Timing of preoperative antibiotic prophylaxis in 54,552 patients and the risk of surgical site infection

A systematic review and meta-analysis

Stijn Willem de Jonge, MD, Sarah L. Gans, MD, PhD, Jasper J. Atema, MD, PhD, Joseph S. Solomkin, MD, Patchen E. Dellinger, MD, Marja A. Boermeester, MD, PhD*

Abstract
The aim of the study was to assess the effect of timing of preoperative surgical antibiotic prophylaxis (SAP) on surgical site infection (SSI) and compare the different timing intervals.

The benefit of routine use of SAP prior to surgery has long been recognized. However, the optimal timing has not been defined. For the purpose of developing recommendations for the World Health Organization guideline for SSI prevention, a systematic review and meta-analysis of all relevant evidence was conducted.

Major medical databases were searched from 1990 to 2016. The primary outcome was SSI after preoperative-SAP comparing different timing intervals. Adjusted odds ratios (OR) with 95% confidence intervals (CI) were extracted and pooled for each comparison with a random effects model.

Fourteen papers with 54,552 patients were included in this review. In a quantitative analysis, there was no significant difference when SAP was administered 120–60 minutes prior to incision compared to administration 60–0 minutes prior to incision. Studies investigating different timing intervals within the last 60 minutes time frame reported contradictory results. The risk of SSI almost doubled when SAP was administered after first incision (OR:1.89; 95%CI:[1.05–3.40]) and was 5 times higher when administered more than 120 minutes prior to incision (OR5.26; 95%CI:[3.29–8.39]).

Administration of antibiotic prophylaxis more than 120 minutes before incision or after incision is associated a higher risk of surgical site infections than administration less than 120 minutes before incision. Within this 120-minute time frame prior to incision, no differential effects could be identified. The broadly accepted recommendation to administer prophylaxis within a 60-minute time frame prior to incision could not be substantiated.

Abbreviations: CABG = Coronary artery bypass graft, CDC = Center for Disease Control and Prevention, CENTRAL = Cochrane Central Register of Controlled Trials, CI = confidence interval, CINHAL = Cumulative Index to Nursing and Allied Health Literature, GRADE = Grading of recommendations, assessment and evaluations, MeSH = Medical Subject Headings, OR = odds ratio, RCT = randomized controlled trial, SAP = surgical antibiotic prophylaxis, SSI = surgical site infection, WHO = World Health Organization.

Keywords: antibiotic prophylaxis, guideline, meta analysis, surgery, surgical site infection, systematic review, WHO

1. Introduction
Surgical site infections (SSI) are a dreadful complication in surgery. SSI is one of the most common nosocomial infections accounting for 21.8% of the total in the United States and causes increased morbidity, mortality, readmissions, and prolonged hospital stay.[1,2] As a result, SSI increase healthcare costs up to 1.6 billion dollar a year.[2] Since the introduction of the antisepsis theory by Semmelweis and Lister in the late 18th century, the administration of routine antibiotic prophylaxis in non-clean and implant surgery has been the biggest breakthrough in SSI prevention. The relevance of timing has been proved in experimental and clinical studies.[3,4] However, the optimal timing of administration remains under debate. Classen’s landmark study was the first clinical study, describing the least infections when antibiotic prophylaxis was administered within 120 minutes prior to incision. Since then many efforts have been made to define an optimal timing interval within 120 minutes with conflicting results.[3,6] Recently, in a large retrospective cohort, no significant association between timing of AP and SSI was described.[7] Current guidelines issued by professional societies or national authorities, such as the American Society of Health-System Pharmacists,[8] the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America,[9] the Royal College of Physicians of Ireland,[10] or Health Protection Scotland[11] recommend administration within 60 minutes prior to incision. However, these recommendations are not based upon systematic reviews of the literature and
meta-analysis or a rigorous evaluation of the quality of the available evidence. The contradictory results in previous studies leave the importance of adherence to these guidelines open to discussion. For the purpose of developing recommendations for the new World Health Organization (WHO) SSI prevention guidelines, a systematic literature review and meta-analysis were conducted on the effectiveness of different timing for administration of SAP to reduce SSI in indicated surgical procedures.

