Guidelines for the management of pregnant and breastfeeding women in the context of Ebola virus disease
Families and communities across several countries have endured Ebola virus disease in recent years. The image on the front cover of these guidelines is based on a picture from the Democratic Republic of the Congo.
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February 2020

World Health Organization
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Acronyms and abbreviations

AFRO Regional Office for Africa (at WHO)

CDC Centers for Disease Control and Prevention (the United States of America)

CT cycle threshold

DSMB Data and Safety Monitoring Board

EBOV Ebola virus

ETC Ebola treatment centre

EtD evidence-to-decision

EVD Ebola virus disease (acute EVD refers to laboratory-confirmed (positive viremia) and symptomatic Ebola virus disease)

GCP good clinical practice

GDG Guideline Development Group

GSC Guideline Steering Committee

GRADE Grading of Recommendations Assessment, Development and Evaluation

GRC Guideline Review Committee

HQ headquarters

IPC infection prevention and control

MCA Department of Maternal, Newborn, Child and Adolescent Health (at WHO)

MEURI Monitored Emergency Use of Unregistered and Investigational Interventions

NIH National Institutes of Health

PPE personal protective equipment

PECO population (P), exposure (E), comparator (C), outcome (O)

PICO population (P), intervention (I), comparator (C), outcome (O)

RCT randomized controlled trial

RHR Department of Sexual and Reproductive Health and Research (at WHO)

RNA ribonucleic acid

RT-PCR reverse transcriptase polymerase chain reaction

SAGE Strategic Advisory Group of Experts (SAGE) on Immunization

UN United Nations

UNFPA United Nations Population Fund

UNICEF United Nations International Children’s Emergency Fund

WHO World Health Organization
Executive summary

The Democratic Republic of Congo is currently experiencing the second largest Ebola outbreak in history (1), following a 2014-2016 outbreak in western Africa that had an estimated 28,000 cases. Investigational treatment and vaccination trials are ongoing, but data in the context of pregnancy and breastfeeding are limited (2,3). A paucity of scientific evidence exists on how to best treat pregnant or breastfeeding women with suspected or confirmed Ebola virus disease (EVD). Historical reports suggest that, among women who acquire EVD during pregnancy, there is increased mortality and morbidity, and a near 100% rate of adverse pregnancy outcomes (4,5).

To save the lives of mothers and their babies, mitigate complications, and limit the spread of disease, it is critical that recommendations are made on the prevention, treatment, and surveillance of women who are exposed to EVD, acquire EVD during pregnancy or breastfeeding, or survive EVD with ongoing pregnancies. These guidelines are the first to provide such recommendations. They also cover the surveillance and management of ongoing pregnancies and adverse pregnancy-related events, the handling of bodily and pregnancy-related fluids during acute maternal infection and following recovery, and the management of subsequent pregnancies in Ebola survivors.

These guidelines will be of interest to health policy-makers, emergency preparedness and response teams, and healthcare providers who work with pregnant or breastfeeding women in the context of Ebola. The guidelines are relevant to the WHO goal of ensuring one billion people are better protected from health emergencies by impacting maternal mortality, neonatal survival, and the transmission of Ebola virus in the context of an Ebola epidemic.

Specific recommendations cover 6 topics. These are: (i) the management of acute EVD in pregnant women, (ii) the management of pregnancies in women who develop EVD during pregnancy and those who survive EVD with an ongoing pregnancy, (iii) infection prevention and control (IPC) measures for pregnant women with acute EVD or who have recovered from EVD with ongoing pregnancies (with conception prior to EVD), (iv) IPC for women who become pregnant after recovering from EVD (with conception after EVD), (v) breastfeeding women with acute EVD or who have recovered from EVD, and (vi) vaccination recommendations for pregnant women who are at risk of acquiring EVD. Of note, some recommendations apply to both specific situations and in the context of rigorous research, such as the use of investigational therapeutics in pregnant women.

Guidelines were developed in accordance with the WHO Handbook for Guideline Development, supported by a special WHO Guideline Steering Committee and a Guideline Development Group of international experts to formulate the recommendations. Scoping thematic discussions determined focus areas and key questions that were addressed in a systematic review. The quality of the evidence for key outcomes was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, followed by the use of an evidence-to-decision framework to analyse the available evidence relating to specific questions. An expert technical consultation of the Guideline Development Group took place on 4-5 June 2019 in Geneva, Switzerland. Prior to the technical consultation, WHO Declaration of Interest forms were reviewed and approved. The Guideline Development Group evaluated the draft guidelines and external reviewers’ reports prior to the WHO Guideline Review Committee approval of the final version.
Guidelines for the management of pregnant and breastfeeding women in the context of Ebola virus disease

Recommendation categories:

1. Recommended: The intervention or option should be implemented.
2. Not recommended: The intervention or option should not be implemented.
3. Insufficient evidence to recommend: The intervention or option lacks sufficient evidence to determine if implementation would be beneficial.
4. Recommendation only in specific contexts: The intervention or option is applicable only in specific conditions, settings, or populations and should only be implemented in these contexts.
5. Recommended only in the context of rigorous research: There are important uncertainties about the intervention or option. In such instances, it should be implemented on a large-scale if in the form of research that is able to address unanswered questions and uncertainties related to effectiveness, acceptability, and feasibility.

Key recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Recommendation category</th>
<th>Strength of recommendation</th>
<th>Quality assessment</th>
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<tbody>
<tr>
<td>Treatment of pregnant women with acute EVD</td>
<td></td>
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</tr>
<tr>
<td>1. Clinical management for all pregnant women should include optimized supportive care.</td>
<td>Recommended</td>
<td>Strong</td>
<td>Very low quality evidence</td>
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<tr>
<td>2. In the context of rigorous research or in accordance with the MEURI protocol (6), the use of the investigational therapies REGN-EB3 and mAb 114 may be offered to pregnant women with EVD (6,12,51).</td>
<td>Recommended in the context of rigorous research or specific contexts</td>
<td>Strong</td>
<td>Very low quality evidence</td>
</tr>
<tr>
<td>Induced abortion and induction of labour in women with acute EVD or following recovery</td>
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<tr>
<td>3. Labour should not be induced for foetal indications in pregnant women with acute EVD.</td>
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</tr>
<tr>
<td>Infection prevention and control measures for pregnant women with EVD</td>
<td></td>
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<tr>
<td>4. Invasive procedures should not be performed for foetal indications in pregnant women with acute EVD.</td>
<td>Recommended</td>
<td>Strong</td>
<td>Very low quality evidence</td>
</tr>
<tr>
<td>5. All pregnant women with acute EVD should be managed using both standard precautions and Ebola-specific IPC measures.</td>
<td>Recommended</td>
<td>Strong</td>
<td>Very low quality evidence</td>
</tr>
<tr>
<td>6. All pregnant women who have recovered from EVD (with conception prior to EVD) should be enabled and encouraged to attend frequent antenatal care. If there is no risk of exposure to pregnancy-related fluids during the visit, only standard precautions are required. Childbirth and pregnancy complications should be managed at ETCs and Ebola IPC measures should be used in addition to standard precautions (53,54).</td>
<td>Recommended</td>
<td>Strong</td>
<td>Very low quality evidence</td>
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(Continued on next page)
7. Among women who become pregnant after EVD (with conception after acute EVD), standard IPC precautions should be used. | Recommended | Strong | Very low quality evidence |

8. Surgically removing foetal tissue from the uterus following maternal demise from EVD (occasionally termed ‘post-mortem caesarean’) may pose a risk of transmission to contacts and should be strongly discouraged. | Recommended | Strong | Very low quality evidence |

### Infection prevention and control measures for breastfeeding women in the context of EVD

9. Breastfeeding should be stopped if acute EVD is suspected or confirmed in lactating women or in a breastfeeding child. The child should be separated from the breastfeeding woman and provided a breastmilk substitute as needed. | Recommended | Strong | Very low quality evidence |

10. Children without confirmed Ebola virus (EBOV) infection who are exposed to breastmilk of women with confirmed EVD should be considered contacts. The child should stop breastfeeding, be given a breastmilk substitute as needed, and undergo close monitoring for signs and symptoms of EVD for 21 days. Post-exposure prophylaxis for EVD can be considered for children exposed to breastmilk of women infected with EBOV on a case-by-case basis and in accordance with existing research protocols. | Recommended | Conditional | Very low quality evidence |

11. If a breastfeeding woman and her child are both diagnosed with EVD, breastfeeding should be discontinued, the pair should be separated, and appropriate breastmilk substitutes provided. However, if the child is under six months of age and no safe and appropriate breastmilk substitutes are available, or the child cannot be adequately cared for, then the option to not separate and continue breastfeeding may be considered. | Recommended | Conditional | Very low quality evidence |

12. A woman who has recovered from EVD, cleared viremia and wants to continue breastfeeding should wait until after two consecutive negative EBOV breastmilk tests by RT-PCR, separated by 24 hours. During this time, the child should be given a breastmilk substitute. | Recommended | Strong | Very low quality evidence |

### Use of the rVSV-ZEBOV-GP Ebola vaccine in pregnant women

13. Pregnant and breastfeeding women should be offered vaccination with the prequalified Ervebo (Merck) live-replicating rVSV-ZEBOV vaccine during an active Zaire EBOV outbreak in affected areas, in the context of rigorous research or in accordance with a compassionate use protocol. Vaccination should occur with informed consent and in compliance with good clinical practice. | Recommended in the context of rigorous research or specific contexts | Conditional | Very low quality evidence |
Producing the guidelines

These guidelines were developed using universal guiding principles on sexual and reproductive health and rights. They were formed in accordance with the WHO Handbook for Guideline Development, led by a WHO Guideline Steering Committee and a Guideline Development Group consisting of international experts.

Gathering the evidence

A scoping review of evidence was performed that identified key PICO/PECO (population, intervention/exposure, comparison, and outcome) questions and informed the design of the systematic review. Due to the limited quality evidence revealed from the initial scoping review, additional key PECO questions were added to provide more evidence-based background for the framework process. Key PICO/PECO questions included the following:

Key questions

1. Among pregnant women with acute EVD, does being treated with investigational therapies (ZMapp, REGN-EB3, Remdesivir, mAb114) in addition to supportive care, as compared to not being treated with investigational therapies, improve maternal, pregnancy or neonatal outcomes?

