

Tracking the Spread of CRE between Facilities –The Use of Genomics in Regional Surveillance

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Whole genome sequencing (WGS) to track multi-drug resistant organisms

- WGS has been shown to provide unparalleled resolution for typing of healthcare pathogens
- This resolution has been applied to track the spread of MDROs at scales ranging from single center outbreaks to global transmission networks
- To date little has been done at the level of regional healthcare networks

Genomic insights into the spread of infections within and between hospitals

1. Tracking a regional outbreak of carbapenem resistant *Klebsiella pneumoniae*
2. Understanding regional spread of carbapenem resistant *Klebsiella pneumoniae* in an endemic region

Genomic insights into the spread of infections within and between hospitals

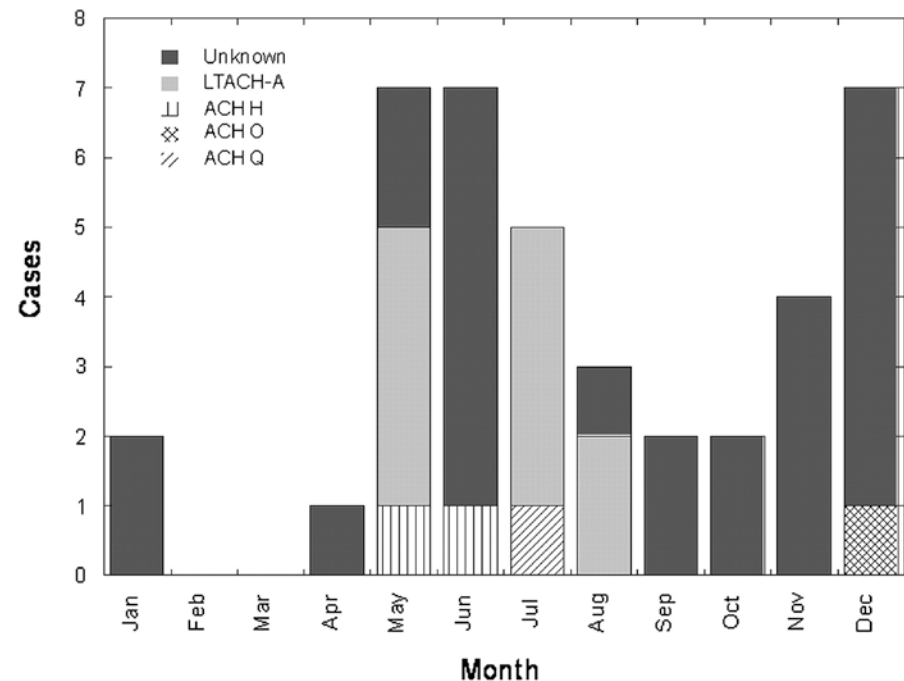
1. Tracking a regional outbreak of carbapenem resistant *Klebsiella pneumoniae*
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How do multi-drug resistant organisms spread throughout a region?

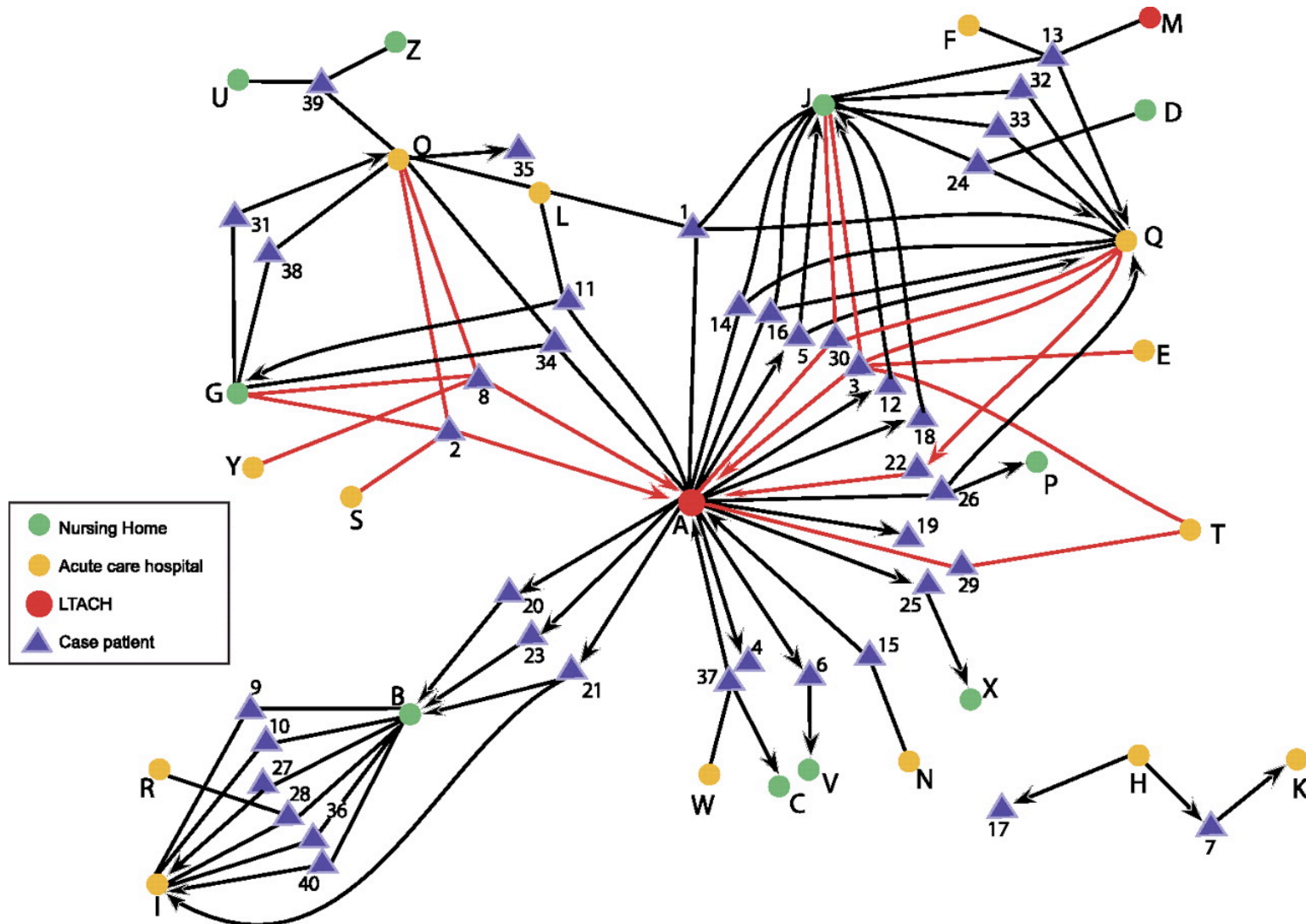
- Patients are often exposed to multiple facilities in a healthcare network as part of their care
- Role of patient transfers in regional spread supported by observation that hospitals with high transfer rates have higher infection rates
- Most studies documenting inter-facility transmission were limited to a handful of patient transfer events

Regional outbreak of CRKP

- CRKP first observed in late 2007
- Subsequent regional outbreak in 4 adjacent counties of Indiana and Illinois spanning 2008
- Affected a total of 40 patients who were exposed to 26 healthcare facilities



Network of patient transfers link affected healthcare facilities



Limitations of social network approach

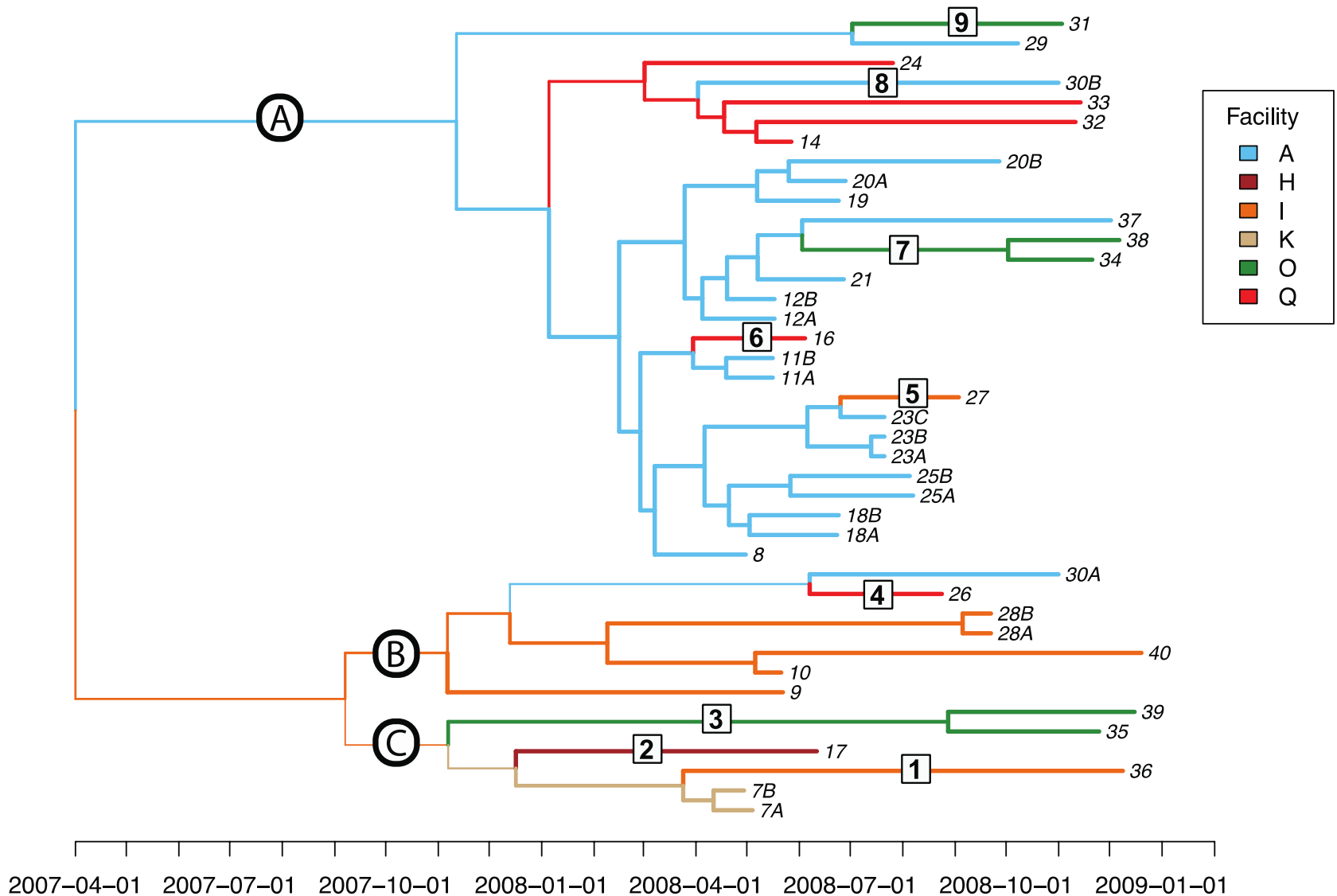
- Even if patient transfer is primary mode of regional dissemination, it remains unclear which transfer events actually drove the outbreak
- Such a detailed epidemiological investigation is only feasible for small clonal outbreaks
- Patient transfer networks are largely static, limiting their utility in evaluating the impact of interventions

Whole genome sequencing to track regional CRKP outbreak

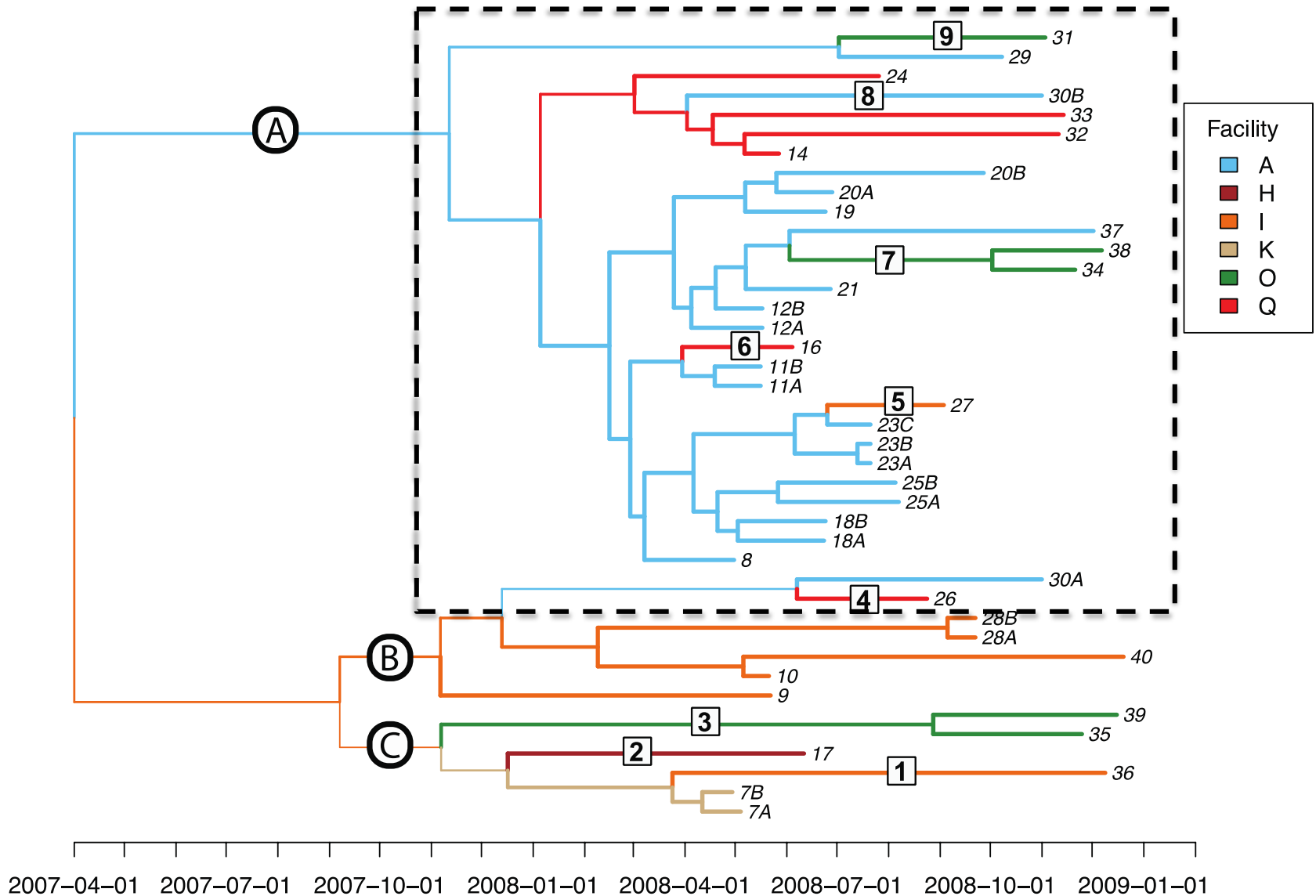
- Does whole genome sequencing provide resolution necessary to define inter-facility transmission?
- Does genomic transmission network support patient transfers having driven regional spread?
- What is the potential for genome sequencing to guide regional interventions?

