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 optimise 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 1st January 1980 to 31st 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 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.

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**Introduction**

In response to the global threat of antimicrobial resistance (AMR),[1] a range of antimicrobial stewardship (AMS) 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 AMR.[6–9] To address this challenge, electronic clinical decision support systems (CDSS) have 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 (EMR) 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 healthcare 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 1980’s 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 optimising 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 optimise the effectiveness of CDSS reporting within this field.

**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 1st January 1980 to 31st October 2015 using the search criteria described in **Supplementary Table 1**. Search criteria were broad and intended to capture all information technology products which have been labelled as “clinical decision support systems” for antimicrobial management.

*Study selection*

Prospective and retrospective articles in English that reporting original research on clinical patient or product outcomes of CDSS for antimicrobial management in primary and secondary care were included. Randomised (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 has been demonstrated to significantly improve patient outcomes.[16–20] Therefore, these CDSS interventions may not be utilised 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 to 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 kappa statistic. Where there was disparity between opinions, the authors discussed these to reach a consensus.

*Decision support system grouping & 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 synthesised 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 (i) development; (ii) feasibility and piloting; (iii) evaluation of the system; and (iv) 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]

*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 includes Randomised Control Trials (RCT’s) (including cluster-RCT’s), 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 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% 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 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*

**Figure 1** describes the screening and eligibility checking process which 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 kappa for agreement was 0.88. These 58 studies described 38 different CDSS. **Table 2** summarises the attributes of the CDSS identified. **Supplementary Table 2** 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, MRSA, *Clostridium difficile* infection).[47–85] Other decision support provided by CDSS for antimicrobial management included; electronic prompts / alerts (7/38; 18%); optimising 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 (EMR) (28/38;74%), via web-based platforms (5/38;13%), via personal digital assistants (3/38;9%), and as standalone 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 and colleagues 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 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 and colleagues 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] 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 and colleagues, 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 rates of prescribing of antibiotics either overall or for a defined syndrome. These studies demonstrated zero to minor clinically significant 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 (ITT) analysis, with poor uptake of the CDSS intervention by clinicians cited as the major driver for this.[30,41] For example, Linder and colleagues, reported a cluster-RCT investigating the use of a rule based (guideline driven) CDSS embedded in a primary care practice’s EMR for antimicrobial prescribing in ARI’s.[32] During the intervention period of the study 21,961 visits were made by patients with ARI’s. 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 vs 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 and colleagues testing the Clinical Prediction Rules (CPR) 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 to detected organisms 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 ITT 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-RCT’s.[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 ITT 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 McDermott *et al*. and Litvin *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 which influenced engagement with the intervention; physician engagement was similarly found to be an issue by Zaidi and colleagues, 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 **Figure 2***.* 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 to 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 organisation level to reduce the cost of antimicrobial therapy, as supported by the RCT reported by McGregor and colleagues 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 and colleagues reported a RCT which implemented clinical decision algorithms within a primary care EMR 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 (ADE’s), healthcare associated infections (HCAI’s), 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.

Whilst 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 individualised 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 optimisation 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 facilitate communication across the environments that they are going to be deployed.[86–88]

Secondly, current study design and outcome reporting requires addressing to promote a standardised view of CDSS. Current investigations of CDSS for antimicrobial management primarily involve the selection of heterogeneous, non-standardised, 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. Whilst several different measures of prescribing were used these often revolved around total number of prescriptions, not taking into account the nature of the presentation and other factors which 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 either 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 AMR; many of which would require longitudinal follow up of individuals across healthcare pathways. Whilst 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 organisations are designed. 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. Young *et al.,* investigated the impact of a hospital wide decision support system to restrict the use of broad spectrum antimicrobials on rates of AMR in their intensive care unit (ICU), observing that despite antimicrobial prescribing levels remaining stable in the ICU, 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 AMR up-stream 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 a 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 AMS 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]

Whilst, several of the challenges described above are not unique to CDSS for antimicrobial prescribing, we support the conclusions drawn by Eichner and Das. 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 that should be considered when developing and reporting CDSS for antimicrobial management (**Table 3**). These focus on (i) a clear description of the systems technical attributes; (ii) 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 (iii) clear justification of rationale for the study design used to evaluate the CDSS, including consideration of outcome measures used to demonstrate effectiveness.

