



# Recherche et Actions Humanitaires

## Leçons apprises des épidémies en Guinée et RDC

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Dpt des Maladies Infectieuses, CHU Montpellier



# Contexte de la MVE



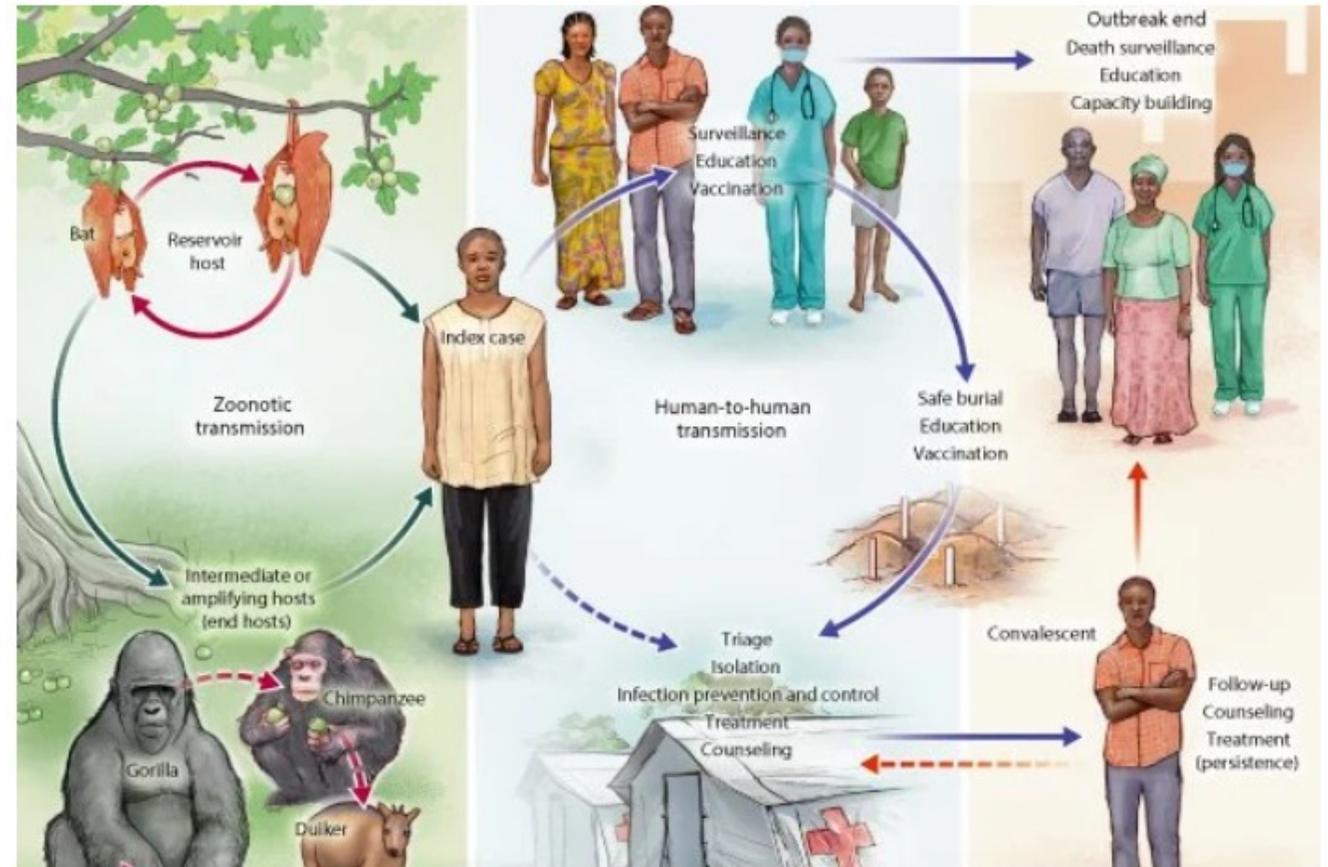
**1976**  
Première découverte au Soudan, et à Yambuku en RD Congo

## Maladie à Virus Ebola –

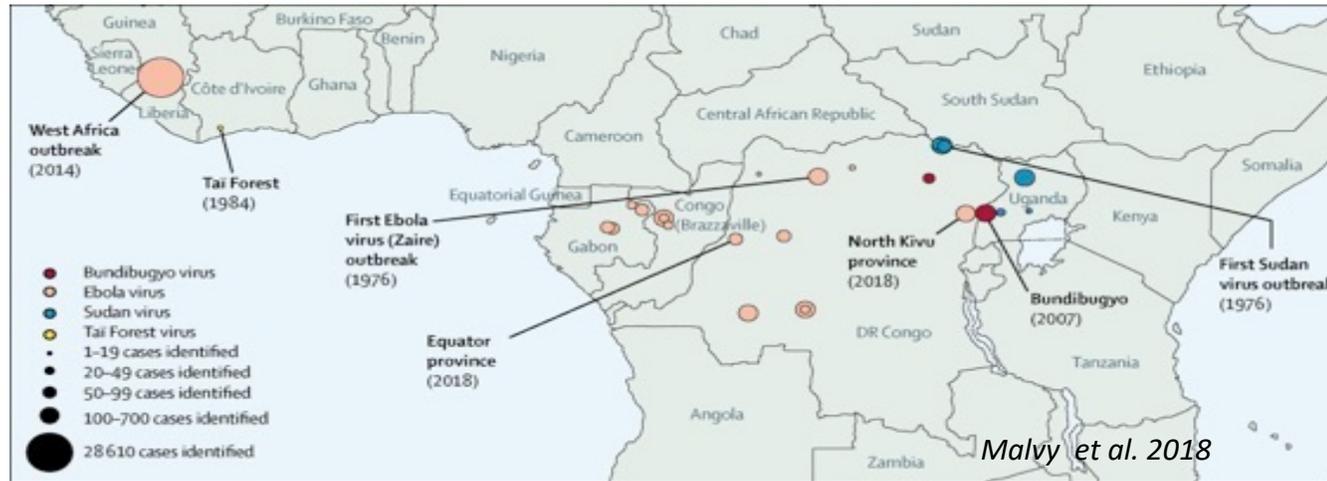
Fièvre hémorragique d'origine virale causée par le **Virus Ebola** (*Orthoebolavirus*), maladie grave souvent mortelle pouvant atteindre des taux de létalité de 50 à 90%



## Transmission et évolution de la MVE



# Ebola: 30 outbreaks since 1976



1976-1978: 3 outbreaks

1994-1996: Ivory Coast, DRC, Gabon

rural/semi-rural areas

Limited number of victims

2014-2016:

**Major outbreak in West Africa**

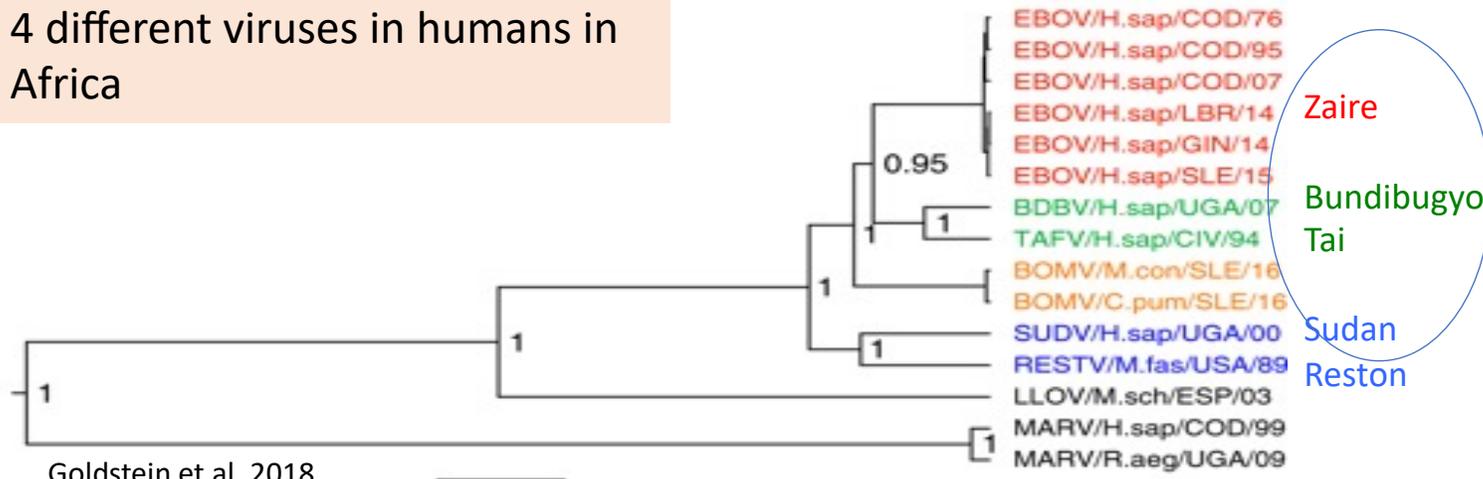
10 X victims than all previous outbreaks

**Increasing frequency**

4 outbreaks in DRC (5/2017-8/2019-2020)

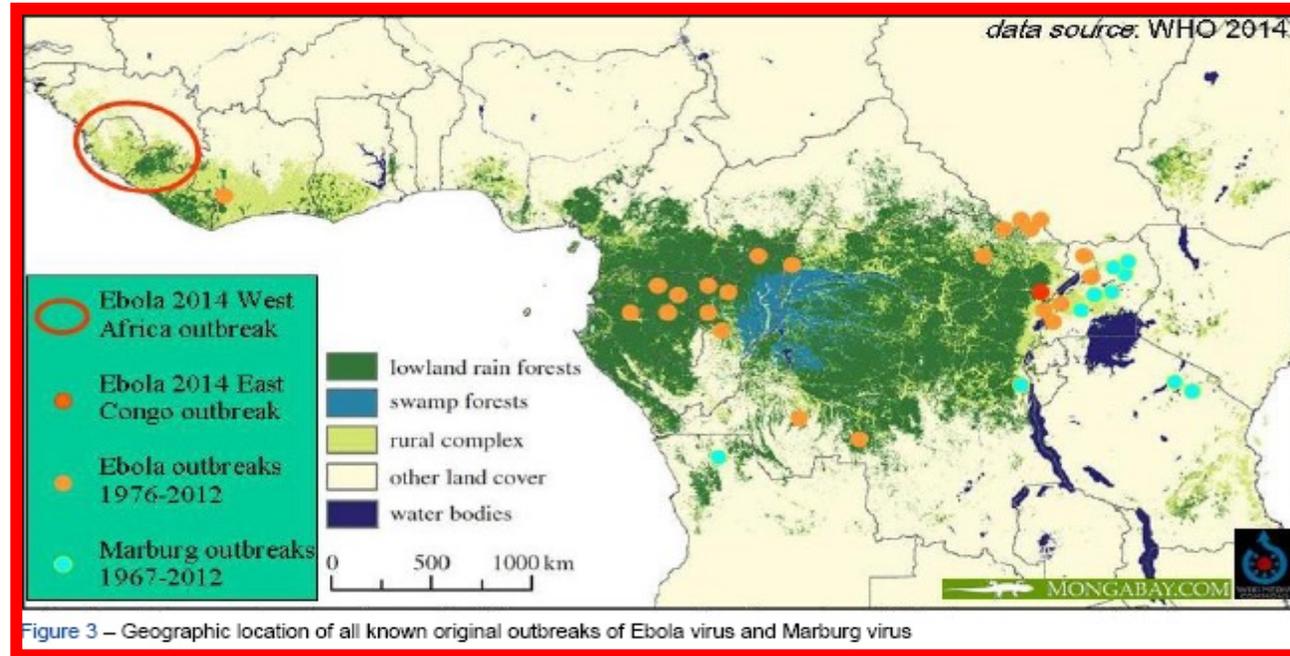
**Major Outbreak in North Kivu & Ituri**

4 different viruses in humans in Africa



Goldstein et al. 2018

# Ebola en 2014 après 28 « outbreaks » depuis 1976



**Treatment:** O

**Vaccin:** O

**Diagnosis:** home-based

**Clinical consequences :** « death »

**Origin:** Spillover ... bats but ...

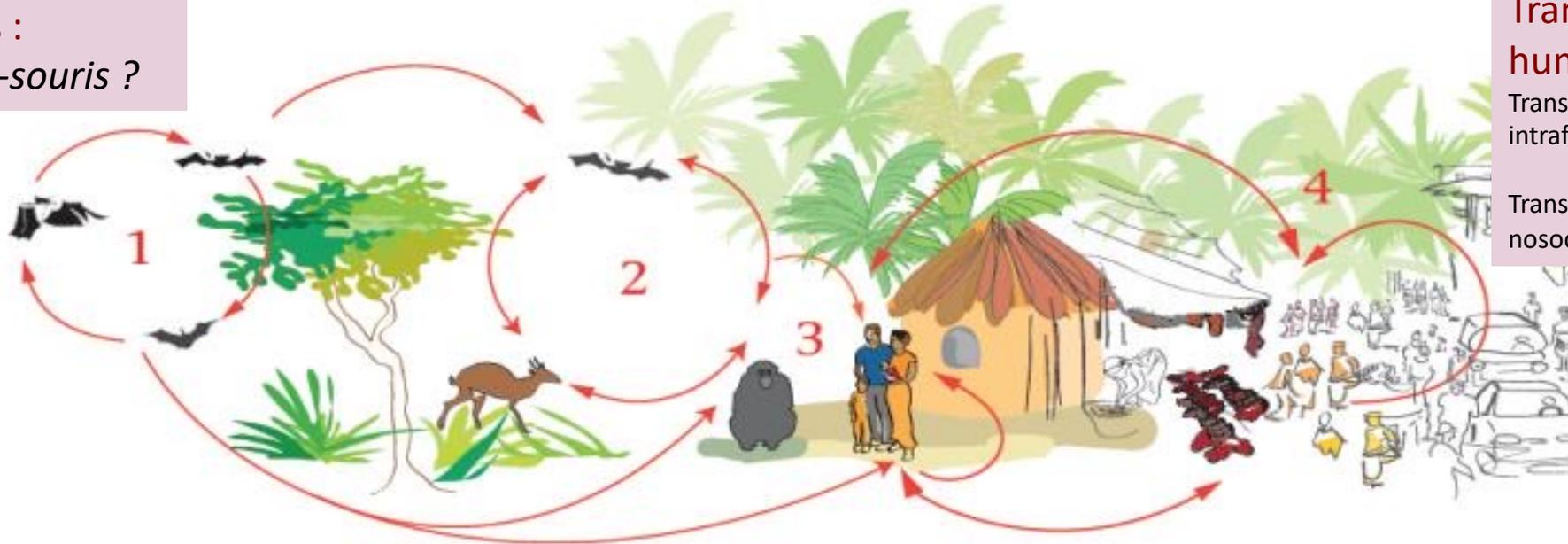
« a minor public health threat for Africa ... »

# Origine des épidémies

*Chaque épidémie chez les humains = événement de transmission zoonotique indépendant*

Ebola virus circulation and transmission within a forest socio-ecosystem:  
(1) bats (2) wildlife (3) contact between man and wildlife (4) human communities © D. Guard-Lavastre/CIRAD, after CDC:  
<http://www.cdc.gov/vhf/ebola/resources/virus-ecology.html>

1. réservoirs :  
*Chauves-souris ?*



4. Transmission humaine  
Transmission intrafamiliale  
Transmission nosocomiale

2. Hôtes intermédiaires ou amplificateur:  
*Primates non-humains, antilopes, autres*

3. Transmission inter-espèces  
*de la faune sauvage à l'homme*

© CIRAD, January 2015

# Comment l'homme s'infecte-t-il?

## Exposition au sang ou organes infectés

Viande de brousse et chasse (réservoirs ou hôtes réservoirs intermédiaires)

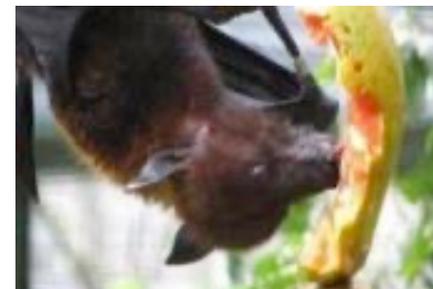
Animaux morts trouvés dans la forêt

Primates non-humains, chauves-souris, antilopes, etc.



