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Systematic review

A systematic review of clinical decision support systems for antimicrobial management: are we failing to investigate these interventions appropriately?

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ABSTRACT

Objectives: Clinical decision support systems (CDSS) for antimicrobial management can support clinicians to optimize antimicrobial therapy. We reviewed all original literature (qualitative and quantitative) to understand the current scope of CDSS for antimicrobial management and analyse existing methods used to evaluate and report such systems.

Method: PRISMA guidelines were followed. *Medline*, *EMBASE*, *HMIC Health and Management* and *Global Health* databases were searched from 1 January 1980 to 31 October 2015. All primary research studies describing CDSS for antimicrobial management in adults in primary or secondary care were included. For qualitative studies, thematic synthesis was performed. Quality was assessed using Integrated quality Criteria for the Review Of Multiple Study designs (ICROMS) criteria. CDSS reporting was assessed against a reporting framework for behaviour change intervention implementation.

Results: Fifty-eight original articles were included describing 38 independent CDSS. The majority of systems target antimicrobial prescribing (29/38;76%), are platforms integrated with electronic medical records (28/38;74%), and have a rules-based infrastructure providing decision support (29/38;76%). On evaluation against the intervention reporting framework, CDSS studies fail to report consideration of the non-expert, end-user workflow. They have narrow focus, such as antimicrobial selection, and use proxy outcome measures. Engagement with CDSS by clinicians was poor.

Conclusion: Greater consideration of the factors that drive non-expert decision making must be considered when designing CDSS interventions. Future work must aim to expand CDSS beyond simply selecting appropriate antimicrobials with clear and systematic reporting frameworks for CDSS interventions developed to address current gaps identified in the reporting of evidence. **T.M. Rawson, Clin Microbiol Infect 2017;23:524**

Introduction

In response to the global threat of antimicrobial resistance [1], a range of antimicrobial stewardship programmes have been developed that tend to focus on reducing high rates of inappropriate antimicrobial use described widely across care pathways and clinical specialties [2–5]. An important facet of this approach has been the development of decision support mechanisms for those who prescribe antimicrobials. These interventions are based on evidence that the majority of antimicrobial prescribing is done by individuals who are not experts in infection management and therefore, may have a limited understanding of antimicrobials and the evidence on antimicrobial resistance [6–9]. To address this challenge, electronic clinical decision support systems (CDSS) have

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been devised with the aim of providing the prescriber with easy and rapid access to information, which is required to make therapeutic decisions at the point-of-prescription [10,11]. With the expanding use of electronic medical records and developments in information technology, the role of CDSS has become an area of great interest with a wide variety of interventions now labelled as such.

In medicine, CDSS have been demonstrated to reduce medical errors and improve the quality of health care provided by promoting the practice of evidence-based medicine [12]. Therefore, it seems logical that in a field where we have a need to improve the practice of evidence-based antimicrobial management CDSS may be an effective avenue to promote this. CDSS were first developed to support antimicrobial management in the 1980s and since then several systematic reviews of experimental and quasi-experimental studies have explored the potential of CDSS to improve antimicrobial management at different levels of care [11,13,14]. However, these reviews have only tended to focus on single care pathways, such as the hospital setting or primary care and fail to include qualitative studies evaluating CDSS. Through these reviews, a minor to moderate benefit of CDSS for optimizing antimicrobial management has been demonstrated with a number of gaps in knowledge remaining to be answered [11,13,14]. We performed a systematic review of original literature (qualitative and quantitative) to try to understand the current scope of CDSS for antimicrobial management and analyse existing methods used to evaluate and report such systems. This will be used to create a pragmatic picture of CDSS for antimicrobial management and produce recommendations for future research and interventions, which may optimize the effectiveness of CDSS reporting within this field.

Materials and method

Search strategy

This systematic review was performed following PRISMA guidelines [15]. The Medline, EMBASE, HMIC Health and Management, and Global Health databases were searched from 1 January 1980 to 31 October 2015 using the search criteria described in the Supplementary material (Table S1). Search criteria were broad and intended to capture all information technology products that have been labelled as 'clinical decision support systems' for antimicrobial management.

