



Un an d'épidémie de maladie à virus Ebola en Afrique de l'Ouest

Point d'étape au 27 Mars 2015

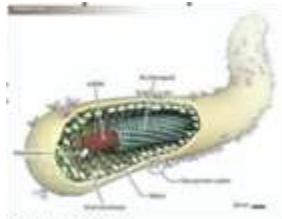
Denis MALVY

*Service des Maladies Infectieuses et Tropicales,
CHU de Bordeaux & INSERM 897, Université de Bordeaux*

Pas de conflits d'intérêt



CEMI 20 - Colloque sur le Contrôle Epidémiologique des Maladies Infectieuses
27 mars 2015 - Institut Pasteur Paris



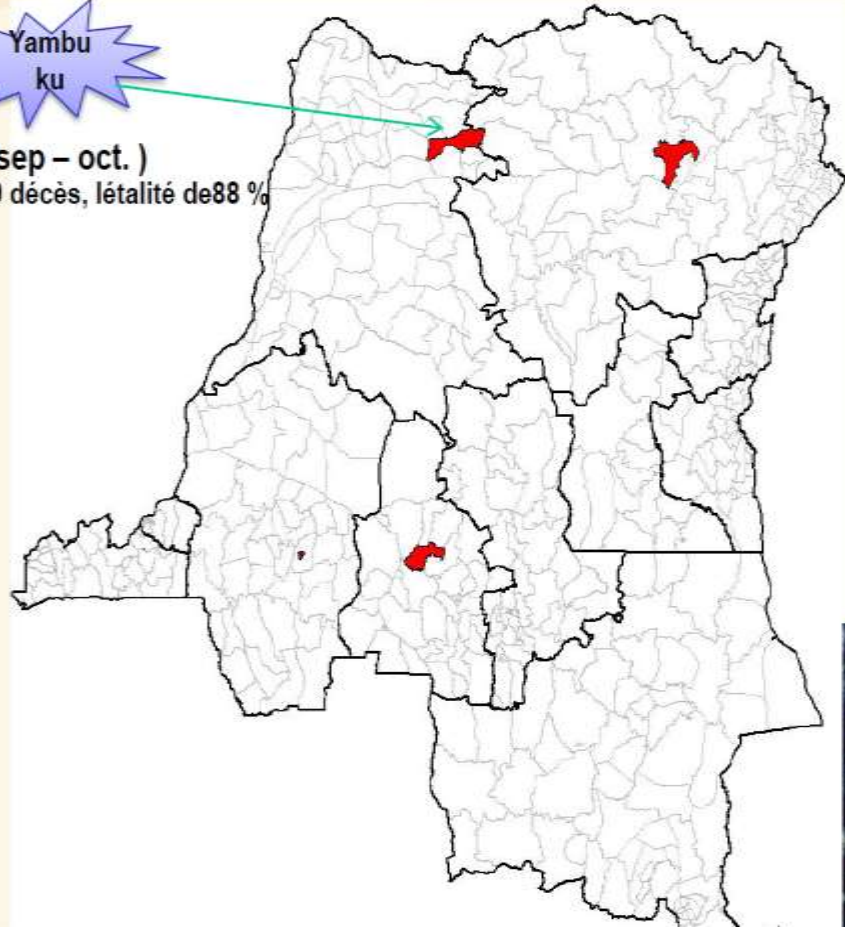
Feldmann, NEJM, 2014

"The feeling was overpowering. Ebola is like a sickness from a different planet. It comes with so much pain." - SALOME KARWAH, EBOLA SURVIVOR



Yambu
ku

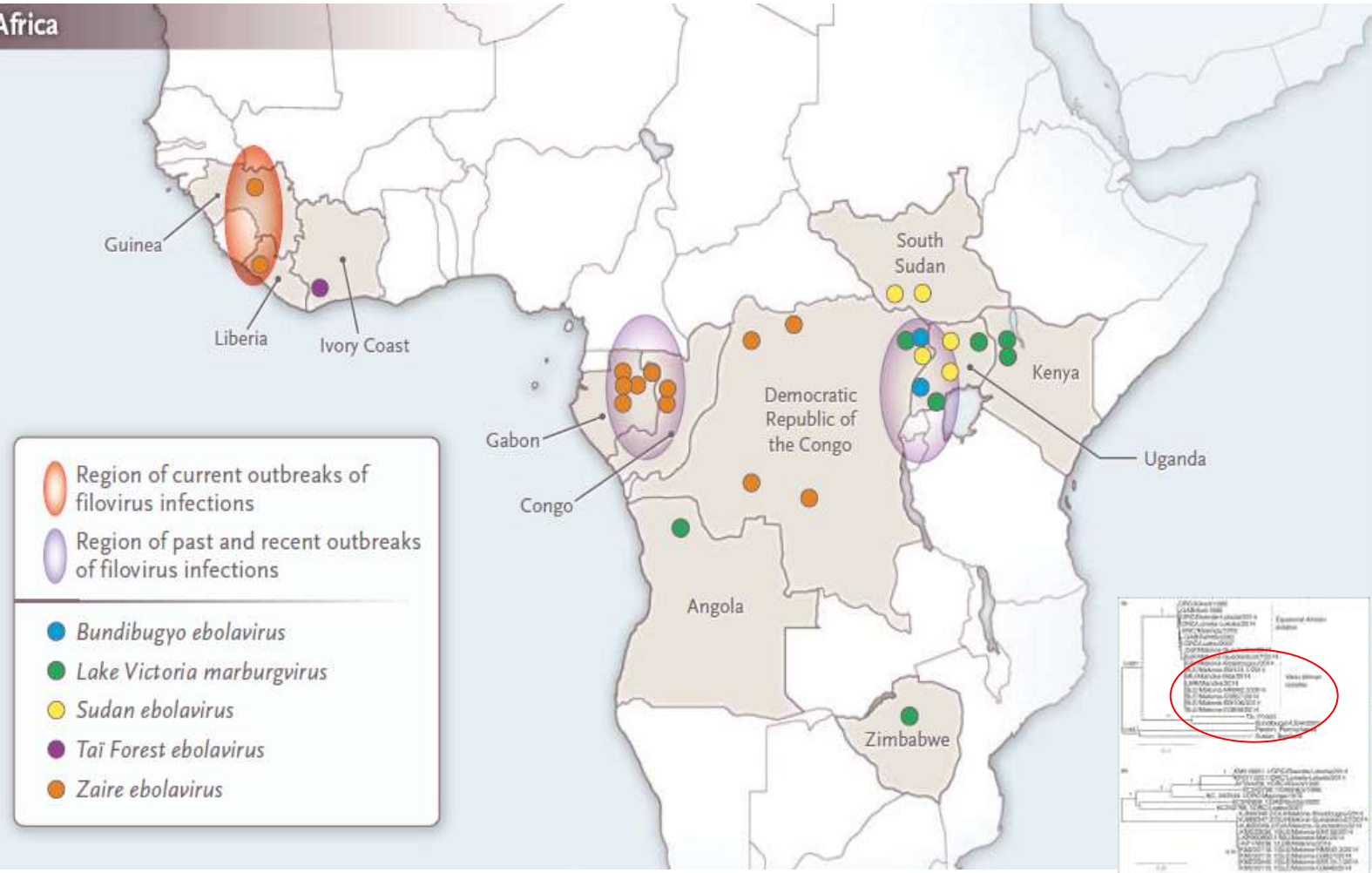
Yambuku 1976(sep – oct.)
318 cas ,280 décès, létalité de 88 %



Ebola river



Africa



La transmission du virus Ebola Zaïre

Des pathogènes très contagieux par contact

Transmission réservoir-homme

~ contact étroit avec sang/tissus de chauve-souris frugivore ?

Transmission inter-humaine

~ contact étroit avec le sang, vomissures, urine, salive, sperme, larmes d'un malade ou les excréta d'un décédé

~ Nosocomiale par voie parentérale

Transmission grand singe-homme

~ contact étroit avec sang/tissus d'un singe infecté



~ **Déforestation**, Chasse et activités forestières
~ Manipulation et dépeçage viande de brousse

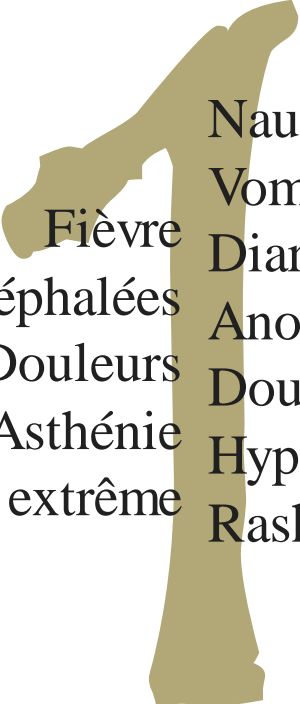
~ Soins aux malades
~ Rites funéraires
~ Vie quotidienne/familiale
~ Transmission liée au soin



Nécessité d'un contact physique proche pour la transmission inter-humaine

Tableau clinique de la fièvre hémorragique à virus Ebola

Incubation: 3 à 21 jours
4 – 7 jours le plus souvent



Fièvre
Céphalées
Douleurs
Asthénie
extrême

Nausées
Vomissements
Diarrhée
Anorexie
Douleurs abdom.
Hyperémie conj.
Rash cutané

Une évolution biphasique



Méléna
Hématurie
Gingivorragie
Hématémèse
Epistaxis

Saignements
Hémoptysie
Anurie
Hoquet

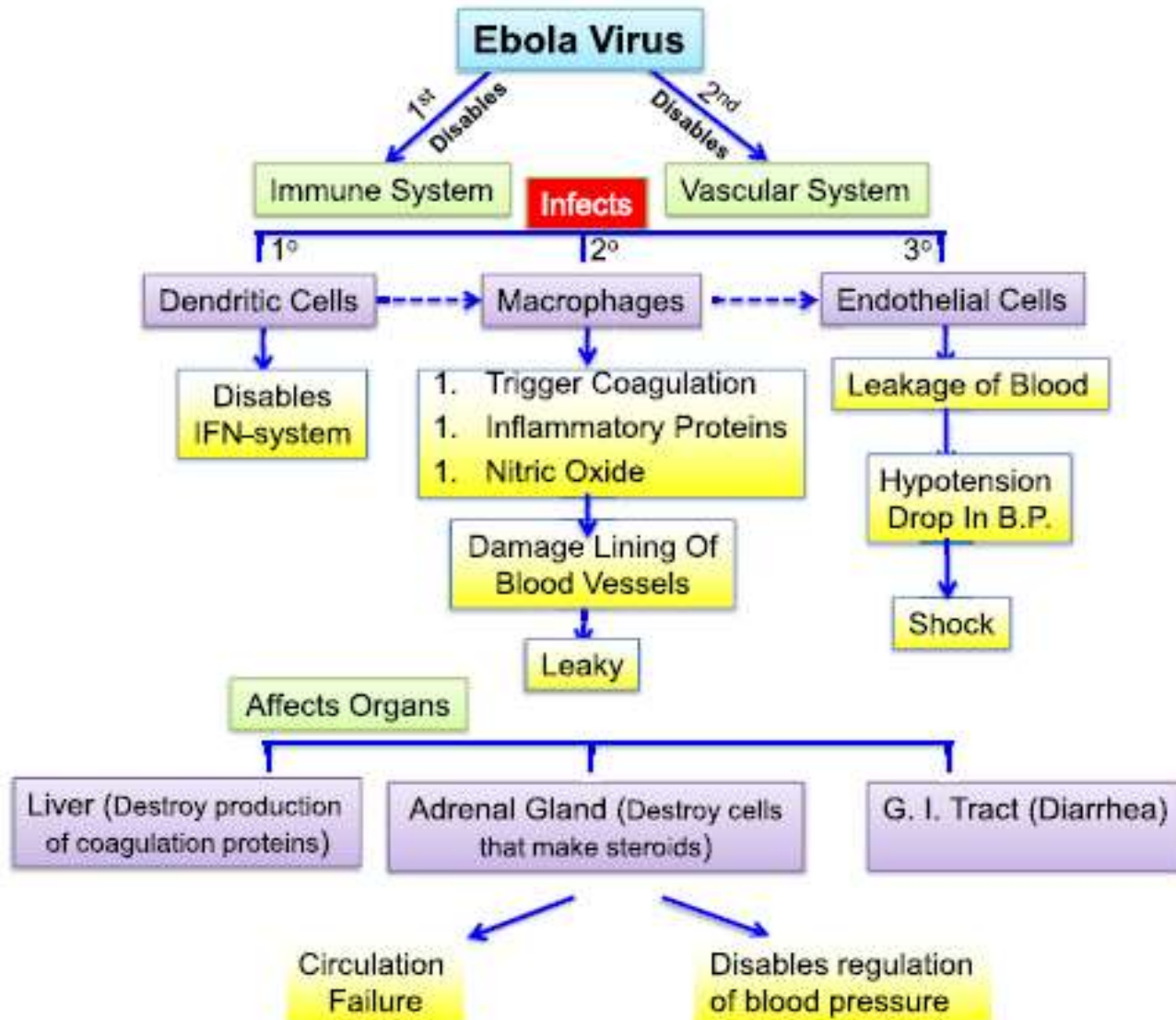
Méléna
Hématurie
Selles sanglantes
hémoptysie

