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The secondary use of data from hospital electronic prescribing and pharmacy systems to support the quality and safety of antimicrobial use: a systematic review

Running title: Systematic review - secondary use of data

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Abstract

Background:

Electronic prescribing (EP) and electronic hospital pharmacy (EHP) systems are increasingly common. A potential benefit is the extensive data in these systems that could be used to support antimicrobial stewardship, but there is little information on how such data are currently used to support the quality and safety of antimicrobial use.

Objectives:

To summarise the literature on secondary use of data (SuD) from EP and EHP systems to support quality and safety of antimicrobial use, to describe any barriers to secondary use, and to make recommendations for future work in this field.

Methods:

We conducted a systematic search within four databases; we included original research studies that were (1) based on SuD from hospital EP or EHP systems, and (2) reported outcomes relating to quality and/or safety of antimicrobial use, and/or qualitative findings relating to SuD in this context.

Results:

Ninety-four full-text articles were obtained; 14 met our inclusion criteria. Only two described interventions based on SuD; seven described SuD to evaluate other antimicrobial stewardship interventions, and five described descriptive or exploratory studies of potential applications of SuD. Types of data used were: quantitative antibiotic usage data (n=9 studies); dose administration data (n=3) and user log data from an electronic dashboard (n=1). Barriers

included data access, data accuracy and completeness, and complexity when using data from multiple systems or hospital sites.

Conclusions:

Literature suggests that SuD from EP and EHP systems is potentially useful to support or evaluate antimicrobial stewardship activities; greater system functionality would help realise these benefits.

Introduction

Increasing antimicrobial resistance is a global phenomenon, mainly attributable to increases in antimicrobial consumption in human, veterinary and agricultural sectors. Public health bodies worldwide advocate the use of antimicrobial stewardship programmes as a strategy to help combat antimicrobial resistance and curb the selection and proliferation of resistant micro-organisms. Monitoring antimicrobial consumption is a key component of these strategies.[1-4]

The UK Five Year Antimicrobial Resistance Strategy 2013-2018[5] lists seven key areas that need to be addressed to tackle the burden of antimicrobial resistance, one of which, '*optimising prescribing practice*', includes as a priority '*identifying the optimum arrangements for recording and reporting of data (including the use of electronic prescribing), as well as analysis of data on antibiotic use, resistance and clinical outcomes'*. Other large-scale antimicrobial stewardship programs in the US and UK similarly promote the use of information technology to help monitor antimicrobial usage.[1,6]

A potential benefit of both electronic prescribing (EP) and electronic hospital pharmacy (EHP) systems is that data on medication use is recorded as part of the system, creating the potential for secondary use of data (SuD) to understand, monitor and subsequently improve antimicrobial use. Although likely to support antimicrobial stewardship, little is known about the extent to which this potential benefit has been realised. Previous systematic reviews have focussed on the benefits of using EP to reduce medication errors and adverse drug events[7-10] and on the use of clinical decision support systems (CDSS) to support antibiotic use.[11] A more recent review focused on the effectiveness of information technology in general in improving hospital antimicrobial prescribing but did not specifically include SuD.[12] Another focused on hospital EP systems in promoting appropriate use of antibiotics but examined

only experimental studies published since 1997, most of which involved prompts and reminders aimed at individual patient care.[13] The authors of this study specifically highlight the need to more thoroughly explore interventions that draw on SuD as these are likely to present the biggest returns on investment.[13] No systematic review has explored the use of data from EP and EHP systems for antimicrobial stewardship.

Our objectives were to review the literature on SuD from EP and EHP systems to support quality and safety of antimicrobial use in the hospital setting, to describe any barriers to secondary use, and to make recommendations for future work in this field.

Methods

Search Strategy

Our search strategy was based on four facets: (1) electronic data systems and surveillance, (2) anti-infectives, (3) quality and safety, and (4) hospitals. Following piloting of the sensitivity and specificity of various search strategies, we used Medical Subject Headings and keywords for each of the four facets based on the following Boolean logic: (1 AND 2 AND [3 OR 4]) OR ("*secondary use adj4 data*"). The final search term was used to help capture articles that focused on SuD but may not have included the other search terms.

One researcher (NC) conducted the search on 15 August 2014 using the following databases: International Pharmaceutical Abstracts, Cumulative Index to Nursing and Allied Health Literature, Medline, and Excerpta Medica (Embase). The full search strategies used for each database are provided in Table S1.

Inclusion and exclusion criteria

We defined SuD as "*the reuse of aggregated electronic (clinical or operational) data from an electronic prescribing or electronic hospital pharmacy system for purposes other than direct patient care or for its original purpose,*" (Chaudhry et al 2016, unpublished data).

We included any original research based on SuD from EP and/or EHP systems that included antimicrobial data and reported safety and/or quality outcomes relating to antimicrobials, and/or qualitative findings relating to SuD, in the hospital setting. We were primarily interested in evidence supporting the effectiveness of interventions based on SuD, but also more broadly in how data from EP and EHP systems were being used to support antimicrobial stewardship. Reviews, conference proceedings, letters and opinion papers were excluded, as were studies based on paper-based prescribing or databases other than EP or EHP. There were no limits by study design, year or country. Table S2 presents full inclusion and exclusion criteria.

Study selection

One researcher (CM) screened titles and abstracts (or titles only if abstracts were unavailable) to identify those for potential inclusion. A sample of the titles and abstracts (n=50) were then screened by a second (NC) and third reviewer (BDF) and any disagreements resolved through discussion. For final study selection, the full-text papers were assessed by the primary reviewer (CM) and those recommended for inclusion plus, any for which there was any uncertainty were screened independently by NC and BDF. Reference lists of full-text papers selected for inclusion were screened to identify any further eligible studies.

Data extraction and analysis

An electronic data collection form was completed by CM for each included study. Extracted data comprised: data collection period, country and setting, type of study, aim/objectives, EP

/ EHP system, how the data were extracted and used, methods, and main outcomes. Data from each study were then extracted to inform a descriptive analysis; the anticipated heterogeneity of the studies precluded meta-analysis. In addition, any reported barriers to effective SuD were documented. Data extraction was checked by BDF and any discrepancies resolved via discussion.

The review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[14] The protocol was registered with the PROSPERO international prospective register of systematic reviews (registration CRD42016042955).

