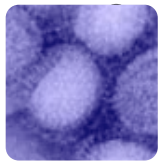
the open-source outbreak: H1N1, the olympics and new directions for public health

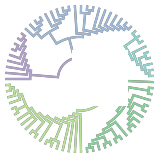
dr. jennifer gardy
bc centre for disease control
genome research laboratory

outline



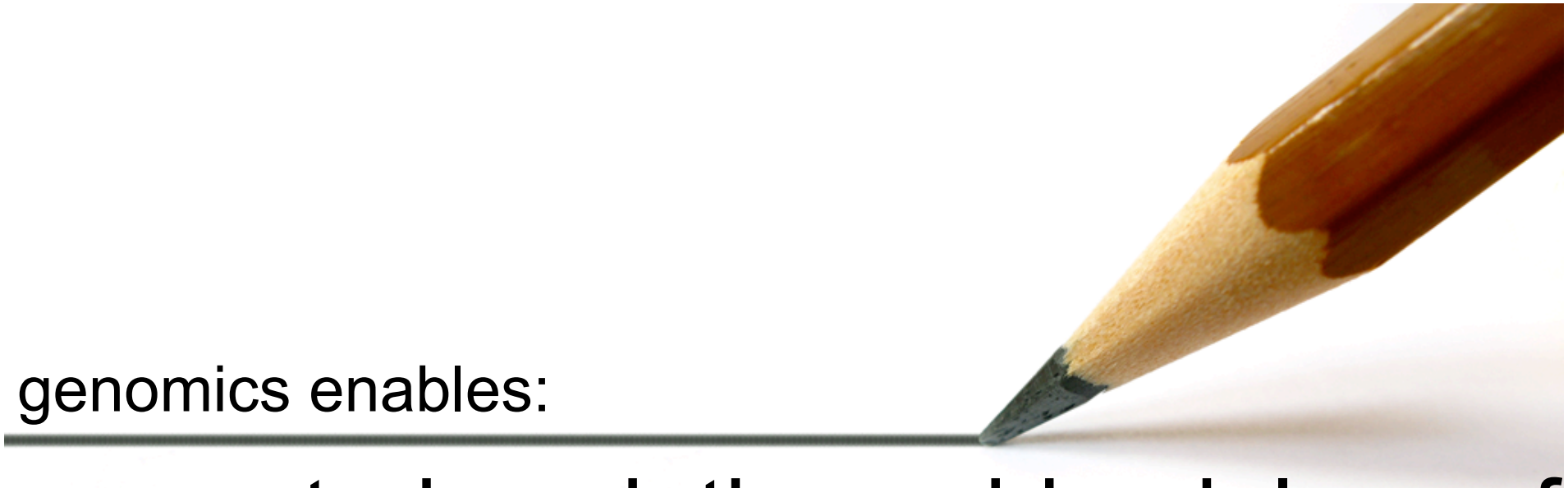
pandemic H1N1: the first open-source outbreak

H1N1/Olympics research project



descriptive epidemiology

predictive epidemiology

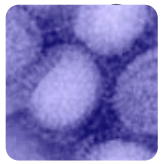


genomics enables:

present: descriptive epidemiology of a bacterial/viral pathogen

future: predictive epidemiology via genome surveillance

part 1

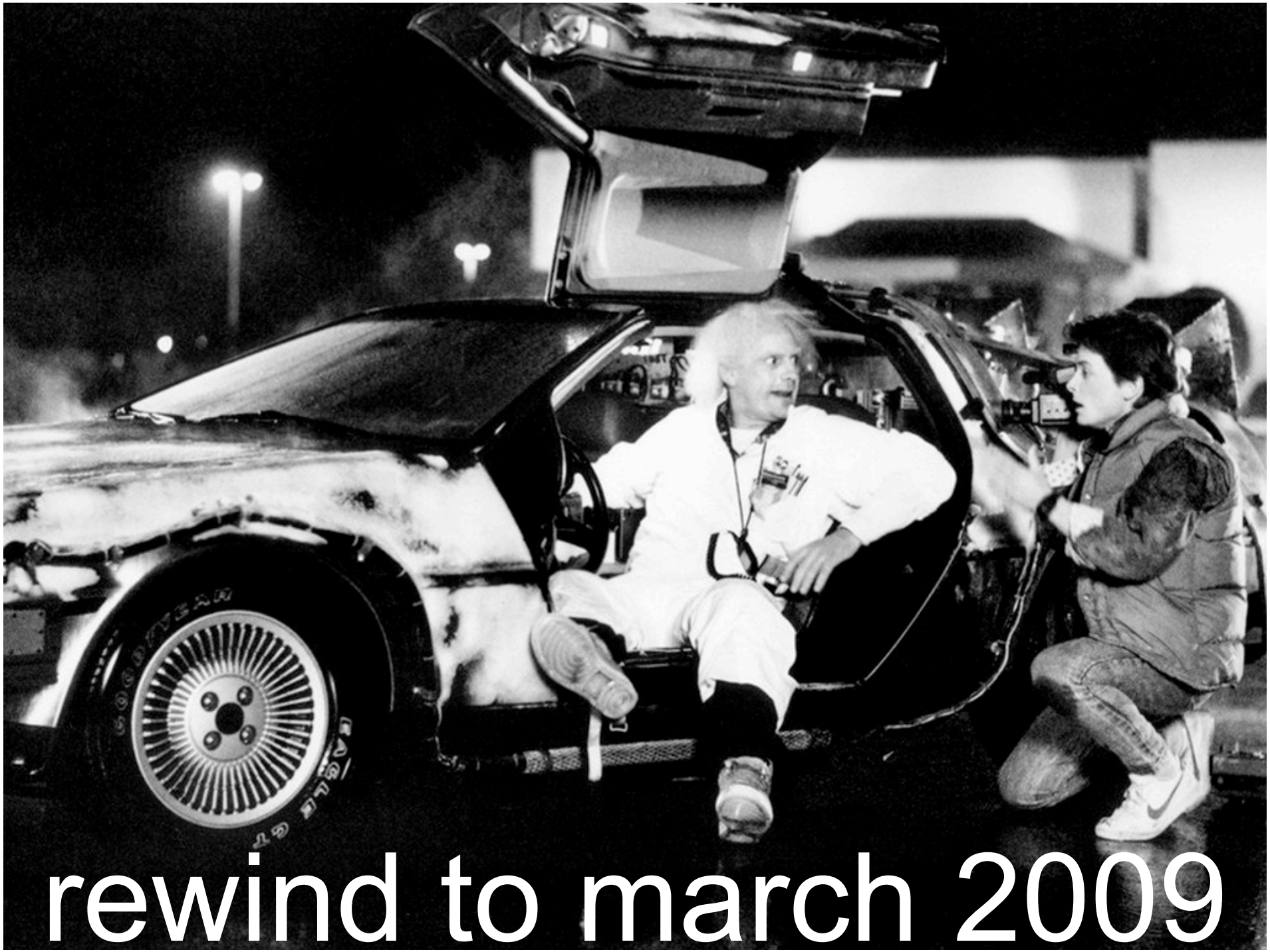


pandemic H1N1: the first open-source outbreak

H1N1/Olympics research project

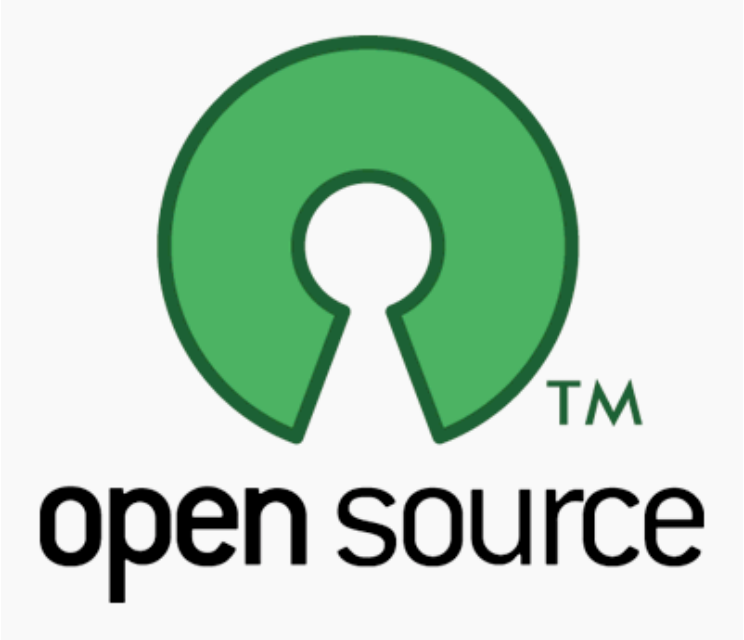
descriptive epidemiology

predictive epidemiology


rewind to march 2009


Sunday Monday Tuesday Wednesday Thursday Friday Saturday
increased flu activity in Mexico
CDC
California
WHO
APRIL 2009
M T W T F S S
JUNE
S M T W T F S
pandemic!

open source outbreak




sharing germs,
sharing genomes


Sunday Monday Tuesday Wednesday Thursday Friday Saturday
increased flu activity in Mexico
CDC
California
WHO
april 25: 1st genome
APRIL 2009
M T W T F S S
JUNE
S M T W T F S
pandemic!

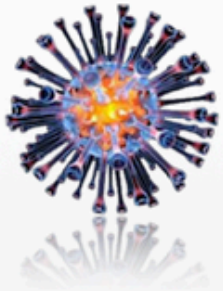
Human/Swine H1N1 Influenza

wiki blog mail

Tags +

Edited Aug 26, 2009 6:41 AM by Andrew Rambaut...

Human/Swine A/H1N1 Influenza Origins and Evolution



These pages exist to enable the rapid dissemination of results resulting from the analysis of genetic data from the ongoing Influenza A/H1N1 outbreak attributed to swine flu. All data used, unless otherwise specified, was made available by GISAID or NCBI and can be obtained directly from these sites.
All analysis should be considered preliminary and results are conditional on the correct labelling and annotation of genetic sequences. Additionally, results may be influenced by limited and biased sampling of isolates. Given the rapid posting of these data, we expect corrections to be made.

- *News 21-Aug-2009:* Public Library of Science has just launched PLoS Currents: Influenza a moderated website based on Google's Knol system allowing rapid and open sharing of new results in influenza research.

Front Page

Analysis and results:

- Phylogenetic analysis and reassortment history
- Molecular epidemiology and molecular clock analysis
- Ph
- Mo

Oth

- Us
- Us
- Co
- Archive of superseded results
- Miscellaneous

Sections

- Phylogeography
  September 1, 2009 9:40 AM
- Molecular Evolution and Adaptation
  July 10, 2009 5:55 PM
- Phylogenetic analysis and reassortment history
  June 12, 2009 12:34 AM
- Epidemiology and molecular clock analysis
  May 10, 2009 2:29 PM

What's Hot

- H1N1: Origins and evolution of the current epidemic
  July 8, 2009 7:53 AM
- PB2-627K & PB2-701N in A/Shanghai /71T/2009
  June 28, 2009 9:11 AM

rk (HA
mas

& MP

ne) -

May 8, 2009 5:59 AM

april 26: international wiki
13 people, 8 institutes, 4 countries
http://tree.bio.ed.ac.uk/groups/influenza

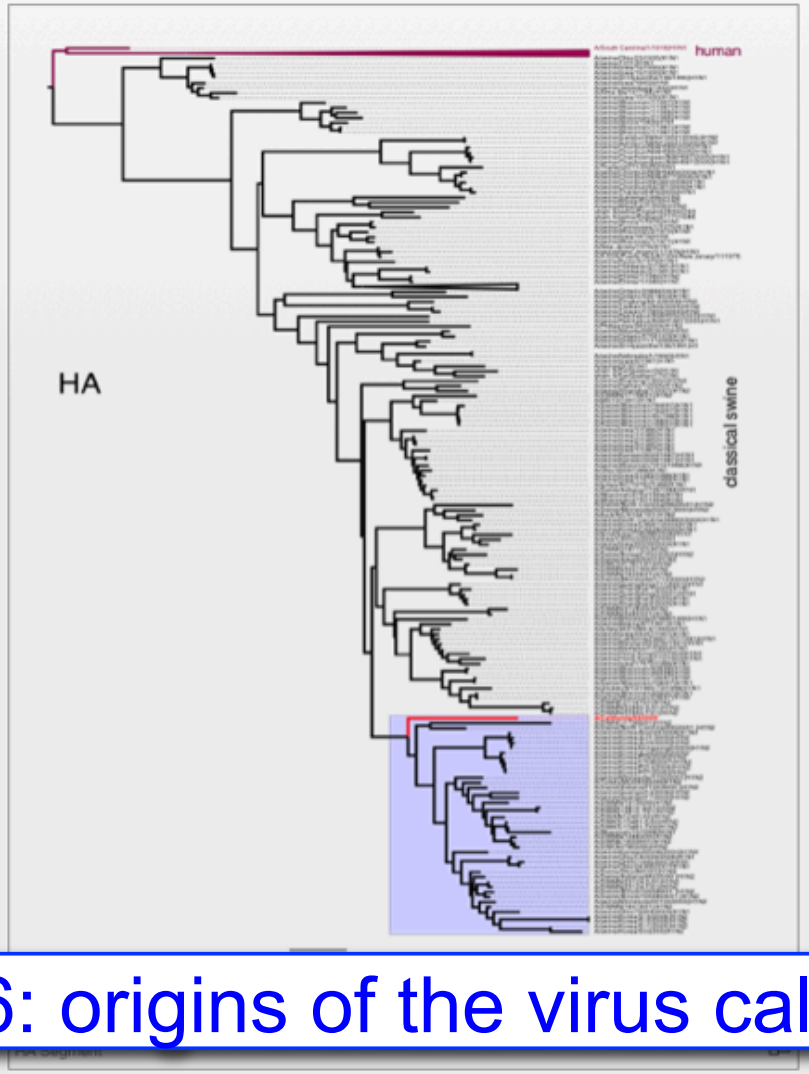
Phylogenetic position of A/California/04/2009 for each genomic segment.

Analysis by Andrew Rambaut 26 Apr 2009

Preliminary Neighbor-Joining trees using the HKY distance metric.

Blue and green shading denote clades of related strains although extensive reassortment and heterogenous sampling means that these clades contain different sets of strains.

See below for PDF versions of all these trees.



