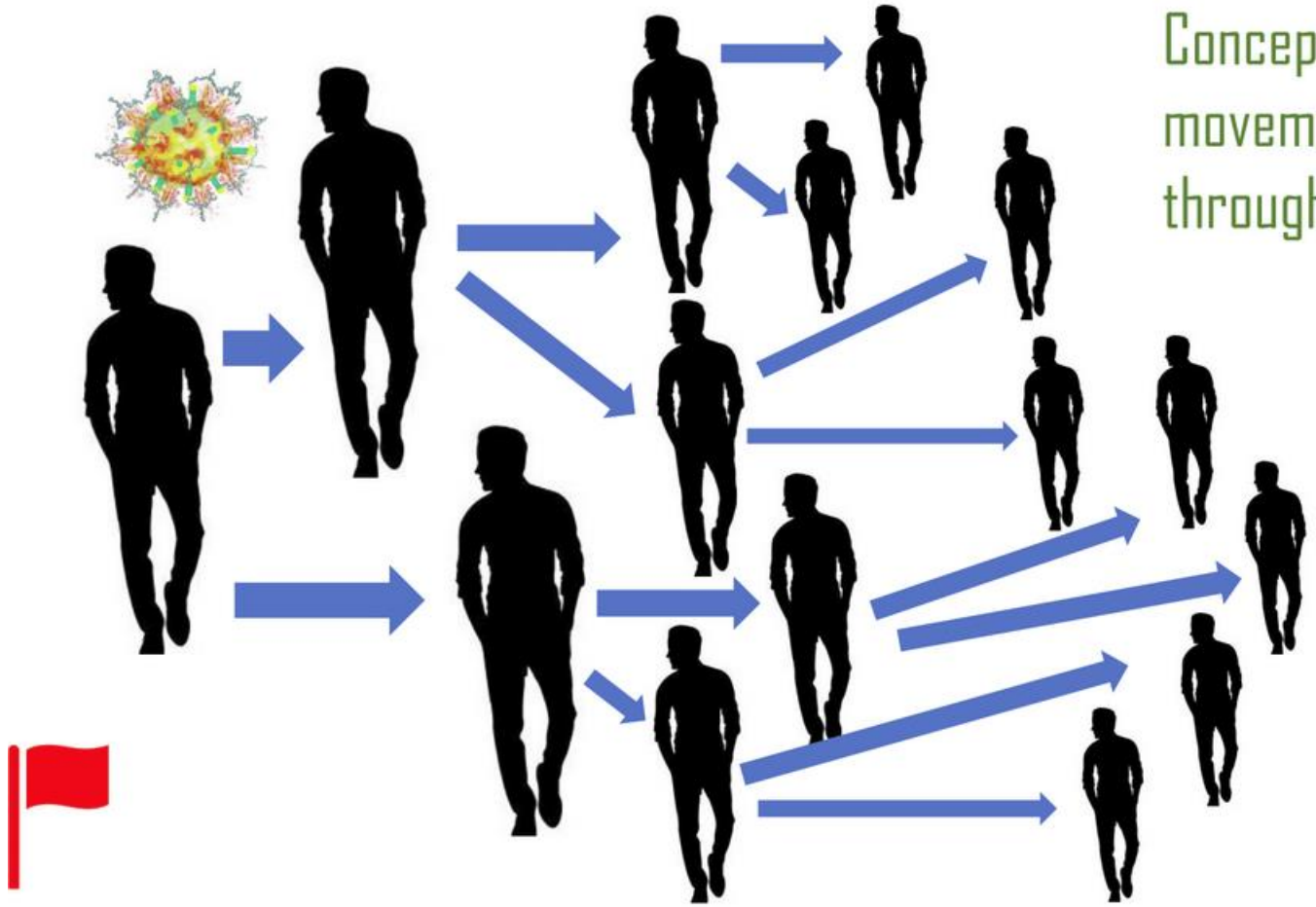
Session 1

Genomic epi overview

Epidemiology & Disease Ecology focus on the population-level

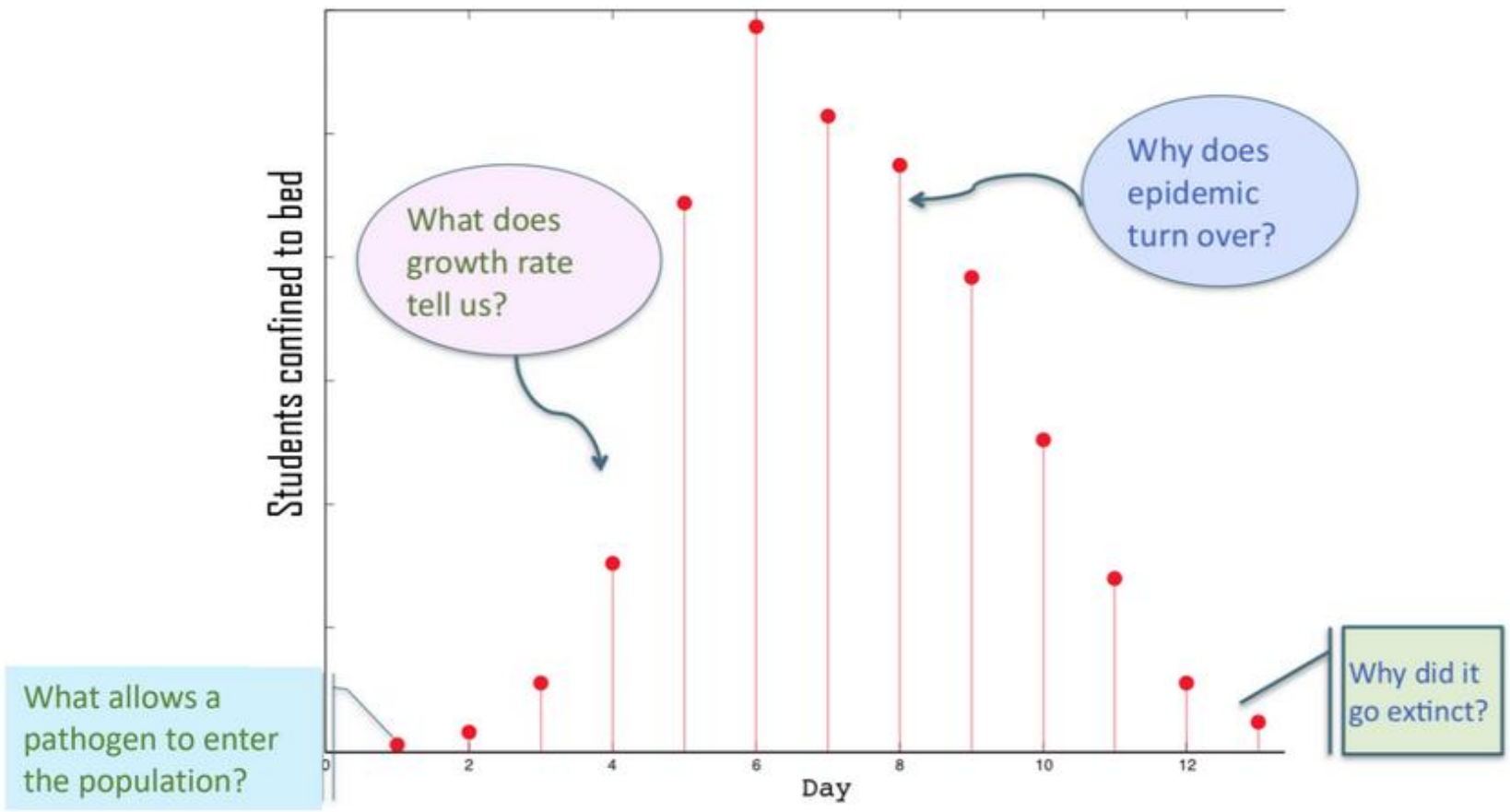


Concept: We can track the movement of pathogens throughout populations

A transmission chain is the set of infection events that occur as a pathogen moves through a population.

