



Ebola Virus Disease: 2019 and Beyond

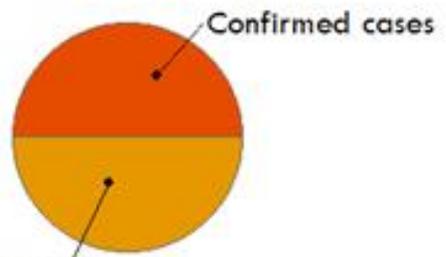
Colleen S. Kraft, MD, MSc

Associate Professor, Pathology and
Laboratory Medicine; Division of Infectious
Diseases

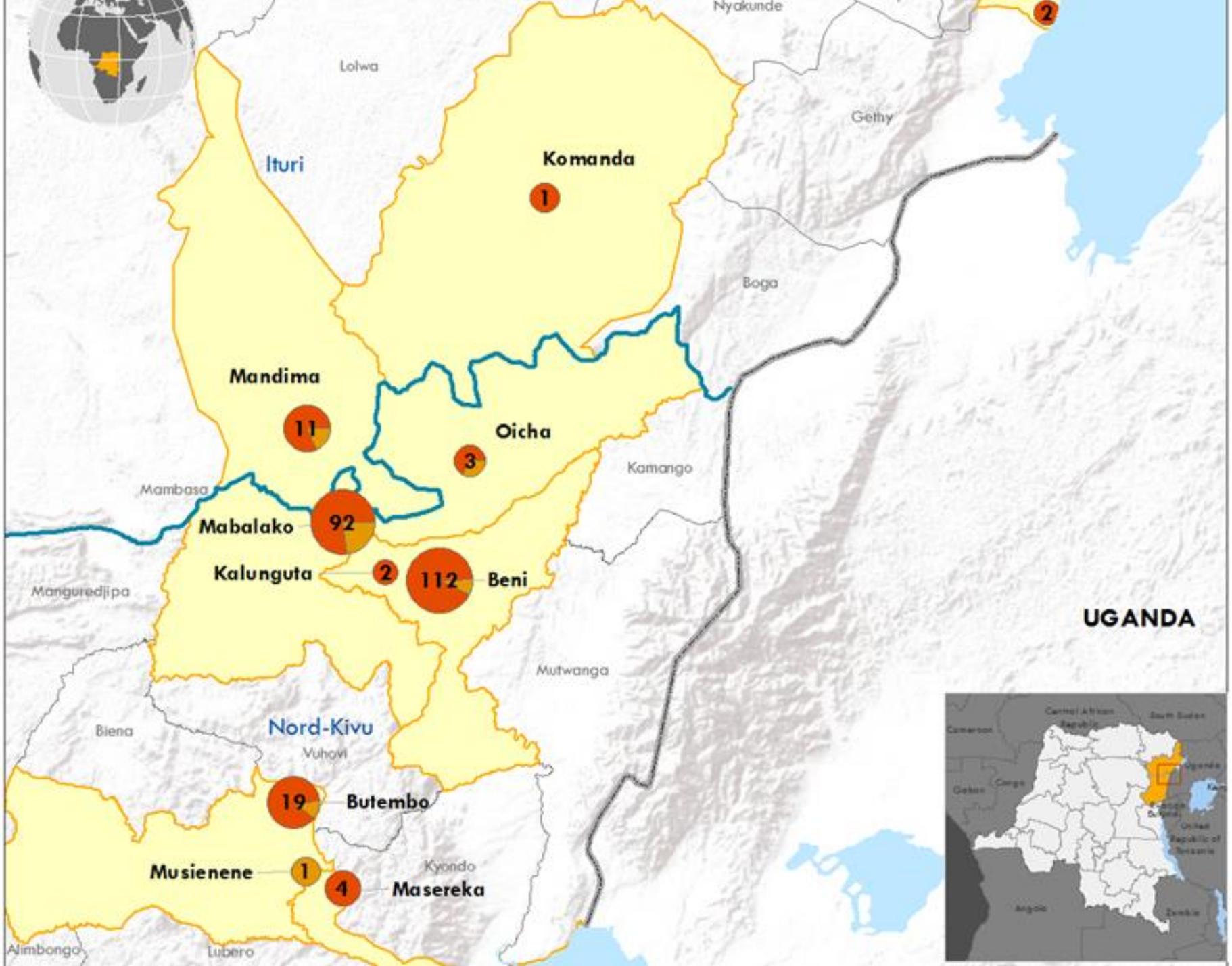
Associate Medical Director, Serious
Communicable Diseases Unit

Emory University School of Medicine

Subject to confirmation



- Major city
- Health Zone reporting probable or confirmed cases
- Health Zone
- Province
- National boundary



Therapeutics currently being deployed in the Democratic Republic of the Congo



- 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



Low yield

Efforts to test therapies and vaccines during the West African Ebola epidemic provided few clear-cut results.

INTERVENTION	MECHANISM	TRIAL LOCATION	STATUS
Brincidofovir	Nucleotide analog	Liberia	Stopped by Chimerix after four patients, reasons unclear
Favipiravir	Viral enzyme inhibitor	Guinea	Completed, more than 200 patients included, putative signal of efficacy
Plasma	Antibodies from survivors	All three countries	Liberia: Stopped after six patients Sierra Leone: Stopped after three patients Guinea: Completed, 102 patients included
Whole blood	Antibodies from survivors	Liberia	Stopped, status unclear
ZMapp	Ebola antibody cocktail	All three countries and the U.S.	About 70 patients enrolled in ongoing RCT
TKM-Ebola	RNA inhibitor	Sierra Leone	Stopped after 14 patients, drug deemed unlikely to work
Interferon-β	Non-specific immune enhancement	Guinea	Stopped after nine patients
GSK and Merck vaccines	Adaptive immunity	Liberia	Suspended after 500 volunteers received each vaccine
Merck vaccine	Adaptive immunity	Guinea	Ring study: More than 4000 vaccinated, efficacy demonstrated Frontline worker study: 2000 vaccinated
Merck vaccine	Adaptive immunity	Sierra Leone	Frontline worker study: 8000+ vaccinated

G. GRULLON/SCIENCE

Serious Communicable Diseases Unit, Emory University Hospital



First civilian
biocontainment unit in
the United States



Funded in 2002 essentially
as Occupational Health for
CDC employees in the
field or laboratory



Contracted to be able to
be activated within 1 hour
of notification



Nurses,
physicians/physician
assistant, laboratorians
on-call 24/7/365



Patient care room

EMORY
HEALTHCARE
We all belong here.

11/12



Patient care experience at Emory Hospital



4 patients
with Ebola
virus disease



3 individuals
admitted for
post-exposure
prophylaxis



1 patient with
Lassa fever virus
in March 2016



Approximately
25 individuals
ruled out for
Ebola

Experimental
therapies
administered
at Emory
under eIND
from FDA

ZMapp (Patients
1 and 2)

Convalescent
Plasma (Patients
2 and 3 and 4)

TKM-Ebola
(Patient 3 and
Exposure 1)

Favipiravir
(Patient 3)

Brincidofovir
(Patient 4)

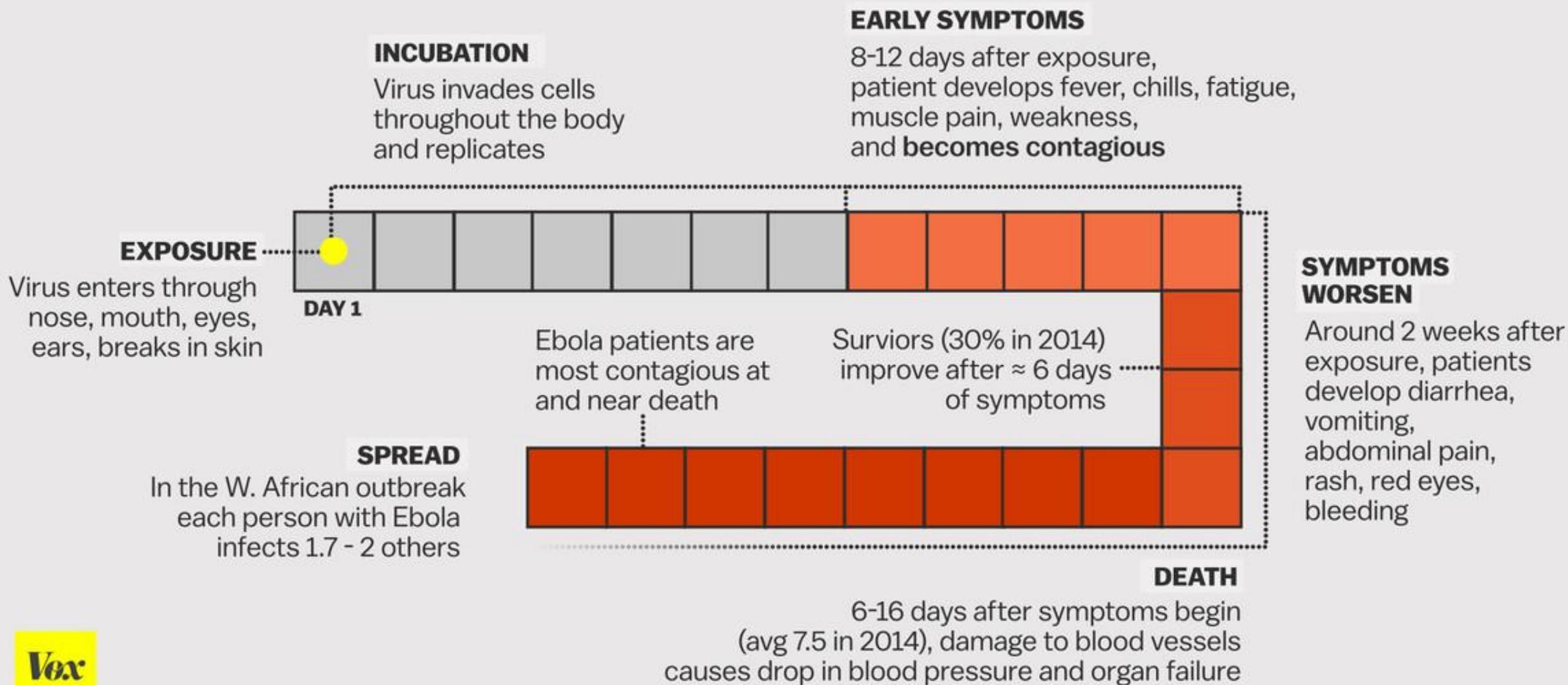
VSV vaccine
(Exposure 2, 3)

