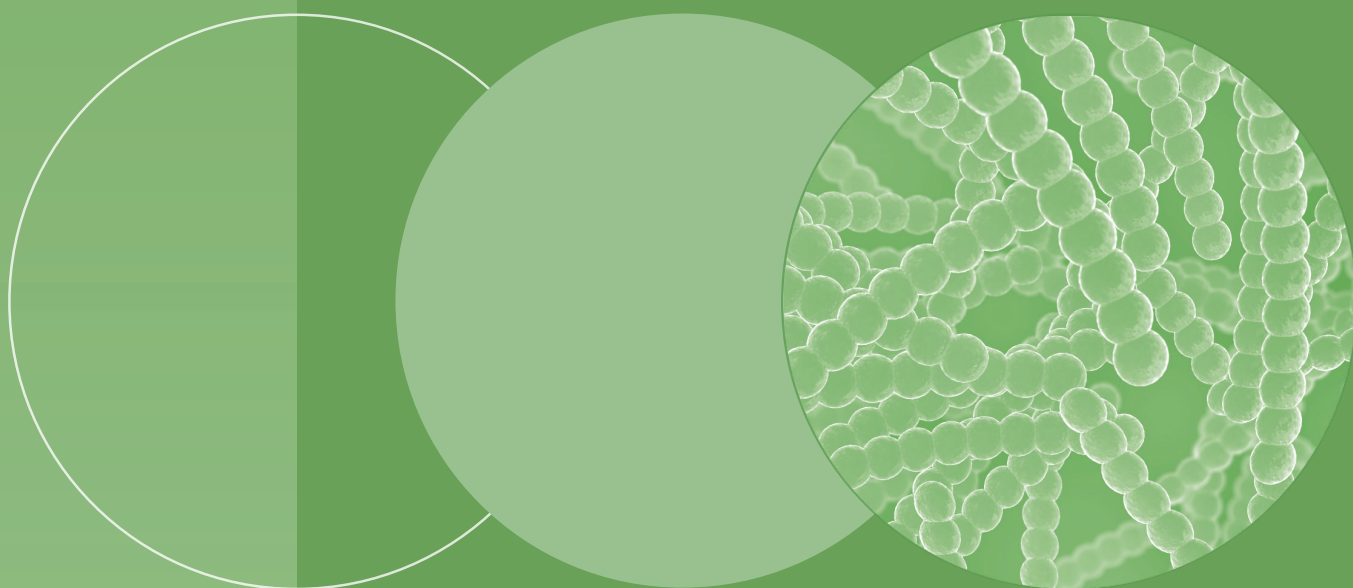


WHO recommendations for prevention and treatment of maternal peripartum infections



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The standardized criteria used in grading the evidence and GRADE tables are not included in this document although table numbers (prefixed with EB) are included for ease of reference. The tables have been published in a separate document – *WHO recommendations for prevention and treatment of maternal peripartum infections: evidence base* – which can be accessed online at www.who.int/reproductivehealth/publications/maternal_perinatal_health/peripartum-infections-guidelines.

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Acronyms and abbreviations

CI	confidence interval
CS	caesarean section
EB	evidence base
GBS	group B Streptococcus
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GREAT	Guideline development, Research priorities, Evidence synthesis, Applicability of evidence, Transfer of knowledge (a WHO project and international partnership)
hr	hour
HIV	human immunodeficiency virus
IM	intramuscular
IV	intravenous
MCA	[WHO Department of] Maternal, Newborn, Child and Adolescent Health
MD	mean difference
NICU	neonatal intensive care unit
OR	odds ratio
PICO	population, intervention, comparison, outcome
PPROM	preterm prelabour rupture of membranes
PROM	prelabour rupture of membranes
RCT	randomized controlled trial
RHR	[WHO Department of] Reproductive Health and Research
RR	relative risk
UK	United Kingdom
USA	United States of America
WHO	World Health Organization

Executive summary

Introduction

Bacterial infections around the time of childbirth account for about one tenth of the global burden of maternal death. Although the majority of these deaths are recorded in low-income countries, childbirth-related infections are also an important direct cause of maternal mortality in high-income countries. Apart from severe morbidity and death, women who experience peripartum infections are also prone to 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 have been associated with increased risk of maternal peripartum infections, including pre-existing maternal conditions (e.g. malnutrition, diabetes, obesity, severe anaemia, bacterial vaginosis, and group B streptococcus infections) and spontaneous or provider-initiated conditions during labour and childbirth (e.g. prolonged rupture of membranes, multiple vaginal examinations, manual removal of the placenta, and caesarean section). As such, the strategies to reduce maternal peripartum infections and their short- and long-term complications have been largely directed at preventive measures where such risk factors exist.

Globally, the most common intervention for preventing morbidity and mortality related to maternal infection is the use of antibiotics for prophylaxis and treatment. However, the misuse of antibiotics for obstetric conditions and procedures that are thought to carry risks of maternal infection is common in clinical practice. Such inappropriate use of antibiotics among women giving birth has implications on global efforts to contain the emergence of resistant bacteria strains and, consequently, on global health. 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. Therefore, appropriate guidance 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 would align with the WHO strategy and, ultimately, improve maternal and newborn outcomes.

The goal of the present guideline is to consolidate guidance for effective interventions that are needed to reduce the global burden of maternal infections and their complications around the time of childbirth. This forms part of WHO's efforts to improve the quality of care for leading causes of maternal death, especially those clustered around the time of childbirth, in the post-MDG era. Specifically, it presents evidence-based recommendations on interventions for preventing and treating genital tract infections during labour, childbirth or the puerperium, with the aim of improving outcomes for both mothers and newborns.

Target audience

The primary audience for this guideline is health professionals who are responsible for developing national and local health protocols and policies, as well as managers of maternal and child health programmes and policy-makers in all settings. The guideline will also be useful to those directly providing care to pregnant women, including obstetricians, midwives, nurses and general practitioners. The information in this guideline will be useful for developing job aids and tools for both pre- and inservice training of health workers to enhance their delivery of care to prevent and treat maternal peripartum infections.

Guideline development methods

The development of this guideline was guided by standard operating procedures in accordance with the process described in the *WHO handbook for guideline development*. Briefly, these included: (i) identification of priority questions and critical outcomes; (ii) retrieval of the evidence; (iii) assessment and synthesis of the evidence; (iv) formulation of recommendations; and (v) planning for the dissemination, implementation, impact evaluation and updating of the guideline. The scientific evidence supporting the recommendations was synthesized using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Up-to-date systematic reviews were then used to prepare evidence profiles for the prioritized questions. Then WHO convened a technical consultation in April 2015 where an international group of experts – the Guideline Development Group (GDG) – formulated and approved the recommendations based on the synthesized evidence.

Recommendations

The WHO technical consultation adopted 20 recommendations covering prioritized questions related to the prevention and treatment of maternal peripartum infections. The prevention aspect of the recommendations focuses on the routine use of minor procedures (e.g. perineal/pubic shaving), antimicrobial agents for vaginal and caesarean birth, and antibiotic prophylaxis for preventing infection in infection-prone conditions and obstetric procedures (prelabour rupture of membranes, meconium-stained amniotic fluid, perineal tears, manual removal of the placenta, operative vaginal birth and caesarean section). The recommendations on treatment of maternal peripartum infections are specific to antibiotic management of chorioamnionitis and postpartum endometritis. For each recommendation, the overall quality of evidence was graded as very low, low, moderate or high. The GDG qualified the direction and strength of each recommendation by considering this quality of evidence and other factors,

including the balance between benefits and harms, values and preferences of stakeholders, and resource implications of the intervention. To ensure that each recommendation is correctly understood and applied in practice, the contributing experts provided additional remarks as needed. Guideline users should refer to these remarks and the evidence summaries in the full version of the guideline if there is any doubt as to the basis of any of the recommendations and how to best implement them.

The WHO recommendations on interventions to prevent and treat maternal peripartum infections are summarized in the table below. In accordance with WHO guideline development procedures, these recommendations will be constantly reviewed and updated following identification of new evidence, with major reviews and updates at least every five years. WHO welcomes suggestions regarding additional questions for inclusion in future updates of the guideline.

Summary list of WHO recommendations for prevention and treatment of maternal peripartum infections

Context	Recommendation	Strength of recommendation and quality of evidence
Prevention of peripartum infections	1. Routine perineal/pubic shaving prior to giving vaginal birth <i>is not</i> recommended.	Conditional recommendation based on very low-quality evidence
	2. Digital vaginal examination at intervals of four hours is recommended for routine assessment of active first stage of labour in low-risk women.	Strong recommendation based on very low-quality evidence
	3. Routine vaginal cleansing with chlorhexidine during labour for the purpose of preventing infectious morbidities <i>is not</i> recommended.	Strong recommendation based on moderate-quality evidence
	4. Routine vaginal cleansing with chlorhexidine during labour in women with group B Streptococcus (GBS) colonization <i>is not</i> recommended for prevention of early neonatal GBS infection.	Conditional recommendation based on very low-quality evidence
	5. Intrapartum antibiotic administration to women with group B Streptococcus (GBS) colonization is recommended for prevention of early neonatal GBS infection.	Conditional recommendation based on very low-quality evidence
	6. Routine antibiotic prophylaxis during the second or third trimester for all women with the aim of reducing infectious morbidity <i>is not</i> recommended.	Strong recommendation based on very low-quality evidence
	7. Routine antibiotic administration <i>is not</i> recommended for women in preterm labour with intact amniotic membranes.	Strong recommendation based on moderate-quality evidence
	8. Antibiotic administration is recommended for women with preterm prelabour rupture of membranes.	Strong recommendation based on moderate-quality evidence
	9. Routine antibiotic administration <i>is not</i> recommended for women with prelabour rupture of membranes at (or near) term.	Strong recommendation based on low-quality evidence

Context	Recommendation	Strength of recommendation and quality of evidence
Prevention of peripartum infections (continued)	10. Routine antibiotic administration <i>is not</i> recommended for women with meconium-stained amniotic fluid.	Conditional recommendation based on low-quality evidence
	11. Routine antibiotic prophylaxis is recommended for women undergoing manual removal of the placenta.	Strong recommendation based on very low-quality evidence
	12. Routine antibiotic prophylaxis <i>is not</i> recommended for women undergoing operative vaginal birth.	Conditional recommendation based on very low-quality evidence
	13. Routine antibiotic prophylaxis is recommended for women with a third- or fourth-degree perineal tear.	Strong recommendation based on very low-quality evidence
	14. Routine antibiotic prophylaxis <i>is not</i> recommended for women with episiotomy.	Strong recommendation based on consensus view
	15. Routine antibiotic prophylaxis <i>is not</i> recommended for women with uncomplicated vaginal birth.	Strong recommendation based on very low-quality evidence
	16. Vaginal cleansing with povidone-iodine immediately before caesarean section is recommended.	Conditional recommendation based on moderate-quality evidence
	17. The choice of an antiseptic agent and its method of application for skin preparation prior to caesarean section should be based primarily on the clinician's experience with that particular antiseptic agent and method of application, its cost and local availability.	Conditional recommendation based on low-quality evidence
	18.0 Routine antibiotic prophylaxis is recommended for women undergoing elective or emergency caesarean section.	Strong recommendation based on moderate-quality evidence
	18.1 For caesarean section, prophylactic antibiotics should be given prior to skin incision, rather than intraoperatively after umbilical cord clamping.	Strong recommendation based on moderate-quality evidence
	18.2 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.	Conditional recommendation based on very low-quality evidence
Treatment of peripartum infections	19. A simple regimen such as ampicillin and once-daily gentamicin is recommended as first-line antibiotics for the treatment of chorioamnionitis.	Conditional recommendation based on very low-quality evidence
	20. A combination of clindamycin and gentamicin is recommended as first-line antibiotics for the treatment of postpartum endometritis.	Conditional recommendation based on very low-quality evidence

1. Background

Bacterial infections during labour and the puerperium are among the leading causes of maternal mortality worldwide, accounting for about one tenth of the global burden of maternal deaths (1, 2). While the number of deaths arising from these infections has decreased considerably in high-income settings, the situation has not improved in resource-limited settings. Most of the estimated 75,000 maternal deaths occurring worldwide yearly as a result of infections are recorded in low-income countries (3). Although the reported incidence in high-income countries is relatively low (between 0.1 and 0.6 per 1000 births), it is nonetheless an important direct cause of maternal mortality (3, 4).

Apart from deaths and acute morbidities associated with infections during or following childbirth, long-term disabilities such as chronic pelvic pain, fallopian tube blockage and secondary infertility can also occur. Maternal infections around childbirth also have a considerable impact on newborn mortality, and an estimated 1 million newborn deaths are associated with such infections annually (5, 6). In addition, infection-related morbidities and prolonged hospitalization can interfere with mother–infant bonding in the first days after birth.

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) and spontaneous or provider-initiated conditions during labour and childbirth (e.g. prolonged rupture of membranes, multiple vaginal examinations, manual removal of the placenta, operative vaginal birth and caesarean section) (3, 7). Caesarean section is notably the most important risk factor for infection in the immediate postpartum period, with a five- to 20-fold increased risk compared to vaginal birth. As such, the strategies to reduce maternal and newborn infections and their short- and long-term complications have been largely directed at avoiding common risk factors and promoting good infection control practices both within and outside the hospital environment.

Globally, the most common intervention for reducing morbidity and mortality related to maternal infection is the use of antibiotics for prophylaxis and treatment. Antibiotics are widely used (and misused) for obstetric conditions and procedures that are thought to carry substantial risks of infection to the mother. In many low-income countries, the use of broad-spectrum antibiotics without confirmation of the infective bacterial agent is common. Treatment

of infection according to antibiotic sensitivity in this setting is constrained by poor diagnostic facilities and the need to promptly administer antibiotics to prevent severe complications. Apart from poor outcomes associated with such practice, there is increasing concern that inappropriate use and misuse of antibiotics among women giving birth could compromise public health through the emergence of resistant bacteria strains.

According to the 2014 global report on surveillance of antimicrobial resistance, resistance to common bacteria has reached alarming levels in many parts of the world (8). 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 (9). Therefore, appropriate guidance 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 would align with the WHO strategy and, ultimately, improve maternal and newborn outcomes.

Definitions and terms

Various definitions and terms have been proposed for childbirth-related infections, but none are used universally. Maternal sepsis, genital tract sepsis, puerperal fever, puerperal sepsis and puerperal infection are common terms used synonymously in the literature without clarity in their definitions. A WHO technical working group defined puerperal sepsis as infection of the genital tract occurring at any time between the onset of rupture of membranes or labour and the 42nd day postpartum in which two or more of the following are present: pelvic pain, fever, abnormal vaginal discharge, abnormal smell/foul odour discharge or delay in uterine involution (10). While this definition captures well the characteristics of infections related to giving birth, the use of the term “puerperal” suggests that the onset of infection is only limited to the puerperium. Moreover, epidemiological data on childbirth-related infections have been complicated by the inclusion of other extragenital infections such as infections of the breast or urinary tract and localized or incidental infections that are unrelated to childbirth.

For clarity, the current guideline adopted the use of the term “maternal peripartum infection” to account for both intrapartum (intra-amniotic infection occurring before birth) and postpartum (or

puerperal) bacterial infections related to childbirth. In this context, maternal peripartum infection is defined as bacterial infection of the genital tract or its surrounding tissues occurring at any time between the onset of rupture of membranes or labour and the 42nd day postpartum in which two or more of the following are present: pelvic pain, fever, abnormal vaginal discharge, abnormal smell/foul odour discharge or delay in uterine involution. This definition builds on an existing definition but with additional considerations for infections related to childbirth procedures or conditions (e.g. caesarean section, episiotomy and perineal tears).

Rationale and objectives

In many parts of the world, peripartum infections continue to cause avoidable deaths, not only because of inadequate access to care during childbirth but also because of poor quality of care in health facilities. Compared to other childbirth complications, the case fatality rates for childbirth-related sepsis remains very high, with rates between 4% and 50% reported in sub-Saharan Africa and South East Asia (11). The coverage of evidence-based interventions for preventing and treating maternal infectious morbidities is generally suboptimal and varies largely within and across countries. As an example, the WHO MultiCountry Survey showed that institutional coverage of antibiotic prophylaxis for caesarean birth differs considerably across and within countries, and was more related to use of clinical guidelines and audits than to the institution's size or location or the country's developmental index (12). These findings suggest considerable gaps in the quality of care and the need for development and implementation of evidence-based guidance for prevention and treatment of maternal infection at the global level. However, the few available guidelines on maternal infections are limited in scope or specific to particular context and cannot serve the interests of populations that could benefit the most.

The goal of the present guideline is to consolidate guidance for effective interventions that are needed to reduce the global burden of maternal infection and its complications around the time of childbirth. This forms part of WHO's efforts to improve the quality of care for leading causes of maternal death, especially those clustered around the time of childbirth, in the post-MDG era. The guideline is evidence-informed and covers topics related to interventions selected and prioritized by an international, multidisciplinary group of health care professionals, consumer representatives and other stakeholders. Specifically, it presents evidence-based recommendations for preventing and treating genital tract infections during

labour, childbirth or puerperium, with the aim of improving outcomes for mothers and newborns. These recommendations are expected to form the basis for the development of global standards and indicators that could be adapted by WHO Member States for monitoring and improving the quality of care for maternal infections. The recommendations are intended to inform the development of relevant clinical protocols and health policies and not to provide a comprehensive practical guide for prevention and management of maternal peripartum infections.

Target audience

The target audience for this guideline includes health professionals responsible for developing national and local health protocols and policies, as well as managers of maternal and child health programmes and public health policy-makers in all settings. For policy-makers, the guideline will provide justification and support for the formulation of relevant policies and guide subsequent allocation of resources, especially in settings where a significant proportion of maternal and newborn deaths are due to complications of peripartum infections. The guideline will also be useful to those directly providing care to pregnant women, such as obstetricians, midwives, nurses and general practitioners. In settings where an inadequate health workforce has necessitated task-shifting of health worker roles, the guideline may also help mid-level providers to choose appropriate interventions to prevent or treat maternal peripartum infection before referral to higher levels of care.

Scope of the guideline

The population affected by this guideline includes pregnant women or women who have recently given birth suspected of being at risk of, or diagnosed with, bacterial infection of the genital tract or its surrounding tissues during or following vaginal or caesarean birth in a primary, secondary or tertiary care setting. The guideline will also impact on their fetus or newborn. Women with infections arising from viral, fungal, other infectious agents or bacterial infections in other areas remote from the genital tract are outside the scope of this guideline. Likewise, the guideline does not cover critical interventions for managing severe sepsis (i.e. acute organ dysfunction secondary to infection) and septicæmic shock (i.e. hypotension due to severe sepsis not reversed with fluid resuscitation).

2. Methods

This document represents WHO's normative support for using evidence-informed policies and practices in all countries. The guideline was developed using standard operating procedures in accordance with the process described in the *WHO handbook for guideline development* (13). In summary, the process included: (i) identification of priority questions and critical outcomes; (ii) retrieval of the evidence; (iii) assessment and synthesis of the evidence; (iv) formulation of recommendations; and (v) planning for the dissemination, implementation, impact evaluation and updating of the guideline.

The guideline development process involved the formation of five main groups to guide the process, with their specific roles as described in the following sections.

Contributors to the guideline

WHO Steering Group

The Steering Group, comprising WHO staff members from the Departments of Reproductive Health and Research (RHR) and Maternal, Newborn, Child and Adolescent Health (MCA), guided and managed the entire guideline development process. The group drafted the initial scope of the guideline and drafted key recommendation questions in PICO format and identified the systematic review team, guideline methodologists and guideline development and external review groups. In addition, the group supervised the synthesis and retrieval of evidence, organized the guideline panel meeting, drafted and finalized the guideline document and managed guideline dissemination, implementation and impact assessment. The members of the Steering Group are listed in Annex 1.

Guideline Development Group

The Steering Group identified 15 external experts and relevant stakeholders from each of the six WHO regions to constitute the Guideline Development Group (GDG). This was a diverse group of individuals with expertise in research, guideline development methods, and clinical policy and programmes relating to interventions to prevent and manage childbirth-related infections. The group also included representatives of women who will be affected by the recommendations. The members were selected in a way that ensured geographic representation and gender balance and avoided important conflicts of interest. Selected members of this group provided input into the drafting of the guideline scope and

the PICO questions, and participated in prioritizing outcomes that guided the evidence reviews. Additionally, the GDG appraised the evidence that was used to inform the guideline, advised on the interpretation of this evidence, formulated the final recommendations based on the draft prepared by the Steering Group, and reviewed and approved the final guideline document. The members of the GDG are listed in Annex 1.

External Review Group

This group included six technical experts and stakeholders with sufficient interest in the provision of evidence-based maternal and newborn care. The group was geographically balanced and gender-representative, and none of its members declared any conflict of interest. The group reviewed the final guideline document to identify any errors of fact and commented on the clarity of the language, contextual issues and implications for implementation. The External Review Group ensured that the guideline decision-making processes considered and incorporated the contextual values and preferences of potential users of the recommendations, health care professionals and policy-makers. It was not within the group's remit to change the recommendations formulated by the GDG. The members of the External Review Group are listed in Annex 1.

Systematic review team and guideline methodologists

Cochrane systematic reviews maintained by the Pregnancy and Childbirth Group of the Cochrane Collaboration were the primary source of evidence on the effectiveness of interventions included in this guideline. The Cochrane Pregnancy and Childbirth Group based in Liverpool, UK, provided input to the scoping of the guideline and coordinated the updating of all relevant systematic reviews based on the standard process of Cochrane Collaboration. The updating of Cochrane systematic reviews for this guideline was a collaborative process between authors of the individual reviews, staff of the Cochrane Pregnancy and Childbirth Group and technical staff of the Department of Health Policy, National Center for Child Health and Development (NCCHD) based in Tokyo, Japan. Where necessary, non-Cochrane systematic reviews were conducted afresh by the technical staff of the Department of Health Policy, NCCHD, Japan, with input from members of the WHO Steering Group. The WHO

Steering Group worked closely with guideline methodologists from the Departments of Health Policy, NCCHD, Japan, to appraise the evidence from systematic reviews using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. The guideline methodologists are listed in Annex 1.

External partners and observers

Representatives of the International Federation of Gynaecology and Obstetrics (FIGO), International Confederation of Midwives (ICM), United Nations Population Fund (UNFPA), United States Agency for International Development (USAID), Bill and Melinda Gates Foundation and the National Institute for Health and Clinical Excellence (NICE) participated in the final guideline development meeting as observers. All these organizations are potential implementers of the proposed guideline with a long history of collaboration with the WHO Department of Reproductive Health and Research in guideline dissemination and implementation. The list of observers who participated in the final technical consultation is presented in Annex 1.

Identification of priority questions and critical outcomes

In consultation with members of the GDG, the systematic review team and guideline methodologists, the WHO Steering Group first drafted a list of recommendation questions and potential critical and important outcomes related to interventions to prevent and treat maternal peripartum infections. The potential outcomes were identified through a search of key sources of existing clinical guidelines and relevant systematic reviews. This exercise generated a total of 34 potential outcomes relating to various interventions for preventing and treating maternal peripartum infections. WHO then consulted a larger group of international experts and stakeholders (including midwives, obstetricians, neonatologists, researchers, experts in health care programmes and representatives of user groups) to rank the outcomes for each guideline question through an electronic survey. Survey participants were asked to rank the relative importance of outcomes on a nine-point scale ranging from 1 (not important) to 9 (critical). The median score was calculated for each outcome based on the participants' responses, to determine outcomes that are "critical" (median score ≥ 7) and "important but not critical" (median score 4–6) for making decisions about the recommendations. To ensure consistency, the Steering Group reviewed the final list of critical and important outcomes for each

guideline question. The prioritized outcomes rated critical and important were included in the scope of this document for evidence searching, retrieval, grading and formulation of recommendations. The list of critical and important outcomes according to the prioritized questions is provided in Annex 2.

Identification and retrieval of evidence

The systematic review team and guideline methodologists, in collaboration with the WHO Steering Group, retrieved evidence for each recommendation question from Cochrane reviews of randomized controlled trials and systematic reviews of non-randomized studies, as needed. The Steering Group provided the methodologists with standard operating procedures and a briefing on the desired output of the systematic reviews, and together agreed on the format and timelines for reporting. Using the assembled list of recommendation questions and prioritized outcomes from the scoping exercise, the WHO Steering Group, along with the systematic review team, identified systematic reviews that were either relevant or potentially relevant and assessed whether they needed to be updated. A systematic review was considered out of date if the last search date was two years or more prior to the date of assessment. For reviews found to be out of date, their authors were requested to update them within a specified time period. In instances where the authors were unable to do so, the updates were undertaken by the external team of systematic reviewers, in consultation with the WHO Steering Group.

Cochrane systematic reviews were the primary source of evidence for the recommendations included in this guideline.¹ The Cochrane reviews relating to interventions to prevent and treat maternal peripartum infections were based on studies identified from searches of the Cochrane Pregnancy and Childbirth Group's Trials Register. The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Coordinator and contains trials identified from: monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL); weekly searches of MEDLINE; weekly searches of EMBASE; hand

¹ As part of the Cochrane pre-publication editorial process, reviews are commented on by three peers (one editor and two referees external to the editorial team) and the Group's Statistical Adviser (see <http://www.cochrane.org/cochrane-reviews>). *The Cochrane Handbook for Systematic Reviews of Interventions* describes in detail the process of preparing and maintaining Cochrane systematic reviews on the effects of health care interventions.

searches of 30 journals and the proceedings of major conferences; and weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts. The details of the search strategies for key databases such as CENTRAL, MEDLINE and EMBASE, the list of hand-searched journals and conference proceedings and the list of journals reviewed via the current awareness service can be found in the “Specialized Register” section within the editorial information about the Cochrane Pregnancy and Childbirth Group. Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Coordinator at the Cochrane Centre searches the register for each review using the topic list rather than keywords.

The assessment of the quality of individual studies included in Cochrane reviews of intervention studies follows a specific and explicit method of assessing the risk of bias. Briefly, two review authors independently assess the risk of bias using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* along six domains (14). Each included study is assessed and rated as being at low, high or unclear risk of bias for random sequence generation, allocation concealment, blinding of study personnel, participants and outcome assessors, attrition, selective reporting and other sources of bias such as publication bias. The assessment along these domains provides an overall risk of bias that indicates the likely magnitude and direction of the bias and how it is likely to impact on the review findings. All Cochrane reviews are preceded by the publication of a peer-reviewed protocol describing the review’s proposed methods and search strategy.

The WHO Steering Group and methodologists worked together to determine the appropriateness and suitability of each systematic review in providing evidence for the priority questions by assessing its relevance, timeliness and quality. Relevance was ascertained by examining whether the population, intervention, comparisons and outcomes (PICO) considered in the full text of the review were compatible with those in the guideline question. The quality of each review was determined by assessing the clarity of its primary question with respect to the PICO; comprehensiveness of the search strategies and databases; potential for bias in the study selection and data extraction processes; methods of risk-of-bias assessment; and methods of data synthesis and reporting.

In situations where there were no suitable systematic reviews (Cochrane and non-Cochrane) or where the

reviews lacked relevant data for specific guideline questions, new systematic reviews were conducted to inform the development of the recommendations. In such cases, the systematic review team was asked to prepare a standard protocol with a clear PICO question, and criteria for identification of studies, including search strategies for different bibliographic databases, methods for assessing risk of bias and a data analysis plan before embarking on the review. Then, the Steering Group reviewed and endorsed the protocol. To identify relevant studies, systematic searches of various electronic sources were conducted, including MEDLINE, EMBASE, CENTRAL, CINAHL, Popline, NLM Gateway and WHO regional databases. The search strategies employed to identify the studies and the specific criteria for inclusion and exclusion of studies were described in the individual systematic reviews. Studies from low-, middle- and high-income countries were considered, and there were no language restrictions. The entire systematic review development process was iterative, with the systematic reviewers and guideline methodologists constantly communicating with the WHO Steering Group to discuss challenges and agree on solutions.

