Second-Line Antituberculosis Drugs in Children: A Commissioned Review for the World Health Organization 19th Expert Committee on the Selection and Use of Essential Medicines

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1 Introduction

1.1 Multidrug-resistant tuberculosis in children – an overview and public health need

Children account for an estimated 10-15% of the global burden of disease caused by *Mycobacterium tuberculosis* (*Mtb*) with an estimated 490,000 cases reported annually and more than 60 000 deaths in 2011 (1, 2). Multidrug-resistant (MDR) tuberculosis (TB), defined as disease caused by *Mtb* resistant to at least both rifampicin (R; RMP) and isoniazid (H; INH), is increasing worldwide, with an estimated 630,000 prevalent cases in 2011 (2). Extensively drug-resistant TB (XDR-TB), defined as resistance to isoniazid, rifampicin, a fluoroquinolone, and one of the second-line injectable (SLI) drugs (amikacin, kanamycin, and capreomycin), has now been identified in 84 countries and accounts for 9.0% of MDR-TB cases globally (2, 3). Possibly due to challenges with confirming the diagnosis in younger ages, lack of awareness of the disease, limited experience in its management, and lack of access to child-friendly or otherwise adequate drugs, few children are being diagnosed and treated for MDR-TB. Assuming that 10-15% of the disease burden is in children, this translates into a conservative estimate of 63,000 prevalent cases of MDR-TB per year in children. A recently published review of TB surveillance data submitted to the World Health Organization (WHO) from 1994-2011 concluded that the proportion of children and adults with MDR-TB was similar in many settings, and in some countries there was actually an association of age <15 years with MDR-TB (4). Among children with culture-confirmed TB between 2007 and 2009 in the Western Cape Province, South Africa, 8.9% were MDR-TB (5). Despite what is likely a large global disease burden, there is a paucity of published experience on paediatric MDR-TB. A recent systematic review identified 8 cohorts describing the outcomes of 318 children with MDR-TB in the literature (6). The pooled estimate for treatment success was 81.7%, with 39.1% of children having an adverse event (6). Though outcomes in children with MDR-TB are generally good in expert hands, treatment regimens are more complicated, expensive, longer, and associated with more toxicity than first-line regimens (6, 7).

There is a growing recognition of the importance of drug-resistant TB in younger ages. The Sentinel Project on Pediatric Drug-Resistant Tuberculosis (http://sentinel-project.org) is a recently formed global collaboration of researchers, caregivers, and advocates drawing attention to childhood MDR-TB and working to prevent child deaths from this treatable disease. In 2012 the Sentinel Project spearheaded the production of a Field Guide (8) and published practical guidance for the management of children with MDR-TB (9). These developments are timely, as new diagnostic tools such as the Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) will likely increase the number of children diagnosed with MDR-TB and needing treatment (10-14).

1.2 Second-line antituberculosis drugs in children

Despite the growing awareness and knowledge, there is still much to be learned about the best treatment of MDR-TB in children. Key among areas requiring urgent evaluation is the appropriate use of second-line antituberculosis drugs, which are critical to ensuring safe, effective treatment and good outcomes. A recent review of the paediatric use of second-line antituberculosis drugs highlighted many gaps in our knowledge (15).

The WHO groups the antituberculosis drugs into five groups, as shown in Table 1.1 (16). The most recent guidelines from the WHO on the dosing of the second-line antituberculosis drugs in children are listed in Table 1.2 (16). These guidelines are generally consistent with those recommended by other organizations (17, 18). Frequent TB-HIV co-infection adds additional complexity, and potential drug-interactions and additive toxicities between the second-line antituberculosis drugs and antiretrovirals also must be considered. These potential interactions and toxicities have been recently summarized (15) and are presented in Table 1.3. Current MDR-TB guidelines recommend including a second-line injectable agent from Group 2, a fluoroquinolone from Group 3, and then adding additional drugs from Groups 4 and 5 to create a treatment regimen with at least 4-5 active drugs (16, 19).

Table 1.1 – Drug groups for the treatment of drug-resistant TB

Group	Group Name	Drugs	Abbreviations
1	First-line oral agents	Isoniazid	H or INH
		Rifampicin	R or RMP
		Ethambutol	E or EMB
		Pyrazinamide	Z or PZA
		Rifabutin	Rfb or Rbt
		Rifapentine	Rfp or Rpt
2	Injectable agents	Kanamycin	Km
		Amikacin	Am
		Capreomycin	Cm
		Streptomycin	S
3	Fluoroquinolones	Moxifloxacin	Mfx
		Levofloxacin	Lfv
		Ofloxacin	Ofx
4	Oral bacteriostatic second-line agents	Ethionamide	Eto or ETH
		Prothionamide	Pto or PTH
		Cycloserine	Cs
		Terizidone	Trd
		Para-aminosalicylic acid	PAS
5	Agents with unclear efficacy or concerns regarding usage	Clofazimine	Cfz
		Linezolid	Lzd
		Amoxicillin-clavulanic acid	Amx/Clv
		Thiacetazone	Thz
		Meropenem-clavulanic acid	Mrp/Clv
		Imipenem/cilastatin	Imp/Cln
		High-dose isoniazid	High-dose H
		Clarithromycin	Clr

Table 1.2 – Summary of the recommended dose and formulations of the second-line antituberculosis drugs (16)

Drug	Dose Recommended	Maximum Dose	Formulation Size
Kanamycin	15-30 mg/kg once daily	1 gram	1 g vial
Amikacin	15-22.5 mg/kg once daily	1 gram	100 mg, 250 mg, 500 mg, and 1 g vials
Capreomycin	15-30 mg/kg once daily	1 gram	1 g vial
Ofloxacin	15-20 mg/kg once daily	800 mg	200 mg, 400 mg
Levofloxacin	7.5 - 10 mg/kg once daily *(twice daily for <5 years)†*	750 mg	250 mg, 500 mg
Moxifloxacin	7.5-10 mg/kg once daily	400 mg	400 mg
Ethionamide/Prothionamide	15-20 mg/kg once daily	1 gram	125 mg and 250 mg tabs
Cycloserine/Terizidone	10-20 mg/kg once or twice daily	1 gram	250 mg capsules
PAS	150 mg/kg granules daily in 2-3 divided doses	12 grams	Sachets of 4 g
Clofazimine	*(3-5 mg/kg once daily)‡*		50 mg tabs, 100 mg tabs/caps
Linezolid	*(10 mg/kg twice daily (once daily for >10 years of age)‡*		600 mg tabs and syrup
Amoxicillin-clavulanic acid, Meropenem-clavulanic acid, and Imipenem/cilastin	As for bacterial infections		
Thiacetazone	5-8 mg/kg once daily		150 mg tabs
High-dose isoniazid	15-20 mg/kg once daily		100 mg tabs
Clarithromycin	7.5-15 mg/kg twice daily		500 mg tabs

† Indicates bracketed recommended by some experts, but differs from formal WHO guideline

‡ No formal paediatric dose recommended in WHO guidelines, so presented dose based on experience and expert opinion(15)

As data on these and new drugs grow, it will be important to ensure not only that child-friendly formulations of these drugs are produced, but also that these drugs are made available to children regardless of where they live. In this review we will highlight what is known regarding the second-line antituberculosis drugs for the treatment of children, and make recommendations for drugs to be included as essential medicines, based on the available literature, clinical experience and expert opinion.

Table 1.3 Potential drug-interactions and combined toxicities between the second-line antituberculosis drugs and antiretrovirals†

	Drug-drug interactions	Potential combined toxicities
Amikacin, kanamycin, capreomycin	Unlikely	Nephrotoxicity with tenofovir
Ofloxacin, levofloxacin, moxifloxacin	Moxifloxacin concentration may be reduced by ritonavir Moxifloxacin concentration may be increased by unboosted atazanavir* Buffered didanosine may reduce oral absorption of all fluoroquinolones	Psychiatric symptoms with efavirenz Hepatitis with nevirapine, efavirenz or protease inhibitors Prolongation of the QT interval with protease inhibitors and efavirenz
Ethionamide, prothionamide	Unknown	Peripheral neuropathy with stavudine or didanosine Psychiatric symptoms with efavirenz Hepatitis with nevirapine, efavirenz or protease inhibitors GI intolerance with zidovudine or protease inhibitors
Cycloserine, terizidone	Unlikely, though renally cleared so nephrotoxicity caused by tenofovir could affect serum concentrations	Peripheral neuropathy with stavudine or didanosine Psychiatric symptoms with efavirenz Stevens Johnson Syndrome with nevirapine and efavirenz
PAS	Unlikely	Hepatitis with nevirapine, efavirenz or protease inhibitors GI intolerance with zidovudine or protease inhibitors
Linezolid	Unlikely	Peripheral neuropathy with stavudine or didanosine GI intolerance with zidovudine or protease inhibitors Lactic acidosis with stavudine, didanosine or zidovudine Bone marrow toxicity with zidovudine
Clofazimine	May increase etravirine* and protease inhibitor concentrations	GI intolerance with zidovudine or protease inhibitors

† Adapted from table in Seddon JA, et al (15)
*not currently recommended for use in children

1.3 Review – Structure and Rationale

The current list of second-line antituberculosis drugs for children in the 2011 WHO List of Essential Medicines include the following: amikacin, capreomycin, cycloserine, ethionamide, kanamycin, ofloxacin and p-aminosalicylic acid (20). This review will include all of these drugs, and based on the WHO Group 2, 3, and 4 drugs, will also include levofloxacin, moxifloxacin, and terizidone. Currently all of these drugs have an important role in the management of children with MDR-TB, and will

continue to do so for the foreseeable future. The WHO Group 5 drugs have uncertain activity against *Mtb* and their role in the treatment of MDR-TB remains to be elucidated. A recent review of the Group 5 drugs noted that existing evidence supports activity of linezolid, clofazimine, and the β-lactams, though their role in the management of drug-resistant TB needs further evaluation (21). As clofazimine and linezolid are increasingly being used in the management of XDR-TB and possibly in future shortened MDR-TB treatment regimens, we will review these drugs here as well. For each drug reviewed, we assessed the evidence for the drug's efficacy, tolerability and safety, pharmacokinetics and pharmacodynamics, and existing formulations and recommendations for its use.

Efficacy

The evaluation of the efficacy of antituberculosis drugs has generally relied on microbiologic endpoints. Because of differences in the pathophysiology of TB in children, especially the paucibacillary nature of the majority of paediatric disease, and difficulties with obtaining sputum specimens, the evaluation of microbiologic endpoints in children is more challenging. There are few trials of antituberculosis drugs in children. Despite this, there is generally no reason to presume that agents shown to be efficacious in adults will not also be efficacious in children (22). The evaluation of the efficacy of these drugs is complicated by a lack of randomized trials in MDR-TB and the difficulty in assigning the contribution of individual drugs in multidrug regimens. Though we have not provided an exhaustive review of the efficacy of each agent, we have attempted to summarize the evidence for the efficacy of each drug against *Mtb in vitro*, in animals, and in human studies, both adult and paediatric where available.

The early bactericidal activity (EBA) of a drug is defined as the fall in colony forming units (CFU) per ml of sputum per day during the first two days of treatment (23), with the extended EBA measuring CFUs after day 2 and up through days 7 or 14. This is generally accepted as a measure of a drug's ability to kill rapidly metabolizing organisms, and important in effecting rapid clinical improvement and rendering patients non-infectious. It may also be an indicator of the drug's ability to protect companion drugs from developing resistance. Sterilizing activity is the ability of a drug to kill all of the bacilli in lesions, including persistent or dormant organisms, and is generally measured by the ability of the drug to sterilize organs in experimental animal models of TB, and in humans by a drug's ability to effect negative cultures at 2 months and to prevent relapses after chemotherapy is stopped (24). A drug's sterilizing ability also indicates whether it may contribute to shortening of therapy. Where the data is available, we specifically include information on each drug's bactericidal and sterilizing activity, though few of the second-line antituberculosis drugs have had thorough such assessments.

As there is a large amount of adult literature on many of these drugs, we did our best to summarize and synthesize the key information; a formal systematic review of this adult data was beyond the scope of this document.

Pharmacokinetics

The pharmacokinetics of many drugs are known to differ in children and adults, and this includes the antituberculosis medications (25-27). Drug absorption, distribution, metabolism, and excretion are all subject to age-related changes (28-30), some of which are due to age-related changes in enzyme maturation and expression (31-33).

As a general approach to dosing of antituberculosis drugs in children, paediatric drug doses should be used that result in the same drug exposure as that associated with efficacious and recommended doses in adults (22, 30). As such, we also present studies of the pharmacokinetics of each drug in adults with TB, and where possible in children with TB. Where there was limited pharmacokinetic data for a drug in children for a TB indication, we have also presented pharmacokinetic data in children for diseases other than TB.

We attempted to more systematically review the available pharmacokinetic literature for these drugs, particularly with regards to paediatric data, which is quite limited for many of these medications.

Safety

Though the adverse effects of most drugs in children will likely be similar to adults, there may be considerable variation in severity, frequency, and toxic effect. The toxicity of a drug may occasionally be greater in children, such as the increased adverse effects of chloramphenicol in infants due to immature enzyme systems, but more often is lower than in adults (30). It is thus important to specifically evaluate the safety profile of drugs in children of different ages (22, 30). We have summarized the toxicity of each drug in adults, with a focus on the prolonged courses used in MDR-TB treatment, and presented the paediatric data as we were able to identify, which was often limited.

Recommendations

Finally, we conclude each section with our assessment of the existing evidence, and in combination with our clinical experience and expert opinion make a recommendation about the appropriateness of the drug to be considered as an essential medicine.

1.4 Search strategy

To evaluate the drugs in this review, we performed a structured review of the literature. We performed our searches in Pubmed, without date or language restrictions, though we were generally only able to review English-language references. Additionally, we reviewed the reference lists of identified articles for additional relevant reports. We also examined other sources well known to the authors, and relied heavily on a review of the second-line antituberculosis drugs in children, recently published by this group and other experts in the field (15).

For each drug reviewed, we performed two searches. The first was a more general search for information on the drug's efficacy in the treatment of TB and its safety profile in adults and children. The second search was focused on the pharmacokinetics in adults with TB, and children with TB and other conditions, and used a published sensitive search string for children (34). From these searches, we reviewed reports that discussed the efficacy of each drug against *Mtb in vitro*, in animals, and in humans, both adult and pediatric where available. We summarized the safety profile of these agents in adult TB treatment. We included reports of the safety of each drug in children, primarily with TB, but also in the treatment of other conditions where data in TB was more limited. Lastly, we included studies that reported pharmacokinetic data in these drugs in adults with TB. We also included all available studies that reported pediatric pharmacokinetic data of these agents, ideally in children with TB, but because of the limited data we also included pharmacokinetic data for non-TB indications in children. We excluded reports that provided pharmacokinetic data only in neonates, or in specific circumstances that were unlikely to routinely exist in patients treated for TB, such as extensive burns or renal failure, unless other data was unavailable. The pharmacokinetic data was extracted in a standardized fashion and presented in table format, with a summary in the text where appropriate. The specific search terms used for each drug are listed in Appendix 2.

Because of time constraints, the number of drugs to be reviewed, and lack of access to some of the early literature, this review is not exhaustive, but the structured approach increases the reproducibility and rigor of the findings and conclusions.

2 – Fluoroquinolones – Ofloxacin, Levofloxacin, and Moxifloxacin

2.1 Background

2.1.1 Overview

Ofloxacin, levofloxacin, and moxifloxacin are fluorinated quinolones, a synthetic class of antibiotics. The fluoroquinolones (FLQs) target the topoisomerase enzymes DNA gyrase and Topoisomerase IV, though other mechanisms of action may exist (35, 36). DNA gyrase is made of two A and two B subunits, encoded by the genes *gyrA* and *gyrB*, and is responsible for introducing negative superhelical twists into bacterial DNA, which is important for the initiation of DNA replication and the transcription of many genes (35). Inhibition of DNA gyrase results in disruption of bacterial DNA synthesis and subsequent rapid cell death (35). The FLQs generally have broad-spectrum activity against gram-negative and gram-positive organisms that varies depending on the individual agent. *Mtb* does not have the enzyme Topoisomerase IV, so inhibition of DNA gyrase is the mechanism of action against *Mtb* (37).

Levofloxacin is the *l*-isomer and more active component of the racemate ofloxacin (38), and therefore has approximately twice the activity of ofloxacin against most bacterial pathogens (39-41). Moxifloxacin has an added methoxy-group, which increases its affinity for DNA gyrase and Topoisomerase IV (36). Ofloxacin is generally considered to be a second-generation FLQ, levofloxacin a second or third-generation, and moxifloxacin a fourth-generation FLQ.

2.1.2 Approved Indications

Ofloxacin, levofloxacin, and moxifloxacin are all approved in the U.S. for treatment of various bacterial infections, but have not received an approved TB indication from a stringent regulatory authority (42).

2.1.3 Cost

Table 2.1 – Price of ofloxacin, levofloxacin, and moxifloxacin by manufacturer (Price in U.S. dollars of the lowest unit – one capsule, one tablet, or one vial) (42)

	Cipla	Hetero	Macleods	Medo-chemie	Micro labs	Bayer	GDF pooled procurement price
Ofloxacin 200 mg tab	0.055	--	0.060	0.095	0.060	--	0.050 (Cipla)
Ofloxacin 400 mg tab	0.099	--	--	--	0.110	--	0.090 (Cipla)
Levofloxacin 250 mg tab	0.061	0.060	0.060	--	0.090	--	0.050 (Cipla)
Levofloxacin 500 mg tab	0.085	0.092	0.075	--	0.160	--	0.080 (Cipla)
Levofloxacin 750 mg tab	†	--	--	--	--	--	--
Moxifloxacin 400 mg tab	1.850	1.10	1.60	--	--	†	1.68 (Cipla) 1.50 (Macleods)

GDF = Global Drug Facility
†Manufacturer did not agree to publish price in source document

2.2 Summary of efficacy data

2.2.1 In vitro activity against Mycobacterium tuberculosis

The *in vitro* activity of the FLQs against *Mtb* has been well demonstrated (43-59). Though not exhaustive, some of the published studies of the Minimum Inhibitory Concentrations (MIC) for

ofloxacin, levofloxacin, and moxifloxacin are listed in Table 2.2. Taken together, these data indicate that the potency of the FLQs against *Mtb* is as follows: moxifloxacin > levofloxacin > ofloxacin, with levofloxacin generally having at least twice the activity of ofloxacin. Of note, the activity of ofloxacin and levofloxacin against bacterial pathogens are decreased 4 to 16 fold at an acidic pH of 5.0 (41).

Table 2.2 Minimum inhibitory concentrations (MIC in µg/ml) † for ofloxacin, levofloxacin, and moxifloxacin against *Mycobacterium tuberculosis*

	Mtb strains	Lowenstein-Jensen medium	Middlebrook 7H10	Middlebrook 7H11	Bactec460	MGIT960
Ofloxacin						
Gorzynski EA, et al. 1989 (51)	Clinical isolates	--	1.3, 2.4	--	--	--
Truffot-Pernot C, et al. 1991 (52)	H37Rv, Clinical isolates, DR and DS	1.0-2.0, 2.0	--	--	--	--
Ji B, et al. 1991 (55)	H37Rv, Clinical isolates, DS	--	--	1.0, 2.0		
Saito H, et al. 1994 (50)	--	--	--	0.78, 0.78		
Ji B, et al. 1995 (47)	Clinical isolates, DS	--	--	1.0, 1.0	--	--
Saito H, et al. 1995 (44)	--	--	--	0.78, 0.78	--	--
Rastogi N, et al. 1996 (59)	Clinical isolates, DS and DR	--	--	--	1.0‡	--
Guilleman I, et al. 1998 (53)	H37Rv	--	--	1.0*	--	--
Vacher S, et al. 1999 (49)	--	--	--	0.5, 1.0	--	--
Ruiz-Serrano MJ, et al. 2000 (56)	Clinical isolates, DS and DR	--	1.0, 2.0	--	--	--
Rodriguez JC, et al. 2001(43)	Clinical isolates, DS	--	--	1.0, 2.0	--	--
Levofloxacin						
Ji B, et al. 1995 (47)	Clinical isolates, DS	--	--	0.5, 1.0	--	--
Saito H, et al. 1995 (44)	--	--	--	0.39, 0. 39	--	--
Rastogi N, et al. 1996 (59)	Clinical isolates, DS and DR	--	--	--	0.5‡	--
Hofner SE, et al. 1997 (45)	Clinical isolates, DS and DR	--	--	1 – 2#	--	--
Guilleman I, et al. 1998 (53)	H37Rv	--	--	0.5*	--	--
Ruiz-Serrano MJ, et al. 2000 (56)	Clinical isolates, DS and DR	--	0.5, 1.0	--	--	--
Tomioka H, et al. 2000 (48)	Clinical isolates, DS	--	--	0.39, 0.39	--	--
	Clinical isolates, DR	--	--	3.13, 6.25	--	--
Rodriguez JC, et al. 2001 (43)	Clinical isolates, DS	--	--	0.5, 1.0	--	--
Rodriguez JC, et al. 2002 (54)	Clinical isolates, DS and DR	--	--	0.25, 0.5	--	--
Moxifloxacin						
Ji B, et al. 1998 (46)	H37Rv, clinical isolates, DS & DR	--	--	0.5, 0.5		
Rodriguez JC, et al. 2001 (43)	Clinical isolates, DS	--	--	0.5, 1.0	--	--
Rodriquez JC, et al. 2002 (54)	Clinical isolates, DS and DR	--	--	0.25, 0.5	--	--
Alvirez-Freites EJ, et al. 2002 (58)	Clinical isolates	--	0.062, 0.125	--	--	--
Kam KM, et al. 2006 (57)	Clinical isolates, DR/OFX-S	--	--	--	--	0.5, 0.5
	Clinical isolates DR/OFX-R	--	--	--	--	1.0, 2.0

† = expressed as MIC_{50}, MIC_{90} respectively, unless otherwise specified; ‡ = MIC_{90}; * = inhibited all strains; # range of MICs
DS = drug-susceptible; DR = drug-resistant, to at least isoniazid and rifampicin; OFX-S = ofloxacin susceptible; OFX-R = ofloxacin-resistant

The WHO 2008 critical concentrations for drug susceptibility testing (DST) of *Mtb* are listed in Table 2.3 (60). Angeby and colleagues determined the wild-type MICs, also referred to as Epidemiological Cut-Off (ECOFF) values for ofloxacin, levofloxacin, and moxifloxacin in 90 consecutive clinical isolates, which are listed in Table 2.3 (61). As they noted, ECOFFs may underestimate the critical concentrations or clinical breakpoints, if strains with higher MICs are still treatable with recommended doses (61). They also noted good correlations between the MICs in Middlebrook 7H10 and in Bactec460 and MGIT960 (61). Combining the clinical history with the laboratory data from over 200 isolates from six international sites, Kam and colleagues recommended critical concentrations for ofloxacin and other second-line drugs (Table 2.3) (62). Critical concentrations for levofloxacin have also been recommended by Sanders and colleagues (See Table 2.3) (63). Table 2.3 also lists results from a preliminary summary of a 2012 WHO Expert Group Meeting on drug susceptibility testing, which made tentative recommendations for some changes, though as yet a formal report with final recommendations is not available (64).

Table 2.3 Suggested critical concentrations for drug susceptibility testing of ofloxacin, levofloxacin, and moxifloxacin (in µg/ml)†

	Lowenstein-Jensen medium	Middlebrook 7H10	Middlebrook 7H11	Bactec460	MGIT960
Ofloxacin					
Angeby KA, et al. 2010 (61)	--	1.0	--	--	--
Kam KM, et al. 2010 (62)	3.0	1-1.5	--	0.5-1.0	--
WHO 2008 (60)	2.0	2.0	2.0	2.0	2.0
WHO 2012 (64)	*4.0*	*2.0*	*2.0*	--	*2.0*
Levofloxacin					
Sanders CA, et al. 2004 (63)	--	1.0	--	2.0	2.0
Angeby KA, et al. 2010 (61)	--	0.5	--	--	--
WHO 2008 (60)	--	2.0	--	--	2.0
WHO 2012 (64)	--	*1.0*	--	--	*1.5*
Moxifloxacin					
Angeby KA, et al. 2010 (61)	--	0.5	--	--	--
WHO 2008 (60)	--	--	--	0.5	0.25
WHO 2012 (64)	--	*0.5/2.0 ‡*	--	--	*0.5/2.0 ‡*

† Tentative updated recommendations in *italics*
‡ Two levels established

The FLQs have also shown *in vitro* activity against intracellular *Mtb* (44, 48, 49, 65). They are known to concentrate in macrophages, and Skinner and colleagues demonstrated potent activity of levofloxacin and sparfloxacin in mouse macrophages (66). Using multiple *in vitro* models of rifampicin-tolerant persistent *Mtb*, Hu and colleagues demonstrated that ofloxacin had little activity, whereas moxifloxacin consistently showed more activity than ofloxacin or levofloxacin, suggesting its sterilizing potential (67). Potential sterilizing activity in an acid model of persistent *Mtb* has also been demonstrated for levofloxacin (68) and moxifloxacin (68, 69), and in other *in vitro* models of dormant or stationary phase *Mtb* (70). In an *in vitro* model of dormant *Mtb*, moxifloxacin was an important component of effective drug-combinations (71).

2.2.2 Activity in animal models

Ofloxacin has shown dose-dependent activity against *Mtb* in a mouse model (47, 55, 72, 73), with a dose equivalent to 600mg in humans having activity similar to ethambutol (52). Levofloxacin has potent dose-dependent bactericidal activity in murine TB, with activity equivalent to twice that of ofloxacin (47, 72, 74, 75).

Moxifloxacin has been more extensively evaluated, and has consistently shown potent dose-dependent bactericidal activity in the mouse model, with daily doses of 100-400 mg/kg of moxifloxacin

as bactericidal as 25 mg/kg of isoniazid (46, 58, 76, 77). Weekly doses of 50-400 mg/kg of moxifloxacin showed limited bactericidal activity (76), but substantial sterilizing ability, with relapse rates in mice of 15% and 61% after a continuation phase of weekly INH-rifapentine-moxifloxacin versus INH-rifapentine-streptomycin respectively (78). In a report by Nuermberger and colleagues in murine TB, the combination of rifampicin-moxifloxacin-pyrazinamide (RMZ) for 2 months followed by rifampicin-moxifloxacin (RM) for 4 months, was much more effective than standard treatment (79). In this study, the combination of RMZ/RM had more potent killing of *Mtb* at 2 months in lungs, and resulted in nearly complete culture conversion in lungs at 3 months, whereas mice receiving standard treatment required 5 months of treatment before culture negativity (79). A follow-up study again in mice showed that treatment with 2RMZ/2RM resulted in cure and no relapses, while 6 months of treatment with the standard regimen (2RHZ/4RH) was required to eliminate relapse, confirming the ability of the RMZ regimen to shorten treatment duration in mice (80).

Two studies evaluated FLQs in combination with other existing second-line anti-TB drugs in mice. In a study of mice infected with *Mtb* strains resistant to isoniazid (INH) and rifampicin, the addition of ethionamide to moxifloxacin showed increased bactericidal activity over moxifloxacin alone, whereas the addition of cycloserine, thiacetazone, capreomycin, PAS, or linezolid did not add activity to moxifloxacin-monotherapy (81). A second study evaluated the relative activities of ofloxacin 200 mg, levofloxacin 200 mg, and moxifloxacin 100 mg each in a 2 month intensive phase with amikacin, ethionamide, and pyrazinamide and a 10 month continuation phase paired with ethionamide, in mice infected with a the H37rv *Mtb* strain (82). At 2 months, the bactericidal activity of the ofloxacin and levofloxacin containing regimens did not differ from the standard regimen of INH-rifampicin-pyrazinamide, and the moxifloxacin-containing regimen was more bactericidal than all three (82). After the 12 months of total treatment though, the spleens and lungs were culture positive in the ofloxacin group in 7/8 and 7/8 respectively, compared to 5/9 and 1/9 in the levofloxacin group (82). In the moxifloxacin group no organs were culture positive after 9 months of total treatment, which was comparable to 6 months of standard treatment (82). Also highlighting the relative potencies of the FLQs, in this same study, FLQ-resistant isolates were recovered from all surviving control mice treated with levofloxacin-monotherapy and moxifloxacin-monotherapy, whereas all the mice treated with ofloxacin-monotherapy died earlier with ofloxacin-susceptible organisms (82).

Moxifloxacin has also been evaluated in animals in numerous combinations with rifapentine and newer drugs, including TMC207 and PA-824, where it appears likely to be an important component of possible future drug regimens (83-89).

2.2.3 Activity in human TB

Multiple studies of the Early Bactericidal Activity (EBA) in TB of the FLQs have been reported, and a 2008 review summarized this and other published EBA reports (23). Three studies reporting the EBA_{0-2} of 600-800 mg ofloxacin consistently reported values of 0.32-0.38 (23, 90, 91). Gosling and colleagues reported mean EBA for days 0-2 of 0.53 for moxifloxacin 400 mg, 0.77 for INH 300 mg, and 0.28 for rifampicin 600 mg (92). The EBA_{0-2} of INH was higher than that of rifampicin (p=0.006), but there was no statistical difference between the moxifloxacin EBA_{0-2} and that of either INH or rifampicin (92). A follow-up study by this group reported an EBA_{0-2} of 0.60 for the combination of 300 mg isoniazid with 400 mg moxifloxacin, similar to the values of each drug alone, suggesting neither additive benefit nor antagonism of the combination (93). In a study by Pletz and colleagues there was no significant difference between the EBAs for days 0-5 for moxifloxacin 400 mg (0.27) and isoniazid 6mg/kg (0.209) (94).

Johnson and colleagues reported mean EBA for days 0-2 of 0.67 for INH 300 mg, 0.45 for levofloxacin 1000 mg, 0.35 for gatifloxacin 400 mg, 0.33 for moxifloxacin 400 mg (95). In their analysis, the EBA_{0-2} of INH was significantly higher than that of gatifloxacin (p =0.01) and moxifloxacin (p=0.02), but the difference between levofloxacin and INH was not statistically significant (p=0.14) (95). Most recently, in a 14-day EBA study evaluating multiple combinations containing new drugs, the combination of moxifloxacin 400 mg, PA-824, and pyrazinamide had an EBA_{0-2} of 0.315 and an EBA_{0-14} of 0.233, higher than the other combinations including the combination of PA-824-pyrazinamide, and at least

comparable to the EBA_{0-2} (0.177) and EBA_{0-14} (0.140) of standard treatment with INH, rifampicin, pyrazinamide, ethambutol (96). In their EBA study, Johnson and colleagues also reported on the extended EBA days 2-7, a marker of possible sterilizing activity, and found that there was no difference between INH, levofloxacin, gatifloxacin, or moxifloxacin, though the pooled EBA_{2-7} of these FLQs was lower than that of INH (p=0.036) (95).

