Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and *Clostridium difficile* infection: a systematic review and meta-analysis

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Summary

Background Antibiotic stewardship programmes have been shown to reduce antibiotic use and hospital costs. We aimed to evaluate evidence of the effect of antibiotic stewardship on the incidence of infections and colonisation with antibiotic-resistant bacteria.

Methods For this systematic review and meta-analysis, we searched PubMed, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, and Web of Science for studies published from Jan 1, 1960, to May 31, 2016, that analysed the effect of antibiotic stewardship programmes on the incidence of infection and colonisation with antibiotic-resistant bacteria and *Clostridium difficile* infections in hospital inpatients. Two authors independently assessed the eligibility of trials and extracted data. Studies involving long-term care facilities were excluded. The main outcomes were incidence ratios (IRs) of target infections and colonisation per 1000 patient-days before and after implementation of antibiotic stewardship. Meta-analyses were done with random-effect models and heterogeneity was calculated with the I^2 method.

Findings We included 32 studies in the meta-analysis, comprising 9 056 241 patient-days and 159 estimates of IRs. Antibiotic stewardship programmes reduced the incidence of infections and colonisation with multidrug-resistant Gram-negative bacteria (51% reduction; IR 0·49, 95% CI 0·35–0·68; p<0·0001), extended-spectrum β-lactamase-producing Gram-negative bacteria (48%; 0·52, 0·27–0·98; p=0·0428), and meticillin-resistant *Staphylococcus aureus* (37%; 0·63, 0·45–0·88; p=0·0065), as well as the incidence of *C difficile* infections (32%; 0·68, 0·53–0·88; p=0·0029). Antibiotic stewardship programmes were more effective when implemented with infection control measures (IR 0·69, 0·54–0·88; p=0·0030), especially hand-hygiene interventions (0·34, 0·21–0·54; p<0·0001), than when implemented alone. Antibiotic stewardship did not affect the IRs of vancomycin-resistant enterococci and quinolone-resistant and aminoglycoside-resistant Gram-negative bacteria. Significant heterogeneity between studies was detected, which was partly explained by the type of interventions and co-resistance patterns of the target bacteria.

Interpretation Antibiotic stewardship programmes significantly reduce the incidence of infections and colonisation with antibiotic-resistant bacteria and *C difficile* infections in hospital inpatients. These results provide stakeholders and policy makers with evidence for implementation of antibiotic stewardship interventions to reduce the burden of infections from antibiotic-resistant bacteria.

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Introduction

In view of the increasing number of infections caused by antibiotic-resistant bacteria, restriction of unnecessary antibiotic use and optimisation of infection control measures are of the utmost importance.[1,2] Strategies for optimal antibiotic use are highly recommended among measures to limit the increasing expansion of antibiotic-resistant bacterial populations at both hospital and community levels.[2–5] Antibiotic stewardship programmes include heterogeneous interventions, such as auditing, restriction of specific antibiotics, restriction of treatment duration, and antibiotic cycling or mixing.[6] The implementation of these measures has been shown to significantly reduce hospital costs and use of antibiotics.[7,8]

Four systematic reviews and meta-analyses have summarised the evidence of the effects of antibiotic stewardship programmes in hospital inpatients.[7,9–11] Feazel and colleagues[10] focused on *Clostridium difficile* infections and showed a reduction of 52% in the incidence of these infections after implementation of antibiotic stewardship, although with significant heterogeneity; the sources of heterogeneity were not explained. Schuts and colleagues[9] analysed the effect of 14 stewardship objectives. Implementation of six of these objectives (use of empirical therapy according to guidelines, de-escalation of therapy, switching from intravenous to oral treatment, therapeutic drug monitoring, restriction of antibiotics, and bedside

Research in context

Evidence before this study

We searched PubMed, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, and Web of Science from Jan 1, 1960, to May 31, 2016. We included studies analysing the effect of antibiotic stewardship programmes on the incidence of infection and colonisation due to antibiotic-resistant bacteria and *Clostridium difficile* infections among hospital inpatients, with the exclusion of long-term care facilities. The search terms used included ("antibiotic AND stewardship" OR "antibiotic AND intervention AND resistance") and ("meticillin/methicillin OR gram negative OR escherichia coli OR clostridium difficile OR ESBL OR extended-spectrum-beta-lactamase OR pseudomonas OR acinetobacter OR vancomycin OR enterococcus"). Reference lists of included studies were also screened. No restriction on study type was applied. Four systematic reviews analysed the effects of antibiotic stewardship programmes in hospital inpatients. Schuts and colleagues focused on clinical outcomes, adverse events, and costs. Karanika and colleagues analysed antimicrobial consumption and costs. The incidence of antibiotic resistance was analysed in seven studies reporting on both antibiotic consumption and resistance. Feazel and colleagues analysed the effect of antibiotic stewardship programmes on *C difficile* infections, but neither incidence rates nor incidence ratios were reported. Davey and colleagues focused on 20 interrupted time-series studies and found that antibiotic stewardship was associated with consistent reductions in the incidence of *C difficile* infections but inconsistent effects on antibiotic-resistant bacteria.

Added value of this study

This systematic review and meta-analysis showed, for the first time, the effectiveness of antibiotic stewardship programmes in reducing the incidence of infections and colonisation due to multidrug-resistant Gram-negative bacteria, extended-spectrum β-lactamase (ESBL)-producing Gram-negative bacteria, meticillin-resistant *Staphylococcus aureus*, and *C difficile*. The effect was increased in haematology-oncology settings and if antibiotic stewardship was co-implemented with hand-hygiene improvement measures.

Implications of all the available evidence

This meta-analysis provides stakeholders and policy makers with evidence for the effectiveness of antibiotic stewardship programmes in reducing the incidence of infection and colonisation with antibiotic-resistant bacteria, in particular ESBL-producing and carbapenem-resistant Gram-negative bacteria. The evidence of increased effect when co-implemented in association with interventions targeting hand hygiene provides important information for new antibiotic stewardship programmes.

consultation) was associated with significant benefits in terms of clinical outcomes, adverse events, and costs. In particular, guideline-adherent empirical therapy was associated with a relative risk reduction of 35% for mortality.[9] Karanika and colleagues[7] focused on five antibiotic-resistant bacteria in seven studies and showed significant reductions in the absolute risk differences for meticillin-resistant *Staphylococcus aureus* (MRSA), imipenem-resistant *Pseudomonas aeruginosa*, and extended-spectrum β-lactamase (ESBL)-producing *Klebsiella pneumoniae*. That study[7] did not analyse the incidence of infection, and the overall percentage change in infection rates among studies was not significant. Davey and colleagues[11] analysed 20 interrupted time-series studies and reported a significant reduction in risk of 49% for *C difficile* infections and non-significant reductions in risk of 13% for resistant Gram-negative bacteria and 19% for resistant Gram-positive bacteria.