Quality assessment and grading of the evidence

Quality assessment of the body of evidence for each outcome was performed using the GRADE approach (15). Using this approach, the quality of evidence for each outcome was rated as “high”, “moderate”, “low” or “very low” based on a set of criteria. The final rating of quality of evidence was dependent on the further consideration of the factors briefly described below:

Study design limitations: The risk of bias was first examined at the level of individual study and then across studies contributing to the outcome. For randomized trials, quality was rated as is (i.e. “high”) or downgraded by one (“moderate”) or two (“low”) levels depending on the minimum quality 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 from different studies. The quality of evidence was not downgraded when the directions of the findings were similar and confidence limits overlapped, whereas the quality was downgraded when the results were in different directions and confidence limits showed minimal or no overlap.

Indirectness: The quality of evidence was downgraded where there were serious or very serious concerns regarding the directness of the evidence – i.e. whether there were important differences between the research reported and the context for which the recommendations are 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: Quality 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. We considered downgrading evidence by one level if we had a strong suspicion of publication bias.

GRADE profiler software was used to construct summary of findings tables for each question: these tables include the assessment and judgements on the elements described above for each outcome and the estimated risks. Relevant information and data were extracted in a consistent manner from the systematic reviews relating to each key question by applying the following procedures: first, up-to-date review documents and/or data (e.g. RevMan file) were obtained from the review authors or the Cochrane Pregnancy and Childbirth Group. Second, analyses relevant to the critical and important outcomes were identified and selected. The data were then imported from the RevMan file (for Cochrane reviews) or manually entered into the GRADE profiler software (for non-Cochrane systematic reviews). For each outcome, GRADE assessment criteria (as described above) were applied to evaluate the quality of evidence. In the final step of the assessment process, GRADE evidence profiles were generated for each guideline question.

Formulation of recommendations

The GRADE framework was applied to formulate each recommendation based on the synthesized evidence. For each guideline question, the WHO Steering Group used the corresponding summaries of evidence for the critical outcomes, overall quality of the evidence, balance between benefits and risks, values and preferences, and resource implications to draft the recommendations. The

draft recommendations, evidence summaries, the corresponding GRADE tables and other related documents were provided in advance to members of the GDG, who were then asked to comment on the document in tracked mode. The GDG members and other participants were then invited to attend a technical consultation (see Annex 1 for the full list of participants) organized at WHO headquarters in Geneva, Switzerland, in April 2015. At the technical consultation, the GDG members systematically reviewed and discussed these documents to finalize the recommendations and determine their direction and strengths.

Declaration of interests by external contributors

According to WHO regulations, all experts must declare their relevant interests prior to participation in WHO guideline development process and meetings. All GDG members and external contributors were, therefore, required to complete a standard WHO Declaration of Interest (DOI) form before engaging in the guideline development process and before participating in guideline-related meetings. The WHO Steering Group reviewed all declarations before finalizing experts' invitations to participate in the guideline development. Where any conflict of interest was declared, the Steering Group determined whether such conflicts were serious enough to affect the expert's objective judgement on the guideline development process and recommendations. To ensure consistency, the Steering Group applied the criteria for assessing the severity of conflict of interests in the *WHO handbook for guideline development* (13) for all experts. All findings from the DOI statements received were managed in accordance with the WHO DOI guidelines on a case-by-case basis and communicated to the experts.

The procedures for the management of declared conflicts of interests were undertaken in accordance with the *WHO guidelines for declaration of interests (WHO experts)*. Where a conflict of interest was not considered significant enough to pose any risk to the guideline development process or reduce its credibility, the experts were only required to openly declare such conflict at the beginning of the GDG meeting, and no further actions were taken. Conflict of interest that warranted actions by the WHO staff arose where experts had obtained funding from a body or an institution to perform primary research or had performed a systematic review directly related to any of the guideline recommendations. At the GDG meeting, the concerned experts were restricted from participating in discussions and/or formulating

recommendations pertaining to their academic conflicts of interest. Annex 3 shows a summary of the DOI statements and how the Steering Group managed declared conflicts of interest.

Decision-making during the technical consultation

The technical consultation process was guided by the following protocol: the meeting was designed to allow participants to discuss each of the recommendations drafted by the WHO Steering Group. Where necessary, each of these recommendations was revised, as needed, through group discussion. The final adoption of each recommendation was made by consensus – defined as the agreement by three quarters or more of the participants – provided that those who disagreed did not feel strongly about their position. Strong disagreements would have been recorded as such in the guideline (there was no record of such disagreement throughout the technical consultation). If the participants were unable to reach a consensus, the disputed recommendation, or any other decision, would be put to a vote. Voting is by a show of hands by members of the GDG. A recommendation or decision stands if a simple majority (more than half of the participants) vote in support of it, unless the disagreement is related to a safety concern, in which case the WHO Secretariat would choose not to issue a recommendation at all. WHO staff at the meeting, external technical experts involved in the collection and grading of the evidence, and observers were not eligible to vote. If the issue to be voted on involves primary research or systematic reviews conducted by any of the participants who have declared an academic conflict of interest, the participants in question would be allowed to participate in the discussion but would not be allowed to vote on the subject of discussion. In addition to evaluating the scientific evidence and its quality, values and preferences, relevant applicability issues and costs were also taken into consideration when formulating the final recommendations.

The technical consultation also determined the strength of each recommendation. By default, the strength of the recommendations discussed

was aligned initially with the quality of the evidence (i.e. at the start of the discussion, “strong recommendations” were based on evidence of “moderate” and “high” quality, while “conditional recommendations” were based on evidence of “low” and “very low” quality). In addition to the quality of the evidence, the following factors were considered when determining the strength and direction of the final recommendations: the balance of benefits versus harms, values and preferences, and resource implications. The consideration of values and preferences was based on the experience and opinions of members of the GDG. Cost evaluation relied on reported estimates obtained during the evidence retrieval process as well as experiences and opinions of members of the GDG. Evidence-to-decision tables were used to note and synthesize these considerations and record the reasons for changes made to the default strength of the recommendations.

Document preparation and peer review

Prior to the technical consultation, the WHO Steering Group prepared a draft version of evidence summaries and corresponding recommendations. The draft document was made available to the participants in the technical consultation two weeks before the meeting for their comments. During the meeting, the draft recommendations were modified in line with participants’ deliberation and remarks. Following the meeting, members of the Steering Group drafted a full guideline document with revisions to accurately reflect the participants’ deliberations and decisions. The draft guideline document was sent electronically to GDG members for further comments before it was sent to the External Review Group for peer review. The Steering Group carefully evaluated the inputs of the peer reviewers for inclusion in the guideline document accordingly. After the technical consultation and peer review, the modifications made by the Steering Group to the guideline were limited to correcting factual errors and improving language to address any lack of clarity. The revised final version was returned electronically to participants in the technical consultation for their final approval.

3. Results

In total, 24 systematic reviews summarized in 57 GRADE tables provided the evidence base for the recommendations included in this guideline. The following sections outline the recommendations and the corresponding narrative summaries of evidence for the prioritized questions. The corresponding GRADE tables for the recommendations are separately presented in the electronic appendix to this document (see the “*WHO recommendations for prevention and treatment of maternal peripartum infection: evidence base*” at www.who.int/reproductivehealth/publications/maternal_perinatal_health/peripartum-infections-guidelines). Balance worksheets summarizing the quality of evidence, values and preferences, balance between benefits and harms and resource implications that were considered in determining the strength and direction of the recommendations are presented in Annex 4.

Guiding principles

The participants in the technical consultation agreed that the following overarching principles are applicable to all recommendations in this guideline. These principles were based on 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. They also draw attention to fundamental and cross-cutting issues relating to the prioritized questions in this guideline. 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 guideline in a range of contexts and settings:

- Standard infection prevention and control measures should be observed in the provision of maternity care to optimize the effects of interventions recommended in this guideline. These measures should include:
 - 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 (e.g. diabetes) during antenatal care; promoting hand hygiene and use of clean products (e.g. blood products); 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); and general improvement of hospital environments (e.g. clean water, appropriate waste disposal and sanitation). Local protocols on infection prevention and control practices should be developed and implemented in accordance with existing WHO guidance (16).

- 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.
 - Reduction of nosocomial transmission of infections by barrier nursing of women with peripartum infections. However, such women should be provided with care and support by health care staff as appropriate, and should not be left in an “isolation ward” unattended.
 - 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.
- This guideline does not provide guidance on the management of severe sepsis (i.e. acute organ dysfunction secondary to infection) and septic shock (i.e. hypotension due to severe sepsis not reversed with fluid resuscitation). Given that there is a high risk of maternal mortality from these conditions, every facility providing maternity care should have in place a protocol for prompt recognition and acute management of severe sepsis and septic shock by a multidisciplinary team. This protocol should be informed by internationally recommended guidelines (17) and adapted to the local obstetric population and available skills and resources.

- 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 (9).
- 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.

Evidence and recommendations

The WHO technical consultation adopted 20 recommendations covering prioritized questions related to the prevention and treatment of maternal peripartum infections. The prevention aspect of the recommendations is focused on routine use of minor procedures (e.g. perineal/pubic shaving), antiseptic agents for vaginal and caesarean birth, and antibiotic prophylaxis for preventing bacterial infection in infection-prone conditions and obstetric procedures prelabour rupture of membranes, meconium-stained amniotic fluid, perineal tears, manual removal of the placenta, operative vaginal birth and caesarean section. When there was evidence of effectiveness regarding the use of any antibiotic, the comparative effectiveness and safety of different classes or regimens of antibiotics were considered to issue additional recommendations. The recommendations on the treatment of maternal peripartum infections are specific to antibiotic management of chorioamnionitis and postpartum endometritis.

The quality of the supporting evidence rated as "very low", "low", "moderate" or "high" and the strength of each recommendation assessed as "strong" or "conditional" are indicated. To ensure that each recommendation is correctly understood and

appropriately implemented in practice, additional "remarks" reflecting the summary of the discussion by GDG are included under the recommendation where necessary.

Prevention of maternal peripartum infections

RECOMMENDATION 1

Routine perineal/pubic shaving prior to giving vaginal birth is not recommended. (*Conditional recommendation based on very low-quality evidence*)

REMARKS

- This recommendation applies to all hair shavings around the female external genital area within the context of vaginal birth. It does not apply to women being prepared for caesarean section.
- The decision regarding perineal/pubic shaving should be left to the woman and not her health care giver. In situations where a woman chooses to have perineal/pubic shaving prior to birth, she could be advised to shave wherever, and by whomever she is most comfortable with (e.g. at home shortly before the time of labour and childbirth).

Review question:

Among pregnant women in labour (P), does routine perineal/pubic shaving prior to giving vaginal birth (I), compared with no perineal/pubic shaving (C), prevent infectious morbidities and improve outcomes (O)?

Summary of evidence

- Evidence on routine perineal/pubic shaving before childbirth for the prevention of maternal and neonatal infectious morbidities was extracted from a Cochrane systematic review of three randomized trials involving 1039 women (18). The trials were conducted in hospitals in the USA (Baltimore, Dallas) and Thailand (Bangkok).
- All trials included women admitted to hospital prior to giving birth. The trials compared perineal shaving versus no perineal shaving (which included clipping or cutting of perineal hair). In two trials (involving 650 women), skin preparation was performed in both intervention and control groups by scrubbing the external genitalia and inner thighs with soap and water or povidone-iodine spray; or with 4% chlorhexidine and rinsing with 1:100 savlon solution.

Perineal shaving versus no perineal shaving (EB Table 1)

- Compared to no perineal shaving, perineal shaving did not reduce the risk of maternal febrile morbidity (relative risk (RR) 1.14, 95% confidence interval (CI) 0.73 to 1.76; 3 trials, 997 women). There were no differences in the number of women who were colonized by gram-positive bacteria (RR 1.16, 95% CI 0.82 to 1.64; 1 trial, 150 women), although there was a reduction in the number of women who were colonized by gram-negative bacteria (RR 0.83, 95% CI 0.70 to 0.98; 1 trial, 150 women).
- There were no significant differences between comparison groups for perineal wound infection (defined as pain and erythema of the margins of perineal or episiotomy wound with/without serious or purulent discharge) (RR 1.47, 95% CI 0.80 to 2.70; 1 trial, 458 women) or perineal wound dehiscence (RR 0.33, 95% CI 0.01 to 8.00; 1 trial, 458 women).
- No neonatal infections were reported in either group (1 trial, 458 women).
- Women's satisfaction as measured by a five-point Likert scale did not show any difference between the comparison groups (mean difference 0.00, 95%CI -0.13 to 0.13, 1 trial, 458 women).
- None of the trials reported on other critical outcomes such as cost of care, and side-effects of perineal shaving (e.g. perineal discomfort, pain during hair regrowth).

Considerations related to the strength of the recommendation

Quality of the evidence

The quality of the evidence was graded from very low and moderate. Overall the quality of evidence was graded as very low.

Balance of benefits and harms

There is no evidence of any clinical benefit of routine perineal (or pubic) shaving before childbirth, although the quality of evidence is very low. Potential complications of perineal shaving, such as irritation and redness of the perineum, multiple superficial scratches from the razor, vulval itching and burning sensation, are not clinically serious but can be discomforting to women. Non-clinical outcomes that are considered very important to women such as embarrassment during the procedure and discomfort during hair regrowth were not reported by any of the studies. In the absence of any clinical benefits, it is reasonable to conclude that perineal shaving

has a higher potential of leading to undesirable consequences for women.

Values and preferences

Routine shaving is a procedure that is no longer practised in some countries but is still being performed in health facilities across all settings, often as part of maintenance of obstetric tradition. The clinical implications of the substantial variations in the currently available shaving methods across contexts (e.g. shaving creams/gel versus razor) are not known. Women's preferences about perineal shaving might differ between individual women and between religious and cultural settings. Pregnant women are likely to place a high value on maintaining their autonomy and dignity and avoid possible embarrassment from being shaved by a health care provider. Therefore, most women would prefer a policy that respects their values and preferences rather than one that mandates all women to have perineal shaving prior to childbirth.

Resource implications

Implementation of this recommendation is likely to reduce costs associated with resources required for shaving women on admission into the labour room.

RECOMMENDATION 2

Digital vaginal examination at intervals of four hours is recommended for routine assessment of active first stage of labour in low-risk women. (Strong recommendation based on very low-quality evidence)

REMARKS

- There is currently no direct evidence on the most appropriate frequency of vaginal examinations to prevent infectious morbidity in the mother and baby, and this recommendation was based on consensus reached by the GDG, and in agreement with an existing recommendation in the *WHO recommendations for augmentation of labour* (19).
- The recommended time intervals are consistent with timing of vaginal examination on the partograph and further reinforce the importance of using partograph as an essential tool to implement this practice. Priority must be given to restricting the frequency and total number of vaginal examinations. This is particularly crucial in

(Continued)

situations where there are other risk factors for infection (e.g. prolonged rupture of amniotic membranes and long duration of labour).

- The GDG acknowledged that the frequency of vaginal examinations is dependent on the context of care and the progress of labour. The group agreed that vaginal examinations at intervals more frequent than specified in this recommendation may be warranted by the condition of the mother or the baby.
- Vaginal examinations of the same woman by multiple care givers around the same time or at different time points should be avoided. The group noted that this practice is common in teaching settings where multiple cadres of staff (or students) perform vaginal examinations for learning purposes.

Review question:

Among pregnant women undergoing labour monitoring (P), does routine vaginal examination at intervals of four hours (I), compared with shorter intervals (C), prevent infectious morbidities and improve outcomes (O)?

Summary of evidence

- Evidence on the intervals of vaginal examination during labour was extracted from a Cochrane systematic review evaluating the effectiveness of vaginal examination at term for assessing labour progress (20). The review included two trials, each examining a different comparison. One trial conducted in Ireland in 307 women with ruptured membranes compared routine vaginal examinations (every one or two hours) with rectal examinations to assess progress in labour. A trial in the UK compared two-hourly with four-hourly vaginal examinations in nulliparous women in labour (150 women randomized, 109 included in the analysis).

Two-hourly versus four-hourly vaginal examinations in labour (no GRADE table included)

- In the UK trial with 109 women comparing two- versus four-hourly vaginal examination to assess progress in labour, no maternal or neonatal critical outcomes related to infection were reported. However, the trial reported no significant differences between the two intervals for duration of labour, caesarean section, operative vaginal birth and use of labour augmentation.

Considerations related to the strength of the recommendation

Quality of evidence

The quality of evidence was graded as very low.

Balance of benefits and harms

There is no evidence from randomized controlled trials to evaluate the relationship between the intervals of vaginal examinations during labour and maternal and newborn infectious morbidities. Multiple vaginal examinations are recognized contributors to infectious morbidities associated with prolonged labour, so it is scientifically plausible that vaginal examinations more frequent than every four hours could potentially increase the risk of infection for both the mother and the infant. In the absence of any evidence of benefits in relation to other clinical outcomes unrelated to infections, the undesirable consequences of more frequent vaginal examinations for women are likely to overcome the potential benefits. Evidence and recommendations related to routine vaginal examination for assessing the progress of labour were included in the *WHO recommendations for augmentation of labour* (19), which recommends four-hour intervals for assessing the progress of labour.

Values and preferences

Pregnant women across all settings are likely to place a high value on minimal labour interventions, including less invasive procedures such as vaginal examinations. Women are unlikely to accept frequent vaginal examinations in the absence of any clinical maternal or fetal indication.

Resource implications

Implementation and adherence to this recommendation is likely to save costs related to staff time and materials that would be required to perform vaginal examinations at intervals more frequent than every four hours.

RECOMMENDATION 3

Routine vaginal cleansing with chlorhexidine during labour for preventing infectious morbidities is not recommended. (*Strong recommendation based on moderate-quality evidence*)

REMARKS

- This recommendation applies to women in whom vaginal birth is anticipated.

- Vaginal cleansing in this context refers to vaginal douching or any mechanical irrigation or washing of the vaginal canal and cervix with chlorhexidine solution or vaginal application of chlorhexidine gel.
- The infectious morbidities considered in the evidence base did not include GBS and HIV-related infections. However, this intervention is also not recommended for preventing early neonatal GBS infection in women with GBS colonization (see *Recommendation 4*).

Review question:

Among pregnant women in labour (P), does routine vaginal cleansing with an antiseptic agent (I), compared with no vaginal cleansing with an antiseptic agent (C), prevent infectious morbidities and improve outcomes following vaginal birth (O)?

Summary of evidence

- Evidence on routine vaginal cleansing with an antiseptic agent during labour for the prevention of maternal and neonatal infections was extracted from a Cochrane systematic review of three trials involving 3012 women (21). All included studies were conducted in hospitals in the USA between 1997 and 2003. The trials included women admitted to the hospital prior to birth, ≥ 24 weeks pregnant and excluded women with GBS infections or known allergy to chlorhexidine. The intervention was chlorhexidine vaginal douching during labour versus sterile water. Two of the studies used 200 ml of 0.2% of chlorhexidine, while the third study used 20 ml of 0.4% chlorhexidine for vaginal irrigation during labour.

Chlorhexidine vaginal douching during labour versus placebo (EB Table 2)

- No differences were observed in the incidence of chorioamnionitis (RR 1.10, 95% CI 0.86 to 1.42; 3 trials, 3012 women) or postpartum endometritis (RR 0.83, 95% CI 0.61 to 1.13; 3 trials, 3012 women). No side-effects from the use of chlorhexidine were observed among women in the two groups (2 trials, 2065 women).
- There was no difference in perinatal mortality between the two groups (RR 1.00, 95% CI 0.17 to 5.79; 2 trials, 2017 neonates).
- For neonatal outcomes, there were no differences between groups for neonatal sepsis (RR 0.75, 95% CI 0.17 to 3.35; 3 studies, 2987 neonates), blood cultures confirming neonatal infections, (RR

0.75, 95% CI 0.17 to 3.35; 2 trials, 2077 neonates), neonatal pneumonia (RR 0.33, 95% CI 0.01 to 8.09, 1 trial, 910 neonates) or neonatal meningitis (RR 0.34, 95% CI 0.01 to 8.29, 1 trial, 1024 neonates). No difference was observed between groups of newborns who received antibiotic treatment (RR 1.65, 95% CI 0.73 to 3.74, 1 trial, 910 neonates).

- The included trials did not report on any other critical outcomes.

Considerations related to the strength of the recommendation

Quality of evidence

The quality of the evidence was graded as moderate for reported critical outcomes.

Balance of benefits and harms

There is no evidence of clinical benefits to support routine vaginal cleansing with chlorhexidine during labour in women giving vaginal birth. The possible side-effects were not reported by any of the studies. Other systematic reviews evaluating the routine use of chlorhexidine for preventing HIV and GBS infections following vaginal birth did not show any clinical benefits either. Although vaginal douching with chlorhexidine is relatively inexpensive, can be performed within minutes and is unlikely to interfere with the women's labour, the use of an additional intervention with no clinical benefit further undermines the natural process of birth. Additionally, the unnecessary use of medical disinfectants in general might contribute to antimicrobial resistance, although such a situation rarely emerges with chlorhexidine even after long-term use.

Values and preferences

Women are likely to prefer minimal interference with the process of labour, and some women may find the procedure invasive and discomforting. Health care providers and policy-makers across settings are likely to place a higher value on saving health care costs and, therefore, choose not to use the intervention.

Resource implications

Although chlorhexidine is relatively cheap, and it is technically feasible to perform vaginal cleansing during labour with minimal increase in resource use, the intervention is not cost-effective, as there is no added benefits for mother and baby.

RECOMMENDATION 4

Routine vaginal cleansing with chlorhexidine during labour in women with group B Streptococcus (GBS) colonization is not recommended for prevention of early neonatal GBS infection. (Conditional recommendation based on very low-quality evidence)

REMARKS

- This recommendation was based on the lack of clinical benefits for the neonate and not on the potential effect of the intervention on GBS-related maternal infectious morbidity.
- The GDG acknowledged the considerable variations in policies regarding the screening for GBS colonization in pregnant women. Therefore, the group agreed that this recommendation should be implemented within the context of local policy and guidance on screening for GBS colonization.

Review question:

Among pregnant women with vaginal, rectal or urethral colonization with group B Streptococcus (GBS) (P), does routine vaginal cleansing with an antiseptic agent during labour (I), compared with no vaginal cleansing with an antiseptic agent (C), prevent neonatal infectious morbidities and improve neonatal outcomes (O)?

Summary of evidence

- Evidence on the use of antiseptic agents for routine vaginal cleansing with an antiseptic agent in GBS-colonized women during labour to prevent neonatal infectious morbidities and improve neonatal outcomes was extracted from a Cochrane systematic review of four trials that included 1125 preterm and term infants (22). The trials were conducted in Belgium, the Netherlands, Norway, Sweden and the UK.
- Rapid screening or culture tests were used to diagnose GBS colonization. Most of the trials excluded women who received antibiotics before delivery, planned caesarean sections and fetal deaths. The interventions were different methods of application and preparations of chlorhexidine: vaginal wash, lubricated gloves with cream, or gel application around the vaginal fornices. Comparison groups included mechanical wash with placebo (sterile water) or no treatment.
- The trials did not report on maternal morbidities, cost of care or maternal satisfaction.

Chlorhexidine (vaginal wash or gel/cream) versus placebo or no treatment (EB Table 3)

- The two trials reporting the incidence of early onset GBS-related neonatal morbidities within the first seven days of life found no differences between groups: GBS sepsis and/or meningitis (RR 2.32, 95% CI 0.34 to 15.63; 2 trials, 987 infants) or GBS pneumonia (RR 0.35, 95% CI 0.01 to 8.60; 2 trials, 987 infants). The number of infants colonized with GBS within the first seven days of life did not differ between the chlorhexidine and placebo or no treatment groups (RR 0.65, 95% CI 0.36 to 1.18; 3 trials, 328 infants).
- No neonatal deaths due to early-onset GBS infection were reported (1 trial, 190 infants).
- In the three trials that reported on maternal side-effects, a significantly greater number of mothers developed minor side-effects (stinging and irritation) related to the use of chlorhexidine (RR 8.5, 95% CI 1.60 to 45.28; 3 trials, 1066 women). No adverse effects were observed in infants in either groups (3 trials; 1066 infants).

Considerations related to the strength of the recommendation**Quality of evidence**

The quality of evidence was graded as very low for almost all critical outcomes reported. Overall, the quality of evidence was graded as very low.

Balance of benefits and harms

There is no clear evidence that routine vaginal cleansing with chlorhexidine during labour is effective in preventing early onset GBS-related disease in preterm and term neonates. Given the very low-quality evidence, there is little certainty about the estimates derived from these trials. Routine vaginal cleansing with chlorhexidine appears to increase the occurrence of stinging sensation and irritation in the vagina of treated women. Without proof of any clinical benefits, such undesirable consequences of chlorhexidine treatment are likely to be a major determinant in clinical decision-making. Although chlorhexidine has a low impact on antimicrobial resistance even with prolonged use, unnecessary use on a large scale may contribute to decreasing sensitivity of microorganisms to antimicrobial agents in the long term.

Values and preferences

The values and preferences of health care providers and women colonized with GBS may vary according to the emphasis on GBS neonatal disease in their

settings. Acceptance of the minor side-effects and discomfort associated with the intervention for a relatively rare neonatal disease is also likely to vary across settings.

Resource implications

Implementation of this recommendation is likely to save costs required to perform vaginal cleansing for all women with GBS colonization during labour.

RECOMMENDATION 5

Intrapartum antibiotic administration to women with group B Streptococcus (GBS) colonization is recommended for prevention of early neonatal GBS infection. *(Conditional recommendation based on very low-quality evidence)*

REMARKS

- This recommendation was made based on clinical benefits for the neonates, as there was insufficient evidence on the effect of antibiotic administration on maternal infectious morbidities.
- As the evidence came from studies that tested ampicillin or penicillin G, either antibiotic should first be considered for treatment except where there are contraindications (e.g. allergy history) or GBS strain has been microbiologically shown to be penicillin-resistant.
- The GDG noted that although women with urethral GBS colonization were not included in the trials, the recommendation should also be applied to such women because urinary colonization is often persistent following identification and treatment during pregnancy.
- The GDG acknowledged the challenges of implementing GBS screening for all pregnant women, particularly in low-resource countries and in settings where the prevalence of maternal colonization is low, coupled with the limitations in providing appropriate preventive measures and follow-up to the majority of the women screened positive. Therefore, the group agreed that this recommendation should be implemented within the context of local policy and guidance on screening for GBS colonization.

In deciding whether or not to administer antibiotics during labour to GBS-colonized women, clinicians should balance the risk and benefits of the use of antibiotics, taking into account different factors (e.g. colonization rates and factors associated with increased transmission).

Review question:

Among pregnant women with vaginal, rectal or urethral colonization with group B Streptococcus (GBS) (P), does routine administration of antibiotics during labour (I), compared with no antibiotics (C), prevent neonatal infectious morbidities and improve maternal and neonatal outcomes (O)?