2. Among pregnant women with acute EVD, does induced abortion, as compared to no induced abortion, improve outcomes from acute EVD?

3. (a) Among pregnant EVD survivors, should Ebola-specific IPC measures be sustained until the termination of pregnancy to reduce risk of household and healthcare-associated EVD transmission?

4. (b) Among EVD survivors conceiving after acute EVD, should Ebola-specific IPC measures be sustained until the termination of pregnancy to reduce risk of household and healthcare-associated EBOV transmission?

5. Among pregnant women who are exposed to patients with acute EVD or his/her body fluids, does receiving the rVSV-ZEBOV Ebola vaccine against EBOV during pregnancy, as compared to not receiving the rVSV-ZEBOV Ebola vaccine against EBOV, decrease the risk of acute EVD?

Background questions

1. Among reproductive-aged women with acute EVD, does being pregnant alter the outcome of the acute EVD?

2. Among pregnant women, how does acute EVD alter maternal, pregnancy, and neonatal outcomes?

3. Among EVD survivors, does being pregnant, postpartum or post-abortion alter EBOV persistence in body fluids such as breastmilk and other pregnancy-related body fluids and tissues?

4. Among women infected with EBOV, does a history of EVD alter subsequent pregnancy outcomes?
5. Are individuals who are exposed to breastmilk of women with acute or prior EVD at increased risk of acquiring EVD?

6. What are the characteristics of diagnostic assays used for EVD in pregnant women?

7. For women exposed to patients with acute EVD, does being pregnant increase the risk of EBOV infection?

A systematic review of literature searched medical research databases (e.g. Cinahl, Cochrane Library, Embase, Global Health, Medline, Popline, Web of Science Core Collection, and WHO Global Index Medicus) and reference lists of key articles and recent publications were reviewed. A parallel review of grey literature searched other databases, health organization websites, conference proceedings, clinical registries, internet search engines, and experts were directly contacted. Two reviewers then independently highlighted key studies through screening, assessed the quality of the research, and synthesized the data. An additional scoping review was performed (including 13 papers in total) that addressed one or several of the following topics: resource use, recommendation feasibility and applicability, and implementation considerations.

**Quality of evidence**

The quality of evidence describes the extent to which one can be confident that an estimate of effect or association is correct. For the purposes of the GRADE process, evidence is categorized as high, moderate, low or very low. Low or very low quality of evidence does not necessarily imply that the studies were conducted poorly, but that study design or data were not optimal for answering a PICO question and developing the recommendation.

An evidence-to-decision framework (Annex 5) guided discussions and decision-making. Risk-benefit analysis tables were compiled for the four key PICO questions, covering: (i) the available evidence and its quality; (ii) the balance between desirable and undesirable effects for the intervention in question; (iii) values and preferences related to interventions for different stakeholders and in different settings; (iv) resource use; (v) feasibility of recommendations; (vi) applicability; (vii) implementation considerations; and (viii) research priorities.

The Guideline Development Group reviewed evidence around the four key PICO questions, their corresponding GRADE analyses, and proposed recommendations. There was a general paucity of published and grey literature that was considered pertinent to the PICO questions, and all outcomes were considered to have evidence profiles of low to very low quality. The proposed recommendations were reviewed with consideration of the GRADE analyses, risk-benefit aspects, and implementation considerations, and consensus sought on each recommendation. Discussions were held in group sessions with all members present. Consensus was sought on each recommendation, including recommendation strength and evidence quality, as outlined. Disagreements were debated during group sessions.

The guideline was reviewed by external reviewers. Recommendations finalized by the Guideline Development Group were not changed by external reviewers other than providing clarity and readability. In addition, the external review provided
structured feedback on accuracy, presentation, and the overall usefulness of the guidelines. With representation from different regions, countries and perspectives, the peer-review process confirmed overall strong support for the proposed recommendations. Suggestions and comments were incorporated and the draft recommendations and risk-benefit tables were finalized. The guidelines were approved by the WHO Guideline Review Committee in December 2019.

**Plans for updating**

WHO will closely monitor emerging data that pertains to topics discussed in the guidelines. The full guideline document will be reviewed again in 2024, unless significant new evidence warrants an earlier review.

**Dissemination, adaptation, implementation and evaluation**

The World Health Organization, together with other UN agencies and implementing partners, plans for rapid dissemination and implementation of the new recommendations in these guidelines. Key steps in the dissemination include the following:

1. Online publication of the guidelines with a limited print edition in English.
2. A French translation of the executive summary and full guidelines will be made available online. Further translation into other languages can be supported from WHO Headquarters following requests from WHO Regional Offices.
3. Adaptation tools will be developed to assist countries in prioritizing limited resources and facilitating effective implementation over time. This will be supported through planning meetings, workshops, and conferences including national and international partners. WHO will closely monitor emerging data that pertains to topics discussed, and this will be reviewed again in 2024 unless significant new evidence warrants an earlier review.

**Recommendation categories**

Recommendations were formulated by the Guideline Development Group, that used the following categories to classify the recommendations.

1. **Recommended**: The intervention or option should be implemented.
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be implemented on a large-scale if in the form of research that is able to address unanswered questions and uncertainties related to effectiveness, acceptability, and feasibility.

* Note: In these guidelines, certain recommendations are made to be applied in both specific contexts and in the context of rigorous research. These recommendations specifically apply to the use of investigational therapeutics in pregnant women, which is recommended for use both under the MEURI protocol and in research situations.

**Recommendations**

**Guiding principles**

Equitable and respectful care should be provided. Women should be given the opportunity to make reproductive health choices regarding the continuation or termination of pregnancy after being presented with all the available options. Decisions should include careful consideration of the risks pertaining to EVD in pregnancy, and they should incorporate both a woman’s personal values and individual situation. Women should be supported in the choices they make.

1. **Treatment of pregnant women with acute Ebola virus disease**

<table>
<thead>
<tr>
<th>RECOMMENDATION #1: Clinical management for all pregnant women should include optimized supportive care.</th>
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<th>RECOMMENDATION #2: In the context of rigorous research or in accordance with the MEURI protocol, the use of the investigational therapies REGN-EB3 or mAb114 may be offered to pregnant women with EVD.</th>
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<tbody>
<tr>
<td><strong>Recommendation strength:</strong> strong. Very low quality evidence.</td>
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</table>

**Remarks**

1. Optimized supportive care includes systematic assessment and re-assessment of patients with EVD, fluid resuscitation, electrolyte monitoring and correction, glucose monitoring and management, treatment of potential co-infections, and nutritional support. Symptomatic care, as well as prevention and management of complications, should always be provided (8).

2. Based on evidence from general adult populations, applying the principles of optimized supportive care to pregnant populations with EVD will likely decrease mortality and confer a beneficial impact on disease outcomes (8).

3. The use of fluid resuscitation in pregnant women with EVD, such as oral rehydration and parenteral administration of clinically appropriate fluids, has not been specifically evaluated. However, among adults with EVD, correction of intravascular depletion through adequate fluid resuscitation likely improves survival (8).

(Continued on next page)
Summary of evidence and considerations

Optimized supportive care

In 2018, a multidisciplinary panel of international experts formulated evidence-based recommendations for delivering optimized supportive care to individuals with acute EVD. Recommendations were formulated based on the quality of evidence as well as benefits, harms, values, and preferences. The majority of recommendations, including rehydration therapy, systematic vital sign assessment, and biochemistry assessment were strongly recommended to all patients with suspected, probable or confirmed EVD as steps to reduce mortality and optimize care (7). These recommendations were adapted for the WHO guidance document “Optimized supportive care for Ebola virus disease” for adults and children (8).

Investigational therapies

Three published reports described investigational therapeutic use in pregnant women with acute EVD (3, 9, 10). During the 2014-2016 outbreak, van Griensven et al. conducted a non-randomized comparative study using convalescent plasma. Among 84 participants, eight pregnant women were treated with convalescent plasma in addition to supportive care. Mortality was 25% among pregnant women and 32% among non-pregnant individuals after receiving plasma treatment. Compared to historical controls with EVD, one of the two (50%) pregnant women died from EVD, but pregnancy in the control group was incompletely documented (3).

A pregnant woman with EVD was also treated with favipiravir in addition to supportive care during the 2014-2016 (9, 10). The woman went into preterm labour and died from haemorrhagic shock. Her newborn child tested positive for EBOV and was treated with investigational therapies. The child became the first known survivor of congenitally-acquired EVD, and an examination at 12 months of age revealed normal development and a complete recovery from EVD (9, 10).

4. Where available, intensive critical care such as non-invasive ventilation, intubation with mechanical ventilation, central venous line insertion with vasopressor support, or renal replacement therapy will likely benefit pregnant women with EVD similar to that observed in adults with EVD.

5. The Monitored Emergency Use of Unregistered and Investigational Interventions (MEURI) expert panel recommends that “access to and use of investigational therapeutics under MEURI be carefully considered for each individual patient, including for vulnerable populations such as pregnant women and paediatric patients, as appropriate given the available data.” In general, the expert panel recommends consideration of factors such as disease severity and risks/benefits of investigational therapy (including adverse effects in pregnant or paediatric populations) (6).

6. Pregnant women with acute EVD who are not treated with investigational or compassionate use agents experience very high (>95%) rates of spontaneous abortion, foetal or neonatal death.

* Further information regarding recommendations 1 and 2 can be found in the WHO publications: “Optimized Supportive Care for Ebola virus disease: Clinical management standard operating procedures” (8), “Notes for the record: Consultation on Monitored Emergency Use of Unregistered and Investigational Interventions (MEURI) for Ebola virus disease” (6), and “Guidance for managing ethical issues in infectious disease outbreaks” (51).
The safety and efficacy of certain investigational therapeutics (ZMapp, Remdesivir, mAb114, REGN-EB3) are being evaluated in an ongoing randomized study. Pregnancy was not used as exclusion criteria in this study (11). Interim analyses noted improved outcomes resulting from treatments including REGN-EB3 or mAb114, and because of this, early termination of the trial was recommended. The efficacy of these treatments in pregnant women specifically is not yet known (12).

