Zika virus pathogenesis in macaques

Dave O’Connor

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Key applications of macaque models of virus pathogenesis

- Longitudinal sampling
- Kinetics of virus replication and antiviral immunity
- Invasive tissue sampling
- Preclinical evaluation of interventions
- Rapid and cost-effective results

Why did we begin studying Zika virus in macaques?

Expected features of pre-zoonotic pathogens

- Microbial agents ——— RNA viruses
- Animal hosts ——— Primates
- Human exposure ——— Highly likely
    - High prevalence in natural hosts
    - High viral load in natural hosts
    - Frequent animal-human contact
- Genetic diversity ——— High
- History of cross-species transmission ——— Yes

February 2012
Kibale, Uganda

http://www.sciencemag.org/news/2016/02/zika-s-long-strange-trip-limelight

examine cross-species pathogenesis of African primate viruses in Asian macaque monkeys

July, 2005
Rio de Janeiro, Brazil

October 19, 2015
Florianópolis, Brazil

http://www.ibtimes.co.uk/zika-virus-brazil-parents-babies-born-microcephaly-demand-answers-1540558

http://www.northcountrypublicradio.org/news/npr/467318839/colombian-clinic-probes-a-mystery-is-zika-triggering-a-rare-disc

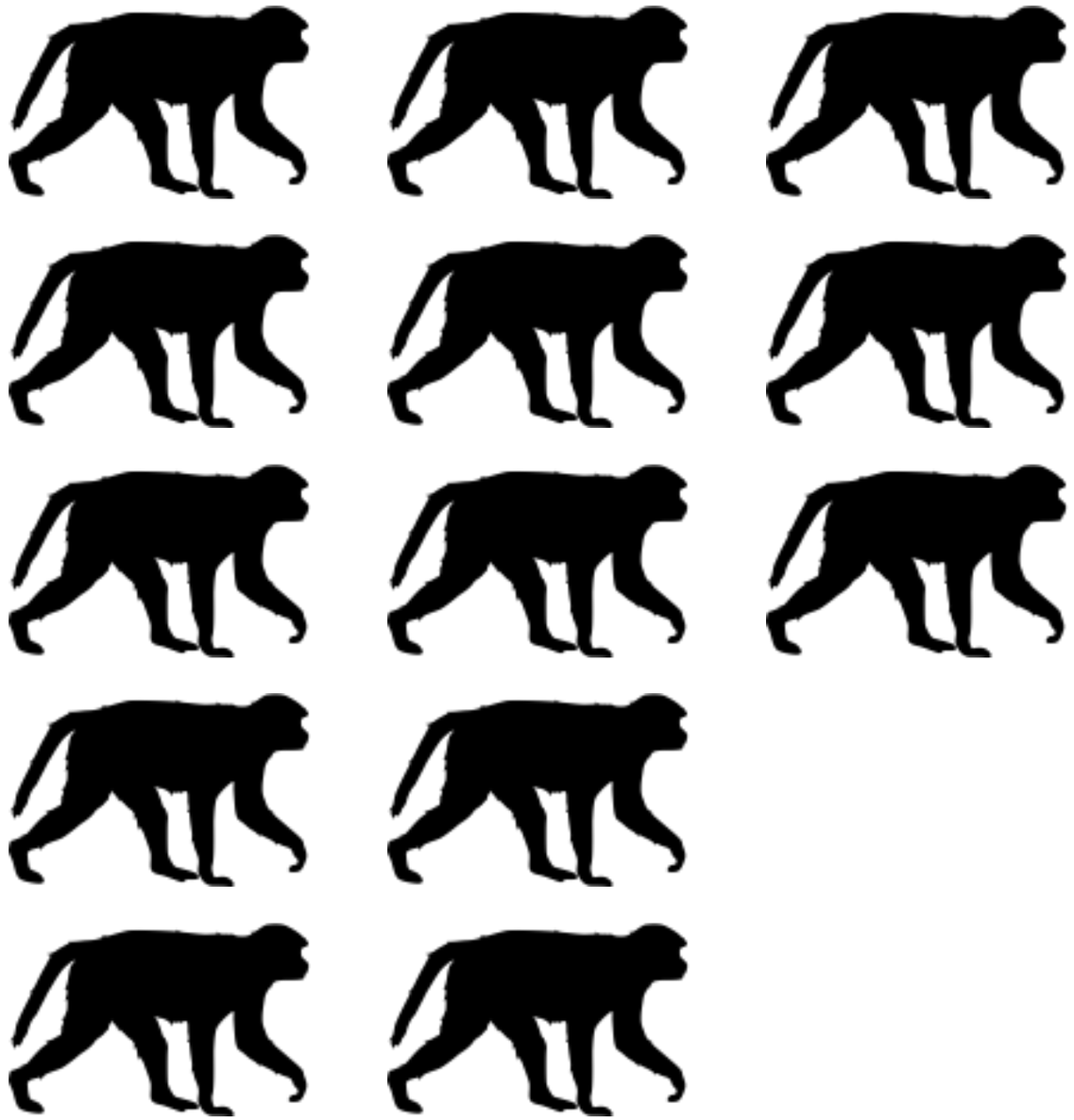
Are macaques appropriate models for Zika virus pathogenesis?

Key questions

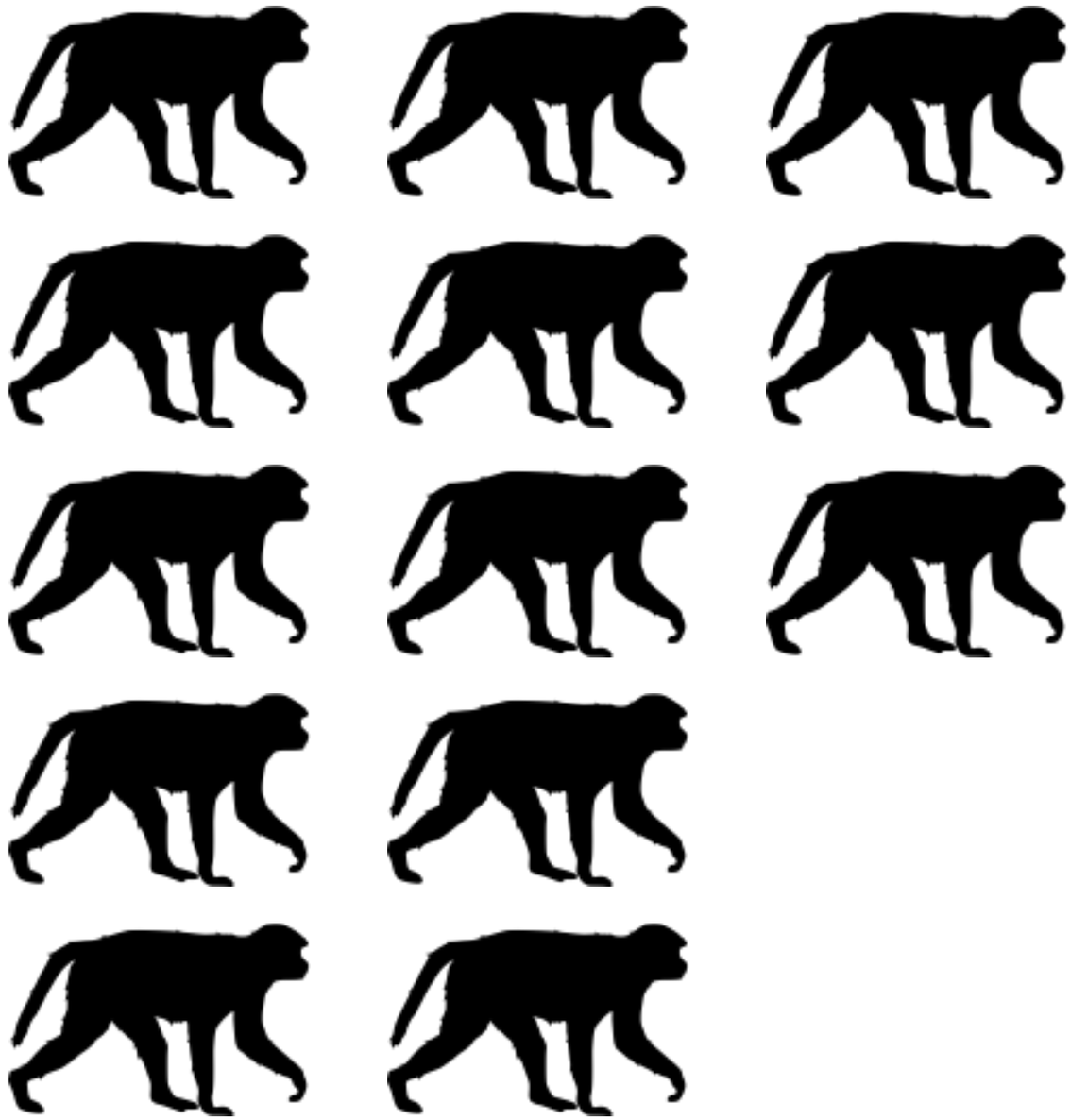
- Can macaques be infected with Zika virus?
  - via physiologic routes and with physiologic doses of virus?
  - with strains similar to those circulating in the Americas?
- Do macaques develop disease similar to humans?
  - rash, asymptomatic infection in non-pregnant macaques?
    - rare complications such as GBS hard to detect
  - fetal abnormalities in pregnant macaques?