april 26: origins of the virus calculated

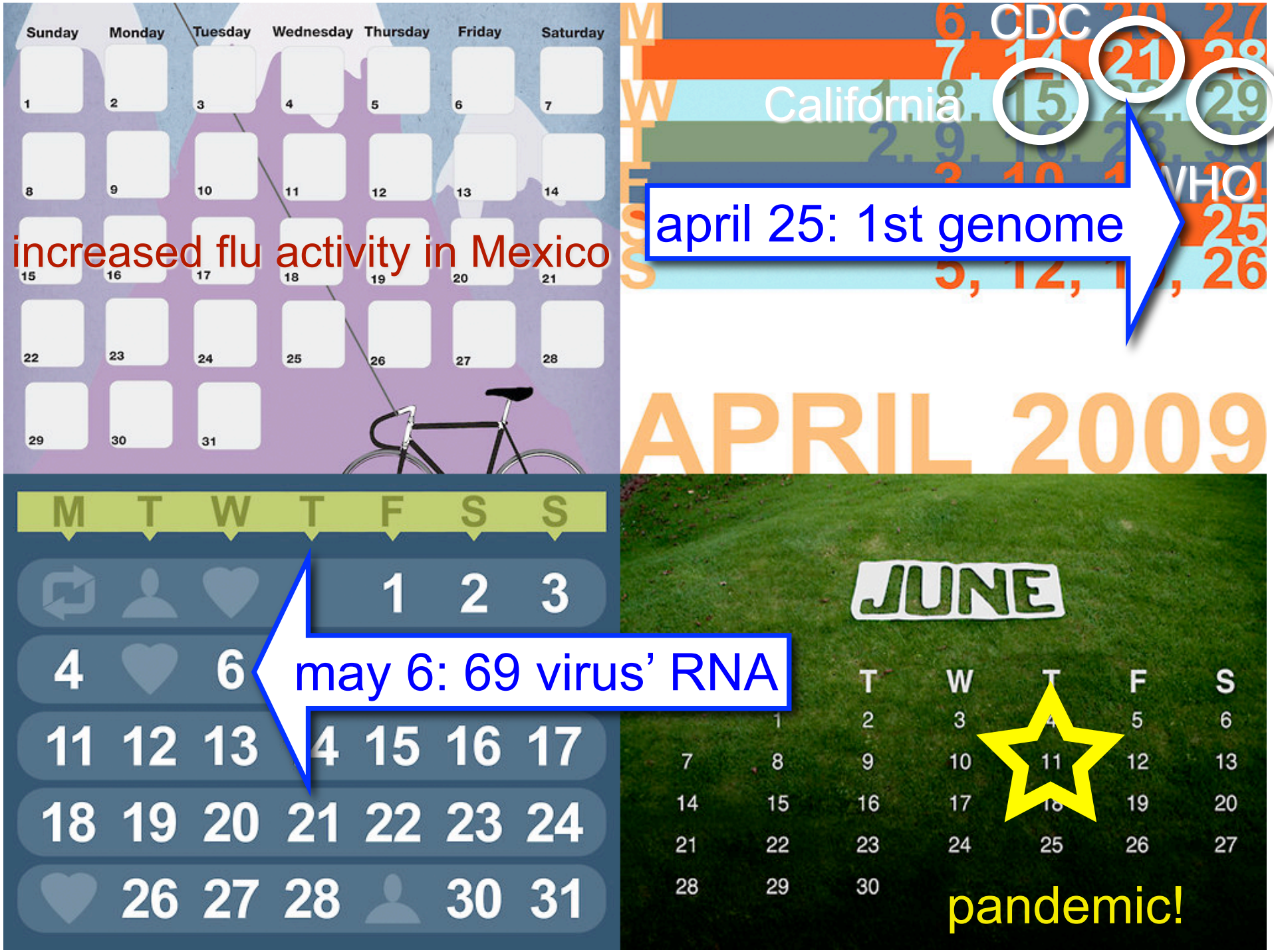
april 30: origins data published

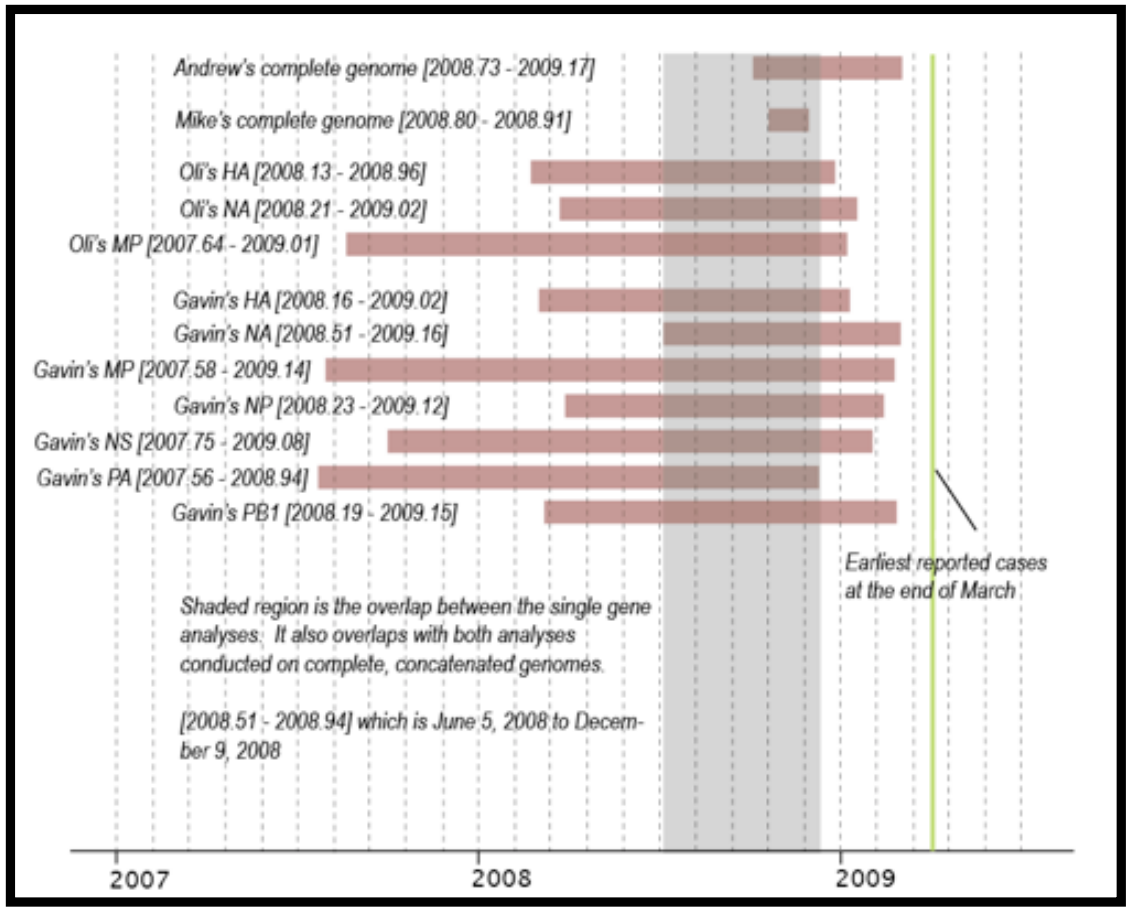
Rapid communications

THE ORIGIN OF THE RECENT SWINE INFLUENZA A(H1N1) VIRUS INFECTING HUMANS

V Trifonov[1], H Khiabanian[1], B Greenbaum[2], R Rabadan (rabadan@dbmi.columbia.edu)[1]
1. Department of Biomedical Informatics, Center for Computational Biology and Bioinformatics, Columbia University College of Physicians and Surgeons, New York, United States
2. The Simons Center for Systems Biology, Institute for Advanced Study, Princeton, United States

5 days from sequence to open-access paper


increased flu activity in Mexico
CDC
California
WHO
april 25: 1st genome
APRIL 2009
may 6: 69 virus' RNA
JUNE
pandemic!



virus entered human population late 08/early 09

may 5: first major paper submitted

Sciencexpress Report

Pandemic Potential of a Strain of Influenza A (H1N1): Early Findings

Christophe Fraser,[1]* Christl A. Donnelly,[1]* Simon Cauchemez,[1] William P. Hanage,[1] Maria D. Van Kerkhove,[1] T. Déirdre Hollingsworth,[1] Jamie Griffin,[1] Rebecca F. Baggaley,[1] Helen E. Jenkins,[1] Emily J. Lyons,[1] Thibaut Jombart,[1] Wes R. Hinsley,[1] Nicholas C. Grassly,[1] Francois Balloux,[1] Azra C. Ghani,[1] Neil M. Ferguson[1]†;

Andrew Rambaut,[2] Oliver G. Pybus[3];

Hugo Lopez-Gatell,[4] Celia M Apluche-Aranda,[5] Ietza Bojorquez Chapela,[4] Ethel Palacios Zavala[4];

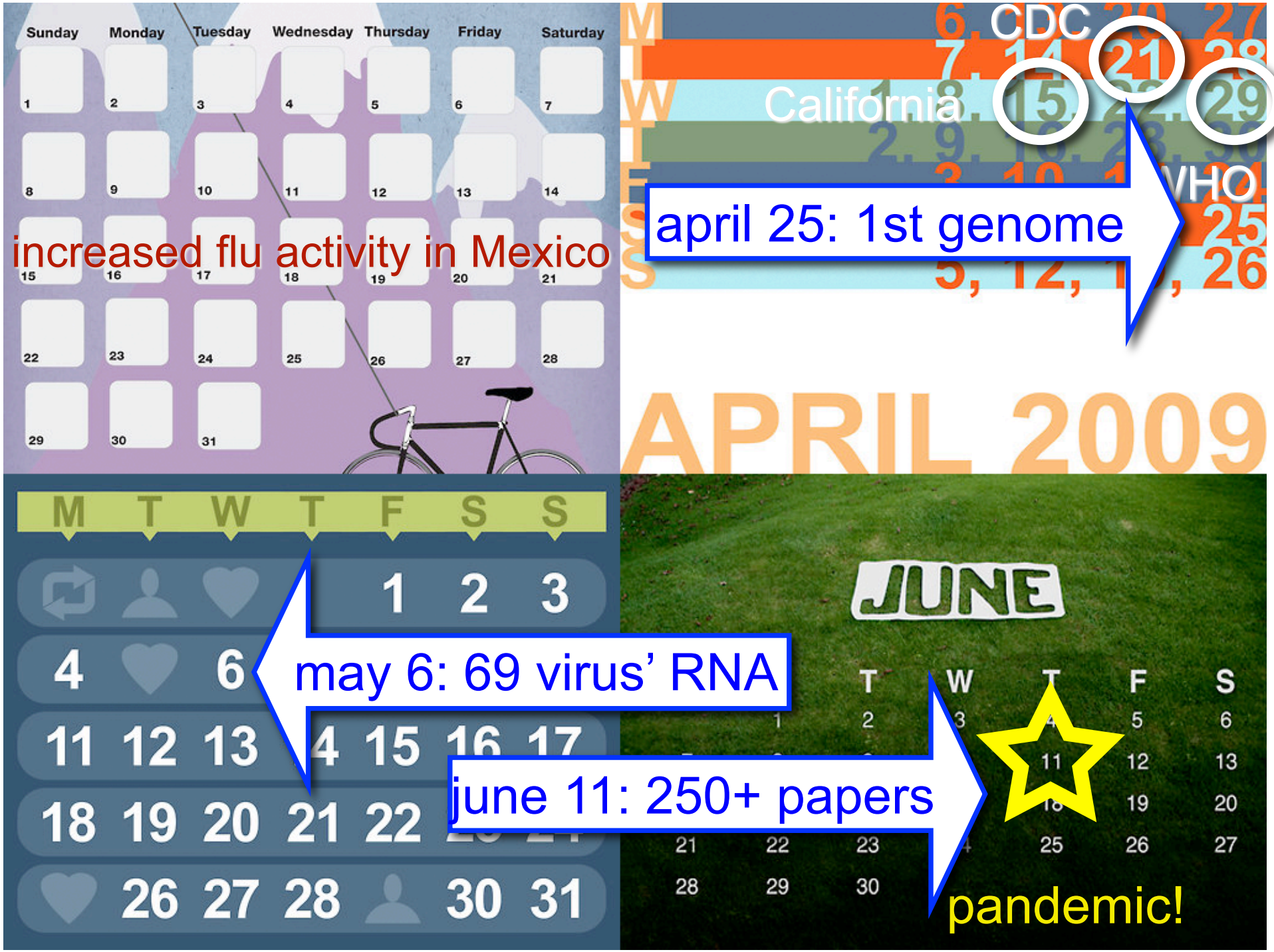
Dulce Ma. Espejo Guevara[6];

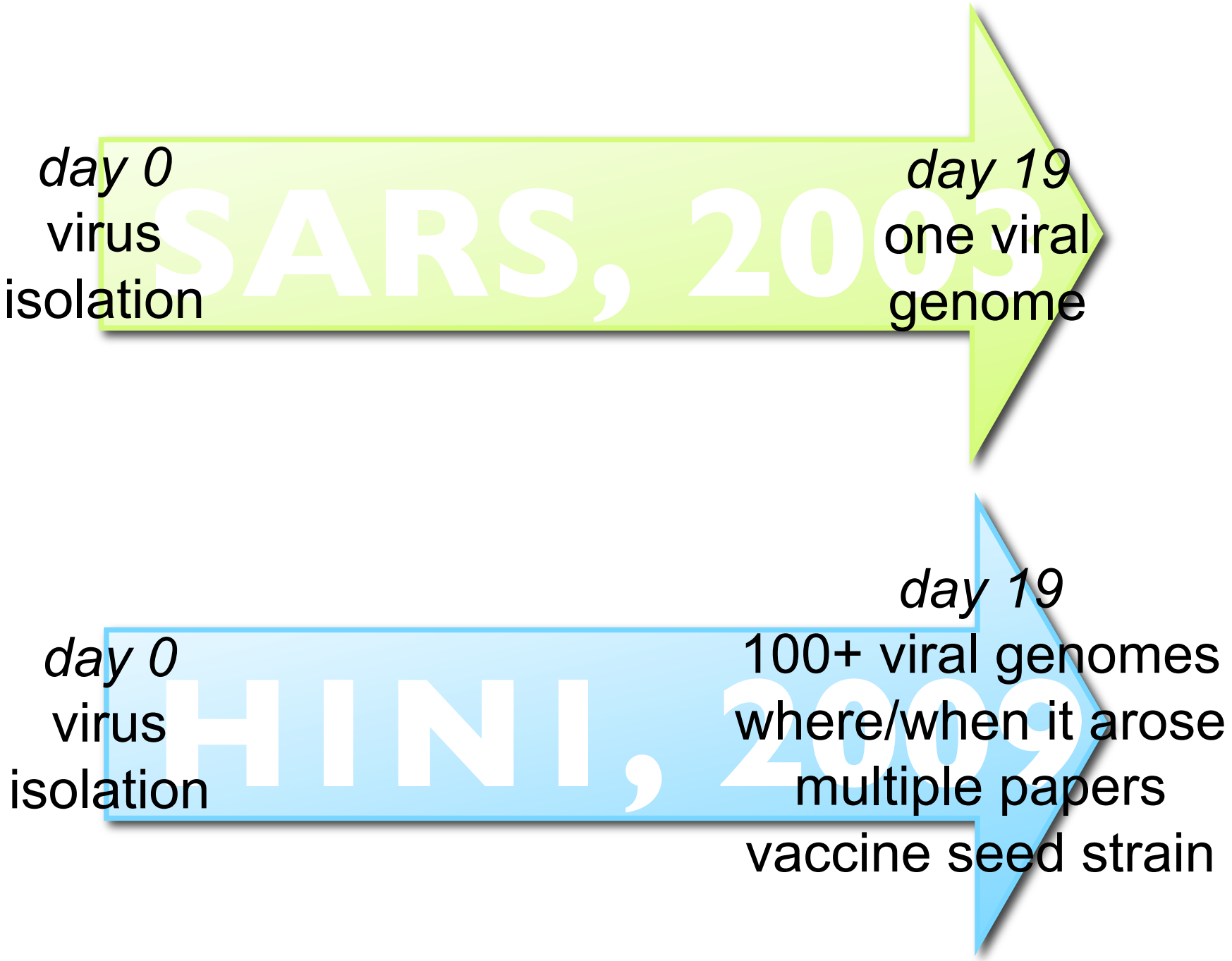
Francesco Checchi,[7] Erika Garcia,[7] Stephane Hugonnet,[7] Cathy Roth[7]

The WHO Rapid Pandemic Assessment Collaboration‡

[1]MRC Centre for Outbreak Analysis & Modelling, Department of Infectious Disease Epidemiology, Imperial College London, Faculty of Medicine, Norfolk Place, London W2 1PG, UK. [2]Institute of Evolutionary Biology, University of Edinburgh, Ashworth Laboratories Edinburgh EH9 3JT, UK. [3]Department of Zoology, University of Oxford, South Parks Road, Oxford OX1 3PS, UK. [4]Directorate General of Epidemiology, FCO. De P. Miranda 177 5th Floor, Mexico City, 01480, Mexico. [5]National Institute of Epidemiological Diagnosis and Reference, Prolongación Carpio No. 470 (3° piso), Col Santo Tomás, México City, C.P. 11340, Mexico. [6]Secretaría de Salud - Servicios de Salud de Veracruz Soconusco No. 36 Colonia Aguacatal C.P. 910 Xalapa, Veracruz, México State. [7]World Health Organization, 20 Av. Appia, 1211 Geneva, Switzerland.

may 11: first major paper published


increased flu activity in Mexico
CDC
California
WHO
april 25: 1st genome
APRIL 2009
may 6: 69 virus' RNA
june 11: 250+ papers
JUNE
pandemic!


day 0
virus
isolation
SARS, 2003
day 19
one viral
genome
day 0
virus
isolation
HINI, 2009
day 19
100+ viral genomes
where/when it arose
multiple papers
vaccine seed strain

how?

technological advances

shift in scientists' attitudes

genomes = easy, cheap, fast

human genome project (1990)

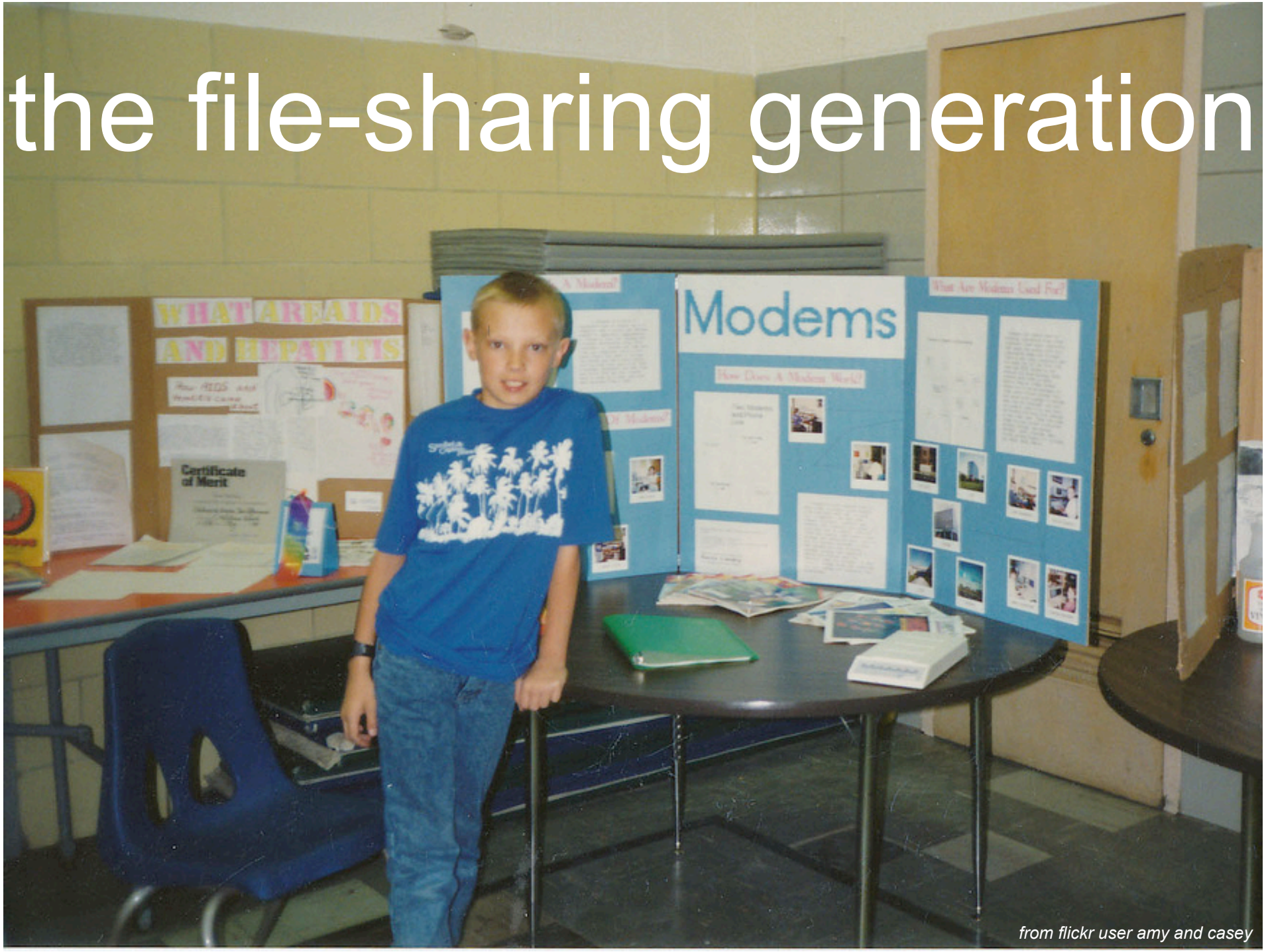
10 years to draft
3 more to complete
$3 billion
100s of people

