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Review

Utility of healthcare-worker-targeted antimicrobial stewardship interventions in hospitals of low- and lower-middle-income countries: a scoping review of systematic reviews

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Background: Antimicrobial stewardship (AMS) initiatives in hospitals often include the implementation of clustered intervention components to improve the surveillance and targeting of antibiotics. However, impacts of the individual components of AMS interventions are not well known, especially in low- and lower-middle-income countries (LLMICs).
Objective: A scoping review was conducted to summarize evidence from systematic reviews (SRs) on the impact of common hospital-implemented healthcare-worker-targeted components of AMS interventions that may be appropriate for LLMICs.
Methods: Major databases were searched systematically for SRs of AMS interventions that were evaluated in hospitals. For SRs to be eligible, they had to report on at least one intervention that could be categorized according to the Effective Practice and Organisation of Care taxonomy. Clinical and process outcomes were considered. Primary studies from LLMICs were consulted for additional information.
Results: Eighteen SRs of the evaluation of intervention components met the inclusion criteria. The evidence shows that audit and feedback, and clinical practice guidelines improved several clinical and process outcomes in hospitals. An unintended consequence of interventions was an increase in the use of antibiotics. There was a cumulative total of 547 unique studies, but only 2% (*N*=12) were conducted in hospitals in LLMICs. Two studies in LLMICs reported that guidelines and educational meetings were effective in hospitals.
Conclusion: Evidence from high- and upper-middle-income countries suggests that audit and feedback, and clinical practice guidelines have the potential to improve various clinical and process outcomes in hospitals. The lack of evidence in LLMIC settings prevents firm conclusions from being drawn, and highlights the need for further research.

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Introduction

Antimicrobial stewardship (AMS) is defined as 'A coherent set of actions which promote the responsible use of antimicrobials' [1], while ensuring that the right patient receives effective treatment at the right time, minimizing harms resulting from the use of antimicrobials [2]. AMS programmes have been gaining momentum globally due to the increasing rates of antimicrobial-resistant organisms, and the inability of modern medicine to manage them effectively [1]. There is growing evidence demonstrating the successful implementation of AMS interventions across high-income countries [3]. Several systematic reviews (SRs) have assessed the impact of bundled AMS interventions, and presented broad summaries of effectiveness [4–7].

Components used in bundled interventions, such as digital interventions, have been recommended as evidence suggests that they can optimize antibiotic prescribing [8,9]. Point-of-care testing, specifically procalcitonin-guided therapy, has also been widely used and has been shown to significantly reduce exposure to antibiotics and costs associated with their use in high- and upper-middle-income countries [10–13]. However, the cost-effectiveness of using such point-of-care testing in low- and lower-middle-income countries (LLMICs) has not been well studied [14]. Given the shortcomings in LLMICs, including insufficient basic infrastructure, poor management commitment, limited policies and programmes, inadequately funded health systems, diagnostic/laboratory challenges and shortages of experienced laboratory/infectious disease personnel [14,15], point-of-care testing and digital interventions may not be sustainable. It has been noted that the content, delivery and function of each intervention component should be evaluated to understand how they might perform in different settings [16]. A recent scoping review collated information on the components of AMS interventions in general practice [17], while an SR provided detailed information on intervention components based on their functions [18]. However, only one LLMIC was included in the updated version [19]. To date, the successes and unintended consequences of intervention components in LLMICs have not been well reported, and this makes it challenging for hospitals in these settings to design feasible and sustainable interventions.

There is no single classification of health system interventions; however, the Effective Practice and Organisation of Care (EPOC) taxonomy of health systems interventions provides a uniform way to classify interventions based on conceptual or practical similarities [20]. In this taxonomy, interventions categorized under the domain 'implementation strategies' (e.g. audit and feedback, education) can potentially change amenable behaviours, and may be appropriate and sustainable in low-resource settings. Behaviour change interventions have shown modest worthwhile effects in AMS programmes; however, success depends on well-designed interventions that consider the target population, environmental factors, the local context, and the use of collaborative team-based approaches [16,21,22].

