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REVIEW

Hearing loss in patients on treatment for drug-resistant tuberculosis

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ABSTRACT: **The treatment of drug-resistant (DR)-tuberculosis (TB) necessitates the use of second-line injectable anti-TB drugs which are associated with hearing loss. Hearing loss affects communication and the development of language and social skills in children. This review describes the pathophysiology of hearing loss and the testing methodologies that can be employed. It is the first paper to systematically review the literature regarding hearing loss in those treated for DR-TB. In the studies identified, the methodology used to test for and to classify hearing loss is inconsistent and children and those with HIV are poorly represented. This review describes existing guidelines and suggests management strategies when hearing loss is found. It describes the challenges of testing hearing in the developing world contexts where the majority of patients with DR-TB are treated. Finally it makes the recommendation that a standardised testing methodology and classification system should be used.**

KEYWORDS: **Drug resistant, hearing loss, ototoxicity, systematic review, tuberculosis**

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The World Health Organization (WHO) estimates that there are 650,000 cases globally of multidrug-resistant (MDR) tuberculosis (TB) (*Mycobacterium tuberculosis* resistant to rifampicin and isoniazid) [1]. A small proportion of these cases are diagnosed and appropriately treated but with the imminent roll-out of newer molecular diagnostic tools [2, 3], a much larger proportion is likely to be treated. The treatment of drug-resistant (DR)-TB requires the use of second-line anti-TB medications many of which are associated with significant adverse events [4]. The injectable drugs, aminoglycosides and polypeptides are associated with a risk to renal function, hearing and the vestibular system. Nephrotoxicity is generally reversible but damage to the auditory and vestibular systems is usually permanent. The monitoring of hearing loss is important for two reasons. First, if detected early it may be possible to alter the regimen to stop or reduce the dose of the responsible drug, preventing progression of hearing loss to the point where it would impact on communication. Secondly, if significant hearing loss has developed and is detected, interventions can be implemented to assist in communication. These include hearing aids, cochlear implants or other hearing impaired tools, teaching and training. Despite the increasing literature on DR-TB over the last 20 yrs, few studies have investigated hearing loss in patients undergoing treatment. Existing studies have used varied case definitions, making comparisons between studies challenging.

Here we review how hearing is tested and assess the implications of testing in resource-limited settings, where the majority of patients with DR-TB are likely to be treated. We describe testing of young children who are not old enough to cooperate with the pure tone audiometry procedure. We systematically review the literature which has assessed hearing in patients undergoing treatment for DR-TB, as well as existing international guidelines. We discuss the different components of hearing loss and potential interventions upon identification of hearing loss. Finally we propose a standardisation in the classification of hearing loss for academic studies in adults and children treated for DR-TB.

THE PHYSIOLOGY OF HEARING AND BALANCE

Sounds, in the form of vibrations, impact on the pinna of the ear and are transmitted down the auditory channel to the tympanic membrane. The vibrations are transmitted through the auditory ossicles (the malleus, incus and stapes) onto the hair cells of the basilar membrane within the organ of corti, situated within the cochlea. Signals

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are transmitted by the cochlear nerve to the brainstem and from there to the cortex where they are interpreted into meaningful sounds. Blockages within the channel, such as wax or discharge can impede this process. Perforations of the tympanic membrane or effusions behind it (otitis media with effusion) and acute or chronic otitis media, can also affect transmission. Both chronic otitis media and tympanic perforations are common in HIV-infected patients and since many of those on treatment for DR-TB are HIV-infected, hearing evaluation must take this into consideration.

The vestibular component of balance is located in the vestibule, located near the cochlea, within the inner ear. Movement of fluid through the three semi-circular canals, as well as the maculae of the saccule and utricle, stimulates hair cells which in turn create signals in the vestibular nerve. This nerve runs with the cochlear nerve as the vestibulocochlear, or eighth cranial nerve, to the brainstem and from there to the cortex, where signals are interpreted as movement and acceleration.

The injectable anti-TB drugs selectively destroy the basal hair cells of the basilar membrane, which are required for high-frequency hearing [5]. This occurs by reacting with transition metal ions to produce reactive oxygen species which in turn damage the cells through an oxidative process. Hearing loss in those treated with aminoglycosides and polypeptides usually starts with high-frequency loss first, with later progression to the frequencies more associated with speech communication. Damage is usually permanent. These drugs can also destroy the hair cells of the vestibule [6].

THE TESTING OF HEARING

If hearing testing is available in the developing world, it is targeted to those who report problems with communication. If this strategy is employed when assessing the hearing of patients treated with injectable medications for DR-TB, hearing loss will only be detected once some degree of irreversible damage has occurred to the frequencies necessary for communication. This is also the case with clinical testing techniques [7]. Hearing screening must start at the beginning of treatment and be carried out regularly, using audiological equipment. If high-frequency hearing loss is detected, it may be possible to stop the drug before hearing loss progresses to the frequencies needed for speech communication, without impairing successful therapy. Hearing testing is particularly important in children, who are still developing and acquiring skills, language and education. Hearing loss during childhood can have critical effects on development [8–14]. If hearing loss is detected in children, the importance of early identification and educational intervention is crucial [15, 16].

