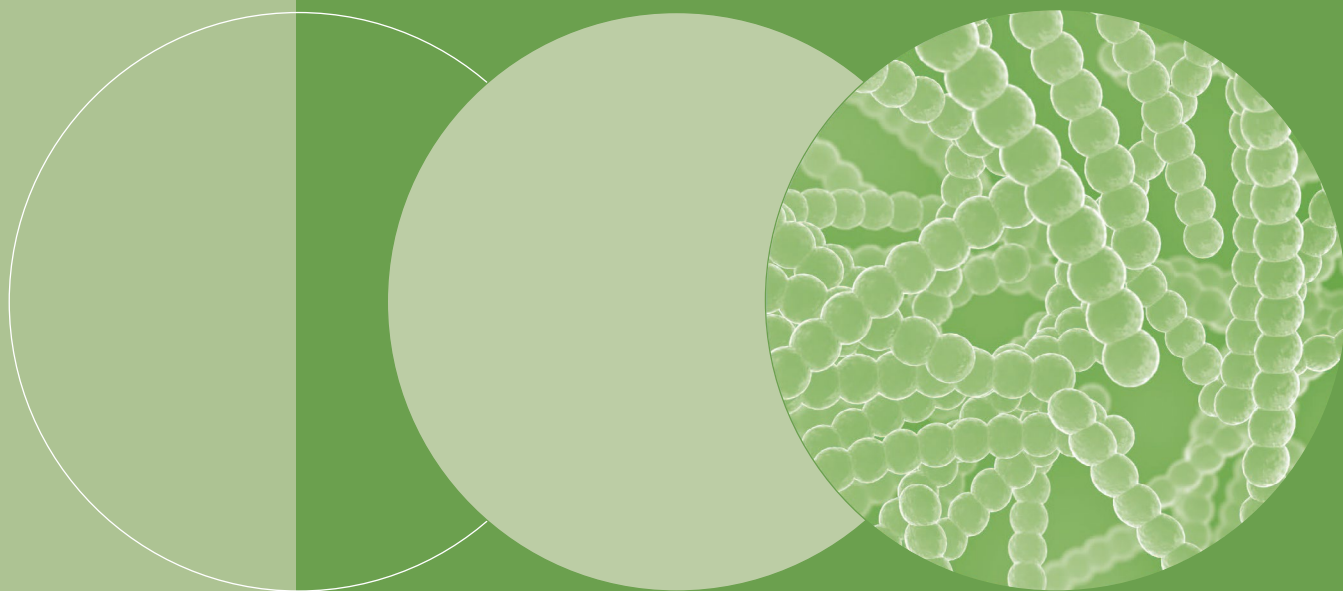


WHO recommendation on **Prophylactic antibiotics for women undergoing caesarean section**



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Acronyms and abbreviations

CerQUAL	Confidence in the Evidence from Reviews of Qualitative Research
CHEC	Consensus Health Economic Criteria
DOI	declaration of interest
ERG	Evidence Review Group
ESG	Evidence Synthesis Group
EtD	evidence-to-decision
FIGO	International Federation of Gynecology and Obstetrics
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GSG	Guideline Steering Group
HRP	UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction
ICM	International Confederation of Midwives
IU	international units
IV	intravenous
MPH-GDG	Maternal and Perinatal Health Guideline Development Group
PICO	population (P), intervention (I), comparator (C), outcome (O)
UNDP	United Nations Development Programme
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
WHO	World Health Organization

Executive summary

Introduction

Direct maternal infections around the time of childbirth account for about one tenth of the global burden of maternal death. Women who develop peripartum infections are also prone to severe morbidity, long-term disabilities such as chronic pelvic pain, fallopian tube blockage and secondary infertility. Maternal infections before or during childbirth are also associated with an estimated 1 million newborn deaths annually.

Several factors increase the risk of maternal peripartum infections, including pre-existing maternal conditions (e.g. malnutrition, diabetes, obesity, severe anaemia, bacterial vaginosis and group B streptococcus infections), as well as prolonged prelabour rupture of membranes, multiple vaginal examinations, manual removal of the placenta, operative vaginal birth and caesarean section. As such, the strategies to reduce maternal peripartum infections and their short- and long-term complications have been directed at improving infection prevention and control practices.

Globally, an effective intervention for preventing morbidity and mortality related to maternal infection is the prophylactic and therapeutic use of antibiotics. However, the misuse of antibiotics for obstetric conditions and procedures is common in many settings. Inappropriate antibiotic use has implications for the global effort to prevent and reduce antimicrobial resistance. The *WHO global strategy for containment of antimicrobial resistance* underscores the importance of appropriate use of antimicrobials at different levels of the health system to reduce the impact of antimicrobial resistance, while ensuring access to the best treatment available. WHO guidelines for health professionals and policy-makers on the need for antibiotics – and the type of antibiotics – for the prevention and treatment of maternal peripartum infections align with the WHO strategy and, if implemented, will improve maternal and newborn outcomes.

In 2019, the Executive Guideline Steering Group (GSG) for World Health Organization (WHO) maternal and perinatal health recommendations prioritized updating of the existing WHO recommendation on prophylactic antibiotics for women undergoing caesarean section in response to the availability of new evidence. The recommendation in this document thus supersedes the previous WHO recommendation on prophylactic antibiotics for women undergoing caesarean section as published in the 2015 guideline *WHO recommendations for the prevention and treatment of maternal peripartum infections*.

Target audience

The primary audience for this recommendation includes health professionals who are responsible for developing national and local health-care guidelines and protocols (particularly those related to the prevention and treatment of peripartum infections) and those involved in the provision of care to women and their newborns during labour and childbirth, including midwives, nurses, general medical practitioners and obstetricians, as well as managers of maternal and child health programmes, and relevant staff in ministries of health and training institutions, in all settings.

Guideline development methods

The updating of this recommendation was guided by standardized operating procedures in accordance with the process described in the *WHO handbook for guideline development*. The recommendation was initially developed and updated using this process, namely: (i) identification of priority questions and outcomes; (ii) retrieval of evidence; (iii) assessment and synthesis of evidence; (iv) formulation of the recommendations; and (v) planning for the dissemination, implementation, impact evaluation and future updating of the recommendation.

The scientific evidence supporting the recommendation was synthesized using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. An updated systematic review was used to prepare the evidence profiles for the prioritized question. WHO convened a meeting on 19–20 October 2020 where the Guideline Development Group (GDG) members reviewed, deliberated and achieved consensus on the strength and direction of the recommendation presented herein. The recommendation was formulated under one of the following categories: recommended, not recommended, recommended only in specific contexts (the intervention is applicable only to the condition, setting or population specified in the recommendation), recommended only in the context of rigorous research (implementation of the recommendation can still be undertaken provided it takes the form of research that addresses unanswered questions). Through a structured process, the GDG reviewed the balance between the desirable and undesirable effects and the overall certainty of supporting evidence, values and preferences of stakeholders, resource requirements and cost-effectiveness, acceptability, feasibility and equity.

Recommendation

The GDG issued the recommendation on prophylactic antibiotics for women undergoing caesarean section with remarks and implementation considerations. To ensure that the recommendation is correctly understood and applied in practice, guideline users may want to refer to the remarks, as well as to the evidence summary, including the considerations on implementation.

WHO recommendation on prophylactic antibiotics for women undergoing caesarean section

Recommendation: For antibiotic prophylaxis for caesarean section, a single dose of first-generation cephalosporin or penicillin should be used in preference to other classes of antibiotics. (*Recommended*)

Remarks:

Antibiotic classes

- The Guideline Development Group noted that the available evidence on the effectiveness of antibiotics for caesarean section was largely derived from trials that tested first- or second-generation cephalosporins or penicillins in the 1980s and 1990s. Based on consensus, the Guideline Development Group favoured these classes of antibiotics over other classes of antibiotics, as they have a broad spectrum of activities and are widely available in all settings. While the Guideline Development Group members acknowledged the lack of clear difference between first- and second-generation cephalosporins, they noted that the evidence suggests that third-generation cephalosporins may be less effective than penicillins for this indication, and therefore suggests that this class of antibiotics should be avoided.
- The Guideline Development Group noted that first-generation cephalosporins are the preferred antibiotic class for prophylaxis in general surgery, as part of efforts to contain antimicrobial resistance.
- In acknowledgement of the lack of evidence on the comparative effectiveness of different classes of antibiotics, the Guideline Development Group concluded that when the recommended antibiotic classes are not available, other classes of antibiotics may also be used. The Guideline Development Group noted that the choice of an antibiotic class should be informed by local antimicrobial resistance guidance, local bacteriologic patterns of post-caesarean infectious morbidity, safety profile, the clinician's experience with that particular class of antibiotics, availability and cost.

Regimen

- The Guideline Development Group emphasized the importance of using a simple and short (single dose, 30–60 minutes before surgery) antibiotic regimen for prophylaxis. There are other clinical factors (e.g. high maternal body mass index, prolonged labour, prolonged duration of surgery, extensive surgical manipulation or massive blood loss) that might increase the risk of developing post-caesarean infections. Clinical judgement is needed to evaluate if a different regimen (higher dose, second dose) of prophylactic antibiotics is warranted in the presence of risk factors.

Risk of necrotizing enterocolitis

- Due to the increased risk of necrotizing enterocolitis among preterm babies exposed to amoxicillin plus clavulanate, the use of amoxicillin plus clavulanate for antibiotic prophylaxis should be avoided before cord clamping for caesarean section of preterm infants.

Timing and provision

- The Guideline Development Group acknowledged that for caesarean section, prophylactic antibiotics are recommended for women undergoing elective or emergency caesarean section and should be given 30–60 minutes prior to skin incision, rather than intraoperatively after umbilical cord clamping, consistent with recommendation No. 18.1 of the 2015 *WHO recommendations for prevention and treatment of maternal peripartum infections*.

Previous recommendation

- This recommendation revalidates recommendation No. 18.2 of the 2015 *WHO recommendations for prevention and treatment of maternal peripartum infections*, where this was considered a strong recommendation based on moderate-quality evidence.

1. Introduction

1.1 Background

In 2017, an estimated 11.9 million cases of direct maternal infections occurred worldwide (1). Maternal deaths due to infection occur mainly through maternal sepsis, a life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion or postpartum period (2). In 2017, an estimated 5.7 million women developed sepsis during pregnancy, childbirth or the postpartum period (3). Infections during or following childbirth not only increase maternal mortality and short-term morbidities, but also can lead to long-term disabilities such as chronic pelvic pain, fallopian tube blockage and secondary infertility (4). Maternal infections around childbirth also have a considerable impact on newborn mortality, causing an estimated 1 million newborn deaths annually (5, 6). Infection-related morbidities and prolonged hospitalization can interfere with mother-infant bonding in the first days after birth (7).

Several factors have been associated with increased risk of maternal infections, including pre-existing maternal conditions (e.g. malnutrition, diabetes, obesity, severe anaemia, bacterial vaginosis and group B streptococcus infections), as well as prolonged prelabour rupture of membranes, multiple vaginal examinations, manual removal of the placenta, severe perineal trauma, operative vaginal birth and caesarean section (8, 9).

Caesarean section is notably the most important risk factor for infection in the immediate postpartum period, with a five-fold to 20-fold increased risk compared to vaginal birth (8, 9). Peripartum infections associated with caesarean section include infection at the wound/incision site, endometritis and urinary tract infection. Rarer, more serious complications include pelvic abscesses, bacteraemia, septic shock, necrotising fasciitis and septic pelvic vein thrombophlebitis, which can lead to death (10). Serious peripartum infections typically require therapeutic antibiotics, prolonged hospital stays and potentially additional surgery (11). Globally, the incidence of post-caesarean infection varies from 2.5% to 20.5% (12). The risk of infection can be reduced through sound surgical techniques, correct use of topical antiseptic agents and antibiotic prophylaxis.

The prevention, early diagnosis and prompt management of sepsis are key factors in reducing sepsis-related morbidity and mortality, as reflected in the 2017 *WHA70.7 Resolution: Improving the prevention, diagnosis and clinical management of sepsis* (13). Globally, an effective intervention for reducing morbidity and mortality related to maternal infection is the prophylactic and therapeutic use of antibiotics. Antibiotics are widely used (and misused) for obstetric conditions (14, 15). For example, in many countries the use of broad-spectrum antibiotics without confirmation of the causative agent is commonplace (14, 15). In many limited-resource settings, poor diagnostic facilities are a further constraint to prompt diagnosis and appropriate use of antibiotics. Apart from poor outcomes associated with such practices, there is increasing concern that inappropriate use and misuse of antibiotics among women giving birth could compromise public health through the emergence of antibiotic-resistant bacterial strains.