Results

Initial screening of titles and abstracts yielded 233 records from a total of 2,331 de-duplicated titles/abstracts. Following review by NC and BDF, 92 were identified for full-text review. Full-text screening of these 92 papers resulted in twelve that met our inclusion criteria. Reasons for exclusion are provided in Figure 1. Two further studies were identified from manual review of reference lists, giving a total of fourteen included studies (Table 1).

Characteristics of included studies

Of the fourteen studies, only two described interventions based on SuD,[15,16] one was an uncontrolled before-and-after evaluation of an antimicrobial audit and feedback intervention and one tested four sequential interventions, one of which involved real time clinical data dashboards, using interrupted time series analysis (also based on SuD). Seven described the reuse of EP/EHP data to evaluate other interventions[17-23] and five described descriptive or exploratory studies of SuD[24-28]. Of the seven evaluative studies, one evaluated a randomised

controlled trial,[17] four were uncontrolled before-and-after studies,[18-20,21] two were time series studies[16,23] and one a descriptive evaluation.[21] We did not identify any qualitative studies that met our inclusion criteria.

The majority of studies (eight)[17-22,25-26] were conducted in the USA. Three were from the UK,[16,23,27] and one each from Germany,[24] South Korea[28] and Australia.[15] The majority (eleven) were single-centre studies.[15-24,28] Three specifically focused on paediatric hospitals.[19-20,25]

Type of data used

Most studies included only antimicrobials; three included other drugs but separately reported antimicrobials.[16,21,28] There was wide heterogeneity between studies in how data were generated and from which systems (Table 1). Ten used data from EP systems, one from an EHP system, and three from both. Of the 14 studies, four combined data from EP and/or EHP systems with other electronic data: from the hospital information system,[18, 28] laboratory system[25,28] and an automated dispensing machine.[18] Two further studies additionally used data from handwritten records.[15,22]

The types of data used fell into three categories: 1) antibiotic prescribing or usage data (nine studies), 2) dose administration data (three studies), and 3) user log data (one study).

Antibiotic usage data

One of the two interventions based on SuD was an Australian study[15] that used data generated from an EP system to audit doctors` antimicrobial prescribing choices according to local guidance and provide feedback to prescribers; the study did not reveal any significant change in prescribing practice. Others used EP and/or EHP systems to obtain data such as numbers of antimicrobial medication orders, dispensing volumes, course durations and doses,

either to evaluate interventions (all US studies),[17-20] or to explore the use of the data for benchmarking or quality improvement, with studies from USA,[25-26] Germany[24] and South Korea.[28]

Dose administration data

The second study that evaluated an SuD intervention was a UK study of four sequential interventions, one of which involved a real time dashboard showing omission rates for antibiotics, non-antibiotics, and dietary supplements, plus weekly feedback emails. Introduction of the dashboard was associated with a significant reduction in the level ($p=0.001$) and trend ($p<0.001$) for antibiotic dose omission rates, using segmented regression analysis.[16] A second UK study used EP data to explore use of antimicrobial dose omission data for benchmarking among hospitals.[27] Two further studies focused on delays in dose administration and evaluated interventions to reduce time to administration of MRSA-decolonizing therapy in a UK hospital[23] and to reduce time to first dose of intravenous antimicrobials in a US hospital.[22]

User log data

A US study[21] made use of user log data to evaluate how real-time surveillance dash-boards for high-risk medications (including aminoglycosides) were being used by pharmacists to inform clinical practice.

Barriers

Several studies[15,21,22,24,26-28] suggested that data extraction was sometimes a complex or tedious process, often requiring informatics specialists, and that quality and completeness of information input into electronic systems was critical.[15,21,24-25] The available data may not include all the information required, such as data required to assess outcomes or

appropriateness.[16,17,24] Authors noted that systems were often localized, and so studies may not be generalizable to other hospital settings.[21,23] Two studies took place across multiple sites with different EP systems; this contributed to increased complexity and additional data validation requirements.[26-27] Baysari et al[15] specifically recommended that vendors of EP systems could do more to facilitate generation of SuD from their systems.

Discussion:

Key findings

We identified fourteen relevant studies, only two of which described interventions based on SuD.[15,16] Others were descriptive or exploratory studies of SuD or used SuD to evaluate other interventions and suggest potential benefits in using such large datasets. Studies suggest that data extraction from EP and EHP was not straightforward, may require linkage of data from more than one system, and may be further limited by the quality of clinical information entered.

Comparison with previous literature

Previous ethnographic research[29,30] has studied SuD for the purposes of driving improvements in quality and safety in healthcare more generally. One paper[29] describes a study of an organisation that used SuD from an EP system to obtain real-time information on a variety of quality indicators and generate intelligence on performance of individuals, teams, and clinical services, as well as to identify and evaluate interventions. Measures such as the prevalence of omitted doses showed marked improvement. Potential unintended consequences were identified, including the risk of focusing attention on aspects of patient safety made visible by the system at the expense of less measurable issues. This issue was not

identified in our review, most likely due to different types of SuD and lack of studies using qualitative methods. A second study[30] identified that extra work was required for SuD, with ambiguity over who should be responsible for this extra work. While we identified that generation of useful data requires significant investment, appropriate infrastructure and dedicated informatics specialists, ambiguity around responsibility was not specifically identified, again likely to reflect the types of study included.

Strengths and limitations

Strengths include use of a systematic approach,[14] including independent review of each stage of screening and data extraction. Limitations include the wide range of terms used in relation to SuD; this may account for two of the included studies[17,22] being identified from reference lists of other publications and it is therefore possible that we missed further papers in our search. Other studies included insufficient detail as to how data were generated and had to be excluded.[31-33] International variation in terminology and practice around EP and EHP systems also introduced challenges in interpreting the literature although we believe we were able to address these through the combined experience of our team. We did not formally assess risk of bias in included studies due to the heterogeneous nature of included studies and the paucity of interventions based on SuD. We did not identify any qualitative studies that met our inclusion criteria.

Implications for practice

National Institute for Health and Care Excellence (NICE) guidance on antimicrobial stewardship,[34] which applies to England and Wales, lists EP as a specific area needed to drive quality improvement. Our work has identified that data suitable for secondary use is currently being generated from EP (and EHP) systems in hospital settings and is being used to identify areas for quality improvement and to monitor the impact of antimicrobial stewardship

initiatives. However, the best approaches to SuD are not yet clear. While the primary functions of EP/EHP systems receive considerable attention from vendors and implementation teams, the difficulties and challenges that some authors report in obtaining data for secondary use highlight the need for potential secondary uses to be considered. Data quality at point of input also constrains downstream opportunities for effective SuD, suggesting a need for local commitment to accurate data entry and quality assurance. Adequate investment in health service infrastructure (including informatics specialists) is required, with consideration to a whole healthcare economy approach. This may include linkage with other systems to aid assessment of antimicrobial choice.