2. Methods

The report of this systematic review is drafted in accordance with the MOOSE guidelines for reporting meta analysis of observational studies.[12] As this concerns a literature study, no ethical approval was required. No review protocol for this meta-analysis was published or registered before this study was undertaken. This systematic review is part of the evidence that formed the basis for the recommendations of the WHO guidelines for SSI prevention.

2.1. Search strategy

A clinical librarian was consulted on the search strategy. A systematic search in Medline (PubMed); Excerpta Medica Database (EMBASE); Cumulative Index to Nursing and Allied Health Literature (CINAHL); Cochrane Central Register of Controlled Trials (CENTRAL); and WHO regional medical databases was conducted. The time limit for the review was between January 1st 1990 and August 13th 2014. The search was updated on August 12th 2016. Language was restricted to English, French, German, and Spanish. A comprehensive list of search terms was used, including Medical Subject Headings (MeSH) (Appendix 1, http://links.lww.com/MD/B734).

2.2. Study selection

Two independent reviewers (SW and SG) screened titles and abstracts of retrieved references for potentially relevant studies. Any disagreements were solved through discussion or, when necessary, after consultation of the senior author (MB). The full text of all potentially eligible articles was obtained and reviewed for eligibility based on predefined inclusion criteria. All clinical studies comparing the outcome of surgical site infection with different timing intervals of preoperative antibiotic prophylaxis in indicated procedures were considered for eligibility. This comprised all clean contaminated, contaminated and implant surgery in all surgical fields. Duplicates, congress abstracts, experimental studies, studies with insufficient data for comparison and studies without clear description of the compared timing intervals where excluded from the analysis. This included studies that did not differentiate agents with a prolonged infusion time such as vancomycin or fluoroquinolones from fast infusion antibiotics like cephalosporins as timing is generally measured form the moment of administration and a delay to full infusion is anticipated in these drugs. When full text was not available or presented results were incomplete the corresponding author was contacted. When all relevant full text papers were gathered each reference list was reviewed for any omitted studies

2.3. Study quality assessment

Two reviewers (SL, SW), critically appraised each study using the Newcastle–Ottawa Quality Assessment Scale for cohort studies. This is a 8 item scoring system, which is validated in the quality assessment of observational cohort studies in systematic reviews.[13] Any disagreements were resolved through discussion or, when necessary, after consultation of the senior author (MB).

2.4. Data extraction

The 2 reviewers (SL, SW) extracted data in a predefined evidence table. The 2 tables were then compared. Any disagreements were resolved through discussion or after consultation of the senior author (MB). Data collection from each table included; design, scope, number of participants, type of surgery, SSI definition, follow-up duration, antibiotics used, duration of procedure and re-dosing, antibiotic continuation, compared timing intervals, SSI rates, adjusted odds ratios, the variables adjusted for, and quality assessment score.

2.5. Outcome measures

The primary outcome of interest was the incidence of surgical site infection after the administration of antibiotic prophylaxis within different timing intervals from the first incision in non-clean and implant surgical procedures.

2.6. Statistical analysis

All statistical analyses were conducted using Review Manager (RevMan, Version 5.3. Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014) as appropriate. To account for heterogeneity between studies and confounding variables within studies only adjusted odds ratios where used for the statistical analysis. Adjusted odds ratios (OR) with 95% confidence intervals (CI) were extracted and pooled for each comparison using the generic inverse variance method in a random effects model. When adjusted odds rates were not available unadjusted crude data were used as a surrogate. We assessed statistical heterogeneity with $I^2$ statistics.

2.7. Publication bias

Publication bias was assessed using a funnel plot.[14]

2.8. GRADE assessment

All data from the eligible studies were analyzed using the grading of recommendations assessment and evaluations methodology (GRADE) with the GRADEpro guideline development tool (http://gdt.guidelinedevelopment.org/), to define the quality of the evidence.[15]

3. Results

3.1. Systematic review

The search retrieved 3177 records of possible relevance. Eleven additional records were identified through other sources. After removal of duplicates 1999 records were screened and 1959 were excluded based on title and abstract. A total of 40 full text articles were assessed for eligibility. Fourteen adhered to the predefined selection criteria and were included in the review; 26 were excluded (Fig. 1, Appendix 2, http://links.lww.com/MD/B734).

