The safety and tolerability of the second-line injectable antituberculosis drugs in children

Anthony J. Garcia-Prats, H. Simon Schaaf & Anneke C. Hesseling

To cite this article: Anthony J. Garcia-Prats, H. Simon Schaaf & Anneke C. Hesseling (2016) The safety and tolerability of the second-line injectable antituberculosis drugs in children, Expert Opinion on Drug Safety, 15:11, 1491-1500, DOI: 10.1080/14740338.2016.1223623

To link to this article: http://dx.doi.org/10.1080/14740338.2016.1223623

Accepted author version posted online: 12 Aug 2016.
Published online: 22 Aug 2016.

Article views: 72

View related articles

View Crossmark data
The safety and tolerability of the second-line injectable antituberculosis drugs in children

Anthony J. Garcia-Prats, H. Simon Schaaf and Anneke C. Hesseling

Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, South Africa

ABSTRACT

1. Introduction

There is a substantial global burden of multidrug-resistant tuberculosis (MDR-TB), defined as TB resistant to at least both isoniazid and rifampicin. Accurate figures of cases in children are lacking, however, two models have provided similar estimates of 32,000 pediatric cases of MDR-TB in 2010 [1] and 27,500 cases in 2014 [2]. Although a small percentage of children with MDR-TB are appropriately diagnosed and treated, there are ongoing efforts to reduce and eliminate this ‘treatment gap’ [3]. Thus, more children will be accessing MDR-TB treatment in coming years.

The treatment of MDR-TB relies on the so-called second-line antituberculosis medications. Current guidance from the World Health Organization (WHO) on MDR-TB treatment recommends building a regimen with at least four TB medications confirmed or likely to have activity, which should include a second-line injectable medication for a minimum duration of 8 months [4]. The second-line injectable antituberculosis drugs collectively refer to the aminoglycosides amikacin, kanamycin, and the cyclic polypeptide capreomycin. These are considered together because of their similar characteristics, including mechanism of action of protein synthesis inhibition, pharmacokinetics, administration requirements, and adverse effect profiles [5]. All of these medications are rapidly degraded when given orally, so must be administered intravenously or by intramuscular injection. Given the current limited existing treatment options for MDR-TB, despite recent registration of the novel drugs bedaquiline and delamanid for use in adults with MDR-TB, the injectables have traditionally been considered key components of current regimens [4]. Even a shortened 9-month regimen which has demonstrated good outcomes in observational studies in adults, and is being evaluated in an ongoing clinical trial, still includes an injectable drug for 4 months [6].

As opposed to adults for whom MDR-TB treatment outcomes remain poor, outcomes in children with MDR-TB are generally good, with successful outcomes reported in 80% of children and higher in some cohorts [7,8]. However, current treatment regimens are associated with frequent and potentially severe adverse effects [8]. The second-line injectables can cause a number of serious adverse effects including nephrotoxicity, electrolyte abnormalities, vestibular toxicity, and most importantly permanent sensorineural hearing loss [5]. Additionally, their requirement to be given by intramuscular injection in many settings makes them poorly tolerated, resulting in substantial pain, distress, and local injection-related complications. An overview of the second-line injectables is shown in Table 1. A thorough understanding of the adverse effects of the second-line injectables is important for
healthcare workers caring for children with MDR-TB, and for persons designing and evaluating novel MDR-TB treatment regimens.

The carbapenem antimicrobials meropenem, imipenem, and ertapenem, when combined with a β-lactamase inhibitor such as clavulanate, have demonstrated antimycobacterial activity. However, because of the limited efficacy data in humans, high cost, and the need for multiple daily intravenous doses, these medications have been mostly used in salvage regimens for patients with very limited treatment options in higher-resourced settings. There may be renewed interest in the carbapenems as antituberculosis medications, as a recent study has now shown a substantial early bactericidal activity of meropenem/amoxicillin-clavulanate [9].

The objective of this review is to examine current knowledge of the adverse effects of the second-line injectable antituberculosis medications and the carbapenems in children, and to highlight knowledge gaps and priority questions for future research.

Table 1. Overview of the second-line injectable antituberculosis medications.

