IIIe Cours d'Automne de Chimiothérapie
Anti-infectieuse et de Vaccinologie

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Les Pensières
74290 Veyrier-du-Lac

Maladie à Virus Ebola : Quelles Leçons ?

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A Well Known Statement… and Emerging Diseases

- Dr William H. Stewart : US Surgeon General (1965–1969) [1]:

  « It is time to close the book on infectious diseases, and declare the war against pestilence won ».

- Since :
  - AIDS, HCV, Anthrax, SARS, West Nile virus, **Chikungunya**, avian flu A(H5N1), **MERS-CoV**, pandemic flu A(H1N1)pdm09, **Ebola virus diseases** (EBOV), **Zika virus**…
  - and vancomycin resistant *Enterococcus*, multiresistant bacteria, multiresistant tuberculosis, colimycin resistant *E.coli* ...
- Emerging Infectious Disease
  - WHO[2] :
    - One that has appeared in the population for the first time, or that may have existed previously but is rapidly increasing incidence or geographic range.
  - The Centers for Disease Control and Prevention (CDC)[2] :
    - New infections resulting from changes in or evolution of existing organisms.
    - Known infections spreading to new geographic areas or populations.
    - Previously unrecognized infections appearing in areas undergoing ecologic transformation. Old infections re-emerging as a result of antibiotic resistance in known agents or breakdowns in public health measures.

1 : http://cid.oxfordjournals.org/content/47/2/294.1.full 2 : WHO http://www.who.int/topics/emerging_diseases/en/
3 : CDC http://wwwnc.cdc.gov/eid/page/background-goals

Emerging Infectious Diseases : Definition

- WHO[1] :
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1 : WHO http://www.who.int/topics/emerging_diseases/en/
2 : CDC http://wwwnc.cdc.gov/eid/page/background-goals

Ebola Virus Disease

Ebola Virus Disease in West Africa.
Situation Report, WHO, June 10, 2016

- Public Health Emergency of International Concern was lifted on 29 March 2016
- In the latest cluster, 7 confirmed and three probable cases of Ebola virus disease (EVD) reported between 17 March and 6 April in south-eastern Guinea.
- 3 confirmed cases reported between 1 and 5 April in Liberia.
- 42 days since last case tested negative required (two times incubation period) to declare the end of an outbreak

28 616 cases
(confirmed, probable & suspected)

11 310 deaths

Case-fatality rate : 50%.
(25-90% in past outbreaks)

10 000 survivors

3 Objectives :
To interrupt all remaining chains of Ebola transmission.
To respond to the consequences of residual risks.
To work on health systems recovery

http://apps.who.int/iris/bitstream/10665/208883/1/ebolasitrep_10Jun2016_eng.pdf?ua=1

Ebola Virus Disease Transmission

- Direct contact through broken skin or mucous membranes (eyes, nose, or mouth) with :
  - Blood or body fluids (including but not limited to urine, saliva, sweat, feces, vomit, breast milk, and semen) of a person who is sick with or has died from Ebola.
  - Objects (like needles and syringes) that have been contaminated with body fluids from a person who is sick with Ebola.
  - Body of a person who has died from Ebola.
  - Infected fruit, bats or primates (apes and monkeys).
- Not spread through the air, by water, or in general, by food.
  - However, in Africa, Ebola may be spread as a result of handling bushmeat (wild animals hunted for food) and contact with infected bats.
- Possibly from contact with semen from a man who has recovered from Ebola (oral, vaginal, anal sex).
- Mosquitoes or other insects : no evidence for transmission.
- Only a few species of mammals (e.g., humans, bats, monkeys, and apes) have shown the ability to become infected with and spread Ebola virus.
- **HCW** providers caring for Ebola patients and close contacts with Ebola patients are at the **highest risk of getting EBV**.

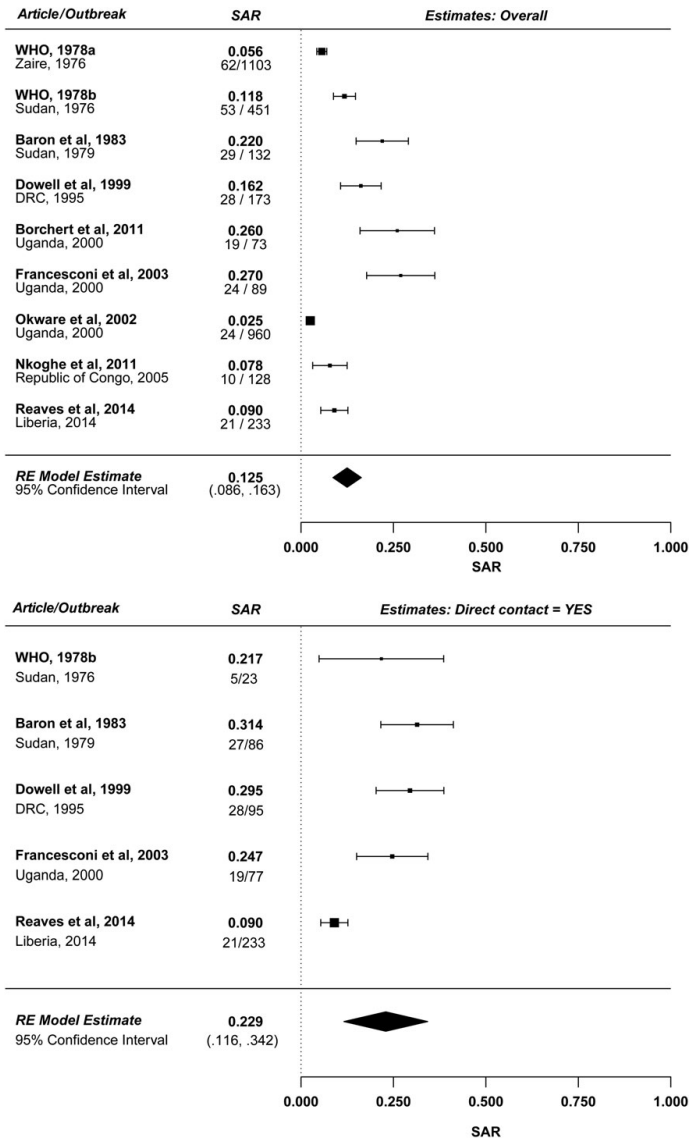
More than 860 HCW infected with Ebov during the 2014 West Africa outbreak

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

Transmissibility and Pathogenicity of Ebola Virus: Household Secondary Attack Rate and Asymptomatic Infection

- Meta-analysis of Ebola household secondary attack rate (SAR), disaggregating by type of exposure :
  - Direct contact.
  - No direct contact.
  - Nursing care.
  - Direct contact but no nursing care.
- Estimated overall household SAR:
  - 12.5% [95% CI, 8.6%–16.3%].
- Transmission driven by direct contact, with little transmission occurring in its absence :
  - SAR, 0.8% [95% CI, 0%–2.3%].
- Greatest risk factor = the provision of nursing care SAR : 47.9% [95% CI, 23.3%–72.6%].
- Rate of asymptomatic Ebola Infections estimated as 27.1% [95% CI, 14.5%–39.6%].

Surveillance and containment measures should be effective for controlling Ebola.