3.2. Study characteristics

Characteristics are summarized in Table 1. All studies were observational; no randomized controlled trials (RCT) were
found. Of the observational studies, 1 was a case control study,[16] 2 were retrospective cohorts,[17,18] and 11 were prospective cohorts.[4,6,19–26] Most studies included a variety of surgical procedures. Represented surgical procedures were gastrointestinal, orthopedic, vascular, traumatology gynecology, and cardiac surgery. All but two studies reported the use of the center of disease control and prevention (CDC) or similar standardized criteria for surgical site infection. Only 1 study specified categories of SSI (superficial, deep, organ space) per timing category and reported a similar distribution across timing categories.[3] Four studies considered SSI as an infection occurring before discharge,[4,20,24] 1 before removal of stitches[26] and 9 within 30 days after surgery (or 1 year in the case of implantation of a foreign body).[5,6,17,23] Nine studies reported postoperative antibiotic continuation with a varying duration up to 48 hours.[4–6,17,18,21–23,27] Five studies did not report on postoperative antibiotic regimen.[6,16,19,20,25,26] Four studies reported a re-dosing regimen within 4 hours after incision versus pre-incision,[4,5,16,17,23] 7 more than 120 minutes prior to incision versus within 120 minutes,[4,19,20] 120–60 versus 60–0 minutes[4–6,21–23] and 60–30 minutes versus 30–0 minutes prior to incision[4,5,17,23] (Table 2). 54,552 patients were included in this review of which 21,072 could be included in the meta-analyses. In some cases, participants could be included in several comparisons.

3.3. Critical appraisal

Critical appraisal of the 14 studies showed some differences in methodological quality. All studies were observational and quality was assessed with the Newcastle–Ottawa scale (Table 3). Thirteen were assessed according to the criteria for observational cohort studies.[4–6,17–26] One was assessed according to the criteria for case control study.[16]

Observational cohort studies[4–6,17–26]—approximately half of the cohorts were representative for a variety of surgical specialties.[4–6,19,20,25] The other half included 1 specific specialty or procedure.[17,18,21–24,26] In all the studies, the non-exposed cohort was drawn from the same community as the exposed cohort and ascertainment of exposure was done by review of a secure record like surgical records. All studies demonstrated that the outcome of interest was not present at the start of the study. All but five cohort studies were comparable on the basis of design

