Enhancing Genomic Epidemiology Capacity on the Frontlines

Hayley D. Yaglom, MS, MPH

Genomics Epidemiologist

Translational Genomics Research Institute (TNorth)

NHICEP | September 16, 2022

Established April 2007
Flagstaff, AZ

We have 15-year history of applying pathogen genomics to public health and clinical medicine.

COVID-19 TGEN GENOMIC FIRST RESPONDER

Pathogen genomics is widely use in Public Health

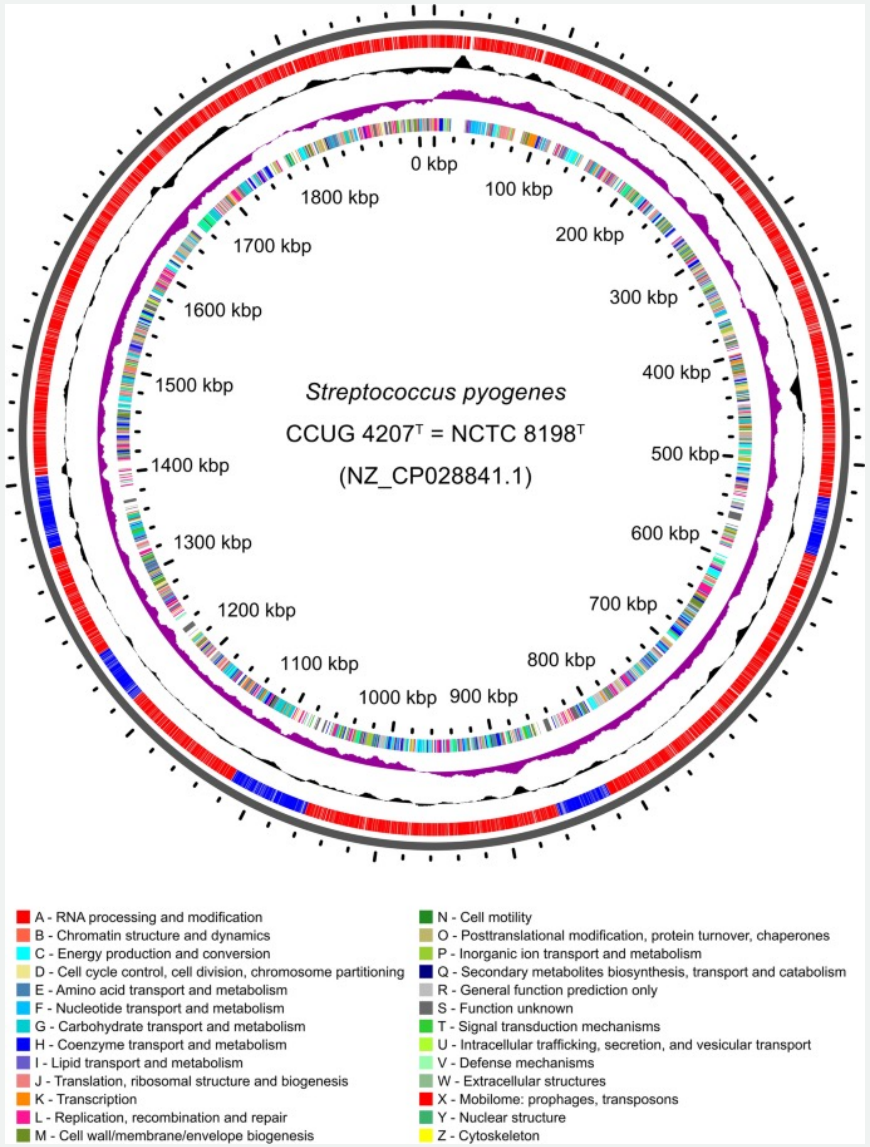
- COVID-19: track variants
- Food safety: identify and investigate outbreaks
- **Antimicrobial resistant organisms**
  - **infer resistance**
  - **better understand transmission**
- Influenza: strain surveillance
- Tuberculosis: identify and investigate clusters
- **Group A *Streptococcus:* investigate outbreaks in healthcare settings**
- Malaria: monitor resistance and other clinically important traits

NEJM 2019; 381:2569-80.

Science Behind Pathogen Genomics

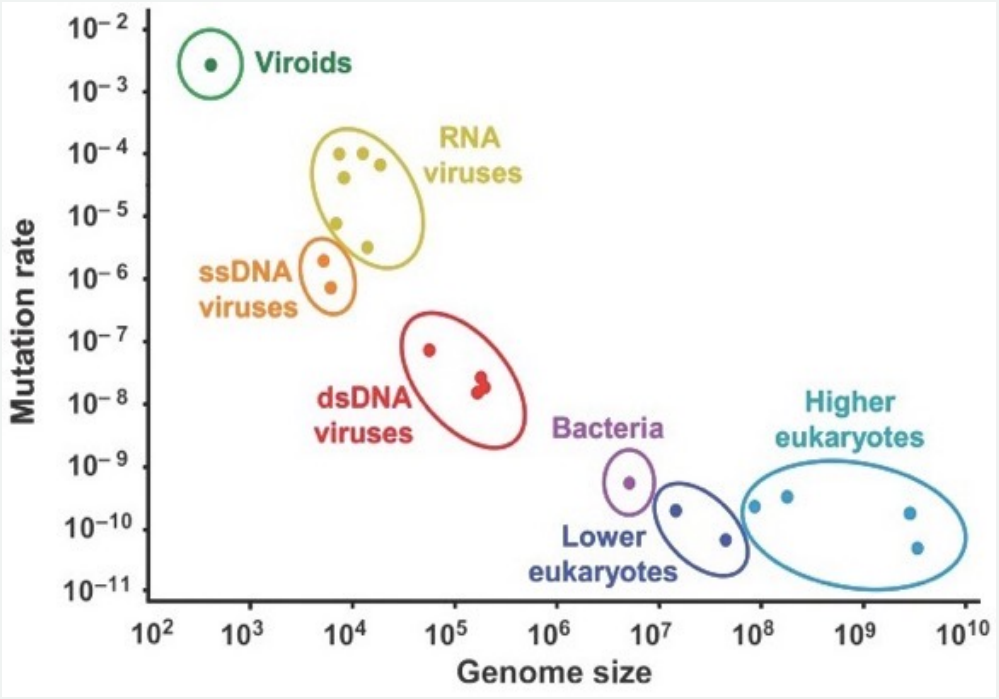
Microbial pathogens are diverse.

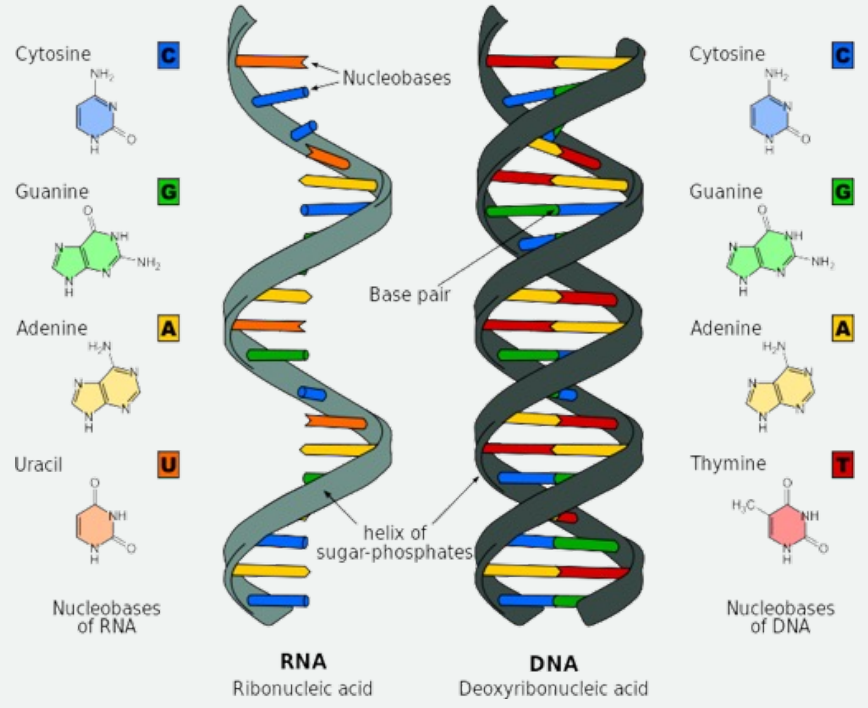
Almost every microbial pathogen has a genome.



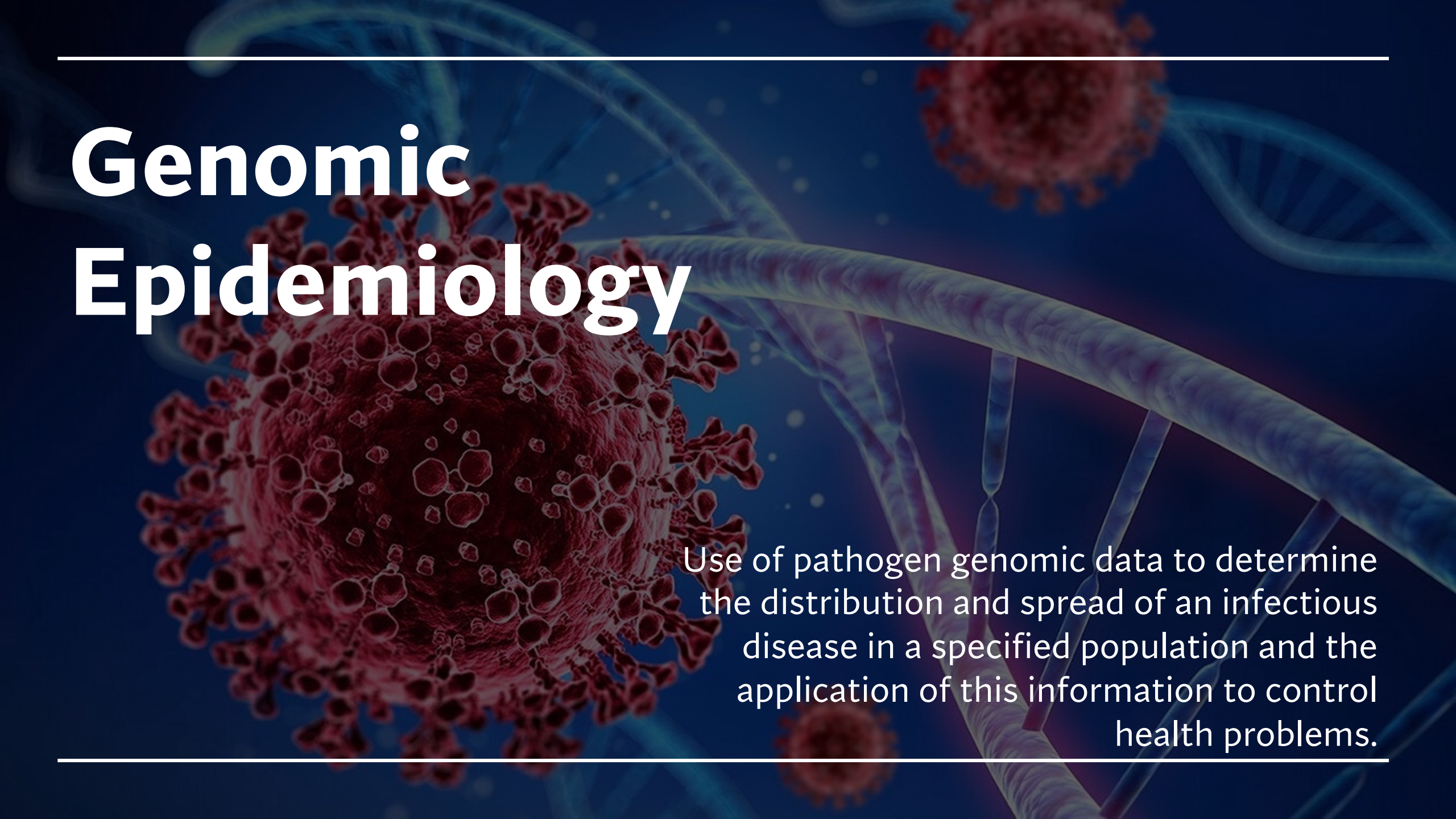
Science Behind Pathogen Genomics

Analyze DNA and RNA of important pathogens for mutations that are significant for public health and healthcare.

