Systematic Review

Risk of gentamicin toxicity in neonates treated for possible severe bacterial infection in low- and middle-income countries: Systematic Review

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Abstract

OBJECTIVES   To assess the risk of gentamicin toxicity and potential number of neonates exposed annually to this risk, through treatment with WHO-recommended first-line antibiotics (gentamicin with penicillin) for the 6.9 million neonates with possible serious bacterial infection (PSBI).
METHODS   Systematic literature review and assessment of the evidence using Cochrane and GRADE criteria. Meta-analysis was undertaken for pooled estimates where appropriate.
RESULTS   Eleven studies (946 neonates) were included (nine randomised controlled trials and two prospective cohort studies). Six trials reported consistently measured ototoxicity outcomes in neonates treated with gentamicin, and the pooled estimate for hearing loss was 3% (95% CI 0–7%). Nephrotoxicity could not be assessed due to variation in case definitions used. Estimates of the number of neonates potentially affected by gentamicin toxicity were not undertaken due to insufficient data.
CONCLUSION   Given wider scale-up of outpatient-based and lower-level treatment of PSBI, improved data are essential to better assess the risks from neonatal gentamicin treatment without assessment of blood levels, to maximise benefit and reduce harm.

keywords gentamicin, toxicity, neonates, sepsis, bacterial infection, systematic review

Introduction

Neonatal infections account for an estimated 580 000 newborn deaths globally each year (2012), with the greatest burden in low- and middle-income countries (LMICs) [1]. Cases of neonatal possible serious bacterial infection (PSBI) in 2012 were estimated at 6.9 million (uncertainty range 5.5–8.3 million), in neonates over 32 weeks gestation (or >1500 g) in South Asia (SA), sub-Saharan Africa (sSA) and Latin America and the Caribbean (LAC) [2]. These neonates are assessed for treatment using sensitive but non-specific clinical criteria, as described in the World Health Organization's (WHO) Integrated Management of Childhood Illness (IMCI) programme [3, 4].

Current WHO guidelines recommend gentamicin with ampicillin or penicillin as first-line therapy for all cases of neonatal sepsis [5]. The United Nations Commission on

Life Saving Commodities (UNCoLSC) [6] has listed parenteral antibiotics for newborns' infections as a priority, and investment is increasing for scaling-up of treatment including at lower levels of the health system. Recently published multicountry studies suggest that simplified antibiotic regimes, still including gentamicin, could be administered on an outpatient basis where referral was not possible, and WHO have changed their guidelines to reflect this, although concerns have been raised about the sample size required for true equivalence [7, 8]. Some countries with poor access to facility-based care are already scaling-up community-based management of neonatal PSBI; for example, Ethiopia is in process of national scale-up, using Health Extension Workers [9].

Gentamicin is an aminoglycoside antibiotic widely used due to its efficacy, low cost and availability [10]. However, it has the potential for toxicity, particularly ototoxicity and nephrotoxicity [11–13]. In adults,

ototoxicity is irreversible affecting both cochlear and vestibular systems, but gentamicin is predominantly vestibulotoxic [14–17]. Studies of gentamicin-associated toxicity are difficult in neonates, as hearing loss and renal impairment after severe bacterial infection are often multifactorial in origin (Figure 1). Sepsis, poor feeding and asphyxia commonly cause acute kidney injury (AKI), and hearing impairment can follow neonatal meningitis and tetanus [18–20, 21]. Other factors associated with infection, such as hypoxia and hyperbilirubinaemia, are also associated with hearing loss [17, 20, 22–24].