Despite the importance of antibiotic resistance, the effect of antibiotic stewardship programmes on the incidence of antibiotic-resistant bacteria has not yet been systematically reviewed. The primary goal of this systematic review and meta-analysis was to determine the effectiveness of antibiotic stewardship in reducing the incidence of infections and colonisation with antibiotic-resistant bacteria and that of *C difficile* infections in hospital inpatients.

Methods

Search strategy and selection criteria

We did a systematic literature review and meta-analysis of the effectiveness of antibiotic stewardship programmes in reducing the incidence of antibiotic-resistant bacterial infections and colonisation in hospital inpatients, in accordance with PRISMA recommendations.[12] We searched PubMed, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, and Web of Science from Jan 1, 1960, to May 31, 2016, with the search terms "antibiotic AND stewardship" OR "antibiotic AND intervention AND resistance" and "meticillin/methicillin OR gram negative OR escherichia coli OR clostridium difficile OR ESBL OR extended spectrum beta-lactamase OR pseudomonas OR acinetobacter OR vancomycin OR enterococcus" (appendix). We also searched the reference lists of retrieved articles. No study type or language restriction was applied. Two authors (DB, FF) independently assessed the eligibility of trials and extracted data. In the case of disagreement, a third author (ET) was consulted. Inclusion and exclusion criteria were established a priori. Studies reporting (or for which the authors, when contacted, were able to provide) the number of events (ie, resistant infections, colonisation) and patient-days were included in the meta-analysis and systematic review. Studies reporting interventions in the community

See Online for appendix

or in long-term care facilities and nursing homes were excluded.

Data analysis

Information collected included author, corresponding author, country, year of publication, year of study, study duration, type of study, setting, and population. Information collected about the intervention included description of the antibiotic stewardship programme (objectives, outcomes, components, and duration); type or class of antibiotics; antibiotic-resistant bacteria targeted; results before and after the intervention, according to the authors' outcome definitions; incidence of infections and colonisation with the targeted antibiotic-resistant bacteria; and total patient-days. When data for total patient-days of follow-up were not available, total patient-days was calculated from the product of the mean length of follow-up and the number of patients followed up for the specific period. Clinical breakpoints were extracted as reported by the authors of the included studies. Antibiotic class was stratified according to the third level of the WHO Anatomical Therapeutic Chemical Classification System, and resistance to single antibiotics was used as the unit of analysis.[13]

Since the definition of resistance has changed over time, we devised criteria to define ESBL-producing bacteria and multidrug-resistant (MDR) bacteria. Criteria to define ESBL-producers were resistance to ceftazidime, ceftriaxone, or both (the two drugs might have had heterogeneous breakpoints, which might have changed over time); phenotypic confirmation (eg, with β-lactamase inhibitor combination); and gene identification with real-time PCR. Criteria to define MDR bacteria were resistance to carbapenem or resistance to at least three anti-pseudomonal antibiotic classes. When more than one antibiotic for each antibiotic class was tested, we only extracted resistance data for predefined drugs in each class to avoid duplicate counting of single isolates (appendix). Infection and colonisation were classified as defined by the authors of the included studies. Data from each study were recorded with standardised forms, verified for consistency and accuracy, and entered into a computerised database. The researchers were not blinded to study authors or location. If needed, authors were contacted via email to request additional information.

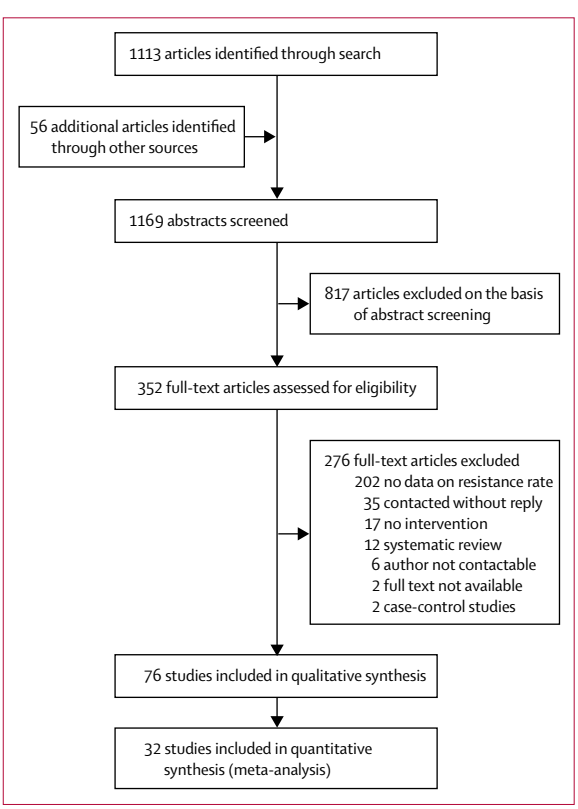

Figure 1: **Study selection**

The primary outcome was the change in the incidence of infection and colonisation with antibiotic-resistant bacteria and *C difficile* infections in hospital inpatients after implementation of antibiotic stewardship. The primary outcome was measured as the incidence ratio (IR), calculated as the ratio between the incidence (ie, the number of antibiotic-resistant bacteria isolated per 1000 patient-days) of colonisation or infection with the targeted antibiotic-resistant bacteria or *C difficile* infection before and after implementation of an antibiotic stewardship programme. Secondary outcomes were the IRs by study settings, type of antibiotic stewardship intervention, and concomitant implementation of infection control measures.