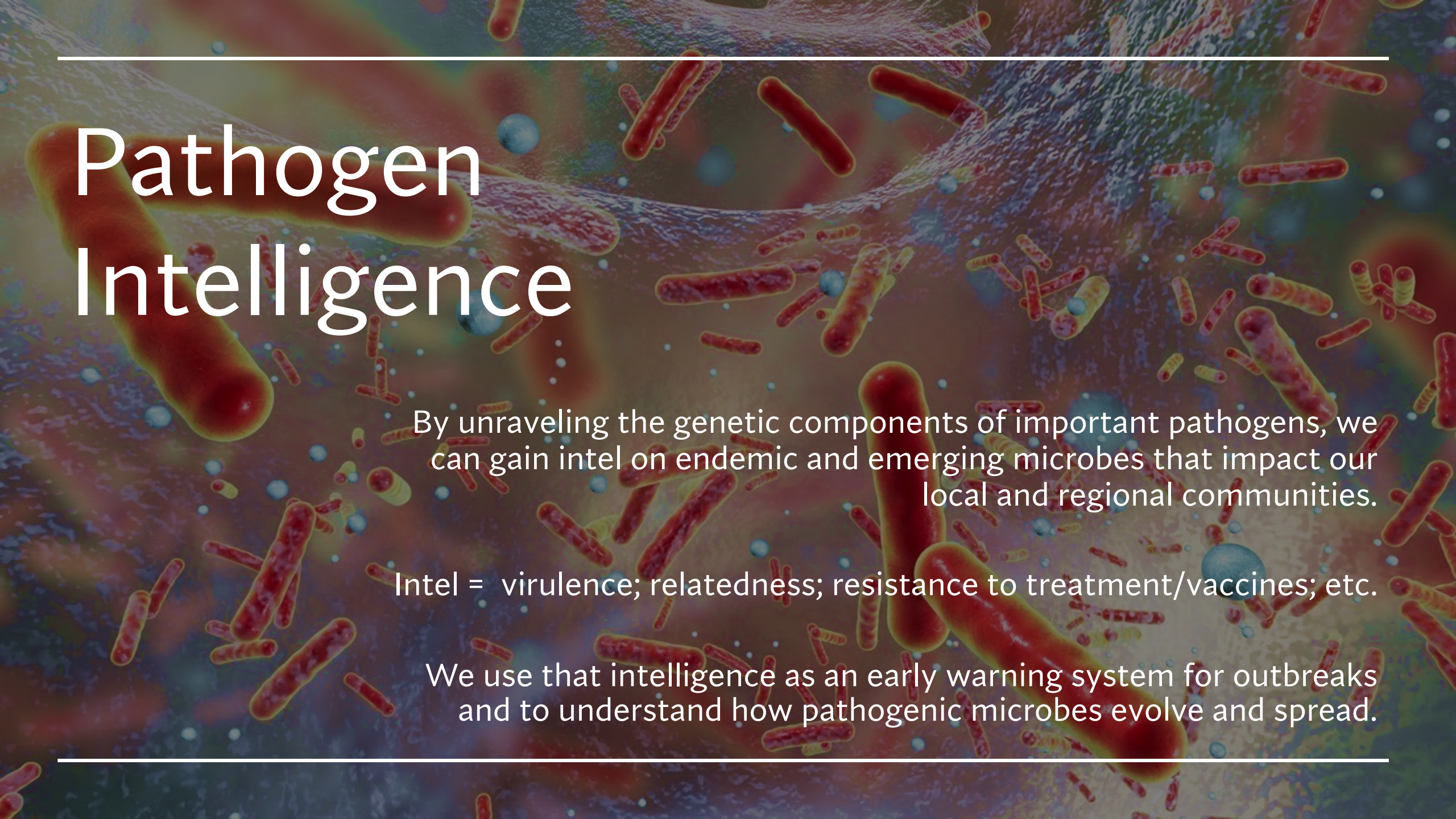




Genomic Epidemiology



Use of pathogen genomic data to determine the distribution and spread of an infectious disease in a specified population and the application of this information to control health problems.



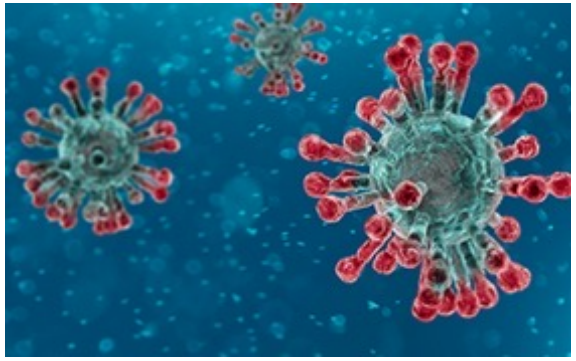
Pathogen Intelligence

By unraveling the genetic components of important pathogens, we can gain intel on endemic and emerging microbes that impact our local and regional communities.

Intel = virulence; relatedness; resistance to treatment/vaccines; etc.

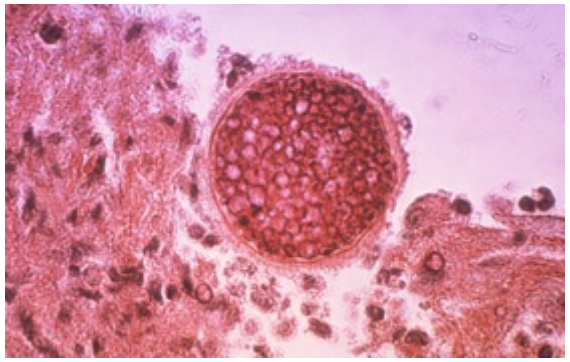
We use that intelligence as an early warning system for outbreaks and to understand how pathogenic microbes evolve and spread.

Focus Areas



Bacterial & Viral Pathogens

Fungal Pathogens



Enteric Disease Surveillance

Wastewater-based Epidemiology

Environmental Surveillance

Antibiotic Resistance

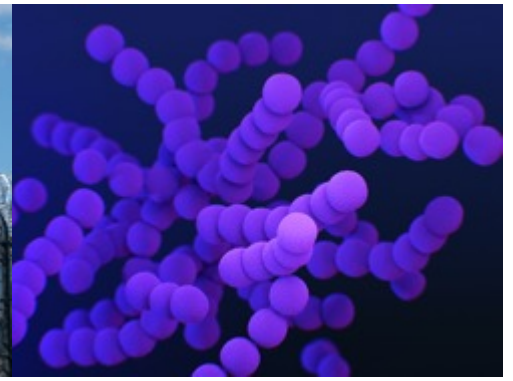
Vector-borne and Zoonotic Diseases

Focus Areas

Healthcare Epidemiology

Healthcare Associated Infections

Regional and Border Health



Special Populations (Detention Centers)

Tribal Health

Burden of Healthcare-Associated Infections

~2 million patients suffer with HAIs in the USA

Fifth leading cause of death in US acute-care hospitals

Overall direct cost to hospitals ranges from $28-45 billion

Costs increase with AMR microorganisms

Critical Pathogens

Acinetobacter

Burkholderia cepacia

Candida auris

Clostridioides difficile

Enterobacterales (carbapenem-resistance)

ESBL-producing Enterobacterales

Klebsiella

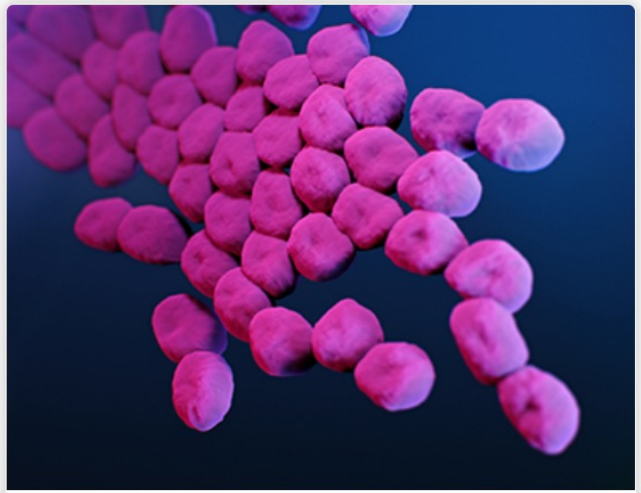
Methicillin-resistant *Staphylococcus aureus* (MRSA)

Pseudomonas aeruginosa

Vancomycin-resistant Enterococci (VRE)

Report provides the latest **antibiotic resistance burden estimates (infections and deaths)** for human health in the United States, including a list of **18 germs listed on level of concern to human health—urgent, serious, and concerning.**

www.cdc.gov/DrugResistance/Biggest-Threats

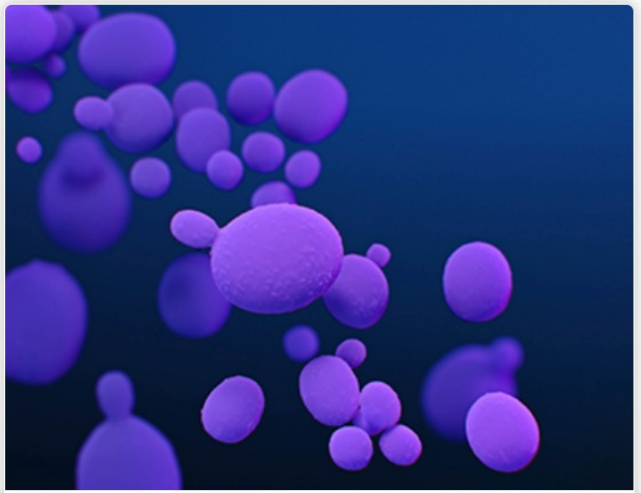


Carbapenem-resistant *Acinetobacter*

Acinetobacter bacteria causes pneumonia and wound, bloodstream, and urinary tract infections. Nearly all infections happen in patients who recently received care in a healthcare facility.

8,500 estimated cases in hospitalized patients in 2017

700 estimated deaths in 2017



Drug-resistant *Candida auris*

C. auris is an emerging multidrug-resistant yeast (fungi). It can cause severe infections and spreads easily between hospitalized patients and nursing home residents.

323 clinical cases in 2018

Clostridioides difficile

C. difficile, or *C. diff*, bacteria causes life-threatening diarrhea and colitis (an inflammation of the colon), mostly in people who have had both recent medical care and antibiotics.

223,900 infections per year

12,800 deaths per year

Carbapenem-resistant Enterobacterales (CRE)

CRE bacteria are a major concern for patients in healthcare facilities. Some Enterobacterales are resistant to nearly all antibiotics, leaving more toxic or less effective treatment options.

- **1,100** estimated deaths in 2017
- **13,100** estimated cases in hospitalized patients in 2017

Drug-resistant Gonorrhea

Gonorrhea is caused by the bacteria *Neisseria gonorrhoeae*. It is a sexually transmitted disease that can result in life-threatening ectopic pregnancy and infertility, and can increase the risk of getting and giving HIV.