Due to concerns about potential toxicity, in well-resourced settings, therapeutic drug monitoring (serum levels) is used to reduce the likelihood of toxicity. Trough levels >2 µg/ml and peak levels>10 µg/ml are associated with increased risk [12, 25, 26], but these ranges have been extrapolated from adult literature and their appropriateness is not completely clear [27, 28]. Neonatal toxicity risk is likely increased by repeat courses, exposure to trough concentrations >2 µg/ml for more than 10 days and baseline renal impairment [29]. Genetic factors also influence susceptibility to gentamicin ototoxicity [30–32].
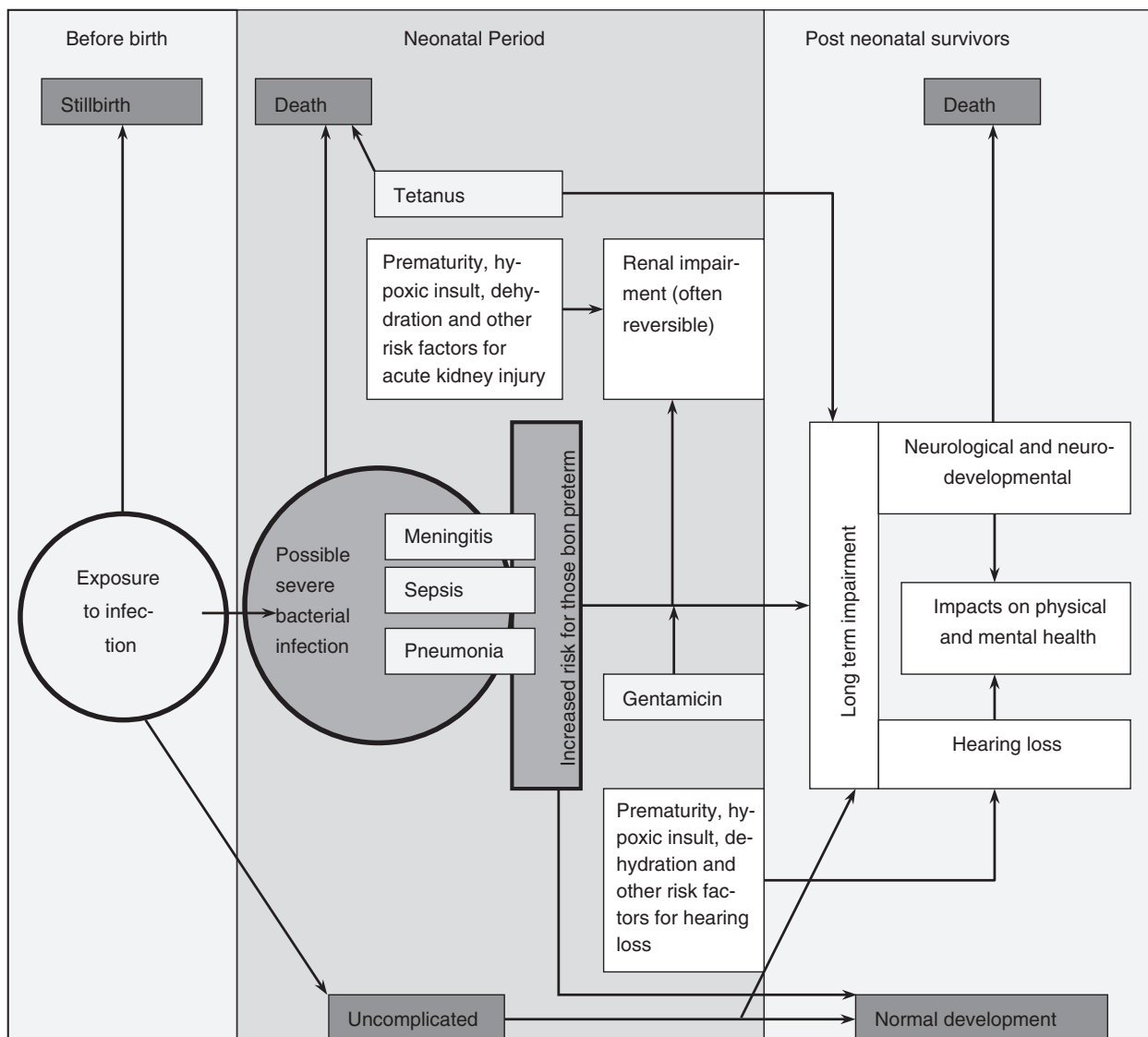

Figure 1 Disease schema for renal and hearing impairment following possible severe bacterial infection in neonates. Figure adapted from Seale *et al.* [21], http://creativecommons.org/licenses/by-nc-sa/3.0/.

The high case fatality risk of neonatal PSBI in LMICs demands that neonatal PSBI cases are treated and delays avoided to reduce neonatal mortality. However, as case management is scaled-up, including outside of hospital care, it is important to consider the risks of treatment, especially when drug levels are unmonitored. Over-treatment of neonatal PSBI may lead to toxicity even amongst neonates who do not have true bacterial infection, and this review focuses on assessing the risk of gentamicin toxicity in neonates.

We aimed to assess risks of gentamicin toxicity in neonates, through systematic literature review and meta-analysis, to enable estimation of the number of neonates at risk of gentamicin toxicity, given recent estimates of 6.9 million neonates in South Asia, Latin America and sub-Saharan Africa needing treatment [2].

Methods

Searches

The following databases were searched without date or language restrictions to identify published data on risks of gentamicin toxicity in neonates and risk of exposure to inaccurate dosing: MEDLINE, EMBASE, Cochrane Libraries and WHO regional databases (Lilacs, EMRO, AFRO, Figure 2). The 'human' limit was applied on MEDLINE and EMBASE. Combinations of the following terms were used as follows: 'gentamicin', 'neonate', 'toxicity' and 'dosing error'. Medical subject heading terms were used where available. Searches were last updated on 3 March 2015. Studies potentially fulfilling the predefined inclusion criteria were selected for full text review after initial screening of titles and abstracts. Further literature was identified through snowball searching.

Inclusion/exclusion criteria and definitions

The PICO format (population, intervention, comparison, outcomes) was applied as follows. The *population* of interest was neonates with suspected or proven sepsis or bacterial infection. Neonatal PSBI was defined as any one of the following reported clinical signs or symptoms; temperature of 37.5 °C or more, temperature of 35.5 °C or less, poor feeding, moving only in response to stimulation, significant chest indrawing, increased rate of respiration and history of convulsions. This definition was derived from the Young Infants Clinical Signs Study [33]. Studies which listed suspected or proven sepsis as the indication for treatment without providing a specific case definition were not excluded on this basis as this was not the focus of the review.

The *intervention* under review was treatment with gentamicin. The *comparison* was no treatment or use of an alternative antibiotic; however, due to the paucity of data quantifying gentamicin toxicity in neonates, studies comparing different aminoglycosides or gentamicin dosing regimens were also considered.

The *outcomes* of interest were nephrotoxicity and ototoxicity occurring as a consequence of gentamicin use and exposure to gentamicin dosing errors. Nephrotoxicity was defined as increments in serum creatinine (SCr) levels as per the thresholds specified in each individual study. Studies using serum or urinary biomarkers to quantify nephrotoxicity were not included as they are the subject of research, and studies evaluating these biomarkers used serum creatinine as the gold standard comparison test [34–36]. Ototoxicity was subclassified as auditory and vestibular toxicity. Auditory toxicity was defined as hearing loss or impairment detected by any validated hearing test. Vestibulotoxicity was defined as vestibular dysfunction detected by any validated vestibular function test.

