# REVIEW OF STREPTOMYCIN-ASSOCIATED OTOTOXICITY IN BRUCELLOSIS CASES

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**Abstract.** Brucellosis is a zoonotic infectious disease with a worldwide distribution and one of the challenges with its treatment is the risk of ototoxicity associated with aminoglycoside-containing regimens. In this study we aimed to review streptomycin-containing brucellosis treatment cases in order to determine the incidence of streptomycin-induced ototoxicity in the study population in order to inform treatment efforts. We conducted a single-center retrospective cohort study. Study subject inclusion criteria were being aged ≥18 years, having been diagnosed with brucellosis at the study institution during 10 January 2023-31 March 2024, having normal tympanic membranes on otoscopy, receiving a treatment regimen containing streptomycin and having undergone pure tone audiometry assessing air conduction at 500, 1000, 2000 and 4000 Hz. Hearing loss was classified as mild (26-40 dB), moderate (41-55 dB), moderately severe (56-70 dB), severe (71-90 dB) and profound (≥91 dB). Study subject exclusion criteria were pregnancy or lactation, chronic renal failure, receiving ongoing chemotherapy for a malignancy, use of known ototoxic medications (excluding nonsteroidal anti-inflammatory drugs) within the previous 3 months, having the presence of severe hearing loss at baseline prior to treatment and having missing data. A total of 70 subjects were included in our study, 60% ($n$ = 42) females. The mean (±standard deviation (SD)) age of study subjects was 43 (±14) (range: 19-70) years. At baseline the number of subjects with hearing loss was 9 (13%); during treatment 7 (10%); 5 (71%), 1 (14%), 0 (0%), 1 (14%) and 0 (0%) had mild, moderate, moderately severe, severe and profound hearing loss, respectively; at completion 0 subjects (0%) had hearing loss. The mean (±SD) age of subjects who developed temporary high-frequency hearing loss during treatment was 57 (±4) years, significantly higher ($p$-value = 0.030) than the age of subjects without hearing loss, which was 43 (±2) years. In summary, among our

study subjects, streptomycin-associated ototoxicity during standard brucellosis treatment was uncommon and reversible. However, older subjects were at greater risk of developing temporary but reversible ototoxicity. We conclude streptomycin is safe to use in brucellosis-treatment regimens in the study population. However, caution should be used in older adults and may warrant audiological testing during and at the end of treatment among older patients. Further testing is needed to determine at what age such testing may be considered.

**Keywords:** *Brucella,* brucellosis, hearing loss, ototoxicity

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## INTRODUCTION

Brucellosis is a zoonotic infectious disease present worldwide (Ghssein *et al*, 2025). The number of brucellosis cases is higher in endemic regions, such as Türkiye (Lavigne *et al*, 2025; Qureshi *et al*, 2023). The estimated annual global incidence of brucellosis is approximately 2.1 million cases (Laine *et al*, 2023).

Since *Brucella* species are intracellular microorganisms, treatment requires long-term, combination antibiotic therapy (Lavigne *et al*, 2025; Marchesini *et al*, 2024). For brucellosis in adults, the recommended treatment regimen if no organ involvement is: streptomycin 1 g intramuscularly for 3 weeks combined with doxycycline 100 mg twice daily for 6 weeks or streptomycin 1 g intramuscularly for 3 weeks combined with doxycycline 100 mg twice daily for 6 week and rifampicin at a dose of 15 mg/kg (600-900 mg) daily for 6 weeks, and if there is organ involvement the recommended treatment is streptomycin 1 g intramuscularly daily for 3 weeks combined with

doxycycline 100 mg twice daily for at least 3 months or streptomycin 1 g intramuscularly daily for 3 weeks combined with doxycycline 100 mg twice daily for at least 3 months and rifampicin at a dose of 15 mg/kg (600-900 mg) daily for at least 3 months (Ariza *et al*, 2007; WHO, 2020). Organ involvement requires longer duration of treatment durations and/or the addition of a third drug (Qureshi *et al*, 2023).

Aminoglycoside antibiotics, including streptomycin, have been reported to cause hearing loss (Duan *et al*, 2025). They can cause both cochlear and vestibular toxicity. Permanent hearing loss may occur due to damage to cochlear hair cells and the stria vascularis (Adeyemo *et al*, 2024). Aminoglycoside-induced ototoxicity initially affects high-frequency hearing, followed by lower frequencies (Human *et al*, 2010). In the literature, the incidence of aminoglycoside-associated ototoxicity has been reported to range between 28% and 37% (Peloquin *et al*, 2004; Sturdy *et al*, 2011). The risk of aminoglycoside-induced ototoxicity increases with higher doses and longer duration of administration (Xie *et al*, 2011).

