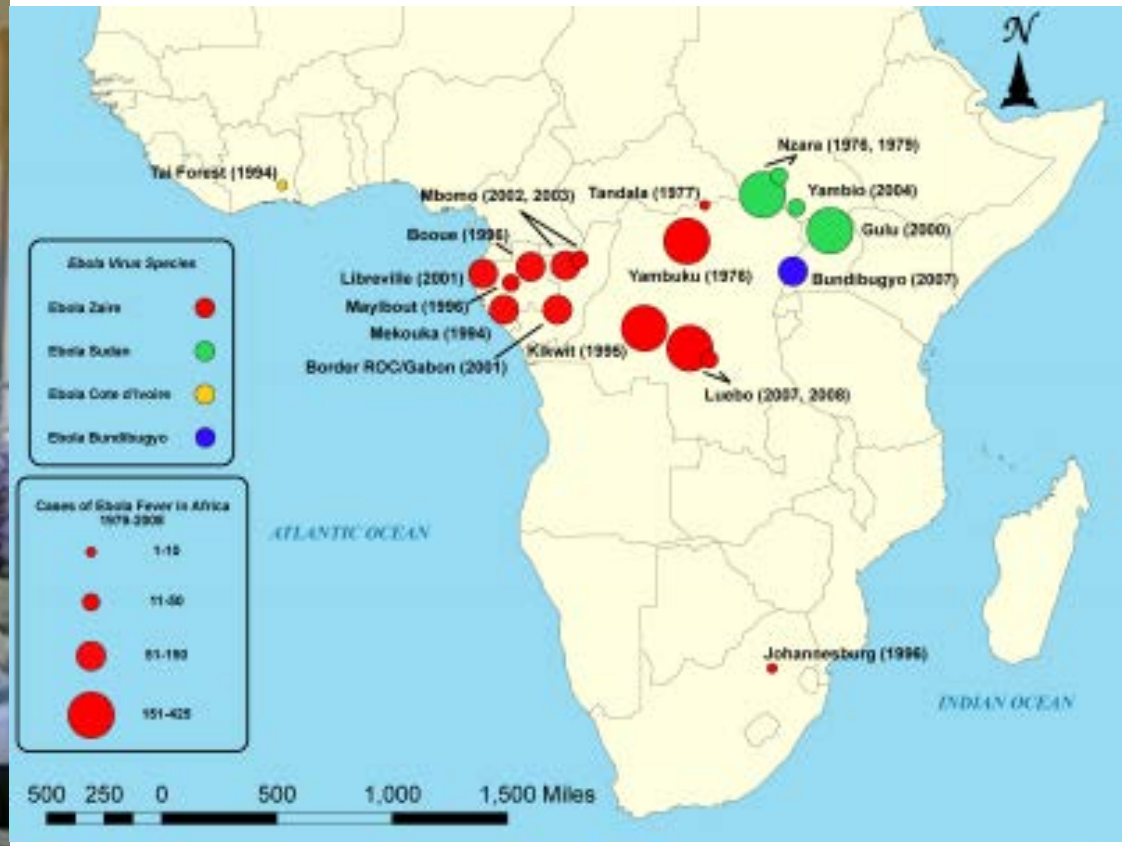
Acute Care Management of Viral Hemorrhagic Fevers