<table>
<thead>
<tr>
<th>Medications</th>
<th>Key characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin and kanamycin (aminoglycosides)</td>
<td></td>
</tr>
<tr>
<td>Capreomycin (cyclic polypeptide)</td>
<td></td>
</tr>
<tr>
<td>Administration intravenously or intramuscular injection</td>
<td></td>
</tr>
<tr>
<td>All have similar pharmacokinetics and similar spectrum of adverse effects</td>
<td></td>
</tr>
<tr>
<td>To be included in all treatment regimens in adults and children for at least 4 months</td>
<td></td>
</tr>
<tr>
<td>Ototoxicity, resulting in permanent sensorineural hearing loss</td>
<td></td>
</tr>
<tr>
<td>Vestibular toxicity, resulting in vertigo and balance problems</td>
<td></td>
</tr>
<tr>
<td>Nephrotoxicity, resulting in oliguric renal failure</td>
<td></td>
</tr>
<tr>
<td>Electrolyte abnormalities, hypokalemia, hypomagnesemia most frequent</td>
<td></td>
</tr>
<tr>
<td>Injection pain and local injection site complications</td>
<td></td>
</tr>
</tbody>
</table>

2. Ototoxicity and vestibulotoxicity

2.1. Overview of ototoxicity

Ototoxicity is a well-known complication of the second-line injectables, and aminoglycoside-induced ototoxicity has been studied in depth. An understanding of the pathophysiology helps provide improved understanding of many of the clinical findings of ototoxicity in injectable-treated patients.

Very early after administration, the injectable antituberculosis medication enters the cochlear hair cells through a membrane channel [10]. This channel acts like a one-way valve, trapping the injectable medication in the hair cell where they are not metabolized; the half-life for disappearance of aminoglycosides from hair cells appears to be >30 days [11]. This results in accumulation of injectable medication in the hair cells over time, and explains why hearing loss can occur or progress after their discontinuation. Once in the hair cells, the injectable medications form complexes with iron (Fe), generating reactive oxygen species; along with direct interactions between the injectable medication and hair cell mitochondrial rRNA; this results in disruption of mitochondrial integrity which ultimately results in apoptotic cell death [10]. This cell death begins at hair cells responsible for recognizing higher-frequency sounds, above the speech threshold, and progresses to lower frequencies [10]. This has important implications for clinical management, as hair cell damage may occur prior to any perceived loss of hearing by participants. As such, subjective patient report cannot be relied on for detection of ototoxicity; audiological testing which includes high frequencies, at least 6000–8000 kHz or higher, is therefore important for early identification of ototoxicity and prompt management.

Studies exploring potential risk factors for aminoglycoside-associated ototoxicity have reported conflicting results. Trough concentrations of injectables have been associated with ototoxicity in some studies, but not in others; older age, duration of use, and cumulative dose are associated with hearing loss in some, but not in others [12–15]. A number of genetic mutations have been identified which increase the risk of injectable-associated ototoxicity [10,16–18]. These mutations are in the gene (MT-RNR1) encoding the mitochondrial 12 s rRNA, making it more similar to bacterial rRNA and increasing its affinity for aminoglycosides, with a resultant...
increase in mitochondrial protein synthesis [10,16–18]. When present, severe hearing loss can occur rapidly, even after a few doses. However, these mutations are relatively infrequent in the general population, present in anywhere from 0–1.8% of populations representing a broad geographic distribution; no specific populations to date have been identified with a particularly high prevalence of these mutations [10,16,19]. In a cohort of South African adults with MDR-TB, none of 153 patients with hearing loss had any of these known mutations, demonstrating that the overall contribution of these genetic predisposition to ototoxicity in MDR-TB treatment is likely small [16,19].

The most important risk factor for ototoxicity appears to be cumulative drug exposure. A number of elegant studies in guinea pigs provided some important insights into this relationship, which appears to be consistent with experience in humans [20,21]. In guinea pigs treated with continuous amikacin infusions at various rates, ototoxicity was closely associated with total dose and total cumulative drug exposure (total area under the time–concentration curve [AUC]) [20,21]. The infusion rate and plasma concentrations were not associated with ototoxicity and did not affect the total dose or total AUC at which ototoxicity occurred. This may explain the limited value of peak and trough measurements as predictors of ototoxicity. This also has important implications for dosing strategies, and suggests that intermittent dosing (thrice weekly versus daily) will not impact on the risk of ototoxicity. In addition to an association with incidence of ototoxicity, the total dose and total AUC were also associated with the magnitude of hearing loss. There was also a significant negative relationship between total dose/total AUC with the hearing frequency at which hearing loss occurred, meaning ototoxicity occurs at higher frequencies at a lower total dose/total AUC, and progresses to lower frequencies as the total dose/total AUC increases. This is consistent with clinical experience in humans. The relationship between total dose/total AUC and ototoxicity fit a sigmoid curve which had a very steep slope, which could result in large differences in incidence and magnitude of ototoxicity over relative small ranges in total dose/total AUC, and could partly explain the large variability and unpredictability of ototoxicity in humans. The proposed explanation for all of these findings was that aminoglycosides enter hair cells at a rate that is linearly related to the plasma concentration through an essentially one-way process, accumulating over time and resulting in ototoxicity once a certain threshold concentration is reached [20,21].