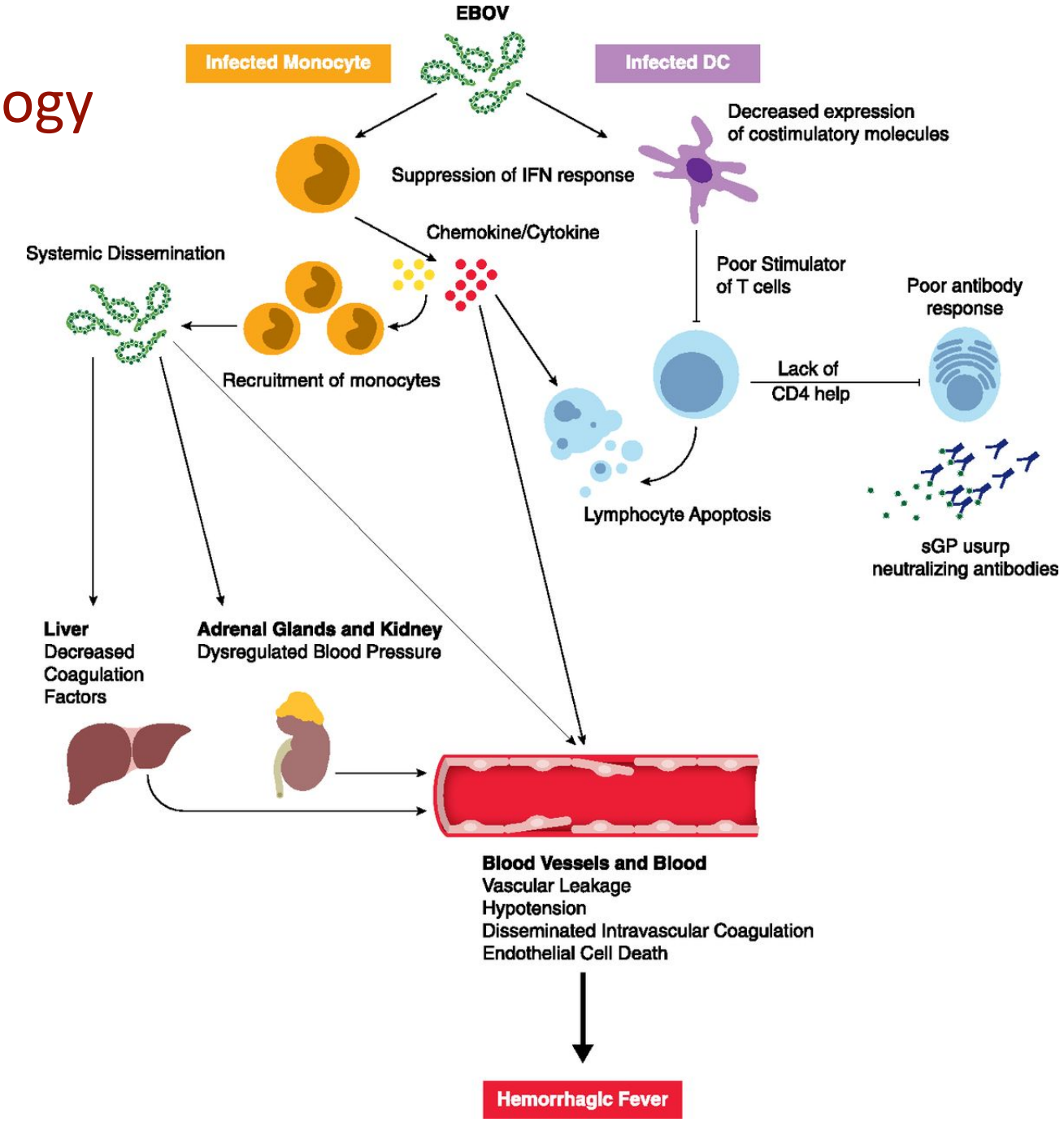


Dean NE Clin Infect Dis 2016 ;62 :1277-86 DOI: 10.1093/cid/ciw114

EVD : Clinical Aspects from 2014-15 Outbreak

	Bah El	Barry M	Bai CQ*	Dallatomasina S	Schieffelin JS	Xu Z
Countries	Guinea	Guinea	Sierra Leone	Sierra Leone	Sierra Leone	Sierra Leone
N	37	90	124	245	106	139
Age (mean, Years)	38 (28–46)	34 ± 14	27-30	28	29.5 (14.6)	29 (0.5-75)
Male	24 (65)	57 (63%)	54	(51)	40%	62 (44.6)
Clinical signs n (%)						
Fever	31/37 (84%)	65 (72%)		87 %	89%	77 (55,4%)
Asthenia	24/37 (65%)	72 (80%)		77 %	66%	114 (82.0%)
Dysphagia			58	26 %	34%	31 (22.3%)
Hiccups		6 (7%)	45	15 %		33 (23.7%)
Pain						
Headache	12/21 (57%)	47 (52%)		73 %	80 %	50 (36.0)
Abdominal pain		24 (27%)	88	51 %	40%	
Myalgia		21 (13%)				
Arthralgia		12 (6%)	90	56 %		
Thoracic pain			79	44 %		
Digestive signs						
Anorexia/weight loss	16/37 (43%)		109	72 %		98 (70.5%)
Nausea/vomiting	21/37 (57%)	54 (60%)		46 %	34%	
Diarrhea	23/37 (62%)	31 (34%)		48 %	51%	81 (58.3%)
Rash / conjunctivitis			- / 143	3 % / 2%	2% / 32%	
Respiratory signs/Dyspnea		13 (14%)	143			
Cough			72	40 %	35%	
Breathing problems			71	20 %		
Bleeding		23 (26%)		5 %	1%	15 (10.8%)
Confusion			70	9%		

EVD : Physiopathology



Rivera A J Leukoc Biol 20126;100:889-904

Séquelles de la MVE (I)

- Musculo-squelettiques
  - Arthralgies (50-75%), ténosynovites, chondrite costale
- Ophtalmologiques :
  - Douleurs, érythème, sécheresse, sensibilité à la lumière, vision floue
  - Uvéite cataracte, atteintes rétiniennes et du nerf optique
- Auditives : 25%
- Perte d'audition, labyrinthite, otite,
- Douleurs abdominales

http://www.who.int/csr/disease/ebola/response/infographic/fr/

Séquelles de la MVE (II)

- Neurologiques
  - Céphalées, troubles de la mémoire, de l'attention, neuropathie périphérique,…
- Santé mentale
- Santé sexuelle
  - Dysfonction erectile, douleur testiculaire, dyspareunie, douleur pelvienne, ménmetrorragies, aménorrhée
- Persistance virale
  - Sites protégés : oeil SNC, testicules, glandes mammaires,
- Risque de résurgence

http://www.who.int/csr/disease/ebola/response/infographic/fr/

EVD : Sequeleae (2015-16)

	Qureshi AI 2015, Guinea	Mattia JG 2016, Sierra Leone	Tiffany 2016, Sierra Leone	Scott JT 2016, Sierra Leone	Mohammed H 2017, Sierra Leone	Etard JF 2017, Guinea
Survivors, n	105	277	166	44	115	802
Male	71 (67%)	114 (41%)	92 (55%)	11		360 (45%)
Female	34 (32%)	163 (59%)	74 (44%)	23	70 (60%)	442 (55%)
Age (median)	38.9 ± 11.9	29 (IQR 20–36)	24.7 ± 12.7	35 (8–70)	28 (0,25–70)	28.4 (1.0–79.9)
Median time from discharge, d	103.5 ± 47.9	121 (82-151)	51.1 ± 41.2	21	261	350
General symptoms						324 (40%)
Fever		255 (92%)		3 (6,8%)		209 (26%)
Asthenia			116 (69.8%)			190 (24%)
Anorexia	103		43 (25.9%)	3 (7%)		89 (11%)
Pain						
Headache			87 (52.4%)	21 (47,7%)	50.4%	278 (37%)
Thoracic pain	31 (30.7%)			4 (9%)	7.6%	
Arthalgia	91 (86.7%)	210 (76%)	129 (77%)	14 (31%)	31.1%	254 (38%)
Myalgia	28 (26.7%)			31 (70%)	43,7%	303 (38%)
Back pain	48 (45.7%)		54 (32.5%)	4 (9%)		56 (7%)
Abdominal pain	33 (31.7%)		90 (54.2%)	4 (9%)		198 (25%)
Manifestations						
Ocular		167 (60%)	94 (56.6%)	6 (13%)	9.2%	124 (18%)
Uveitis		50 (18%)	58 (34.9%)			
Conjunctivitis		207 (75%)				
Auditory		67 (24%)	5 (0.3%)		0.8%	19 (2%)
Digestives	17 (32.3)		9 (5.4%)		5.1%	
Urologic/Sexual/STD	45 (43.1)		38 (22.8%)		7.8%	
Respiratory			45 (27.1%)	5 (11%)	12.6%	
Cardiac			19 (11.4%)			
Skin			81 (48.8%)	6 (13.5%)	10.5%	
Neurosensitive						298 (37%)
Insomnia			30 (18%)	3 (7%)	16.4%	

Sequelae of Ebola Virus Disease

Postebogui cohort[1]

- 375 survivors (dec 15, 2015)
- 1 081 events reported from 296 (79 %) survivors :
  - General signs (39 %) : asthenia, fever, anorexia.
  - Neurologic signs (32 %): headache.
  - Rheumatologic signs (46 %).
  - Ocular symptoms (16 %): conjunctivitis, iridocyclitis, impaired vision.
  - Infectious signs (22 %).
  - Pelvic pain (21 %).
  - Anemia (13 %).

Sierra Leone cohort[2]

- 277 survivors (114 males), median age 29 yrs (IQR 20-36), median time from discharge 121 days (82-151)
  - Arthralgia (210, 76 %),
  - New ocular symptoms (167, 60 %), uveitis (50, 18 %),
  - Auditory symptoms (67, 24 %).
- High EBOV viral load at acute EVD presentation independently associated with
  - Uveitis (adjusted OR : 3,33, 95% IC 1,97-5,91).
  - New ocular symptoms (adjusted OR 3,04, 95% IC 1,87-4,94).

1 : Etard JF. CROI 2016, Boston 22-25 février 2016 Abstract 73LB 2 : Mattia JG Lancet Infect Dis 2015 doi: 10.1016/S1473-3099(15)00489-1

EVD and Pregnancy: A Retrospective Cohort Study of Pts Managed at 5 Ebola Treatment Units in West Africa

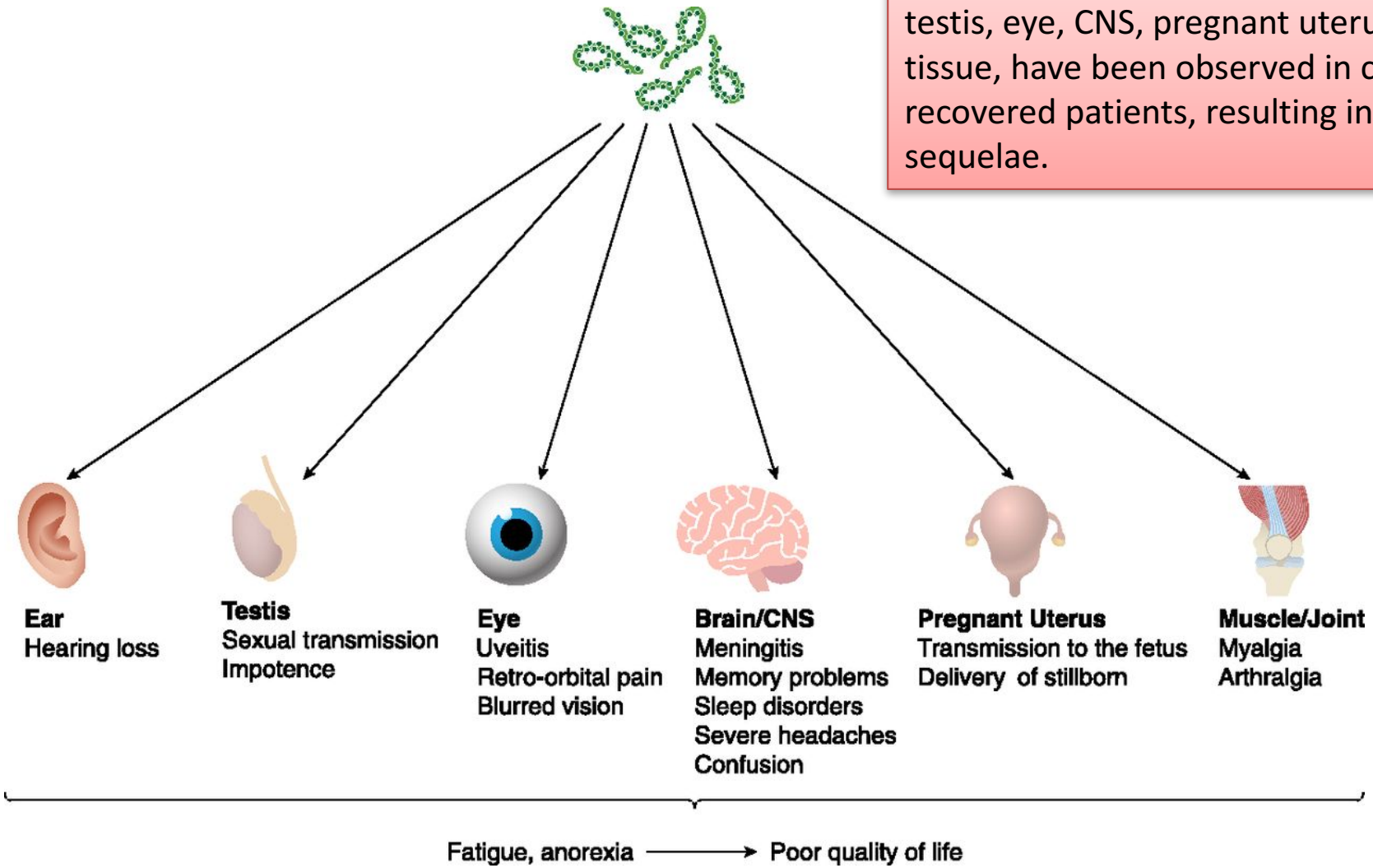
- Retrospective cohort study :
- Reproductive-aged women presenting to 5 West African ETUs:
  - 729 enrolled;
  - 44 (6%) pregnant.
  - 13/44 (30%) EVD +.
  - 6/13 (46%) died.
- Mortality :
  - All-cause mortality : 14% vs 19%, *P* = 0.39.
  - EVD specific mortality : 46% vs 54%, *P* = 0.60.
  - Not significantly different between pregnant and nonpregnant women.
- Limited data suggest poor fetal and neonatal outcomes in EVD-affected pregnancies.

