Le plus important concernant les voyages

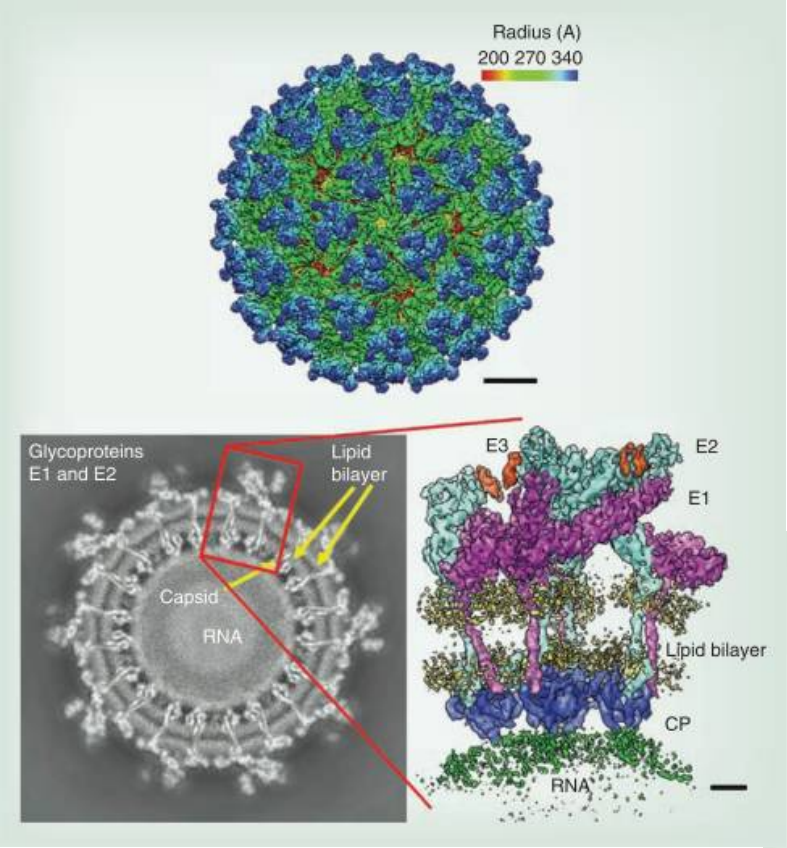
Liens d'intérêt : voyages /congrès offerts par l'industrie

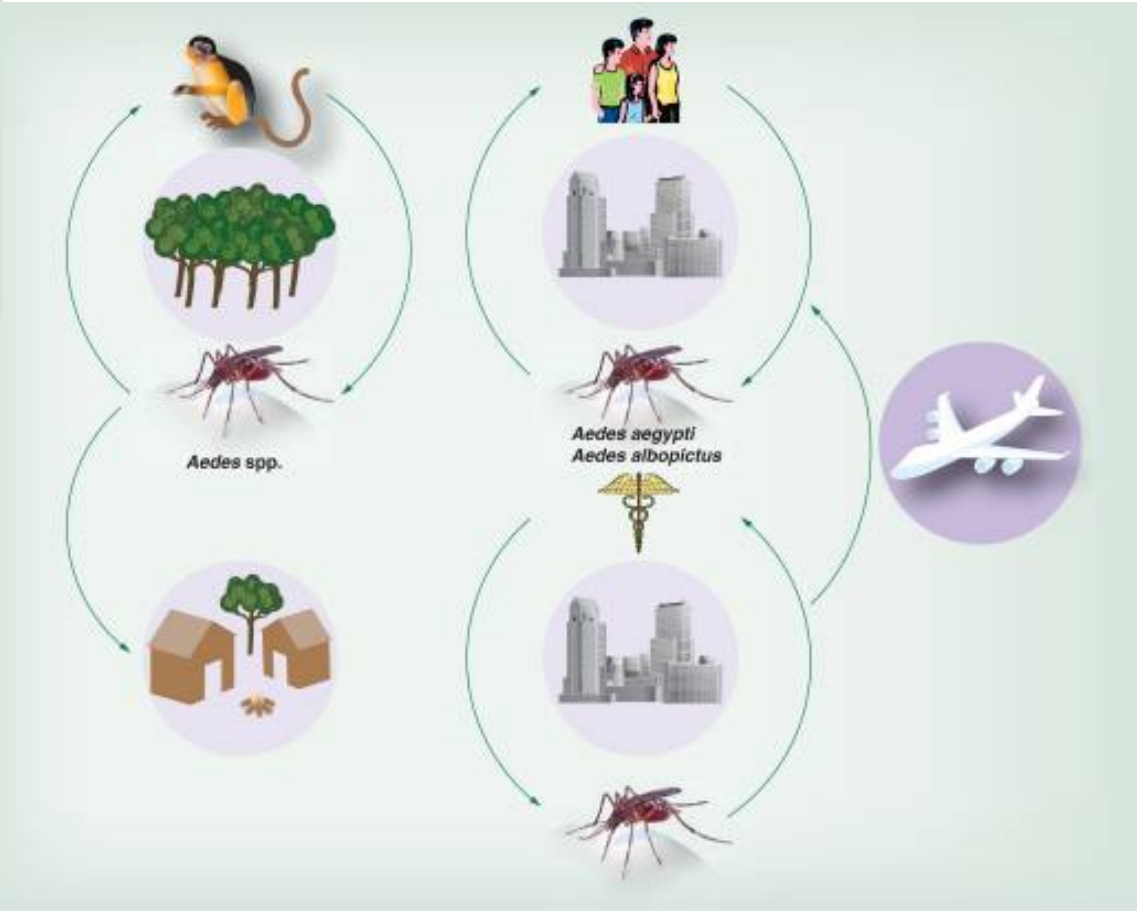
Le voyageur : une vraie sentinelle épidémiologique

Parashar D. , Cherian S .

Antiviral perspectives for chikungunya virus

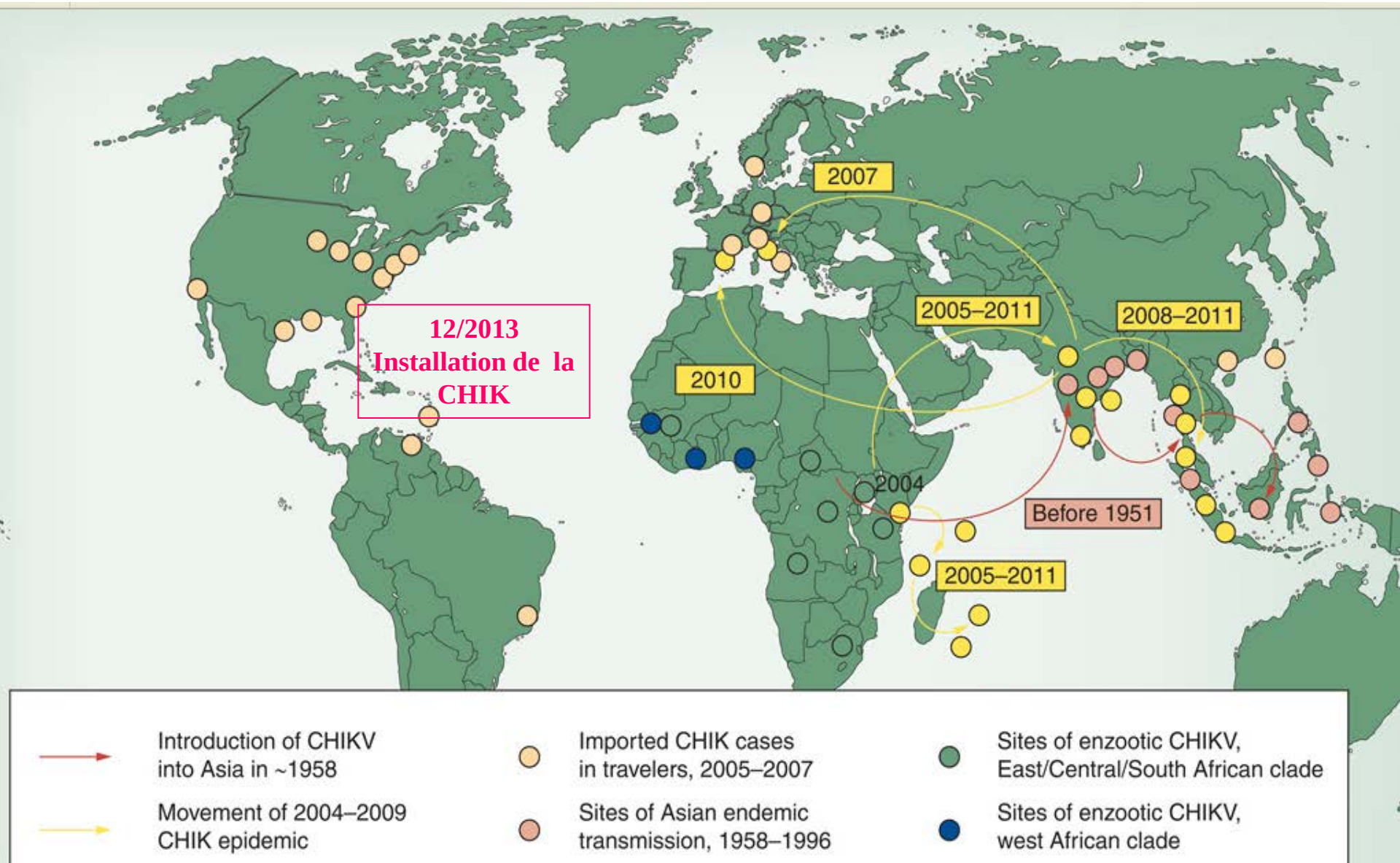
Biomed. Res. Int. 2014;:631642.





Introduit en France en 2004

Le CHIK


2007
2005–2011
2008–2011
2010
2004
Before 1951
2005–2011
12/2013
Installation de la
CHIK
Introduction of CHIKV into Asia in ~1958
Movement of 2004–2009 CHIK epidemic
Imported CHIK cases in travelers, 2005–2007
Sites of Asian endemic transmission, 1958–1996
Sites of enzootic CHIKV, East/Central/South African clade
Sites of enzootic CHIKV, west African clade

Parashar . Antiviral perspectives for chikungunya virus Biomed. Res. Int 2014;2014:631642.

Table 1: Major tested anti-CHIKV chemical compounds.