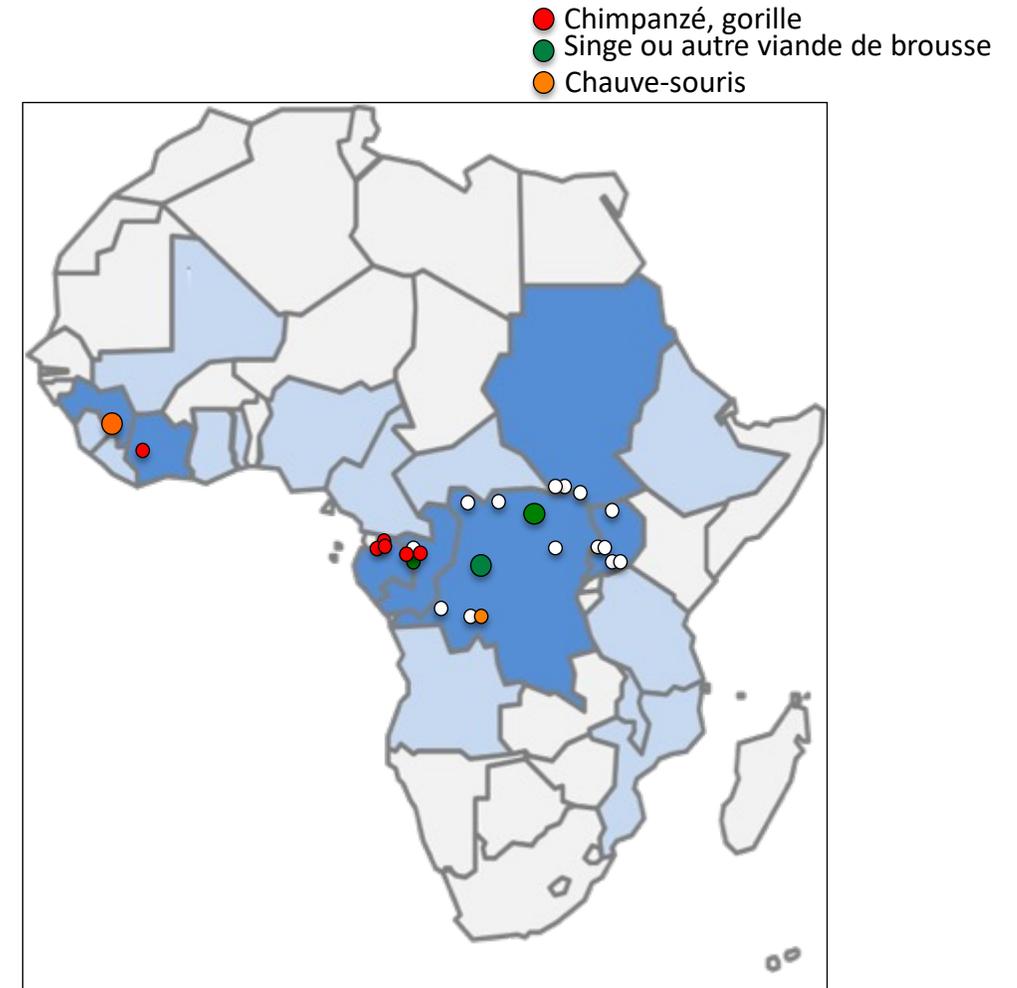
## Exposition aux produits biologiques infectés (urine, salive, selle, etc.)

Ex. Fruits contaminés par la salive des chauves-souris, etc.



# Origine zoonotique identifiée/suspectée dans certaines épidémies

- **Contact avec les chimpanzés et gorilles**  
*présence de l'ARN viral*
  - Cote d'Ivoire : 1994
  - Gabon et Congo: 1996-2003
- **Contact avec le singe ou autre viande de brousse**
  - RDC: 1976, 2014, 2017?
  - Congo: 2003?
- **Contact avec les chauves-souris**
  - RDC: 2007, 2008 ?
  - Guinée: 2014?



# Role of bats suspected in 2 outbreaks

- **Exposure to bushmeat**

In 2007 in Luebo, DRC (Leroy et al, 2009)



- **Indirect exposure to infected bats:**

2013 Guinea

the burnt tree that housed a bat colony in Meliandou where the index case ( 2years old child) could have been infected



(Marí Saéz et al. EMBO Mol Med. 2015)

(Marí Saéz et al. EMBO Mol Med. 2015)

# Transmission des « FHV » (Ebola)

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- Un patient contaminé asymptomatique n'est pas contagieux
- Tous les liquides biologiques sont contagieux : sang, selles, vomissements, urines, ...
- La contagiosité augmente avec la progression de la maladie (charge virale)

# Transmission des « FHV » (Ebola)

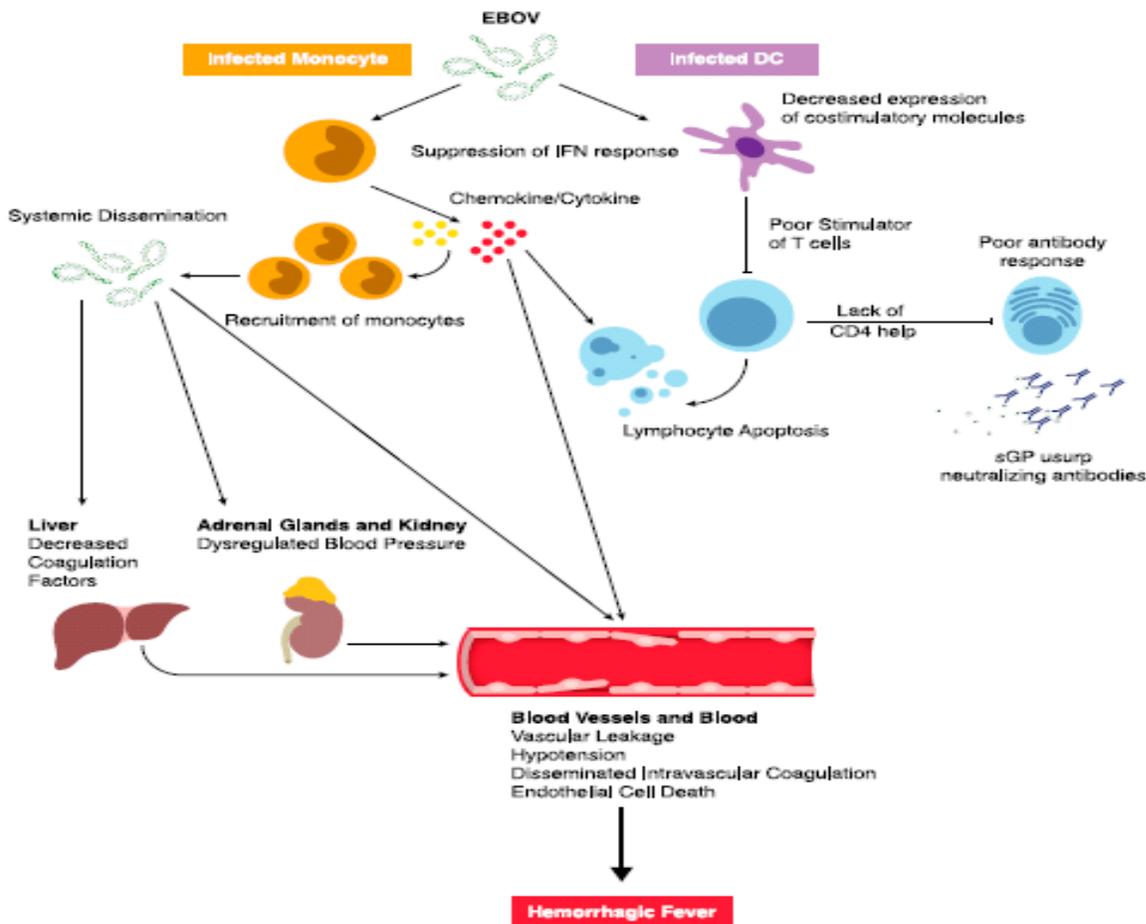
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- Le virus ne franchît pas la peau saine
- Contact sur peau lésée ou sur les muqueuses
- L'environnement peut être contaminé (persistance plusieurs heures)
- La transmission aérienne n'est pas authentifiée (transport en avion)

# La maladie à virus Ébola (avant 2014...)



- La maladie aiguë
- Forme sévère



Incubation: 2 à 21J le plus souvent de 4 à 9 jours  
CRF: >80%...

	Time since symptom onset	Clinical features	Typical patient
Early febrile or mild stage	0–3 days	Non-specific features: fever, weakness, lethargy, and myalgia	Ambulatory, able to compensate for fluid losses; no indication for intravenous fluid administration
Gastrointestinal involvement	3–10 days	Same as early stage plus diarrhoea, vomiting, or both, or abdominal pain	Unable to compensate for fluid losses because of emesis or large volume losses; indication for intravenous fluid administration
Complicated stage	7–12 days	Same as gastrointestinal involvement stage plus haemorrhage, shock, organ failure, and neurological complications	Critically ill, usually hypovolaemic, often with confusion or seizures

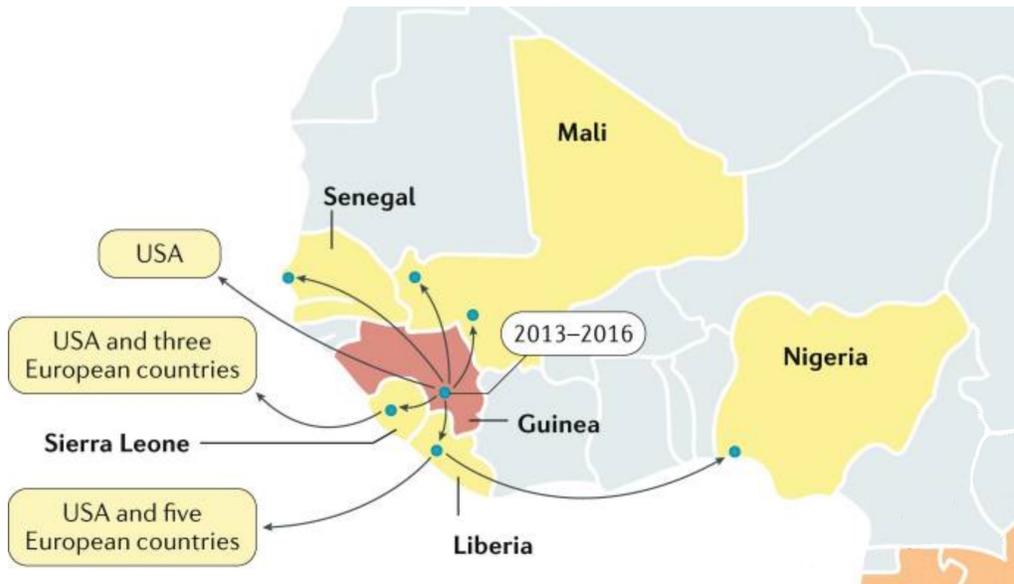
Adapted from Chertow and colleagues<sup>63</sup> and Hunt and colleagues.<sup>64</sup>

**Table 1: Ebola virus disease presentation by stage**

# En 2014: mobilisation internationale

## Epidémie en Afrique de l'Ouest

- 28000 cas / > 11000 décès
- Crainte d'une pandémie



## Ebola: time to act

*Governments and research organizations must mobilize to end the West African outbreak.*

11 SEPTEMBER 2014 | VOL 513 | NATURE | 143



### Head JF Delfraissy

A large portfolio of projects : Clinical Trial (« Jiki »), Vaccine (« PREVAC »), Social Sciences, Diagnosis,...

