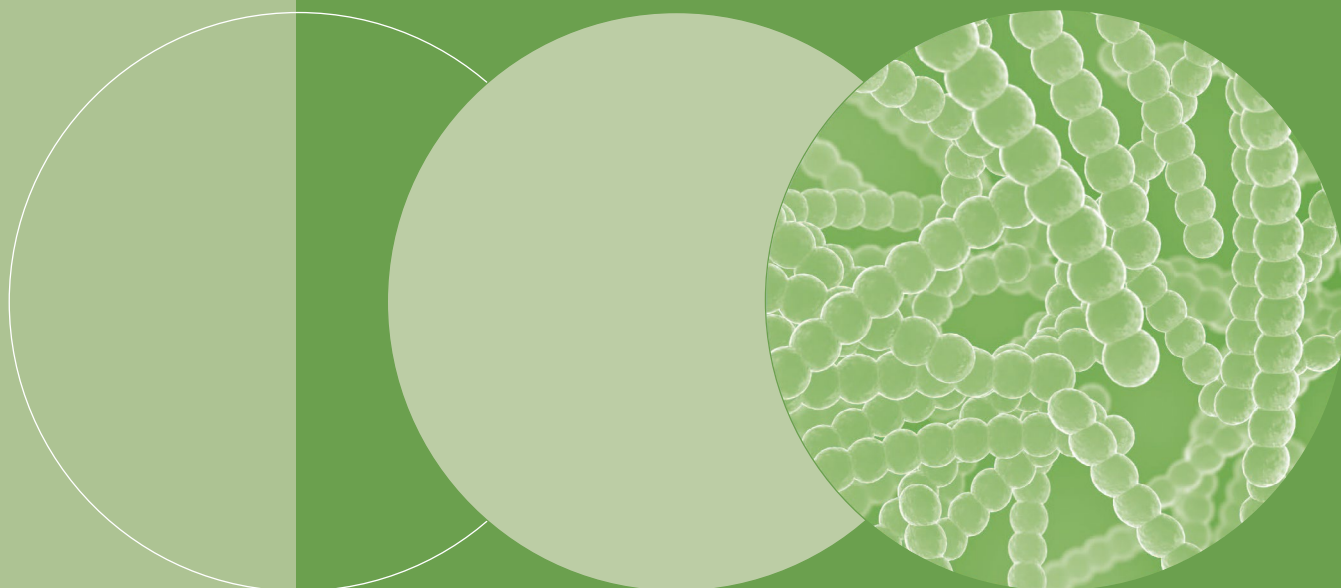


WHO recommendation on **Routine antibiotic prophylaxis for women undergoing operative vaginal birth**



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for women undergoing operative
vaginal birth**

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Contents

Acknowledgements	v
Acronyms and abbreviations	vi
Executive summary	vii
Introduction	vii
Target audience	vii
Guideline development methods	vii
Recommendation	viii
1. Introduction	1
1.1 Background	1
1.2 Rationale and objectives	2
1.3 Target audience	2
1.4 Scope of the recommendation	2
1.5 Persons affected by the recommendation	2
2. Methods	3
2.1 Contributors to the guideline	3
2.2 Identification of priority questions and outcomes	4
2.3 Evidence identification and retrieval	5
2.4 Certainty assessment and grading of the evidence	5
2.5 Formulation of the recommendation	6
2.6 Management of declarations of interests	8
2.7 Decision-making during the GDG meeting	8
2.8 Document preparation	9
2.9 Peer review	9
3. Guiding principles, best practice, recommendation and supporting evidence	10
3.1 Guiding principles and best practice	10
3.2 Recommendation and supporting evidence	11
4. Dissemination, adaptation and implementation of the recommendation	13
4.1 Recommendation dissemination	13
4.2 Adaptation	13
4.3 Implementation considerations	14
5. Research implications	14
6. Applicability issues	15
6.1 Anticipated impact on the organization of care and resources	15
6.2 Monitoring and evaluating guideline implementation	15
7. Updating the recommendations	16
8. References	17
Annex 1. External experts and WHO staff involved in the preparation of the recommendation	21
Annex 2. Priority outcomes used in decision-making	24
Annex 3. Summary and management of declared interests from GDG members	25
Annex 4. Evidence-to-decision framework	26

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Acronyms and abbreviations

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

Executive summary

Introduction

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

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

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

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

Target audience

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

Guideline development methods

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

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

Recommendation

The GDG issued the recommendation on routine antibiotic prophylaxis for women undergoing operative vaginal birth with remarks and implementation considerations. To ensure that the recommendation is correctly understood and applied in practice, guideline users may want to refer to the remarks, as well as to the evidence summary, including the considerations on implementation.

WHO recommendation on routine antibiotic prophylaxis for women undergoing operative vaginal birth

Recommendation: Routine antibiotic prophylaxis is recommended for women undergoing operative vaginal birth. (*Recommended*)

Remarks

- “Operative vaginal birth” is the term used to describe delivery of the fetal head assisted by either vacuum extractor or forceps.
- The Guideline Development Group noted that the available evidence, from high-income countries, strongly supports the use of a single dose of intravenous amoxicillin (1 g) and clavulanic acid (200 mg) administered as soon as possible after birth and no more than 6 hours after birth. The effects of other antibiotics and routes of administration for this indication are unknown.
- The Guideline Development Group recognized that intravenous amoxicillin and clavulanic acid may not be readily available or feasible to use in resource-limited settings and suggested that where this combination is not available, providers should consider the use of an appropriate class of antibiotics with similar spectrum of activity, based on local antimicrobial resistance patterns, safety profile (including allergies), the clinician’s experience with that class of antibiotics, availability and cost.
- The risk of postpartum infections and side-effects of antibiotics should be discussed with all women undergoing operative vaginal birth at the earliest time possible before or after birth.
- This recommendation was based on agreement by the Guideline Development Group that the improved health outcomes for women were clinically significant and outweighed the potential effects on emerging antimicrobial resistance.