Summary of evidence

- Evidence on the use of antibiotics during labour or delivery for known maternal GBS colonization to prevent infectious morbidity from GBS was extracted from a Cochrane systematic review of four trials including 852 women (23).
- Trials included women with vaginal and/or rectal GBS colonization ascertained by cultures in three trials, at different postmenstrual ages, or by rapid latex agglutination test at the time the mother was giving birth in one trial. Two trials included women at 36 weeks of gestation or more. The included trials were conducted in Finland, Spain and the USA.
- Two trials excluded women with rupture or prolonged rupture of membranes, and two trials excluded women undergoing planned caesarean section. Other relevant exclusion criteria varied between trials: antibiotic intake within the preceding seven days, fever prior to delivery or fetal death prior to labour.
- Two trials compared ampicillin versus no treatment – using different antibiotics regimens (2 g of ampicillin IV followed by 1 g every four hours until giving birth or 500 mg of ampicillin IV every six hours until delivery). One trial compared penicillin with no treatment (5 million units of penicillin G IV every six hours during labour, and if labour lasted more than 18 hours, 1 million units of penicillin orally every eight hours until parturition). One trial compared ampicillin with penicillin.
- The included trials did not report on antimicrobial resistance or maternal satisfaction.

Intrapartum antibiotics versus no treatment for GBS-positive women (EB Table 4)

- Only one trial reported maternal outcomes. No significant reduction was observed between comparison groups for maternal sepsis in the peri/postpartum period (RR 0.31, 95% CI 0.01 to 7.49; 1 trial, 160 women) or puerperal infections (RR 0.16, 95% CI 0.01 to 3.03; 1 trial, 121 women).
- In one small trial, intrapartum antibiotic administration did not show reductions in neonatal mortality from all causes (RR 0.19, 95% CI 0.01 to 3.82; 164 infants), neonatal mortality from early onset GBS infection (RR 0.31, 95% CI 0.01 to 7.50; 164 infants) or neonatal mortality from infections caused by bacteria other than GBS (RR 0.31, 95% CI 0.01 to 7.50; 164 infants).
- There was a statistically significant reduction in the incidence of early-onset (postnatal age <7 days) GBS neonatal infection (RR 0.17, 95% CI 0.04 to 0.74; 3 trials, 488 infants, number needed to treat to benefit = 25) and probable early infection (RR 0.17, 95% CI 0.03 to 0.91; 2 trials, 324 infants). There was no difference on the late onset (≥ 7 days) and GBS neonatal infection (RR 0.36, 95% CI 0.01 to 8.69; 2 trials, 289 infants).
- Analysis of the incidence of other neonatal infectious morbidities such as neonatal sepsis, meningitis, urinary tract infection or pneumonia due to bacterial organisms other than GBS showed no difference between the two comparison groups (RR 1.00, 95% CI 0.15 to 6.79; 2 trials, 289 infants).

Considerations related to the strength of the recommendation

Quality of the evidence

The quality of the evidence was graded as very low for all critical outcomes. Overall, the quality of the evidence was graded as very low.

Balance of benefits and harms

There is some evidence of reduced risk of early neonatal GBS sepsis, but with no reduction in all cause or GBS-related neonatal mortality. This lack of effect on neonatal mortality may be the result of the large size needed to demonstrate differences between the comparison groups. Available evidence was limited to three studies with relatively small sample sizes and largely at high risk of bias. In addition, most of the studies included in the review did not report on maternal or neonatal side-effects of the administration of antibiotics. Administration of antibiotics to all colonized women might expose mothers and newborns to potential side-effects of

antibiotics and contribute to antimicrobial resistance. The decision to recommend the administration of antibiotics to prevent GBS also needs to take into consideration other factors related to the incidence of GBS colonization, screening and transmission of GBS from the mother to the baby. GBS vaginal colonization rates vary between populations and are not always associated with clinical symptoms in the mother or the infant. In addition, the transmission rate of GBS from the mother to her baby is known to be very low.

The available evidence is insufficient to assess the balance of benefits and harms for subgroups of women who may be at a higher risk of transmission, such as women in preterm labour, women with ruptured membranes or those with a previous baby with neonatal GBS sepsis. The current evidence was derived from high-income countries, and it is possible that the baseline incidence of GBS colonization and neonatal transmission might confer higher clinical benefits for women treated with antibiotics during labour.

Values and preferences

Pregnant women in all settings are likely to place a high value on a reduced risk of perinatal transmission of GBS, and a low value on possible side-effects of prophylactic antibiotics. However, there is likely to be significant variability in the values and preferences of health care providers and policy-makers across settings in terms of the balance between the rate of perinatal transmission of neonatal GBS infection and the potential impact of antimicrobial resistance on public health.

Resource implications

The use of antibiotics during labour for GBS-colonized women is likely to slightly increase health care costs, particularly in settings where women are routinely screened during pregnancy and labour. However, the implementation of this recommendation is likely to result in cost savings related to the management of potential adverse outcomes (e.g. intensive care admission, prolonged hospital stay) among newborns born to GBS-colonized mothers.

RECOMMENDATION 6

Routine antibiotic prophylaxis during the second or third trimester to all women with the aim of reducing infectious morbidity is not recommended. (Strong recommendation based on very low-quality evidence)

REMARKS

- This recommendation applies to an unselected population of pregnant women in the second or third trimester of pregnancy.
- The GDG noted that prophylactic antibiotic use may be necessitated in a clearly defined group of women with high-risk pregnancy, but the description in the systematic review is inadequate to identify such a group.
- The GDG identified the evaluation of the effects of routine antibiotics in specific groups of women with high-risk pregnancy as a research priority.

Review question:

Among women in the second or third trimester of pregnancy (P), does routine antibiotic prophylaxis (I), compared with no antibiotic prophylaxis (C), prevent infectious morbidities and improve outcomes (O)?

Summary of evidence

- Evidence on the administration of prophylactic antibiotics to pregnant women during the second or third trimester for the prevention of infectious morbidities was extracted from a Cochrane systematic review of eight trials involving approximately 4300 women (3663 included in the analysis) (24).
- One trial each was conducted in Belgium, the Netherlands and Malawi, and two trials each in India and the USA. In addition, one single-country and one multicountry trial also included data from Kenya.
- Women in their second or third trimester of pregnancy (between 14 and 34 weeks of gestation) who were not in labour were eligible for inclusion in the trials. In three trials, women with high-risk pregnancies (defined variously as a history of preterm birth, low birthweight, stillbirth or early perinatal death, pre-pregnancy weight < 50 kg or previous preterm birth who had bacterial vaginosis diagnosis in current pregnancy). Women receiving antibiotics due to infection were excluded.

- Trials used a range of antibiotics and administration routes: oral cefetamet-pivoxil, cephalixin, metronidazole, azythromycin or erythromycin, intramuscular (IM) ceftriaxone or clindamycin vaginal cream.
- Subgroup analyses were performed on women who might be at higher risk of presenting with adverse outcomes. Authors defined high-risk women as those who had a previous spontaneous preterm delivery, history of low birthweight, a diagnosis of bacterial vaginosis in the current pregnancy (BV identified after enrolment and antibiotics used only for prophylaxis before knowing if the participant had BV or not) or a pre-pregnancy weight less than 50 kg.
- There were no data reported on side-effects of antibiotics, antimicrobial resistance or cost of care.

Prophylactic antibiotics versus placebo (EB Table 5)

- There was a significant reduction in postpartum endometritis (RR 0.53, 95% CI 0.35 to 0.82; 3 trials, 627 women) in the group receiving antibiotics compared to the placebo group, but no significant difference between groups regarding chorioamnionitis (RR 0.62, 95% CI 0.10 to 3.62; 1 trial, 229 women). A reduction was observed for prelabour rupture of membranes (RR 0.34 95% CI 0.15, 0.78; 1 trial, 229 women), but not for preterm prelabour rupture of membranes (RR 0.31 95% CI 0.06, 1.49; 1 trial, 229 women).
- There was no significant difference between groups for perinatal mortality (RR 0.83, 95% CI 0.57 to 1.20; 4 trials, 2710 infants).
- There was no significant difference between groups for preterm birth (RR 0.88 95% CI 0.72, 1.09; 6 trials, 3663 women), low birthweight (RR 0.86 95% CI 0.53, 1.39; 4 trials, 978 women) or mean birthweight (RR 41.60, 95% CI -78.20 to 161.40; 4 trials, 978 women).
- The included trials did not report any serious adverse effects of antibiotic prophylaxis.

Prophylactic antibiotics versus placebo: unselected pregnant women

- There were no significant reductions in the incidence of postpartum endometritis (RR 0.51 95% CI 0.24 to 1.08; 2 trials, 431 women) or chorioamnionitis (RR 0.62 95% CI 0.10 to 3.62; 1 trial, 229 women) among unselected women.
- There was no significant difference between groups on perinatal mortality (RR 0.84, 95%

CI 0.57 to 1.23; 2 trials, 2315 infants) among unselected women.

- There were no differences in the risk of low birthweight (RR 1.07; 95% CI 0.71 to 1.63; three trials, 725 women), small for gestational age (RR 1.29 95% CI 0.42 to 3.96; one trial, 229 women) or congenital anomalies (RR 1.49 95% CI 0.20 to 11.14; two trials, 463 women).

Prophylactic antibiotics versus placebo: high-risk women

- There was a significant reduction in postpartum endometritis in high-risk pregnant women (women with a history of preterm birth, low birthweight, stillbirth or early perinatal death) (RR 0.55; 95% CI 0.33 to 0.92; 1 trial, 196 women) and postpartum detected gonococcal infection (RR 0.35, 95% CI 0.13 to 0.94; 1 trial, 204 women) in the group receiving antibiotics compared to the placebo group.
- There were no differences between subgroups of high-risk pregnant women on preterm delivery, except in the subgroup of pregnant women with a previous preterm birth who had bacterial vaginosis during the current pregnancy (RR 0.64, 95% CI 0.47 to 0.88; 1 trial, 258 women, subgroup differences $P = 0.08$).
- There was no significant difference between groups on perinatal mortality among different high-risk groups (in women with a history of preterm birth, low birthweight, stillbirth or early perinatal death) (RR 0.53 95% CI 0.13 to 2.18; 1 trial, 253 infants) or in women with a history of preterm delivery alone (RR 3.08 95% CI 0.13 to 74.46; 1 trial, 142 women).
- The risk of low birthweight was reduced in the subgroup of high-risk women who received antibiotics compared to a placebo (RR 0.57; 95% CI 0.37 to 0.88; 1 trial, 253 women).
- There was no difference between control and intervention groups on neonatal sepsis (RR 11.31; 95% CI 0.64 to 200.79; 1 trial, 142 infants)

Considerations related to the strength of the recommendation

Quality of evidence

The quality of evidence was graded as very low for most critical outcomes. Overall, the quality of evidence was graded as very low.

Balance of benefits and harms

There is insufficient evidence to recommend the routine use of antibiotics during the second or third

trimester of pregnancy to reduce infectious morbidity or adverse outcomes. Evidence suggesting some clinical benefits was observed as a result of the inclusion of women with high-risk pregnancies, based on trials with limited study design and small sample sizes. In addition, this group was heterogeneous, and it was unclear from the data which of the included conditions accounted for the observed reduction in postpartum endometritis. No data were available to evaluate the potential side-effects or impact of prolonged antibiotic treatment of the mother or the newborn, including the development of antimicrobial resistance. In the light of the available evidence, potential benefits related to the use of antibiotics during pregnancy to prevent infectious morbidities do not appear to outweigh potential harms, particularly for women who are not carrying a high-risk pregnancy.

Values and preferences

Health care providers and policy-makers in all settings are likely to place a high value on the potential public health impact of administering antibiotics to an unselected population of women during their second or third trimester in the absence of evidence of any clinical benefits. Mothers will prefer to avoid the inconvenience and side-effects of antibiotic use. The panel is confident that there is no variation in this value among health care providers, policy-makers and mothers in low-, middle- and high-income settings.

Resource implications

Implementation of this recommendation is likely to significantly reduce health care costs in settings where low-risk obstetric populations are routinely provided with antibiotics during pregnancy. In the long term, adherence to this recommendation will prevent significant health care costs that might be required to combat bacterial resistance in both obstetric and the general populations.

RECOMMENDATION 7

Routine antibiotic administration is not recommended for women in preterm labour with intact amniotic membranes. (*Strong recommendation based on moderate-quality evidence*)

REMARKS

- This recommendation is in keeping with the WHO guideline on interventions to improve preterm birth outcomes (25).

- The GDG placed its emphasis on the potential risk of harm to the baby (i.e. cerebral palsy) and less value on the minimal benefit to mothers; therefore, it recommended against the intervention.
- It is critical for women with any diagnostic or clinical signs of infection to be treated accordingly with antibiotics.

Review question:

Among pregnant women in preterm labour with intact amniotic membranes (P), does routine antibiotic prophylaxis (I), compared with no routine antibiotic prophylaxis (C), prevent infectious morbidities and improve outcomes (O)?

Summary of evidence

- Evidence on the administration of prophylactic antibiotics to women in preterm labour with intact membranes for the prevention of maternal and neonatal infection was extracted from a Cochrane systematic review of 14 trials involving 7837 women (26).
- Trials were conducted in the 1990s in low-, middle- and high-income countries: six in the USA, and one each in Canada, Chile, Denmark, Germany, Iran, South Africa, the UK and Uruguay. All included trials used similar definitions of preterm labour, which included the presence of uterine contractions and cervical dilatation, with intact membranes. Trials included women with gestational ages between 20 and 36 weeks, with a mean of 30–32 weeks. However, the majority of the women gave birth at term. All trials excluded women with symptoms or signs suggestive of overt clinical infection of the mother or fetus. Four trials included women with multiple pregnancies.
- Use of tocolytics or antenatal steroids was part of the clinical protocol for the majority of the included trials (13 and 12 trials, respectively). Four of the seven trials reporting on GBS colonization reported intrapartum antibiotic administration for women with a positive GBS culture, in addition to the study drug. Only one trial reported on long-term follow-up of children.
- The intervention was oral or intravenous administration of antibiotics compared to either no treatment or a placebo. Antibiotic regimes varied between trials. Seven trials used only intravenous methods, three used only oral administration, and four combined the two sequentially. Ten trials used a combination of antibiotics. The duration of treatment varied between three and 10 days, with the majority of studies using courses of five to seven days.
- Trials did not report on maternal severe infectious morbidity, maternal death or antibiotic resistance.

Any antibiotics versus no antibiotics (or placebo) (EB Table 6)

- Women receiving antibiotics had significantly reduced rates of maternal infection, including chorioamnionitis/endometritis (RR 0.74, 95% CI 0.63 to 0.86, number needed to treat to benefit = 34, 95% CI 24 to 63; 10 trials, 7371 women). There was no significant difference between groups for adverse drug reaction requiring cessation of treatment (RR 1.32, 95% CI 0.92 to 1.89; 5 trials, 626 women).
- No statistically significant difference was found in perinatal mortality (RR 1.22, 95% CI 0.88 to 1.69; 10 trials, 7304 women) or stillbirths (RR 0.73, 95% CI 0.43 to 1.26; 8 trials, 7080 infants).
- There was a trend towards an increased risk of neonatal death among those receiving prophylactic antibiotics (RR 1.57, 95% CI 1.03 to 2.40; 9 trials, 7248 infants). There was no significant difference between groups on the need for mechanical ventilation (RR 1.02, 95% CI 0.84 to 1.24; 1 trial, 6241 infants); respiratory distress syndrome (RR 0.99, 95% CI 0.84 to 1.16; 9 trials, 7200 infants); neonatal positive blood culture (RR 1.01, 95% CI 0.69 to 1.49; 3 trials, 6526 infants); or neonatal sepsis (RR 0.86, 95% CI 0.64 to 1.16; 10 trials, 7386 infants) and other preterm-related morbidities such as intraventricular haemorrhage, major cerebral abnormality, necrotizing enterocolitis or chronic lung disease. No difference was found on admission to neonatal intensive care unit (NICU) or special care (RR 0.82, 95% CI 0.62 to 1.10; 5 trials, 6875 infants).
- One trial reported on outcomes at seven years of age and found no difference in infant deaths (RR 1.06, 95% CI 0.68 to 1.67; 4654 children), any functional impairment (RR 1.10, 95% CI 0.99 to 1.23; 3052 children) or moderate to severe impairment (RR 1.07, 95% CI 0.89 to 1.28; 3052 children). There was a trend towards an increased risk of cerebral palsy in the treated group (RR 1.82, 95% CI 0.99 to 3.34; 3173 children).

Considerations related to the strength of the recommendation

Quality of evidence

The evidence was graded from moderate to high. Overall, the quality of the evidence was graded as moderate.

Balance of benefits and harms

The potential harms as shown in the review, including neonatal deaths and cerebral palsy, in association with the use of routine antibiotic prophylaxis outweigh the clinical benefits of antibiotics in terms of reducing maternal infectious morbidity.

Values and preferences

Health care providers, policy-makers and pregnant women and their families in all settings are likely to place a high value on preterm survival without long-term morbidity, and less value on clinical benefits in terms of reducing maternal infection. The panel is confident that there is no variation of this value among mothers, health care providers or policy-makers in any setting.

Resource implications

Implementation of this recommendation is likely to reduce health care costs where routine antibiotic prophylaxis for women with preterm labour and intact membranes is currently the norm.

RECOMMENDATION 8

Antibiotic administration is recommended for women with preterm prelabour rupture of membranes. (*Strong recommendation based on moderate-quality evidence*)

REMARKS

- This recommendation is in keeping with the WHO guideline on interventions to improve preterm birth outcomes (25).
- For near-term (i.e. ≥ 36 weeks) PPROM where the clinical policy of immediate or early labour induction (within 12 hours of rupture) is in place, antibiotic use does not confer any benefit and should not be used (see *Recommendation 9* in this guideline).
- Erythromycin is recommended as the antibiotic of choice for prophylaxis in women with preterm prelabour rupture of membranes according to the *WHO recommendations on interventions to improve preterm birth outcomes* (25).

- To avoid inadvertent antibiotic administration to women with intact amniotic membranes, antibiotics should not be prescribed unless a definite diagnosis of PPROM has been made. Therefore, a policy to prescribe antibiotics for women with PPROM should be accompanied by a protocol to reliably diagnose PPROM.
- Long latent phase (interval between rupture of membranes and onset of preterm labour) could predispose to intrauterine infection. Therefore, women should be closely monitored for signs of clinical chorioamnionitis.

Review question:

Among pregnant women with preterm prelabour rupture of membranes (PPROM) (P), does routine antibiotic prophylaxis (I), compared with no routine antibiotic prophylaxis (C), prevent infectious morbidities and improve outcomes (O)?

Summary of evidence

- Evidence for routine administration of prophylactic antibiotics to women with PPROM was extracted from a Cochrane systematic review of 22 trials involving 6872 women (27).
- The majority of the trials included in the review were conducted in high-income countries: 14 in the USA, and one each in Finland, Germany and Spain. One trial was conducted in Turkey, one in Zimbabwe and one multi-country trial in Chile and the USA. Results on short- and long-term outcomes were dominated by one trial conducted in the UK. Trials were conducted in the 1990s and early 2000s.
- Women were recruited between 20 and 37 weeks of gestation. Clinical definitions and methods for diagnosis of PPROM varied between trials. The majority of the women were not in active labour.
- Included trials compared different antibiotic regimens with placebo, other antibiotic class or no treatment, using different routes of administration (oral alone, intravenous alone or a combination).

Any prophylactic antibiotics versus placebo (all women and babies) (EB Table 7)

- Sixteen trials compared any antibiotic with placebo and randomized 6300 women. These trials tested a broad spectrum of penicillins, beta-lactam, macrolide (erythromycin) and other antibiotics (clindamycin, gentamycin) either alone or in combination.

- There was a statistically significant reduction in chorioamnionitis (RR 0.66, 95% CI 0.46 to 0.96; 11 trials, 1559 women).
- There was no difference in perinatal deaths for all antibiotic comparisons (RR 0.93, 95% CI 0.76 to 1.14; 12 trials, 6301 infants), but there was a significant reduction in neonatal infections, including pneumonia, for all antibiotic comparisons (for any antibiotics (RR 0.67, 95% CI 0.52 to 0.85; 12 trials, 1680 infants), all penicillins, excluding co-amoxiclav (RR 0.81, 95% CI 0.68 to 0.98; five trials, 521 infants), and other antibiotics (RR 0.71, 95% CI 0.53 to 0.95; 3 trials, 763 infants)). There was a significant reduction in the number of positive neonatal blood culture (RR 0.79, 95% CI 0.63 to 0.99; 3 trials, 4961 infants).
- There was a significant reduction in the number of infants receiving surfactant (RR 0.83, 95% CI 0.72 to 0.96; 1 trial, 4809 infants), of infants requiring oxygen therapy (RR 0.88, 95% CI 0.81 to 0.96, 1 trial, 4809 infants) and of infants with abnormal cerebral ultrasound scans before discharge (RR 0.81, 95% CI 0.68 to 0.98; 12 trials, 6289 infants) in the treated group compared with placebo. The duration of NICU admission was shorter in the treated group than in the placebo group (mean difference (MD) -5.05 days, 95% CI -9.77 to -0.33; 3 trials, 255 infants).
- No differences were observed for neonatal respiratory distress syndrome (RR 0.95, 95% CI 0.83 to 1.09, 12 studies, 6287 infants), the number of babies requiring ventilation (RR 0.90, 95% CI 0.80 to 1.02, 2 studies, 4924 infants), neonatal oxygenation > 28 days (RR 0.79, 95% CI 0.61 to 1.03, 3 studies, 5487 infants) or necrotizing enterocolitis (RR 1.09, 95% CI 0.65 to 1.83, 6229 infants). However, the incidence of necrotizing enterocolitis appeared to be increased only with the use of beta-lactam antibiotics (including co-amoxiclav) (RR 4.72, 95% CI 1.57 to 14.23; 2 trials, 1880 infants).
- Regarding long-term outcomes, one trial showed that antibiotics seemed to have little effect on serious childhood disability at seven years (RR 1.01, 95% CI 0.91 to 1.12; 3171 children).
- Maternal deaths, serious maternal morbidities, puerperal sepsis, neonatal encephalopathy, major adverse drug reactions or antibiotic resistance were not reported.

Considerations related to the strength of the recommendation

Quality of evidence

The quality of evidence was graded from moderate to high for all outcomes. Overall, the quality of the evidence was graded as moderate.

Balance of benefits and harms

Compared with placebo, antibiotics for PPROM reduced the risk of chorioamnionitis in the mother. Antibiotics also reduced the risk of neonatal infections, including pneumonia, and cerebral abnormality, and were associated with a shorter stay in neonatal intensive care. On the other hand, antibiotics did not appear to have an impact on other infant mortality or severe morbidity or on longer-term outcomes. Overall, there are desirable short-term benefits for the mother and preterm infants without evidence of harms on short- or long-term.

Values and preferences

Health care providers, policy-makers and pregnant women and their families in all settings are likely to place a high value on the benefits of short-term outcomes for the mother and infant (reduction in maternal and neonatal infection). The panel is confident that there is no variation of this value among mothers, health care providers and policy-makers in any setting.

Resource implications

Antibiotics are widely available in both oral and parenteral forms in all settings. It is feasible to include prophylactic antibiotic therapy into existing health structures that are designed to manage women at risk of imminent preterm birth with minimal costs.

RECOMMENDATION 9

Routine antibiotic administration is not recommended for women with prelabour rupture of membranes at (or near) term. (*Strong recommendation based on low-quality evidence*)

REMARKS

- "Routine" use implies administration of antibiotics in the absence of clinical signs of infection or any additional risk factors for infection.
- "Near term" in this context refers to 36 weeks gestation and above.

(Continued)

- Evidence for this recommendation was based on studies that included women with duration of ruptured membranes less than 12 hours. The GDG noted that while the available evidence clearly indicates that antibiotics do not confer any benefits under a clinical policy of immediate or early induction (within 12 hours of rupture), it is less clear for a policy of expectant or delayed induction longer than this timeframe. Nevertheless, the generally low rate of maternal infection in the control population in the included studies (< 5%) further supports the restriction of antibiotic use to women with PROM and clinical evidence of infections.
- The GDG noted that evidence is lacking on the potential benefits of antibiotic prophylaxis for women with prolonged rupture of membranes (> 18 hours) and active labour where the baseline risk of infection may be higher. As the risk of infection increases with the duration of labour, it is possible that women with prolonged labour and ruptured membranes may benefit from antibiotic prophylaxis, and this underlies the common clinical practice. The group acknowledges that in the light of current obstetric practice, it is unlikely that a randomized controlled trial will address the important question on the effect of antibiotic prophylaxis in prolonged prelabour rupture of membranes at term (> 12 hours) or prolonged labour with ruptured membranes.
- The GDG put its emphasis on potential side-effects of antibiotics, particularly long-term effects among exposed children, as well as bacterial resistance and, therefore, made a strong recommendation.

Review question:

Among pregnant women with prelabour rupture of membranes at or near term (P), does routine antibiotic prophylaxis (I), compared with no routine antibiotic prophylaxis (C), prevent infectious morbidities and improve outcomes (O)?

Summary of evidence

- Evidence on the use of prophylactic antibiotics for women with prelabour rupture of membranes (PROM) at 36 weeks gestation or beyond for preventing infectious morbidities was extracted from a Cochrane systematic review of four trials involving 2639 women (28).
 - The trials were conducted in Chile, Egypt, Portugal and Spain.
 - Gestational age inclusion criteria varied slightly between trials (≥ 36 weeks in two trials and ≥ 37 weeks in two trials). All studies excluded women with multiple pregnancy and major obstetric complications. All studies used consistent criteria for diagnosis of membrane rupture and had protocols that attempted to minimize vaginal examinations. Pregnancy management protocols varied slightly between settings, mainly for induction policies.
 - The trials did not report on antibiotic side-effects and antibiotic resistance.
- Any antibiotic versus placebo or no antibiotic (all women) (EB Table 8a)**
- Two trials compared antibiotics with placebo, and two other trials compared antibiotics versus no treatment. All trials compared different antibiotics and routes of administration. Two trials tested IV ampicillin with IV or IM gentamycin, one trial tested parenteral ampicillin/sulbactam, and one trial intravenous cefuroxime and clindamycin for 48 hours then oral cefuroxime and clindamycin for a further 24 hours.
 - There were no significant differences between groups for maternal infectious morbidities: suspected or proven chorioamnionitis (RR 0.65, 95% CI 0.34 to 1.26; 4 trials, 2639 women), endometritis (RR 0.34, 95% CI 0.05 to 2.31; 4 trials, 2639 women) or wound infection (RR 0.79, 95% CI 0.36 to 1.72; 3 trials, 1906 women). Data on postpartum pyrexia had high levels of heterogeneity ($I^2 = 93\%$) and were presented separately for two trials (RR 0.97, 95% CI 0.58 to 1.61; RR 0.11, 95% CI 0.01 to 0.88). There was no difference in reported maternal adverse effects (RR 2.93 95% CI 0.12 to 71.63; 4 trials, 2639 women). There were no cases of serious maternal outcome, postpartum septicaemia or maternal deaths reported in any of the trials.
 - There was no significant difference between groups in perinatal mortality (RR 1.98, 95% CI 0.60 to 6.55; 4 trials, 2639 infants), though two studies had no cases. Furthermore, no difference in stillbirth was shown when comparing antibiotics with placebo or no antibiotics (RR 3.00, 95% CI 0.61 to 14.82; 3 trials, 1906 infants). There were no cases of neonatal mortality in the three trials reporting this outcome (1906 infants).
 - There was no significant difference in probable early-onset neonatal sepsis (RR 0.69, 95% CI 0.21 to 2.33; 4 trials, 2639 babies) or definite

early-onset neonatal sepsis (RR 0.57, 95% CI 0.08 to 4.2; 4 trials, 2639 babies). There were no significant differences for neonatal meningitis (RR 0.33, 95% CI 0.03 to 3.11; 4 trials, 2639 infants), neonatal pneumonia (RR 0.33, 95% CI 0.01 to 7.96; 4 trials, 2639 infants), admission to NICU (RR 1.23, 95% CI 0.82 to 1.85; 3 trials, 1906 infants) or length of hospitalization in NICU (MD 0.05 days, 95% CI -0.09 to 0.19; 1 trial, 1640 infants). There were no cases of respiratory distress syndrome in two studies.

