TECHNICAL REPORT

Systematic review and evidence-based guidance on perioperative antibiotic prophylaxis

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This report was commissioned by the European Centre for Disease Prevention and Control (ECDC), coordinated by Anna-Pelagia Magiorakos and produced by the Institute of Hygiene and Environmental Medicine, Charité – University Medicine Berlin (service contract ECD/10/015).

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All authors have declared that they had no conflict of interest that would have influenced their opinion in producing this report.

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Additional information on the characteristics of the included studies and a methodological assessment of bias is available in a digital format. If you wish to receive an email with this information, write to info@ecdc.europa.eu and cite 'Systematic review and evidence-based guidance on perioperative antibiotic prophylaxis' in the subject line of your email.

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Abbreviations

AHRQ	Agency for Healthcare Research and Quality
AM team	Antimicrobial management team
CABG	Coronary artery bypass graft
CBA	Controlled before-after study
CDC	Centres for Disease Control and Prevention
CDI	Clostridium difficile infection
CI	Confidence interval
ECDC	European Centre for Disease Prevention and Control
EPOC	Effective Practice and Organisation of Care
EU	European Union
GNB	Gram-negative bacteria
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICU	Intensive care unit
ITS	Interrupted time-series analysis
MDRO	Multidrug-resistant organism
MRSA	Meticillin-resistant *Staphylococcus aureus*
Non-CBA	Non-controlled before-after study
OR staff	Operating room staff
OR	Odds ratio
PAP	Perioperative antibiotic prophylaxis
PREZIES	Preventie Ziekenhuisinfecties door Surveillance
RR	Relative risk
SCIP	Surgical Care Improvement Project
SSI	Surgical site infection
TRAPE	Trial to Reduce Antimicrobial Prophylaxis Errors
VRE	Vancomycin-resistant *enterococci*

Glossary

Audit: A quality improvement process that seeks to improve patient care and outcomes through a systematic review of all aspects of care against explicit criteria and the implementation of change. Where indicated, changes are implemented at an individual, team, or service level and further monitoring is used to confirm improvement in healthcare delivery [1].

European Union-wide applicability: Applicability of a key component across the European Union in terms of adaptability and adoption in the context of potential barriers at a national level related to finances, culture, or healthcare structures.

Healthcare professionals: Clinical staff who have regular contact with patients. This includes physicians, nurses, pharmacists, paramedical professionals (e.g. occupational therapists, physiotherapists, radiographers, ambulance workers and porters), and students in these disciplines.

Implementation: Implementation is a deliberate action performed to put a plan (intervention) or system into operation within an organisation [2,3].

Infection control professional: Clinical staff trained in infection control, including nurses, physicians, and microbiologists.

Multidisciplinary: This term refers to a group of individuals who represent different professional backgrounds and is usually used in the context of multidisciplinary teams.

Perioperative antibiotic prophylaxis: Administration of systemic antibiotics before or during a surgical procedure.

Surgical site infection: Infection of superficial or deep tissue or organs at the surgical site or related to the site of the surgical procedure. Case definitions for surgical site infections are those from Commission Implementing Decision 2012/506/EU of 8 August 2012 amending Decision 2002/253/EC laying down case definitions for reporting communicable diseases to the Community network under Decision No 2119/98/EC of the European Parliament and of the Council (notified under document C(2012) 5538) and the Centers for Disease Control and Prevention (CDC) from the United States of America. Good concordance between the EU and US definitions was shown in: Hansen S, Sohr D, Geffers C, Astagneau P, Blacky A, Koller W et al. Concordance between European and US case definitions of healthcare-associated infections. Antimicrob Resist Infect Control. 2012 Aug 2;1(1):28. doi: 10.1186/2047-2994-1-28.

Surveillance: The ongoing systematic collection, analysis, and interpretation of health data essential to the planning, implementation, and evaluation of public health practice; closely integrated with the timely dissemination of these data to relevant stakeholders [4].

Executive summary

Background

Perioperative antibiotic prophylaxis (PAP) has been shown to be an effective measure for preventing surgical site infections (SSIs). The use of PAP contributes considerably to the total amount of antibiotics used in hospitals and has been shown to be associated with increases in antibiotic resistance and healthcare costs. Because of the benefits of PAP and the importance of using it correctly, the European Centre for Disease Prevention and Control (ECDC) issued a call for tender entitled 'Systematic review and evidence-based guidance on perioperative antibiotic prophylaxis'. The objectives of this project were: 1) to identify the effectiveness of key modalities of perioperative antibiotic prophylaxis from a systematic review and 2) to develop five key PAP modalities and process indicators for monitoring their implementation on the basis of scientific evidence and expert opinion.

Key modalities of the effectiveness of perioperative antibiotic prophylaxis

The systematic review identified five key PAP modalities that were shown to improve compliance of healthcare professionals with appropriate administration, timing, dosage and duration of PAP for the prevention of SSI. The five modalities were: 1) forming a multidisciplinary team to develop, implement and update a PAP protocol, conduct an audit of compliance, and provide feedback; 2) ensuring administration of PAP within 60 minutes prior to incision; 3) assigning responsibility for timely administration of PAP to the anaesthesiologist; 4) administering only a single dose of PAP; and 5) to discontinue PAP at the end of surgery.

Indicators for monitoring five key PAP modalities in hospitals

As it is important to monitor implementation of these modalities, indicators were subsequently developed by expert consensus. These indicators included frequency of administration of PAP by an anaesthesiologist or another designated professional when indicated, presence and frequency of meetings of the multidisciplinary team, as well as other measures to improve compliance.

Potential barriers to EU-wide implementation of key PAP modalities

Identified barriers to EU-wide implementation of the PAP modalities include, among others, lack of education, psychological barriers, fear of litigation, lack of awareness regarding local antimicrobial resistance patterns, hierarchical problems, and lack of professional regulations. Identifying potential barriers could pave the way for the key modalities to be implemented in a uniform manner across the EU.

Conclusions

Adopting or adapting these five key modalities and indicators when creating local policies for antibiotic use would be an important step for hospitals across Europe. All five key modalities support the harmonisation of administration of PAP and increase awareness in hospitals, which would eventually lead to a decrease in antibiotic use and antibiotic resistance. Barriers for the implementation of both modalities and indicators should be addressed. Administrative support based on local, national or EU-wide strategies would be helpful to overcome barriers to the EU-wide implementation of the PAP modalities discussed in this document.

Perioperative antibiotic prophylaxis modality	Indicators for each modality
Modality #1: Multidisciplinary antimicrobial management teams	
Hospitals should establish a multidisciplinary AM team (including surgeons, anaesthesiologists, nurses, pharmacists, infection control specialists, and clinical microbiologists) who should develop and implement a protocol of appropriate PAP. *Compliance with this protocol should be audited regularly and the results should be fed back to the antimicrobial prescribers and decision-makers, e.g. chief of surgery, quality committee, AM team.* *The protocol should be reviewed and updated regularly. It should consider adjustment of PAP for patients who are at risk for SSI due to MDROs or who have a BMI over 30. The hospital's local antibiotic susceptibility patterns should also be taken into account.*	The presence of a multidisciplinary AM team which is responsible for developing, implementing and regularly updating the PAP protocol; in charge of regularly updating the local AB protocol; and responsible for regularly analysing and auditing compliance with appropriate PAP.

Perioperative antibiotic prophylaxis modality	Indicators for each modality
Modality #2: Responsibility for appropriate timing of perioperative antibiotic prophylaxis	
To ensure appropriate timing, antibiotic prophylaxis before and during surgery should be the responsibility of the anaesthesiologist*. ** This recommendation is supported by the best available evidence. If there is no anaesthesiologist available, another professional present at the time of surgery should be designated.*	Measurement of the presence of an anaesthesiologist or another designated professional at surgery who is responsible for applying PAP.
Modality #3: Timing of perioperative antibiotic prophylaxis	
PAP should be administered within 60 minutes before incision (except when administering vancomycin and fluoroquinolones), ideally at the time of anaesthetic induction.	Rate of compliance with the administration of PAP within 60 minutes.
Modality #4: Dosing and duration of perioperative antibiotic prophylaxis	
Although a single dose of PAP is preferred, subsequent doses should be given depending on the duration of the procedure and the half-life of the antibiotic, and if significant blood loss occurs during surgery.	Rate of compliance with indication, selection and dosage of PAP according to protocol.
Modality #5: Duration and termination of perioperative antibiotic prophylaxis	
Continuing antibiotic prophylaxis after the end of surgery is not recommended*. ** Hospitals should use a reminder/stop order system (e.g. computer system, checklist) in order to encourage appropriate duration and dosage of PAP.*	Rate of compliance with discontinuation of PAP within 24 hours after initiation of surgery.

1 Introduction

Surgical site infections (SSIs) are the third most common type of hospital-acquired infections and, on average, account for 17% of their total (based on data from point prevalence surveys performed in industrialised countries in recent years) [5]. Perioperative antibiotic prophylaxis (PAP) is considered an effective measure for prevention of SSIs because the vast majority of SSIs are caused by endogenous translocation of the patient's intestinal microbiota [6]. Bowater et al. analysed data from 21 meta-analyses based on randomised controlled trials (RCT) that included 48 909 patients from 250 hospitals [7]. The authors demonstrated that the administration of PAP had a significant effect on the prevention of SSIs, irrespective of the contamination of the wound and type of surgical procedure (relative risk from 0.19 to 0.82). This is significant as up to 80% of SSIs could be reduced by appropriate PAP administration.

The use of PAP contributes considerably to the total amount of antibiotics used in hospitals and has been shown to be associated with increases in antibiotic resistance and healthcare costs. Studies have shown that approximately 15% of all antibiotics in hospitals are prescribed for surgical prophylaxis [8,9]. Furthermore, a survey of European hospitals reported that half of the surgical patients in 2006 had received PAP for more than 24 hours after the end of surgery without a reason [8]. In a recent study involving 14 hospitals, adherence to local PAP guidelines ranged widely from 5 to 85% [10]. Many studies have demonstrated non-compliance with PAP guidelines in up to 88% of patients [11,12], indicating that there is room for improvement in PAP in many European hospitals.

In May 2010, the European Centre for Disease Prevention and Control (ECDC) issued a call for tender entitled 'Systematic review and evidence-based guidance on perioperative antibiotic prophylaxis'. The tender called for a systematic literature review, supplemented by the input of an expert group, identifying 10 effective key PAP modalities and to subsequently produce a guidance document which ranks the five most important and effective modalities, along with compliance indicators. This guidance could then be adopted by hospitals across Europe as an essential step in decreasing the inappropriate administration of PAP.

2 Methodology

2.1 Systematic review

2.1.1 Objectives

The objective of the systematic review was to identify the effectiveness of key modalities of PAP delivery and to provide a shortlist of 10 PAP modalities.

Effectiveness is defined as the effect of an already established efficacious therapy [13] at the population level, reflecting real-life circumstances. In contrast, *efficacy* is characterised by strong control, in that a standardised programme is delivered in a uniform fashion to a specific, often narrowly defined, homogeneous target audience. Due to the strict standardisation of efficacy trials, any positive (or negative) effect can be directly attributed to the intervention being studied [14].

Questions addressed

In this systematic review effectiveness of PAP was evaluated by addressing the following questions:

- Is the appropriate use of PAP associated with a decrease in the incidence of SSI?
- What are the factors that contribute to increased compliance with PAP?
- What are the obstacles that prevent the implementation of adequate PAP?
- Does timing, dosage or duration of PAP have an influence on the incidence of SSIs?
- Does PAP have an impact on the incidence of *Clostridium difficile* infection (CDI) and the development of antimicrobial resistance?

2.1.2 Inclusion/exclusion criteria

Included studies (in general)

All prospective RCTs were included, as were non-randomised clinical trials, such as controlled before–after studies (CBA), non-controlled before–after studies (non-CBA), interrupted-time-series analyses (ITS), case-control studies, cohort studies and other observational cohort studies, in addition to all systematic reviews and meta-analyses.

Excluded studies

Exclusion criteria were developed for articles identified in the systematic search[1]. Thus, studies retrieved from the systematic review were excluded if any of the following were present:

- Antibiotics were administered as treatment for known or suspected infection.
- Retrieved studies were conference papers without detailed descriptions of methods and results.
- Pre-operative antibiotic prophylaxis was administered topically (i.e. ear drops, irrigation with antimicrobial solution, etc.).
- Antibiotic prophylaxis was started postoperatively and not pre- or perioperatively.
- PAP administration extended for longer than 72 hours after surgery.
- Antibiotics were administered for selective digestive decontamination.
- Preoperative antibiotic prophylaxis was administered in burn patients.
- The outcome of the studies was not the incidence of SSIs, but calculation of the antibiotic concentration in various organ compartments.

Inclusion criteria for the type of surgery

The following surgical procedures for which the efficacy of PAP has been previously shown were included in the search strategy:

- Neurosurgery, including craniotomy, spinal and shunt surgery.
- Orthopaedic surgery, including hip, long bone and open limb fractures.
- Gastrointestinal surgery, including endoscopic retrograde cholangiopancreatography (ERCP), hernia repair with placement of a mesh plug, percutaneous endoscopic gastrostomy (PEG) placement, colorectal surgery, and appendectomy.
- Gynaecological surgery, including caesarean section and breast cancer surgery.
- Urological surgery, including transrectal prostate biopsy.
- Vascular surgery, including arterial reconstruction.
- Cardiothoracic surgery.

[1] For a list of excluded studies, please see Annex 2.

Exclusion criteria for the type of surgery

The following surgical procedures or non-surgical interventions were excluded:

- Ophthalmologic surgery
- Oral and maxillofacial surgery
- Dermatological surgery
- Intravascular catheter insertion (i.e. non-tunnelled and tunnelled central venous catheter).

2.1.3 Defining the population, intervention, comparison and outcome (PICO) for each question/objective

Objective 1: Is the appropriate use of PAP associated with a decrease in the incidence of SSI?

Appropriate use of PAP was defined as any of the following:

- Appropriate selection of antibiotic according to type of surgery and suspected microorganisms.
- Timely administration of antibiotics (60 minutes before incision and 120 minutes for glycopeptides or fluoroquinolones).
- Correct redosing of antibiotics according to the pharmacokinetic properties and duration of surgery.
- Discontinuation of PAP after surgery.

Types of studies included and excluded for Objective 1:

Included study types	Excluded study types
• RCTs • CBAs • Non-CBAs • Interrupted-time-series analyses • Observational retrospective or prospective cohort studies (if they provided a control, or, in case of risk factor analysis, a multivariate analysis of risk factors for SSI) • Systematic reviews and meta-analysis which evaluated the primary outcomes	• Surveillance studies without an intervention • CBAs or non-CBAs in which additional measures aside from PAP for preventing SSIs were applied at the same time • Studies employing questionnaires to analyse compliance • Observational studies without a control • Non-systematic reviews • All studies published before 2000

PICO for Objective 1	
Population	All adult and non-adult patients undergoing day, outpatient or inpatient surgery who received systemic PAP
Intervention	All interventions improving the quality of selection, timing, dosage and duration of PAP
Comparison	Patients with inappropriate administration of PAP
Outcome	Primary outcome: • SSI (The diagnosis of SSIs continues to vary between studies. Therefore, the definitions used by the original authors in the included studies were used). • Compliance with appropriate administration of PAP (primary or secondary outcome) Secondary outcome: • Mortality (any cause) • Adverse side effects (allergic reactions, diarrhoea, CDI)

Objective 2: What are the factors that contribute to increased compliance with PAP?

Types of studies included and excluded for Objective 2:

Included study types	Excluded study types
• RCTs • CBAs • Non-CBAs • Interrupted-time-series analyses • Observational retrospective or prospective cohort studies (if control was reported or, in case of risk factor analysis, if a multivariate analysis of risk factors for SSI was reported) • Systematic reviews and meta-analysis evaluating primary outcomes	• Surveillance studies without an intervention • Studies employing questionnaires to analyse compliance • Observational studies without a control • Non-systematic reviews • All studies published before 2000

PICO for Objective 2	
Population	All healthcare professionals involved in administering PAP for surgical procedures
Intervention	All interventions improving quality of PAP administration
Comparison	Healthcare professionals administering inappropriate selection, timing, dosage or duration of PAP
Outcome	Primary outcomes: • Compliance with guidelines or bundles that included PAP • Compliance with individual process measures such as indication, timing, dosage, duration of PAP

Objective 3: What are the obstacles that prevent the implementation of adequate PAP?