Additionally, the WHO convened an expert panel regarding investigational therapeutics using the MEURI ethical framework. The panel recommended that among vulnerable populations such as pregnant women, investigational therapeutics should be considered, and that until evidence suggests otherwise, pregnant women should be offered similar treatments to the non-pregnant population. Given that very few infants born to women with EVD survive, teratogenic effects were considered secondary to the mother’s health; however, risks and benefits should be highlighted in informed consent procedures (6).

2. Induced abortion and induction of labour in women with acute EVD

RECOMMENDATION #3: Labour should not be induced for foetal indications in pregnant women with acute EVD.

**Recommendation strength:** strong. Very low quality evidence.

**Remarks**

1. There is insufficient evidence to determine if induced abortion or induction of labour impacts maternal outcomes of acute EVD. No recommendation can be made.

2. Pregnant women with acute EVD or following recovery (with conception before EVD) who undergo an induced, incomplete, or spontaneous abortion should be provided with post-abortion care as described in the WHO guidelines “Safe abortion: technical and policy guidance for health systems” (13). Women should be provided instructions on how to handle potentially infectious specimens (such as products of conception) using Ebola-specific IPC measures and personal protective equipment (PPE).

3. Pregnant women recovering from EVD should be provided with counselling and necessary information pertaining to the risks of EVD that affect pregnancy outcomes, such as the risk for persistent infectivity of pregnancy-related fluids and tissues after EVD recovery. This information is necessary for women to make an informed decision regarding their choice to continue the pregnancy or undergo induced abortion.

4. Health authorities should take steps to expand access to all relevant reproductive options to women during an Ebola outbreak including safe abortion and contraceptive access. Health authorities should also ensure that access to reproductive options are not limited by a woman’s socioeconomic, cultural, racial, or religious status (55).

5. Women who have recovered from EVD but who wish to terminate a pregnancy should receive accurate information about their options and have access to safe abortion and post-abortion care (13,45). They should be supported in the choices they make regarding continuation or termination of pregnancy.

(Continued on next page)
6. Pregnant women who have recovered from EVD (with conception prior to EVD) may choose to proceed with an induced abortion. Due to the risk of viral persistence in pregnancy-related fluids and tissues, medical abortion (use of medications including misoprostol +/- mifepristone when possible) is preferred to surgical abortion (use of trans-cervical procedures), as surgical abortion may increase risk of EBOV transmission due to the invasiveness of the procedure.

7. Follow-up after an uncomplicated medical abortion using mifepristone and misoprostol is not required for obstetric indications. If only misoprostol is used, a follow-up visit is recommended to assess for completion of the abortion. Follow-up visits can be used to monitor symptoms, recovery, and assess the need for contraceptive services (45).

8. Induced abortions should be performed and managed at ETCs or healthcare facilities that are able to follow standard precautions in addition to Ebola-specific IPC measures, and that have the capability to provide obstetric care. Women who proceed with an induced abortion should stay at the facility in which the operation was performed until the abortion is completed due to the potential risk of infection from pregnancy-related fluids and tissues.

9. PPE (e.g. double gloves, face mask, gown or coverall and apron, head cover, eye protection (goggles or face shield) and boots (53)) in addition to standard precautions (52) should be used when handling pregnancy-related fluids and tissues from women with acute EVD or following recovery (if conception was prior to EVD), given the potential for disease transmission (53,54).

10. Products of conception should be tested for EBOV using reverse transcriptase polymerase chain reaction (RT-PCR), and should be handled and disposed of using PPE in accordance with established recommendations (52).

11. Women discharged from ETCs should receive Ebola-specific advice and counselling related to pregnancy, abortion, post-abortion care, breastfeeding, and sexual transmission.

12. Engagement from multiple stakeholders such as national authorities, epidemic response, UNFPA, UNAIDS and WHO is recommended to provide adequate sexual and reproductive healthcare within the context of Ebola.

Summary of evidence and considerations

One study found that uterine evacuation of pregnant women with acute Lassa fever was associated with improved survival from viral haemorrhagic fever (14). There were no studies of women with acute EVD undergoing induced abortion, though two studies included outcome data from four women who underwent induced abortion after recovering from EVD (15,16). The first was a retrospective cohort investigation by Henwood et al from 2014-2015 including 13 pregnant women with laboratory-confirmed EVD, one of which underwent induced abortion on the day of her discharge from the ETC (15). Similarly, in another retrospective cohort study of 77 pregnant women with laboratory-confirmed EVD, Caluwaerts et al reported results from three women who underwent induced abortion after recovering from EVD (16), but other evidence of induced abortion during acute EVD was limited to unpublished individual case reports and were not included.
3. Infection prevention and control measures for pregnant women with EVD

**RECOMMENDATION #4:** Invasive procedures should not be performed for foetal indications in pregnant women with acute EVD.


**RECOMMENDATION #5:** All pregnant women with acute EVD should be managed using both standard precautions and Ebola-specific IPC measures.


**RECOMMENDATION #6:** All pregnant women who have recovered from EVD (with conception prior to EVD) should be enabled and encouraged to attend frequent Antenatal Care (ANC). If there is no risk of exposure to pregnancy-related fluids during the ANC visit, only standard precautions are required. Complications associated with childbirth and pregnancy should be managed at ETCs and Ebola IPC measures should be used in addition to standard precautions.


**RECOMMENDATION #7:** Among women who become pregnant after EVD (with conception after acute EVD), standard IPC precautions should be used.


**RECOMMENDATION #8:** Surgically removing foetal tissue from the uterus following maternal demise from EVD (occasionally termed ‘post-mortem caesarean’) may pose a risk of transmission to contacts and should be strongly discouraged.


**Remarks**

1. Although the actual risk of EVD transmission from pregnant women following recovery is unclear, there is evidence that Ebola RNA can remain detectable in amniotic fluid, placental tissue, foetal tissue, and vaginal secretions. This evidence enables WHO to make strong recommendations regarding the necessity of Ebola-specific IPC measures for pregnant women who have recovered from EVD (with conception prior to EVD) in situations with potential for pregnancy-related fluid or tissue exposure. However, if the pregnancy was conceived after EVD, there is no known risk of EVD transmission with exposure to pregnancy-related fluids and tissues, and therefore only standard precautions are necessary.

2. Effective IPC measures require a hierarchy of engineering, environmental and administrative controls in order to block viral spread in healthcare facilities. In addition to PPE, IPC includes, but is not limited to, barrier nursing, hand hygiene, and waste management (56).

3. EVD transmission has been linked to traditional funeral ceremonies. Similarly, there is likely a high risk of transmission from post-mortem caesareans for pregnant women who have died from EVD. Guidelines on how to conduct safe and dignified burials for patients with suspected or confirmed EVD should be followed in the event of a maternal death from EVD, including the recommendation that only trained personnel should handle human remains, handling should be minimal, and cultural and religious considerations should be taken into account (46).
4. Actions (such as an invasive procedure) should not be taken in the event of foetal distress in pregnant women with acute EVD. As such, foetal monitoring during labour is not necessary.

* Further information regarding recommendations 5, 6, and 7 can be found in the WHO publications: “Interim guidance: Interim infection prevention and control guidance for care of patients with suspected or confirmed filovirus haemorrhagic fever in healthcare settings, with focus on Ebola” (53), “Interim guidance: Clinical care for survivors of Ebola virus disease” (54), and “Standard precautions in health care. Aide-memoir” (52). Further information regarding recommendation 8 can be found in the WHO publication “Interim guidance: How to conduct safe and dignified burial of a patient who has died from suspected or confirmed Ebola or Marburg virus disease” (46).

4. Infection prevention and control for breastfeeding women in the context of EVD

**RECOMMENDATION #9:** Breastfeeding should be stopped if acute EVD is suspected or confirmed in a lactating woman or in a breastfeeding child. The child should be separated from the breastfeeding woman and provided a breastmilk substitute as needed.


**RECOMMENDATION #10:** Children without confirmed EBOV infection who are exposed to the breastmilk of women with confirmed EVD should be considered contacts. The child should stop breastfeeding and should undergo close monitoring for signs and symptoms of EVD for 21 days. The child should be given a breastmilk substitute as needed. Post-exposure prophylaxis for EVD can be considered for children exposed to the breastmilk of EBOV-infected women on a case-by-case basis and in accordance with existing research protocols.


**RECOMMENDATION #11:** If a lactating woman and her breastfeeding child are both diagnosed with EVD, breastfeeding should be discontinued, the pair should be separated, and appropriate breastmilk substitutes should be provided. However, if the child is under six months of age and does not have safe and appropriate breastmilk substitutes, or the child cannot be adequately cared for, then the option to not separate and continue breastfeeding can be considered.


**RECOMMENDATION #12:** A woman who has recovered from EVD, cleared viremia, and wants to continue breastfeeding should wait until she has had two consecutive negative RT-PCR breastmilk tests for EBOV by, separated by 24 hours. During this time, the child should be given a breastmilk substitute.


**Remarks**

1. The recommendation to discontinue breastfeeding in the event that both the breastfeeding woman and the breastfed child have acute EVD is based on a hypothetical risk of viral ‘boosting’ between two infected individuals. This viral boosting could theoretically increase disease severity through additional viremic exposure. Evidence to directly support this recommendation is lacking.
2. Infants younger than 6 months of age should be provided with a breastmilk substitute (eg, ready-to-use infant formula) that is acceptable, feasible, affordable, sustainable, and safe. Infants and young children between 6 months and 23 months of age should be provided with a ready-to-use infant formula or ultra-high temperature full-cream (or whole) cow’s milk along with complementary feeding (this food can be supplemented with micronutrient powders if the nutrient content is expected to be inadequate).

3. Rapid testing of breast milk of women with recovered EVD, who would like to continue to breastfeed, should be prioritized.

4. Women’s choices related to stopping breastfeeding, or continuing after EVD recovery and testing of breast-milk, should be respected and supported by health care workers to facilitate the choice.

Summary of evidence and considerations

Disease transmission

Among studies describing the role of IPC measures at time of childbirth for EVD-positive women, multiple lapses in IPC measures likely contributed to the transmission of EBOV from pregnant women to others. These included inadequate and improper use of PPE such as using contaminated material for multiple patients, point of care exposure from patients with unrecognized EVD, and lack of proper isolation procedures (17–19). Contacts who subsequently contracted EVD after lapses in IPC measures included healthcare workers and caregivers (18), and other patients at healthcare facilities (19).