Study selection

Prospective and retrospective articles in English that reported original research on clinical patient or product outcomes of CDSS for antimicrobial management in primary and secondary care were included. Randomized (including cluster), observational (including case–control, cross-sectional, cohort, before–after and interrupted time series), diagnostic, development reports (including data), mixed-methods, and qualitative (survey, semi-structured interview or ethnographic) studies were all included. Interventions focusing predominantly on critical care were excluded as these CDSS are often used by doctors in a controlled setting, where close working relationships with infection specialists have been demonstrated to significantly improve patient outcomes [16–20]. Therefore, these CDSS interventions may not be used in a similar way to other areas, where they are often used to supplement this expert support. Moreover, CDSS designed specifically for paediatric antimicrobial management were excluded given the differences in prescribing compared with adult antimicrobial management. If studies did not present original data, they were not carried forward. Two authors (TMR plus either LSPM, EC or ECS) independently screened study titles and abstracts against the inclusion and exclusion criteria described above and extracted data (described below). On completion of this process, inter-rater reliability was assessed by calculating Cohen's κ statistic. Where there was disparity between opinions, the authors discussed these to reach a consensus.

Decision support system grouping and data extraction

Following study selection, two authors (TMR plus either LSPM, EC or ECS) independently reviewed each study, grouping those for each CDSS described and extracting data. Data recorded included the characteristics of the CDSS (decision support provided, platform, and system infrastructure), the study design(s) used to evaluate the CDSS, and any comparator used. Primary and secondary outcomes were recorded when presented in the manuscript, as was the outcome of these. Qualitative studies were analysed using a thematic synthesis approach [21]. Qualitative studies were synthesized using an inductive approach with line by line coding of the text to draw out descriptive themes (carried out by one author, TMR). Manuscripts were then re-coded and discussed by the researchers (TMR, LSPM, EC, ECS) to agree upon analytical themes from within the text [21]. Finally, the CDSS systems were evaluated against an analytical framework adapted from the Stage Model of Behaviour Intervention Development [22] and the Medical Research Council's Developing and Evaluating complex interventions guidance [23]. The framework is outlined in Table 1. The four domains of the framework used to evaluate the CDSS were (a) development; (b) feasibility and piloting; (c) evaluation of the system; and (d) implementation. When included within reporting of such systems these criteria will allow the reader to understand holistically the rationale for why and how a CDSS was developed and how its effectiveness was evaluated [22,23].

Table 1
Analytical framework for the assessment of clinical decision support systems applied to the studies in this review

Domain 1: Development	Domain 2: Feasibility and Piloting	Domain 3: Evaluation	Domain 4: Implementation
Literature describing a system should demonstrate:	**Literature describing a system should outline:**	**Literature describing a system should demonstrate:**	**Literature describing a system should outline:**
A definition of stakeholder behaviours that are being targeted and how stakeholders have been engaged with during the development phase	How pilot testing was performed and the findings of this	Efficacy testing in a 'real-world' setting	How it was tested in the real world with real-world providers
A rationale for how the intervention may influence these behaviours	An understanding of the mechanism of behaviour change witnessed and how the intervention may be having its effect	High levels of control maintained to confirm internal validity of intervention	Strategies for implementation and adoption of intervention that were used and how these may have impacted on observations
An outline of how the system was developed		Confirm how the intervention changes practice and quantify its impact	Plans for (or evidence of) long-term surveillance / follow up of the system

Analytical framework adapted from Stage Model of Behaviour Intervention Development [22] and the Medical Research Council's Developing and Evaluating complex interventions guidance [23].

Quality assessment

Given the heterogeneity of studies included within this review, we opted to use the Integrated quality Criteria for the Review Of Multiple Study designs (ICROMS) criteria [24]. ICROMS aims to facilitate the review of behaviour change interventions in the field of infection, such as clinical decision support tools. It facilitates the review of multiple study designs that include randomized control trials (RCTs) (including cluster-RCTs), cohort, before–after and interrupted time series studies, as well as qualitative studies [24]. For studies that were not included in ICROMS, we quality assessed these using validated criteria from the literature. These were the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria for cross-sectional studies and case–control studies [25]; the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) criteria for economic evaluations [26]; and the Standards for Reporting Diagnostic Accuracy Studies (STARD) criteria for diagnostic studies [27]. For development reports, we were unable to assign a quality criterion (and these were therefore labelled as high risk of bias).

