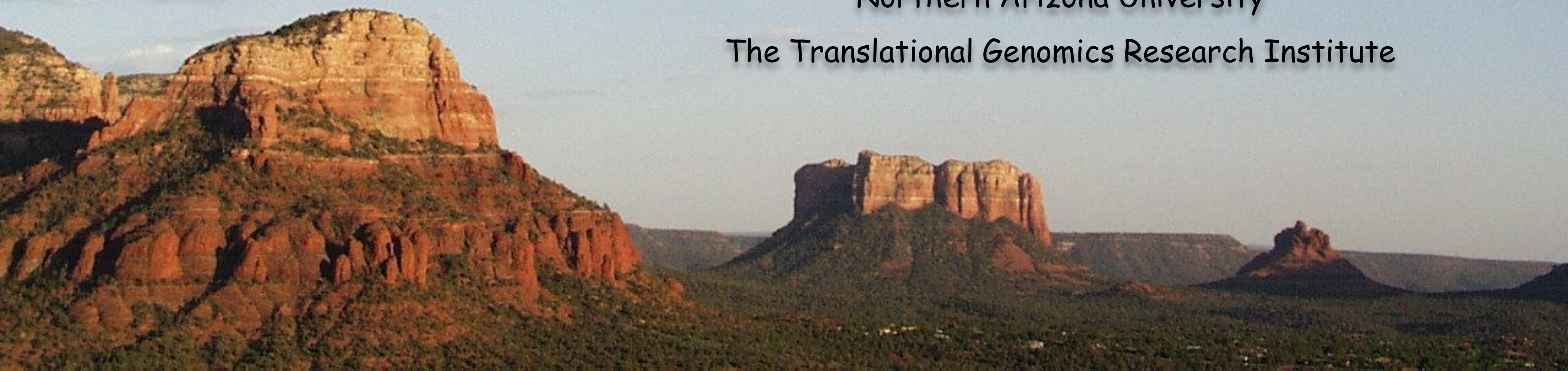
NORTHERN ARIZONA UNIVERSITY

TGEN

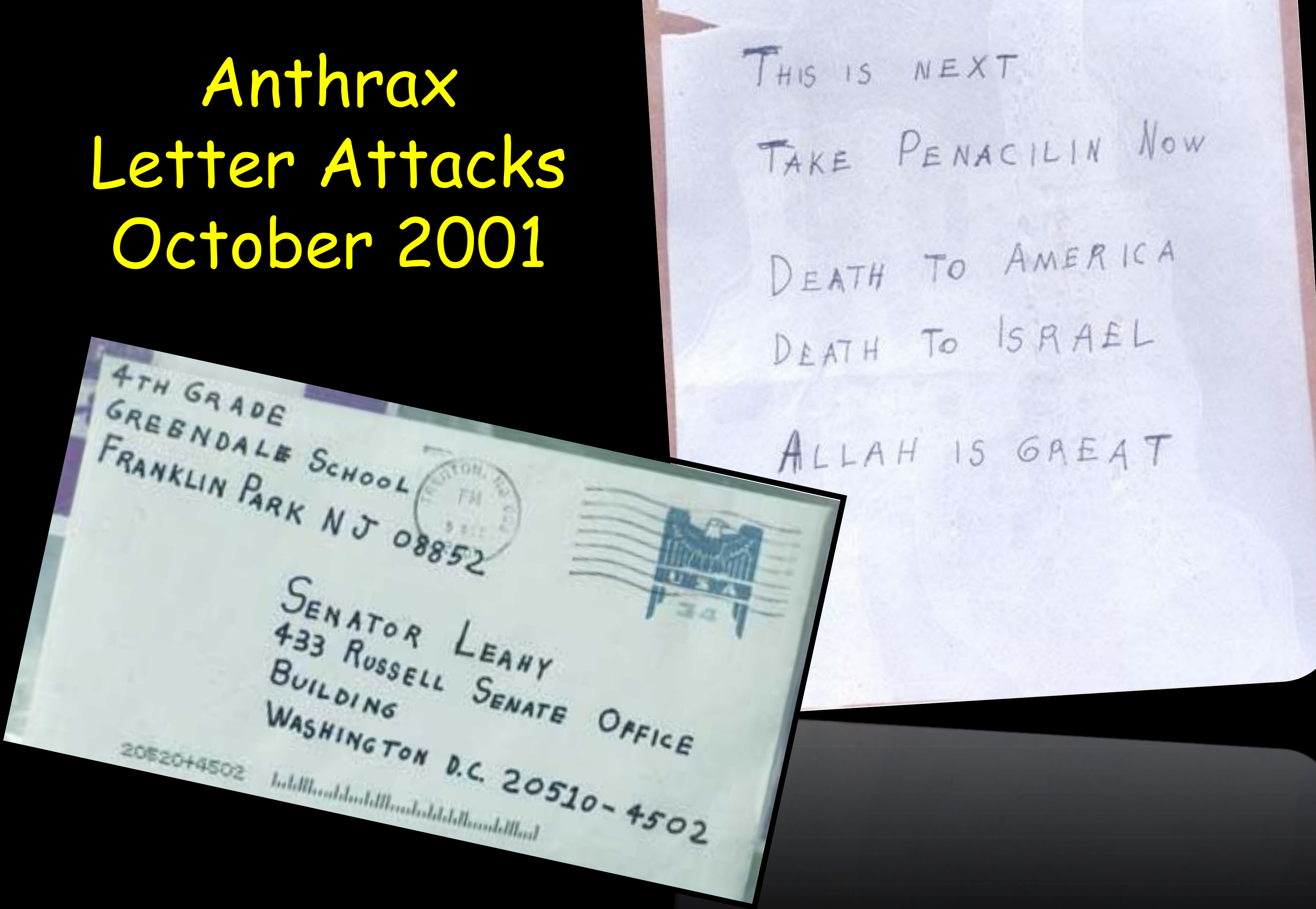
Genomics and a New Age in Global Disease Tracking

Paul Keim, PhD

Northern Arizona University
The Translational Genomics Research Institute



Anthrax Letter Attacks October 2001



4TH GRADE
GREENDALE SCHOOL
FRANKLIN PARK NJ 08852

SENATOR LEAHY
433 RUSSELL SENATE OFFICE
BUILDING
WASHINGTON D.C. 20510-4502

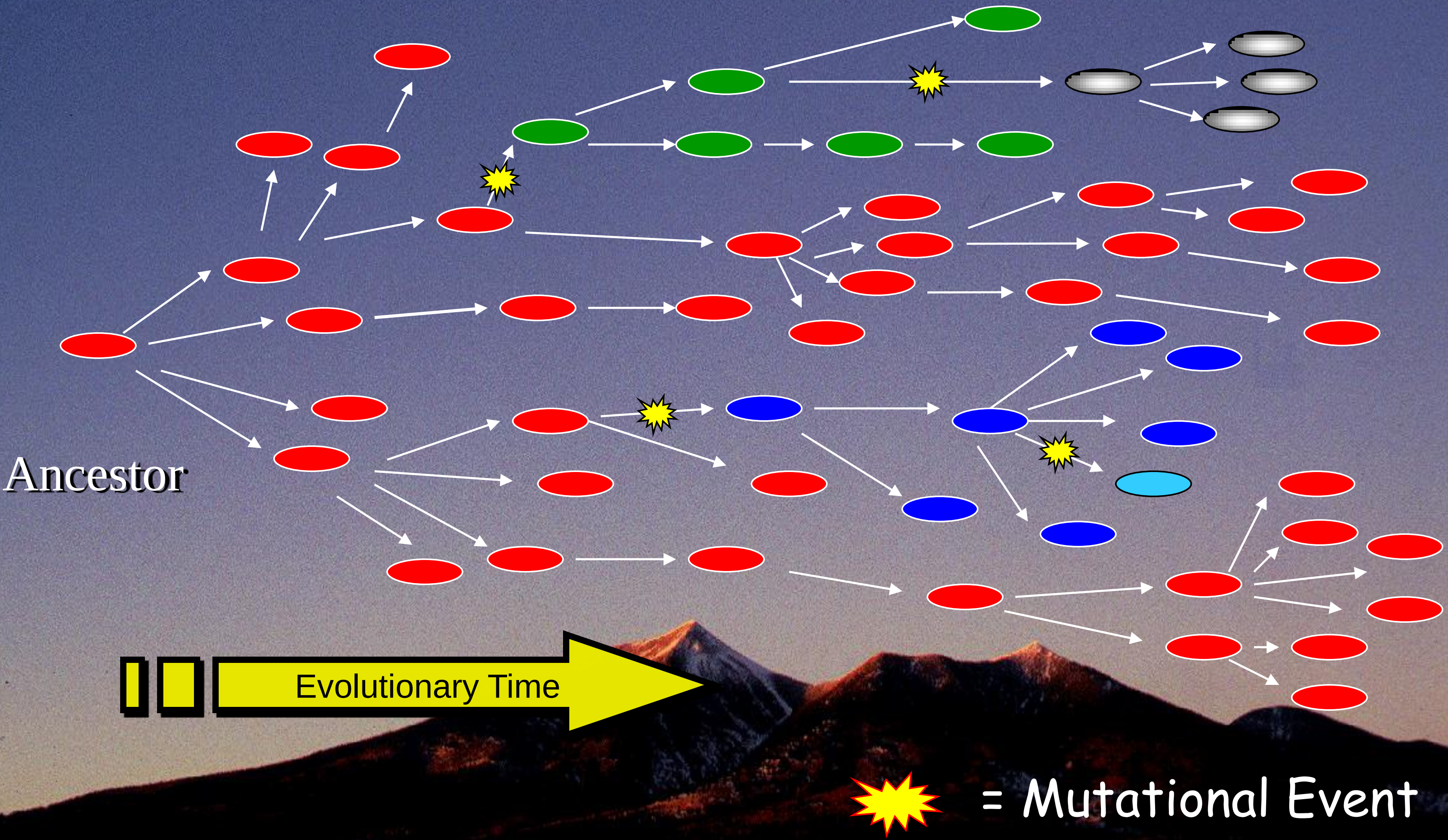
20520+4502

THIS IS NEXT
TAKE PENACILIN NOW

DEATH TO AMERICA
DEATH TO ISRAEL

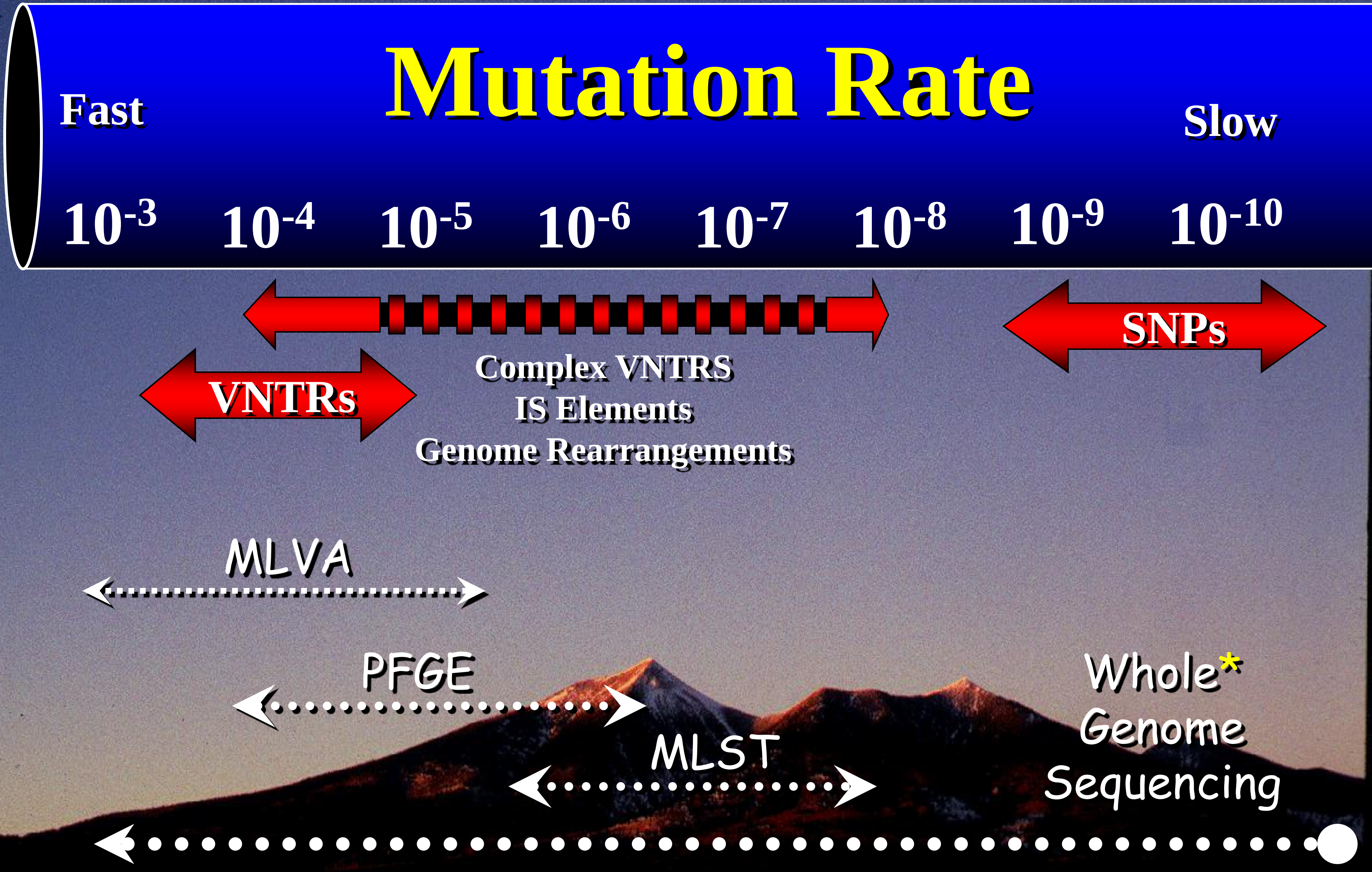
ALLAH IS GREAT

Diversity Generation in an Idealized Clonally Propagating Pathogen



A Genome is a Big Place!