September 1, 2022

Colleen S. Kraft, MD, MSc

Emory University Hospital

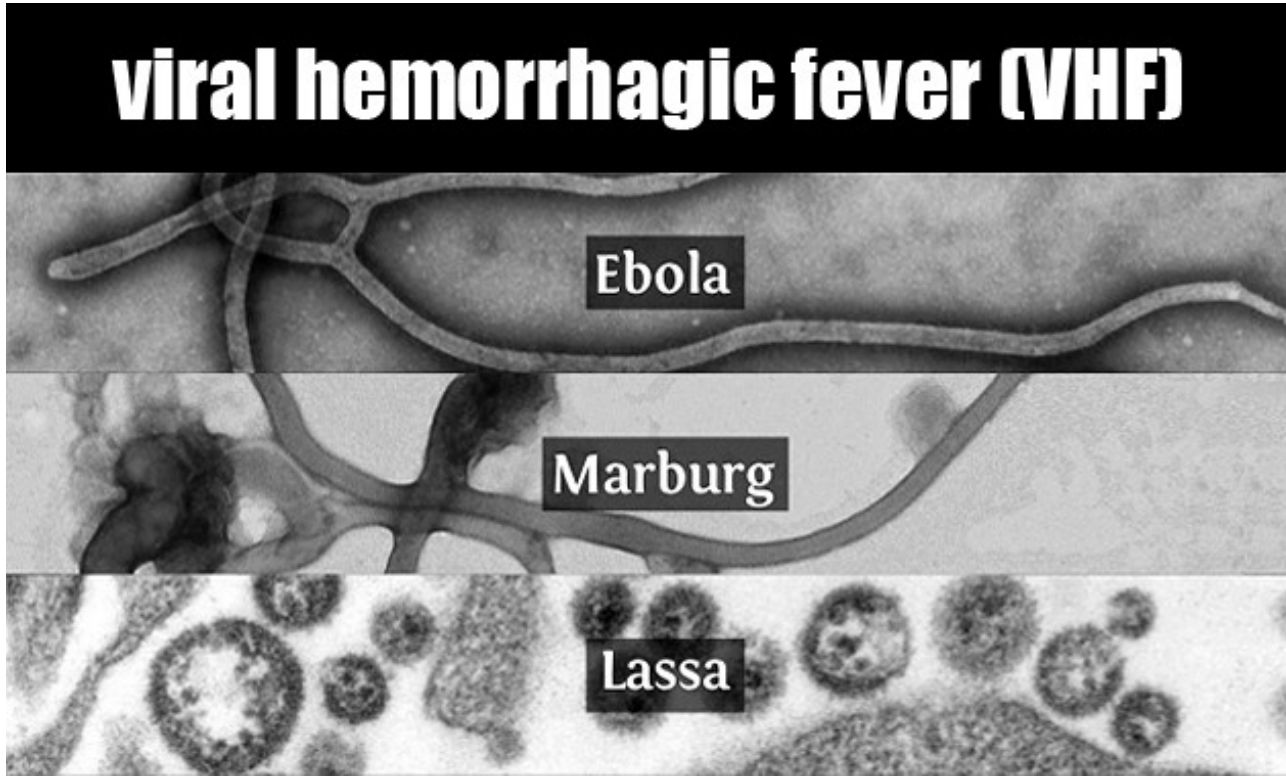
Before 2014, Ebola virus disease was a rural disease and containment worked



File:Ebola outbreak in Gulu Municipal Hospital.jpg

Description of VHF

- They are RNA viruses
- They are enveloped, in a lipoprotein outer layer, making it easier to destroy these viruses
- They naturally exist in animal or insect populations, restricted to the geographical areas where the host species live
- They spread to people when a person encounters an infected animal or insect host
- Outbreaks of VHFs in people can be difficult to prevent since they can occur sporadically and cannot be easily predicted