Types of studies included and excluded for Objective 3:

Included study types	Excluded study types
• All CBAs • Non-CBAs • Observational retrospective or prospective cohort studies, including studies with/without control group and questionnaire-based studies on PAP non-compliance • Systematic reviews and meta-analysis which evaluated the primary outcomes • No restrictions regarding the year of publication	Non-systematic reviews

PICO for Objective 3	
Population	All healthcare professionals involved in administering PAP for surgical procedures
Intervention	All interventions detrimental to appropriate administration of PAP
Comparison	All healthcare professionals administering PAP appropriately
Outcome	Primary outcomes: • Barriers for implementation of appropriate PAP • Non-compliance with guidelines or bundles addressing PAP • Non-compliance with individual process measures such as indication, timing, dosage, duration of PAP • Hospital-dependent organisational or structural barriers

Objective 4: Do timing, dosage or duration of PAP as process indicators have an influence on the incidence of SSIs?

Types of studies included and excluded for Objective 4:

Included study types	Excluded study types
• All CBAs • Non-CBAs • Interrupted-time-series analyses • RCTs • Observational retrospective or prospective cohort studies (if control group was reported or, in case of risk factor analysis, if a multivariate analysis of risk factors for SSI was reported) • Systematic reviews and meta-analysis evaluating primary outcomes • No restrictions for year of the study's publication; the majority of eligible clinical studies were conducted before 2000	• All studies not reporting SSI • All surveillance studies • Observational studies without a control • Non-systematic reviews

PICO for Objective 4	
Population	All adult and non-adult patients undergoing day, outpatient or inpatient surgery who received systemic PAP
Intervention	All interventions investigating selection, timing, dosage and duration of PAP administration
Comparison	Surgical procedures in which administration of PAP varied with respect to: • the selection of alternative antibiotics • premature or delayed timing of PAP • the administration of multiple doses of PAP • a longer duration of PAP
Outcome	Primary outcomes were defined as: • SSI • Timing and/or dosage and/or duration of PAP • Selection according to local antimicrobial susceptibility pattern

Objective 5: Does the use of PAP have an effect on the incidence of CDI and the development of antimicrobial resistance?

Types of studies included and excluded for Objective 5:

Included study types	Excluded study types
• All CBAs • Non-CBAs • Interrupted-time-series studies • Observational retrospective or prospective cohort studies (as long as a control group was reported) • Surveillance studies (as long as a multivariate analysis of risk factors for those outcomes was performed and included) • Systematic reviews and meta-analysis evaluating outcomes • No restriction regarding the year of publication	• All studies which provide neither identification nor antimicrobial susceptibility testing of bacterial isolates • Observational studies not reporting a control group • Non-systematic reviews

PICO for Objective 5	
Population	All adult and non-adult patients undergoing day, outpatient or inpatient surgery who received systemic PAP
Intervention	The selection of various antibiotics for PAP (i.e. broad-spectrum antibiotics), the administration of multiple doses of PAP, or prolonged administration of PAP after surgery
Comparison	Patients receiving narrow-spectrum antibiotics (i.e. first or second generation cephalosporins), a single dose of PAP, or a short-course of PAP
Outcome	Primary or secondary outcomes: • Occurrence of CDI • Detection of multi-drug resistant bacteria (MDR bacteria) • SSI

2.1.4 Search strategy and study selection

General search strategy for the identification of studies

CENTRAL (Cochrane Database Clinical Trials), Cochrane Database of Systematic Reviews, PubMed, Ovid MEDLINE, Ovid EMBASE, and the Database of Abstracts of Reviews of Effectiveness (DARE) were searched for this systematic review. A hand search of the bibliographic references of studies, textbooks, review articles and meta-analyses was conducted in order to find additional citations not identified by the electronic searches. The grey literature for eligible studies was also searched. Grey literature was defined according to the 'Luxembourg definition' as:

> information produced and distributed on all levels of government, academics, business and industry in electronic and print formats not controlled by commercial publishing, i.e. where publishing is not the primary activity of the producing body [15].

For Objectives 1, 2 and 5 the data sources were screened from 2000 until the end of December 2011, and for Objectives 3 and 4 from 1970 to the end of December 2011. Significant changes in hospital policy [16], surgical techniques (increasing importance of minimal, invasive surgery at the expense of open abdominal surgery) [17], and antibiotic resistance in recent years, made it necessary to put a publication year restriction on Objectives 1, 2 and 5 [18]. Other important studies retrieved for Objectives 3 and 4 that were conducted before 2000 were still valid, and were, therefore, retained [19].

The search was restricted to publications in English, French, Spanish, German and Swedish.

Search strategies for Objectives 1 to 5

Search strategies for Objectives 1–5 in MEDLINE, Embase and Ovid can be found in Annex 1, Tables 1.1–1.6.

2.1.5 Study selection from results of systematic review

After the systematic search, titles and abstracts of the retrieved search results were screened for eligibility according to the pre-defined inclusion and exclusion criteria (see Table 2.1.2). A full-text assessment by two reviewers followed.

Study selection from the screened titles and abstracts of the retrieved search results

The reviewers independently screened all retrieved titles and abstracts by using the inclusion and exclusion criteria outlined in Section 2.1.2 (please see Figure 2 for PRISMA flowchart of selection process). If reviewers disagreed on the ex-/inclusion of a title/abstract, the full text of the study was analysed. In addition to the pre-defined exclusion criteria, studies were excluded if:

- PAP was not mentioned in either the abstract or title; and
- there was no mention of whether a surgical procedure had been performed.

Titles and abstracts meeting inclusion criteria were retained for full-text analysis (Figure 2).

Studies whose full-text articles met the inclusion criteria were retained for further data extraction. A data extraction form for the assessment of study quality and outcomes was developed and tested prior to extracting data from all included studies. Each reviewer extracted the data from the full text individually, and any discrepancies between the two reviewers were discussed. Disagreements between the two main reviewers were resolved by the project leader, who acted as a third reviewer[2].

2.1.6 Quality assessment of included studies

The methodological quality of the studies was assessed using specific criteria for each study design. Study design was evaluated by using the criteria developed by the Cochrane Effective Practice and Organisation of Care (EPOC) Review Group [20]. Grading was done by using the Grading of Recommendations Assessment, Development and

[2] Further information is available upon request. See p. ii for details.

Evaluation working group (GRADE working group) criteria [21,22]. In addition, grading of CBAs and non-CBAs was done using the criteria developed by the Stanford-UCSF Evidence-based Practice Centre (EPC) and the Agency for Healthcare Research and Quality (AHRQ), which published the 'Critical Analysis of Quality Improvement Strategies' [23].

The quality of evidence of the included studies was assessed using the GRADE approach, which assigns high, moderate, low, and very low quality ratings to studies. The highest quality rating is for RCTs [22,24], which can be downgraded to moderate, low or even very low quality evidence, depending on the presence of limitations, indirectness of evidence, unexplained heterogeneity, imprecision or inconsistency of results or publication bias.

Although observational studies are rated as low quality due to study design, , they can – in accordance with GRADE – be upgraded to moderate study quality if mitigating factors are present, for example the magnitude of a treatment effect or the presence of a dose-response gradient [25][3].

Quality assessment for randomised control trials (RCT) or meta-analyses/systematic reviews of RCTs

Randomised control trials are by default rated as high quality and are downgraded if they meet any of the five criteria listed in Table 1. Furthermore, if serious limitations are present in RCTs, the quality is decreased to low quality [20,22][3].

No serious limitations	Studies employed a randomisation method that did not allow the investigator/participant to know or influence the intervention group before an eligible participant entered the study, performed blinding of patients and personnel as well as blinding of outcome detection (if method was not described, likelihood was assumed), and revealed a low risk of attrition bias.
Serious limitations	High risk of performance and detection bias (i.e. studies performed no blinding of patients, personnel, and outcome detection). Studies performed blinding, but demonstrated a high risk of attrition or reporting bias or were pre-terminated.
Very serious limitations	Studies revealed three or more high risks of bias, i.e. studies performed no blinding of patients, personnel and outcome detection, and demonstrated a high risk of attrition or reporting bias.
Unclear limitations	No information was provided on the methods of randomisation; blinding of patients, personnel and outcome detection; and characterisation of study participants.

Table 1. Limitations in study design suggesting a high likelihood of bias

The study consisted at least of two intervention sites and two control sites.
The timing of the study period for the control and intervention group was comparable (i.e. the pre- and post-intervention periods of measurement for the control and intervention groups should be the same).
The intervention and control groups were comparable for their key characteristics.
There was a clearly defined point in time at which the intervention occurred and this was reported by the researchers.
At least three data points before and three after the introduction of the intervention was collected.

Quality assessment for CBAs, ITS and observational studies

CBA studies were evaluated according to the by EPOC[3].

a) If CBA studies fulfilled the following three key criteria, they were graded assigned moderate quality of evidence [20,22].

b) ITS were evaluated by the EPOC Review Group and GRADE and were assigned moderate quality of evidence if they met the following two key criteria [20,22].

c) If an observational cohort study accumulated 80–100% of the maximum point value outlined by GRADE, the study quality was considered 'good' and the quality of evidence was rated as 'moderate'; if it accumulated ≥60–<80% and was of 'moderate' quality, it was rated as 'low; if it accumulated <60% and was considered 'poor', the study quality was rated as 'very low' (according to GRADE criteria) [25].

The best grade that can be given to observational cohort studies is 'moderate' (GRADE criteria).

Quality assessment for non-CBA studies

GRADE does not assess the methodological quality of non-CBA studies as is only applied to controlled or observational studies [24,25]. In order to evaluate the internal and external validity of the studies included in this review, the approach proposed by Ranji et al. was used [23].

In their report 'Closing the Quality Gap: A Critical Analysis of Quality Improvement Strategies', Ranji et al. acknowledged that many studies were likely to employ a non-controlled before-after design (non-CBA)[23] and developed specific quality criteria to identify studies where – within the limitations of the study design – causality could be more reliably attributed to the intervention. In this review, several quality criteria were used for grading

[3] Further information is available upon request. See p. ii for details.

non-CBA studies. The criteria outlined below were used to rate the studies by answering the following questions with a 'YES', 'NO' or 'Unclear' (if insufficient information was provided).

Questions to address to assess the internal validity of studies were:

- Was the intervention performed independently of other QI efforts or other changes?
- Did the study report data on more than one point in time before and after the intervention?
- If the study reported infection rates, were process measurements also reported?

Factors affecting the external validity of the studies answered to the following two questions:

- Did the study report infection rates and use CDC/NNIS methodology for measuring infections that developed after hospital discharge?
- If the study reported infection rates, was surveillance for infections performed after discharge from the hospital?

The quality of the included studies was evaluated and grades were assigned ('good,' 'moderate' or 'poor'). In general, studies meeting the above criteria for external validity, as well as a minimum of two of the above criteria for internal validity, were considered to be of stronger internal and external validity; studies with serious flaws affecting internal validity (none of the three criteria met) were considered to have poor internal validity.

After the application of the quality criteria, the studies were graded and grouped as follows:

- Good quality: study fulfilled ≥4 criteria
- Moderate quality: study fulfilled at least 3 criteria
- Poor quality: Study fulfilled <3 criteria.

According to the GRADE guidelines, non-CBA studies with 'good' external and internal validity are considered to have moderate quality of evidence, while 'moderate' external and internal validity is considered to yield a low quality of evidence. Studies with 'poor' external and internal validity are considered to have very low quality of evidence (Table 2).

Table 2. Equivalency levels of Ranji et al.'s grades to the grades assigned by the GRADE approach [22-25]

Type of study	Grading of the study's external and internal validity according to Ranji et al.	Grading the quality of evidence according to the GRADE approach
RCT	Not applicable	• No limitations: high quality • Serious limitations: moderate quality • Very serious limitations: low quality
CBA	• Good validity • Moderate validity • Poor validity	• Moderate quality • Low quality • Very low quality
ITS	• Good validity • Moderate validity • Poor validity	• Moderate quality • Low quality • Very low quality
Non-CBA	• Good validity • Moderate validity • Poor validity	• Moderate quality • Low quality • Very low quality
Observational studies	Not applicable	• Moderate quality • Low quality • Very low quality

In order to simplify the assessment of studies, points were assigned to the four grades used by GRADE approach:

- High quality: 4 points
- Moderate quality: 3 points
- Low quality: 2 points
- Very low quality: 1 point

Assessment of 10 PAP modalities from the results of the systematic review for the shortlist

The ECDC call for tender specified that a shortlist of 10 PAP modalities be derived from the summary of evidence collected in the systematic review. This process was achieved as follows:

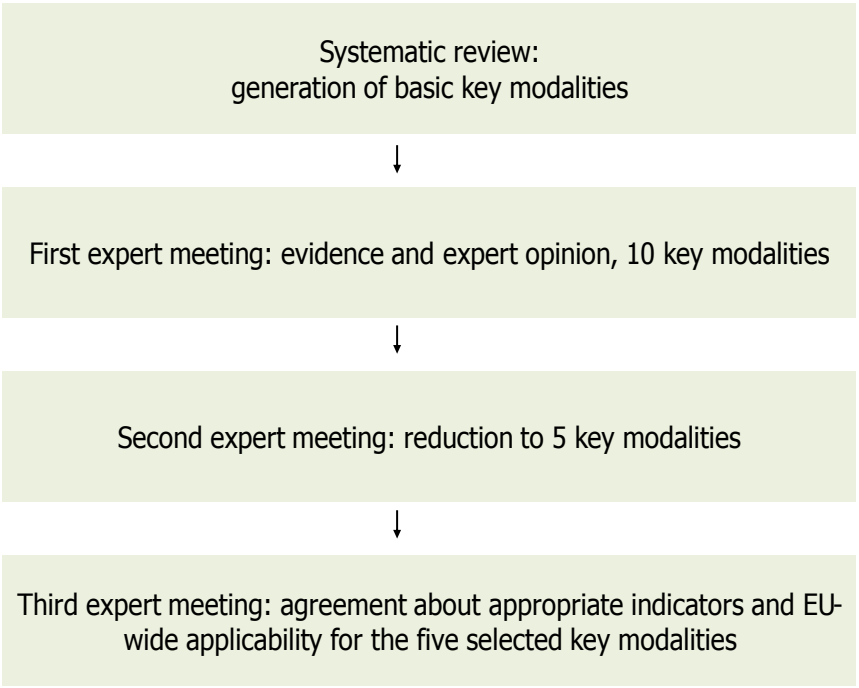
First, results for all PAP modalities were collected from each objective's results and duplicates were removed. Second, the modalities of similar content (e.g. audit and feedback, different interventions for administering or ending PAP, etc.) were summarised and grouped by content. Third, the PAP modalities derived from this process were ranked according to the quality of evidence of the studies supporting them.

PAP modalities supported by high- and moderate-quality studies were ranked first, followed by those supported by low-quality studies. Only the 10 modalities ranked highest were retained; lower-ranking modalities were discarded.

2.2 Key PAP modalities: indicators and barriers to implementation

In three one-day consensus workshops, an expert group ranked and narrowed down the 10 PAP modalities to five. The experts developed a consensus-based guidance on key modalities and defined quality indicators for PAP. The names of the expert group members, their institutional affiliations and their areas of expertise are provided above; Figure 1 gives an overview of the process.

Figure 1. Flowchart: developing five key modalities for PAP



2.2.1 First expert meeting

The goal of the first expert meeting in Berlin was to review the results of the systematic review and to review the experts' scores of the 10 PAP modalities. Prior to the meeting, the experts had received the systematic review and the results, the 10 PAP modalities and an evaluation form, which allowed them to score the 10 PAP modalities on quality of evidence, EU-wide applicability and implementability. The 10 modalities were then further broken down into 15 questions or components, so that each item could be clearly described and scored individually, thus minimising the risk of misinterpreting the individual components of each PAP modality[4].

2.2.2 Second expert meeting

The second expert meeting was also held in Berlin. The aim was to narrow down the 10 PAP modalities to five by ranking them according to quality of evidence and assessing their EU-wide applicability.