Evolutionary Scale & Subtyping



Mutation Rate

Fast

Slow

10^{-3} 10^{-4} 10^{-5} 10^{-6} 10^{-7} 10^{-8} 10^{-9} 10^{-10}

VNTRs

Complex VNTRS
IS Elements
Genome Rearrangements

SNPs

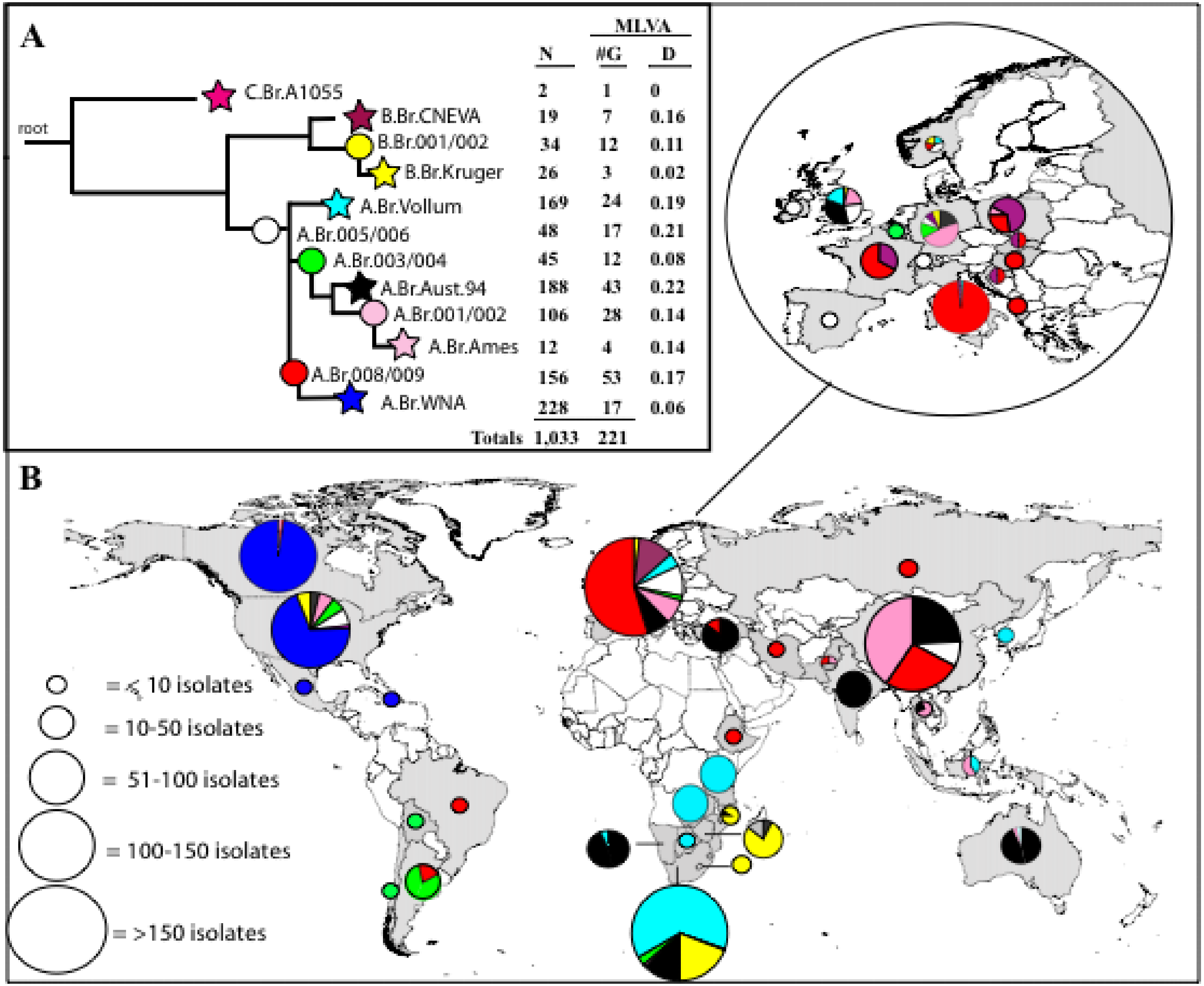
MLVA

PFGE

MLST

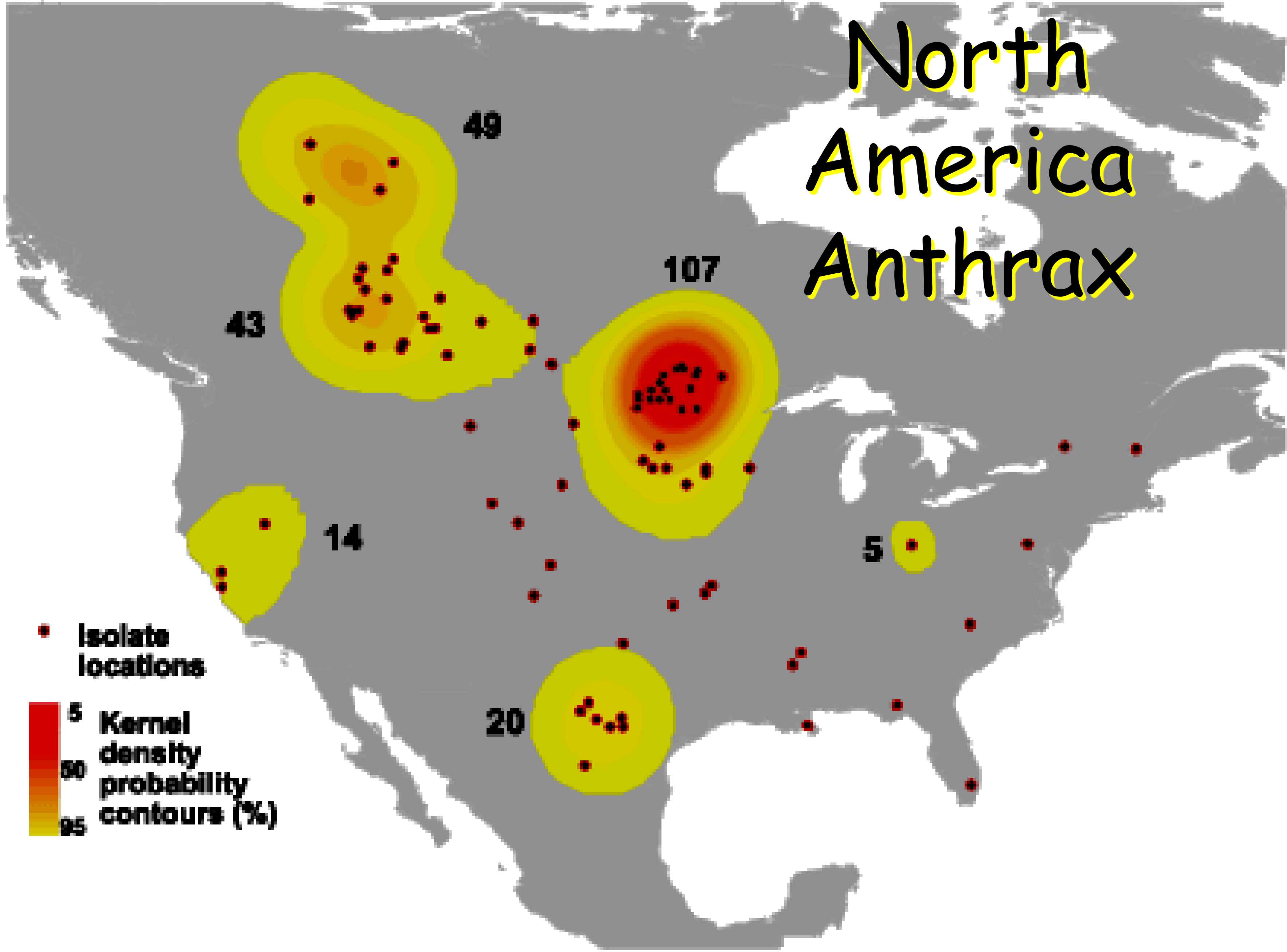
Whole*
Genome
Sequencing

Anthrax Evolution and Ecology



		MLVA	
	N	#G	D
C.Br.A1055	2	1	0
B.Br.CNEVA	19	7	0.16
B.Br.001/002	34	12	0.11
B.Br.Kruger	26	3	0.02
A.Br.Vollum	169	24	0.19
A.Br.005/006	48	17	0.21
A.Br.003/004	45	12	0.08
A.Br.Aust.94	188	43	0.22
A.Br.001/002	106	28	0.14
A.Br.Ames	12	4	0.14
A.Br.008/009	156	53	0.17
A.Br.WNA	228	17	0.06
Totals	1,033	221	