In this study we aimed to review streptomycin-containing brucellosis treatment cases in order to determine the incidence of streptomycin-induced ototoxicity in the study population in order to inform treatment efforts.

## MATERIALS AND METHODS

We conducted a single-center retrospective observational cohort study among patients diagnosed with and treated for brucellosis during 1 October 2023-31 March 2024 at Ağrı Training and Research Hospital Training and Research Hospital, Ağrı Province, Türkiye.

### Patient selection and evaluated parameters

Study subjects were all those patients who were diagnosed with and treated for brucellosis at the study institution during the study period. Study subject inclusion criteria were being aged ≥18 years, having been diagnosed with brucellosis at the study

institution during 10 January 2023-31 March 2024, having normal tympanic membranes on otoscopy, receiving a treatment regimen containing streptomycin and having undergone pure tone audiometry. Exclusion criteria were pregnancy or lactation, chronic renal failure, receiving ongoing chemotherapy for a malignancy, use of known ototoxic medications (excluding nonsteroidal anti-inflammatory drugs) within the previous 3 months, having the presence of severe hearing loss on baseline prior to treatment and having missing data.

In each study subject, we obtained the following data from the hospital electronic medical record: subject age, gender, presence of comorbid medical conditions, pure tone audiometry (PTA) results, treatment-related adverse effects and treatment duration.

The diagnosis of brucellosis was made based on a combination of clinical presentation and laboratory results. Symptoms consistent with brucellosis were: fever, fatigue, night sweats, weight loss, headache, musculoskeletal pain, and a history of suspected exposure to *Brucella* (contact with tissues or secretions of infected animals, consumption of raw or unpasteurized milk and dairy products, or inhalation of potentially infected aerosols). Laboratory used to confirm the diagnosis of brucellosis required at least one of the following criteria: (1) a *Brucella* Coombs gel test (BCGT, ODAK, Toprak Medical, İstanbul, Turkey) having a titer ≥1:160; (2) a fourfold or greater rise in the *Brucella* titer over a two-week period; or (3) isolation of *Brucella* species from blood culture. Patients not having both the clinical presentation and confirmatory laboratory testing were excluded from the study.

Streptomycin was administered as part of dual or triple combination therapy was given at a dose of 1 g/day intramuscularly, with dose adjustments made when clinically indicated. For dual regimens, streptomycin was combined with doxycycline (100 mg orally twice daily). For triple regimens,

streptomycin was combined with both doxycycline (100 mg twice daily) and rifampicin (600 mg once daily) (Bosilkovski *et al*, 2021). The planned duration of streptomycin therapy was 3 weeks unless there was an adverse reaction to a component of treatment or inadequate response to treatment. The total duration of therapy was 6 weeks in patients without organ involvement and at least 12 weeks in those with organ involvement, depending on the affected system.

**Pure tone audiometry (PTA)**

Otoscopy was conducted on all subjects prior to inclusion in the study. Subjects with normal otoscopy were evaluated with PTA by certified audiologists from the Otorhinolaryngology Department at initiation, during (on Days 7, 14 and 21 of treatment if possible) and at the end of treatment. Air- and bone-conduction thresholds were measured using a calibrated Madsen Itera II pure tone audiometer (Otometrics, Taastrup, Denmark) assessing hearing at 500, 1000 2000, and 4000 Hertz (Hz) in both ears. In this study, hearing loss was defined as a change in hearing to a greater hearing loss category after exposure to streptomycin (Clark, 1981).

Hearing loss was classified as described previously (Clark, 1981): where normal hearing was having a hearing threshold of ≤25 dB, mild hearing loss was 26-40 dB, moderate was 41-55 dB, moderately severe was 56-70 dB, severe was 71-90 dB and profound was ≥91 dB. In cases of asymmetrical hearing loss, the ear with the greater degree of hearing loss was used for analysis. The 4000 Hz frequency was used to identify high-frequency hearing loss.

**Outcome definitions**

The primary outcome of the study was finding hearing loss. The secondary outcome was reversibility of hearing loss by the end of treatment but the occurrence of high-frequency hearing loss during follow-up.