Antibiotics versus no antibiotics: by timing of induction of labour (EB Table 8b)

- Three trials involving 2478 women were included in the subgroup analysis of timing of induction of labour
- There was no significant difference between comparison groups for early (< 12 hr) or late (≥ 12 hr) induction subgroups with respect to chorioamnionitis and/or endometritis (early induction: RR 1.15, 95% CI 0.64 to 2.08; 1 trial, 1640 women; late induction: RR 0.34, 95% CI 0.08 to 1.47; 2 trials, 838 women).
- No significant differences were found between comparison groups in the subgroups for perinatal mortality (early induction: RR 3.00, 95% CI 0.61 to 14.82; 1 trial, 1640 infants; late induction: RR 0.98, 95% CI 0.14 to 6.89; 2 trials, 838 infants). Data on stillbirths were only available for the early induction subgroup, for which no statistically significant difference was found (RR 3.00, 95% CI 0.61 to 14.82; 1 trial, 1630 women).
- There were no significant differences between comparison groups in the two subgroups with respect to neonatal mortality.

Considerations related to the strength of the recommendation

Quality of evidence

The quality of evidence was low for the majority of critical outcomes in the main comparison. For the subgroup analysis, the quality of evidence was moderate to low for critical outcomes reported for the early induction subgroup and very low for all late induction subgroups. The overall quality of evidence was based on the main comparison (i.e. all women) and, therefore, was graded as low.

Balance of benefits and harms

There is no convincing evidence of benefits for the mothers or neonates from the routine administration of antibiotics to women with PROM at or near term. Severe maternal and neonatal morbidity or deaths

were infrequent in both the intervention and the control groups. Early or late induction of labour to expedite birth does not seem to affect maternal and neonatal infection outcomes. There were no data to assess the risk of short- and long-term harms of routine antibiotic use, particularly with respect to the development of antibiotic resistance. Although the evidence is limited to women with singleton pregnancies, there is no reason to suggest that the findings would be different for women with multiple pregnancies.

Values and preferences

Health care providers and policy-makers are likely to place a high value on the potential impact of antibiotic use on antibiotic resistance, and, in the absence of evidence of effectiveness, would chose not to use the intervention. The panel is confident that there is no variation in this value across settings.

Resource implications

Implementation of this recommendation is likely to reduce health care costs in settings where routine antibiotics prophylaxis for all cases of ruptured amniotic membranes is currently the norm.

RECOMMENDATION 10
<p>Routine antibiotic administration is not recommended for women with meconium-stained amniotic fluid. <i>(Conditional recommendation based on low-quality evidence)</i></p>
REMARKS
<ul style="list-style-type: none"> ■ In the absence of convincing evidence, the GDG puts its emphasis on the public health impact of routine administration of antibiotics (in terms of increasing antibiotic resistance) for a relatively common condition in labour and decided to recommend against the intervention. ■ Antibiotics should be used in a situation where the passage of meconium by the fetus may be triggered by antepartum or intrapartum infectious morbidity – e.g. chorioamnionitis — or when the characteristics of the liquor suggest intrapartum infection. ■ It is important that a personnel experienced in neonatal resuscitation attends the delivery of all infants in whom thick meconium liquor is noted, as the risk of meconium aspiration syndrome is higher in this situation.

Review question:

Among pregnant women with meconium-stained amniotic fluid during labour (P), does routine administration of antibiotics (I), compared with no routine antibiotics (C), prevent infectious morbidities and improve outcomes (O)?

Summary of evidence

- Evidence for the routine use of prophylactic antibiotics among women presenting with meconium-stained amniotic fluid during labour was extracted from a Cochrane systematic review of two trials involving 362 women (29). The two trials were led by the same investigator. One trial was reported only as a conference abstract with little methodological detail.
- Both trials were conducted in the USA. The trials excluded women with evidence of active infection or allergy to penicillin and/or cephalosporin.
- The two trials compared 3 g of intravenous ampicillin-sulbactam (one trial repeated every six hours until delivery) with intravenous normal saline as placebo.

Antibiotics versus placebo or no treatment (EB Table 9)

- The incidence of chorioamnionitis was significantly reduced in the treated group compared with placebo (RR 0.36, 95% CI 0.21 to 0.62; 2 trials, 362 women), but no difference was observed in the incidence of postpartum endometritis (RR 0.5, 95% CI 0.18 to 1.38; 1 trial, 120 women).
- No difference was found in the incidence of neonatal sepsis (RR 1.00, 95% CI 0.21 to 4.76; 1 trial, 120 infants) or NICU admission (RR 0.83, 95% CI 0.18 to 1.38; 1 trial, 120 infants).
- No serious adverse effects were reported.
- The trials did not report on maternal severe infectious morbidities, maternal or neonatal mortality, or antibiotic resistance.

Considerations related to the strength of the recommendation**Quality of evidence**

The quality of evidence was graded as low for all outcomes except chorioamnionitis, which was moderate in quality. Overall, the quality of evidence was graded as low.

Balance of benefits and harms

Available evidence from trials included in the review is insufficient to support the use of prophylactic antibiotics in preventing maternal and neonatal infectious morbidities among women presenting with meconium-stained amniotic fluid during labour. Antibiotic appears to reduce the risk of chorioamnionitis but has no effect on neonatal outcomes. Data on postpartum endometritis was too small to support or refute the findings regarding chorioamnionitis. Overall, the evidence should be interpreted with caution due to its low quality and the small sample size. In the absence of clear evidence of clinical benefits, the potential risks to public health of routinely administering antibiotics for a relatively common condition during labour outweigh the potential benefits.

Values and preferences

Health care providers and policy-makers are likely to place a high value on the potential impact of antibiotic use on emerging antibiotic resistance, and, in the absence of convincing evidence of effectiveness, would choose not to use the intervention. The panel is confident that there is no variation in this value across settings.

Resource implications

Implementation of this recommendation is likely to reduce health care costs in settings where routine antibiotic prophylaxis for women with meconium-stained liquor during labour is currently the policy.

RECOMMENDATION 11

Routine antibiotic prophylaxis is recommended for women undergoing manual removal of the placenta. (*Strong recommendation based on very low-quality evidence*)

REMARKS

- Although there is no clear indication of benefits from the available evidence, the GDG decided to recommend prophylactic antibiotic use for this condition based on consensus after considering the potentially higher risk of infection related to the invasive nature of intrauterine manipulation required for manual placental removal. The group also considered indirect evidence of the benefit of prophylactic antibiotics from studies of caesarean section and abortion, as well as observational studies of other intrauterine manipulations.

- This recommendation is based on updated evidence and is consistent with existing WHO guidance on the treatment of postpartum haemorrhage which recommends a single dose of antibiotics (ampicillin or first-generation cephalosporin) for manual placental removal (30).
- In addition to antibiotic use, health care providers should take into account other factors that could decrease the risk of infection, such as observing good hygiene and general aseptic technique during the procedure and prevention or treatment of anaemia in the woman.
- This question was considered a research priority for settings in which prophylactic antibiotics are not routinely administered and those where the baseline risk of infectious morbidity is low. However, the GDG acknowledged that conducting a randomized trial may be challenging given the current clinical practice.

Review question:

Among women undergoing manual removal of retained placenta following vaginal birth (P), does antibiotic prophylaxis (I), compared with no antibiotic prophylaxis (C), prevent infectious morbidities and improve outcomes (O)?

Summary of evidence

- An updated Cochrane review that evaluated this question did not find any eligible randomized controlled trial to include (31). Evidence was extracted from a systematic review of non-randomized studies which included three retrospective cohort studies of 567 women (32). This review considered only women undergoing vaginal deliveries and excluded women with prior history of fever.
- The studies were conducted in Germany, Norway and Bulgaria, and all compared outcomes among women receiving antibiotic prophylaxis with no intervention.
- Only two critical outcomes (endometritis and puerperal fever > 37.5 °C, > 24 hours) were reported.

Antibiotic prophylaxis versus no treatment (EB Table 10)

- Compared with no antibiotic prophylaxis, antibiotic prophylaxis was not associated with significant differences in the number of women with puerperal fever [odds ratio (OR) 0.93, 95% CI 0.38 to 2.27; 1 study, 302 women] or endometritis (OR 0.84 95% CI 0.38 to 1.85; 3 studies, 567 women).

Considerations related to the strength of the recommendation

Quality of evidence

The overall quality of evidence was graded as very low.

Balance of benefits and harms revise wording

There is no evidence from randomized controlled trials to determine the effect of antibiotic use prior to manual placental removal on infectious morbidities. Low-quality evidence from observational studies in high-income countries also shows inconclusive evidence of benefits, although the odds of endometritis and puerperal fever were reduced when antibiotics were used. There was no information about potential harms of the intervention. The effect of routine use of antibiotics on antibiotic resistance is likely to be insignificant considering the very low incidence of manual removal of the placenta in women giving birth.

Values and preferences

Health care providers and policy-makers in low-income settings (where the baseline risk of infectious morbidity is high) are likely to place a high value on the potential clinical benefits of antibiotic use for an intrauterine manoeuvre and would chose to adhere to the recommendation. The panel acknowledged that there might be variation in this value in high-income settings where infection control standard is high.

Resource implications

Implementation of this recommendation is likely to require additional costs for antibiotics. However, these added costs are justified by cost savings for treatment of severe infectious morbidities that could result from an invasive intrauterine manipulation.

RECOMMENDATION 12

Routine antibiotic prophylaxis is not recommended for women undergoing operative vaginal birth. (Conditional recommendation based on very low-quality evidence)

REMARKS

- "Operative vaginal birth" is the term used to describe delivery of the fetal head assisted by either vacuum extractor or forceps.
- Prophylactic antibiotics may be useful for other maternal conditions that could result from prolonged second stage of labour or the use of an instrument for vaginal birth (e.g. third- or fourth-degree perineal tear).

Review question:

Among women undergoing operative vaginal birth (P), does routine antibiotic prophylaxis (I), compared with no prophylaxis (C), prevent infectious morbidities and improve outcomes (O)?

Summary of evidence

- Evidence regarding the routine administration of prophylactic antibiotics to women undergoing operative vaginal birth (vacuum or forceps) was extracted from a Cochrane systematic review (33). Only one trial with a sample size of 393 women reported on critical outcomes. The trial was conducted in the USA. Women with evidence of other inflammatory infections or allergies to penicillin class of drugs were excluded.
- The evidence was supplemented with another systematic review of non-randomized studies which included three retrospective cohort studies of 1293 women (34). Two of the studies were performed in Germany, and one in France.

Antibiotic prophylaxis versus no treatment (randomized controlled trials) (EB Table 11a)

- The trial investigated the use of 2 g of cefotetan intravenously after umbilical cord clamping versus no treatment in women undergoing instrumental deliveries.
- The trial found no differences between the treatment and control groups regarding the incidence of endomyometritis (RR 0.07; 95% CI 0.00 to 1.21) or length of maternal hospital stay (MD 0.09 days; 95% CI -0.23 to 0.41).
- The included trial did not report any other critical outcomes.

Antibiotic prophylaxis versus no treatment (non-randomized studies) (EB Table 11b)

- Prophylactic antibiotic regimes varied between studies. One study used 4 g ampicillin or 4 g cephalexin or cefalotin, administered for at least five days. One study used 1 g of clomoxyl administered intravenously during an intrauterine procedure or during umbilical cord clamping and repeated two and six hours later plus 0.5 g of ornidazole. One study used mebacid sulfamerazine or 2 g chloramphenicol daily for six to 10 days.
- There were no differences between the treated and untreated group in the incidence of endometritis (OR 0.67; 95% CI 0.07 to 6.04; 2 studies, 1091 women), maternal septicaemia (OR 0.32; 95% CI 0.01 to 7.90, 1 study, 336 women) or wound infection (episiotomy abscess) (OR 0.35; 95% CI 0.06 to 2.06; 2 studies, 540 women).

Considerations related to the strength of the recommendation**Quality of the evidence**

Overall, the quality of evidence from both sources was graded as very low.

Balance of benefits and harms

There is low-quality evidence to suggest that antibiotic prophylaxis does not reduce the risk of maternal infections after operative vaginal birth. Neonatal outcomes were not reported in the studies included in the reviews.

Values and preferences

Health care providers and policy-makers are likely to place a high value on the potential impact of antibiotic use on antibiotic resistance, and, in the absence of evidence of effectiveness, would choose not to use the intervention. The panel is confident that there is no variation in this value across settings.

Resource implications

Implementation of this recommendation is likely to reduce additional costs for antibiotics where routine use of antibiotics for all operative births is an established practice.

RECOMMENDATION 13

Routine antibiotic prophylaxis is recommended for women with third- or fourth-degree perineal tear. (*Strong recommendation based on very low-quality evidence*)

REMARKS

- Despite the insufficient evidence of benefits, the GDG agreed that women with third- or fourth-degree perineal tear are at higher risk of infection in the postpartum period and took a consensus view to recommend the routine use of antibiotic prophylaxis for these conditions. The group puts its emphasis on the reduction in wound infection which might aggravate long-term consequences of third- or fourth-degree perineal tears (e.g. involuntary loss of flatus and/or faeces which affects quality of life) and, therefore, made a strong recommendation.
- This recommendation is consistent with the WHO postnatal care guideline on treatment of third- or fourth-degree perineal tears (35).
- The GDG acknowledged that antibiotic administration following third- or fourth-degree tears is already a common clinical practice and, therefore, did not consider the question a research priority.

Review question:

Among women with third- or fourth-degree perineal tear after birth (P), does routine antibiotic prophylaxis (I), compared with no antibiotic prophylaxis (C), prevent maternal infectious morbidities and improve outcomes (O)?

Summary of evidence

- Evidence on the effectiveness and safety of routine administration of prophylactic antibiotics post-delivery to women with third- or fourth-degree perineal tear was extracted from a Cochrane systematic review that included only one trial with 147 women (36).
- The trial was conducted in the USA. Women who were less than 18 years of age, GBS- or HIV-positive, had chorioamnionitis, history of inflammatory bowel disease or were already on antibiotics at the moment of inclusion were excluded from the study. The trial planned to recruit 310 women but was terminated early because of its inability to achieve the sample size within a reasonable time period. The rate of loss to

follow-up at two and six weeks following discharge among women who participated in the trial was 27.2%.

- Women in the treatment arm received a single dose of second-generation cephalosporin (cefotetan, cefoxitin or penicillin, or clindamycin if allergic to penicillin), while those in the control arm received placebo. In both groups, wound disruption or purulent discharge of the perineum after repair was assessed at two and six weeks postpartum.

Antibiotic prophylaxis versus placebo (EB Table 12)

- The trial showed a significant reduction in the number of women who had wound infection two weeks after delivery (RR 0.34, 95% CI 0.12 to 0.96; 107 women). However, there was no difference between the groups at six weeks after delivery (RR 0.38, 95% CI 0.13 to 1.09; 128 women).
- The trial did not report on severe maternal infectious morbidity, puerperal sepsis, local discomfort, sexual dysfunction, duration of hospital stay, side-effects of antibiotics or antibiotic resistance.

Considerations related to the strength of the recommendation

Quality of evidence

Overall, the quality of evidence was graded as very low.

Balance of benefits and harms

The available evidence is insufficient to conclude on the clinical benefits of routine administration of prophylactic antibiotics in women with third- or fourth-degree perineal tear postpartum. The small sample size and high dropout rate limits the quality of the evidence. However, there is indirect evidence of benefit for prophylactic antibiotics from potentially contaminated wounds (considering the bacteria flora in the rectum) in surgical practice, and it would be reasonable to use antibiotics to reduce the risk of infection.

Values and preferences

Health care providers and policy-makers are likely to place a high value on the potential impact of antibiotic use on preventing wound complications and long-term consequences of poorly healed severe perineal tears. The panel is confident that there is no variation in this value across settings.

Resource implications

Implementation of this recommendation is likely to minimally increase health care costs (for antibiotics) where routine antibiotic use is not the current practice. However, these added costs are justified by cost savings for treatment of long-term morbidities (e.g. poor quality of life) of obstetric anal sphincter injuries when they are complicated by perineal infections.

RECOMMENDATION 14

Routine antibiotic prophylaxis is not recommended for women with episiotomy.

(Strong recommendation based on consensus view)

REMARKS

- The above recommendation was based on a consensus of the GDG in view of a high rate of episiotomy and the potential impact of antibiotics, in the absence of clinical benefits on public health. The GDG puts its emphasis on avoidance of emerging antimicrobial resistance at the global level and, therefore, made a strong recommendation.
- This recommendation applies to the use of antibiotics before or immediately after episiotomy repair following vaginal birth. Antibiotics should be administered when there are clinical signs of infection of an episiotomy wound.
- The GDG emphasized the need for health systems to adopt a policy of restrictive rather than routine use of episiotomy to reduce its potential complications and the use of additional resources for its treatment.
- Second-degree perineal tear is anatomically similar to an episiotomy and does not warrant the use of prophylactic antibiotics.
- In a situation where an episiotomy wound extends to become a third- or fourth-degree perineal tear, prophylactic antibiotics should be administered as recommended in this guideline (see *Recommendation 13*).

Review question:

Among women who had an episiotomy for vaginal birth (P), does routine antibiotic prophylaxis (I), compared with no routine antibiotic prophylaxis (C), prevent maternal infectious morbidities and improve outcomes (O)?

Summary of evidence

- A systematic review was conducted to evaluate the effectiveness of antibiotic prophylaxis on infectious morbidity following episiotomy in women giving vaginal birth. Based on a pre-specified protocol, a detailed search was conducted in MEDLINE, EMBASE, CENTRAL and the CINAHL databases for randomized and non-randomized studies that addressed these questions. Of the 831 citations generated by these search strategies, 38 full-text articles were retrieved for further assessment. None of these studies met the inclusion criteria for this review (37).

Considerations related to the strength of the recommendation

Quality of evidence

There is no direct evidence on the impact of antibiotics on infectious morbidity in women with episiotomy.

Balance of benefits and harms

There is a complete lack of evidence from randomized trials and observational studies to determine the benefit or harm of routine administration of antibiotics to women who receive an episiotomy for vaginal birth. Carefully performed episiotomies generally have a low rate of infection in settings where infection control measures are well observed. The relatively high global episiotomy rates (> 50%) means that many mothers will be exposed to antibiotics without clear evidence of benefit but a huge impact on public health in terms of emerging antimicrobial resistance.

Values and preferences

Health care providers and policy-makers in all settings are likely to place a high value on the potential public health impact of administering antibiotics to large proportion of women giving birth, in the absence of evidence of any clinical benefits. Mothers will prefer to avoid the inconvenience and side-effects of antibiotic use. The panel is confident that there is no variation in this value among health care providers, policy-makers and mothers in low-, middle- and high-income settings.

Resource implications

The implementation of this recommendation is likely to save considerable health system costs in view of the high rate of episiotomy worldwide and the widespread use of prophylactic antibiotics in women with episiotomy.

RECOMMENDATION 15

Routine antibiotic prophylaxis is not recommended for women with uncomplicated vaginal birth. (Strong recommendation based on very low-quality evidence)

REMARKS

- The GDG was concerned about the potential public health implication of the high rate of routine use of antibiotics following vaginal birth without any specific risk factors in some settings. The group puts its emphasis on the negative impact of such policy on the global efforts to contain antimicrobial resistance and, therefore, made a strong recommendation against routine antibiotic prophylaxis.
- “Uncomplicated vaginal birth” in this context connotes vaginal birth in the absence of any specific risk factor for or clinical signs of maternal peripartum infection.
- Careful monitoring of all women after birth is essential to promptly identify any sign of endometritis and institute appropriate antibiotic treatment (see *Recommendation 20*).
- Recommendations on antibiotic use for common intrapartum conditions or interventions that often raise concerns about increased risk of infection are available in this guideline.

Review question:

Among pregnant women with uncomplicated vaginal birth (P), does antibiotic prophylaxis after birth (I), compared with no prophylaxis or placebo (C) prevent infectious morbidities and improve outcomes (O)?

Summary of evidence

- Evidence on the impact of antibiotic prophylaxis in women with uncomplicated (“normal”) vaginal birth was extracted from a systematic review which identified two eligible randomized controlled trials involving 1653 women (38). The two trials compared antibiotic prophylaxis with no prophylaxis. The trials were conducted in France and Japan.
- One of the trials described women with “uncomplicated vaginal birth” as those who had vaginal delivery, no fever ($> 38^{\circ}\text{C}$) during labour or the hour following delivery, an interval of < 24 hours between rupture of membranes and labour onset, no evidence of extragenital infection (e.g.

urinary tract infection) and no known allergy to Amox-CA or betalactam. The study excluded women with evidence of amniotic fluid infection at the time of admission. The second trial excluded women with a history of hypersensitivity to the tested antibiotics (cefteram or cephem), fourth-degree perineal lacerations, birth after PROM at term, underlying medical conditions such as gestational hypertension and diabetes mellitus and at the discretion of the physician.

- One trial used a single dose of Amox-CA 1 g intravenously, while the other trial used oral 300 mg cefteram pivotal for three or five days.
- In terms of outcomes, one of the trials used clinical and/or laboratory criteria for diagnosing endometritis: pyrexia $> 38^{\circ}\text{C}$ confirmed on two separate occasions and accompanied by pain on mobilizing the uterus and/or fetid lochia, and/or leucocytosis of more than $10\,000/\text{mm}^3$. The other trial used only clinical criteria that included the occurrence of “fever more than 37°C for more than two days, or infected lochia, or low abdominal pain detected and diagnosed by the doctor in charge, after 24 hours from birth”.

Antibiotic prophylaxis versus no prophylaxis/ placebo (EB Table 13)

- Women receiving antibiotic prophylaxis after uncomplicated vaginal birth experienced significantly reduced incidence of endometritis (RR 0.26, 95% CI 0.09 to 0.73; 2 trials, 1653 women). However, no statistically significant difference was observed in the risks of puerperal fever (RR 0.26, 95% CI 0.02 to 3.97, 2 trials, 1653 women), wound infection (RR 0.80, 95% CI 0.07 to 8.68; 1 trial, 362 women), urinary tract infection (RR 0.51, 95% CI 0.18 to 1.45; 1 trial, 1291 women) and duration of hospital stay (MD -0.15 days, 95% CI -0.31 to 0.01; 1 trial, 1291 women).
- All other outcomes reported in the review were not prespecified as critical outcomes for this recommendation question.

Considerations related to the strength of evidence

Quality of evidence

The quality of evidence was graded as very low for four out of the five critical outcomes reported. Overall the quality of evidence was graded as very low.

Balance of benefits and harms

There is very low-quality evidence of clinical benefit in terms of reduction in postpartum endometritis in women who received antibiotics following

uncomplicated vaginal birth. No clinical benefits were observed for other critical outcomes. The studies contributing data to the endometritis outcome were at high risk of bias because of lack of blinding, given that the diagnosis of endometritis in the studies was in part subjective.

Additionally, fever, a more objective measure, which was also included as part of the diagnosis of endometritis, was not different between intervention and control arms of the trial. The incidence of postpartum endometritis in the control population of the studies was 2.2%, suggesting that only a small proportion of women were at risk of endometritis. The number needed to treat to benefit (i.e. to avoid one case of endometritis) is 58. In view of the very low rate of endometritis and the fact that endometritis in itself is more of an early sign of severe pelvic infection when left untreated, unnecessary exposure of about 98% of women who are unlikely to develop this condition will negatively impact on public health in terms of increasing antimicrobial resistance.

Values and preferences

Health care providers and policy-makers in all settings are likely to place a high value on the potential negative public health impact of administering antibiotics to a very large proportion of women giving birth who are unlikely to develop peripartum infection. Mothers will also prefer to avoid the inconvenience and side-effects of antibiotic use. The panel is confident that there is no variation in this value among health care providers, policy-makers and mothers in low-, middle- and high-income settings.

Resource implications

The implementation of this recommendation is likely to save health care costs in settings where antibiotics are routinely given to women with uncomplicated vaginal birth. Additionally, adherence to this recommendation could potentially contribute to significant reduction in health care costs related to combating antimicrobial resistance in the larger population.

RECOMMENDATION 16

Vaginal cleansing with povidone-iodine immediately before caesarean section is recommended. (*Conditional recommendation based on moderate-quality evidence*)

REMARKS

- The recommendation of the use of povidone-iodine out of the common antiseptics was because it was the only agent tested in all randomized controlled trials that evaluated the review question.
- The GDG noted that the main clinical benefit (reduction in post-caesarean endometritis) demonstrated in the review was largely driven by women at higher baseline risk of infections (i.e. those who were already in labour and those with ruptured membranes). However, in consideration of the similarity in the statistical findings between subgroups and the entire study population, the group acknowledged that women at lower baseline risk of infection are also likely to benefit from the intervention.
- Due to the staining of surrounding tissues, vaginal cleansing in this context may be regarded as a potentially invasive procedure, and implementation might not be easy.
- The GDG considers further evaluation of the benefits in high-risk women and potential adverse effects (especially among women with ruptured membranes and those planning to breastfeed) a research priority. Additionally, the group considers it essential to identify the most appropriate timing of the intervention to achieve benefit with minimal harm and whether other antiseptic agents (e.g. chlorhexidine) have similar beneficial effects. The group noted that shorter application and contact time are likely to be associated with less maternal and fetal exposure. Therefore, the group suggested vaginal application of povidone-iodine very close to the start of caesarean section (e.g. following bladder catheterization) to minimize the discomfort to the woman. The specified duration of vaginal cleansing with povidone-iodine in three of the seven included studies in the Cochrane review was 30 seconds.
- The use of a high concentration and/or repeated applications of povidone-iodine should be avoided to minimize maternal and fetal exposure and possible interference with the results of neonatal thyroid screening.

Review question:

Among pregnant women with indications for caesarean section (P), does vaginal cleansing with an antiseptic agent prior to caesarean delivery (I), compared with no vaginal cleansing with an antiseptic agent (C), prevent post-operative maternal infectious morbidities (O)?

Summary of evidence

- Evidence on vaginal preparation with antiseptic agent before caesarean section for preventing postoperative infectious morbidities was extracted from a Cochrane systematic review of seven trials involving 2816 women (2635 analysed) (39).
- Trials were conducted in low-, middle- and high-income countries: one trial each in Iran, Pakistan and Turkey, and four trials in the USA.
- All seven trials compared preoperative povidone-iodine solution preparation with a control group. Where specified, the concentration of povidone-iodine applied ranged from 1% to 10%. Control group was no vaginal cleansing in six trials and saline vaginal wash in one trial.
- Most trials included women undergoing either a scheduled or emergency caesarean delivery. Two trials excluded women with chorioamnionitis. Prophylactic antibiotics were used in all trials.
- None of the trials reported severe maternal infectious morbidity, side-effects of antiseptic agent or the cost of care.

