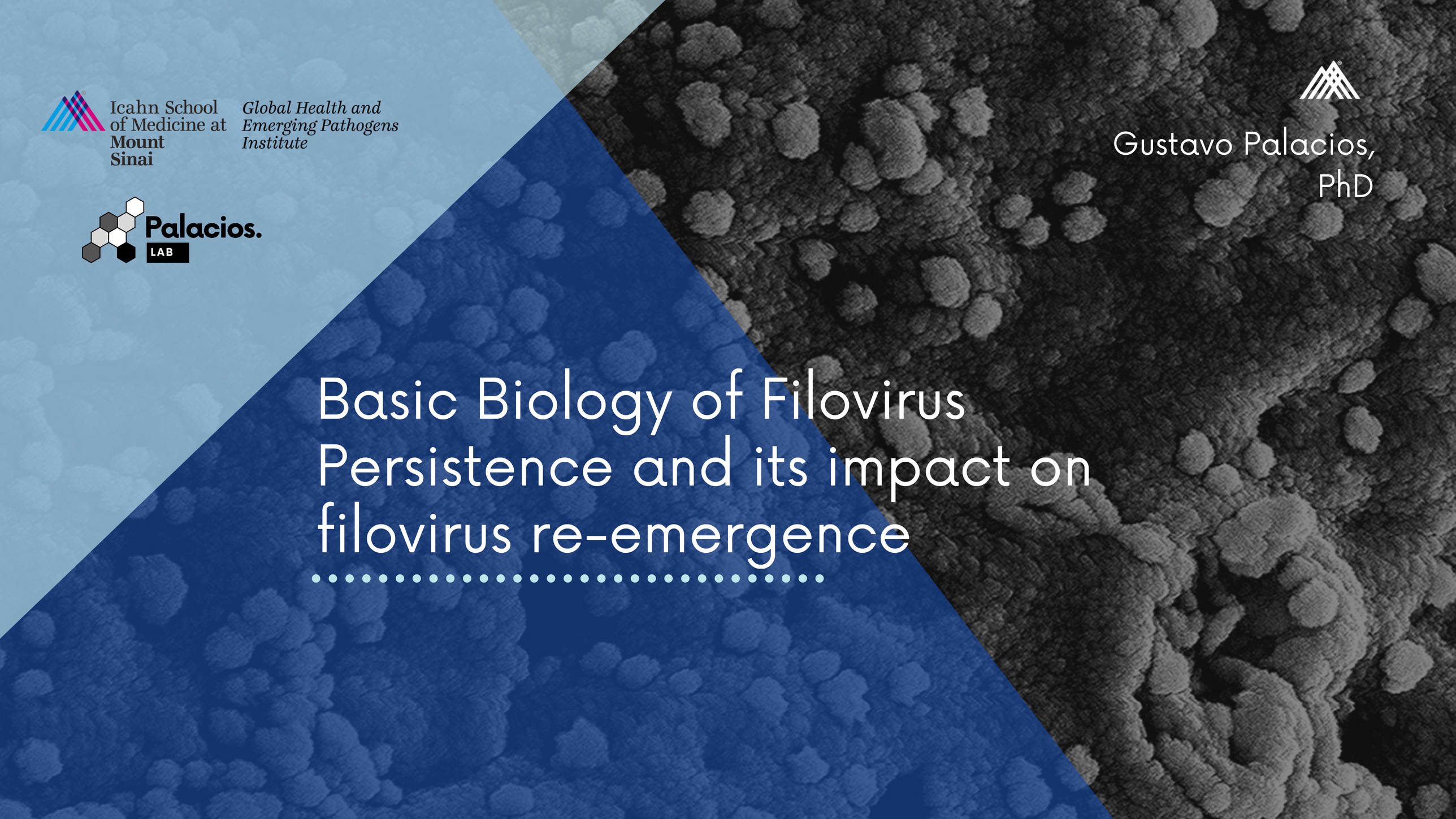

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Gustavo Palacios, PhD

Basic Biology of Filovirus Persistence and its impact on filovirus re-emergence

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Historical Background Ebolavirus

- EBOV discovered in 1976.
- Only latest outbreak resulted in enough EVD survivors to study EVD sequelae.
- The presence of EBOV RNA and, rarely, infectious virus during convalescence had been documented previously as early as 1976.
- EBOV genomic RNA was detected in seminal fluid of survivors of a 1995 EVD outbreak with successful EBOV isolation from a single sample.
- In addition to scarce human data, no indication of EBOV persistence was collected in the almost universally lethal EVD animal models used for medical countermeasure development.
- Identifying the immune-privileged sites that harbor EBOV and the molecular mechanisms governing persistence within and transmission from people are essential for improved containment of future outbreaks.

Martini et al., 1968. Klin Wochenschr
Kuming and Kokoris, 1977. Br J Ophthalmol
Bausch et al., 2007. J Infect Dis
Rodriguez et al., 1995. J Infect Dis
Rowe et al., 1999. J Infect Dis

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MARTINI ET AL., 1968. KLIN WOCHENSCHR
Kuming and Kokoris, 1977. Br J Ophthalmol
Bausch et al., 2007. J Infect Dis
Rodriguez et al., 1995. J Infect Dis
Rowe et al., 1999. J Infect Dis

Other filoviruses:

- The first report of sex transmission of MARV from an MVD survivor to his wife in 1967.
- MARV was isolated from the aqueous fluid of the eye of a 1975 MVD survivor with uveitis.
- MVD recurred in a previous MVD survivor in 1991
- SUDV was isolated from seminal fluid of an EVD survivor in 1977 and from seminal fluid and breast milk of two survivors in 2000.

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March 24, 2015

The New York Times | http://nyti.ms/1DWHRcp

AFRICA

Exposure Concerns Grow in Liberia After Diagnosis of First Ebola Case in Weeks

By SHERI FINK MARCH 24, 2015

Worries have widened in recent days over the number of people in Liberia who may have been exposed to the country's first Ebola case in more than two weeks, a street vendor who lived in a one-bathroom house shared with 52 others in a Monrovia suburb and who had sold food at a school where more than 1,900 students are enrolled.

The patient, identified as Ruth Tugbah, 44, had been in contact with a range of people, including her children and a pastor who had sought to comfort her, after she developed a fever and was contagious, aid workers said Tuesday.

Ms. Tugbah received a diagnosis of Ebola on Friday, ending a short-lived period of optimism that Liberia would be the first of three afflicted West African countries to emerge from the worst epidemic of the deadly virus in history.