Fluoroquinolones have been investigated in humans for treatment of both drug-susceptible and drug-resistant TB. Tsukumura and colleagues reported one of the earliest evaluations of ofloxacin use for the clinical treatment of TB in 19 adults (97). In this study of 19 adults with chronic DR-TB most of whom were effectively receiving monotherapy with ofloxacin 300 mg, 26% became culture negative, with many of those failing treatment developing ofloxacin resistance (97). Numerous other studies followed, many of which were reviewed in 2003 by Ginsberg and colleagues, and showed generally good efficacy of the FLQs in TB though little advantage to adding or substituting them in standard-treatment regimens for drug-susceptible TB (98, 99). A 2008 Cochrane Review of randomized trials of FLQs used in the treatment of TB, mostly drug-susceptible, reported no statistically significant difference in trials substituting ciprofloxacin, ofloxacin, or moxifloxacin for first-line drugs in relation to cure, treatment failure, or clinical or radiological improvement, though ciprofloxacin use was associated with increased risk of relapse and longer time to sputum culture conversion in HIV-infected individuals (100). A few notable studies of FLQs for the treatment of drug-susceptible TB are discussed further below. A randomized trial from India evaluating multiple ofloxacin-containing first-line regimens suggested the potential for the FLQs for treatment-shortening, though this study did not include a standard-treatment control group (101). In a TB Trials Consortium (TBTC) trial in adults, substitution of moxifloxacin for ethambutol in the intensive phase of standard treatment for drug-susceptible TB did not affect 2 month-culture negativity, though higher rates of culture-negativity at 4 weeks in the moxifloxacin group do provide some evidence for its sterilizing activity (102). A similar Phase II study (OFLOTUB) to assess the sterilizing activity of FLQs by the substitution of ofloxacin, gatifloxacin, or moxifloxacin for ethambutol in the standard-treatment of adults with drug-susceptible TB reported significantly increased bacillary elimination for moxifloxacin and gatifloxacin, but not ofloxacin (103). In a trial comparing standard therapy versus standard therapy with the addition of levofloxacin 500 mg in adults with TB-HIV co-infection, there was no difference in 2 month culture conversion though there was a statistically non-significant increase in 1 month culture conversion in the levofloxacin arm (104). In another TBTC trial in adults, substitution of moxifloxacin for INH in the standard intensive phase resulted in a small but statistically non-significant increase in 2-month culture negativity in the moxifloxacin group (60.4% moxifloxacin versus 54.9% INH) (105). An ongoing study (REMox TB) is evaluating two 4-month moxifloxacin-containing treatment regimens for treatment shortening (ClinicalTrials.gov Identifier: NCT00864383).

In addition to the initial study by Tsukumura and colleagues, a large number of observational studies have documented the role of FLQs in the treatment of MDR-TB, though the previously mentioned Cochrane Review did not identify any randomised trials of FLQs specifically for MDR-TB treatment (100). Multiple systematic reviews also did not identify any randomized trials in MDR-TB, but did synthesize the many observational studies (106-108). Two recent individual patient data (IPD) meta-analyses used reports identified in these systematic reviews to provide a more detailed analysis. The first included data from 9,153 patients from 32 observational cohorts, and reported improved treatment success with the use of a later-generation FLQ versus no FLQ (adjusted Odds Ratio [aOR] 2.8, 95% CI 1.3-6.1) and versus ofloxacin (aOR 2.1, 95% CI 1.2-3.9), and with the use of ofloxacin versus no FLQ (aOR 2.0, 95% CI 1.2-3.3) (106). A second IPD meta-analysis found that the adjusted odds ratios of treatment success versus treatment failure, relapse or death, for those with MDR-TB and second-line-injectable-resistance, MDR-TB and FLQ resistance, and XDR-TB, compared to MDR-TB alone were 0.6, 0.4, and 0.2 respectively (109). In a retrospective observational study comparing ofloxacin and levofloxacin for MDR-TB treatment in adults, levofloxacin was more efficacious, with increased treatment success in ofloxacin-susceptible isolates (96.2% for levofloxacin versus 87.5% for ofloxacin) and in ofloxacin-resistant isolates (78.6% for levofloxacin versus 45.5% for ofloxacin) (110).

Existing evidence also supports a potential role for the later-generation FLQs in the treatment of XDR-TB. A systematic review of adults with XDR-TB reported that use of later-generation FLQs was associated with improved outcomes (111). In a cohort of adults with XDR-TB from South Africa, use of moxifloxacin was protective against death (hazard ratio 0.11, 95% CI 0.01-0.82) (112). A recent study reported improved treatment outcomes for an intensified regimen for the treatment of TB meningitis in adults, which included higher-dose rifampicin and moxifloxacin, though receipt of moxifloxacin was not associated with the outcome in this study (113). These reports highlight the importance and increasing role of the later-generation FLQs in TB treatment.

Data in paediatric MDR-TB is limited, but is supportive of FLQs for this indication. In a systematic review of children treated for MDR-TB, FLQs were an important component of the treatment regimen in all included studies, which had a pooled treatment success of 81.67% (6). More recently, in a cohort of children with MDR-TB in which a FLQ was a key component of the treatment regimen, 137/149 (92%) had cure or probable cure, further supporting its use (114). The later generation FLQs levofloxacin and moxifloxacin were efficacious in two small case series of 8 children with MDR-TB (115, 116).

2.2.4 Resistance

Mycobacterial resistance to the FLQs occurs most commonly via mutations in *gyrA* gene, in a highly conserved region called the Quinolone Resistance Determining Region (QRDR) (98). Single mutations can result in ofloxacin MICs >2.0 µg/ml, with high-grade resistance usually requiring two or more mutations (117). Different mutations are associated with different levels of resistance (57, 117-119), and there is broad cross-resistance among the FLQs, though differing degrees of resistance from one drug to another (57, 119, 120). Of particular clinical importance in MDR-TB, moxifloxacin retains significant activity in many ofloxacin-resistant isolates, with MICs of moxifloxacin being 4 to 8-fold lower than those of ofloxacin (57, 119, 121). In a study by Kam and colleagues, the moxifloxacin MIC_{90} among ofloxacin-resistant *Mtb* clinical isolates was 2.0 µg/ml, with only 2/35 isolates having a moxifloxacin MIC of 4.0 µg/ml (57), highlighting the potential use of high-dose FLQs in the management of FLQ-resistant *Mtb* (122). In mice infected with FLQ-resistant strains of *Mtb* with different MICs, treatment with moxifloxacin was able to cure those infected with a resistant strain with an MIC of 0.5 µg/ml (123). Moxifloxacin treatment prevented mortality but had limited impact on lung CFUs among those infected with a strain with an MIC of 2.0 µg/ml, but did not affect survival or lung CFUs among those infected with strains with an MIC of 4.0 µg/ml (123). Despite this evidence, the role for later-generation FLQs in the context of ofloxacin-resistance remains controversial.

FLQ-resistant mutants have been reported to appear spontaneously at frequencies of $2x10^{-6}$ to $1x10^{-8}$ (120), and it is well demonstrated that FLQ-resistance in *Mtb* can emerge rapidly when used without other drugs to protect it (97, 98, 120, 124-126). In a the 2 year follow-up of a randomized-controlled clinical trial of TMC207 (bedaquiline) in adults with MDR-TB, 4/18 in the control arm receiving placebo and the standard MDR-TB ofloxacin-containing regimen developed ofloxacin-resistance during the course of their MDR treatment (127). Of note, among the FLQs moxifloxacin has been shown to have the lowest probability of generating resistant mutants, when considering its pharmacokinetics and mutant prevention concentration (128).

In addition to *gyrA* mutations, FLQ-resistance may develop as a result of decreased intracellular drug accumulation due to efflux pumps (117). Efflux-pump-related ofloxacin-resistance has been shown to be induced by co-administration of rifampicin in rifampicin-resistant *Mtb* isolates (129). Additional work is needed to further elucidate the role of efflux-pumps and their clinical significance in *Mtb* FLQ-resistance.

2.3 Pharmacokinetics and Pharmacodynamics

2.3.1 Pharmacokinetics

General

The fluoroquinolones are generally well-absorbed after oral administration, with bioavailabilities of 85-95% for ofloxacin (130, 131), ≥99% for levofloxacin (132, 133), and 86 - 91.2% for moxifloxacin in healthy adult volunteers (134). Absorption of the FLQs is substantially reduced by the co-administration of the multivalent cations $Zn^{++,}$ Al^{++}, and Fe^{++}, but not Ca^{++} (135, 136). When given with sucralfate, the moxifloxacin AUC and C_{max} were reduced to 40% and 45% respectively compared to expected, and when given with iron the AUC and C_{max} were reduced to 61% and 41% respectively (137). Food has been shown to delay absorption and slightly lower the C_{max} (135, 138), but generally does not affect the AUC of the FLQs (135). Ofloxacin and levofloxacin have concentration-independent protein binding of roughly 25% at the doses studied (139, 140), with moxifloxacin protein binding estimated to be 25-50% (140, 141), though there may be substantial inter-individual differences (142). Ofloxacin, levofloxacin (143), and moxifloxacin all generally have good penetration into body fluids (144), including into the cerebrospinal fluid (145). The reported ratio of CSF to plasma AUC_{0-24} for levofloxacin is 0.74 (146) and for moxifloxacin is 0.71-0.82 (147, 148). Ofloxacin and levofloxacin penetrate lung fluids well, with concentrations in lung epithelial lining fluids exceeding those in serum (149, 150), and with pleural fluid to serum concentration ratios of 0.82-0.92 (151).

The elimination and metabolism of the FLQs varies with each agent. Ofloxacin (139) and levofloxacin are primarily excreted unchanged in the urine, with <5% metabolized in the liver (132). The absorption (C_{max} and T_{max}) of the enantiomers of racemic ofloxacin are not significantly different, though the *l*-isomer has been shown to have a slightly, but statistically significant, greater AUC and slower clearance than the *r*-isomer (152). Moxifloxacin has multiple routes of elimination, with roughly 50% undergoing glucuronide (153) and sulphate conjugation (154) in the liver (37), 25% excreted unchanged in the faeces (37), and 20-25% excreted unchanged in the urine (37, 134). Moxifloxacin is not metabolized by the cytochrome p450 system and is not known to inhibit cyp450 enzymes (37), though the involvement of p-glycoprotein (155) and other enzyme systems in moxifloxacin metabolism can result in drug interactions, including with rifamycins (153, 154).

Ofloxacin

In healthy adults, the following normalized pharmacokinetic (PK) parameters have been reported for ofloxacin: $t_{1/2}$ 4-5 hours, C_{max} 4.0 µg/ml/70kg, and AUC_{24} 48 µg*h/ml/70kg (98). Our search identified 3 studies of the pharmacokinetics of ofloxacin in adults with TB (see Appendix 1, Table A-1) (138, 156, 157). Stambaugh and colleagues evaluated the pharmacokinetics of ofloxacin in a cohort of TB patients, using both intensive and sparse sampling methods, and reported PK parameters generally consistent with those of healthy adults (See Appendix 1, Table A-1) (156). They noted that the AUC and C_{max} values increased proportionally with dose, and delayed absorption was relatively common, but not consistently found in most patients having multiple samplings (156). The two children aged 2.5 and 17 years included in this study were described to have similar PK parameters to the adults, though their data was not separately reported (156). The three HIV-infected patients in this cohort were noted to have slower absorption, but otherwise had similar PK parameters to HIV-infected individuals (156). Chigutsa and colleagues describe the pharmacokinetics of an 800 mg oral dose of ofloxacin in adults with MDR-TB in 2 locations in South Africa (Table A-2) (138). Administration of ofloxacin with a meal resulted in delayed absorption (138). HIV-infection was not found to be a statistically significant pharmacokinetic covariate in this study (138). Similar findings to the first two studies were reported among adults with drug-resistant TB in Thailand (157).

Our search did not identify any studies of pharmacokinetic studies of ofloxacin in children with TB. We identified a single study of ofloxacin in children with multidrug-resistant typhoid fever (Appendix 1, Table A-1) (130). Seventeen children with a mean age of 10.4 years (range 5-14 years) with multidrug-resistant typhoid fever, were enrolled in a randomized cross-over study comparing oral and IV ofloxacin (130). After a 7.5 mg/kg oral dose, the following values were noted: C_{max} 5.73 µg/ml, T_{max} 1.39 hours, t ½ 3.26 hours, and AUC_{0-12} 26.5 mg*h*L (130). The authors noted that while the T_{max}, t ½, and volume of distribution were similar to those in healthy adults, the systemic clearance was more rapid (130). Preliminary results presented at the 2012 Union World Conference on Lung Health in

Kuala Lumpur, Malaysia, from an ongoing study of the pharmacokinetics of the second-line anti-TB drugs in children are also presented in Appendix 1, Table A-1.

Levofloxacin

In healthy adults, the following normalized pharmacokinetic parameters have been reported for levofloxacin: $t_{1/2}$ 6-8 hours, C_{max} 6.21 µg/ml/70kg, and AUC_{24} 44.8 µg*h/ml/70kg (98). Our search identified one study evaluating the pharmacokinetics of levofloxacin in adults with TB, using a dose of 1000 mg once daily (See Appendix 1, Table A-2) (141). In a study evaluating FQNs in TB meningitis, Thwaites and colleagues reported levofloxacin AUC_{0-24} of 155 (range 81.1-284) for a 500mg dose given twice daily (146). HIV infection has been shown not to affect the pharmacokinetics of levofloxacin (158-160), and no interactions were shown between levofloxacin and the antiretrovirals zidovudine (160), efavirenz or nevirapine (158).

Our search did not identify any studies of levofloxacin pharmacokinetics in children with TB, though we found 1 other non-tuberculosis paediatric study (See Appendix 1, Table A-2) (133). Chien and colleagues evaluated over 80 children, in five different age stratifications, given a single-dose of IV or oral levofloxacin (133). All pharmacokinetic parameters were similar between age groups and to published adult data, with the exception of clearance, which was inversely related to age (133). Consistent with the known age-related development of glomerular filtration, levofloxacin clearance decreased up until 10 years of age, at which point it was only slightly higher than but approximating that of adults (133). The most rapid change in clearance was noted in the first 2 years of life, though even children less than 5 years of age cleared levofloxacin almost twice as fast as adults (0.28L/h/kg vs 0.14L/h/kg) (133). Based on their data, the authors recommended a dose of 10mg/kg twice daily for children less than 5 years of age, and 10mg/kg once daily for children older than 5, in order to approximate adult C_{max} and AUC parameters for recommended adult doses (133). Using the above pharmacokinetic data (133), Li and colleagues used a pharmacometric approach, in the context of treatment for postexposure inhalational anthrax, to conclude that levofloxacin doses of 8mg/kg twice daily for children <50kg and 500mg once daily for children ≥50kg best approximated the levofloxacin exposure in adults after a 500mg dose (161).

Moxifloxacin

In healthy adults, the following normalized pharmacokinetic parameters have been reported for moxifloxacin: $t_{1/2}$ 10.7-13.3 hours, C_{max} 4.34 µg/ml/70kg, and AUC_{24} 39.3 µg*h/ml/70kg (98). Our search identified six studies evaluating the pharmacokinetics of moxifloxacin in adults with TB, presented in Appendix 1, Table A-3 (113, 141, 142, 162-164). Pranger and colleagues described lower values for the C_{max} and AUC then other studies, though a high proportion of patients with rifampicin co-administration may partly explain some of these differences (142). Most recently, the pharmacokinetics of moxifloxacin 400 mg and 800 mg were reported as part of a study of intensified treatment for TB meningitis (113).

Our search identified a single case study of the pharmacokinetics of moxifloxacin in one child with *Mycoplasma hominis* meningitis (165). In this 1 month old 1000 gram former 28-week premature infant, a 5 mg/kg IV dose of moxifloxacin gave a C_{max} of 1.7µg/ml and AUC_{0-24} of 16.5 µg/ml, which the authors noted were lower than adult values (165). We did not identify any pharmacokinetic studies of moxifloxacin in children with TB.

The rifamycins and moxifloxacin have been shown to have pharmacokinetic interactions. High-dose intermittent rifapentine increased moxifloxacin clearance by 8-30% and reduced the AUC by approximately 8%- 17% (162, 166). Rifampicin appears to have a larger effect on moxifloxacin, increasing clearance by 45% and decreasing the C_{max} by 32% and AUC by 27-31% (163, 167). The clinical significance of these reductions in moxifloxacin exposure is unknown.

2.3.2 Pharmacodynamics

A C_{max}/MIC ratio of 8-10 and AUC/MIC ratio of 100-125 are associated with fluoroquinolone activity in bacteria and presumably in *Mtb* as well (98, 168). In a dose-fractionation study in a murine model of TB, the AUC/MIC ratio was the most important pharmacodynamic (PD) parameter (169). In this same study, moxifloxacin had better pharmacodynamics than ofloxacin, sparfloxacin, or ciprofloxacin (169). Based on known pharmacokinetics and MICs for the fluoroquinolones, calculated expected pharmacodynamic parameters indicated that a 400 mg dose of moxifloxacin would be the most potent (C_{max}/MIC of 9, AUC_{24}/MIC of 96), followed by 500 mg levofloxacin (C_{max}/MIC of 5-7, AUC_{24}/MIC of 40-50), and 400 mg ofloxacin (C_{max}/MIC of 2, AUC_{24}/MIC of 24) (168). Based on published pharmacokinetics and wild-type MICs of *Mtb* determined in their studies, Angeby and colleagues estimated a more favourable *free*AUC/MIC ratio for levofloxacin 750 mg than moxifloxacin 400 mg (61).

In simulations, compared with ofloxacin doses of 400 mg twice daily and 600 mg once daily, an ofloxacin dose of 800 mg once daily gave the most favorable AUC/MIC (156). The probability of target attainment (PTA) is a method which combines human pharmacokinetic data and pharmacodynamic data, to determine the probability of attaining a certain pharmacodynamic index in a population using Monte Carlo simulations (138). Chigutsa and colleagues found that based on the ofloxacin MICs and pharmacokinetics of ofloxacin in South African adults MDR-TB patients, a critical concentration of 2.0µg/ml, and a target pharmacodynamic index of *free*AUC/MIC of 100, very few patients achieved a PTA of 0.9 with an 800 mg oral dose of ofloxacin (138). In simulations, higher doses were more likely to reach a PTA of 0.9 (138). The authors concluded that an 800 mg dose of ofloxacin was inadequate for the treatment of MDR-TB in South African adults, and that the use of higher ofloxacin doses or alternate fluoroquinolones should be considered (138).

Peloquin and colleagues demonstrated that a levofloxacin dose of 1000 mg achieved median ratios of free-AUC to actual MIC (0.5-1.0 µg/ml), and free-AUC to published MIC_{90} (1.0 µg/ml) of 187.67 and 96.51 respectively, with nine of 10 patients having a free AUC/MIC_{actual} >125 (141). In the same study, a moxifloxacin dose of 400 mg resulted in median ratios of free-AUC to MIC_{actual} (0.5 µg/ml) and free-AUC to published-MIC_{90} (0.5 µg/ml) of 59.35, which was below 100 for all nine patients (141). In their EBA and pharmacokinetics study, Johnson and colleagues reported the most favorable pharmacodynamics for levofloxacin 1000 mg (95). Using MICs of 1.0 µg/ml for levofloxacin and 0.5 µg/ml for moxifloxacin they reported AUC_{0-24}/MIC ratios of 129.1 for levofloxacin 1000 mg and 110.5 for moxifloxacin 400 mg (95). The C_{max}/MIC ratios were 15.6 for levofloxacin 1000 mg and 12.3 for moxifloxacin 400 mg (95). A target C_{max} of 8-12 has been proposed for ofloxacin and levofloxacin (170).

2.4 Safety Data

Despite well-known adverse effects of the fluoroquinolones, most of those in clinical use, including ofloxacin, levofloxacin, and moxifloxacin are generally well-tolerated in short courses in adults (35). Concerns about the effect of fluoroquinolones on cartilage in children have limited their use, and as such there is a relative paucity of data in children, particularly for prolonged courses. Increasingly these drugs are being recognized as safe in younger ages and gaining more widespread use where other treatment options are limited, including for the treatment of DR-TB. In general, the toxicity profile of FLQs in children is similar to that of adults (171). High-quality data on the toxicity of these drugs in adults and children used in the doses and prolonged courses used in the treatment of MDR-TB is more limited, though it is reassuring to note that among children receiving ciprofloxacin, there was no difference in risk of toxicity among those receiving treatment durations of <30 days, 30-60 days, and >60 days (172).

Gastrointestinal adverse effects

Gastrointestinal (GI) events including anorexia, nausea, vomiting, abdominal pain, and diarrhea, are the most common adverse effects, reported in 3-17% of adults in clinical trials, but are generally mild

and rarely require discontinuing the drug (35). *Clostridium difficile*-associated diarrhea can occur uncommonly (35, 173), may be associated with prolonged FLQ use (174), and there is some evidence that moxifloxacin may carry a higher risk than levofloxacin (175). Mild, self-limited gastrointestinal adverse effects were the most commonly reported toxicity in children treated with ciprofloxacin (171) with diarrhea, vomiting, and nausea each occurring in 2% of children (172), but limited data is available for other FLQs. Our search did not identify any reports of FLQ-related *C. difficile*-associated diarrhea in children. In a systematic review and meta-analysis of children with MDR-TB, ofloxacin was potentially implicated as a cause of nausea among some patients in one of the included reports (6). In a cohort of children receiving ofloxacin, ethambutol, and high-dose isoniazid as part of MDR-TB preventive therapy, 31 and 1 of 193 reported Grade 1 or 2 vomiting respectively, 18 and 1 of 193 reported Grade 1 or 2 diarrhea, and 17 and 10 of 193 reported Grade 1 or 2 appetite loss/nausea (176). Only two Grade 3 GI-related events were reported (appetite loss/nausea), and no Grade 4 events (176).

Central Nervous System adverse effects

Central nervous system (CNS) adverse effects are well described (177), and occur in 0.9 – 11% of adults taking fluoroquinolones depending on the agent (35). The CNS manifestations of FLQ toxicity are quite variable and include insomnia, dizziness, headaches, confusion, somnolence, delirium, psychosis, and muscle jerks, many of which may ultimately be related to inhibition of GABA or activation of NMDA-receptors (178) by the FLQs (175, 177, 179). Sleep disturbance has been reported in up to 4.7% of patients taking FLQs (177). Seizures have been described to occur with ofloxacin (180) and levofloxacin (181, 182), may be related to drug-interactions with non-steroidal anti-inflammatory drugs, antidepressants, metoclopramide, and theophylline, and are more common in those with seizure disorders, electrolyte abnormalities, the elderly, and those with renal failure, but overall occur in less than 1% of patients (178, 179, 182). Many rare CNS adverse effects have also been described (177, 183).

Two cases of seizure associated with overdose of nalidixic acid in children have been reported (184, 185), but our review did not identify any reports of seizures attributed to ofloxacin, levofloxacin, or moxifloxacin in children. Sleep disorders, nightmares, and insomnia have been well-described in children taking ofloxacin (186). A systematic review reporting the adverse effects in 182 children with MDR-TB did not describe any CNS effects attributed to fluoroquinolones (6). In the recently reported cohort of children receiving an ofloxacin-containing MDR-TB preventive treatment regiment, 9/193 and 4/193 experienced Grade 1 or 2 mood/sleep disturbances (176). Three children had Grade 3 mood/sleep disturbances, including hallucinations, probably related to accidental misdosing of ofloxacin (176). In our experience, mild sleep disturbance and nightmares are not uncommon in children taking ofloxacin, but are generally mild, more frequent at the initiation of therapy and resolve spontaneously without interrupting treatment.

Prolongation of QT interval

The fluoroquinolones are known to prolong the QT interval in a dose-dependent manner by inhibition of potassium channels, specifically the delayed rectifier potassium current I_{KR}, encoded by the HERG gene (175, 187). QT interval prolongation predisposes to Torsades de Pointes, which may result in sudden death. Though there is variability between agents, the prolongation is minimal for most drugs, averaging 3-6 ms, and the clinical significance of such small degrees of QT prolongation is questionable (187, 188). Though all the FLQs are known to have this effect, individual agents vary in the strength of their inhibition of these channels and in their effect on the QT interval (189, 190). In a study evaluating the inhibition of I_{KR} HERG channels by FLQs using *in vitro* patch-clamp electrophysiology, the rank order of inhibition was sparfloxacin > grepafloxacin > moxifloxacin (IC_{50} 129 µM) > gatifloxacin > levofloxacin (IC_{50} 915 µM) > ciprofloxacin > ofloxacin (IC_{50} 1420 µM) (189).

The clinical evidence is generally consistent with this rank order, and among the FLQs in use for TB treatment moxifloxacin has the greatest effect on QT interval, though it is still a relatively small absolute effect and the clinical relevance remains unknown (191-193). Despite relative small absolute

effects for most patients, an abnormally prolonged QT interval (>470 ms in females; >450 ms in males) occurred in 4.3% of patients pre-dose and 12.8% post-dose receiving 800 mg of moxifloxacin, compared to 8.5% pre-dose and 6.4% post-dose for placebo (193). In this same study, prolongation of the QT interval more than 60 ms above baseline, a marker for increased risk of slowed ventricular repolarization, occurred in 12 instances among 5 subjects, of which nine instances among 4 subjects were in those receiving 800 mg of moxifloxacin (193). Levofloxacin has shown very little effect on the QT interval in clinical studies, even at doses of 1000 mg and 1500 mg (191, 193, 194). Noel and colleagues found that after doses of 500, 1000, and 1500 mg of levofloxacin, corrected QT intervals (QTc) were unchanged from baseline, though transient increases in heart rate were noted (194). Despite these documented QT prolonging effects, documented cases of Torsades de Pointes are rare. Search of an FDA database showed that between 1996-2001 in the US 37 individual cases of Torsades de Pointes were reported in association with FLQs (195). The rates of FLQ-associated Torsades de Pointes per 10 million prescriptions were as follows: ciprofloxacin 0.3, ofloxacin 2.1, levofloxacin 5.4, gatifloxacin 27, moxifloxacin 0 (195). More recent studies linking FLQ use with cardiac arrhythmias have been generally consistent with these findings (196, 197).

Though the absolute effect of FLQs on the QT interval appears to be minimal, this may be more clinically important in combination with other known risk factors for Torsades de Pointes (192), which include female gender, familial long QT syndromes, other heart disease, electrolyte abnormalities such as hypokalemia, hypomagnesemia, and hypocalcemia, renal and liver dysfunction, and interactions with multiple drugs that prolong the QT (187). In the report from the FDA database, nineteen of the 37 patients with reported FLQ-associated Torsades de Pointes were taking other drugs known to prolong the QT interval, and some additional patients had other predisposing conditions, such as hypokalemia (195). An additional consideration for patients on MDR-TB treatment is the frequent drug-induced hypothyroidism related to PAS or ethionamide. Hypothyroidism and subclinical hypothyroidism are associated with prolongation of the QT interval (198, 199), and treatment of these conditions with L-thyroxine has been shown to normalize the QT interval (200, 201). We did not identify any reports of QT prolongation or arrhythmias related to the combination of FLQs and hypothyroidism, though there would theoretically be an increased risk, which might support the use of L-thyroxine in this context. An additional important consideration in malaria endemic areas is the QT prolonging effects of many existing malaria treatment (202). The use of many of these antimalarials in combination with FLQs is currently contraindicated, though additional data on the potential clinical significance is needed (202).

Our review did not identify any reports of the effect of FLQs on the QT interval in children or any reports of FLQ-associated arrhythmia or sudden death in children, though awareness of this potentially significant adverse effect would be important, particularly in children with known risk factors for prolonged QT. Based on existing knowledge though, concern about QT prolongation should not limit FLQ use in children.

Arthropathy

Concern about arthropathy has been the main factor limiting FLQ use in children. FLQ-induced damage to the cartilage of weight-bearing joints has been observed in all animal models tested, with multiple proposed mechanisms for this damage, including magnesium chelation by the FLQs (203). The most important risk factor is young age, and juvenile dogs appear to be the most sensitive, with beagle puppies treated with nalidixic acid developing arthropathy at half the dose recommended for children (203). In animals, the clinical manifestations of FLQ-induced arthropathy improve over time, but consistently fail to resolve completely (203). Multiple reviews of fluoroquinlone safety in children have been published, and consistently conclude that there may be some association between FLQs and reversible arthralgia in children but there is no evidence for severe or irreversible arthropathy (36, 171, 172, 204-208). Burkhardt and colleagues reviewed 31 published reports of 7,045 children treated with generally short courses of nalidixic acid, norfloxacin, pefloxacin, ciprofloxacin, and ofloxacin and found no reports of arthropathy beyond the severity of what would be expected from the underlying disease process (203). In this review most reported arthropathy was mild/moderate and completely reversible, and the authors estimated a risk of severe arthropathy, similar to the damage seen in

juvenile animals, to be <0.04% (203). In a prospective non-blinded long-term follow-up of 2,345 children treated with short courses of levofloxacin, Noel and colleagues reported a statistically significant increase in musculoskeletal disorders, primarily subjective arthralgia, occurring in 2.1-3.4% of children treated with levofloxacin (209). The authors note that the lack of blinding may have biased these results, particularly as the difference was mainly related to subjective parental reports of arthralgia (209). It has been noted that there is no prospective clinical experience of levofloxacin safety and tolerability in children for treatment lasting more than 14 days (161). Yee and colleagues reported no increased risk of tendon or joint complaints in over 6000 children treated with ciprofloxacin, ofloxacin, or levofloxacin, compared to azithromycin-treated children (210). In studies reporting on joint imaging after FLQ use, no long term abnormalities having been demonstrated in any children (203).