In Sierra Leone, investigators performed contact tracing of a pregnant woman with EVD after she presented in labour. She delivered via caesarean at a general hospital and developed EVD symptoms two days following delivery. She died shortly after and a post-mortem buccal swab confirmed the diagnosis of EVD. The infant developed symptoms at three days of life and died seven days later. Investigators identified 46 individuals who had contact with the pregnant woman during her stay at the healthcare facilities, and among these individuals, six contracted laboratory-confirmed EVD. In this study, investigators revealed that the nurses, hospital cleaning staff and caregivers did not have access to recommended PPE. Other potential contributors to the high risk of exposure from this case included a lack of recognition of EVD infection, exposure from infected bodily fluids, and lack of isolation precautions (18).

Similarly, Connolly and Young performed contact tracing on a pregnant woman with undiagnosed EBOV who delivered in a maternity ward in 2014. Investigators identified multiple lapses in IPC measures that likely contributed to EVD infection for two maternity ward patients and their infants. One of the maternity patients who contracted EVD was delivered by the same nurse as the index patient; PPE used by the nurse was both incomplete and contaminated from the index patient. Further, the maternity patient’s delivery suite was the same as the index case and was not cleaned between deliveries. The second maternity patient was likely infected because of a lack of standard precaution procedures, as she was placed next to the index case during her delivery and subsequent haemorrhage (20).

Detectable EBOV RNA has been identified in amniotic fluid (21,22), placental tissue (21,23,24), foetal tissue (17, 21, 25, 26,27), vaginal secretions (28), and even in pregnant women with mild or unrecognized disease (17,27).
**Viral persistence in pregnancy-related fluids and tissues**

Persistence of EBOV has been documented in pregnancy-related fluids and tissues after clearance of the virus from blood has occurred (17,21) (Table 1). EBOV was successfully isolated from a foetal tissue sample in a woman who delivered a stillborn foetus one month after being exposed to EVD (17). Similarly, a woman from Sierra Leone delivered a stillborn foetus who tested positive for EBOV RNA, yet denied EVD or exposure to it. Her blood was EBOV RNA negative, IgM antibody negative, and IgG antibody positive for EBOV (27).

In reproductive tract specimens from non-pregnant individuals, EBOV RNA was detected up to 36 days following symptom onset for EVD (29), but all samples from menstrual blood in non-pregnant women tested negative (30).

**Ebola in breastmilk**

EBOV RNA has been detected in the breastmilk of women with acute and convalescent EVD up to 26 days after symptom onset (31,32), as well as in women with asymptomatic EVD (33,34) (Table 1). Two lactating women were evaluated after their infants died from laboratory-confirmed EVD. EBOV RNA was detected in their breastmilk by RT-PCR despite negative testing in blood (33,34).

Of 25 infants who were breastfed by mothers with EVD, 68% developed presumed or laboratory-confirmed EVD, with a mortality rate of 82%. Eight infants were breastfed by EVD-positive women but did not become ill (31-38). Other studies of four breastfed infants did not identify if the mother or infant developed EVD first (31,33,34). However, Bower *et al* (35) found that of 14 mothers who clearly acquired EVD prior to their breastfed infants, 86% (n=12) of the exposed infants contracted EVD, with EVD status proving to be the greatest risk. Breastfeeding alone was not identified as a risk factor for EVD transmission.

Table 1. Viral persistence in pregnancy-related fluids/tissues and breastmilk, of Ebola virus RNA (detected by RT-PCR) and if viral isolation was attempted and successful.

<table>
<thead>
<tr>
<th>Specimens</th>
<th>Positive specimens (n)</th>
<th>Duration after symptom onset, RT-PCR</th>
<th>Duration after viral clearance from blood, RT-PCR (days)</th>
<th>Initial CT (cycle threshold)*</th>
<th>Viral isolation*</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amniotic fluid</td>
<td>9</td>
<td>Not stated</td>
<td>0-32</td>
<td>16-25</td>
<td>Not attempted</td>
<td>Caluwaerts [21]</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>38 days (from first positive blood sample)</td>
<td>32</td>
<td>22</td>
<td>Not attempted</td>
<td>Caluwaerts [26]</td>
</tr>
<tr>
<td>Placenta</td>
<td>3</td>
<td>Not stated</td>
<td>2-31</td>
<td>19-25</td>
<td>Not attempted</td>
<td>Caluwaerts [21]</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>38 days (from ETC admit)</td>
<td>31</td>
<td>19</td>
<td>Not stated</td>
<td>Caluwaerts [26]</td>
</tr>
</tbody>
</table>

*(Continued on next page)*
<table>
<thead>
<tr>
<th>Specimens</th>
<th>Positive specimens (n)</th>
<th>Duration after symptom onset, RT-PCR</th>
<th>Duration after viral clearance from blood, RT-PCR (days)</th>
<th>Initial CT (cycle threshold)*</th>
<th>Viral isolation*</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foetal tissue</td>
<td>4</td>
<td>Not stated</td>
<td>0-4</td>
<td>16-21</td>
<td>Not stated</td>
<td>Caluwaerts [21]</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Unclear, no maternal blood positivity documented</td>
<td>Unclear, no maternal blood positivity documented</td>
<td>16</td>
<td>Successful isolation</td>
<td>Bower [17]</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Unclear, no maternal blood positivity documented</td>
<td>Unclear, no maternal blood positivity documented</td>
<td>21</td>
<td>Not stated</td>
<td>Okoror [27]</td>
</tr>
<tr>
<td>Vaginal swab</td>
<td>1 (of 6)</td>
<td>33 days</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Unsuccessful isolation / culture</td>
<td>Rodriguez [28]</td>
</tr>
<tr>
<td></td>
<td>1 (of 1)</td>
<td>20 days</td>
<td>0 (day of viral clearance from blood)</td>
<td>33</td>
<td>Not stated</td>
<td>Oduyebo [23]</td>
</tr>
<tr>
<td></td>
<td>0 (of 44)</td>
<td>N/A (no positive samples by ELISA)</td>
<td>N/A (no positive samples by ELISA up to 21 months convalescence)</td>
<td>N/A</td>
<td>Unsuccessful isolation / culture</td>
<td>Rowe [39]</td>
</tr>
<tr>
<td></td>
<td>0 (of 21)</td>
<td>N/A (no positive samples)</td>
<td>N/A, (no positive samples 40+ days after discharge from ETC)</td>
<td>N/A</td>
<td>N/A</td>
<td>Green [40]</td>
</tr>
<tr>
<td></td>
<td>2 (of 6), from same individual</td>
<td>36 days</td>
<td>Not stated</td>
<td>28</td>
<td>Unsuccessful isolation</td>
<td>Liu [30]</td>
</tr>
<tr>
<td></td>
<td>3 (of 5), from same individual</td>
<td>28 days</td>
<td>10</td>
<td>Not stated</td>
<td>Unsuccessful isolation</td>
<td>Mora-Rillo [41]</td>
</tr>
<tr>
<td></td>
<td>0 (of 2)</td>
<td>N/A (no positive samples)</td>
<td>N/A (no positive samples 4 days after convalescence)</td>
<td>N/A</td>
<td>Unsuccessful isolation</td>
<td>Liddell [42]</td>
</tr>
<tr>
<td></td>
<td>1 (of 1)</td>
<td>2 days</td>
<td>N/A (no samples during convalescence)</td>
<td>-27</td>
<td>Not stated</td>
<td>Akerlund [43]</td>
</tr>
<tr>
<td>Menstrual blood</td>
<td>2 (of 6), from same individual</td>
<td>N/A (no positive samples)</td>
<td>N/A (no positive samples 42-246 days after convalescence)</td>
<td>37</td>
<td>Unsuccessful isolation</td>
<td>Liu [30]</td>
</tr>
</tbody>
</table>

(Continued on previous page)
### 5 Use of rVSV-ZEBOV-GP Ebola vaccine in pregnant women

**RECOMMENDATION #13:** Pregnant and breastfeeding women should be offered vaccination with the prequalified Ervebo (Merck) live-replicating rVSV-ZEBOV-GP vaccine during an active Zaire EBOV outbreak in affected areas, in the context of rigorous research or in accordance with a compassionate use protocol. Vaccination should occur with informed consent and in compliance with good clinical practice.

*Recommendation strength:* conditional.  
*Very low quality evidence*

**Remarks**

1. The WHO prequalified the injectable Ebola vaccine Ervebo (manufactured by Merck) in November 2019 after the vaccine was deemed compliant with WHO standards for quality, safety and efficacy. This decision followed the European Medicines Agency (EMA) announcement recommending a conditional marketing authorization for the rVSV-ZEBOV-GP vaccine.

2. The Strategic Advisory Group of Experts (SAGE), the principal advisory group to WHO on vaccinations, recommends that pregnant and lactating women be included in research within the framework of clinical trial vaccine protocols. SAGE notes that protocols must include provisions for safety monitoring and documentation of EVD cases among vaccinated individuals, as well as follow-up of pregnant women and their offspring.

### Table: Specimen Testing Results

<table>
<thead>
<tr>
<th>Specimens</th>
<th>Positive specimens (n)</th>
<th>Duration after symptom onset, RT-PCR</th>
<th>Duration after viral clearance from blood, RT-PCR (days)</th>
<th>Initial CT (cycle threshold)*</th>
<th>Viral isolation*</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breastmilk</td>
<td>2 (of 2), from same individual</td>
<td>15 days</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Successful isolation</td>
<td>Bausch [31]</td>
</tr>
<tr>
<td></td>
<td>3 (of 3), from same individual</td>
<td>26 days</td>
<td>Not stated</td>
<td>21.6</td>
<td>Not stated</td>
<td>Nordenstedt [32]</td>
</tr>
<tr>
<td></td>
<td>1 (of 1)</td>
<td>Unclear, no maternal blood positivity documented</td>
<td>Unclear, no maternal blood positivity documented</td>
<td>23.3</td>
<td>Not stated</td>
<td>Sissoko [33]</td>
</tr>
<tr>
<td></td>
<td>2 (of 2), from same individual</td>
<td>Unclear, no maternal blood positivity documented</td>
<td>Unclear, no maternal blood positivity documented</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Arias [34]</td>
</tr>
<tr>
<td></td>
<td>0 (of 1)</td>
<td>N/A (no positive samples)</td>
<td>N/A (no positive samples)</td>
<td>N/A</td>
<td>Not attempted (Caluwaerts S, pers. comm., 2019)</td>
<td>Moreau [37]</td>
</tr>
</tbody>
</table>

Note: (i) While RT-PCR can detect viral particles in specimens, infectivity potential can only be confirmed by viral isolation, a diagnostic method that uses viral culture techniques to confirm the presence of infectious viral specimens; (ii) cycle threshold (CT) is inversely related to viral load (i.e. a lower CT indicates a higher viral load).
3. The MEURI expert panel recommends that “access to and use of investigational therapeutics under MEURI be carefully considered for each individual patient, including for vulnerable populations such as pregnant women and paediatric patients, as appropriate given the available data”. In general, the expert panel recommends that factors including disease severity, available information on risks and benefits for the investigational therapy (including any available information on adverse effects in pregnancy or paediatrics) be considered.

