What to Know About Ebola in the Age of COVID

Dr. Bruce Ribner, MD, MPH

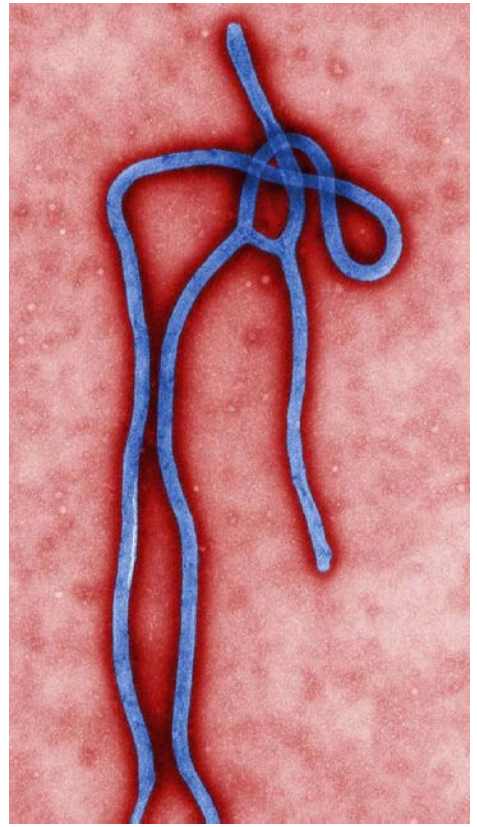
EMORY UNIVERSITY SCHOOL OF MEDICINE

Serious Communicable Diseases Program

Project ECHO

Background on Ebola

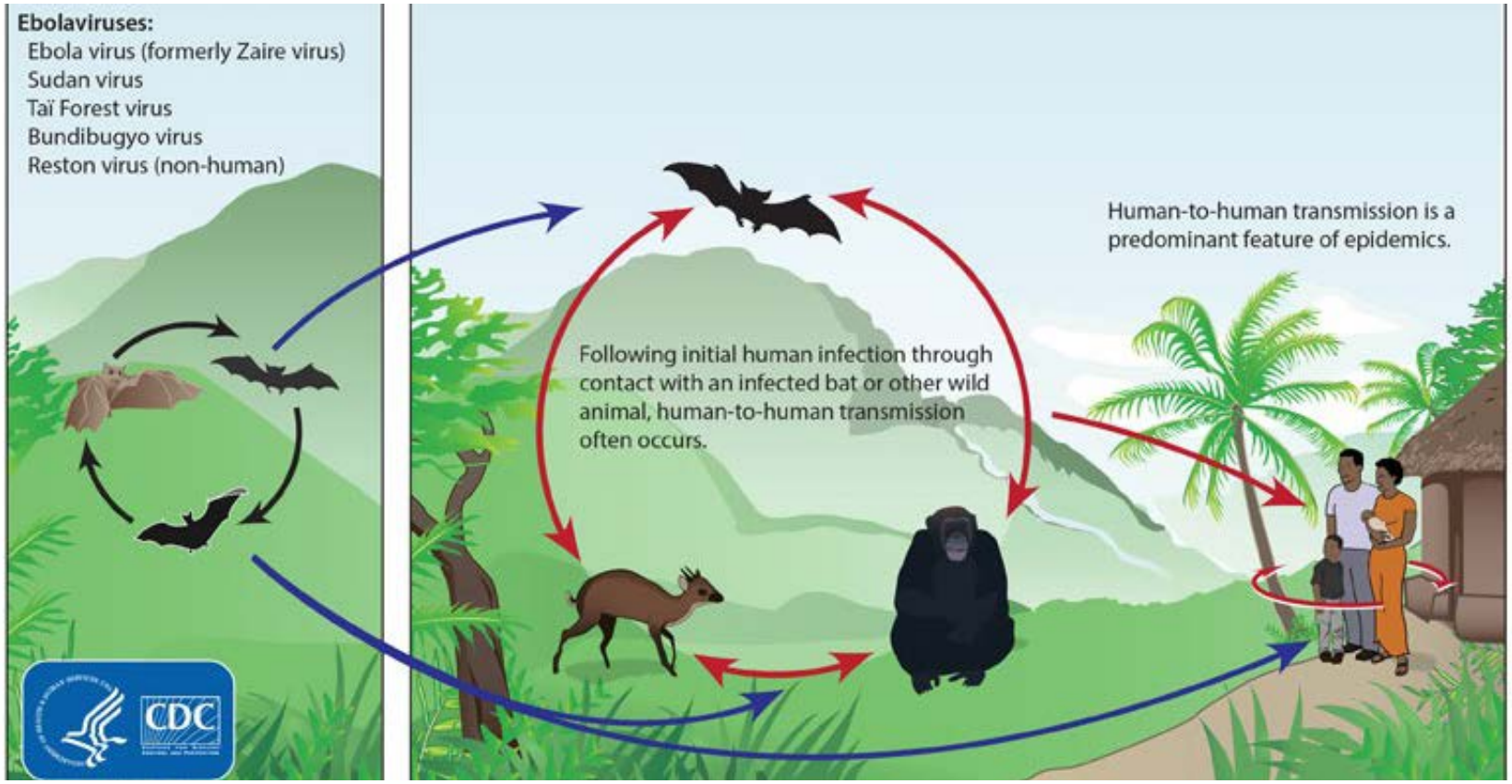
- Family Filoviridae
  - Two genera: *marburgvirus* and *ebolavirus*
  - Enveloped, negative, single-stranded RNA viruses
- Five species of Ebola viruses
  - Ebola (EBOV)
  - Sudan (SUDV)
  - Tai Forest (TAFV)
  - Bundibugyo (BDBV)
  - Reston (RESTV)
- Transmitted by contaminated body fluids
- Mortality from Ebola virus disease (EVD) historically has ranged from 40-88%



