Using Whole Genome Sequencing to Investigate the Outbreak of Carbapenamase-Producing Bacteria

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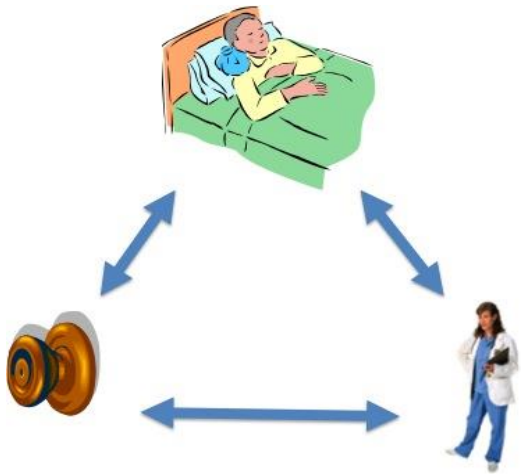
MDROs have become an enormous problem, for hospitals treating seriously immunosuppressed patients

How are MDRO spread in healthcare?

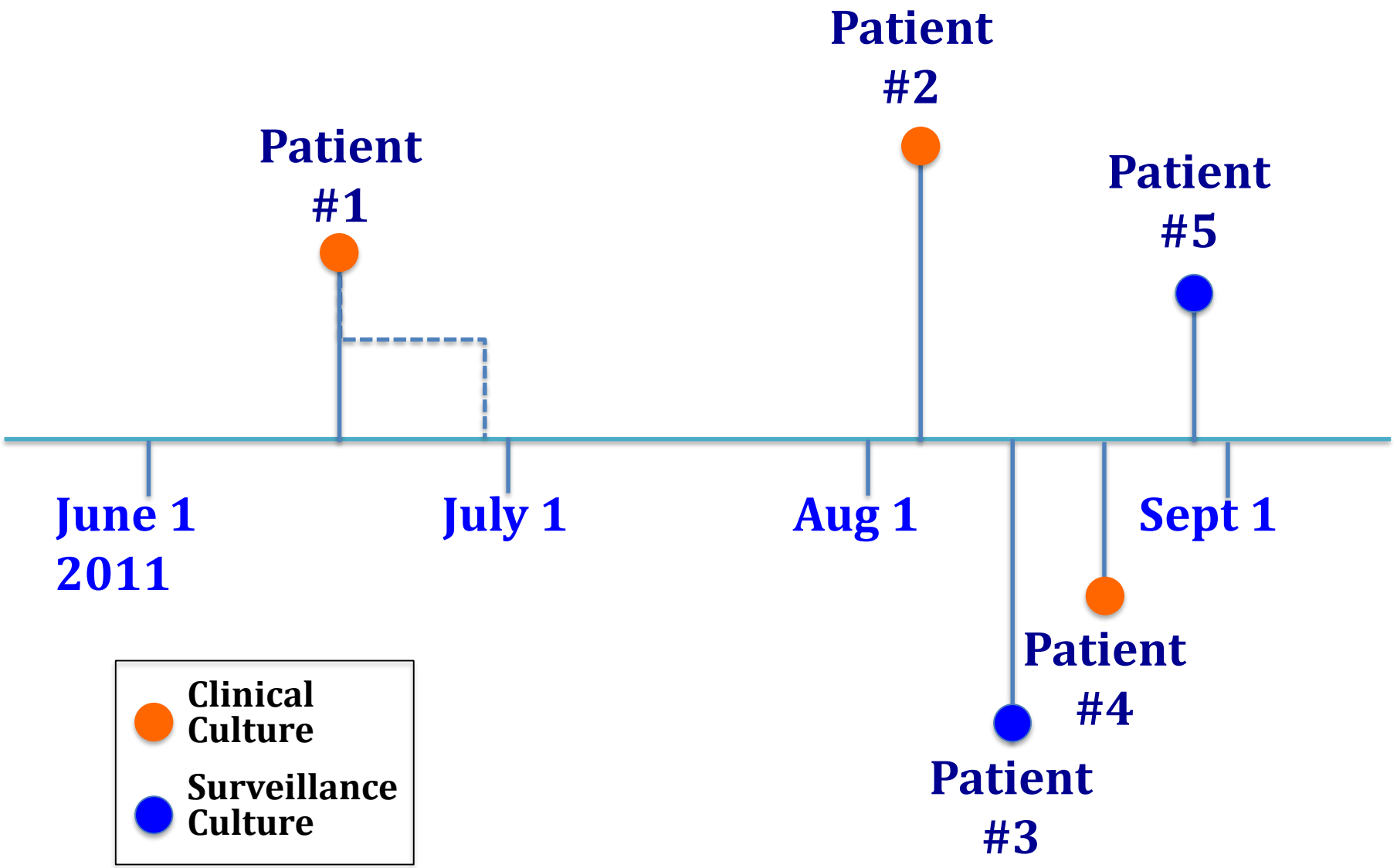
- No direct, ironclad data (diffuses accountability)
  - Hands of health care workers
  - Contaminated equipment
  - Other fomites
  - Environmental contamination
- Which routes of transmission occur most commonly?
- Where should prevention efforts be targeted?



Index Case

A patient known to be infected with a carbapenemase-producing isolate of *K. pneumoniae* was admitted to the NIH Clinical Center on 13 June, 2011. Enhanced isolation procedures were immediately implemented, and no spread of the bacteria was seen for the month she was in the hospital. Although all seemed well, a few weeks later on August 5th, a second patient was discovered to be infected with a similar pathogen, followed by a series of other patients identified as either infected or colonized –– about 1 per week to a total of 18 by the end of the year. Seven people ultimately died as a result of CRE infection.