These guinea pig studies are consistent with and explain many of the findings in human studies. In a study comparing the impact of dosing strategy on ototoxicity in adults, there was no difference in risk of ototoxicity between persons treated with a daily dose of streptomycin, kanamycin, or amikacin of 15 mg/kg/dose (5 days a week) compared to those receiving a three times weekly dose of 25 mg/kg/dose [22]. Neither maximum plasma concentration nor trough concentration were associated with risk of hearing loss. However older age, total dose and the related duration of treatment, were associated with ototoxicity, with a 6.9-fold increase in ototoxicity for every 10-fold increase in total dose received [22]. These confirm the limited value of intermittent dosing and measuring peak/trough concentrations for reducing ototoxicity risk, and confirm the importance of cumulative dose. In a cohort of 28 adults with MDR-TB in Botswana treated with amikacin 750–1000 mg/day, 11 (39%) had hearing loss [23]. Amikacin peak and trough concentrations were not associated with hearing loss, however cumulative days of therapy and cumulative amikacin AUC were predictive of hearing loss. As in the animal studies, the relationship between cumulative AUC and cumulative days of therapy was a sigmoid curve; the modeled estimated risk of hearing loss began to sharply increase around 6 months of cumulative therapy and was nearly 100% at 9 months of therapy.

The relative risk of ototoxicity between the different second-line injectables has not been well characterized, but could potentially be clinically relevant. Although not a second-line injectable, streptomycin was found to be less ototoxic than kanamycin or amikacin in one adult study [22]. In a retrospective review of adults with MDR-TB treated with either amikacin or kanamycin in routine care, the risk of hearing loss was higher with amikacin, with an adjusted odds ratio (aOR) of 2.3 (95% CI 1.0–5.4); the association of amikacin with more severe hearing loss was even higher, with an aOR of 4.0 (95% CI 1.5–10.8) [24]. Duration of treatment and total dose were not reported or controlled for in this study, however, these results are suggestive of a higher ototoxicity risk with amikacin. In some sources, it has been stated that capreomycin is less ototoxic than amikacin or kanamycin, however, evidence for this assertion is limited and somewhat conflicting. In a cohort of adults with MDR-TB in the UK, 11 of 29 (38%) treated with amikacin had ototoxicity, however, none of 11 treated only with capreomycin as their injectable agent experienced ototoxicity [25]. In a small Irish cohort, 1 of 4 (25%) adults treated with capreomycin had hearing loss, compared to 7 of 34 (20.6%) treated with amikacin and 4 of 26 (15.4%) treated with kanamycin [26]. These reports should be interpreted with caution given the small numbers and retrospective observational design. We have observed clinicians substituting capreomycin for other injectables in MDR-TB patients once early hearing loss has been detected, or suggesting a preferential use of capreomycin presuming a reduced risk of ototoxicity; we would suggest caution in using such approaches in the absence of better evidence, as there is still a risk of ototoxicity with capreomycin, and other serious adverse effects may be related to capreomycin use as discussed below [27]. The injectables have concentration-dependent activity against Mycobacterium tuberculosis, with the ratio of the maximum plasma concentration (Cmax) to the minimum inhibitory concentration (MIC) being the pharmacodynamics measure most closely associated with efficacy [5]. Amikacin has been consistently shown to be the more potent second-line injectable against M. tuberculosis in vitro, with a lower MIC compared to kanamycin and capreomycin [5], and for that reason may be the injectable of choice for MDR-TB treatment. This is a consideration that should be weighed against a potentially higher risk of ototoxicity with amikacin.

Other factors have been shown to increase the risk of ototoxicity, and clinicians should at least be aware of them. The concomitant use of loop diuretics has been shown to
increase aminoglycoside ototoxicity in animals, and there are descriptions in adults [28–30]. Although the risk in adults and children has been poorly characterized, clinicians should at least be aware of the theoretical increased potential for ototoxicity with co-treatment with these two classes of medications. Concomitant administration of iron also increases ototoxicity risk in gentamicin-treated guinea pigs; it was postulated that this was related to the role of Fe in the generation of reactive oxygen species and free radicals [31]. The contribution of these factors relative to other risk factors, like cumulative drug exposure, is not entirely clear.