Implications for research

We found that there is a lack of robust evidence around SuD as an intervention to improve antimicrobial stewardship; we found only two studies that tested intervention based on SuD, one of which demonstrated benefits in the outcome measure assessed[16] and one of which did not[15]. There is therefore an urgent need for the public health and research community to target this topic, as currently very little information is available to help define, develop and implement interventions using SuD. Future evaluation of SuD interventions should include use of qualitative and mixed methods designs, in order to understand mechanisms and processes governing effective reuse of data, including enablers as well as barriers and the effects of local organisational context, in addition to impact upon outcomes.

Conclusions:

Our study suggests that the current paucity of evaluative interventional evidence may be due to immaturity in secondary use functions in current systems, which in turn hinders replication and evaluation of SuD for antimicrobial stewardship. SuD from EP and EHP systems may be useful to support or evaluate antimicrobial stewardship interventions in hospital settings.

However, SuD is often a complex process, especially where multiple systems are used, necessitating informatics specialists and careful consideration of data quality. Greater system functionality may also help realise the benefits. Studies of antimicrobial stewardship interventions based on SuD are lacking, representing a key area where future research is needed.

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388 **Table 1: Summary of included studies**

Study reference	Study setting	Study design, brief details and outcome measures where relevant	Data used, system(s) from which obtained, and purpose of use	Main findings
Shojania et al, 1998[17]	720 bed tertiary teaching hospital, USA	Evaluation of randomised controlled trial of an intervention to improve vancomycin prescribing based on display of vancomycin guidelines within an EP system. Evaluation included uncontrolled before-and-after comparison of primary outcome measures (number and duration of vancomycin orders) and interrupted time series analysis of secondary outcome measures (number of patients who received at least one dose of vancomycin; amount of vancomycin dispensed), using retrospectively obtained data.	Data from **hospital pharmacy system** and **EP system** (not specified) used to **evaluate** the effectiveness of the intervention over the 9 month study period.	The intervention resulted in a significant reduction in vancomycin use, with fewer orders and shorter duration of use. The authors highlight a key limitation in that the data used to evaluate the effectiveness of the intervention did not allow assessment of appropriateness of use, nor identification of any adverse outcomes.
Botwin et al, 2001[18]	500 bed teaching hospital, USA	Uncontrolled before and after study of an intervention aimed at reducing the duration of surgical prophylaxis, based on restricting nurses' access to automated dispensing machines. Evaluated with uncontrolled before-and-after comparison using retrospectively obtained data to assess effect on outcome measure (compliance with policy)	Data from the **hospital pharmacy system** (Digimedics) on course duration, together with data from Pyxis automated dispensing machines and hospital information system, used to **evaluate** the effectiveness of the intervention, with three months' data extracted pre-intervention and a further three months' data post-intervention.	The 24hr stop-order policy for prophylactic antimicrobials was complied with in 31% of 137 cases pre-intervention and 63% of 146 cases post-intervention, representing significant improvement. No specific findings reported relating to the practicalities of secondary use of data for these purposes
Hartmann et al, 2004. [24]	14-bed adult surgical ICU at a university hospital, Germany	Retrospective descriptive analysis of data to explore feasibility of use for clinical audits and quality improvement as well as to explore whether using antibiotic therapy as a surrogate for infection correlates with mortality.	Patient data management system used as an electronic patient record for surgical ICU patients, which included both **EP** and electronic medication administration records. Retrospective **exploratory study**, using 15 months' data on drug administrations, and the number and duration of courses, to explore how these data could be used.	Of a total of 2,053 patients, 58.0% received antibiotics, with 36.7% receiving one antibiotic, 14.1% two antibiotics and 7.2% three or more. Duration of antibiotic (OR 1.46) and number of antibiotics used (OR 2.15) significantly correlated with hospital mortality. Data interpretation was limited by the data being truncated if patients were transferred from the ICU to another ward, and by no data being recorded on indications for the antibiotics (e.g. prophylaxis, empirical or organism-specific treatment).
Voit et al, 2005. [25]	Children's hospital, USA, plus three matched hospitals	Retrospective descriptive cohort study of 1,493 children who underwent 1,630 inpatient surgical procedures during a one-year period, together with comparison to similar data obtained from three matched children's hospitals, to identify opportunities for improving compliance with surgical prophylaxis protocols as the outcome measure.	Data on administration and duration of antibiotics obtained from **EP** system (Meditech), plus patient and laboratory data from a second hospital system, and merged to create an electronic surveillance system. Data for a sample of 201 children were validated by chart review. Equivalent details not given for the three matched hospitals. Retrospective **exploratory study**, using a year's data, of whether these data could be used for quality improvement.	Surgical antibiotic prophylaxis was not compliant with national guidance for nearly half of all procedures, most commonly involving prolonged antimicrobial administration in clean surgical procedures. Overall, 90% of procedures that were classified by the electronic surveillance system as opportunities for improvement at the index hospital were confirmed by medical chart review, suggesting reasonable validity. It was noted that antimicrobials may be used for indications that could not be captured by the dataset available, thus limiting the validity of the data.