Focus on The POSTBOGUI Project

# Les soignants ++



**Table 1. Demographic Characteristics and Signs and Symptoms in Confirmed and Probable Ebola Case Patients with a Definitive Clinical Outcome in Guinea, Liberia, Nigeria, and Sierra Leone.\***

Variable	All Patients	Patients Who Died	Patients Who Recovered	Odds Ratio (95% CI)†
		<i>no./total no. (%)</i>		
<b>Demographic characteristics</b>				
Male sex	685/1415 (48.4)	515/1056 (48.8)	170/359 (47.4)	0.93 (0.73–1.19)
Age group				
<15 yr	190/1378 (13.8)	145/1021 (14.2)	45/357 (12.6)	1.18 (0.83–1.71)
15–44 yr	838/1378 (60.8)	577/1021 (56.5)	261/357 (73.1)	0.48 (0.36–0.62)
≥45 yr	350/1378 (25.4)	299/1021 (29.3)	51/357 (14.3)	2.47 (1.79–3.46)
Health care worker	158/1429 (11.1)	112/1067 (10.5)	46/362 (12.7)	0.86 (0.60–1.27)

# « Postebogui »: Accompagnement et évaluation des patients déclarés guéris en Guinée

Promoteur : INSERM/Reacting

Principaux Investigateurs : Saliou Sow, Abdoulaye Touré, Alpha Keita, Mounié Barry  
JF Etard, Ph Msellati,, M Peeters, A Ayoub, A Desclaux, B Taverne, E Delaporte

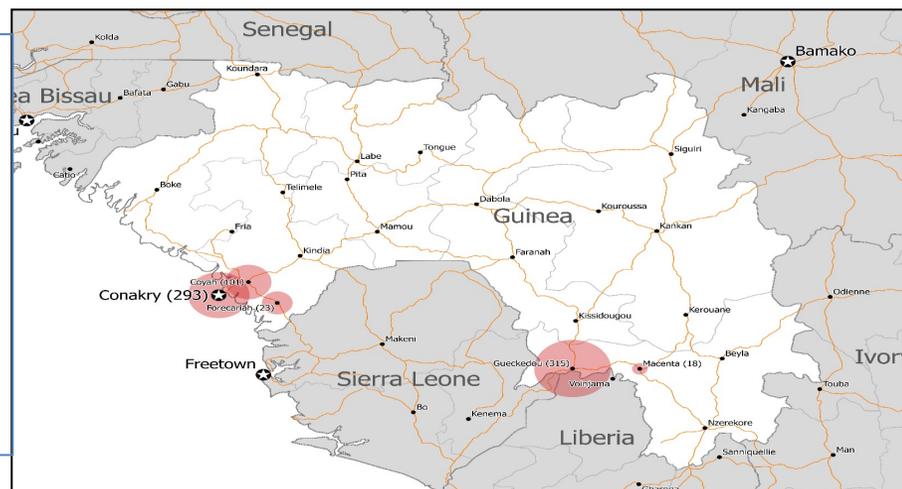
Objectif général : Améliorer les connaissances sur les conséquences cliniques, biologiques et sociales de la maladie

Méthode : **Etude de cohorte multicentrique pluridisciplinaire et études ancillaires**

Paquet d'accompagnement :

- Renforcement des infrastructures avec un service dédié à la prise en charge pluridisciplinaire des patients
- Renforcement des capacités des associations de patients guéris
- Mise en place d'un continuum des soins gratuits et de prise en charge des complications éventuelles

- **Guinée**
- 3811 cas, 2536 morts
- 1270 survivants (33%)
- PostEbogui 802 survivants suivis dans 4 sites



# Multidisciplinary assessment of post-Ebola sequelae in Guinea (Postebogui): an observational cohort study



Jean-François Etard\*, Mamadou Saliou Sow\*, Sandrine Leroy\*, Abdoulaye Touré\*, Bernard Taverne, Alpha Kabinet Keita, Philippe Msellati, N'Fally Magassouba, Sylvain Baize, Hervé Raoul, Suzanne Izard, Cécé Kpamou, Laura March, Ibrahima Savane, Moumié Barry, Eric Delaporte, and the Postebogui Study Group†

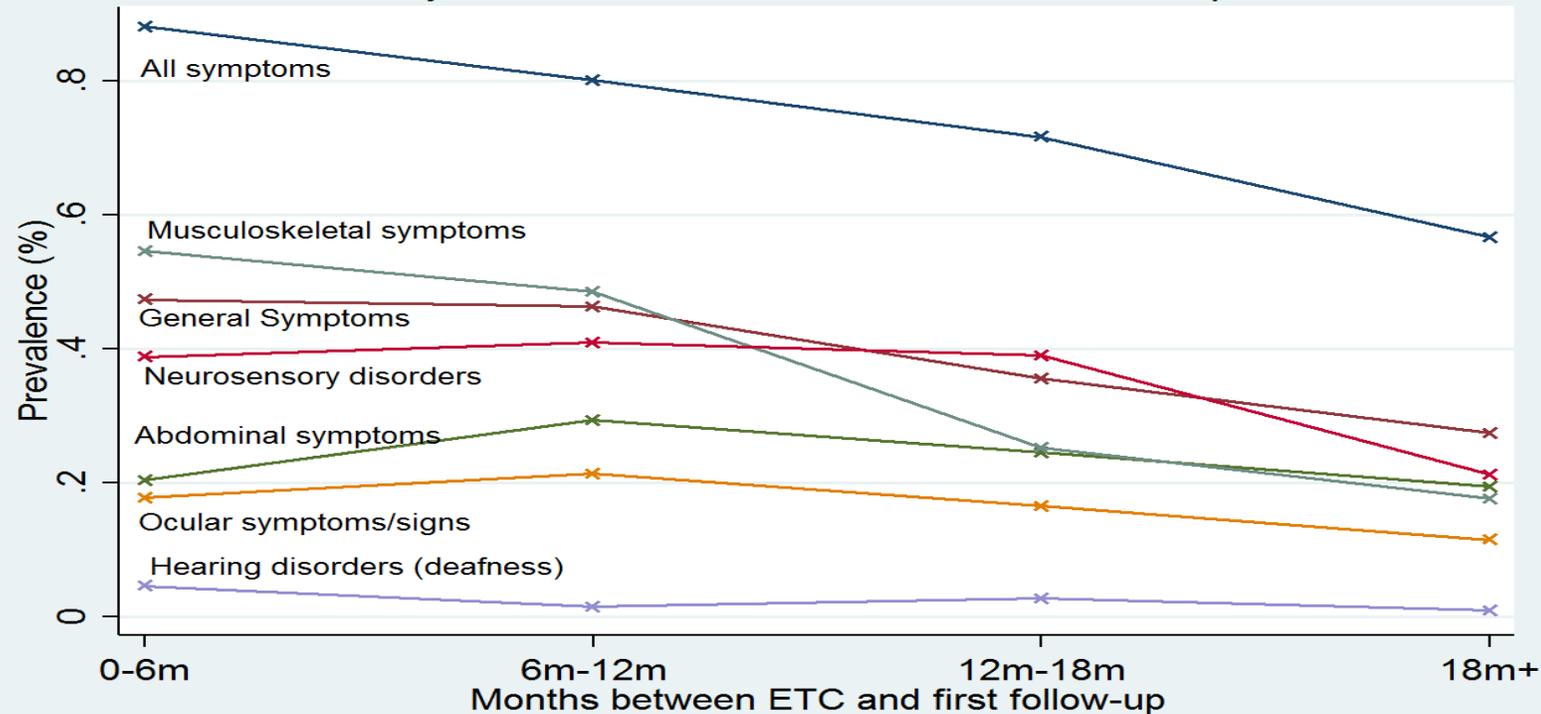
## Summary

**Background** The high number of survivors from the 2013–16 west African outbreak of Ebola virus disease (EVD) has raised several new issues: long-term clinical complications, psychosocial consequences, risks of EVD reactivation, and secondary transmission due to viral persistence in body fluids. We aimed to assess long-term clinical, psychosocial, and viral outcomes in EVD survivors in Guinea.

*Lancet Infect Dis* 2017; 17: 545–52

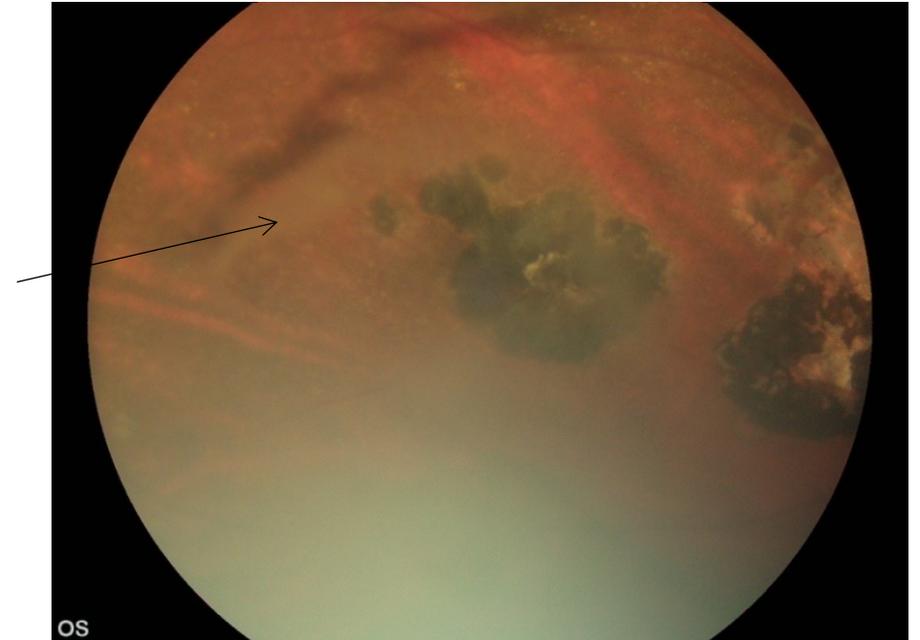
Published Online  
January 13, 2017  
[http://dx.doi.org/10.1016/S1473-3099\(16\)30516-3](http://dx.doi.org/10.1016/S1473-3099(16)30516-3)

Prevalence of signs and symptoms reported at POSTEBOGUI inclusion by months between ETC and first follow-up



# Focus on ophthalmology

- 157 patients examined (slit lamp, dilated funduscopy):
  - 24 uveitis (48% ant, 76% unilat)
  - 4 episcleritis
  - 2 keratitis
- 2 blindness due to cataract among two children → surgery



Source: Esther Hereth

## Ocular Complications in Survivors of the Ebola Outbreak in Guinea



ESTHER HERETH-HEBERT, MAMADOU OURY BAH, JEAN FRANÇOIS ETARD, MAMADOU SALIOU SOW,  
SERGE RESNIKOFF, CHRISTINE FARDEAU, ABDOULAYE TOURE, ALEXIS NIOUMA OUENDENO,  
ISAAC CEUGNA SAGNO, LAURA MARCH, SUZANNE IZARD, PIERRE LOUIS LAMA, MOUMIÉ BARRY, AND  
ERIC DELAPORTE, FOR THE POSTEBOGUI STUDY GROUP

→ Overall abnormal examination = 19 %

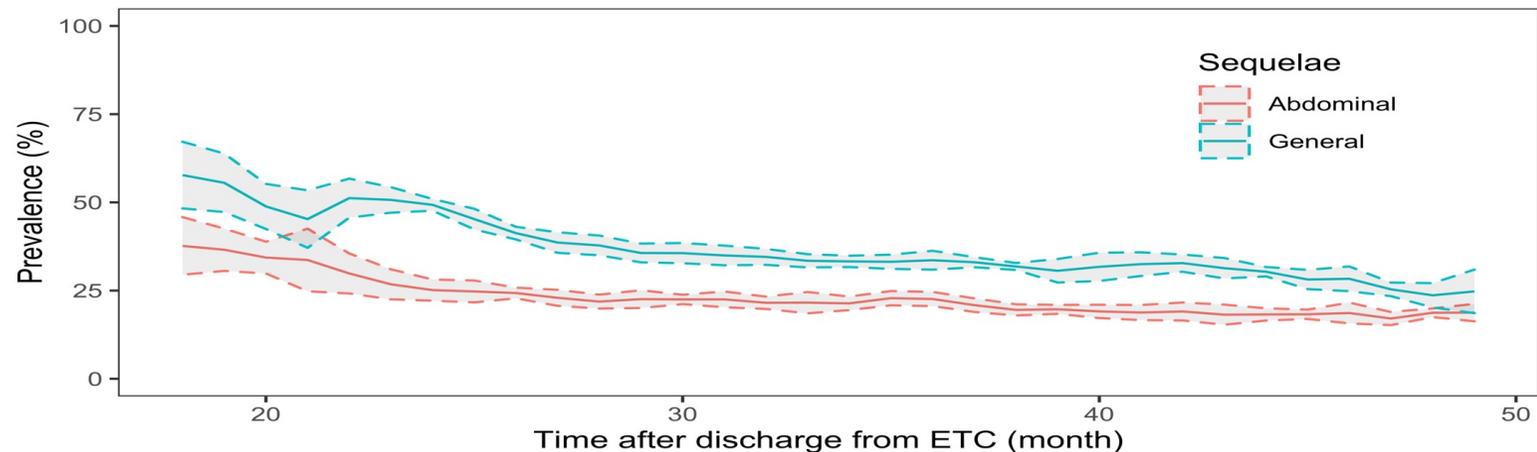
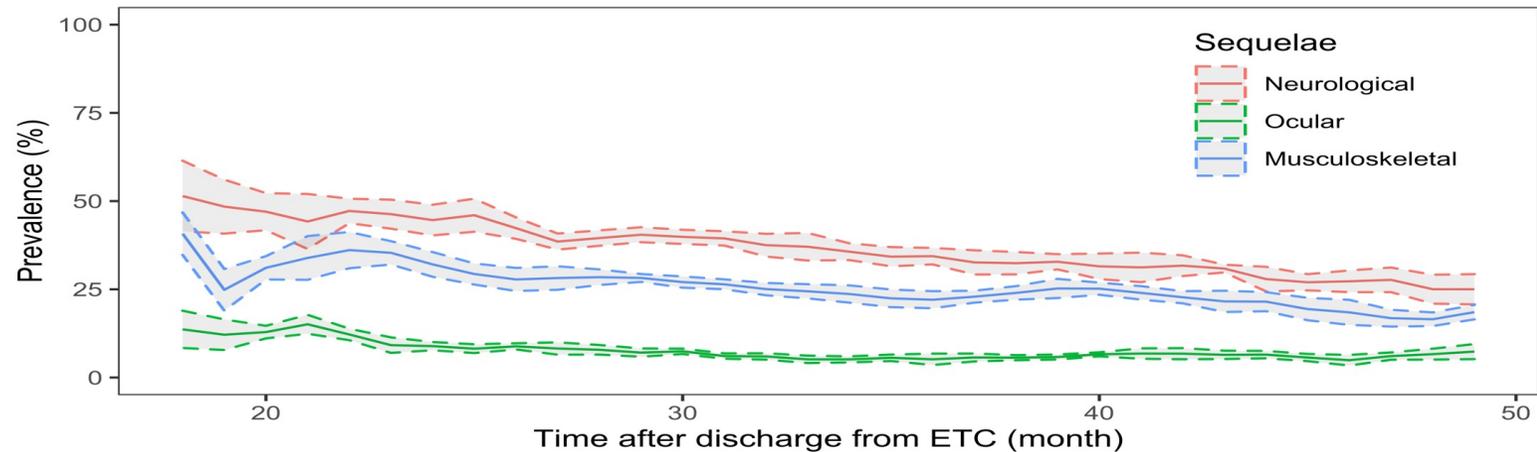
# Ebola-long .....