- **550,000** estimated drug-resistant infections per year

Infection Control & Hospital Epidemiology

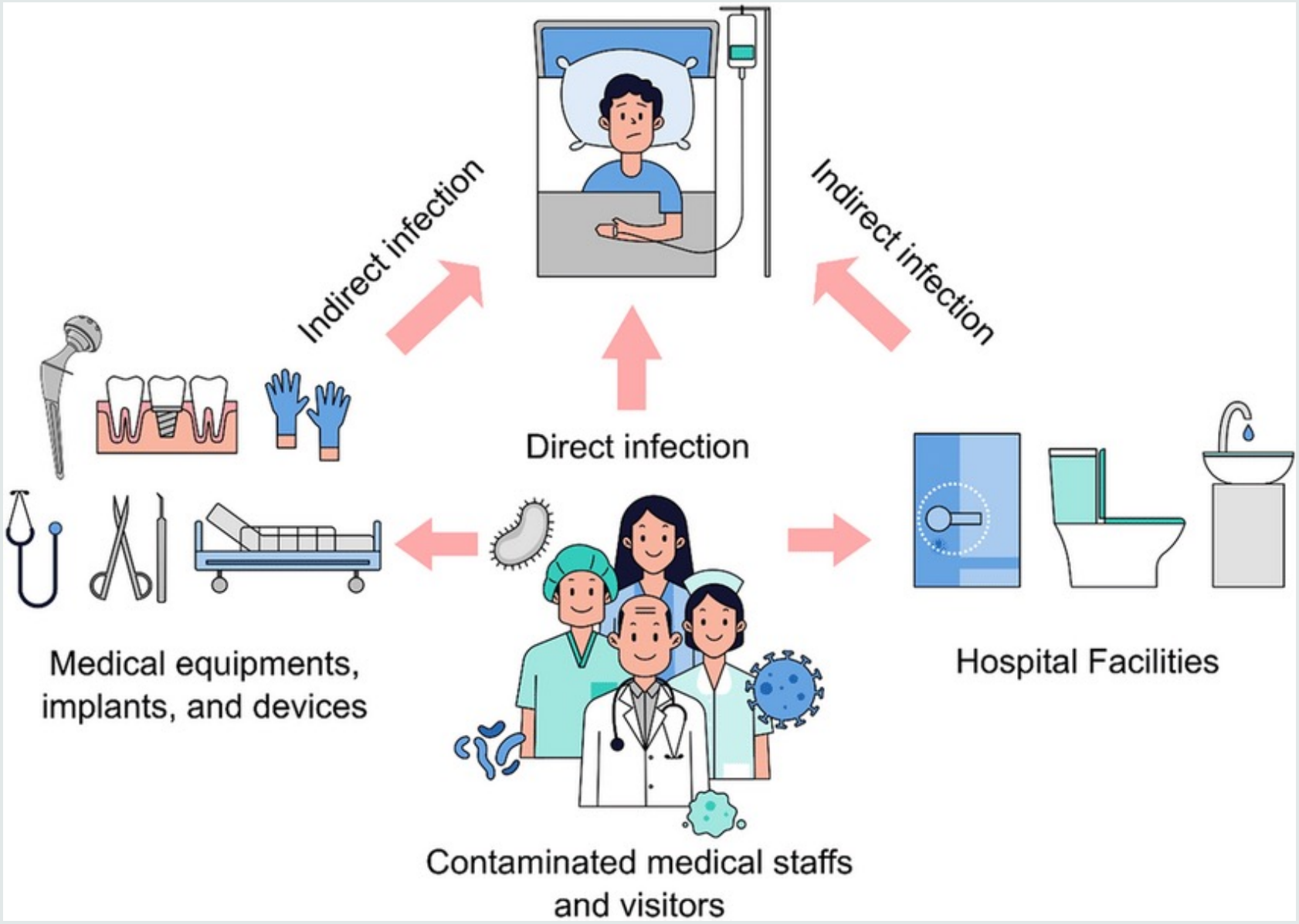
Volume 43, No 8
August 2022

ICHE

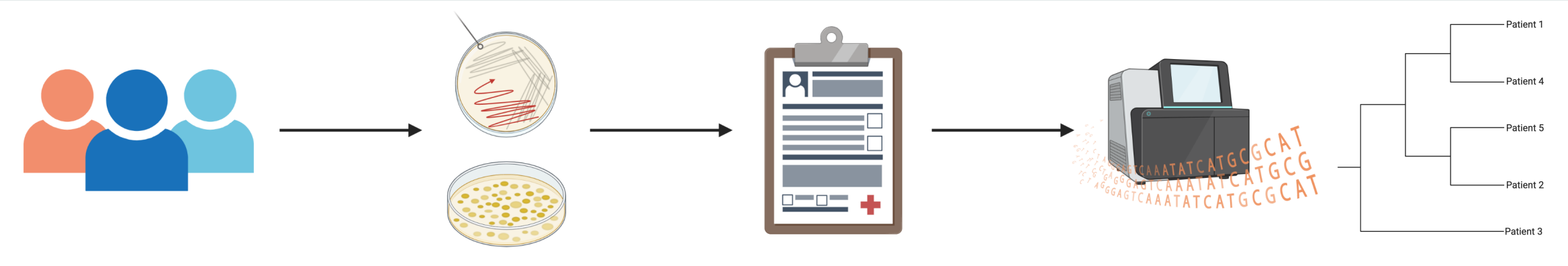
Artist: Lona Mody

SHEA
The Society for Healthcare Epidemiology of America

CAMBRIDGE UNIVERSITY PRESS


Indirect infection
Indirect infection
Direct infection
Medical equipments, implants, and devices
Contaminated medical staffs and visitors
Hospital Facilities

How can genomics be useful in the healthcare setting?



How can genomics be useful in the healthcare setting?

Is it always clear how cases are related?

Or what the source is?

Or if transmission in the facility really occurred?

Are cases identified months earlier or months later a part of the cluster/outbreak?

What if the genomics came first, identified clusters of cases early, and informed the infection prevention response?

RESEARCH Open Access

Whole genome SNP typing to investigate methicillin-resistant *Staphylococcus aureus* carriage in a health-care provider as the source of multiple surgical site infections

Chandler C. Roe[1*], Kimberly S. Horn[2], Elizabeth M. Driebe[1], Jolene Bowers[1], Joel A. Terriquez[2], Paul Keim[1] and David M. Engelthaler[1]

Abstract

Background: Prevention of nosocomial transmission of infections is a central responsibility in the healthcare environment, and accurate identification of transmission events presents the first challenge. Phylogenetic analysis based on whole genome sequencing provides a high-resolution approach for accurately relating isolates to one another, allowing precise identification or exclusion of transmission events and sources for nearly all cases. We sequenced 24 methicillin-resistant *Staphylococcus aureus* (MRSA) genomes to retrospectively investigate a suspected point source of three surgical site infections (SSIs) that occurred over a one-year period. The source of transmission was believed to be a surgical team member colonized with MRSA, involved in all surgeries preceding the SSI cases, who was subsequently decolonized. Genetic relatedness among isolates was determined using whole genome single nucleotide polymorphism (SNP) data.

Results: Whole genome SNP typing (WGST) revealed 283 informative SNPs between the surgical team member's isolate and the closest SSI isolate. The second isolate was 286 and the third was thousands of SNPs different, indicating the nasal carriage strain from the surgical team member was not the source of the SSIs. Given the mutation rates estimated for *S. aureus,* none of the SSI isolates share a common ancestor within the past 16 years, further discounting any common point source for these infections. The decolonization procedures and resources spent on the point source infection control could have been prevented if WGST was performed at the time of the suspected transmission, instead of retrospectively.

Conclusions: Whole genome sequence analysis is an ideal method to exclude isolates involved in transmission events and nosocomial outbreaks, and coupling this method with epidemiological data can determine if a transmission event occurred. These methods promise to direct infection control resources more appropriately.

Keywords: Nasal carriage, Surgical site infections, MRSA, Transmission, Whole genome sequencing

MRSA in Surgeon & Patients with SSI

- 24 MRSA isolates were sequenced to retrospectively investigate a suspected point source of three surgical site infections that occurred over 1 year.
- Source was believed to be a surgical team member colonized with MRSA.
- Phylogenetic analysis revealed that the surgical team member was not the source of numerous surgical site infections.

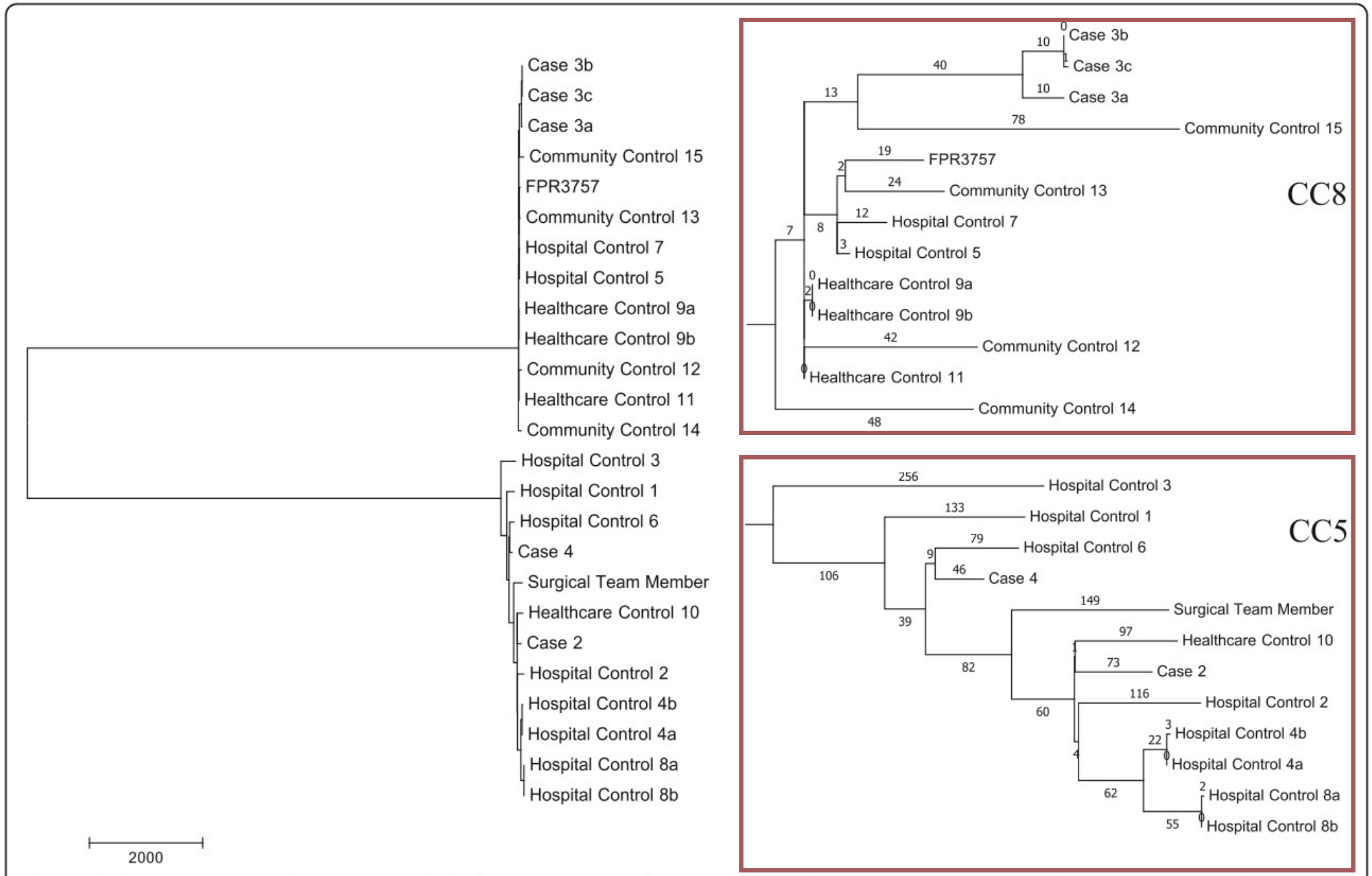
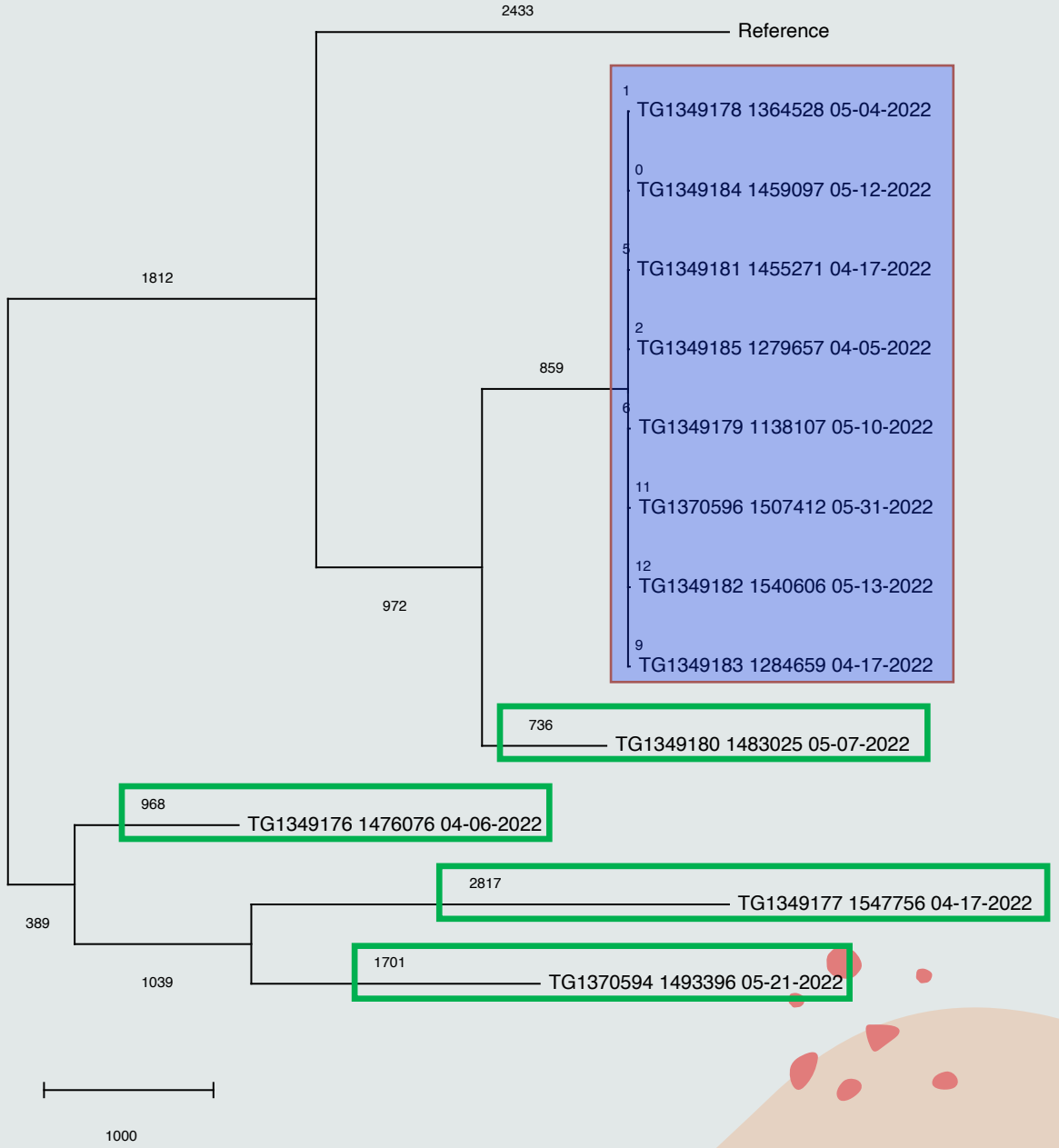