Study reference	Study setting	Study design, brief details and outcome measures where relevant	Data used, system(s) from which obtained, and purpose of use	Main findings
Sheen et al, 2008.[28]	1,080 bed tertiary teaching hospital, South Korea	Retrospective, descriptive study of prescription and laboratory data for 56 drugs (including antimicrobials among other drugs) that may require dose adjustment in renal insufficiency.	Four years' data on drugs and doses obtained from **EP** system (not specified), together with data from laboratory system and hospital information system, and collated in a 'data mart'. Retrospective **exploratory study**, with data used for descriptive analysis of overdose rates and identification of factors associated with overdose.	A total of 28,954 patients were evaluated; 22,981 (5.3%) overdoses were identified from 431,991 medication orders for drugs that require dose adjustment in renal insufficiency. Of the 20 most frequently overdosed drugs, 13 were antimicrobials. Amoxicillin had the highest overdose rate (71.9% of all medication orders for amoxicillin were classed as overdoses, accounting for 6.9% of all overdoses), followed by piperacillin-tazobactam (10.3%; 6.9%) and cefotetan (9.8%; 5.4%). It was noted that the secondary use of data allowed analysis of a very large dataset; limitations included that the dose administered may have differed from the dose prescribed but the database captured only the latter.
Di Pentima et al, 2010.[19]	180 bed paediatric tertiary care teaching hospital, USA	Uncontrolled before and after study of a suite of antimicrobial stewardship interventions aimed at reducing vancomycin use and vancomycin prescription errors. Effect on these two outcome measures evaluated using retrospectively obtained data.	Data from **EP** system (Cerner) used to **evaluate** the effectiveness of the intervention. Four years' data (one year baseline and three years' post-intervention) obtained and used to assess monthly density of antimicrobial use, calculated as doses administered per 1,000 patient-days per year.	Vancomycin utilisation significantly decreased from 378 doses administered per 1,000 patient days to 255 doses per 1,000 patient days in the last year of the study, representing a significant improvement despite an increase in *S.aureus* infections. The decrease in vancomycin use was not associated with increases in any other antibiotics. The rate of vancomycin prescribing errors also decreased. No specific findings relating to the secondary use of data for these purposes.
Di Pentima et al, 2011.[20]	180 bed paediatric tertiary care teaching hospital, USA	Uncontrolled before and after study of a suite of antimicrobial stewardship interventions. Effect on compliance with antimicrobial stewardship recommendations evaluated using retrospectively obtained data.	Data from **EP** system (Cerner) used to **evaluate** the interventions. Data used to calculate annual data on doses administered per 1,000 patient-days over a six year period (three years baseline and three years post-intervention).	Rate of compliance with antimicrobial stewardship recommendations increased from 83 to 92% of interventions over three years. Total antimicrobial use peaked at 3,089 doses per 1,000 patient-days per year pre-intervention and decreased to 1,904 doses per 1,000 patient-days per year post-intervention. Authors noted as a limitation the lack of a standard metric for measuring antimicrobial use in children.
Schwartz et al, 2011. [26]	ICUs from four academic medical centres, USA	Retrospective descriptive study with the aim of deriving and validating uniform ICU antimicrobial utilization measures based on computerized data. Electronic data were obtained and compared with observation and manual review of medication administration records to assess validity.	Antimicrobial use data obtained from different systems: Hospital A: **hospital pharmacy system** and then **EP** data; Hospital B: data extracted from eMAR Hospital C: **hospital pharmacy system** Hospital D: EP data **Exploratory study** of data use for benchmarking, based on 36 months' data.	Bedside observations revealed more than 95% concordance between observed dose administrations and eMAR records. Comparison between manual record review and computerised data showed over-estimations in antimicrobial days and patient days on antimicrobials ranged from < 1% to 17.7% among study hospitals. The hospital for which numerator data were derived from eMAR had the least discrepant results. Programming of antimicrobial utilisation measures based on computerised pharmacy and administrative data was complex and error-prone. Problems commonly related to misunderstandings between programmers and investigators. The study highlights the complexity of generating reliable data from a diverse set of electronic medication systems. For example, eMAR data were available in a format amenable to analysis only at hospital B, which was able to distinguish antimicrobial doses that were administered from those that were ordered but not administered.

Study reference	Study setting	Study design, brief details and outcome measures where relevant	Data used, system(s) from which obtained, and purpose of use	Main findings
Waitman et al, 2011. [21]	University medical centre, USA	Retrospective descriptive evaluation of a real-time monitoring and surveillance tool designed to identify patients at increased risk of an adverse drug event. Includes analysis of 869 patients on aminoglycosides during a six month study period (as well as patients receiving warfarin and heparin/enoxaparin). Outcome measures based on pharmacist review of at-risk patients.	Six months' user log data obtained from **EP** (not specified) and used to evaluate the effectiveness of the surveillance tool in a **descriptive evaluation**.	23 of 51 pharmacists used the aminoglycoside dashboard, which had a higher usage rate than those for warfarin and heparin/enoxaparin. All patients on aminoglycosides were reviewed at least once with a mean of 8 reviews per case. Pharmacists generated comments for 100% of aminoglycoside patients, with more than three comments per case. Pharmacy comments were detailed, often summarizing patient, order and laboratory data. There were frequent interventions with relevant documentation reflecting the action taken. A limitation of the evaluation was that some pharmacists' interventions may not have been documented and therefore could not be analysed.
Panosh et al, 2012 [22]	Adult patients admitted to cardiology, oncology or general medicine in a university hospital, USA	Retrospective uncontrolled before and after study to evaluate the impact of introducing a direct 'closed loop' link between an EP system and a pharmacy order-entry system on the time to administer initial doses of intravenous antimicrobials. Evaluated using retrospectively obtained data.	Data on the time of order entry were obtained retrospectively from the **hospital pharmacy system** (Horizon Meds Manager), based on data in the **EP** system (Horizon) and compared with handwritten administration times documented on medication administration records to **evaluate** the intervention. Used five months' data pre-intervention and five months' data post-intervention.	Introduction of the closed loop link reduced the mean time to administration from 3.2 to 2.0 hours, representing a significant improvement. Limitations included: (1) handwritten antimicrobial administration times were sometimes documented in broad terms e.g. 8am, 1pm rather than precise times; (2) documented administration times may not represent the time medication arrived from pharmacy; (3) they did not exclude doses administered in emergency department or as prophylaxis as this would have entailed the evaluation of data from multiple computer systems.
Baysari et al, 2013[15]	320 bed teaching hospital, Australia	Uncontrolled before-and-after study of an audit and feedback intervention based on secondary use of data, exploring impact on compliance with antimicrobial policy relating to prescribing of restricted antimicrobials.	Prescribing data (dose, duration, prescriber details) for selected restricted antimicrobials obtained from **EP** system (MedChart); data obtained each week, for the previous week, for 12 weeks, and used as part of the **audit and feedback intervention**. Evaluated using data on compliance with local antimicrobial policy and interviews with feedback recipients.	No significant change in antimicrobial policy compliance following implementation of the intervention (0% of 20 relevant antibiotics had approval pre-intervention, and 11.9% of 101 post-intervention). Interviews revealed various practical problems with the policy. Determining the indication for each antimicrobial proved to be challenging as prescribers rarely documented indications for use. It was noted that data extraction was not easy and that greater system functionality was required to enable data to be extracted for real time review and feedback.
Carruthers et al, 2013[27]	Three hospitals with 1234, 424 and 1472 beds respectively, UK	Descriptive time series analysis of data on omitted doses of antibiotics in three hospitals using EP.	One year's data extracted retrospectively from each of the three **EP** systems (Hospital 1: locally developed Prescribing Investigation and Communications System; Hospital 2: Meditech; Hospital 3: JAC). **Exploratory study**; data used for benchmarking.	The rate of omitted antibiotic doses ranged from 5.9% of 448,716 prescribed doses in one hospital to 10.3% of 573,538 in another. The percentage of missed doses with no recorded reason varied from 26.7% at one hospital to 61.7% at another. The study demonstrated that large data sets from different EP and medicines administration systems can be used to quantify the incidence of omitted antibiotic doses. A limitation is that some clinical areas in the study hospitals did not use EP.