Risk of bias was assessed independently by two authors (DB, FB) using the National Institutes of Health's Quality Assessment Tool for Before–After (Pre–Post) Studies With No Control Group.[14] The tool was adapted to our study by removing the criteria (not applicable to our specific subset of data) regarding blinding (no 8), follow-up (no 9), and individual-level data adjustment (no 12), resulting in nine assessment criteria (appendix). Studies were classified as low quality (fewer than four points), moderate quality (four to six points), or high quality (more than six points). The meta-analysis was done following the Cochrane Collaboration recommendations and reported in accordance with the PRISMA guidelines (appendix).[12,15] Studies with no events before and after the intervention were excluded from the analysis. The pooled estimates of IRs and 95% CIs were obtained by combining the logarithms of the IRs by use of the generic inverse-variance method and random-effect models of meta-analysis. The I^2 statistic was used to quantify statistical heterogeneity. The potential sources of heterogeneity studied with meta-regression were bacterial species, resistance pattern, type of intervention and infection control measures, infection, colonisation, length of follow-up, year of study, and geographical location. The overall significance testing was done with Wald's test adjusted with the Bonferroni correction. Sensitivity analyses were done for study quality

and study design. Reporting and publication bias were examined with a funnel plot and tested with Egger's test. All statistical analyses were done using Stata, version 14.0. The protocol is available online.

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Our literature search identified 1113 studies, and an additional 56 articles were identified through other sources (figure 1). After applying inclusion and exclusion criteria at the abstract level, 817 of these 1169 studies were excluded. We retrieved full texts for the remaining 352 articles for further review. We contacted authors of 45 articles by email to request additional information. Ten authors responded, of whom four were able to provide data that were included in the final review. In total, 76 articles were reviewed in further detail (appendix) and 32 were included in the meta-analysis. Two (6%) studies were of high quality, 26 (81%) were of moderate quality, and four (13%) were of low quality (appendix). Overall, we analysed 9 056 241 patient-days and 159 IR estimates. The study characteristics are summarised in the table. The studies were done between 1992 and 2014 in 20 countries. Countries most represented were the USA (five studies), Japan (four studies), and Germany and France (three studies each). The most common study designs were before–after studies (17 [53%] studies), cohort studies (seven [22%] studies), and interrupted time-series studies (six [19%] studies; table). About half of the interventions were done in the entire hospital (15 [47%] studies), whereas for 17 (53%) studies the interventions were focused on specific wards. The most frequent antibiotic stewardship interventions were audits (19 [59%] studies) and implementation of restrictive policies (15 [47%] studies). In ten (31%) studies, antibiotic stewardship programmes were co-implemented with infection control measures, most frequently hand hygiene

For the **protocol** see www.medizin.uni-tuebingen.de/uktmedia/EINRICHTUNGEN/Kliniken/Medizinische+Klinik/Innere+Medizin+I/PDF_Archiv/AG+Tacconelli/ASP_StudyProtocol2015

	Years	Country	Study design	Setting	Infection or colonisation	Intervention	Infection control measures	Main objective	Results
Borde et al[16]	2013–14	Germany	ITS	Hospital	Infection	Audit, guideline implementation	No change	Reduction of antibiotic use	Reduced RDD per 1000 patient-days; no effect on incidence of *Clostridium difficile* infection
Cruz-Rodriguez et al[17]	2012–13	Mexico	Before–after	Orthopaedics	Infection	Antibiotic restriction, audit	Hand hygiene	Reduction of clindamycin use and incidence of *C difficile* infection	Reduced DDD per 1000 patient-days and incidence of *C difficile* infection
Apisarnthanarak et al[18]	2010–12	Thailand	Before–after	Medical ICU	Infection and colonisation	Audit, feedback	Isolation, environmental cleaning, hand hygiene, chlorhexidine bathing	Reduction of incidence of XDR *Acinetobacter baumannii*	Reduced incidence of XDR *A baumannii*
Lübbert et al[19]	2010–12	Germany	Before–after	Hospital	Infection and colonisation	Guideline implementation	No change	Reduction of antibiotic use and incidence of antibiotic resistance and *C difficile* infection	Reduced DDD per 1000 patient-days, VRE rates, and incidence of *C difficile* infection
Zou et al[20]	2009–13	China	ITS	Hospital	Infection and colonisation	Audit	No change	Reduction of antibiotic use and incidence of antibiotic resistance	Reduced DDD per 100 patient-days; decreased or stable incidence of antibiotic resistance
Dubrovskaya et al[21]	2009–11	USA	Before–after	Surgery	Infection	Guideline implementation	No change	Reduction of antibiotic use and incidence of *C difficile* infections	Reduced DDD per 1000 patient-days; no effect on incidence of *C difficile* infection
Leung et al[22]	2009–10	Canada	Before–after	ICU	Infection	Audit, education	No change	Reduction of use of drugs targeting *Pseudomonas aeruginosa*, costs, and incidence of *C difficile* infection	Reduced antibiotic use and costs; no effect on incidence of *C difficile* infection
Yeo et al[23]	2009–10	Singapore	ITS	Haematology-oncology	Infection	Audit	No change	Reduction of antibiotic use and incidence of antibiotic resistance	Reduced DDD per 100 patient-days; no effect on incidence of antibiotic resistance
Chong et al[24]	2008–11	Japan	Before–after	Haematology-oncology	Infection	Antibiotic cycling	No change	Reduction of incidence of antibiotic-resistant Gram-negative bacteria	Reduced incidence of cefepime-resistant Gram-negative bacteria
Niwa et al[25]	2008–11	Japan	Before–after	Hospital	Infection	Audit, guideline implementation	Education, hand hygiene	Reduction of antibiotic use, costs, and incidence of antibiotic resistance	Reduced DDD per 1000 patient-days and incidence of MRSA and antibiotic-resistant *Serratia marcescens*

(Table continues on next page)