Characteristic	EVD Positive, Not Pregnant	EVD Positive, Pregnant	*P*
All patients	93 (162)	7 (13)	…
Age, y, median (IQR)	33 (24–42)	24 (20–32)	.02
Clinical symptoms at triage			
Days of symptoms, median (IQR)	3 (2–6)	3 (2–3)	.36
Abdominal pain	51 (82)	54 (7)	.82
Anorexia	67 (109)	54 (7)	.37
Asthenia	75 (122)	77 (10)	1.00
Bleeding	8 (13)	15 (2)	.31
Diarrhea	57 (89)	27 (3)	.06
Dyspnea	28 (45)	23 (3)	1.00
Fever	73 (119)	62 (8)	.35
Headache	64 (104)	54 (7)	.55
Hiccups	13 (21)	15 (2)	.68
Jaundice	2 (3)	8 (1)	.27
Myalgia or arthralgia	68 (110)	23 (3)	.00
Nausea	43 (42)	20 (2)	.20
Throat pain	26 (42)	8 (1)	.19
Vomiting	52 (85)	15 (2)	.02
Epidemiological characteristics			
Contact with someone ill	79 (112)	67 (8)	.33
Initial Ct value, median (IQR)	23 (20–27)	26 (19–35)	.17
Outcome			
Length of stay, d, median (§IQR)	7 (4–14)	10 (2–17)	.69
Mortality	54 (87)	46 (6)	.60

Henwood P C Clin Infect Dis 2017 DOI: 10.1093/cid/cix290

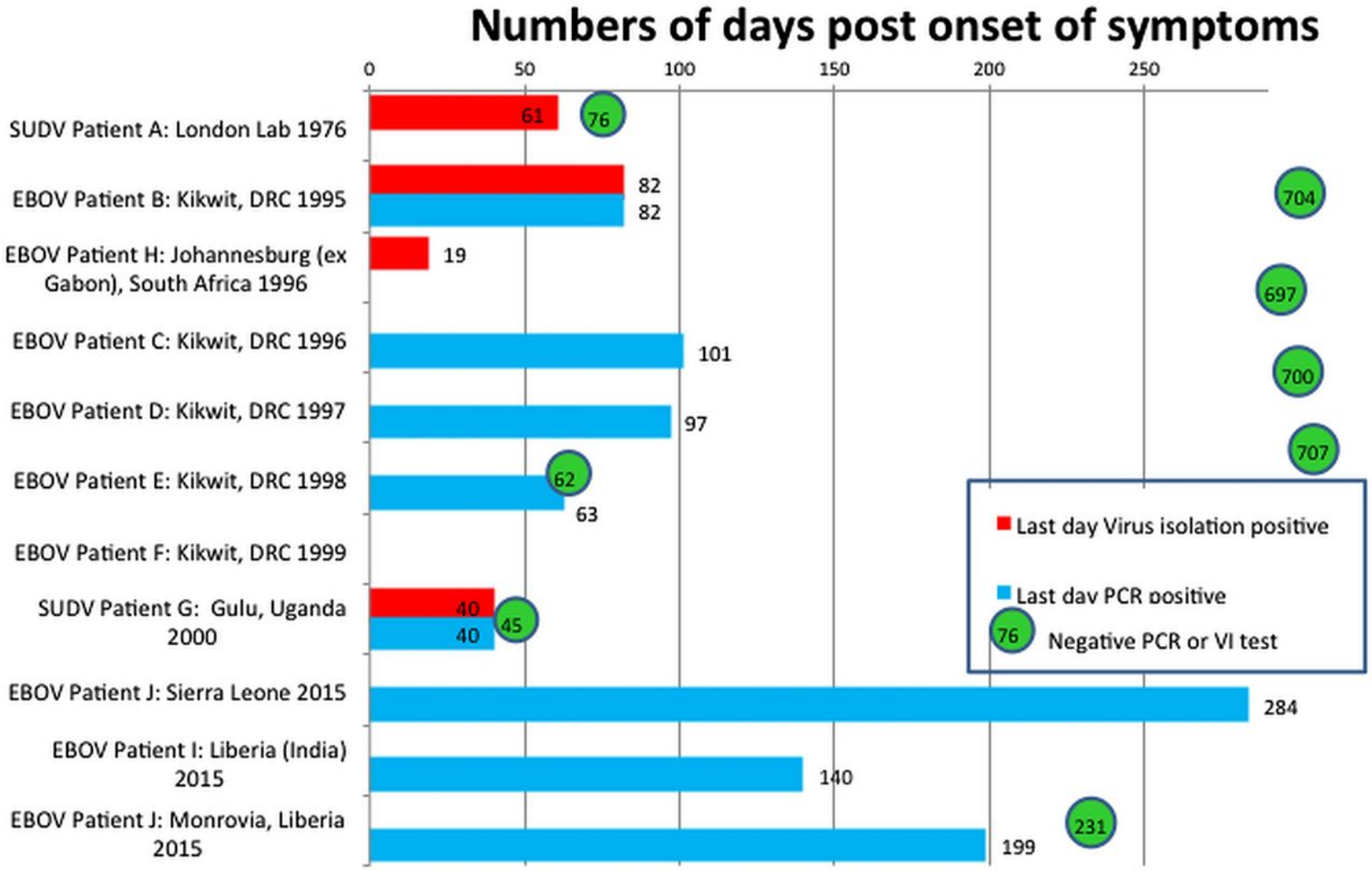
Long-Term Post-EBOV Consequences

EBOV entry and persistence into organs that are immune privileged, including the ear, testis, eye, CNS, pregnant uterus, and muscle tissue, have been observed in clinically recovered patients, resulting in Ebola disease sequelae.



Riviera A J Leukoc Biol 2016;100:889-904

Persistence of Ebola Virus and Ebola Virus RNA in Semen



Thorson A BMJ Open 2016 ;6:e008859 doi:10.1136/bmjopen-2015-008859

Virus Isolation and RT-PCR Findings in Other Body Fluids in Recovered Patients

EBOV	Faeces or rectal swabs	Throat swabs or saliva	Sweat	Urine	
Patient 1, London, 1976	EBOV	−VI days 14–27	−VI days 14–27	NA	−VI days 14–27
29 Recovered patients, Kikwit, DRC, 1995	EBOV	−VI days 11–57	−VI days 11–57	NA	−VI days 11–57
8 Recovered patients, Kikwit, DRC, 1995	EBOV	−RT-PCR days 11–33 (total 18 specimens) + RT-PCR days 22 and 29 (total 2 specimens, same woman−RT-PCR days 25 and 33)	−RT-PCR days 11–33 (total 20 specimens)	NA	−RT-PCR days 11–33 (total 19 specimen)
4 Patients, Gulu, Uganda, 2000	SUDV	NA	−RT-PCR days 12–23	NA	−RT-PCR days 12–23
Patient 1, Sierra Leone, 2014	EBOV	−VI after day 17 (negative blood test day 17)	−VI after day 17 (negative blood test day 17)	−VI + RT-PCR until day 40	+ VI repeatedly until day 26 + RT-PCR until day 30

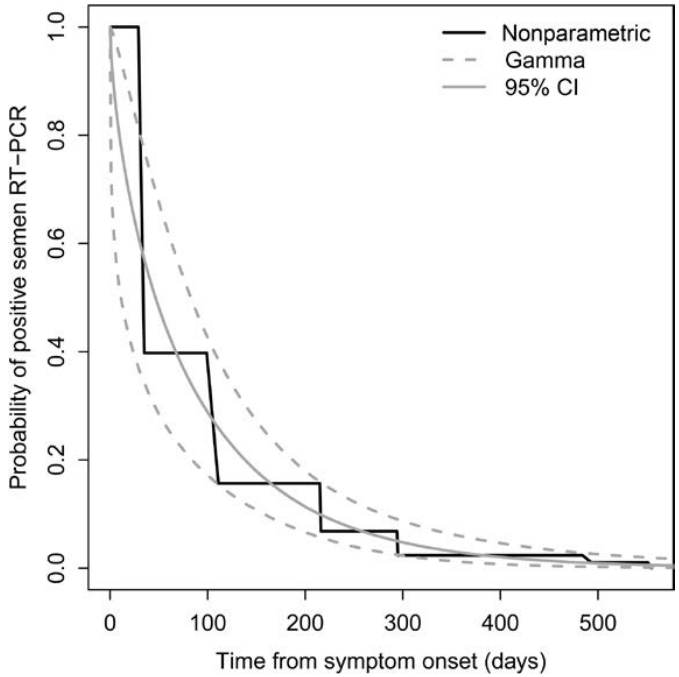
EBOV: Persistence in Semen

- Mate SE[1]
  - Case report Liberia.
  - Evidence of sexual transmission of EBOV.
  - Evidence of the persistence of infective EBOV in semen for 179 days or more after the onset of EVD.
- Soka MJ[2]
  - 466 survivors enrolled in a follow up program after discharged.
  - Real-time RT-PCR results available from 429 participants.
  - 38 (9%) : at least one semen specimen positive for Ebola virus RNA.
  - Of these, 24 (63%) provided semen specimens positive 12 months or longer after EVD recovery.
- Diallo B[3]
  - Case report sexual.
  - Persistence of Ebola virus in seminal fluid 531 days after onset of disease.
  - Sexual transmission 470 d after onset of symptoms.
  - caused a new cluster of EVD in Guinea and Liberia.

1 : Mate SE N Engl J Med 2015;373:2448-54 DOI: 10.1056/NEJMoa1509773 2 : Soka MJ Lancet Glob Health 2016; 4: e736–43 http://dx.doi.org/10.1016/ S2214-109X(16)30175-9 3 : Diallo B Clin Infect Dis 2016;63(10):1353–6

Dynamics of Ebola RNA Persistence in Semen: A Report From the Postebogui Cohort in Guinea

- Postebogui study includes Ebola survivors from 4 study centers in Guinea.
- Follow-up visits scheduled :
  - At inclusion.
  - And 1, 3, 6, 9, 12, 18, and 24 months after inclusion.
- Semen samples :
  - Collected from men ≥ 15 years of age at each visit.
  - Tested by RT-PCR for the presence of EBOV RNA.
- 315 men included at the time of data extraction:
  - 188 provided at least 1 semen sample.
  - With a total of 409 samples.