Study reference	Study setting	Study design, brief details and outcome measures where relevant	Data used, system(s) from which obtained, and purpose of use	Main findings
Coleman et al, 2013 [16]	1200 bed teaching hospital, UK	Retrospective time-series analysis of data on omitted doses of all medications; four sequential interventions introduced.	239 weeks' data on omitted doses extracted retrospectively from **EP** (locally developed Prescribing Investigation and Communications System). Data for antibiotics presented separately. Data used to **evaluate** a series of four sequential interventions, one of which was based on secondary use of data and involved a **real time dashboard intervention** showing omission rates for antibiotics, non-antibiotics, and dietary supplements, plus weekly feedback emails.	Omission rates for antibiotics reduced from 10.3 to 4.4% of doses over the period of the study, a reduction of 57% ($p<0.001$). Introduction of the dashboard was specifically associated with a significant reduction in the level ($p=0.001$) and trend ($p<0.001$) for missed antibiotic doses, using segmented regression analysis. Rates of omitted antibiotic doses also decreased significantly following the instigation of executive-led overdue doses root cause analysis meetings and the publication of an associated Rapid Response Alert. Implementing a visual indicator for overdue doses was not associated with a significant change. Limitations noted include possible documentation discrepancies and the inclusion of 'legitimate' omissions such as patient refusal in the dataset.
Brooks et al, 2014 [23]	1,200 bed teaching hospital, UK	Retrospective time series analysis of time between hospital admission and first administration of MRSA decolonisation therapy for patients colonised with MRSA.	Six years' data on time of administration of MRSA decolonization therapy obtained retrospectively from **EP** (locally developed Prescribing Investigation and Communications System). Data used to **evaluate** any changes following various national and local interventions.	Of a 1,403 identified cases, 94% had the time of hospital admission and time of first administration of MRSA decolonisation therapy documented. Significant decrease of 15% per year (95% CI: 11.1-18.7%) in time from patient admission to administration of decolonisation treatment for MRSA positive patients. It was noted that MRSA bacteraemia cases had to be excluded as a result of differences in the time needed for colonization and bacteraemia samples to be cultured in the laboratory.

Studies are presented in chronological order. Abbreviations: eMAR: electronic medication administration record; CI: confidence interval; EP: electronic prescribing; ICU: intensive care unit; VRE: vancomycin-resistant *Enterococci*

393 **Figure 1: PRISMA flow chart**

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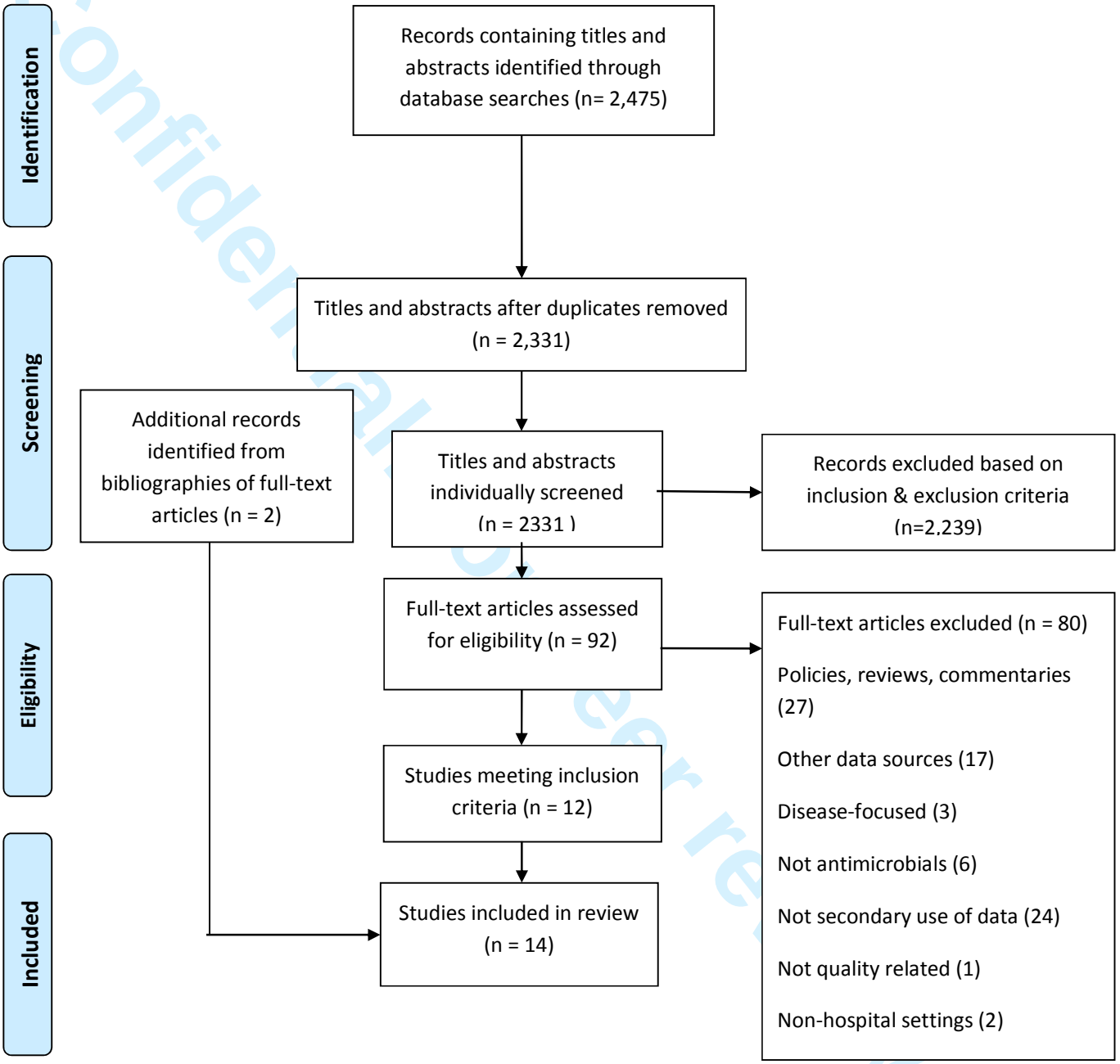