Hearing loss can be conductive or sensorineural and before hearing can be tested, the status of the auditory channel and tympanic membrane must be determined. This is performed with a combination of otoscopy and tympanometry. Otoscopy involves the visual inspection of the channel for signs of infection, wax, foreign bodies or other obstruction using an otoscope. It is also vital to assess the tympanic membrane for perforation or middle ear fluid collections and infections. Tympanometry should ideally be carried out to document middle ear function. In this procedure, a tympanometer probe is placed in the participant's auditory channel and the compliance of the tympanic membrane measured. If pathology exists either in the channel, the tympanic membrane or in the middle ear, the results of hearing testing may not be reliable.

For adults and older children (those able to cooperate with testing) the current preferred method for testing hearing is audiometry. Testing occurs in a sound-proof room or booth with headphones placed over the patient's ears. The patient is asked to raise a hand or press a button when they hear a sound. For both ears and for a range of frequencies, the minimum volume or amplitude is recorded at which the patient responds. Frequencies tested are in the range of 125–8,000 Hz [17]. An audiogram is created such as the one shown in figure 1. Frequencies above 2,000 Hz are considered high frequency. This technique requires cooperation and concentration but should be possible in all developmentally normal patients >5 yrs. In expert hands, with the use of play techniques, even younger children can be encouraged to participate. However, it may not be possible to engage them, as concentration spans can be short; for very young children this approach is not possible.

For those unable to cooperate with testing, it may be necessary to measure the patency of the neuronal auditory circuit. Otoacoustic emissions (OAEs) are small sounds produced constantly by a functioning cochlea. They are produced spontaneously but can also be stimulated. OAE testing determines the difference between a stimulus waveform and a recorded waveform following stimulation. These tests can determine the patency of the auditory circuit within the cochlea but do not establish if the patient can actually hear. As the hearing loss associated with anti-TB drug use affects the cochlea, this approach is likely to be satisfactory. Although OAEs can give some information regarding the degree of hearing loss and the frequencies likely to be affected they should be viewed as a screening tool.

To test OAEs a probe is placed in the auditory channel with the patient still and in a quiet room. It takes a few seconds and results are available immediately. Advantages include the rapidity of the test, the possibility that the test can be performed at the patient bedside if they are too unwell or weak to visit the audiology department and the fact that patient concentration is not required. The patient does, however, have to be still for the test, which in small children can be challenging. In addition, ambient noise levels must be low. Auditory brainstem evoked response (ABER) testing measures the entire length of the sensorineural pathway. A probe is placed in the auditory channel and auditory stimulation is provided in the form of a click. Electrodes are placed at various points on the scalp and the electrical activity is detected in the same way as an electroencephalogram. Young children typically need to be sedated to perform this test and it is usually undertaken in specialist centres. The middle ear must be healthy.

CATEGORISING HEARING LOSS

The major components of hearing loss are the frequency, the amplitude, whether it is unilateral or bilateral and whether it is sensorineural, conductive or a combination of the two. The frequency refers to the pitch or tone at which the patient has lost hearing. Human hearing is typically in the range 20 Hz (a low pitch sound) to 20,000 Hz (a high pitch sound). The amplitude refers to the degree of hearing loss or the loudness (expressed in decibels (dB)) required for the sound to be heard. A number of

