Instituts thématiques

Inserm

Institut national
de la santé et de la recherche médicale

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RÉPUBLIQUE FRANÇAISE

sponse to Ebola :
a crisis situation

issy

f the « Task Force

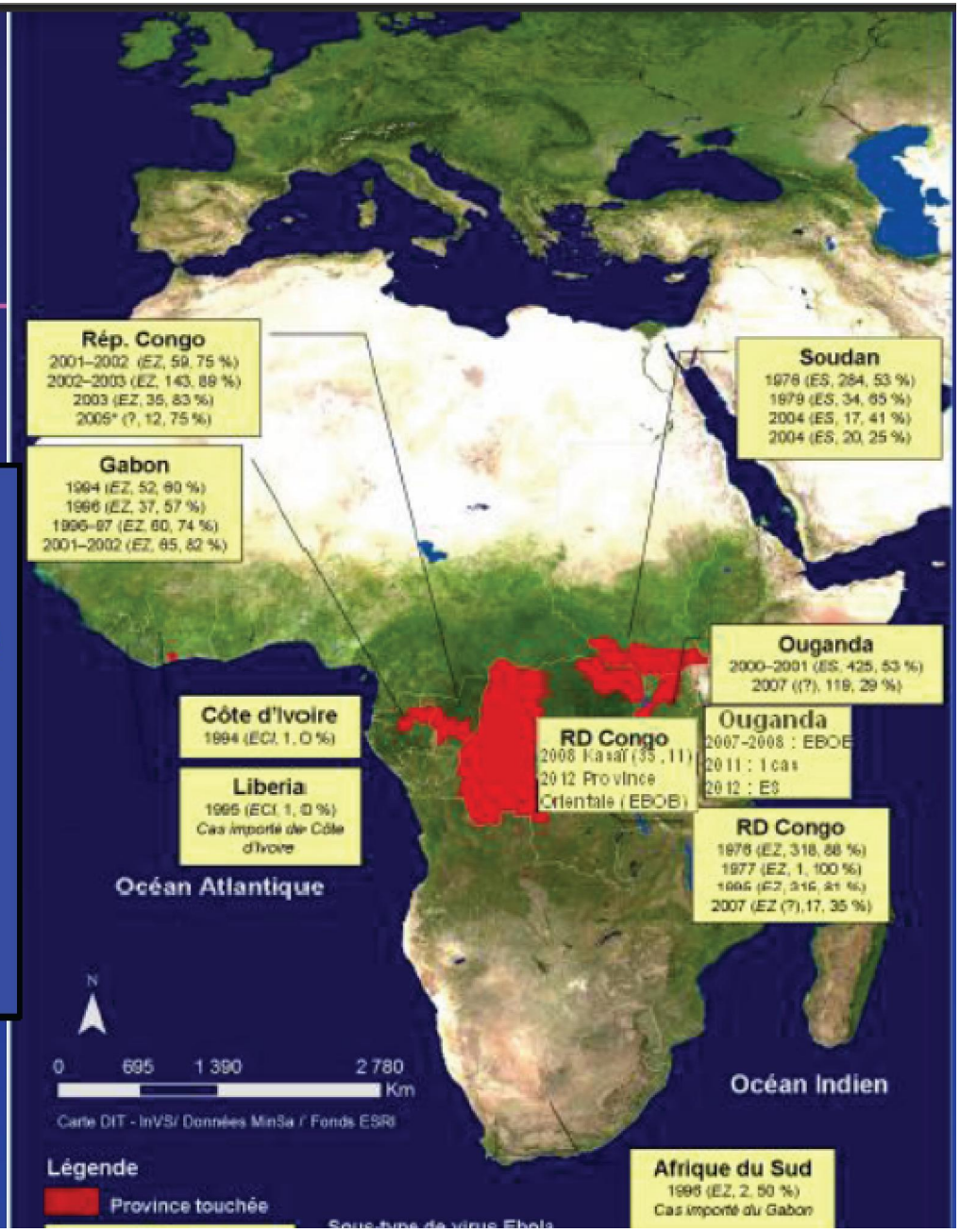
érielle de la lutte contre

aviesan
alliance nationale
pour les sciences de la vie et de la santé

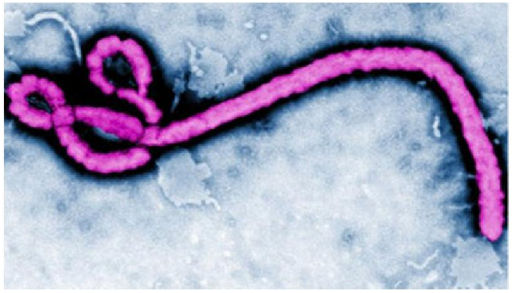
ITMO Microbiologie
et maladies infectieuses

March 10, 2015

- Afrique centrale
- Epidémies de faible taille
- Milieu rural



Filovirus: classification



Filovirus

Genre: *Ebolavirus*

5 Espèces:
Zaire ebolavirus
Sudan ebolabirus
Côte d'Ivoire ebolavirus
Bundibugyo ebolavirus
Reston ebolavirus

Genre: *Marburgvirus*

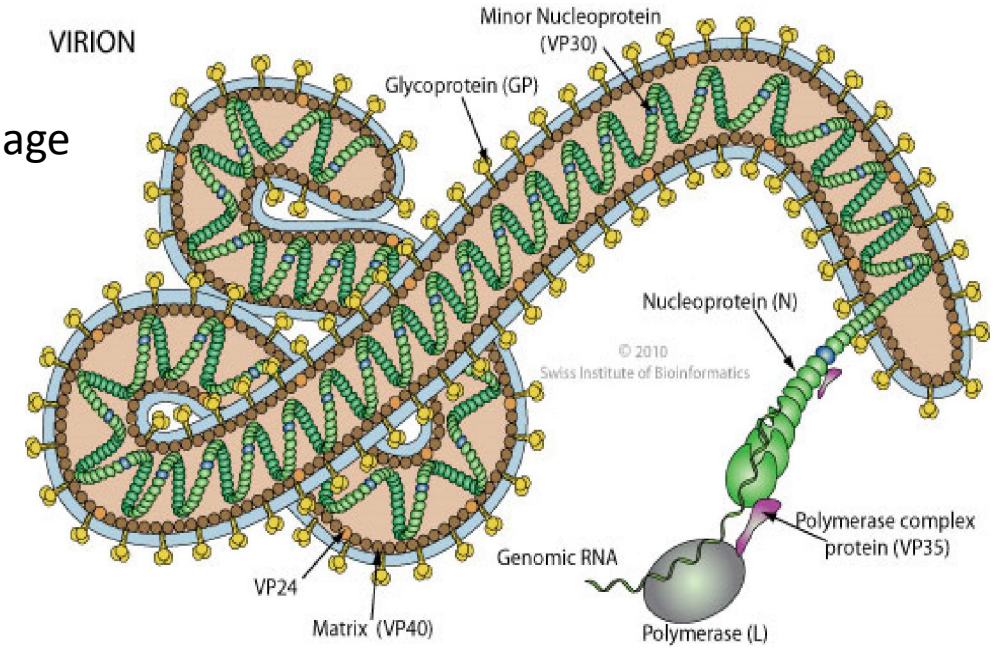
1 Espèce: *Marburg marburgvirus*

- Marburg virus (MARV)
- Ravn virus (RAVV)

Virus Ebola

- Virus ARN simple brin
- Glycoprotéine de surface, cible des anticorps neutralisants
- **Virus enveloppé a priori fragile et sensible à la plupart des désinfectants (eau de javel et ses dérivés et solutions hydro alcooliques) à condition de respecter le temps de contact**
- **Negative-stranded RNA linear genome: 18-19kb, 7 proteins**

GP=Glycoprotéine transmembranaire
NP=Nucléoprotéine nécessaire à l'assemblage de la Capside
VP24= inhibiteur antiviral
VP35= inhibe la production d'IFN
VP30=Transcription anti-terminator
VP40= nécessaire pour assemblage et bourgeonnement de la capside
L-Viral RNA Polymerase



The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Emergence of Zaire Ebola Virus Disease in Guinea — Preliminary Report

Sylvain Baize, Ph.D., Delphine Pannetier, Ph.D., Lisa Oestereich, M.Sc., Toni Rieger, Ph.D., Lamine Koivogui, Ph.D., N'Faly Magassouba, Ph.D., Barrè Soropogui, M.Sc., Mamadou Saliou Sow, M.D., Sakoba Keïta, M.D., Hilde De Clerck, M.D., Amanda Tiffany, M.P.H., Gemma Dominguez, B.Sc., Mathieu Loua, M.D., Alexis Traoré, M.D., Moussa Kolié, M.D., Emmanuel Roland Malano, M.D., Emmanuel Heleze, M.D., Anne Bocquin, M.Sc., Stephane Mély, M.Sc., Hervé Raoul, Ph.D., Valérie Caro, Ph.D., Dániel Cadar, D.V.M., Ph.D., Martin Gabriel, M.D., Meike Pahlmann, Ph.D., Dennis Tappe, M.D., Jonas Schmidt-Chanasit, M.D., Benido Impouma, M.D., Abdoul Karim Diallo, M.D., Pierre Formenty, D.V.M., M.P.H., Michel Van Herp, M.D., M.P.H., and Stephan Günther, M.D.

