Effectiveness of antimicrobial stewardship programmes in neonatology: a systematic review

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ABSTRACT

Introduction Antimicrobial stewardship programmes (ASPs) are recommended to improve antibiotic use in healthcare and reduce antimicrobial resistance (AMR). Our aim was to investigate the effectiveness of ASPs in reducing antibiotic consumption, use of broad-spectrum/restricted antibiotics, antibiotic resistance and healthcare-associated infections (HAIs) in neonates.

Methods We searched PUBMED, SCIELO, EMBASE and the Cochrane Database (January 2000–April 2019) to identify studies on the effectiveness of ASPs in neonatal wards and/or neonatal intensive care units (NICUs). Outcomes were as follows: reduction of antibiotic consumption overall and of broad-spectrum/target antibiotics, inappropriate antibiotic use, antibiotic resistance and HAIs. ASPs conducted in settings other than acute care hospitals, for children older than 1 month, and ASPs addressing antifungal and antiviral agents, were excluded.

Results The initial search identified 53 173 titles and abstracts; following the application of filters and inclusion criteria, a total of six publications were included in the final analysis. All studies, of which one was multi-centre study, were published after 2010. Five studies were conducted exclusively in NICUs. Four articles applied multimodal interventions. Reduction of antibiotic consumption overall and/or inappropriate antibiotic use were reported by four articles; reduction of broad-spectrum/targeted antibiotics were reported by four studies; No article evaluated the impact of ASPs on AMR or the incidence of HAI in neonates.

Conclusion ASPs can be effectively applied in neonatal settings. Limiting the use of broad-spectrum antibiotics and shorting the duration of antibiotic treatment are the most promising approaches. The impact of ASPs on AMR and HAI needs to be evaluated in long-term studies.

What is already known on this topic?

- Antimicrobial stewardship programmes (ASPs) are an important tool to reduce antibiotic consumption in paediatrics, but little know is reported about impact on neonatal population.
- Evaluation of ASP impact in hospitals is usually performed using aggregated patient data, making identification of ASP effect in neonatal populations difficult.
- Antibiotic consumption in neonates has a different pattern compared with that in older children and adults.

What this study adds?

- ASPs are effective to reduce overall antibiotic consumption in hospitalised neonates.
- The impact of ASPs for hospitalised neonates on reduction of antibiotic resistance has not been established.
- The contribution of ASPs to reduction of healthcare-associated infections in neonatology has not been evaluated in hospitalised neonates.

INTRODUCTION

Antimicrobial resistance (AMR) is a phenomenon that existed and was recognised even before the widespread use of the first antibiotic for human use, penicillin.[1] AMR is a naturally occurring and transmissible survival mechanism in bacteria, and thus, large-scale use of antibiotics drives rapid increase in the global burden of AMR, threatening the medical benefit of these drugs.[2]

Children and neonates are arguably the most affected human population, as AMR combined with a limited pipeline of newly developed antibiotic agents and classes limits the therapeutic options to treat infections due to multidrug-resistant bacteria.[3] In 2018, not one single new antibiotic of the total 59 new drugs approved for human use by the US Food and Drug Administration was licensed for paediatric use.[4] In the absence of new antibiotics and owing to a lack of pharmacokinetic data to guide effective and safe use of many existing agents such as colistin and polymyxin B, antibiotics are often prescribed 'off-label', potentially contributing to the emergence of multi-resistant bacteria.[5]

Antimicrobial stewardship programmes (ASPs) help to improve antimicrobial use and potentially extend the effective lifespan of these agents, while new antibiotics are in development. The core components of an ASP differ between institutions, but as a minimum, should include (1) monitoring of antibiotic prescribing patterns, (2) AMR surveillance and (3) post-prescription review.[6]

Implementation of ASP in neonatal wards and neonatal intensive care units (NICUs) is important, owing to long hospital stays and the risk to develop hospital-acquired infections (HAIs) in this population, particularly in preterm and low birthweight infants. Use of antibiotics in neonatal care is