2.2. Incidence of ototoxicity in second-line injectable-treated adults and children with MDR-TB

The incidence of hearing loss reported among adults with MDR-TB treated with second-line injectables is quite variable; this may be related at least in part to the inconsistency in the quality of reporting, methods of assessments, and definitions of ototoxicity [32]. In a 2012 systematic review of hearing loss in drug-resistant TB patients, the percent of reported hearing loss ranged from 2.6–61.5% [32]. In cohorts reported after this systematic review, the stated risk of ototoxicity remains quite variable. However, among studies in which comprehensive audiology assessments are done and reported, the risk of hearing loss is high and quite concerning. In a South African cohort of adults, 57% developed hearing loss [19]. HIV-infected persons in this study had a higher risk of hearing loss; HIV-infected persons might receive longer injectable treatment because of more severe disease or slow treatment response, however, duration of injectable treatment was not controlled for in this analysis. In 12 adults with MDR-TB in the UK treated with amikacin (15 mg/kg once daily) who received careful audiometry assessments, 7 (58%) had documented hearing loss, 3 reported tinnitus; 8 (67%) had their amikacin interrupted because of these abnormalities, and 4 patients had further progression of hearing loss after this interruption [33]. A large cohort of adults with MDR-TB treated with amikacin (15–25 mg/kg daily, maximum 1000 mg) in Botswana reported similar results, with 270 of 437 (62%) reporting hearing loss, with 147 (54%) of these confirmed by audiology; dose and duration of treatment were associated with hearing loss [34]. A similar risk was reported in a Namibian adult cohort, with overall 58% having any hearing loss, with 10% of these having severe and 15% having profound hearing loss [24].

Given the prolonged half-life of the injectables in cochlear hair cells, recent previous treatment with streptomycin, as in patients receiving a WHO Category II regimen, would be expected to increase the risk of hearing loss with subsequent injectable-containing MDR-TB treatment. This has not been well quantified, but clinicians should be aware of this potential increased risk.

Data on ototoxicity in children treated for MDR-TB is more limited. This may in part be due to the challenges with accurately assessing hearing in young children, and the limited published reports of pediatric MDR-TB in the literature. Young children often cannot cooperate with the pure tone audiometry (PTA) assessments used in adults and older children. Alternative methods of hearing testing are available for younger ages, including otoacoustic emission (OAE) testing, which is feasible with the appropriate equipment in most settings. Other audiology testing used in young children, such as auditory brainstem evoked response (ABER), play audiometry, and conditioned response audiometry requires more specialized training and equipment, and access may be limited in many settings. A detailed discussion of these different testing modalities, approaches to audiological assessment in different ages, interpretation of results and classification of hearing loss is beyond the scope of this review, but important and has been previously written in about in detail [32,35,36].

The lack of capacity for audiological testing in many high-burden settings, particularly for children, is problematic. In a 2009 survey of 18 sub-Saharan African countries, only South Africa, had more than 1 audiologist per 100,000 population, and many had no audiologist. Only 2 of 18 countries had an audiology training program, and access to services such as basic audiology, ABER, and routine hearing screening was rated as nil to poor in most countries and where present was centralized and not widely accessible [37]. This contributes to the limited data, and results in inadequate monitoring of children treated with the second-line injectables, putting them at risk for more severe hearing loss.

Taking a conservative approach and using a strict definition of hearing loss, 24% of children in a retrospective cohort of children treated for MDR-TB had confirmed hearing loss [38]. A high proportion of children with hearing loss was reported in the same setting in a follow-up prospective cohort study [8]. In this study, 25 of 142 (17.6%) children treated for MDR-TB had hearing loss; however in this cohort, only 94 (66%) children (those with more severe MDR-TB disease) were treated with an injectable, and the median duration of injectable use was only 4 months (interquartile range 4–6). This therefore likely underestimates the risk of hearing loss in children receiving the current routinely recommended 6 months of injectable treatment. Two other pediatric cohorts reported a lower risk of ototoxicity, with hearing loss in 2 of 38 (6.7%) and 1 of 10 (10%), however, audiological monitoring was not well described in these studies [7,39,40].

Children are known to have a higher clearance of aminoglycosides, resulting in lower drug exposure relative to adults given the same mg/kg dose [5]. If cumulative drug exposure is the most predictive risk factor for injectable-associated ototoxicity, then children would be expected to have a lower risk compared to adults treated for the same duration and same mg/kg dose of injectable. However, children younger than 6 months of age may have a reduced aminoglycoside clearance relative to older children and adults due to immature renal function, resulting in higher drug exposures and a potentially higher risk of ototoxicity. Although devastating at any age, hearing loss in young children is particularly harmful as it occurs during critical periods of neurodevelopment and may have a profound impact on speech development.

