From Zika to AIDS

WISCONSIN
UNIVERSITY OF WISCONSIN–MADISON

Doherty
Institute

Disclosures

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BMS
Amgen
Emergent BioSolutions
Ionis Pharmaceuticals

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Pacific Biosciences
Roche/Nimblegen

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Battelle
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University of Melbourne:
Stephen Kent

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I am profoundly grateful for the guidance, support, and participation of volunteers who make our studies possible and have provided the rationale for undertaking preclinical nonhuman primate studies

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NIH P01AI132132
NIH P51OD011106

2005

2015

source: University of Wisconsin-Madison

Nearly nothing was known about Zika virus before the American outbreak in 2016.

Developing the research agenda for understanding Zika virus led us to re-evaluate what is possible when we study HIV/SIV.

Lesson 1: We can understand acute HIV/SIV infection better

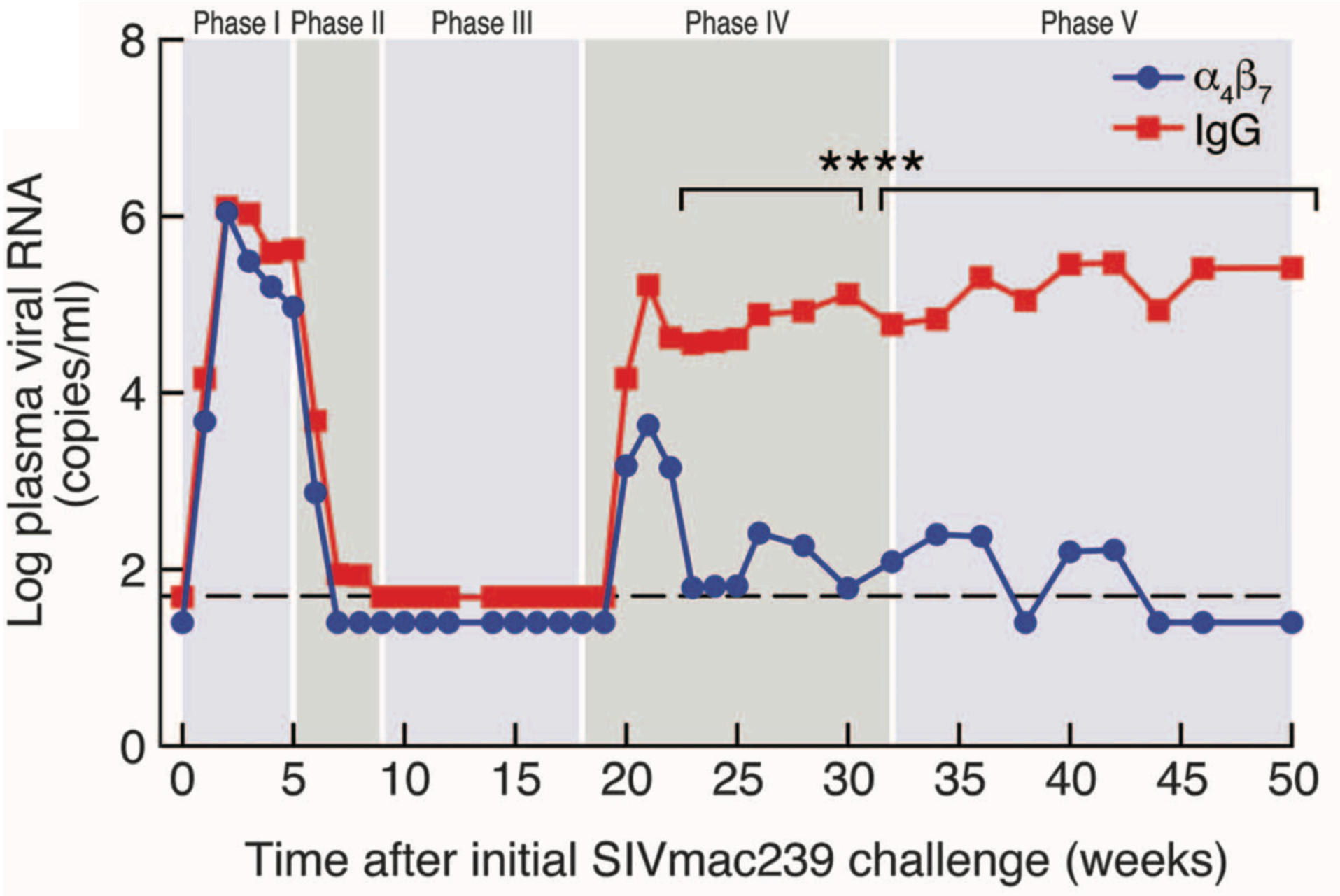
- Acute infection is extremely challenging to study in people, since most people do not know when they are exposed or infected

- Macaque models excel at studying acute simian immunodeficiency virus (SIV) infections

- Infect animals at specific times with exact doses of sequence-defined viruses via different routes

- Longitudinal studies with frequent sampling are simplified

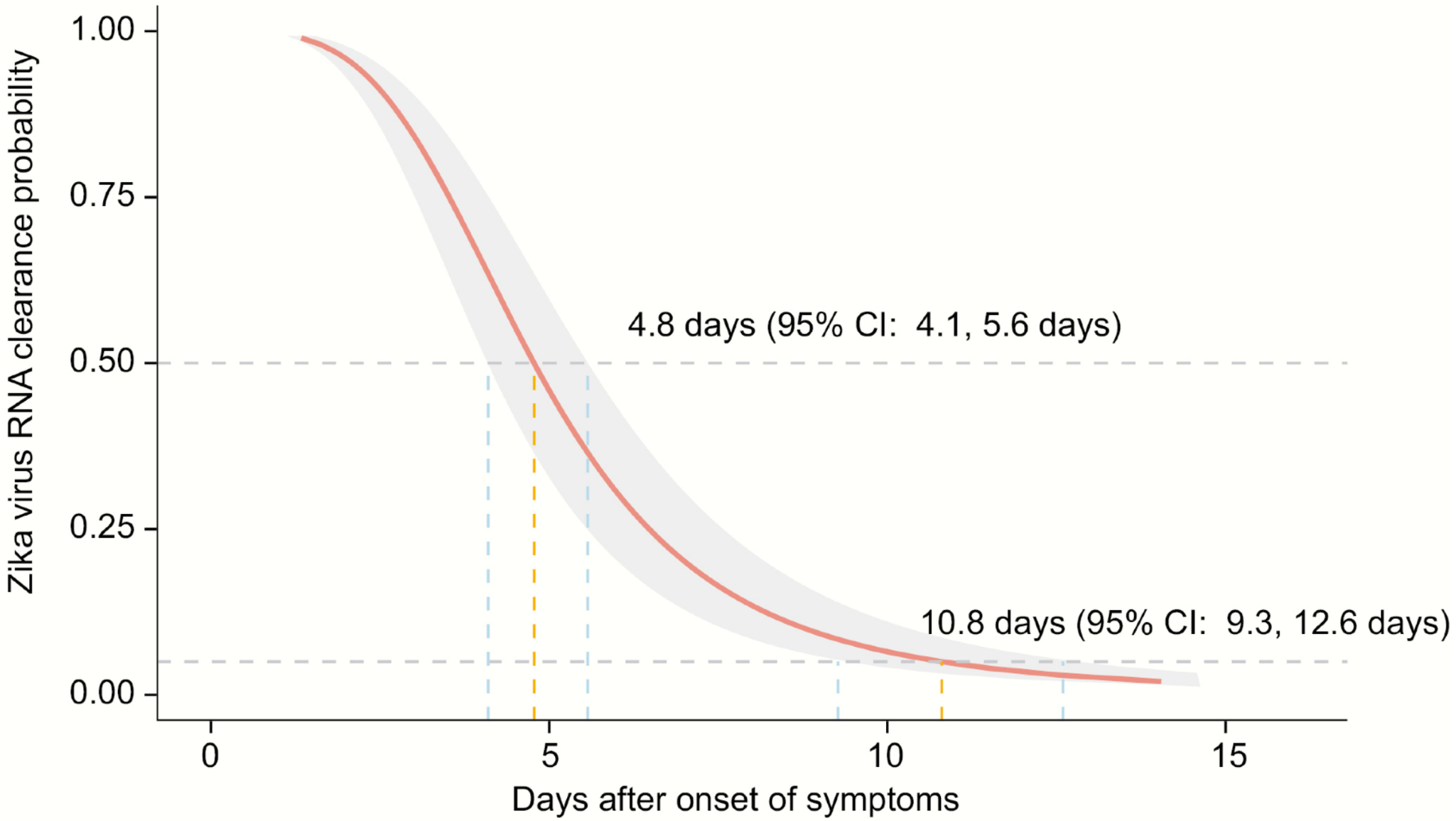
Why do SIV studies only sample animals once or twice a week during acute infection?