	Years	Country	Study design	Setting	Infection or colonisation	Intervention	Infection control measures	Main objective	Results
(Continued from previous page)									
Malani et al[26]	2008–10	USA	Cohort	Hospital	Infection	Audit	No change	Reduction of antibiotic use, costs, and incidence of *C difficile* infection	Reduced antibiotic use, cost, and incidence of *C difficile* infection
Price et al[27]	2007–09	UK	ITS	Hospital	Infection	Antibiotic restriction	Patient cohort (dedicated ward), hand hygiene	Reduction of antibiotic use and incidence of *C difficile* infection	Reduced DDD per 1000 patient-days (cephalosporin, quinolone), increased use of antibiotics targeting *P aeruginosa* and penicillins, and reduced incidence of *C difficile* infection
Schön et al[28]	2007–08	Sweden	Point prev-alence survey	Hospital	Infection	Antibiotic restriction, guideline implementation	No change	Reduction of antibiotic use and incidence of *C difficile* infection	Reduced antibiotic use; no effect on incidence of *C difficile* infection
Ramirez et al[29]	2006–10	Spain	Cohort	Haematology-oncology, neurosurgery, angiology, nephrology	Infection and colonisation	Audit	No change	Reduction of incidence of antibiotic-resistant Gram-positive bacteria	Reduced DDD per 1000 patient-days (linezolid) and incidence of antibiotic-resistant Gram-positive bacteria
Mimica Matanovic et al[30]	2006–07	Croatia	Before–after	Hospital	Infection	Antibiotic restriction	No change	Reduction of use of amoxicillin and clavulanic acid and incidence of *Escherichia coli* resistant to amoxicillin and clavulanic acid	Reduced DDD per 100 bed-days and incidence of *E coli* resistant to amoxicillin and clavulanic acid
Marra et al[31]	2006–07	Brazil	Before–after	ICU	Infection	Antibiotic restriction, audit	No change	Reduction of antibiotic therapy duration (to <14 days)	Reduced antibiotic use and imipenem-resistant *Klebsiella pneumoniae* and *A baumannii*
Takesue et al[32]	2005–08	Japan	Before–after	Hospital	Infection	Antibiotic cycling, antibiotic restriction, audit	No change	Reduction of infection due to MDR Gram-negative bacteria	Reduced incidence of MDR Gram-negative bacteria; no effect on incidence of ESBL producers
Schultsz et al[33]	2004–06	Vietnam	Before–after	Tetanus ICU	Colonisation	Antibiotic mixing	Hand hygiene, education, barrier precaution, patient screening	Reduction of incidence of MDR Gram-negative bacteria and MRSA	Reduced incidence of MRSA and ESBL-producing bacteria
Meyer et al[34]	2002–06	Germany	ITS	Surgical ICU	Infection	Restriction of a single antibiotic, education	No change	Reduction of antibiotic use (surgical prophylaxis) and incidence of antibiotic resistance	Reduced DDD per 1000 patient-days and incidence of MRSA rates; increased incidence of third-generation cephalosporin-resistant *E coli*
Lee et al[35]	2002–03	South Korea	Case-control	Neurosurgical ICU	Colonisation	Audit	No change	Reduction of cephalosporin use and incidence of ESBL-producing *K pneumoniae*	Reduced DDD per 100 patient-days and incidence of ESBL- producing *K pneumoniae*
Arda et al[36]	2002–03	Turkey	Cohort	ICU	Infection	Antibiotic restriction, audit	No change	Reduction of antibiotic use and costs	Reduced DDD per 1000 patient-days, costs, and antibiotic-resistant *K pneumoniae*; increased incidence of amikacin-resistant *A baumannii*
Cook and Gooch[37]	2001–13	USA	Cohort	Hospital	Infection	Antibiotic restriction, audit, decision support system	Screening of patients for MRSA or VRE, isolation of high-risk patients	Long-term benefits of antibiotic stewardship	Reduced DDD per 1000 patient-days, MRSA infection, *C difficile* infection, and incidence of quinolone-resistant and carbapenem-resistant *P aeruginosa*
Grohs et al[38]	2001–12	France	ITS	Hospital	Colonisation	Restriction of a single antibiotic	No change	Reduction of Enterobacteriaceae harbouring high-level expression of AmpC β-lactamase	Reduced antibiotic use; stable incidence of Enterobacteriaceae harbouring high-level expression of AmpC β-lactamase
Miyawaki et al[39]	2001–07	Japan	Cohort	Hospital	Infection	Audit	No change	Reduction of antibiotic use and drugs targeting MRSA	Reduced DDD per 1000 patient-days and MRSA infections

(Table continues on next page)

	Years	Country	Study design	Setting	Infection or colonisation	Intervention	Infection control measures	Main objective	Results
(Continued from previous page)									
Mach et al[40]	2001–04	Czech Republic	Cohort	Hospital	Infection	Antibiotic restriction, guideline implementation	No change	Reduction of antibiotic use and incidence of antibiotic resistance	Reduced RDD per 1000 bed-days; no effect on incidence of resistance
Chalfine et al[41]	2000–09	France	Before–after	Hospital	Infection and colonisation	Antibiotic restriction, audit, education	Hand hygiene, isolation, education	Reduction of incidence of MRSA	Reduced DDD per 1000 patient-days and incidence of MRSA infection
Peto et al[42]	2000–05	Hungary	Before–after	Surgical ICU	Infection	Antibiotic restriction, audit	No change	Reduction of antibiotic use	Reduced DDD per 100 patient-days
Aubert et al[43]	2000–02	France	Before–after	ICU	Infection and colonisation	Antibiotic restriction	Patient screening	Reduction of quinolone use and incidence of resistant bacteria	Reduced quinolone use and incidence of resistant *P aeruginosa*
Smith et al[44]	1997–2003	USA	Before–after	Surgical ICU	Infection	Antibiotic cycling	No change	Reduction of incidence of MRSA and VRE	Reduced incidence of MRSA; no effect on incidence of VRE
Leverstein-van Hall et al[45]	1996–97	Netherlands	Cohort	Neurology, neurosurgery	Infection and colonisation	Antibiotic restriction	Hand hygiene, patient or staff screening	Reduction of MDR Enterobacteriaceae	Reduced incidence of MDR Enterobacteriaceae
McNulty et al[46]	1994–95	UK	Before–after	Geriatrics	Infection	Antibiotic restriction, audit	Hand hygiene, environmental cleaning	Reduction of incidence of *C difficile* infection	Reduced incidence of *C difficile* infection
Frank et al[47]	1992–94	USA	Before–after	Hospital	Infection and colonisation	Antibiotic restriction, audit, education	No change	Reduction of antibiotic use and incidence of resistance	Reduced antibiotic use, Gram-negative bacteraemia, and incidence of MRSA; no effect on incidence of *C difficile* infection

ITS=interrupted time series. XDR=extremely drug-resistant. RDD=recommended daily dosage. DDD=defined daily dose. ICU=intensive care unit. VRE=vancomycin-resistant enterococci. MRSA=meticillin-resistant *Staphylococcus aureus*. MDR=multidrug-resistant. ESBL=extended-spectrum β-lactamase.

Table: **Summary of studies included in the meta-analysis (n=32)**

(eight [25%] studies) and patient screening (four [13%] studies; table). 21 (66%) studies assessed the effect of antibiotic stewardship programmes on infection only, three (9%) on colonisation only, and eight (25%) on both infection and colonisation.