2.3. Otoprotective strategies

Understanding the cellular and molecular pathogenesis of ototoxic drug-induced hair cell loss, has led to exploration of a number of potential antidotes or preventive treatments,
mainly focusing on counteracting reactive oxygen species and free radicals [10]. Iron chelators such as deferoxamine may inhibit formation of reactive oxygen species, and in animals such agents reduce aminoglycoside-induced ototoxicity [10,41,42]. Acetylsalicylate has the dual benefit of being an iron chelator and an antioxidant, and reduces gentamicin-induced ototoxicity in animals [10]. Many other antioxidants, including D-methionine, glutathione, N-acetylcysteine (NAC) have also demonstrated benefit in animal models [10]. There is some evidence for the benefit of a number of these agents in humans for prevention of ototoxicity. In a randomized controlled trial in adults receiving short courses of gentamicin for acute infections, ototoxicity was shown in 13% receiving placebo and 3% of those receiving aspirin (3 grams daily, divided doses) [43,44]. This study acts as a proof of concept, and demonstrates the potential benefits of coadministration with the widely available aspirin. Concerns, however, particularly with long-term high-dose aspirin treatment, include the risk of tinnitus from aspirin itself, an association of Reye syndrome with aspirin use in children with viral infections, and a risk of gastrointestinal ulcerations and bleeding. A recent systematic review assessed the safety and otoprotective potential of NAC [45]. There is no data in MDR-TB; however, in this review, aminoglycoside-treated dialysis patients receiving NAC had a substantially reduced risk of ototoxicity, though numbers were small and overall quality of evidence was low. The safety of NAC when given for at least 6 weeks duration was also evaluated, and it was found that abdominal pain, nausea, vomiting, diarrhea, and arthralgia were more common in NAC-treated groups compared to controls, however, severe adverse events were limited. NAC may be an attractive otoprotective agent in MDR-TB and should therefore be evaluated in children with MDR-TB.

2.4. Vestibulotoxicity

The vestibular system located in the inner ear and composed of the utricle and sacule which detect linear movement, and the semicircular canals which detect rotational movement, is responsible for balance and spatial orientation. Treatment with the injectables can also result in vestibulotoxicity through effects on the hair cells of the vestibular system, however, this has been less studied than ototoxicity. It may occur in the absence of ototoxicity. It may present with feelings of dizziness, vertigo, lightheadedness, which may be subtle at the onset [46]. In adults treated for MDR-TB, vestibulotoxicity is variably reported. In one study of adults receiving long-term injectable treatment, objective measures of vestibular dysfunction were documented in 8 of 87 (9%); there may be some reversibility of symptoms over time, but changes may persist [22]. Subjective vestibular symptoms were much more common in this cohort, with 41% reporting subjective balance changes and 47% reporting dizziness; these were mostly mild, associated with the injectable infusion and resolved over time [22]. In a cohort of 53 South African adults treated for MDR-TB, vestibular complaints were common, with vertigo reported in 45%, sensation of falling in 38% and imbalance in 26%; information about progression or resolution over time was not provided [47]. There is little data on vestibulotoxicity in children treated for MDR-TB. In our experience, we have not seen clinically apparent vestibulotoxicity, however, this may be related to difficulties in eliciting symptoms in young children and it is possible that this is an under-recognized adverse effect.

3. Nephrotoxicity and electrolyte abnormalities

3.1. Nephrotoxicity

The second-line injectables are well known for their potential to cause renal impairment. The injectables elicit renal injury primarily by causing renal tubular dysfunction [48,49]. After glomerular filtration, the injectables enter renal tubular cells and accumulate there, ultimately resulting in renal tubular cell death via apoptosis or necrosis through an as yet unspecified mechanism. In addition to tubular dysfunction, the injectables have also been shown to induce altered glomerular filtration and reduced renal blood flow [49]. The clinical result of these effects is oliguric renal failure, however, this may be preceded by more subtle evidence of tubular dysfunction such as mild wasting of glucose, protein, and electrolytes [48,49]. This renal injury is generally reversible after discontinuation of the injectable.