Using these quality criteria, studies were scored as advised within ICROMS [24]. A study was awarded 2 points if a specific criterion was met, 0 points if the criterion was not met, and 1 point if it was unclear. The sum of the quality criterion was then given to represent a *global quality score* for each study. Based on recommendations from ICROMS scores <60% of the maximum attainable score for that criterion were labelled high risk of bias / low reliability (defined 'high risk') [24]. Scores of 60%–80% of the total for that study type were labelled medium risk of bias / medium reliability ('medium risk') and studies with >80% of the total score for that study type were labelled low risk of bias / high reliability ('low risk'). Given that our objectives were to capture all relevant literature, we did not exclude data based on the quality of evidence provided.

Summary measures

Following extraction and synthesis, data were reviewed by all researchers to identify current barriers and facilitators to success in practice. All major primary outcome measures described within the studies were grouped and classified into either patient level, prescriber level or unit/hospital level outcomes. These were tabulated and the level of evidence for overall achievement of each primary outcome demonstrated within the literature for these groups was graded using Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria [28].

Results

Study selection and characteristics

Fig. 1 describes the screening and eligibility checking process that was undertaken. An initial electronic search identified 402 individual titles and abstracts for screening. Of these, 131/402 (33%) abstracts were carried forward for eligibility screening and 58/131 (44%) were included in the review. Cohen's κ for agreement was 0.88. These 58 studies described 38 different CDSS. Table 2 summarizes the attributes of the CDSS identified. Supplementary material (Table S2) outlines the full evaluation of the 38 CDSS. On assessment of the risk of bias of included studies using ICROMS, the majority of studies in primary care were found to be low to medium risk (7/18; 39% and 8/18; 44%, respectively), whereas the majority of studies reported from secondary care were medium to high risk (15/40; 38% and 22/40; 55%, respectively) of bias.

Decision support systems reported in the literature

The majority of CDSS in the literature target antimicrobial prescribing (29/38; 76%). The 11 systems focused on antimicrobial prescribing in primary care provided decision support for specific syndromic presentation in adults. The conditions targeted were acute respiratory tract infections (ARIs), with two CDSS also including urinary tract infections (UTIs) [29–46]. In contrast, systems supporting antimicrobial prescribing in secondary care targeted broader populations with interventions tending to focus on empirical and prophylactic antimicrobial prescribing rather than individual syndromes (exceptions included pneumonia, UTI, methicillin-resistant *Staphylococcus aureus*, *Clostridium difficile* infection) [47–85,95]. Other decision support provided by CDSS for antimicrobial management included electronic prompts/alerts (7/38; 18%); optimizing antimicrobial dosing (3/38; 8%); supporting antimicrobial de-escalation (2/38; 5%); surveillance (2/38; 5%); and prescriber feedback (1/38; 3%).

Several platforms for delivering CDSS were reported, including systems being integrated into hospital electronic medical record (28/38; 74%), via web-based platforms (5/38; 13%), via personal digital assistants (3/38; 9%), and as stand-alone software (2/38; 5%). The reported infrastructure providing decision support was predominantly rules based (29/38; 76%). There were also a number of machine learning tools reported including; use of neural networks (2/38; 5%), association rule learning algorithms (1/38; 3%) and predictive models (1/38; 3%). These were all reported in secondary care.

Analysis of CDSS development & pilot and feasibility testing domains

On comparison with domains 1 and 2 of our defined analytical framework (Table 1), a paucity of evidence exists to describe stakeholder involvement in the development processes for CDSS. This includes a lack of evidence supporting pre-intervention stakeholder analysis, evidence exploring user decision processes, and how interventions will fit into routine clinical workflow. For example, Andreassen *et al.* describe the development of an intelligent CDSS using Causal Probabilistic Networks (TREAT) for use in secondary care [67]. Within this report, much detail is placed on the construction of a pathophysiological model for the diagnosis of infection and antimicrobial selection. However, no evidence is provided to describe prescriber's decision pathways and how the system will integrate into this process in clinical practice. In contrast, McDermott *et al.* report during the development of the eCRT study engagement with a small number of stakeholders ($n = 33$) in the design of the intervention based on behaviour change theories [42,94]. However, post-implementation review of this intervention identified problems with variations in individuals prescribing behaviours, lack of end-user engagement with implementation, and rigidity of the guidelines incorporated limiting the use of the system [40]. These aspects of the clinician's decision-making process were not explored during the development phase. This observation is supported by Zaidi *et al.*, who highlighted workflow-related issues of their CDSS with junior medical staff during the post-intervention qualitative evaluation of their product [79].