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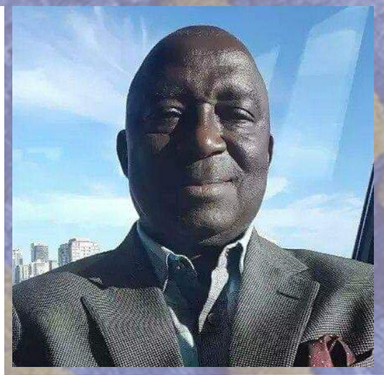
The NEW ENGLAND JOURNAL of MEDICINE

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



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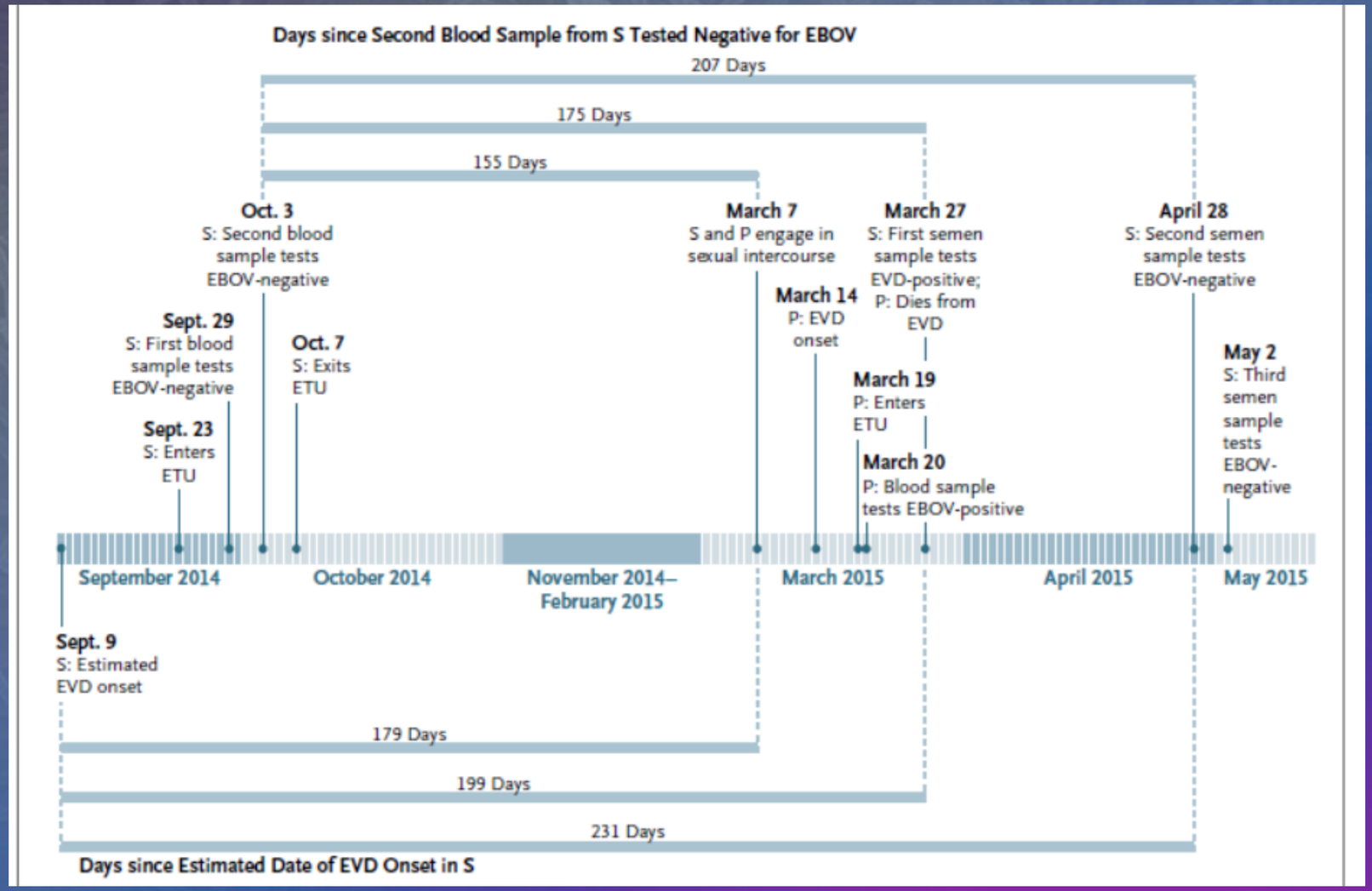
Timeline



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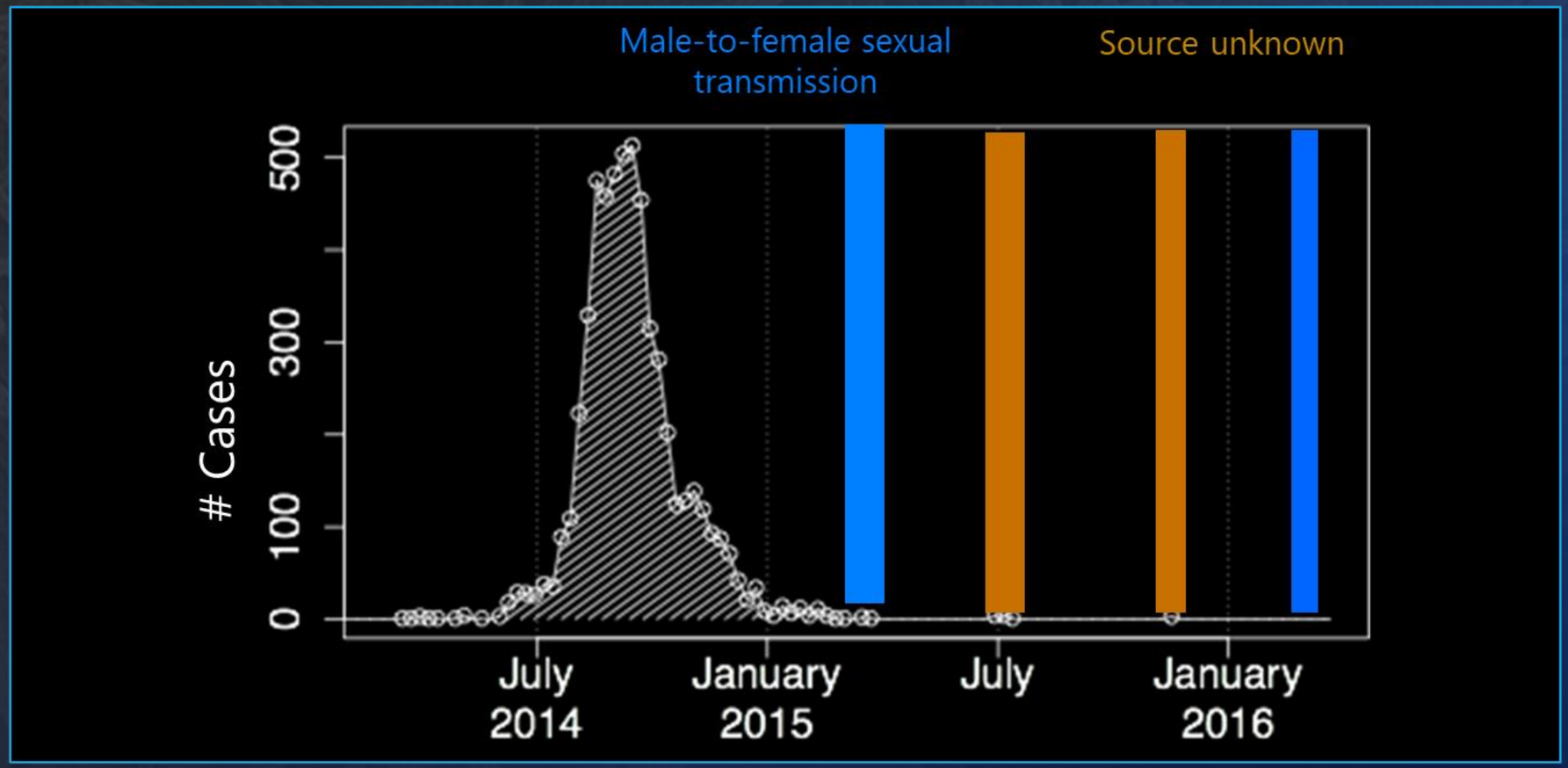
Potential for additional mechanisms to generate flare-ups