spring 2009
four weeks
$48,000 worth of reagents
three-person team

stephen quake, stanford bioengineering

data = easy, cheap, fast

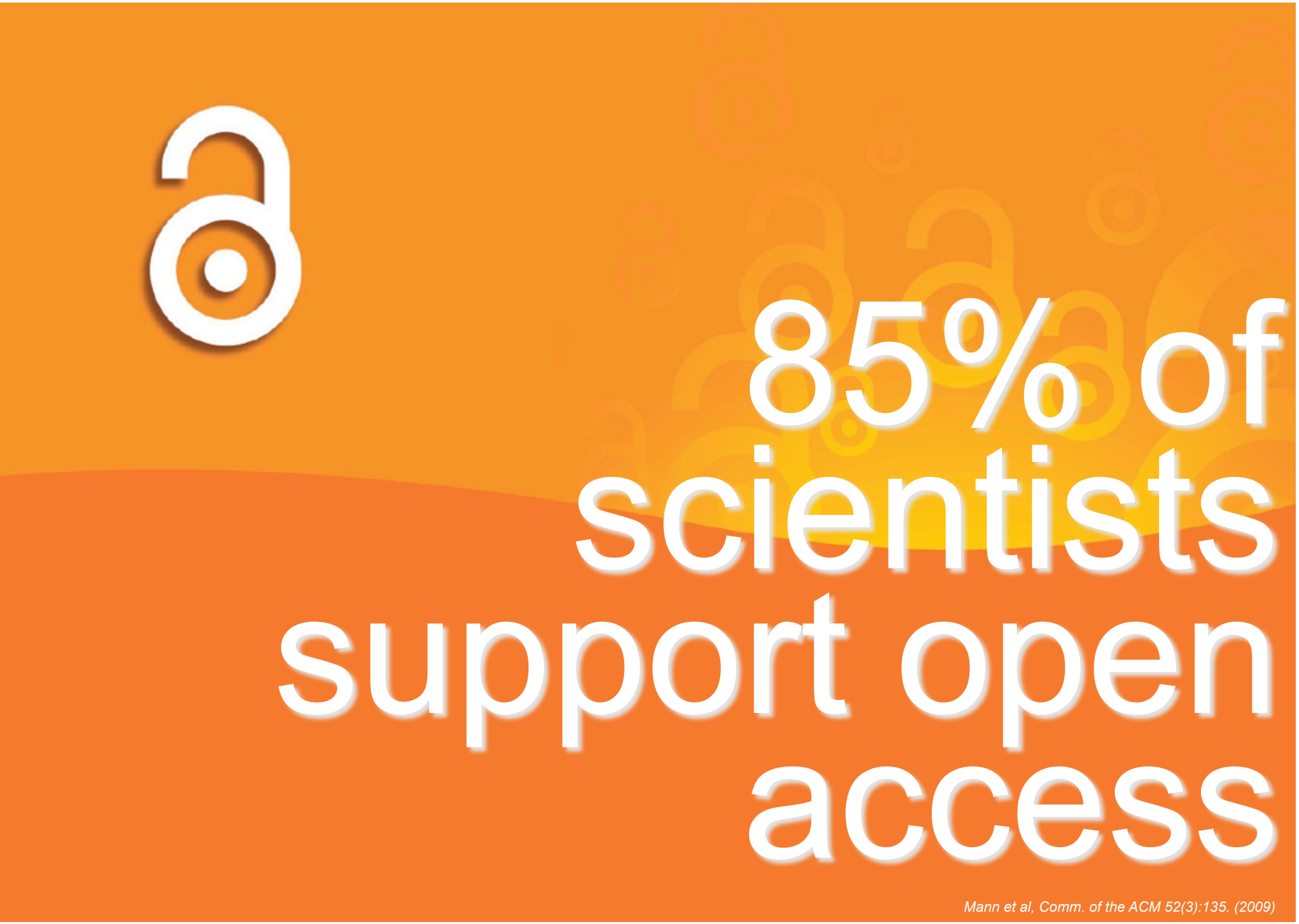
the file-sharing generation



from flickr user amy and casey

Open Access Week - October 19-23, 2009

To broaden awareness and understanding of Open Access


85% of
scientists
support open
access
Mann et al, Comm. of the ACM 52(3):135. (2009)

collaboration

believed to be the same as his 'Funduszellen', types (c) and (d) being the 'Mündungszellen'.

The type IV alveoli (Fig. 1*A* and *B*) are found in adult males only, scattered amongst type III. They are composed of a number of similar cells, type (*g*), which become filled with purple-staining granules after the tick starts to feed.

A more detailed description of the salivary alveoli and of the changes which they undergo during the life-cycle of the tick will be published at a later date.

I am indebted to Mr. M. Ulrich of the Photographic Department, South African Institute for Medical Research, for the photomicrographs.

W. M. Till

Department of Entomology,
South African Institute of Medical Research,
Johannesburg.
June 22.

1 Bonnet, M. A., *C. R. Acad. Sci.*, **142**, 296 (1906).
2 Douglas, J. R., *Univ. Calif. Pub. Ent.*, **7**, 207 (1943).
3 Robinson, L. E. and Davidson, J., *Parasitol.*, **6**, 217 (1913).
4 Nordenskiold, E., *Zool. Anz.*, **28**, 478 (1905).

BACTERIOLOGY

Bacteriophage Typing Applied to Strains of *Brucella* Organisms

Surface antigens usually limited to one taxonomic group are the main factors determining the bacteriophage sensitivity of bacterial species[1]. By such sensitivity, species of *Salmonella* can be distinguished[2] and the degree of sensitivity is used for typing strains of *S. typhi* [3,4,5] and strains of other bacteria[6].

Brucella phages were discovered only after rigorous search[7] and they have apparently not yet been described in detail. A *Brucella* phage grown on strain 19 *Brucella abortus* in a shake flask culture has now been found to be active on cultures of *Br. abortus* laboratory strains, but not on *Br. melitensis* and *Br. suis*. This phage was obtained by growing a single plaque taken from the end point dilution of a phage suspension kindly supplied by Dr. A. W. Stableforth from Weybridge, England.

The phage produces irregular plaques of small diameter, the smallest only being recognized as spots in the bacterial mat on 'Albimi' agar. These spots and the edges of the plaques appear to consist of extremely rough colonies of the *Brucella* strain attacked.

The technique found most practical is as follows: A 72-hr. aerated liquid culture of phage is cleared by centrifugation at 3,000 r.p.m. for 75 min. and the supernatant heated at 60° C. for 60 min. to destroy any remaining bacteria. The phage suspension is stored at 4° C. and serially diluted ten-fold before use. The phage dilutions are spotted on dry 'Albimi' agar plates by means of a 1 mm. diameter platinum loop. After drying the spots are covered with a suspension of young cells taken from surface culture and made up to a density of approximately Brown's tube 1, in a diluent of distilled water containing 0.1 per cent (w/v) carboxy-methyl-cellulose. The 0.02-ml. dropper pipette is used for depositing the suspension over the site of the phage spot. After standing in the dark for 1 hr. the plates are incubated at 37° C. in inverted position for 24 hr. or longer and if necessary in an atmosphere of 10 per cent carbon dioxide. An example of the results is given in Table 1.

Table 1. Differential Susceptibility

Titration of *Brucella* Bacteriophage

Phage dilution	*M* 16*M*	*A* 544	*S* 1330	*A* 819	*Ev.* Sh. Sem.
Undiluted	—	+ + + +	—	+ + + +	—
10^{-1}	—	+ + + +	—	+ + + +	—
10^{-2}	—	+ + +	—	+ + +	—
10^{-3}	—	+ +	—	+ +	—
10^{-4}	—	+	—	+	—
10^{-5}	—	—	—	—	—
10^{-6}	—	—	—	—	—

+ + + +, confluent lysis.
+ + +, plaques and spots.
+ +, spots.
+, less than 5 spots.
−, no phage activity.

Here it was found that *Br. melitensis* strain 16*M* and *Br. suis* strain 1330 which are World Health Organization reference strains were completely resistant as was also a stock culture of a local *Brucella* variant isolated from sheep semen.

The aerobic *Br. abortus* strain 19, and the carbon dioxide dependent *Br. abortus* strain 544 which is a World Health Organization reference strain were equally susceptible to the phage.

These results show that phage typing may have important taxonomic and possibly also epidemiological value in the field of *Brucellosis* research.

Acknowledgments are due to Dr. R. A. Alexander, director of veterinary services, for permission to publish this report and to Mr. P. V. Mulders for technical assistance.

G. C. van Drimmelen

Faculty of Veterinary Science,
University of Pretoria

1 Burnet, F. M., *Brit. J. Exp. Path.*, **8**, 121 (1927).
2 Schmidt, A., *Zbl. Bakt.*, **12**, 202, 207 (1931).
3 Craigie, J., and Brandon, K. F., *J. Path. Bact.*, **4**, 233 (1936).
4 Craigie, J., and Yen, C. H., *Canad. Pub. Health J.*, 484 (1938).
5 Crocker, C. G., *J. Hyg.* (Camb.), **45**, 118 (1947).
6 Coetzee, J. N., *S.A. J. Lab. and Clin. Med.*, **4**, 147 (1948).
7 Pickett, J., and Nealon, E. L., *J. Hyg.* (Camb.), **48**, 500 (1950).

Induction of Phage Formation in the Lysogenic *Escherichia coli* K-12 by Mitomycin C

Mitomycin *C*, a newly isolated antibiotic, is receiving special attention because of its anti-neoplastic activity as well as its selective inhibitory action on the synthesis of bacterial deoxyribonucleic acid.[1] It has also been observed that the impaired deoxyribonucleic acid synthesis of cells of *Escherichia coli B* treated with mitomycin *C* can be promptly restored by infection with the bacteriophage *T2r*$^+$. These properties suggested that this antibiotic could induce the development of active phage from the prophage state in lysogenic bacteria, since they are similar to ultra-violet effects. This communication concerns the lytic process of *Escherichia coli K*–12 induced by mitomycin *C* added externally.

Cells growing in salts-glucose synthetic medium were harvested at the logarithmic phase of growth, resuspended in a similar fresh medium in the presence of various concentrations of mitomycin *C*, and incubated at 37° with vigorous shaking. Samples were taken at intervals, and turbidity was measured photometrically at 660mμ. When exposed to 0·05 μgm. of mitomycin *C* per ml., growth proceeded at

nature Vol 461|1 October 2009|doi:10.1038/nature08356

ARTICLES

Tankyrase inhibition stabilizes axin and antagonizes Wnt signalling

Shih-Min A. Huang[1], Yuji M. Mishina[1], Shanming Liu[1], Atwood Cheung[1], Frank Stegmeier[1], Gregory A. Michaud[1], Olga Charlat[1], Elizabeth Wiellette[1], Yue Zhang[1], Stephanie Wiessner[1], Marc Hild[1], Xiaoying Shi[1], Christopher J. Wilson[1], Craig Mickanin[1], Vic Myer[1], Aleem Fazal[1], Ronald Tomlinson[1], Fabrizio Serluca[1], Wenlin Shao[1], Hong Cheng[1], Michael Shultz[1], Christina Rau[2], Markus Schirle[2]†, Judith Schlegl[2], Sonja Ghidelli[2], Stephen Fawell[1], Chris Lu[1], Daniel Curtis[1], Marc W. Kirschner[3], Christoph Lengauer[1]†, Peter M. Finan[1], John A. Tallarico[1], Tewis Bouwmeester[2]†, Jeffery A. Porter[1], Andreas Bauer[2]† & Feng Cong[1]

The stability of the Wnt pathway transcription factor β-catenin is tightly regulated by the multi-subunit destruction complex. Deregulated Wnt pathway activity has been implicated in many cancers, making this pathway an attractive target for anticancer therapies. However, the development of targeted Wnt pathway inhibitors has been hampered by the limited number of pathway components that are amenable to small molecule inhibition. Here, we used a chemical genetic screen to identify a small molecule, XAV939, which selectively inhibits β-catenin-mediated transcription. XAV939 stimulates β-catenin degradation by stabilizing axin, the concentration-limiting component of the destruction complex. Using a quantitative chemical proteomic approach, we discovered that XAV939 stabilizes axin by inhibiting the poly-ADP-ribosylating enzymes tankyrase 1 and tankyrase 2. Both tankyrase isoforms interact with a highly conserved domain of axin and stimulate its degradation through the ubiquitin-proteasome pathway. Thus, our study provides new mechanistic insights into the regulation of axin protein homeostasis and presents new avenues for targeted Wnt pathway therapies.

The evolutionarily conserved Wnt/β-catenin signal transduction pathway controls many biological processes[1]. A key feature of the Wnt pathway is the regulated proteolysis of the downstream effector β-catenin by the β-catenin destruction complex. The principal constituents of the β-catenin destruction complex are adenomatous polyposis coli (APC), axin and glycogen synthase kinase 3α/β (GSK3α/β). In the absence of Wnt pathway activation, cytosolic β-catenin is constitutively phosphorylated and targeted for degradation. On Wnt stimulation the β-catenin destruction complex dissociates, leading to the accumulation of nuclear β-catenin and transcription of Wnt pathway-responsive genes.

Inappropriate activation of the Wnt pathway has been observed in many cancers[2,3]. Notably, truncating mutations of the tumour suppressor APC are the most prevalent genetic alterations in colorectal carcinomas[4–6]. The efficient assembly of the multi-protein destruction complex is dependent on the steady-state levels of its principal constituents. Axin has been reported to be the concentration-limiting factor in regulating the efficiency of the β-catenin destruction complex[7,8] and overexpression of axin induces β-catenin degradation in cell lines expressing truncated APC[9–11]. Thus, it is likely that axin protein levels need to be tightly regulated to ensure proper Wnt pathway signalling. In fact, Wnt signalling itself regulates the level of axin at several steps, with *AXIN2* being a major transcriptional target of the β-catenin–T-cell factor (TCF) complex and Wnt signalling promoting the degradation of axin[12,13]. However, the molecular mechanisms that regulate protein homeostasis of destruction complex components and complex assembly remain elusive.

In this study we used chemical-genetic and -proteomic approaches to search for novel modulators of the Wnt signalling pathway. We identified a low molecular mass compound that can prolong the half-life of axin and promote β-catenin degradation through inhibiting tankyrase (TNKS). Our study uncovers a new mechanism that controls axin protein stability and Wnt pathway signalling, and its therapeutic exploitation holds promise for treating Wnt-pathway-dependent cancers.

XAV939 inhibits Wnt signalling by increasing axin levels

XAV939 was identified as a small molecule inhibitor of the Wnt/β-catenin pathway from a high-throughput screen using a Wnt-responsive Super-Topflash (STF) luciferase reporter assay in HEK293 cells (Fig. 1a). XAV939 strongly inhibited Wnt3a-stimulated STF activity in HEK293 cells, but did not affect CRE, NF-κB or TGF-β luciferase reporters (Fig. 1b). In contrast, LDW643, a close structural analogue of XAV939 (Fig. 1a), had no effect on the Wnt3a-induced STF reporter (Fig. 1b). XAV939 treatment blocked Wnt3a-induced accumulation of β-catenin in HEK293 cells (Fig. 1c), indicating that the compound modulates Wnt signalling upstream of β-catenin. Interestingly, XAV939 also inhibited STF activity in SW480 cells, a colorectal cancer cell line harbouring a truncated APC (Fig. 1d). XAV939 decreased β-catenin abundance, but significantly increased β-catenin phosphorylation (S33/S37/T41) in SW480 cells (Fig. 1e), indicating that XAV939 promotes the phosphorylation-dependent degradation of β-catenin by increasing the activity of the destruction complex.

