SOGC Committee Opinion on the Management of a Pregnant Woman Exposed to or Infected With Ebola Virus Disease in Canada

Abstract

Objective: To review the evidence and provide recommendations on the general management of a pregnant woman exposed to or infected with Ebola virus disease (EVD).

Outcomes: Outcomes evaluated include general principles of approach and specific aspects of management of EVD relevant to pregnancy.

Evidence: Published literature was retrieved through searches of Medline, EMBASE, and CINAHL in October 2014 using appropriate controlled vocabulary and key words (Ebola and pregnancy; hemorrhagic fever and pregnancy). Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies published in English. Searches were updated and incorporated in the guideline to November 7, 2014. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology assessment-related agencies, clinical practice guideline collections, and national and international medical specialty societies.

Values: The quality of evidence in this document was rated using the criteria described in Report of the Canadian Task Force on Preventive Health Care (Table 1).

Conclusion: Individuals incubating EVD but who do not yet have symptoms are not infectious. The chance of a pregnant woman presenting with EVD in Canada is minimal, as are the chances of her infecting others if reasonable precautions are in place. Evidence of maternal–fetal transmission is limited and anecdotal.

Key words: Ebola, hemorrhagic fever, pregnancy
The committee opinion has been written as a supplemental document to provide guidance to obstetric care providers in Canada in the extremely unlikely event a pregnant woman with EVD is seen in a Canadian setting. This opinion was written in the midst of an extensive outbreak of EVD in specific countries in West Africa and in the context of rapidly changing guidelines on public health practices, personal protection advice, and clinical management advice available through international and national documents produced by WHO, PHAC, United States Centers for Disease Control and Prevention, provincial and regional health organizations, and many others. It is important to refer to the most up-to-date version of those guidelines for recommendations on personal protection, general management, and public health policy. As of November 7, 2014, the outbreak of the Zaire strain of EVD in West Africa, ongoing since December 2013, has resulted in 13,268 people with documented illness and 4960 deaths worldwide. The outbreak continues in Guinea, Sierra Leone, and Liberia. Nigeria and Senegal have not had any new cases for more than 21 days, and there was 1 case in Mali. In addition, there have been 5 cases outside of Africa with 4 in the US and 1 in Spain. This is the largest outbreak of EVD ever recorded and it is not yet under control in West Africa.

Given that women of reproductive age are being infected in the outbreak countries, and that women of reproductive age from Canada are part of teams of health care providers and scientists assisting with the effort, it is conceivable that a pregnant woman with EVD exposure or infection could present for care in Canada. This article attempts to prepare Canadian perinatal care providers for this very unlikely eventuality.

**Ebola Virus**

Ebola virus, 1 of 5 strains of a filoviridae family of viruses, is an RNA virus with a protein envelope. The 4 types confirmed to have caused human disease are Ebola Zaire, Ebola Sudan, Ebola Ivory Coast, and Ebola Bundibugyo. The reservoir for Ebola virus appears primarily to be in fruit bats, but the spread to humans likely occurs through the consumption or handling of meat from infected animals such as rodents or primates. Human-to-human transmission can then occur.

**Epidemiology**

EVD was first discovered in an outbreak in the Democratic Republic of the Congo in 1976 with the Ebola Zaire strain. Since then there have been a number of small, contained outbreaks in Africa. In 2014, an outbreak of EVD in West Africa led to a unprecedented number of cases and deaths.

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**ABBREVIATIONS**

EVD  Ebola virus disease
MSF  Médecins Sans Frontières
PCR  polymerase chain reaction
PHAC  Public Health Agency of Canada
PPE  personal protective equipment
WHO  World Health Organization
outbreaks (Table 2) until the 2014 outbreak, which is not only the largest but the most geographically extensive. Case fatality rates reported in Table 2 apply to West Africa and areas with limited health care infrastructure and generally very limited resources. In resource rich countries, there has been a 20% mortality associated with EVD (of 5 cases, 1 person died, 3 recovered, and 1 was still in treatment at the time of writing).