Table S1: Keywords used for search strategy in all 4 databases (NB: 'adj' function used in Medline and Embase only, for IPA and CINAHL 'adj' was substituted with 'N')

Keywords in 4 different databases:				
Facet:	**Keywords used:**	**Number of articles retrieved from Embase and Medline**	**Number of articles retrieved from Cinahl**	**Number of articles retrieved from IPA**
Facet 1: Electronic data systems and surveillance	Secondary* data* or Secondary* use* or Secondary* adj4 data* or secondary* adj3 EHR* or secondary* adj3 electronic* health* record*.	63,778	17,643	13,280
	Surveillance* adj3 information* system* or ((computer* or electronic*) adj3 (detect* or surveillance*)) or Medication* adj1 monitor* or Medicine* adj1 monitor* or Technovigilance* or Computer* adj4 surveillance* or Computer* adj4 monitor*			
	Electronic* prescri* or E-Prescri* or ePrescri* or prescri* adj3 data* or Decision* support* system* or Computer* prescri* support* system* or Computer* adj3 prescri* or electronic* adj3 prescri* or Automat* prescri* or Prescri* automat* screen* system*			
	Computer* information* or Computer* adj4 Adverse* drug* or Computer* adj4 patient* information*			
	Computer* physician* decision* support* or CPOE or Computer* physician* order* or physician* order* entry* or Computer* provider* order* or provider* order* entry* or Computer* prescriber* order* or prescriber* order* entry* or Computer* prescription* order* or prescription* order* entry* or Medication* order* entry* or Medicine* order* entry* or drug*order* entry*			
	dispen* adj2 data* or Hospital* dispen* or Pharmacy* adj2 dispen* or Clinic* adj2 information* system* or computer* pharmacy* record*			
	Electronic* medication* adj1 administration* record*or			

	Electronic* medication* adj1 administration* system* or Electronic* drug* adj1 administration* record* or Electronic* drug* adj1 administration* system* or administration* data* or Medication* administration* system* or EPMA* or EMAR*			
	hospital* computer* program* or hospital* information* system* or hospital* data* or electronic* health* record* or electronic* clinical* system* or pharmacy* computer* system*			
	(Electronic* or computer*) adj2 discharg* or ((electronic* database*) and (clinical* data*))			
	((pharmacy* or medication* or medicine*) adj1 (system*or data*) and (monitor* or access* or assess* or surveillance* or vigilance* or collect* or review* or identif* or analys* or examin* or investigat* or intervention* or compare*))			
Facet 2: Anti-infective	Healthcare* associa* infection* or health* care* associa* infection* or healthcare* relat* infection* or health* care* relat* infection* or hospital* associa* infection* or hospital* relat* infection* or hospital* acquire* infection* or anti-microbial* or antimicrobial* or antibiotic* or anti-infective* or anti* infective* or anti-viral* or anti* viral*	754,021	36,245	39,164
Facet 3: Quality and safety	quality* adj2 safety* measurement* or quality* adj2 healthcare* or quality* adj2 health* care* or quality* improvement* or patient* safety* or (improv* quality* adj2 (efficiency* or care* or safety*)) or improv* care* or Prevent* adj2 harm* or Reduc* adj2 harm* or Safety* adj1 Improv*	121,858	95,547	10,713
Facet 4: Hospital	Hospital* or Tertiary* care* or Secondary* care* or acute* care* or Inpatient* or ward* or emergency* department* or secondary*	2,402,529	300,832	78,512

	healthcare* or tertiary* healthcare* or intensive* care* unit* or ICU or ITU or critical* care* unit*			
Facet 5:	(secondary* use* adj4 data*).ti,ab,kw.	221	19	1
Search combination	Facet combination: 1 and 2 and (3 or 4) or 5	**1121** (15/08/2014)	**269** (15/08/2014)	**707** (15/08/2014)

MeSH terms used for search strategy in Embase

EMBASE search:			
Facet:	**Boolean term used:**	**MeSH Term**	**Total number of articles found with each facet from 15/08/2014 search**
1). Electronic data systems and surveillance	OR	electronic prescribing/	Number of articles found after all the MeSH terms in facet 1 combined: **44,462**
	OR	computerized provider order entry/	
	OR	Electronic medical record/	
	OR	*hospital information system/	
	OR	*Decision support system/	
	OR	(medical audit/ or feedback system/) and (information system/)	
	OR	computer assisted drug therapy/	
2). Anti-infective	OR	Exp antiinfective agent/	Number of articles found after all the MeSH terms in facet 2 combined: **2,448,322**
	OR	Healthcare associated infection/	
	OR	Hospital infection/	
	OR	*infection/	
3). Quality and safety	OR	*Risk reduction/	Number of articles found after all the MeSH terms in facet 3 combined: **130,050**
	OR	*Healthcare quality/	
	OR	*Patient safety/	
	OR	Quality Improvement/	
	OR	*Risk management/	
	OR	*Risk assessment/	
4). Hospital	OR	hospital/	Number of articles found after all the
	OR	secondary health care/	
	OR	tertiary health care/	

	OR	Hospital discharge	MeSH terms in facet 4 combined: **451,936**
	OR	hospital patient/	
Search combination		[Facet 1 and facet 2 and (facet 3 or facet 4)]	**533**

