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ORIGINAL REPORT

Differences in VigiBase® reporting of aminoglycoside and capreomycin-suspected ototoxicity during tuberculosis treatment

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ABSTRACT

Purpose To evaluate the association between the use of streptomycin, amikacin, kanamycin and capreomycin in tuberculosis (TB) treatment and the pharmacovigilance reporting of ototoxicity (deafness or hearing loss, tinnitus and vertigo). Second, to analyze patient demographic and geographic factors that influence the reporting of ototoxicity in TB treatment.

Methods A case/non-case disproportionality analysis of the VigiBase® individual case safety reports (ICSRs) of patients treated for TB using multidrug regimens that contain either of streptomycin, amikacin, kanamycin or capreomycin. Cases were reports of ototoxicity; non-cases were other adverse drug reactions (ADRs). The unit of analysis was the drug–ADR pair. We calculated reporting odds ratios (RORs) and their 95% confidence intervals (CI). The referent drug was streptomycin.

Results By June 2014, there were 3361 drug–ADR pairs in VigiBase® (1693 ICSRs) where the parenteral administration of the four drugs for TB treatment was suspected of causing the reported ADRs. Deafness, tinnitus and vertigo were reported in 576 drug–ADR pairs (cases), the rest being other ADRs (non-cases). Reporting of deafness was most disproportionately associated with amikacin use (ROR 9.3; 95%CI 3.8–23.0), followed by kanamycin use (ROR 4.3; 95%CI 1.3–14.2). Reporting of vertigo was inversely associated with capreomycin use (ROR 0.1; 95%CI 0.01–0.4). Geographic region affected the reporting of ototoxicity while age and sex did not.

Conclusion Spontaneous reporting of deafness cases within VigiBase® was most disproportionately associated with amikacin use, followed by kanamycin. There were regional variations in the global reporting of ototoxicity. These findings should be verified through a follow up study. Copyright © 2016 John Wiley & Sons, Ltd.

KEY WORDS—drug-resistant tuberculosis; hearing loss; pharmacoepidemiology; pharmacovigilance; disproportionality analysis; drug safety

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INTRODUCTION

Ototoxicity (deafness or hearing loss, tinnitus and vertigo) is an important public health problem that is associated with substantial disability, economic and societal costs.[1–3] It can be caused by several factors, including the use of medications like aminoglycosides (e.g. amikacin, kanamycin and streptomycin) or glycopeptides (e.g. capreomycin), which are currently the cornerstone of multidrug-resistant tuberculosis (MDR-TB) treatment, worldwide.[4,5] The prolonged use of aminoglycosides or capreomycin for MDR-TB treatment augments patients' risk of ototoxicity, making the patients prone to this preventable adverse effect if risk mitigation measures are not put in place.[6,7]

The literature on the occurrence and on the comparative risk of the ototoxicity of aminoglycosides and capreomycin in MDR-TB treatment is limited. Previous studies on this subject have focused on the use of various aminoglycosides and capreomycin in experimental animals; on their use for none-TB indications; or have compared the safety of two or three of these drugs but not all the four drugs simultaneously; or sometimes the studies have included other aminoglycosides that are not indicated for tuberculosis treatment.[7,8] Besides, the review by Frymark and colleagues reveals that most of the safety and efficacy studies on these drugs were conducted in the period

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between the 1970s and 1990s when the prevalence of MDR-TB globally was still low.[7] The global TB epidemiologic circumstances have since changed, and larger numbers of patients diagnosed with MDR-TB are now being treated with amikacin, kanamycin and capreomycin than before, especially in the developing countries.[9,10] The widespread use of aminoglycosides in MDR-TB has made both clinicians and researchers alike to revisit the question of the comparative otological safety of these drugs in real-life clinical use.

There is currently a wealth of untapped information that has accumulated over time in pharmacovigilance databases on the safety of drug use in real life clinical practice that could help to elucidate on differences in the ototoxicity of these drugs in tuberculosis treatment. An example is the World Health Organization (WHO) global database of individual case safety reports (ICSRs), called VigiBase®,[11] which is a repository of readily available data on reported adverse effects of medicines used in actual clinical practice from around the globe.