Modes of Transmission

Human-to-human transmission can occur through very direct contact with the secretions and excretions of infected symptomatic patients or cadavers. Exposure to heavily contaminated bedding and clothing with vomitus, blood, and/or feces has also been a source of infection. The virus requires a mucosal surface or break/abrasion in the skin, or parenteral spread. It is not spread through the aerosol route. Health workers are typically infected from needle stick injuries or protocol breaches in the use of personal protective equipment and techniques. These protocol breaches occur when individuals do not properly don impermeable PPE or contaminate themselves while doffing the equipment. Emerging data from WHO suggest that health care workers in outbreak areas have frequently been infected in other aspects of their lives through individuals they live with, care for at home, or have as sexual partners.

CLINICAL TIP

Individuals incubating Ebola virus who do not yet have symptoms (sudden fever, fatigue, muscle pain, headache, sore throat, and gastrointestinal symptoms of nausea, vomiting, diarrhea, and abdominal pain) are not infectious. Infectivity potential increases with the degree of illness and patients are more highly infectious when they are more symptomatic. Once patients recover, it is important to document clearance in the blood. The virus has been detected in breast milk, but it is unclear for how long after recovery breast milk may still be infectious. Reports

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Species</th>
<th>Cases</th>
<th>Case fatality rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012/2013 to present (data to 07/11/2014)</td>
<td>Guinea, Liberia, Sierra Leone, Nigeria (cleared), Senegal (cleared), Mali, Spain, US</td>
<td>Zaire</td>
<td>13,268</td>
<td>37.4 (4960 deaths)</td>
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<tr>
<td>2012</td>
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<td>Bundibugyo</td>
<td>57</td>
<td>51</td>
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<td>Sudan</td>
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</tr>
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<td>83</td>
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<tr>
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<td>Zaire</td>
<td>143</td>
<td>90</td>
</tr>
<tr>
<td>2001–2002</td>
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<td>75</td>
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<tr>
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<td>100</td>
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<td>Gabon</td>
<td>Zaire</td>
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<td>315</td>
<td>81</td>
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<tr>
<td>1994</td>
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<td>Tai Forest</td>
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<td>0</td>
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<td>Zaire</td>
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<td>60</td>
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<td>1979</td>
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<td>65</td>
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<td>100</td>
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<tr>
<td>1976</td>
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<td>Sudan</td>
<td>284</td>
<td>53</td>
</tr>
<tr>
<td>1976</td>
<td>Democratic Republic of the Congo</td>
<td>Zaire</td>
<td>318</td>
<td>88</td>
</tr>
</tbody>
</table>

The information in this table is adapted from the WHO tables “Ebola response roadmap situation report update” and “Chronology of previous Ebola virus disease outbreaks.” The mortality rates are based on deaths per reported cases; not all cases were confirmed at the time of writing.
suggest an effect in breast milk lasting for 15 to 40 days.\textsuperscript{9,10} Of note, semen may still contain the virus up to 7 weeks post-recovery.\textsuperscript{6,11}

**CLINICAL PRESENTATION AND DIAGNOSIS**

The incubation period for EVD is 2 to 21 days (mean 4 to 10 days).\textsuperscript{6} First symptoms include the sudden onset of fever (usually high at > 38.6 °C), fatigue, muscle pain, headache, sore throat, and gastrointestinal symptoms of nausea, vomiting, diarrhea, and abdominal pain.\textsuperscript{12} Other less common features include cough, maculopapular rash, and conjunctival injection.\textsuperscript{13} Towards the end of the first week of symptomatic disease, hemorrhagic features of petechia, blood loss from venipuncture sites, bruising, and gastrointestinal bleeding may occur in up to 18% of patients.\textsuperscript{3,14} Laboratory findings include leukopenia, thrombocytopenia and elevated liver enzymes.\textsuperscript{6} PT and PTT can be prolonged and fibrin degradation products can be elevated. As the disease progresses, severe hypovolemic shock and multi-organ failure occurs, usually between days 6 and 16 from symptom onset.\textsuperscript{15} Seizures and coma usually precede death in those with terminal illness.