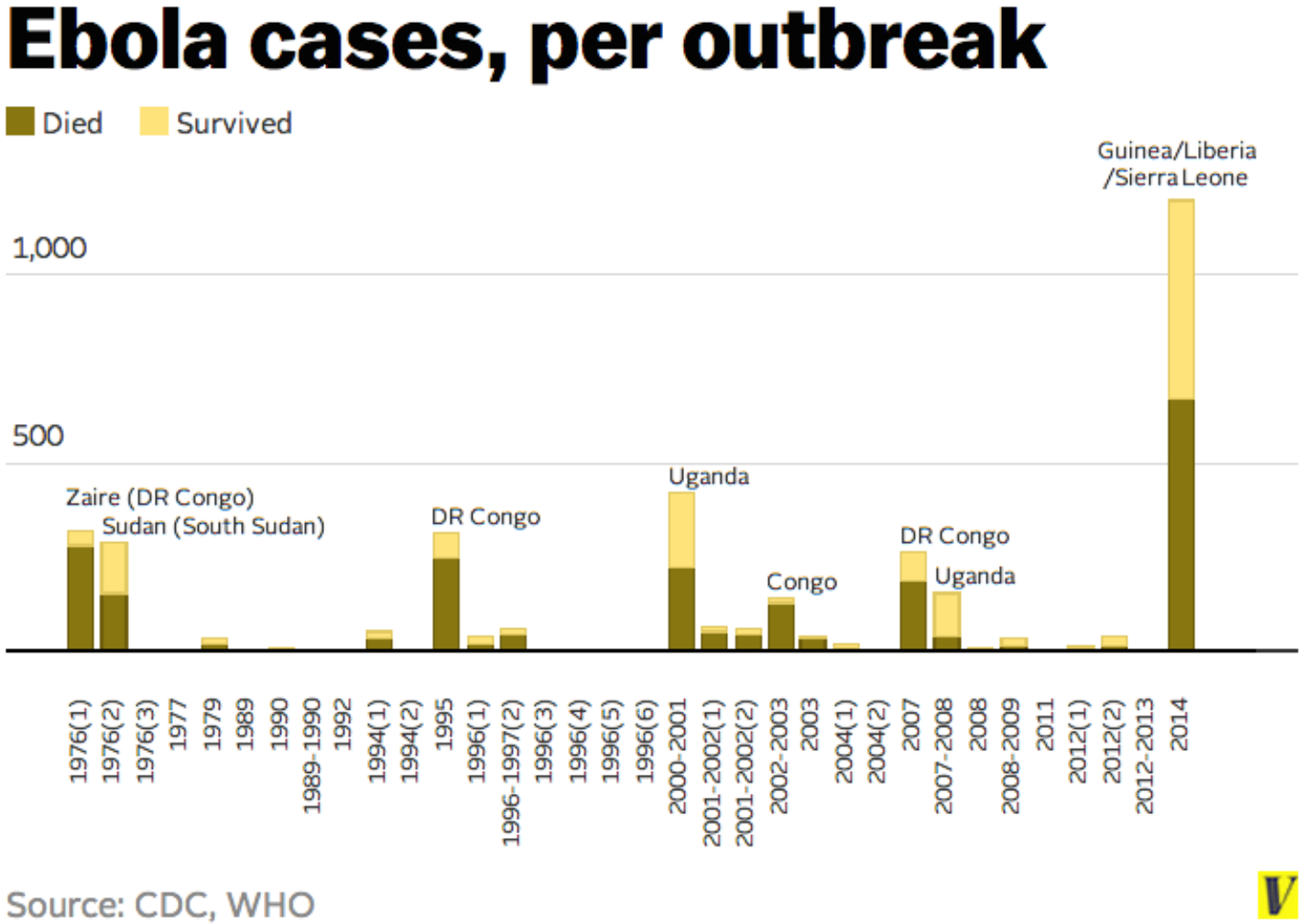
Cynthia Goldsmith/CDC

Ebola Transmission

- Zoonotic infection
  - Natural reservoir is likely the fruit bat
  - Can be transmitted to other mammals, including primates
  - Human acquisition contact with infected animal, then human-human transmission



Ebola 1976-2014



Ebola Cases and Deaths* as of March 09, 2016

	Total Cases (Suspected, Probable, and Confirmed)	Confirmed Cases	Total Deaths
Guinea	3,804	3344	2,536
Sierra Leone	14,122	8,704	3,955
Liberia	10,666	3,157	4,808
Italy	1	1	0
United Kingdom	1	1	0
Nigeria	20	19	8
Spain	1	1	0
Senegal	1	1	0
United States	4	4	1
Mali	8	7	6
TOTAL	28,603	15,239	11,301

Updated case counts available at http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/case-counts.html.
* Total cases include probable, suspected, and confirmed cases. Reported by WHO using data from ministries of health

Ebola Outbreaks- They Never Went Away

Ebola Virus Outbreaks				
Country	Cases	Deaths	Species	Year
Dem. Rep. of the Congo	130	55	Zaire ebolavirus	2020
Dem. Rep. of the Congo, Uganda ǂ	3470	2287	Zaire ebolavirus	2018-2020
Dem. Rep. of the Congo	54	33	Zaire ebolavirus	2018
Dem. Rep. of the Congo	8	4	Zaire ebolavirus	2017
Dem. Rep. of the Congo	66	49	Zaire ebolavirus	2014
Multiple countries	28646	11323	Zaire ebolavirus	2014-2016

Ebola Virus - Current Outbreak - DRC

- 7 February 2021, DRC declared an outbreak of Ebola in North Kivu province

Current situation

12 total cases **6 total deaths**

- The outbreak is located near the city of Butembo
- Vaccination of contacts, and contacts of contacts – using the rVSV-ZEBOV vaccine – is underway
- Over 10,873 people vaccinated so far
- Declared over May 4, 2021