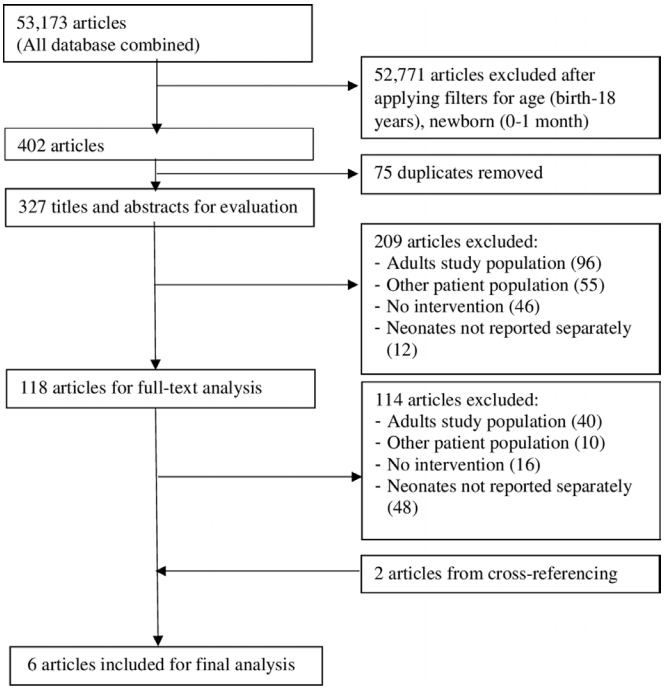

Figure 1 Systematic review profile.

unavoidable for both prophylaxis of risk factors for sepsis and surgical procedures, and life-saving treatments of severe bacterial infections. However, antibiotic use in neonates is associated with short-term and long-term adverse consequences due to emerging AMR, both for the individual patient and neonatal settings as a whole. Often, pathogens of clinical bacterial infections are not identified in neonates, which limits targeted treatment; and thus, antibiotic prescriptions for clinical sepsis or suspected bacterial infections in neonates is often large.[7]

Considering these aspects, we aimed to identify studies on effective ASPs in reducing antibiotic consumption, use of broad-spectrum/restricted antibiotics, AMR, and HAIs in neonatal wards and/or NICUs.

METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses statements of evaluations of healthcare interventions.[8]

Search strategy

We searched publications in PUBMED, SCIELO, EMBASE and the Cochrane Database of Systematic Review from 1 January 2000 to 30 April 2019 using the search terms 'antimicrobial stewardship', 'antimicrobial stewardship and antibiotic use', antimicrobial stewardship and neonates', 'antimicrobial stewardship and neonatal intensive care unit', 'antimicrobial stewardship and C-reactive protein', 'antimicrobial stewardship and interleukin 6' and 'antimicrobial stewardship and interleukin 8', and applying filters for age (children from birth to less than 18 years, and newborns to 1 month). There were no language restrictions. The complete search strategy is presented in online supllementary file (search strategy for databases).

Eligibility criteria

Inclusion criteria: Studies were eligible for full-text review if they were conducted in hospitalised neonates, including neonatal wards and NICUs, and when clearly defined ASP actions were the main intervention. Antimicrobial stewardship was defined according to the Infectious Disease Society of America and the Society for Healthcare Epidemiology of America.[9] Only quantitative studies, such as randomised controlled trials, controlled and non-controlled before-and-after studies, controlled and non-controlled interrupted time series analyses and cohort studies were included. Previous systematic reviews were also analysed for cross-referencing.

Exclusion criteria: Reviews, case series, letters, notes, conference abstracts and opinion articles were excluded, as well as interventions in outpatient care, in paediatric settings other than neonatal, emergency departments, primary care, long-term care facilities or a combination of these. We also excluded quantitative studies applying ASPs in both adults and children/neonates, where extraction of neonatal data was not possible. Finally, studies focusing on antiviral and antifungal agents were excluded as well.

Study searching and selection

All search steps were conducted independently by three investigators (ARAS, MF and CBB). Disagreements were resolved by consensus. After applying the search criteria and filters to each database, we conducted three rounds of article analysis before selecting the final list of publications for inclusion:

1. First-round: Exclusion of duplicate articles.
2. Second-round: Screening of the titles and abstracts.
3. Third round: Reading of eligible full-text articles.

Articles from the reference sections of full-text articles were scrutinised and included for analysis, if eligibility criteria were met.