According to the 2015 *WHO global action plan on antimicrobial resistance*, the global consumption of antibiotics in humans has risen in the past two decades, primarily driven by an increased use in low- and middle-income countries (14, 15). The action plan underscores the importance of appropriate use of antimicrobials at different levels of the health system to reduce the impact of antimicrobial resistance, while ensuring access to the best treatment available (16). WHO guidelines for health-care professionals and policy-makers on the need for antibiotics – and the type of antibiotic regimens – for the prevention and treatment of maternal infections align with the WHO strategy and, ultimately, improve maternal and newborn outcomes.

1.2 Rationale and objectives

WHO has established a new process for prioritizing and updating maternal and perinatal health recommendations, whereby an international group of independent experts – the Executive Guideline Steering Group (GSG) – oversees a systematic prioritization of maternal and perinatal health recommendations in most urgent need of updating (17, 18). Recommendations are prioritized for updating on the basis of changes or important new uncertainties in the underlying evidence based on benefits, harms, values placed on outcomes, acceptability, feasibility, equity, resource use, cost-effectiveness or factors affecting implementation. The Executive GSG prioritized updating of the existing WHO recommendation on prophylactic antibiotics for women undergoing caesarean section after the publication of new evidence on this intervention.

This updated recommendation was developed in accordance with the standards and procedures in the *WHO handbook for guideline development*, including synthesis of available research evidence, use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE)¹ and GRADE Confidence in the Evidence from Reviews of Qualitative Research (GRADE-CerQUAL)² methodologies, and formulation of recommendations by a Guideline Development Group (GDG) composed of international experts and stakeholders (19). The recommendation in this document thus supersedes the previous WHO recommendation on prophylactic antibiotics for women undergoing caesarean section as published in the 2015 guideline *WHO recommendations for the prevention and treatment of maternal peripartum infections* (20). The primary aim of this recommendation is to improve the quality of care and outcomes for women giving birth, as they relate to peripartum infection and its complications. This recommendation thus provides a foundation for sustainable implementation of effective antibiotic prophylaxis for women undergoing caesarean section.

1.3 Target audience

The primary audience includes health professionals who are responsible for developing national and local health-care guidelines and protocols (particularly those related to the prevention and treatment of peripartum infections) and those involved in the provision of care to women during labour and childbirth, including midwives, nurses, general medical practitioners and obstetricians, as well as managers of maternal and child health programmes, and relevant staff in ministries of health and training institutions, in all settings.

This recommendation will also be of interest to women giving birth, as well as members of professional societies involved in the care of pregnant women, staff of nongovernmental organizations concerned with promoting people-centred maternal care, and implementers of maternal and perinatal health programmes.

1.4 Scope of the recommendation

Framed using the population (P), intervention (I), comparator (C), outcome (O) (PICO) format, the question for this recommendation was:

- Among women receiving routine antibiotic prophylaxis for caesarean section (P), is the use of a particular class of antibiotics (I), compared with other classes of antibiotics (C), more effective in preventing post-operative infectious morbidities (O)?

1.5 Persons affected by the recommendation

The population affected by this recommendation includes all pregnant women in labour.

¹ Further information is available at: <http://www.gradeworkinggroup.org/>.

² Further information is available at: <https://www.cerqual.org/>.

2. Methods

The recommendation was developed using standardized operating procedures in accordance with the process described in the *WHO handbook for guideline development* (19). In summary, the process included: (i) identification of the priority question and critical outcomes; (ii) retrieval of evidence; (iii) assessment and synthesis of evidence; (iv) formulation of the recommendation; and (v) planning for the dissemination, implementation, impact evaluation and updating of the recommendation.

In 2019, the question relating to which class of antibiotics should be used as prophylaxis for women undergoing caesarean section was identified by the Executive GSG as a high priority for development of an updated recommendation, in response to new evidence on this question. Six main groups were involved in this process, with their specific roles described below.

2.1 Contributors to the guideline

2.1.1 Executive Guideline Steering Group (GSG)

The Executive GSG is an independent panel of 14 external experts and relevant stakeholders from the six WHO regions: African Region, Region of the Americas, Eastern Mediterranean Region, European Region, South-East Asia Region and Western Pacific Region. The Executive GSG advises WHO on the prioritization of new and existing PICO questions in maternal and perinatal health for development or updating of recommendations (17, 18).

2.1.2 WHO Steering Group

The WHO Steering Group, comprising WHO staff members from the Department of Sexual and Reproductive Health and Research, the Department of Maternal, Newborn, Child and Adolescent Health and Ageing and the Antimicrobial Resistance Division and Infection Prevention & Control Technical and Clinical Hub managed the process of updating the recommendations. The WHO Steering Group drafted the key recommendation questions in PICO format, engaged the systematic review teams and guideline methodologists (that is, the Evidence Synthesis Group [ESG]), as well as the members of the GDG and the External Review Group (ERG) (see below). In addition, the WHO Steering Group supervised the retrieval and syntheses of evidence, organized the GDG meetings, drafted and finalized the guideline document, and will also manage the guideline dissemination, implementation and impact assessment. The members of the WHO Steering Group are listed in Annex 1.

2.1.3 Guideline Development Group (GDG)

The WHO Steering Group identified a pool of approximately 50 experts and relevant stakeholders from the six WHO regions to constitute the WHO Maternal and Perinatal Health Guideline Development Group (MPH-GDG). This pool consists of a diverse group of experts who are skilled in the critical appraisal of research evidence, implementation of evidence-informed recommendations, guideline development methods, and clinical practice, policy and programmes relating to maternal and perinatal health, as well as a consumer representative. Members of the MPH-GDG are identified in a way that ensures geographic representation and gender balance, and there were no perceived or real conflicts of interest. Members' expertise cuts across thematic areas within maternal and perinatal health.

From the MPH-GDG pool, 16 external experts and relevant stakeholders were invited to participate as members of the GDG for updating this recommendation. Those selected were a diverse group with expertise in research, guideline development methods, gender, equity and rights, clinical practice, policy and programmes, and consumer representatives relating to prevention and treatment of peripartum infection.

The GDG members for this recommendation were also selected in a way that ensured geographic representation and gender balance, and there were no important conflicts of

interest. The GDG appraised the evidence that was used to inform the recommendation, advised on the interpretation of this evidence, formulated the final recommendation based on the draft prepared by the WHO Steering Group and reviewed and reached unanimous consensus for the recommendation in the final document. The members of the GDG are listed in Annex 1.

2.1.4 Evidence Synthesis Group (ESG)

WHO convened an ESG composed of guideline methodologists and systematic review teams to conduct or update systematic reviews, appraise the evidence and develop the evidence-to-decision (EtD) frameworks. A systematic review on the effects of the intervention was updated, which was supported by the Cochrane Pregnancy and Childbirth Group (21). The WHO Steering Group reviewed and provided input into the updated protocol and worked closely with the Cochrane Pregnancy and Childbirth Group and the guideline methodologist to appraise the evidence using the GRADE methodology. Representatives of the Cochrane Pregnancy and Childbirth Group and a methodologist attended the GDG meeting to provide an overview of the available evidence and GRADE tables and to respond to technical queries from the GDG.

All members of the ESG attended the GDG meetings to provide an overview of the synthesized evidence and to respond to technical queries from the GDG. The members of the ESG are listed in Annex 1.

2.1.5 External partners and observers

Representatives of the United States Agency for International Development (USAID), the International Confederation of Midwives (ICM), the International Federation of Gynecology and Obstetrics (FIGO) and the Bill & Melinda Gates Foundation participated in the GDG meetings as observers. These organizations, with their long history of collaboration with WHO in maternal and perinatal health guideline dissemination and implementation, were identified as potential implementers of the recommendations. The list of observers who participated in the GDG meetings is included in Annex 1.

2.1.6 External Review Group (ERG)

The ERG included eight technical experts with interests and expertise in the prevention and treatment of peripartum infections. The group was geographically diverse and gender balanced, and the members had no important conflicts of interest. The experts reviewed the final document to identify any factual errors and commented on the clarity of language, contextual issues and implications for implementation. They ensured that the decision-making processes had considered and incorporated contextual values and the preferences of persons affected by the recommendation, health-care professionals and policy-makers. It was not within the remit of this group to change the recommendation that was formulated by the GDG. Members of the ERG are listed in Annex 1.

2.2 Identification of priority questions and outcomes

The priority outcomes were aligned with those from the 2015 *WHO recommendations for the prevention and treatment for maternal peripartum infections* (20). These outcomes were initially identified through a search of scientific databases for relevant, published systematic reviews and a prioritization of outcomes by the GDG for the 2015 guideline. In recognition of the importance of women's experiences of care, two additional outcomes – maternal well-being and maternal satisfaction – were included for this update to ensure that evidence synthesis and recommendation decision-making by the GDG were driven by outcomes that are important to women and to ensure that the final set of recommendations would be woman-centred. All the outcomes were included in the scope of this document for evidence searching, retrieval, synthesis, grading and formulation of the recommendation. The list of priority outcomes is provided in Annex 2.

2.3 Evidence identification and retrieval

Evidence to support this update was derived from several sources by the ESG working in collaboration with the WHO Steering Group.

2.3.1 Evidence on recommendation of prophylactic antibiotics for women undergoing caesarean section

An existing systematic review on prophylactic antibiotics for women undergoing caesarean section was updated (21). This systematic review was the primary source of evidence of effectiveness for this recommendation. Four studies involving 856 women were added since the previous review. Randomized controlled trials relevant to the key question were screened by the review authors, and data on relevant outcomes and comparisons were entered into the Review Manager 5 (RevMan) software. The RevMan file was retrieved from the Cochrane Pregnancy and Childbirth Group and customized to reflect the key comparisons and outcomes (those that were not relevant to the recommendation were excluded). The RevMan file was then exported to the GRADE profiler (GRADEpro) software, and GRADE criteria were used to critically appraise the retrieved scientific evidence (22). Finally, evidence profiles (in the form of GRADE summary of findings tables) were prepared for comparisons of interest, including the assessment and judgements for each outcome and the estimated risks.

2.3.2 Evidence on values, resource use and cost-effectiveness, equity, acceptability and feasibility

A mixed-methods systematic review was the primary source of evidence on values, acceptability and feasibility as they relate to the EtD framework for prophylactic antibiotics for women undergoing caesarean section (23). This review included the views and experiences of women and providers with antibiotic prophylaxis during labour and childbirth and included nine studies pertaining to the use of prophylactic antibiotics at caesarean section. A number of factors affecting the use of antibiotics by providers around the time of birth were identified. Additionally, a systematic review of qualitative studies evaluating “what women want” from intrapartum care was used to further inform the values and equity domains (24). Two studies pertaining to the availability and quality of antibiotics internationally were also used to inform the equity domains (25, 26).

The primary source of evidence for resources and cost-effectiveness were two trials included in the systematic review for this recommendation (21). The first study compared cephalosporin (ceftriaxone) versus a mixed nitroimidazole plus aminoglycoside triple drug regimen (metronidazole and ampicillin plus cloxacillin and gentamicin) in the prevention of caesarean section infections (27). The second study was conducted in a tertiary hospital in China and compared the effectiveness of a cephalosporin plus nitroimidazole regimen (cefazolin sodium plus metronidazole) versus a nitroimidazole plus penicillin control group (metronidazole plus ampicillin sodium and benzylpenicillin sodium) and included the outcome cost of drugs (28). Available evidence was assessed as low quality according to the Consensus Health Economic Criteria (CHEC) checklist (29).

2.4 Certainty assessment and grading of the evidence

The certainty assessment of the body of evidence on effects for each outcome was performed using the GRADE approach (30). Using this approach, the certainty of evidence for each outcome was rated as “high”, “moderate”, “low” or “very low” based on a set of established criteria. The final rating of certainty of evidence was dependent on the factors briefly described below.

Study design limitations: The risk of bias was first examined at the level of each individual study and then across the studies contributing to the outcome. For randomized trials, certainty was first rated as “high” and then downgraded by one (“moderate”) or two (“low”) levels, depending on the minimum criteria met by the majority of the studies contributing to the outcome.

Inconsistency of the results: The similarity in the results for a given outcome was assessed by exploring the magnitude of differences in the direction and size of effects observed in different studies. The certainty of evidence was not downgraded when the directions of the findings were similar and confidence limits overlapped, whereas it was downgraded when the results were in different directions and confidence limits showed minimal or no overlap.

Indirectness: The certainty of evidence was downgraded when there were serious or very serious concerns regarding the directness of the evidence, that is, whether there were important differences between the research reported and the context for which the recommendation was being prepared. Such differences were related, for instance, to populations, interventions, comparisons or outcomes of interest.

Imprecision: This assessed the degree of uncertainty around the estimate of effect. As this is often a function of sample size and number of events, studies with relatively few participants or events, and thus wide confidence intervals around effect estimates, were downgraded for imprecision.