The purpose of this scoping review was to summarize evidence from SRs that reported on the impact of individual components of AMS interventions targeting healthcare workers (HCWs) in hospitals. Hospitals were selected for this scoping review, as approximately 50% of antibiotics are prescribed inappropriately in this setting, which hosts a majority of patients with the likelihood of poor clinical outcomes [23,24]. Methods used to collect and analyse data, and practice and research implications of AMS studies conducted in LLMICs will also be explored.

Methods

The protocol was registered at Figshare. The Manual for Evidence Synthesis published by the Joanna Briggs Institute (JBI) and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Extension for Scoping Reviews were used to guide protocol development and review reporting [25,26].

Eligibility criteria

SRs evaluating HCW-targeted AMS interventions in hospitals were eligible for inclusion. Cochrane's EPOC taxonomy for interventions targeting HCWs [20] was used to categorize and describe interventions to simplify reporting. Details of the eligibility criteria are presented in Table I.

Search methods

The JBI three-step approach was used to search the literature [27]. Limited searches were conducted in OVID Medline, CINAHL and the Cochrane Library to locate existing SRs on AMS. A librarian (NR) used the titles, abstracts, keywords and subject headings acquired from this preliminary search to develop the final search strategy, as seen in Appendix A (see online supplementary material). Google Scholar and ProQuest Dissertations and Theses were searched for unpublished literature, and the reference lists of retrieved SRs and scoping reviews were searched for additional SRs. No language filters were applied, but screening was done for publications written or translated in English as the resources and time needed for translating were unavailable. The final search was done on 27th May 2022. The electronic database search strategies presented in Appendix A (see online supplementary material) were reported according to PRISMA-S, an extension for reporting literature searches in SRs [28].

Selection of reviews

Two reviewers (TW and WWS) independently screened the titles and abstracts of retrieved studies, and disagreements were arbitrated by a third reviewer (JWB). Selected full-text articles were independently assessed against the inclusion criteria by two reviewers (TW and JWB). Discrepancies were resolved via discussion.

Table I
Inclusion/exclusion criteria

	Inclusion	Exclusion
Population	Hospital-assigned healthcare workers	General practitioners, other healthcare workers in outpatient settings
Concept	Evaluated healthcare-worker-targeted interventions that can be categorized according to the EPOC taxonomy. Outcomes of interest include clinical outcomes (length of stay, mortality, infection rate, etc.) and process outcomes (adherence to guidelines, duration of treatment, etc.)	Interventions that may not be feasible for low-resource settings – technologically advanced interventions, point-of-care testing (procalcitonin-guided therapy and C-reactive protein), electronic surveillance systems, artificial intelligence etc. Restrictive interventions – automatic stop order, expert approval, formulary restrictions etc. Microbiological, financial and summary outcomes
Context	Hospitals – secondary care settings that provide health care to hospitalized patients	Outpatient, field hospitals, long-term care facilities including nursing homes
Sources	Published or unpublished systematic reviews (with or without meta-analysis) conducted from 2000 to 2021	Primary studies, conference abstracts, commentaries, editorials, overviews, non-systematic literature reviews, qualitative reviews, scoping reviews

EPOC, Effective Practice and Organisation of Care.

Data extraction

A modified and piloted version of the JBI's template source of evidence details, characteristics and results extraction instrument was used to extract data from included SRs [27]. Two reviewers (TW and HW) independently extracted information on primary objectives, search methods, number of included studies based on gross national income status per capita, search time frames, intervention components that could be classified according to the EPOC taxonomy, and key findings related to clinical and process outcomes. Primary articles from LLMICs included in SRs were retrieved, and information on data collection and analysis methods, and practice and research implications were collected. Disagreements were resolved through discussion. The World Bank list of economies (June 2020) – LLMICs [29] was used to identify LLMICs included in the selected SRs.

Quality assessment

Using the Assessment of Multiple Systematic Reviews (AMSTAR) tool [30], two reviewers (TW and JWB) independently assessed the quality of the included SRs. The total possible score for the AMSTAR tool is 11. TW and JWB independently examined the level of evidence for included primary studies using the Oxford Centre for Evidence-Based Medicine: Levels of Evidence (OCEBM) tool, which is a systematic approach to appraise research evidence rapidly [31,32]. Discrepancies were resolved via discussion; if consensus could not be reached, a third reviewer (IJO) arbitrated.

