Background

Mary Choi, MD, MPH
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

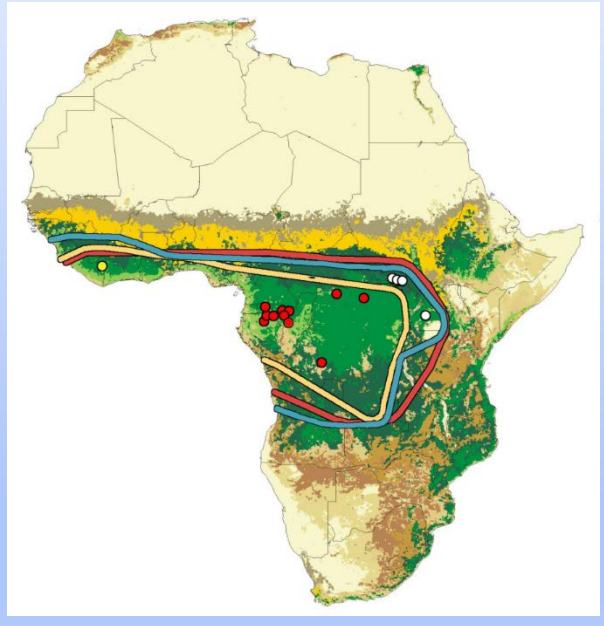
- Ebola virus disease (EVD) in humans is a deadly disease caused by infection with one of 4 viruses within the genus *Ebolavirus,* family *Filoviridae*
  - **Ebola virus *(*species *Zaire ebolavirus)***
  - Sudan virus *(*species *Sudan ebolavirus)*
  - Tai Forest virus *(*species *Tai Forest ebolavirus)*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

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

- * 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



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

Hypsignathus monstrosus
fruit bat

PCR+ **4/21**
IgG+ **4/17**

Epomops franqueti
fruit bat

PCR+ **5/117**
IgG+ **8/117**

Myonycteris torquata
fruit bat

PCR+ **4/141**
IgG+ **4/58**

Ebola virus reservoir search in Gabon 2002-2003

Does not exist in the United States

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

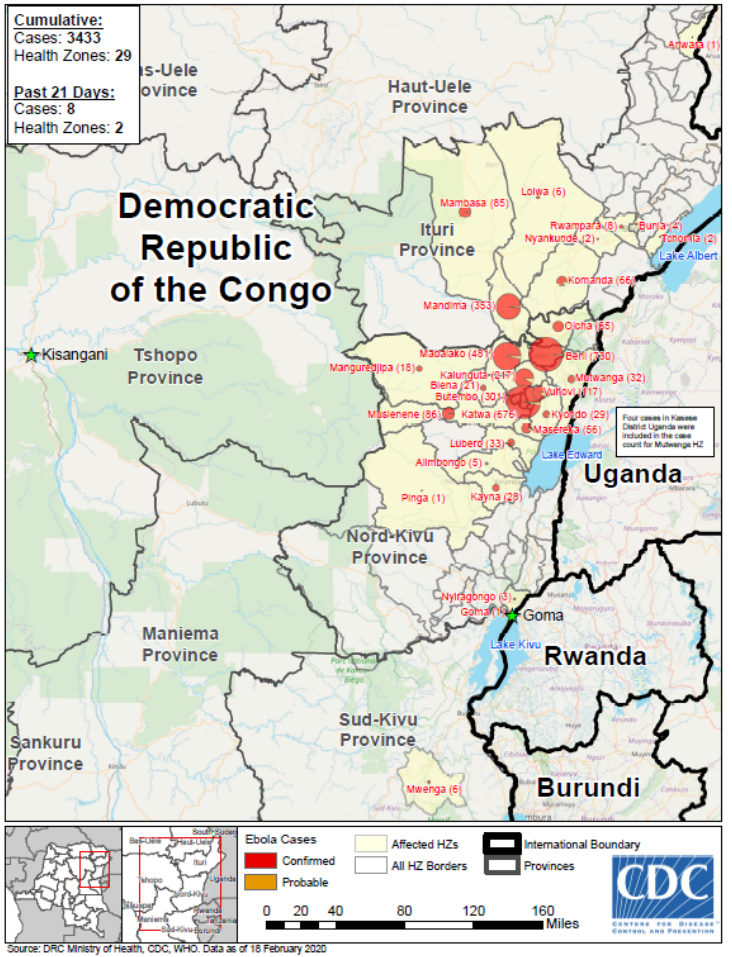
- Incidence of sequelae amongst EVD survivors unknown
- Most commonly reported symptoms:
  - Arthralgia, uveitis, myalgia, abdominal pain, fatigue, [1,2]
- Within one year of discharge, Ebola survivors have 5-fold greater mortality than the general population[3]
- Ebola virus persistence in immune-privileged 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
2. Prevail III Study Group. A longitudinal study of Ebola sequelae in Liberia
3. Keita et al. Subsequent mortality in survivors of Ebola virus disease in Guinea: a nationwide retrospective cohort study Lancet Infect Dis. 2019