There were several potential limitations to this study. For example, the use of cluster-RCT design for experimental studies does not allow individualisation of data, therefore meta-analysis of interventions is difficult to perform. Secondly, many CDSS interventions are implemented with a number of other AMS-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 in order 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 utilised. 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 optimisation, 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 finalisation of the final iteration for submission.

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**Competing interests**

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

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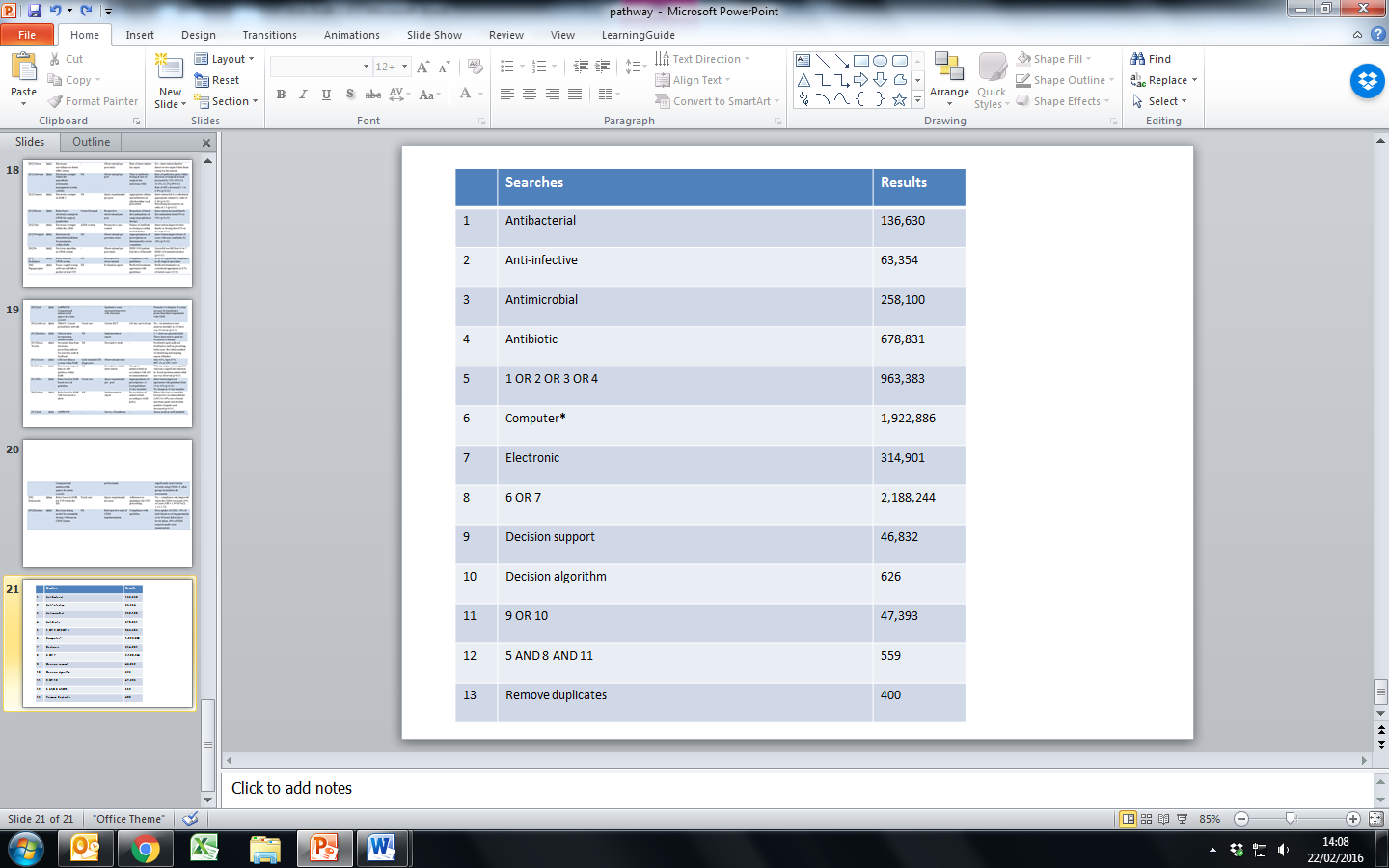
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**Supplementary table 1.** Search criteria used for systematic review of clinical decision support systems for antimicrobial prescribing



