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The Non Human Primate as a model for EBOLA virus infection

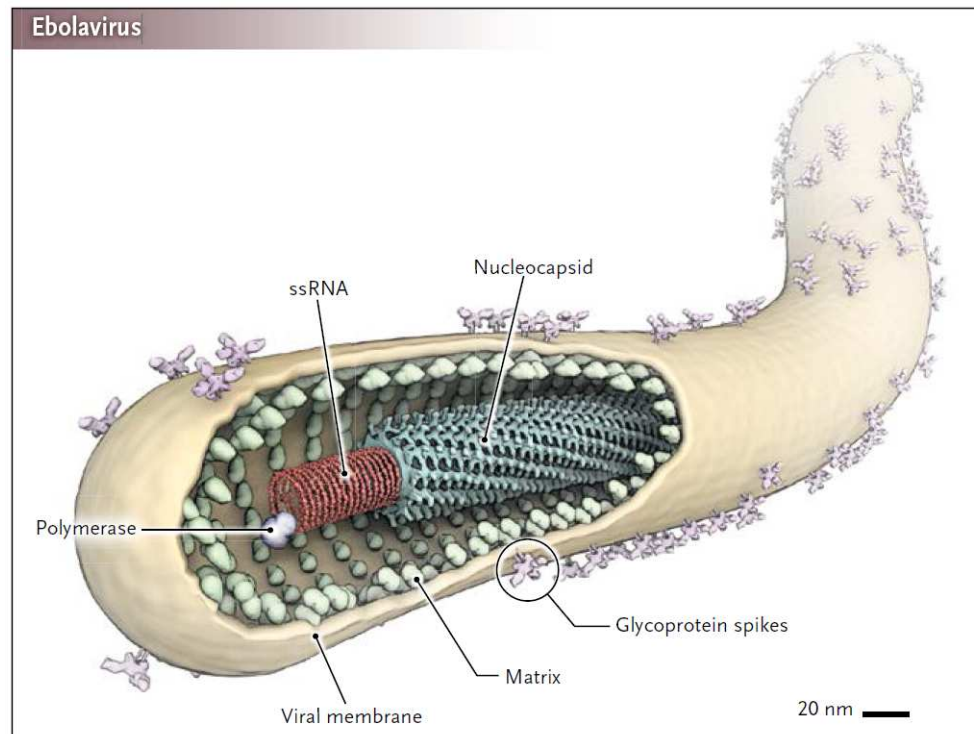
**SAC Meeting on Emerging and
Reemerging Infectious Diseases**

September 14 – 15, 2015

Fondation Mérieux Les Pensières Conference Centre

Ebola Virus

- Family : *Filoviridae*
- Genus : *Filovirus*
- Genome : single-stranded, Negative linear RNA, encapsidated



From DOI: 10.1056/NEJMp1405314, Heinz Feldmann

➤ Specific filamentous morphology

➤ Important polymorphism

➤ Nucleocapside - 4 proteins

NP

VP30

VP35

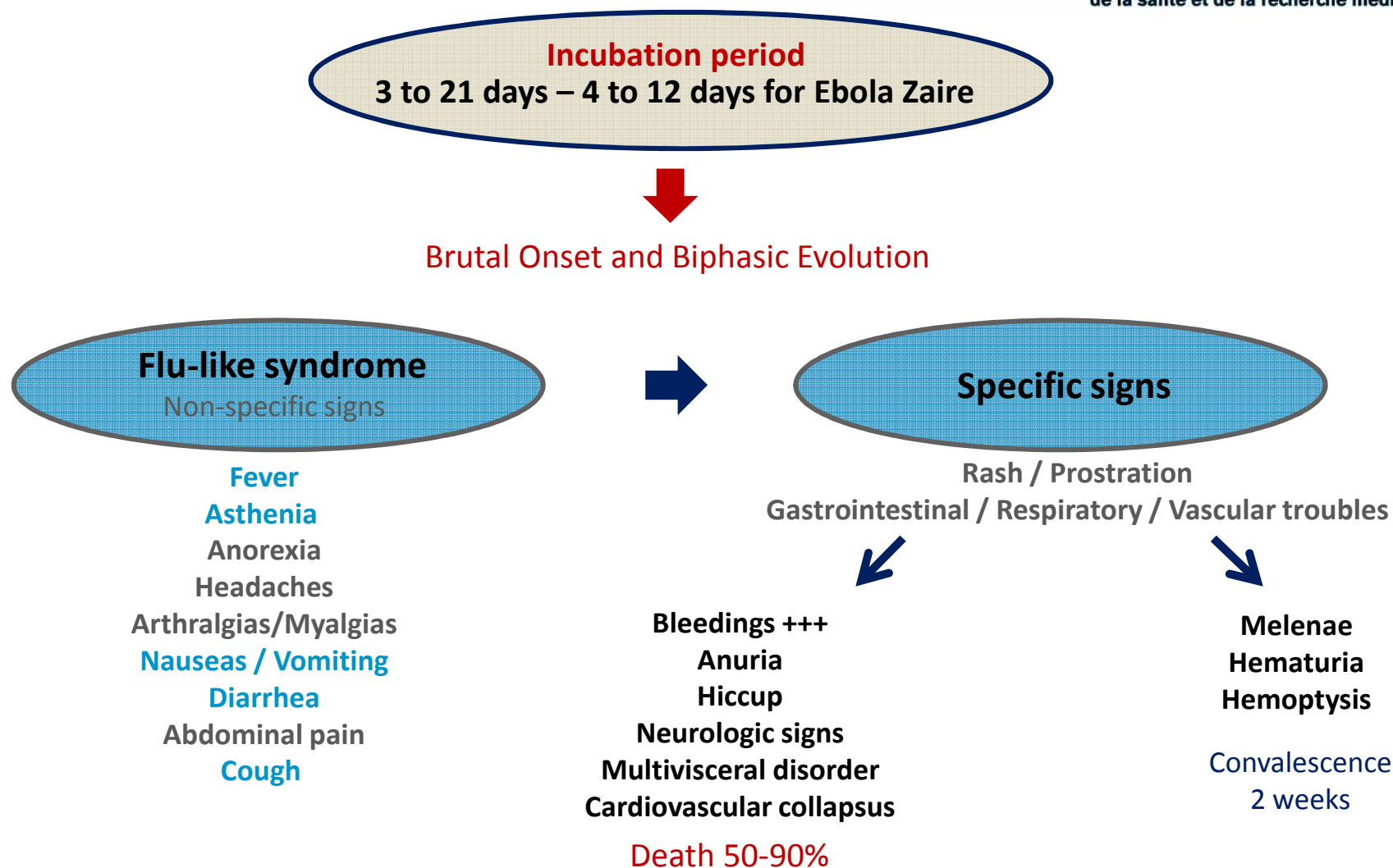
L (RNA polymerase)