Analysis of evidence domain

For analysis of framework domain 3, examination of experimental design studies in primary care reveals primary outcome measures were heterogeneous and tended to focus on the rates of prescribing of antibiotics either overall or for a defined syndrome. These studies demonstrated zero to minor clinically significant

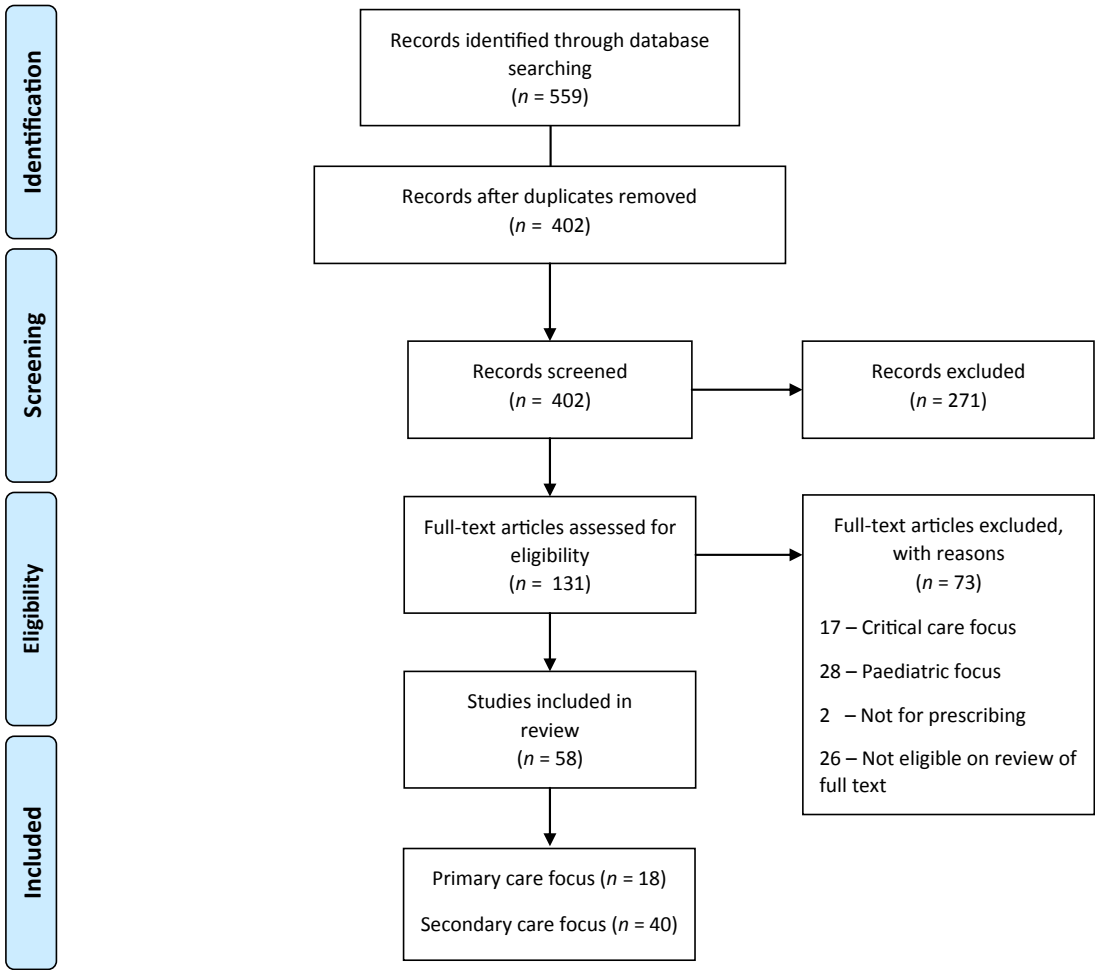

Fig 1. PRISMA flow diagram outlining study selection for inclusion within the systematic review of clinical decision support for infection management in primary and secondary care.