4. There are no available studies that have determined the efficacy of rVSV-ZEBOV-GP vaccine in pregnant women; however, the vaccine is considered to have very good efficacy in the general population.

Summary of evidence and considerations

In 2015, Samai et al conducted a randomized, phase 2/3 trial to evaluate the safety and efficacy of the rVSV-ZEBOV vaccine among 8,651 healthcare and frontline Ebola response workers. Participants in the immediate vaccination cohort (n=4,319) were compared to participants in whom vaccination was delayed until 8-24 weeks after enrolment (n=4,332). Although pregnancy was part of the exclusion criteria and testing was required for women of reproductive age, 43 vaccinated women became pregnant during the study timeframe. Researchers were unable to assess the efficacy of rVSV-ZEBOV among pregnant women or among study participants because none developed laboratory-confirmed EVD, and exposure after enrolment was not detailed in the study.

In 2018, Edmunds and Jarvis performed an analysis of vaccinating pregnant women with rVSV-ZEBOV based on available data. The authors identified 11 studies, seven of which were randomized controlled trials and four were cohort studies, in the Democratic Republic of Congo, Gabon, Guinea, Kenya, Liberia, Sierra Leone, Spain and the United States of America. There were 98 pregnancies in the vaccinated group with 93 known pregnancy outcomes, of which 67% had a live birth and 27% had a pregnancy loss. Data on spontaneous abortions, induced abortions, and preterm births were available for 41 vaccinated pregnant women, of which 10% experienced a spontaneous abortion, 6% had an induced abortion, and 2% had a preterm birth.

One study provided comparison information for pregnant women who were vaccinated or unvaccinated. In this, 60 unvaccinated women were pregnant or became pregnant during the trial (with outcome data available for 46), compared to 43 vaccinated women (with outcome data available for 40), and a pregnancy loss rate of 43% among the vaccinated women and 44% among the unvaccinated women.

Considerations for implementation

1. Treatment of pregnant women with suspect or acute EVD

a. It is important to prioritize rapid diagnostic testing and confirmatory laboratory testing in pregnant women with suspected EVD, as they may require acute obstetric care and may pose a risk of EVD transmission from pregnancy-related fluids and tissues.
b. There may be considerable overlap in symptoms between early EVD and pregnancy-related conditions in pregnant women. As such, evaluation of pregnant women by obstetric and Ebola-response trained healthcare providers is essential, and clinical management should be informed by risk of exposure to EVD, symptom history, and an obstetric evaluation.

c. Pregnant women with suspected or confirmed EVD should be evaluated and treated in designated spaces within ETCs with measures to ensure privacy.

d. Appropriate resources and personnel trained in obstetric and neonatal care should be available at ETCs in order to avoid treatment delays or risks associated with transporting pregnant women. Specialist support can be provided by a mobile team who can come to the ETC or via telemedicine/telephone.

e. The decision to manage obstetric complications in order to save the life of a pregnant woman with confirmed or suspected acute EVD requires a case-by-case evaluation that takes into account maternal and not foetal indications, individual patient characteristics, as well as personnel and resource availability. Shared decision-making involving the patient, family members and healthcare workers is encouraged.

f. Ebola-specific IPC measures and personal protective equipment (PPE) should be used when performing surgery or invasive procedures (53). If feasible, minimally invasive procedures are preferable. Consideration should also be given to the healthcare worker’s ability and willingness to operate.

g. Performing obstetric surgery in PPE may present unique challenges (such as blurred vision increasing exposure risks for healthcare workers), and should only be performed by those who are familiar and confident with the procedure, and able to do so safely in PPE. If surgery is performed, full decontamination of the site must be conducted afterwards (58).

2. Induced abortion and induction of labour in women with acute EVD or following recovery

a. Following recovery from EVD, it is important to offer pregnant women comprehensive counselling on the risk of an adverse pregnancy outcomes and pregnancy management options. A woman may choose to proceed with an induced abortion, pregnancy induction, or expectant management.

b. If an induced abortion is desired, the gestational age and the presence or absence of prior uterine surgeries should be taken into consideration. Guidance on medically induced abortions, including medication regimens, can be found in the WHO guideline “Medical management of abortion” (45). Products of conception should be assumed to be potentially infectious until EBOV testing has resulted. Because of this, it is necessary to use Ebola-specific PPE (double gloves, face mask, gown or coverall and apron, head cover, eye protection (goggles or face shield) and boots (53)), as well as standard precautions (52).

c. Induction of labour or induced abortion should occur in a private area within the ETC.

d. Guidance on the induction of labour, including induction regimens, can be found in the WHO guideline “WHO recommendations for induction of labour” (46). Given the poor pregnancy outcomes associated with EVD in pregnancy, psychosocial support should be offered. Necessary supplies and medications should be stocked and readily available prior to beginning the induction. The induction should occur under the supervision of a healthcare provider with expertise in obstetric and neonatal medicine.
a. The act of surgically removing foetal tissue from the uterus of a demised pregnant woman with EVD holds cultural significance in some communities but poses significant risk for disease transmission. Similar to implementing safe and dignified burials for those who die from EVD, modifications may be considered to ensure an opportunity to honour cultural traditions and burial practices while limiting risk of disease transmission. Guidance on safe and dignified burials can be found in the WHO interim guidance, “How to conduct safe and dignified burial of a patient who has died from suspected or confirmed Ebola or Marburg virus disease” (47).

b. After a pregnant woman recovers from EVD (with conception prior to EVD), she should be offered counselling on the increased risk of spontaneous abortion, preterm labour, stillbirth, or neonatal death associated with EVD during pregnancy. She should be informed that there is a risk of transmission if others are exposed to pregnancy-related fluids or tissues, such as amniotic fluid, placental or foetal tissue.

c. A pregnant woman with a history of EVD (with conception prior to EVD) and an ongoing pregnancy may desire pregnancy continuation. It is important to closely manage such cases, as there is an elevated risk of spontaneous abortion, preterm labour, and EVD transmission. Depending on gestational age and obstetric assessments, women may be provided the option to continue inpatient care at ETCs. Alternatively, follow-up can be offered with outpatient ANC and post-EVD care if the following criteria is fulfilled: the individual is deemed stable, has a closely monitored follow up plan, gestational age is less than 36 weeks, reliable transportation is available, and the patient is able to seek medical care quickly and safely (59). Pregnant women who fulfil the criteria for outpatient management should be readmitted to an ETC for delivery to limit potential EVD transmission.

Outpatient management of EVD survivors with ongoing pregnancies (with conception prior to EVD) who desire pregnancy continuation

- Regular and frequent ANC follow-up visits should be planned, preferably with obstetric staff or maternal service providers linked to ETCs, or if not feasible, at an obstetric clinic with providers that are informed about appropriate IPC measures required for these pregnancies (59).

- The first follow-up visit should occur within 3 days of ETC discharge. Continued visits every 7–10 days should be planned for the duration of the pregnancy.

- The woman, her partner, and family should receive individualized information and counselling on the risk of adverse pregnancy outcomes and transmission, how to reduce transmission risks, early warning signs of adverse pregnancy outcomes, delivery or abortion preparedness, and abstinence from sexual intercourse (or use of condoms if not possible).

- Home delivery kits (including gloves, disinfectant solution, and disposal bags) and education on proper handling of pregnancy-related fluids and tissues using IPC measures should be provided to women in the event of an unavoidable home birth or spontaneous abortion.

- Women who recover from EVD with a viable pregnancy should be considered high-risk, and as such, should be cared for at a facility equipped to handle obstetric procedures and Ebola IPC measures starting at 36 weeks gestation to mitigate risks of adverse events and minimize transmission risks. Admission can be to an ETC or a similarly equipped facility. Admission at 36 weeks can follow standard IPC precautions unless signs of labour or adverse events occur. When labour or adverse events occur, the woman should be offered care within Ebola-specific isolation areas (hot/red zone).

(Continued on next page)
4. Infection prevention and control measures for breastfeeding women with EVD (54)

a. In order to reduce the possible risk of EVD transmission through breastfeeding, it is important to offer testing of breastmilk by RT-PCR to all lactating women who have recovered from EVD.

b. Women wanting to breastfeed after EVD recovery should be supported to do so, and should be educated on safe handling and disposal of breastmilk to prevent EBOV transmission, hand hygiene and the need for subsequent breastmilk testing to confirm negativity. Breastfeeding women who would like to discontinue, should be supported, counselled and offered lactation inhibition (see Annex 2 for technical guidance, and the flowchart opposite).
5. Use of the rVSV-ZEBOV Ebola vaccine in pregnant women

a. National authorities in countries with outbreaks of Zaire EBOV should introduce the rVSV-ZEBOV-GP vaccine and offer it to pregnant women within the framework of research, using informed consent and a transparent, evidence-based process. Ervebo (Merck) has been prequalified and meets WHO quality, efficacy and safety standards.

b. Ring vaccination and other strategies may be used during an epidemic to define priority populations for vaccination. Pregnant women should be included and specifically addressed within these strategies given their vulnerability to adverse EVD-related pregnancy events.

Research priorities

1. Treatment of pregnant women with acute EVD

a. Determine the efficacy and safety of investigational therapies (REGN-EB3 and mAb114) in pregnant women with acute EVD.

b. Investigate pregnancy and neonatal outcomes among women receiving investigational therapeutics to treat acute EVD, including assessment of viral persistence in pregnancy-related tissues and fluids.

