

The Impact of Antimicrobial Stewardship in Children in Low- and Middle-income Countries

A Systematic Review

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Background: Antimicrobial stewardship (AMS) is central to the World Health Organisation Global Action Plan against antimicrobial resistance (AMR). If antibiotics are used without restraint, morbidity and mortality from AMR will continue to increase. In resource-rich settings, AMS can safely reduce antibiotic consumption. However, for children in low- and middle-income countries (LMIC), the impact of different AMS interventions is unknown.

Aim: To determine the impact of different AMS interventions on antibiotic use and clinical and microbiologic outcomes in children in LMIC.

Methods: MEDLINE, Embase and PubMed were searched for studies of AMS interventions in pediatric population in LMIC settings. Controlled trials, controlled before-and-after studies and interrupted time series studies were included. Outcomes assessed were antibiotic use, multidrug-resistant organism (MDRO) rates, clinical outcomes and cost.

Results: Of 1462 studies, 34 met inclusion criteria including a total population of >5,000,000 in 17 countries. Twenty were in inpatients, 2 in ED, 10 in OPD and 2 in both. Seven studies were randomized controlled trials. All types of interventions reported a positive impact on antibiotic prescribing. AMS bundles with education, and clinical decision tools appeared more effective than guidelines alone. AMS interventions resulted in significantly decreased clinical infections (4/4 studies) and clinical failure (2/2) and reduced MDRO colonization rate (4/4). There was no concomitant increase in mortality (4/4 studies) or length of stay (2/2).

Conclusion: Multiple effective strategies exist to reduce antibiotic consumption in LMIC. However, marked heterogeneity limit conclusions regarding the most effective approach, particularly regarding clinical outcomes. Overall, AMS strategies are important tools in the reduction of MDRO-related morbidity in children in LMIC.

Key Words: antimicrobial stewardship, low-middle income, prescribing, antibiotic

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Antimicrobial resistance (AMR) poses a huge threat to global health, and effective antibiotics to treat multidrug-resistant organisms (MDRO) are limited, particularly in low- and middle-income countries (LMICs). Half of deaths in neonates attributable to resistant pathogens occur in just 5 LMICs.¹ Access to antibiotics is a continuing problem in many LMIC settings, and more deaths are attributed to limited and delayed access than to infections with resistant organisms.¹ However, antibiotic consumption has rapidly increased in countries such as China and India, with a shift toward broad-spectrum antibiotic use.¹ Consequently, the World Health Organization (WHO) has outlined a global action plan to combat AMR. A key objective includes monitoring and optimization of antimicrobial use at national and local levels.²

Antimicrobial stewardship (AMS) interventions are effective in increasing adherence to antibiotic policy, reducing antibiotic duration and reducing infection rates with MDROs and *Clostridium difficile*.^{3,4} However, the large majority of studies are from high-income countries, so findings may not be applicable to LMIC settings. A consensus has been published on core necessary elements for hospital AMS programs (ASPs) which could be applied to both high- and low/middle-income settings, and the WHO has developed a toolkit for ASPs in LMIC.^{5,6} However, specific guidelines are lacking for ASPs in children.

Implementing ASPs for children in LMIC has specific challenges. Infections are the leading cause of death in children under 5 years old in LMIC, particularly in neonates, so the impetus to prescribe antibiotics is high.^{1,7} Limited access to microbiology laboratory services, and specifically antibiotic susceptibility testing, means that broad-spectrum antibiotics have been used frequently, with low incentive to change in these high-mortality settings.⁸ Although poor access to antibiotics is a tangible problem in LMIC, the irony is that untargeted prescribing has worsened the problem by increasing AMR, leading to antibiotics becoming less effective.¹ There has been one previous systematic review of AMS in children.⁹ Only 1 of the 9 studies was in an LMIC, and outpatients and neonatal intensive care units (NICUs) were excluded. The only review of AMS interventions in LMIC was limited to hospital settings and did not consider pediatrics specifically.¹⁰

This systematic review aimed to determine, for children accessing hospital and/or community healthcare in LMIC, the impact of different AMS interventions on antibiotic use, clinical outcomes, AMR and cost.

METHODS

This systematic review of the impact of AMS interventions in children in LMIC followed PRISMA guidelines. The review protocol was registered at the PROSPERO International Prospective Register

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of Systematic Reviews (available at <http://www.crd.york.ac.uk>): Registration number CRD42020153776. The search terms are outlined in Supplemental Digital Content 1, <http://links.lww.com/INF/E516>.

