ÉBOLA: UNE ÉPIDÉMIE APRÈS L'AUTRE

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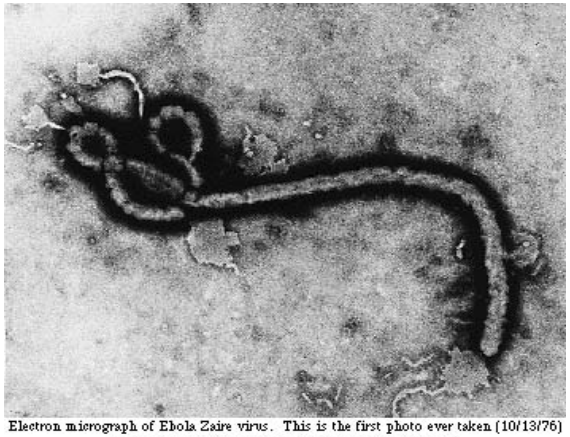
Collège de France (2018-9)

Yambuku, Zaïre (RDC), 1976

(Ebola river)



Electron micrograph of Ebola Zaire virus. This is the first photo ever taken (10/13/76) by Dr. F.A. Murphy, now at UC Davis, then at CDC.
Diagnostic specimen in cell culture at 160,000X magnification.

(Yambuku)

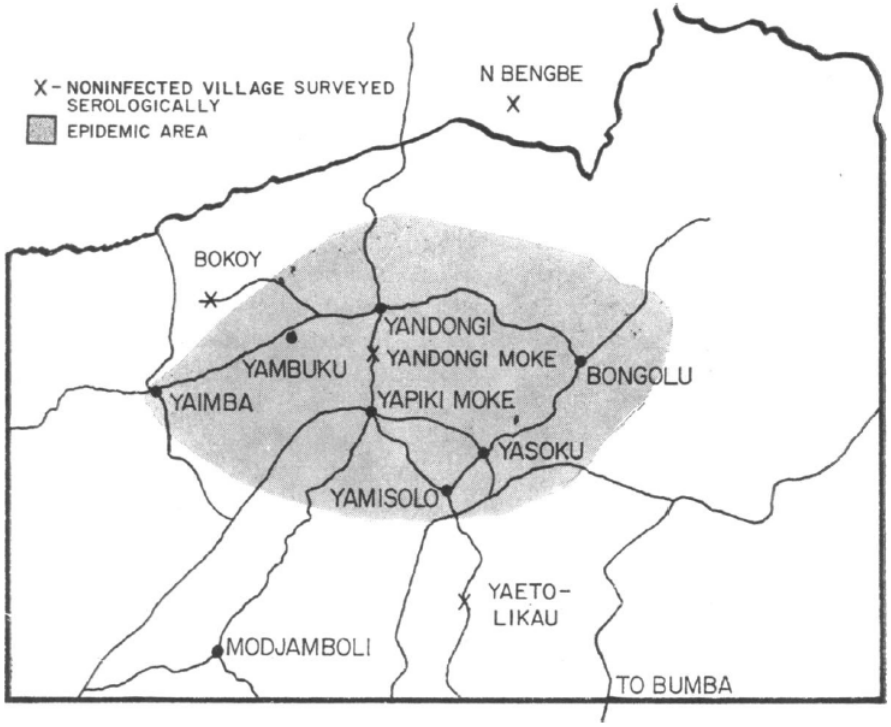
(Images: CDC Public Health Image Library) (Texte: Marc Gozlan et Paul Benkimoun, Le Monde)

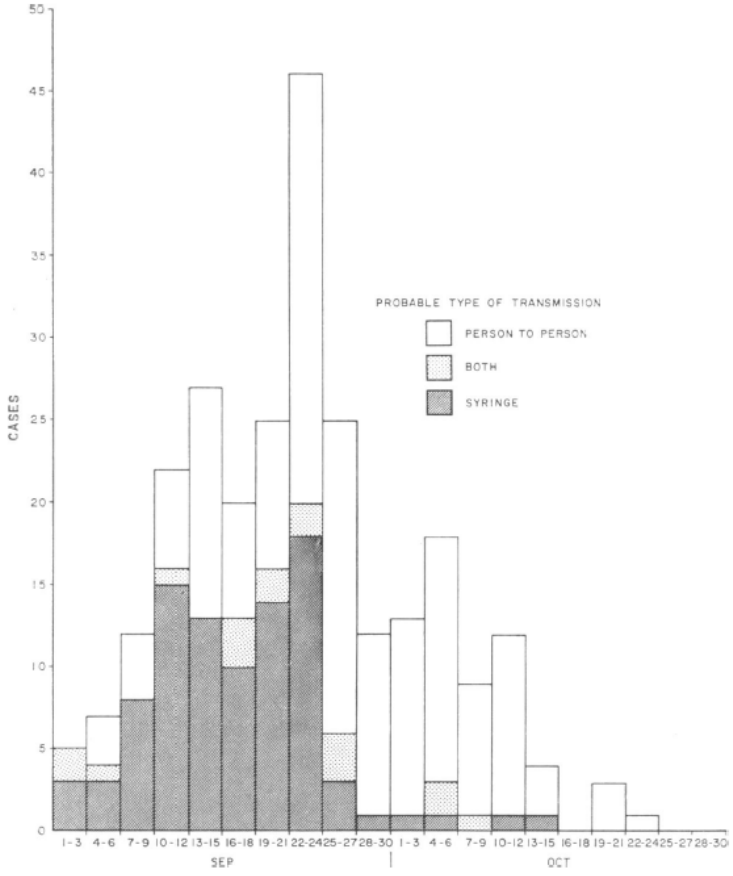
Yambuku hospital, Zaïre (RDC), 1976

(CDC/Joel G. Breman, M.D., D.T.P.H)

(CDC Public Health Image Library)

Enquête, Yambuku, 1976





Patient 0: 26 août 1976
318 patients, taux de létalité: 88%
55/550 villages touchés
Rôle des injections

(Report International Commission, Bull OMS, 1978)

Yambuku, Zaïre (RDC), 1976

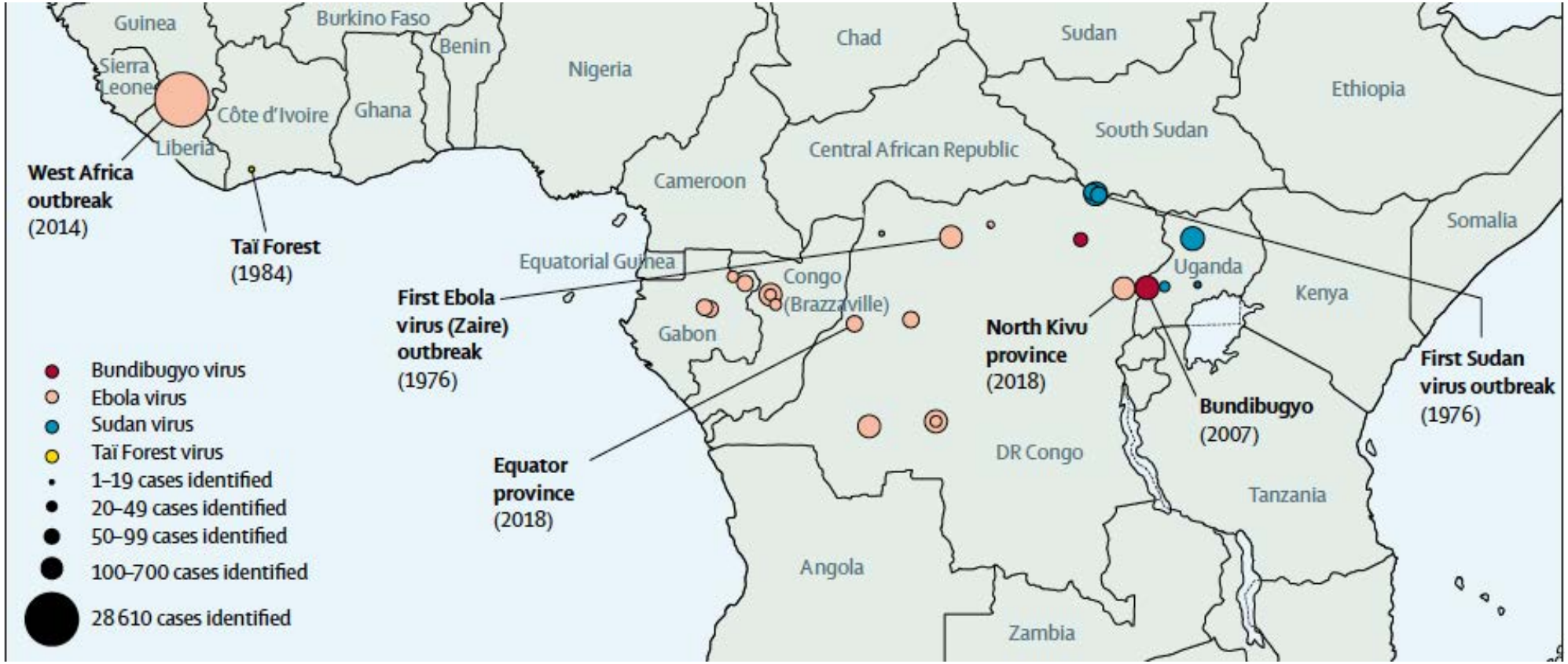
(CDC/Joel G. Breman, M.D., D.T.P.H)

(CDC Public Health Image Library)

Bilan de l'épidémie, Yambuku, 1976

- Durée d'incubation: 1 semaine
- Durée des symtômes: 1 semaine
- Evolution clinique:
  - 3-4 jours non spécifiques
  - Puis douleurs pharyngées, éruption cutanée, douleurs abdominales hémorragies notamment intestinales
- Rôle des injections et contacts interpersonnels dans la transmission
- Surveillance active dans les villages, isolement, quarantaine,
- Equipement protecteur, décontamination, enterrement des cadavres dans linceuls imprégnés de formol
- Transfusion de plasma de convalescents à 2 patients

Epidémies d'Ebola, 1976-2018



(Malvy et coll., Lancet, 2019)

Kikwit, RDC,1995

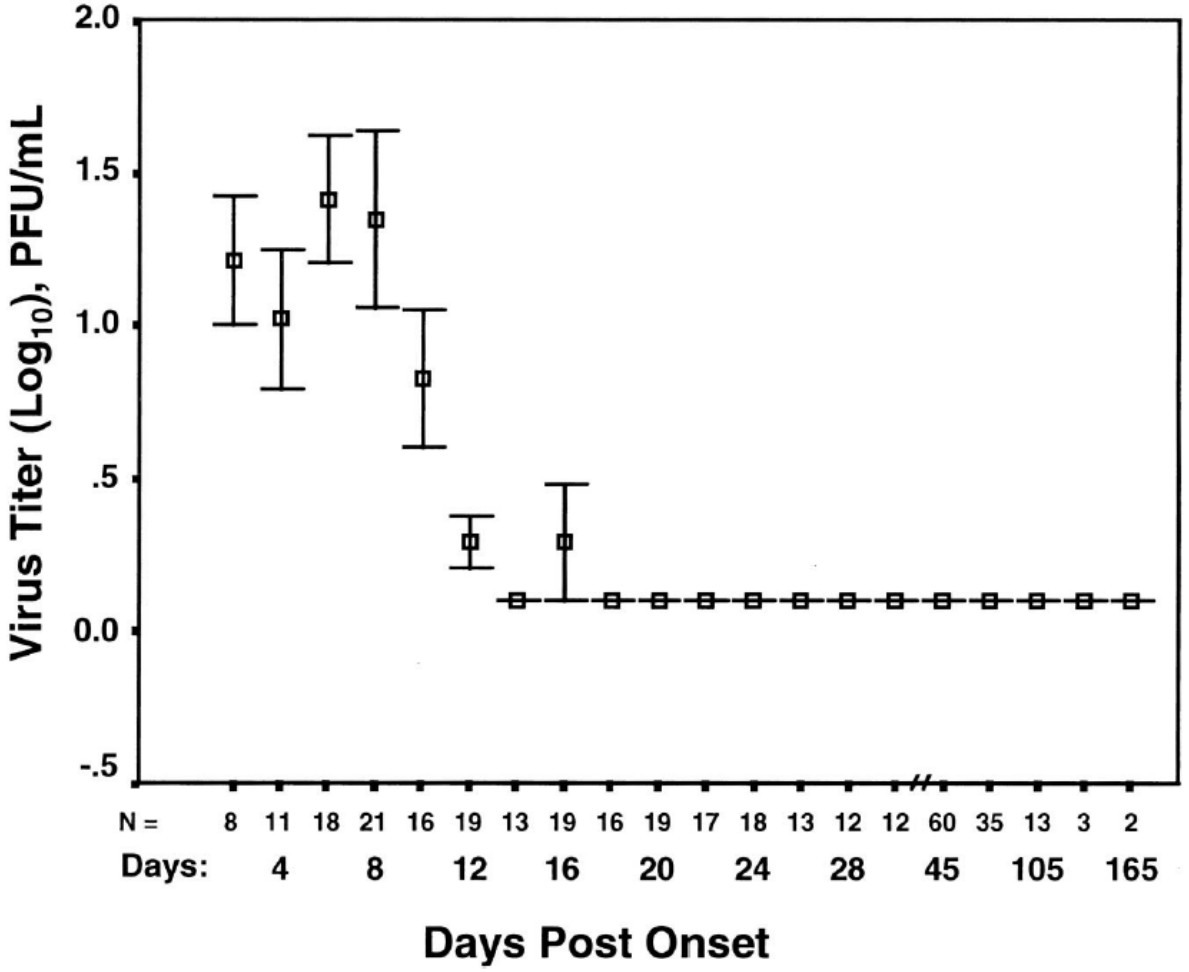
(Marielle Furrer)

Symptômes, patients Ebola, Epidémie de Kikwit, 1995 (n=103)

	%
Fièvre	95
Asthénie	87
Diarrhée	86
Nausées, vomissements	72
Douleurs abdominales	63
Douleurs pharyngées, dysphagie	56
Arthralgies	55
Anorexie	44
Eruption cutanée	14
Saignements gingivaux	12
Hématémèse	11
Méléna	9

(Bwaka, JID, 1999)

Virémie (titres) chez les patients Ebola, épidémie de Kikwit, 1995



(Kziazek, JID, 1999)

Transfusion de sang de survivants, Kikwit, 1995

Table 2. Characteristics of 8 Ebola-infected female convalescent blood transfusion recipients.