**Legend:** \* wildcard

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

Studies included in review  
(n = 58)

Full-text articles assessed for eligibility  
(n = 131)

Records excluded  
(n = 271)

Records screened  
(n = 402)

Records after duplicates removed  
(n = 402)

Records identified through database searching  
(n = 559)

## Identification

## Screening

Full-text articles excluded, with reasons  
(n = 73)

17 – Critical care focus

28 – Paediatric focussed

2 – Not for prescribing

26 – not eligible on review of full text

## Eligibility

## Included

Primary care focus (n = 18)

Secondary care focus (n = 40)

*From:*  Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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

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

**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 optimisation | 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) |
|  | Standalone software | 2 (5) |
|  |  |  |
| **System Attributes** |  |  |
|  | Rule based\* | 29 (76) |
|  | Causal Probabilistic Networks | 1 (3) |
|  | Drug-bug logic | 1 (3) |
|  | Pharmacokinetic modelling\* | 2 (5) |
|  | Fuzzy cognitive mapping | 1 (3) |
|  | Guidelines | 2 (5) |
|  | Predictive models | 1 (3) |
|  | N/A | 2 (5) |
|  |  |  |

**Legend:** \* = 1 system had multiple attributes

**Figure 2.** Primary outcome measures identified from systematic review of the literature of CDSS for infection management in primary and secondary care

|  |  |  |  |
| --- | --- | --- | --- |
| **PRIMARY OUTCOME MEASURE** | **Total number** | **No achieving outcome** | **Quality of evidence** |
| Disease specific antimicrobial prescribing rate (e.g. in total ARI visits) | **6** | **3** | **H** |
| Rate of antimicrobial prescribing (drug e.g. DDD/1000 patient bed days) | **3** | **3** | **M** |
| Economic benefit of CDSS | **3** | **1** | **M** |
|  |  |  |  |
| Mortality (e.g. 30 & 180 days) | **1** | **1** | **L** |
| Patient specific complications (SSI’s / ADE’s / HCAI) | **1** | **1** | **L** |
| Diagnostic accuracy  e.g. Infection type (e.g. ARI / UTI), Predicting probability of blood stream infection, or predict causative organism | **3** | **3** | **L** |
| Individualised dose optimisation | **1** | **1** | **L** |
|  |  |  |  |
| Appropriate emperical 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** | **-** |

**UNIT LEVEL**

**PRESCRIBER**

**PATIENT**

**Legend:** DDD = Daily defined doses; ARI = Acute respiratory tract infection; HCAI = Healthcare Associated Infection; CDI = *C.difficile* infection; ADE = Adverse drug event

|  |  |  |
| --- | --- | --- |
| **Criteria** | **Sub-heading** | **Comment** |
| **Description of Decision Support Tool** |  |  |
|  | Type of decision support provided | *e.g. Antibiotic prescribing*  *Dose optimisation*  *Feedback*  *Surveillance* |
|  | Platform it is provided on | *e.g. Integrated into EMR*  *Web-based*  *Standalone software* |
|  | Infrastructure | *e.g. Rule based*  *Machine learning*  *(with description)* |
| **System development** |  |  |
|  | Rationale for development | *e.g. Were stakeholders involved in defining a need & 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 the evaluation is undertaken in*  *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 & 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)* |

**Table 3.** Recommended reporting criteria for consideration when describing and evaluating clinical decision support systems for antimicrobial management

**Supplementary table 2.** Summary of Clinical Decision Support Systems for antibiotic prescribing and evidence supporting aspects of behavioural intervention development