Table 2
Summary of clinical decision support systems evaluated

CDSS characteristics	*n* (%)
System setting	
Primary care	11 (29)
Secondary care	27 (71)
Types of decision support	
Antibiotic prescribing	29 (76)
Physician feedback	1 (3)
Alerts / prompts	7 (18)
Dose optimization	3 (8)
De-escalation	2 (5)
Surveillance	2 (5)
CDSS Platform	
Integrated into EMR	28 (74)
On PDA device	3 (8)
Web-based application	5 (13)
Stand-alone software	2 (5)
System Attributes	
Rule based[a]	29 (76)
Causal probabilistic networks	1 (3)
Drug-bug logic	1 (3)
Pharmacokinetic modelling[a]	2 (5)
Fuzzy cognitive mapping	1 (3)
Guidelines	2 (5)
Predictive models	1 (3)
N/A	2 (5)

Abbreviations: CDSS, clinical decision support systems; EMR, electronic medical records; N/A, not avilable; PDA, personal digitl assistant.
[a] One system had multiple attributes.

improvements in antimicrobial use [29–31,37,39,41,42]. Failures in demonstrating primary outcome measures were often reported as being due to the intention-to-treat analysis, with poor uptake of the CDSS intervention by clinicians cited as the major driver for this [30,41]. For example, Linder *et al.*, reported a cluster-RCT investigating the use of a rule-based (guideline-driven) CDSS embedded in a primary care practice's electronic medical records for antimicrobial prescribing in ARIs [32]. During the intervention period of the study 21 961 visits were made by patients with ARIs. A total of 11 954 visits were in primary care clinics where the CDSS had been implemented. Of these visits, the CDSS intervention was only used 6% of the time [31]. The study did not demonstrate improvement in reducing overall rates of prescribing for ARI visits (43% in control versus 39% in intervention (OR 0.8, 95% CI 0.6–1.2). In experimental interventions where primary outcomes were met, such as the RCT reported by McGinn *et al.* testing the Clinical Prediction Rules CDSS, outcomes focused on a rules-based system designed for specific types of ARI and demonstrated a 10% reduction in antimicrobial prescribing for these conditions (adjusted RR 0.74, 95% CI 0.60–0.92) [39]. However, clinical outcomes and unintended consequences of reducing antimicrobial prescribing for this cohort were not investigated. CDSS adoption rates in this study were reported as 62.8% [39]. Therefore, there is a large variation in uptake of such interventions between studies, which appears to influence the achievement of clinical and statistical outcomes.

In secondary care, three experimental studies were identified reporting CDSS evaluation. These evaluated two systems. Again, outcome measures were extremely variable, making comparison between interventions difficult. One trial, reported by McGregor *et al.* described an electronic alert system for antimicrobial management teams demonstrated a significant financial benefit, with the trial stopped early after the authors demonstrated savings of over $84,000 during a 3-month study period where the intervention was used on 359 patients versus 180 controls [80]. The remaining two experimental studies reported did not show significant improvements in primary outcomes following adjustment. These studies both used a CDSS incorporating Causal-Probabilistic Networks (TREAT). Primary outcome measures were the appropriateness of empirical prescribing and 180-day survival following treatment, respectively [69,71]. Where primary outcome looked at the appropriateness of empirical therapy compared with detected organism sensitivity, TREAT did demonstrate a 9% improvement in appropriateness of prescribing [69]. However, once findings were adjusted for medical ward clustering and site, using multivariate regression, the findings did not reach significance (OR 1.48, 95% CI 0.95–2.29). This may have been partly due to under-powering of the study, due to financial and time constraints, cited by the authors [69]. Furthermore, in the second trial assessing 180-day survival, failures were once again in the intention-to-treat analysis, with significant benefits identified on per-protocol analysis (6% increase in survival, p 0.04), suggesting that clinical uptake of interventions may once again be a contributing factor, along with appropriate powering of cluster-RCTs [71].