This study aimed at evaluating the association between the use of four parenteral drugs (amikacin, kanamycin, streptomycin and capreomycin) and the global pharmacovigilance reporting of ototoxicity (deafness, tinnitus and vertigo) in VigiBase®. At the time of conducting the study, these four drugs were recommended by the WHO for the re-treatment of drug-susceptible TB (streptomycin) or for the treatment of drug-resistant TB (amikacin, kanamycin and capreomycin).[6] Second, we analyzed patient demographic (age and sex) and geographic factors that influenced the reporting of ototoxicity in TB treatment.

METHODS

Setting

The Uppsala Monitoring Centre (UMC) is the WHO Collaborating Centre for International Drug Monitoring that maintains VigiBase®.[11,12] The UMC collects, stores and routinely analyses pharmacovigilance data on reported suspected adverse drug reactions (ADRs) from all the continents of the world, to identify drug safety signals. At a national level, ADRs are reported by healthcare professionals and in some countries by pharmaceutical companies or patients. An ICSR submitted to the database typically contains anonymous patient demographic characteristics (such as age and sex), the suspected drug(s), concomitant medication, one or more reported ADRs and other relevant clinical information, although detailed clinical information is often lacking in many of the reports.[11] These reports are forwarded electronically by the various collaborating national centers to the UMC for analysis and filing in VigiBase®.

Within VigiBase®, the reported ADRs are coded using the WHO Adverse Drug Reaction Terminology (WHO-ART) or the Medical Dictionary for Regulatory Activities (MedDRA®).[13,14] Drugs suspected of causing the ADR are classified according to the WHO Drug Dictionary, which is linked to the WHO Anatomical Therapeutic Chemical (ATC) system for classifying medicinal drugs. We used medical product codes of the WHO Drug Dictionary to retrieve the records of the drugs of interest.

Study design

We conducted a case/non-case disproportionality analysis of all ICSRs in VigiBase® between 1968 and June 2014 where streptomycin, amikacin, kanamycin or capreomycin was indicated for TB treatment as part of a multidrug regimen and was the principal drug suspected of causing the reported ADR. We used the therapeutic indications stated on the ICSRs to select the records where the drugs were used for the treatment of TB. These anti-TB drugs were identified in VigiBase® using their respective medical product codes. Only records where the drugs were specified to have been administered parenterally (intramuscular, intravenous, subcutaneous or intradermal) were included in the analysis because these are the main routes by which the drugs are administered in TB treatment. Within this selection of ICSRs, we identified all drug–ototoxicity combinations (cases). Ototoxicity was defined as hearing loss or deafness, tinnitus, vertigo or non-specific ototoxicity, using the relevant MedDRA® high level terms and the associated preferred terms.[14] All the other drug and non-ototoxic ADR combinations were considered as non-cases. Patient or reporter consent was not required because the ICSRs in VigiBase® are anonymous.

Covariates

Covariates were limited to the variables that could be retrieved from the standardized structured fields of VigiBase®. These variables included patients' age, sex and the country reporting the suspected ADR. No information was obtained from the free text fields of VigiBase®.

Data analysis

For a particular ICSR in VigiBase®, a drug could be reported with more than one suspected ADR. Likewise, several suspected drugs could be associated with

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the same ADR. Thus, the unit of analysis for this study was the drug–ADR combination, rather than the unique ICSR itself.

We used frequency counts, percentages, as well as statistical measures of central tendency and dispersion to summarize the basic patient demographic variables and other characteristics of the drug–ADR combinations. Categorical variables were compared using the chi-square test.

Logistic regression analysis was used to assess the strength of the association between the parenteral use of amikacin, kanamycin or capreomycin in TB treatment and the reporting of ototoxicity and other suspected ADRs. Streptomycin was the referent drug because it is mainly used for re-treatment of drug susceptible *Mycobacterium tuberculosis* and not for the drug-resistant strains. The magnitude of the association was expressed as the reporting odds ratio (ROR), with 95% confidence intervals (CI). The ROR is a measure of disproportionality in pharmacovigilance databases.[15–18]

We also analyzed whether the age, sex and geographic location of the patient was associated with the reporting of ototoxicity. The Statistical Package for the Social Sciences (SPSS) software, version 12.0.1 (IBM SPSS software, New York, USA) was used for data analysis.