Data on the risk of arthropathy in children on long-term FLQ therapy is limited, but beginning to emerge. A systematic review reporting on adverse effects in 182 children with MDR-TB described a single case of temporary Achilles tendonitis in a child potentially associated with levofloxacin (6). In recently presented data on children receiving ofloxacin 15-20 mg/kg generally for 6 months duration for MDR-TB preventive treatment, 5/189 reported Grade 1 joint/muscle/bone pain, 1/189 Grade 2, and 0/189 Grade 3 or 4 (176). A 2011 review of fluoroquinolone use and safety in children commissioned by the WHO and endorsed by the WHO Essential Medicine Committee, concluded that existing information was sufficient to support their appropriate use in infants and children, and recommended their wide availability for use in children with clear clinical indication in combination with close monitoring (211).

FLQ-associated arthropathy has also been described in adults receiving ofloxacin (212, 213) and moxifloxacin (214) for treatment of TB.

Other

Other adverse effects, including Steven Johnson Syndrome and Toxic Epidermal Necrolysis (175), and dysglycemia (175, 215), have been described but are uncommon with ofloxacin, levofloxacin, and ofloxacin. Hepatotoxicity has been described, but is uncommon, with an estimated incidence of <1 per 100,000, and FDA data reports acute liver failure events per 10 million prescriptions of 2.1 for levofloxacin and 6.6 for moxifloxacin (175). The FLQs are generally considered to be well tolerated in the context of liver disease. Ofloxacin been shown to be safe for use in patients with chronic liver disease (216, 217) and moxifloxacin and levofloxacin in those with anti-TB drug induced hepatitis (218, 219). We did not identify reports of severe skin reactions, dysglycemia, or liver failure or acute liver injury in children receiving FLQs.

Overall Toxicity in TB Treatment Regimens

Though not as robust as the toxicity data for short term FLQ use, there is increasing published experience of the adverse effects associated with prolonged courses of the FLQs in TB treatment regimens in adults. In the treatment of latent TB in adults, multiple studies have reported poor tolerance of the combination of pyrazinamide with ofloxacin (220) or levofloxacin (221, 222), though as previously described, the combination of ofloxacin, high-dose INH, and ethambutol was very well tolerated for MDR-TB preventive therapy in children (176).

Of 53 adults receiving long-term ofloxacin and 10 levofloxacin for MDR-TB, only one patient had an adverse effect necessitating discontinuation of their ofloxacin (223). A case-control study in adults receiving levofloxacin versus those receiving standard first-line TB treatment, found no statistically significant difference in risk of adverse events, despite the fact that many of the patients receiving levofloxacin had experienced previous drug-related adverse events (224). Addition of levofloxacin 500 mg to standard 4-drug treatment in HIV-infected adults did not result in an increase in adverse effects (104). There was no difference in adverse effects between ofloxacin and levofloxacin-containing regimens for a cohort of adult MDR-TB patients (110). No adverse effects were reported in a series of 4 adults with MDR-TB receiving levofloxacin 500 mg twice daily for 9-24 months (225). Moxifloxacin

has generally been safe and well-tolerated in adult TB regimens. The reported risk of moxifloxacin discontinuation is variable, with some cohorts reporting few (142, 226), but others reporting from 10.5 - 21.3% (227, 228). In two TBTC clinical trials, evaluating moxifloxacin substituted in the intensive phase for isoniazid or ethambutol respectively, there was no statistically significant difference in discontinuations between moxifloxacin (14%) and isoniazid (10.7%) (105), or moxifloxacin (10%) and ethambutol (10%) (102). Among 655 Korean adults being treated with first or second-line anti-TB regimens, 112 (17%) patients experienced at least one major adverse drug reaction, though of 377 patients receiving FLQ only 1 (0.003%) experienced a major FLQ-related adverse drug reaction (229). A Cochrane Review of FLQs in the treatment of TB reported no difference in adverse events in FLQ-containing regimens evaluated, except a slightly higher risk of total adverse events (Risk Ratio 1.34, 95% Confidence Interval 1.05-1.72) where a FLQ was substituted for ethambutol in the standard regimen (100).

What data is available suggests that the long term use of FLQs in children with TB is safe and well-tolerated. No adverse effects were reported for a 23-month old and an 11-month old with MDR-TB receiving long-term therapy with moxifloxacin 10 mg/kg once daily (116). In a series of 6 children with MDR-TB treated with moxifloxacin or levofloxacin, 1 child had levofloxacin permanently interrupted because of bilateral metacarpophalangeal polyarthritis, and a second child had bilateral ankle arthralgia which resolved without changing treatment (115). In a systematic review of children with MDR-TB, the majority received FLQs which appeared to be well-tolerated, though the specific risk of FLQ-related adverse effects or drug discontinuations was not reported (6).

2.5 Existing recommendations for the use of oxfloxacin, levofloxacin, and moxifloxacin in paediatric DR-TB

In assessing the systemic use of FLQs in children, an expert panel of the American Academy of Pediatrics (AAP) concluded that FLQs could be used in children where benefits outweigh the risks and no alternative agents are available, in which they included *Mycobacterial* infections known to be susceptible to FLQs (230). Despite what was assessed as Very Low quality of evidence, taking into consideration the risks and benefits, the WHO 2010 Rapid Advice on the Treatment of TB in Children gives a Strong Recommendation for the use of FLQs in the treatment of DR-TB (231). These recommendations did not specify the use of one FLQ over another (231). The current WHO guidelines on the management of DR-TB give a Strong Recommendation to include a fluoroquinolone in the treatment for MDR-TB, based on Very Low Quality evidence, and give a Conditional Recommendation to include a later-generation rather than an earlier-generation FLQ, based on Very Low Quality Evidence (16, 232). No specific recommendations were made in regards to children (232).

Dosing recommendations are in Table 1.2. Ofloxacin is available as 200 and 400 mg tabs, and the recommended dose for children is 15-20 mg/kg given once daily, with a maximum dose of 800 mg (16). Levofloxacin is generally available as 250 or 500 mg tabs. The levofloxacin dose recommended in WHO 2008 guidelines for the management of drug-resistant TB is 7.5-10 mg/kg once daily with a maximum dose of 750 mg (16), though based on age-related differences in levofloxacin pharmacokinetics, others recommend a dose of 7.5-10 mg/kg given once daily for children over five years of age and twice daily for those under 5 years of age (19). A levofloxacin suspension (25 mg/ml) does exist but is not widely available (42). Moxifloxacin is only widely available as 400 mg tabs, with a recommended dose range of 7.5-10 mg/kg with a maximum dose of 400 mg (16). Achieving recommended dosing with the existing tablet formulations requires breaking tablets at times into quarters, which can be challenging, particularly for the smallest children. Moxifloxacin tablets when broken or crushed are very bitter and poorly tolerated.

2.6 Future or Ongoing Studies in Children

A search of www.clinicaltrials.gov and the WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/) identified no registered studies of ofloxacin, levofloxacin, or moxifloxacin in children with TB. A registered study titled "Moxifloxacin in Pediatric Subjects With Complicated Intra-abdominal Infection (MOXIPEDIA)" (NCT01069900) is currently recruiting to evaluate the safety and efficacy of moxifloxacin in children 3 months – 17 years of age with intra-abdominal infection. The Phase I study "Safety, Tolerability and Pharmacokinetics of Single Dose Intravenous Moxifloxacin in Pediatric Patients" (NCT01049022) will evaluate the pharmacokinetics of a single IV dose of moxifloxacin in children aged 3 months to 14 years. Two other registered studies in adults, "A Study to Evaluate the Bioequivalence of an Oral Suspension Formulation, an Oral Solution Formulation, and the Marketed Tablet Formulation of Levofloxacin in Healthy Subjects" (NCT00602589) and "Bioavailability, Food Effect and Safety, Tolerability of a New Oral Suspension in Comparison to the Marketed Moxifloxacin Tablet in Healthy Adults" (NCT01073891) may help to inform future studies of pediatric dosing of levofloxacin and moxifloxacin suspensions.

An ongoing study in Cape Town, South Africa is evaluating the pharmacokinetics, safety, and tolerability of second-line antituberculosis drugs in children, including ofloxacin, levofloxacin, and moxifloxacin. Preliminary data will be disseminated during 2013.

2.7 Conclusions and Recommendations

As demonstrated in this review, the efficacy of ofloxacin, levofloxacin, and moxifloxacin against *Mtb* has been extensively evaluated and consistently demonstrated *in vitro*, in animals, and in humans. These data have also shown the higher potency of the later-generation FLQs levofloxacin and moxifloxacin, relative to ofloxacin. Despite a lack of randomized trials of the FLQs in the treatment of MDR-TB in adults or children, their strong bactericidal and sterilizing activity, favourable pharmacokinetics and toxicity profile have made them the most important component of existing MDR treatment regimens, and they are being used extensively for this indication globally. Depending on data from ongoing trials, it is possible that moxifloxacin may be part of a shorter treatment regimen for drug-susceptible TB, and will likely also be a component of future treatment regimens involving new drugs.

Despite initial concerns about the safety of FLQs in children, the available data to date has not demonstrated serious arthropathy, or other severe toxicity. The FLQs are generally well-tolerated by adults receiving the prolonged treatment required for MDR-TB. The data on extended administration of FLQs to children has not demonstrated serious adverse effects, and based on existing knowledge there is no reason to expect such.

Additional data is needed in regards to paediatric dosing of the FLQs in MDR-TB, particularly for levofloxacin and moxifloxacin, though a current study of the pharmacokinetics of the second-line anti-TB drugs in children with MDR-TB has already presented preliminary data on ofloxacin pharmacokinetics, while evaluation of levofloxacin (in younger) and moxifloxacin (in older children) is ongoing.

In weighing the risks and benefits, the WHO and the AAP have identified drug-resistant TB as an important indication for the use of FLQs in children. Based on this up-to-date summary of the risk and benefits of ofloxacin, levofloxacin, and moxifloxacin in the treatment of drug-resistant TB in children, we would recommend inclusion of levofloxacin and moxifloxacin on the Essential Medicine List, and further recommend that levofloxacin or moxifloxacin be the preferred FLQ for treatment of DR-TB in children. We would recommend that ofloxacin remain on the Essential Medicine List for DR-TB in children, but be used as an alternative agent only where levofloxacin and moxifloxacin are unavailable. We acknowledge that pharmacokinetic data to inform the most appropriate dosing in children of these drugs is urgently needed, and likely to be forthcoming from ongoing studies. We recommended an ofloxacin dose of 15-20 mg/kg once daily. We recommend a levofloxacin dose of

10-15 mg/kg once daily. Pharmacokinetic data would suggest twice daily levofloxacin dosing for children <5 years of age, though with the difficulty in achieving this dose with existing tablet formulations and adherence with twice daily dosing make this challenging. Where levofloxacin suspension is available and adherence assured, the dose could be divided twice daily. We recommend a moxifloxacin dose of 7.5-10 mg/kg once daily, though this can be difficult to achieve in younger children with tablet formulations.

Existing formulations of these drugs are difficult to appropriately dose and administer to children. A suspension formulation of levofloxacin does exist, but is not widely available. We recommend that child-friendly formulations of these drugs, especially for levofloxacin and moxifloxacin be developed and made widely available to children with DR-TB.

3 Aminoglycosides and Cyclic-polypeptides – Amikacin, Kanamycin, and Capreomycin

3.1 Background

3.1.1 Overview

The antibiotics amikacin, kanamycin, and capreomycin are WHO Group II drugs (16), generally considered together because of their similar mechanism of action, pharmacology, requirement for intravenous (IV) or intramuscular (IM) route of administration, and adverse effect profiles. In the context of treatment for drug-resistant TB, they are often referred to together as the second-line injectable (SLI) drugs.

Kanamycin is a product of the *Streptomyces* species of soil bacteria (233). Amikacin is an aminoglycoside antibiotic, which is a semi-synthetic derivative of kanamycin (234). The mechanism of action of aminoglycosides is tight binding to the 16S rRNA in the 30S ribosomal subunit, resulting in a conformational change in the rRNA subunit which prevents mRNA translation and translocation, thus inhibiting protein synthesis (233, 235). Aminoglycosides are minimally protein bound and highly water-soluble, explaining their limited ability to cross lipid-containing membranes (233). Their activity is limited in acidic environments (233, 236). In addition to their demonstrated activity against *Mycobacterium tuberculosis* (*Mtb*), amikacin and kanamycin have good activity against aerobic gram-negative organisms, and may have synergistic activity when used in combination with β-lactam antibiotics (235).

Capreomycin is a cyclic polypeptide antibiotic isolated from *Streptomyces capreolus*, and chemically similar to viomycin (237-239). Despite the fact that capreomycin has been known to have activity against *Mtb* and *Mycobacterium avium* since the 1960s by the inhibition of protein synthesis, the exact mechanism of action has been unclear (237). Only more recently has it been determined that capreomycin binds to sites on the 16s and 23s rRNA subunits, inhibiting translocation by stabilization of tRNA in the A-site of the ribosome, though there may be additional mechanisms of action (240, 241). Binding of capreomycin and viomycin requires methylation of these rRNA sites by the enzyme encoded by the *tlyA* gene, a recent discovery important in understanding the molecular resistance patterns of the SLI drugs (242, 243).

3.1.2 Approved indications

Amikacin was first approved by the U.S. FDA, with an Abbreviated New Drug Application approved in 1981 (42). The approved indication in the U.S. is the short-term treatment of serious infections due to susceptible strains of Gram-negative bacteria (42). Kanamycin was first approved by the U.S. FDA, with an Abbreviated New Drug Application approved in 1973 (42). The approved indication is the short term treatment of serious infections caused by susceptible strains of micro-organisms (42). Capreomycin was first approved by the U.S. FDA in 1971 for the indication of use in pulmonary infections caused by capreomycin-susceptible strains of Mtb when the primary agents have been ineffective or cannot be used because of toxicity or the presence of resistant bacilli (42).

3.1.3 Cost

The costs of amikacin, kanamycin, and capreomycin are listed below in Table 3.1 (42). In addition to the 500 mg/2 ml solution for injection, amikacin also exists as 500 mg/2ml and 100 mg/2 ml solution for injection, and 100 mg, 500 mg & 1 gram powder for injection, though prices were not listed for these formulations (42). Kanamycin is also available as 1 gram/4 ml, 500 mg/2 ml, and 1 gram/3 ml solution for injection, and as 1 gram powder for injection (42).

Table 3.1 – Price of amikacin, kanamycin, and capreomycin by manufacturer (Price in U.S. dollars of the lowest unit – one capsule, one tablet, or one vial) (42)

	Cipla	Medo-chemie	Mac-leods	Pan-pharma	Micro labs	Akom	Vianex	GDF pooled procurement price
Amikacin 500 mg/2 ml solution for injection	3.250	0.990	--	--	--	--	--	0.962 (Medochemie) 2.950 (Cipla)
Kanamycin 1gram powder for injection	--	--	1.510	0.748	--	--	--	0.790 (Panpharma)
Kanamycin 1 gram/4 ml solution for injection	--	--	--	--	--	--	--	2.580 (Meiji)
Capreomycin 1 gram powder for injection	--	--	7.720	--	--	6.250	†	8.000 (Akorn) 5.340 (Vianex)*

GDF = Global Drug Facility
† Manufacturer did not agree to publish price in source document

3.2 Summary of efficacy data

3.2.1 In vitro activity against Mycobacterium tuberculosis

The SLI drugs have potent *in vitro* activity against *Mtb* strains, with amikacin generally having stronger activity than kanamycin, streptomycin, and capreomycin (244-253). Against *Mtb* H37Rv, amikacin had a Minimum Inhibitory Concentration (MIC) of 0.2 µg/ml and an Minimum Bactericidal Concentration (MBC) of 0.4µg/ml, which was equivalent to that for isoniazid, 4-fold lower than that of kanamycin and 16-fold lower than streptomycin (245). A separate study attributed less potency to amikacin than streptomycin and equivalent to kanamycin, based on *in vitro* MIC (246). In an evaluation of aminoglycoside and aminocyclitol *in vitro* activity against clinical *Mtb* isolates by Ho and colleagues, streptomycin and amikacin showed equivalent activity, with MIC_{90} of 1 µg/ml, which were 2 and 4-fold lower than for capreomycin and kanamycin respectively (248). In a report from de Steenwinkel et al, amikacin had strong concentration-dependent and rapid killing of *Mtb*, that was superior in comparison with other agents in its effect against organisms with both high and low metabolic activity (249). Jureen and colleagues found that among drug-susceptible *Mtb* clinical isolates, the epidemiological cut-off value (ECOFF) in Middlebrook 7H10 medium for amikacin (1 µg/ml) was lower than that for kanamycin (4 µg/ml), capreomycin (4 µg/ml), streptomycin (2 µg/ml) and viomycin (2 µg/ml), resulting in favorable pharmacodynamics for amikacin for almost all susceptible strains based on known pharmacokinetics (250). Early *in vitro* experiments with capreomycin showed it to have about half the inhibitory activity of streptomycin or kanamycin, and a tenth the activity of INH (254).

The WHO recommended critical concentrations for DST for amikacin, kanamycin, and capreomycin are listed in Table 3.2 (60, 64).

Table 3.2 Suggested critical concentrations for drug susceptiblity testing of amikacin, kanamycin, and capreomycin (in µg/ml)†

	Lowenstein-Jensen medium	Middlebrook 7H10	Middlebrook 7H11	Bactec460	MGIT960
Amikacin					
WHO 2008 (60)	--	--	--	1.0	1.0
WHO 2012 (64)	*30.0*	*4.0*	--	--	*1.0*
Kanamycin					
WHO 2008 (60)	30.0	5.0	6.0	4.0	--
WHO 2012 (64)	*30.0*	*5.0*	*6.0*	--	*2.5*
Capreomycin					
WHO 2008 (60)	40.0	10.0	10.0	1.25	2.5
WHO 2012 (64)	*40.0*	*4.0*	--	--	*2.5*

† Tentative updated recommendations in *italics*

Sterilizing activity is dependent on the ability to kill dormant or nonreplicating persistent *Mtb*. In an *in vitro* model of persistent organisms, Heifets and colleagues showed that among all the antituberculosis drugs, which included amikacin, only capreomycin and metronidazole had activity against non-replicating *Mtb* in anaerobic conditions (255). A subsequent study demonstrated that both amikacin and capreomycin had low-level activity against dormant *Mtb in vitro*, suggesting that protein synthesis does occur in non-replicating dormant organisms and that these drugs may have activity in this context (71). In addition, amikacin and capreomycin made key contributions in combination with rifampicin, moxifloxacin, and metronidazole to the complete killing of organisms in this in-vitro model of dormant *Mtb* (71). Again amikacin and capreomycin were shown to have relatively potent activity against nonreplicating persisters in anaerobic conditions, with amikacin having the same MIC of 0.5 µg/ml in both aerobic and anaerobic conditions (247). The limited ability to target intracellular organisms means that the SLI drugs have poor activity against *Mtb* residing within host macrophages, which may explain the lack of sterilizing activity *in vivo*, though much remains unknown in this regard (236, 247, 251).

3.2.2 Activity in animal models

In a murine model of TB, a 10 mg/kg dose of amikacin was shown to be more potent than a 25 mg/kg dose of streptomycin, as measured by macroscopic surface lung lesions and lung *Mtb* colony forming units (245). Further evaluation showed that a 10 mg/kg dose of amikacin was 5-fold and 17-fold more effective than 10 mg/kg doses of streptomycin and kanamycin respectively, as measured by *Mtb* lung colony forming units (245). Additionally, amikacin appeared to show increasing effectiveness with progressively larger doses, up to 15 mg/kg, the highest dose evaluated in this study (245). Lounis et al. obtained similar results showing that amikacin was more bactericidal in mice than streptomycin, kanamycin, or isepamicin at the same doses (72). A study of streptomycin in a mouse model of chronic TB, even in very high doses, added very little sterilizing activity when used in combination with isoniazid and rifampicin, and long term results in mice treated with isoniazid and rifampicin were much better than in those treated with much longer courses of isoniazid and streptomycin (256). In early evaluations of capreomycin, TB infected mice treated with doses of capreomycin of 250 mg/kg, 500 mg/kg, 1000 mg/kg, had much reduced mortality, lung necrosis, and TB bacilli on lung histology, compared to untreated mice and those receiving a 5 mg/kg dose (257).

3.2.3 Activity in human TB

Though *in vitro* and animal studies consistently demonstrated the activity of amikacin, kanamycin, and capreomycin against *Mtb*, studies in humans have been less clear. A study of the early bactericidal activity (EBA) of amikacin in a group of adult patients found just detectable EBAs of 0.0405, 0.0453, and 0.0518 respectively for amikacin doses of 5 mg, 10 mg, and 15 mg (258). The authors postulated that this finding, contrasting with *in vitro* and animal studies, may be related to the reduced activity of aminoglycosides in the acidic environment present in cavities with active TB and ongoing inflammation, inactivation of aminoglycosides by leukocytes, and poor penetration into fibrosclerotic cavities (258-260). It was suggested that amikacin and other aminoglycosides may have improved activity further into the treatment period, when inflammation has reduced and the environment may become more neutral or alkaline (258). Data has demonstrated that streptomycin, and presumably amikacin, kanamycin, and capreomycin, play a role in preventing the emergence of resistance to companion drugs during combination therapy (24, 256).

Despite *in vitro* evidence of bactericidal activity against *Mtb* which is dormant or with low metabolic activity, the clinical evidence suggests limited *in vivo* sterilizing activity of the SLI agents (24). A study of bactericidal and sterilizing activities of antituberculosis drugs in the first 14 days of treatment attributed a small degree of potentially sterilizing activity to streptomycin in multivariate analysis, noted in the first 2-6 days of treatment (261). This is consistent with an increased rate of culture conversion at one month in adults given streptomycin in addition to isoniazid, rifampicin, and pyrazinamide, though there was no difference at two months in the two groups (262). In a careful review of studies

carried out by the British Medical Research Council, streptomycin appeared to have slight sterilizing activity as measured by relapse rates in some studies, but which never reached statistical significance (263).

An early study of amikacin in the treatment of TB in a small number of patients was disappointing, with 4/4 patients failing to respond to amikacin-containing treatment and with amikacin-resistance emergence in 3/4 (264). Though not effective in the treatment of these patients, the emergence of resistance implies some activity of amikacin, as it generated sufficient pressure to select for resistant mutants. This small series should be interpreted cautiously, as the amikacin doses were low, with three of the patient receiving a dose of 500 mg daily, and the fourth initially at 750 mg daily then at 250 mg daily (264).

Perhaps the most compelling evidence for the role of these drugs in current TB management comes from the worse outcomes in patients with multidrug-resistant (MDR)-TB who have additional resistance to the SLI drugs. Patients with extensively drug-resistant TB (XDR-TB), which includes resistance to one of the second-line injectable drugs (3), consistently have worse outcomes than patients with MDR-TB susceptible to the fluoroquinolones and the SLI (265-267). An evaluation of the impact of SLI-resistance among adults with MDR-TB showed that additional capreomycin-resistance was associated with an increased risk of treatment failure and death, though the risk of unfavourable outcomes among patients with amikacin- or kanamycin-resistance was not increased (268). A small adult cohort from the U.S. demonstrated that those with MDR-TB and those with MDR with additional resistance to a fluoroquinolone and streptomycin had roughly equivalent outcomes, and both had much better treatment success than those with XDR-TB, suggesting an important role for the SLI drugs (269). In a larger cohort from South Korea, those with MDR-TB with additional resistance to a SLI had lower rates of successful treatment and increased all-cause mortality relative to those with MDR-TB with SLI-susceptibility (265). Three recent individual patient data (IPD) meta-analyses add some additional information. The first included data from 9,153 patients from 32 observational cohorts, and reported that the use of kanamycin or amikacin or capreomycin versus no injectable was not associated with successful treatment outcome, though the small number of patients who did not receive an injectable agent is a limitation of that analysis (106). The second IPD meta-analysis showed that of patients with XDR-TB, those who had resistance to both an aminoglycoside (kanamycin or amikacin) and to capreomycin had a significantly lower odds of success compared to those with XDR alone (aOR 0.4, 95% Confidence Interval 0.2-0.8), which would suggest an important role of these drugs in XDR-TB (270). The third IPD meta-analysis found that the adjusted odds ratios of treatment success versus treatment failure, relapse or death, for those with MDR-TB and SLI-resistance, MDR-TB and fluoroquinolone resistance, and XDR-TB, compared to MDR-TB alone were 0.6, 0.4, and 0.2 respectively (109). There is little data in children, though in a subgroup analysis in a systematic review of paediatric MDR-TB, treatment success was higher in studies in which most patients received injectables compared to studies where they were uncommonly used (87.2% versus 62.6%, p=0.02) (6). Despite some discrepancies, taken together these data provide some evidence for the current role of amikacin, kanamycin, and capreomycin in the treatment of drug-resistant TB in adults and children.

3.2.4 Resistance

There is little cross-resistance of the SLI drugs to other antituberculosis drugs (271). Amikacin, kanamycin, and capreomycin generally retain activity in streptomycin-resistant strains. Amikacin and kanamycin have high-levels of cross-resistance with each other, and variable rates of cross-resistance to capreomycin (264), though there is still much unknown about the resistance of *Mtb* to these drugs (272).

3.3 Pharmacokinetics and Pharmacodynamics

3.3.1 Pharmacokinetics

The pharmacokinetics of capreomycin, amikacin, kanamycin, and streptomycin are very similar and the same general approach can be used for dosing and monitoring these drugs (170, 273-276). A major disadvantage of the SLI drugs is that they are rapidly degraded when given orally, and can only be given intramuscularly or intravenously. Aminglycosides are generally absorbed completely after intramuscular injection, and the pharmacokinetics of IV and IM amikacin are essentially the same, though for IM dosing there is not as strong of a linear relationship between increasing dose and Cmax, possibly related to variability in absorption (233, 277, 278). Aminoglycosides are known to cross poorly into the cerebrospinal fluid in the absence of inflamed meninges, and do diffuse into bronchial secretions, but don't achieve levels as high as plasma, with plasma/sputum ratios of roughly 0.25 (233, 279-281). Of particular relevance in TB, penetration of capreomycin and kanamycin into fibro-sclerotic tuberculous cavities is poor (260). Over 99% of aminoglycosides are excreted unchanged by the kidney (233), with age-related changes in renal clearance being important in the pediatric pharmacokinetics (282). Large interpatient variability in the pharmacokinetics may make therapeutic drug monitoring a potentially valuable strategy (282-284).

The pharmacokinetics of amikacin have been shown to vary in children according to age, and one study showed that among 6 neonates (6-25 days old), 10 infants (4-18 months) and 8 young children (3-11 years), the t½ of IV amikacin was 2.812, 1.803 and 1.196 h, respectively (285). Though there is pharmacokinetic data on amikacin and kanamycin in children, to our knowledge evaluations in children with TB have not been previously reported. Appendix 1, Table A-4 shows some of the published pharmacokinetics of amikacin in adults with TB, and in children with other conditions (235, 258, 274, 279-281, 286-294). Appendix 1, Table A-5 shows the published pharmacokinetics of kanamycin in adults with TB and in children with other conditions (295-298). There are some published studies of capreomycin pharamacokinetcs in animals (299-304), but limited human data (see Appendix 1, Table A-6) (237, 254, 276). We are unaware of published pharamacokinetics of capreomycin in children. Preliminary data from an ongoing study of the pharmacokinetics of amikacin in children with DR-TB presented at the 2012 Union World Conference on Lung Health in Kuala Lumpur, Malaysia, is shown in Appendix 1 Table A-4. With a dose of 20 mg/kg IM, C_{max} values were above the suggested adult targets of 35-45 µg/ml for a large percentage of the patients. Considering these relatively high values in the context of the substantial risk of hearing loss in our patient population, we are now evaluating the pharamacokinetics and safety with dosing amikacin at 15 mg/kg IM daily, which we think may be sufficient.

3.3.2 Pharmacodynamics

Aminoglycosides generally show concentration-dependent killing (305). Against gram-negative organisms, pharmacodynamic parameters most closely associated with efficacy were the ratio of area under the concentration-time curve (AUC) to minimum inhibitory concentration (MIC) (AUC/MIC), and maximum serum concentration to MIC (C_{max}/MIC), though specific data for *Mtb* is lacking (305-309). A ratio of C_{max}/MIC >12 is thought to result in maximum killing, with a ratio of >8-10 giving effective bactericidal activity, and a ratio of <4 resulting in poor activity (309). Aminoglycosides have a substantial post-antibiotic effect, meaning they continue to suppress bacterial growth after limited exposure to the agent, though at least some of this effect may be due to continued activity of AGs even when below the MIC (sub-MIC effect) and post-antibiotic leukocyte effect, in which organisms pretreated with antibiotics are more susceptible to leukocyte killing (305). It has been suggested that in the treatment of TB, dosing of amikacin and other aminoglycosides should target a C_{max} of 35-45 µg/ml for daily administration, and 65-80 µg/ml for twice-weekly administration, though precise targets based on pharmacokinetic-pharmacodynamic data in humans are not known (170).

3.4 Safety Data

The aminoglycosides and cyclic-polypeptides are well known to cause nephrotoxicity, ototoxicity, vestibular toxicity, and electrolyte abnormalities, with other more rare adverse effects seen occasionally (310). An early review of aminoglycoside-associated toxicity in children concluded that

toxicity in infants and children has not been rigorously evaluated, but that a lack of reports of well-known adverse effects in children suggests that they are generally well-tolerated (311). This assertion is supported by more recent systematic reviews in neonates and in patients with cystic fibrosis which report limited toxicity of short courses of aminoglycosides (312, 313), but limited data exists on the more prolonged courses used in MDR-TB treatment.

Nephrotoxicity and Electrolyte Abnormalities

Aminoglycoside-induced nephrotoxicity is reversible, and is related to uptake of aminoglycosides by renal tubular cells after glomerular filtration, with intracellular accumulation and subsequent tubular necrosis by an as yet undetermined mechanism, generally resulting in oliguric renal failure (314). The uptake into tubular cells is a saturable process, suggesting that higher, less frequent dosing might attenuate nephrotoxicity (314), which has been confirmed by studies of extended-interval dosing of aminoglycosides in adults (315). A meta-analysis of extended-interval aminoglycoside dosing in children did not demonstrate any difference in nephrotoxicity between extended-interval and more frequent dosing, though because this adverse effect is less common in children demonstrating a difference would be difficult (316, 317). In 2 adult cohorts treated for MDR-TB, 9.8% (318) and 9.3% (319) had nephrotoxicity during treatment by their different definitions. Nephrotoxicity has generally not been a common problem among children with MDR-TB, with 1 of 182 children in recent systematic review reported to have an asymptomatic elevation in creatinine (6). In our anecdotal experience nephrotoxicity is very unusual.