Products	Assay type	Hypothesized target	Pros	Cons	References
Chloroquine	*In vitro* (vero cells)	Disrupted endosome-mediated CHIKV internalization, possibly through the prevention of endosomal acidification.	*In vitro* study proved that it blocks the production of proinflammatory cytokines and the proliferation of monocytes, macrophages, and lymphocytes.	*In vivo* study required.	Delogu and de Lamballerie, 2011 [50] Khan et al., 2010 [41]
Ribavirin	Human	Can interact with the intracellular viral RNA production.	Faster resolution of joint and soft tissue manifestations.	Involvement of a small number of patients and lack of planning as randomly distributed patients were not compared with a placebo group.	Ravichandran and Manian, 2008 [44]

Parashar . Antiviral perspectives for chikungunya virus Biomed. Res. Int 2014;2014:631642.

6-Azauridine	*In vitro* (vero cells)	Inhibition of orotidine monophosphate decarboxylase, an enzyme involved in the de novo biosynthesis of pyrimidine, cytidine, and thymidine.	Showed a significant inhibition of CHIKV at a low concentration.	The antiviral activity has been difficult to replicate *in vivo*.	Briolant et al., 2004 [46]
Arbidol **Antigrippal**	*In vitro* (vero and primary human fibroblast cells)	Inhibition of virus mediated fusion and blocking of the viral entry into the target cells through inhibition of glycoprotein conformational changes that are essential for the fusion process.	Well-tolerated with minimal side effects.	Not tested in *in vivo* system.	Delogu et al., 2011 [48]
Harringtonine	*In vitro* (BHK21 cells)	Affects CHIKV RNA production inside the infected cell as well as viral protein expression such as the nsP3 and the E2 proteins.	Minimal cytotoxicity.	Not tested in *in vivo* system.	Kaur et al., 2013 [49]

Post transcriptionnel

Sélection de MR

Analogues 3e et 3f prometteurs

Bioorg Med Chem. 2014 Sep 16

Parashar . Antiviral perspectives for chikungunya virus Biomed. Res. Int 2014;2014:631642.

Table 2: Some of the major cellular inhibitors against chikungunya virus.

Cellular factors	Assays	Target/effectors	Pros	Cons	References
Furin inhibitors	*In vitro* (myoblast cells).	Intracellular furin-mediated cleavage of viral envelope glycoproteins: the E2E3 or p62 precursor.	Able to induce a stronger inhibition of viral infection.	Not tested in *invivo* system.	Ozden et al., 2008 [54]
2′,5′-Oligoadenylate synthetase (OAS3)	Human epithelial HeLa cell lines.	Affects CHIKV replication through a RNase L-dependent pathway.	Ability of OAS3 to inhibit alphavirus growth may be important for the development of antiviral molecules against CHIKV.	Cannot rule out the possibility that OAS3-mediated inhibition of CHIKV was also due to a block early in virus life cycle, for example, viral entry and uncoating of virus particles.	Bréhin et al., 2009 [56]
Cellular IMPDH enzyme	*In vitro* (vero cells).	Depletion of intracellular guanosine pool.	CHIKV utilizes IMPDH activity for its growth and multiplication which is a potential and effective target to prevent its infection.	It would be useful to explore similar findings by targeting IMPDH in case of other alphaviruses which are more lethal than chikungunya like Sindbis virus, Semliki forest virus, and so forth.	Khan et al., 2011 [62]

Le vaccin contre le Chik se fait attendre !

- Vaccins tués, atténués , chimériques, ADN, peptidiques , recombinants (adénovirus)
  - Le vaccin VLP : mais plusieurs injections !
  - MVA - CHIKV (Gènes CHIK C,E3, E2 , 6 K et E1 ..)

Le Chik : Phase aiguë

- Antalgiques, salicylés , AINS, plantes
  - Même efficacité des anti- COX et AINS (associés aux protecteurs gastriques)
  - Tolérance : hépatique …
- Ribavirine + INF ou Peg INF
  - Etudes ?
- Nouvelles cibles / avenir

Prévention anti-vectorielle +++

Le Chik: Phase chronique

- PR ou Rhumatisme post chikungunya
  - Stéroïdes
  - Chloroquine
  - MTX

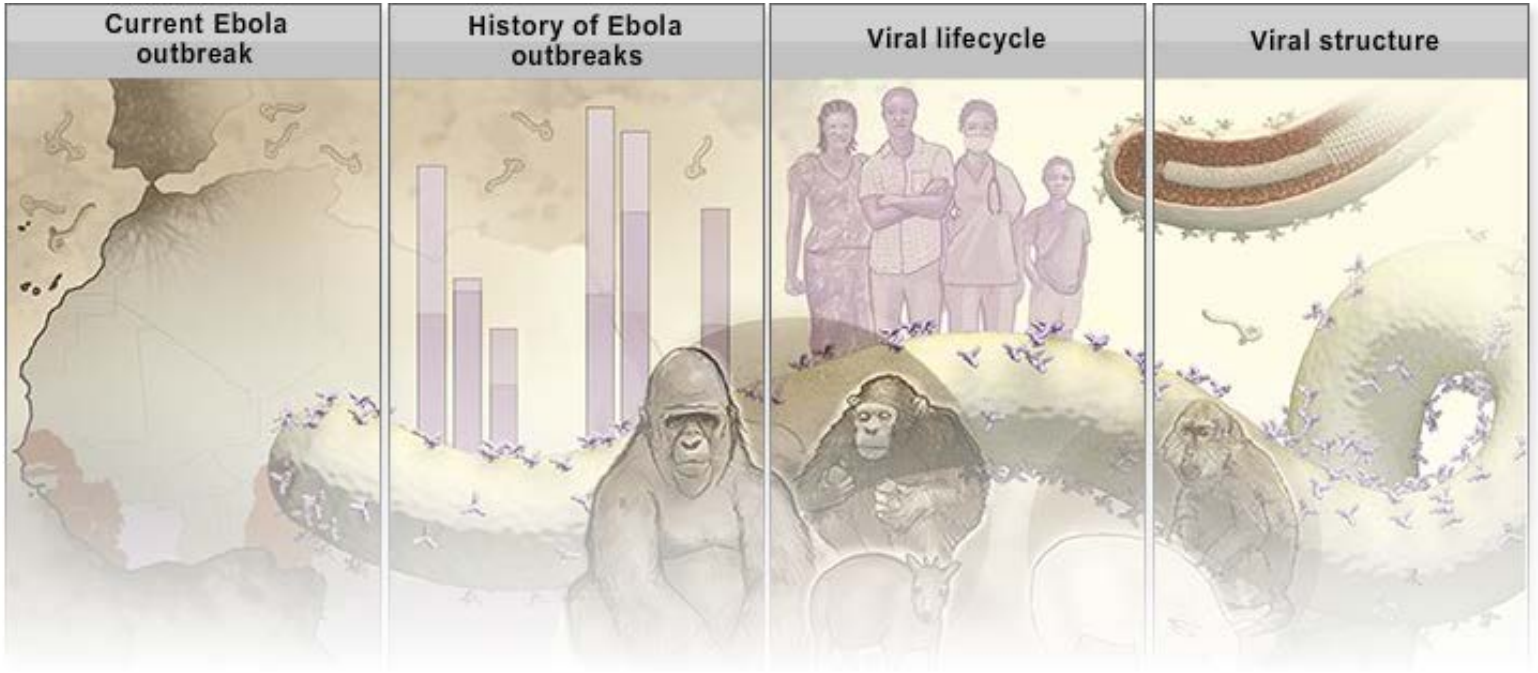
Prévention anti-vectorielle +++

Ebola … Ebola… Ebola…

Un déluge de publications , d'images …

Ebola Virus Disease — Current Knowledge

Rupa Kanapathipillai, N Engl J Med 2014; 371



Ebola virus disease is an RNA virus of the filovirus family. Five subspecies have been identified: *Zaire ebolavirus, Bundibugyo ebolavirus, Taï Forest ebolavirus, Sudan ebolavirus*, and *Reston ebolavirus*; all but the last cause disease in humans.[1]

Zaire ebolavirus, the cause of the current epidemic in West Africa,[2] has previously had a mortality rate of 90%, but the current mortality rate is estimated to be 70%.[3]

Ebola's animal reservoir is thought to be the fruit bat; transmission to humans is thought to occur after direct contact with infected tissues or bodily fluids.[4]

Human-to-human transmission also occurs through direct contact with infected bodily fluids. The incubation period is typically 11 days. Diagnosis is made with polymerase chain reaction, which usually becomes positive 1 day before symptom onset. Symptoms are nonspecific but typically include fever, weakness, and diarrhea.[5]

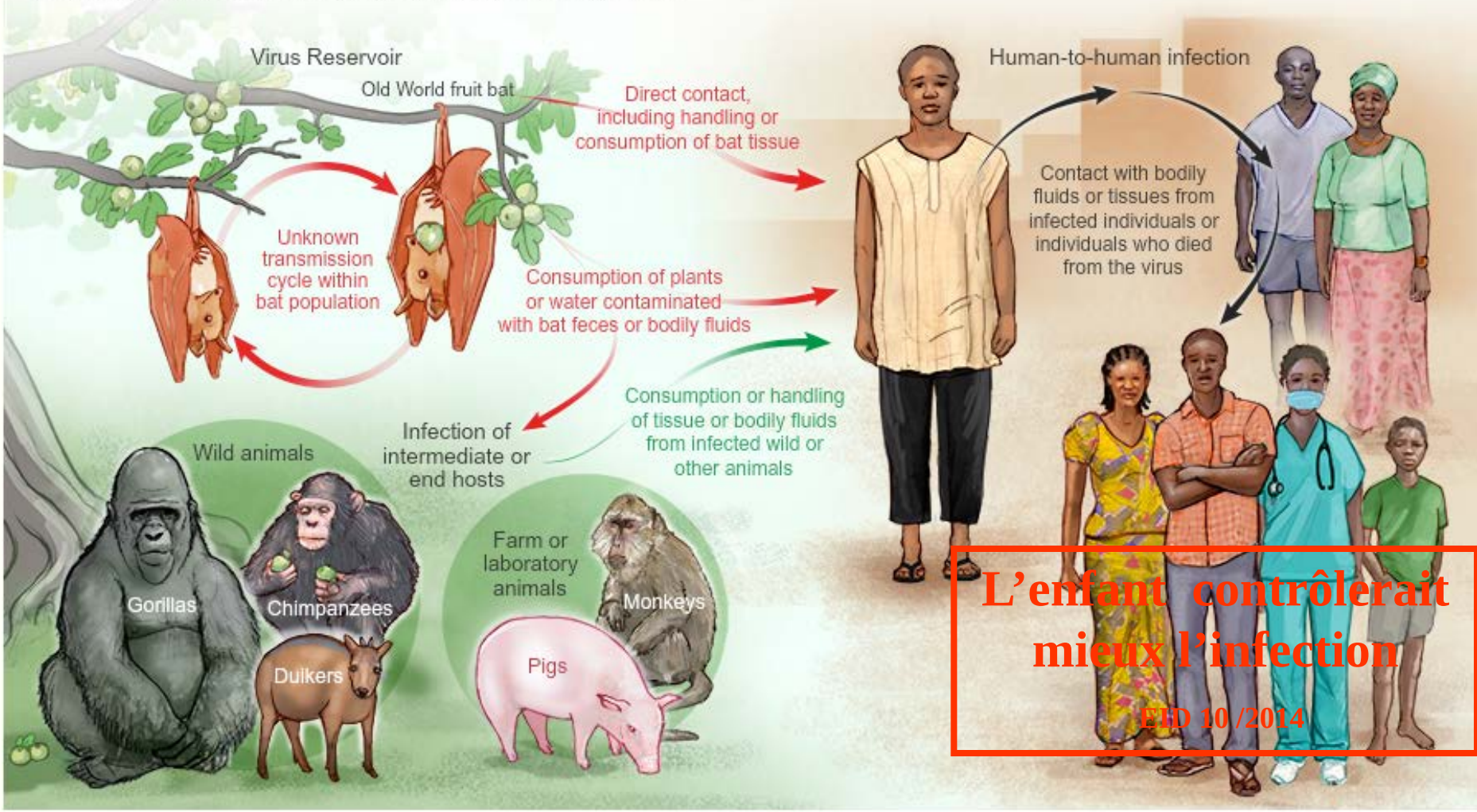
Transmission can be prevented by isolation and treatment of patients and by tracing and monitoring of contacts. Supportive care, including management of fluid and electrolytes levels, nutritional support, and treatment of bacterial superinfections, improves the likelihood of survival.[6]