Publication bias: The certainty rating could also be affected by perceived or statistical evidence of bias to underestimate or overestimate the effect of an intervention as a result of selective publication based on study results. Downgrading evidence by one level was considered where there was strong suspicion of publication bias.

Certainty of evidence assessments are defined according to the GRADE approach:

- **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty:** We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty:** Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
- **Very low certainty:** We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

The findings of the qualitative reviews were appraised for quality using the GRADE-CERQual tool (31). The GRADE-CERQual tool, which uses a similar conceptual approach to other GRADE tools, provides a transparent method for assessing and assigning the level of confidence that can be placed in evidence from reviews of qualitative research. The systematic review team used the GRADE-CERQual tool to assign a level of confidence (high, moderate, low and very low) to each review finding according to four components: methodological limitations of the individual studies; adequacy of data; coherence; and relevance to the review question of the individual studies contributing to a review finding. Findings from individual cost-effectiveness studies were reported narratively for each comparison of interest. Available evidence was assessed using the CHEC checklist (29).

2.5 Formulation of the recommendation

The WHO Steering Group supervised and finalized the preparation of summary of findings tables and narrative evidence summaries in collaboration with the ESG using the GRADE EtD framework. EtD frameworks include explicit and systematic consideration of evidence on prioritized interventions in terms of specified domains: effects, values, resources, equity, acceptability and feasibility. For the priority questions, judgements were made on the impact of the intervention on each domain to inform and guide the decision-making process. Using the EtD framework template, the WHO Steering Group and ESG created summary documents for each priority question covering evidence on each domain:

- **Effects:** The evidence on the priority outcomes was summarized in this domain to answer the questions: “What are the desirable and undesirable effects of the intervention?” and “What is the certainty of the evidence on effects?” Where benefits clearly outweighed

harms for outcomes that are highly valued by women, or vice versa, there was a greater likelihood of a clear judgement in favour of or against the intervention, respectively. Uncertainty about the net benefits or harms, or small net benefits, usually led to a judgement that did not favour the intervention or the comparator. The higher the certainty of the evidence of benefits across outcomes, the higher the likelihood of a judgement in favour of the intervention. In the absence of evidence of benefits, evidence of potential harm led to a recommendation against the intervention. Where the intervention showed evidence of potential harm and was also found to have evidence of important benefits, depending on the level of certainty and the likely impact of the harm, such evidence of potential harm was more likely to result in a context-specific recommendation, with the context explicitly stated within the recommendation.

- **Values:** This domain relates to the relative importance assigned to the outcomes associated with the intervention by those affected, how such importance varies within and across settings, and whether this importance is surrounded by any uncertainty. The question asked was: “Is there important uncertainty or variability in how much women value the main outcomes associated with the intervention?” When the intervention resulted in benefit for outcomes that most women consistently value (regardless of setting), this was more likely to lead to a judgement in favour of the intervention. This domain, together with the “effects” domain (see above), informed the “balance of effects” judgement.
- **Resources:** For this domain, the questions asked were: “What are the resources associated with the intervention?” and “Is the intervention cost-effective?” The resources required to implement a specific class of antibiotics as prophylaxis for women undergoing caesarean section, training, and monitoring and evaluation. A judgement in favour of or against the intervention was likely where the resource implications were clearly advantageous or disadvantageous, respectively.
- **Acceptability:** For this domain, the question was: “Is the intervention acceptable to women and health-care providers?” The lower the acceptability, the lower the likelihood of a judgement in favour of the intervention.
- **Feasibility:** The feasibility of implementing this intervention depends on factors such as the resources, infrastructure and training requirements, and the perceptions of health-care providers responsible for administering it. The question addressed was: “Is it feasible for the relevant stakeholders to implement the intervention?” Where major barriers were identified, it was less likely that a judgement would be made in favour of the intervention.
- **Equity:** This domain encompasses evidence or considerations as to whether or not the intervention would reduce health inequities. Therefore, this domain addressed the question: “What is the anticipated impact of the intervention on equity?”. The intervention was likely to be recommended if its proven (or anticipated) effects reduce (or could reduce) health inequalities among different groups of women and their families.

For each of the above domains, additional evidence of potential harms or unintended consequences are described in the Additional considerations subsections. Such considerations were derived from studies that might not have directly addressed the priority question but provided pertinent information in the absence of direct evidence. These were extracted from single studies, systematic reviews or other relevant sources.

The WHO Steering Group provided the EtD framework, including evidence summaries, summary of findings tables and other documents related to the recommendation, to GDG members two weeks in advance of the GDG meeting. The GDG members were asked to review and provide comments (electronically) on the documents before the GDG meeting. During the GDG meeting (19–20 October 2020), which was conducted under the leadership of the GDG chairperson, the GDG members collectively reviewed the EtD framework, and any comments received through preliminary feedback, and formulated the recommendations. The purpose of the meeting was to reach consensus on the recommendation and the specific context, based on explicit consideration of the range of

evidence presented in the EtD framework and the judgement of the GDG members. The GDG was asked to select one of the following categories for the recommendation:

- **Recommended:** This category indicates that the intervention should be implemented.
- **Not recommended:** This category indicates that the intervention should not be implemented.
- **Recommended only in specific contexts (“context-specific recommendation”):** This category indicates that the intervention is applicable only to the condition, setting or population specified in the recommendation and should only be implemented in these contexts.
- **Recommended only in the context of rigorous research (“research-context recommendation”):** This category indicates that there are important uncertainties about the intervention. With this category of recommendation, implementation can still be undertaken on a large scale, provided it takes the form of research that addresses unanswered questions and uncertainties related both to effectiveness of the intervention or option, and its acceptability and feasibility.

2.6 Management of declarations of interests

WHO has a robust process to protect the integrity of its normative work, as well as to protect the integrity of individual experts with whom it collaborates. WHO requires that experts serving in an advisory role disclose any circumstances that could give rise to actual or ostensible conflict of interest. The disclosure and the appropriate management of relevant financial and non-financial conflicts of interest of GDG members and other external experts and contributors, including external reviewer, are a critical part of guideline development at WHO. According to WHO regulations, all experts must declare their interests prior to participation in WHO guideline development processes and meetings according to the guidelines for declaration of interest (DOI) for WHO experts (19). All GDG members and ERG members were therefore required to complete a standard WHO DOI form before engaging in the guideline development process and before participating in the guideline-related processes. The WHO Steering Group reviewed all declarations before finalizing the experts’ invitations to participate. Where any conflict of interest was declared, the WHO Steering Group determined whether such conflicts were serious enough to affect an expert’s objective judgement in the guideline and recommendation development process. To ensure consistency, the WHO Steering Group applied the criteria for assessing the severity of conflict of interests as outlined in the *WHO handbook for guideline development* to all participating experts (19). All findings from the DOI statements received were managed in accordance with the WHO procedures to assure the work of WHO and the contributions of its experts is, actually and ostensibly, objective and independent. The names and biographies of individuals were published online two weeks prior to the meeting. Where a conflict of interest was not considered significant enough to pose any risk to the guideline development process or to reduce its credibility, the experts were only required to openly declare such conflicts of interest at the beginning of the GDG meeting, and no further actions were taken. Annex 3 shows a summary of the DOI statements and how conflicts of interest declared by invited experts were managed by the WHO Steering Group.

2.7 Decision-making during the GDG meetings

During the meeting, the GDG reviewed and discussed the evidence summary and sought clarification. In addition to evaluating the balance between the desirable and undesirable effects of the intervention and the overall certainty of the evidence, the GDG applied additional criteria based on the GRADE EtD framework to determine the direction and strength of the recommendation. These criteria included stakeholders’ values, resource implications, acceptability, feasibility and equity. Considerations were supported by evidence from a literature search as described in section 2.3.2 and on the experience and opinions of the GDG members. EtD tables were used to describe and synthesize these considerations.

Decisions were made based on consensus, defined as the agreement by three quarters or more of the participants. None of the GDG members expressed opposition to the recommendation.

2.8 Document preparation

Prior to the online meeting, the WHO Steering Group prepared a draft version of the GRADE evidence profiles, the evidence summary and other documents relevant to the GDG's deliberation. The draft documents were made available to the participants of the meeting two weeks before the meeting for their comments. During the meeting, these documents were modified in line with the participants' deliberations and remarks. Following the meeting, members of the WHO Steering Group drafted a full guideline document to accurately reflect the deliberations and decisions of the participants. The draft document was sent electronically to the GDG and the ERG for their final review and approval.

2.9 Peer review

Following review and approval by the GDG members, the final document was sent to eight external independent experts of the ERG who were not involved in the guideline panel for peer review. The WHO Steering Group evaluated the inputs of the peer reviewers for inclusion in this document. After the meeting and external peer review, the modifications made by the WHO Steering Group to the document consisted only of the correction of factual errors and improving language to address any lack of clarity.

3. Guiding principles, best practice, recommendation and supporting evidence

3.1 Guiding principles and best practice

The participants in the 2015 technical consultation on prevention and treatment of peripartum infection agreed that the following overarching principles were applicable to the recommendations on prevention and treatment of peripartum infections. These guiding principles and best practice statements were adopted by the 2020 GDG panel. The principles and best practice statements were based on expert consensus and were not derived from a systematic process of evidence retrieval, synthesis and grading. They conform with the principles of good clinical practice that are needed to improve care related to the prevention or treatment of infectious morbidities around the time of childbirth. In addition to the strategies for implementation, monitoring and impact assessment presented later in this document, these principles are expected to guide end-users in the process of adapting and implementing this recommendation in a range of contexts and settings:

- Avoidance of infection by identifying and correcting predisposing factors to infection (e.g. by providing nutritional advice and addressing nutritional deficiencies, anaemia and other maternal medical conditions such as diabetes) during antenatal care.
- Standard infection prevention and control precautions should be observed in the provision of maternity care to optimize the effects of interventions recommended in this guideline (32). These measures should include:
 - Promoting high quality standards of hand hygiene for the sterilization and storage of instruments and supplies and use of clean equipment; promoting aseptic surgical practices (e.g. following standard skin preparation techniques and proper use of antiseptic agents for surgical site preparation); use of personal protection equipment (e.g. gloves and aprons or surgical gowns); and use of safe products (e.g. blood products). Local protocols on infection prevention and control practices should be developed and implemented in accordance with existing WHO guidance (33).
 - Improvement of health-care facilities physical environments (e.g. clean water, appropriate waste disposal and sanitation)
 - Clinical monitoring of women for signs of infection throughout labour and the postpartum period and early detection of infection by laboratory investigation as needed. This is particularly crucial for women who present with any form of illness around the time of childbirth, as poor monitoring and late detection of severe infection are known contributory factors to infection-related severe maternal morbidity and death. Before hospital discharge, women should be counselled on how to identify and promptly seek care for any danger signs of infection during the postpartum period (34).
 - Clear guidance and protocols are needed for the prompt recognition, timely management and transfer to specialized services (e.g. intensive care unit) of women with maternal sepsis (organ dysfunction resulting from infection) and septic shock (hypotension due to sepsis not reversed with fluid resuscitation) and ensure availability of a protocol on resuscitation, antimicrobial therapy and subsequent supportive therapies. This protocol should be informed by internationally recommended guidelines and adapted to the local obstetric population and available skills and resources.
 - When transmission-based precautions are necessary to reduce or prevent nosocomial transmission of infections for women with peripartum infections, women should be provided care and support while in an isolation ward by appropriately trained health-care staff.

- Care should be organized in a way that facilitates staff behavioural change and encourages compliance with the hospital infection control measures. These should include, but not be limited to, staff training and feedback, use of information and educational materials, appropriate distribution of infection control equipment and materials, establishment of local protocols, infection surveillance, and clinical audit and feedback.
- National health systems need to ensure reliable supply systems, sustain availability and equitable access to good-quality, affordable antibiotics that are listed in the *WHO model list of essential medicines* for use in maternal and perinatal health-care (35), and ensure that the necessary equipment are available wherever maternity services are provided. They also need to ensure that the core list of first-line and second-line antibiotics on the *WHO model list of essential medicines* are available at maternity care facilities. This includes establishing robust and sustainable regulatory, procurement and logistics processes that can ensure good-quality medicines and equipment are obtained, transported and stored correctly.
- As part of the global efforts to reduce antimicrobial resistance, antibiotics should be administered only when there is a clear medical indication (as recommended in this guideline) and where the expected benefits outweigh the potential harms within the local context. It is essential to establish a hospital committee that monitors antimicrobial usage, including the quantity and patterns of use, feeds back the results to the prescribers and regularly updates the hospital antimicrobial formularies (36).
- To the extent possible, prophylactic and therapeutic use of antibiotics should be informed by the narrowest antibacterial spectrum, the woman's history (including drug intolerance), the simplest effective dose in terms of antibiotic class and regimen, cost-effectiveness, bacterial agents most likely to cause infection and local susceptibility patterns in the hospital and in the community. Bacterial culture samples should be obtained before initiating antibiotics therapy, but this should not prevent prompt administration of antibiotics. Additionally, the choice of antiseptics and antibiotics should be guided by maternal conditions and aimed at avoiding adverse effects. Ideally, the use of antimicrobials in any setting should be informed by local or national resistance surveillance data and treatment guidelines.