Probability for Ebola virus disease survivors' semen to test positive for Ebola virus

Parametric survival models adjusted to estimate the probability of positive RT-PCR result over time, using exponential, Weibull, Gompertz, log-logistic, log-normal, gamma, and inverse Gaussian distributions

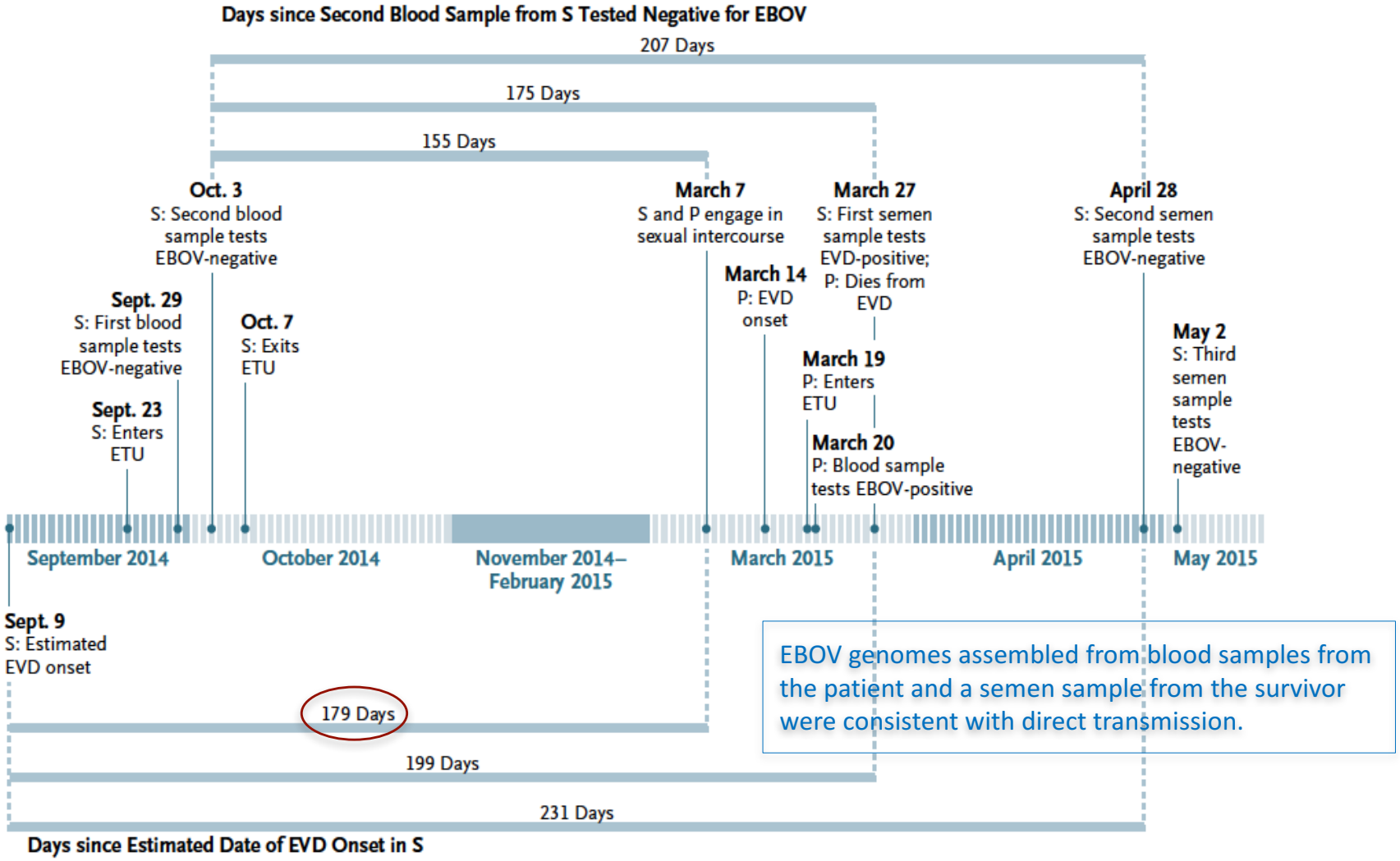
Estimated probability of remaining positive for EBOV RNA in semen :
- 31.6% (95% CI, 18.6%–46.0%) at 3 months
- 13.5% (95% CI, 7.8%–21.0%) at 6 months
- 2.9% (95% CI, 1.1%–5.7%) at 12 months
- 0.7% (95% CI, 0.1%–2.0%) at 18 months

Results emphasize the importance of the WHO recommendations for survivors' management.

Subtil F Clin Infect Dis 2017 DOI: 10.1093/cid/cix210

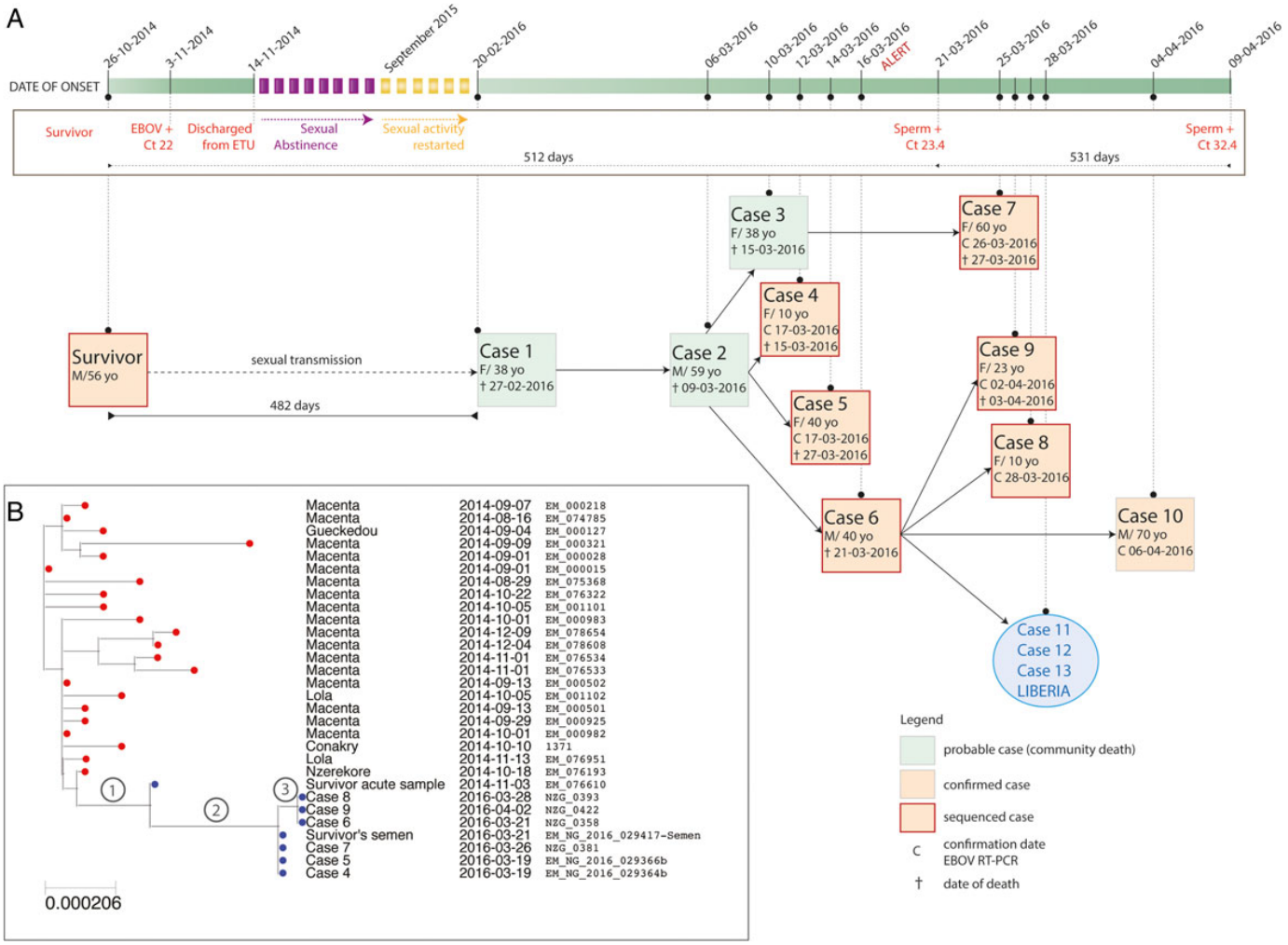
Molecular Evidence of Sexual Transmission of Ebola Virus

Clinical Timelines for the Patient and the Survivor, from September 2014 through May 2015



Mate SE N Engl J Med 2015;373:2448-54.DOI: 10.1056/NEJMoa1509773

Resurgence of EVD in Guinea Linked to a Survivor With Virus Persistence in Seminal Fluid > 500 Days



Chains of transmission within the new Ebola virus disease cluster (**A**) and maximum likelihood phylogenetic analysis of the sequences from the new EVD cluster in historical and geographical context (**B**).

Late Ebola Virus Relapse Causing Meningoencephalitis: A Case Report

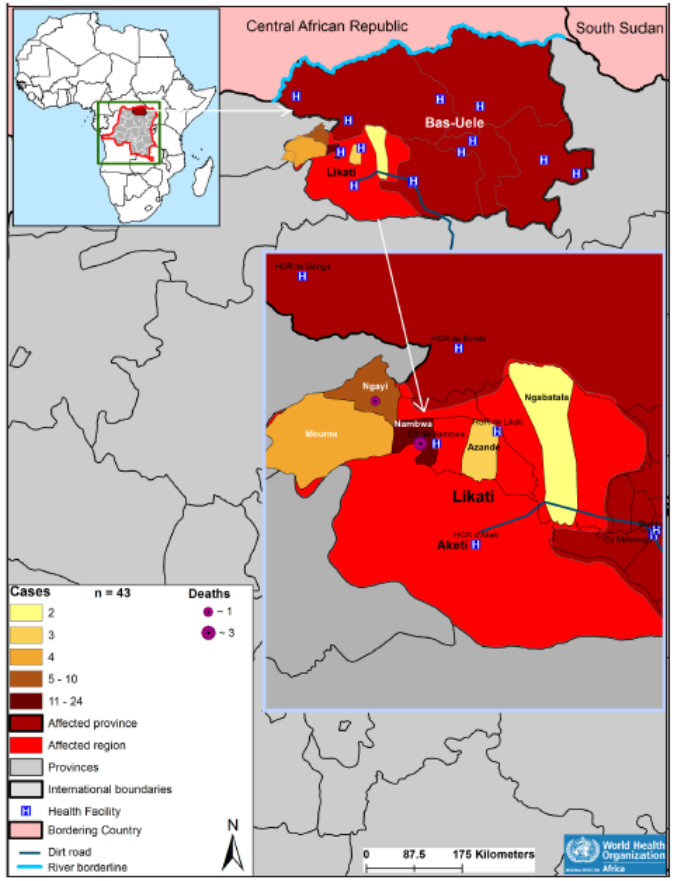
- 39-year-old female nurse from Scotland.
- EVD in Sierra Leone.
  - Received intensive supportive treatment and experimental antiviral therapies.
  - Discharged with undetectable Ebola virus RNA in peripheral blood.
- Readmitted to hospital 9 months after discharge with symptoms of acute meningitis.
  - RT-PCR : Ebola virus RNA at a higher level in CSF than plasma.
  - Infectious virus recovered from CSF.
  - Meningoencephalitis, cranial neuropathies and radiculopathy.
  - GS-5734 treatment + high-dose corticosteroids.
  - CSF Ebola virus RNA undetectable following 14 days of treatment with GS-5734.

