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Identification of outcomes reported for hospital antimicrobial stewardship interventions using a systematic review of reviews

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Background: Randomized trials of hospital antimicrobial stewardship (AMS) interventions aimed to optimize antimicrobial use contribute less to the evidence base due to heterogeneity in outcome selection and reporting. Developing a core outcome set (COS) for these interventions can be a way to address this problem. The first step in developing a COS is to identify and map all outcomes.

Objectives: To identify outcomes reported in systematic reviews of hospital AMS interventions.

Methods: Cochrane Database of Systematic Reviews, MEDLINE and Embase were searched for systematic reviews published up until August 2019 of interventions relevant to reducing unnecessary antimicrobial use for inpatient populations in secondary care hospitals. The methodological quality of included reviews was assessed using AMSTAR-2, A (revised) MeaSurement Tool to Assess systematic Reviews. Extracted outcomes were analysed using deductive and inductive thematic analysis. A list of overarching (unique) outcomes reflects the outcomes identified within the systematic reviews.

Results: Forty-one systematic reviews were included. Thirty-three (81%) systematic reviews were of critically low or low quality. A long list of 1739 verbatim outcomes was identified and categorized under five core areas of COMET (Core Outcome Measures in Effectiveness Trials) taxonomy: 'resources use' (45%), 'physiological/clinical' (27%), 'life impact' (16%), 'death' (8%) and 'adverse events' (4%). A total of 421 conceptually different outcomes were identified and grouped into 196 overarching outcomes.

Conclusions: There is significant heterogeneity in outcomes reported for hospital AMS interventions. Reported outcomes do not cover all domains of the COMET framework and may miss outcomes relevant to patients (e.g. emotional, social functioning, etc.). The included systematic reviews lacked methodological rigour, which warrants further improvements.

Introduction

The loss of effectiveness of any anti-infective medicine, defined as antimicrobial resistance,[1] is a global public health problem.[2] Tackling antimicrobial-resistant infections in hospitals is problematic because bacteria are prone to become resistant to several antibiotics and disinfectants at once, leading to serious infections that are difficult to treat. Such infections result in prolonged hospital stays, increased healthcare costs and a higher incidence of mortality.[3] Evidence suggests that overuse or inappropriate use of antimicrobials is responsible for the emergence of antimicrobial-resistant infections.[4] Recognizing the association between antimicrobial exposure and antimicrobial resistance, the WHO initiated a Global Action Plan on antimicrobial resistance with optimizing the use of antibiotics as one of its strategic objectives.[2] A key approach to optimizing the use of antibiotics is the deployment of antibiotic stewardship programmes.

Hospital antibiotic stewardship programmes typically include multiple interventions aimed at optimizing antimicrobial use by selecting the right antibiotic, in the right dose and duration to ensure effective treatment for patients with infectious conditions and supporting professionals to reduce unnecessary use to minimize collateral damage.[2] Antimicrobial stewardship (AMS) interventions can have multiple targets, such as de-escalation of therapy based on culture, dose adjustment according to renal

function, or use of technology to assist prescribing, and others. AMS interventions in hospitals require healthcare professionals to implement a coherent set of actions that promote responsible use of antibiotic agents.[5]

A wealth of research projects and published systematic reviews on AMS interventions are available.[6] Still, despite these efforts, the evidence for which specific interventions are effective (in terms of mortality, length of stay and quality of life) remains surprisingly weak.[7,8] This could be due to heterogeneity in outcome selection and reporting in trials evaluating the effectiveness of these interventions.

One approach to addressing heterogeneity in outcome selection and reporting studies on the topic is establishing a core outcome set (COS). Core outcomes are an agreed standardized set of outcomes that should be measured and reported as a minimum in all effectiveness trials within a specific clinical area.[9,10] Use of a COS is suggested to benefit the systematic review process by increasing the amount of usable information for use in a meta-analysis.[11] The development of a COS generally involves working with key stakeholders such as health professionals and patients to prioritize outcomes and achieve consensus on the core set. The first stage of developing a set of core outcomes is to identify outcomes reported in the existing literature.[12] Currently, there is no consensus as to which outcomes should be selected and reported for evaluation of hospital AMS interventions.