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**Figure 1.** Flowchart of the study selection process. Numbers between parentheses represent the results of the initial search before the update in August 2016 represented by the numbers outside the parentheses. To avoid drug toxicity, vancomycin and fluoroquinolones have to be infused over a prolonged period of time (>60min) compared to other antibiotics. As timing is measured from the moment of administration and a delay to full infusion is anticipated with the above-mentioned antibiotics, we considered it necessary to differentiate these from fast infusion antibiotics (for example, cephalosporins). Studies that did not have this differentiation were excluded due to unclear timing categories.
| Author, year, reference | Design | N   | Population (age, % female) | Type of surgery | SSI definition, follow-up duration | Antibiotic used | Redosing | Antibiotic continuation | Variables adjusted for | NOS |
|-------------------------|--------|-----|----------------------------|-----------------|-----------------------------------|----------------|----------|------------------------|------------------------|-----|
| Olesen et al, 1992[4]   | Single center OBS-P | 2847 | 53 (11–97); 62% | Hysterectomy, cholecystectomy, bowel resection, gastric bypass, hip, knee. | NA, until discharge | Gentamicin; cefonicid; cefotaxim; cefamandole | NA        | 24–48 h               | Age, procedure type, procedure duration, sex, underlying disease, surgeon, hospital service, attending physician, nursing service, postoperative procedures | 7   |
| Munoz et al, 1995[19]   | Single center OBS-P | 2083 | 55.8 ± 20.6; 52% | Clean-contaminated, contaminated and clean. | CDC, until discharge | Gentamicin; clindamycin + gentamicin; gentamicin + metronidazole; ceftriaxone; cefotaxime; ceftazim; cefoxitin + gentamicin, cefotin | NA        | NA                    | Procedure duration, diabetes, wound classification | 7   |
| Uzan Garcia et al, 1997[20] | Single center OBS-P | 1983 | 48 ± 23; 47% | Clean, clean-contaminated, contaminated, dirty. | CDC, Until discharge | According to the hospital clinical infections commission | NA        | NA                    | Age, procedure duration, wound classification, stay prior to surgery, emergency procedure, ICU stay, malignant neoplasm, diabetes, staple use for skin closure, antikoagulationprophylaxis | 7   |
| Trick et al, 2000[16]   | Single center CCTIHL | 120  | NA; NA | CABG | CDC DSS, 30 d/1 y | Cefuroxime | NA        | NA                    | Diabetes, staple use for skin closure, antimicrobial agent | 7   |
| Garey et al, 2006[21]   | Single center OBS-P | 2048 | 64 ± 12; 32% | CABG + valve replacement | CDC, 30 d | Vancomycin | NA        | 24 hr                  | Age, procedure type, diabetes, comorbidities, emergency surgery, race, atherosclerosis, obesity | 7   |
| Kasatpibal et al, 2006[22] | Multi center OBS-P | 1972 | 26 IQR 16–39; 53.1% | Open uncomplicated appendectomy | CDC, 30 d | Meropenem + gentamicin | NA        | 24 hr                  | Age, procedure type, procedure duration, sex, length of preoperative stay, ASA score, diabetes, obesity | 7   |
| Van Kasteren et al, 2007[23] | Multi center OBS-P | 1922 | 68.8 ± 10.8; 69% | Hip and knee arthroplasty | CDC, 30 d | Rifampicin; clindamycin; cefamandole; amoxicillin; gentamicin | NA        | Yes                   | Age, procedure duration, sex, aSA score, duration of propranolol, use of antibiptic-impregnated bone cement | 7   |
| Weber et al, 2008[24]   | Single center OBS-P | 3836 | NA; 49% | Vascular, vascular, trauma | CDC, 30 d | Cefuroxime + metronidazole | NA        | Yes                   | Procedure duration, age, procedure type, sex, diabetes, wound classification, aSA score, intraoperative body temperature, body mass index, preoperative antibiotic prophylaxis | 8   |

(continued)
| Author, year, reference | Design | N  | Population (age, % female) | Type of surgery | SSI definition, follow-up duration | Antibiotic used | Redosing | Antibiotic continuation | Variables adjusted for | NOS |
|--------------------------|--------|----|---------------------------|-----------------|-----------------------------------|----------------|---------|------------------------|------------------------|-----|
| Steinberg et al, 2009[6] | Single center OBS-P | 3656 | NA; NA | Cardiac, hysterectomy, hip and knee, arthroplasty | CDC, 30 d/1 y | Cephalexin and other short infusion time antibiotics | >4 hr | 12-24 hr | Therapy, smoking status, immunosuppression, Procedure duration, procedure type | 8 |
| Ho et al, 2011[17] | Single center OBS-R | 605 | 59.7±17.8; 52% | Colon and rectal surgery with anastomosis | CDC, 30 d | Cefazolin + metronidazole; cefoxitin; fluoroquinolone + metronidazole | >4 hr | 24 hr | Type of surgery, wound class, comorbidities, underlying disease, surgeon, ICU admission, intraoperative hypothermia, transfusion, history of radiation, serum albumin concentration, intraoperative hypotension, postoperative glycem control, year | 7 |
| Koch et al, 2012[24] | Single center OBS-P | 28250 | 65±12; 28% | Cardiac surgical procedures involving median sternotomy | STS, discharge | Cefuroxime; vancomycin | NA | 36 hr | NA | 6 |
| El-Mahallawy et al, 2013[26] | Single center OBS-P | 200 | NA; 31.5% | Cystectomy, gastrectomy, colorectal surgery | CDC, Until removal of stitches | Cefepime + gentamicin; clindamycin + amikacin | >2 hr | NA | NA | 5 |
| Koch et al, 2013[27] | Single center OBS-P | 4453 | 54 IQR 42-65; NA | General surgery | NSQIP, 30 d | Cefazolin; ampicillin; cefotaxime; metronidazole; clindamycin; piperacillin | No | NA | NA | 8 |
| Wu et al, 2014[28] | Single center OBS-R | 577 | NA; NA | Appendectomy | NA, 30 d | Cefazolin; gentamicin; Metronidazole; cefotaxime; cefmetazole | NA | <24 hr | NA | 6 |