- Understanding the long-term evolution and predictors of sequelae of Ebola virus disease survivors in Guinea: A 48-month prospective, longitudinal cohort study (PostEboGui)

Mamadou Saliou Kalifa Diallo<sup>1,2</sup>, Abdoulaye Toure<sup>2,3</sup>, Mamadou Saliou Sow<sup>4</sup>, Cécé Kpamou<sup>2</sup>, Alpha Kabinet Keita<sup>1,2</sup>, Bernard Taverne<sup>1</sup>, Martine Peeters<sup>1</sup>, Philippe Msellati<sup>1</sup>, Thierno Alimou Barry<sup>2</sup>, Jean-Francois Etard<sup>1</sup>, René Ecochard<sup>5,6,7,8</sup>, Eric Delaporte<sup>1</sup> for the PostEboGui Study Group

*Clinical Infectious Diseases*, 2021

1/3 des suivis présentaient encore des symptômes



# Séquelles associées à la maladie à virus Ebola: Etude PREVAIL

NEJM 2019

Baisse de la fréquence des signes cliniques à 12 mois par rapport à 6 mois

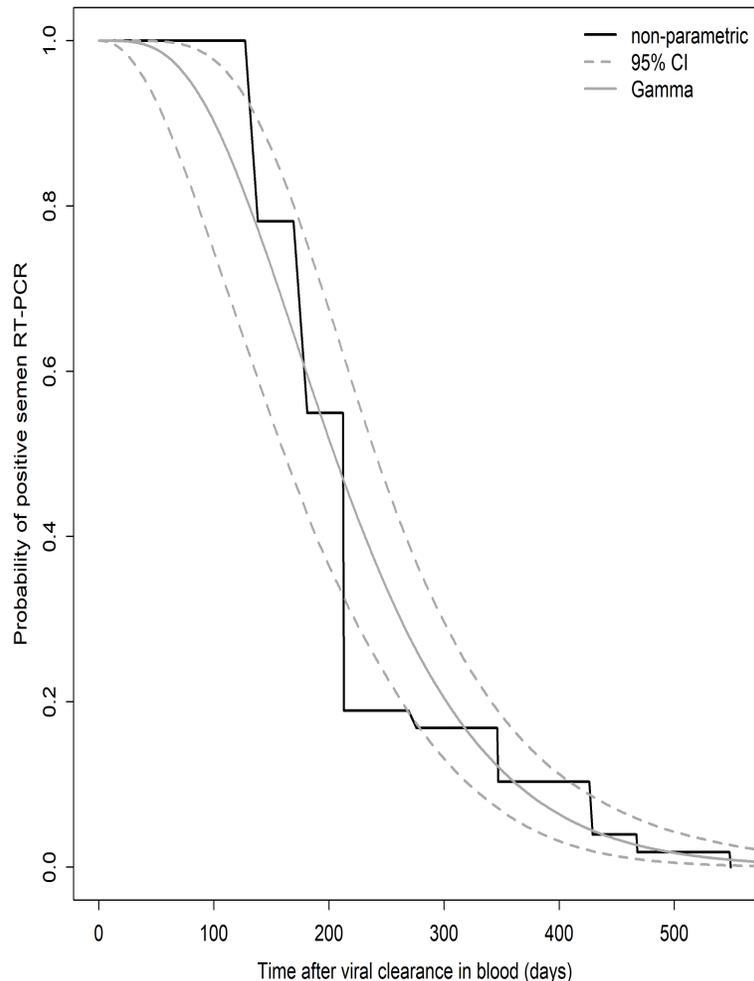
**Table 2. Selected Symptoms and Findings on Physical Examination among Survivors and Close Contacts over Time.\***

Symptom or Finding	Baseline Visit			6-Month Visit			12-Month Visit			P Value†
	Survivors (N=966)	Contacts (N=2350)	Odds Ratio (95% CI)	Survivors (N=851)	Contacts (N=2137)	Odds Ratio (95% CI)	Survivors (N=860)	Contacts (N=2053)	Odds Ratio (95% CI)	
	no. (%)			no. (%)			no. (%)			
Urinary frequency	142 (14.7)	81 (3.4)	5.9 (3.9–7.8)	21 (2.5)	35 (1.6)	1.7 (0.7–2.6)	18 (2.1)	18 (0.9)	2.7 (0.9–4.4)	<0.001
Headache	460 (47.6)	837 (35.6)	1.5 (1.2–1.7)	322 (37.8)	498 (23.3)	1.8 (1.5–2.1)	280 (32.6)	262 (12.8)	3.0 (2.4–3.6)	<0.001
Fatigue	178 (18.4)	149 (6.3)	3.1 (2.4–3.8)	75 (8.8)	61 (2.9)	3.0 (1.9–4.1)	44 (5.1)	23 (1.1)	4.3 (2.2–6.5)	0.41
Muscle pain	223 (23.1)	238 (10.1)	3.4 (2.6–4.1)	118 (13.9)	205 (9.6)	1.8 (1.3–2.2)	110 (12.8)	154 (7.5)	2.1 (1.6–2.7)	<0.001
Memory loss	282 (29.2)	113 (4.8)	8.2 (6.4–10.5)	89 (10.5)	12 (0.6)	19.7 (10.5–36.9)	40 (4.7)	3 (0.1)	31.2 (9.5–102.6)	0.009
Joint pain	459 (47.5)	411 (17.5)	4.0 (3.3–4.8)	298 (35.0)	253 (11.8)	3.6 (2.9–4.3)	237 (27.6)	182 (8.9)	3.5 (2.6–4.3)	0.50
Chest findings	41 (4.2)	48 (2.0)	2.3 (1.3–3.2)	16 (1.9)	35 (1.6)	1.2 (0.5–1.9)	12 (1.4)	13 (0.6)	2.4 (0.5–4.2)	0.16
Joint findings	42 (4.3)	46 (2.0)	2.1 (1.2–3.1)	21 (2.5)	26 (1.2)	1.9 (0.8–3.0)	20 (2.3)	21 (1.0)	2.1 (0.8–3.4)	0.91
Neurologic findings	43 (4.5)	35 (1.5)	2.7 (1.4–4.0)	23 (2.7)	16 (0.7)	3.2 (1.1–5.2)	13 (1.5)	13 (0.6)	2.0 (0.4–3.7)	0.51
Muscle findings	44 (4.6)	29 (1.2)	4.6 (2.8–7.6)	15 (1.8)	8 (0.4)	5.6 (2.3–13.7)	5 (0.6)	8 (0.4)	1.7 (0.5–5.3)	0.14
Abdominal findings	100 (10.4)	150 (6.4)	1.9 (1.3–2.4)	56 (6.6)	99 (4.6)	1.6 (1.0–2.1)	44 (5.1)	68 (3.3)	1.7 (1.0–2.4)	0.67
Eye examination findings‡										
Uveitis	149 (26.4)	77 (12.1)	2.5 (1.7–3.2)	—	—	—	172 (33.3)	90 (15.4)	2.5 (1.8–3.2)	0.77
Cataracts	78 (13.8)	81 (12.8)	0.9 (0.6–1.2)	—	—	—	71 (13.8)	67 (11.4)	0.9 (0.6–1.2)	0.52
Moderate-to-severe visual loss	14 (2.5)	12 (2.0)	1.2 (0.2–2.2)	—	—	—	16 (3.1)	11 (1.9)	1.2 (0.3–2.2)	0.54
Blind	10 (1.8)	9 (1.5)	1.1 (0.1–2.2)	—	—	—	12 (2.3)	9 (1.6)	1.2 (0.1–2.2)	0.46

**Autres signes** : orchite, alopecie, troubles de l'audition, paresthésie

**Autres signes neurologiques** : anorexie, confusion, insomnie, anxiété (Howlett PJ, Emerg Infect Dis 2018)

# POSTEBOGUI: Etudes des fluides



Clinical Infectious Diseases

## BRIEF REPORT

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

Fabien Subtil,<sup>1,2,3\*</sup> Charlotte Delaunay,<sup>1,2,3\*</sup> Alpha Kabinet Keita,<sup>1</sup> Mamadou Saliou Sow,<sup>4</sup> Abdoulaye Touré,<sup>1,5</sup> Sandrine Leroy,<sup>1</sup> Philippe Msellati,<sup>1</sup> N'Fally Magassouba,<sup>6</sup> Sylvain Baize,<sup>7</sup> Hervé Raoul,<sup>8</sup> René Ecochard,<sup>2,3</sup> Moumié Barry,<sup>4</sup> Eric Delaporte,<sup>1</sup> and Jean-François Etard<sup>1</sup>; for the Postebogui Study Group

Open Forum Infectious Diseases

## MAJOR ARTICLE

### A 40-Month Follow-Up of Ebola Virus Disease Survivors in Guinea (PostEbogui) Reveals Long-Term Detection of Ebola Viral Ribonucleic Acid in Semen and Breast Milk

Alpha Kabinet Keita,<sup>1,2\*</sup> Nicole Vidal,<sup>1,\*</sup> Abdoulaye Toure,<sup>2,3</sup> Mamadou Saliou Kalifa Diallo,<sup>2</sup> N'Fally Magassouba,<sup>4</sup> Sylvain Baize,<sup>5,6</sup> Mathieu Mateo,<sup>5,6</sup> Herve Raoul,<sup>7</sup> Stephane Mely,<sup>7</sup> Fabien Subtil,<sup>8,9</sup> Cécé Kpamou,<sup>2</sup> Lamine Koivogui,<sup>3</sup> Falaye Traore,<sup>3</sup> Mamadou Saliou Sow,<sup>2,10</sup> Ahidjo Ayouba,<sup>1</sup> Jean Francois Etard,<sup>1</sup> Eric Delaporte,<sup>1</sup> and Martine Peeters<sup>1,\*</sup>; for the PostEbogui Study Group

Semen (n=1368), urine, feces, cervicovaginal fluid, saliva, breast milk

Breast milk : rare but up to 500 days after discharge..

Semen: probability of RNA +, 93% à 3 mois, 60% à 6 mois

(positivité associée à taux AC , œil, douleurs articulaires)

Clinical Microbiology and Infection 23 (2017) 412–413



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journal homepage: [www.clinicalmicrobiologyandinfection.com](http://www.clinicalmicrobiologyandinfection.com)



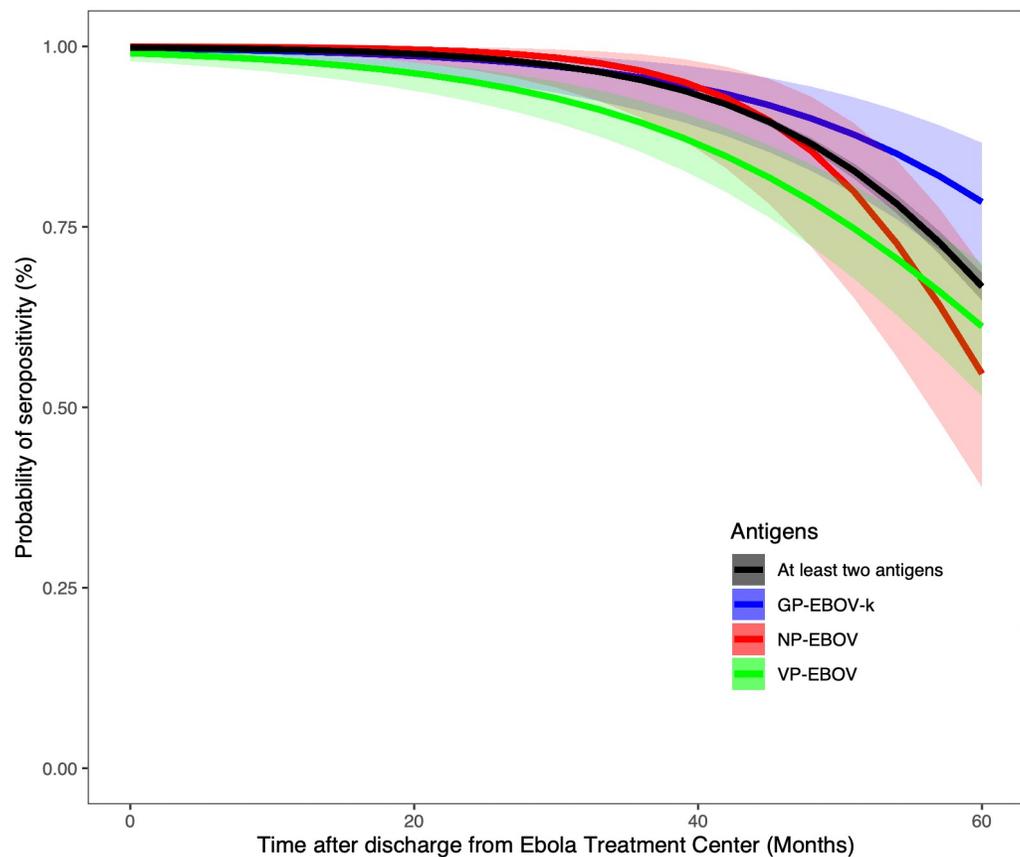
Letter to the Editor

Extraordinary long-term and fluctuating persistence of Ebola virus RNA in semen of survivors in Guinea: implications for public health



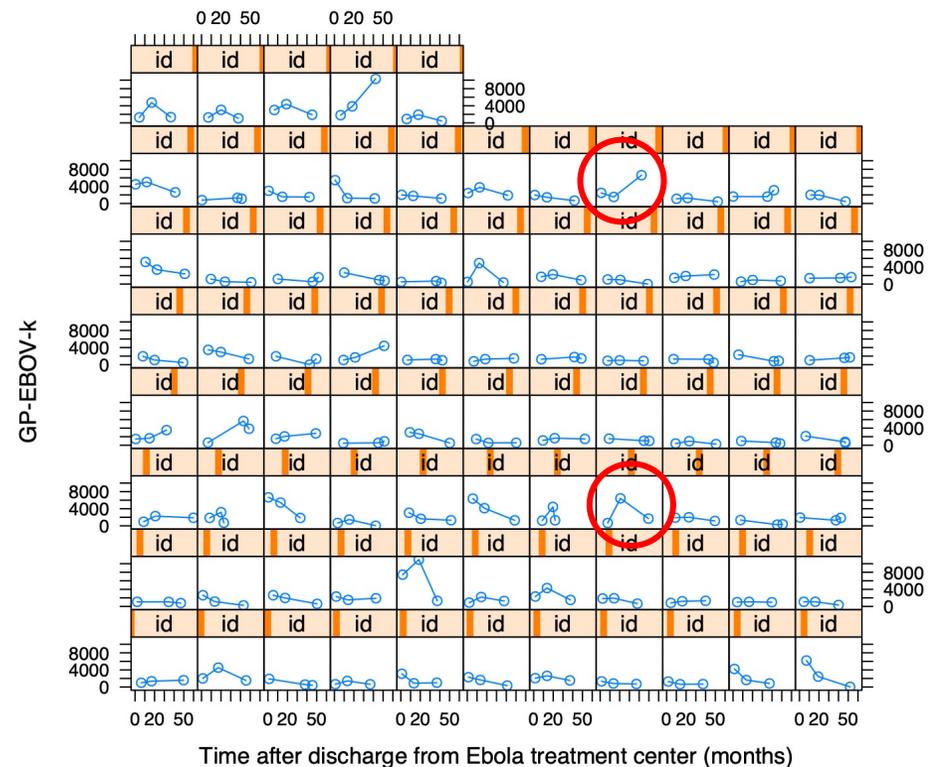
# Temporal evolution of the humoral antibody response after Ebola virus disease in Guinea: a 60-month observational prospective cohort study

Mamadou Saliou Kalifa Diallo, Ahidjo Ayouba, Alpha Kabinet Keita, Guillaume Thaurignac, Mamadou Saliou Sow, Cécé Kpamou, Thierno Alimou Barry, Philippe Msellati, Jean-François Etard, Martine Peeters\*, René Ecochard\*, Eric Delaporte\*, Abdoulaye Toure\*, for the PostEbogui Study Group†



5 years after discharge  $\frac{3}{4}$  had Ab  
Association RNA semen and high Ab concentrations

GP-EBOV-k = Zaire strain Kissidougou 2014 glycoproteins



The y axis represents the quantitative value of the antigens expressed in MFI/100 beads