Results

By June 2014, out of the total 8 658 133 reports filed in VigiBase®, there were 1693 unique ICSRs with 3361 drug–ADR pairs where streptomycin, amikacin, kanamycin or capreomycin was reported to have been parenterally used for the treatment of *M. tuberculosis* infection (Fig. 1). Primarily, these four drugs were used for the treatment of pulmonary tuberculosis, basing on the ICSRs where information on the treatment indications was available.

Table 1 presents a description of the drug–event pairs that were included in the analysis. Majority (94%) of the patients were treated with streptomycin-based regimens. The reported types of ototoxicity were deafness ($n=71$), tinnitus ($n=91$), vertigo ($n=394$) and non-specific ototoxicity ($n=20$). The median (interquartile range) patient age was 42 (30–57) years, and males accounted for 1900 (56 %) of the pairs. These reports originated from 56 countries mainly in Asia ($n=2034$, 60%) and Europe ($n=897$, 27%).

In Table 2, we show the specific reported ototoxic adverse reactions (cases) and examples of the non-ototoxic adverse reactions (non-cases) that occurred during TB treatment where amikacin, kanamycin, streptomycin or capreomycin was the main suspected drug. It can be seen that the non-ototoxic adverse reactions were diverse in nature, ranging from general, non-specific symptoms such as electrolyte disturbances, pain, fever, malaise and fatigue, to organ-specific injury, such as visual impairment, thyroid dysfunction, hepatic failure and renal disorders.

Table 3 shows the crude RORs for the association between the VigiBase® reporting of ototoxicity and the use of amikacin, kanamycin or capreomycin in

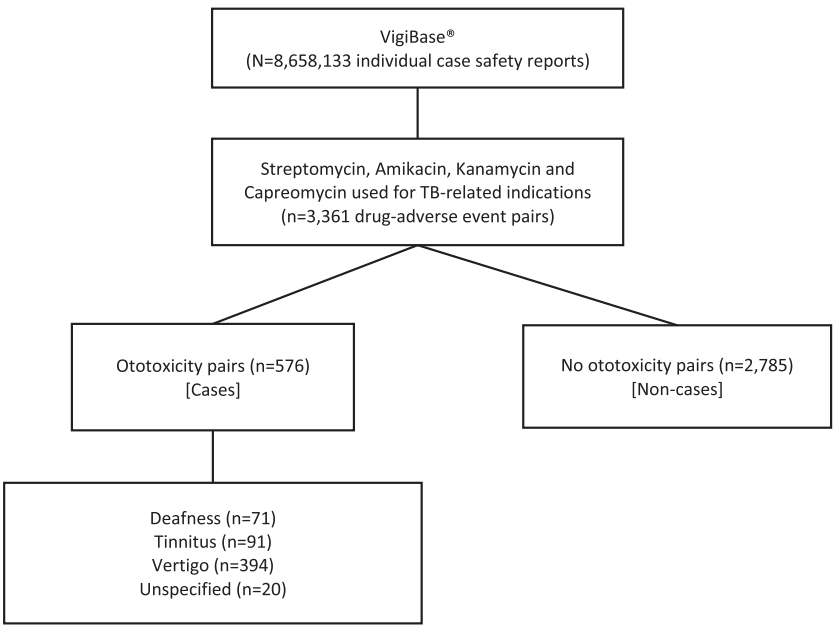

Figure 1. The study flow diagram

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Table 1. Characteristics of the reported suspected drug–adverse reaction pairs

Variable	Categories	Values
Aminoglycoside or capreomycin:	Streptomycin, *n* (%)	3164 (94%)
	Kanamycin, *n* (%)	40 (1%)
	Amikacin, *n* (%)	40 (1%)
	Capreomycin, *n* (%)	117 (4%)
Adverse reaction:	Deafness, *n* (%)	71 (2%)
	Tinnitus, *n* (%)	91 (3%)
	Vertigo, *n* (%)	394 (12%)
	Unspecified ototoxicity, *n* (%)	20 (1%)
	Other adverse reactions, *n* (%)	2785 (83%)
Age:	Median (IQR), years	42 (30 – 57)
Sex:	Male, *n* (%)	1900 (56%)
	Female, *n* (%)	1415 (42%)
	Missing, *n* (%)	46 (2%)
Region:	Africa, *n* (%)	164 (5%)
	Americas, *n* (%)	211 (6%)
	Asia, *n* (%)	2034 (60%)
	Europe, *n* (%)	897 (27%)
	Oceania, *n* (%)	55 (2%)

n = count; % = percent; IQR = interquartile range.