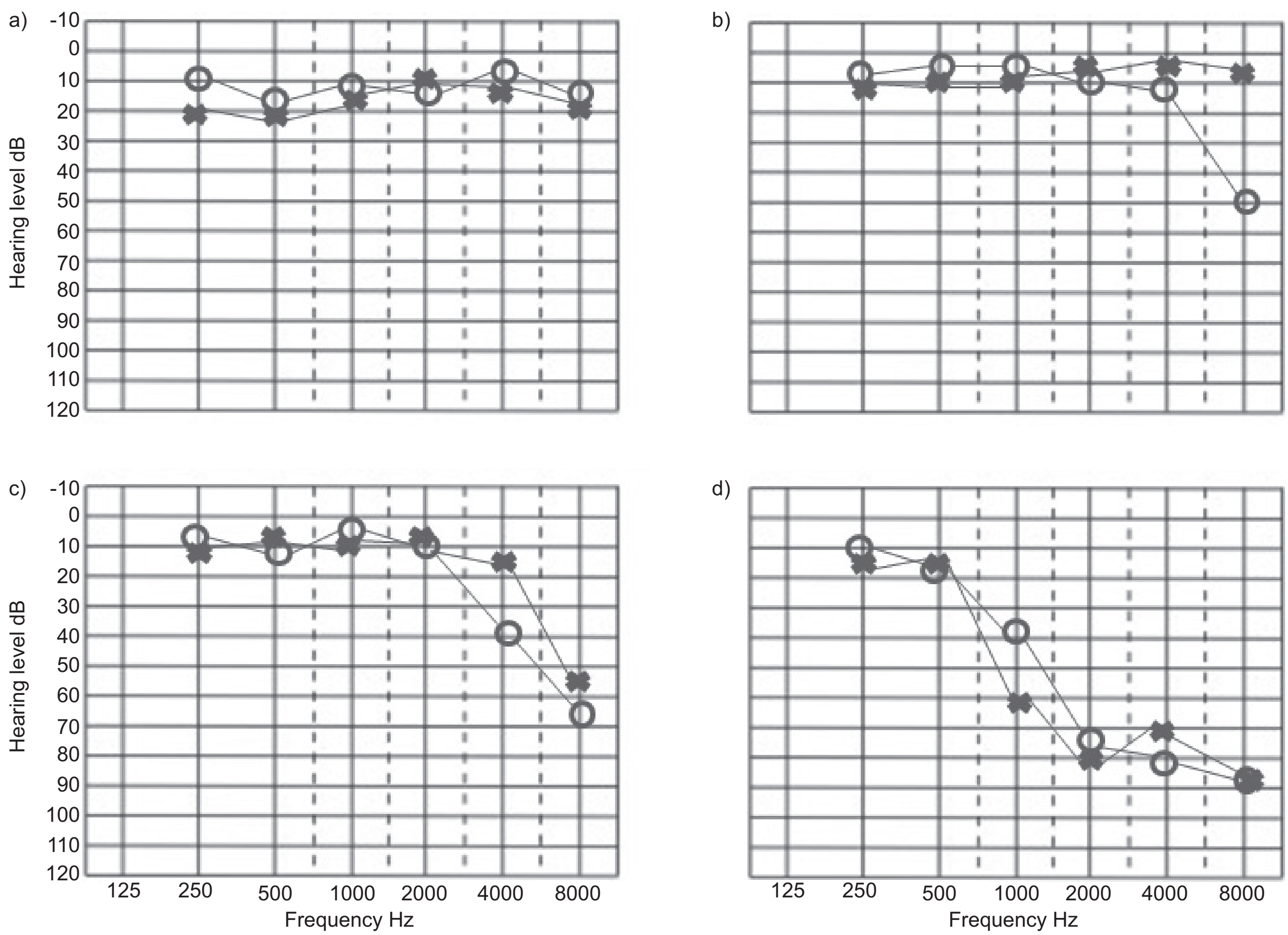

FIGURE 1. Audiograms demonstrating hearing assessment in a patient receiving treatment for drug-resistant tuberculosis with progressive hearing loss. Circles demonstrate responses to sounds presented in the right ear and crosses to those presented in the in left. a) Normal hearing, b) moderate unilateral high-frequency hearing loss; c) moderately severe bilateral high-frequency hearing loss and d) severe bilateral hearing loss including high and mid frequencies.

authorities classify normal hearing as the patient being able to hear sounds presented at an amplitude of <25 dB, with mild impairment 26-40 dB, moderate 41–55 dB, moderately severe 56–70 dB, severe 71–90 dB and profound >90 dB [18, 19]. Hearing loss can be unilateral or bilateral and the two ears can either have the same pattern of hearing loss or different patterns. Finally, using otoscopy and tympanometry, together with masking and bone conduction audiometry techniques, it is possible, to some degree, to determine whether the hearing impairment is caused by a conductive component or by a sensorineural element. To accurately describe hearing loss it is necessary to include some component of all of these aspects.

STUDIES AND GUIDELINES

A systematic review of the literature was conducted to identify studies of hearing loss in those treated for MDR-TB. The search terms and databases consulted are documented later in this review and in figure 2. In addition, we assessed the references from two systematic reviews that looked at treatment outcomes for MDR-TB, looking for articles that documented hearing assessment in those treated for MDR-TB [20, 21]. A large number of studies that analysed treatment outcomes for MDR-TB did not included any mention of hearing testing. The studies that did describe hearing testing are described in tables 1 and 2. In table 1 we present the studies which describe the use of a standardised method for hearing screening and classification. However, in the majority of studies a standardised method was either not used or not described and these studies are shown in table 2. Some studies used clinical definitions, some used audiometry and others used a combination. Often the criteria to register an adverse event were in situations severe enough to warrant changing or discontinuing treatment. This may mean that early high-frequency hearing loss was detected and treatment changed but in most cases, where monitoring is less robust, it is likely to mean that treatment was changed when deafness was noted by the patient.