Ebola Virus – Current Outbreak - DRC

https://www.cdc.gov/vhf/ebola/outbreaks/drc/2021-february.html

Ebola Virus – Current Outbreak - Guinea

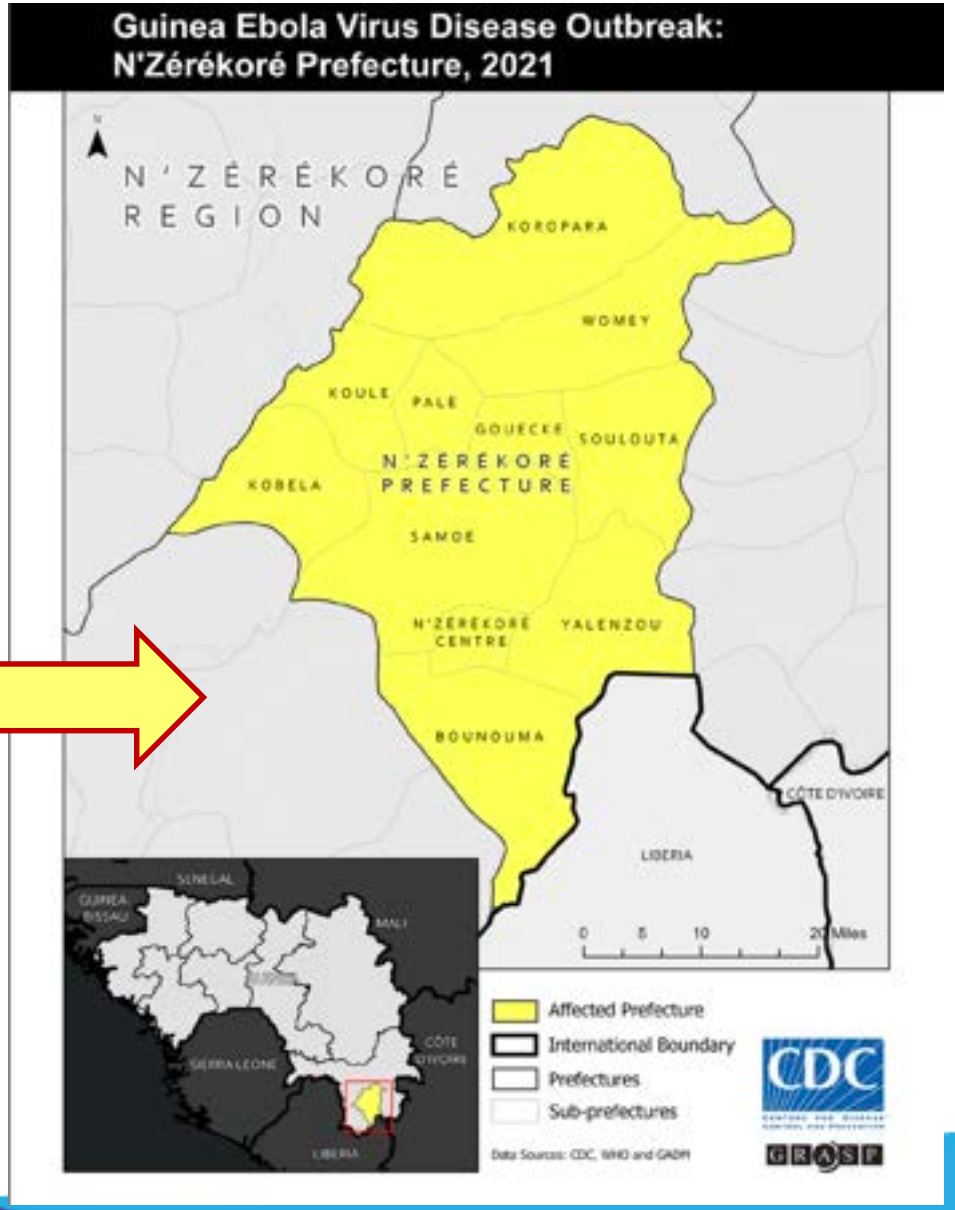
- Early January - cases of Ebola detected in Gouecke, a rural community in N'Zerekore prefecture

Current situation

23 total cases **12 total deaths**

- Ring vaccination campaign using the rVSV-ZEBOV vaccine is underway
- Over 1000 people vaccinated so far
- Will be over June 18, 2021 if no new cases

Ebola Virus – Current Outbreak - Guinea



https://www.cdc.gov/vhf/ebola/outbreaks/guinea/2021-february.html

Ebola Virus – Current Outbreak - Guinea

- Guinea outbreak detected after a 51-year-old nurse, who had originally been diagnosed with typhoid and malaria, died in late January
    - Several people who attended her funeral fell ill, including members of her family and a traditional healer who had treated her. Four died
    - Researchers suspected Ebola might have caused the deaths, and in early February they discovered the virus in the blood of the nurse's husband
    - Ebola outbreak was officially declared on 13 February, with the nurse the likely index case
- Genomic analysis revealed that the virus causing the new outbreak differs barely from the strain seen 5 to 6 years ago, suggesting that the virus lay dormant in a survivor of the epidemic all that time. It is hypothesized that the virus reactivated in a survivor, likely laying dormant in an immunologically protected site

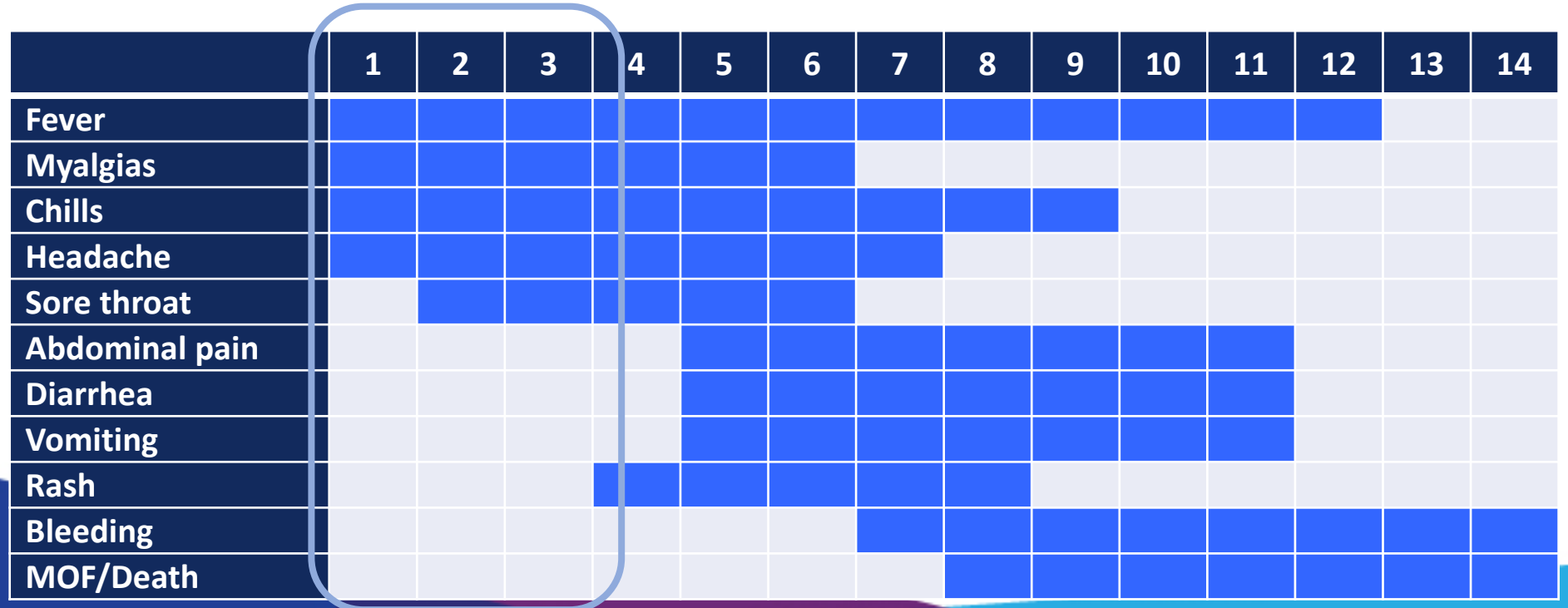
Ebola- it’s not over when it’s over

Residual virus in immune privileged body sites

- semen
- amniotic fluid
- eye
- central nervous system

Clinical Course of EVD

- **Latency of 2-21 days (most 8-10)**
- **Prodromal phase – day 1-3**
  - Fever, malaise/fatigue, headache, myalgias
  - Leukopenia (esp lymphopenia) & thrombocytopenia
  - Limited viral shedding and negative blood PCR