STAGES OF EBOLA VIRUS DISEASE

Contagious through bodily fluids = 

Not contagious = 

SOURCE: CDC



Ebola as a critical illness: “Patient 3”

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



Critical role of nursing and supportive care

- 24/7 one-on-one nurses allowed for rapid response to changes and adjustment of care
- Critical care nurses had the ability to support patients in nutrition, physical therapy, and self care
- Limited consultants from being in the room
- Emotional support/Family support
- Provider-centered patient care

Successful Delivery of RRT in Ebola Virus Disease

Michael J. Connor Jr,^{*†} Colleen Kraft,^{‡§} Aneesh K. Mehta,[‡] Jay B. Varkey,[‡] G. Marshall Lyon,[‡]
Ian Crozier,^{||} Ute Ströher,^{||} Bruce S. Ribner,[‡] and Harold A. Franch^{†**}

- All RRT effluent should be non-infectious
- Virus/RNA too big to fit through membrane
- Tested effluent multiple days by PCR to confirm



Post-Ebola syndrome

- Long term medical sequelae have been documented with all 4 types of Ebola virus
- Types of sequelae include
 - Rheumatologic
 - Ocular
 - Neurologic
 - Skin
 - Reproductive organs

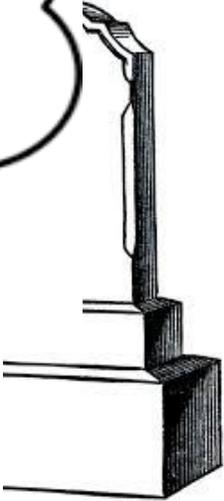




*Viral
persistence*



*Sexual
transmission*



*Subclinical
disease*

Persistence of Ebola Virus in Ocular Fluid during Convalescence

Jay B. Varkey, M.D., Jessica G. Shantha, M.D., Ian Crozier, M.D., Colleen S. Kraft, M.D., G. Marshall Lyon, M.D., Aneesh K. Mehta, M.D., Gokul Kumar, M.D., Justine R. Smith, M.B., B.S., Ph.D., Markus H. Kainulainen, Ph.D., Shannon Whitmer, Ph.D., Ute Ströher, Ph.D., Timothy M. Uyeki, M.D., M.P.H., M.P.P., Bruce S. Ribner, M.D., M.P.H., and Steven Yeh, M.D.

Late Ebola virus relapse causing meningoencephalitis: a case report

Michael Jacobs, Alison Rodger, David J. Bell, Sanjay Bhagani, Ian Cropley, Ana Filipe, Robert J. Gifford, Susan Hopkins, Joseph Hughes, Farrah Jabeen, Ingolfur Johannessen, Drosos Karageorgopoulos, Angie Lackenby, Rebecca Lester, Rebecca S N Liu, Ailsidair MacConnachie, Tabitha Mahungu, Daniel Martin, Neal Marshall, Stephen Mepham, Richard Orton, Massimo Palmarin, Monika Patel, Colin Perry, S Erica Peters, Duncan Porter, David Ritchie, Neil D Ritchie, R Andrew Seaton, Vattipally B Sreenu, Kate Templeton, Simon Warren, Gavin Swindle, Maria Zambon, Robin Gopal, Emma C Thomson

Organs of persistence

Central nervous system

Seminal fluid

Placenta

Eye – aqueous/vitreous



Ebola Hemorrhagic Fever and Pregnancy

Kibadi Mupapa, Woliere Mukundu, Mpia Ado Bwaka, Mungala Kipasa, Ann De Roo, Kivudi Kuvula, Kapay Kibadi, Matondo Massamba, Djuma Ndaberey, Robert Colebunders, and J. J. Muyembe-Tamfum

Ebola RNA Persistence in Semen of Ebola Virus Disease Survivors — Preliminary Report

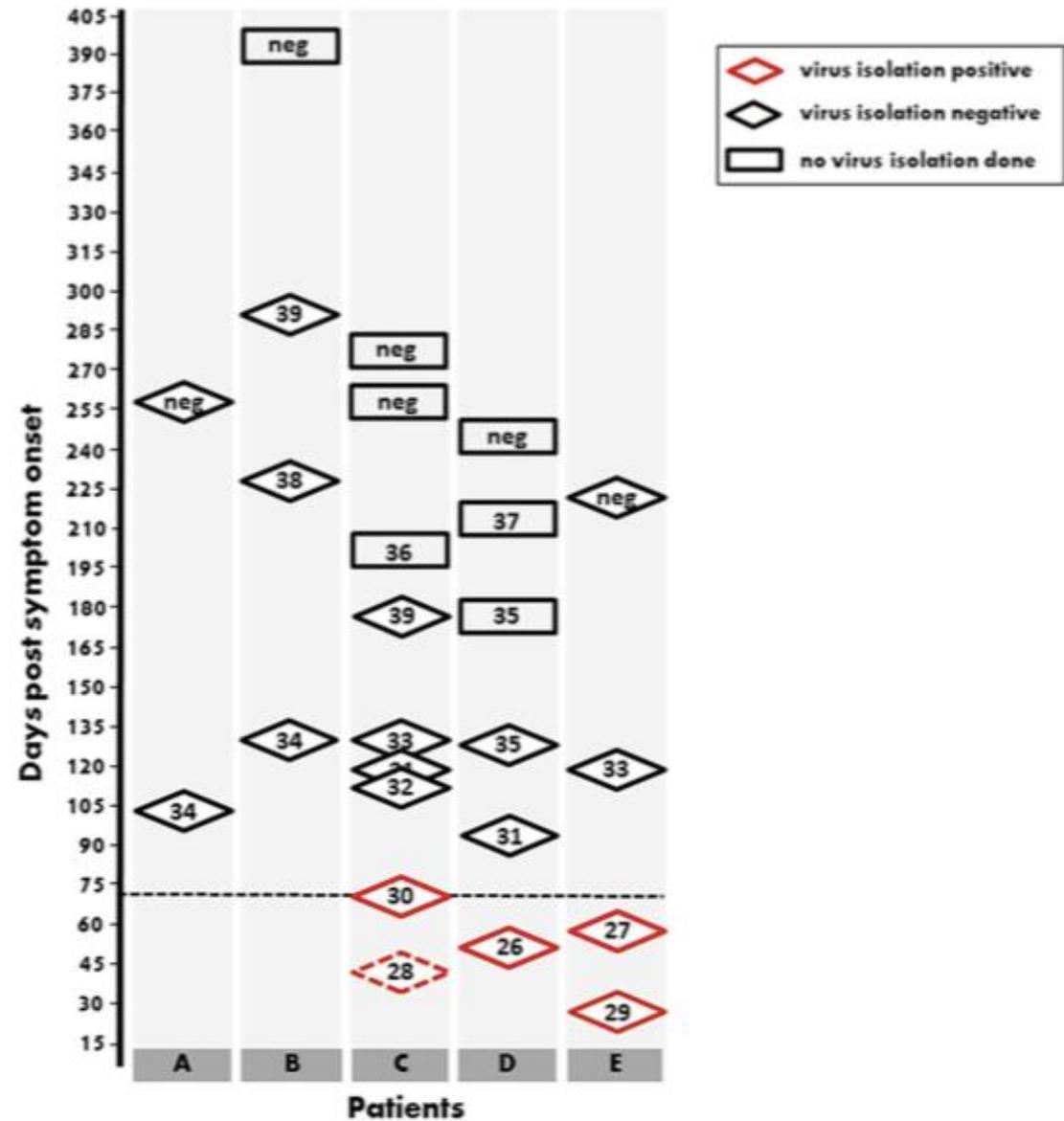
G.F. Deen, B. Knust, N. Broutet, F.R. Sesay, P. Formenty, C. Ross, A.E. Thorson, T.A. Massaquoi, J.E. Marrinan, E. Ervin, A. Jambai, S.L.R. McDonald, K. Bernstein, A.H. Wurie, M.S. Dumbuya, N. Abad, B. Idriss, T. Wi, S.D. Bennett, T. Davies, F.K. Ebrahim, E. Meites, D. Naidoo, S. Smith, A. Banerjee, B.R. Erickson, A. Brault, K.N. Durski, J. Winter, T. Sealy, S.T. Nichol, M. Lamunu, U. Ströher, O. Morgan, and F. Sahr