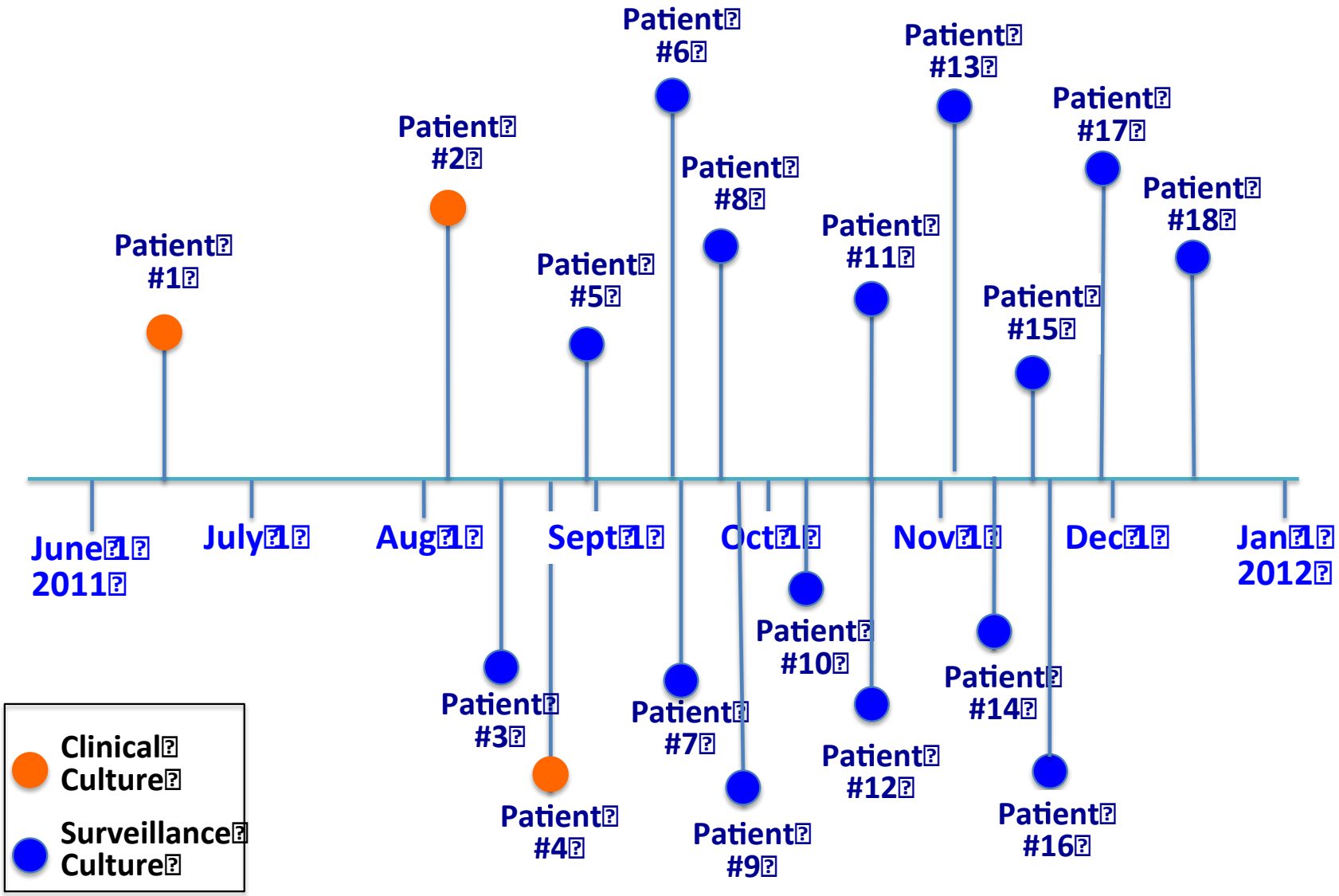
Initial KPC Cases: June – September



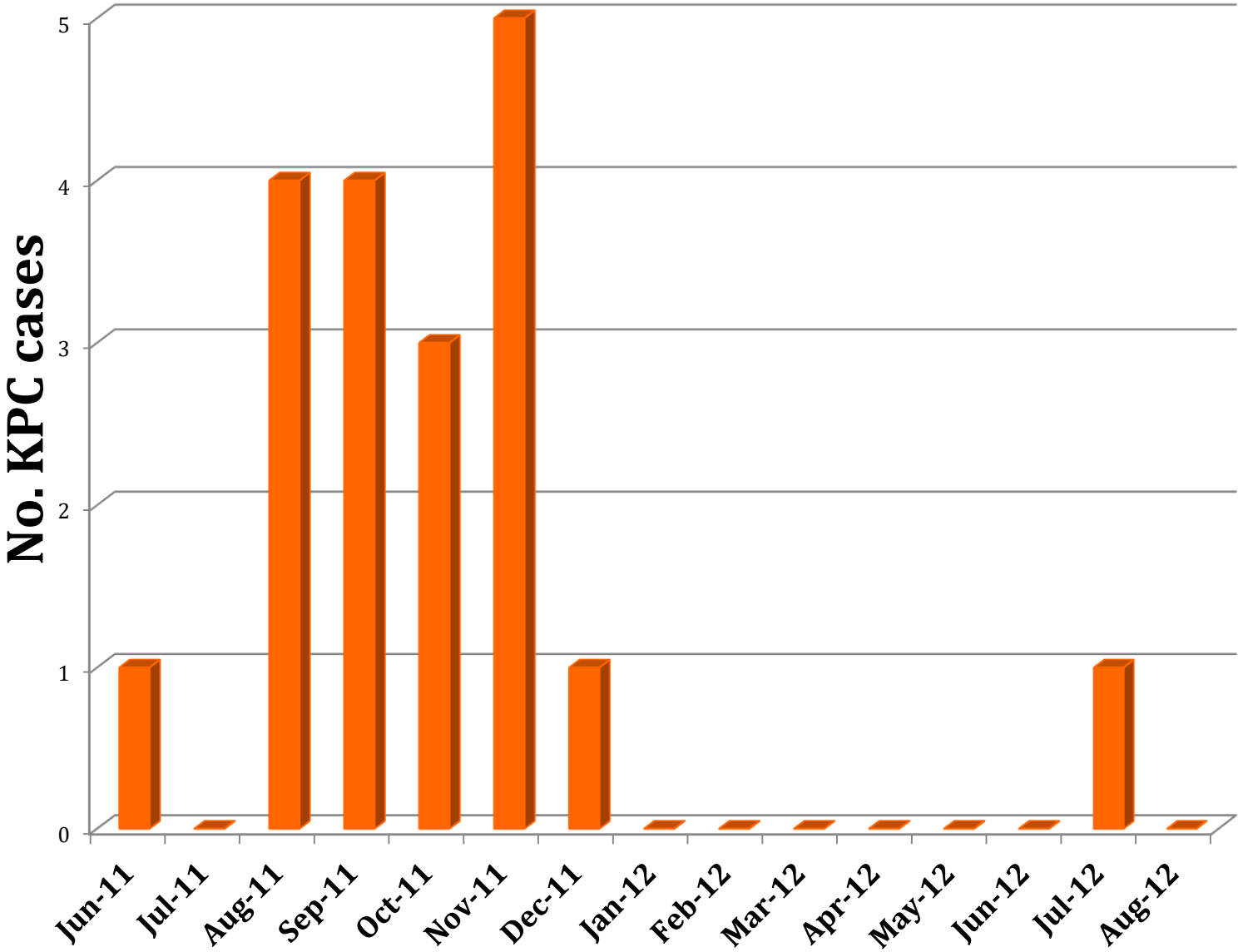
Characteristics of Clinical Center patients who acquired the outbreak strain

Demographic characteristics (18 pts)	
Median age (yrs)	44
Underlying malignancy	9
HSCT recipients	6
Outcome	
Only colonized with CRE	9
Developed CRE infection (bloodstream)	9
Died from CRE	7
Died from underlying condition	4

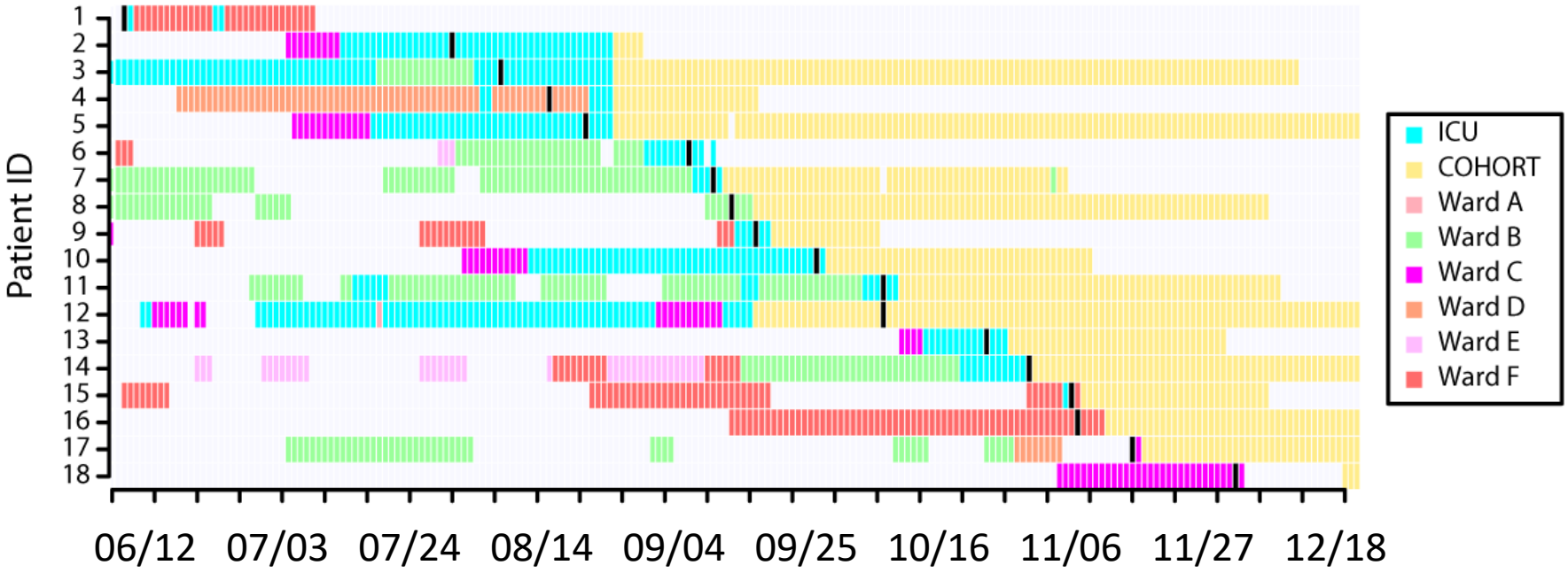
How can we begin to understand how this outbreak unfolded?