TB treatment. The reporting of "any ototoxicity" was not disproportionately associated with the use of amikacin or kanamycin, compared to streptomycin use. However, it was associated with a statistically significant lower reporting odds for capreomycin use relative to streptomycin use (ROR 0.3; 95%CI 0.1–0.5).

When assessed by the specific type of ototoxicity as shown in Table 4, the reporting of deafness was disproportionally higher for amikacin use relative to streptomycin use (ROR 9.3; 95%CI 3.8–23.0), followed by kanamycin use (ROR 4.3; 95%CI 1.3–14.2). On the other hand, the reporting of vertigo was inversely associated with the use of capreomycin compared to streptomycin (ROR 0.1; 95%CI 0.01–0.4). However, the reporting of tinnitus in VigiBase® was not significantly disproportionately associated with amikacin, kanamycin or capreomycin use, relative to streptomycin use.

Geographical variations in the global reporting of ototoxicity are noticeable in Table 5. Compared to Africa, there was a disproportionately higher reporting of ototoxicity by the Americas (ROR 4.0; 95%CI 1.7–9.3), Asia (ROR 5.1; 95%CI 2.4–11.0) and Europe (ROR 4.8; 95%CI 2.2–10.4). Deafness or tinnitus was the predominant type of ototoxicity reported from the Americas (ROR 5.0; 95%CI 1.4–17.3), while

Table 2. Examples of adverse reactions in VigiBase®, suspected to be caused by amikacin, kanamycin, streptomycin or capreomycin use, during tuberculosis treatment

Ototoxic adverse reactions (cases)	Non-ototoxic adverse reactions (non-cases)
1. Hearing impaired (deafness)	14. Dysphagia
2. Tinnitus	15. Eye pain and visual impairment
3. Vertigo	16. Electrolyte disturbances (e.g. hypokalemia)
4. Vestibular disorder	17. Fatigue
Non-ototoxic adverse reactions (non-cases)	18. Fever
1. Abdominal pain	19. Gait disturbance
2. Allergic reaction	20. Gastritis
3. Anaphylaxis	21. Hepatic failure
4. Ascites	22. Hyperthyroidism
5. Cardiac arrest	23. Hypothyroidism
6. Cheilitis	24. Injection site reaction
7. Chills	25. Malaise
8. Conjunctivitis	26. Multi-organ failure
9. Constipation	27. Nausea
10. Dermatitis and skin rash	28. Pain
11. Diarrhea	29. Pericardial effusion
12. Disseminated intravascular coagulation	30. Photophobia
13. Dyspepsia	31. Renal disorders
	32. Vomiting

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Table 3. Reporting odds ratios (RORs) for "any ototoxicity" by type of suspected drug

Suspected drug	Total drug–ADR combinations ($N = 3361$)	Any ototoxicity ($n = 576$)	Other ADRs ($n = 2785$)	Crude ROR (95%CI)
Streptomycin	3164	556	2608	Reference
Kanamycin	40	4	36	1.4 (0.7–2.6)
Amikacin	40	10	30	0.7 (0.3–1.7)
Capreomycin	117	6	111	0.3 (0.1–0.5)

ADR = adverse drug reaction; ROR = reporting odds ratio; 95%CI = 95% confidence interval.

Table 4. Reporting odds ratios (RORs) of specific categories of ototoxicity and the suspected drug

Suspected drug	Deafness ($n = 71$)	Tinnitus ($n = 91$)	Vertigo ($n = 394$)
Streptomycin ($n = 3164$)	Reference	Reference	Reference
Kanamycin ($n = 40$)	4.3 (1.3–14.2)	0.9 (0.1–6.8)	N/A
Amikacin ($n = 40$)	9.3 (3.8–23.0)	2.9 (0.9–9.7)	0.2 (0.02–1.3)
Capreomycin ($n = 117$)	1.4 (0.4–4.5)	0.6 (0.2–2.6)	0.1 (0.01–0.4)

The numbers in the cell represent the point estimates for the reporting odds ratios (ROR) and their 95% confidence intervals in brackets. N/A = not possible to calculate because of some cells containing zero values.

vertigo was mostly reported by countries in Asia (ROR 6.6; 95%CI 2.4–17.9). Europe had almost similar reporting of deafness/tinnitus (ROR 3.8; 95%CI 1.2–12.4) and vertigo (ROR 4.6; 95%CI 1.7–12.6).