To explore how XAV939 may increase the activity of the destruction complex, we investigated whether compound treatment alters the protein levels of known Wnt pathway components. Notably, the

[1]Novartis Institutes for Biomedical Research, 250 Massachusetts Avenue, Cambridge, Massachusetts 02139, USA. [2]Cellzome AG, Meyerhofstrasse 1, D-69117 Heidelberg, Germany. [3]Department of Systems Biology, Harvard Medical School, Boston, Massachusetts 02115, USA. †Present addresses: Novartis Institutes for Biomedical Research, CH-4002 Basel, Switzerland (T.B., A.B.); Novartis Institutes for Biomedical Research, Cambridge, Massachusetts 02139, USA (M. Sc.); Sanofi-Aventis, 94403 Vitry-sur-Seine, France (C.L.).

pandemic H1N1: the first open-source outbreak

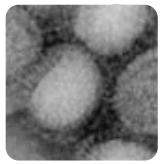
new model for rapid response

fast, open genomic data

collaborative process

open access to results

part 2



pandemic H1N1: the first open-source outbreak

H1N1/Olympics research project

descriptive epidemiology

predictive epidemiology

BC Centre for Disease Control

An agency of the Provincial Health Services Authority

DISEASES & CONDITIONS | FOOD & YOUR HEALTH | HEALT ENVI

You are here: Home > About BCCDC > Divisions

Text Size: S M L

IN THIS SECTION

- About BCCDC
  - Mission & Vision
  - Divisions
    - Epidemiology Services
    - Vaccine and Pharmacy Services
    - Hepatitis Services
    - STI/HIV Prevention and Control
    - Tuberculosis Control
    - Mathematical Modeling Unit
    - Public Health and Emergency Management
    - Environmental Health Services
    - UBC Centre for Disease Control
  - Annual Reports
  - Partners
  - Global Health
  - Careers
  - Accreditation
  - How Are We Doing?
- Contact Us

surveillance, detection, diagnosis, treatment, & prevention of IDs

Divisions

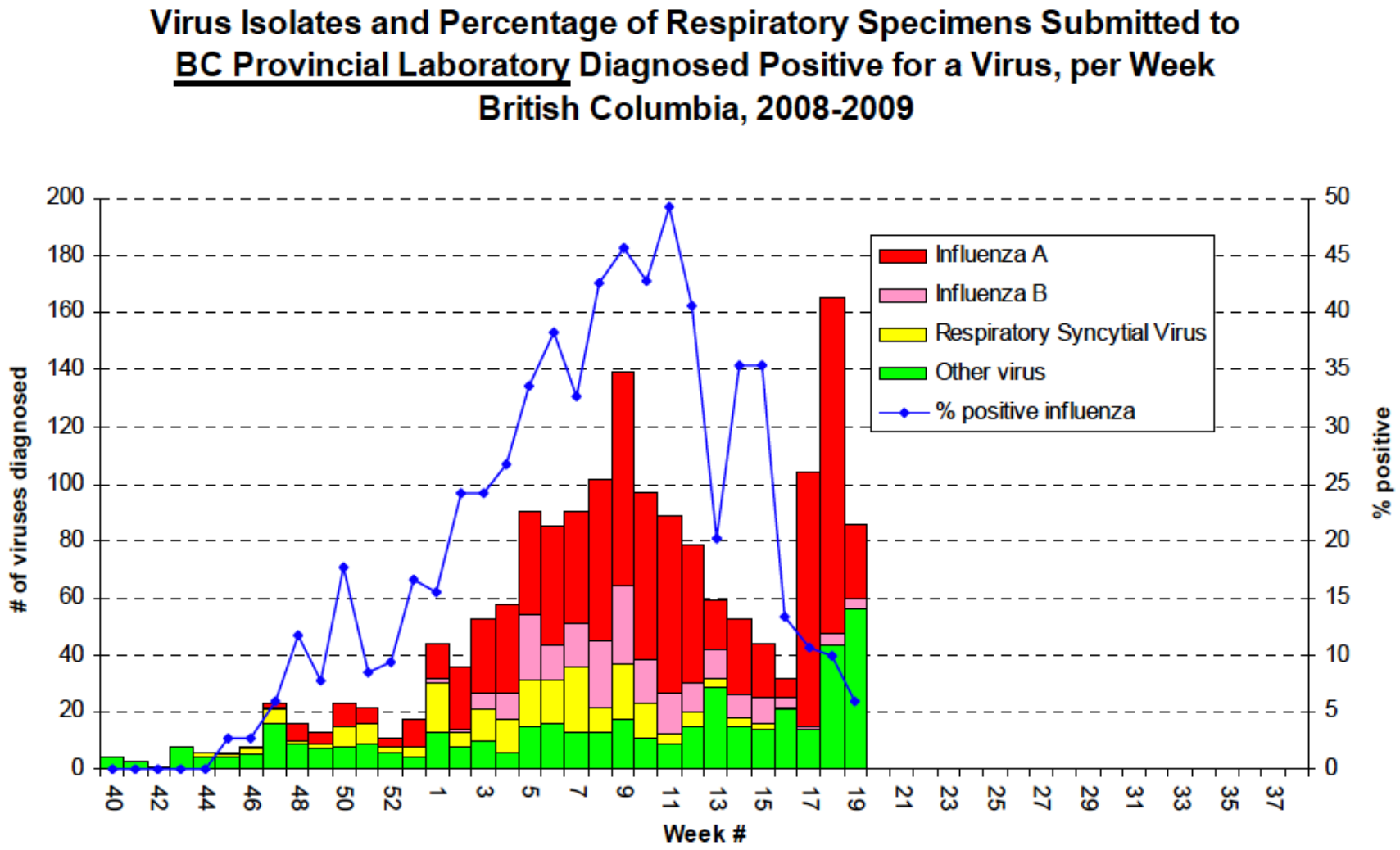
The day to day public health work of the BC Centre for Disease Control is done in support of regional health authorities, the BC Ministry of Health and the Provincial Health Officer.
Scientific and technical support is provided by the following specialized, yet integrated, operating divisions:

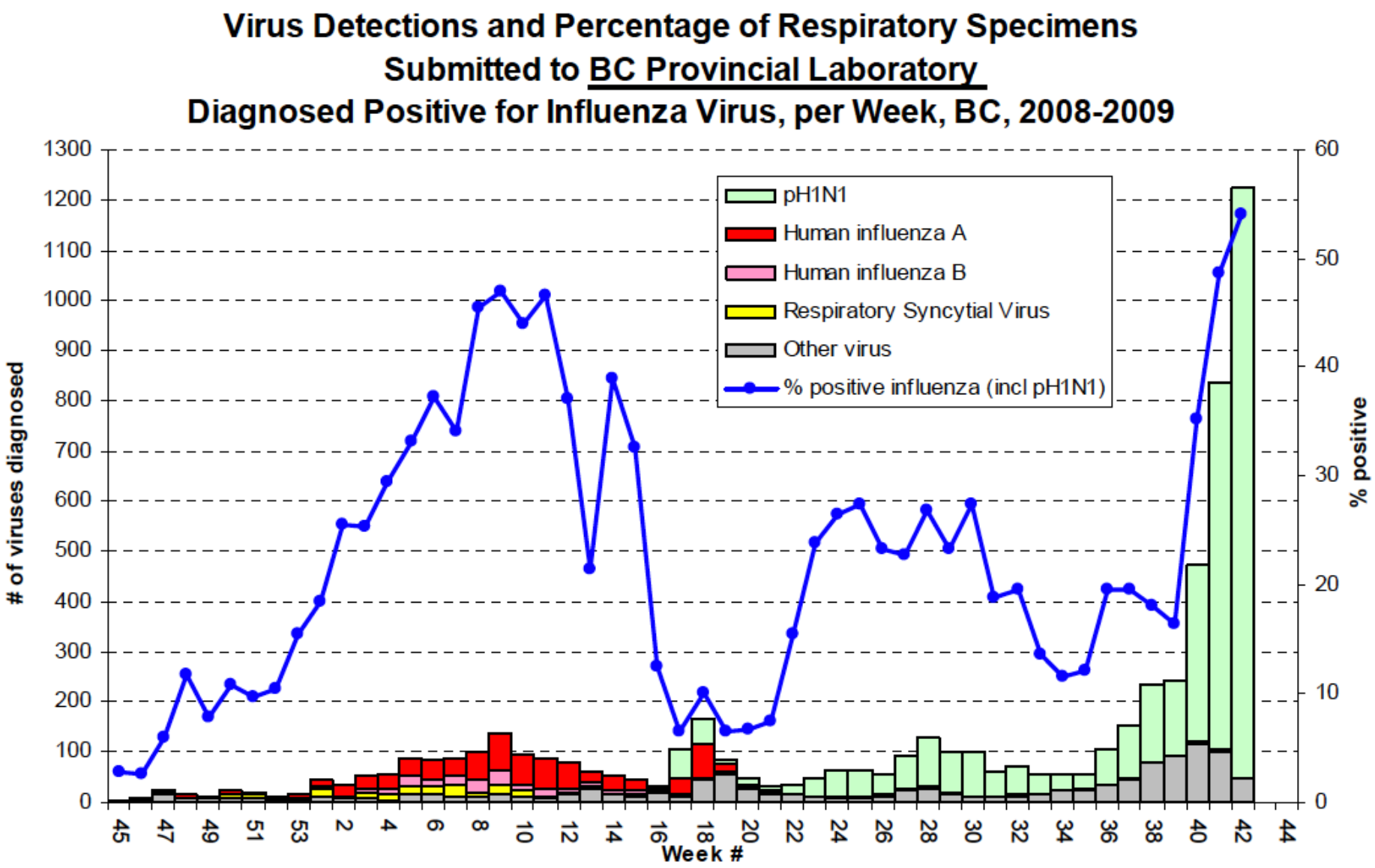
- Epidemiology Services
- Vaccine and Pharmacy Services
- Hepatitis Division
- STI/HIV Prevention and Control
- Tuberculosis Control
- Mathematical Modeling Unit
- Public Health Emergency Management
- Environmental Health Services
- UBC Centre for Disease Control

Formerly BCCDC Laboratory Services, the BCCDC Public Health & Microbiology Reference Laboratory is a service of PHSA Laboratories.

BCCDC & pH1N1: lab testing

- april/may: surge in lab test volume




Virus Detections and Percentage of Respiratory Specimens
Submitted to BC Provincial Laboratory
Diagnosed Positive for Influenza Virus, per Week, BC, 2008-2009
# of viruses diagnosed
% positive
Week #
pH1N1
Human influenza A
Human influenza B
Respiratory Syncytial Virus
Other virus
% positive influenza (incl pH1N1)
0
100
200
300
400
500
600
700
800
900
1000
1100
1200
1300
0
10
20
30
40
50
60
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47
49
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38
40
42
44

BCCDC & pH1N1: research & activities

- "one-stop pandemic shop"
  - sero-epi survey
  - vaccine uptake campaign
  - mathematical modelling
  - informatics infrastructure
  - genomics

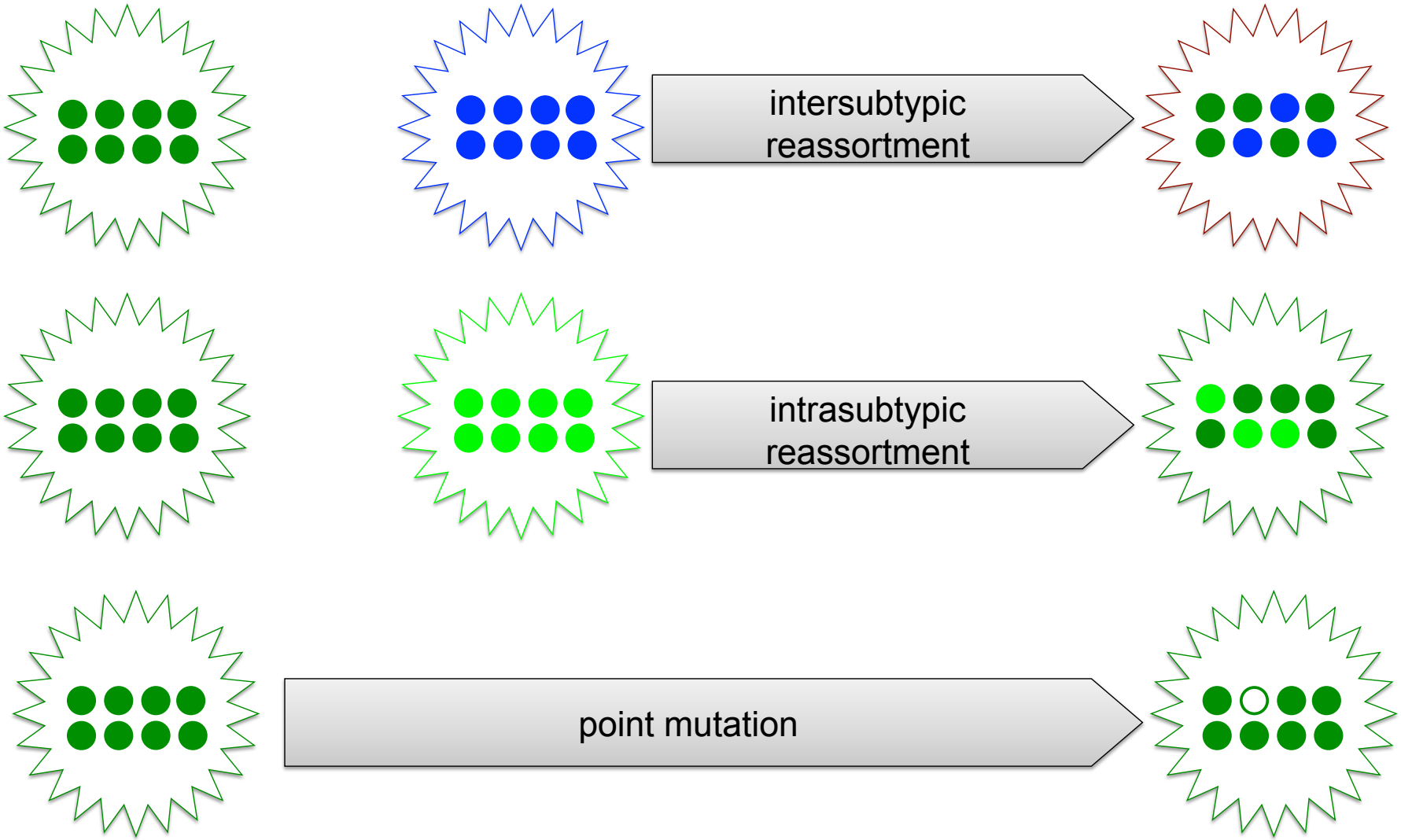
GenomeBritishColumbia

BC Centre for Disease Control
AN AGENCY OF THE PROVINCIAL HEALTH SERVICES AUTHORITY

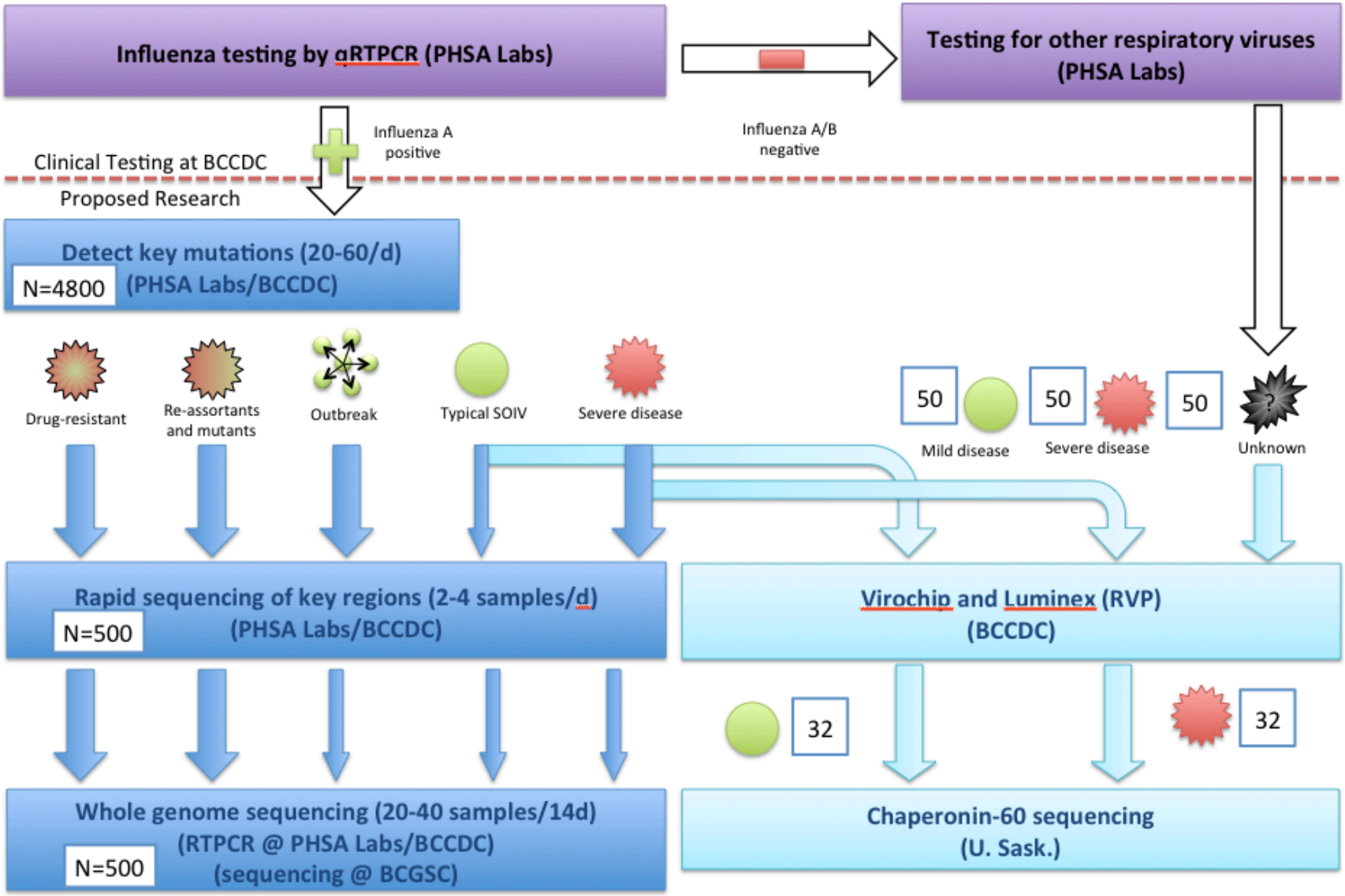
sequence 400-500 H1N1 genomes,
observe viral evolution in real-time.