Select a panel above

Ebola Virus Disease — Current Knowledge

Rupa Kanapathipillai, N Engl J Med 2014; 371

Ebola virus is thought to persist in reservoir species in areas where it is endemic. Humans, apes, and other mammalian species develop severe disease and are therefore considered end hosts rather than reservoir species.[11] Viral antibodies and RNA have been identified in three species of fruit bats from the Pteropodidae family (*Hypsignathus monstrosus, Epomops franqueti,* and *Myonycteris torquata*). Rodents are also potential reservoirs.[15] Reston ebolavirus has been identified in domestic pigs in the Phillipines.[18] Other species may serve as viral reservoirs. Once humans are infected, person-to-person transmission occurs after direct contact with infected bodily fluids or tissues.

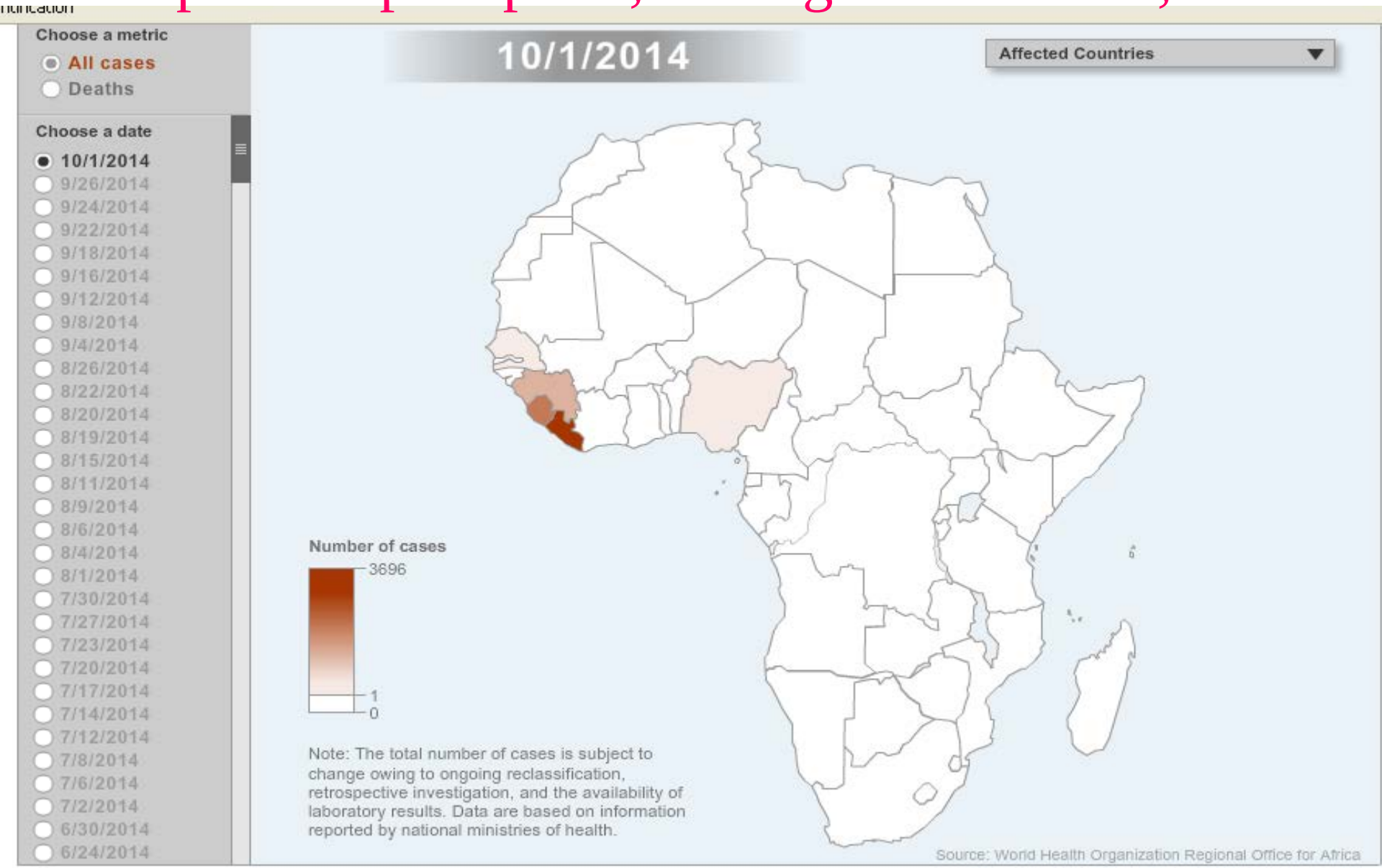


L'enfant contrôlerait mieux l'infection

EID 10 /2014

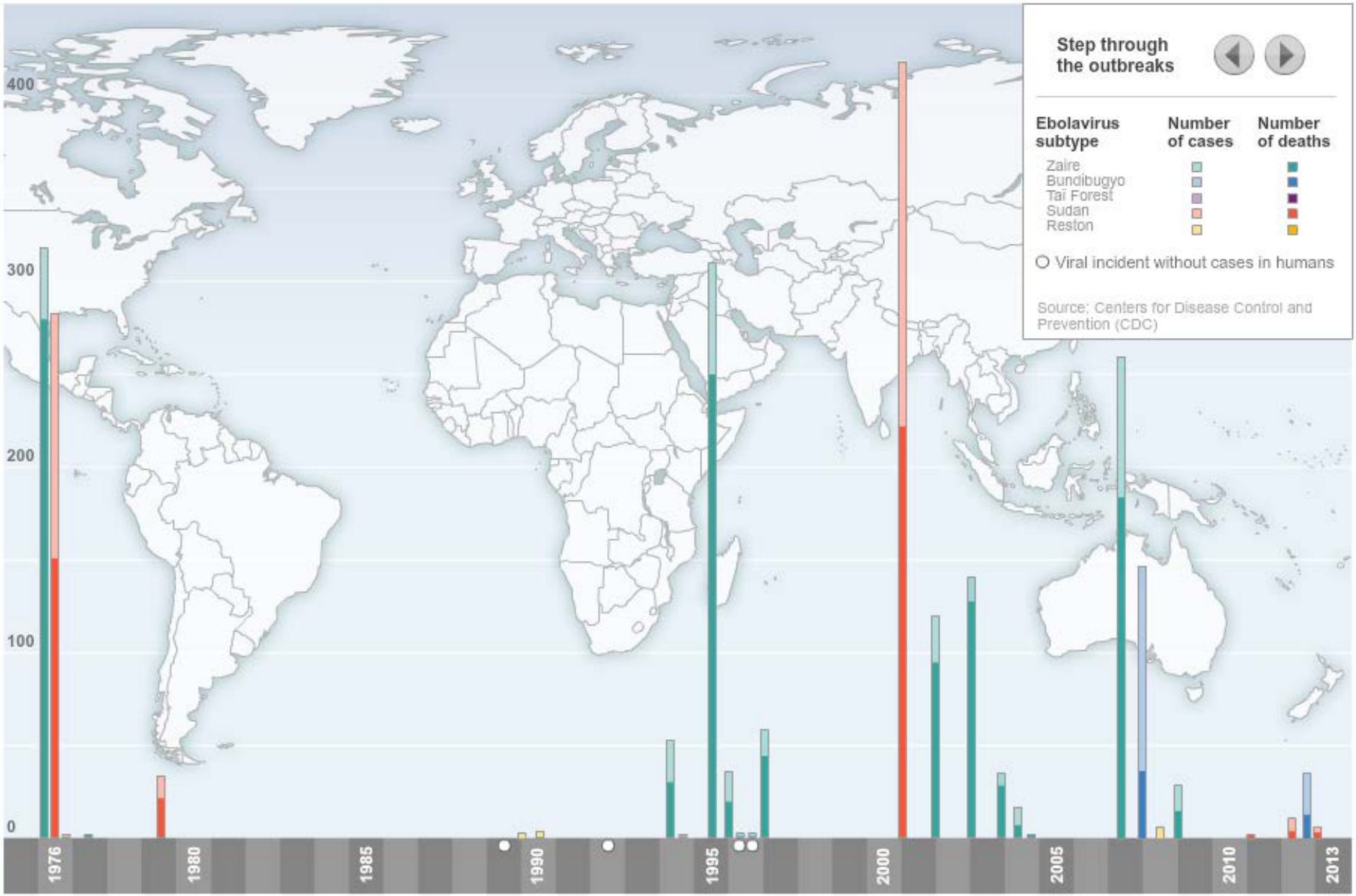
Ebola Virus Disease — Current Knowledge

Rupa Kanapathipillai, N Engl J Med 2014; 371



Ebola Virus Disease — Current Knowledge

Rupa Kanapathipillai, N Engl J Med 2014; 371