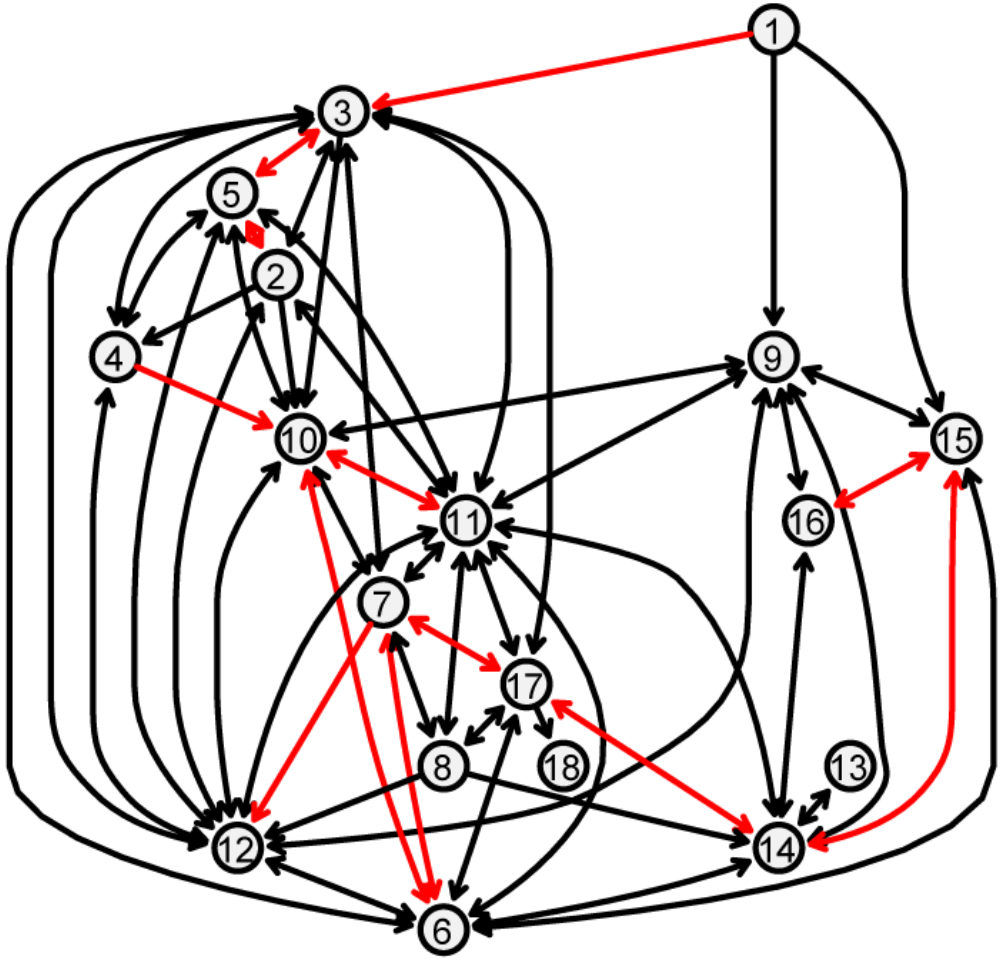
Epidemic curve of Clinical Center Clustered KPC-Klebsiella cases



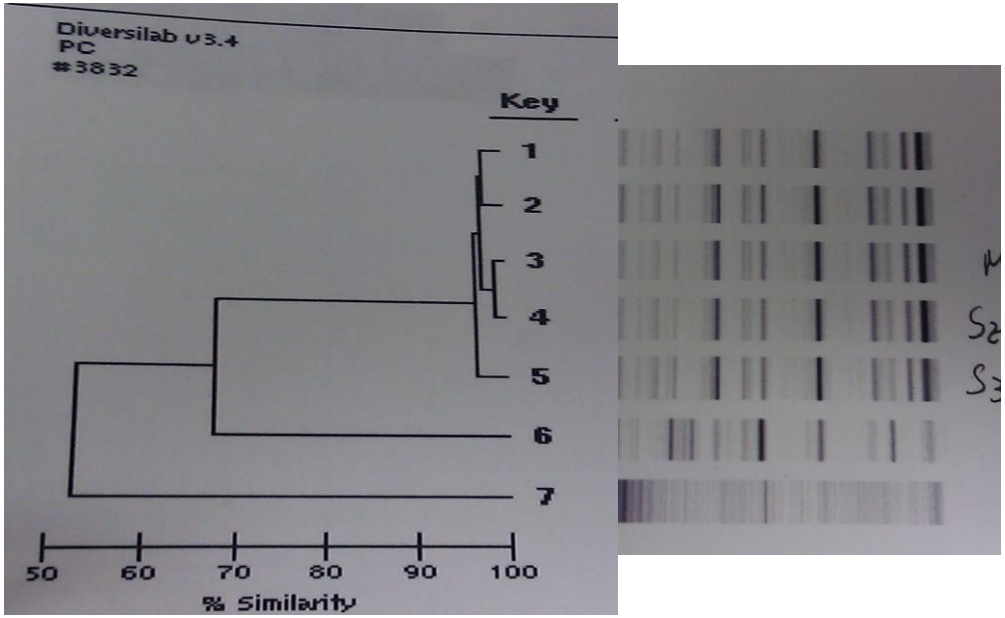
Can we use 'Shoe-Leather Epidemiology' (i.e., patient overlap) to reconstruct transmission?



Patient overlap does not provide clear picture of how outbreak unfolded



PFGE and Rep-PCR did not distinguish isolates



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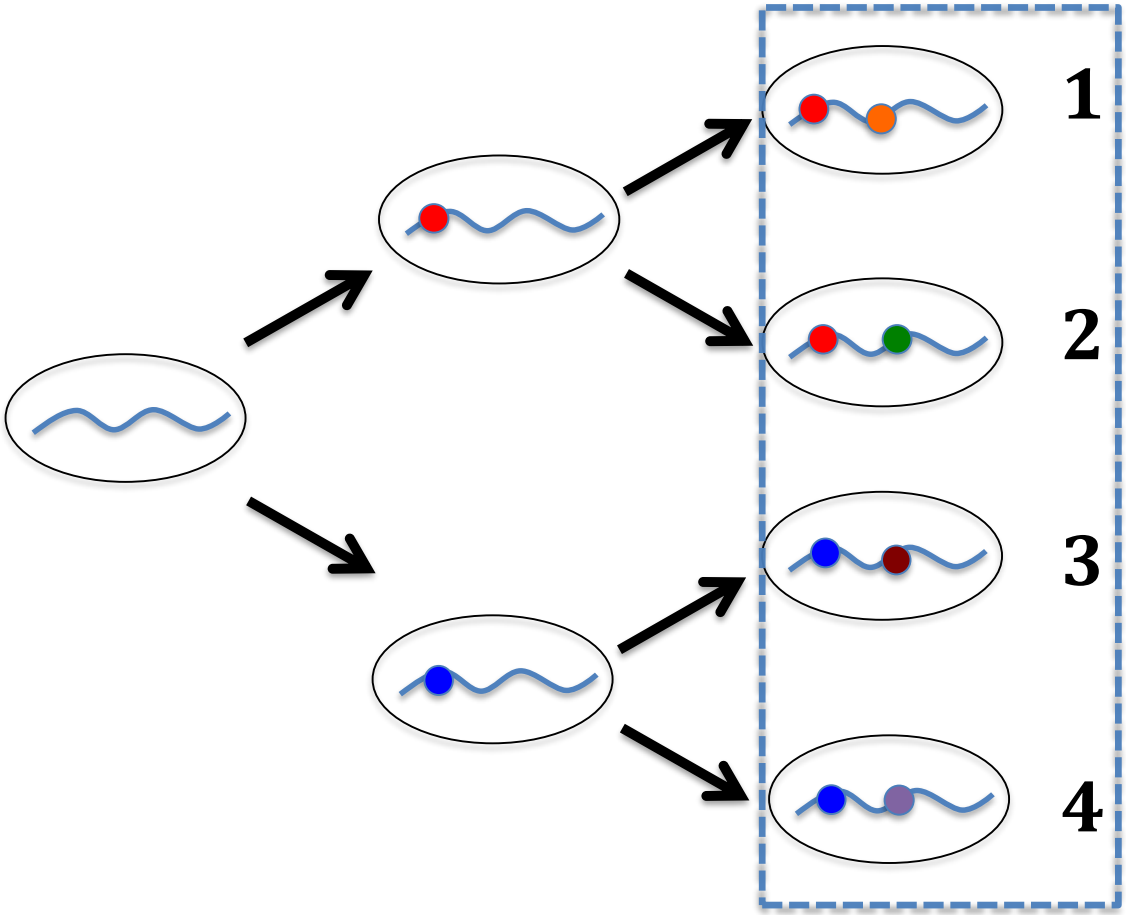
Differences in organism's genomes can be used to recreate their history