➤ Viral envelope

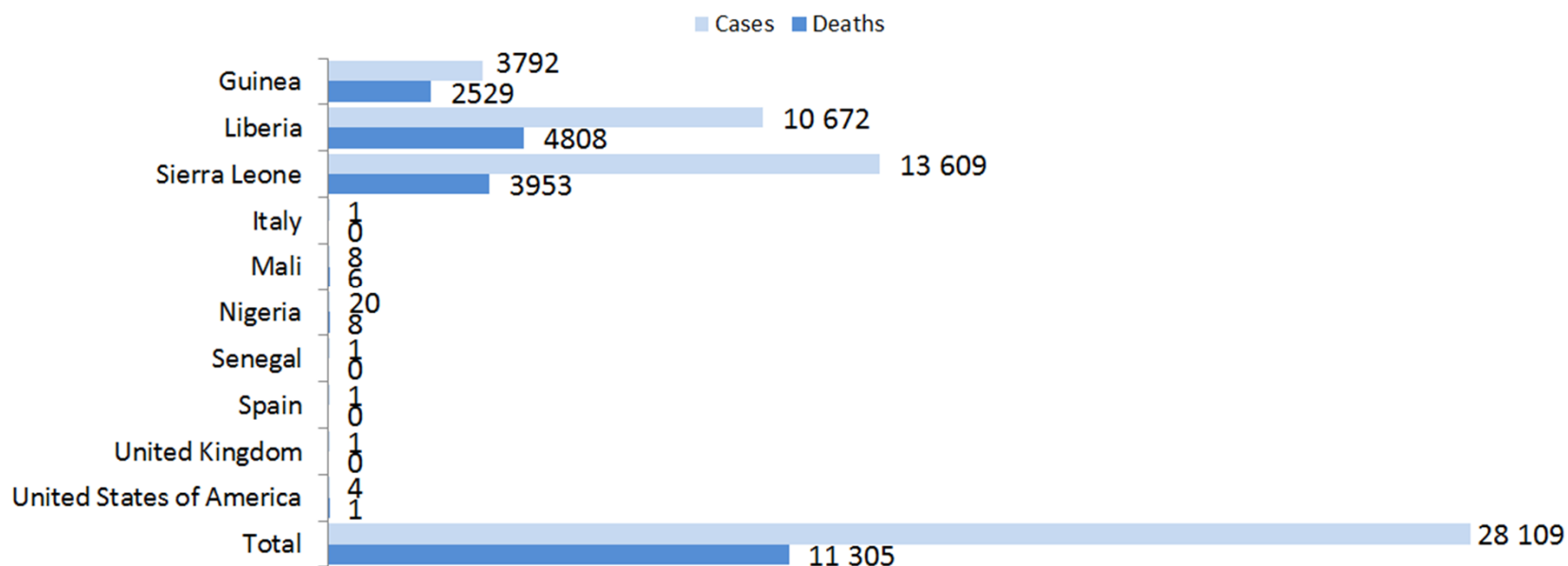
VP24

VP40

GP (spikes, trimeric oligomerisation)



Confirmed, probable and suspected EVD cases worldwide (data up to 30 August 2015)



Data available on WHO website :