The main objective of this systematic review was to identify all outcomes from published systematic reviews of hospital AMS interventions and describe the variability of outcomes.

Methods

The protocol for this systematic review was registered with PROSPERO (CRD42020162800).

Search strategy

A comprehensive search strategy was developed, using the search strategy used by Davey *et al.*,[13] with the help of an information specialist, by employing syntax and vocabulary related to systematic reviews of AMS interventions. The complete search strategy is available in Supplementary data.

Information sources

We searched MEDLINE and Embase databases from 1946 and 1974, respectively, to 6 August 2019, and the Cochrane Database of Systematic Reviews (Issue 12) for relevant systematic reviews.

Study selection

One review author (S.Y.) independently screened 100 titles and abstracts resulting from the search to identify relevant publications. Two review authors (C.R. and M.R.) double-screened 50 randomly selected titles and abstracts independently for quality assurance. An 80% or greater agreement rate between the three reviewers (C.R., M.R. and S.Y.) was required for S.Y. to screen all titles and abstracts.

One review author (S.Y.) obtained and screened 100 full-text articles independently to identify potential reviews for inclusion. Three other reviewers (C.R., E.D. and M.R.) independently double-screened a random 10% sample. We compared the results of the screening and resolved any disagreements by discussion. A minimum 80% agreement level between all reviewers was required for S.Y. to screen all full-text articles for inclusion.

Inclusion and exclusion criteria

Study type

1. Review explicitly described the study as a 'systematic review' (i.e. stated as such in the title, abstract or full text of the study report).
2. Review that reported a comprehensive search strategy (i.e. reported full search strategies for one or more databases, including any limits applied, submitted as an appendix or published as a supplementary file for online readers).

Population

1. Any inpatient population from secondary care hospitals (such as hospital wards, emergency departments, intensive care units, community hospitals, university hospitals or district hospitals).
2. Reviews inclusive of inpatients from other settings such as tertiary care/long-term care/and primary care patients were also eligible. In such cases, outcome data specific to secondary care hospital inpatients only were extracted.

Intervention

Any intervention relevant to improving antimicrobial drug use in secondary care hospitals. The intervention strategies assessed by included reviews were categorized using the practical guide on antibiotic prescribing for healthcare workers in hospitals.[14]

Outcomes

According to availability, all outcomes and outcome measurements from the main body of the text and tables of review methods and results sections were extracted. No language restriction was applied. We intended to translate full-text articles written in any of our research staff's languages (e.g. Spanish, Portuguese, Italian, Polish, German, French, Bengali, Hindi and Urdu).

Reviews assessing AMS interventions conducted in long-term care facilities were excluded from this review.

Data extraction

We developed an electronic data extraction form to extract information on review author, review population of interest, intervention(s) of interest, clinical settings and verbatim outcome names from text and tables of review methods and results sections.

One reviewer (S.Y.) independently extracted relevant data from the included reviews, and three other reviewers (C.R., M.R. and E.D.) independently performed the duplicate data abstraction for a 5% sample of included reviews for quality assurance. We compared the results of data extraction and resolved any disagreements by discussion. A minimum 80% agreement rate between the reviewers was required for S.Y. to extract data from all included reviews.

Quality assessment

The methodological quality of included reviews was assessed using AMSTAR-2, A (revised) MeaSurement Tool to Assess systematic Reviews, a 16-item questionnaire for critical appraisal of systematic reviews of randomized and non-randomized studies of healthcare interventions.[15] Two reviewers independently assessed the quality of each included review (S.Y./C.R., S.Y./E.D. and S.Y./M.R.). Disagreements were resolved by one-on-one discussion and, when required, resolved by discussing with all reviewers.