Ebola virus infection can relapse from a reservoir site

- Relapsed with meningoencephalitis 9 months after being discharged
- PCR positive at a low Ct in the CSF (23.7), and also in the plasma (31.3)
- Treated with GS-5743, steroids, supportive care and recovered
- Had Ebola virus-specific antibodies detected after her initial illness in January of 2015
- No changes in the coding region of the virus to suggest immune escape



Ebola virus disease is present longer than originally thought in semen



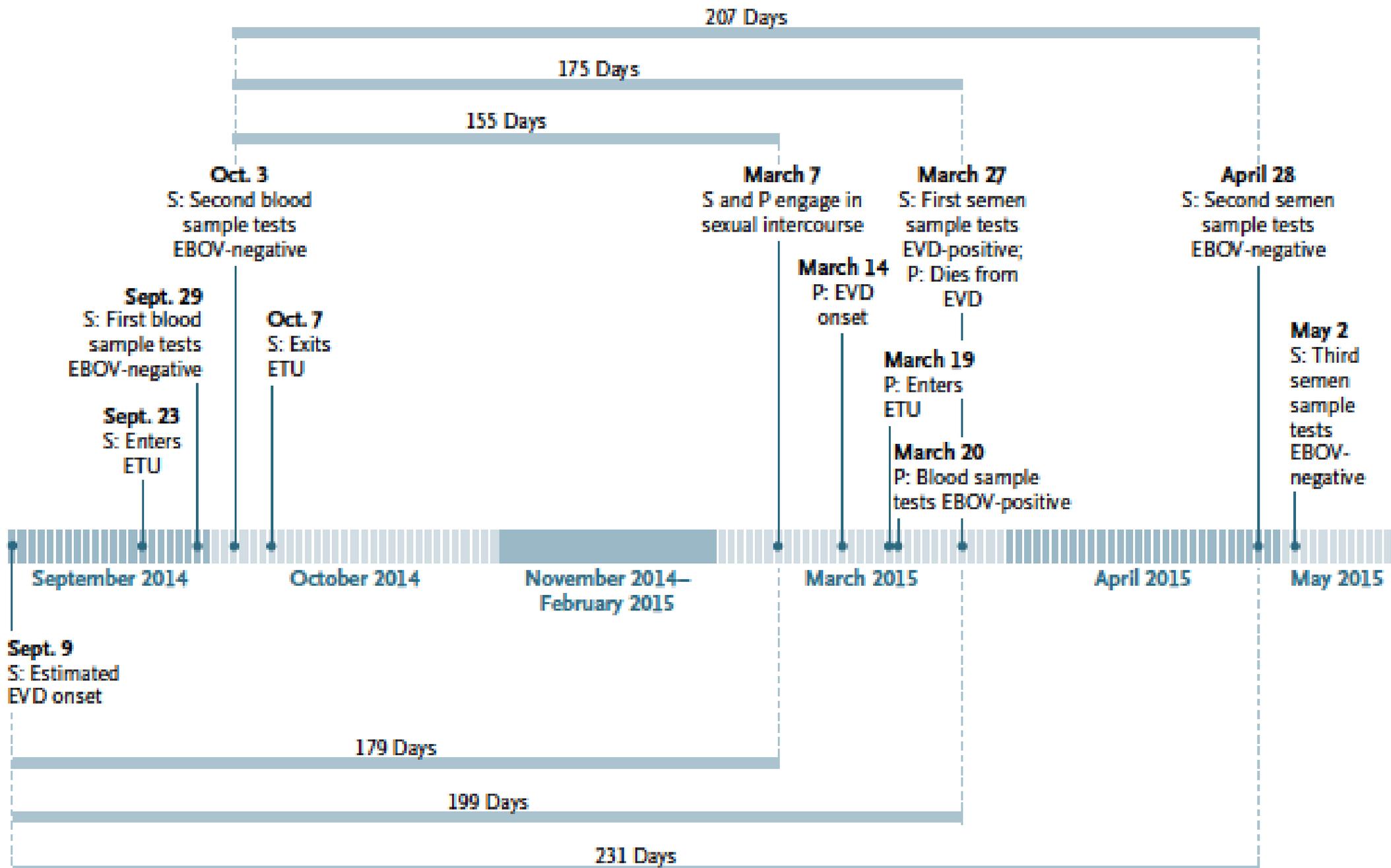
BRIEF REPORT

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



Days since Estimated Date of EVD Onset in S

Persistence of Ebola virus after the end of widespread transmission in Liberia: an outbreak report



Emily Kainne Dokubo, Annika Wendland*, Suzanne E Mate*, Jason T Ladner*, Esther L Hamblion, Philomena Raftery, David J Blackley, A Scott Laney, Nuha Mahmoud, Gloria Wayne-Davies, Lisa Hensley, Eric Stavale, Lawrence Fakoli, Christopher Gregory, Tai-Ho Chen, Augustine Koryon, Denise Roth Allen, Jennifer Mann, Andrew Hickey, John Saindon, Mehboob Badini, April Baller, Peter Clement, Fatorma Bolay, Yatta Wapoe, Michael R Wiley, James Logue, Bonnie Dighero-Kemp, Elizabeth Higgs, Alex Gasasira, Desmond E Williams, Bernice Dahn, Francis Kateh, Tolbert Nyenswah, Gustavo Palacios†, Mosoka P Fallah†*

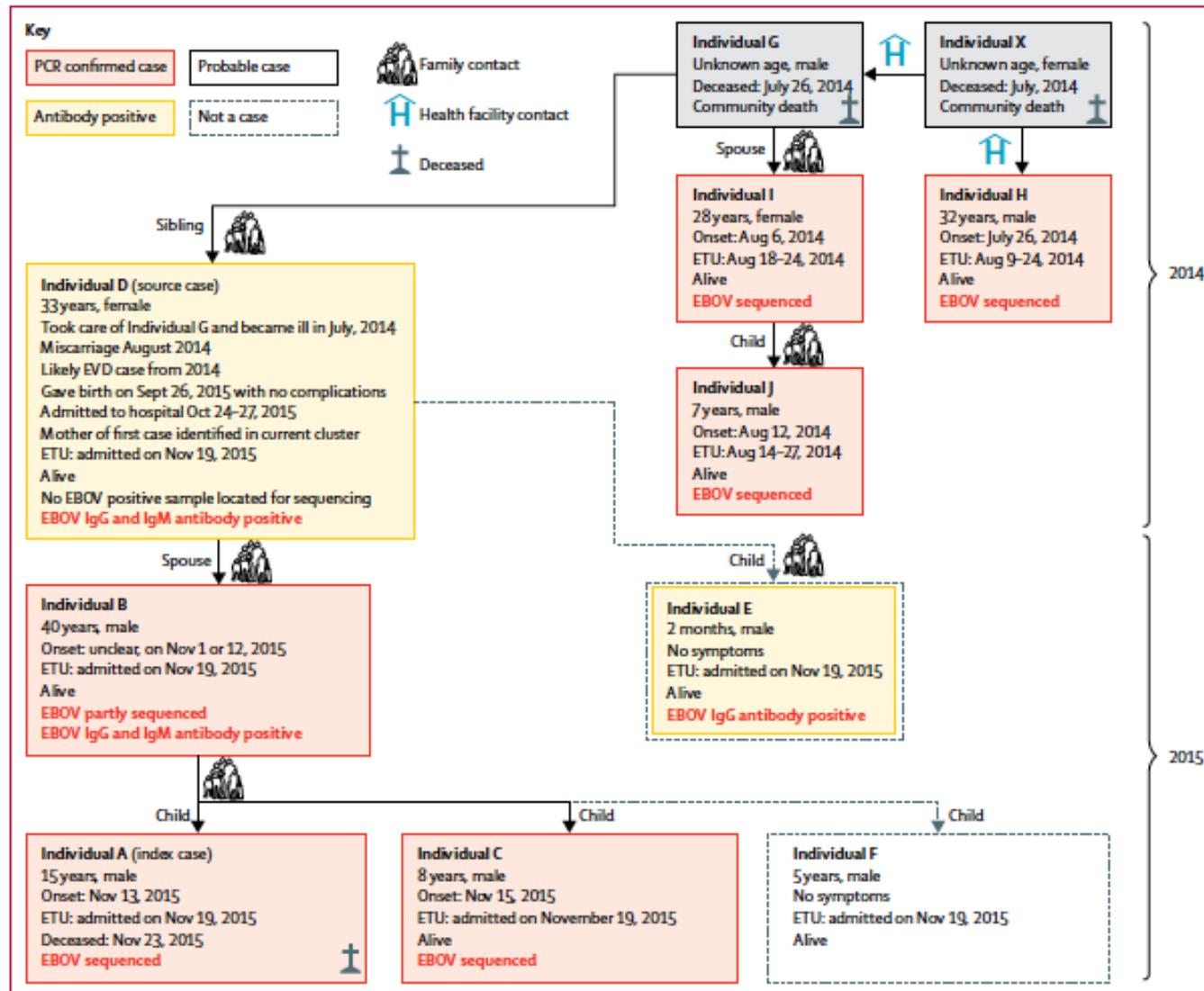
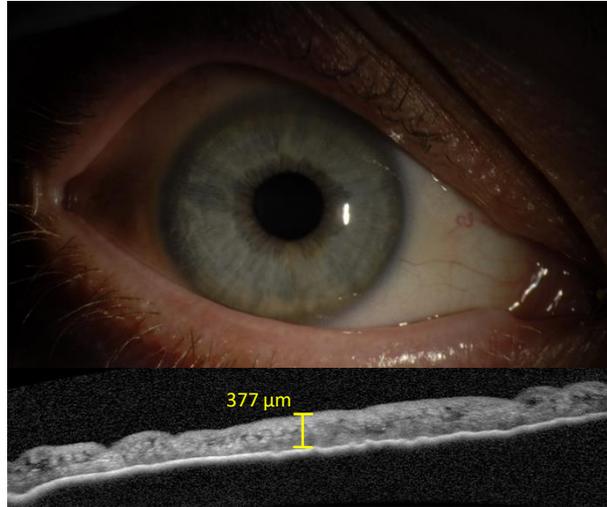