<http://maps.who.int/mapjournal/?appid=435a2088687742c4b64aca38914195d4&webmap=521e32fa65d34269b47c9f1d08a3bf68>

The primate model

Animal models are needed in the frame of:

- Basic sciences
 - To study the physiopathology mechanisms
 - To study the host/pathogen interactions
 - ...
- Preclinical studies
 - To test the efficacy of therapeutic tools
 - To test the efficacy of prophylactic tools
 - To test diagnosis tools

A good animal model must:

- Be closed to the infectious process observed in humans
- Reflect the disease observed in humans

The primate model

Animal models available to study Ebola virus infection and disease:

- Adapted viral strains:
 - Mice, Guinea pigs
- Genetically modified animals:
 - IFNAR -/- mice, STAT-1 mice
- Unmodified animals and WT viral strains
 - **Non Human Primates (cynomolgus and rhesus macaques)**
 - Ferrets

Constraints associated to experimental Ebola virus infection in NHPs:

- Limited number of animals
- Availability of biosafety officer
- Anesthesia before handling of animal
- At least four protective gloves
- Exclusion/limitation of hazardous tools
- Daily care

The primate model

Protocol implemented in the Lyon-Mérieux P4 laboratory:

- NHPs: cynomolgus macaques
 - **Origin: Mauritius, SW Indian Ocean**
- Viral strain: Ebola Zaire, Gabon 2001 p7
- Challenge dose: 1000, **100, 10** pfus
- Route of infection: IM
- Daily observation & blood sampling 3 time a week

Criteria used for NHP euthanasia:

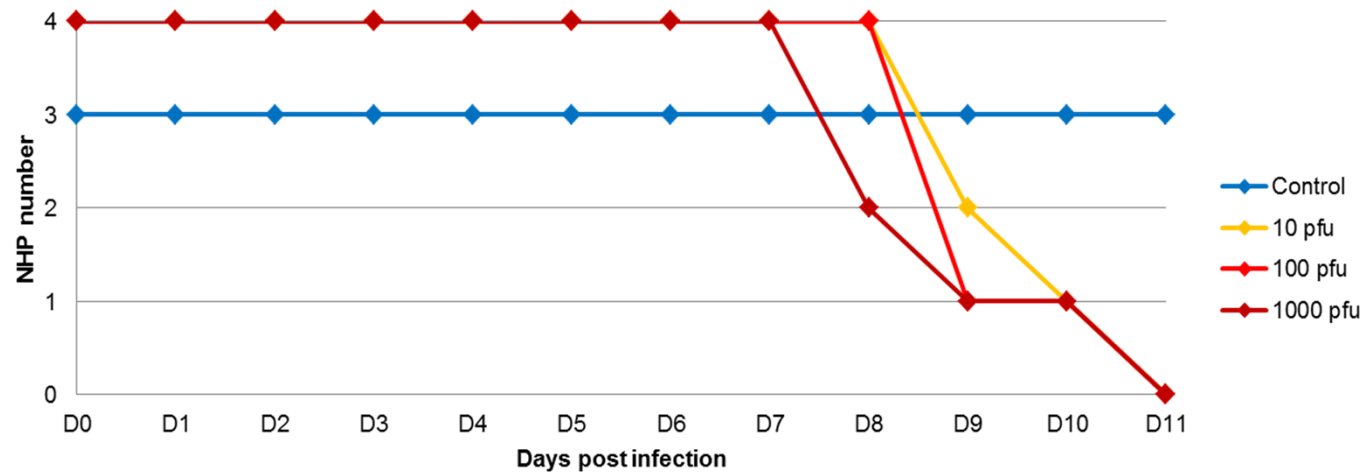
- Weight loss >15% (reference: D0)
- Fever (> 40° C) for more than 3 days
- Anorexia for more than 4 days
- Epistaxis
- Haemorrhagic and mucosal diarrhea

Analysis performed:

- Virus load (infectious particles & viral RNA)
- Genomics of virus populations (NGS)
- Blood count
- Biochemistry (liver, renal, inflammation markers...)

The primate model

Lethality observed in NHP challenged with 10, 100 & 1000 pfu (IM)