An ancestral reconstruction approach to tracking regional transmission

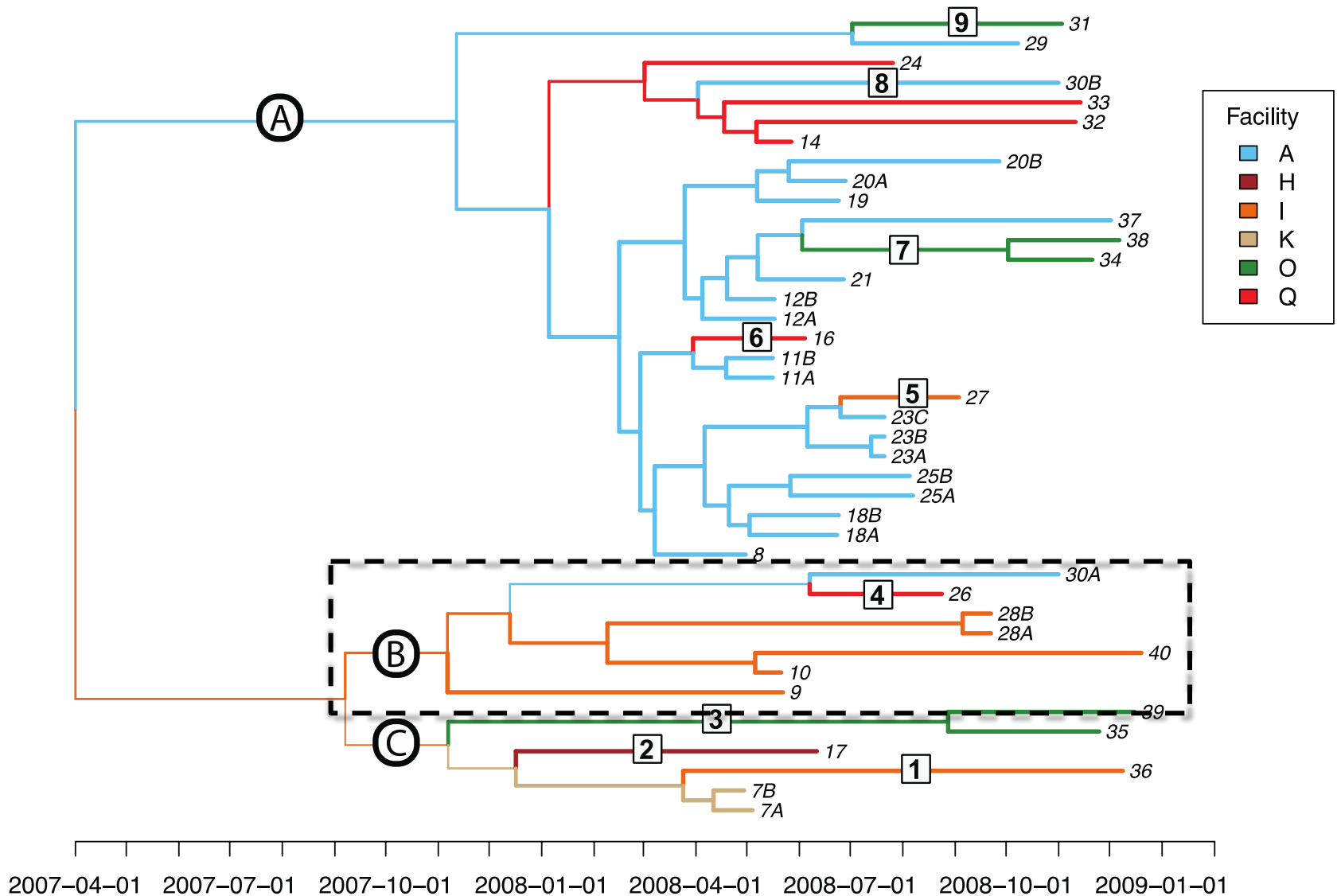
Genomic analysis provides a high-resolution picture of transmissions underlying outbreak



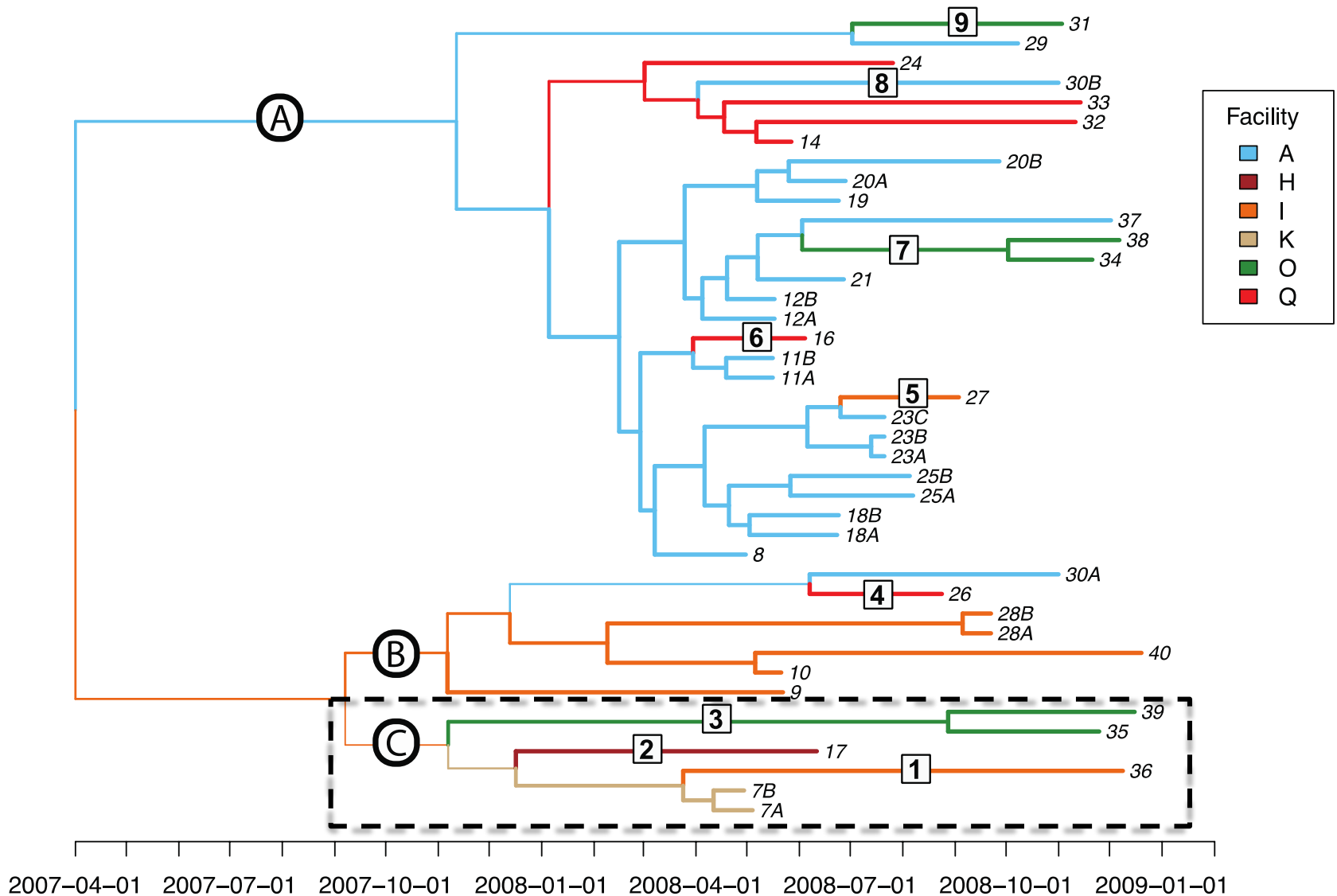
LTACH A was a key driver of regional spread



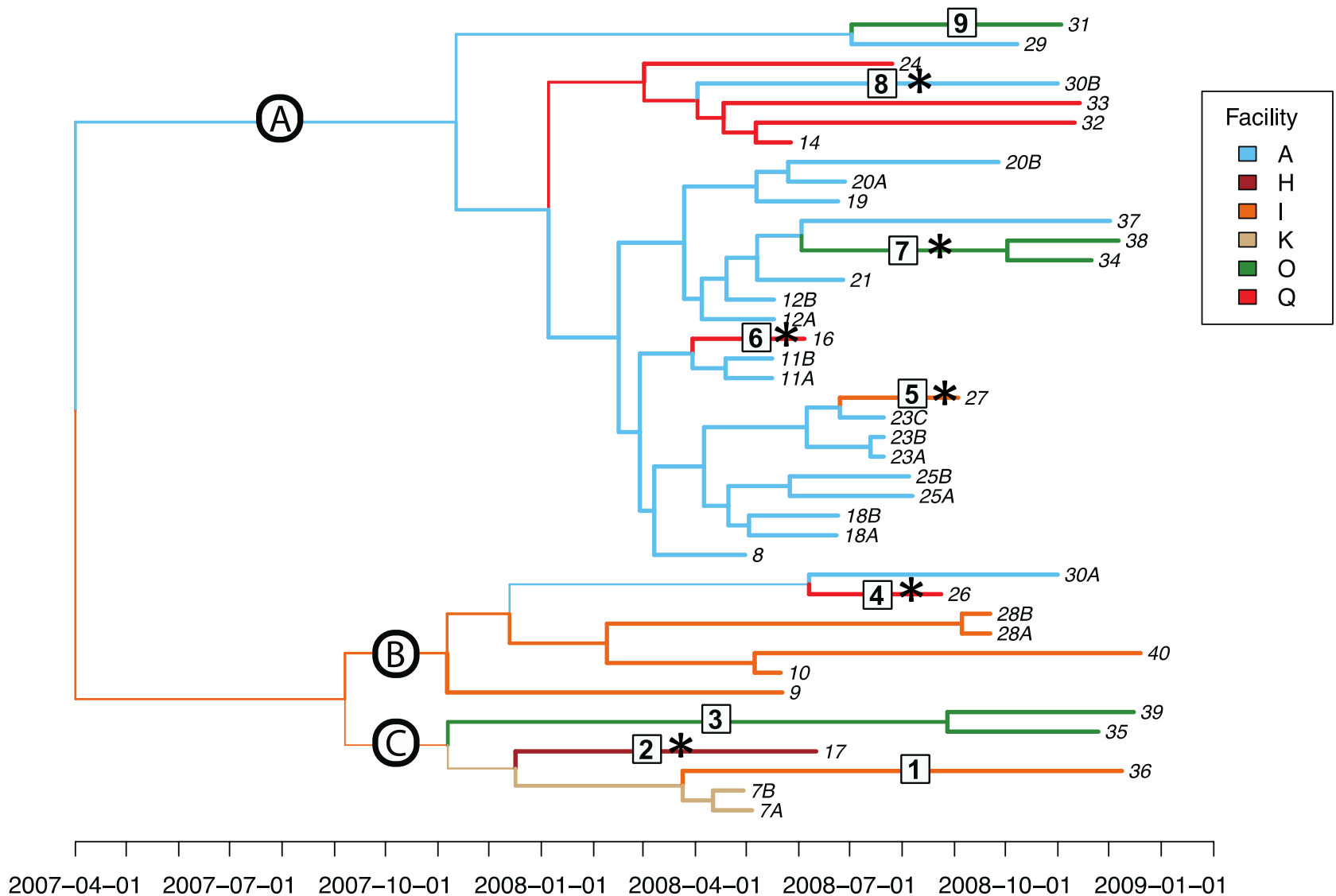
Early involvement of ACH-I was previously unappreciated