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

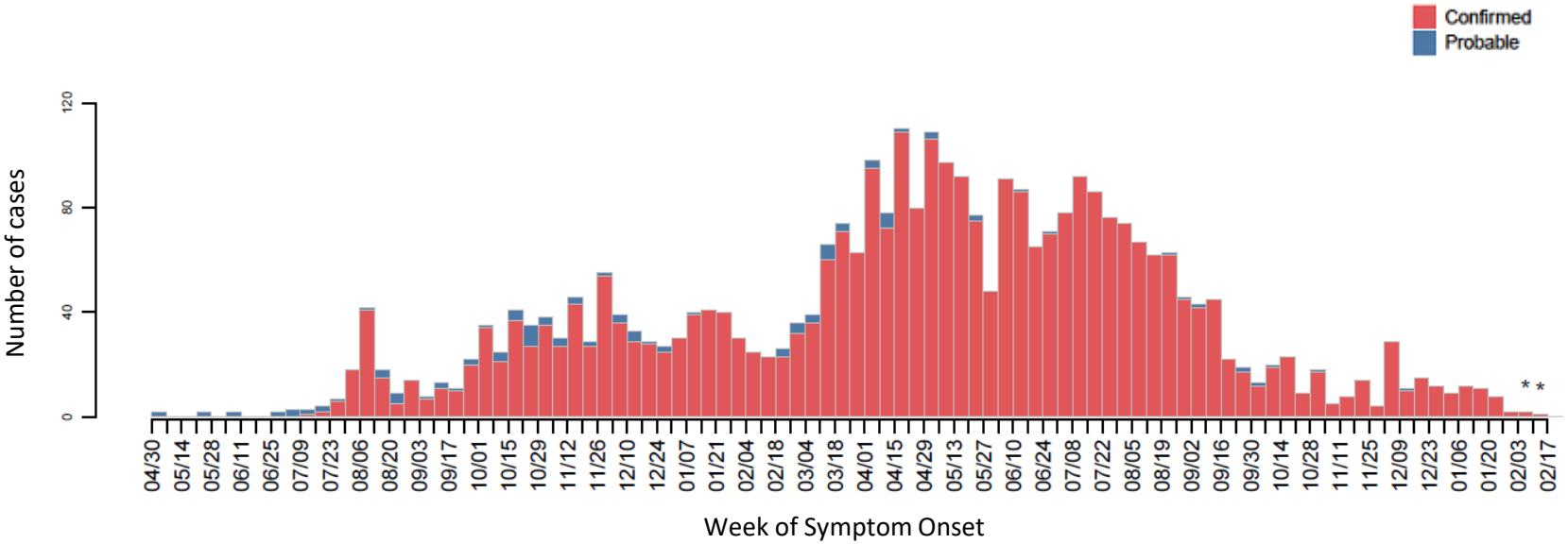
Cases of Ebola Virus Disease, DRC, 18 February 2020