Can macaques be infected with Zika virus?

13 Indian rhesus macaques challenged subcutaneously



All 13 animals had detectable virus in blood



Are Zika virus challenge doses physiologic?

10^4 PFU of Zika virus reliably establishes infection

10^6 PFU 

10^5 PFU 

10^4 PFU 

10^4 PFU 

10^4 PFU 

mosquitos transmit up to 10^4 PFU per blood meal

sexual transmission dose currently unknown

Do American Zika virus strains infect macaques?

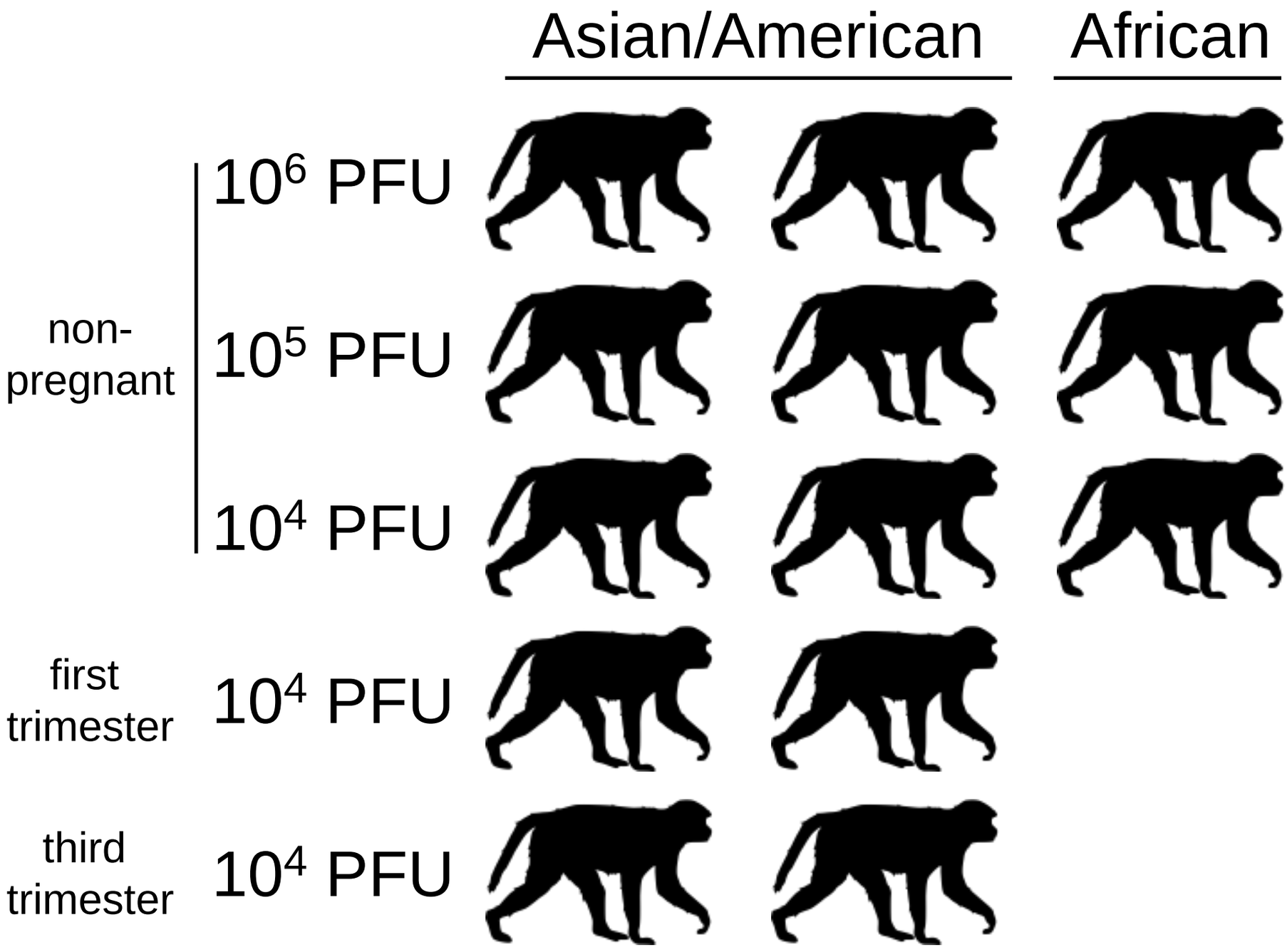
Asian/American and African Zika virus infect macaques

	Asian/American		African
10^6 PFU			
10^5 PFU			
10^4 PFU			
10^4 PFU			
10^4 PFU			

Colleagues have infected macaques with Puerto Rican (Bioqual/Whitney/ONPRC) and Brazilian Zika virus (UC-Davis)

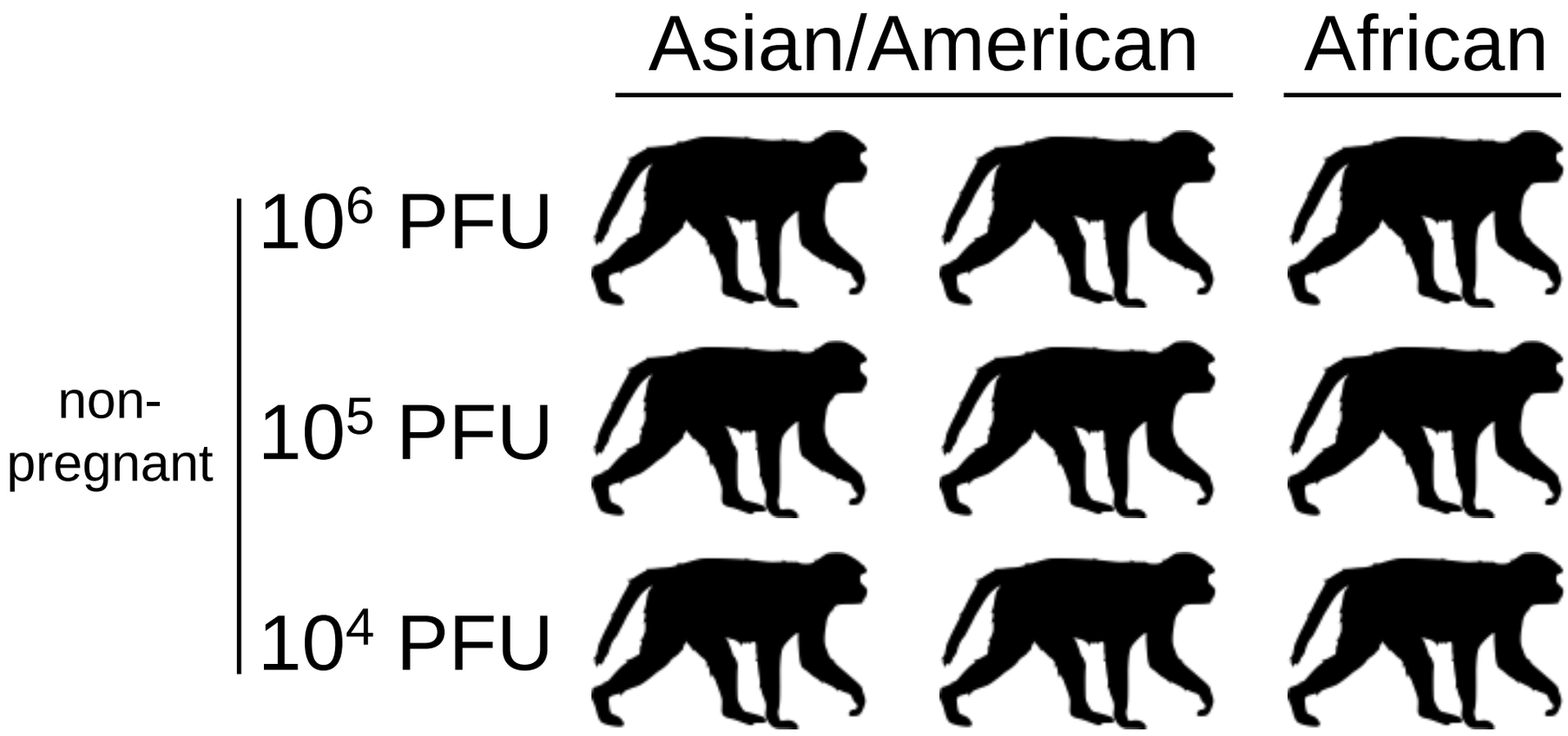
Do macaques develop disease similar to humans?