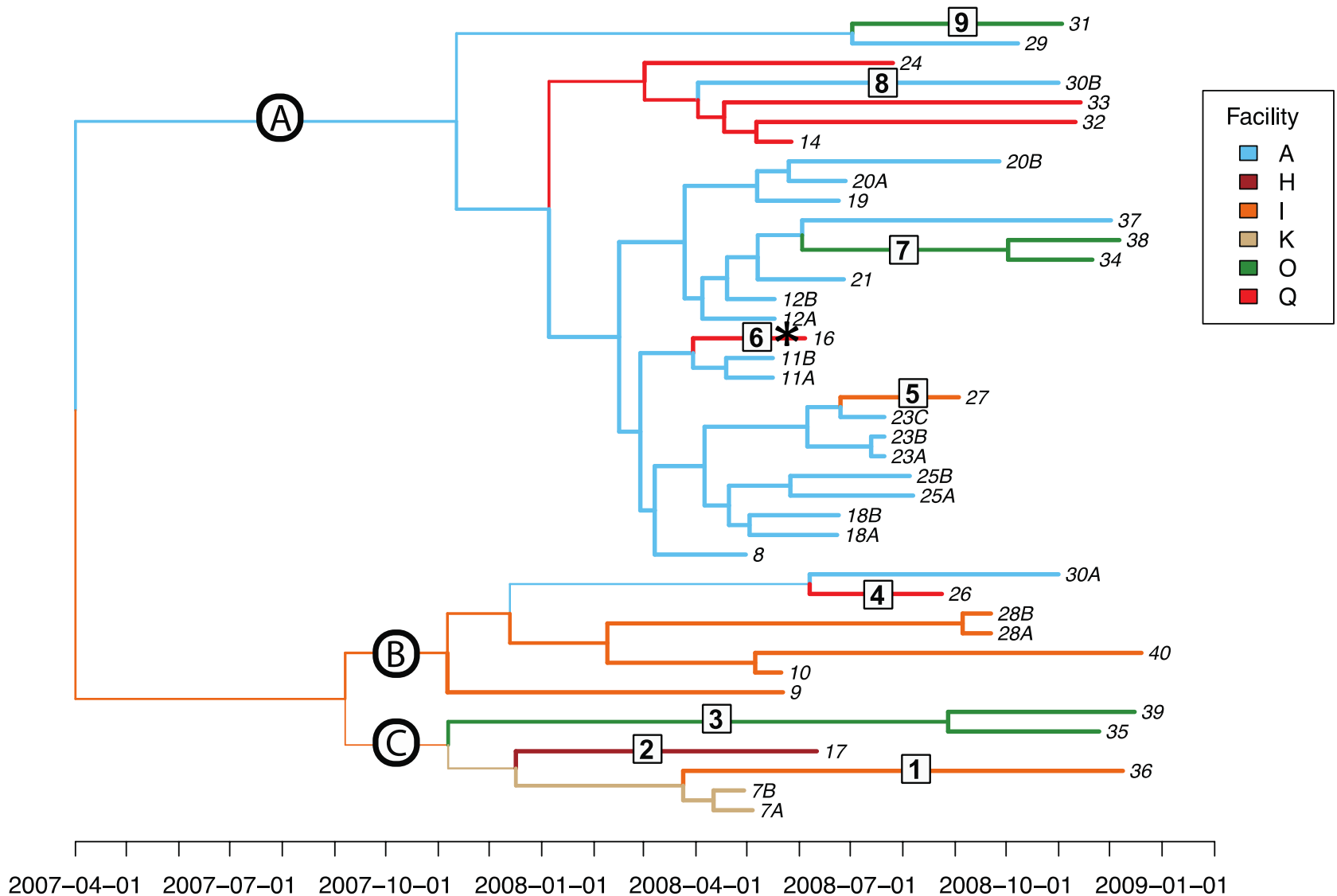
Genomic analysis highlights group of patients not consistent with patient-sharing network



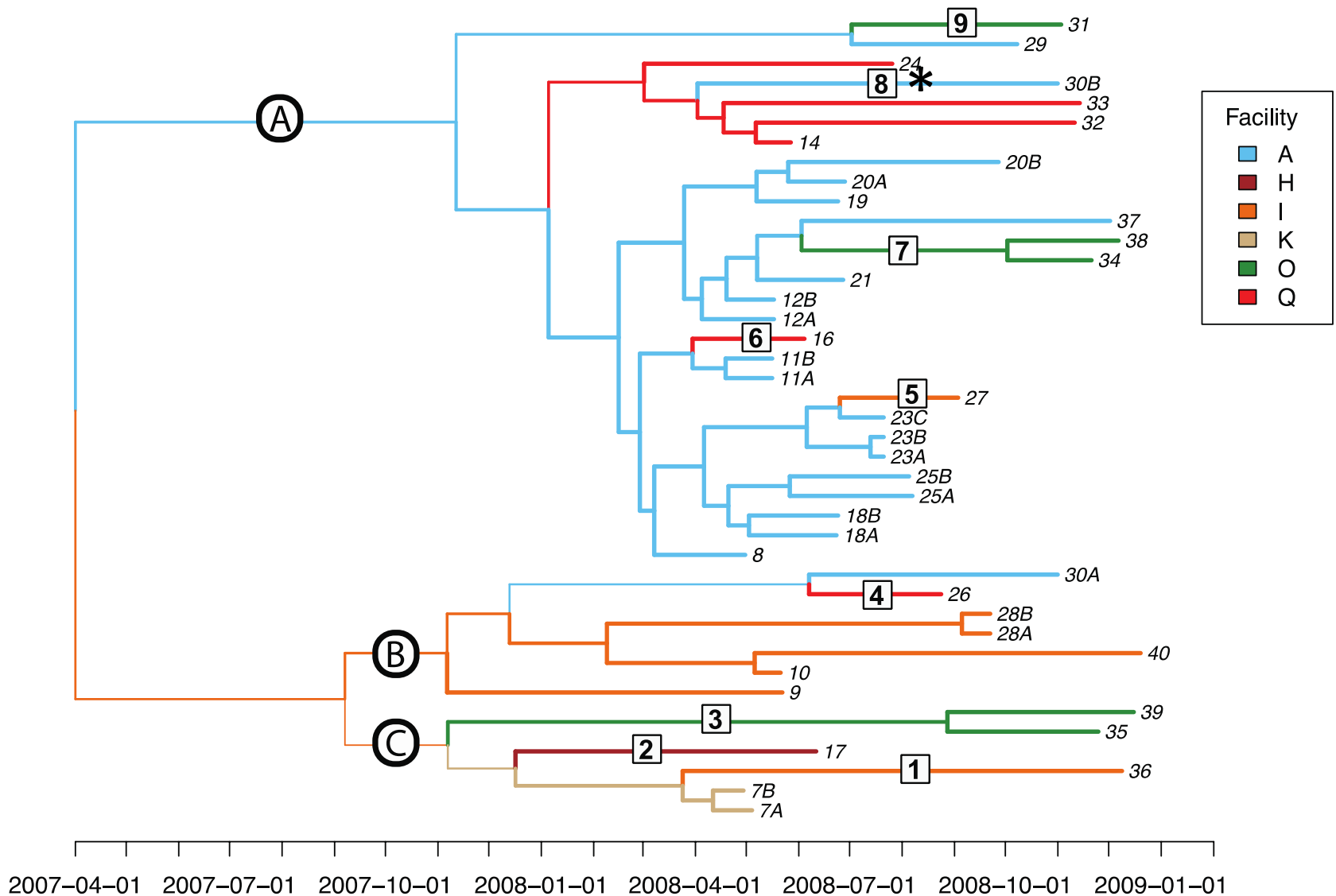
Most of genomic inter-facility transmission linkages have patient sharing explanations



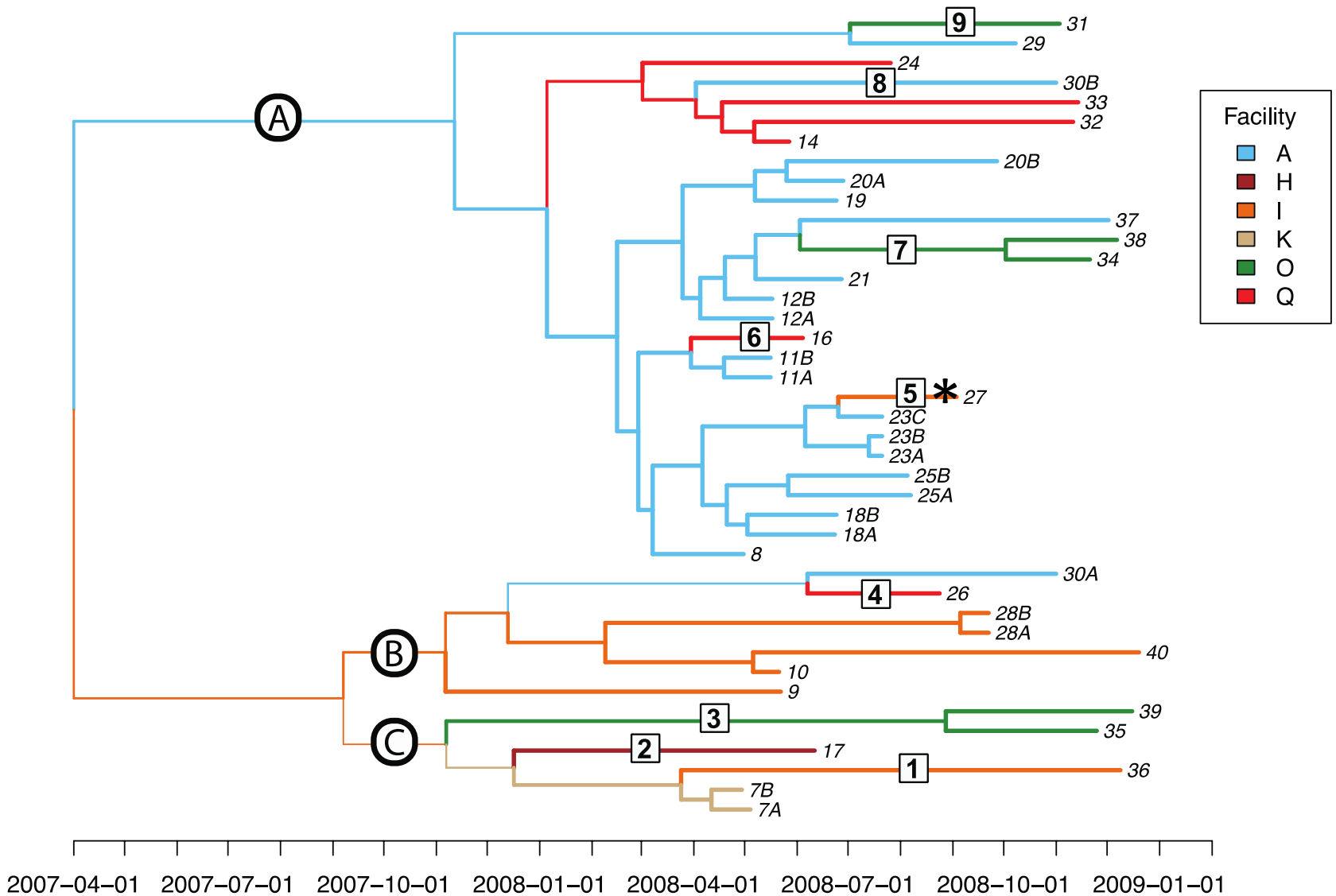
Patient 16 was in facility A (blue) before going to Q (red)



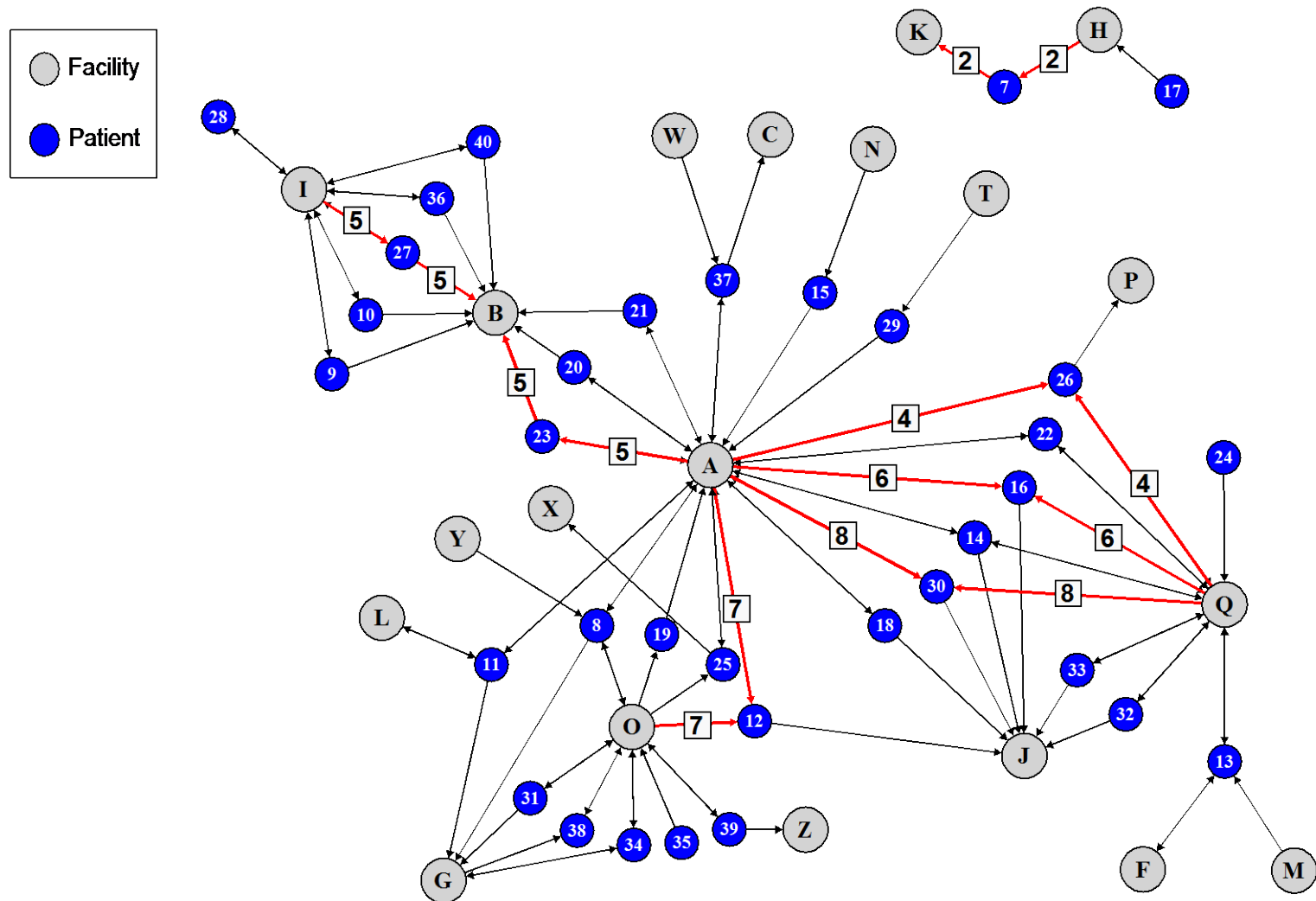
Patient 30 was in facility Q (red) before going to A (blue)