Each item was rated either a 'yes' or 'no' (items 1, 3, 5, 6, 7, 10, 16); or a 'yes' or 'no' or 'partial yes' (items 2, 4, 8, 9); or a 'yes' or 'no' or 'no meta-analysis conducted' (items 11, 12, 15). We rated an item as not applicable (N/A) when it was not relevant to the review (e.g. item 8, 'Did the review authors describe the included studies in adequate detail?' was not relevant when a systematic review had zero included studies). We rated an item as 'no' when any of its subitems were 'no'. During the overall quality rating of a review, we weighted 'partial yes' as a 'yes' and did not consider 'not applicable' items.

In line with AMSTAR-2 guidance, a substituted set of critical items was used to appraise included reviews. Items related to the estimates of study effects (e.g. item 13: Risk of bias when interpreting the results of review) were regarded as non-critical. After interpreting weaknesses detected in critical and non-critical items, the methodological quality of included reviews was rated as high, moderate, low and critically low following their definitions.[15]

We compared differences in proportions between Cochrane and non-Cochrane reviews using Fisher's exact test.

Outcome data synthesis

We extracted verbatim outcome names from included reviews and arranged them in alphabetical order into a spreadsheet to develop an initial long list of outcomes. We then analysed outcomes using a three-step approach, including deductive and inductive methods (Figure 1).

Step 1: categorizing outcomes into relevant domains (deductive method)

All identified verbatim outcomes were mapped to the relevant outcome domains of the taxonomy framework developed by the COMET (Core Outcome Measure in Effectiveness Trails) initiative.[16] The framework consists of 38 outcome domains spread across the five core areas (death, pathophysiology/clinical manifestation, life impact, resource use and adverse events).

We then applied consistent spellings for verbatim outcomes (e.g. 'LOS' to 'length of stay'; 'CDI' or 'C. diff. infection' to '*Clostridium difficile* infection') and removed identically worded verbatim outcomes from each domain.

Step 2: identifying and retaining conceptually different outcomes

Within each domain, the identified outcomes were kept in verbatim whereas those that were found to be conceptually identical, i.e. outcomes addressing the same concept but defined/measured differently or using different terminology, were grouped together under the same outcome name (keeping the wording verbatim). We referred to it as 'conceptually different outcome' to aid analysis. For example, outcomes identified as 'Total cost of antimicrobials in 12-mo period', 'Cost of antimicrobial therapy per 1000 patient-days', 'antimicrobial expenditure', 'antibiotic cost', etc. were grouped under one outcome name 'Hospital antimicrobial expenditure' (verbatim). All conceptually different outcomes were retained in the list for analysis. We removed the time points identified for conceptually different outcomes in this step. For instance, 'twenty-eight-day mechanical ventilation-free days', was retained as 'mechanical ventilation-free days'.

Step 3: developing unique outcomes

Inductive analysis, i.e. analysing patterns in the data and developing a general conclusion, was used to condense the extensive outcome data. One author (S.Y.) read each 'conceptually different outcome' and grouped together the ones with common wording (pattern). An overarching outcome label was created (a so-called 'unique outcome') to represent the grouped set of outcomes, or if applicable, a verbatim outcome name was used as a label (provided it captured the other outcomes in this group well) (see Table 1 for example). Two reviewers (E.D. and M.R.) independently assessed the grouping and labelling of a subset of outcome data to ensure consistency.

Results

Agreement between the reviewers

There was 100% and 83% agreement between three reviewers (C.R., M.R. and S.Y.) for the title and abstract screening and the full-text screening, respectively. An agreement level for data abstraction was 85% between all four reviewers.

Search results

The summary of all literature search results is shown in Figure 2. The search of databases resulted in 5855 citations. After removing 952 duplicate search records and screening titles and abstracts, 410 full-text articles were appraised for inclusion, of which 369 were excluded. The main reason for exclusion was that the article was not a systematic review ($n=229$). One full-text eligible review identified in standard Chinese language was excluded because the translation was not feasible.[17] Forty-one systematic reviews (including a total of 1484 primary studies) were included in this systematic review. A list of all excluded reviews and reasons for exclusion is available upon request.