vancouver 2010
vancouver 2010
IPC
#1
VANCOUVER2010.COM

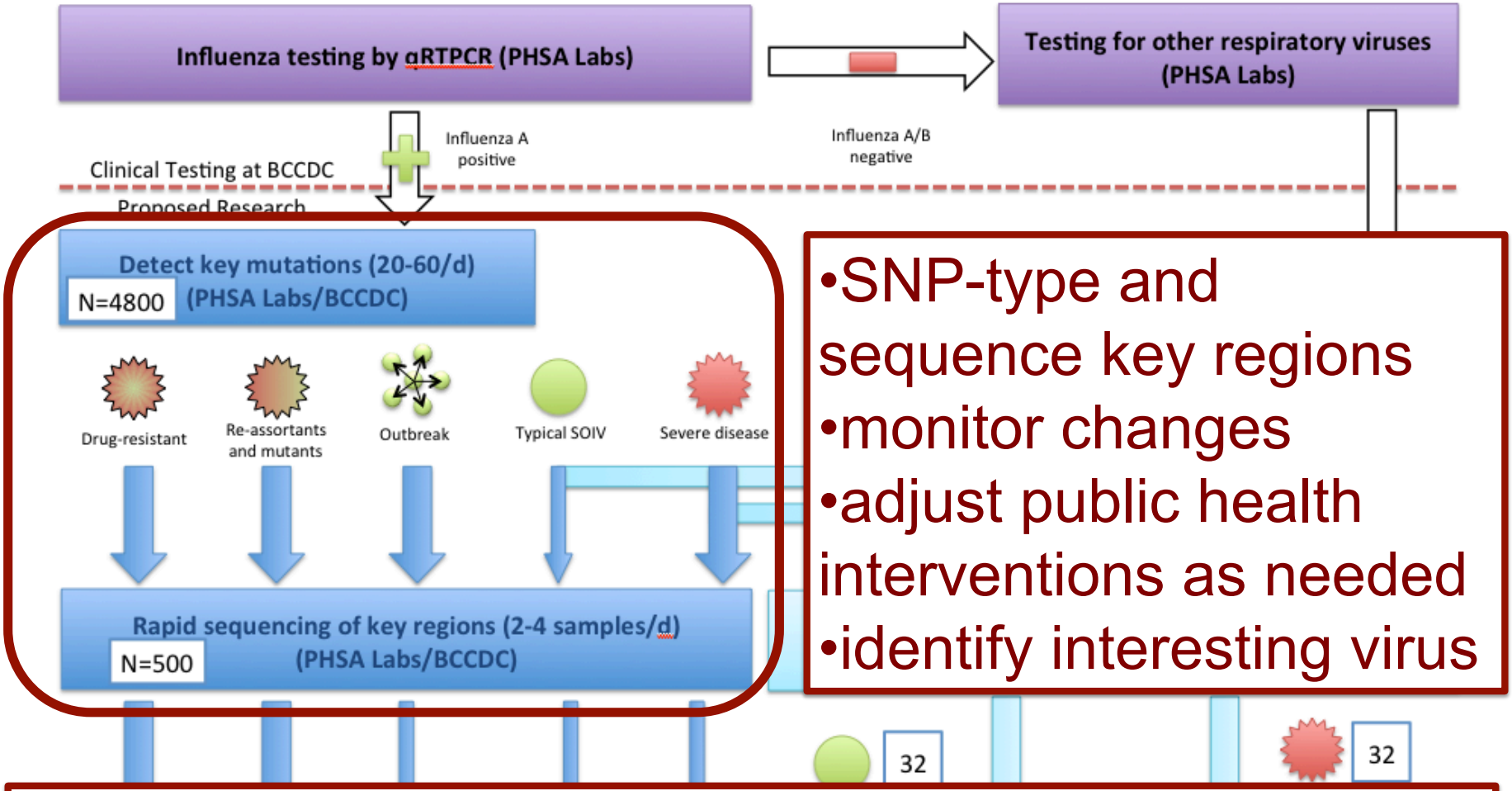
"influenza virus is sloppy, capricious and promiscuous" – world health organization



H1N1 genomics project overview



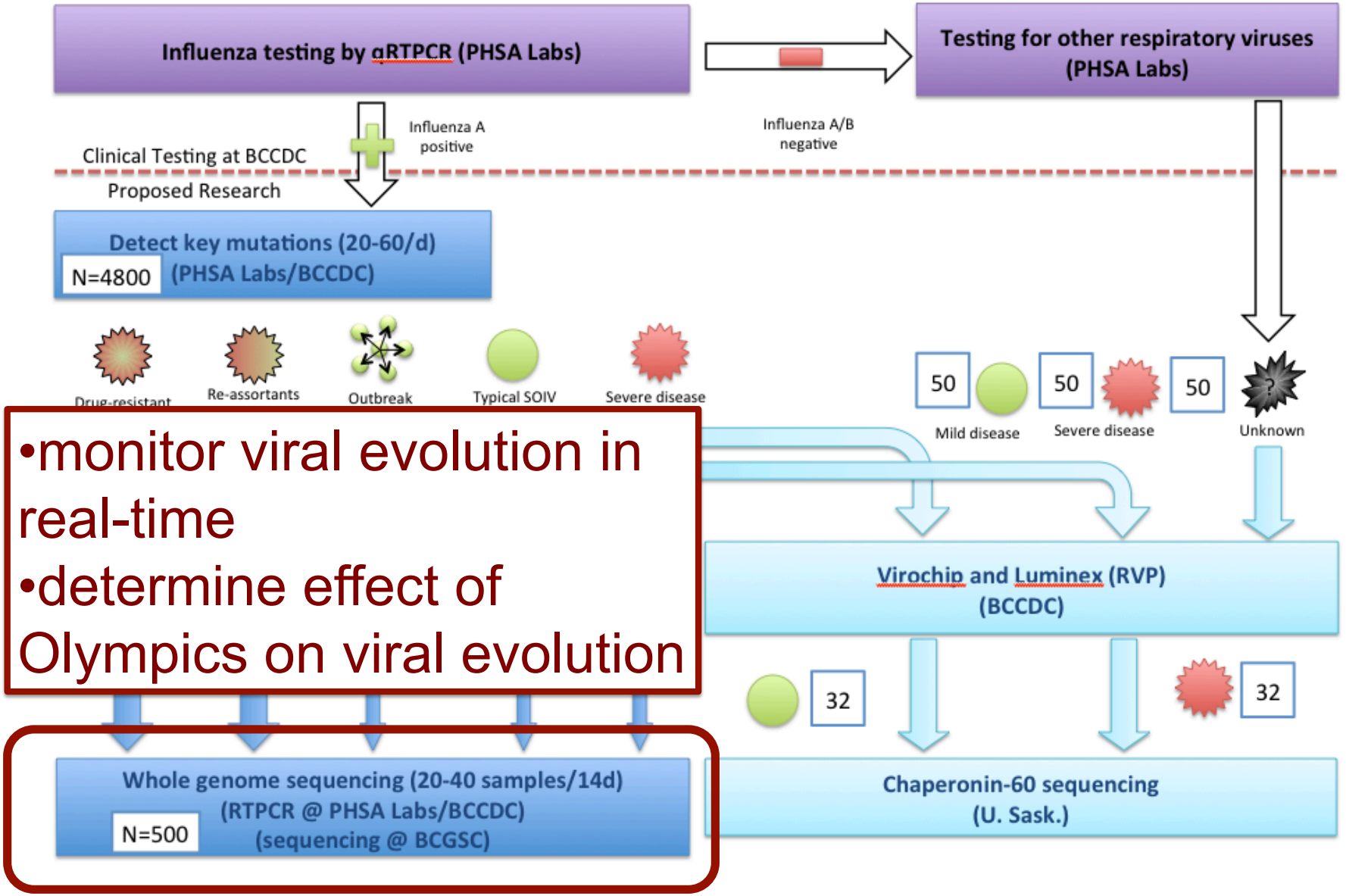
1. targeted sequencing: public health outcomes



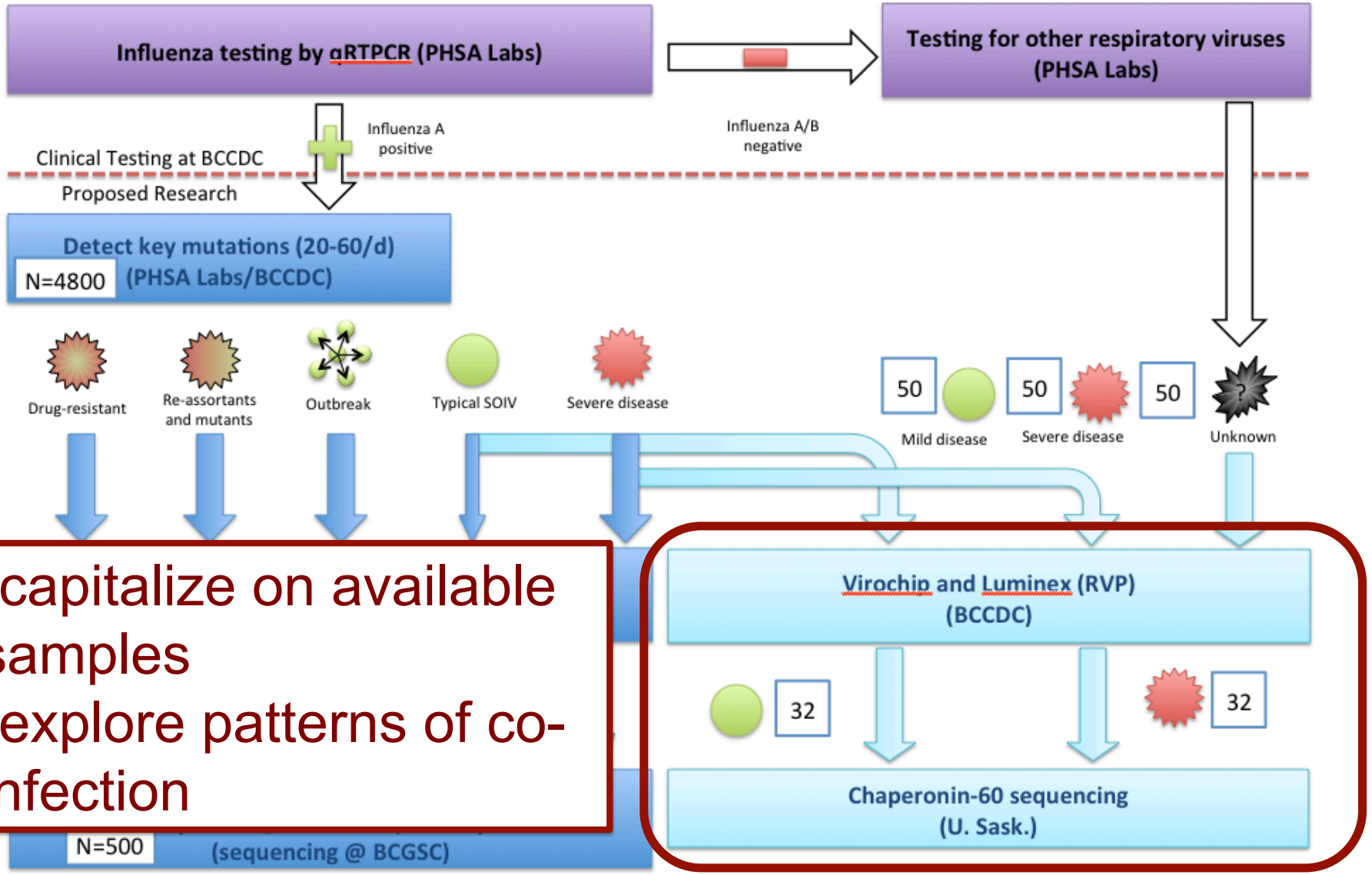
- SNP-type and sequence key regions
- monitor changes
- adjust public health interventions as needed
- identify interesting virus

e.g. 4 samples with point mutations in M gene rendered typing assay probe ineffective = new probe.

2. whole-genome sequencing: evolution



3. metagenomics: co-infections

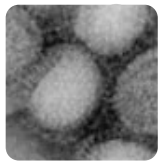


- capitalize on available samples
- explore patterns of co-infection

BCCDC's H1N1 genomics project

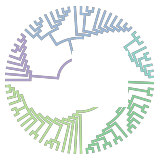
- all sequence will be made publicly available
- collaborating with social scientists, FNIH, GSC, international group of phylodynamics researchers using orwik, GoogleWave

part 3



pandemic H1N1: the first open-source outbreak

H1N1/Olympics research project



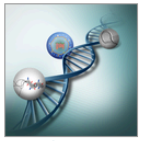
descriptive epidemiology

predictive epidemiology

what is descriptive epidemiology of a pathogen?

where did it come from, how is it spreading, what makes it pathogenic?

Genomics of Emerging Infectious Disease



View large image

This collection of essays, perspectives, and reviews from six PLoS Journals provides insights into how genomics can revolutionize our understanding of emerging infectious disease.

Collection Editor: Jonathan A. Eisen, PhD, is a Professor at the University of California, Davis, in Davis, California. His laboratory is in the UC Davis Genome Center, and he holds appointments in the Section of Evolution and Ecology and the Department of Medical Microbiology and Immunology.

Staff Editor: Catriona J. MacCallum; **Developmental Editor:** Carol Featherstone, PhD (Freelance Science Editor and Writer); **Copy Editor:** Maggie Brown.

Downloads: Audio interview (22 minutes; 10 MB MP3) with Jonathan Eisen, Siv Andersson, and Raj Gupta, led by Kirsten Sanford; Complete collection (6.7 MB PDF).

Produced with support from Google.org. The PLoS Journal editors have sole responsibility for the content of this collection.

Image Credit: Illustration by Pat Margis (PLoS) of a double helix with superimposed images from articles in this collection. Top: a human helminth (*Strongyloides stercoralis*) from Brindley et al., *PLoS Negl Trop Dis* 3(10) e538. Center: a schematic representation of an influenza A virion from McHardy et al., *PLoS Pathog* 5(10) e1000566. Bottom: the bacterium *Helicobacter pylori* from Dorer et al., *PLoS Pathog* 5(10) e1000544.

Editorial Top

Genomics of Emerging Infectious Disease: A PLoS Collection

Jonathan A. Eisen, Catriona J. MacCallum

PLoS Biology:
Published 26 Oct 2009 | info:doi/10.1371/journal.pbio.1000224

PNAS PNAS PNAS

The comparative genomics of viral emergence

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Edited by Stephen Curtis Stearns, Yale University, New Haven, CT, and accepted by the Editorial Board September 28, 2009 (received for review July 8, 2009)

RNA viruses are the main agents of emerging and re-emerging diseases. It is therefore important to reveal the evolutionary processes that underpin their ability to jump species boundaries and establish themselves in new hosts. Here, I discuss how comparative genomics can contribute to this endeavor. Arguably the most important evolutionary process in RNA virus evolution, abundant mutation, may even open up avenues for their control through "lethal mutagenesis." Despite this remarkable mutational power, adaptation to diverse host species remains a major adaptive challenge, such that the most common outcome of host jumps are short-term "spillover" infections. A powerful case study of the utility of genomic approaches to studies of viral evolution and emergence is provided by influenza virus and brought into sharp focus by the ongoing epidemic of swine-origin H1N1 influenza A virus (A/H1N1pdm). Research here reveals a marked lack of surveillance of influenza viruses in pigs, coupled with the possibility of cryptic transmission before the first reported human cases, such that the exact genesis of A/H1N1pdm (where, when, how) is uncertain.

evolution | influenza | RNA virus | lethal mutagenesis | mutation rate

discovery allowed characterization of much of the microbial flora carried by honey bees, encompassing viruses, bacteria, fungi, and others. In short, the generation and analysis of complete genome sequence data are close to becoming the default way of characterizing new viral pathogens (9).

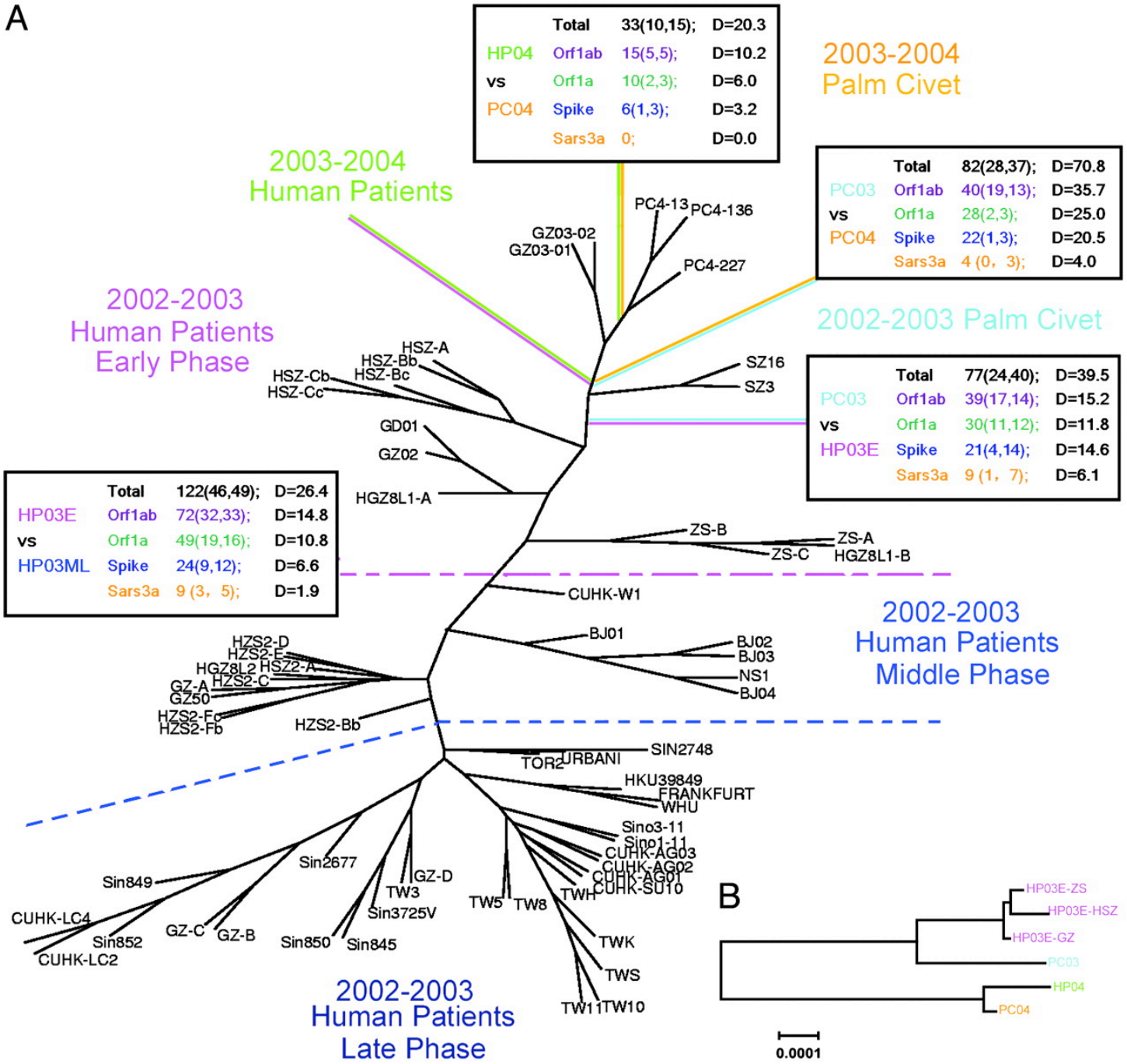
The aim of this article is to demonstrate how new genomic-scale approaches are able to provide unique insights into the processes that govern the emergence and evolution of RNA viruses. In doing so I make general statements about the nature of RNA virus evolution and highlight some of the key evolutionary lessons learned from the ongoing A/H1N1pdm pandemic in particular. As a sidebar, this work illustrates the increasingly important role played by evolutionary biology in the study of infectious disease.