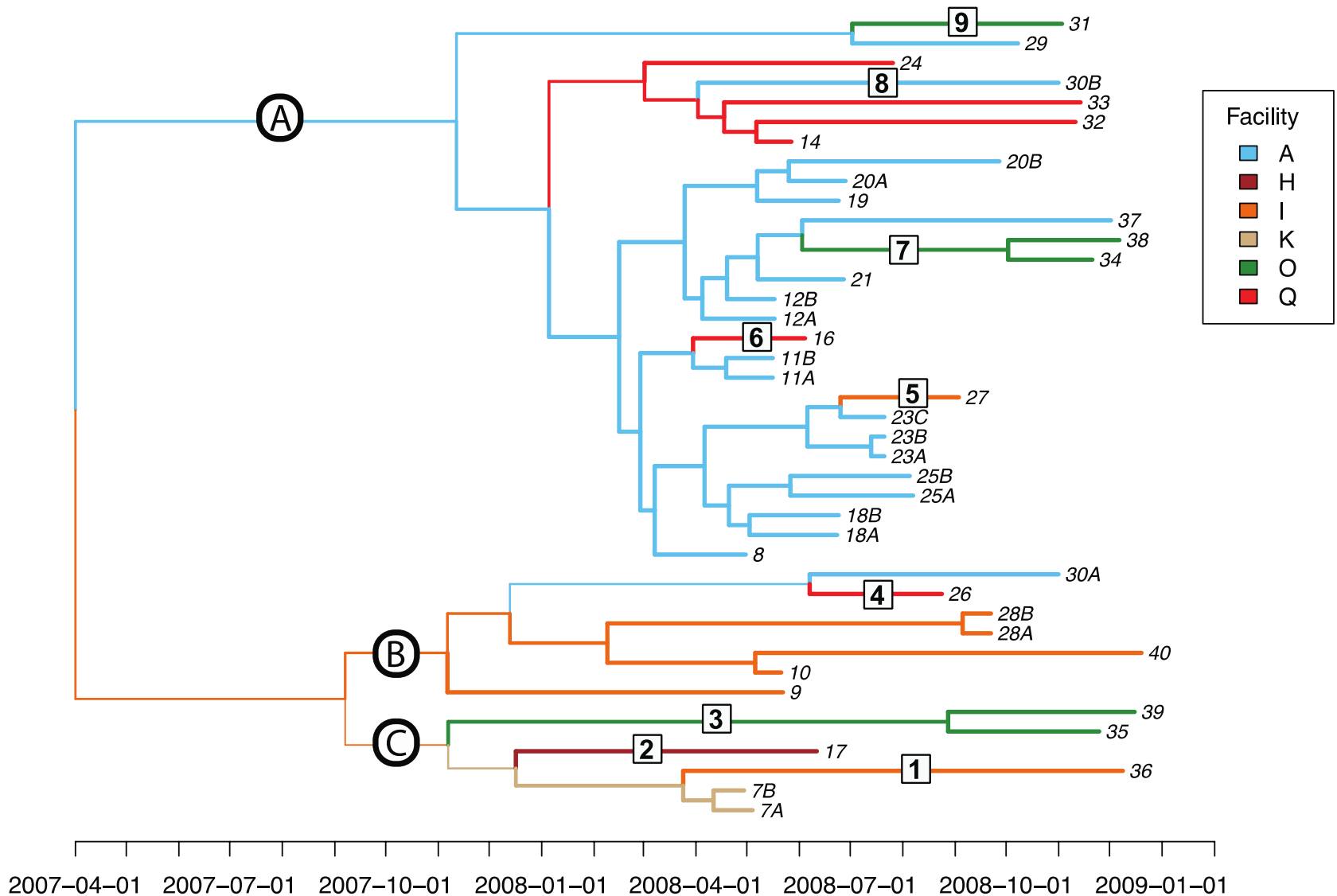
Patient 27 and 23 spent time in a common facility – NH-B



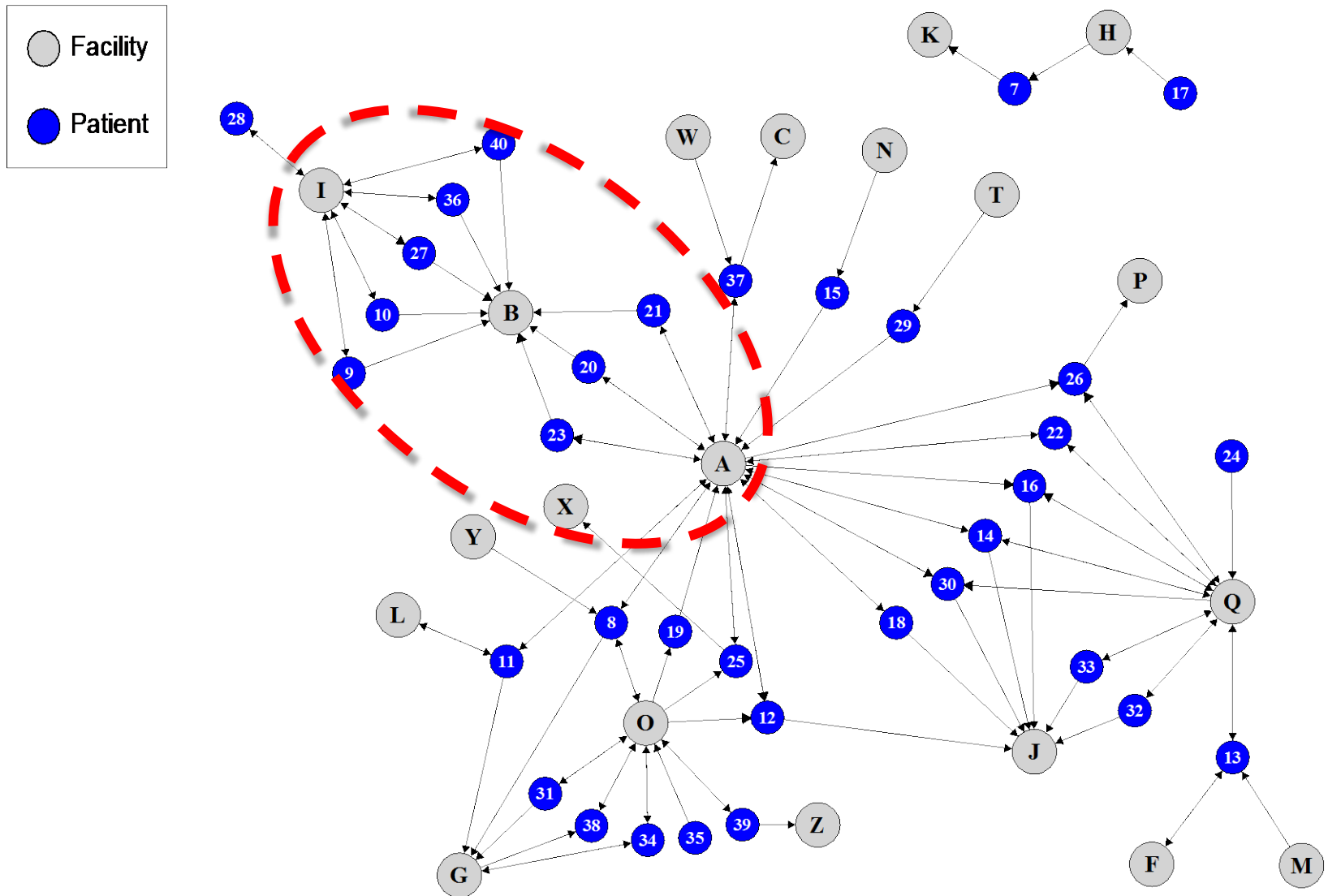
A subset of patient transfers is sufficient to explain regional spread



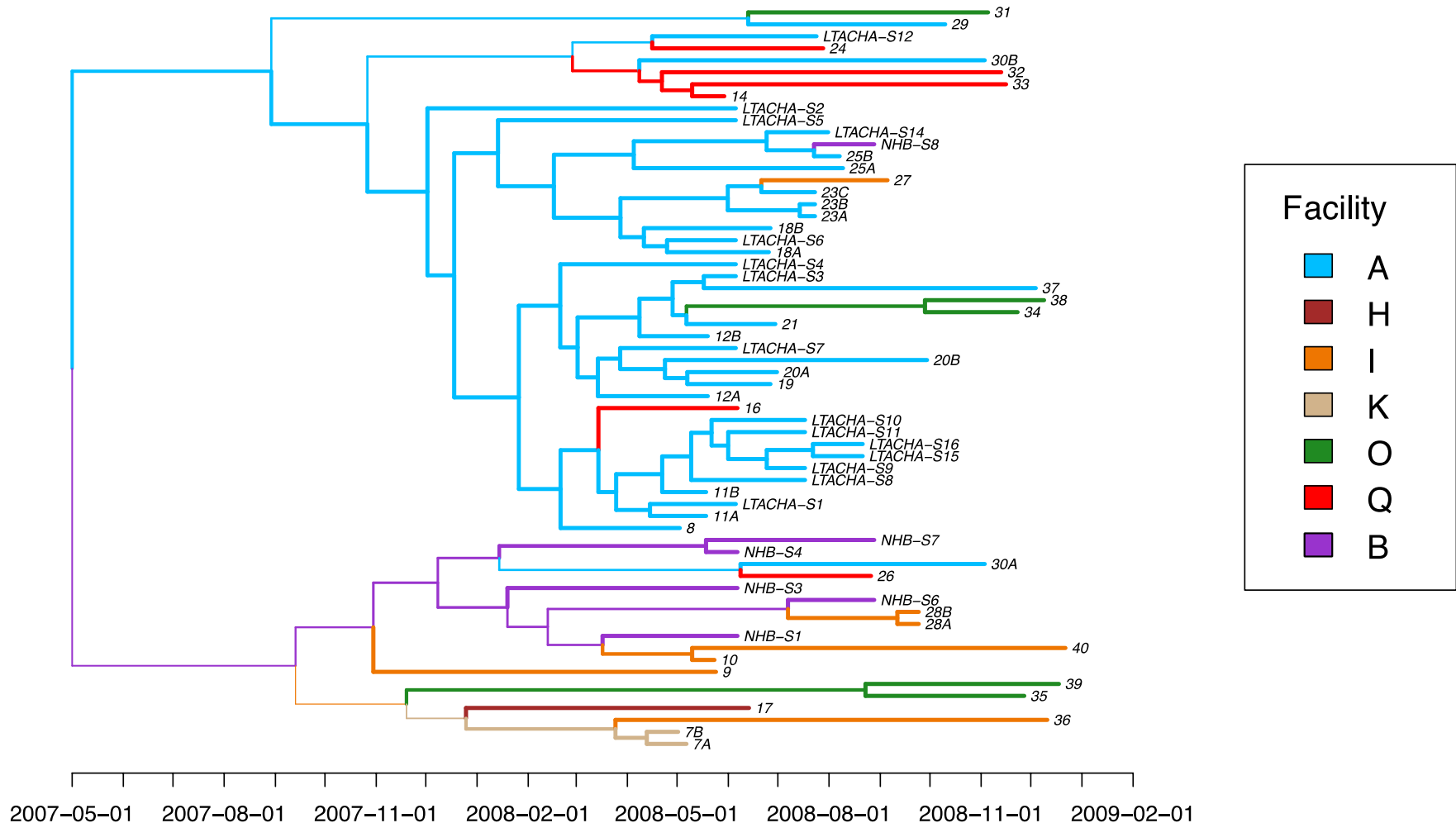
Is there any relationship between ACH-I and LTACH-A that could explain early transmissions?