Aminoglycosides and capreomycin are thought to produce hypokalemia, hypomagnesemia, and hypocalcemia by inducing renal wasting of these electrolytes, and by induction of secondary hypoaldosteronism which results in urinary loss of magnesium and potassium (320). These electrolyte abnormalities have been associated with high cumulative doses of these drugs, and occur at a frequency of about 4.5% for aminoglycosides (320, 321). The risk appears to be higher with capreomycin, occurring in between 4-15% of patients on prolonged capreomycin (320, 322, 323). In a cohort of 115 adults with MDR-TB, 34.8% had an electrolyte abnormality during the course of treatment, with 31.3% having hypokalemia, 15.7% hypomagnesemia, and 12.2% both (320). Despite the frequency of magnesium abnormalities, it generally accompanied hypokalemia and followed 2-3 months after, which led the authors to conclude that screening for serum potassium was sufficient (320). Among those receiving capreomycin 68.2% had hypokalemia, and in multivariable analysis use of capreomycin and low baseline weight were associated with hypokalemia (320). Hypokalemia was noted in 33.2% of an adult MDR-TB cohort in Russia, resulting in the discontinuation of capreomycin in 7.4% of patients (318). In a cohort of XDR-TB patients in South Africa, 6 of 67 patients died due to the presumed capreomycin-associated adverse events of rapidly progressive renal failure (n=5) and hypokalemia (n=1), a median of 14 days after starting capreomycin (112). In contrast to adults, electrolyte abnormalities in children treated for MDR-TB are unusual, and were reported in 1 of 182 children in a recent systematic review (6). Despite routine screening of serum potassium every two months in children on aminoglycosides or capreomycin, electrolyte abnormalities are rare in our experience.

Ototoxicity

Though much is known about the mechanism of aminoglycoside-induced ototoxicity, many questions still remain. Aminoglycosides enter cochlear hair cells very early after infusion, through a membrane channel which may act as a one way valve, and as they are not metabolized, can remain in hair cells for prolonged periods of time (324). Similarly to the kidneys, uptake into inner ear tissues appears to be a saturable phenomenon, with continuous infusion resulting in markedly higher inner ear tissue levels than discontinuous dosing in rats (325-327). Through generation of reactive oxygen species formed by the creation of aminoglycoside complexes with Fe, as well as by interactions with the 12s subunit of mitochondrial rRNA, aminoglycosides result in disruption of hair cell mitochondrial integrity and leakage of pro-apoptotic factors into the cytoplasm resulting in cell death (324). This damage begins at high frequencies, above the range of normal speech, and progresses to lower frequencies over time, explaining why patients may not report subjective hearing difficulty early on (324). To date,

at least 6 genetic mutations in the mitochondrial gene encoding 12s rRNA (*MT-RNR1*) have been identified which confer an increased risk of ototoxicity (324, 328-330). Interestingly, these mutations appear to increase the similarity of mitochondrial to bacterial rRNA, which results in an increased affinity of aminoglycosides to mitochondrial rRNA with resultant decreased mitochondrial protein synthesis (324).

The identification of factors able to reliably classify individuals at higher risk for ototoxicity remains elusive. A study among adult patients with cystic fibrosis receiving aminoglycosides demonstrated hearing loss in 7/38 (18%), which was associated in multivariate analysis with trough concentrations >10µg/ml for amikacin or >2µg/ml for gentamicin/tobramycin (331). In other evaluations, neither peak nor trough concentrations appear to be related to ototoxicity, though age, duration of use, and cumulative dose have been associated (326, 332). In a study of hearing loss in 3 combined trials of aminoglycosides, trough concentration and age were associated with ototoxicity in univariate analysis, but only age remained associated in multivariate analysis (333). Despite the animal data suggesting that extended interval dosing of aminoglycosides might decrease their ototoxicity (325, 327, 334), data in humans have not shown such a benefit (274, 315). In a study comparing a daily dose of streptomycin, kanamycin, or amikacin of 15 mg/kg (5 days a week) versus a three-times weekly dose of 25 mg/kg, there was no difference in risk of hearing loss between the daily and thrice-weekly groups (274). Neither dose size in mg/kg nor C_{max} were associated with risk of hearing loss (274). All patients had 24 hour troughs below 2µg/ml, and all had calculated troughs below 0 at 48 hours (274). Older age, total dose and the related duration of treatment, were associated with ototoxicity (274). For every 10-fold increase in total dose received, the risk of hearing loss increased 6.9-fold (274). Streptomycin was much less ototoxic than kanamycin or amikacin in this study, though the risk of ototoxicity of the agents relative to each other varies in the literature (274). Concomitant use of loop diuretics (335, 336), or iron (337) with aminoglycosides may increase the risk of ototoxicity, while aspirin (338, 339), iron chelating agents (340, 341), and other antioxidants may play a protective role, though further evaluation is needed (324).

Data on the toxicity of prolonged courses of SLI agents given to patients with drug-resistant-TB is limited, but growing. A recent review of hearing loss in patients treated for MDR-TB demonstrated high variability in the quality of reporting, methods of assessments, and definitions of ototoxicity, limiting the ability to draw robust conclusions (342). Though most of these studies reported less than 10% of patients experiencing hearing loss, there was a wide range, with rates as high as 50% reported (342). In a cohort of 153 South African MDR-TB patients treated with SLIs, 57% developed high-frequency hearing loss, with HIV-infected individuals having a higher risk (70%) (343). Despite the known association of hearing loss with mitochondrial mutations, none of these 153 had mutations in the *MT-RNR1* gene, and given the population frequency of these mutations, it is unlikely that they are implicated in the majority of patients having ototoxicity (328, 343).

Using a strict definition of hearing loss, a recent retrospective analysis of a cohort of children treated for MDR-TB reported that 24% had documented hearing loss, highlighting the frequency and importance of this adverse event (344). In two other cohorts, 2/38 (6.7%) and 1/10 (10%) of children were reported to have hearing loss (6, 345, 346). Accurately assessing hearing in young children can be a challenge. Though less frequent than in adults with MDR-TB, hearing loss in children during critical periods of language development may have a more profound impact on speech and overall development, and strategies which maintain the efficacy of MDR-TB treatment regimens but limit ototoxicity are therefore urgently needed.

3.5 Existing recommendations for the use of amikacin, kanamycin, and capreomycin in paediatric DR-TB

Kanamycin and capreomycin are available as 1 gram vials. Amikacin is available in vials ranging from 100 mg up to 1 gram, which is an advantage for efficient dosing in children. The recommended dose

for amikacin is 15-22.5 mg/kg once daily, and for kanamycin and capreomycin is 15-30 mg/kg once daily (See Table 1.2).

The most up-to-date guidance from the World Health Organization recommends an 8-month long intensive phase, increased from 6 months in previous guidelines, which would generally include a SLI drug (232), though children will rarely require treatment with a SLI drug beyond 6 months, and often do equally well with shorter courses (114) (Unpublished data – James Seddon, H Simon Schaaf, et al).

3.6 Future or Ongoing Studies in Children

A search of www.clinicaltrials.gov and the WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/) revealed no registered studies of amikacin, kanamycin, or capreomycin in children with TB. An ongoing study in Cape Town, South Africa is evaluating the pharmacokinetics, safety, and tolerability of second-line antituberculosis drugs in children, including amikacin (in addition to data presented in Appendix 1 Table A-4 data will be disseminated during 2013).

3.7 Conclusions and Recommendations

Despite some inconsistencies, the abundance of the current evidence supports the current important role of kanamycin, amikacin, and capreomycin in the treatment of MDR and XDR-TB in children. The appropriate treatment of most children with MDR-TB will require one of the SLI drugs, which should be made available for children. Nephrotoxicity and electrolyte abnormalities are rare in children. Ototoxicity appears to be less frequent than in adults, but is still an important and serious adverse effect in a substantial proportion of children. Strategies to limit the toxicity, including optimizing the dose and duration of these drugs, need urgent evaluation.

We recommend that amikacin, kanamycin, and capreomycin remain Essential Medicines for the treatment of drug-resistant TB in children. Based on the preliminary data presented here showing high amikacin concentrations in children with a 20 mg/kg dose relative to proposed target values, we would recommend a dose range for these drugs of 15-20 mg/kg, and would not routinely exceed 20 mg/kg/dose when giving them once daily.

Despite differences in their *in vitro* potency, all three drugs are generally considered equivalent for treatment of MDR-TB, and those caring for children with DR-TB should use whichever is available in their setting. In our practice we use amikacin most commonly in children, first because it seems to have a lower MIC compared with kanamycin and capreomycin, and second because of the smaller vial sizes for less wasteful dosing, though others have suggested amikacin be the last choice among these drugs (347). We recommend capreomycin be made available for children who have XDR-TB resistant to amikacin and kanamycin.

4 – Ethionamide and Prothionamide

4.1 Background

4.1.1 Overview

2-ethyl thioisonicotinamide, now ethionamide, was synthesized in 1956 by Grumbach and colleagues and later reported to have anti-mycobacterial activity (348). Prothionamide is the propyl analog of ethionamide (349). Ethionamide (ETH) and prothionamide (PTH) are structurally similar to isoniazid (350). Both are prodrugs which are activated by the flavin monoxygenase enzyme EthA, encoded by the *ethA* gene (350). The activated ETH and PTH form adducts with NAD which are tight binding inhibitors of the InhA enzyme in *Mtb*, also the target of isoniazid, and inhibit mycolic acid synthesis (350, 351). ETH and PTH are generally considered interchangeable, and in addition to their use in treatment of *Mtb* are also used in the treatment of leprosy (350).

4.1.2 Approved indications

Ethionamide first received U.S. FDA approval in 1965, and is approved for the treatment of active TB resistant to isoniazid or rifampicin, or where the patient is intolerant of other drugs (42). Prothionamide was first marketed in Germany in the 1970s but registered in the framework of posterior registration process in Germany in 2005 and approved by the German Federal Institute for Drugs and Medical Devices for the following indications: treatment of all forms and stages of pulmonary and extrapulmonary TB as second-line drug in the case of proven multidrug-resistance against first-line drugs; treatment of diseases caused by ubiquitous (atypical) mycobacteria; treatment of leprosy in the context of modified therapy regimens (42).

4.1.3 Cost

Table 4.1 – Price of ethionamide and prothionamide (Price in U.S. dollars of the lowest unit – one capsule, one tablet, or one vial) (42)

	Cipla	Lupin	Macleods	Micro-labs	Pfizer	Fatol	Olain-farm	GDF pooled procure-ment price
Ethionamide 250 mg tab	0.091	†	0.095	0.078	†	--	--	0.080 (Cipla) 0.073 (Macleods) 0.0079 (Lupin)
Prothionamide 250 mg tab	--	†	--	0.080	--	0.126	0.140	0.127 (blister) (Fatol) 0.080 (bottle) (Lupin)

GDF = Global Drug Facility
†Manufacturer did not agree to publish prices in source document

4.2 Summary of efficacy data

4.2.1 In vitro activity against Mycobacterium tuberculosis

Ethionamide and prothionamide have shown bactericidal activity *in vitro* against *Mtb*, with PTH MICs usually reported as either equal to or half that of ETH (251, 348, 352-356). Proposed critical concentrations for ethionamide are listed in Table 4.2 (60, 62, 64, 357). Schon and colleagues also reported ethionamide wild-type MICs, or ECOFFS, also listed in Table 4.2 (354). Rastogi and colleagues suggested critical concentrations for ethionamide in Bactec460 of ≤1.25 for susceptible, 2.5 for intermediate, and ≥5.0 for resistant (251). Reproducibility of ETH and PTH MICs is known to be problematic (354).

Ethionamide has shown intracellular activity against *Mtb* in human macrophages (251).

Table 4.2 Proposed critical concentrations (in µg/ml) for ethionamide and prothionamide against *Mycobacterium tuberculosis*

	Lowenstein-Jensen medium	Middlebrook 7H10	Middlebrook 7H11	Bactec460	MGIT960
Ethionamide					
Pfyffer GE, et al. 1999 (357)	--	5.0	--	1.25	--
Rusch-Gerdes S, et al. 2006 (355)	--	--	--	2.5	5.0
Schon T, et al. 2011 (354)	--	2.0	--	--	--
Kam KM, et al. 2010 (62)	40	2.0-3.0	--	1.0	--
WHO 2008 (60)	40	5.0	10.0	2.5	5.0
WHO 2012 (64)	40	5.0	10.0	--	5.0
Prothionamide					
Rusch-Gerdes S, et al. 2006 (355)	--	--	--	1.25	2.5
Schon T, et al. 2011 (354)	--	1.0	--	--	--
WHO 2008 (60)	40	--	--	1.25	2.5
WHO 2012 (64)	40	--	--	--	2.5

4.2.2 Activity in animal models

Multiple studies have shown activity of ETH and PTH in animals (58, 81, 358, 359). In a mouse model of TB, the combination of gatifloxacin and ethionamide was not different than isoniazid and rifampicin, which suggested the potential of a fluoroquinolone-ethionamide combination (360). Similarly, Fattorini and colleagues demonstrated enhanced activity over moxifloxacin alone when moxifloxacin was combined with ethionamide, which was not shown with other second-line drugs tested (81).

4.2.3 Activity in human TB

After discovery of its activity against *Mtb in vitro* and in animals, ethionamide was evaluated in a number of studies in multiple different combinations, often in patients with resistance to streptomycin, PAS, and INH, where it was found to have some activity when combined with other drugs, but its use was often limited by poor tolerabilitiy (361-366). In a trial in adults comparing ethionamide 500 mg in two divided doses versus prothionamide 500 mg in two divided doses in combination with INH and streptomycin, there was no difference in treatment efficacy, with 98% and 96% respectively having negative cultures at 6 months (367).

As with many of the other older second-line agents, as other more active and well-tolerated drugs were developed, ETH and PTH use declined significantly, though the growing burden of MDR-TB has led to resurgence in interest in them. The contribution of ETH/PTH to current MDR treatment regimens was highlighted in an individual-patient meta-analysis of over 9,153 patients with MDR-TB, in which use of ETH or PTH was associated with an increased odds of treatment success versus failure or relapse (aOR 1.7, 95% CI 1.3-2.3) and versus failure, relapse or death (aOR 1.7, 95% CI 1.4–2.1) (106) .

In children, ETH has been well-tolerated and efficacious when used at a dose of 20 mg/kg in an intensive regimen for treatment of TB meningitis (368). ETH was a component of the usual treatment regimens in all the cohorts included in a recent systematic review of children with MDR-TB, which reported a pooled treatment success of 81.67% (6).

4.2.4 Resistance

ETH and PTH are generally considered to have complete cross-resistance (369). Even in very early descriptions of the antimycobacterial activity of ETH, it was noted that the risk for resistance development is high and ETH should be given with other tuberculostatic drugs (348, 353). Ethionamide resistance may result from mutations in the *ethA* gene, in the *inhA* promoter region, or

less commonly mutations in the *inhA* structural gene (370). Mutations in the *inhA* promoter region or structural gene result in low/intermediate resistance to isoniazid, but there is no cross-resistance with *ethA* mutations (370-372).

4.3 Pharmacodynamics and Pharmacokinetics

4.3.1 Pharmacokinetics

Both ETH and PTH are rapidly absorbed after oral administration and have relatively short half-lives of roughly 2 hours (373). The sulphoxide, the main metabolite, which has anti-mycobacterial properties, is further converted to multiple other metabolites (373). Less than 1-2% of ETH or PTH or their sulphoxide metabolites are recovered in urine or faeces, and some other metabolites have been recovered in urine, though there is still much unknown about the specifics of ETH/PTH elimination (373). ETH has good tissue penetration, with a ratio of epithelial lining fluid to serum concentration of 9.7 in a study by Conte and colleagues (374). Cerebrospinal fluid (CSF) penetration was shown to be good (145). An early study in adults documented later CSF peak concentrations relative to serum, around 3 hours, and that overall CSF concentrations were similar to serum regardless of meningeal inflammation (375). An evaluation in children, CSF ethionamide concentrations exceeded a target concentration of 2.5 µg/ml in 11 of 13 occasions (85%) after a dose of 20 mg/kg, compared to 7 of 26 occasions (26%) after a 15 mg/kg dose (376).

In healthy volunteers, the T_{max} was slightly prolonged when ethionamide was given with antacid or with food (2.3 to 2.6 hours) compared to when it was given on an empty stomach or with orange juice, but this was not statistically significant (377). There was no statistically significant difference in Cmax or AUC when ethionamide was given under fasting conditions, with orange juice, food, or antacids (377). Adults with TB had lower AUCs compared to healthy volunteers, and absorption was highly variable, with delayed absorption and flat concentration-time curves seen commonly (378).

In a single study of prothionamide and ethionamide in healthy adult volunteers, prothionamide had a slightly shorter $t_{1/2}$, and slightly lower plasma concentrations than ethionamide (369). In adults with TB, there was no substantial difference in prothionamide pharmacokinetic parameters in those with low BMI compared to a normal BMI (379).

A single study describes the pharmacokinetics of ethionamide in children with TB (380). Children less than 2 years of age had significantly lower AUC and C_{max}, and more rapid absorption and elimination, compared to older children (380). HIV-infection was associated with reduced exposure, but not with delay in absorption or elimination (380). Pharmacokinetic parameters were not affected by rifampicin co-administration, body mass index, mid-upper-arm circumference, or weight-for-age Z-scores (380). With a dose of 15-20 mg/kg, the mean serum level of ethionamide was above 2.5 µg/ml in all age groups, though there was substantial inter-individual variation, and after 4 months of therapy 7/31 children had a C_{max} below this level (380). In the two children included in a study by Zhu and colleagues, a 12.3 year old had a C_{max} of 0.48 µg/ml and AUC of 1.00 µg-h/ml after a 250mg dose, and a 6.7 year old had a C_{max} of 1.11 µg/ml and an AUC of 9.88 µg-h/ml after a 250mg dose (378). We are not aware of any pharmacokinetic studies of prothionamide in children.

Appendix 1, Tables A-7 and A-8 show the results of published pharmacokinetic evaluations of ethionamide and prothionamide respectively in adults and children with TB (349, 369, 378-380).

4.3.2 Pharmacodynamics

The pharmacodynamics of ethionamide and prothionamide in TB are not well described. Target levels of 2.5 µg/ml, and between 1 – 5 µg/ml have been suggested (170, 380), but precise targets are not known. Based on a population pharmacokinetic model, 250mg given twice or three times daily failed to achieve a C_{max}/MIC>1, AUC>MIC, or %Time>MIC (378). A dose of 750 mg once daily achieved the highest AUC>MIC, followed by a 500 mg twice daily dose (378).

4.4 Safety Data

Gastrointestinal adverse effects

Gastrointestinal (GI) intolerance is a well-known adverse effect of both ethionamide and prothionamide. In an early evaluation of retreatment regimens containing ethionamide at a dose of 750-1000 mg divided 3-4 times daily, Kass and colleagues reported that almost all patients reported some degree of GI intolerance which usually improved or resolved within 2-3 weeks without dose adjustment (381). In 26% of their patients the GI intolerance was sufficiently serious to switch to the suppository form of ethionamide (381). The GI intolerance had immediate and delayed components, consisting of anorexia, metallic taste, nausea, vomiting, sialorrhea, upper abdominal discomfort, and diarrhea (381). GI intolerance is known to be a common adverse effect of ETH in children as well, but has not been rigorously described. In the first few weeks of treatment, giving the once daily dose twice daily has been recommended to improve tolerability in children (19).

There is a suggestion that prothionamide may be better tolerated than ethionamide (379). In an early study, among adults taking ethionamide 375 mg twice daily, 24/48 (50%) reported GI symptoms with 9/48 (19%) being severe, compared to 17/53 (32%) with any and 3/53 (6%) with severe GI symptoms for those taking prothionamide 375 mg twice daily (382). This trend towards worse GI intolerance with ethionamide was not statistically significant (382). A similar trend in improved GI tolerability was seen in a trial comparing ETH- and PTH- containing regimens, with GI intolerance reported in 33.5% on ETH vs 25.6% on PTH, though there was no difference in the groups in discontinuation of the drug for adverse effects (367). Interestingly, in a comparison of ethionamide 250 mg or 500 mg once daily with prothionamide 250 mg or 500 mg once daily for treatment of leprosy, GI intolerance was infrequently reported in either group (383).

Hypothyroidism

Hypothyroidism is a known reversible adverse effect of prolonged therapy with ETH and PTH (384-386). ETH, which is structurally similar to methimazole, is thought to inhibit organification of idiodine and possibly to block uptake of iodine (384, 387). In a cohort of 186 adults with MDR-TB in which 96.2% were treated with both ETH or PTH and PAS, 129 (69%) had hypothyroidism defined as a TSH>10mIU/L (388). Hypothyroidism was reported in 73/213 (34.2%) in a retrospective cohort from Botswana, 5/7 (71.4%) in a cohort from the UK, and 11/52 (21%) in an Indian cohort who also described one death from myxedema coma in one patient (389-391).

In a cohort of ETH-treated children with MDR-TB, 79/137 (58%) had abnormal thyroid functions, with at least 41% of those with abnormalities likely due to ETH-treatment (387).

An increased risk of hypothyroidism is associated with ETH/PTH and PAS co-treatment (387), and with HIV in a paediatric cohort (387) but not in an adult cohort (388).

Other

Hepatitis (392), pellagra-like rash (393), central nervous system effects (394, 395), and gynecomastia (396, 397) have been rarely associated with ETH or PTH, mostly in case reports (349, 369).

4.5 Existing recommendations for the use of ethionamide and prothionamide in paediatric DR-TB

Ethionamide and prothionamide are available as 250 mg tabs. The recommended dose in children 15-20 mg/kg once daily to a maximum daily dose of 15-20 mg/kg (see Table 1.2) (16). Because of their relatively high bactericidal activity and low cost, it has been recommended that ETH or PTH be the first Group IV drugs added when designing a treatment regimen for MDR-TB (398).

4.6 Future or Ongoing Studies in Children

A search of www.clinicaltrials.gov and the WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/) identified no registered studies of ethionamide or prothionamide in children with TB. A large ongoing study in Cape Town, South Africa is evaluating the pharmacokinetics, safety, and tolerability of second-line antituberculosis drugs in children, including ethionamide.

4.7 Conclusions and Recommendations

Ethionamide and prothionamide have both consistently demonstrated potent activity against *Mtb in vitro* and *in vivo*. Though GI intolerance and hypothyroidism are relatively frequent adverse effects, life-threatening toxicity is rare. Because of the pattern of cross-resistance with INH, the combination of high-dose INH and ethionamide will provide at least one active drug for most strains. ETH or PTH are key components of existing treatment regimens of DR-TB in adults and children.

Ethionamide is currently listed as an Essential Medicine for adults and children (20). For the foreseeable future ETH or PTH will remain important components of the treatment of DR-TB in children, and we would therefore recommend that ethionamide remains an Essential Medication. Prothionamide is not currently listed as an Essential Medicine for adults or children (20), but is used interchangeably throughout the world and should be considered an alternative to ETH.

For MDR-TB, we recommend a dose for ethionamide and prothionamide of 15-20 mg/kg once daily, with a maximum dose of 1000 mg.

5 – Cycloserine and Terizidone

5.1 Background

5.1.1 Overview

D-Cycloserine is a cyclic analog of the amino acid D-alanine, discovered in the 1950s (399). The antimycobacterial activity of cycloserine (CS) is related to its inhibition of two enzymes needed for the synthesis of peptidoglycan, a key component of the cell wall of *Mtb* (399-402). Cycloserine inhibits the action of both D-alanine:D-alanine ligase, which synthesizes D-alanine pentapeptides, and of D-alanine racemase, which converts L-alanine to D-alanine (400-402). Terizidone (TZD) is a Schiff-base of two molecules of D-cycloserine combined with terephthalic di-aldehyde (403).

5.1.2 Approvals

Cycloserine was first approved by the U.S. FDA in June 1964, for the indication of treatment of active pulmonary and extra-pulmonary TB when the causative organisms are susceptible to this drug and when treatment with primary medications has proved inadequate (42). Terizidone was first approved by German Federal Institute for Drugs and Medical Devices (BfArM), where it was first marketed in Germany in the 1970s and is still in the process of the posterior registration process there (42). The approved indication in Germany is the treatment of TB in adults and adolescents aged 14 or older (42).

5.1.3 Cost

Table 5.1 – Price of cycloserine and terizidone by manufacturer (Price in U.S. dollars of the lowest unit – one capsule, one tablet, or one vial) (42)

	Aspen	Chao Center / Purdue	Lupin	Mac-leods	Fatol	GDF pooled procurement price
Cycloserine 250 mg cap	†	0.580	†	0.593	--	0.580 (blister) (Macleods) 0.780 (bottle 100) (Aspen) 0.800 (bottle 40) (Chao Center)
Terizidone 250 mg cap	--	--	--	--	1.489	1.494 (Fatol)

GDF = Global Drug Facility
† Manufacturer did not agree to publish price in source document

5.2 Summary of efficacy data

5.2.1 In vitro activity against Mycobacterium tuberculosis

The *in vitro* activity of D-cycloserine was extensively evaluated early after its discovery. More recently, the MIC of CS was shown to be generally between 25-75 µg/ml in Bactec460 (251). In a model of intracellular TB in human macrophages, cycloserine had only moderate bactericidal activity, less than the other first and second-line antituberculosis drugs evaluated, except for clarithromycin (251). The 2008 WHO recommended critical concentration for DST for cycloserine was 40 µg/ml on Lowenstein-Jensen medium (60), but has tentatively been lowered to 30 µg/ml in informal guidance in 2012 (64). There are no recommendations for terizidone (60).

5.2.2 Activity in animal models

In a guinea pig model, cycloserine used alone was not effective in controlling TB, though the combination of cycloserine with isoniazid showed slightly increased efficacy compared to isoniazid alone (404-408). We are not aware of published English-language literature on the activity of terizidone in animal models.

5.2.3 Activity in human TB

Despite disappointing results in animal models, initial trials in the 1950s of cycloserine in humans reported clinical, radiological, and bacteriologic improvement in adults with both acute and chronic drug-resistant pulmonary TB (409, 410). Subsequent reports were more mixed and suggested its most appropriate use was in combination with other more active agents (411-415). Schwartz and colleagues reported poor outcomes in 6 of 12 adults with advanced chronic pulmonary TB treated with INH 100 mg three time daily and CS 250 mg twice daily, and noted that responses were slower than with the combinations of INH-PZA and INH-Streptomycin (412). Additionally, resistance to isoniazid emerged rapidly in a number of the cases, highlighting the limited ability of CS to protect companion drugs against the development of resistance (412). Another study comparing ethionamide-pyrazinamide with ethionamide-cycloserine showed less frequent and delayed ethionamide-resistance when paired with CS 500-1000mg daily, though ETH-resistance did still emerge (361). Among 46 adults with chronic pulmonary TB resistant to all other agents, CS in doses of 500 or 750 mg induced rapid improvement in a large percentage of patients, with 54% having negative sputum smear and culture at 6 months, but only 27% remaining negative at 12 months (413). Cycloserine fell out of favor partly because of the improved activity of new agents, but also because of its substantial toxicity at the doses required for clinically relevant activity (412). Only recently has it again found a role in the management of MDR-TB (16). Caminero and colleagues suggested that when constructing an MDR treatment regimen, cycloserine should be the second choice, after ethionamide, among the Group 4 drugs (347). The published early paediatric experience consists of two small series in the 1960s which described the use of cycloserine in combination with isoniazid in the treatment of 29 children, and report generally good outcomes and few adverse effects (404, 416, 417).

There is very little English-language literature on the use of terizidone for TB. In combination with other drugs, TZD at a dose of 250 mg three times daily was shown to be well tolerated and effective for the treatment of urogenital TB in 51 adults, though the clinical characteristics, outcomes, and adverse events were not well described (418). Data presented at the 4th South African AIDS Conference in 2009 suggested that replacing ethambutol with terizidone in HIV infected adults with MDR-TB could result in faster culture-conversion, though this has yet to be published to our knowledge (419).

5.3 Pharmacodynamics and Pharmacokinetics

5.3.1 Pharmacokinetics

Cycloserine and terizidone are thought to be well absorbed after oral administration and to distribute widely to most body fluids and tissue, including cerebrospinal fluid (145, 420). They are primarily excreted unchanged in the urine (420). After a single oral dose of 500 mg of cycloserine under fasting conditions in 12 healthy adult volunteers the C_{max} was 12-30 µg/ml and the T_{max} was 0.25-2.5 hrs (421). The C_{max} and T_{max} were delayed by consumption of a high-fat meal, but the AUC was unaffected. Orange juice and antacid did not have a significant effect on any pharmacokinetic parameters (421).

We are aware of one English-language study that compared the pharmacokinetics of cycloserine with terizidone in adults with TB (403). Absorption and excretion in urine of both drugs were more rapid in younger adults (403). At all doses, the concentrations of terizidone were generally higher than cycloserine, but this was statistically significant at only some time points (403). The ratio of cycloserine to terizidone did not correspond to two molecules of cycloserine contained in the terizidone, except at 30 hours after drug administration, which the authors hypothesize may be related to the slow hydrolysis of terizidone into cycloserine in the organism (403). Additionally, doses above 500 mg did not result in a proportional increase in serum concentrations of either drug (403). The means for T_{max}, t½ and C_{max} were not specifically reported in the study, but the T_{max} for both CS and TZD were between 2 to 3 hours (403). Based on visual inspection of the concentration-time curves, rough estimates for the C_{max} for CS at doses of 250 mg, 500 mg, and 750 mg were 8-9 µg/ml, 14-15

µg/ml, and 16-17 µg/ml respectively (403). Rough estimates for the C_{max} for TZD at doses of 250 mg, 500 mg, and 750 mg were 8-9 µg/ml, 16-17 µg/ml, and 18-19 µg/ml respectively (403).

