

Genomic Epidemiology: Objectives of genomic data in enhancing surveillance activities

Laboratory Response Team

PAHO-IMST

Health Emergencies Department



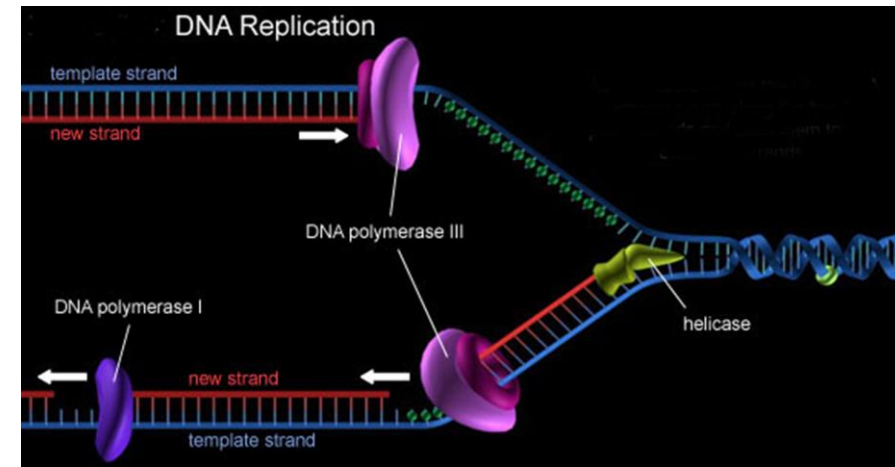
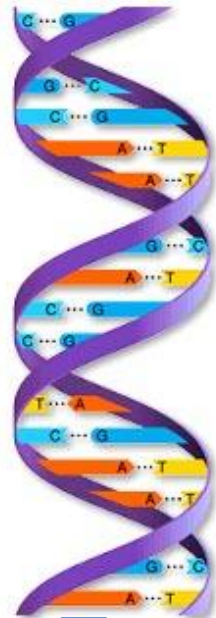
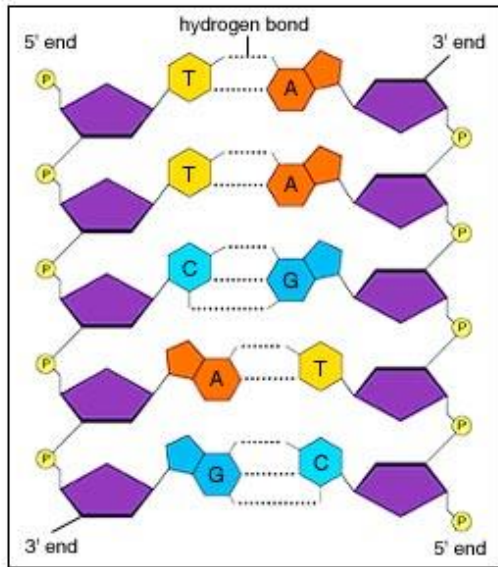
Molecular Epidemiology

Background and definitions

- **Epidemiology** aims to study the distribution, determinants, and causes of health-related problems in order to prevent and control them effectively.
- **Molecular Epidemiology** integrates the use of techniques and fundamentals of molecular biology (**characterization of nucleic acids** and **amino acid content**), for the study of the distribution (time and place) and determining factors (transmission, manifestations and progression) of the occurrence of a disease

Molecular Epidemiology

Molecular bases of change:
From the DNA to the proteins

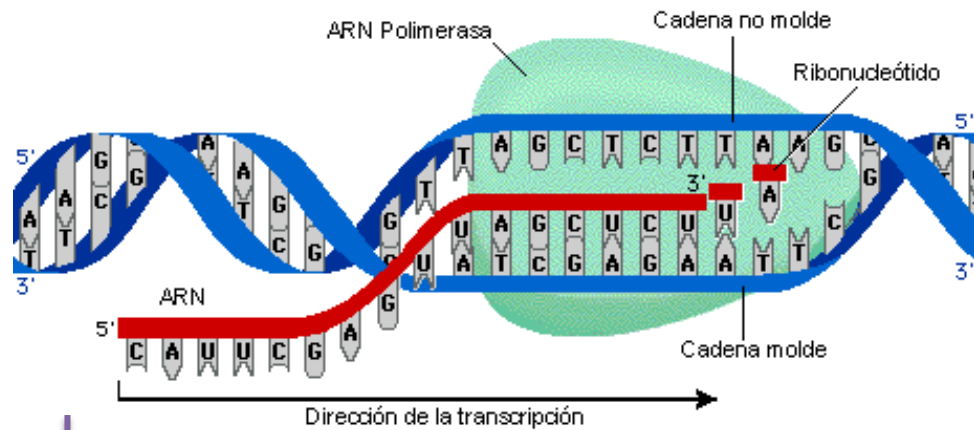


DNA Replication

Errors = Mutation

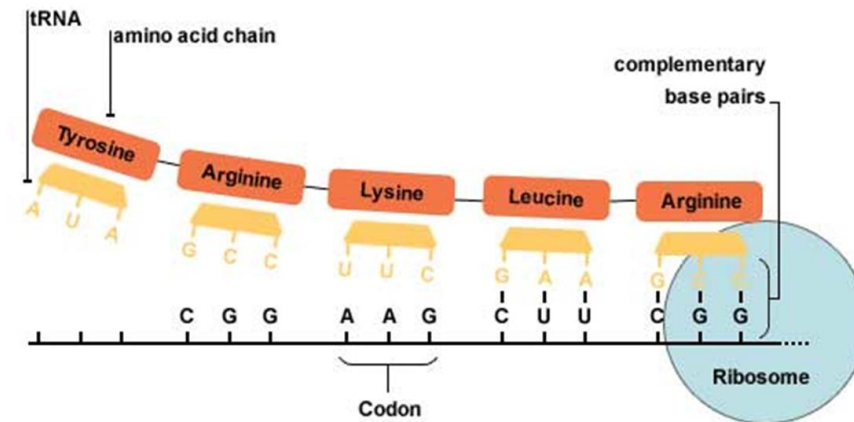
Molecular Epidemiology

Molecular bases of change:
From the DNA to the proteins



RNA Transcription

Errors =
Mutation

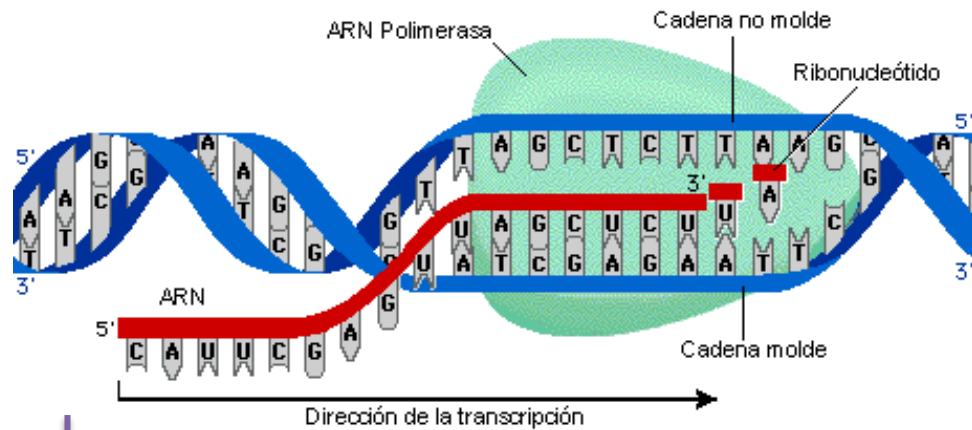


Protein Translation



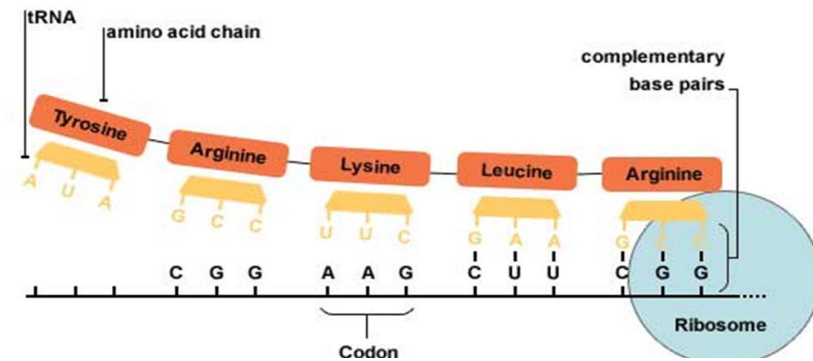
Molecular Epidemiology

Molecular bases of change: From the DNA to the proteins



RNA Transcription

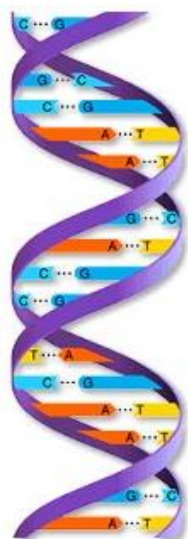
Errors =
Mutation



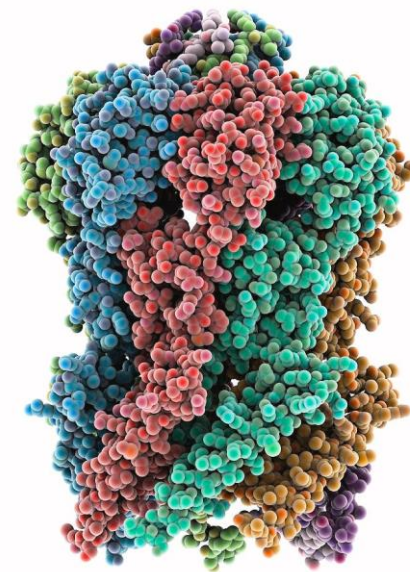
		1st base					
		U	C	A	G		
2nd base	U	UUU Phenylalanine UUC Phenylalanine UUA Leucine UUG Leucine	UCU Serine UCC Serine UCA Serine UCG Serine	UAU Tyrosine UAC Tyrosine UAA Stop UAG Stop	UGU Cysteine UGC Cysteine UGA Stop UGG Tryptophan	U C A G	
	C	CUU Leucine CUC Leucine CUA Leucine CUG Leucine	CCU Proline CCC Proline CCA Proline CCG Proline	CAU Histidine CAC Histidine CAA Glutamine CAG Glutamine	CGU Arginine CGC Arginine CGA Arginine CGG Arginine	U C A G	
	A	AUU Isoleucine AUC Isoleucine AUA Isoleucine AUG Methionine (Start)	ACU Threonine ACC Threonine ACA Threonine ACG Threonine	AAU Asparagine AAC Asparagine AAA Lysine AAG Lysine	AGU Serine AGC Serine AGA Arginine AGG Arginine	U C A G	
	G	GUU Valine GUC Valine GUA Valine GUG Valine	GCU Alanine GCC Alanine GCA Alanine GCG Alanine	GAU Aspartic Acid GAC Aspartic Acid GAA Glutamic Acid GAG Glutamic Acid	GGU Glycine GGC Glycine GGA Glycine GGG Glycine	U C A G	
		Nonpolar, aliphatic	Polar, uncharged	Aromatic	Positively charged	Negatively charged	

Molecular Epidemiology

Molecular bases of change:
From the DNA to the proteins



Genomic changes



Protein changes

- **Molecular Epidemiology** integrates the use of techniques and fundamentals of molecular biology (**characterization of nucleic acids** and **amino acid content**), for the study of the distribution (time and place) and determining factors (transmission, manifestations and progression) of the occurrence of a disease

Molecular Epidemiology

THE JOURNAL OF INFECTIOUS DISEASES • VOL. 127, NO. 4 • APRIL 1973
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SPECIAL ARTICLE

The Molecular Epidemiology of Influenza

Edwin D. Kilbourne

*From the Department of Microbiology, Mount Sinai
School of Medicine of the City University of
New York, New York*

Molecular Epidemiology

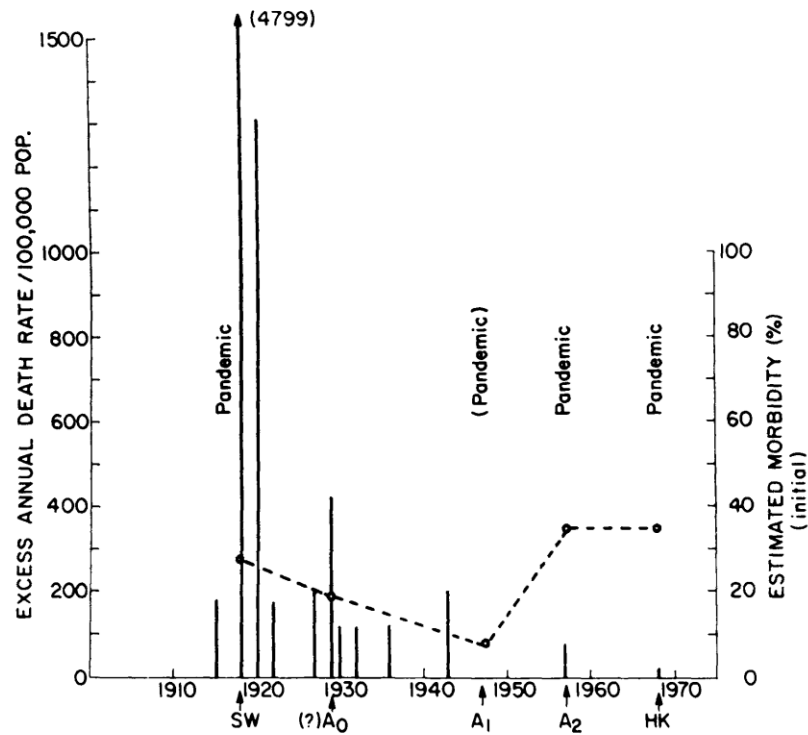


Figure 1. Profile of major epidemics of influenza in the United States during the 20th century. (○---○) = estimated morbidity in initial wave; (-----) = excess annual death rate per 100,000 population. (From data of S. D. Collins. Public Health Monograph no. 48, 1957 and A. D. Langmuir, *In* Influenza: Its Epidemiology. Hospital Practice Vol 6: 103–108, 1971.

“Influenza viruses only present minor antigenic variation during interepidemic period”

In contrast, the pandemic spread of virus in 1947, 1957, and 1968 has been associated with dramatic and radical changes in viral antigenic structure so that, in effect, the global population is presented with a new infective agent—a kind of Andromeda strain¹ to which young and old alike are susceptible.