Testing for the Ebola virus in blood by reverse transcription PCR is the most definitive and rapid test and will return a positive result within 3 days of the onset of symptoms.\textsuperscript{15} Time to get this result back will vary from site to site depending on access to trained laboratory personal and transportation of specimens (the test itself takes approximately 4 hours). This results in a potential clinical window in which results of PCR testing in an infected person may be negative (in the first 3 days of symptoms). Therefore, in probable cases of infection (see Table 3)\textsuperscript{16} repeating PCR testing in 3 to 4 days is recommended. It is important to consider other diagnoses for high fevers found in travelers returning from West Africa, such as malaria or typhoid.\textsuperscript{15,17} In Canada, influenza and other seasonal viral illnesses are common and should also be ruled out.

**PRECAUTIONS AND TREATMENT**

The primary focus for health facilities that could deal with EVD (Table 3) must be on the protection of health care workers with appropriate use of PPE. In addition, if a diagnosis of EVD is confirmed, public health and infection control experts should be involved in contact tracing where appropriate and terminally cleaning areas contaminated with the infected individual’s bodily fluids.\textsuperscript{15,17} Isolation of individuals with probable or confirmed EVD is paramount, and each province and region has detailed plans for where these individuals are to be assessed and treated. These plans are in evolution, so the local medical health officers and infection control services are the best source for up-to-date regional specific information. Obstetric care providers need to ensure that they have been trained in donning and doffing PPE, and follow recommended guidelines including appropriate training and monitoring for use of PPE should they work in a facility that is a designated Ebola testing or treatment facility.\textsuperscript{15,17,18}

In the situation of a confirmed case of Ebola, the focus of therapy is on supportive care with maintenance of intravascular volume, correction of electrolyte and metabolic abnormalities, correction of coagulation abnormalities, nutrition and antimicrobial therapy of secondary bacterial infections.\textsuperscript{13,15} Currently no proven antiviral therapies or vaccines are available for clinical use; however, corrections of electrolyte and metabolic abnormalities are usually effective in supporting the individual through this self-limited viral illness.\textsuperscript{19} Detailed guidelines drafted by critical care and infectious diseases experts to guide management in the intensive care setting are available on the PHAC website.\textsuperscript{17}

**Specific Considerations in Pregnancy**

Since many health care workers and adult women in the affected countries are women of child bearing age, the possibility of EVD in pregnancy exists. In any given population, 2% to 5% of persons are estimated to be pregnant. Data from the current outbreak that could inform health care providers are limited, but some data from prior EVD outbreaks are available.\textsuperscript{20}

Early data from 1976 suggests outcomes for pregnant and non-pregnant women did not differ, with mortality rates of 89% and 88%, respectively.\textsuperscript{7} However, more recent data from a small series in 1995 suggested that pregnant women were at higher risk of mortality than the general population.\textsuperscript{21} MSF reports fetal outcomes to have been very poor, with most women presenting with intrauterine fetal demise.

**Antepartum considerations**

If a woman presents to a Canadian health care setting with a history consistent with Ebola exposure and is asymptomatic, the standard adult protocols for evaluation and monitoring should be used. A plan for management at the onset of symptoms should be established, part of which should include ensuring ambulance access to a designated Ebola containment hospital. Work is being done in Canada to arrange for safe air transport, but in many areas road ambulance is the only safe transportation option.

