Ebola Virus Disease

PHO Grand Rounds

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Outline

1. Classification of Ebola virus
   Dr. Jonathan Gubbay

2. Reservoir and transmission to humans
   Dr. Jonathan Gubbay

3. Pathogenesis
   Dr. Gary Garber

4. Clinical presentation and prognosis
   Dr. Gary Garber

5. History of past Ebola outbreaks
   Michael Whelan

6. Overview of current outbreak
   Michael Whelan

7. Social impact and response
   Dr. Bryna Warshawsky

8. Post-exposure prophylaxis and vaccines
   Dr. Bryna Warshawsky

9. Public Health Ontario response
Dr. Jonathan Gubbay

• Classification of Ebola virus
• Reservoir and transmission to humans
Classification of Ebola virus

- **Order Mononegavirales**
  - Enveloped, nonsegmented, negative strand RNA viruses

- **Family Filoviridae contains 3 genera:**
  - *Ebolavirus* (1976)
  - *Marburgvirus* – Lake Victoria marburgvirus (1967)
  - *Cuevavirus* – Lloviu virus (bats, Spain, 2002)
**Ebola virus species**

- Sudan ebolavirus: 1976, Sudan.
- Taï Forest ebolavirus (formerly *Côte d’Ivoire ebolavirus*): 1994, Ivory Coast.
  - Single case, veterinary worker handling primate.
  - Macaques, swine.
  - Human laboratory workers seropositive but no clinical disease.
Ebolavirus virion

- Genome 19kb long.
- Diameter 80nm; length 960nm to 1200nm.
- Four viral proteins: polymerase (L), nucleoprotein (NP), and proteins VP35 and VP30.
- Spikes formed by GP1/GP2 complexes (envelope glycoprotein)
- VP24 (membrane protein) associated with envelope
- Secretory GP: binds to antibody, possible antineutrophil activity.
Ebolavirus secretory glycoprotein (SGP)

- N terminal 300 amino acids identical to surface glycoprotein.
- Found in high levels in serum.
- May counteract action of anti-ebola antibodies.
- Possible antineutrophil activity.

*Figure 40.5* Features of the GP (top) and SGP (bottom) proteins of EBOV-Z (1976). N-linked glycosylation sites (Y) and cysteine residues (~S) are identified along the sequences. The basic features of GP are essentially the same for all filoviruses.

Guinea strain forms a new clade (subgroup) of Zaire ebolavirus

Suggests evolution of Guinea strain in parallel with strains from DRC and Gabon from recent ancestor

Not introduced directly to Guinea from above countries.

Reservoir and transmission to humans

- Fruit bats reservoir of virus - Drop partially eaten fruits
- Bats infect chimpanzees, gorillas, forest antelopes, porcupines
- Humans handle and eat bush meat (bats, chimpanzees, gorillas)
- Infected human passes from person to person

Centers for Disease Control and Prevention; Virus Ecology Graphic
Dr. Gary Garber

- Pathogenesis
- Clinical presentation and prognosis
Pathogenesis of Ebola - transmission

• Among 173 household contacts of 27 patients with confirmed Ebola, the transmission rate was only 16% despite none of the standard infection control precautions routinely employed in U.S. hospitals being used

• Of 78 contacts who reported no physical contact with the infected patient, none became infected

• Among those who did have physical contact, risk for Ebola was highest after contact with the patients’ blood

• Large HCW transmission in Sierra Leone associated with infected woman in labour

Pathogenesis - transmission

• Fastest incubation period has been reported associated with needle stick injury.

• Viral load may correlate with disease severity and survival

• This is NOT an airborne disease. Thus the pulmonary disease is hemorrhage and ARDS associated with severe sepsis.
Pathogenesis - how does Ebola cause disease?

• Virus enters the body via infected blood/body fluid in contact with a mucosal surface or a break in intact skin.

• Virus replicates preferentially in monocytes/macrophages and dendritic cells which facilitate dissemination of the virus throughout the body via lymphatic system.

• Other cells are secondarily infected and there is rapid viral growth in hepatocytes, endothelial and epithelial tissues.