Systematic reviews, randomised controlled trials and observational studies were included. Duplicate reports and studies that did not fulfil the inclusion criteria were excluded. Longitudinal, case–control and cross-sectional studies that did not control for confounding were not included.

Abstraction and analyses

Data from all studies fulfilling the inclusion criteria were abstracted onto a standardised form by a single reviewer. The risk of bias in each study was assessed according to Cochrane guidelines [37]. The quality of the body of evidence for each outcome of interest was assessed using GRADE criteria [38] and the available evidence summarised according to each outcome of interest. Meta-analyses were undertaken where appropriate using STATA version 13.0 [39]. Heterogeneity was assessed using the I^2 statistic. Random effects models were used if there was sufficient evidence of heterogeneity ($I^2 > 10\%$) [40]. A summary proportion estimate and corresponding 95% confidence intervals (CI) are reported.

Modelling approach

A three-step compartmental model (Figure 3) was developed for estimation of the number of neonates annually at risk of gentamicin toxicity following treatment for pSBI in South Asia (SA), sub-Saharan Africa (sSA) and Latin America and the Caribbean (LAC), adapted from previous work on impairment after neonatal infections
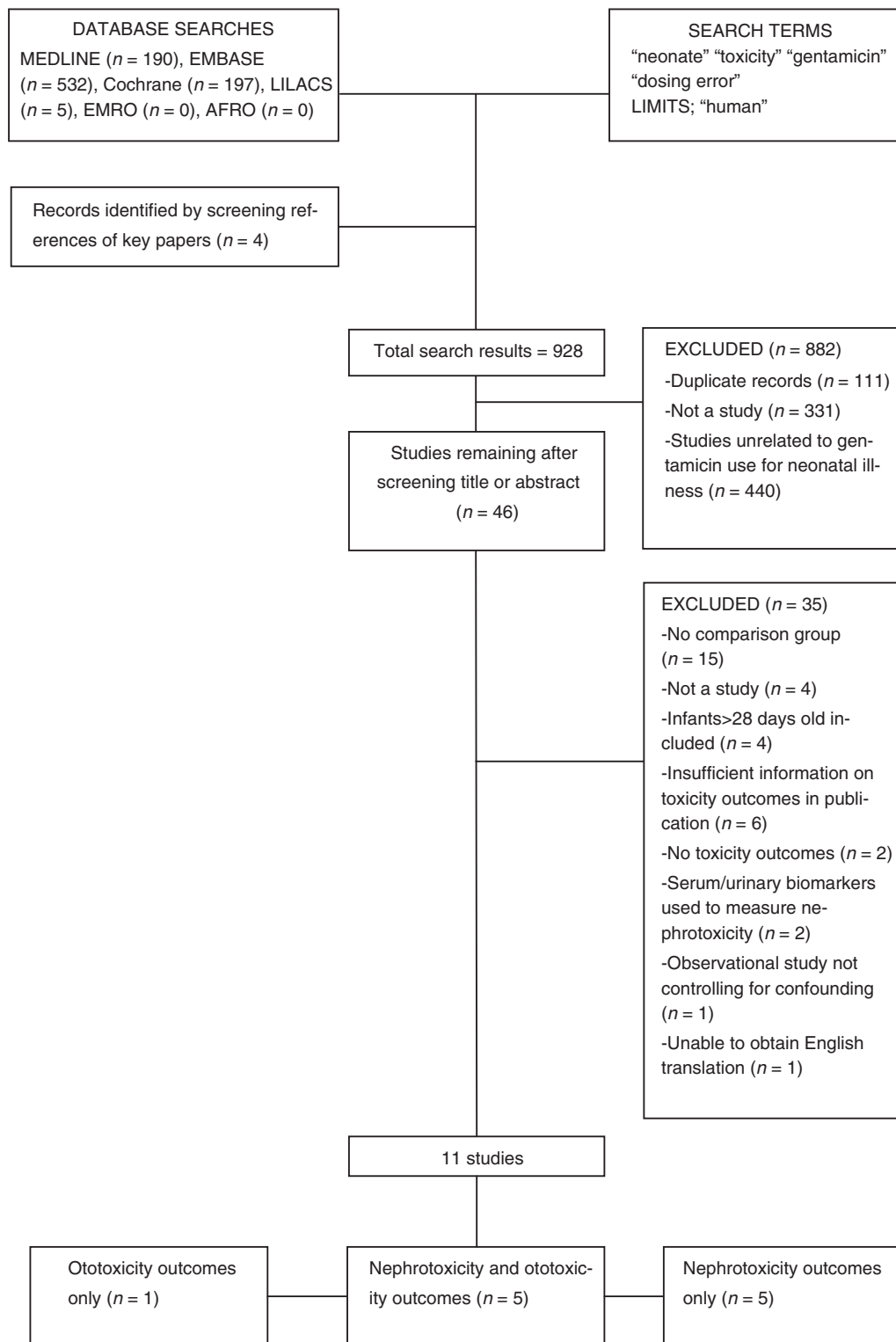
1595

DATABASE SEARCHES
MEDLINE (*n* = 190), EMBASE
(*n* = 532), Cochrane (*n* = 197), LILACS
(*n* = 5), EMRO (*n* = 0), AFRO (*n* = 0)

SEARCH TERMS
"neonate" "toxicity" "gentamicin"
"dosing error"
LIMITS; "human"

Records identified by screening references of key papers (*n* = 4)

Total search results = 928

EXCLUDED (*n* = 882)
-Duplicate records (*n* = 111)
-Not a study (*n* = 331)
-Studies unrelated to gentamicin use for neonatal illness (*n* = 440)

Studies remaining after screening title or abstract
(*n* = 46)

EXCLUDED (*n* = 35)
-No comparison group
(*n* = 15)
-Not a study (*n* = 4)
-Infants>28 days old included (*n* = 4)
-Insufficient information on toxicity outcomes in publication (*n* = 6)
-No toxicity outcomes (*n* = 2)
-Serum/urinary biomarkers used to measure nephrotoxicity (*n* = 2)
-Observational study not controlling for confounding (*n* = 1)
-Unable to obtain English translation (*n* = 1)

11 studies

Ototoxicity outcomes only (*n* = 1)

Nephrotoxicity and ototoxicity outcomes (*n* = 5)

Nephrotoxicity outcomes only (*n* = 5)

Figure 2 Study selection and results.