## Long-lasting severe immune dysfunction in Ebola virus disease survivors

Aurélie Wiedemann<sup>1</sup>, Emile Foucat<sup>1</sup>, Hakim Hocini<sup>1</sup>, Cécile Lefebvre<sup>1</sup>, Boris P. Hejblum<sup>2</sup>, Mélyny Durand<sup>2</sup>, Miriam Krüger<sup>2</sup>, Alpha Kabinet Keita<sup>3,4</sup>, Ahidjo Ayouba<sup>3</sup>, Stéphane Mély<sup>5</sup>, José-Carlos Fernandez<sup>1</sup>, Abdoulaye Touré<sup>3,4,6</sup>, Slim Fourati<sup>7</sup>, Claire Lévy-Marchal<sup>8</sup>, Hervé Raoul<sup>5</sup>, Eric Delaporte<sup>3</sup>, Lamine Koivogui<sup>6</sup>, Rodolphe Thiébaud<sup>2,9</sup>, Christine Lacabaratz<sup>1,11</sup>, Yves Lévy<sup>1,10,11</sup> & PostEboGui Study Group\*

### 2 years after EVD, Ebola Survivors exhibit:

- Increased **activation/inflammation** markers in blood
- Increased activated CD8 T cells, activated/exhausted B cells, non-classical NK cells and activated DC
- Up-regulation of pathways implicated in **antiviral response** (IFN signaling, Complement System and PRR signaling pathways)

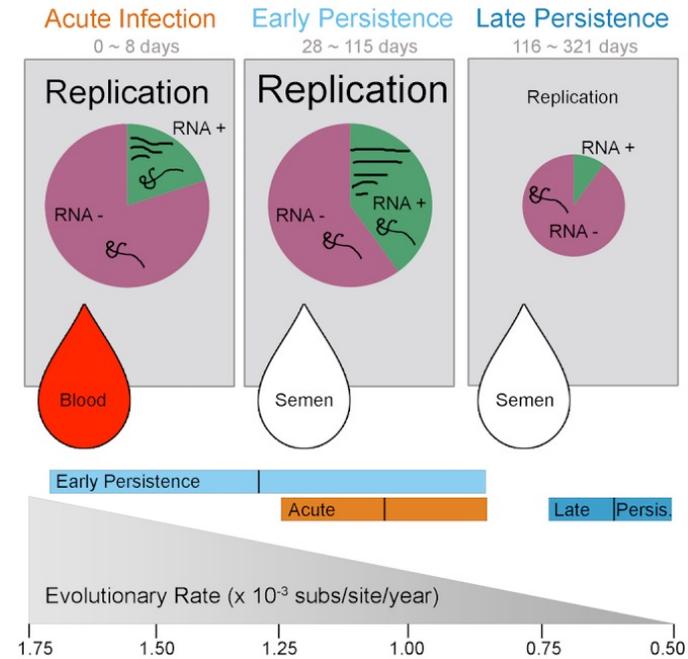
EBOV-associated immune activation

- **Microbial translocation** from a leaky gut
- **Ab responses** and robust and polyfunctional memory **EBOV-specific T cell responses**

“Chronic Ebola Virus Disease”

Possible maintenance of EBOV in immune-privileged sites

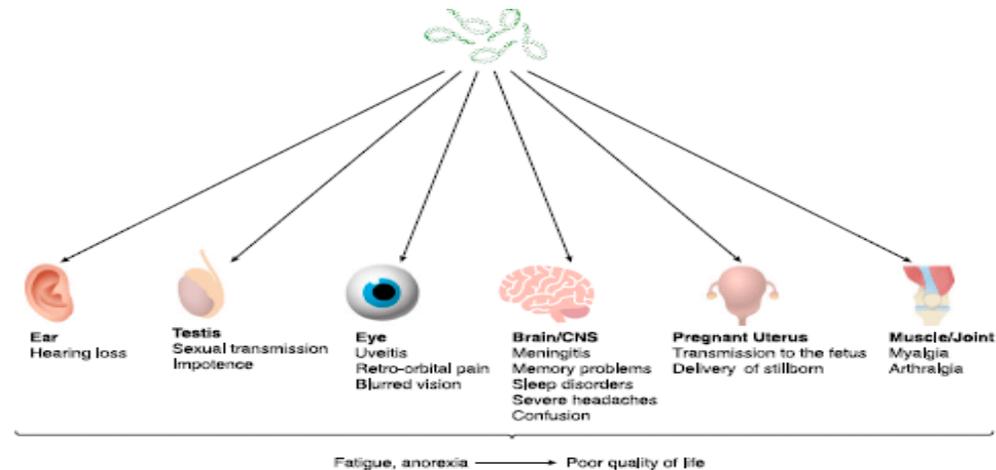
# Persistence versus Latence virale



**During persistence, active EBOV replication/transcription continued**, but decreased with time, consistent with viral persistence (i.e., long-term viral genome maintenance with active transcription/replication) rather than viral latency (i.e., long-term viral genome maintenance without active replication and low/no transcription)

# Interprétation

Persistance du virus Ebola au niveau de lieux de « privilèges immuns »



*J. Leukoc. Biol.* 100: 889–904; 2016.

**Séquelles liées aux atteintes viscérales de la phase aigue**

(qs Insuffisance rénale)

**Conséquences liées au stress de la phase aigue**

(dépression-douleurs-asthénie)

# Etude des « contacts » :



**Prevalence of infection among asymptomatic and paucisymptomatic contact persons exposed to Ebola virus in Guinea: a retrospective, cross-sectional observational study**

*Lancet Infect Dis* 2019; 19: 308-16

Published Online February 11, 2019

Mamadou Saliou Kalifa Diallo\*, Muriel Rabilloud\*, Ahidjo Ayouba\*, Abdoulaye Touré\*, Guillaume Thaurignac, Alpha Kabinet Keita, Christelle Butel, Cécé Kpamou, Thierno Alimou Barry, Mariama Djouldé Sall, Ibrahima Camara, Sandrine Leroy, Philippe Msellati, René Ecochard, Martine Peeters, Mamadou Saliou Sow, Eric Delaporte, Jean-François Etard, on behalf of the Contacteboqui Study Group†

Mise en évidence de formes cliniques a-et pauci-symptomatiques avec une séroconversion chez les contacts selon le degré d'exposition aux risques de 3 à 17 %

## Clinical sequelae among individuals with pauci-symptomatic or asymptomatic Ebola virus infection and unrecognised Ebola virus disease in Liberia: a longitudinal cohort study



J Daniel Kelly, Collin Van Ryn, Moses Badio, Tamba Fayiah, Kumblytee Johnson, Dehkontee Gayedyu-Dennis, Sheri D Weiser, Travis C Porco, Jeffery N Martin, Michael C Sneller, George W Rutherford, Cavan Reilly, Mosoka P Fallah, J Soka Moses



# Conséquences :réactivation de l'infection

The NEW ENGLAND JOURNAL of MEDICINE

## BRIEF REPORT

### 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.

Severe unilateral uveitis 14 w after with EBOV in aqueous humor

Initial TT : **convalescent plasma**, plus TKM



### 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, Alisdair MacConnachie, Tabitha Mahungu, Daniel Martin, Neal Marshall, Stephen Mephram, Richard Orton, Massimo Palmarini, Monika Patel, Colin Perry, Erica Peters, Duncan Porter, David Ritchie, Neil D Ritchie, R Andrew Seaton, Vattipally B Sreenu, Kate Templeton, Simon Warren, Gavin S Wilkie, Maria Zambon, Robin Gopal, Emma C Thomson

**Lancet 2016; 388: 498-503**

Acute meningitis 9 months after with EBOV in CSF

Initial admission: **passive immunotherapies** (plasma; monoclonal Ab combination, ZMab)

# Conséquences : Transmission

The Journal of Infectious Diseases

SUPPLEMENT ARTICLE



## Ebola Virus Transmission Caused by Persistently Infected Survivors of the 2014–2016 Outbreak in West Africa

Lorenzo Subissi,<sup>1</sup> Mory Keita,<sup>2</sup> Samuel Mesfin,<sup>2</sup> Giovanni Rezza,<sup>3</sup> Boubacar Diallo,<sup>4</sup> Steven Van Gucht,<sup>1</sup> Emmanuel Onuche Musa,<sup>4</sup> Zabulon Yoti,<sup>4</sup> Sakoba Keita,<sup>5</sup> Mamoudou Harouna Djingarey,<sup>2</sup> Amadou Bailo Diallo,<sup>2</sup> and Ibrahima Soce Fall<sup>4</sup>

**Table 1. Summary of the Episodes of EVD Re-Emergence From Persistently Infected Survivors**

Flare-up	Country	Date of Confirmation of Index Case	Size of Cluster	Days After Ebola-Free Declaration	Months From ETU Release (Recovery) of Survivor	Most Suspected Body Fluid	Route of Transmission	Virus Isolation	Reference
1	Liberia	March 20, 2015	1	N/A	5	Semen	Sex	Unsuccessful	[11]
2	Liberia	June 29, 2015	7	51	10 <sup>c</sup>	Unidentified	Possibly sex	N/A	[30]
3	Guinea	August 25, 2015	1	N/A	Unknown	Breast milk	Mother-to-child	Unattempted	[15]
4a <sup>a</sup>	Sierra Leone	August 29, 2015	6 (total)	N/A	1.5	Semen	Sex	Unknown	[5]
4b <sup>a</sup>	Sierra Leone	September 3, 2015				Semen	Close contact with body fluids		[5]
5	Guinea	October 13, 2015	1	N/A	11.5	Semen	Close contact with body fluids	Unattempted	[31]
6	Liberia	November 22, 2015	3	80	Unknown	Unidentified	Unidentified	Unknown	[32, 33]
7	Sierra Leone	January 14, 2016	2	68	14 <sup>c</sup>	Unidentified	Unidentified	N/A	[34]
8 <sup>b</sup>	Guinea (Liberia)	March 16, 2016 (April 1, 2016)	10 3	78 (78)	17	Semen	Sex	Unattempted	[35]

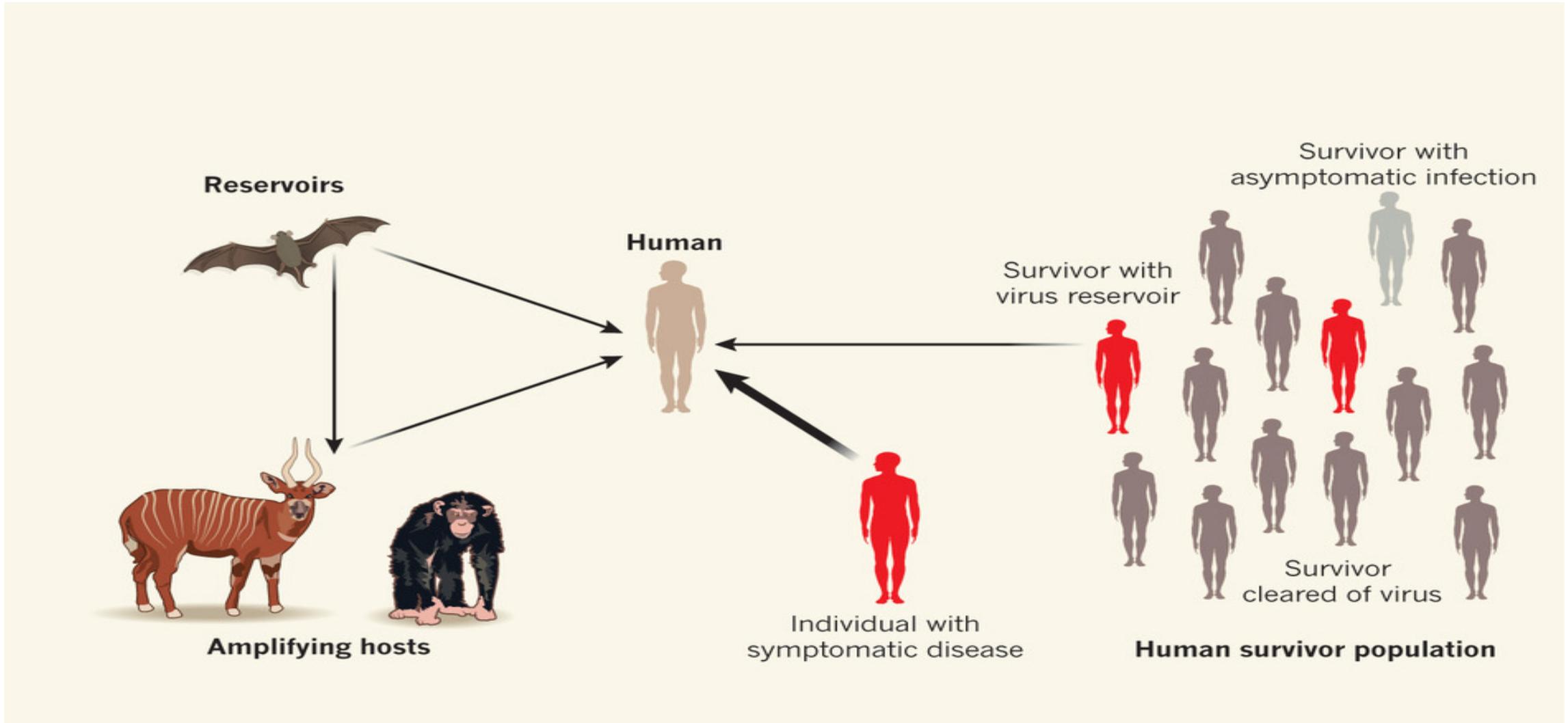
Abbreviations: EBOV, Ebola virus; ETU, Ebola treatment unit; EVD, EBOV disease; N/A, not applicable.

<sup>a</sup>This flare-up is subdivided into 2 because the same survivor is likely to have simultaneously infected 2 relatives (ie, 2 index cases).

<sup>b</sup>Liberia is in brackets because EVD reappearance in the country was not due to EBOV transmission from persistently infected survivor but EVD cases from the Guinean cluster moving to Liberia.