Before the second meeting, the experts received a questionnaire with the 10 agreed-upon PAP modalities (Table 20) from the first meeting and were asked to score them again (Table 21). The submitted scores were then presented at the second meeting. Each modality was discussed individually and was ranked according to the experts' score. Consensus was achieved by unanimous agreement on the five final key PAP modalities.

2.2.3 Third expert meeting

The third expert meeting was held in Stockholm. The aim was to develop five quality-of-care indicators for the monitoring of the implementation of the five PAP modalities and to identify barriers for EU-wide applicability.

Selection of quality indicators

[4] Further information is available upon request. See p. ii for details.

Before the third meeting, a short literature search was performed to identify published indicators for the monitoring of PAP. These were sent to the experts via e-mail for input and further comment. The studies derived from the search were not evaluated for quality of evidence because indicators were selected based on expert opinion.

At the third meeting, the proposed indicators for the five PAP modalities were presented and discussed. By the end of the meeting, the experts had reached a consensus on the final indicators.

After the meeting, the authors of this literature review identified numerators and denominators for each indicator and further developed these for Indicators 2 to 5. In addition, they also developed a checklist for Indicator 1. The completed list of indicators was sent to all members of the expert group for further comments. Following expert feedback, a revised list of the final indicator list was sent to the experts for confirmation and agreement. The experts unanimously agreed on the final list of indicators.

Barriers

Experts agreed to use the median score for the identification of barriers for the implementation of PAP since this score best represented the collective opinion of the small expert group. After the median scores were presented, the experts re-examined each modality, taking into account the identified barriers and comparing the results of the grading. Grades 3 and 4 were considered a 'potential barrier', grades 5 and 6 a 'major barrier', while grades 1, 2, and 'not applicable' were not considered a barrier. However, 'not applicable' was considered to require further discussion. Agreement among experts was achieved when six of the ten experts voted for the same grade or higher. If eight or more of ten experts voted for the same grade or higher, 'strong' agreement was achieved. During the discussion, no votes were changed to avoid the influence of opinion leaders. It became clear during the meeting that barriers 9, 10, 11 and 12 were not uniformly understood, especially regarding key modality 1. Therefore these barriers were rephrased and barrier 12 was split into two separate barriers, resulting in a total of thirteen barriers. After the meeting, experts were asked to re-grade these barriers and submit their results via e-mail[5].

[5] Further information is available upon request. See p. ii for details.

3 Results

3.1 Results of the systematic review

3.1.1 Search strategy

The systematic search in EMBASE, OVID Medline and PubMed, CENTRAL, and the Cochrane Database of Systematic Reviews yielded 663 records. In addition, another 24 records were identified by hand search. The number of removed duplicate records was 36, leaving 651 abstracts for further screening. Of these, 491 abstracts were excluded according to the exclusion criteria, leaving 160 studies for full text analysis. A further 50 studies were excluded because pre-defined exclusion criteria were applied, which left 110 studies to be included and analysed further (Figure 2).

Figure 2. PRISMA flowchart: identified, screened, and included/excluded studies

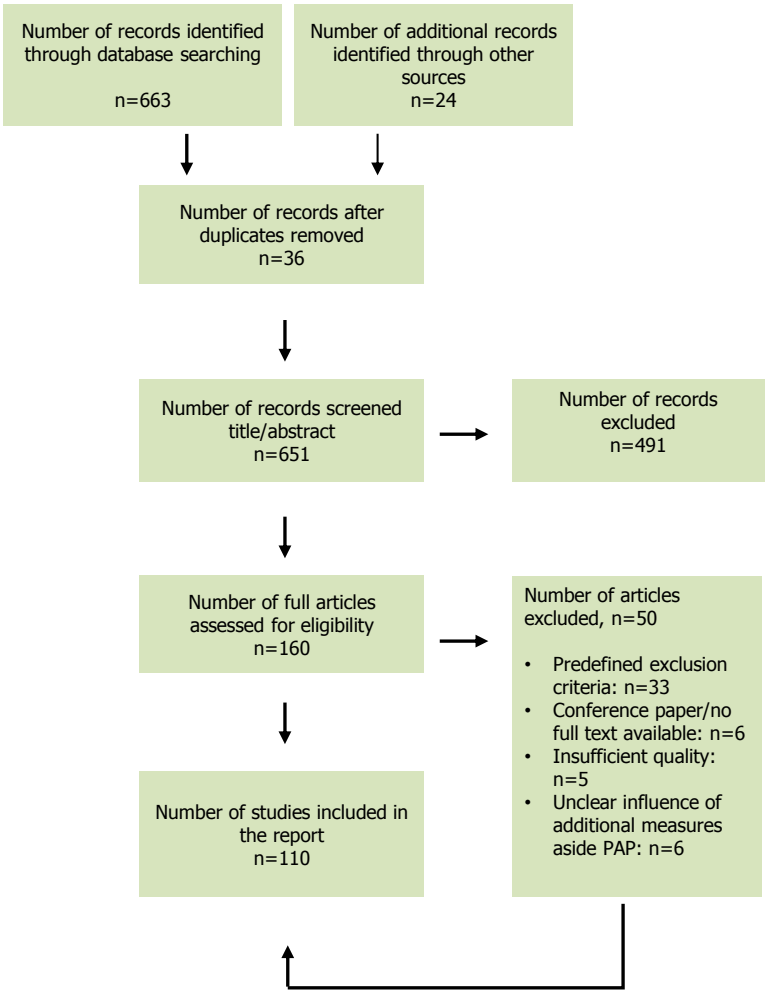


Table 3. Distribution of included study designs and geographical location of studies, by continent

Distribution of study designs, n (%)	Distribution (world regions)
Non-CBAs: n=48 (43.6%)	North America: n=64
Observational cohort studies: n=31 (28.2%)	Europe: n=20
Systematic reviews/meta-analyses: n=13 (11.8%)	Asia: n=12
RCTs: n=12 (10.9%)	South America: n=5
ITS: n=3 (2.72%)	Australia/New Zealand: n=4
CBAs: n=2 (1.82%)	Middle East: n=3
Questionnaire: n=1 (0.9%)	Central America: n=2
Total: n=110	

Objective 1: Is the appropriate use of PAP associated with a decrease in the incidence of surgical site infections?

Forty studies, all published after 2000, evaluated compliance with the adequate selection, timing and duration of PAP; these studies also evaluated the association of PAP with SSI rates. Details on distribution can be found in in Table 4. The characteristics of each study, their results, and their quality grades were summarised[6].

Table 4. Distribution of included study design and geographical location of included studies, Objective 1

Type of study	Distribution (world regions)
Non-CBAs: n=24 (60%)	North America: n=21
Observational cohort studies: n=12 (30%)	Europe: n=7
ITS: n=2 (1.82%)	Asia: n=6
CBAs: n=2 (1.82%)	South America: n=4
	Central America: n=2
Total: N=40	

Four large cohort studies retrospectively analysed the influence of appropriate PAP selection, timing and duration on the SSI rate [26-29]. Hawn et al. showed a significant association between timing and appropriate selection of PAP and the incidence of SSI in an unadjusted risk analysis [26]. The authors analysed the data of 9 195 colorectal and vascular procedures, hip and knee arthroplasty, performed in 95 US Veterans' Affairs (VA) hospitals between 2005 and 2006 [26]. However, when adjusting the analysis for patient and procedure factors associated with SSI, this significant association disappeared [28]. Three years later, in 2011, the authors presented an enlarged database with data from 60 853 surgeries performed in 112 VA hospitals between 2005 and 2009, including patients who underwent cardiac surgery and hysterectomies [28]. The authors measured the compliance rate of administrating appropriate PAP in respect to timing, selection and duration. They demonstrated a significant increase in the compliance rate with appropriate PAP administration over the observed study period, but neither the absolute nor the risk-adjusted SSI rates improved significantly. This was confirmed by Stulberg et al. in a retrospective cohort study [29] which analysed the hospital discharge data of 405 720 patients from 398 hospitals in the USA and examined the relationship between the US-American Surgical Care Improvement Project (SCIP) measures and postoperative infection rates [29]. None of the individual measures such as timing, selection and duration of PAP were significantly associated with a lower probability of infection.

Ingraham et al. analysed the association between SCIP measures and risk-adjusted outcomes like SSI in a cross-sectional study of > 600 000 surgical procedures performed in 200 US acute-care hospitals (non-VA hospitals) [27]. The authors found a significant relationship between appropriate selection of PAP (SCIP 2) with SSI rate ($r=-0.20$, $p=0.004$). Timely administration of PAP within 60 minutes prior to incision (SCIP 1) was not associated with better outcomes ($p=0.08$).

What measures can be taken to increase the adherence to appropriate administration of PAP has been shown in several, mostly non-controlled intervention studies. However, the quality of evidence in many of these studies is limited [12,30-33].

Three of the controlled studies [34-36] were considered of good and one of moderate [37] methodological quality with regard to internal and external validity. Five of the 24 identified non-controlled before/after studies (non-CBAs) demonstrated good internal and external validity [38-42]. Most of the other non-CBA were of moderate to poor methodological quality [43-45]. This lack of well-designed trials on appropriate PAP compliance has also been reported in the critical analysis of quality improvement strategies by the US-American Agency for Healthcare Research and Quality [23].

Several studies investigated the impact of forming a multidisciplinary team for implementing a PAP protocol on the incidence of SSI rates [39,46-56].

One of the well-designed controlled studies, an interrupted time series analysis by Weinberg et al., used a continuous quality improvement (CQI) methodology to target post-operative infections among women undergoing caesarean sections in two maternity hospitals in Columbia [36]. A multidisciplinary team (obstetrician, nurses, pharmacist and administrator) was trained in CQI methods and formulated a protocol which structured the process of ordering and administering PAP; feedback on infection rates was given to hospital administrators. Grading of the study showed that the internal and external validity were good because the investigators collected data at multiple time points, performed appropriate ITS statistical analysis, measured two relevant process parameters (use of PAP and appropriate timing of PAP) and used CDC/NNIS measurement standards for defining SSIs. The intervention achieved significant improvement of compliance for adequate administration of PAP and demonstrated a significant reduction of SSIs. Compliance with administration of PAP increased from 71% to 95% after intervention in

[6] Further information is available upon request. See p. ii for details.

Hospital A (p<0.001) and from 36% to 89% in Hospital B (p<0.001). PAP was administered timely in 24% of cases before and in 96% of cases after the intervention (p<0.001) in Hospital A, and in 50% of cases before and 96% of cases after intervention in Hospital B (p<0.001). The SSI rate was 10.5/100 procedures before the intervention and could be reduced to 0/100 procedures afterwards in Hospital A (p<0.001); SSI reduction in Hospital B was not significant (before: 6.1/100 procedures, after: 4.4/100 procedures) [36].

The interrupted time series study by van Kasteren et al. was conducted in 13 hospitals in the Netherlands which participated in a national surveillance network of nosocomial infections (preventie van ziekenhuisinfecties door surveillance [PREZIES]) [35]. In each hospital, study participants formed multidisciplinary teams consisting of surgeons, anaesthetists, microbiologists, pharmacists, nurses, and local antibiotic policy committees, performed an audit, presented the audit results, and recommended measures for improvement. They also organised educational meetings for physicians and nurses, emphasising guideline adherence and appropriate use of prophylactic antibiotics. The study demonstrated good internal and external quality. The study revealed statistically significant improvement in the appropriate selection of PAP (before intervention 3.9%, after intervention 63.5%, p<0.01), appropriate timing of PAP (before intervention 49.5%, after intervention 60.6%, p<0.01) and appropriate duration of PAP (before intervention 45.8%, after intervention 68.6%, p<0.01). With respect to SSIs, the study demonstrated a non-significant trend towards reduced SSIs (before intervention 5.4%, after intervention 4.6%, p=NS). The investigators followed CDC recommendations for SSI post-discharge surveillance and standard prophylactic antibiotic protocols, thus enabling the study's results being transferrable to other settings.

Dellinger et al. reported on a National Surgical Prevention Collaborative in which 44 US hospitals participated for one year, covering a total of 35 543 surgical procedures [46]. Each hospital formed a multidisciplinary team which participated in four two-day training sessions, receiving instructions on the appropriate administration of PAP. These multidisciplinary teams implemented PAP protocols in their hospitals, reported monthly SSI rates, and submitted data about the proportion of patients receiving PAP with the appropriate antibiotic, given within 1 h prior to incision and no longer than 24 hours after surgery. Overall SSI rate decreased significantly from 2.28% in the first quarter (215 infections/9 435 surgeries) to 1.65% (158 infections/9 584 surgeries) in the fourth quarter (p <0.001).

One of the non-CBA revealing good quality regarding internal and external validity was Forbes et al. [39]. The authors demonstrated that developing and implementing a protocol of perioperative antibiotic prophylaxis according to guidelines by a multidisciplinary working group including anaesthesiologists, surgeons, nurses and pharmacists resulted in significant improvement of compliance with the administration of PAP within 60 minutes before incision (before intervention only 5.9% of patients received timely PAP versus 92.6% after intervention (p <0.001). The SSI rate improved after the intervention but did not reach statistical significance (SSI rate pre-intervention vs. post-intervention: 14.3% vs. 8.7%, p=0.21). This finding was confirmed in another non-CBA of moderate study quality by Pastor et al. [50]. The authors showed a significant increase in compliance by implementing a multidisciplinary AM team, but also could not influence the SSI rates (compliance with redosing: before intervention 83% vs 91% after intervention, p<0.01; compliance with PAP duration: before intervention 70% vs 84% after intervention, p<0.01).

The value of audit and feedback was evaluated in several studies [12,39,47-50,52,53,55,57-59]. The methodologically well-performed non-CBA by Liau et al. considered all clean and clean-contaminated elective gastrointestinal/hernia operations and analysed the effect of implementing a PAP protocol and an audit system with feedback on the SSI rate [60]. It showed a decrease in the SSI rate from 3.1% to 0.5% (p<0.001) after the intervention. For the study, a multidisciplinary team developed and distributed antibiotic guidelines to operating room (OR) staff, and anaesthesiologists were in charge of reference and compliance, focusing on the selection of the type of antibiotic and the administration of PAP within 30 minutes before incision (including redosing after four hours if surgery was prolonged, and stopping prophylaxis within 24 h after surgery). An interim analysis of outcomes and compliance data was conducted every six months [60].

Education of healthcare professionals about appropriate administration of PAP was also the scope of some investigations [38,40,49,52,60-62]. The methodologically well performed non-CBA study by Gomez et al. analysed an intervention consisting of education of OR staff and introduction of an antibiotic prophylaxis request form that included an automatic stop of prophylaxis within 24 h after surgery [40]. A total of 3 496 surgical procedures including cardiovascular, gastrointestinal, gynaecological, neurosurgical, orthopaedic and urologic surgery were analysed before intervention; 3 982 procedures were assessed after the intervention. Adequate administration of PAP was predefined according to guidelines, i.e. timing of PAP <2 h before incision. This intervention significantly reduced the inadequate selection, timing and duration of antibiotic prophylaxis and achieved a significant reduction of risk of SSI rates (RR 0.59; 95% CI, 0.44–0.79; p<0.01).

Some studies investigated if the administration of PAP should be the responsibility of the anaesthesiologist in order to guarantee timeliness [49,54,55]. The non-CBA study by Kanter et al. formed a multidisciplinary team consisting of anaesthesiologists, surgeons, operating room nurses, and infectious disease specialists that developed guidelines [49]. The responsibility of administrating the antibiotic prophylaxis was shifted from the nurses to the anaesthesiologist. Compliance was measured by monitoring antibiotic selection, duration, and time of administration, and reported monthly to the OR staff. The adherence to appropriate PAP administration improved:

compliance with adequate timing increased from 11% to 91%, and compliance with adequate duration from 10% to 92%. SSIs after cardiovascular surgery decreased from 3.8% before the intervention to 1.4% (no information about p-value provided). Although the study demonstrated good external validity, it revealed limitations in the description of the statistical analysis resulting in a lack of testing for significance and also demonstrated moderate internal validity due to lack of reporting for more than one time point before intervention. Trussell et al. also transferred the responsibility of PAP administration to the anaesthesiologist, in addition to implementing a multidisciplinary AM team and performing audits and feedback [54]. The study demonstrated an increase in PAP compliance and reduction of SSI rates (improvement in compliance regarding timing of PAP: 72% vs 92% ($p<0.001$), selection of PAP: 90% vs 95% ($p=0.2$), discontinuation of PAP within 24 h: 67% vs. 85% ($p<0.001$); reduction of SSI: before the intervention 3.5% and afterwards 1.5%; $p=0.001$) [54].