source: Byrareddy et al. Science, 2016

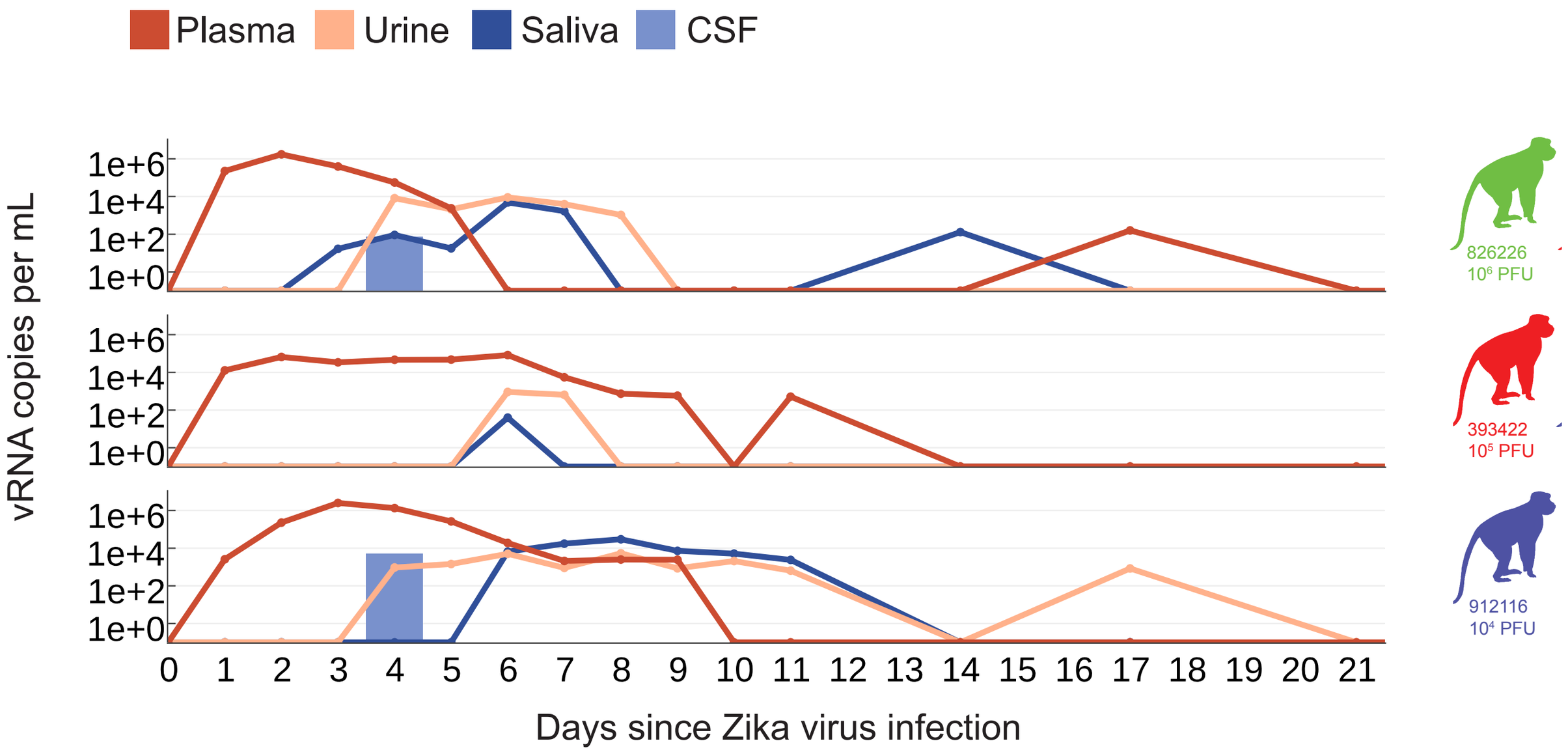
In 20 years, it never occurred to me to ask if we could take more frequent samples to more accurately profile viral dynamics in acute SIV infection

Zika virus is only detected in the blood for ~ 1 week



source: Fontaine et al. Clinical Infectious Diseases, 2018

To study Zika virus in monkeys we sampled every day for the first 10 days



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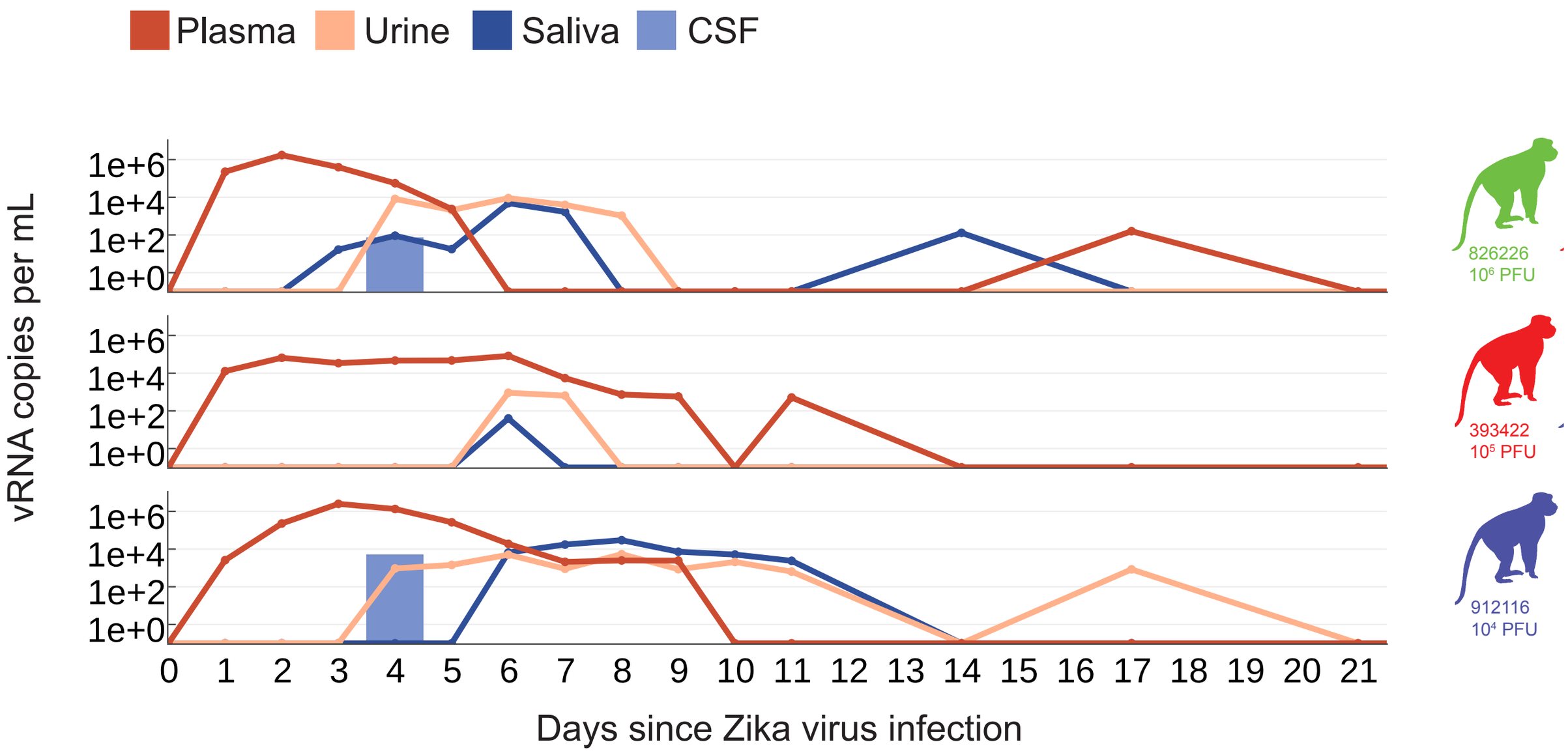

Daily or near-daily sampling is logistically challenging but possible without compromising animal health

The NIH Director

Photo Gallery

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Articles

Statements

May 13, 2014

NIH Takes Steps to Address Sex Differences in Preclinical Research

NIH

Over the past two decades, we have learned a great deal about how men and women respond differently to medications. This knowledge came after a concerted effort in the early '90s to increase the number of women in NIH-funded clinical research. Today, just over half of NIH-funded clinical research participants are women. Unfortunately, experimental design in cell and animal research has not always followed suit. An over-reliance on male animals, and neglect of attention to the sex of cells, can lead to neglect of key sex differences that should be guiding clinical studies, and ultimately, clinical practice. NIH is taking action to address this shortfall as outlined by Janine A. Clayton, M.D., Director of the NIH Office of Research on Women's Health, and me in the *Nature* Comment below.

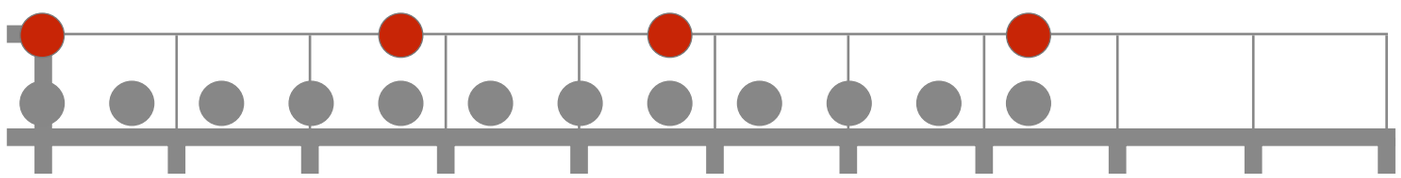
Francis S. Collins, M.D., Ph.D.
Director, National Institutes of Health

Nature Comment: NIH to balance sex in cell and animal studies
Reference: Clayton, J.A., Collins, F.S. NIH to balance sex in cell and animal studies. Nature. 509, 282-283 (2014)

Guidance issued for FY2017 funding

We realized that no studies had compared acute SIV plasma viral load dynamics between male macaques infected intrarectally, female macaques infected intravaginally