The studies in tables 1 and 2 were conducted in diverse geographical locations and under varying programmatic conditions. Some report national programme results and others report on treatment provided by non-governmental organisations. The earliest study describes patients treated in the 1970s and there have been increasing numbers of investigations since 2000. The proportion of patients experiencing hearing loss is variable. All studies described that some patients developed hearing loss and in many it was <10%. However, in other

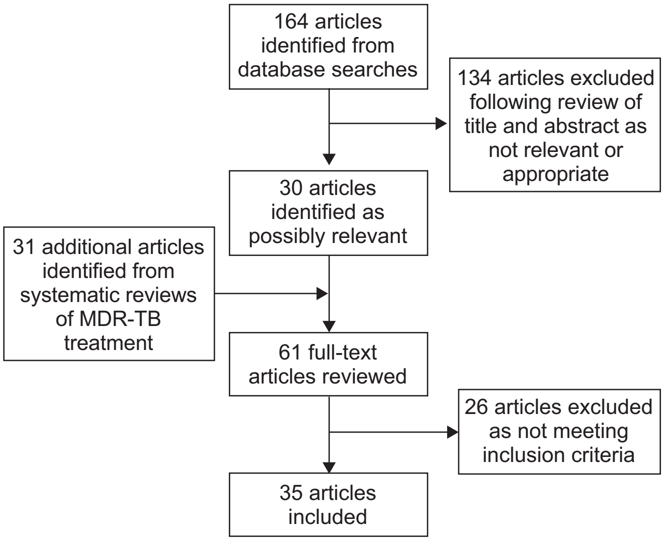

FIGURE 2. Details of the systematic review. MDR-TB: multidrug-resistant tuberculosis.

studies the frequency of ototoxicity approaches or exceeds 50%. This may be a function of the sensitivity of the testing methodology, the patient population studied, previous treatment, the drugs used, dosages, duration of treatment or comorbid conditions. Due to the large variability in testing methodology, recording and classification, formal meta-analysis is not possible. However, it is interesting to note that the proportion of patients with hearing loss seems to be greater in the studies where standardised hearing assessments have been conducted. This might mean that either clinically nonsignificant hearing loss is being detected when a standardised methodology is used or that a large number of patients with hearing loss are being missed when less robust assessments are carried out. From the review of these studies, it is evident that children and HIV-infected patients are poorly represented and, in many instances, excluded. The documentation of the drugs used, as well as the dose and duration, are also infrequently provided.

Few studies have assessed risk factors for hearing loss on DR-TB treatment. PELOQUIN *et al.* [26] described the use of streptomycin, kanamycin and amikacin given both daily and three times a week. They found that streptomycin caused less ototoxicity than the other two drugs but that the size or frequency of dosage did not affect toxicity. Older age and cumulative dose were associated with an increased risk and median onset of hearing loss was 9 weeks in both patients treated daily and three times a week. Three patients experienced hearing loss after completing treatment. DE JAGER *et al.* [22] were unable to demonstrate an association between any clinical or treatment factors and the incidence of hearing loss. 45 of the 61 patients studied were given kanamycin; five were given streptomycin, two amikacin and nine a combination of aminoglycosides. No difference in the incidence of hearing loss was detected between the different drugs. STURDY *et al.* [27] found that increased age, the use of amikacin and decreased renal function were associated with ototoxicity. The number of patients given capreomycin in this study was only 11, however, so it is difficult

TABLE 1 Studies that have examined ototoxicity among patients treated for drug-resistant tuberculosis and assessed hearing loss using standardised testing and classification methodology

First author [ref.]	Year of study	Country	Type of testing and classification of hearing loss	Patients n	Ototoxicity n (%)	Age range yrs	HIV-infected patients n or n/n (%)
DE JAGER [22]	1995–2000	The Netherlands	15 dB at two adjacent frequencies or 20 dB at one frequency. Testing frequencies 250–8000 Hz	61	11 (18.0)	10–83	Not specified
DUGGAL [23]	2000–2006	India	10 dB at two adjacent frequencies, 20 dB at any one frequency or loss of response at three consecutive frequencies where responses were previously obtained. Testing frequencies 250–8000 Hz	64	12 (18.8)	17–65	Not specified
KENNEDY [24]	2004–2009	Ireland	Audiograms every 6 weeks. Classification based on article by BRUMMETT and FOX [25]	13	8 (61.5)	24–82	1/7 (14.3)
PELOQUIN [26]	1991–1998	USA	20 dB at any frequency and 15 dB at two adjacent frequencies both assessed. Audiometry tested at 250–8000 Hz	87	32–28# (36.8–32.2)	19–79	Not specified
STURDY [27]	2004–2009	UK	10 dB at two adjacent frequencies, 20 dB at any one frequency or clinical symptoms of hearing loss. Frequencies not specified	50	9 (18.0)	34.6±12.8¶	5 (10)

#: unclear from the article; ¶: mean±SD is presented as the age range was unavailable.