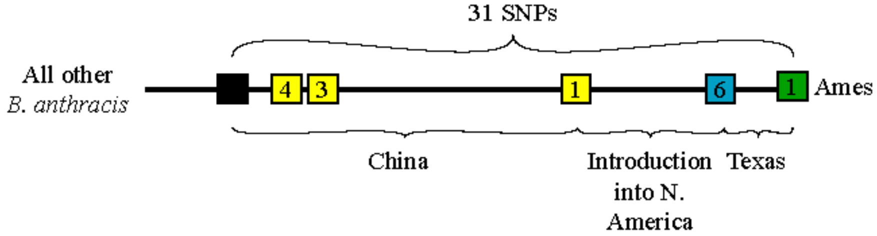
North America Anthrax



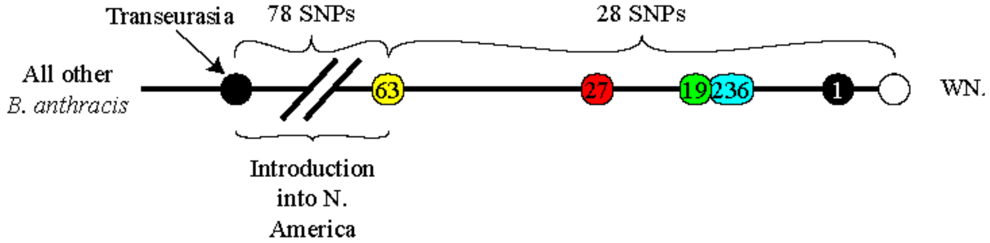
Anthrax in North America

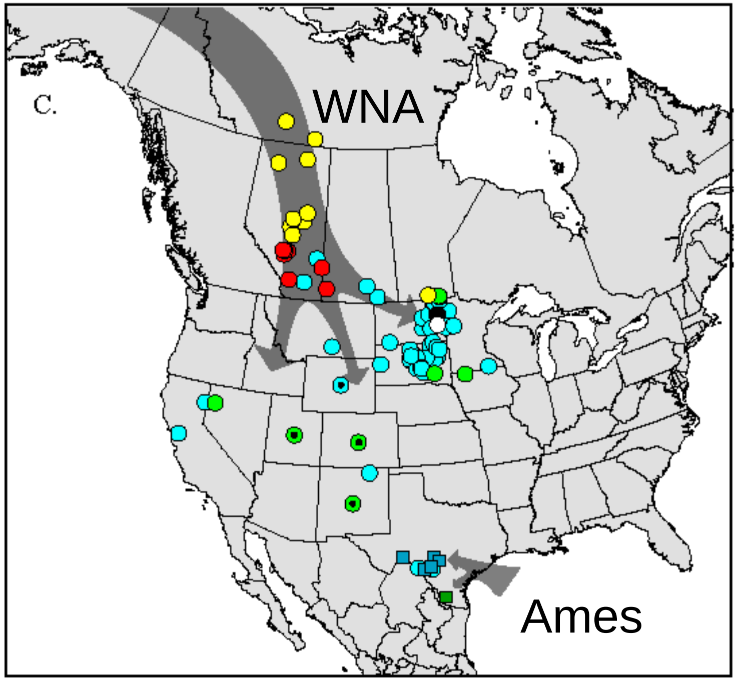
Two Important Migrations

Ames



WNA



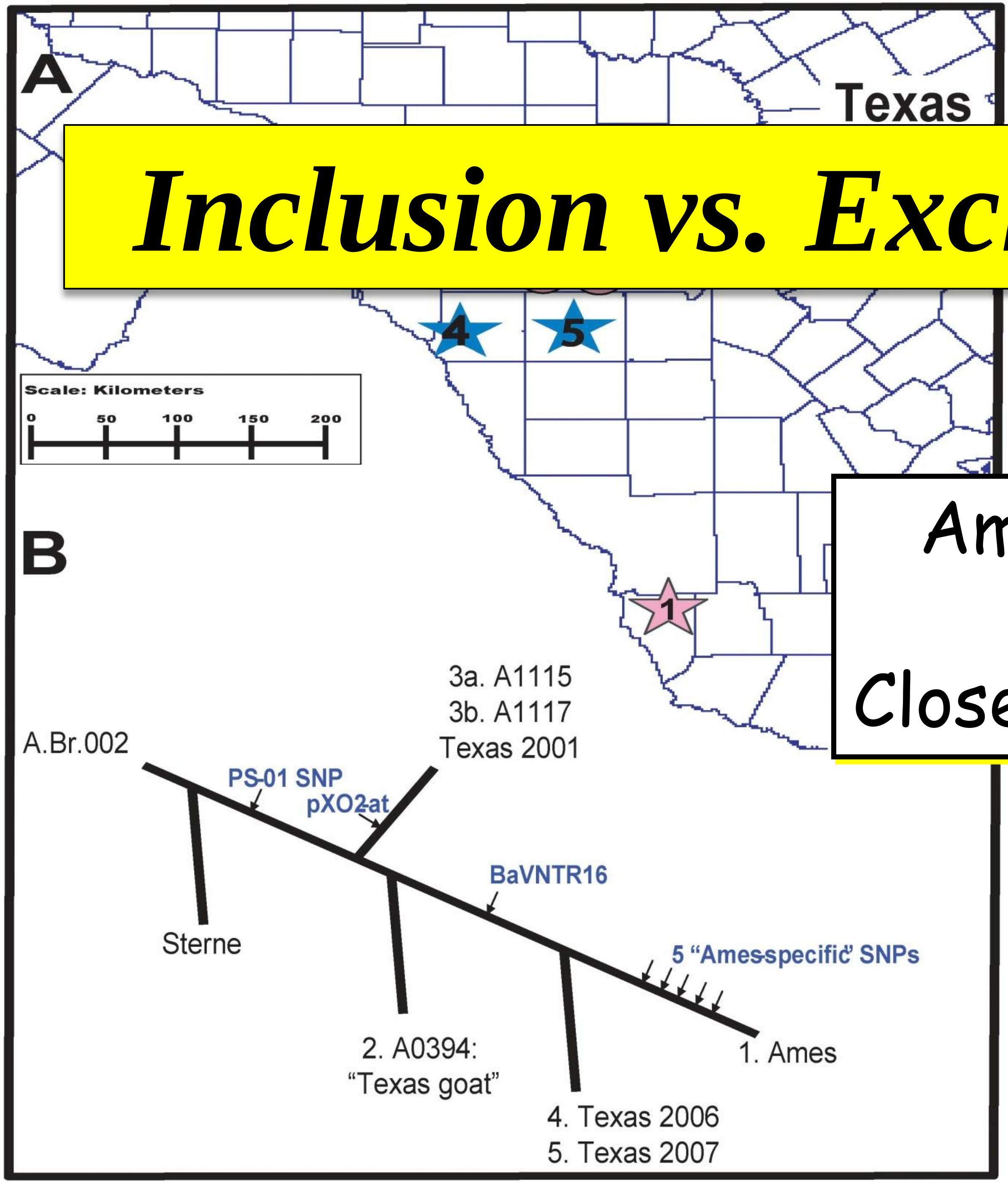


Pearson et al. 2004. PNAS

Kenefic and Pearson et al. 2009. PLoS One

Pearson et al. 2009. IGE

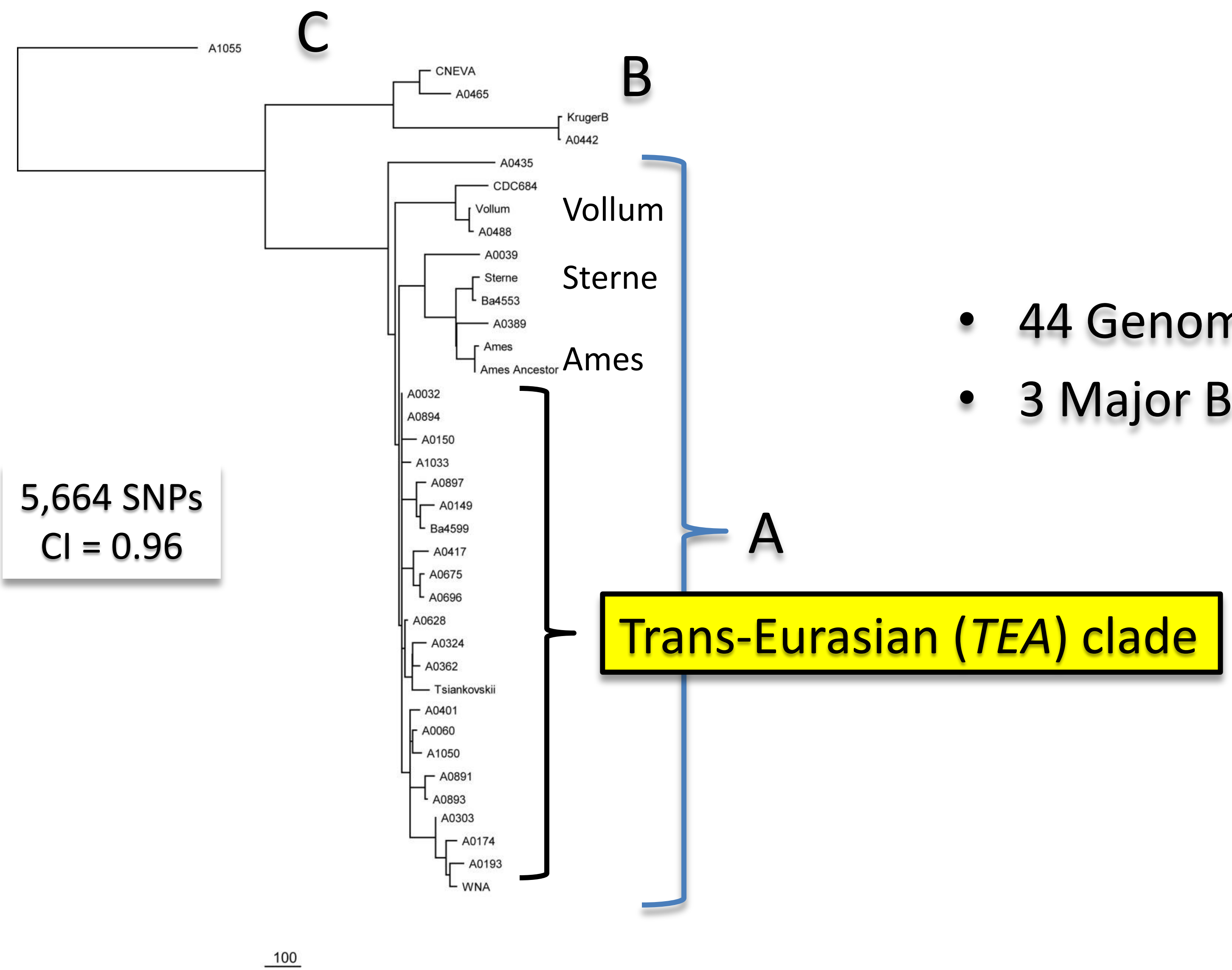
Inclusion vs. Exclusion



Ames strains
And Its
Closest Relatives

Kenefic et. al. 2008
EID **14:**1494-6

Bacillus anthracis Whole Genome Phylogeny



5,664 SNPs
CI = 0.96

- 44 Genomes
- 3 Major Branches

Anthrax and Heroin Users in Scotland

ANTHRAX

IS KILLING HEROIN USERS
ACROSS SCOTLAND

READ THIS -
IT MAY SAVE YOUR LIFE

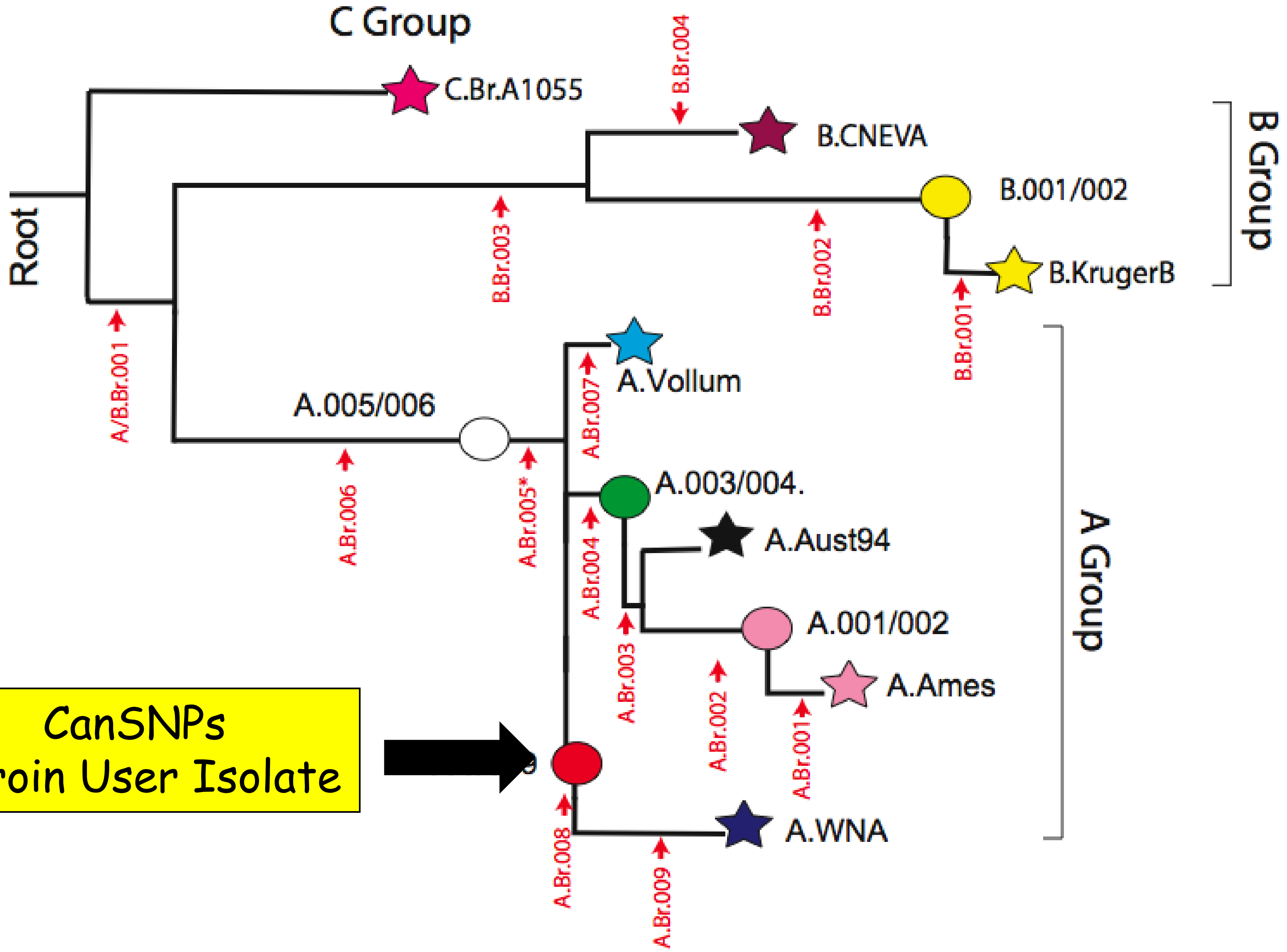
*EARLY TREATMENT WITH ANTIBIOTICS
CAN BE LIFE SAVING.*

ScottishdrugsForum

NHS
SCOTLAND

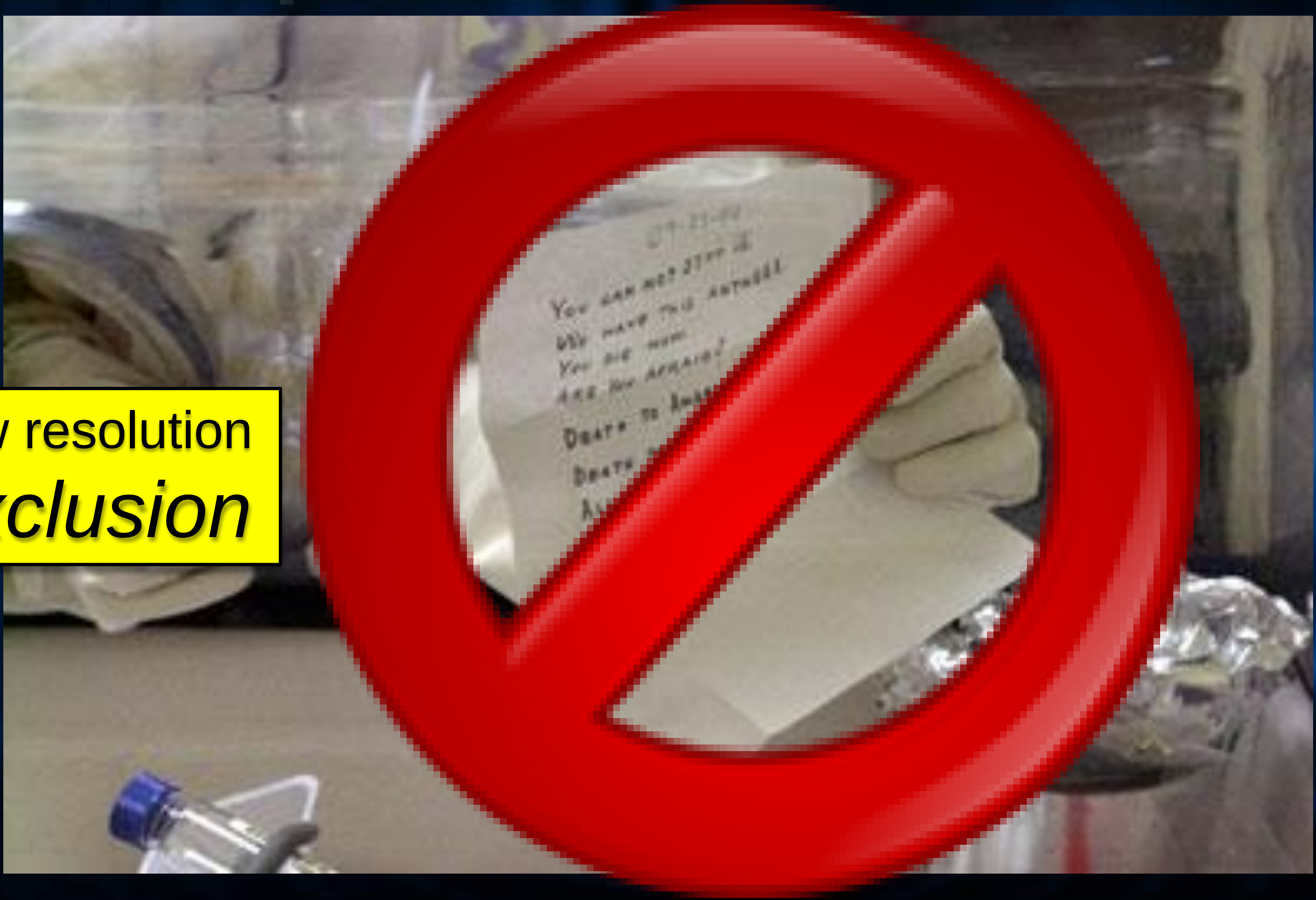
Injectional Anthrax

- ~200 suspected Cases
- ~100 confirmed cases
- ~ 17 deaths
- Scotland, England, Germany