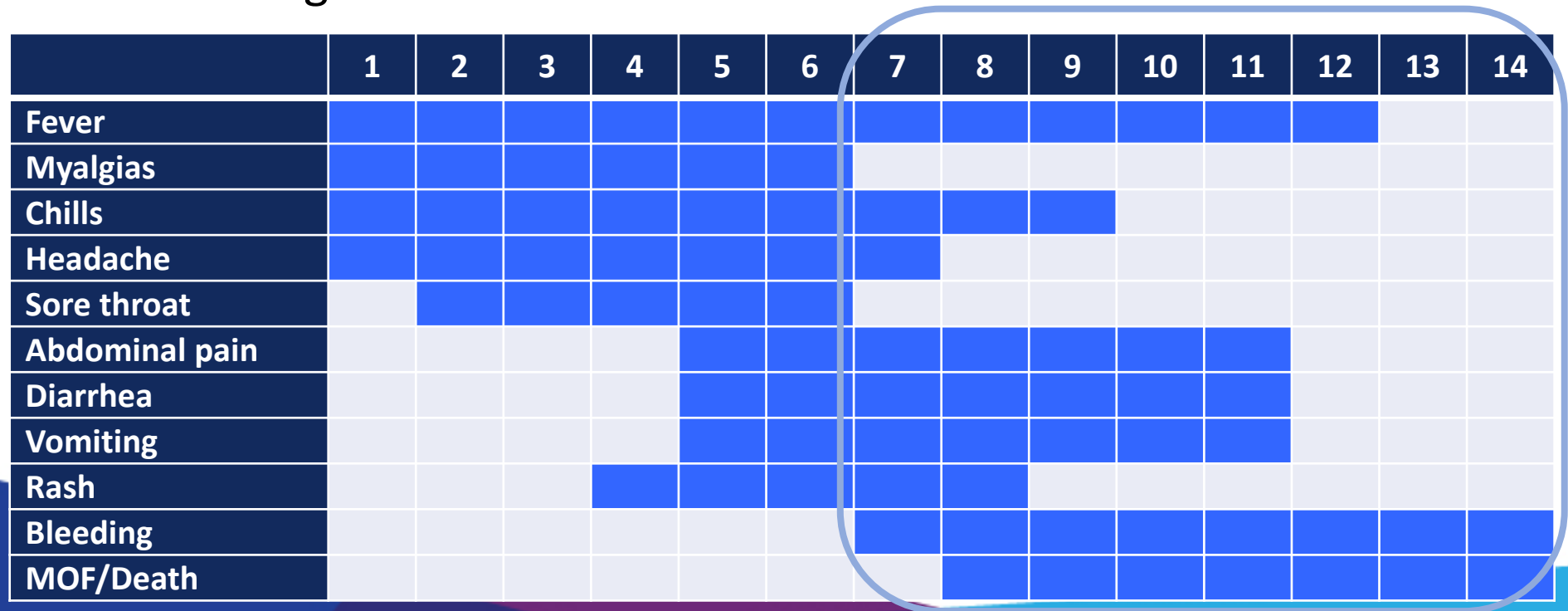


Clinical Course of EVD

- **Fever + Gastroenteritis/hepatitis – day 3-4 to 8-12**
  - Vomiting, diarrhea → volume depletion, electrolyte loss
  - Metabolic acidosis
  - Elevated AST > ALT but minimal hyperbilirubinemia

Critical Illness in EVD

- Respiratory distress/failure
- Renal Failure
- Encephalopathy/encephalitis
- Severe Shock
- Severe Hemorrhage



Clinical Pearls: Volume and Electrolytes

- Patients will be hypovolemic even while their body weight increases by 10-20 kg
  - low albumin + vascular damage → third spacing
- Large volume losses: 5-10 liters/day
- Marked electrolyte abnormalities and nutritional deficiency
  - Regardless of when received or severity of illness
  - Hypokalemia, hypocalcemia and hyponatremia to varying marked degrees
  - Required both intravenous and oral replacement

Medical Countermeasures against Ebola: Therapeutics and Vaccines

Dr. Aneesh Mehta, MD

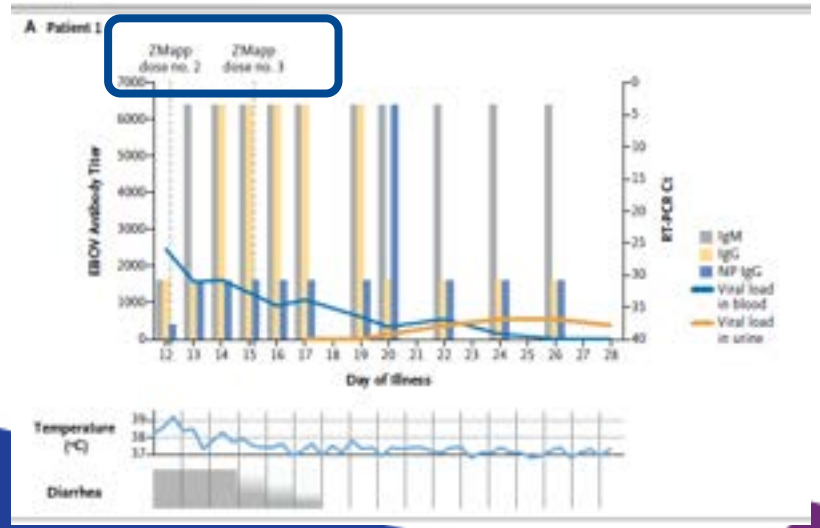
In 2014, we knew nothing, but we tried many things…

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Clinical Care of Two Patients with Ebola Virus Disease in the United States

G. Marshall Lyon, M.D., M.M.Sc., Aneesh K. Mehta, M.D., Jay B. Varkey, M.D., Kent Brantly, M.D., Lance Plyler, M.D., Anita K. McElroy, M.D., Ph.D., Colleen S. Kraft, M.D., Jonathan S. Towner, Ph.D., Christina Spiropoulou, Ph.D., Ute Ströher, Ph.D., Timothy M. Uyeki, M.D., M.P.H., M.P.P., and Bruce S. Ribner, M.D., M.P.H., for the Emory Serious Communicable Diseases Unit*



Administration of Brincidofovir and Convalescent Plasma in a Patient With Ebola Virus Disease

Diana F. Florescu, Andre C. Kalil, Angela L. Hewlett, Amy J. Schuh, Ute Stroher, Timothy M. Uyeki, Philip W. Smith

Clinical Infectious Diseases, Volume 61, Issue 6, 15 September 2015, Pages 969–973, https://doi.org/10.1093/cid/civ395

Clinical features and viral kinetics in a rapidly cured patient with Ebola virus disease: a case report

…etter*, Pascal Cherpillod, Tom J Petty, Samuel Cordey, Gaël Vieille, Sabine Yerly, Claire-Anne Siegrist, Kaveh Samii, …acquier, Evgeny M Zdobnov, Andrew J H Simpson, Paul S C Rees, Felix Baez Santa, Yvan Gasche, François Chappuis, …me Pugin†, Laurent Kaiser†

…l description of viral kinetics, duration of virus shedding, and intraviral evolution in different …d to understand Ebola virus pathogenesis. Patients with Ebola virus infections admitted to …rovide a unique opportunity to do such in-depth virological investigations. We describe the …l virological follow-up of a case of Ebola virus disease.