Reduced rate of evolution observed in flare-ups

Science Advances

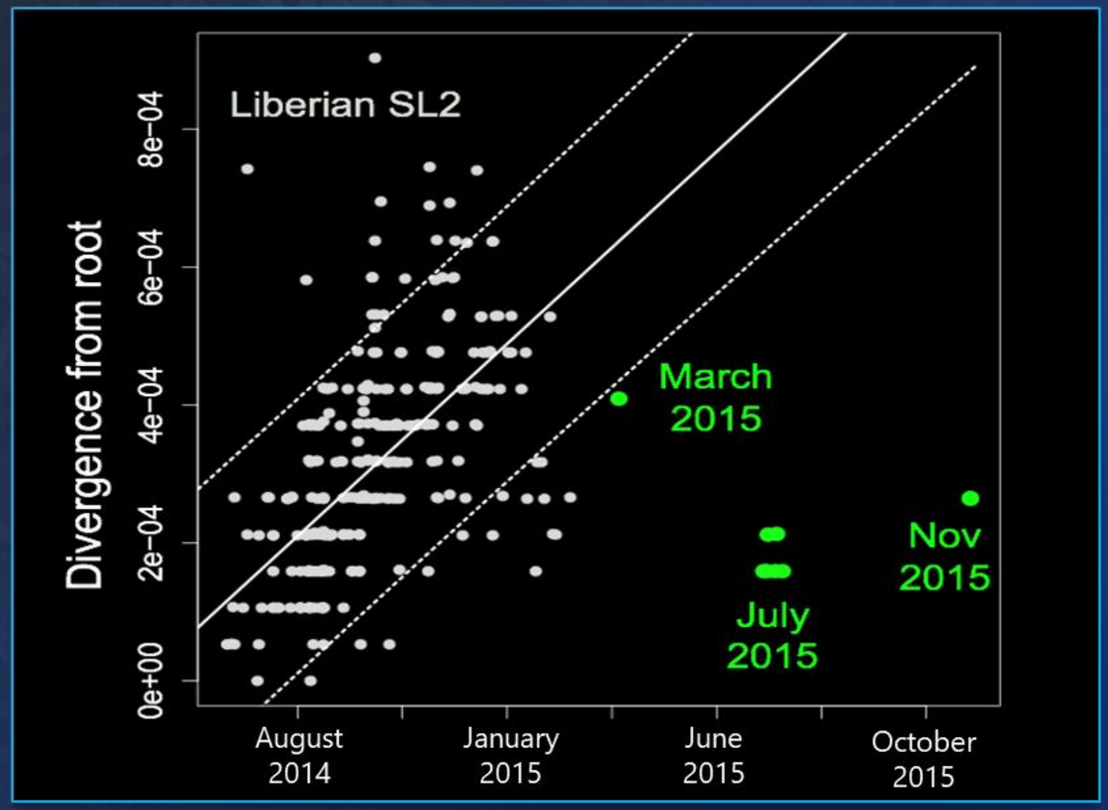
RESEARCH ARTICLE

EPIDEMIOLOGY

Reduced evolutionary rate in reemerged Ebola virus transmission chains

10.1126/sciadv.1600378

David J. Blackley,[1]* Michael R. Wiley,[2]* Jason T. Ladner,[2]* Mosoka Fallah,[3]* Terrence Lo,[1] Merle L. Gilbert,[2] Christopher Gregory,[1] Jonathan D'ambrozio,[2] Stewart Coulter,[1] Suzanne Mate,[2] Zephaniah Balogun,[1] Jeffrey Kugelman,[2] William Nwachukwu,[1] Karla Prieto,[2] Adolphus Yeiah,[3] Fred Amegashie,[3] Brian Kearney,[2] Meagan Wisniewski,[2] John Saindon,[1] Gary Schroth,[4] Lawrence Fakoli,[5] Joseph W. Diclaro II,[6] Jens H. Kuhn,[7] Lisa E. Hensley,[7] Peter B. Jahrling,[7] Ute Ströher,[1] Stuart T. Nichol,[1] Moses Massaquoi,[3] Francis Kateh,[3] Peter Clement,[8] Alex Gasasira,[8] Fatorma Bolay,[5] Stephan S. Monroe,[1] Andrew Rambaut,[9,10,11] Mariano Sanchez-Lockhart,[2] A. Scott Laney,[1] Tolbert Nyenswah,[3†] Athalia Christie,[1†] Gustavo Palacios[2†]



Ebola carriers? Why the virus keeps coming back April 29, 2016

We might now know why Ebola keeps popping up in West Africa May 1, 2016

Ebola se cache dans le corps des malades pour survivre May 18, 2016

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Impact in Vaccines and Therapeutics