[21, 41]. However, data were judged to be insufficient to derive formal estimates of the number of neonates annually at risk of gentamicin toxicity.

Results

There were 924 articles identified in the systematic literature search, and an additional four articles identified through snowball searching. After initial screening of titles and abstracts, 46 articles were selected for full text review and 11 studies fulfilling the pre-specified inclusion criteria were identified; nine prospective randomised studies [42–50] and two prospective cohort studies [51, 52]

(Figure 2). These 11 studies were conducted between 1979 and 2004 in the United States, Thailand, India and Germany.

Intravenous gentamicin was used in 10 studies and one study [44] used intramuscular gentamicin. The pharmacokinetic properties of gentamicin are equivalent for both intravenous and intramuscular routes of administration so this would be unlikely to influence the outcome [29]. Eight studies [42, 43, 45, 47–51] compared different gentamicin dosing regimens, thus both intervention and comparison groups received gentamicin. Hearing assessments were reported in six trials [42–45, 51, 52], and vestibular function was assessed in one study [52]. Ten studies [42–51] measured and reported serum creatinine. No
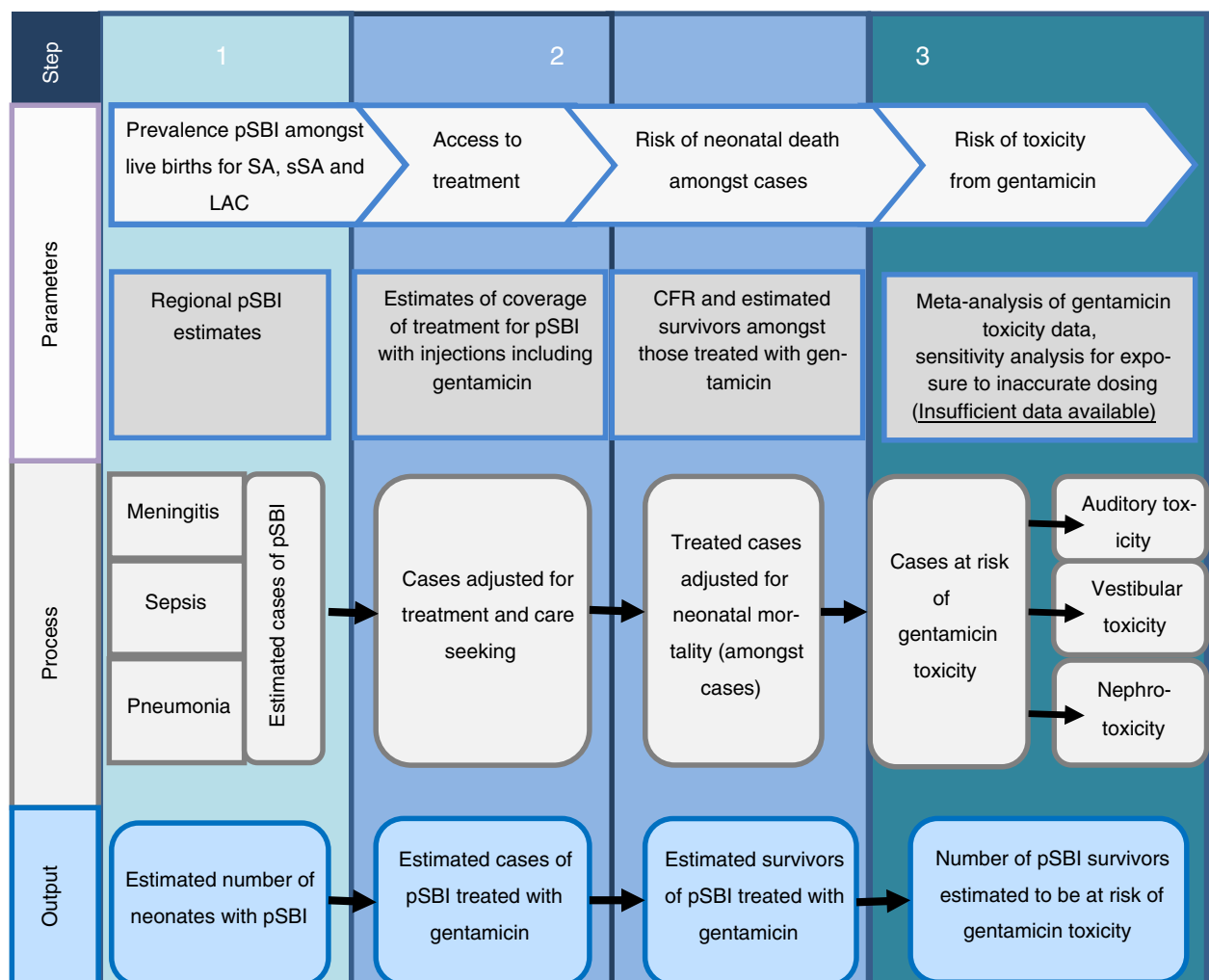

Figure 3 Outline of parameters required and three-step compartmental model for estimation of the number of neonates annually at risk of gentamicin toxicity in low- and middle-income countries. CFR, case fatality risk; SA, South Asia; sSA, sub-Saharan Africa; LAC, Latin America and the Caribbean, pSBI; possible severe bacterial infection. Figure adapted from Seale *et al.* [21], http://creative-commons.org/licenses/by-nc-sa/3.0/.

data were identified on frequency of dosing errors. The study characteristics and Cochrane risk of bias assessment for each individual trial are summarised in Table 1, and the GRADE quality assessment is detailed in Table 2.