Methods A 43-year-old medical doctor who contracted an Ebola virus infection in Sierra Leone on Nov 16, 2014 (day 1), was airlifted to Geneva University Ho…, Geneva, Switzerland, on day … after disease onset. The patient received an experimental antiviral treatment o… monoclonal antibodies (ZMAb) and favipiravir. W… monitored daily viral load kinetics, estimated viral clearance, ca…lculated the half-life of the virus in plasma, and analysed the viral genome via high-throughput sequencing, in addition to clinical and biological signs.

The Use of TKM-100802 and Convalescent …ients With Ebola Virus Disease in …es

Summary

Background In the current epidemic of Ebola virus disease in western Africa, many aid workers have become infected. Some of these aid workers have been transferred to specialised hospitals in Europe and the USA for intensified treatment, providing the potential for unique insight into the clinical course of Ebola virus disease under optimised supportive measures in isolation units.

Methods A 38-year-old male doctor who had contracted an Ebola virus infection in Sierra Leone was airlifted to University Hospital Frankfurt, Germany, on day 5 after disease onset. Within 72 h of admission to the hospital's high-level isolation unit, the patient developed signs of severe multiorgan failure, including lungs, kidneys, and gastrointestinal tract. In addition to clinical parameters, the diagnostic work-up included radiography, ultrasound, pulse contour cardiac output technology, and microbiological and clinical chemistry analyses. Respiratory failure with pulmonary oedema and biophysical evi… of vascular leak syndrome needed mechanical ventilation. The patient received a 3 day treatment course with …FX06 (MChE-F4Pharma, Vienna, Austria), a fibrin-derived peptide under clinical development for vascular leak sy… After FX06 administration and … detection of Ebola virus-specific antibodies and a fall in viral load, vascular leak syndrome and respiratory parameters substantially improved. We gave broad-spectrum empiric antimicrobial therapy and the patient needed intermittent renal replacement therapy. The patient fully recovered.

…t,[1,3*] Scott Koepsell,[4] Anne M. Winkler,[1] Christopher J. Kratochvil,[5] LuAnn Larson,[6] Marshall Lyon III,[2] Rachel J. Friedman-Moraco,[7] Vincent C. Marconi,[7] Charles E. Hill,[1] …on,[7] Steven J. Lisco,[7] Mark J. Mulligan,[7] Timothy M. Uyeki,[8] Anita K. McElroy,[8] …tina Spiropoulou,[8] Ute Ströher,[8] Ian Crozier,[9] Richard Sacra,[10] …blinwong,[11] Harold A. French,[12] Philip W. Smith,[3] and Bruce S. Ribner[2]; for …nd the Emory Serious Communicable Diseases Unit[2]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Clinical Management of Ebola Virus Disease in the United States and Europe

Timothy M. Uyeki, M.D., M.P.H., M.P.P., Aneesh K. Mehta, M.D., Richard T. Davey, Jr., M.D., Allison M. Liddell, M.D., Timo Wolf, M.D., Pauline Vetter, M.D., D.T.M.&H., Stefan Schmiedel, M.D., Thomas Grünewald, M.D., Ph.D., Michael Jacobs, M.B., B.S., Ph.D., D.T.M.&H., Jose R. Arribas, M.D., Laura Evans, M.D., Angela L. Hewlett, M.D., Arne B. Brantsaeter, M.D., Ph.D., M.P.H., Giuseppe Ippolito, M.D., Christophe Rapp, M.D., Ph.D., Andy I.M. Hoepelman, M.D., Ph.D., and Julie Gutman, M.D. for the Working Group of the U.S.–European Clinical Network on Clinical Management of Ebola Virus Disease Patients in the U.S. and Europe*

What we learned…

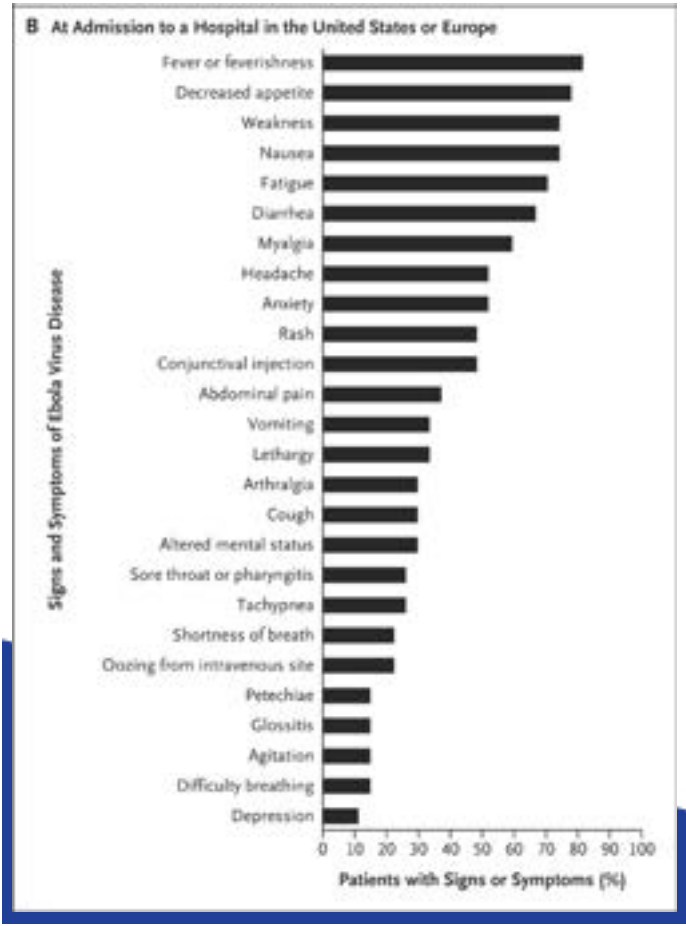


Table 4. Results of Virologic Testing.*

Variable	No. of Patients	Value	No. of Days after Onset of Illness
		median (range)	
EBOV RNA level at admission			
RT-PCR cycle-threshold value	19	24.0 (16.6–34.9)	5 (2–15)
EBOV RNA level — copies/ml	13	27×10^6 ($0.114–1200\times10^6$)	6.5 (5–11)
Peak viral detection			
Lowest RT-PCR cycle-threshold value	21	22.3 (13.2–39.5)	7 (2–15)
Highest EBOV RNA level — copies/ml	14	73×10^6 ($0.5–2100\times10^6$)	7 (2–11)
Duration of viremia — days†	22		17.5 (5–27)