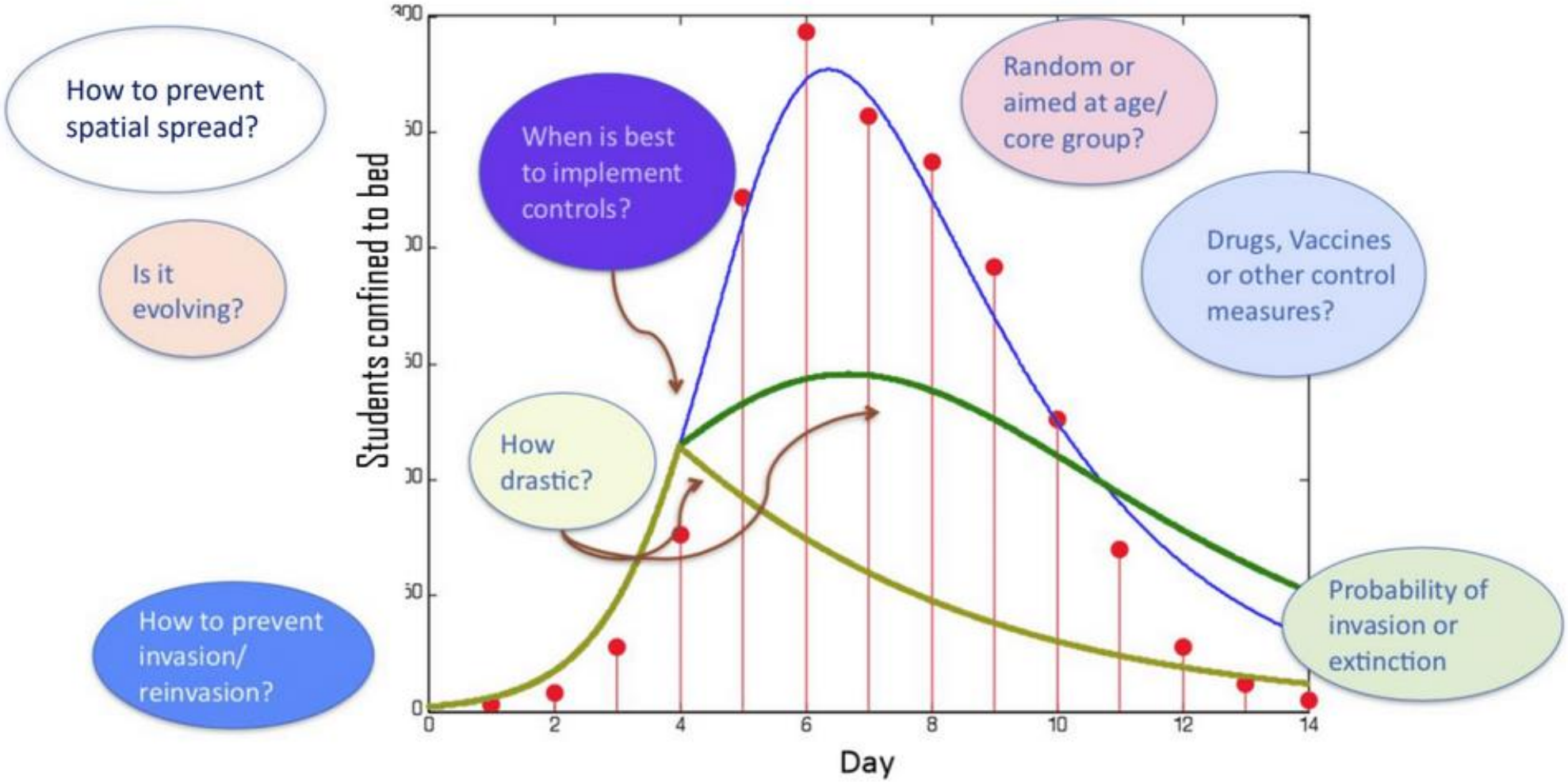
slides in part adapted from Pej Rohani& John Drake's SISMID 2019 course materials and Micaela Martinez's SIMSID 2021 lectures

Biological questions we can ask of time series



slides in part adapted from Pej Rohani& John Drake's SISMID 2019 course materials and Micaela Martinez's SIMSID 2021 lectures

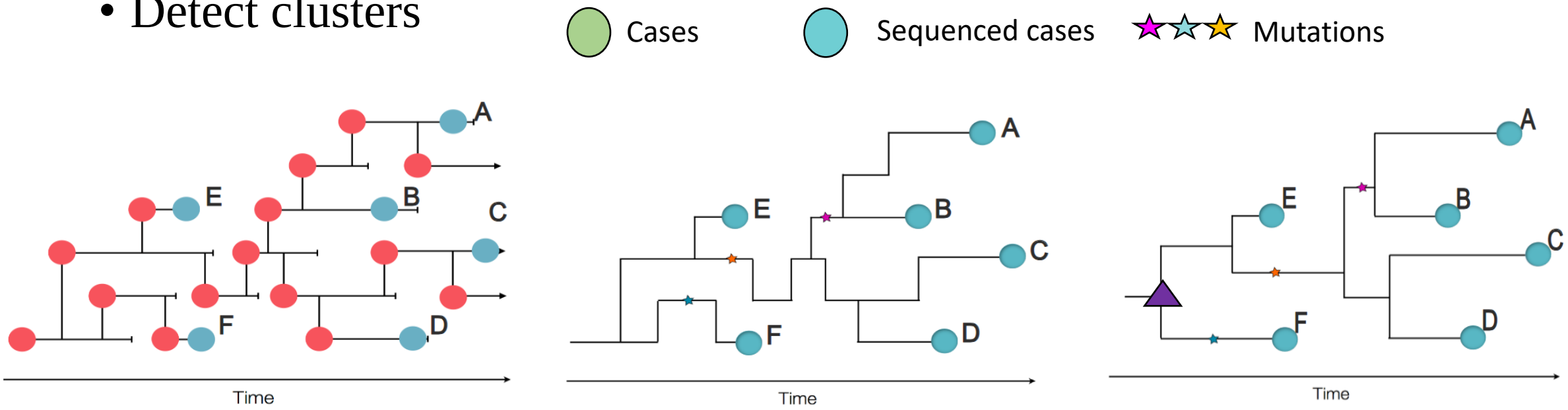
Questions about interventions we can ask of time series



slides in part adapted from Pej Rohani& John Drake's SISMID 2019 course materials and Micaela Martinez's SIMSID 2021 lectures

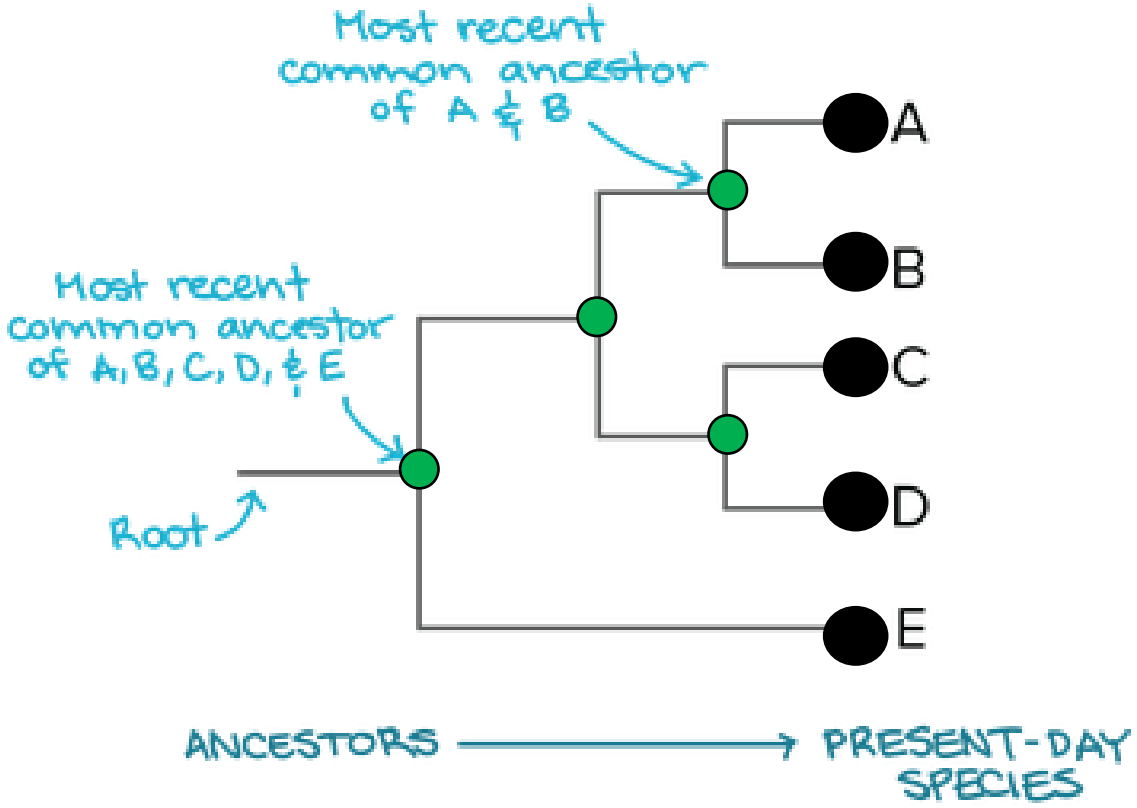
Genomic epidemiology is a powerful tool

- Outbreak investigation and surveillance
- Distinguish pathogen lineages
- Reveal unobserved transmission processes
- Detect clusters