CanSNPs
Heroin User Isolate

Not the Ames strain



Low resolution

Exclusion

Previous Scottish Anthrax

- n maker 6)
  Ghanaian
  Non M TEA

  W s (1950'
  nard Isla
  Match n

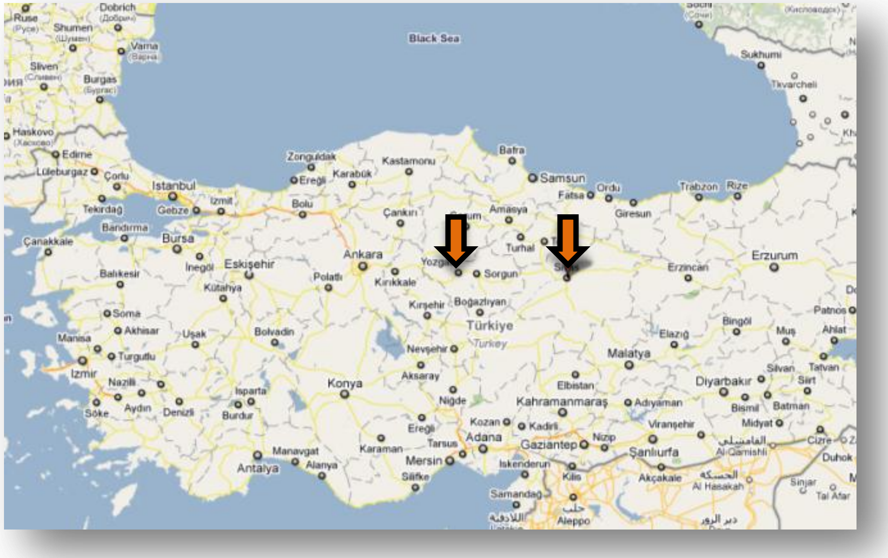
Low Resolution
Exclusion

Low Resolution
Exclusion

Scottish heroin-user *B. anthracis*
New CanSNP analysis

- It is a member of the TEA subtype
- "canSNP match" to two natural isolates from Turkey

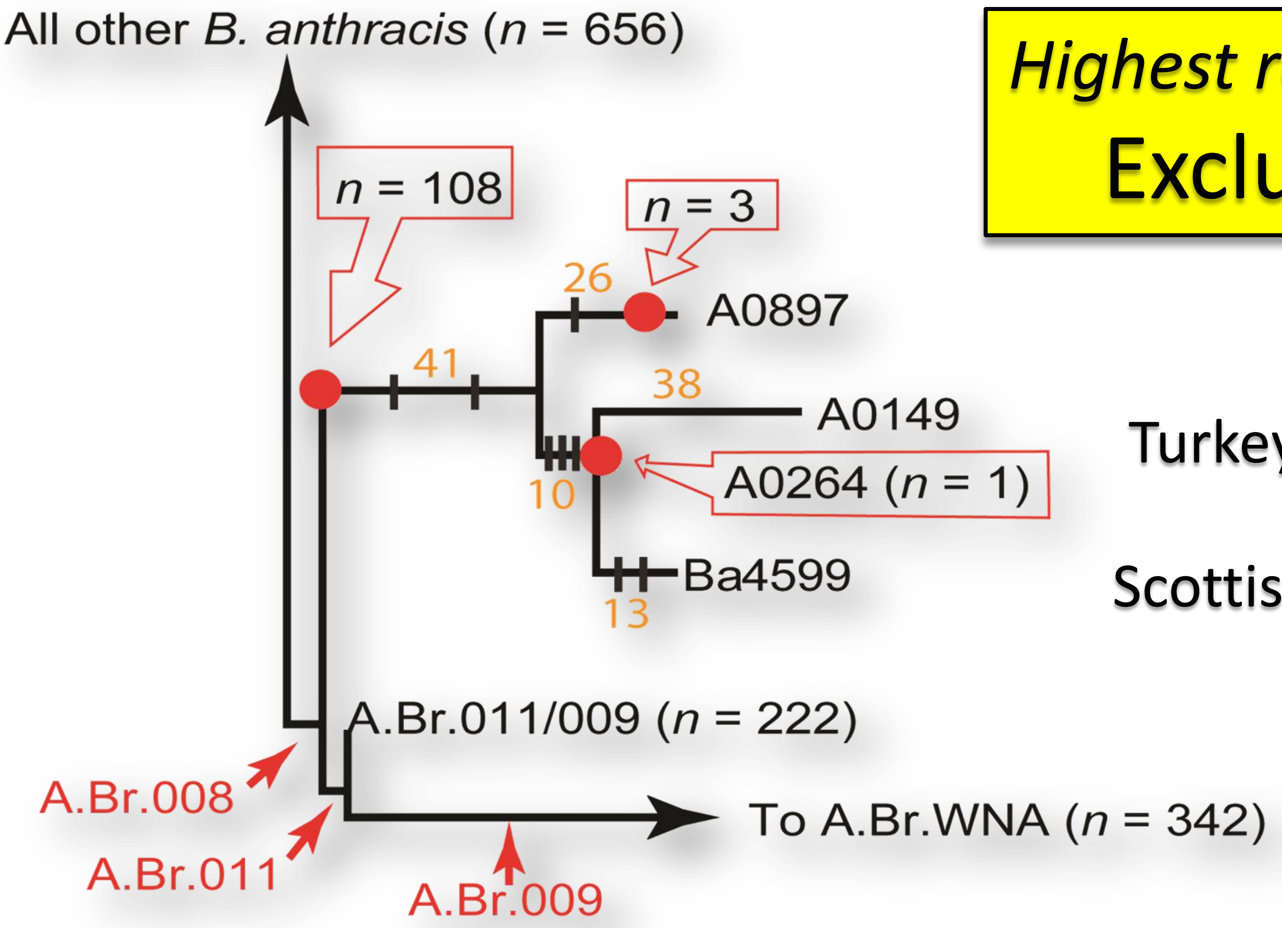
Turkey



High Resolution

Inclusion

Heroin-user associated strain



Highest resolution

Exclusion

Turkey Isolates

Scottish Drug User

Outbreak Samples Matching "Heroin" *B. anthracis* Genome

- 2 "strain specific" canSNP assays
  - Ancestral allele for diversity of strains (global)

- 22 isolates from culture-positive anthrax cases
- 18 clinical culture-negative anthrax cases
  - Scotland, England, Germany

Highest resolution
Inclusion

Heroin-associated Anthrax: Conclusions

- The heroin *B. anthracis* strains are not members of:
  - The Ames group
  - The Vollum group, including natural isolates from Afghanistan
  - Groups containing other common strains
- They are members of:
  - The Trans-Eurasian (TEA) group
  - A subgroup within TEA that also contains natural isolates from Turkey
- But they are still distinct from the Turkey isolates
- Possible scenario: Contaminated bone meal or animal hide along the smuggling route.