Presentation of findings

Findings were presented in tabular format and narrative summary, categorized according to the EPOC taxonomy of interventions targeting HCWs [20].

Results

In total, 6519 citations were retrieved. Of these, 35 full-text records were screened for eligibility. Eighteen SRs met the inclusion criteria. The process for inclusion is illustrated in Figure 1. The list of excluded articles (N=17) and reasons for exclusion can be found in Appendix B (see online supplementary material).

All included SRs were published within the last 10 years, and one SR [19] included a publication dating back to 1976 [33]. Although there was a cumulative total of 547 unique studies, only 2% (N=12) were conducted in hospitals in LLMICs. The characteristics of the SRs are described in Appendix C (see online supplementary material). One SR (5%) was judged to be of high quality, five (28%) were judged to be of moderate quality (5–8), and 12 (67%) were judged to be of low quality (0–4) (Appendix D, see online supplementary material).

Evidence for intervention components

Across the 18 SRs, seven types of AMS components that could be classified according to the EPOC taxonomy were identified. Audit and feedback (78%; N=14) and clinical practice guidelines (61%; N=11) were addressed most frequently. Various outcomes were evaluated for these components, and evidence of effectiveness and unintended consequences are shown in Table II.

Three SRs conducted meta-analyses [19,34,35]. Based on the findings of 14 randomized controlled trials (RCTs) (3318 participants), a significant reduction in mean treatment duration [1.95 days, 95% confidence interval (CI) 2.22–1.67; high-certainty evidence] was reported by one SR following a HCW-targeted AMS intervention [19]. Inpatient *Clostridioides difficile* infections were reduced significantly following an AMS intervention in another SR (incidence ratio 0.68, 95% CI 0.53–0.88; P<0.0029) [34], and the pooled decrease in