Source: DRC Ministry of Health, CDC, WHO. Data as of 18 February 2020

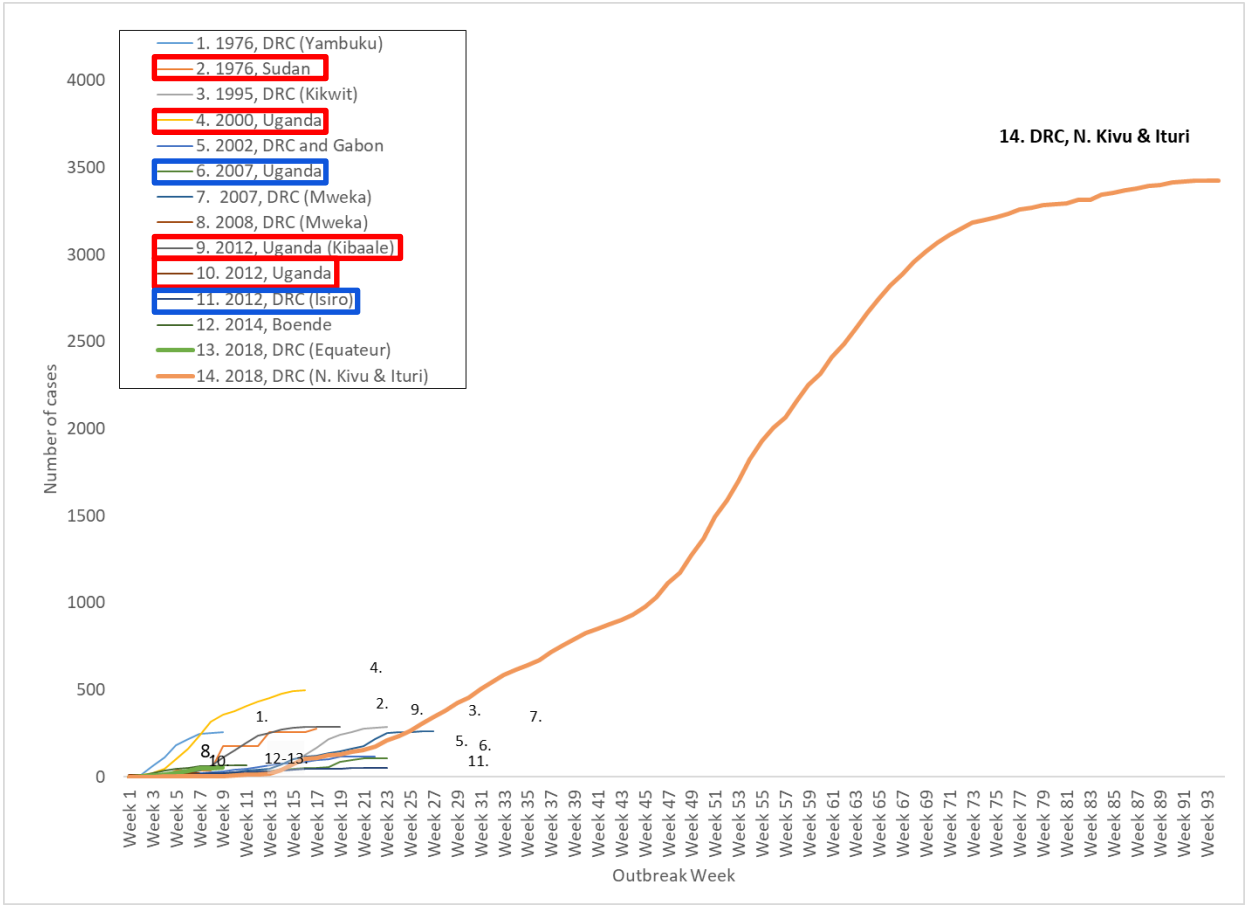
Case Counts as of February 18, 2020

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



*Due to reporting lag, the recent trend should be interpreted with caution

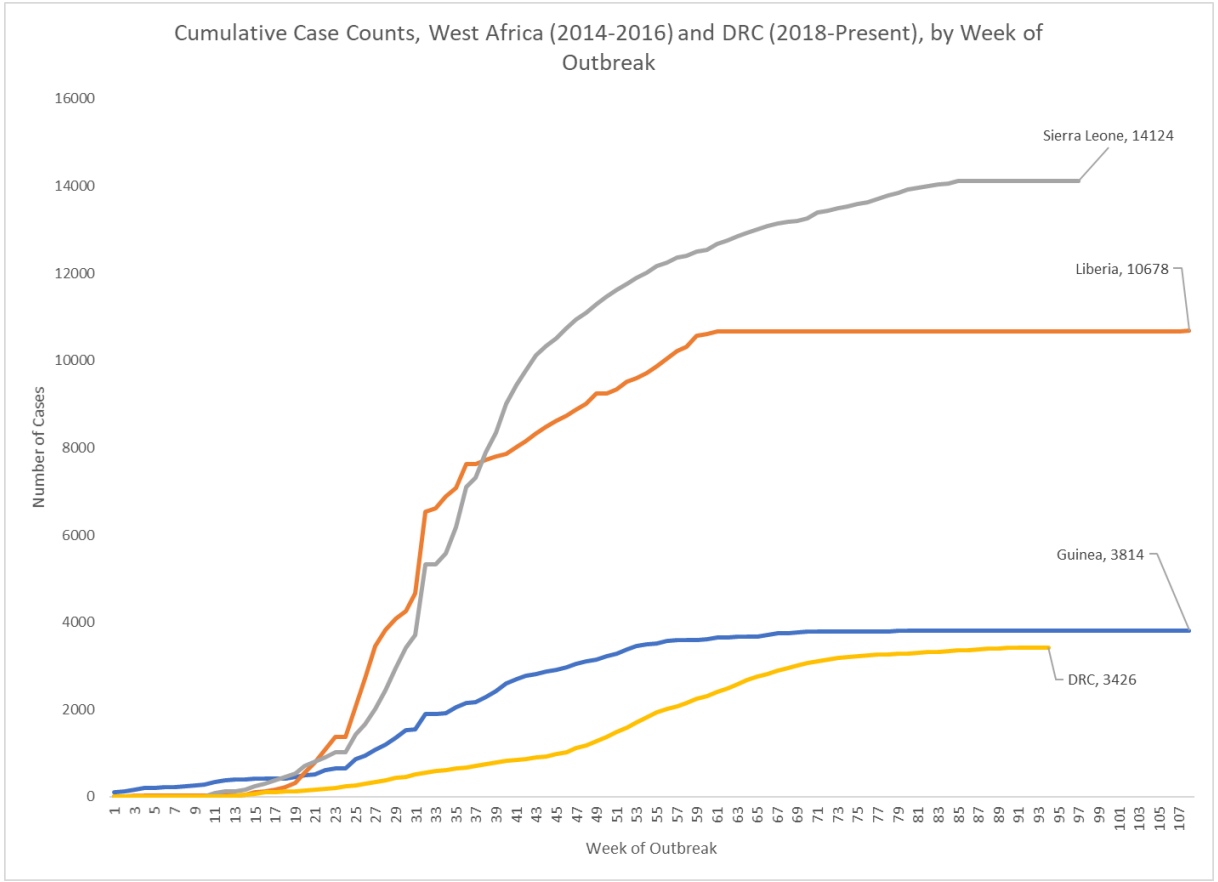