Ebola Virus Disease — Current Knowledge

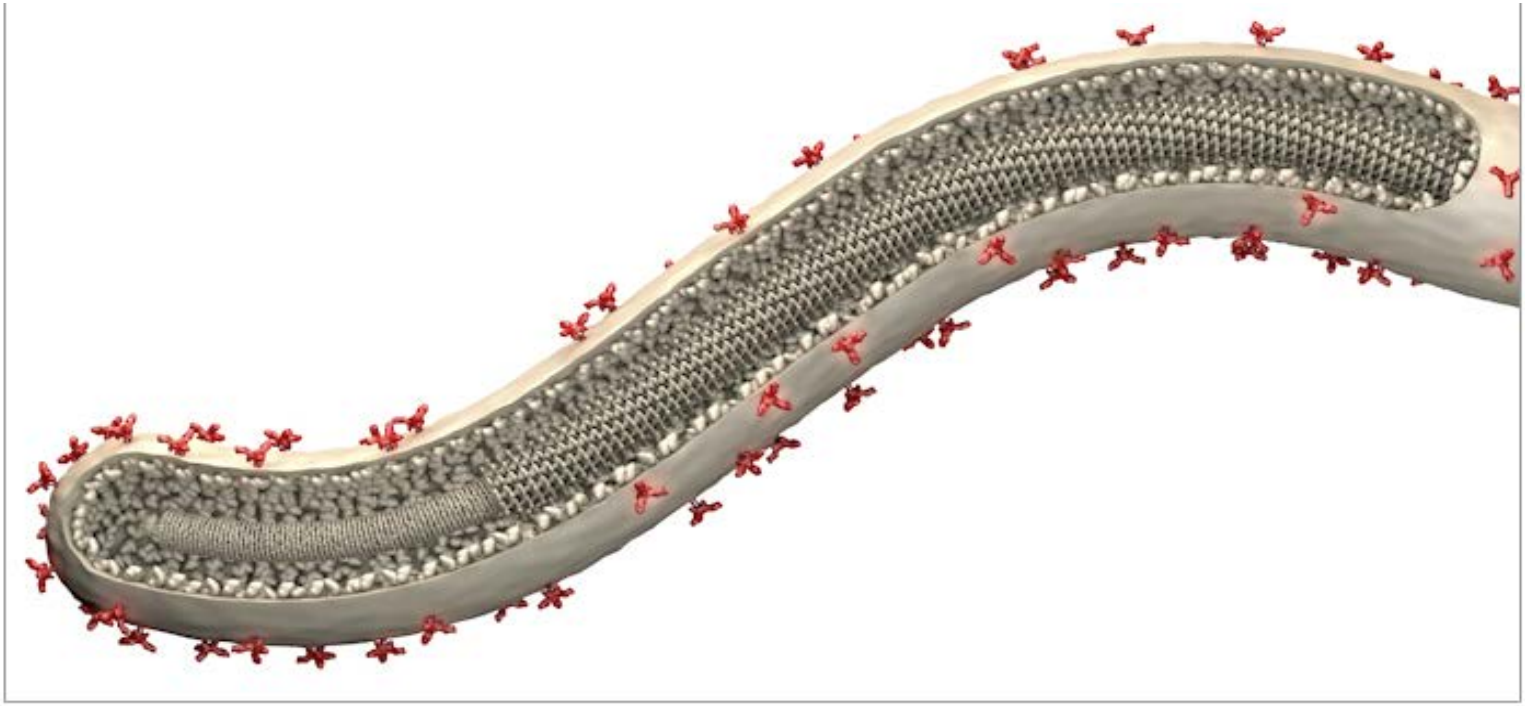
Rupa Kanapathipillai, N Engl J Med 2014; 371

Ebola structure

- ○ Whole virus
- ○ Cut virus

Internal structures

- ○ Viral membrane
- ◉ **Transmembrane glycoproteins**
- ○ Matrix (VP40 and VP24)
- ○ Nucleocapsid (VP30 and nucleoproteins)
- ○ Negative-sense RNA
- ○ Polymerase complex (VP35 and L proteins)

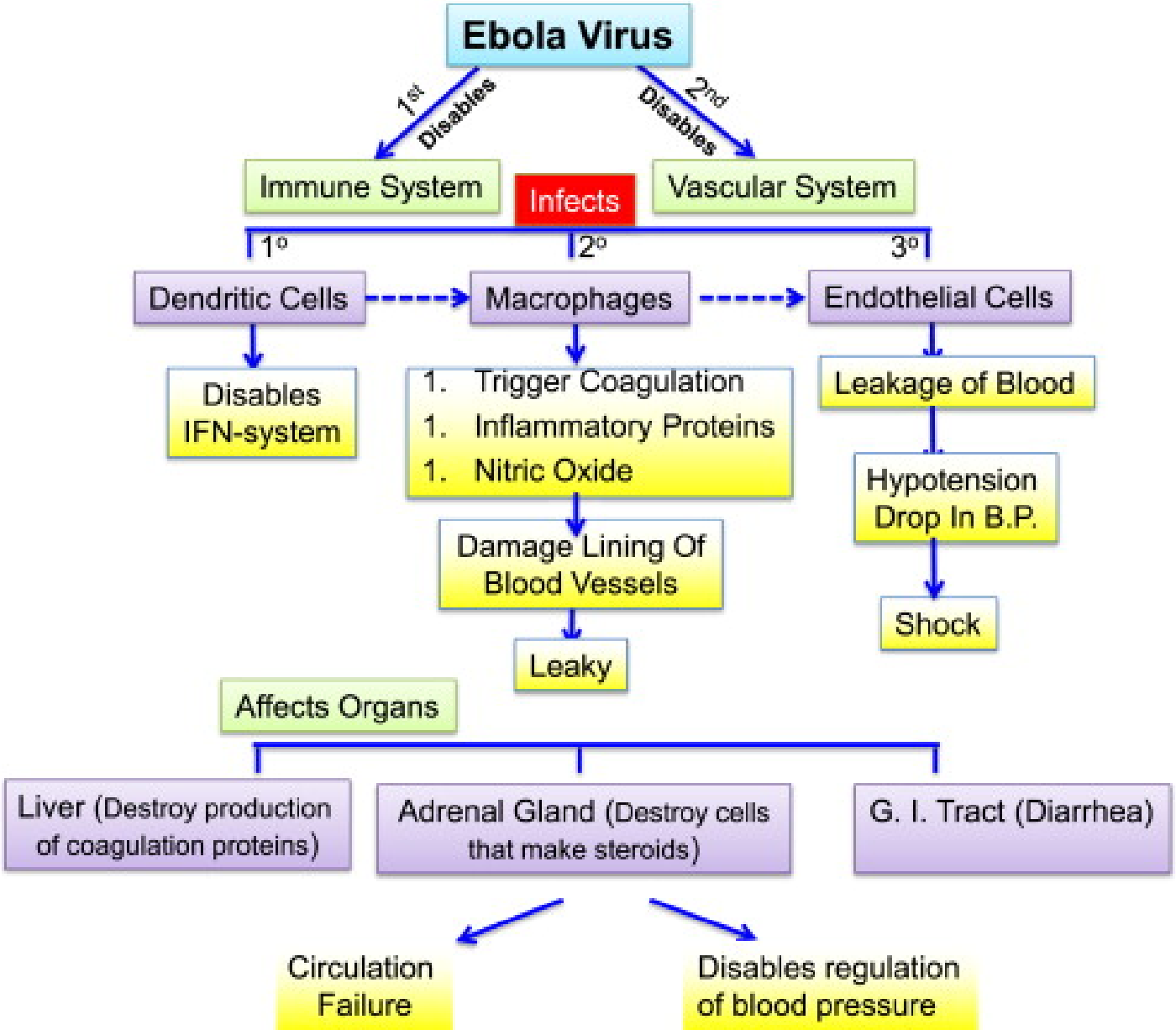


Ebola virus, like Marburg virus, belongs to the Filoviridae family.[19] Filoviruses have a filamentous structure and are negative-sense, enveloped RNA viruses; ebola virus particles typically have a diameter of 80 nm, with various lengths up to 14000 nm.[19] The virus genome is 19 kb in length and composed of seven genes. The glycoprotein is a transmembrane surface protein that is critical for viral attachment to host cells.[21] The ribonucleoprotein complex (RNA genome encapsulated by a nucleoprotein) facilitates replication, transcription, evasion from interferon, and particle formation.[20,22,23]

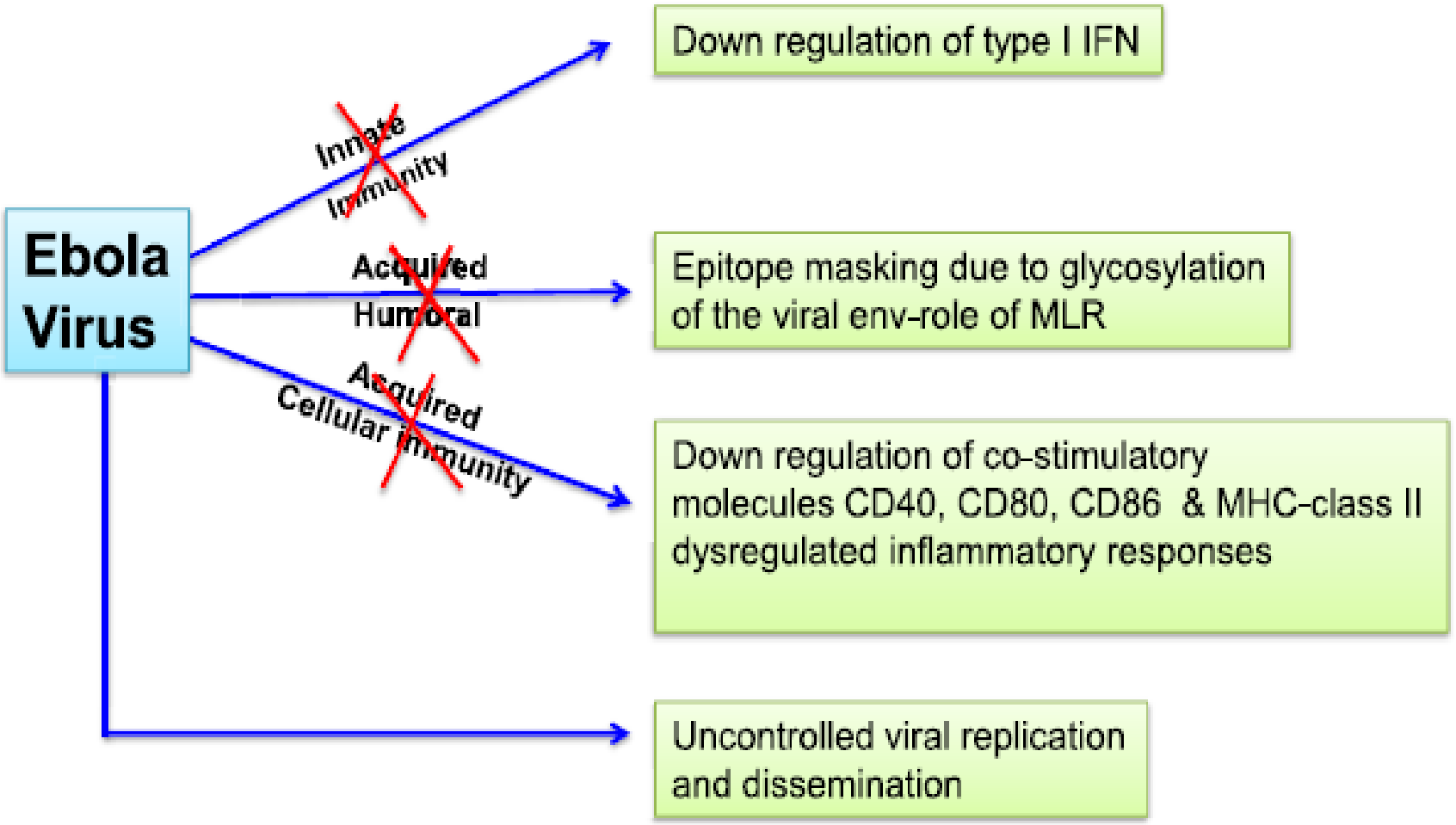
Clincal Features and Pathobiology of Ebolavirus infection