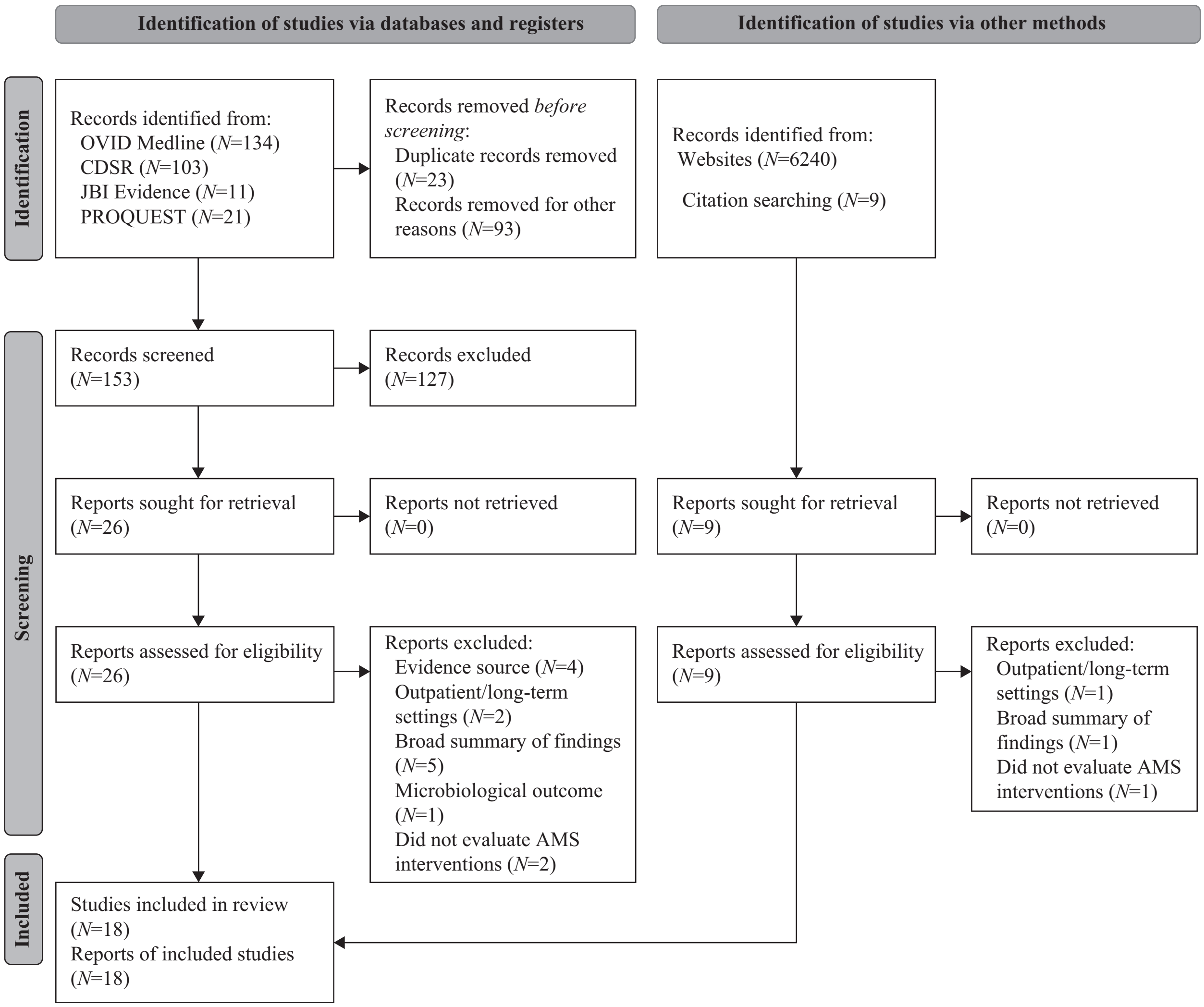

Figure 1. Prisma flow diagram showing the review selection process. AMS, antimicrobial stewardship; CDSR, Cochrane Database of Systematic Reviews.

antimicrobial consumption after AMS implementation in the third SR was 19.9% (95% CI 12.1–27.7; four studies) and 20.9% (95% CI 15.0–30.5, 12 studies) in the USA and Europe [35]. Pooled results from the three SRs and meta-analyses were not specific to unique intervention components.

Audit and feedback

SRs reported that the use of audit and feedback was successful in reducing the duration and rate of inappropriate antibiotic prescribing, with rates reduced to zero following implementation [36–38]. Compliance with hang time (time elapsed between written antibiotic order and administration) improved from 41.2% to 78.4% following audit and feedback [39]. Improvements in the appropriate use of antibiotics were documented, but it was noted by the SR authors that while an RCT showed effectiveness, an interrupted time series study showed no difference following audit and feedback [36,37]. Antibiotic therapy was discontinued for 90% of patients whose doctors received formal feedback [40]. Reductions were seen in total antibiotic consumption, which was most frequently measured using daily defined doses, and one study indicated that there was no compensatory increase of other antibiotics [40]. Contrarily, it was documented that antibiotic use increased following audit and feedback, and patient outcomes were reported as unchanged in two SRs [19,36].

Clinical practice guidelines

Clinical practice guidelines were used to guide the administration of surgical antibiotic prophylaxis, improving the use and initiation of first-line therapy, and reducing the use of broad-spectrum antibiotics. Reduced use of antibiotics and improved compliance with guidelines were discussed benefits of using clinical practice guidelines [38,40–43]. The effect on the incidence of *C. difficile* infections following guideline implementation varied [34,36,41,42,44].

Low- and lower-middle-income countries

Of 12 primary studies from LLMICs, eight studies that met the inclusion criteria were included in this scoping review