Evaluation of challenge route and sex impacts on acute SIV plasma viral loads



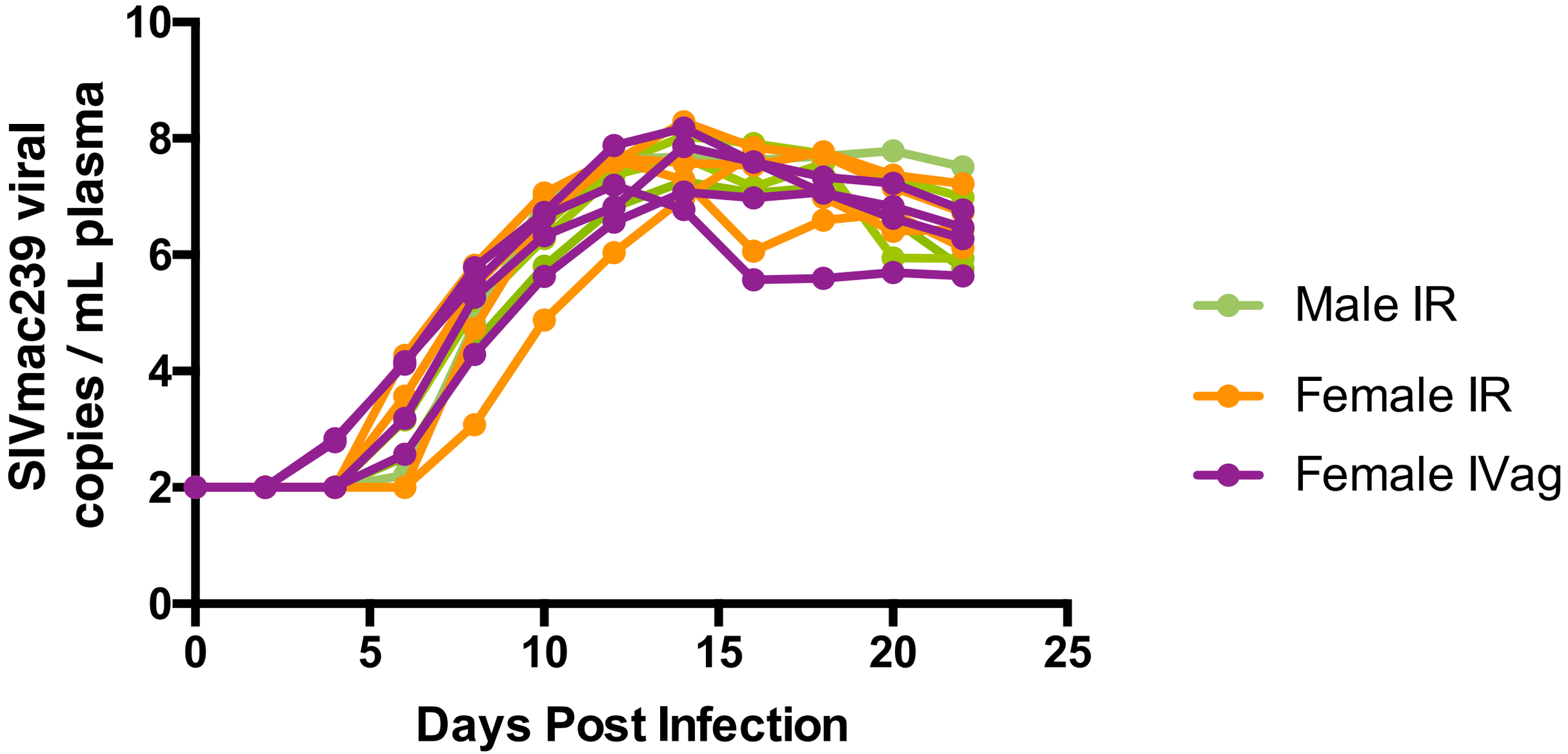
Days post-SIVmac239 infection

Four **males** challenged **intrarectally**

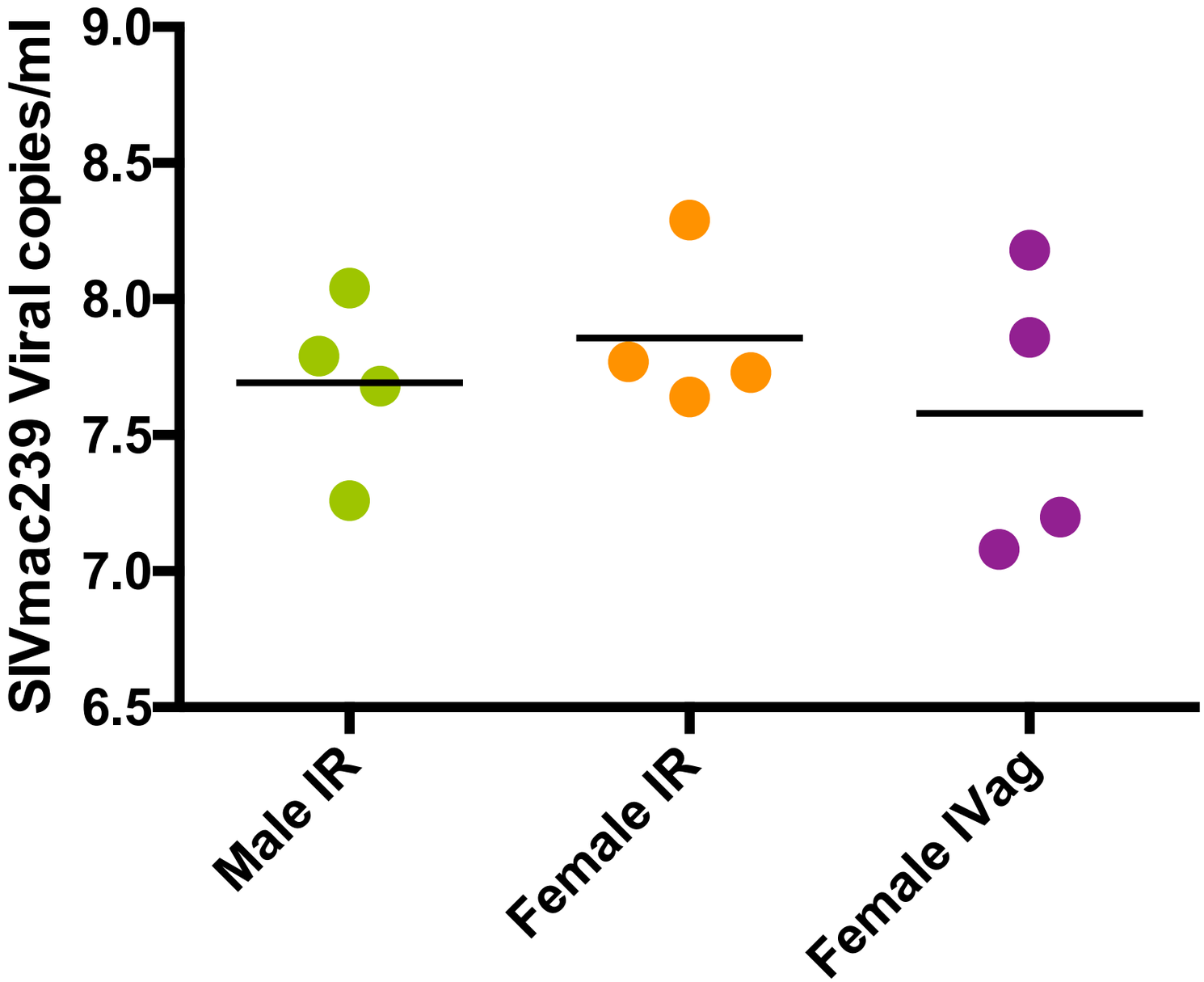
Four **females** challenged **intrarectally**