Quality of articles and risk of bias

The quality of the selected articles was assessed using the integrated quality criteria for systematic review of multiple study designs (ICROMS) tool.[10] Briefly, the tool consists of two distinct parts: (1) The first one is a list of quality criteria specific for each study design, as well as criteria applicable across all study designs using a scoring system. Criteria components include aspects about aims, study justification, management of bias, analytical rigour and ethical aspects. (2) The second part is the 'decision matrix', which specifies the robustness of the study by identifying minimum requirements according to the study type and the relevance of the study to the review question. Only studies meeting the minimum score and the mandatory criteria according to the ICROMS methodology were included for the final analysis.

Data collection

Data were extracted using a standardised data-extraction form, which summarised the study details including authors, year of publication, settings, country or countries where the study was performed, time frame of the study, aim, interventions and summary of key findings. The following outcomes were assessed: reduction of total antibiotic consumption; reduction of inappropriate antibiotic use; reduction of broad spectrum and/or target antibiotic use; reduction of AMR and reduction of HAI. Inappropriate antibiotic use was defined as use of a broad-spectrum antibiotic when the infection episode and/or pathogen could have been successfully treated with a narrow-spectrum antibiotic/s; or when treatment time exceeded the recommended treatment duration.[11]

RESULTS

A total of 53 173 articles were identified. After applying filters for age and patient type, 402 publications remained, of which

Table 1 Antimicrobial stewardship programme in neonatal settings: a systematic review (January 2000–April 2019)

Authors	Study design	Setting	City, country, study period	Aims	Interventions	Summary of key findings
Chiu et al[12]	NCITS	Two tertiary NICUs; 50 and 18 beds	Boston, USA; 2005 to 2008	To evaluate effectiveness and safety of a guideline restricting vancomycin use	▶ Introduction of an electronic guideline restricting vancomycin use	▶ Change of vancomycin use from 6.9/1000 PD to 4.5/PD in hospital 1 (p=0.01), and from 17/1000 PD to 6.4/1000 PD in Hospital 2 (p<0.0001) ▶ Change of infants exposed to vancomycin from 5.2/1000 PD to 3.1/1000 PD (p=0.008) in hospital 1, and from 10.8/1000 PD to 5.5/1000 PD in hospital 2 (p=0.009)
Ting et al[16]	NCBA	Single NICU	Vancouver, Canada; 2010 to 2015	To evaluate the effectiveness of ASP on antibiotic prescription practices	▶ Audit and feedback ▶ Revision of antibiotic guideline ▶ Education on judicious antimicrobial use ▶ New technology to reduce time of microbiological diagnosis	▶ Change of inappropriate meropenem antibiotic—days from 1.89 to 1.96 (RR (95% CI): 1.04 (0.70–1.52)) per 1000 DOT ▶ Change of inappropriate cefotaxime antibiotic—days from 3.56 to 1.73 (RR (95% CI): 0.49 (0.33–0.71)) per 1000 DOT ▶ Change of inappropriate vancomycin antibiotic—days from 2.70 to 1.01 (RR (95% CI): 0.37 (0.22–0.60)) per 1000 DOT ▶ No improvement of inappropriate antibiotic prescriptions in very low birthweight infants ▶ No changes in inappropriate courses of linezolid
Nzegwu et al[13]	NCITS	Single level IV NICU; 54 beds	Boston, USA; 2011–2016	To evaluate an ASP on prescription practices	▶ Development of clinical guidelines on the treatment of common neonatal infections ▶ Audit and feedback by a multidisciplinary ASP team ▶ Education on judicious antibiotic use	▶ Change of monthly antibiotic use from 270.4 to 258.8 DOT/1000 PD (p=0.669) ▶ Change of monthly ampicillin use from 118.6 to 103.4 DOT/1000 PD (p=0.037) ▶ No significant changes of vancomycin, cefotaxime and gentamicin/tobramycin ▶ Decrease of late-onset sepsis evaluation and prescription events per 100 NICU days (p<0.0001), with an average reduction of 2.65 evaluations per year per provider Clinical guidelines adherence of 98.75%
Lee et al[14]	NCITS	Single paediatric centre, NICU; 60 beds	Memphis, USA; 2010 to 2013	To evaluate the effectiveness of a new guideline about antimicrobial use for common infections and early-onset sepsis on antimicrobial use	▶ Development of a guideline taking into account local antibiograms ▶ Education on judicious antimicrobial use ▶ Regular audits and feedback	▶ Change of antibiotic use from 448 to 367 DOT/1000 PD ▶ Change of targeted broad-spectrum antibiotics from 70 to 27 DOT/1000 PD
Mc Carthy *et al*[17]	NCBA	Single NICU; 50 beds	Cork, Ireland; September 2016 to March 2017	To evaluate the effectiveness of a local guideline in combination with audits and electronic prescribing on antimicrobial use	▶ Development of a local guideline on antibiotic prescription ▶ Education on judicious antimicrobial use ▶ Electronic prescribing ▶ Audit and feedback ▶ Multidisciplinary round	▶ Change of antibiotic use from 572 to 417 DOT/1000 PD (p<0.0001) ▶ Change of prolonged antibiotic use (>36 hours) from 82 to 7.5 DOT/1000 PD (p=0.0004) ▶ Change of prolonged antibiotic use (>5 days) from 46.5 to 7 DOT/1000 PD (p=0.0009)