TABLE 2 Studies that have examined ototoxicity among patients treated for drug-resistant tuberculosis using unspecified testing and classification methodology

First author [ref.]	Year of study	Country	Type of testing and classification of hearing loss	Patients n	Ototoxicity n (%)	Age range yrs	HIV-infected patients n or n/n (%)
BAGHAEI [28]	2006–2009	Iran	Hearing testing by audiometry Technique and classification not specified	80	8–14 (10.0–17.5)	14–81	4 (5.0)
BLOSS [29]	2000–2004	Latvia	Audiometry carried out monthly on patients determined by clinicians to be at risk of adverse events Testing technique and classification not specified	1027	195 (19.0)	13–83	32 (3.1)
BURGOS [30]	1982–2000	USA	World Health Organization definitions of adverse effects used Testing technique not specified	48	2 (4.2)	22–78	11 (22.9)
CHAN [31]	1984–1998	USA	Not specified	205	39 (19.0)	2–85	NS
CODECASA [32]	2001–2003	Italy	Not specified	38	1 (2.6)	43.6±17.3[#]	2 (5.3)
DHEDA [33]	2002–2008	South Africa	Not specified	161	10 (6)	<16 yrs excluded	82/174 (47.1)
DROBAC [34]	1999–2003	Peru	Audiometry if on an injectable for >6 months Audiometry techniques and classification not specified	30	2 (6.7)	2–14	2/38 (5.3)
FURIN [35]	1996–1998	Peru	Hearing loss confirmed by physical examination or audiometry Audiometry techniques or classification not specified	60	4 (6.7)	12–60	1 (1.7)
GEERLIGS [36]	1985–1998	The Netherlands	Adverse effects considered if necessitating a change in medication Hearing testing technique not specified	40	0–6[¶] (0–15)	10–82	0
GOBLE [37]	1973–1983	USA	Hearing loss requiring treatment to be stopped. Testing modality not specified	171	13 (7.6)	17–79	NS
ISAAKIDIS [38]	2007–2011	India	Hearing testing by audiometry Technique and classification not specified	58	5 (8.6)	11–61	58 (100)
JACOB [39]	2002–2007	Belgium	Hearing testing by audiometry. Technique and classification not specified	22	11 (50.0)	21–76	1/21 (4.8)
JOSEPH [40]	2006–2007	India	Not specified	38	1 (2.6)	<18 yrs excluded	+
KARAGOZ [41]	1995–2000	Turkey	Audiometric tests performed at the beginning of treatment and whenever complaints about hearing were detected	110	24 (22.0)	16–65	0
KEAL [42]	2006–2011	UK	Not specified (abstract only)	18	5 (27.8)	10–80	1 (5.6)
KESHAVJEE [43]	2000–2004	Russia	Not specified	608	78 (12.8)	XDR: 33.9±11.1[#] MDR: 35.9±11.3[#]	5 (0.8)
KIM [44]	1996–2005	Republic of Korea	Hearing testing not specified but toxicity defined as prompting change or cessation of treatment medication	211	8 (3.8)	13–91	+
LEIMANE [45]	2000	Latvia	Not specified	204	58 (28.4)	17–78	1/197 (0.5)
MALLA [46]	2005–2006	Nepal	Not specified	125	12 (9.6)	33.6±12.5[#]	NS
MASJEDI [47]	2002–2006	Iran	Not specifed	43	20 (46.5)	15–83	0
NATHANSON [48]	1998–2002	Estonia, Latvia, Peru, Philippines, Russia	Variable across the sites but not specified	818	98 (12.0)	NS	NS
PALMERO [49]	1996–1999	Argentina	Hearing testing not specified but toxicity defined as requiring definitive discontinuation of offending drug	74	5 (6.8)	<16 excluded 36.0±13.0[#]	+
SHIN [50]	2000–2002	Russia	Hearing loss confirmed by physical examination or audiometry Audiometry testing technique and classification not specified	244	38 (15.6)	17–65	NS
TAHAOĞLU [51]	1992–1999	Turkey	Not specified	158	45 (28.5)	15–68	+
TELZAK [52]	1991–1994	USA	Not specified	17[$]	1 (5.9)	<25 yrs: 2; ⩾25 yrs: 23	+
TÖRÜN [53]	1992–2004	Turkey	Tinnitus, hearing loss confirmed by audiometry or presence of disequilibrium Audiometry techniques or classification not specified	263	110 (41.8)	14–68	+
TUPASI [54]	1999–2002	Philippines	Not specified	117	22 (18.8)	15–24 yrs: 11; ⩾25 yrs: 106	Unable to test HIV status
UFFREDI [55]	1998–1999	France	Hearing testing not specified but the drug is recorded as having to have been withdrawn	45	2 (4.4)	17–77	9 (20)
VAN DEUN [56]	1997–2007	Bangladesh	Not specified	427	19 (4.4)	<25 yrs: 108; >25 yrs: 319	Not tested
YEW [57]	1990–1997	Hong Kong	Vertigo, tinnitus and impaired hearing grouped together Testing technique not specified	63	9 (14.3)	12–77	0