Characteristics of included reviews

Seventeen included reviews (45%) assessed AMS interventions on inpatients of secondary care hospitals [13,18–34] and 12 (29%) on inpatient and outpatient populations of hospitals.[8,35–45] The remaining 12 (29%) assessed interventions on ICU/Emergency Department inpatients only.[46–57]

Fifteen reviews (36%) considered rapid diagnostics and biomarkers strategies including microbiology,[31,46] viral testing,[36,54] antimicrobial allergy testing,[28,44] procalcitonin[35,38,40,45,50–53] and C-reactive protein[41] biomarkers. Nine reviews (22%) considered multiple (i.e. more than one) intervention strategies.[8,13,21–23,30,32,33,39] Six reviews (15%) assessed multiple health information technology interventions including alerts/prompts, stand-alone software, surveillance systems, etc. to optimize antimicrobial prescribing[18–20,26,42] or explicitly to personalize antibiotic dose calculations for the patient.[37] Four reviews (10%) assessed antimicrobial review strategies, including de-escalation of therapy[24,25,49] and conversion from IV to oral route.[27] Four reviews (10%) assessed antimicrobial prescribing policies including delayed therapy[34,43] and duration of therapy.[29,55] Two studies (5%) assessed a pharmacokinetic/pharmacodynamic-based antibiotic dose optimization strategy[48,56] and one review (2%) assessed a prospective audit and feedback strategy.[57] Intervention strategies identified in this systematic review are presented in Figure 3.

Three reviews (7%) applied country restrictions, of which two were restricted to studies from Asia [21,39] and one review (2%) was restricted to studies from low-middle-income countries (LMICs).[30]

Detailed characteristics of each included review can be found in Table S1.

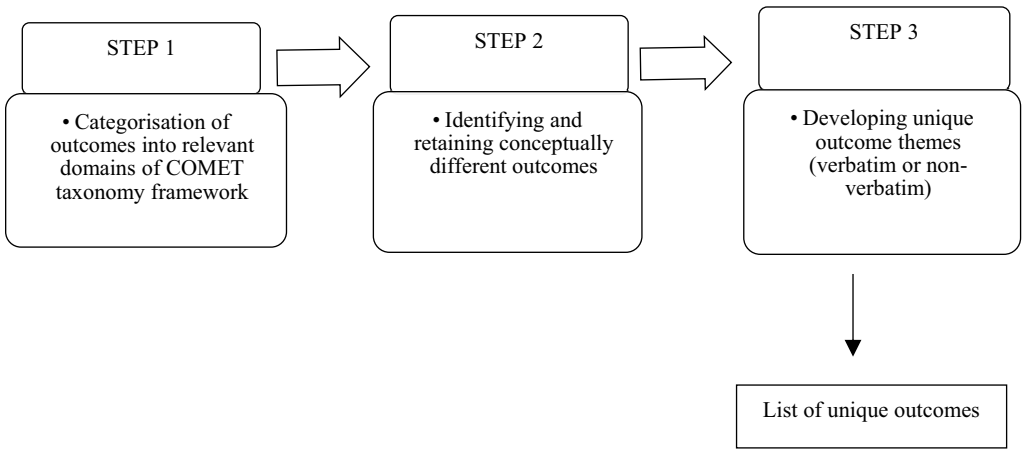

Figure 1. An overview of the method of outcome data synthesis.

Quality assessment of included reviews

Agreement between reviewers for quality assessment of included reviews was 82%.

The summary of AMSTAR 2 quality assessment results for the 41 included reviews is presented in Table S2. PICO components were included in the inclusion criteria of 88% ($n=36$) of reviews. Fifty-three percent of reviews ($n=22$) reported prior established methods. Only 58% ($n=24$) of reviews used a comprehensive search strategy. Eighty-five percent ($n=35$) of reviews performed study selection in duplicate but only 56% ($n=23$) performed data abstraction in duplicate. Seventy-seven percent ($n=31$) described included studies in adequate detail, and 97% ($n=40$) reported funding sources and conflicts of interest. The quality assessment results of each included review are displayed in Table S2.