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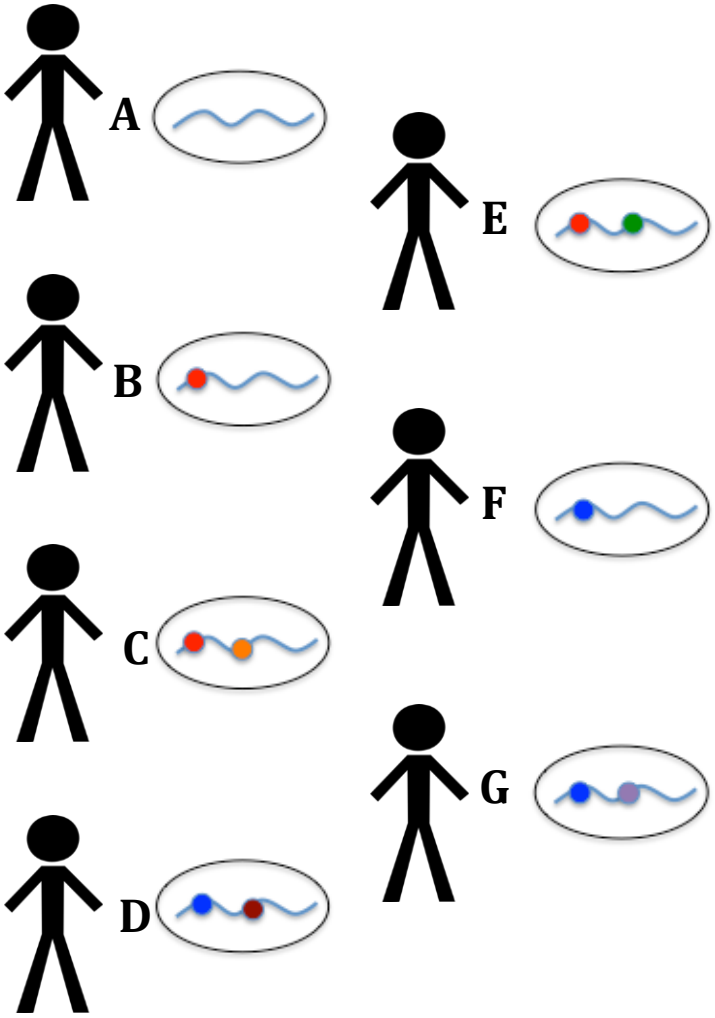
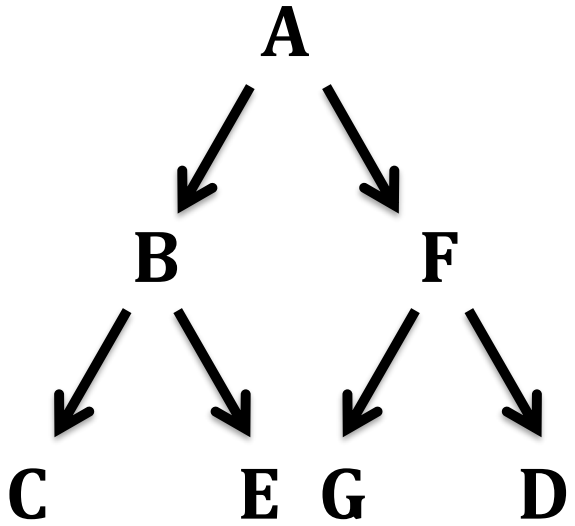
This same concept is what we hoped to use to track the spread of infectious disease





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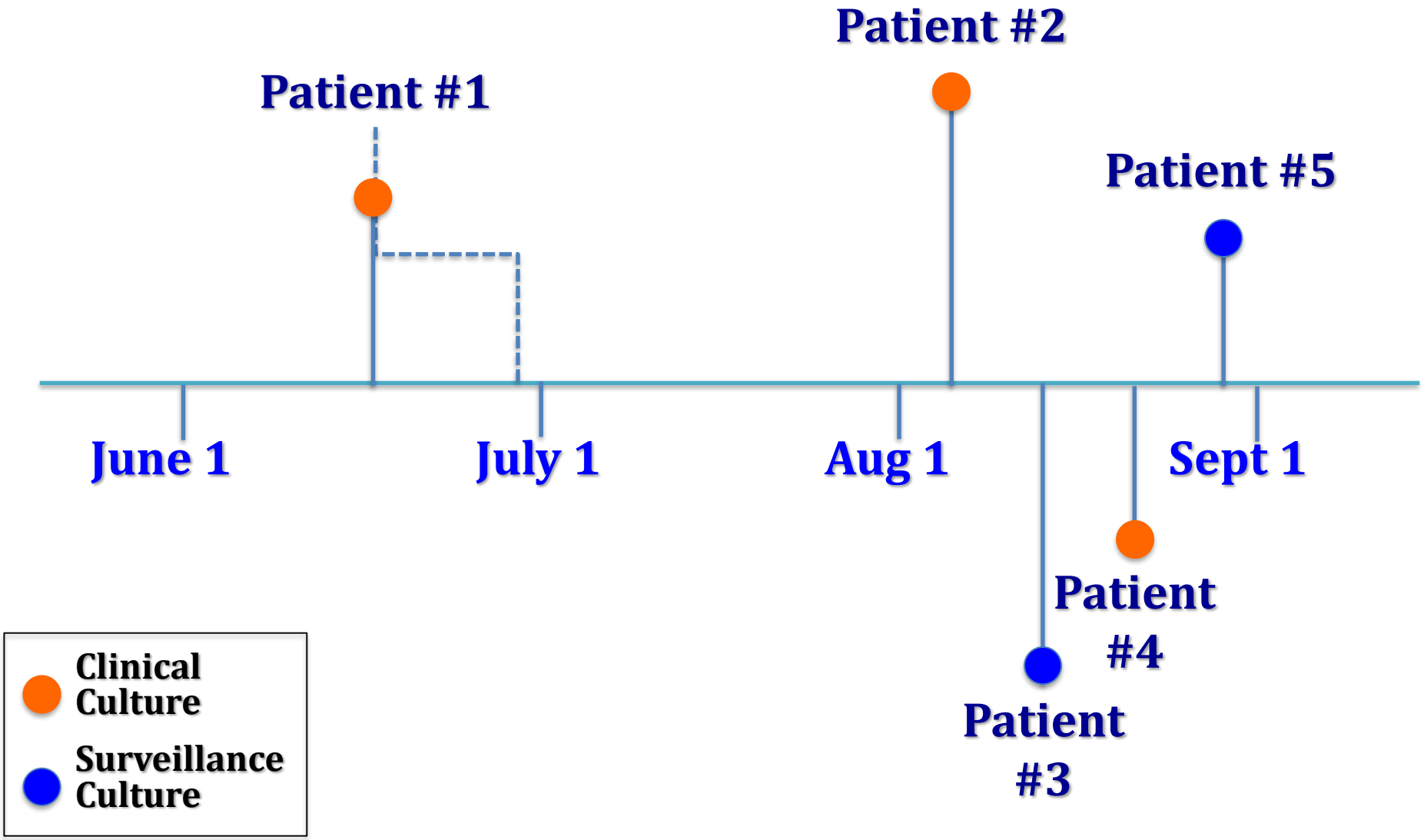
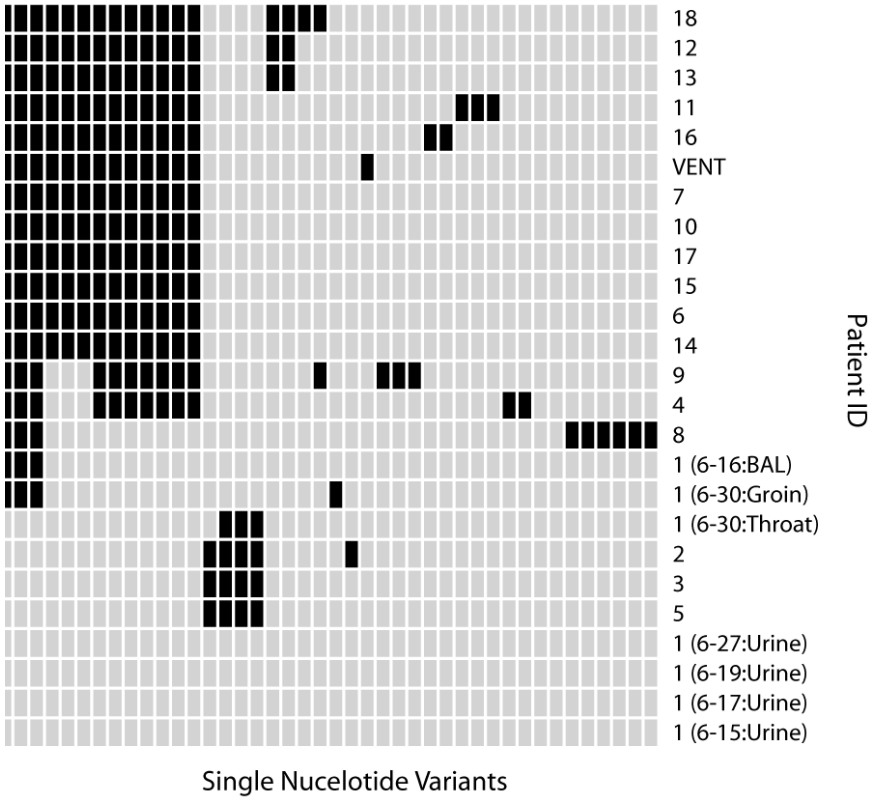
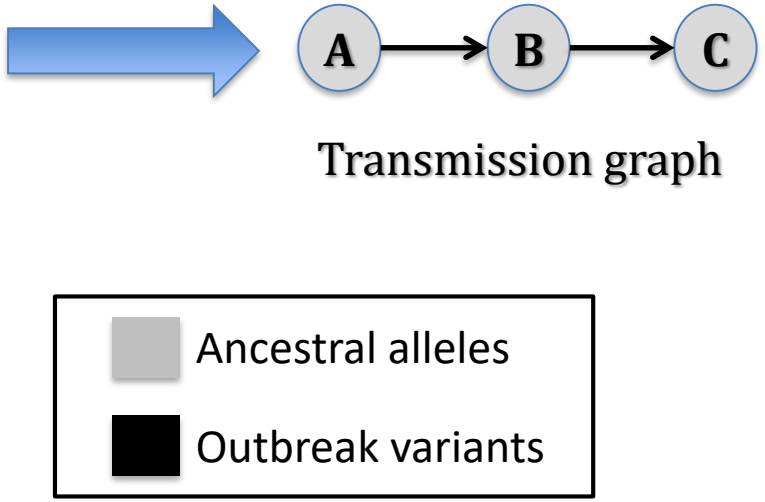
One major question – Does *Klebsiella* evolve fast enough to track spread over weeks?