Forme sévère
Défaillance
d'organe, choc

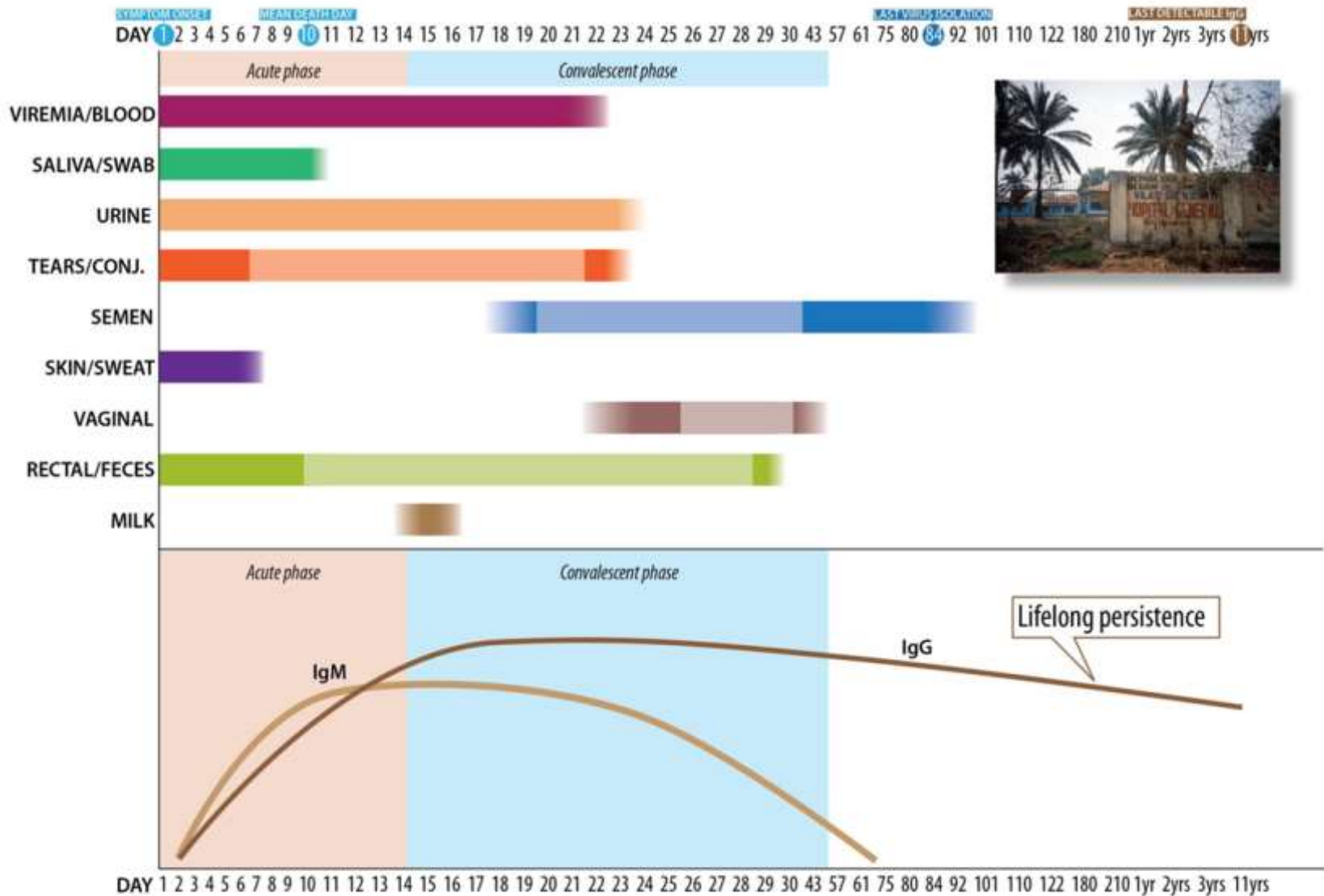


6-14 jours

Forme résolutive
Complications
tardives
Pathologies
sociales
(stigmatisation)



Ebola Hemorrhagic Fever



Pourquoi cette épidémie est différente des précédentes

- **Nombre de cas très important:**
> 24 623 (dont 10 169 décès au 01/03/2015)
- **Durée prolongée:** plus de un an
- **Extension à plusieurs pays** d'Afrique de l'Ouest
- **Circulation virus dans zones urbaines**
plus difficiles à surveiller
- **Débordement des structures sanitaires**
locales et des ONG spécialisées

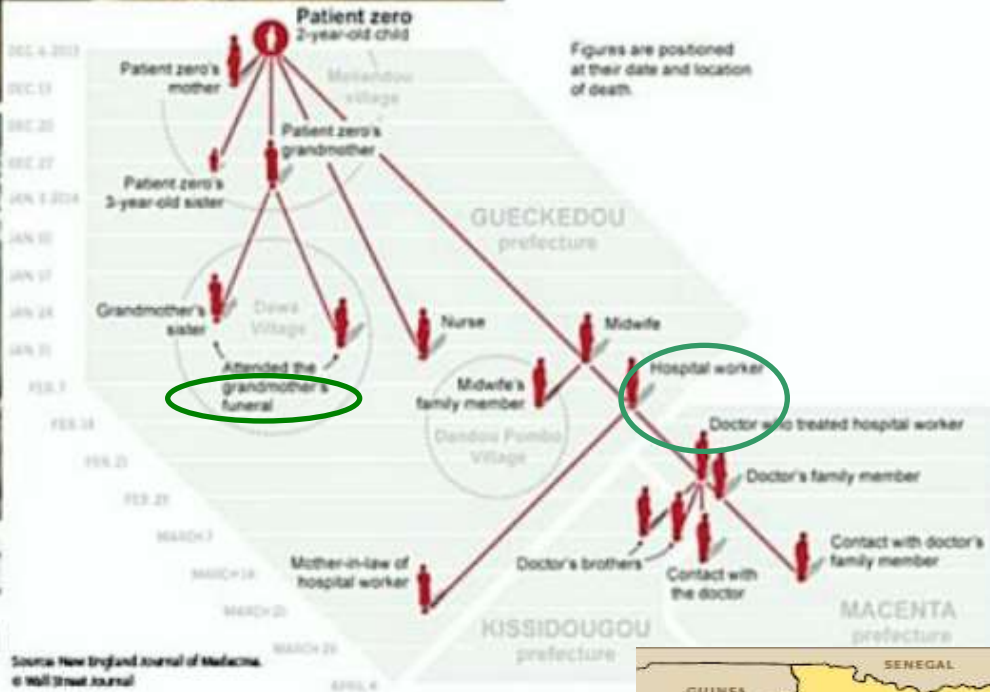
Ebola outbreak: Guineans in shock

2014-04-11 13:19



Figure 3. The families and the burial tree that traced a fatality
 A: The village of Melandou.
 B-D: The burial tree (see text) of the woman who died at a funeral.

Saez, EMBO Molecu



Source: *New England Journal of Medicine*.
 © Wall Street Journal



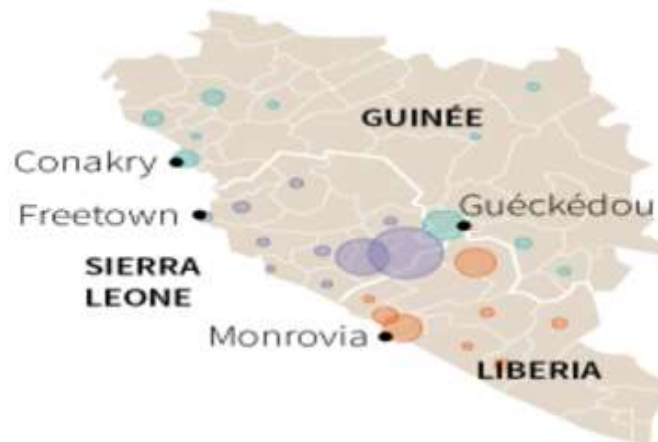
NOMBRE MOYEN DE CAS PAR SEMAINE, PAR DISTRICT 5 20 50

Du 30 décembre 2013 au 4 mai 2014



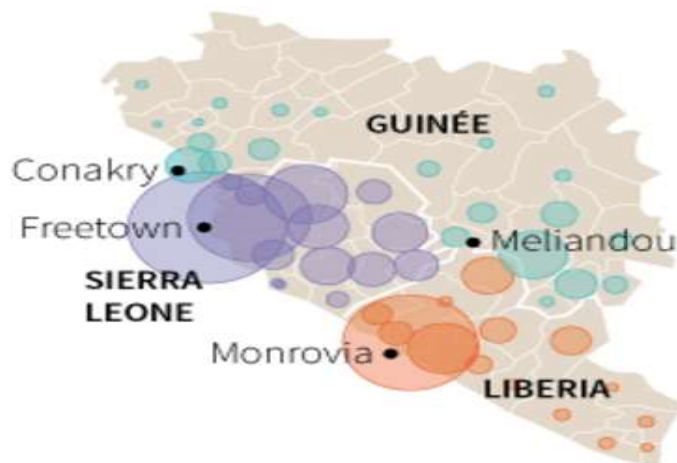
L'épidémie aurait débuté en décembre dans le village guinéen de Meliandou, près de la frontière avec le Liberia et la Sierra Leone.

Du 5 mai au 3 août 2014



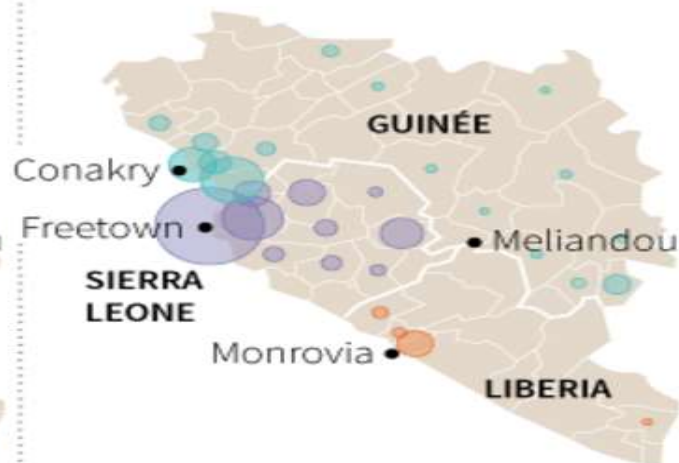
A partir de l'épicentre de Guéckédou d'autres foyers de cas surgissent très à distance et touchent les trois pays.

Du 4 août 2014 au 4 janvier 2015



L'OMS sonne l'alarme alors que les trois capitales sont touchées et que l'on dénombre plus de 1000 cas par semaine.

Du 5 janvier au 15 mars 2015



L'épidémie décline, mais les mouvements de population entretiennent l'épidémie, surtout en Sierra Leone.