**Statistical analysis**

Continuous variables were assessed for normality using the Shapiro-Wilk test. Normally

distributed data were presented as means (±standard deviation (SD)) and compared using the Student's t-test. Non-normally distributed variables were expressed as medians (with interquartile ranges) and compared using the Mann-Whitney U test. Categorical variables were summarized as numbers and percentages and compared using the Chi-square test or Fisher's exact test, where appropriate. The McNemar test was used to compare categorical variables before and after treatment. All analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 26 (IBM Corp, Armonk, NY). A p-value ≤0.05 was considered statistically significant.

Given the retrospective nature of the study, some follow-up audiometric data were unavailable at some periods while undergoing treatment and for these, we did not use imputation methods to provide these data. Analyses were conducted using a complete-case approach for each comparison, based on the availability of audiometric data at the corresponding treatment period. Missing data were assumed to be missing at random, as data unavailability was primarily related to routine clinical follow-up patterns rather than patient outcomes.

**Ethical approval and consent to participate**

The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval for the study was obtained from the Ağrı İbrahim Çeçen University Clinical Research Ethics Committee (decision no. 119 on 28 March 2024).

Written informed consent was waived by the institutional ethics committee due to the retrospective nature of the study. All data were analyzed anonymously, and patient confidentiality was strictly maintained.

## RESULTS

A total of 70 subjects were included in the study, 42 (60%) female (Fig 1). The mean (±SD) age of study subjects was 43 (±14) (range: 19-70) years. At least one comorbid