CCTRL = case-control study; CDC = Centers for Disease Control and Prevention; CI = confidence interval; CABG = coronary artery bypass graft; DSSI = deep sternal site infection; hr = hour; NSQIP = national surgical quality improvement programme; NOS = Newcastle-Ottawa scale; NA = not available; OBS-P = prospective observational cohort; OBS-R = retrospective observational cohort; QR = interquartile range; (): Range; ±: standard deviation; STS = Society of Thoracic Surgeons; SSI = surgical site infection; risk of bias.
and analysis.\cite{4,6,17,19,21,23} One study used no prophylaxis as the reference category.\cite{22} Three studies used a different statistical approach for the analysis.\cite{18,24,25} One study is originally a randomized controlled trial investigating the effect of 2 different agents for antibiotic prophylaxis.\cite{26} The effect of timing was also described, but randomization was done on the basis of the different antibiotic agents and thus we described the study as observational. Assessment of outcome was done by independent

| Author, year, reference | Timing categories | Before/after first incision (−/+) | Time | SSI/total (%) | Adjusted odds ratio (95% confidence interval) | Included in comparison |
|-------------------------|------------------|---------------------------------|------|----------------|---------------------------------------------|-----------------------|
| Classen et al, 1992\cite{4} | – | 1440–102 min | 14/369 (3.8) | 4.3 (1.8–10.4) | 1,2,3a |
| | + | 120–0 min | 10/1708 (0.6) | 1 |
| | + | 0–180 min | 4/282 (1.4) | 2.1 (0.6–7.4) |
| Muroz et al, 1995\cite{19} | + | 180–1440 min | 16/488 (3.3) | 5.8 (2.4–13.8) | 2 |
| | – | > 120 min | 24/107 (22.4) | 5.82 (3.12–10.84) |
| | + | < 120 min | 28/754 (3.7) | 3.2 (2.04–5.1) |
| Lizanc Garcia et al, 1997\cite{20} | + | After surgery | 94/1222 (7.7) | 5.3 (1.56–17.93) |
| | – | > 120 min | 5/56 (9.2) | 5.28 (1.56–17.93) |

Table 2
Results per timing category.

\* = prior to incision, + = after incision, min = minute, NA = not available, SSI = surgical site infection. Second column for vancomycin timing.
Table 3

Quality assessment, Newcastle–Ottawa scale for nonrandomized studies.

| Study                  | Case control study | Control study | Year | Selection of cases and controls | Ascertainment of controls | Comparability of groups | Definition of outcome | Ascertainment of outcome | Non-response rate | Total |
|------------------------|--------------------|---------------|------|---------------------------------|---------------------------|-------------------------|----------------------|------------------------|---------------------|-------|
| Trick et al, 1998[19]  | Yes                | Yes           | 1998 | Yes                              | Yes                       | Yes                     | Yes                  | Yes                    | 0.01                | 1     |
| El-Mahallawy et al, 2009[22] | Yes                | Yes           | 2009 | Yes                              | Yes                       | Yes                     | Yes                  | Yes                    | 0.01                | 1     |
| Koch et al, 2012[23]   | Yes                | Yes           | 2012 | Yes                              | Yes                       | Yes                     | Yes                  | 0.01                   | 1     |
| Koch et al, 2013[24]   | Yes                | Yes           | 2013 | Yes                              | Yes                       | Yes                     | Yes                  | 0.01                   | 1     |
| Garey et al, 2006[25]  | Yes                | Yes           | 2006 | Yes                              | Yes                       | Yes                     | Yes                  | Yes                    | 0.01                | 1     |
| Weber et al, 2008[26]  | Yes                | Yes           | 2008 | Yes                              | Yes                       | Yes                     | Yes                  | Yes                    | 0.01                | 1     |
| Steinberg et al, 2012[27] | Yes            | Yes            | 2012 | Yes                              | Yes                       | Yes                     | Yes                  | Yes                    | 0.01                | 1     |
| Ho et al, 2013[28]     | Yes                | Yes           | 2013 | Yes                              | Yes                       | Yes                     | Yes                  | Yes                    | 0.01                | 1     |

