

Management of Ebola virus disease (EVD) survivors in Ontario

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Public Health Ontario

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Overview

This document will review the epidemiology of Ebola virus disease (EVD), the current understanding of Ebola virus persistence in survivors and the risk of Ebola virus exposure in Ontario. Recommendations for the care of EVD survivors and when to use infection prevention and control (IPAC) precautions for EVD are outlined. Additional information related to IPAC precautions for EVD and other Viral Haemorrhagic Fevers (VHFs) can be found in the document entitled “Guidance for Patients with Suspect or Confirmed Viral Haemorrhagic Fevers (VHF) in Acute Care Settings”.

The following two resources provide very good guidance on the care of EVD survivors and potential risks from contact with blood and body fluids, and should be consulted for additional information:

- World Health Organization (WHO). Interim Guidance: Clinical care for survivors of Ebola virus diseases. [Internet][accessed 2016 March 23]. Available from: <http://www.who.int/csr/resources/publications/ebola/guidance-survivors/en/>
- Centers for Disease Control and Prevention (CDC). Interim Guidance for Management of Survivors of Ebola Virus Disease in U.S. Healthcare Settings. [Internet][accessed 2016 March 23]. Available from <http://www.cdc.gov/vhf/ebola/healthcare-us/evaluating-patients/guidance-for-management-of-survivors-ebola.html>

Background

EPIDEMIOLOGY

As of March 30, 2016 there have been 28,610 reported confirmed, probable and suspected Ebola Virus Disease (EVD) cases among identified West African countries with intense EVD transmission (Guinea, Liberia and Sierra Leone) and 11,308 deaths reported (39.5% mortality rate).¹ The majority of cases reported within these countries occurred prior to December 2014 (17,908 cases (62.6%) were reported by December 7, 2014)² when rapid scale-up operations focusing on improving surveillance, contact tracing and community interventions were implemented.¹

Due to successful control efforts, the World Health Organization (WHO) stated on January 14, 2016 that all known EVD chains of transmission have been stopped in West Africa. For the first time in almost two years, all three of the most affected countries reported no new cases.³ Although this news is promising, the WHO warns of expected flare-ups in the coming months and a flare up in Sierra Leone was reported shortly thereafter. As of April 1, 2016, there have been 12 documented episodes of EVD flare-ups, likely related to the virus persisting in some body fluids of EVD survivors. The WHO indicates strong surveillance and response efforts are necessary to ensure control over any flare-ups that may occur.³ None of the flare-ups that have occurred to date have resulted in intense, widespread EVD transmission and it is expected, as time progresses, the potential for flare-ups will decrease. Based on the data released by the WHO on January 20, 2016, of the confirmed cases with available information, 81.2% were 15 years of age or older and 48.9% were male.⁴ Applying these proportions to the approximately 17,300 EVD survivors, it can be estimated that there are approximately 6,900 male survivors 15 years of age or older.

In Ontario from November 10, 2014 to February 5, 2016 there were 981 individuals identified at a Canadian border with history of travel to an EVD affected region in the preceding 21 days who were issued an Order under the Federal Quarantine Act to report to public health for monitoring for symptoms associated with EVD. Of these individuals, 2% (21/981) went on to develop symptoms associated with EVD that required further investigation, all with negative results for EVD. Even when there was active transmission of EVD in Guinea, Sierra Leone and Liberia, there was very little exportation of infection with only nine individuals acquiring infection in these countries and bringing their infection to another country (excluding individuals with known infections who were transported to other countries for care).¹ Therefore the likelihood of exportation when there is almost no transmission in West Africa is remote.

RISK OF PERSISTENT INFECTION FROM VARIOUS SOURCES

Ebola virus has been found to persist in convalescent EVD patients in sites that are harder for the immune system to reach (immunologically privileged sites). In EVD survivors, the following are considered immunologically privileged sites and fluids from these sites are potentially infectious:

- the eyes – ocular fluids (but not tears)
 - central nervous system (spinal cord and brain) – cerebral spinal fluid (CSF)
 - male reproductive tract including the testicles - semen
 - mammary glands – breast milk
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EVD survivors can experience joint pain but it is currently uncertain if synovial fluid from joints can contain Ebola virus. Synovial fluid of an EVD survivor will be considered potentially infectious for purposes of these recommendations.