There is limited pediatric pharmacokinetic data available for cycloserine. Two case series including 29 children reported a cycloserine level of 3-36 µg/ml after a 15 mg/kg dose (416), and concentrations of 10-35 µg/ml after a 20mg/kg dose (404, 417), though the timing of these concentrations and the study methods were not well described. In a single child with MDR TB meningitis, 14 days after starting treatment cycloserine serum concentration after a dose of 250 mg twice daily (15mg/kg) was 16.5 µg/ml 9 hours after the dose (422). In this same child at more than 100 days into treatment, cycloserine concentration after a dose of 125 mg twice daily (7 mg/kg) was 23.9 µg/ml 9 hours post-dose, and in a third sampling at a dose of 125 mg twice daily (6.4 mg/kg) were 24 µg/ml 2.25 hours post-dose with a trough of 8.40 µg/ml 12 hours post-dose (422). We are unaware of any additional pharmacokinetic studies of cycloserine or terizidone in children.

Appendix 1 Table A-9 shows the results of published pharmacokinetic studies of cycloserine and terizidone respectively, in adults with TB (403, 420).

5.3.2 Pharmacodynamics

The pharmacodynamics of cycloserine and terizidone in TB are not well described. For cyclcoserine, a target C_{max} of 20-35 µg/ml has been proposed, with the recommendation to adjust doses for levels less than 15 µg/ml or greater than 40 µg/ml (170). The most important pharmacodynamic parameter for CS and TZD is not known, though since the mechanism of action parallels that of penicillin, which has time-dependent killing, it has been proposed that optimizing the time-above-MIC would be advisable (421). Based on the pharmacokinetic parameters estimated by Zhu and colleagues and using an MIC of 10 µg/ml, with 500 mg once daily dosing of CS serum concentrations would exceed MIC for 8 hours, and with 500 mg 12 hourly serum concentrations would exceed MIC for the majority of the period (421).

5.4 Safety Data

Cycloserine is well-known to have central nervous system adverse effects, which generally occur in 20-33% of patients (179), but have been reported to affect up to half of treated patients (423). The neurologic manifestations are variable, and include excitation, dizziness, headache, tremor, slurred speech, insomnia, anxiety, lethargy, inability to concentrate, as well as more serious effects including severe depression, suicidal ideation, psychosis, seizures, and encephalopathy (170, 179, 424). The neurotoxicity is generally felt to be dose-related, with more serious toxicity associated with higher serum levels (170). In a study by Holmes and colleagues, when cycloserine doses were titrated to maintain serum levels between 20-40µg/ml, clinical response was maintained and only 4/60 patients had neuropsychiatric events (425). In all four of those patients with neurologic side effects, cycloserine levels were above 40 µg/ml (425), though it has been noted that toxicity may occur even at low serum levels (170). The nervous system side-effects of cycloserine are generally reversible, and respond to reducing the dose or discontinuing the drug. Cycloserine is thought to be a pyridoxine antagonist and to increase the renal excretion of pyridoxine, which can result in neuropathy and as such it should be prescribed in combination with pyridoxine (145). It has been suggested that the neuropsychiatric effects of cycloserine may be ameliorated by co-administration of pyridoxine, though this remains controversial and unproven (179). Complicating the evaluation of neuropsychiatric events in MDR-TB is the high prevalence of baseline psychiatric disorders in this group of patients (426). In a cohort of 75 adult MDR-TB patients in Lima, Peru, 52.2% and 8.7% had depression and anxiety respectively at baseline, with 13.3%, 12.0%, and 12.0% experiencing incident depression, anxiety, and psychosis respectively during treatment which included cycloserine in 74 of the 75 (426). Despite these adverse effects, with aggressive management including psychiatric pharmacotherapy, cycloserine was safely continued in all but one of the patients (426). Cycloserine has also been

associated with other more rare side effects, including encephalopathy (424) and dermatologic reactions including Stevens-Johnson syndrome in an HIV-infected person (427, 428).

Multiple sources quote that terizidone has fewer adverse effects (around 1%) than cycloserine (around 11%) (403, 429, 430), though this assertion should be interpreted with caution as no additional detail is provided nor is the original source of the data (an unpublished study by the author of reference 430) cited by any of these references.

Limited pediatric safety data exists either for cycloserine or terizidone. The two pediatric cases series of cycloserine treatment were notable for the absence of any toxic effects reported in either (404, 416, 417). In a recent systematic review 6 of 182 children treated for MDR-TB had adverse effects attributed to cycloserine, which included depression, anxiety, hallucinations, transitory psychosis, and blurred vision (6). In our anecdotal experience, terizidone at a dose of 20 mg/kg once daily is very well tolerated by children, with few adverse effects.

5.5 Existing recommendations for the use of cycloserine and terizidone in paediatric DR-TB

Cycloserine and Terizidone are available in 250 mg capsules, and are recommended to be given at 10-20 mg/kg divided once or twice daily (See Table 1.2). The capsule formulation makes dosing in children a challenge, as capsules cannot be easily split or cut, though partial doses can be given by opening the capsules and separating the powder or dissolving the powder in water. In our anecdotal experience, terizidone has been well tolerated in children at a dose of 20mg/kg once daily.

5.6 Future or Ongoing Studies in Children

A search of www.clinicaltrials.gov and the WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/) revealed no registered studies of terizidone or cycloserine in children with TB. An ongoing large study in Cape Town, South Africa is evaluating the pharmacokinetics, safety, and tolerability of second-line antituberculosis drugs in children, including terizidone.

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5.7 Discussion, Conclusions and Recommendations

Though there remain questions about the efficacy of cycloserine, concerns about its well-known neurotoxicity, and a paucity of published information on terizidone, because of the limited current treatment options these drugs will remain important in the treatment of MDR-TB for the foreseeable future. Despite limited data on the pharmacokinetics of these agents in children and the lack of child-friendly formulations, cycloserine and terizidone can be feasibly given to children. The few published reports on the safety of these drugs suggests that side effects are less frequent in children, which is consistent with our anecdotal experience that they are well-tolerated by children. Published English-language literature on terizidone is limited, but in our substantial experience with it in children it has been safe and effective. The CSF penetration of many of the second-line agents is limited, so the excellent CSF penetration of these drugs also makes them important agents in patients with MDR TB meningitis.

As such, we recommend that cycloserine remain an Essential Medicine for children with MDR-TB, and we would recommend that terizidone be an alternative to cycloserine. Either cycloserine or terizidone will be an important component of existing treatment regimens for DR-TB in children, and clinicians should use whichever of these two drugs is available to them. We would recommend terizidone and cycloserine doses of 15 mg/kg once daily, with a range of 10-20 mg/kg.

6 – Para-aminosalicylic Acid (PAS)

6.1 Background

6.1.1 Overview

PAS was one of the first antituberculosis drugs developed, first given to a human with TB in March 1944 (431). Despite the fact PAS has been in use for over 60 years, its exact mechanism of action against *Mtb* remains unclear. The inhibitions of folate synthesis and iron utilization have both been hypothesized (432-435). As PAS is structurally similar to the sulfonamides, the inhibition of dihydropteroate synthase (DHPS), a key enzyme in the pathway for folate synthesis and the target enzyme of the sulfonamides, was postulated to be the likely mechanism of action (436). Other evidence points to the primary activity of PAS being inhibition of salicylic acid conversion to mycobactin, a critical molecule in iron acquisition by *Mtb.* (433, 437) Because of the potential for developing novel agents with similar mechanisms of action, there is a renewed interest in describing in more detail the antimycobacterial activity of PAS. Most of this new data points toward a role for PAS in folate biosynthesis (436, 438), though this remains controversial. Recent studies have reported that rather than inhibit DHPS (439), PAS is a prodrug metabolized by it, and that the products of PAS metabolism by DHPS and other subsequent enzymes, competitively inhibit multiple downstream enzymes in the folate metabolism pathway in *Mtb* (440).

PAS has existed in multiple forms, but remains most commonly available today as the acid salt, para-aminosalicylic acid (PAS) and the sodium salt, para-aminosalicylate sodium (PAS-sodium) (347, 432). Though largely falling out of favor related to its poor tolerability and the development of more active agents, there has been a renewed interest in PAS because of the global increase in drug-resistant TB.

6.1.2 Approved indications

PAS has been approved by the U.S. FDA for the indication of treatment of TB in combination with other active agents, with PAS-sodium first registered in the U.S. in 1950 and PAS in 1994 (42).

6.1.3 Cost

Table 6.1 – Price of PAS (Price in U.S. dollars of the lowest unit – one capsule, one tablet, or one vial) (42)

	Jacobus	Macleods	Olainfarm	GDF pooled procurement price
PAS 4 gram sachet	1.567	--	--	1.530 (Jacobus)
PAS-sodium - 60% w/w granules – 9.2g sachet	--	1.510	--	1.450 (Macleods)
PAS-sodium - 60% w/w granules – 100g jar	--	16.270 (1.497 for 9.2g)	--	16.000 (Macleods) (1.472 for 9.2g)
PAS-sodium - powder for solution – 5.25g sachet	--	--	1.550	1.500 (Olainfarm)

GDF = Global Drug Facility

6.2 Summary of efficacy data

6.2.1 In vitro activity against Mycobacterium tuberculosis

In 1946 Lehman reported the bacteriostatic activity of PAS from among 50 benzoic acid derivatives he screened for anti-TB activity (431), which was confirmed by follow-up studies (441). PAS has been reported to have an MIC reported as <1 µg/ml against 9 clinical strains (432). Recommended critical concentrations from WHO for PAS against *Mtb* for DST are presented in Table 6.2, along with

suggested breakpoints from a study by Kam and colleagues combining clinical and laboratory data on over 198 clinical strains (60, 62, 64).

Table 6.2 Proposed critical concentrations (in µg/ml) for para-aminosalicylic acid (PAS) against *Mycobacterium tuberculosis*

	Mtb strains	Lowenstein-Jensen medium	Middlebrook 7H10	Middlebrook 7H11	Bactec460	MGIT960
Kam KM, et al. 2010	Clinical strains	1.0	0.5-1.0	--	0.5-1.0	--
WHO 2008 (60) and 2012 (64)	--	1.0	2.0	8.0	--	4.0

6.2.2 Activity in animal models

PAS administered to mice was demonstrated to suppress the effect of experimental TB, and the combination of PAS and streptomycin showed more activity (441).

6.2.3 Activity in human TB

At the same time he first reported the *in vitro* activity of PAS, Lehman also reported its initial use in humans (431). Administration of 15 grams to adults with TB resulted in weight gain, defervescence, and drop in the erythrocyte sedimentation rate (431, 442) and sputum culture conversion in 28% (442). Based on its demonstrated efficacy in early studies, PAS was extensively evaluated in multiple combinations in the 1950s and 1960s. One of the first studies evaluating combination treatment, a trial reported in 1950 by the British Medical Research Council (BMRC), compared PAS (20 grams daily in 4 divided doses) versus streptomycin (SM) (1 gram daily) versus the combination of PAS-SM, and reported the proportions with negative sputum culture at 6 months were 8% for PAS, 19% for SM, and 33% for PAS-SM (443). The addition of PAS to SM greatly reduced the emergence of SM-resistance, with 33/49 in the SM group having SM-resistance, compared with 5/48 in the PAS-SM group (443). Despite its limited ability to effect culture conversion, among those receiving PAS alone a higher proportion had clinical and radiologic improvement and a lower proportion died, compared to a control group receiving bed rest only in a previous trial of streptomycin (443). In a follow-up study evaluating different doses of PAS (5 grams versus 10 grams versus 20 grams daily) in combination with SM, negative cultures at 6 months of treatment were reported in 18-31% of patients, with no statistically significant differences between the doses (444). The lower doses of PAS were less effective at preventing the emergence of SM-resistance, with SM-resistance at 6 months occurring in 36% on SM-PAS 5 g, 30% on SM-PAS 10 g, and 7% on SM-PAS 20g (444).

PAS was also studied in combinations with isoniazid after its development. In a study in India comparing 12-month regimens of INH-PAS versus 3 regimens of isoniazid-monotherapy, the proportion of those who were culture-negative in at least the last 3 consecutive months of treatment was 86% for the INH-PAS group, compared to 44-67% for the INH groups (445). In this same study, PAS delayed the development of INH-resistance, but by 6 months of treatment nearly all the positive cultures were resistant to INH in all groups (445). Five of the 6 with baseline INH-resistance in the PAS-INH group had an unfavourable outcome (445, 446). Taken together these findings highlight the role of PAS as a drug to be used in combination with other active agents, mainly to protect companion drugs against the development of resistance. Because of its poor tolerability and after studies showing the value of rifampicin, pyrazinamide, and ethambutol, the use of PAS declined substantially.

The early bactericidal activity of PAS has been evaluated in a single study involving 4 patients (23, 447). In this study, a dose of 15 grams of PAS resulted in an EBA_{0-2} of 0.259 and an EBA_{2-14} of 0.076 (447).

Undoubtedly many children were treated with PAS after its discovery, though reports of its efficacy in children are limited. Lorber and colleagues reported a 2 year survival of 73.7% for a cohort of children with TB meningitis treated with streptomycin and PAS, compared to 46.1% for a historical control from

the same centre treated with streptomycin alone (448). In a cohort of children in the U.S., the addition of PAS to streptomycin slightly reduced mortality relative to streptomycin alone, and it was described as generally well tolerated in doses of 200-400 mg/kg/day (449).

Despite few studies evaluating the specific role of PAS in MDR/XDR-TB treatment in adults or children, the lack of other available effective agents has led to resurgence in its use for this indication (16). A recent individual-patient meta-analysis evaluating the impact of second-line drug resistance in patients with XDR-TB reported that, relative to those with XDR alone, patients with XDR and additional resistance to at least one Group IV drug had an adjusted Odds Ratio of treatment failure or death of 2.6 (95% CI 1.1, 6.7) (270). All of the patients in the above group had resistance to all Group IV agents tested, including PAS, so the contribution of the individual Group IV drugs to this result was unable to be explored (270). Good outcomes have been reported in a number of paediatric cohorts in which children received PAS as a component of their MDR-TB treatment regimen, though no conclusions were made about the specific contribution of PAS (6, 450).

6.2.4 Resistance

Resistance to PAS was noted early in its clinical use, particularly in patients treated with prolonged courses of PAS alone, but noted to be less severe and less frequent than in patients taking streptomycin, and less frequent when PAS was used in combination therapy (442, 451, 452). Much more recently the molecular genetics of PAS resistance has been explored. A mutation in the *thyA* gene has been associated with PAS-resistance (436, 438). The *thyA* gene encodes the enzyme thymidylate synthetase, important in DNA repair in synthesis, and a major consumer of tetrahydrofolate (THF) and thus determinant of intracellular folate concentrations (438). Mathys and colleagues noted that 37% of PAS-resistant clinical isolates had *thyA* gene mutations (453). Interestingly, investigation of nine other genes involved in folate metabolism did not reveal other PAS-resistance associated mutations (453). In an evaluation of 188 consecutive clinical strains of *Mtb*, *thyA* mutations had a positive predictive value of 89.3% for PAS-resistance, but much lower negative predictive values (454). Additional work is needed to further elucidate mechanisms of PAS resistance.

6.3 Pharmacokinetics and Pharmacodynamics

Lehman provided some initial observations on the pharmacology of PAS. PAS is rapidly absorbed with a T_{max} of 1/2 to 1 hour, and rapidly excreted with a 4 gram oral dose excreted in 3-4 hours (442). Enteric-coated PAS granules resulted in max serum concentrations after about 2 hours, and delayed the excretion of oral doses to 5-6 hours (442, 455). The acid-resistant coating of the granules is thought to prevent the rapid release of PAS in the stomach, which may be partially responsible for the GI-intolerance and erratic pharmacokinetics, and allows more gradual release and absorption in the more neutral small intestine (456). PAS is 50-60% protein bound (15, 457). Roughly 70% of absorbed PAS is acetylated to N-acetyl-*p*-aminosalicylate (APAS) by N-acetyltransferase-1 (NAT-1), with 25% conjugated with glycine to form *p*-aminosalicyluric acid (PAA) (458). There is considerable metabolism in the gut and liver resulting in a large first pass effect (459). Early studies evaluating the effect of PAS in TB meningitis reported PAS concentrations in the CSF to be 1/3 to 1/4 that in the serum (442). Even in the presence of meningitis PAS concentrations in the CSF are low, which may be related to active transport of PAS by the choroid plexus, though it has been noted that the addition of PAS to streptomycin in early regimens did result in improved outcomes (145).

The results of early studies of PAS-sodium and other non-granule forms of PAS are presented in Appendix 1 Table A-10 (458, 460). In adults, the T_{max} after a 4 gram dose of PAS granules was around 6 hours (455). The $t_{½}$ of the drug in blood is 45-60 minutes, so serum levels fall rapidly after absorption is complete (455). PAS given as 4 grams once daily resulted in serum concentrations below the MIC of 1 µg/ml for a part of the dosing period. A flat concentration time curve was obtained for PAS granules given as 4 grams twice daily, and maintained serum levels above the MIC of 1 µg/ml for the entire dosing period in 81 of 88 adult TB patients (455). As such, the authors recommended

twice daily dosing of PAS granules, though other older studies showed once-daily to be as effective as twice-daily dosing (461, 462). Co-administration of PAS with a high-fat meal has been shown to delay the T_{max} and increase the C_{max} and AUC, while co-administration with antacids or orange juice did not affect he PK parameters (463). Our anecdotal observation is that patients seem to prefer once daily to twice daily dosing of PAS.

Our search identified two reports of the pharmacokinetics of PAS in children. Until this year, only a single English-language report provided data on PAS pharmacokinetics in 4 children with TB given PAS-sodium 300 mg/kg/day, divided into 5 doses (457, 464). Based on interpretation of the graphically represented data, after doses of 50-60 mg/kg, the C_{max} was roughly 5-10 µg/ml, with the T_{max} occurring at roughly 1 hour followed by a rapid decline in blood concentrations (457, 464). A report published during 2012 presented results of a study comparing the pharmacokinetics of slow-release PAS granules given to 10 children as 75 mg/kg twice daily or 150 mg/kg once daily, and to adults as 4 grams twice daily. A higher mean C_{max} and AUC_{0-12} were noted for the 150 mg/kg compared to the 75mg/kg paediatric doses, but the small number of patients limited the ability to detect statistically significant differences (457). The authors reported no statistically significant differences between any of the dosing regimens, but consistent with a previous adult study, they noted a high degree of intra-group variance, with coefficients of variance for the PK parameters ranging from 39.1-79.7 (457).

Appendix 1 Table A-10 shows the results of published pharmacokinetic studies of PAS in adults with TB and children (432, 455, 457).

6.3.2 Pharmacodynamics

Because PAS has bacteriostatic activity and a limited post-antibiotic effect, it has been suggested that serum concentrations should be maintained above the MIC (1 µg/ml) for as much of the dosing period as possible (170). After a 4 gram dose a target serum concentration of 20-60 µg/ml has been proposed, with dose increases for C_{max} below 10 µg/ml, but the precise pharmacodynamics of PAS in the treatment of TB are unknown (170).

6.4 Safety Data

Gastrointestinal Intolerance

GI-intolerance with vomiting, diarrhea, anorexia, and abdominal discomfort were noted as frequent adverse effects in the first clinical evaluations of PAS (442, 465), and occurring in up to 50% of patients in some reports (466). This effect was noted to be less when PAS was given as enteric-coated granules (442, 455). A few drops of opiate or a teaspoon of magnesium oxide given just before PAS were also noted to decrease the GI adverse effects (442). The use of antrenyl, an anti-cholinergic with antimotility and antispasmodic properties, was shown to decrease the GI-adverse effects of PAS in a small group of adults (465). Antimotility agents also may help alleviate PAS-associated diarrhea. In current MDR-TB treatment regimens, GI adverse effects are very commonly reported, but because of the multi-drug regimens it is difficult to attribute these effects to any single agent. In a large cohort of 244 adults treated for MDR-TB, 88.9% of whom were treated with PAS, PAS was permanently discontinued in 9 because of nausea and vomiting, 3 because of diarrhea, 3 because of hepatotoxicity, and 1 because of joint complaints (318).

Hypothyroidism

Hypothyroidism is a known adverse effect of PAS described in multiple case series and reports early after its introduction into clinical use (467-469), including a case of symptomatic hypothyroidism in an 8 year-old child (470). MacGregor and colleagues reported a goiter in 20 of 83 patients (23%) treated with 20 grams PAS daily, with the earliest onset five months after starting treatment (471). They also noted resolution of the goiter and any symptoms of hypothyroidism with administration of thyroid

extract or discontinuation of PAS (471). It is thought to be due to the blocking of the organification of iodide in the thyroid (471-473). A resurgence of its use for prolonged durations in MDR-TB treatment regimens has renewed awareness of this adverse effect (385). The combination of treatment with PAS and ethionamide, also known to cause hypothyroidism (384), may result in a higher risk of hypothyroidism (388). In a retrospective study of adults with MDR-TB in Lesotho, 129/186 (69%) had laboratory evidence of hypothyroidism (Thyroid Stimulating Hormone [TSH] >10 miU/L) during treatment (388). In this study, 179/186 were on both PAS and ethionamide/prothionamide, so it was not possible to determine the individual contribution of these drugs to the hypothyroidism (388). In an evaluation of ethionamide-associated hypothyroidism in a cohort of South African children with MDR-TB, those on a regimen containing both PAS and ethionamide were more than twice as likely to have hypothyroidism compared to those on ethionamide alone (387). A high-risk of hypothyroidism has also been reported in another cohort of PAS-treated children with MDR-TB (450).

Hypersensitivity reactions

An early thorough review of the topic by Matsaniotis and colleagues reported that hypersensitivity occurred in about 2-3% of adults (474). The majority of occurrences are reported within 2-6 weeks of starting PAS, but it has been reported as soon as 8 days and as late as 73 days, and symptoms are usually of acute onset (474). The symptoms are highly variable, but most commonly include fever and rash, which is usually maculopapular but may take many other forms including exfoliative dermatitis (474). Other common symptoms are chills, malaise, generalized lymphadenopathy, joint pain, and various hematologic abnormalities (474). Less commonly hepatitis and jaundice can be seen (474). PAS-associated hypersensitivity reactions have been described in children in two reports, and similar to the frequency in adults was reported in 3 of a cohort of 100 children treated with PAS (474, 475). When there are limited other drug options, desensitization with ascending doses of PAS is possible has been successfully reported in adults and children as well (456, 474).

Other

PAS has been shown to mildly prolong the prothrombin time, which is reversible with administration of Vitamin K, though rarely is this clinically relevant in otherwise healthy individuals (441, 476).

6.5 Existing recommendations for the use of PAS in paediatric DR-TB

PAS is a WHO Group IV drug, and depending on local guidelines may be used as a component of MDR-TB treatment regimens (16). The recommended dose for children is 150 mg/kg per day divided into 2-3 doses (Table 1.2) (16), though as noted pharmacokinetic data in children is limited. Measuring the dose accurately in children is difficult, and can be aided with the use of measuring spoons for PAS-sodium or graduated scoops for PAS granules (42). The slow-release PAS granule formulation may offer the benefit over the PAS-sodium formulation of improved tolerability and sustained drug concentrations above the MIC (457). Though not a formal recommendation, one expert opinion is that when constructing an MDR treatment regimen, PAS would be the third choice of the three WHO Group IV drugs to include (347).

The slow-release PAS granules require refrigeration below 15 C, though may be stored for up to 4-8 weeks at 40 C and 75% humidity (42).

6.6 Future or Ongoing Studies in Children

A search of www.clinicaltrials.gov and the WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/) revealed no registered studies of PAS in children with TB. An ongoing study in Cape Town, South Africa is evaluating the pharmacokinetics, safety, and tolerability of second-line antituberculosis drugs in children, including PAS.

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6.7 Discussion, Conclusions and Recommendations

Slow release PAS granules and PAS-sodium are included as second-line anti-TB drugs in the 2011 WHO 3rd List of Essential Medicines for Children (20). Though not a potent drug, its efficacy against *Mtb* has been well established in adults, particularly in protecting companion drugs against resistance. Based on existing data, experience, and recommendations, many children with MDR-TB will be successfully treated without PAS, though for children with additional drug resistance, including Pre-XDR or XDR-TB, drug options are much more limited and PAS will be an important component of treatment regimens in that context. Though known to be poorly tolerated because of its substantial GI-irritation, severe or life-threatening adverse effects are rare. Pharmacokinetic data in children is currently emerging that will better inform paediatric dosing.

We recommend that PAS granules and PAS-sodium remain Essential Medicines for children with drug-resistant TB. We recommend a dose of 150-200 mg/kg day in children, which can be given as a single dose or divided doses. We recommend the slow-release PAS granules as the preferred formulation, because of its pharmacokinetic benefits and improved tolerability, though either is acceptable to use depending on local availability.

We also recommend the development of more accurate dosing methods for the granules. The graded measuring scoops should be made widely available for all children requiring PAS granules, possibly by including a scoop in each box of sachets. A simple solution that should be considered is repackaging PAS granules into smaller dosing sachets to facilitate more accurate and efficient paediatric dosing.

7 – Linezolid

7.1 Background

7.1.1 Overview

Linezolid belongs to the oxazolidinone class of antibiotics (477). The oxazolidinones bind to the 50S ribosomal subunit, inhibiting formation of the initiation complex and preventing translation and protein synthesis (477-479). This novel mechanism of action means there is no cross-resistance with other protein-synthesis inhibitors and makes them an attractive antibiotic for drug-resistant infections (477). Linezolid is active against gram-positive organisms, and most commonly used in short-courses for treatment of skin and soft tissue infections, nosocomial pneumonia, and resistant gram-positive infections (477).

7.1.2 Approved indications

Linezolid has been approved by the U.S. FDA for the indication of treatment susceptible strains of some microorganisms for nosocomial pneumonia, and for skin and skin structure infections, and was first registered in the U.S. in 2000 (42). Linezolid does not have an official indication for treatment of drug-resistant TB (42).

7.1.3 Cost

Recently published unit costs for linezolid are listed in Table 7.1. Patent coverage of linezolid in the U.S. and other countries, along with a lack of quality-assured alternative producers, has resulted in prohibitively high costs of linezolid (42). The cost of linezolid in South Africa in the private sector is 81 U.S. dollars per tablet, resulting in a cost of 60,000 U.S. dollars for one patient for a 2 year course that would be indicated for the treatment of MDR/XDR-TB (42).

Table 7.1 – Price of Linezolid (Price in U.S. dollars of the lowest unit – one capsule, one tablet, or one vial) (42)

	Hetero	Pfizer	GDF pooled procurement price
Linezolid 600 mg tab	2.500	†	--
Linezolid powder for suspension 100mg/5 ml	--	†	--

GDF = Global Drug Facility
†Manufacturer did not agree to publish prices in source document

7.2 Summary of efficacy data

7.2.1 In vitro activity against Mycobacterium tuberculosis

The *in vitro* activity of linezolid against *Mtb* has been consistently demonstrated, and MICs from published studies are listed in Table 7.2 (54, 355, 480-485). Using Middlebrook 7H9 media to test 67 drug-susceptible and drug-resistant isolates, the MIC_{50} and MIC_{90} of linezolid were 1.0 µg/ml and 2.0 µg/ml respectively (486). For 33 MDR and 34 non-MDR clinical strains, Ermertcan and colleagues reported MIC_{50}, MIC_{90} of 0.5 µg/ml, 0.5 µg/ml for both groups, but did not specify the test medium used (487). Huang and colleagues evaluated the linezolid MICs for *Mtb* clinical isolates over the course of 10 years, and despite a lack of linezolid exposure, reported a trend of higher MICs to linezolid in MDR isolates over time, which was associated with resistance to the FLQs (except levofloxacin) and to kanamycin (488). Using a test concentration of 6 µg/ml linezolid on 295 MDR clinical isolates including 9 which were XDR, only 2 isolates were found to be resistant (489), though the clinical relevance of that breakpoint is not clear.

Table 7.2 Minimum inhibitory concentrations (MIC) (in µg/ml)† for linezolid against *Mycobacterium tuberculosis*

	Mtb strains	Lowenstein-Jensen medium	Middlebrook 7H10	Middlebrook 7H11	Bactec460	MGIT960
Zurenko GE, et al. 1996 (480)	Clinical isolates, DS	--	0.5 *	--	--	--
	Clinical isolates, DR	--	0.5-2.0 #	--	--	--
Rodriguez JC, et al. 2002 (54)	Clinical isolates, mostly DS	--	--	0.5, 1.0	--	--
Alcala L, et al. 2003 (481)	Clinical isolates, DS and DR	--	0.5, 1.0	--	--	--
Erturan Z, et al. 2005 (482)	Clinical isolates, DR	--	--	--	4.0, 8.0	--
Sood R, et al. 2005 (483)	Clinical isolates, DR	--	--	1.0, 32.0	--	--
Tato M, et al. 2006 (484)	Clinical isolates, DS and DR	--	0.25, 0.5	--	--	--
Yang C, et al. 2011 (485)	Clinical isolates, DS and DR	--	0.125, 0.5	--	--	--

† = expressed as MIC_{50}, MIC_{90} respectively, unless otherwise specified; * = inhibited all strains; # range of MICs
DS = drug-susceptible; DR = drug-resistant, to at least isoniazid or rifampicin, or both;

Current WHO recommended critical concentrations for linezolid are listed in Table 7.3 (60, 64) along with proposed breakpoints from Rusch-Gerdes and colleagues (355). Wild-type MICs or epidemiological cut-off values (ECOFFS) for linezolid proposed by Schon and colleagues are also listed in Table 7.3 (354).

Table 7.3 Proposed critical concentrations (in µg/ml) for linezolid against *Mycobacterium tuberculosis*

	Lowenstein-Jensen medium	Middlebrook 7H10	Middlebrook 7H11	Bactec460	MGIT960
Rusch-Gerdes S, et al. 2006 (355)	--	--	--	1.0	1.0
Schon T, et al. 2011 (354)	--	0.5	--	--	--
WHO 2008 (60)	--	--	--	1.0	1.0
WHO 2012 (64)	--	--	--	--	*1.0*

In a study assessing *in vitro* combinations of drugs against *Mtb*, linezolid showed synergistic activity with rifampicin but not the fluoroquinolones (490). Linezolid has shown intracellular activity against *Mtb*, with activity in a murine macrophage model less than that of rifampicin but greater than isoniazid (483). Linezolid was bactericidal against drug-susceptible strains in the exponential growth phase, but against non-replicating *Mtb* in a latent growth phase, only the highest concentrations showed any bactericidal activity, suggesting limited sterilizing ability (491).