- The Guideline Development Group noted the WHO recommendation against the use of antenatal amoxicillin and clavulanic acid combination (co-amoxiclav) for women with preterm prelabour rupture of membranes, on the basis of an increased risk of necrotizing enterocolitis in preterm newborns. However, the group agreed that the administration of a single dose of intravenous amoxicillin (1 g) and clavulanic acid (200 mg) in the largest trial demonstrating evidence occurred after birth (precluding intrauterine exposure to the newborn) and that such use is unlikely to carry risk of necrotizing enterocolitis.
- This recommendation relates to the use of antibiotics for women who are undergoing operative vaginal birth and who are not receiving postpartum antibiotics for other indications.
- This recommendation supersedes recommendation No. 12 of the 2015 *WHO recommendations for prevention and treatment of maternal peripartum infections*, where this was considered a conditional recommendation based on very low-quality evidence.

1. Introduction

1.1 Background

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

Several factors have been associated with increased risk of maternal infections, including pre-existing maternal conditions (e.g. malnutrition, diabetes, obesity, severe anaemia, bacterial vaginosis and group B streptococcus infections), as well as prelabour rupture of membranes, multiple vaginal examinations, manual removal of the placenta, severe perineal trauma, operative vaginal birth and caesarean section (8, 9). As such, the strategies to reduce maternal and newborn infections and their short- and long-term complications have been largely directed at preventive measures, particularly the promotion of good infection control practices both within and outside the hospital environment.

The prevention, early diagnosis and prompt management of sepsis are key factors in reducing sepsis-related morbidity and mortality, as reflected in the 2017 *WHA70.7 Resolution: Improving the prevention, diagnosis and clinical management of sepsis* (10). Globally, an effective 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 (11, 12). For example, in many countries the use of broad-spectrum antibiotics without confirmation of the causative agent is commonplace (11, 12). In many limited-resource settings, poor diagnostic facilities are a further constraint to prompt diagnosis and appropriate use of antibiotics. Apart from poor outcomes associated with such practices, there is increasing concern that inappropriate use and misuse of antibiotics among women giving birth could compromise public health through the emergence of antibiotic-resistant bacterial strains.

According to the 2015 *WHO global action plan on antimicrobial resistance*, the global consumption of antibiotics in humans has risen in the past two decades, primarily driven by an increased use in low- and middle-income countries (11–13). The action plan underscores the importance of appropriate use of antimicrobials at different levels of the health system to reduce the impact of antimicrobial resistance, while ensuring access to the best treatment available (13). WHO guidelines for health professionals and policy-makers on the need for antibiotics – and the type of antibiotics – for the prevention and treatment of maternal peripartum infections align with the WHO strategy and, if implemented, will improve maternal and newborn outcomes.

Operative vaginal birth (sometimes described as an instrumental birth or assisted vaginal birth) is the use of vacuum extractor or forceps to assist the delivery of the fetal head during vaginal birth. Operative vaginal birth is performed due to suspicion of immediate or potential fetal compromise, to shorten the second stage of labour for maternal benefit (when a woman is fatigued or when prolonged expulsive efforts are inadvisable), or due to inadequate progress or prolonged second stage of labour (14). When used appropriately, operative vaginal birth can reduce the rate of caesarean delivery (14).

In women undergoing operative vaginal birth, the risk of infection is increased due to bladder catheterisation, vaginal examination and instrumentation during the procedure, as well as the risk of tissue trauma. Infection may present as fever, infection of the uterus or surrounding tissues, an infected episiotomy or vaginal tear, or urinary tract infection (15).

Estimates from high-income settings suggest that 0.7% to 16% of operative vaginal births may result in an infectious complication (15). One strategy to prevent peripartum infection occurring after an operative birth is the use of antibiotic prophylaxis.

1.2 Rationale and objectives

WHO has established a new process for prioritizing and updating maternal and perinatal health recommendations, whereby an international group of independent experts – the Executive Guideline Steering Group (GSG) – oversees a systematic prioritization of maternal and perinatal health recommendations in most urgent need of updating (16, 17). Recommendations are prioritized for updating on the basis of changes or important new uncertainties in the underlying evidence based on benefits, harms, values placed on outcomes, acceptability, feasibility, equity, resource use, cost-effectiveness or factors affecting implementation. The Executive GSG prioritized updating of the existing WHO recommendation on routine prophylactic antibiotics for women undergoing operative vaginal birth after the publication of new evidence on this intervention.

This updated recommendation was developed in accordance with the standards and procedures in the *WHO handbook for guideline development*, including synthesis of available research evidence, use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE)¹ and GRADE Confidence in the Evidence from Reviews of Qualitative Research (GRADE-CerQUAL)² methodologies, and formulation of recommendations by a Guideline Development Group (GDG) composed of international experts and stakeholders (18). The recommendation in this document thus supersedes the previous WHO recommendation for routine antibiotic prophylaxis for operative vaginal birth as published in the 2015 guideline *WHO recommendations for prevention and treatment of maternal peripartum infections* (19). The primary aim of this recommendation is to improve the quality of care and the outcomes for women giving birth, as they relate to peripartum infection and its complications. This recommendation thus provides a foundation for sustainable implementation of routine antibiotic prophylaxis for women undergoing operative vaginal birth.

1.3 Target audience

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

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

1.4 Scope of the recommendation

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

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

1.5 Persons affected by the recommendation

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

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

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

2. Methods

The recommendation was developed using standardized operating procedures in accordance with the process described in the *WHO handbook for guideline development* (18). In summary, the process included: (i) identification of the priority question and critical outcomes; (ii) retrieval of evidence; (iii) assessment and synthesis of evidence; (iv) formulation of the recommendation; and (v) planning for the dissemination, implementation, impact evaluation and updating of the recommendation.

In 2019, antibiotic prophylaxis for operative vaginal birth was identified by the Executive GSG as a high priority for development of an updated recommendation, in response to new evidence on this question. Six main groups were involved in this process, with their specific roles described below.

2.1 Contributors to the guideline

2.1.1 Executive Guideline Steering Group (GSG)

The Executive GSG is an independent panel of 14 external experts and relevant stakeholders from the six WHO regions: African Region, Region of the Americas, Eastern Mediterranean Region, European Region, South-East Asia Region and Western Pacific Region. The Executive GSG advises WHO on the prioritization of new and existing PICO questions in maternal and perinatal health for development or updating of recommendations (16, 17).