Patient	Age (years)	No. of days between onset of symptoms and transfusion	Blood volume (cm^3)	Received blood from donor no.	Outcome
1	27	7	400	1	Survived
2	12	11	150	2	Survived
3	15	13	150	3	Survived
4	54	9	250	2	Survived
5	44	15	250	4	Survived
6	25	13	250	4	Survived
7	40	11	450	5	Survived
8	48	4	400	2	Died

(Mupapa, JID, 1999)

Transmission intra-maisonnée, Kikwit, 173 contacts de 27 patients, 28 cas secondaires

Risk factor	Adjusted RR	95% CI	*P*
Female sex	1.0	0.5–2.1	NS
Spouse of index case	1.3	0.7–2.5	NS
Age >18 years	3.6	1.3–10.1	.02
Exposures during incubation period			
Conversation	0.7	0.2–3.0	NS
Sharing a bed	1.4	0.8–2.4	NS
Touching	0.8	0.4–1.8	NS
Exposures during early illness			
Sharing a meal	1.2	0.5–2.7	NS
Conversation	0.7	0.3–2.0	NS
Sharing a bed	1.3	0.7–2.5	NS
Exposures during late illness			
Sharing a meal	2.2	1.2–4.0	.009
Conversation	3.9	1.2–12.2	.02
Sharing a bed	2.2	1.2–4.2	.009
Exposure to cadaver			
Viewed	1.6	0.5–4.9	NS
Touched	2.1	1.1–4.2	.03

(Dowell, JID, 1999)

Transmission inter-humaine

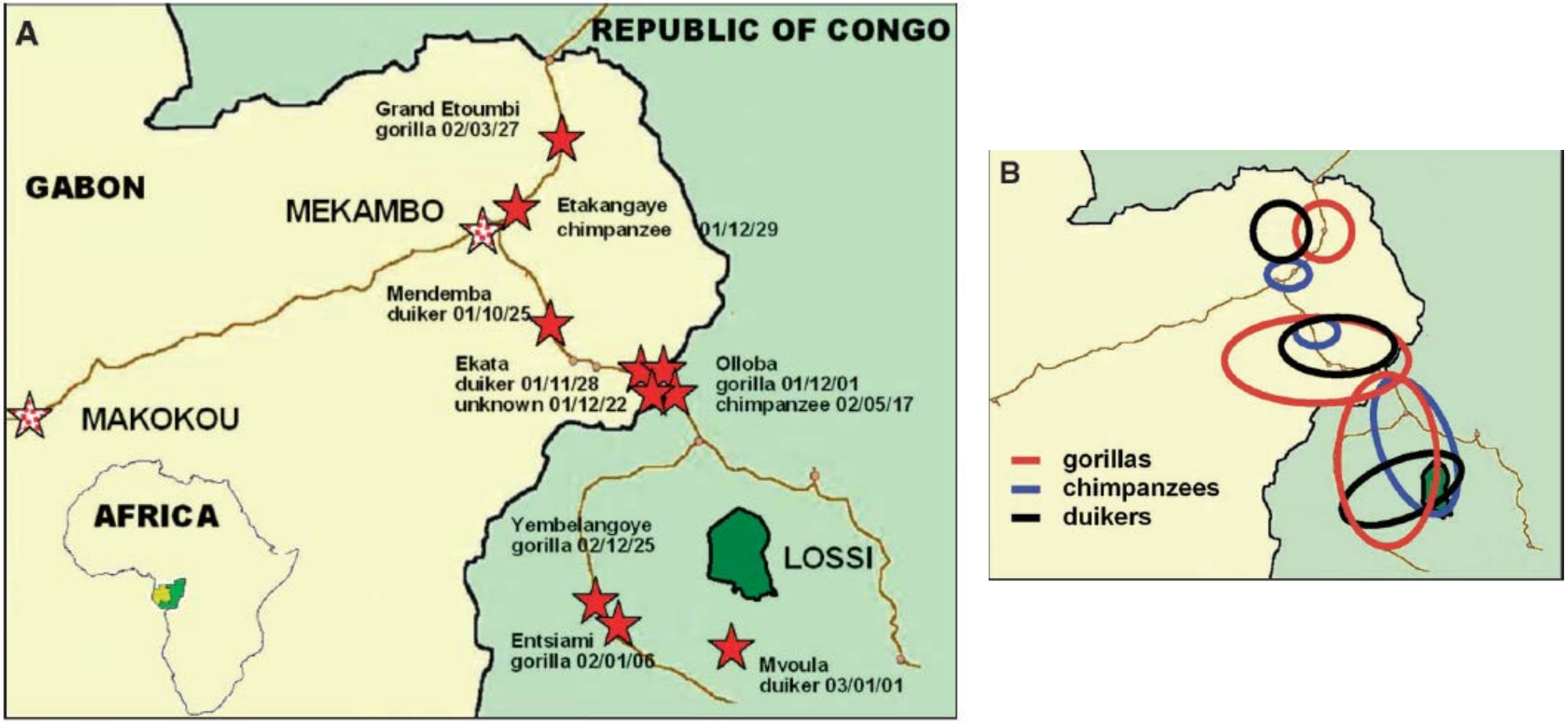
- Via les fluides corporels: soins aux patients, et rites funéraires
- Contagion après le début des symptômes, et plus importante en phase terminale
- La transmission inter-humaine par aerosols n’a pas été mise en évidence

Recherche de virus Ebola par PCR dans le sperme, Kikwit, 1995

Identification no. of convalescent, age (years)	Sample 1	Sample 2	Sample 3
2060, 27			
Days after illness onset	52	82	697
RT-PCR	+	+	−
2032, 25			
Days after illness onset	47	91	ND
RT-PCR	+	+	
96, 29			
Days after illness onset	63	97	698
RT-PCR	+	−	−
11, 33			
Days after illness onset	63	701	ND
RT-PCR	+	−	
2110, 32			
Days after illness onset	62	ND	ND
RT-PCR	−		

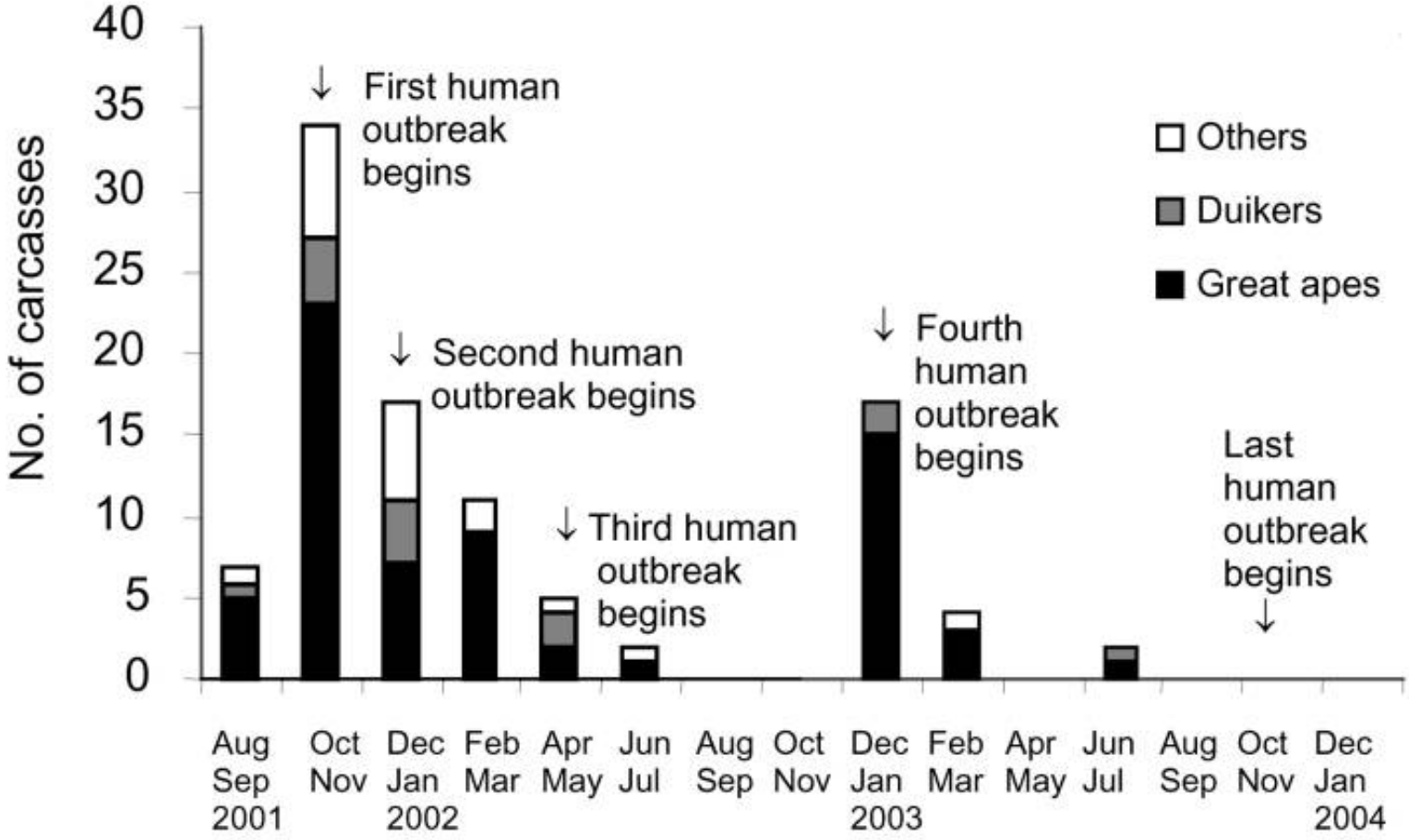
(Rowe, JID, 1999)

Epidémies d'Ebola rattachées à des animaux infectés, Gabon et RDC, 2001-2003



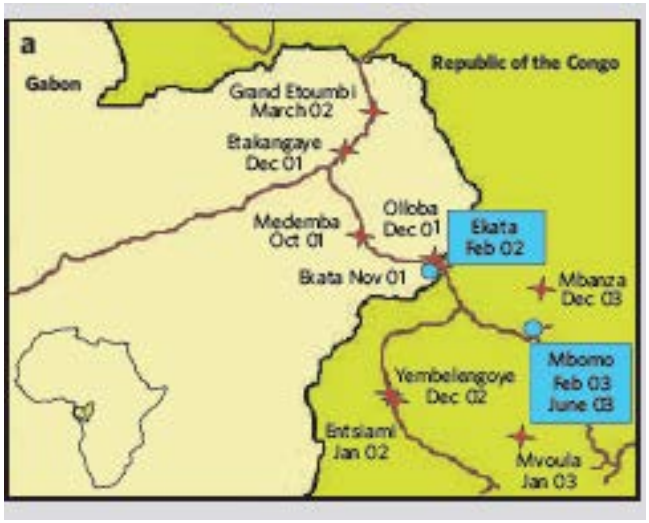
(Leroy, Science, 2003)

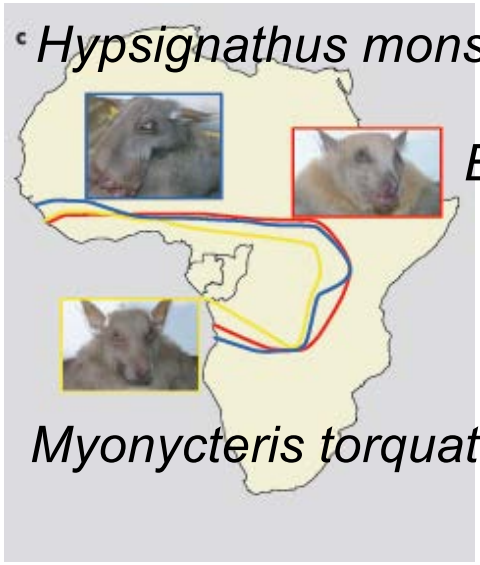
Carcasses animales et épidémies d'Ebola Gabon et Congo, 2001-3

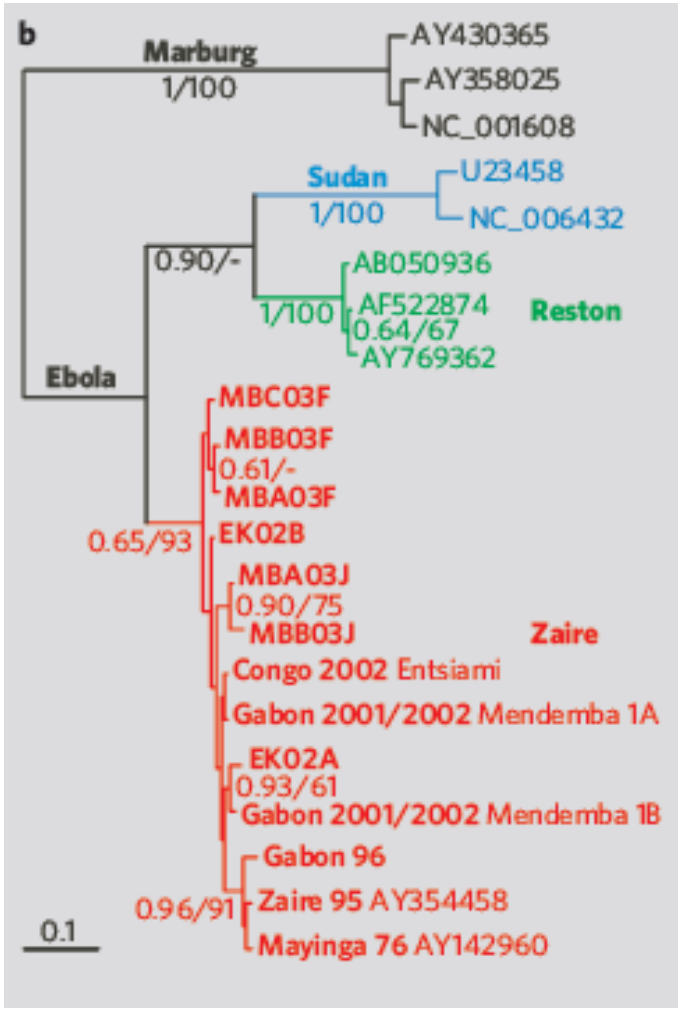


(Rouquet, EID, 2005)

Réservoir: chauve-souris?

