Background

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Viral Special Pathogens Branch
Centers for Disease Control and Prevention

Advisory Committee on Immunization Practices

February 26, 2020
Overview

- Ebola virus disease
- rVSVΔG-ZEBOV-GP vaccine
- Parameters for WG discussions
Background

- Ebola virus disease (EVD) in humans is a deadly disease caused by infection with one of 4 viruses within the genus *Ebolavirus*, family *Filoviridae*
  - Ebola virus (species *Zaire ebolavirus*)
  - Sudan virus (species *Sudan ebolavirus*)
  - Tai Forest virus (species *Tai Forest ebolavirus*)
  - Bundibugyo virus (species *Bundibugyo ebolavirus*)
Background

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  - **Ebola virus (species Zaire ebolavirus)**
  - Sudan virus (species *Sudan ebolavirus*)
  - Tai Forest virus (species *Tai Forest ebolavirus*)
  - Bundibugyo virus (species *Bundibugyo ebolavirus*)
**Ebola virus (species *Zaire ebolavirus*)**

- Responsible for the majority of reported EVD outbreaks* including the 2 largest outbreaks in history
  - 2014-2016 West Africa (28,652 cases/11,325 deaths)
  - Current eastern Democratic Republic of Congo (DRC)
- In total, Ebola virus (species *Zaire ebolavirus*) has infected >31,000 persons and resulted in >12,000 deaths**
- Untreated, mortality rates 70-90%
- No FDA-approved treatment

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* Total of 28 EVD outbreaks reported, 18/28 (64%) due to Ebola virus (species *Zaire ebolavirus*)
** Total numbers of infections and deaths due to Ebola virus (species *Zaire ebolavirus*) but excluding the ongoing 2018 eastern DRC EVD Outbreak
Ebola virus reservoir search in Gabon 2002-2003

Myonycteris torquata
fruit bat

PCR+ 4/141
IgG+ 4/58

Epomops franqueti
fruit bat

PCR+ 5/117
IgG+ 8/117

Hypsignathus monstrosus
fruit bat

PCR+ 4/21
IgG+ 4/17

E. M. Leroy et al., Fruit bats as reservoirs of Ebola virus
Nature 438, 575-576 (December 2005) (adapted)
Ebola virus reservoir search in Gabon 2002-2003

Does not exist in the United States

E. M. Leroy et al., Fruit bats as reservoirs of Ebola virus
Nature 438, 575-576 (December 2005)
Signs and Symptoms

- Signs and symptoms of EVD include:
  - Fever
  - Headache
  - Fatigue
  - Muscle pain/Joint pain
  - Bleeding (epistaxis, injection sites)
  - Abdominal pain
  - Rash
  - Diarrhea
  - Vomiting
Person-to-Person Transmission

- In infected individuals, Ebola virus can be found in all body fluids:
  - Blood
  - Feces/Vomit
  - Urine
  - Tears
  - Saliva
  - Breast milk
  - Amniotic fluid
  - Vaginal secretions
  - Sweat
  - Semen

- Contact (through broken skin or non-intact skin or mucosal membranes) with the body fluids of a person that is sick or has died of EVD
EVD Sequelae

- Incidence of sequelae amongst EVD survivors unknown
- Most commonly reported symptoms:
  - Arthralgia, uveitis, myalgia, abdominal pain, fatigue, $^{1,2}$
- Within one year of discharge, Ebola survivors have 5-fold greater mortality than the general population$^3$
- Ebola virus persistence in immune-privileged sites (e.g., testes, eyes, brain, placenta); in some instances has resulted in continued disease transmission and disease recrudescence

1. Rowe et al. Clinical, virologic, and immunologic follow-up of convalescent Ebola hemorrhagic fever patients and their household contacts, Kikwit, Democratic Republic of Congo
2018 EVD Outbreak, Eastern DRC

- August 1, 2018, an EVD outbreak was declared in eastern DRC
- Ebola virus (species *Zaire ebolavirus*)
- 10th outbreak in DRC; largest outbreak to ever have occurred there
- July 2019: outbreak declared a “Public Health Emergency of International Concern” (PHEIC); reaffirmed February 2020
Case Counts as of February 18, 2020

- Cases reported in 29 health zones; 3 provinces
- >3000 cases; >2000 deaths

*Due to reporting lag, the recent trend should be interpreted with caution*
Cumulative Case Counts, Selected EVD Outbreaks 1976-2019
Epidemic Curve, 2014-2016 West Africa Outbreak and Current DRC Outbreak