Slides modified from my dissertation

Phylogenetic Trees 101

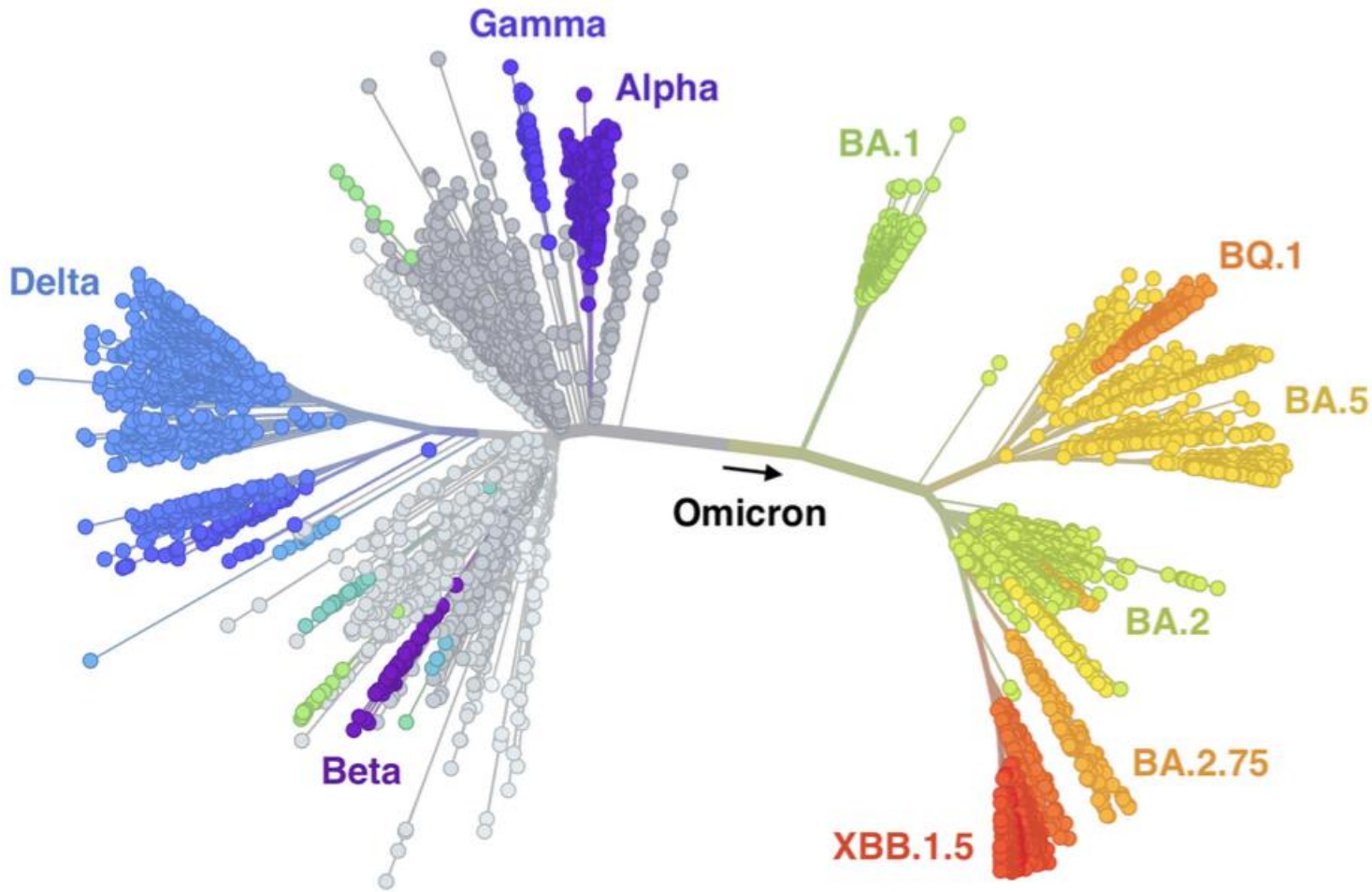


- Evolutionary relationships among organisms
- Tips: sequences
- Internal nodes: divergence events
- Branches: connections between nodes and tips

Image adapted from Khan Academy

Slides modified from my dissertation

Genetic relationships of globally sampled SARS-CoV-2 to present



Adapted from SISMID course materials by Trevor Bedford and Sarah Cobey: https://bedford.io/projects/sismid/

Application of phylogenies

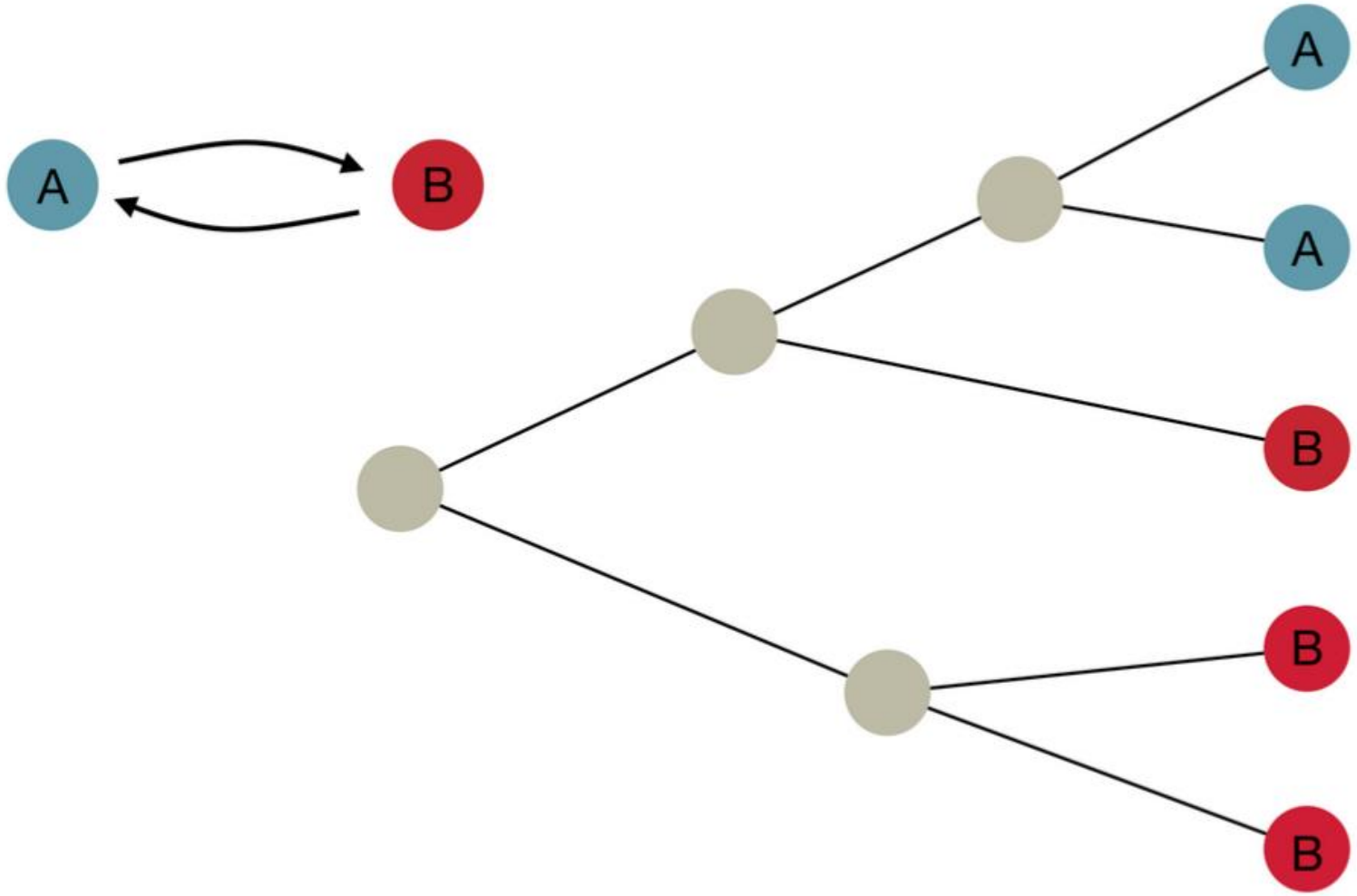
Phylogenies are used very commonly in biology, but also many other disciplines where biology plays a role.