2.1.2 WHO Steering Group

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

2.1.3 Guideline Development Group (GDG)

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

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

The GDG members for this recommendation were also selected in a way that ensured geographic representation and gender balance, and there were no important conflicts of interest. The GDG appraised the evidence that was used to inform the recommendation,

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

2.1.4 Evidence Synthesis Group (ESG)

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

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

2.1.5 External partners and observers

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

2.1.6 External Review Group (ERG)

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

2.2 Identification of priority questions and outcomes

The priority outcomes were aligned with those from the 2015 *WHO recommendations for prevention and treatment of maternal peripartum infections* (19). These outcomes were initially identified through a search of scientific databases for relevant, published systematic reviews and a prioritization of outcomes by the GDG for the 2015 guideline. In recognition of the importance of women's experiences of care, two additional outcomes – maternal well-being and maternal satisfaction – were included for this update to ensure that evidence synthesis and recommendation decision-making by the GDG were driven by outcomes that are important to women and to ensure that the final set of recommendations would be woman-centred. All the outcomes were included in the scope of this document for evidence searching, retrieval, synthesis, grading and formulation of the recommendation. The list of priority outcomes is provided in Annex 2.

2.3 Evidence identification and retrieval

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

2.3.1 Evidence on recommendation of routine antibiotic prophylaxis for women undergoing operative vaginal birth

An existing systematic review on routine antibiotic prophylaxis for operative vaginal birth was updated (20). This systematic review was the primary source of evidence of effectiveness for this recommendation. Since the previous systematic review of evidence, one additional trial of 3420 women was included. Randomized controlled trials relevant to the key question were screened by the review authors, and data on relevant outcomes and comparisons were entered into the Review Manager 5 (RevMan) software. The RevMan file was retrieved from the Cochrane Pregnancy and Childbirth Group and customized to reflect the key comparisons and outcomes (those that were not relevant to the recommendation were excluded). The RevMan file was then exported to the GRADE profiler (GRADEpro) software, and GRADE criteria were used to critically appraise the retrieved scientific evidence (21). Finally, evidence profiles (in the form of GRADE summary of findings tables) were prepared for comparisons of interest, including the assessment and judgements for each outcome and the estimated risks.

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

A mixed-methods systematic review was the primary source of evidence on values, acceptability and feasibility as they relate to the EtD framework for routine antibiotic prophylaxis for operative vaginal birth (22). This review included the views and experiences of women and health-care providers with antibiotic prophylaxis during labour and childbirth. A number of factors affecting the use of antibiotics by health-care providers around the time of birth were identified through studies pertained to using antibiotics for other conditions (such as caesarean section, preterm prelabour rupture of membranes and group B streptococcal infection). Additionally, a systematic review of qualitative studies evaluating “what women want” from intrapartum care was used to further inform the values and equity domains (23). Several studies pertaining to the availability and quality of antibiotics internationally were also used to inform the equity domains (24–27). The primary source of evidence for resources and cost-effectiveness was a trial included in the Cochrane systematic review that compared antibiotic prophylaxis (amoxicillin and clavulanic acid) to placebo (saline solution) for operative vaginal birth, which reported cost-effectiveness outcomes in terms of health-care resources and drug costs (28). This evidence was assessed as high quality according to the Consensus Health Economic Criteria (CHEC) checklist.

2.4 Certainty assessment and grading of the evidence

The certainty assessment of the body of evidence on effects for each outcome was performed using the GRADE approach (29). Using this approach, the certainty of evidence for each outcome was rated as “high”, “moderate”, “low” or “very low” based on a set of established criteria. The final rating of certainty of evidence was dependent on the factors briefly described below.

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

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

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

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

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

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

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

The findings of the qualitative reviews were appraised for quality using the GRADE-CERQual tool (30). The GRADE-CERQual tool, which uses a similar conceptual approach to other GRADE tools, provides a transparent method for assessing and assigning the level of confidence that can be placed in evidence from reviews of qualitative research. The systematic review team used the GRADE-CERQual tool to assign a level of confidence (high, moderate, low and very low) to each review finding according to four components: methodological limitations of the individual studies; adequacy of data; coherence; and relevance to the review question of the individual studies contributing to a review finding. Findings from individual cost-effectiveness studies were reported narratively for each comparison of interest, and evidence was assessed using the CHEC checklist.

2.5 Formulation of the recommendation

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

- **Effects:** The evidence on the priority outcomes was summarized in this domain to answer the questions: “What are the desirable and undesirable effects of the intervention?” and “What is the certainty of the evidence on effects?” Where benefits clearly outweighed harms for outcomes that are highly valued by women, or vice versa, there was a greater likelihood of a clear judgement in favour of or against the intervention, respectively. Uncertainty about the net benefits or harms, or small net benefits, usually led to a judgement that did not favour the intervention or the comparator. The higher the certainty of the evidence of benefits across outcomes, the higher the likelihood of a judgement in favour of the intervention. In the absence of evidence of benefits, evidence of potential

harm led to a recommendation against the intervention. Where the intervention showed evidence of potential harm and was also found to have evidence of important benefits, depending on the level of certainty and the likely impact of the harm, such evidence of potential harm was more likely to result in a context-specific recommendation, with the context explicitly stated within the recommendation.

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

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

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

- **Recommended:** This category indicates that the intervention should be implemented.
- **Not recommended:** This category indicates that the intervention should not be implemented.

- **Recommended only in specific contexts ("context-specific recommendation"):** This category indicates that the intervention is applicable only to the condition, setting or population specified in the recommendation and should only be implemented in these contexts.
- **Recommended only in the context of rigorous research ("research-context recommendation"):** This category indicates that there are important uncertainties about the intervention. With this category of recommendation, implementation can still be undertaken on a large scale, provided it takes the form of research that addresses unanswered questions and uncertainties related both to effectiveness of the intervention or option, and its acceptability and feasibility.