Cochrane reviews on hospital AMS interventions had higher AMSTAR-2 scores than the non-Cochrane reviews (Fisher exact test $P \leq 0.001$).

Identified outcomes

A total of 1752 verbatim outcomes were extracted from the 41 included reviews. A total of 318 identically worded outcomes were identified and removed as exact duplicates. Each of the remaining 1434 verbatim outcomes was reviewed and arranged across the COMET taxonomy domains presented under the five core areas. A total of 421 conceptually different outcomes were identified (step 2) and consolidated into 196 overarching outcomes called unique outcomes (step 3), covering 18 of 38 domains of the taxonomy framework (see Table S3). The summary of unique outcomes is presented in Figure 4.

Total number of outcomes identified for each core area and their domains with highest number of outcomes are discussed below.

Table 1. Example for step 3: Developing unique outcomes

Conceptually different outcomes	Unique outcome
Hospital antimicrobial expenditure cost of non-restricted antimicrobial use per 1000 patient-days cost of restricted antimicrobial use per 1000 patient-days	**Cost of antimicrobial use per hospital patient**

Death: mortality/survival outcomes

One-hundred-and-eight (8%) verbatim outcomes were related to death (i.e. mortality/survival) identified from 33 included reviews (80.4%). During analysis, 18 conceptually different outcomes were identified (step 2) and grouped into 11 unique outcomes (step 3).

The commonly reported verbatim outcomes were related to 'In-hospital mortality' ($n=40$) and 'all-cause inpatient mortality' ($n=22$).

Physiological/clinical: infection and infestation outcomes

A total of 386 (27%) verbatim outcomes were classified under the core area 'physiological/clinical'. Of these, 207 (54%) were related to the 'infection and infestation' domain, reported in 29 reviews (71%). During analysis, 40 conceptually different outcomes were identified (step 2), which were grouped into 22 unique outcomes (step 3).

The commonly reported verbatim outcomes were related to 'antimicrobial resistance' ($n=45$); e.g. 'incidence of methicillin-resistant *Staphylococcus aureus* infection' ($n=17$).

Life impact: delivery of care outcomes

A total of 230 (16%) verbatim outcomes were classified under the core area 'Life impact'. Of these, 218 (15.3%) were related to the delivery of care domain and reported in 26 reviews (63.4%). During analysis, 71 conceptually different outcomes were identified (step 2) and grouped into 45 unique outcomes (step 3).

The commonly reported verbatim outcomes were related to 'treatment response' ($n=42$) and 'adherence to guidelines for appropriate antibiotic therapy' ($n=18$).