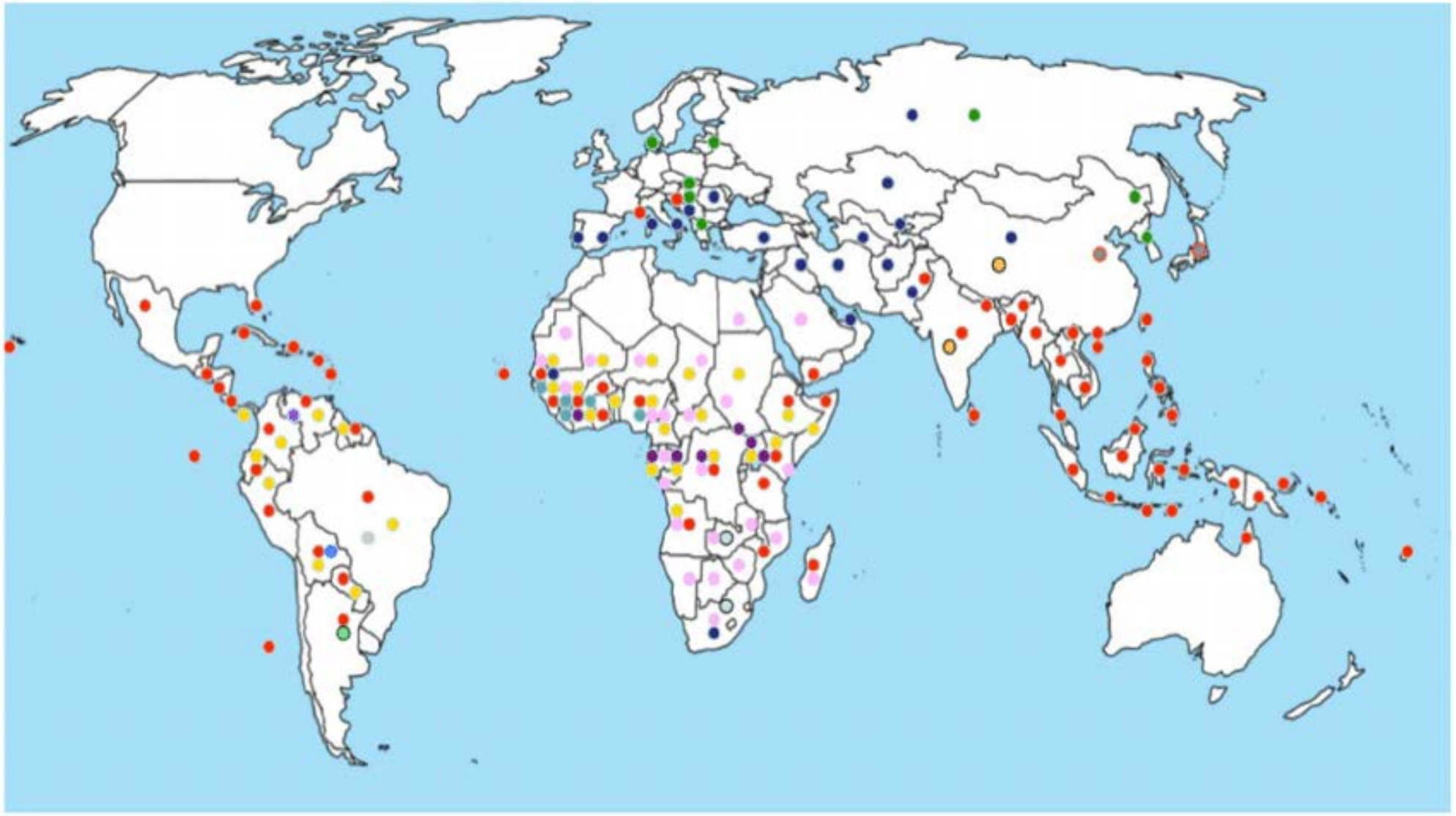


What are VHFs? | Viral Hemorrhagic Fevers (VHFs) | CDC

Unique clinical challenges with VHF

- More of the world's population is at risk for VHFs
- Person-to-person transmission of some VHFs can occur
- Confirmation of VHF cases can take time
- Prevention of VHF outbreaks is difficult
- Availability of vaccines and treatments are limited

Viral hemorrhagic fevers (VHFs) | CDC



Geographical distribution of Viral Hemorrhagic Fevers (VHF). This map... | Download Scientific Diagram (researchgate.net)

Ebola virus disease as a critical illness?

44 year old health care worker evacuated from Kenema, Sierra Leone in early September

- Admitted to Emory Hospital on day 5; received first dose of experimental medication in country
- High fever, rigors, copious diarrhea, high transaminases, mild coagulopathy, encephalopathy

Day 6: Severe gastroenteritis and hepatitis

Day 9: Acute kidney injury and respiratory distress

- Intubation and Mechanical ventilation

Day 11: Cardiac arrhythmias and worsening acidosis

- Continuous Renal Replacement Therapy

Day 21: Extubated → Delirium

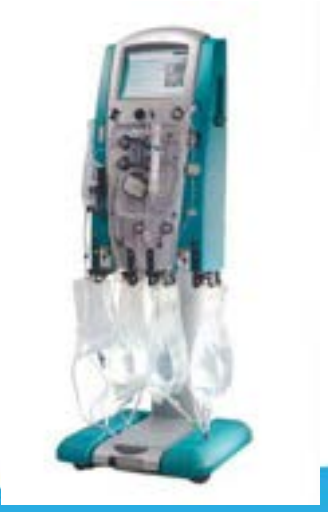
Day 29: Improving mental status

Day 35: Dialysis held

- Blood tests negative for EBOV by RT-PCR

Day 40: Discharged home

- 30 lb weight loss, easy fatigability, proximal muscle weakness + unsteady gait → difficulty ambulating, word-finding difficult