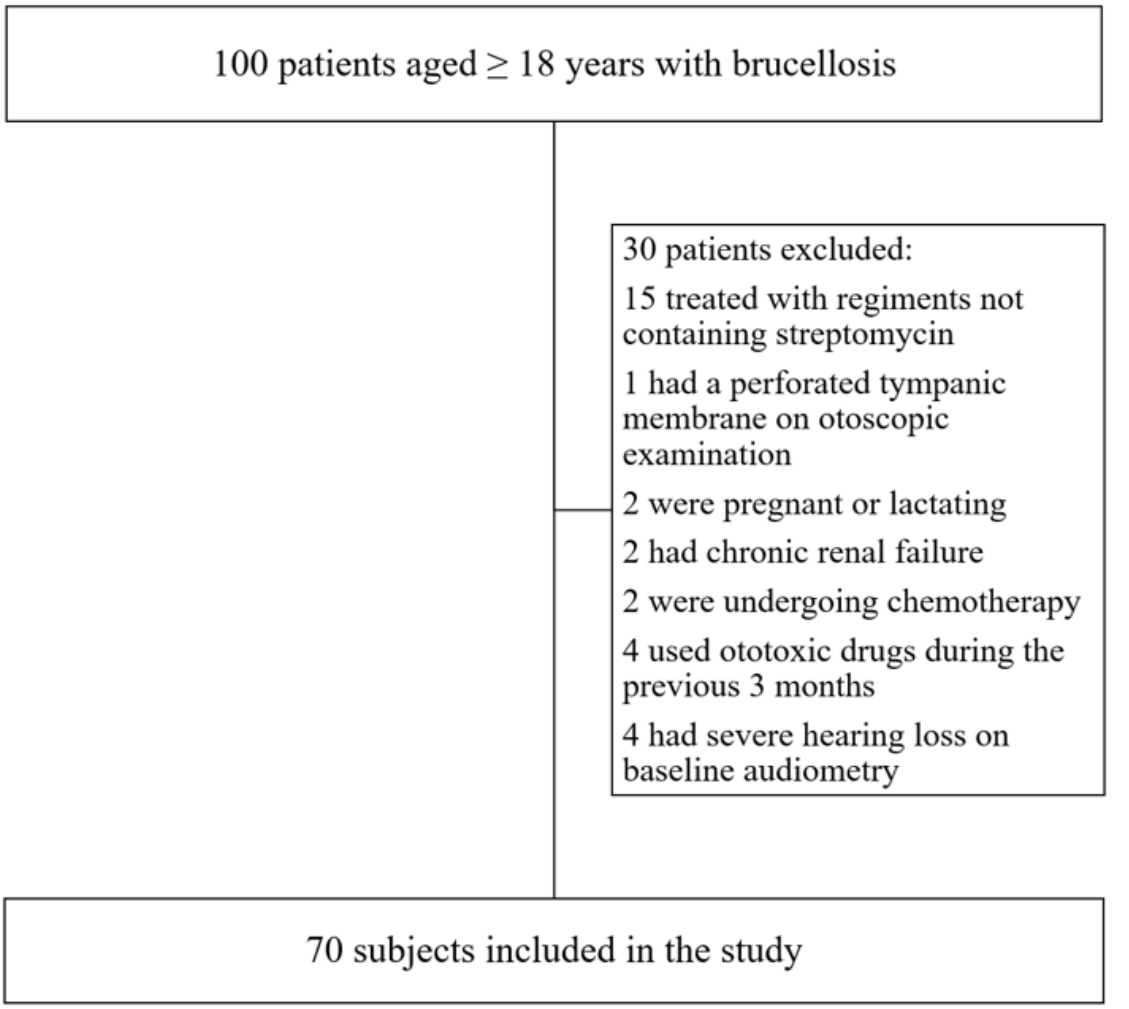


Fig 1 - Flow diagram for study subject selection

condition was documented in 27 patients (39%).

Audiometric data at baseline were available for 68 subjects (97%), during the early treatment period for 68 subjects (97%), during the mid-treatment period for 64 subjects (91%), during the late treatment period for 47 subjects (67%) and at the end of treatment for 47 subjects (67%) (Tables 1, 2 and 3).

Table 1

Baseline pure tone audiometry results (N = 70)

| Pure tone audiometry | Frequency *n* (%) |
|---|---|
| Overall air conduction | |
| Normal (≤25 dB) | 61 (87) |
| Mild hearing loss (26-40 dB) | 7 (10) |
| Moderate hearing loss (41-55 dB) | 2 (3) |
| High frequency (4000 Hz) | |
| Normal (≤25 dB) | 49 (70) |
| Mild hearing loss (26-40 dB) | 12 (17) |
| Moderate hearing loss (41-55 dB) | 3 (4) |
| Moderate-severe hearing loss (56-70 dB) | 6 (9) |

dB: decibel; Hz: hertz

No statistically significant overall hearing loss ($p$-value >0.05) was identified by the end of treatment compared with the baseline at the onset of treatment. None of the patients who subjectively reported hearing loss had audiometrically confirmed hearing impairment. An increase in air conduction thresholds was most frequently seen during the second week of treatment ($n$ = 3, 4%). High-frequency (4000 Hz) hearing loss during the second week of treatment was seen in 4 subjects (6%). A total of 7 subjects (10%) had hearing loss during treatment but the hearing returned to baseline in all these subjects by the end of treatment with streptomycin (Table 4).

At baseline the number of subjects with hearing loss was 9 (13%), during treatment this number was 7 (10%); (5 (71%), 1 (14%),

Table 2

Hearing loss or complaints during treatment

| During treatment | Number of subjects with available data | Hearing loss identified (*n*, %) | High-frequency hearing loss identified (*n*, %) | Subjective hearing complaints (*n*, %) | Number of subjects with other adverse events | Remarks |
|---|---|---|---|---|---|---|
| Early treatment (first week) | 68 | 1 (1) | 4 (6) | 1 (1) | None | 2 subjects had no available follow-up data |
| Mid treatment (second week) | 64 | 2 (3) | 1 (2) | 6 (9) | None | 5 subjects had no available follow-up data; 1 subject requested oral only treatment regimen |
| Late treatment (third week) | 47 | 0 (0) | 0 (0) | 6 (13) | Neurological (4)<br>DRESS (1)<br>Thrombocytopenia (1) | 15 subjects had no available follow-up data; 1 subject requested oral only treatment regimen |
| At completion of treatment | 47 | 0 (0) | 1 (2) | 2 (4) | None | Same as previous period |

DRESS: drug rash with eosinophilia and systemic symptoms

Table 3

Comparison of pure tone audiometry results at baseline, during and at the end of treatment

| Pure tone audiometry | Baseline frequency *n* (%) | Follow-up frequency *n* (%) | *p*-value |
|---|---|---|---|
| Early treatment period (first week) (N = 68) | | | |
| Overall air conduction | 9 (13) | 7 (10) | 0.625 |
| Mild (26-40 dB) | 7 (10) | 6 (9) | |
| Moderate (41-55 dB) | 2 (3) | 1 (1) | |
| High frequency (400 Hz) | 21 (31) | 16 (24) | 0.180 |
| Mild (26-40 dB) | 12 (18) | 6 (9) | |
| Moderate (41-55 dB) | 3 (4) | 5 (7) | |
| Moderate-severe (56-70 dB) | 6 (9) | 4 (6) | |
| Severe (71-90 dB) | 0 (0) | 1 (1) | |
| Mid treatment period (second week) (N = 64) | | | |
| Overall air conduction | 8 (13) | 8 (13) | 1 |
| Mild (26-40 dB) | 6 (9) | 6 (9) | |
| Moderate (41-55 dB) | 2 (3) | 2 (3) | |
| High frequency (4000 Hz) | 20 (31) | 14 (22) | 0.070 |
| Mild (26-40 dB) | 12 (19) | 5 (8) | |
| Moderate (41-55 dB) | 3 (5) | 4 (6) | |
| Moderate-severe (56-70 dB) | 5 (8) | 4 (6) | |
| Severe (71-90 dB) | 0 (0) | 1 (2) | |