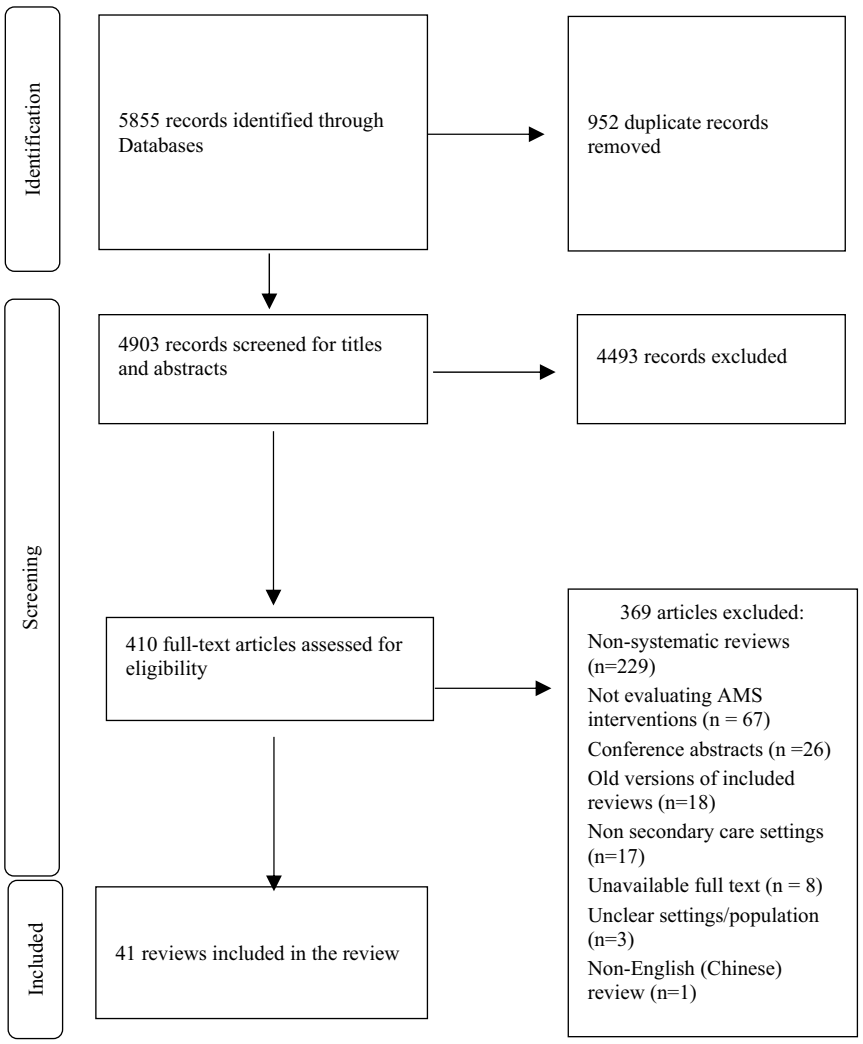

Figure 2. Flow diagram for the summary of search results. AMS, antimicrobial stewardship.

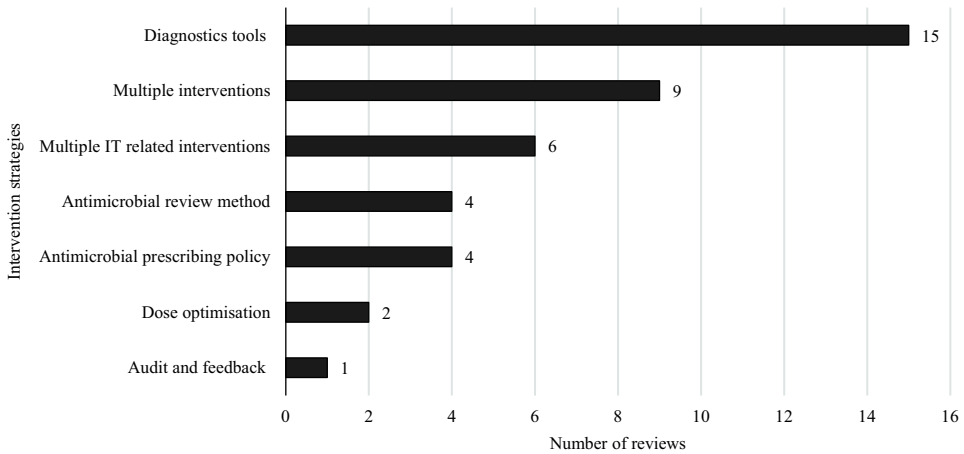

Figure 3. Types of intervention strategies identified from included reviews. IT, information technology.