Molecular Epidemiology

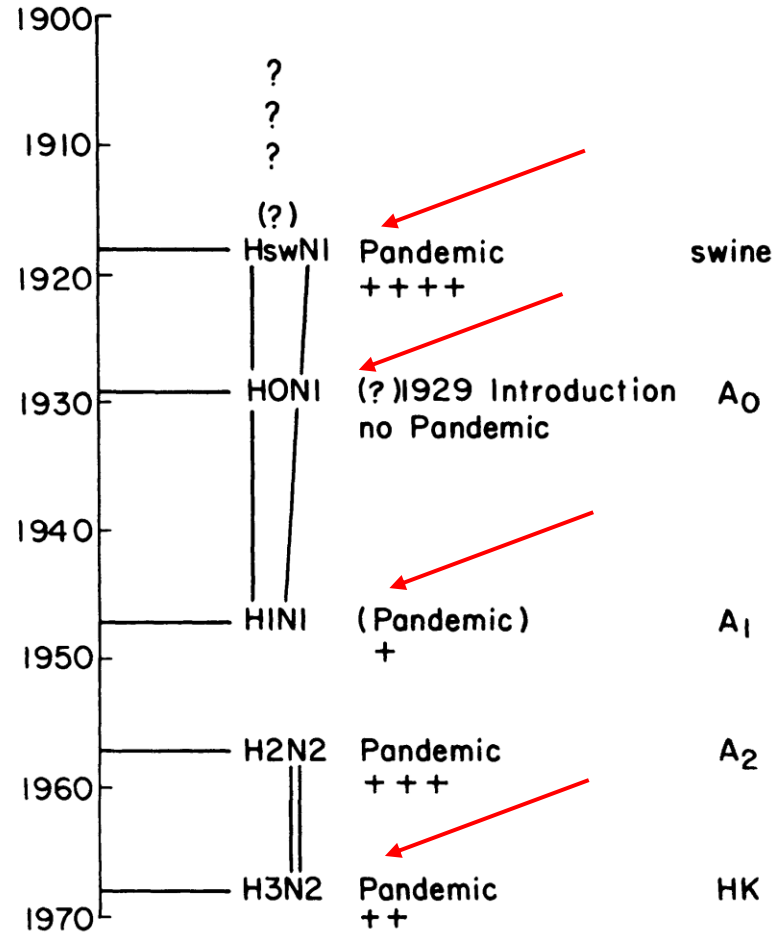


Figure 2. Antigenic variation and pandemic severity of influenza. H = hemagglutinin and N = neuraminidase antigen. Vertical connecting lines indicate antigenic relatedness (i.e., shared antigenic determinants). Double vertical lines indicate close similarity. H0N₁ is new subtype designation for A₀, etc.

- *Why does pandemic severity vary?*
- *Why do pandemics now occur at shorter intervals?*
- *Whence come the pandemic variants and how they arise?*

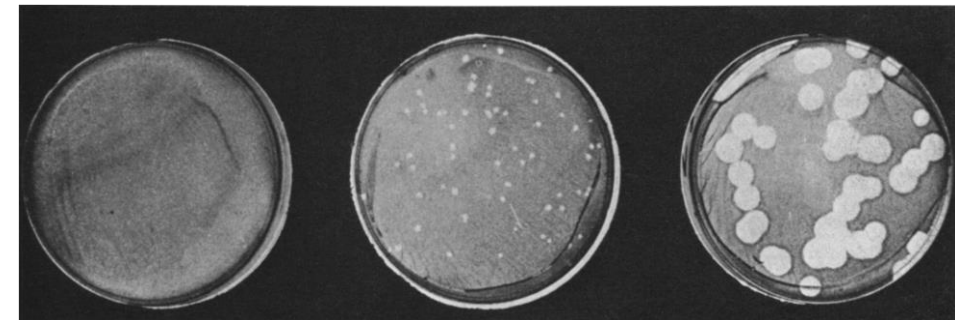


Figure 4. Different effects of antibodies to hemagglutinin (anti-HA) and neuraminidase (anti-NA) on the development of influenza-virus plaques in monolayer cultures of clone 1-5C-4 cells. Right, plaques in the absence of specific antibody; left, complete plaque inhibition with anti-HA; middle, reduction in plaque size, but not in plaque number, by anti-NA.

Molecular Epidemiology

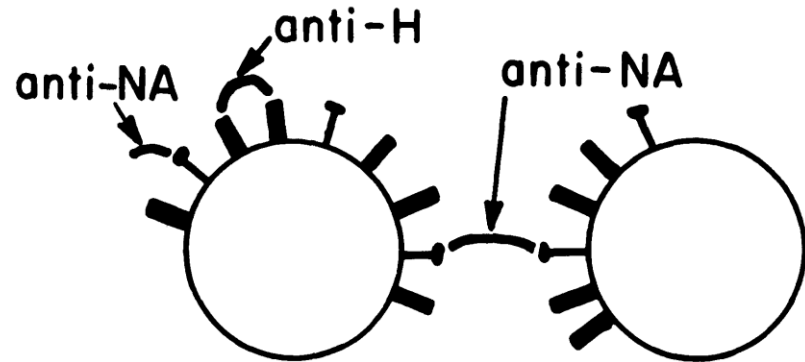


Figure 6. Presumed structural (molecular) basis for different effects of antibody to hemagglutinin (anti-H) and neuraminidase (anti-NA). Divalent binding of anti-H to virion will neutralize viral attachment and infectivity. For steric reasons anti-NA cannot bind divalently to single virion but can bridge adjacent virions to aggregate particles (hypothetical).

Table 3. Antigenic variations in hemagglutinin (HA) and neuraminidase (NA) of the virus and pandemic severity of influenza.

Year	Virus	Change in	Extent of change	Result	
1918	H-SW N1	?	?	Pandemic (severe)	
192?	H0	N ₁	HA NA	++ +	No pandemic
1947	H1	N ₁	HA NA	++ +	Pandemic (mild)
1957	H ₂	N ₂	HA NA	+++ +++	Pandemic (severe)
1968	H ₃	N ₂	HA	+++	Pandemic (moderate)

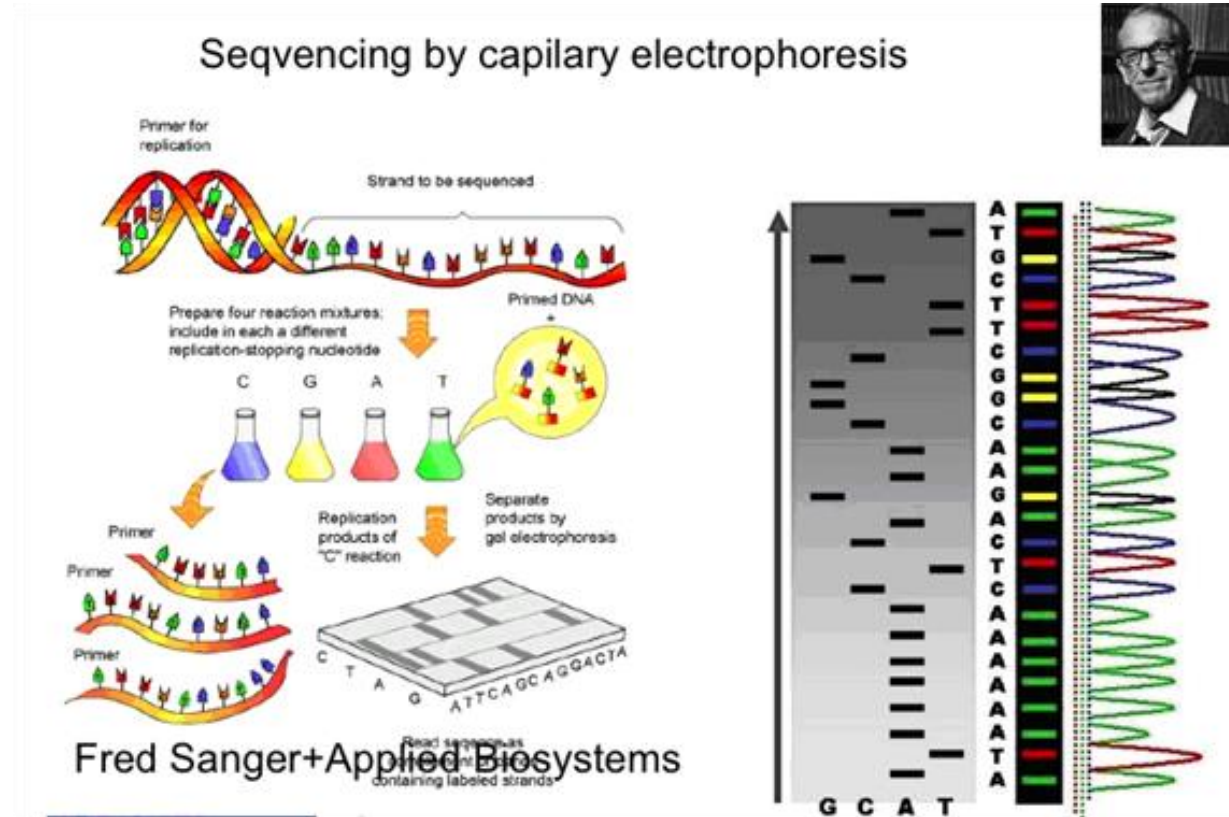
- *Observation at molecular level: Antigen vs Antibody interaction*

- *Differences in neutralization may impact severity of outbreak*

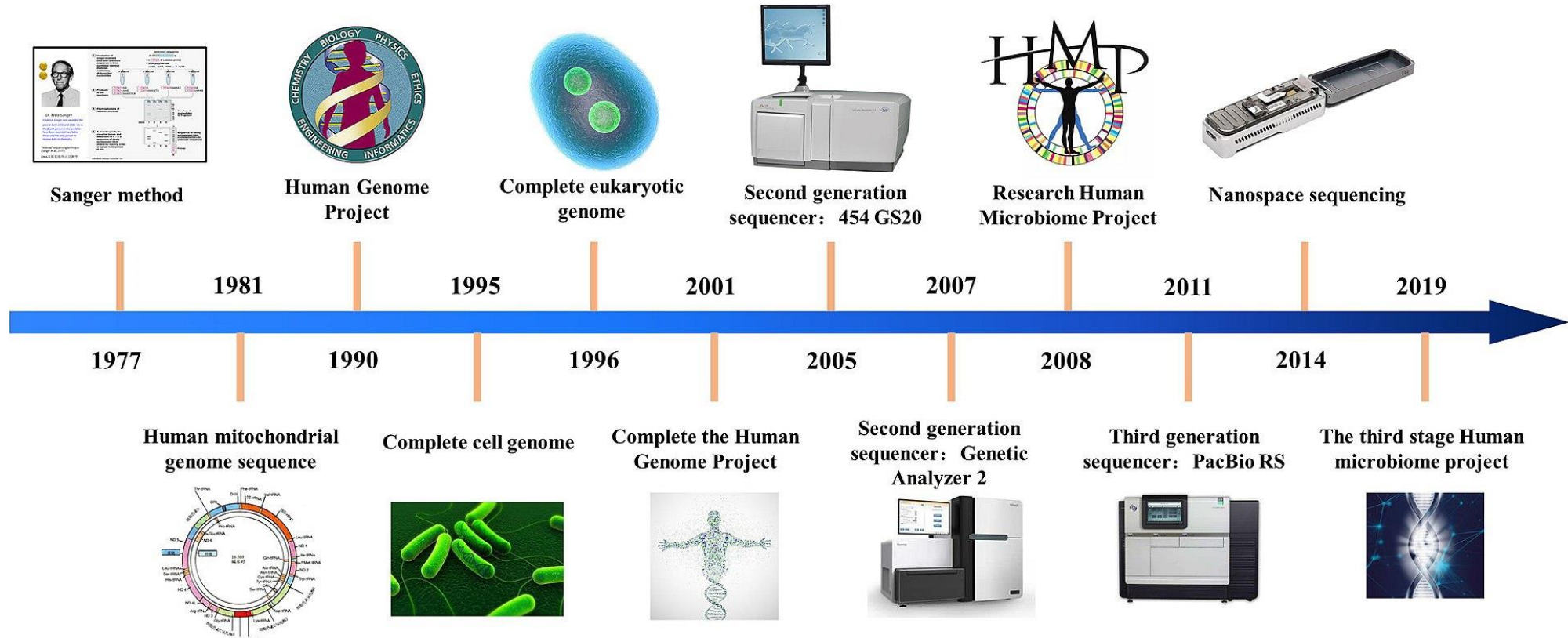
Genomic Epidemiology

First attempts to sequence DNA/RNA

- Robert Holley, 1965: tRNA
- Walter Fiers, 1972: Coat protein gene MS2
- Frederick Sanger, 1977: developed the first DNA sequencing method that utilized radiolabelled partially digested fragments called “chain termination method



Genomic Epidemiology

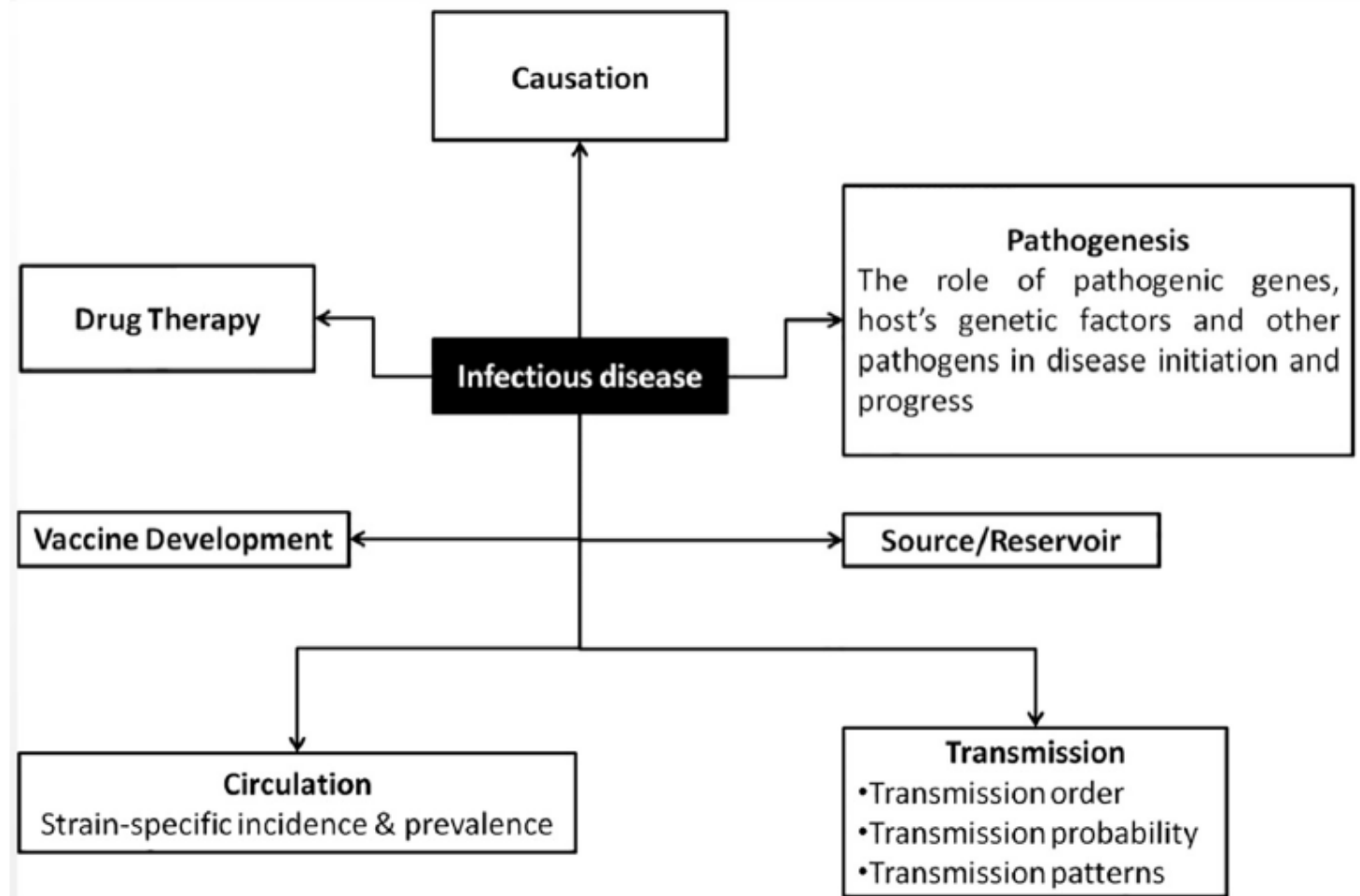


By Aimin Yang, Wei Zhang, Jiahao Wang, Ke Yang, Yang Han and Limin Zhang - [1] doi:10.3389/fbioe.2020.01032, CC BY-SA 4.0, <https://commons.wikimedia.org/w/index.php?curid=101041189>