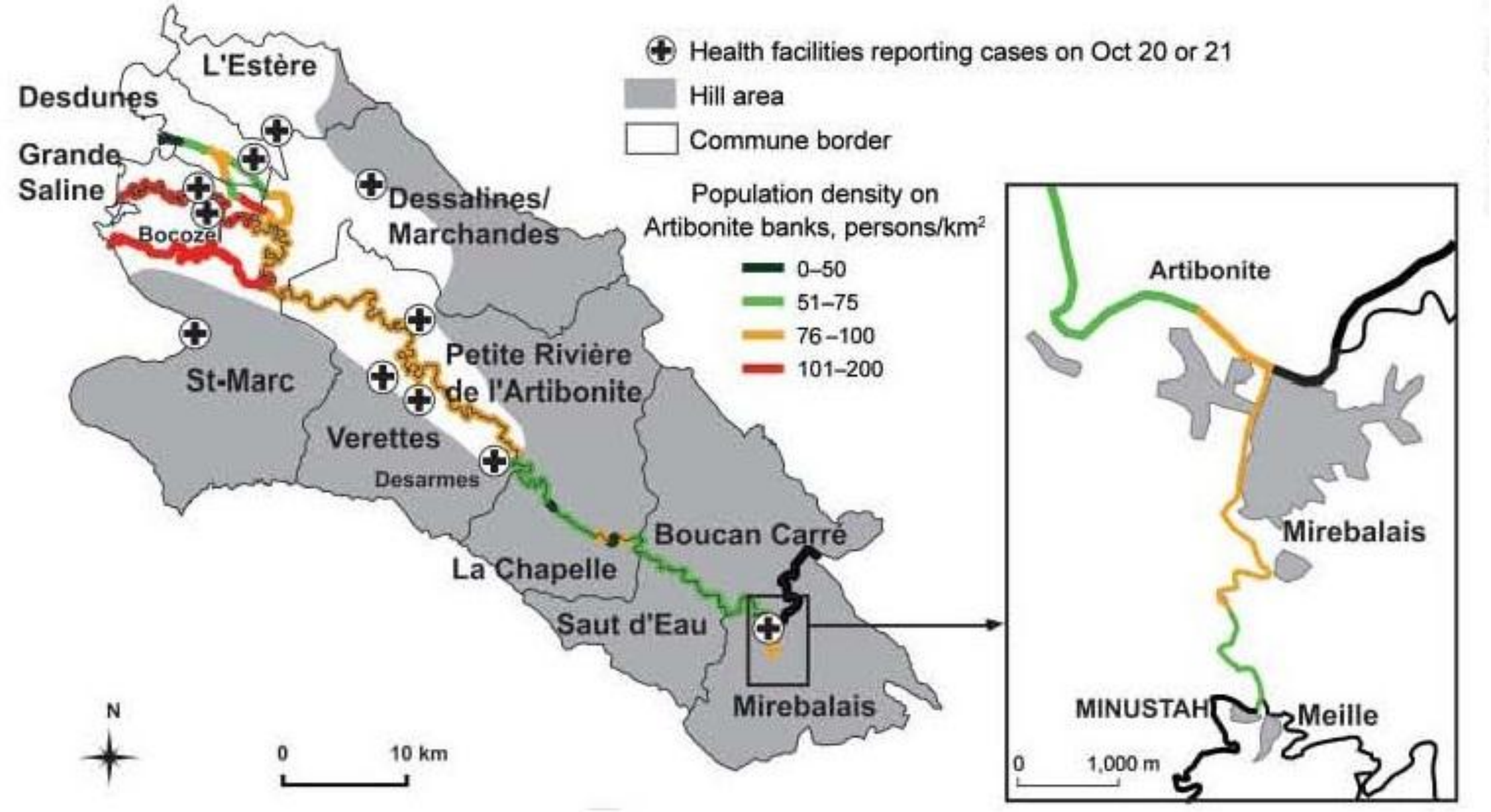
Price *et al*. in review

Haitian cholera

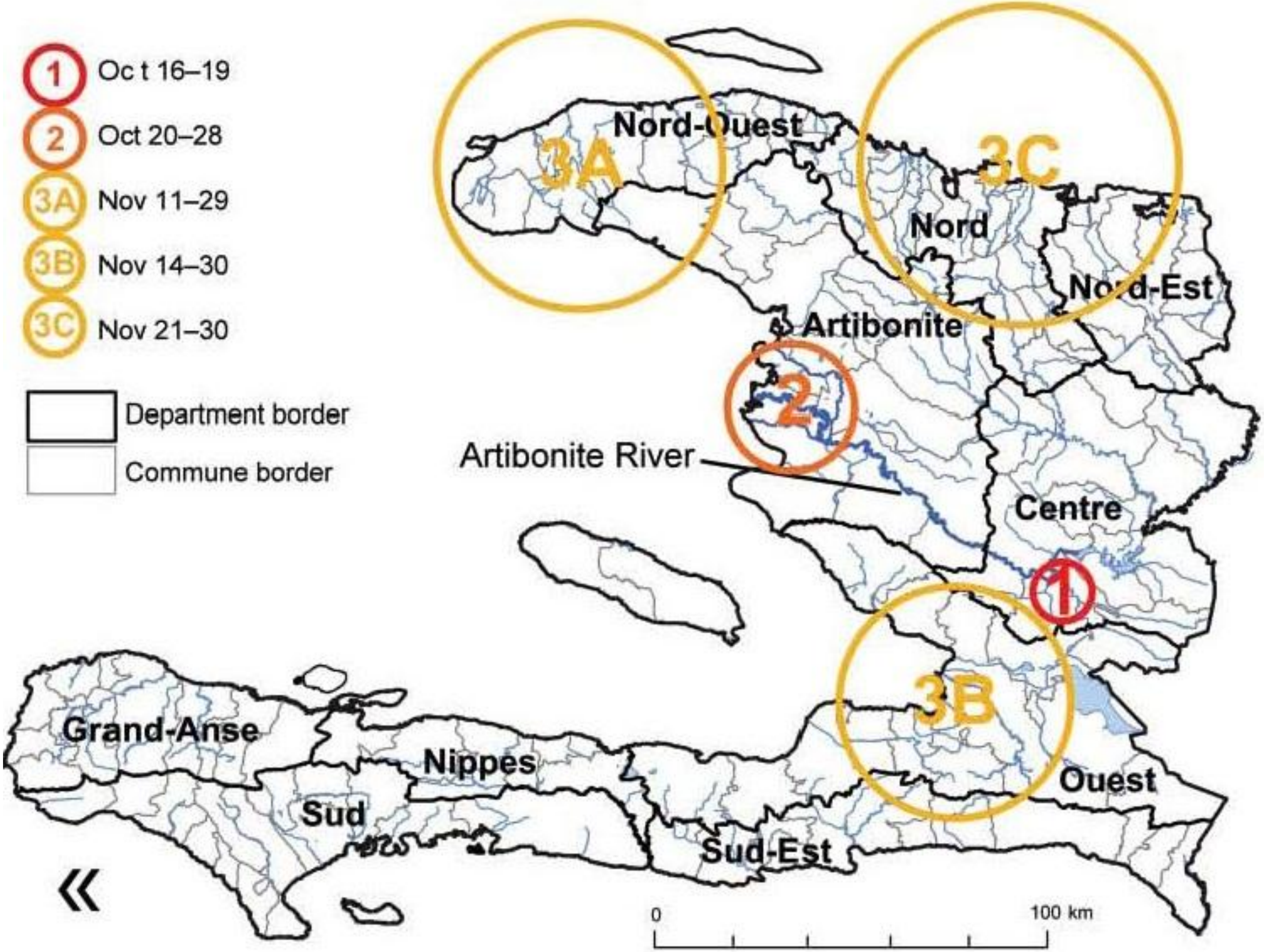
- > 300,000 cholera cases
- > 6,000 cholera deaths

- Nepalese UN peacekeepers implicated

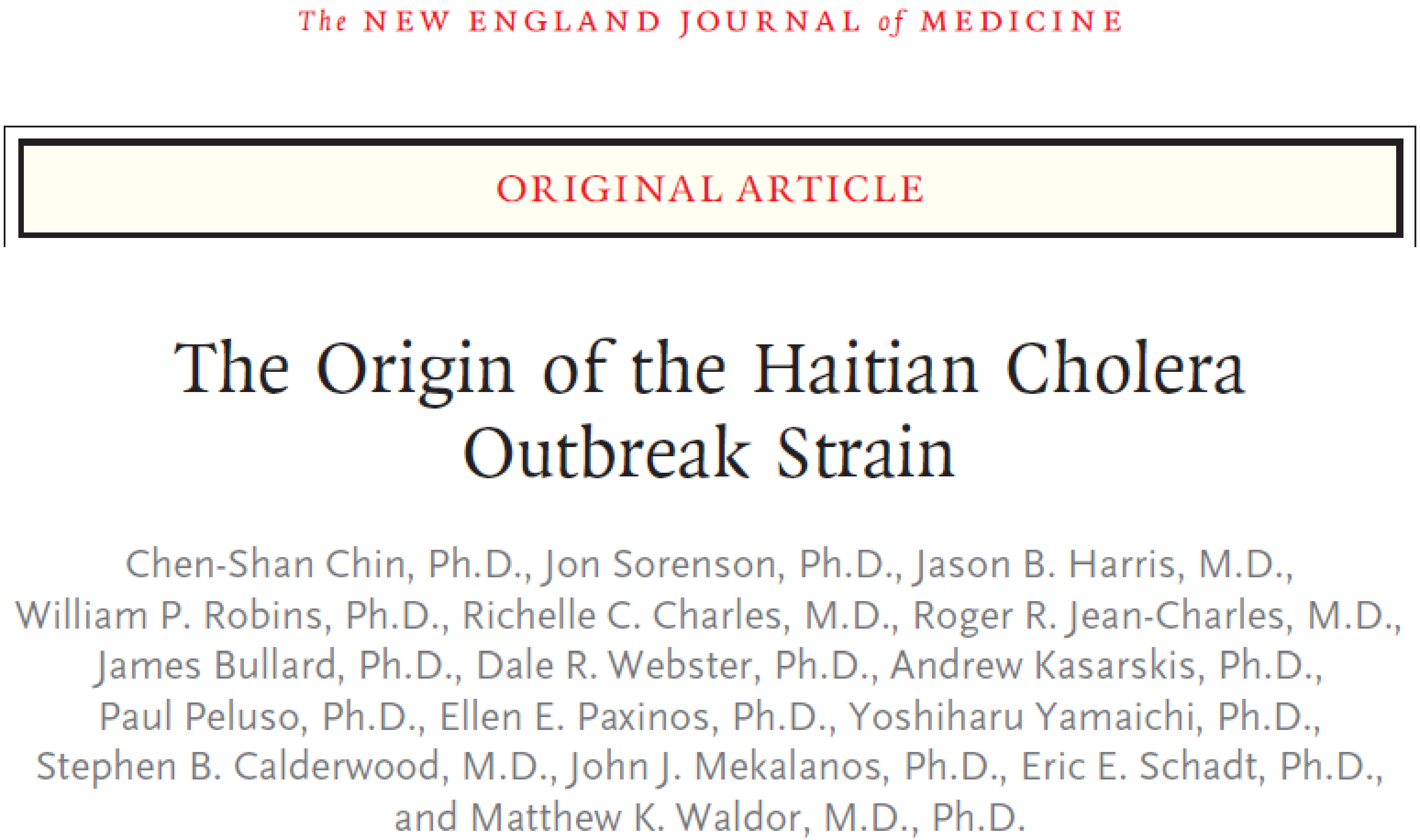
Fig 1



Piarroux et al. 2011. *EID* 17:1161-7



Piarroux et al. 2011. *EID* 17:1161-7



The NEW ENGLAND JOURNAL of MEDICINE

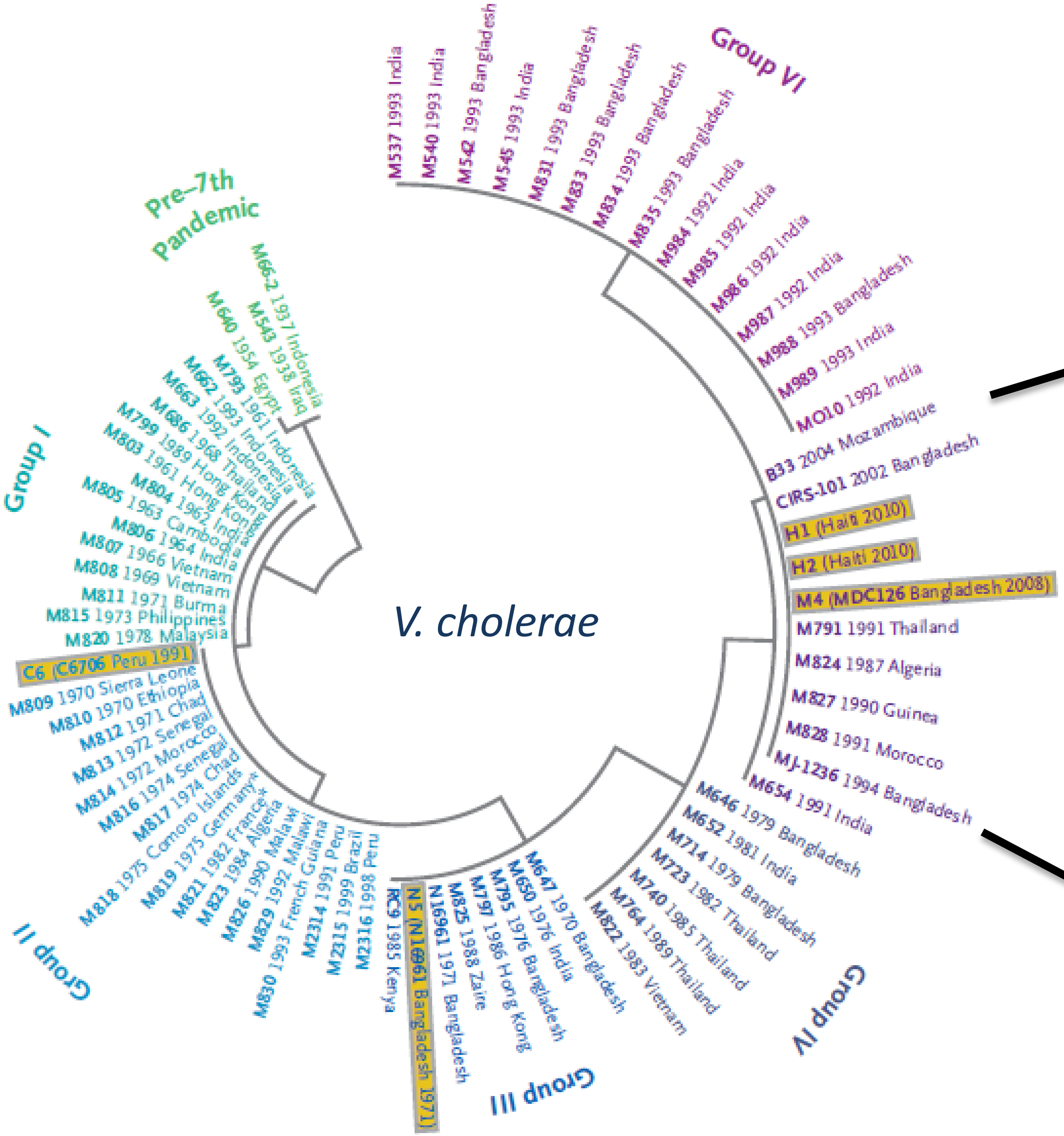
ORIGINAL ARTICLE

The Origin of the Haitian Cholera Outbreak Strain

Chen-Shan Chin, Ph.D., Jon Sorenson, Ph.D., Jason B. Harris, M.D., William P. Robins, Ph.D., Richelle C. Charles, M.D., Roger R. Jean-Charles, M.D., James Bullard, Ph.D., Dale R. Webster, Ph.D., Andrew Kasarskis, Ph.D., Paul Peluso, Ph.D., Ellen E. Paxinos, Ph.D., Yoshiharu Yamaichi, Ph.D., Stephen B. Calderwood, M.D., John J. Mekalanos, Ph.D., Eric E. Schadt, Ph.D., and Matthew K. Waldor, M.D., Ph.D.

Chin et al. 2011. *N Engl J Med.* 364:33-42

SNP - Group V



- Mozambique
- Bangladesh
- Haiti*
- Haiti*
- Bangladesh*
- Thailand
- Algeria
- Guinea
- Morocco
- Bangladesh

Chin et al. 2011. *N Engl J Med.* 364:33-42

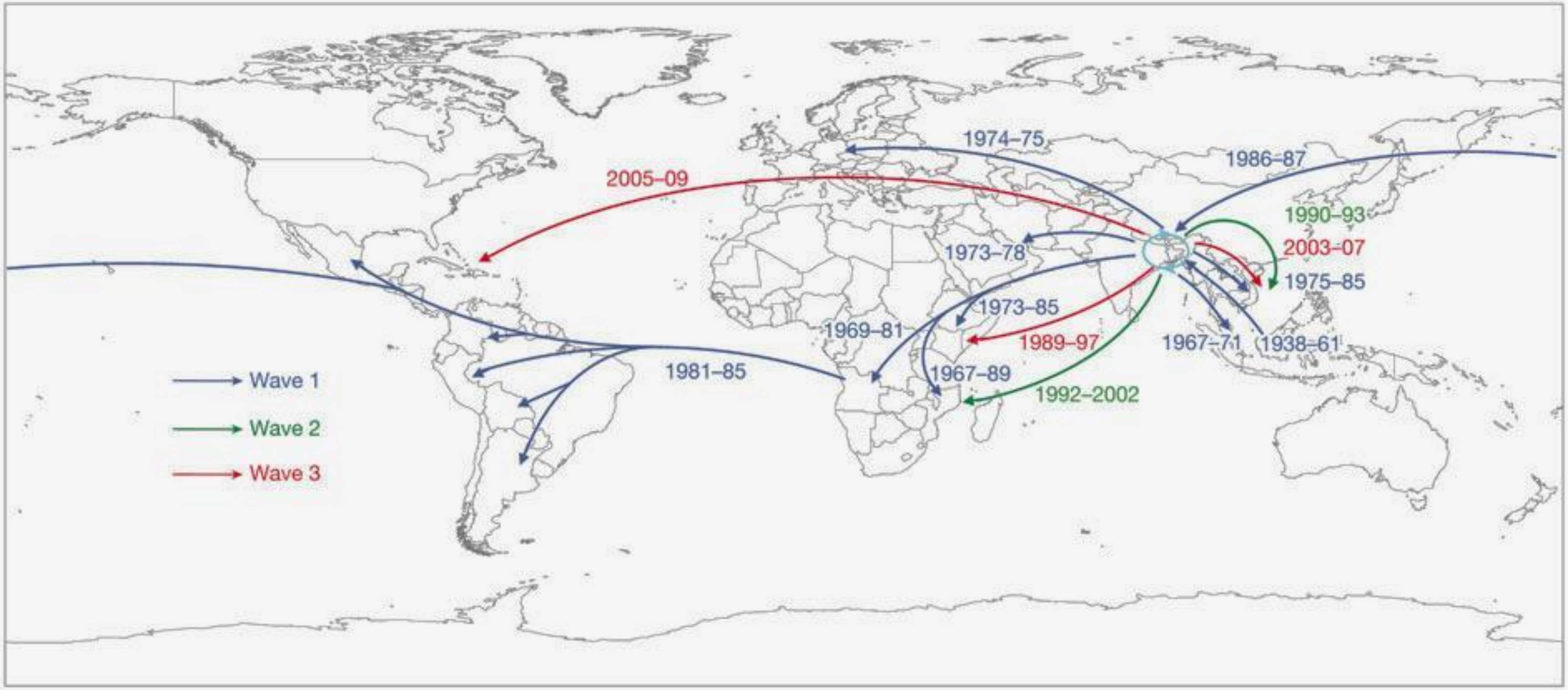
after

Lam et al. 2010. *EID* 16:1130-2

V. cholerae SNP Group V

Based upon: Lam et al. 2010. *EID* 16:1130-2.