Pooled analysis of eligible studies showed that antibiotic stewardship implementation was associated with significant reductions in the incidence of MDR Gram-negative bacteria (51% reduction; IR 0·49, 95% CI 0·35–0·68; p<0·0001; figure 2), ESBL-producing Gram-negative bacteria (48%; 0·52, 0·27–0·98; p=0·0428; appendix), MRSA (37%; 0·63, 0·45–0·88; p=0·0065; figure 3), and *C difficile* infections (32%; 0·68, 0·53–0·88; p=0·0029; figure 4) in hospital inpatients. The reduction in the incidence of the MDR Gram-negative bacteria was also confirmed in the subgroup of studies focusing on carbapenem resistance (43%; 0·57, 0·40–0·81; p=0·0018; appendix). The incidence of aminoglycoside-resistant (IR 0·82, 95% CI 0·56–1·20; p=0·3028) and quinolone-resistant (0·74, 0·50–1·11; p=0·1435) Gram-negative bacteria was not significantly reduced (appendix). The incidence of aminoglycoside-resistant (1·00, 0·86–1·16; p=0·9701) and quinolone-resistant (1·10, 0·82–1·48; p=0·5416) Gram-positive bacteria was also not significantly changed.

Although not significantly changed, after stratification by type of Gram-negative bacteria, the reduction in incidence was greatest for carbapenem-resistant *Acinetobacter baumannii* (56% reduction; IR 0·44, 95% CI 0·17–1·13; p=0·0864) and *P aeruginosa* (29%; 0·71, 0·46–1·10; p=0·1254). One study reporting the incidence of carbapenem-resistant *K pneumoniae* showed a reduction of 48% (IR 0·52, 95% CI 0·13–2·09; p=0·3639). Among the Gram-positive bacteria, the IR of vancomycin-resistant enterococci was not significantly changed after implementation of antibiotic stewardship programmes (1·40, 0·81–2·43; p=0·2233; appendix).

Substantial heterogeneity (>50%) was noted between the studies (the specific heterogeneity for antibiotic-resistant bacteria is reported in each figure). Heterogeneity assessment, done by meta-regression, showed that the bacterial species (I^2 residual 90·2%; adjusted R^2 19·2%; p=0·0006) and resistance patterns (94·5%; 10·3%; p=0·0116) were the primary contributors to the high between-study variability. The other study characteristics that contributed to heterogeneity were length of follow-up after an antibiotic stewardship programme (adjusted R^2 7·2%; p=0·0017), presence or absence of hand-hygiene co-implementation (5·5%; p=0·0007), and interventions of audits and feedback (4·5%; p=0·0044).

Figure 5 shows the summary forest plot of the pooled estimates of IRs for antibiotic resistance among the various subgroups according to study characteristics. When stratifying by setting, antibiotic stewardship

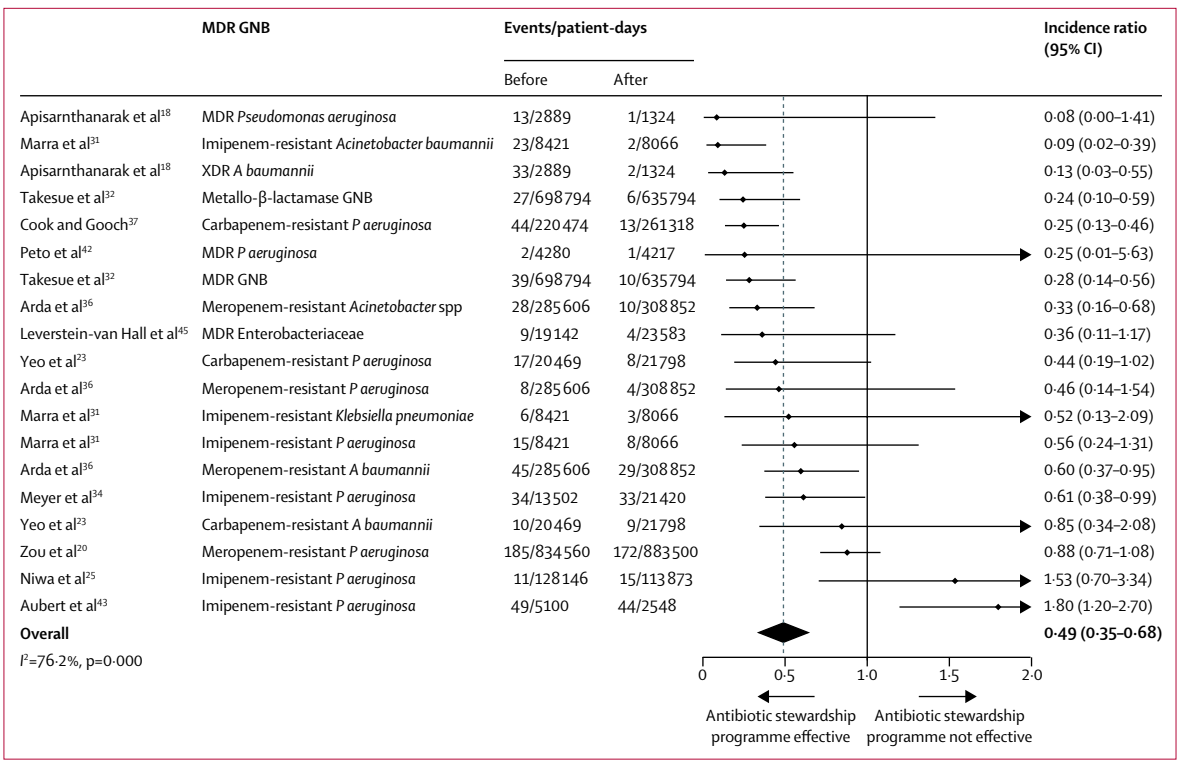

Figure 2: **Forest plot of the incidence ratios for studies of the effect of antibiotic stewardship on the incidence of MDR GNB**
GNB=Gram-negative bacteria. MDR=multidrug-resistant. XDR=extensively drug-resistant.

interventions were associated with reduced IRs in haematology-oncology departments (59% reduction; IR 0·41, 95% CI 0·20–0·85; p=0·0166), intensive care units (23%; 0·77, 0·66–0·89; p=0·0003), and medical departments (22%; 0·78, 0·66–0·91; p=0·0024).

