in adults using the currently recommended doses of second-line drugs, as has been found in several studies [34,36,38,130]. Adverse events may therefore increase as higher TB drug doses are recommended because many adverse events are dose related; this should be prospectively monitored. The aim is to dose a drug at its maximum effective concentration, but keeping adverse events to a minimum; to determine this optimal benefit vs. risk ratio, careful long-term prospective clinical studies of safety and tolerability and pharmacokinetic/pharmacodynamics in children are needed.

New and innovative methods may be necessary to better evaluate adverse events of antituberculosis drugs in children. Body mapping (drawing a life-size ‘self’ and writing on it what children experience) was used in a recent study with older children and teenagers to express what they feel; this helped children to articulate adverse events and experiences while on MDR-TB therapy [131]. Exploration of these and other innovative methods of adverse event assessment in children may improve our understanding of the safety profile of these drugs.

Regimens for DR-TB are changing; new drugs are becoming available, and new combinations to shorten treatment duration and exclude the injectable agents are currently being evaluated in adults and will soon follow in children. Careful pharmacovigilance is needed to document adverse events, of which some may be unexpected or new. Special investigations such as electrocardiogram monitoring and additional
laboratory tests will be required to determine optimal and safe drug use in new MDR-TB regimens in children.

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Papers of special note have been highlighted as either of interest (•) or of considerable interest (–) to readers.
• Recent estimate of the numbers of children with tuberculosis infection and disease, both drug susceptible and drug resistant.
• Consensus statement about how to involve children earlier in drug trials.
• A good overview of management of children with drug-resistant tuberculosis.
• A retrospective study showing high rates of hearing loss in children on injectable agents.
• Prospective study confirming safety of preventive therapy including ofloxacin in children who were MDR-TB contacts.
• An excellent review of fluoroquinolone use in children.
• A review of fluoroquinolone safety.
A study showing the long-term safety of fluoroquinolones regarding cartilage and bone growth in children.

A comprehensive review of ethionamide and prothionamide use in children.

A large pharmacokinetic and safety study of ofloxacin in children.

A meta-analysis of cycloserine/terizidone safety.

A nice overview of antituberculosis drug penetration into the CSF.

- A review on current knowledge regarding linezolid in antituberculosis treatment in children.


- A comprehensive review on second-line antituberculosis drugs in children.


- Meta-analysis of safety of clofazimine in antituberculosis treatment in adults.


- Good overview of ongoing antituberculosis drug trials.


- A timely review on para-aminosalicylic acid.