Uptake of the injectables into renal tubular cells is a saturable phenomenon at clinically relevant concentrations [48]. This phenomenon has been exploited through a strategy of higher less-frequent dosing to potentially reduce nephrotoxicity. In a randomized trial of once vs. twice daily dosing of aminoglycosides in adults, nephrotoxicity occurred in 15% of adults receiving twice-daily therapy, and in 0% of those receiving once-daily therapy; the dosing strategy was closely associated with occurrence of nephrotoxicity, as was AUC [50]. Meta-analyses in adults have shown no difference in efficacy with once- vs. multiple-daily dosing strategies of aminoglycosides, however, there are conflicting results with regard to nephrotoxicity, with one showing a reduced incidence with extended interval dosing [51] but others showing no difference [52,53]. A meta-analysis of extended interval dosing in children found no difference in nephrotoxicity [54,55]. Given the programmatic simplicity and benefits for cost and adherence, in MDR-TB treatment the injectables are therefore given as once-daily or thrice-weekly doses.

The proportion of adults treated for MDR-TB with reported renal impairment ranges from <1% to 9.8% [27,56–60]; this may reflect the heterogeneity in definitions, monitoring, and treatment approaches between studies. The risk of nephrotoxicity in children has not been well described, but appears to be low. In a systematic review of children treated for MDR-TB, only 1 of 182 children was reported to have any renal impairment, an asymptomatic elevation of creatinine [7]. In our personal experience, renal impairment is quite uncommon in children with once-daily administration of the recommended doses of injectables. In a prospective observational cohort study of children treated for MDR-TB [8], no cases of abnormal renal function were seen among injectable-treated children, although this was not specifically reported in the paper (personal communication, H.S. Schaaf).
There are no direct comparisons of the relative risk of nephrotoxicity between the second-line injectables, however, the limited existing evidence does point to a higher risk with capreomycin. In a cohort of 151 patients in South Africa with extensively drug-resistant TB (XDR-TB), 61 (58%) experienced a total of 161 adverse events during treatment [27]. In total, 6 of the 161 adverse events resulted in death, and all 6 were due to capreomycin (5 cases of renal failure, 1 case of hypokalemia); 5 of these 6 were in HIV-infected persons. The deaths occurred at a median of 14 days after starting capreomycin (range 9–73) [27]. This high risk of death due to capreomycin-associated renal failure is concerning, and there should be close monitoring of renal function when capreomycin use is required.

3.2. Electrolyte abnormalities

Hypokalemia, hypomagnesemia, and hypocalcemia are well-described adverse effects of the injectables, most likely due to renal electrolyte wasting, although other mechanisms may also contribute [56,61]. Reported risk factors for the development of electrolyte abnormalities include cumulative dose, low body weight, and choice of injectable. The available evidence suggests a substantially higher risk of electrolyte abnormalities with capreomycin [61–63]. The most comprehensive description in MDR-TB treatment is from a cohort of 115 adults in Peru, where 34.8% had an electrolyte abnormality detected [61]. Hypokalemia was the most frequent, found in 31.3%, with hypomagnesemia detected in 15.7% and with 12.2% of patients having both abnormalities; capreomycin-treated patients had a higher risk, with 68.2% having hypokalemia. In multivariable analysis, hypokalemia was associated with capreomycin use and low body weight. Capreomycin-attributed hypokalemia was responsible for one death in a cohort of South African XDR-TB patients, and in this cohort capreomycin was the most frequent drug discontinued because of adverse effects [27].

A systematic review of children treated for MDR-TB reported only one episode of electrolyte abnormality in 182 children [7]. This is consistent with our experience; our practice is routine monitoring of electrolytes every 4–8 weeks in children with MDR-TB during their injectable treatment, however, we have identified few abnormalities. Given the concerns in adults, particular care may be warranted in children treated with capreomycin, with more frequent monitoring of electrolytes prudent (every 2–4 weeks if feasible).

4. Injection site adverse events

Local site adverse effects of the injectable agents, including infection, pain, subcutaneous and muscle abscess formation, muscle contracture and fibrosis, and neurovascular injury have been poorly reported to date. Although the risk of an adverse effect after a single injection is low, given the very large total number of injections over the treatment course, adverse effects would be expected to occur regularly [64]. A painful, inflamed injection site was reported as an adverse effect in 4% of an adult MDR-TB cohort, with abscess formation in <1% [58], but most published MDR-TB cohort data does not report on such effects. This has similarly not been well described in children. The smaller size and lower muscle mass introduces additional challenges in children, and some injection-related adverse effects would be expected to be more common in children, such as neurovascular injury. Suggested best practices for intramuscular injections in children exist, but this has not carried over into MDR-TB treatment recommendations [64]. This is a common challenge for frontline healthcare workers, and guidance would be valuable given the large number of required injections and age-related changes in optimal injection site.