Vaginal preparation with antiseptic agent versus control: all women (EB Table 14a)

- Women receiving vaginal cleansing with povidone-iodine experienced significantly reduced risk of post-caesarean endometritis (RR 0.45, 95% CI 0.25 to 0.81; 7 trials, 2635 women).
- There was no significant difference between the comparison groups for postoperative fever (RR 0.90, 95% CI 0.74 to 1.10; 6 trials, 2475 women), wound infection (RR 0.86, 95% CI 0.54 to 1.36; 6 trials, 2205 women) or any wound complication (RR 0.63, 95% CI 0.37 to 1.07; 2 trials, 729 women).

Vaginal preparation with antiseptic agent versus control: by presence or absence of labour before caesarean section (EB Table 14b)

- Four trials stratified data for women according to whether they were in labour or not before the caesarean section.

- Women in labour who received vaginal preparation with povidone-iodine solution preoperatively had lower risk of endometritis (RR 0.56, 95% CI 0.34 to 0.95; 3 trials, 523 women), but there were no differences observed for postoperative fever (RR 0.68, 95% CI 0.42 to 1.08; 2 trials, 307 women) or wound infection (RR 0.72, 95% CI 0.24 to 2.21, 2 trials, 307 women).
- Among women who were not in labour, no significant differences were observed between the intervention and the control groups for post-caesarean endometritis (RR 0.89, 95% CI 0.52 to 1.54; 3 trials, 871 women), postoperative fever (RR 0.96, 95% CI 0.61 to 1.49; 2 trials, 658 women) or wound infection (RR 0.64, 95% CI 0.27 to 1.56; 2 trials, 652 women).
- However, the test for subgroup differences did not show evidence of any differences between the subgroups.

Vaginal preparation with antiseptic agent versus control: by status of amniotic membranes (EB Table 14c)

- Four trials stratified data for women according to the status of amniotic membranes.
- Women with ruptured membranes who received vaginal preparation with povidone-iodine solution had lower risk of post-caesarean endometritis (RR 0.24, 95% CI 0.10 to 0.55; 3 trials, 272 women), but there were no differences observed for postoperative fever (RR 0.62, 95% CI 0.34 to 1.12; 2 trials, 200 women) or wound infection (RR 1.22, 95% CI 0.46 to 3.20, 3 trials, 272 women).
- Among women with intact membranes, no significant differences were observed between the intervention and the control groups for post-caesarean endometritis (RR 0.63, 95% CI 0.36 to 1.06; 3 trials, 857 women), postoperative fever (RR 0.93, 95% CI 0.63 to 1.36; 2 trials, 769 women) or wound infection (RR 0.72, 95% CI 0.35 to 1.52; 3 trials, 857 women).
- There was evidence of subgroup differences only for post-caesarean endometritis.

Considerations related to the strength of the recommendation

Quality of the evidence

The quality of the evidence for critical outcomes was graded as moderate or high. Overall, the quality of the evidence was graded as moderate.

Balance of benefits and harms

Vaginal preparation with povidone-iodine solution immediately prior to caesarean birth has the potential to reduce postoperative endometritis, particularly in women with ruptured membranes or those who are already in labour. This benefit was demonstrated in the context of prophylactic antibiotic cover. No adverse effects were reported by any of the trials. It is likely that the clinical benefits in terms of reduced endometritis observed in the overall analysis of the review apply to both emergency and scheduled or planned caesarean sections. However, the noted reduction in post-caesarean endometritis does not appear to influence postpartum maternal febrile morbidity, which was not significantly different between women who received and those who did not receive vaginal antiseptic before caesarean birth.

The balance between harm and benefits is limited by the lack of reporting on the maternal and infant side-effects of vaginal antiseptic application, although such side-effects are known to be rare. For neonates, a few studies have reported increased iodine levels in the first few days after birth but without any important clinical consequences. Such changes in iodine levels can affect the interpretation of results of neonatal thyroid screening in settings where this is routinely performed.

The findings of this Cochrane review are limited to the use of povidone-iodine preparations, and the effect of other popular antiseptics such as chlorhexidine as a vaginal disinfectant prior to caesarean birth is unknown.

Values and preferences

Health care providers, policy-makers and pregnant women and their families are likely to place a high value on the benefits of this intervention in terms of reduction in post-caesarean endometritis and a low value on the possible inconvenience associated with vaginal cleansing. This value is unlikely to substantially vary regardless of clinical situations and baseline risk of ascending infection (e.g. intact versus ruptured membranes, elective versus emergency caesarean section).

Resource implications

Implementation of this recommendation is likely to slightly increase costs where it is not currently in practice. However, the low costs of povidone-iodine, ready availability in all settings and low resources in terms of staff time or skill needed to implement this recommendation suggest that this intervention is likely to be cost-effective.

RECOMMENDATION 17

The choice of an antiseptic agent and its method of application for skin preparation prior to caesarean section should be based primarily on the clinician's experience with that particular antiseptic agent and method of application, its cost and local availability.

(Conditional recommendation based on low-quality evidence)

REMARKS

- Skin preparation is a vital part of the overall care that must be given to women undergoing surgery, to prevent surgical site infections before caesarean section. However, there is no strong evidence to recommend the use of one specific antiseptic agent over another.
- Maternal allergy to the preparation must be excluded prior to surgery.
- A standard preoperative skin preparation technique that is appropriate for the intended skin incision must be followed.

Review questions:

(i) Among pregnant women undergoing caesarean delivery (P), is the use of a particular antiseptic agent for preoperative skin preparation (I), compared with other antiseptic agent(s) (C), more effective in preventing post-caesarean infectious morbidities (O)?

(ii) Among pregnant women undergoing caesarean delivery (P), is the use of a particular method of antiseptic application for preoperative skin preparation (I), compared with other methods of antiseptic application (C), more effective in preventing post-caesarean infectious morbidities (O)?

Summary of evidence

- Evidence for the comparative effectiveness of different methods of application of antiseptic agents (e.g. scrub, paint, drape) was extracted from a Cochrane systematic review of six trials including 1522 women (40). For the comparison of the use of drape versus no drape (where one trial used iodine and other used chlorhexidine), two trials conducted in Denmark and South Africa included 1294 women undergoing elective or emergency caesarean section.
- Evidence on the comparative effectiveness of different antiseptic agents (e.g. alcohol, povidone-iodine) for skin preparation prior to caesarean

section was extracted from the same Cochrane systematic review with data from four small trials (194 women) (40). Three of these trials were conducted in the USA, and one in France. Trials tested different forms and concentrations of antiseptics agents. For each comparison only one trial of small sample size contributed data.

- The included trials did not report on many critical outcomes: severe maternal infectious morbidity, maternal death, side-effects, maternal satisfaction, neonatal infection or severe neonatal morbidity.

Comparison of different antiseptic preparations (EB 15a-15c)

Alcohol scrub plus iodophor drape versus iodophor scrub (1 trial, 79 women)

- One trial compared a one-minute scrub with 70% isopropyl alcohol followed by application of iodophor-impregnated adhesive film in the experimental group, with a five-minute iodophor scrub followed by application of iodophor solution in the control group.
- No significant difference between groups was reported in the incidence of endometritis (RR 1.62, 95% CI 0.29 to 9.16).
- The trial reported no wound infection in either group.

Chlorhexidine 0.5% versus 70% alcohol plus iodophor drape (IOBAN 2) (1 trial, 22 women)

- This trial reported only on neonatal outcomes and did not contribute any data to any of the comparisons included in the systematic review. Cord blood iodine concentration was significantly higher in the iodine group (18.38 ± 20.34 versus 6.44 ± 0.66 $\mu\text{g}/100$ ml, $P < 0.05$) than in the alcohol plus iodophor drape group. There was no significant difference in neonatal 48-hour urine iodine excretion and thyroid-stimulating hormone levels at five days.

Parachlorometaxylenol plus iodine versus iodine alone (1 trial, 50 women)

- One trial compared a five-minute scrub with parachlorometaxylenol followed by povidone-iodine scrub and normal saline irrigation of the pelvis and subcutaneous tissue at uterine closure and fascial closure with povidone-iodine surgical scrub (7.5%) followed by povidone-iodine (10%) and normal saline irrigation of the pelvis and subcutaneous tissue at uterine and fascial closure.
- There was no significant difference between groups in the incidence of endometritis (RR 0.88,

95% CI 0.56 to 1.38) or wound infection (RR 0.33, 95% CI 0.04 to 2.99).

Chlorhexidine gluconate versus povidone-iodine (1 trial, 60 women)

- There was no significant difference between groups for wound infection at two weeks after birth (RR 2.10, 95% CI 0.20 to 21.42), although the chlorhexidine gluconate group had significantly reduced bacterial growth at 18 hours after caesarean section (RR 0.23, 95% CI 0.07 to 0.70).

Methods of application: drape versus no drape (EB Tables 15d-15e)

- Two trials compared drape with no drape using different methods for preoperative skin disinfection. Incisional plastic drape was applied to the skin after preoperative skin disinfection. Preoperative skin disinfection was performed with 0.5% chlorhexidine in 80% alcohol solution for 30 seconds in one trial, and 2.5% iodine in 70% ethanol in the other trial. Rates of antibiotics prophylaxis were similar between intervention (10.7%) and control arms (8.2%) in one trial.
- The comparison showed no significant differences between groups for wound infection (RR 1.29, 95% CI 0.97 to 1.71; 2 trials, 1294 women) or reduction of skin colony counts (MD 0.07 colony forming unit per plate; 95% CI -0.34 to 0.48, 1 trial, 79 women).
- There was no significant difference between groups for length of hospital stay (MD 0.10 days, 95% CI -0.27 to 0.46, 1 trial, 603 women).

Considerations related to the strength of the recommendation

Quality of the evidence

The quality of evidence was graded as low for all critical outcomes for comparisons between antiseptics and for methods of application. Overall the quality of evidence was graded as low.

Balance of benefits and harms

There is insufficient evidence to demonstrate that one antiseptic agent or one method of application is better than the other for skin preparation for caesarean section. Available trials involved small number of participants and were mostly underpowered to detect statistical differences between comparison groups. Although one study showed considerable reduction in skin bacteria colony counts when chlorhexidine was used compared to povidone-iodine, the finding did not translate to reduced risk of wound infection.

Values and preferences

The choice of antiseptic preparation and the method of application of antiseptic preparation are likely to be guided by the clinician's experience, locally available options and locally common bacterial skin flora and antimicrobial sensitivity. The preferences of health care providers, policy-makers and pregnant women are likely to vary considerably across settings.

Resource implications

Antiseptic agents that are used for skin preparation are relatively cheap and available in all settings with the capacity to perform caesarean section. The implementation of this recommendation does not require a specific change in existing practice and is, therefore, unlikely to change health care costs in settings where the same preparation continues to be used. However, health care costs might be reduced in settings where the health systems choose to use a cheaper preparation that meets the criteria specified in the recommendation.

RECOMMENDATION 18.0

Routine antibiotic prophylaxis is recommended for women undergoing elective or emergency caesarean section. (*Strong recommendation based on moderate-quality evidence*)

REMARKS

- Antibiotic prophylaxis in this context refers to antibiotic use prior to the initiation of/or during caesarean section in the absence of clinical signs of infection. The GDG noted that it is essential for clinicians to be clear about this description to avoid using antibiotic regimens that are most applicable for treating confirmed infection – i.e. therapeutic antibiotic use.
- The intravenous route should be used for antibiotic administration given that the evidence underpinning this recommendation was based on findings from trials where the majority used this route.
- The GDG emphasized the importance of using the simplest and shortest antibiotic regimen for prophylaxis. As the evidence suggests that single-dose regimens are as effective as multiple-dose regimens, the GDG favoured single-dose antibiotic regimens which can easily be given prior to/during caesarean section, rather than multiple-dose regimens which sometimes extend to the postoperative period. Clinical judgement is needed to

evaluate other factors that might increase the risk of developing post-caesarean infections and are, therefore, more likely to benefit from multiple antibiotic doses (e.g. prolonged duration of surgery (long “skin-to-skin” interval), difficult surgical manipulation or massive blood loss).

Review question:

Among women undergoing caesarean section (P), does routine antibiotic prophylaxis (I), compared with no antibiotic prophylaxis (C), prevent infectious morbidities and improve outcomes (O)?

Summary of evidence

- Evidence for the routine use of prophylactic antibiotics for preventing infection and improving outcomes in women undergoing caesarean sections was extracted from a Cochrane systematic review of 95 trials including over 15 000 women (41).
- Trials were conducted in low-, middle- and high-income countries: 39 in the USA, six in Germany, four in Mexico, three studies each in Canada, Finland, Israel, Italy, South Africa and the UK; two studies each in Austria, France, Greece, Hong Kong, Malaysia, Nigeria, Sweden and the United Arab Emirates; and one study each in China, Denmark, Hungary, Kenya, the Netherlands, New Zealand, Saudi Arabia, Spain, Sudan, Tunisia, Turkey and Zimbabwe.
- The antimicrobial agents most often used in the trials included ampicillin, first-generation cephalosporin (usually cefazolin), second-generation cephalosporin (cefamandole or cefuroxime), cefamycin (cefoxitin, cefotetan), metronidazole, penicillins with an extended spectrum of activity (e.g. ticarcillin, mezlocillin or piperacillin), beta-lactam/beta-lactamase inhibitor combination and aminoglycoside-containing combination. Antibiotics were in a majority of cases delivered intravenously. In one study, antimicrobial prophylaxis was administered by rectal suppository. In four studies, follow-up doses were administered by rectal suppository or vaginal tablet. The duration of the postoperative treatment course varied from a single intravenous dose to as long as a week.
- A large proportion of the studies (n = 59, 8500 women) gave no information on the type of surgery performed. Clinical definitions for evaluated outcomes were broadly consistent

across trials, except for febrile morbidity and serious infectious morbidity. No study reported on baseline risk of infection before the intervention.

Any antibiotic prophylaxis versus no antibiotic prophylaxis (EB Table 16a)

- There was a reduction in cases of serious infectious complications (RR 0.31, 95% CI 0.20 to 0.49; 32 trials, 6159 women), maternal febrile morbidity (RR 0.45, 95% CI 0.40 to 0.51; 56 trials, 9046 women), endometritis (RR 0.38, 95% CI 0.34 to 0.42; 83 trials, 13 548 women), wound infections (RR 0.40, 95% CI 0.35 to 0.46; 82 trials, 14 407 women) and maternal urinary tract infections (RR 0.56, 95% CI 0.49 to 0.65; 66 trials, 10 928 women). Adverse events (rash, phlebitis at the site of the intravenous infusion) were more frequent in the treated group (RR 2.43; 95% CI 1.00 to 5.90; 13 trials, 2131 women). There were no serious drug-related adverse events reported. Maternal length of hospital stay was shorter in the treated group (MD -0.46, 95% CI -0.65 to -0.28; 19 trials, 3168 women) compared with controls.
- The majority of the trials did not report on neonatal outcomes. Those trials reporting them declared few neonatal deaths but no relationship to the use of antibiotics (two trials), no complications related to drug administration (two trials) or any neonatal morbidity (five trials).
- Subgroup analyses based on whether single dose only or multiple dose or either antibiotic regimens were used showed similarity in terms of effect size and direction for all maternal critical outcomes (as shown by the interaction tests) except for endometritis:
 - Febrile morbidity: single dose (RR 0.50, 95% CI 0.42 to 0.60, 27 trials, 5410 women); multiple doses (RR 0.41, 95% CI 0.35 to 0.49, 26 trials, 3192 women); both (RR 0.33, 95% CI 0.21 to 0.53, 3 trials, 444 women); $P = 0.13$.
 - Wound infection: single dose (RR 0.45, 95% CI 0.38 to 0.54, 27 trials, 7937 women); multiple doses (RR 0.35, 95% CI 0.28 to 0.43, 42 trials, 6208 women); both (RR 0.27, 95% CI 0.07 to 0.98, 2 trials, 262 women); $P = 0.15$, $I^2 = 47.6\%$; serious infectious complications: single dose (RR 0.50, 95% CI 0.25 to 1.0, 15 trials, 3819 women); multiple doses (RR 0.24, 95% CI 0.13 to 0.43, 17 trials, 2340 women); $P = 0.11$.
 - Urinary tract infection: single dose (RR 0.60, 95% CI 0.49 to 0.72, 33 trials, 6941 women); multiple doses (RR 0.51, 95% CI 0.41 to 0.64, 32 trials, 3805 women); both (RR 0.70, 95% CI

0.21 to 2.39, 1 trial, 282 women); $P = 0.58$.

- Maternal hospital stay: single dose (MD -0.39 days, 95% CI -0.60 to -0.19, 12 trials, 2369 women); multiple doses (MD -0.65 days, 95% CI -1.01 to -0.30, 7 trials, 799 women); $P = 0.21$.
- Adverse effects: single dose (RR 2.12, 95% CI 0.66 to 6.75, 7 trials, 1329 women); multiple doses (RR 2.94, 95% CI 0.73 to 11.76, 6 trials, 802 women); $P = 0.72$.
- Endometritis: A significant reduction in endometritis was observed for both dosing types; however, the interaction tests showed a significant difference between subgroups: single dose (RR 0.43, 95% CI 0.38 to 0.50, 41 trials, 8487 women); multiple dose (RR 0.32, 95% CI 0.27 to 0.37, 40 trials, 4799 women); both (RR 0.36, 95% CI 0.17 to 0.73, 2 trials, 262 women); $P = 0.02$, $I^2 = 75.3\%$ – although in the same direction. Multiple-dose antibiotic prophylaxis significantly was associated with a 68% reduction in the risk of endometritis compared to a 57% reduction for single-dose antibiotics.

Antibiotic prophylaxis versus no antibiotic prophylaxis: by antibiotic class (EB Table 16b)

- Approximately two thirds of studies evaluated treatment with a first- or second-generation cephalosporin, including cefamycins, or ampicillin. No study reported on monotherapy with a penicillinase-resistant penicillin, fourth-generation cephalosporin, carbapenem, tetracycline, macrolide and aminoglycosides.
- There were reductions in maternal outcomes for all antibiotics subgroups, without differences between subgroups for serious infection outcomes ($P = 0.93$; $I^2 = 0\%$) and wound infection ($P = 0.17$; $I^2 = 26.8\%$). Interaction tests indicated potentially significant differences among subgroups for febrile morbidity ($P < 0.001$; $I^2 = 73.8\%$) and endometritis ($P = 0.07$; $I^2 = 38.6\%$). The smallest reduction in febrile morbidity was seen for cefamycins (RR 0.73, 95% CI 0.61 to 0.88; 9 trials, 1894 women), and the largest for other regimens (RR 0.23, 95% CI 0.07 to 0.76; 1 trial, 118 women). The smallest reduction in endometritis was seen for beta-lactamase inhibitor combinations (RR 0.67, 95% CI 0.27 to 1.66; 5 trials, 788 women), though this was insignificant, and the largest reduction for natural penicillins (RR 0.19, 95% CI 0.05 to 0.65; 1 trial, 66 women).

Antibiotic prophylaxis versus no antibiotics: by type of caesarean section (EB Table 16c)

- Seventeen studies (3500 women) included data on women undergoing elective caesarean sections, according to the review definition, while 22 studies (2500 women) included non-elective procedures. Two studies included both. Three subgroups were compared: elective, non-elective and both elective and non-elective or undefined caesarean section.
- Interaction tests showed a significant difference ($P = 0.001$; $I^2 = 85.2\%$) between subgroups for wound infection (elective CS: RR 0.62, 95% CI 0.47 to 0.82; non-elective CS: RR 0.39, 95% CI 0.27 to 0.58; undefined caesarean section: RR 0.34 95% CI 0.28 to 0.40) and maternal urinary tract infection (elective CS: RR 0.92, 95% CI 0.57 to 1.50; non-elective CS: RR 0.44 95% CI 0.31 to 0.60; undefined caesarean section: RR 0.59 95% CI 0.49 to 0.70). There were no differences between subgroups for febrile morbidity ($P = 0.79$; $I^2 = 0\%$), endometritis ($P = 0.84$; $I^2 = 0\%$), febrile morbidity ($P = 0.79$; $I^2 = 0\%$) or serious infectious maternal outcomes ($P = 0.73$; $I^2 = 0\%$).

Considerations related to the strength of the recommendation

Quality of evidence

The quality of evidence was graded as moderate for most critical outcomes. Certain subgroups of antibiotics had lower-quality evidence, ranging from low to very low. Overall, the quality of the evidence for the main comparison was graded as moderate.

Balance of benefits and harms

There is moderate-quality evidence demonstrating the clinical benefits of using prophylactic antibiotics for women undergoing caesarean section, regardless of drug class and regimen or type of caesarean section (elective or non-elective). No antibiotic class or regimen seems to be more effective than the other. Subgroup analyses according to drug regimen and time of administration were observational in nature and not part of a randomized trial or meta-analysis. Serious maternal adverse effects related to the use of antibiotics were rare. However, there is little information about the impact of prophylactic antibiotic treatment on the neonates, although it is unlikely that any potential neonatal risk would outweigh maternal benefits.

Values and preferences

Health care providers, policy-makers and pregnant women and their families in all settings are likely to place a high value on the reduction in serious maternal infectious complications with minimal risk of adverse effects. The panel is confident that there is no variation in this value among mothers, health care providers and policy-makers in low-, middle- and high-income settings.

Resource implications

Antibiotics used for surgical prophylaxis in women undergoing caesarean section are inexpensive, easy to administer and readily available in all settings. It is possible that additional costs related to the use of antibiotics for caesarean section may depend on the overall caesarean section rates across settings. However, these added costs are outweighed by the cost savings for treating short- and long-term complications of post-caesarean infections (e.g. costs related to ICU admission, long hospital stay) to the woman and her family.

RECOMMENDATION 18.1

For caesarean section, prophylactic antibiotics should be given prior to skin incision, rather than intraoperatively after umbilical cord clamping. (Strong recommendation based on moderate-quality evidence)

REMARKS

- The GDG highlighted the importance of administering prophylactic antibiotics at least 15–60 minutes prior to skin incision in optimizing tissue and blood antibiotic concentrations. Based on the pharmacokinetics of common intravenous antibiotics, maximal benefit can be expected when administered between 30 and 60 minutes before skin incision.
- The GDG acknowledged that evidence also supports the effectiveness of prophylactic antibiotics after umbilical cord clamping for the prevention of post-caesarean infectious morbidities. Therefore, antibiotics are still beneficial when used outside the suggested timeframe (i.e. 15–60 minutes before incision) and should be applied as circumstances demand. This is particularly important in cases of emergency caesarean section where the available time to administer a prophylactic antibiotic might be limited.

- There are no data on the effects of preoperative administration on possible longer-term effects of antibiotic exposure on the baby, and women should be counselled as appropriate. The GDG considers this question a research priority and suggested that opportunities for longer-term follow-up of babies from previous trials should be explored.

Review question:

Among women receiving antibiotic prophylaxis for caesarean section (P), is preoperative administration of antibiotics (I), compared with intraoperative administration of antibiotics (after umbilical cord clamping) (C), more effective in preventing maternal and neonatal infectious morbidities (O)?

Summary of evidence

- Evidence on appropriate timing (preoperative versus intraoperative) for the administration of prophylactic antibiotics for preventing infectious morbidities following caesarean section was extracted from a Cochrane systematic review of 10 trials involving 5589 women (5041 analysed) (42).
 - Trials were conducted in low-, middle- and high-income countries: five in the USA, two in India and one each in Austria, Egypt and Turkey.
 - The target population was women undergoing caesarean section, predominantly elective and non-emergency procedures. All but two trials excluded emergency caesarean section. Most of the trials excluded women with chorioamnionitis or other signs of infection, those who had received antibiotics prior to delivery, with ruptured membranes or who delivered preterm. Two trials excluded multiple pregnancies.
 - Antibiotics for prophylaxis were given intravenously either before the incision or after clamping of the neonatal umbilical cord. Studies administering antibiotics before incision used different timeframes, with the majority ranging from 15 to 60 minutes.
 - The antibiotics used were different regimens of cephalosporins: seven trials used first-generation cephalosporin (cefazolin 1 g or 2 g), while the other three trials used third-generation cephalosporin (ceftriaxone 1 g or 2 g). Clindamycin was typically the agent of choice for women who had known allergy to cephalosporins.
- Prophylactic antibiotics before skin incision versus after umbilical cord clamping (EB Table 17)**
- Compared with administration after umbilical cord clamping, preoperative antibiotic administration was associated with a 43% reduction in the incidence of endomyometritis (RR 0.54, 95% CI 0.36 to 0.79; 10 trials, 5041 women) and a 41% reduction in the incidence of wound infection (RR 0.59, 95% CI 0.44 to 0.81; 10 trials, 5041 women). These findings were consistent between trials testing first- and second-generation cephalosporins.
 - There were no significant differences between the group receiving antibiotics before incision versus after umbilical cord clamping in the incidence of urinary tract infection (RR 1.02, 95% CI 0.65 to 1.59; 8 trials, 4001 women), pelvic abscesses (RR 1.00, 95% CI 0.06 to 15.97; 1 trial, 741 women), respiratory infections (e.g. pneumonia) (RR 2.30, 95% CI 0.34 to 15.45; 4 trials, 1849 women) or febrile illness (RR 0.93, 95% CI 0.63 to 1.35; 4 trials, 2650 women).
 - Two trials (1274 women) collected information on septic pelvic thrombophlebitis, and one trial (874 women) on septic shock and maternal death, but reported no events.
 - There was evidence of a significant reduction in maternal hospital stay among women receiving antibiotics preoperatively compared with women receiving it during caesarean section (MD -0.17, 95% CI -0.30 to -0.04; 2 trials, 1342 women).
 - For the neonate, there was no statistically significant difference between the group receiving antibiotics before incision versus after umbilical cord clamping regarding the incidence of neonatal sepsis (RR 0.76, 95% CI 0.51 to 1.13; 5 trials, 2907 neonates), neonatal sepsis workup (RR 0.92, 95% CI 0.69 to 1.23; 4 trials, 1170 neonates), infection with a resistant organism (RR 0.70, 95% CI 0.12 to 4.14; 1 trial, 379 neonates) febrile illness (RR 0.67, 95% CI 0.28 to 1.62, 1 trial, 953 neonates), ICU admission (RR 0.91, 95% CI 0.74 to 1.13; 6 trials, 3708 neonates) or duration of ICU stay (MD -0.07 days, 95% CI -2.60 to 2.46; 3 trials, 1731 neonates). Neonatal mortality was not reported by any of the trials.
 - Other critical outcomes were not reported.
- Considerations related to the strength of the recommendation**
- Quality of evidence**
- The majority of critical outcomes were graded as being of moderate to high quality. Overall, quality of evidence was graded as moderate.

Balance of benefits and harms

Preoperative (pre-incision) antibiotic administration is more effective than intraoperative administration for reducing infectious morbidities in women undergoing caesarean section, without evidence of adverse neonatal outcomes. The theoretical concerns regarding antibiotic exposure of the neonate were not demonstrated by the review, although the results were limited only to short-term outcomes. Given the increasing evidence of the importance of appropriate bacterial colonization after birth for infant health and immune system development, it remains unclear whether the demonstrated reduction in the risk of wound infection/endometritis outweighs the longer-term effect of prenatal antibiotic exposure on the baby.

Values and preferences

Health care providers, policy-makers and pregnant women and their families in all settings are likely to place a high value on the added clinical benefits of preoperative antibiotic administration in terms of further reduction in endomyometritis and wound infection, without adverse effects on neonatal infections. The panel is confident that there is no variation in this value among mothers, health care providers and policy-makers in low-, middle- and high-income settings.

Resource implications

Antibiotics are widely available in parenteral forms in all settings where caesarean sections are performed. The timing of antibiotic administration for caesarean section prophylaxis is unlikely to impact the health care costs needed to implement the intervention.