Fig. 1 Phylogenetic SNP analysis. Unrooted phylogenetic SNP analysis based on whole genome sequence data of 24 MRSA isolates using the maximum parsimony algorithm

Suspected VRE Outbreak

- >25 cases of VRE in a 7-month timeframe
- No clear epidemiologic or clinical links between patients
- 13 isolates received for sequencing
- 4 isolates are not related – green
- There is an evolving and circulating strain of VRE in the hospital, but no indication of direct patient to patient transmission or a single source of infection.



Genomics in Other HAI Outbreaks

Multistate Outbreak of *Burkholderia cepacia* Infections Associated with Contaminated Ultrasound Gel

Background

CDC is assisting the Food and Drug Administration (FDA) and several state and local health departments with an ongoing investigation of *Burkholderia cepacia* complex (Bcc) infections in healthcare facilities. Patients have developed Bcc infections, including bloodstream infections, after likely having undergone ultrasound-guided procedures in which **MediChoice® M500812 ultrasound gel** was used.

MediChoice® M500812 ultrasound gel was likely used to guide ultrasonography in preparation for or du

- placement of central and peripheral intravenous catheters, and
- transcutaneous procedures, such as paracentesis.

RESEARCH ARTICLE

NOSOCOMIAL INFECTION

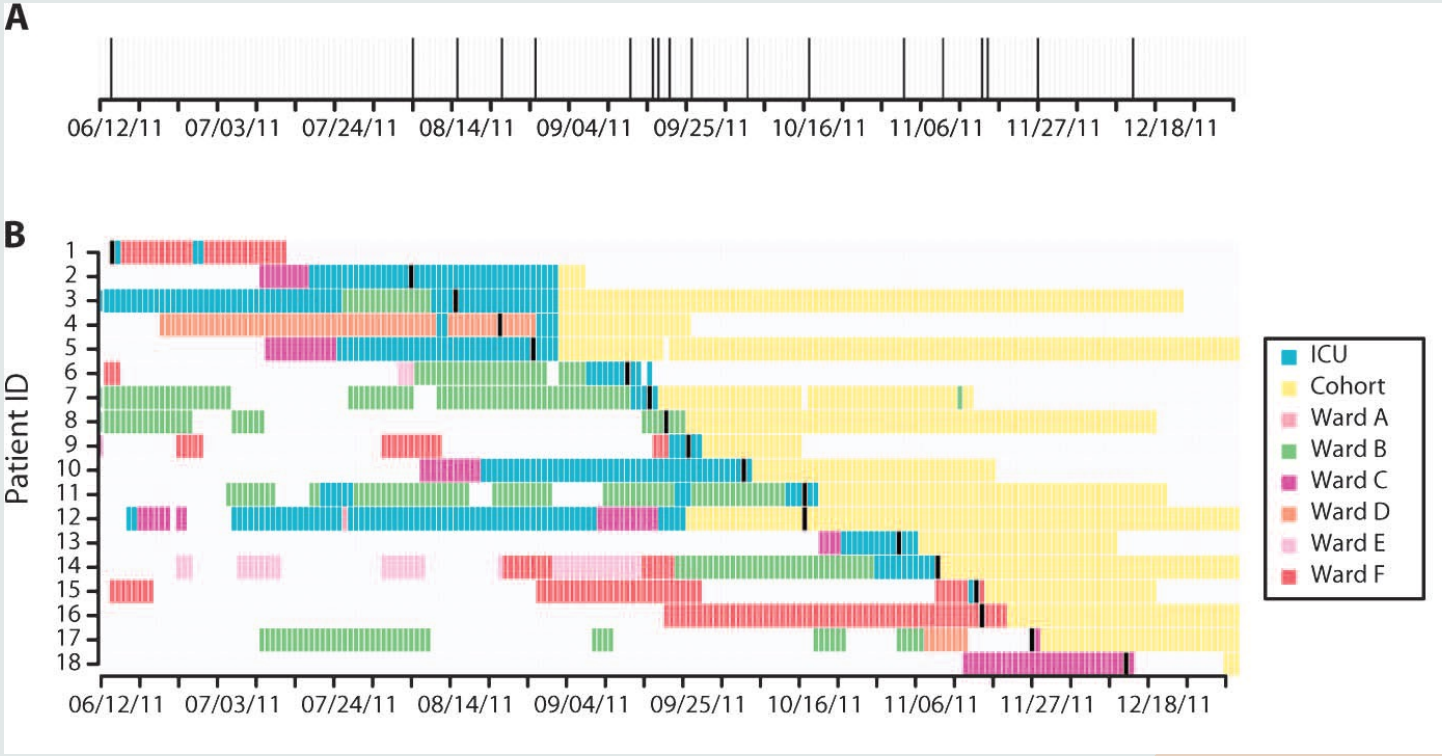
Tracking a Hospital Outbreak of Carbapenem-Resistant *Klebsiella pneumoniae* with Whole-Genome Sequencing

Evan S. Snitkin,[1] Adrian M. Zelazny,[2] Pamela J. Thomas,[1] Frida Stock,[2] NISC Comparative Sequencing Program,[3] David K. Henderson,[2] Tara N. Palmore,[2]* Julia A. Segre[1]*

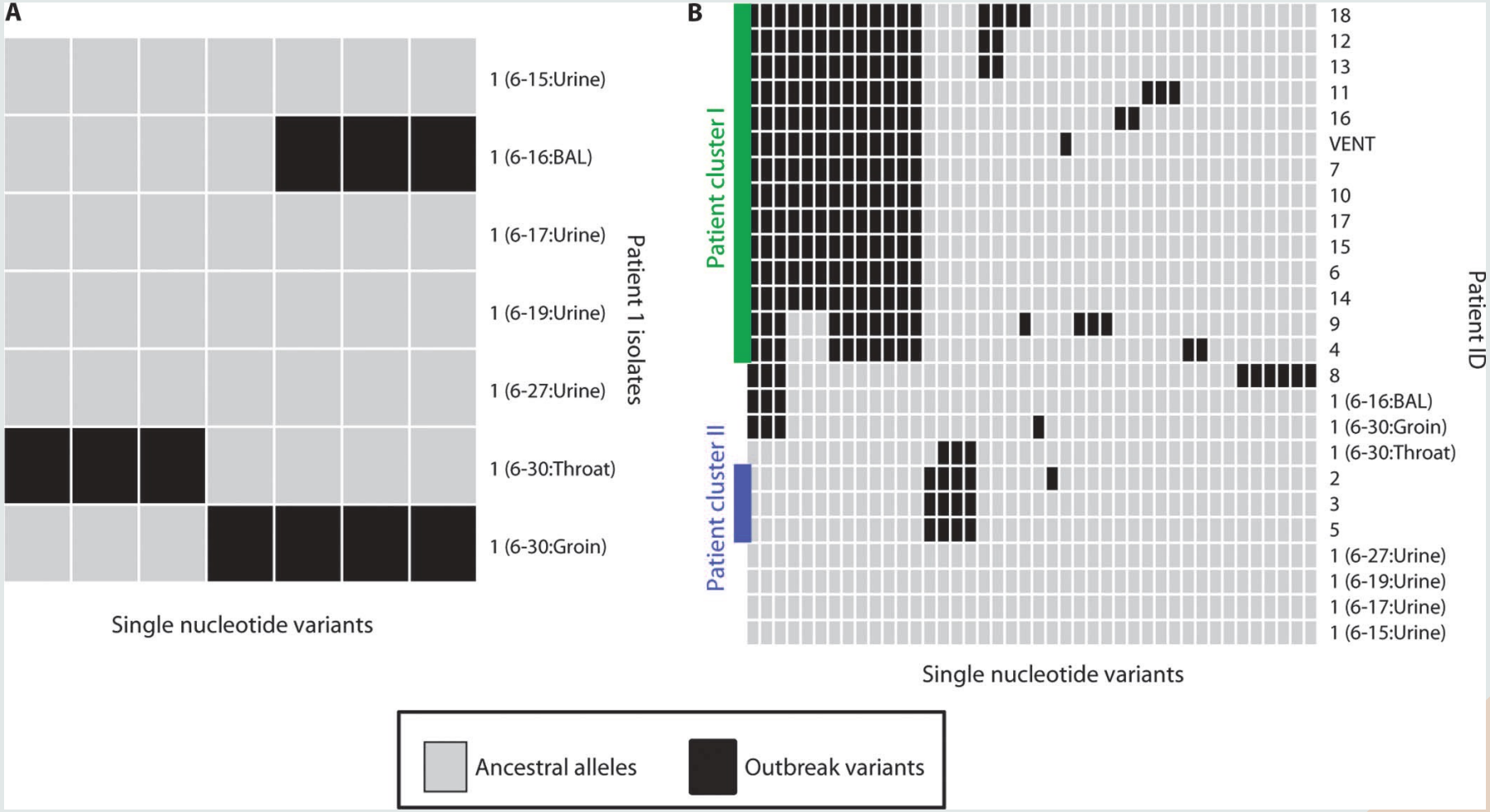
The Gram-negative bacteria *Klebsiella pneumoniae* is a major cause of nosocomial infections, primarily among immunocompromised patients. The emergence of strains resistant to carbapenems has left few treatment options, making infection containment critical. In 2011, the U.S. National Institutes of Health Clinical Center experienced an outbreak of carbapenem-resistant *K. pneumoniae* that affected 18 patients, 11 of whom died. Whole-genome sequencing was performed on *K. pneumoniae* isolates to gain insight into why the outbreak progressed despite early implementation of infection control procedures. Integrated genomic and epidemiological analysis traced the outbreak to three independent transmissions from a single patient who was discharged 3 weeks before the next case became clinically apparent. Additional genomic comparisons provided evidence for unexpected transmission routes, with subsequent mining of epidemiological data pointing to possible explanations for these transmissions. Our analysis demonstrates that integration of genomic and epidemiological data can yield actionable insights and facilitate the control of nosocomial transmission.