Ansari . Journal of Autoimmunity 2014; 30 ; 1-9

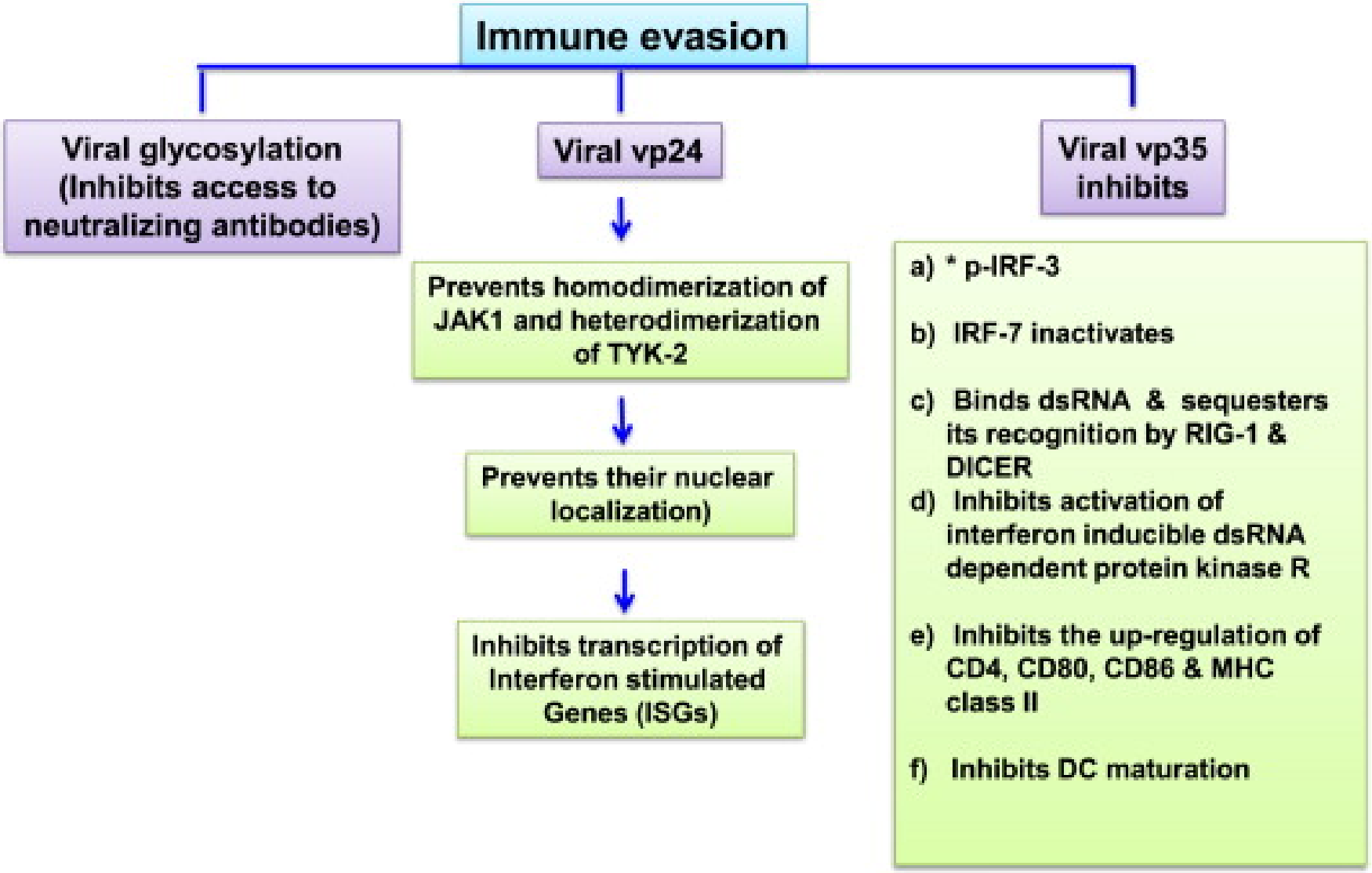
Infection rapidement sévère: Cascade pathologique



Le virus vainqueur !



Un système immunitaire dévasté

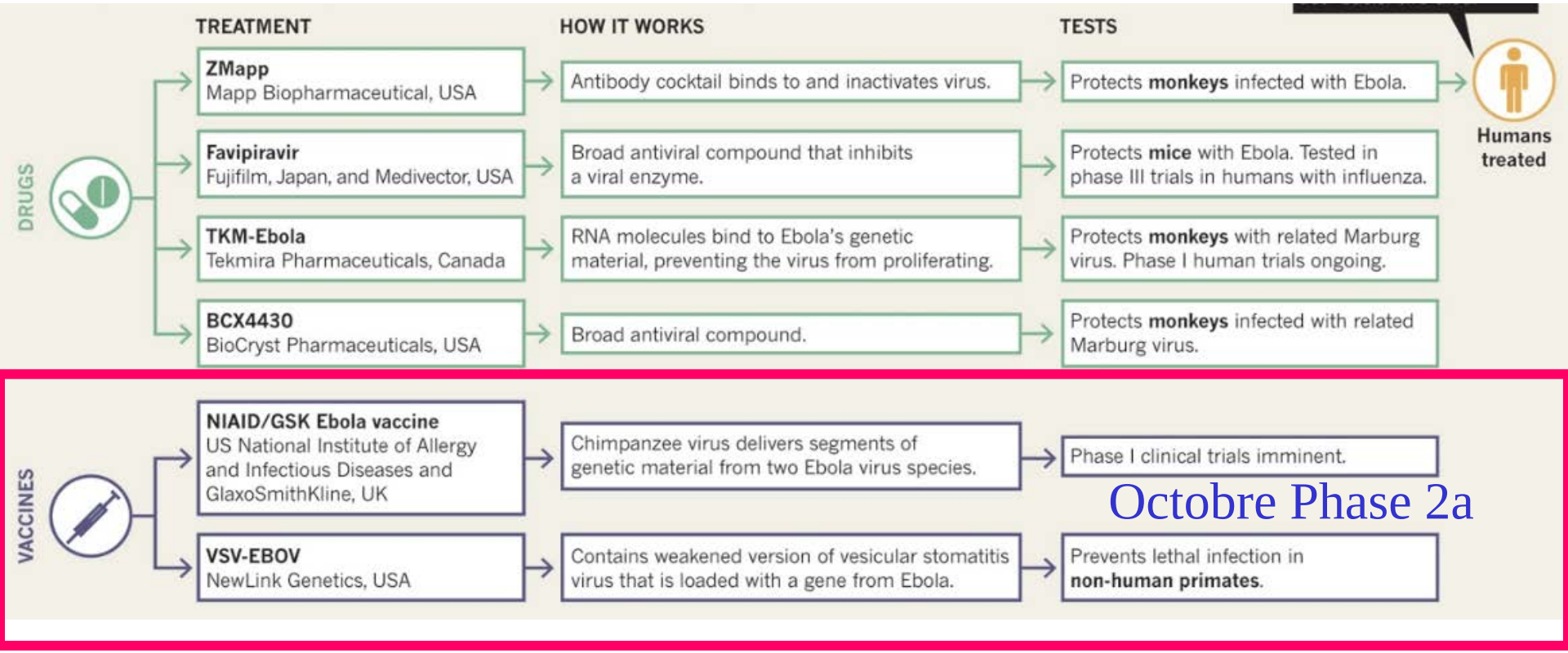


L’épidémie de la peur et du drame sanitaire

- Virus facilement - difficilement transmissible !!