Analysis of implementation and prescriber engagement with systems

On analysis of framework domain 4, we identified that many of the CDSS interventions investigated in experimental studies failed in the intention-to-treat analysis, with poor physician uptake of the intervention appearing to be a contributing factor. This finding is supported on review of published qualitative studies investigating CDSS implementation in both primary and secondary care. Here, a common theme emerges describing barriers to physician engagement with such systems. In primary care, a number of patient, physician and technical aspects causing a lack of engagement with interventions were identified by Litvin *et al.* and McDermott *et al.* [34,40]. For example, both studies cite technical aspects, like usability and work flow of the intervention in normal clinical practice as potential barriers to use, especially when it was felt to reduce time with or detract from engagement with the patient [34,40]. Moreover, physician factors such as perceived level of clinical experience and agreement with conventional CDSS were cited as factors that influenced engagement with the intervention; physician engagement was similarly found to be an issue by Zaidi *et al.*, who assessed the implementation of a CDSS in an Australian hospital [78,79]. However, of note was the paucity of information available describing mechanisms to support implementation and adoption of CDSS as well as a lack of stakeholder follow up and long-term surveillance of interventions to support such observations.

Review of reported primary outcome measures of CDSS

Major primary outcome measures identified in this review are outlined in Table 3. Outcome measures were classified based on demonstration of results at the hospital/unit, patient, or prescriber level. Evidence was rated as medium to high at supporting the benefit of CDSS at the hospital and prescriber level, but was poor to support the impact of CDSS on patient level outcomes, including mortality and experience of complications. As discussed above, outcome measures tended to be proxy indicators of success, such as appropriateness compared with guidelines or rates of prescribing. They often failed to investigate direct patient outcomes from implementation of CDSS.

Overall, evidence is low to medium for the majority of clinical outcomes. However, there is high-quality evidence supporting CDSS at a unit/healthcare organization level to reduce the cost of antimicrobial therapy, as supported by the RCT reported by

Table 3
Primary outcome measures identified from systematic review of the literature of clinical decision support systems for infection management in primary and secondary care

Primary outcome measure	Total number	Number achieving outcome	Quality of evidence[a]
Unit level			
Disease specific antimicrobial prescribing rate (e.g. in total ARI visits)	6	3	H
Rate of antimicrobial prescribing (e.g. DDD/1000 patient bed days)	3	3	M
Economic benefit of CDSS	3	1	M
Patient level			
Mortality (e.g. 30 and 180 days)	1	1	L
Patient specific complications (SSIs / ADEs / HCAI)	1	1	L
Diagnostic accuracy e.g. Infection type (e.g. ARI / UTI), Predicting probability of bloodstream infection, or predict causative organism	3	3	L
Individualized dose optimization	1	1	L
Prescriber level			
Appropriate empirical prescribing—against subsequent bug sensitivity	3	3	H
Individual changes in prescribing behaviour (including de-escalation)	4	4	M
Adherence to local guidelines	9	7	M
Appropriate prescribing—duration / timing of therapy	2	2	M
Acceptance of CDSS	2	1	L
Compliance with dosing guidance	2	0	-

Abbreviations: ADE, adverse drug event; ARI, acute respiratory tract infection; CDI, *Clostridium difficile* infection; DDD, daily defined doses; HCAI, healthcare-associated infection; SSI, skin and soft-tissue infection; UTI, urinary tract infection.

[a] H, high quality; M, medium quality; L, low quality.

McGregor *et al.* in secondary care [80]. At the prescriber level, high quality evidence is available to suggest that CDSS have the potential to directly influence individual prescribing behaviours. For example, McGinn *et al.* reported an RCT which implemented clinical decision algorithms within a primary care electronic medical record system. This demonstrated significant reductions in antimicrobial prescribing and investigations ordered at the individual physician level [39]. However, there remains a paucity of high-quality evidence for patient specific outcome measures, such as mortality or complications of treatment selection, such as adverse drug events, healthcare-associated infections and other unintended consequences. This type of evidence is probably not currently available due to the need for longitudinal follow up of individuals across complex care pathways and difficulties with powering such studies.

Discussion

Within this review of CDSS for antimicrobial management of adults in primary and secondary care, we have identified a heterogeneous and disjointed approach to investigating and reporting CDSS interventions. This has included a paucity of supporting information to justify the development and deployment of many CDSS interventions reported, variable study designs, outcome measures that tend to be of low quality, and a lack of consideration of supportive measures required to promote prescriber engagement and use of these interventions, such as audit and feedback during implementation.