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | CDSS Characteristics | |  |  |  | CDSS reporting on aspects of system development | |  |  |  | Summary of supporting studies | |  |  |  |
|  | **Setting** | **CDSS** | | **Platform** | **Infrastructure** | **Development** | **Feasibility & Piloting** | | **Evaluation** | **Implementation** | **Study type** | **Primary outcome** | | **Outcome met** | **Risk of Bias** |
| [29] Flottorp | PC | Antibiotic prescribing for ARI & UTI | | Software integrated into EMR | Rule based | *-* | *-* | | *Small decrease in prescribing in ARI*  *No effect on UTI* | *-* | cRCT | Rate prescribing | | UTI – no  ARI – 3% ↓ | Low |
| [44] Rubin | PC | Antibiotic prescribing for ARI | | PDA device | Rule based | *Algorithms translated from paper to electronic form after demonstration of success* | *Paper based algorithms proved successful in RCT* | | *High adherence to guidelines* | *Training provided to providers before deployment & incentives used.* | CS | - | | 76% guideline adherence | Med |
| [45] Madaras-Kelly | PC | Antibiotic prescribing for ARI | | PDA device | Rule based | *-* | *-* | | *-* | *Failed to gain patient consent for inclusion* | NCBA | Average cost of treatment  CDSS acceptance | | No  No | High |
| [30–32] ARI Smart Form / Quality Dashboard | PC | Antibiotic prescribing for ARI & UTI  Physician feedback | | Integrated into EMR | Rules based | *Based intervention on evidence based guidelines*  *Identified need to improve accuracy of diagnosis of ARI & UTI in practice* | *Demonstrated high sensitivity & specificity for diagnosing ARI & UTI* | | *No effect observed* | *Poor engagement with intervention by prescribers* | CSS  cRCT  cRCT | Accuracy of diagnosis & Prescribing  Rate of prescribing  Rate of prescribing | | Yes  No  No | Med  Low  Low |
| [33] Rattinger | PC | Antibiotic prescribing for ARI | | Integrated into EMR | Rules based | *Attempted to integrate CDSS into natural workflow of care (stakeholders and methods not identified)*  *Translation of pharmacy processes into CDSS* | *-* | | *Improvements in adherence to guidelines* | *-* | CBA | Warranted vs. unwarranted AU | | Yes – AU improved | Low |
| [34–36] ABX-TRIP | PC | Antibiotic prescribing for ARI | | Integrated into EMR | Rules based | *Based on evidence based guidelines for ARI* | *-* | | *Potential to reduce inappropriate prescribing in ARI* | *Poor engagement with intervention by prescribers*  *Number of barriers to uptake identified* | Qu  CS  CITS | No  Appropriate AU  Inappropriate prescribing | | -  No  Yes | Med  High  Low |
| [37] [38] Gonzales &  Michaelidis | PC | Antibiotic prescribing for ARI | | Integrated into EMR | Rules based | *-* | *-* | | *Reduced rate of antimicrobial prescribing* | *More expensive to implement than PDSS, which is equally as effective*  *Implementation was supported by implementing with physician training and reinforcement through audit & feedback* | cRCT  EA | Rate of prescribing  Cost of intervention vs PDSS | | Yes  No | Low  Med |
| [39] CPR tool | PC | Antibiotic prescribing for ARI | | Integrated into EMR | Rules based | *Based on evidence that CPR improve quality of practice* | *-* | | *Reduction in individual prescribing rates / changes in prescribing behaviour* | *-* | RCT | Changes in individual prescribing behaviour | | Yes – NNT =11 | High |
| [40–42] eCRT | PC | Antibiotic prescribing for ARI  Electronic prompts | | Integrated into EMR | Rules based | *Stakeholders engaged in intervention design for feedback*[94]  *National guidelines followed* | *-* | | *Small reduction in rate of prescribing for ARI* | *Poor engagement with intervention by prescribers*  *Reasons preventing engagement identified and explored* | cRCT  cRCT  Qu | Proportion of ARI consultation with antibiotic prescribed | | No  Yes - ↓1.85% | Med  Med  Low |