Genomic Epidemiology

Genomic epidemiology studies have provided information about infectious diseases:

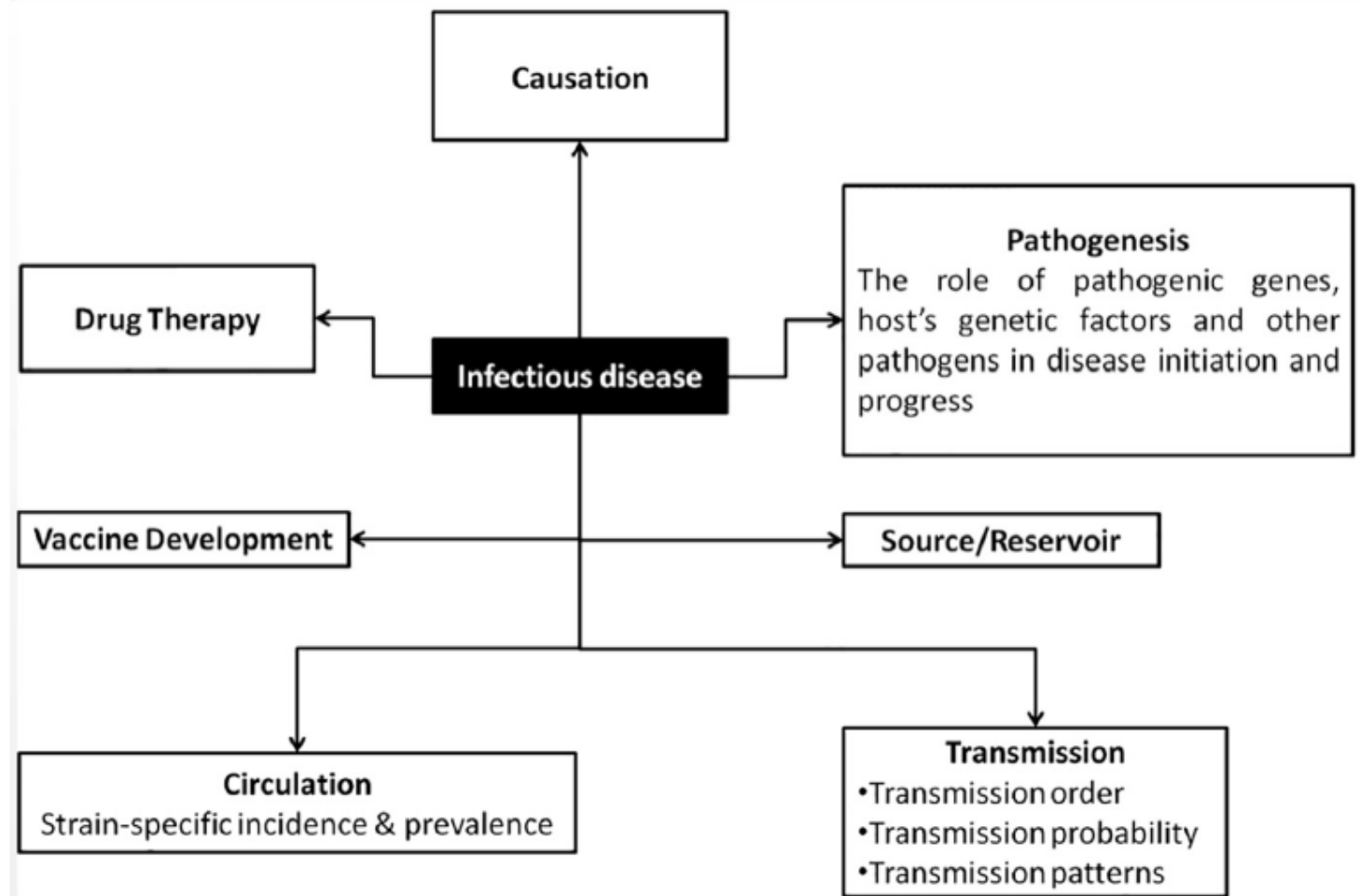
- causality
- pathogenesis
- circulation patterns
- transmission
- prevention
- therapy



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Antecedentes Virus Chapare en Bolivia

- Dic 2003 – Ene 2004
 - Conglomerado de casos de fiebre hemorrágica cerca al Rio Chapare en Cochabamba, Bolivia
- 1 Caso fatal confirmado (hombre de 22 años, cultivador de coca)
 - Sin contacto conocido con otros casos
 - Clínica: fiebre, dolor de cabeza, signos múltiples de hemorragia
 - Muerte 14 días después de inicio de síntomas
 - Por secuenciación, se confirma un virus nuevo: Chapare



Brote de Fiebre hemorrágica en Bolivia, 2019

OPS



Organización
Panamericana
de la Salud



Organización
Mundial de la Salud
Américas

Alerta Epidemiológica Fiebre Hemorrágica por Arenavirus en Bolivia

18 de julio de 2019

En el Estado Plurinacional de Bolivia, se encuentra en curso la investigación de un brote de fiebre hemorrágica causado por un Arenavirus, con casos reportados en personal de salud; ante ello la Organización Panamericana de la Salud / Organización Mundial de la Salud (OPS / OMS) recuerda a los Estados Miembros sobre la necesidad de permanecer vigilantes y fortalecer la implementación de las medidas de prevención y control de infecciones, en todos los niveles de atención en los servicios de salud.

Resumen de la situación

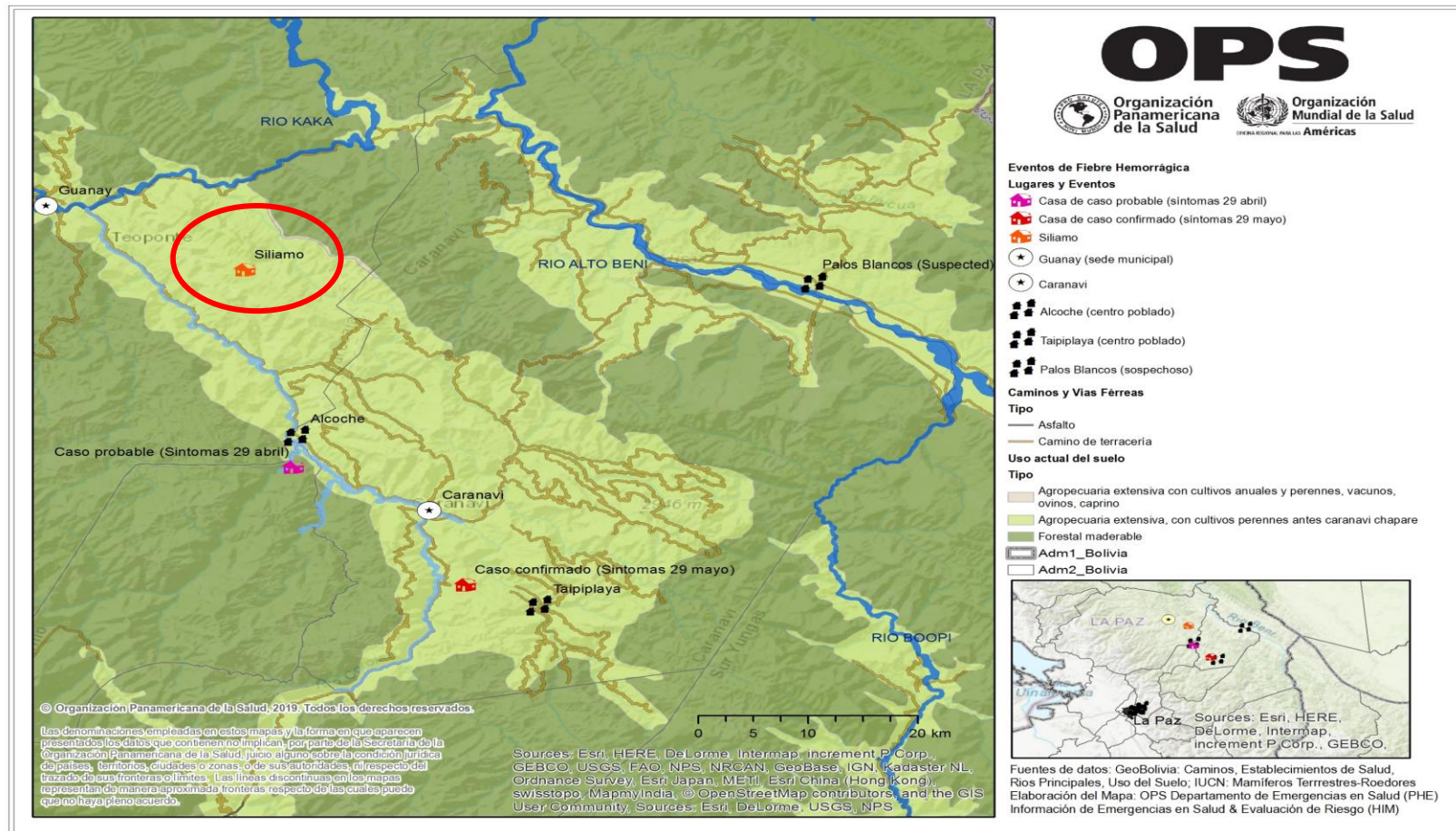
El 28 de junio de 2019, el Ministerio de Salud del Estado Plurinacional de Bolivia recibió el reporte de 3 casos de síndrome febril hemorrágico de etiología desconocida, con sospecha de transmisión de persona a persona. Hasta el 17

Fiebres hemorrágicas por Arenavirus

Son una zoonosis producida por un virus perteneciente al género Arenavirus de la familia de *Arenaviridae*, asociados generalmente a enfermedades transmitidas por roedores en humanos. Entre los 21 Arenavirus del Nuevo Mundo conocidos, cinco se han vinculado con fiebres hemorrágicas en humanos y dos de ellos en



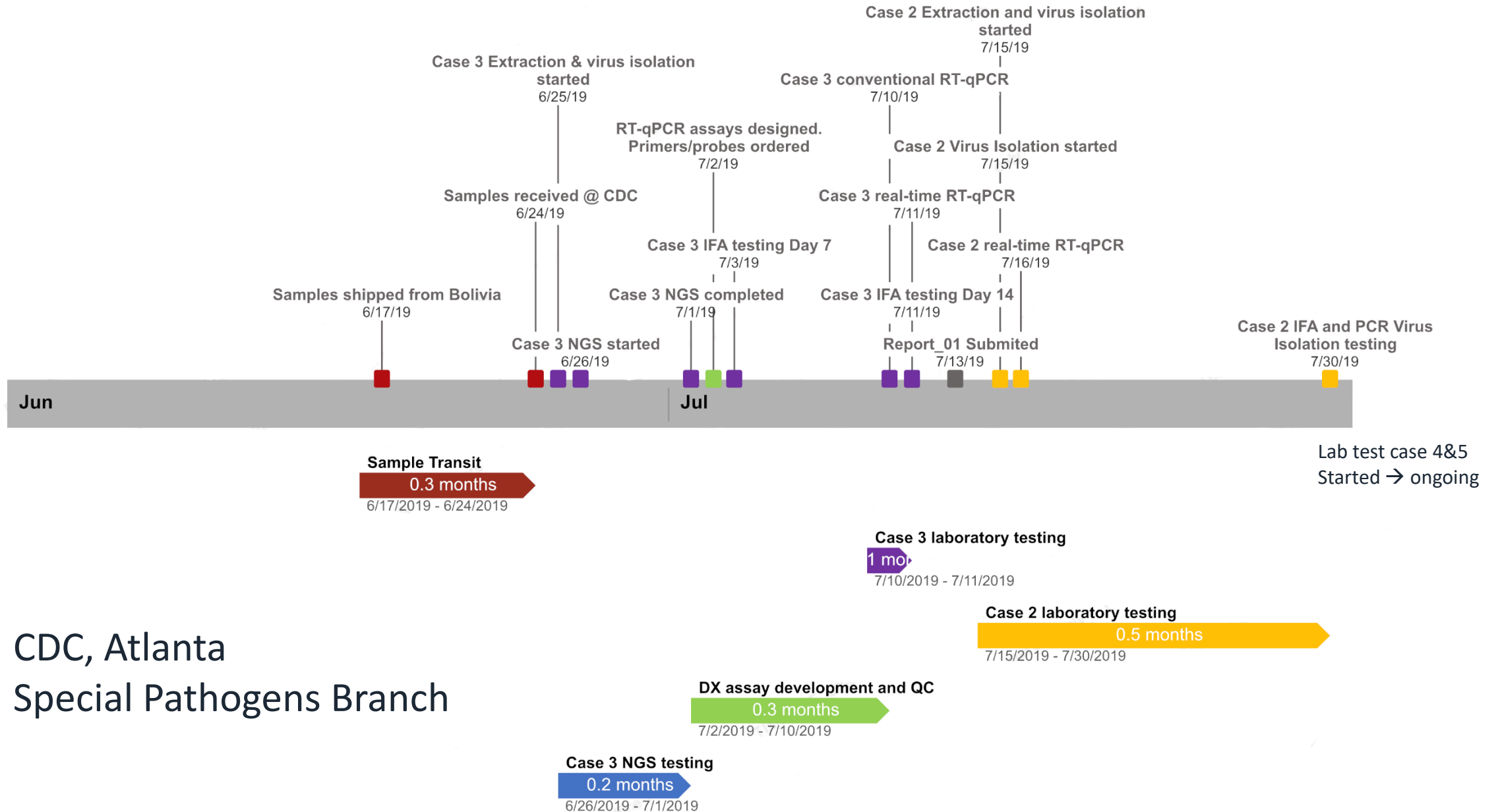
Características geográficas del área de exposición de los casos con probable transmisión zoonótica



- Arroz (en Guanay existen 57 pequeños centros de acopio) - Café - otros
- Caranavi a Guanay – 2 horas.