Summary of evidence for Objective 1: Is the appropriate use of PAP associated with a decrease in the incidence of surgical site infections?

The summary of evidence for Objective 1 can be found below. All studies were observational and exhibited considerable methodological variability. All studies reported SSI rates as either the primary or the secondary outcome. The following studies showed a decrease in SSIs [27,30,32,34,36,37,40,42-46,48,53,57,60-65] when there was an increase in compliance with PAP.

Studies which did not show significant reductions in SSIs showed either a non-significant (or non-reported statistical value) decrease in SSIs, no change, an increase or incomplete reporting[7].

The included studies, which showed significant reduction in SSIs, were extremely heterogeneous since different methods and study designs were used; interventions and reporting methods differed considerably, and the studies were performed on heterogeneous populations in different healthcare settings. Due to this large variability, a meta-analysis was not performed, in order to assess whether there was an overall significant reduction in SSI rates following an increased compliance with PAP.

Compliance with the following interventions was found to demonstrate a significant decrease in SSIs in the studies:

- A multidisciplinary AM team (including surgeons, anaesthesiologists, nurses, pharmacist, infection control specialists and clinical microbiologists) should be formed. The AM team should implement a protocol of adequate PAP (selection of antibiotic, dosage and duration) for each surgical procedure [30,36,45-47,60,65].
- Trained personnel in infectious diseases, prevention and control should perform regular educational meetings for surgeons, anaesthesiologists and OR nursing staff about adequate PAP, risk factors for surgical site infections, and provide updates on guidelines [30,36,45,57,60,62,63].
- An audit of OR staff (surgeons, anaesthesiologists, nursing staff) and feedback should be performed regularly in order to control compliance with appropriate PAP (selection, timing, dosage and duration) [30,49,60,62].
- A computer-assisted decision support system, an automatic reminder system, a surgical patient safety checklist, or a 'time-out' procedure should be implemented in order to guarantee appropriate administration of PAP [27,34,46,61,62].
- Administration of perioperative prophylaxis should be the responsibility of the anaesthesiologist [49].
- A computer-assisted automatic stop order of PAP should be implemented in order to guarantee an appropriate duration of prophylaxis [40,64].
- In order to guarantee appropriate redosing, an acoustic reminder should be implemented [37].
- Pre-operative screening of patients at risk for MDRO colonisation should be considered [42,63].
- Standardised order forms for PAP should be implemented [30,36,40,49,51,62].
- The PAP protocol should be stratified by patient's specific factors (i.e. weight, underlying diseases, etc.) [53,65].

Objective 2: What are the factors that contribute to increased compliance with PAP?

Twenty-four included studies, all published after 2000, evaluated measures intended to improve compliance with administration of adequate PAP (e.g. selection, timing, and duration). Details on distribution can be found in Table 5.

The characteristics of the studies, their results and the grading of methodological quality/quality of evidence were summarised[7].

Table 5. Distribution of included study design and geographical location of included studies, Objective 2

Type of study	Distribution (world regions)
Non-CBAs: n=16 (66.7%)	North America: n=15
Observational cohort studies: n=5 (20.8%)	Europe: n=6
RCTs: n=1 (4.2%)	Asia: n=1
ITS: n=1 (4.2%)	Australia/New Zealand: n=1
Scoping review: n=1 (4.2%)	Middle East: n=1
Total: N=24	

A scoping review identified factors and interventions that can influence PAP administration [66]. A scoping review is conducted with rigor comparable to a systematic review, but examines a broader question by reviewing a wide range of study designs. Gagliardi et al. included five studies which evaluated compliance with appropriate administration of PAP as primary outcome, but did not evaluate the impact on SSI rate [66]. They concluded that the following measures improve compliance with appropriate PAP: implementation of multidisciplinary protocols/pathways; education or individualised performance feedback addressing clinician knowledge, attitudes, beliefs and behaviours; implementation of computerised decision-support programmes; and written orders for PAP kits, or pharmacist preparation of individualised PAP kits [66].

In a RCT, Kritchevsky et al. investigated whether the implementation of a quality-improvement collaborative combined with comparative feedback of performance data would increase compliance [67]. They included 44 US acute-care hospitals, each of which randomly sampled approximately 100 selected surgical cases (cardiac surgery, hip or knee replacement, hysterectomy) at both the baseline and re-measurement phases. All hospitals received a comparative feedback report. Hospitals randomly assigned to the intervention group (n=22) participated in a quality improvement collaborative comprising two in-person meetings led by experts, monthly teleconferences, and receipt of supplemental materials over nine months. The groups did not differ in the change in proportion of patients who received a properly timed antimicrobial prophylaxis dose (−3.8 percentage points [95% CI, −13.9–6.2]) after adjustment for region, hospital size, and surgery type. Similarly, the groups did not differ in individual measures of antibiotic duration; use of appropriate drugs; receipt of a single preoperative dose; or an all-or-none measure combining timing, duration and selection. The authors assumed that the hospitals volunteered for the effort were motivated to change. They concluded that all included hospitals improved their compliance data for these PAP measures by receiving a performance feedback that could not significantly improve by additional participation in a quality-improvement collaborative.

A CBA study by Ritchie et al. with moderate study quality was conducted in the orthopaedic service of two hospitals in New Zealand [68]. In order to reduce non-indicated, prolonged administration of PAP >24 h in patients undergoing hip fracture surgery, a pre-printed prescription sticker was introduced and applied to the medication chart by the anaesthetist when the initial dose of antibiotic was given. The number of patients who received three doses according to the hospital guidelines increased from 29% to 74% ($p<0.001$). In the control hospital, the number of patients who received a three-dose course of PAP was 20% in the pre-intervention period and 26% in the post-intervention period ($p=0.37$) [68].

A moderate-quality non-CBA study by Rosenberg et al. used a time-out procedure (documented on a time-out sheet) to verify antibiotic administration prior to incision. This sheet not only served as a reminder but also documented that the patient received PAP in a timely manner [69]. The compliance rate of appropriate timing of PAP in patients undergoing spine surgery, total knee or hip joint arthroplasty increased from 65% pre-intervention to 99.1% post-intervention ($p<0.0001$). Independent audits in the 18 months following the completion of the study demonstrated significantly better compliance with timing of PAP in patients with orthopaedic surgery [69]. A non-CBA by Nemeth et al. could not confirm these results [70]. The authors evaluated the effects of a time-out with oral verification of antibiotic administration on the compliance to timely PAP administration [70]. In the pre-intervention group, 87 of 97 cases (90%) demonstrated timely antibiotic administration. In the post-intervention group, only 163 of 193 cases (85%) received timely antibiotic prophylaxis. Although pre-intervention compliance was slightly better than post-intervention, this difference was not significant ($p=0.223$). The authors concluded that the addition of preoperative verification to timely antimicrobial prophylaxis does not improve compliance with the prophylaxis guidelines [70].

Clinical education of surgeons, anaesthesiologists and nursing staff was implemented by Ozgun et al. in a non-CBA study (good internal and external validity) [71]. The authors demonstrated a significant decrease in inappropriate selection, timing and duration of PAP after the intervention.

[7] Further information is available upon request. See p. ii for details.

A non-CBA study by Alerany et al. (good internal and external validity) with 586 patients in a single ambulatory surgical centre in Israel analysed the appropriateness of PAP after forming a multidisciplinary team which implemented a PAP protocol including international guideline recommendations on antibiotic selection, timing and duration of prophylaxis. In addition, an integrated dispensing system was established which included a specific medication set for each surgical procedure, a medication information sheet, and a discharge report. The appropriateness of PAP increased to 94.9% post-intervention as compared to 50.9% pre-intervention ($p<0.01$) [72].

Bratzler et al. analysed 34 133 randomly selected patients undergoing cardiothoracic, vascular, colorectal, gynaecologic surgeries, and knee or hip arthroplasty. They demonstrated that in only 55.7% of the procedures, PAP was administered within 60 minutes before incision. Patients undergoing cardiac or orthopaedic surgery were more likely to receive PAP in time. The authors assumed that this can be explained by the more common use of pre-printed care plans or order forms (50.0% of patients undergoing hip or knee arthroplasty, and 36.6% of patients undergoing cardiac surgery, as compared to 4.0% of colorectal cases, 4.5% of hysterectomy cases, and 5.3% of vascular surgery cases) [73]. A prospective cohort study by Turnbull et al. analysed a total of 4 835 patients admitted for surgical procedures who required antimicrobial prophylaxis. Turnbull et al. demonstrated an effective first prophylactic dose for all cases when an order was written (OR 19.7; CI 95%, 9.1–42.7; $P<0.001$) and given in the operating room (OR 13.9; CI 95%, 7.5–25.6; $P<.001$). Factors that influence an effective first prophylactic dose negatively were beta-lactam allergy (OR 0.49; CI 95%, 0.4–0.61; $P<0.001$) and same-day surgery (OR 0.57; CI 95%, 0.4–0.82; $P<0.001$) [74].

Carlès et al. demonstrated in a non-CBA study that the use of a personalised antibiotic kit could significantly increase adherence to guidelines regarding appropriate selection of antibiotics (82% vs 41%, $P<0.001$), appropriate timing of administration (12% vs 24%, $P=0.003$), and duration of PAP (1.5% vs 22%, $P<0.001$) [75].

A disadvantage of this approach was that personalised kits could only be provided for patients with elective surgery, as kits had to be prepared in the hospital pharmacy, which required advance information on patients and surgery.

Summary of evidence for Objective 2: What are the factors that contribute to increased compliance with PAP?

The following list summarises measures which increased compliance with appropriate PAP administration.

- A multidisciplinary antimicrobial management team should be formed; the team should implement a protocol of adequate PAP (selection of antibiotic, dosage and duration) for each surgical procedure [66,76-80].
- In order to guarantee appropriate administration of PAP, one of the following should be implemented: computer-assisted decision support, a pre-printed order form, an automatic reminder system, or a checklist for optimised timing [66,72,81,82].
- In order to guarantee appropriate and timely administration of PAP, a time-out with oral verification of antibiotic administration should be performed before incision; alternatively, a surgical patient safety system checklist should be implemented [69,81].
- Administration of perioperative prophylaxis should be the responsibility of the anaesthesiologist [79].
- Pre-printed stickers for stopping PAP or a computer-based antibiotic order set with an automatic stop order for PAP can be implemented [68,83].
- Training/education of surgeons, anaesthesiologists and OR nursing staff [71,80,81].
- Implementation of the local PAP protocol according to guidelines; standardised orders for PAP [81].
- Use of a personalised surgical antibiotic kit prepared in the hospital pharmacy (only feasible for elective surgery) [75].
- Institution of a computerised reminder system for optimal redosing of PAP [84].

The following studies demonstrated a significantly increased compliance with adequate PAP in respect to selection, timing and duration by several interventions, but could not demonstrate that the observed decrease in SSI rate was statistically significant. The measures included:

- implementation of a multidisciplinary management team [39,48,50-52,55,56];
- education/training [52];
- shifting the responsibility of PAP administration to the anaesthesiologist [55];
- audit and feedback [12,39,48,50,52,55,58]; and
- implementation of standardised order form [51].

Two studies demonstrated that significant improvement in compliance in administering a single dose of PAP – as opposed to prolonged continuation of PAP – did not increase the SSI rate and thus did not harm the patients [38,59].

Objective 3: What are the obstacles that prevent the implementation of adequate PAP?

Five of the included studies analysed obstacles for compliance with the appropriate administration of PAP. One of these studies was already included in Objective 2. Details on distribution can be found in Table 6. The characteristics of each study, the results and the grading of quality were summarised[8].

Table 6. Distribution of included study design and geographical location of included studies, Objective 3

Type of study	Distribution (world regions)
Observational cohort studies: n=3 (60%)	North America: n=2
Non-CBAs: n=1 (20%)	Europe: n=2
Questionnaire: n=1 (20%)	Middle East: n=1
Total: N=5	

A well-designed prospective cohort study by Al-Momany et al. enrolled 236 patients who were admitted for cardiac surgery in the only official referral hospital for cardiac surgery in Jordan [85]. The investigators analysed the adherence to international PAP guidelines for cardiac surgery in their hospital. They demonstrated that adherence to international guidelines for antibiotic selection was low (1.7%). It was also low with respect to dosage (27.9%) and duration (39.4%), whereas the adherence for timely administration of PAP was high at 99.1%. The authors concluded that the absence of standardised antimicrobial practice guidelines was responsible for a lack of communication between anaesthesiologists and surgeons, thus producing poor monitoring and non-adherence. They proposed that hospital guidelines be developed and that the clinical pharmacist be given a central role in administration, monitoring and intervention of PAP [85].

Another well-designed study by Tan et al. reported on semi-structured interviews conducted with anaesthesiologists, surgeons and perioperative administrators in two large academic Canadian hospitals and highlighted workflow, unpredictable and unanticipated changes to the workflow, and role perception as the dominant obstacles in guideline observance [86]. Another important barrier to appropriate prescribing was the low priority assigned to timely antimicrobial administration, organisational communication, and inconvenience of administration.

A prospective, multi-centre audit of 1763 elective procedures was performed in 13 Dutch hospitals (the study is part of the PREZIES project) and published by van Kasteren et al. [87]. The objectives of this study were to analyse the adherence to local hospital guidelines for PAP and explore the reasons for non-adherence. The study identified the following barriers: lack of awareness due to ineffective distribution of the most recent version of the guidelines, lack of agreement by surgeons with local hospital guidelines, and factors such as organisational constraints in the surgical suite and the ward.

The study by Turnbull et al. identified same-day surgery and ß-lactam allergy as significant risk factors for inappropriate compliance with the proper timing of PAP [74].

Although the non-CBA study by Brusaferro et al. had some serious limitations in respect to internal and external validity, it provided interesting information about non-compliance [88]. In this study, a protocol for appropriate PAP was implemented and the reasons for non-compliance were investigated. The authors identified deficiencies in hospital policy, protocol definition, and cultural behaviour of healthcare workers as reasons for non-compliance.

Summary of evidence for Objective 3: What are the obstacles that prevent the implementation of adequate PAP?

The following list summarises the obstacles or barriers for implementation of appropriate PAP:

- Absence of standardised local guidelines and lack of awareness of the most recent version of the guidelines [86,87]
- Workflow and organisational constraints [86-88]
- Disagreement with guidelines [86,87]
- Same-day surgery and ß-lactam allergy [74].

Objective 4: Do selection, timing, dosage or duration of PAP as process indicators have an influence on the incidence of SSIs?

A total of 44 studies were included. All evaluated the appropriate selection, timing and duration of PAP administration and its association with SSI rates. Details on distribution can be found in Table 7.

The characteristics of each study, results, and the grading of quality were summarised[8].

[8] Further information is available upon request. See p. ii for details.

Table 7. Distribution of included study design and geographical location of included studies, Objective 4

Type of study	Distribution (world regions)
Systematic reviews/meta-analyses: n=12 (27.3%)	North America: n=25
RCTs: n=11 (25%)	Europe: n=8
Observational cohort studies: n=11 (25%)	Asia: n=5
Non-CBAs: n=10 (22.7%)	Australia/New Zealand: n=3
	South America: n=2
	Middle East: n=1
Total: N=44	

Adequate selection of antibiotics for PAP

Four studies were included: one systematic review [89], one double-blinded RCT [90], one non-CBA [42], and one ITS [91]. Two of the studies were performed in Europe and two in the USA.

A systematic review by Cranny et al. investigated whether a switch was indicated from non-glycopeptide to glycopeptide antibiotics for perioperative prophylaxis in surgical settings with a high risk of MRSA infections [89]. The review included 16 RCTs published between 1990 and 2002. There was no evidence that the use of glycopeptides prevented more SSIs than the use of non-glycopeptides. The systematic review concluded that there was insufficient evidence supporting the choice of antibiotic prophylaxis because most studies either did not report the baseline prevalence of MRSA at the participating surgical units or failed to report MRSA infections as outcome. The authors concluded that future research was needed to predict the pattern of drug resistance and its implications for postsurgical clinical outcomes.