MeSH terms used for search strategy in Medline

Medline search:			
Facets:	**Boolean term used:**	**MeSH Term**	**Total number of articles found with each facet from 15/08/2014 search**
1). Electronic data systems and surveillance	OR	Clinical pharmacy information systems/	Number of articles found after all the MeSH terms in facet 1 combined: **15,794**
	OR	Electronic prescribing/	
	OR	*Decision Support Systems, Clinical/	
	OR	Decision Making, Computer-Assisted/	
	OR	Drug Therapy, Computer-Assisted/	
	OR	(information systems/) and (clinical audit/ or Medical audit/ or feedback/)	
	OR	Medical order entry systems/	
	OR	Electronic Health Records/	
2). Anti-infectives	OR	community-acquired infections/ or cross infection/	Number of articles found after all the MeSH terms in facet 2 combined: **1,322,236**
	OR	Exp antiinfective agent/	
	OR	*infection/	
3). Quality and safety	OR	*Safety management/	Number of articles found after all the MeSH terms in facet 3 combined: **72,818**
	OR	*Quality of healthcare/	
	OR	*Patient safety/	
	OR	Quality Improvement/	
	OR	*Risk management/	
	OR	*Risk assessment/	
4). Hospital	OR	Hospitals/	Number of articles found after all the MeSH terms in
	OR	Secondary Care/	
	OR	Tertiary Healthcare/	
	OR	Inpatients/	

		Patient discharge/	facet 4 combined: **84,736**
Search combination		[Facet 1 and facet 2 and (facet 3 or facet 4)]	**41**

MeSH terms used for search strategy in CINAHL

CINAHL search:			
Facet:	**Boolean term used:**	**MeSH Term**	**Total number of articles found with each facet from 15/08/2014 search**
1). Electronic data systems and surveillance	OR	**Electronic order entry**	Number of articles found after all the MeSH terms in facet 1 combined: **10,359**
	OR	*Computerised patient record	
	OR	*Nursing information systems	
	OR	*hospital information systems	
	OR	Clinical pharmacy information systems	
	OR	(Audit or feedback) and information systems	
	OR	*decision support systems, clinical	
	OR	*data collection, computer assisted	
		Drug therapy computer assisted	
2). Anti-infectives	OR	MH "Antiinfective Agents+"	Number of articles found after all the MeSH terms in facet 2 combined: **121,409**
	OR	MH "Community-Acquired Infections+"	
	OR	MH "Cross Infection+"	
	OR	MH "Infection+"	
3). Quality and safety	OR	*quality of healthcare /	Number of articles found after all the MeSH terms in facet 3 combined: **64,390**
	OR	*Patient safety/	
	OR	Quality Improvement/	
	OR	*Risk management/	
	OR	*Risk assessment/	
4). Hospital	OR	Hospital units/	Number of articles found
	OR	secondary health care/	

	OR	tertiary health care/	after all the MeSH terms in facet 4 combined: **61,176**
	OR	Transfer discharge/	
	OR	inpatients/	
Search combination		[Facet 1 and facet 2 and (facet 3 or facet 4)]	**49**

Table S2: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Hospital focused research – includes inpatients, outpatients, and/or discharge. Also includes community hospitals and Outpatient Parenteral Antimicrobial Therapy from hospitals.	Any non-hospital based setting e.g. primary care, care/nursing homes (includes long-term care facilities), state agencies, clinical registries, clinical trials of drugs, out-of-hours centres, general practices and private offices (clinics).
Data used from electronic prescribing and/or hospital pharmacy data systems(s), either alone or in combination with other data. Electronic prescribing systems were taken to include the prescribing component of computerised prescriber order entry (CPOE) systems that may allow ordering of tests and treatment other than medication, as well as any medication administration data obtained from electronic prescribing systems.	Non-electronic surveillance/monitoring data collection methods Electronic databases looking at surveillance of diseases (including infectious diseases) and epidemiological investigations without any mention of antimicrobials, prevalence studies of diseases, human factors studies, links between two or more diseases, patient costs, animal studies, pharmacokinetic or pharmacodynamics studies, pharmacovigilance reports, studies of non-prescribed medication, post-marketing drug surveillance and electronic systems intended for non-healthcare professionals. If a study did not include information on how electronic data has been generated, then the study was excluded
Focuses on secondary use of data (defined as the reuse of aggregated electronic [clinical or operational] data from an electronic prescribing or electronic hospital pharmacy system for purposes other than direct patient care or for its original purpose).	The following were excluded: • Trigger tools * (includes electronic tools and alerts) • Bar code technologies, including Bar Code Medication Administration (BCMA) systems • Medical Devices, e.g. smart pumps, infusion devices, unit-dose systems, IV drug-delivery systems, being used for their primary purpose • Incident reporting systems (these fulfil their primary purpose which is to reduce errors and raise awareness, hence will be excluded in this systematic review) • Studies describing the development or evaluation of clinical decision support systems (CDSS) and alerts, in-built as part of the CDSS software. CDSS is defined as "*software that is designed to be a direct aid to clinical decision-making, in which the characteristics of an individual patient are matched to a computerized clinical knowledge base and patient-specific assessments or recommendations are then presented to the clinician or the patient for a decision*"**.However, any research articles which are based on the secondary use of data from CDSS/alerts systems which otherwise meet the inclusion criteria will be included. • Studies based solely on electronic hospital/pharmacy data being used for direct patient care, such as to identify lists of patents for clinical pharmacists' follow up, were excluded.
Original research conducted in any country	Papers that were not original research e.g. reviews, Conference Proceedings, Editorials, Case-reports, Book Chapters, Extracts, Notes (unless original research is presented), Case-studies at the individual patient level (case-studies on a hospital or similar level are included), Policy and opinion papers (includes commentaries), and letters to the Editor were excluded
Research papers available in English	Full text article unavailable in English
Includes data on ANTIMICROBIAL use (prescribing, administration, transcription, monitoring, dispensing, overall hospital use, antimicrobial safety/use in general) **Studies focusing on a wider range of medications are included, if data specific to one of more antimicrobials were reported separately**	Research that did not present data for antimicrobials
Quality outcomes measured in the study clearly defined AND/OR a qualitative study examining secondary use of data	None of the outcome measures are related to antimicrobial medication, use or safer use of antimicrobial medication
Research in adults and/or paediatrics and/or neonates and includes any aspect of prophylaxis and/or treatment with antimicrobials	

* where trigger tools are defined as the use of sets of triggers or 'clues', to identify patients who may have suffered adverse events (ADEs) either in real time or retrospectively. ** Adapted from Sim I, Gorman P, Greenes RA *et al*. Clinical decision support systems for the practice of evidence-based medicine. *J Am Med Inform Assoc*. **2001** ;8(6):527-34.