(Continued on next page)
2. Induced abortion or induction of labour in women with acute EVD or following recovery

a. Optimize reporting of outcomes for pregnant women with EVD if induced abortion is performed during acute EVD.
b. Investigate values and preferences regarding reproductive choices, including pregnancy continuation versus induced abortion, among pregnant women in the context of EVD.
c. Explore and analyse how information is perceived regarding counselling on pregnancy outcomes and treatment with investigational therapeutics and vaccines in research contexts. Determine optimal communication strategies for counselling in the context of EVD and pregnancy.

d. Evaluate strategies to optimize pregnancy outcomes and best care for women with suspected EVD in whom diagnostic evaluation is pending.

3. Infection prevention and control measures in pregnant women with EVD

a. Analyse and adapt diagnostic algorithms to improve the specificity of EBOV screening in pregnant women with EVD symptoms.
b. Determine persistence and infectivity risk of pregnancy-related fluids and tissues in women with acute or convalescent EVD, particularly among those who are treated with investigational therapies.
c. Investigate the relationship between positive RT-PCR EBOV testing to live infectious virus in pregnancy-related fluids and tissues over time.
d. Explore culturally acceptable alternatives to the practice of post-mortem caesarean delivery.
e. Explore investigational therapies to reduce mother-to-child transmission of EBOV.
f. Investigate the risk and determinants of adverse maternal or pregnancy outcomes among survivors of EVD (with conception after EVD).
g. Explore the effects of information fatigue on the operational side of IPC measures for Ebola efforts, including health workforce readiness, and what factors can motivate and sustain efforts to support pregnant women during ongoing epidemics.

4. Infection prevention and control measures in breastfeeding women with EVD

a. Determine the infectivity potential of breast milk in women with acute or convalescent EVD.
b. Investigate rapid diagnostic testing performance in breastmilk.
c. Investigate the relationship between positive RT-PCR EBOV testing to live infectious virus in breast milk over time.
d. Determine the optimal management of EBOV-exposed infants.
### 5. Use of the rVSV-ZEBOV-GP Ebola vaccine use in pregnant women

- a. Evaluate the understanding and risk perception among pregnant and breastfeeding women regarding investigational treatment and vaccination for EVD through comprehension testing of informed consent.

- b. Determine the efficacy and safety of the rVSV-ZEBOV-GP vaccine in pregnant women, particularly in regards to the Ervebo vaccine (Merck), prequalified by WHO.

- c. Investigate which vaccines optimize maternal, pregnancy and neonatal outcomes when administered to pregnant women.

- d. Investigate vaccine efficacy for different EBOV strains or in the event of a viral mutation in the current strain.

- e. Determine the acceptability of investigational vaccine use among pregnant or lactating women in different communities.

- f. Determine the impact of vaccine use on traditional IPC measures and prevention response efforts to reduce EVD transmission.

### Funding

Development of these guidelines was funded by the WHO and the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), hosted by the Department of Sexual and Reproductive Health and Research, World Health Organization, Geneva, Switzerland.

### References


2. Edmunds J, Jarvis C. Benefits risk analysis of vaccination of pregnant women with rVSV-ZEBOV as part of expanded access programme. London School of Hygiene and Tropical Medicine; 2018.


47. Interim guidance: How to conduct safe and dignified burial of a patient who has died from suspected or confirmed Ebola or Marburg virus disease. Geneva: World Health Organization; 2017;1-17.


Annex 1. Additional considerations for implementation: Management of breastfeeding and pregnant women with acute or recovered EVD (with conception prior to EVD)

These represent summarized additional considerations for implementation of recommendations, please see also earlier section in this Guideline as well as other indicated sources for further advice on clinical management of related conditions.

Delivery, induced labour and pregnancy complications during or after acute EVD

- Delivery and management of pregnancy complications in women with ongoing or recovered EVD, should happen within the ETC in an area designated for the care of pregnant women, allowing for privacy and dignity, and safe healthcare worker access. Care should be provided by health care staff with relevant expertise such as in obstetrics and Ebola management.

- All the anticipated drugs and equipment needed, are best placed placed near the patient in the designated delivery/obstetrics ETC area. Ideally, a pre-prepared “obstetric-box” or similar, with relevant drugs and equipment should be readily available in case of the acute admission of a woman in labour with EVD.

- If intravenous access can be obtained safely, following IPC protocol, it should be secured as early as possible.

- Foetal monitoring is not necessary.

- Spontaneous vaginal delivery should be anticipated.

- Vaginal examinations should be minimized, and artificial rupture of membranes avoided.

- Treatment to prevent post-partum haemorrhage after delivery should be provided as per WHO recommendations (48). Depending on local resources, individual circumstances, and a feasible and safe administration route, this can be given as oxytocin, or else as misoprostol or another recommended and available substance, please see “WHO recommendations: Uterotonics for the prevention of postpartum hemorrhage. Geneva: World Health Organization; 2018 “ (48).

- Avoid standing directly in front of a patient during delivery of foetus or placenta to avoid unnecessary exposure to body fluids.

- Surgical procedures on critical maternal indications, during acute EVD, need careful individual considerations from health care workers and patients’ perspective alike, and should if needed, be performed by a person with clinical expertise and confident to do so with the physical restrictions of full PPE.

- Placenta and any pregnancy related tissue or fluids must be disposed of following Ebola-specific IPC protocol for potentially infectious material.

- The newborn is assumed EVD-positive and care provided should be in accordance with full PPE and IPC protocols. Rapid RT-PCR Ebola testing of the newborn should be prioritized.

- The cord can be clamped using disposal plastic cord clamps and cut with disposable scissors.

- If there is a stillbirth/the foetus is not born alive, the cord does not need to be clamped or cut. Guidance on safe and dignified burials can be found in the WHO interim guidance, “How to conduct safe and dignified burial of a patient who has died from suspected or confirmed Ebola or Marburg virus disease” (47).

- Pregnant women with EVD may experience an intrauterine foetal death or other pregnancy related complications. If a woman has recovered from EVD with negative RT-PCR testing from a blood specimen and is in need of induced labour or other invasive or surgical procedures, these should also be managed inside the ETC and follow similar IPC considerations.
• For further and more comprehensive recommendations of management of pregnancy and delivery complications, please revert to the below WHO publications.

**Breastfeeding**

• If a woman, with acute or recovered EVD, does not wish to breastfeed in the context of a risk of transmitting EBOV, to suppress lactation, medication such as Cabergoline may be suggested to a pregnant or breastfeeding woman. In a pregnant woman this is ideally offered soon after delivery/pregnancy termination. Another option, in case medication is not available or suitable, the woman may be instructed on how to use a breast-pump and how to safely dispose of milk until lactation has stopped.

• A breastmilk substitute that meets the conditions of acceptability, feasibility, affordability, sustainability, and safety should be provided.

**Counselling**

Pregnant or breastfeeding women with acute or recovered EVD may benefit from counselling addressing aspects of their sexual and reproductive health and rights, in relation to their disease experiences and choices made.

**Comprehensive recommendations on prevention and treatment of postpartum hemorrhage, induction of labour, complications management and safe abortion including medical management of abortion and post-abortion care, can be found in the below WHO publications:**


- Health worker roles in providing safe abortion care and post-abortion contraception


The following publications have additionally informed the annex: (61,62)
Annex 2. Evidence-to-decision tables

A) PICO 1

Among pregnant women with acute EVD, does being treated with investigational therapies (ZMapp, REGN-EB3, Remdesivir, mAb114) in addition to supportive care, as compared to not being treated with investigational therapies, improve maternal, pregnancy or neonatal outcomes?

**Problem:** Improving recovery from acute EVD in pregnant women

**Perspective:** Clinical practice recommendation - population perspective, evidence-generation perspective

**Population:** Pregnant women with EVD

**Intervention:** Investigational therapies (ZMapp, REGN-EB3, Remdesivir, mAb114)

**Comparison:** Supportive care only

**Setting:** Ebola treatment centre

**Subgroups:** Women undergoing vaginal birth; women undergoing caesarean section

**Priority outcomes** (used in the development of the recommendations):

**Critical outcomes**
- Maternal death
- Foetal death or spontaneous abortion
- Newborn death

Definition of foetal death (ICD-11): Intrauterine demise of foetus during the pregnancy, also referred to as a stillbirth if demise occurred during last half of pregnancy. *Note: this term was not always defined in the included literature.*

Definition of spontaneous abortion (ICD-11): Non-induced foetal or embryonic death, or passage of products of conception <20 weeks gestation or <500 grams. *Note: this term was not always defined in the included literature.*

**Important outcomes**
- Severe maternal morbidity (including obstetric bleeding and shock)
- Induced abortion
- Preterm birth
- Breastfeeding
- Treatment side-effects and adverse outcomes (nausea, vomiting, headache, abdominal pain, hypertension, shivering, fever and diarrhoea)
- Maternal well-being and satisfaction

**Included studies** (n=4)
- Case report/series: 2 studies
- Prospective cohort: 1 study
- Randomized controlled study: 1 study
**GRADE TABLE**

<table>
<thead>
<tr>
<th>Outcome (# included studies)</th>
<th>Factors that may decrease certainty of evidence*</th>
<th>Overall certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Limitations</td>
<td>Indirectness</td>
<td>Inconsistency</td>
</tr>
<tr>
<td><strong>Maternal death</strong> (3)</td>
<td>Serious</td>
<td>Serious</td>
<td>Cannot determine**</td>
</tr>
<tr>
<td><strong>Foetal death or spontaneous abortion</strong> (3)</td>
<td>Serious</td>
<td>Serious</td>
<td>Cannot determine**</td>
</tr>
<tr>
<td><strong>Neonatal death</strong> (3)</td>
<td>Serious</td>
<td>Serious</td>
<td>Cannot determine**</td>
</tr>
<tr>
<td><strong>Composite morbidity</strong> (2)</td>
<td>Serious</td>
<td>Serious</td>
<td>Cannot determine**</td>
</tr>
<tr>
<td><strong>Maternal well-being and satisfaction</strong> (0)</td>
<td>No studies identified</td>
<td>No studies identified</td>
<td>No studies identified</td>
</tr>
</tbody>
</table>

* Composite morbidity includes the following important outcomes: Severe maternal morbidity, neonatal morbidity, preterm birth/preterm premature rupture of membranes, breastfeeding, induced abortion, treatment side-effects and adverse outcomes

** Cannot determine inconsistency due to small sample size

---

**CRITICAL OUTCOMES**

For all critical outcomes (maternal death, foetal death, spontaneous abortion and newborn death), when compared with standard supportive care, existing evidence is unable to determine survival benefit with the addition of investigational therapies for pregnant women with EVD. Only four studies reported on the use of investigational therapies in pregnant women with EVD, and no studies were designed to evaluate the efficacy of treatment in pregnant women.