The Evolutionary Genetics of Viral Emergence

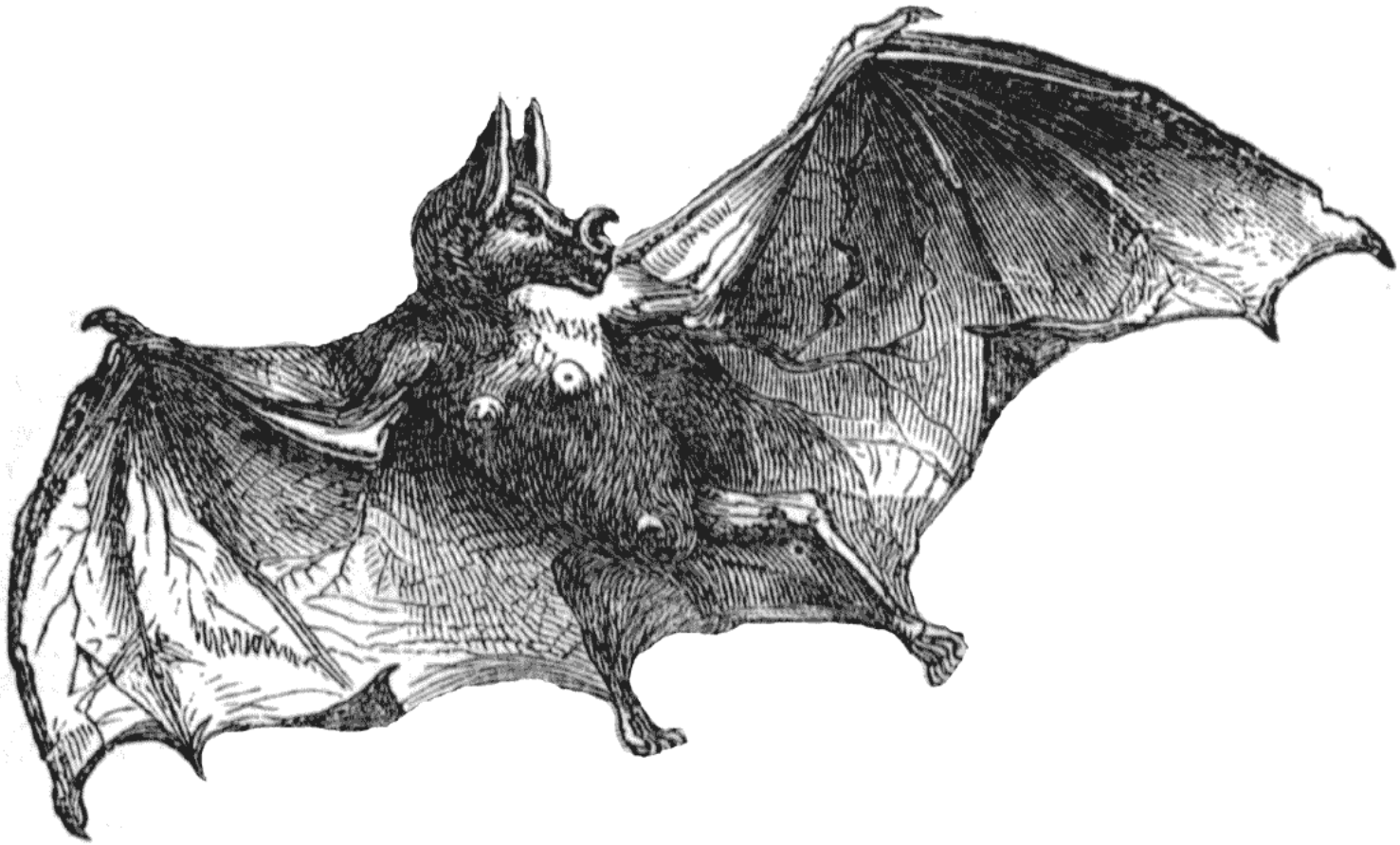
Even allowing for their relative abundance, RNA viruses seem particularly prone to causing emerging diseases in humans and other animals (10). Although these infectious agents have defining characteristics, perhaps the most important from the perspective of their evolution is their capacity for mutation. The vast majority of estimates of mutation rates in RNA viruses are

story 1: where did it come from? **SARS**

- first novel EID of 21st century
  - Nov. 2002 – atypical pneumonia, China
  - March 2003 – international spread
  - July 2003 – containment (~800 deaths)
- suspected animal origin
- sequenced by BCCDC & others


A
Total 33(10,15); D=20.3
HP04 Orf1ab 15(5,5); D=10.2
vs Orf1a 10(2,3); D=6.0
PC04 Spike 6(1,3); D=3.2
Sars3a 0; D=0.0
2003-2004 Palm Civet
2003-2004 Human Patients
Total 82(28,37); D=70.8
PC03 Orf1ab 40(19,13); D=35.7
vs Orf1a 28(2,3); D=25.0
PC04 Spike 22(1,3); D=20.5
Sars3a 4 (0, 3); D=4.0
2002-2003 Human Patients Early Phase
2002-2003 Palm Civet
Total 77(24,40); D=39.5
PC03 Orf1ab 39(17,14); D=15.2
vs Orf1a 30(11,12); D=11.8
HP03E Spike 21(4,14); D=14.6
Sars3a 9 (1, 7); D=6.1
Total 122(46,49); D=26.4
HP03E Orf1ab 72(32,33); D=14.8
vs Orf1a 49(19,16); D=10.8
HP03ML Spike 24(9,12); D=6.6
Sars3a 9 (3, 5); D=1.9
2002-2003 Human Patients Middle Phase
2002-2003 Human Patients Late Phase
PC4-13
PC4-136
PC4-227
GZ03-02
GZ03-01
HSZ-A
HSZ-Bb
HSZ-Bc
HSZ-Cb
HSZ-Cc
SZ16
SZ3
GD01
GZ02
HGZ8L1-A
ZS-B
ZS-A
ZS-C
HGZ8L1-B
CUHK-W1
BJ01
BJ02
BJ03
NS1
BJ04
HZS2-D
HZS2-E
HGZ8L2
HSZ2-A
HZS2-C
GZ-A
GZ50
HZS2-Fc
HZS2-Fb
HZS2-Bb
SIN2748
TOR2
URBANI
HKU39849
FRANKFURT
WHU
Sino3-11
Sino1-11
CUHK-AG03
CUHK-AG02
CUHK-AG01
CUHK-SU10
TWH
TW5
TW8
TWK
TWS
TW11
TW10
Sin2677
GZ-D
TW3
Sin3725V
Sin849
CUHK-LC4
Sin852
CUHK-LC2
GZ-C
GZ-B
Sin850
Sin845
B
HP03E-ZS
HP03E-HSZ
HP03E-GZ
PC03
HP04
PC04
0.0001

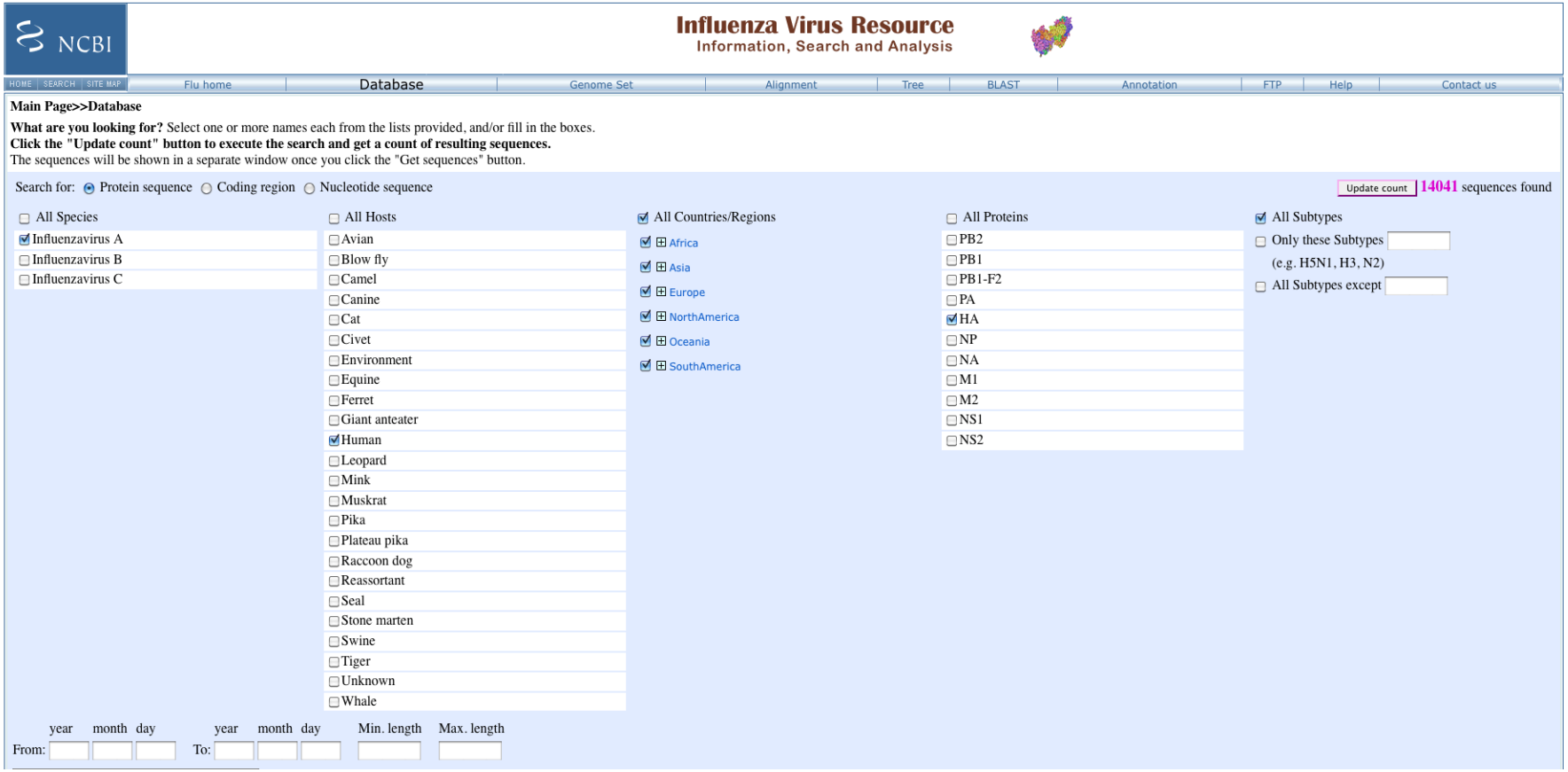
but… high nucleic acid identity, not found in wild civets



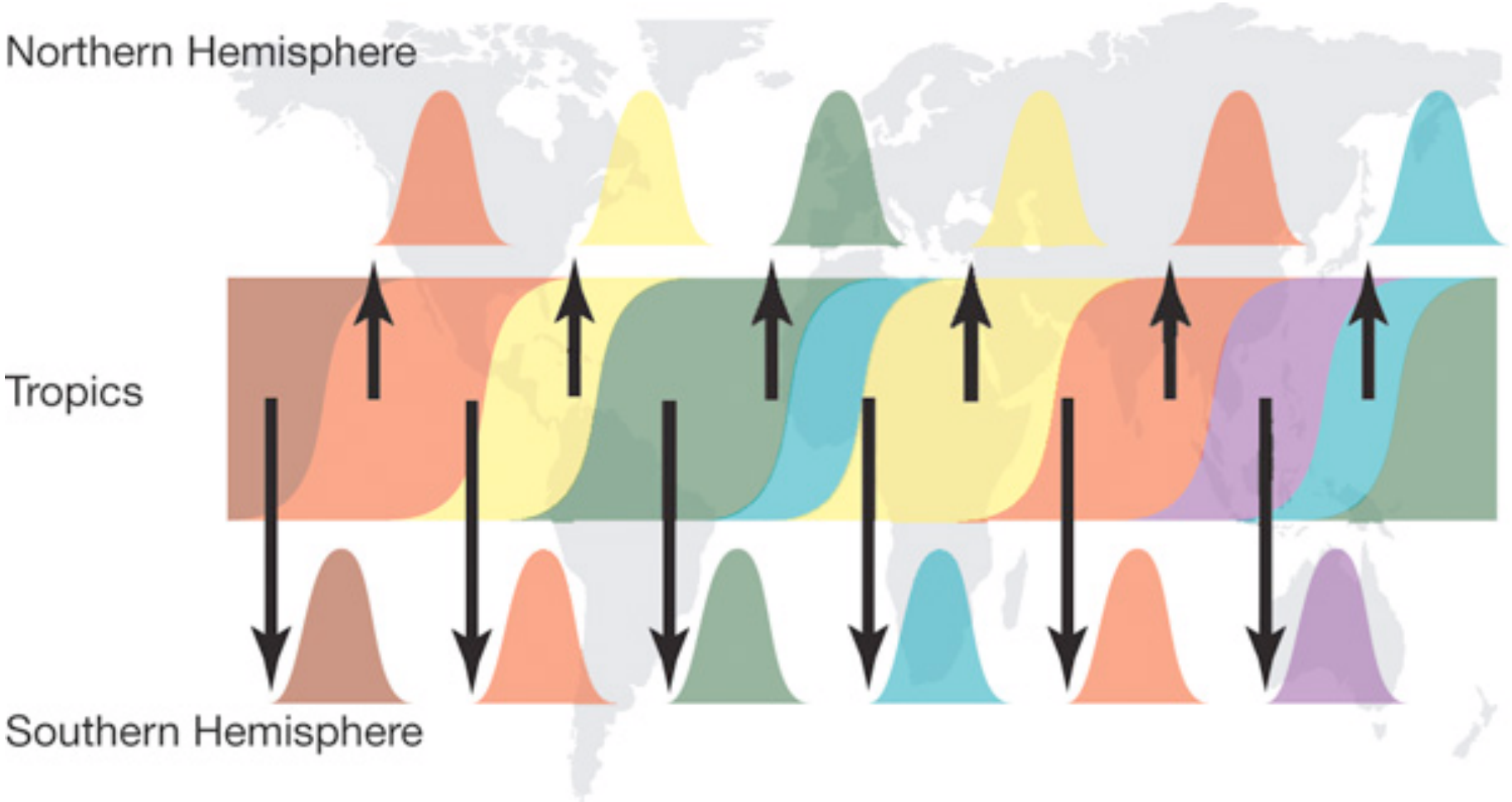
- SARS CoV and others found in bats
- older, evolutionarily stable
- endemic since mid-1980s