Table 2. Proportion of Patients with Abnormal Laboratory Values at Admission or at Any Time during Hospitalization in the United States or Europe.*

Abnormal Laboratory Result	At Admission	During Hospitalization	Treatment Received during Hospitalization†
	no./total no. tested (%)		*no./total no. (%)*
Hyponatremia (sodium <135 mmol/liter)‡	12/27 (44)	21/27 (78)	21/21 (100)
Hypokalemia (potassium <3.5 mmol/liter)	10/27 (37)	18/27 (67)	18/18 (100)
Hypocalcemia (total calcium <8 mmol/liter)	10/16 (62)	15/20 (75)	10/15 (67)
Hypomagnesemia (magnesium <0.85 mmol/liter)	9/10 (90)	14/17 (82)	10/14 (71)
Hypoalbuminemia (albumin <3.5 g/dl)	20/25 (80)	25/25 (100)	7/25 (28)
Elevated creatinine (>1.3 mg/dl)	5/27 (19)	11/27 (41)	
Elevated bilirubin (>1.5 mg/dl)	2/22 (9)	14/26 (54)	
Elevated aspartate aminotransferase (>98 U/liter)§	20/26 (77)	25/25 (100)	
Elevated alanine aminotransferase (>110 U/liter)¶	14/26 (54)	26/27 (96)	
Leukocytosis (white-cell count ≥15,000/μl)‖	3/25 (12)	17/27 (63)	
Leukopenia (white-cell count <3500/μl)‖	8/26 (31)	13/27 (48)	
Neutropenia (absolute neutrophil count <1500/μl)	3/23 (13)	4/23 (17)	
Lymphopenia (absolute lymphocyte count <1500/μl)	14/23 (61)	20/23 (87)	
Anemia (hemoglobin <11 mg/dl)**	1/27 (4)	16/27 (59)	3/16 (19)
Thrombocytopenia (platelet count <150,000/μl)	22/26 (85)	26/27 (96)	5/26 (19)
Thrombocytosis (platelet count >450,000/μl)††	6/26	9/27 (33)	2/9 (22)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Clinical Management of Ebola Virus Disease in the United States and Europe

Timothy M. Uyeki, M.D., M.P.H., M.P.P., Aneesh K. Mehta, M.D., Richard T. Davey, Jr., M.D., Allison M. Liddell, M.D., Timo Wolf, M.D., Pauline Vetter, M.D., D.T.M.&H., Stefan Schmiedel, M.D., Thomas Grünewald, M.D., Ph.D., Michael Jacobs, M.B., B.S., Ph.D., D.T.M.&H., Jose R. Arribas, M.D., Laura Evans, M.D., Angela L. Hewlett, M.D., Arne B. Brantsaeter, M.D., Ph.D., M.P.H., Giuseppe Ippolito, M.D., Christophe Rapp, M.D., Ph.D., Andy I.M. Hoepelman, M.D., Ph.D., and Julie Gutman, M.D. for the Working Group of the U.S.–European Clinical Network on Clinical Management of Ebola Virus Disease Patients in the U.S. and Europe*

What we did not learn anything from…

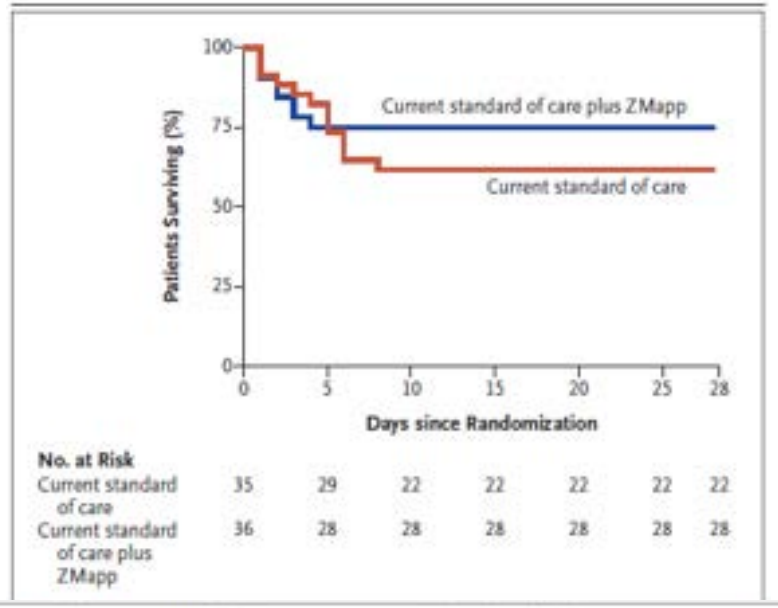
Table 3. Use of Investigational Therapies.*

Investigational Therapy	Received at Least 1 Dose (N=27)	Completed Course†	Adverse Reactions	Suspected Adverse Reactions
	number of patients (percent)			
ZMapp or MIL77	8 (30)	2 (25)	4 (50)	Fever, hypotension, agitation, tachycardia, tachypnea, flushing, palmar pruritus, rash
ZMab	5 (19)	1 (20)	2 (40)	Fever, urticaria, serum sickness
TKM-Ebola	5 (19)	1 (20)	5 (100)	Fever, chills, hypotension, the systemic inflammatory response syndrome, nausea, lipemia
Favipiravir	10 (37)	5 (50)	3 (30)	Nausea, vomiting, elevated aspartate aminotransferase, neutropenia, QTc prolongation
Brincidofovir	7 (26)	1 (14)	4 (57)	Diarrhea, nausea, vomiting, elevated aminotransferase levels, severe fatigue
FX06	2 (7)	NA	0	
Convalescent plasma‡	10 (37)	NA	3 (33)	Transfusion-related acute lung injury
Convalescent whole blood	1 (4)	NA	0	
Amiodarone§	2 (7)	NA	1 (50)	Bradycardia
Melanocortin	1 (4)	NA	0	

- At least 10 different off-label or compassionate use therapies were tried
  - 70% received more than one.
- We saw likely side effects
- We did not learn anything about efficacy of any of these medications.