In women who were infected while pregnant, the virus may persist in the fetus, amniotic fluid, placenta and breast milk. Women who become pregnant after recovering from EVD infection are not considered infectious from the fetus, amniotic fluid or placenta. It is possible for the Ebola virus to remain in breast milk in women who had EVD either while pregnant or before becoming pregnant. There is currently no available evidence to indicate the time period between the EVD infection and pregnancy that is associated with no risk of Ebola virus in breast milk.⁵

After an EVD-Zaire outbreak in 1995 in Kikwit, Democratic Republic of the Congo, follow up of survivors and their household contacts over 21 months was completed. Over a three month period, body fluids from 28 convalescent patients were tested for the presence of Ebola virus in tears, sweat, feces, urine, saliva, conjunctival fluid, vaginal secretions and semen. Blood and semen were also collected at the 21 month visit. All tears, sweat, feces, urine, saliva, conjunctival fluid, and vaginal specimens were obtained 12 to 157 days after symptom onset and were negative for viral isolation and ELISA. Semen was also negative by virus isolation but had RNA detected by reverse transcriptase polymerase chain reaction (RT-PCR) testing for up to 91 days, when the last specimen was tested from this individual. The earliest negative semen sample by RT-PCR was obtained 62 days after symptom onset.⁶

Another study from the 1995 Kikwit outbreak assessed body fluids from 12 survivors. In this study one patient tested positive by RT-PCR from conjunctival fluid at 22 days, a rectal specimen at 29 days and vaginal fluids at 33 days post symptom onset. In addition, four of five men were positive by RT-PCR from semen, with the longest positive result obtained at 101 days post symptom onset. Virus was isolated from one semen specimen at 82 days⁷ (Note that this case was also reported in the preceding article about the Kikwit outbreak - Rowe et al.⁶).

In the recent EVD outbreak in West Africa, preliminary findings based on testing of 93 men from Sierra Leone indicated that semen was positive by RT-PCR for 100% of samples (9 of 9) tested within the first three months of symptom onset, 65% (26 of 40) of samples collected four to six months post symptom onset and 26% (11 of 43) of specimens in those seven to nine months post symptom onset. The shortest and longest time from symptom onset to testing RT-PCR negative was 128 days (four months) and 284 days (nine months), respectively, although no participants with onset more than 10 months previously were included in the study. Additional studies are being done to determine if the virus in semen remains viable.⁸ Sexual transmission has been documented, although its occurrence is rare.^{5,8}

The Centers for Disease Control and Prevention (CDC) in the United States have summarized the longest time periods from illness onset that EVD RNA or antigen have been detected in various body fluids, as well the longest time period that infectious Ebola virus has been detected in these body fluids (see Table 1: <http://www.cdc.gov/vhf/ebola/healthcare-us/evaluating-patients/guidance-for-management-of-survivors-ebola.html>). The longest time intervals noted for isolation of Ebola virus are as follows:

- aqueous humor from the eye – 98 days;
 - cerebral spinal fluid – 282 days;
 - semen – 82 days;
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- breast milk – 15 days;
- urine - 26 days;
- vomit – 8 days;

with viral RNA being detected for a similar or longer period of time.⁹ The World Health Organization reports the presence of Ebola virus in breast discharge for nine months from symptom onset.⁵ Research regarding the presence and infectivity of Ebola virus in the vaginal fluids of recovered women is ongoing. Ebola virus RNA has been isolated in vaginal fluid up to 33 days after symptom onset, but live virus has never been found. To date, there have been no cases of female-to-male sexual transmission of EVD and therefore routine testing of vaginal fluids is not recommended.⁵ Reactivation of disease from an immunologically privileged site appears to be possible, but rare. In the current West African outbreak, meningitis developed nine months after a patient recovered from EVD. The virus was detected by PCR from the cerebral spinal fluid (CSF) and also at lower levels in the blood, where virus from the CSF appears to have leaked.⁵

Recommendations for the care of survivors

Due to the decline in the outbreak, efforts now focus on reducing the likelihood of flare-ups by providing care to survivors in an effort to ensure they no longer pose a risk of transmitting EVD to others.