Search Strategy

MEDLINE, EMBASE, and PUBMED databases (inception to February 2020) were searched for original studies, and the Cochrane Database was searched for systematic reviews. Additional records were identified through reference checking. Participants were children 0–18 years of age in inpatient, ED or outpatient settings. LMICs were defined based on gross national income per capita as published by the World Bank.¹²

AMS interventions reviewed were those that constitute one of the core or supplemental strategies in an ASP defined according to the Infectious Diseases Society of America and Society for Healthcare Epidemiology of America⁹: audit and feedback, formulary restriction and preauthorization, education, guidelines and clinical pathways and antimicrobial cycling. Clinical decision support (point-of-care [POC] test or decision support algorithm) was also included as the latter may be feasible to institute in LMIC. Interventions of interest were those that targeted healthcare professionals, but if studies also targeted parents they were included.

Inclusion Criteria

Studies were included for full-text review if they were randomized or nonrandomized controlled trials, before-after studies or interrupted time series. Studies could be of single or bundled interventions. There needed to be one or more of the following outcomes: antibiotic prescription rate and appropriateness (compliance with antibiotic guidelines and reduction in use of nontargeted antibiotics, decision to treat, total duration³); clinical outcomes (infection, clinical failure, morbidity/mortality and length of hospital stay); microbiologic outcomes (reduction in resistant bacterial colonization or infection); and cost.

Exclusion Criteria

Exclusion criteria were studies solely related to antifungal, antimalarial or antiretroviral medication, studies without outcome measures and studies with adults where pediatric data could not be evaluated separately. Case series, editorials and reviews without primary data were excluded.

Study Selection Process

Two reviewers independently conducted the database searches and reviewed the title and/or abstract of each study. Full text was reviewed by the authors if articles appeared to meet study inclusion, and any discrepancy was discussed and resolved between the reviewers

Data Extraction

Data were extracted independently and compiled in a PRISMA format table, including: study design, setting, number of participants, population, intervention group, comparison group, outcomes and risk of bias (Supplemental Digital Content, <http://links.lww.com/INF/E516>). Studies were grouped by intervention type. A meta-analysis was not done as the disparity in study design, interventions and outcomes prevented combining of data from different studies. Study bias was assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.¹³

RESULTS

Thirty-four studies met inclusion criteria with total population of >5,000,000 children in 17 countries; China (14 studies),^{14–28} Argentina (2),^{29,30} Bangladesh (2),^{31,32} India (2),^{33,34} Tanzania (2),^{35,36} Brazil,³⁷ Cuba,³⁸ Indonesia,³⁹ Iran,⁴⁰ Kenya,⁴¹ Korea,⁴² Peru,⁴³ Pakistan,⁴⁴ Russia,⁴⁵ Serbia,⁴⁶ Turkey⁴⁷ and Vietnam⁴⁸

(Table 1, see Table 1, Supplemental Digital Content 2, <http://links.lww.com/INF/E516>).

The majority of study designs were uncontrolled before-after series (17)^{14,22–24,26–28,30,31,34,37–39,42,44,46} or RCTs (7).^{21,29,35,38,41,43,48} Additionally, there were 3 uncontrolled interrupted time series,^{15,17,33} 3 controlled before-after studies,^{16,19,45} 2 non-RCTs,^{36,47} 2 studies assessing long-term follow-up²⁰ and cost-effectiveness of an RCT.²⁵ The majority of studies were at medium (12) or high (16) risk of bias (Table 2).

Fourteen studies were of AMS bundles^{14,17,19–21,26,28,30–32,37–39,41,44,46} (multiple interventions applied at once, further described below), 2 of which also included infection prevention and control measures.^{37,39} The remaining interventions were: a clinical decision tool (7),^{22,29,35,36,43,47,48} implementation of a guideline (7),^{16,24,27,33,34,42,45} financial disincentives for antibiotic prescribing (2),^{15,23} audit and feedback (1)⁴⁰ and cost-effectiveness (1).²⁵

Settings in which ASP were implemented varied between inpatient wards (13 studies),^{22,24,26,28,30,32,39–42,45,46} outpatient clinics (11),^{16,19,21,23,27,29,31,35,36,38,48} intensive care (NICU 4^{17,33,34,37} and PICU 3^{14,30,44}) combined inpatient and outpatient (2)^{15,23} and ED (2).^{43,47} The outcomes measured were markedly heterogeneous (see Table, Supplemental Digital Content 3, <http://links.lww.com/INF/E516>).

Antibiotic Prescribing Results According to Intervention AMS Bundles

Sixteen studies assessed effectiveness of the implementation of an AMS bundle, 6 of which were from China and 14 of which had a medium/high risk of bias. AMS bundles as a minimum included policy or guideline implementation plus education. Some also included audit and feedback, an AMS committee, restrictions for overprescribing, antibiotic resistance reporting, prior authorization, point of prescription interventions (automatic stop after 48 hours), and parental education. Outcomes assessed were heterogeneous (Table 1).