2.6 Management of declarations of interests

WHO has a robust process to protect the integrity of its normative work, as well as to protect the integrity of individual experts with whom it collaborates. WHO requires that experts serving in an advisory role disclose any circumstances that could give rise to actual or ostensible conflict of interest. The disclosure and the appropriate management of relevant financial and non-financial conflicts of interest of GDG members and other external experts and contributors, including external reviewers, are a critical part of guideline development at WHO. According to WHO regulations, all experts must declare their interests prior to participation in WHO guideline development processes and meetings according to the guidelines for declaration of interest (DOI) for WHO experts (18). All GDG and ERG members were therefore required to complete a standard WHO DOI form before engaging in the guideline development process and before participating in the guideline-related processes. The WHO Steering Group reviewed all declarations before finalizing the experts' invitations to participate. Where any conflict of interest was declared, the WHO Steering Group determined whether such conflicts were serious enough to affect an expert's objective judgement in the guideline and recommendation development process. To ensure consistency, the WHO Steering Group applied the criteria for assessing the severity of conflict of interests as outlined in the *WHO handbook for guideline development* to all participating experts. All findings from the DOI statements received were managed in accordance with the WHO procedures to assure the work of WHO and the contributions of its experts is, actually and ostensibly, objective and independent. The names and biographies of individuals were published online two weeks prior to the meeting. Where a conflict of interest was not considered significant enough to pose any risk to the guideline development process or to reduce its credibility, the experts were only required to openly declare such conflicts of interest at the beginning of the GDG meeting, and no further actions were taken. Annex 3 shows a summary of the DOI statements and how conflicts of interest declared by invited experts were managed by the WHO Steering Group.

2.7 Decision-making during the GDG meeting

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

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

2.8 Document preparation

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

2.9 Peer review

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

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

3.1 Guiding principles and best practice

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

- Avoidance of infection by identifying and correcting predisposing factors to infection (e.g. by providing nutritional advice and addressing nutritional deficiencies, anaemia and other maternal medical conditions such as diabetes) during antenatal care.
- Standard infection prevention and control precautions should be observed in the provision of maternity care to optimize the effects of the intervention recommended in this guideline (31). These measures should include:
 - Promoting hand hygiene, high quality standards for the sterilization and storage of instruments and supplies and use of clean equipment; promoting aseptic surgical practices (e.g. following standard skin preparation techniques and proper use of antiseptic agents for surgical site preparation); use of personal protection equipment (e.g. gloves and aprons or surgical gowns); and use of safe products (e.g. blood products). Local protocols on infection prevention and control practices should be developed and implemented in accordance with existing WHO guidance (32).
 - Improvement of health-care facilities physical environments (e.g. clean water, appropriate waste disposal and sanitation).
 - Clinical monitoring of women for signs of infection throughout labour and the postpartum period and early detection of infection by laboratory investigation as needed. This is particularly crucial for women who present with any form of illness around the time of childbirth, as poor monitoring and late detection of severe infection are known contributory factors to infection-related severe maternal morbidity and death. Before hospital discharge, women should be counselled on how to identify and promptly seek care for any danger signs of infection during the postpartum period (33).
 - Clear guidance and protocols are needed for the prompt recognition, timely management and transfer to specialized services (e.g. intensive care unit) of women with maternal sepsis (organ dysfunction resulting from infection) and septic shock (hypotension due to sepsis not reversed with fluid resuscitation) and ensure availability of a protocol on resuscitation, antimicrobial therapy and subsequent supportive therapies. This protocol should be informed by internationally recommended guidelines and adapted to the local obstetric population and available skills and resources.
 - When transmission-based precautions are necessary to reduce or prevent nosocomial transmission of infections for women with peripartum infections, they should be provided care and support, while in an isolation ward, by appropriately trained health-care staff.

- Care should be organized in a way that facilitates staff behavioural change and encourages compliance with the hospital infection control measures. These should include, but not be limited to, staff training and feedback, use of information and educational materials, appropriate distribution of infection control equipment and materials, establishment of local protocols, infection surveillance and clinical audit and feedback.
- National health systems need to ensure reliable supply systems and sustain availability and equitable access of good-quality, affordable antibiotics for use in maternal and perinatal health-care listed in the *WHO model list of essential medicines* and to ensure that the necessary equipment are available wherever maternity services are provided. They also need to ensure that the core list of first-line and second-line antibiotics on the *WHO model list of essential medicines* are available at maternity care facilities. This includes establishing robust and sustainable regulatory, procurement and logistics processes that can ensure good-quality medicines and equipment are obtained, transported and stored correctly.
- As part of the global efforts to reduce antimicrobial resistance, antibiotics should be administered only when there is a clear medical indication (as recommended in this guideline) and where the expected benefits outweigh the potential harms within the local context. It is essential to establish a hospital committee that monitors antimicrobial usage, including the quantity and patterns of use, feeds back the results to the prescribers and regularly updates the hospital antimicrobial formularies (34).
- To the extent possible, prophylactic and therapeutic use of antibiotics should be informed by the narrowest antibacterial spectrum, the woman's history (including drug intolerance), the simplest effective dose in terms of antibiotic class and regimen, cost-effectiveness, bacterial agents most likely to cause infection and local susceptibility patterns in the hospital and in the community. Bacterial culture samples should be obtained before initiating antibiotics therapy, but this should not prevent prompt administration of antibiotics. Additionally, the choice of antiseptics and antibiotics should be guided by maternal conditions and aimed at avoiding adverse effects. Ideally, the use of antimicrobials in any setting should be informed by local or national resistance surveillance data and treatment guidelines.