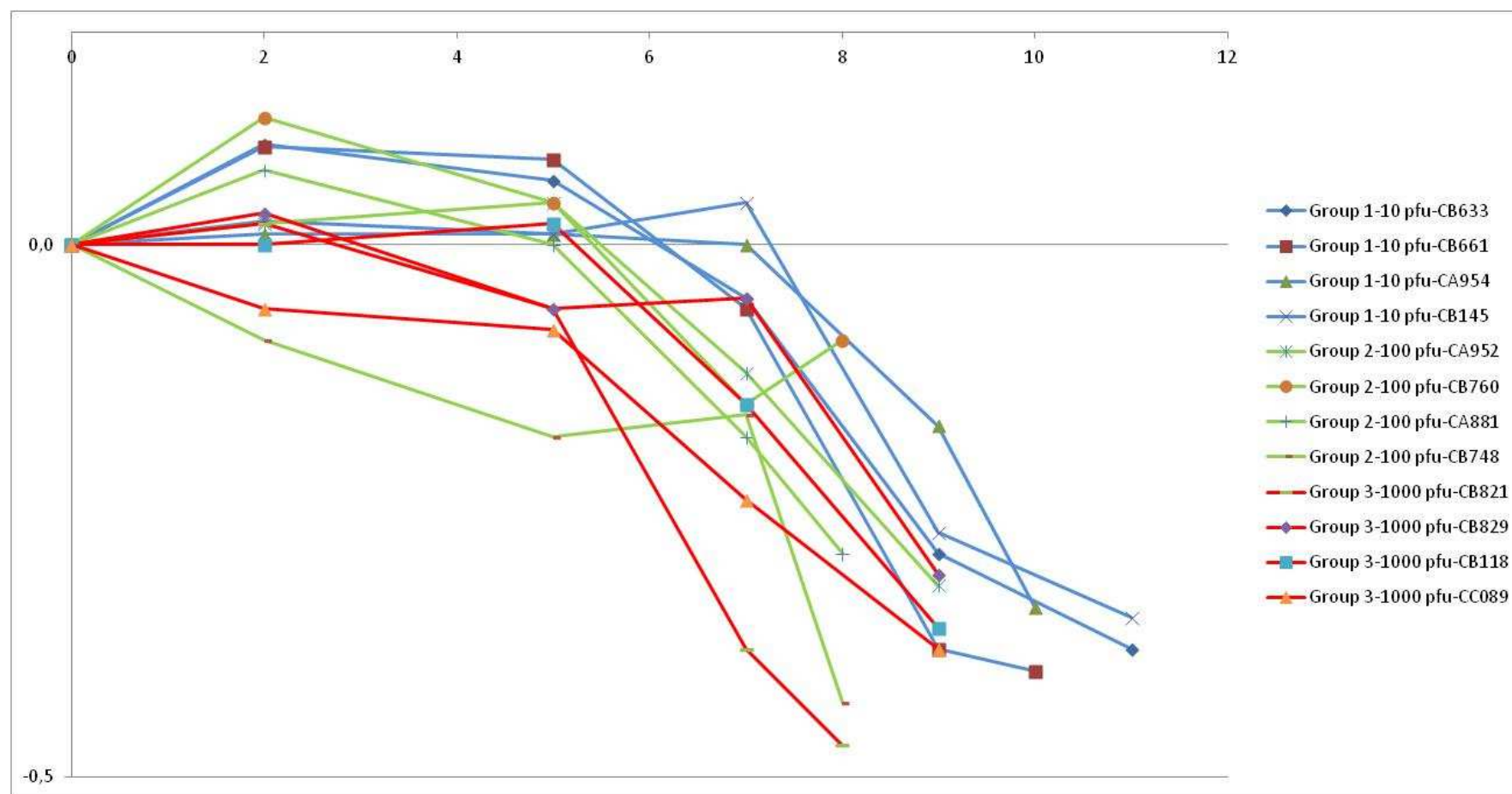
Symptoms

- D5 PI: Fever (40-41° C)
- D6 PI: Anorexia (no consumption of food and water).
- D7 PI: Petechiae (inguinal + saphenous areas)
- D8 PI: Petechiae on the whole body
- D8 PI: Haemorrhagic and mucosal diarrhea
- D9-10 PI: Prostration, hypothermia.