Infection of non-pregnant and pregnant macaques



Do we observe rash, asymptomatic infection in non-pregnant macaques?

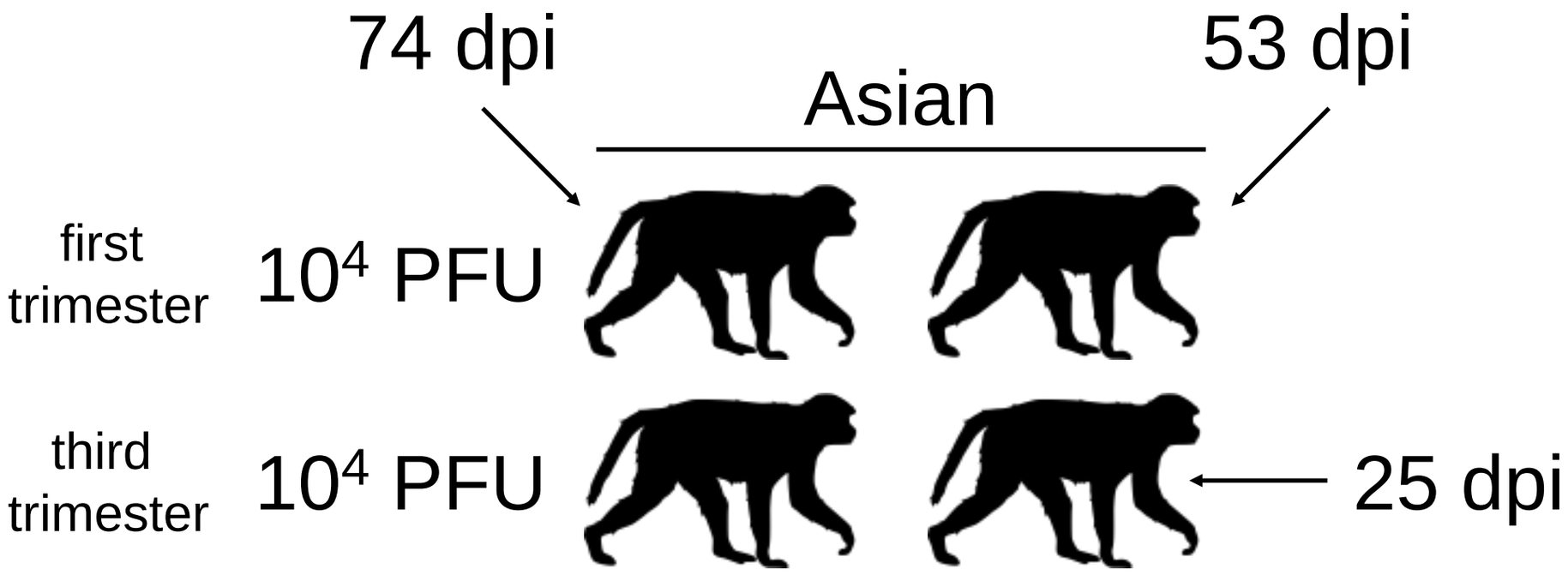
Mild, asymptomatic infection in non-pregnant macaques



- animals appeared healthy throughout experiments
- mild rash observed at infection site in few WNPRC animals
- prominent descending rash noted in macaques infected with Puerto Rican Zika virus (ONPRC)

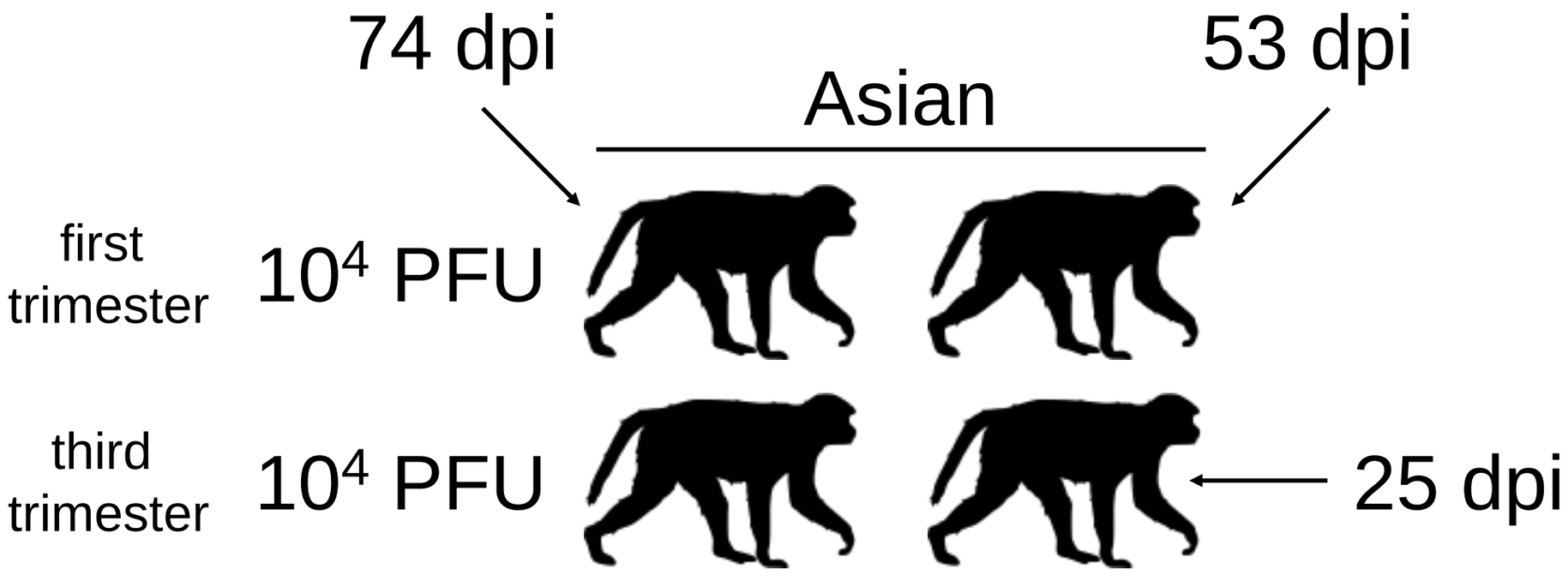
Are there fetal abnormalities in pregnant macaques?

Infection of non-pregnant and pregnant macaques



Infection of non-pregnant and pregnant macaques

- mothers remained healthy throughout pregnancy
- head circumference ~ 2 standard deviations below normal; placental calcification at 42 dpi



Both fetuses from 1st trimester infections are small

	biparietal diameter	**head circumference**	**femur length**
3/23/16	1.3 SD below mean	1.8 SD below	---
3/30/16	1 SD below	1.7 SD below	0.6 SD below
4/12/16	0.7 SD below	1.7 SD below	0.5 SD below
4/19/16	1.2 SD below	2.4 SD below	0.5 SD below
4/26/16	0.7 SD below	1.3 SD below	0.4 SD below
5/3/16 (**58 dpi**)	0.7 SD below	1.4 SD below	0.2 SD below

4/19/16	1 SD below	2.3 SD below	1 SD below
4/26/16	3 SD below	2.4 SD below	1 SD below
5/3/16 (**37 dpi**)	2.4 SD below	2.4 SD below	1 SD below

all values are shown as standard deviations (SD) below normal projected growth

Need for caution

- fetuses **are** small, but are they pathogenically small due to ZIKV infection?
  - we do not know right now - more animals and more data will resolve more clearly

- head circumference and biparietal diameter would likely merit follow-up in pregnant women who have travelled to areas with high ZIKV prevalence