Hospital Outbreak of Carbapenem-Resistant Klebsiella pneumoniae

- June 13 – patient 1 was transferred to ICU from a previous hospital and discharged on July 15
- Patient 1 colonized with CRE – placed in enhanced contact isolation, PPE for staff/visitors
- August 5 – CRE cultured from tracheal aspirate of patient 2



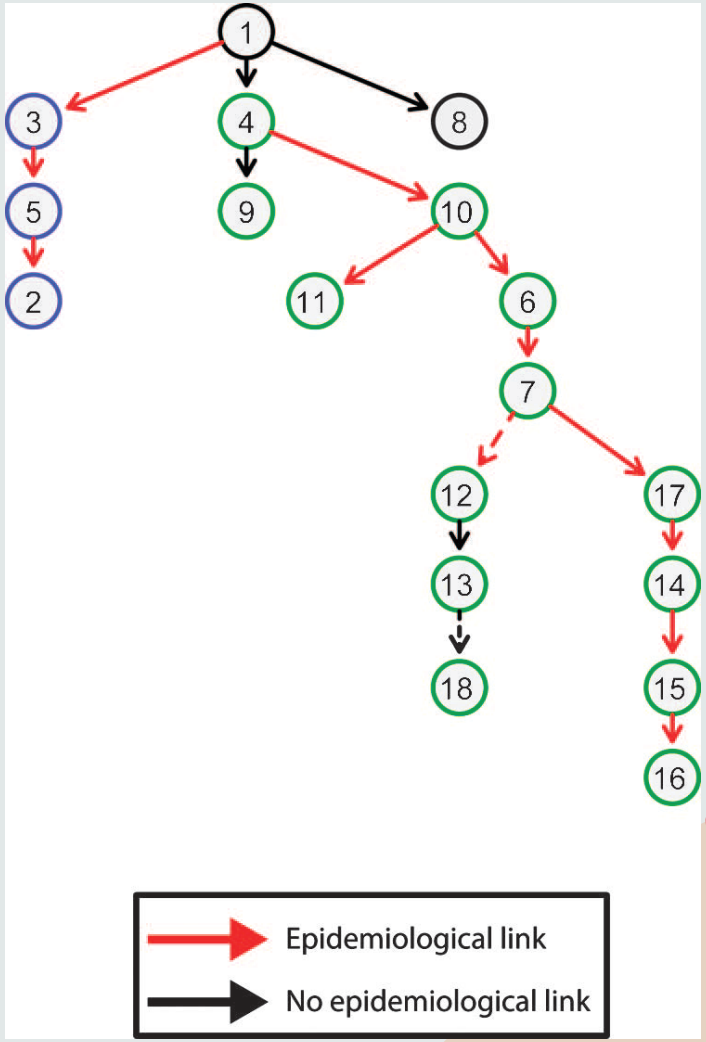
Hospital Outbreak of Carbapenem-Resistant Klebsiella pneumoniae



Hospital Outbreak of Carbapenem-Resistant Klebsiella pneumoniae

1. Genetically distinct isolates from patient 1 were transmitted to other patients.

2. Not only is patient 1 linked to the outbreak but also three independent transmission events from this patient led to hospital-wide dissemination of the outbreak strain.



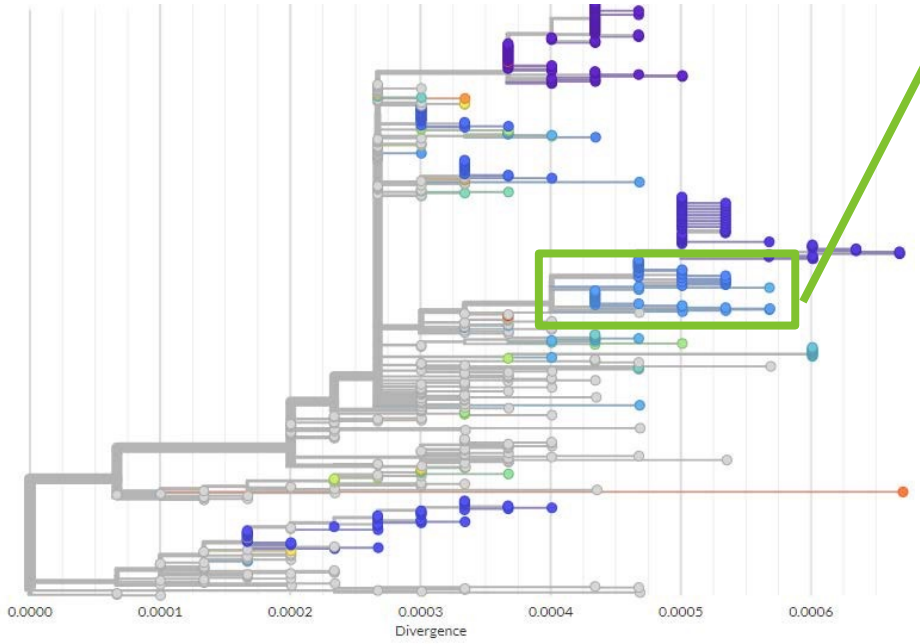
COVID-19 outbreaks at two skilled nursing facilities

- 2 skilled nursing facilities in the same metropolitan area contacted the Minnesota Department of Health (MDH) after identifying confirmed COVID-19 cases in residents and health care personnel (HCP)
  - Facility A
  - Facility B
- During April – June 2020, facility-wide, serial testing was implemented at both facilities to:
  - Identify residents with SARS-CoV-2 infection
  - Inform mitigation efforts

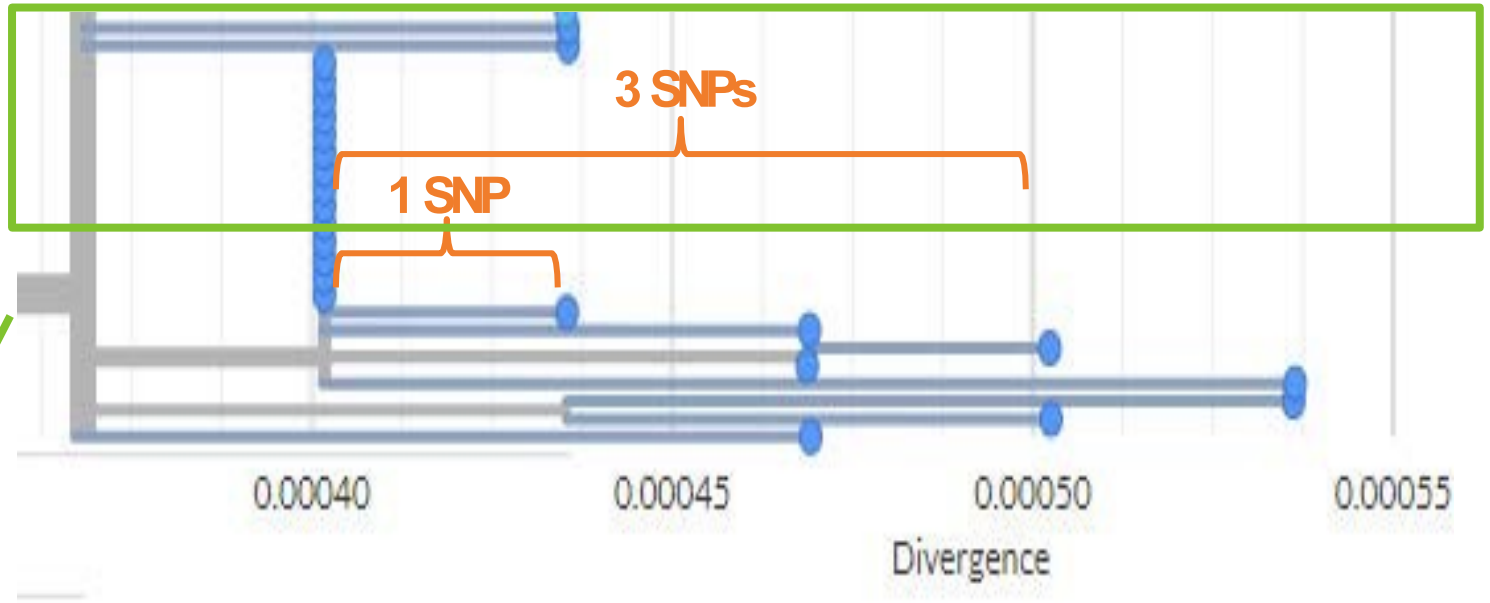
Cases whose samples were sequenced

- **Facility A**
  - 18 (35%) residents' specimens were sequenced
  - 6 (18%) HCP's specimens were sequenced
- **Facility B**
  - 75 (66%) residents' specimens were sequenced
  - 5 (7%) HCP's specimens were sequenced