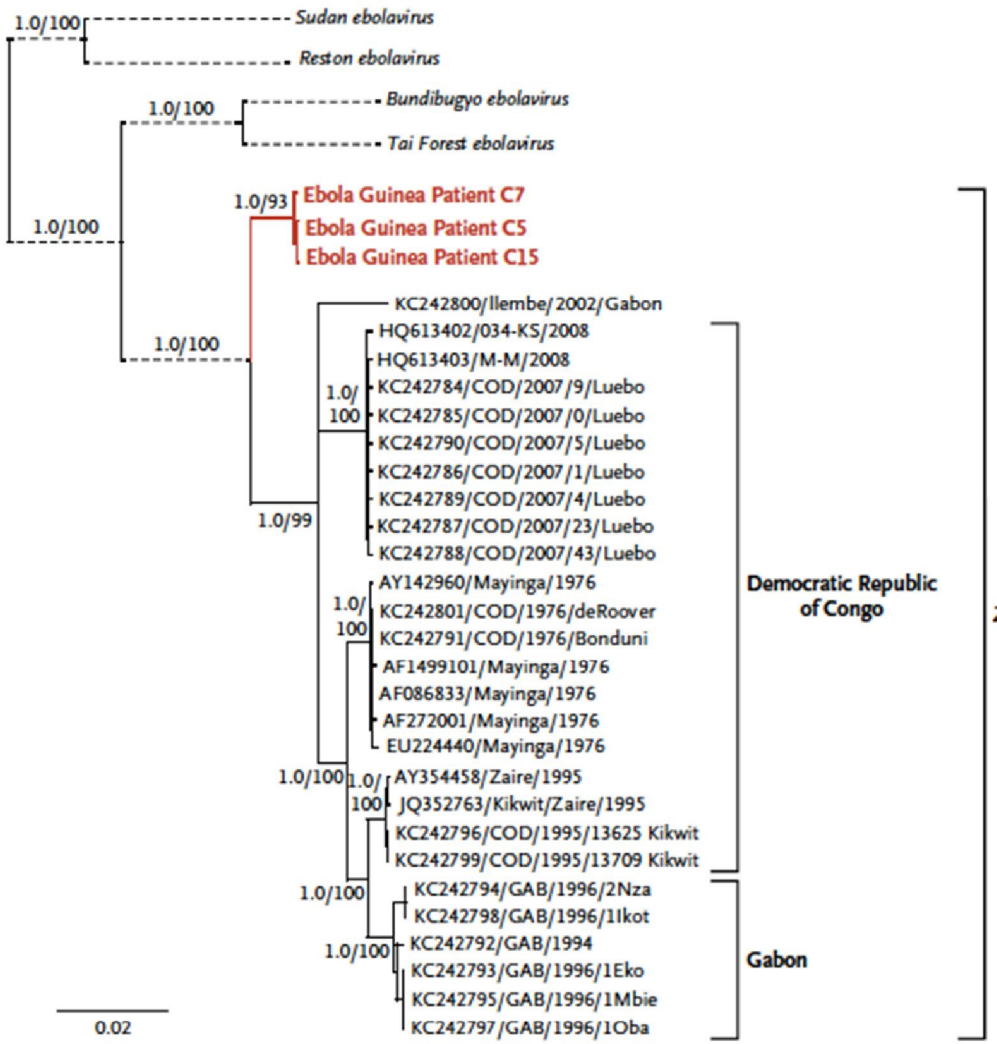


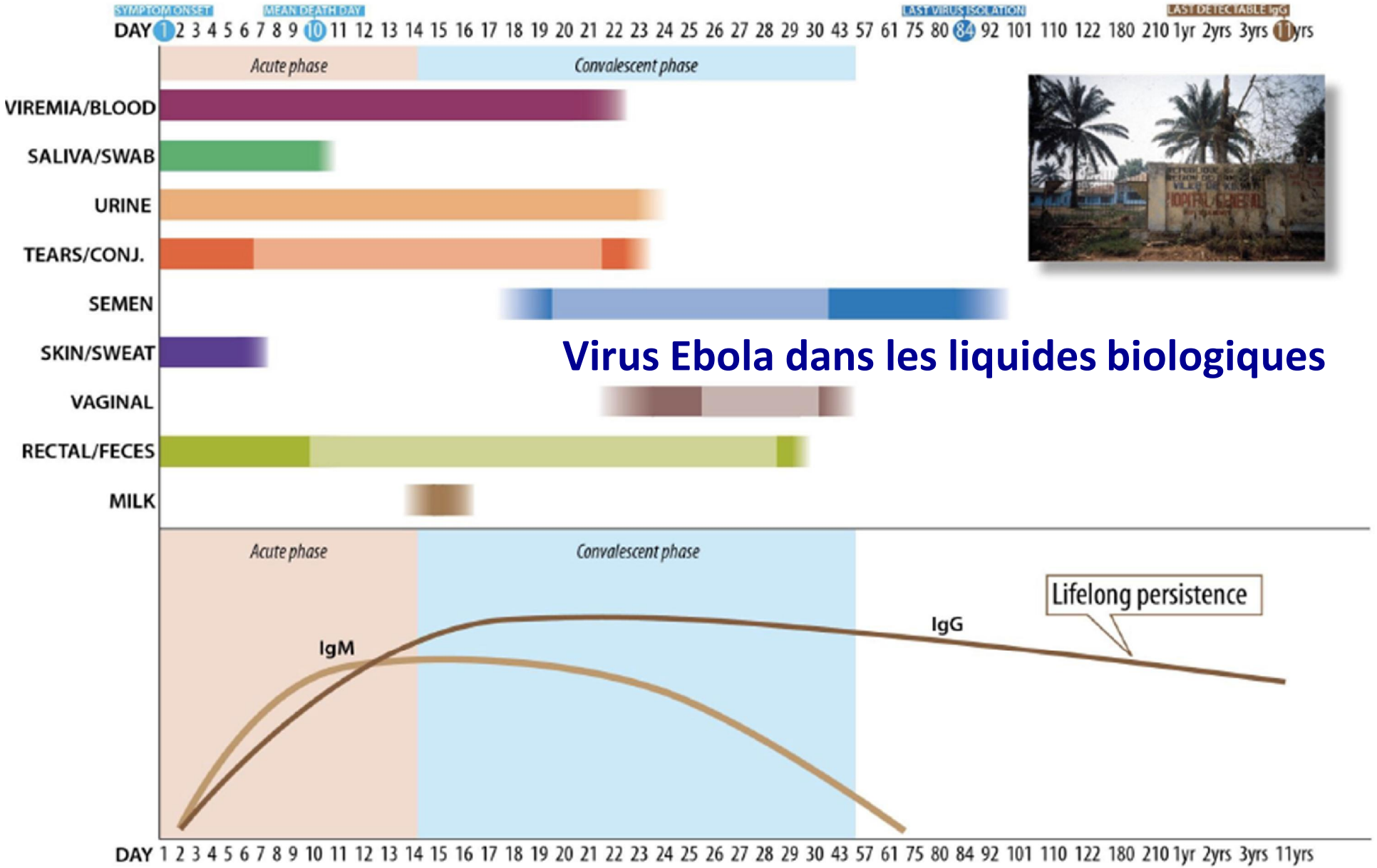
Figure 3. Phylogenetic Analysis of the Ebolavirus Genus, Including the EBOV Strains from Guinea.

The phylogenetic tree was inferred with the use of the Bayesian Markov Chain Monte Carlo method. A second tree that was inferred for the same set of sequences with a maximum-likelihood method confirmed the Bayesian tree (data not shown). Bayesian posterior probabilities and bootstrap percentages (1000 replicates of the maximum-likelihood tree) are shown on the branches. For clarity of presentation, the branches for the non-EBOV species were shortened and condensed (dashed branches). The GenBank accession number, strain designation, country of origin, and year of isolation are indicated on the EBOV branches. The EBOV Guinea strain is available from the European Virus Archive (www.european-virus-archive.com).

Virus variability, impact on MAbs treatments, on diagnostic tests, clinical presentation, …

Laboratoire P4 Jean Mérieux-Inserm, Lyon

Ebola Hemorrhagic Fever



Virus Ebola dans les liquides biologiques

OPEN ACCESS Freely available online

PLOS | PATHOGENS

Shed GP of Ebola Virus Triggers Immune Activation and Increased Vascular Permeability

Beatriz Escudero-Pérez, Valentina A. Volchkova, Olga Dolnik, Philip Lawrence, Viktor E. Volchkov*

Molecular Basis of Viral Pathogenicity, CIRI, INSERM U1111- CNRS UMR5308, Université de Lyon, Université Claude Bernard Lyon 1, Ecole Normale Supérieure de Lyon, Lyon, France

Abstract

During Ebola virus (EBOV) infection a significant amount of surface glycoprotein GP is shed from infected cells in a soluble form due to cleavage by cellular metalloprotease TACE. Shed GP and non-structural secreted glycoprotein sGP, both expressed from the same GP gene, have been detected in the blood of human patients and experimentally infected animals. In this study we demonstrate that shed GP could play a particular role during EBOV infection. In effect it binds and activates non-infected dendritic cells and macrophages inducing the secretion of pro- and anti-inflammatory cytokines (TNFα, IL1β, IL6, IL8, IL12p40, and IL1-RA, IL10). Activation of these cells by shed GP correlates with the increase in surface expression of co-stimulatory molecules CD40, CD80, CD83 and CD86. Contrary to shed GP, secreted sGP activates neither DC nor macrophages while it could bind DCs. In this study, we show that shed GP activity is likely mediated through cellular toll-like receptor 4 (TLR4) and is dependent on GP glycosylation. Treatment of cells with anti-TLR4 antibody completely abolishes shed GP-induced activation of cells. We also demonstrate that shed GP activity is negated upon addition of mannose-binding sera lectin MBL, a molecule known to interact with sugar arrays present on the surface of different microorganisms. Furthermore, we highlight the ability of shed GP to affect endothelial cell function both directly and indirectly, demonstrating the interplay between shed GP, systemic cytokine release and increased vascular permeability. In conclusion, shed GP released from virus-infected cells could activate non-infected DCs and macrophages causing the massive release of pro- and anti-inflammatory cytokines and effect vascular permeability. These activities could be at the heart of the excessive and dysregulated inflammatory host reactions to infection and thus contribute to high virus pathogenicity.

Citation: Escudero-Pérez B, Volchkova VA, Dolnik O, Lawrence P, Volchkov VE (2014) Shed GP of Ebola Virus Triggers Immune Activation and Increased Vascular Permeability. PLoS Pathog 10(11): e1004509. doi:10.1371/journal.ppat.1004509

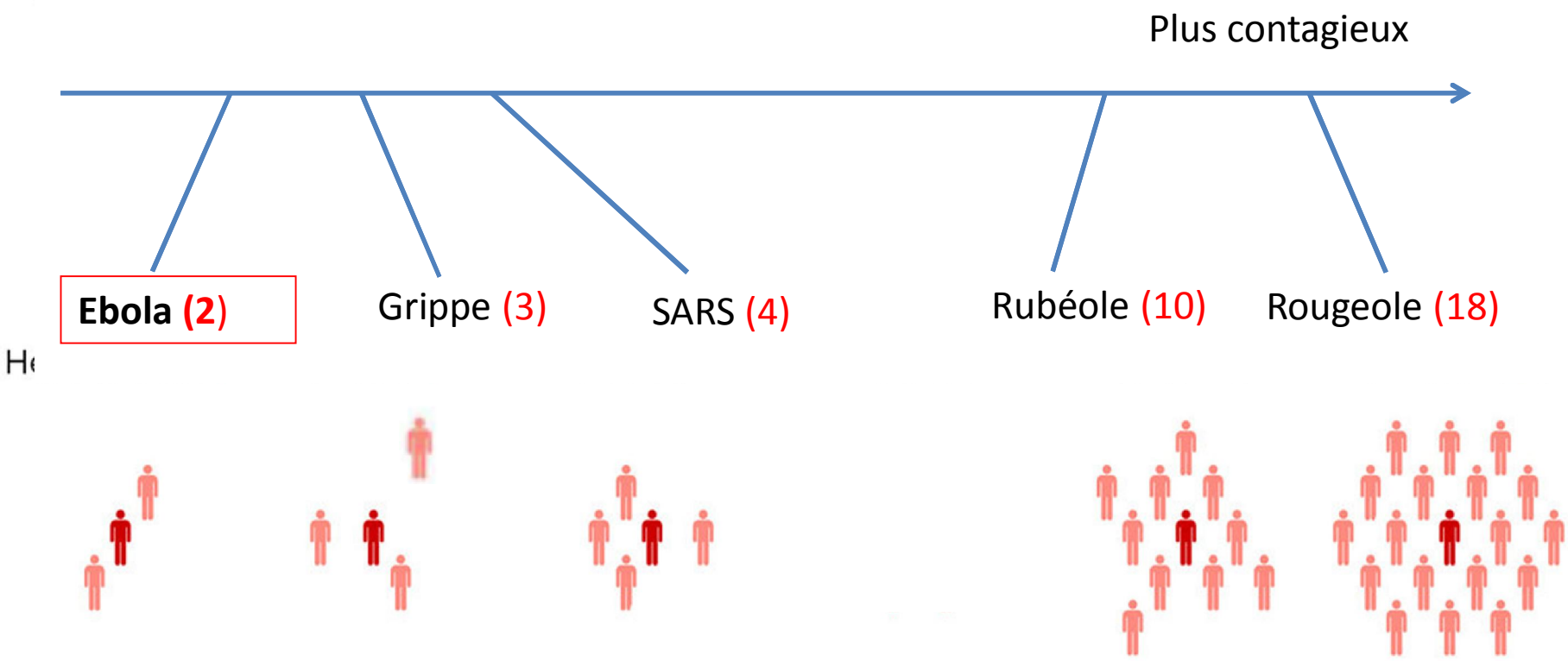
Editor: Jens H. Kuhn, Division of Clinical Research, United States of America

Received May 16, 2014; **Accepted** October 9, 2014; **Published** November 20, 2014

Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. All relevant data are within the paper and its