Cumulative Case Counts, Selected EVD Outbreaks 1976-2019



Sudan virus

Bundibugyo virus

Epidemic Curve, 2014-2016 West Africa Outbreak and Current DRC 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)

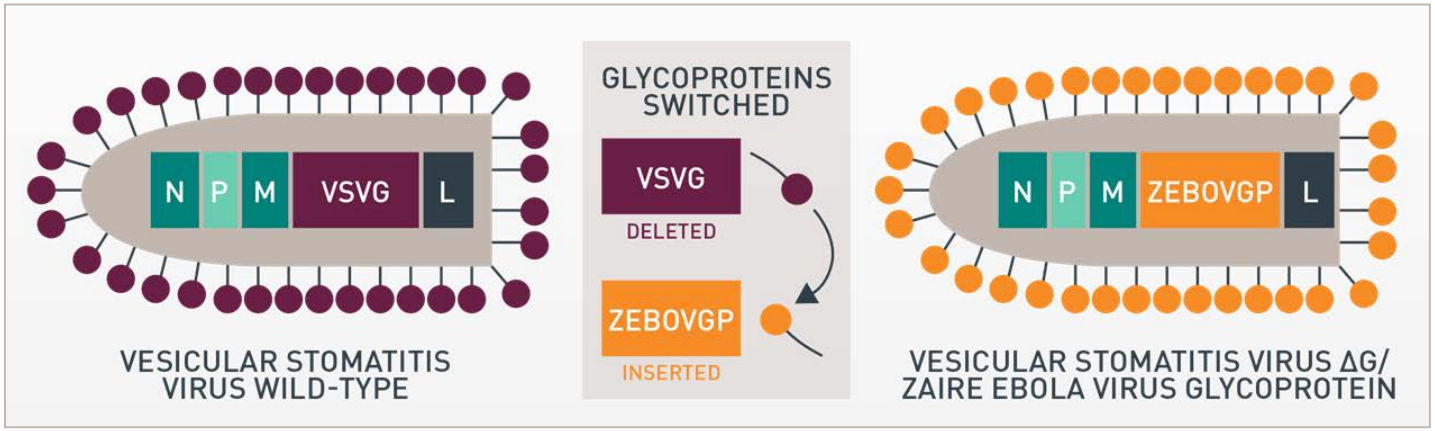
*Bellevue, NIH, University of Nebraska, Emory University

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.