The primate model

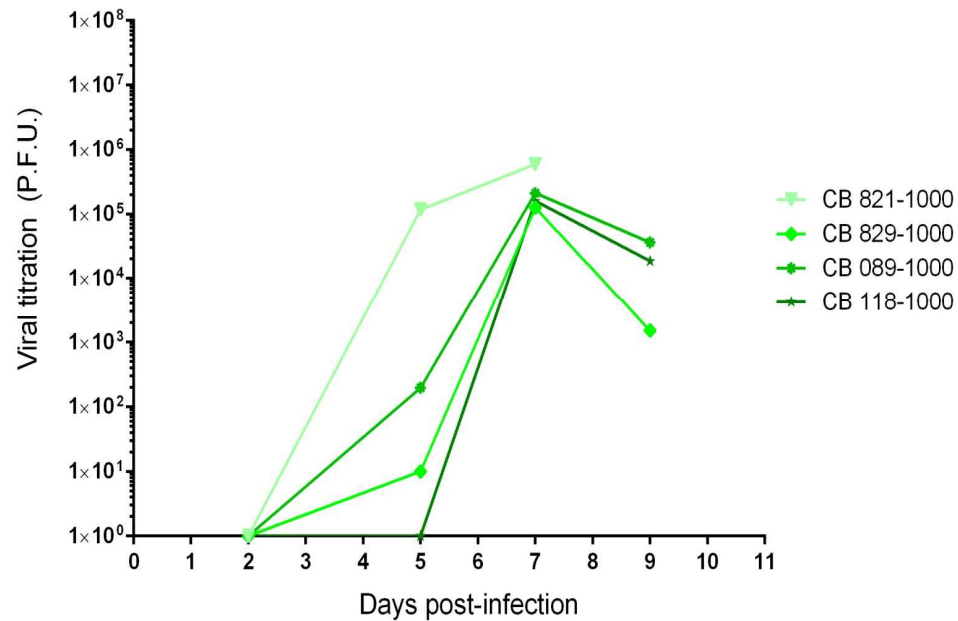
WEIGHT LOSS



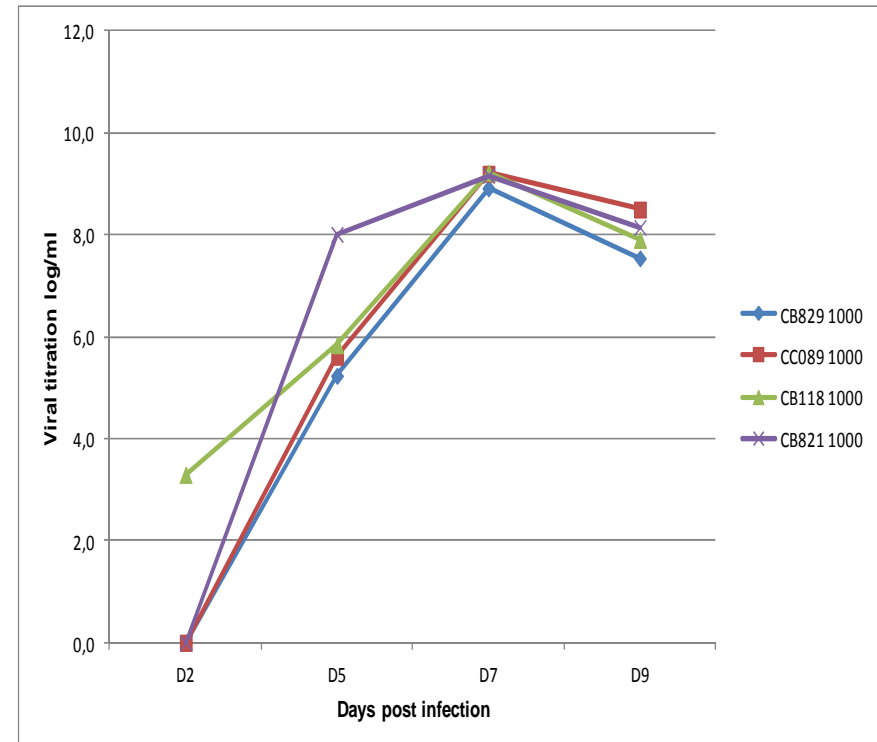
The primate model

Viral loads for the challenge dose: 1000 pfus

Pfus/ml