Although many of the CDSS interventions reported within this study are based on decision pathways or guidelines, very few interventions report pre-deployment stake-holder analysis or prescriber decision mapping to justify intervention design. With many devices built based on expert infection opinion, developers may be missing a valuable opportunity to explore and understand how non-expert prescribers' decision pathways differ when prescribing antimicrobial therapy. A deeper understanding of these aspects would allow for more individualized design of interventions to target specific steps in the prescriber's workflow as well as justifying development of specific user interface designs. Moreover, a greater understanding of the challenges within the routine prescriber's workflow may provider greater insight into other aspects of decision support that would warrant inclusion with CDSS for antimicrobial management. These may include specific dose optimization platforms, patient engagement tools or surveillance modules. This has been supported by several technical reports analysing key lessons in developing future clinical decision support systems with pre-deployment stakeholder engagement being reported to provide justification for defining the goals and clinical objectives of the device, allowing critical consideration of individual workflow, and facilitating communication across the environments where they are going to be deployed [86–88].

Second, current study design and outcome reporting require addressing to promote a standardized view of CDSS. Current investigations of CDSS for antimicrobial management primarily involve the selection of heterogeneous, non-standardized, proxy outcome measures, such as total amounts of antimicrobial prescribing or what is determined 'appropriate' antimicrobial prescribing. In primary care, primary outcomes focused on the rate of antimicrobial prescribing for the syndrome being investigated, namely ARI. Several different measures of prescribing were used but these often revolved around total number of prescriptions, not taking into account the nature of the presentation and other factors that may have influenced the physician's decision, such as delayed prescribing. In secondary care, many studies focused on whether the antimicrobial prescribed was 'appropriate', based on local guidelines, expert opinion, or identified organism sensitivities. As proxy measures, these outcomes do not directly measure clinical benefit to the individual or society, such as mortality, adverse events and development of antimicrobial resistance; many of which would require longitudinal follow up of individuals across healthcare pathways. Although addressed as secondary outcomes in several studies, these tended to be part of subgroup analysis where minor significance may be demonstrated but no statistical correction was described in the methodology, such as the Bonferroni correction. Therefore, the rigor of these results cannot be fully assessed. Future investigators of CDSS for antimicrobial management need to ensure that clear outcome measures that are sufficiently powered to demonstrate direct benefit for patients, prescribers, or healthcare organizations. This may mean that there is a need for larger, multi-centred collaborations to be set up to facilitate appropriate sample sizes.

With the growing need to promote cross-specialty engagement and the joining up of care pathways between primary and secondary care, a more appropriate way of comparing CDSS may be through analysis of different intervention types. Studies in primary care currently fail to assess the effect of changes in prescribing on secondary care, where patients who fail antimicrobial therapy in the community may subsequently present to hospital; similarly, studies based in secondary care may fail to investigate the unintended consequences of actions in hospital on patients discharged to primary care services. Indeed, much of the impact of changes in prescribing in both primary and secondary care may currently be missed by failing to look across the entire patient care pathway. Yong *et al.*, investigated the impact of a hospital-wide decision support system to restrict the use of broad-spectrum antimicrobials on rates of antimicrobial resistance in their intensive care unit, observing that despite antimicrobial prescribing levels remaining stable in the intensive care unit, there was an increase in susceptibility of Gram-negative organisms to broad-spectrum agents [89]. This would suggest that prescribing behaviours in another area of the patient pathway, where significant decreases in prescribing were described, may have influenced the observed changes in antimicrobial resistance upstream from the setting. These findings would support the requirement for longitudinal follow up of individuals receiving antimicrobials and the need for combining of primary and secondary care interventions to truly assess the impact of CDSS at a societal level.

Finally, the role of CDSS on its own is unlikely to be of significant clinical benefit, requiring synergistic interventions to be implemented in support of it. Given the current lack of evidence to support CDSS implementation in non-expert prescribers' work flow and the significant lack of engagement with CDSS interventions reported within the literature it is likely that implementation with education, regular feedback on device use, and other antimicrobial stewardship-related interventions will be required to generate interest and use of any CDSS. Therefore, study design must consider these facets and account for them to allow interventions to be assessed both separately and as multi-modal interventions, as is more likely to be the case in clinical practice. This would further be supported by the development of a suitable reporting framework to guide the reporting of CDSS intervention studies, similar to the outbreak reports and intervention studies for non-interventional trials (ORION) guidelines for healthcare-associated infection reporting [90]. These guidelines have helped to raise the standards of research and publication in hospital epidemiology through setting standards for design and reporting of studies, allowing for greater generalizability of findings reported in studies [90].