**Maternal death** - For maternal death, although a statistically significant survival benefit was not detected with the addition of convalescent plasma to supportive care for pregnant women, this outcome was limited by a very small sample size of pregnant women in the study and historical control group. Investigators did not describe or account for potential confounders such as pregnancy characteristics, maternal comorbidities, or treatments administered to the historical control group. Maternal benefit (or lack thereof) from the addition of favipiravir to supportive care was unable to be determined because the evidence consisted of a single case report of one individual.

**Foetal death/spontaneous abortion** - For foetal death or spontaneous abortion, although all pregnant women treated with convalescent plasma in addition to supportive care experienced a spontaneous abortion while at the ETC, investigators were unable to detect a significant difference in foetal outcomes because they were unknown in the control group. Further, the study and control groups were severely limited by small sample sizes and lack of characterization.

**Newborn death** - Only a single case report on favipiravir investigational therapy in addition to supportive cares for the mother was included. The child was a rare congenital survivor of EVD. A survival benefit for newborn children was unable to be determined because it is a single case report and the child was also treated with investigational therapies after birth.

**IMPORTANT OUTCOMES**

For all important outcomes, including maternal and neonatal morbidity, preterm birth, breastfeeding, rates and timing of induced abortion, treatment side-effects and adverse outcomes, maternal well-being and satisfaction, existing evidence is unable to determine if the addition of investigational therapies improves outcomes for pregnant women with EVD when compared with standard supportive care.
EVIDENCE-TO-DECISION TABLE

| Balance of benefits and harms | (a) Potential benefit - EVD has a very high fatality rate of around 50% (based on 2014-2016 West Africa outbreak data of women exposed to protocolized supportive care), and >90% foetal or newborn deaths if only supportive treatment is offered. Investigational therapies have potential to improve survival in pregnant women.  
(b) Potential harm - There may be a risk of teratogenicity to the foetus following use of investigational therapies that have not been thoroughly evaluated in pregnant populations. It is unclear if such therapies in pregnant women are associated with higher rates of adverse drug events, side-effects, or additional harm. |
| Values and preferences | Given the high rate of maternal mortality and adverse pregnancy outcomes associated with EVD, pregnant women may value access to investigational therapies. |
| Resource use | Treatment with investigational therapies would likely require significant resource use as it requires reliable and consistent access to medications and supplies, as well as support from individuals with expertise in administering and monitoring these therapies. |
| Feasibility/applicability | There is no direct evidence investigating acceptability of supportive and investigational therapies for EVD among pregnant women. However, selective use of investigational therapies for adults with EVD are commonplace in affected communities. |

A) PICO 2

Among pregnant women with acute EVD, does induced abortion, as compared to no induced abortion, improve outcomes from acute EVD?

Problem: Improving recovery from acute EVD in pregnant women

Perspective: Clinical practice recommendation - population and evidence-generation perspective

Population: Pregnant women with EVD

Intervention: Induced abortion

Comparison: No induced abortion

Setting: ETC

Subgroups: None

Priority outcomes:

Critical outcomes
- Maternal death
- Severe maternal morbidity
- Severe EVD

Important outcomes
- EVD transmission from pregnancy-related tissues and fluids
- Complications from induced abortion (including secondary infections and haemorrhage)
- Maternal well-being and satisfaction

Included studies (n=0)
- None identified
GRADE TABLE

<table>
<thead>
<tr>
<th>Outcome (# included studies)</th>
<th>Factors that may decrease certainty of evidence*</th>
<th>Overall certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Limitations</td>
<td>Indirectness</td>
<td>Inconsistency</td>
</tr>
<tr>
<td>Maternal death (0)</td>
<td>No studies identified</td>
<td>No studies identified</td>
<td>No studies identified</td>
</tr>
<tr>
<td>Severe maternal morbidity (0)</td>
<td>No studies identified</td>
<td>No studies identified</td>
<td>No studies identified</td>
</tr>
<tr>
<td>Severe EVD (0)</td>
<td>No studies identified</td>
<td>No studies identified</td>
<td>No studies identified</td>
</tr>
<tr>
<td>EVD transmission (0)</td>
<td>No studies identified</td>
<td>No studies identified</td>
<td>No studies identified</td>
</tr>
<tr>
<td>Complications from induced abortion (0)</td>
<td>No studies identified</td>
<td>No studies identified</td>
<td>No studies identified</td>
</tr>
<tr>
<td>Maternal well-being and satisfaction (0)</td>
<td>No studies identified</td>
<td>No studies identified</td>
<td>No studies identified</td>
</tr>
</tbody>
</table>

CRITICAL OUTCOMES

For all critical outcomes (maternal death, severe maternal morbidity, severe EVD), when compared to no induced abortion, existing evidence is unable to determine if induced abortion during acute EVD is associated with improved maternal survival, improved maternal outcomes or decreased disease severity. Among the two studies that reported maternal and disease outcomes in women with EVD who underwent induced abortion, there was no evaluation on the impact of induced abortion during acute illness.

IMPORTANT OUTCOMES

For all important outcomes (including EVD transmission, complications from induced abortion, maternal well-being and maternal satisfaction), when compared to no induced abortion, existing evidence is unable to determine if induced abortion is associated with differential transmission rates of EVD, induced abortion-related complications, or maternal satisfaction and well-being. These outcomes were not described in the studies that reported on induced abortion among women with EVD.

EVIDENCE-TO-DECISION TABLE

<table>
<thead>
<tr>
<th>Balance of benefits and harms</th>
<th>(a) Potential benefits</th>
<th>(b) Potential harm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Evacuation of the pregnancy may confer a theoretical survival benefit to the mother by decreasing viral load and eliminating a potential source for viral persistence (although this has not been specifically reported on for EVD in the literature).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Given the near 100% foetal or neonatal mortality rate associated with EVD infection during pregnancy, induced abortion may confer a psychological benefit for some mothers.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Given the potential for EVD-positive women to have viral persistence in pregnancy-related fluids and tissues after achieving convalescence, performing induced abortion in a controlled environment with proper IPC measures in place would likely reduce the risk for disease transmission.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>· If induced abortion is performed for a mother with acute EVD, she may experience infection-related complications such as increased bleeding, shock, or more severe disease.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>· Induced abortion may confer increased risks to healthcare providers who perform the procedure given the risk of exposure to infectious pregnancy-related fluids and tissues.</td>
<td></td>
</tr>
</tbody>
</table>

(Continued on next page)
Guidelines for the management of pregnant and breastfeeding women in the context of Ebola virus disease

Values and preferences

- Induced abortion may be the preferred management for some pregnant women given the near 100% associated foetal and neonatal mortality rate. This eliminates the potential risk of viral persistence in pregnancy-related fluids/tissues.
- Induced abortion may be contrary to the beliefs or value systems of individuals, as well as against certain laws and policies.

Resource use

- Performing an induced abortion would involve additional resources including medication (such as misoprostol, although this medication is low cost), use of an ETC and full PPE for delivery, and trained healthcare personnel to carry out the induced abortion.

Feasibility

- Induced abortion is feasible given the availability of associated medications, but it is also resource-intensive due to the requirements for induced abortion to take place in an ETC with full PPE and attendance by a trained healthcare worker.

Applicability

- Highly applicable

A) PICO 3

Among pregnant survivors of EVD, should Ebola-specific IPC measures be sustained until delivery/abortion to reduce risk of healthcare associated and household transmission of EVD?

Problem: Transmission risk of EBOV for pregnant survivors of EVD

Perspective: Clinical practice recommendation - population and evidence-generation perspective

Population: Pregnant survivors of EVD

Intervention: IPC measures at delivery

Comparison: Non-pregnant survivors of EVD

Setting: ETCs, healthcare centres, households

Subgroups: None

Priority outcomes:

Critical outcomes

- Transmission of EBOV at healthcare centres, households, and ETCs

Important outcomes

- Delivery or abortion complications (such as haemorrhage, obstructed labour, other maternal morbidity) associated with ongoing IPC measures
- Healthcare worker acceptability of ongoing need for PPE
- Maternal well-being and maternal satisfaction

Included studies (n=21)

- Case report/series: 11 studies
- Prospective cohort: 1 study
- Retrospective cohort: 6 studies
- Cross-sectional: 3 studies
<table>
<thead>
<tr>
<th>Outcome (# included studies)</th>
<th>Factors that may decrease certainty of evidence*</th>
<th>Overall certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmission of EBOV at healthcare centres, households, and ETCs (21)</td>
<td>Serious</td>
<td>Serious</td>
<td>Serious</td>
</tr>
<tr>
<td>Childbirth/abortion complications associated with IPC (0)</td>
<td>No studies identified</td>
<td>No studies identified</td>
<td>No studies identified</td>
</tr>
<tr>
<td>Healthcare worker acceptability of ongoing need for PPE (0)</td>
<td>No studies identified</td>
<td>No studies identified</td>
<td>No studies identified</td>
</tr>
<tr>
<td>Maternal well-being and satisfaction (0)</td>
<td>No studies identified</td>
<td>No studies identified</td>
<td>No studies identified</td>
</tr>
</tbody>
</table>

** Cannot determine inconsistency due to small sample size

**CRITICAL OUTCOMES**

Healthcare centre, household, and ETC transmission of EVD

- Among pregnant women who survive EVD with ongoing pregnancies, there were no documented cases of EVD transmission at time of delivery or abortion procedures in healthcare, household or ETC settings in deliveries with or without IPC measures in place. However, multiple studies have demonstrated EBOV RNA persistence in pregnancy-related fluids and tissues among pregnant survivors. Furthermore, the virus was successfully isolated from foetal tissue in a woman with serological evidence of prior asymptomatic EVD, suggesting the possibility of ongoing infectivity. Findings were limited by a small number of included studies, the quality of the study design, and the possibility of reporting bias regarding EVD transmission in healthcare and household settings.