| [46] Fernández | PC | Antibiotic prescribing | | Web-based guideline | Rules based | *National guidelines identified* | *-* | | *Improvement in guideline adherence* | *-* | NCITS | Adherence to guidelines | | Yes – 21%↑ | Med |
| [43] McCullough | PC | Antibiotic prescribing for ARI  Electronic prompts | | Integrated into EMR | Rules based | *Designed intervention based on a hypothesis of how CDSS will act to change behaviours. (Stakeholders not engaged)* | *Reduction in antimicrobial usage* | | *-* | *-* | CS | - | | CDSS use reduced AU | Med |
|  |  |  | |  |  |  |  | |  |  |  |  | |  |  |
| [47–50] Antimicrobial Consultant | SC | Antibiotic prescribing  Electronic prompts | | Integrated into EMR | Rules based | *Based on local guidelines for therapy* | *Reduction in mortality and reduction in DDD/100 occupied bed days*  *Reduction in pharmacy spending on antimicrobials* | | *Improved timing of prophylactic dosing*  *Improved appropriate selection of therapy in ICU* | *-* | NCBA  NCBA  CS  CS | Improvement in prophylaxis  Appropriate selection of therapy  Detection of mismatch between abx & organism sensitivity  - | | Yes - improved timing  Yes – 17%↑  Yes  - | High  Med  High  Med |
| [67–71,95]TREAT | SC | Antibiotic prescribing | | Standalone software | Causal Probabilistic Networks | *Defining causal probabilistic networks focusing on organism* | *Ability to predict BSI*  *Ability to predict micro-organism*  *Appropriate empirical therapy recommendations* | | *Appropriate empirical therapy recommendations* | *-* | DR  DE    DE  CS  CS/cRCT    cRCT | -  ROC pred. BSI  Organism predication  Appropriate empirical therapy  Appropriate empirical therapy  180 day survival rate | | -  Yes - ROC 0.68 (0.63-0.73)  Yes - ROC >0.5 for all organisms  Yes - Improved by 20% (p<0.01)  Yes - Improved by 13% (p<0.01)  No - ITT – 3% lower (p=0.2) | High  Med  High  High  Low    Med |
| [72,73] Mullett | SC | Antibiotic prescribing | | Standalone software | Drug-bug logic matrix | *Allows expansion of susceptibility data points* | *Improved appropriateness of antimicrobial selection* | | *-* | *-* | CS  CS | -  Appropriate empirical therapy | | -  Yes - 20% improvement (p<0.01) | Med  High |
| [84] Hwang | SC | Gentamicin dose optimisation | | Standalone on PDA | Pharmacokinetic model | *PK principles explored to provide rationale*  *PK model constructed* | *Improved plasma concentration target attainment* | | *-* | *Found CDSS inconvenient to navigate / use* | CCS | Steady state peak and trough target concentration attainment | | Yes - Target peak (p=0.04) and trough (p<0.01) targets met more frequently | High |
| [51] WizOrder | SC | IV to PO switch for quinolones | | Integrated into EMR | Rules based | *Based on evidence of safety and effectiveness of early iv to oral switch* | *-* | | *Improvement in oral quinolone ordering* | *-* | NCITS | Proportion of weekly PO orders | | Yes - 5.6% (2.8-8.4%) ↑ in weekly orders (p<0.01) | Med |
| [52] Bernstein | SC | Generic antibiotic prescribing  Electronic prompts | | Integrated into EMR | Rules based | *-* | *-* | | *Improve prescribing of prescriptions to self-paying patients* | *Supported with 30 minute didactic lecture* | NCBAS | Proportion correct prescriptions to self-paying patients | | Yes - 22% improvement (p=0.03) | Med |
| [53] Webb | SC | Prophylactic antimicrobial prescribing and delivery | | Integrated into EMR | Rules based | *Based on evidence that appropriate timing of prophylaxis reduces incidence of SSI*  *Paper preoperative order form converted* | *Improved timely administration of prophylactic antibiotics* | | *-* | *-* | DR | Timing of administration of therapy in relation to surgical site incision | | Yes - Timely administration improved from 51 to 95% | High |