Applications:

- Reconstruction of evolutionary relationships
- Reconstruction of population dynamics (over time / space)
- Outbreak analysis
- Typing of strains/variants

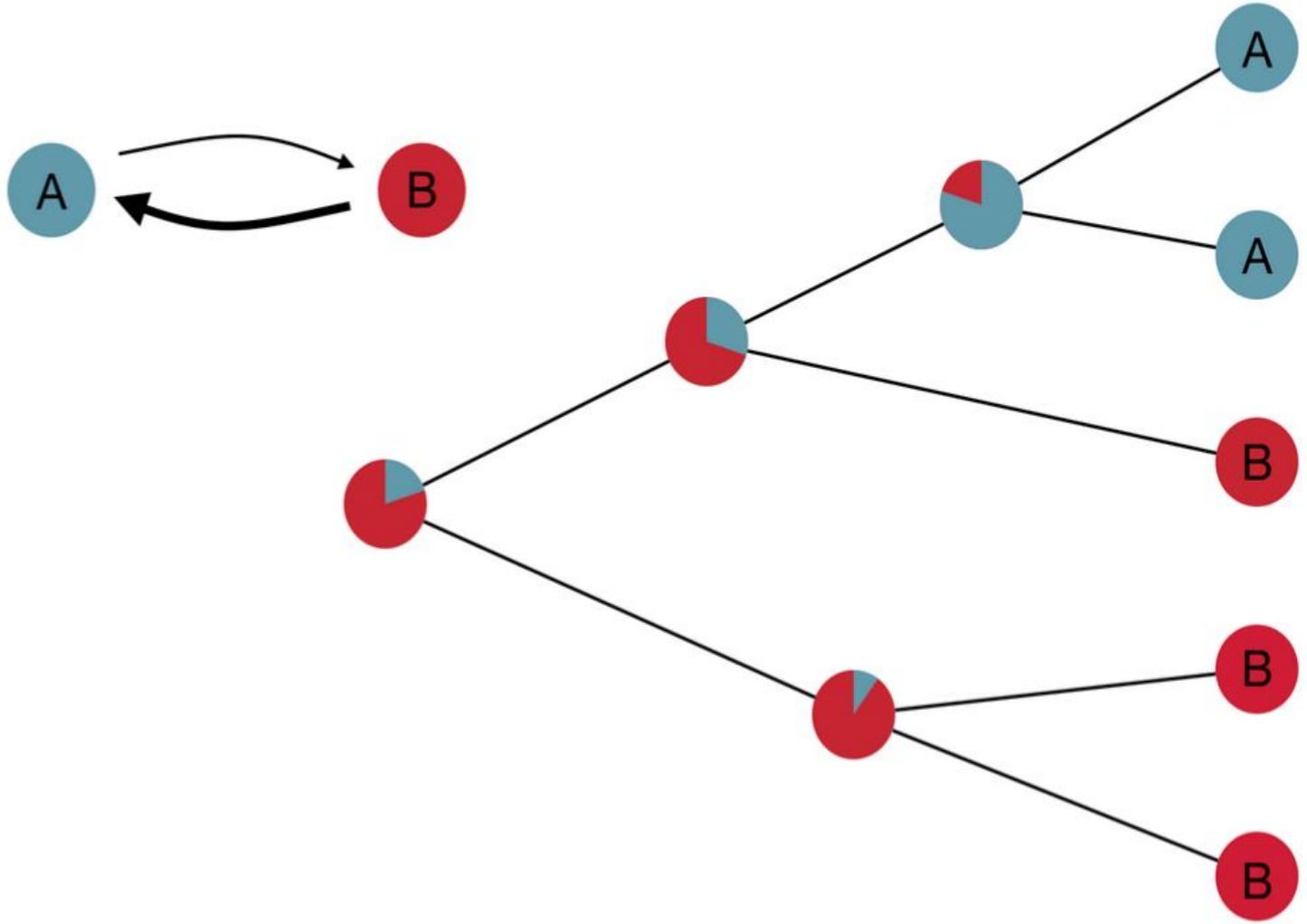
Adapted from GenEpi-BioTrain-Training Materials: Course: GenEpi-BioTrain - Training Materials on Genomic Epidemiology and Public Health Bioinformatics - Bridging the gaps

- When we have additional metadata, such as host or location, we can integrate those traits into evolutionary models



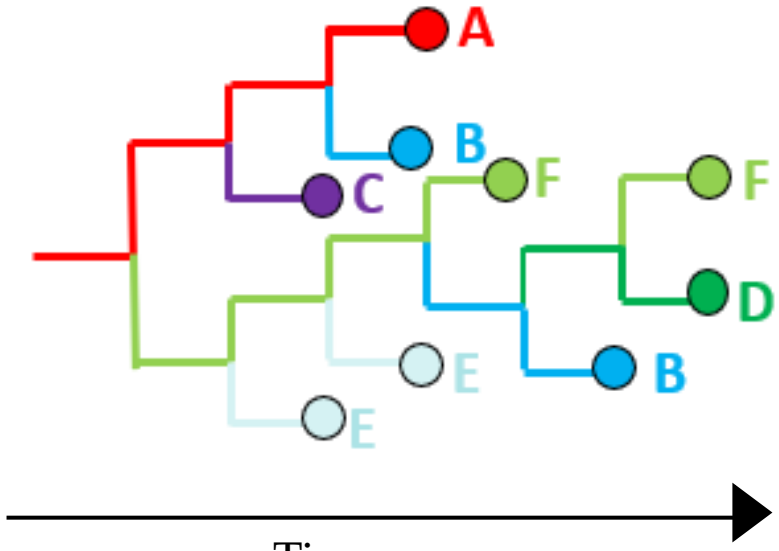
Adapted from SISMID course materials by Trevor Bedford and Sarah Cobey: https://bedford.io/projects/sismid/

- We can apply a social network model to infer the transition matrix and ancestral states



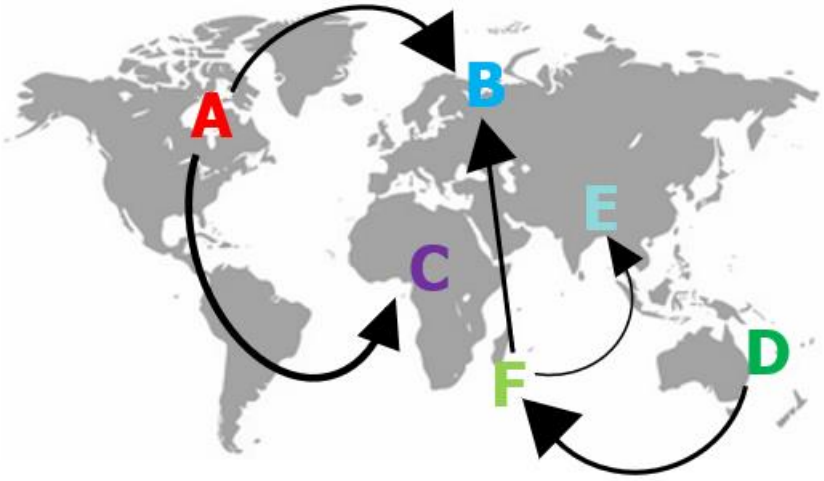
Adapted from SISMID course materials by Trevor Bedford and Sarah Cobey: https://bedford.io/projects/sismid/