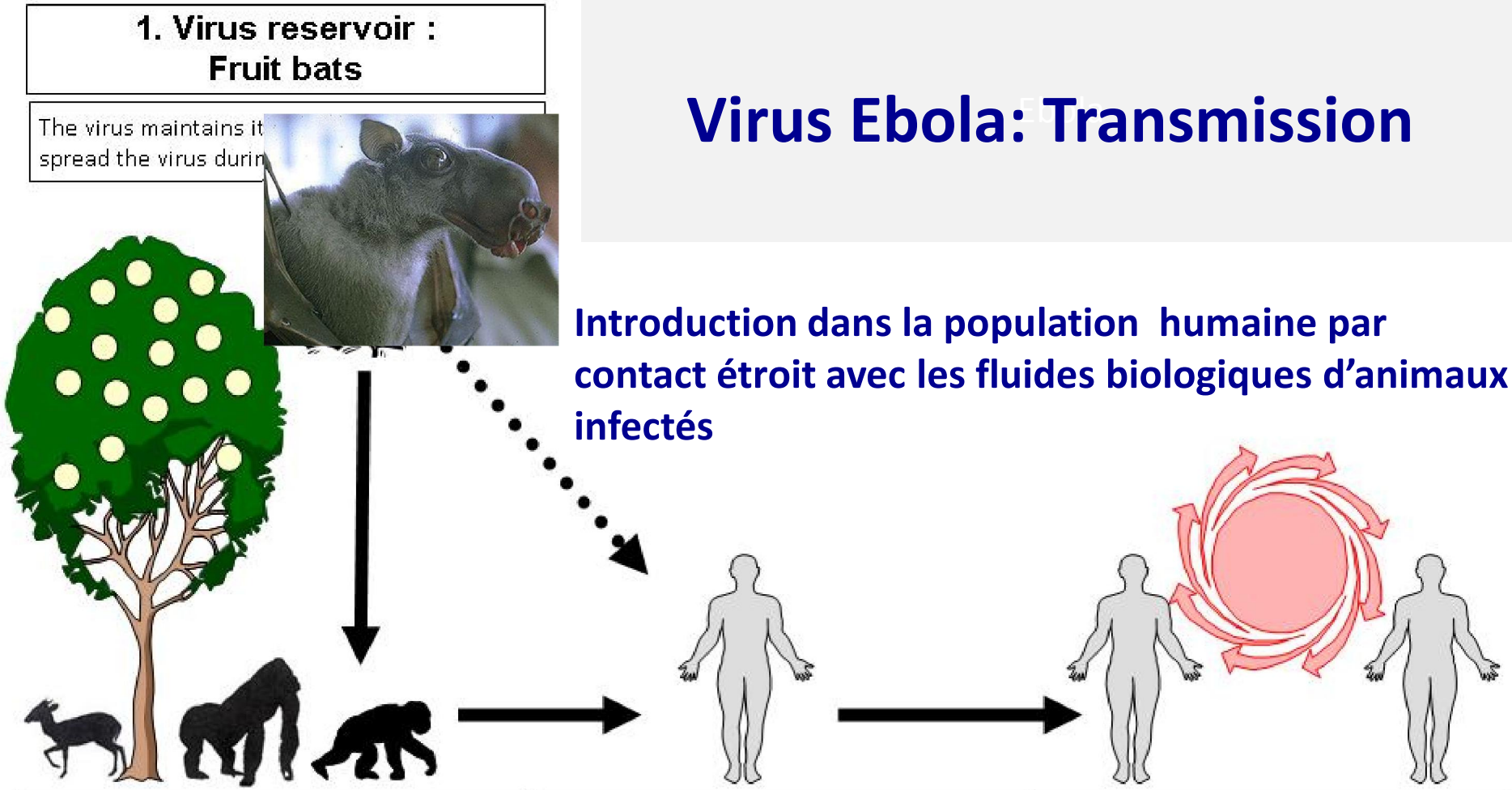
R_0: une « échelle de Richter » pour les maladies transmissibles

R_0: nombre moyen de nouveaux cas générés par personnes malades



Nishira. Euro Surveil 2014

Virus Ebola: Transmission



Introduction dans la population humaine par contact étroit avec les fluides biologiques d'animaux infectés

2. Epizootic in primates	3. Primary human infection	4. Secondary transmission
Infected fruit bats enter in direct or indirect contact with other animals and pass on the infection, sometimes causing large-scale epidemics in gorillas, chimpanzees and other monkeys or mammals (e.g. forest antelopes).	Humans are infected either through direct contact with infected bats (rare event), or through handling infected dead or sick animals found in the forest (more frequent)	Secondary human-to-human transmission occurs through direct contact with the blood, secretions, organs or other body fluids of infected persons. High transmission risk when providing direct patient care or handling dead bodies (funerals).

Sciencexpress

Genomic surveillance elucidates Ebola virus origin and transmission during the 2014 outbreak

- Le virus a diffusé à partir de l'Afrique Centrale par des animaux infectés au cours des 10 dernières années
- Puis transmission interhumaine

"In memoriam: Tragically, five co-authors, who contributed greatly to public health and research efforts in Sierra Leone, contracted EVD in the course of their work and lost their battle with the disease before this manuscript could be published. We wish to honor their memory."

JVI Journals.ASM.org

March 2015 Volume 89 Number 5

Ebola Virus and Severe Acute Respiratory Syndrome Coronavirus Display Late Cell Entry Kinetics: Evidence that Transport to NPC1$^+$ Endolysosomes Is a Rate-Defining Step

Rebecca M. Mingo, James A. Simmons, Charles J. Shoemaker,* Elizabeth A. Nelson, Kathryn L. Schornberg, Ryan S. D'Souza, James E. Casanova, Judith M. White

JVI Journals.ASM.org

January 2015 Volume 89 Number 1

Simian Hemorrhagic Fever Virus Cell Entry Is Dependent on CD163 and Uses a Clathrin-Mediated Endocytosis-Like Pathway

Yingyun Cai,[a] Elena N. Postnikova,[a] John G. Bernbaum,[a] Shuiqing Yu,[a] Steven Mazur,[a] Nicole M. Delulis,[a] Sheli R. Radoshitzky,[b] Matthew G. Lackemeyer,[a] Adam McCluskey,[c] Phillip J. Robinson,[d] Volker Haucke,[e] Victoria Wahl-Jensen,[a] Adam L. Bailey,[f] Michael Lauck,[f] Thomas C. Friedrich,[f] David H. O'Connor,[f] Tony L. Goldberg,[f] Peter B. Jahrling,[a] Jens H. Kuhn[a]

ELSEVIER

Contents lists available at ScienceDirect

Virology

journal homepage: www.elsevier.com/locate/yviro

Cell entry by a novel European filovirus requires host endosomal cysteine proteases and Niemann–Pick C1

Melinda Ng[a], Esther Ndungo[a], Rohit K. Jangra[a], Yingyun Cai[b], Elena Postnikova[b], Sheli R. Radoshitzky[c], John M. Dye[c], Eva Ramírez de Arellano[d], Ana Negredo[d], Gustavo Palacios[c], Jens H. Kuhn[b], Kartik Chandran[a,*]

Available online 11 October 2014

ELSEVIER

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

A polymorphism of the TIM-1 IgV domain: Implications for the susceptibility to filovirus infection

Makoto Kuroda[a], Daisuke Fujikura[b], Osamu Noyori[a,1], Masahiro Kajihara[a], Junki Maruyama[a], Hiroko Miyamoto[a], Reiko Yoshida[a], Ayato Takada[a,c,d,*]

Available online 4 November 2014

JVI Journals.ASM.org

April 2014 Volume 88 Number 8

Role of Phosphatidylserine Receptors in Enveloped Virus Infection

Kouki Morizono,[a,b] Irvin S. Y. Chen[a,b,c]

Division of Hematology and Oncology, Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, California, USA[a]; UCLA AIDS Institute, David Geffen School of Medicine, University of California, Los Angeles, California, USA[b]; Departments of Microbiology, Immunology, and Molecular Genetics, David Geffen School of Medicine, University of California, Los Angeles, California, USA[c]

EBOLA RECEPTORS ?

Update : 02.2015

The NEW ENGLAND JOURNAL of MEDICINE

April 2014

BRIEF REPORT

Emergence of Zaire Ebola Virus Disease in Guinea

Sylvain Baize, Ph.D., Delphine Pannetier, Ph.D., Pharm.D., Lisa Oestereich, M.Sc., Toni Rieger, Ph.D., Lamine Koivogui, Ph.D., N'Faly Magassouba, Ph.D., Barrè Soropogui, M.Sc., Mamadou Saliou Sow, M.D., Sakoba Keïta, M.D., Hilde De Clerck, M.D., Amanda Tiffany, M.P.H., Gemma Dominguez, B.Sc., Mathieu Loua, M.D., Alexis Traoré, M.D., Moussa Kolié, M.D., Emmanuel Roland Malano, M.D., Emmanuel Heleze, M.D., Anne Bocquin, M.Sc., Stephane Mély, M.Sc., Hervé Raoul, Ph.D., Valérie Caro, Ph.D., Dániel Cadar, D.V.M., Ph.D., Martin Gabriel, M.D., Meike Pahlmann, Ph.D., Dennis Tappe, M.D., Jonas Schmidt-Chanasit, M.D., Benido Impouma, M.D., Abdoul Karim Diallo, M.D., Pierre Formenty, D.V.M., M.P.H., Michel Van Herp, M.D., M.P.H., and Stephan Günther, M.D.

SUMMARY

In March 2014, the World Health Organization was notified of an outbreak of a communicable disease characterized by fever, severe diarrhea, vomiting, and a high fatality rate in Guinea. Virologic investigation identified *Zaire ebolavirus* (EBOV) as the causative agent. Full-length genome sequencing and phylogenetic analysis showed that EBOV from Guinea forms a separate clade in relationship to the known EBOV strains from the Democratic Republic of Congo and Gabon. Epidemiologic investigation linked the laboratory-confirmed cases with the presumed first fatality of the outbreak in December 2013. This study demonstrates the emergence of a new EBOV strain in Guinea.

Souche du virus Ébola en Guinée

- Souche Ébola-Zaïre, variant Makona : **EBOV/Mak**
  - Ebola virus/H.sapiens-wt/GIN/2014/Makona

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Emergence of Zaire Ebola Virus Disease in Guinea

Rivière Makona

(Kuhn JH, Andersen KG, Baize S et *al. Viruses* 2014;6:4760-99)

Pourquoi cette épidémie est différente des précédentes

- **Nombre de cas très important :** > 23 000 cas au 24/01/2015 **Environ 9 000 décès**
- **Durée prolongée :** > 1 an
- **Extension à plusieurs pays** d'Afrique de l'Ouest
- **Circulation virus dans zones urbaines :** échanges nombreux, zones plus difficiles à surveiller
- **Débordement des structures sanitaires** locales et des ONG spécialisées
- **Aspects Culturels**