Jacobs M. Lancet 2016;388:498-503 http://dx.doi.org/10.1016/S0140-6736(16)30386-5

WHO. Ebola Situation Report (May 24, 2017)
New Cluster in the Democratic Republic of Congo

- A total of two confirmed cases have been reported, three probable cases and 38 suspected cases from five health areas :
  - Nambwa : 24 cases* and 3 deaths.
  - Muma : 4 cases.
  - Ngayi : 10 cases* and 1 death.
  - Azande : 3 cases.
  - Ngabatala : 2 cases.
- No HCW affected to date.
- The majority of the cases presented with fever, vomiting, bloody diarrhoea and other bleeding symptoms and signs.
- As of 24 May :
  - 520 contacts listed.
  - 226 completed 21 days of contact monitoring.
  - 294 contacts under daily follow up for signs and symptoms of Ebola.

Figure 1. Geographical distribution of cases in the current EVD outbreak in the Democratic Republic of Congo as of 21 May 2017



As this is a rapidly changing situation, the reported number of cases and deaths, contacts being monitored and the laboratory results are subject to change due to enhanced surveillance, contact tracing activities, on-going laboratory investigations, reclassification, and case, contact and laboratory data consolidation.

http://www.afro.who.int/en/ebola/ebola-situation-reports.html

Ebola Virus Disease
Specific Treatment and Vaccine

Evaluation of Convalescent Plasma for Ebola Virus Disease in Guinea

- Nonrandomized, comparative study
- 99 pts with confirmed EVD
- 2 consecutive transfusions
  - 200 to 250 ml of ABO-compatible convalescent plasma
  - initiated on the day of diagnosis or up to 2 days later
- Control group :
  - 418 pts from the same center
  - During the previous 5 months

Conclusions :
The transfusion of up to 500 ml of convalescent plasma with unknown levels of neutralizing antibodies in 84 patients with confirmed EVD was **not associated** with a significant improvement in survival

Table 2. Primary Outcome Analysis.*

Variable	Convalescent Plasma (N=84)	Control (N=418)	P Value for Interaction†
Death 3 days to 16 days after diagnosis — no. (%)	26 (31)	158 (38)	
Odds ratio for death (95% CI)			
Unadjusted	0.74 (0.45–1.22)	1.00	
Adjusted for age and cycle-threshold value	0.88 (0.51–1.51)	1.00	
Adjusted for cycle-threshold value according to age group			0.92
<5 yr	0.18 (0.02–2.12)	1.00	
5–15 yr	0.75 (0.08–7.41)	1.00	
16–44 yr	0.86 (0.44–1.68)	1.00	
≥45 yr	1.52 (0.48–4.88)	1.00	
Adjusted for age according to cycle-threshold value			0.43
<25 cycles	0.87 (0.34–2.22)	1.00	
25–29.9 cycles	0.81 (0.37–1.76)	1.00	
≥30 cycles	1.11 (0.31–3.97)	1.00	

* The primary outcome was the risk of death in the 14 days after the administration of convalescent plasma. Included in the analysis were all deaths that occurred up to 16 days after PCR confirmation of EVD on real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay in the two groups to allow for plasma administration up to and including the second day after RT-PCR confirmation. Patients who had died before the third day after confirmation of EVD on RT-PCR were excluded from the analysis to provide a similar starting point for measuring survival. The unadjusted between-group difference in the convalescent-plasma group was −7 percentage points (95% confidence interval [CI], −18 to 4), and the adjusted between-group difference was −3 percentage points (95% CI, −13 to 8).

† P values, calculated with the use of likelihood ratio tests, are for the comparison of models that included terms for the interaction of study group with the factor of interest with models that did not include interaction terms.

Van Griensven J NEJM 2016;374:33-42 DOI: 10.1056/NEJMoa1511812

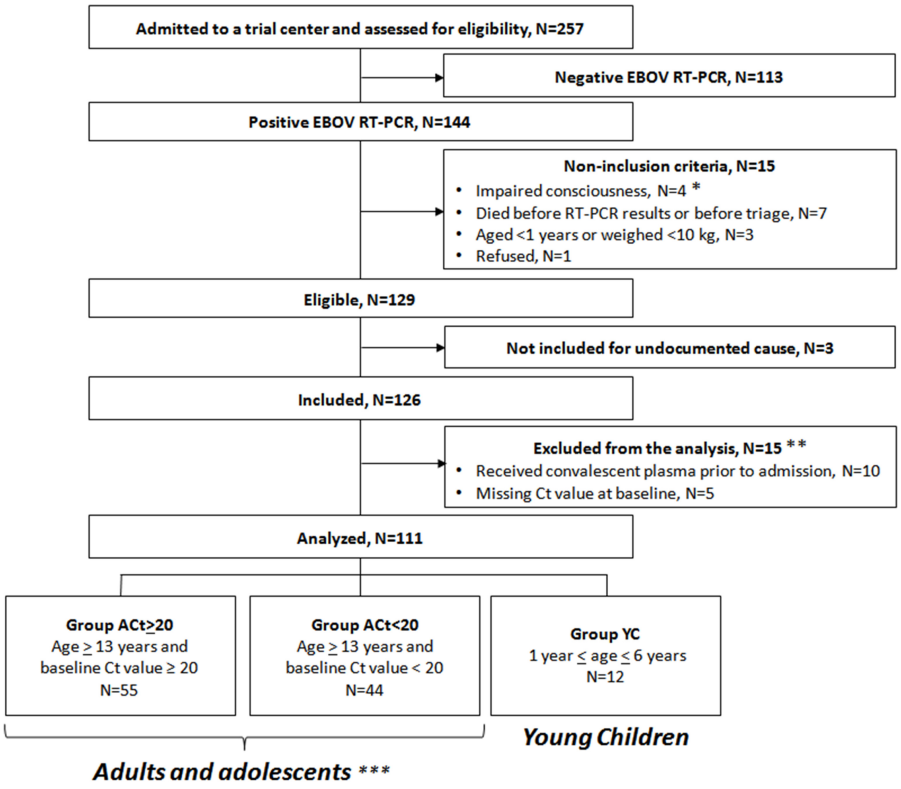
Experimental Treatment with Favipiravir for Ebola Virus Disease (the JIKI Trial), Guinea

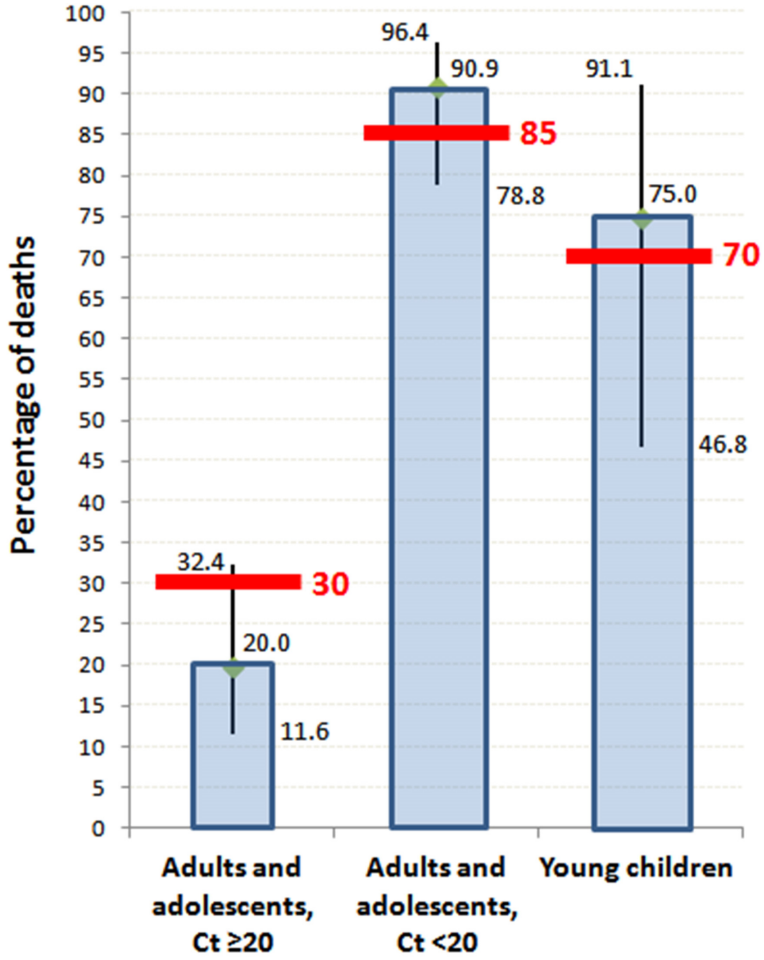
- Non-randomized trial.
  - Context of an outbreak at its peak.
  - Crowded care centers.
  - Randomization with an experimental drug not judged appropriate.
- No conclusion on the efficacy of the drug.
- Significant improvement in the Ct ≥ 20 group.
- Frequency of renal dysfunction and the powerful prognostic value of low Ct values.
- Prognostic value of renal failure (creatinine level).

Drug trials in EVD should systematically stratify analyses by baseline Ct value, as a surrogate of viral load.
Favipiravir monotherapy merits further study in patients with medium to high viremia, but not in those with very high viremia.