Patient age and sex had no influence on the reporting of cases of deafness that were suspected to be caused by the use of aminoglycoside or capreomycin for TB treatment, as shown in Table 6.

DISCUSSION

We observed some similarities and differences in the RORs of the association between the global reporting of ototoxicity in VigiBase® and the parenteral use of streptomycin, amikacin, kanamycin and capreomycin for the treatment of tuberculosis. The reporting of deafness was significantly disproportionately associated with amikacin use, followed by kanamycin, but not with capreomycin use. However, for vertigo, capreomycin use was significantly associated with lower reporting odds relative to streptomycin use.

Table 5. Geographic variation in the reporting of ototoxicity associated with the use of amikacin, kanamycin, streptomycin or capreomycin during tuberculosis treatment

Region	Any ototoxicity ($n = 576$)	Deafness/ tinnitus ($n = 162$)	Vertigo ($n = 394$)
Africa ($n = 164$)	Reference	Reference	Reference
Americas ($n = 211$)	4.0 (1.7–9.3)	5.0 (1.4–17.3)	2.0 (0.6–6.5)
Asia ($n = 2034$)	5.1 (2.4–11.0)	2.2 (0.7–7.0)	6.6 (2.4–17.9)
Europe ($n = 897$)	4.8 (2.2–10.4)	3.8 (1.2–12.4)	4.6 (1.7–12.6)
Oceania ($n = 55$)	0.8 (0.2–4.2)	1.0 (0.1–9.7)	0.7 (0.1–6.8)

The numbers in the cell represent the point estimates for the reporting odds ratios (ROR) and their 95% confidence intervals in brackets.

Aminoglycosides and capreomycin exhibit selective ototoxicity by damaging different parts of the inner ear, causing hearing problems (cochleotoxicity)[19,20] or postural disorders (vestibulotoxicity).[8] Amikacin, kanamycin and capreomycin predominantly cause auditory damage.[2,21–24] To date, there is no firm evidence on the comparative risk of these three drugs in causing specific ototoxicity, especially for deafness, during tuberculosis treatment.[23] The question still remains: *between amikacin, kanamycin and capreomycin, which one causes more deafness*? Our findings suggest that amikacin has a greater risk of deafness than kanamycin,[25] which in turn has a greater risk of deafness than capreomycin. Peloquin *et al.* compared the incidence of deafness in patients treated for MDR-TB with amikacin, kanamycin or streptomycin and found that amikacin had a greater risk of causing deafness than kanamycin, while streptomycin had the lowest risk.[26] Although our results corroborate those of Peloquin *et al.*, they are still tentative, given the nature and limitations of the spontaneous pharmacovigilance data reported in VigiBase®,[27,28] upon which the current study was based.

Although patient age was not significantly associated with the reporting of deafness, advanced age is a known risk factor for aminoglycoside-induced ototoxicity. This has been previously reported by Sturdy

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Table 6. Influence of patient age and sex on the reporting of deafness suspected to be caused by the use of aminoglycosides or capreomycin in tuberculosis treatment

Variable	Category	Cases (deafness)	Non-cases	ROR (95%CI)	*P*-value
Age (years)	<65	13	503	Reference	
	≥65	57	2692	1.2 (0.7–2.2)	0.52
Sex	Female	33	1382	Reference	
	Male	36	1864	0.8 (0.5–1.3)	0.38

ROR = reporting odds ratio; 95%CI = 95% confidence intervals; *numbers may not add up to 3, 361 because of missing values.

et al., Peloquin *et al*. and Sedon *et al*. in their studies of aminoglycoside-induced hearing loss in tuberculosis treatment.[23,26,29] The age-related loss of hearing could be because of the apoptotic loss of the auditory sensory hair cells of the organ of Corti that is associated with advancing age.[30] Additionally, our finding of lack of association between biological sex and the occurrence of aminoglycoside-induced ototoxicity in TB treatment is consistent with the literature.[26]