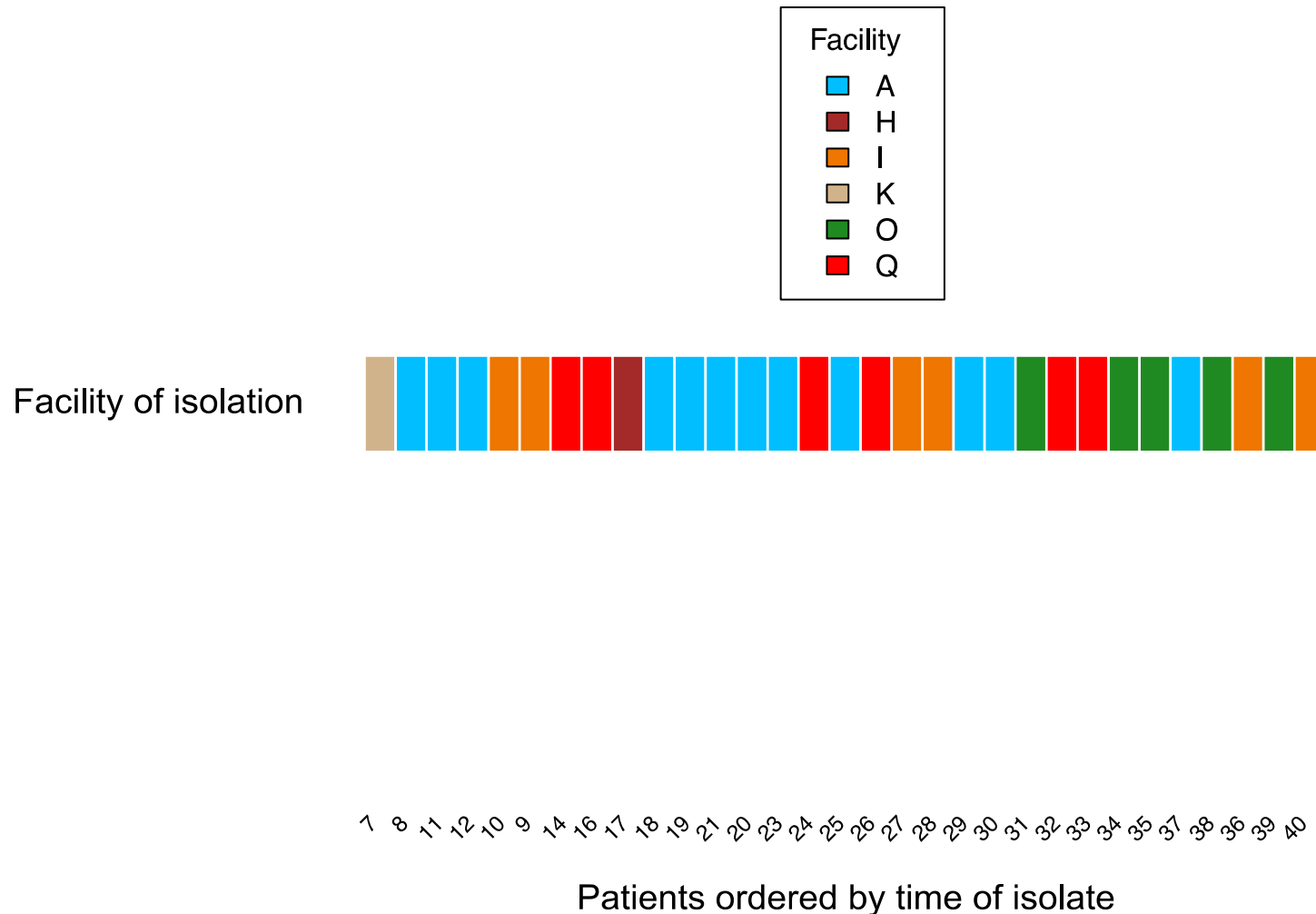
LTACH-A and ACH-I are connected by NH-B



Surveillance isolates from NH-B are inter-mixed with isolates from ACH-I and LTACH-A



Simulation of real-time data yields accurate predictions of isolate origin



Conclusions from regional outbreak investigation

- WGS provides sufficient resolution to discern intra- and inter-facility transmission events
- Comparison of genomic and patient-sharing networks supports inter-facility transfers having driven regional outbreak
- Integrated analysis of genomic and patient sharing networks facilitates epidemiologic hypothesis testing
- Genomic surveillance has the potential to aid in real-time control of regional outbreaks

Genomic insights into the spread of infections within and between hospitals

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How can we prioritize healthcare facilities for regional intervention?

- Facilities that are maximal intra-facility amplifiers of regional MDRO burden (e.g. those with highest transmission rates)
- Facilities whose connections to other facilities lead to maximal amplification of MDRO burden in other facilities

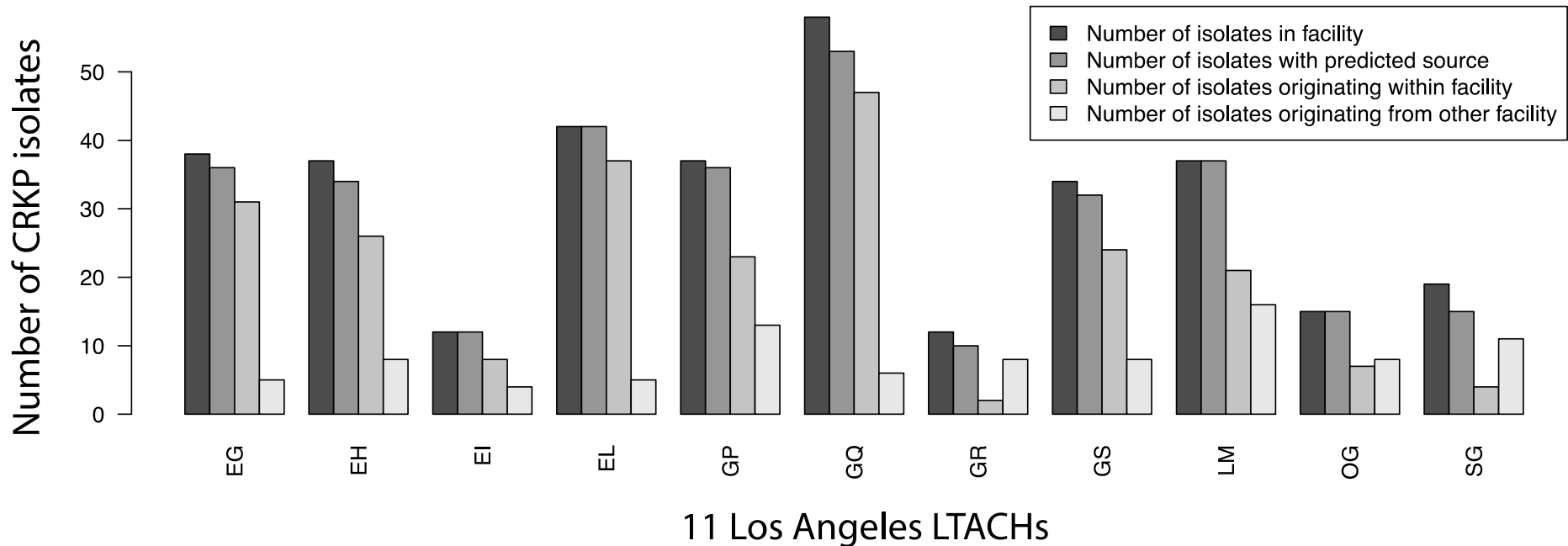
Long-term acute care hospitals at the center of the *CRKP* epidemic

- Long-term acute care hospitals (LTACHs) are increasingly recognized as reservoirs and amplifiers of drug resistance
 - High acuity and long stay patient population
 - Heavy antibiotic usage
 - Reduced resources for infection prevention
- Study in Chicago region found 4% prevalence of CRKP in acute care hospitals and > 30% in LTACHs
- Study in same region found that sharing patients with LTACHs was associated with a two-fold increase in infection rates

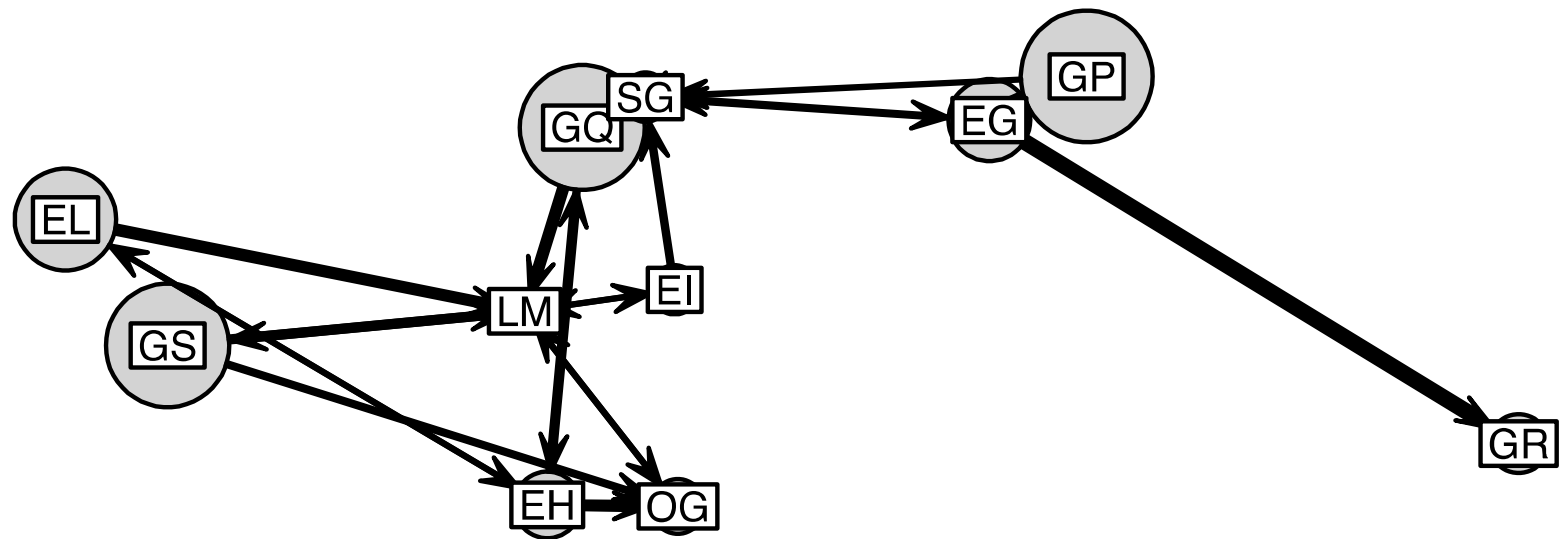
WGS to track regional spread of CRKP across Los Angeles LTACHs

- 11 LA area LTACHs where CRKP is endemic
 - Collected >400 clinical isolates of CRKP during 1-year study
- Key proof of concept questions
 - Can WGS distinguish intra- and inter-facility transmissions?
 - Can WGS inform how CRKP moves between LTACHs
 - Does CRKP importation LTACHs drive infection rates?

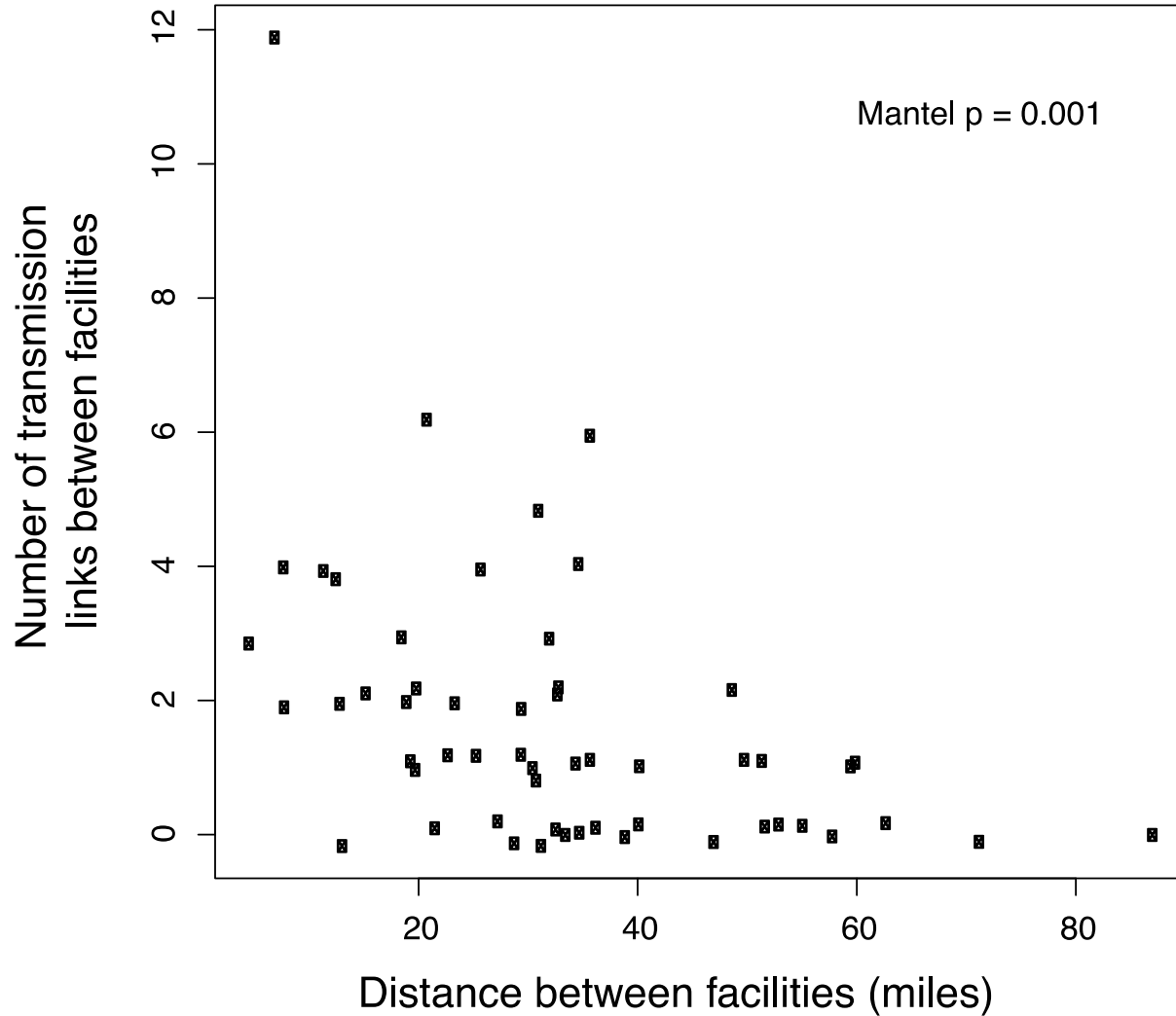
LTACHs vary in CRKP prevalence and relative burden associated with outside importation