Courtesy of Merck; adapted

Single Dose Protects NHPs Against IM EBOV Challenge Across a Range of Vaccine Dose Levels

USAMRIID study number AP-14-009 (III)	IM Vaccine Dose (pfu)	day of IM challenge	survival
Vaccine immunogenicity and efficacy in cynomolgus macaques at doses of $3x10^6$ to $1x10^8$ pfu	$1x10^8$	42	8/8 100%
	$2x10^7$	42	7/7 100%
	$3x10^6$	42	7/8 88%
	None (saline)	42	0/3 0%

44/45 overall survival across all doses

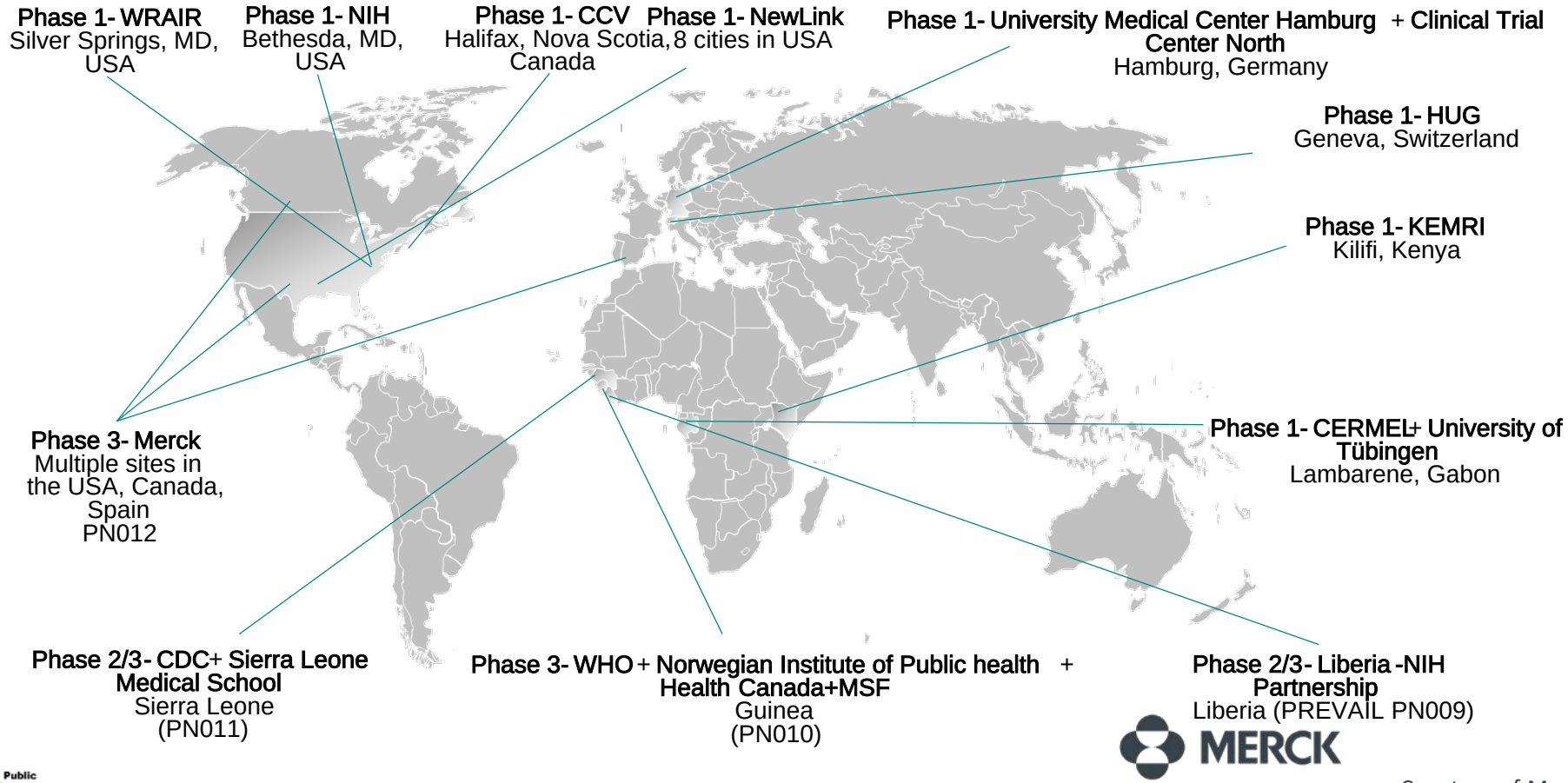
USAMRIID study number AP-15-001-02	IM Vaccine Dose (pfu)	day of IM challenge	survival
Vaccine immunogenicity and efficacy in cynomolgus macaques at doses of $3x10^2$ to $3x10^6$ pfu	$3x10^6$	42	4/4 100%
	$3x10^5$	42	4/4 100%
	$3x10^4$	42	4/4 100%
	$3x10^3$	42	5/5 100%
	$3x10^2$	42	5/5 100%
	None (saline)	42	0/2 0%