Phylogenetic tree of SARS-CoV-2 case genomes



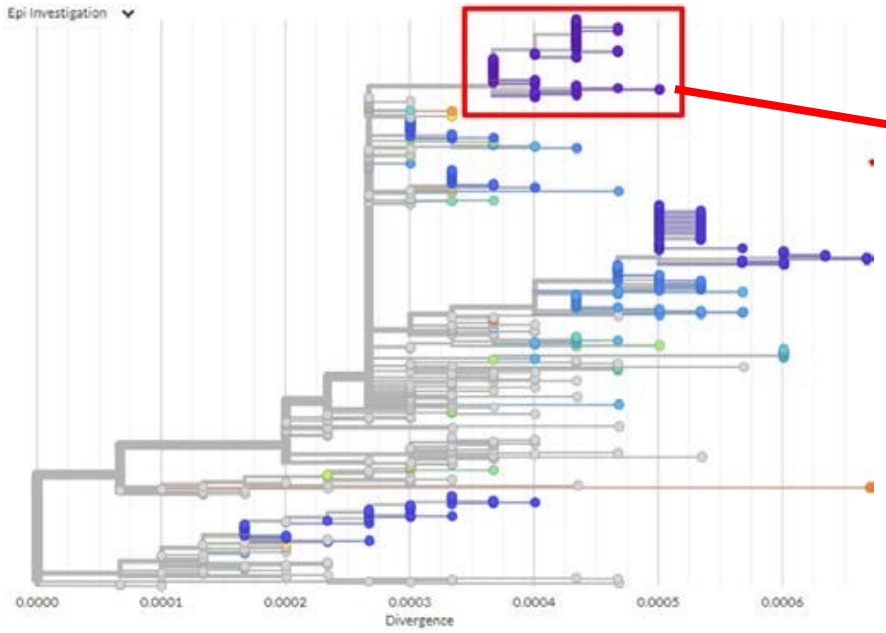
Facility A

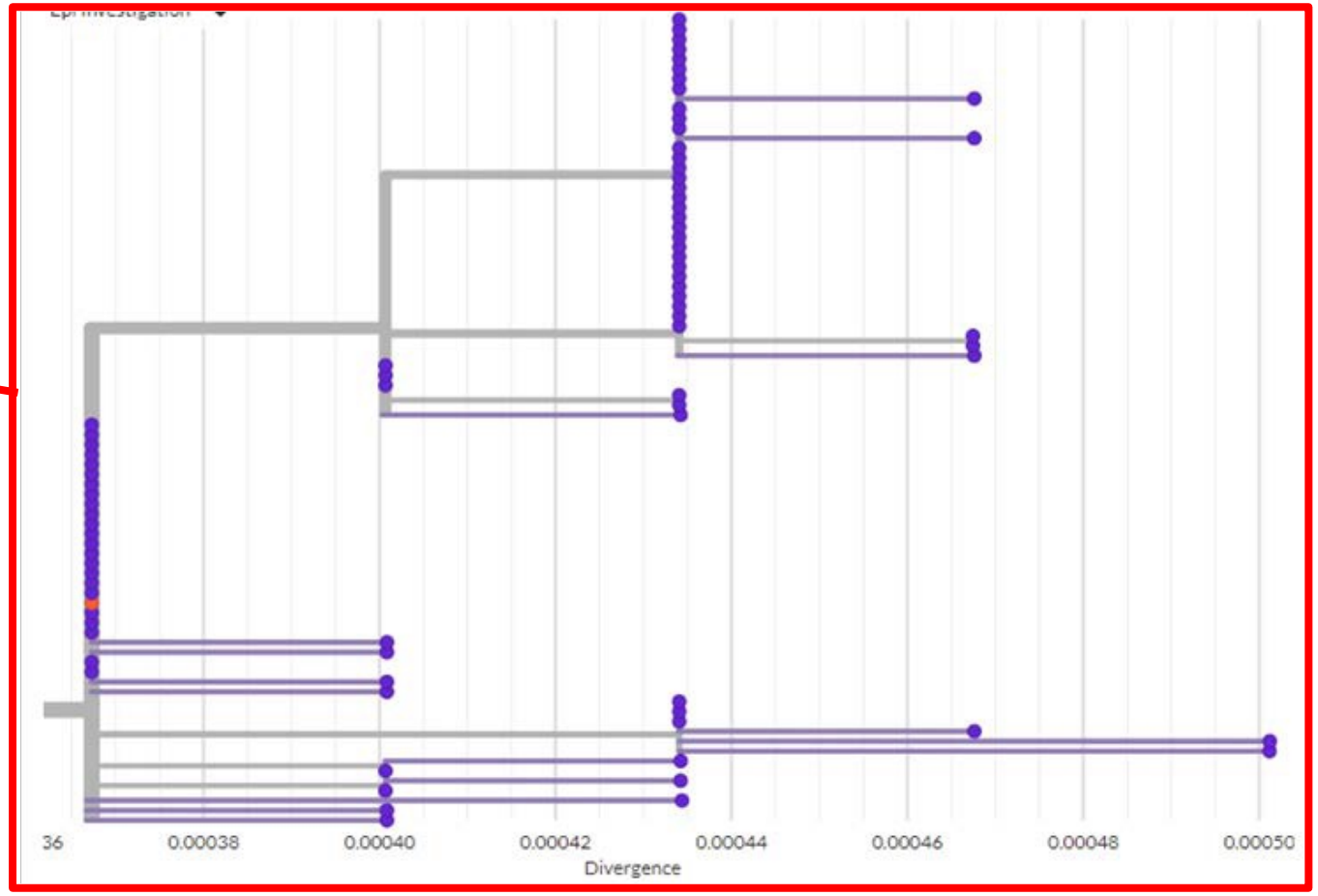


Trees drawn with Nextstrain

Phylogenetic tree of SARS-CoV-2 case genomes

Facility B





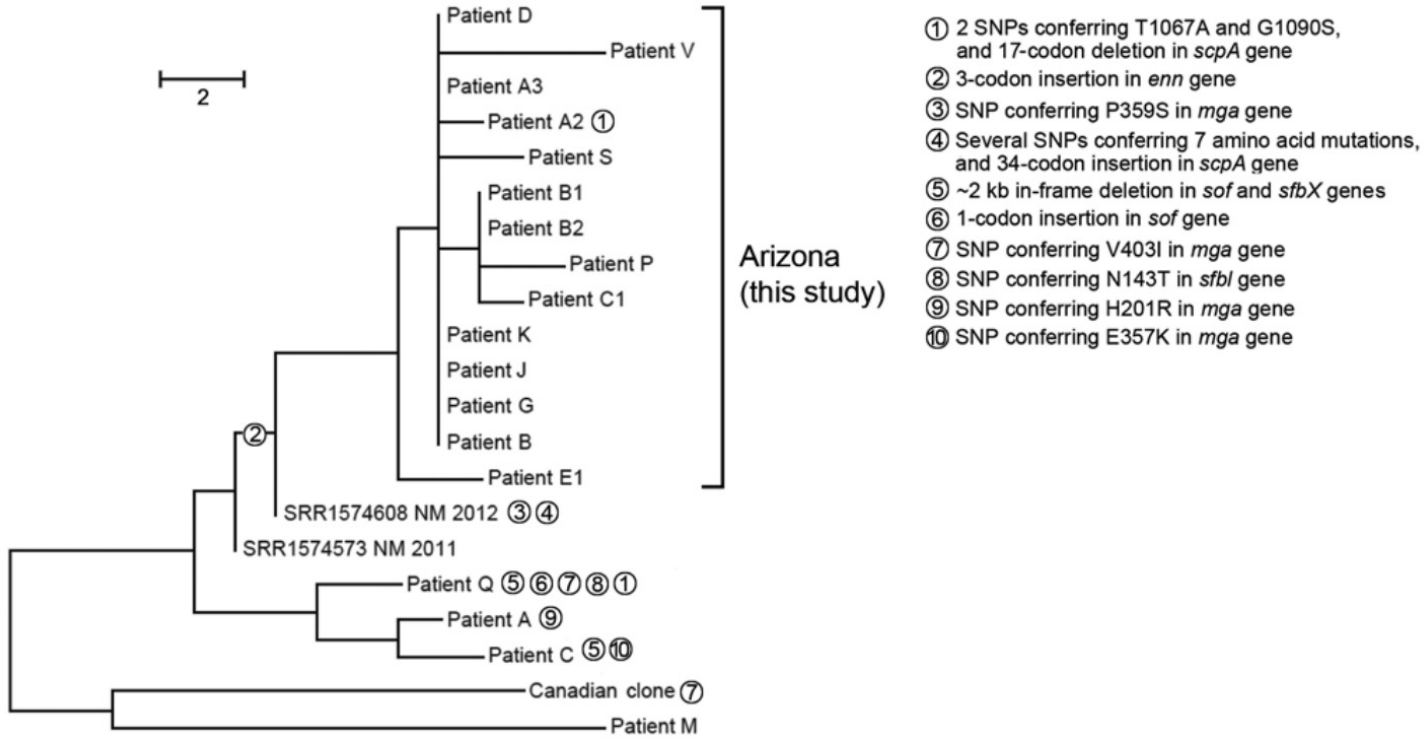
Invasive Group A Strep *emm59*

The hypervirulent *emm59* genotype of invasive group A *Streptococcus* was identified in Northern Arizona. This strain was eventually associated with a homeless shelter and a local jail outbreak.

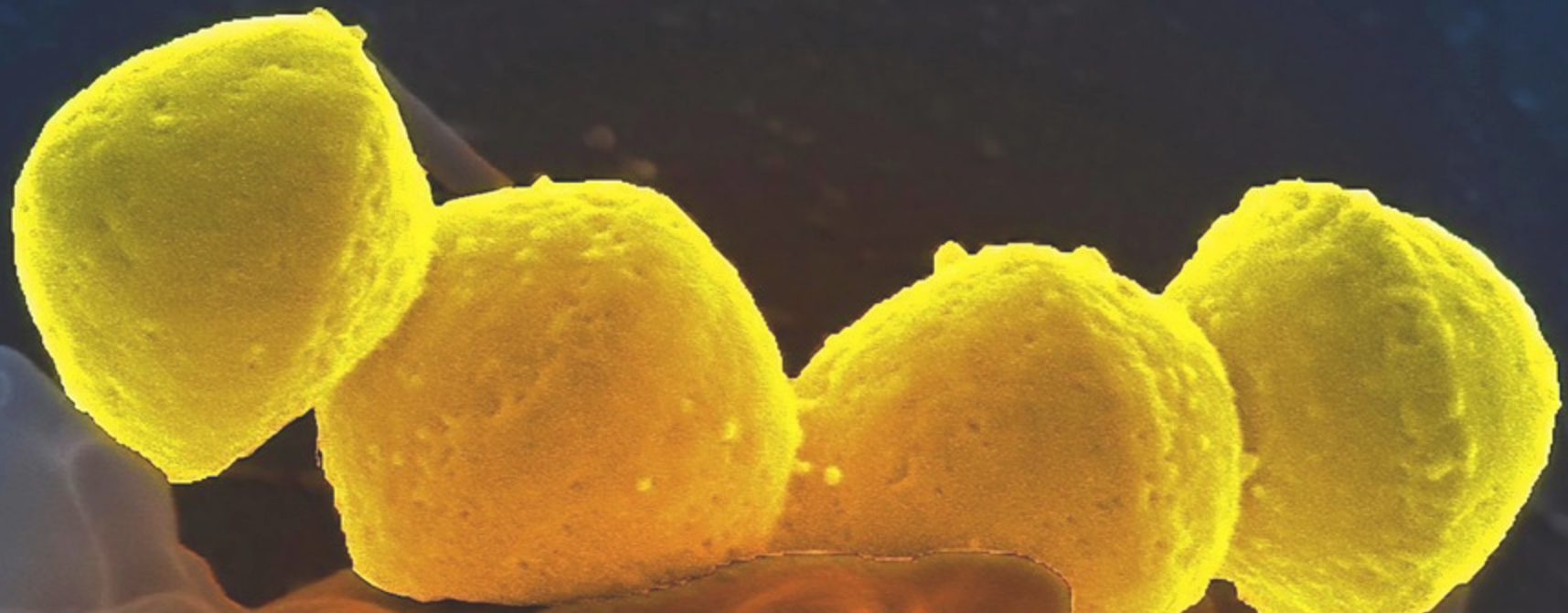
Outbreak of Hypervirulent Strain of emm59 - 2015

Genomic sequencing and phylogenetic analysis revealed a distinct clone consisting of 14/18 emm59 isolates that were separated by 0-4 SNP's, supporting the presence of an ongoing outbreak.

These individuals were also epidemiologically linked, providing further evidence of transmission of the emm59 iGAS clone.

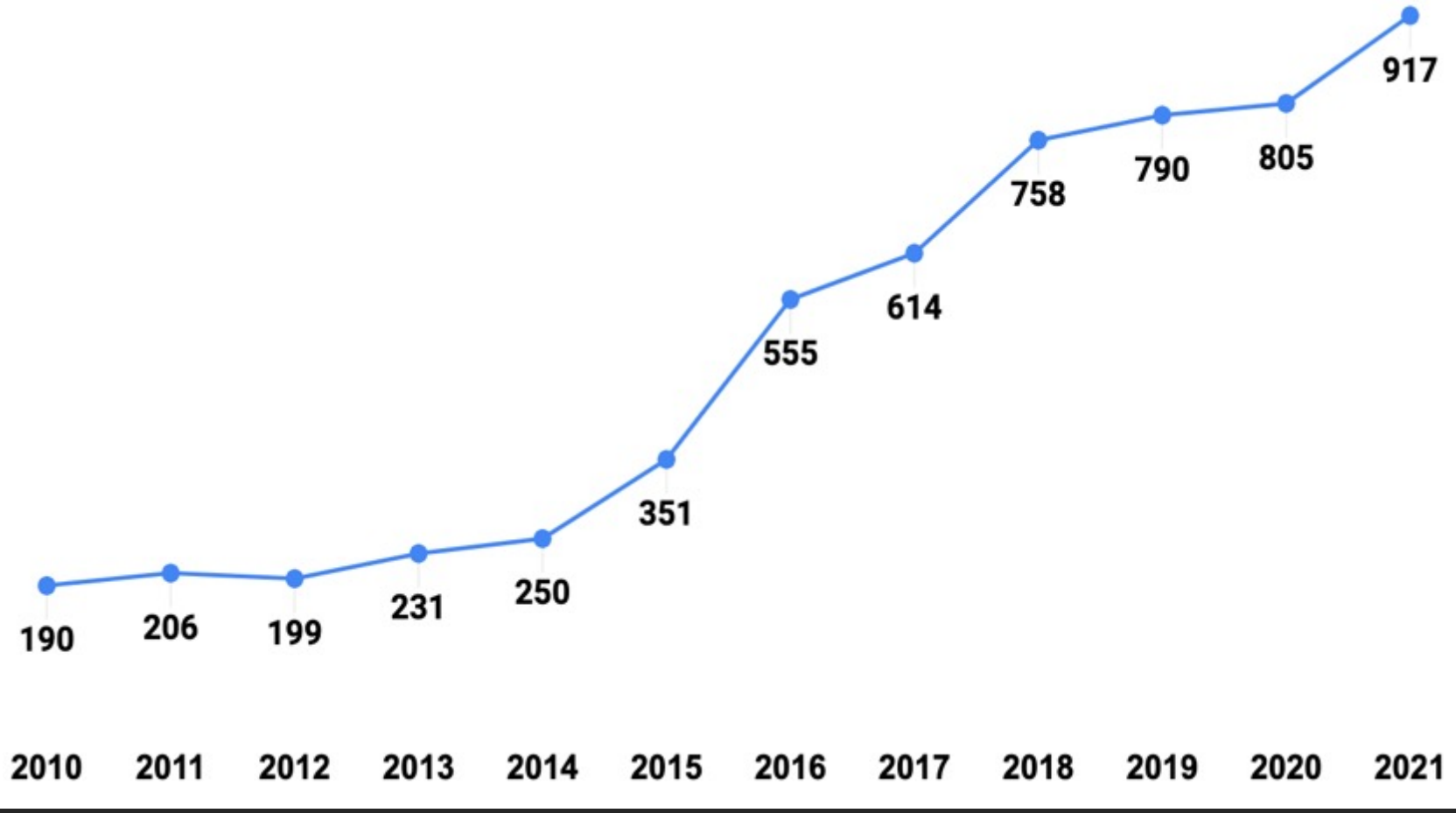


Invasive Group A Strep *emm49*



A statewide genomic surveillance system for invasive Group A *Streptococcus* was developed and implemented to identify emerging strains and clusters of infections that warrant public health action. This serves as a model for the next generation of public health surveillance.

Arizona has experienced a 4-fold increase in Invasive Grp A Streptococcus (iGAS).



Building a statewide system for iGAS.

ARIZONA DEPARTMENT OF HEALTH SERVICES

Arizona State Public Health Laboratory
Clinical Laboratory Newsletter
Summer 2019

LRN LABORATORY RESPONSE NETWORK

ADHS requests isolates of *Streptococcus* group A for genetic study

The Arizona Department of Health Services, pursuant to Arizona Administrative Code R9-6-204, is requesting that all isolates of *Streptococcus* group A from a normally sterile site be submitted to the Arizona State Public Health Laboratory (ASPHL) effective July 1, 2019. Isolates should be sent to 250 N 17th Ave, Phoenix, Arizona 85007 within one working day of isolating the organism and must be accompanied by a completed ASPHL lab submission form (instructions for completing can be found at: www.azdhs.gov/preparedness/state-laboratory/index.php#shipping-receiving-forms).