Four **females** challenged **intravaginally**

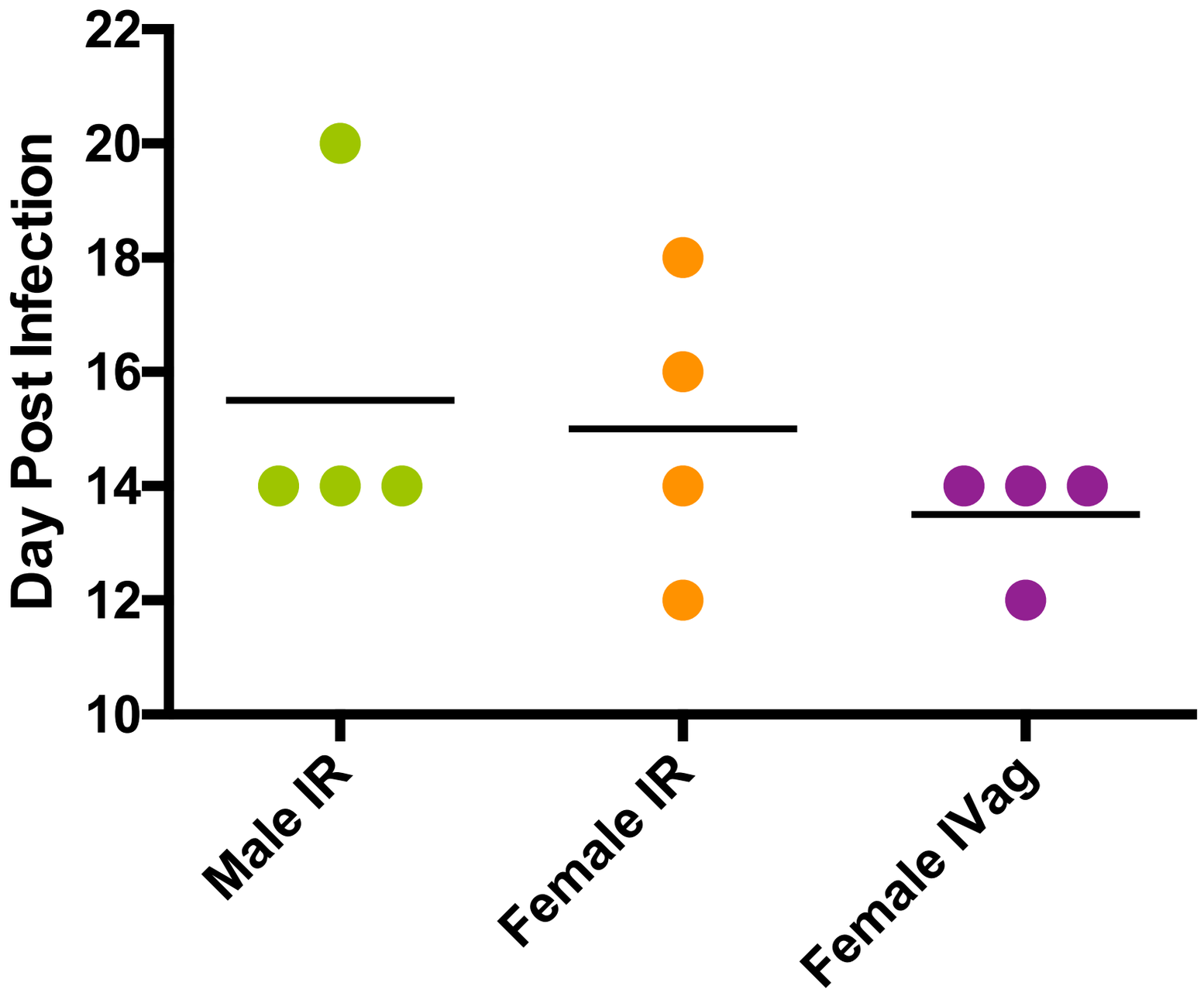
All three groups showed similar acute phase SIV viral load dynamics



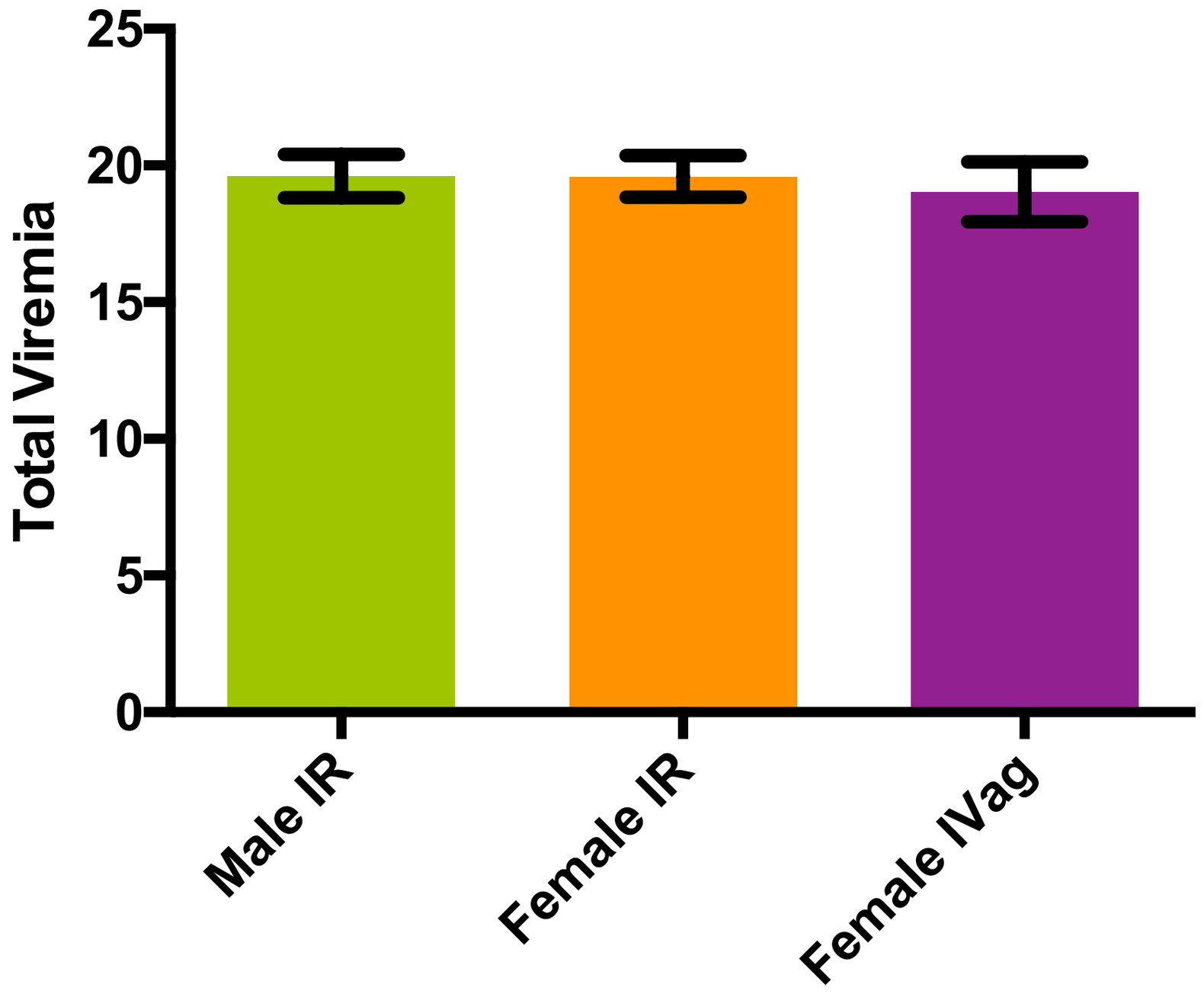
Peak SIV viral load did not differ significantly between groups



Number of days to peak viremia did not differ significantly between groups



Total viremia (area under the curve) did not differ significantly between groups



Lesson #1 summary

- **The basic biology of HIV/SIV replication during acute infection does not appear to be strongly impacted by sex or infection route when high dose of virus is used**

- **For studies where acute phase SIV viral dynamics (peak viral load, time to peak viral load, total viremia) are primary readouts, sex and route of SIV infection are unlikely to significantly impact results**

- **Do not necessarily need separately powered male and female groups for vaccine and cure studies where these are primary endpoints (though interventions might behave differently in males and females; intrarectal challenge of equal numbers of males and females may be sufficient for many studies)**

Live poll #1 - for scientists and clinicians

Which of the following best describes how and when data collected in your studies are typically made available to others?

A. In or near real-time, as soon as the data is available

B. At conferences and meetings, months **before** submission to peer-reviewed journals

C. At the time of submission to peer-reviewed journals, via pre-print archives such as Biorxiv

D. Results and data are available upon publication of peer-reviewed manuscripts that are freely available

E. I publish results in peer-reviewed journals but do not typically consider whether the journal can be accessed freely by others because most papers are eventually made publicly available via Pubmed Central after an embargo period.

F. I work for an organization that rarely publishes or divulges research results

Live poll #2 - for everyone else

Which of the following best describes how and when you would like data from HIV studies to be made available?

A. In or near real-time, as soon as the data is available

B. At conferences and meetings, months **before** submission to peer-reviewed journals

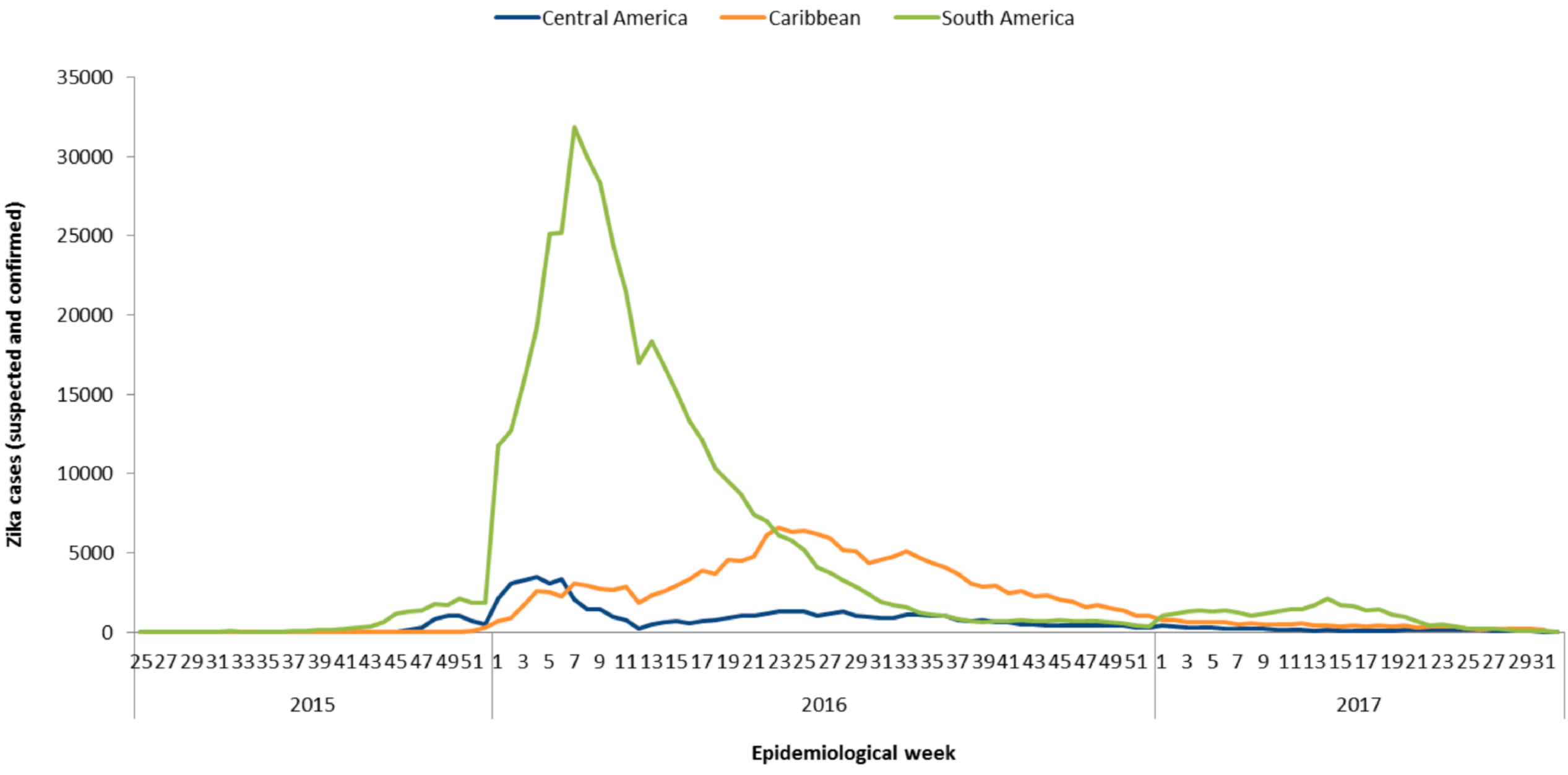
C. At the time of submission to peer-reviewed journals, via pre-print archives such as Biorxiv