RECOMMENDATION 18.2

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.

(Conditional recommendation based on very low-quality evidence)

REMARKS

- The GDG noted that the available evidence on the effectiveness of antibiotics came largely from trials that tested first-generation cephalosporin or penicillin. Based on consensus, the 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.

- In acknowledgement of the lack of evidence on the comparative effectiveness of different classes of antibiotics, the GDG concluded that when the recommended antibiotic classes are not available, other classes of antibiotics may also be used. The group noted that the choice of such antibiotic class should be informed by the local bacteriologic patterns of post-caesarean infectious morbidity, the availability of such antibiotic class, the woman's allergy history, the clinician's experience with that particular class of antibiotics, and its cost.
- Due to the high risk of necrotizing enterocolitis among preterm babies, the use of "co-amoxiclav" for antibiotic prophylaxis should be avoided not only for caesarean delivery of preterm infants, but it might also be safer to avoid its use for caesarean delivery of term babies.

Review question:

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 postoperative infectious morbidities (O)?

Summary of evidence

- Evidence on the comparative effectiveness and safety of different classes of antibiotics to prevent infectious morbidity in women undergoing caesarean section was extracted from a Cochrane systematic review of 35 trials (with 31 trials providing data for 7697 women) (43).
- Trials were conducted in low-, middle- and high-income countries: 12 studies in the USA, four in India, three in Italy, two in Thailand, and one each in the following countries: Argentina, Canada, Greece, Finland, the Netherlands, Malaysia, Mozambique, Rwanda, South Africa, Sudan, Switzerland, the UK, the United Arab Emirates and Zimbabwe.
- The trials included women undergoing either elective or non-elective caesarean section. All but five trials administered prophylactic antibiotics after umbilical cord clamping. Antibiotics were administered preoperatively in four trials, and information about the timing of antibiotic administration was not available for one trial.
- The comparisons considered in the review were those between two or more antibiotics of different

classes. Comparisons of different drugs or drug regimens within the same class were excluded. The majority of the trials included compared cephalosporin with penicillin. The overall data for any cephalosporin versus any penicillin were not pooled but analysed according to the following subgroups: single cephalosporin versus single penicillin, single cephalosporin versus penicillin combination, cephalosporin combination versus single penicillin and cephalosporin combination versus penicillin combination. Three trials compared a cephalosporin or penicillin with another class of antibiotics. Few studies compared mixed antibiotic regimens (which do not include a cephalosporin or penicillin) with cephalosporin or penicillin.

Cephalosporin versus penicillin (EB Tables 18a-18j)

Single cephalosporin versus single penicillin (13 trials, 4010 women)

- There were no cases of maternal sepsis in 346 women involved in two trials.
- There were no significant differences between cephalosporin and penicillin regimens for endometritis (RR 1.11, 95% CI 0.81 to 1.52; 9 trials, 3130 women), maternal febrile morbidity (RR 0.89, 95% CI 0.61 to 1.30; 7 trials, 1344 women), wound infection (RR 0.83, 95% CI 0.38 to 1.81; 9 trials, 1497 women) or urinary tract infection (RR 1.48, 95% CI 0.89 to 2.48, 7 trials, 1120 women). There were no significant differences between antibiotic classes on a maternal composite of adverse effects (RR 2.02, 95% CI 0.18 to 21.96; 3 trials, 1902 women).
- No cases were reported in the two trials evaluating a composite outcome of maternal serious infectious morbidity.
- None of the included studies reported neonatal sepsis.

Single cephalosporin versus penicillin combination (12 trials, 2875 women)

- There were no significant differences between comparison groups for maternal sepsis (RR 2.37, 95% CI 0.10 to 56.41; 1 trial, 75 women), endometritis (RR 0.90, 95% CI 0.60 to 1.35, 10 trials, 2134 women), maternal febrile morbidity (RR 0.92, 95% CI 0.56 to 1.49; 6 trials, 1824 women), wound infection (RR 0.72, 95% CI 0.40 to 1.30; 7 trials, 1608 women) or maternal urinary tract infection (RR 0.66, 95% CI 0.17 to 2.55; 6 trials, 1361 women). There were no significant differences between antibiotic classes on maternal composite adverse effects (RR 0.96, 95% CI 0.09 to 10.50; 4 trials, 1333 women).

- None of the included studies reported neonatal sepsis.

Cephalosporin combination versus single penicillin (1 trial, 147 women)

- From one study involving 139 women, there were no differences observed between groups for endometritis (RR 2.70, 95% CI 0.63 to 11.55), maternal febrile morbidity (RR 2.36, 95% CI 0.84 to 6.62) or wound infection (RR 2.02, 95% CI 0.42 to 9.63). The other critical outcomes were either not reported by the study or there were no events.

Cephalosporin combination versus penicillin combination (2 trials, 363 women)

- There were no significant differences between groups in maternal sepsis (RR 3.21, 95% CI 0.34 to 30.45; 1 trial, 232 women), endometritis (RR 0.33, 95% CI 0.01 to 7.77; 1 trial, 83 women), maternal fever (RR 1.57, 95% CI 0.69 to 3.60; 2 trials, 315 women) or wound infection (RR 1.23, 95% CI 0.42 to 3.58; 2 trials, 315 women).

Cephalosporins versus penicillins: comparison by type of caesarean section (22 trials, 5788 women)

- Most of the trials included women undergoing either elective or emergency caesarean sections.
- There was no significant difference between women undergoing elective or emergency caesarean section for maternal sepsis (RR 2.91, 95% CI 0.47 to 18.10; 4 trials, 653 women).
- There was a significant difference between subgroups for endometritis ($I^2 = 61.4\%$). Penicillins showed a trend towards superior effectiveness compared with cephalosporins for reducing endometritis among women undergoing non-elective caesarean section (RR 1.33, 95% CI 1.01 to 1.75, 6 trials, 2362 women). The differences were not significant for elective caesarean section (RR 2.06, 95% CI 0.66 to 6.39; 3 trials, 461 women) or when type of caesarean section was not differentiated (RR 0.85, 95% CI 0.60 to 1.19; 11 trials, 2567 women).

Cephalosporins versus penicillins: comparison by timing of administration (22 trials, 5788 women)

- All but two trials administered antibiotics before umbilical cord clamping. Two trials did not report on the timing of antibiotic administration.
- There were no significant differences between antibiotics for maternal sepsis (RR 2.91, 95% CI 0.47 to 18.10; 4 trials, 653 women) or endometritis (RR 1.11, 95% CI 0.90 to 1.37; 20 trials, 5390 women).

Cephalosporins versus penicillins: comparison by route of administration (22 trials, 5788 women)

- Twenty trials compared antibiotics given intravenously. Two studies compared the antibiotics when administered as a lavage/irrigation during surgery.
- There were no significant differences between antibiotic classes for maternal sepsis (RR 2.90, 95% CI 0.46 to 18.17, 4 trials, 653 women) or endometritis (RR 1.12, 95% CI 0.92 to 1.37, 20 trials, 5390 women) in relation to the route of administration.

First-generation cephalosporins versus extended-spectrum penicillins (2 trials, 822 women)

- Extended-spectrum penicillins were more efficient in preventing endometritis than first-generation cephalosporins (RR 2.18, 95% CI 1.30 to 3.66; 2 trials, 814 women). However, no differences were reported in maternal fever (RR 2.36, 95% CI 0.84 to 6.62; 1 trial, 139 women) or wound infection (RR 2.02, 95% CI 0.42 to 9.63; 1 trial, 139 women).

First-generation cephalosporins versus aminopenicillins (8 trials, 1882 women)

- There were no significant differences between groups for endometritis (RR 1.09, 95% CI 0.69 to 1.71; 7 trials, 1487 women), maternal febrile morbidity (RR 0.78, 95% CI 0.40 to 1.51; 5 trials, 883 women), wound infection (RR 0.85, 95% CI 0.36 to 2.01; 5 trials, 626 women) or urinary tract infections (average RR 1.41, 95% CI 0.54 to 3.70; 5 trials, 626 women).
- A reduction in the maternal length of hospital stay was observed in the group receiving cephalosporins compared to aminopenicillins (MD -1.50, 95% CI -2.46 to -0.54; 1 trial, 132 women).

Second-generation cephalosporins versus extended spectrum penicillins (6 trials, 2077 women)

- There were no significant differences between groups for endometritis (RR 1.10, 95% CI 0.78 to 1.54; 4 trials, 1334 women), maternal febrile morbidity (RR 1.08, 95% CI 0.79 to 1.47; 4 trials, 850 women), wound infection (RR 2.37, 95% CI 0.64 to 8.73; 2 trials, 438 women) or urinary tract infection (RR 1.43, 95% CI 0.67 to 3.07, 3 trials, 567 women). There were no reported events of maternal sepsis (1 trial, 287 women), post-discharge infections (3 trials, 305 women) or maternal composite adverse effects (RR 2.02, 95% CI 0.18 to 21.96; 2 trials, 1030 women).

Second-generation cephalosporins versus aminopenicillins (8 trials, 1921 women)

- There were no significant differences between groups in maternal sepsis (RR 2.37, 95% CI 0.10 to 56.41; 1 trial, 75 women), endometritis (RR 1.01, 95% CI 0.75 to 1.35; 8 trials, 1890 women), maternal febrile morbidity (RR 1.17, 95% CI 0.64 to 2.15; 3 trials, 387 women), wound infection (RR 1.14, 95% CI 0.47 to 2.78; 5 trials, 638 women), maternal urinary tract infection (RR 0.63, 95% CI 0.11 to 3.66; 4 trials, 462 women) or maternal composite of adverse effects (RR 1.92, 95% CI 0.18 to 20.82; 3 trials, 1130 women).

Third-generation cephalosporins versus extended-spectrum penicillins (2 trials, 359 women)

- Extended-spectrum penicillins were more efficient than third-generation cephalosporins in preventing endometritis (RR 2.14, 95% CI 1.14 to 4.00; 1 trial, 300 women). Other considered outcomes reported no events.

Third-generation cephalosporins versus aminopenicillins (7 trials, 1904 women)

- There were no significant differences between groups for endometritis (RR 1.47, 95% CI 0.89 to 2.42; 5 trials, 1472 women), maternal febrile morbidity (RR 1.12, 95% CI 0.69 to 1.83; 3 trials, 1060 women), maternal urinary tract infection (RR 0.52, 95% CI 0.10 to 2.80; 2 trials, 233 women) or length of maternal hospital stay (MD -0.03, 95% CI -0.14 to 0.08; 1 trial, 746 women).
- Wound infections were reduced in the group receiving third-generation cephalosporins (RR 0.49 95% CI 0.27 to 0.90; 6 trials, 1556 women).

Fluoroquinolones versus penicillin or cephalosporin (EB Tables 18k-18l)

- Two very small trials tested ciprofloxacin versus ampicillin/sulbactam (72 women) or cefotetan (81 women).
- No differences were found between these antibiotics regarding maternal sepsis, endometritis or wound infection.

Other antibiotic regimens versus penicillin or cephalosporins (EB Tables 18m-18n)

- There were other comparisons between other antibiotic class combinations versus penicillin or cephalosporin:
 - Lincosamide plus aminoglycoside versus penicillin (1 trial, 88 women)
 - Beta-lactam versus cephalosporin (2 trials, 118 women)

- There were no differences observed between the comparison groups for the outcomes reported: wound infection and endometritis.

Aminoglycoside plus nitroimidazole versus standard antibiotic cocktail (EB Table 18o)

- One trial involving 241 women compared gentamicin (aminoglycoside) plus metronidazole (nitroimidazole) with a standard cocktail of antibiotics (containing penicillin, nitroimidazole and macrolide). There was no significant difference between the two groups with regard to endometritis (RR 0.81, 95% CI 0.29 to 2.26; 1 trial, 241 women), maternal fever (RR 1.12, 95% CI 0.69 to 1.83; 3 trials, 1060 women), wound infection (RR 3.23, 95% CI 0.34 to 30.64; 1 trial, 241 women) or maternal urinary tract infection (RR 1.08, 95% CI 0.07 to 17.03; 1 trial, 241 women).

Considerations related to the strength of the recommendation

Quality of the evidence

Several critical outcomes were graded as very low-quality evidence for the various comparisons. Overall, the quality of evidence was graded as very low.

Balance of benefits and harms

There is no evidence to demonstrate that any specific class of antibiotic is better than the other for prophylaxis in women undergoing caesarean section. However, first-generation cephalosporins and penicillin have an advantage over other classes of antibiotics in terms of cost and wide availability in all settings.

Values and preferences

Health care providers and policy-makers are likely to vary in their choice of antibiotic class for prophylaxis at caesarean section. These choices are likely to vary widely across settings but would often be dependent on local bacteriological patterns of post-caesarean infectious morbidity, patterns of bacterial resistance, availability and cost of antibiotics and common indications for caesarean section.

Resource implications

First-generation cephalosporin and penicillin are relatively cheaper than newer antibiotics, easy to administer, and readily available in all settings with the capacity to perform caesarean sections. The implementation of this recommendation is likely to save health care costs related to multiple doses of antibiotics where such practice is currently the norm.

Treatment of maternal peripartum infection

RECOMMENDATION 19:

A simple regimen such as ampicillin and once-daily gentamicin is recommended as first-line antibiotics for the treatment of chorioamnionitis. *(Conditional recommendation based on very low-quality evidence)*

REMARKS

- There is insufficient evidence to support the use of any antibiotic over another. Based on consensus, the GDG favoured a regimen that is simple, can be administered over a short duration and follows the principles of antibiotic use to reduce emergence of resistant strains of bacteria.
- Although there is no clear evidence as to whether antibiotics should be discontinued after birth or continued in the postpartum period, the GDG noted that women who remain symptomatic are likely to benefit from longer antibiotic treatment for at least 24 to 48 hours after the symptoms and signs of infection (e.g. fever, uterine tenderness) have subsided.

Review question:

Among women receiving antibiotic treatment for intra-amniotic infection/chorioamnionitis (P), is the use of a particular antibiotic regimen (I), compared with other regimens (C), more effective in improving maternal and neonatal outcomes (O)?

Summary of evidence

- Evidence on comparative effectiveness and safety of different antibiotics regimens for treatment of women diagnosed with intra-amniotic infection/chorioamnionitis was extracted from a Cochrane systematic review of 11 trials involving 1296 women (44).
- All trials were conducted in the USA except one which was conducted in Italy.
- The definition of chorioamnionitis varied between trials, but in all trials the definition included the presence of fever. Other conditions considered for diagnosis were maternal tachycardia, fetal tachycardia, uterine tenderness, purulent or foul amniotic fluid and maternal leucocytosis.
- Women were followed up until discharge from hospital, and six trials reported follow-up between one and six weeks after discharge. Six trials included women who delivered by caesarean

section. Four trials excluded women ≤ 34 weeks of gestation. Most of the trials excluded women who received antibiotics prior to delivery and those with other sources of infection.

- Trials tested a range of IV antibiotics regimens, doses, frequency, duration of administration, combinations and timing of administration. Four trials compared antibiotics during labour, six trials compared antibiotics after birth, and one compared antibiotic administration before and after birth. The following antibiotics were used in the included trials: ampicillin, ampicillin/sulbactam, gentamicin, clindamycin and cefotetan.

Intrapartum antibiotics (EB Table 19a)

Ampicillin plus daily gentamicin versus ampicillin plus thrice-daily gentamicin (2 trials, 163 women)

- 2 g IV ampicillin six-hourly plus 5.1 mg/kg (every 24 hours) of gentamicin were compared with 2 g IV ampicillin six-hourly plus 80 mg of gentamicin eight-hourly.
- There were no differences between groups in the rates of endometritis (RR 0.86, 95% CI 0.27 to 2.70). One of the trials (125 women) reported no differences between groups in initial successful response to antibiotics (RR 1.05, 95% CI -0.45 to 1.25), maximum maternal temperature (MD 1.05, 95% CI 0.94 to 1.17) and maternal postpartum hospital stay (MD 0.00, 95% CI -0.43 to 0.43). No maternal death was reported in any of the treatment groups.
- There were no differences between groups for neonatal sepsis (RR 1.07, 95% CI 0.40 to 2.86). One of the trials (125 women) reported no differences between groups for respiratory distress syndrome (RR 1.69, 95% CI 0.42 to 6.78, 1 study, 125 neonates) or duration of neonatal antibiotic use (in days) (MD 0.20 days, 95% CI -0.37 to 0.77, 1 study, 125 neonates).

Dual-agent therapy (ampicillin/gentamicin) versus triple-agent therapy (ampicillin/gentamicin/clindamycin) (1 trial, 133 women)

- There were no statistical differences between groups in the incidence of postpartum endometritis (RR 1.86, 95% CI 0.67 to 5.14), postpartum endometritis after vaginal delivery (RR 9.63, 95% CI 0.55 to 167.95; 73 women) or postpartum endometritis after caesarean section (RR 1.0, 95% CI 0.32 to 3.10; 60 women).
- There were no statistical differences for neonatal sepsis (RR 0.93, 95% CI 0.06 to 14.52), neonatal deaths (RR 1.39, 95% CI 0.24 to 8.06), intraventricular haemorrhage (RR 4.64, 95% CI

0.23 to 94.90), respiratory distress syndrome (RR 1.11, 95% CI 0.36 to 3.47; 125 neonates) or neonatal seizures (RR 0.93, 95% CI 0.06 to 14.52).

Ampicillin/sulbactam versus cefotetan (1 trial, 19 women)

- One small trial compared ampicillin/sulbactam versus cefotetan and reported no failure of antibiotic treatment for women with chorioamnionitis and no maternal deaths.

Postpartum antibiotics (EB Tables 19b-19e)

Ampicillin during labour plus postpartum clindamycin/gentamicin versus no treatment during the postpartum period, 1 trial, 116 women

- No significant differences were observed for postpartum endometritis (RR 1.48, 95% CI 0.68 to 13.24), and wound infection (RR 0.37, 95% CI 0.04 to 3.45) between the postpartum treated and untreated groups.
- There were no differences in neonatal deaths (RR 3.32, 95% CI 0.14 to 79.88), neonatal sepsis (RR 1.11, 95% CI 0.23 to 5.27) or transient tachypnoea (RR 0.83, 95% CI 0.19 to 3.55).

Once daily versus thrice-daily gentamicin/clindamycin in the postpartum (1 trial, 131 women)

- No differences were observed between groups in the rate of treatment failure, defined as elevated temperature after 72 hours treatment (RR 1.02, 95% CI 0.27 to 3.89), or length of antibiotic treatment (days) (MD -0.30 days, 95% CI -0.90 to 0.30). No cases of nephrotoxicity were observed.

Short versus long duration of treatment (2 trials, 401 women)

- Two trials compared continuation of intrapartum antibiotic administration with either a postpartum short-course or longer-course antibiotic treatment. In both trials women received ampicillin and gentamicin when chorioamnionitis was diagnosed during labour. In one trial, there was no further treatment in the intervention arm after delivery, while in the control arm, the intrapartum schedule of ampicillin and gentamicin was continued postpartum until the women were afebrile and asymptomatic for 24 hours. In the second trial, women in the short-course arm received a single dose of cefotetan within one hour of delivery, while those in the long-course arm received cefotetan every 12 hours for a minimum of 48 hours.
- No significant differences were observed between the postpartum short- and long-course treatment

in the overall rate of treatment failure (RR 1.31, 95% CI 0.42 to 4.02; 1 trial, 292 women) or after stratification by mode of delivery (vaginal delivery: RR 1.46, 95% CI 0.39 to 5.51; 2 trials, 284 women; caesarean delivery: RR 3.31, 95% CI 0.38 to 28.75; 1 trial, 117 women). There were no differences in the incidence of wound infection (RR 1.87, 95% CI 0.17 to 20.37; 1 trial, 292 women) or pelvic abscess (RR 2.80, 95% CI 0.12 to 68.24; 1 trial, 292 women). Mean duration of hospital stay (in days) was reduced in the shorter arm of treatment compared to the longer arm (MD -0.90 days, 95% CI -1.64 to -0.16; 1 trial, 292 women).

- Intrapartum versus postpartum ampicillin/gentamicin (1 trial, 45 women)
- No differences were found between the group receiving antibiotics intrapartum versus postpartum in maternal bacteraemia (RR 2.19, 95% CI 0.25 to 19.48) or maximum maternal temperature postpartum (MD -0.50, 95% CI -1.08 to 0.08).
- Mothers and neonates in the intrapartum antibiotic group tended to have significantly shorter hospital stays (maternal postpartum hospital stay (days): MD -1.00 day, 95% CI -1.94 to -0.06; neonatal hospital stay: MD -1.90 days, 95% CI -3.31 to -0.49).
- There were no difference between groups in the incidence of early neonatal sepsis (RR 0.08, 95% CI 0.00 to 1.44) or sepsis and pneumonia combined (RR 0.06, 95% CI 0.00 to 0.95).

Considerations related to the strength of the recommendation

Quality of evidence

Overall, the quality of evidence was graded as very low.

Balance of benefits and harms

There is insufficient evidence to demonstrate the most appropriate antimicrobial regimen for the treatment of women with intra-amniotic infection; whether antibiotics should be continued during the postpartum period; and which regimen and what treatment duration should be used. Available trials generally involved a small number of participants and were mostly underpowered to detect statistical differences between comparisons of interest.

Values and preferences

Preferences for antibiotic regimens are likely to vary according to existing policy in a particular setting, the clinicians' experience and knowledge about

common local bacterial causes of infection and patterns of antimicrobial resistance, maternal allergy and availability of drugs. Women are likely to prefer not to receive further antibiotics in the postpartum period, to reduce their hospital stay.

Resource implications

Ampicillin and gentamicin are widely available in all facilities. This antibiotic regimen is cheaper than other available regimens. Therefore, implementation of this recommendation is likely to reduce health system costs in those settings not using ampicillin and once-daily gentamicin regimen.

RECOMMENDATION 20

A combination of clindamycin and gentamicin is recommended for the treatment of postpartum endometritis. (*Conditional recommendation based on very low-quality evidence*)

REMARKS

- The GDG acknowledged that availability and costs of clindamycin might be limiting factors in low-resource settings, and suggested the use of a penicillin class of drug as alternative treatment in such contexts.
- In the majority of studies that demonstrated benefits of clindamycin and gentamicin over other regimens, clindamycin was administered as 600 mg IV every six to eight hours, and gentamicin was administered as 1–1.5 mg/kg or 60–80 mg IV or IM every eight hours. Although the exact duration of the treatment was not specified in most cases, treatment was continued for as long as clinical symptoms and signs persisted. Similar to the remark regarding the treatment for chorioamnionitis, the GDG suggested that antibiotic treatment should continue for at least 24–48 hours after complete resolution of clinical signs and symptoms (e.g. fever, uterine tenderness, purulent lochia, leucocytosis).

Review question:

Among women receiving antibiotic treatment for postpartum endometritis (P), is the use of a particular antibiotic regimen (I), compared with other regimen(s) (C), more effective in improving maternal outcomes (O)?

Summary of evidence

- Evidence on the use of different antibiotics regimens to treat postpartum endometritis was extracted from a Cochrane systematic review. Forty-two trials including 4240 women were included (although 40 trials and 4240 women were included in the analysis) (45).
- Trials were mostly conducted in high-income countries, particularly in the USA: 33 trials were conducted in the USA, two in Mexico, and one in each of Colombia, France, Italy and Peru. One study was a multi-centre study conducted in many countries including the USA.
- Clinical criteria used to define endometritis were consistent across trials and included fever and uterine tenderness. Some trials also considered pelvic pain, purulent lochia, parametrial tenderness, leucocytosis, absence of other foci of infection or, in contrast, included women with chorioamnionitis or salpingitis or pelvic cellulitis after caesarean section. The definition of fever varied between trials in the criteria used for height of fever, intervals between febrile episodes and from the operative procedure. Some variations existed in the definition of serious morbidities, which included bacteraemia, pelvic thrombophlebitis, pelvic abscess and peritonitis.
- Trials included women who developed endometritis within the six weeks following delivery, but the majority of women were enrolled about 48 hours post-delivery. In half of the trials, only women who developed endometritis after caesarean section were included, but in four trials information on the mode of delivery was not reported. Inclusion of women who delivered by caesarean section and received prophylactic antibiotics varied between trials. Cefazolin was the main prophylactic agent used except in one trial in which cefoxitin was used.
- Antibiotic regimens were classified into 12 groups. In half of the trials (20 trials, 1918 women), the use of clindamycin plus an amino glycoside was compared with another regimen; in the others, different antibiotic regimens were compared.
- No trial reported on maternal mortality. The review did not consider long-term complications such as subfertility or uterine adhesions.

Clindamycin plus aminoglycoside versus other regimens (EB Table 20a)

- Analyses of clindamycin plus an aminoglycoside (most often gentamicin) resulted in a significant reduction in the rate of treatment failure compared

with penicillins (RR 0.65, 95% CI 0.46 to 0.90; 7 trials, 689 women) and cephalosprins (RR 0.69, 95% CI 0.49 to 0.99; 8 trials, 872 women). Concerning the other regimens tested, there were no significant differences observed between lincosamides when compared to quinolones (RR 0.72, 95% CI 0.38 to 1.37; 3 trials, 176 women) or monobactams (RR 2.25, 95% CI 0.60 to 8.43; 2 trials, 181 women), although the trials were much smaller. After antibiotic prophylaxis for caesarean section, there were no differences in treatment failure between lincosamides and penicillins (RR 1.12, 95% CI 0.63 to 1.98; 2 trials, 229 women).

- Analyses of severe complications showed no differences among the different subgroups: lincosamide versus cephalosporins (RR 2.40, 95% CI 0.30 to 19.19; 4 trials, 476 women), monobactams (no events; 1 trial, 62 women), penicillins (RR 0.33, 95% CI 0.09 to 1.18; 5 trials, 422 women) or quinolones (RR 2.89, 95% CI 0.31 to 27.20; 2 trials, 160 women).
- There was a decrease in wound infection with the use of clindamycin plus aminoglycoside compared with cephalosporins (RR 0.53, 95% CI 0.30 to 0.93; 4 trials, 500 women) and a trend towards reduction when compared to penicillins (RR 0.46, 95% CI 0.21 to 1.00; 3 trials, 339 women). No differences were shown within the other subgroups: lincosamides versus monobactams (RR 0.95, 95% CI 0.06 to 14.85; 1 trial, 119 women) or quinolones (RR 0.51, 95% CI 0.05 to 5.45; 1 trial, 97 women).
- No differences were found in side-effects among the various groups (diarrhoea, allergic reactions) or length of hospital stay.

Aminoglycoside plus penicillin or ampicillin versus any other regimen (EB Table 20b)

- Two trials compared gentamicin plus penicillin or ampicillin versus other regimens. These trials showed statistically significant heterogeneity ($P = 0.03$, $I^2 = 78\%$) for treatment failure and were analysed separately. The trial (200 women) comparing gentamicin plus penicillin versus gentamicin/clindamycin showed significantly more treatment failures (RR 2.57, 95% CI 1.48 to 4.46) for those treated with gentamicin plus penicillin, but the trial comparing gentamicin plus ampicillin versus piperacillin/tazobactam showed no significant differences between groups (RR 0.56, 95% CI 0.15 to 2.03; 56 women).
- No differences were found when aminoglycoside plus penicillin were compared with gentamicin/clindamycin in the incidence of severe

complications (RR 0.11, 95% CI 0.01 to 2.04; 1 trial, 200 women), wound infections (RR 0.50, 95% CI 0.22 to 1.12; 1 trial, 200 women), diarrhoea (RR 5.00, 95% CI 0.24 to 102; 1 trial, 200 women) or allergic reactions (RR 1.00, 95% CI 0.14 to 6.96).