BRIEF REPORT

Ebola Virus Transmission Initiated by Relapse of Systemic Ebola Virus Disease

P. Mbala-Kingebeni, C. Pratt, M. Mutafali-Ruffin, M.G. Pauthner, F. Bile, A. Nkuba-Ndaye, A. Black, E. Kinganda-Lusamaki, M. Faye, A. Aziza, M.M. Diagne, D. Mukadi, B. White, J. Hadfield, K. Gangavarapu, N. Bisento, D. Kazadi, B. Nsunda, M. Akonga, O. Tshiani, J. Misasi, A. Ploquin, V. Epaso, E. Sana-Paka, Y.T.T. N'kasar, F. Mambu, F. Edidi, M. Matondo, J. Bula Bula, B. Diallo, M. Keita, M.R.D. Belizaire, I.S. Fall, A. Yam, S. Mulangu, A.W. Rimion, E. Salfati, A. Torkamani, M.A. Suchard, I. Crozier, L. Hensley, A. Rambaut, O. Faye, A. Sall, N.J. Sullivan, T. Bedford, K.G. Andersen, M.R. Wiley, S. Ahuka-Mundeke, and J.-J. Muyembe Tamfum

Table 1. Diagnostic Test Results in Samples Obtained during the First and Second Episodes of EVD in the Patient in 2019.*

Sample and Laboratory Identifiers†	Date Sample Collected	Sample Type	Glycoprotein Ct Value	Nucleoprotein Ct Value	Glycoprotein IgG EC_{50} Titer	Virus Sequenced‡
Sample d1: MAN4194	June 15	Serum	32.5	29.9	Negative	Yes
MAN4337	June 18	Serum	Negative	41.7	—	—
MAN4434	June 20	Serum	41.3	39.2	—	—
MAN4524	June 22	Serum	Negative	38.5	—	—
MAN4694	June 25	Serum	Negative	38.0	—	—
MAN4796	June 27	Serum	Negative	Negative	—	—
Sample d14: MAN4907	June 29	Serum	Negative	Negative	1:77,579	—
Identifier unknown	Aug. 27	Semen	Negative	Negative	—	—
Sample d171: MAN12309	Dec. 3	Serum	33.3	30.1	1:164,609	Yes
Sample d173: MAN12369	Dec. 5	Oral swab	28.7	24.8	—	Yes

* The glycoprotein and nucleoprotein targets of Ebola virus RNA were detected with the use of GeneXpert diagnostic quantitative reverse-transcriptase–polymerase-chain-reaction assays (Xpert Ebola Assay, Cepheid) and are expressed as cycle-threshold (Ct) values. Glycoprotein binding titers were assessed with the use of an enzyme-linked immunosorbent assay (Alpha Diagnostic International) with a readout for the anti-Ebola glycoprotein IgG EC_{50} (the concentration at which there is a 50% decrease in antigen binding). EVD denotes Ebola virus disease.
† Sample identifiers were assigned only to the samples described in this article.
‡ Samples from which full viral genomes were determined are indicated.

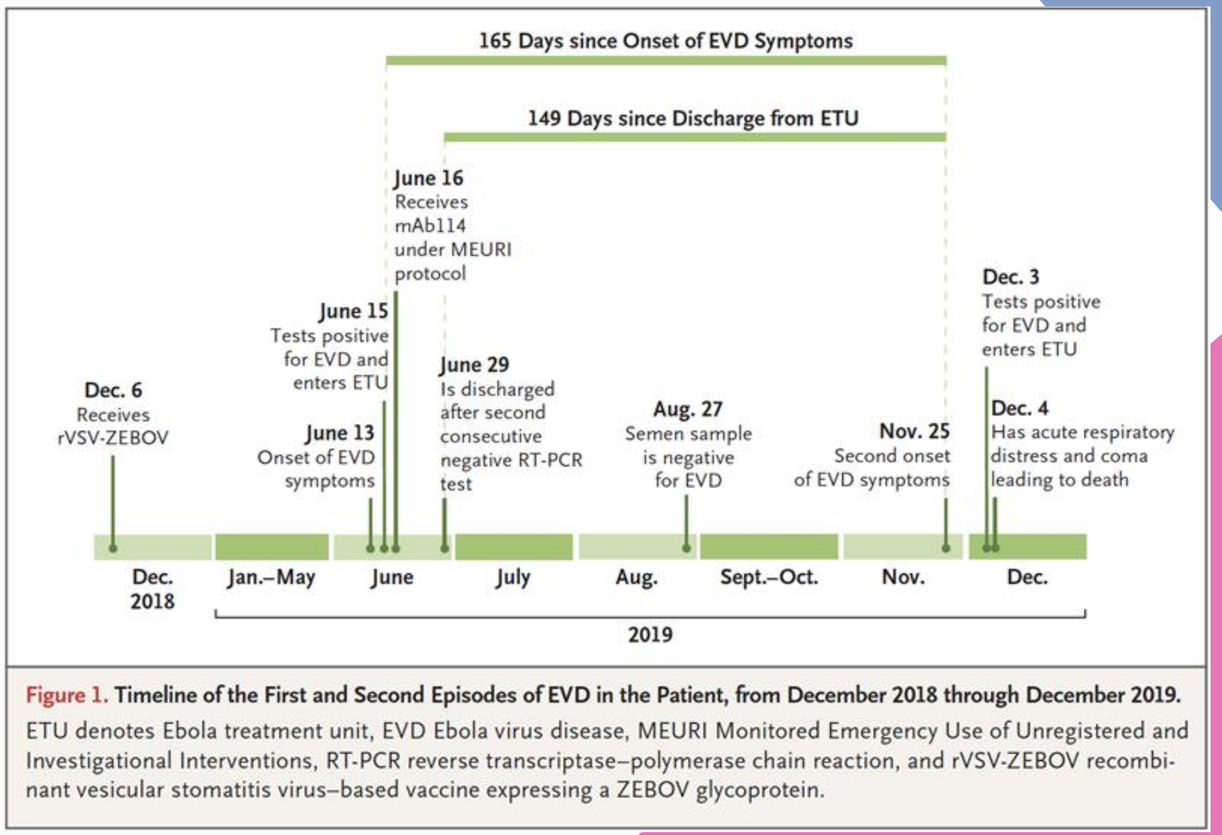

Figure 1. Timeline of the First and Second Episodes of EVD in the Patient, from December 2018 through December 2019.
ETU denotes Ebola treatment unit, EVD Ebola virus disease, MEURI Monitored Emergency Use of Unregistered and Investigational Interventions, RT-PCR reverse transcriptase–polymerase chain reaction, and rVSV-ZEBOV recombinant vesicular stomatitis virus–based vaccine expressing a ZEBOV glycoprotein.