SOURCES : OMS ; THE NEW YORK TIMES

3 waves = 3 missed opportunities

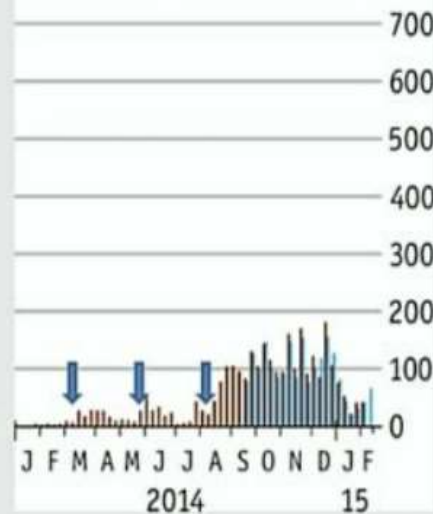
New cases* of Ebola infection per week

To February 8th 2015

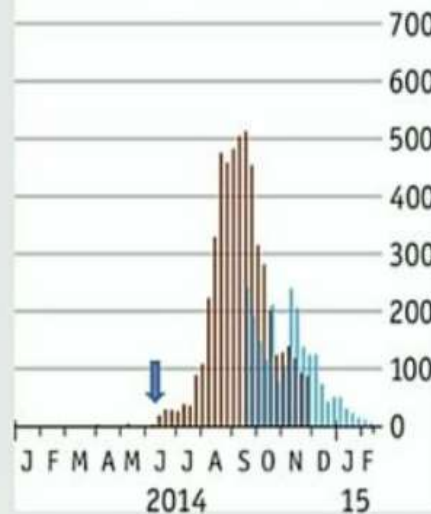
■ Patient database

■ WHO Situation Report

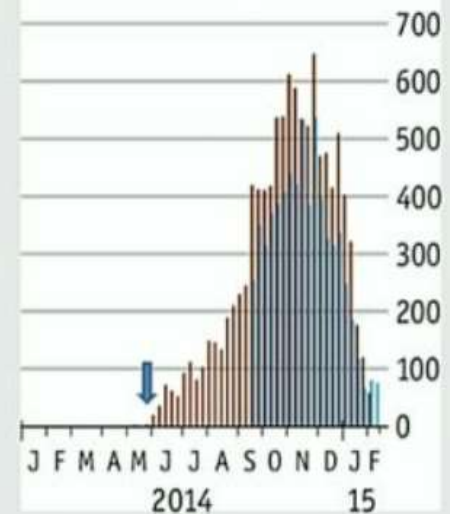
Guinea



Liberia



Sierra Leone

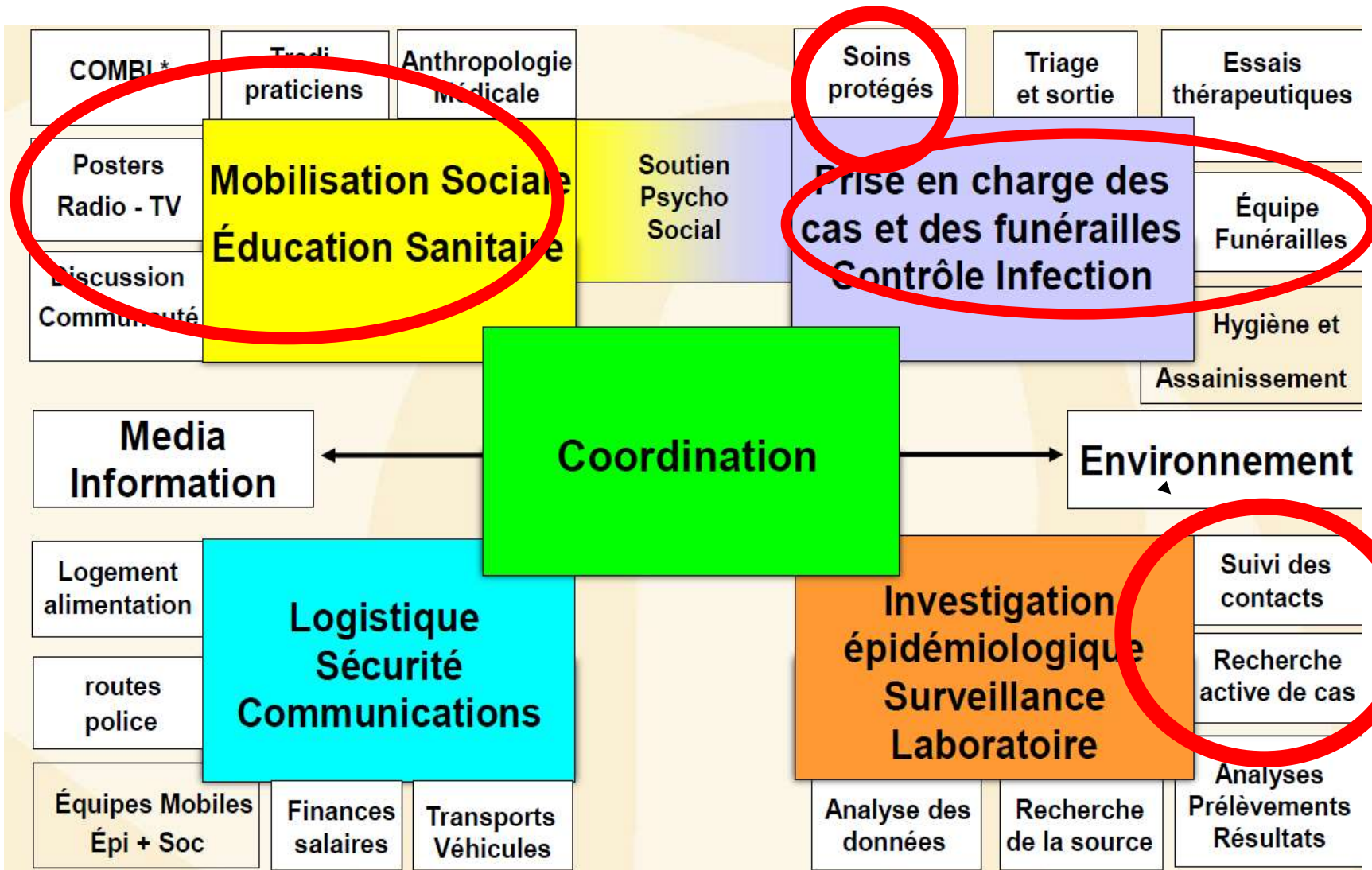


Sources: WHO

*Confirmed and probable

Quelques Facteurs favorisant la **diffusion** de l'épidémie

- Retard aux mesures de contrôle de l'épidémie
- Circulation majeure des personnes (zones frontières, noeuds routiers)
- Non confiance de la population dans les structures de santé et dans les autorités sanitaires
- Coutumes funéraires



Mobilisation communautaire

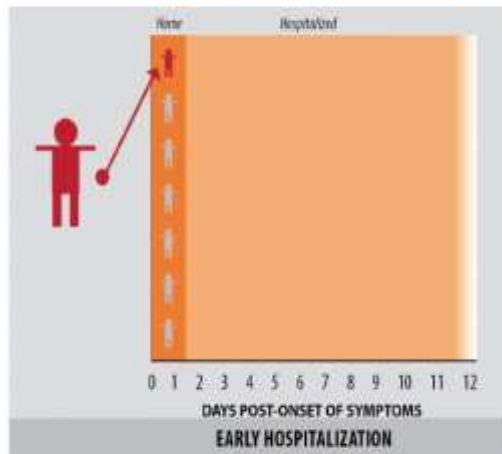
- **Relais d'information** (comités veille villageois)
- **Appui aux enfants vulnérables et personnes guéries**
- **Gestion de l'hostilité et des actes de malveillance ou stigmatisation** vis à vis des soignants et équipes de lutte (suivi, funérailles)
- **Gestion des poches de réticences 'réservoir' épidémique:** Identification communautaire des cas suspects et des contacts; notification des décès communautaires; gestion des rumeurs, dénis, réticences; surveillance des mouvements de population

Investigation des cas et traçabilité des contacts

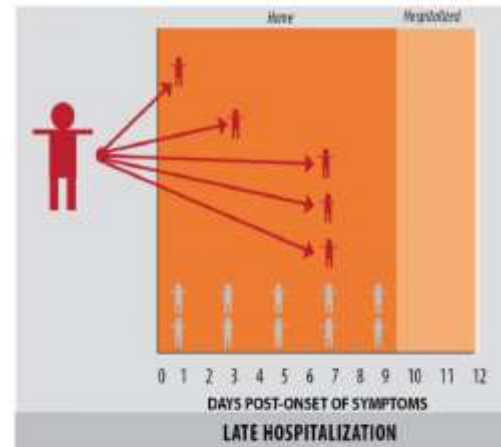
Référence rapide (et isolement) des cas suspects

- Au fur et à mesure que le nombre de cas augmente, la transmission échappe aux seules chaînes de transmission péri-domiciliaires (cluster) et évolue de l'échelle de la concession vers la communauté (circulation occulte en population)
- Intervention rapide 'critique'
- Mars 2015:
- % nouveaux cas
parmi contacts identifiés:
Guinée~15%, Sierra Leone?
Liberia 100%

***Ebola transmission dynamics:
early hospitalization vs. late hospitalization***



**Fewer contacts
Less risk of transmission
Better survival**



**Multiple contacts
High risk of transmission**

Funérailles sécurisées

dignes et rassurantes

- **Mesure fondamentale**
Consommatrice de ressources
humaines et matérielles
(temps, véhicules)
- **Mesure difficile:** incidents avec équipes
de sécurité
- **Mars 2015, Guinée:** ~15 enterrements non sécurisés par semaine
60% des nouveaux décès sont communautaires (non pas en CTE)

Soins protégés

Personal Protective equipment (PPE)