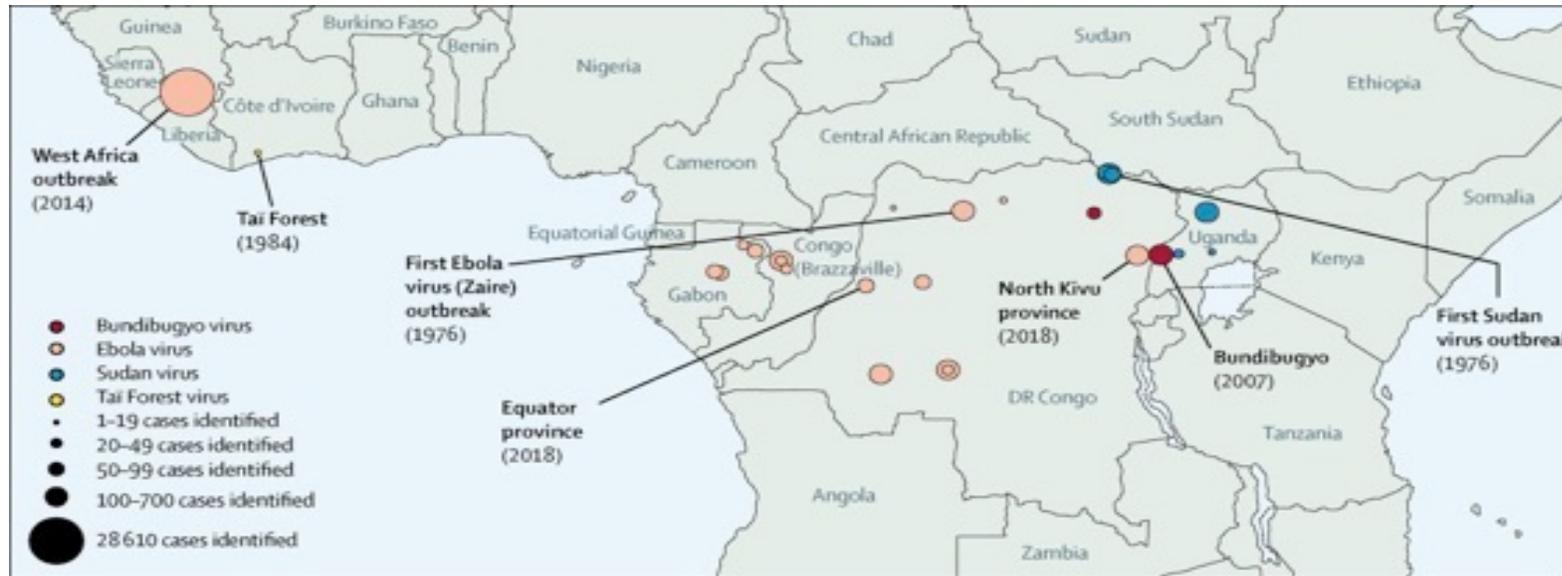
<sup>c</sup>The persistently infected survivor could not be identified: the number of months refers to the time between the dates of EBOV confirmation of the sample with closest EBOV sequence and the sample of the index case.

# Un réservoir humain.....



Ebola infection dynamics in animals and humans.

# Ebola:After 2014- 2016



The West Africa outbreak with 10 X victims than all previous outbreaks represented a paradigm shift in particular for research

**Treatment:** From Favipiravir , ZmApp to the Palm Study in RDC

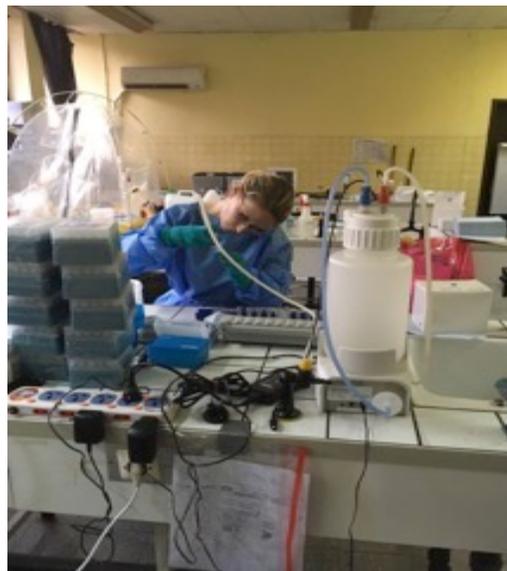
**Vaccin:** Validation of the Merck vaccin and its use to control the outbreak in RDC, evaluation of the J& J vaccin also (PREVAC study)

**Diagnosis:** Developpement of operationnal real time PCR tests, NGS, Luminex serology, ..

**Clinical consequences :**Asymptomatic, acute and standard of care, « chronic »

# Technical support to virology laboratory of INRB

(A.Ayoub, C.Butel, A. Lacroix, M Peeters, L.Serrano)



- **New diagnostic tools**
  - MagPix (High throughput serology)
  - NGS sequencing « Minlon »
- **Training of laboratory staff**
  - Aziza Amouri
  - Junior Bulabula
  - Placide Mbala
- **Implementation of new tools**
  - Antibody screening of clinical suspect cases neg with Xpert
  - Antibody screening of contacts
  - Amplicon sequencing of Ebola strains from the outbreak with Minlon

# Installation des laboratoires de terrain pour la detection et caracterisation rapide des virus Ebola (Bikoro, Itipo, Mbandaka)



# Séquençage de Nouvelle Génération

Préparation de la librairie



1. Nanopore (Minion)

2. Hiseq

3. Miseq

# Séquençage sur terrain : caractérisation rapide des souches virales

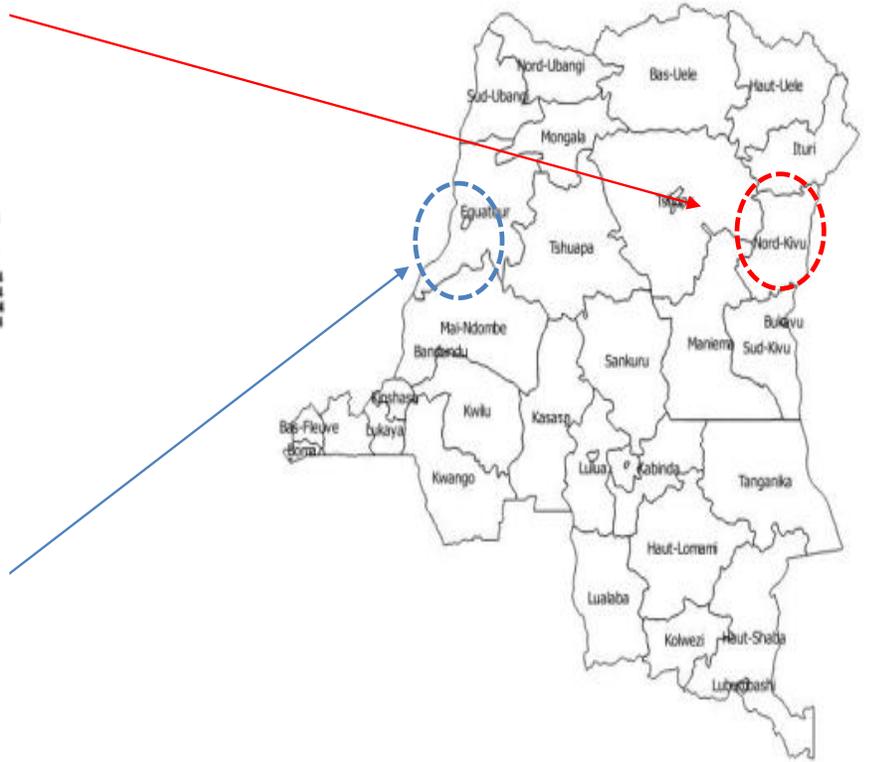
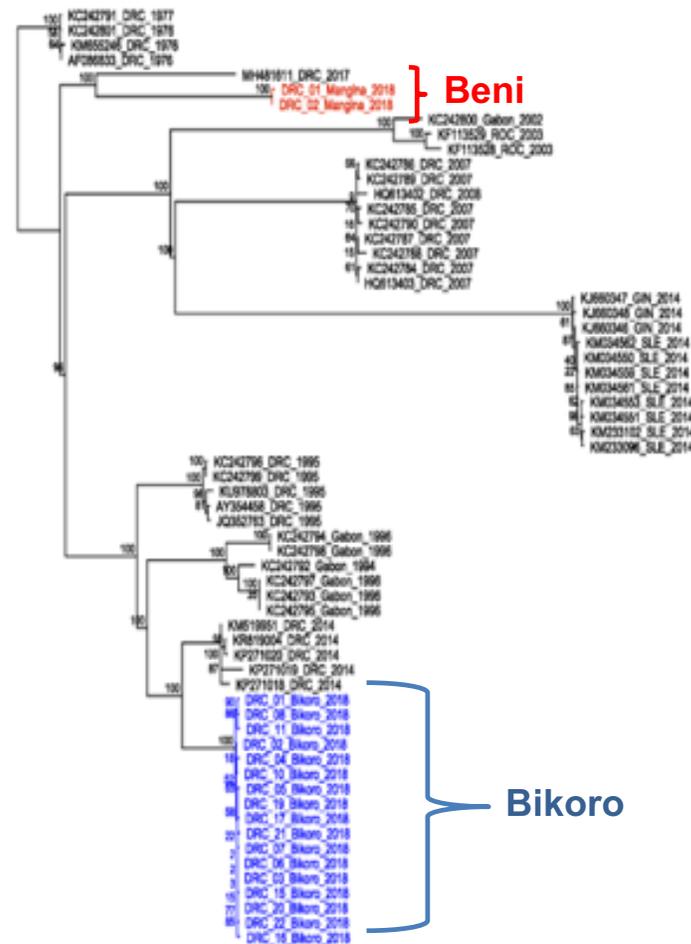
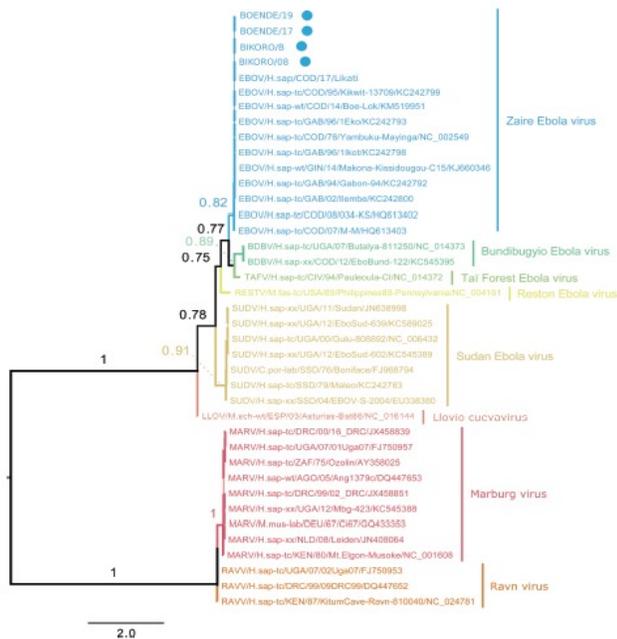
Clinical Infectious Diseases

BRIEF REPORT

## 2 épidémies différentes causées par le virus Ebola

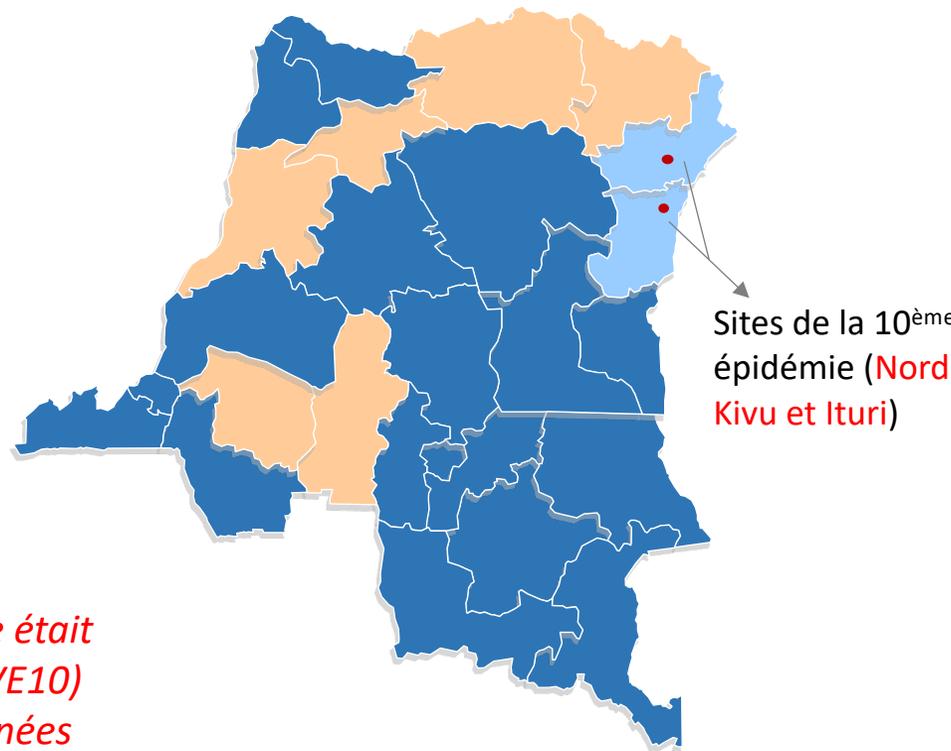
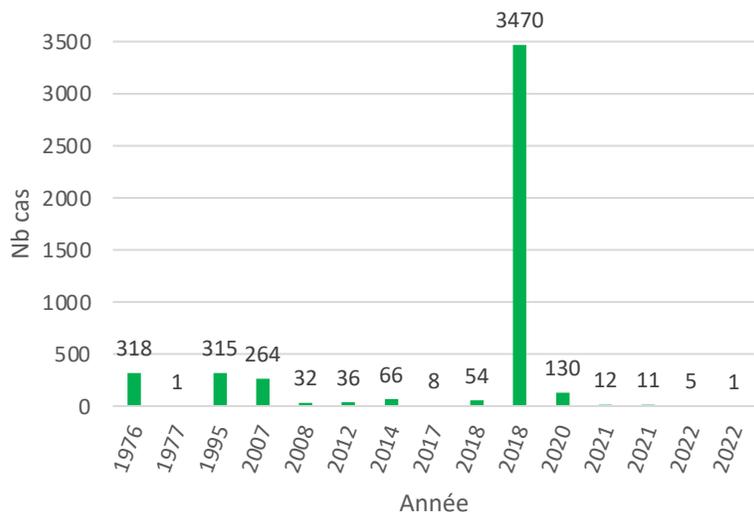
Rapid Confirmation of the Zaire Ebola Virus in the Outbreak of the Equateur Province in the Democratic Republic of Congo: Implications for Public Health Interventions

Placide Mbala-Kingebeni,<sup>1,2,3</sup> Christian-Julian Villabona-Arenas,<sup>3</sup> Nicole Vidal,<sup>3</sup> Jacques Likofata,<sup>4</sup> Justus Nsio-Mbete,<sup>5</sup> Sheila Makiala-Mandanda,<sup>1,2</sup> Daniel Mukadi,<sup>1,2</sup> Patrick Mukadi,<sup>1,2</sup> Charles Kumakamba,<sup>1,6</sup> Bathe Djokolo,<sup>5</sup> Ahidjo Ayouba,<sup>3</sup> Eric Delaporte,<sup>3</sup> Martine Peeters,<sup>3</sup> Jean-Jacques Muyembe Tamfum,<sup>1,2</sup> and Steve Ahuka-Mundede<sup>1,2</sup>



# La MVE en République Démocratique du Congo

Evolution des cas Ebola par année en RDC



*! Sur les 15 épidémies, la plus importante était celle de 2018-2020 (10<sup>ème</sup> épidémie MVE10) 8 résurgences durant les 5 dernières années*