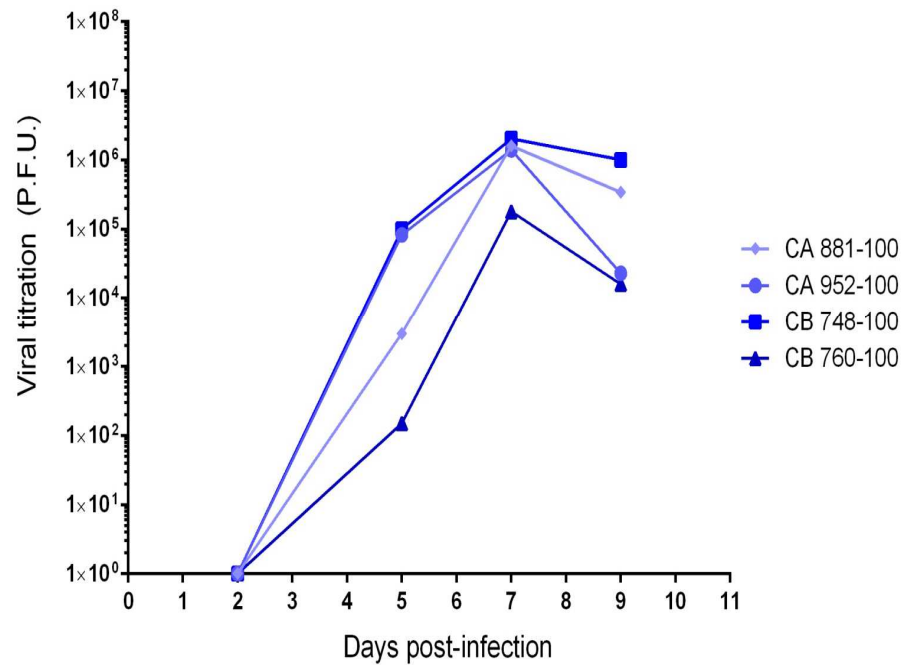
Log genomes/ml



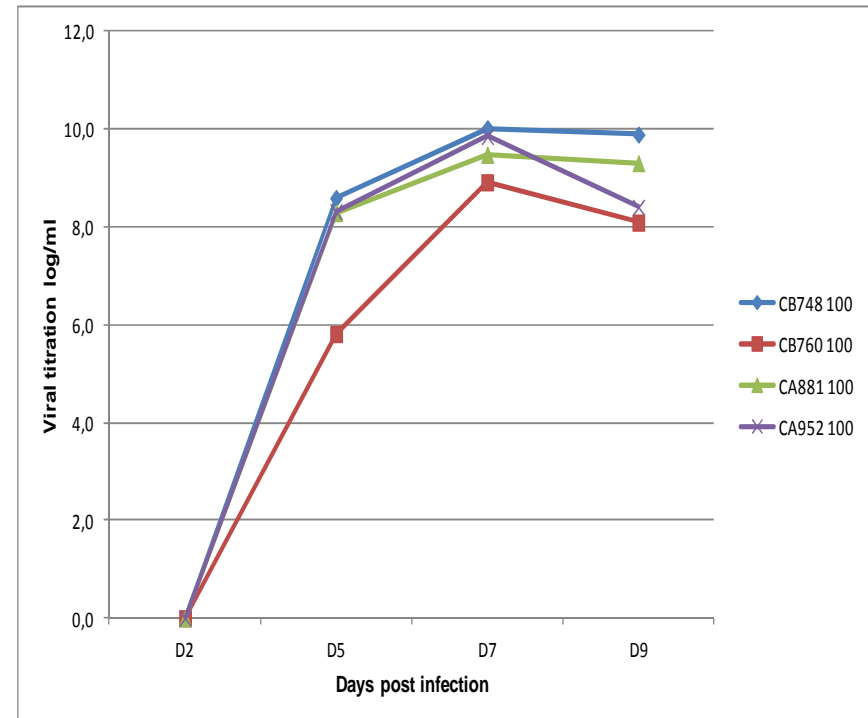
The primate model

Viral loads for the challenge dose: 100 pfus

Pfus/ml



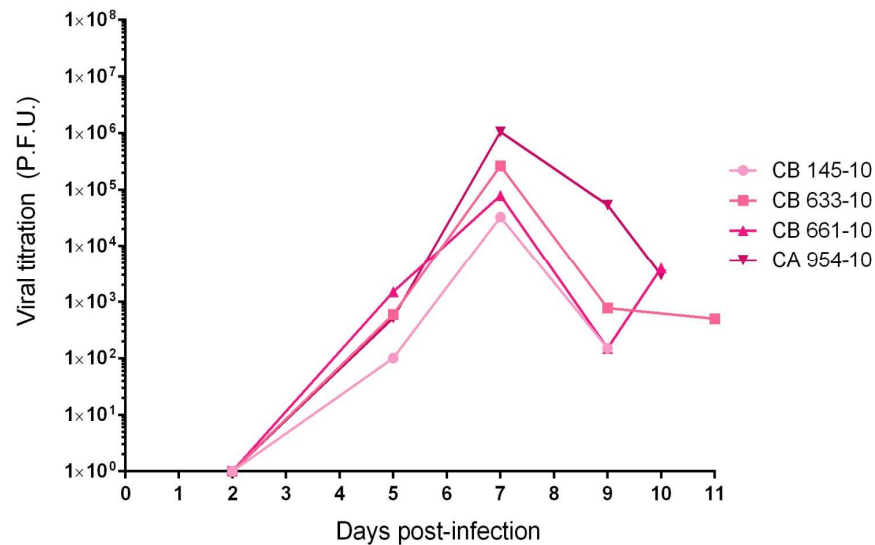