Antibiotic stewardship programmes implemented with infection control measures had a greater effect on reduction of antibiotic resistance (31%; IR 0·69, 95% CI 0·54–0·88; p=0·0030) than did implementation of antibiotic stewardship programmes alone (19%; 0·81, 0·67–0·97; p=0·0210; figure 5). In particular, interventions that co-implemented hand hygiene together with antibiotic stewardship were associated with a greater reduction in the IR of antibiotic resistance (66%; 0·34, 0·21–0·54; p<0·0001; figure 5) than those without hand-hygiene intervention (17%; 0·83, 0·71–0·98; p=0·0304; appendix). The magnitude of effect was dependent on the type of antibiotic stewardship programme implemented. A significant effect was found for antibiotic cycling (51% reduction in antibiotic resistance; 0·49, 0·34–0·72; p=0·0030), followed by audits and feedback (34% reduction; 0·66, 0·52–0·83; p=0·0006) and antibiotic restriction (23% reduction; 0·77, 0·67–0·89; p=0·0003). Use of implementing guidelines for antibiotic stewardship programmes (IR 1·03, 95% CI 0·85–1·25; p=0·7496) and focusing on one antibiotic class (1·28, 0·68–2·41; p=0·4527) did not lead to significant changes in IRs (appendix). Interventions generally became more effective over time: 10% reduction in antibiotic resistance for 1980–2000 (IR 0·90, 95% CI 0·60–1·36; p=0·6226), 21% reduction for 2001–05 (0·79, 0·69–0·90; p=0·0006), and 32% reduction for 2006–13 (0·68, 0·49–0·95; p=0·0223; figure 5).

Sensitivity analysis based on the quality of the studies revealed no notable difference in IRs, even after exclusion of the low-quality studies. The pooled-effect size estimate based on prospective studies revealed an increased protective effect (IR 0·64, 95% CI 0·49–0·83; p=0·0008). We did not find any evidence of effects for small studies (Egger's test p=0·836) or publication bias (appendix).

Discussion

Our study findings show that implementation of antibiotic stewardship programmes is associated with a reduction in the IRs of infection and colonisation with antibiotic-resistant bacteria and *C difficile* infections in hospital inpatients. The largest reductions were seen in the incidence of infection or colonisation with MDR Gram-negative bacteria, followed by the incidence of infection or colonisation with ESBL-producing Gram-negative bacteria and MRSA, and the incidence of *C difficile* infections. Notably, antibiotic stewardship was found to be highly effective in haematology-oncology settings and when implemented alongside infection control measures. Co-implementation of improved hand hygiene had a beneficial effect on the

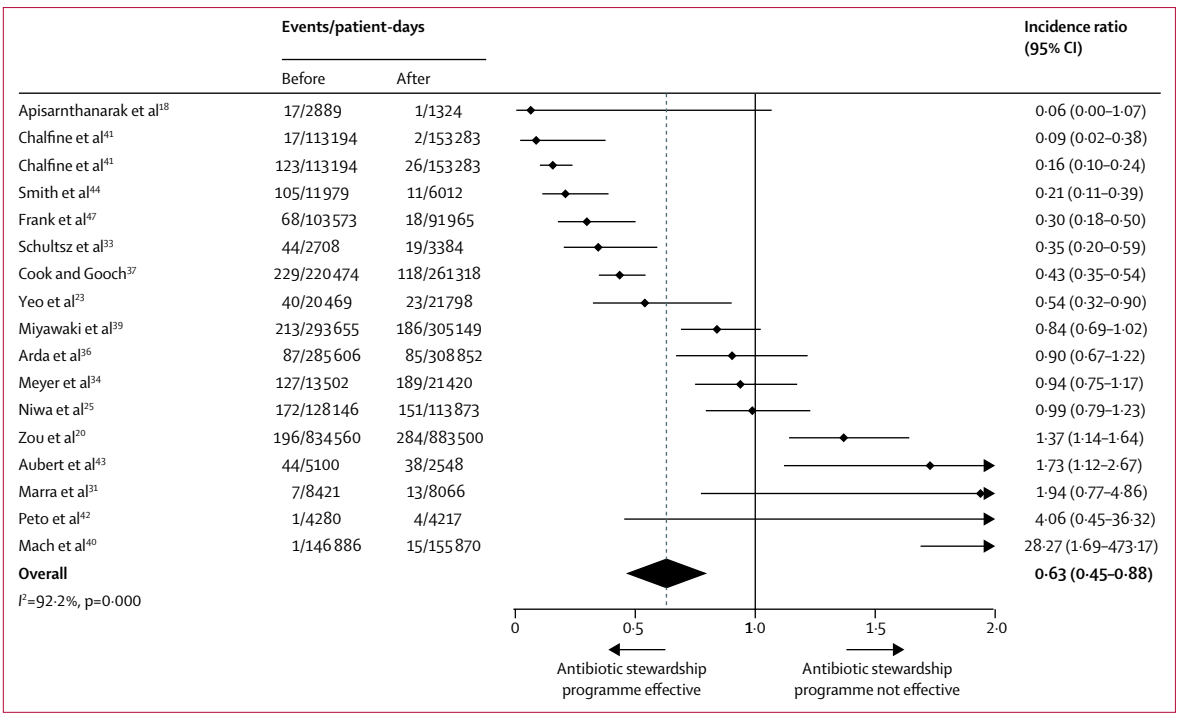

Figure 3: **Forest plot of the incidence ratios for studies of the effect of antibiotic stewardship on the incidence of meticillin-resistant *Staphylococcus aureus***