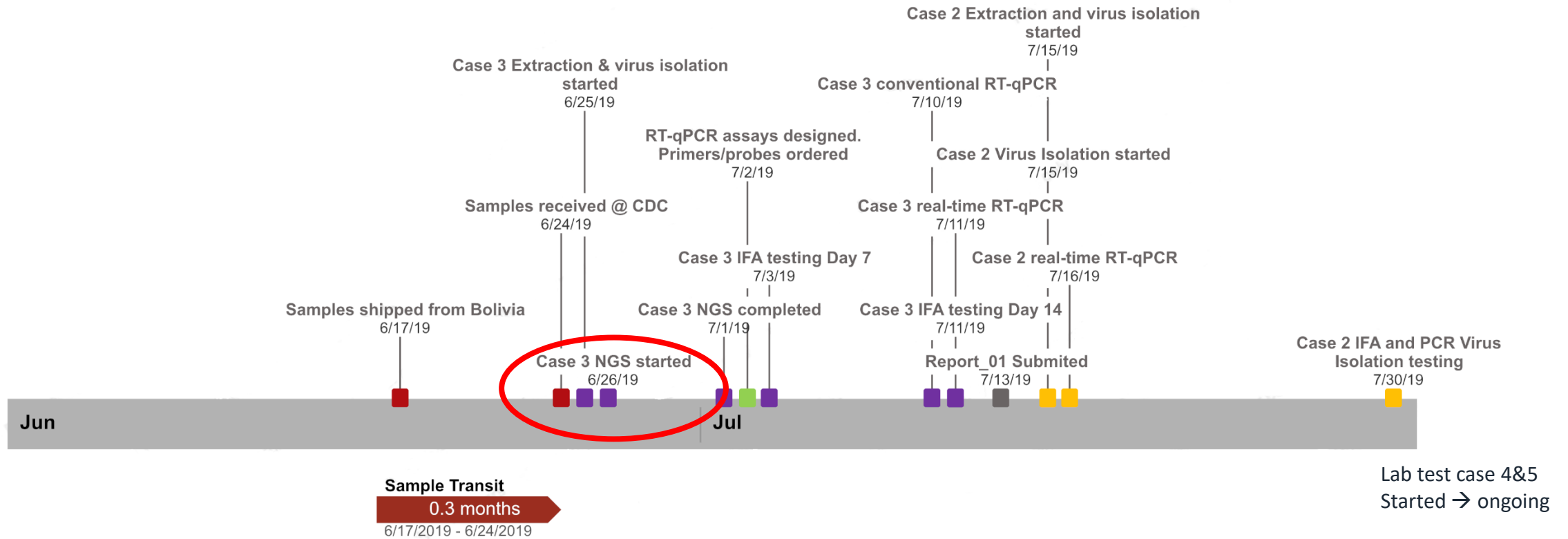
Dr. Joao Toledo; Dra. Alison Paredes,
OPS/PHE

Diagnóstico NWA, Bolivia 2019



CDC, Atlanta
Special Pathogens Branch

Diagnóstico NWA, Bolivia 2019



Different virus that 2002

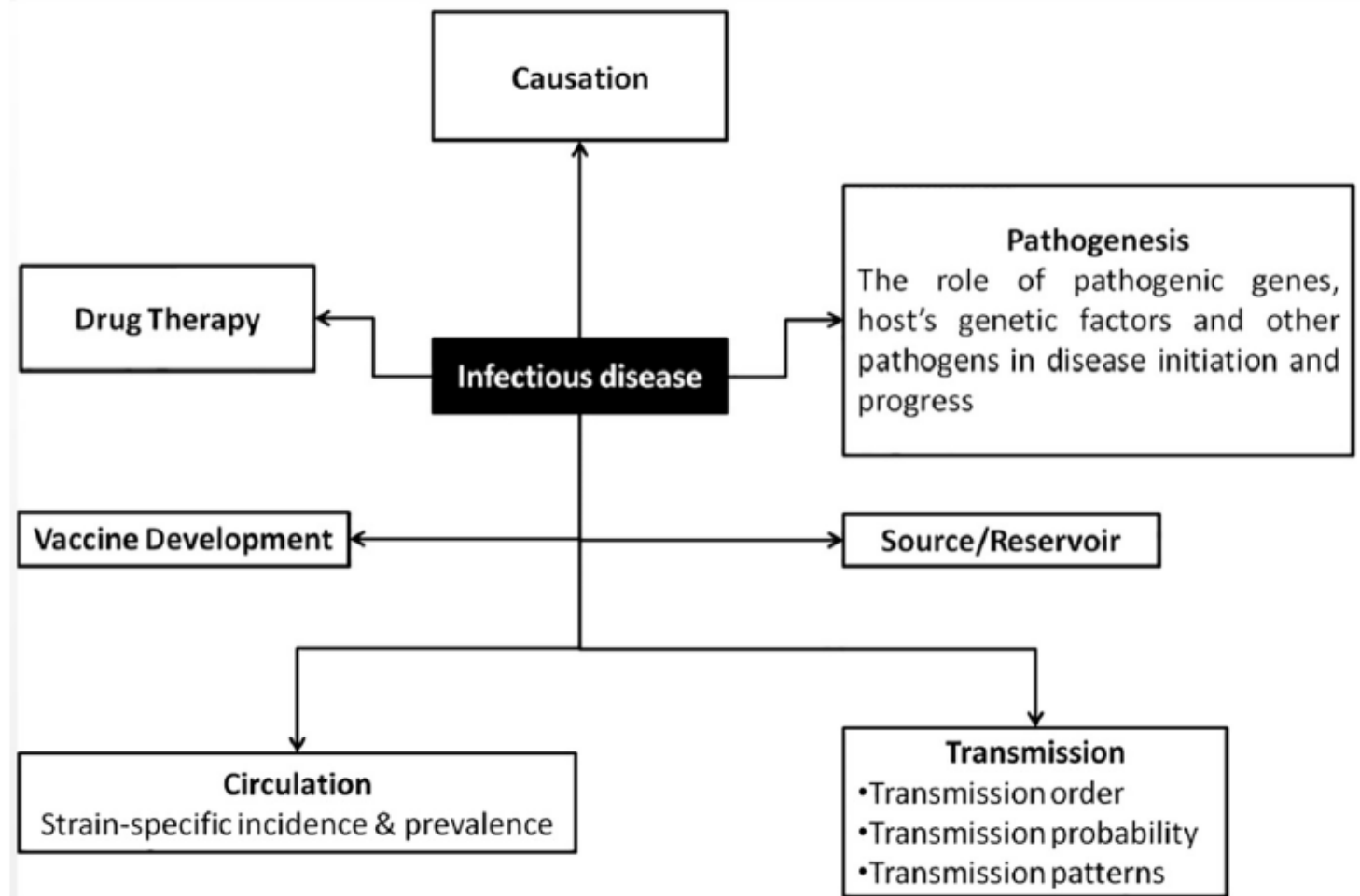
CDC, Atlanta
Special Pathogens Branch

New World Arenavirus was
described: Chapare-2019

Genomic Epidemiology

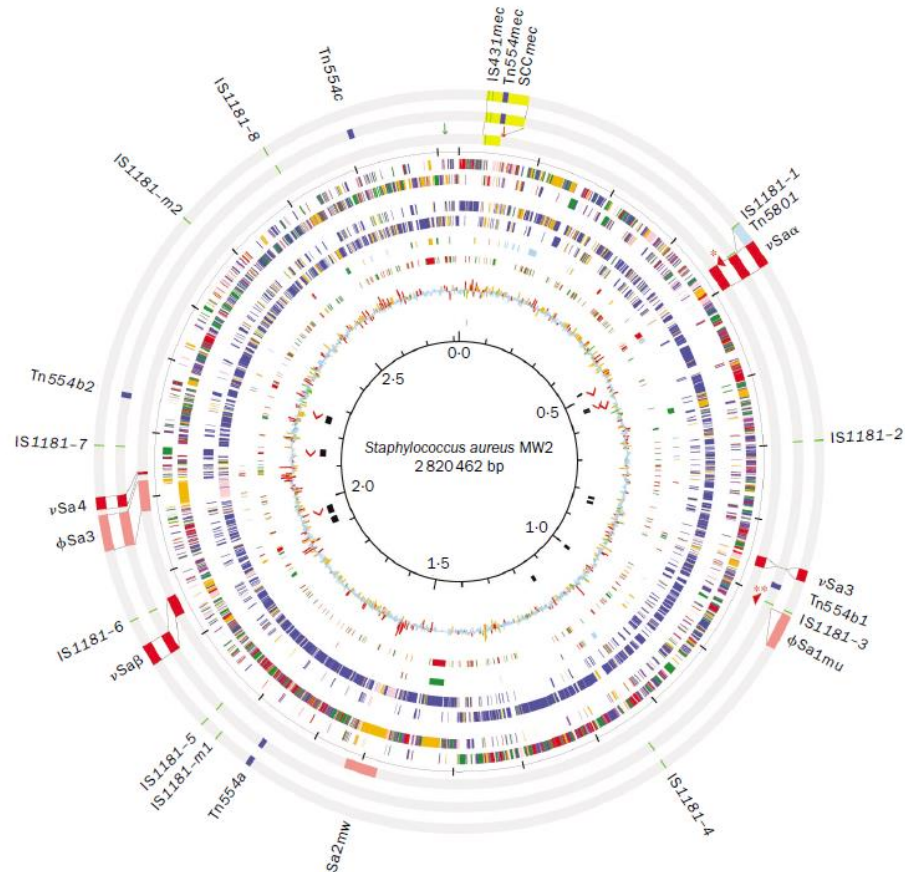
Genomic epidemiology studies have provided information about infectious diseases:

- causality
- **pathogenesis**
- circulation patterns
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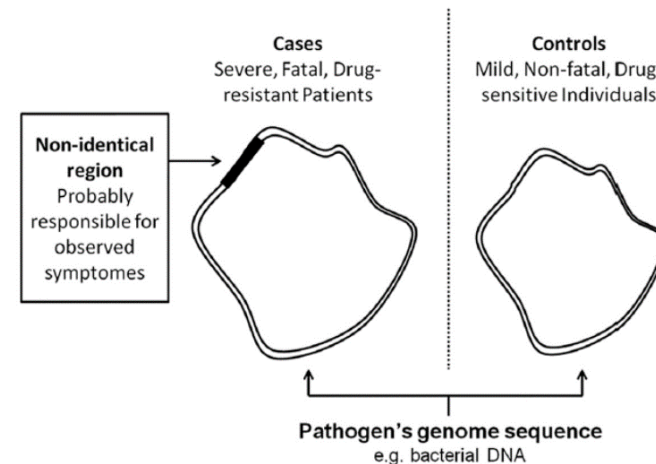


Genomic Epidemiology

By comparing the genome sequencer of a particular pathogen between severe, fatal or drug resistant cases, it is possible to find out if there is any difference between genomes and identify genetic markers involved

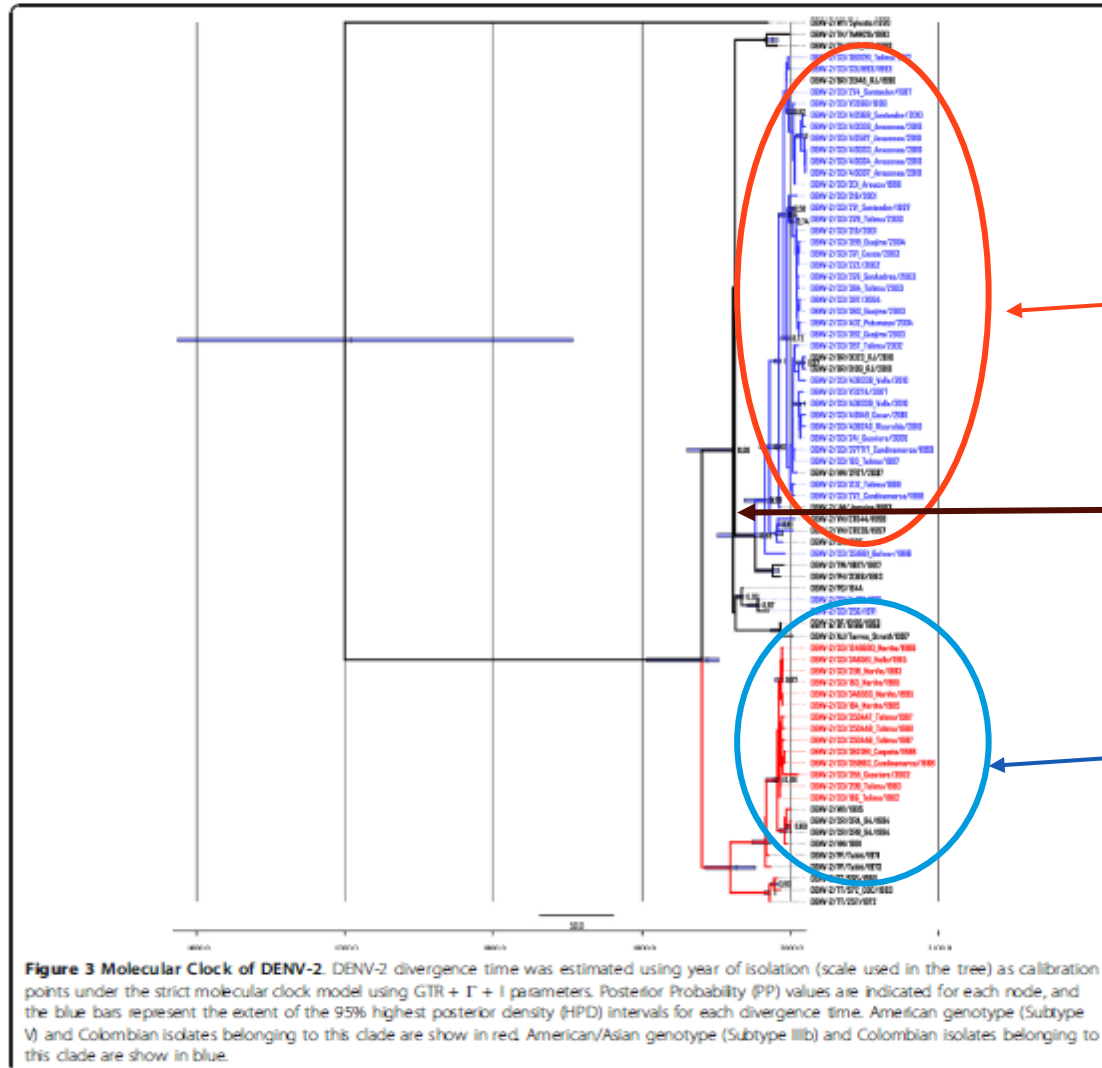


- New type of methicillin-resistant *Staphylococcus aureus* (MRSA) was identified to cause community-acquired MRSA with high fatality rate (*Baba et al., 2002*)
- Comparison of whole genomes from fatal cases and mild cases demonstrated 7 genomic islands responsible for the increased pathogenicity



Genomic Epidemiology

DENV-2 Asian genotype has been associated to increased risk of Hemorrhagic manifestation



American/Asian genotype (IIIb)

Introduction and replacement around the end of 80's coinciding with the first hemorrhagic cases in Colombia

American genotype (V)