Le risque de transmission aux soignants est important

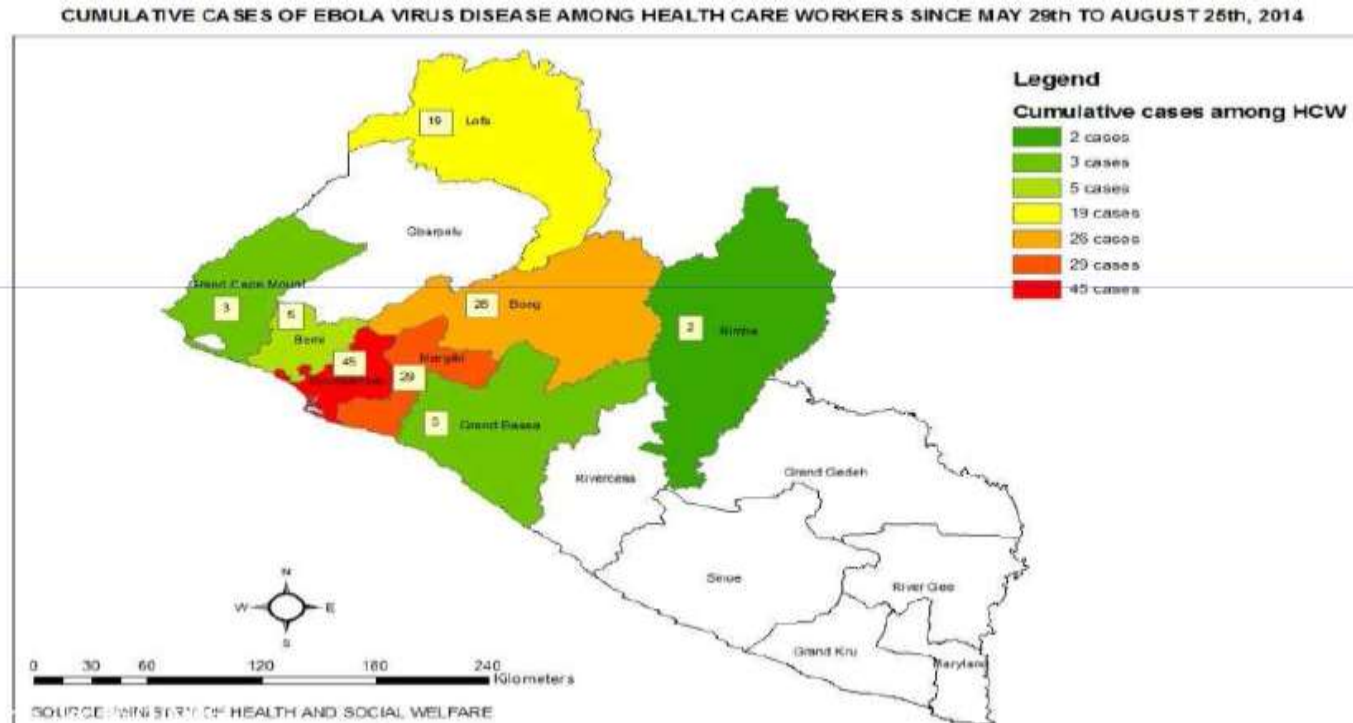
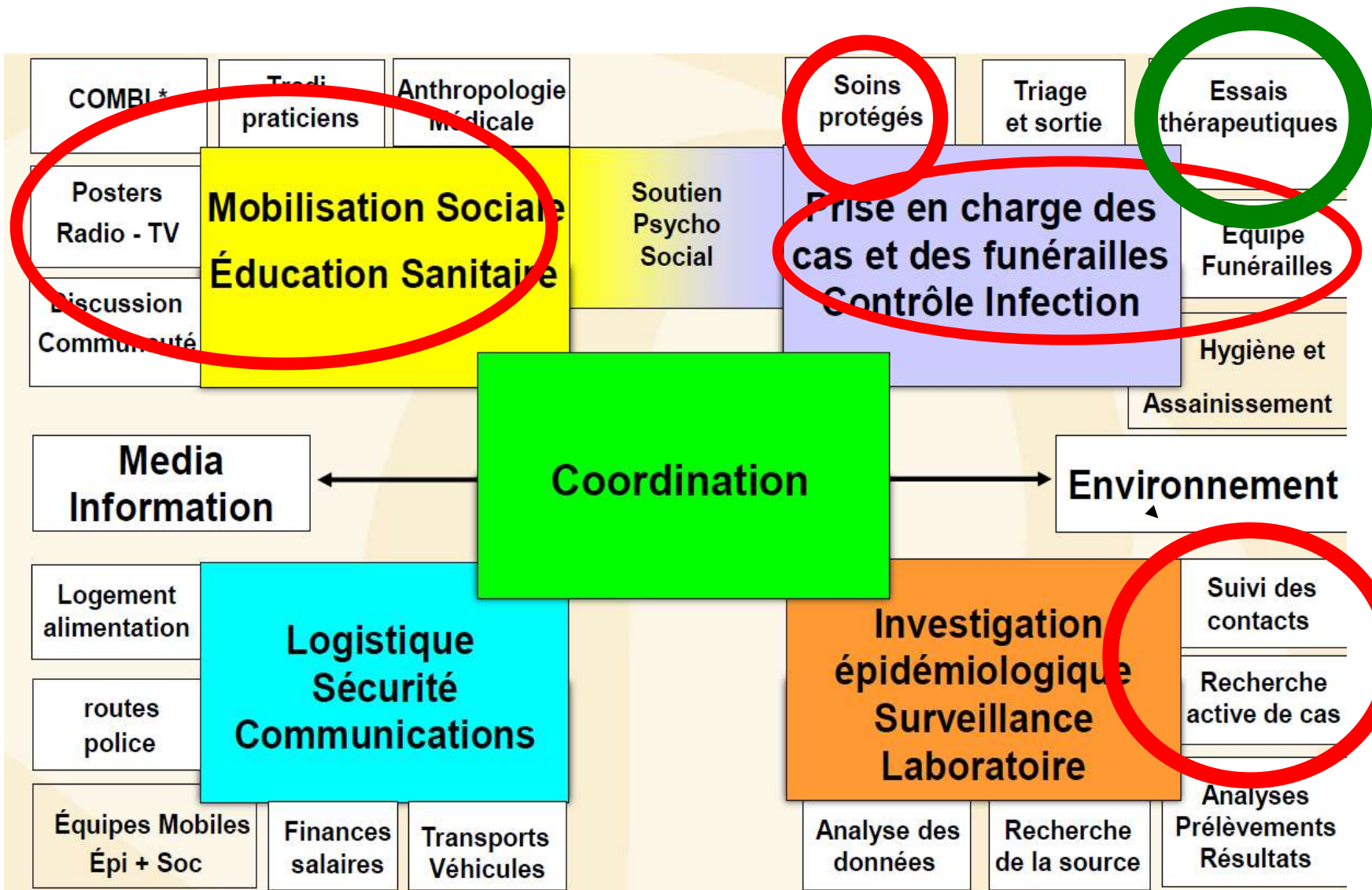


Table 3: Ebola virus disease infections in health workers in the three countries with intense transmission

Country	Cases	Deaths
Guinea	166	88
Liberia	371	179
Sierra Leone	293	221
Total	830	488

Data are confirmed cases and deaths only, apart from deaths in Sierra Leone, which include confirmed, probable, and suspected deaths

Source: WHO, 18 February 2015



The two lead candidate vaccines currently under clinical evaluation

A-rVSV-ZEBOV – recombinant vesicular stomatitis virus

The rVSV vaccine aims to induce EVD-specific immune responses.

NewLink Pharmaceuticals/Public Health Agency of Canada

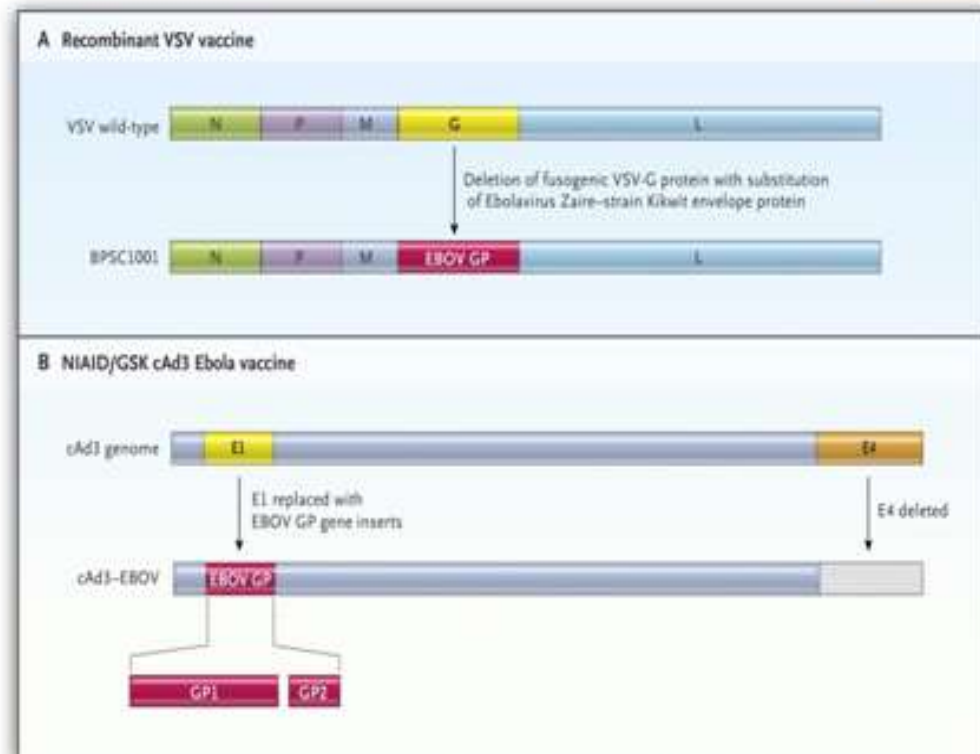
800 vials donated to WHO by the Government of Canada

B -ChAd3-ZEBOV – chimpanzee adenovirus 3

Uses a chimpanzee adenovirus that does not grow, containing the gene for EVD surface protein.

GSK/NIAID

25 000 doses by December 2014



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

Candidate vaccines were selected on the basis of protection in nonhuman primates post-lethal challenge (100%) and availability of GMP-grade vaccine.

Additional candidate vaccines are also in the pipeline, but at a less advanced stage of development.

Principles underlying Phase 1

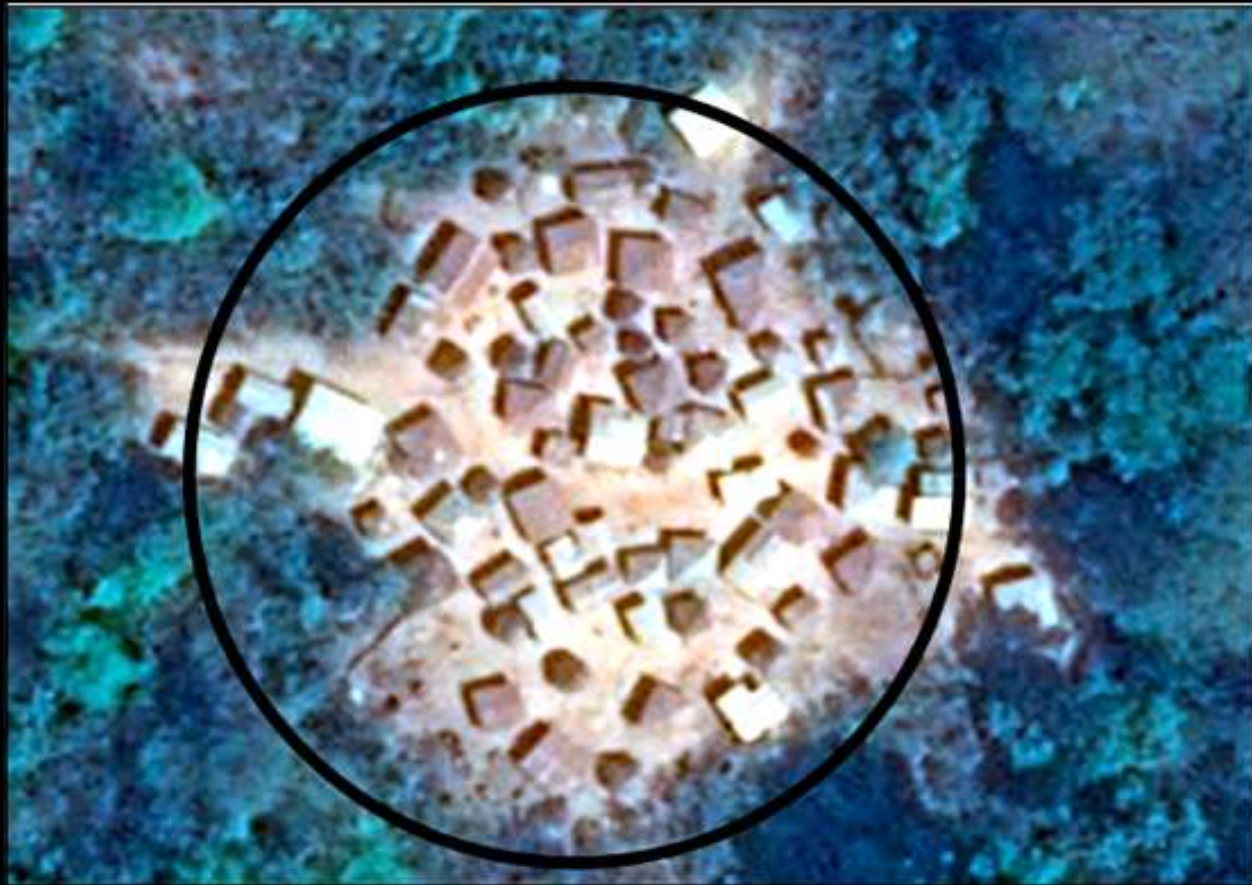
- **Quality and safety were considered paramount considerations throughout evaluation**
- Safety and reactogenicity may differ between African and non-African populations
- Immunogenicity may differ between African and non-African populations
- Therefore Phase 1 data from African populations are desirable in addition to data from Europe and North America