3.2 Recommendation and supporting evidence

The following section outlines the recommendation and the corresponding narrative summary of evidence for the prioritized question. The EtD table, summarizing the balance between the desirable and undesirable effects and the overall certainty of the supporting evidence, values and preferences of stakeholders, resource requirements, cost-effectiveness, acceptability, feasibility and equity that were considered in determining the strength and direction of the recommendation, is presented in the EtD framework (Annex 4).

The following recommendation was adopted by the GDG. Evidence on the effectiveness of this intervention was derived from the updated systematic review and summarized in GRADE tables (Annex 4).

To ensure that the recommendation is correctly understood and appropriately implemented in practice, additional remarks reflecting the summary of the discussion by the GDG are included under the recommendation.

Recommendation: For antibiotic prophylaxis for caesarean section, a single dose of first-generation cephalosporin or penicillin should be used in preference to other classes of antibiotics. (Recommended)

Remarks:

Antibiotic classes

- The Guideline Development Group noted that the available evidence on the effectiveness of antibiotics for caesarean section was largely derived from trials that tested first- or second-generation cephalosporins or penicillins in the 1980s and 1990s. Based on consensus, the Guideline Development Group favoured these classes of antibiotics over other classes of antibiotics, as they have a broad spectrum of activities and are widely available in all settings. While the Guideline Development Group members acknowledged the lack of clear difference between first- and second-generation cephalosporins, they noted that the evidence suggests that third-generation cephalosporins may be less effective than penicillins for this indication and, therefore, suggests that this class of antibiotics should be avoided.
- The Guideline Development Group noted that first-generation cephalosporins are the preferred antibiotic class for prophylaxis in general surgery, as part of efforts to contain antimicrobial resistance.
- In acknowledgement of the lack of evidence on the comparative effectiveness of different classes of antibiotics, the Guideline Development Group concluded that when the recommended antibiotic classes are not available, other classes of antibiotics may also be used. The Guideline Development Group noted that the choice of an antibiotic class should be informed by local antimicrobial resistance guidance, local bacteriologic patterns of post-caesarean infectious morbidity, safety profile, the clinician's experience with that particular class of antibiotics, availability and cost.

Regimen

- The Guideline Development Group emphasized the importance of using a simple and short (a single dose, 30–60 minutes before surgery) antibiotic regimen for prophylaxis. There are other clinical factors (e.g. high maternal body mass index, prolonged labour, prolonged duration of surgery, extensive surgical manipulation or massive blood loss) that might increase the risk of developing post-caesarean infections. Clinical judgement is needed to evaluate if a different regimen (higher dose, second dose) of prophylactic antibiotics is warranted in the presence of risk factors (37).

Risk of necrotizing enterocolitis

- Due to the increased risk of necrotizing enterocolitis among preterm babies exposed to amoxicillin plus clavulanate (38), the use of amoxicillin plus clavulanate for antibiotic prophylaxis should be avoided before cord clamping for caesarean section of preterm infants.

Timing and provision

- The Guideline Development Group acknowledged that prophylactic antibiotics are recommended for women undergoing elective or emergency caesarean section and should be given 30–60 minutes prior to skin incision, rather than intraoperatively after umbilical cord clamping, consistent with recommendation No. 18.1 of the 2015 *WHO recommendations for prevention and treatment of maternal peripartum infections* (20).

Previous recommendation

- This recommendation revalidates recommendation No. 18.2 of the 2015 *WHO recommendations for prevention and treatment of maternal peripartum infections*, where this was considered a strong recommendation based on moderate-quality evidence.

4. Dissemination, adaptation and implementation of the recommendation

The dissemination and implementation of this recommendation are to be considered by all stakeholders involved in the provision of care for pregnant women at the international, national and local levels. There is a vital need to increase women's access to maternal health-care at community level and to strengthen the capacity at health-care facilities of all levels to ensure they can provide high-quality services and information to all women giving birth. It is therefore crucial that this recommendation be translated into care packages and programmes at country, health-care facility and community levels, where appropriate.

4.1 Recommendation dissemination

The recommendation will be disseminated through WHO regional and country offices, ministries of health, professional organizations, WHO collaborating centres, other United Nations agencies and nongovernmental organizations, among others. This recommendation will also be available on the WHO website and the WHO Reproductive Health Library.¹ Updated recommendations are also routinely disseminated during meetings or scientific conferences attended by WHO maternal and perinatal staff.

The executive summary and recommendation from this publication will be translated into the six United Nations languages and disseminated through the WHO regional offices.

4.2 Adaptation

National and subnational subgroups may be established to adapt and implement this recommendation based on an existing strategy. This process may include the development or revision of existing national guidelines or protocols based on the updated recommendation.

The successful introduction of evidence-based policies (relating to updated recommendations) depends on well-planned and participatory consensus-driven processes of adaptation and implementation. These processes may include the development or revision of existing national or local guidelines and protocols, often supported by ministries of health, United Nations agencies, local professional societies and other relevant leadership groups. An enabling environment should be created for the use of this recommendation, including changes in the behaviour of health-care practitioners to enable the use of evidence-based practices.

This recommendation should be adapted into documents and tools that are appropriate for different locations and contexts to meet the specific needs of each country and health service. Modifications to the recommendations, where necessary, should be justified in an explicit and transparent manner.

In the context of humanitarian emergencies, the adaptation of the current recommendation should consider the integration and alignment with other response strategies. Additional considerations to the unique needs of women in emergency settings, including their values and preferences, should be made. Context-specific tools and toolkits may be required in addition to standard tools to support the implementation of the recommendation in humanitarian emergencies by stakeholders.

4.3 Implementation considerations

- This recommendation should be implemented in line with the guiding principles and best practice statements outlined in this recommendation.

¹ Available at: www.who.int/rhl.

- Training is needed to ensure that injectable antibiotics are used appropriately and safely. This includes safe injection practices and disposal. Special attention needs to be given to correct dosage and safe use of antibiotics for this indication, and efforts are needed to ensure that antibiotics are not misused for other indications.
- Antibiotics should be stored and used as per the manufacturer instructions.
- Women should be adequately counselled and engaged in shared decision-making around the use of prophylactic antibiotics for caesarean section, including side-effects of antibiotics and breastfeeding.
- Consideration can be given to increased doses for obese pregnant patients.

5. Research implications

The GDG identified important knowledge gaps that need to be addressed through primary research, which may have an impact on this recommendation. The following questions were identified as those that demand urgent priority:

- What is the comparative effectiveness of different classes of antibiotics for prophylaxis at caesarean section on important neonatal health outcomes and neonatal microbiome?
- What are the main outcomes that women (and their families) value in relation to the use of antibiotics to prevent infection at caesarean section?

6. Applicability issues

6.1 Anticipated impact on the organization of care and resources

A number of factors (barriers) may hinder the effective implementation and scale-up of this recommendation. These factors may be related to the behaviours of patients (women or families) or health-care professionals and to the organization of care or health service delivery. As part of efforts to implement this recommendation, health system stakeholders may wish to consider the following potential barriers to their application:

- lack of understanding of the value of a specific class of antibiotic as prophylaxis for women undergoing caesarean section among women giving birth, families or communities;
- lack of human resources with the necessary training and skills to deliver a specific class of antibiotic as prophylaxis for women undergoing caesarean section;
- concerns from skilled care personnel and system managers regarding the safety of a specific class of antibiotic as prophylaxis for women undergoing caesarean section, including antimicrobial resistance;
- lack of reliable supply systems and sustained availability and equitable access to antibiotics for use in obstetrics listed in the WHO model list of essential medicines;
- lack of current systems in place to monitor the use of antibiotics and antimicrobial resistance;
- lack of effective referral mechanisms and care pathways for women identified as needing additional care.

6.2 Monitoring and evaluating guideline implementation

The implementation and impact of this recommendation will be monitored at the health service, country and regional levels, as part of broader efforts to monitor and improve the quality of maternal and newborn care. The WHO document *Standards for improving quality of maternal and newborn care in health facilities* (39) provides a list of prioritized input, output and outcome measures that can be used to define quality of care criteria and indicators and that should be aligned with locally agreed targets. In collaboration with the monitoring and evaluation teams of the WHO Department of Sexual and Reproductive Health and Research and the WHO Department of Maternal, Newborn, Child and Adolescent Health and Ageing, data on country- and regional-level implementation of the recommendation can be collected and evaluated in the short to medium term to assess its impact on national policies of individual WHO Member States.

Information on recommended indicators can also be obtained at the local level by interrupted time series or clinical audits. In this context, the GDG suggests the following indicators to be considered:

- Proportion of women giving birth by caesarean section who received antibiotic prophylaxis (by class of antibiotics), calculated as the number of women who receive antibiotic prophylaxis for caesarean section divided by the total number of women giving birth by caesarean section.
- Incidence of peripartum infection among women giving birth by caesarean section, calculated as the number of women with peripartum infection after caesarean section divided by the total number of women giving birth by caesarean section.

The first indicator provides an assessment of the use of evidence-based practices among women considered at higher risk of infection around childbirth, while the second indicator provides information on the efficacy of the intervention. WHO has developed specific guidance for evaluating the quality of care for severe maternal complications (including sepsis) based on the near-miss and criterion-based clinical audit concepts (40).

7. Updating the recommendation

The Executive GSG convenes annually to review WHO's current portfolio of maternal and perinatal health recommendations and to help WHO prioritize new and existing questions for recommendation development and updating. Accordingly, this recommendation will be reviewed along with other recommendations for prioritization by the Executive GSG. If new evidence that could potentially impact the current evidence base is identified, the recommendation may be updated. If no new reports or information is identified, the recommendation may be revalidated.

Following publication and dissemination of the updated recommendation, any concerns about the validity of the recommendation should be promptly communicated to the guideline implementers, in addition to any plans to update the recommendation.

WHO welcomes suggestions regarding additional questions for inclusion in the updated recommendation. Please email your suggestions to srhmph@who.int.

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Annex 2. Priority outcomes used in decision-making

Priority outcomes (O):¹

Critical outcomes:

- Severe infectious morbidity (sepsis, septic shock, laparotomy/ hysterectomy for infection, maternal intensive care unit admission)
- Puerperal infection (endometritis with/without myometritis with/without salpingitis causing maternal febrile morbidity)
- Wound infection
- Side-effects of antibiotics
- Antimicrobial resistance

Important outcomes:

- Maternal death
- Maternal well-being
- Maternal satisfaction
- Cost of care
- Neonatal mortality
- Neonatal infection

¹ These outcomes reflect the prioritized outcomes used in the development of this recommendation, in the 2015 *WHO recommendations for prevention and treatment of maternal peripartum infections*. The outcomes "maternal well-being" and "maternal satisfaction" have been added as part of this update. The labels of the outcomes "severe infectious morbidity" and "puerperal infection" were updated to reflect the current WHO maternal sepsis definition.

Annex 3. Summary and management of declared interests from GDG members

Name	Expertise contributed to guideline development	Declared interest	Management of conflict of interest
Fatima Adamu	Content expert and end-user	None declared	Not applicable
Subha Sri Balakrishnan	Content expert and end-user	Senior Technical Officer, Centre for Maternal and Newborn Health (CMNH), Liverpool School of Tropical Medicine (March 2018–March 2020). CMNH received grants from United Nations Children’s Fund (UNICEF), WHO India and National Health Mission Madhya Pradesh during this period.	The conflict was not considered serious enough to affect Guideline Development Group (GDG) membership or participation.
Michelle Bazari	Women’s representative	None declared	Not applicable
Maria Laura Costa	Content expert and end-user	None declared	Not applicable
Jemima Dennis-Antwi	Content expert and end-user	None declared	Not applicable
Hadiza Galadanci	Content expert and end-user	None declared	Not applicable
David Lissauer	Content expert and end-user	None declared	Not applicable
Pisake Lumbiganon	Content expert and end-user	None declared	Not applicable
Ashraf Nabhan	Content expert and end-user	None declared	Not applicable
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Hiroshi Obara	Content expert and end-user	None declared	Not applicable
Alfred Osofi	Content expert and end-user	None declared	Not applicable
Haroon Saloojee	Content expert and end-user	None declared	Not applicable
Sadia Shakoor	Content expert and end-user	None declared	Not applicable
Rachel Smith	Content expert and end-user	None declared	Not applicable
Joseph Solomkin	Content expert and end-user	None declared	Not applicable

Annex 4. Evidence-to-decision framework

Question

The question of interest in PICO (population (P), intervention (I), comparator (C), outcome (O)) format:

- Among women receiving routine antibiotic prophylaxis for caesarean section (P), is the use of a particular class of antibiotics (I), compared with other classes of antibiotics (C), more effective in preventing post-operative infectious morbidities (O)?