7.2.2 Activity in animal models

In one of the first *in vivo* evaluations, Cynamon and colleagues showed substantial dose dependent activity of linezolid in a murine model of *Mtb*, based on lung and spleen colony forming units (CFU) in comparison to untreated controls (492). Interestingly, also evaluated in this study was PNU-100480, another oxazolidinone antibiotic, which at a dose of 100 mg/kg showed activity equivalent to isoniazid 25 mg/kg, with both PNU-100480 and INH having statistically significant greater activity than linezolid (492). A subsequent study confirmed the activity of linezolid in murine TB, but surprisingly at doses approximating the clinically relevant linezolid exposure in humans the bactericidal activity was limited (493). This study again confirmed the much higher relative activity of PNU-100480 alone and in combination with other first and second-line drugs (493). A follow-up study of longer treatment with linezolid in a mouse model actually showed antagonistic activity when linezolid was added to isoniazid, rifampicin, and pyrazinamide, and suggested the possibility of shortened treatment with addition of PNU-100480 to standard treatment (494). In another mouse study, addition of linezolid to moxifloxacin did not increase activity over moxifloxacin alone (81).

7.2.3 Activity in human TB

A single study has evaluated the EBA of linezolid at doses of 600 mg once daily and 600 mg twice daily (495). The EBA_{0-2} was 0.26 for linezolid twice daily and 0.18 once daily, compared to 0.67 for INH 300 mg, demonstrating modest early bactericidal activity for linezolid (495). The values for the extended EBA_{2-7} were 0.09 for twice daily and 0.04 for once daily linezolid, and 0.16 for isoniazid, which suggests minimal sterilizing activity though that should be interpreted with caution (495).

In one of the first clinical studies of linezolid in drug-resistant TB, Fortun and colleagues reported good clinical success with the use of linezolid in 3 patients with MDR-TB with resistance to other second-line agents, but also substantial toxicity (496). Multiple other small case series and observational studies would report similar results, with good treatment success in patients with substantial drug-resistance and limited treatment options, but with frequent adverse events (497-509).

These and other reports were evaluated in two systematic reviews published in 2012 which reported on the safety and efficacy of linezolid for the treatment of drug-resistant TB in adults, with similar results (510, 511). The first by Cox and Ford included 11 studies representing 148 patients (510). The pooled percentage of patients with treatment success was 67.99% (95% CI 58.00-78.99) (510). There was no significant difference in pooled treatment for success in studies with a mean duration of treatment >7 months versus ≤7 months, or for studies that used >600 mg daily versus ≤600 mg daily (510). Among the 9 studies reporting it, the pooled proportion of culture conversion while on linezolid was 97.86% (95% CI 95.19-100%) (510). The second systematic review by Sotgiu and colleagues included 207 patients in 12 studies, many but not all the same studies as the first review, and reported similar findings (511). Of 121 patients with definite treatment outcomes, 82% (95% CI 74-88%) had successful treatment outcomes, with 93% (95% CI 86-97%) having sputum smear conversion and 93% (95% CI 87-97%) having culture conversion (511). In a subgroup analysis, there were no statistically significant differences in treatment outcomes between those receiving ≤600mg daily versus those receiving >600 mg (511).

Two more recent cohorts have reported similar findings to previous studies (512, 513).

Lee and colleagues reported the results of a clinical trial of linezolid in 39 highly-treatment experienced patients with chronic XDR-TB in which patients were randomized to immediate versus delayed addition of linezolid to their existing failed background regimen (514). By 4 months, 79% in the immediate group compared to 35% in the delayed group had culture conversion, though by 6 months 87% of all the patients had culture converted (514). At the time of study publication, 8/38 patients had withdrawn from the study due to treatment failure (n = 4), personal reasons (n=1), and adverse events (n=3), while 17/38 were still receiving the study treatment (514). Thirteen had successfully completed treatment with no relapse to date, suggesting at least some sterilizing potential for linezolid (514). These results are much improved relative to existing reported outcomes for XDR-TB and suggest a role for linezolid in some patients (514).

In 2011, Garazziano and Tozo reviewed the clinical experience with linezolid in children, and though there is less experience than in adults, a significant body of literature does exist for short courses (515). They identified four clinical trials in the literature describing linezolid use in 611 children up to 17 years of age, in which linezolid was found to be effective for complicated skin and soft tissue infections, nosocomial and community-acquired pneumonia, and resistant gram-positive infections, and well-tolerated for treatment durations less than 28 days (515). Also identified were 14 case series and 43 case reports describing linezolid use in another 206 children where it was generally effective for a variety of indications and usually used for durations less than 28 days (515).

Experience with linezolid use in children with drug-resistant TB is more limited, and our search identified 7 reports including 16 children [one patient was included in two reports (516, 517)] treated with linezolid for drug-resistant TB (116, 498, 509, 516-519). Results of these reports are summarized in Table 7.4. All 16 patients had culture conversion, most within 1-3 months, and 14 of 16 (87.5%) had a successful long-term outcome, with 1 lost-to-follow-up and 1 death. The only death was from

respiratory failure, and the patient was culture-negative at the time of death (498). In many of these patients, the good outcomes were despite extensive disease with positive cultures, substantial drug resistance, and prolonged culture positivity and failed treatment with other second-line drugs prior to linezolid use for periods as long as 9 months (509), 7 months (516), and 6-12 months (517).

Table 7.4 Published reports of linezolid use in children with drug-resistant TB

	Age (yrs) & Gender	HIV	TB resistance profile	Dose and duration of linezolid treatment	Culture conversion	Treatment outcome
Park IN, et al. 2006 (498)	17 F	Neg	H, R, E, CLOS, KM, OFX, PAS, PTH	600 mg once daily, 8 months	Yes, 147 days	Death (respiratory failure)
Condos R, et al. 2008 (509)	10 F	Pos	H, R, E, Z, S, CIP, AM, AUG, RB, PAS, CAP	600 mg OD, 25 months	Yes, 29 days	Successful
Schaaf HS, et al. 2009 (516) and Rose PC et al. 2012 (517)	0.9 F	Neg	H, R, E, OFX, AM	10-12 mg/kg BD, 19 months	Yes, 23 days	Successful
Pinon M, et al. 2010 (116)	1.9 F	--	(H, R, E, Z, S, KM) †	10 mg/kg BD, 13 months	Yes, 1 month	Successful
	0.9 M	--	(H, R, E, Z, S, ETH, PAS, CS) †	10 mg/kg BD, 3 months	Yes, 2 months	Lost-to-follow-up
Dauby N, et al. 2011 (518)	14 F	Neg	H, R, RB, E, OFX, Z, AM, CS, PTH	600 mg OD, 8 months	Yes, 11 weeks	Successful
Kjollerstrom P, et al. 2011 (519)	14 M	Neg	H, R, Z, E, S, RB, ETH, CAP, AM	600 mg BD, 9 months	Yes, 12 weeks	Successful
	12 F	Neg	H, R, Z, S, RB, ETH, CS, PAS, KM, OFX	600 mg BD, 6 months	Yes, 6 weeks	Successful
	4 F	Neg	H, R, S, ETH	10 mg/kg BD, 6 months	Yes, 12 weeks	Successful
	17 M	Pos	H, R, Z, E, S	(Dose not stated)11 months	Yes, 12 weeks	Successful
Rose PC, et al. 2012 (517)	13 M	Neg	H, R, AM	300 mg OD, 23 months	Yes, 3 months	Successful
	10 M	Pos	H, R, E, AM, OFX	300 mg OD, 20 months	Yes, 4 months	Successful
	13 F	Neg	H, R, E, AM, ETH, OFX	300 mg OD, 15 months	Yes, 2.5 months	Successful
	0.6 M	Neg	H, R, E, AM, OFX	10 mg/kg BD, 15 months*	Yes, 3 months	Successful
	10 F	Pos	H, R, E, ETH, KM, S	300 mg BD, 24 mnths; 200 mg BD, 3 months*	Yes, 18 months	Successful
	5 F	Pos	H, R, E, KM, S, OFX	300 mg once daily, 7 months	NA (negative prior to linezolid)	Successful

H = isoniazid, R = rifampicin, E = ethambutol, Z = pyrazinamide, ETH = ethionamide, PTH = prothionamide, PAS = para-aminosalicylic acid, KM = kanamycin, AM = amikacin, CAP = capreomycin, OFX = ofloxacin, CIP = ciprofloxacin, RB = rifabutin, AUG = augmentin, CS = cycloserine, OD = once daily, BD = twice daily

†Resistance profile of source case reported

*Treatment ongoing at time of report

7.2.4 Resistance

There is some *in vitro* evidence that it is difficult to induce resistance to linezolid in *Mtb*. Following repeated *in vitro* exposures of 13 *Mtb* isolates to linezolid, a slight increase in MIC was noted among 11, but all were within 2 dilutions and all remained susceptible to linezolid with MICs of 0.25 µg/ml or less (491). Linezolid also was shown to have a low mutant-prevention concentration (MPC_{90} = 1.2 µg/ml) comparable to that of moxifloxacin, supporting its potent activity against *Mtb* (128).

Some reports have suggested elevated linezolid MICs in MDR isolates (480, 483, 488), with two studies reporting some degree of apparent cross-resistance between the fluoroquinolones and linezolid (54, 488), but other studies have reported equivalent linezolid MICs in the majority of drug-susceptible, MDR, and XDR clinical isolates (481, 484, 485, 489).

Richter and colleagues identified 4 out of 210 *Mtb* clinical isolates as resistant (MIC >1 µg/ml) to linezolid, all among linezolid-exposed patients (520). Based on further evaluation of these isolates, no specific gene mutations were identified, and efflux pumps were not responsible for the resistance (520). Hillemann and colleagues reported linezolid-resistant mutants to appear at a frequency *in vitro* of 2×10^{-8} to 5×10^{-9}, and identified two classes of mutants (521). One class had much higher MICs (>16-32 µg/ml in this study) and identifiable mutations in the 23S rRNA, which also was associated with impaired growth indicating a possible loss of fitness (521). The other class had lower MICs, generally between 4-8 µg/ml, and did not have any identifiable mutation, suggesting a non-ribosomal mechanism of resistance, and did not have impaired growth *in vitro* (521). These findings were consistent with the characteristics of linezolid-resistant *Mycobacterium smegmatis* previously described (522). Very recently, the *rplC* T460C mutation, which encodes the ribosomal protein L3 which is known to interact with the 50s rRNA (523), has been identified in linezolid-resistant mutants and may be responsible for lower-level resistance (524).

In the clinical trial reported by Lee and colleagues of linezolid in chronic XDR, of the 4 of 38 patients who did not have culture conversion, all 4 acquired linezolid resistance, with increased MICs by a factor of 8-32 from baseline (514). Gene sequencing identified mutations in the 23S rRNA in two patients, and the *rplC* T460C mutation in the remaining two patients (514).

7.3 Pharmacokinetics and Pharmacodynamics

7.3.1 Pharmacokinetics

Linezolid is well absorbed, with oral availability approaching 100%, and equally good absorption with the oral suspension and tablet formulation (477, 525). In healthy volunteers the T_{max} is 0.5-2 hours. Co-administration with a high fat meal may delay the T_{max} and slightly reduce the C_{max}, but does not affect the AUC (525). Protein binding is reported to be 31% (477, 525). Linezolid has complex metabolism with two primary and multiple minor metabolites (525). The rate-limiting step in linezolid clearance is the non-enzymic formation of the primary metabolite, and both renal and non-renal routes are involved in elimination (525). The primary route of elimination is non-renal, accounting for roughly 65% (526). In healthy volunteers the mean C_{max} after steady state dosing with 600 mg varies from 16.3-21 µg/ml and the mean AUC_{0-12} from 107-138 µg*h/ml (525). Increased clearance and decreased AUC has been noted in ill patients relative to healthy volunteers, as well as substantial inter-patient variability which has raised the question of the role of therapeutic drug monitoring (527, 528).

Linezolid has good tissue penetration (525, 529), including into lung and epithelial lining fluid (530), with a mean epithelial lining fluid to serum ratio of 8.35 in one study (531), and ratio that varied from 2.3-4.2 over 12 hours in another (530). Penetration into CSF was 18-38% in rabbit models of meningitis, but a small study in humans reported a CSF-to-plasma ratio of linezolid of 0.7 (525). A subsequent study in adult neurosurgery patients showed a similar mean CSF-to-serum ratio of 0.66 (532). In the same study, mean PK parameters for linezolid 600 mg twice daily dosing in the CSF were C_{max} 10.8 µg/ml, C_{min} 6.1 µg/ml, AUC 101.6 µg*h/ml, and t1/2 19.1 h, all of which suggest excellent pharmacodynamics in the CSF (532). A single study in children and adolescents reported on ventricular fluid linezolid concentrations (533). PK parameters in ventricular fluid with 10 mg/kg 12 hourly were C_{max} 7.54 µg/ml, C_{min} 1.26 µg/ml, AUC_{0-12} 31.7 µg*h/ml, with a VF-to-plasma ratio of 0.98 (533). PK parameters in ventricular fluid with 10 mg/kg 8 hourly were C_{max} 5.84 µg/ml, C_{min} 1.94 µg/ml, AUC_{0-8} 16.4 µg*h/ml, with a VF-to-plasma ratio of 0.95 (533). The authors noted that meningeal inflammation did not appear to influence CSF penetration in their study. A review reporting

successful outcomes in over 90% of patient treated with linezolid for central nervous system infections adds additional support to the pharmacokinetic findings (534).

Our search identified 2 studies of linezolid pharmacokinetics in adults with TB, with results reported in Table 7.5 (495, 499, 535, 536). In their trial of linezolid for chronic XDR, Lee and colleagues reported mean AUC_{0-24} of 91.1 for 300 mg once daily, and 180.4 for 600 mg once daily (514). In the same study, in all those taking 600 mg daily the serum concentration exceeded the MIC for the entire dosing period, but the trough was below the MIC for 9/16 taking 300 mg once daily, including the 2 patients who developed linezolid resistance (514).

Our search did not identify any studies of linezolid pharmacokinetics in children with TB. A review by Jungbluth and colleagues summarized the paediatric pharmacokinetic data on linezolid from four clinical trials which included over 180 children (526). In newborns linezolid clearance approximates that in adults, but increases to 2-3 times adult values by the first week of life, gradually declining over time until around 12 years of age when it and other PK parameters approximate that of adults . The increased clearance results in shorter t1/2 and smaller AUCs relative to adults (526). It was recommended that in order to approximate the adult dose of 600 mg twice daily, to give a dose of 10 mg/kg 8 hourly in children <12 years of age, and for adolescents ≥ 12 years of age to give adult doses (526).

Appendix 1 Table A-11 list results of these pharmacokinetic studies.

7.3.2 Pharmacodynamics

Linezolid appears to have both time and concentration dependent killing, with the result that both the AUC/MIC ratio and % time above MIC (%T>MIC) have been correlated with linezolid activity against gram-positive bacteria (537, 538). Suggested target for gram-positive bacteria are AUC/MICs>80-120, with a target %T>MIC of 100%, though specific values for *Mtb* have not been established (536, 537). The post-antibiotic effect (PAE) of linezolid was reported to be 4 hours in a single study, which was less than that of gatifloxacin, and much less than that of rifampicin and capreomycin which were also evaluated in the same study (539). This moderate PAE would support maintaining concentrations above the MIC throughout the entire treatment period, though the clinical importance of this in Mtb is not known.

Dietze and colleagues noted excellent values for both fAUC/MIC and time over MIC (T>MIC) for both a 600 mg once and twice daily dosing, though there was no correlation between either of these measures and the EBA_{0-2} or EBA_{2-7} in their study (495). Based on values obtained from this study, McGee and colleagues calculated favorable pharmacodynamic parameters for both linezolid 600 mg twice daily (C_{max}/MIC 16.2, AUC_{0-12}/MIC 121.6, AUC_{0-24}/MIC 243.2, and %T>MIC 100.0), and 600 mg once daily (C_{max}/MIC 20.0, AUC_{0-12}/MIC 107.8, AUC_{0-24}/MIC 116.2, and %T>MIC 62.8) (536). Using a lower dose of linezolid of 300 mg twice daily, Alffenaar and colleagues reported an AUC_{0-24}/MIC from 167-667 for 7 of 8 patients with a ratio >100, and T%>MIC of 100% for all patients, suggesting that lower doses may maintain efficacy while hopefully limiting toxicity (535). In the clinical trial reported by Lee and colleagues, neither the linezolid C_{max} nor the trough was associated with time to culture conversion (514).

7.4 Safety Data

Though linezolid is generally considered to be well tolerated in short courses, a number of important adverse effects are associated with its use, some of which are dose- and time-dependent (540, 541). In general, adverse effects are reported less in linezolid treated children than adults (515, 542). Inhibition of mitochondrial protein synthesis by linezolid was been demonstrated, and may be the cause of many of linezolid's adverse effects (540).

Gastrointestinal toxicity

Gastrointestinal adverse effects are some of the most commonly described toxicities associated with linezolid use, though rarely are serious enough to require alteration or discontinuation of the drug (541). In phase III clinical trials in adults, the most common drug-related adverse events were nausea (3.4%) and diarrhea (4.3%) (541). In a review of clinical trials of short durations of linezolid in children, diarrhea (3.8 - 9.1%), vomiting (1.2 - 4.2%), and loose stools (1.2 - 3.5%) were the most common drug-related adverse events, though in the comparator-controlled trials there was no difference between linezolid and the comparator for any of these (543).

Hematologic toxicity

Both dose and time dependent myelosuppression were noted in pre-clinical evaluations of linezolid in animals (541). A review of adult clinical trial data of linezolid courses <28 days showed no statistical difference in hematologic toxicity between the linezolid and comparator groups, though there was a trend towards increased mild anaemia and thrombocytopaenia in the linezolid group for those treated for more than 2 weeks (541, 544). There have been more reports of anaemia in more prolonged courses of linezolid, thought to be related to a bone marrow suppression due to inhibition of mitochondrial protein synthesis (541). Subsequent studies have been variable in adults but suggest a slight risk of thrombocytopaenia that is increased with longer duration of linezolid, but is reversible with cessation of the drug (541). The exact mechanism of thrombocytopaenia is unknown, but an immune-mediated phenomenon has been proposed (541). Reversible leukopaenia and pancytopaenia have been described but appear to be rare (541). A single report suggested that linezolid-associated cytopaenias may be responsive to vitamin B6, though this remains to be definitively demonstrated (545). In contrast to short courses of linezolid, a systematic review of prolonged linezolid treatment of MDR-TB reported anaemia in 38.1% and thrombocytopaenia in 11.8% (511), with higher linezolid doses significantly associated with these adverse effects in a small clinical trial in XDR-TB (514).

Paediatric data from clinical trials of short courses of linezolid was similar to adults, with a trend towards mild reversible thrombocytopaenia in children treated >14 days but no statistical difference in hematologic adverse events between the linezolid and comparator groups (546).

Neurotoxicity

Peripheral neuropathy was not noted in clinical trials of linezolid, but has been well described among patients on prolonged durations of linezolid (541, 547). It usually presents as paresthesia and numbness in distal extremities in a “stocking and glove” distribution, with lower extremities affected more commonly than upper (541), and is generally not reversible after cessation of linezolid (541, 547) and not responsive to vitamin B6 (545). Linezolid is also associated with toxic optic neuropathy, with painless, bilateral central vision loss, often of sudden onset, and gradual progressive loss of color vision and visual acuity (541). Onset of symptoms is generally 3-12 months, and existing evidence suggests optic neuropathy will improve with discontinuation of linezolid, but can result in permanent visual deficits (541). In a systematic review of linezolid-treated adults with MDR-TB, 47.1% reported peripheral neuropathy and 13.2% optic neuritis (511).

In addition to the cases of peripheral neuropathy among linezolid-treated children with DR-TB described below, a recent review identified 8 cases of neuropathy in children – 5 with peripheral neuropathy alone, 1 with optic neuropathy, and 2 with both peripheral and optic neuropathy (548). Seven of 8 were on prolonged courses from a range of 4 weeks to 7 months at the time on onset, and 5 of 5 in which the outcome was reported had improvement or resolution of symptoms after discontinuation of linezolid (548). A single case of possible auditory nerve neuropathy has been described in a neonate (549).

Other

Hyperlactatemia and lactic acidosis have been described in association with linezolid, with a 2009 review reporting 9 adult cases in the literature (541). Patients may be asymptomatic or have non-specific symptoms, though nausea and vomiting are commonly reported (541). Discontinuation of linezolid will generally result in resolution of the hyperlactatemia over the course of 1-2 weeks (541).

Yogev and colleagues described metabolic acidosis in 2 of 79 (2.5%) children receiving linezolid in a randomized trial, though both had significant other comorbidities (550). Three additional cases were described in children with liver disease and other comorbidities (551), and more recently a case was described in a children receiving long-term linezolid for DR-TB (517).

A case of rhabdomyolosis has also been reported in an adult on linezolid for DR-TB (552). Linezolid is a weak monoamine oxidase inhibitor (MAOI), and in combination with other drugs such as selective serotonin reuptake inhibitors (SSRIs) may rarely precipitate serotonin syndrome (541). A single suspected case has been described in a child (553).

Toxicity in MDR/XDR-TB treatment regimens

In the systematic review of linezolid for DR-TB by Cox and Ford, the pooled percentage of adverse events was 61.48% (95% CI 40.15-80.80%), with pooled percentages of neuropathy of 36.12% (95%CI 19.09–53.16) and bone marrow suppression of and 28.47% (95%CI 14.80–42.14), and 36.23% (95%CI 20.67–51.79) stopping linezolid because of adverse effects (510). In this review, there was a trend towards increased risk of adverse events in those receiving linezolid >600 mg [49.85% (37.31–62.38)] versus ≤600 mg [34.40% (95%CI 23.02–45.77)] (p=0.07), and a statistically significant difference in those discontinuing linezolid because of adverse effects for those on >600 mg [60.75% (95%CI 42.69–78.81)] versus ≤600 mg [29.49% (95%CI 3.24–55.74)] (p=0.05) (510).

In the systematic review by Sotgiu and colleagues, 59% (95% CI 49-68%) experienced and adverse event, of which 69% (95% CI58-79%) required linezolid discontinuation or dose adjustment (511). The most common adverse events were anaemia (38.1%), peripheral neuropathy (47.1%), gastrointestinal disorder (16.7%), optic neuritis (13.2%), and thrombocytopenia (11.8%) (511). In a subgroup analysis there was a statistically increased risk in adverse events for those receiving >600 mg daily (74.5%) compared with those receiving ≤600 mg daily (46.7%) (511). The higher dose was also associated with statistically increased risk of some specific adverse events, including anaemia (60% vs 2.5%), leukopaenia (17.1% vs 2.0%), and GI symptoms (29.4% vs 8.0%) despite a much shorter duration of treatment in the higher dose group (511).

In the clinical trial of linezolid for chronic XDR-TB, 33/38 (87%) of the patients had a clinically significant adverse event, of which 31/38 were possibly or probably related to linezolid (514). After a second randomization in this study to continuation with 300 mg versus 600 mg linezolid, the 600 mg group was 2.7 times more likely to experience an adverse event compared to the 300 mg group, though still 11/16 patients in the 300 mg group experienced an adverse event (514).

Table 7.5 lists the adverse events among published reports of children on linezolid for drug-resistant TB. At least one adverse event was reported for 7 of 16 children (43.8%), with 4 of 16 (25%) requiring a linezolid dose-reduction, and 2 of 16 (12.5%) permanently discontinuing linezolid. Peripheral neuropathy was the most common, occurring in 4/16 (25%), but was reported to resolve after dose reduction or discontinuation of linezolid in each case. The association of linezolid with anaemia reported in 2/16 (12.5%) is unclear, as the episodes were attributed primarily to a vaso-occlusive crisis in a child with co-morbid sickle-cell disease in one case, and HIV in the other. The single life-threatening adverse event was a case of severe pancreatitis and lactic acidosis described by Rose and colleagues (517). Three of 5 (60%) known HIV-infected children experienced adverse events, compared to 4 of 9 (44.4%) known HIV-uninfected, though the sample is too small to draw any robust conclusions about different risk between the two groups.

Table 7.5 Adverse events among published reports of children on linezolid for drug-resistant TB

	Age (yrs) & Gender	HIV	Dose and duration of linezolid treatment	Adverse Event/s	Action and Outcome
Park IN, et al. 2006 (498)	17 F	Neg	600 mg OD, 8 months	None	
Condos R, et al. 2008 (509)	10 F	Pos	600 mg OD 25 months	None	
Schaaf HS, et al. 2009 (516) and Rose PC, et al. 2012 (517)	0.9 F	Neg	10-12 mg/kg BD, 19 months	None	
Pinon M, et al. 2010 (116)	1.9 F	--	10 mg/kg BD, 13 months	None	
	0.9 M	--	10 mg/kg BD, 3 months	None	
Dauby N, et al. 2011 (518)	14 F	Neg	600 mg OD, 4 months, 300 mg OD, 4 months	Moderate peripheral neuropathy after 4 months	Improved with dose reduction to 300 mg once daily
Kjollerstrom P, et al. 2011 (519)	14 M	Neg	600 mg OD, 9 months	Severe progressive peripheral neuropathy after 9 months	Completely resolved after discontinuation of linezolid
	12 F	Neg	600 mg OD, 6 months	Peripheral neuropathy after 4 months	Responded to dose reduction to 300 mg once daily
				Severe anaemia requiring transfusion	Anaemia probably related to co-morbid sickle cell disease, so linezolid continued
	4 F	Neg	10 mg/kg BD, 6 months	Urticarial rash	Resolved after dose reduced to half
	17 M	Pos	(Dose not stated)11 months	None	
Rose PC, et al. 2012 (517)	13 M	Neg	300 mg OD, 23 months	None	
	10 M	Pos	300 mg OD, 20 months	Pancreatitis at 8 months	Attributed to d4T, anticonvulsant, high-fat diet, and possibly linezolid; linezolid continued
	13 F	Neg	300 mg OD, 15 months	None	
	0.6 M	Neg	10 mg/kg BD, 15 months*	None	
	10 F	Pos	300 mg BD, 24 months, 200 mg BD, 3 months*	Peripheral neuropathy at 24 months	Linezolid dose reduced, d4T changed to ABC, terizidone dose reduced, pyridoxine increased; symptoms resolved
				Mild anaemia and leukopaenia at 25 months,	Anaemia, leukonpaenia attributed to HIV
	5 F	Pos	300 mg once daily, 7 months	Severe pancreatitis and lactic acidosis requiring ICU admission at 7 months	Attributed to linezolid which was discontinued, fully recovered

OD = once daily, BD = twice daily

7.5 Existing recommendations for the use of linezolid in paediatric DR-TB

The WHO 2008 guidelines recommend the use of Group 5 drugs, of which linezolid is one, only when a regimen containing 4 drugs with likely activity cannot be created from Groups I-IV, though no other specific recommendations regarding linezolid were made (16). The recommended linezolid dosage is 600 mg twice daily for 4-6 weeks, then 600 mg once daily (16). The WHO 2011 guidelines update did not specifically address linezolid (232). There are no specific recommendations for linezolid use in children in these documents (16, 232). We are unaware of any other formal recommendations for the use of linezolid in children with DR-TB.

Though there are no formal recommendations for paediatric dosing of linezolid for DR-TB, 10 mg/kg twice daily for those <10 years, and 10 mg/kg once daily for those ≥10 years has been suggested

(517), and is the dose most commonly used in published linezolid-treated paediatric DR-TB cases to date.

7.6 Future or Ongoing Studies in Children

A search of www.clinicaltrials.gov and the WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/) revealed no registered studies of linezolid in children with TB. An ongoing study in Cape Town, South Africa is evaluating the pharmacokinetics, safety, and tolerability of second-line antituberculosis drugs in children, including linezolid, when used in children with XDR-TB.

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7.7 Conclusions and Recommendations

The activity of linezolid against *Mtb in vitro* has been well demonstrated. Emerging data in adults and children has also shown it to be effective in difficult cases of DR-TB, with high rates of culture conversion and good long-term outcomes despite substantial anti-TB drug resistance and prolonged periods of culture positivity on second-line drugs prior to linezolid. These benefits are offset by its high cost, and frequent and often severe time- and dose-dependent toxicity.

Because of the high cost, considerable toxicity, and very good clinical outcomes with existing treatment regimens for children with MDR-TB, existing evidence does not support the routine use of linezolid for such children. For children with MDR-TB with additional resistance or with XDR-TB, linezolid may however make the difference between a successful or poor outcome, as demonstrated in many of the paediatric cases described to date. Because of its good CSF penetration, linezolid may also be an important option for children with MDR-TB meningitis, for which outcomes are often poor and other drugs with potent antituberculosis activity and good CSF penetration are limited. The risk versus benefit in these cases favors linezolid, and we would recommend linezolid as an Essential Medicine for children with MDR-TB with additional FLQ or second-line-injectable resistance, or XDR-TB. We recommend a dose of 10 mg/kg per dose twice daily in children <10 years of age, and 10 mg/kg once daily in children ≥10 years of age.

We would also support calls for lowering linezolid costs and making it available, including in suspension form for children, with that indication (42). We would also recommend urgent evaluation of linezolid pharmacokinetics in children with DR-TB to provide more guidance on the most appropriate dosing for this indication.

8 – Clofazimine

8.1 Background

8.1.1 Overview

Clofazimine is a member of the riminophenazines class of compounds, and was first noted to have *in vitro* activity against *Mtb* in the 1950s (554, 555). Investigations for this indication were largely abandoned after it showed limited *in vivo* efficacy in guinea pigs and monkeys (554). Later studies showed activity against *Mycobacterium leprae* and clofazimine therefore remains a key component of anti-leprosy treatment regimens (554, 556). In addition to its role in leprosy, clofazimine has also been used in the treatment of *Mycobacterium avium* complex (MAC) infections, and because of its unique pharmacologic characteristics and anti-inflammatory and anti-cancer properties has been evaluated in some cancers, Crohn's disease, and various other inflammatory and dermatologic conditions (557).

It was later shown that the limited activity shown in guinea pigs and monkeys was likely related to poor absorption of the drug, and that there was in fact *in vivo* activity against *Mtb* in hamsters and mice where clofazimine was well-absorbed (554). With the increase in drug-resistant TB, there has been resurgence in interest in clofazimine in TB treatment.

Multiple possible mechanisms of action for clofazimine have been postulated, including generation of intracellular hydrogen peroxide, binding to guanine bases in DNA, stimulation of phospholipase A_2 activity leading to intracellular accumulation of lysophospholipds (554), generation of reactive oxygen species (558, 559), and interference with electron transport (555), though to date this remains unclear.