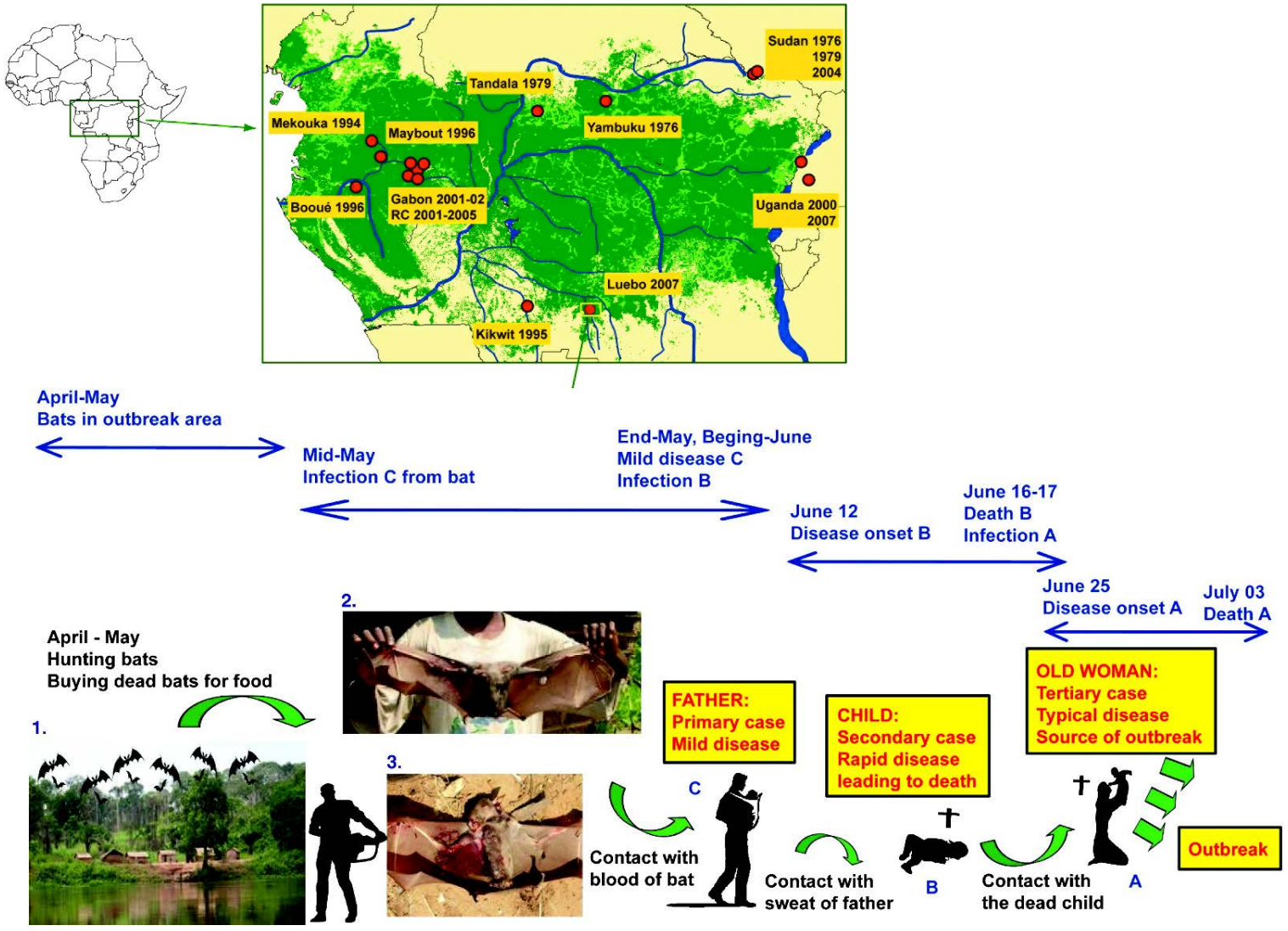






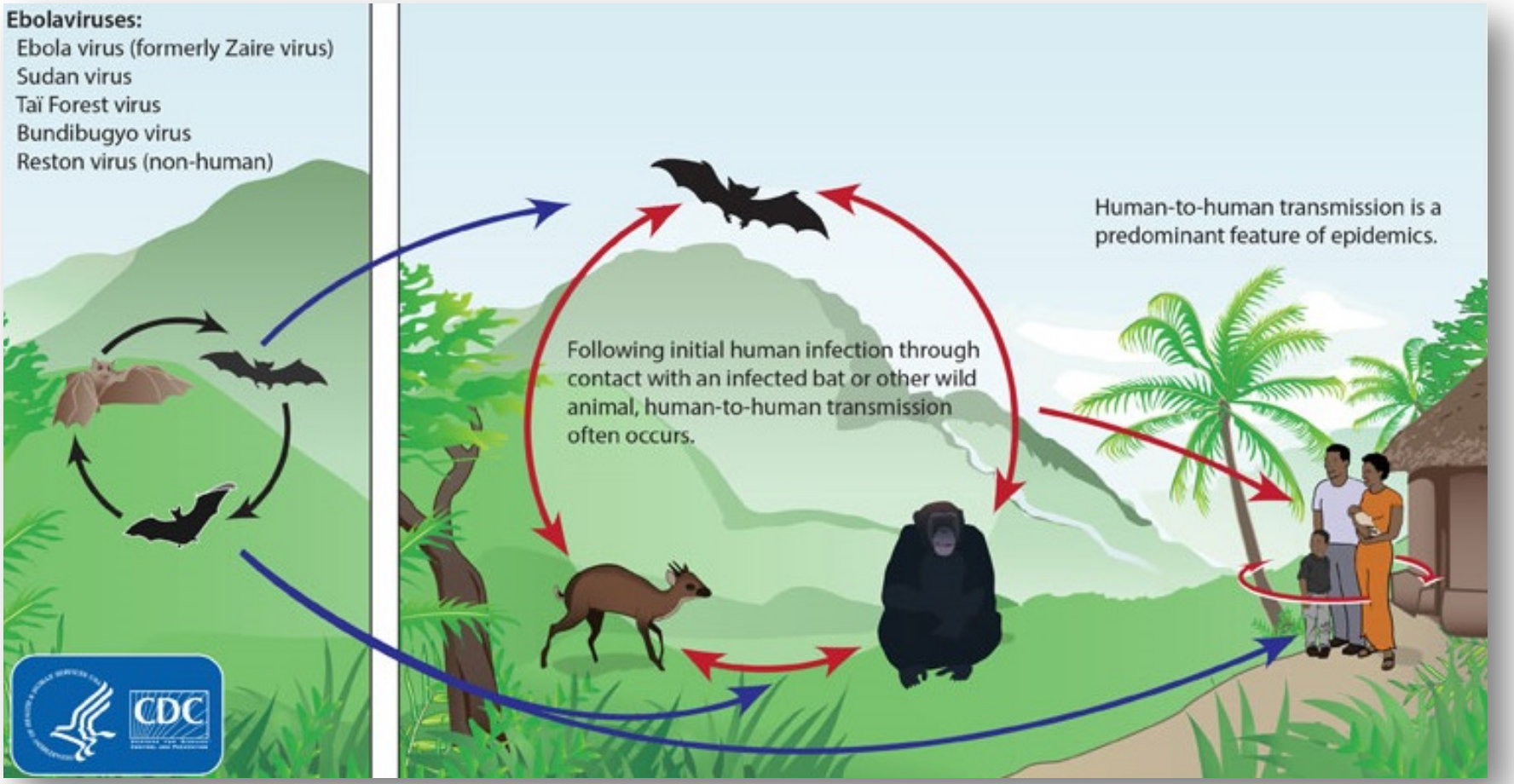
(Leroy et coll. Nature, 2005)

Contamination par chauves-souris
Epidémie Luebo, RDC, 2007

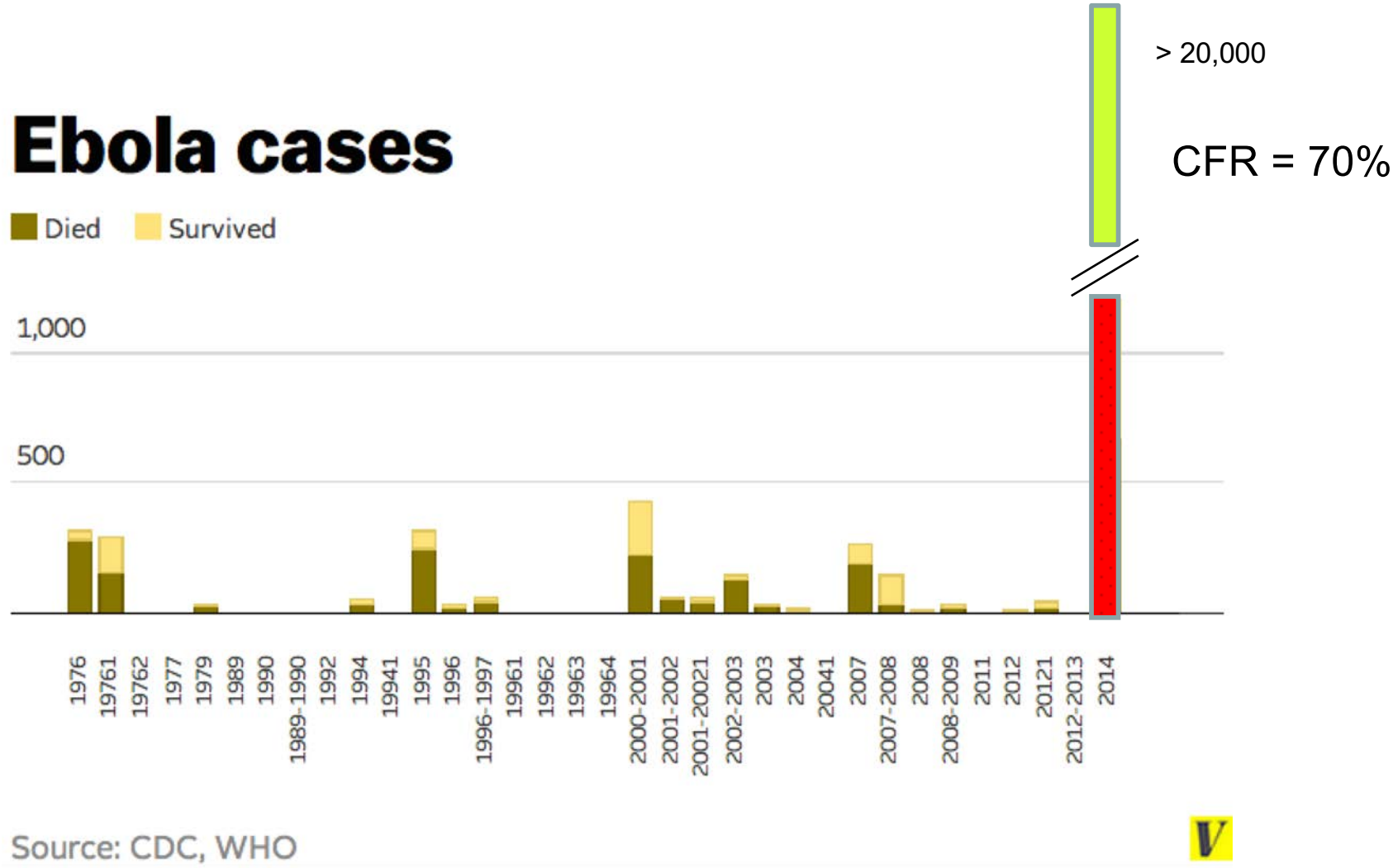


(Leroy, Vector-Borne and Zoonotic Diseases, 2009)

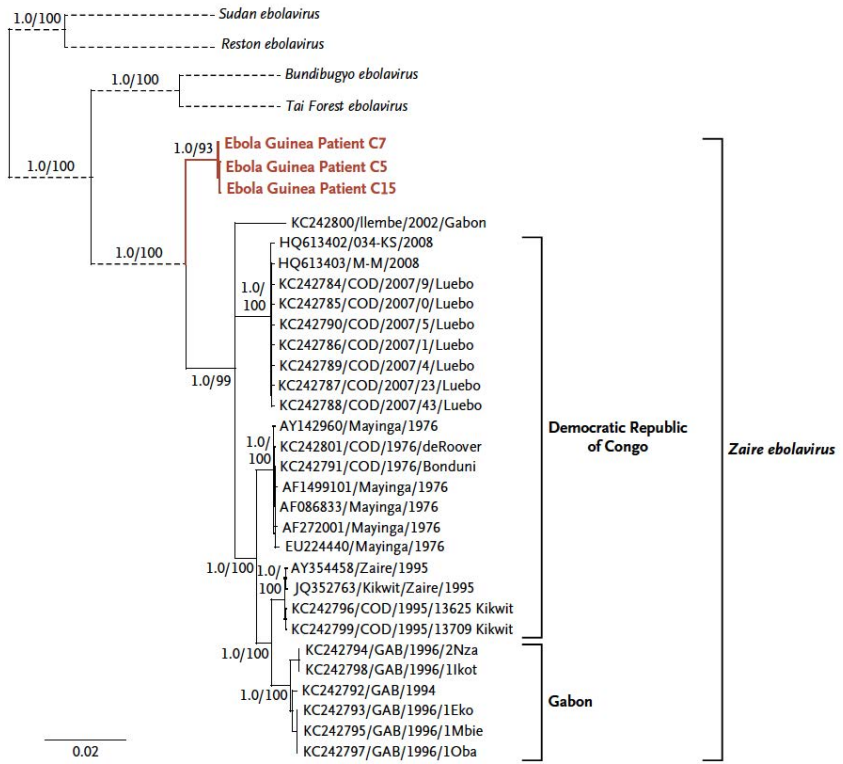
Cycle du virus Ebola



Number of cases per Ebola outbreak

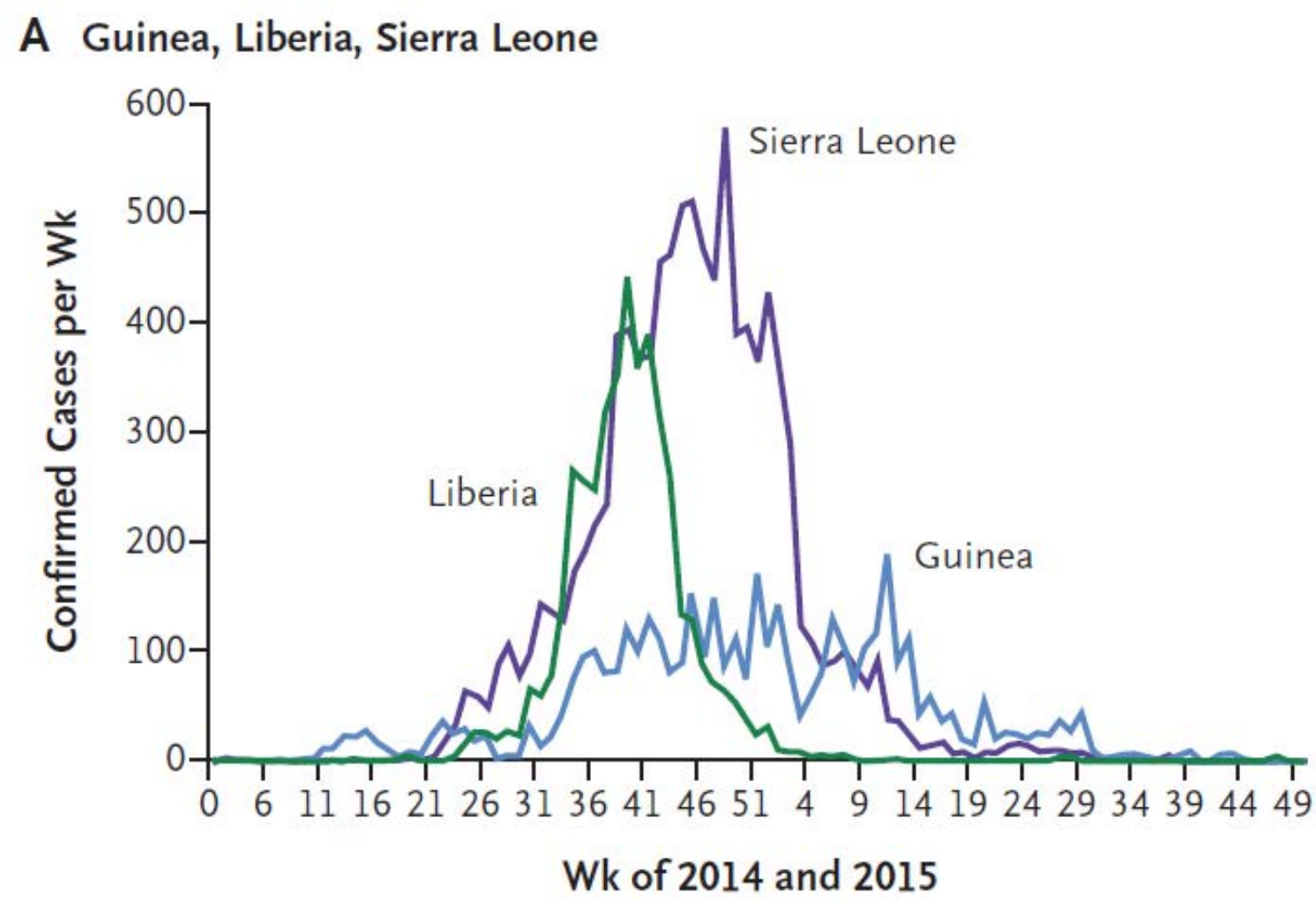


Epidémie d'Ebola, Afrique de l'Ouest, 2013-5



(Baize, NEJM, 2014)