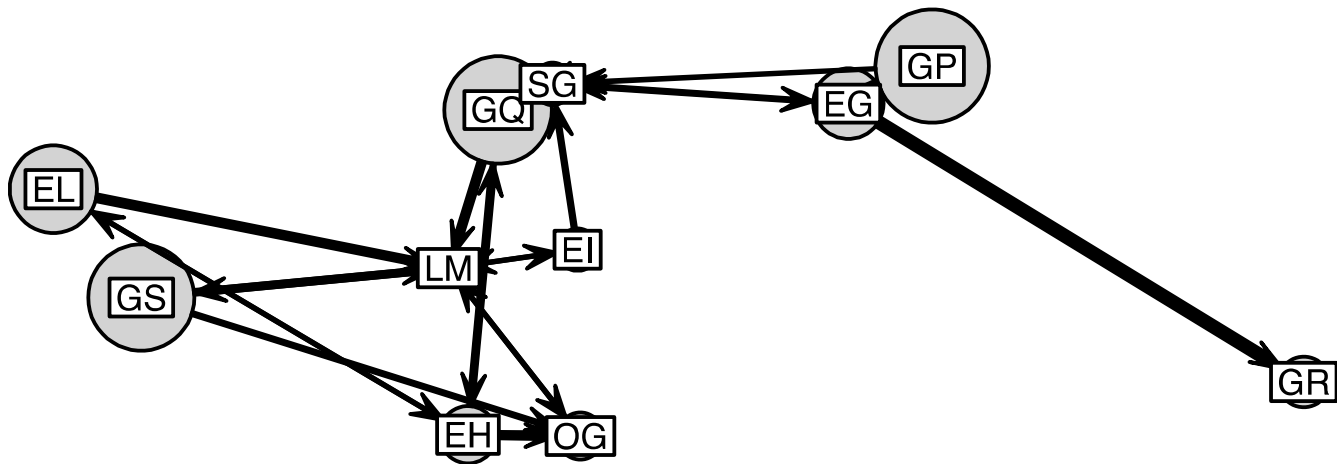
Genomic transmission map for 11 LA-area LTACHs



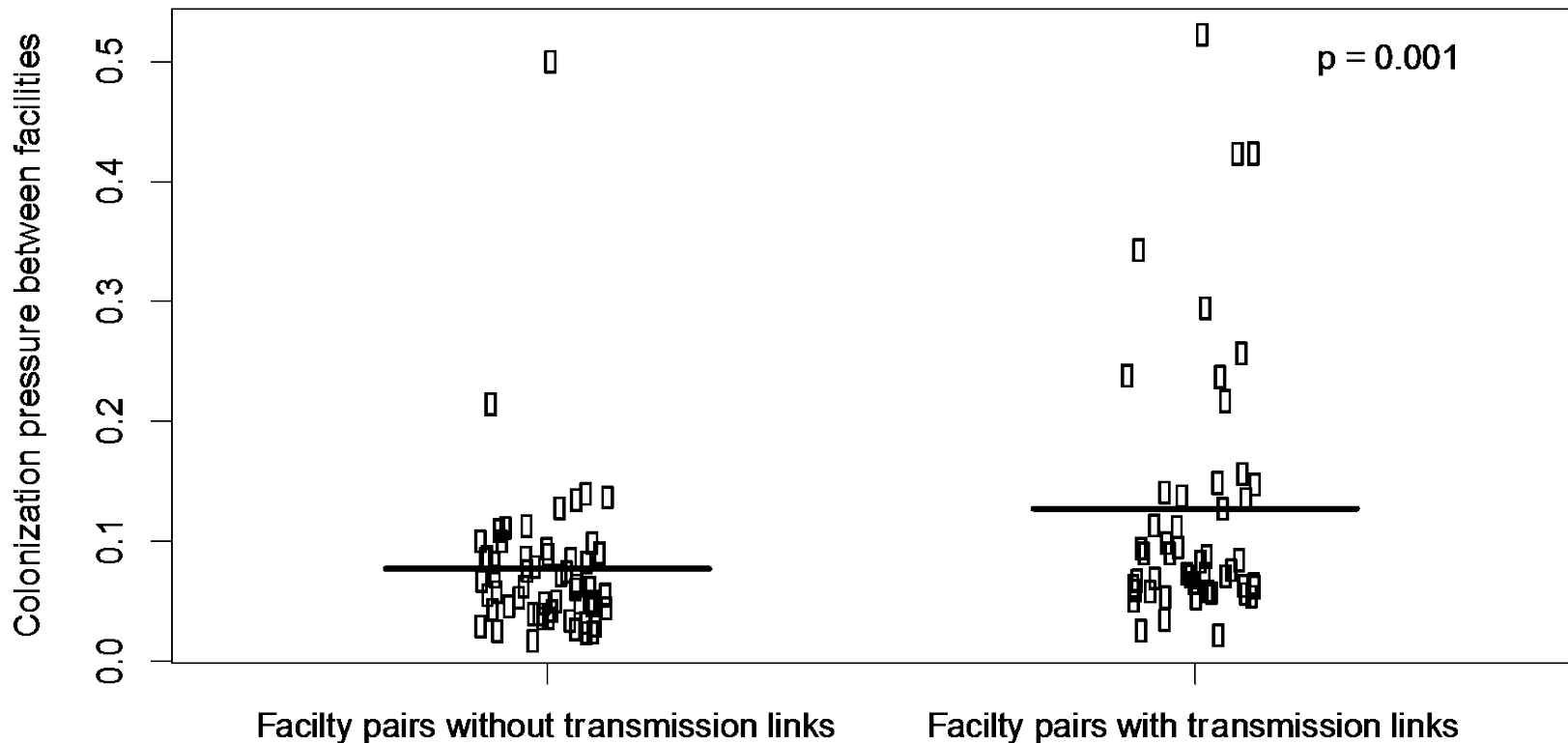
Transmissions occur between geographically proximate facilities



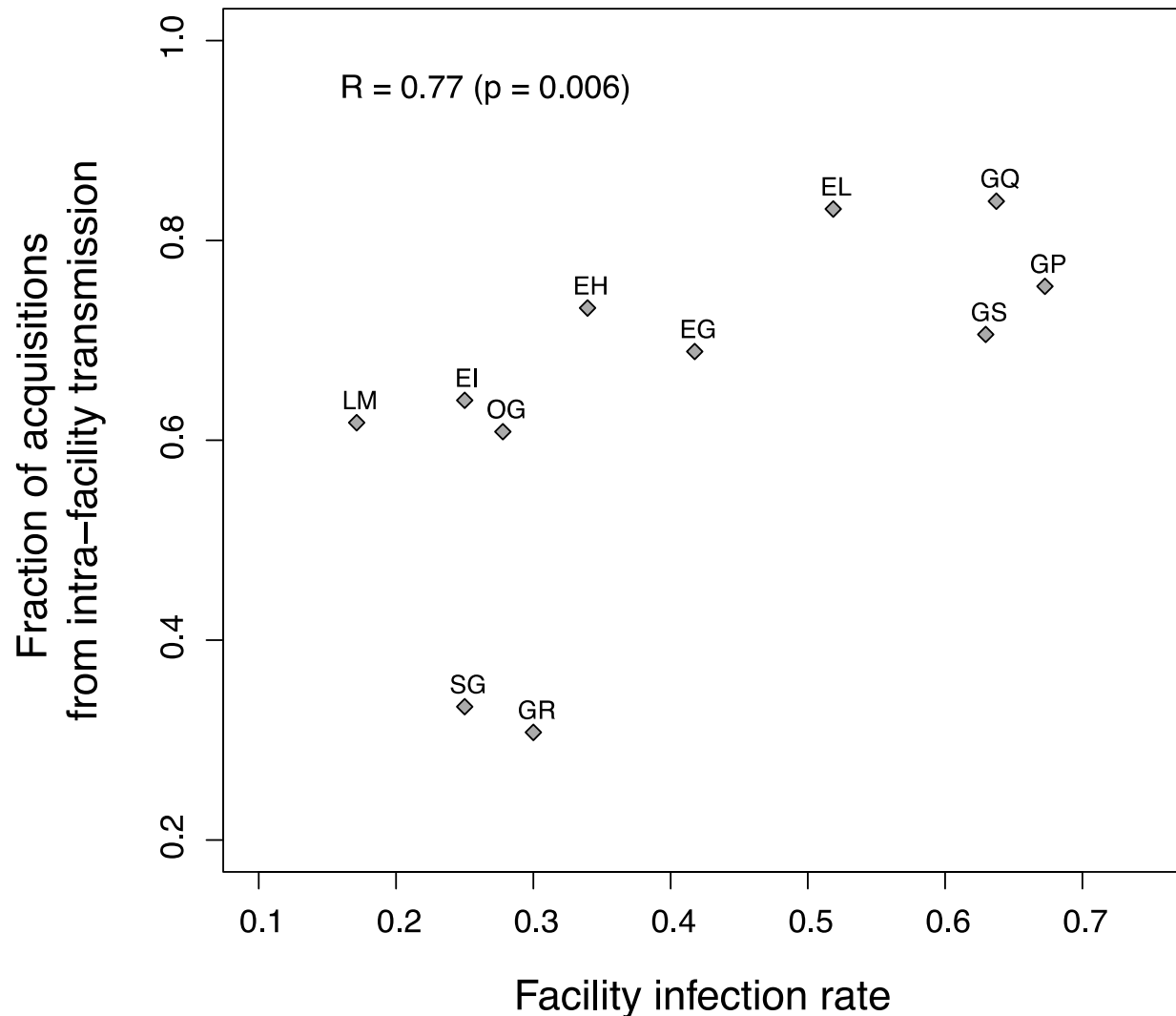
Its not just proximity – but also CRKP
prevalence at proximate facilities



Transmissions originate from facilities imposing higher colonization pressure



CRKP burden within facilities is associated with intra-facility transmission rate



Conclusions from regional LTACH study

- Whole genome sequencing allows for insight into the regional movement of endemic organisms
- CRKP transmissions between LTACHs can be detected, but prevalence is driven by local transmission rates
- Genomic surveillance has the potential to guide targeted interventions by identifying high-transmission facilities and regional reservoirs