D. Results and data are available upon publication of peer-reviewed manuscripts that are freely available

E. In peer-reviewed journals, whether or not they are freely available. Most results are eventually released from embargo by Pubmed Central and made available for free.

F. I do not particularly care how and when research results are made available

Zika virus spread explosively in the Americas in early 2016



August 25, 2017 Pan American Health Organization

Lesson 2: Norms around data sharing in emerging disease outbreaks are changing

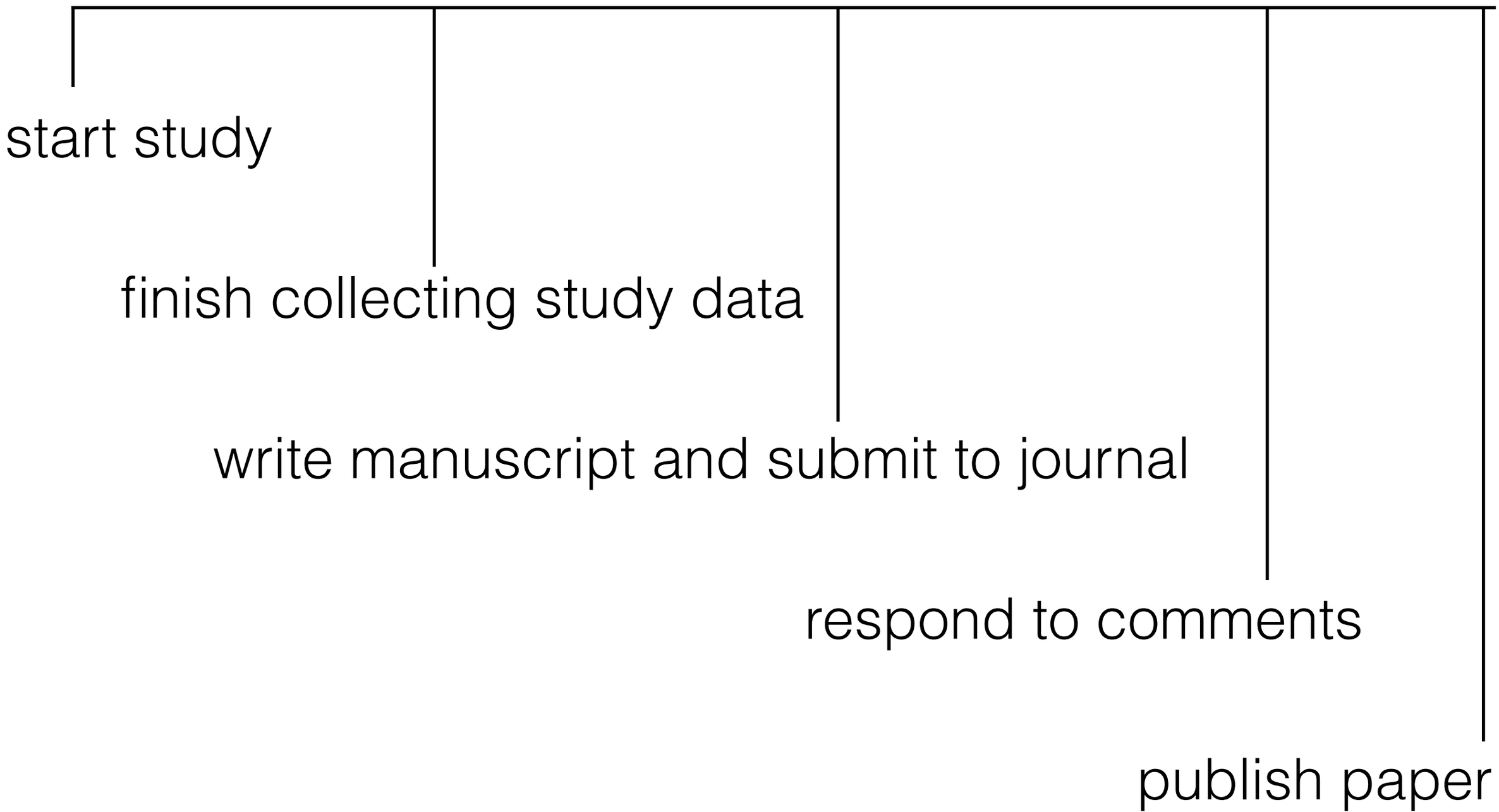
- **Journals commit to making Zika virus research free to access**

- **Funders will require researchers to share data with the community**

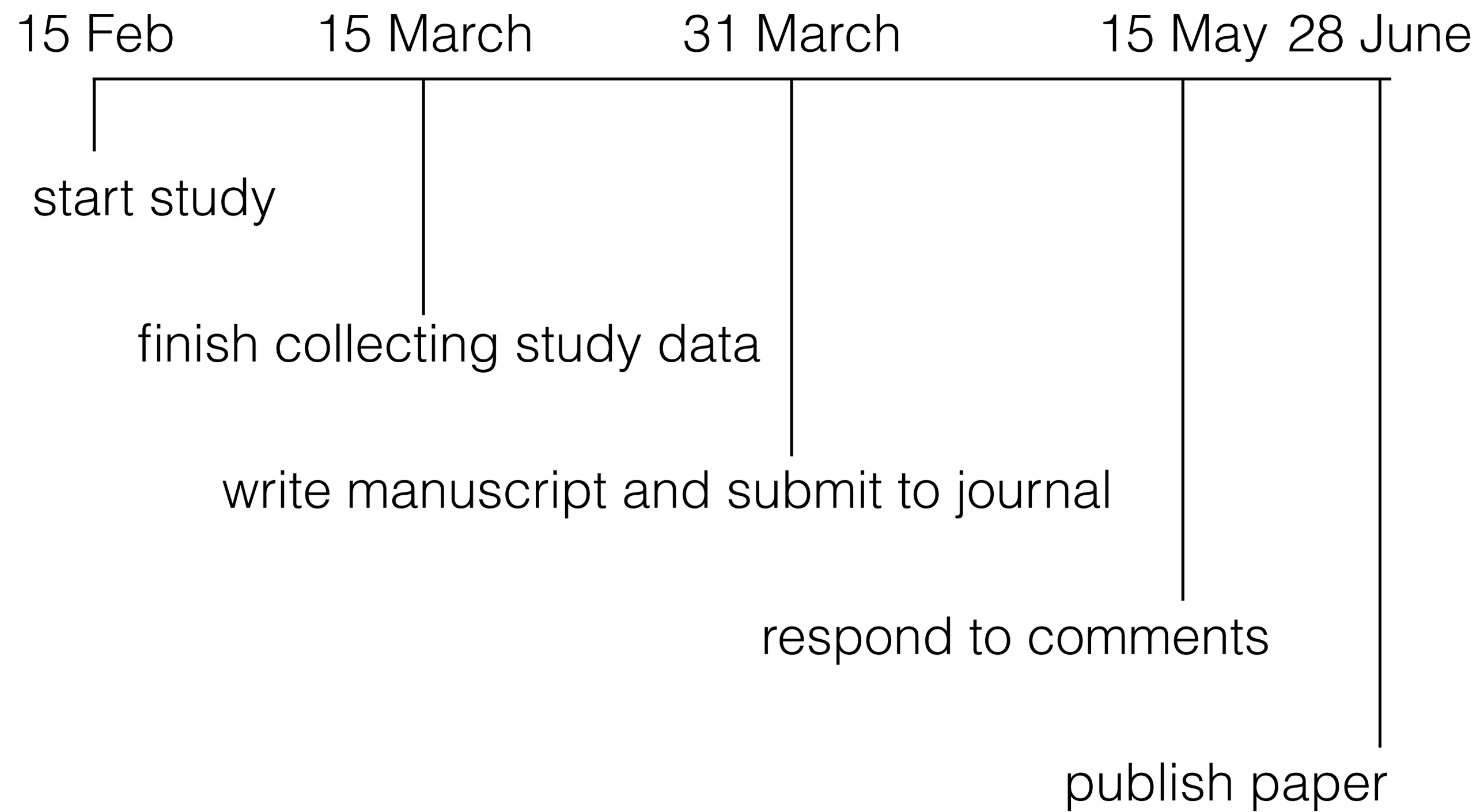
- **https://blogs.plos.org/plos/2016/02/statement-on-data-sharing-in-public-health-emergencies/**