If variants clearly stratify patients into groups: Can we infer transmission paths from sequence variants?





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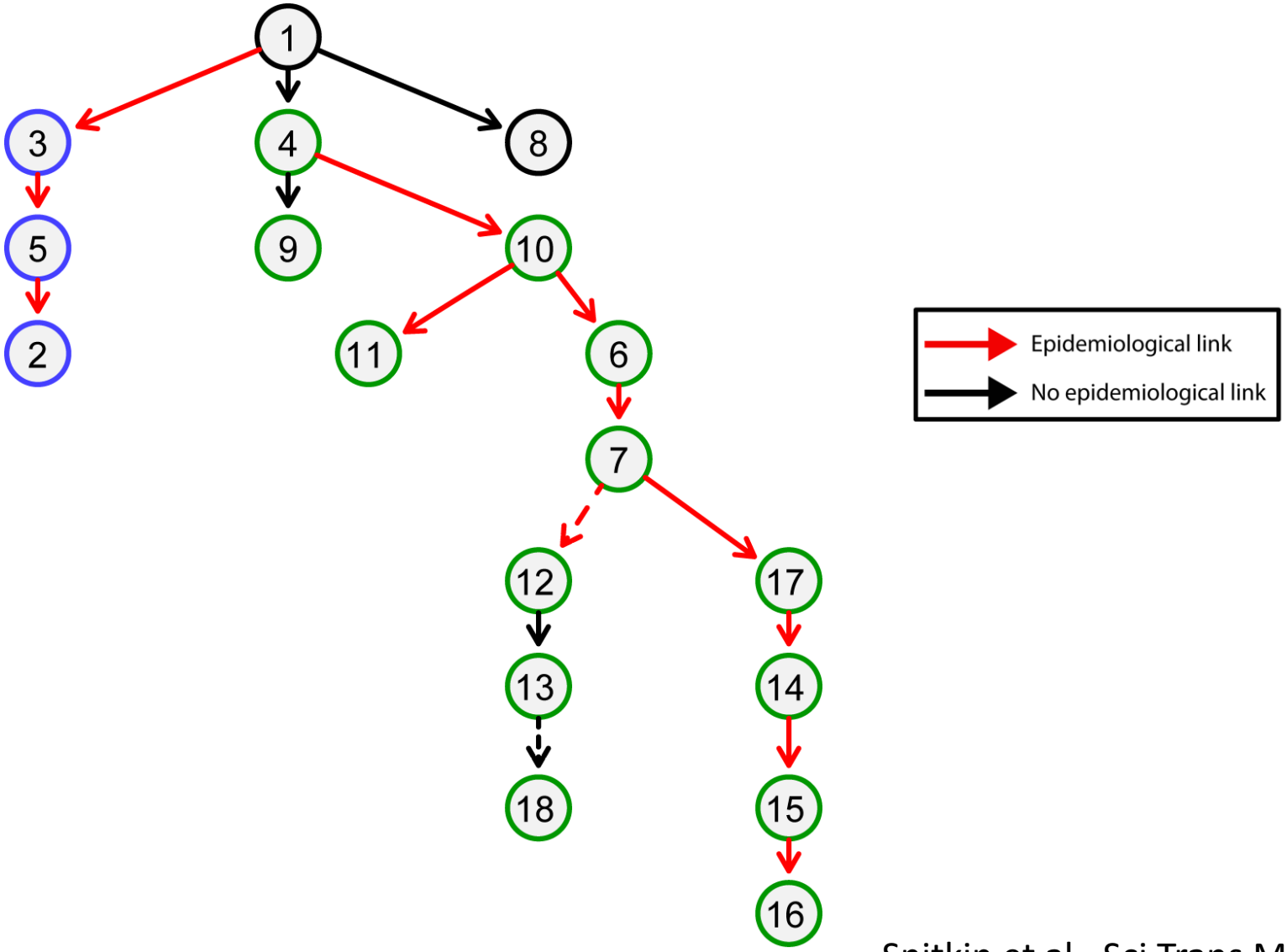
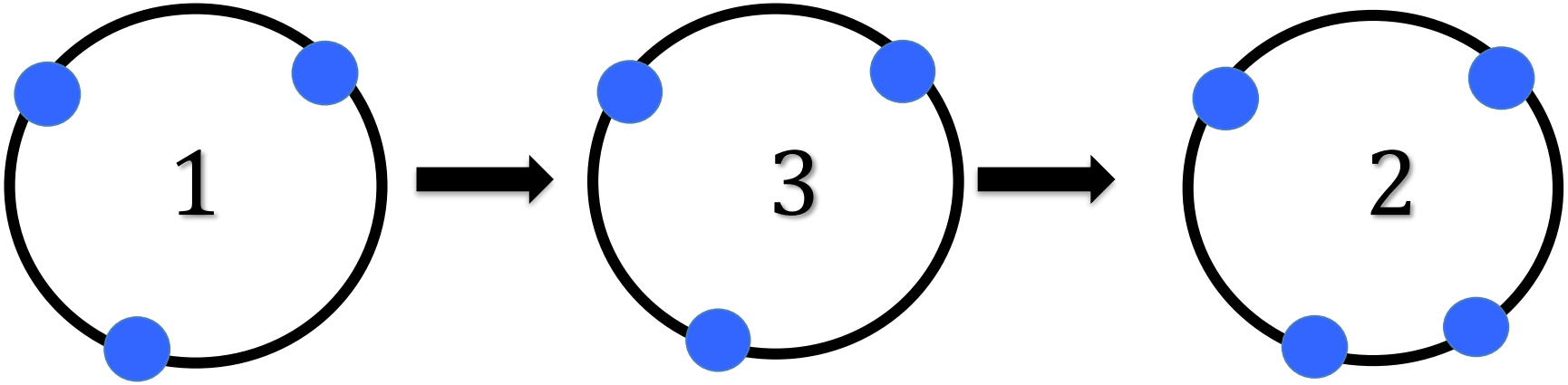
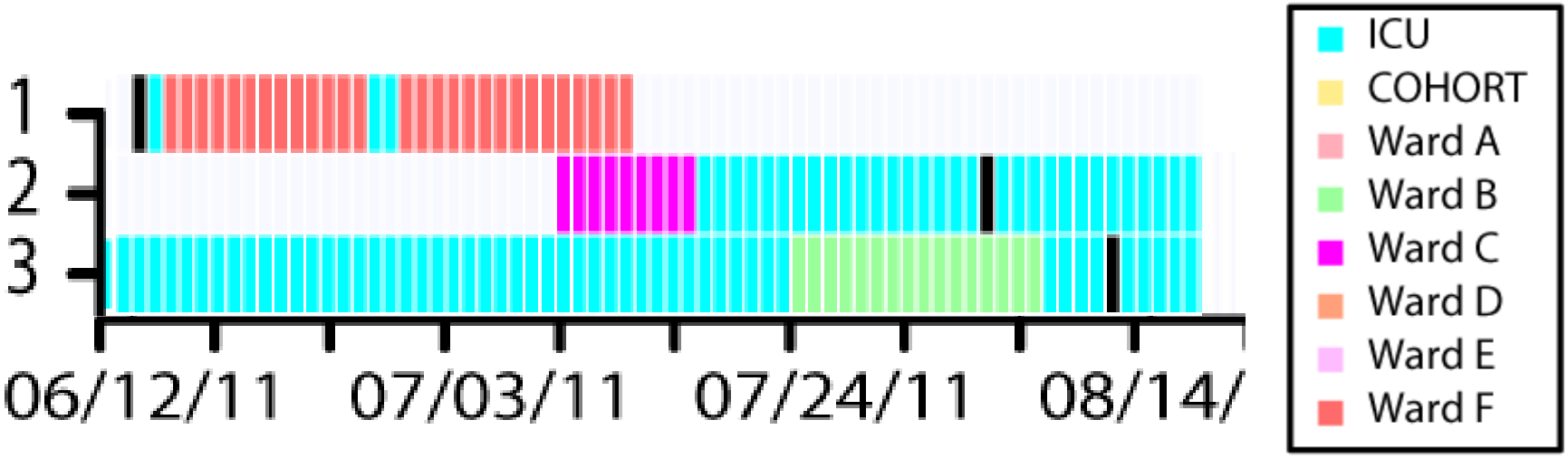
Reconstructing transmission using both genomic and epidemiologic data