Ct : cycle threshold

Experimental Treatment with Favipiravir for Ebola Virus Disease (the JIKI Trial), Guinea



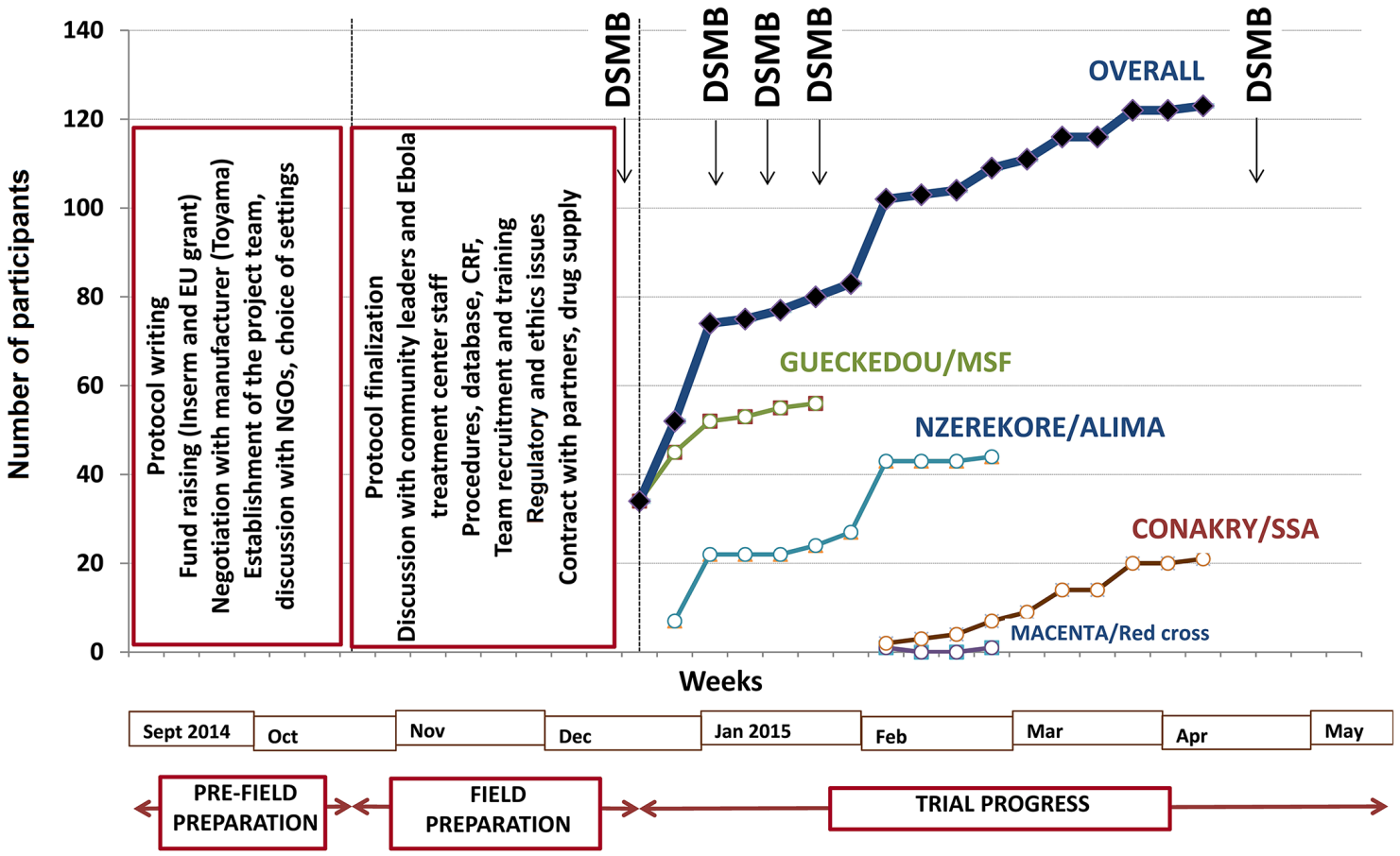


Ct = 20 corresponding to RNA viral load = 7.7 $\log_{10}$ genome copies/ml

N of patients	55	44	12
N of deaths	11	40	9

JIKI trial mortality, according to age and baseline RT-PCR Ct value

Experimental Treatment with Favipiravir for Ebola Virus Disease (the JIKI Trial), Guinea

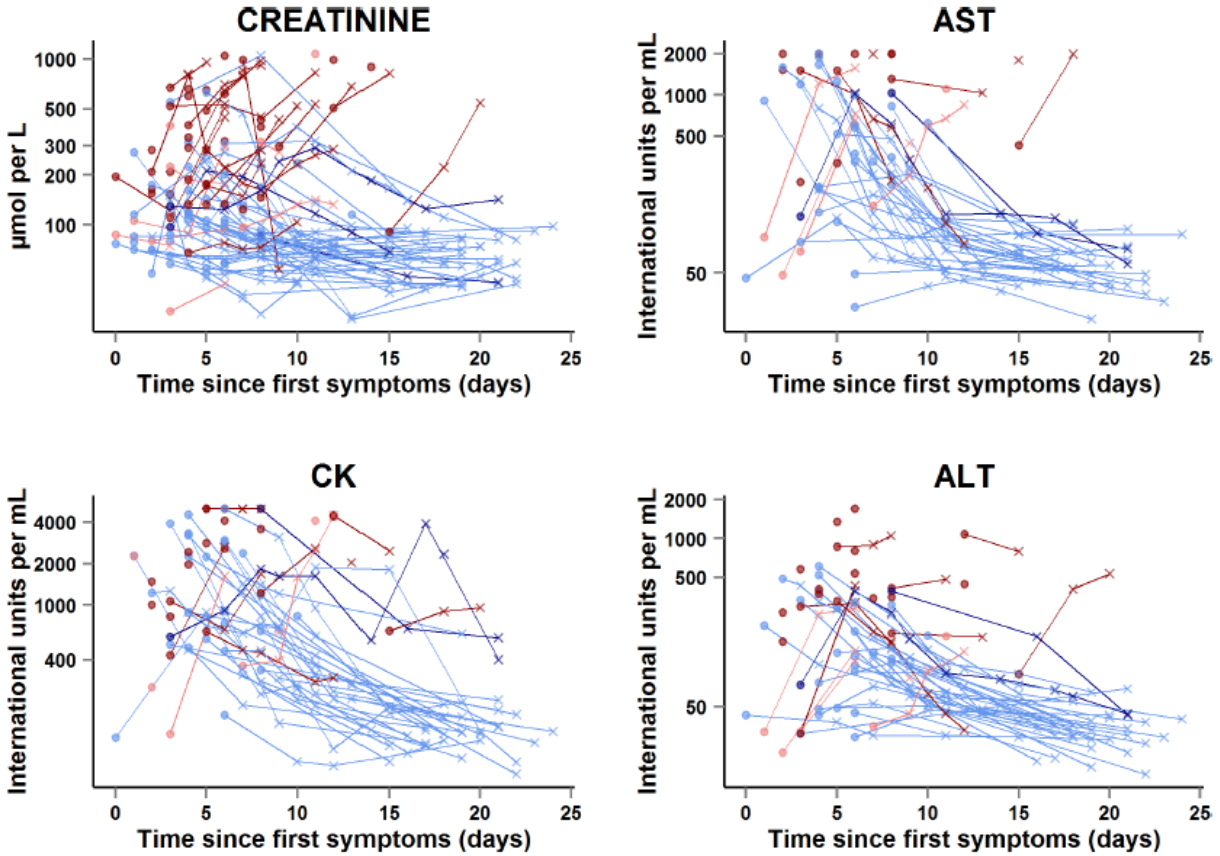


JIKI trial progress

Sissoko D Plos Medicine 2016 DOI:10.1371/journal.pmed.1001967

Experimental Treatment with Favipiravir for Ebola Virus Disease (the JIKI Trial), Guinea

Evolution of serum creatinine, aspartate aminotransferase, alanine aminotransferase, and creatine phosphokinase in adolescents and adults

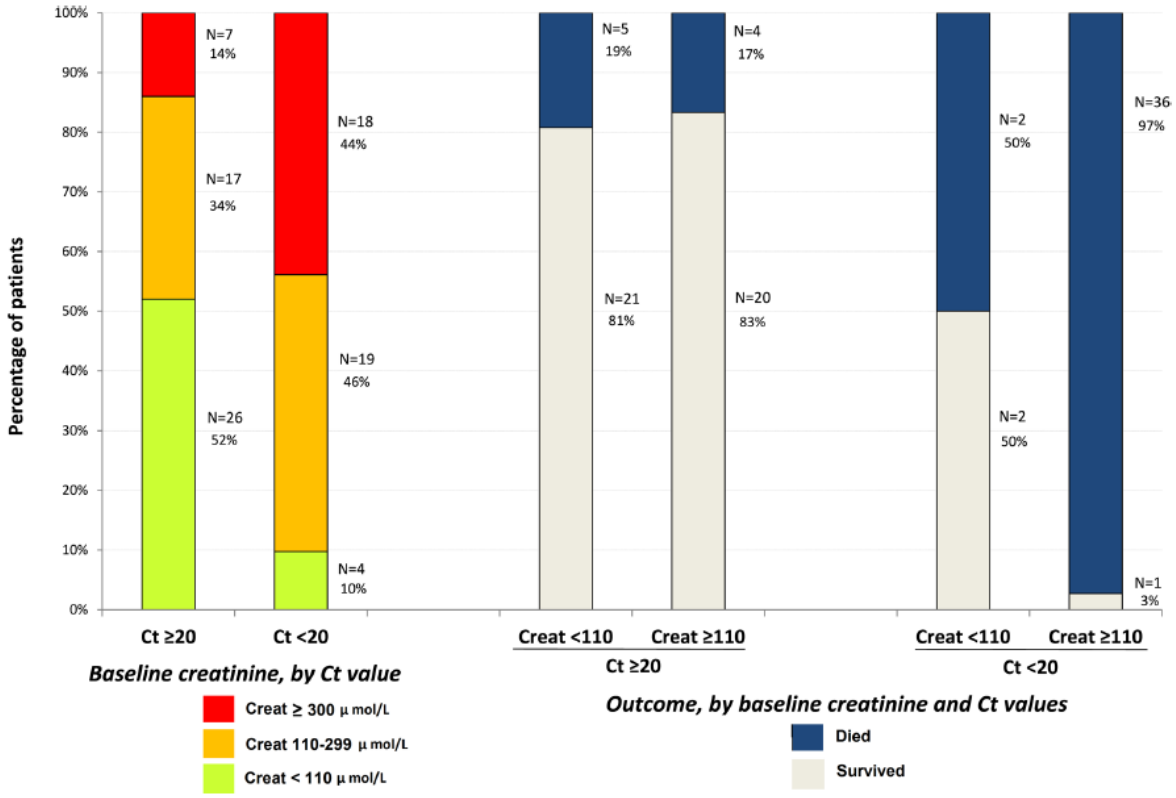


Red symbols represent patients who died; blue symbols represent patients who survived. Dark red lines represent patients with baseline Ct < 20 who died, light red lines represent patients with baseline Ct 20 who died, dark blue lines represent patients with baseline Ct < 20 who survived, and light blue lines represent patients with baseline Ct 20 who survived.

Sissoko D Plos Medicine 2016 DOI:10.1371/journal.pmed.1001967

Experimental Treatment with Favipiravir for Ebola Virus Disease (the JIKI Trial), Guinea

Baseline serum creatinine in adolescents and adults and outcomes according to baseline values.