Cumulative Case Counts, West Africa (2014-2016) and DRC (2018-Present), by Week of Outbreak
Ebola Virus Disease in the United States

- 11 individuals treated for EVD in the United States
  - All associated with 2014-2016 West Africa outbreak
  - 9 were infected in West Africa
  - 2 (18%) died

- 1 imported case of EVD resulted in secondary transmission in the U.S. (2014)

- Additional individuals repatriated to the U.S. following high-risk exposures to Ebola virus; none tested positive (2014-2016 West Africa, 2018 eastern DRC)

*Bellevue, NIH, University of Nebraska, Emory University*
rVSVΔG-ZEBOV-GP Vaccine
Recombinant Vesicular Stomatitis Virus-Based Ebola Virus Vaccine (rVSVΔG-ZEBOV-GP)

- Live-attenuated recombinant vesicular stomatitis virus vaccine
- Vaccine cannot cause Ebola virus infection
- Initially developed by Public Health Agency Canada and New Link Genetics; Merck holds intellectual rights
- Protects only against Ebola virus (species Zaire ebolavirus)
- December 2019: FDA approved for individuals 18 years of age or older for the prevention of Ebola virus disease
Vaccine Construct

- VSV envelope protein was deleted and replaced (ΔG) by inserting only the envelope glycoprotein (GP) of Zaïre ebolavirus (Kikwit)
- Administered as a 1.0 mL dose by the intramuscular route
- Stored between -80°C and -60°C. It can be stored at 2°C to 8°C for up to 2 weeks. Once thawed it cannot be refrozen.
Single Dose Protects NHPs Against IM EBOV Challenge Across a Range of Vaccine Dose Levels

<table>
<thead>
<tr>
<th>USAMRIID study number AP-14-009 (III)</th>
<th>IM Vaccine Dose (pfu)</th>
<th>day of IM challenge</th>
<th>survival</th>
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<tr>
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<td>$2 \times 10^7$</td>
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<td>7/7</td>
</tr>
<tr>
<td></td>
<td>$3 \times 10^6$</td>
<td>42</td>
<td>7/8</td>
</tr>
<tr>
<td></td>
<td>None (saline)</td>
<td>42</td>
<td>0/3</td>
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<table>
<thead>
<tr>
<th>USAMRIID study number AP-15-001-02</th>
<th>IM Vaccine Dose (pfu)</th>
<th>day of IM challenge</th>
<th>survival</th>
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<tbody>
<tr>
<td>Vaccine immunogenicity and efficacy in cynomolgus macaques at doses of $3 \times 10^2$ to $3 \times 10^6$ pfu</td>
<td>$3 \times 10^6$</td>
<td>42</td>
<td>4/4</td>
</tr>
<tr>
<td></td>
<td>$3 \times 10^5$</td>
<td>42</td>
<td>4/4</td>
</tr>
<tr>
<td></td>
<td>$3 \times 10^4$</td>
<td>42</td>
<td>4/4</td>
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<tr>
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<td>5/5</td>
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<tr>
<td></td>
<td>$3 \times 10^2$</td>
<td>42</td>
<td>5/5</td>
</tr>
<tr>
<td></td>
<td>None (saline)</td>
<td>42</td>
<td>0/2</td>
</tr>
</tbody>
</table>

44/45 overall survival across all doses

Challenge with 1000 pfu of wild type Zaïre ebolavirus

Courtesy of Merck; adapted
Rapidly Initiated Clinical Trial Evaluation Across 10 Countries

Phase 1 - HUG
Geneva, Switzerland
Phase 1 - KEMRI
Kilifi, Kenya
Phase 1 - CERMEL + University of Tübingen
Lambarene, Gabon
Phase 2/3 - Liberia - NIH Partnership
Liberia (PREVAIL PN009)
Phase 2/3 - CDC + Sierra Leone Medical School
Sierra Leone (PN011)
Phase 1 - WRAIR
Silver Springs, MD, USA
Phase 1 - NIH
Bethesda, MD, USA
Phase 1 - CCV
Halifax, Nova Scotia, 8 cities in USA
Phase 1 - NewLink
Canada
Phase 1 - University Medical Center Hamburg + Clinical Trial Center North
Hamburg, Germany
Phase 1 - Merck
Multiple sites in the USA, Canada, Spain
PN012
Phase 2/3 - WHO + Norwegian Institute of Public health Health Canada + MSF
Guinea (PN010)
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Liberia (PREVAIL PN009)
Safety