Snitkin et al., Sci Trans Med 2012

Chain of Transmission: Patient 1➔3➔2
Genetic and epidemiology data agree





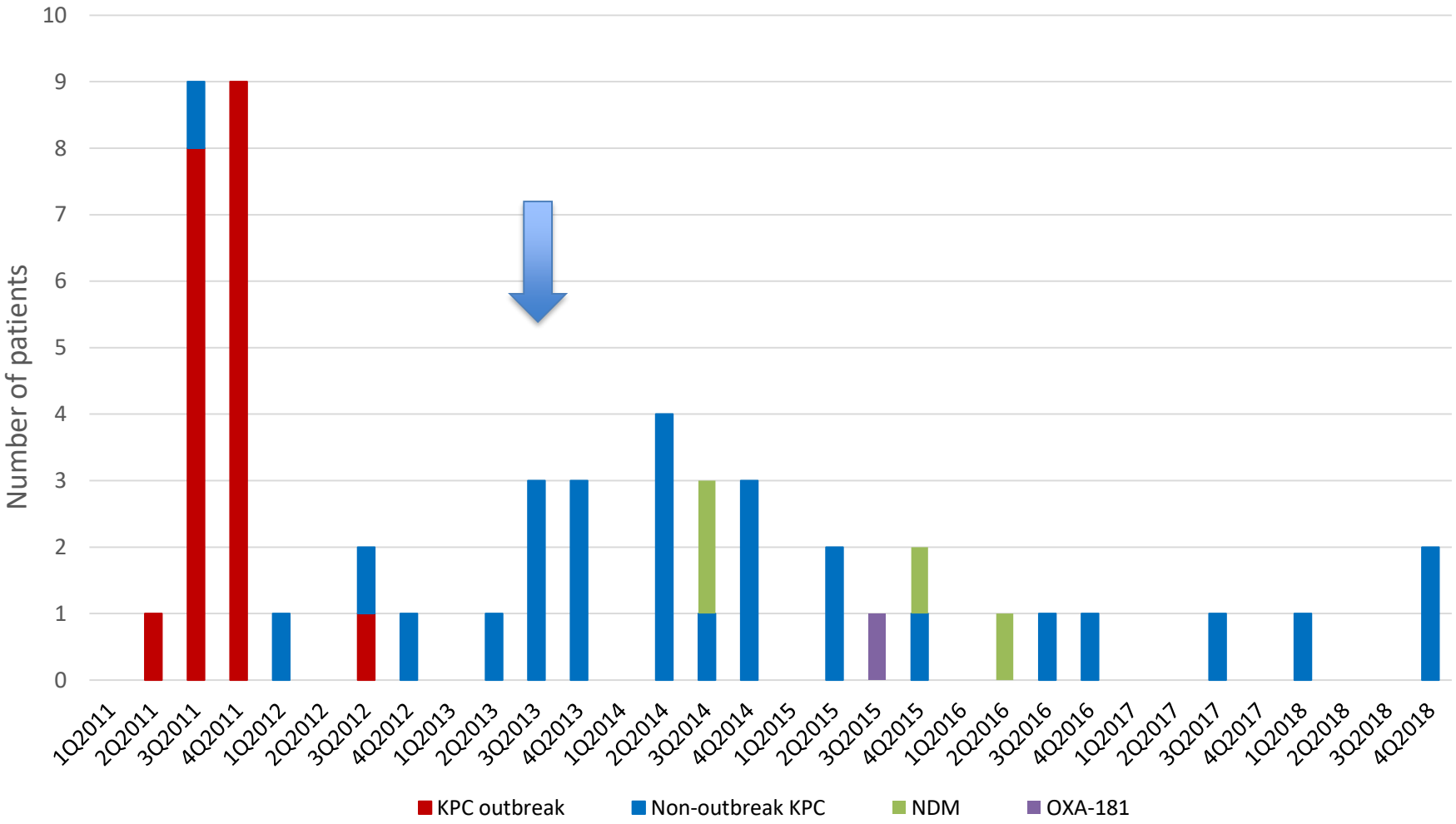
Practical application of WGS to issues of relevance to healthcare epidemiology

- Using WGS and advanced molecular methods:
  - to assess isolates detected as asymptomatic colonization to characterize the development and expansion of MDRO?
  - to detect asymptomatic MDRO colonization reliably
  - to inform our understanding of mechanisms of MDRO transmission
  - to determine the role of asymptomatically colonized patients in transmission
  - based on findings from these studies, to create targeted interventions, and assess their efficacy
  - to assess why some MDROs are expanding more rapidly than others.

What did we learn from our outbreak?

- The outbreak was clearly clonal, originating from patient 1;
- Klebsiella outbreaks can spread undetected from individuals who are silently colonized
- Rectal surveillance is critical for detection of silently colonized patients and stemming transmissions, though not sensitive enough;
- Genetic sequencing offers promise as a more sensitive fingerprinting technique and may provide a mechanism to investigate specific instances of transmission.