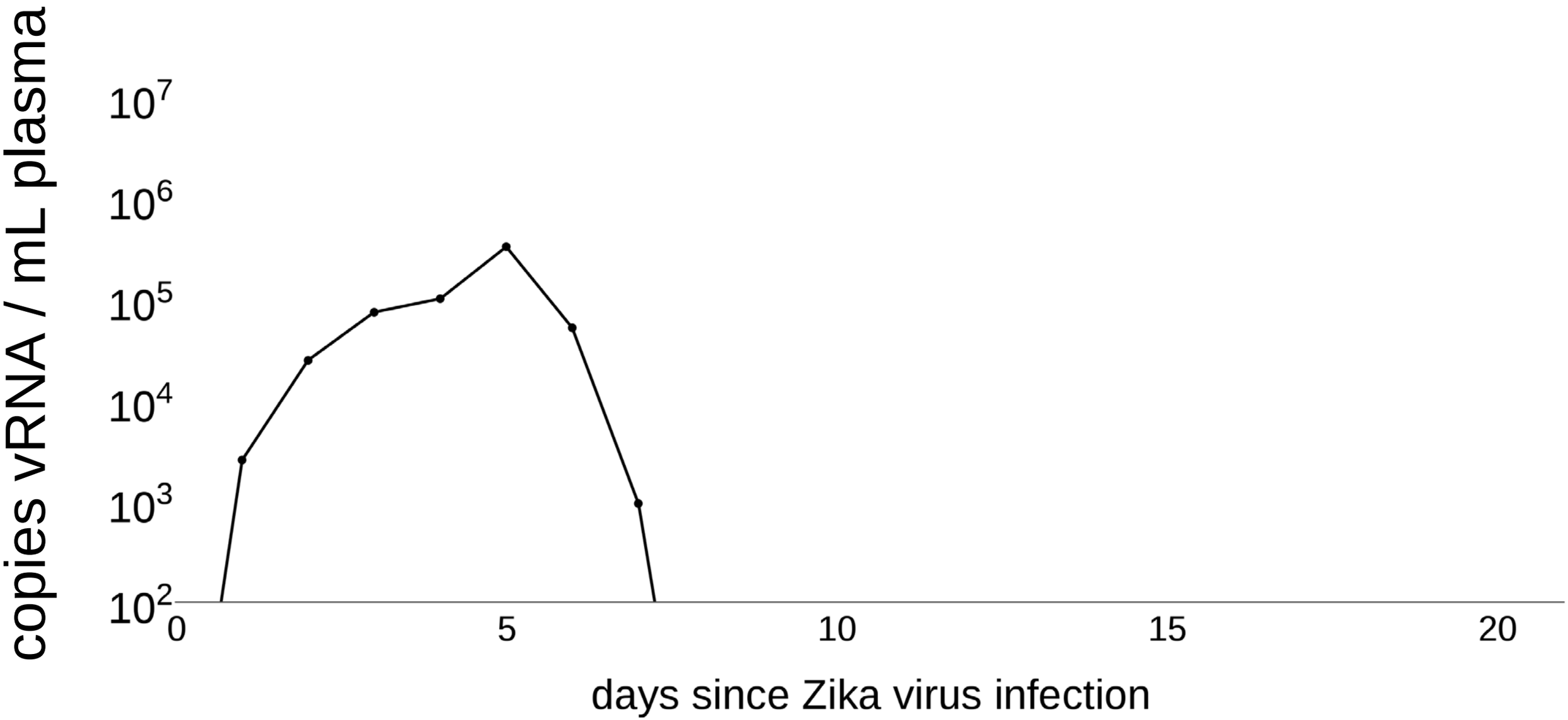
Macaques recapitulate key aspects of Zika virus pathogenesis

High priority questions in Zika virus research

- What is the natural history of Zika virus infection
  - when is viremia detected and cleared?
  - how much Zika virus is in different fluids throughout infection?
  - is there a difference between African and Asian strains?
- Do immune responses to Zika virus completely protect from re-infection?
- Does Zika virus infect or establish sanctuary in the nervous system?

When is viremia detected and cleared?