Genomic analyses will be performed on submitted isolates to better inform public health understanding of transmission patterns of invasive *Streptococcus* group A in Arizona and to ensure rapid implementation of appropriate control measures. ADHS will send an additional notification if the submission of isolates is no longer needed.

If you have questions related to invasive Streptococcus group A isolate submission or reporting, please contact the ADHS Office of Infectious Disease Services: (602) 364-3676 or HAI@azdhs.gov.

GC-117-PHS-EDC: Guidance on Clinical Laboratory Submission of Isolates or Specimens

ADHS

Laboratory Guidelines for Submission of Isolates or Specimens

The intent of this document is to help clinical laboratories interpret which isolates or specimens should be submitted to the Arizona State Laboratory as part of the Arizona Administrative Code (A.A.C.) R9-6-204. For information on which laboratory results should be reported, please visit https://azdhs.gov/labreporting.

An **isolate of the organism** for each positive culture, if available, or a **specimen** for each positive test result should be submitted to the Arizona State Laboratory **within one working day** for the organisms listed below:

- *Bacillus anthracis*
- *Brucella* spp.
- *Burkholderia mallei* and *B. pseudomallei*
- Carbapenem-resistant Enterobacteriaceae (CRE), submit isolates only[1]
- *Escherichia coli*, *Shiga* toxin-producing
- *Francisella tularensis*
- *Haemophilus influenzae*, from a normally sterile site for individuals <5 years of age
- *Legionella* spp., submit isolates only
- *Listeria* spp., from a normally sterile site
- Measles virus and anti-measles-IgM serologies
- Mumps virus and anti-mumps-IgM serologies
- *Mycobacterium tuberculosis* complex and its drug sensitivity pattern[2]
- *Neisseria meningitidis*, from a normally sterile site
- Rabies virus from a human
- Rubella virus and anti-rubella-IgM serologies
- *Salmonella* spp.
- *Streptococcus* group A, from a normally sterile site, submit isolates only[1]
- Vancomycin-resistant or Vancomycin-intermediate *Staphylococcus aureus*
- Variola virus (smallpox)
- *Vibrio* spp.
- Viral hemorrhagic fever agent
- Yellow fever virus
- *Yersinia pestis* (plague)
- *Yersinia* spp. (other than *Y. pestis*)
- Zika virus

[1] According to A.A.C. R9-6-204, these isolates must be submitted only by request. **ADHS is requesting isolates for all positive tests at this time.**

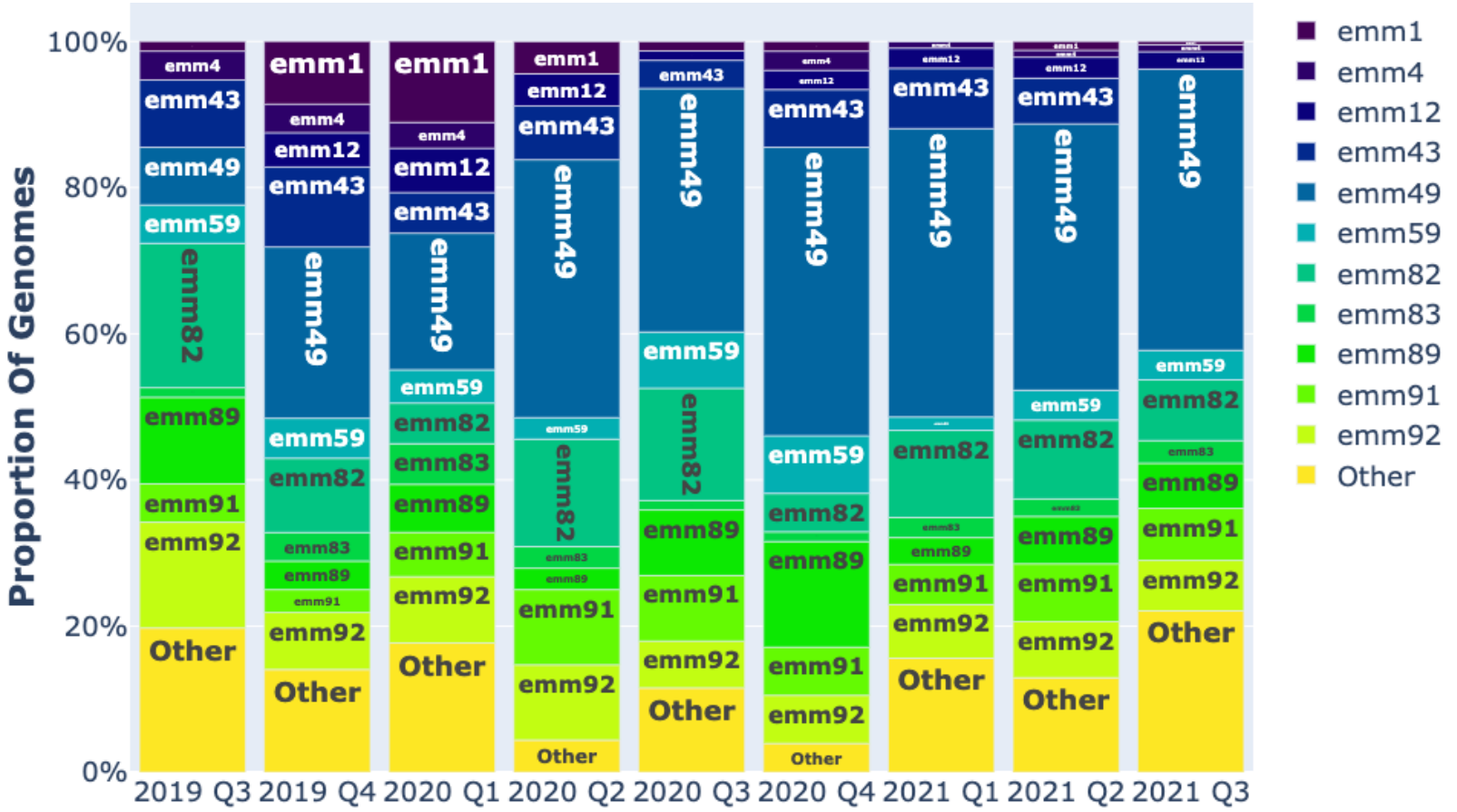
[2] Submit an isolate or specimen of the organism, as applicable, only when an initial positive result is obtained for an individual, when a change in resistance pattern is detected, or when a positive result is obtained ≥ 12 months after the initial positive result is obtained for an individual.

ADHS may also request isolates or specimens for organisms other than those listed above to be submitted to the Arizona State Laboratory on a case-by-case basis, including for emerging or exotic disease agents.

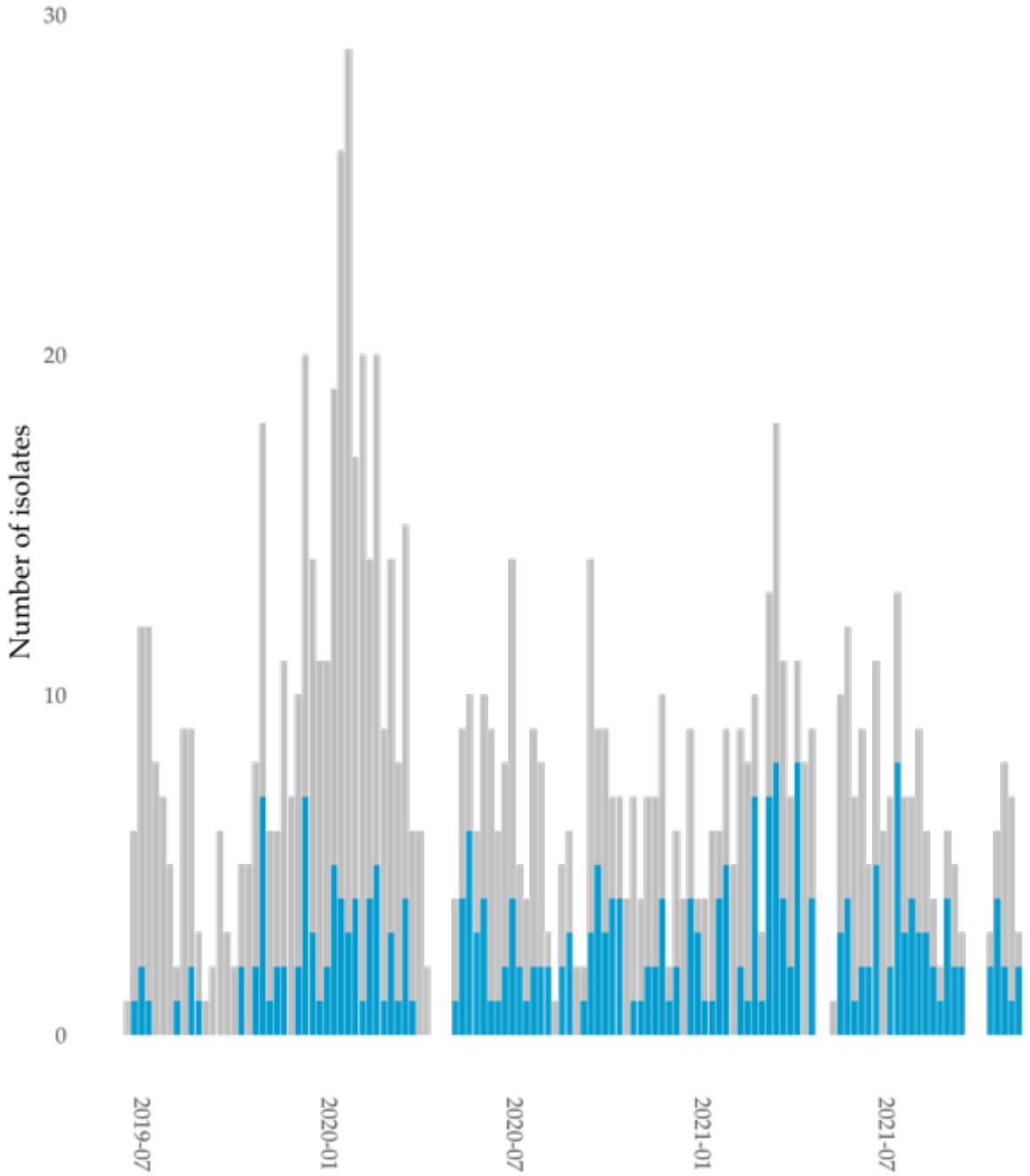
For example, submission of specimens testing positive for Candida spp. (other than *C. albicans*) will help detect a new emerging/exotic infection, *Candida auris*, to enable public health investigation and control.

Guidance document effective 07/17/2019 | http://azdhs.gov/labreporting | A.A.C. R9-6-204 Effective 01/01/2018

iGAS genomic surveillance identified endemic and emerging strains types.



iGAS genomic surveillance identified endemic and emerging strains types.



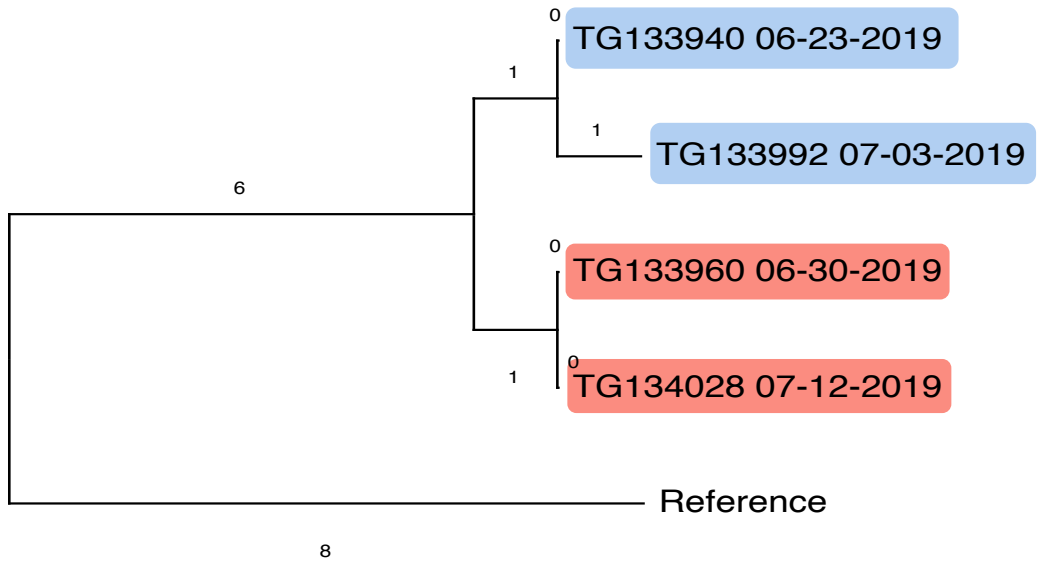
Outbreaks of iGAS in healthcare facilities associated with with emm49.