A well-designed, high-quality, double-blind RCT by Dhadwal et al. analysed the SSI rates in high-risk patients (obesity or diabetes) undergoing sternotomy for primary isolated coronary artery bypass graft (CABG). The study group received a combination of vancomycin, gentamicin and rifampicin, while the control group received the same number of doses of a mono-prophylaxis with cefuroxime. The combination therapy significantly reduced the SSI rate in high-risk patients, without increasing the incidence of MDROs. The authors concluded that patient-related factors such as weight or diabetes and procedure-related factors should be considered in the selection of antibiotic prophylaxis [90].

A non-CBA study by Nunez-Pereira et al. (good internal and external validity) included patients undergoing spinal surgery for which an individualised antibiotic prophylaxis was administered. The selection of the antibiotic was based on the results of urine screening in pre-surgical patients [42]. Although the difference in overall rate of SSIs in the two cohorts did not reach statistical significance, the percentage of SSIs due to Gram-negative bacteria decreased significantly after the intervention (68.2% in cohort A versus 33.4% in cohort B, $p<0.05$) [42].

An ITS study by Garey et al. was identified in which the intervention was changed from cefuroxime to vancomycin in 6 465 patients undergoing coronary artery bypass graft (CABG) surgery or valve replacement over a 4-year period [92]. The average monthly SSI rate in patients undergoing CABG surgery decreased by 2.1 cases per 100 surgeries after the switch from cefuroxime to vancomycin ($p=0.04$). The control group was patients undergoing valve replacement surgery. The change of antibiotic prophylaxis was associated with a decrease only in SSIs caused by MRSA and coagulase-negative staphylococci; the incidence of SSIs caused by Gram-negative or other Gram-positive bacteria was not affected. Although the study had a large sample size, a long observation period, and used a control group to evaluate other factors possibly influencing the change in SSI rates, the study showed serious limitations in internal validity due to testing effects; differences between the study and the control group with respect to gender, race, national nosocomial infection surveillance (NNIS) risk score, and type of surgery. Thus, further studies are still needed before recommending vancomycin as appropriate antibiotic selection in cardiac surgery. This point of view is supported by a systematic review by Cranny at al. demonstrating that there is insufficient evidence to recommend a threshold of MRSA prevalence at which it would be appropriate to switch from non-glycopeptide to glycopeptide antibiotics for perioperative antibiotic prophylaxis. In addition, there was also a lack of evidence from RCTs to conclude that glycopeptide antibiotics are more effective than non-glycopetides in preventing SSIs [89].

Adequate timing of PAP

Five RCTs were analysed with respect to adequate timing of PAP: one RCT published before, four published after 2000 [19] [93,94] . Furthermore, one meta-analysis [94], three non-CBA [59,61,95], seven cohort studies [69,73,96-100], and one case-control study [101] were included.

The four RCTs performed within the last 12 years included 1 490 women undergoing elective cesarean section. The administration of cefazolin before incision was compared with administration at cord clamping. Three of these RCTs were included in a meta-analysis by Constantine et al. [94]; an additional double-blind RCT by Witt et al. was identified here [93]. The pooled data demonstrated a non-significant trend towards lower risk of surgical site infections (wound infection or endometritis) when PAP was administered perioperatively (RR 0.72; 95% CI 0.41–1.25). All trials were published between 1997 and 2011 and showed low risks of selection, performance and

detection bias. A nested case-control study in children undergoing spinal fusion procedures found that inappropriate timing of PAP, defined as administration >60 min before incision, was significantly associated with deep SSI (adjusted OR 3.5 [95% CI 1.7–7.3]) [101].

The non-CBA study by Mannien et al. of methodologically good quality, demonstrated that administration of PAP <30 minutes before incision and a restrictive antibiotic policy (single dose of cefazolin ± metronidazole) had no detrimental effect on the outcome (measured by SSI rate) in 1 953 patients undergoing clean or clean-contaminated surgery [59].

Several guidelines, such as the advisory statement from the National Surgical Infection Prevention Project and the guideline for prevention of SSI published by the CDC Hospital Infection Control Practices Advisory Committee, recommended initiating PAP within 60 minutes before incision if beta-lactam antibiotics are chosen [73]. The rationale is to be found in the experimental work by Burke, published in 1961, and the clinical trials from Stone et al. and Classen et al. [19,96,102]. Generally, the best agent, which is both safe and effective, should be selected and the correct dose should be administered at the right time to achieve serum and/or tissue concentration that exceeds the minimal inhibitory concentrations of these bacteria likely to contaminate the operation field.

A double-blinded RCT published by Stone et al. in 1976 demonstrated a significant reduction of SSI in 400 patients undergoing elective gastric, biliary, and colonic surgery, when PAP was delivered 1 h before operation as compared to post operation or placebo [19]. No significant difference in SSI rate was observed if PAP was applied 8–12 h before surgery as compared to 1 h before surgery. The study's generalisability to current surgical practice in Europe is questionable since the study is over 30 years old [19].

A more recent prospective cohort study by Weber et al. analysed the incidence of SSI in respect to timing of PAP in 3 836 surgeries [98]. They found that administration of PAP between 30 and 60 minutes before incision was more effective in preventing SSI than administration within 30 minutes before incision if cefuroxime was used.

Adequate dosage of antibiotics for PAP

Four Cochrane systematic reviews [103-106], four other systematic reviews [107-110], one RCT [37] and one non-CBA study [111] were included; all publications analyse PAP dosage (single dose vs multiple doses).

A systematic review by Gillespie et al. analysed data from two studies in which the participants underwent either hip fracture surgery or a range of different closed fracture fixation procedures. Data for deep SSI were pooled from these two studies (921 participants), one of which dominated the analysis by virtue of its size. A single dose of cefamandole was less effective than multiple doses in preventing deep surgical site infection (RR 7.89, 95% CI 1.01–61.97) and superficial SSI (RR 4.82, 95% CI 1.08–21.61) after surgery for closed fracture [103].

Another systematic review by Nelson et al. analysed single dose versus multiple dose treatment in 3 589 patients undergoing colorectal surgery [104]. In this review, 25 trials published between 1984 and 2000 were analysed. As compared to single-dose administration, no advantage with longer dosing could be observed when multiple doses were given (RR1.06, 95% CI 0.89–1.27 (p=0.51)). In a sub-group analysis, three studies that specifically compared a single preoperative dose of antibiotic to either a second intra-operative dose, or early post-operative dose, or both, also showed no advantage with extended dosing (p=0.58). The quality of 19 of the 25 studies included was low in respect to selection and allocation bias, because only six of the included trials (24%) were actually randomised.

A systematic review by Zani et al. analysed single-dose versus multiple-doses of PAP in patients undergoing transrectal prostate biopsy in seven trials [105]. No differences with regard to fever and urinary tract infections were found when multiple doses of antibiotic prophylaxis were given versus a single-dose. The quality of evidence was high due to a low risk of various biases, including selection, performance and detection bias of the included studies.

Zanetti et al. looked at compliance with regard to redosing PAP and its effect on the rate of SSI of in a RCT performed in a US university hospital that had a pre-existing integrated computerised physician order entry system [37]. Patients were randomised to receive a computerised audible and visual reminder if prophylactic antibiotics needed redosing during long surgery. Implementing the reminder significantly increased the number of appropriate redosing (40% before intervention to 68% afterwards; p<0.001) while the occurrence of SSIs only moderately decreased from 6% to 4% (p=0.042). According to the authors, the incidence of SSI during the six month preceding the study period was 10% higher than the incidence during the pre-intervention period. The study quality is moderate due to an unclear risk of selection bias and a high risk of performance bias.

In a non-CBA study, Wagner et al. implemented an automatic optimisation programme for adjusting the antibiotic dosage based on patient weight [106]. Compliance significantly increased when there were guidelines for patients weighing ≥80 kg. Although the SSI rate was defined as secondary outcome, no data were presented on the incidence of SSIs during the study period. This made it impossible to say whether adjusting the antibiotic dosage according to body weight influenced the incidence of SSIs.

Adequate duration of PAP

Five systematic reviews analysing short-term versus long-term antibiotic prophylaxis were identified [103,105,107-109].

A systematic review by Gillespie et al. included two small studies in which 224 participants undergoing hip fracture surgery were randomised to receive multiple doses of parenteral antibiotics either administered over ≤24 hours or a longer period [103]. Data for deep SSI were pooled from these two studies and demonstrated no evidence of difference between the two types of regimen for the outcomes of deep (RR 1.10, 95% CI 0.22 to 5.34) or superficial surgical site infection (RR 0.57, 95% CI 0.17 to 1.93).

A second systematic review by Stewart et al. compared short versus longer PAP in 531 patients undergoing peripheral arterial reconstruction [107]. Continuing prophylactic antibiotics for longer than 24 h did not reduce SSIs significantly (RR 1.28; 95% CI: 0.82, 1.98). In their systematic review, Stewart et al. analysed three trials, which were published between 1984 and 1998 and revealed variable risks in respect to selection, performance and detection bias.

The systematic review by Zani et al. analysed short- (one day) versus long-term (three days) PAP in patients undergoing transrectal prostate biopsy in six trials [105]. The authors demonstrated that long-course treatment is not superior to short-course treatment for the outcomes: fever (RR 2.84, 95% CI 0.99–8.16), bacteraemia (RR favouring short course: 0.33, 95% CI 0.01–7.86) and urinary tract infection (RR 1.40, 95% CI 0.73–2.68). Only for the outcome bacteriuria the authors found that long-course treatment – in three trials with considerable heterogeneity (I2=34%) – was associated with a lower risk of bacteriuria (RR 2.09, 95% CI 1.17–3.73).

Thus, the authors concluded that there is no definitive data to confirm that antibiotics for long-course treatments (three days) are superior to short-course treatments (one day), or that multiple-dose treatment is superior to single dose treatment.

A prospective cohort study by Harbarth et al. compared short-term (≤ 48 h) with long-term (>48 h) PAP in 2 641 patients undergoing coronary artery bypass graft (CABG) surgery with or without valve replacement [110]. After adjustment for possible confounding factors (i.e. obesity, co-morbidities, ASA score IV, duration of surgery, etc.) prolonged PAP was not associated with a decreased risk of SSI (adjusted OR: 1.2; 95% CI: 0.8–1.6) but was correlated with an increased risk of acquiring antibiotic resistance (adjusted OR: 1.6; 95% CI 1.1–2.6). The authors concluded that the maximum clinical benefit of prophylaxis is achieved by administration of antibiotics 48 hours post-surgery; the administration of antibiotics for more than 48 hours is ineffective in further reducing SSI. The study reveals some limitations. The incidence of mediastinitis was not reported. There was no mention of a difference in mortality or length of stay in the two groups. In addition, the choice of antibiotics had not been identical in the two groups [110].

Mertz et al. showed the opposite in a systematic review and meta-analysis comparing the efficacy of short-term (≤24 h) versus long-term (>24 h) antibiotic prophylaxis in open heart surgery [108]. In this review, the selected 12 RCTs involving 7 893 patients were published between 1972 and 2008. The meta-analysis demonstrated a risk reduction of sternal SSI in the long-term compared to the short-term antibiotic prophylaxis (RR=1.38 [95% CI: 1.13–1.69]). However, the findings are limited due to the heterogeneity of the antibiotic regimen used and also by the fact that more than 50% of the 12 studies revealed a severe risk of selection, performance and detection bias. Thus, the authors stated that no definitive conclusion can be drawn from the evidence available and they recommend the need for a rigorous, large RCT [108].

De Chiara et al. observed in a methodologically well-performed prospective cohort study with 358 patients undergoing clean and clean and clean-contaminated general surgery that prolonged PAP did not reduce the SSI rate in patients with risk factors. If PAP was applied longer than 24 hours, it was an independent risk factor for intra-hospital or post-hospital SSI, regardless of the presence of patients' risk factors (OR 3.39; 95% CI 1.11–10.35; p=0.032 and OR 5.39; 95% CI 1.64–17.75; p=0.006, respectively) [111].

Summary of evidence for Objective 4: Do selection, timing, dosage or duration of PAP as process indicators have an influence on the incidence of SSIs?

The following list summarises the effect of appropriate selection, timing, dosage and duration of PAP on SSI prevention.

- PAP should be applied 30 to 60 minutes before incision (120 minutes before incision if a glycopeptide is administered) [59,73,85,97,101,112].
- If surgery lasts <4 h and no significant blood loss occurs, a single dose of PAP should be preferred over multiple doses ([37,103,104,109,113-115].
- The selection and dosage of PAP should be adjusted according to patient factors (e.g. the weight of the patient, diabetes mellitus, etc.) [90,106,116,117].
- The duration of PAP should not exceed 24 hours after the end of surgery [103,105,108-111,116,118].
- The selection of antibiotics should be selected according to the patient's colonisation with multidrug-resistant microorganisms [42,119].

Objective 5: Does the use of PAP have an effect on the incidence of Clostridium difficile*-associated diarrhoea (CDAD) or the development of antimicrobial resistance?*

The number of well-designed studies about the association of perioperative antibiotic prophylaxis is limited and incidence rates for CDAD and/or MDROs are rarely reported. One systematic review [89], two RCTs [120-122], three cohort study [110,123,124] and one non-CBA study were included [125] (Table 8).

Table 8. Distribution of included study design and geographical location of included studies, Objective 5

Type of study	Distribution (world regions)
Observational cohort studies: n=3 (42.8%)	North America: n=4
RCTs: n=2 (14.3%)	Asia: n=3
Systematic reviews/meta-analyses: n=1 (14.3%)	
Non-CBAs: n=1 (14.3%)	
Total: N=7	

Two RCTs reported on incidence of CDAD in patients undergoing colorectal surgery [120,121].

Itani et al. assessed the efficacy and safety of PAP with ertapenem compared with cefotetan in 901 patients undergoing elective colorectal surgery [120,122]. The study measured the occurrence of CDAD and looked at SSI as a primary outcome. Although ertapenem was more effective than cefotetan in the prevention of SSI, the overall incidence of CDAD was 1.7% in the ertapenem group and 0.6% in the cefotetan group (p=0.02). The study was a well-designed RCT and showed low risk of bias [120,122].

The second RCT by Fujita et al. compared single dose versus multiple doses of cefmetazole as antibiotic prophylaxis in 384 patients. Two patients (1.1%) with postoperative CDAD were in the multiple dose groups and none in the single dose group [121]. Although randomisation was performed adequately, the quality of the study was poor due to high risk of bias (performance bias, selection bias and reporting bias) [121].

In a well-designed retrospective cohort study with good methodological quality, Carignan et al. reported a significant increase in the occurrence of CDAD due to PAP from 2003 to 2005 as compared with 1999 to 2002 (14.9 cases/1000 procedures versus 0.7 cases/1000 procedures; p <0.001)[123]. Independent risk factors associated with CDAD in patients given PAP were only age <65 yrs, cefoxitin rather than cefazolin alone or in combination with another drug, and the year of surgery.

The study by Harbarth et al. found in their study of 2 641 patients undergoing CABG or valve surgery or both that antibiotic prophylaxis for more than 48 hours increased antimicrobial resistance [110]. Specifically, patients receiving greater than 48 hours of antibiotics were 1.6 times more likely to harbour resistant organisms compared with those having a regimen of less than 48 hours. However, only 41% of patients were cultured, and the site from which the culture was taken was not specified [110]

In a non-CBA study by Paul et al., CDAD was considered a secondary outcome. Short-term PAP, using a single dose of cefazolin plus a single dose of vancomycin intraoperatively, was replaced by a protocol using a prolonged PAP with cefazolin up to 24 h in patients undergoing cardiac surgery [125]. The incidence of SSI did not decrease significantly (3.8%–2.6%; p=0.27). The incidence of CDAD increased slightly but not significantly from 4.6% to 5.9% (p=0.313). The quality of the study revealed good external validity but demonstrated limitations in internal validity due to differences in operative characteristics for control and study group [125].