story 2: how is it spreading? **influenza**

- IGSP: 4000 influenza genomes across time, space, species, type



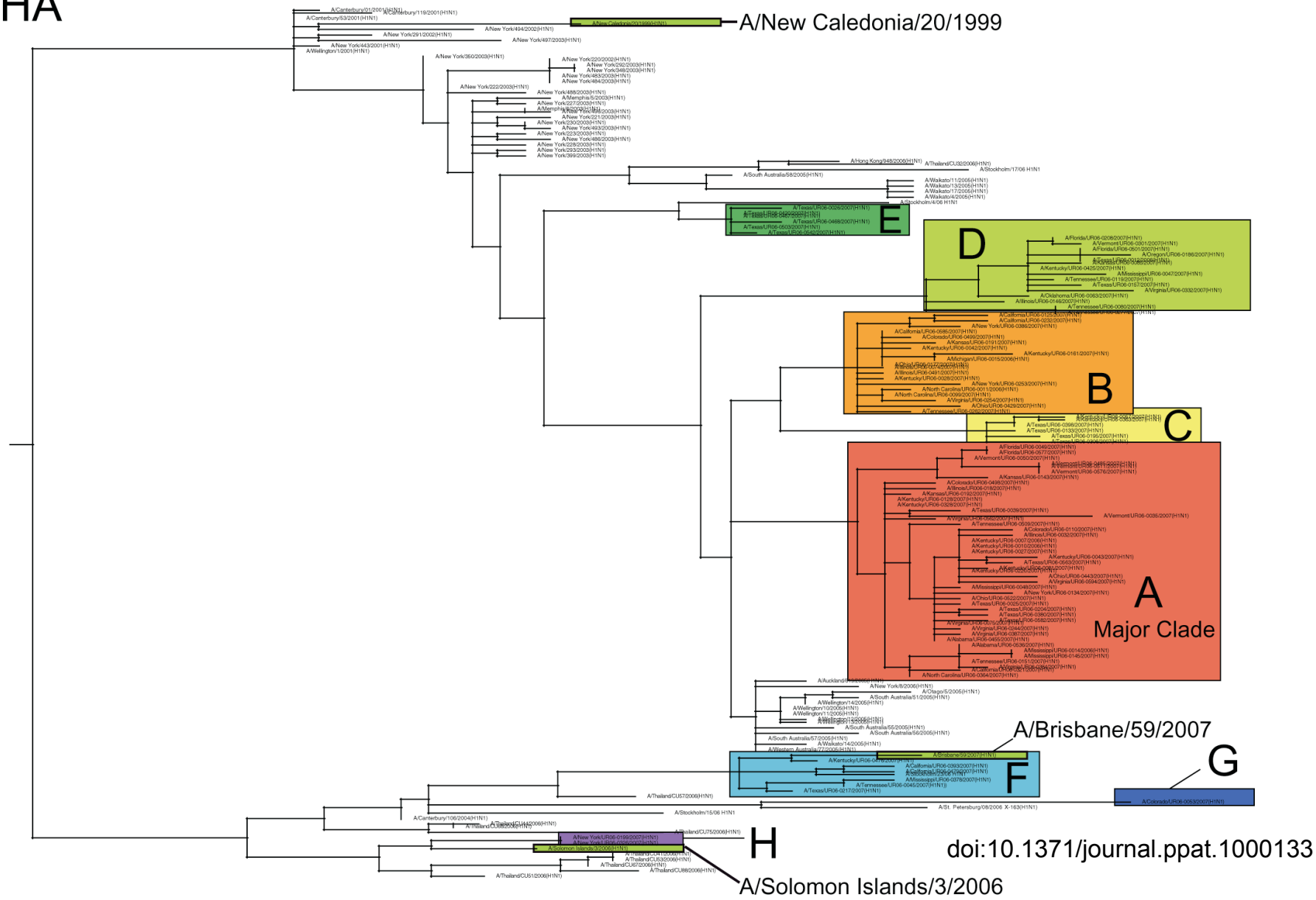
source-sink model of emergence



doi:10.1038/nature06945

co-circulating lineages w/ reassortment

HA



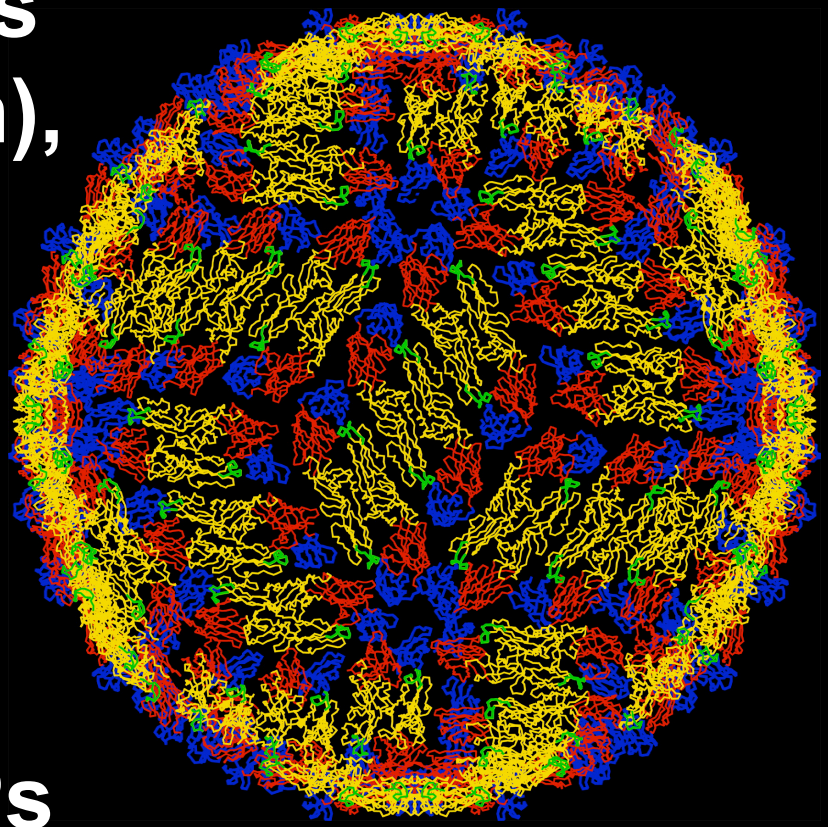
doi:10.1371/journal.ppat.1000133

antiviral resistance is dynamic

story 3: what makes it pathogenic? **Dengue**

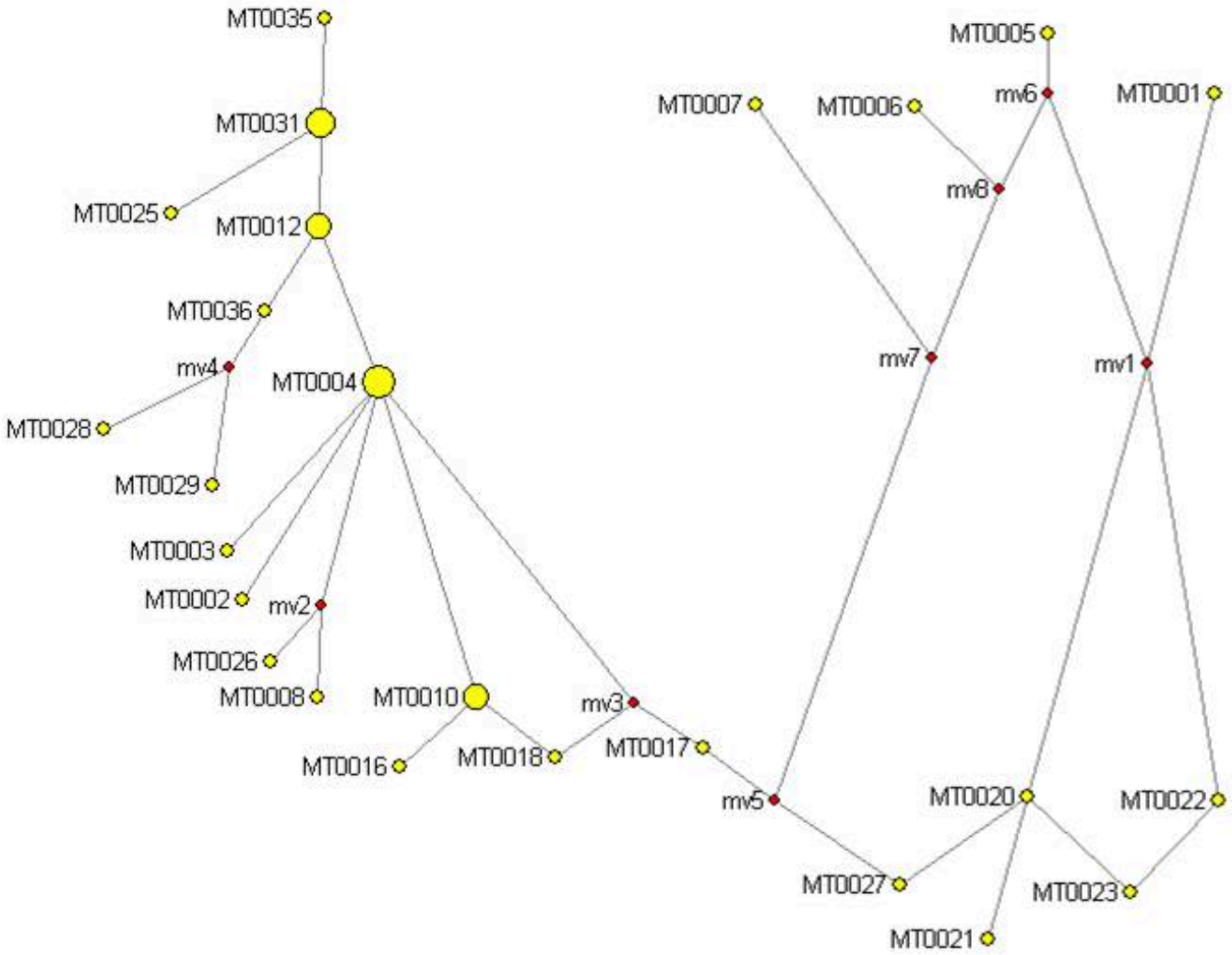
- 50-100 million infections per year
- four serotypes, each with multiple genotypes, geographic distribution
- large-scale sequencing effort underway (target= 3500 genomes)
- genomic correlates of severity

- DENV-2 SE Asian genotype replaced DENV-2 American
- mutations in E genes (receptor interaction), NS1, NS5, multiple UTRs (translation, replication)
- human genetic correlates: HLA (susceptibility), SNPs (severity)



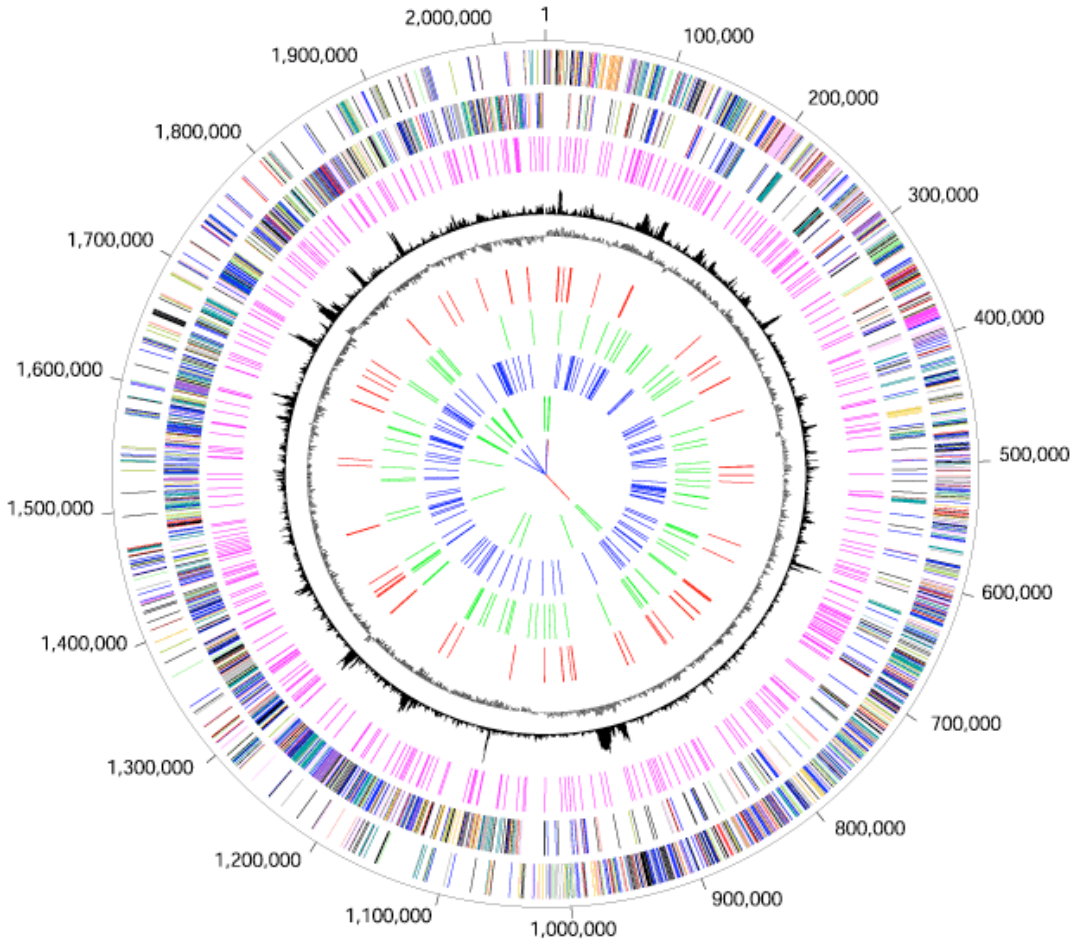
bccdc story 1: outbreak evolution **TB**

- 36 complete *M. tuberculosis* genomes from VI outbreak to compare molecular evolution vs. field epidemiology data



bccdc story 1: unusual isolate *S. pneumo*

- genome from serotype 5 DTES outbreak contains an unusual genomic island (sugar usage?)



descriptive epidemiology: the future

- can answer questions around origins, evolution, pathogenicity, but not clinically-relevant questions
  - effect of co-infections? links between evolution of co-infecting pathogens? role of immunity? viral quasispecies within an individual? epistatic interactions? genomes of most common pathogens? virus discovery?
- genome data must be collected along with extensive host, co-infection data

Recommended essential minimum data for SARI surveillance

General information
- Unique identification number
- Medical record number
- Name (of patient and parent's name, if a minor)
- Date of birth
- Sex
- Address
- Date of onset of symptoms
- Date of collection of epidemiologic data
- Suspected novel influenza case
- Inpatient or outpatient

Clinical signs and symptoms
- Fever >38°C
- Cough
- Sore throat
- Shortness of breath/difficulty breathing
- Other clinical danger signs (*19,22,23*)

Type of specimen collected and date of collection
- Throat swab specimen, date of collection
- Nasal swab specimen, date of collection
- Other specimen (if collected), date of collection

Preexisting medical conditions
- Liver disease
- Kidney disease
- AIDS, cancer, or other immunocompromised state
- Neuromuscular dysfunction
- Diabetes
- Heart disease
- Lung disease
- Smoking history

Optional data collection for SARI surveillance

General information
- Diarrhea
- Encephalopathy

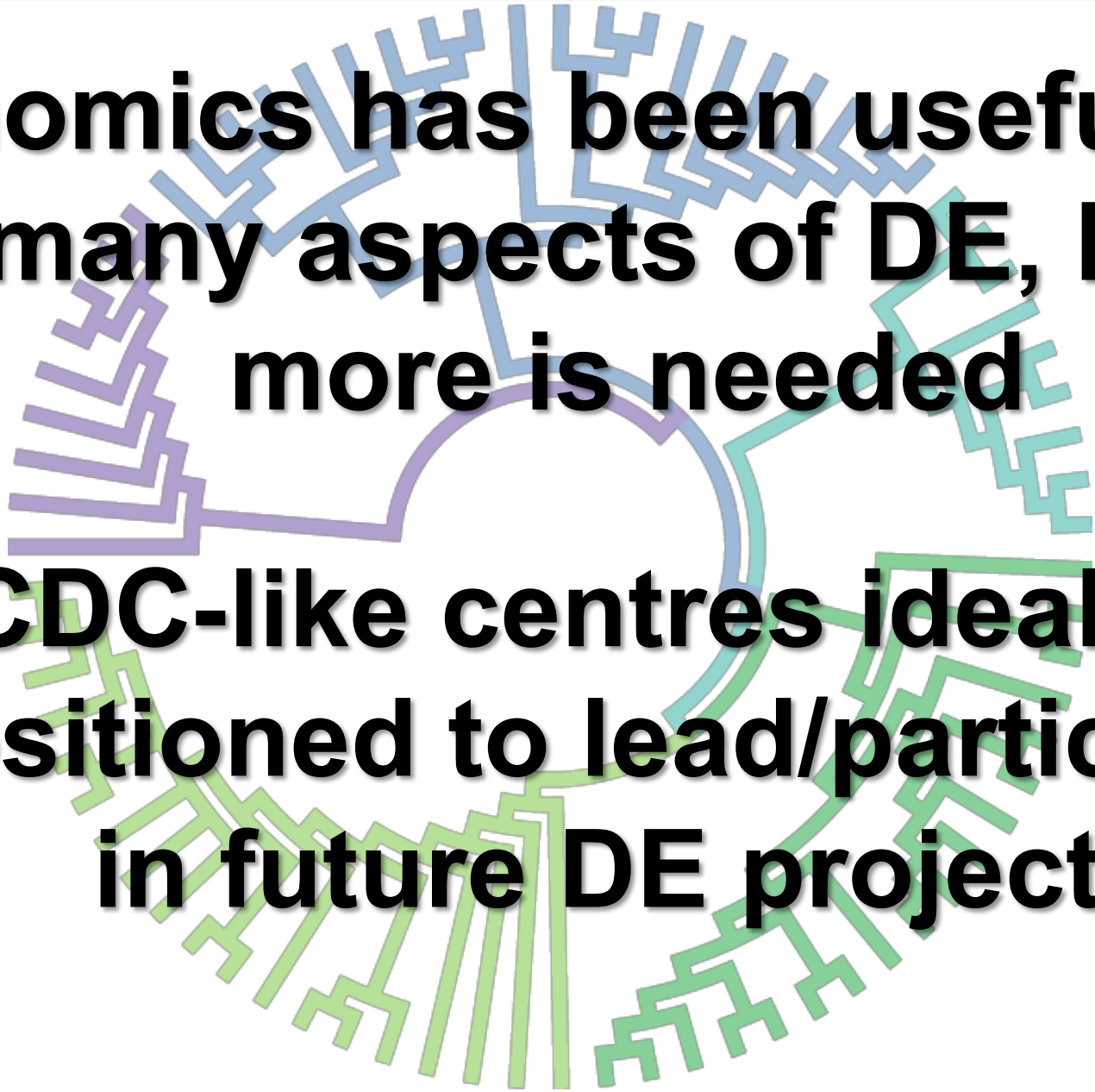
Exposure
- Occupation of patient
- Part of an outbreak investigation
- Contact with sick or dead poultry or wild birds
- Contact with friend or family who has SARI
- Travel in an area known to have endemic circulation of avian influenza (H5N1)
- Other high-risk exposure (e.g., eating raw or undercooked poultry products in an area of influenza virus [H5N1] circulation)

Vaccine/treatment history
- Vaccination against influenza within the past year
- Currently taking antiviral medicine

*SARI, severe acute respiratory infection; ILI, influenza-like illness.