Problem: Which antibiotic option to use for preventing infection at caesarean section

Perspective: Clinical practice recommendation – population perspective

Population (P): Women receiving routine antibiotic prophylaxis for caesarean section

Intervention (I): Particular class of antibiotics

Comparators (C): Other classes of antibiotics

Setting: Hospital setting

Subgroups: by type of caesarean section

Priority outcomes (O):¹

Critical outcomes:

- Severe infectious morbidity (sepsis, septic shock, laparotomy/ hysterectomy for infection, maternal intensive care unit admission)
- Puerperal infection (endometritis with/without myometritis with/without salpingitis causing maternal febrile morbidity)
- Wound infection
- Side-effects of antibiotics
- Antimicrobial resistance

Important outcomes:

- Maternal death
- Maternal well-being
- Maternal satisfaction
- Cost of care
- Neonatal mortality
- Neonatal infection

¹ These outcomes reflect the prioritized outcomes used in the development of this recommendation, in the 2015 *WHO recommendations for prevention and treatment of maternal peripartum infections*. The outcomes “maternal well-being” and “maternal satisfaction” have been added as part of this update. The labels of the outcomes “severe infectious morbidity” and “puerperal infection” were updated to reflect the current WHO maternal sepsis definition.

Summary of interventions and comparisons

Comparison class or subclass of antibiotics	Intervention class or subclass of antibiotics	Single class administered			Multiple classes administered			
		Anti-staphylococcal cephalosporins (1st and 2nd generations)	Minimally anti-staphylococcal cephalosporins (3rd generation)	Broad-spectrum penicillins plus beta-lactamase inhibitors	Lincosamide plus amino-glycoside	Anti-staphylococcal cephalosporins (1st and 2nd generation) plus nitroimidazole	Aminoglycoside plus nitroimidazole	Minimally anti-staphylococcal cephalosporins (3rd generation) plus nitroimidazole
Single class administered	Broad-spectrum penicillins plus beta-lactamase inhibitors	8 trials (1540 women)	2 trials (865 women)		No trials	1 trial (83 women)	No trials	No trials
	Non-anti-staphylococcal penicillins (natural and broad spectrum)	10 trials (3476 women) ^a	4 trials (854 women)	Comparison not within scope of review	1 trial (88 women)	1 trial (139 women)	No trials	No trials
	Broad-spectrum penicillins and anti-staphylococcal penicillins	No trials	1 trial (200 women)	Comparison not within scope of review	No trials	No trials	No trials	No trials
	Fluoroquinolones	1 trial (81 women)	No trials	1 trial (72 women)	No trials	No trials	No trials	No trials
	Carbapenems	No trials	1 trial (48 women)	No trials	No trials	No trials	No trials	No trials
	Macrolides	1 trial (70 women)	No trials	No trials	No trials	No trials	No trials	No trials
	Broad-spectrum penicillins plus anti-staphylococcal penicillins plus aminoglycoside plus nitroimidazole	No trials	1 trial (200 women)	Comparison not within scope of review	No trials	No trials	No trials	No trials
	Anti-staphylococcal penicillins plus aminoglycoside	No trials	1 trial (200 women)	Comparison not within scope of review	No trials	No trials	No trials	No trials
	Natural penicillins plus nitroimidazole plus macrolide	No trials	No trials	Comparison not within scope of review	No trials	No trials	1 trial (241 women)	No trials
Multiple classes administered	Non-anti-staphylococcal penicillins (natural and broad spectrum) plus nitroimidazole	No trials	No trials	Comparison not within scope of review	No trials	2 trials (256 women)	No trials	No trials
	Non-anti-staphylococcal penicillins (natural and broad spectrum) plus nitroimidazole plus amphenicol	No trials	No trials	Comparison not within scope of review	No trials	No trials	No trials	1 trial (232 women)

^a This total includes nine trials (3093 women) that administered antibiotics systemically, and one trial (383 women) that administered antibiotics by lavage/irrigation. In the Cochrane review, trials using systemic administration were analysed separately from those using lavage/irrigation; for all comparisons, this evidence summary only includes results from trials that administered antibiotics systemically.

Assessment

Effects of interventions

What is the effect of a particular class of antibiotics, compared to other classes of antibiotics, when used for women receiving antibiotic prophylaxis for caesarean section?

Research evidence

Summary of evidence

Source and characteristics of studies

Evidence on the effects of different classes of antibiotics for antibiotic prophylaxis at caesarean section was derived from a Cochrane systematic review (1) that included 39 trials. Six trials did not contribute any data to the analysis, therefore analyses are based on the data from 33 trials (8073 women). Since the previous review update in 2014, four trials have been added, and substantive changes have been made to the structure of the comparisons.

Overall, the review included 26 comparisons of single or multiple classes of antibiotics (Table 1). In this review update, there was no overall comparison of penicillins versus cephalosporins. Subclasses of penicillins and cephalosporins with similar actions against agents that are the principle causes of infection at caesarean section (Gram-positive cocci particularly, including *Staphylococcus aureus* and streptococci; anaerobes; and Gram-negative bacilli) were grouped together. Subclasses with known variation in potential action against these causative agents were separated into different comparisons.

This evidence summary focuses on four comparisons of subclasses of cephalosporins versus subclasses of penicillins. For the remaining 22 comparisons, evidence was available for fewer than 300 women (all but one comparison included only a single small study), limited outcomes (of very low certainty data) were available, and there was no clear evidence reported of benefit/harm/no difference between interventions.

The four comparisons of cephalosporins versus penicillins are:

- Anti-staphylococcal cephalosporins (1st and 2nd generation) versus broad-spectrum penicillins plus beta-lactamase inhibitors (8 trials, 1540 women);
- Anti-staphylococcal cephalosporins (1st and 2nd generation) versus non-anti-staphylococcal penicillins (natural and broad spectrum) (9 trials, 3093 women);
- Minimally anti-staphylococcal cephalosporins (3rd generation) versus broad-spectrum penicillins plus beta-lactamase inhibitors (2 trials, 865 women);
- Minimally anti-staphylococcal cephalosporins (3rd generation) versus non-anti-staphylococcal penicillins (natural and broad spectrum) (4 trials, 854 women).

Twenty trials (5933 women) contributed data to these four comparisons of cephalosporins versus penicillins. These 20 trials were published between 1982 and 2014 and conducted in Brazil, Canada, Greece, India (two trials), Italy, Rwanda, South Africa, Switzerland, Thailand (two trials) and the United States of America (USA) (nine trials). Three trials had more than two arms and contributed to two of these comparisons.

One trial included women undergoing elective caesarean section only (122 women); seven trials included non-elective caesarean section only (2922 women); five trials included both elective and non-elective caesarean section (1635 women). Seven trials were unclear about type of caesarean section (1254 women).

All trials used parenteral administration of antibiotics. Eleven trials (3808 women) administered single intravenous (IV) doses to women in both groups, and four trials (803 women) administered multiple IV doses to women in both groups. One trial (400 women) compared a single IV dose of cephalosporin (1st generation) versus multiple intramuscular doses of natural penicillins. Four trials (922 women), three of which administered multiple doses and one a single dose in both groups, did not describe the route used.

Sixteen trials administered the antibiotics at, or immediately after, cord clamping (5217 women). Two trials administered the antibiotics preoperatively: one trial up to 60 minutes before the incision (132 women) and one immediately before the incision (59 women). Two trials did not describe timing (525 women).

Please see Appendix 1 for:

- a. Overview of the subclasses of cephalosporins and penicillins given to women in the four comparisons of cephalosporins and penicillins listed above;
- b. Detailed information on specific drugs, doses, and routes of administration for each of the four comparisons.

Effects of interventions

1) Anti-staphylococcal cephalosporins (1st and 2nd generation) versus broad-spectrum penicillins plus beta-lactamase inhibitors

Severe infectious morbidity: It is unclear whether anti-staphylococcal cephalosporins (1st and 2nd generation) reduce maternal sepsis when compared with broad spectrum penicillins plus beta-lactamase inhibitors (*very low certainty evidence*).

Puerperal infection: Low certainty evidence suggests that anti-staphylococcal cephalosporins (1st and 2nd generation) may make little or no difference to the incidence of **endometritis** (7 trials; 1161 women; RR 1.10, 95% CI 0.76 to 1.60) or **maternal fever (febrile morbidity)** (3 trials; 678 women; 30/342 vs 27/336; RR 1.07, 95% CI 0.65 to 1.75).

Wound infection: It is unclear whether anti-staphylococcal cephalosporins (1st and 2nd generation) reduce rates of **wound infection** when compared with broad-spectrum penicillins plus beta-lactamase inhibitors (*very low certainty evidence*).

Side-effects of antibiotics: It is unclear whether anti-staphylococcal cephalosporins (1st and 2nd generation) reduce rates of **maternal composite adverse effects** or **maternal allergic reactions** when compared with broad-spectrum penicillins plus beta-lactamase inhibitors (*very low certainty evidence*). Low certainty evidence suggests anti-staphylococcal cephalosporins (1st and 2nd generation) may make little or no difference to rates of maternal skin rash (3 trials; 591 women; 4/348 vs 3/243; RR 1.08, 95% CI 0.28 to 4.11).

The priority outcomes **antimicrobial resistance**, **maternal well-being**, **maternal satisfaction** and **neonatal mortality** were not included in the Cochrane review; while **maternal death**, **cost of care** and **neonatal infection** were not reported by any included studies.

Subgroup analysis: Effects by type of caesarean section

Although the Cochrane review included subgroup analysis by type of caesarean section for the outcomes maternal sepsis and maternal endometritis, there were a relatively small number of studies, and too few studies defined the type of caesarean section for the results of the subgroup analysis to be meaningful.

2) Anti-staphylococcal cephalosporins (1st and 2nd generation) versus non-anti-staphylococcal penicillins (natural and broad spectrum)

Puerperal infection: Low certainty evidence suggests that anti-staphylococcal cephalosporins (1st and 2nd generation) may make little or no difference to rates of **endometritis** when compared with non-anti-staphylococcal penicillins (natural and broad spectrum) (6 trials; 2147 women; 190/1462 vs 61/685; average RR 0.91, 95% CI 0.49 to 1.66).

Low certainty evidence suggests that anti-staphylococcal cephalosporins (1st and 2nd generation) may make little or no difference to rates of **maternal fever (febrile morbidity)** when compared with non-anti-staphylococcal penicillins (natural and broad spectrum), though the 95% confidence interval is quite wide (5 trials; 798 women; 43/381 vs 55/417; average RR 0.74, 95% CI 0.39 to 1.41).

Wound infection: Low certainty evidence suggests anti-staphylococcal cephalosporins (1st and 2nd generation) may make little or no difference to rates of **wound infection** when compared with non-anti-staphylococcal penicillins (natural and broad spectrum) (6 trials; 915 women; 16/434 vs 15/481; RR 1.15, 95% CI 0.59 to 2.26).

Side-effects of antibiotics: It is unclear whether anti-staphylococcal cephalosporins (1st and 2nd generation) reduce rates of **maternal composite adverse effects** or **maternal allergic reactions** when compared with non-anti-staphylococcal penicillins (natural and broad spectrum) (*very low certainty evidence*).

Cost of care: Low certainty evidence suggests anti-staphylococcal cephalosporins (1st and 2nd generation) may reduce **maternal length of hospital stay** (1 trial; 132 women; mean difference (MD) 1.5 days shorter (2.46 days shorter to 0.54 day shorter).

The priority outcomes **antimicrobial resistance**, **maternal well-being**, **maternal satisfaction** and **neonatal mortality** were not reported in the Cochrane review; while **maternal serious infectious morbidity**, **maternal death** and **neonatal infection** were not reported by any included studies.

Subgroup analysis: Effects by type of caesarean section

For the outcomes eligible for subgroup analysis by type of caesarean section in the Cochrane review, none of the included studies reported data on women giving birth by elective caesarean section (in two trials, all women had non-elective caesarean section, and in the remaining four, type of caesarean section was mixed or not defined).

3) Minimally anti-staphylococcal cephalosporins (3rd generation) versus broad-spectrum penicillins plus beta-lactamase inhibitors

Severe infectious morbidity: It is unclear whether minimally anti-staphylococcal cephalosporins (3rd generation) reduce **maternal composite serious infectious complications** (including **maternal death attributed to infection**) when compared with broad-spectrum penicillins plus beta-lactamase inhibitors (*very low certainty evidence*).