3.4. Unpooled results

Five studies[16,18,24,25] were not included in any meta-analyzed comparison. Trick et al conducted a case control study in a single center, a different methodology than the other observational studies included in the meta-analysis, and could therefore not be pooled. They included 120 coronary artery bypass graft (CABG) procedures and compared administration more than 120 minutes before incision versus within 120 minutes before incision showing significant increased risk of SSI with administration more than 120 minutes before incision (OR: 5.00; 95%CI [1.40–17.00]) (Tables 1 and 2, Fig. 2).[16] El Mahallawy et al, Wu et al and 2 studies by Koch et al could not be included in the meta-analysis because adjusted odds ratios could not be derived from their results (Tables 1 and 2, Fig. 2). Koch et al[24,25] conducted 2 observational studies. One prospectively evaluating 28,250 cardiac surgical procedures involving median sternotomy investigated different timings of antibiotic prophylaxis and showed that predicted SSI rates were lowest when cefuroxime was administered 15 minutes prior to incision and vancomycin 30 minutes and the latter evaluated difference between 30 and 60 minutes versus 0 to 30 minutes in 4453 general surgery procedures and showed that administration within 30–60 minutes had a 30% higher risk as compared to administration within 0 to 30 minutes (11.7% vs 9%). This difference was significantly different (P = 0.01). Wu et al compared 577 patients undergoing appendectomy in four 30-minute timing categories ranging from 0 to 30 up to more than 120 minutes prior to surgery and found no significant difference in the SSI rate between the groups. Finally, El Mahallawy et al[26] compared timing of antibiotic prophylaxis more than 30 minutes prior to incision with within 30 minutes in 200 surgical procedures. No significant difference in the SSI rate was found.

In Fig. 2 we have visualized our summary findings.

3.5. Meta-analysis

In 4 separate comparisons, the risk of SSI with different timing intervals could be assessed with meta-analysis. Due to the absence of studies using a 0 to 60 minute interval as reference category we were unable to compare adjusted outcomes for this interval in the analysis. We used unadjusted crude data as a surrogate for this comparison. When crude data was meta-analyzed in the other comparisons it resulted in the same outcome but a smaller effect size as compared to adjusted odds (Appendix 3, http://links.lww.com/MD/B734).
There was no significant difference in the risk of surgical site infection comparing 120–60 minutes versus 60–0 minutes (OR: 1.22; 95%CI: [0.92–1.61]; Table 2, Fig. 3C). When timing intervals within the last 60 minutes prior to incision, 60–30 minutes versus 30–0 minutes, were compared there was also no significant difference (OR: 1.07; 95%CI: 0.53–2.17; Table 2, Fig. 3D). However, results of individual studies were contradictory and considerable heterogeneity was apparent ($I^2$=85%).

When antibiotic prophylaxis was administered after incision the risk of a surgical site infection was almost twice as high (OR: 1.89; 95%CI: [1.05–3.40]; Table 2, Fig. 3A) as compared to administration before incision and resulted in 25 more infections per 1000 treated patients (from 1 more to 65 more).

Administration of AP more than 120 minutes prior to incision increased the risk of SSI more than 5 times as compared to administration within 120 minutes (OR: 5.26; 95%CI: 3.29–8.39; Table 2, Fig. 3B).

3.6. Publication bias

Funnel plots are presented in Appendix 4, http://links.lww.com/MD/B734. None of the analyses reached the minimally required 10 included studies for adequate assessment of publication bias. As a result no conclusions can be drawn on the presence or absence of publication bias.

3.7. Grade assessment

GRADE tables with full assessment of the individual comparisons are presented in Table 4. Overall the quality of evidence was very low to moderate due to imprecision, inconsistency and large effect.

4. Discussion

The quality of the retrieved evidence was assessed with the use of GRADE methodology. Overall, moderate to low quality of evidence shows that administration of SAP more than 120 minutes prior to incision, or after incision respectively, is associated with a higher risk of SSI as compared with administration within 120 minutes prior to incision. Within these time limits, no significant difference between timing intervals for SAP administration was demonstrated.