Challenge with 1000 pfu of wild type Zaïre ebolavirus

MERCK

Courtesy of Merck; adapted

Rapidly Initiated Clinical Trial Evaluation Across 10 Countries



MERCK

Courtesy of Merck

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

Specimen Type	Detected by RT-PR ?* If yes, longest duration reported	Virus Isolation attempted?	Virus isolation result
Blood	Yes; 14 days p.v. [3,a]	Yes [10]	Neg [10]
Urine	Yes; 7 days p.v. [3,a]	No	-
Saliva	Yes; 14 days p.v. [3,a]	No	-
Synovial fluid [b]	Yes; 17 days p.v. [4,6,10,b]	Yes [10]	Neg [10]
Skin vesicles [c]	Yes; 17 days p.v. [4,10,c]	Yes [10]	Pos; 9 days [10]

*p.v: post-vaccination

[a] Specimens tested for a 28 days; [b] Specimens tested for 23 days; [C] 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)

MERCK

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

Courtesy of Dr. Henao-Restrepo

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

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

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 [3] https://archive.defense.gov/news/newsarticle.aspx?id=123935
[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

• **CDC, GA**	• **Galveston National Laboratory, TX**
• **Georgia State, GA**	• **Shope Laboratory, TX**
• **NIH, MD**	• **Texas Biomedical Research Institute, TX**
• **USAMRIID, MD**	• **Rocky Mountain Laboratories, MT**
• **National Emerging Infectious Disease Laboratories, MA**	• **National Biodefense Analysis and Countermeasures Center, MD**

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

• **Emory University, GA**	• **Nebraska Medical Center, NE**
• **HHC Bellevue Hospital Center, NY**	• **Denver Health Medical Center, CO**
• **Johns Hopkins Hospital, MD**	• **Cedars-Sinai Medical Center, CA**
• **University of Minnesota Medical Center, MN**	• **Providence Sacred Heart Medical Center and Children's Hospital, WA**
• **University of Texas Medical Branch at Galveston, TX**	• **NIH, MD**
• **Massachusetts General Hospital, MA**	