PLOS | PATHOGENS

Table 1. Similarities between Severe and Fatal EBOV and Classical Sepsis.*

Parameter	Similarities	References
Systemic Inflammation	Increased levels of pro-inflammatory cytokines (e.g., interleukin 6 [IL-6]), chemokines (IL-8), and the anti-inflammatory cytokine IL-10	**Classical Sepsis:** [5,10,11]; **EBOV:** [17,19,20]
Immune Dysfunction	Increased susceptibility to secondary bacterial infections, lymphocyte apoptosis	**Classical Sepsis:** [4,14]; **EBOV:** [23,28]
Coagulopathy	Increased D-dimers, thrombomodulin, ferritin, disseminated intravascular coagulation, thrombocytopenia	**Classical Sepsis:** [9,12]; **EBOV:** [17,18,20]
Endothelial Dysfunction	Vascular leak with hypovolemia	**Classical Sepsis:** [13]; **EBOV:** [23–25,27]
Organ Dysfunction	Renal insufficiency, hepatic dysfunction, respiratory failure, neurologic dysfunction	**Classical Sepsis:** [6,8,11]; **EBOV:** [21–25]

* Classical sepsis is defined as bacterial and fungal sepsis

doi:10.1371/journal.ppat.1005088.t001

Addressing the Complications of Ebola and Other Viral Hemorrhagic Fever Infections: Using Insights from Bacterial and Fungal Sepsis - PubMed (nih.gov)