Ototoxicity

Six studies assessed auditory toxicity; devices used for assessment and findings are summarised in Table 2. Three studies reported no hearing impairment in both intervention and comparison groups. [42–44] Three trials reported hearing loss in both intervention and comparison groups [45, 51, 52], and gentamicin was used in both intervention and comparison groups in two of these studies [45, 51]. Only one study assessed vestibular toxicity [52]. Vestibular function was evaluated using the Barany rotational test; one infant in the intervention (gentamicin) group had vestibular dysfunction at 3 years of age. There was no vestibular dysfunction noted in the comparison groups where gentamicin was not used.

In the meta-analysis of intervention group data (gentamicin therapy in combination with an additional antibiotic) from six studies [42–45, 51, 52], hearing loss after neonatal treatment with gentamicin was estimated to be 3% ((95% CI 0–7%), Figure 4). This estimate does not take into account the auditory toxicity events in the comparison groups.

Nephrotoxicity

Nephrotoxicity was assessed in ten studies; case definitions and findings are summarised in Table 2. Five studies [42, 45, 48–50] reported no nephrotoxic events in both intervention and comparison groups. One study [43] reported no difference in serum creatinine between intervention and comparison groups, but did not specifically state whether or not renal impairment was noted during the course of treatment. Three studies reported nephrotoxic events in both intervention and comparison groups [44, 46, 51], and gentamicin was used in both intervention and control groups in one of these studies [51]. One study comparing two gentamicin dosing regimens reported a single nephrotoxic event in the comparison group; this infant received concurrent indomethacin [47]. Due to the variations in case definitions, meta-analysis of nephrotoxicity data was not performed.

Estimates of burden of gentamicin toxicity in neonates with PSBI

In 2012, there were an estimated 6.9 million (uncertainty range 5.5–8.3 million) cases of PSBI in LMICs worldwide [2]. The overall case fatality risk for PSBI in LMICs was estimated to be 0.098 (95% CI 0.074–0.122) [2], and the proportion seeking care was estimated to be 59%; the median value obtained from a recent review of care-seeking behaviour in LMICs [53]. However, there were insufficient data on gentamicin toxicity in neonates for modelling, thus estimates of the numbers of neonates annually at risk of gentamicin toxicity in LMICs were not made.

Discussion

This study shows that despite the high burden of neonatal infection needing treatment, and plans to scale-up care, there are insufficient data to assess whether there is potential for harm in terms of toxicity associated with gentamicin treatment. This is of particular concern given the lack of specificity in diagnosing possible serious bacterial infection. The recent Antenatal Corticosteroids Trial (ACT) whereby lower-level workers prescribed steroids for presumed preterm labour, with four of every five women treated then not delivering preterm, and an increase in neonatal mortality, underlines the critical importance of ensuring that the principle of 'do no harm' is considered [54]. Innovation is critical to reach the poorest families who are often outside the health system, but as we work to increase access to PSBI treatment for neonates, we must also assess and minimise the potential for harm.

In the data available for hearing loss after gentamicin treatment, 3% (0–7%) of neonates were estimated to be affected. However, the data were limited; there were six studies, three with no events, and the remaining three all had limitations. In the first of these three, there were five auditory toxicity events in control groups not treated with gentamicin, compared to eight in the group treated with gentamicin [52]. In the second, more than half (57%) of the study population had indirect hyperbilirubinaemia which would increase risk of hearing loss [17, 51], and in the third study, all participants were preterm and thus more susceptible to hearing loss associated with PSBI [21, 45]. Despite the evidence that in adults, gentamicin is predominantly vestibulotoxic, only one study reported vestibular testing in infants after treatment with gentamicin. [15–17, 52] This may be, in part, a result of the longer follow-up time required for quantitative vestibular function testing and the complexity of the assessment [55], but it is important that this question is answered.

There were ten studies that considered renal function; however, case definitions of nephrotoxicity were very variable, limiting the extent to which results from different studies could be compared. A standard case definition

Table 1 Studies of hospitalised neonates included in the systematic review of gentamicin toxicity in neonates