Guidelines and quality control programs have adopted a 60-minute interval for SAP, but the origin of this 60-minute interval is arbitrary. The first published guideline that describes this interval refers to a pharmacokinetic study and a paper investigating the combined results of 2 randomized controlled clinical trials on multidose versus single dose prophylaxis. However, this study was not designed to assess the optimal timing of SAP and very little details about the data and methods are reported. The first clinical study designed to investigate the relevance of timing described the least infections when antibiotic prophylaxis was administered within 120 minutes prior to incision. Regardless of the effect, there was no significant difference with administration 180 minutes after incision. Since then many efforts have been made to define an optimal timing interval within 120 minutes with contradictory results. Some studies suggest that administration of SAP should be within 30 minutes of first incision, whereas other studies have demonstrated an optimal interval between 75 and 30 minutes or describe no relationship at all between timing of SAP and SSI. Although the 60-minute interval is part of daily practice and an important aspect of quality control, not 1 prospective study has confirmed its superiority and a strong evidence based substantiation for its use is lacking. In the current systematic review, we aggregate all the available evidence to find an evidence-based answer to the issue of optimal timing of preoperative SAP.

The limitations of the present study are generally allocated to the individual studies. The risk of SSI is a complex and multifactorial problem and therefore prone to confounding. Especially when assessed in observational studies where no randomization is in place to evenly distribute known and unknown confounders across study groups. In this systematic
review and meta-analysis, all identified studies were observational. No randomized studies have been performed on this topic. As a result, design and outcome measures differed limiting inclusion in the meta-analysis, the comparing groups were of unequal size and, while included data are adjusted for measured confounders, model building strategies, and the variables adjusted for varied across studies. Although important variables such as procedure duration, procedure type, and wound classification were included in the majority of the studies, they were not in all. In addition, regardless of the variables included in the models, there is always a risk of unmeasured residual confounding. Therefore inferences on these data are strictly associational, not causal. Also, some of the retrieved evidence is over 20 years old and preferred agents and minimally inhibitory concentrations may have changed. Lastly, among the included studies a substantial heterogeneity was apparent with regard to the antibiotic regimen: all studies used multiple agents with varying half-lives; all studies reported the time of administration, but information on infusion time was lacking in many resulting in the exclusion of all studies that did not differentiate agents with prolonged infusion times such as vancomycin from fast infusing antibiotics such as cephalosporins; the duration of the procedure and re-dosing protocol varied; when a re-dosing protocol was applied, it was based on the duration of the procedure rather than on the time after the first dose, thus leading to a high risk of inadequate re-dosing; and postoperative antibiotic duration was not the same. These are all aspects that potentially influence the effect of timing of SAP on SSI and thereby impede the results. However, despite these limitations, the present systematic review is the first and only to address all the available data on this topic using meta-analysis to aggregate the evidence and GRADE methodology to assess its quality in order to find an evidence-based answer to this issue.

Figure 3. Meta analyses (A) Comparison 1: administration of surgical antibiotic prophylaxis post- versus pre- incision. (B) Comparison 2: Administration of surgical antibiotic prophylaxis more than 120 min prior to incision versus within 120 min prior to incision. (C) Comparison 3a: Administration of surgical antibiotic prophylaxis 120–60 min prior to incision versus 60–0 min prior to incision. ∗Crude unadjusted data were used in the meta analyses. (D) Comparison 3b: Administration of surgical antibiotic prophylaxis 60–30 min prior to incision versus 30–0 min prior to incision.
**Table 4**

Comparison 1: Administration of surgical antibiotic prophylaxis post- vs pre-incision

| Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | No. of studies | Surgical site infection |
|--------------|--------------|---------------|--------------|-------------|----------------------|----------------|------------------------|
| Observational studies | Not serious | Not serious | Not serious | Not serious | None | 4 | 18/439 (4.1%) / 116/3852 (3.0%) | OR: 1.89 (1.05–3.40) / 25 more per 1000 (from 1 more to 65 more) |

Comparison 2: Administration of surgical antibiotic prophylaxis more than 120 minutes prior to incision vs within 120 minutes prior to incision

| Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | No. of studies | Surgical site infection |
|--------------|--------------|---------------|--------------|-------------|----------------------|----------------|------------------------|
| Observational studies | Not serious | Not serious | Not serious | Strong association | None | 3 | 287/4437 (6.5%) / 43/484 (8.9%) | OR: 5.26 (3.29–8.39) / 250 more per 1000 (from 154 more to 361 more) |

Comparison 3a: Administration of surgical antibiotic prophylaxis 120-60 minutes prior to incision vs 60-0 minutes prior to incision

| Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | No. of studies | Surgical site infection |
|--------------|--------------|---------------|--------------|-------------|----------------------|----------------|------------------------|
| Observational studies | Not serious | Not serious | Serious | None | None | 6 | 122/3659 (3.3%) / 279/9964 (2.8%) | OR: 1.22 (0.92–1.61) / 6 more per 1000 (from 2 fewer to 16 more) |

Crude unadjusted data were used in the meta-analyses.