- Peur d’être malade , de voir l’autre malade
- Peur de la stigmatisation

- Vite un vaccin préventif et thérapeutique



Octobre Phase 2a

02/09 /2014 Nature

The NEW ENGLAND JOURNAL of MEDICINE

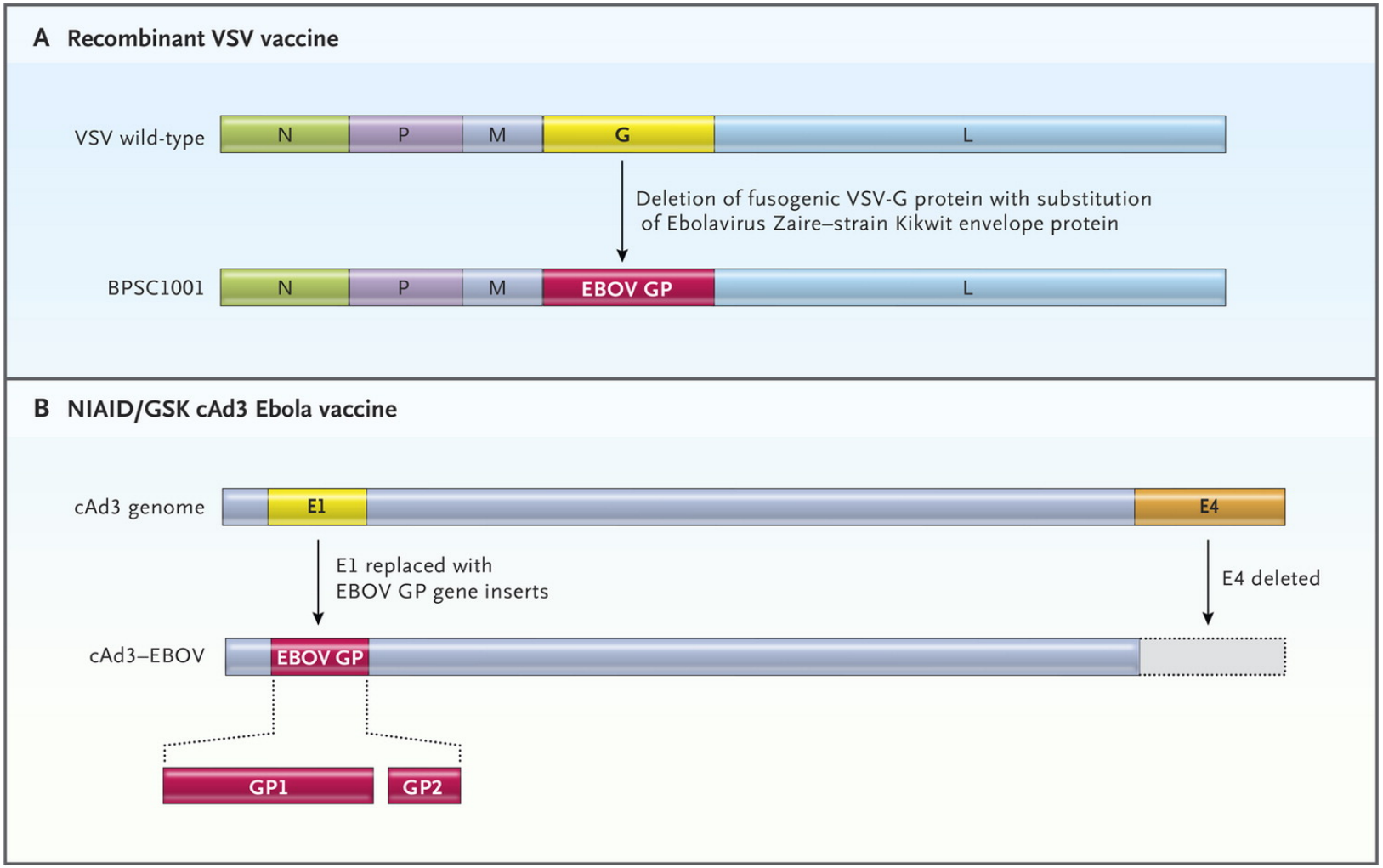
Perspective

Ebola Vaccine — An Urgent International Priority

Rupa Kanapathipillai, M.D., Ana Maria Henao Restrepo, M.D., Patricia Fast, M.D., Ph.D., David Wood, Ph.D., Christopher Dye, D.Phil., Marie-Paule Kieny, Ph.D., and Vasee Moorthy, B.M., B.Ch., Ph.D.

October 7, 2014 | DOI: 10.1056/NEJMp1412166

Structures of Ebola Vaccine Candidates rVSV (Panel A) and cAd3 (Panel B).



Kanapathipillai R et al. N Engl J Med 2014. DOI: 10.1056/NEJMp1412166

Les pèlerins de retour du Hajj
MERS - Cov ? Quel risque ?

Mass gathering medicine. 2014 Hajj and Umra prépararin as a leading

Jaffar . Intern. J. Infect. Dis . 2014; 27; 26-31

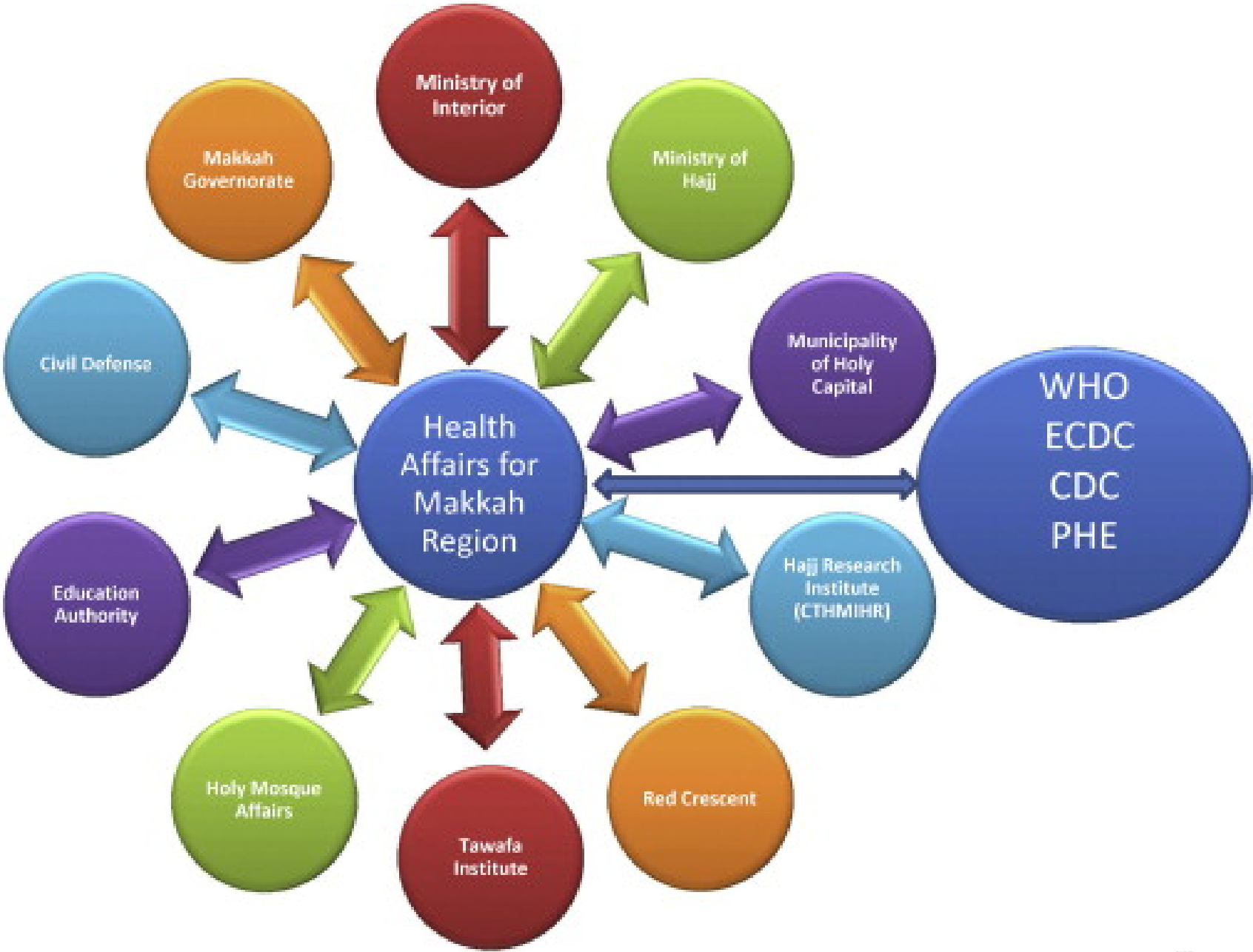
Hajj – Umra = Regroupement

- 10 millions pèlerins / an
- Venant de 184 pays

- Les infections importées / épidémies

- Organisation et vigilance constantes
- 24 comités et 7 hôpitaux
  - Comité de prévention médicale
  - …..

Early Coordination for Hajj Plan



Preventive Program Framework

At Higher Government Level

Supreme Hajj Committee
(seeks to coordinate the activities of various governmental ministries and agencies)

At Ministry of Health Level

Supervisory Committee for Preventive Medicine Program

At Makkah Region Level

Executive Committee for Preventive Medicine Program

Table 1
Diseases under surveillance at Hajj and the application of paper and/or mobile surveillance systems

	Disease	Mobile system	Paper-based system
1	Novel coronavirus	Yes	Yes
2	Meningococcal meningitis	Yes	Yes
3	Viral hemorrhagic fever (Ebola Virus Disease, Rift Valley fever, dengue fever, Crimean-Congo hemorrhagic fever and others)	Yes	Yes
4	Plague	Yes	Yes
5	Yellow fever	Yes	Yes
6	Cholera	Yes	Yes
7	Food-borne illness	Yes	Yes
8	Polio	Yes	Yes
9	Influenza-like illness	Yes	-

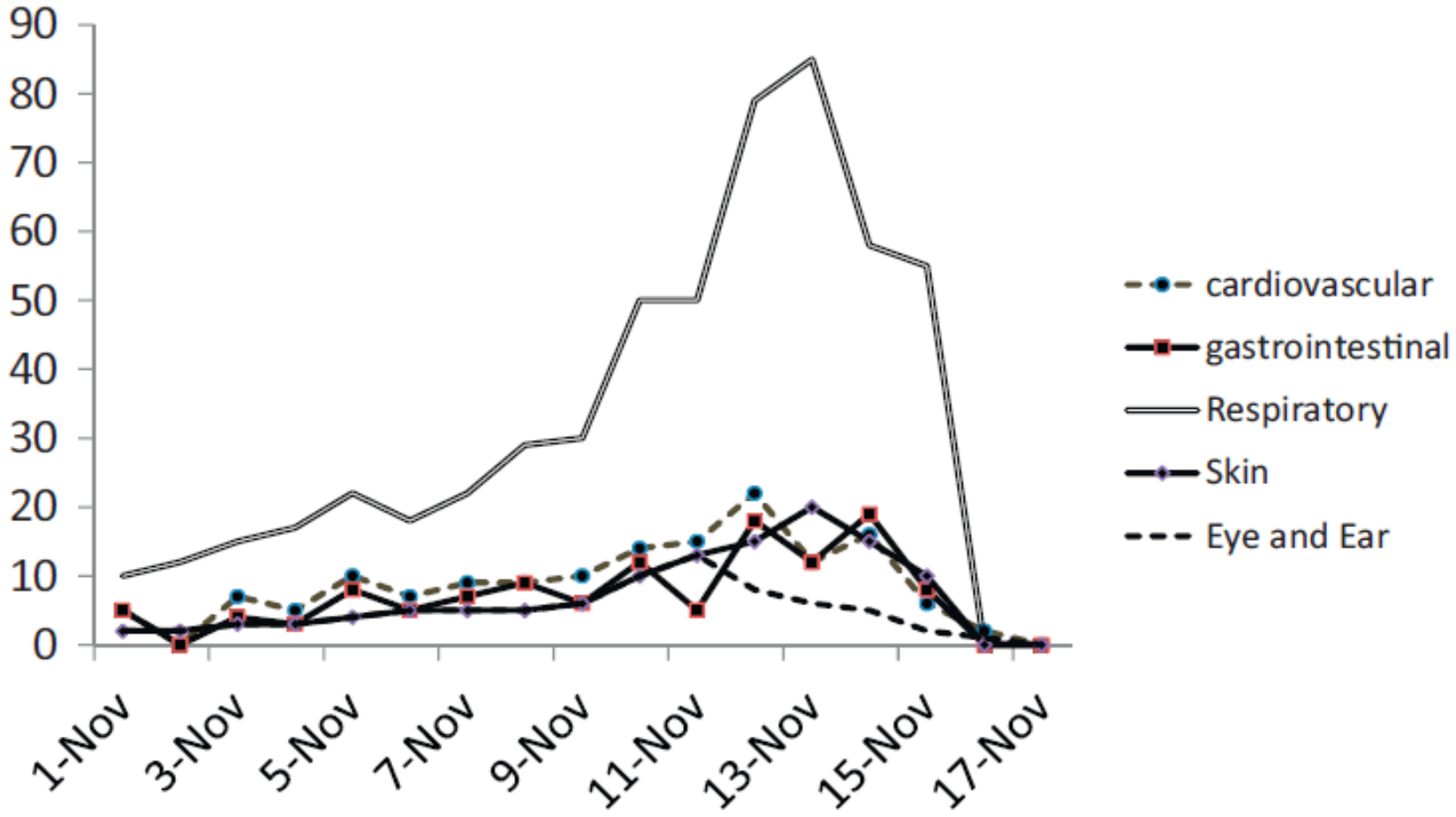


Figure 3. An example of data produced using digital pens to monitor the categories of diagnoses of patients visiting primary care clinics during the 2013 Hajj season.