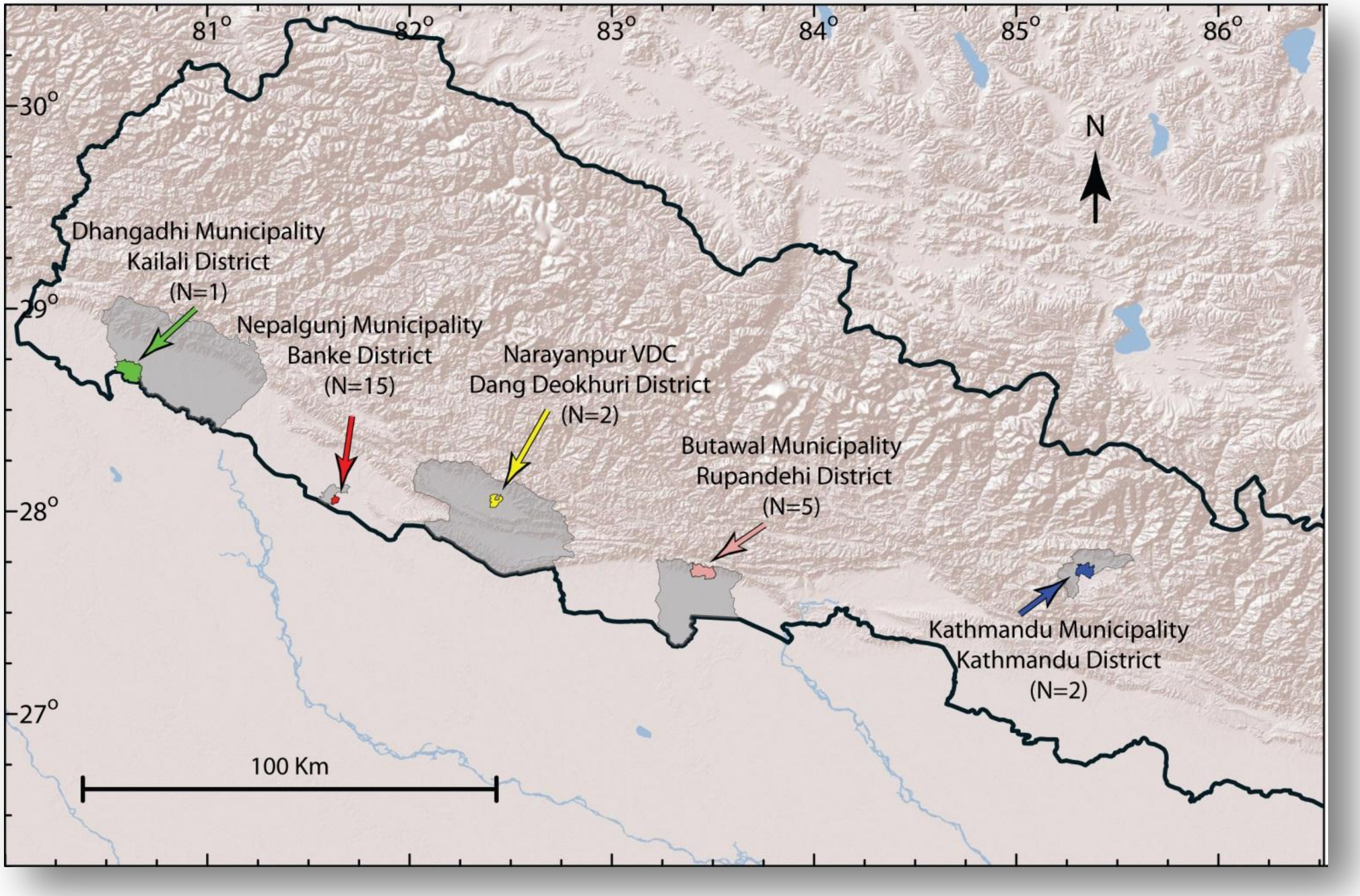
Transmission events inferred for the seventh-pandemic phylogenetic tree, drawn on a global map.



nature

A Mutreja *et al*. *Nature (*2011) 477:462-5.

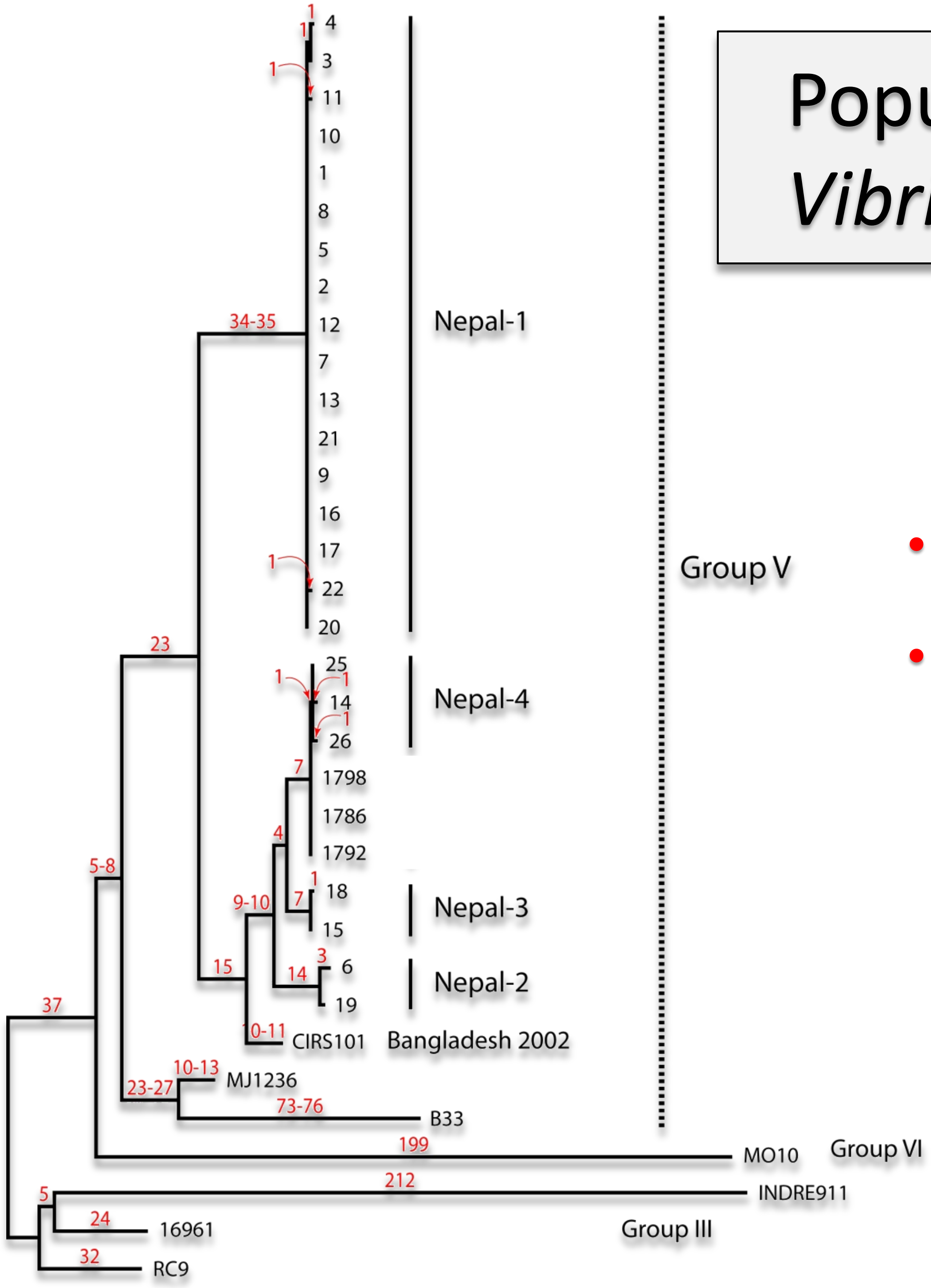
Cholera in Nepal



Rene S. Hendriksen, L. Price, P. Keim, Geeta Shakya, Frank M. Aarestrup, & others
mBio 2011

Danish Technical University - Copenhagen
TGen – Flagstaff, Arizona
National Public Health Laboratory, Katmandu, Nepal

Population Genetics of *Vibrio cholera* in Nepal

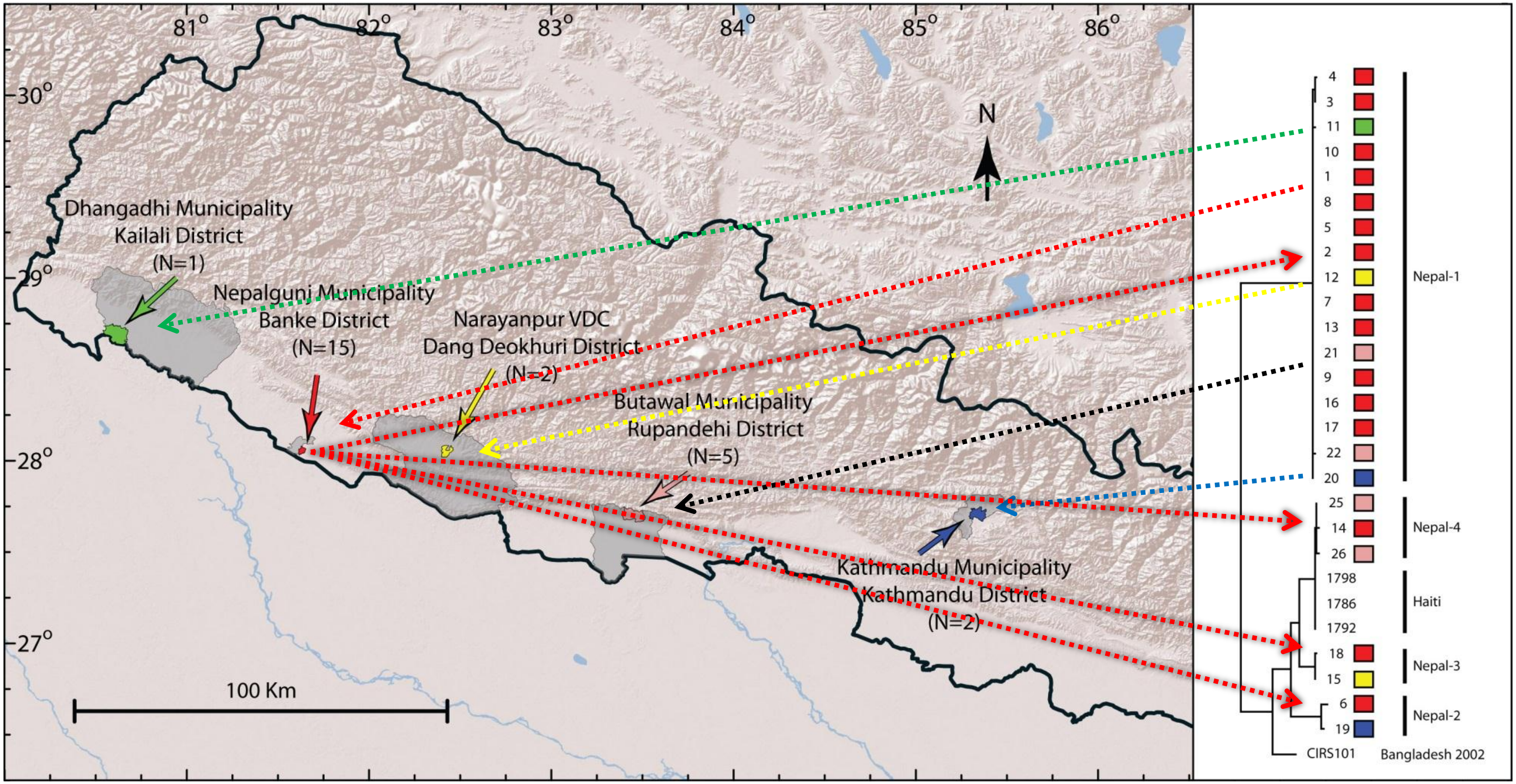


- 24 *V. cholera* Genomes
- 2 major Nepalese Clades
  - Nepal-1 has low diversity

Rene S. Hendriksen, L. Price, P. Keim,
Geeta Shakya, Frank M. Aarestrup, & others
2011 (*mBio*)

Danish Technical University - Copenhagen
TGen – Flagstaff, Arizona
National Public Health Laboratory, Katmandu