CRE Surveillance Since KPC-Klebsiella outbreak



Arrow - Admission surveillance begins

Acknowledgements

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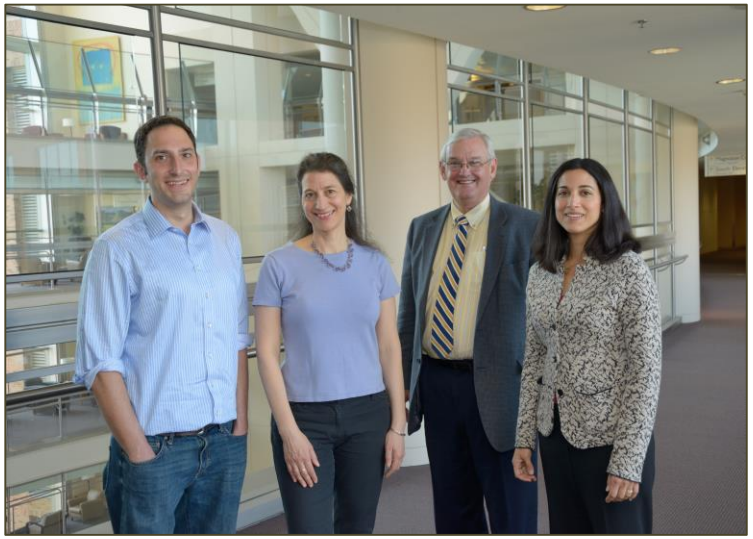

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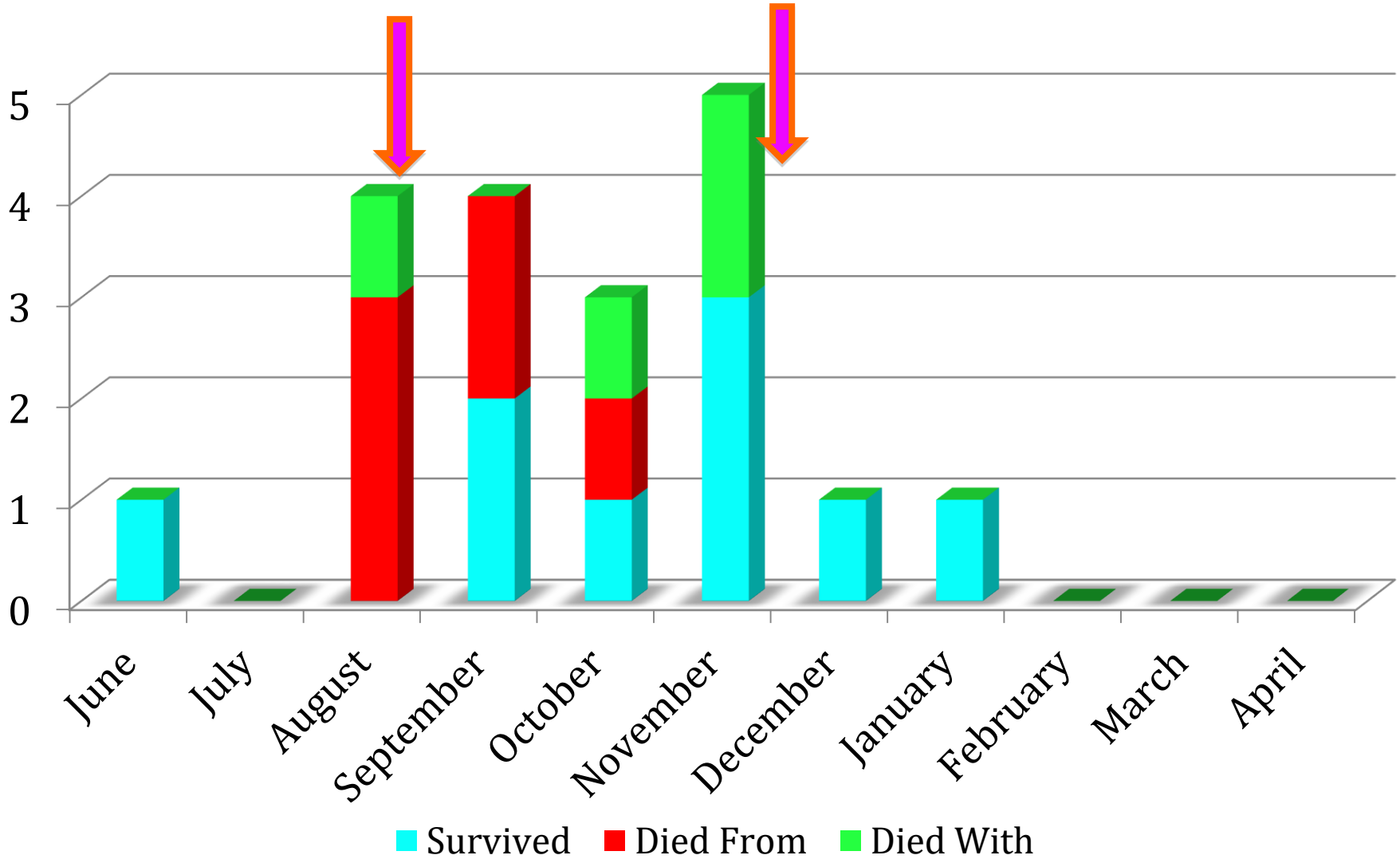
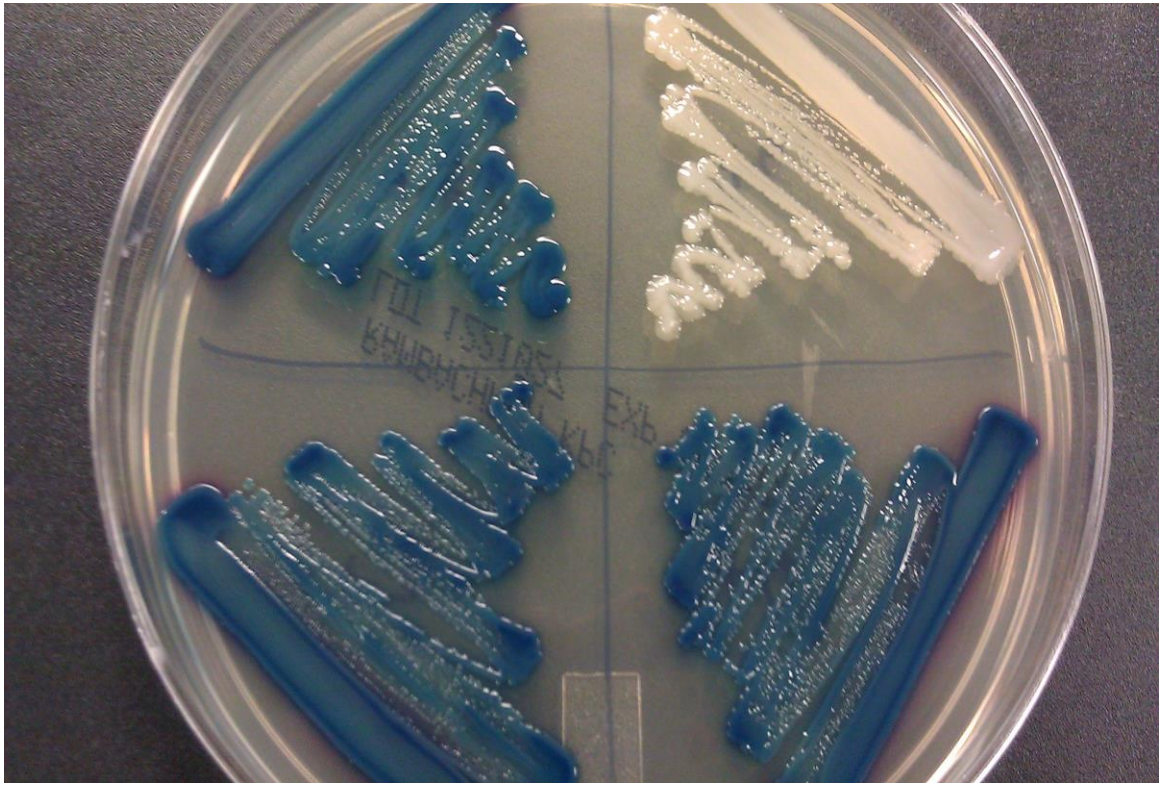
Outcomes of Clinical Center KPC-Klebsiella Cases, 2011-12



Surveillance cultures



Blue: *Klebsiella, Enterobacter, Citrobacter*
Dark pink: *E. coli*
Cream/white: *Pseudomonas, Acinetobacter*