- Mild to moderate transient reactogenicity commonly reported within 24-48 hrs. of vaccination; resolved within 7 days
  - Injection site pain, swelling, erythema
  - Fever/subjective fever
  - Muscle aches, malaise, headache
- Arthralgia and arthritis reported in some vaccinees
- Vaccine-related SAEs are rare
Detection of rVSV Vaccine Virus

- Virus dissemination and replication can occur and persist for up to 2-3 weeks after vaccination

<table>
<thead>
<tr>
<th>Specimen Type</th>
<th>Detected by RT-PR?* If yes, longest duration reported</th>
<th>Virus Isolation attempted?</th>
<th>Virus isolation result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>Yes; 14 days p.v. ³,a</td>
<td>Yes ¹⁰</td>
<td>Neg ¹⁰</td>
</tr>
<tr>
<td>Urine</td>
<td>Yes; 7 days p.v. ³,a</td>
<td>No</td>
<td>-</td>
</tr>
<tr>
<td>Saliva</td>
<td>Yes; 14 days p.v. ³,a</td>
<td>No</td>
<td>-</td>
</tr>
<tr>
<td>Synovial fluid ⁵</td>
<td>Yes; 17 days p.v. ⁴,6,10,⁵</td>
<td>Yes ¹⁰</td>
<td>Neg ¹⁰</td>
</tr>
<tr>
<td>Skin vesicles ⁶</td>
<td>Yes; 17 days p.v. ⁴,10,⁶</td>
<td>Yes ¹⁰</td>
<td>Pos; 9 days ¹⁰</td>
</tr>
</tbody>
</table>

* p.v: post-vaccination

₀ Specimens tested for a 28 days; ⁵ Specimens tested for 23 days; ⁶ Specimens tested for 35 days
Immunogenicity

- No immune correlate for protection
- A measure of the immune response that confers protection against EVD is unknown
- Protective effect conferred by immunization likely a combination of innate and adaptive immune response activation
- As measured by ELISA, EBOV-GP-specific IgG antibodies begin to rise 14 days and can persist through 24 months post-vaccination
rVSVΔG-ZEBOV-GP Use in Outbreak Settings: Ça Suffit

- Two part, Phase 3, cluster-randomized, open-label ring vaccination

- Took place in Guinea, at a time when the EVD outbreak was waning
  - Ring vaccination design chosen in part to generate robust data on vaccine efficacy in the setting of a waning outbreak

- Defined a cluster around a confirmed case of EVD

- Primary outcome: Incidence of EVD with onset 10 days or more from randomization
  - Account for incubation period of EVD and unknown time for the vaccine to develop protective immunity
 Ça Suffit: “Interim”

- Clusters randomized to immediate vaccination or delayed vaccination (21 days after randomization)
- Vaccine efficacy: 100% (95%CI: 74.7-100, p=0.0036)
Ça Suffit: “Final”

- July 2015, randomization discontinued at the recommendation of the data and safety monitoring board, all subsequent clusters offered immediate vaccination
- Reported vaccine efficacy for randomized and non-randomized clusters
- Vaccine efficacy: 100% (95%CI: 68.9-100, p=0.0045)*

*Efficacy calculation based on randomized participants (all immediately vaccinated vs all eligible in delayed vaccinated) who developed EVD ≥ 10 day after randomization

Courtesy of Merck; adapted
rVSVΔG-ZEBOV-GP Use in Outbreak Settings: DRC

- Ring vaccination started 1 week after the outbreak was declared
- Ring strategy has evolved over time
- >200,000 vaccinated
Parameters for Work Group Discussions
Considerations

- Suspected virus reservoir does not exist in the U.S.
- 9/11 individuals treated for EVD in the U.S. were individuals responding to a foreign EVD outbreak
- Ongoing EVD outbreak in eastern DRC (PHEIC)
- No EVD outbreak in the United States
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- Ongoing EVD outbreak in eastern DRC (PHEIC)
- No EVD outbreak in the United States

Deliberations focused on pre-exposure vaccination in U.S. populations at immediate occupational risk
Populations of Focus