Quelques Facteurs favorisants la diffusion de l'épidémie

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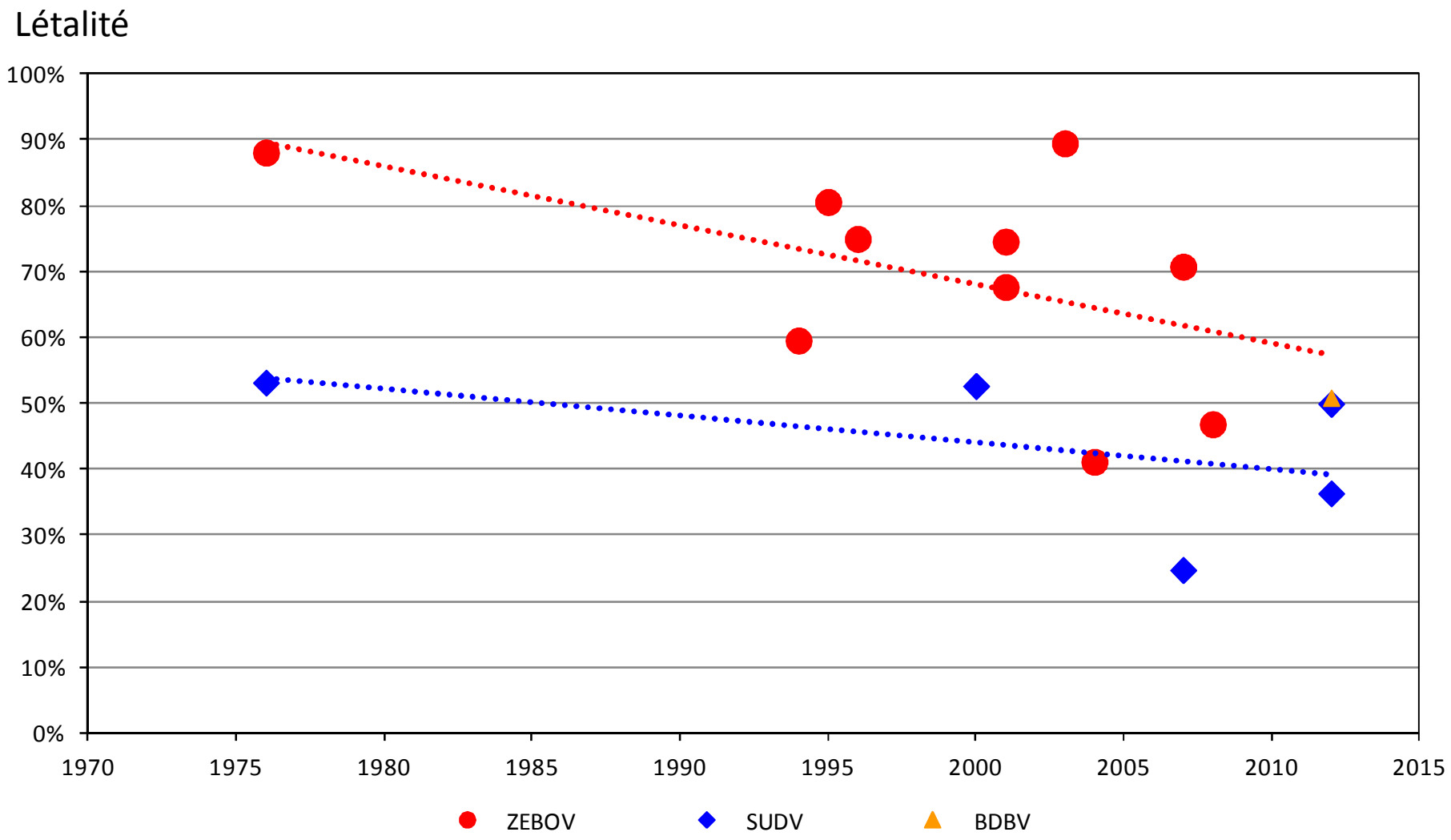
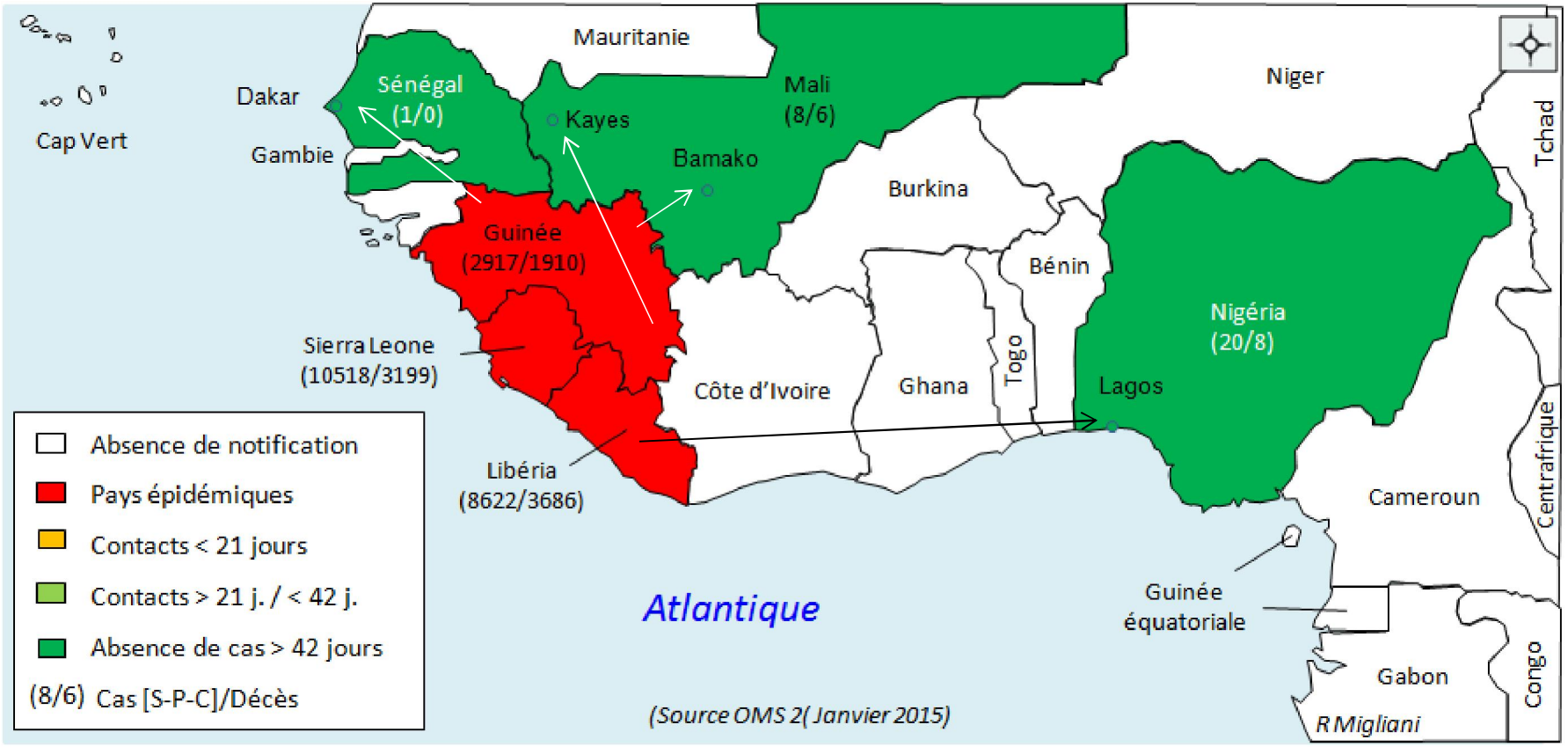
- Apparue dans un zone d'Afrique jusque là indemne, donc non préparée
  - méconnaissance de la maladie dans la population
  - d'où retard aux mesures de contrôle de l 'épidémie
- Non confiance de la population dans les structures de santé et dans les autorités sanitaires
- Coutumes funéraires
- Déforestation
- Augmentation du niveau de vie et de l'utilisation des taxis brousse

Maladie à létalité élevée



ZEBOV : souche Zaïre Ebolavirus , SUDV : souche Sudan Ebolavirus, BDBV : souche Bundibugyo virus

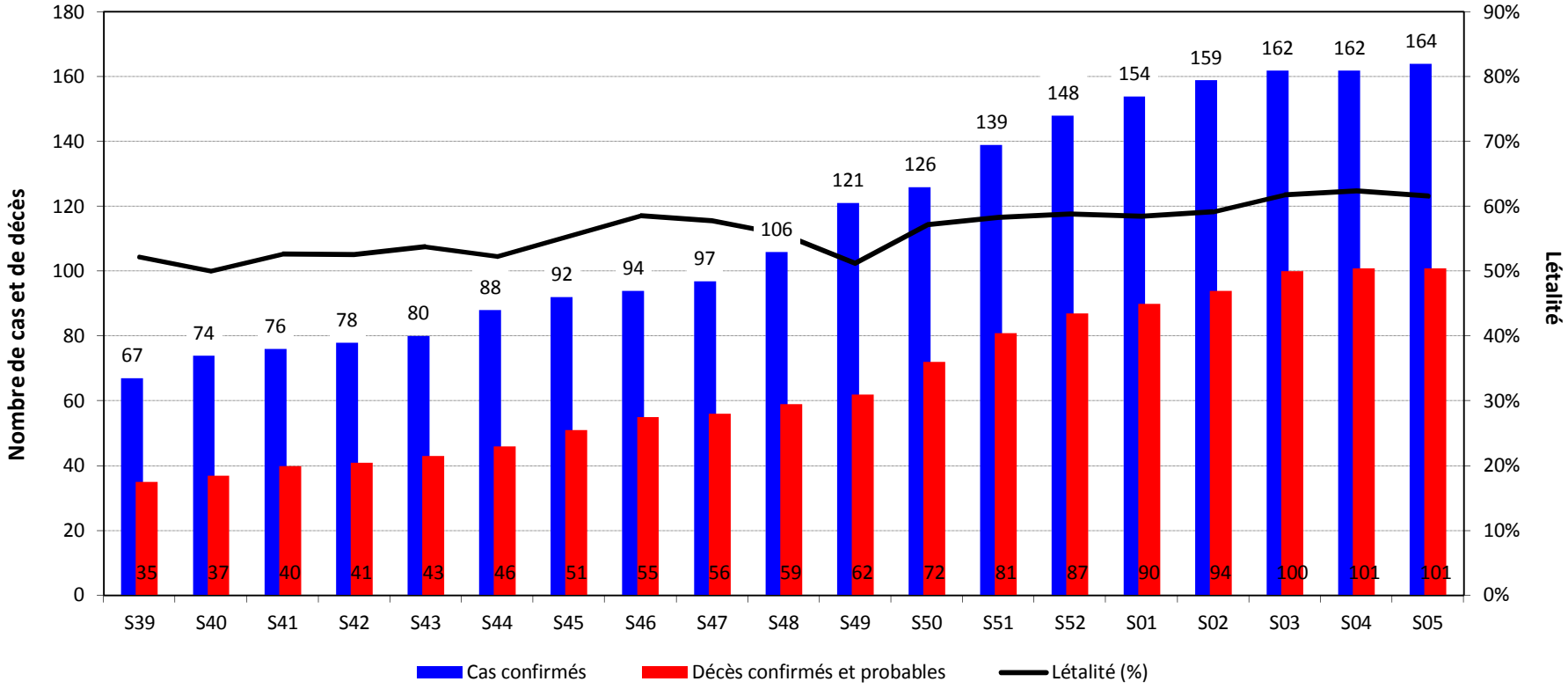
Situation de l'épidémie d'Ébola en Afrique de l'Ouest



Le Mali a éliminé officiellement Ebola (« Ebola free ») depuis le 18 janvier

Exportation de cas dans les pays frontaliers

Personnels de santé infectés par Ébola en Guinée depuis la semaine 39/2014



Une incidence difficilement maitrisable en novembre-décembre (~5-10 cas/semaine)

Baisse s'est amorcée fin janvier

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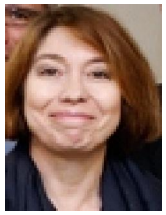
RÉPUBLIQUE FRANÇAISE
Premier ministre

French Task Force on Ebola (Oct 2014)

National Coordinator

Pr Jean François Delfraissy,

Under the authority of the Prime Minister



Diplomacy

Mrs Christine Fages,

Diplomat

Health

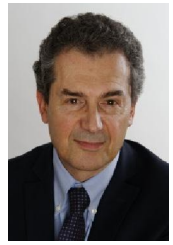
Pr Thierry Debord,
Professor of Medicine

Interior/Security

M. Pierre Lieutaud, Prefect

Research

Pr Yves Levy, CEO of Inserm,
President of AVIESAN



Administrative Chief Officer : Anne-Claire Amprou

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RÉPUBLIQUE FRANÇAISE
Premier ministre

French Task Force on Ebola

Main tasks in october 2014 :

- Avoid possible contamination in France
- Support affected countries to curb the epidemic dynamics
- Prevent the spread of the disease to neighboring countries
- Coordination and funding of translational research on Ebola