3.2 Recommendation and supporting evidence

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

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

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

Recommendation: Routine antibiotic prophylaxis is recommended for women undergoing operative vaginal birth. (*Recommended*)

Remarks

- “Operative vaginal birth” is the term used to describe delivery of the fetal head assisted by either vacuum extractor or forceps.
- The Guideline Development Group noted that the available evidence, from high-income countries, strongly supports the use of a single dose of intravenous amoxicillin (1 g) and clavulanic acid (200 mg) administered as soon as possible after birth and no more than 6 hours after birth. The effects of other antibiotics and routes of administration for this indication are unknown.
- The Guideline Development Group recognized that intravenous amoxicillin and clavulanic acid may not be readily available or feasible to use in resource-limited settings and suggested that where this combination is not available, providers should consider the use of an appropriate class of antibiotics with similar spectrum of activity, based on local antimicrobial resistance patterns, safety profile (including allergies), the clinician’s experience with that class of antibiotics, availability and cost.
- The risk of postpartum infections and side-effects of antibiotics should be discussed with all women undergoing operative vaginal birth at the earliest time possible before or after birth.
- This recommendation was based on agreement by the Guideline Development Group that the improved health outcomes for women were clinically significant and outweighed the potential effects on emerging antimicrobial resistance.
- The Guideline Development Group noted the WHO recommendation against the use of antenatal amoxicillin and clavulanic acid combination (co-amoxiclav) for women with preterm prelabour rupture of membranes, on the basis of an increased risk of necrotizing enterocolitis in preterm newborns. However, the group agreed that the administration of a single dose of intravenous amoxicillin (1 g) and clavulanic acid (200 mg) in the largest trial demonstrating evidence occurred after birth (precluding intrauterine exposure to the newborn) and that such use is unlikely to carry risk of necrotizing enterocolitis.
- This recommendation relates to the use of antibiotics for women who are undergoing operative vaginal birth and who are not receiving postpartum antibiotics for other indications.
- This recommendation supersedes recommendation No. 12 of the 2015 *WHO recommendations for prevention and treatment of maternal peripartum infections*, where this was considered a conditional recommendation based on very low-quality evidence.

4. Dissemination, adaptation and implementation of the recommendation

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

4.1 Recommendation dissemination

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

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

4.2 Adaptation

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

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

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

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

¹ Available at: www.who.int/rhl.

4.3 Implementation considerations

- This recommendation should be implemented in line with the guiding principles and best practice statements outlined in this document.
- Training is needed to ensure injectable antibiotics are used appropriately and safely. This includes safe injection practices and disposal. Special attention needs to be given to correct dosage and safe use of antibiotics for this indication, and efforts are needed to ensure that antibiotics are not misused for other indications.
- Antibiotics should be stored and used as per manufacturer instructions. For instance, amoxicillin and clavulanic acid powder for injection should be stored below 25 °C and used immediately after reconstitution (within 20 minutes). Vials are not suitable for multidose use (35).
- Women should be adequately counselled and engaged in shared decision-making around the use of prophylactic antibiotics for operative vaginal birth, including side-effects of antibiotics and breastfeeding.

5. Research implications

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

- What are the comparative effects of intravenous amoxicillin and clavulanic acid combination versus other classes of (cheaper and more widely available) antibiotics when used for antibiotic prophylaxis for operative vaginal birth?
- Which is the most effective route of antibiotic administration for antibiotic prophylaxis for operative vaginal birth?
- What are the views and perspectives of women regarding the use of antibiotics for operative vaginal birth?

6. Applicability issues

6.1 Anticipated impact on the organization of care and resources

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

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

6.2 Monitoring and evaluating guideline implementation

The implementation and impact of this recommendation will be monitored at the health service, country and regional levels, as part of broader efforts to monitor and improve the quality of maternal and newborn care. The WHO document *Standards for improving quality of maternal and newborn care in health facilities* (36) provides a list of prioritized input, output and outcome measures that can be used to define quality of care criteria and indicators and that should be aligned with locally agreed targets. In collaboration with the monitoring and evaluation teams of the WHO Department of Sexual and Reproductive Health and Research and the WHO Department of Maternal, Newborn, Child and Adolescent Health and Ageing, data on country- and regional-level implementation of the recommendation can be collected and evaluated in the short to medium term to assess its impact on national policies of individual WHO Member States.

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

- Proportion of women undergoing operative vaginal birth who receive antibiotic prophylaxis, calculated as the number of women who receive antibiotic prophylaxis for operative vaginal birth divided by the total number of women undergoing operative vaginal birth.
- Incidence of peripartum infection among women undergoing operative vaginal birth, calculated as the number of women with peripartum infection after operative vaginal birth divided by the total number of women undergoing operative vaginal birth.

The first indicator provides an assessment of the use of evidence-based practices among women considered at higher risk of infection around childbirth, while the second indicator provides information on the efficacy of the intervention. WHO has developed specific guidance for evaluating the quality of care for severe maternal complications (including sepsis) based on the near-miss and criterion-based clinical audit concepts (37).

7. Updating the recommendations

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

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

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

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Annex 1. External experts and WHO staff involved in the preparation of the recommendation

A. Participants at the WHO Guideline Development Group (GDG) meeting (19–20 October 2020)

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Annex 2. Priority outcomes used in decision-making

Priority outcomes (O):¹

Critical outcomes

- Severe infectious morbidity (sepsis, septic shock, laparotomy or hysterectomy for infection, or maternal intensive care unit admission)
- Puerperal infection (endometritis with/without myometritis and with/without salpingitis causing maternal febrile morbidity)
- Wound infection (episiotomy, perineal or vaginal)
- Antimicrobial resistance

Important outcomes

- Side-effects of antibiotics
- Cost of care
- Maternal satisfaction
- Maternal well-being
- Neonatal sepsis
- Neonatal mortality

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

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

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

Annex 4. Evidence-to-decision framework

Question

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

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

Problem: Preventing maternal infection at operative vaginal birth

Perspective: Clinical practice recommendation – population perspective

Population (P): Pregnant women who are undergoing operative vaginal birth

Intervention (I): Prophylactic antibiotic (regardless of timing of administration)

Comparator (C): No prophylactic antibiotic or placebo

Setting: Hospital setting

Subgroup: Type of instrument used in operative vaginal birth

Priority outcomes (O):¹

Critical outcomes

- Severe infectious morbidity (sepsis, septic shock, laparotomy or hysterectomy for infection, or maternal ICU admission)
- Puerperal infection (endometritis with/without myometritis and with/without salpingitis causing maternal febrile morbidity)
- Wound infection (episiotomy, perineal or vaginal)
- Antimicrobial resistance

Important outcomes

- Side-effects of antibiotics
- Cost of care
- Maternal satisfaction
- Maternal well-being
- Neonatal sepsis
- Neonatal mortality

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

Assessment

Effects of interventions

What are the effects of prophylactic antibiotics compared to placebo or no prophylactic antibiotic when given to women for operative vaginal birth?