Courbes épidémiques Ebola
Guinée, Sierra Leone et Libéria, 2014-5



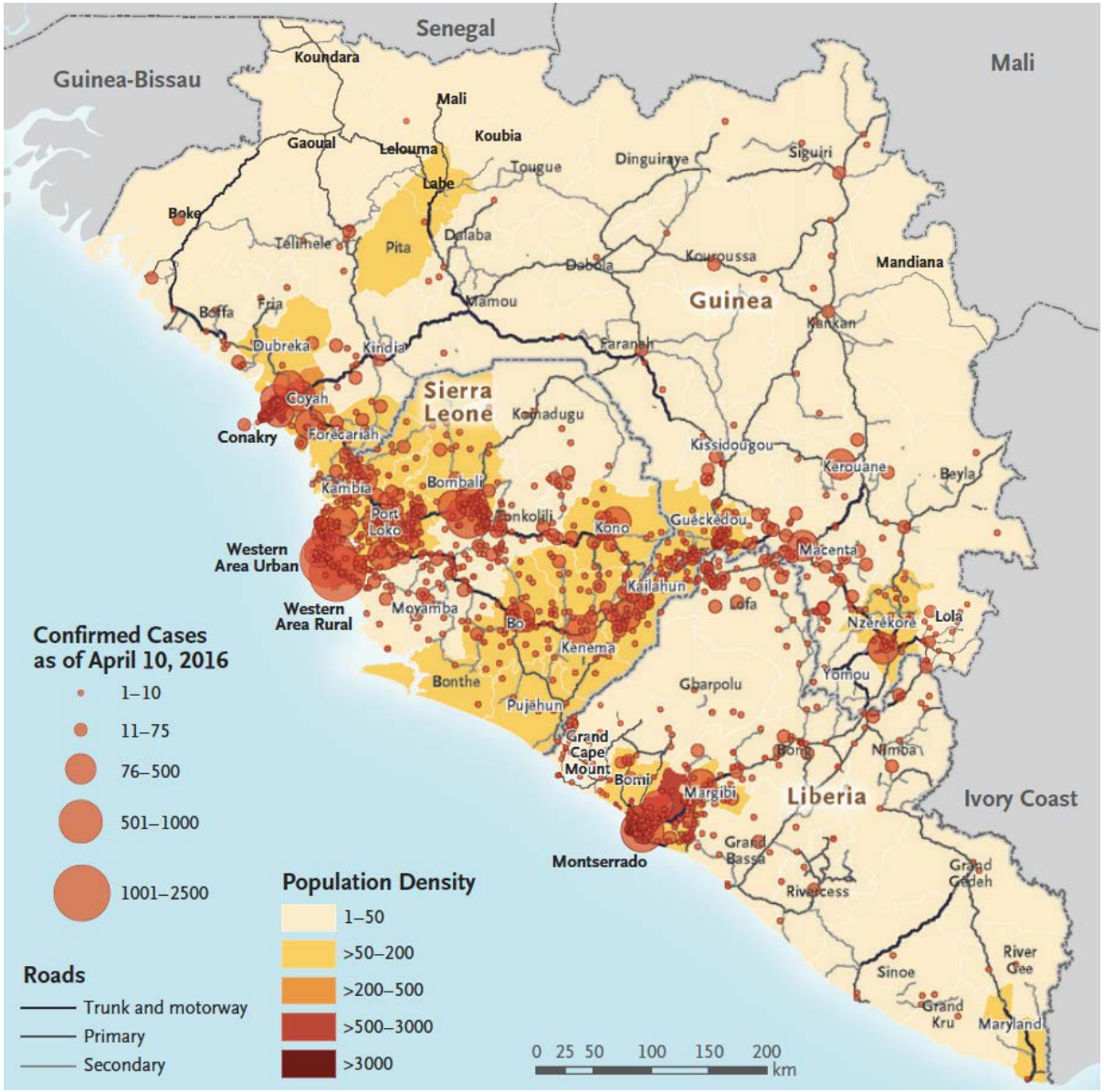
(WHO response team, NEJM, 2016)

How Ebola Roared Back

Kevin Sack, Sheri Fink, Pam Belluck, Adam Nossiter,
New York Times, 29 déc 2014

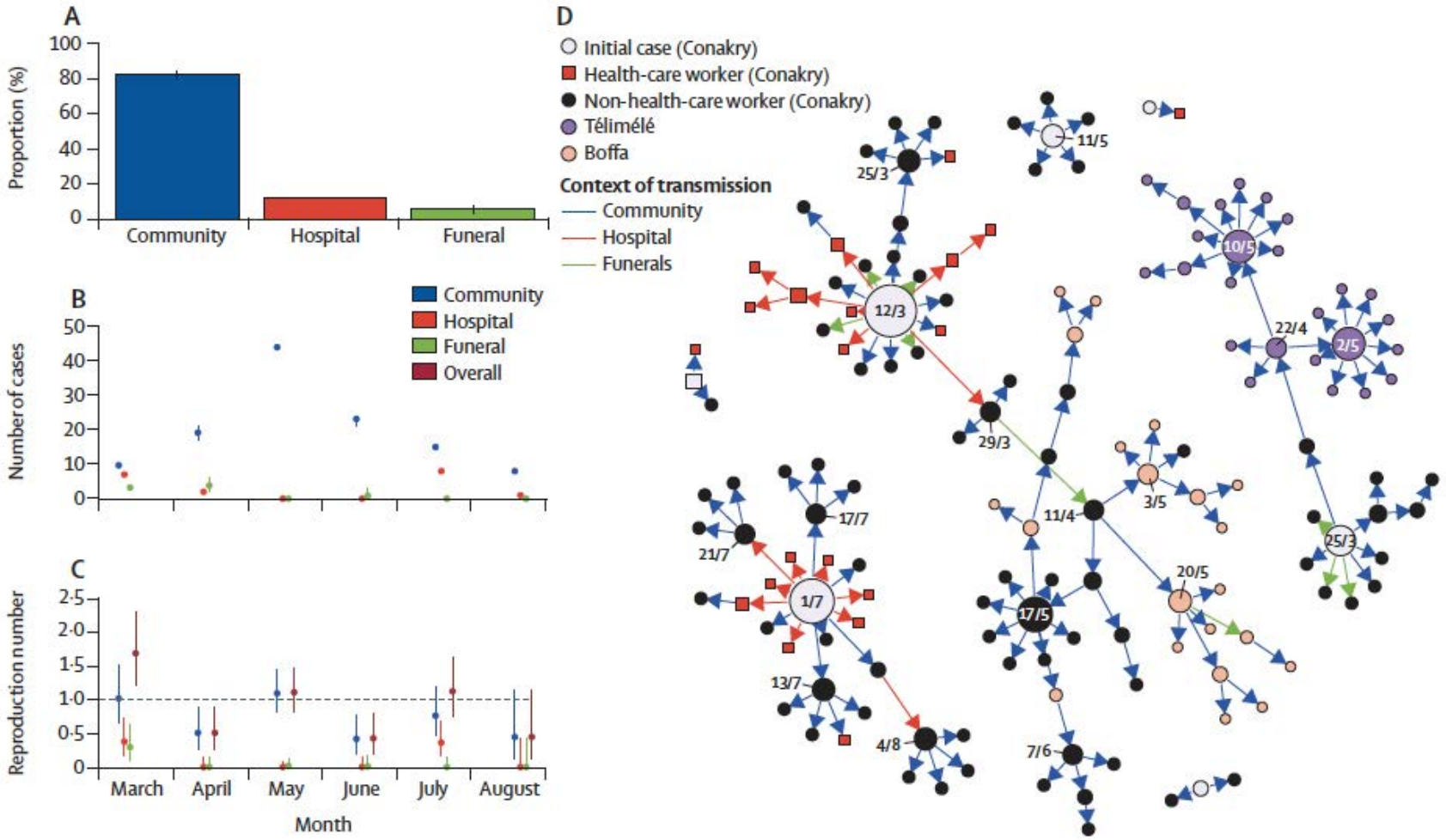
(Daniel Berehulak for The New York Times)

Epidémie d'Ebola, Afrique de l'Ouest, 2013-5



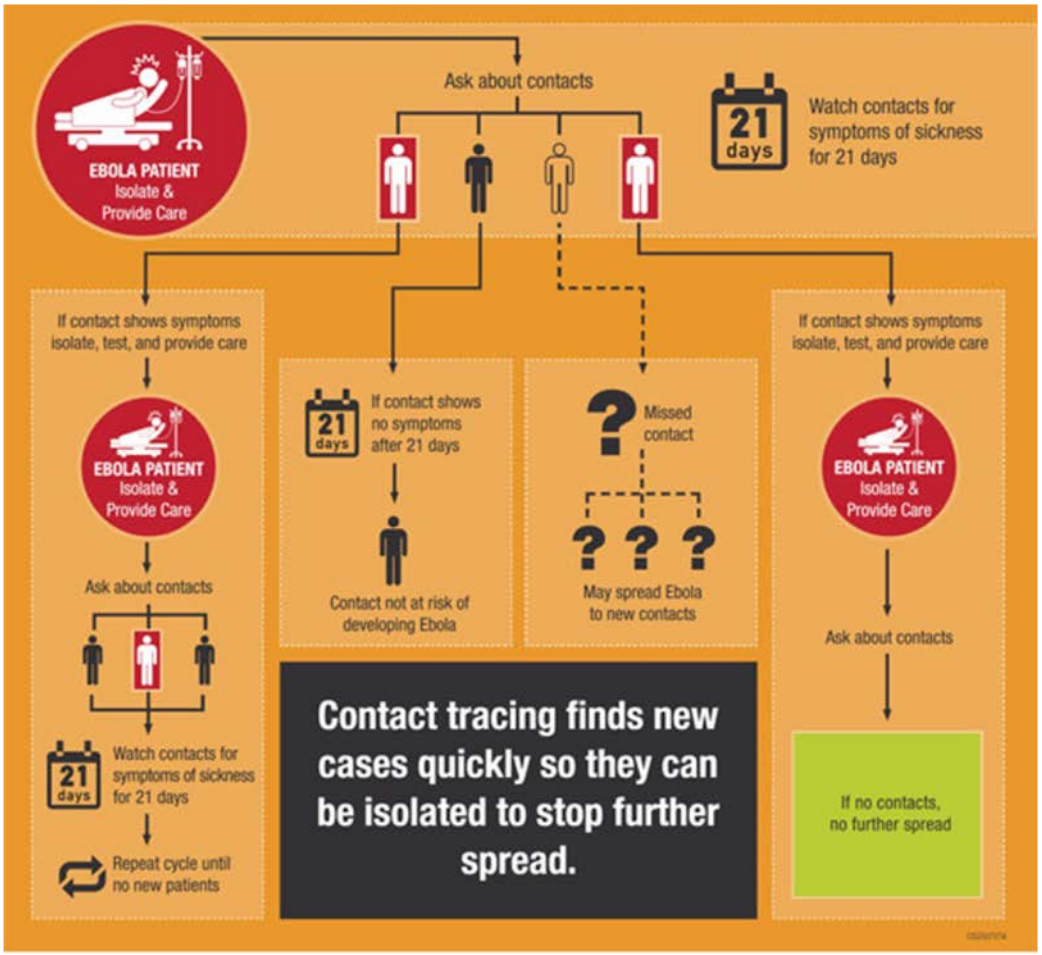
(WHO response team, NEJM, 2016)

Chaînes de transmission, Ebola, Conakry, Guinée, 2014



(Faye et coll., Lancet infect Dis, 2015)

Contrôle en communauté

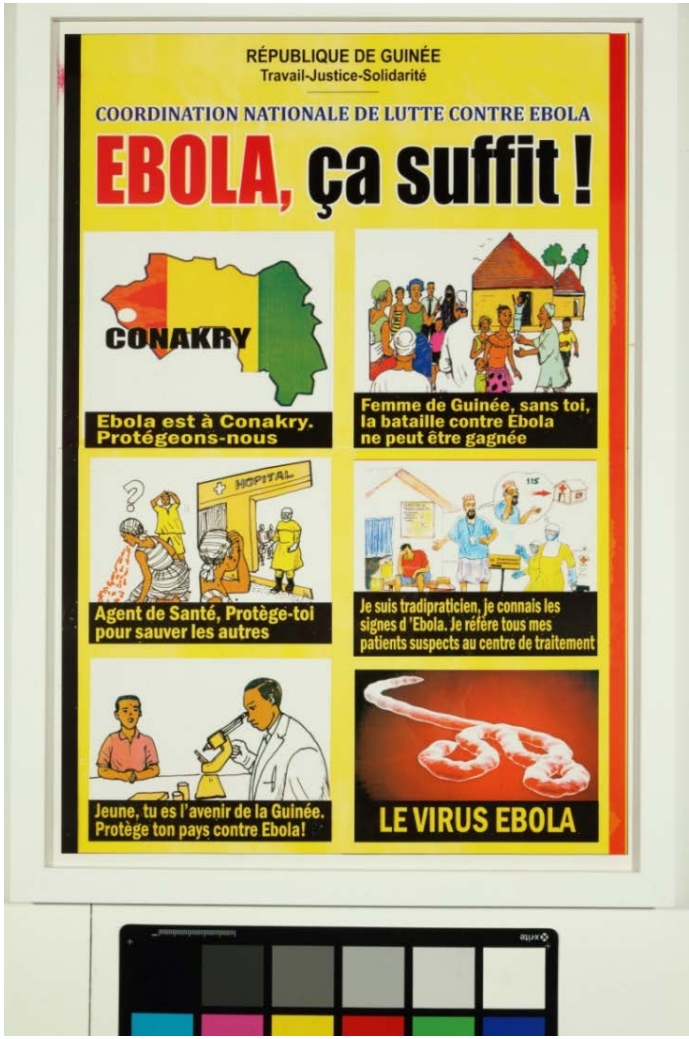


Contact tracing, source CDC

(Cellou Binani / AFP/Archives)

(Zoom Doso/AFP)