Coordinated response in Guinea :

- Support political coordination in Guinea
- HWs mobilisation, training, and protection
- Diagnosis and Treatment
- Sensitization, education and prevention
- Disease control measures

Diagnosis - Care

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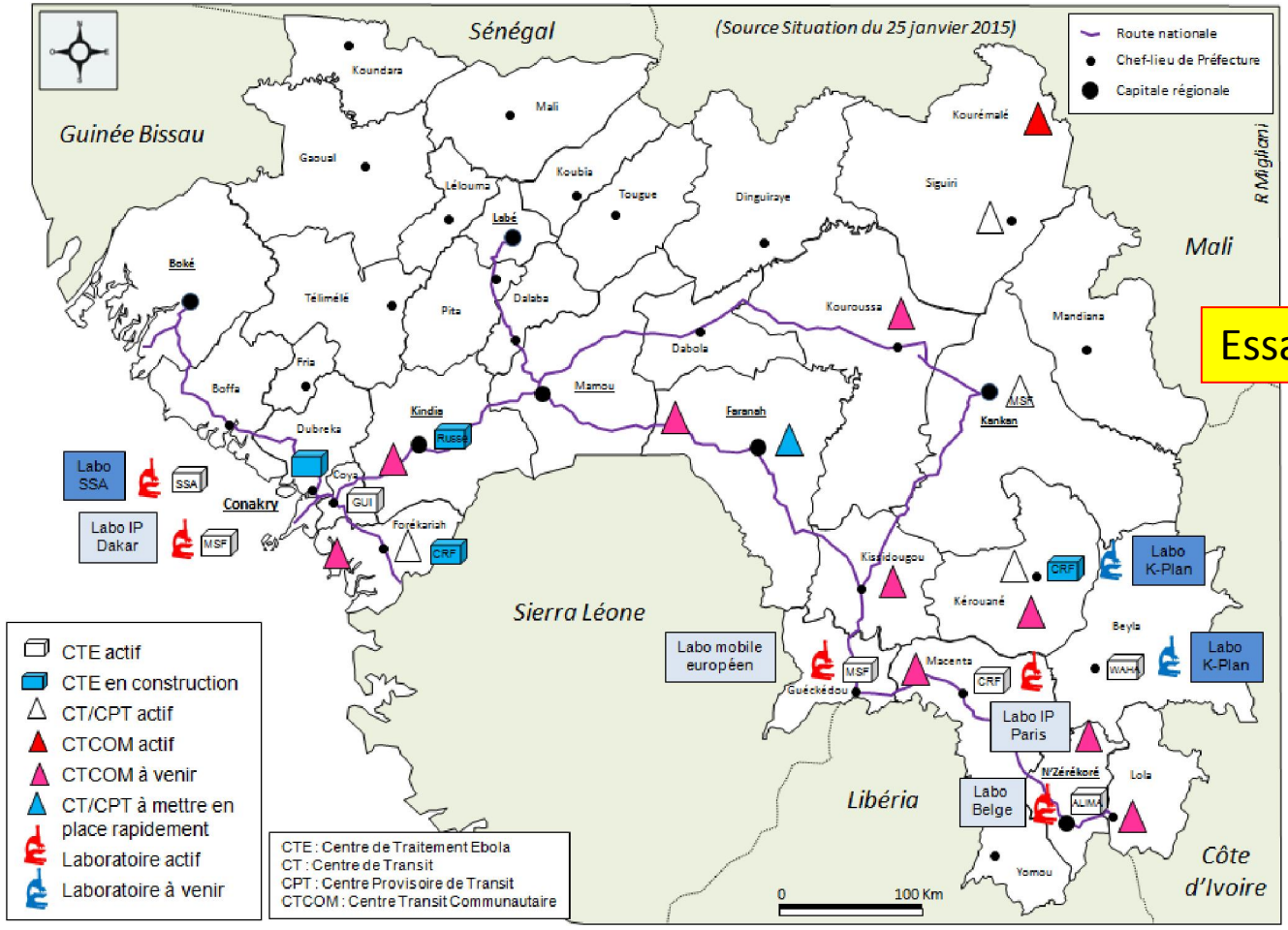
- Laboratories
  - Donka de Conakry
  - Mobile EU lab Guéckédou (additional mobile EU lab in development)
  - Macenta ETU
  - Beyla ETU – under construction
  - Kerouane ETU - under construction
  - Institut Pasteur – under construction (2016)
- ETU
  - Macenta (50 beds, opens 14 November); *FRC – French Red Cross*
  - Beyla (30-50 beds, opens mid-December) ; *WAHA – Women and Health Alliance International*
  - Kérouané (30-50 beds, opens early January); *FRC – French Red Cross*
  - Renovating the Forecariah transit center (20 beds, completion mid-December); *FRC – French Red Cross*
  - *N'zérékoré (40 beds, opens end of November) ; ALIMA – The Alliance for International Medical Action*

Structures de prise en charge des cas d'Ébola en Guinée en février 2015



Augmentation du nombre de structures :

- 2 CTE, 1 CT = 150 lits → 5 CTE, 1 CTS, 4 CT, 1 CTCOM = 444 lits
- 2 laboratoires → 5 laboratoires = <1% Cas suspects +++

Centre de Traitement des Soignants (CTS) inauguré le 19 janvier – fonctionnel le 23 janvier

Visite du CTS en Guinée le 7 février 2015

FRENCH EBOLA RESPONSE

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Premier ministre

More than **115** MILLIONS Euros

EBOLA RESPONSE IN WEST AFRICA

GUINEA

ETUs

- Macenta (50 beds)
- Beyla (20-30 beds)
- Kérouané (30-50 beds)
- Forecariah (20 beds)
- N'zérékoré (40 beds)

Financing by French Gov 150 French HCW & 800 Guinean

Training Center

- France & Guinea
- 7days, 50 instructors for each
- 200 trainees/month
- First course Nov 15th

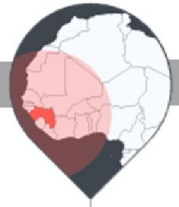
Conakry Medical Unit

- 20 beds
- 30 French HCW & 50 Guinean
- Estimate Opening Dec

Supply PPE and medical assets

Supply extra food aid

Strengthen basic health services



WEST AFRICA

Financing of prevention plans EBOLA outbreak (Mali , Cameroun & Ivory Coast)

Strengthen labs in 7 countries in West AFRICA

More than **110** MILLIONS Euros

INTERNATIONAL ORGANIZATIONS

Technical Assistance

- French Experts embedded in UNMEER
- Financing extra support to WHO

More than **5** MILLIONS Euros

MEDICAL EVACUATION

- **Medical evacuation within Guinea**
- **MEDEVAC coordination through EU Mechanism**
- **Emergency transport and hospitalization in France**

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Premier ministre

ORGANIZATION OF THE « RESEARCH » POLE

RESEARCH IN A PUBLIC HEALTH CRISIS 'THE EBOLA MODEL'

ORGANIZATION OF THE « RESEARCH » POLE (72,5 M€)

Global program responsibility : Y. Levy (Pdt Aviesan)

- Coordination of the pole "research"
- Strategic and programmatic orientations
- Identification of priorities
- Selection of projects and actions
- Consolidated view of budgets
- Organization of the French institutional representation
- Coordinating communication
- Interactions with funding agencies and other institutions involved

Scientific Committee
Evaluation
Scientific monitoring of projects

Animation and scientific watch: Y. Yazdanpanah (IMMI) - REACTing

- International Scientific watch
- scientific Expertise
- Animation of research teams
- Proposals for action and research programs
- Scientific monitoring of projects (results and publications)

Operational management of projects

- Up to each institution responsible for a project
- Implementation of research projects (budget, legal, human resources ...)

RESPONSE TO EBOLA EPIDEMIC: 2014

- **Diagnostic: NRC for VHF/INSERM P4 lab in Lyon**

  Emergence of Zaire Ebola Virus Disease in Guinea-Preliminary Report

  Baize S et al, N Engl J Med. 2014 Apr 16.

- **First meeting, July 17th : assessment of French research teams involved and of on-going research projects**

- **Following meetings: 5 and 19 August, 2 and 26 September, 20 October, 18 November**

  - ✓ Research priorities: Diagnostic, Treatment, Vaccination, clinical research, Social and Human sciences
  - ✓ Funding: seed money from Aviesan and additional funding

PROJECTS LAUNCHED

- **Diagnostic:**
  - ✓ Standardisation of a secure qualitative and quantitative molecular diagnosis protocol for filovirus infections; *University Aix-Marseille; Institut Pasteur; CIRMF-Gabon*
- **Treatment:**
  - ✓ Identification of molecules that could inhibit EBOV replication and be rapidly transfered to clinic; *Enyo-Pharma; Inserm*
- **Clinical trial:**
  - ✓ Efficacy of favipiravir in humans; *Inserm; Ministry of Health Guinea; Institut Pasteur*
- **Social and Human Sciences:**
  - ✓ Ebola Epidemic and social production of trust in Senegal; *IRD; CNRS; UCAD and Ministry of Health, Senegal*
  - ✓ Rumors, disputes and controversies: perspectives from the digital world; IRD; McGill University; Columbia University; WHO
- **Vaccines : Coll J&J/Inserm/LSHTM (IMI2); DC-based vaccines (Inserm); measles live vaccine (IP)**

Les produits qui semblent prometteurs

Classe	Exemple	Données d'inocuité	Efficacité chez l'animal	Problèmes potentiels
Anticorps monoclonaux	Zmapp	Données historiques sur les Mabs	Macaque 100%	Disponibilité
Antiviral (petite molecule)	Favipiravir	Enregistré pour la grippe	faible	Oral : 18-36 comprimés/jour
Antiviral (petite molecule)	Brincidofovir	Phase III pour CMV	In vitro	Données chez l'animal
Antiviral (ARN)	siRNA	Phase I administration unique	Macaque 100%	Disponibilité
Stinulateur le la réponse immunitaire	Interféron	Enregistré pour les hépatites	Faible	Fièvre
Contrôle de l'hémorrhagie	FX06	Phase II en cardiologie	Théorique	Pas de données

Les médicaments à tester en priorité

- Deux médicaments enregistrés pour d'autres indications sont proposées parce qu'ils sont efficaces contre le virus Ebola en culture de cellules (in vitro)
  - Le **favipiravir** est en cours d'étude en Guinée depuis décembre. Des résultats préliminaires sont disponibles
  - Une étude avec le **brincidofovir** a commencé au Libéria en janvier, mais elle a été interrompue en février
- Deux produits développés spécifiquement contre la maladie à Ebola sont prêts pour entrer en clinique, peut-être en Sierra Leone
  - le cocktail d'anticorps monoclonaux **ZMapp** (Leafbio, USA)
  - le **siRNA** de Tekmira, USA, Canada