The greatest risk of flare-ups is male-to-female sexual transmission as semen has tested positive by RT-PCR for as long as 9 months post symptom onset and viable virus has been detected in semen as long as 82 days post symptom onset.^{7,8,9} To mitigate the risk of EVD flare-ups associated with sexual transmission, the CDC and the WHO suggest EVD survivors refrain from sexual activity or use condoms. The WHO recommends the semen of male survivors be tested for the presence of EVD beginning at three months after disease onset. If the man has two consecutive negative results one week apart, normal sexual activity can resume without concern about EVD transmission. For males whose semen is positive for EVD at three months, testing should be repeated every month until two consecutive negative results one week apart are received. For males who are unable to undergo testing, safe sexual practices are encouraged for at least 12 months after symptom onset.¹⁰ Essential health services for survivors are available in Guinea, Sierra Leone, and Liberia.¹

Research regarding the presence and infectivity of Ebola virus in the vaginal fluids of recovered women is ongoing. Ebola virus RNA has been isolated in vaginal fluid up to 33 days after symptom onset, but live virus has never been found. To date, there have been no cases of female-to-male sexual transmission of EVD and therefore routine testing of vaginal fluids is not recommended.⁵ The risk of transmission of Ebola virus through the breast milk of EVD survivors is also being investigated. Females who were pregnant or lactating when infected have had Ebola virus isolated from their breast milk up to two months after infection. At this time, it is recommended EVD survivors have their breast milk tested for Ebola virus.⁵ In Ontario, EVD survivors may resume breast feeding if they have two consecutive negative tests of their breast milk 48 hours apart.

Potential sources of introduction to Ontario and risk associated with each source

There are three potential sources of EVD introduction into Ontario:

1. a flare-up in West Africa or elsewhere resulting in exportation to Ontario from an incubating or acutely infectious case;
2. a convalescent case who travels to Ontario and causes transmission in Ontario;
3. a new EVD outbreak that arises anywhere in the world and results in exportation to Ontario.

As outlined below, the risk from any of these sources is extremely low.

1. A flare-up in West Africa or elsewhere resulting in exportation to Ontario from an incubating or acutely infectious case:
 - Twelve flare-ups have been documented in West Africa as of March 29, 2016,¹¹ the most recent of which involved Guinea and Liberia.¹² Due to rapid response, strict contact tracing and surveillance, none of the flare-ups have resulted in intense/widespread transmission
 - Risk of flare-ups will decrease with time as convalescent individuals clear the virus from immunologically privileged sites such as semen
 - Diligent response efforts reduce the risk of widespread transmission from flare-ups
 - Even when there was intense transmission in West Africa, there were only nine instances of exportations of EVD; therefore the risk of exportations from a flare-up is remote even with the lifting of travel restrictions and exit screening
 2. A convalescent case who travels to Ontario and causes transmission in Ontario:
 - Of the approximately 6,900 males survivors 15 years of age and over, approximately 62.6% of cases occurring over a year ago. Therefore, approximately 2,580 male survivors who are 15 years of age and over were likely infected between December 8, 2014 and January 20, 2016
 - Based on ongoing research, just over half of male survivors have EVD RNA in semen four to six months after symptom onset and approximately one quarter were positive for RNA at seven to nine months after symptom onset
 - Considering the low number of travellers who have arrived in Ontario compared to the population of the affected West African countries and the number of potentially infectious men, the risk a potentially infectious man arriving in Ontario is very low and will continue to decrease over time as infection clears in convalescent men
 3. A new EVD outbreak begins in any part of the world and results in exportation to Ontario:
 - There have been 26 EVD outbreaks recorded since 1976
 - Risk of a new outbreak is very low and the risk of introduction into Ontario much lower
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General recommendations with regard to EVD risks in Ontario