Continued

Table 1 Continued

Authors	Study design	Setting	City, country, study period	Aims	Interventions	Summary of key findings
Cantey *et al*[15]	NCITS	Single level 3C NICU; 90 beds	Texas, USA; March 2012 to June 2014	To inform ASP strategies in a NICU, determining areas where antibiotic use could be reduced safety	▶ Extension of ruled-out sepsis courses beyond 48 hours ▶ Treatment duration for culture-negative pneumonia ▶ Treatment duration for culture-negative sepsis	▶ Change of antibiotic use from 343.2 to 252.2 DOT/1000 PD (p<0.0001) ▶ Change of 48 hours rule-out courses (percentage discontinued <48 hours) from 32% to 95% (p<0.0001) ▶ Change of infants with culture-negative sepsis treated <5 days from 31% to 62% (p=0.04) ▶ Change of pneumonia treatments<5 days from 36% to 72% (p<0.0001)

ASP, antimicrobial stewardship program; DOT, days of therapy; NCBA, non-controlled before-and-afterstudy; NCC, non-controlled cohort study; NCITS, non-controlled time-series analysis; NICU, neonatal intensive care unit; PD, patient-day.

75 were duplicates (figure 1). A total of 118 full-text articles were reviewed, of which six were eligible for final analysis. Four articles were from the USA,[12–15] one from Canada and one from Ireland.[16 17] All articles fulfilled the minimum and mandatory ICROMS quality criteria (scores for each article according to the ICROMS methodology are presented in online supplementary annex 1-3).

All studies were published after 2010 and only one included patients from two or more different hospitals.[12] The remaining articles reported interventions conducted in single centres.

Interventions in neonates only were conducted exclusively in NICUs.[12 13 15–17] One article addressed interventions to the NICU, the paediatric intensive care unit (PICU) and the cardiac intensive care unit.[14]

ASPs of four studies used a multimodal implementation strategy,[13 14 16 17] while a single ASP intervention was tested in the other two studies.[12 15] Table 1 summarises the findings of the six articles.

Table 2 presents the outcomes assessed in studies of ASP intervention in neonates.

Reduction of overall antibiotic use and/or inappropriate prescription was reported by three studies.[13–15 17] However, such reduction was statistically significant in two studies only.[15 17]

Four articles reported reductions in the use of broad-spectrum or target antibiotics.[12–14 16] However, such reduction was statistically significant in one study only.[12] Antibiotic classes targeted for reduction included carbapenems (meropenem), glycopeptides (vancomycin), oxazolidinones (linezolid), third-generation and fourth-generation cephaloporins, and broad-spectrum penicillins (piperacillin–tazobactam).

No article assessed the impact of ASP on the incidence of AMR or HAI.