Genomic epidemiology is even more powerful with additional metadata



	A	B	C	D	E	F
A	-	**1**	**1.8**	0.5	0.3	0.1
B	0.7	-	0.6	0.2	0.1	2
C	5	0.1	-	0.1	0.2	0.1
D	1.5	1.2	0.5	-	0.9	**1.2**
E	2	2.2	2.7	0.1	-	1.2
F	3	**1**	2.2	2.1	**3**	-

Rate (transitions per year)



Slides modified from my dissertation

This allows us to ask important questions around who, what, where, when, and why

- When did the outbreak emerge, and where did it come from?
- Which lineages are circulating in a community?
- How are viruses moving between locations?
- What are the key predictors of viral diffusion?
- Is this outbreak sustained by local transmission, or is it frequently being re-seeded from other locations?

Slides modified from my dissertation

Genomic epi does not replace the traditional epi investigation. It complements it.

- Corroborate suspicions in an investigation
- Refute hypotheses thereby encouraging more investigation

Adapted from StaPH-B Monthly Webinar – August, 2020:
https://www.youtube.com/embed/C3YCm3WOY0A?autoplay=1

Let’s put outbreaks into context

Transmission Heterogeneity

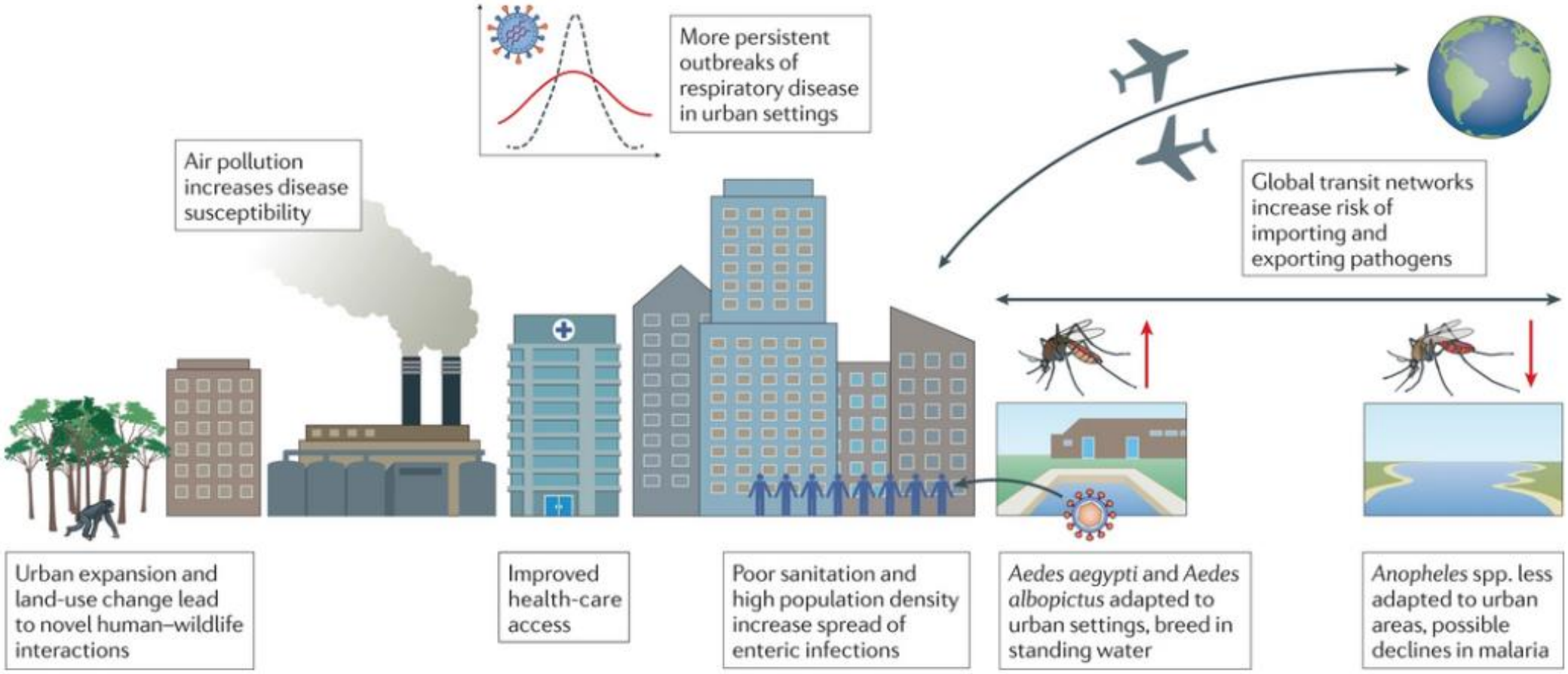
- Some individuals are more infectious, or some are more likely to get infected, as a result of host biology or site of infection (e.g., immunocompromised individuals)
- Some individuals are more likely to get infected, and pass on infection, as a result of behavior (e.g., children, patients in a hospital)
- Some strains of the infection are more infectious than others, as a result of pathogen biology

Adapted from SISMID course materials by the Martinez lab: https://memartinez.org/sismid-2021-course-materials/

One Health

- One health is a collaborative, multisectoral, and transdisciplinary approach with the goal of achieving optimal health outcomes recognizing the interconnection between people, animals, and their shared environment

Drivers of Transmission (example)



Interactions between urbanization and infectious disease are complex, with increased urbanization driving both positive and negative changes to global disease burden.

https://www.nature.com/articles/s41579-021-00639-z/figures/2

Global health

- Global health is the area of study, research, and practice that places a priority on improving health and achieving equity in health for all people worldwide. This includes reduction of disparities and protection against **global threats** that **disregard national borders**

Determinants of health

"The context of people's lives determine their health, and so blaming individuals for having poor health or crediting them for good health is inappropriate. Individuals are unlikely to be able to directly control many of the determinants of health. These determinants—or things that make people healthy or not—include the above factors, and many others:"

- The social and economic environment,
- The physical environment, and
- The person's individual characteristics and behaviors