Johnson & Johnson Phase 1 trials

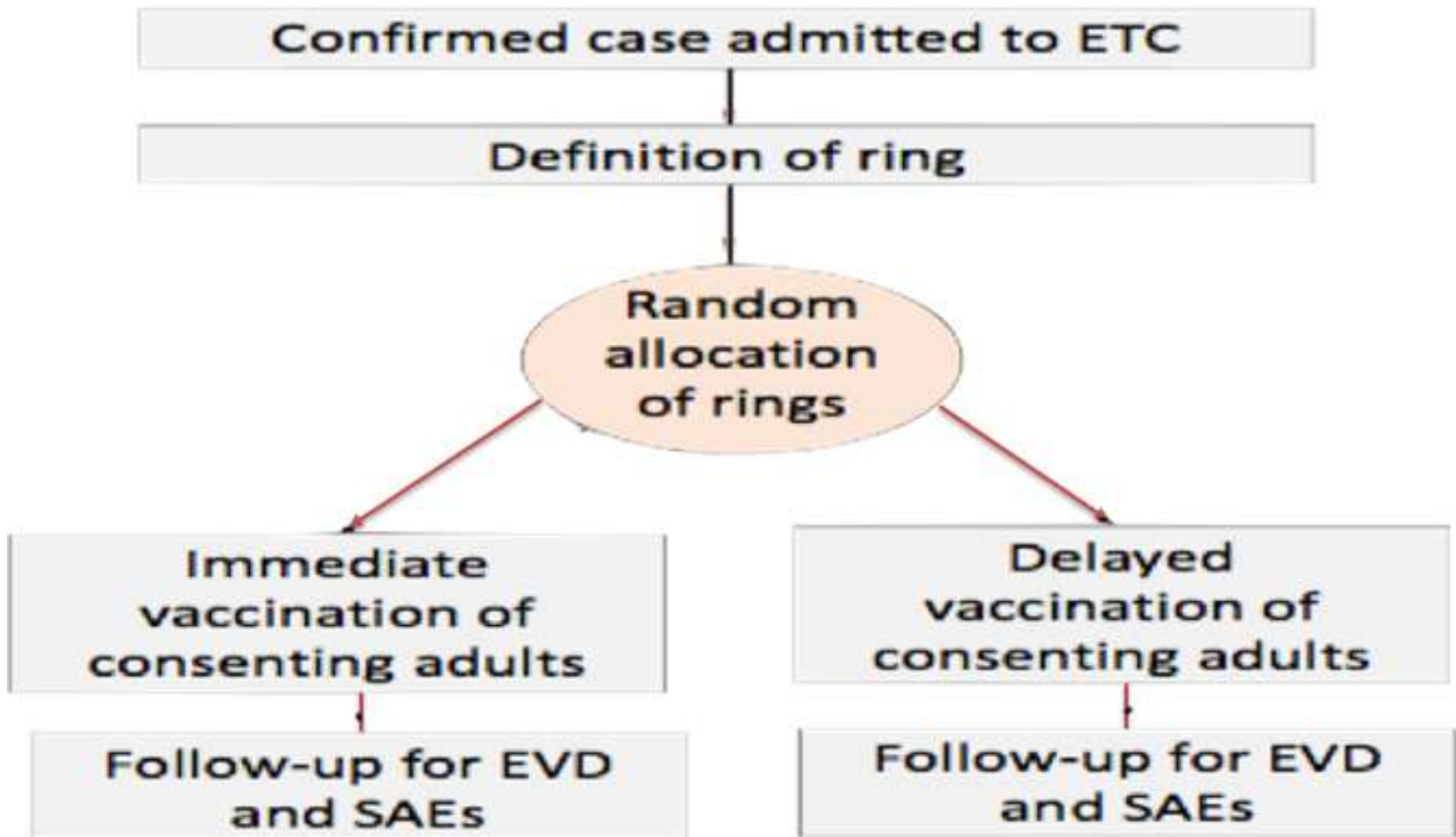
- **Ad26/MVA based approach with 100% NHP efficacy after the booster dose**
- **First Phase 1 trial started in January 2015 in UK**
- **Phase 1 clinical trials planned for USA and Africa soon**
- **Major commitments from company for accelerated development and scaled-up manufacturing, with Phase 2-3 planned for 2015**

Phase 3 efficacy trial designs

- Liberia: Randomized controlled 3-arm trial in the community
- Sierra Leone: Stepped-wedge trial with health care workers
- Guinea: 2 protocols: Ring vaccination trial and immunization of frontline workers



Ring vaccination study design



Comparison of rates of EVD

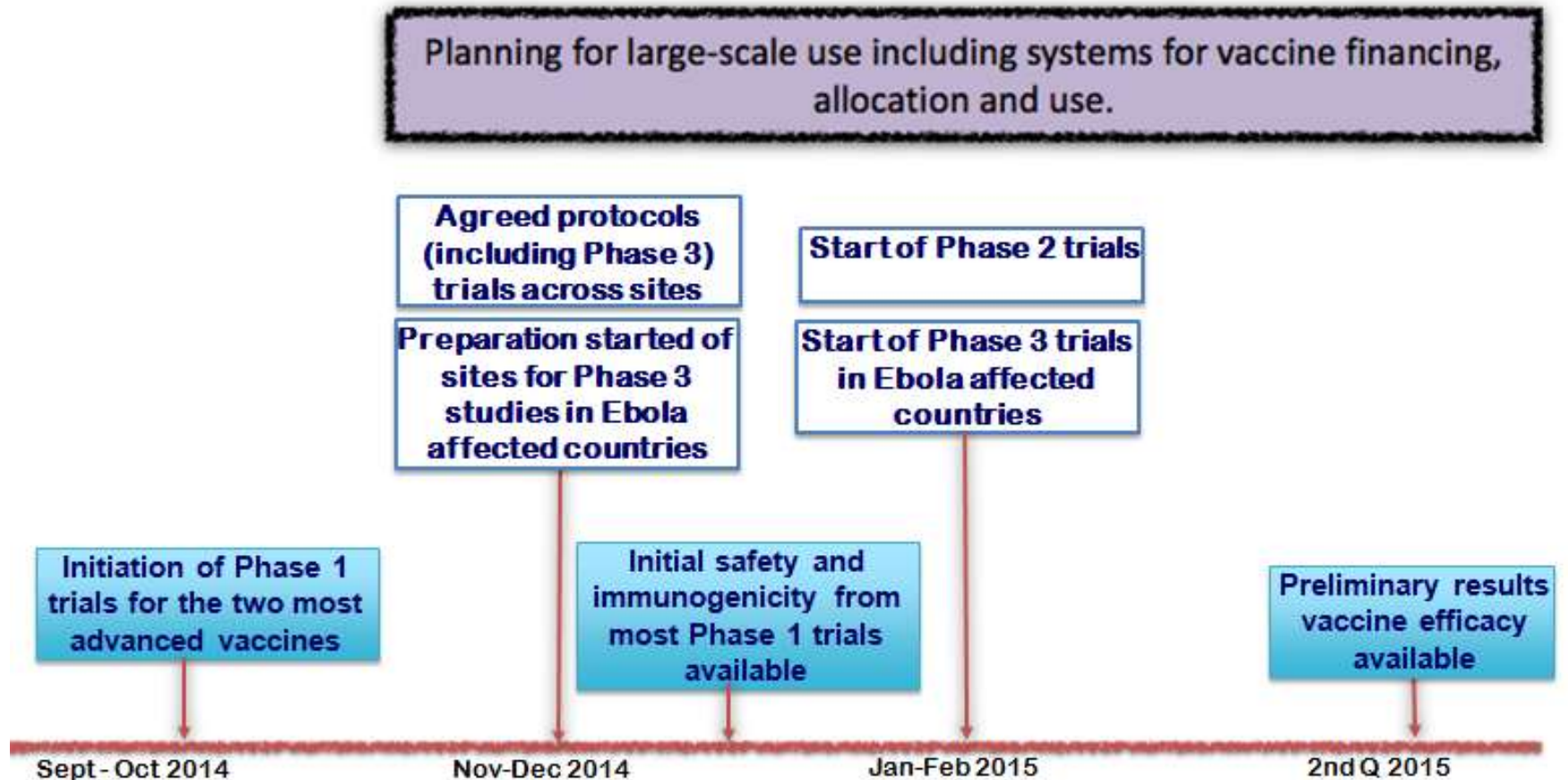
Un premier vaccin contre la maladie à virus Ebola est testé dans les villages affectés, un an après le début de l'épidémie, 25 mars 2015

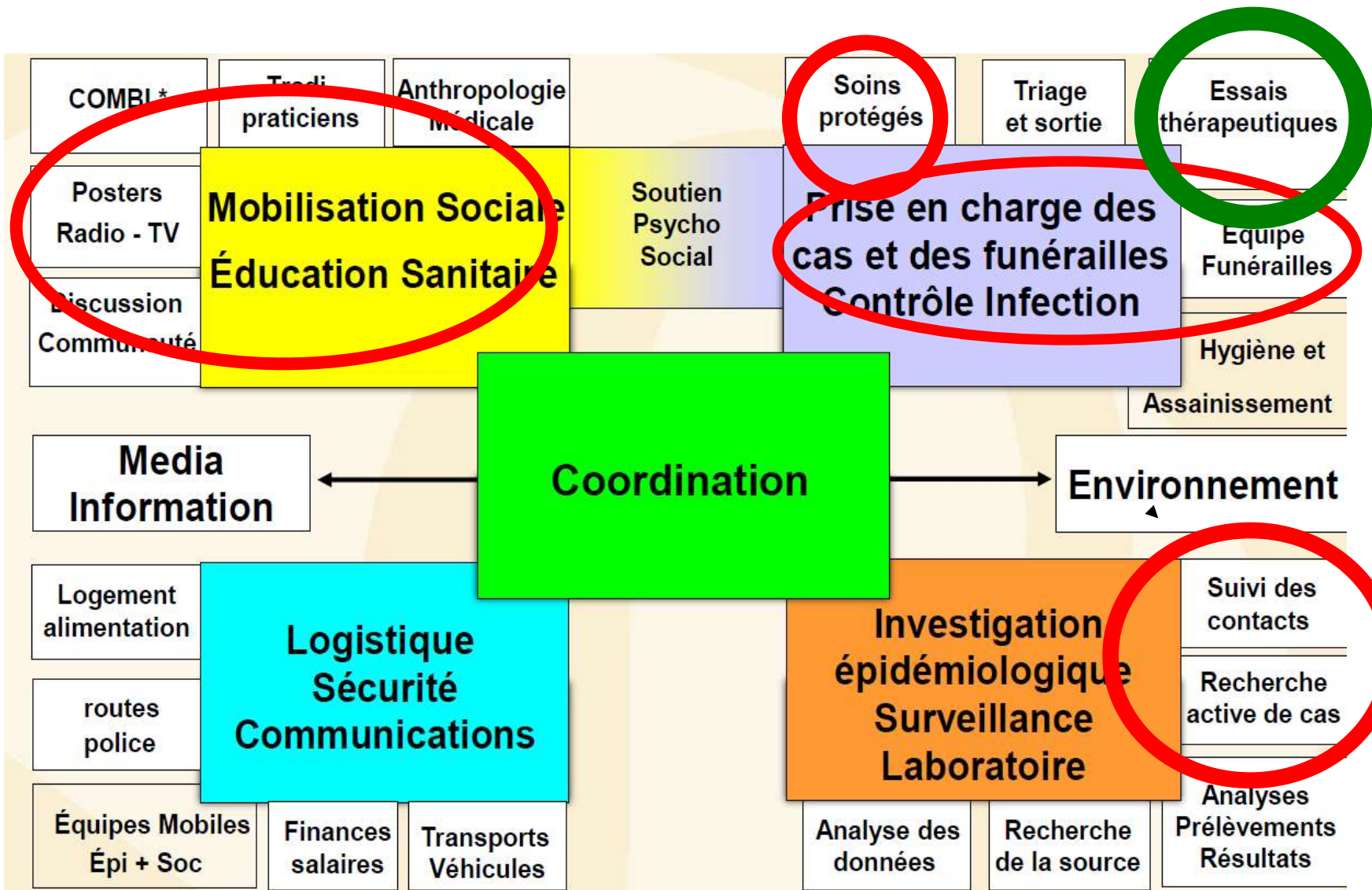
La vaccination dite « en ceinture » débute à Coyah, en Guinée

Conakry (Guinée), 25 mars 2015 (OMS): Le Gouvernement guinéen et l'Organisation mondiale de la Santé (OMS) ont lancé hier la toute première vague d'essais cliniques d'un vaccin contre la maladie à virus Ebola dans un village touché par l'épidémie en Basse-Guinée, l'une des zones du pays où l'on trouve le plus de cas d'Ebola.

Ces tests de vaccinations dites « en ceinture » du vaccin VSV-EBOV, développé par l'Agence de la Santé Publique du Canada, ont été très bien accueillis dans un village rural de la préfecture de Coyah, où l'équipe médicale est arrivée le 23 mars...