Five studies targeted antibiotic prescribing for specific conditions: patients with intussusception after air enema reduction,²⁸ respiratory tract infection^{20,21,31,38} and acute nonbloody diarrhea.⁴¹ When applied to specific conditions, all AMS bundles substantially reduced inappropriate antibiotic prescribing,^{20,21,28,38,41} with 4 of 5 statistically significant.⁴¹

In inpatient wards and PICU, AMS bundles significantly reduced overall antibiotic consumption (except for one study in PICU, although empiric use reduced¹⁴) and antibiotic resistance rates,^{14,26} and increased adherence to guidelines.²⁰ An AMS bundle applied in a PICU in China resulted in significant reduction in use of the third generation cephalosporins from 53% to 17% ($P < 0.01$), increased use of beta-lactam/beta-lactamase-inhibitors (BL/BLIs) from 4% to 44% ($P < 0.01$), and no change in carbapenem use.¹⁴ In addition, there was a reduction in bacterial resistance in *Pseudomonas aeruginosa* and Enterobacteriaceae. When applied in NICUs, AMS bundles led to reduction in empiric and overall antibiotic use^{17,33,34} and resistance rates,^{17,34,37} without increase in late-onset sepsis or mortality.¹⁷

One outpatient study followed up 14 of 25 primary health-care facilities 12 months after completing an RCT of an AMS bundle to reduce antibiotics in acute URTI.²⁰ Compared with the preintervention rate of 84%, antibiotic prescribing 6 months postimplementing the intervention was 37% ($P \leq 0.01$), and at 18 months 54% ($P \leq 0.01$) (ie, some rebound), compared with control facilities where it remained stable at approximately 75%.

Two of the AMS bundle studies additionally included infection prevention and control interventions. One from Indonesia found a reduction in HAI from 23% to 9% ($P < 0.01$) in addition to significant reductions in inappropriate prescriptions and all-cause

Table 1. Study and Type of Outcomes Assessed (Primary Outcome Unless Stated Secondary, 2°)

Study Type Author, Year	Antibiotic Consumption	Antibiotic Type	Antibiotic Indication	Antibiotic Prescribing Rate	Cost	MDRO Isolation	Mortality (All Cause)	Other Clinical Outcome
Implementation of AMS Bundle, n = 16								
Zou et al, 2015 ²⁸								
Wei et al, 2017 ¹⁹								
Ding et al, 2008 ¹⁴								
Wei et al, 2017 ²¹								
Wei et al, 2019 ²⁰								
Zhang et al, 2018 ²⁵								
Zhang et al, 2018 ²⁶								
Lu et al, 2019 ¹⁷						2°	2°	2°
Kalaba et al, 2018 ⁴⁶						2°		
Ruvinsky et al, 2014 ³⁰								
Opondo et al, 2011 ⁴¹								
González Ochoa et al, 1996 ³⁸								
Haque et al, 2017 ⁴⁴							2°	
Sultana, 2017 ³²								
Chowdhury et al, 2018 ³¹								
Murni et al, 2015 ³⁹			2°				2°	
Calil et al, 2001 ³⁷								
Guideline or policy implementation, n = 7								
Zhang et al, 2008 ¹⁸		2°						
Zhang et al, 2008 ²⁴								
Liang et al, 2014 ¹⁶								
Jinka et al, 2017 ³³		2°					2°	2°
Berild et al, 2008 ⁴⁵							2°	2°
Lee et al, 2007 ⁴²							2°	
Murki et al, 2009 ³⁴							2°	
Clinical decision tool, n = 7								
Shao et al, 2015 ³⁶								
Keitel et al, 2017 ³⁵				2°			2°	
Do et al, 2016 ⁴⁸							2°	2°
Bucher et al, 2012 ⁴³								
Ozkaya et al, 2009 ⁴⁷								
Torres et al, 2014 ²⁹							2°	2°
Wu et al, 2017 ²²							2°	
Antibiotic restriction and financial disincentive, n = 2								
Gong et al, 2016 ¹⁵								
Xu et al, 2019 ²³								
Audit and feedback on restricted antibiotics, n = 1								
Rahbarimanesh et al, 2019 ⁴⁰								
Total outcomes	14	10	11	10	9	8	8	11

mortality.³⁹ The other in an NICU in Brazil showed a reduction in multidrug-resistant (MDR) *Enterobacter cloacae* colonization and all MDRO infections.³⁷

Antibiotic Guidelines or Policy

Seven studies assessed the effectiveness of guidelines, and 5 had a high risk of bias. Three from China implemented the national guidelines^{16,18,24} and the others implemented local guidelines/policy.^{33,34,42,45} Combined, the number of participants studied was large, including multiple different inpatient specialty units, and the follow-up period of assessment of intervention was 12–24 months.