Puerperal infection: It is unclear whether minimally anti-staphylococcal cephalosporins (3rd generation) reduce **endometritis** when compared with broad-spectrum penicillins plus beta-lactamase inhibitors (*very low certainty evidence*). Low certainty evidence suggests that minimally anti-staphylococcal cephalosporins (3rd generation) may make little or no difference to **maternal fever** when compared with broad-spectrum penicillins plus beta-lactamase inhibitors (1 trial, 746 women; 20/372 vs 17/374; RR 1.18, 95% CI 0.63 to 2.22).

Wound infection: It is unclear whether minimally anti-staphylococcal cephalosporins (3rd generation) reduce rates of **wound infection** when compared with broad-spectrum penicillins plus beta-lactamase inhibitors (*very low certainty evidence*).

Side-effects of antibiotics: It is unclear whether minimally anti-staphylococcal cephalosporins (3rd generation) reduce rates of **maternal composite adverse effects, allergic reactions, nausea, vomiting, diarrhoea, or skin rash** when compared with broad-spectrum penicillins plus betalactamase inhibitors (no events for all outcomes; *very low certainty evidence*).

Cost of care: Low certainty evidence suggests that minimally anti-staphylococcal cephalosporins (3rd generation) may make little or no difference to **maternal length of hospital stay** when compared with broad-spectrum penicillins plus beta-lactamase inhibitors (1 trial; 746 women; MD 0.01 day shorter (0.12 day shorter to 0.1 day longer)).

The priority outcomes **antimicrobial resistance, maternal well-being, maternal satisfaction** and **neonatal mortality** were not reported in the Cochrane review; while **maternal serious infectious morbidity** and **neonatal infection** were not reported by any included studies.

Subgroup analysis: Effects by type of caesarean section

For the only outcome where subgroup analysis was undertaken by type of caesarean section in the Cochrane review (endometritis), the type of caesarean section was either not clearly reported, or the results were not stratified by elective/non-elective caesarean section.

4) Minimally anti-staphylococcal cephalosporins (3rd generation) versus non-anti-staphylococcal penicillins (natural and broad spectrum)

Puerperal infection: Moderate certainty evidence suggests that minimally anti-staphylococcal cephalosporins (3rd generation) probably increase rates of **endometritis** when compared with non-anti-staphylococcal penicillins (natural and broad spectrum) (2 trials, 562 women; 30/200 vs 34/362; RR 1.74, 95% CI 1.10 to 2.75). However, it is unclear whether minimally anti-staphylococcal cephalosporins (3rd generation) reduce **maternal fever (febrile morbidity)** when compared with non-anti-staphylococcal penicillins (natural and broad spectrum) (*very low certainty evidence*).

For all other reported outcomes (**severe infectious morbidity, wound infection, side-effects of antibiotics**) it was unclear whether minimally anti-staphylococcal cephalosporins (3rd generation) improved outcomes when compared with non-anti-staphylococcal penicillins (natural and broad spectrum) (*very low certainty evidence*).

The priority outcomes **antimicrobial resistance, maternal well-being** and **maternal satisfaction** were not included in the Cochrane review; while **cost of care, neonatal mortality** and **neonatal infection** were not reported by any included studies.

Subgroup analysis: Effects by type of caesarean section

For the outcomes eligible for subgroup analysis by type of caesarean section in the Cochrane review (maternal sepsis and endometritis), all women had the same type of caesarean section for each outcome.

Additional considerations

For comparison 2 – anti-staphylococcal cephalosporins (1st and 2nd generation) versus non-anti-staphylococcal penicillins (natural and broad spectrum) – the Cochrane review authors noted that there was substantial statistical heterogeneity in the results for endometritis, maternal fever and maternal urinary tract infection. This heterogeneity appeared to be explained by one small outlying study. This study was the only one that gave antibiotics before skin incision (rather than at or after cord clamping). However, the review authors emphasized that further investigation would be required to confirm whether timing of administration was an important explanatory factor.

Desirable effects

How substantial are the desirable anticipated effects?

Judgement

✓ Don't know	— Varies	— Trivial	— Small	— Moderate	— Large
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Undesirable effects

How substantial are the undesirable anticipated effects?

Judgement

✓ Don't know	— Varies	— Large	— Moderate	— Small	— Trivial
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Certainty of the evidence

What is the overall certainty of the evidence on effects?

— No included studies	✓ Very low	— Low	— Moderate	— High
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Values

Is there important uncertainty about, or variability in, how much women (and their families) value the main outcomes?

Research evidence

A systematic review on the perspectives and experiences of women and providers with antibiotics for preventing infection at birth was conducted (2). The review identified one qualitative study with 21 women who had undergone caesarean section in the United Kingdom (3). Women's descriptions of caesarean section recovery focused on their experiences of pain, the impact on mobility and caregiving and their concerns on the risks of wound infection or non-healing. Women described receiving inadequate information on the risk of post-operative infections, not being aware that endometritis was a possible complication or that endometritis could be prevented through vaginal cleansing.

A 2018 systematic review of qualitative studies of "what women want" from intrapartum care found that most women want a positive birth experience (with good outcomes for mother and baby) but acknowledge that medical intervention may sometimes be necessary (*high confidence*) (4). Most women, especially those giving birth for the first time, are apprehensive about labour and birth (*high confidence*) and wary of medical interventions, although in certain contexts and/or situations, women welcome interventions to address recognized complications (low confidence). Where interventions are introduced, women would like to receive relevant information from technically competent health-care providers who are sensitive to their needs (*high confidence*).

Additional considerations

A 2018 core outcome set for caesarean delivery maternal infectious morbidity outcomes was proposed on the basis of a systematic review of outcomes in 452 trials and a Delphi survey of 40 review authors (5). The proposed core outcome set included endometritis (primary outcome), maternal mortality, wound infection, wound complications, febrile morbidity and neonatal morbidity.

Judgement

—	—	✓	—
Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability

Balance of effects

Does the balance between desirable and undesirable effects favour a particular class of antibiotics?

Judgement

✓	—	—	—	—	—	—
Don't know	Varies	Favours no particular class of antibiotics	Probably favours no particular class of antibiotics	Does not favour either	Probably favours one class of antibiotics	Favours one class of antibiotics

Resources

How large are the resource requirements (costs)?

Research evidence

Two out of 46 trials included in the Cochrane review comparing different classes of antibiotics to prevent infection at caesarean section reported cost outcomes (6, 7).

One study compared the effectiveness of a cephalosporin (ceftriaxone) versus a mixed nitroimidazole plus aminoglycoside triple drug regimen (metronidazole and ampicillin plus cloxacillin and gentamicin) in the prevention of caesarean section infections and included the outcomes duration of hospital stay and cost of antibiotic therapy (6).

This study was assessed as low quality according to the Consensus Health Economic Criteria (CHEC) checklist (8). It was set in two tertiary hospitals in Nigeria and reported a difference in the mean cost of antibiotic treatment between ceftriaxone and a triple regimen (US\$9 for ceftriaxone; \$15 for the triple regimen). There was no difference in length of hospital stay (or other maternal outcomes). The authors concluded that the use of the cheaper single dose antibiotic was as effective as the more expensive triple regimen. Other cost-effectiveness outcomes were not measured.

The second study was conducted in a tertiary hospital in China and compared the effectiveness of a cephalosporin plus nitroimidazole regimen (cefazolin sodium plus metronidazole) versus a nitroimidazole plus penicillin control group (metronidazole plus ampicillin sodium and benzylpenicillin sodium) and included the outcome cost of drugs (7). The intervention group received 2 g of cefazolin sodium plus 200 mL of 0.5% metronidazole during and after caesarean section. The control group received 3 g of ampicillin sodium plus 200 mL of 0.5% metronidazole during caesarean section, plus 200 mL of 0.5% metronidazole, 3 g of ampicillin sodium and 4 × 10⁴ IU of benzylpenicillin sodium after caesarean section.

Cost of antibacterial agents and total drug costs were lower in the intervention group compared to the control group; there were no differences in maternal outcomes.

An additional single-centre study set in the USA was identified in the Cochrane review (9). Data on costs was not included in the review from this study due to the cost of each course of treatment not being specified and several other factors being included in the calculation of cost failure. This study was low quality according to CHEC checklist (8). The cost of failure for a prophylactic antibiotic to prevent post-caesarean infection was US\$ 5026 (in 1986) based on daily charges for hospital room, laboratory tests and fees, costs of drugs, pharmacy preparations and intravenous equipment. This value was then applied to the failure rate of each antibiotic investigated for 100 patients (ampicillin: \$140 833; cephalothin: \$79 074; and piperacillin: \$26 358).

Additional considerations

A 2017 systematic review assessed cost analyses in the use of prophylactic antibiotics to prevent surgical site infections, including caesarean section (10); however, this review reported no additional direct evidence for different classes of antibiotics for caesarean section. An updated literature search (May 2019) did not provide any additional evidence.

Main resource requirements

Resource	Description
Staff	Skilled health-care professional is required to administer the antibiotic intravenously.
Training	Training to administer intravenous antibiotics, and to monitor and manage expected and unexpected side-effects, is part of standard maternity staff training. Refresher trainings on safe injection practices, safe sharp disposal, hand hygiene, antimicrobial stewardship and antimicrobial resistance, including different regimens and classes of antibiotics.
Supplies	Antibiotics are generally inexpensive, with median prices typically ranging from US\$ 0.0039 to US\$ 0.53 per 1 g vial or 1 mL solution (11). The median cost of selected antibiotics are presented below: <ul style="list-style-type: none"> ■ Ceftriaxone: 1 g vial at US\$ 0.42 ■ Gentamicin: 40 mg/mL ampoule at US\$ 0.06 ■ Metronidazole: 5 mg/mL vial at US\$ 0.0039 ■ Cefazolin sodium: 1 g vial at US\$ 0.48 ■ Ampicillin: 1 g vial at US\$ 0.19 ■ Benzylpenicillin sodium: 5 M IU powder at US\$ 0.53 IV administration: <ul style="list-style-type: none"> ■ Hand hygiene: water and soap, towels, alcohol-containing preparation (liquid, gel or foam) ■ Gloves ■ Skin preparation: alcohol-based solution, single-use swab or cotton wool ball ■ Sterile IV cannula and giving/infusion set ■ IV fluids ■ Sharps container
Equipment and infrastructure	Minimal
Time	Minimal
Supervision and monitoring	Supervision and monitoring are required for health-care professionals administering antibiotic.

Resources required

Judgement

— Don't know	✓ Varies	— Large costs	— Moderate costs	— Negligible costs or savings	— Moderate savings	— Large savings
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Certainty of the evidence on required resources

What is the certainty of the evidence on costs?

Judgement

— No included studies	— Very low	✓ Low	— Moderate	— High
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Cost-effectiveness

Judgement

✓ Don't know	— Varies	— Favours no particular class of antibiotics	— Probably favours no particular class of antibiotics	— Does not favour either	— Probably favours one class of antibiotics	— Favours one class of antibiotics
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Equity

What would be the impact on health equity?

Research evidence

No direct evidence on the effects of health equity of different classes of antibiotics for preventing infection at caesarean section were identified.

However, as a strategy to prevent microbial resistance, the 2019 *WHO model list of essential medicines* includes a core set of first- and second-line antibiotics that should be available everywhere (i.e. access antibiotics) to treat common or severe clinical syndromes (12). These antibiotics have the properties of narrow-spectrum agents, having a low risk of resistance selection as well as adverse effects. It includes cefazolin and metronidazole as first choice and amoxicillin plus clavulanic acid, gentamicin and cefuroxime as second choice for surgical prophylaxis.

Additional considerations

The availability of antibiotics is likely to affect equitable access and use of antibiotics in many low- and middle-income countries. A study of 13 561 health-care facilities in low- and middle-income countries found that 17 priority antibiotics were stocked by fewer than 50% of facilities (13). The third generation IV cephalosporins ceftriaxone and cefotaxime were available in a median of ~50% and 8% of facilities, respectively. However, this study assessed the availability of antibiotics in health centres, clinics and dispensaries – the availability of cephalosporins for prophylactic use at higher-level facilities (where caesarean section is available) may be higher.

A 2020 systematic review found the quality of some antibiotics in low- and middle-income countries to be low, with the prevalence of failed injectable antibiotics (18 studies, 1090 samples) at 13.4% (14). The failure rate for injectable cefazolin was 16.0% (2 studies, 449 samples), and 2.9% for injectable metronidazole (3 studies, 34 samples).

Judgement

✓ Don't know	— Varies	— Reduced	— Probably reduced	— Probably no impact	— Probably increased	— Increased
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Acceptability

Is the intervention acceptable to key stakeholders?