Study ID, design and location	Intervention	Comparison	Outcomes	Risk of bias				
				Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting
Agarwal G et al. (2002) [43]† RCT; USA	4 mg/kg gentamicin every 24 hour + ampicillin (n = 20)	2.5 mg/kg gentamicin every 12 hour + ampicillin (n = 21)	Nephrotoxicity and ototoxicity	Low risk; computerised generator used	Low risk; sealed envelopes	High risk; no blinding	Low risk; 7% loss to follow-up	Low risk§
Adelman RD et al. (1987) [46] RCT; USA	2.5 mg/kg gentamicin 12 or 8 hourly + ampicillin (n = 45)	75 mg/kg mezlocillin 12, 8 or 6 hourly (n = 45)	Nephrotoxicity	Low risk; computerised generator used	Unclear; insufficient information in publication	High risk; no blinding	High risk; 18% loss to follow-up	Low risk§
Chotigeat U et al. (2001) [47] RCT; Thailand	4–5 mg/kg gentamicin once daily (n = 27)‡	2–2.5 mg/kg gentamicin twice daily (n = 27)‡	Nephrotoxicity	Unclear; insufficient information in publication	Unclear; insufficient information in publication	High risk; no blinding	Low risk; no loss to follow-up	Low risk§
Finitzo-Hieber T et al. (1979) [52]† Prospective cohort; USA	5–6 mg/kg/day genamicin (n = 116)‡	15 mg/kg/day kanamycin (n = 118)‡ or no therapy (n = 113)	Ototoxicity	Low risk; table of randomised drug regimens used	High risk; no concealment	High risk; no blinding	High risk; 75% loss to follow-up at 4 years	Low risk§
Itsarayoungyen S et al. (1982) [44]† RCT; USA	2.5 mg/kg gentamicin 12 hourly + penicillin/ampicillin/methicillin (n = 35)	2.5 mg/kg to bramycin 12 hourly + penicillin/ampicillin/methicillin (n = 26)	Nephrotoxicity and ototoxicity	Low risk; random numbers table used	Unclear; insufficient information in publication	Low risk; double blinded	High risk; 18% loss to follow-up	Low risk§
Kosalaraksa P et al. (2004) [48] RCT; Thailand	5 mg/kg gentamicin 24 hourly + penicillin/ampicillin/cloxacillin (n = 33)	2.5 mg/kg gentamicin 12 hourly penicillin/ampicillin/cloxacillin (n = 31)	Nephrotoxicity	Low risk; computerised generator used	Low risk; sealed envelopes used	High risk; no blinding	Low risk; no loss to follow-up	Low risk§
Krishnan L et al. (1997) [49] RCT; India	4 mg/kg gentamicin 24 hourly + ampicillin/ cloxacillin/crystalline penicillin/ceftazidime (n = 9)	2.5 mg/kg gentamicin 12 hourly + ampicillin/ cloxacillin/crystalline penicillin/ceftazidime (n = 9)	Nephrotoxicity	Unclear; insufficient information in publication	Unclear; insufficient information in publication	High risk; no blinding	Low risk; no loss to follow-up	Low risk§

Table 1 (*Continued*)

Study ID, design and location	Intervention	Comparison	Outcomes	Risk of bias				
				Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting
Lundergan FS *et al.* (1999) [51]† Prospective cohort; USA	5 mg/kg gentamicin loading dose then 4 mg/kg 24 hourly (term neonates), 2.5 mg/kg 24 hourly (all others) + ampicillin/additional antimicrobial (*n* = 64)	Historic cohort, gentamicin 2.5 mg/kg 24 hourly (weight <2000 g), 5 mg/kg 12 hourly (weight >2000 g) no loading doses (*n* = 57)	Nephrotoxicity and ototoxicity	High risk; treatment initiated at discretion of clinician, historical cohort	High risk; no concealment	High risk; no blinding	Low risk; no loss to follow-up	Low risk§
Mercado CK *et al.* (2004) [45]† RCT; USA	4–5 mg/kg gentamicin 48 hourly + ampicillin (*n* = 19)	2–2.5 mg/kg gentamicin twice daily + ampicillin (*n* = 21)	Nephrotoxicity and ototoxicity	Unclear; insufficient information in publication	Low risk; sealed envelopes used	High risk; no blinding	Low risk; no loss to follow-up	Low risk§
Rastogi *et al.* (2002) [42]† RCT; USA	48-h gentamicin dosing schedule + ampicillin (*n* = 30)	24-h gentamicin dosing schedule + ampicillin (*n* = 28)	Nephrotoxicity and ototoxicity	Low risk; computerised generator used	High risk; list of random numbers	High risk; no blinding	Low risk; no loss to follow-up	Low risk§
Wiese G (1988) [50] RCT; Germany	5 mg/kg gentamicin daily in 2 doses + azlocillin (*n* = 25)	5 mg/kg gentamicin daily in 2 doses + ceftriaxone (*n* = 24)	Nephrotoxicity	Unclear; insufficient information in publication	Unclear; insufficient information in publication	High risk; no blinding	Low risk; 8% loss to follow-up	Low risk§

†Included in meta-analysis.
‡Unclear if additional antibiotic used, not specified in publication.
§Outcomes specified in objectives assessed and reported.

Table 2 Studies of gentamicin toxicity in hospitalised neonates assessed by adapted GRADE evidence profile

Number of studies (Design)	Quality assessment				Generalisability			Summary of findings		Events in intervention group (total in group at end of study)	Events in comparison group (total in group at end of study)	Overall quality of evidence
	Limitations	Inconsistency	Imprecision	Indirectness	To population of interest	To intervention of interest		Study ID	Hearing test/ vestibular function test/definition of nephrotoxicity			
Auditory toxicity defined as hearing loss detected by validated hearing test:												
6 (4 RCTs, 2 cohort) [42–45, 51, 52]	No serious limitations	Heterogeneity present	Serious imprecision (few events, small sample sizes)	Serious indirectness (4 trials comparing different gentamicin dosing regimens)	Hospitalised neonates	Yes		Agarwal (2002) [43]†	Natus ALGO screen	0 (20)	0 (21)	Low
								Finitzo-Hieber (1979) [52]	Year 1 – Denver development test; year 2 – behavioural response audiometry, visual reinforcement audiometry; year 3 – audiometry, impedance, vestibular assessment; year 4 – Illinois Test of psycholinguistic abilities, Beery test of visual motor Integration, Peabody picture vocabulary test.	8 (59)	Kanamycin group; 3 (59) Control (no treatment) group; 5 (44)	
								Itsarayounyen (1982) [44]	Behavioural screen, ABR or both	0 (20)	0 (30)	
								Lundergan (1999) [51]†	Natus ALGO screen	2 (64)	1 (57)	
								Mercado (2004) [45]†	Natus ALGO 2 screen, follow-up ABR if abnormal	2 (19)	1 (21)	
								Rastogi (2002) [42]†	Natus ALGO screen, follow-up ABR if abnormal	0 (30)	0 (28)	
Vestibular toxicity defined as vestibular dysfunction detected by a validated vestibular function test:												
1 (cohort) [52]	Significant loss to follow-up (75% at 4 years), single study	N/A	Small sample size, few events	Undetected	Hospitalised neonates	Yes		Finitzo-Hieber (1979) [52]	Barany rotational test	1 (59)	Kanamycin group; 0 (59) Control (no treatment) group; 0 (44)	Very low