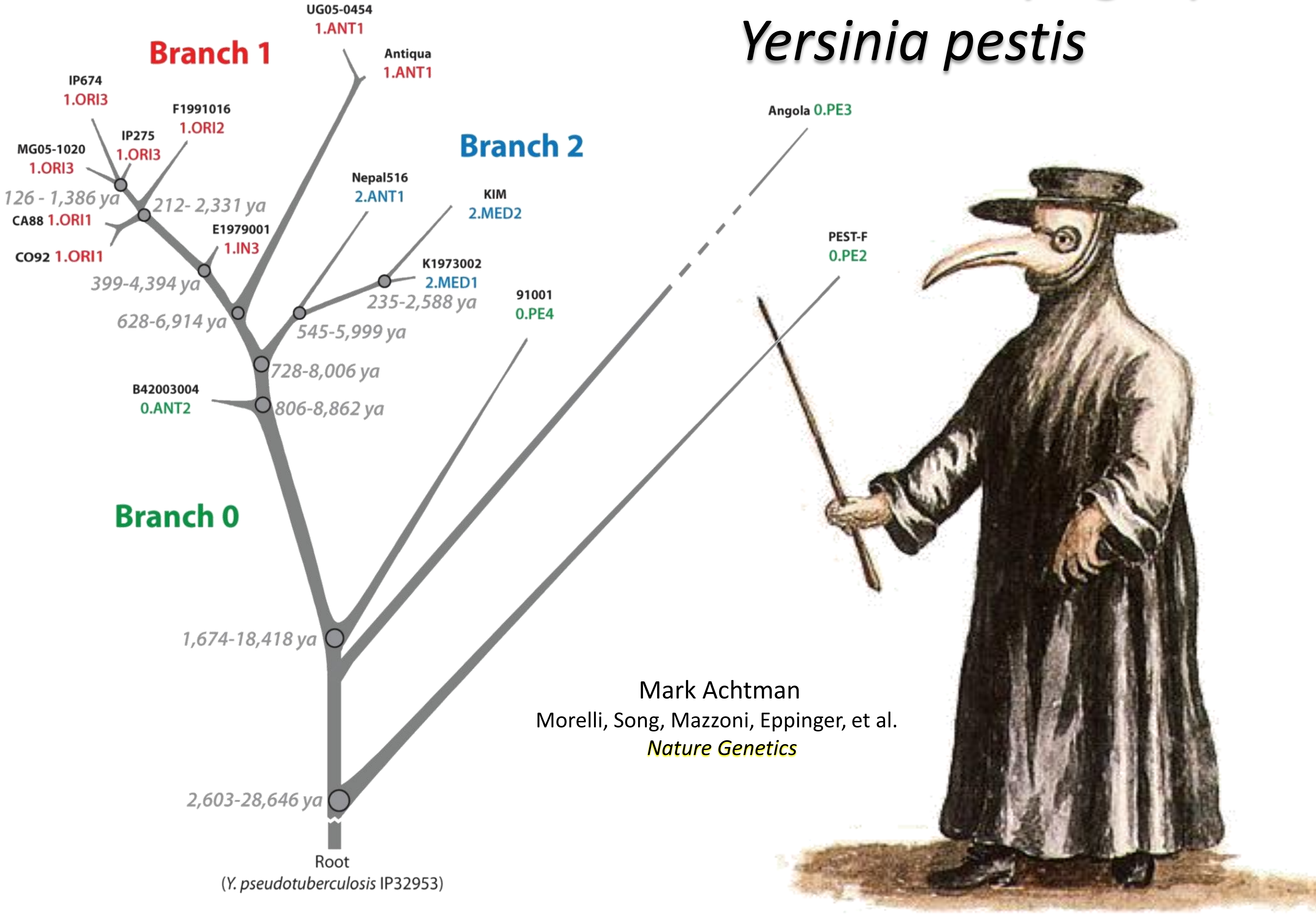
Phylogeography of Nepalese *V. cholerae*



Rene S. Hendriksen, L. Price, P. Keim, Geeta Shakya, Frank M. Aarestrup, & others
mBio 2011

EPIDEMIOLOGY

Whole Genome Phylogeny of *Yersinia pestis*

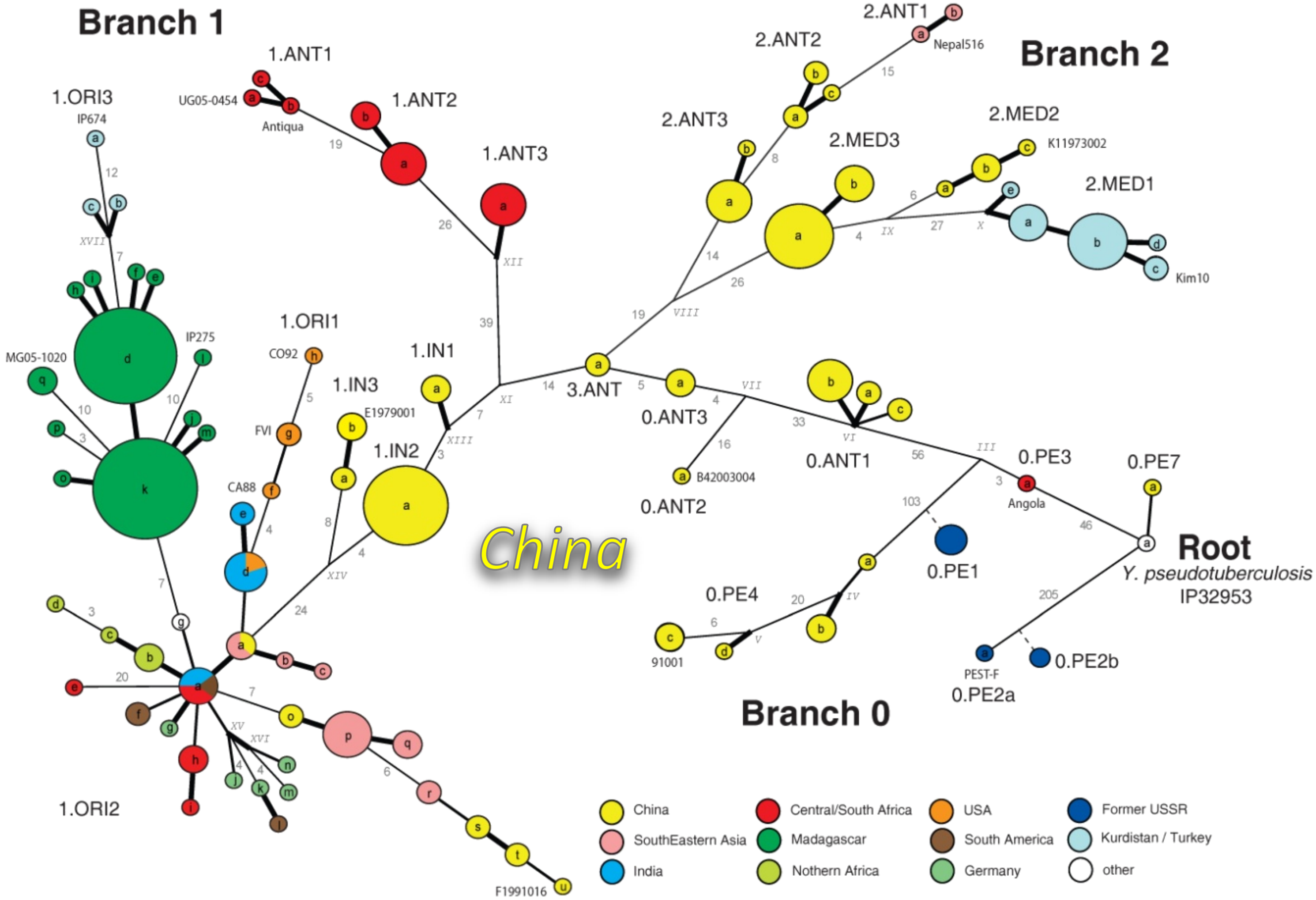


Mark Achtman

Morelli, Song, Mazzoni, Eppinger, et al.

Nature Genetics

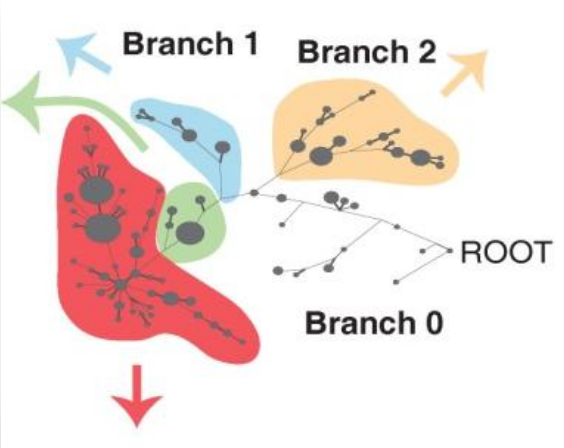
Global Population Genetic Structure



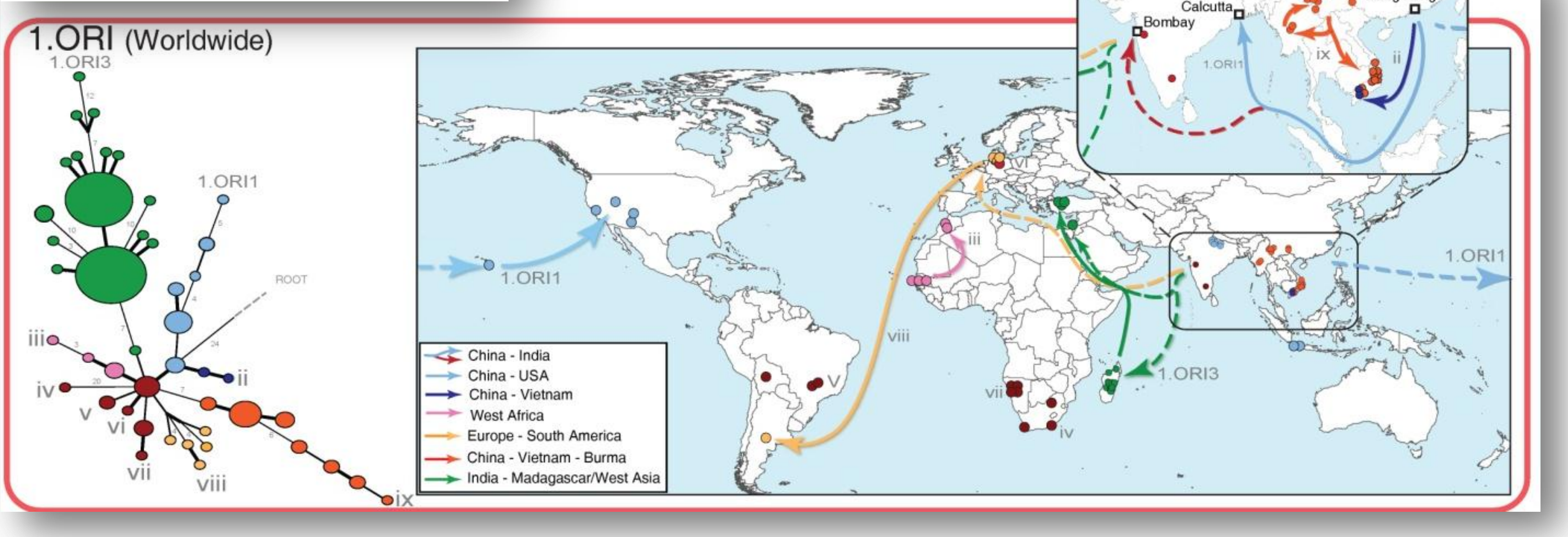
Mark Achtman
Morelli, Song, Mazzoni, Eppinger, et al.
Nature Genetics 2010

Total = 933 SNPs
289 *Y. pestis* isolates

Branch 1.ORI – China to the World



Mark Achtman
Morelli, Song, Mazzoni, Eppinger, et al.
Nature Genetics 2010

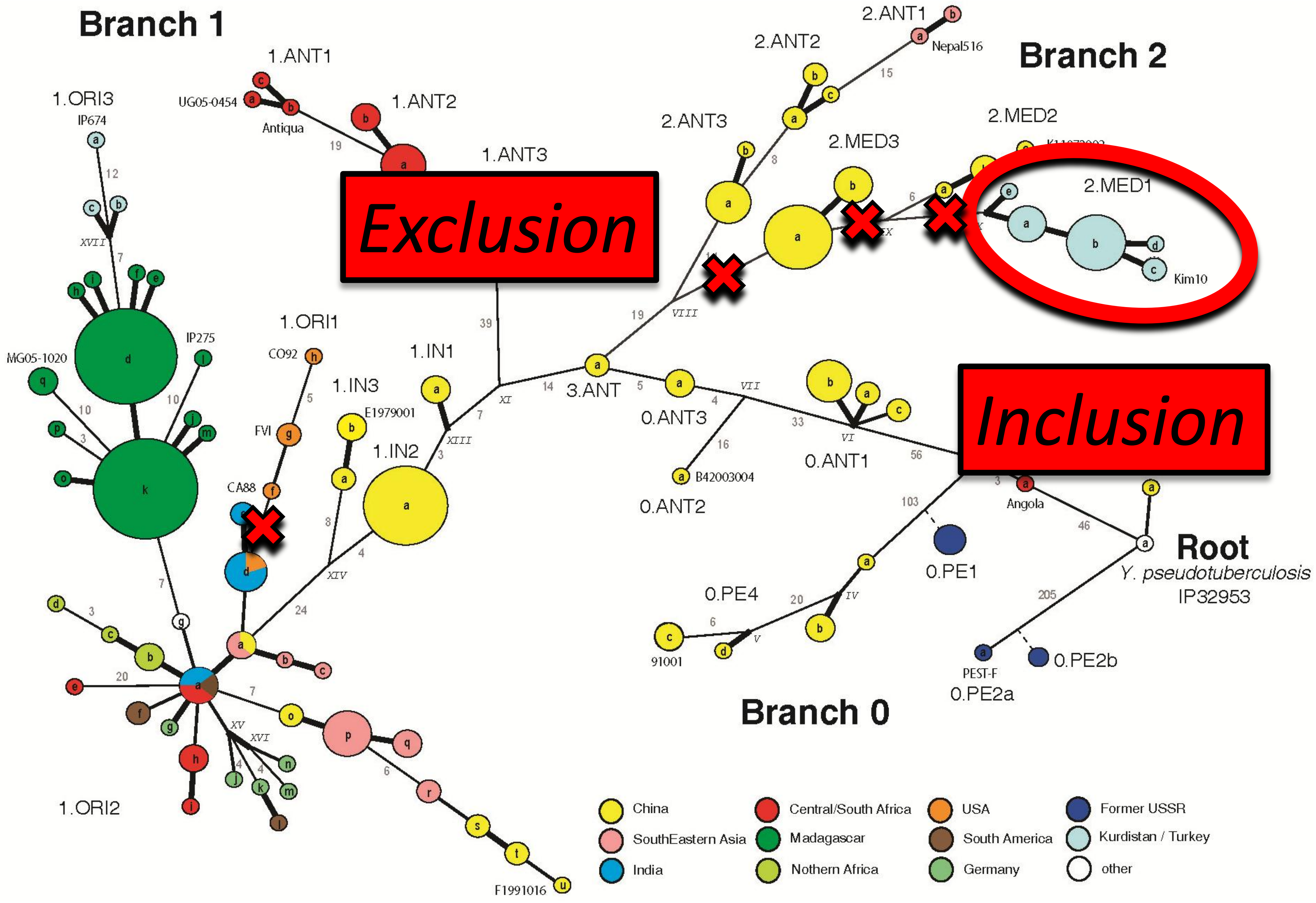


Case History:
A University Scientist

- 60 year old, diabetic male
- Dies 13 hours after presentation in the emergency room
- Worked in Infectious Disease Research – no virulent strains

Frank et al. In prep.