If a pregnant woman becomes symptomatic, arrangements should be made for containment in an appropriate
Table 3. Public Health Agency of Canada’s case definitions

<table>
<thead>
<tr>
<th>Person under investigation</th>
<th>A person with EVD-compatible symptoms not attributed to another medical condition AND with laboratory results pending AND at least 1 of the following epidemiologic risk factors within the 21 days before the onset of symptoms:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• residence in or travel to an area where EVD transmission is active;</td>
</tr>
<tr>
<td></td>
<td>• health care worker wearing PPE and adhering to appropriate infection prevention and control precautions with no safety breaches, who directly or indirectly cared for a probable or confirmed case of EVD (direct patient care or contact with the environment or fomites of a case);</td>
</tr>
<tr>
<td></td>
<td>• other patient or visitor without high-risk exposures, as defined below, who spent time in a health care facility where probable or confirmed cases of EVD were being treated;</td>
</tr>
<tr>
<td></td>
<td>• household member of a probable or confirmed case of EVD without high-risk exposures, as defined below;</td>
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<tr>
<td></td>
<td>• laboratory worker processing bodily fluids of probable or confirmed cases of EVD with appropriate PPE and standard biosafety precautions and no safety breaches;</td>
</tr>
<tr>
<td></td>
<td>• direct exposure (e.g. through participation in funeral or burial rites) to human remains with appropriate PPE and no safety breaches in a geographic area where the outbreak was occurring;</td>
</tr>
<tr>
<td></td>
<td>• direct unprotected contact with bats or primates from an EVD-affected country.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Probable case</th>
<th>A person with EVD-compatible symptoms not attributed to another medical condition AND at least 1 of the following high-risk exposures within the 21 days before the onset of symptoms:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• percutaneous or mucous membrane exposure or direct skin contact with body fluids of a confirmed or probable case of EVD;</td>
</tr>
<tr>
<td></td>
<td>• sexual contact with a probable or confirmed EVD case;</td>
</tr>
<tr>
<td></td>
<td>• laboratory worker processing body fluids of probable or confirmed EVD cases without appropriate PPE or standard biosafety precautions;</td>
</tr>
<tr>
<td></td>
<td>• health care worker not wearing PPE and/or not adhering to appropriate infection prevention and control precautions, who directly or indirectly cared for a probable or confirmed case of EVD (e.g. direct patient care or contact with environment or fomites of a case);</td>
</tr>
<tr>
<td></td>
<td>• direct exposure without appropriate PPE to human remains (e.g. through participation in funeral or burial rites) in a geographic area where an outbreak was occurring</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Confirmed case</th>
<th>A person with laboratory confirmation of EVD infection using at least 1 of these methods:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• isolation and identification of virus from an appropriate clinical specimen (e.g., blood, serum, tissue, urine specimens, or throat secretions);</td>
</tr>
<tr>
<td></td>
<td>• detection of virus-specific RNA by reverse-transcriptase PCR from an appropriate clinical specimen (e.g., blood, serum, tissue) using 2 independent targets or 2 independent samples;</td>
</tr>
<tr>
<td></td>
<td>• demonstration of virus antigen in tissue (e.g., skin, liver, or spleen) by immunohistochemical or immunofluorescent techniques AND another test (e.g., PCR);</td>
</tr>
<tr>
<td></td>
<td>• demonstration of specific IgM AND IgG antibody by EIA, immunofluorescent assay, or Western Blot;</td>
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<tr>
<td></td>
<td>• demonstration of a 4-fold rise in IgG serum antibody by EIA, immunofluorescent assay, or Western Blot from serial samples.</td>
</tr>
</tbody>
</table>

This table is adapted from PHAC’s national case definition. EIA: enzyme immunoassay
medical facility, and immediate testing for EVD should be conducted by PCR. If her condition and symptoms are consistent with the case definition for EVD, but PCR test results for EVD are negative and symptom onset was less than 3 days prior, she should be considered a probable case until a repeated PCR also returns negative results. In a case such as this, workup for other causes of fever including malaria smears and blood cultures for typhoid (if they can be safely performed in the laboratory) should be performed. Clinical evaluation and laboratory testing for common respiratory viral diseases in Canada, particularly influenza, is very important. Adherence to local laboratory protocols for the safe handling of potentially Ebola-infected blood is essential. If the pregnancy is at a pre-viable gestational age, assessment of pregnancy status is warranted, but if fetal demise is diagnosed, induction of labour or evacuation of the uterus should not be initiated until the potential window phase has passed or until repeat PCR negative results are available.