XDR: extensively drug-resistant; MDR: multidrug-resistant; NS, not specified. [#]: mean±SD is presented as the age range was unavailable. [¶]: unclear from the article. [+]: HIV-infected patients excluded from the study. [$]: of the 25 patients studied only 17 received injectable drugs.

to be confident of the implications of these findings. Finally, a study by DUGGAL *et al*. [23] divided the patients into those who were treated with amikacin, kanamycin and capreomycin. Seven out of 34 patients treated with amikacin, four out of 26 given kanamycin and one out of four treated with capreomycin developed hearing loss. Patients were followed up for a year after discontinuing treatment and all ototoxicity was found to be permanent. From these studies, in spite of small patient numbers, it appears that hearing loss is usually permanent and that older age, renal impairment and cumulative dose are associated with toxicity. The differences in relative toxicity between the individual drugs require further investigation.

Current international DR-TB guidelines and expert opinion provides limited detailed advice regarding the monitoring, classification and management of hearing loss. A consensus is lacking. The WHO simply states that hearing loss should be documented and compared with baseline results if audiometry is available. If hearing loss is detected, options include changing from an aminoglycoside to capreomycin, decreasing the frequency/dose, or discontinuing the suspected agent if this can be performed without compromising the regimen. No mention is made in the guidelines of how hearing should be tested, how frequently it should be performed or what classifies as hearing loss [4]. The non-governmental organisation, Partners in Health, provides similar recommendations [58, 59]. The Francis J Curry National Tuberculosis Center suggests performing a baseline audiogram and repeating it monthly, monitoring the ability of the patient to participate in normal conversation and converting the injectable drug dosage to three times weekly after the first 3 or 4 months if mycobacterial cultures remain negative. Finally, they advise avoiding concomitant loop diuretics, as they are associated with ototoxicity [60].

The British Society of Audiology (BSA) provides a standardised guideline for hearing testing in adults [17] and the American Speech-Language-Hearing Association (ASHA) have well-developed guidelines regarding hearing screening for adults and children of different ages [61, 62]. They also provide a guideline for management of individuals receiving cochleotoxic drug therapy [63]. This guideline suggests that testing should be carried out at 250–8,000 Hz at octave intervals, at baseline and, for ototoxic antibiotics, testing should be weekly. Testing should continue until the end of therapy and at 3 and 6 months following discontinuation of treatment. Frequencies 9,000–20,000 Hz can be included to increase sensitivity but this can be time-consuming and the patient may become fatigued. Hearing loss should always be compared to baseline measurements and ototoxicity is defined as any of: 1) a 20 dB decrease at any one frequency, 2) a 10 dB decrease at any two adjacent frequencies or 3) loss of response at three consecutive test frequencies where responses were previously obtained. The use of OAEs and ABERs is discussed for testing children and individuals who are unable to cooperate, but evidence is limited regarding their ability to screen for ototoxicity. Other proposed classifications employ grading systems, one from the US National Cancer Institute, termed the Common Terminology Criteria for Adverse Events (CTCAE) [64], the second proposed by BROCK *et al*. [65] and the third by CHANG and CHINOSORNVATANA [66]. All of these suggest grades from zero to four, the CTCAE classification [64] suggesting that higher grades indicate increasing amplitude loss with the BROCK *et al.* [65] and CHANG and CHINOSORNVATANA [66] classifications suggesting higher grades indicate that more frequencies are involved. These are detailed in table 3. The American Academy of Audiology has issued a position statement and clinical practice guideline regarding ototoxic monitoring [67]. In this, they discuss the challenges to testing and the use of audiometry, OAE and also high-frequency audiometry. Additionally, they discuss hearing loss classification, suggesting that the ASHA classification should be used. A final aspect of both the BSA and the ASHA guidelines is the testing environment and the permitted background noise. Testing should normally be conducted in a sound-proofed room but if testing is carried out at the patient bedside then the ambient noise level should be recorded. These guidelines do not, however, advise on the screening of patients in low-resource settings where the majority of DR-TB patients live.