Academy of Medical Sciences, UK
Bill and Melinda Gates Foundation
Biotechnology and Biological Sciences Research Council (BBSRC)
The British Medical Journal (BMJ)
Bulletin of the World Health Organization
Canadian Institutes of Health Research
The Centers for Disease Control and Prevention
Chinese Academy of Sciences
Chinese Centre for Disease Control and Prevention
The Department of Biotechnology, Government of India
The Department for International Development (DFID)
Netherlands Organisation for Health Research and Development
Deutsche Forschungsgemeinschaft (DFG)
eLife
The Economic and Social Research Council (ESRC)
F1000
Fondation Mérieux
Fundação Oswaldo Cruz (Fiocruz)
The Institut Pasteur
Japan Agency for Medical Research and Development (AMED)
The JAMA Network
The Lancet
Médecins Sans Frontières/Doctors Without Borders (MSF)
National Academy of Medicine
National Institutes of Health, USA
National Science Foundation, USA
The New England Journal of Medicine (NEJM)
PLOS
Science Journals
South African Medical Research Council
Springer Nature
UK Medical Research Council
Wellcome Trust
ZonMw - The

Study publication timeline



Study publication timeline



Study publication timeline

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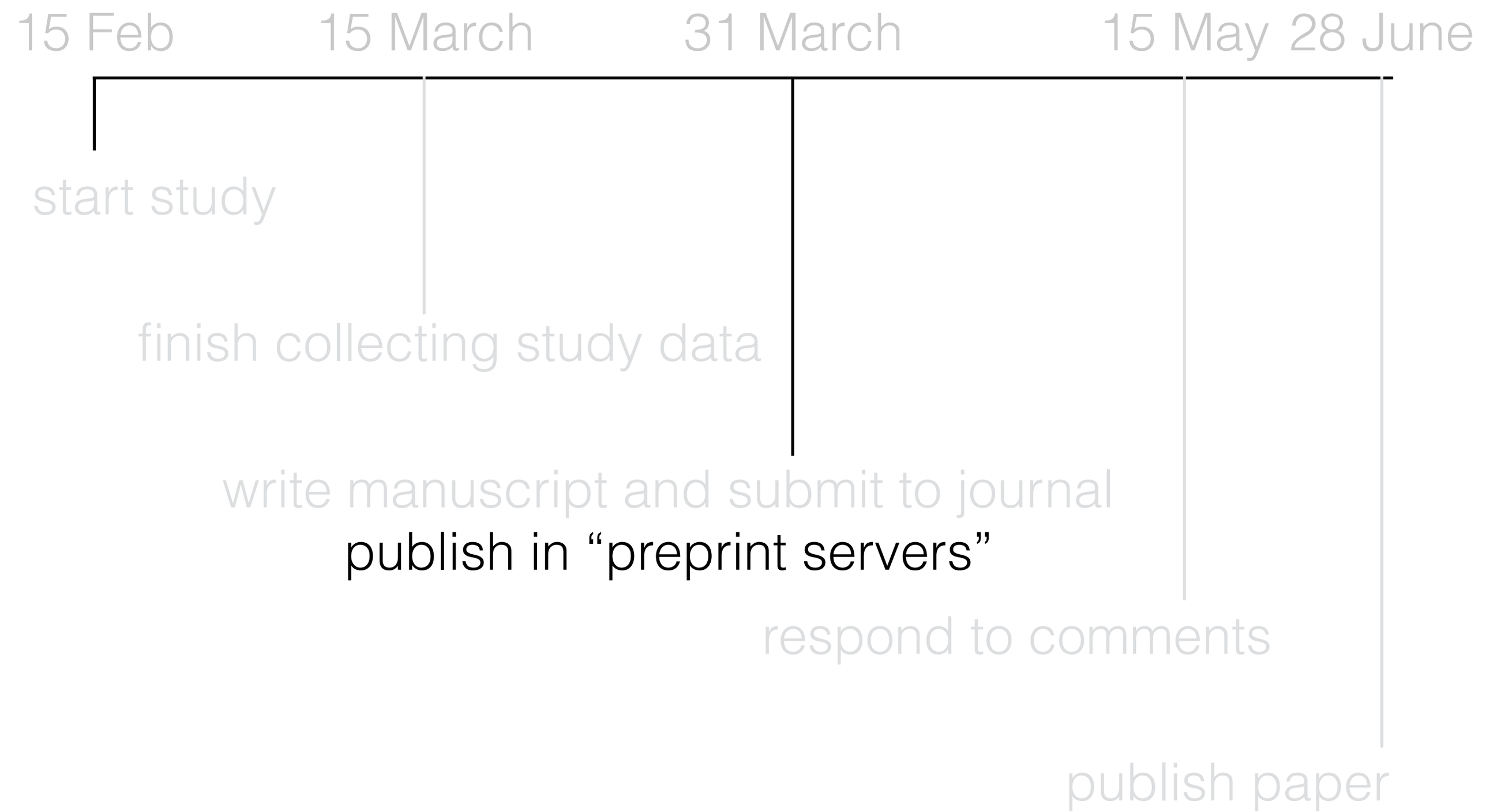

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View by Month

Proudly supported by CHAN ZUCKERBERG INITIATIVE

New Results

A rhesus macaque model of Asia lineage Zika virus infection

Dawn M. Dudley, Matthew T. Aliota, Emma L. Mohr, Andrea M. Weiler, Gabrielle Lehrer-Brey, Kim L. Weisgrau, Mariel S. Mohns, Meghan E. Breitbach, Mustafa N. Rasheed, Christina M. Newman, Dane D. Gellerup, Louise H. Moncla, Jennifer Post, Nancy Schultz-Darken, Michele L. Schotkzo, Jennifer M. Hayes, Josh A. Eudailey, M. Anthony Moody, Sallie R. Permar, Shelby L. O'Connor, Eva G. Rakasz, Heather A. Simmons, Saverio Capuano, Thaddeus G. Golos, Jorge E. Osorio, Thomas C. Friedrich, David H. O'Connor

doi: https://doi.org/10.1101/046334

This article is a preprint and has not been peer-reviewed [what does this mean?].

ARTICLE INFORMATION

doi https://doi.org/10.1101/046334

History May 10, 2016.

ARTICLE VERSIONS

Older version (March 30, 2016 - 20:38).

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Study publication timeline

15 Feb — start study

15 March — write manuscript and submit to journal

31 March — publish in “preprint servers”

15 May — respond to comments

28 June — publish paper

We took Zika virus data sharing one step further

zika.labkey.com
Zika public portal | Inbox | Gmail | EHR | dholk | Technology | News | Social | OC Servers | Science | MSN Radar | Inbox
Estim | www.cdc.g | wisconsin na... | sallie permar... | zest zika - G... | David O'Con... | Keynote | Start Page: /...

Zika Open-Research Portal

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Introduction

Welcome to the Zika experimental science team (ZEST) data portal. Given the urgency of the ongoing Zika virus epidemic, we are making our study results available in real-time. Each study and its available data are shown below. For example, the first study performed by the ZEST team is ZIKV-001. If there are data you would like but are not available, please contact us. We are also happy to answer questions about the data as best as possible, but we apologize in advance if we do not have time to answer each and every question.

Questions or comments can be directed to Dave O'Connor dhoconno@wisc.edu. You can also follow the O'Connor lab (@dho_lab) or Dave (@dho) on Twitter.

LabKey (long-time technology partners of the O'Connor Lab) has launched the Zika Open-Research Portal to help facilitate collaborative research. This portal provides researchers with a platform to share raw data, study commentary and results with the public in real-time. Projects are freely available to investigators.

If you are interested in making your research publicly available through the portal, please contact LabKey to get started.