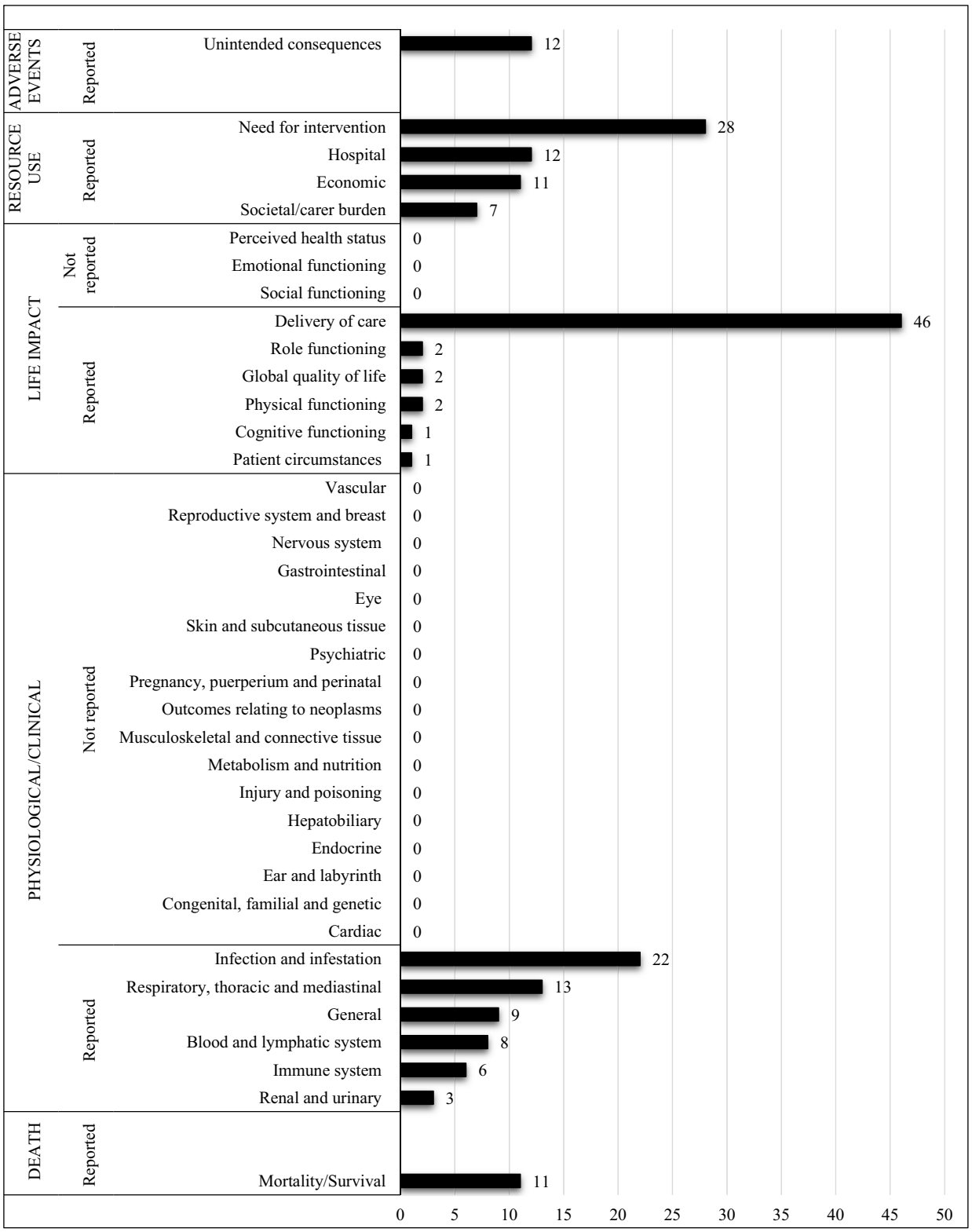

Figure 4. Summary of identified outcomes ($N = 196$), across the five core areas of the COMET taxonomy framework.

Resource use: need for further intervention outcomes

A total of 645 (45%) verbatim outcomes were classified under the core area 'resources use'. Of these, 326 (23%) verbatim outcomes were related to the 'Need for further intervention' domain, reported in 39 reviews (95%); moreover, 79 conceptually different outcomes were identified (step 2), which were grouped into 28 unique outcomes (step 3).

The commonly reported verbatim outcomes were related to 'duration of antimicrobial treatment' ($n=65$) and 'quantity (volume) of antimicrobial agents prescribed' ($n=39$).