RESEARCH

Open Access

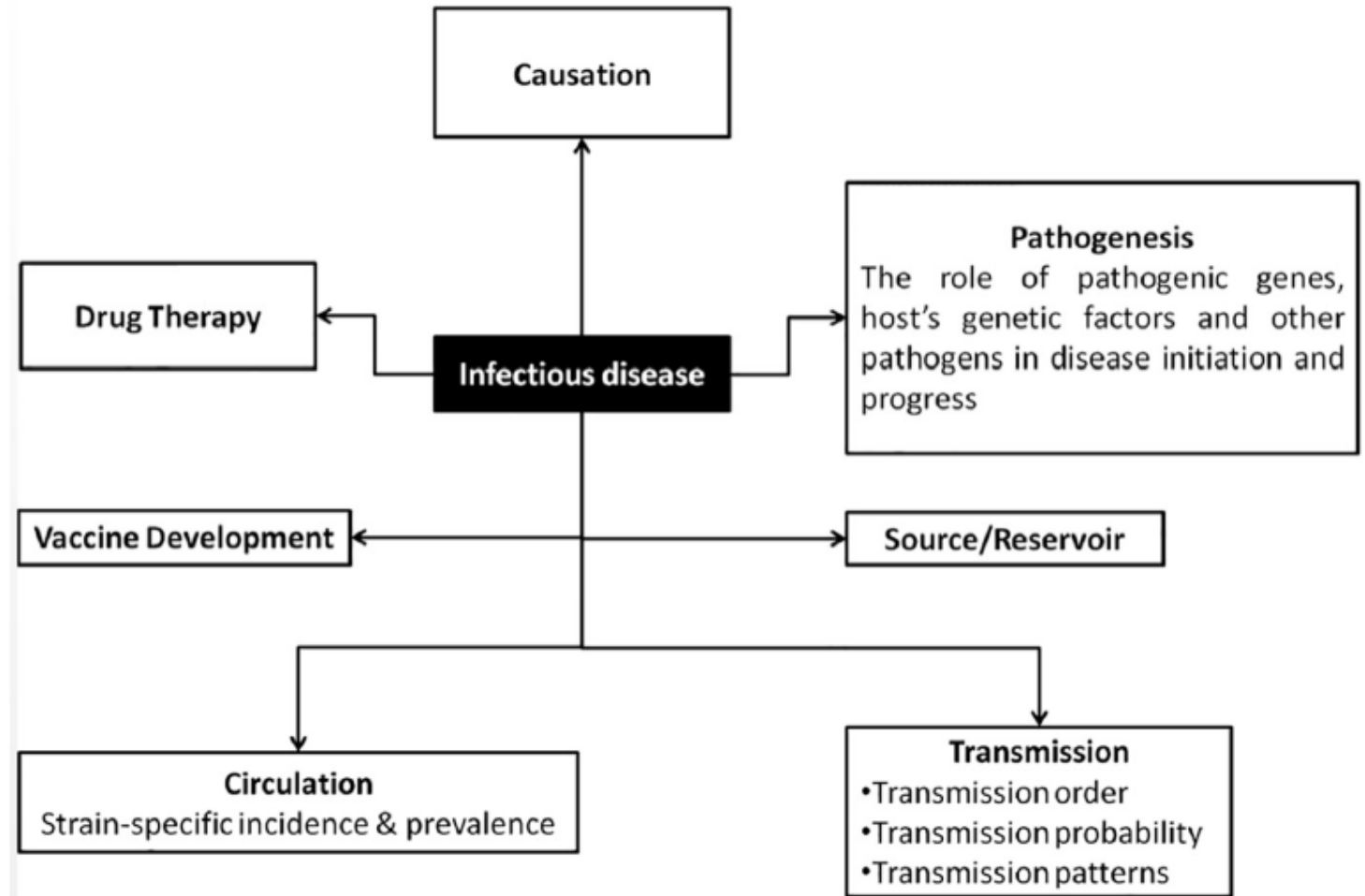
Phylogenetic reconstruction of dengue virus type 2 in Colombia

Jairo A Méndez^{1,3*}, José A Usme-Ciro², Cristina Domingo^{4,5}, Gloria J Rey¹, Juan A Sánchez³, Antonio Tenorio⁴ and Juan C Gallego-Gomez²

Genomic Epidemiology

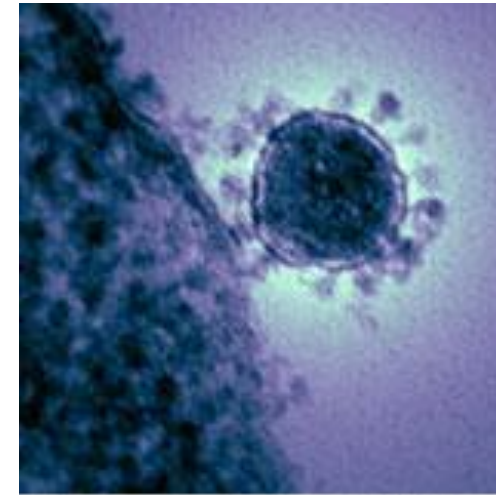
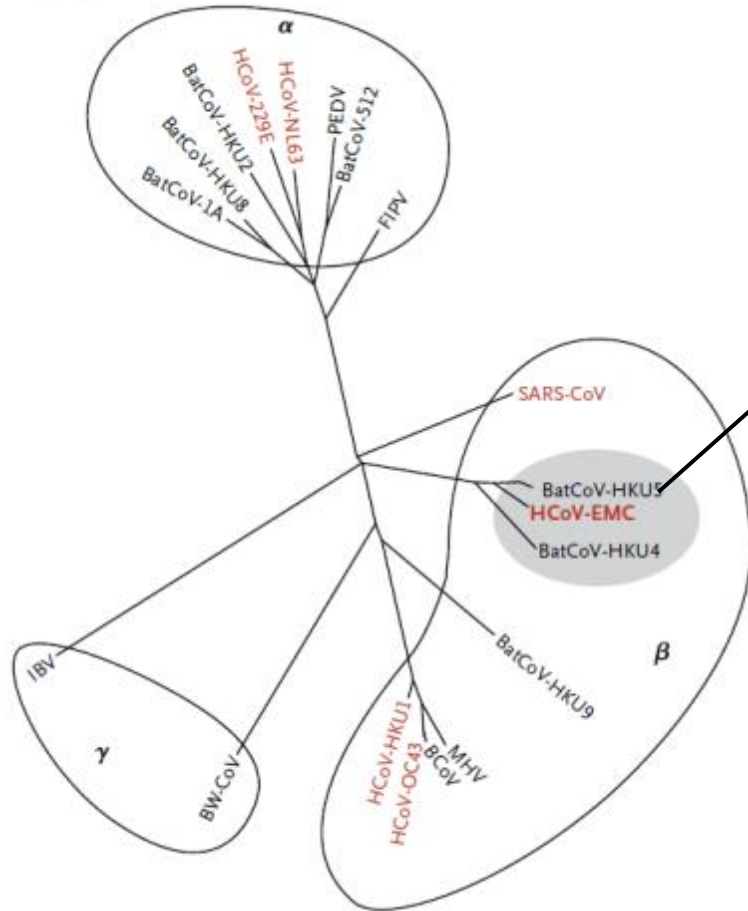
Genomic epidemiology studies have provided information about infectious diseases:

- causality
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- **transmission**
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- therapy



2012: MERS CoV

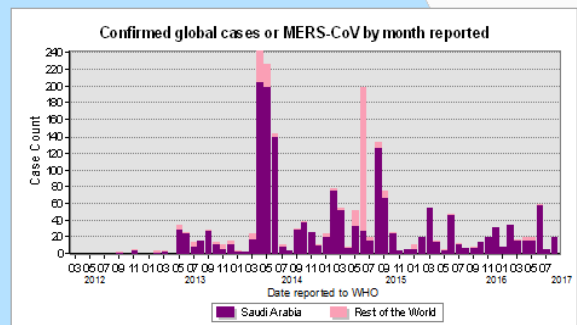
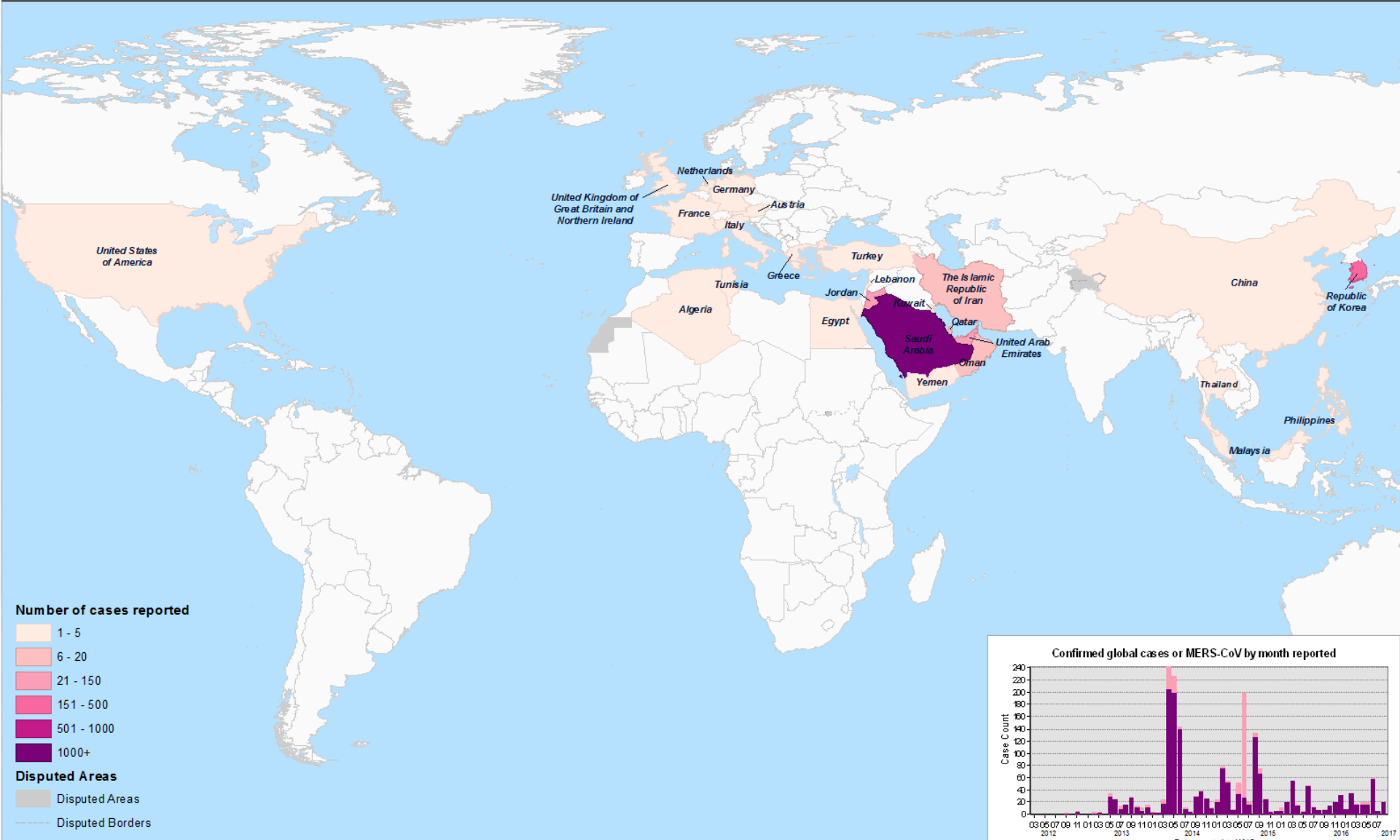
B Phylogenetic Tree



Microscopic view of MERS.
Photo: National Institute of
Allergy & Infectious Diseases

**Nuevo Virus diferente al
SARS Co-V**

CONFIRMED GLOBAL CASES OF MERS-COV 2012 - 2017



Map Scale (A3): 1:1,109,175,783
 1 cm = 11,092 km
 Coordinate System: GCS WGS 1984
 Datum: WGS 1984
 Units: Degree

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

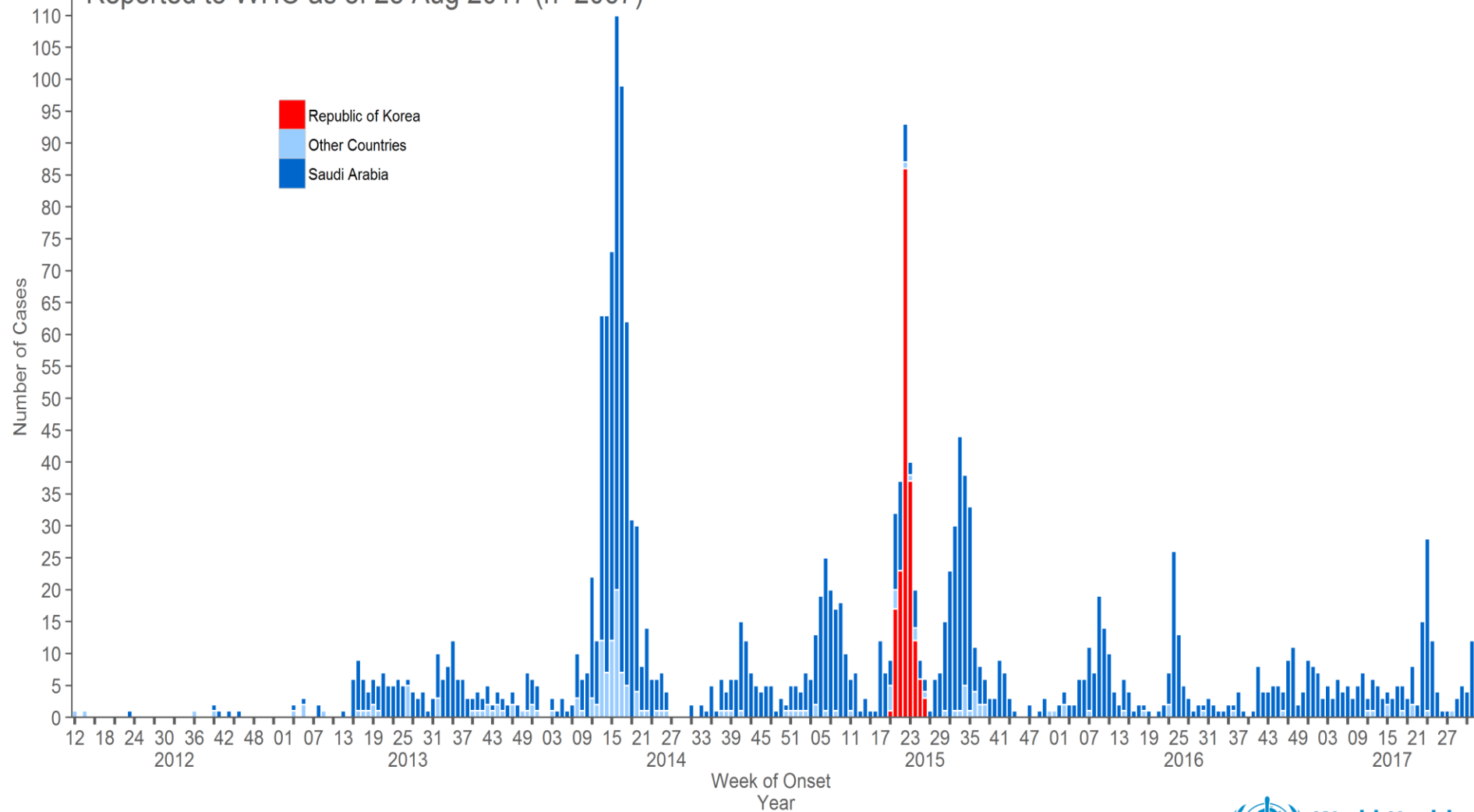
Data Source: World Health Organization
 © WHO 2017. All rights reserved.
 Map date: 25/08/2017