Guideline/policy implementation alone significantly reduced antibiotic consumption in only 2 studies^{16,45} and in 1 of 3 hospitals in another study.²⁴ While not all studies showed reduction in this specific measure, there were frequently reductions in other antibiotic measures, such as proportion of neonates in an Indian NICU treated with antibiotics (58%–46%, $P < 0.001$) and use of third generation cephalosporins (41%–7%, $P < 0.01$).³³ There were other impacts as well, such as significant reduction in ESBL rates (47%–25%, $P = 0.04$), also found after guideline implementation in a Korean hospital which resulted in significant reduction in ESBL *Klebsiella pneumoniae* (64%–26%; $P < 0.01$).⁴²

Table 2. Risk of Bias Assessment of AMS Intervention Studies by Type in Children in LMICs¹³

Study Type	Risk of Bias Criteria*														Overall Risk†
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	
Interrupted time series															
Gong et al, 2016 ¹⁵	U	L	L	L	H	L	L	NA	NA	NA	NA	NA	NA	L	Medium
Jinka et al, 2017 ³³	U	L	L	L	L	U	L	NA	NA	NA	NA	NA	NA	L	Medium
Lu et al, 2019 ¹⁷	U	L	L	L	L	U	L	NA	NA	NA	NA	NA	NA	L	Medium
Rahbarimanesht et al, 2019 ⁴⁰	H	L	L	L	L	H	H	NA	NA	NA	NA	NA	NA	H	High
Cluster RCT															
Opondo et al, 2011 ⁴¹	NA	NA	NA	NA	NA	U	L	H	L	U	U	L	L		High
González Ochoa et al, 1996 ³⁸	NA	NA	NA	NA	NA	U	L	H	L	L	H	H	L	H	High
Wei et al, 2017 ²¹	NA	NA	NA	NA	NA	L	L	L	L	L	L	L	L	L	Low
Wei et al, 2019 ²⁰	NA	NA	NA	NA	NA	L	U	L	L	L	L	L	L	L	Medium
Case-control/controlled and uncontrolled^U before-after studies															
Liang et al, 2014 ¹⁶	NA	NA	NA	NA	NA	H	L	H	H	U	U	L	L	L	High
Berild et al, 2008 ⁴⁵	NA	NA	NA	NA	NA	U	U	H	H	L	U	L	H	L	High
Wei et al, 2017 ¹⁹	NA	NA	NA	NA	NA	U	L	H	H	H	H	L	L	L	High
Murki et al ^U , 2009 ³⁴	NA	NA	NA	NA	NA	H	U	H	H	L	L	H	U	H	High
Chowdhury et al ^U , 2018 ³¹	NA	NA	NA	NA	NA	L	L	H	H	L	L	L	L	L	Medium
Sultana ^U , 2017 ³²	NA	NA	NA	NA	NA	U	U	H	H	L	H	U	U	L	High
Wu et al ^U , 2017 ²²	NA	NA	NA	NA	NA	L	L	H	H	L	L	L	L	L	Medium
Murni et al ^U , 2015 ³⁹	NA	NA	NA	NA	NA	L	L	H	H	L	L	L	L	L	Medium
Ruvinsky et al ^U , 2014 ³⁰	NA	NA	NA	NA	NA	U	L	H	H	U	H	L	L	H	High
Calil et al ^U , 2001 ³⁷	NA	NA	NA	NA	NA	L	U	H	H	L	L	L	L	L	Medium
Lee et al ^U , 2007 ⁴²	NA	NA	NA	NA	NA	L	L	H	H	L	L	L	L	L	Medium
Xu et al ^U , 2019 ²³	NA	NA	NA	NA	NA	L	L	H	H	L	L	L	L	L	Medium
Zhang et al ^U , 2008 ²⁴	NA	NA	NA	NA	NA	L	L	H	H	U	L	L	L	U	High
Zhang et al ^U , 2008 ²⁸	NA	NA	NA	NA	NA	L	L	H	H	U	L	L	L	U	High
Zou et al ^U , 2015 ²⁸	NA	NA	NA	NA	NA	U	L	H	H	L	L	L	L	L	Medium
Ding et al ^U , 2008 ¹⁴	NA	NA	NA	NA	NA	U	L	H	H	L	L	L	L	L	Medium
Kalaba et al ^U , 2018 ⁴⁶	NA	NA	NA	NA	NA	H	L	H	H	U	U	L	L	H	High
Zhang et al ^U , 2018 ²⁶	NA	NA	NA	NA	NA	U	H	H	H	L	L	L	L	L	High
RCT															
Bucher et al, 2012 ⁴³	NA	NA	NA	NA	NA	U	L	U	U	U	L	L	H	L	High
Shao et al, 2015 ³⁶	NA	NA	NA	NA	NA	L	L	L	L	L	H	L	L	L	Medium
Keitel et al, 2017 ³⁵	NA	NA	NA	NA	NA	L	L	L	L	L	L	L	L	L	Low
Do et al, 2016 ⁴⁸	NA	NA	NA	NA	NA	L	L	L	L	L	L	L	L	L	Low
Torres et al, 2014 ²⁹	NA	NA	NA	NA	NA	L	L	L	L	U	L	L	H	L	Medium
Non-RCT															
Ozkaya et al, 2009 ⁴⁷	NA	NA	NA	NA	NA	L	L	U	U	U	L	U	H		High
Haque et al, 2017 ⁴⁴	NA	NA	NA	NA	NA	L	L	L	L	L	L	L	L	L	Low