Research evidence

Summary of evidence

Source and characteristics of studies

Evidence on the effects of prophylactic antibiotics compared to placebo or no treatment at operative vaginal birth is from an updated Cochrane review that includes two trials involving 3813 women (1). Both trials were conducted in high-income countries. The first was a multicentre trial conducted in 27 hospitals in the United Kingdom of Great Britain and Northern Ireland (United Kingdom) between 2016 and 2018, involving 3420 women and 3440 newborns at 36 weeks gestation or above (2). Women were not eligible if they had any other indication for antibiotics following the birth, third- or fourth-degree tears, had received antibiotics antenatally or had intrapartum antibiotics with ongoing antibiotic administration postnatally. Of these, 2234 were births by forceps and 1196 by vacuum extraction (10 were spontaneous births). Antibiotics (1 g amoxicillin plus 200 mg clavulanic acid, intravenous) were compared with 20 mL of intravenous sterile 0.9% saline placebo, given as soon as possible after birth and no more than 6 hours after birth.

The second trial was a single-centre trial conducted in the United States of America (USA) between 1986 and 1988 involving 393 women (3). Of these women, 170 underwent a forceps delivery and 223 had vacuum extractions. This trial included women with third- and fourth-degree tears, but excluded those showing signs of chorioamnionitis or other infections. The intervention group received a dose of 2 g cefotetan intravenously, immediately after cord clamping, compared with no treatment.

Comparison 1: Any antibiotic(s) versus no prophylactic antibiotic or placebo.

Data from both trials contributed to this comparison.

Severe infectious morbidity

Serious infectious complications: High certainty evidence suggests that antibiotic prophylaxis after operative vaginal birth reduces the risk of severe infectious complications (defined in the systematic review as the occurrence of any of: bacteraemia, systemic infection, septic shock, septic thrombophlebitis, necrotising fasciitis or maternal death attributed to infection) compared to placebo or no treatment (one trial, 3420 women; RR 0.44, 95% CI 0.22 to 0.89).

Puerperal infection

Endometritis: Moderate certainty evidence suggests that antibiotic prophylaxis after operative vaginal birth probably makes little or no difference to the risk of endometritis compared to placebo or no treatment (two trials, 3813 women; RR 0.32, 95% CI 0.04 to 2.64).

Other confirmed or suspected maternal infection: High certainty evidence suggests that antibiotic prophylaxis after operative vaginal birth reduces the risk of other confirmed or suspected maternal infection compared to placebo or no treatment (one trial, 3420 women; RR 0.58, 95% CI 0.49 to 0.69).¹

Wound infection (episiotomy, perineal or vaginal)

Infected episiotomy/laceration (organ or space infection): Low certainty evidence suggests that the use of antibiotic prophylaxis after operative vaginal birth may make little or no difference on the risk of infected episiotomy/laceration (organ or space

infection), when compared to placebo or no treatment (one trial, 3420 women; RR 0.11, 95% CI 0.01 to 2.05).

Infected episiotomy/laceration (superficial perineal wound infection): High certainty evidence suggests that the administration of prophylactic antibiotics after operative vaginal birth reduces the risk of superficial perineal wound infection compared to placebo or no treatment (one trial, 3420 women; RR 0.53, 95% CI 0.40 to 0.69).

Infected episiotomy/laceration (deep perineal wound infection): High certainty evidence suggests that the administration of prophylactic antibiotics after operative vaginal birth reduces the risk of deep perineal wound infection compared to placebo or no treatment (one trial, 3420 women; RR 0.46, 95% CI 0.31 to 0.69).

Infected episiotomy/laceration (wound breakdown): High certainty evidence suggests that the administration of prophylactic antibiotics after operative vaginal birth reduces the risk of wound breakdown compared to placebo or no treatment (one trial, 2593 women; RR 0.52, 95% CI 0.43 to 0.63).

Side-effects of antibiotics

Maternal adverse reactions: Low certainty evidence suggests that the use of antibiotic prophylaxis after operative vaginal birth may make little or no difference on the risk of maternal adverse reactions when compared to placebo or no treatment (one trial, 2593 women; RR 2.00, 95% CI 0.18 to 22.05).

Cost of care

Cost (£): High certainty evidence suggests that the use of prophylactic antibiotics after operative vaginal birth decreases the cost of care when compared to placebo or no treatment (one trial, 2539 women; the mean costs with any antibiotics was £52.60 less, from £97.26 less to £7.94 less).

Maternal well-being

Maternal health-related quality of life: High certainty evidence suggests that the administration of prophylactic antibiotics after operative vaginal birth increases maternal health-related quality of life (one trial, 2539 women; mean difference 0.01 higher, 95% CI 0.00 to 0.02 higher).

The outcomes **antimicrobial resistance, maternal satisfaction, neonatal sepsis and neonatal mortality** were not reported in the included studies.

Subgroup analysis

The Cochrane review did not report on the subgroup of type of instrument used in operative vaginal birth.

In the United Kingdom multicentre trial, the primary outcome (confirmed or suspected maternal infection within six weeks of delivery) was overall significantly lower in the treatment group (RR 0.58, 95% CI 0.49–0.69). A post-hoc analysis of the primary outcome according to mode of operative birth was not significantly different between the subgroups ($P = 0.727$):

- Forceps: RR 0.62 (99% CI 0.45 to 0.86)
- Vacuum: RR 0.56 (99% CI 0.39 to 0.80)

In the USA single-centre trial, results were not reported by type of instrument.

Additional considerations

None.

Desirable effects

How substantial are the desirable anticipated effects?

Judgement

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

How substantial are the undesirable anticipated effects?

Judgement

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

What is the overall certainty of the evidence on effects?

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

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

Research evidence

A systematic review on the perspectives and experiences of women and providers on antibiotics and antiseptics for preventing infection at birth identified no direct evidence on this question (4).

However, a 2018 systematic review of qualitative studies of “what women want” from intrapartum care found that most women want a positive birth experience (with good outcomes for mother and baby) but acknowledge that medical intervention may sometimes be necessary (*high confidence*) (5). Most women, especially those giving birth for the first time, are apprehensive about labour and birth (*high confidence*) and wary of medical interventions, although in certain contexts and/or situations, women welcome interventions to address recognized complications (*low confidence*). Where interventions are introduced, women would like to receive relevant information from technically competent health-care providers who are sensitive to their needs (*high confidence*).