- Identified 3 U.S. populations at highest risk for potential occupational exposure to Ebola virus (species *Zaire ebolavirus*) for whom potential policy options are most urgent:
  - Individuals responding to an outbreak of EVD due to Ebola virus (species *Zaire ebolavirus*)
  - Individuals who work as laboratorians and support staff at biosafety-level 4 (BSL-4) facilities that handle replication-competent Ebola virus (species *Zaire ebolavirus*)
  - Healthcare personnel\(^1\) (HCP) at a federally-designated Ebola Treatment Centers involved in the care and transport of confirmed EVD patients

\(^1\) see slide 37
WG Activities and Discussions Since October 2019

- Additional populations with potential risk for occupational exposure include:
  - HCP at state/jurisdictionally-designated Ebola Treatment Centers
  - HCP at Ebola Assessment Hospitals
  - HCP at Frontline Hospitals

- WG discussions on recommendations for additional populations at potential occupational risk are continuing
Individuals Responding to EVD Outbreaks

- Number of organizations responding to an outbreak will vary by size and location of the outbreak

- > 4,000 U.S. government (USG) deployers to 2014-2016 West Africa EVD outbreak (including domestic EVD cases)

- U.S. responders to the current eastern DRC outbreak
  - ~200 NGOs personnel
  - ~300 governmental personnel (CDC, NIH, USAID)

1 https://www.cdc.gov/mmwr/volumes/65/su/pdfs/su6503.pdf  

4 Update on the U.S. Public Health Response to the Ebola Outbreak
Biosafety Level 4 (BSL-4) Laboratory Personnel in the U.S.

- 10 BSL-4 laboratories in the U.S ~350-400 lab and support staff
- Currently 8 laboratories handle replication-competent Ebola virus

<table>
<thead>
<tr>
<th>CDC, GA (GA)</th>
<th>Galveston National Laboratory, TX (TX)</th>
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<tbody>
<tr>
<td>Georgia State, GA (GA)</td>
<td>Shope Laboratory, TX (TX)</td>
</tr>
<tr>
<td>NIH, MD (MD)</td>
<td>Texas Biomedical Research Institute, TX (TX)</td>
</tr>
<tr>
<td>USAMRIID, MD (MD)</td>
<td>Rocky Mountain Laboratories, MT (MT)</td>
</tr>
<tr>
<td>National Emerging Infectious Disease Laboratories, MA (MA)</td>
<td>National Biodefense Analysis and Countermeasures Center, MD (MD)</td>
</tr>
</tbody>
</table>
Federally-designated Ebola Treatment Centers in the U.S.

- Specialized high-level isolation units equipped with infrastructure, laboratory capabilities, staff to care for patients with highly hazardous communicable diseases

- ~ 500 healthcare workers/support staff

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<tbody>
<tr>
<td>Emory University, GA</td>
<td>Nebraska Medical Center, NE</td>
</tr>
<tr>
<td>HHC Bellevue Hospital Center, NY</td>
<td>Denver Health Medical Center, CO</td>
</tr>
<tr>
<td>Johns Hopkins Hospital, MD</td>
<td>Cedars-Sinai Medical Center, CA</td>
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<tr>
<td>University of Minnesota Medical Center, MN</td>
<td>Providence Sacred Heart Medical Center and Children’s Hospital, WA</td>
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<td>University of Texas Medical Branch at Galveston, TX</td>
<td>NIH, MD</td>
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<tr>
<td>Massachusetts General Hospital, MA</td>
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</table>
Healthcare Personnel Definition

1. Healthcare personnel (HCP) refers to all paid and unpaid persons serving in healthcare settings who have the potential for direct or indirect exposure to patients or infectious materials, including body substances (e.g., blood, tissue, and specific body fluids); contaminated medical supplies, devices, and equipment; contaminated environmental surfaces; or contaminated air. These HCP include, but are not limited to, emergency medical service personnel, nurses, nursing assistants, physicians, technicians, clinical laboratory personnel, autopsy personnel, therapists, phlebotomists, pharmacists, students and trainees, contractual staff not employed by the healthcare facility, and persons not directly involved in patient care, but who could be exposed to infectious agents that can be transmitted in the healthcare setting (e.g., clerical, dietary, environmental services, laundry, security, engineering and facilities management, administrative, billing, and volunteer personnel).

Adapted from https://www.cdc.gov/infectioncontrol/guidelines/healthcare-personnel/index.html
References


For more information, contact CDC
1-800-CDC-INFO (232-4636)

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.