Phylogenetic tree of emm49, July 19
4 isolates

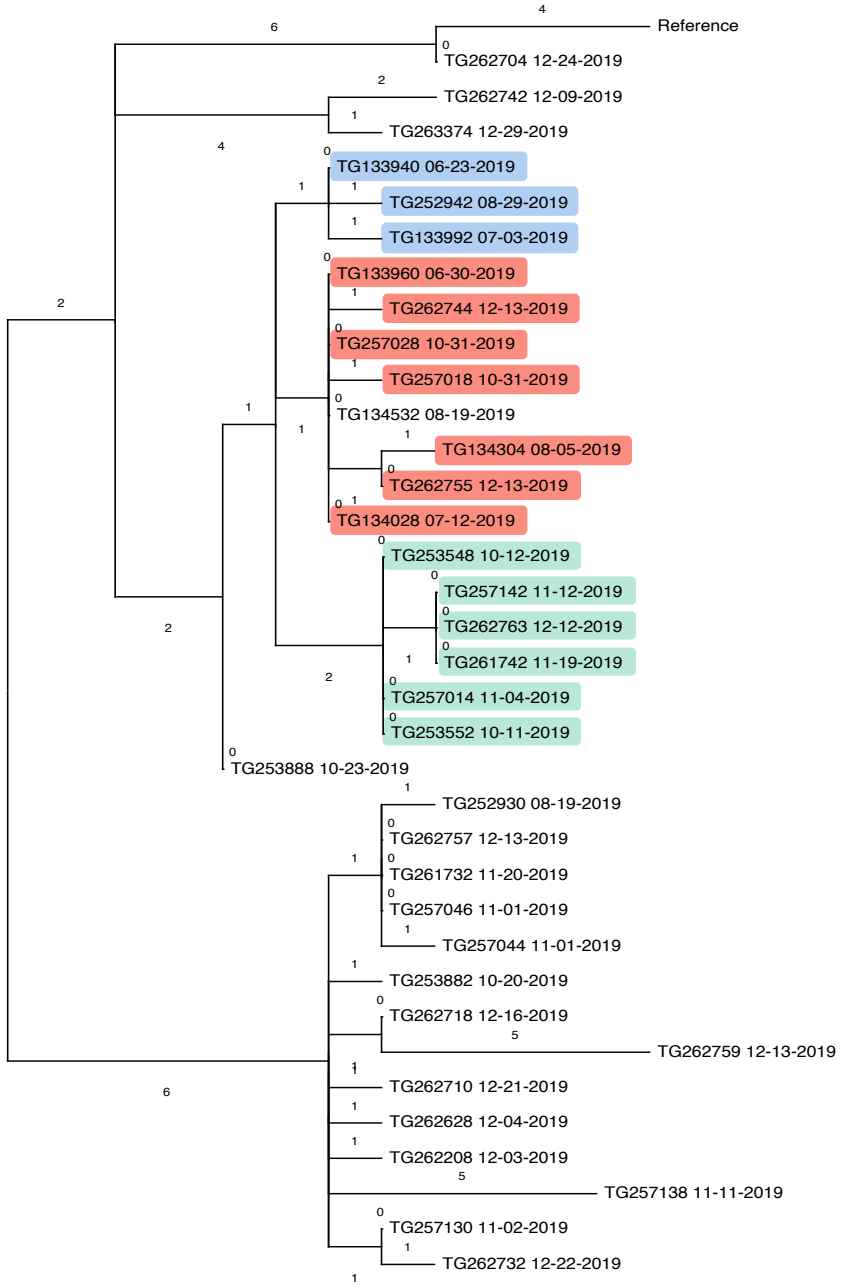
Blue: Skilled Nursing Facility

Red: Long-Term Care Facility

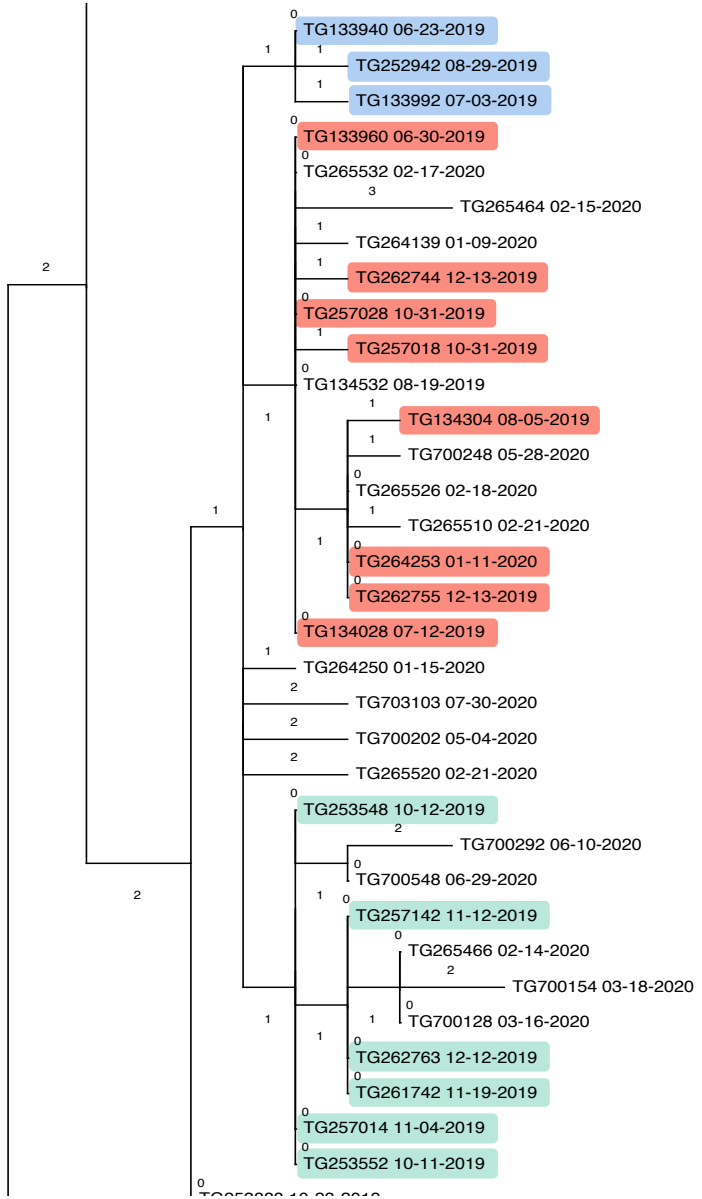
Green: Assisted Living Memory Care

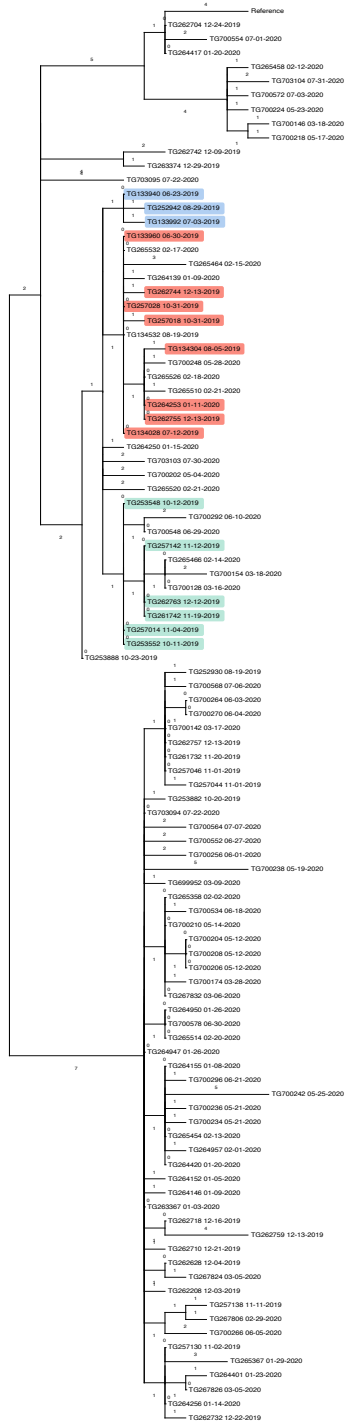


Phylogenetic tree of emm49, Dec 2019
35 isolates



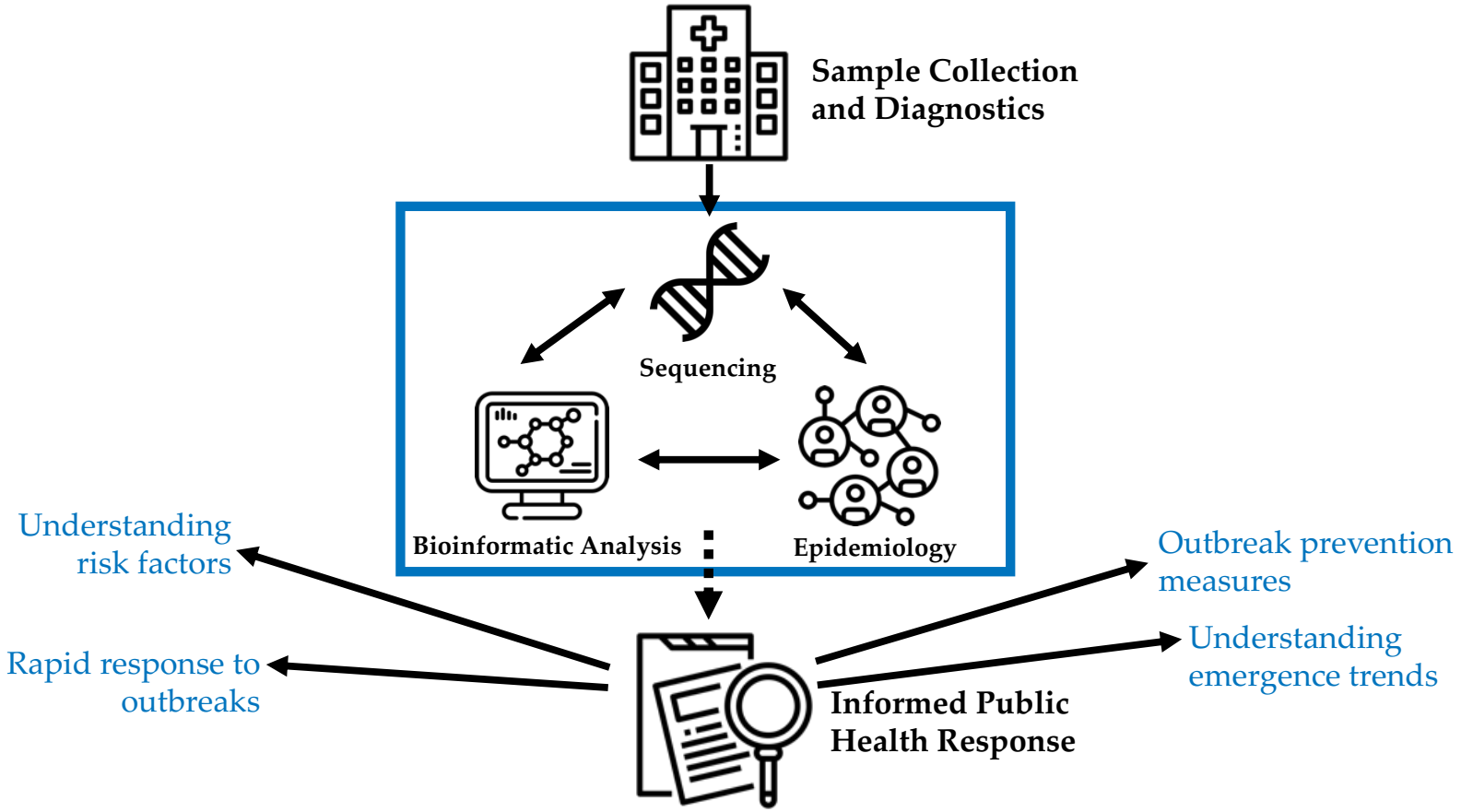
Phylogenetic tree of emm49, July 2020
100 isolates





Public health investigations confirms the connected between patients.

Genomics can significantly advance the state of infectious disease surveillance.



Thank you!

hyaglom@tgen.org

tgen® NORTH
AN AFFILIATE OF City of Hope.

ARIZONA DEPARTMENT
OF HEALTH SERVICES