Table 2 (*Continued*)

Nephrotoxicity defined as increase in serum creatinine (SCr) as per thresholds specified in each individual study:

Quality assessment					Generalisability		Summary of findings				
Number of studies (Design)	Limitations	Inconsistency	Imprecision	Indirectness	To population of interest	To intervention of interest	Study ID	Hearing test/ vestibular function test/definition of nephrotoxicity	Events in intervention group (total in group at end of study)	Events in comparison group (total in group at end of study)	Overall quality of evidence
10 (9 RCTs, 2 cohort) [42–51]	No serious limitations	Difficult to assess due to heterogeneous case definitions	Serious imprecision (small sample sizes, few events)	Serious indirectness (8 trials comparing different gentamicin dosing regimens)	Hospitalised neonates	Yes	Adelman (1987) [46]	Increase in SCr ≥ 0.3 mg/dl	26% (38)	12% (36)	Moderate
							Agarwal (2002) [43]†	SCr of 1 mg/dl or 0.5 mg/dl increase	Unclear (20)‡	Unclear (30)‡	
							Chotigeat (2001) [47]†	Increase in SCr (threshold not specified)	0 (27)	1 (27)	
							Itsarayoungyen (1982) [44]	Increase in SCr 0.4 mg% or more during treatment	3 (20)	4 (30)	
							Kosalaraksa (2004) [48]†	Increase in SCr (threshold not specified)	0 (33)	0 (31)	
							Krishnan (1997) [49]†	Increase in SCr (threshold not specified)	0 (9)	0 (9)	
							Lundergan (1999) [51]†	Increase in SCr by 0.5 mg/dl	27% (64)	26% (57)	
							Mercado (2004) [45]†	'Normal' SCr defined as level < 1 mg/dl	0 (19)	0 (21)	
							Rastogi (2002) [42]†	Increase in SCr by 0.5 mg/dl	0 (30)	0 (28)	
							Wiese (1988) [50]†	Increase in SCr (threshold not specified)	0 (23)	0 (22)	

RCT, Randomised controlled trial; ABR, Auditory brainstem responses.
†Gentamicin administered to both intervention and comparison groups.
‡No differences in SCr between the two groups, unclear if nephrotoxic events occurred as not specified in publication.
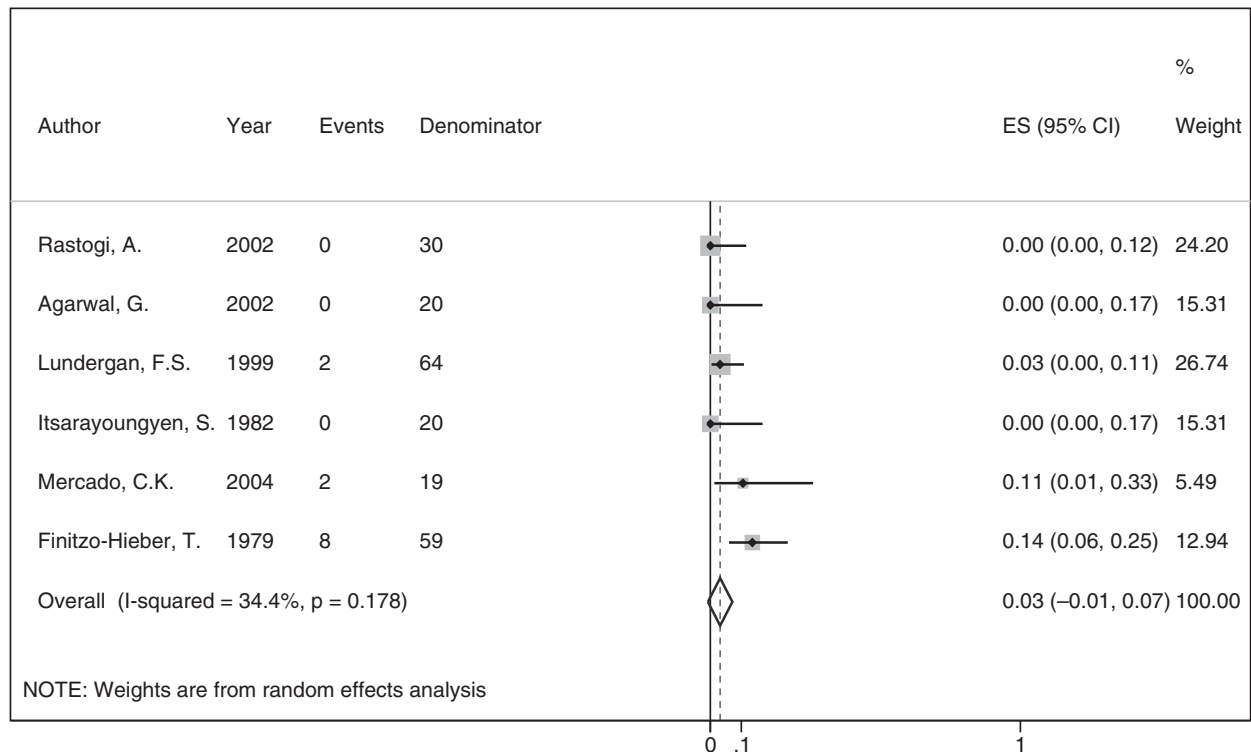
Author	Year	Events	Denominator	ES (95% CI)	% Weight
Rastogi, A.	2002	0	30	0.00 (0.00, 0.12)	24.20
Agarwal, G.	2002	0	20	0.00 (0.00, 0.17)	15.31
Lundergan, F.S.	1999	2	64	0.03 (0.00, 0.11)	26.74
Itsarayoungyen, S.	1982	0	20	0.00 (0.00, 0.17)	15.31
Mercado, C.K.	2004	2	19	0.11 (0.01, 0.33)	5.49
Finitzo-Hieber, T.	1979	8	59	0.14 (0.06, 0.25)	12.94
Overall (I-squared = 34.4%, p = 0.178)				0.03 (−0.01, 0.07)	100.00