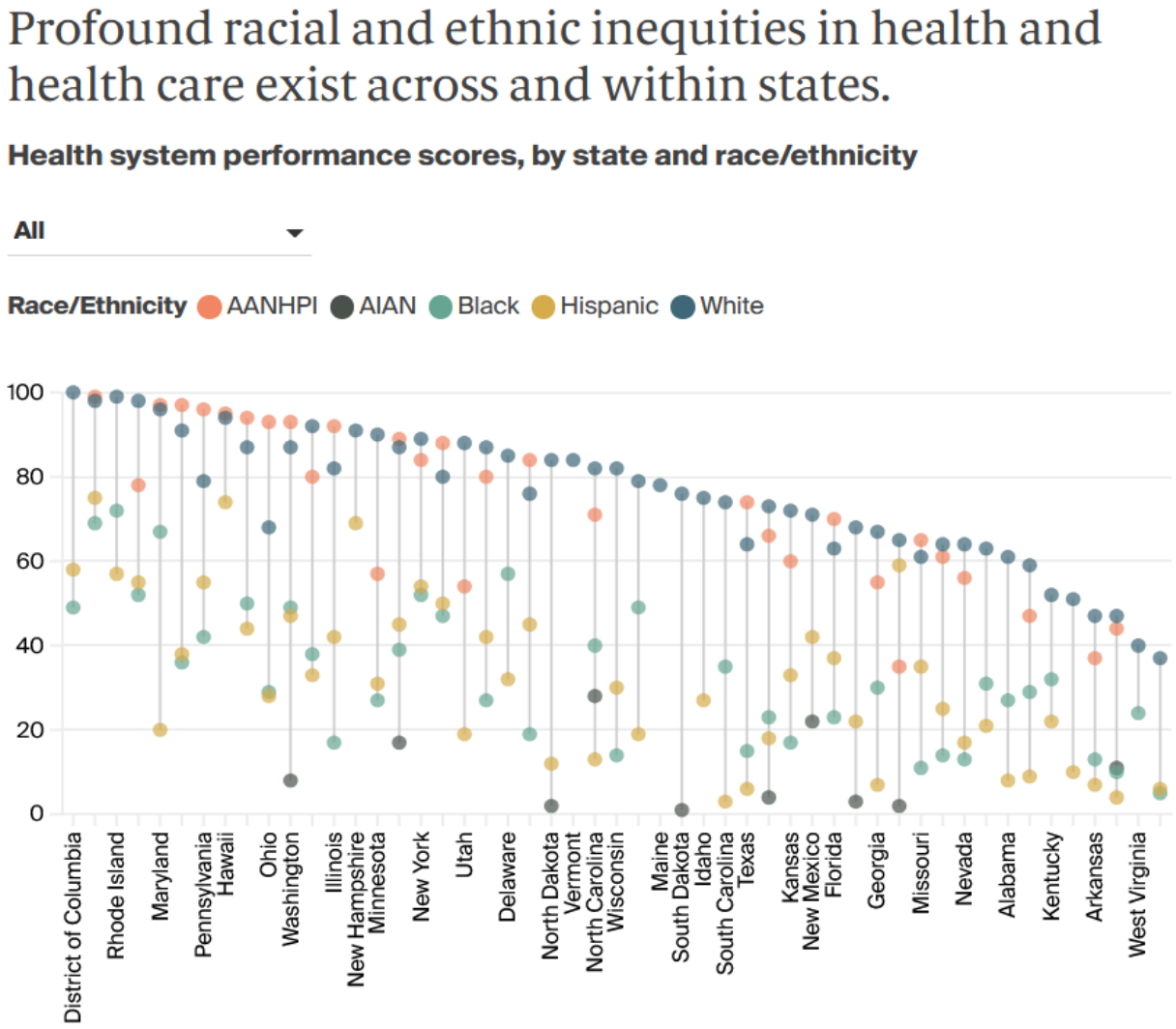
https://www.who.int/news-room/questions-and-answers/item/determinants-of-health

- **Income and social status** - higher income and social status are linked to better health. The greater the gap between the richest and poorest people, the greater the differences in health.
- **Education** – low education levels are linked with poor health, more stress and lower self-confidence.
- **Physical environment** – safe water and clean air, healthy workplaces, safe houses, communities and roads all contribute to good health. Employment and working conditions – people in employment are healthier, particularly those who have more control over their working conditions
- **Social support networks** – greater support from families, friends and communities is linked to better health. Culture - customs and traditions, and the beliefs of the family and community all affect health.
- **Genetics** - inheritance plays a part in determining lifespan, healthiness and the likelihood of developing certain illnesses. Personal behavior and coping skills – balanced eating, keeping active, smoking, drinking, and how we deal with life's stresses and challenges all affect health.
- **Health services** - access and use of services that prevent and treat disease influences health
- **Gender** - Men and women suffer from different types of diseases at different ages.

https://www.who.int/news-room/questions-and-answers/item/determinants-of-health

Unequal distribution of social, political, economic, and environmental resources contribute to health disparities and affect health equity

- What does this look like?
  - Lower literacy levels and higher dropout rates
  - Higher rates of illness and worse health outcomes
  - Lower access to healthy food
  - Higher rates of infant mortality, mental health disorders, lower life expectancy, etc.



https://www.cdc.gov/health-equity/what-is/index.html

Research Article

Microbiology and Infectious Disease

Repeated introductions and intensive community transmission fueled a mumps virus outbreak in Washington State

Louise H Moncla, Allison Black, Chas DeBolt, Misty Lang, Nicholas R Graff, Ailyn C Pérez-Osorio, Nicola F Müller, Dirk Haselow, Scott Lindquist, Trevor Bedford

Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, United States; Department of Epidemiology, University of Washington, United States; Office of Communicable Disease Epidemiology, Washington State Department of Health, United States; Arkansas Department of Health, United States

Case study: Mumps

Mumps outbreak

- “In 2016 and 2017, mumps virus swept the United States in the country’s largest outbreak since the pre-vaccine era (CDCMMWR, 2019). Washington State was heavily affected, reporting 889 confirmed and probable cases.”

https://elifesciences.org/articles/66448

Hypothesis: waning immunity?

- “Longitudinal studies (Davidkin et al., 2008), epidemiologic outbreak investigations (Cardemil et al., 2017), and epidemic models (Lewnard and Grad, 2018) suggest that mumps vaccine-induced immunity wanes over 13–30 years”

https://elifesciences.org/articles/66448

What do we know?

- “Among the infected school-aged children in Arkansas and Washington, >90% had previously received two doses of MMR vaccine (Fields et al., 2019)”
- “Unusually though, while most US outbreaks in 2016/2017 were associated with university settings…incidence in Washington was highest among children aged 10–18 years, younger than expected given waning immunity”
- “The outbreak was also peculiar in that approximately 52% of the total cases were Marshallese, an ethnic community that comprises ~0.3% of Washington’s population. These same phenomena were also observed in Arkansas.”

https://elifesciences.org/articles/66448

- “The high proportion of vaccinated cases, younger-than-expected age at infection, disproportionate impact on the Marshallese community, and epidemiologic link to Arkansas suggest that factors beyond waning immunity are necessary to explain mumps transmission during this outbreak in Washington.”

https://elifesciences.org/articles/66448

What do we know about this population?

- “Between 1947 and 1986, the United States occupied the Republic of Marshall Islands and detonated the equivalent of >7000 Hiroshima size nuclear bombs as part of its nuclear testing program (Barker, 2012).”
- “Marshallese individuals inhabiting the targeted atolls were forcibly moved to other islands, and many were exposed to nuclear fallout (Abella et al., 2019) that persists on the Islands today (Bordner et al., 2016).”
- “Significant concern remains within the community regarding long-term health impacts of nuclear exposure and its potential impacts on immune function.”

https://elifesciences.org/articles/66448

Hypotheses?

- “Marshallese individuals living on and off the Islands experience significant health disparities including a higher burden from infectious diseases and chronic health conditions
- Compounding these disparities, from 1996 to 2020 (Hirono, 2019), Marshallese individuals were specifically excluded from Medicaid eligibility despite legal residency in the US permitted under the Compact of Free Association (COFA) Treaty. As a result, many US-residing Marshallese are uninsured, with poor access to healthcare (McElfish et al., 2015).
- Marshallese households are more likely to be multigenerational and tend to be larger on average (Harris and Jones, 2005; US Census Bureau, 2021), potentially increasing the number and intensity of interactions among individuals.
- These factors combined mean that Marshallese individuals may be at increased risk of respiratory virus infection.”