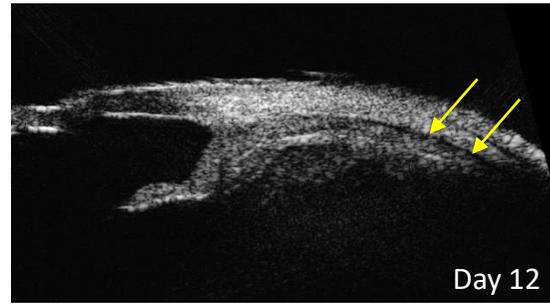
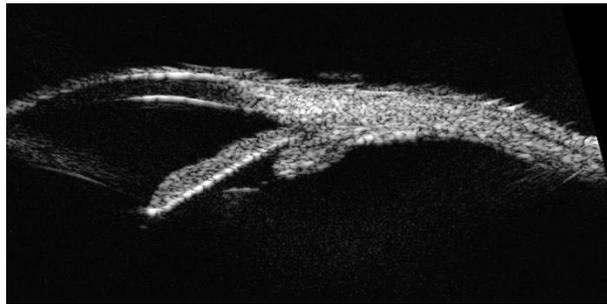
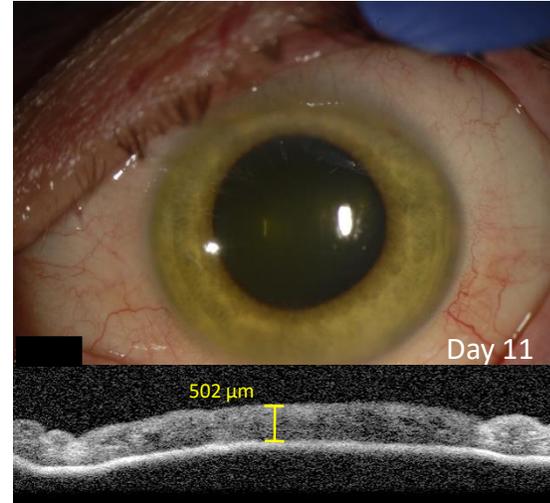
Figure 1: Transmission chain for Ebola cluster (November, 2015)
 EBOV-Ebola virus. ETU-Ebola treatment unit. EVD-Ebola virus disease.

Panuveitis with Iris Heterochromia

Right eye



Left Eye



Treatment Summary

- Oral favipiravir (eIND to FDA)
- Periocular corticosteroid
- Topical corticosteroid
- Oral prednisone taper

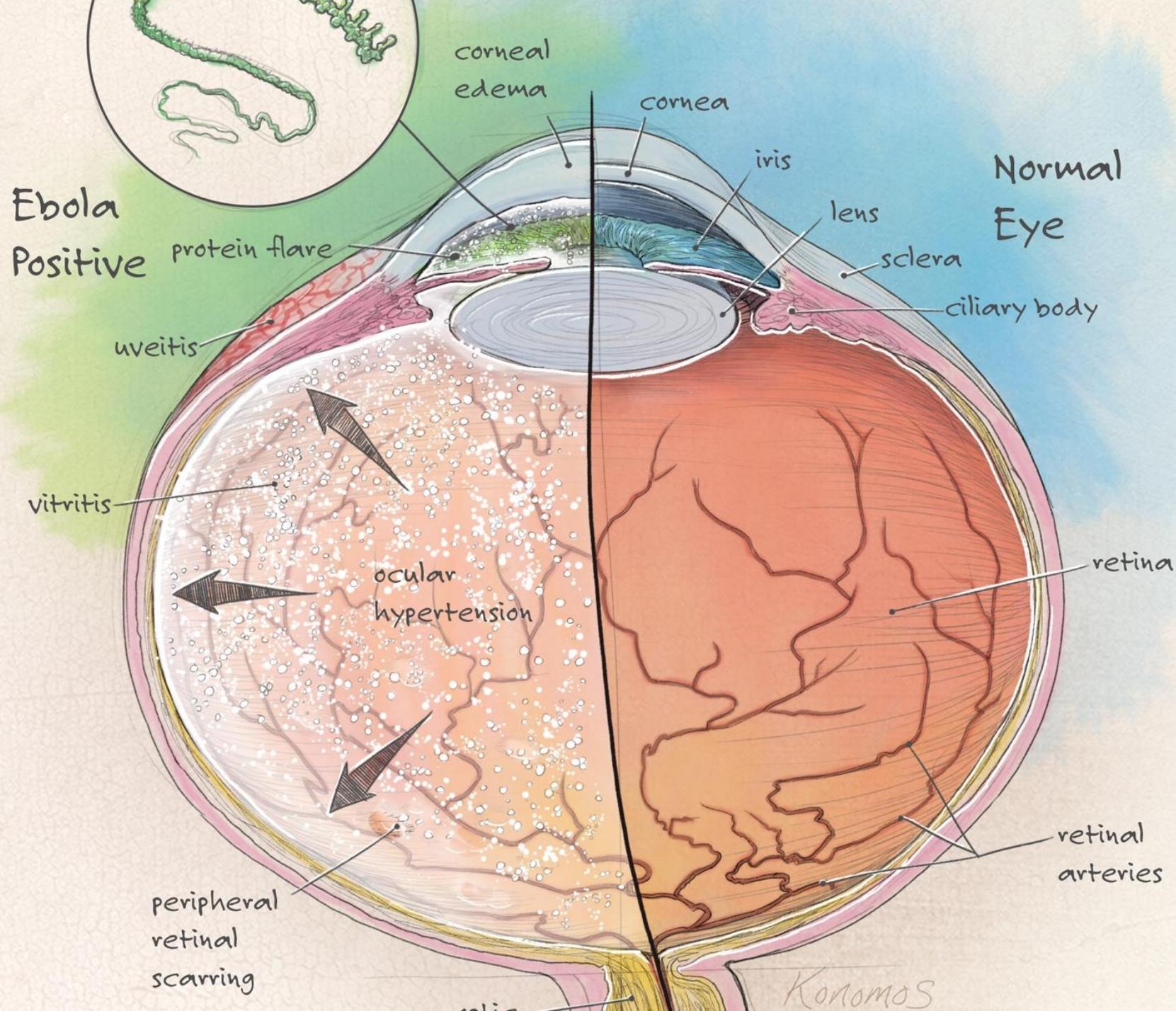
Eye manifestations

- Described after 1995 outbreak in DRC
- Post-Ebola syndrome now recognized after this large scale outbreak
- Out of 277 survivors in Sierra Leone who underwent ophthalmologic screening, 18% with uveitis

	Number of survivors (%)
Arthralgias (symptom onset during ETU or after discharge)	210 (76%)
Any auditory symptoms (tinnitus, aural fullness, hearing loss) that started during ETU or after discharge	67 (24%)
Ocular symptoms (onset during ETU or after discharge)	167 (60%)
Blurry vision	104 (38%)
Light sensitivity	86 (31%)
Itchy eye	86 (31%)
Tearing	79 (29%)
Pain	72 (26%)
Foreign body sensation	68 (25%)
Floaters	46 (17%)
Redness	46 (17%)
Flashes of light	43 (16%)
Dry eye	39 (14%)
Burning sensation	29 (10%)
Loss of vision	7 (3%)
Uveitis diagnosed on slit-lamp and dilated fundoscopic examination* (68 eyes involved among 50 patients)	50 (18%)
Anterior uveitis	31 (46%)
Posterior uveitis	18 (26%)
Intermediate uveitis	2 (3%)
Panuveitis	17 (25%)

ETU=Ebola treatment unit. *A patient could have more than one type of uveitis if both eyes were involved.