- No differences were found when aminoglycoside plus ampicillin were compared to piperacillin/tazobactam in the incidence of wound infection (RR 2.44, 95% CI 0.13 to 44.57; 1 trial, 56 women). No severe complications, diarrhoea or allergic reactions were reported in this trial.

Penicillin plus beta-lactamase inhibitor versus any other regimen (EB Table 20c)

- Twelve trials including 1007 women compared penicillin plus beta-lactamase inhibitor with any other regimen. For all comparisons, no significant differences were observed in the incidence of treatment failure: penicillin plus beta-lactamase inhibitor versus lincosamides (RR 1.07, 95% CI 0.70 to 1.64; 6 trials, 495 women), versus cephalosporins (RR 1.08, 95% CI 0.39 to 43.93; 2 trials, 52 women), versus penicillins (RR 1.24, 95% CI 0.90 to 1.05; 2 trials, 155 women), versus carbapenems (RR 0.97, 95% CI 0.90 to 1.05; 1 trial, 238 women) and versus nitroimidazoles (RR 1.09, 95% CI 0.24 to 5.04; 1 trial, 67 women).
- Two trials reported on severe complications. One compared penicillin plus beta-lactamase inhibitor versus lincosamides and found no differences between groups (RR 4.32, 95% CI 0.51 to 36.95; 3 trials, 160 women). No events were reported in a small trial comparing penicillin plus beta-lactamase inhibitor versus penicillin (56 women).
- Two small trials reported on wound infection. No differences were found when penicillin plus beta-lactamase inhibitor was compared to penicillins (RR 0.41, 95% CI 0.02 to 7.47; 1 study, 56 women). The other study (77 women) reported no events. For diarrhoea there were no differences between penicillin plus beta-lactamase inhibitor versus lincosamides (RR 1.08, 95% CI 0.29 to 4.01; 3 trials, 160 women) or penicillin plus beta-lactamase inhibitor versus cephalosporins (RR 0.54, 95% CI 0.06 to 5.26; 1 trial, 27 women). One small trial (56 women) reported no events.
- Four trials reported on allergic reactions and reported no differences when comparing penicillin plus beta-lactamase inhibitor versus penicillins (RR 0.98, 95% CI 0.06 to 15.23; 2 trials, 155 women). The two trials comparing penicillin plus beta-lactamase inhibitor versus lincosamides reported no events. Length of hospital stay did not differ when a penicillin plus beta-lactamase

inhibitor was compared to penicillin (MD 0.80, 95% CI -0.09 to 1.69; 1 trial, 99 women).

Aztreonam plus clindamycin versus any other regimen (EB Table 20d)

- Two trials each compared aztreonam plus clindamycin versus trospectomycin plus aztreonam or versus gentamicin plus clindamycin.
- No differences were found among subgroups in the incidence of treatment failure when aztreonam plus clindamycin was compared to trospectomycin plus aztreonam (RR 1.49, 95% CI 0.78 to 2.84; 2 trials, 422 women) or gentamicin plus clindamycin (RR 0.45, 95% CI 0.12 to 1.67; 2 trials, 181 women).
- There were no differences in the incidence of allergic reactions (RR 1.04, 95% CI 0.52 to 2.09; 2 trials, 181 women) in the aztreonam plus clindamycin group compared to gentamicin plus clindamycin. Only one trial comparing aztreonam plus clindamycin versus gentamicin plus clindamycin reported on other outcomes and found no difference in the incidence of wound infection (RR 1.09, 95% CI 0.07 to 17.00; 1 trial, 117 women), diarrhoea (RR 2.10, 95% CI 0.20 to 22.58; 1 trial, 119 women) or length of hospital stay (MD -0.45 days, 95% CI -1.15 to 0.25; one trial, 119 women). No cases of severe complications were reported.

Cephalosporin with longer half-life versus cephalosporin with shorter half-life (EB Table 20e)

- Two trials compared different half-life cephalosporins: cefoxitin administered every six hours was compared with either cefmetazole administered every eight hours or cefotetan administered every 12 hours.
- The rate of treatment failure was lower in the group treated with the longer half-life compared to the shorter half-life (RR 0.61, 95% CI 0.40 to 0.92; 2 trials, 484 women). For other outcomes, no differences were found between the groups for severe complication (RR 0.27, 95% CI 0.02 to 2.89; 1 trial, 355 women), wound infection (RR 0.70, 95% CI 0.13 to 3.68, 2 trials, 484 women), diarrhoea (RR 1.43, 95% CI 0.42 to 4.84; 1 trial, 129 women), allergic reaction (RR 0.78, 95% CI 0.22 to 2.72; 1 trial, 377 women) or length of hospital stay (MD -0.60 days, 95% CI -1.45 to 0.25; 1 trial, 129 women).

Metronidazole plus gentamicin versus penicillins (EB Table 20f)

- Only one trial (67 women) compared metronidazole plus gentamicin versus penicillins (ampicillin plus sulbactam). The study found no difference in the rate of treatment failure (RR 0.91, 95% CI 0.20 to 4.21).

Once-daily versus thrice-daily gentamicin (EB Table 20g)

- Four studies compared once-daily versus thrice-daily (eight-hourly) gentamicin. Once-daily gentamicin tended to reduce the likelihood of treatment failure compared with a thrice-daily regimen (RR 0.70, 95% CI 0.49 to 1.00; 4 trials, 463 women).
- There were no differences in antibiotic adverse effects reported (nephrotoxicity: RR 3.04, 95% CI 0.13 to 73.43; 3 trials, 353 women) or in the length of hospital stay (MD -0.73 days, 95% CI -1.27 to -0.20; 3 trials, 322 women).

Continued oral versus no treatment after intravenous antibiotic course (EB Table 20h)

- Three trials tested continued oral antibiotics (ampicillin, ampicillin/clavulanic or penicillin) versus no treatment after initial intravenous antibiotic course.
- No differences were found between treatment groups for treatment failure (RR 1.46, 95% CI 0.34 to 6.18; 1 trial, 109 women), wound infection (RR 3.38, 95% CI 0.14 to 80.70; 1 trial, 81 women), recurrence of endometritis (RR 2.91, 95% CI 0.12 to 68.81; 3 trials, 253 women) or length of hospital stay (MD -0.21 days, 95% CI -1.44 to 1.02; 1 trial, 63 women).

Poor activity against penicillin-resistant anaerobic bacteria versus good activity (EB Table 20i)

- Trials showed a significantly higher rate of treatment failure (RR 1.94, 95% CI 1.38 to 2.72; 7 trials, 774 women) and wound infection (RR 1.88, 95% CI 1.17 to 3.02; 6 trials, 740 women) in the group treated with antibiotic regimens with poor activity against penicillin-resistant anaerobic bacteria, compared with the good activity group (six out of the seven trials tested clindamycin/gentamicin combination).
- No differences were found in the incidence of severe complications (RR 1.68, 95% CI 0.45 to 6.29; 5 trials, 671 women), diarrhoea (RR 0.29, 95% CI 0.08 to 1.04; 6 trials, 743 women), allergic reactions (RR 1.34, 95% CI 0.34 to 5.36; 5 trials,

628 women) or length of hospital stay (MD 0.37 days, 95% CI -1.44 to 0.73; two trials, 267 women).

Oral ofloxacin/clindamycin versus intravenous clindamycin/gentamicin (EB Table 20j)

- One small trial reported treatment failure when comparing oral ofloxacin/clindamycin versus intravenous clindamycin/gentamicin treatment. No difference was observed between the two groups (RR 0.67, 95% CI 0.15 to 2.98; 1 trial, 16 women).

Considerations related to the strength of the recommendation**Quality of the evidence**

The quality of the evidence was graded from low to very low. Overall, the quality of evidence was graded as very low.

Balance of benefits and harms

Compared to cephalosporins and penicillins, the combination of clindamycin plus an aminoglycoside (especially gentamicin) appears more effective in the successful treatment of postpartum endometritis. Although more information is required about the side-effects to fully understand the balance between the shown benefits and potential harms, clindamycin plus an aminoglycoside are generally not known to be associated with serious adverse effects in clinical practice. There was also no information regarding costs to determine the comparative cost-benefits of the various regimens, but it is recognized that clindamycin is associated with consistently higher costs or less attractive cost-effectiveness in a variety of settings.

Values and preferences

Health care providers and policy-makers in high-income setting are likely to place a high value on the added benefit of clindamycin and gentamicin over the two popular classes of antibiotics in terms of better treatment outcome and comparative side-effects. However, health care providers in low-income settings are likely to place a lower value on these added benefits because of cost and accessibility issues. The panel is uncertain regarding to what extent these values will vary across settings and populations. It is likely that preference for antibiotic regimens will vary according to existing policy in a particular setting, the clinicians' experience and knowledge about local antimicrobial resistance pattern, maternal allergy and availability and cost of the antibiotics.

Resource implications

It is technically feasible to include both clindamycin and gentamicin treatment into existing protocols for postpartum endometritis in health facilities. However, while gentamicin is cheap and readily available in all settings, clindamycin is comparatively more expensive and currently not readily available in all settings. The use of clindamycin is likely to increase health care costs, particularly in low-resource settings.

4. Research implications

Despite the burden of maternal peripartum infections, the quality of the evidence backing the recommendations made in this guideline was generally rated low or very low. For evidence rated low or very low, the GRADE methodology suggests that further research is very likely to have an impact on the direction and/or strength of the recommendation. In contrast, for evidence rated high or moderate, new research is not a priority.

Based on this approach, the GDG identified critical gaps in current evidence regarding the prevention and treatment of infectious conditions around childbirth. These knowledge gaps were prioritized according to their potential to improve maternal and/or neonatal outcomes and quality of care, incremental value, feasibility and likelihood to address equities. It was also noted that evidence is lacking regarding some widely used practices, such as the use of prophylactic antibiotics to prevent infectious morbidities in women with episiotomy or women having normal low-risk labour. In no order of priority, the following were the research gaps identified during the guideline development process:

- What is the comparative effectiveness and safety of chlorhexidine and povidone-iodine for vaginal cleansing among women undergoing caesarean section in preventing maternal infection morbidities?
 - What are the effects of vaginal cleansing immediately before caesarean section among women at potentially higher risk of infection (e.g. women with ruptured membranes)?
 - Is there any difference in the incidence of maternal infection morbidities between vaginal cleansing performed before or immediately after caesarean section?
- What are the potential adverse effects of the use of iodine containing antiseptics for vaginal cleansing for the newborn if the mother is planning to breastfeed?

- What are women's views and preferences (including satisfaction) about perineal/pubuc shaving prior to vaginal birth?
- What is the incidence of immediate and short-term complications (razor, vulval itching and burning sensation, discomfort during hair regrowth) after perineal/pubuc shaving in postpartum?
- What are the effects of routine prophylactic antibiotics on perineal wound infection morbidity among women with episiotomy?
- What are the effects of routine prophylactic antibiotics on preventing infection morbidity among women with normal (uncomplicated) vaginal birth?
- What are the effects of routine prophylactic antibiotics during the second and third trimester on women carrying high-risk pregnancies (e.g. history of preterm birth, low birthweight, previous preterm birth with bacterial vaginosis in the current pregnancy)?
- What is the contribution of the duration of rupture of membranes and length of labour on maternal and neonatal infectious morbidity among women with PROM at term?
- What are the benefits of initiating prophylactic antibiotics after prolonged rupture of membranes at term?
- What is the effect of administration of antibiotics prior to initiation of caesarean section on antibiotic resistance patterns in the neonates and longer-term infant health?

5. Dissemination and implementation of the guideline

The overall goal of this guideline is to improve maternal and neonatal health outcomes and the quality of care. Dissemination and implementation of recommendations in this guideline are to be considered by all actors implicated in the provision of care for pregnant women (clinicians, policy-makers) at the international, national and local levels.

Guideline dissemination and evaluation

The recommendations made in this guideline 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 guideline will also be available on the WHO website and in the WHO Reproductive Health Library. To increase awareness of the guideline, a short commentary will be published in a peer-reviewed journal. The guideline will also be disseminated during meetings or scientific conferences attended by staff of the RHR department. The executive summary will be translated into the six UN languages and disseminated through the WHO regional offices. Technical assistance will be provided to any WHO regional office willing to translate the full guideline into any of the six UN languages.

The guideline was evaluated using the AGREE-II appraisal instrument (www.agreetrust.org/agree-ii/) to ensure that it meets international quality standards and reporting criteria.

Guideline implementation

The Maternal and Perinatal Health team of the WHO RHR department will support national and local groups to adapt and implement the guideline based on the strategy used by the GREAT (Guideline-driven, Research priorities, Evidence synthesis, Application of evidence, and Transfer of knowledge) Network (www.greatnetworkglobal.org). The GREAT Network uses a unique evidence-based knowledge translation approach to support low- and middle-income countries in the adaptation and implementation of guidelines relating to reproductive, maternal, perinatal and newborn health, and has been successfully employed for other guidelines in many countries. Specifically, the GREAT Network brings together relevant stakeholders of the health care system to identify and assess the priorities, barriers and facilitators to guideline implementation, and supports the efforts of stakeholders to develop adaptation and guideline implementation strategies tailored to the local context. This includes technical support for local guideline implementers in the development of training manuals, flow charts and quality indicators as well as participation in stakeholder meetings.

In addition, WHO will update the Integrated Management of Pregnancy and Childbirth (IMPAC) manual in line with the recommendations in this guideline.

6. Applicability issues

Anticipated impact on the organization of care and resources

The evidence-based recommendations for the prevention and treatment of maternal infections in this guideline can be achieved with the use of relatively inexpensive practices and drugs. The GDG noted that the following issues should be considered to increase the impact and facilitate implementation of the recommendations made in this guideline:

- Ensure adequate WASH (water availability and quality, presence of sanitation facilities and availability of soap and water for hand washing) services at the facility level as an essential component of provision of care and infection prevention.
- Establish effective hygiene and infection prevention and control measures, based on current best practice at the facility level, including housekeeping and waste disposal.
- Health systems should ensure reliable supply systems and sustain availability and equitable access to antiseptics and antibiotics for use in obstetrics listed in the WHO Model List of Essential Medicines.
- Ensure high quality standards for the sterilization and storage of instruments and supplies used for labour- and childbirth-related procedures (e.g. episiotomy, vacuum- and forceps-assisted vaginal birth and caesarean section).
- Establish protocols to maintain fundamental surgical aseptic techniques (e.g. appropriate skin preparation, sterile drapes and instruments, gentle tissue handling, and haemostasis) when performing a caesarean section to reduce postoperative complications, including infection.
- Provide clear guidance for timely transfer of women to an obstetric-led facility for management of maternal and newborn peripartum infections.
- Provide clear guidance for timely transfer of women to specialized services (e.g. intensive care unit) for the management of maternal severe sepsis and septic shock and ensure availability of a protocol on resuscitation, antimicrobial therapy and subsequent supportive therapies.
- Provide standard postpartum care and follow-up, both at the facility and in the community, as required by the context, to ensure early identification and treatment of puerperal infections.

Monitoring and evaluating the guideline implementation

The implementation and impact of the recommendations in this guideline should be monitored at the health-service, regional and country levels based on clearly defined criteria and indicators that are associated with locally agreed targets. The recommended set of outcomes, measures and indicators can be adapted by regional and country levels to assess the impact of implementing and adherence to the guideline recommendations.

In collaboration with the WHO RHR and MCA departments' monitoring and evaluation team, data on country- and regional-level implementation of the recommendations will be collected and evaluated in the short to medium term to assess its impact on the national policy 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 undergoing caesarean section who receive antibiotic prophylaxis, calculated as the number of women who receive antibiotic prophylaxis for caesarean section divided by the total number of women undergoing caesarean section.
- Proportion of women with PPRM who receive antibiotic prophylaxis, calculated as the number of women with PPRM who receive antibiotic prophylaxis divided by the total number of women with PPRM.
- Incidence of surgical wound infection among women undergoing caesarean section, calculated as the number of women with surgical wound infection after caesarean section divided by the total number of women undergoing caesarean section.

The first two indicators provide an assessment of the use of evidence-based practices among women considered at higher risk of infection around childbirth, while the last indicator provides information on the efficacy of the intervention. The use of other locally developed indicators (e.g. use of practices that are not recommended, such as routine use of antibiotics for episiotomy and uncomplicated vaginal birth) may be necessary to better assess the quality of care related to prevention and treatment of peripartum infection morbidity.

7. Updating the guideline

In accordance with the concept of WHO's GREAT project (www.greatnetworkglobal.org), which employs a systematic and continuous process of identifying and bridging evidence gaps following guideline implementation, the proposed guideline will be updated five years after publication unless significant new evidence emerges which necessitates earlier revision. The Steering Group will continue to follow the research development in the area of maternal peripartum infections, particularly relating to those questions for which no evidence was found and those that are supported by low-quality evidence, where new recommendations or a change in the published recommendation may be warranted, respectively. Following publication and dissemination of the guideline, any concerns about the validity of any recommendation will be promptly communicated to guideline implementers, in addition to plans to update the recommendation.

As the guideline nears the end of its proposed five-year validity period, the responsible technical officer (or another designated WHO staff), in conjunction with the Steering Group, will assess the currency of the recommendations and the need for new guidance on the topic. Where there are concerns about the validity of a particular recommendation based on new evidence, the systematic review addressing the primary question will be updated. To update the review, the existing search strategy used for the initial review will be applied, possibly by the same systematic review team or another team if the initial review team is no longer available. Any new questions identified following the scoping exercise at the end of five years will undergo a similar process of evidence retrieval, synthesis and grading in accordance with the WHO standards for guideline development.

WHO welcomes suggestions regarding additional questions for inclusion in the updated guideline. Please email your suggestions to: mpa-info@who.int or reproductivehealth@who.int.

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Annex 2. Critical and important outcomes for decision-making

KEY QUESTIONS	PRIORITY OUTCOMES C=Critical outcomes; I=Important outcomes
1. Among pregnant women in labour (P), does routine perineal/pubuc shaving prior to giving birth (I), compared with no perineal/pubuc shaving (C), prevent infectious morbidities and improve outcomes (O)?	<p>Puerperal sepsis (endometritis with/without myometritis and with/without salpingitis causing maternal febrile morbidity) (C) Wound infection (episiotomy, perineal or vaginal) (C) Local discomfort (perineal irritation/allergy) (C)</p> <p>Maternal satisfaction with care (I) Cost of care (I) Neonatal infection (I)</p>
2. Among pregnant women undergoing labour monitoring (P), does routine vaginal examination at intervals of four hours (I), compared with shorter intervals (C), prevent infectious morbidities and improve outcomes (O)?	<p>Puerperal sepsis (endometritis with/without myometritis and with/without salpingitis causing maternal febrile morbidity) (C) Chorioamnionitis or maternal intrapartum infection (C) Wound infection (episiotomy, perineal or vaginal) (C) Neonatal infection (C) Severe neonatal morbidity (e.g. neonatal ICU admission) (C) Perinatal mortality (C)</p> <p>Maternal death (I) Severe infectious morbidity (septicaemia, septic shock, laparotomy/hysterectomy for infection, maternal ICU admission) (I) Maternal satisfaction (I) Maternal hospital stay (I) Cost of care (I)</p>
3. Among pregnant women in labour (P), does routine vaginal cleansing with an antiseptic agent (I), compared with no vaginal cleansing with an antiseptic agent (C), prevent infectious morbidities and improve outcomes following vaginal birth (O)?	<p>Puerperal sepsis (endometritis with/without myometritis and with/without salpingitis causing maternal febrile morbidity) (C) Chorioamnionitis or maternal intrapartum infection (C) Side-effects (vaginal irritation/allergic reaction) (C) Wound infection (episiotomy, perineal or vaginal) (C) Perinatal mortality (C) Severe neonatal morbidity (e.g. neonatal ICU admission) (C) Neonatal infection (C)</p> <p>Severe infectious morbidity (septicaemia, septic shock, laparotomy/hysterectomy for infection, maternal ICU admission) (I) Maternal death (I) Cost of care (I)</p>
4. Among pregnant women with vaginal, rectal or urethral colonization with group B Streptococcus (P), does routine vaginal cleansing with an antiseptic agent during labour (I), compared with no vaginal cleansing with an antiseptic agent (C), prevent neonatal infectious morbidities and improve neonatal outcomes (O)?	<p>Local discomfort (vaginal irritation/allergic reaction) (C) Neonatal death (C) Neonatal infection (C) Severe neonatal morbidity (e.g. neonatal ICU admission) (C)</p> <p>Puerperal sepsis (endometritis with/without myometritis and with/without salpingitis causing maternal febrile morbidity) (I) Cost of care (I) Maternal satisfaction (I) Chorioamnionitis or maternal intrapartum infection (I) Wound infection (episiotomy, perineal or vaginal) (I)</p>

KEY QUESTIONS	PRIORITY OUTCOMES C=Critical outcomes; I=Important outcomes
5. Among pregnant women with vaginal, rectal or urethral colonization with group B Streptococcus (P), does routine administration of antibiotics during labour (I), compared with no antibiotics (C), prevent neonatal infectious morbidities and improve neonatal outcomes (O)?	<p>Antimicrobial resistance (C) Perinatal mortality (C) Neonatal infection (C) Severe neonatal morbidity (e.g. neonatal ICU admission) (C)</p> <p>Puerperal sepsis (endometritis with/without myometritis and with/without salpingitis causing maternal febrile morbidity) (I) Maternal satisfaction (I) Chorioamnionitis or maternal intrapartum infection (I) Wound infection (episiotomy, perineal or vaginal) (I) Side-effects of antibiotics (I) Cost of care (I)</p>
6. Among women in the second or third trimester of pregnancy (P), does routine antibiotic prophylaxis (I), compared with no antibiotic prophylaxis (C), prevent infectious morbidities and improve outcomes (O)?	<p>Puerperal sepsis (endometritis with/without myometritis and with/without salpingitis causing maternal febrile morbidity) (C) Wound infection (episiotomy, perineal or vaginal) (C) Chorioamnionitis or maternal intrapartum infection (C) Severe maternal infectious morbidity (septicaemia, septic shock, laparotomy or hysterectomy for infection, maternal ICU admission) (C) Side-effects of antibiotics (C) Antimicrobial resistance (C) Perinatal mortality (C) Severe neonatal morbidity (e.g. neonatal ICU admission) (C) Neonatal infection (C)</p> <p>Cost of care (I)</p>
7. Among pregnant women in preterm labour with intact amniotic membranes (P), does routine antibiotic prophylaxis (I), compared with no routine antibiotic prophylaxis (C), prevent infectious morbidities and improve outcomes (O)?	<p>Puerperal sepsis (endometritis with/without myometritis with/without salpingitis causing maternal febrile morbidity) (C) Chorioamnionitis or maternal intrapartum infection (C) Maternal death (C) Severe maternal infectious morbidity (septicaemia, septic shock, laparotomy or hysterectomy for infection, or maternal ICU admission) (C) Perinatal mortality (C) Severe neonatal morbidity (e.g. neonatal ICU admission) (C) Side-effects of antibiotics (C) Antimicrobial resistance (C)</p>
8. Among pregnant women with preterm prelabour rupture of membranes (P), does routine antibiotic prophylaxis (I), compared with no routine antibiotic prophylaxis (C), prevent infectious morbidities and improve outcomes (O)?	<p>Puerperal sepsis (endometritis with/without myometritis and with/without salpingitis causing maternal febrile morbidity) (C) Chorioamnionitis or maternal intrapartum infection (C) Maternal death (C) Severe maternal infectious morbidity (septicaemia, septic shock, laparotomy or hysterectomy for infection, or maternal ICU admission) (C) Side-effects of antibiotics (C) Antimicrobial resistance (C) Perinatal mortality (C) Severe neonatal morbidity (e.g. neonatal ICU admission) (C)</p>

KEY QUESTIONS	PRIORITY OUTCOMES C=Critical outcomes; I=Important outcomes
9. Among pregnant women with prelabour rupture of membranes at (or near) term (P), does routine antibiotic prophylaxis (I), compared with no routine antibiotic prophylaxis (C), prevent infectious morbidities and improve outcomes (O)?	<p>Puerperal sepsis (endometritis with/without myometritis and with/without salpingitis causing maternal febrile morbidity) (C)</p> <p>Chorioamnionitis or maternal intrapartum infection (C)</p> <p>Maternal death (C)</p> <p>Severe maternal infectious morbidity (septicaemia, septic shock, laparotomy or hysterectomy for infection, or maternal ICU admission) (C)</p> <p>Side-effects of antibiotics (C)</p> <p>Antimicrobial resistance (C)</p> <p>Perinatal mortality (C)</p> <p>Severe neonatal morbidity (e.g. neonatal ICU admission) (C)</p>
10. Among pregnant women with meconium-stained amniotic fluid during labour (P), does routine administration of antibiotics (I), compared with no routine antibiotics (C), prevent infectious morbidities and improve outcomes (O)?	<p>Severe infectious morbidity (septicaemia, septic shock, laparotomy/ hysterectomy for infection, maternal ICU admission) (C)</p> <p>Chorioamnionitis or maternal intrapartum infection (C)</p> <p>Puerperal sepsis (endometritis with/without myometritis and with/without salpingitis causing maternal febrile morbidity) (C)</p> <p>Side-effects of antibiotics (C)</p> <p>Antimicrobial resistance (C)</p> <p>Neonatal mortality (C)</p> <p>Neonatal infection (C)</p> <p>Severe neonatal morbidity (e.g. neonatal ICU admission) (C)</p> <p>Cost of care (I)</p>
11. Among women undergoing manual removal of retained placenta following birth (P), does antibiotic prophylaxis (I), compared with no antibiotic prophylaxis (C), prevent infectious morbidities and improve outcomes (O)?	<p>Severe maternal infectious morbidity (septicaemia, septic shock, laparotomy or hysterectomy for infection, or maternal ICU admission) (C)</p> <p>Maternal death (I)</p> <p>Puerperal sepsis (endometritis with/without myometritis and with/without salpingitis causing maternal febrile morbidity) (C)</p> <p>Side-effects of antibiotics (I)</p> <p>Antimicrobial resistance (C)</p> <p>Wound infection (episiotomy, perineal, or vaginal) (I)</p> <p>Cost of care (I)</p>
12. Among women undergoing operative vaginal delivery (P), does routine antibiotic prophylaxis (I), compared with no prophylaxis (C), prevent infectious morbidities and improve outcomes (O)?	<p>Severe infectious morbidity (septicaemia, septic shock, laparotomy/ hysterectomy for infection, maternal ICU admission) (C)</p> <p>Puerperal sepsis (endometritis with/without myometritis and with/without salpingitis causing maternal febrile morbidity) (C)</p> <p>Wound infection (episiotomy, perineal, or vaginal) (C)</p> <p>Antimicrobial resistance (C)</p> <p>Side-effects of antibiotics (I)</p> <p>Cost of care (I)</p> <p>Neonatal sepsis (I)</p> <p>Neonatal mortality (I)</p>
13. Among women with third- or fourth-degree perineal tear after birth (P), does routine antibiotic prophylaxis (I), compared with no antibiotic prophylaxis (C), prevent maternal infectious morbidities and improve outcomes (O)?	<p>Wound infection (perineal) (C)</p> <p>Puerperal sepsis (endometritis with/without myometritis and with/without salpingitis causing maternal febrile morbidity) (C)</p> <p>Local discomfort (C)</p> <p>Sexual dysfunction (C)</p> <p>Severe maternal infectious morbidity (septicaemia, septic shock, laparotomy or hysterectomy for infection, or maternal ICU admission) (I)</p> <p>Duration of hospital stay (I)</p> <p>Side-effects of antibiotics (I)</p> <p>Cost of care (I)</p>