*Criteria: A: intervention independent of other changes, B: shape of intervention prespecified, C: intervention unlikely to affect data collection, D: knowledge of allocated interventions adequately prevented during study, E: seasonality taken into account, F: incomplete outcome data adequately addressed, G: study free from selective outcome reporting, H: random sequence generation, I: allocation concealment, J: baseline outcome measures similar, K: baseline characteristics similar, L: any blinding reported, M: study protected against contamination, N: other risk of bias.

†The risk of bias was considered low if all criteria were scored as low, medium if 1 or 2 criteria were scored as unclear or high and high if >2 criteria were scored as unclear or high. Risk of bias criteria: H, high risk of bias; L, low risk of bias; NA, not applicable to this study design; U, unclear risk of bias.

Clinical Decision Tools

Seven studies evaluated the impact of a clinical decision tool or algorithm, 4 of which had a low risk of bias. Two controlled trials from Tanzania used a clinical algorithm³⁶ and an electronic POC test³⁵ to assess acute febrile illness. The new ALMANACH algorithm was compared with standard practice and resulted in a significantly lower prescribing rate on day 0

(15% vs. 84%, $P < 0.001$) and a higher percentage of cure on day 7 (97% vs. 92%, $P < 0.001$).³⁶ Although the reduction in prescribing rate in the ALMANACH arm looks striking, it is worth noting that the 2 arms recruited in 2 different primary care facilities where there were differences in baseline bacterial infection rate. Subsequently, an RCT compared ePOCT, an algorithm using clinical signs plus POC tests (eg, malaria, hemoglobin and

oximetry), to ALMANACH. Clinical failure on day 7 in ePOCT was 2.3% versus 4.1% in ALMANACH ($P = 0.005$) with significantly reduced antibiotic prescribing of 12% versus 30% ($P < 0.001$).³⁵ In a smaller RCT from Argentina, a clinical score was assessed for outpatients 3–60 months of age with nonsevere pneumonia, finding that antibiotic prescriptions were reduced from 87% to 47% with no increase in poor outcomes (hospitalization, PICU and death) at day 10.²⁹

POC tests alone without clinical components have been subject to a few studies. Use of CRP,³⁸ a fecal rotavirus plus fecal leucocyte POC test for acute diarrhea in <5-year-olds,⁴³ and an influenza POC test for mild influenza-like illness in 3- to 14-year-olds⁴⁷ reduced antibiotic prescriptions by 14% ($P < 0.001$), 21% ($P = 0.03$) and 32% ($P = 0.01$), respectively. In contrast, measuring procalcitonin at day 1 and repeated during admission, resulted in no difference in prescribing rate or antibiotic duration.²²

Financial Disincentive

Two studies from China assessed the impact of financial disincentive, rewarding prescription of desired antibiotics and/or penalizing undesired antibiotics. Outpatient prescriptions reduced by 59% ($P \leq 0.01$), and in inpatients prescriptions reduced by 15% with preauthorization alone, and a further 28% after adding “financially punished” audit and feedback ($P < 0.001$).¹⁵ Another study implemented incentive/disincentive per prescription and found a sustained decrease in antibiotic usage year on year over a 7-year period and reduction in MDRO colonization rate.²³ No clinical outcomes were assessed in either study.

Audit and Feedback

Audit and immediate feedback on meropenem and vancomycin prescriptions resulted in significant reduction in use of these antibiotics compared with the preintervention period: meropenem 10% to 1.5% ($P < 0.05$) and vancomycin 36% to 4% ($P < 0.05$). There was also a significant reduction in mortality from 28% to 6% ($P = 0.001$) with significantly fewer positive blood cultures during the intervention period (24% to 4%) ($P = 0.01$).⁴⁰

Results According to Outcome

Thirteen studies evaluated clinical outcomes after implementing an AMS intervention^{17,22,29,33–36,39,40,42,44,45,48} (Table 1). In 7, this was a primary outcome, and of these only 4 were low to medium risk of bias.