Comparison 3b: Administration of surgical antibiotic prophylaxis 60-30 minutes prior to incision vs 30-0 minutes prior to incision

| Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | No. of studies | Surgical site infection |
|--------------|--------------|---------------|--------------|-------------|----------------------|----------------|------------------------|
| Observational studies | Serious | Not serious | Serious | None | None | 4 | 153/3785 (4.0%) / 222/4728 (4.7%) | OR: 1.07 (0.53–2.17) / 3 more per 1000 (from 22 fewer to 50 more) |

CI = confidence interval, OR = odds ratio, RR = relative risk, RRR = relative risk reduction, SAP = surgical antibiotic prophylaxis.

1 Quality of evidence was upgraded to moderate for large effect size.
2 Optimal information size is met but CI overlaps no effect and fails to exclude considerable benefit or harm (RR or RRR of 25%).
3 High heterogeneity, $I^2 = 85\%$.
4 Optimal information size is met but CI crosses no effect and fails to exclude considerable benefit or harm (RR or RRR of 25%).
Although it has been shown to be very hard to find significant differences between timing categories in individual studies, the pooled analyses of the aggregated show a strong association with harm of inadequate timing.

Our findings indicate that adequate tissue concentrations of the antibiotic should be present at the time of the incision and throughout the procedure for SAP to be effective. This necessitates administration prior to incision. Further evidence shows that low tissue concentration of antibiotics at the time of wound closure is associated with higher SSI rates.\textsuperscript{13,31} Although based on the available evidence it is not possible to more precisely establish the optimal timing within the 120-minute interval, antibiotics with short half-lives may be less effective if given early in this time interval than when administered closer to the time of incision, and there is no evidence that administration close to the incision is inferior.\textsuperscript{12} It is therefore recommended to take into account the half-life of the administered antibiotics in order to establish the exact time of administration within 120 minutes preincision. (e.g., administration closer to the incision time [<60 minutes] for antibiotics with a short half-life, such as cefazolin, cefoxitin, and penicillins in general) The same attention about the single antibiotic half-life should be paid when considering re-dosing during prolonged surgery, which should occur with the timing based on the time of preoperative administration and not simply on duration of the operation. Concerns about antibiotic protein binding may arise when choosing highly bound antimicrobials, such as ceftriaxone, teicoplanin or ertapenem. Under particular pathophysiological conditions, such drugs disposition may indeed be affected: any situation with low level of serum proteins, such as critically ill or very aged patients, malnourishing, cachexia, or renal diseases with protein loss may yield to suboptimal antibiotic exposure through increased antibiotic clearance in the presence of normal or augmented renal function as well as to overexposure and potential toxic effects in the presence of severely impaired renal function. Difficulties in adherence to recommended timing intervals are seen in various studies.\textsuperscript{36–41} The use of SURPASS, a surgical safety checklist, leads to better compliance with regard to timing of antibiotic prophylaxis.\textsuperscript{42}

Surgical antibiotic prophylaxis should be administered within 120 minutes prior to incision, when indicated according to the type of operation. Administration before 120 minutes of incision is associated with a higher risk of surgical site infection. The exact optimal timing within this timeframe cannot be defined according to the available evidence but half-life and protein-binding of the antibiotic should be taken in to account, also according to the underlying conditions of the individual patient. The broadly accepted recommendation to administer AP within 60 minutes prior to incision could not be substantiated. However the evidence comes from studies with limited methodological quality and definitive randomized controlled trials are still needed. Future research should well describe and standardize aspects affecting the effect of timing. Also different pharmacokinetic properties should be taken in to account. A protocol for a randomized control trial has been published earlier in 2015.\textsuperscript{43} We curiously await the results of this trial. No financial support has been received for this study.

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