Les deux vaccins les plus avancés sur le plan de l'évaluation clinique

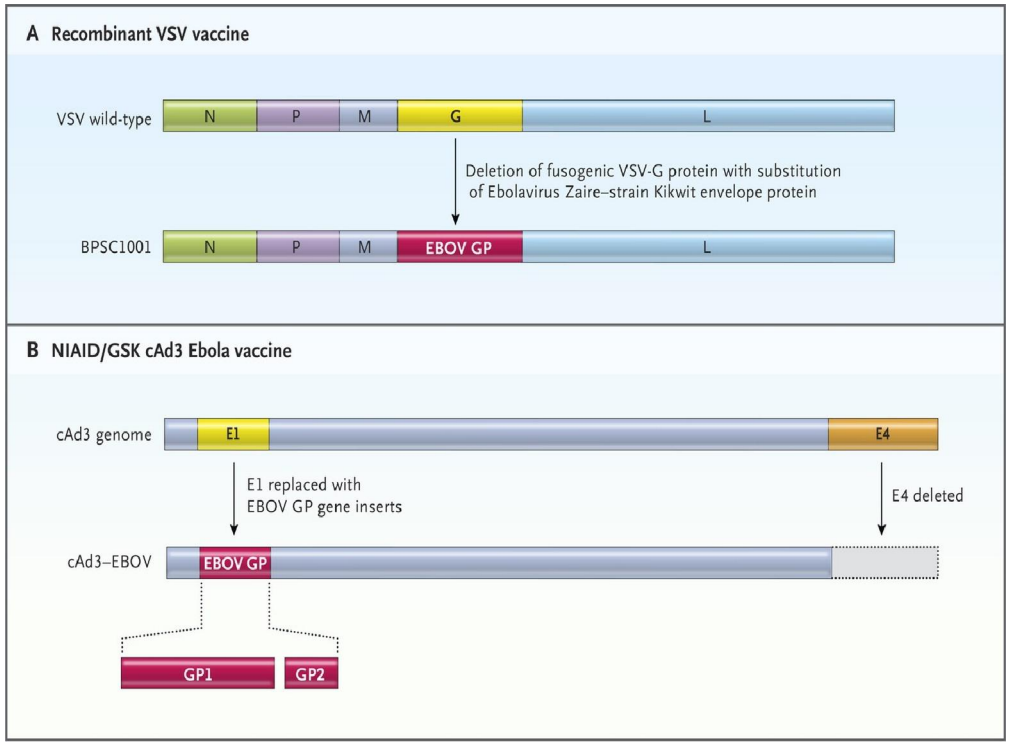
A- rVSV-ZEBOV – Virus de la stomatite vesiculaire recombinant

Merck Vaccines/NewLink Pharmaceuticals/Public Health Agency of Canada

800 flacons donnés à l'OMS par le gouvernement du Canada en août 2014

B - ChAd3-ZEBOV – Adenovirus 3 du chimpanzee

GSK/NIAID



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

World Health Organization

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

- **Coordinator:** Hervé Raoul, BSL4 lab in Lyon
- **Participants:** Inserm, MOH Guinea, Bernhard-Nocht Institute, Institut Pasteur, ENS, Aix Marseille University, Ruprecht-Karls University Heidelberg, University Amsterdam, University Utrecht, UCAD, Public Health England
- **Total budget:** 2 892 171 euros

JIKI TRIAL

Sponsor

- ✓ **Inserm**: ITMO Santé Publique - Pôle Recherche Clinique, Claire Levy-Marchal

Principal Investigators

- ✓ **Denis Malvy** (Head of Infectious diseases department, Bordeaux Univ Hospital & Inserm unit 897, Bordeaux)
- ✓ **Sakoba Keita** (Guinea's national coordinator for the fight against Ebola, Ministry of health, Conakry)

Scientific Coordonators

- ✓ **Xavier Anglaret** (Programme PACCI/site ANRS, Abidjan, Côte d'Ivoire & Inserm unit 897, Bordeaux)
- ✓ **France Mentré** (Inserm unit 1137, IAME & CM Nord REACTing, Paris)

JIKI TRIAL

- **Hypotheses**
  - ✓ Efficacy of favipiravir correlates negatively with time since first symptoms
  - ✓ Favipiravir for EVD should be given at higher doses than that previously tested in studies in human with influenza

- **Primary objective:** efficacy of high-dosed favipiravir in reducing mortality in humans with EVD

- **Secondary objectives**
  - ✓ Evolution of EBOV plasma RNA and infectious loads under treatment;
  - ✓ Tolerance of favipiravir;
  - ✓ Viral micro-diversity of EBOV;
  - ✓ Trough concentrations of favipiravir;
  - ✓ Factors associated with mortality , cure at Day 30, toxicity

The drug favipiravir will be tested in clinical trials against Ebola next month

- **Social and Behavioral Science study**
  - ✓ To ensure that the trial is culturally sensitive, gender-aware and reflexive

JIKI TRIAL

- **Design:** non-comparative, proof-of-concept, phase II trial
- **Settings:** three EVD care centers in Guinea
  - ✓ December 2014: MSF EVD care center in Gueckedou
  - ✓ January 2015: French Red Cross EVD care center in Macenta and ALIMA EVD care center in Nzerekore

- **Inclusion criteria:**
  - ✓ Age ≥1 year
  - ✓ EVD confirmed by a positive qualitative PCR test
  - ✓ Informed consent
- **Non inclusion-criteria:**
  - ✓ Pregnancy (emergency use)
  - ✓ Inability to take the drug (encephalopathy; severe vomiting)

JIKI TRIAL

- **Primary outcome:** mortality by Day 14

- **Secondary outcomes:**
  - ✓ Evolution of EBOV plasma RNA and infectious loads
  - ✓ Grade 3-4 adverse events
  - ✓ Viral micro-diversity of EBOV (including resistance mutations)
  - ✓ Trough concentrations of favipiravir
  - ✓ Cure at Day 30
    - 4 days without fever or significant symptoms AND
    - able to feed and walk independently AND
    - two consecutive negative qualitative PCR

Favipiravir in patients with Ebola Virus Disease: early results of the JIKI trial in Guinea

(Inserm C1463 - EEUU H2020 666092)

Daouda SISSOKO, Elin FOLKESSON, M'lebing ABDOUL, Abdoul Habib BEAVOGUI, Stephan GUNTHER, Susan SHEPHERD, Christine DANEL, France MENTRE, Xavier ANGLARET, Denis MALVY

Inserm U897, University of Bordeaux, France
Médecins Sans Frontières (MSF), Belgium
Alliance for International Medical Action (ALIMA), France
Centre de Formation et de Recherche en Santé Rurale de Maférinyah, Guinea
Bernhard-Nocht-Institut für Tropenmedizin, Germany
Inserm U1137, Paris Diderot University, France

All authors declared no conflict of interest

COHORT OF RECOVERED PATIENTS FROM EBOLA IN GUINEA

- **Sponsor:** Inserm
- **Principal Investigators:**
  - ✓ Dr Mounié Barry; CHU Donka-Ministry of Health, Guinea
  - ✓ Pr Eric Delaporte; IRD-Inserm, France
- **Main objective:** evaluate clinical, biological (immuno and virology) and social outcomes of Ebola Virus Disease (EVD)
- **General Design:**
  - ✓ Multidisciplinary, multicentric prospective observational cohort study of adults and children who recovered from EVD.
  - ✓ Three hundred patients followed 18 months
- **Beginning:** February 2015

DEVELOPEMENT OF DENDRITIC CELL-BASED PROPHYLACTIC AND THERAPEUTIC EBOLA VACCINES

- **Principal Investigators:**
  - ✓ Pr Yves Lévy; VRI/inserm/Upec, Créteil, France
  - ✓ Dr Hervé Raoul, BSL - 4 Inserm Mérieux, France
- **Main objective:** Development of recombinant antibodies (rAb) targeting dendritic cells (DC) and fused to Ebola antigen (Ag), in order to favor activation of antiviral specific immune responses
- **General Design:**
  - ✓ Evaluation of immune responses and protection conferred by the DC-based vaccine candidates in non-human primates
  - ✓ Test therapeutic vaccination with anti-DC Ebol rAbs in combination with antiviral T-705 prophylaxis
  - ✓ Phase I/II safety and immunogenicity study in healthy volunteers
  - ✓ Elicitation of Ig-specific responses following Immunization of healthy volunteers with anti-DC Ebol rAbs

IMI2 PROJECT

- **Objective**: Clinical development of prime-boost vaccine based on Ad26.ZEBOV and MVA-BN-Filo
- **Consortium**: Janssen, Inserm, LSHTM
- **Response to call submitted on Dec 1, 2014**
- **Inserm**:
  - ✓ Coordinator of EBOVAC-2 project in Topic 1 (Phase II trials)
  - ✓ Partner of EBOVAC-1 project in Topic 1 (Phase 1 & 3 trials)
  - ✓ Partner in Topic 5 (Rapid diagnosis)

EBOVAC2

➢ **Objective:** Phase II clinical development in Europe and non-endemic African countries of a two component prime-boost vaccine for prophylaxis against Ebola: Ad26.ZEBOV prime + MVA-BN-Filo boost

➢ **Candidate vaccines (Janssen Crucell, Bavaria Nordic):**

- ✓ Ad26.ZEBOV: monovalent Ad26 vaccine expressing Mayinga Ebola GP
- ✓ MVA-BN-Filo: multivalent MVA with ZEBOV, SEBOV, Marburg GP and Tai Forest nucleoprotein insert
- ✓ GP of the current strain circulating in West Africa shares 97% homology with ZEBOV GP used in this strategy
- ✓ Complete protection in macaques study with trivalent Ad26 mixture prime (ZEBOV, SEBOV, Marburg) and MVA-BN-Filo boost and Ebola Zaire Kikwit challenge

➢ **Main endpoints:** immunogenicity; safety

OTHER PROPOSALS TO CONSIDER

- **Social and human sciences: Characteristics and care's trajectories of patients with suspected Ebola infection in France**
- **Diagnostic:** Development and evaluation of rapid diagnostic test for the detection of Ebola virus in blood or urine (CEA & BioFire).
- **Prevention: initiation of fast development of Ebola preventive vaccine derived from measles live vaccine**
- **Treatments:**
  - ✓ Development and evaluation of the efficacy of hyperimmunes Igs.
  - ✓ Identification of new molecules and vaccines based on different approaches including lentiviral vector (Institut Pasteur).

ChAd3 : Résumé des essais de Phase 1 chez les adultes en bonne santé

Site	*Nombre*	*Début du recrutement*	*Fin du recrutement*	*Résultats prelim.*
VRC – USA (Bivalent)	20	2 Septembre 2014	Octobre	Publié NEJM Nov 2014
Oxford – UK	60	17 Septembre 2014	Novembre	Publié NEJM Fev 2015
CVD – Mali	91	8 Octobre 2014	Décembre	Jan 2015
Lausanne, Suisse	120	31 Octobre 2014	Décembre	Jan 2015
Univ. du Maryland, USA	20	31 Octobre 2014	Deéembre	Jan 2015

rVSV : Résumé des essais de Phase 1 chez les adultes en bonne santé

Site	Nombre	Début	Fin du recrutement	Résultats prelim.
WRAIR – USA	30	17 Octobre 2014	Déc 2014	Déc 2014
NIAID – USA	30	24 Octobre 2014	Déc 2014	Déc 2014
Genève Suisse	100	10 Nov 2014	Jan 2015	Jan 2015
Allemagne	30	17 Nov 2014	Jan 2015	Jan 2015
Gabon	60	21 Nov 2014	Jan 2015	Jan 2015
Kenya	40	Déc 2014	Jan 2015	Fév 2015
Canada	30	Déc 2014	Dec 2014	Jan 2015
Total volontaires vaccinés Phase I = 320				

A retenir des essais cliniques de Phase 1 à ce jour 9 February 2015

- Pas d'effets secondaires sérieux liés à la vaccination
- Des cas d'arthrite ont été mis en évidence à Genève dans l'essai de Phase 1 de rVSV-ZEBOV. Effet secondaire peu sévère, transitoire. Pas de signes d'autoimmunité
- Il est essentiel de poursuivre l'étude de la sécurité des deux vaccins

Approches pour les essais d'efficacité (Phase 3)

- Liberia: Essai randomisé controlé avec 3 groupes, dans la population générale
- Sierra Leone: Essai stepped-wedge, pour les personnels de santé
- Guinée: 2 protocoles: Vaccination en ceinture et immunisation des travailleurs de première ligne