***MMWR* (2011) 60;201-205**



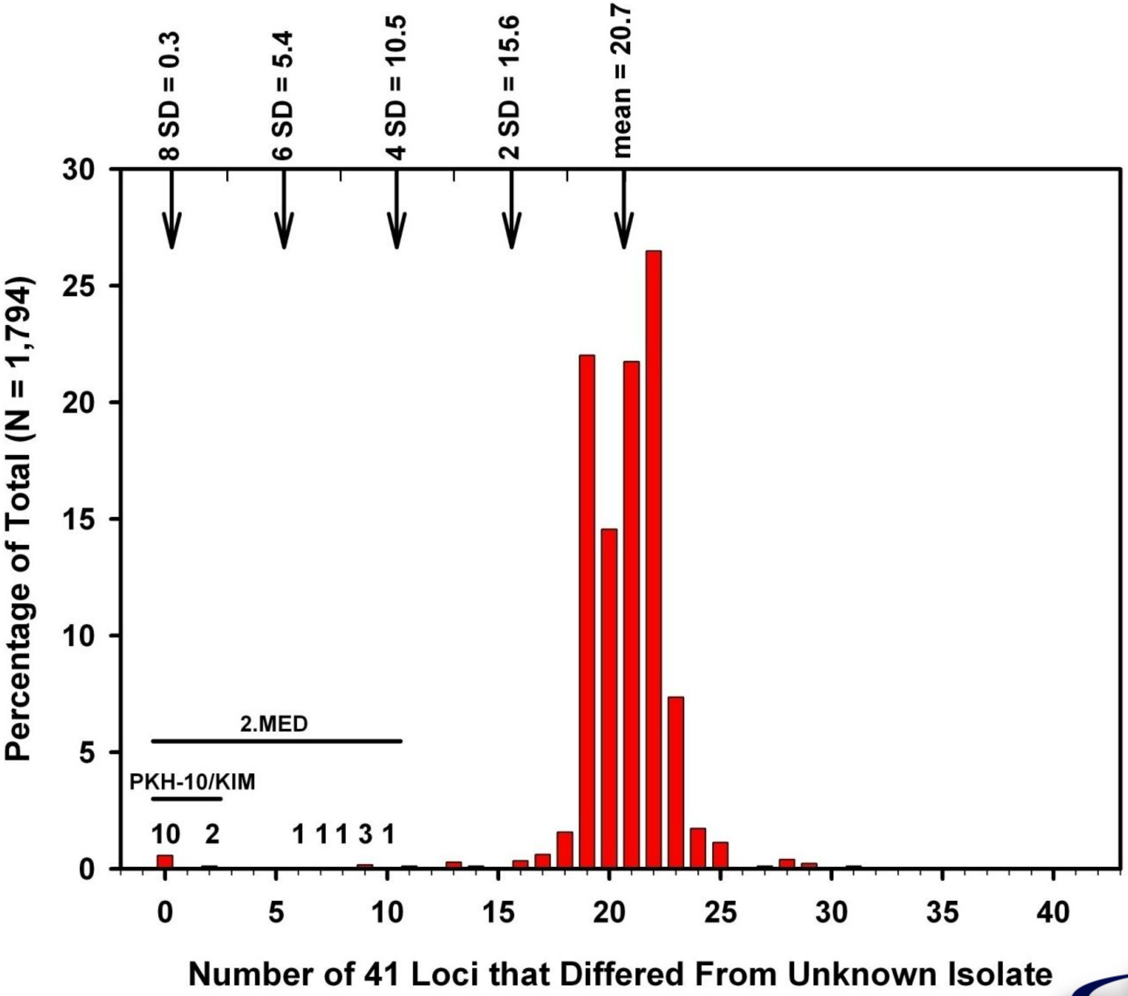
Exclusion

Inclusion

✖ = analyzed canSNP

Morelli *et al*. Nature Genetics *2010*

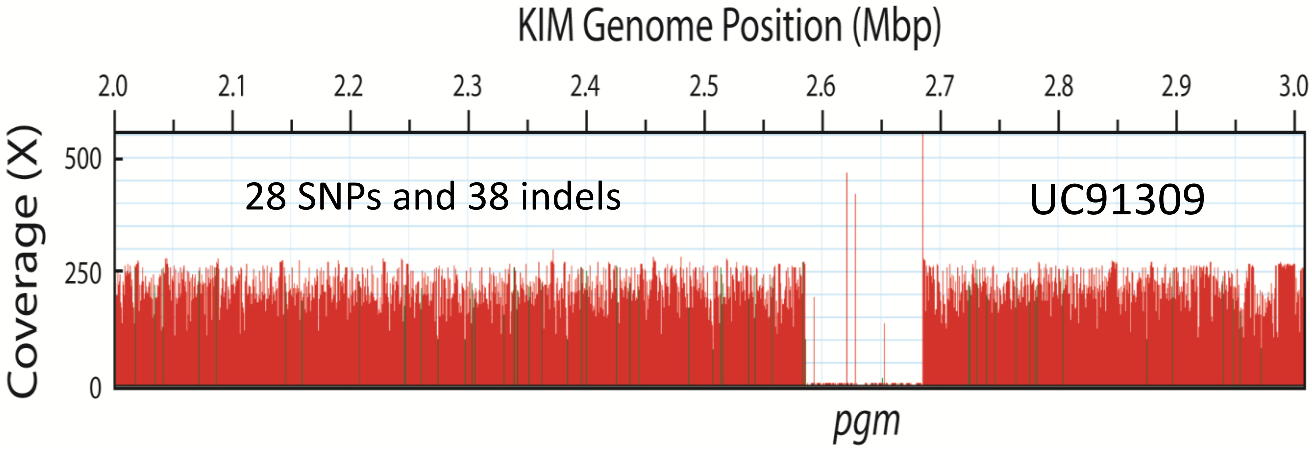
VNTR Database Match for Lab Acquired Plague Infection



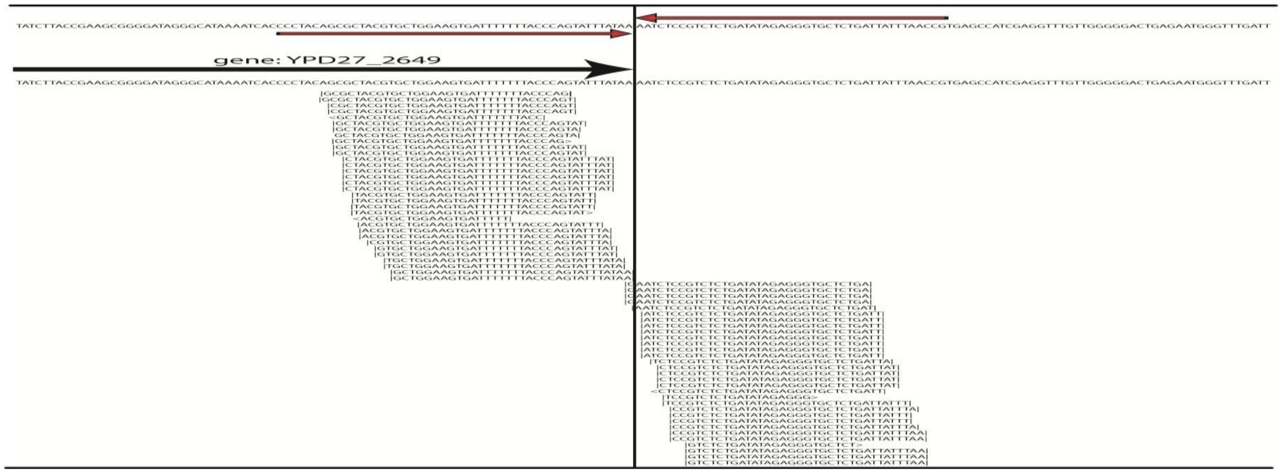
Wagner *et al*. Unpublished Data

Whole Genome Sequencing

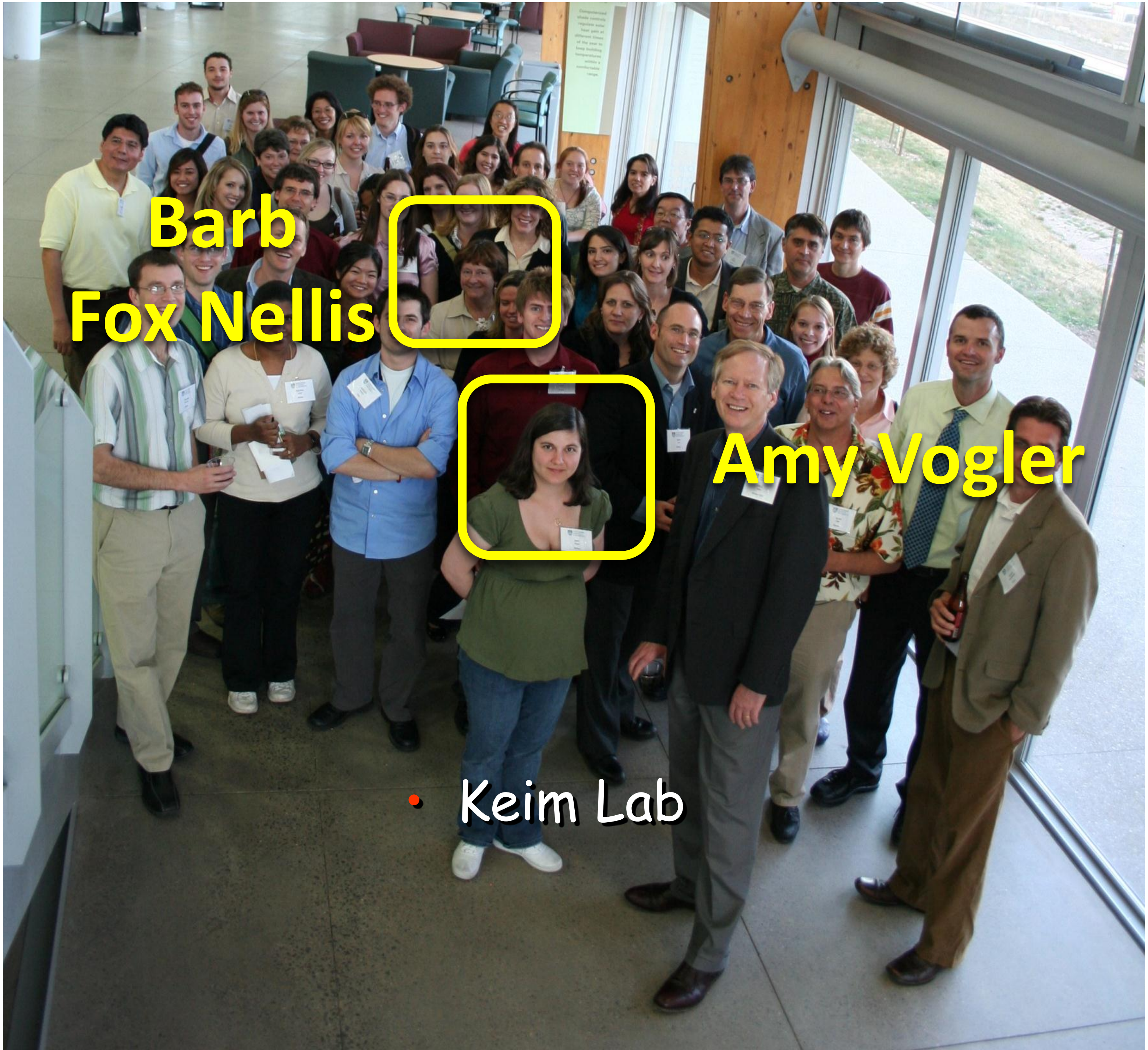
A.
Attenuation
Defect
Unaltered



B.
Genetically
Engineered
Strain
(cam-R)



Frank et al. In Prep.



Barb Fox Nellis

Amy Vogler

- Keim Lab

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