DISCUSSION

The balance between adequate and unnecessary antibiotic use in neonates remains a challenge. Due to the vulnerability of neonates, and particularly of pre-term infants, antibiotics are frequently described in this population.[18] On a given day, 39.1% of infants of a level III NICU receive one or more antibiotics,[19] although there is considerable variation in the overall use of antibiotics overall,[20] as well as the selection of antibiotic agents.[21 22] The studies in this systematic review show that reduction of antibiotic use is possible and still safe for neonates, as verified previously in an analysis of secular trends of antibiotic use in this population.[23]

Effectiveness of ASPs in paediatric inpatient populations other than neonates has been summarised by two systematic reviews.[24 25] The first review identified nine studies in various US paediatric inpatient settings,[24] the second review focused on paediatric intensive care, and identified nine studies from the US, Germany, Indonesia and Singapore.[25] All studies reported reductions in the use of antibiotics overall and broad-spectrum/restricted antibiotics in particular.[25] One study even reported HAI reductions, but the only study investigating AMR could not find statistically significant differences.

Table 2 Outcomes reported in studies of antimicrobial stewardship in neonatology (January 2000–April 2019)

Author	Outcomes			
	Reduction of antibiotic use or inappropriate prescription	Reduction of broad-spectrum or target antibiotics	AMR reduction	HAI reduction
Chiu *et al*[12]	ND		ND	ND
Ting *et al*[16]	ND		ND	ND
Nzegwu *et al*[13]			ND	ND
Lee *et al*[14]			ND	ND
Mc Carthy *et al*[17]		ND	ND	ND
Cantey *et al*[15]		ND	ND	ND

Reduction with statistical significance.
Reduction without statistical significance.
Reduction by simple comparison.
ND, not done.

Despite an increasing number of studies on ASPs in literature, only a few were performed in neonatal care. This is of concern because antibiotic use in neonates not only is linked to AMR but is associated with potential other risks such as necrotising enterocolitis or invasive fungal diseases.[26 27] Although we included studies in neonates only, our search came across a number of reports on applying ASPs in the entire paediatric population, including neonates.[28–34] Although the principles of ASPs are applicable in both neonates and other paediatric patients, details must be adapted. Neonates differ from other paediatric patients in many ways, but mostly by the fact that infections are predominantly healthcare related of which the majority are bloodstream infections.[35] ASPs should always address neonatal populations separately, as the indications and drivers of antimicrobial use are different from infants and children. When comparing the impact of ASP in NICU versus paediatric ICU settings, NICU ASPs appear to achieve more reduction in antibiotic consumption and use of broad-spectrum/restricted agents.[25] However, there are extremely few published reports of NICU ASP and recent reports from PICUs that have achieved reduced antibiotic consumption and use of broad-spectrum antibiotics.[25 36 37]

When evaluating antibiotic consumption in neonates, days of therapy (DOT) or DOT/1000 patient-days are the two most commonly used metrics[12–15 17]; furthermore, the proportion of antimicrobial agents prescribed from each of the WHO Access, Reserve and Watch (AWaRE) classes should be included in future research reporting neonatal prescribing and ASP.[38]

Prolonged courses of empiric, broad-spectrum antibiotics (eg, vancomycin in combination with third-generation cephalosporins) are common in NICUs due to the lack of gold standards in diagnosing neonatal sepsis. Culture-confirmed early-onset sepsis is not frequent, particularly not in term infants.[39] Targeting or discontinuing antibiotics is challenging in neonates due to the unreliability of blood culture sampling in this population.[40 41] In the absence of reliable markers to guide antibiotic therapy, effects of ASPs are limited in neonates. Effects on overall antibiotic use reported by the studies of this systematic review were limited,[13 14 17] and the difference was statistically significant in two of them.[15 16] Effects are mainly due to reducing therapy duration.[17] Audit and feedback, but even more, regular multidisciplinary rounds with neonatologists and infectious diseases specialists offer confidence in ASPs, and results may be seen in the long-term rather than in short-term.[23]

Only one article was able to demonstrate statistically significant reduction of selected broad-spectrum antibiotics.[12] Although ASPs may not substantially reduce overall antibiotic use in neonates, effects on limiting broad-spectrum antibiotics may be more interesting, and even be beneficial in reducing colonisation with multidrug-resistant *Enterobacter cloacae*,[42 43] or in reducing candidiasis.[27] Adapting the choice of antibiotic agents[13] to local antibiogrammes and avoiding broad-spectrum antibiotics may be the most promising element of ASPs in the neonatal population.