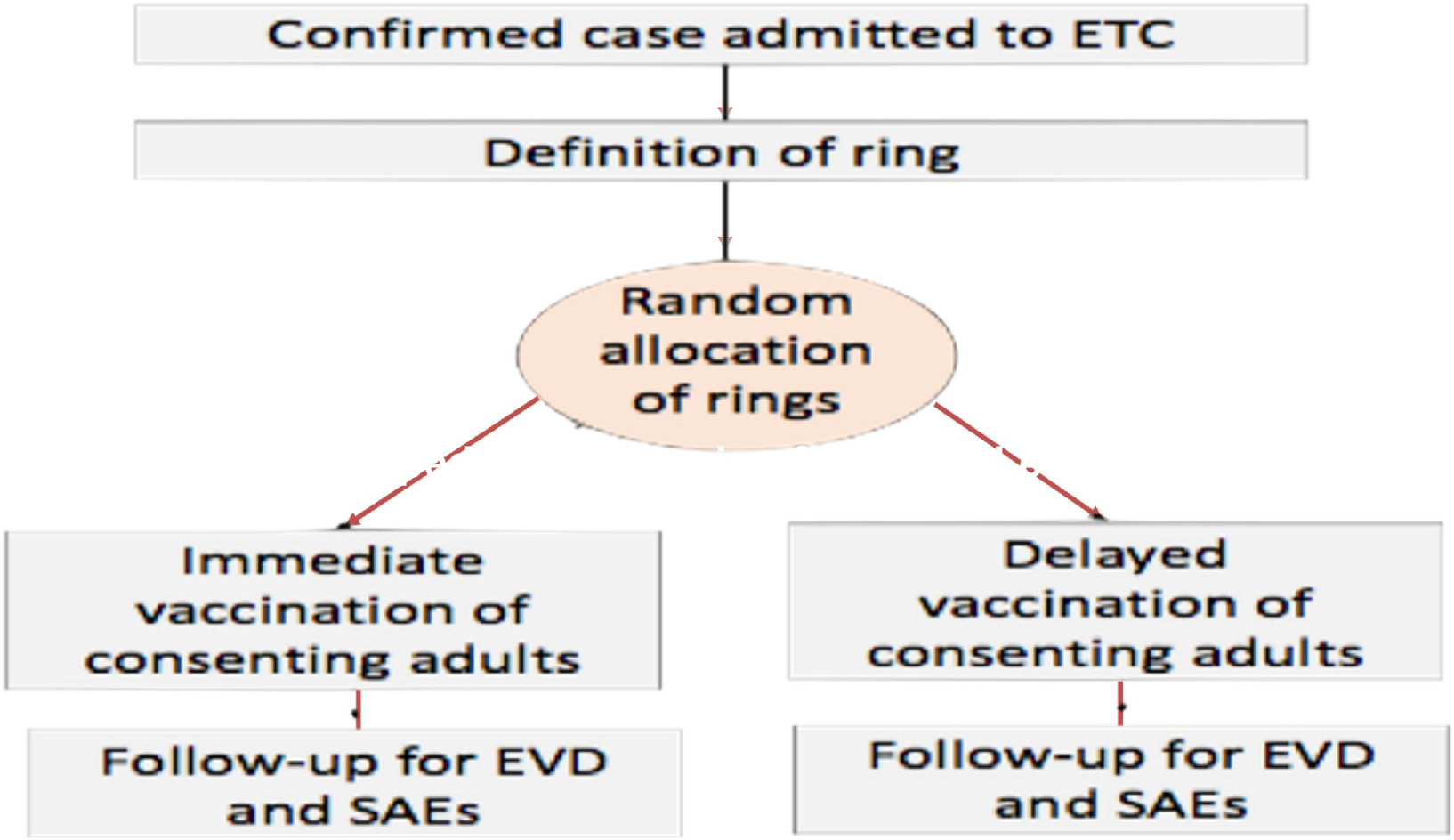
Essai de Phase 3 au Liberia

- Essai randomisé contrôlé en double-aveugle
- Trois groupes: 1:1:1 (rVSV:placebo:cAd3)
- Essai de Phase 2 inclu dans l'étude de Phase 3: 600 sujets
- N ~ 28,000
- Démarré le 26 janvier 2015

Essai de Phase 3 au Sierra Leone

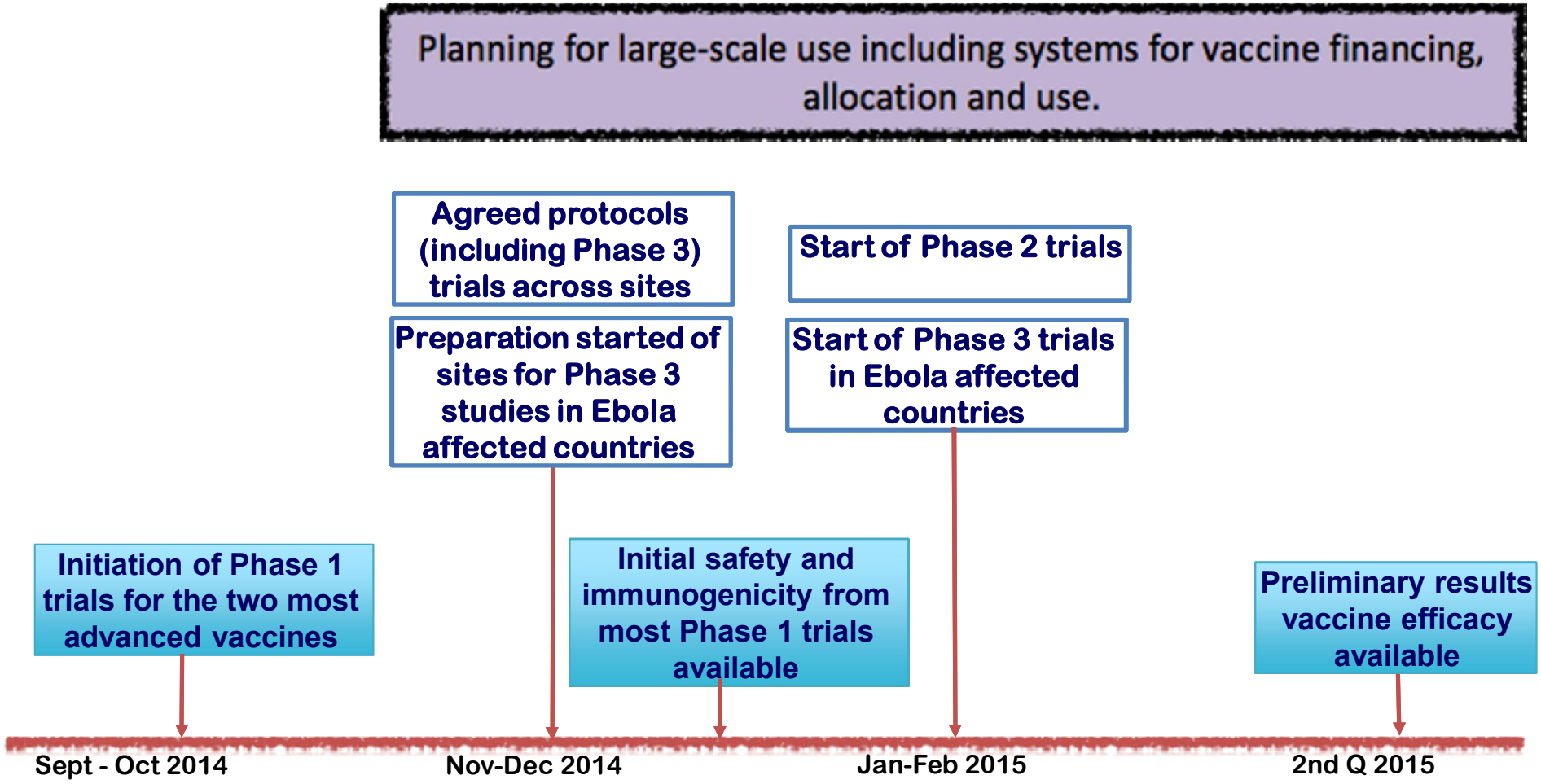
- Utilise un recrutement par paliers pour évaluer l'efficacité du vaccin
- Les groupes cibles (e.g. hospitaux/cliniques, centres de traitement Ebola, équipes en charge des enterrements) sont randomisés pour être vaccinés pendant une période de 18 semaines
- Le suivi des cohortes commence à t=0 pour tous les participants, indépendemment de la date de vaccination
- Les participants passeront du status non-vacciné au statut vacciné pendant la semaine qui leur a été attribuée de façon aléatoire pour la vaccination

Vaccination en ceinture pour la Guinée



Comparaison des taux d'infection avec le virus Ebola

Vaccins Ebola – Etapes clé



World Health Organization

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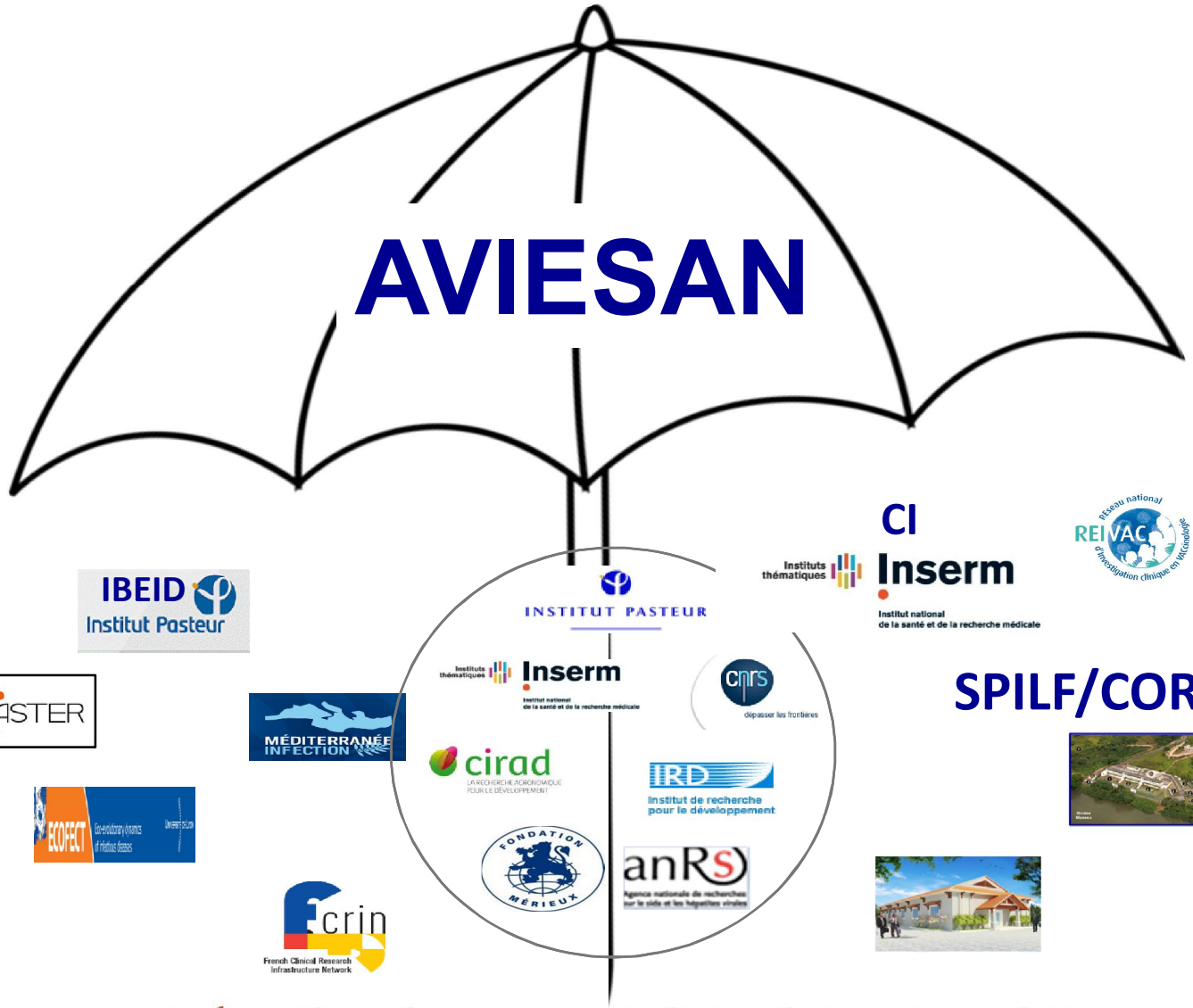
RÉPUBLIQUE FRANÇAISE
Premier ministre