Table 2: Ebola virus disease sequelae at first convalescent clinic visit in 277 survivors





Research Paper

Ebola Virus Persistence in Ocular Tissues and Fluids (EVICT) Study: Reverse Transcription-Polymerase Chain Reaction and Cataract Surgery Outcomes of Ebola Survivors in Sierra Leone[☆]

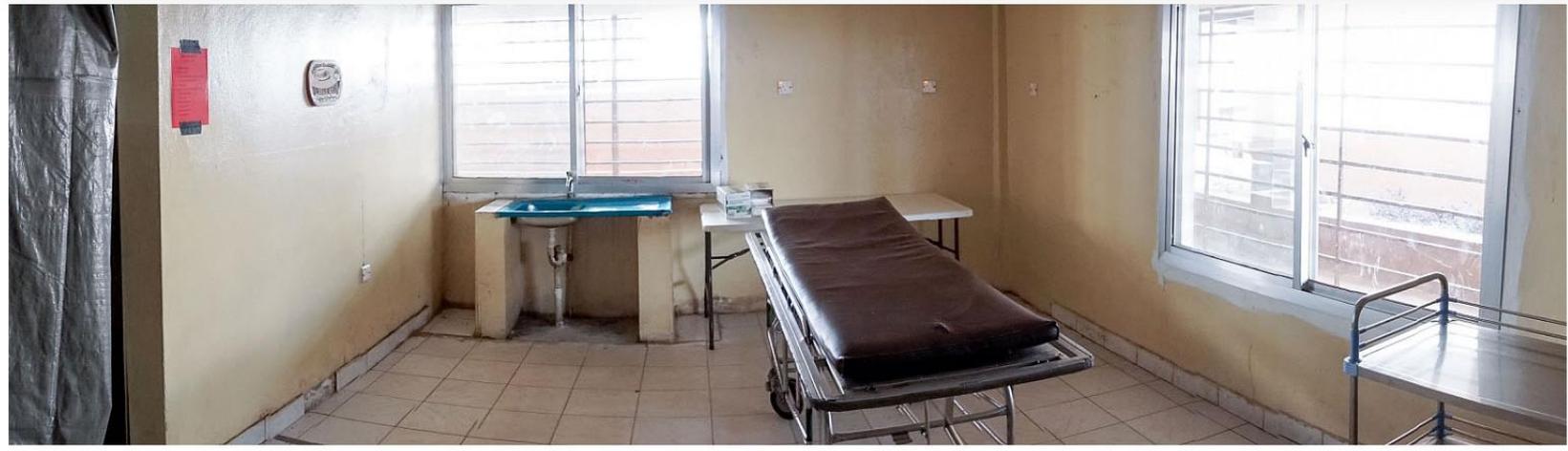


Jessica G. Shantha^{a,b}, John G. Mattia^{c,1}, Augustine Goba^d, Kayla G. Barnes^{e,f}, Faiqa K. Ebrahim^g, Colleen S. Kraft^h, Brent R. Hayek^a, Jessica N. Hartnettⁱ, Jeffrey G. Shaffer^j, John S. Schieffelinⁱ, John D. Sandi^d, Mambu Momoh^d, Simbirie Jalloh^d, Donald S. Grant^{d,y}, Kerry Dierberg^k, Joyce Chang^k, Sharmistha Mishra^l, Adrienne K. Chan^l, Rob Fowler^l, Tim O'Dempsey^m, Erick Kalumaⁿ, Taylor Hendricksⁿ, Roger Reiners^o, Melanie Reiners^o, Lowell A. Gess^o, Kwame O'Neill^p, Sarian Kamara^p, Alie Wurie^p, Mohamed Mansaray^q, Nisha R. Acharya^b, William J. Liu^r, Sina Bavari^s, Gustavo Palacios^s, Moges Teshome^{o,t}, Ian Crozier^u, Paul E. Farmer^k, Timothy M. Uyeki^v, Daniel G. Bausch^w, Robert F. Garryⁱ, Matthew J. Vandy^{p,1}, Steven Yeh^{a,x,*}

^a Emory Eye Center, Emory University School of Medicine, Atlanta, GA, United States

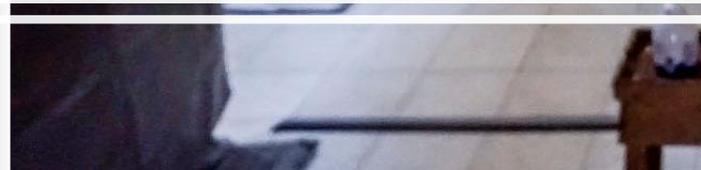
^b University of California San Francisco, Proctor Foundation, San Francisco, CA, United States

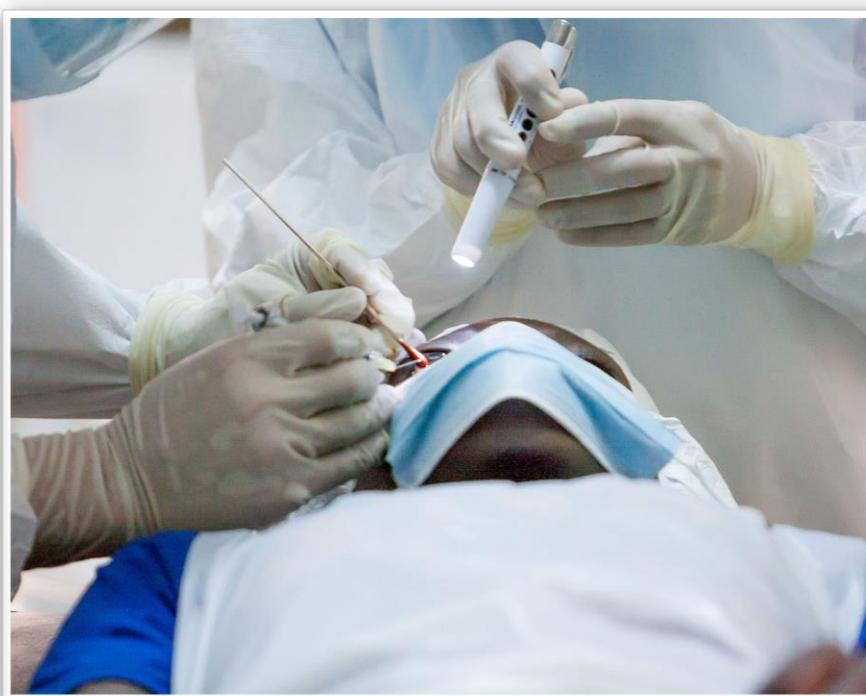
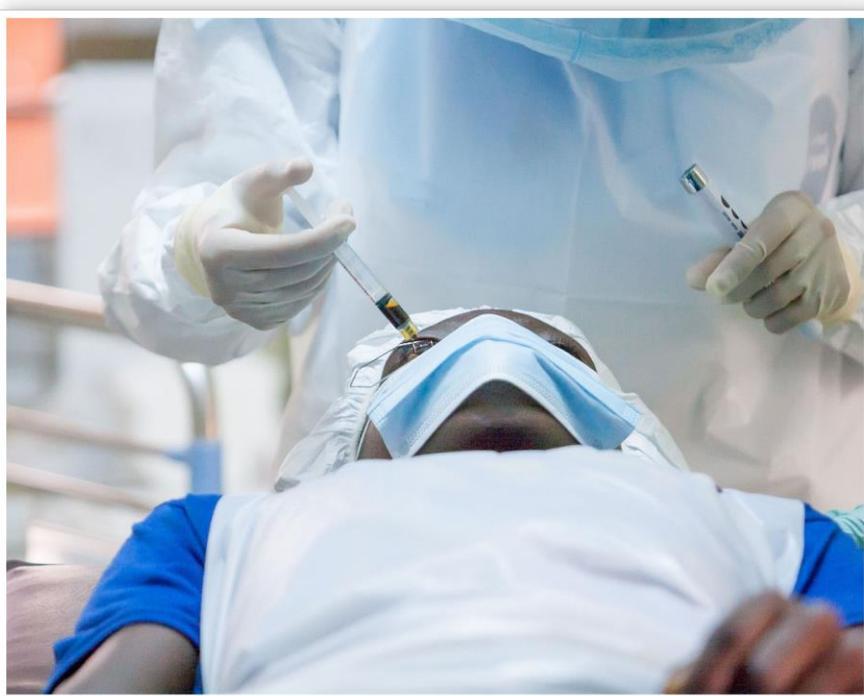
^c Lunsar Baptist Eye Hospital, Port Loko, Sierra Leone



Recapitulating unidirectional flow in Sierra Leone

1. Approach red line
2. Remove apron
3. Remove one boot and step into chemical
4. Remove outer gloves (breaking seal)
5. Sanitize hands
6. Remove tape
7. Remove tape
8. Sanitize inner gloves
9. Remove coverall
10. Sanitize inner gloves
11. Enter anteroom





Human Factors Risk Analyses of a Doffing Protocol for Ebola-Level Personal Protective Equipment: Mapping Errors to Contamination