| [80] PharmWatch | SC | Electronic alerts for patients requiring change in antimicrobial theapy | | Web-based application | Rules based | *Developed based on evidence in favour of post-prescription review & CDSS for improving efficacy in other fields* | *-* | | *Economic benefit from use of CDSS* | *-* | RCT | Antimicrobial treatment costs ($) | | Yes - Stopped early – saved $84,000 in 3 months | Med |
| [75] Buising | SC | Antibiotic prescribing in CAP | | Web-based application | Rules based | *-* | *-* | | *Improved appropriateness of prescribing* | *Supported with academic detailing with education and advertising campaign in ED* | NCITS | Appropriate prescribing for CAP cf. local guidelines | | Yes - Improved appropriateness (OR:1.99, 1.07-3.69; p=0.02) | Med |
| [76–79] iAPPROVE | SC | Prescribing of restricted antibiotics | | Web-based application | Rules based | *Based on evidence for impact of restrictive policies on antimicrobial prescribing* | *-* | | *Consumption of cephalosporin’s reduced*  *AMR to cephalosporin’s & MRSA fell* | *Detailed that formative evaluation of system use would help promote engagement*  *Barriers to engagement from staff identified* | NCBA  NCITS  Qu  Qu | -  Change 3/4th Ceph use  -  - | | -  Yes - 38.3 DDD/1000 bed days fall in use  Formative evaluation may be of benefit  Senior staff ID more barrier to uptake | High  Med  Low  Low |
| [81] Vincent | SC | Electronic pharmacy support with dosing | | Integrated within EMR | - | *Based on evidence for drug protocol management services and efficacy of CDSS in other clinical areas* | *Increased time from requests to dosing support being provided* | | *-* | *-* | CCS | Uptake & time from request to dose | | No - Time ↑ from 20 to 37 minutes (p=0.03) | High |
| [54,55] Smart Anaesthesia Messenger (SAM) | SC | Prophylactic antimicrobial prescribing and delivery | | Integrated within Anaesthesia information management system (AIMS) | Rules based | *Based on evidence surrounding effective timing of prophylactic therapy* | *Improved compliance with prophylactic antimicrobial administration & re-dosing* | | *-* | *Roll out with feedback and distributing monthly reports had an additive effect at improving compliance* | DR  CCS | Guideline compliance  Failure of antibiotic re-dosing | | Yes - Stepwise improvement to 100%  Yes - Improve timely re-dosing from 63%-84% (p<0.01) | High  High |
| [82] Nelson | SC | Detection of SIRS with electronic alerts | | Integrated within EMR | Rules based surveillance system | *Developed surrounding the need to increase speed of detection & intervention for sepsis* | *-* | | *Failed to improve speed of intervention for sepsis* | *-* | NCBA | Rate of interventions for sepsis | | No – slower than human detection and intervention | High |
| [56] Schwann | SC | Prophylactic antimicrobial prescribing and delivery  Electronic prompts | | Integrated within Anaesthesia information management system (AIMS) | Rules based | *Based on evidence surrounding effective timing of prophylactic therapy*  *Developed on evidence that POCEPs may elicit specific behaviour-responses (stakeholders not engaged)* | *-* | | *Improved timeliness of antimicrobial prophylaxis administration*  *Rate of SSI reduced* | *-* | NCITS | Time to antibiotic dosing  Rates of SSI | | Yes - 31% ↑ in appropriate timing (p<0.01)  SSI ↓ from 1.1 to 0.8% (p<0.01) | Med |
| [61] Carman | SC | Clinical alerts for detection of MRSA result | | Integrated in EMR | - | *Based on inconsistent management of MRSA and evidence supporting CDSS for improving adherence to guidelines* | *-* | | *Improved prescribing and inappropriate culturing for community acquired MRSA* | *-* | NCBA | Appropriate management of MRSA | | Yes - ↓ inappropriate cultures (OR 0.69 – p<0.01)  ↑ (OR 2.4, p<0.01) Prescribing | High |