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Impact in Spillover?

nature
International weekly journal of science

Article

Resurgence of Ebola virus in 2021 in Guinea suggests a new paradigm for outbreaks

https://doi.org/10.1038/s41586-021-03901-9

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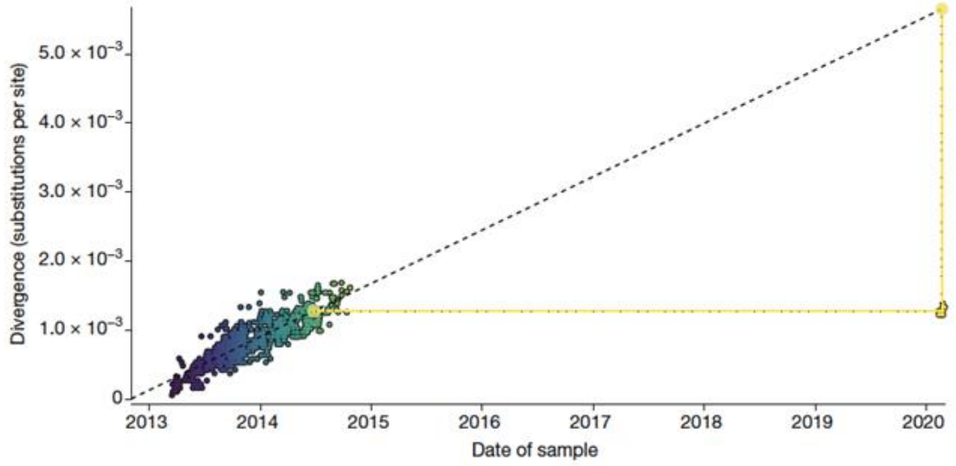
Check for updates

Alpha Kabinet Keita[1,2,26], Fara R. Koundouno[3,4,26], Martin Faye[5,26], Ariane Düx[6,26], Julia Hinzmann[4,7,8,26], Haby Diallo[1], Ahidjo Ayouba[2], Frederic Le Marcis[1,2,9], Barré Soropogui[3], Kékoura Ifono[3,4], Moussa M. Diagne[5], Mamadou S. Sow[1,10], Joseph A. Bore[3,11], Sebastien Calvignac-Spencer[6], Nicole Vidal[2], Jacob Camara[3], Mamadou B. Keita[12], Annick Renevey[4,7], Amadou Diallo[5], Abdoul K. Soumah[1], Saa L. Millimono[3,4], Almudena Mari-Saez[6], Mamadou Diop[5], Ahmadou Doré[3], Fodé Y. Soumah[10], Kaka Kourouma[12], Nathalie J. Vielle[4,13], Cheikh Loucoubar[5], Ibrahima Camara[1], Karifa Kourouma[3,4], Giuditta Annibaldis[4,13], Assaïtou Bah[3], Anke Thielebein[4,7], Meike Pahlmann[4,7], Steven T. Pullan[8,11], Miles W. Carroll[8,11], Joshua Quick[14], Pierre Formenty[15], Anais Legand[15], Karla Pietro[16], Michael R. Wiley[16,17], Noel Tordo[16], Christophe Peyrefitte[5], John T. McCrone[18], Andrew Rambaut[18], Youssouf Sidibé[20], Mamadou D. Barry[20], Madeleine Kourouma[20], Cé D. Saouromou[20], Mamadou Condé[20], Moussa Baldé[10], Moriba Povogui[1], Sakoba Keita[21], Mandiou Diakite[22,23], Mamadou S. Bah[22], Amadou Sidibe[9], Dembo Diakite[10], Fodé B. Sako[10], Fodé A. Traore[10], Georges A. Ki-Zerbo[13], Philippe Lemey[24], Stephan Günther[4,7,13], Liana E. Kafetzopoulou[4,7,24], Amadou A. Sall[5], Eric Delaporte[2,25], Sophie Duraffour[4,7,13,27], Ousmane Faye[5,27], Fabian H. Leendertz[6,27], Martine Peeters[2,27], Abdoulaye Toure[1,12,27] & N'. Faly Magassouba[3,27]



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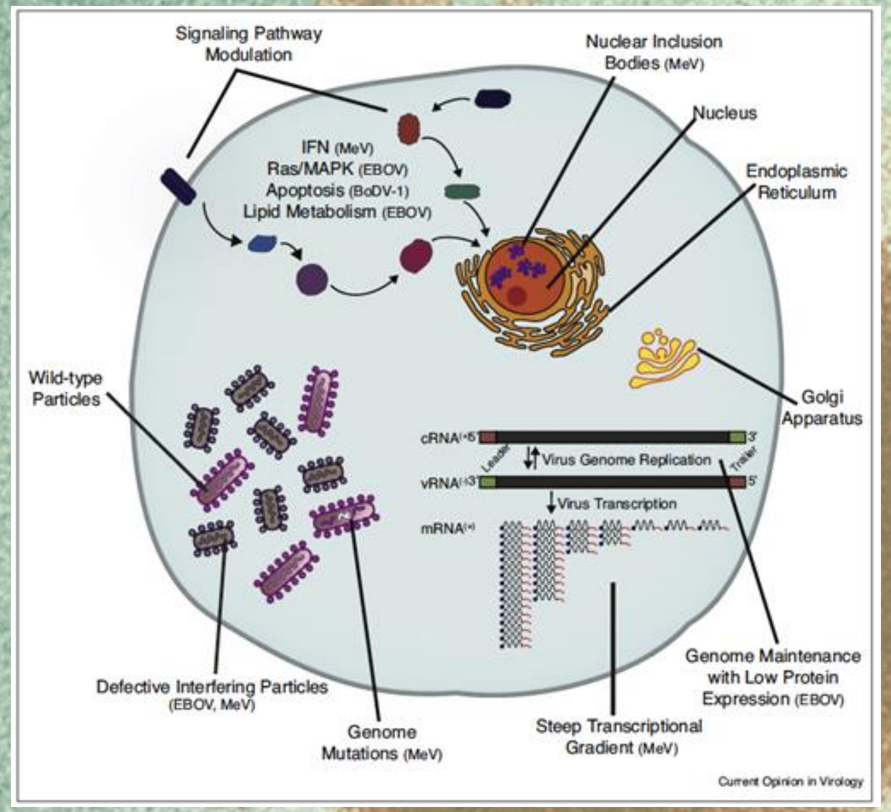