Table II
Impact of antimicrobial stewardship interventions

Commonly used interventions (EPOC taxonomy)	Definitions (EPOC taxonomy)	Evidence of effectiveness	Evidence of adverse outcomes
Audit and feedback	A summary of health workers' performance over a specified period of time, given to them in a written, electronic or verbal format. The summary may include recommendations for clinical action	Reduced rate of inappropriate antimicrobial use Reduced duration of inappropriate antibiotic use Decreased total antibiotic use Reduced use of broad-spectrum antibiotics Improved rate of appropriate antibiotic use IV antimicrobial use switched on the appropriate day Decrease in hospital length of stay Reduced risk for CDI Reduction in the number of DDD antibiotics/100 days of hospitalization Decrease in overall antimicrobial cost Reduced time to antimicrobial therapy modification Reduced duration of IV use Reduced use of audited and evaluated antimicrobials Improved compliance with hang time (time elapsed between intravenous antibiotic order and actual administration) Increased compliance with guidelines Enhanced therapy due to early detection of errors Increased appropriate discontinuation of antibiotic therapy Increased compliance with ASP recommendations Improved appropriate initial use	Increase in antibiotic use
Clinical practice guidelines[a]	Clinical guidelines are systematically developed statements to assist healthcare providers and patients to decide on appropriate health care for specific clinical circumstances (US IOM)	Reduced incidence of HCAI Reduced use of targeted broad-spectrum antibiotics Reduced antibiotic consumption DDD per 1000 days Reduced antibiotic cost Increased use of targeted narrow-spectrum antibiotics Reduced antibiotic use Increased appropriate first-line therapy	Increase in antibiotic use Increased mortality rate in ICU intervention group

(*continued on next page*)

Table II (*continued*)

Commonly used interventions (EPOC taxonomy)	Definitions (EPOC taxonomy)	Evidence of effectiveness	Evidence of adverse outcomes
		Increased use of surgical prophylaxis for caesarean section Decrease in incorrect timing of surgical antibiotic prophylaxis Improved initiation of antimicrobial use within 8 h of presentation Reduced treatment duration Reduced length of stay No increase in attributable morbidity or mortality after guideline implementation Reduced percentage of treatment failure	
Continuous quality improvement	An iterative process to review and improve care that includes involvement of healthcare teams, analysis of a process or system, a structured process improvement method or problem-solving approach, and use of data analysis to assess changes	Improved use of appropriate first-line therapy Reduced IV antibiotics Reduced nursing time Reduction in cost of intravenous antibiotics Improved adherence to clinical practice guidelines Decreased antimicrobial consumption	None reported
Educational materials	Distribution to individuals, or groups, of educational materials to support clinical care, i.e. any intervention in which knowledge is distributed	Decreased antibiotic use Reduced antibiotic cost per patient	Increase in antibiotic use
Educational meetings[a]	Courses, workshops, conferences or other educational meetings	Reduced antibiotic use Reduced MRSA bacteraemia Reduced MRSA colonization Increased appropriate antimicrobial therapy for pneumonia and diarrhoea	Decreased number of women receiving surgical antibiotic prophylaxis before a caesarean section
Educational outreach visits or academic detailing	Personal visits by a trained person to health workers in their own settings, to provide information with the aim of changing practice	Reduced antibiotic use Decreased duration of IV antibiotics Increased percentage of days of adequate antibiotic treatment Reduced duration of therapy Reduction in dosing Increase inappropriate IV to oral switch Reduced inappropriate antibiotic use Reduced targeted antibiotic use Reduced IV antibiotic use Increased compliance with AMS programmes Reduced length of stay Reduced mortality rate Decreased CDI rate	Increased prophylactic antibiotic use for <24 h Increased dose-related prescription errors during the first year of the AMS programme Increased length of stay Increased mortality

Reminders	Manual or computerized interventions that prompt health workers to perform an action during a consultation with a patient, for example computer decision support systems	Reduced IV DOT Reduced rate of multi-drug-resistant infections Reduced DOT for restricted antimicrobials Reduced inappropriate dosing Increased appropriate administration of surgical prophylaxis Decreased days of IV therapy Reduced duration of treatment	None reported

AMS, antimicrobial stewardship; CDI, *Clostridiodes difficile* infection; DDD, defined daily doses; EPOC, Effective Practice and Organisation of Care; HCAI, healthcare-associated infection; ICU, intensive care unit; IV, intravenous; DOT, days of therapy; MRSA, meticillin-resistant *Staphylococcus aureus*.
[a] Reported as effective in low- and lower-middle-income countries (two studies).

[45–52]. Three were conducted in Kenya [46,48,50] and two were conducted in India [49,52]. Levels of evidence according to the OCEBM tool ranged from 2 to 4, with levels 3 and 4 accounting for six of the studies. Intervention periods ranged from 2 to 18 months. Two studies reported that components, educational meetings and clinical practice guidelines were effective [47,49]. For the other six studies, bundled interventions with educational components were used [45,46,48,50–52]. An interrupted time-series design was used in three studies, which assessed the longitudinal effects of the interventions using segmented regression analysis [46,49,52]. Rates and proportions were reported in studies evaluating the appropriateness of antibiotic therapy compared with standard treatment guidelines [47,48,50,51]. Methods for data collection and analysis, and implications for research and practice are summarized in Table III.