| [60] Haynes | SC | Prescribing surgical prophylaxis | | Integrated into EMR | Rules based | *Based on evidence surrounding effective timing of prophylactic therapy & for CDSS to reduce adverse events* | *-* | | *Improvement in timely discontinuation of prophylactic antimicrobials* | *-* | CITS | Timely discontinuation of antibiotic prophylaxis | | Yes - ↑ timely discontinuation from 39% - 56% (p<0.01) | Med |
| [59] Westphal | SC | Antibiotic prescribing for pneumonia | | Integrated into EMR | Rules based | *Based on evidence that making guidelines available during prescribing can improve practice* | *-* | | *Improved adherence to guidelines* | *-* | NCITS | Appropriateness of prescriptions | | Yes – improved rate or non-conformity to guidelines by 18% (p<0.01) | High |
| [58] Po | SC | Linezolid prescribing | | Integrated into EMR | Rules based | *Based on evidence of CPOE reducing errors* | *-* | | *Reduced the use of linezolid* | *-* | NCITS | DDD/1000 patient bed days of linezolid | | Yes - Use ↓ from 44 to 7 DDD/1000 bed days (p<0.01) | High |
| [57] Rodrigues | SC | Prescribing surgical prophylaxis | | Integrated into EMR | Rules based | *-* | *High compliance with antimicrobial prophylaxis guidelines* | | *-* | *-* | CS | Compliance with guidelines | | Yes - >90% compliance with guidelines | High |
| [74] Papageorgiou | SC | Diagnosis and treatment of UTI | | Integrated into EMR | Fuzzy-cognitive map software | *Probabilistic networks and need to incorporate multiple variables in decision process explored. (Stakeholders not engaged with)* | *Predict appropriate treatment for UTI’s in accordance with guidelines* | | *-* | *-* | DR | Agreement with guidelines | | Yes - Predicted treatment appropriate in 87% | High |
| [62] Beaulieu | SC | Clinical alerts advising on de-escalation / escalation of therapy | | Integrated into EMR | Rules based system | *Critical needs assessment performed by ASP specialists (MDT).* | *Generated alert’s daily, which tended to prompt de-escalation of therapy* | | *-* | *System integrated into a closed-loop medication safety process* | DR | - | | - | HIgh |
| [83] Cooper | SC | CDI surveillance | | Integrated into EMR | Predictive model | *Developed due to high risk nature of CDI and requirement for early diagnosis* | *High sensitivity and specificity of system. Low PPV, high NPV* | | *-* | *-* | DE | - | | High sens, spec, & NPV. Low PPV (4%) | High |
| [63] Antibiocarte | SC | Prescribing guidelines and infection management support | | Web-based | Rules based | *Simple interface type and ease of navigation was preferred* | *-* | | *-* | *-* | DR | Acceptance of 2 interfaces evaluated | | Simple “at a glance” interface preferred | High |
| [64] Filice | SC | Antibiotic prescribing | | Integrated into EMR | Electronic guidelines | *-* | *Improved appropriateness of prescribing to guidelines* | | *-* | *-* | CS | Appropriateness of prescriptions  30 day mortality | | Yes -11% improvement (p=0.01)  No change | Med |
| [65] Best Practice Alert tool | SC | Antibiotic prescribing | | Integrated into EMR | Rules based | *Based on local AMS guidelines* | *Acceptance of best BPA’s led to improvements in de-escalation of therapy* | | *-* | *-* | DR | De-escalation according to policy | | Yes – significant improvement when engaged with (p<0.01) | High |
| [66] Demonchy | SC | Antibiotic prescribing in UTI | | Integrated into EMR | Electronic guidelines | *CDSS integrated into EMR workflow*  *Developed based on previous reported CDSS success* | *CDSS use appeared to improved antimicrobial prescribing* | | *-* | *Poor engagement with CDSS by physicians* | CBA | Adherence to guidelines | | No – poor use. Adherence did improve when CDSS used | Med |
| [85] Diasinos | SC | Dose & TDM optimisation in aminoglycoside therapy | | Integrated into EMR | Bayesian prediction software and  Rules based alerts | *Based on guidelines for dosing* | *-* | | *-* | *Poor uptake of intervention.* | MM | Compliance with guidelines | | No – poor uptake | Med |