MVE 1- 9, 11, 15

MVE 10 -12- 13

## ❖ 10<sup>ème</sup> épidémie en RDC ( 2018-2020)

- 3470 cas
- 2287 décès
- 2<sup>ème</sup> plus grande épidémie mondiale

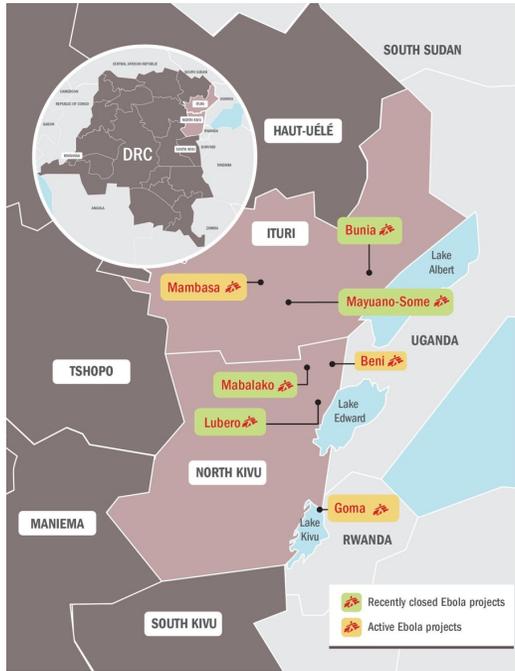
## ❖ Gestion complexe

- Zone urbaine
- Expansion nationale
- USSPI en juillet 2019
- Insécurité et conflits armés
- Faible acceptation de la communauté
- Faiblesse et épuisement du Système de Santé

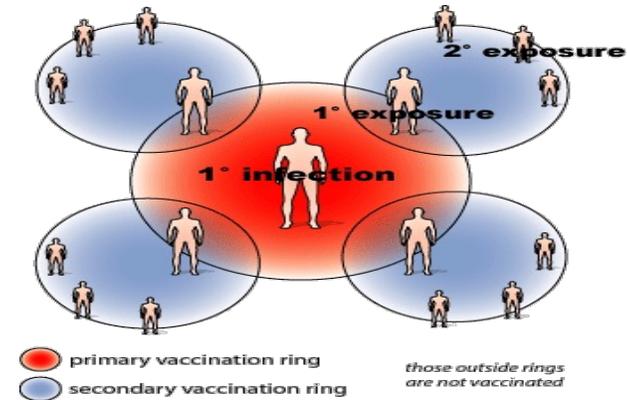
## ❖ Appui international +++

- Vaccinations
- Essais thérapeutiques expérimentaux
- Innovation diagnostic

# Dixième Epidémie de MVE en RDC 2018



- ❖ Cas confirmés : 3470
- ❖ Décès: 2287
- ❖ Survivants: 1183



## Facteurs d'extension



## Mesures de contention

- ❖ Insécurité
- ❖ Attaques contre eq. de riposte
- ❖ Niveau bas de PCI
- ❖ Rites et coutumes morts



Traitements expérimentaux  
Protocole MEURI et essai clinique



# Destruction du CTE de la ZS BIENA



# Piliers de la riposte à une épidémie de la MVE

- Détection des cas
- Isolement des malades
- Suivi des contacts
- Enterrements Dignes et sécurisés

Depuis 2018 :

- Vaccination en ceinture (autour des cas)
- Utilisation des traitements







# Evaluation et accompagnement des patients déclarés guéris d'une infection par le virus Ebola et de leurs contacts en République Démocratique du Congo « Les Vainqueurs d'Ebola »

Question par rapport à PostEbogui : Quel Impact des traitements sur séquelles et réservoir ?

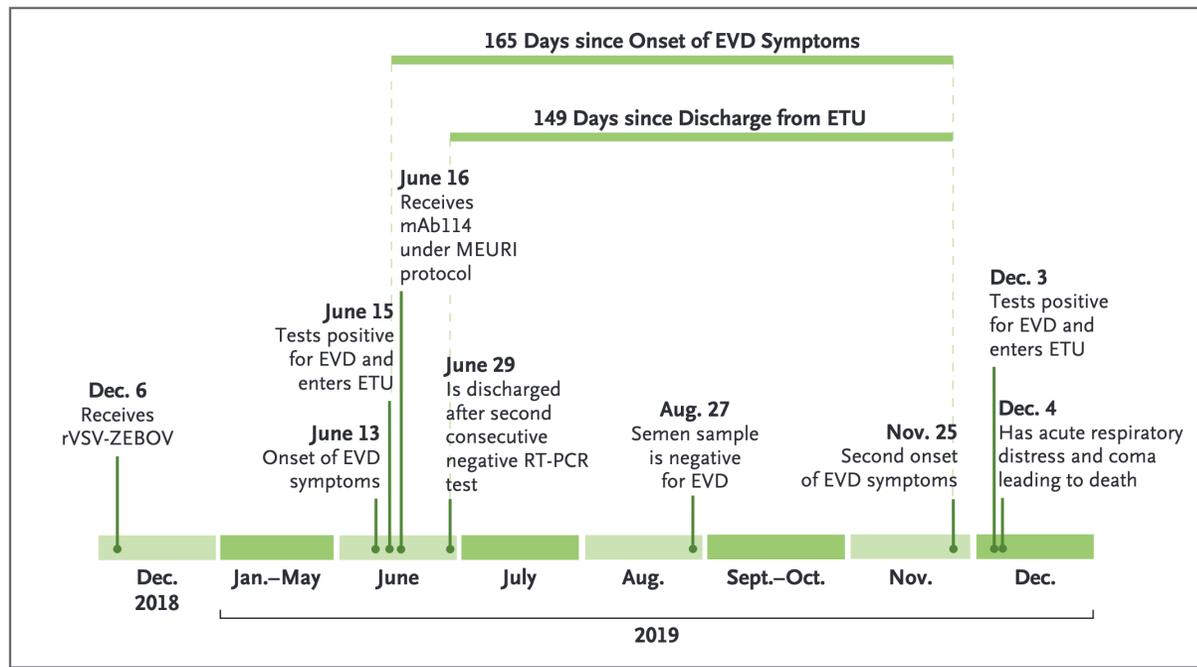


Promoteur

BRIEF REPORT

# Ebola Virus Transmission Initiated by Relapse of Systemic Ebola Virus Disease

P Mbala-Kingebeni et al

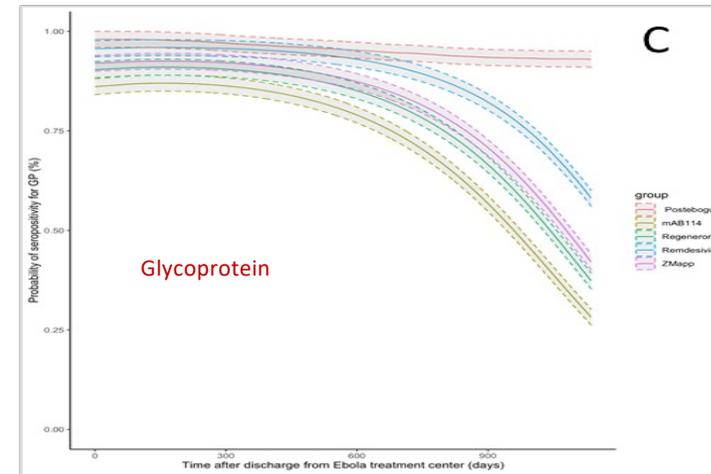
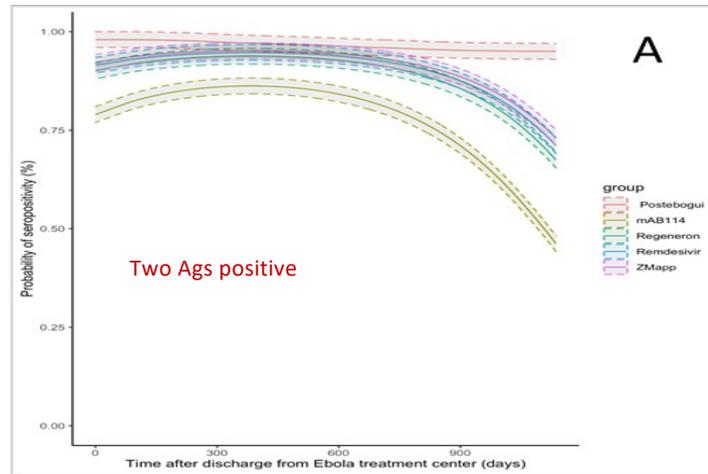


**Figure 1.** Timeline of the First and Second Episodes of EVD in the Patient, from December 2018 through December 2019. ETU denotes Ebola treatment unit, EVD Ebola virus disease, MEURI Monitored Emergency Use of Unregistered and Investigational Interventions, RT-PCR reverse transcriptase–polymerase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

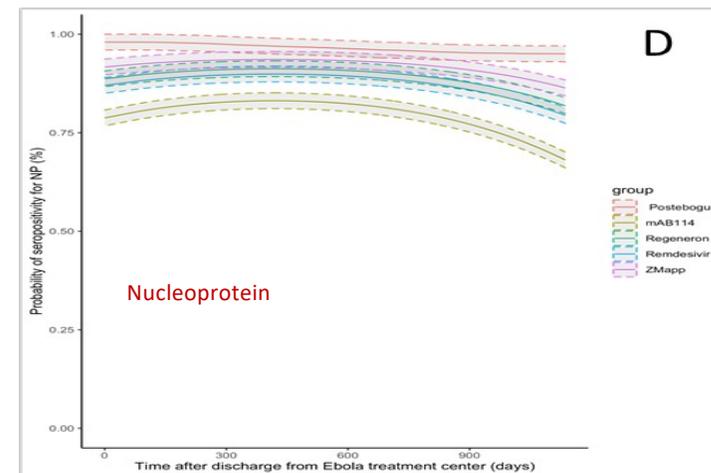
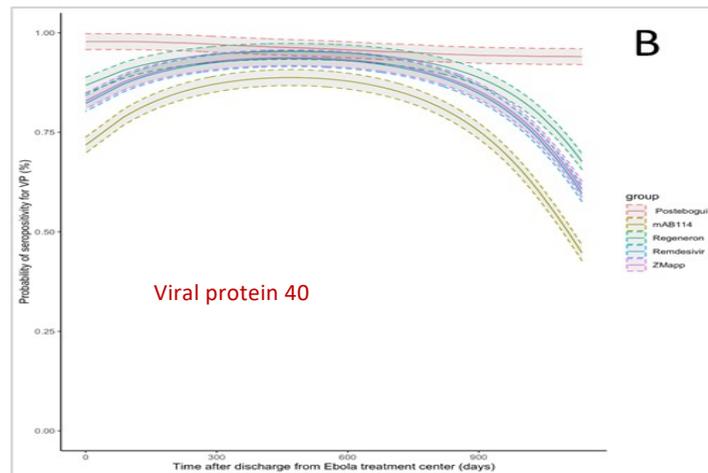
Molecular investigation: Relapse and not reinfestation

- Led to a transmission chain of 91 patients

# Réponse humorale chez les « vainqueurs » en fonction des traitements reçus



Patients non traités



Probability of being positive to Ebola antigens among survivors who received specific treatment according to time after discharge from the Ebola treatment Center.

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

Jun Liu<sup>1†</sup>, John C. Trefry<sup>1†</sup>, April M. Babka<sup>1</sup>, Christopher W. Schellhase<sup>1</sup>, Kayla M. Coffin<sup>1</sup>, Janice A. Williams<sup>1</sup>, Jo Lynne W. Raymond<sup>1</sup>, Paul R. Facemire<sup>1</sup>, Taylor B. Chance<sup>1</sup>, Neil M. Davis<sup>1</sup>, Jennifer L. Scruggs<sup>1‡</sup>, Franco D. Rossi<sup>1</sup>, Andrew D. Haddow<sup>1§</sup>, Justine M. Zelko<sup>1</sup>, Sandra L. Bixler<sup>1</sup>, Ian Crozier<sup>2</sup>, Patrick L. Iversen<sup>1</sup>, Margaret L. Pitt<sup>1</sup>, Jens H. Kuhn<sup>3</sup>, Gustavo Palacios<sup>1||</sup>, Xiankun Zeng<sup>1\*</sup>

### **RESULTS**

**EBOV persists in the brain ventricular system of mAb-treated rhesus macaque survivors**

**Fatal recrudescence associated with EBOV ventricular persistence in mAb-treated macaque survivors**

# Guinée Ebola 2021

Investigation pluridisciplinaire immédiate  
 Diagnostic de l'épidémie en 2 jours en Guinée  
 Mise en place immédiate des mesures de contrôle  
**La préparation çà marche !**

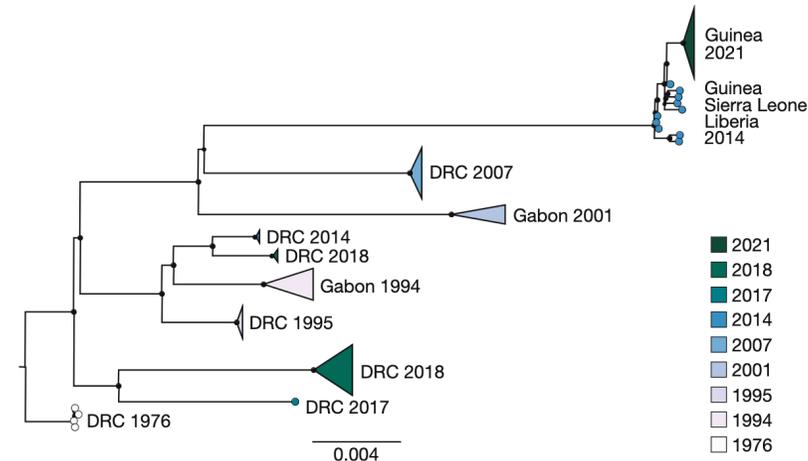


Article

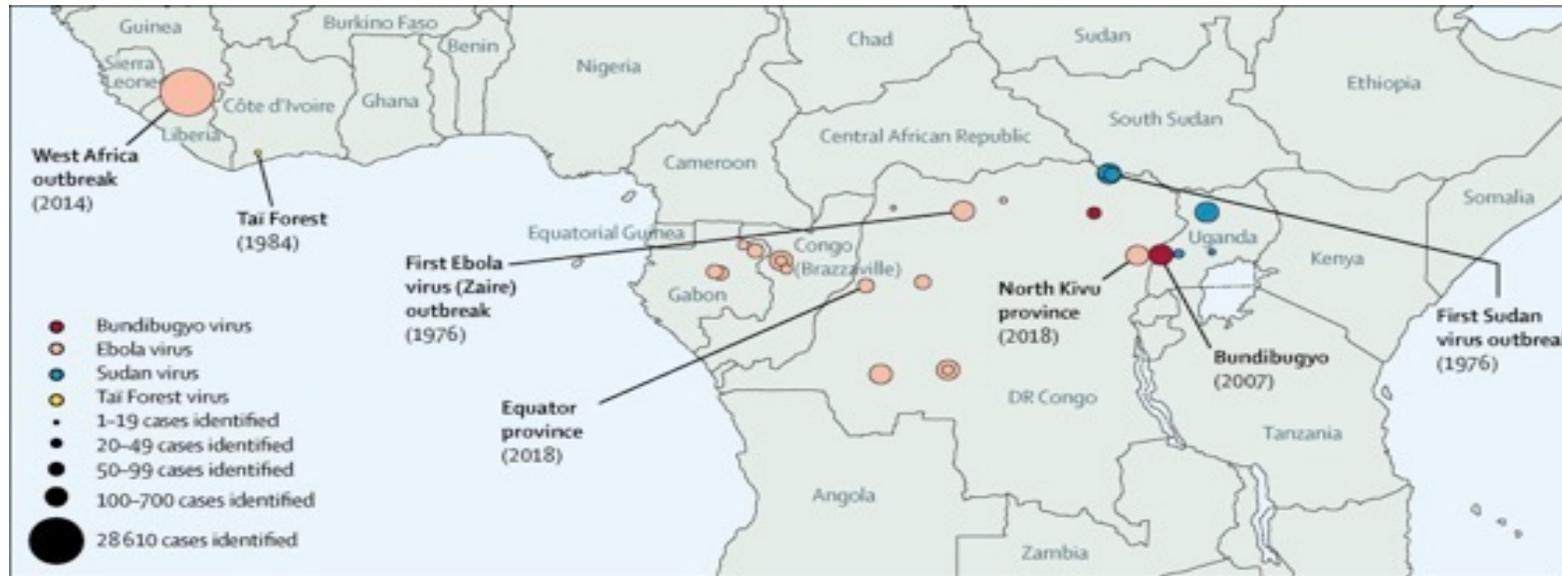
Nature | Vol 597 | 23 September 2021

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

Nouvelle épidémie > 5 ans après  
 Souche EBOV 2014-2016  
 Origine « réservoir humain »  
 et non « spillover »!