However, the limited body of evidence demonstrates that there is an urgent need for well-designed trials analysing toxicity and bacterial resistance due to the administration of perioperative antibiotic prophylaxis.

Summary of evidence for Objective 5: Does the use of PAP have an effect on the incidence of *Clostridium difficile*-associated diarrhoea (CDAD) or the development of antimicrobial resistance?

The following measures could prevent an increase in the development of multidrug-resistant bacteria or an increase of incidence of *C. difficile* infections due to PAP:

- In order to adapt the antibiotic prophylaxis to a patient's individual colonisation with MDROs, a screening should be performed pre-operatively [57].
- Surveillance data of MDROs should be analysed periodically by an AM team to adjust selection of antibiotic prophylaxis [63,65,121,122].
- Active surveillance of MDROs (e.g. MRSA, ESBL-positive *Enterobacteriacae* and toxin-producing *Clostridium difficile*) should be performed regularly on surgical wards by trained personnel (infection control personnel or clinical microbiologists) [123].

Supporting evidence for deriving the initial 10 PAP modalities

- Twenty-seven conclusions were derived from the summary of evidence from Objectives 1–5. Thereafter, by removing eight duplicates, combining modalities with similar content, and scoring these modalities according to their level of evidence as described above, the following list of 10 PAP modalities was sent to the expert group prior to the first expert meeting.

Modality 1

A multidisciplinary AM team should develop and implement a protocol of appropriate PAP.

Table 9. Studies supporting Modality 1 and quality of evidence

Author and design of study	Quality of study in respect to internal and external validity (Ranji et al. [23])	Quality of evidence according to the GRADE approach* [24]
Forbes et al. 2008, non-CBA	Good	3
Van Kasteren et al. 2005, non-CBA	Good	3
Weinberg et al. 2001, ITS study	Good	3
Hedrick et al. 2007, non-CBA	Moderate	2
Liau et al. 2010, non-CBA	Moderate	2
Pastor et al. 2009, non-CBA	Moderate	2
Pons-Busom et al. 2004	Moderate	2
Sun et al. 2009	Moderate	2
Thompson et al. 2011, non-CBA	Moderate	2
Trussell et al. 2001, non-CBA	Moderate	2
Webb et al. 2006, non-CBA	Moderate	2
White et al. 2007, non-CBA	Moderate	2
Young et al. 2011, non-CBA	Moderate	2
Zvonar et al. 2008, non-CBA	Moderate	2

** Quality of evidence according to the GRADE approach: 4=high quality, 3=moderate quality, 2=low quality, 1=very low quality*

Modality 2

A multidisciplinary AM team should update the PAP protocol regularly according to standard, approved guidelines.

Table 10. Studies supporting Modality 2 and quality of evidence

Author and type of study	Quality of study in respect to internal and external validity (Ranji et al. [23])	Quality of evidence according to the GRADE approach* [24]
Gomez et al. 2006, non-CBA	Good	3
Geubels et al. 2004, non-CBA	N.A.	2
Pons-Busom et al. 2004, non-CBA	Moderate	2

** Quality of evidence according to the GRADE approach: 4=high quality, 3=moderate quality, 2=low quality, 1=very low quality*

N.A. = not applicable

Modality 3

To control the appropriate selection of antibiotics, as well as timing and duration of prophylaxis, a multidisciplinary AM team should perform an annual audit of surgeons, anaesthesiologists and OR nursing staff and provide, if necessary, structured feedback and education to healthcare staff and decision-makers.

Table 11. Studies supporting Modality 3 and quality of evidence

Author and design of study	Quality of study in respect to internal and external validity (Ranji et al. [23])	Quality of evidence according to the GRADE approach* [24]
Kritchevsky et al. 2008, RCT	N.A.	4
Forbes et al. 2008, non-CBA	Good	3
Van Kasteren et al. 2005, non-CBA	Good	3
Weinberg et al. 2001, ITS study	Good	3
Hedrick et al. 2007; non-CBA	Moderate	2
Liau et al. 2010, non-CBA	Moderate	2
Pastor et al. 2009, non-CBA	Moderate	2
Thompson et al. 2011, non-CBA	Moderate	2
Trussell et al. 2001, non-CBA	Moderate	2
Webb et al 2006, non-CBA	Moderate	2
White et al. 2007; non-CBA	Moderate	2
Young et al. 2011, non-CBA	Moderate	2

** Quality of evidence according to the GRADE approach: 4=high quality, 3=moderate quality, 2=low quality, 1=very low quality*

N.A. = not applicable

Modality 4

To encourage appropriate duration and dosage of PAP one of the following should be implemented: a computer-assisted decision support system, an automatic reminder system, a patient checklist, or a time-out procedure.

Table 12. Studies supporting Modality 4 and quality of evidence

Author and design of study	Quality of study in respect to internal and external validity (Ranji et al. [23])	Quality of evidence according to the GRADE approach* [24]
De Vries et al. 2010	Good	3
Forbes et al. 2008, non-CBA	Good	3
Haynes et al. 2011, ITS	Good	3
Van Kasteren et al. 2005, non-CBA	Good	3
Weinberg et al. 2001, ITS study	Good	3
Hedrick et al. 2007, non-CBA	Moderate	2
Larochelle et al. 2011, non-CBA	Moderate	2
Liau et al. 2010, non-CBA	Moderate	2
Pastor et al. 2009, non-CBA	Moderate	2
Thompson et al. 2011, non-CBA	Moderate	2
Trussell et al. 2001, non-CBA	Moderate	2
Webb et al. 2006, non-CBA	Moderate	2
White et al. 2007; non-CBA	Moderate	2
Young et al. 2011, non-CBA	Moderate	2

** Quality of evidence according to the GRADE approach: 4=high quality, 3=moderate quality, 2=low quality, 1=very low quality*

Modality 5

Perioperative prophylaxis should be the responsibility of the anaesthesiologist.

Table 13. Studies supporting Modality 5 and quality of evidence

Author and design of study	Quality of study in respect to internal and external validity (Ranji et al. [23])	Quality of evidence according to the GRADE approach* [24]
Kanter et al. 2008; non-CBA	Moderate	2
Trussell et al. 2001, non-CBA	Moderate	2
Webb et al. 2006, non-CBA	Moderate	2
Zvonar et al. 2008, non-CBA	Moderate	2

** Quality of evidence according to the GRADE approach: 4=high quality, 3=moderate quality, 2=low quality, 1=very low quality*

Modality 6

Perioperative antibiotic prophylaxis should be administered 30 to 60 minutes before incision, ideally at the time of anaesthetic induction (except for vancomycin and fluoroquinolones).

Table 14. Studies supporting Modality 6 and quality of evidence

Author and design of study	Quality of study in respect to internal and external validity (Ranji et al. [23])	Quality of evidence according to the GRADE approach* [24]
Witt et al. 2011, double-blinded RCT	N.A.	4
Mannien et al. 2006, non-CBA	Good	3
Van Kasteren et al. 2005, non-CBA	Good	3
Weinberg et al.201 l., ITS study	Good	3
Weber et al. 2008, cohort study	Good	3
Larochelle et al. 2011, non-CBA	Moderate	2
Liau et al. 2010, non-CBA	Moderate	2
Young et al. 2011, non-CBA	Moderate	2

** Quality of evidence according to the GRADE approach: 4=high quality, 3=moderate quality, 2=low quality, 1=very low quality*
N.A. = not applicable

Modality 7

Although a single dose of perioperative antibiotic prophylaxis is preferred, subsequent doses should be given depending on the duration of the procedure and the half-life of the antibiotic, and if significant blood loss occurs during surgery.

Table 15. Studies supporting Modality 7 and quality of evidence

Author and design of study	Quality of study in respect to internal and external validity (Ranji et al. [23])	Quality of evidence according to the GRADE approach [24]*
Zani et al. 2011, , Cochrane systematic review + meta-analysis	N.A.	4
Gillespie et al. 2010, Cochrane systematic review + meta-analysis	N.A.	3
McDonald et al. 1998, systematic review + meta-analysis	N.A.	3
Meijer et al. 1990 systematic review + meta-analysis	N.A.	3
Nelson et al. 2009, Cochrane systematic review + meta-analysis	N.A.	3
Slobogean et al. 2008, systematic review + meta-analysis	N.A.	3

Author and design of study	Quality of study in respect to internal and external validity (Ranji et al. [23])	Quality of evidence according to the GRADE approach [24]*
Southwell-Keely et al. 2004 systematic review + meta-analysis	N.A.	3
Zannetti et al. 2003, RCT	N.A.	3

** Quality of evidence according to the GRADE approach: 4=high quality, 3=moderate quality, 2=low quality, 1=very low quality*
N.A. = not applicable

Modality 8

Prolonging prophylaxis after the end of surgery is not recommended.

Table 16. Studies supporting Modality 8 and quality of evidence

Author and design of study	Quality of study in respect to internal and external validity (Ranji et al. [23])	Quality of evidence according to the GRADE approach [24]*
Zani et al. 2011, Cochrane systematic review + meta-analysis	N.A.	4
Gillespie et al. 2010, Cochrane systematic review + meta-analysis	N.A.	3
Nelson et al. 2009, Cochrane systematic review + meta-analysis	N.A.	3
Southwell-Keely 2004, systematic review + meta-analysis	N.A.	3
Stewart 2008, systematic review + meta-analysis	N.A.	3
Harbarth 2000; prospective cohort study	N.A	3

** Quality of evidence according to the GRADE approach: 4=high quality, 3=moderate quality, 2=low quality, 1=very low quality*
N.A. = not applicable

Modality 9

The perioperative antibiotic protocol should take into account individual patient factors like BMI, underlying diseases, or colonisation with resistant pathogens.

Table 17. Studies supporting Modality 9 and quality of evidence

Author and design of study	Quality of study in respect to internal and external validity (Ranji et al. [23])	Quality of evidence according to the GRADE approach* [24]
Dhadwal et al. 2007, double blind RCT	Good	4
Núnez-Pererira et al. 2011, non-CBA	Good	3
Garey et al. 2008, ITS study	Moderate	2
Kato et al. 2007, non-CBA	Moderate	2
Wagner et al. 2011, non-CBA	Moderate	2
Linam et al. 2010, case-control study	Moderate	2
Schelenz et al. 2005, non-CBA	Poor	1
Sharma et al. 2009, non-CBA	Poor	1

** Quality of evidence according to the GRADE approach: 4=high quality, 3=moderate quality, 2=low quality, 1=very low quality*
N.A. = not applicable

Modality 10

In surgical departments, patterns of MDROs and incidence of *Clostridium difficile* infections should be monitored proactively so PAP can be appropriately adjusted.

Table 18. Studies supporting Modality 10 and quality of evidence

	Quality of study in respect to internal and external validity (Ranji et al. [23])	Quality of evidence according to the GRADE approach [24]*
Itani et al. 2008, RCT	N.A.	4
Carignan et al. 2008, retrospective cohort study	N.A.	3
Kato et al. 2007, non-CBA	Moderate	2

** Quality of evidence according to the GRADE approach: 4=high quality, 3=moderate quality, 2=low quality, 1=very low quality*
N.A. = not applicable

3.2 Results of the expert meetings

3.2.1 First expert meeting, Berlin, Germany

Before the first meeting took place, the experts were asked to comment on the initial PAP modalities as derived from the systematic review. The results of the experts' replies to the initial 10 PAP modalities are shown in Figure 3.

The systematic review was presented at the first expert meeting, and experts were asked to comment. Comments and discussion were recorded. The 10 PAP modalities were ranked by the authors of this literature review and discussed with regard to EU-wide applicability and implementability.

At the end of the first expert meeting, the experts agreed unanimously on the following 10 PAP modalities (Table 19).

Figure 3. Expert grading of the proposed PAP modalities

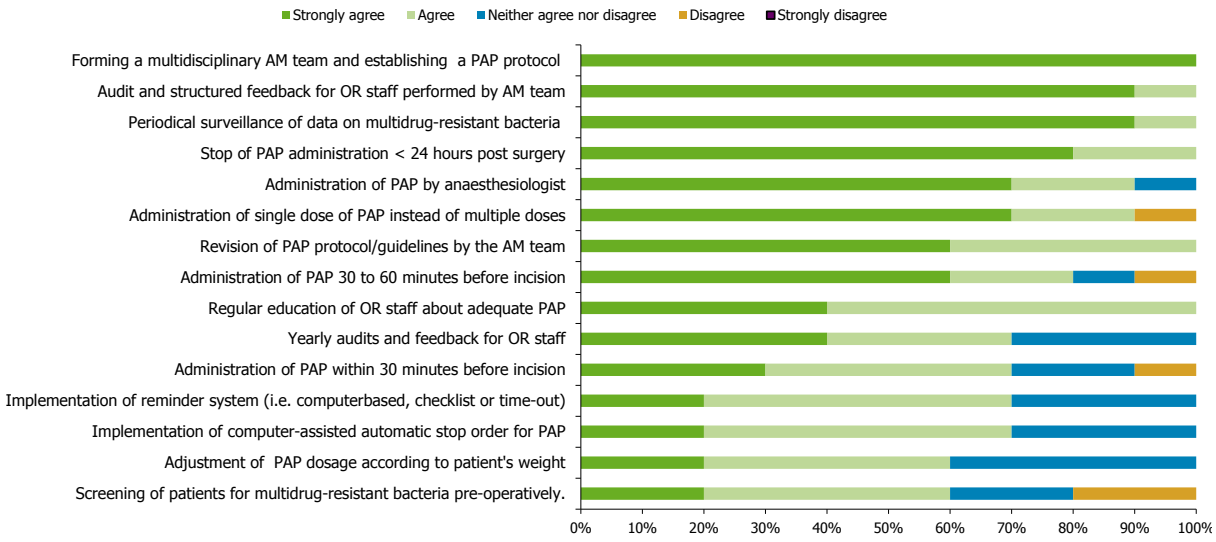


Figure 4. Summary of the experts' recommendation to proposed PAP modalities

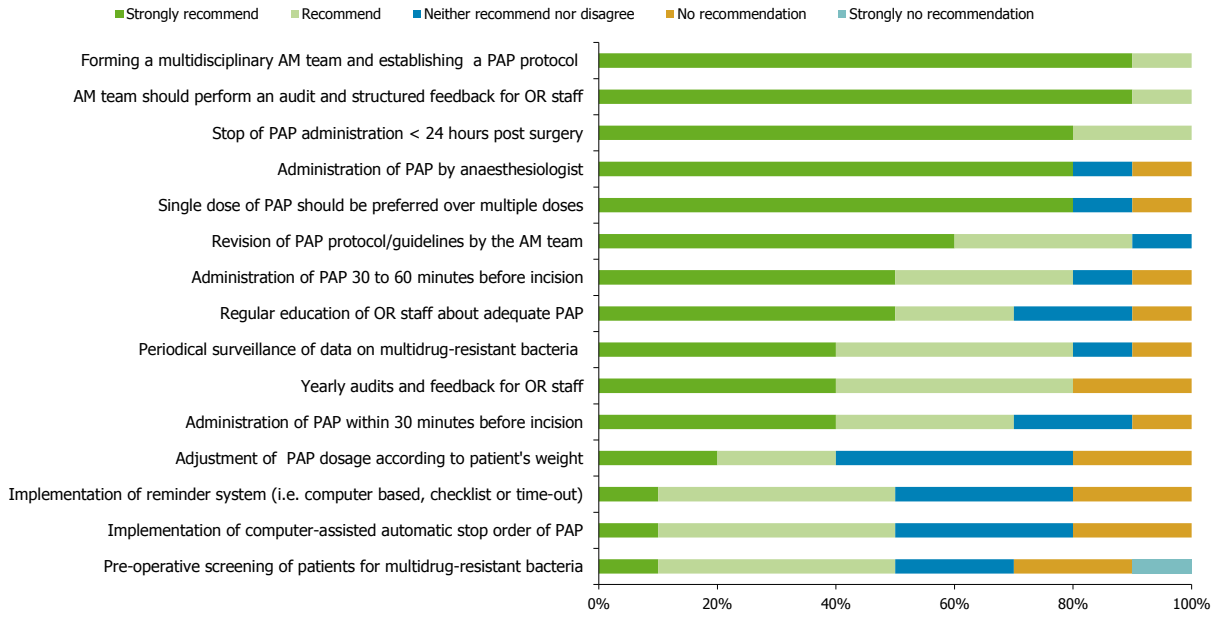


Table 19. PAP modalities as outlined at the first expert meeting

10 modalities of perioperative antibiotic prophylaxis	
1	A multidisciplinary AM team (including surgeons, anaesthesiologists, nurses, pharmacists, infection control specialists, and clinical microbiologists) should develop and implement a protocol of appropriate PAP.
2	A multidisciplinary AM team should regularly update the PAP protocol according to standard, approved guidelines.
3	To control the appropriate selection of antibiotics, as well as timing and duration of prophylaxis, a multidisciplinary AM team should perform an audit of surgeons, anaesthesiologists and OR nursing staff and provide, if necessary, structured feedback and education to healthcare staff and decision-makers.
4	In order to encourage appropriate duration and dosage of PAP, a computer-assisted decision support system and automatic reminder system should be implemented.
5	PAP should be the responsibility of the anaesthesiologist.
6	PAP should be administered within 30–60 minutes before incision (except for vancomycin and fluoroquinolones), ideally at the time of anaesthetic induction.
7	Although a single dose of PAP is preferred, subsequent doses should be given depending on the duration of the procedure and the half-life of the antibiotic, and if significant blood loss occurs during surgery.
8	Prolonging prophylaxis after the end of surgery is not recommended.
9	The PAP protocol should take into account individual patient factors like BMI, underlying diseases, or colonisation with resistant pathogens.
10	In surgical departments, patterns of MDROs and incidence of *Clostridium difficile* infections should be monitored proactively so PAP can be appropriately adjusted.