• There is strong cytokine/inflammatory mediator release of TNF-a and inflammatory cascade.
Pathogenesis - inflammatory response

• Leads to endothelial damage, increased vascular permeability and shock.

• This results in the end organ damage and multi-organ dysfunction

• Diffuse intravascular coagulopathy (DIC) with platelet and coagulation factor consumption which leads to hemorrhage.

• IgM starts forming in 2 day and IgG in 5-8 days post infection. Immunologic response correlates with survival.

• Thus the observation that those who live >1 week are more likely to survive.
Clinical Manifestations

- Incubation period 8-10 days (range 2-21)
- Sudden onset of Fever >38.6°C
- Flu-like symptoms: chills, myalgias, and malaise, sore throat
- Nausea, vomiting, abdominal pain, diarrhea
- Respiratory symptoms of chest pain, shortness of breath and cough
- CNS symptoms: Headache, confusion and coma
Clinical Manifestations

- Rash occurs around day 5
- Hypotension, peripheral edema
- Bleeding manifestations develop in >50% (internal/external)
- Can vary from petechiae & easy bruising, to mucosal hemorrhage, uncontrolled bleeding and massive GI blood loss
- Multi-organ dysfunction: kidneys and Liver
- Laboratory abnormalities
  - Thrombocytopenia and leukopenia
  - Elevated transaminases (AST > ALT), amylase, D-dimer
  - Reduced albumin
Immunity and Survival

- Treatment is supportive care
- IgG response appears to be protective
- Survivors may have persistent high antibody titres and associated sequelae of hepatitis, uveitis, muscle weakness etc.
- Previous observation was that serum from an Ebola survivor was therapeutic
- Anecdotal reports of Mab therapy being successful
- **Caution**, in a disease with 50% survival, any anecdotal observation can be a chance event
- It does support the potential role of vaccination
Michael Whelan

• History of past Ebola outbreaks
• Overview of current outbreak
Ebola Outbreaks prior to 2014

• First identified in 1976, causing two outbreaks
  • One in Sudan
  • One in Democratic Republic of Congo (previously Zaire)
  • Both had several hundred cases

• Multiple, mostly limited outbreaks over the years since then
  • Over 20 outbreaks since the first in 1976
  • Only 5 with more than 100 cases
  • Mainly in countries in Central Africa

## Ebola Outbreaks prior to 2014

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Ebola virus species</th>
<th>Cases</th>
<th>Deaths</th>
<th>Case fatality</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>Democratic Republic of Congo</td>
<td>Bundibugyo</td>
<td>57</td>
<td>29</td>
<td>51%</td>
</tr>
<tr>
<td>2007</td>
<td>Uganda</td>
<td>Bundibugyo</td>
<td>149</td>
<td>37</td>
<td>25%</td>
</tr>
<tr>
<td>2007</td>
<td>Democratic Republic of Congo</td>
<td>Zaire</td>
<td>264</td>
<td>187</td>
<td>71%</td>
</tr>
<tr>
<td>2003 (Jan-Apr)</td>
<td>Congo</td>
<td>Zaire</td>
<td>143</td>
<td>128</td>
<td>90%</td>
</tr>
<tr>
<td>2000</td>
<td>Uganda</td>
<td>Sudan</td>
<td>425</td>
<td>224</td>
<td>53%</td>
</tr>
<tr>
<td>1995</td>
<td>Democratic Republic of Congo</td>
<td>Zaire</td>
<td>315</td>
<td>254</td>
<td>81%</td>
</tr>
<tr>
<td>1976</td>
<td>Sudan</td>
<td>Sudan</td>
<td>284</td>
<td>151</td>
<td>53%</td>
</tr>
<tr>
<td>1976</td>
<td>Democratic Republic of Congo</td>
<td>Zaire</td>
<td>318</td>
<td>280</td>
<td>88%</td>
</tr>
</tbody>
</table>

Origins of current outbreak in West Africa

• Initial (suspect) cases occurred in a family in Guéckédou, Guinea
  • December 2013 / January 2014

• Spread to a number of health care workers and then among their family members
  • January to March 2014