Outbreaks have led to modernization of treatment

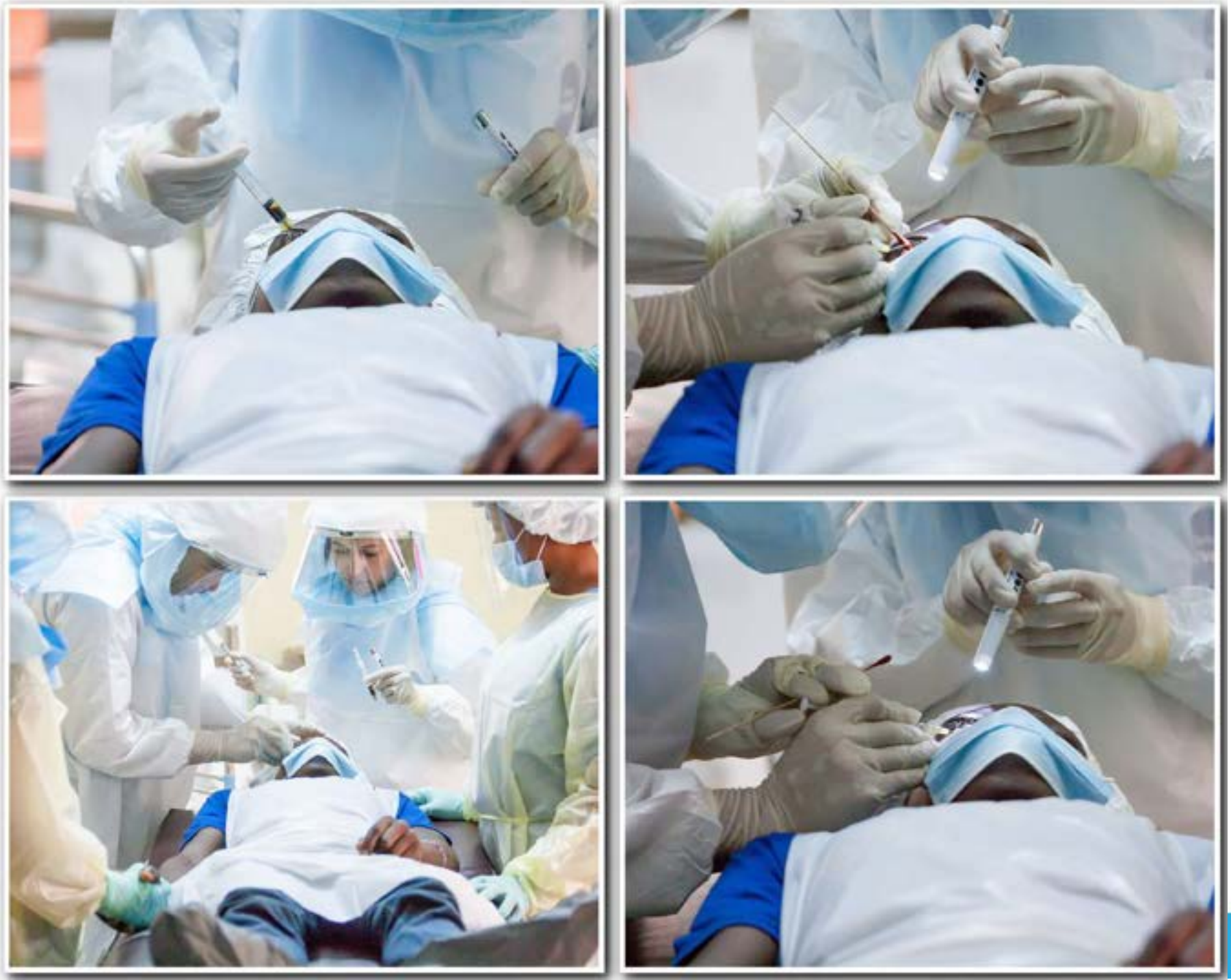
Pamoja Tulinde Maisha (PALM) trial

- Zmapp™ (MappBio) - 3 antibodies, c13C6FR1, c2G4, and c4G7, expressed in a species of tobacco, Nicotiana benthamiana
- Remdesivir (Gilead Sciences) – novel nucleotide analog prodrug
- MAb114 (Merck) - human IgG1 MAb targeted to the Zaire ebolavirus (EBOV) glycoprotein (GP)
- REGN-EB3 (Regeneron) – 3 antibodies

Ebola-specific therapies

- Atoltivimab, maftivimab, and odesivimab (REGN-EB3) and ansuvimab (mAb114) are two antibody-based therapies that are effective for the treatment of *Zaire ebolavirus* infection. The WHO included the use of these antibodies in its response to an outbreak of Ebola virus disease in the DRC in 2021, and these antibodies are both approved for use by the US Food and Drug Administration.
  - **Atoltivimab, maftivimab, and odesivimab (REGN-EB3)** – In October 2020, the US Food and Drug Administration (FDA) approved the triple-monoclonal antibody (mAb) product, which contains atoltivimab, maftivimab, and odesivimab (sold as Inmazeb). This combination of three mAbs targets three nonoverlapping epitopes on the Ebola virus surface glycoprotein, providing potent virus neutralization.
  - Ansuvimab **(mAb114)** – In December 2020, the FDA approved the monoclonal antibody ansuvimab (sold as Ebanga). This mAb was isolated from a survivor of Ebola virus disease and neutralizes the virus.