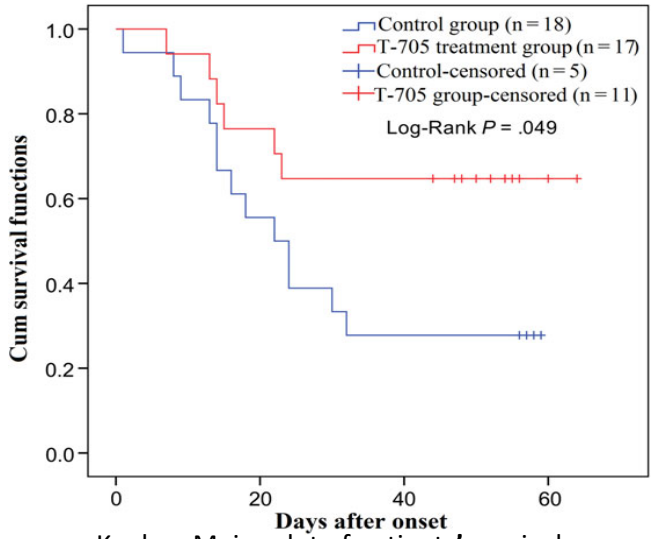


Sissoko D Plos Medicine 2016 DOI:10.1371/journal.pmed.1001967

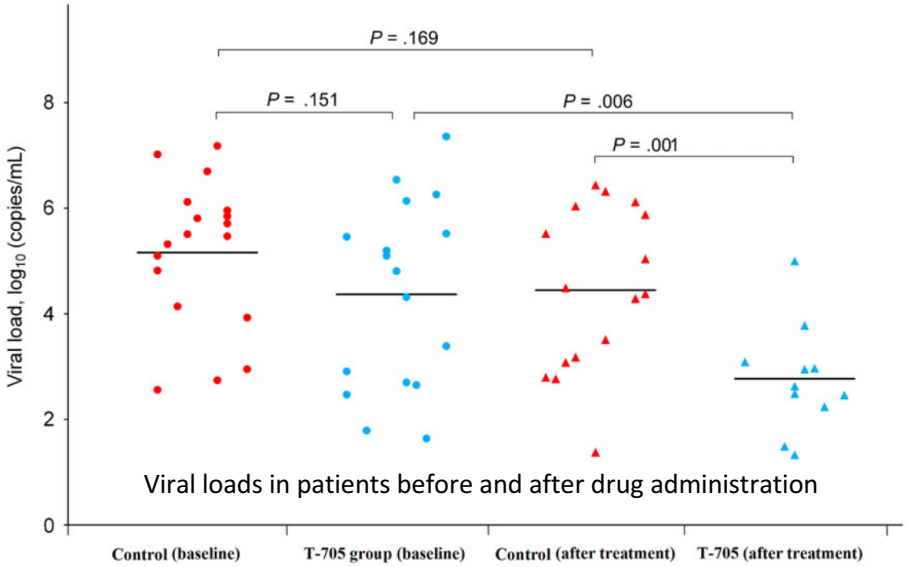
Clinical and Virological Characteristics of EVD Patients Treated With Favipiravir (T-705)—Sierra Leone, 2014

- Retrospective clinical case series, Sierra Leone.
- Confirmed EVD pts enrolled and treated:
  - WHO–recommended supportive therapy (control group).
  - WHO-recommended therapy + favipiravir (T-705).
- Survival and virological characteristics were observed for 85 patients in the control group and 39 in the T-705 treatment group.
- Survival rate :
  - Overall T-705 *vs* control group : 56.4% (22/39) vs 35.3% (30/85); *P* = 0.027).
  - Among 35 pts who complete the T-705 treatment : 64.8% (11/17) vs 27.8% (5/18).
- Average survival time :
  - T-705 (46.9 ± 5.6 days) *vs* control group (28.9 ± 4.7 days).
- >100-fold viral load reduction :
  - 52.9% of T-705 treated pts vs 16.7% of patients in control group.

Treatment of EVD with T-705 associated with prolonged survival and markedly reduced viral load.



Kaplan–Meier plot of patients' survival



Viral loads in patients before and after drug administration

BAI CQ Clin Infect Dis 2016;63:1288-94 DOI: 10.1093/cid/ciw571

Experimental Treatment of EVD with TKM-130803: A Single-Arm Phase 2 Clinical Trial

- TKM-130803 :
  - a small interfering RNA lipid nanoparticle product
  - Effective in primate model of infection
- Single-arm phase 2 trial
  - Adults with confirmed EVD
  - 0.3 mg/kg of TKM-130803 by IV infusion once daily for up to 7 d.
  - Pts enrolled into a concurrent observational cohort.
  - Primary outcome : survival to day 14
- The probability that a TKM-130803 pt survive to day 14 was estimated to be 0.27 (95% CI 0.06, 0.58).

Table 2. Timelines, TKM-130803 doses received, and outcomes.

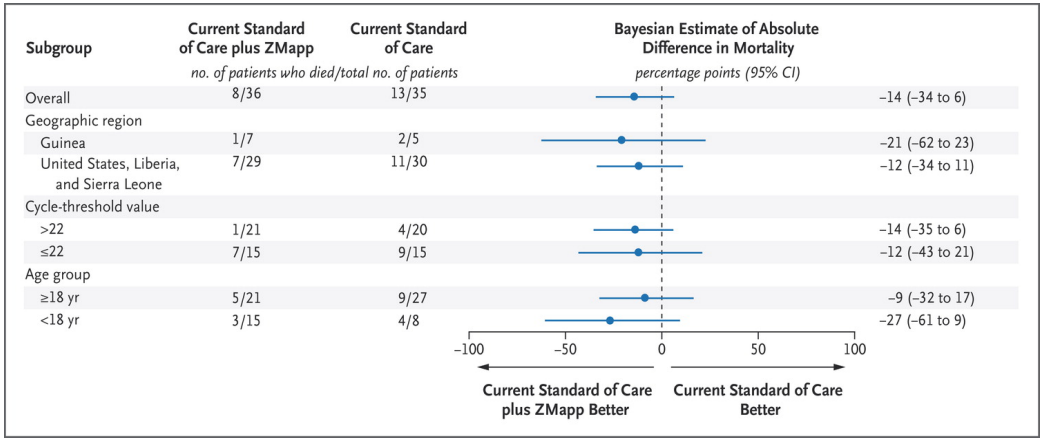
Patient ID	Cohort	Day of Onset	DOA	DOA +1	DOA+2	DOA +3	DOA+4	DOA +5	DOA+6	DOA +7	DOA +8	Outcome
203-001	TKM	-4	EVD+	Dose1*	Dose2	Dose3*	Dose4	Dose5	Dose6	Dose7		Alive & Discharged DOA +15
203-002	OBS	Day of onset unknown	EVD+			Died						Died
203-003	OBS	-4	EVD+			Died						Died
203-004	TKM	-2		EVD+		Dose1 Died						Died
203-005	TKM	-4		EVD+	Dose1	Dose2	Dose3 Died					Died
203-006	OBS	-6	EVD+									Alive & Discharged DOA +9
203-007	TKM	-3	EVD+		Dose1	Dose2	Dose3	Dose4	Dose5	Dose6	Dose7	Alive & Discharged DOA +13
203-020	TKM	-1	EVD+	Dose1	Dose2	Dose3	Dose4	Died				Died
203-021	TKM	-1	EVD+	Dose1	Dose2	Dose3	Dose4	Died				Died
203-022	TKM	-2		EVD+	Dose1	Dose2	Died					Died
203-025	TKM	-2	EVD+	Dose1	Dose2 Died							Died
203-027 †	TKM	-1	EVD+	Dose1	Died							Died
203-028	TKM	-1	EVD+	Dose1	Dose2*	Dose3	Dose4	Dose5	Dose6	Dose7		Alive & Discharged DOA +11
203-030 †	TKM	-3	EVD+	Dose1*	Died							Died
203-031	TKM	0		EVD + Dose 1	Dose2	Dose3	Dose4	Dose5	Dose6	Dose7 Died		Died
203-032	TKM	Day of onset unknown		EVD + Dose 1	Dose2	Dose3	Dose4	Dose5	Dose6	Dose7 Died		Died
203-034	TKM	-1	EVD+	Dose1	Dose2	Dose3 Died						Died

TKM-130803 given once daily at the dose used in this trial did not improve survival in patients with EVD compared to historic controls (survival greater than 0.55)

Dunning J Plos Medicine 2016 http://dx.doi.org/10.1371/journal.pmed.1001997

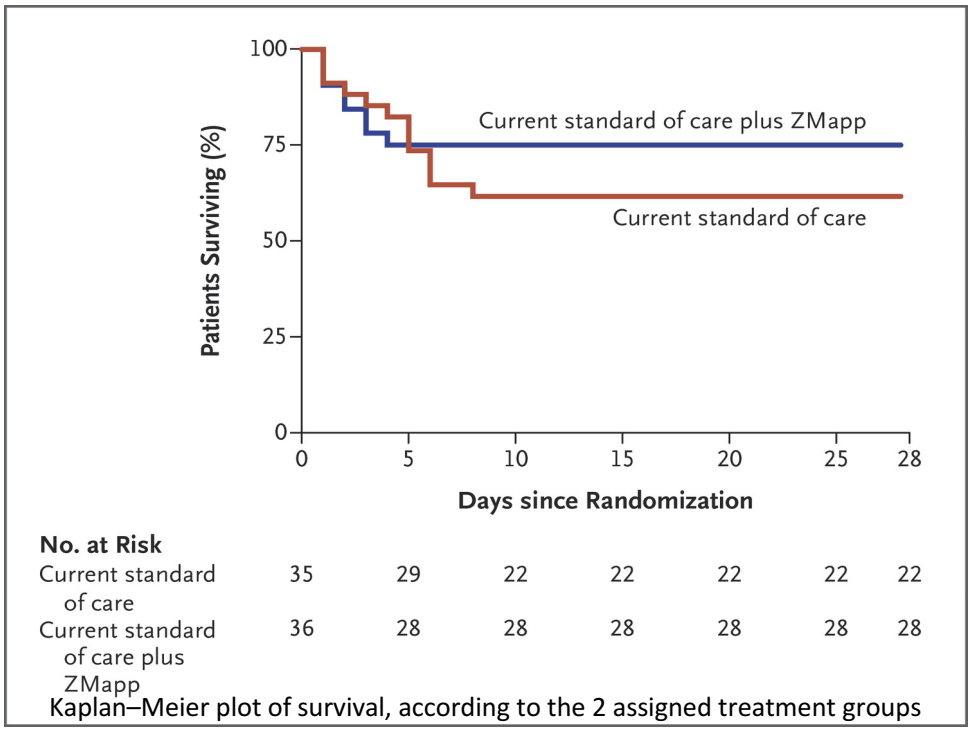
A Randomized, Controlled Trial of ZMapp for EVD (Multi-National PREVAIL II Study)

- Randomized, controlled trial.
  - Zmapp + current standard of care.
  - *versus* current standard of care alone.
  - Patients with confiermed EVD.
- ZMAPP : 50 mg/kg, IV, every third day.
- Primary end point : mortality at 28 days.
- 72 pts enrolled, stratification :
  - According to baseline PCR cycle-threshold value for the virus (≤ 22 *vs* > 22).