- Among breastfeeding women with acute or convalescent EVD, there is a suspected high risk of transmission through breastmilk that may persist for longer than one month after symptom onset, as documented by viral persistence and successful viral isolation from breastmilk in women with acute and convalescent EVD. Findings were limited by small sample sizes with significant methodological limitations. In all studies, the close contact that inherently occurs with breastfeeding potentially confounded transmission routes between mothers and infants.

**IMPORTANT OUTCOMES**

Delivery or abortion complications with ongoing IPC measures

- Among pregnant survivors of EVD in which IPC measures are continued at time of delivery or abortion, existing evidence is unable to determine if IPC measures are associated with increased rates of delivery or abortion-related complications. No studies remarked specifically on delivery or abortion outcomes among pregnant survivors with or without IPC measures in place.

Healthcare worker acceptability of ongoing need for PPE, maternal well-being, maternal satisfaction

- Among pregnant survivors of EVD who undergo delivery or abortion, existing evidence is unable to determine the degree of acceptability for healthcare workers regarding use of PPE, maternal well-being or maternal satisfaction with continued IPC measures at time of delivery or abortion compared to no continued IPC measures. There were no studies that investigated these outcomes.
### EVIDENCE-TO-DECISION TABLE

<table>
<thead>
<tr>
<th>Balance of benefits and harm</th>
<th>(a) Potential benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Given the consistent finding of detectable Ebola viral RNA in pregnancy-related fluids and tissues in some individuals after maternal convalescence, and evidence of viral isolation from foetal tissue, there is a potential risk for infectivity. By recommending use of full PPE and IPC measures during delivery or obstetric procedures for pregnant survivors of EVD (if EVD was diagnosed during the current pregnancy), disease transmission to healthcare workers and community members may be reduced.</td>
</tr>
<tr>
<td></td>
<td>- Disease transmission may be reduced to breastfeeding infants if breastfeeding is stopped in women with suspected or confirmed EVD given evidence for viral particles in breastmilk.</td>
</tr>
<tr>
<td></td>
<td>(b) Potential harm</td>
</tr>
<tr>
<td></td>
<td>- Delivery with full PPE and following IPC measures may be difficult given the unpredictable nature and timing of delivery/pregnancy loss, significant resources needed (such as delivery in an ETC), and requirement for trained healthcare providers with experience in EVD transmission. Requiring delivery of pregnant EVD survivors in ETCs may be difficult for some individuals, as ETCs may be far away and it may not be feasible for pregnant women to relocate to/near an ETC for delivery (i.e. due to cost, childcare/household responsibilities, inability to work while relocated, etc).</td>
</tr>
<tr>
<td></td>
<td>- If the proper healthcare facility (such as an ETC) or PPE supplies are not available at time of delivery, some providers may refuse to provide care, given the potential infectious risk from pregnancy-related fluids and tissues and that may be life-threatening for women who experience complications.</td>
</tr>
<tr>
<td></td>
<td>- Fear of exposure to infectious pregnancy-related fluids and tissues may limit a provider’s willingness to perform indicated obstetric procedures such as caesarean delivery or repair of vaginal lacerations.</td>
</tr>
<tr>
<td></td>
<td>- Stopping breastfeeding may expose the infant to metabolic derangements or infection if appropriate breast-milk substitute is not used. Appropriate breast-milk substitute may be costly and/or difficult to obtain.</td>
</tr>
</tbody>
</table>

| Values and preferences | EVD survivors with ongoing pregnancies may be unwilling or unable to take the necessary precautions to deliver at appropriate healthcare facilities (and that may also require relocation). |
|                        | Mothers may prefer delivery using traditional methods. |
|                        | Healthcare providers may not feel comfortable administering obstetric care if full PPE is not used, given the potential infectious risk of pregnancy-related fluids and tissues. |
|                        | Community members may be at risk of infection if delivery does not occur in a controlled setting following IPC measures. |
|                        | Mothers with acute EVD or who are EVD survivors may be unwilling to stop breastfeeding if they cannot find an appropriate breast-milk substitute. Mothers may not be easily able to provide breastmilk for EBOV testing. |

| Resource use | Significant resources will be required for all pregnant survivors of EVD (with EVD diagnosed in the current pregnancy) to undergo delivery or obstetric procedures in an appropriate healthcare facility (such as an ETC), with full PPE and IPC. This may include relocation to near an ETC for many, and the availability of trained healthcare workers for delivery or obstetric procedures. |
|             | In breastfeeding women with continued viral persistence in breastmilk, breastmilk substitutes may be costly and difficult to obtain. |

| Feasibility/applicability | To ensure delivery at designated centres and attended by trained healthcare workers, relocation of pregnant survivors for a prolonged period of time may be required. The use of PPE and IPC at time of delivery or obstetric procedure requires adequate supplies and has associated costs. |
A) PICO 4

Among pregnant women who are exposed to patients with acute EVD or his/her body fluids, does receiving the rVSV-ZEBOV Ebola vaccine against EBOV during pregnancy, as compared to not receiving the rVSV-ZEBOV Ebola vaccine against EBOV, decrease the risk of acute EVD?

**Problem:** Decreasing rates of EVD infection among pregnant women

**Perspective:** Clinical practice recommendation - population and evidence-generation perspective

**Population:** Pregnant women without EVD

**Intervention:** Vaccination

**Comparison:** Non-pregnant individuals without EVD

**Setting:** Community, healthcare centres, ETCs

**Subgroups:** Healthcare workers and front-line Ebola workers that are pregnant

**Priority outcomes:**

**Critical outcomes**
- Vaccine efficacy among pregnant women
- Vaccines safety

**Important outcomes**
- Risk of teratogenicity from vaccine
- Maternal well-being and satisfaction

**Included studies (n=2)**
- Benefits-risk analysis: 1 study
- Prospective randomized controlled study: 1 study

**GRADE TABLE**

<table>
<thead>
<tr>
<th>Outcome (# included studies)</th>
<th>Factors that may decrease certainty of evidence</th>
<th>Overall certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Limitations</td>
<td>Indirectness</td>
<td>Inconsistency</td>
</tr>
<tr>
<td>Vaccine efficacy (1)</td>
<td>Unable to determine*</td>
<td>Unable to determine*</td>
<td>Unable to determine*</td>
</tr>
<tr>
<td>Vaccine safety (2)</td>
<td>Serious</td>
<td>Serious</td>
<td>Serious</td>
</tr>
<tr>
<td>Risk of teratogenicity (1)</td>
<td>Serious</td>
<td>Serious</td>
<td>Serious</td>
</tr>
<tr>
<td>Maternal well-being and satisfaction (0)</td>
<td>No studies identified</td>
<td>No studies identified</td>
<td>No studies identified</td>
</tr>
</tbody>
</table>

* Only one study aimed to evaluate vaccine efficacy among pregnant women, but there were no cases of EVD in the study or control group.
CRITICAL OUTCOMES

Vaccine efficacy
- Among women who received the rVSV-ZEBOV vaccine during or just prior to pregnancy, compared to pregnant women who did not receive the rVSV-ZEBOV vaccine, existing evidence is unable to determine vaccine efficacy. One study aimed to evaluate vaccine efficacy among pregnant women and non-pregnant individuals, but there were no cases of EVD in the study or control group.

Vaccine safety
- Among women who received the rVSV-ZEBOV vaccine during or just prior to pregnancy, existing evidence is unable to determine vaccine safety in pregnant women due to limited data and small sample sizes. One study compared data from vaccinated and unvaccinated pregnant women, but there was no significant increase risk of pregnancy loss.

IMPORTANT OUTCOMES

Risk of teratogenicity from vaccine
- Among women who received the rVSV-ZEBOV vaccine during or just prior to pregnancy, compared to pregnant women who did not receive the rVSV-ZEBOV vaccine, existing evidence is unable to determine if the rVSV-ZEBOV confers a risk of teratogenicity in pregnancy. One study specifically evaluated for teratogenicity among pregnant women with vaccine exposure, and among 38 infants, no teratogenic malformations were noted, though this study was limited by small sample size and the short length of follow up in infants.

Maternal well-being and satisfaction
- Among women who received the rVSV-ZEBOV vaccine during or just prior to pregnancy, compared to pregnant women who did not receive the rVSV-ZEBOV vaccine, existing evidence is unable to determine maternal well-being and satisfaction with vaccine administration. There were no studies that evaluated these outcomes.

EVIDENCE-TO-DECISION TABLE

<table>
<thead>
<tr>
<th>Balance of benefits and harm</th>
<th>(a) Potential benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In the general population, rVSV-ZEBOV is highly effective at preventing EVD.</td>
</tr>
<tr>
<td></td>
<td>Administration of the vaccine to pregnant women can help prevent infection and potentially mortality in mothers, as well as associated near 100% pregnancy loss/neonatal death in foetuses.</td>
</tr>
<tr>
<td></td>
<td>Delivery of a pregnant woman with acute EVD is associated with high risk of transmission to healthcare providers and community members. Prevention of infection in pregnant women eliminates this risk.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>(b) Potential harm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rVSV-ZEBOV is a live-attenuated replication-competent viral vector. Live attenuated vaccines pose a theoretical risk to foetuses and historically have not been recommended for pregnant women.</td>
</tr>
<tr>
<td></td>
<td>Safety data of rVSV-ZEBOV in pregnant women is not well characterized given the limited number of pregnant women in vaccine trials. Adverse effects may or may not be increased in pregnant women.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Values and preferences</th>
<th>Given the limited safety data for rVSV-ZEBOV in pregnant women, relevant stakeholders may not agree with administration of the vaccine in pregnant populations. Pregnant women and/or their family members may not be willing to have the vaccine administered during pregnancy.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Offering the vaccine to pregnant women is consistent with the principle of autonomy.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resource use</th>
<th>Administering rVSV-ZEBOV in pregnant individuals would increase resources used, including the demand for rVSV-ZEBOV, healthcare workers to administer the vaccine, and costs.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>If vaccine administration reduces cases of EVD in pregnant women, then treatment resources and costs would decrease.</td>
</tr>
</tbody>
</table>

| Feasibility/applicability | Offering rVSV-ZEBOV for pregnant women is feasible and applicable in areas that are undergoing ring vaccination. |
Annex 3. Contributors

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