NOTE: Weights are from random effects analysis

Figure 4 Meta-analysis of ototoxicity as detected by validated hearing test in intervention groups treated with different gentamicin regimes ($N = 212$). See Tables 1 and 2 for details of the six studies.

of nephrotoxicity in neonates (or acute kidney injury) is needed, but this is in part hampered by difficulties in interpreting tests. New biomarkers to detect neonatal renal impairment are being investigated, but serum creatinine (SCr) is currently the gold standard test [34–36]. However, levels in the first 72 h of life can reflect the maternal SCr, and in fact, half of all neonatal renal function can be lost before changes in SCr are noted [35].

The limitations in the data in this review are all in the direction of underestimation of the true incidence of neonatal gentamicin toxicity. In eight studies, gentamicin was administered to both intervention and comparison groups [42, 43, 45, 47–51]. All trials were conducted in hospitalised neonates, where experienced clinicians, therapeutic drug monitoring, neonatal intensive care facilities and routine blood monitoring were available. This limits the generalisability of the data, as this standard of care is not universally accessible even in upper middle-income countries such as Thailand and without this care, the likelihood of toxicity is increased. [47, 48, 56, 57] If outpatient management is implemented at scale in LMICs, sick, preterm neonates with undetected impaired renal function will be at much higher risk of toxicity.

Although there are significant data limitations, as described previously, the importance of prevention of auditory toxicity and early identification of infants with hearing impairment cannot be overstated. Hearing loss is a leading cause of moderate and severe disability worldwide [58]. Children with hearing impairment in LMICs are more likely to be marginalised and subject to physical abuse [59]. Additionally, significant hearing loss increases risk of poor academic performance due to hindered speech and language development [60].

Programmatic implications

Where hospital treatment of PSBI is not accessible or feasible, outpatient management with antibiotic injections is associated with reduced neonatal mortality, especially in high burden settings [61]. Decisions on changes to future case management guidelines should include consideration of the potential for toxicity associated with treatment as well as changes in resistance patterns. Alternatives include cephalosporins, particularly for neonates at increased risk of toxicity (preterm, low birth weight or and jaundiced). Whilst therapeutic drug monitoring may not be feasible in all healthcare facilities where treatment

G. M. Musiime *et al.*   **Risk of gentamycin toxicity in neonates**

is provided, monitoring should be undertaken where resources are more readily available, in larger hospitals. Additionally, systems should be put in place to ensure that dosing errors are avoided [62, 63].

Implementation of widespread neonatal hearing screening in LMICs would be challenging with high costs of equipment and the deficit of skilled healthcare workers. Targeted hearing screening of high-risk neonates, such as those exposed to gentamicin, may be possible in the short to medium term. If supported by treatment, this would confer long-term benefit to the infants as speech and language development is improved with early identification of hearing impairment and appropriate rehabilitation [64].

Recommendations for further research

There is a need for well-designed prospective cohort studies assessing the frequency of toxic levels of gentamicin using current standard of care in LMICs. In addition, a multicentred, well-designed, adequately powered randomised controlled trial evaluating outcomes after either first-line treatment with aminoglycosides or a third generation cephalosporin for neonatal PSBI is needed.

Innovative approaches to assessing gentamicin levels and to measuring ototoxicity are also key areas for research, possibly through public–private partnerships. A possible method to facilitate serum gentamicin level measurement is microsampling, using filter paper to collect blood from finger or heel pricks. Microsamples on filter paper are simple to collect and transport. Further research is required to determine agreement with results from larger volume samples [65, 66].

In the meantime, when workers at any level of the health system are using gentamicin for neonatal PSBI, [61,67] investments are urgently required to improve coverage data [68] and for implementation research to improve accuracy of prescribing and administration particularly for preterm, sick neonates where overdoses will do the most damage.

Conclusion

The lack of data on gentamicin toxicity risk in neonates, for ototoxicity and nephrotoxicity, is striking, particularly in LMICs where the disease burden, and need for antibiotic treatment is greatest. Particularly with expansion of outpatient management in settings where access to hospital-based care is limited, more attention and further research is essential to ensure that much needed scale-up to ensure access to treatment does not result in also doing harm.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Study identifiers and context.
Table S2. Study Design and Methodology.
Table S3. Study Limitations.
Table S4. Participants.
Table S5. Intervention.
Table S6. Ototoxicity.
Table S7. Nephrotoxicity and Dosing errors.

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