No articles evaluated the impact of ASPs on HAI. ASPs alone may be limited to impact on HAI, but in combination with infection prevention and control interventions have been shown to be beneficial. Such a comprehensive strategy reduced HAIs from 22.6% to 8.6% in a single centre in Indonesia.[44]

Our study has limitations. First, four databases were searched and some articles may have been missed, even with inclusion of all languages in the search criteria. To minimise this problem, we used cross-referencing to identify missed eligible articles. Second, although used already in the nineties, 'antimicrobial stewardship' is a relative new term and by applying it in our search strategy, particularly older studies not using this term may have been missed. However, cross-referencing identified studies, which did not use the term 'antimicrobial stewardship' as a key word.[13] Third, no randomised controlled trials were identified. Although considered the gold standard in measuring effectiveness, ASPs are behaviour interventions, and thus, the findings are not surprising. The closest behaviour change interventions come to randomised controlled trials is a stepped-wedge cluster-randomised controlled trial design.[45]

CONCLUSION

ASPs can be effectively applied in neonatal settings. Limiting the use of broad-spectrum antibiotics and shorting the duration of antibiotic treatments are the most promising approaches. The impact of ASPs on AMR and HAI needs to be evaluated in long-term studies.

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Annex 1-Quality criteria for application per study design- Integrated quality criteria for review of multiple study designs (ICROMS)

Quality criteria			Study design [b]						
Dimension		Specific criteria [a]	RCT	CBA	CITS	NCITS	NCBA	CS	QUAL
1.	Clear aims and justification	a. Clear statement of the aims of research?	++	++	++	++	++	++	++
		b. Rationale for number of pre-and post-intervention points or adequate baseline measurement	x	x	+	++	++	x	x
		c. Explanation for lack of control group	x	x	x	+	+	x	x
		d. Appropriateness of qualitative methodology	x	x	x	x	x	x	+
		e. Appropriate study design	x	x	x	x	x	x	++
2.	Managing bias in sampling or between groups	a. Sequence generation	++	x	x	x	x	x	x
		b. Allocation concealment	++	x	x	x	x	x	x
		c. Justification for sample choice	x	x	x	++	++	x	x
		d. Intervention and control group selection designed to protect against systematic difference/selection bias	x	++	x	x	x	x	x
		e. Comparability of groups	x	x	x	x	x	++	x
		f. Sampling and recruitment	x	x	x	x	x	x	++
3.	Managing bias in outcome measurements and blinding	a. Blinding	++	x	x	x	x	x	x
		b. Baseline measurement- protection against selection bias	x	++	x	x	x	x	x
		c. Protection against contamination	x	++	x	x	x	x	x
		d. Protection against secular changes	x	x	++	x	x	x	x
		e. Protection against detection bias: blinded assessment of primary outcome measures	+	+	+	+	+	+	x
		f. Reliable primary outcome measures	+	+	+	+	+	+	+
		g. Comparability of outcomes	x	x	x	x	x	++	x
4.	Managing bias in follow-up	a. Follow-up of subjects (protection against exclusion bias)	+	x	x	x	x	x	x
		b. Follow-up of patients of episodes of care	+	x	x	x	x	x	x
		c. Incomplete outcome data addressed	+	+	+	+	+	++	+
5.	Managing bias in other study aspects	a. Protection against detection bias: intervention unlikely to affect data collection	+	+	+	+	+	x	x
		b. Protection against information bias	x	x	x	x	x	+	x
		c. Data collection appropriate to address research aims	x	x	x	x	x	x	+
		d. Attempts to mitigate effects of no control	x	x	x	++	++	x	x
6.	Analytical rigour	a. Sufficient data points to enable reliable statistical inference	x	x	++	x	x	x	x
		b. Shaping of intervention effect specified	x	x	+	x	x	x	x
		c. Analysis sufficiently rigorous/free from bias	+	+	+	+	+	+	+
7.	Managing bias in reporting/ethical considerations	a. Free of selective outcome reporting	+	+	+	+	+	+	+
		b. Limitations addressed	+	+	+	+	+	+	+
		c. Conclusions clear and justified	+	+	+	+	+	+	+
		d. Free of other bias	+	+	+	+	+	+	+
		e. Ethics issues addressed	+	+	+	+	+	+	+

[a] Applicability of quality criteria to each study design: + Criteria to be included in quality assessment for study design; ++ Mandatory criteria to be met quality assessment; x Criteria not to be applied in quality assessment for study design.