Joel M. Mumma,¹ Francis T. Durso,¹ Ashley N. Ferguson,¹ Christina L. Gipson,¹ Lisa Casanova,² Kimberly Erukunuakpor,² Colleen S. Kraft,^{3,4} Victoria L. Walsh,³ Craig Zimring,⁵ Jennifer DuBose,⁵ and Jesse T. Jacob,⁵ for the CDC Prevention Epicenters Program, Division of Healthcare Quality Promotion

¹School of Psychology, Georgia Institute of Technology, ²School of Public Health, Georgia State University, ³Division of Infectious Diseases, Department of Medicine, Emory University School of Medicine, ⁴Department of Pathology and Laboratory Medicine, Emory University, and ⁵School of Architecture, Georgia Institute of Technology, Atlanta

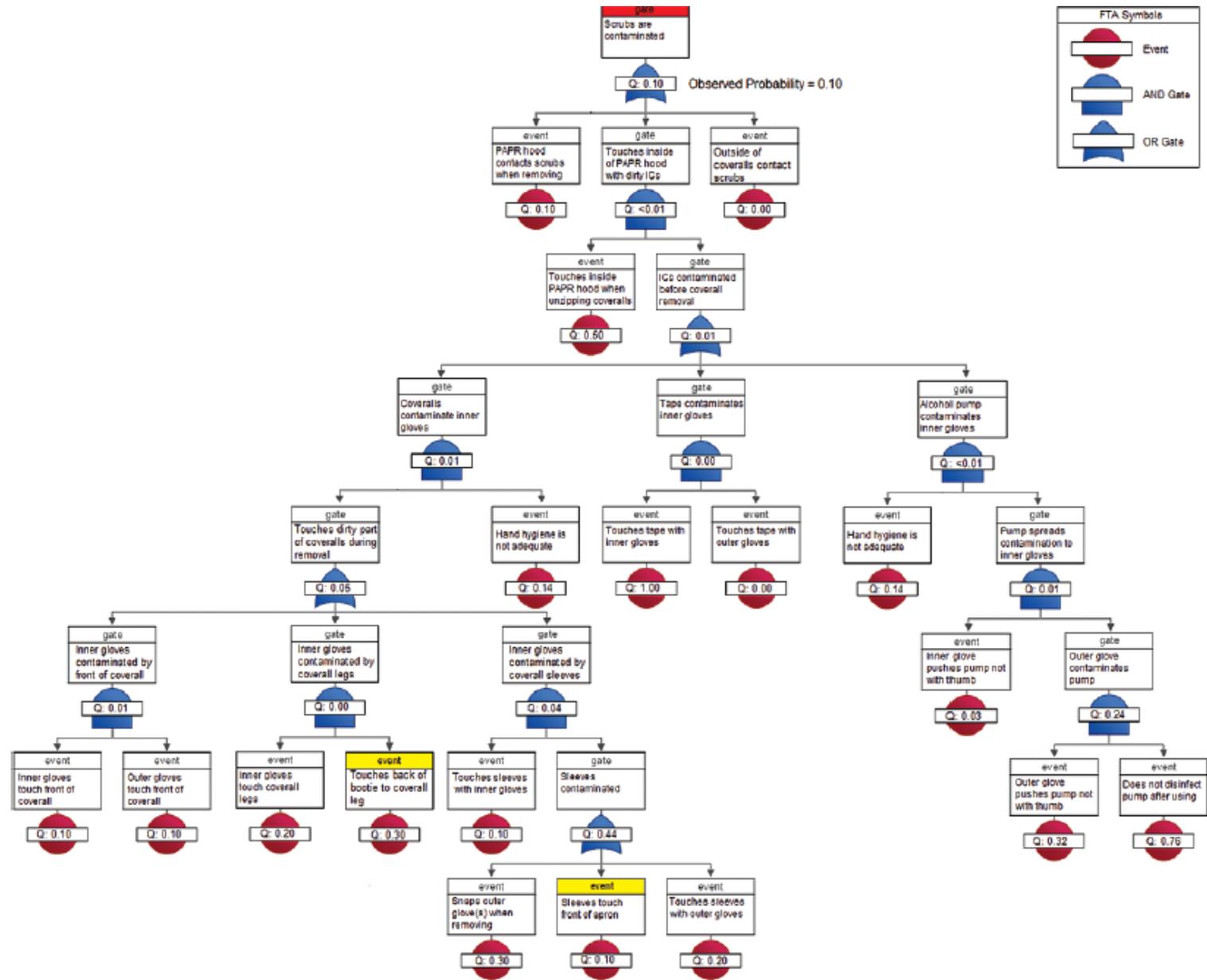
Assessing Viral Transfer During Doffing of Ebola-Level Personal Protective Equipment in a Biocontainment Unit

Lisa M. Casanova,¹ Kimberly Erukunuakpor,¹ Colleen S. Kraft,² Joel M. Mumma,³ Francis T. Durso,³ Ashley N. Ferguson,³ Christina L. Gipson,³ Victoria L. Walsh,⁴ Craig Zimring,⁵ Jennifer DuBose,⁵ and Jesse T. Jacob,⁴ for the Centers for Disease Control and Prevention Epicenters Program, Division of Healthcare Quality Promotion

¹Division of Environmental Health, School of Public Health, Georgia State University, ²Department of Pathology and Laboratory Medicine, Emory University, ³School of Psychology, Georgia Institute of Technology, ⁴Division of Infectious Diseases, Department of Medicine, Emory University School of Medicine, and ⁵School of Architecture, Georgia Institute of Technology, Atlanta

Study to evaluate errors in doffing

Failure Modes Effect Analysis

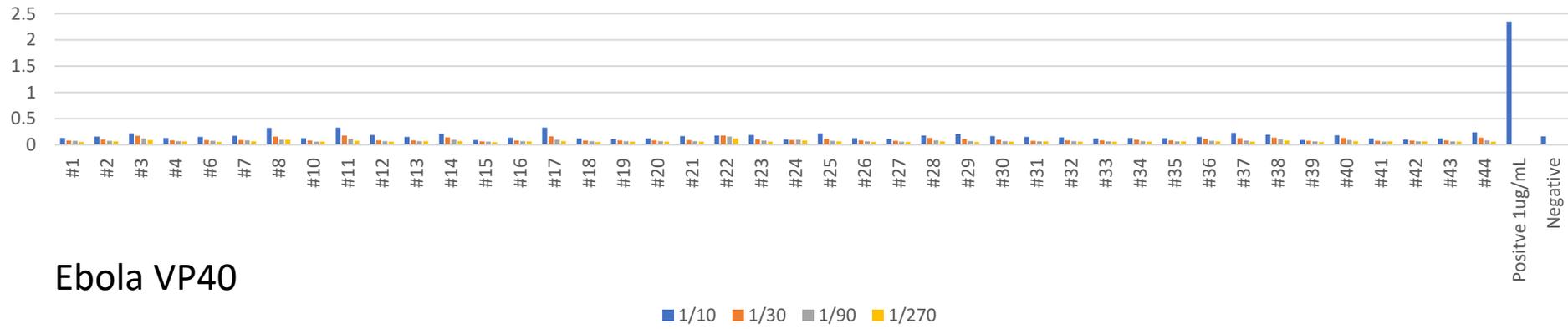
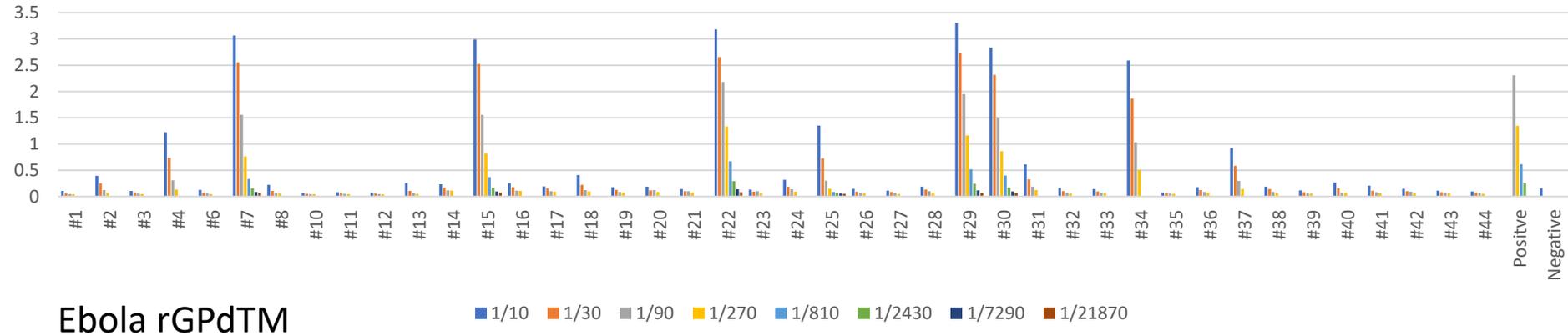