Infections and Clinical Failure

In 2 studies that implemented an AMS bundle including infection control, there was a significant reduction in HAI from 23% to 9% ($P < 0.001$)³⁹ and reduction of nosocomial infections due to MDRO from 18 to 2 cases per year (no P value).³⁷ A further AMS bundle implemented in a large NICU reduced late-onset sepsis from 11% to 7% ($P = 0.01$).¹⁷ An audit and feedback strategy to manage selected antibiotics resulted in a reduction in bacteremia from 24% to 4% ($P = 0.001$).⁴⁰ Introducing a clinical algorithm and measuring clinical outcomes at day 7, there was a reduction in clinical failure from 4.1% to 2.3% ($P = 0.005$) in one study,³⁵ and an increase in proportion of cure at day 7 from 92% to 97% ($P < 0.001$) in another that also used a POC.³⁶ Use of POC CRP in primary care for children with acute respiratory infection reduced immediate antibiotic use without resulting in increased hospitalization from severe infection.⁴⁸

MDRO Colonization or Infection

Eight studies evaluated reduction in MDRO colonization and/or infection from implementation of an AMS intervention.^{14,17,23,26,34,37,42,46} In 6, this was a primary outcome^{14,23,26,37,42}

and all were medium to high risk of bias. Differences in reporting included whether bacteria were colonizing, causing invasive infection, both or unspecified; and whether MDROs were multiple specified bacteria, single bacterial types or unspecified, making summarizing MDRO outcomes difficult. Overall, in the 4 studies measuring MDRO colonization, all showed significant reduction ranging from 29% to 66%, including MRSA, VRE, ESBL-producing and carbapenem-resistant Enterobacteriaceae.^{17,23,26,37} In the 4 studies measuring MDRO invasive infection, 3 showed reductions ranging from 22% to 89%, including unspecified MDRO and ESBL-producing Gram-negative bacteria.^{34,37,42} In the fourth study, there was a significant reduction of 44% overall in MDRO, but no reduction in CRE.¹⁷

Most commonly, when studies assessed the impact on multiple specific MDRO, they found reductions in all of them, for example, implementation of an AMS bundle found reductions in all of carbapenem-resistant *P. aeruginosa* and ESBL-producing *Escherichia coli* and *K. pneumoniae*.¹⁴ The only divergence from this was in another study implementing an AMS bundle, in which there was a 96% reduction in MRSA colonization and/or infection but no change in ESBL-producing *E. coli*.⁴⁶

Mortality

Eleven studies measured mortality as an outcome, the majority as a secondary outcome. Only two showed a reduction in mortality—implementation of an AMS bundle resulted in a reduction from 10% to 8% ($P < 0.05$), most likely related to a reduction in HAI,³⁹ and audit and feedback reduced all-cause mortality from 28% to 6% ($P = 0.001$), likely related to reduction in bacteremia.⁴⁰ In the majority, the salient finding was that better management of antibiotics did not increase mortality, through either AMS bundles,^{17,34,44} guidelines^{33,42,44,45} or decision tools.^{35,48} This was shown in different settings, including NICU,^{17,33,34} PICU,⁴⁴ general inpatients,⁴⁵ outpatients^{29,35} and primary care.⁴⁸

Inappropriate Prescribing

Appropriateness of prescribing was measured in 4 studies, and all involved implementation of AMS bundles. Two studies showed a significant reduction in overall inappropriateness compared with preintervention (43% decreased to 21%)³⁹ or the control group (53% vs. 77%).⁴¹ In contrast, one study showed no significant reduction in inpatient inappropriateness (51% to 42%),¹⁹ but because all 3 studies introduced AMS bundles, it is impossible to know which components may have contributed to this difference. Additionally, one study showed a specific increase in appropriateness of ceasing antibiotics within 48 hours in culture-negative sepsis from 6% to 45% ($P < 0.0001$).⁴⁴

Length of Stay

Length of stay in hospital was a secondary outcome in 4 studies. Two very different studies—one implementing a broad AMS bundle in NICU¹⁷ and one specific use of procalcitonin in LRTI²²—found no change in median length of stay, remaining at 7 and 10 days, respectively. In contrast, a study specifically addressing meropenem and vancomycin use in PICU with a much higher baseline length of stay of 23 days, showed a significant reduction to 16 days ($P = 0.02$).⁴⁰

Cost-effectiveness

There was one cost-effectiveness study from China of an AMS bundle applied to 2- to 14-year-old outpatients with URTI (from a previous RCT²¹).²⁵ Incremental cost-effectiveness ratios were measured using costs of consultation (time cost of doctor), prescription monitoring process, peer-review meetings (time cost of participants) and medication costs. They found an incremental