• Not all initial cases were definitively linked

• [Click for map](http://www.nejm.org/doi/full/10.1056/NEJMoа1404505#t=article)

Progression of outbreak up to August 25, 2014

### Case counts and deaths in current outbreak in West Africa up to August 26, 2014

<table>
<thead>
<tr>
<th>Country</th>
<th>Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liberia</td>
<td>1,378</td>
<td>694</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>1,026</td>
<td>422</td>
</tr>
<tr>
<td>Guinea</td>
<td>648</td>
<td>430</td>
</tr>
<tr>
<td>Nigeria</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td>3,069</td>
<td>1,552</td>
</tr>
</tbody>
</table>

**Cases in Nigeria not widespread, mainly limited to the city of Lagos**

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Location of cases: up to August 25, 2014

Dr. Bryna Warshawsky

• Social impact and response
• Post-exposure prophylaxis and vaccines
## Context for outbreak

<table>
<thead>
<tr>
<th>Country</th>
<th>Population 2012 (millions)</th>
<th>Median age 2012 (years)</th>
<th>Literacy levels 2010 or 2012 (percent)</th>
<th>Expenditures on health 2012 (per capita total expenditures at average exchange rate - US)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guinea</td>
<td>11.5</td>
<td>18.5</td>
<td>25 / 41</td>
<td>$ 32</td>
</tr>
<tr>
<td>Liberia</td>
<td>4.2</td>
<td>18.4</td>
<td>61</td>
<td>$ 66</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>6</td>
<td>20</td>
<td>43</td>
<td>$ 96</td>
</tr>
<tr>
<td>Canada</td>
<td>34.8</td>
<td>40</td>
<td></td>
<td>$ 5741</td>
</tr>
</tbody>
</table>

Context for outbreak

- Widespread on multiple fronts
- Affected large cities
- Weak and fragile infrastructure
- Lack of knowledge of the disease
- Distrust of government and foreigners
- Not seeking health care
- Social rituals / burial rituals
- Delayed response; more resources needed
Impact on social determinants of health

• Trading, industry, agriculture, tourism
• Worsening poverty
• Hunger
• Orphans
• Stigma
• School closures
• Other diseases not being treated
• Lack of preventive care: prenatal care, vaccination
Response – World Health Organization Roadmap

• Actual number 2-4 times higher

• Case count could exceed 20,000

• Objectives targeted at countries:
  ➢ With widespread and intense transmission
  ➢ With an initial case(s) or with localized transmission
  ➢ Sharing land borders with an intense transmission area and those with international transportation hubs

• Elements of the response:
  ➢ Treatment centres, referral centres, laboratory access, surveillance and contact tracing, safe burial, social mobilization

• Estimated cost $ 490 million

WHO ethics panel

• WHO convened ethics panel on August 11 regarding use of unapproved vaccines and medications

• Determined ethical in special circumstances

• Moral duty to evaluate these interventions in the best possible studies under the circumstances

• Lots of issues:
  - Conducting research in the midst of the outbreak
  - Who gets drugs
  - Payment
  - Consent
  - Protection from liabilities
Post-exposures prophylaxis / treatment

• ZMapp - “Secret Serum” – PHAC and others
  ➢ Three monoclonal antibodies against parts of the glycoprotein
  ➢ Grown in tobacco plants
  ➢ Suppress viremia and viral spread
  ➢ Effective in non-human primates – 3 doses starting on day 3 to 5
  ➢ Post-exposure, used in seven people - 2 of 7 died

Xiangguo Qiu et al. Reversion of advanced Ebola virus disease in nonhuman primates with Zmapp, Nature
http://www.nature.com/nature/journal/vnfv/ncurrent/pdf/nature13777.pdf
Post-exposure prophylaxis

Tekmira – TKM – Ebola – Burnaby, British Columbia

- Small interfering RNAs
- Formulated in stable nucleic acid lipid particle (SNALP)
- Inhibits the replications of the virus
- Post-exposure prophylaxis in non-human primates given in multiple doses (30 minutes after infection and then either day 1, 3 and 5 or daily for 6 days)
- Tested in humans, put on hold then released
- Also a Marburg variety