Plasma viremia lasts approximately 10 days in non-pregnant macaques



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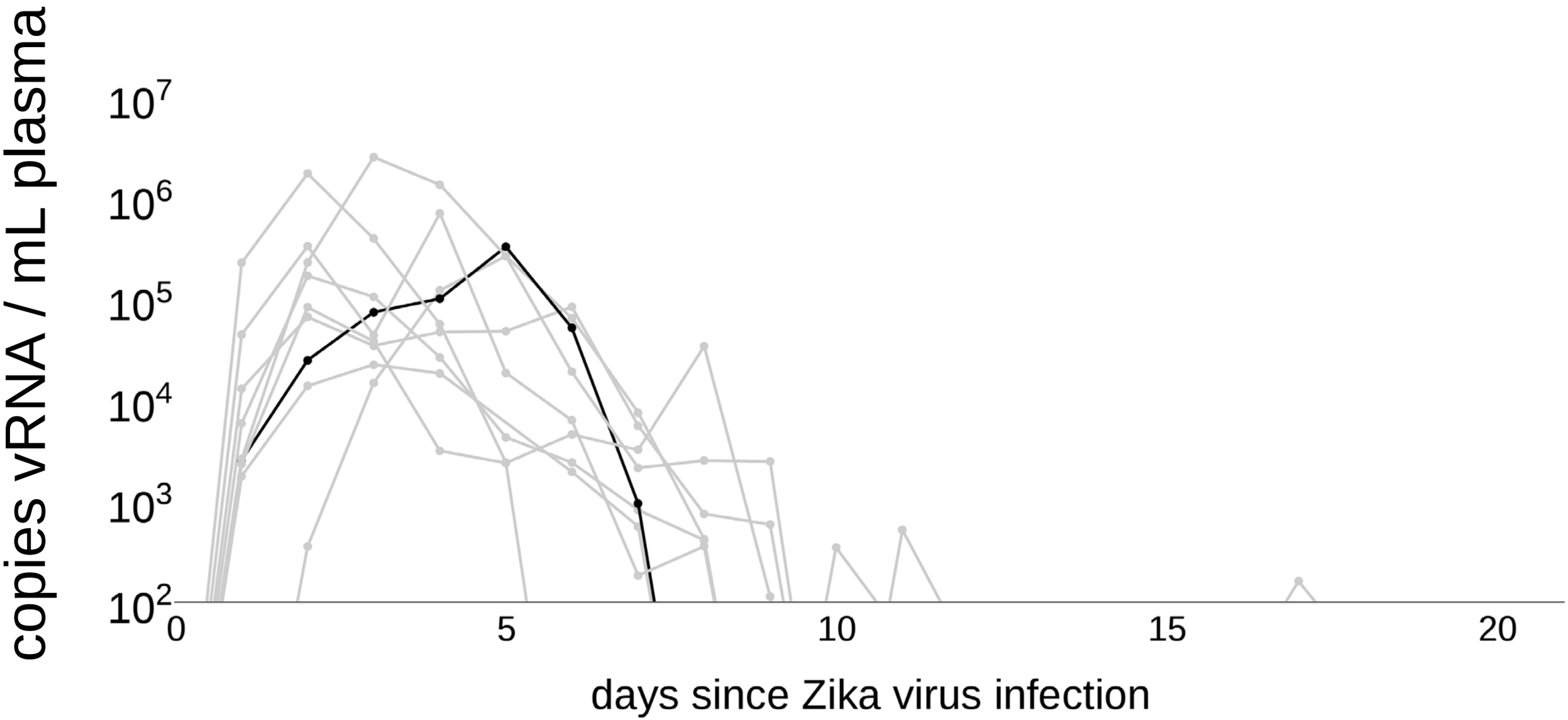
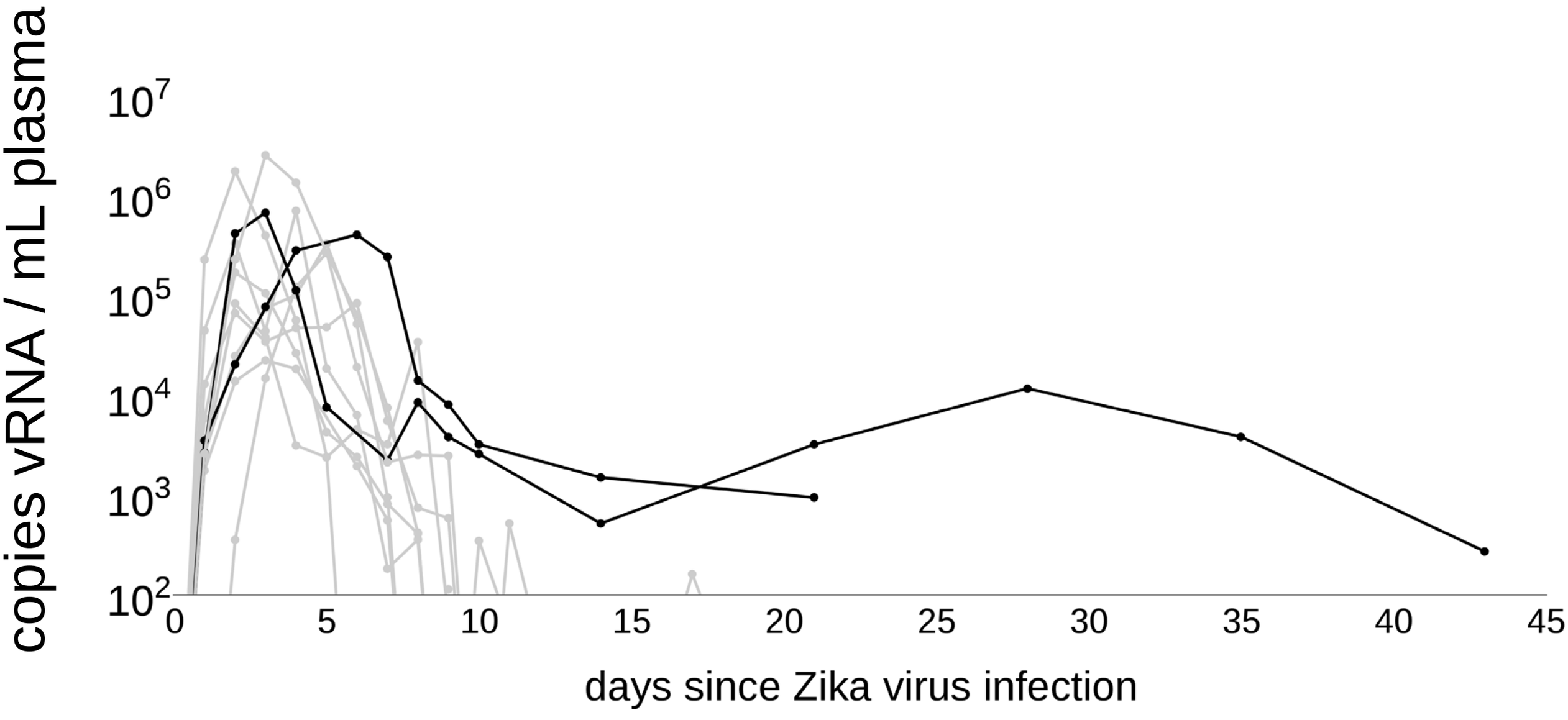
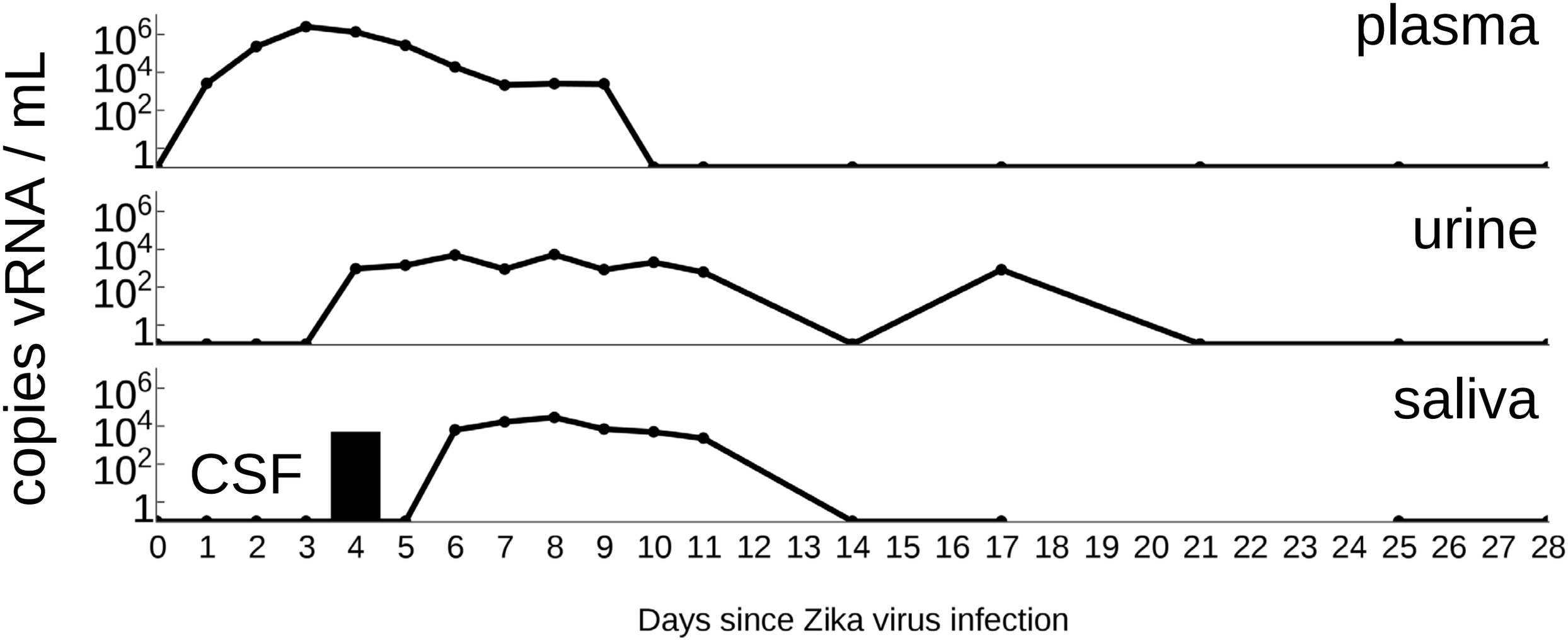


Plasma viremia is extended in pregnant macaques



How much Zika virus is in different fluids throughout infection?

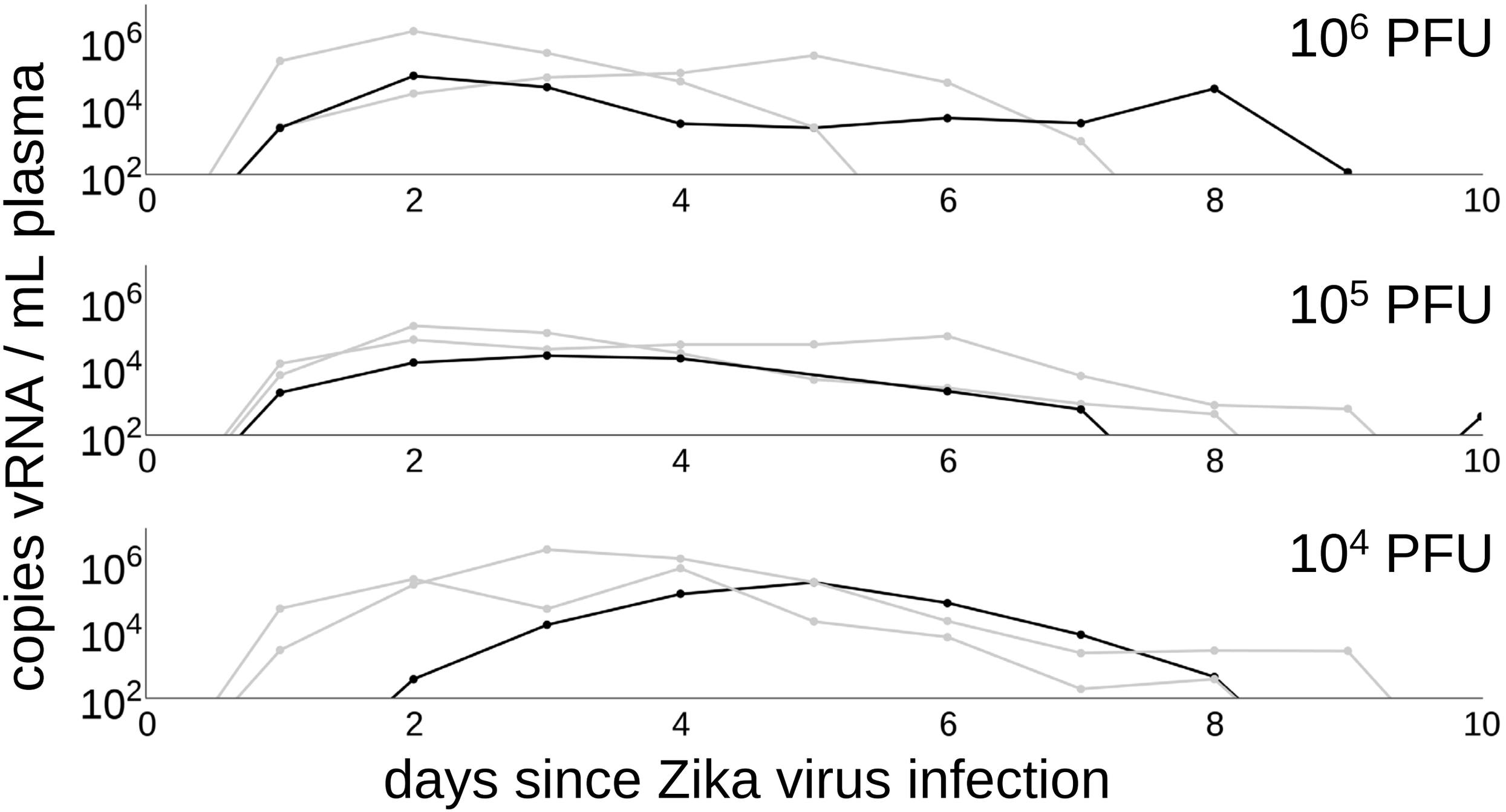
Zika virus is detectable in blood, saliva, urine, and CSF