case definition of MERS-CoV. The main objectives were the following: to monitor MERS-CoV closely during this mass gathering event, to detect any cases among pilgrims and local residents in a timely manner, and to collect information about the virus in the area in which the first case was located if this were to occur. Clinical samples were taken from all suspected cases during 2013 Hajj season and tested for all possible viral etiologies including MERS-CoV; all samples tested negative for MERS-CoV.[15]

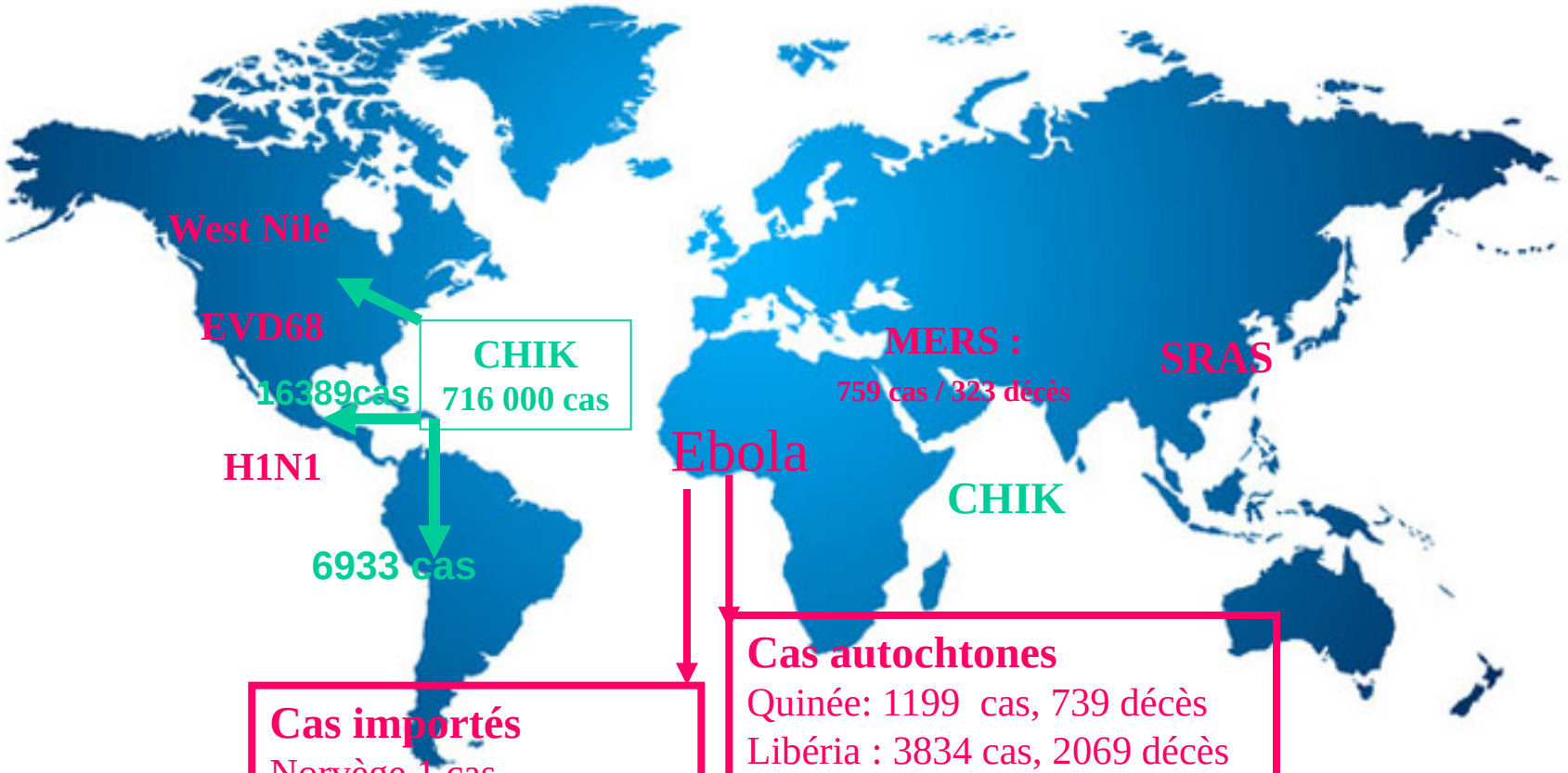
In addition, following the 2013 Hajj, a cohort of 129 French Hajj pilgrims were systematically sampled with nasal swabs prior to returning to France and were screened for MERS-CoV. The majority of them (90.7%) had respiratory symptoms and none tested positive for MERS-CoV.[16]

Respiratory illnesses are common among pilgrims. The most common viral respiratory tract infections are influenza and rhinovirus.[17] The estimated incidence of upper respiratory tract infections (URTIs) during the Hajj ranges from 20% to 80%, depending on the type of method used to confirm the diagnosis.[15]

Les pèlerins de retour

- Vigilance jusque fin octobre
  - Symptômes respiratoires + fièvre …

Cas importés et risque de cas secondaires

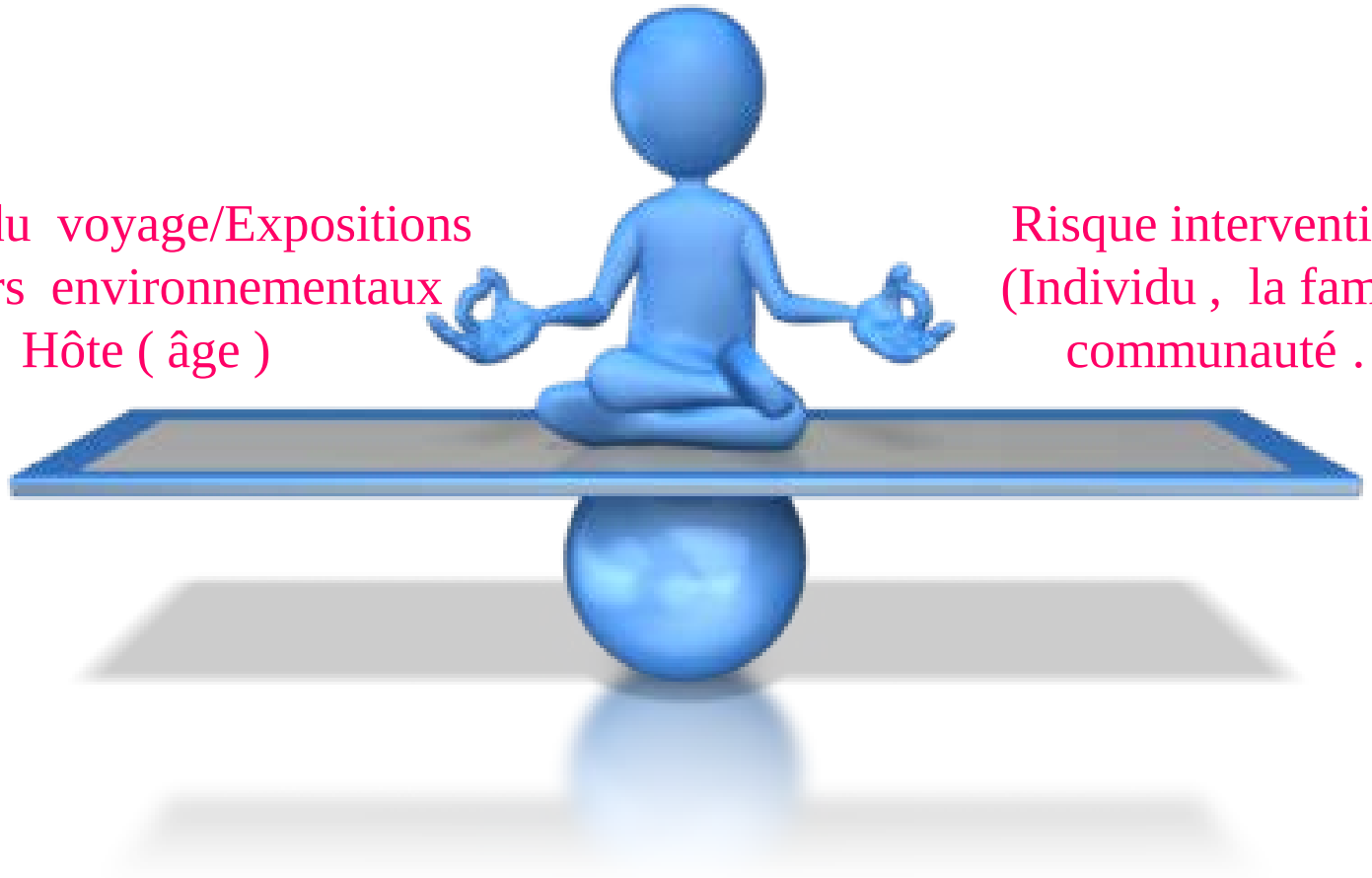


Cas importés
Norvège 1 cas
USA : 1 cas Nebrasca ,
1 Texas décédé
France 1 cas (IDE)
Allemagne : 1 cas

Cas autochtones
Quinée: 1199 cas, 739 décès
Libéria : 3834 cas, 2069 décès
S. Leone : 2437 cas 623 décès
Nigéria 20 cas 8 décès
Sénégal : 1 cas
Espagne : 1 cas (07/10)
USA : 1 cas (28/09)

Le personnel de santé

Risque du voyage/Expositions
Dangers environnementaux
Hôte (âge)



Risque interventionnel
(Individu , la famille la communauté ….)