Post-exposure prophylaxis / treatment

BCX-4430 – BioCryst Pharmaceuticals

- Small molecule
- Adenosine analogue, inhibits viral RNA polymerase function
- Broad antiviral inhibitor 20 viruses
- Within 48 hours after exposure and then twice daily for 14 days

Favipiravir - Fujifilm

- Small molecule, nucleotide analogue
- Targets the polymerase to stop viral replication; Effective 6 days post infection
- Approved to treat influenza in Japan

Sarepta

- Binds to viral RNA and stops replication


Thomas Reuters Disease Briefing: Ebola Hemorrhagic Fever
http://www.whiov.cas.cn/xwdt_105286/kydt/201408/W020140822749968603837.pdf
Vaccines

**VSV-EBOV**

- **Public Health Agency of Canada**
  - Recombinant vesicular stomatitis virus
  - Replace glycoprotein with Ebola – Zaire, Ebola - Sudan or Marburg
  - Live vaccine; single dose
  - Pre-exposure and possibly post-exposure – used in one laboratory worker
  - Canada donating 800-1000 doses

**GlaxoSmithKline/National Institute of Allergy and Immunology**

- Combined with chimp adenovirus 3
- Bivalent – Zaire and Sudan, Univalent – Zaire
- Inactivated vaccine; single dose ??

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Public Health Ontario Response

- Public health  
  Dr. Bryna Warshawsky
- Infection prevention and control  
  Dr. Gary Garber
- Laboratory testing  
  Dr. Jonathan Gubbay
PHO EVD resource page

http://www.publichealthontario.ca/ebola

Laboratory

TESTING INFORMATION

*Ebola Virus Disease (EVD)* - Sample collection and submission guide

TESTING FLOW CHART

Testing flow for *Ebola Virus Disease (EVD)* in Ontario

Resources

EBOLA GUIDANCE DOCUMENTS

Infection Prevention and Control Guidance for Patients with Suspected or Confirmed *Ebola Virus Disease (EVD)* in Ontario Health Care Settings

*Ebola Virus Disease (EVD)* - Frequently Asked Questions

*Ebola Virus Disease (EVD)* - Fact Sheet

*Ebola Virus Disease (EVD)* - Interim Risk Assessment and Evaluation of Returning Travellers

Related Links

ONTARIO MINISTRY OF HEALTH AND LONG-TERM CARE

*Ebola Virus Disease* (Public information)

PUBLIC HEALTH AGENCY OF CANADA

Viral haemorrhagic fever

*Ebola Virus Disease*

Ebola outbreak in west Africa: Travel health notice

CENTERS FOR DISEASE CONTROL AND
Key Ebola Virus Disease Facts

• Only spread by direct contact with blood and body fluids; not airborne

• Incubation 2-21 days; usually 8-10 days

• Only infectious when symptomatic

• Increasingly infectious as get sicker
Perspectives on risk assessment

• Ebola virus disease confined to well-defined geographic areas
  ➢ Guinea, Liberia, Sierra Leone, Nigeria (Lagos and Port Harcourt only), Democratic Republic of Congo (Equateur province)

• Most infected individuals likely to have known exposures (not unrecognized exposures)

• Most infected individuals, other than aid and health care workers, not likely to travel to Ontario

• Common things are common
  ➢ Malaria, typhoid fever, influenza, meningococcal, much more likely diagnoses
## Interim Risk Assessment of Returning Travellers

<table>
<thead>
<tr>
<th>EVD risk level</th>
<th>Criteria</th>
<th>Action for asymptomatic patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>No risk</td>
<td>Not in affected country/area</td>
<td>No action</td>
</tr>
<tr>
<td>Very low risk</td>
<td>No known exposures</td>
<td>Self-monitoring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No public health action</td>
</tr>
<tr>
<td>Low risk</td>
<td>In a health care facility OR Near a person with EVD but no direct contact</td>
<td>Self-monitoring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intermittent public health follow-up</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>Direct contact WITH full PPE</td>
<td>Self-monitoring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Daily public health follow-up</td>
</tr>
<tr>
<td>High risk</td>
<td>Direct contact WITHOUT full PPE</td>
<td>Self-monitoring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Daily public health follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Review daily activities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stay in town</td>
</tr>
</tbody>
</table>
Interim Risk Assessment for Returning Traveller Action for the Symptomatic Patient