also detected low levels in vaginal swabs;
semen not yet tested

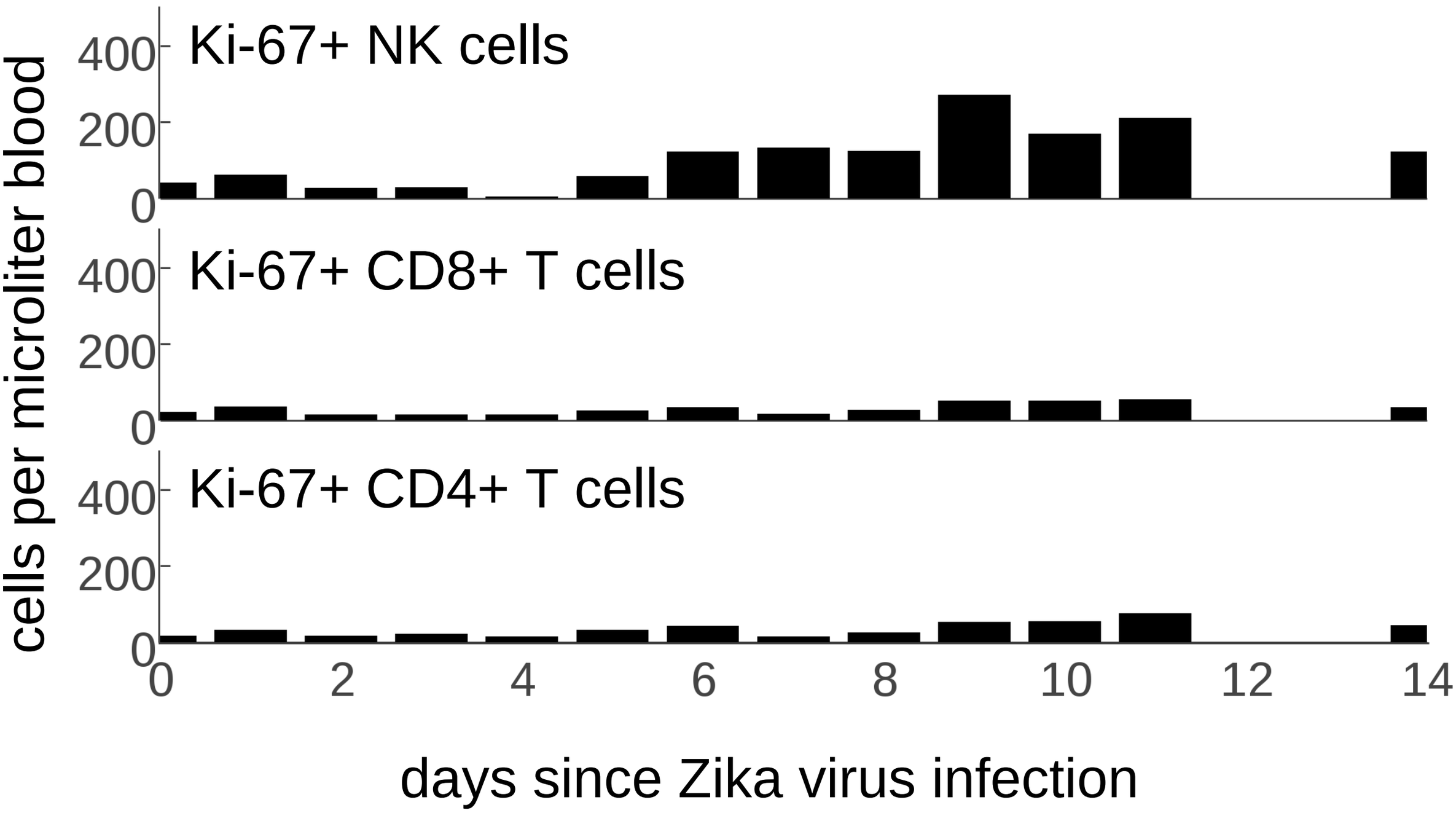
Is there a difference between African and Asian strains?

Lower viral loads in macaques challenged with African virus

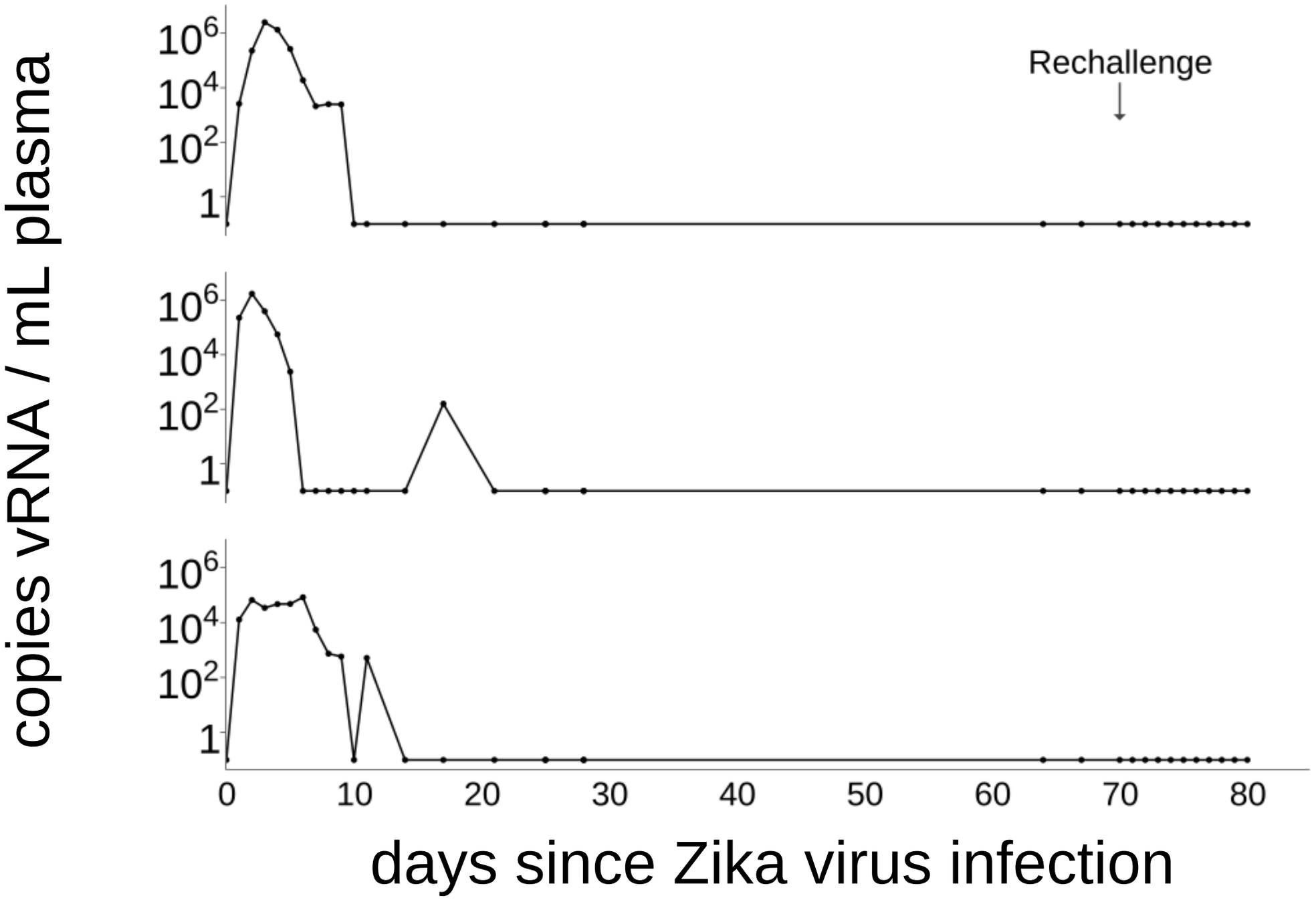


Do immune responses to Zika virus completely protect from re-infection?