Countermeasure	Description	Efficacy
Adenovirus-based vaccine	Recombinant, replication-incompetent adenovirus expressing the Ebola virus glycoprotein	- 100% protection in NHPs after a single vaccination 4 weeks prior to challenge - Progressed into clinical trials
Vesicular stomatitis virus-based vaccine	Recombinant, replication-competent vesicular stomatitis virus expressing the Ebola virus glycoprotein	- 100% protection in NHPs after a single vaccination 4 weeks prior to challenge - 50% to 100% protection in NHPs if given 20 minutes post-challenge - Used in one human after a potential laboratory exposure; no adverse effects other than fever
Antibody treatment	Three monoclonal antibodies against the Ebola virus glycoprotein, plus interferon alpha	- 75 to 100% protection in NHPs with treatment starting 5 days post-challenge (that is, after the onset of detectable viremia)
siRNA treatment	siRNAs targeting the Ebola virus polymerase L, the polymerase cofactor VP35 and the nucleocapsid-associated protein VP24	- 100% protection in NHPs with treatment starting 30 minutes post challenge

OMS : 8 thérapies

- TKM Ebola : inhibe la réplication : Tekmira /Canada
- Avi 75 37: survie 60 -80% des singes: Sarepta/Canada

- Favipiravir (T705) Toyamma Chemicals Medivector /Fujji Film /Japon : 300 mg /kg /j
  - - 4 log (IC90 à 110 µM) , clairance en 4 jours

- BCX4430, analogue synthétique de l'adénosine : puissante activité in vitro and et in vivo
- INF: rallonge la survie , ne baisse pas la mortalité

OMS : 8 thérapies

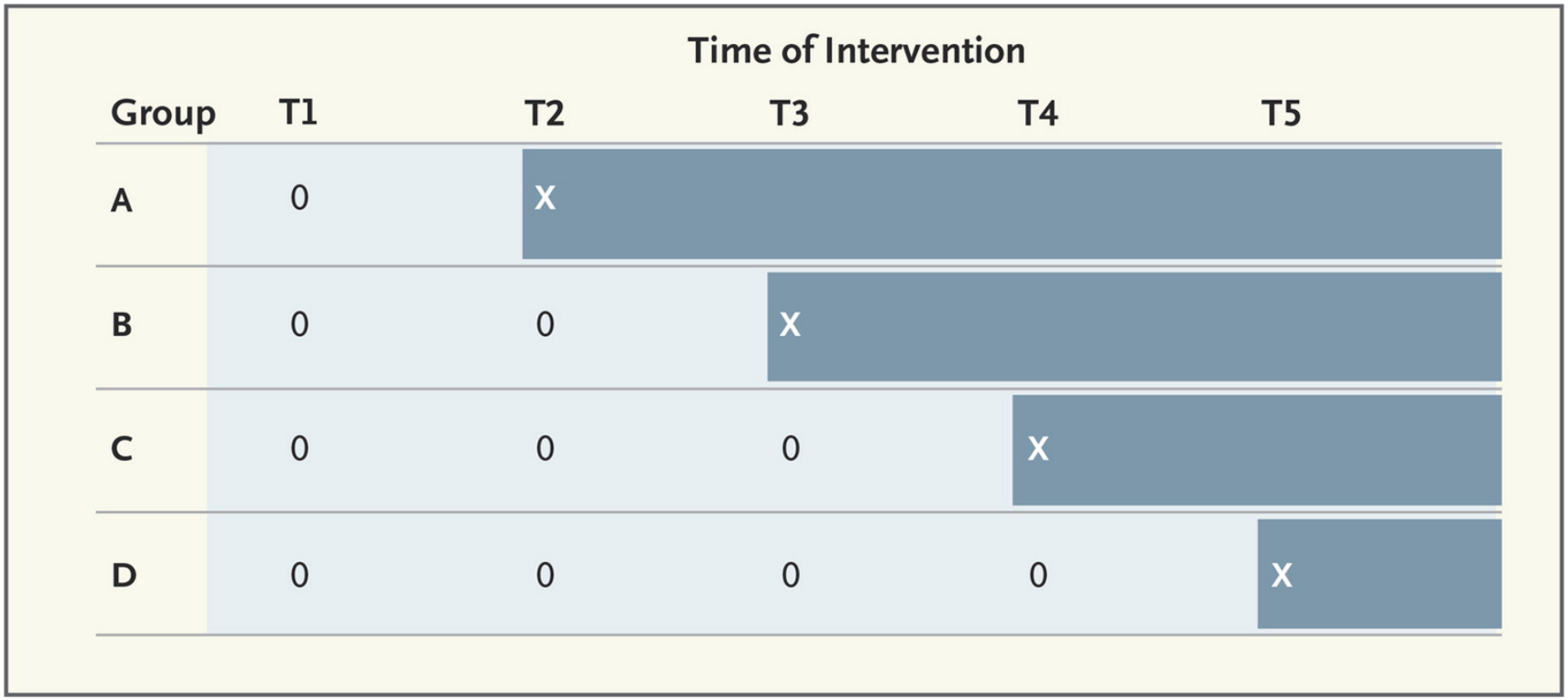
- Le plasma des survivants (Transfusions !!)
- Le « ZMapp Laboratoire Biocryst : (US) : BCX4530
  - Cocktail de 3 anticorps humanisés cible différentes parties de la particule virale / Singe ++ non homologué/ usage compassionnel
- Globulines hyper-immunes humaines et animales : Fab'Entech / France / Test sérum de cheval

OMS : 1er candidat vaccin

- Chimp -Adeno 3 (GSK , National Institute of Allergy and Infectious Diseases -NIAID)
  - Résultats encourageants chez l'animal, y compris chez des primates / 16/ 16 animaux protégés
  - Indication de l'OMS :
    - sujets à haut risque de contamination,
  - Eude de phase I. août, GSK : mise en place accélérée Bonne tolérance
    - 15.000 doses prévues disponibles fin 2014.

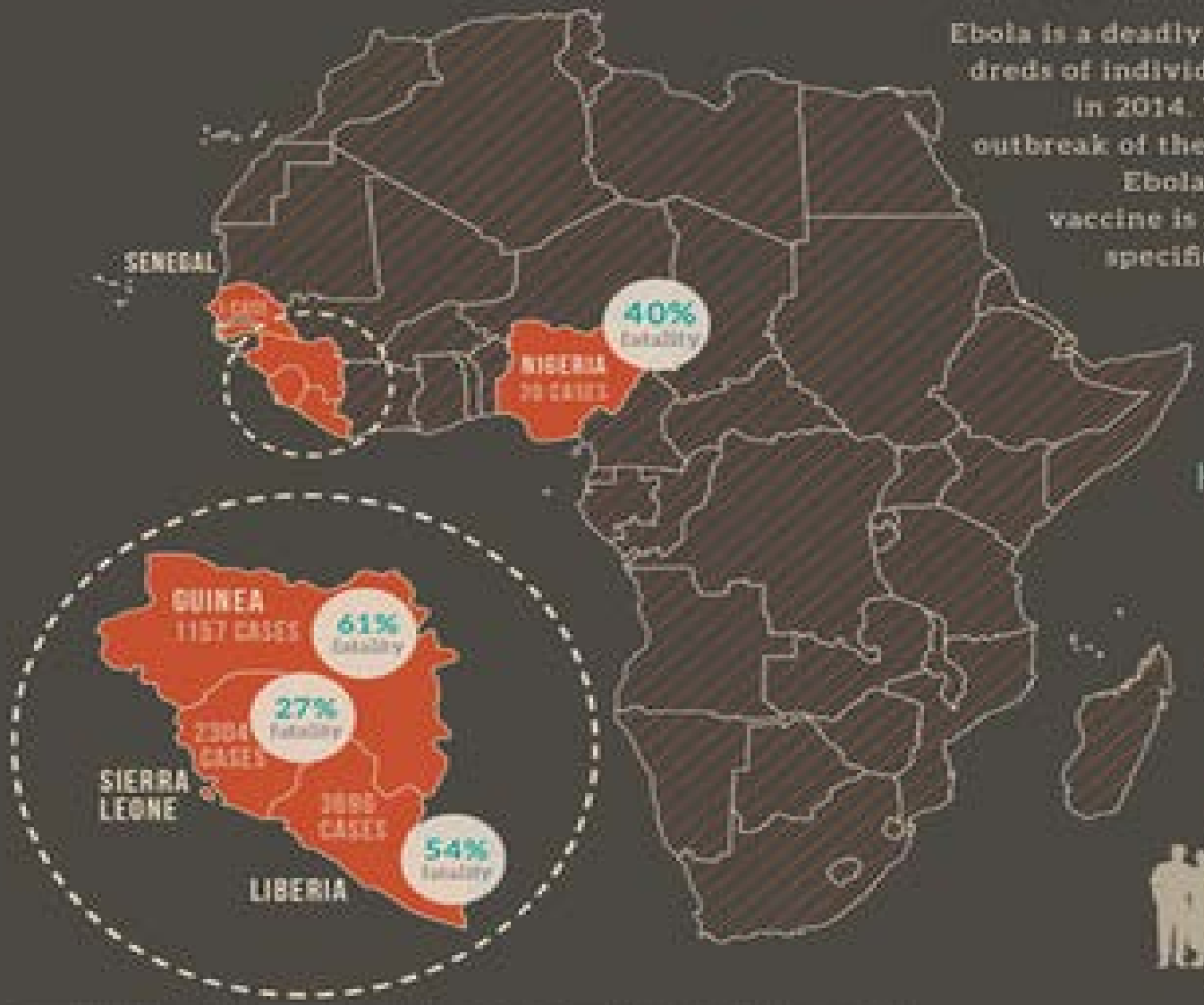
OMS : 2ème candidat vaccin

- rVSV (New Link Genetics) :
  - Le vaccin a été testé avec 100% de succès chez 20 primates et 80 adultes
  - Un essai de phase I dont le lancement a été autorisé jeudi par la FDA.
  - 800 doses ont été données à l'OMS.
  - *Actif en post exposition*
  - *Durée de protection …*



Kanapathipillai R et al. N Engl J Med 2014. DOI: 10.1056/NEJMp1412166

2014 EBOLA OUTBREAK



Ebola is a deadly virus that has killed hundreds of individuals in West Africa so far in 2014. This is the worst recorded outbreak of the virus. The fatality rate of Ebola can be as high as 90%. No vaccine is available, nor is there any specific treatment. Originating in Guinea, Sierra Leone and Liberia, cases have now been confirmed in Nigeria and Senegal.

HOW DOES EBOLA SPREAD?

Bats may be the natural host for ebola viruses.

Transmission to wild animals such as monkeys and gorillas occurs

Human to Human transmission can occur by direct contact with body fluids of infected individuals

Sources: World Health Organization (w.h.o.int), Centers for Disease Control and Prevention (cdc.gov)