Mobilisation sociale



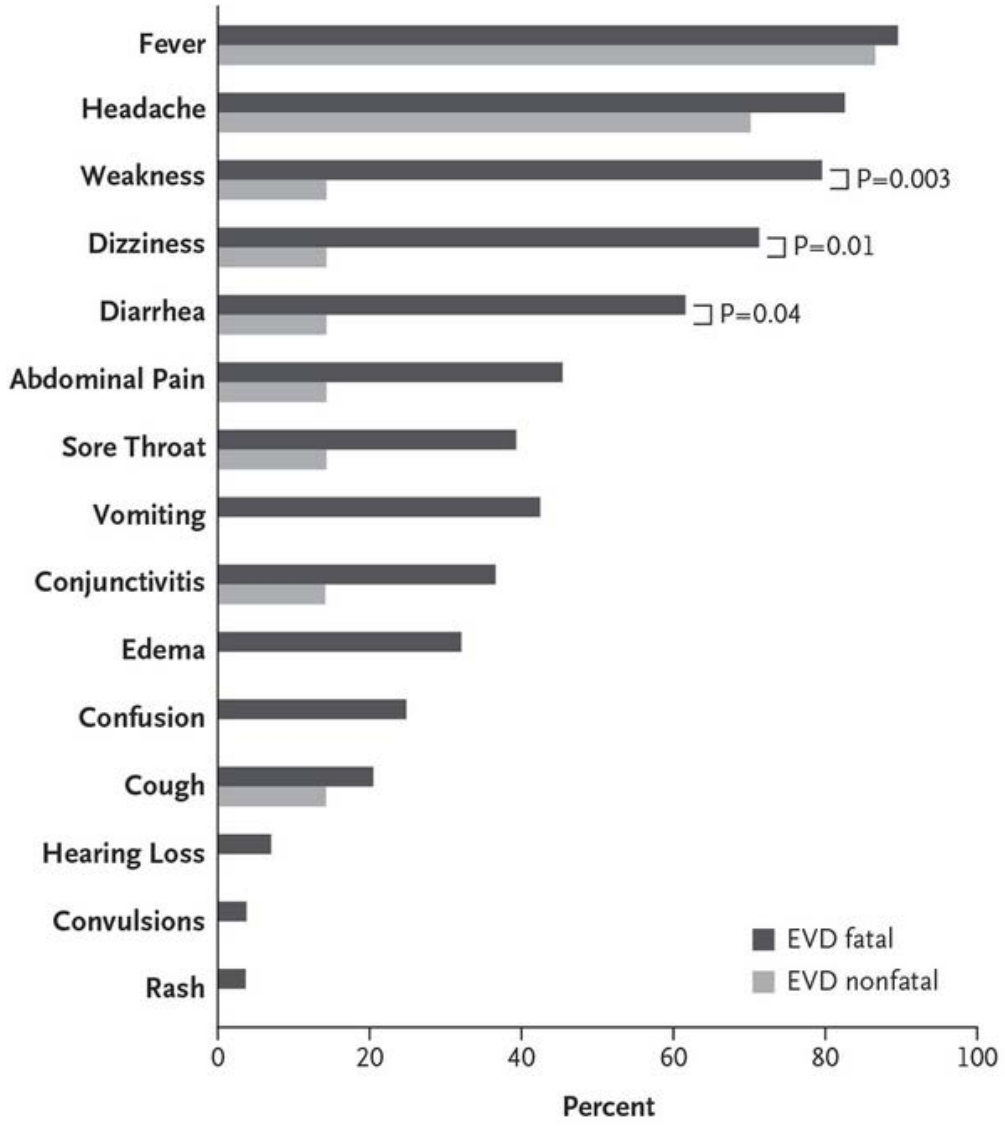
(Youssouf Bah, AP)

Rites funéraires, enterrements sécurisés et dignes

(Kieran McConville)

(Goran Tomasevic/Reuters)

Symptômes à l'admission, Sierra Leone, 2014 (n=44)



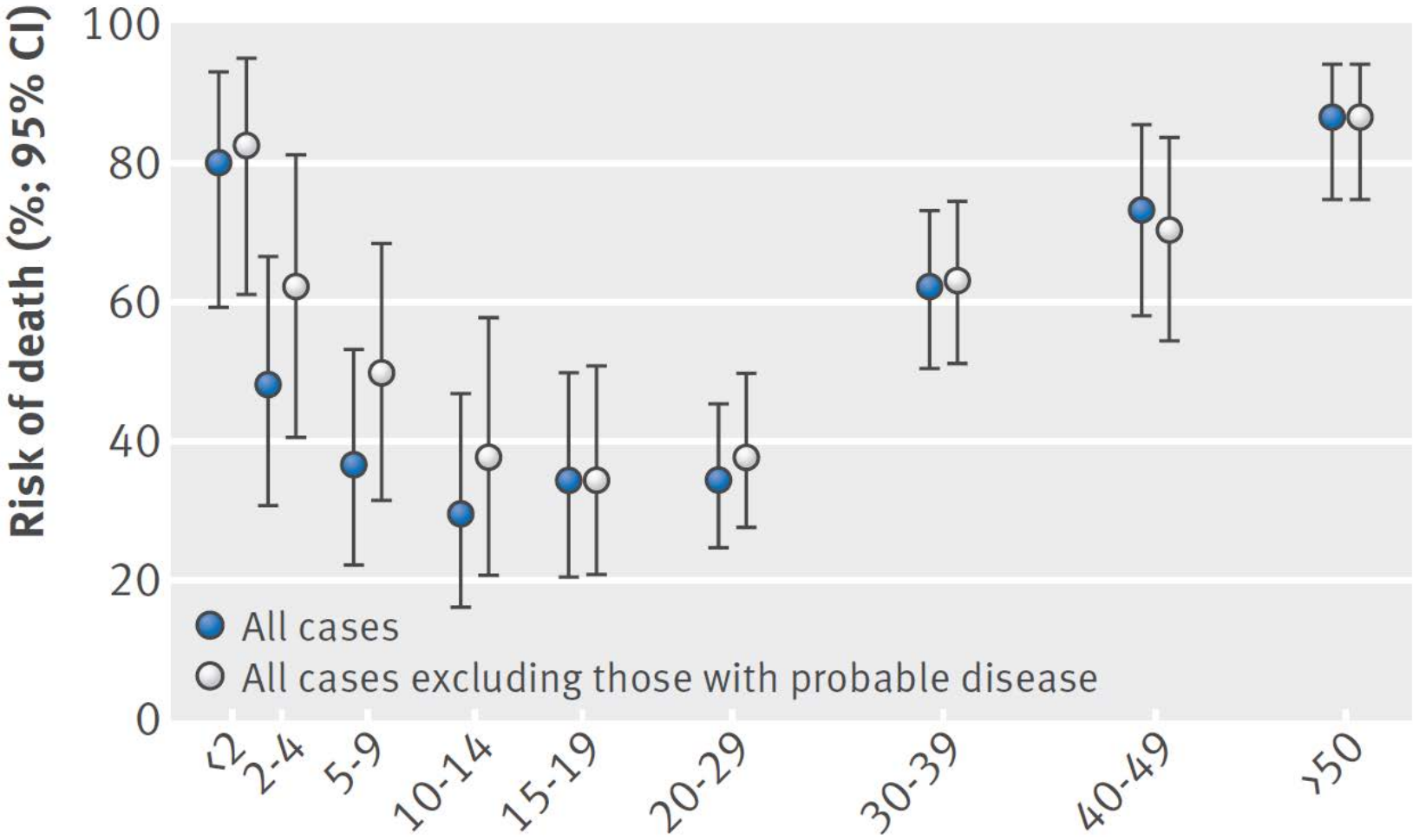
(Schieffelin, NEJM, 2014)

Evolution clinique

- Incubation: 8–10 jours (étendue: 2–21 jours)
- Symptômes:
  - Début: fièvre, frissons, douleurs musculaires, malaise, anorexie
  - Après 5 jours: symptômes gastro-intestinaux, comme nausées, vomissements, diarrhée aqueuse, douleurs abdominales
  - Autres: maux de tête, conjonctivite, hoquet, eruption cutanée, douleurs thoraciques, troubles respiratoires, confusion, crises d'épilepsie
  - Symptômes hémorragiques: 18% des cas

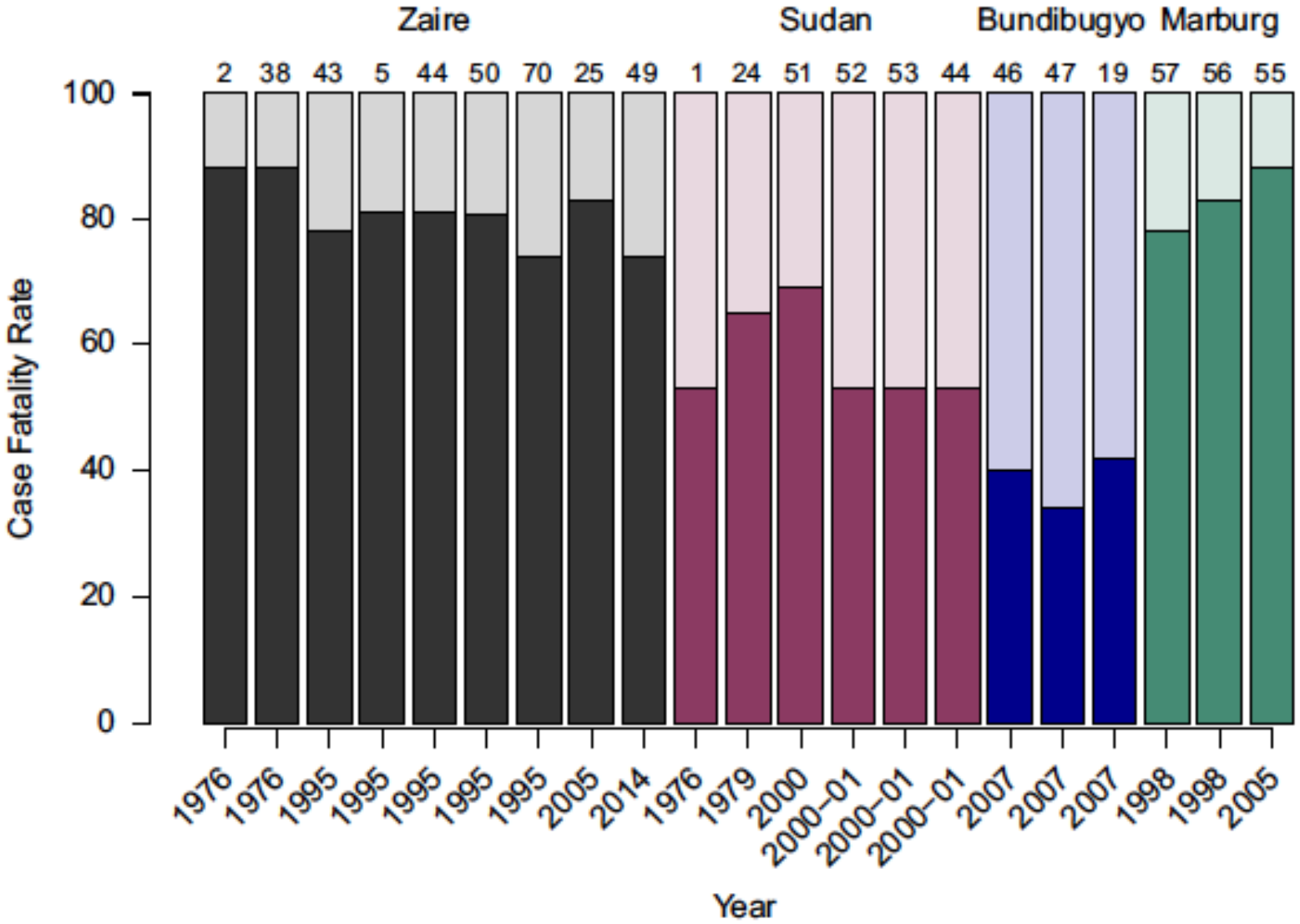
(WHO Ebola Response team. *NEJM*. 2014)

Taux de létalité par âge
Ebola, Sierra Leone, 2014-5



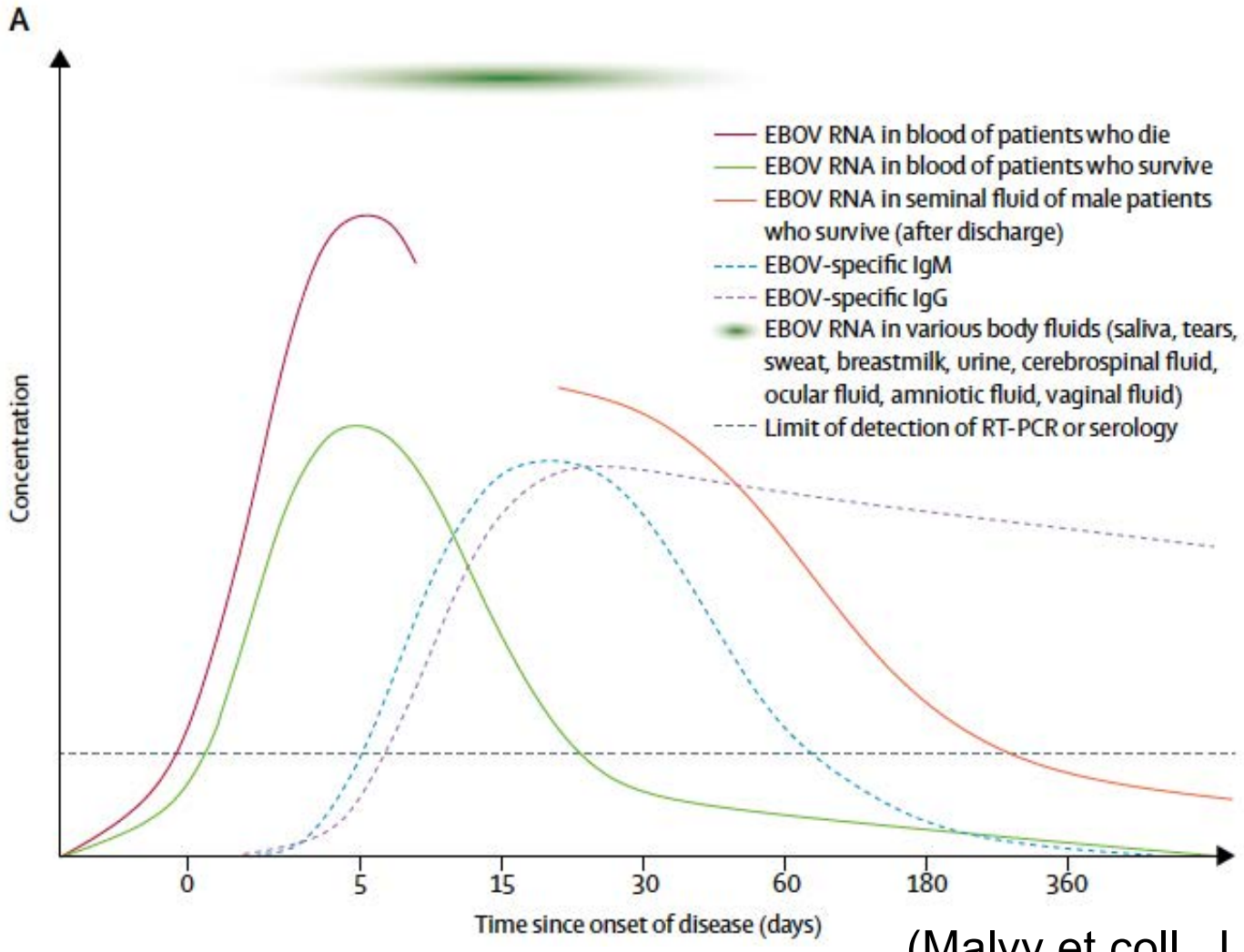
(Bower et coll., BMJ, 2016)