TABLE 3 Published classification systems for hearing loss

Classification system	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
CTCAE [64]		Adult (with monitoring): threshold shift of 15–25 dB averaged at two contiguous test frequencies in at least one ear Adult (without monitoring): subjective change in hearing Paediatric: threshold shift >20 dB at 8000 Hz in at least one ear	Adult (with monitoring): threshold shift of >25 dB averaged at two contiguous test frequencies in at least one ear Adult (without monitoring): hearing loss but hearing aid/intervention not indicated Paediatric: threshold shift >20 dB at 4000 Hz and above in at least one ear	Adult (with monitoring): threshold shift of >25 dB averaged at three contiguous test frequencies in at least one ear Adult (without monitoring): hearing loss with hearing aid/intervention indicated Paediatric: loss requiring intervention/aids Threshold shift >20 dB at 3000 Hz and above in at least one ear	Adult: Decrease in hearing to profound bilateral loss (>80 dB at 2000 Hz and above) Paediatric: cochlear implants indicated
BROCK [65]	Hearing thresholds <40 dB at all frequencies	Thresholds ⩾40 dB at 8000 Hz	Thresholds ⩾40 dB at 4000–8000 Hz	Thresholds ⩾40 dB at 2000–8000 Hz	Thresholds ⩾40 dB at 1000–8000 Hz
CHANG [66]	⩽20 dB hearing loss at 1000, 2000 and 4000 Hz	1a: ⩾40 dB hearing loss at any frequency 6000–12000 Hz 1b: ⩾20 dB and <40 dB hearing loss at 4000 Hz	2a: ⩾40 dB hearing loss at 4000 Hz and above 2b: >20 dB and <40 dB hearing loss at any frequency <4000 Hz	Hearing loss of ⩾40 dB at ⩾2000 Hz	Hearing loss of ⩾40 dB at ⩾1000 Hz
ASHA [63]	1) 20 dB decrease at any one frequency, 2) 10 dB decrease at any two adjacent frequencies or 3) Loss of response at three consecutive test frequencies where responses were previously obtained				

CTCAE: Common Terminology Criteria for Adverse Events; ASHA: American Speech and Hearing Association.

Search strategy

The search terms ''TB'', ''tuberculosis'', ''audio*'', ''hearing'', ''resistant'', ''mdr'' were used to search the following databases: Medline, Embase, CINAHL Plus, Cochrane Library, Web of Science, and Academic Search Premier and Africa-Wide Information. The databases were searched from their inception until January 2012 without language restrictions. Abstracts were assessed and appropriate full-text articles retrieved. Reviews or case series of fewer than 10 patients were excluded and all articles included if they documented the assessment of hearing in patients being treated for MDR-TB. This is detailed in figure 2.

CHALLENGES TO HEARING ASSESSMENT

Due to high rates of HIV co-infection in settings where DR-TB is highly prevalent, chronic middle ear infections, outer ear infections and perforations of the tympanic membrane are common. These can complicate the testing and its interpretation. If, following otoscopy and tympanometry, evidence of a middle ear infection is found, the patient should be prescribed a course of antibiotics and reassessed in a week or two. If it is persistent, the patient should be assessed by an ear, nose and throat surgeon as, in this context, hearing testing is unlikely to be reliable.

In regions where the majority of patients with DR-TB live, resources are limited and full audiological testing is usually not possible. Facilities are frequently not adequately designed or appropriately constructed; sound-proofing is poor with ambient noise levels too high for optimal testing. Testing equipment is often not present and trained staff rarely available. In the absence of optimal conditions, however, it is still possible to carry out hearing screening with basic facilities, equipment and training. For example, the Médecins San Frontières team in Khayelitsha (Cape Town, South Africa), who are piloting a decentralised model of care for the treatment of DR-TB, have trained a lay, non-audiologist to carry out a testing protocol in a makeshift testing booth [68]. Patients with abnormal test results are then referred to hospital-based audiologists for formal testing. Another option is mobile testing stations, driven from clinic to clinic, with audiologists effectively performing an outreach service. Even with these forms of testing it is possible to apply high standards and evaluate patients in a systematic and rigorous manner.

STANDARDISED HEARING ASSESSMENT

It is important to standardise the assessment of hearing for patients being treated for DR-TB. Such an approach improves clinical case management within TB programmes, allows for the appropriate allocation of staffing and resources and permits the comparison of studies conducted in different settings. Standardisation should include the schedule and duration of testing as well as the testing methodology.

For individual clinical care, the frequency, laterality, amplitude and aetiology (conduction or sensorineural) should be included in the description. These must be monitored and assessed for change over time with comparisons made to baseline results. This allows an informed decision regarding their clinical management. Both the degree of absolute hearing impairment and hearing change over time (caused by ototoxic drugs) are important. For research studies, as well as documenting individual clinical findings, it is also important to classify the hearing loss in a systematic manner using a graded (Brock *et al.* [65], CTCAE [64] or Chang and Chinosornvatana [66]) or binary (ASHA [63]) system.