The observed geographic differences in the reporting of ototoxicity across the globe could be related to the global epidemiologic distribution of TB cases; differences in the relative use of specific aminoglycosides or capreomycin in TB treatment according to national clinical guidelines; the strength of the pharmacovigilance systems in the countries comprising the regional blocks, and the quality of ICSRs from these countries. For example, although sub-Sahara Africa has a large burden of TB, there were disproportionately too few ICSRs reported in VigiBase® from this region, presumably because of the nascent or weak pharmacovigilance systems in many of the countries in sub-Saharan Africa.[31–34] For Europe, where most countries have functional pharmacovigilance systems, most ICSRs came from the Eastern countries like Romania and the Czech Republic where the burden of TB is still high.[35,36] Asia reported the most cases of vertigo because of the predominant use of streptomycin by some of the countries in this region as reported in VigiBase®, while the Americas reported relatively more cases of deafness in VigiBase® because of the disproportionately greater use of amikacin and kanamycin compared to streptomycin or capreomycin.

We believe that our findings reflect real differences in the relative ototoxicity of these drugs in clinical practice. The findings could inform the treatment choices of clinicians and managers of TB treatment programs. Globally, amikacin and kanamycin are still an integral part of MDR-TB treatment, a disease that afflicts an estimated 480 000 people, living mostly in developing countries.[6,10] The current scaled-up use of these drugs for TB treatment drives upwards the occurrence of aminoglycoside and capreomycin-induced deafness. Therefore, measures should be put in place to mitigate the risk of developing this drug-induced deafness; otherwise, countries will begin dealing with growing numbers of people suffering from avoidable hearing disabilities.

Considering known limitations of disproportionality analysis in pharmacovigilance,[37,38] we carefully restricted our data analysis solely to those ICSRs involving the use of the study drugs specifically for TB-related indications. Because the treatment indications were not stated for many ICSRs, we analyzed only the subset where this information was available.

Secondly, spontaneous pharmacovigilance data often lack information on the total number of patients treated with the drug being studied; hence, we were unable to calculate event rates in the absence of denominators.[28] Besides, the existence of under- or over-reporting of suspected ADRs and missing data is a typical problem of spontaneous reporting, making it susceptible to reporting bias.[27] We could not adjust for the effect of other important variables on the reporting of ototoxicity, such as renal impairment and the cumulative doses of the studied drugs, because of a lack of this information in the structured fields of VigiBase®. Last, too few reports for some of the subgroups diminished the power of the study.

CONCLUSION

The reporting of deafness in VigiBase® was mainly disproportionately associated with amikacin use, followed by kanamycin. Geographic differences in the reporting of ototoxicity could be a reflection of the global TB epidemiology; and the extent of development and level of functionality of pharmacovigilance systems of the countries in those regions. Future studies with prospective designs are needed to confirm the comparative risk and the determinants of the types of ototoxicity that occur in the

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long-term treatment of multidrug-resistant tuberculosis using amikacin, kanamycin and capreomycin.

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Caveat statement

The information reported to the Uppsala Monitoring Centre (UMC) comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug related is not the same in all cases. Second, the information in this paper does not represent the opinion of the World Health Organization or the UMC.

CONFLICT OF INTEREST

The authors declare no conflict of interest relevant to this study.

KEY POINTS

- Aminoglycosides and capreomycin are regaining importance in the treatment of drug-resistant tuberculosis. These drugs are potentially ototoxic, some with a propensity for auditory toxicity and some for vestibular toxicity. Whether amikacin, kanamycin, streptomycin or capreomycin is the more ototoxic drug is still not very clear.
- Based on spontaneous reports of suspected adverse reactions filed in the global pharmacovigilance database (VigiBase®), amikacin appears to be the most cochleotoxic, followed by kanamycin, while capreomycin is the least.
- This information, although not yet conclusive, may help in selecting the preferred injectable drug for inclusion into national clinical tuberculosis treatment guidelines, especially in developing countries where the incidence of drug-resistant TB is on the rise.

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AUTHOR CONTRIBUTIONS

Evans Sagwa conceived and designed the study; analyzed the data; and drafted, finalized and submitted the manuscript. PC Souverein was involved in the design of the study, data management,and review of the manuscript; I Ribeiro collected and analyzed the preliminary data for the study and reviewed the manuscript; HGM Leufkens reviewed the study protocol and manuscript. Aukje Mantel-Teeuwisse contributed to the design of the study, the interpretation of the study findings, provided guidance on writing of the manuscript and critically reviewed all drafts of the manuscript.

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