KEY QUESTIONS	PRIORITY OUTCOMES C=Critical outcomes; I=Important outcomes
14. Among women who had an episiotomy for vaginal birth (P), does routine antibiotic prophylaxis (I), compared with no routine antibiotic prophylaxis (C), prevent maternal infectious morbidities and improve outcomes (O)?	<p>Wound infection (C) Wound dehiscence (C) Puerperal sepsis (endometritis with/without myometritis and with/without salpingitis causing maternal febrile morbidity) (C)</p> <p>Severe maternal infectious morbidity (septicaemia, septic shock, laparotomy or hysterectomy for infection, maternal ICU admission) (I) Discomfort/pain at episiotomy wound site (I) Cost of care (I) Maternal hospital stay (I) Antimicrobial resistance (I)</p>
15. Among pregnant women with uncomplicated vaginal birth (P), does antibiotic prophylaxis after birth (I), compared with no prophylaxis or placebo (C) prevent infectious morbidities and improve outcomes (O)?	<p>Severe maternal infectious morbidity (septicaemia, septic shock, laparotomy or hysterectomy for infection, maternal ICU admission) (C) Puerperal sepsis (endometritis with/without myometritis and with/without salpingitis causing maternal febrile morbidity) (C) Wound infection (C) Urinary tract infection (C) Maternal hospital stay (C) Side-effects of antibiotics (C) Antimicrobial resistance (C)</p> <p>Cost of care (I)</p>
16. Among pregnant women with indications for caesarean section (P), does vaginal cleansing with an antiseptic agent prior to caesarean delivery (I), compared with no vaginal cleansing with an antiseptic agent (C), prevent postoperative maternal infectious morbidities (O)?	<p>Severe maternal infectious morbidity (septicaemia, septic shock, laparotomy or hysterectomy for infection, maternal ICU admission) (C) Puerperal sepsis (endometritis with/without myometritis and with/without salpingitis causing maternal febrile morbidity) (C)</p> <p>Wound infection (I) Side-effects of antiseptics (vaginal irritation/allergy) (I) Cost of care (I)</p>
17. (i) Among pregnant women undergoing caesarean delivery (P), is the use of a particular antiseptic agent for preoperative skin preparation (I), compared with other antiseptic agent(s) (C), more effective in preventing post-caesarean infectious morbidities (O)? (ii) Among pregnant women undergoing caesarean delivery (P), is the use of a particular method of antiseptic application for preoperative skin preparation (I), compared with other methods of antiseptic application (C), more effective in preventing postcaesarean infectious morbidities (O)?	<p>Wound infection (C) Puerperal sepsis (endometritis with/without myometritis and with/without salpingitis causing maternal febrile morbidity) (C) Severe maternal infectious morbidity (septicaemia, septic shock, laparotomy or hysterectomy for infection, maternal ICU admission) (C)</p> <p>Maternal death (I) Cost of care (I) Allergy/irritation at operation site (I) Maternal satisfaction (I) Neonatal infection (I) Severe neonatal morbidity (e.g. neonatal ICU admission) (I)</p>

KEY QUESTIONS	PRIORITY OUTCOMES C=Critical outcomes; I=Important outcomes
18.0 Among women undergoing caesarean section (P), does routine antibiotic prophylaxis (I), compared with no antibiotic prophylaxis (C), prevent infectious morbidities and improve outcomes (O)?	<p>Maternal death (C) Severe infectious morbidity (septicaemia, septic shock, laparotomy/hysterectomy for infection, maternal ICU admission) (C) Puerperal sepsis (endometritis with/without myometritis with/without salpingitis causing maternal febrile morbidity) (C) Wound infection (C) Antimicrobial resistance (C)</p> <p>Neonatal sepsis (I) Neonatal mortality (I) Side-effects of antibiotics (I) Cost of care (I)</p>
18.1 Among women receiving antibiotic prophylaxis for caesarean section (P), is preoperative administration of antibiotics (I), compared with intraoperative administration of antibiotics after umbilical cord clamping (C), more effective in preventing maternal and neonatal infectious morbidities (O)?	<p>Severe infectious morbidity (septicaemia, septic shock, laparotomy/hysterectomy for infection, maternal ICU admission) (C) Puerperal sepsis (endometritis with/without myometritis with/without salpingitis causing maternal febrile morbidity) (C) Wound infection (C) Severe neonatal morbidity (e.g. neonatal ICU admission) (C)</p> <p>Maternal death (I) Side-effects of antibiotics (I) Cost of care (I) Antimicrobial resistance (I) Neonatal infection (I) Neonatal mortality (I)</p>
18.2 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 postoperative infectious morbidities (O)?	<p>Severe infectious morbidity (septicaemia, septic shock, laparotomy/hysterectomy for infection, maternal ICU admission) (C) Puerperal sepsis (endometritis with/without myometritis with/without salpingitis causing maternal febrile morbidity) (C) Wound infection (C) Side-effects of antibiotics (C) Antimicrobial resistance (C)</p> <p>Maternal death (I) Cost of care (I) Antimicrobial resistance (I) Neonatal mortality (I) Neonatal infection (I)</p>
19. Among women receiving antibiotic treatment for intra-amniotic infection / chorioamnionitis (P), is the use of a particular antibiotic regimen (I), compared with other regimens (C), more effective in improving maternal and neonatal outcomes (O)?	<p>Severe infectious morbidity (septicaemia, septic shock, laparotomy/hysterectomy for infection, maternal ICU admission) (C) Puerperal sepsis (endometritis with/without myometritis and with/without salpingitis causing maternal febrile morbidity) (C) Side-effects of antibiotics (C) Antimicrobial resistance (C) Neonatal mortality (C) Neonatal infection (C)</p> <p>Maternal death (I) Cost of care (I)</p>
20. Among women receiving antibiotic treatment for postpartum endometritis (P), is the use of a particular antibiotic regimen (I), compared with other regimens (C), more effective in improving maternal outcomes (O)?	<p>Severe infectious morbidity (septicaemia, septic shock, laparotomy/hysterectomy for infection, maternal ICU admission) (C) Duration of hospital stay (C) Side-effects of antibiotics (C) Antimicrobial resistance (C) Long-term complications e.g. subfertility, uterine adhesions (C)</p> <p>Maternal death (I) Cost of care (I)</p>

Annex 3 Summary and management of declared interests of Guideline Development Group members

NAME AND EXPERTISE CONTRIBUTED TO THE GUIDELINE DEVELOPMENT	DECLARED INTEREST(S)	MANAGEMENT OF CONFLICT(S) OF INTEREST
Dr Subha Sri Balakrishnan Expertise: End-user and women's representative	None declared	None
Ms Beverly Chambers Expertise: Women's representative	None declared	None
Dr Maria Laura Costa Expertise: Content expert and end-user	None declared	None
Professor Malik Goonewardene Expertise: Content expert and end-user	None declared	None
Ms Sonja Henderson Expertise: Methodologist	None declared	None
Dr Julia Hussein Expertise: Content expert and end-user	Research grants, consultancies and travel expenses for meetings from private non-profit organizations, including MacArthur Foundation and PATH, amounting to approx. \$600,000 from 2009 to 2013.	Research grants covered maternal health service research for leading causes of maternal death and morbidity in general, and not specific to maternal sepsis. Her research interests were not considered to conflict with her interests in this guideline development.
Ms Chowa Kasengele Expertise: Content expert and end-user	Consultancies for Jhpiego to train health workers on elimination of mother-to-child HIV transmission and mentorship of nursing staff in family planning in Zambia.	The declared interests were not considered relevant to this guideline.
Professor Pisake Lumbiganon Expertise: Content expert and end-user	Co-author of five Cochrane systematic reviews used in this guideline.	The declared academic conflict was not considered significant enough to affect GDG membership or participation in the technical consultation. Nevertheless, Professor Lumbiganon was restricted from participating in the discussions and formulation of recommendations related to the Cochrane reviews that he co-authored.
Professor Ashraf Nabhan Expertise: Content expert and end-user	None declared	None
Professor Ruta Nadisauskiene Expertise: Content expert and end-user	None declared	None
Professor James Neilson Expertise: Content expert and end-user	None declared	None

NAME AND EXPERTISE CONTRIBUTED TO THE GUIDELINE DEVELOPMENT	DECLARED INTEREST(S)	MANAGEMENT OF CONFLICT(S) OF INTEREST
Dr Alfred Osoti Expertise: Content expert and end-user	None declared	None
Professor Xu Qian Expertise: Content expert and end-user	None declared	None
Professor Haroon Saloojee Expertise: Content expert and end-user	None declared	None
Dr Jeffrey Smith Expertise: Content expert and implementer	Employee of Jhpiego, which works to promote quality of care and reduction of maternal and newborn mortality. Receives a salary from Jhpiego and programme support from USAID and other donors for research and programmatic work in the area of quality of care. Amount of USAID support for the Maternal and Child Survival Program is approximately \$50 million for all areas in 2015.	His organizational and personal conflicts of interests were not considered significant enough to pose any risk to the guideline development process or reduce its credibility. Dr Smith, through support from Jhpiego and USAID, has been a key partner in promoting and implementing all published WHO guidelines relating to maternal and newborn health since the late 1990s.
Professor Adewale Sule-Odu Expertise: Content expert and end-user	None declared	None

Annex 4. Summary of the considerations related to the strength of the recommendations (balance worksheets)

RECOMMENDATION	1	2	3	4	5
Intervention	Perineal/public shaving prior to vaginal birth	Digital vaginal examination at intervals of four hours for routine assessment of active labour	Vaginal cleansing with chlorhexidine for preventing infections during labour	Vaginal cleansing with chlorhexidine for GBS-colonized women during labour	Intrapartum prophylactic antibiotics for GBS-colonized women
Quality of the evidence	<input type="checkbox"/> High <input type="checkbox"/> Moderate <input type="checkbox"/> Low <input checked="" type="checkbox"/> Very low	<input type="checkbox"/> High <input type="checkbox"/> Moderate <input type="checkbox"/> Low <input checked="" type="checkbox"/> Very low	<input type="checkbox"/> High <input checked="" type="checkbox"/> Moderate <input type="checkbox"/> Low <input type="checkbox"/> Very low	<input type="checkbox"/> High <input type="checkbox"/> Moderate <input type="checkbox"/> Low <input checked="" type="checkbox"/> Very low	<input type="checkbox"/> High <input type="checkbox"/> Moderate <input type="checkbox"/> Low <input checked="" type="checkbox"/> Very low
Values and preferences	<input type="checkbox"/> No significant variability <input checked="" type="checkbox"/> Significant variability	<input checked="" type="checkbox"/> No significant variability <input type="checkbox"/> Significant variability	<input checked="" type="checkbox"/> No significant variability <input type="checkbox"/> Significant variability	<input type="checkbox"/> No significant variability <input checked="" type="checkbox"/> Significant variability	<input type="checkbox"/> No significant variability <input checked="" type="checkbox"/> Significant variability
Balance of benefits versus disadvantages	<input type="checkbox"/> Benefits outweigh disadvantages <input type="checkbox"/> Benefits and disadvantages are balanced <input checked="" type="checkbox"/> Disadvantages outweigh benefits	<input checked="" type="checkbox"/> Benefits outweigh disadvantages <input type="checkbox"/> Benefits and disadvantages are balanced <input type="checkbox"/> Disadvantages outweigh benefits	<input type="checkbox"/> Benefits outweigh disadvantages <input type="checkbox"/> Benefits and disadvantages are balanced <input checked="" type="checkbox"/> Disadvantages outweigh benefits	<input type="checkbox"/> Benefits outweigh disadvantages <input type="checkbox"/> Benefits and disadvantages are balanced <input checked="" type="checkbox"/> Disadvantages outweigh benefits	<input checked="" type="checkbox"/> Benefits outweigh disadvantages <input type="checkbox"/> Benefits and disadvantages are balanced <input type="checkbox"/> Disadvantages outweigh benefits
Resource use	<input checked="" type="checkbox"/> Less resource intensive <input type="checkbox"/> More resource intensive	<input checked="" type="checkbox"/> Less resource intensive <input type="checkbox"/> More resource intensive	<input checked="" type="checkbox"/> Less resource intensive <input type="checkbox"/> More resource intensive	<input checked="" type="checkbox"/> Less resource intensive <input type="checkbox"/> More resource intensive	<input type="checkbox"/> Less resource intensive <input checked="" type="checkbox"/> More resource intensive
Recommendation direction	<input type="checkbox"/> In favour of the intervention <input checked="" type="checkbox"/> Against the intervention	<input checked="" type="checkbox"/> In favour of the intervention <input type="checkbox"/> Against the intervention	<input type="checkbox"/> In favour of the intervention <input checked="" type="checkbox"/> Against the intervention	<input type="checkbox"/> In favour of the intervention <input checked="" type="checkbox"/> Against the intervention	<input checked="" type="checkbox"/> In favour of the intervention <input type="checkbox"/> Against the intervention
Overall ranking	<input type="checkbox"/> Strong recommendation <input checked="" type="checkbox"/> Conditional recommendation	<input checked="" type="checkbox"/> Strong recommendation <input type="checkbox"/> Conditional recommendation	<input checked="" type="checkbox"/> Strong recommendation <input type="checkbox"/> Conditional recommendation	<input type="checkbox"/> Strong recommendation <input checked="" type="checkbox"/> Conditional recommendation	<input type="checkbox"/> Strong recommendation <input checked="" type="checkbox"/> Conditional recommendation

RECOMMENDATION	6	7	8	9	10
Intervention	Prophylactic antibiotics during the second or third trimester	Prophylactic antibiotics for preterm labour with intact membranes	Prophylactic antibiotics for preterm prelabour rupture of membranes	Prophylactic antibiotics for prelabour rupture of membranes at (or near) term	Prophylactic antibiotics for women with meconium-stained amniotic fluid
Quality of the evidence	<input type="checkbox"/> High <input type="checkbox"/> Moderate <input type="checkbox"/> Low <input checked="" type="checkbox"/> Very low	<input type="checkbox"/> High <input checked="" type="checkbox"/> Moderate <input type="checkbox"/> Low <input type="checkbox"/> Very low	<input type="checkbox"/> High <input checked="" type="checkbox"/> Moderate <input type="checkbox"/> Low <input type="checkbox"/> Very low	<input type="checkbox"/> High <input type="checkbox"/> Moderate <input checked="" type="checkbox"/> Low <input type="checkbox"/> Very low	<input type="checkbox"/> High <input type="checkbox"/> Moderate <input checked="" type="checkbox"/> Low <input type="checkbox"/> Very low
Values and preferences	<input checked="" type="checkbox"/> No significant variability <input type="checkbox"/> Significant variability	<input checked="" type="checkbox"/> No significant variability <input type="checkbox"/> Significant variability	<input checked="" type="checkbox"/> No significant variability <input type="checkbox"/> Significant variability	<input checked="" type="checkbox"/> No significant variability <input type="checkbox"/> Significant variability	<input checked="" type="checkbox"/> No significant variability <input type="checkbox"/> Significant variability
Balance of benefits versus disadvantages	<input type="checkbox"/> Benefits outweigh disadvantages <input type="checkbox"/> Benefits and disadvantages are balanced <input checked="" type="checkbox"/> Disadvantages outweigh benefits	<input type="checkbox"/> Benefits outweigh disadvantages <input type="checkbox"/> Benefits and disadvantages are balanced <input checked="" type="checkbox"/> Disadvantages outweigh benefits	<input checked="" type="checkbox"/> Benefits outweigh disadvantages <input type="checkbox"/> Benefits and disadvantages are balanced <input type="checkbox"/> Disadvantages outweigh benefits	<input type="checkbox"/> Benefits outweigh disadvantages <input type="checkbox"/> Benefits and disadvantages are balanced <input checked="" type="checkbox"/> Disadvantages outweigh benefits	<input type="checkbox"/> Benefits outweigh disadvantages <input type="checkbox"/> Benefits and disadvantages are balanced <input checked="" type="checkbox"/> Disadvantages outweigh benefits
Resource use	<input checked="" type="checkbox"/> Less resource intensive <input type="checkbox"/> More resource intensive	<input checked="" type="checkbox"/> Less resource intensive <input type="checkbox"/> More resource intensive	<input type="checkbox"/> Less resource intensive <input checked="" type="checkbox"/> More resource intensive	<input checked="" type="checkbox"/> Less resource intensive <input type="checkbox"/> More resource intensive	<input checked="" type="checkbox"/> Less resource intensive <input type="checkbox"/> More resource intensive
Recommendation direction	<input type="checkbox"/> In favour of the intervention <input checked="" type="checkbox"/> Against the intervention	<input type="checkbox"/> In favour of the intervention <input checked="" type="checkbox"/> Against the intervention	<input checked="" type="checkbox"/> In favour of the intervention <input type="checkbox"/> Against the intervention	<input type="checkbox"/> In favour of the intervention <input checked="" type="checkbox"/> Against the intervention	<input type="checkbox"/> In favour of the intervention <input checked="" type="checkbox"/> Against the intervention
Overall ranking	<input checked="" type="checkbox"/> Strong recommendation <input type="checkbox"/> Conditional recommendation	<input checked="" type="checkbox"/> Strong recommendation <input type="checkbox"/> Conditional recommendation	<input checked="" type="checkbox"/> Strong recommendation <input type="checkbox"/> Conditional recommendation	<input checked="" type="checkbox"/> Strong recommendation <input type="checkbox"/> Conditional recommendation	<input type="checkbox"/> Strong recommendation <input checked="" type="checkbox"/> Conditional recommendation

RECOMMENDATION	11	12	13	14	15
Intervention	Prophylactic antibiotics for women undergoing manual removal of the placenta	Prophylactic antibiotics for women undergoing operative vaginal delivery	Prophylactic antibiotics for women with third- or fourth-degree perineal tear	Prophylactic antibiotics for women with an episiotomy	Prophylactic antibiotics for women with uncomplicated vaginal birth
Quality of the evidence	<input type="checkbox"/> High	<input type="checkbox"/> High	<input type="checkbox"/> High	<input type="checkbox"/> High	<input type="checkbox"/> High
	<input type="checkbox"/> Moderate	<input type="checkbox"/> Moderate	<input type="checkbox"/> Moderate	<input type="checkbox"/> Moderate	<input type="checkbox"/> Moderate
	<input type="checkbox"/> Low	<input type="checkbox"/> Low	<input type="checkbox"/> Low	<input type="checkbox"/> Low	<input type="checkbox"/> Low
	<input checked="" type="checkbox"/> Very low	<input checked="" type="checkbox"/> Very low	<input checked="" type="checkbox"/> Very low	<input checked="" type="checkbox"/> Very low	<input checked="" type="checkbox"/> Very low
Values and preferences	<input type="checkbox"/> No significant variability	<input checked="" type="checkbox"/> No significant variability	<input checked="" type="checkbox"/> No significant variability	<input checked="" type="checkbox"/> No significant variability	<input checked="" type="checkbox"/> No significant variability
	<input checked="" type="checkbox"/> Significant variability	<input type="checkbox"/> Significant variability	<input type="checkbox"/> Significant variability	<input type="checkbox"/> Significant variability	<input type="checkbox"/> Significant variability
Balance of benefits versus disadvantages	<input checked="" type="checkbox"/> Benefits outweigh disadvantages	<input type="checkbox"/> Benefits outweigh disadvantages	<input checked="" type="checkbox"/> Benefits outweigh disadvantages	<input type="checkbox"/> Benefits outweigh disadvantages	<input type="checkbox"/> Benefits outweigh disadvantages
	<input type="checkbox"/> Benefits and disadvantages are balanced	<input type="checkbox"/> Benefits and disadvantages are balanced	<input type="checkbox"/> Benefits and disadvantages are balanced	<input type="checkbox"/> Benefits and disadvantages are balanced	<input type="checkbox"/> Benefits and disadvantages are balanced
	<input type="checkbox"/> Disadvantages outweigh benefits	<input checked="" type="checkbox"/> Disadvantages outweigh benefits	<input type="checkbox"/> Disadvantages outweigh benefits	<input checked="" type="checkbox"/> Disadvantages outweigh benefits	<input checked="" type="checkbox"/> Disadvantages outweigh benefits
		<input type="checkbox"/> Less resource intensive	<input checked="" type="checkbox"/> Less resource intensive	<input type="checkbox"/> Less resource intensive	<input checked="" type="checkbox"/> Less resource intensive
Resource use	<input checked="" type="checkbox"/> More resource intensive	<input type="checkbox"/> More resource intensive	<input checked="" type="checkbox"/> More resource intensive	<input type="checkbox"/> More resource intensive	<input type="checkbox"/> More resource intensive
		<input checked="" type="checkbox"/> In favour of the intervention	<input type="checkbox"/> In favour of the intervention	<input type="checkbox"/> In favour of the intervention	<input type="checkbox"/> In favour of the intervention
Recommendation direction	<input type="checkbox"/> Against the intervention	<input checked="" type="checkbox"/> Against the intervention	<input type="checkbox"/> Against the intervention	<input checked="" type="checkbox"/> Against the intervention	<input checked="" type="checkbox"/> Against the intervention
	<input checked="" type="checkbox"/> Strong recommendation	<input type="checkbox"/> Strong recommendation	<input checked="" type="checkbox"/> Strong recommendation	<input checked="" type="checkbox"/> Strong recommendation	<input checked="" type="checkbox"/> Strong recommendation
Overall ranking	<input type="checkbox"/> Conditional recommendation	<input checked="" type="checkbox"/> Conditional recommendation	<input type="checkbox"/> Conditional recommendation	<input type="checkbox"/> Conditional recommendation	<input type="checkbox"/> Conditional recommendation

RECOMMENDATION	16	17	18.0	18.1	18.2
Intervention	Vaginal cleansing with an antiseptic agent before caesarean section	Choice of antiseptic agent and its method of application for skin preparation prior to caesarean section	Prophylactic antibiotics for women undergoing caesarean section	Timing of antibiotic prophylaxis for caesarean section	Class of antibiotic prophylaxis for caesarean section
Quality of the evidence	<input type="checkbox"/> High <input checked="" type="checkbox"/> Moderate <input type="checkbox"/> Low <input type="checkbox"/> Very low	<input type="checkbox"/> High <input type="checkbox"/> Moderate <input checked="" type="checkbox"/> Low <input type="checkbox"/> Very low	<input type="checkbox"/> High <input checked="" type="checkbox"/> Moderate <input type="checkbox"/> Low <input type="checkbox"/> Very low	<input type="checkbox"/> High <input checked="" type="checkbox"/> Moderate <input type="checkbox"/> Low <input type="checkbox"/> Very low	<input type="checkbox"/> High <input type="checkbox"/> Moderate <input type="checkbox"/> Low <input checked="" type="checkbox"/> Very low
Values and preferences	<input checked="" type="checkbox"/> No significant variability <input type="checkbox"/> Significant variability	<input type="checkbox"/> No significant variability <input checked="" type="checkbox"/> Significant variability	<input checked="" type="checkbox"/> No significant variability <input type="checkbox"/> Significant variability	<input checked="" type="checkbox"/> No significant variability <input type="checkbox"/> Significant variability	<input type="checkbox"/> No significant variability <input checked="" type="checkbox"/> Significant variability
Balance of benefits versus disadvantages	<input checked="" type="checkbox"/> Benefits outweigh disadvantages <input type="checkbox"/> Benefits and disadvantages are balanced <input type="checkbox"/> Disadvantages outweigh benefits	<input checked="" type="checkbox"/> Benefits outweigh disadvantages <input type="checkbox"/> Benefits and disadvantages are balanced <input type="checkbox"/> Disadvantages outweigh benefits	<input checked="" type="checkbox"/> Benefits outweigh disadvantages <input type="checkbox"/> Benefits and disadvantages are balanced <input type="checkbox"/> Disadvantages outweigh benefits	<input checked="" type="checkbox"/> Benefits outweigh disadvantages <input type="checkbox"/> Benefits and disadvantages are balanced <input type="checkbox"/> Disadvantages outweigh benefits	<input checked="" type="checkbox"/> Benefits outweigh disadvantages <input type="checkbox"/> Benefits and disadvantages are balanced <input type="checkbox"/> Disadvantages outweigh benefits
Resource use	<input type="checkbox"/> Less resource intensive <input checked="" type="checkbox"/> More resource intensive	<input type="checkbox"/> Less resource intensive <input checked="" type="checkbox"/> More resource intensive	<input type="checkbox"/> Less resource intensive <input checked="" type="checkbox"/> More resource intensive	<input type="checkbox"/> Less resource intensive <input checked="" type="checkbox"/> More resource intensive	<input type="checkbox"/> Less resource intensive <input checked="" type="checkbox"/> More resource intensive
Recommendation direction	<input checked="" type="checkbox"/> In favour of the intervention <input type="checkbox"/> Against the intervention	<input checked="" type="checkbox"/> In favour of the intervention <input type="checkbox"/> Against the intervention	<input checked="" type="checkbox"/> In favour of the intervention <input type="checkbox"/> Against the intervention	<input checked="" type="checkbox"/> In favour of the intervention <input type="checkbox"/> Against the intervention	<input checked="" type="checkbox"/> In favour of the intervention <input type="checkbox"/> Against the intervention
Overall ranking	<input type="checkbox"/> Strong recommendation <input checked="" type="checkbox"/> Conditional recommendation	<input type="checkbox"/> Strong recommendation <input checked="" type="checkbox"/> Conditional recommendation	<input checked="" type="checkbox"/> Strong recommendation <input type="checkbox"/> Conditional recommendation	<input checked="" type="checkbox"/> Strong recommendation <input type="checkbox"/> Conditional recommendation	<input type="checkbox"/> Strong recommendation <input checked="" type="checkbox"/> Conditional recommendation

RECOMMENDATION	19	20
Intervention	Antibiotic regimens for the treatment of chorioamnionitis	Antibiotic regimens for the treatment of postpartum endometritis
Quality of the evidence	<input type="checkbox"/> High <input type="checkbox"/> Moderate <input type="checkbox"/> Low <input checked="" type="checkbox"/> Very low	<input type="checkbox"/> High <input type="checkbox"/> Moderate <input type="checkbox"/> Low <input checked="" type="checkbox"/> Very low
Values and preferences	<input type="checkbox"/> No significant variability <input checked="" type="checkbox"/> Significant variability	<input type="checkbox"/> No significant variability <input checked="" type="checkbox"/> Significant variability
Balance of benefits versus disadvantages	<input checked="" type="checkbox"/> Benefits outweigh disadvantages <input type="checkbox"/> Benefits and disadvantages are balanced <input type="checkbox"/> Disadvantages outweigh benefits	<input checked="" type="checkbox"/> Benefits outweigh disadvantages <input type="checkbox"/> Benefits and disadvantages are balanced <input type="checkbox"/> Disadvantages outweigh benefits
Resource use	<input type="checkbox"/> Less resource intensive <input checked="" type="checkbox"/> More resource intensive	<input type="checkbox"/> Less resource intensive <input checked="" type="checkbox"/> More resource intensive
Recommendation direction	<input checked="" type="checkbox"/> In favour of the intervention <input type="checkbox"/> Against the intervention	<input checked="" type="checkbox"/> In favour of the intervention <input type="checkbox"/> Against the intervention
Overall ranking	<input type="checkbox"/> Strong recommendation <input checked="" type="checkbox"/> Conditional recommendation	<input type="checkbox"/> Strong recommendation <input checked="" type="checkbox"/> Conditional recommendation

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