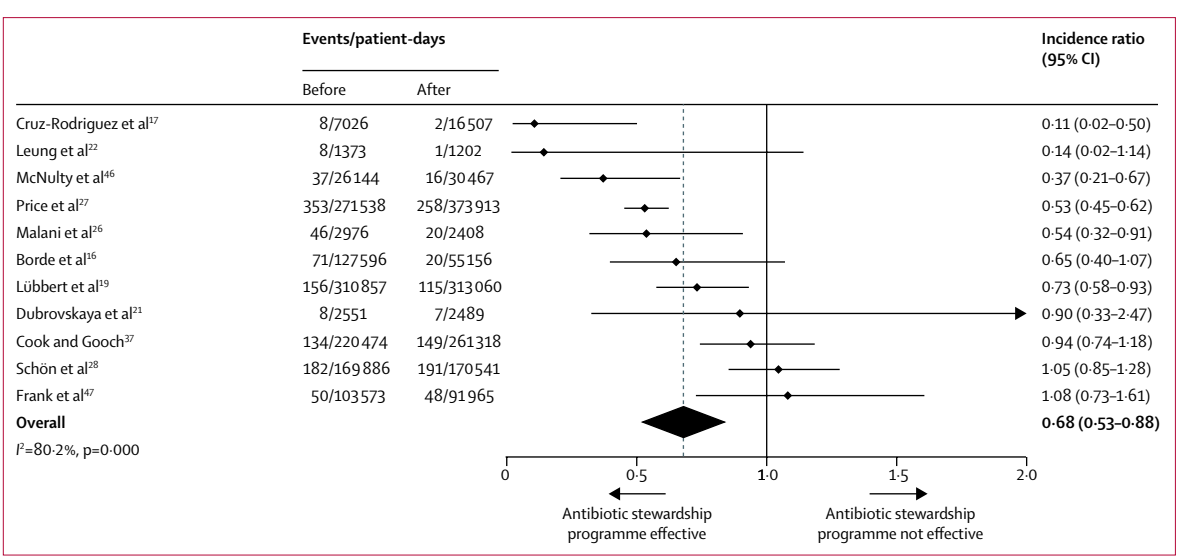

Figure 4: **Forest plot of the incidence ratios for studies of the effect of antibiotic stewardship on the incidence of *Clostridium difficile* infections**

overall success of the interventions, reducing resistance rates by two-thirds. Among the different types of antibiotic stewardship interventions, antibiotic cycling was found to be the most effective, followed by audits and feedback, and antibiotic restriction. The interventions became more effective over time, ranging from 10% reduction of antibiotic resistance for 1980–2000 to 32% reduction for 2006–13.

An effect for antibiotic stewardship on other outcomes (eg, mortality, antibiotic costs) has already been shown. Karanika and colleagues[7] analysed the effect of antibiotic stewardship programmes in seven studies published up to July, 2015, and showed a significant decrease in antibiotic resistance among MRSA, imipenem-resistant *P aeruginosa*, and ESBL-producing *K pneumoniae* isolates, with a 4·5% reduction in overall resistance. Because that study[7] reported only absolute risk differences for specific bacteria, comparison of their results with the results of this study is difficult. The 2016 systematic review by Schuts and colleagues[9] analysed stewardship objectives

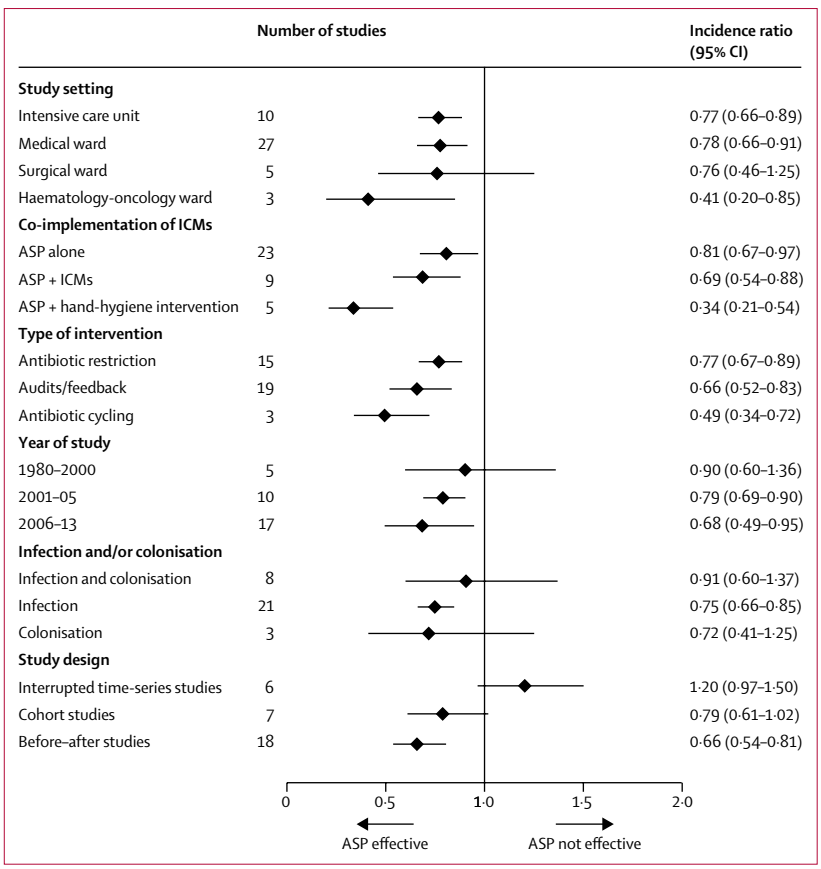

Figure 5: **Summary forest plot of the incidence ratios for studies investigating the effect of ASPs on antibiotic resistance, according to study characteristics**
ICM=infection control measure. ASP=antibiotic stewardship programme.

and showed a 56% reduction in mortality with guideline-adherent empirical therapy and a 35% reduction in mortality with de-escalation interventions. Feazel and colleagues,[10] when investigating the effect of antibiotic stewardship programmes on the incidence of *C difficile* infections, estimated a protective effect of 52%. In this meta-analysis and systematic review, we estimated a protective effect of 32% for *C difficile* infections, and this difference might be attributed to our more conservative approach, with use of IRs, and also to our inclusion of eight studies that were not analysed in the review by Feazel and colleagues.[10]

Our findings clearly show that antibiotic stewardship programmes, when implemented alongside infection control measures, are more effective than implementation of antibiotic stewardship alone. In particular, studies co-implementing a hand-hygiene programme with an antibiotic stewardship programme have reported a reduction of 66% in antibiotic resistance versus 17% in studies without co-implementation of hand-hygiene interventions, thus supporting the so-called butterfly effect of hand hygiene. The hand-hygiene measures implemented in the studies included in our meta-analysis varied from education to replacement of handwashing with alcohol-based hand rubbing and substitution of hand-directed soap dispensers with elbow-directed soap dispensers.[33,41,44,46] It is important to emphasise that the effect of infection control and hand hygiene was observed not only for infections due to MRSA but also for those due to antibiotic-resistant Gram-negative bacteria. This finding seems to support the importance of verifying the level of hand-hygiene compliance and adherence to basic infection control measures, with simultaneous implementation of antibiotic stewardship and integration of infection control experts into the antibiotic stewardship programme teams.