Table 3 (cont)

| Pure tone audiometry | Baseline frequency *n* (%) | Follow-up frequency *n* (%) | *p*-value |
|---|---|---|---|
| Late treatment period (third week) (N = 47) | | | |
| Overall air conduction | 6 (13) | 5 (11) | 1 |
| Mild (26-40 dB) | 4 (9) | 4 (9) | |
| Moderate (41-55 dB) | 2 (4) | 1 (2) | |
| High frequency (4000 Hz) | 16 (34) | 11 (23) | 0.125 |
| Mild (26-40 dB) | 10 (21) | 4 (9) | |
| Moderate (41-55 dB) | 2 (4) | 4 (9) | |
| Moderate-severe (56-70 dB) | 4 (9) | 3 (6) | |
| End of treatment period (N = 47) | | | |
| Overall air conduction | 6 (13) | 3 (6) | 0.250 |
| Mild (26-40 dB) | 4 (9) | 2 (4) | |
| Moderate (41-55 dB) | 2 (4) | 1 (2) | |
| High frequency (4000 Hz) | 16 (34) | 11 (23) | 0.125 |
| Mild (26-40 dB) | 10 (21) | 5 (11) | |
| Moderate (41-55 dB) | 2 (4) | 3 (6) | |
| Moderate-severe (56-70 dB) | 4 (9) | 3 (6) | |

dB: decibel; Hz: hertz

Table 4

Audiometric characteristics of subjects in whom hearing loss was identified during treatment

| Parameters | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 |
|---|---|---|---|---|---|---|---|
| Age in years | 57 | 30 | 69 | 66 | 38 | 48 | 58 |
| Sex | Female | Male | Male | Female | Male | Female | Male |
| Presence of comorbid condition(s) | None | None | Yes | Yes | None | None | Yes |
| Baseline AC (dB), R/L | 22/20 | 18/20 | 27/23 | 37/37 | 15/13 | 18/18 | 17/17 |
| Early treatment AC in dB, R/L | 26/28 | 17/24 | 25/25 | 38/35 | 12/17 | 15/15 | 17/17 |
| Mid treatment AC in dB, R/L | 27/29 | 17/28 | 18/27 | 38/35 | 13/16 | 18/15 | 18/18 |
| Late treatment AC in dB, R/L | 26/28 | N/A | 20/27 | N/A | 12/15 | 20/15 | 18/19 |
| End of treatment AC in dB, R/L | 24/23 | N/A | 18/25 | N/A | 12/15 | 23/15 | 17/20 |
| Baseline high frequency (4000 Hz) in dB, R/L | 30/20 | 25/25 | 70/70 | 70/55 | 25/15 | 20/25 | 45/40 |
| Early treatment high frequency in dB, R/L | 30/45 | 10/20 | 55/70 | 75/60 | 20/30 | 20/30 | 45/40 |
| Mid treatment high frequency in dB, R/L | 30/45 | 10/20 | 55/70 | 75/60 | 15/20 | 20/30 | 45/45 |
| Late treatment high frequency in dB, R/L | 30/45 | N/A | 55/70 | N/A | 15/20 | 20/30 | 45/45 |
| End of treatment high frequency in dB, R/L | 30/20 | N/A | 55/70 | N/A | 15/20 | 20/25 | 45/40 |

AC: air conduction audiometry; dB: decibel; Hz: hertz; N/A: data not available; R/L: right/left

0 (0%), 1 (14%) and 0 (0%) with mild, moderate, moderately severe, severe and profound hearing loss, respectively) and at completion this total number was 0 (0%).

The mean (±SD) age of subjects with high-frequency hearing loss during treatment was 57 (±4) years and the mean (±SD) age of subjects without high-frequency hearing loss during treatment was 43 (±2) years; this difference was statistically significant ($p$-value = 0.030).