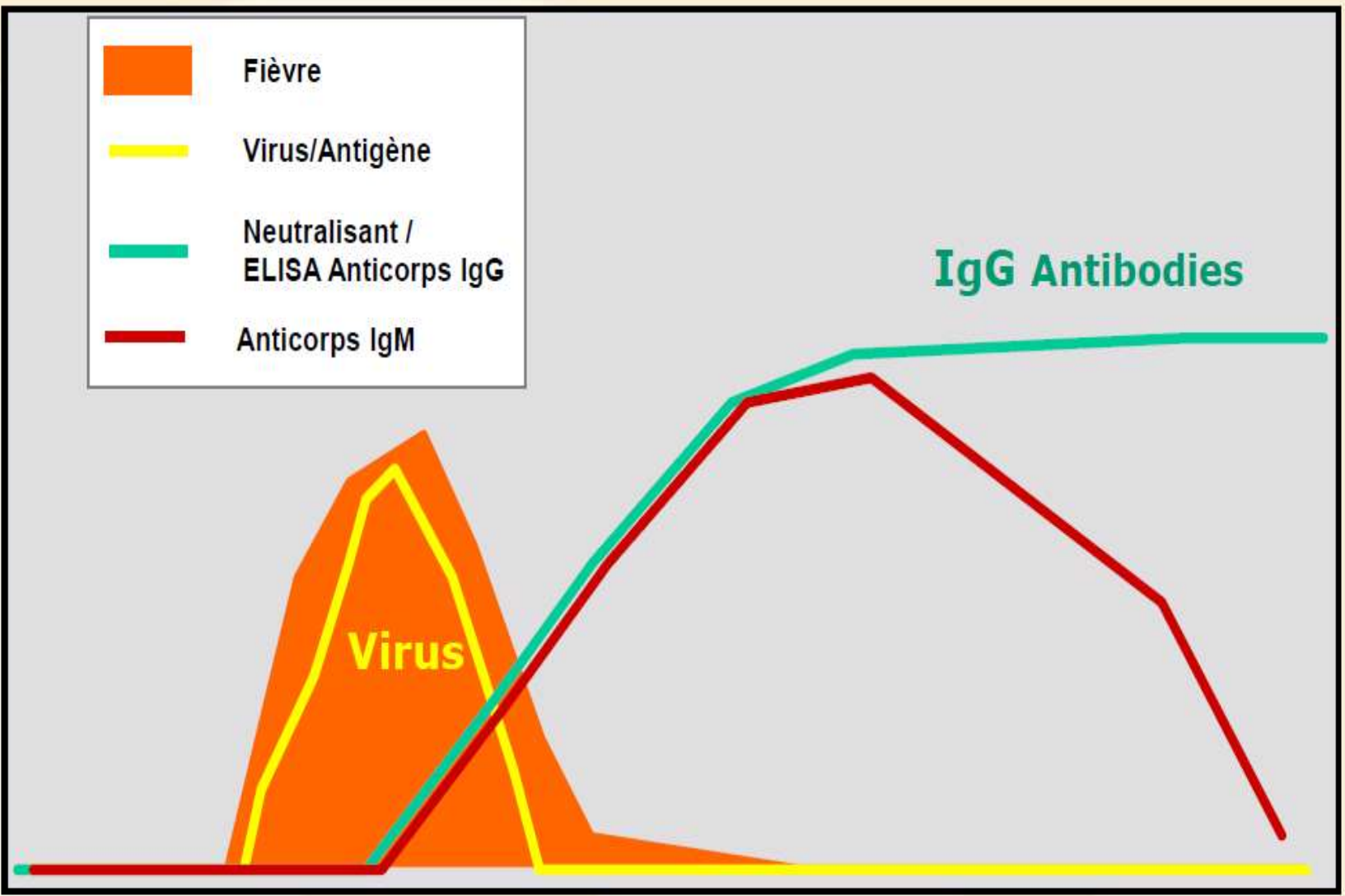
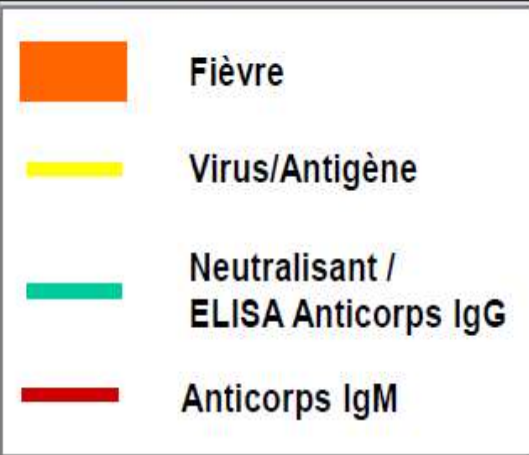
Ebola Vaccines - Key milestones





Traitements systématiques non spécifiques

- **Référence sans délais du patient suspect en vue du diagnostic et de la prise en charge**
- **Traitement de soutien :**
 - Restauration volémique IV, correction troubles électrolytiques,
 - Traitement symptomatique intensif, drogues vaso-pressives
 - Prise en charge de la douleur (et de la dépression)
 - Traitement antibiotique pré-emptif
 - Traitement présomptif du paludisme
 - Thérapeutique nutritionnelle



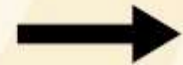
IgG Antibodies

Virus

Incubation

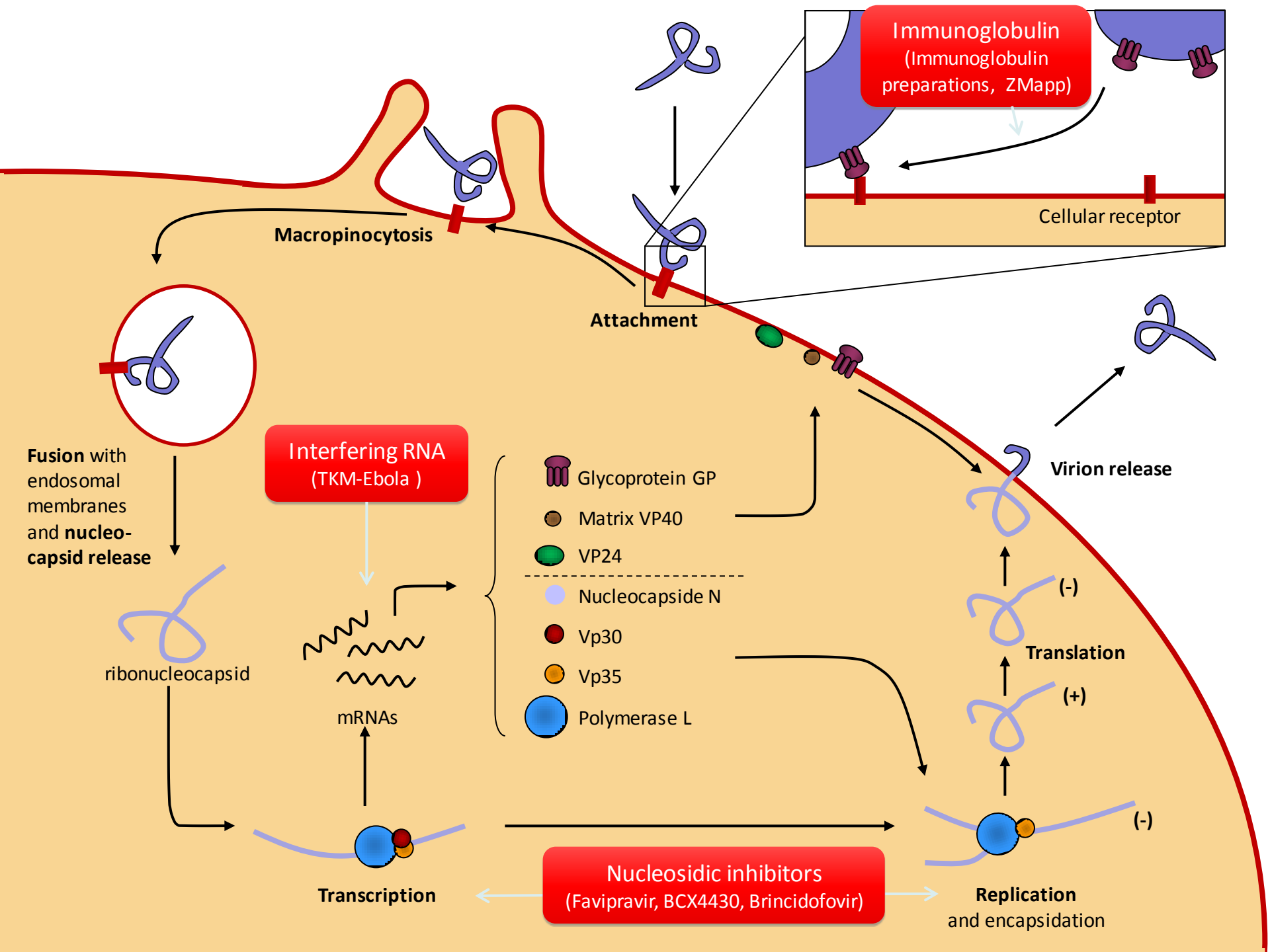
Diseases

Time



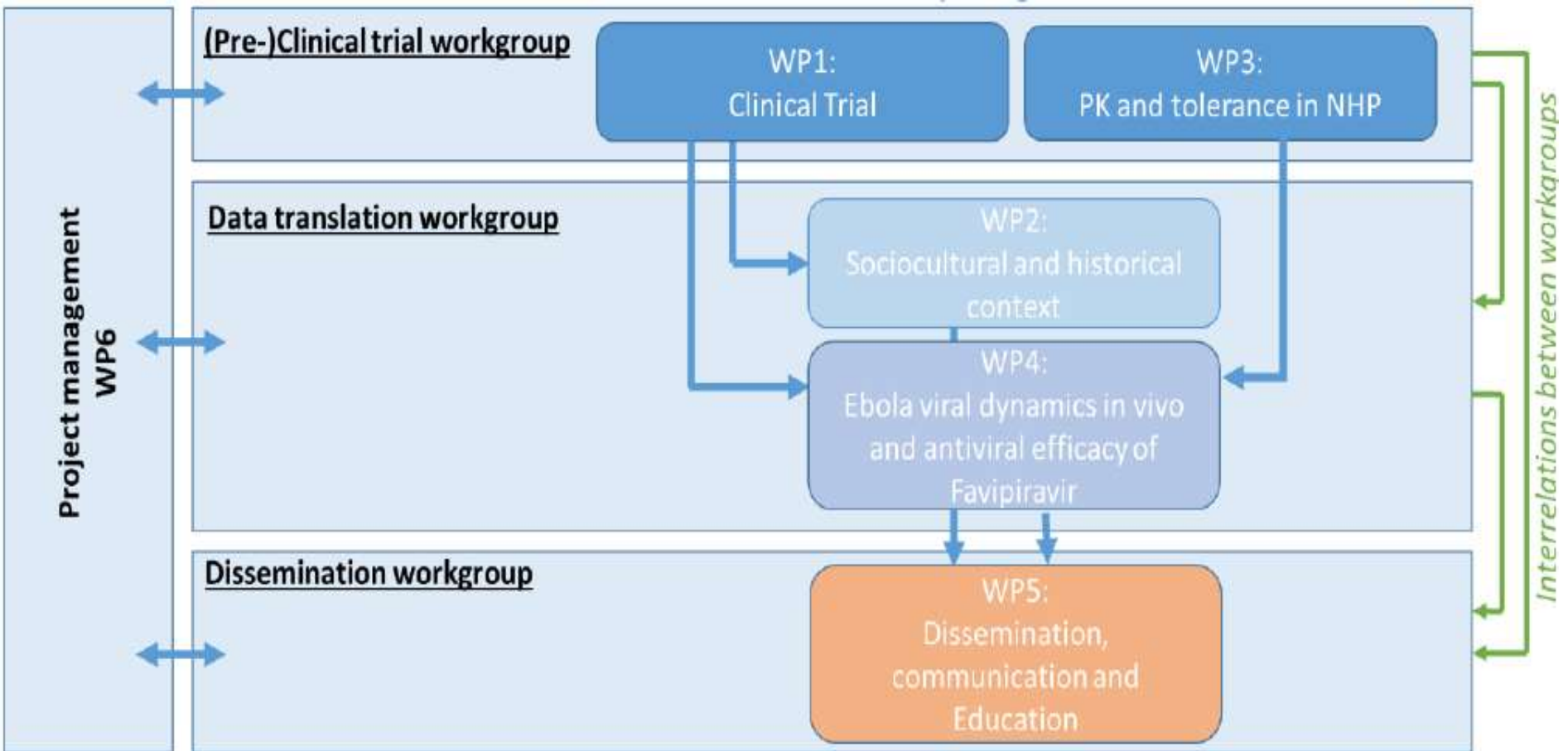
Arguments in favour of convalescent blood or plasma for management of Ebola

- Serum therapies have an extensive history of successful use in certain settings (e.g. diphtheria, pneumococcal pneumonia, anthrax, etc.) and remain important treatments for some conditions (e.g. CMV, parvovirus B19, Argentine Hemorrhagic Fever, etc.).
- Infrastructures for collection of blood do exist, and transfusion already is an adjunctive therapy for hypovolemic, coagulopathic and hemorrhagic conditions in affected regions. Whole blood could provide single unit equivalent plasma if found effective.
- Anecdotal evidence (Mupupa, et al. J Inf Dis 1999) and some animal studies (Dye, et al. PNAS 2012) suggest possible efficacy of convalescent plasma in Ebola.
- Monoclonal Abs are effective in animal models, but may be less available and more costly than transfusion therapy.