Research evidence

A mixed-methods systematic review on the perspectives and experiences of women and providers with antibiotic prophylaxis at birth was conducted (2). A number of factors affecting the use of antibiotics by providers around the time of birth were identified in studies pertained to use of prophylactic antibiotics at caesarean section (9 studies), in women with preterm prelabour rupture of membranes or in women with group B streptococcal infection.

Factors affecting use of antibiotics by providers included:

- Some providers felt that the risk of infection varies depending on the environment, affecting their antibiotic use (*low confidence*).
- Some providers were concerned about unnecessary antibiotic use due to the potential for unwanted side-effects and medicalisation of birth, while others considered the risk of adverse effects to be outweighed by the benefits of avoiding infection (*low confidence*).
- Some providers are motivated to use antibiotics by a fear of postpartum infection and associated medico-legal risk (*very low confidence*). There was varying level of concern about antimicrobial resistance (*low confidence*).
- Antibiotic prescribing practices by providers are influenced by information from written reference materials (*low confidence*), professional norms (*very low confidence*) and personal experience. Some consider trial evidence from other countries to not be applicable to their local setting, preferring evidence from local trials (*low confidence*).
- Some providers considered cost-effectiveness and affordability of antibiotics when deciding whether to prescribe and when choosing an antibiotic agent (*low confidence*).

No studies were identified on women's perspectives on the acceptability of this intervention.

Additional considerations

None.

Judgement

— Don't know	— Varies	— No	— Probably No	✓ Probably Yes	— Yes
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Feasibility

Is the intervention feasible to implement?

Research evidence

A systematic review on the perspectives and experiences of women and providers with antibiotic prophylaxis at birth was conducted (2). None of the findings suggested that antibiotic use at caesarean section was not feasible. However, some identified factors may possibly affect feasibility:

- Providers' views on the woman's underlying risk of infection, whether they consider antibiotics to be effective for this indication, the risk of side-effects and the risk of antibiotic resistance (*low confidence*), though views were mixed as to whether guidelines had a substantial impact on antibiotic use.
- Local guidelines and professional norms around antibiotic use (*low confidence*).
- Antibiotic cost-effectiveness and affordability (*moderate confidence*).

No studies were identified on women's perspectives on the feasibility of this intervention.

Additional considerations

None.

Judgement

— Don't know	— Varies	— No	— Probably No	— Probably Yes	✓ Yes
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Summary of judgements table

Desirable effects	✓ Don't know	— Varies		— Trivial	— Small	— Moderate	— Large
Undesirable effects	✓ Don't know	— Varies		— Large	— Moderate	— Small	— Trivial
Certainty of the evidence	— No included studies			✓ Very low	— Low	— Moderate	— High
Values				— Important uncertainty or variability	— Possibly important uncertainty or variability	✓ Probably no important uncertainty or variability	— No important uncertainty or variability
Balance of effects	✓ Don't know	— Varies	— Favours no particular class of antibiotics	— Probably favours no particular class of antibiotics	— Does not favour either	— Probably favours one class of antibiotics	— Favour one class of antibiotics
Resources required	— Don't know	✓ Varies	— Large costs	— Moderate costs	— Negligible costs or savings	— Moderate savings	— Large savings
Certainty of the evidence on required resources	— No included studies			— Very low	✓ Low	— Moderate	— High
Cost-effectiveness	✓ Don't know	— Varies	— Favours no particular class of antibiotics	— Probably favours no particular class of antibiotics	— Does not favour either	— Probably favours one class of antibiotics	— Favour one class of antibiotics
Equity	✓ Don't know	— Varies	— Reduced	— Probably reduced	— Probably no impact	— Probably increased	— Increased
Acceptability	— Don't know	— Varies		— No	— Probably No	✓ Probably Yes	— Yes
Feasibility	— Don't know	— Varies		— No	— Probably No	— Probably Yes	✓ Yes

Summary:

- Several antibiotic classes have been evaluated for preventing infection at caesarean section, though there is currently insufficient evidence to conclude which class of antibiotics is superior for this indication. Moderate certainty evidence suggests that minimally anti-staphylococcal cephalosporins (3rd generation) probably increase rates of **endometritis** when compared with non-anti-staphylococcal penicillins (natural and broad spectrum).
- There is also a lack of evidence on neonatal outcomes, maternal side-effects, well-being and satisfaction, and antimicrobial resistance.
- The cost-effectiveness of different antibiotic classes is likely to vary. Various antibiotic regimens are probably acceptable and feasible to use at caesarean section, though cost-effectiveness and the impacts on equity are unknown.

Summary of findings tables

Question: Anti-staphylococcal cephalosporins (1st and 2nd generation) compared to broad-spectrum penicillins plus beta-lactamase inhibitors for preventing infection at caesarean section

Setting: Hospital (USA, India, Greece)

Bibliography: Williams MJ, Carvalho Ribeiro do Valle C, Gyte GML. Different classes of antibiotics given to women routinely for preventing infection at caesarean section. Cochrane Database Syst. Rev. 2021; 3:CD008726. doi: 10.1002/14651858.CD008726.pub3.

No. of studies	Study design	Certainty assessment						Effect		Certainty	Importance	
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anti-staphylococcal cephalosporins (1st and 2nd generation)	No. of women	Broad-spectrum penicillins plus beta-lactamase inhibitors			Relative (95% CI)
SEVERE INFECTIOUS MORBIDITY: SEPSIS												
1	randomized trial	serious ^a	not serious	not serious	very serious ^{b,c,d}	none	1/42 (2.4%)	0/33 (0.0%)	RR 2.37 (0.10 to 56.41)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊖⊖⊖ VERY LOW	CRITICAL
PUERPERAL INFECTION: ENDOMETRITIS												
7	randomized trials	serious ^e	not serious	not serious	serious ^b	none	60/638 (9.4%)	41/523 (7.8%)	RR 1.10 (0.76 to 1.60)	8 more per 1000 (from 19 fewer to 47 more)	⊕⊕⊖⊖ LOW	CRITICAL
PUERPERAL INFECTION: MATERNAL FEVER (FEBRILE MORBIDITY)												
3	randomized trials	serious ^e	not serious	not serious	serious ^b	none	30/342 (8.8%)	27/336 (8.0%)	RR 1.07 (0.65 to 1.75)	6 more per 1000 (from 28 fewer to 60 more)	⊕⊕⊖⊖ LOW	CRITICAL
WOUND INFECTION												
4	randomized trials	serious ^e	not serious	not serious	very serious ^{b,c}	none	8/277 (2.9%)	10/266 (3.8%)	RR 0.78 (0.32 to 1.90)	8 fewer per 1000 (from 26 fewer to 34 more)	⊕⊖⊖⊖ VERY LOW	CRITICAL

No. of studies	Certainty assessment						Effect			Importance		
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anti-staphylococcal cephalosporins (1st and 2nd generation)	Broad-spectrum penicillins plus beta-lactamase inhibitors	Relative (95% CI)		Absolute (95% CI)	Certainty
SIDE-EFFECTS OF ANTIBIOTICS: MATERNAL COMPOSITE ADVERSE EFFECTS												
2	randomized trials	serious ^e	not serious	not serious	very serious ^{b,c}	none	2/282 (0.7%)	1/186 (0.5%)	RR 0.96 (0.09 to 10.50)	0 fewer per 1000 (from 5 fewer to 51 more)	⊕⊖⊖⊖ VERY LOW	CRITICAL
SIDE-EFFECTS OF ANTIBIOTICS: MATERNAL ALLERGIC REACTIONS												
2	randomized trials	serious ^d	not serious	not serious	very serious ^g	none	0/181 (0.0%)	0/192 (0.0%)	not estimable	—	⊕⊖⊖⊖ VERY LOW	CRITICAL
SIDE-EFFECTS OF ANTIBIOTICS: MATERNAL SKIN RASH												
3	randomized trials	not serious	not serious	not serious	very serious ^{b,c}	none	4/348 (1.1%)	3/243 (1.2%)	RR 1.08 (0.28 to 4.11)	1 more per 1000 (from 9 fewer to 38 more)	⊕⊕⊖⊖ LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

^a The pooled effect provided by study "B".

^b Wide confidence interval crossing the line of no effect.

^c Fewer than 30 events.

^d Less than 300 women.

^e Most of the pooled effect provided by studies "B".

^f Statistical heterogeneity (I² > 60%).

^g No events.

Question: Anti-staphylococcal cephalosporins (1st and 2nd generation) compared to non-anti-staphylococcal penicillins (natural and broad spectrum) for preventing infection at caesarean section

Setting: Hospital (Brazil, Canada, Rwanda, Thailand, USA)

Bibliography: Williams MJ, Carvalho Ribeiro do Valle C, Gyte GML. Different classes of antibiotics given to women routinely for preventing infection at caesarean section. Cochrane Database Syst. Rev. 2021; 3:CD008726. doi: 10.1002/14651858.CD008726.pub3.

No. of studies	Certainty assessment					No. of women			Effect		Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anti-staphylococcal cephalosporins (1st and 2nd generation)	Non-anti-staphylococcal penicillins (natural and broad spectrum)	Relative RR (95% CI)	Absolute (95% CI)		
PUERPERAL INFECTION: ENDOMETRITIS												
6	randomized trials	serious ^a	not serious	not serious	serious ^b	none	190/1462 (13.0%)	61/685 (8.9%)	Average RR 0.91 (0.49 to 1.66)	8 fewer per 1000 (from 45 fewer to 59 more)	⊕⊕⊕⊕ LOW	CRITICAL
PUERPERAL INFECTION: MATERNAL FEVER (FEBRILE MORBIDITY)												
5	randomized trials	serious ^a	not serious	not serious	serious ^b	none	43/381 (11.3%)	55/417 (13.2%)	Average RR 0.74 (0.39 to 1.41)	34 fewer per 1000 (from 80 fewer to 54 more)	⊕⊕⊕⊕ LOW	CRITICAL
WOUND INFECTION												
5	randomized trials	serious ^a	not serious	not serious	serious ^b	none	16/434 (3.7%)	15/481 (3.1%)	RR 1.15 (0.59 to 2.26)	5 more per 1000 (from 13 fewer to 39 more)	⊕⊕⊕⊕ LOW	CRITICAL
SIDE-EFFECTS OF ANTIBIOTICS: MATERNAL COMPOSITE ADVERSE EFFECTS												
2	randomized trials	serious ^a	not serious	not serious	very serious ^{b,c}	none	2/1263 (0.2%)	1/435 (0.2%)	RR 2.02 (0.18 to 21.96)	2 more per 1000 (from 2 fewer to 48 more)	⊕⊕⊕⊕ VERY LOW	CRITICAL
SIDE-EFFECTS OF ANTIBIOTICS: MATERNAL ALLERGIC REACTIONS												
2	randomized trials	serious ^a	not serious	not serious	very serious ^d	none	0/162 (0.0%)	0/167 (0.0%)	not estimable	—	⊕⊕⊕⊕ VERY LOW	CRITICAL

No. of studies	Certainty assessment						Effect			Certainty	Importance		
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anti-staphylococcal cephalosporins (1st and 2nd generation)	No. of women	Non-anti-staphylococcal penicillins (natural and broad spectrum)			Relative (95% CI)	Absolute (95% CI)
COST OF CARE: MATERNAL LENGTH OF HOSPITAL STAY (DAYS)													
1	randomized trial	serious ^e	not serious	not serious	serious ^f	none	66	66	—	—	MD 1.5 lower (2.46 lower to 0.54 lower)	⊕⊕⊖⊖ LOW	IMPORTANT

CI: Confidence interval; RR: Risk ratio; MD: Mean difference.

^a Most of the pooled effect provided by studies "B".

^b Wide confidence interval crossing the line of no effect.

^c Less than 30 events.

^d No events.

^e The effect provided by study "B".

^f Less than 300 women.

Question: Minimally anti-staphylococcal cephalosporins (3rd generation) compared to broad-spectrum penicillins plus beta-lactamase inhibitors for preventing infection at caesarean section

Setting: Hospital (India and Switzerland)

Bibliography: Williams MJ, Carvalho Ribeiro do Valle C, Gyte GML. Different classes of antibiotics given to women routinely for preventing infection at caesarean section. Cochrane Database Syst. Rev. 2021; 3:CD008726. doi: 10.1002/14651858.CD008726.pub3.