World Health Organization
 Americas

Confirmed global cases of MERS-CoV

Reported to WHO as of 25 Aug 2017 (n=2067)

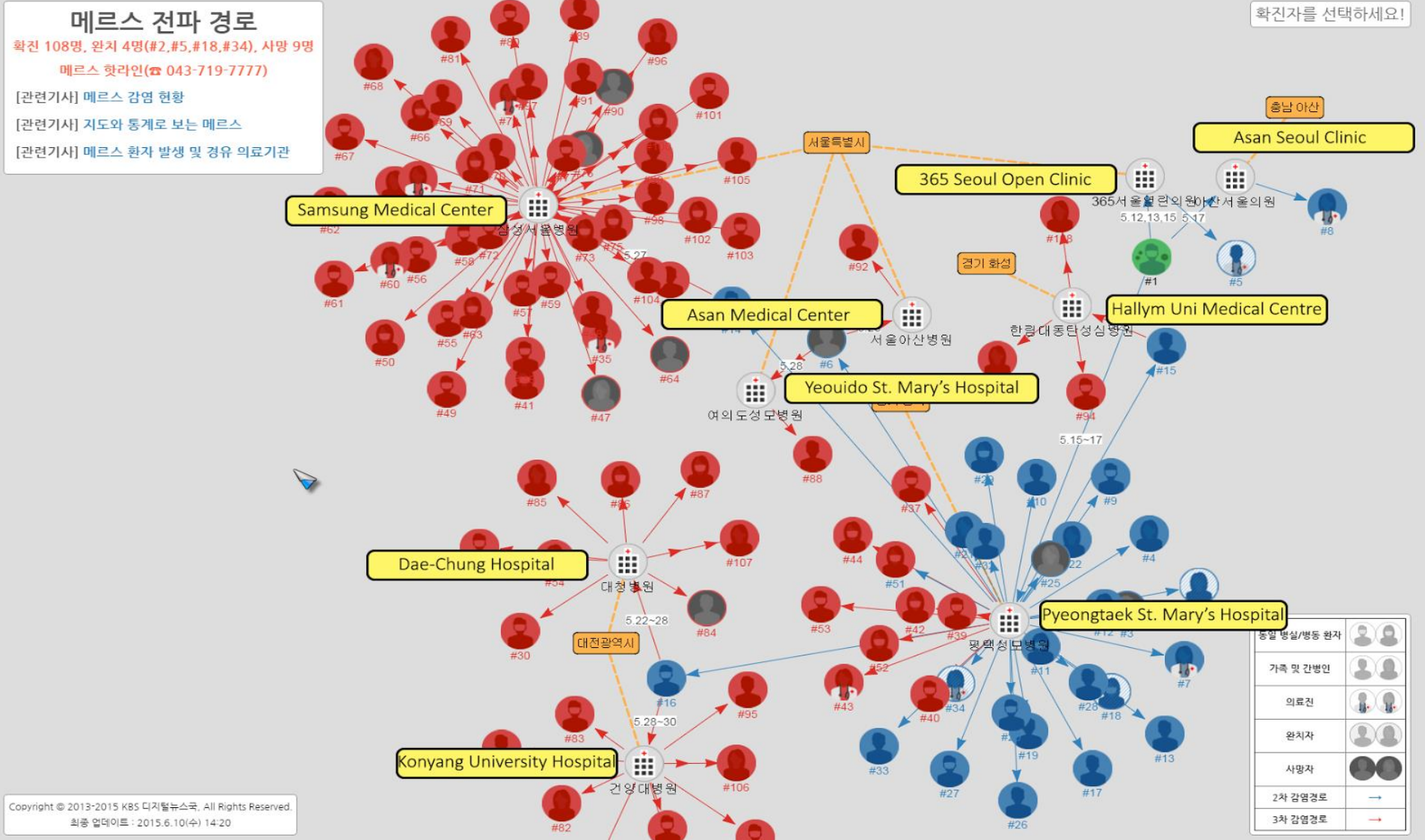


Other countries: Algeria, Austria, Bahrain, China, Egypt, France, Germany, Greece, Iran, Italy, Jordan, Kuwait, Lebanon, Malaysia, Netherlands, Oman, Philippines, Qatar, Thailand, Tunisia, Turkey, United Arab Emirates, United Kingdom, United States of America, Yemen

Please note that the underlying data is subject to change as the investigations around cases are ongoing. Onset date estimated if not available.



Propagación MERS CoV



https://3.bp.blogspot.com/-S2EhY2APzVo/VXguXJhLBUI/AAAAAAAD_A/yR0GgXn2qx4/s1600/Korea-MERS-Hospitals-and-cases_10JUN2015.png



Pan American Health Organization

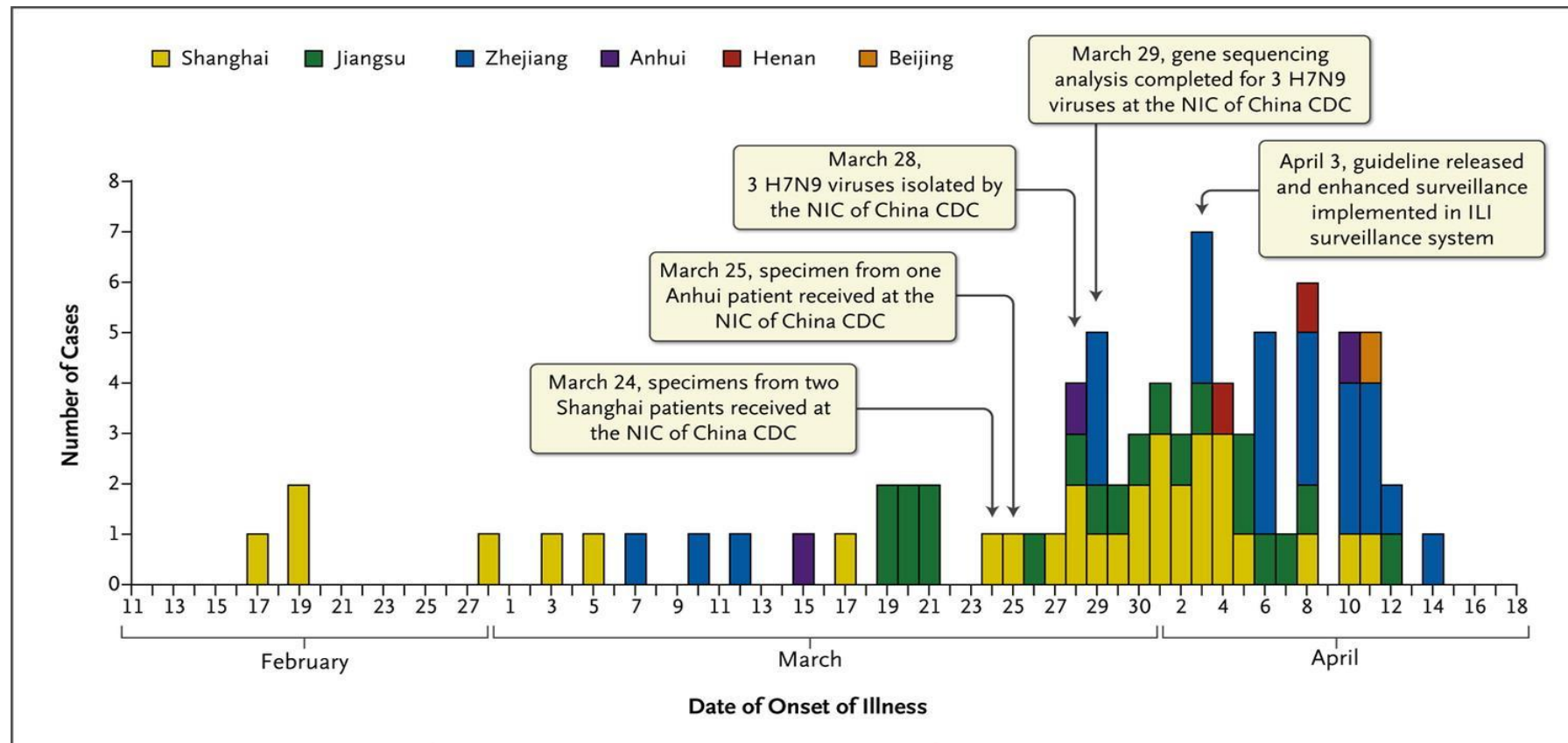


World Health Organization
REGIONAL OFFICE FOR THE Americas

2013: Influenza aviar A(H7N9)

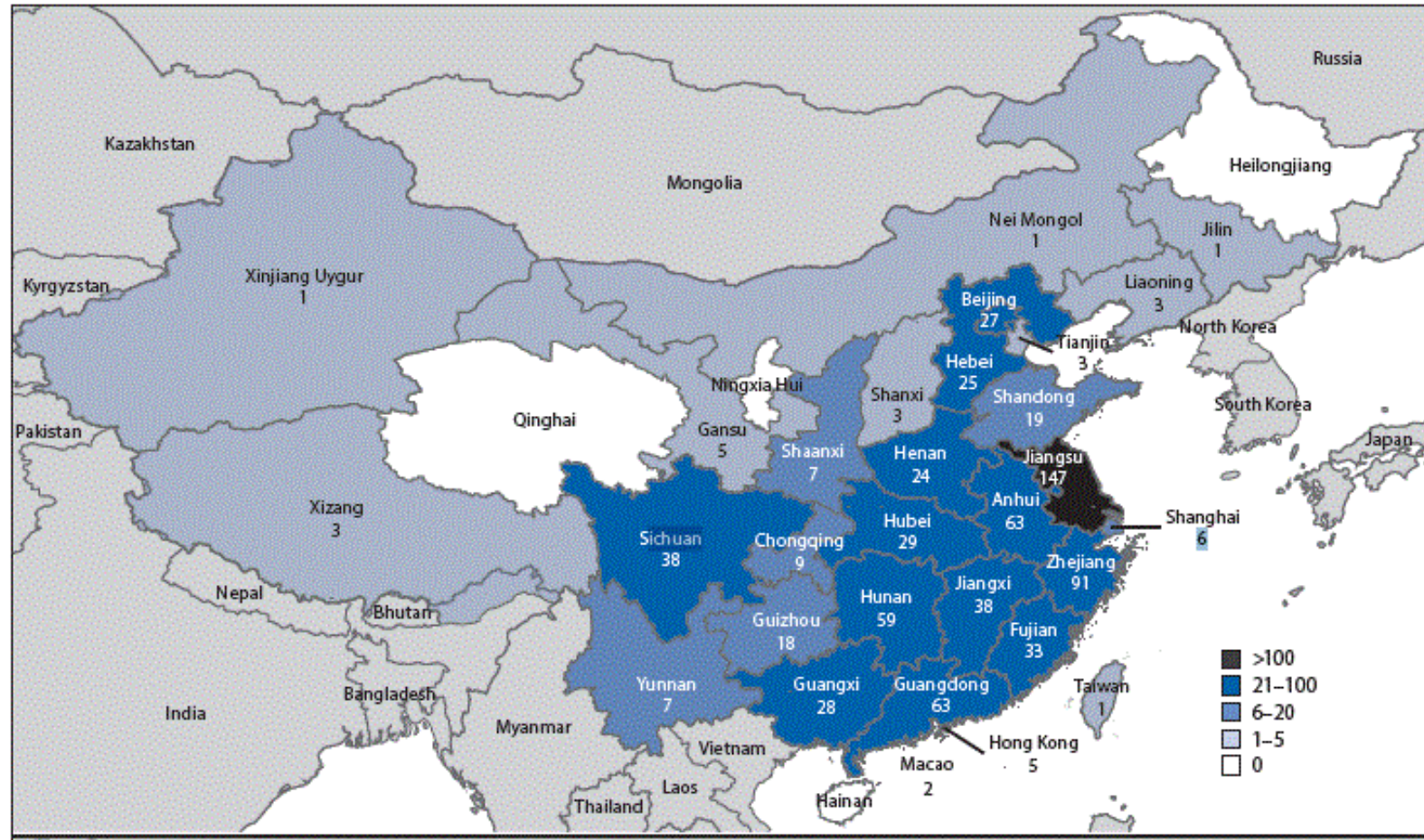
ORIGINAL ARTICLE

Human Infection with a Novel Avian-Origin Influenza A (H7N9) Virus



The NEW ENGLAND JOURNAL of MEDICINE

2013: Influenza aviar A(H7N9)



Distribución geográfica del linaje asiático Infecciones por virus de la influenza aviar A (H7N9) en humanos informadas a la Organización Mundial de la Salud – China (1 de octubre de 2013 al 7 de agosto de 2017)



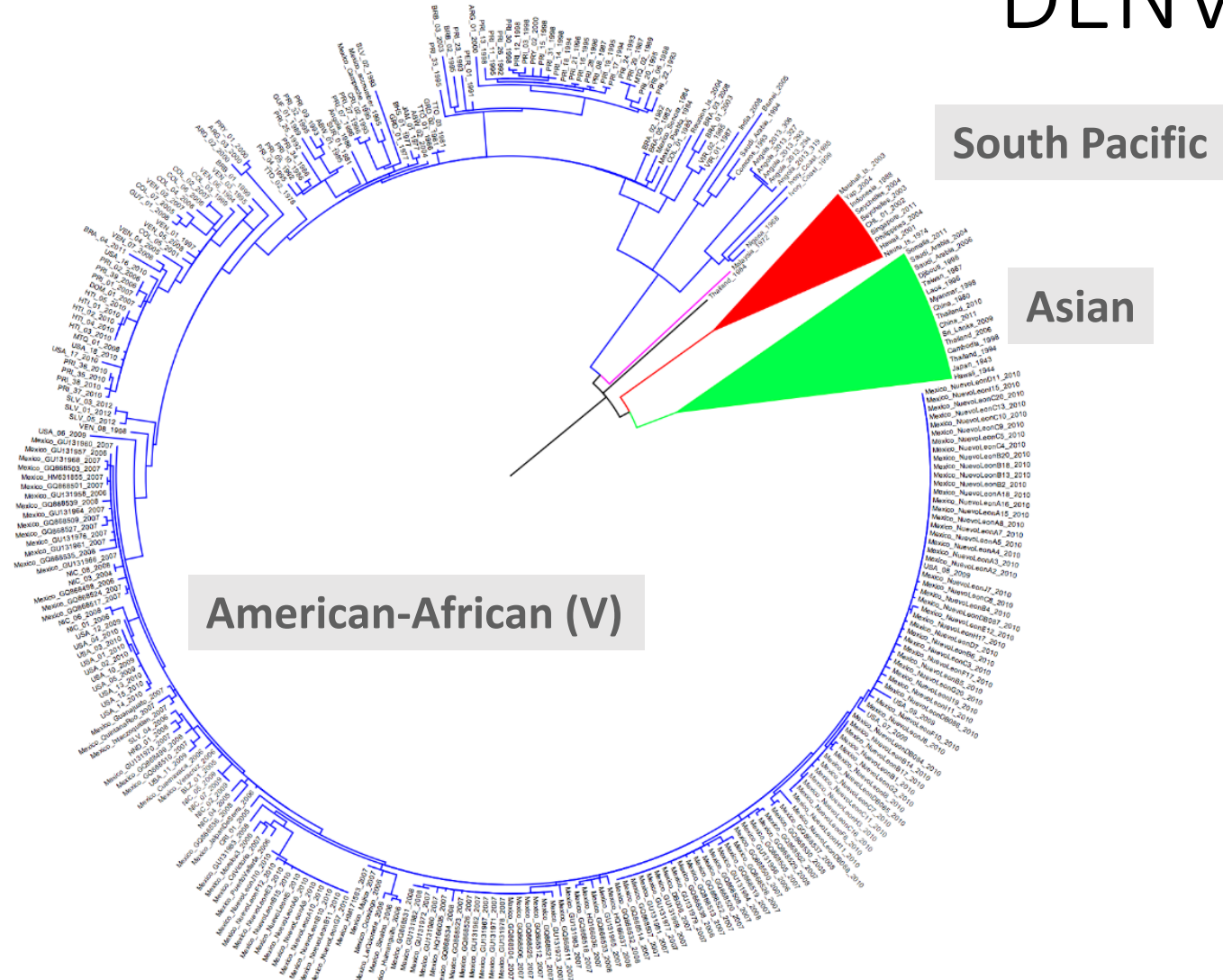
Pan American
Health
Organization



World Health
Organization

REGIONAL OFFICE FOR THE Americas

DENV-1 Phylogeny



South Pacific

Asian

American-African (V)