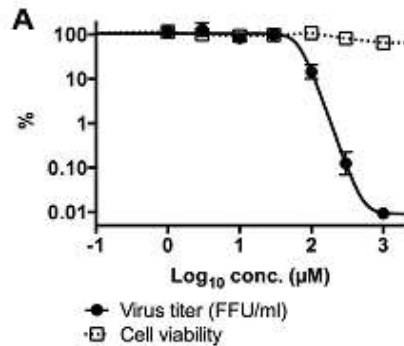


Evaluation of efficacy and antiviral activity of favipiravir in non-human primates & humans



Why favipiravir?

- Favipiravir is a nucleoside polymerase inhibitor with strong activity against several RNA viruses
- It is the only drug with proven activity in vitro against Ebola virus



Oesterreich *et al.*, Antivir Res (2014)

B		95% CI
IC ₅₀	67 µM (10.5 µg/ml)	56 – 75 µM
IC ₉₀	110 µM (17 µg/ml)	83 – 143 µM
IC ₉₉	186 µM (29 µg/ml)	132 – 265 µM

Fig. 1. Antiviral activity of T-705 against EBOV in cell culture. (A) Vero E6 cells were infected with EBOV and T-705 was added 1 h p.i. After 5 days, the concentration of infectious viral particles in the cell culture supernatant was measured by immunofocus assay. A sigmoidal dose-response curve was fitted to the data using Prism GraphPad 6.0 (GraphPad Software). Cell viability was measured by the MTT method. (B) The IC₅₀, IC₉₀ and IC₉₉ values for T-705 with 95% confidence interval (95% CI) were calculated from the sigmoidal function.

The JIKI trial in Guinea

Settings: 4 Ebola treatment centers in Guinea

Sponsor/funding: Inserm/EEUU

Objective: to assess the efficacy of high-dose favipiravir in decreasing mortality in humans with EVD

Design: non-comparative, “proof-of-concept”, phase II trial

Inclusion criteria: Age ≥ 1 year, able to take pills, positive EBOV test, informed consent,

Treatment: Favipiravir, Toyama Chemical Co., Ltd (oral tablets 200 mg), 10 days (*Mentre et al., Lancet Infect Dis 2014, Frange et al., Lancet 2015*)

Primary outcome: Mortality at Day 14

Secondary outcomes: Evolution of EBOV plasma RNA and infectious loads, grade 3-4 adverse events, resistance mutations, trough concentrations of favipiravir

Analysis: Reference = pre-trial mortality (MSF/EMLab database, Sept 15- Dec 14, 2015), with same team, same procedures and same laboratory

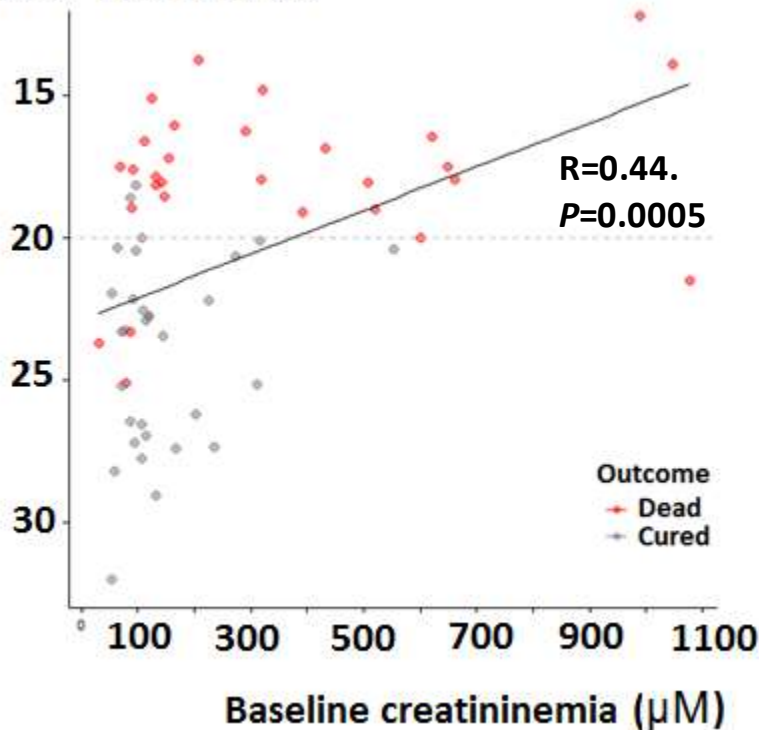
Report: Favipiravir in patients with Ebola Virus Disease: early results of the JIKI trial in Guinea. D. SISSOKO, et al. CROI 2015, Feb. 25, Seattle, USA, Abstr 103ALB (oral presentation)



Outcome by baseline serum creatinine and RT-PCR Ct value

First 69 adult participants, JIKI trial, 17 DEC 2014 – 20 JAN 2015

Baseline RT-PCR Ct value



Creatinine at baseline***	Outcome = Death	
	n (column %)	n (row %)
Baseline Ct <20		
<110 µM	5 (19%)	3 (60%)
110-299 µM	10 (37%)	10 (100%)
≥300 µM	12 (44%)	12 (100%)
	81%	100%
Baseline Ct ≥20		
<110 µM	19 (58%)	3 (16%)
110-299 µM	10 (30%)	0 (0%)
≥300 µM	4 (12%)	1 (25%)
	42%	7%

*** 9 missing values

Ebola haemorrhagic fever in Sudan, 1976

Report of a WHO/International Study Team ¹

A large outbreak of haemorrhagic fever (subsequently named Ebola haemorrhagic fever) occurred in southern Sudan between June and November 1976. There was a total of 284 cases; 67 in the source town of Nzara, 213 in Maridi, 3 in Tembura, and 1 in Juba. The outbreak in Nzara appears to have originated in the workers of a cotton factory. The disease

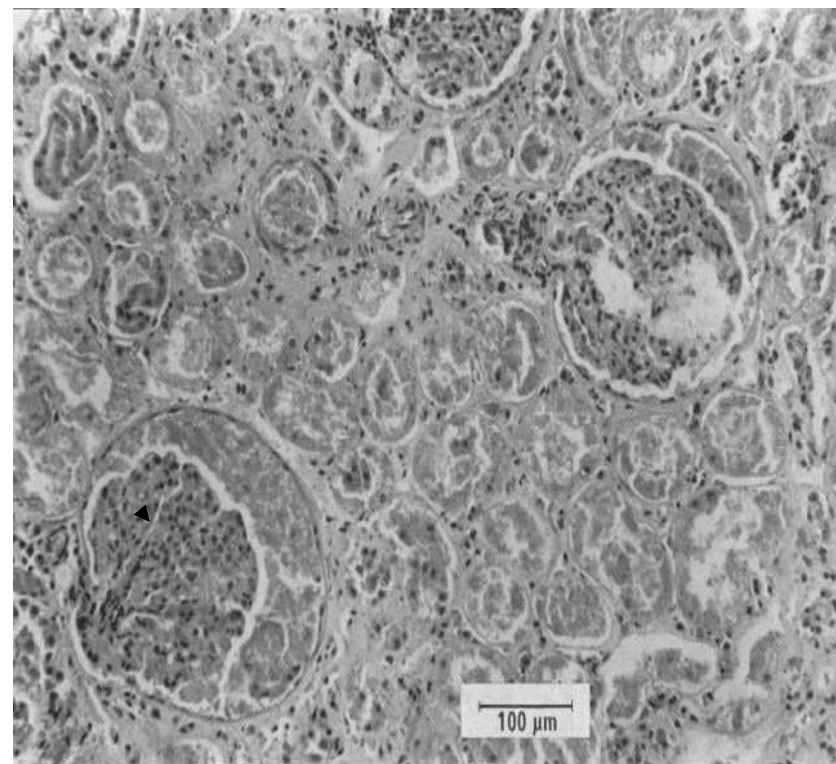


Fig. 7. Kidney. Area of tubular necrosis and exceptionally profuse precipitate in Bowman's spaces. (The small specks are formalin pigment, not nuclear debris or inclusions. (Case 2).

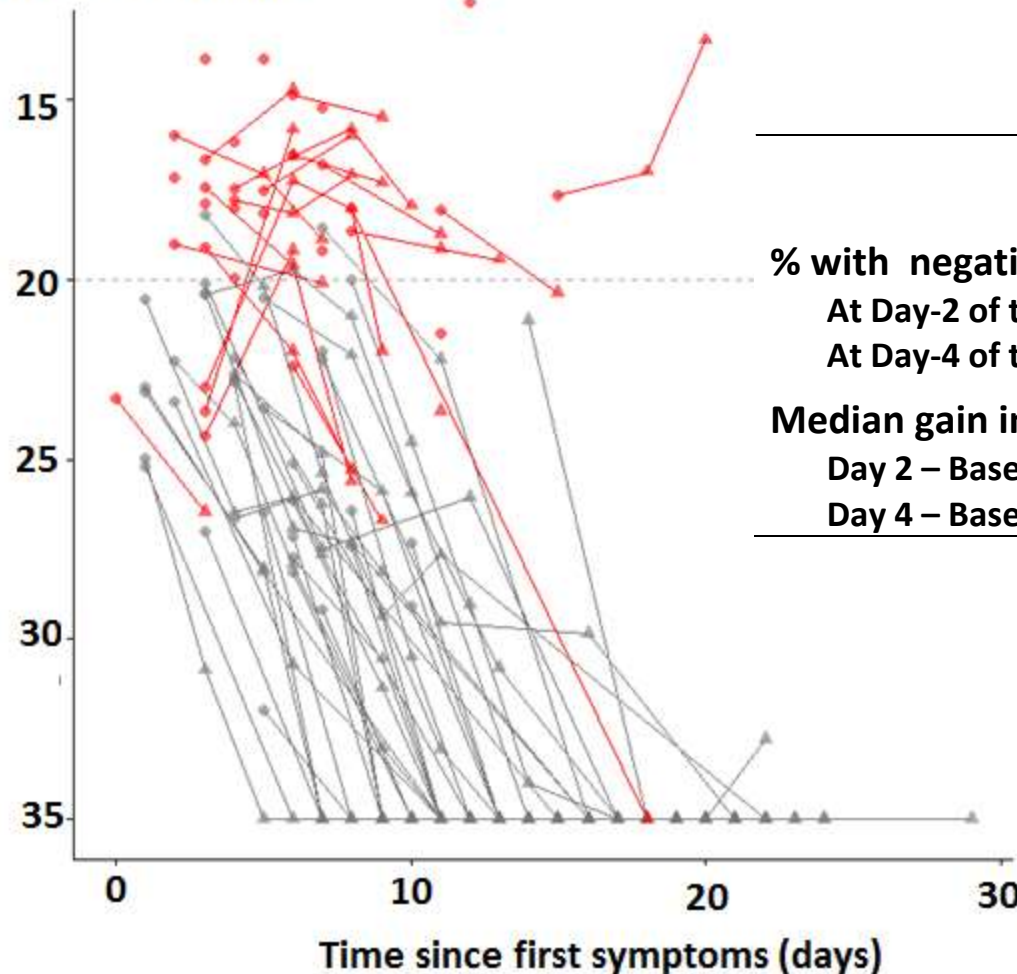
Two post mortems were carried out on patients in November 1976. The histopathological findings resembled those of an acute viral infection and although the features were characteristic they were not exclusively diagnostic. They closely resembled the features described in Marburg virus infection, with focal eosinophilic necrosis in the liver and destruction of lymphocytes and their replacement by plasma cells. One case had evidence of renal tubular necrosis.