• Consider:
  • Presenting symptoms
  • Ebola virus disease (EVD) risk level

• If needed, consult with infectious disease and/or public health

• In hospital, notify Infection Prevention and Control (IPAC)

• Notify public health of symptomatic returning traveller from country/area affected by EVD, even if EVD not suspected after assessment
  • Public health will arrange additional follow-up
Screening tools

• Screening for travel to affected country/area and presence of symptoms

• Recommended action for:
  • Primary health care providers
  • Emergency departments – algorithm
  • Community laboratories
  • Dental and allied health care professional offices
  • Emergency medical services

• Communications to post-secondary schools
Public Health Ontario Response

- Public health Dr. Bryna Warshawsky
- Infection prevention and control Dr. Gary Garber
- Laboratory testing Dr. Jonathan Gubbay
IPAC Practices for EVD: Droplet + Contact Precautions

• Patient accommodation:
  • Single room with dedicated bathroom (minimum requirement); door closed
  • consider use of an isolation room that has an anteroom for donning or doffing PPE

• PPE for all staff entering the room:
  • fluid-resistant, long-sleeved, cuffed gown
  • gloves
  • full face protection (face shield)
  • surgical or procedure mask

• Maintain log of all individuals entering the room; only essential people should enter the room
Risk Assessment for EVD

• Use risk assessment to determine the need for additional PPE; as the patient’s condition changes, the risk to HCPs may change.

• The procedure being performed and the presence of clinical symptoms impacts the decision of what PPE to wear.

• Clinical risks may include:
  • Large amounts of blood/body fluids: foot/leg coverings, head coverings, waterproof gowns, or biohazard suits
  • Aerosol generating procedures: N95 respirators
  • Phlebotomy: double gloves

• Ensure adequate training before adding unfamiliar PPE
Other infection prevention and control measures covered in the IPAC document

- Donning and doffing
- Environmental cleaning
- Infection control during laboratory testing
Public Health Ontario Response

- Public health: Dr. Bryna Warshawsky
- Infection prevention and control: Dr. Gary Garber
- Laboratory testing: Dr. Jonathan Gubbay
Testing flow for Ebola virus disease (EVD) in Ontario

This is an excerpt from the *Ebola virus disease (EVD) interim sample collection and submission guide* available on the PHO website at [www.publichealthontario.ca/ebola](http://www.publichealthontario.ca/ebola)

Last updated August 22
# Ebola virus disease (EVD) interim sample collection and submission guide

Table 1: Recommended specimen collection guidelines for diagnosis/detection of Ebola virus disease.

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Test</th>
<th>How to submit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>PCR &amp; viral culture</td>
<td>2-4 mls in tube containing EDTA</td>
</tr>
<tr>
<td>Blood</td>
<td>Serology</td>
<td>2-4 mls in serum separator tube (SST)</td>
</tr>
</tbody>
</table>
Repeat laboratory testing on day 4 of fever

• Ebola virus is only present in blood after onset of fever.

• It may take up to 4 days after fever onset for Ebola virus PCR to be positive.

• If initial testing was done within 4 days of onset of fever, testing should be repeated on day 4 if clinical suspicion is still present.
Ebola PCR testing at the National Microbiology Laboratory, Winnipeg

• NML conducts PCR testing for 2 Ebola virus targets:
  • Polymerase gene
  • Nucleoprotein gene

• Testing currently done within one day of receipt at NML - may change depending on testing demand, level of suspicion that patient has Ebola (pretest probability).
Acknowledgements

Public Health Ontario

• Infection Prevention and Control
• Public Health Ontario Laboratory
• Communicable Disease Prevention and Control
• Emergency Preparedness and Incident Response
• Communications

Ministry of Health and Long-Term Care

Public health units

Health care providers