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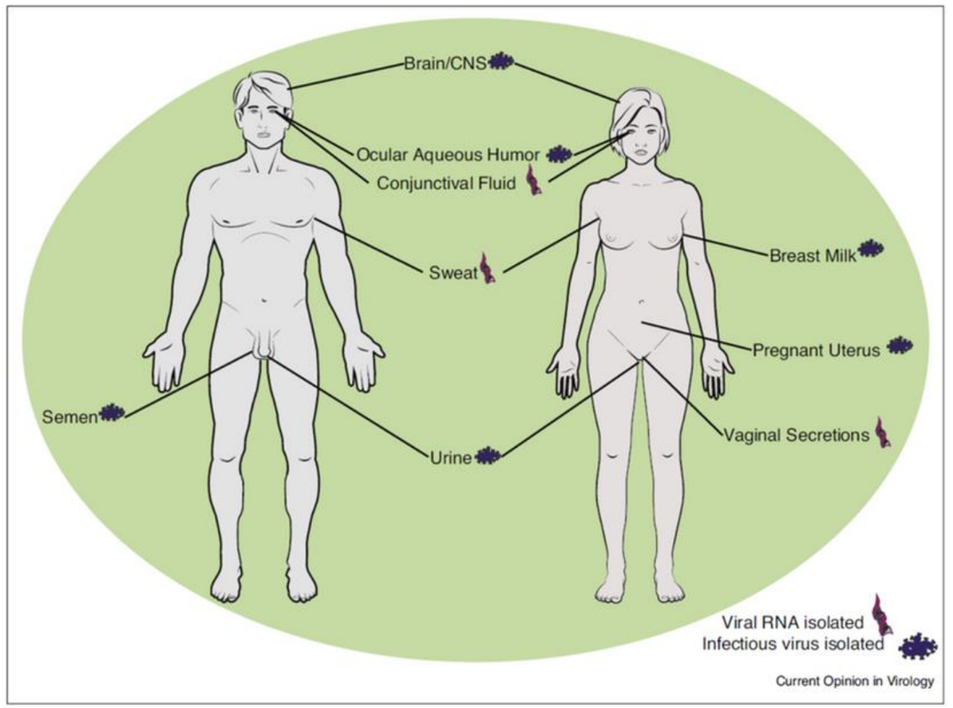
Current Opinion in Virology

Ebola virus persistence as a new focus in clinical research

Katie Caviness[1], Jens H Kuhn[2] and Gustavo Palacios[1]



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Historical In Vitro Models of Persistence

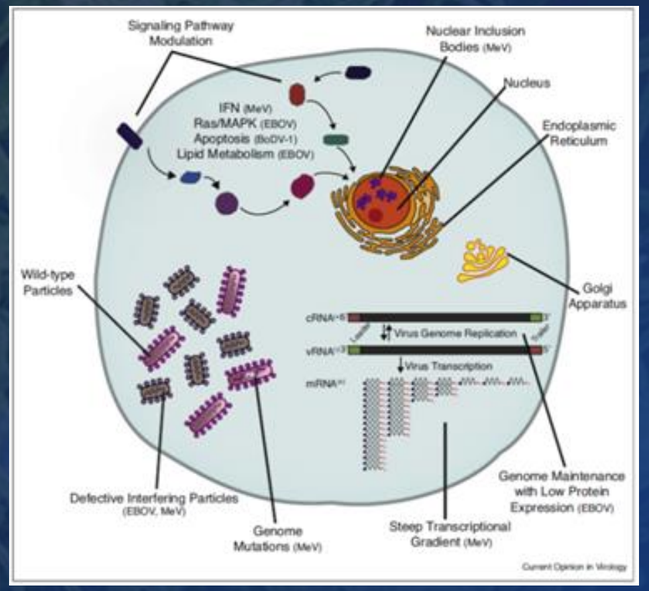
Ebola Virus Defective Interfering Particles and Persistent Infection

Philippe Calain, Martha C. Monroe, and Stuart T. Nichol[1]

Special Pathogens Branch, Division of Viral and Rickettsial Diseases, Centers for Disease Control and Prevention, Mailstop G14, 1600 Clifton Road, N.E., Atlanta, Georgia 30329-4018

Received March 1, 1999; returned to author for revision May 7, 1999; accepted July 20, 1999

Ebola virus (Zaire subtype) is associated with high mortality disease outbreaks that commonly involve human to human transmission. Surviving patients can show evidence of prolonged virus persistence. The potential for Ebola virus to generate defective interfering (DI) particles and establish persistent infections in tissue culture was investigated. It was found that serial undiluted virus passages quickly resulted in production of an evolving population of virus minireplicons possessing both deletion and copyback type DI genome rearrangements. The tenth undiluted virus passage resulted in the establishment of virus persistently infected cell lines. Following one or two crises, these cells were stably maintained for several months with continuous shedding of infectious virus. An analysis of the estimated genome lengths of a selected set of the Ebola virus minireplicons and standard filoviruses revealed no obvious genome length rule, such as "the rule of six" found for the phylogenetically related *Paramyxovirinae* subfamily viruses. Minimal promoters for Ebola virus replication were found to be contained within 156 and 177 nucleotide regions of the genomic and antigenomic RNA 3′ termini, respectively, based on the length of authentic termini retained in the naturally occurring minireplicons analyzed. In addition, using UV-irradiated preparations of virus released from persistently infected cells, it was demonstrated that Ebola virus DI particles could potentially be used as natural minireplicons to assay standard virus support functions.



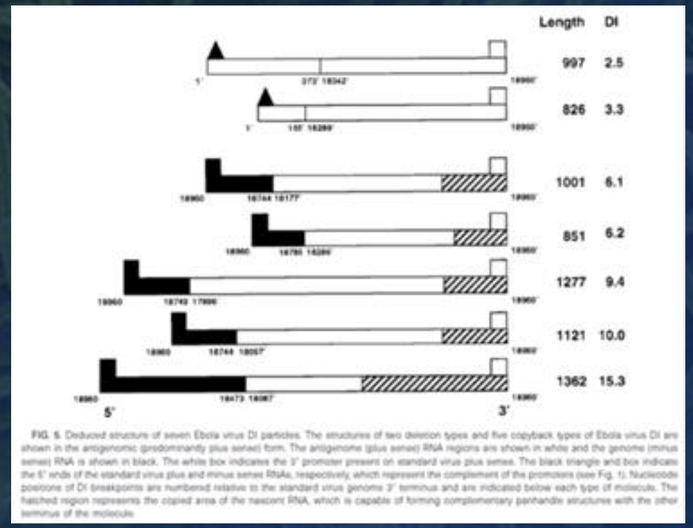
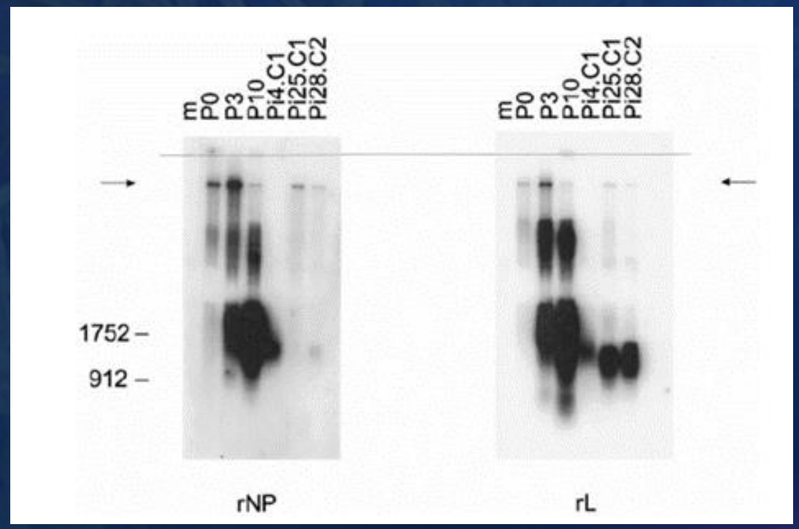