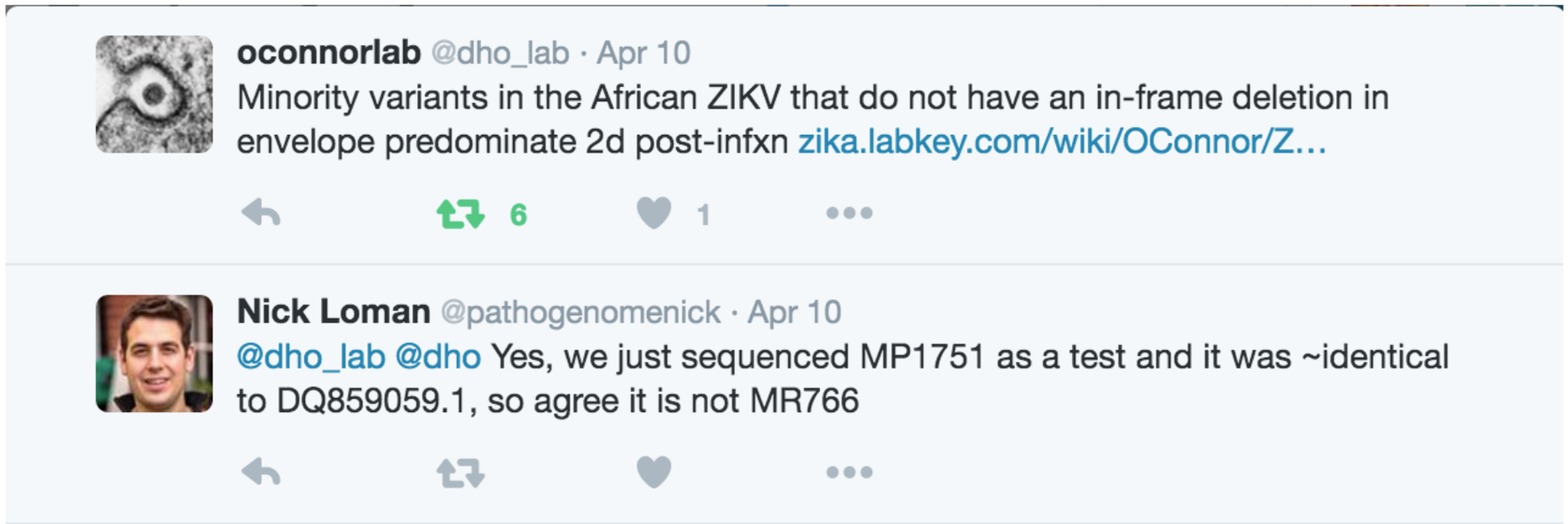
Direct Study Links

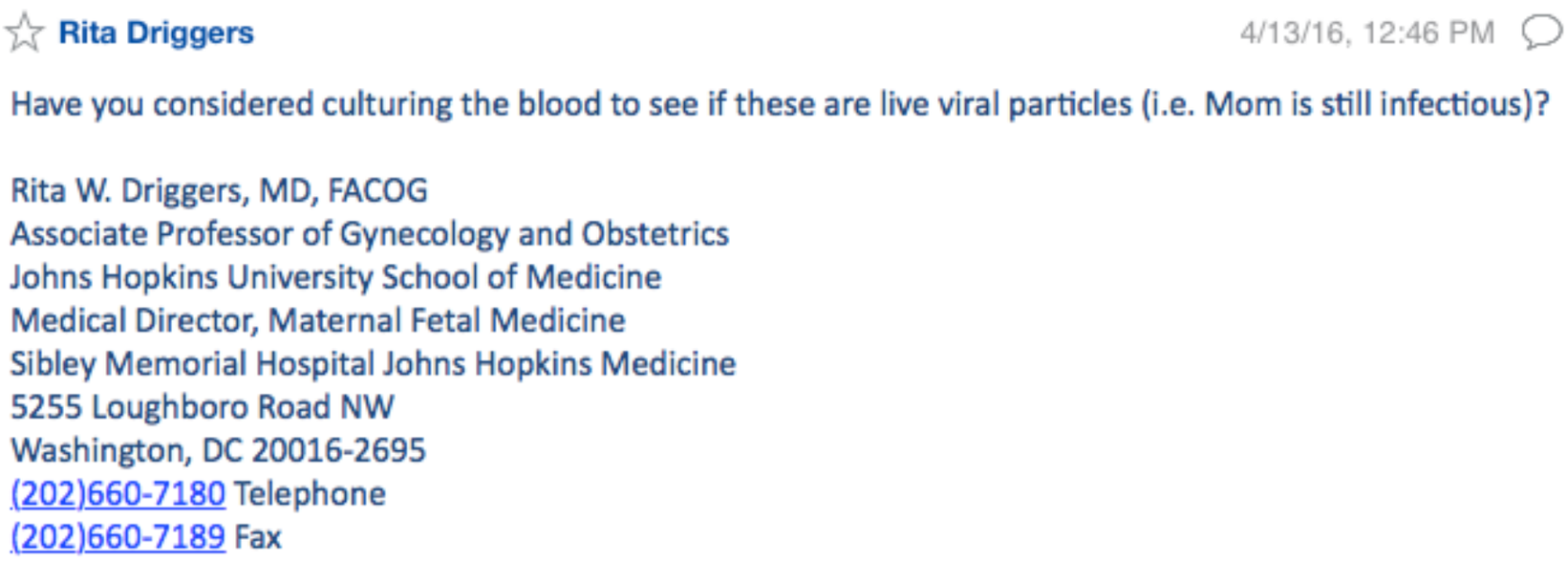
- ZIKV-001
- ZIKV-002
- ZIKV-003

dho_lab
Tweets
oconnorlab @dho_lab
Our paper "Heterologous protection against Asian Zika virus challenge in rhesus macaques" is now posted on bioRxiv. biorxiv.org/content/early/...
oconnorlab @dho_lab
23h
Several tissue biopsies positive for #ZIKA viral RNA despite aviremic plasma. zika.labkey.com/announcements/...
oconnorlab @dho_lab
5d
@MackayIM @nicolamlow @FabiKrauer Also, @marielmohns will be putting other data online this week, but we won't have more fetal info
oconnorlab @dho_lab
5d
@MackayIM @nicolamlow @FabiKrauer It's because the ultrasound data (u/s) which is what we have most doesn't have clear interpretation
oconnorlab @dho_lab
5d
@FabiKrauer @nicolamlow @MackayIM In utero u/s (see portal) suggest somewhat smaller than normal, but equivoca so far.
oconnorlab @dho_lab
5d
@FabiKrauer @nicolamlow @MackayIM Second C-section on animal with sustained viremia this week. 60+ tissues, tho, so analyzing slow
oconnorlab @dho_lab
5d
@FabiKrauer @nicolamlow @MackayIM We only have C-section data on one animal so far, and this animal did not have sustained viremia.
oconnorlab @dho_lab
7d
Confirmed protection from homologous reinfection and pregnancy updates. zika.labkey.com/announcements/...

http://zika.labkey.com

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





ScienceTimes
The New York Times

Zika Data Sent Right To the Web

Online sharing of vital research points to a new way of responding to epidemics.

By DONALD G. McNEIL Jr.

MADISON, WIS. — Of the hundreds of monkeys in the University of Wisconsin's primate center, a few — including rhesus macaque 827577 — are now famous, at least among scientists tracking the Zika virus.

Since February, a team led by David H. O'Connor, the chairman of the center's global infectious diseases department, has been conducting a unique experiment in scientific transparency. The tactic may presage the evolution of new ways to respond to fast-moving epidemics.

Dr. O'Connor and his colleagues have been infecting pregnant female macaques with the Zika virus, minutely recording their symptoms, and giving them blood tests and ultrasounds. But then, instead of saving their data for academic journals, the researchers have posted it almost immediately on a website anyone can visit.

The openness of the process thrills scientists, who say it fosters collaboration and speeds research.

"David's work is very useful," said Dr. Koen Van Rompay, a virologist at the California National Primate Research Center at the University of California, Davis. "We all learn from each other and make sure we don't duplicate each other's work."

Back-to-back epidemics of Ebola and Zika have driven some infectious disease specialists to embrace greater speed and openness. Until now, they felt forced to hoard data and tissue samples: Careers depend on being published in prestigious journals, which often refuse to publish work that has previously been released and may take months to edit papers.

At the same time, Dr. O'Connor's openness has exposed some of the more macabre requirements of scientific research.

Animal rights activists are upset at the brutal reality of infecting female monkeys and dissecting their babies. They argue that the work is unnecessary because scientists have already learned a lot by drawing blood

GREG LOVETT/THE PALM BEACH POST, VIA ASSOCIATED PRESS

Challenges to open data sharing

- **Effort required can be considerable, especially for studies that have complex, interconnected data sets**

- **Vulnerable to initial interpretations being propagated even though newer data can lead to revised interpretations - may not be appropriate for clinical trials**

- **Reluctance of some collaborators (especially industry partners) to share information that could compromise intellectual property claims**

- **Open data sharing is not orthodox; conventional metrics are still used to rate and evaluate scientific careers**

I respectfully submit that these challenges are more than counterbalanced by the good that can come from sharing information freely during a public health emergency

The lifetime cost of care for each baby affected with ZIKV-associated microcephaly is estimated at **$3.8m USD**

As of July 17, 2018, **283** infants have been born in the US and US territories with ZIKV-associated birth defects

In the United States alone, children affected by ZIKV during pregnancy will likely cost the health care system **~1b USD**

Scott Grosse, CDC Research Economist, personal communication August 14. 2018

An estimated **5,000** people are newly infected with HIV each day

Approximately **37,000,000** are living with HIV/AIDS

Between 2000-2015, approximately **$560b** USD was spent on HIV/AIDS worldwide

https://www.hiv.gov/hiv-basics/overview/data-and-trends/global-statistics; https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)30698-6/fulltext

What can HIV/AIDS scientists learn from Zika virus data sharing?

- **Dip your toes in the water - try making your data slightly more available and see if anything bad happens**

- **If you typically present mainly published results at meetings like this, present unpublished studies in progress**

- **Submit your manuscripts to pre-print servers like biorxiv (https://www.biorxiv.org) at the same time as submissions to peer reviewed journals**

    - **In 2018, 106 papers with 'HIV' in title in biorxiv versus 6,739 in NCBI PubMed (1.6%)**

- **Make "negative" data available to others**

As of 5 September 2018

You already share data every day - it’s not hard!