## DISCUSSION

In our study of the effect of streptomycin treatment of brucellosis on hearing, 10% of subjects had transient high frequency hearing loss during treatment but this had resolved completely by the end of treatment in all our subjects.

In a study from sub-Saharan Africa (Adeyemo *et al*, 2024), the incidence and risk factors for ototoxicity were evaluated in 153 patients receiving streptomycin-based antituberculosis treatment by checking weekly PTA during the first 2 months and monthly PTA for the following 6 months and ototoxicity was detected in 34.6% of patients, with a mean onset time of 28 weeks. A significant association was also found between ototoxicity and age and between ototoxicity and cumulative streptomycin dose (Adeyemo *et al*, 2024). In contrast, the incidence of ototoxicity in our study was only 10% during streptomycin treatment and 0% by the end of treatment. Possible reasons for this difference include careful patient selection, limiting streptomycin administration in our study to 3 weeks, exclusion of concomitant ototoxic drug use, and regular audiological monitoring. Our study findings show the risk of ototoxicity increases proportionally with age.

In a study from South Africa (Hong *et al*, 2020) examining the ototoxic effects of aminoglycosides, 379 patients undergoing treatment for drug-resistant tuberculosis were included. A predictive model was developed using logistic regression analysis to estimate the ototoxic

potential of the drug. After six months of treatment, hearing loss of varying degrees was detected in 63% of patients (Hong *et al*, 2020). In contrast, the incidence in our study was 10%, which may be attributed to the relatively lower dose and shorter duration of streptomycin use.

In a study conducted in Colorado, USA during 1991-1998 (Peloquin *et al*, 2004), patients diagnosed with mycobacterial disease and receiving streptomycin- or amikacin-containing regimens were prospectively followed in a randomized manner. The dosage and frequency of drug administration were not associated with the incidence of ototoxicity but older age and cumulative drug dosage were associated with ototoxicity in 37% of subjects.

In our study, complaints of hearing problems were not associated with significant hearing loss, similar to the results of another study which reported subjective complaints of hearing problems were not associated with objective hearing abnormalities (Peloquin *et al*, 2004). Possible explanations for this discrepancy could be a placebo effect, poor patient education or the inability of audiology to detect mild hearing changes.

The ototoxic potential of aminoglycosides, such as streptomycin, necessitates caution in clinical use, as they can cause irreversible damage to cochlear and vestibular structures (Adeyemo *et al*, 2024). In the literature, the incidence of aminoglycoside-associated ototoxicity has been reported to vary widely, often associated with prolonged use, high-dose administration or the presence of concomitant use of ototoxic medications (Adeyemo *et al*, 2024; Ganesan *et al*, 2018; Peloquin *et al*, 2004; Sturdy *et al*, 2011). The relatively low incidence observed in our study may be explained by the elimination of some of these risk factors, the short duration of treatment and the lower dosage used.

Our study had several limitations. First, its retrospective

observational design precludes causal inference and may be subject to information bias. Second, the study was conducted at a single center with a relatively limited sample size, which may restrict the generalizability of the findings. The small number of subjects who developed hearing loss also limited the ability to perform robust subgroup analyses. Third, hearing assessment was based on standard pure tone audiometry and ultra-high-frequency audiometry was not performed; therefore, subtle or early cochlear changes may not have been detected. Finally, audiometric follow-up was limited to the treatment period and delayed-onset ototoxicity after treatment completion cannot be excluded. Despite these limitations, the study provides clinically relevant data on the audiological safety of short-course streptomycin therapy for brucellosis.

In summary, among our study subjects, streptomycin-associated ototoxicity during standard brucellosis treatment was uncommon and reversible. However, some older subjects did develop transient ototoxicity during treatment. We conclude streptomycin is safe to use in brucellosis-treatment regimens in the study population. However, caution should be used in older adults and may warrant audiological testing during and at the end of treatment. Further testing is needed to determine at what age such testing may be considered and longer term follow up testing should be done to rule out delayed onset ototoxicity. Further multicenter prospective studies, with complete case follow-ups and the inclusion of otoacoustic emission tests, could provide further information about streptomycin-induced ototoxicity.

## CONFLICT OF INTEREST DISCLOSURE

The authors declare no conflict of interest.

## ARTIFICIAL INTELLIGENCE STATEMENT

An artificial intelligence–based language tool (ChatGPT, OpenAI)

was used solely for translation and language editing. The authors take full responsibility for the accuracy and integrity of the content.

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