Partnership for Research on Ebola Virus in Liberia (PREVAIL)

- A Randomized, Controlled Trial of ZMapp versus standard of care for Ebola Virus Infection
  - Started in March 2015
- 72 patients in Liberia, Sierra Leone, Guinea, and the US
  - However, as the outbreak came to an end in these areas, the trial was not able to fully enroll
- Mortality was 37% with current standard of care alone and 22% with standard of care plus Zmapp
  - Not statistically better though, potential due to not enough data
- Baseline viral load was strongly predictive of both mortality and duration of hospitalization in all age groups.



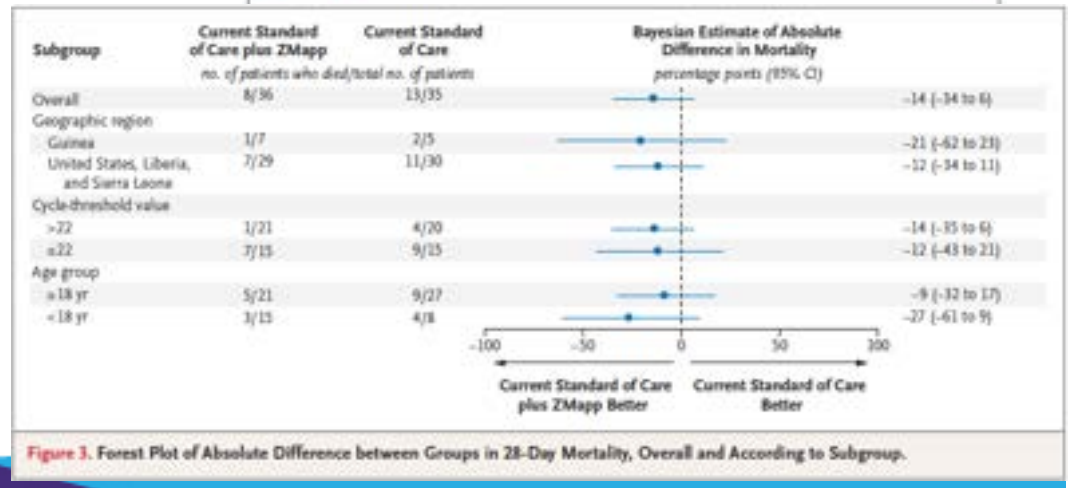


Figure 3. Forest Plot of Absolute Difference between Groups in 28-Day Mortality, Overall and According to Subgroup.

https://www.nejm.org/doi/10.1056/NEJMoa1604330

Then came the PALM trial

- After the 2014-16 Ebola outbreak ended, WHO, NIH, and others designed a platform trial to evaluate medication for Ebola
- During the 2018 outbreak in the DRC, this was launched as the PALM trial
  - ZMapp used in 2014-16
  - Remdesivir (a RNA polymerase inhibitor)
  - MAb114 (a single human monoclonal antibody derived from an Ebola survivor)
  - REGN-EB3 (a coformulated mixture of three human IgG1 monoclonal antibodies by Regeneron)

https://www.nejm.org/doi/full/10.1056/NEJMoa1910993

PALM results

- 681 patients were enrolled from November 2018 to August 2019
  - Data and Safety Monitoring Board (DSMB) essentially stopped trial early because there were some significant differences.
- At 28 days, death had occurred in 35.1% in the MAb114 group vs 49.7% in the ZMapp group and 33.5% in the REGN-EB3 group

https://www.nejm.org/doi/full/10.1056/NEJMoa1910993

FDA Approved medications for Ebola!

- Two treatments approved to treat EVD caused by *Zaire ebolavirus*
  - Neither have been evaluated against species other than Zaire ebolavirus
  - Both adults and children
- REGN-EB3 → atoltivimab, maftivimab, and odesivimab-ebgn (Inmazeb™ [Regeneron]) in October 2020
  - 50/50/50 mg/kg as a single intravenous infusion over 2-4 hours
  - Side effects: fever, chills, tachycardia, tachypnea, and vomiting
- MAb114 → Ansuvimab-zykl (Ebanga™ [Ridgeback]) in December 2020
  - 50 mg/kg as a single intravenous infusion over 60 minutes
  - Side-effects: fever, tachycardia, diarrhea, vomiting, hypotension, tachypnea and chills

Even better… we have a vaccine!