Discussion

Summary of main findings

This scoping review describes a range of evaluated hospital-implemented HCW-targeted AMS intervention components that could be categorized according to the implementation strategies of the EPOC taxonomy for health system interventions. The most frequently reported components in the included SRs were audit and feedback (78%), and clinical practice guidelines (61%), which seem to improve clinical and prescribing outcomes in hospitals. Unintended consequences resulting from the implementation of these components were documented by three SRs [19,36,43]. The included SRs incorporated few primary studies (2% of all included studies) from LLMICs, and it was shown that educational meetings and guidelines were effective in these settings.

Comparison with the literature

Audit and feedback was most frequently reported in the reviewed research evidence. Generally, audit and feedback was documented as a principal AMS intervention in low- and middle-income-countries [53], and as a universal component in AMS frameworks of general practice [17]. However, in a study confined to Latin America and the Caribbean, educational interventions were most often reported [54]. Consistent with this scoping review, antimicrobial consumption was the most frequently reported outcome in the literature [53,54]. While this scoping review focused primarily on persuasive and educational components, the emphasis of recently conducted evidence syntheses was on restrictive (pre-authorization and automatic stop orders) and structural AMS interventions. Point-of-care testing, specifically procalcitonin-guided therapy, was reported as an intervention for improving prescribing practices [11,12,55,56]. Other recently evaluated interventions included the impact of smartphone applications, computer decision support systems, and electronic surveillance systems on antibiotic prescribing [57–60]. It is anticipated that future evidence syntheses on AMS interventions will focus increasingly on technologically

Table III
Collated information from studies in low- and lower-middle-income countries

Parameters	Summary from primary studies
Geographical context	Kenya India Bangladesh Nigeria
Types of studies	Before–after with interrupted time series NRCT without cross-contamination control Uncontrolled before–after Segmented time series analysis Cluster-randomized controlled, with pre- and post-intervention period Uncontrolled before–after Interrupted time series
Study year (range)	2009–2017
Baseline surveillance (range)	2 weeks–18 months
Interventions	Guidelines Educational meetings Bundled interventions
Target population(s)	Medical, nursing, theatre staff Doctors from surgical specialties Physicians of paediatric wards Prescribers, pharmacists, nurses and other healthcare workers Surgeons and anaesthesiologists
Data collection methods	Surveys and standardized data collection forms Audit tools – Joanna Briggs Institute Practical Application of Clinical Evidence System audit tool Documents and records Information systems
Data analysis methods	Segmented regression analysis Proportions and rates Regression analysis adapted for segmented time series Pearson's Chi-square Logistic regression models Segmented regression analysis of interrupted time series data
Implications for practice	1. Educational interventions may be used in hospitals to improve appropriate prescribing for common illnesses 2. Education and training combined with audit and feedback can be used to improve compliance with evidence-based criteria for oral to intravenous switch 3. Antibiotic use can be reduced following the implementation of clinical practice guidelines, but effectiveness is dependent on the mode of implementation, the appropriateness of guidelines, and the duration of dissemination 4. Intervention bundles can improve prescribing for both common and life-threatening illnesses in hospitals 5. Educational and audit and feedback interventions targeting surgical staff can optimize surgical prophylaxis 6. AMS should be included in medical school curriculums since backend approaches to AMS are not very impactful in the short term and impact is poorly sustainable in the longer term. Therefore, policies and restrictive interventions are necessary for healthcare settings 7. Implementing locally developed surgical prophylaxis policies can reduce postoperative intravenous antibiotic use and increase pre-operative use. Factors such as the availability of antimicrobials, buy-in from hospital management, and staff awareness of policies must be addressed
Research implications	1. Availability of antimicrobials in hospital pharmacies should be considered in future AMS research 2. Prospective medical record review will provide the most accurate

Table III (*continued*)