The pain associated with the intramuscular injections is an important source of distress for MDR-TB patients, and is often mentioned by patients as one of the worse aspects of treatment [65]. Strategies to reduce the pain associated with daily intramuscular injections of the second-line injectables are needed. The addition of a local anesthetic has been shown to reduce the pain of intramuscular injections of penicillin and ceftriaxone without substantially altering their pharmacokinetics [66–68]. A similar strategy is being evaluated in a randomized blinded crossover study of the effect of added lignocaine on pain and pharmacokinetics of intramuscular amikacin in older children and adolescents with MDR-TB (PACTR201401000670381), with results expected soon. Implanted catheters or peripherally inserted central venous cannulas may be used in some settings, and would clearly eliminate the need for intramuscular injections. However, this approach has its own risks, including complications of line placement and line infection. In most high TB-burden settings, the regular use of such long-term venous access is not feasible due to a lack of capacity for line placement and the difficulty in caring for lines.

5. Carbapenems for TB treatment

The carbapenems are generally well tolerated, with the most common adverse events being diarrhea, rash, and nausea/vomiting, which are mostly mild [69–71]. As with other β-lactams, there is a risk of hypersensitivity (anaphylactic) reactions that may be severe. Imipenem in particular has been associated with seizures, with a higher risk in those with existing central nervous system disease or meningitis, although the absolute risk is low [70,72,73]. A systematic review of carbapenem-containing regimens for MDR-TB identified nine eligible studies; carbapenem-attributed adverse events were reported in 0–13.5% of patients depending on the cohort, with 0–40% of these adverse events resulting in at least temporary interruption of the carbapenem [74]. This review is limited by the high variability in treatment regimens, disease and drug-resistance spectrum, specific carbapenem used and dose. These cohorts only included two children, so no conclusions can be drawn regarding long-term carbapenem safety in children with MDR-TB from the existing data. In addition to data on the safety of carbapenems, adverse effects related to the need for long-term vascular access in children would also need to be considered given the lack of a current orally administered carbapenem and the need for multiple-daily dosing for most of these agents. Complications from central lines or peripherally inserted central venous catheters are not infrequent in children [75].
6. Conclusion

The second-line injectable antituberculosis medications remain a component of currently recommended treatment regimens for MDR-TB. Their clinically important adverse effects include ototoxicity, vestibulotoxicity, nephrotoxicity, electrolyte abnormalities, and injection site complications. However, the incidence of these adverse effects and risk factors for their occurrence have not been well described in children with MDR-TB. Clinicians caring for children with MDR-TB should be aware of these potential adverse effects, so that appropriate screening and management can occur, to ensure that MDR-TB treatment is as safe as possible.

7. Expert opinion

Although there is a substantial body of evidence on the safety of the second-line injectable antituberculosis medications, mostly in adults, a number of priority areas remain for future research, including improved characterization of adverse effects in children treated with injectables for MDR-TB, development of strategies to reduce or eliminate the need for injectables in MDR-TB treatment, and evaluation of strategies to reduce the risk of injectable-related adverse effects when they are truly required to be used in MDR-TB regimens (Table 2).

There is limited high-quality data on the risk of adverse effects due to the second-line injectables in children treated for MDR-TB. There is likely systematic under-detection and under-reporting in children of some injectable-related adverse effects, such as ototoxicity, local injection site complications, and pain and distress due to injections; this may be partly related to challenges in assessing some of these effects in children. For other potential adverse effects, such as nephrotoxicity and electrolyte abnormalities, the risk in children may be relatively low. Improved data would help inform practical guidance for monitoring of adverse effects in children treated for MDR-TB, would make a case for devoting resources for appropriate safety monitoring in children, such as equipment and training for audiological monitoring in young children, and ultimately could provide motivation for urgently identifying MDR-TB treatment strategies that exclude the use of injectables.

The most obvious approach to reducing the risk of second-line injectable-related adverse effects is to limit or eliminate their use in MDR-TB treatment altogether. As described above, children with non-severe MDR-TB can be successfully treated without injectable treatment or at a minimum, with reduced duration of injectables [8]. Such a strategy should be employed wherever possible, and updated treatment recommendations should reflect the potential of such a strategy when carefully employed. This would rely on early identification of MDR-TB in children before progression to more severe disease, which is much more likely when children are identified by active contact investigation of infectious MDR-TB cases. In adults, multiple trials are underway to evaluate novel regimens for MDR-TB treatment, most of which include one of the new TB medications bedaquiline or delamanid, and many of which do not use an injectable medication. However, efficacy data on these regimens is unlikely to be available soon. A shortened, all oral MDR-TB treatment regimen for children is a research priority, but data on such a regimen would likewise be unavailable for some time. In the interim, an important way forward may be the careful exploration of whether another TB drug or drugs, such as delamanid, bedaquiline, or even linezolid, could be substituted for the injectable in pediatric MDR-TB treatment regimens.