Adverse events: unintended consequences outcomes

Sixty-five (4%) verbatim outcomes were related to unintended consequences identified from six reviews (15%). During analysis, 29 conceptually different outcomes were identified (step 2) and grouped into 14 unique outcomes (step 3).

The commonly reported verbatim outcomes were related to 'Unintended effects of antibiotic use' ($n=15$).

Discussion

The first key finding of this study is that many heterogeneous outcomes have been used to assess the impact of hospital AMS interventions. With such wide variations in outcome selection and reporting, synthesizing the evidence on the effectiveness of these interventions is challenging. The results demonstrate that outcome reporting has been commonly focused on 'life impact-delivery of care' (e.g. adherence to policy) and 'resource use' (e.g. duration of hospital stay) and rarely focused on 'life impact-patient functioning' (e.g. role functioning, physical functioning, cognitive functioning). This may indicate that researchers often do not assess the effects of these interventions in terms of functional, social and emotional wellbeing,[58] which requires patient involvement. We understand that certain outcomes (e.g. relating to psychiatry, metabolism and nutrition, etc. of taxonomy) are not relevant to AMS interventions and for this reason no outcomes were reported.

The second finding is that patient self-reported outcomes are underreported in the existing literature, and there is a need to get further patient/public perspectives on outcomes of hospital AMS interventions. Patient/public perspectives could be gained from qualitative research with members of the public/patients to identify outcomes that matter to them in the context of hospital AMS interventions. The outcome list generated through this review, combined with outcomes identified by the qualitative research, could be used to develop questionnaire items for a COS Delphi study.

The third finding is that systematic reviews related to these interventions often lacked methodological rigour, despite conceptual and practical advances in the science of systematic reviews. Although the Cochrane reviews on hospital AMS interventions were of high quality compared with non-Cochrane reviews, there were still weaknesses identified within Cochrane reviews, including a failure to explain the selection of study designs for inclusion (item 3). Despite the increasing use of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist by journals, there remains a need to improve the reporting of reviews in this area.

The fourth finding is that limited studies have reviewed the evidence on effectiveness of hospital AMS interventions in LMICs, and those that did have found included studies to be low in quality.[30] Feasibility of evaluation of hospital AMS interventions in LMICs may be studied as assessing certain outcomes can be challenging in these countries.

This review's strength is the robust methodology, including the prior registration of the protocol in PROSPERO and transparent reporting. A limitation is that we could not assess included reviews for outcome reporting bias. Future COS development studies may consider the approach suggested by Dwan *et al.*[59] to assess outcome reporting bias in reviews. Other COS developers reviewing primary studies of hand[60] and cancer surgery[61] have explored this and found a high risk of outcome reporting bias. We did not determine the overlap of primary studies across included reviews, and this may have influenced the number of duplicate outcomes in the list. In the absence of an agreed formal definition of a systematic review, for use in a systematic review of reviews studies, we used a locally agreed definition of a systematic review.[62] An international consensus on systematic review definition may be helpful to fill this taxonomic gap and improve the robustness of future systematic reviews of reviews.

Conclusions

There are currently no minimum core outcomes for trials evaluating hospital AMS interventions. The identified long list of outcomes shows a significant heterogeneity in outcome measures used by effectiveness studies of AMS interventions in hospitals. The outcome measures commonly reported do not cover all the domains within the COMET framework and may have missed some outcomes relevant to patients (e.g. perceived health status, emotional functioning and social functioning). Research to identify outcomes that matter to patients relevant to AMS interventions can help identify potentially overlooked outcomes important to them.

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Transparency declarations

The authors report no conflicts of interest in this work.

Author contributions

C.R., E.D. and M.R. conceived the research and S.Y. collected and analysed the data under their supervision. All members participated in the eligibility screening, data abstraction and analysis. S.Y. wrote the first draft of the manuscript, and all authors contributed to writing and shaping the final paper.

Supplementary data

Tables S1 to S3 are available as Supplementary data at *JAC* Online.

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