1. Specific screening for Ebola is no longer necessary due to the virtual elimination of documented transmission in West Africa. The very low risk of flare-ups will decrease over time. Flare-ups in West Africa should be monitored closely; screening recommendations can be re-assessed if widespread or uncontrolled transmission in West Africa reoccurs.
 2. Patients who present with clinically compatible symptoms of EVD should be asked about travel history as per usual practice and also asked about contact with an Ebola survivor. Should EVD be suspected based on clinically compatible symptoms and a history of potential exposure, appropriate EVD-specific infection control precautions should be used. See document entitled “Guidance for Patients with Suspect or Confirmed Viral Haemorrhagic Fevers (VHF) in Acute Care Settings.”
 3. Although very unlikely to occur, patients who identify as being previously infected with EVD and present for care in Ontario, including those presenting with a possible relapse, should be assessed based on the recommendations outlined below and the [WHO Interim Guidance: Clinical Care for survivors of Ebola virus disease](#).⁵ Should a relapse be suspected in an EVD survivor, or should contact with an immunologically privileged site of an EVD survivor be required, appropriate EVD-specific infection control precautions should be used. Additional details are provided below and in the document entitled “Guidance for Patients with Suspect or Confirmed Viral Haemorrhagic Fevers (VHF) in Acute Care Settings.”
 4. The Provincial Infectious Diseases Advisory Committee [Routine practices and Additional Precautions in All Health Care Settings, 3rd Edition](#) should be followed with all patients.
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Infection prevention and control (IPAC) recommendations when caring for EVD survivors

The following outlines when Routine Practices and Additional Precautions are required when caring for EVD survivors and when EVD-specific precautions are required. The elements of EVD-specific IPAC recommendations are outlined in the document entitled “Guidance for Patients with Suspect or Confirmed Viral Haemorrhagic Fevers (VHF) in Acute Care Settings”. The following outlines which type of IPAC precautions are recommended under two circumstances:

1. EVD survivors presenting for care that is NOT related to an EVD relapse
2. EVD survivors presenting for care that IS OR MAY be related to an EVD relapse

1) EVD survivors presenting for care that is NOT related to an EVD relapse

Body fluids that are NOT from immunologically privileged sites: As per usual, Routine Practices and Additional Precautions (and not EVD-specific precautions) are required for potential exposure to blood, urine, feces, vomit, saliva, tears, sputum, sweat and vaginal fluid.

Body fluids from immunologically privileged sites: EVD-specific precautions are required if contact is expected with fluids from immunologically privileged sites (i.e., intraocular fluid, cerebral spinal fluid, semen, breast milk or synovial fluid). EVD-specific precautions would no longer be required for fluids that have been tested for Ebola virus RNA by RT-PCR and have been found to be negative on two consecutive tests.

Delivery and handling of newborns: EVD-specific precautions are required for the delivery and handling of the newborn baby from a woman who had EVD while pregnant. Routine Practices and Additional Precautions are required for the delivery and handling of a baby if the woman became pregnant after recovering from EVD. In both women who had EVD during pregnancy or became pregnant after recovering from EVD, EVD-specific precautions would be required if handling breast milk or if the woman is receiving an epidural or spinal anesthetic, because of the potential exposure to CSF.

Elective surgery: If surgery on immunologically privileged sites (eyes, brain or spinal cord, breasts, male genitourinary tract including testes, prostate and seminal vesicles and joints) is elective and can be postponed, it is recommended that it be delayed for one year post resolution of acute EVD. If surgery on any of these sites must be performed, EVD-specific precautions will be required, even if beyond a year from EVD symptom onset. During surgery, a swab for Ebola virus testing should be taken from the implicated site to assist with IPAC management post-operatively.⁵

2) EVD survivor presenting for care that IS OR MAY be related to an EVD relapse

Patient experiencing a relapse may present with fever, eye symptoms, or neurologic symptoms such as headache, neck stiffness, photophobia, altered mental status, and/or seizures. When examining a patient who is or may be having a relapse, EVD-specific IPAC precautions are required until EVD is ruled out by testing of blood and specific body sites as indicated based on symptoms (e.g.: CSF for neurologic symptoms).

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