Taux de létalité, épidémies d'Ebola



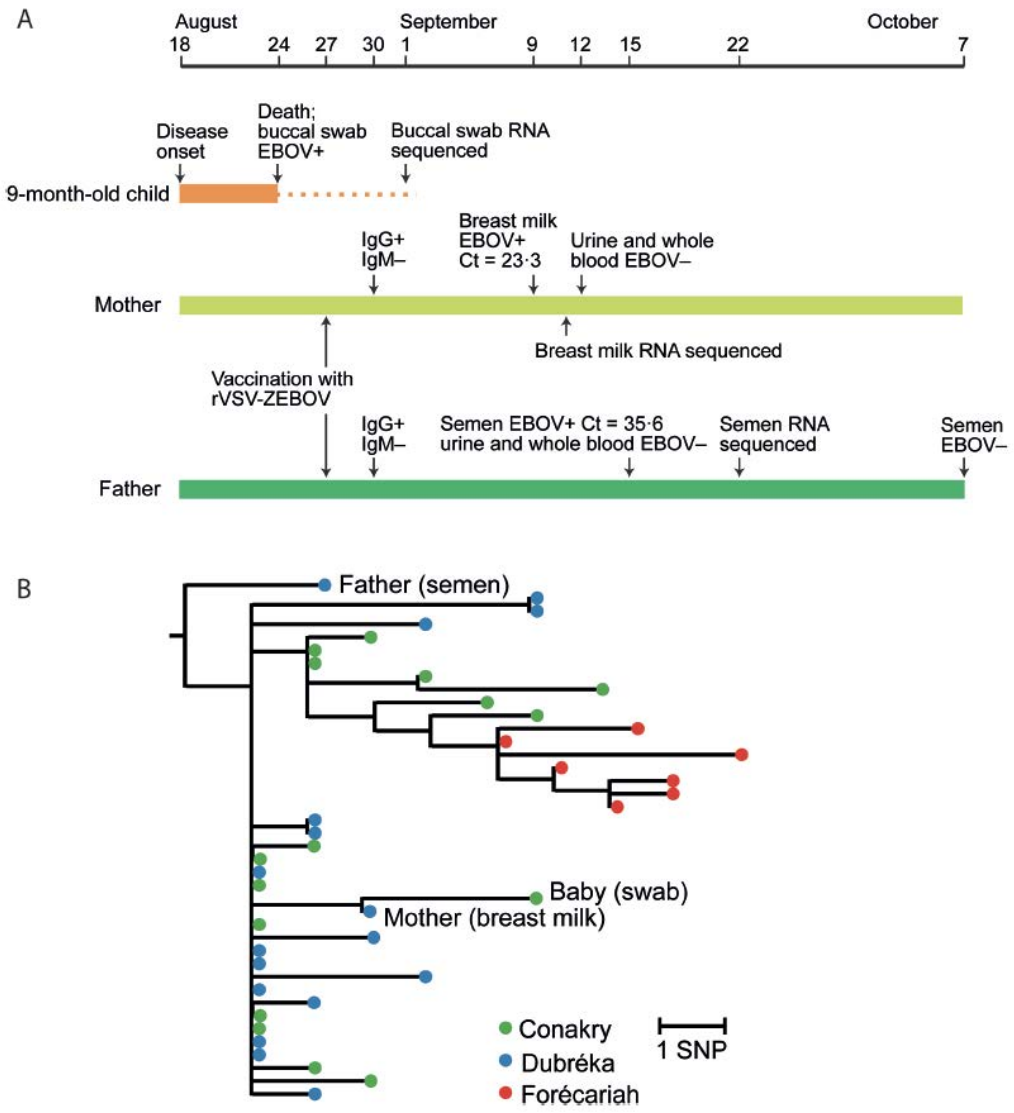
(Van Kerkhove, Scientific data, 2015)

Présence du virus dans les fluides corporels



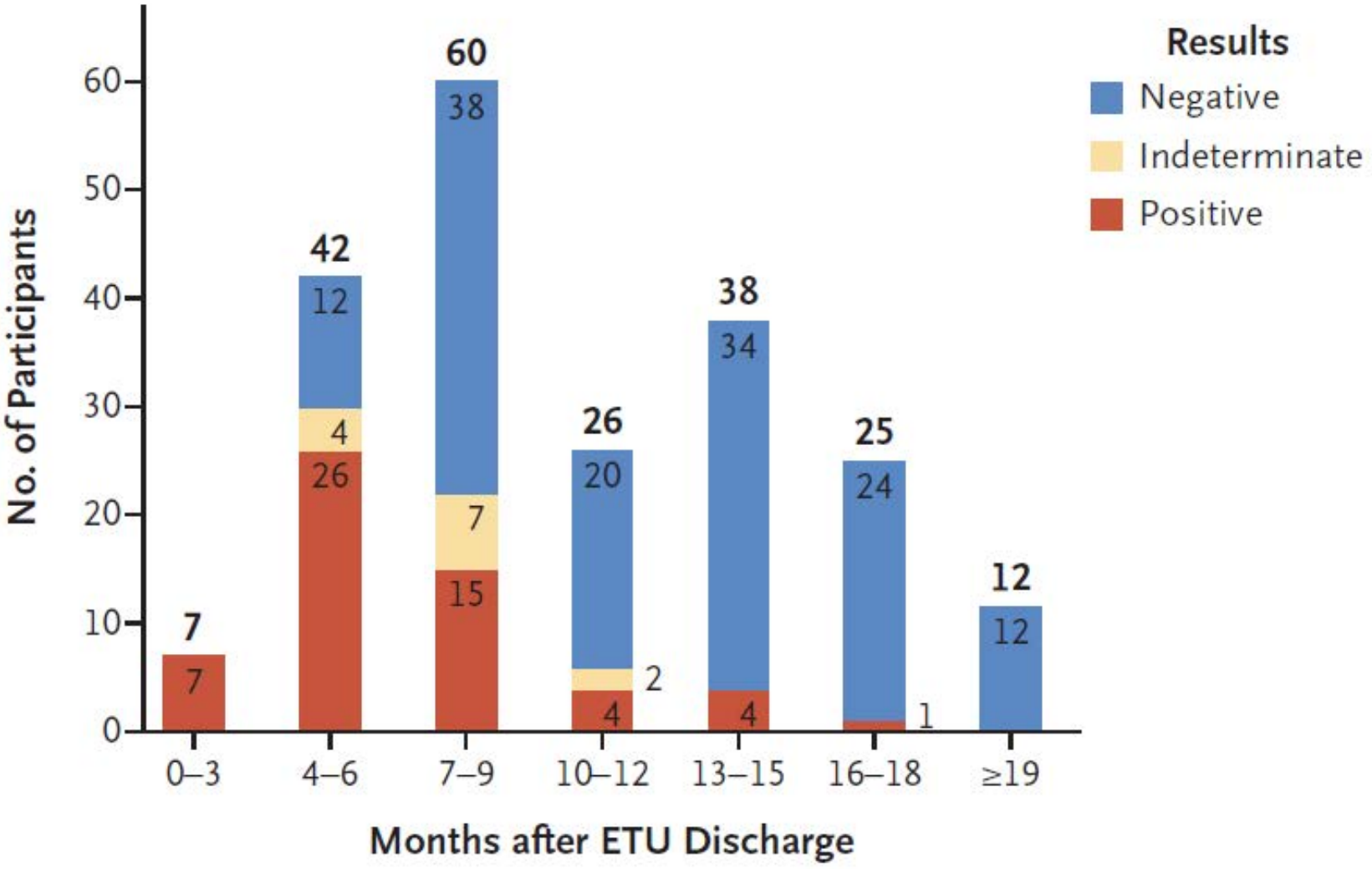
(Malvy et coll., Lancet, 2019)

Transmission par le lait maternel Guinée, 2015



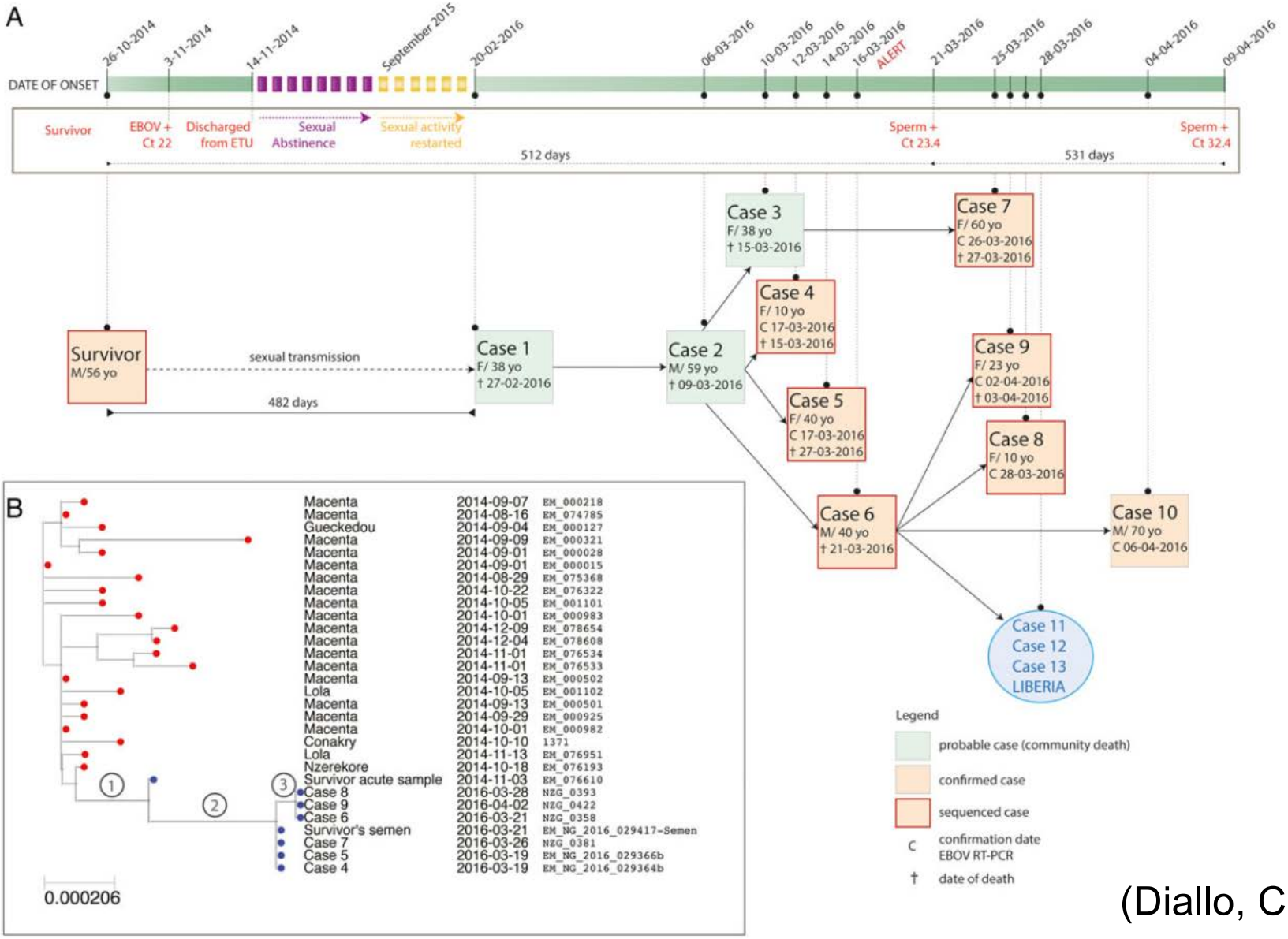
(Sissoko, CID, 2017)

Présence du virus dans le sperme Sierra Leone,



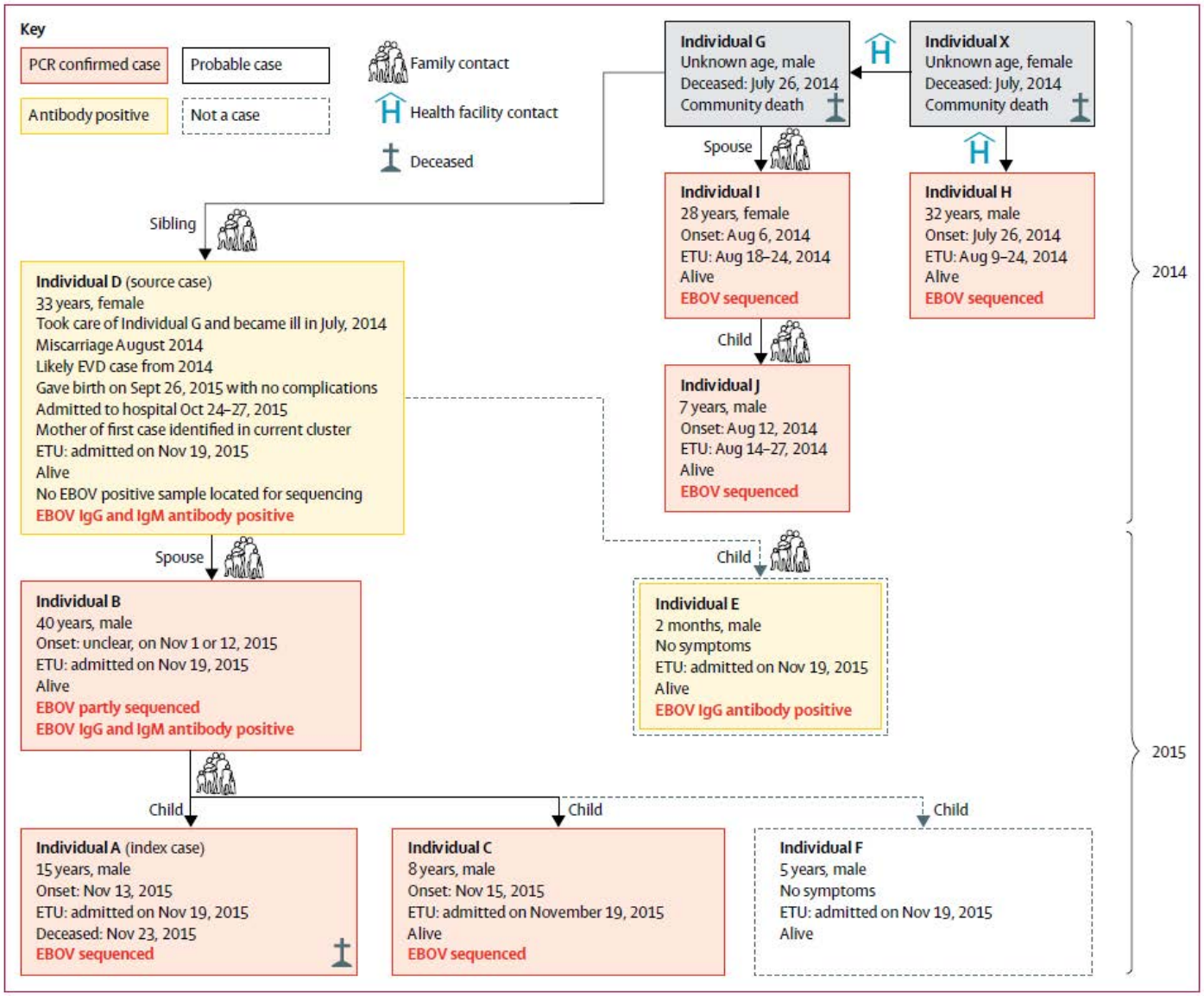
(Deen et coll, NEJM, 2017)

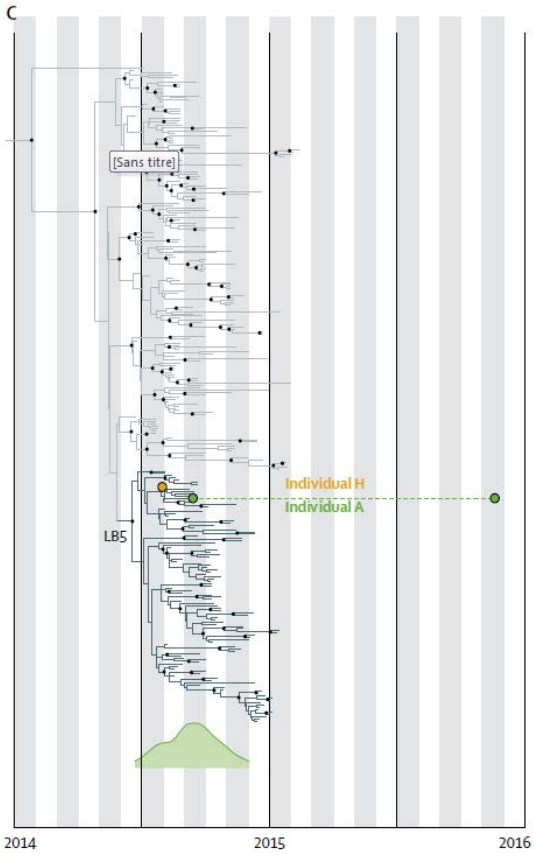
Transmission sexuelle près de 500 jours après guérison, Guinée, 2014-5