In addition to efforts to eliminate or reduce second-line injectable use, strategies to reduce the risk of injectable-related adverse effects should be pursued in parallel. It is likely that the injectables will continue to play a role in MDR-TB treatment for the foreseeable future, while data, experience with, and access to novel regimens accumulate. Additionally, resistance to novel agents may develop with their more widespread use [76], and the injectables may again become important agents in future salvage regimens. Improved risk reduction approaches aimed at making the injectables safer and more tolerable when their use is required, should be pursued in parallel to strategies of eliminating or reducing their use. Many such risk reduction strategies are relatively

---

Table 2. Summary of research priorities related to the safety and tolerability of the second-line injectable antituberculosis medications in children with multidrug-resistant tuberculosis (MDR-TB).

| Improved characterization of incidence of injectable-associated adverse effects in children with MDR-TB |
| Cohort data on incidence and severity of adverse effects in children |

**Strategies to eliminate or reduce the duration of injectable treatment of MDR-TB**

- Trials of all oral MDR-TB regimens
- Omission of injectable use in children with non-severe MDR-TB
- Reduced duration of injectable use in children with non-severe MDR-TB
- Substitution of injectable with novel or repurposed TB drugs in otherwise standard MDR-TB treatment regimens

**Reduce the risk of adverse effects when injectables are used for MDR-TB**

- Formal guidance on safe intramuscular injection in children, including age-appropriate injection site selection
- Addition of local anesthetic (lignocaine) to intramuscular injections for pain reduction
- Use of potentially otoprotective medications such as N-acetylcysteine, aspirin
- Therapeutic drug monitoring
- Inhaled injectable treatment

---

---

---
simple and straightforward. Formal guidance is needed on safe intramuscular injection techniques in children. The addition of local anesthetic to intramuscular injections as the potential to greatly reduce injection pain, and data is urgently needed. Strategies to reduce the risk of ototoxicity, the most serious and concerning injectable-related adverse effect, are urgently needed. The use of NAC, aspirin, or other antidotes deserves evaluation in trials in adults and/or children, and could be done within the context of other planned studies. Audiological screening of high- and ultra-high frequency hearing, could potentially lead to earlier detection of ototoxicity and discontinuation of injectables prior to more severe hearing loss that would be more likely to affect speech thresholds. Improved capacity to deliver basic audiology services in high TB burden countries is needed. Strategies that utilize age-appropriate testing and can be delivered in a decentralized fashion by non-audiologists with minimal training, such as tele-audiology and the use of smart phone technology, should be explored [77–79]. Although traditional peak and trough measurements are unlikely to predict ototoxicity, appropriately timed therapeutic drug monitoring could potentially help predict the risk of ototoxicity and inform a safer duration of treatment [80]. Inhaled therapy with the second-line injectables may also be a way to deliver these medications to the site of disease while limiting systemic exposures and thus reducing adverse effects [81]. Information on the safety and efficacy of inhaled injectable treatment is relevant, however, the feasibility of delivering inhaled therapy at a programmatic level could be an important limitation. Inhaled therapy targeted to achieve similar systemic exposures as parenteral therapy would negate many of the benefits of inhaled delivery [82].

Work to address these priority issues would greatly improve the overall safety and tolerability of MDR-TB treatment in children.

Funding
This paper was not funded.

Declaration of interest
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References
Papers of special note have been highlighted as either of interest (+) or of considerable interest (+) to readers.

11. An excellent overview of aminoglycoside ototoxicity from a cellular and molecular perspective, including review of risk factors and emerging otoprotective strategies.
22. Animal data which provides important insight into the mechanisms of hearing loss and helps make sense of some clinical observations related to aminoglycoside ototoxicity.
Demonstrates the association of amikacin cumulative exposure with risk of ototoxicity in adults with MDR-TB


Describes severe and fatal adverse effects related to capreomycin in adults with XDR-TB.


One of few pediatric references reporting on detailed audiological assessments in children with MDR-TB; demonstrates high proportion of children with MDR-TB treated with injectables develop hearing loss.


Detailed description of electrolyte abnormalities in adults treated with MDR-TB, including risk factors.


• Describes patient experiences of receiving long-term injectable treatment for MDR-TB.