Log genomes/ml



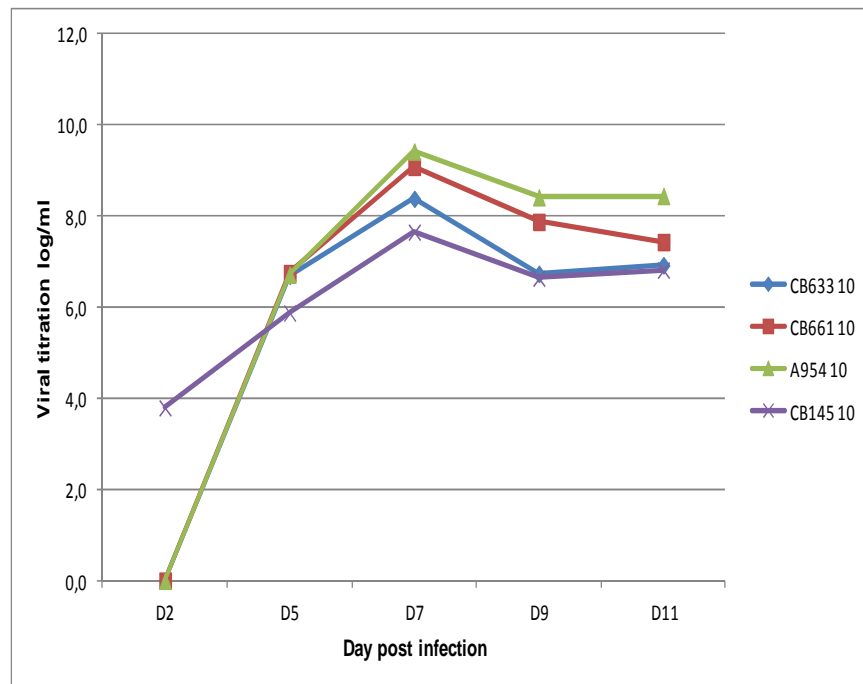
The primate model

Viral loads for the challenge dose: 10 pfus

Pfus/ml

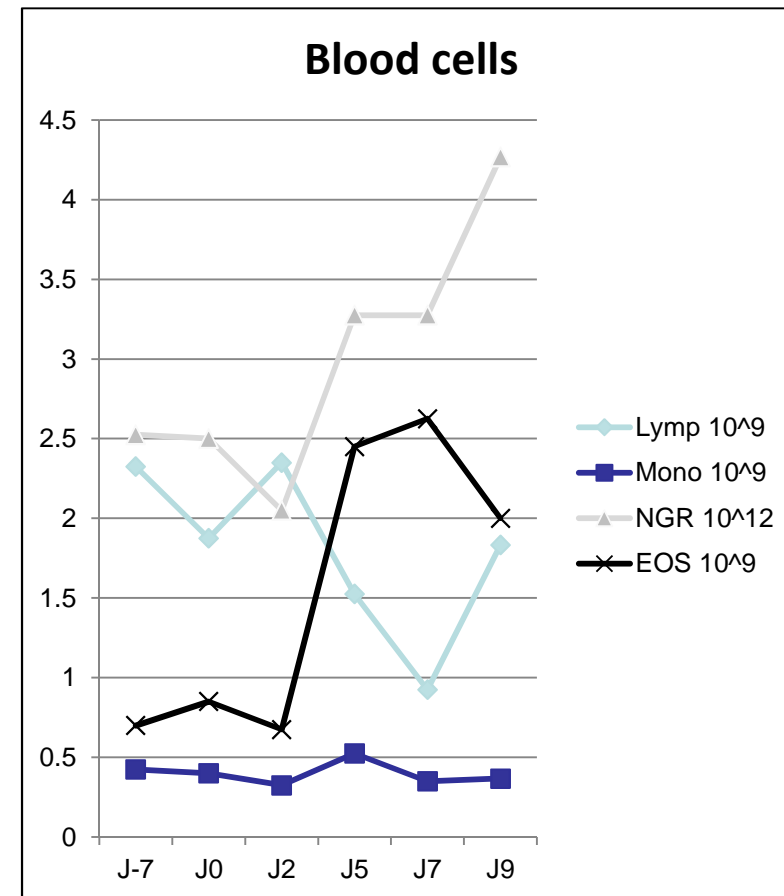
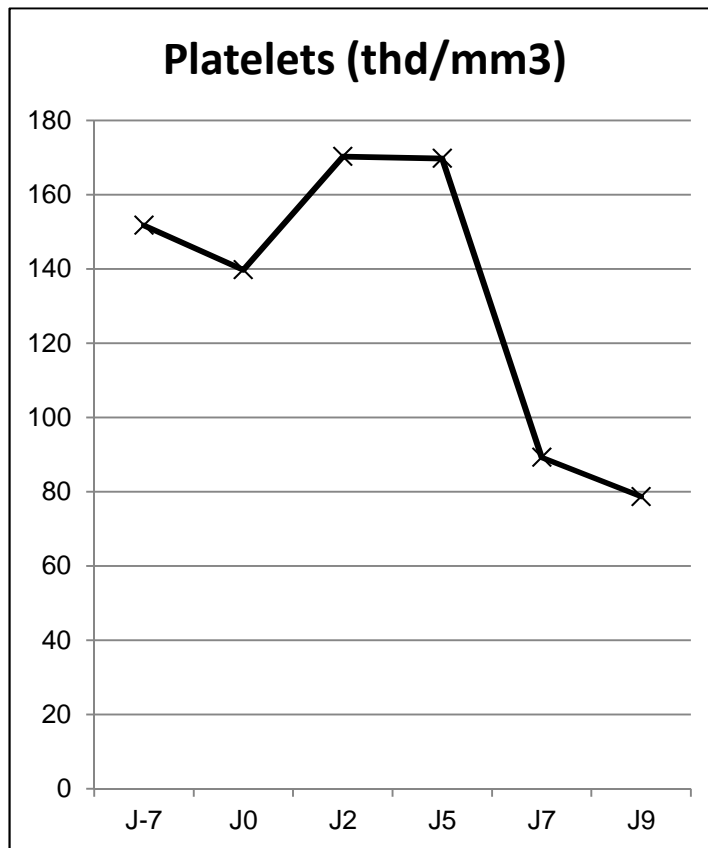