320 E gene sequences

Santiago 2014, unpublished



DENV-1

American-African
genotype
(American sequences)

Central American-North American lineage
(2005-present)

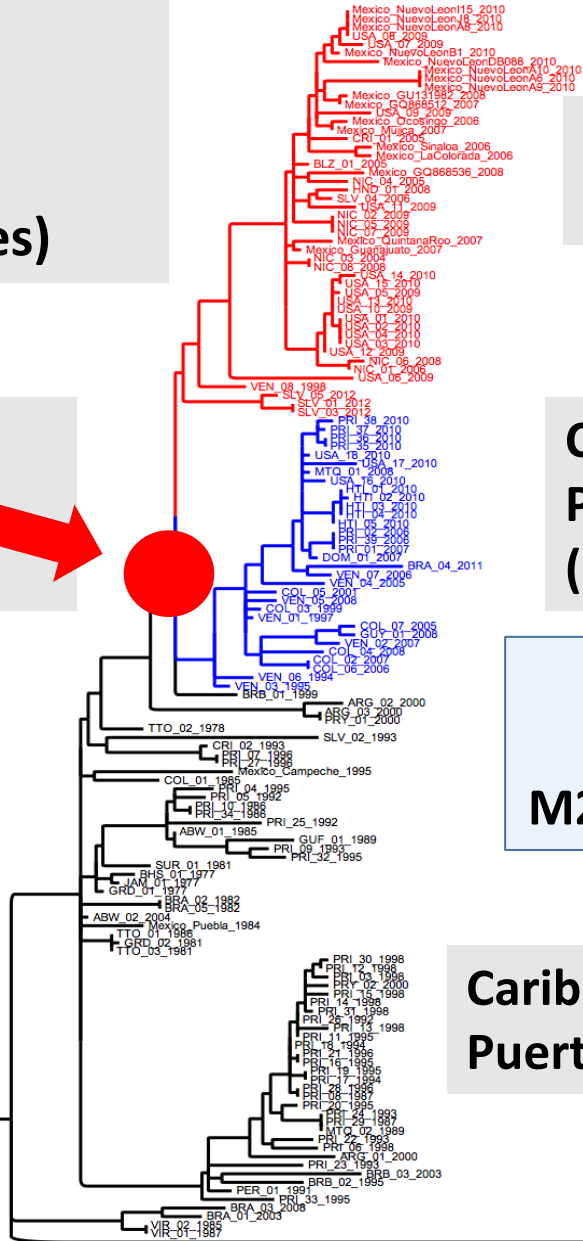
Caribbean and South American lineage
Puerto Rico 2010 epidemic
(~ 1994 – present)

Amino acid changes
V55I conservative EDII
M297T non-conservative EDIII

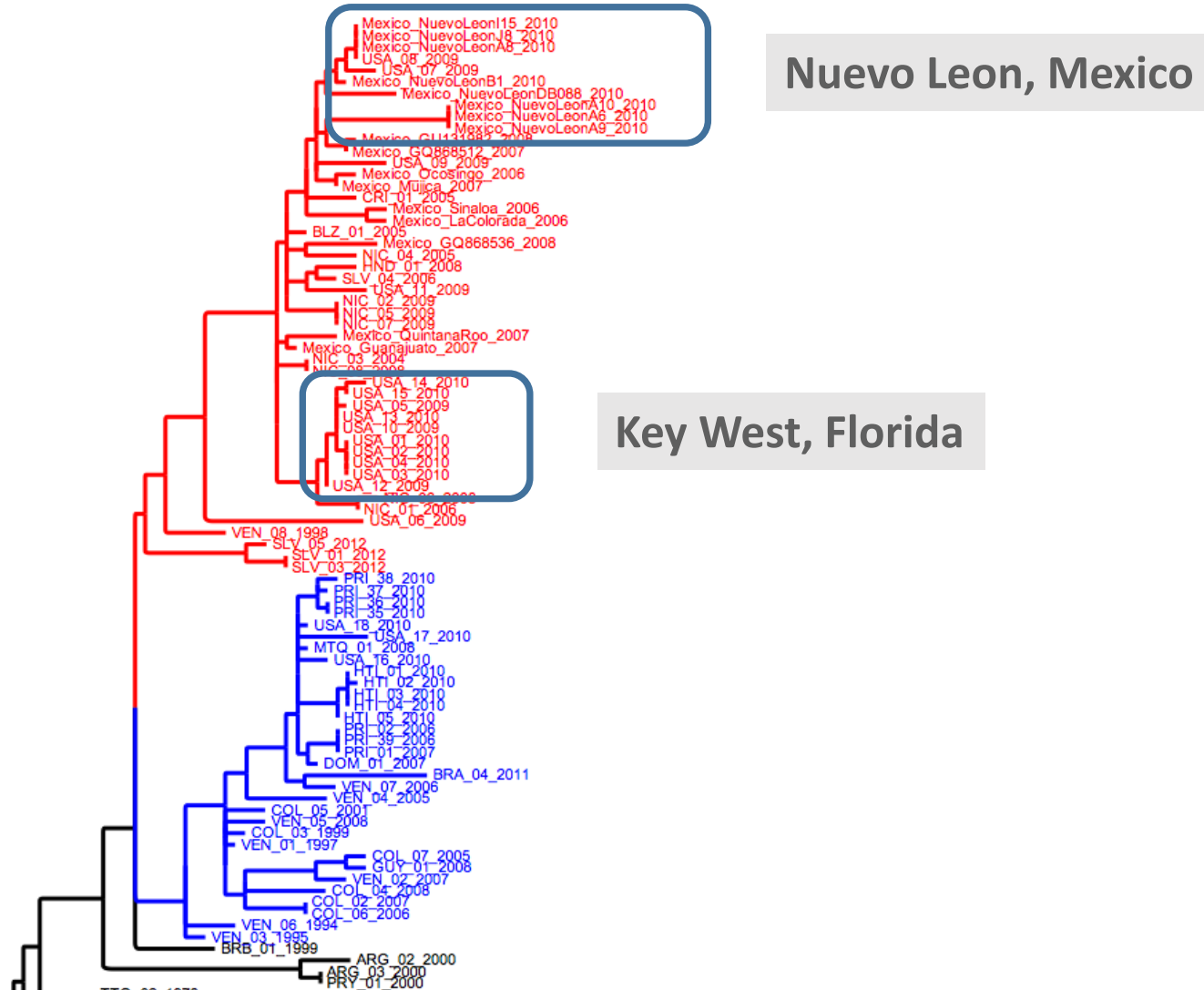
Caribbean and South America
Puerto Rico epidemics (1994-1995 and 1998)

Early American isolates (1980s)

Point of lineage
divergence
1998?