(Diallo, CID, 2016)

Ebola résurgence tardive
Liberia, juillet 2014 – novembre 2015

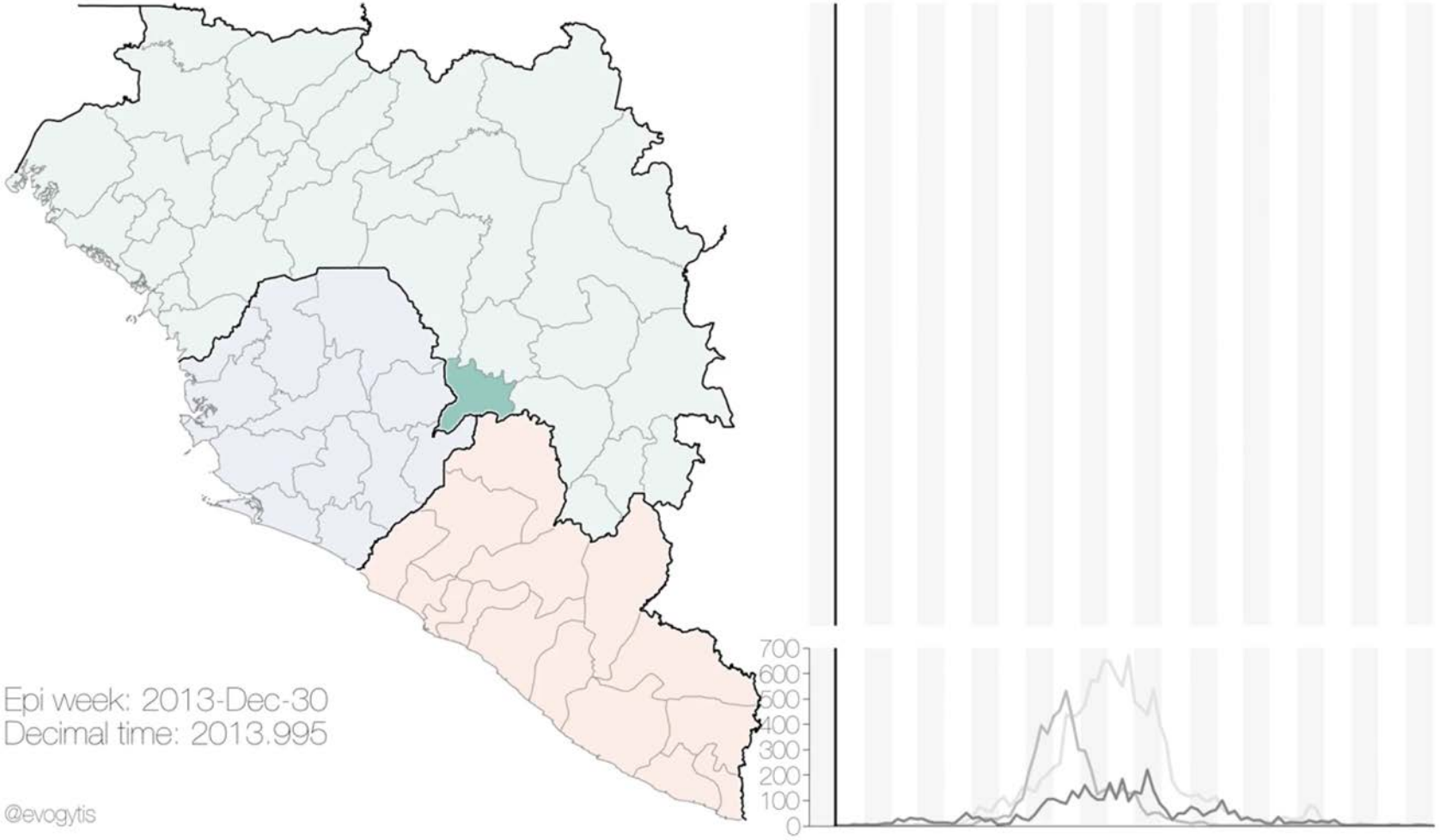




(Dokubo, Lancet Infect Dis 2018)

Epidémie d'Ebola,

Afrique de l'Ouest, 2014-2015



(Gytis Dudas, Bedford lab) https://youtu.be/j4Ut4krp8GQ

Présentation clinique et prise en charge des patients

	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

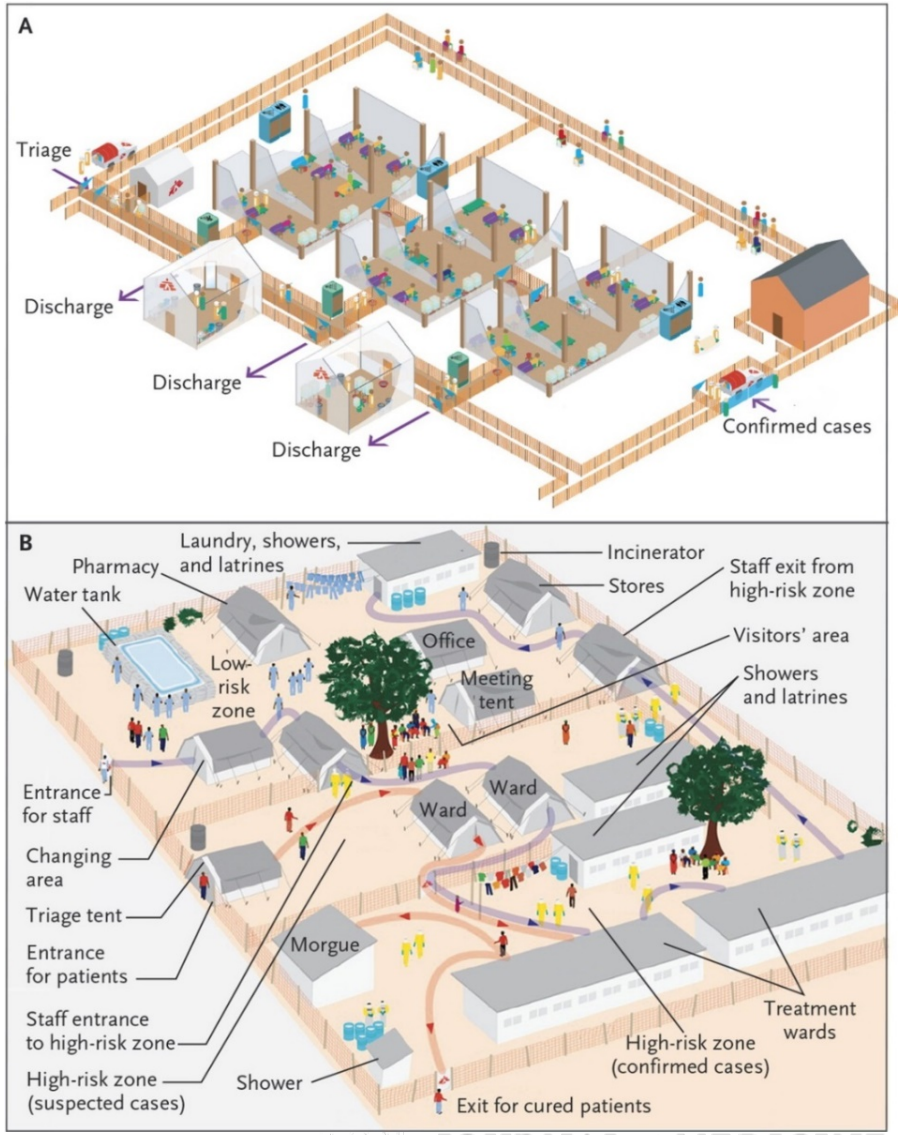
Adapted from Chertow and colleagues[63] and Hunt and colleagues.[64]

(Malvy et coll., Lancet, 2019)

Organisation des soins

(Daniel Berehulak for The New York Times)

(Daniel Berehulak for The New York Times)



(Chertow DS et al. NEJM, 2014)

Essais randomisés, oui ou non?

and mortality is extremely high. This is precisely the problem with Ebola: current conventional care does not much affect clinical outcomes and mortality is as high as 70%. When conventional care means such a high probability of death, it is problematic to insist on randomising patients to it when the intervention arm holds out at least the possibility of benefit. Ethical arguments are not the same for all levels of risk.

(Adebamowo, Lancet, 2014)

Randomisation is essential in Ebola drug trials

In their Correspondence (Oct 18, p 1423),[1] Clement Adebamowo and colleagues suggest that new Ebola drugs should not be assessed with clinical trials that use randomisation.[1] There are at least four reasons to think they are mistaken.

(Shaw, Lancet, 2014)

Produits évalués

- Favipiravir: antiviral (grippe), voie orale, essai à un bras (n=99), mortalité à 20% chez patients avec charge virale basse, 91% avec charge virale élevée; non concluant (groupe contrôle historique).
- Plasma de patients convalescents: deux perfusions, essai à un bras (n=84), mortalité à 31% dans le groupe intervention et 37% dans le groupe contrôle (historique); non concluant.
- ZMapp: anticorps monoclonaux, trois perfusions intraveineuses, essai randomisé (n=72 sur 200 planifiés), mortalité de 22% dans le groupe ZMapp versus 37% dans le groupe contrôle; non concluant.
- TKM: ARN interférents associés avec des nanoparticules lipidiques, essai à un bras (n=12), sept perfusions, mortalité à 25% (après exclusion de deux décès précoces), effets indésirables (cytokines)

(Malvy et coll., Lancet, 2019)

Essai vaccinal en anneau, Guinée, 2015

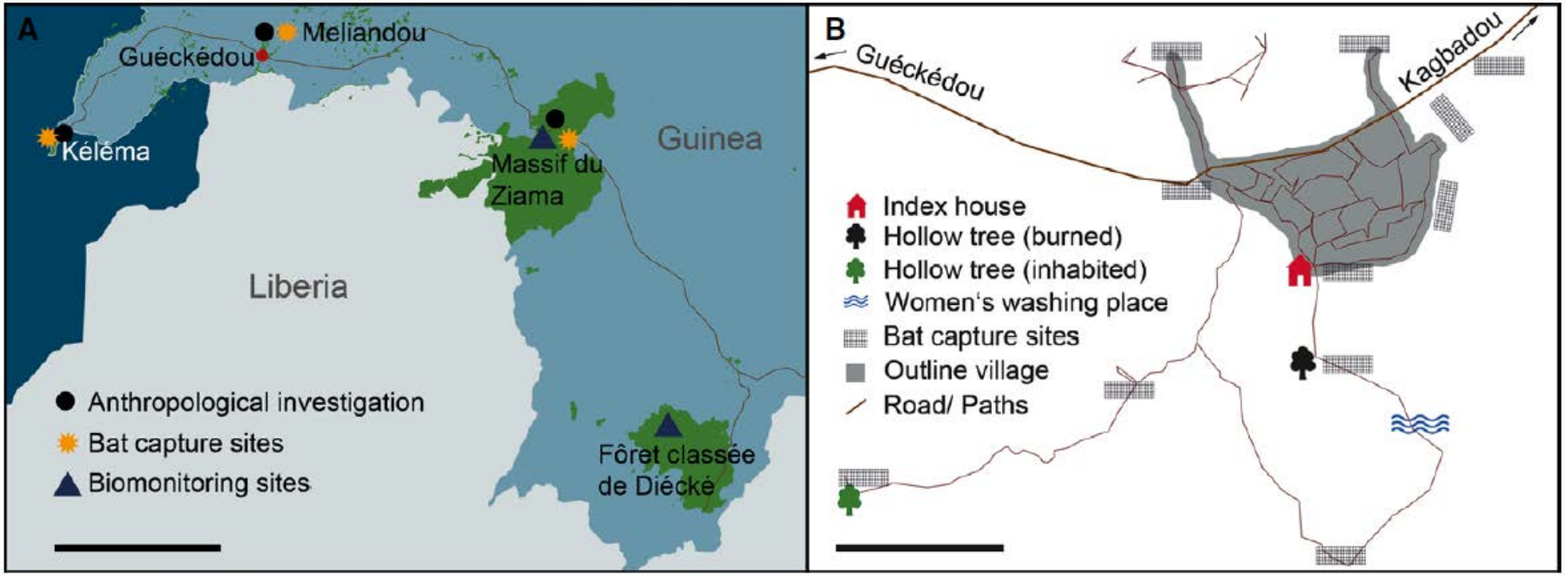
	All vaccinated in immediate versus all eligible in delayed (primary analysis)	All eligible and consented	All eligible (eligible adults, contacts and contacts of contacts)	All (all contacts and contacts of contacts)
Number of individuals (clusters)				
Immediate	2014 (48)	2048 (48)	3035 (48)	4123 (48)
Delayed	2380 (42)	1930 (42)	2380 (42)	3528 (42)
Number of cases at <10 days (affected clusters)				
Immediate	9 (4)	10 (5)	18 (9)	21 (9)
Delayed	16 (12)	6 (5)	16 (12)	25 (13)
Number of cases at ≥10 days (affected clusters)				
Immediate	0 (0)	0 (0)	6* (3)	8* (4)
Delayed	16† (7)	11† (5)	16† (7)	21† (7)
Vaccine efficacy/ effectiveness‡ (%; 95% CI)	100% (74·7 to 100)	100% (70·8 to 100)	75·1% (−7·1 to 94·2)	76·3% (−15·5 to 95·1)
p value§	0·0036	0·0194	0·1791	0·3351

*All cases occurred in unvaccinated individuals. †Four cases were vaccinated and developed symptoms on day 0, 2, 6, or 6 after vaccination. ‡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 (first two columns); from Cox proportional hazards model to estimate vaccine effectiveness (last two columns). §From Fisher's exact test (two-sided).

(Henao-Restrepo, Lancet, 2015)

(Cellou Binani/Stringer)

Origine de l'épidémie de 2013-4 Meliandou, Guéckédou, Guinée



(Saez et coll. EMBO Mol Med, 2015)

Chauve-souris à l'origine?