Log genomes/ml



The primate model

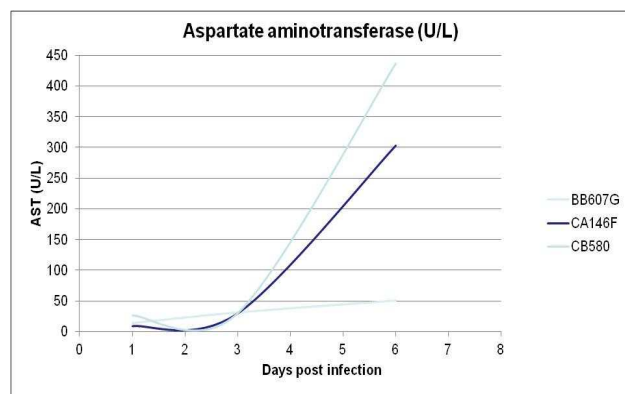
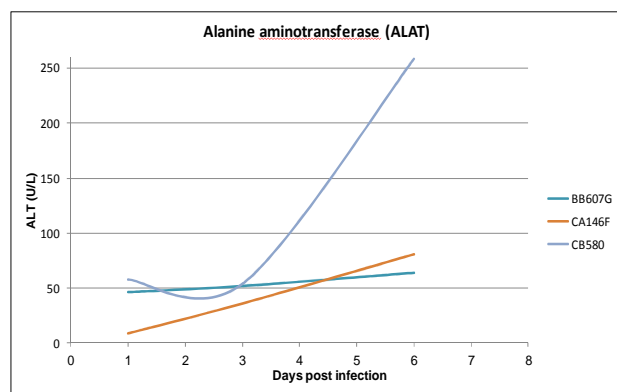
Challenge dose: 1000 pfus



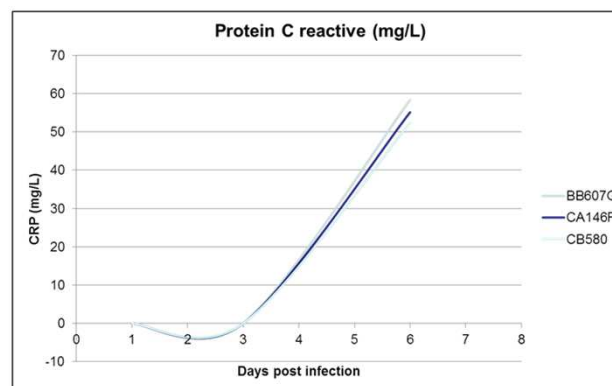
Challenge dose: 1000 pfus

Biochemistry analysis

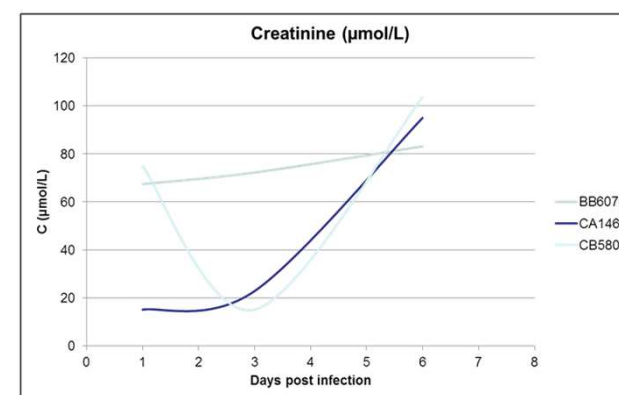
Transaminases



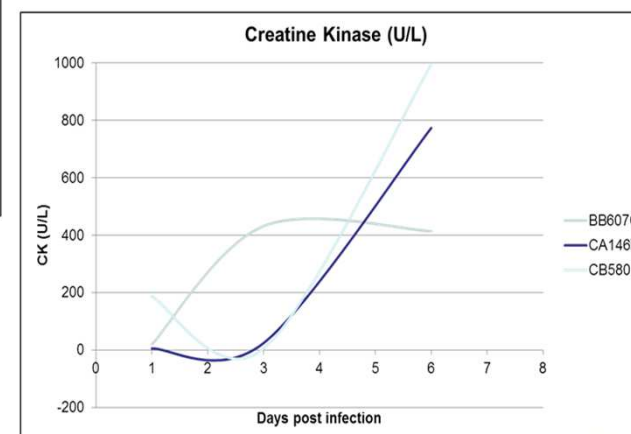
CRP



Creatinine



Creatine kinase



Perspectives

Improvement of the model:

- Challenge doses (lower doses)
- Route of infection (mucosal route)

Example of ongoing programs using this model:

- Evaluation of the antiviral activity of favipiravir
 - ❑ PK studies in mice, macaques and humans
 - ❑ infection/treatment protocols in NHPs
- Combination therapy
- ...



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Acknowledgements to:

Frédéric Jacquot
Laura Barrot
Audrey Vallvé
Stéphane Barron
Guillaume Noel

France Mentré
Jérémie Guedj



St. Luke's International University, Tokyo,
Japan & The Japanese Government (MoH)
for funding support



Delphine Pannetier
Stéphane Mely
Anne Bocquin
Stéphanie Mundweiller
Damien Thomas

Xavier de Lamballerie
Nicolas Salez
Yannik Boehmann
Gilles Quérat
Magali Gilles
Géraldine Piorkowski
Karine Almani



UMR190

Béatrice Labrosse
Christophe Léculier
Alban Pocquet
Jean Lecompte

Sylvain Baize



Bernadette Murgue
Jean-François Delfraissy





The primate model



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Thanks for your attention

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