3.2.2 Second expert meeting, Berlin, Germany

Before the second meeting in Berlin, the experts agreed to re-score the 10 modalities by evaluating the quality and strength of evidence and implementability, this time using a 6-point scale ranging from 1 (strongly disagree) to 6 (strongly agree) in order to facilitate the ranking process (Table 20).

Table 20. Results of the experts' re-scoring by email of 10 PAP modalities prior to the second expert meeting

	PAP modality	Author and design of study	Quality of evidence according to the GRADE approach* [24,25]	Expert grading on strength of evidence; median (range) (1=strongly disagree to 6=strongly agree)	Expert grading of implementability; median (range) (1=strongly discouraged to 6=implementation strongly recommend)
1	A multidisciplinary AM team (including surgeons, anaesthesiologists, nurses, pharmacists, infection control specialists, and clinical microbiologists) should develop and implement a protocol of appropriate PAP.	Forbes 2008, non-CBA Van Kasteren 2005, non-CBA Weinberg 2001, ITS Hedrick 2007, non-CBA Liau 2010, non-CBA Pastor 2009, non-CBA Pons-Busom et al. 2004, non-CBA Sun 2009, non-CBA Thompson 2011, non-CBA Trussell 2001, non-CBA Webb 2006, non-CBA White 2007, non-CBA Young 2011, non-CBA Zvonar 2008, non-CBA	3 3 3 2 2 2 2 2 2 2 2 2 2 2	6 (5-6)	6 (4-6)
2	A multidisciplinary AM team should regularly update the PAP protocol according to standard, approved guidelines.	Gomez 2006, non-CBA Geubels 2004, non-CBA Pons-Busom et al. 2004, non-CBA	3 2 2	5 (4-6)	6 (4-6)
3	To control the appropriate selection of antibiotics, as well as timing and duration of prophylaxis, a multidisciplinary AM team should perform an audit of surgeons, anaesthesiologists and OR nursing staff and provide, if necessary, structured feedback and education to healthcare staff and decision-makers.	Kritchevsky, RCT Forbes 2008, non-CBA Van Kasteren 2005, non-CBA Weinberg 2001, ITS study Hedrick 2007, non-CBA Liau 2010, non-CBA Pastor 2009, non-CBA Thompson 2011, non-CBA Trussell 2001, non-CBA Webb 2006, non-CBA White 2007, non-CBA Young 2011, non-CBA	4 3 3 3 2 2 2 2 2 2 2 2	6 (3-6)	6 (3-6)
4	In order to encourage appropriate duration and dosage of PAP, a computer-assisted decision support system and automatic reminder system should be implemented.	De Vries 2010, CBA Forbes 2008, non-CBA Van Kasteren 2005, non-CBA Weinberg 2001, ITS study Hedrick 2007, non-CBA Larochelle 2011, non-CBA Liau 2010, non-CBA Pastor 2009, non-CBA Thompson, 2011, non-CBA Trussell 2001, non-CBA Webb 2006, non-CBA White 2007, non-CBA Young 2011, non-CBA	3 3 3 3 2 2 2 2 2 2 2 2 2 2	4 (3-6)	4 (3-6)
5	PAP should be the responsibility of the anaesthesiologist.	Kanter 2008, non-CBA Trussell 2001, non-CBA Webb 2006, non-CBA Zvonar 2008, non-CBA	2 2 2 2	5 (3-6)	5 (3-6)
6	PAP should be administered within 30–60 minutes before incision (except for vancomycin and fluoroquinolones), ideally at the time of anaesthetic induction.	Mannien 2006, non-CBA Van Kasteren 2005, non-CBA Weinberg 2001, ITS study Witt 2011, double-blinded RCT Liau 2010, non-CBA Young 2011, non-CBA	3 3 3 3 2 2	6 (4-6)	6 (4-6)

	PAP modality	Author and design of study	Quality of evidence according to the GRADE approach* [24,25]	Expert grading on strength of evidence; median (range) (1=strongly disagree to 6=strongly agree)	Expert grading of implementability; median (range) (1=strongly discouraged to 6=implementation strongly recommend)
7	Although a single dose of PAP is preferred, subsequent doses should be given depending on the duration of the procedure and the half-life of the antibiotic, and if significant blood loss occurs during surgery.	Zani 2011, systematic review McDonald 1998, systematic review Gillespie 2010, Cochrane systematic review Meijer 1990, systematic review Nelson 2009, Cochrane systematic review Slobogean 2008, systematic review Southwell-Keely 2004, systematic review Zannetti 2003, RCT	4 3 3 3 3 3 3 3	6 (4-6)	6 (4-6)
8	Prolonging prophylaxis after the end of surgery is not recommended.	Zani 2011, Cochrane systematic review Gillespie 2010, Cochrane systematic review Nelson et al. 2009, Cochrane systematic review Southwell-Keely 2004, systematic review	4 3 3 3	6 (2-6)	6 (2-6)
9	The PAP protocol should take into account individual patient factors like BMI, underlying diseases, or colonisation with resistant pathogens.	Dhadwal 2007, double blind RCT Núnez-Pererira 2011, non-CBA Garey 2008, ITS study Kato 2007, non-CBA Wagner 2011, non-CBA Linam 2010, case-control study Schelenz 2005, non-CBA Sharma 2009, non-CBA	4 3 2 2 2 2 1 1	5 (2-6)	6 (5-6)
10	In surgical departments, patterns of MDROs and incidence of *Clostridium difficile* infections should be monitored proactively so PAP can be appropriately adjusted.	Itani et al. 2008, RCT Carignan 2008, retrospective cohort study Kato et al. 2007, non-CBA	4 3 2	4 (3-6)	5 (2-6)

** Quality of evidence according to the GRADE approach [24,25]: 4=high quality, 3=moderate quality, 2=low quality, 1=very low quality*

Defining EU-wide applicability/implementability and addressing barriers

In order to facilitate the discussion and the ranking it was necessary to define terms such as 'EU-wide applicability' and 'EU-wide implementability'. The experts were asked to identify key components of these terms so that they could be easily understood and their ranking and consensus transparent and homogeneous. Components such as financial resources, educational aspects, staff resources, cultural issues and hierarchical aspects were some of the identified topics. While discussing these components, the expert also identified several barriers to EU-wide applicability and implementability. It was decided to draw a list of potential barriers for each PAP modality, based on a short literature review and expert input. These barriers were expected to be different in each country, depending on socio-economic and political factors, but the identification of such barriers could be used to fine-tune the implementation details for the PAP modalities.

Final five key modalities

During this second expert meeting, each modality was discussed separately and either rejected, included, or combined with another modality. The final five key PAP modalities are listed in Table 21.

Table 21. Final five key modalities for perioperative antibiotic prophylaxis

Modality #1: Multidisciplinary antimicrobial management teams
Hospitals should establish a multidisciplinary AM team (including surgeons, anaesthesiologists, nurses, pharmacists, infection control specialists, and clinical microbiologists) who should develop and implement a protocol of appropriate PAP. *Compliance with this protocol should be audited regularly and the results should be fed back to the antimicrobial prescribers and decision-makers, e.g. chief of surgery, quality committee, AM team.* *The protocol should be reviewed and updated regularly. It should consider adjustment of PAP for patients who are at risk for SSI due to MDROs or who have a BMI over 30. The hospital's local antibiotic susceptibility patterns should also be taken into account.*
Modality #2: Responsibility for appropriate timing of perioperative antibiotic prophylaxis
To ensure appropriate timing, antibiotic prophylaxis before and during surgery should be the responsibility of the anaesthesiologist*. ** This recommendation is supported by the best available evidence. If there is no anaesthesiologist available, another professional present at the time of surgery should be designated.*
Modality #3: Timing of perioperative antibiotic prophylaxis
PAP should be administered within 60 minutes before incision (except when administering vancomycin and fluoroquinolones), ideally at the time of anaesthetic induction.
Modality #4: Dosing and duration of perioperative antibiotic prophylaxis
Although a single dose of PAP is preferred, subsequent doses should be given depending on the duration of the procedure and the half-life of the antibiotic, and if significant blood loss occurs during surgery.
Modality #5: Duration and termination of perioperative antibiotic prophylaxis
Continuing antibiotic prophylaxis after the end of surgery is not recommended*. ** Hospitals should use a reminder/stop order system (e.g. computer system, checklist) in order to encourage appropriate duration and dosage of PAP.*

3.2.3 Third expert meeting, Stockholm, Sweden

The original objective of the third meeting in Stockholm was to develop indicators for monitoring the five key PAP modalities. The identification of barriers was later added to the agenda of the meeting.

Indicators

The authors of this review conducted a literature search and sent the proposed indicators for the monitoring of PAP to the experts. The studies from where the indicators were taken were not rated or graded.

At the meeting, five indicators were selected, since the call for tender had specified one indicator per modality. Indicators were not further categorised into internal, external, or structural.

The list of the five final key modalities and their respective indicators can be found in Table 22.

Table 22. Final five key PAP modalities and corresponding indicators

Perioperative antibiotic prophylaxis modality	Indicators for each modality
Modality #1: Multidisciplinary antimicrobial management teams	
Hospitals should establish a multidisciplinary AM team (including surgeons, anaesthesiologists, nurses, pharmacists, infection control specialists, and clinical microbiologists) who should develop and implement a protocol of appropriate PAP. *Compliance with this protocol should be audited regularly and the results should be fed back to the antimicrobial prescribers and decision-makers, e.g. chief of surgery, quality committee, AM team.* *The protocol should be reviewed and updated regularly. It should consider adjustment of PAP for patients who are at risk for SSI due to MDROs or who have a BMI over 30. The hospital's local antibiotic susceptibility patterns should also be taken into account.*	The presence of a multidisciplinary AM team which is responsible for developing, implementing and regularly updating the PAP protocol; in charge of regularly updating the local AB protocol; and responsible for regularly analysing and auditing compliance with appropriate PAP.
Modality #2: Responsibility for appropriate timing of perioperative antibiotic prophylaxis	
To ensure appropriate timing, antibiotic prophylaxis before and during surgery should be the responsibility of the anaesthesiologist*. ** This recommendation is supported by the best available evidence. If there is no anaesthesiologist available, another professional present at the time of surgery should be designated.*	Measurement of the presence of an anaesthesiologist or another designated professional at surgery who is responsible for applying PAP.
Modality #3: Timing of perioperative antibiotic prophylaxis	
PAP should be administered within 60 minutes before incision (except when administering vancomycin and fluoroquinolones), ideally at the time of anaesthetic induction.	Rate of compliance with the administration of PAP within 60 minutes.
Modality #4: Dosing and duration of perioperative antibiotic prophylaxis	
Although a single dose of PAP is preferred, subsequent doses should be given depending on the duration of the procedure and the half-life of the antibiotic, and if significant blood loss occurs during surgery.	Rate of compliance with indication, selection and dosage of PAP according to protocol.

Perioperative antibiotic prophylaxis modality	Indicators for each modality
Modality #5: Duration and termination of perioperative antibiotic prophylaxis	
Continuing antibiotic prophylaxis after the end of surgery is not recommended*. ** Hospitals should use a reminder/stop order system (e.g. computer system, checklist) in order to encourage appropriate duration and dosage of PAP.*	Rate of compliance with discontinuation of PAP within 24 hours after initiation of surgery.

Barriers

After the second expert meeting, the authors of this review drew up a list of possible barriers: barriers for professionals, teams/social interaction, organisation, and structures. Experts were asked to submit additional barriers. After a final list of barriers was established, experts were asked to rate the barriers on a 6-point scale (1=no/minor barrier, 6=major barrier). Table 23 gives the final list, as agreed upon at the third expert meeting.

Table 23. Experts' consensus for each proposed barrier

Barriers for		Key modalities				
		1	**2**	**3**	**4**	**5**
Professionals	1. Lack of awareness about SSI rates	pb	NA	NA	pb	pb
	2. Lack of awareness about the extent of multidrug-resistant organisms	pb	NA	NA	mb	mb
	3. Lack of education	mb	NA	pb	mb	mb
	4. Psychological barriers	pb	pb	pb	mb	mb
Teams/social interaction	5. Communication and feedback problems	pb	nb	NA	pb	pb
	6. Hierarchical problems	pb	mb	nb	pb	mb
Organisation	7. Limitation of resources due to hospital size	mb	nb	nb	nb	pb
	8. Limited staff resources and funding	mb	nb	nb	nb	NA
	9. Organisational problems related to the management of care and/or resources	pb	pb	pb	pb	pb
Structures	10. Lack of professional regulations	pb	NA	pb	mb	mb
	11. Lack of empowerment	mb	pb	pb	pb	pb
	12. External pressure	nb	nb	nb	NA	pb
	13. Fear of litigation	nb	NA	nb	pb	mb

Note: Major barriers are shaded in grey: major barrier (mb), potential barrier (pb), no barrier (nb), no agreement (NA)

4 Guidance on five key PAP modalities and corresponding indicators

4.1 Multidisciplinary antimicrobial management teams

Modality 1: Hospitals should establish a multidisciplinary AM team (including surgeons, anaesthesiologists, nurses, pharmacists, infection control specialists, and clinical microbiologists) who should develop and implement a protocol of appropriate PAP.

Compliance with this protocol should be audited regularly and the results should be fed back to the antimicrobial prescribers and decision-makers, e.g. chief of surgery, quality committee, AM team. The protocol should be reviewed and updated regularly. It should consider adjustment of PAP for patients who are at risk for SSI due to MDROs or who have a BMI over 30. The hospital's local antibiotic susceptibility patterns should also be taken into account.

Indicator: Presence of a multidisciplinary AM team which is responsible for developing, implementing and regularly updating PAP, for regularly updating the local AB protocol and regularly analysing and auditing compliance with appropriate PAP.

Table 24. Checklist for Indicator 1

Components of checklist for Indicator 1	Number of points Yes=1 pts. No=0 pts. (maximal 11 pts.)
Is there a multidisciplinary AM team that consists of professionals from relevant areas (i.e. surgery, anaesthesiology, pharmacy, infectious diseases, nursing, infection control, etc.)?	
Does the AM team have one or more annual plenary meetings?	
Is the hospital PAP protocol regularly updated (at least annually)?	
Are patient-specific factors taken into consideration when updating the PAP protocol (i.e. BMI, type of surgery, length of surgery, presence of MDROs, etc.)?	
Is the PAP protocol updated and adapted according to the local antimicrobial susceptibility patterns?	
Were the surgical procedures evaluated according to appropriateness of PAP indication?	
Is a sufficient number of surgical procedures included in an audit of PAP (≥10% of the total annual number of surgical procedures – at least 30 procedures* – for which PAP is indicated)? ** The Haute Autorité de Santé (French National Authority for Health) recommends a minimum of 30 procedures for any type of audit.*	
Were one or more audits for compliance with the PAP protocol performed?	
Are data on compliance fed back to the surgical departments?	
Are data on compliance fed back to the hospital administration?	
Are measures taken to improve compliance? (Describe the effectiveness of the measures.)	
Total number of points	

4.2 Responsibility for appropriate timing of perioperative antibiotic prophylaxis

Modality 2: To ensure appropriate timing, antibiotic prophylaxis before and during surgery should be the responsibility of the anaesthesiologist[9].