Additional considerations

A 2018 core outcome set for caesarean delivery maternal infectious morbidity outcomes was proposed on the basis of a systematic review of outcomes in 452 trials and a Delphi survey of 40 review authors (6). The proposed outcome set included endometritis (primary outcome), maternal mortality, wound infection, wound complications, febrile morbidity and neonatal morbidity.

Judgement

— Important uncertainty or variability	— Possibly important uncertainty or variability	✓ Probably no important uncertainty or variability	— No important uncertainty or variability
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Balance of effects

Does the balance between desirable and undesirable effects favour antibiotic prophylaxis or no antibiotic prophylaxis?

Judgement

— Don't know	— Varies	— Favours no antibiotic prophylaxis	— Probably favours no antibiotic prophylaxis	— Does not favour either	— Probably antibiotic prophylaxis	✓ Favours antibiotic prophylaxis
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Resources

How large are the resource requirements (costs)?

Research evidence

The Cochrane review included one trial that compared antibiotic prophylaxis (amoxicillin and clavulanic acid) to placebo (saline) for operative vaginal birth and examined the outcome cost-effectiveness in terms of health-care resources and drug cost (2).

This trial was conducted in 27 obstetric units in the United Kingdom and included assessment of cost of care (in addition to health outcomes), evaluating resources required using unit costs from the United Kingdom National Health Service (NHS) perspective. Resources considered were: antibiotic use (intervention and new prescriptions), health-care professional visits, outpatient hospital visits and all-cause hospital readmissions. This study was assessed as high quality according to Consensus Health Economic Criteria (CHEC) checklist (7).

At six weeks postpartum, women in the intervention group used fewer NHS health-care resources compared with women in the placebo group. The mean difference in all categories of resource use favoured the intervention group, with significant mean differences in visits to a general practitioner (mean difference -0.11 visits, 99% CI -0.17 to -0.04), nurse or midwife home visits (-0.18 visits, -0.30 to -0.06), and outpatient hospital visits (-0.14 visits, -0.24 to -0.04). No significant differences were detected in the length of stay for all cause hospital readmissions. The total mean costs at six weeks postpartum was estimated to be £102.50 (standard deviation [SD] £652.40) in the amoxicillin and clavulanic acid group and £155.10 (SD £497.40) in the placebo group - a mean difference of -£52.60 (99% CI -£115.10 to £9.90).

A systematic literature search identified no further studies on the cost effectiveness of this intervention.

Additional considerations

A number of penicillins including amoxicillin/clavulanic acid are under the 'access' category in the *WHO model list of essential medicines*.

Main resource requirements

Resource	Description
Staff	Skilled health personnel to administer antibiotics intravenously.
Training	Training to administer safe injections, and to monitor and manage expected and unexpected side-effects, is part of standard maternity staff training. Refresher trainings on safe injection practices, safe sharp disposal, hand hygiene, antimicrobial stewardship and antimicrobial resistance.
Supplies	The International Medical Products Price Guide (MSH) median price of one vial of 1000 mg of amoxicillin plus 200 mg of clavulanic acid for injection is US\$ 1.45 (8). Intravenous administration: <ul style="list-style-type: none"> ■ Hand hygiene: water and soap, towels, alcohol-containing preparation (liquid, gel or foam) ■ Gloves ■ Skin preparation: alcohol-based solution, single-use swab or cotton wool ball ■ Sterile intravenous cannula and giving/infusion set ■ Intravenous fluids ■ Sharps container
Equipment and infrastructure	Amoxicillin and clavulanic acid powder for injection should be stored below 25 °C and used immediately after reconstitution (within 20 minutes). Vials are not suitable for multidose use (9).
Time	Minimal
Supervision and monitoring	Minimal

Resources required

Judgement

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

What is the certainty of the evidence on costs?

Judgement

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

Judgement

— Don't know	— Varies	— Favours no antibiotic prophylaxis	— Probably favours no antibiotic prophylaxis	— Does not favour either	✓ Probably favours antibiotic prophylaxis	— Favours antibiotic prophylaxis
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Equity

What would be the impact on health equity?

Research evidence

Women who are poor, least educated and who reside in rural areas generally have lower coverage of health interventions (such as facility-based birth and use of antibiotics during operative vaginal birth) and worse health outcomes than more advantaged women (10).

Intravenous antibiotics are widely used internationally and in a range of settings (low- to high-resource settings). However, variable availability of different antibiotics in health-care facilities in low- and middle-income countries is a recognized challenge that likely affects equitable access to this intervention (11–13). For example, a study of 13 561 health-care facilities in low- and middle-income countries found that 17 important antibiotics were stocked by fewer than 50% of facilities (13). There may be unequitable access to the benefits of this intervention in settings where important antibiotics are not routinely stocked or available.

In some low- and middle-income countries, the quality of available antibiotics may be variable – one study estimated the prevalence of inadequate quality injectable antibiotics at 13.4% across 1090 tested samples (14). The presence of poor-quality antibiotics in some settings may mean that the benefits of antibiotic prophylaxis are reduced in some settings. In settings where the cost of the antibiotic is borne by the woman or her family, antibiotic access may be less equitable.

Additional considerations

Overall, this intervention will likely increase health equity by preventing death and serious health consequences of peripartum infection with an inexpensive and easily implemented intervention. However, the benefits of antibiotic prophylaxis may not be fully realized due to the presence of poor-quality antibiotics in some settings and settings where cost of the antibiotic is borne by the woman or her family.

Judgement

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

Is the intervention acceptable to key stakeholders?

Research evidence

A mixed-methods systematic review on the perspectives and experiences of women and providers on antibiotic prophylaxis at birth was conducted (4). A number of factors affecting the use of antibiotics by providers around the time of birth were identified, through studies pertained to using antibiotics for other conditions (such as caesarean section, preterm prelabour rupture of membranes or group B streptococcal infection). No studies were identified relating specifically to antibiotic use at operative vaginal birth.

