Ebola Virus Disease: 2019 and Beyond

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Is Ebola Virus Disease still relevant?

- 8 May 2018, WHO reported an Ebola virus disease outbreak in DRC’s Equateur Province. There were 54 cases (38 confirmed and 16 probable), and the outbreak was declared over on 24 July 2018 (33 deaths, 61% CFR).

- 1 August 2018, an outbreak of Ebola virus disease was confirmed in North-Kivu Province, Democratic Republic of Congo (DRC). As of 19 Feb 2019, a total of 996 cases (745 confirmed and 61 probable) including 505 deaths, have been reported.
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<br>Sierra Leone: Stopped after three patients<br>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<br>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

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

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

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

INCUBATION
Virus invades cells throughout the body and replicates

EARLY SYMPTOMS
8-12 days after exposure, patient develops fever, chills, fatigue, muscle pain, weakness, and becomes contagious

EXPOSURE
Virus enters through nose, mouth, eyes, ears, breaks in skin

SYMPTOMS WORSEN
Around 2 weeks after exposure, patients develop diarrhea, vomiting, abdominal pain, rash, red eyes, bleeding

SPREAD
In the W. African outbreak each person with Ebola infects 1.7 - 2 others

Ebola patients are most contagious at and near death

Survivors (30% in 2014) improve after ≈ 6 days of symptoms

DEATH
6-16 days after symptoms begin (avg 7.5 in 2014), damage to blood vessels causes drop in blood pressure and organ failure

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 $\Rightarrow$ 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 $\Rightarrow$ 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
• 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
Sexual transmission

Viral persistence

Subclinical disease
Organs of persistence

Central nervous system

Seminal fluid

Placenta

Eye – aqueous/vitreous
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.
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. Schoepf, 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
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 Hamblian, 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

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

| Symptom                                | 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* (58 eyes involved among 59 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

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Recapitulating unidirectional flow in Sierra Leone
Study to evaluate errors in doffing
Alone we can do so little... together we can do so much.

—HELEN KELLER
Serology study – healthcare workers

Ebola rGPdTM

Ebola VP40
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 2, 5, and 9 - 16 days post onset
EVD 15 - 3 days post onset

McElroy et al, PNAS, 2015
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, Prof Ira M Longini, PhD, Prof Matthias Egger, MD, Natalie E Dean, PhD, Prof W John Edmunds, PhD, Anton Camacho, PhD, Miles W Carroll, PhD, Moussa Doumbia, MD, Bertrand Draguez, MD, Sophie Duraffour, PhD, Godwin Enwere, FWACP, Rebecca Grais, PhD, Stephan Gunther, MD, Stefanie Hossmann, MSc, Prof Mandy Kader Kondé, PhD, Souleymane Kone, MSc, Eeva Kuiska, PhD, Prof Myron M Levine, MD, Serra Mandal, MD, Gunnstein Norheim, PhD, Ximena Riveros, BSc, Aboubacar Soumah, MD, Svend Trelle, MD, Andrea S Vicari, PhD, Conall H Watson, MFPH, Sakoba Kéita, MD, Dr Marie Paule Kiény, PhD. Prof John-Arne Rettingen, MD

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?