Uptodate: Treatment and prevention of Ebola virus disease



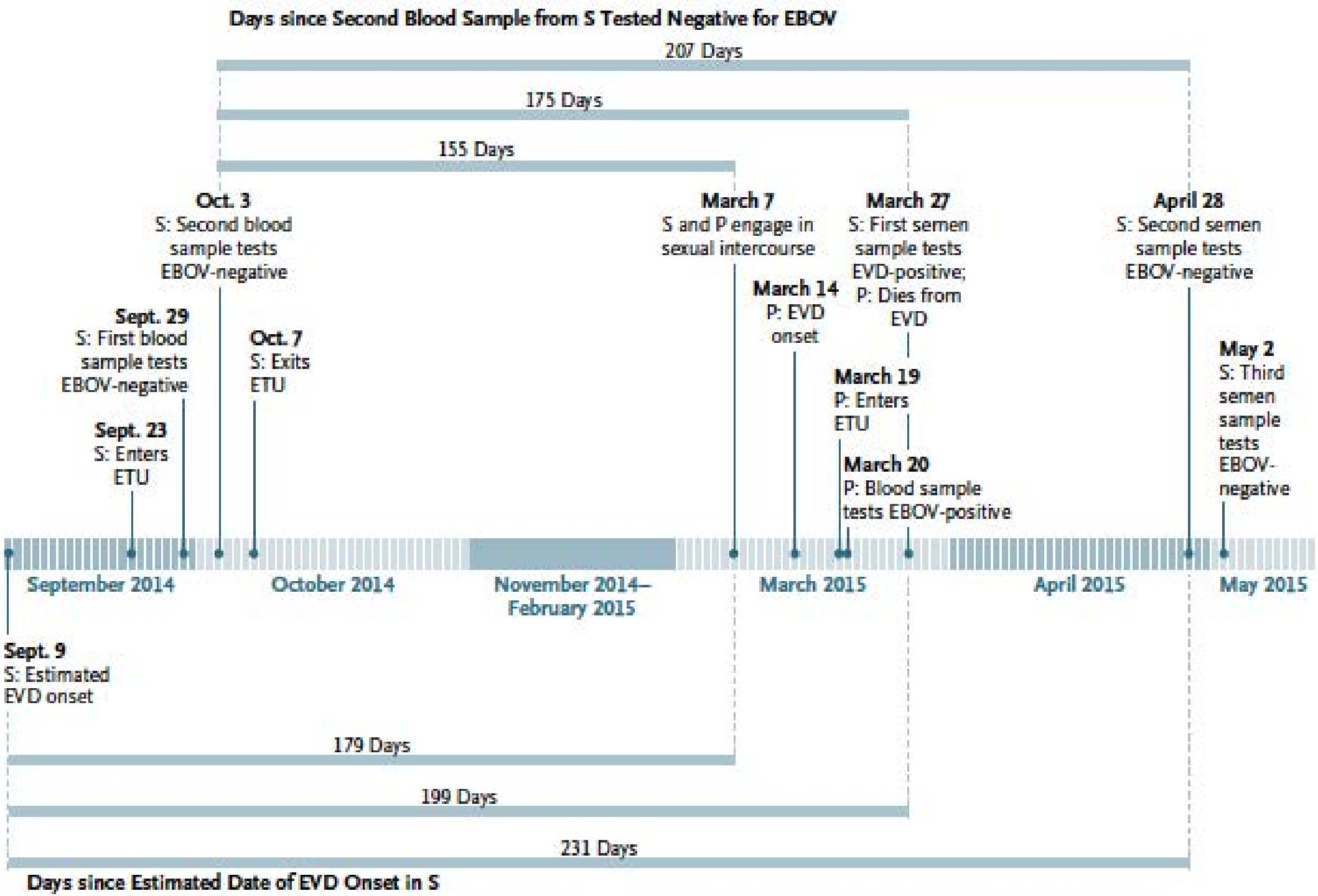
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Molecular Evidence of Sexual Transmission of Ebola Virus

S.E. Mate, J.R. Kugelman, T.G. Nyenswah, J.T. Ladner, M.R. Wiley, T. Cordier-Lassalle, A. Christie, G.P. Schroth, S.M. Gross, G.J. Davies-Wayne, S.A. Shinde, R. Murugan, S.B. Sieh, M. Badio, L. Fakoli, F. Taweh, E. de Wit, N. van Doremalen, V.J. Munster, J. Pettitt, K. Prieto, B.W. Humrighouse, U. Ströher, J.W. DiClaro, L.E. Hensley, R.J. Schoepp, D. Safronetz, J. Fair, J.H. Kuhn, D.J. Blackley, A.S. Laney, D.E. Williams, T. Lo, A. Gasasira, S.T. Nichol, P. Formenty, F.N. Kateh, K.M. De Cock, F. Bolay, M. Sanchez-Lockhart, and G. Palacios