8.1.2 Approved indications

First approved by U.S. FDA in 1986 for the treatment of lepromatous leprosy, including dapsone-resistant lepromatous leprosy and lepromatous leprosy complicated by erythema nodosum leprosum, clofazimine has no official indication for the treatment of drug-resistant TB (42).

8.1.3 Cost

In addition to the 50 mg soft gel cap, clofazimine also exists as a 100 mg soft gel cap formulation (42).

Table 8.1 – Price of clofazimine (Price in U.S. dollars of the lowest unit – one capsule, one tablet, or one vial) (42)

	Novartis	GDF pooled procurement price
Clofazimine 50 mg soft gel cap*	†	--

GDF = Global Drug Facility
†Manufacturer did not agree to publish prices in source document

8.2 Summary of efficacy data

8.2.1 In vitro activity against Mycobacterium tuberculosis

In one of the earliest studies of clofazimine, MIC for *Mtb* was 1.3-3.3 µg/ml in Proskauer and Beck medium (554, 560). Clofazimine MICs in Bactec460 were reported by Rastogi and colleagues as 0.1 – 0.4 µg/ml for all strains (251). They also reported limited bactericidal activity even at concentrations 4-8 times the MIC (251). Reddy and colleagues reported a range of MICs in Bactec460 of 0.06 to 2.0 µg/ml for drug-susceptible and drug-resistant *Mtb* strains, with an MIC_{50} and MIC_{90} of 0.12 µg/ml and 1.0 µg/ml respectively (561).

In 2008 WHO recommended a critical concentration for DST of 4.0 µg/ml for clofazimine in Bactec460, but tentative revised guidance from 2012 does not list any clofazimine critical concentrations (60, 64).

These and other proposed critical concentrations (357) or wild type MICs (ECOFFs) (354) are listed in Table 8.3. Rastogi and colleagues proposed susceptibility breakpoints in Bactec460 of ≤1.0 µg/ml for susceptible, 2.0 µg/ml for intermediate, and ≥4.0 µg/ml for resistant (251).

Table 8.3 Proposed critical concentrations (in µg/ml)† for drug susceptibility testing for clofazimine against *Mycobacterium tuberculosis*

	Lowenstein-Jensen medium	Middlebrook 7H10	Middlebrook 7H11	Bactec460	MGIT960
Pfyffer GE, et al. 1999 (357)	--	1.0	--	0.5	--
Schon T, et al. 2011 (354)	--	0.25	--	--	--
WHO 2008 (60)	--	--	--	4.0	--
WHO 2012 (64)	--	--	--	--	--

Clofazimine has also shown intracellular activity against *Mtb* in human macrophages (561), with one study reporting nearly 99% killing that was roughly equivalent to amikacin, greater than kanamycin, capreomycin, streptomycin, ciprofloxacin, and ethambutol, but less than isoniazid, rifampicin, ethionamide, ofloxacin and sparfloxacin (251). At a concentration of 1 µg/ml, clofazimine showed activity against *Mtb* persisters in an in vitro anaerobic model, which was less than that of rifampicin and moxifloxacin, but greater than that of INH (562).

8.2.2 Activity in animal models

Despite initial concerns about the lack of activity in guinea pigs and monkeys, other early studies showed in vivo activity of clofazimine in hamsters, rabbits, and mice (554, 561). More recent animal studies have confirmed its *in vivo* activity against *Mtb*. In an in vivo model of *Mtb* persisters using mice infected with a low-dose aerosol of *Mtb*, clofazimine had dose dependent activity, with a 20mg/kg dose more effective in reducing *Mtb* CFUs than a 50 mg/kg dose of moxifloxacin at all time points studied (562). A daily dose of 20 mg/kg of clofazimine eradicated all *Mtb* from the lungs after 90 days in all mice, and a 200 mg/kg dose after 60 days (562). Because of the concentrating of clofazimine in tissue and its long half-life, a carry-over effect cannot be ruled out as the cause for these findings (562), though the existence of such an effect remains controversial (563). Some moxifloxacin-resistant mutants were obtained after moxifloxacin exposure, but no clofazimine-resistant mutants were obtained regardless of the clofazimine duration or dose (562). In experiments evaluating multiple bedaquiline drug combinations in a mouse model, bedaquiline-pyrazinamide was most effective when combined with clofazimine, compared to the addition of moxifloxacin, rifapentine, linezolid, or PA-824 (89). Despite attempts to limit carryover effects in this experiment, the authors highlight the need for relapse-based assessments of the sterilizing activity of clofazimine-containing regimens (89). In a follow-up murine study, the combination of clofazimine with rifapentine added the most sterilizing activity to bedaquiline-PZA in relapse-based assessments (564). These more recent studies suggest a possible role for clofazimine in future regimens, though further evaluation is needed.

8.2.3 Activity in human tuberculosis

Clofazimine was a component of a shortened treatment regimen for adults with MDR-TB in Bangladesh, reported by Van Deun and colleagues (565). In this study, a 4 month intensive phase containing kanamycin, gatifloxacin, clofazimine, ethambutol, high-dose isoniazid, pyrazinamide, prothionamide, followed by a 5 month continuation phase containing gatifloxacin, ethambutol, pyrazinamide, and clofazimine, resulted in 87.8% with cure or treatment completion with only 0.5% relapsing (565). An ongoing randomized trial is evaluating a similar regimen in populations with a high HIV prevalence and higher rates of second-line antituberculosis drug resistance (see Section 8.6).

Additional support for clofazimine includes the report of a cohort of adults with XDR-TB, in which more than 60% of patients had a successful treatment outcome with a clofazimine-containing regimen in most (566).

A recent systematic review of clofazimine use in DR-TB identified 12 studies reporting on 3489 MDR- and XDR-TB patients who received clofazimine as part of their treatment regimen (567). There was a wide range of treatment success reported, from 16.5% to 87.8%, with a pooled percent of 61.96% having treatment success (567). Though there was no control in this meta-analysis, the authors note that this percentage of treatment success is in line with overall DR-TB outcomes, and conclude that clofazimine should be considered an alternative treatment option (567).

Our search did not identify any specific studies of clofazimine in children with tuberculosis. In a report of linezolid-containing regimens in children with DR-TB, two children also received clofazimine (517). Neither child was reported to have clofazimine-associated adverse effects and both had successful outcomes, though it is difficult to ascertain the contribution of clofazimine to these multi-drug regimens (517).

8.2.4 Resistance

One of the notable features of clofazimine is the low percentage of resistance among *Mtb* (554). In fact it has been noted that clofazimine-resistance mutants are difficult to generate in the lab or in the clinical setting (555). Little else has been written about clofazimine-resistance in *Mtb*.

8.3 Pharmacokinetics and Pharmacodynamics

8.3.1 Pharmacokinetics

Absorption of clofazimine is reported to be 45-62% after an oral dose, and food may increase the rate and degree of absorption (555) . Nix and colleagues reported absorption was increased with a high-fat meal, and slightly decreased when given with orange juice or antacid (568). Multiple metabolites have been identified which represent less than 1% of the total drug dose, but their antimycobacterial activity is unknown (555, 569). Clofazimine is highly lipophilic, which accounts for its characteristic pharmacologic property of accumulation in tissues, particularly in fatty tissues and the reticuloendothelial system, including macrophages (554, 555). As such, serum levels are generally not affected by dose or duration of treatment (554). Estimates of the half-life with prolonged dosing have ranged from 10-70 days (554, 570, 571). The drug is mainly eliminated in the faeces, and after cessation of treatment the drug slowly releases from tissue into serum and is eliminated (554). Clofazimine may decrease rifampicin absorption (572).

Our search did not identify any studies of clofazimine pharmacokinetics in adults with TB, though it has been studied in leprosy and in healthy volunteers (568, 571). Nix and colleagues reported a mean T_{max} of 5.89-7.07 hrs, a mean C_{max} of 169-369 nanograms/ml, and mean serum $AUC_{0\text{-infinity}}$ of 2422-5144 nanogram*h/ml (568).

Our search did not identify any pharmacokinetic studies of clofazimine in children.

8.3.2 Pharmacodynamics

The low serum levels and high tissue levels make evaluation of clofazimine pharmacodynamics a challenge, and we are unaware of proposed PD targets to date. A 2-hour post-dose value of 0.5-4.0 µg/ml can suggest that the it is being absorbed (170).

8.4 Safety Data

Gastrointestinal adverse effects

Gastrointestinal disturbance is one of the most commonly reported adverse effects associated with clofazimine, with abdominal pain, nausea, vomiting, and diarrhea reported in 40-50% of patients (555).

In an adult cohort treated with clofazimine for leprosy, severe abdominal symptoms were reported in 9 of 84, though this appears to be a higher frequency than usually reported (573). Crystalline deposits of clofazimine have been found in organs where it concentrates, including organs of the GI system, but severe abdominal complications related to this are rare (555, 574). WHO guidelines advise that severe abdominal pain and acute abdomen have been reported with, and would be an indication for discontinuing clofazimine (16).

Specific data on GI adverse effects in children has not been well reported. A 12 year old child being treated for leprosy had clofazimine discontinued after an episode of severe haematemesis, a rare toxicity previously described (575). Severe enteropathy has also been reported in a child (576).

Dermatologic

Dermatologic adverse effects are the most common and striking. Up to 75-100% of patients develop a reddish-black or orange skin discoloration within a few weeks of starting treatment (554, 555). Discoloration of the eyes as well as urine, faeces, sputum, and sweat are also possible (555). The skin color changes are reversible over time ranging from months to years, and traces of clofazimine have been found in skin 1-2 years after its discontinuation (577). This color-change is not dangerous, but can be very distressing to patients. Ichtyiosis has been reported in 8-28% of patients, and other rashes or skin dryness is reported in another 1-5% of patients (555). Interestingly, Ramu and colleagues reported that most patients accepted the skin color change but felt that the ichtyiosis was stigmatizing (573). In one report, co-adminstration of isoniazid appeared to lessen adverse effects, including skin color change (573).

We did not identify specific reports of dermatologic adverse effects in children, but presumably they are similar in frequency and scope in children.

In MDR-TB treatment regimens

Based on results in leprosy, long term treatment with clofazimine is generally well tolerated, with few cases requiring discontinuation (575). Limited data exists regarding its adverse effects in MDR-TB treated adults. Of note, the study by Van Deun and colleagues reported no adverse effects typical for clofazimine during the study (565). In the systematic review of its use in DR-TB, the rate of adverse effects in these studies was high but comparable to other DR-TB cohorts not treated with clofazimine (567). GI intolerance and skin discoloration were the most commonly reported effects (567). One included study reported skin discoloration in 36/44 (81.8%), icthyiosis in 12/44 (27.3%), depression in 1/44 (2.3%), GI disturbance in 21/44 (47.7%) and dizziness in 1/44 (2.3%), but no patient discontinued clofazimine due to adverse effects (567, 578).

8.5 Existing recommendations for clofazimine use in paediatric DR-TB

The WHO 2008 guidelines recommend the use of Group 5 drugs, of which clofazimine is one, only when a regimen containing 4 drugs with likely activity cannot be created from Groups 1-4, though no other specific recommendations regarding clofazimine were made, and a recommended dose was not provided (16). The WHO 2011 guidelines update did not specifically address clofazimine (232). There are no specific recommendations for its use in children in these documents (16, 232). We are unaware of any other formal recommendations for the use of clofazimine in children with DR-TB.

A dose of 3-5 mg/kg has been recommended (19). As the only formulations are soft gel caps, which cannot be given as partial doses, appropriate weight-based dosing can be very challenging in children. Additionally, young children may be unable to swallow the caps.

8.6 Future or Ongoing Studies in Children

A search of www.clinicaltrials.gov and the WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/) revealed no registered studies of clofazimine in children with tuberculosis.

We identified two ongoing registered studies in adults with TB that include clofazimine. The study "Evaluation of Early Bactericidal Activity in Pulmonary Tuberculosis With Clofazimine (C)-TMC207 (J)-PA-824 (Pa)-Pyrazinamide (Z) (NC-003)" (ClinicalTrials.gov Identifier NCT01691534) is evaluating the EBA of multiple different combinations of drugs in adults, including clofazimine. The study "The evaluation of a standardised treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant tuberculosis (MDR-TB): a multi-centre international parallel group randomised controlled trial (STREAM)" (ISRCTN78372190), is evaluating a shortened regimen based on that reported by Van Deun and colleagues (565) compared to existing MDR treatment regimens in adults with MDR-TB.

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8.7 Conclusions and Recommendations

Clofazimine's pharmacologic characteristics, its ability to concentrate in macrophages, its potential sterilizing activity, its lack of cross-resistance with other agents, and its apparent ability to avoid developing resistance, all make it a potentially attractive option for treatment of DR-TB. Clofazimine has shown *in vitro* and *in vivo* activity against *Mtb*, including in combinations with novel agents. Its individual contribution to MDR-TB treatment is unknown, though it has been a component of a successful 9 month treatment regimen. It is known to cause GI adverse effects and skin discoloration, which can be quite disturbing to patients, though serious or life-threatening toxicities are rare. There is limited safety data available for it in MDR-TB treatment regimens, but long-term treatment of leprosy with clofazimine has been generally well-tolerated. Adverse effects in children are poorly described, though the lack of reports of serious toxicity despite its use in the treatment of leprosy suggests no major problems. Clofazimine is listed as an Essential Medicine for adults and children for the treatment of leprosy (20). There is no reason to suspect increased adverse effects in DR-TB, though this remains to be more definitively demonstrated.

Currently there is insufficient evidence to recommend clofazimine for the routine treatment of MDR-TB in children. Where additional resistance exists and treatment options are much more limited, such as in the case of XDR-TB, the risks and benefits favour its use. We recommend clofazimine as an Essential Medicine for the treatment of XDR-TB in children, to be used in centres experienced in the management of complicated paediatric DR-TB. We recommend a dose of 3-5 mg/kg, up to a maximum of 100 mg daily. In younger children, the dose may be given intermittently in order to achieve an average daily dose of 3-5 mg/kg. Because of the limited data in children, we recommend close monitoring and formal reporting of treatment outcomes and any adverse effects in any children receiving clofazimine for DR-TB.

We recommend that studies of clofazimine be conducted in children with DR-TB to inform dosing and adverse effect profiles in different age strata. More child-friendly formulations are needed, particularly if clofazimine is to become a more important component of future treatment regimens.

9.0 Summary

Based on existing estimates of global MDR-TB prevalence and assuming that 10-15% of the disease burden is in children, this translates into a conservative estimate of 63,000 prevalent cases of MDR-TB per year in children. New diagnostics and a growing awareness of this largely unrecognized disease burden will likely result in increasing number of children diagnosed with MDR-TB. Despite gaps in data regarding efficacy, safety, and pharmacokinetics of second-line antituberculosis drugs in children, treatment outcomes reported to date are very good, with more than 80% of children with DR-TB having successful treatment and limited serious toxicity. Access to and appropriate use of second-line antituberculosis drugs are critical to ensuring safe, effective treatment and good outcomes in paediatric DR-TB.

We have reviewed and summarized the evidence for the second-line antituberculosis drugs in children for DR-TB, including efficacy, safety, pharmacokinetics, and existing recommendations for their use. Based on our review of the evidence, our anecdotal experience, and weighing the risks and benefits for each drug, we have made recommendations for drugs to be included in the Essential Medicines List for DR-TB in children, as summarized in Table 9.1.

Table 9.1 Summary of our recommendations for inclusion of second-line antituberculosis drugs for use in children with drug-resistant TB in the Essential Medicines List

	2011 - 3rd WHO Model List of Essential Medicines for Children (1)	2012 - Our recommendations for inclusion in Essential Medicine List
Ofloxacin	Included	Remain included, as alternative where levofloxacin or moxifloxacin are not available
Levofloxacin	As an alternative	Include, as a preferred FLQ for DR-TB
Moxifloxacin	No	Include, as a preferred FLQ for DR-TB
Amikacin	Included	Remain included
Kanamycin	Included	Remain included
Capreomycin	Included	Remain included
Ethionamide	Included	Remain included
Prothionamide	No	Include, as alternative drug where ethionamide is not available
Cycloserine	Included	Remain included
Terizidone	No	Include, as alternative drug where cycloserine is not available
P-aminosalicylic acid (PAS)	Included	Remain included
Linezolid	No	Include, for the indication of XDR-TB, Pre-XDR-TB†, or MDR-TB meningitis
Clofazimine	No *(included for indication of leprosy only)*	Include, for the indication of XDR-TB

†Pre-XDR-TB = MDR-TB with additional resistance to a FLQ or a second-line injectable, but not both
FLQ = fluoroquinolone

As noted in the review, data on the safety and tolerability with the long-term use of some of these drugs is limited in children, and we would recommend that clinicians using these drugs monitor children closely for any adverse effects, and report on the efficacy, safety and tolerability of these drugs in children they are treating, in a standard manner. Ongoing studies on the pharmacokinetics of many of these drugs will soon provide additional information on the most appropriate dosing of many of these drugs. Few of these drugs exist in formulations that allow accurate or easy paediatric dosing and administration, and we urgently recommend the development of child-friendly formulations of all these second-line antituberculosis drugs. Access to these drugs is critical for the successful treatment of children with DR-TB, and we call on all involved stakeholders to ensure that these drugs are made available to children, at reasonable prices, wherever children with DR-TB may be.

Appendix 1 – Results of pharmacokinetic studies of second-line antituberculosis drugs

Table A-1 – Results of pharmacokinetic studies of ofloxacin in adults with TB, and children with TB or other conditions (concentrations in µg/ml, times in hours)

Study	Methods	Disease	HIV	Age in years	N	Dosage	T_{max}	T ½	C_{max}	0	0.5	1	2	4	5	6	8	12	AUC
Adults																			
Zhu M, et al. 2002 (156)	HPLC	TB	3	42 (22-57)	11	800 mg orally (600-1200) [intensive sampling]	1.03 (0.5-6)	7.34 (3.53-28.3)	10.5 (8.0-14.3)	--	--	--	--	--	--	--	--	--	103 (48-755)
			--	43 (2.5-79)	62	600 (200-1000) [sparse sampling]	--	5.70 (0.79-173)	8.52 (1.83-19.9)	--	--	--	--	--	--	--	--	--	68.7 (0.78-374)
Chulavatnatol, S, et al. 2003 (157)	HPLC	DR-TB	--	38.09 (11.97)	11	10 mg/kg orally (once daily)	1.68 (1.21)	8.03 (3.37)	9.61 (2.17)	--	--	--	--	--	--	--	--	--	70.57 (26.4)
Chigutsa E, at al. 2012 (138)	HPLC	MDR-TB (Cape Town)	16	34 (20-63)	38	800 mg orally (with meal)	3	7.8	8.8	--	--	--	--	--	--	--	--	--	--
		MDR-TB (Durban)	13		27	800 mg orally (empty stomach)	1.2		10.4	--	--	--	--	--	--	--	--	--	--
Children																			
Bethal DB, et al. 1996 (130)	HPLC	Multidrug-resistant typhoid fever	--	10.4 (5-14)	17	7.5 mg/kg IV	--	4.45 (3.79-5.10)	9.21 (8.22-10.2)	--	--	--	--	--	--	--	--	--	31.15 (26.1-36.2)
					17	7.5 mg/kg orally	1.39 (0.77-2.05)	3.26 (2.31-3.75)	5.73 (4.87-6.59)	--	--	--	--	--	--	--	--	--	26.5 (25.0-28.0)
Hesseling AC, et al. 2012	Mass spec-trometer	MDR-TB treatment and prophylaxis	--	0-2 yrs group	12	20mg/kg orally	1.42 (0.52)	--	9.54 (8.57-10.6)	--	--	--	--	--	--	--	--	--	45.1 (38.3-47.9) †
			--	2 - 5	21	20 mg/kg orally	1.67 (0.73)	--	8.79 (6.98-9.99)	--	--	--	--	--	--	--	--	--	42.4 (35.6-50.8) †
			--	6-15	10	20 mg/kg orally	2.60 (1.27)	--	7.16 (5.84-7.66)	--	--	--	--	--	--	--	--	--	39.2 (32.1-42.3) †

†AUC 0-8

Table A-2 – Results of pharmacokinetic studies of levofloxacin in adults with TB, and children with TB or other conditions (concentrations in µg/ml, times in hours)

Study	Methods	Disease	HIV	Age in years	N	Dosage	T_{max}	T ½	C_{max}	0	0.5	1	2	4	5	6	8	12	AUC
Adults																			
Peloquin CA, et al. 2008 (141)	HPLC	TB	0/10	44 (30-54)	10	1000 mg orally	1.0 (1.0-4.0)	7.37 (4.14-16.3)	15.55 (8.55-42.99)	--	--	--	--	--	--	--	--	--	131 (52-702)
Levofloxacin in *Tuberculosis* Drug Review 2008 (579)	--	--	--	--	--	750 mg orally	--	7.7-8.9	7-12	--	--	--	--	--	--	--	--	--	71.4-110
Children																			
Chien S, et al. 2005 (133)	HPLC	Bacterial infections	--	0.5 - 2	6	7.0 mg/kg IV	--	4.1 (1.3)	5.19 (1.26)	--	--	--	--	--	--	--	--	--	21.5 (6.1)
				0.5 - 2	8	7.0 mg/kg orally	1.4 (0.4)	5.0 (1.3)	4.21 (1.49)	--	--	--	--	--	--	--	--	--	25.8 (9.2)
				2 - <5	7	7.0 mg/kg IV	--	4.0 (0.8)	6.02 (1.07)	--	--	--	--	--	--	--	--	--	22.7 (4.7)
				2 - <5	8	7.0 mg/kg orally	1.6 (0.5)	1.6 (1.3)	4.56 (0.83)	--	--	--	--	--	--	--	--	--	25.9 (4.8)
				5 - <10	10	7.0 mg/kg IV	--	4.8 (0.8)	7.30 (3.85)	--	--	--	--	--	--	--	--	--	29.2 (6.4)
				5 - <10	8	7.0 mg/kg orally	1.3 (0.4)	5.3 (1.6)	4.64 (0.39)	--	--	--	--	--	--	--	--	--	29.0 (10.0)
				10 - <12	7	7.0 mg/kg IV	--	5.4 (0.8)	6.12 (1.19)	--	--	--	--	--	--	--	--	--	39.8 (11.3)
				10 - <12	8	7.0 mg/kg orally	1.9 (0.9)	5.5 (0.7)	3.99 (0.87)	--	--	--	--	--	--	--	--	--	37.3 (9.8)
				12 - <16	10	7.0 mg/kg IV	--	6.0 (2.1)	6.34 (1.58)	--	--	--	--	--	--	--	--	--	40.5 (7.6)
				12 - <16	8	7.0 mg/kg orally	1.6 (1.0)	5.8 (1.4)	4.76 (0.86)	--	--	--	--	--	--	--	--	--	41.1 (6.8)

Table A-3 – Results of pharmacokinetic studies of moxifloxacin in adults with TB, and children with TB or other conditions (concentrations in µg/ml, times in hours)

Study	Methods	Disease	HIV	Age in years	N	Dosage	T_{max}	T ½	C_{max}	0	0.5	1	2	4	5	6	8	12	AUC
Adult																			
Nijland HMJ, et al. 2007 (163)	HPLC	TB	--	30 (20-55)	19	400 mg orally (with 450 mg rifampicin)	2.5 (0.5-6.0)	7.1 (5.0-9.6)	3.2 (2.5-4.5)	--	--	--	--	--	--	--	--	--	33.3 (25.1-55.5)
					19	400 mg orally	1.00 (0.5-3.0)	9.9 (7.4-14.0)	4.7 (3.4-6.0)	--	--	--	--	--	--	--	--	--	48.2 (37.2-60.5)
Peloquin CA, et al. 2008 (141)	HPLC	TB	--	35 (18-46)	9	400 mg orally	1.0 (1.0-2.0)	6.53 (4.25-10.6)	6.13 (4.47-9.00)	--	--	--	--	--	--	--	--	--	60 (24-140)
Pranger AD, et al. 2011 (142)	HPLC	TB	--	(adults)	16	400 mg orally	1 (1-2)	8 (6-10)	2.5 (2.0-2.9)	--	--	--	--	--	--	--	--	--	24.9 (20.7-35.2)
Zvada SP, et al. 2012 (162)	HPLC	TB	--	40 (21-51)	27	400 mg orally (single dose)	--	--	3.8 (2.1-4.6)	--	--	--	--	--	--	--	--	--	50.8 (31.8-65.3)
Manika K, et al. 2012 (164)	HPLC	MDR/XDR-TB	0/7	40.1 (15.7)	7	400 mg orally	2.36 (0.56)	--	4.59 (2.06)	--	--	--	--	--	--	--	--	--	37.96 (16.5)
Ruslami R, et al. 2013 (113)	--	TB meningitis	--	18-60	19	400 mg orally	2 (1-6)	--	3.9 (3.2-4.8)	--	--	--	--	--	--	--	--	--	28.6 (24.2-33.8)
			--	18-64	16	800 mg orally	2 (1-6)	--	7.4 (5.6-9.6)	--	--	--	--	--	--	--	--	--	60.4 (45.4-80.3)

Table A-4 - Results of pharmacokinetic studies of amikacin in adults with TB, and children with TB or other conditions (concentrations in µg/ml, times in hours)

Study	Methods	Age in years	Disease	HIV	Dosage	N	T_{max}	T ½	C_{max}	0	0.5	1	2	4	5	6	8	12	AUC
Adults																			
Peloquin CA, et al. 2004 (274)	--	51 (27-75)	TB, MAC, NTM	--	15 mg/kg IV	11	--	2.5 (1.7-3.0)	46 (25-54)	--	--	--	--	--	--	--	--	--	--
	--	48 (35-70)	TB, MAC, NTM	--	25 mg/kg IV	11	--	2.1 (1.4-3.3)	79 (84-98)	--	--	--	--	--	--	--	--	--	--
Donald PR, et al. 2001 (258)	Immuno-assay	36 (11)	TB	--	5 mg/kg IM	12	--	--	--	--	--	13.5 (2.7)	7.4 (2.3)	4.4 (1.7)	2.9 (1.2)	--	--	--	--
		37 (8)	TB	--	10 mg/kg IM	13	--	--	--	--	--	26.7 (5.5)	16.1 (3.2)	10.7 (2.2)	6.5 (1.8)	--	--	--	--
		35 (10)	TB	--	15 mg/kg IM	15	--	--	--	--	--	39.2 (9.0)	21.7 (4.5)	14.2 (2.8)	8.8 (2.4)	--	--	--	--
Amikacin review in *Tuberculosis*, 2008 (235)	--	--	--	--	6.3 mg/kg (+/- 1.4)	--	--	2.3	26 (+/- 4)	--	--	--	--	--	--	--	--	--	--
Children																			
Hesseling AC, et al. 2012	--	<2	DR-TB	--	20 mg/kg IM	6	1.00 (0.00)	--	43.65 (42.2-49.2)	--	--	--	--	--	--	--	--	--	103.9 (96.8-119)#
		2-5	DR-TB	--	20 mg/kg IM	7	1.14 (0.38)	--	49.10 (40.7-59.2)	--	--	--	--	--	--	--	--	--	124.2 (97.7-162)#
		>5 years	DR-TB	--	20 mg/kg IM	15	1.13 (0.35)	--	49.60 (40.3-56.4)	--	--	--	--	--	--	--	--	--	159.3 (124-179)#
Khan AJ, et al. 1976 (286)	--	7 (3-12)	UTI	--	7.5 mg/kg IM (first dose)	7	--	--	--	--	--	15.7 (11-20)	--	--	--	--	--	0.75 (0.4-2.7)	--
			UTI	--	7.5 mg/kg IM (after 2-7 days)	5	--	--	--	--	--	19 (15-22)	--	--	--	3.8 (2.6-4.9)	--	0.72 (0.4-0.8)	--
Viscoli C, et al. 1991 (287)	Immuno-assaay (Abbot)	3 (2-13)	Fever and neutropaenia after bone marrow transplant	--	20 mg/kg IV (over 30 min) Day 1	13	--	--	72.3 (11.6)	<3	36.9 (9.55)	--	--	--	--	<3	--	<3	--

					20 mg/kg IV (over 30 min) Day 4	13	--	--	74.0 (19.3)	<3	39.7 (14.1)	--	--	--	--	<3	--	<3	--
Kafetzis DA, et al. 1991 (288)	Immuno-assay (Abbot)	6.8	Severe gram-negative infections	--	20 mg/kg IV (over 15-30 min)	56	--	--	--	--	--	39.8 (8.4)	--	--	--	--	--	--	--
					(subset of above)	13	--	2.02 (0.64)	--	--	--	36.5 (9.1)	20.5 (6.5)	9.5 (4.0)	--	--	2.7 (2.2)	1.0 (1.4)	--
Marik PE, et al. 1991 (289)	Immuno-assay	8 weeks (range 1 – 23)	Severe gram-negative infections	--	20 mg/kg IV (over 3-5 mins)	30	--	5.02 (1.5-11.9	30.1 (4.6)	1.3 (4.6)	--	--	--	--	--	--	--	--	--
		28 weeks (range 24-52)		--	20 mg/kg IV (over 3-5 mins)	30	--	2.86 (0.6 – 6.3)	33.9 (6.5)	0.46 (0.1)	--	--	--	--	--	--	--	--	--
		34 yrs (range 1 - 70)		--	15 mg/kg IV (over 3-5 mins)	40	--	3.45 (1.1 – 6.5)	33.8 (4.8)	0.77 (0.8)	--	--	--	--	--	--	--	--	--
Kafetzis DA, et al. 1979 (290)	Agar well-plate with bacillus subtillus	Infants - 3.5 months	Serious infection	--	7.5 mg/kg IM	10	--	2.15 (0.17)	--	--	17 (3.6)	15.7 (2.8)	10.6 (3.4)	4.2 (1.1)	--	2.6 (0.34)	--	<0.8	--
		Children – 3.1 yrs		--	7.5 mg/kg IV (bolus)	3	--	2.21 (0.15)	--	--	14.7 (4.8)	11.6 (5.1)	8.7 (4.8)	5.1 (3.1)	--	3.8 (0.4)	--	<0.8	--
				--	7.5 mg/kg IM	8	--	2.02 (0.24)	--	--	18.4 (5.4)	17.7 (3.7)	11.6 (4.6)	3.7 (1.4)	--	2.2 (1.0)	--	<0.8	--
				--	7.5 mg/kg IV (bolus)	3	--	2.04 (0.2)	--	--	19.8 (3.2)	13.1 (2.3)	7.8 (0.5)	4.0 (0.1)	--	2.0 (0.3)	--	<0.8	--
Trujillo H, et al. 1991 (580)	Agar diffusion	3 months – 14 years	Serious infection	--	20 mg/kg IV (over 30 min)	25	--	--	--	6.8 (3.4)	--	52 (11.8)	--	--	--	--	--	--	--
		(subset of above)			20 mg/kg IV (over 30 min)	4				2.5 (1.5)	48 (11.5)	48 (5.6)	29.7 (5.8)	14.7 (5.8)	--	--	6.8 (4.2)	4.1 (3.1)	--
El Desoky AS, et al. 1999 (581)	--	1.45 (1.34)	Broncho-pneuonia	--	7.5 mg/kg IV (over 30 min)	11	--	--	--	<0.8	20.0 (4.4)	--	--	--	--	--	--	--	--
					15 mg/kg IV (over 30 min)	10	--	--	--	<0.8 (n=6) 3.6 (1.6) (n=5)	39.4 (9.6)	--	--	--	--	--	--	--	--
Cleary TG, et al. 1979 (291)	Radio-enzymatic assay	1-16	Malignancy, bacterial infection	--	5 mg/kg IV (over 30 min) 8 hourly	12	--	1.24 (0.9)*	--	--	29.3 (5.6)†	13.6 (1.5)†	5.7 (0.7)†	1.5 (0.4)†	--	0.4 (0.1)†	0.4 (0.1)†	--	--
					5 mg/kg IV (over 60 min) 8 hourly	12	--		--	--	--	18.1 (3.2)†	9.0 (1.7)†	4.2 (1.0)†	--	1.6 (0.5)†	0.7 (0.3)†	--	--
					5 mg/kg IV (over 60 min)	22	--		--	--	--	17.2 (1.7)†	8.3 (1.0)†	3.3 (0.7)†	--	1.2 (0.3)†	--	--	--