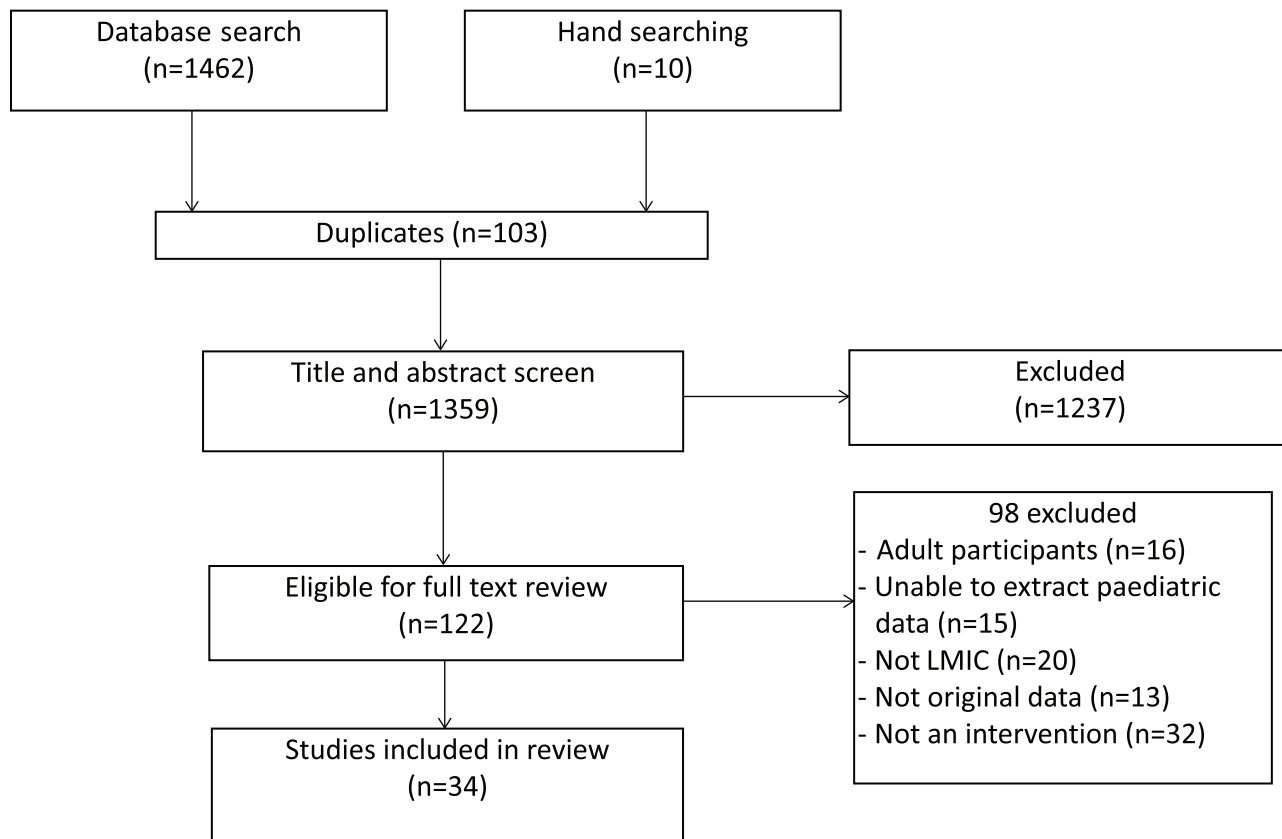


FIGURE 1. Studies included in the review of AMS in children in LMIC.

cost of USD0.03 per percentage point reduction in antibiotic prescribing in addition to a USD390 upfront cost per healthcare facility and concluded that the AMS bundle was “close to cost neutral.”

Seven other studies reported on antibiotic expenditure pre and post AMS intervention. Four found a significant reduction in expenditure ranging from 10% to 75%,^{14–16,44} while one reported a reduction in cost per DDD without *p* values⁴⁶; ceftriaxone had an 85% reduction and meropenem a 56% reduction in cost per DDD between 2010 and 2014. One study found a 16% reduction in average cost per patient on the gastroenterology ward with introduction of a locally developed guideline, but 38% increase on the respiratory ward (no *P* values provided).⁴⁵ A final study found no difference in the cost of prescriptions from introducing an AMS bundle, despite reduction in antibiotic use.²¹

DISCUSSION

AMR poses an increasing threat to global health. This systematic review of AMS interventions in pediatric healthcare settings in LMIC shows that any type of AMS intervention can reduce antibiotic consumption, with more consistent reduction resulting from clinical decision tools and enabling strategies than guideline implementation alone. The variability in outcome measures limits the ability to summarize clinical, AMR and cost outcomes. However, most of these were improved significantly by AMS interventions, most likely due to the poor baseline position in many LMICs.