Suspicious colonies undergo PCR
for *bla*KPC and *bla*NDM-1

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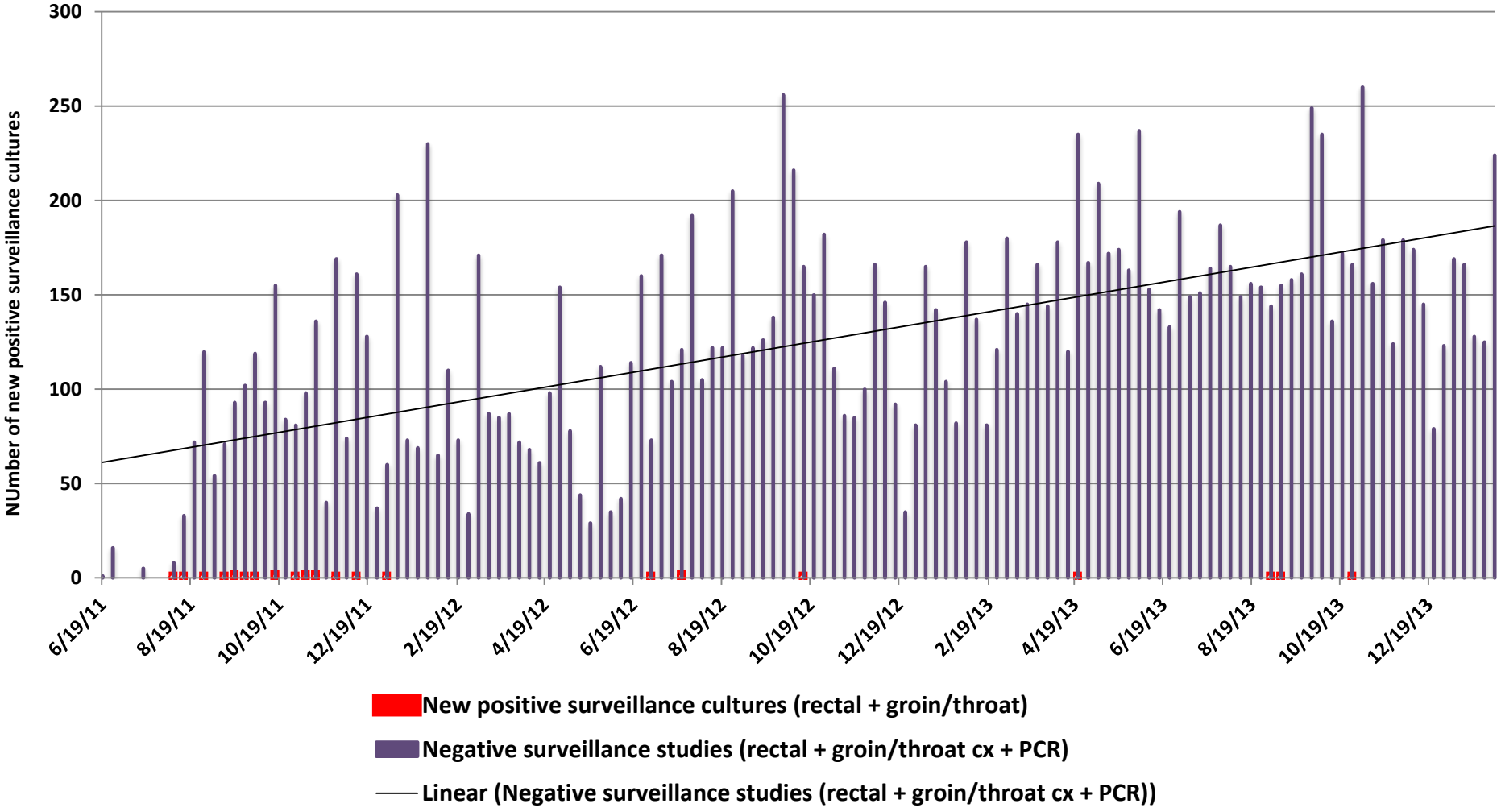
Volume of CRE surveillance cultures by week and by result, June 2011 to February 2014



Surveillance cultures

- Among 11,754 rectal swabs from 3,843 patients (85% compliance), 15 patients had new CRE isolates detected (either by chromogenic selective media or direct PCR).
  - One patient acquired the outbreak KPC+ strain (7/2012).
  - Hospitalized on the same unit as the cohorted area.
  - The 14 others were all completely unrelated (WGS).
- Since August 2011 all "new" CRE isolates have been detected in surveillance cultures; none from clinical cultures.
- Since July 2012 no instances of hospital transmission have been detected.

Environmental cultures

- Among 419 environmental samples, 10 (2.4%) grew KPC-Klebsiella, KPC-Enterobacter, and KPC-Pantoea:
  - One ventilator that had been used by a KPC patient and "triple-cleaned."
  - A high-touch surface in the room of one KPC patient after housekeeping cleaning post-discharge.
  - Five sink drains in rooms previously housing KPC patients.
  - Two handrails, and one medication room counter surface.
- Nonetheless, concern that small inocula might transmit lethal infection to immunosuppressed patients and that inadequate cleaning might foster transmission prompted continued use of hydrogen peroxide vapor decontamination.

Interventions Employed to Combat CRE Spread at the NIH CC – 1

Intervention	Basis	Comment
1. Careful engagement of all stakeholders involved in the care of infected and colonized patients	Guideline (1)	Critical to successful implementation of prevention and control measures
2. Communication with hospital staff, campus staff, local and state public health authorities and patients about issues relating to the outbreak that are relevant to each group.	Guideline (1)	Critical to successful engagement of stakeholders
3. Aggressive microbial surveillance, including:		
➢ Microbial surveillance of all patients who are admitted to medical, surgical or pediatric units, with empirical isolation and additional surveillance of patients who have been hospitalized in the past week or abroad in the past six months.	Guideline (1)	Crucial for identifying new cases and preventing transmission from patients who have had potentially high-risk exposures
➢ Targeted, twice-times weekly microbial surveillance of patients hospitalized on the highest-risk units;	Empirical	Frequency driven by the severity of illness/immunosuppression
➢ Monthly whole house microbial surveillance of all medical/surgical patients;	Guideline (1)	Crucial to identity new cases/transmission
➢ Use selective media to identify resistant pathogens;	Guideline (1)	Selective media are expensive
➢ Sampling multiple sites on each patient to decrease sampling error and capture different pathogens in their respective niches	Empirical	Driven by local microbiology; prior outbreaks of other Multidrug Resistant Organisms
4. Rapid identification of identified resistant organisms (e.g., MALDI-TOF/Mass Spectroscopy)	Routine at NIHCC	Equipment expensive; output extremely rapid and remarkably useful
5. Rapid characterization of resistance mechanisms	Guideline (1)	For example, PCR for carbapenemase genes (KPC, NDM-1, etc.)

Palmore TN, Henderson DK. Ann Intern Med. 2014;160:567-569.

Interventions Employed to Combat CRE Spread at the NIH CC – 2

Intervention	Basis	Comment
6. Whole-genome sequencing to characterize the spread and to investigate mechanisms of healthcare-associated spread	Investigational	Did not 'unravel' our outbreak, but did identify silent transmission and changed our strategy
7. Implementation of enhanced contact precautions for all infected or colonized patients	Empirical	Intensity of the intervention due to the severity of illness/immunosuppression
8. Geographic and personnel cohorting	Guideline (1)	Difficult to implement for some categories of personnel
9. Equipment dedicated to be used solely for cohorted patients, to the extent possible	Guideline (1)	Reduces fomite risk
10. Daily chlorhexidine baths for patients	Guideline (1)	Unable to determine efficacy in our setting
11. Monitoring adherence to all infection control precautions, including ***unwavering attention to adherence to appropriate hand-hygiene procedures***	Empirical	Strategy was useful in prior outbreak (2) and implementation was associated with improved adherence
12. Attention to the details of environmental disinfection, including consideration of use of new decontamination technologies (e.g., hydrogen peroxide vapor, ultraviolet light)	Empirical	Intensity of the intervention due to the severity of illness/immunosuppression of our patients; a minuscule inoculum may ultimately prove lethal

1. *CDC. Guidance for control of carbapenem-resistant Enterobacteriaceae (CRE): 2012 CRE toolkit. Washington, DC: U.S. Department of Health and Human Services; 2013. Accessed at www.cdc.gov/hai/pdfs/cre/CRE-guidance-508.pdf on 24 February 2014.*
2. *Palmore TN, et al. Use of adherence monitors as part of a team approach to control clonal spread of multidrug-resistant Acinetobacter baumannii in a research hospital. Infect Control Hosp Epidemiol 2011;32:1166-72.*

Palmore TN, Henderson DK. Ann Intern Med. 2014;160:567-569.

Environmental cleaning and disinfection