# Ebola: 2021



**Treatment:** Palm Study in RDC ( Ab only)

**Vaccin:** Merck and J&J

**Diagnosis:** Developpement of operationnal real time PCR tests, NGS, Luminex serology, ..

**Clinical consequences :**Asymptomatic, acute and standard of care, « chronic »

**Reservoir:** not only animal...

**Preparadness...:** Diagnosis of the Guinean outbreak in .. 2 days versus 4 months in 2014!

# Conséquences de la persistance virale

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**Séquelles:** Persistance de certaines manifestations cliniques

**Résurgence:** Nouvelle infection symptomatique avec ou non nouvelle chaîne de contamination

**Nouvelles chaînes de transmission** en zone épidémique ou dans une nouvelle zone géographique...

**Impact négatif des traitements Ac monoclonaux ?** Sur la persistance virale et les risques de réinfestation

**Implications de Santé publique :** Suivi des survivants  
Vaccination ?

Un besoin urgent:

**Développer et évaluer des traitements permettant la clairance d' EBOV au niveau des réservoirs**

# Acknowledgements



Montpellier



Abdoulaye Touré, Alpha Keita



INRB, RDC

JJ Muyembe, Steve Ahuka Mundeke, P Mbala



**Inserm**  
La science pour la santé  
From science to health



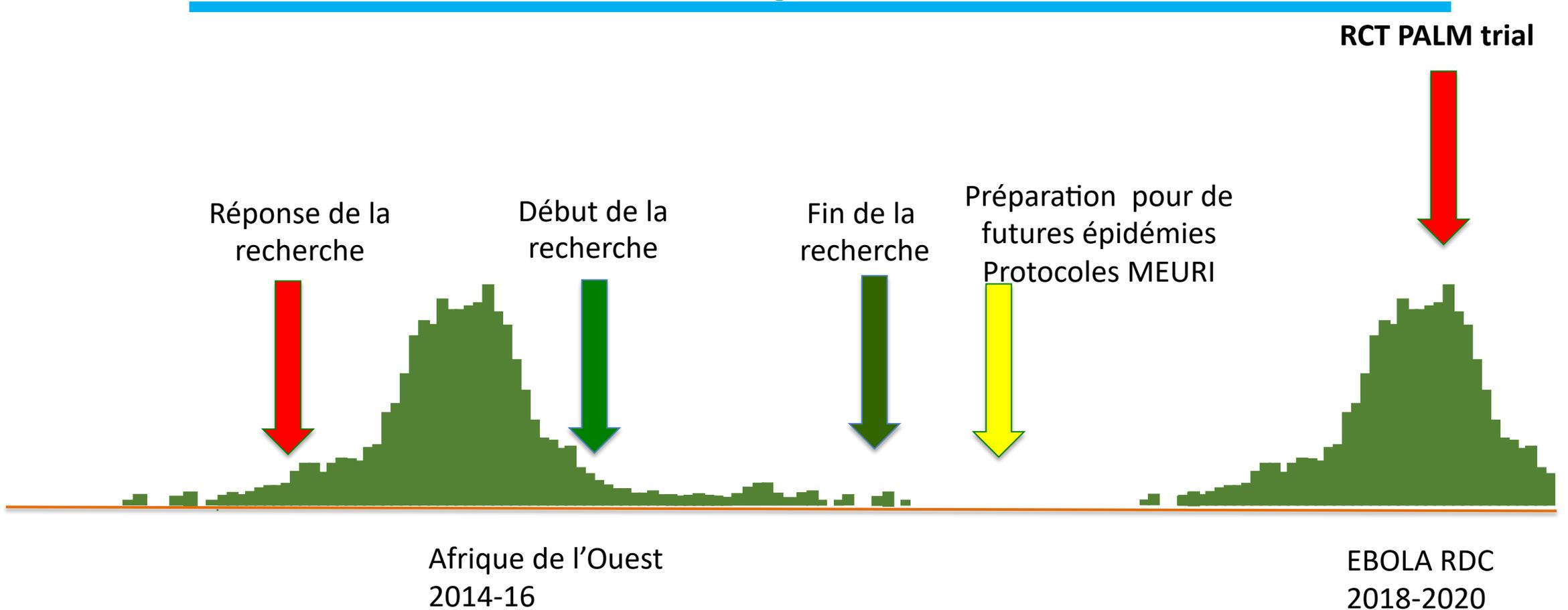
PRISME GUINEE



PRISME RDC

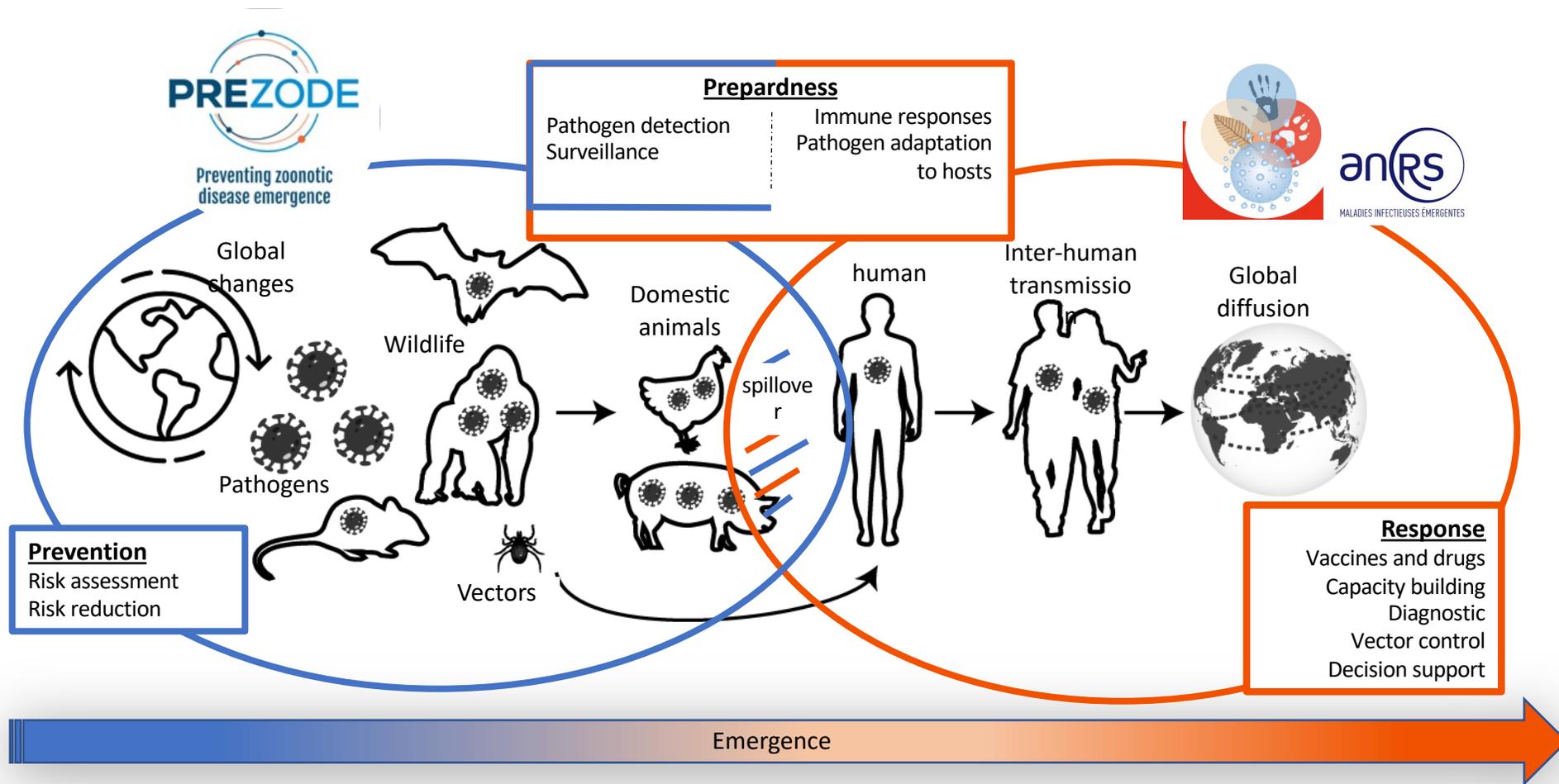


# Recherche thérapeutique en situation de crise aiguë: Exemple Ebola



**La préparation d'une future crise et la capitalisation de l'expérience a permis la mise en place d'un essai randomisé avec 4 stratégies!**

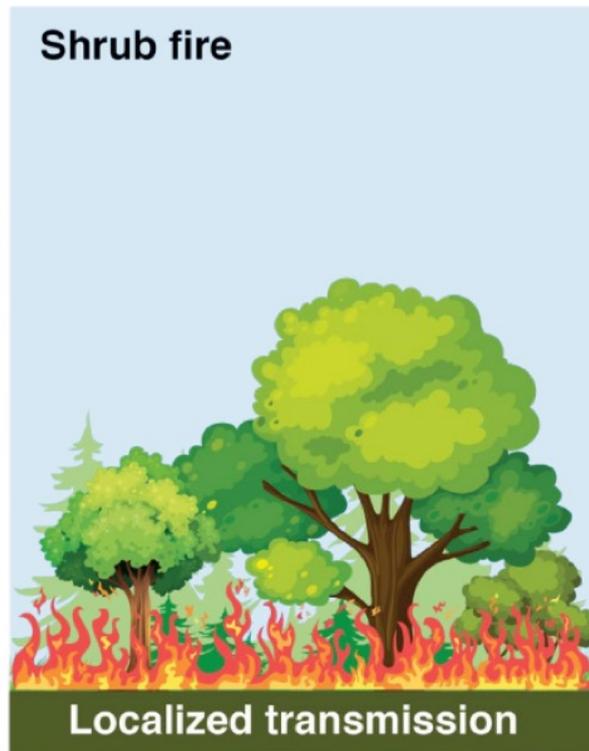
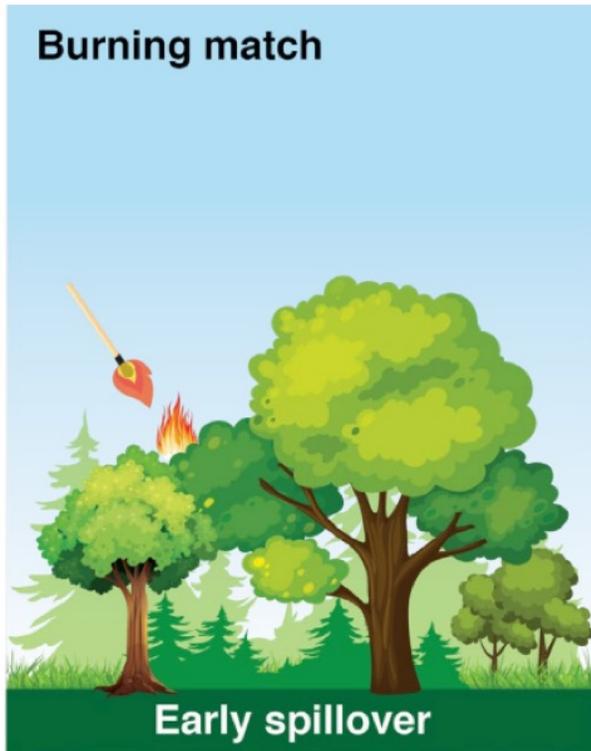
Monitored Emergency Use of Unregistered and Experimental Interventions' (**MEURI**) protocol



Microbe circulation  
in wildlife

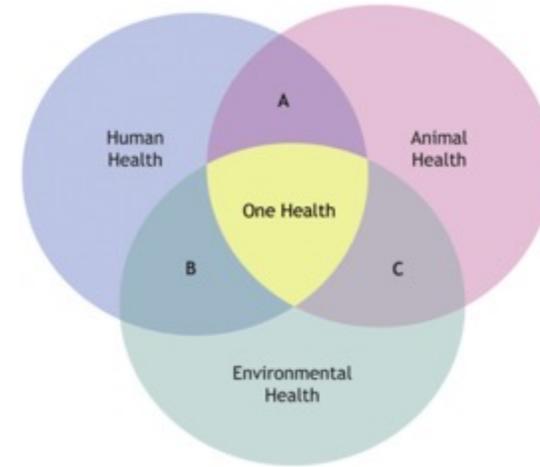
Beggining of  
human  
exposure

Adaptation for  
human transmission



# One Health approach

- Multi-disciplinary approach
  - animal, human, and environmental health
  - **understand the ecology of each emerging zoonotic diseases (>70% of Human Emerging Diseases)**
  - risk assessment, and develop plans for response and control.



**One Health** is the idea that the health of people is connected to the health of animals and our shared environment.

When we protect **one**, we help protect **all**.

[www.cdc.gov/onehealth](http://www.cdc.gov/onehealth)

The illustration shows three overlapping circles. The top circle is orange and contains silhouettes of a family (two adults and two children). The bottom-left circle is blue and contains silhouettes of a chicken, a goat, and a dog. The bottom-right circle is green and contains silhouettes of trees and birds.