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

1. Samai, Mohamed, Seward, Jane F, Goldstein, Susan T, Mahon, Barbara E, Lisk, Durodami Radcliffe, Widdowson, Marc-Alain, Jalloh, Mohamed I, Schrag, Stephanie J, Idriss, Ayesha, Carter, Rosalind J. The Sierra Leone trial to introduce a vaccine against Ebola: an evaluation of rVSVΔ G-ZEBOV-GP vaccine tolerability and safety during the West Africa Ebola outbreak. The Journal of infectious diseases; 2018.
2. Kennedy, Stephen B, Bolay, Fatorma, Kieh, Mark, Grandits, Greg, Badio, Moses, Ballou, Ripley, Eckes, Risa, Feinberg, Mark, Follmann, Dean, Grund, Birgit. Phase 2 placebo-controlled trial of two vaccines to prevent Ebola in Liberia. New England Journal of Medicine; 2017.
3. Heppner Jr, D Gray, Kemp, Tracy L, Martin, Brian K, Ramsey, William J, Nichols, Richard, Dasen, Emily J, Link, Charles J, Das, Rituparna, Xu, Zhi Jin, Sheldon, Eric A. Safety and immunogenicity of the rVSVΔ G-ZEBOV-GP Ebola virus vaccine candidate in healthy adults: a phase 1b randomised, multicentre, double-blind, placebo-controlled, dose-response study. The Lancet Infectious diseases; 2017.
4. Halperin, Scott A, Arribas, Jose R, Rupp, Richard, Andrews, Charles P, Chu, Laurence, Das, Rituparna, Simon, Jakub K, Onorato, Matthew T, Liu, Kenneth, Martin, Jason. Six-Month safety data of recombinant vesicular stomatitis Virus–Zaire Ebola virus envelope glycoprotein vaccine in a phase 3 double-blind, placebo-controlled randomized study in healthy adults. The Journal of infectious diseases; 2017.
5. ElSherif, May S, Brown, Catherine, MacKinnon-Cameron, Donna, Li, Li, Racine, Trina, Alimonti, Judie, Rudge, Thomas L, Sabourin, Carol, Silvera, Peter, Hooper, Jay W. Assessing the safety and immunogenicity of recombinant vesicular stomatitis virus Ebola vaccine in healthy adults: a randomized clinical trial. Cmaj; 2017.
6. Huttner, Angela, Dayer, Julie-Anne, Yerly, Sabine, Combescure, Christophe, Auderset, Floriane, Desmeules, Jules, Eickmann, Markus, Finckh, Axel, Goncalves, Ana Rita, Hooper, Jay W. The effect of dose on the safety and immunogenicity of the VSV Ebola candidate vaccine: a randomised double-blind, placebo-controlled phase 1/2 trial. The Lancet Infectious diseases; 2015.
7. Regules, Jason A, Beigel, John H, Paolino, Kristopher M, Voell, Jocelyn, Castellano, Amy R, Hu, Zonghui, Muñoz, Paula, Moon, James E, Ruck, Richard C, Bennett, Jason W. A recombinant vesicular stomatitis virus Ebola vaccine. New England Journal of Medicine; 2017.
8. Legardy-Williams JK, Carter RJ, Goldstein ST, Jarrett OD, Szefer E, Fombah AE, et al. Pregnancy Outcomes among Women Receiving rVSVΔ-ZEBOV-GP Ebola Vaccine during the Sierra Leone Trial to Introduce a Vaccine against Ebola. Emerg Infect Dis. 2020;26(3):541-548.
9. Henao-Restrepo, Ana Maria, Camacho, Anton, Longini, Ira M, Watson, Conall H, Edmunds, W John, Egger, Matthias, Carroll, Miles W, Dean, Natalie E, Diatta, Ibrahima, Doumbia, Moussa. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!). The Lancet; 2017.
10. Agnandji, S.T., et al., Safety and immunogenicity of rVSVDELTAG-ZEBOV-GP Ebola vaccine in adults and children in Lambarene, Gabon: A phase I randomised trial. PLoS Medicine / Public Library of Science, 2017. 14(10): p. e1002402.
11. Agnandji, S.T., et al., Phase 1 Trials of rVSV Ebola Vaccine in Africa and Europe. New England Journal of Medicine, 2016. 374(17): p. 1647-60.
12. Bolay, F.K., et al., PREVAIL I Cluster Vaccination Study With rVSVDELTAG-ZEBOV-GP as Part of a Public Health Response in Liberia. Journal of Infectious Diseases, 2019. 219(10): p. 1634-1641.
13. Dahlke, C., et al., Dose-dependent T-cell Dynamics and Cytokine Cascade Following rVSV-ZEBOV Immunization. EBioMedicine, 2017. 19: p. 107-118.
14. Gsell, P.S., et al., Ring vaccination with rVSV-ZEBOV under expanded access in response to an outbreak of Ebola virus disease in Guinea, 2016: an operational and vaccine safety report. The Lancet Infectious Diseases, 2017. 17(12): p. 1276-1284.
15. Halperin, S.A., et al., Immunogenicity, Lot Consistency, and Extended Safety of rVSVDELTAG-ZEBOV-GP Vaccine: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study in Healthy Adults. Journal of Infectious Diseases, 2019. 220(7): p. 1127-1135.
16. Henao-Restrepo, A.M., et al., Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial. Lancet, 2015. 386(9996): p. 857-66.
17. Jarrett, O.D., et al., Monitoring Serious Adverse Events in the Sierra Leone Trial to Introduce a Vaccine Against Ebola. Journal of Infectious Diseases, 2018. 217(Supplement 1): p. S24-S32.
18. Juan-Giner, A., et al., Safety of the rVSV ZEBOV vaccine against Ebola Zaire among frontline workers in Guinea. Vaccine, 2019. 37(48): p. 7171-7177.

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

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.