Management of a pregnant woman who has had confirmed EVD
Careful attention to the safety of health providers is needed. It is recommended that multiple providers be identified to maximize the team available for care. Primary medical management should focus on the resuscitation and support of the woman following the published guidelines for fluid resuscitation, management of intravascular coagulopathy, and secondary bacterial infections as outlined for non-pregnant adults. Of note, some of the features of EVD may also be consistent with known complications of pregnancy, including preeclampsia with HELLP, gestational thrombocytopenia, and abruptio placenta (spontaneous bleeding). Clinical management should include consideration of known complications of pregnancy in addition to management of EVD.

Maternal considerations
Data from prior EVD outbreaks suggest that there is no increased susceptibility to EVD acquisition in pregnancy, but the mortality rate in pregnant women may be higher than in non-pregnant adults; the overall case fatality rate in the 2014 outbreak has to date been 37.4% with no documented breakdown in the epidemiology reports of pregnant versus non-pregnant women. High rates of first and second trimester spontaneous pregnancy loss have been reported in prior outbreaks of EVD, with a 23% pregnancy loss in the 1976 outbreak in Zaire. One pregnancy was formally reported in the outbreak in Guinea in a 16-year-old who subsequently had a spontaneous loss, but herself survived. Many anecdotal reports of pregnancies in women infected with EVD have come from MSF, but published reports from epidemiologic studies are lacking because efforts have been concentrated on patient care and infection control.

Neonatal considerations
The few reports on neonates delivered to women with acute EVD suggest the prognosis is very poor. In 1976 in Zaire, the 11 neonates born to pregnant women with EVD all died within 19 days of life, and in the 1995 outbreak 1 live born infant died. However, it is again unknown whether this was a direct effect of EVD in these infants or an effect of other complications in settings with limited resources, high rates of gastrointestinal infections and malaria, and a mother who was acutely ill. Of note, there is no information on outcomes of an EVD-exposed neonate cared for in a high resource setting.

GENERAL RECOMMENDATIONS FOR ANTENATAL, INTRAPARTUM, AND POSTPARTUM MANAGEMENT
A literature search was conducted prior to developing this committee opinion. Very little good evidence was found and the following general recommendations are therefore all classified as level III (opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees)-L (insufficient evidence to make a recommendation; however, other factors may influence decision-making) (Table 1). Each institution should have a plan in place for the management of probable or confirmed cases of Ebola in pregnant or labouring women. The decision as to whether to train all labour and delivery staff in the use of PPE or to have a smaller team of well-trained individuals on call may be decided by individual institutions based on regional plans for designated testing and treatment hospitals.

If a pregnant woman presents with fever, and/or other symptoms of Ebola and has a high-risk contact history (was a resident of or is a health care worker returning from such an affected area), then she should be placed in an appropriate closed hospital room. Health care personnel should follow current infection control procedures before evaluating this patient for possible Ebola infection with blood testing for
Ebola PCR.13,15 If the Ebola PCR is negative and the onset of
the woman’s symptoms occurred within the last 3 days, the
Ebola PCR should be repeated in 3 to 4 days to ensure that it
is a true negative. Isolation of the woman for 3 days is based
upon whether she has had a high- or low-risk exposure.8,17
Management of a pregnant woman with probable but
unconfirmed EVD should involve selective laboratory and
imaging investigations that minimize the risk of exposure to
clinical and laboratory staff. Malaria smear, basic hematology,
liver enzymes, renal function, and coagulation assessments
would be appropriate, as would viral testing for influenza
during the influenza season. Blood cultures should be held
until confirmation that Ebola PCR is negative because the
only facility in Canada operating a Containment Level 4
Laboratory is the PHAC’s National Microbiology Laboratory
in Winnipeg, Manitoba.