SUMMARY

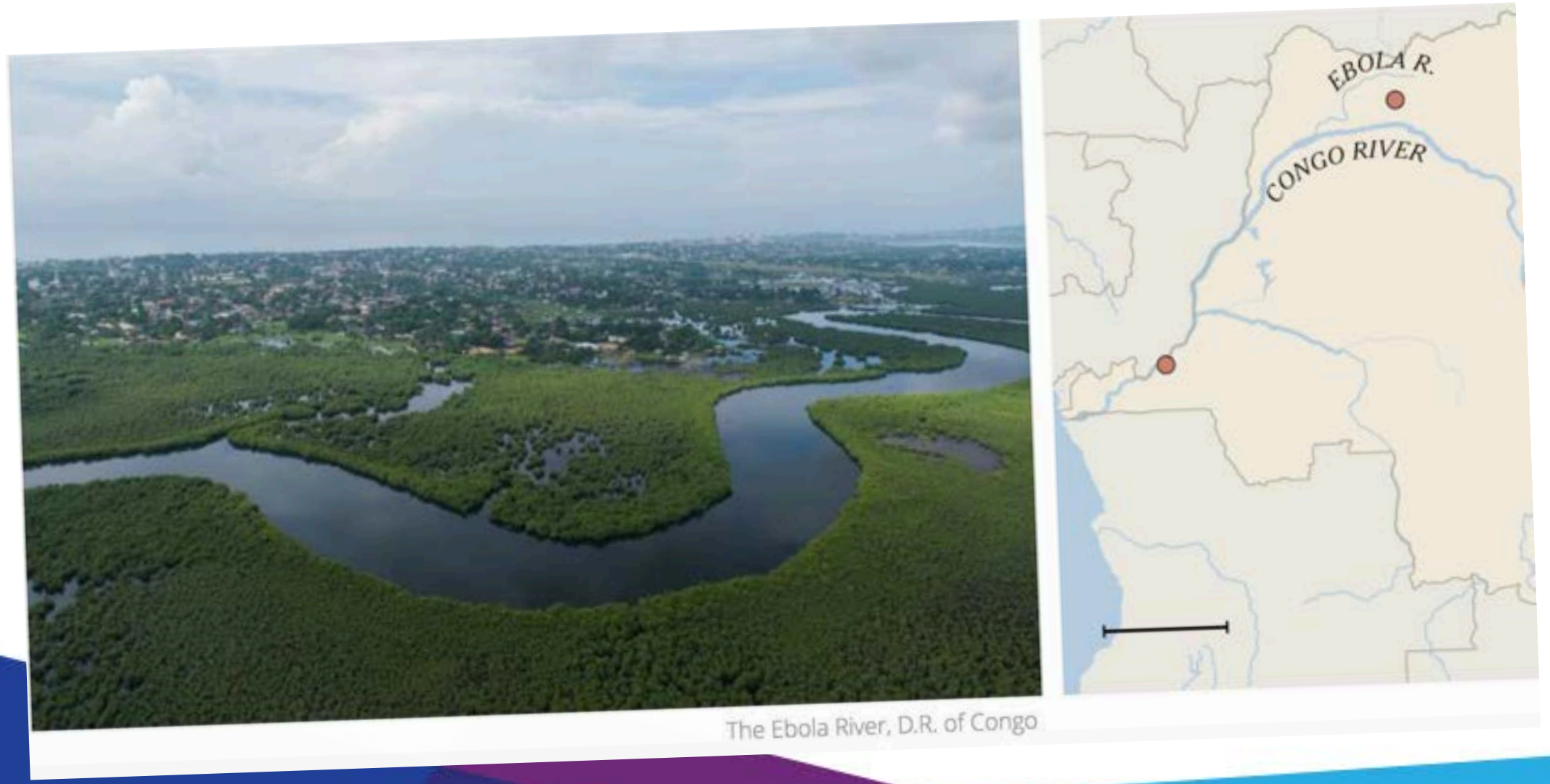

Days since Second Blood Sample from S Tested Negative for EBOV
207 Days
175 Days
155 Days
Oct. 3
S: Second blood sample tests EBOV-negative
March 7
S and P engage in sexual intercourse
March 27
S: First semen sample tests EVD-positive; P: Dies from EVD
April 28
S: Second semen sample tests EBOV-negative
March 14
P: EVD onset
Sept. 29
S: First blood sample tests EBOV-negative
Oct. 7
S: Exits ETU
March 19
P: Enters ETU
May 2
S: Third semen sample tests EBOV-negative
Sept. 23
S: Enters ETU
March 20
P: Blood sample tests EBOV-positive
September 2014
October 2014
November 2014–February 2015
March 2015
April 2015
May 2015
Sept. 9
S: Estimated EVD onset
179 Days
199 Days
231 Days
Days since Estimated Date of EVD Onset in S

Vaccination strategies

- Ervebo® (rVSV-ZEBOV)
  - >350,000 people in Guinea, DRC under compassionate use and safe and effective against Zaire Ebolavirus
  - Global stockpile started January 2021
  - U.S. indications: outbreak response, laboratorians and healthcare personnel
- Zabdeno-and-Mvabea
  - Granted marketing authorization by European Medicines Agency
  - 2 dose regimen, and not suitable for an outbreak response

https://www.who.int/news-room/fact-sheets/detail/ebola-virus-disease

Questions?



The Ebola River, D.R. of Congo