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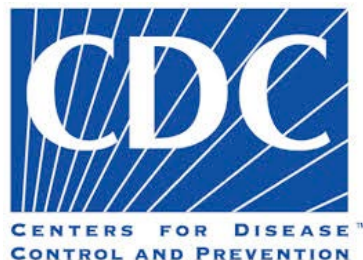
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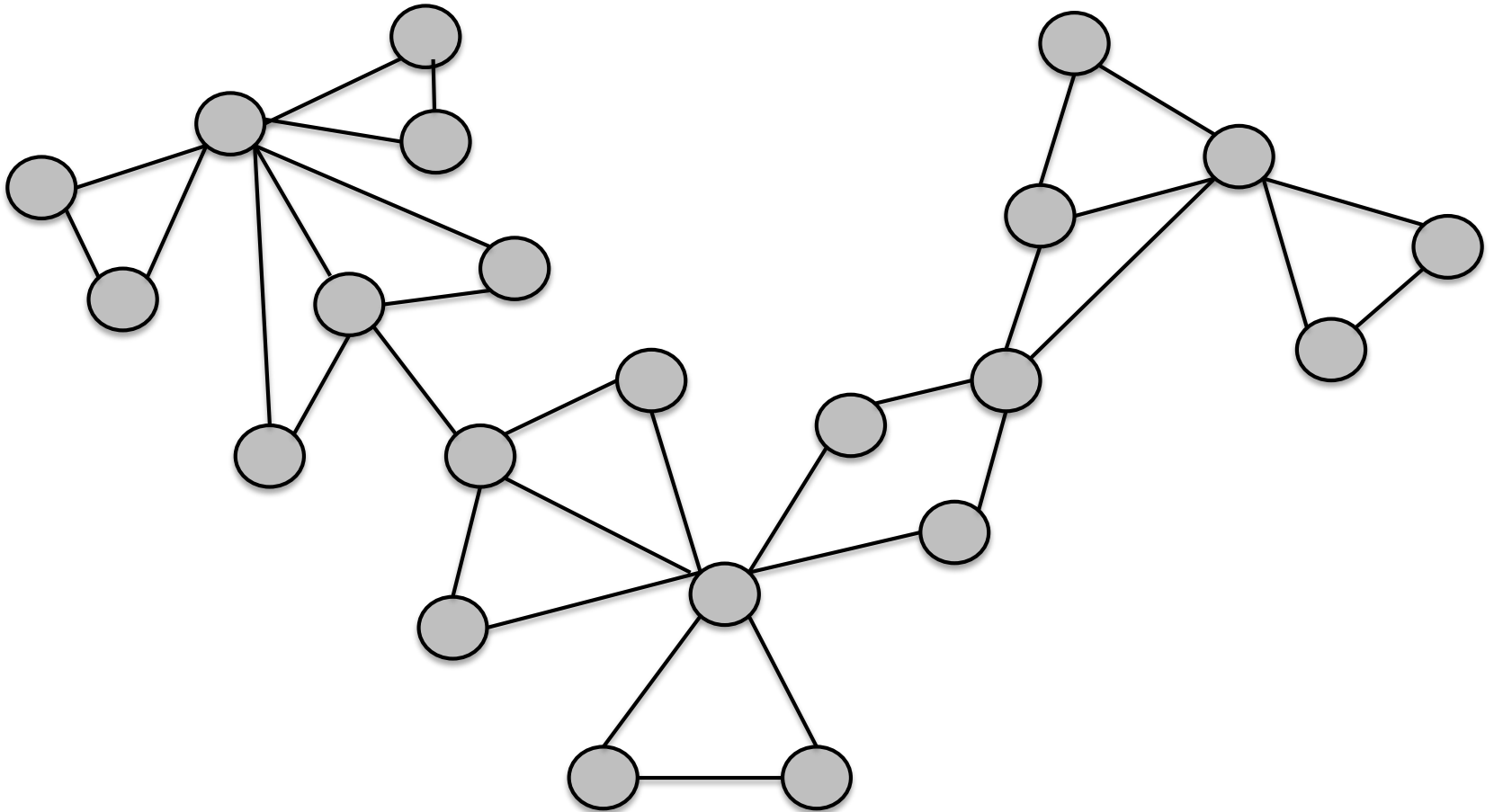
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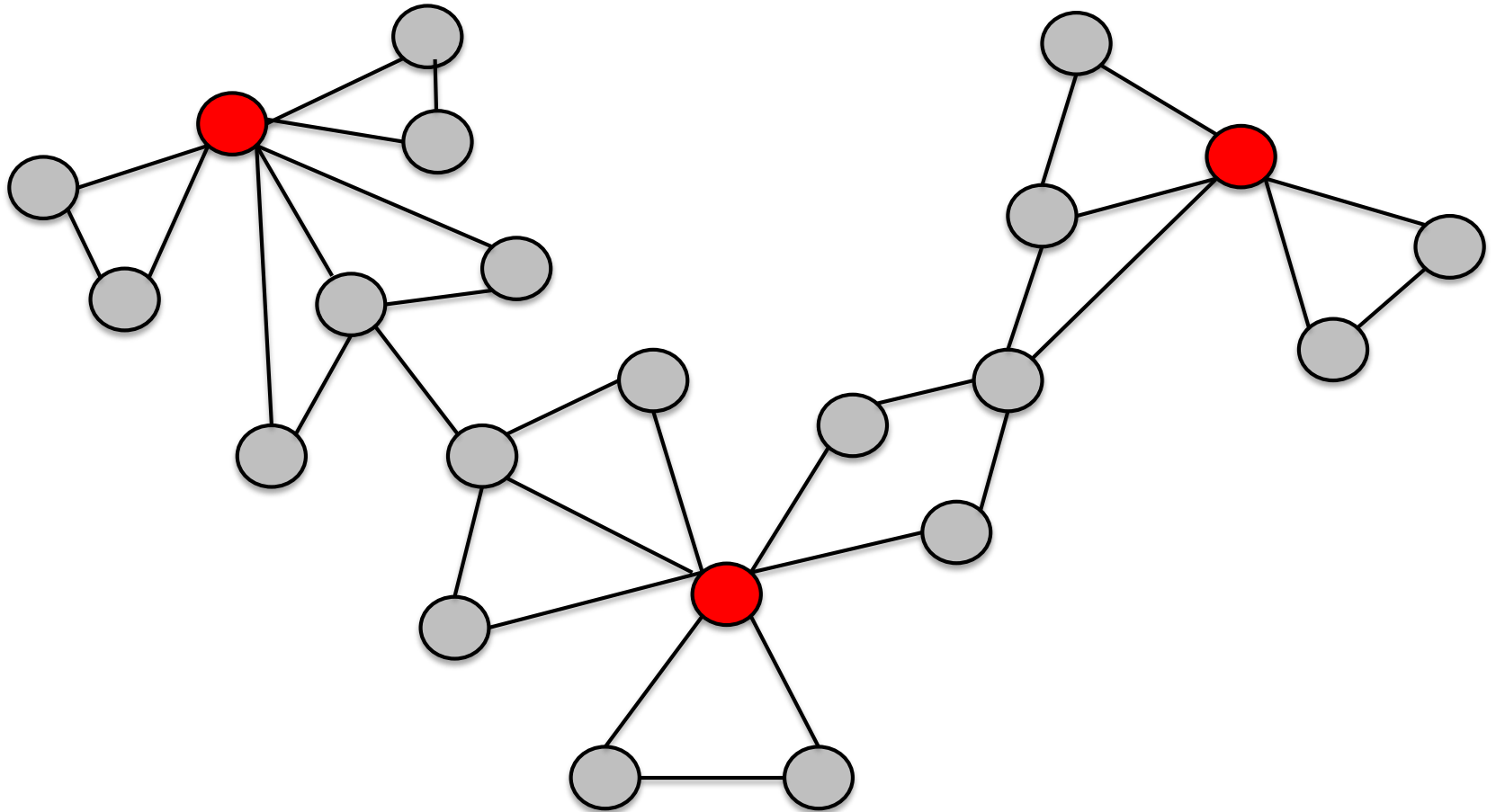
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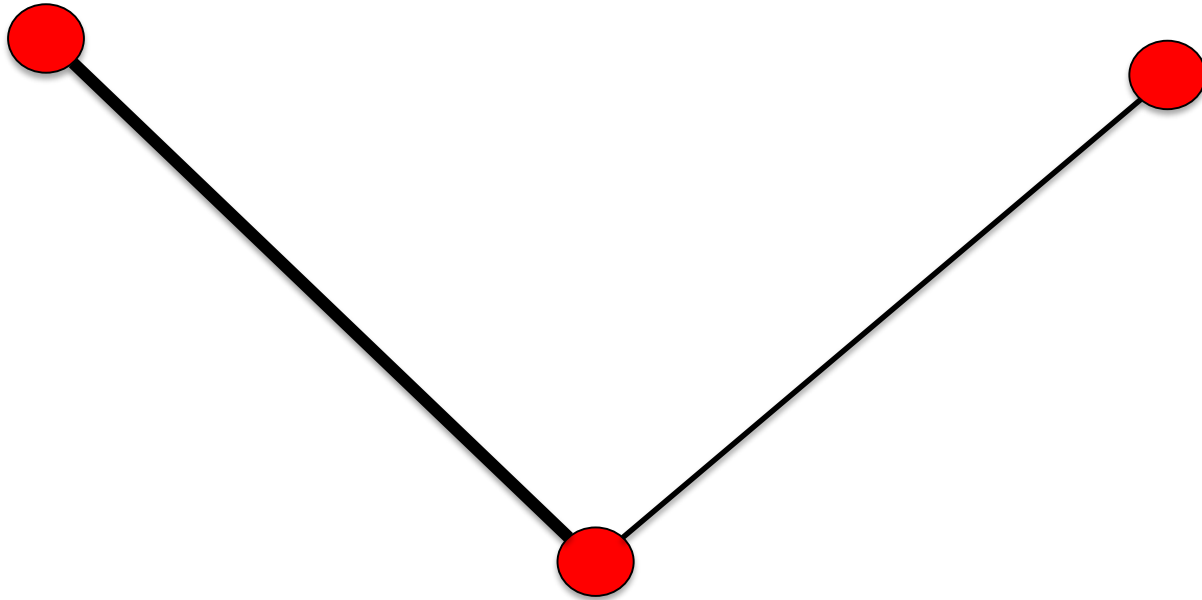
Vision of regional monitoring