Robust pathogen sensing during primary infection



Primary immunity completely protects against homologous rechallenge



From AIDS to ZIKV: maximizing macaque model utility

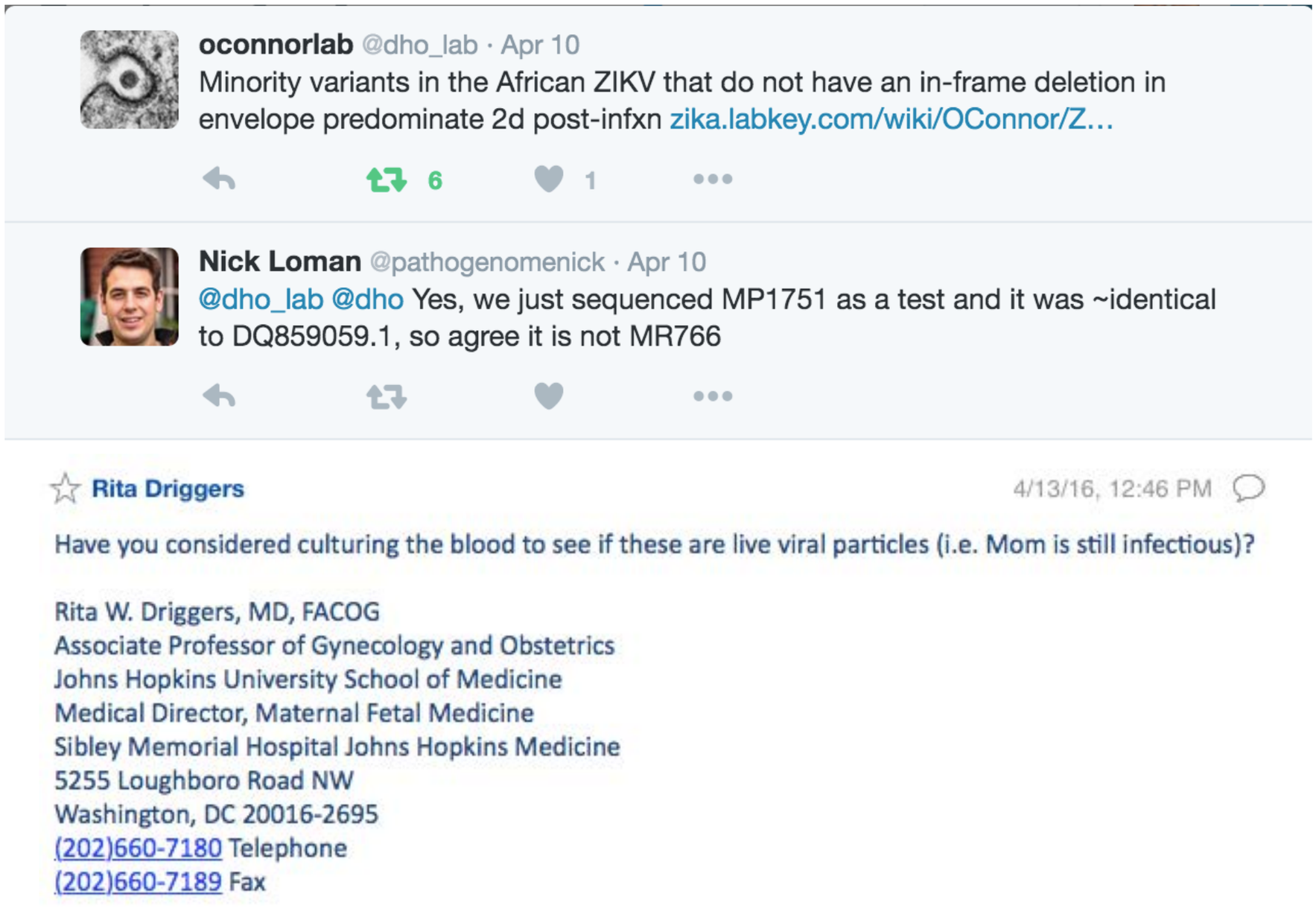
Key points

- Rapid results only matter if communicated quickly
- Experimental reproducibility requires careful coordination between investigators
  - selection and characterization of Zika virus strains for in vivo use
- Access and resources from National Primate Research Centers

Rapid results only matter if communicated quickly

http://zika.labkey.com

Enables stakeholders, scientists, and community to engage in experiments – leads to better, faster research

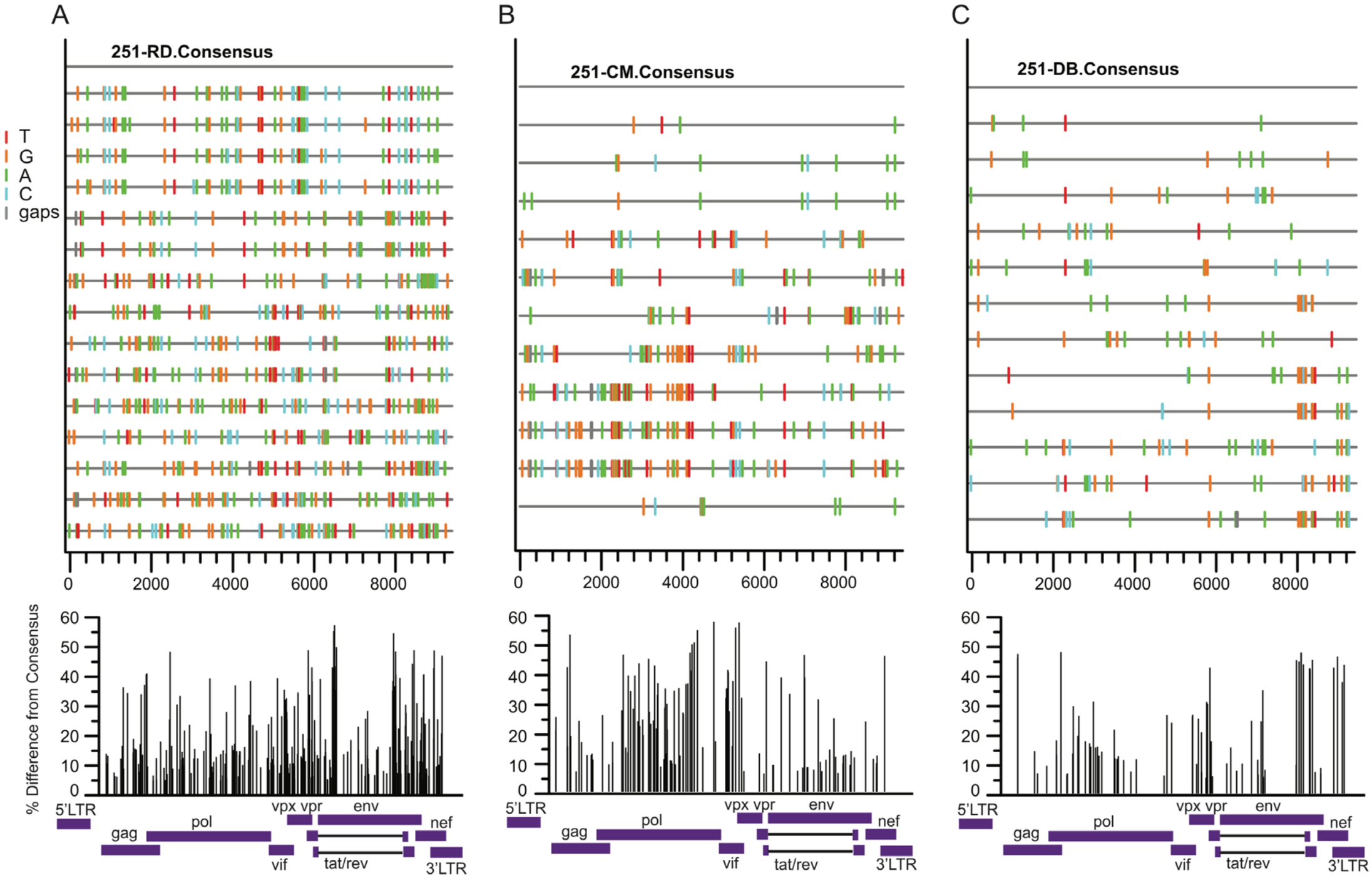


Zika virus real-time data sharing partners

- Wisconsin National Primate Research Center
- California National Primate Research Center
- Oregon National Primate Research Center
- Washington National Primate Research Center
- Sallie Permar, Duke University
- Amilcar Tanuri, Federal University Rio de Janeiro