French Response to Ebola : Research in a crisis situation

- **FIRST LESSONS**
- **MEDIUM AND LONG TERM NEEDS**

REACTING: A NETWORK



ANRS Research Sites involved in EBOLA

- **Sub-Saharan Africa**

  Cameroon,

  Burkina Faso,

  Côte d'Ivoire,

  Senegal

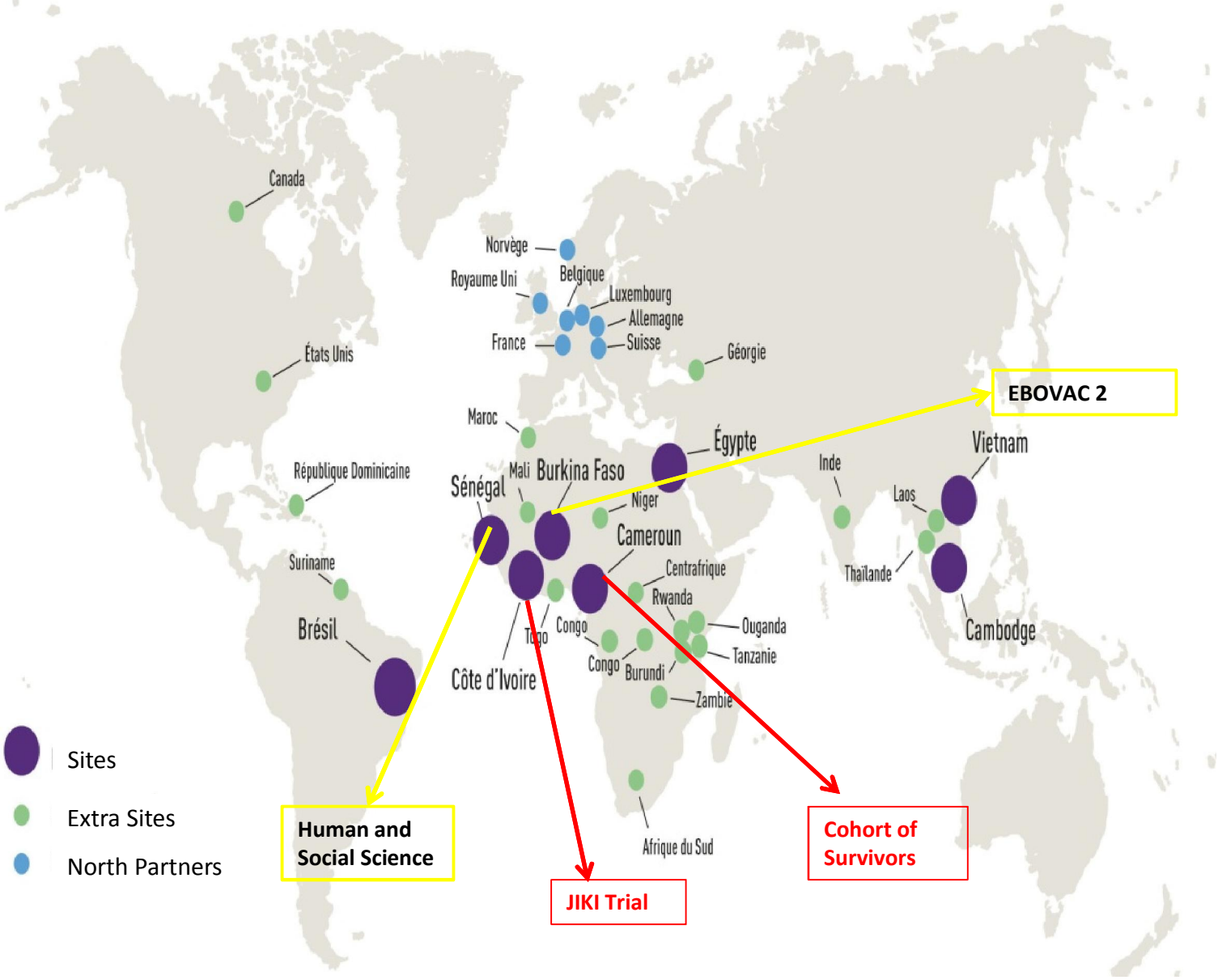
- **South –East Asia**

  Cambodia,

  Vietnam

- **Egypt**

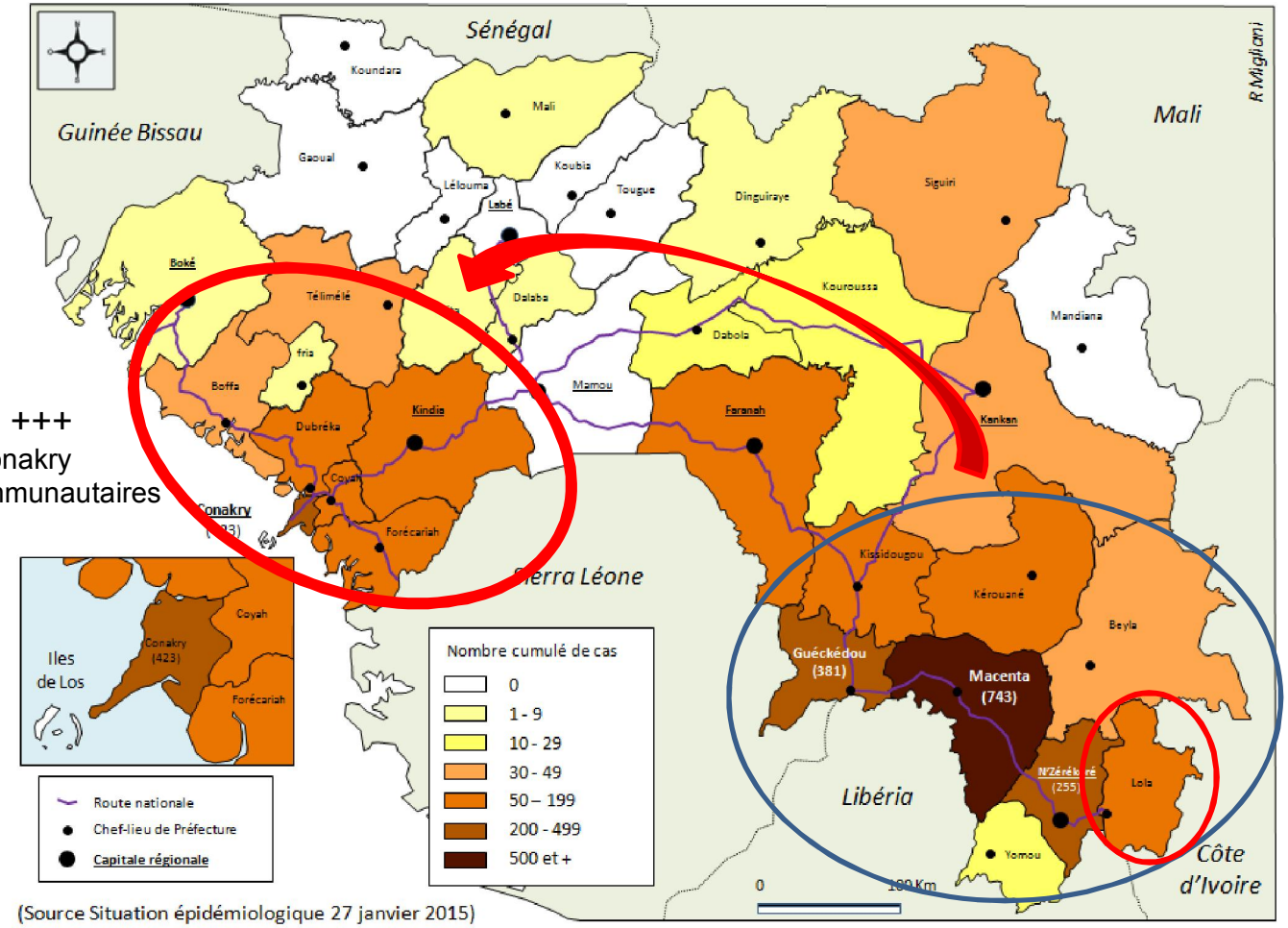
- **Brazil**



Laboratoire P4 Jean Mérieux-Inserm, Lyon

Incidence cumulée Ébola en Guinée - Janvier 2015

Basse Guinée +++
Semaine 3-5 à Conakry
= 69% Décès communautaires



(Source Situation épidémiologique 27 janvier 2015)

Guinée forestière

L'épicentre depuis mars 2014 = Guinée forestière

Défervescence janvier 2015 = Est du pays (sauf Lola)

Bascule de l'épidémie = Basse Guinée +++

Février 2015 : Les défis Sanitaires

- Réticence communautaire +++
- Décès communautaires
- Suivi des personnes contacts
- Prise en charge précoce
- Infection des agents de santé
- Coordination des interventions

FRENCH RESPONSE TO EBOLA
MAIN ISSUES FOR 2015 (1/2)

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1. BRING EBOLA EPIDEMIC UNDER CONTROL BY JUNE 2015

- ✓ In the 3 main countries impacted by Ebola (Guinea, Sierra Leone and Liberia), the epidemic becomes more volatile with spreading sources of infection,
- ✓ but the epidemic has been contained in the epicenters
- ✓ The population is reluctant to visit Ebola care units to get treated

WHAT IS AT STAKE FOR 2015?

- ✓ The response must be in line with the evolution of the epidemic and must get more mobile with the set up of local teams in charge of ringing the bell and delivering quick solutions
- ✓ Make sure that Ebola Care units will be able to react promptly in case of a new outbreak

2. GIVE THE POPULATION ACCESS TO A TREATMENT WHICH HAS BEEN TESTED

- ✓ New treatments have been tested during the epidemic : Favipiravir in Humans and Primates.

WHAT IS AT STAKE FOR 2015?

- ✓ Access to tested treatments (Favipiravir alone or in combination) must be guaranteed in care units to get them more attractive to patients.
- ✓ Support of the phase 4 of cohort of patients treated with Favipiravir in TCU according to scientific protocols

FRENCH RESPONSE TO EBOLA
MAIN ISSUES FOR 2015 (2/2)

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RÉPUBLIQUE FRANÇAISE

3. PREPARE THE TRANSITION PHASE AND PREVENT NEW OUTBREAKS

- ✓ Launching the rebuilding of the health systems affected by the Ebola outbreak
  - Health services have been deeply damaged by the Ebola outbreak
  - Rebuilding and improving health services for primary care will be necessary

- ✓ Improving the supervision with the set-up of an epidemiological network and warning system
  - The Ebola outbreak has highlighted the weakness of the supervision system
  - Setting up a regional network able to prevent new outbreaks must be initiated. France will be able to provide expertise.

- ✓ Building capacities in public health
  - Preventing and controlling epidemic require strong public health skills and expertise
  - Establishing a regional school for public health in West Africa is a key condition of capacity building
  - Supporting the establishment of a “high level” laboratories network for detection of emerging pathogens (Pasteur Institute in Guinea…)

Partners

- IRD, CEA, Inserm, CNRS (Social and Human Science), ANRS, VRI
- IPP
- NGOs, MSF, FRC, ALIMA
- Fondation/Institut Mérieux
- Pharmaceutical companies : Toyama Chemical
- WHO
- European Commission
- French Embassy in Guinea, in Mali
- X Anglaret, F Mentré, D Malvy, E Delaporte, S Baize, H Raoul, X De Lamballerie, les chercheurs guinéens, C Lévy-Marchal, B Murgue, Y Yazdanpanah.

THANK YOU