No. of studies	Certainty assessment						No. of women		Effect		Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minimally anti-staphylococcal cephalosporins (3rd generation)	Broad-spectrum penicillins plus beta-lactamase inhibitors	Relative (95% CI)	Absolute (95% CI)		
PUERPERAL INFECTION: ENDOMETRITIS												
2	randomized trials	serious ^a	not serious	not serious	very serious ^{b,c}	none	1/431 (0.2%)	1/434 (0.2%)	RR 1.02 (0.07 to 15.88)	0 fewer per 1000 (from 2 fewer to 34 more)	⊕⊖⊖⊖ VERY LOW	CRITICAL
MATERNAL FEVER (FEBRILE MORBIDITY)												
1	randomized trial	serious ^d	not serious	not serious	serious ^b	none	20/372 (5.4%)	17/374 (4.5%)	RR 1.18 (0.63 to 2.22)	8 more per 1000 (from 17 fewer to 55 more)	⊕⊕⊖⊖ LOW	CRITICAL
PUERPERAL INFECTION: MATERNAL COMPOSITE SERIOUS INFECTIOUS COMPLICATION												
1	randomized trial	serious ^d	not serious	not serious	very serious ^e	none	0/372 (0.0%)	0/374 (0.0%)	not estimable	—	⊕⊕⊖⊖ VERY LOW	CRITICAL
WOUND INFECTION												
2	randomized trials	serious ^a	not serious	not serious	very serious ^{b,c}	none	11/431 (2.6%)	12/434 (2.8%)	Average RR 0.67 (0.10 to 4.58)	9 fewer per 1000 (from 25 fewer to 99 more)	⊕⊕⊖⊖ VERY LOW	CRITICAL
SIDE-EFFECTS OF ANTIBIOTICS: MATERNAL COMPOSITE ADVERSE EFFECTS												
2	randomized trials	serious ^a	not serious	not serious	very serious ^e	none	0/431 (0.0%)	0/434 (0.0%)	not estimable	—	⊕⊕⊖⊖ VERY LOW	CRITICAL
SIDE-EFFECTS OF ANTIBIOTICS: MATERNAL ALLERGIC REACTIONS												
2	randomized trials	serious ^a	not serious	not serious	very serious ^e	none	0/431 (0.0%)	0/434 (0.0%)	not estimable	—	⊕⊕⊖⊖ VERY LOW	CRITICAL

No. of studies	Certainty assessment							Effect		Importance		
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of women		Relative (95% CI)		Absolute (95% CI)	Certainty
SIDE-EFFECTS OF ANTIBIOTICS: MATERNAL NAUSEA												
1	randomized trial	serious ^d	not serious	not serious	very serious ^{c,ef}	none	Minimally anti-staphylococcal cephalosporins (3rd generation)	Broad-spectrum penicillins plus beta-lactamase inhibitors	not estimable	—	⊕⊖⊖⊖ VERY LOW	CRITICAL
SIDE-EFFECTS OF ANTIBIOTICS: MATERNAL VOMITING												
1	randomized trial	serious ^d	not serious	not serious	very serious ^{c,ef}	none	0/59 (0.0%)	0/60 (0.0%)	not estimable	—	⊕⊖⊖⊖ VERY LOW	CRITICAL
SIDE-EFFECTS OF ANTIBIOTICS: MATERNAL DIARRHOEA												
1	randomized trial	serious ^d	not serious	not serious	very serious ^{c,ef}	none	0/59 (0.0%)	0/60 (0.0%)	not estimable	—	⊕⊖⊖⊖ VERY LOW	CRITICAL
SIDE-EFFECTS OF ANTIBIOTICS: MATERNAL SKIN RASH												
1	randomized trial	serious ^d	not serious	not serious	very serious ^{c,ef}	none	0/59 (0.0%)	0/60 (0.0%)	not estimable	—	⊕⊖⊖⊖ VERY LOW	CRITICAL
COST OF CARE: MATERNAL LENGTH OF HOSPITAL STAY (DAYS)												
1	randomized trial	serious ^d	not serious	not serious	serious ^b	none	372	374	—	MD 0.01 lower (0.12 lower to 0.1 higher)	⊕⊕⊖⊖ LOW	IMPORTANT

CI: Confidence interval; RR: Risk ratio; MD: Mean difference.

^a The pooled effect provided by trials "B".

^b Wide confidence interval crossing the line of no effect.

^c Less than 30 events.

^d The effect provided by trial "B".

^e No events.

^f Less than 300 women.

Question: Minimally anti-staphylococcal cephalosporins (3rd generation) compared to non-anti-staphylococcal penicillins (natural and broad spectrum) for preventing infection at caesarean section

Setting: Hospital (Canada, Italy, South Africa and USA)

Bibliography: Williams MJ, Carvalho Ribeiro do Valle C, Gyte GML. Different classes of antibiotics given to women routinely for preventing infection at caesarean section. Cochrane Database Syst. Rev. 2021; 3:CD008726. doi: 10.1002/14651858.CD008726.pub3.

No. of studies	Certainty assessment							Effect		Certainty	Importance			
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of women		Relative (95% CI)			Absolute (95% CI)		
SEVERE INFECTIOUS MORBIDITY: SEPSIS														
1	randomized trial	serious ^a	not serious	not serious	very serious ^{b,c}	none	Minimally anti-staphylococcal cephalosporins (3rd generation)	Non-anti-staphylococcal penicillins (natural and broad spectrum)	0/27 (0.0%)	0/32 (0.0%)	not estimable	—	⊕⊖⊖⊖ VERY LOW	CRITICAL
PUERPERAL INFECTION: ENDOMETRITIS														
2	randomized trials	serious ^d	not serious	not serious	not serious	none	30/200 (15.0%)	34/362 (9.4%)			RR 1.74 (1.10 to 2.75)	70 more per 1000 (from 9 more to 164 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
PUERPERAL INFECTION: MATERNAL FEVER (FEBRILE MORBIDITY)														
1	randomized trial	serious ^a	not serious	not serious	very serious ^{e,f}	none	5/55 (9.1%)	6/59 (10.2%)			RR 0.89 (0.29 to 2.76)	11 fewer per 1000 (from 72 fewer to 179 more)	⊕⊖⊖⊖ VERY LOW	CRITICAL
PUERPERAL INFECTION: MATERNAL COMPOSITE SERIOUS INFECTIOUS COMPLICATION														
1	randomized trial	serious ^a	not serious	not serious	very serious ^{b,c,e}	none	0/27 (0.0%)	0/32 (0.0%)			not estimable	—	⊕⊖⊖⊖ VERY LOW	CRITICAL
WOUND INFECTION														
3	randomized trials	serious ^d	not serious	not serious	very serious ^{e,f}	none	4/190 (2.1%)	11/216 (5.1%)			RR 0.41 (0.13 to 1.28)	30 fewer per 1000 (from 44 fewer to 14 more)	⊕⊖⊖⊖ VERY LOW	CRITICAL
SIDE-EFFECTS OF ANTIBIOTICS: MATERNAL COMPOSITE ADVERSE EFFECTS														
2	randomized trials	serious ^d	not serious	not serious	very serious ^b	none	0/172 (0.0%)	0/335 (0.0%)			not estimable	—	⊕⊖⊖⊖ VERY LOW	CRITICAL

No. of studies	Study design	Certainty assessment						No. of women			Effect		Certainty	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minimally anti-staphylococcal cephalosporins (3rd generation)	Non-anti-staphylococcal penicillins (natural and broad spectrum)	Relative (95% CI)	Absolute (95% CI)				
SIDE-EFFECTS OF ANTIBIOTICS: MATERNAL ALLERGIC REACTIONS														
1	randomized trial	serious ^a	not serious	not serious	very serious ^{b,c}	none	0/27 (0.0%)	0/32 (0.0%)	not estimable	—	⊕⊖⊖⊖ VERY LOW	CRITICAL		
SIDE-EFFECTS OF ANTIBIOTICS: MATERNAL NAUSEA														
1	randomized trial	serious ^a	not serious	not serious	very serious ^{b,c}	none	0/27 (0.0%)	0/32 (0.0%)	not estimable	—	⊕⊖⊖⊖ VERY LOW	CRITICAL		
SIDE-EFFECTS OF ANTIBIOTICS: MATERNAL VOMITING														
1	randomized trial	serious ^a	not serious	not serious	very serious ^{b,c}	none	0/27 (0.0%)	0/32 (0.0%)	not estimable	—	⊕⊖⊖⊖ VERY LOW	CRITICAL		
SIDE-EFFECTS OF ANTIBIOTICS: MATERNAL DIARRHOEA														
1	randomized trial	serious ^a	not serious	not serious	very serious ^{b,c}	none	0/27 (0.0%)	0/32 (0.0%)	not estimable	—	⊕⊖⊖⊖ VERY LOW	CRITICAL		
SIDE-EFFECTS OF ANTIBIOTICS: MATERNAL SKIN RASH														
1	randomized trial	serious ^a	not serious	not serious	very serious ^{b,c}	none	0/27 (0.0%)	0/32 (0.0%)	not estimable	—	⊕⊖⊖⊖ VERY LOW	CRITICAL		

CI: Confidence interval; RR: Risk ratio.

^a The effect provided by trial "B".^b No events.^c Less than 300 women.^d The pooled effect provided by trials "B".^e Wide confidence interval crossing the line of no effect.^f Less than 30 events.

Appendix 1

a) Overview of the drugs administered

Subclass of cephalosporin or penicillin	Antibiotic administered
1st generation cephalosporins	Cefazolin Cephalothin
2nd generation cephalosporins	Cefonicid Cefotetan Cefoxitin Cefuroxime
3rd generation cephalosporins	Cefotaxime Ceftriaxone Ceftizoxime
Natural penicillins	Benzathine penicillin Procaine penicillin
Broad-spectrum penicillins	Ampicillin Mezlocillin Piperacillin
Penicillins plus beta-lactamase inhibitors	Ampicillin plus sulbactam Co-amoxyclav (amoxicillin plus clavulanic acid) Ticarcillin plus clavulanic acid

b) Comparisons and interventions

All antibiotics for prophylaxis at caesarean section were administered systemically. Unless otherwise indicated, antibiotics were given intravenously, or the route was not described.

Anti-staphylococcal cephalosporins (1st and 2nd generation) (8 trials, 1540 women)				Broad-spectrum penicillins plus beta-lactamase inhibitors					
Drug	Dose	No. of women		Drug	Dose	No. of women			
Cefazolin	1 g single dose	289	VS	Ampicillin plus sulbactam	1 g single dose	87	Anti-staphylococcal cephalosporins (1st and 2nd generation) (9 trials, 3093 women)		
	2 g single dose	67			1.5 g single dose	128			
Cefotetan	1 g single dose	224			Co-amoxycylav (amoxicillin plus clavulanic acid)	3 g single dose		192	
	2 g single dose	96				1.2 g single dose		188	
Cefoxitin	2 g x 3 doses	68			Ticarcillin plus clavulanic acid	2.4 g single dose		55	
Cefuroxime	1.5 g single dose	85		(3 g + 100 mg) x 3 doses		61			
Anti-staphylococcal cephalosporins (1st and 2nd generation) (9 trials, 3093 women)				Non-anti-staphylococcal penicillins (natural and broad spectrum)					
Drug	Dose	No. of women			Drug	Dose		No. of women	
Cefazolin	1 g single dose	283		VS	Ampicillin	2 g single dose		315	Anti-staphylococcal cephalosporins (1st and 2nd generation) (9 trials, 3093 women)
	2 g single dose	161				1 g x 3 doses		113	
	1 g x 3 doses	261	Benzathine penicillin; procaine penicillin ^a		(1 200 000 IU; 400 000 IU) x 5 doses	200			
Cefonicid	1 g	147			Mezlocillin	4 g single dose	51		
	2 g single dose	244	2 g x 3 doses			51			
Cefotetan	1 g single dose	155	Piperacillin		4 g single dose	155			
	2 g single dose	162			2 g x 3 doses	268			
	2 g x 3 doses	278							
Cefoxitin	4 g x 3 doses	49							
	2 g single dose	200							

Minimally anti-staphylococcal cephalosporins (3rd generation) vs broad-spectrum penicillins plus beta-lactamase inhibitors (2 trials, 865 women)			
Minimally anti-staphylococcal cephalosporins (3rd generation)		Broad-spectrum penicillins plus beta-lactamase inhibitors	
Drug	Dose	Drug	Dose
Cefotaxime	1 g single dose	Co-amoxycylav (amoxicillin plus clavulanic acid)	1.2 g single dose
			No. of women
			434
VS			
Minimally anti-staphylococcal cephalosporins (3rd generation) vs non-anti-staphylococcal penicillins (natural and broad spectrum) (4 trials, 854 women)			
Minimally anti-staphylococcal cephalosporins (3rd generation)		Non-anti-staphylococcal penicillins (natural and broad spectrum)	
Drug	Dose	Drug	Dose
Cefotaxime	1 g x 3 doses	Ampicillin	2 g single dose
Ceftizoxime	1 g single dose		1 g x 3 doses
Ceftriaxone	1 g single dose		1 g single dose; then 500 mg x 4 doses
		Mezlocillin	2 g single dose
		Piperacillin	4 g single dose
			No. of women
			148
			59
			125
			32
			155

a Single study; both antibiotics administered intramuscularly.

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