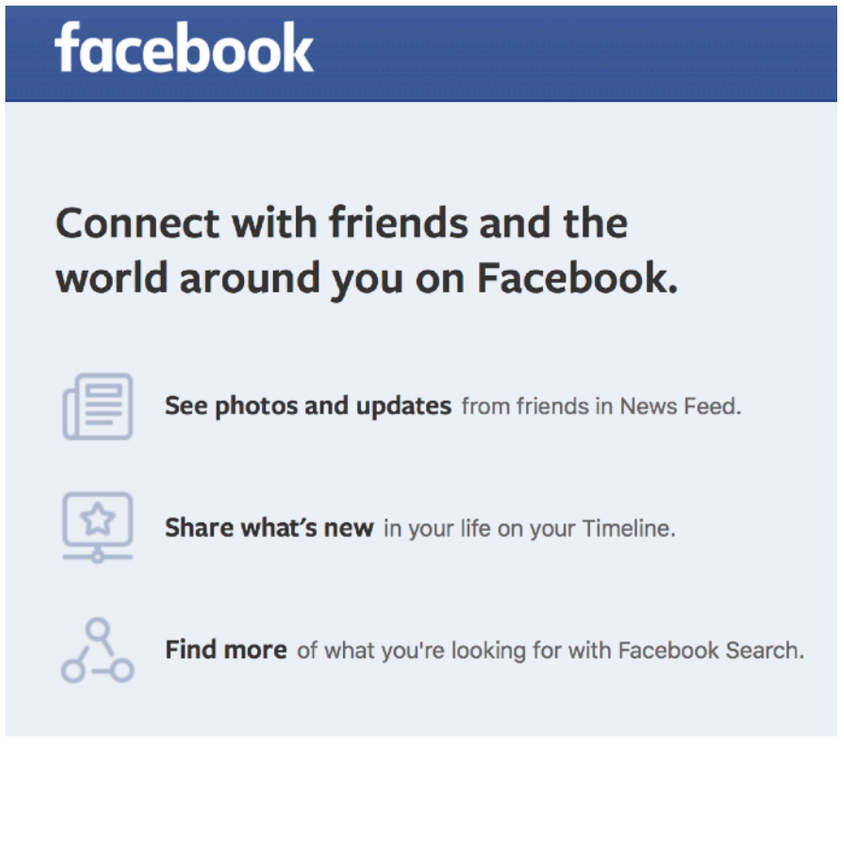
Monday, September 3, 2018

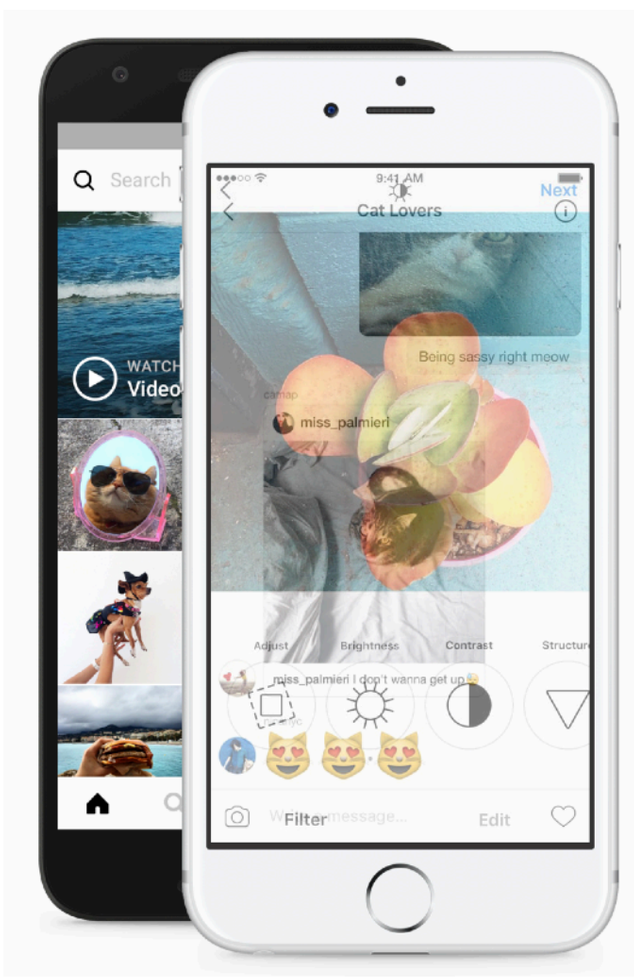
Father's Day -- again!!

In case you didn't know, Father's Day in Australia is in September! Sheesh! Dave claimed TWO Father's Days this year. Oh well, he deserves it. We had a nice Father's Day #2. We took a nice walk in Royal Park and the boys took pictures of birds. Then, we ended up at the Zoo. We became members, which will get us entry into several zoos across Australia during the year, and it means we can just pop into the zoo for an hour or two and not feel like we need to spend the whole day there. Afterwards, we each got to play tennis. I played doubles with folks who play at my level, and Dave got to play with the real experts. Good times were had by all.

On another note - we went to high table at Queen's College tonight and we learned that there are two other kids there, aged 5 and 2. They are a little younger than Eli, but certainly they can be mates for him and introduce him to the wonders of Queen's after we move there.

-- shelby





What can other HIV/AIDS stakeholders do to encourage data sharing?

- **Talk to scientists and clinicians when you consent and participate in studies - studies cannot be done without you and you have agency in how studies are done**
- **Change comes from funding agencies - encourage them to take steps to democratize data access**

European science funders ban grantees from publishing in paywalled journals

By **Martin Enserink** | Sep. 4, 2018 , 3:15 AM

Issued by

National Institutes of Health (NIH)

Purpose

The NIH encourages investigators to use interim research products, such as preprints, to speed the dissemination and enhance the rigor of their work. This notice clarifies reporting instructions to allow investigators to cite their interim research products and claim them as products of NIH funding.

https://go.wisc.edu/6h5m6x

dholk.primate.wisc.edu

Gmail-unread | Zika public portal | EHR | dholk | Technology | News | Social | OC Servers | Science | Sports | Health | Melbourne | Search resul... Abandonware | Flights

Introduction

Human immunodeficiency virus (HIV) replication in blood peaks peaks two to three weeks after infection, typically at orders of magnitude higher than replication during chronic infection. This acute insult causes permanent immunologic damage. Acute viral replication may be particularly important in spreading HIV since the amount of replicating virus is proportional to transmission risk. Yet, little is known about pathologic events that determine the magnitude of peak acute HIV replication.

We study the events of early infection in macaques experimentally infected with simian immunodeficiency virus (SIV). We recently showed that microbial products flux into the blood very early in SIV infection, prior to the peak viral replication. This translocation of microbial products is associated with an increase in CD4+ and CCR5+ cells that are susceptible to SIV, indicating that hyperacute microbial translocation appears to create a permissive environment for systemic SIV replication (Ericsen et al. 2016).

We are now continuing these studies by investigating how quickly hyperacute microbial translocation occurs in male and female macaques infected intrarectally and intravaginally and to determine from which mucosal surfaces translating microbes are derived. These experiments may allow us to establish whether development of novel interventions to limit microbial translocation should be considered to minimize the severity of acute HIV/SIV infections. These experiments will also allow us to examine whether biological sex or route of infection affect peak viremia and/or microbial translocation in acute infection.

Methods in brief

Sixteen animals are used in this study: four males infected intrarectally, four females infected intrarectally, four females infected intravaginally, and four mock-infected females. The infecting strain used was SIVmac239. Doses of 100,000 TCID50 were used for both intrarectal and intravaginal infections. All female animals were treated with injectable medroxyprogesterone to eliminate the potentially confounding effects of animals being in different stages of the menstrual cycle. Blood was collected prior to the start of the study and every 2-3 days in the first 3 weeks following infection. Mucosal samples collected consisted of swabs of the oral cavity, nasal cavity, and vagina, fecal samples, and brochoalveolar lavage (BAL), were collected as described in the "Sample Manifest" file below. Viral loads, 16S sequencing, and 16S qPCR were performed on plasma samples; 16S sequencing was performed on mucosal samples. Flow cytometry was performed on collected peripheral blood mononuclear cells (PBMCs).

Results

Peak acute phase viral load dynamics

Of the twelve infected animals, four males were infected intrarectally, four females were infected intrarectally, and four females were infected intravaginally. In the acute phase, we did not observe differences in time to first detectable viremia, time to peak viremia, peak magnitude of viremia, or total viremia (area under the curve) with regards to challenge route or biological sex.

Microbial translocation

Microbial products in the blood of infected and mock-infected animals are being sequenced using 16S PCR. We are using deep sequencing of 16S microbial products to determine which taxa translocated, and we are using 16S qPCR to quantify translocating microbial products. We will compare the composition of microbes translocating into the plasma with the compositions found in the various mucosal surfaces we have sampled.

Files

Sample manifest.xlsx: This file shows the sampling timeline and the analyses planned for each sample.

CBC data_to 03.09.18.xlsx: This file contains the results of complete blood count (CBC) tests through March 9, 2018.

Viral Load Graphs in Numbers.numbers: This file contains the complete viral load data for all animals along with viral load graphs made in Apple's "Numbers" application.

SIV_viral_loads_acute_infection.xlsx: This file contains the complete viral load data for all animals along with some analysis done in excel.

Attached Files

Sample manifest.xlsx
CBC data_to 03.09.18.xlsx
Viral Load Graphs in Numbers.numbers
SIV_viral_loads_acute_infection.xlsx