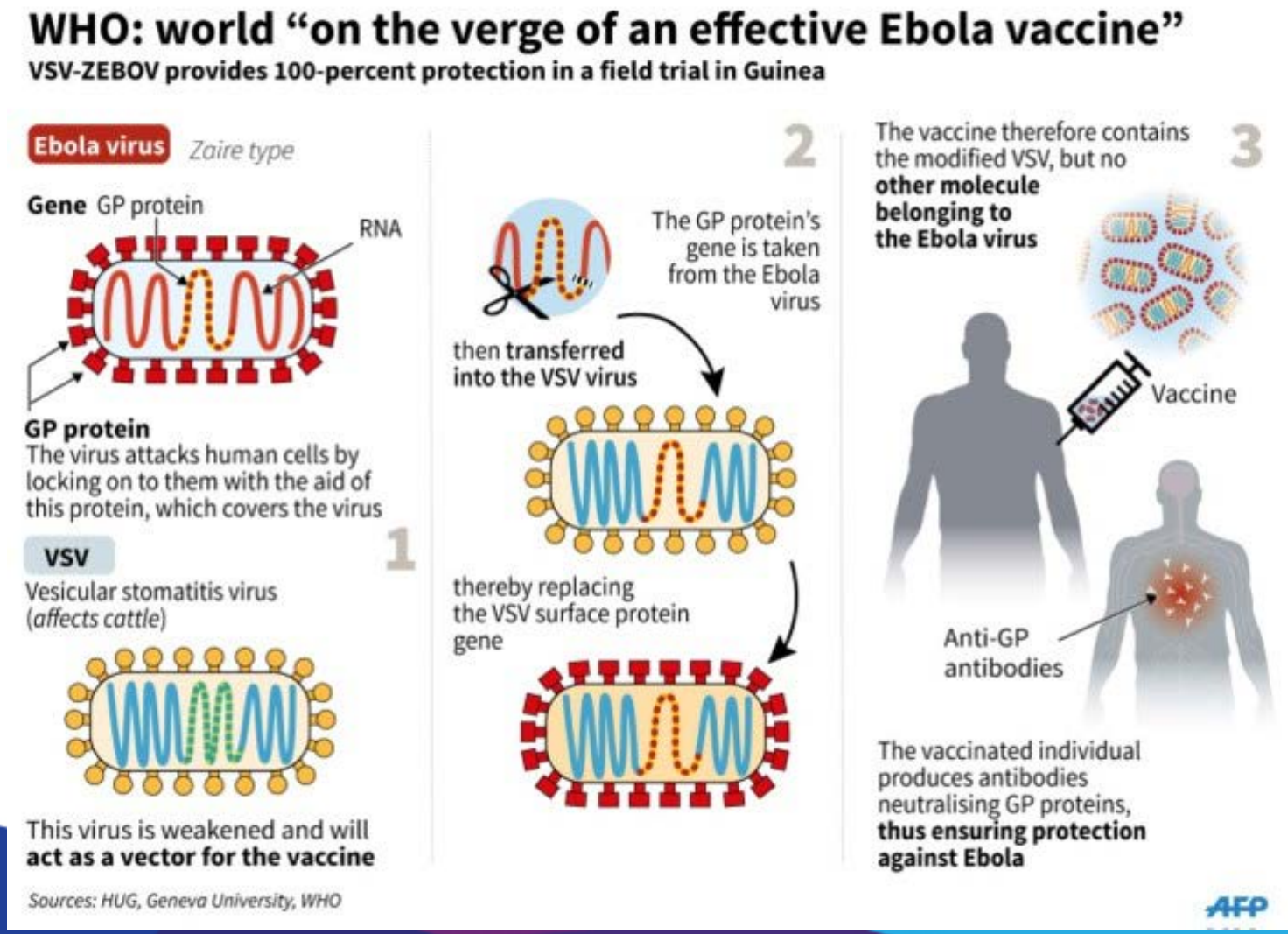
Ebola Vaccines

- FDA approved the Ebola vaccine rVSV-ZEBOV (Ervebo®) in December 2019
  - Single dose vaccine

- A two-dose vaccine regimen of a different vaccine has been studied in the US and during the 2019 Ebola outbreak in the Democratic Republic of the Congo.
  - Ad26.ZEBOV then MVA-BN-Filo “booster” dose 56 days later
  - Not yet been approved by the FDA; approved in EU.

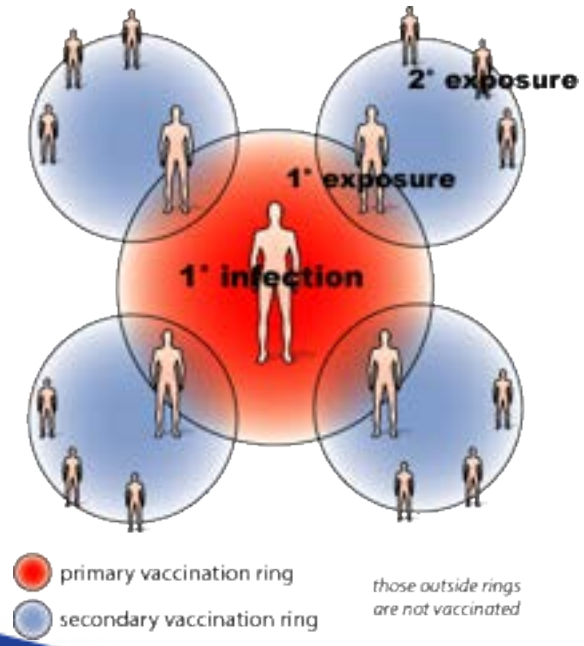
https://www.cdc.gov/vhf/ebola/prevention/index.html

Ebola vaccine rVSV-ZEBOV (Erevbo®)



Ebola vaccine rVSV-ZEBOV (Erevbo®)

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!)



- A ring (cluster) of all their contacts and contacts of contacts
  - Randomly assigned clusters (1:1) to either immediate vaccination or delayed vaccination (21 days later)
  - 4539 contacts and contacts of contacts in 51 clusters randomly assigned to immediate vaccination
  - 4557 contacts and contacts of contacts in 47 clusters randomly assigned to delayed vaccination
- Vaccine efficacy was 100% (95% CI 69–100, p=0·0045),
  - No cases of Ebola virus disease occurred 10 days or more after vaccine
  - 23 cases (11 clusters affected) in delayed or never vaccinated.
- 53.9% reported at least one adverse event
  - generally mild (87.5%): Headache, fatigue, and muscle pain
  - Two serious events: one febrile reaction and one anaphylaxis

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)32621-6

Ebola vaccine rVSV-ZEBOV (Erevbo®)

- FDA approved the Ebola vaccine rVSV-ZEBOV (Ervebo®) in Dec 2019
  - Single dose vaccine
- Advisory Committee on Immunization Practices (ACIP) recommended vaccination with rVSV-ZEBOV for adults ≥ 18 years who are at potential occupational risk of exposure to Zaire ebolavirus.
  - Responding or planning to respond to an outbreak of EVD
  - Laboratorians or other staff working at biosafety-level 4 facilities that work with live Ebola virus
  - Healthcare personnel working at federally designated Ebola Treatment Centers
  - *We anticipate other groups becoming eligible soon*

Ebola vaccine rVSV-ZEBOV (Erevbo®)

- Contraindications for Ervebo®
  - Known severe allergy, such as anaphylaxis, to any component of the vaccine, including rice protein
  - Clinical evidence of a systemic infection or other acute illness
  - Presence of any clinically significant medical condition, past medical history, pre-existing illness that in the opinion of the healthcare provider may place the individual at an unreasonably increased risk of a serious adverse event following vaccination
  - Unwillingness to complete the informed consent process and sign the consent form
- Pregnancy and lactation are not absolute exclusion, determination of whether to receive the vaccine should be made on an individual basis, in consultation with a healthcare provider, based on the benefit/risk of vaccination against the risk of exposure to Ebola
- Laboratory and healthcare workers at risk for occupational exposure to EBOV who receive Ervebo® must continue to adhere to recommended biosafety guidelines and infection prevention and control procedures.

https://www.cdc.gov/vhf/ebola/clinicians/vaccine/precautions.html

Ebola vaccine rVSV-ZEBOV (Erevbo®)

- Administered as intramuscularly (IM) injection
- If frozen, thaw the vaccine vial completely at room temperature until no visible ice is present (approximately 10 to 15 minutes)
  - Do not thaw in a refrigerator as the vaccine is sensitive to slow thawing
  - If not used immediately, the vaccine may be stored for up to 13 days at 2 C to 8 C or for up to three hours at room temperature protected from light
  - Do NOT re-freeze.
- After administration of the vaccine, the used vial and syringe should be disposed of as normal biohazardous waste
  - The product does not contain Ebola virus.

https://www.cdc.gov/vhf/ebola/clinicians/vaccine/precautions.html

The Serious Communicable Diseases Program at Emory

An interdisciplinary program fostering innovative research, advanced education, and training opportunities for healthcare and academic professionals within Emory and across the nation.

Lessons Learned

- Key to management of patients with serious communicable diseases is aggressive support care
- Protecting healthcare workers requires a return to basic infection control principles
- Maximizing our knowledge about the management and prevention of serious communicable diseases will require a preexisting research infrastructure
- Public health infrastructure will be critical in addressing the next outbreak of a serious communicable disease

Thank you!