JAC-2016-1716

The secondary use of data from hospital electronic prescribing and pharmacy systems to support the quality and safety of antimicrobial use: a systematic review

COMMENTS to the Author	RESPONSES
Editor (Dr Hayley Wickens):	
Thank you for submitting this interesting review of published data on use of data from electronic prescribing and pharmacy systems; the paucity of information did not come as a surprise, but was somewhat disappointing. The paper is well-written and robust methodologically, and suitable for publication, subject to addressing the queries raised by the reviewers. I agree that Table 1 should remain in the main body of the paper, as it describes the findings and will be useful for readers.	Thank you for these positive comments We have left table 1 in the main body of the manuscript as suggested.
Supplementary Revision As mentioned in the revision e-mail sent by the Editor, Dr Wickens, (on 20th January 2017) **this document contains specific style requirements and editorial office comments**, which MUST be addressed when you prepare your revised paper.	
IMPORTANT ADVICE: By far the most common proof problems that we have to contact authors about concern a lack of consistency in the numbers of things (patients or isolates for instance) stated in different parts of the article (for example the Abstract might state that there were 46 isolates, but in Table 1 only 40 are listed and so on). Other common related faults are lists of items in the text or Tables that don't add up to the total that is stated, or percentages that don't match the numbers indicated. We understand that articles undergo many rounds of revision before submission and it is easy for these types of inconsistencies to creep in. Now is the best time to take a fresh look at your article, sit down with a calculator and check: (i) that everything is consistent throughout the Abstract, main text, Figures and Tables; (ii) that everything adds up to the correct totals; and (iii) that percentages are correct. **Please make good use of what may be your final opportunity to check your article and make any corrections or redraft portions of the text, Tables or Figures before resubmission. THIS IS EXTREMELY IMPORTANT AS EXTENSIVE OR TRIVIAL REDRAFTING OF ARTICLES AT THE PROOF STAGE IS NOT PERMITTED.**	We have read the paper carefully as advised.

Specific Comments Please move the Figure to the end of the article, after the Reference list and Table.	We have moved the figure as requested.
TITLE PAGE DETAILS AND ABSTRACT FORMAT On the title page, please: -give a short running title (<50 characters in total). -remove the keywords as JAC no longer requires these. -indicate the corresponding author in the list with an asterisk. **To** make it easier to index your article, please put family names of all authors in CAPITALS.	A running title has been added as requested. The keywords have now been removed. An asterisk has been added to indicate the corresponding author. The family names of all authors have been capitalised as requested.
REFERENCE CITATIONS References must be cited in the text in numerical order. Currently, your reference citations skip from 15 to 22.	We have amended the referencing to ensure that all are now given in numerical order.
MAIN TEXT OR & MRSA are allowed abbreviations.	We have removed the explanation of these two abbreviations from the paper.
ACKNOWLEDGEMENTS/FUNDING/CONFLICTS OF INTEREST **Please move the 'Acknowledgements' section to before the 'Funding' section.** **Transparency declarations:** Please note that the declaration MUST cover ALL the authors. You may need to add 'All other authors: none to declare' to achieve this. Please ensure that your Transparency declarations are still up to date. For more information please see the relevant section of our Instructions to Authors (http://www.oxfordjournals.org/jac/for_authors/index.html) for further details.	The acknowledgements section has been moved as requested. We have added this extra clarification to the transparency declaration and can confirm that this section remains up to date.
REFERENCES References to websites. Please check that the URL listed works and leads to the material you have indicated.	We have checked all URLs and can confirm that they are active (as at 25 January 2017)

FIGURES AND TABLES **Table formatting** Please note that Tables should not contain return characters that have been used to create line breaks. Each data item should be in a separate cell. If you have used return characters to create line breaks you will need to add rows to your Table in order to remove the return characters.	We have amended the table slightly to remove return characters.
Referee: 1:	
Interesting (and disppointing) finding that electronic prescribing and data systems might not be as useful as one would want them to be for secondary use of data. Did you identify the reasons why the 2 articles sourced from bibliography were missed in the searches? An explanation might fit in the limitations.	We agree that this was disappointing! It does however represent a considerable opportunity for research and development, which we emphasise in the paper. This is an interesting point; we suspect this relates to the diffuse terminology in this field. We have added a point to this effect in the strengths and limitations section; we have also indicated in the results section of the paper which two papers these were in order to aid transparency in this respect.
Line 191-200 appropriatness would need a reference to the indication for prescription so it should be highly recommended in any new EP software, right? This would help Sud, right? Unfortunately only 2 studies reported on interventions based on SUDs.	As well as the indication, an assessment of appropriateness is likely to need other information such as allergies, concomitant drugs (as anti-infective choices may depend on drug interactions) and concomitant co-morbidities. This is likely to need to go beyond a requirement for indication for anti-infectives prescribed using EP systems and will require data linkage between systems beyond EP and EHP systems; we have now highlighted in this in the discussion section. We already highlight the limitation that only two studies reported interventions based on SuD; we have now added the word “only” to make this more explicit.
In the coclusions and recommendations it might be reasonable to suggest that: 1; EP and EHP systems should be able to identify targets for quality improvement (Stewardship Targets) 2) EP and EHP systems should have algorithms, based on locally followed guidelines so that data entry is not free text so as to avoid missing or inaccurate or incomplete data entry. In addition the indication (diagnosis) should also ideally be part of the electronic prescription so as to allow for evaluation of appropriateness, right?	Thank you for these suggestions. 1) We have added a comment to this effect. 2) The included studies did not suggest that free text data entry was a problem, so while this would be a common sense recommendation, we do not feel that it is appropriate to make this point based on the evidence that we reviewed. We have responded to the point around evaluation of appropriateness above.
Referee: 2:	
I believe that this article is timely due to the current move to incorporate electronic prescribing data into hospital-based quality and safety initiatives. I have a couple of comments that maybe the authors could take into consideration.	Thank you for these positive comments.

I envision that healthcare professionals who would read this article would be interested in utilising secondary data as part of their antimicrobial stewardship programmes, therefore I would like to see some discussion about the enablers related to SuD presented as well as barriers. I think that it is important to present a balanced argument for readers who are interested in SuD.	We have added a recommendation that future work should explore the facilitators as well as barriers to secondary use of data.
Also, I understand that there is a restriction on the word count but I believe that some discussion on whether the types of data used in the studies were effective in improving antimicrobial stewardship in hospitals. For example, were there any positive changes in prescribing behaviour due to the SuD analysis? Were there any implications for implementing and sustaining good stewardship? I think that these points would of interest to those who would read this article.	This information is included within table 1. As highlighted, we found only two intervention studies that were designed to answer the question around whether secondary use of data is helpful; this information is presented in table 1 and in the text of the paper.