					6 hourly														
Kafetzis DA, et al. 2000 (292)	--	2-84 months	Acute pyelo-nephritis	--	7.5 mg/kg IV (over 30 min) 12 hourly	6	--			--	19.1 (12.2-25.9) ††	--	--	--	--	--	--	0.66 (0.1-2.1)	--
Vogelstein B, et al. 1977 (582)	Enzymatic assay	4-16	Infection	--	420 mg/m^2 (over 5 mins) IV 8 hourly	20	--	1.6 (0.4)	--	--	--	28.7	--	--	--	--	--	--	--
Lanao JM, et al. 1981 (293)	Method with bacillus subtillus	3-11	--	--	7.5 mg/kg IV (bolus)	8	--	1.19 (0.19)	--	--	--	--	--	--	--	--	--	--	--
Krivoy N, et al. 1998 (294)	Immuno-assay (Abbot)	5.1 (3.5)	Neutropenic fever	--	10 mg/kg IV (over 30 min) 12 hourly	10	--	2.51 (0.74)	--	--	19.1 (12.3)	--	--	--	--	--	--	0.85 (0.74)	--
		9.2 (5.3)		--	20 mg/kg IV (over 30 min) 24 hourly	13	--	2.85 (0.32)	--	0.18 (0.24)	42.6 (12.6)	--	--	--	--	--	--	--	--	--
Byl B, et al. 2001 (281)	Immuno-assay (Abbot)	19 (10-32)	Cystic Fibrosis (CF)	--	30 mg/kg IV (over 30 min) 24 hourly	12	--	2.6 (1.3)	--	--	116 (37)	--	--	--	--	--	--	--	235 (110)
Autret E, et al. 1986 (279)	Immuno-assay (Abbot)	7.6 (3-15)	CF	--	5 mg/kg IV (over 30 min) 6-8 hourly	9 [27 pks]	--	1.1 (0.26) **	18.5 (4.2)	--	--	--	--	--	--	--	--	--	--
					7.5 mg/kg IV (over 30 min) 6-12 hourly	[6 pks]	--	--	25.95 (10.2)	--	--	--	--	--	--	--	--	--	--
					12.5 mg/kg IV (over 30 min) 12 hourly	[3 pks]	--	--	31.5 (10.8)	--	--	--	--	--	--	--	--	--	--
		6.3 (1-12)	Non-CF Controls	--	5 mg/kg IV (over 30 min) 8 hourly	4	--	0.83 (0.15)	16.8 (4.9)	--	--	--	--	--	--	--	--	--	--
Canis F, et al. 1997 (280)	Immuno-assay (Abbot)	9.8 (1.7-22.2)	CF	--	35 mg/kg IV (over 30 min) 24 hourly	18	--	3.15-16.57	121.4 (37.5)	0.88 (0.62)	--	--	--	--	--	--	--	--	--
Vic P, et al. 1996 (583)	Immuno-assay (Abbot)	9.6 (4.8)	CF	--	35 mg/kg IV (over 30 min) 24 hourly	20	--	--	73 (19)	0.78 (0.55)	--	--	--	--	--	--	--	--	287 (65)

† Concentration as measured at time after start of infusion

* t1/2 was calculated for all 3 groups taken together

†† Concentration as measured 15 minutes after completion of the infusion

** t ½ calculated as mean from all pharmacokinetic studies in these cystic fibrosis patients

#AUC 0-8

Table A-5 – Results of pharmacokinetic studies of kanamycin in adults with TB, and children with TB or other conditions (concentrations in µg/ml, times in hours)

Study	Methods	Disease	HIV	Age in years	N	Dosage	T_{max}	T ½	C_{max}	0	0.5	1	2	4	5	6	8	12	AUC
Adults																			
Peloquin CA, et al. (274)	--	TB, MAC, NTM	--	42 (19-68)	16	15 mg/kg IV	--	2.2 (1.5-3.6)	44 (32-65)	--	--	--	--	--	--	--	--	--	--
	--	TB, MAC, NTM	--	55 (25-76)	17	25 mg/kg IV	--	2.5 (1.6-4.0)	72 (33-113)	--	--	--	--	--	--	--	--	--	--
Kanamycin review in *Tuberculosis*, 2008 (298)	--	--	--	--	--	7.5 mg/kg IV	--	2.5	22	--	--	--	--	--	--	--	--	--	--
Children																			
Berger S, et al. 1958 (297)	Bacillus subtillus method	Various	--	3-23 months	4	5 mg/kg IM	--	--	--	--	--	14 (9-19)	--	--	--	1.3 (1.2-1.3)	--	--	--
			--	2-13 years	3	5 mg/kg IM	--	--	--	--	--	12 (11-18)	--	--	--	0.7 (0.6-0.8)	--	--	--
			--	3-23 months	3	15 mg/kg IM	--	--	--	<1	--	32 (30-40)	--	--	--	2.6 (1.7-3.2)	--	--	--
			--	2-13 years	6	15 mg/kg IM	--	--	--	<1	--	33 (25-100)	--	--	--	5.9 (4.1-10)	--	--	--
			--	3-23 months	4	25 mg/kg IM	--	--	--	<1	--	50 (41-65)	--	--	--	4.2 (2.7-8.2)	--	--	--
			--	2-13 years	4	25 mg/kg IM	--	--	--	<1	--	47 (44-58)	--	--	--	4.8 (3.5-10)	--	--	--
High RH, et al. 1958 (296)	--	--	--	Over 1 week of age	17	5 mkg/kg	--	--	18 (9-31)	--	--	--	--	--	--	--	--	--	--
					26	20 mg/kg	--	--	43 (29-120)	--	--	--	--	--	--	--	--	--	--
Hieber JP, et al. 1976 (295)	Bacillus subtillus method	Post-operative	--	0-6 months	4	5 mg/kg IM	--	2.5	--	--	10.4 (9.2-12)	9.0 (8-10)	6.0 (4.8-7.6)	3.3 (1.8-4.6)	--	--	1.3 (1.0-1.5)	--	--

--	1-12 years	12	5 mg/kg IM	--	1.7	--	--	10.2 (3.6-18)	9.3 (4.4-14)	6.3 (4.0-9.6)	2.8 (1.7-5.2)	--	--	0.6 (0.3-1.2)	--	--
--	0-6 months	2	10 mg/kg IM	--	2.0	--	--	18.0 (16-22)	14.4 (13-16)	9.8 (9.6-10)	2.9 (2.5-3.2)	--	--	0.8 (0.5-1.1)	--	--
--	1-12 years	8	10 mg/kg IM	--	1.5	--	--	14.0 (6-29)	18.4 (8.4 – 30)	13.0 (8.4-20)	5.9 (2.8-8)	--	--	0.9 (0.4-1.3)	--	--

Table A-6 – Results of pharmacokinetic studies of capreomycin in adults with TB, and children with TB or other conditions (concentrations in µg/ml, times in hours)

Study	Methods	Age in years	Disease	HIV	Dosage	N	T_{max}	T ½	C_{max}	0	0.5	1	2	4	5	6	8	12	AUC
Adults																			
Morse WC, et al. 1966 (254)	Bioassay	--	--	--	1 gram IM	29	--	--	--	--	--	--	29.4	--	--	10.4	--	--	--
Black HR, et al. 1966 (276)	Bacillus subtillus method	--	TB	--	1 gram IM	10	--	--	--	0.95	--	29.1	32.7	19.8	--	12.1	--	3.2	--
Capreomycin review in *Tuberculosis*, 2008 (237)	--	--	--	--	1 gram IM	--	--	--	32 (20-47)	--	--	--	--	--	--	--	--	--	--

Table A-7 – Results of pharmacokinetic studies of ethionamide in adults with TB, and children with TB or other conditions (concentrations in µg/ml, times in hours)

Study	Methods	Disease	HIV	Age in years	N	Dosage	T_{max}	T ½	C_{max}	0	0.5	1	2	4	5	6	8	12	AUC
Adults																			
Zhu M, et al. 2002 (378)	HPLC	TB	--	36.2 (12.2-57.6)	5	500 mg (250-500 mg)	2.00 (1.25-2.22)	1.63 (0.23-0.77)	1.35 (0.48-5.63)	--	--	--	--	--	--	--	--	--	2.80 (1.00-8.96)
		TB	--	45.5 (6.7-79.0)	50	500 mg (250-1000)	--	1.94 (0.39-2.76)	--	--	--	--	--	--	--	--	--	--	3.95 (1.47-21.2)
		Healthy volunteers	--	26 (24-47)	12	500 mg	1.50 (0.75-3.00)	1.94 (1.34-3.81)	1.97 (0.99-6.10)	--	--	--	--	--	--	--	--	--	8.00 (5.90-13.3)
Ethionamide review in *Tuberculosis*, 2008 (349)	--	--	--	--	--	250 mg	--	1.92	2.16	--	--	--	--	--	--	--	--	--	7.67
Children																			
Thee S, et al. 2011 (380)	HPLC	TB	2	<2 years	5	15-20 mg/kg	0.97 (0.9-1.0)	0.92 (0.4)	3.79 (1.59)	--	--	--	--	--	--	--	--	--	7.84 (3.74)
		TB – RMP co-trtmnt	2	<2 years	5		0.98 (0.9-1.3)	1.11 (0.33)	3.91 (1.61)	--	--	--	--	--	--	--	--	--	8.75 (3.87)
		TB	2	2-6years	6	15-20 mg/kg	1.11 (0.9-2.1)	(1.30 (0.46)	4.43 (1.23)	--	--	--	--	--	--	--	--	--	11.51 (6.90)
		TB – RMP co-trtmnt	2	2-6 years	5		1.00 (1.0-1.1)	1.08 (0.37)	3.58 (1.36)	--	--	--	--	--	--	--	--	--	8.72 (3.90)
		TB	3	6-12 years	5	15-20 mg/kg	2.00 (1.0-3.0)	1.38 (0.20)	3.62 (1.30)	--	--	--	--	--	--	--	--	--	13.54 (4.96)
		TB – RMP co-trtmnt	1	6-12 years	5		1.97 (1.0-2.1)	1.32 (0.19)	5.44 (1.24)	--	--	--	--	--	--	--	--	--	15.04 (5.50)

Table A-8 – Results of pharmacokinetic studies of prothionamide in adults with TB, and children with TB or other conditions (concentrations in µg/ml, times in hours)

Study	Methods	Disease	HIV	Age in years	N	Dosage	T_{max}	T ½	C_{max}	0	0.5	1	2	4	5	6	8	12	AUC
Adults																			
Lee HW, et al. 2009 (379)	HPLC	MDR-TB	--	38.0 (23-53)	17	250 mg or 375 mg (mean dose 5.9 mg/kg)	3.4 (1.4)	3.0 (0.7)	2.5 (1.3)	--	--	--	--	--	--	--	--	0.2 (0.2)	11.3 (3.9)
Prothionamide review in *Tuberculosis*, 2008 (369)	--	--	--	--	--	250 mg	--	1.38	--	--	--	--	--	--	--	--	--	--	--

Table A-9 – Results of pharmacokinetic studies of cycloserine and terizidone in adults with TB, and children with TB or other conditions (concentrations in µg/ml, times in hours)

Study	Methods	Disease	HIV	Age in years	N	Dosage	T_{max}	T ½	C_{max}	0	0.5	1	2	4	5	6	8	12	AUC
Adult																			
Zitkova L, et al. 1974 (403)	Color-imetric	TB	--	47	10	Cycloserine 250 mg	2-3	25.1	8-9†	--	--	--	--	--	--	--	--	--	--
				49	15	Cycloserine 500 mg	2-3	15.8	14-15 †	--	--	--	--	--	--	--	--	--	--
				47	10	Cycloserine 750 mg	2-3	21.8	16-17 †	--	--	--	--	--	--	--	--	--	--
Cycloserine review in *Tuberculosis*, 2008 (420)	--	--	--	--	--	Cycloserine 250 mg 12 hourly	--	10	25-30	--	--	--	--	--	--	--	--	--	--
Zitkova L, et al. 1974 (403)	Colori-metric	TB	--	47	10	Terizidone 250 mg	2-3	33.1	8-9†	--	--	--	--	--	--	--	--	--	--
				49	15	Terizidone 500 mg	2-3	20.9	16-17 †	--	--	--	--	--	--	--	--	--	--
				47	10	Terizidone 750 mg	2-3	24.8	18-19 †	--	--	--	--	--	--	--	--	--	--

† Rough estimations based on published concentration-time curve

Table A-10 – Results of pharmacokinetic studies of para-aminosalicylic acid (PAS) in adults with TB, and children with TB or other conditions (concentrations in µg/ml, times in hours)

Study	Methods	Disease	HIV	Age in years	N	Dosage	T_{max}	T ½	C_{max}	0	0.5	1	2	4	5	6	8	12	AUC †
Adults																			
Pentikainen P, et al. 1973 (460)	Chroma-tography	Healthy volunteers	--	--	12	4 grams PAS (Parasal)	3.17	--	52.4	--	--	--	--	--	--	--	--	--	222
					12	4 grams PAS-C (Pascorbic)	2.21	--	65.6	--	--	--	--	--	--	--	--	--	271
					12	2 grams PAS-C (Pascorbic)	1.79	--	32.6	--	--	--	--	--	--	--	--	--	177
Wan SH, et al. 1974 (458)	Marshall Method	Healthy volunteers	--	--	12	PAS 4 grams	3.54	--	49.98	--	--	--	--	--	--	--	--	--	209.7
					12	PAS Na salt 2.8 grams	0.83	--	155.4	--	--	--	--	--	--	--	--	--	313.2
					12	PAS Ca salt 2.6 grams	1.02	--	139.5	--	--	--	--	--	--	--	--	--	326.8
					12	PAS K salt 2.6 grams	1.10	--	121.1	--	--	--	--	--	--	--	--	--	313.2
Peloquin CA, et al. 1999 (455)	HPLC	TB	--	40 (18-58)	6	4 grams PAS granules twice daily	--	--	--	--	--	--	--	25.8 (4.2-53.2)	--	--	23.2 (1.6-51.0)	16.4 (5.6-44.5)	--
		TB	--	37 (19-64)	6	4 grams twice PAS granules daily	--	--	--	--	--	--	--	--	--	22.4 (13.1-37.0)	--	--	--
						4 grams PAS granules once daily	--	--	--	0.0 (0.0-0.6)	--	--	--	--	--	23.4 (14.6-30.3)	--	3.7 (13.8-1.6)	--
Liwa AC, et al. 2012 (457)	HPLC	MDR-TB	4/12	27 (18-53)	12	4 grams PAS granules twice daily	5.2 (2.04)	--	51.3 (20.0)	--	--	--	--	--	--	--	--	--	368.0 (194)
PAS review in *Tuberculosis*, 2008 (432)	--	--	--	--	--	4 grams	--	0.75-1	20 (9-35)	--	--	--	--	--	--	--	--	--	--
Children																			
Liwa AC, et al. 2012 (457)	HPLC	MDR-TB	4/10	4 (1-12)	10	75 mg/kg twice daily	4.8 (2.5)	--	45.4 (22.7)	--	--	--	--	--	--	--	--	6.8	233.3 (135)

		PAS granules													
	10	150 mg/kg twice daily PAS granules	4.8 (3.6)	--	56.5 (32.4)	--	--	--	--	--	--	--	--	21.3	277.9 (221)

† AUCs are for hours 0-12

Table A-11 – Results of pharmacokinetic studies of linezolid in adults with TB, and children with TB or other conditions (concentrations in µg/ml, times in hours)

Study	Methods	Disease	HIV	Age in years	N	Dosage	T_{max}	T ½	C_{max}	C_{min}	0.5	1	2	4	6	8	12	AUC 0-12	AUC 0-24
Adults																			
Dietze R, et al. 2008 (495)	HPLC	TB	0/9	45.0 (39.0–48.0)	9	600 mg twice daily	1.0 (1.0-4.0)	4.56 (2.1-7.0)	19.4 (11.8-24.9)	--	--	--	--	--	--	--	--	116.4 (50.4-197)	232.9 (100.8 - 394.4)
			0/10	33.5 (23.0–42.0)	10	600 mg once daily	1.5 (1.0-4.0)	3.20 (1.5-5.0)	15.0 (11.9-21.3)	--	--	--	--	--	--	--	--	87.0 (47.5-119.3)	96.9 (47.8-143.7)
Koh WJ, et al. 2009 (499)	HPLC	MDR/XDR-TB	0/10	--	10	300 mg once daily	--	--	11.6 (4.4)	2.1 (1.3)	--	--	--	--	--	--	--	--	--
Alffenaar JW, et al. 2010 (535)	LCMS/MS assay	MDR/XDR-TB	--	28 (26-38)*	8	300 mg twice daily	1.2 (0.5-1.2)	5.6 (3.0-6.4)	9.5 (7.7-10.1)	1.9 (0.6-2.2)	--	--	--	--	--	--	--	57.6 (38.5-64.2)	--
					8	600 mg twice daily	1.4 (0.8-1.4)	5.8 (4.7-6.0)	20.4 (16.3-21.9)	5.8 (2.7-6.8)	--	--	--	--	--	--	--	145.8(101.2-160.9)	--
Children																			
Jungbluth GL, et al. 2003 # (526)	HPLC	--	--	Newborn, Preterm*, <1 week of age	9	10 mg/kg	--	5.6 (2.4-9.8)	12.7 (9.6-22.2)	--	--	--	--	--	--	--	--	--	108 (41-191)‡
				Newborn, Full term, < 1 week of age	10	10 mg/kg	--	3.0 (1.3-6.1)	11.5 (8.0-18.3)	--	--	--	--	--	--	--	--	--	55 (19-103)‡
				Newborn, Full term ≥1 week ≤28 days	10	10 mg/kg	--	1.5 (1.2-1.9)	12.9 (7.70 21.6)	--	--	--	--	--	--	--	--	--	34 (23-50)‡
				Infants >28 days - <3 months	12	10 mg/kg	--	1.8 (1.2-2.8)	11.0 (7.2-18.0)	--	--	--	--	--	--	--	--	--	33 (17-48)‡
				Young children, 3 months – 11 years	59	10 mg/kg	--	2.9 (0.9-8.0)	15.1 (6.8-36.7)	--	--	--	--	--	--	--	--	--	58 (19-153)‡
				Adolescents 12-17 years	36	10 mg/kg or 600 mg	--	4.1 (1.3-8.1)	16.7 (9.9-28.9)	--	--	--	--	--	--	--	--	--	95 (32-178)‡

All values in this study reported as mean and range; ‡AUC 0-infinity; *Preterm considered <34 weeks gestation

Appendix 2 – Search Terms

1.1 Ofloxacin, Levofloxacin, and Moxifloxacin

General search: "(fluoroquinolone* OR ofloxacin OR levofloxacin OR moxifloxacin) AND tuberculosis"

Pharmacokinetic search:

> #1 – "Infant[MeSH] OR Infant_ OR infancy OR Newborn_ OR Baby_ OR Babies OR Neonat_ OR Preterm_ OR Prematur_ OR Postmatur_ OR Child[MeSH] OR Child_ OR Schoolchild_ OR School age_ OR Preschool_ OR Kid or kids OR Toddler_ OR Adolescent[MeSH] OR Adoles_ OR Teen_ OR Boy_ OR Girl_ OR Minors[MeSH] OR Minors_ OR Puberty[MeSH] OR Pubert_ OR Pubescen_ OR Prepubescen_ OR Pediatrics[MeSH] OR Paediatric_ OR Paediatric_ OR Peadiatric_ OR Schools[MeSH] OR Nursery school_ OR Kindergar_ OR Primary school_ OR Secondary school_ OR Elementary school_ OR High school_ OR Highschool_"
>
> #2 – "fluoroquinolone* OR ofloxacin OR levofloxacin OR moxifloxacin"
>
> #3 – "#2 AND pharmacokinetic* AND (#1 OR tuberculosis)"

1.2 Amikacin

General search: "amikacin AND tuberculosis"

Pharmacokinetic-specific search:

> #1 – "Infant[MeSH] OR Infant_ OR infancy OR Newborn_ OR Baby_ OR Babies OR Neonat_ OR Preterm_ OR Prematur_ OR Postmatur_ OR Child[MeSH] OR Child_ OR Schoolchild_ OR School age_ OR Preschool_ OR Kid or kids OR Toddler_ OR Adolescent[MeSH] OR Adoles_ OR Teen_ OR Boy_ OR Girl_ OR Minors[MeSH] OR Minors_ OR Puberty[MeSH] OR Pubert_ OR Pubescen_ OR Prepubescen_ OR Pediatrics[MeSH] OR Paediatric_ OR Paediatric_ OR Peadiatric_ OR Schools[MeSH] OR Nursery school_ OR Kindergar_ OR Primary school_ OR Secondary school_ OR Elementary school_ OR High school_ OR Highschool_"
>
> #2 - "amikacin AND pharmacokinetic* AND #1"

1.3 Kanamycin

General search: "kanamycin AND tuberculosis"

Pharmacokinetic-specific search:

> #1 – "Infant[MeSH] OR Infant_ OR infancy OR Newborn_ OR Baby_ OR Babies OR Neonat_ OR Preterm_ OR Prematur_ OR Postmatur_ OR Child[MeSH] OR Child_ OR Schoolchild_ OR School age_ OR Preschool_ OR Kid or kids OR Toddler_ OR Adolescent[MeSH] OR Adoles_ OR Teen_ OR Boy_ OR Girl_ OR Minors[MeSH] OR Minors_ OR Puberty[MeSH] OR Pubert_ OR Pubescen_ OR Prepubescen_ OR Pediatrics[MeSH] OR Paediatric_ OR Paediatric_ OR Peadiatric_ OR Schools[MeSH] OR Nursery school_ OR Kindergar_ OR Primary school_ OR Secondary school_ OR Elementary school_ OR High school_ OR Highschool_"
>
> #2 - "kanamycin AND pharmacokinetic* AND #1"

1.4 Capreomycin

General search: "capreomycin AND tuberculosis"

Pharmacokinetic-specific search:

> #1 – “Infant[MeSH] OR Infant_ OR infancy OR Newborn_ OR Baby_ OR Babies OR Neonat_ OR Preterm_ OR Prematur_ OR Postmatur_ OR Child[MeSH] OR Child_ OR Schoolchild_ OR School age_ OR Preschool_ OR Kid or kids OR Toddler_ OR Adolescent[MeSH] OR Adoles_ OR Teen_ OR Boy_ OR Girl_ OR Minors[MeSH] OR Minors_ OR Puberty[MeSH] OR Pubert_ OR Pubescen_ OR Prepubescen_ OR Pediatrics[MeSH] OR Paediatric_ OR Paediatric_ OR Peadiatric_ OR Schools[MeSH] OR Nursery school_ OR Kindergar_ OR Primary school_ OR Secondary school_ OR Elementary school_ OR High school_ OR Highschool_”
>
> #2 - “capreomycin AND pharmacokinetic* AND #1”

1.5 Ethionamide and prothionamide

General search: “(ethionamide OR prothionamide) AND tuberculosis”

Pharmacokinetic-specific search

> #1 – “Infant[MeSH] OR Infant_ OR infancy OR Newborn_ OR Baby_ OR Babies OR Neonat_ OR Preterm_ OR Prematur_ OR Postmatur_ OR Child[MeSH] OR Child_ OR Schoolchild_ OR School age_ OR Preschool_ OR Kid or kids OR Toddler_ OR Adolescent[MeSH] OR Adoles_ OR Teen_ OR Boy_ OR Girl_ OR Minors[MeSH] OR Minors_ OR Puberty[MeSH] OR Pubert_ OR Pubescen_ OR Prepubescen_ OR Pediatrics[MeSH] OR Paediatric_ OR Paediatric_ OR Peadiatric_ OR Schools[MeSH] OR Nursery school_ OR Kindergar_ OR Primary school_ OR Secondary school_ OR Elementary school_ OR High school_ OR Highschool_”
>
> #2 - “(ethionamide OR prothionamide) AND pharmacokinetic* AND (#1 OR tuberculosis)”

1.6 Cycloserine and terizidone

General Search: “(cyloserine OR terizidone) AND tuberculosis”

Pharmacokinetic-specific search

> #1 – “Infant[MeSH] OR Infant_ OR infancy OR Newborn_ OR Baby_ OR Babies OR Neonat_ OR Preterm_ OR Prematur_ OR Postmatur_ OR Child[MeSH] OR Child_ OR Schoolchild_ OR School age_ OR Preschool_ OR Kid or kids OR Toddler_ OR Adolescent[MeSH] OR Adoles_ OR Teen_ OR Boy_ OR Girl_ OR Minors[MeSH] OR Minors_ OR Puberty[MeSH] OR Pubert_ OR Pubescen_ OR Prepubescen_ OR Pediatrics[MeSH] OR Paediatric_ OR Paediatric_ OR Peadiatric_ OR Schools[MeSH] OR Nursery school_ OR Kindergar_ OR Primary school_ OR Secondary school_ OR Elementary school_ OR High school_ OR Highschool_”
>
> #2 - “(cycloserine OR terizidone) AND pharmacokinetic* AND (#1 OR tuberculosis)”

1.7 PAS

General Search: “(p-amino salicylic acid OR para-amino salicylic acid OR PAS) AND tuberculosis”

Pharmacokinetic-specific search

> #1 – “Infant[MeSH] OR Infant_ OR infancy OR Newborn_ OR Baby_ OR Babies OR Neonat_ OR Preterm_ OR Prematur_ OR Postmatur_ OR Child[MeSH] OR Child_ OR Schoolchild_ OR School age_ OR Preschool_ OR Kid or kids OR Toddler_ OR Adolescent[MeSH] OR Adoles_ OR Teen_ OR Boy_ OR Girl_ OR Minors[MeSH] OR Minors_ OR Puberty[MeSH] OR

Pubert_ OR Pubescen_ OR Prepubescen_ OR Pediatrics[MeSH] OR Paediatric_ OR Paediatric_ OR Peadiatric_ OR Schools[MeSH] OR Nursery school_ OR Kindergar_ OR Primary school_ OR Secondary school_ OR Elementary school_ OR High school_ OR Highschool_"

#2 – "p-amino salicylic acid OR para-amino salicylic acid OR PAS"

#3 - "#2 AND pharmacokinetic* AND (#1 OR tuberculosis)"

1.8 Linezolid

General Search: "linezolid AND tuberculosis"

Pharmacokinetic-specific search

#1 – "Infant[MeSH] OR Infant_ OR infancy OR Newborn_ OR Baby_ OR Babies OR Neonat_ OR Preterm_ OR Prematur_ OR Postmatur_ OR Child[MeSH] OR Child_ OR Schoolchild_ OR School age_ OR Preschool_ OR Kid or kids OR Toddler_ OR Adolescent[MeSH] OR Adoles_ OR Teen_ OR Boy_ OR Girl_ OR Minors[MeSH] OR Minors_ OR Puberty[MeSH] OR Pubert_ OR Pubescen_ OR Prepubescen_ OR Pediatrics[MeSH] OR Paediatric_ OR Paediatric_ OR Peadiatric_ OR Schools[MeSH] OR Nursery school_ OR Kindergar_ OR Primary school_ OR Secondary school_ OR Elementary school_ OR High school_ OR Highschool_"

#2 - "linezolid AND pharmacokinetic* AND (#1 OR tuberculosis)"

1.9 Clofazimine

General Search: "clofazimine AND tuberculosis"

Pharmacokinetic-specific search

#1 – "Infant[MeSH] OR Infant_ OR infancy OR Newborn_ OR Baby_ OR Babies OR Neonat_ OR Preterm_ OR Prematur_ OR Postmatur_ OR Child[MeSH] OR Child_ OR Schoolchild_ OR School age_ OR Preschool_ OR Kid or kids OR Toddler_ OR Adolescent[MeSH] OR Adoles_ OR Teen_ OR Boy_ OR Girl_ OR Minors[MeSH] OR Minors_ OR Puberty[MeSH] OR Pubert_ OR Pubescen_ OR Prepubescen_ OR Pediatrics[MeSH] OR Paediatric_ OR Paediatric_ OR Peadiatric_ OR Schools[MeSH] OR Nursery school_ OR Kindergar_ OR Primary school_ OR Secondary school_ OR Elementary school_ OR High school_ OR Highschool_"

#2 - "clofazimine AND pharmacokinetic* AND (#1 OR tuberculosis)"

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