Although several of the challenges described above are not unique to CDSS for antimicrobial prescribing, we support the

conclusions drawn by Eichner and Das [91]. Within their review of the barriers in development and implementation of a CDSS, they call for specific implementation and evaluation tools for CDSS within specific fields to promote better integration within end-user workflow and uptake on implementation [91]. For the role of CDSS in antimicrobial management we propose that the summary of key components for reporting CDSS that have been identified within this review should be considered when developing and reporting CDSS for antimicrobial management (Table 4). These focus on (a) a clear description of the system's technical attributes; (b) consideration and reporting of all four domains of the analytical framework that we have developed for assessing the implementation of these complex interventions for antimicrobial prescribing; and (c) clear justification of rationale for the study design used to evaluate the CDSS, including consideration of outcome measures used to demonstrate effectiveness.

Table 4
Recommended reporting criteria for consideration when describing and evaluating clinical decision support systems for antimicrobial management

Criteria / Sub-heading	Comment
Description of Decision Support Tool	
Type of decision support provided	e.g. Antibiotic prescribing Dose optimization Feedback Surveillance
Platform on which it is provided	e.g. Integrated into EMR Web-based Stand-alone software
Infrastructure	e.g. Rule-based Machine learning (with description)
System development	
Rationale for development	e.g. Were stakeholders involved in defining a need and developing the tool? How? Theory behind the intervention clearly outlined Clear working hypothesis
Previous feasibility / pilot testing	e.g. Pilot testing supporting intervention Pilot test of how system will change behaviour
Evidence supporting evaluation	e.g. Justify the setting in which the evaluation is undertaken How will the authors control for bias?
How the tool is implemented	e.g. What support measures was the tool implemented with to promote adoption (e.g. education/training sessions, audit and feedback)
Study design	
Justification for study design	e.g. What is the study design? Why was this selected? How are confounding factors controlled for (change in guidelines, Hawthorne effect, the effect of implementation strategies for adoption)?
Outcome measure selection	e.g. What is the primary outcome for this study (patient outcomes, change in prescriber behaviour, economic evaluation)? Are direct or proxy measures being used? Are the unintended consequences of this intervention considered? Will stakeholders be involved (qualitative evaluation)

EMR, electronic medical records.

There were several potential limitations to this study. For example, the use of cluster-RCT design for experimental studies does not allow individualization of data, therefore meta-analysis of interventions is difficult to perform. Second, many CDSS interventions are implemented with a number of other antimicrobial stewardship-based interventions, such as educational sessions and prescriber feedback [92,93]. In many cases, it is challenging to dissect the individual merits of each of these facets of the overall intervention, making the direct impact of the CDSS more challenging to determine. Finally, although broad-based search terms were used to try and capture a broad representation of appropriate studies, some may have been missed. This includes commercially developed products that are not reported within the literature and were not within the scope of this review. Our methodology included hand searching of reference lists of identified studies to address this.

In conclusion, CDSS for antimicrobial management currently demonstrate a potential to facilitate improved evidence-based antimicrobial use in adults. However, several key areas must be addressed if the true potential of CDSS in this field is to be effectively explored. CDSS must not be viewed as a magic bullet and as such, interventions must be multi-modal so that potential synergistic effects can be explored to ensure that interventions are used. This requires careful consideration of appropriate study design and the clear and transparent reporting of CDSS interventions with a focus on demonstrating direct patient impact and surveillance for unintended consequences of such interventions. The development of an evidence-based reporting framework for CDSS for antimicrobial management would greatly enhance the quality of evidence available to support such interventions. Furthermore, research must explore broader integration of different CDSS such as linking antimicrobial selection with other modules, like dose optimization, patient engagement tools and automated surveillance mechanisms.

Contribution statement

All authors contributed significantly towards the planning and undertaking of this study. TMR drafted the initial draft of the manuscript with all authors significantly contributing to the development and finalization of the final iteration for submission.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cmi.2017.02.028.

Transparency declaration

AHH and LSPM have consulted for bioMérieux in 2013 and 2014, respectively.

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