FIG. 5. Deduced structure of seven Ebola virus DI particles. The structures of two deletion types and five copyback types of Ebola virus DI are shown in the antigenomic (predominantly plus sense) form. The antigenome (plus sense) RNA regions are shown in white and the genome (minus sense) RNA is shown in black. The white box indicates the 3′ promoter present on standard virus plus sense. The black triangle and box indicate the 5′ ends of the standard virus plus and minus sense RNAs, respectively, which represent the complement of the promoters (see Fig. 1). Nucleotide positions of DI breakpoints are numbered relative to the standard virus genome 3′ terminus and are indicated below each type of molecule. The hatched region represents the copied area of the nascent RNA, which is capable of forming complementary panhandle structures with the other terminus of the molecule.



Center for Genome Sciences

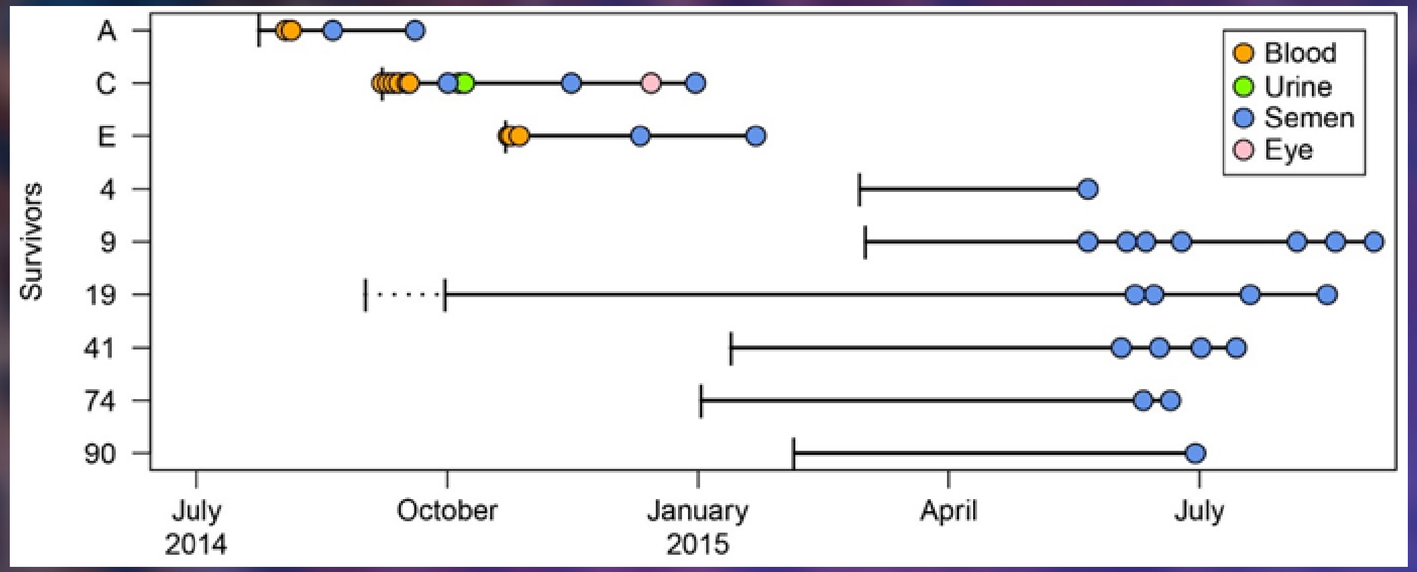
Cell Reports
Report
Active Ebola Virus Replication and Heterogeneous Evolutionary Rates in EVD Survivors

Case Studies of Persistence in Humans
Viral population characterization in a cohort of EVD survivors

Sierra Leone Ebola Virus Persistence Study

- Aim: To investigate the persistence of Ebola virus in body fluids in a cohort of EVD survivors
- Pilot study: cohort of 100 men
- Specimens: semen
- Joint study between CDC, Sierra Leone Ministry of Health and Sanitation, Sierra Leone Armed Forces, and WHO.

Semen-acquired viral sequences ("SAVS")



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Cell Reports 2018 22, 1159-1168DOI: (10.1016/j.celrep.2018.01.008)

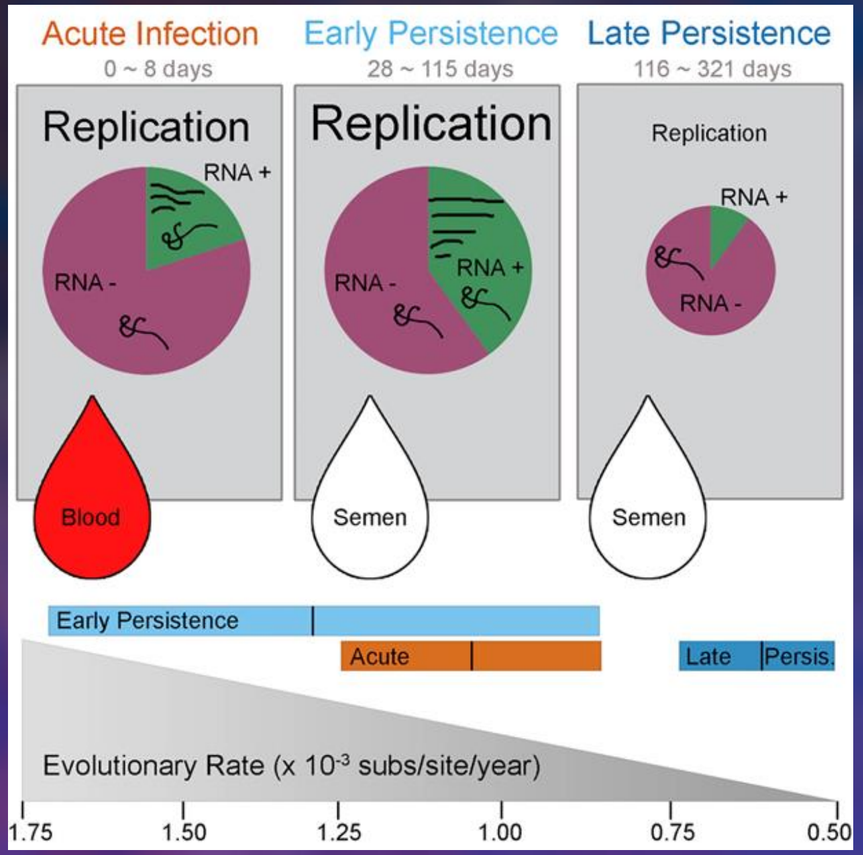
Report

Cell Reports

Active Ebola Virus Replication and Heterogeneous Evolutionary Rates in EVD Survivors