Indicator: Rate of whether an anaesthesiologist (or other designated professional present at the time of surgery) was responsible for the administration of PAP.

$$\text{Indicator 2} = \frac{\text{Number of surgeries where PAP was indicated for which an anaesthesiologist}^{3} \text{ was responsible for PAP}}{\text{Number of all surgeries for which PAP was indicated}}$$

[9] Or another designated professional.
This recommendation is supported by the best available evidence. If there is no anaesthesiologist available, another professional present at the time of surgery should be designated.

4.3 Timing of perioperative antibiotic prophylaxis

Modality 3: PAP should be administered within 60 minutes before incision (except when administering vancomycin and fluoroquinolones), ideally at the time of anaesthetic induction.

Indicator: Rate of compliance with the administration of the antibiotic prophylaxis within 60 minutes before incision.

$$\text{Indicator 3} = \frac{\text{Number of PAP administered within 60 minutes before incision}}{\text{Number of all surgeries where PAP was indicated and administered}}$$

4.4 Dosing and duration of perioperative antibiotic prophylaxis

Modality 4: Although a single dose of PAP is preferred, subsequent doses should be given depending on the duration of the procedure and the half-life of the antibiotic, and if significant blood loss occurs during surgery.

Indicator (applicable to Modality 1 and Modality 4): Rate of compliance with indication, selection and dosage of PAP according to protocol.

$$\text{Indicator 4.1} = \frac{\text{Number of surgeries where PAP was administered when there was an indication}}{\text{Number of all surgeries when PAP was indicated}}$$

$$\text{Indicator 4.2} = \frac{\text{Number of surgeries where PAP was administered when it was NOT indicated}}{\text{Number of all surgeries when PAP was NOT indicated}}$$

$$\text{Indicator 4.3} = \frac{\text{Number of surgeries with appropriate choice of PAP}}{\text{Number of all surgeries when PAP was indicated}}$$

$$\text{Indicator 4.4} = \frac{\text{Number of surgeries with single dosage of PAP}}{\text{Number of all surgeries for which a single dosage of PAP was indicated}}$$

$$\text{Indicator 4.5} = \frac{\text{Number of surgeries for which additional doses of PAP was administered when there was an indication}}{\text{Number of all surgeries for which additional doses of PAP are indicated}}$$

4.5 Duration and termination of perioperative antibiotic prophylaxis

Modality 5: Continuing antibiotic prophylaxis after the end of surgery is not recommended*.

** Hospitals should use a reminder/stop order system (e.g. computer system, checklist) in order to encourage appropriate duration and dosage of PAP.*

Indicator: Rate of compliance with discontinuation of PAP within 24 hours after initiation of surgery.

$$\text{Indicator 5} = \frac{\text{Number of PAP discontinued within 24 hours post-surgery}}{\text{Number of all surgeries when PAP was indicated}}$$

In order to evaluate compliance for indicators 2 to 5, auditing a selected number of surgical procedures in which PAP is indicated is recommended (e.g. colorectal surgery, hip surgery).

5 Limitations

Some limitations of the systematic review and the development of guidance should be noted and taken into account.

In the systematic review, most (71.8%) of the included studies except for Objective 4 (timing and duration of PAP) were non-controlled, for example before/after studies or cohort studies. Since these types of studies are not considered rigorous, they were graded as having a low level of evidence according to GRADE. This limits the amount and strength of included evidence.

Although the European experts who participated in the three consensus meetings and in the development of this report represented many of the disciplines involved in the administration of PAP (surgery, infection control, anaesthesiology, infectious disease, microbiology, pharmacy, nursing, and quality management), they did not represent all EU Member States. The experts' opinions regarding the EU-wide applicability of the proposed PAP modalities most likely reflect the situation in their home countries and cannot necessarily be applied to the rest of Europe.

6 Conclusions

Perioperative antibiotic prophylaxis (PAP) is considered one of the most effective measures for preventing surgical site infections (SSI). Five key PAP modalities were identified by combining a systematic review by ranking the evidence by an expert group according to effectiveness, implementability and EU-wide applicability. Overall guidance and indicators for compliance monitoring were developed by consensus. The five modalities refer to effective measures to improve the compliance of healthcare professionals with appropriate administration, timing, dosage and duration of PAP for preventing SSI.

The indicators identified for monitoring the five key modalities include compliance with the indication, selection, timing, dosage and duration of PAP; the frequency of administration of PAP by an anaesthesiologist or another designated professional when indicated; the presence and frequency of meetings of the multidisciplinary team; and further measures to improve compliance.

Identified barriers to the EU-wide implementation of the PAP modalities include lack of education, psychological barriers, fear of litigation, lack of awareness regarding local antimicrobial resistance patterns, hierarchical problems, and lack of professional regulations. The key PAP modalities could help improve the compliance of healthcare professionals with PAP protocols and thereby reduce inappropriate antibiotic usage and decrease the prevalence of MDROs in hospitals and countries in Europe.

A common strategy within hospitals across Europe including the five key modalities and indicators will ensure and strengthen the adequate administration of PAP. Barriers to implementation should be addressed, analysed and overcome by local, national or EU-wide strategies.

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Annex 1. Table of the search strategies

Table 1.1. Search strategy of MEDLINE via PubMed for Objectives 1, 2 and 3

Search	Query	Items found
#4	Search (((cohort*[TiAb] AND study*[TiAb]) OR observational study*[TiAb] OR controlled before-and-after study*[TiAb] OR CBAs[TiAb] OR interrupted time series[TiAb] OR ITS[TiAb]) AND (antibiotic*[TiAb] OR antimicrobial*[TiAb] OR antiinf*[TiAb]) AND (prophyla*[TiAb] OR preventive*[TiAb] OR prevention*[TiAb] OR preventing[TiAb] OR premedication[TiAb]) AND (wound infection*[TiAb] OR surgical site infection*[TiAb]))	91
#3	Search ((surgical site infection AND preoperative prophylaxis) AND ((compliance) OR (adherence) OR (protocol) OR (program) OR (training) OR (education))) OR ((surgical site infection AND perioperative prophylaxis) AND ((protocol implementation) OR (efficacy) OR (effectiveness) OR (program) OR (improvement) OR (compliance) OR (adherence) OR (training) OR (education) OR (implementation) OR (instruction) OR (bundle) OR (surveillance) OR (appropriateness) OR (guidelines AND compliance) OR (initiative) OR (checklist) OR (impact)))	276
#2	Search (surgical site infection AND preoperative prophylaxis) AND ((compliance) OR (adherence) OR (protocol) OR (program) OR (training) OR (education))	89
#1	Search (surgical site infection AND perioperative prophylaxis) AND ((protocol implementation) OR (efficacy) OR (effectiveness) OR (program) OR (improvement) OR (compliance) OR (adherence) OR (training) OR (education) OR (implementation) OR (instruction) OR (bundle) OR (surveillance) OR (appropriateness) OR (guidelines AND compliance) OR (initiative) OR (checklist) OR (impact))	205

Table 1.2. Search of MEDLINE/Embase via OVID for Objectives 1, 2 and 3

Search	Query	Items found
1	(surgical site infection AND perioperative prophylaxis) AND ((protocol implementation) OR (efficacy) OR (effectiveness) OR (program) OR (improvement) OR (compliance) OR (adherence) OR (training) OR (education) OR (implementation) OR (instruction) OR (bundle) OR (surveillance) OR (appropriateness) OR (guidelines AND compliance) OR (initiative) OR (checklist) OR (impact))	76
2	remove duplicates from 1	58
3	(((cohort* and study*) or observational study* or controlled before-and-after study* or CBAs or interrupted time series or ITS) and (antibiotic* or antimicrobial* or antiinf*) and (prophyla* or preventive or prevention* or preventing or premedication) and (wound infection* or surgical site infection*)).mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, an, sh, tn, dm, mf, dv, kw]	1099
4	compliance.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, an, sh, tn, dm, mf, dv, kw]	254749
5	(adherence or protocol or program or training or education).mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, an, sh, tn, dm, mf, dv, kw]	2586060
6	4 or 5	2766157
7	6 and 3	154
8	remove duplicates from 7	105

Table 1.3. Search of MEDLINE via PubMed for Objective 4

Search	Query	Items found
#1	((cohort* and study*)	191152
#2	observational study*	23804
#3	controlled before-and-after study*	54
#4	CBAs	147
#5	interrupted time series or ITS AND(antibiotic* or antimicrobial* or antiinf*) AND (prophyla* or preventive or prevention* or preventing or premedication) AND (wound infection* or surgical site infection*))	3
#6	#1 OR #2 OR #3 OR #4 OR #5	211974
#7	(antibiotic* or antimicrobial* or antiinf*) AND (prophyla* or preventive or prevention* or preventing or premedication) AND (wound infection* or surgical site infection*))	6324
#8	#6 AND #7	192
#9	Timing	68878
#10	Duration	353595
#11	#9 OR #10	416144
#12	#8 AND #11	61

Table 1.4. Search of MEDLINE via PubMed for Objective 5

Search	Query	Items found
#1	((cohort*[TiAb] AND study*[TiAb] OR (observational study*[TiAb]) OR controlled before-and-after study*[TiAb] OR CBAs[TiAb] OR interrupted time series[TiAb] OR ITS [TiAb])) AND (antibiotic* [TiAb] OR antimicrobial*[TiAb] OR antiinf*[TiAb]) AND (prophyla*[TiAb] OR preventive*[TiAb] OR prevention*[TiAb] OR preventing [TiAb] OR premedication [TiAb]) AND (wound infection*[TiAb] OR surgical site infection*[TiAb].	2531
#2	((multidrug-resistant bacteria) OR (*Clostridium difficile*-associated diarrhoea) OR clostridium difficile))	14661
#3	#1 AND #2	45

Table 1.5. Search of MEDLINE via PubMed for Objective 5

Search	Query	Items found
#1	((cohort*[TiAb] AND study*[TiAb] OR (observational study*[TiAb]) OR controlled before-and-after study*[TiAb] OR CBAs[TiAb] OR interrupted time series[TiAb] OR ITS [TiAb])) AND (antibiotic* [TiAb] OR antimicrobial*[TiAb] OR antiinf*[TiAb]) AND (prophyla*[TiAb] OR preventive*[TiAb] OR prevention*[TiAb] OR preventing [TiAb] OR premedication [TiAb]) AND (wound infection*[TiAb] OR surgical site infection*[TiAb].	2531
#2	((multidrug-resistant bacteria) OR (*Clostridium difficile*-associated diarrhoea) OR clostridium difficile))	14661
#3	#1 AND #2	45

Table 1.6. Search of MEDLINE/Embase via OVID for Objective 5

Search	Query	Items found
#1	surgical wound infection.mp. [mp=ti, ab, ot, nm, hw, ps, rs, ui, sh, tn, dm, mf, dv, kw]	26642
#2	perioperative antibiotic prophylaxis.mp. [mp=ti, ab, ot, nm, hw, ps, rs, ui, sh, tn, dm, mf, dv, kw]	669
#3	clostridium difficile.mp. [mp=ti, ab, ot, nm, hw, ps, rs, ui, sh, tn, dm, mf, dv, kw]	17275
#4	clostridium difficile diarrhea.mp. [mp=ti, ab, ot, nm, hw, ps, rs, ui, sh, tn, dm, mf, dv, kw]	211
#5	multi drug resistant bacteria.mp. [mp=ti, ab, ot, nm, hw, ps, rs, ui, sh, tn, dm, mf, dv, kw]	214
#6	multi drug resistance.mp. [mp=ti, ab, ot, nm, hw, ps, rs, ui, sh, tn, dm, mf, dv, kw]	3099
#7	3 or 4 or 5 or 6	20573
#8	1 and 2	159
#9	8 and 7	1
#10	antibiotic prophylaxis.mp. [mp=ti, ab, ot, nm, hw, ps, rs, ui, sh, tn, dm, mf, dv, kw]	31562
#11	1 and 10	2709
#12	11 and 7	15

Fourteen hits after removing duplicates from #12.

Annex 2. Excluded studies

Table 2.1. Excluded studies

Study	Reason for exclusion
Alkalin et al. 2000	Non-systematic review
Allan et al. 2000	Non-systematic review
Aziz et al. 2010	Unclear role of PAP in the prevention of SSIs since additional measures for their prevention were also reported
Berenguer 2010	Retrospective review without control
Braxton et al. 2010	Questionnaire/surveillance without a control
Bucher et al. 2011	Non-systematic review
Burke et al. 2010	Questionnaire/surveillance without a control
Campell et al. 2008	Questionnaire/surveillance without a control
Castello et al. 2006	No appropriate control provided
Chaberny et al. 2011	Non-systematic review
Charrier et al. 2009	Unclear role of PAP in the prevention of SSIs since additional measures for their prevention were also reported
Davis 2008 et al.	Severe methodological limitations
Delgrado-Rodriguez 2001	Before–after study in a single Spanish hospital in 1989 patients; intervention consisted of reduction of preoperative stay; unnecessary chemoprophylaxis; reinforcement of aseptic management of surgical wound; appropriate management of catheters without any information about the impact of PAP on SSIs as primary outcome. No definition of unnecessary PAP.
Diana et al. 2011	Questionnaire/surveillance without a control
Dull et al. 2008	Severe methodological limitations
El-Badawi et al. 2009	No full text available/no access to full text
Enzler et al. 2011	Non-systematic review
Finkelstein et al. 2005	Unclear role of PAP in the prevention of SSIs since additional measures for their prevention were also reported
Goliembski et al. 2004	Non-systematic review
Gorecki et al. 1999 et al.	Retrospective analysis of appropriate PAP and antibiotic therapy and occurrence of CDAD; results are presented as total use of antibiotics, irrespective of prophylaxis or therapy; no sufficient statistical analysis performed.
Gorevitch et al. 2008	Non-systematic review
Gradl et al. 2011	Non-systematic review
Graf et al. 2009	Unclear role of PAP in the prevention of SSIs since additional measures for their prevention were also reported
Higuchi et al. 2010	Prospective observational study surveying SSI after single PAP dose without a control
Hohmann et al. 2011	Conference abstract; limited information; no full text published
Hübner et al. 2011	Questionnaire/surveillance without a control
Humphrey et al. 2009	Non-systematic review
Hyman et al. 2010	Conference abstract; limited information; no full text published
Jäger et al. 2006	Non-systematic review
Karamboudis et al. 2010	Questionnaire/surveillance without a control
Kim et al. 2010	Conflicting data in the abstract between text and table
Lau et al. 2010	Unclear role of PAP in the prevention of SSIs since additional measures for their prevention were also reported
Lichtenberg et al. 2003	Conference abstract; limited information; no full text published.
Malangoni 2011	Non-systematic review
McHugh et al. 2010	No appropriate control provided
Meyer et al. 2010	Unclear role of PAP in the prevention of SSIs since additional measures for their prevention were also reported
Misteli et al. 2011	Aim of study was evaluation of the microbiology of SSI; no controls
Munoz-Platon et al. 1995	No full text available/no access to full text
O'Reilly et al.	Severe methodological limitations
Pan et al. 2009	Questionnaire/surveillance without a control
Poubothu et al. 2009	No appropriate control provided
Rauk et al. 2010	No PAP
Rosenberger 2011	Non-systematic review
Santini et al. 2009	Conference abstract; limited information; no full text published
Schneeberger et al. 2002	Questionnaire/surveillance without a control
Schweon 2006	Journal article summarising reasons for SSI and prevention strategies (no original study, no systematic review)
Shah et al. 2010	Questionnaire/surveillance without a control
Suljagic et al. 2010	Surveillance of SSI; no analysis of PAP
Vries 2010	Conference abstract, no full text published yet
Wacha et al.	Non-systematic review