(Daniel Berehulak for The New York Times)

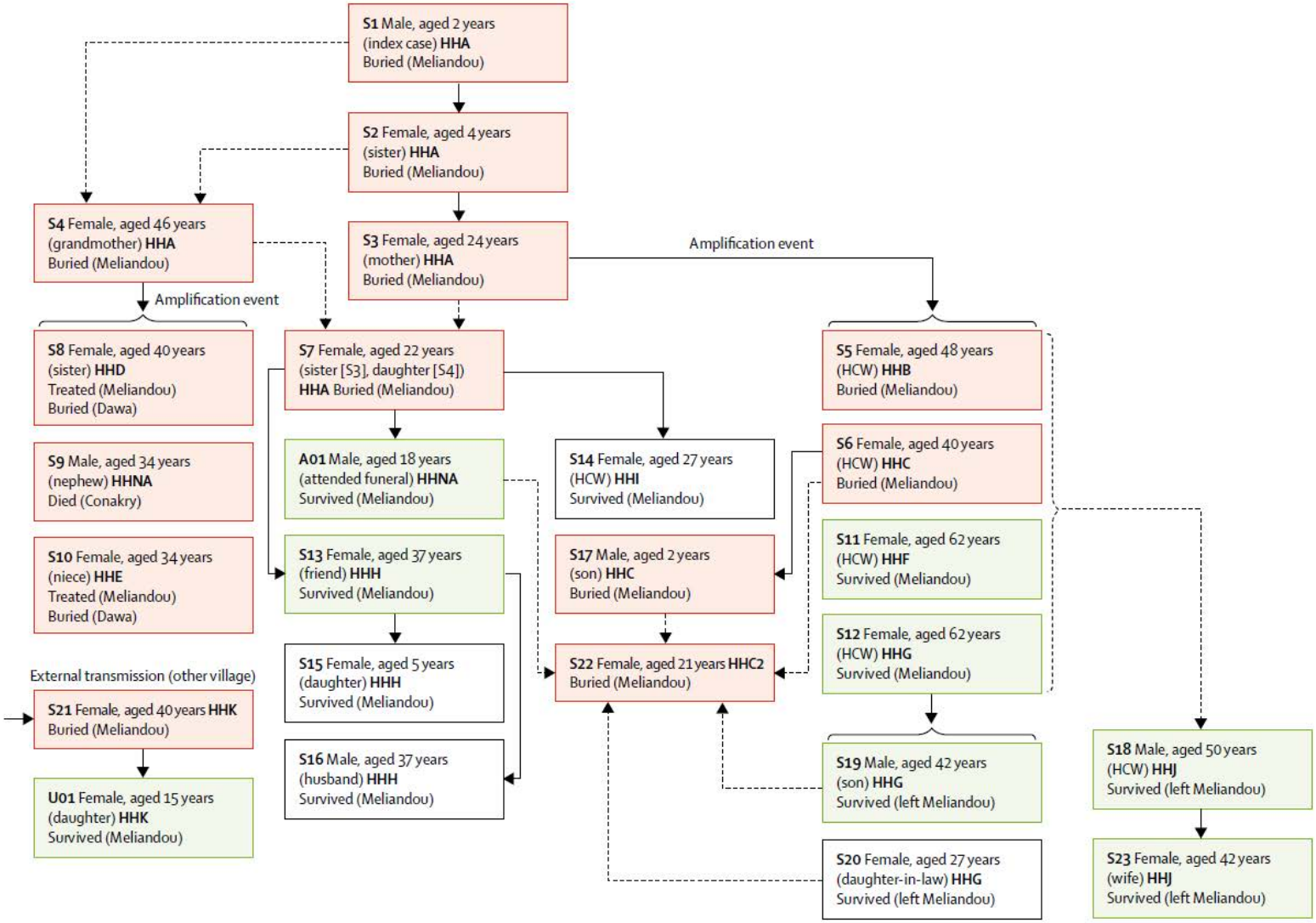
Mops condylurus

(Jakob Fahr)

(Fabian Leendertz)

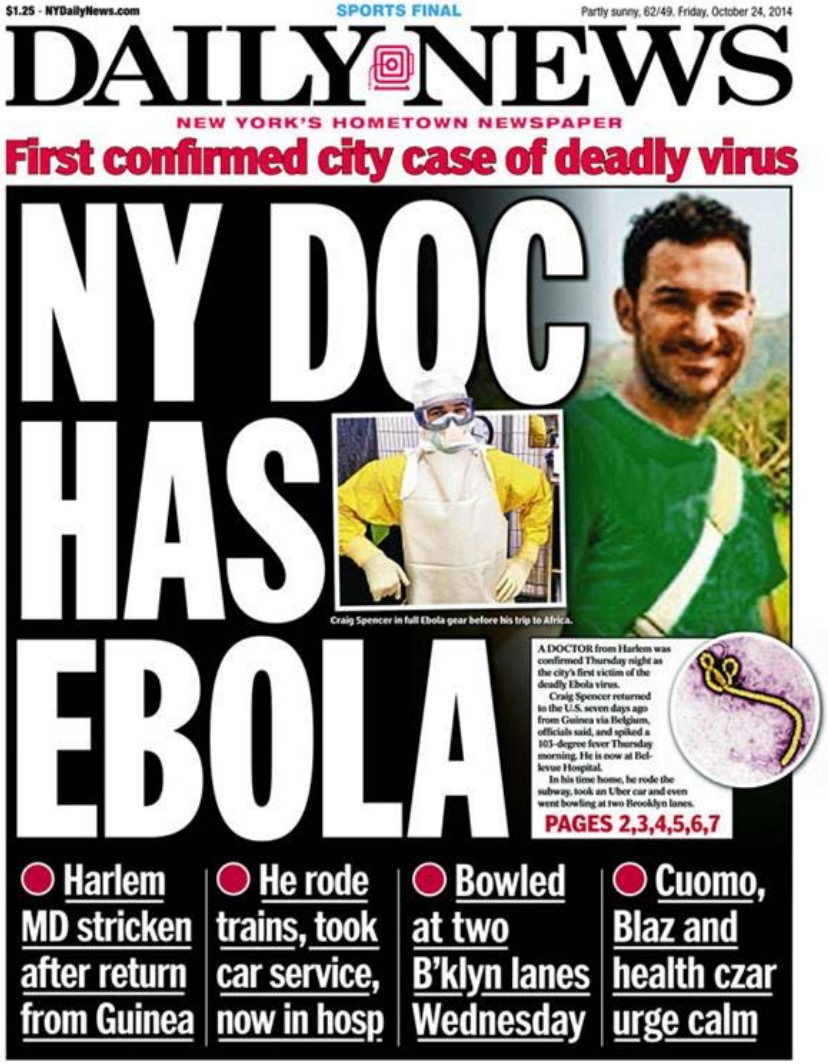
(Saez, EMBO Mol Med, 2014)

Chaînes de transmission Epidémie de Meliandou, Guinée, décembre 2013 – mars 2014



(Timothy, Lancet Infect Dis, 2019)

Autres pays touchés


$1.25 - NYDailyNews.com SPORTS FINAL Partly sunny, 62/49. Friday, October 24, 2014

DAILY NEWS

NEW YORK'S HOMETOWN NEWSPAPER

First confirmed city case of deadly virus

NY DOC HAS EBOLA

Craig Spencer in full Ebola gear before his trip to Africa.

A DOCTOR from Harlem was confirmed Thursday night as the city's first victim of the deadly Ebola virus.

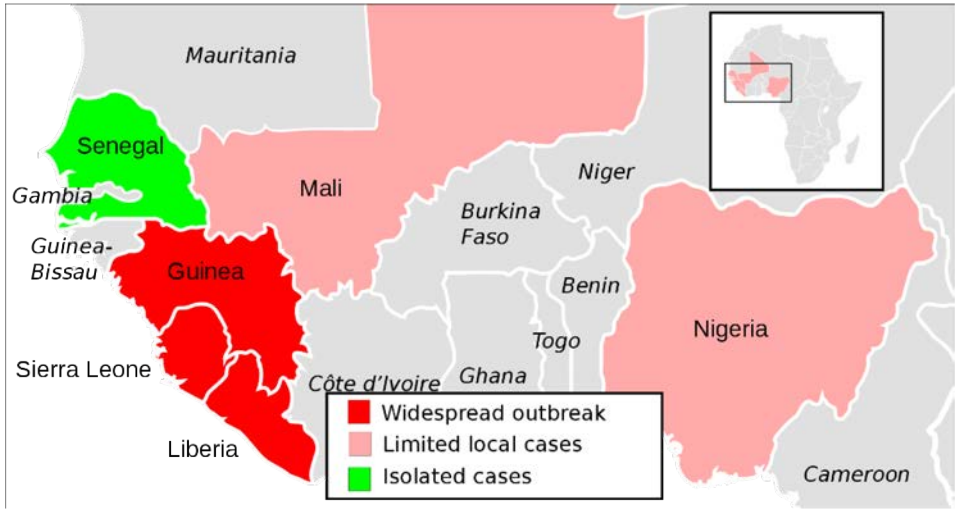
Craig Spencer returned to the U.S. seven days ago from Guinea via Belgium, officials said, and spiked a 103-degree fever Thursday morning. He is now at Bellevue Hospital.

In his time home, he rode the subway, took an Uber car and even went bowling at two Brooklyn lanes.

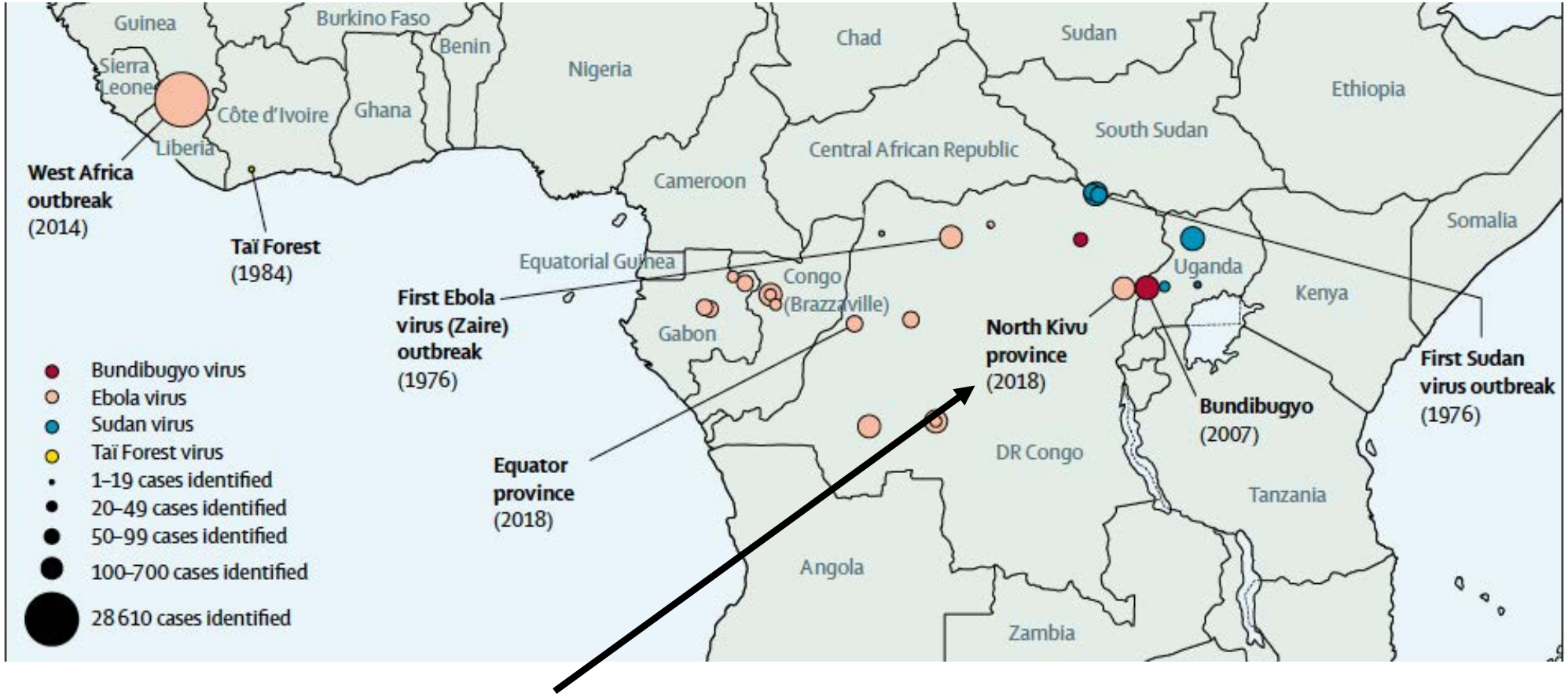
PAGES 2,3,4,5,6,7

- Harlem MD stricken after return from Guinea
- He rode trains, took car service, now in hosp
- Bowled at two B'klyn lanes Wednesday
- Cuomo, Blaz and health czar urge calm

(John Spink/SPINK@AJC.COM)



Epidémies d'Ebola, 1976-2018



Depuis juillet 2018: 936 cas et 591 décès au 15 mars 2019

(Malvy et coll., Lancet, 2019)

Conflits armés et contrôle de l’épidémie

(Laurie Bonnaud/MSF)

(*Al-hadji Kudra Maliro/AP)*

(© 2018 Private)

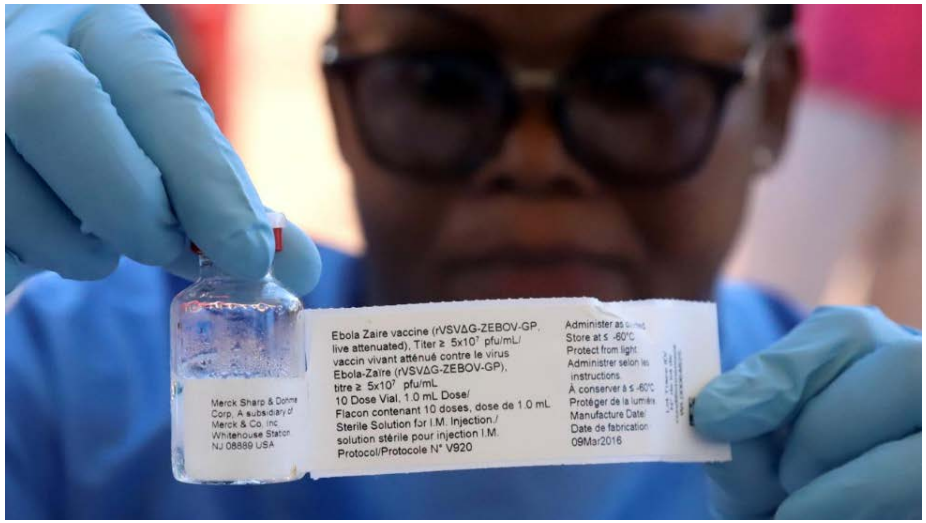
Vaccination des contacts (anneau)

Début mars 2019:
•585 anneaux
•21511 contacts
•63615 contacts de contacts

dont:
•26601 agents de santé
•21135 enfants de 1 à 17 ans

Et depuis peu:
•Femmes enceintes

(Olivia Acland/Reuters)



(Kenny Katombe / Reuters)

Traitements en cours d'évaluation
Essai randomisé à 4 bras

- 112 patients par bras
- Mortalité à J28
- Administration par voie intraveineuse:
  - Mab 114: anticorps monoclonal isolé à partir d'un survivant de l'épidémie de Kikwit (1995); une perfusion intraveineuse de 30 minutes
  - Regeneron: cocktail de trois anticorps monoclonaux
  - Zmapp: cocktail de trois anticorps monoclonaux
  - Remdesivir: antiviral, analogue nucléotidique,

Traitement symptomatique

(John Wessels/Getty Images)

Contrôle de l'épidémie: choix versus coercion

UN Geneva, Violaine Martin / Flickr cc

"We have a striking contradiction:
On the one hand a rapid and large outbreak response
with new medical tools such as vaccines and treatments
that show promising outcomes when people come early
— and on the other hand, people with Ebola are dying in their communities,
and do not trust the Ebola response enough to come forward."

(Joanne Liu, MD, Présidente de MSF International, 6 mars 2019)

Epidémies d'Ebola en Afrique, Changement de paradigme

(Munster, NEJM, 2018)