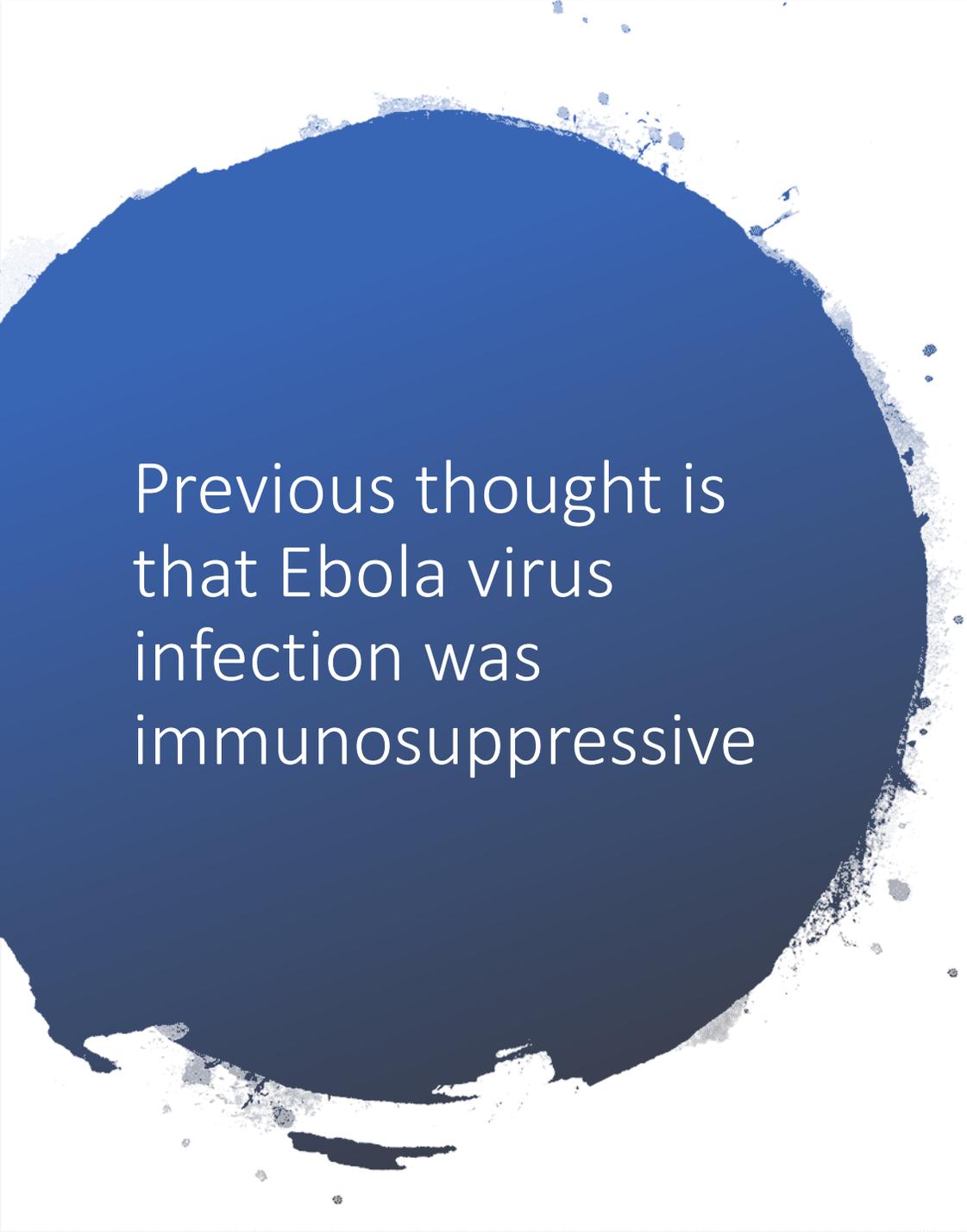
Massachusetts General Hospital ■ Providence Health & Services ■ Emory Medicine ■ Johns Hopkins Medicine
Denver Health ■ University of Nebraska Medical Center ■ UTMB Health ■ University of Minnesota
Cedars-Sinai Medical Center ■ NYC Health + Hospitals/Bellevue
Hospitals/Bellevue



*Alone we can do so little...
together we can do so much.*
—HELEN KELLER

Serology study – healthcare workers





Previous thought is
that Ebola virus
infection was
immunosuppressive

Ebola virus infected dendritic cells were impaired in their ability to produce cytokines and activate T cells

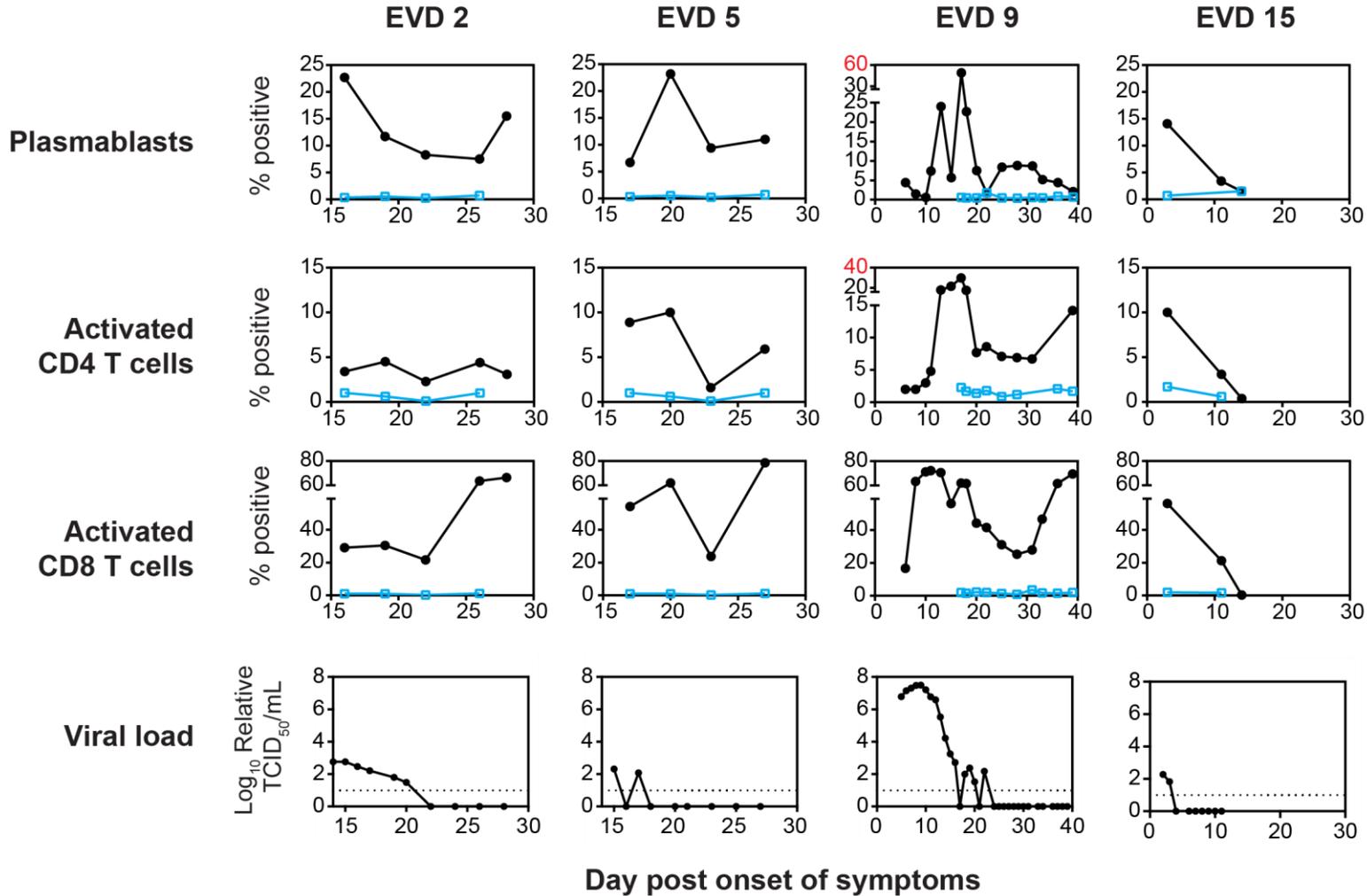
Infected macrophages exhibit impaired maturation

Ebola virus encodes proteins that interfere with the innate immune response

Clinical observations demonstrated T-cell apoptosis, lymphopenia and absent antibody responses in fatal cases