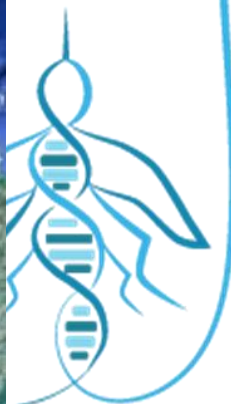
DENV-1 Central American lineage



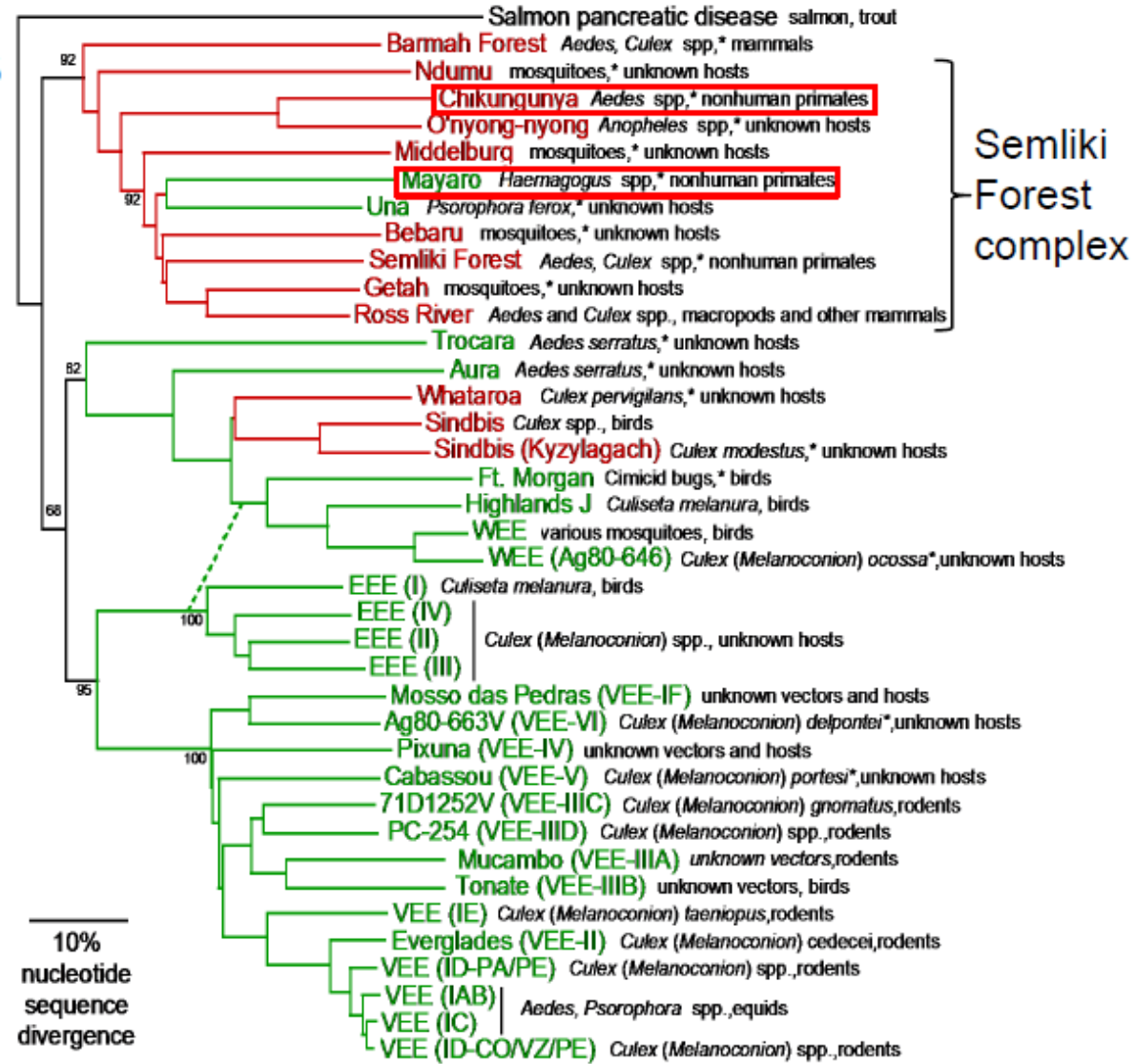


Santiago, 2014 unpublished

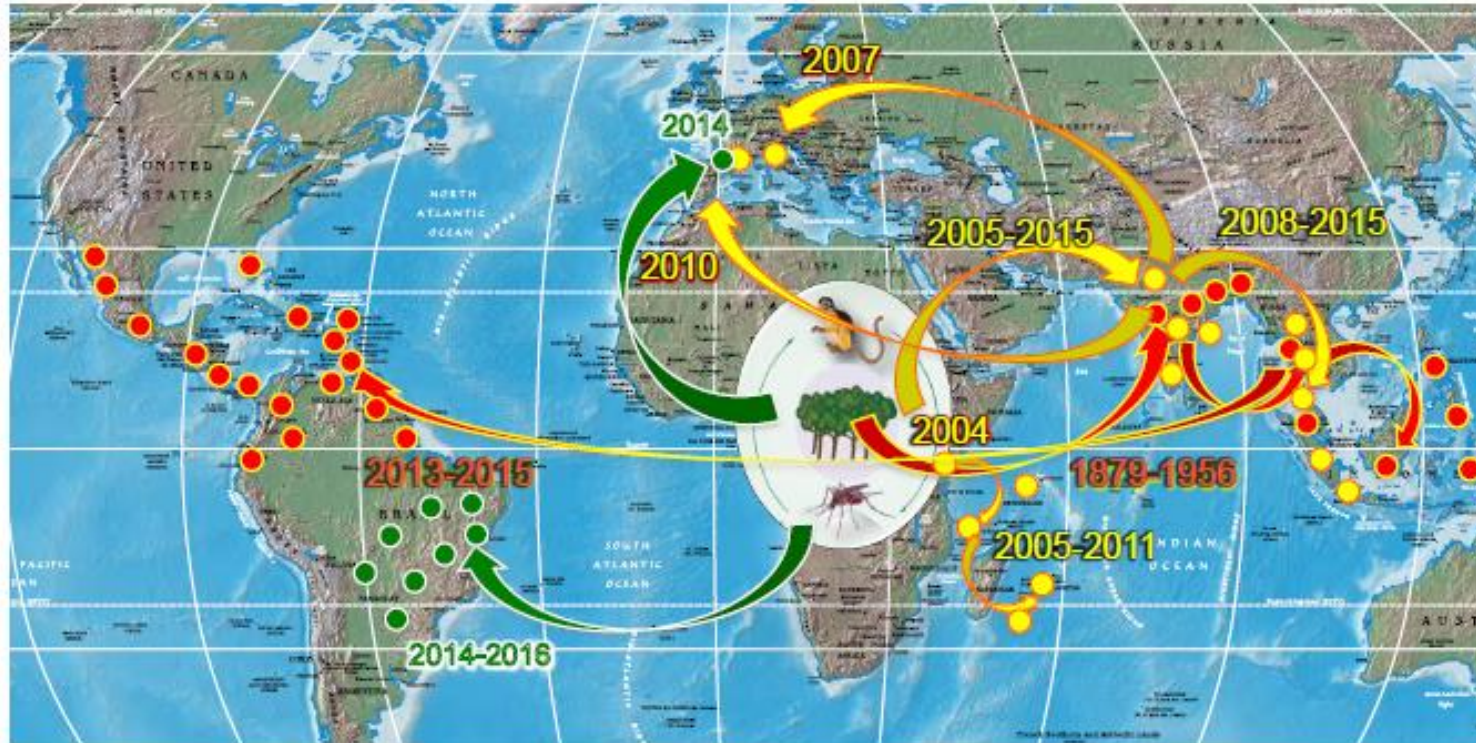
G.A. Santiago 2013



Alphavirus Evolution



History of Chikungunya Virus Emergence



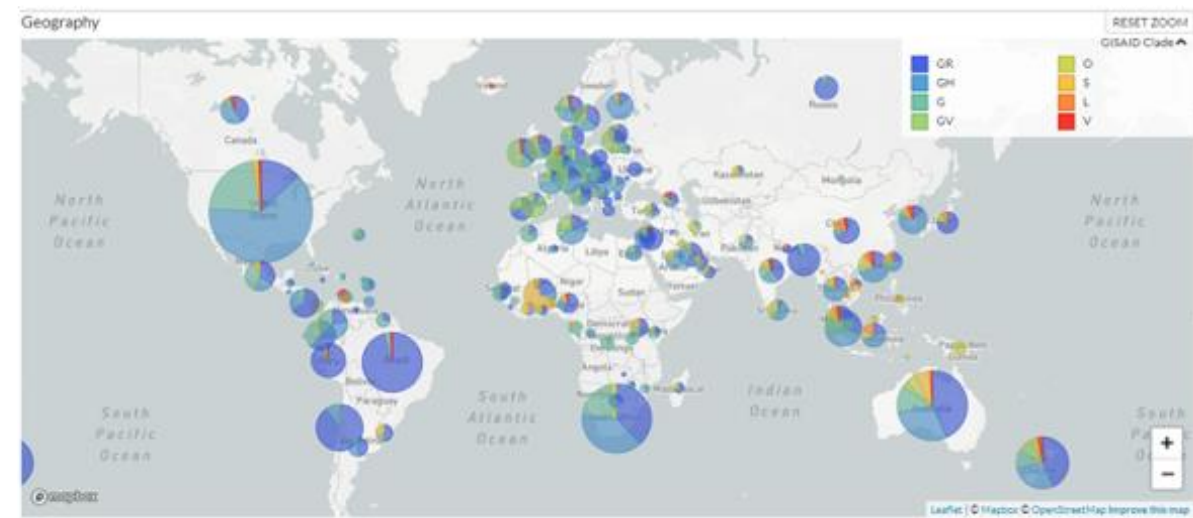
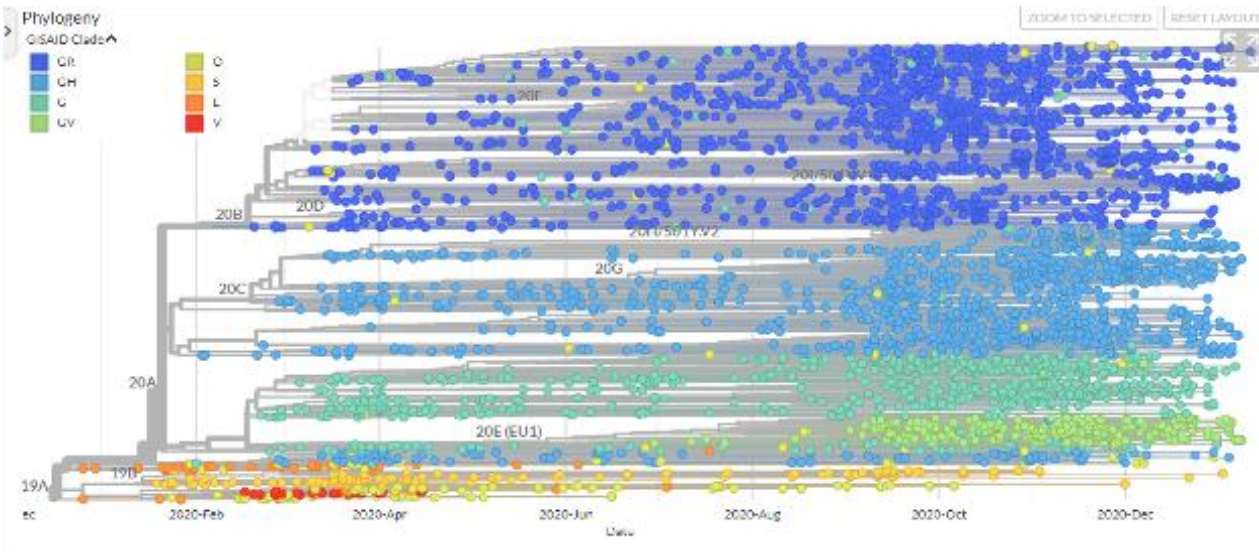
ECSCA lineage

Asian lineage

Indian Ocean Lineage



SARS-CoV-2 Genetic Characterization



<https://www.gisaid.org/phyldynamics/global/nextstrain/>

> 3,645,340 sequences submitted to GISAID

Country/Territory	Alpha	Beta	Gamma	Delta
Anguilla	Yes	No	No	Yes
Antigua and Barbuda	Yes	Yes	Yes	Yes
Argentina	Yes	Yes	Yes	Yes
Aruba	Yes	Yes	Yes	Yes
Bahamas	Yes	No	Yes	Yes
Barbados	Yes	No	Yes	Yes
Belize	Yes	No	Yes	Yes
Bermuda	Yes	Yes	No	Yes
Bolivia	Yes	No	Yes	No
Bonaire	Yes	No	Yes	Yes
British Virgin Islands	Yes	No	Yes	Yes
Brazil	Yes	Yes	Yes	Yes
Canada	Yes	Yes	Yes	Yes
Cayman Islands	Yes	Yes	Yes	Yes
Chile	Yes	Yes	Yes	Yes
Colombia	Yes	No	Yes	Yes
Costa Rica	Yes	Yes	Yes	Yes
Cuba	Yes	Yes	No	Yes
Curacao	Yes	Yes	Yes	Yes
Dominica	Yes	No	No	Yes
Dominican Republic	Yes	No	Yes	No
Ecuador	Yes	No	Yes	Yes
El Salvador	Yes	No	Yes	Yes
Falkland Islands	Yes	Yes	No	No
French Guiana	Yes	Yes	Yes	Yes
Grenada	Yes	No	No	Yes
Guadeloupe	Yes	Yes	Yes	Yes
Guatemala	Yes	yes	Yes	Yes
Guyana	No	No	Yes	yes
Haiti	Yes	No	Yes	Yes
Honduras	Yes	No	Yes	Yes
Jamaica	Yes	No	No	Yes
Martinique	Yes	Yes	Yes	Yes
Mexico	Yes	Yes	Yes	Yes
Montserrat	Yes	No	Yes	Yes
Panama	Yes	Yes	Yes	Yes
Paraguay	yes	No	Yes	Yes
Peru	Yes	No	Yes	Yes
Puerto Rico	Yes	Yes	Yes	Yes
Saba	No	No	No	Yes
Saint Barthélemy	Yes	No	No	No
Saint Kitts and Nevis	No	No	No	Yes
Saint Lucia	Yes	No	No	Yes
Saint Martin	Yes	Yes	No	No
St Vincent and the Grenadines	No	No	Yes	Yes
Saint Pierre et Miquelon	No	No	No	Yes
Sint Maarten	Yes	Yes	yes	Yes
Suriname	Yes	Yes	Yes	Yes
Trinidad and Tobago	Yes	No	Yes	Yes
Turks and Caicos	Yes	No	Yes	Yes
United States of America	Yes	Yes	Yes	Yes
Uruguay	Yes	Yes	Yes	Yes
Venezuela	Yes	No	Yes	Yes
Virgin Islands (US)	Yes	Yes	No	Yes

54 / 56 Countries and Territories have detected at least 1 VOC (September 20)

Alpha = 49

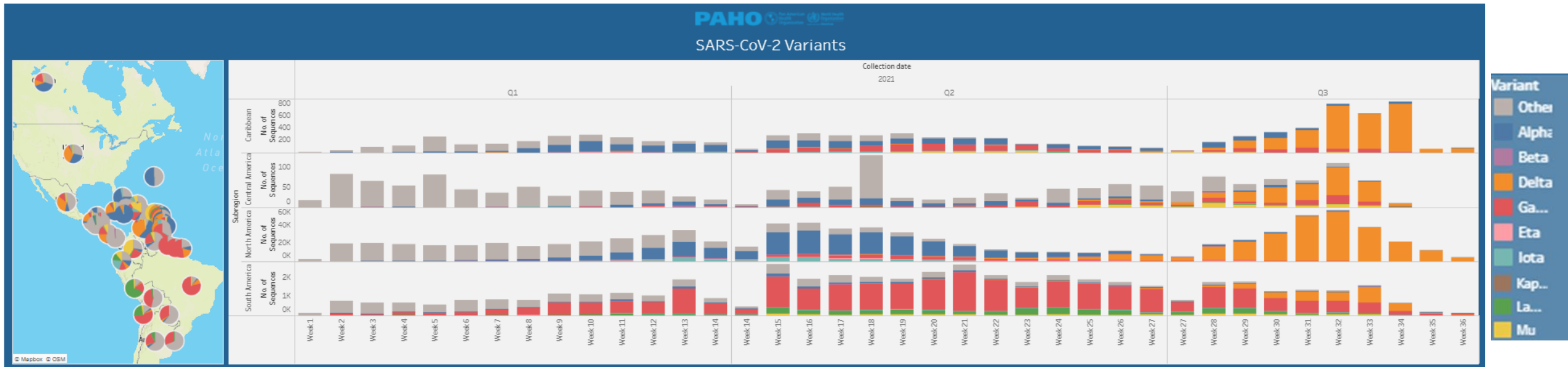
Beta = 25

Gamma = 40

Delta = 52

Regular update on variants at PAHO Region

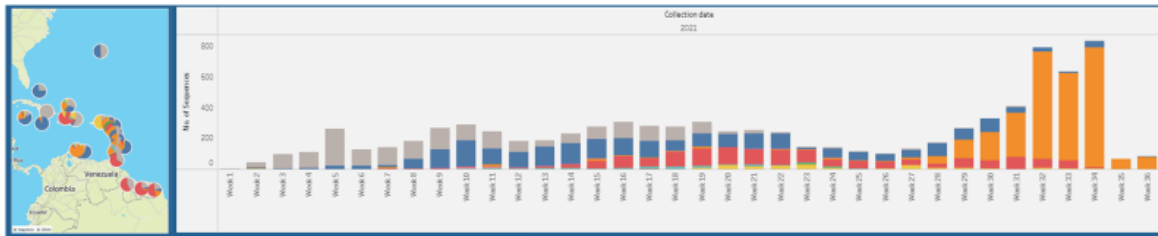
PAHO Region



Dashboard developed by PAHO-IMST

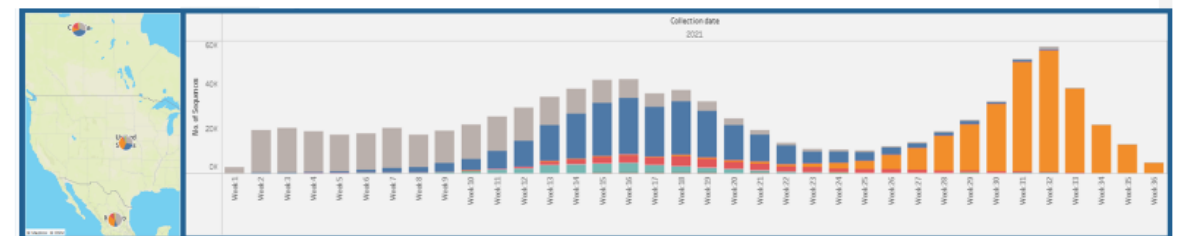
Regular update on variants at PAHO Region

Caribbean Subregion



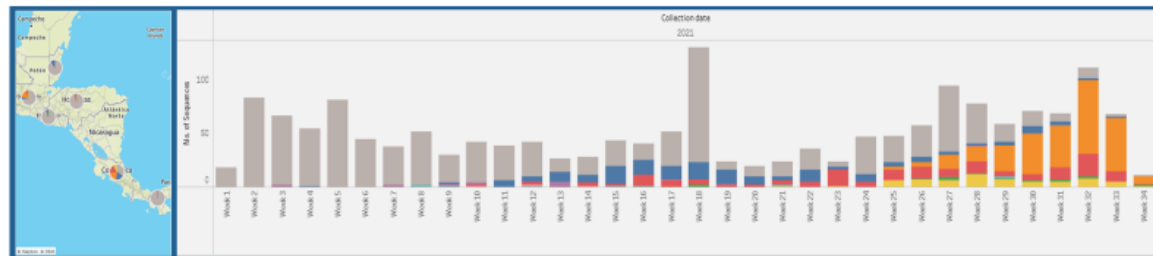
Dashboard developed by PAHO-IMST

North America Subregion



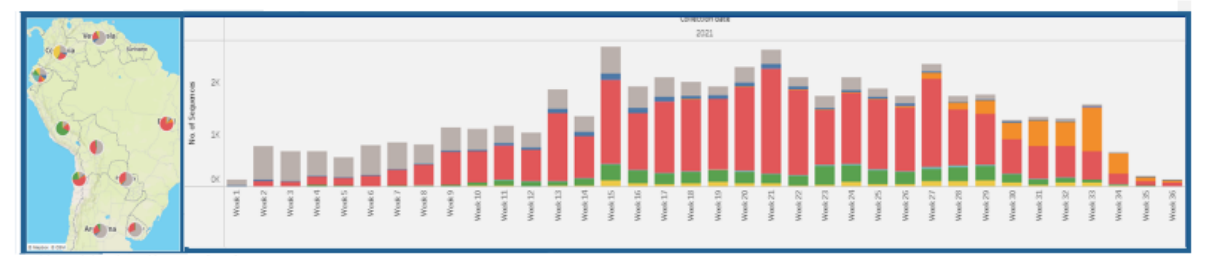
Dashboard developed by Patrick Biche, PAHO-IMST

Central America Subregion



Dashboard developed by Patrick Biche, PAHO-IMST

South America Subregion



Dashboard developed by Patrick Biche, PAHO-IMST

SARS-CoV-2 Genomic Surveillance Network

Challenges...

- Strengthen genomic surveillance in the Region through the PAHO Genomic Surveillance Network is a Priority
- Important gaps in sequencing capacity:
 - Too expensive
 - Sustainability (*do we need sequencing in each country?*)
 - Requires specific expertise
 - Shipping of samples: expensive / customs and exportation process is difficult
- Screening protocols may complement the surveillance

SARS-CoV-2 Genomic Surveillance Network

Challenges...

- Standardized strategies remain a challenge: [Sequencing vs. Genomic surveillance](#)
 - The concept of “molecular epidemiology” should be integrated in surveillance systems
 - Clear surveillance objectives: contact tracing, circulation patterns, clusters in specific population, changes in pathogenesis...
- Surveillance is not only to detect VOI/VOC (political pressures...)

Gracias!!

**PAHO-IMST
Emerging Viruses
Laboratory Response Team**