In this study, antibiotic stewardship programmes were more effective in the haematology-oncology settings than in other settings. This finding is notable because of the serious outcomes of MDR infections in this setting and the scarcity of information about the effectiveness of antibiotic stewardship programmes in haematology-oncology patients.[48,49] The main limitation of this finding is the low number (three) of included studies. Bradley and colleagues[50] did a prospective three-phase sequential study in which ceftazidime was replaced with piperacillin-tazobactam in patients with febrile neutropenia. The intervention reduced colonisation with glycopeptide-resistant *Enterococcus* spp (57% without intervention *vs* 19% with intervention).[50] Chong and colleagues[24] were able to reduce antibiotic resistance rates, in particular cefepime-resistant Gram-negative bacteria, by implementation of an antibiotic cycling regimen in which four primary antibiotic classes were rotated. Yeo and colleagues[23] implemented an audit and feedback antibiotic stewardship programme targeting ceftazidime-resistant *Escherichia coli,* ceftazidime-resistant *K pneumoniae,* carbapenem-resistant *Acinetobacter* spp, and MRSA, resulting in a significant reduction in MRSA rates only. In the intensive care unit setting, a significant effect was also detected in our review, consistent with the observation by Karanika and colleagues[7] of a significant reduction in antibiotic consumption in this setting after implementation of an antibiotic stewardship programme.

Among the types of antibiotic stewardship programmes implemented, we found antibiotic cycling, audits, and antibiotic restriction to be effective. Studies of guideline implementation and single antibiotic classes did not show any effect for these interventions on resistance rates, perhaps because of short follow-up. A meta-analysis[51] of antibiotic cycling showed a significant reduction in the incidence of antibiotic-resistant bacteria per 1000 patient-days after the intervention (reduction of 7·2, 95% CI 0·44–14·00; p=0·037). However, the low number of studies (three) implementing antibiotic cycling in our review restricts the generalisability of the results. The success of this measure is usually dependent on the setting in which it is implemented and the local epidemiology.[24,44] Auditing, with its components of intense communication and feedback, renders antibiotic stewardship programmes effective and seems to be promising in

all settings.[23,41] Across the studies, success was attributed to high compliance among physicians, the additional educational effect of feedback, a closer working relationship between physicians and the antibiotic stewardship team because of audits, control of certain endpoints of infection control by audits in conjunction with antibiotic stewardship programmes, educational effects, and the Hawthorne effect due to putting electronic monitoring systems in place.[23,25,33,39,41] The effectiveness of antibiotic restriction was also shown by Schuts and colleagues[9] who used a restricted antibiotics list targeting specific bacteria.

Our study had some limitations. First, although we had a wide range of eligible studies, we were limited to 32 studies because of the scarcity of essential data in the remaining studies. Incomplete data reporting and absent author responses were the main factors restricting our ability to do a more comprehensive meta-analysis of the clinical efficacy of antibiotic stewardship programmes. However, most of the excluded studies also reported a reduction in their antibiotic resistance rates. Second, we could not investigate the effectiveness of single interventions in greater detail because most of the studies reported comprehensive results of composite antibiotic stewardship programmes implemented together with infection control strategies. Third, we included uncontrolled studies with pre–post data, and we cannot entirely ignore that the observed effect could be due to an underlying secular trend. Fourth, we detected significant heterogeneity between studies. However, analysis of the sources of the heterogeneity showed that 20% of the between-study variance could be explained by the multiple pattern of resistance among included antibiotic-resistant bacteria. The absence of interventions targeting hand hygiene alongside antibiotic stewardship interventions and the type of antibiotic stewardship intervention also contributed to the heterogeneity. Because of the wide array of study designs, different types of antibiotic stewardship programmes, co-implementation of infection control measures, and the focus on different antibiotic-resistant bacteria, the residual heterogeneity in this complex background is, to an extent, understandable. Further investigation of heterogeneity and interactions between contributing factors could not be done because of the small number of studies. Given that antibiotic stewardship programmes are usually implemented in large settings and I^2 tends to be increased when the number of patients or patient-days is variable, it can also be speculated that the large denominator used in the IR calculations could explain the substantial amount of heterogeneity even between individual antibiotic-resistant bacteria.[52]

The principal strength of our study is the analysis of the incidence of infections or colonisation as the primary outcome of the antibiotic stewardship programmes. To the best of our knowledge, this study is the first to use this measure, which takes into account the individual patient-days of follow-up, is easily comprehensible, and is comparable across studies.[20,31,43]

When planning future studies of antibiotic stewardship programmes, it would be advisable to use controlled interventional study designs and data-reporting patterns to enable comparison and generalisation of results. Standards for data reporting are accessible in the literature and include reporting of absolute bacteria numbers, antibiotic consumption represented by defined daily doses, and reporting of patient-days for the study period.[53] Adherence to such reporting policies can provide more reliable and comparable data, an outcome essential in guiding future research and recommendations. An antibiotic stewardship programme should be studied over a sufficiently long period of time to adequately assess its effect. The effects of various types of antibiotic stewardship interventions should be assessed for Gram-negative and Gram-positive bacteria separately.

In conclusion, our meta-analysis shows that antibiotic stewardship programmes have an essential role in combating the development of antibiotic resistance, especially for MDR Gram-negative bacteria, and emphasises the importance of promoting antibiotic stewardship programmes at the hospital level to reduce the spread of antibiotic-resistant bacteria among the inpatient population. Therefore, implementation of these measures should be recommended not only on the basis of the well known cost benefits, but also because of the more relevant, patient-based clinical advantages. Co-implementation of hand-hygiene improvement interventions with antibiotic stewardship programmes has a synergistic effect and is thus recommended for future antibiotic stewardship planning. Good quality intervention studies are needed to help prioritise the various antibiotic stewardship programmes for each specific resistance scenario.

Contributors

ET conceived and designed the study. DB, FB, FF, and SD did the literature review and data collection. BPG, EC, FF, DB, and SD reviewed the data. BPG and EC did the statistical analysis. DB, BPG, and ET wrote the manuscript. All authors contributed to the interpretation of the data and writing of the Article and agree with its content and conclusions.

Declaration of interests

We declare no competing interests.

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