https://elifesciences.org/articles/66448

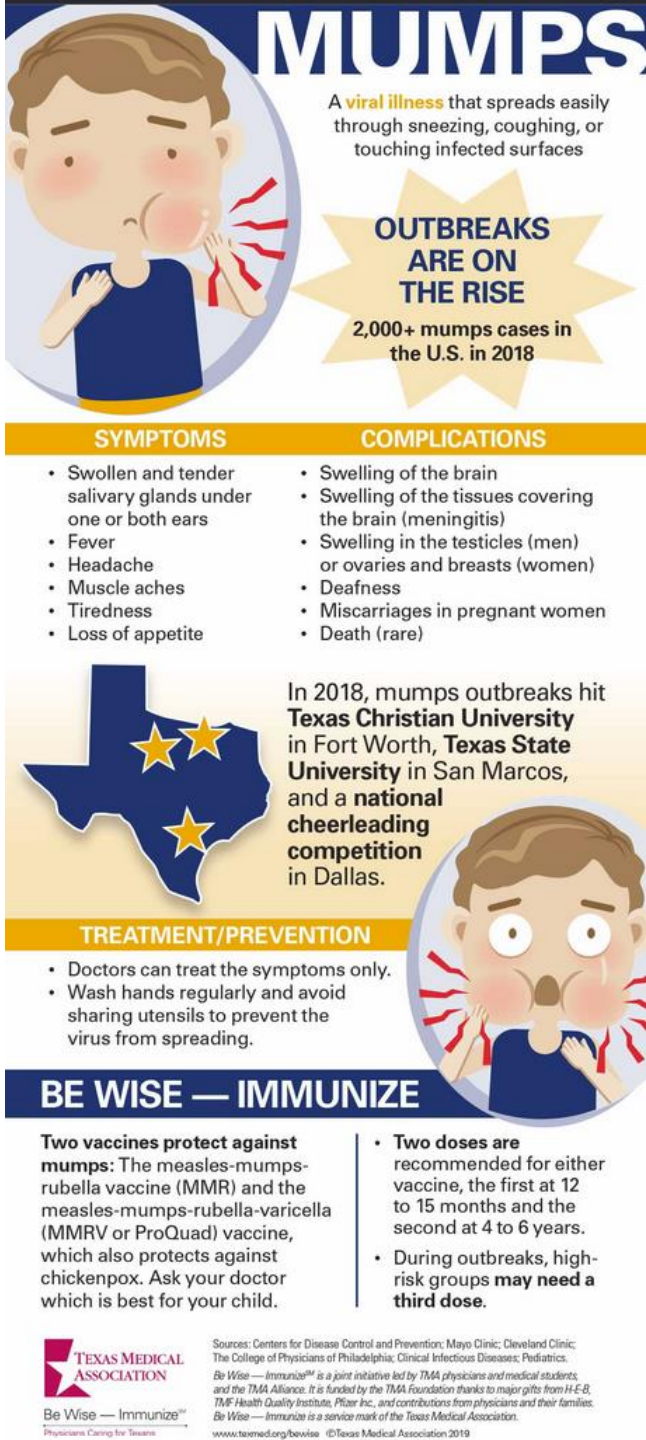
Study motivations

- “Clarifying the determinants of infectious disease transmission is important for prioritizing prevention and mitigation resources.”
- “Estimating the number and timing of viral introductions is important for estimating epidemiologic parameters and evaluating public health surveillance systems, but detecting these dynamics may be challenging with case count data alone”
- “…genomic data to clarify epidemiologic hypotheses”

https://elifesciences.org/articles/66448

What is mumps?

- Infection caused by mumps virus, a paramyxovirus
- Highly contagious
- Transmitted person-to-person through direct contact with saliva or respiratory droplets
- Causes swelling of parotid glands (between ear and jaw) or other salivary glands, usually lasts 3-7 days
- Common complications: hearing loss, meningitis, encephalitis, etc.
- No treatment, except rest and pain relief
- Prevention: measles-mumps-rubella (MMR) childhood vaccine



https://www.texmed.org/Template.aspx?id=50058

We start with a case definition

Case Classification

Suspect

- Meets the clinical criteria but does not meet laboratory or epidemiologic linkage criteria, **OR**
- Meets supportive laboratory evidence but does not meet the clinical criteria **AND** has documentation that mumps was suspected.

Probable

- Meets clinical criteria **AND** epidemiologic linkage criteria, **OR**
- Meets supportive laboratory evidence **AND**
  - Meets clinical criteria of:
    - ≥2-day duration of parotitis or other salivary gland swelling **OR**
    - a mumps-related complication

AND

- Does NOT meet epidemiologic linkage criteria**

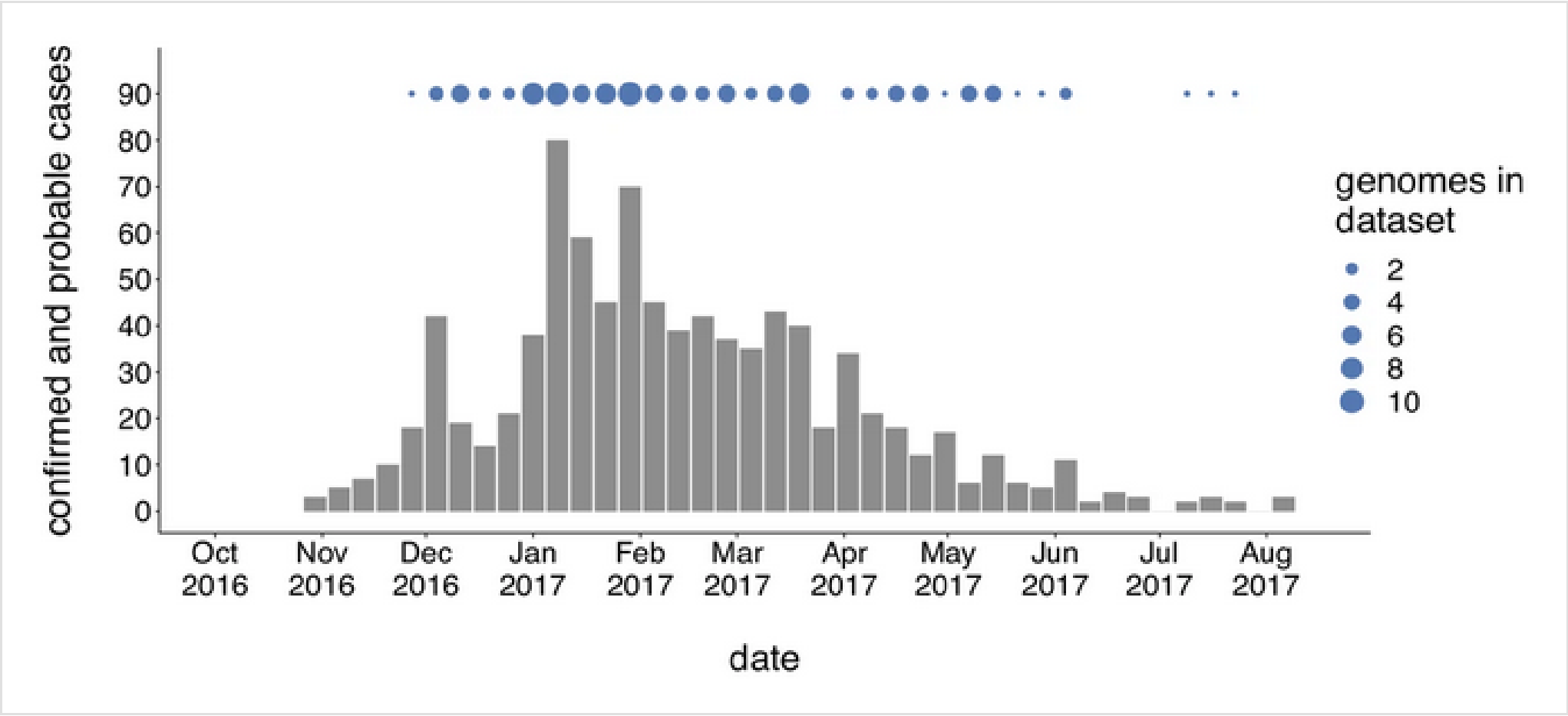
***These are considered sporadic cases.*

Confirmed

- Meets confirmatory laboratory evidence.