Factors affecting provider use of antibiotics included:

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

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

Additional considerations

None.

Judgement

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

Is the intervention feasible to implement?

Research evidence

A systematic review on the perspectives and experiences of women and providers on antibiotic prophylaxis at birth (4) identified no direct evidence relating to antibiotics for operative vaginal birth. However, some evidence relating to feasibility of using antibiotics for other clinical indications at birth (such as preterm prelabour rupture of membranes, caesarean section and group B streptococcus) was available.

None of the findings suggested that antibiotic use at birth was not feasible. However, some identified factors may possibly affect feasibility:

- Providers views on the woman's underlying risk of infection, whether they consider antibiotics to be effective for this indication, the risk of side-effects and the risk of antibiotic resistance (*low confidence*)
- Whether local guidelines and professional norms recommend the use of antibiotics for a given indication or not (*low confidence*), though views were mixed as to whether guidelines had a substantial impact on antibiotic use.
- Antibiotic cost-effectiveness and affordability (*moderate confidence*)

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

Additional considerations

As antibiotics are widely used in maternity care settings for a number of indications, the panel considered that this intervention would likely be feasible to key stakeholders.

Judgement

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

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

Summary of findings tables

Question: Any antibiotics compared to placebo or no treatment for operative vaginal delivery

Setting: United Kingdom and United States of America

Bibliography: Liabsuetrakul T, Choobun T, Peeyananjarassri K, Islam QM. Antibiotic prophylaxis for operative vaginal delivery. Cochrane Database Syst. Rev. 2020; 3:CD004455.

No. of studies		Study design	Certainty assessment				No. of patients		Effect		Certainty	Importance
			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Any antibiotics	placebo or no treatment	Relative (95% CI)		
SERIOUS INFECTIOUS COMPLICATIONS												
1	randomized trial	not serious	not serious	not serious	not serious	none	11/1715 (0.6%)	25/1705 (1.5%)	RR 0.44 (0.22 to 0.89)	8 fewer per 1000 (from 11 fewer to 2 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
ENDOMETRITIS												
2	randomized trials	not serious	not serious	not serious	serious ^a	none	15/1907 (0.8%)	30/1906 (1.6%)	RR 0.32 (0.04 to 2.64)	11 fewer per 1000 (from 15 fewer to 26 more)	⊕⊕⊕⊕ MODERATE	CRITICAL
CONFIRMED OR SUSPECTED MATERNAL INFECTION												
1	randomized trial	not serious	not serious	not serious	not serious	none	180/1715 (10.5%)	306/1705 (17.9%)	RR 0.58 (0.49 to 0.69)	75 fewer per 1000 (from 92 fewer to 56 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
INFECTED EPISIOTOMY/LACERATION (ORGAN OR SPACE INFECTION)												
1	randomized trial	not serious	not serious	not serious	very serious ^{a,b}	none	0/1715 (0.0%)	4/1705 (0.2%)	RR 0.11 (0.01 to 2.05)	2 fewer per 1000 (from 2 fewer to 2 more)	⊕⊕⊕⊖ LOW	CRITICAL
INFECTED EPISIOTOMY/LACERATION (SUPERFICIAL PERINEAL WOUND INFECTION)												
1	randomized trial	not serious	not serious	not serious	not serious	none	75/1715 (4.4%)	141/1705 (8.3%)	RR 0.53 (0.40 to 0.69)	39 fewer per 1000 (from 50 fewer to 26 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

Certainty assessment													
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect		Certainty	Importance	
							Any antibiotics	placebo or no treatment	Relative (95% CI)	Absolute (95% CI)			
INFECTED EPISIOTOMY/LACERATION (DEEP PERINEAL WOUND INFECTION)													
1	randomized trial	not serious	not serious	not serious	not serious	none	36/1715 (2.1%)	77/1705 (4.5%)	RR 0.46 (0.31 to 0.69)	24 fewer per 1000 (from 31 fewer to 14 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL	
INFECTED EPISIOTOMY/LACERATION (WOUND BREAKDOWN)													
1	randomized trial	not serious	not serious	not serious	not serious	none	142/1296 (11.0%)	272/1297 (21.0%)	RR 0.52 (0.43 to 0.63)	101 fewer per 1000 (from 120 fewer to 78 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL	
ANTIMICROBIAL RESISTANCE													
0 ^c									not estimable		—	CRITICAL	
MATERNAL ADVERSE REACTIONS													
1	randomized trial	not serious	not serious	not serious	very serious ^{a,d}	none	2/1296 (0.2%)	1/1297 (0.1%)	RR 2.00 (0.18 to 22.05)	1 more per 1000 (from 1 fewer to 16 more)	⊕⊕⊕⊖ LOW	CRITICAL	
MATERNAL HOSPITAL READMISSION													
1	randomized trial	not serious	not serious	not serious	serious ^a	none	63/1296 (4.9%)	84/1297 (6.5%)	RR 0.75 (0.55 to 1.03)	16 fewer per 1000 (from 29 fewer to 2 more)	⊕⊕⊕⊖ MODERATE	CRITICAL	
COSTS (£)													
1	randomized trial	not serious	not serious	not serious	not serious	none	1296	1297	—	MD 52.6 lower (97.26 lower to 7.94 lower)	⊕⊕⊕⊕ HIGH	CRITICAL	
MATERNAL SATISFACTION													
0 ^c									not estimable		—	CRITICAL	
MATERNAL HEALTH-RELATED QUALITY OF LIFE													
1	randomized trial	not serious	not serious	not serious	not serious	none	1296	1297	—	MD 0.01 higher (0 to 0.02 higher)	⊕⊕⊕⊕ HIGH	CRITICAL	

		Certainty assessment					No. of patients			Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Any antibiotics	placebo or no treatment	Relative (95% CI)	Absolute (95% CI)			
NEONATAL SEPSIS													
0 ^c									not estimable		—	CRITICAL	
NEONATAL MORTALITY													
0 ^c									not estimable		—	CRITICAL	

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

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

^b Even though the sample size is large (over 3000 women), all the data comes from a single study and the confidence interval is extremely wide.

^c No studies included in the review evaluated this outcome.

^d Small sample size and/or few events.

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