Immune response during acute Ebola infection

EVD patient **Healthy control**



EVD 2,5 and 9 - 16 days post onset
EVD 15 – 3 days post onset



THE LANCET

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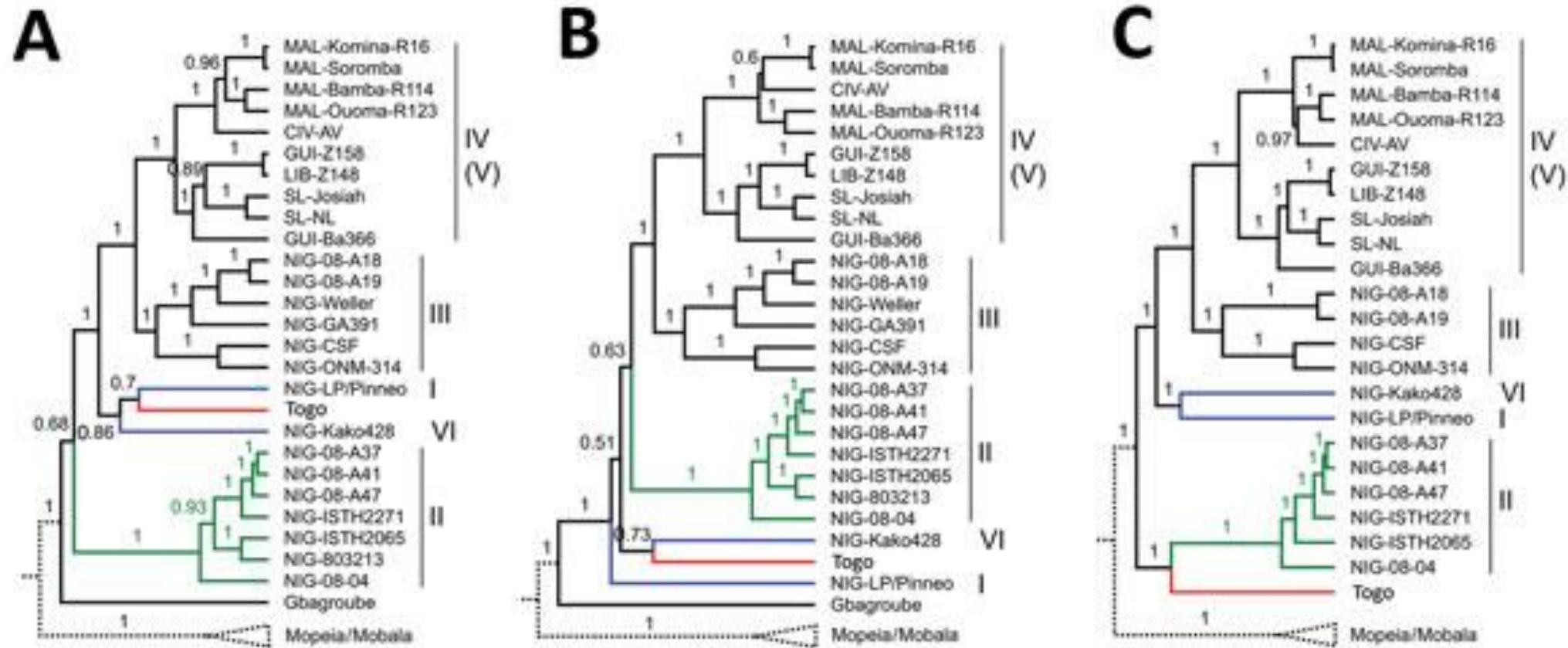
Articles

Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial

Ana Maria Henao-Restrepo, MD^a, Prof Ira M Longini, PhD^b, Prof Matthias Egger, MD^{c, e}, Natalie E Dean, PhD^b, Prof W John Edmunds, PhD^f, Anton Camacho, PhD^f, Miles W Carroll, PhD^{g, h}, Moussa Doumbia, MD^j, Bertrand Draguez, MD^k, Sophie Duraffour, PhD^h, Godwin Enwere, FWACP^a, Rebecca Grais, PhD^l, Stephan Gunther, MD^j, Stefanie Hossmann, MSc^d, Prof Mandy Kader Kondé, PhD^m, Souleymane Kone, MSc^a, Eeva Kuisma, PhD^{g, h}, Prof Myron M Levine, MDⁿ, Sema Mandal, MD^o, Gunnstein Norheim, PhD^p, Ximena Riveros, BSc^a, Aboubacar Soumah, MD^j, Sven Trelle, MD^d, Andrea S Vicari, PhD^a, Conall H Watson, MFPH^f, Sakoba Kéïta, MD^r, Dr Marie Paule Kieny, PhD^{a, †}  , Prof John-Arne Røttingen, MD^{q, s, †}

Available online 3 August 2015

New Lassa strain from Togo



Ebola in 2018



WE ARE INTERNATIONALLY
MORE ATTENTIVE TO
REGIONAL OUTBREAKS



THERAPEUTICS ARE DEPLOYED
MUCH SOONER



EXPERIMENTAL THERAPIES
STILL REQUIRE ADDITIONAL
STUDIES DUE TO NOT
REACHING STATISTICAL
SIGNIFICANCE



AWARENESS OF VIRAL
PERSISTENCE IN IMMUNE
PRIVILEGED SITES, AND
TRANSMISSION FROM THESE
SITES



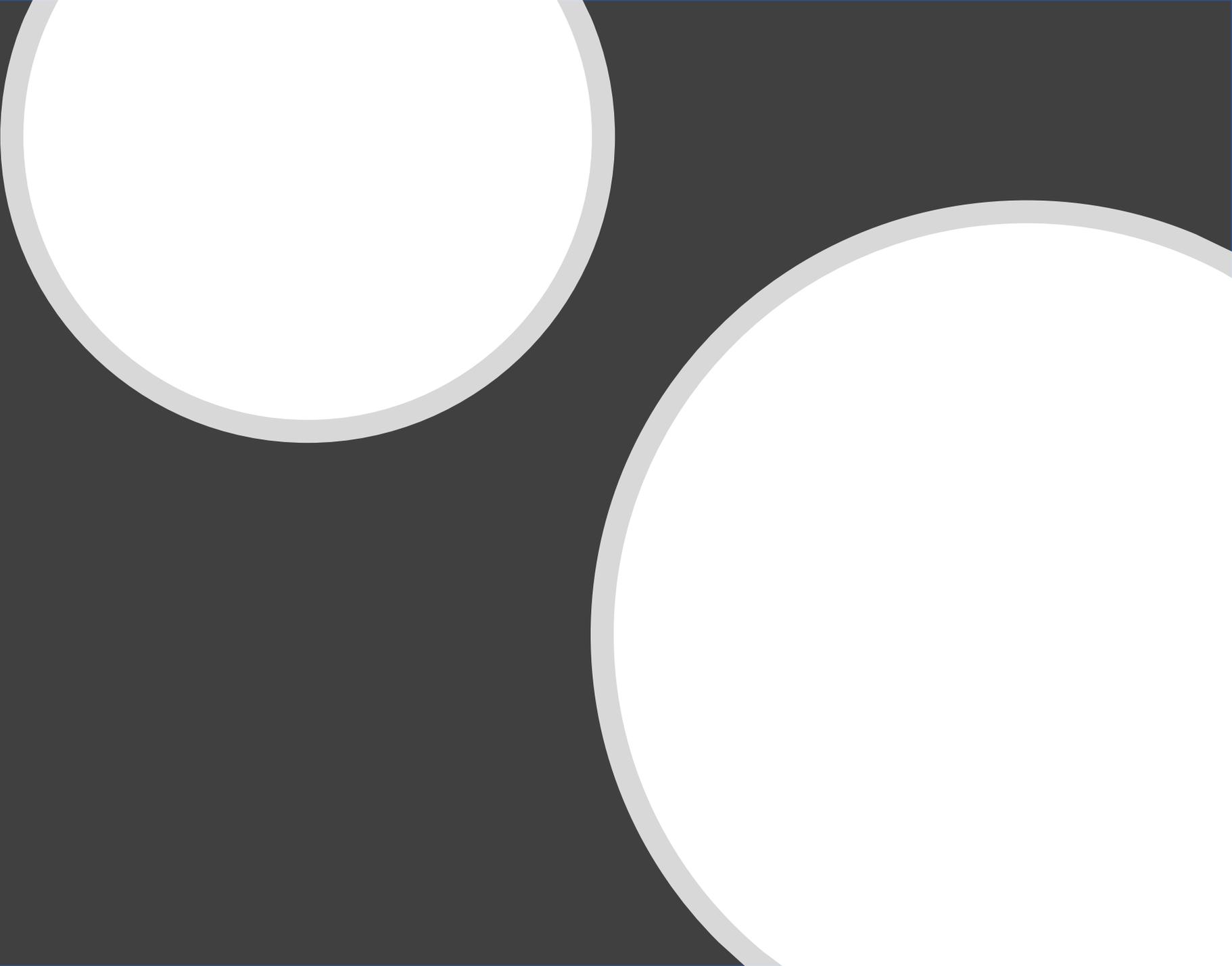
VACCINATION WITH VSV
VACCINE A PROMISE FOR
FUTURE OUTBREAKS

Huge thanks to our very active team

- Nursing
- Pharmacy
- Health and Safety
- Infection Prevention
- Environmental Services
- Emory Medical Laboratories
- Occupational Health
- Administration
- Media Relations
- Pastoral Care
- Faculty and Staff Assistance
- Supplies/Logistics
- Emory Security
- Emory Critical Care
- Emergency Medicine
- Emory CEPAR
- Nephrology

Funding

- CDC, “Clinical Care for Individuals Referred by CDC for Medical Examination and/or Hospitalization,” RFP 2015-N-17184
- ASPR, “National Ebola Training and Education Center”, 1U3REP150549-01-00
- Hospital Preparedness Program
- CDC/NIOSH: 75D30118C02645, Elastomeric respirator feasibility and effectiveness for healthcare worker training



Questions?