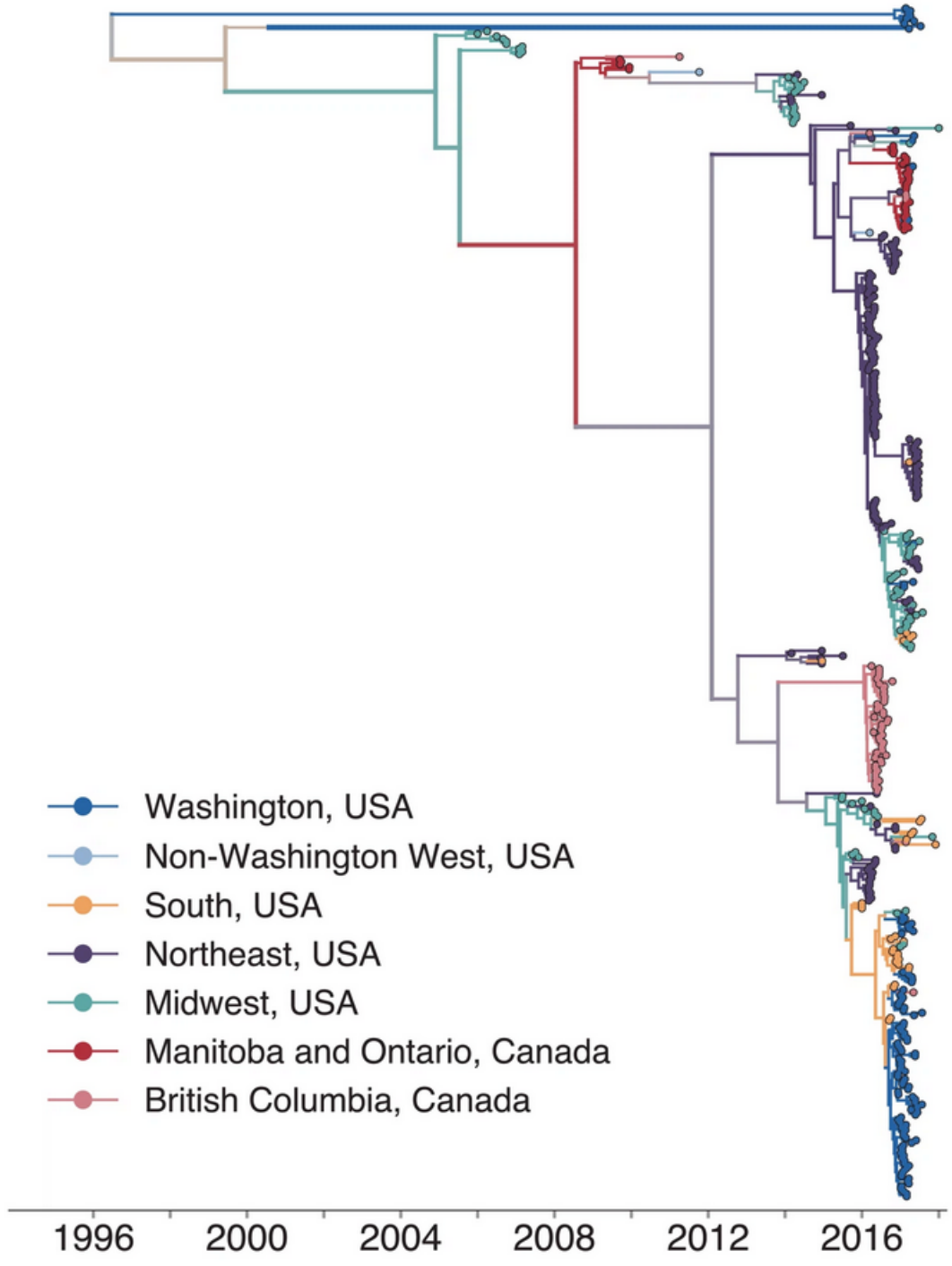
https://ndc.services.cdc.gov/case-definitions/mumps-2024/

And then an epi curve



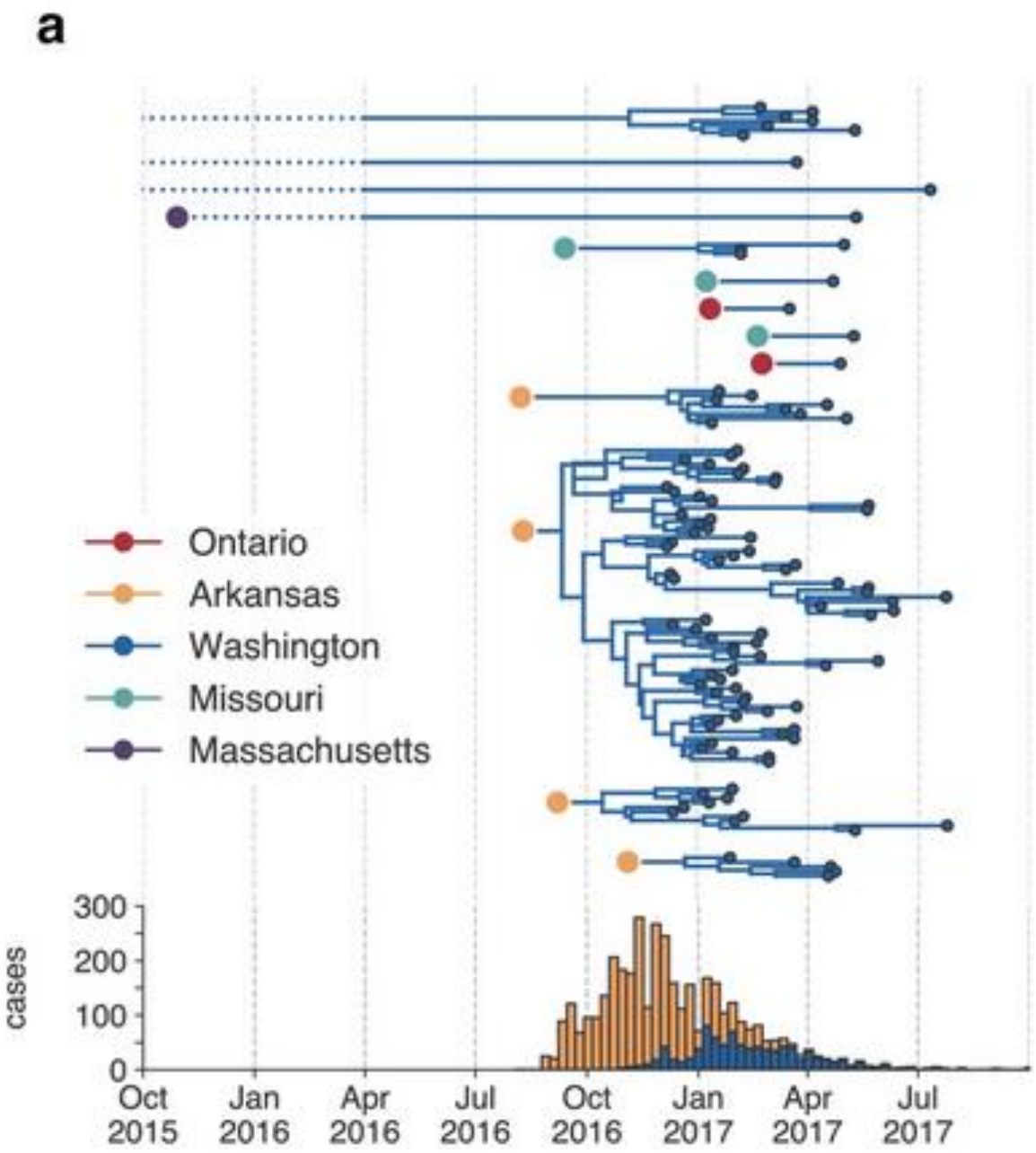
https://ndc.services.cdc.gov/case-definitions/mumps-2024/

Build a tree



https://ndc.services.cdc.gov/case-definitions/mumps-2024/

- Mumps was introduced into WA at least 13 times
- Separated each introduction into WA inferred in the tree and plotted each as its own transmission chain
- Long branch from MA? Likely missing samples
- Introductions from ON and MS led to limited onward transmission
- 4 introductions from AR led to sustained chains of transmission



https://ndc.services.cdc.gov/case-definitions/mumps-2024/

Important context in understanding transmission

- Multigenerational living is common in the Marshallese community
- Marshallese households tend to be larger on average, potentially facilitating more frequent or intense contact
- Social networks may be key risk factor for respiratory virus outbreak, even when vaccine is effective and widely used
- Infection intensity could be exacerbated by “low rates of insurance and poor access to healthcare, hesitancy to seek medical care and health disparities stemming form US occupation, nuclear testing, and exclusion from healthcare services”

https://ndc.services.cdc.gov/case-definitions/mumps-2024/

Conclusions

- “What appeared to be a single outbreak based on case surveillance data was in fact a series of multiple introductions, primarily from Arkansas, sparking overlapping and co-circulating transmission chains”
- “Transmission was overwhelmingly maintained within the Marshallese community…infections seeded into the non-Marshallese community did not sustain prolonged transmission chains”
- “Outbreaks in younger age groups may be possible in sufficiently high-contact settings. Provision of an outbreak dose of mumps-containing vaccine to high-risk groups may therefore be especially effective for limiting mumps transmission in future outbreaks”

https://ndc.services.cdc.gov/case-definitions/mumps-2024/