Two strains of Ebola virus were isolated from acute phase sera collected from acutely ill patients in Maridi hospital during the investigation in November 1976. Antibodies to Ebola

RT-PCR Ct values at baseline and during follow-up

First 69 adult participants, JIKI trial, 17 DEC 2014 – 20 JAN 2015

RT-PCR Ct value



	Baseline Ct value	
	<20	≥20
% with negative RT-PCR		
At Day-2 of treatment	0 (0%)	11 (28%)
At Day-4 of treatment	1 (4%)	20 (51%)
Median gain in Ct		
Day 2 – Baseline	+ 1.5	+ 5.2
Day 4 – Baseline	+ 2.9	+ 12.3

Mortality by baseline CT : Jiki vs. Pre-trial

First 69 adult participants, JIKI trial, 17 DEC 2014 – 20 JAN 2015

	JIKI				3-months Pre-trial				<i>P</i>
	Included		Dead		Admitted		Dead		
	n	(column %)	n	(row %)	n	(column %)	n	(row %)	
Any Ct value*	69	(100%)	33	(48%)	478	(100%)	272	(57%)	0.16
Ct <20	28	(42%)	26	(93%)	232	(48%)	197	(85%)	0.39
Ct ≥20	39	(58%)	6	(15%)	246	(52%)	75	(30%)	0.052
20 ≤ Ct < 25	24	(36%)	6	(25%)	154	(32%)	57	(37%)	
Ct ≥ 25	15	(22%)	0	(0%)	92	(20%)	18	(20%)	

* Including 2 missing Ct values at baseline

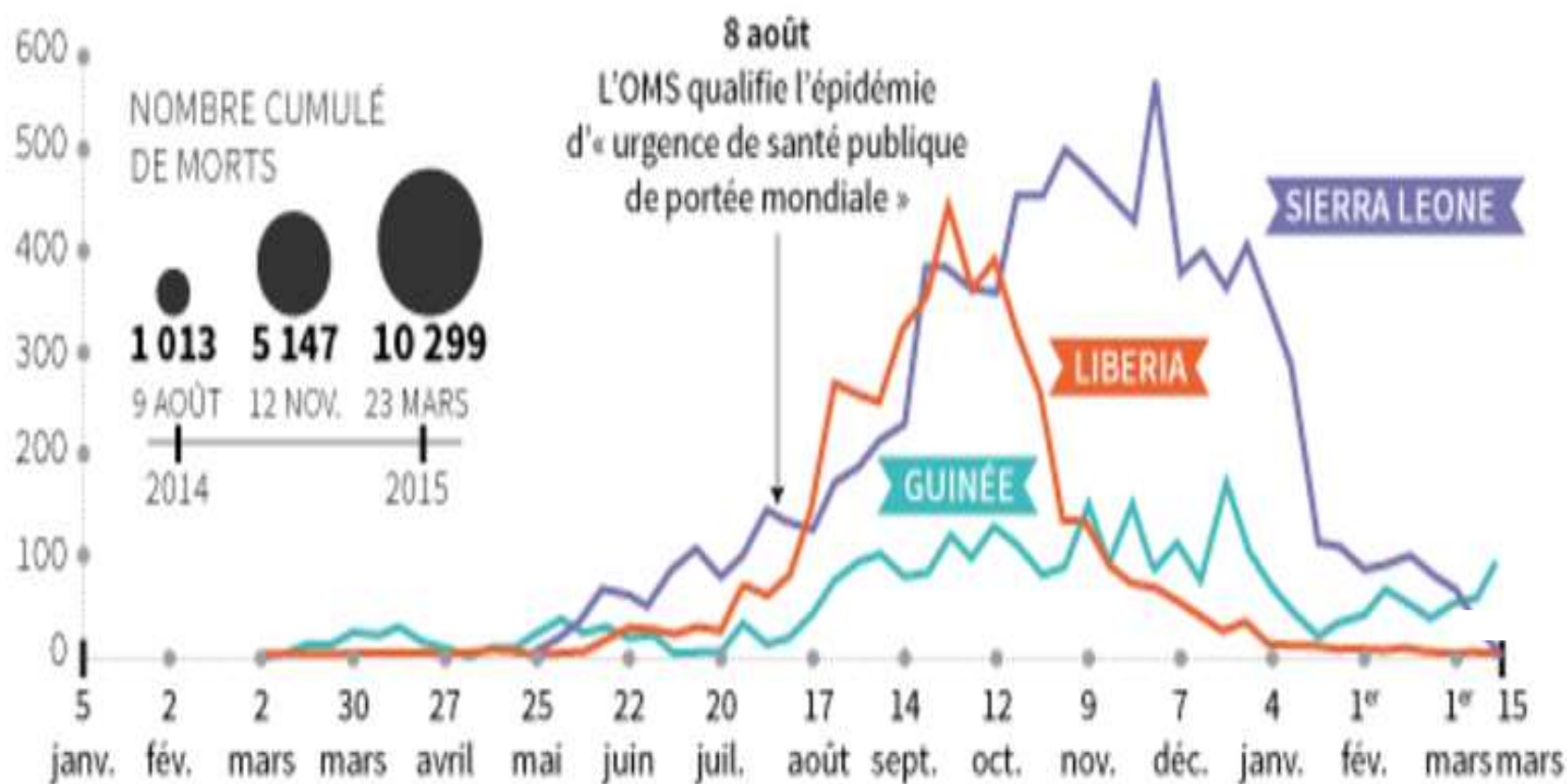
Discussion

- **RT-PCR Ct value and serum creatinine are two excellent markers of disease severity**
 - **50% of patients showed up with a Ct value < 20 (equivalent to 10⁸ copies/ml)**
 - **52% of patients showed up with kidney failure**
 - **81% of patients with baseline Ct < 20 had refractory kidney failure; 100% died**
 - **42% of patients with baseline Ct ≥ 20 had transient kidney failure ; 97% recovered**
- **No indication that monotherapy with favipiravir improves survival in patients with initial Ct < 20**
 - Mortality as high as in 3-month period preceding the trial
 - Modest increase in Ct at Day-2 and Day-4
 - **other interventions should be urgently tested in this population**
- **A « signal » (low level of proof) that monotherapy with favipiravir may improve survival in patients presenting with Ct ≥ 20**
 - Mortality lower by half compared to patients with similar viral load during the 3 month period immediately preceding the trial (same team, same lab)
 - Important increase in Ct at Day-2 and Day-4
 - **we will amend the JIKI trial protocol and include analysis by baseline CT to gather further evidence of favipiravir efficacy**

Plus d'un an d'épidémie

NOMBRE DE CAS CONFIRMÉS PAR SEMAINE, SELON LES PAYS

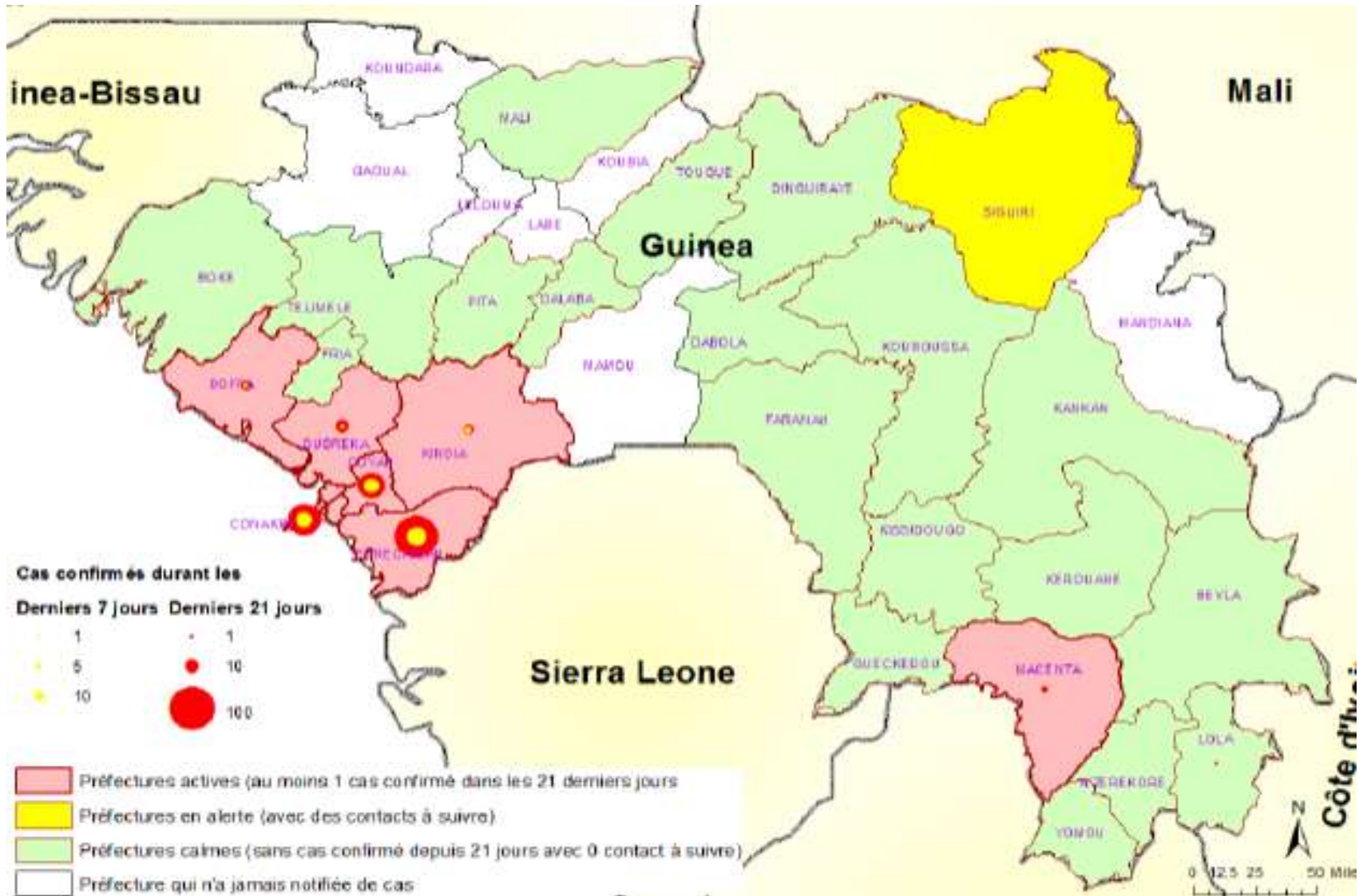
Selon la base de données de l'Organisation mondiale de la santé (OMS) et les données nationales



Le modèle du Libéria

- Ebola : «L'existence du Liberia est gravement menacée»
[AFP](#) 9 septembre 2014
- 1er septembre. Des infirmiers ramènent un patient atteint du virus Ebola, qu'ils ont appréhendé sur un marché de Paynesville, après sa fuite de l'hôpital Elwa de Monrovia, au Liberia, où il était placé en quarantaine. (Photo Reuters TV)

Situation Guinée, 15 mars 2015



Vers le post(péri)-EBOLA?

Chronique annoncée de la deuxième crise

Reduced vaccination and the risk of measles and other childhood infections post-Ebola

Saki Takahashi,¹ C. Jessica E. Metcalf,^{1,2} Matthew J. Ferrari,³ William J. Moss,⁴ Shaun A. Truelove,⁴ Andrew J. Tatem,^{5,6,7} Bryan T. Grenfell,^{1,6} Justin Lessler^{4*}

...additional deaths from measles (15). Measles mortality could be at the high end of this range because of the limited health care services and increased prevalence of malnutrition and vitamin A deficiency associated with the Ebola outbreak (16).

As Ebola fades, a new threat

With health services devastated in the wake of Ebola, experts are bracing for a deadly measles outbreak in West Africa

Un contrôle proche de l'épidémie improbable

Un premier anniversaire sans 'zéro Ebola'

- **Systemes de santé** fragiles ou effondrés
- **Des objectifs individuels et communautaires inconciliables?** Isolement et mesures de protection des soignants vs prise en charge des patients
- **Poids des stratégies délétères** (quarantaines, stigmatisation) et **réticences communautaires**
- Vers une mobilisation internationale et un transfert de compétence dans la reconstruction des systèmes de santé et la préparation aux alertes
- Vers une circulation endémique de bas niveau avec flambées épidémiques limitées et récurrentes?

Il n'y a pas à ce jour de conclusion

- Rapport OMS
18/03/15
- 128 nouveaux cas
- 58 cas en Guinée
- 74 en Sierra Léone
- Augmentation du taux d'incidence
- Expansion géographique
- Aléats de la réponse