Highlights

- During persistence, EBOV exhibits heterogeneous evolutionary rates
- Active EBOV transcription and replication occurs during persistence
- RNA hyper-editing observed during viral persistence
- No evidence for significant selective pressure during persistence



Cell Reports 2018 22, 1159-1168DOI: (10.1016/j.celrep.2018.01.008)

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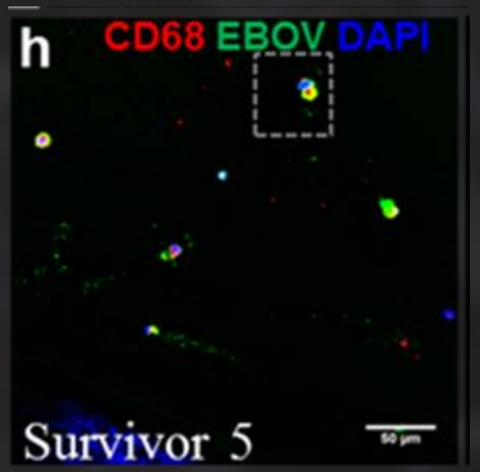
Xiankun Zeng, PhD

USAMRIID
United States Army Medical Research Institute of Infectious Diseases



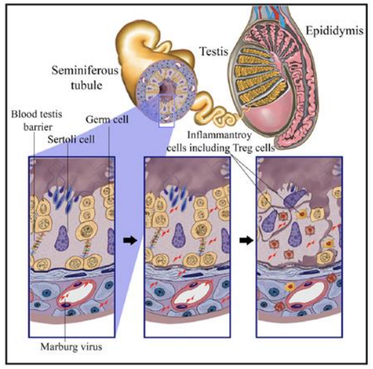
nature microbiology

Altmetric: 138 Citations: 3 More detail »

Article

Identification and pathological characterization of persistent asymptomatic Ebola virus infection in rhesus monkeys

Graphical Abstract



Cell Host & Microbe

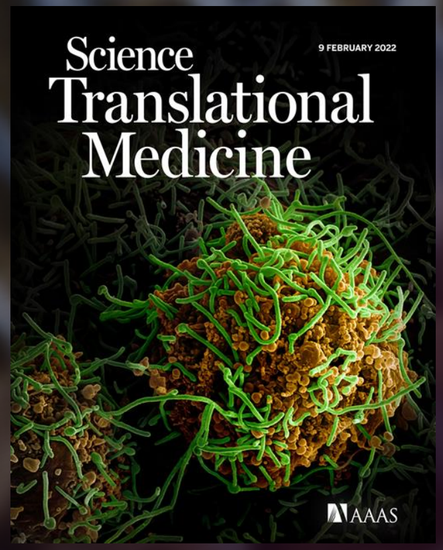
Persistent Marburg Virus Infection in the Testes of Nonhuman Primate Survivors

Science Translational Medicine

Current Issue First release papers

RESEARCH ARTICLE | VIRAL DISEASES

Ebola virus persistence and disease recrudescence in the brains of antibody-treated nonhuman primate survivors



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Historical Data on the effect of antibodies in the treatment of Viral Hemorrhagic Fevers

Journal of Medical Virology 20:207–218 (1986)

Treatment of Junin Virus-Infected Guinea Pigs With Immune Serum: Development of Late Neurological Disease

Richard H. Kenyon, David E. Green, Gerald A. Eddy, and Clarence J. Peters

United States Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, Maryland

Guinea pigs infected with Argentine hemorrhagic fever virus (Junin) were treated with pooled, homologous convalescent sera. Use of 15,000 or 5,000 therapeutic units of immune sera prevented all signs of illness when administered within 24 hr of infection. We could also prevent illness and death in infected guinea pigs as late as 6 days after infection if we used more antisera (30,000 therapeutic units/kg). In some treatment groups, surviving animals developed a late neurological syndrome with prominant rear-limb paralysis. Treated animals typically expressed

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Available online at www.sciencedirect.com

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Antiviral Research 78 (2008) 132–139

Antiviral Research

www.elsevier.com/locate/antiviral

Treatment of Argentine hemorrhagic fever

Delia A. Enria*, Ana M. Briggiler, Zaida Sánchez

Instituto Nacional de Enfermedades Virales Humanas, "Dr. Julio I. Maiztegui", Monteagudo 2510, 2700 Pergamino, Argentina

Received 22 August 2007; accepted 9 October 2007

5.2. Rationale for the evaluation of alternative forms of treatment for AHF

Some arguments give the rationale for the evaluation of alternative forms of treatment in AHF:

- The lack of efficacy of the immune plasma in patients with more than 8 days of evolution (Enria and Maiztegui, 1994).
- The risk of transfusion-borne diseases (Saavedra et al., 1997).
- The presentation of a late neurological syndrome in around 10% of the treated AHF survivors (Maiztegui et al., 1979; Enria et al., 1985; Enria, 2005).
- The difficulties with the maintenance of an adequate stock of immune plasma.

One of the most puzzling secondary events associated with the treatment of immune plasma is the LNS. From the very first description of AHF it was recognized that some patients could present a neurological disease after the acute phase of the illness. The disease was known among inhabitants of the endemic area as "relapse," but this entity was then named Late Neurological Syndrome of AHF. Several physiopathogenic mechanisms have

The search for Junin virus by isolation attempts, even by co-cultivation, and by RT-PCR from blood, lymphoid tissues and CSF has been consistently negative. The higher titers of neutralizing antibodies and the CSF-serum antibody ratio in LNS cases suggest the possibility of a more prolonged antigenic stimulation, probably through a longer persistence of virus or antigens in the central nervous system.

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Conclusions

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- The frequency of EBOV persistent infections in primates is more frequent than previously expected.
- Most survivors show a reduced rate of evolution during persistent infection.
- There is evidence of active replication in both human and NHPs.
- Filovirus persistence is also common in Marburg infections

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Gustavo Palacios, PhD

Thanks!

Questions?