Ideally, hearing should be tested before any ototoxic drug is given to provide a baseline assessment. As many patients with DR-TB will have been previously given a retreatment regimen, sometimes repeatedly, baseline hearing loss due to previous streptomycin use is common in adults. In patients with hearing loss at baseline it is still important to regularly monitor their hearing to detect any further deterioration. It is also important to include such patients in research studies. After initial assessment, hearing testing should be carried out monthly at a minimum. Less frequent testing may allow early changes to be missed with hearing loss only detected once mixed frequencies (*i.e.* high frequencies and the frequencies needed for communication) have become affected. If abnormalities are detected, consideration should be given to testing fortnightly. Testing should continue monthly for the full duration of the time that the patient is on the injectable drug and then at 6 months after finishing the injections. Although no intervention to ameliorate the effects can be made once the drug is stopped, hearing loss can continue after the withdrawal and it is important to detect this ongoing loss in order to offer hearing aids or assistance and to provide an accurate research assessment of toxicity.

At each assessment, otoscopy and tympanometry should be carried out. If the patient is able to cooperate then audiometry should be conducted and in the absence of other international guidelines, the existing ASHA guidelines should be followed. For research studies, we suggest that hearing loss should be designated according to the ASHA criteria so that when the audiogram changes sufficiently from baseline (20 dB decrease at any one frequency, 10 dB decrease at any two adjacent frequencies or loss of response at three consecutive test frequencies where responses were previously obtained) the patient is classified as having hearing loss. The time at first detection of hearing loss should be recorded. If patients, such as young children, are unable to cooperate, then following otoscopy and tympanometry, they should have OAE assessment, again according to ASHA guidelines. This should be seen as a screening test and should be reported as pass or fail. Failure does not necessarily imply hearing loss but that it was not possible to determine if the hearing was normal.

MANAGING HEARING LOSS

Recently a number of genes have been identified that show a strong association with aminoglycoside-induced hearing loss [69–73]. These genes are uncommon, however, occurring in $<1\%$ of those tested in a South African population [70]. Although it is not practical in the majority of settings to test for these at the start of therapy, it may be possible to do so in the future when our understanding has evolved. If specific genes are detected, clinicians might consider either other drug options or more frequent monitoring. As the damage to the hair cells of the cochlea is caused by reactive oxygen species, it is theoretically possible to mitigate these effects by iron chelation or co-administration of an anti-oxidant [6]. A recent study in China has demonstrated a protective effect of aspirin in adults treated with gentamicin [74]. Although more research is required into this, consideration should be given to starting patients on this concomitant treatment.

The options available if hearing loss is detected are to stop the drug, reduce the dose, increase the dose interval, or retain current therapy while increasing the frequency of monitoring to identify further deterioration early. The choice will depend largely on disease severity and response, the duration for which the injectable has already been given, the drug-resistance profile of the organism (and consequently which other drugs may be effective) and availability of alternative drugs. In addition, the nature of the hearing loss and the speed at which it has occurred must be considered.

One final factor that can be considered is the monitoring of drug concentrations in the blood. Therapeutic drug monitoring (TDM) should play a far greater role in the management of patients on injectable treatment for DR-TB. In most contexts where patients are being treated for DR-TB, patients receive their injectable medications intramuscularly. There is very little data on the distribution and bioavailability of aminoglycosides and polypeptides delivered in this manner. Also, in these areas, peak and trough concentrations are rarely measured. Review of the available literature reveals that there is little documented regarding the drug exposure that patients experience following injectable drug use, given at WHO-advised dosages, and there is almost nothing for patients being treated for DR-TB [75]. It is also unclear what the target range should be, both for efficacy and for toxicity. Although TDM may not be practical in many places, where possible it should be used to titrate the dose to provide optimal anti-mycobacterial activity while limiting toxicity. Peak injectable drug concentrations can be used to adjust the dose while trough concentrations (taken prior to the subsequent dose) can be used to adjust dosing schedule.

CONCLUSIONS

A large proportion of patients treated for DR-TB are developing hearing loss, a significant adverse event that can impair their quality of life. The effects on the development of children are profound. Additionally, WHO recently recommended extending the duration of injectable drug use from 6 to 8 months, as longer use of injectables has been found to be associated with more successful treatment outcomes [76]. Although the flippant expression ''better deaf than dead'' is frequently employed, it is rarely such a simple decision. Clinicians must carry out a risk assessment whereby the risk of hearing loss is weighed against the risk of treatment failure from stopping or not using an injectable drug. Patients need to be informed of the risks of treatment and the risks of not using injectables and permitted input into treatment decisions. New, alternative drugs are urgently needed.

Few studies have systematically assessed the hearing of patients on DR-TB treatment and differing methodologies have been used. A more systematic approach to hearing screening in patients with DR-TB is required for both adults and children. More research is needed to allow comparisons between patients, and interventions to reduce the incidence of drug-induced deafness need further investigation.

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STATEMENT OF INTEREST

None declared.

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