[b] Study designs: RCT =randomised controlled trial; CBA =controlled before-after; CITS ¼ controlled interrupted time series; CS = cohort study; NCITS =non-controlled interrupted time series; NCBA =non-controlled before-after; QUAL = qualitative.

Annex 2 -Decision matrix including mandatory criteria and minimum score for study type to be analysed in review.

Study Design [a]	Mandatory criteria [b]	Minimum score
RCT, cRCT	1A, 2A, 2B, and 3A	22
CBA	1A, 2D, 3B and 3C	18
CITS	1A, 3D and 6A	18
NCITS	1A, 1B, 2C and 5D	22
NCBA	1A, 1B, 2C and 5D	22
Cohort	1A, 2E, 3G and 4C	18
Qualitative	1A, 1E and 2F	16

[a] Study Designs: RCT = randomised controlled trial; CBA =controlled before-after; CITS = controlled interrupted time series; cRCT =cluster-randomized controlled trial; NCITS = noncontrolled interrupted time series; NCBA =non-controlled before-after.

[b] Scores applicable to each criteria: Yes (criterion met) =2 points; Unclear (unclear whether or not the criterion is met) =1 point; No (criterion not met) = 0 points.

Adapted from Zingg W et al. Innovative tools for quality assessment: integrated quality criteria for review of multiple study designs (ICROMS). Public Health 2016;133:19-37.

Annex 3- Score attributed to selected articles. Effectiveness of antimicrobial stewardship programmes in neonatology. A systematic review

Reference	Study design	Minimum score required	Article Score
Chiu, 2011	NCITS	22	32
Ting, 2019	NCBA	22	31
Nzegwu, 2017	NCITS	22	30
Lee, 2016	NCITS	22	30
Mc Carthy, 2018	NCBA	22	22
Cantey 2016	NCITS	22	28

NCITS: noncontrolled interrupted time series; NCBA : non-controlled before-after.

SUPPLEMENTARY MATERIAL – SEARCH STRATEGY FOR DATABASES

Database	**PUBMED**
Strategy	
#1	("antimicrobial stewardship"[MeSH Terms] OR ("antimicrobial"[All Fields] AND "stewardship"[All Fields]) OR "antimicrobial stewardship"[All Fields])
#2	(("antimicrobial stewardship"[MeSH Terms] OR ("antimicrobial"[All Fields] AND "stewardship"[All Fields]) OR "antimicrobial stewardship"[All Fields]) AND ("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "neonates"[All Fields])
#3	(("antimicrobial stewardship"[MeSH Terms] OR ("antimicrobial"[All Fields] AND "stewardship"[All Fields]) OR "antimicrobial stewardship"[All Fields]) AND ("anti-bacterial agents"[Pharmacological Action] OR "anti-bacterial agents"[MeSH Terms] OR ("anti-bacterial"[All Fields] AND "agents"[All Fields]) OR "anti-bacterial agents"[All Fields] OR "antibiotic"[All Fields])
#4	(("antimicrobial stewardship"[MeSH Terms] OR ("antimicrobial"[All Fields] AND "stewardship"[All Fields]) OR "antimicrobial stewardship"[All Fields]) AND ("intensive care units, neonatal"[MeSH Terms] OR ("intensive"[All Fields] AND "care"[All Fields] AND "units"[All Fields] AND "neonatal"[All Fields]) OR "neonatal intensive care units"[All Fields] OR ("neonatal"[All Fields] AND "intensive"[All Fields] AND "care"[All Fields] AND "unit"[All Fields]) OR "neonatal intensive care unit"[All Fields])
#5	(("antimicrobial stewardship"[MeSH Terms] OR ("antimicrobial"[All Fields] AND "stewardship"[All Fields]) OR "antimicrobial stewardship"[All Fields]) AND C-protein[All Fields] AND reactive[All Fields])
#6	(("antimicrobial stewardship"[MeSH Terms] OR ("antimicrobial"[All Fields] AND "stewardship"[All Fields]) OR "antimicrobial stewardship"[All Fields]) AND ("interleukin-6"[MeSH Terms] OR "interleukin-6"[All Fields] OR "interleukin 6"[All Fields])
#7	(("antimicrobial stewardship"[MeSH Terms] OR ("antimicrobial"[All Fields] AND "stewardship"[All Fields]) OR "antimicrobial stewardship"[All Fields]) AND ("interleukin-8"[MeSH Terms] OR "interleukin-8"[All Fields] OR "interleukin 8"[All Fields])) AND (("2000/01/01"[PDAT] : "2019/04/30"[PDAT])
#8	(("2000/01/01"[PDAT] : "2019/04/30"[PDAT])
#9	("infant, newborn"[MeSH Terms] OR ("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms])))
#10	((Classical Article[ptyp] OR Clinical Study[ptyp] OR Clinical Trial[ptyp] OR Comparative Study[ptyp] OR Controlled Clinical Trial[ptyp] OR Historical Article[ptyp] OR Meta-Analysis[ptyp] OR Multicenter Study[ptyp] OR Observational Study[ptyp] OR Pragmatic Clinical Trial[ptyp] OR systematic[sb])]
#11	" humans" [MeSH Terms]
#12	(#1 OR #2 OR # 3 OR # 4 OR #5 OR # 6 OR #7) AND # 8 AND # 9 AND #10 AND #11