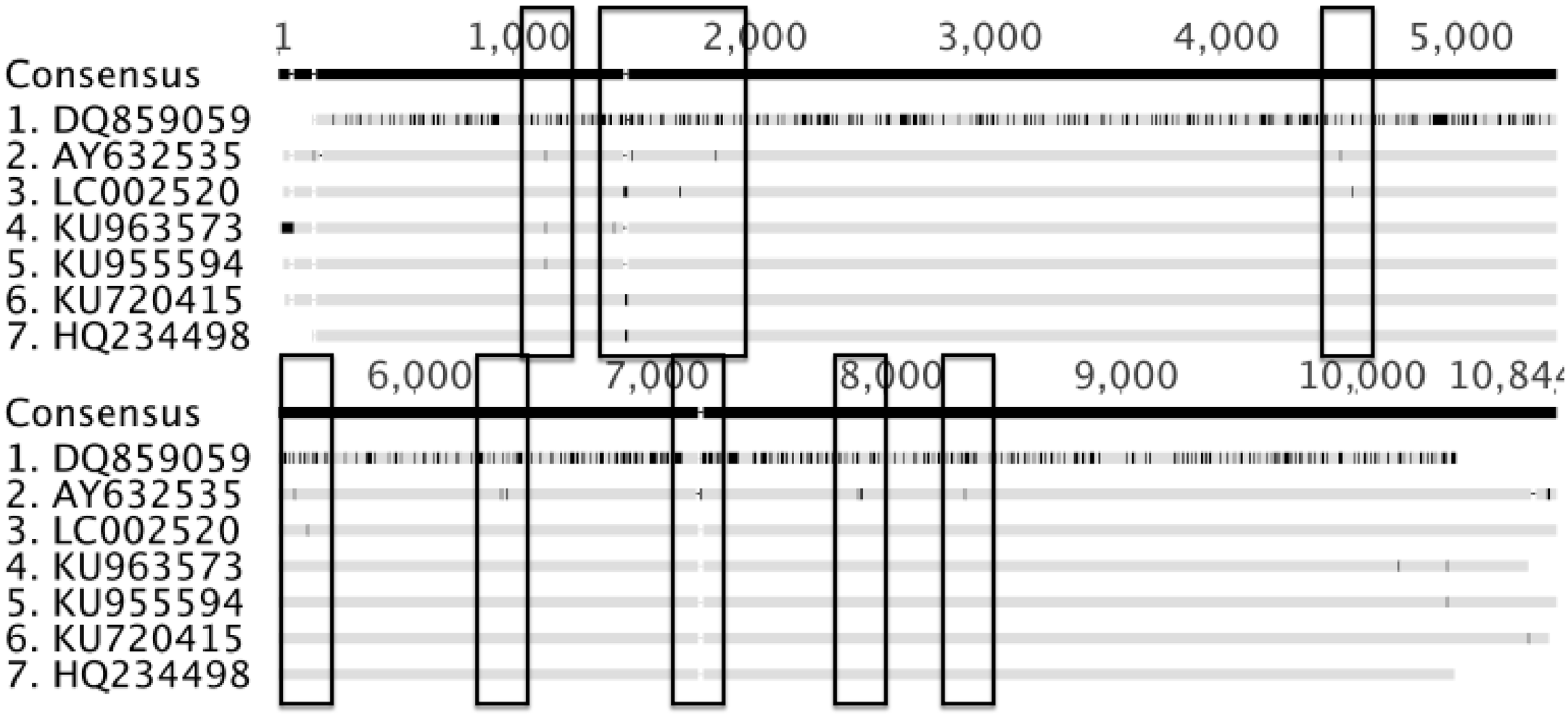
Experimental reproducibility requires careful coordination between investigators

“SIVmac251”



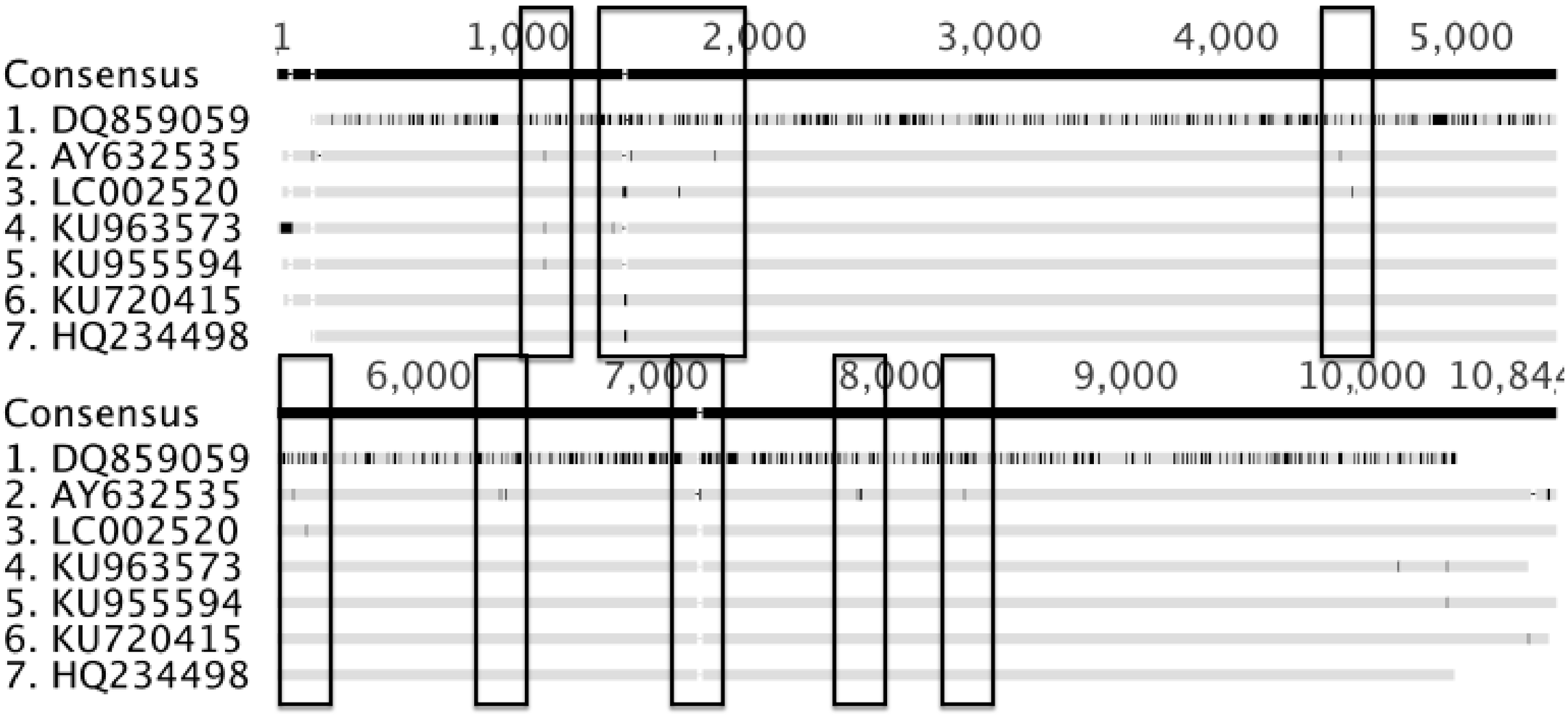
Del Prete et al., J. Virol 2013

“MR766”



Seven different sequences are all called ZIKV “MR766” (Uganda 1947) in Genbank

“MR766”



In vitro passage could impact biology — consider distribution of standardized “ready-to-use” viruses and challenge protocols for in vivo studies

Access and resources from National Primate Research Centers

Coordinated management of NPRC resources will be essential

- HIV/AIDS investigators, reproductive biologists, and neurobiologists all interested in studying Zika virus

- Breeding needs directly conflict with studying Zika virus in pregnant macaques
  - importing macaques for pregnancy studies logistically difficult

- Outdoor colonies may be susceptible to locally acquired Zika virus infections
  - need for accurate, inexpensive reagents to identify Zika virus and dengue virus SPF animals

Macaque studies are an important component of the response to the Zika virus threat

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