There are a number of differences between the AMS interventions in LMIC in this review and those in children in HIC.^{9,49} In HIC, the majority of AMS studies include audit and feedback³⁹;

however, only 7 of 32 in this review used this. This is likely because this strategy is very labor intensive without access to an electronic medical record, a luxury not available in most LMIC healthcare settings. Another review found that use of locally developed empiric guidelines was much more common in HIC.⁴⁹ This is likely because of access to microbiologic culture and susceptibility testing, without which it is impossible to develop local antibiograms.⁵⁰ While national/international guidelines can be effective in reducing antibiotic consumption, without accounting for local resistance patterns, they may represent a blunter tool against the development of AMR. In contrast, clinical decision tools have been subjected to more study in LMIC than HIC,⁴⁹ and this review suggests they are highly effective in reducing antibiotic use. Care should therefore be taken not to presume that AMS interventions that are successful in HIC are automatically applicable to LMIC.

The importance of outcomes of AMS may also differ between LMIC and HIC. In LMIC, where infections are the leading cause of under-5 mortality, it is critical to know whether interventions that reduce antibiotic prescribing result in increased morbidity or mortality. Only a minority of studies addressed mortality or clinical failure and most were not powered for these outcomes and/or had a high risk of bias. In addition, only 6 studies included NICU or PICU, where there are high rates of broad-spectrum antibiotic prescribing^{16,51} and resistance in LMIC.¹ For evidence to impact on sustained practice,⁵² mortality and behavioral change in these high prescribing settings both need to be addressed.

The impact on MDRO colonization and infection was investigated more frequently than has been reported for children in HIC, where only one study found no change with the AMS intervention.⁴⁷ In the 8 studies identified in this review, 3 in ICU, MDRO

rates were significantly reduced in all. While this likely reflects high baseline rates of MDRO in LMIC,¹ this very fact means this outcome is important. In 2 studies, MDRO remained low several years after implementation of the intervention.^{23,37} Surveillance to ensure gains are sustained depends on access to ongoing antibiotic susceptibility testing.

That there was only one cost-effectiveness study identified²⁵ highlights a major gap in studies of pediatric healthcare in LMIC where scarce resources frequently result in lack of oversight of broad-spectrum antibiotic prescribing. Simple, potentially inexpensive interventions may offer the greatest cost savings, as has been shown for the management of childhood pneumonia and neonatal infection.⁵³ Without high-quality cost-effectiveness analyses to inform broader health economic benefits of reducing morbidity and mortality, necessary rationing of resources in LMIC settings may mean that AMS is avoided.

The WHO recommends that ASPs should be implemented in a stepwise manner, build on existing structures and reporting, maximize teamwork, and encourage champions and clinical staff to participate: “start small and keep it simple and doable.”⁶ The findings in this review provide evidence to support this approach: ASPs that included education of clinical staff as part of the AMS bundle were successful in reducing prescribing rate, and those that were adapted to existing structures, such as clinical decision algorithms, were successfully implemented and achieved positive results. The WHO approach could be coupled with the suggestion to identify conditions with frequent antibiotic use to prioritize targets of ASPs.⁵⁴

A limitation of this review was the low quality of many of the included studies which limits the ability to determine which interventions are the most successful. Adult reviews excluded a large proportion of studies due to bias limitations of uncontrolled before-after studies. However, these may be the only feasible option for LMIC with high volumes of prescriptions, for example, in hospitals in China, or with limited access to funding. Therefore, these studies were included as important pragmatic examples in this review. Ideally, if an RCT is not possible, studies should use a controlled interrupted time series methodology to confidently determine which interventions are most successful.⁵⁵ Beyond a simple measure of antibiotic consumption, many included studies did not evaluate appropriateness of antibiotic use including route and duration of antibiotics for specific infections.⁵⁶

CONCLUSION

Controlling excessive antibiotic use is an important tool in the effort to combat rising AMR with its consequent impact on morbidity and mortality. It is important to put this in the context of pressures in LMIC of high childhood mortality from infection and frequent antibiotic shortages, by tailoring interventions and outcome measures appropriately.⁵⁷ This means incorporating the review findings of the success of AMS bundles and clinical decision tools into existing systems.⁵⁸ It also means that key outcomes of reduction of HAI and MDRO infection should be prioritized in studies above the easier measure of antibiotic consumption, as only addressing these comprehensively in a broad public health approach will reduce mortality from MDRO in a cost-effective and sustainable way.

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