Database	**EMBASE**
Strategy	
#1	"antimicrobial stewardship": ab, ti
#2	"neonates": ab, ti
#3	"neonatal intensive care unit":ab,ti
#4	"antibiotic use": ab, ti
#5	"C-reactive protein": ab, ti
#6	"interleukin 6": ab, ti

#7	"interleukin 8":ab,ti
#8	''clinical study'/exp OR 'clinical trial':ti,ab OR 'clinical trials':ti,ab OR 'controlled study'/exp OR 'evaluation'/exp R 'cross-sectional study'/exp OR 'cross sectional':ab,ti OR 'evaluation study':ab,ti OR 'evaluation studies':ab,ti OR 'intervention study':ab,ti OR 'intervention studies':ab,ti OR 'case control':ab,ti OR 'cohort analysis'/exp OR cohort:ab,ti OR longitudinal*:ab,ti OR prospective:ab,ti OR prospectively:ab,ti OR retrospective:ab,ti OR 'follow up'/exp OR 'follow up':ab,ti OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR 'comparative study':ab,ti OR 'comparative studies':ab,ti) NOT ('case report'/exp OR 'case study'/exp OR 'editorial'/exp OR 'letter'/exp OR 'note'/exp OR [conference abstract]/lim) AND [2000–2019]/py AND [humans]/lim AND [embase]/lim NOT [medline]/lim
#9	(#1 AND #2) OR (#1 AND #3) OR (#1 AND #2 AND #4) OR (#1 AND #2 AND #5) OR (#1 AND #2 AND #6) OR (#1 AND #2 AND #7) OR (#1 AND #2 AND #8) AND #8

Database	**SCIELO**
Strategy	
#1	"antimicrobial stewardship"
#2	"antimicrobial stewardship AND neonates"
#3	"antimicrobial stewardship and neonatal intensive care unit"
#4	"antimicrobial stewardship and neonates and C-reactive protein"
#5	"antimicrobial stewardship and neonates and interleukin 6"
#6	"antimicrobial stewardship and neonates and interleukin 8"
#7	type:("research-article" OR "rapid-communication")
#8	(#1 OR #2 OR # 3 OR #4 OR #5 OR #6) AND #7

Database	**COCHRANE DATABASE OF SYSTEMATIC REVIEWS**
Strategy	
#1	(antimicrobial stewardship): ti, ab, kw
#2	(antimicrobial stewardship and neonates): ti,ab, kw
#3	(antimicrobial stewardship and neonatal intensive care unit): ti,ab, kw
#4	(antimicrobial stewardship and neonates and C-reactive protein): ti, ab, tw
#5	(antimicrobial stewardship and neonates and interleukin 6): ti, ab, kw
#6	(antimicrobial stewardship and neonates and interleukin 8): ti, ab, kw
#7	with Publication Year from 2000 to 2019, with Cochrane Library publication date from Jan 2000 to Apr 2019, in Trials (Word variations have been searched)
#8	# 1 OR #2 OR #3 OR #4 OR #5 OR #6 AND #7