The number of staff in contact with the patient should be
kept to a minimum, and PHAC guidelines and provincial
and regional infection control protocols, including the
appropriate use of personal protective equipment, should
be followed carefully.15,17

If a pregnant woman is deemed to be infected with
Ebola based on symptoms and a positive Ebola PCR test,
guidelines for general care of the infected adult patient
should be followed.15 Care and management should occur
in a regionally dedicated facility for adult care of EVD in the
case of intrauterine fetal demise; expectant management or
the most non-invasive management of the evacuation of
the uterus should be preferred over surgical management
and followed by primarily medical management of uterine
contractions and blood loss.15,24,25 If a woman is near term
and has been exposed to Ebola virus but is not yet infected,
induction of labour or elective Caesarean section should be
considered in order to deliver the infant prior to the onset
of viremia and maternal illness. If the woman subsequently
becomes ill with EVD, the infant should be isolated from
the mother, breastfeeding should be discontinued, and the
mother should be cared for without the complications of
pregnancy impeding medical management.

If a woman with probable or confirmed EVD presents
in labour, careful management of the labour with
consideration of both the health status of the mother and
the safety of the care providers is paramount. Management
of care should be conducted with obstetricians, intensivists,
infectious disease specialists, anaesthesiologists, nurses,
and pediatricians as core members of a multidisciplinary
team. Early establishment of adequate intravenous access
and administration of antibiotics to prevent or treat
chori amnionitis and endometritis should be considered.
Fetal monitoring should be external only; no fetal scalp or
scalp gas monitoring should be performed.24 There should
be multidisciplinary team input about the appropriateness
of an emergency Caesarean section based on the prognosis
for the woman considering her overall medical status and
the ability of the team to conduct a safe surgical delivery.
Caesarian section may only be appropriate when it is likely
to save the life of the mother. There should be antenatal
consultation with the pediatric/neonatal team to determine
a plan of care for the newborn and to discuss whether an
unwell newborn should be actively resuscitated given the
poor chance of an infant born to an infected mother to
survive and the increased risk of exposure of health care
workers.

During a vaginal delivery, rupture of membranes should
be induced only if controlled rupture seems prudent
to avoid significant fluid contamination of health care
providers. Protection of the staff conducting the delivery
should be paramount. In the event of a tear or episiotomy,
repair should be conducted only to control excessive
bleeding and only by an experienced obstetrician using
an instrument-only technique. No cord traction and no
cord blood draws should be performed. Placental delivery
should be permitted to occur naturally without traction,
and postpartum hemorrhage should be managed medically
whenever possible.

Management of the Neonate Born to a
Mother With Probable or Confirmed EVD

Ebola transmission to infants has not clearly been
described as transplacental or peripartum and the rate of
transmission is unknown. Neonatal survival has not been
described nor has a case of an Ebola-exposed neonate
cared for in a facility with advanced neonatal intensive
care resources. Neonates born to mothers with probable
or confirmed EVD must be considered to be infected and
cared for using appropriate precautions and PPE in an
Ebola-designated facility. The neonate should be assessed
by experienced pediatric medical and nursing staff, with
care taken to clean maternal secretions from the infant
prior to any invasive care or monitoring. In addition to any
other evaluations of care, infant venipuncture for Ebola
PCR should be done in consultation with a specialist in
pediatric infectious diseases at birth, at 3 days of life, and
any time within 21 days of birth that the infant becomes
unwell or symptomatic. Ideally, to minimize the risk of
peripartum transmission, an asymptomatic term infant
should be isolated from the mother until she is cleared
of EVD. Protocol for isolation and management of sick
term or preterm infants with suspected EVD, including
location, equipment, intra-facility transport, diagnostic
tests and procedures, and staff responsibilities and training
should be developed at each Ebola-designated institution. Although treatment and prevention of Ebola disease is of paramount importance, medical teams (obstetric, pediatric, and neonatal) should maintain standards of good communication and family-centred care.

Postpartum management should include advice on the use of condoms for at least 3 months post-survival from Ebola for either the male or female partner.6,11 Women should be advised to use secure contraception (pills or injection) for at least 3 to 6 months after surviving EVD.

Overall it is deemed highly unlikely that pregnant women with EVD will need care in Canada, but should this occur recommendations for care may vary over time as further information becomes available.

REFERENCES