Parameters	Summary from primary studies
	evidence 3. Examining associations between antibiotic use and antimicrobial resistance rates, and clinical outcomes such as mortality rates would be useful for future research 4. Research should focus on the association between the thorough documentation of signs by physicians and adherence to prescribing guidelines 5. Other AMS interventions need to be considered for improving the optimal duration of use 6. Clinical cure of patient and infection-free days would be useful indicators 7. Individual-level data analysis should be undertaken 8. Impact of multiple focus group discussions over extended periods should be assessed 9. For the evaluation of deep or organ-space SSI rate following the introduction of surgical prophylaxis, sample size, study duration, patient follow-up and physician experience are critical factors that must be considered

AMS, antimicrobial stewardship; SSI, surgical site infection.

advanced interventions. This indicates the possibility of a reduced number of SRs evaluating the effectiveness of interventions that are feasible for LLMICs.

Strengths and limitations

To the authors' knowledge, this is the first scoping review to summarize evidence from SRs on commonly used and reported hospital-based AMS intervention components with added focus on unintended consequences, and evidence from LLMICs including research and practice implications. The authors searched the literature extensively using strategies designed by an information specialist, and assessed the quality of the included SRs rigorously using the AMSTAR tool. A limited amount of evidence from LLMICs was available in the included SRs, but the authors were able to extract and summarize evidence on study designs and methods used to collect and analyse data in resource-poor locations. Collated evidence on research and practice implications in the represented LLMICs was also documented. Although the authors conducted a comprehensive search of the scientific literature, potentially eligible SRs may have been missed.

The literature describes health systems in LLMICs as poorly funded and ill-equipped [15], and it was impractical for the authors to verify these claims by obtaining an inventory of AMS resources in these regions given the available time and resources. Therefore, this scoping review focused on interventions that can employ a behavioural change approach with the possibility of long-term sustainability, hence the emphasis on interventions that can be classified according to the EPOC taxonomy [20]. For many of the studies included in the SRs, it was noted that interventions were bundled, and it was not common for the SR authors to report on the effectiveness of unique components of interventions, and how components interacted with the context in which they were implemented. This made it difficult to determine how and why interventions were successful, especially as this scoping review was reporting on the evidence as synthesized in the included SRs. Furthermore, the quality of some of the included SRs may reduce the credibility of the evidence they presented. In some SRs, it was not clear what taxonomy was used for categorizing intervention components, and post-study categorization of components was challenging as many intervention details were not presented by included SRs. This detail must be considered when examining the findings of this scoping review. Inconsistencies with AMS terminology are especially problematic when the effectiveness of components is being synthesized to inform future interventions [54]. Standardization of definitions would allow for comparability across settings.

Implications for research

More primary research evaluating AMS intervention components needs to be conducted in LLMICs, as the replication of components across settings has the potential to accumulate much-needed evidence on unintended consequences and effectiveness. As the components examined principally targeted behaviour change, further research addressing the application of behavioural change theories and the use of behaviour change techniques may be useful to explain variations in the effectiveness of these components, and the advancement of AMS interventions in LLMICs. Emphasis should be placed on the local culture and context for the development of an optimal model which may prove effective and sustainable.

In conclusion, evidence from high- and upper-middle-income countries suggests that audit and feedback, and clinical practice guidelines have the potential to improve various clinical and process outcomes in hospitals. Limited evidence suggests that educational outreach and clinical practice guidelines are effective in LLMICs. More quality research on

AMS is needed in LLMICs, and findings should be incorporated in evidence syntheses.

Conflict of interest statement

CH holds grant funding from the NIHR School of Primary Care Research Evidence Synthesis Working Group (PROJECT 390) and the NIHR BRC Oxford. He receives expenses for teaching EBM and is also paid for his general practice work in NHS out of hours (contract Oxford Health NHS Foundation Trust). He is the Director of CEBM, Editor in Chief of *BMJ Evidence-Based Medicine*, and an NIHR Senior Investigator. TW is currently employed in the Infectious Disease/Employee Health Division at the Sir Lester Bird Medical Centre (formerly known as Mount St. John's Medical Centre). This division is responsible for AMS, and infection prevention and control. IO, NR, JWB, WWS, HW and VW declare no conflict of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2022.09.008.

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