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

Although the estimated effect of ZMapp appeared to be beneficial, the result did not meet the prespecified statistical threshold for efficacy.



Kaplan–Meier plot of survival, according to the 2 assigned treatment groups

Table 2. Comparison of 28-Day Mortality According to Treatment Group.*

Variable	Current Standard of Care Alone	Current Standard of Care plus ZMapp	Bayesian Estimate of Absolute Difference	Bayesian Estimate of Relative Risk	Posterior Probability That ZMapp Was Superior
			percentage points (95% CI)	*value (95% CI)*	%
No. of patients alive	22	28			
No. of patients who died	13	8			
No. of patients lost to follow-up	1	0			
28-Day mortality — %	37†	22†	−14 (−34 to 6)	0.62 (0.29 to 1.24)	91.2

* CI denotes credible interval.
† These are crude non-Bayesian estimates.

Davey RT N Engl J Med 2016; 375:1448-1456 DOI: 10.1056/NEJMoa1604330

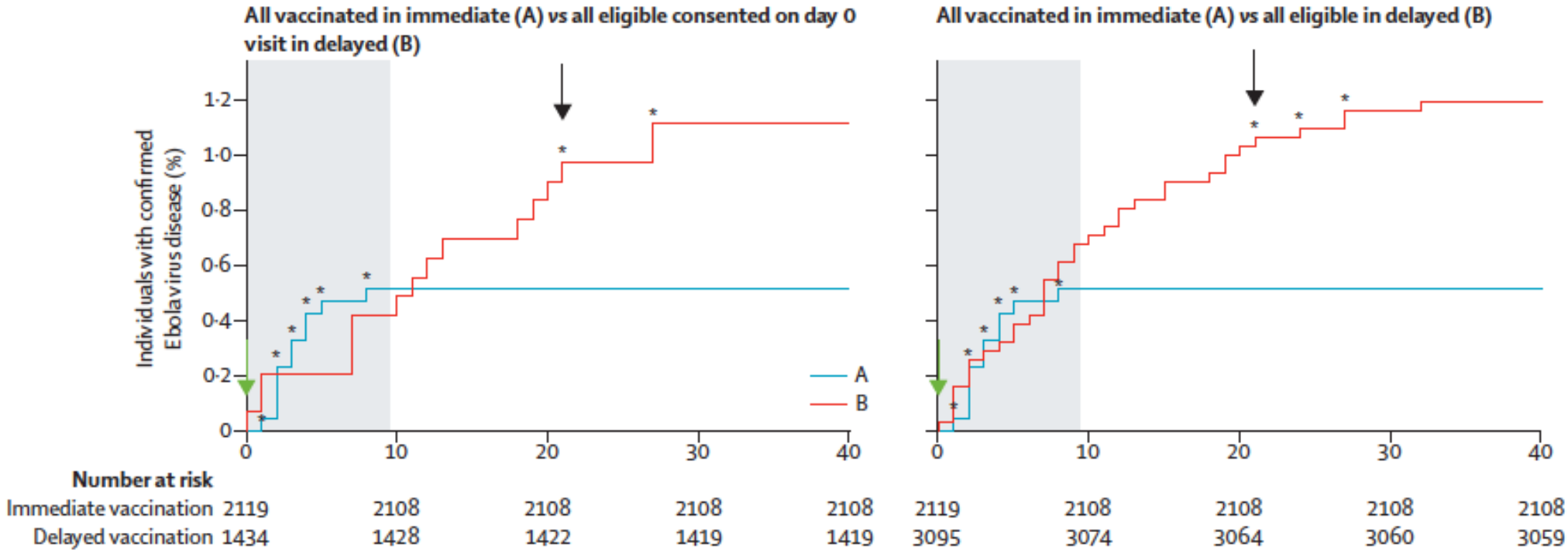
Efficacy and Effectiveness of an rVSV-Vectored Vaccine in Preventing EVD

- Final Results from the Guinea Ring Vaccination, Open-label, Cluster-Randomized Trial (Ebola Ça Suffit!);
- rVSV-ZEBOV :
  - A recombinant, replication competent vesicular stomatitis virus-based candidate vaccine.
  - Expressing a surface glycoprotein of Zaire Ebolavirus.
- Clusters (contacts and contacts of contacts of recently confirmed EVD).
  - Randomly assigned to either immediate vaccination.
  - or delayed vaccination (21 days later) of all eligible individuals.
  - Single IM dose of rVSV-ZEBOV in the prevention of laboratory confirmed EVD.
- Primary outcome :
  - Confirmed case of EVD with onset 10 days or more from randomization.
- Results :
  - No cases of Ebola virus disease occurred 10 days or more after randomization among randomly assigned contacts and contacts of contacts vaccinated in immediate clusters.
  - *versus* 16 cases (7 clusters affected) among all eligible individuals in delayed clusters.
  - Vaccine efficacy : 100% (95% CI 68.9–100.0, p=0.0045).

Henao-Restrepo AM Lancet 2017 Feb 4; 389(10068): 505–518 doi: 10.1016/S0140-6736(16)32621-6

Efficacy and Effectiveness of an rVSV-Vectored Vaccine in Preventing EVD

Kaplan-Meier plots for confirmed cases of EVD in different study populations



Arrows show time of vaccination (at day 0 or day 21); the plus signs denote cases among non-eligible children and the stars denote cases among vaccinated individuals; the shaded area denotes the a priori defined lag time of 0–9 days.

Henao-Restrepo AM Lancet 2017 Feb 4; 389(10068): 505–518 doi: 10.1016/S0140-6736(16)32621-6

Efficacy and Effectiveness of an rVSV-Vectored Vaccine in Preventing EVD

	All clusters*				Randomised clusters†			
	1	2	3	4	5	6	7	8
	All vaccinated in immediate (group A) *vs* all contacts and contacts of contacts in delayed plus all never-vaccinated in immediate or non-randomised (group B)	All vaccinated in immediate (group A) *vs* all eligible in delayed plus all eligible never-vaccinated in immediate (group B)	All contacts and contacts of contacts in immediate (group A) *vs* delayed (group B)	All vaccinated in immediate (group A) *vs* all eligible never vaccinated in immediate (group B)	All vaccinated in immediate (group A) *vs* all eligible and consented on day 0 visit in delayed (group B)	All vaccinated in immediate (group A) *vs* all eligible in delayed (group B)	All eligible in immediate (group A) *vs* all eligible delayed (group B)	All contacts and contacts of contacts in immediate (group A) *vs* all contacts and contacts of contacts in delayed (group B)
Group A								
Number of individuals (clusters)	3775 (70)	3775 (70)	7241 (70)	3775 (70)	2108 (51)	2108 (51)	3212 (51)	4513 (51)
Cases of Ebola virus disease (clusters affected)	0 (0)	0 (0)	12 (7)	0 (0)	0 (0)	0 (0)	7 (4)	10 (5)
Attack rate	0%	0%	0·17%	0%	0%	0%	0·22%	0·22%
Group B								
Number of individuals (clusters)	7995 (116)	4507 (104)	4529 (47)	1432 (57)	1429 (46)	3075 (47)	3075 (47)	4529 (47)
Cases of Ebola virus disease (clusters affected)	34 (15)	23 (11)	22 (8)	7 (4)	10 (4)	16 (7)	16 (7)	22 (8)
Attack rate	0·43%	0·51%	0·49%	0·49%	0·7%	0·52%	0·52%	0·49%
Vaccine effect								
Vaccine efficacy/ effectiveness‡ (%, 95% CI)	100% (77·0 to 100·0)	100% (79·3 to 100·0)	70·1% (−4·9 to 91·5)	100% (−51·5 to 100·0)	100% (63·5 to 100·0)	100% (68·9 to 100·0)	64·6% (−46·5 to 91·4)	64·6% (−44·2 to 91·3)
p value§	0·0012	0·0033	0·2759	0·125	0·0471	0·0045	0·344	0·3761

*Randomly assigned and non-randomly assigned individuals who were allocated to immediate vaccination were combined. †Non-randomised immediate clusters are excluded from this analysis. ‡From fitting a β-binomial distribution to the cluster-level numerators and denominators and using an inverted likelihood ratio test to identify the lower bound for vaccine efficacy (columns 1, 2, 5, and 6); from a Cox proportional hazards model (column 3, 7, and 8); from signed test (two-sided): probability of observing endpoints in control groups among treatment–control mismatched pairs and under the null hypothesis that the vaccine has no efficacy (column 4). §From Fisher's exact test (two-sided), which is approximate for columns 1 and 2. From signed test (two-sided): probability of observing endpoints in control groups among treatment–control mismatched pairs and under the null hypothesis that the vaccine has no efficacy (column 4).

***Table 3*: Effect of vaccine on cases of Ebola virus disease in different study populations**

Henao-Restrepo AM Lancet 2017 Feb 4; 389(10068): 505–518 doi: 10.1016/S0140-6736(16)32621-6

EVD Prevention : Healthcare Workers and Settings

- Preparing for Ebola – A Tiered Approach
- Personal Protective Equipment (PPE)
- Evaluating Patients
- Cleaning and Disinfecting Healthcare Environments
- Emergency Services
- Hospitals
- Outpatients and Ambulatory Care Settings
- Laboratories

https://www.cdc.gov/vhf/ebola/healthcare-us/

Lesson From Ebola Virus Disease: The Rich and the Poor

Begin Military Hospital, Paris, France

Ebola treatment unit for HCW, Conakry, Guinea

Photography Pr C Rapp

Lesson From Ebola Virus Disease

- Case-fatality rate around 50% (25-90% in past outbreaks).
- Zoonotic disease : important animal reservoir.
- Direct transmission by contact with sick or dead people or contaminated fluids : HCW at high risk.
- Sexual transmission documented.
- Post-EVD period characterized by clinical sequelae, delayed viral clearance in immunologically protected sites (semen), psychological distress, and social impact.
- High viral load at onset predictive of sequelae and lack of response to antiviral treatment.
- Late relapse described.
- Vigilance to be maintained : surveillance in at risk area, training of HCW for all Ebola-related infection control practices and procedures.

Emerging Infectious Diseases : an Old Concept

- 1926 :
  - *“I am very concerned at the idea of what would become of a unscathed so far population, if a new, infectious agent, were to spread”.*
- 1935 :
  - *“Infectious diseases will never disappear. It comes always to news; some of them will disappear slowly; those who remain won't show more in the form we know today”.*

Charles Nicolle. Le destin des Maladies Infectieuses. 1926 et 1935