Strategy to Enhance Influenza Surveillance Worldwide[1]

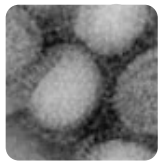
Justin R. Ortiz, Viviana Sotomayor, Osvaldo C. Uez, Otavio Oliva, Deborah Bettels, Margaret McCarron, Joseph S. Bresee, and Anthony W. Mounts



genomics has been useful for many aspects of DE, but more is needed

CDC-like centres ideally positioned to lead/participate in future DE projects

part 4



pandemic H1N1: the first open-source outbreak

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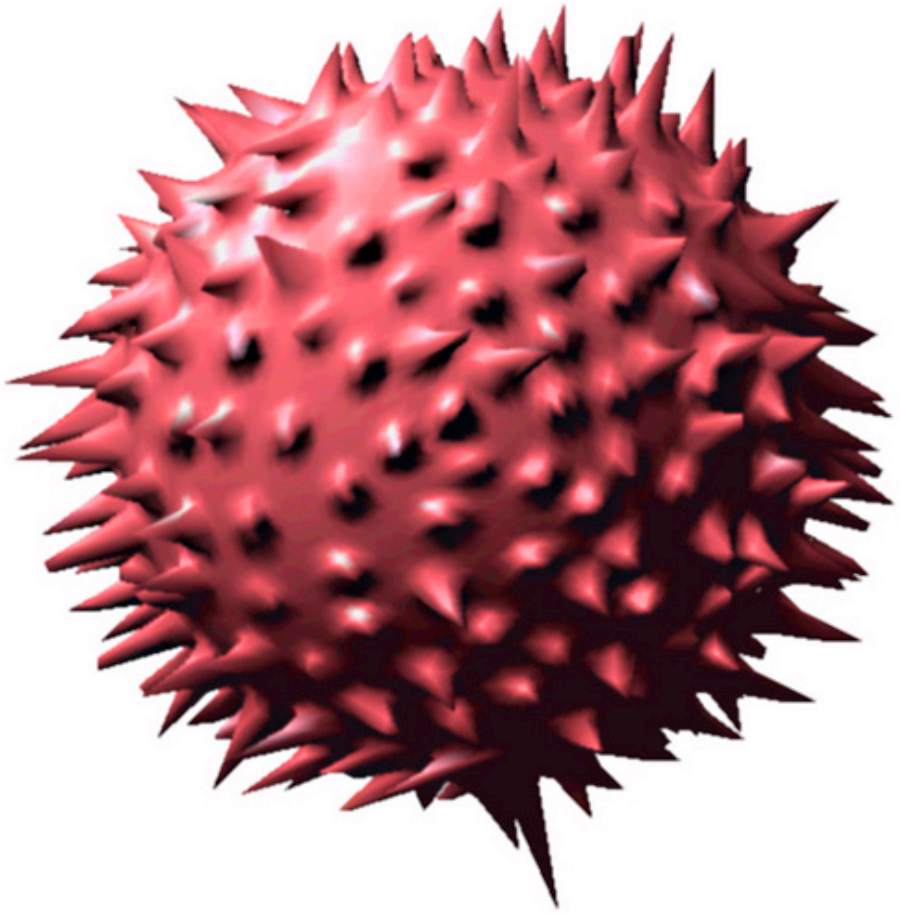
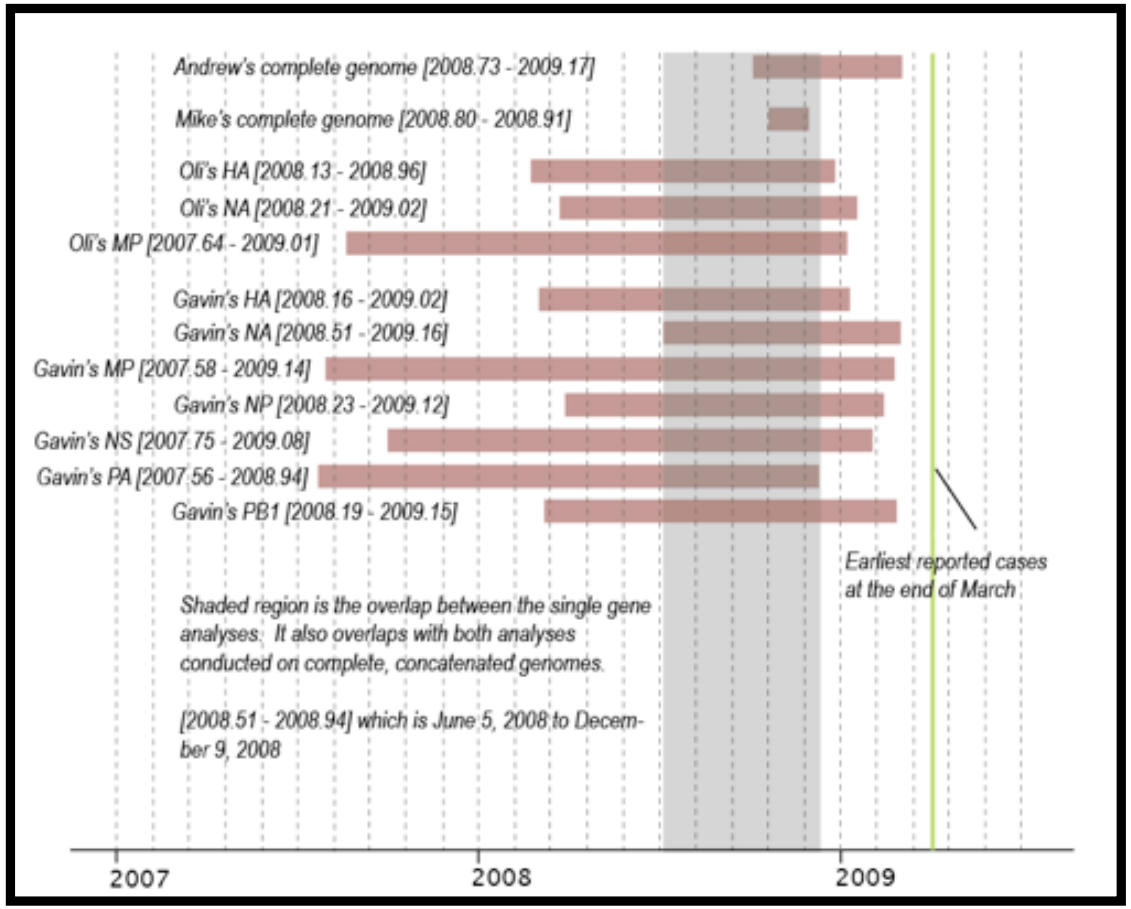


stopping the
next outbreak
before it starts



months of undiscovered circulation in people

sometimes cover-ups, infrastructure problems

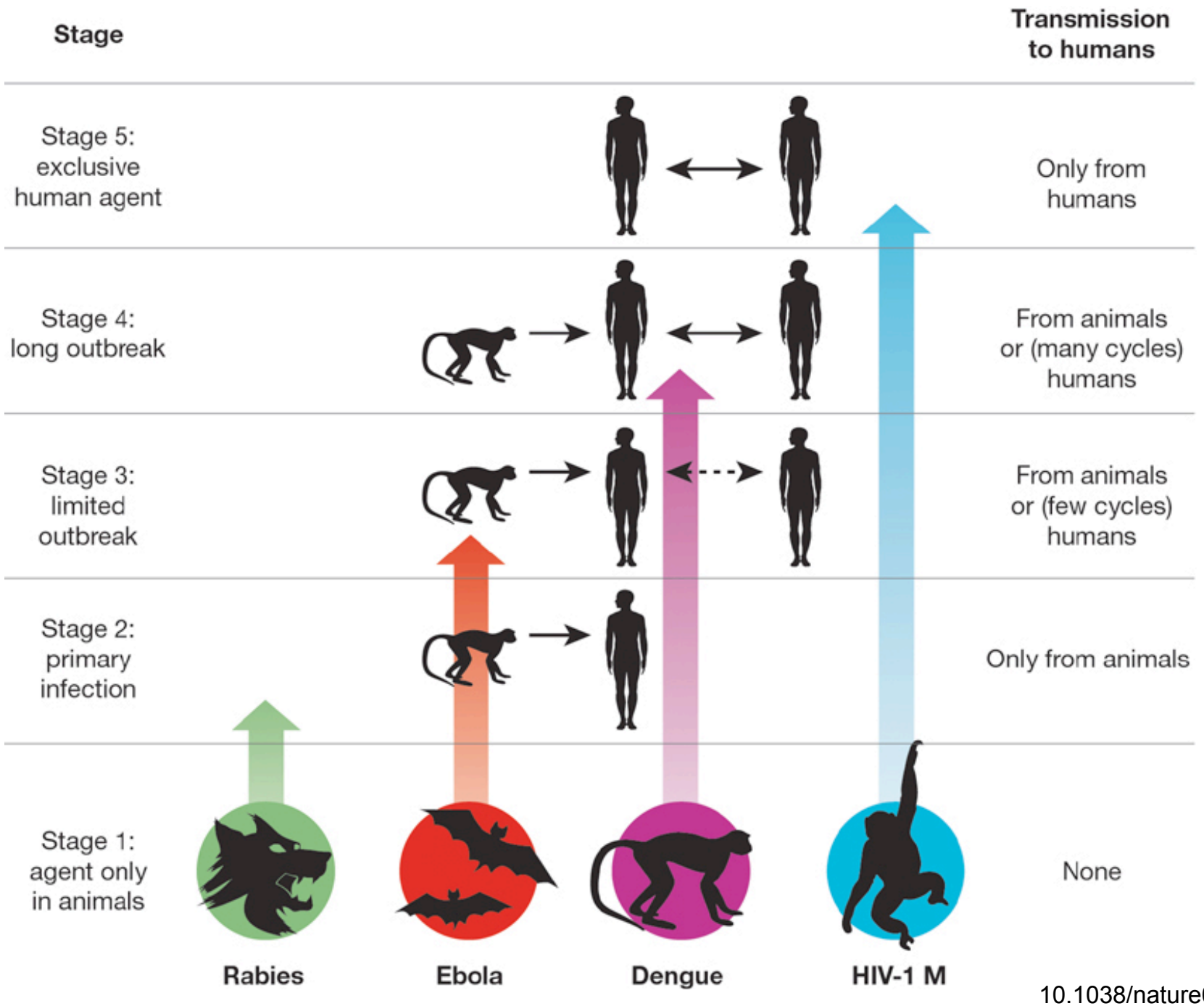
most often poor surveillance, novel pathogens


genome
surveillance

population sampling to pick up threats before the lab or clinic

predictive epidemiology: genome surveillance

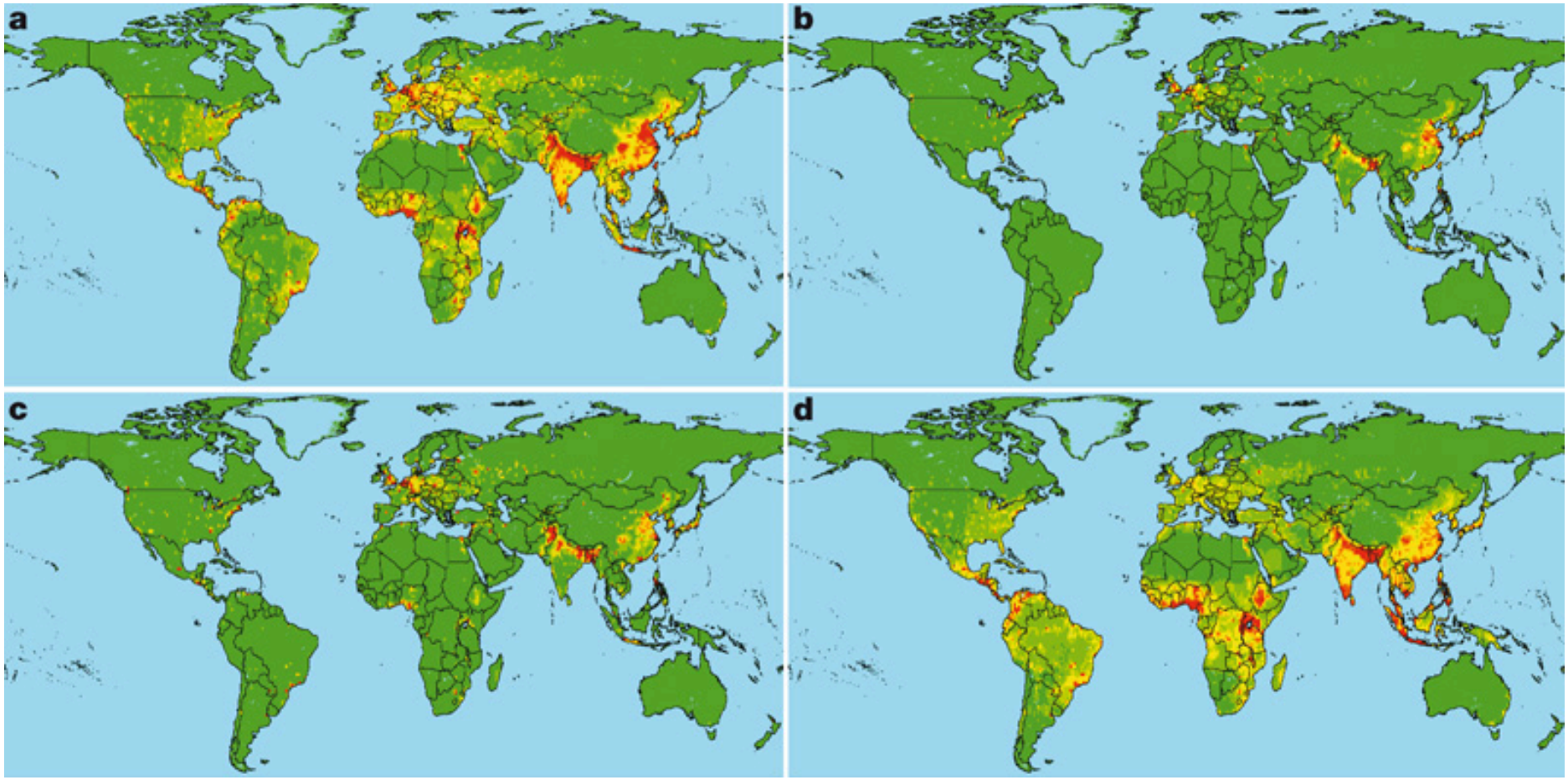
- genomics technology exists, global sentinel system is the roadblock
  - needs infrastructure, standards, reporting
- local/national sentinel systems effective, start by incorporating genomics into these
- must ultimately consider diverse species, geography, demographics over time to be effective



10.1038/nature05775

wildlife

other animals



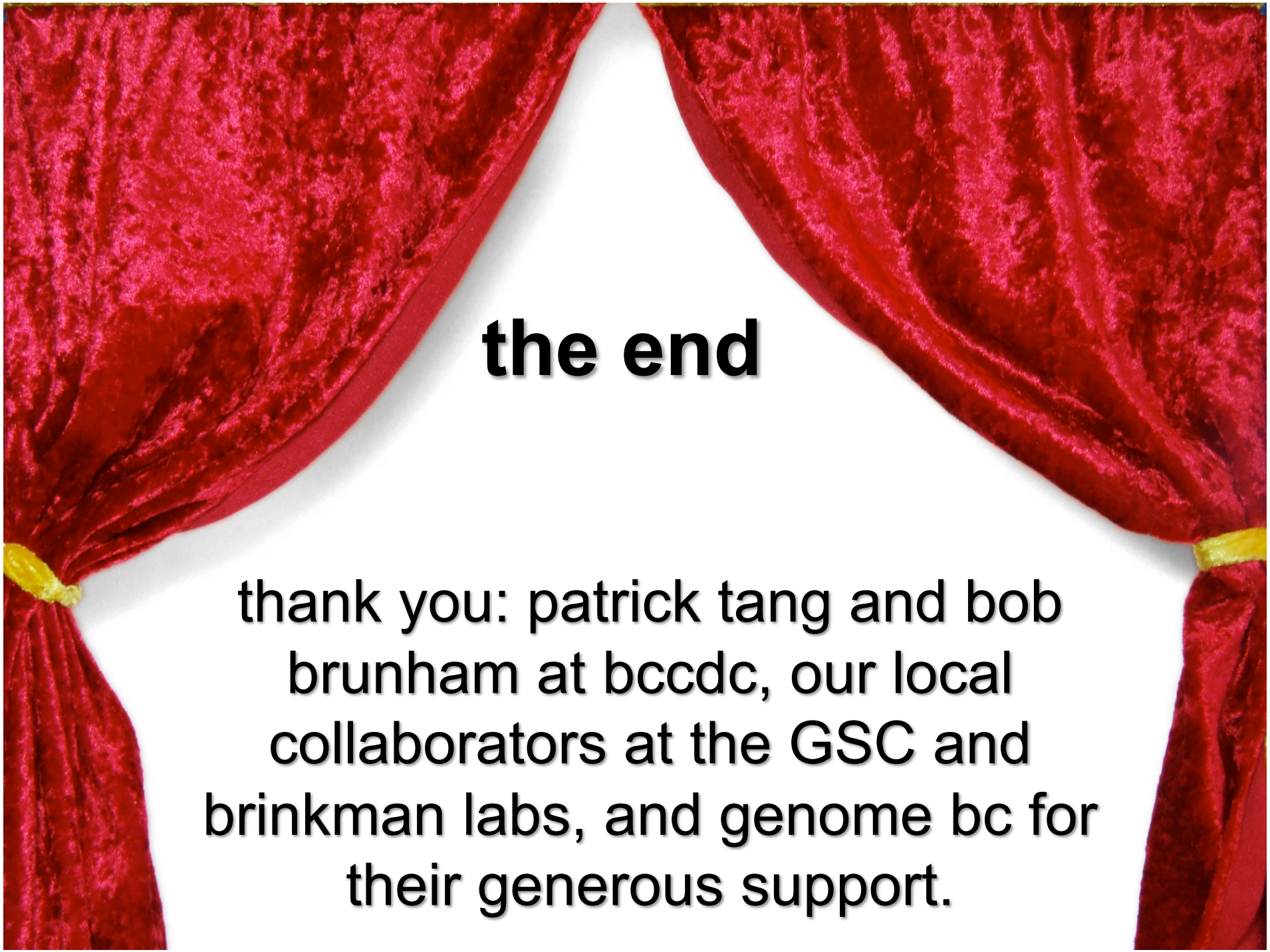
antimicrobial resistance

vector-borne

0.1038/nature06536

sewagenomics

from flickr user stuck in customs


the end
thank you: patrick tang and bob brunham at bccdc, our local collaborators at the GSC and brinkman labs, and genome bc for their generous support.