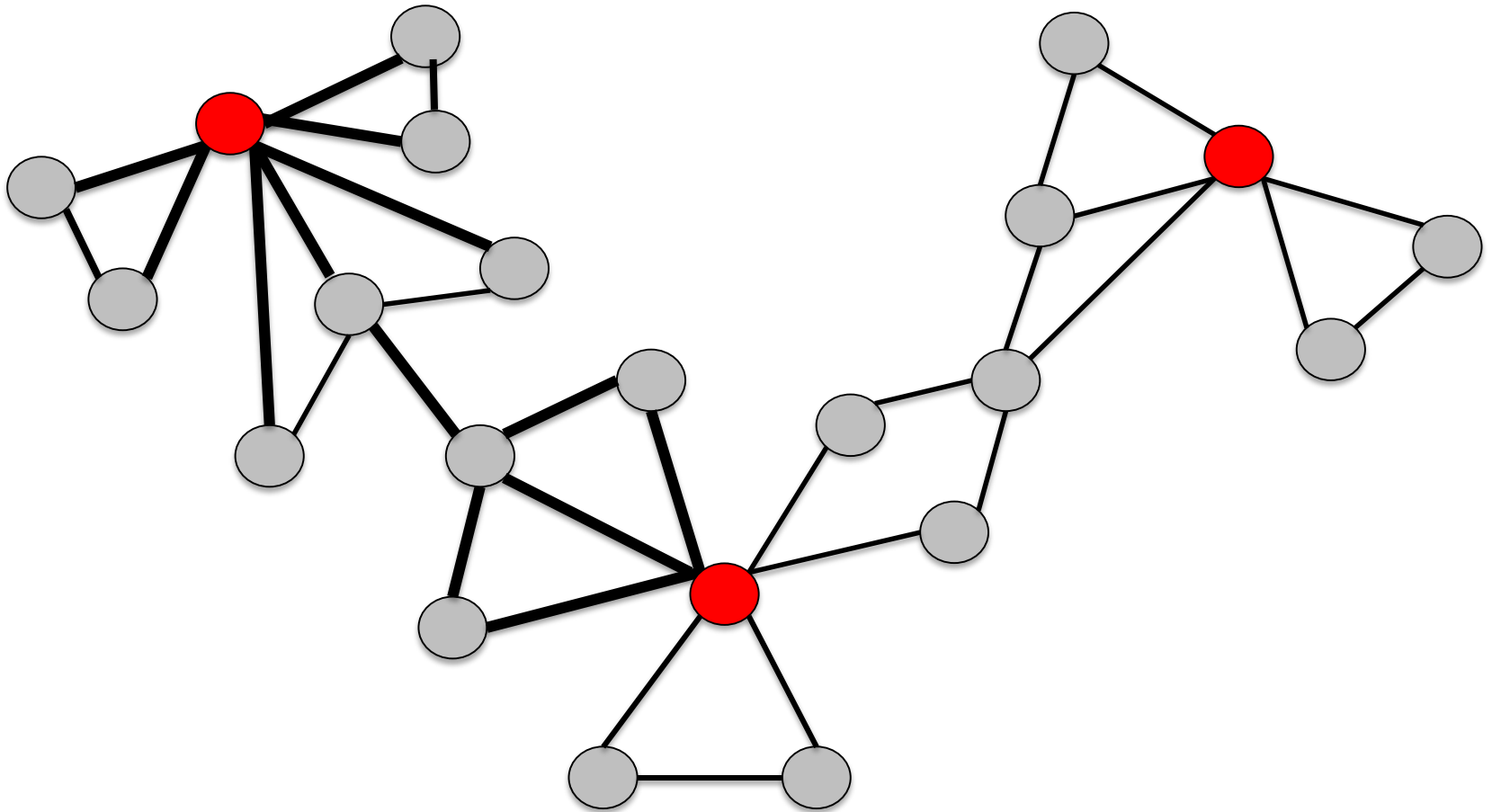
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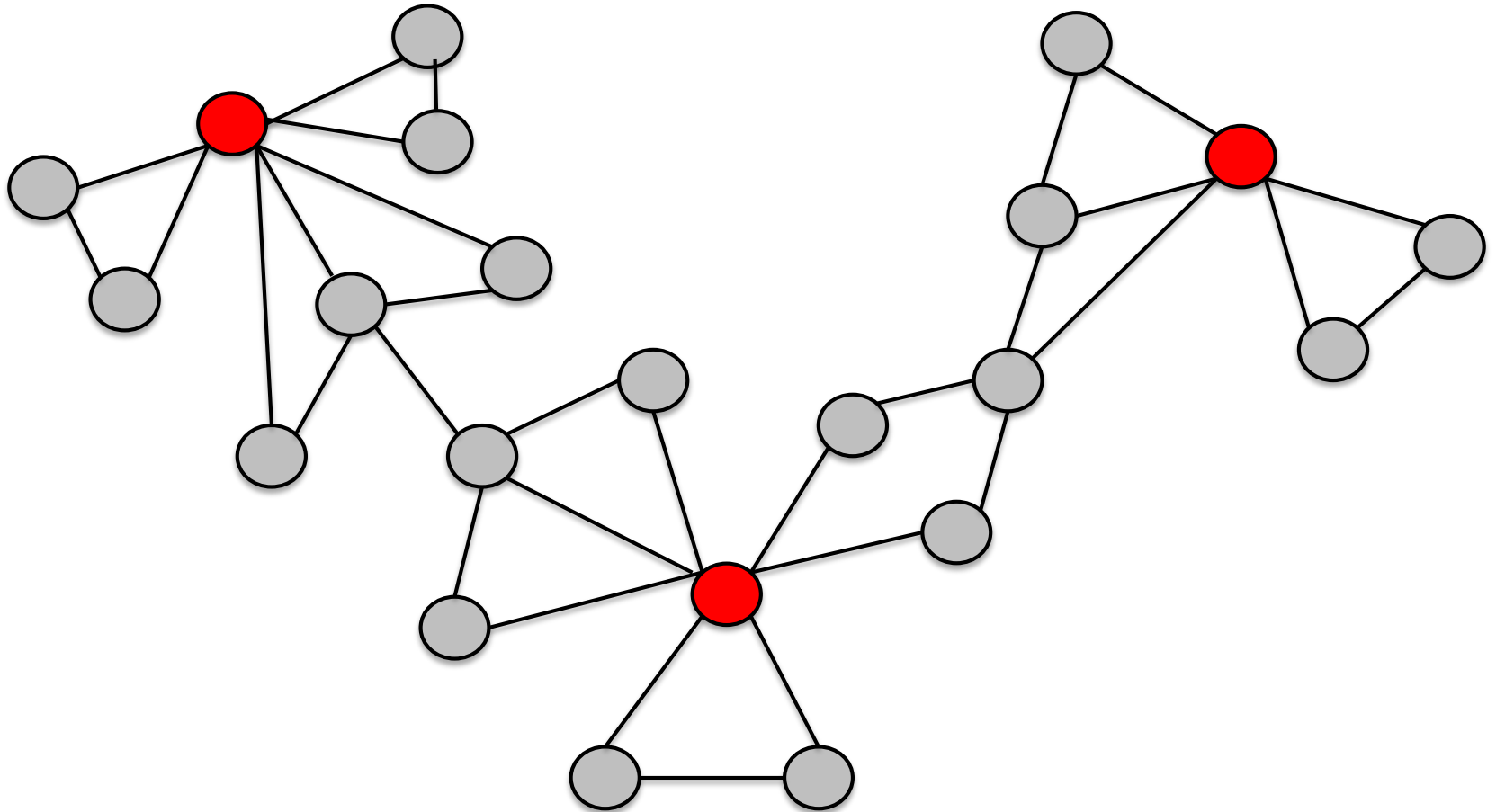
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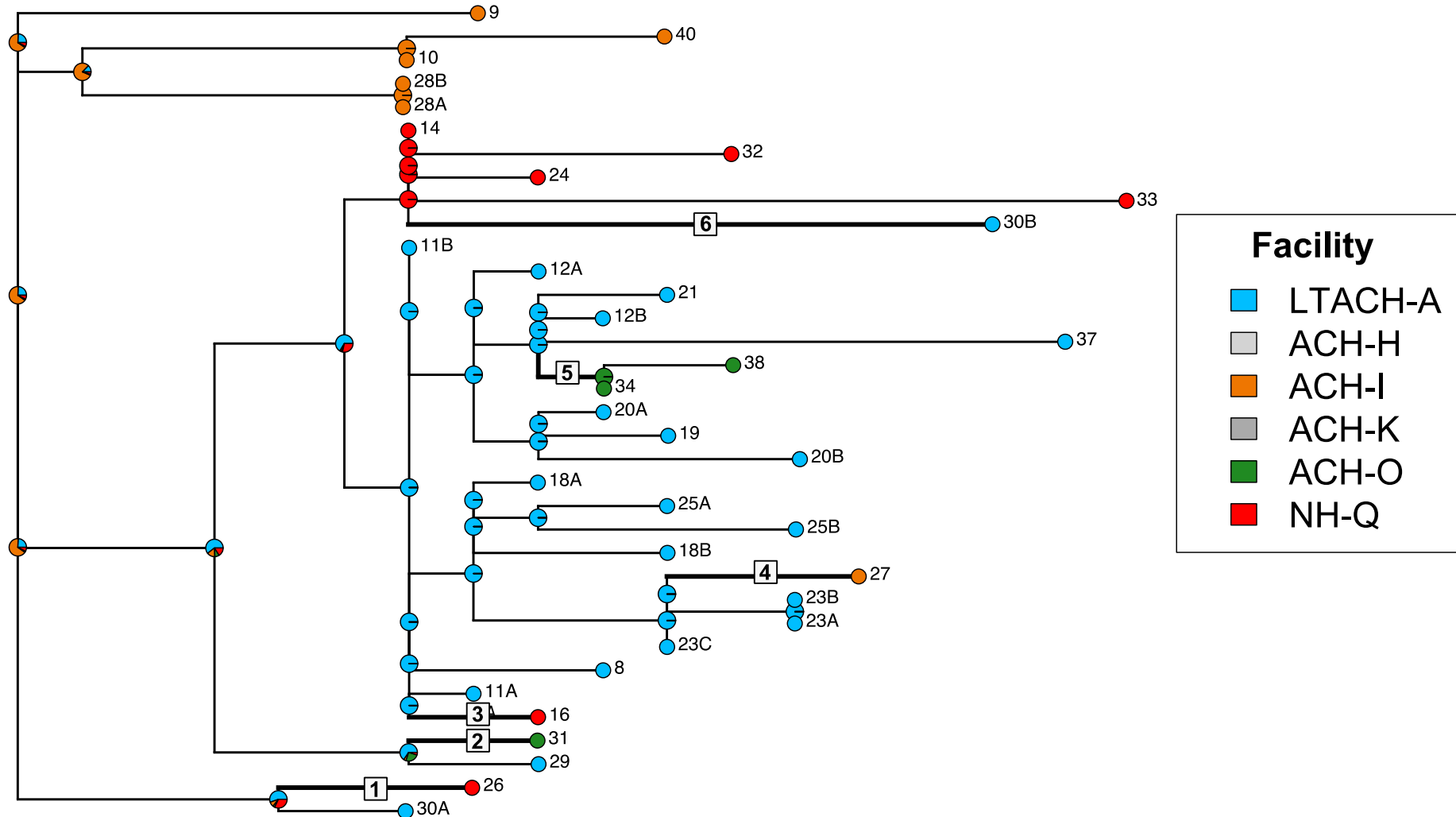
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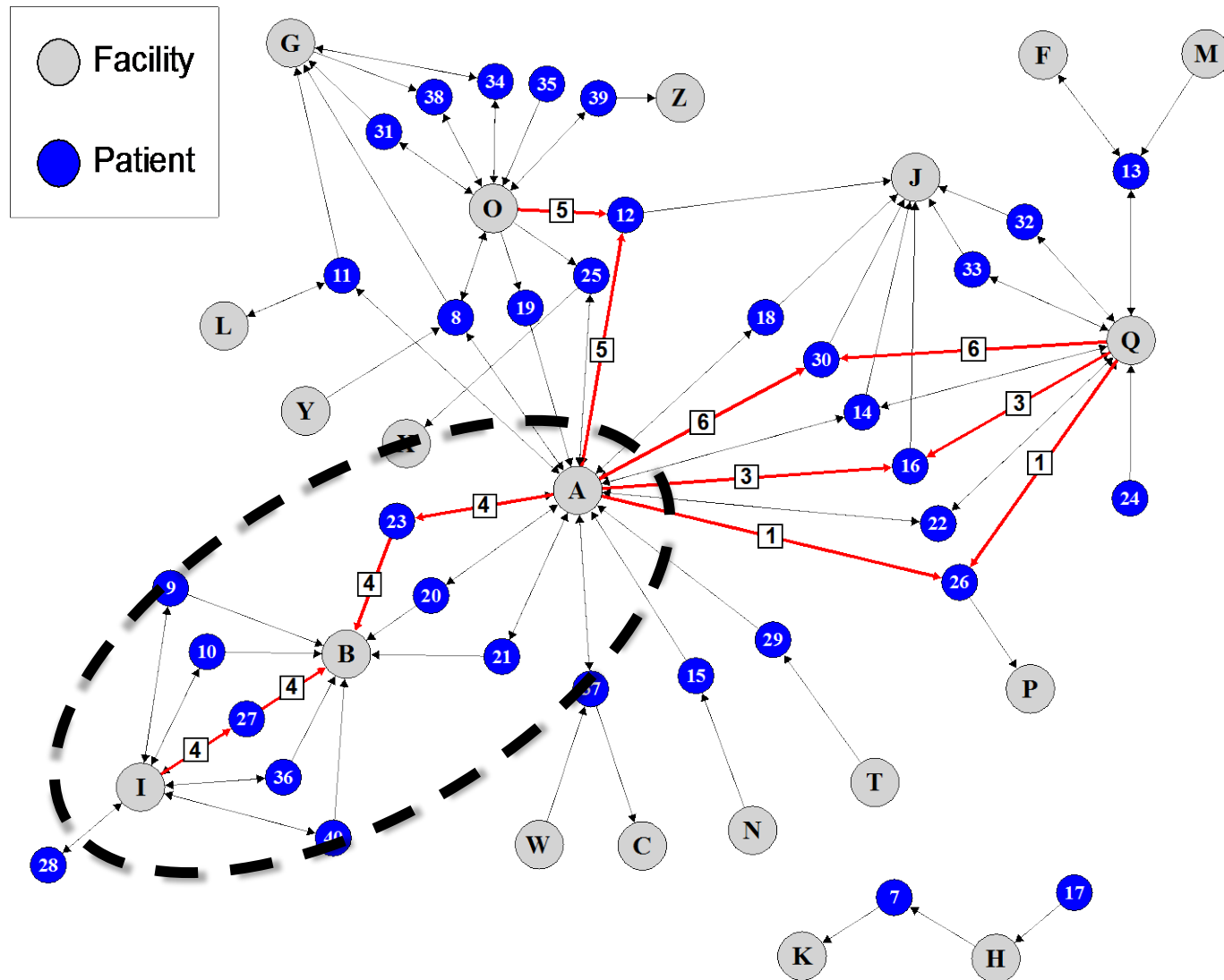
Does amount of importation from outside facilities determine infection rates?



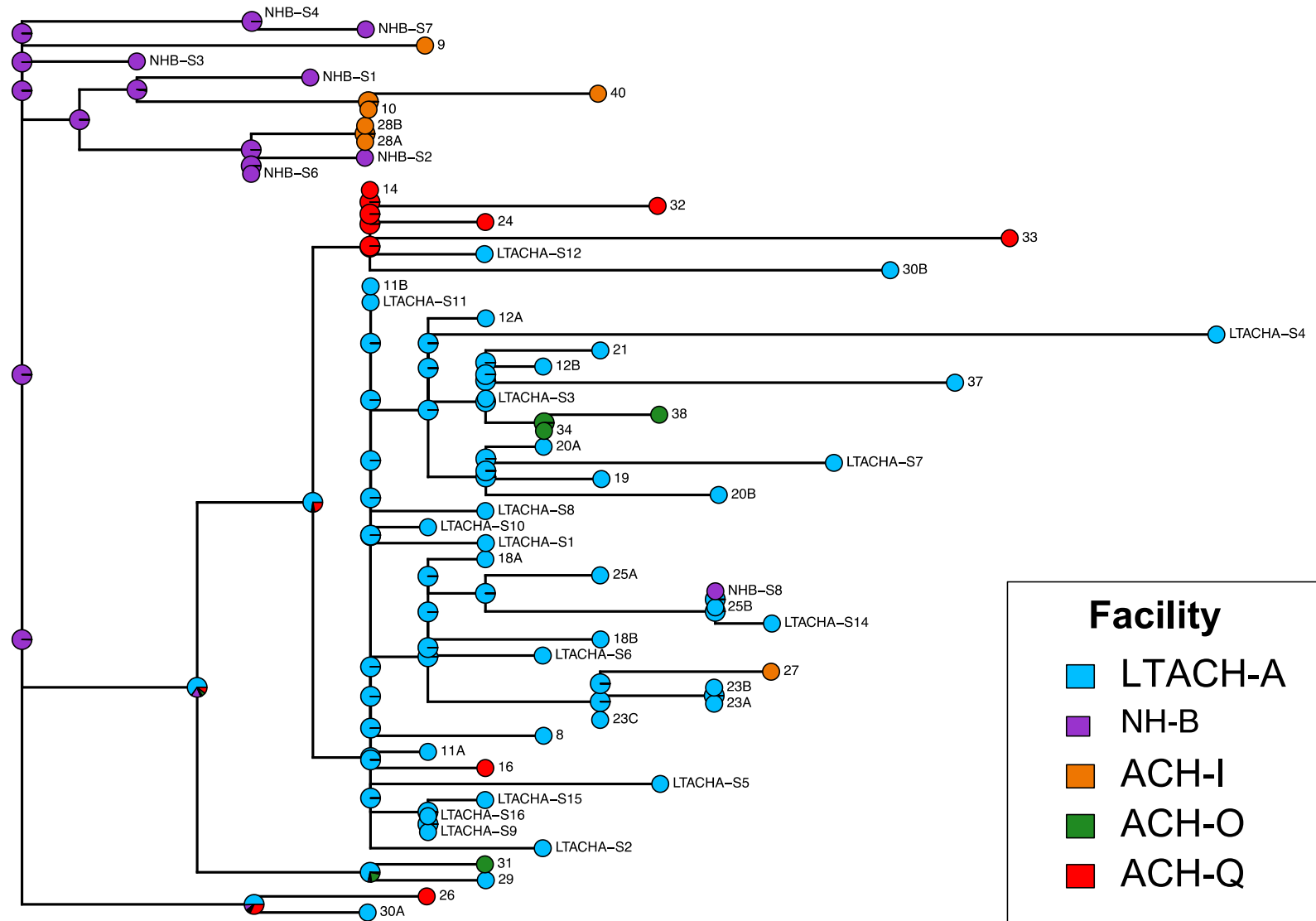
Can we understand events that transpired at the beginning of the outbreak?



LTACH-A and ACH-I are connected via NH-B



WGS confirms NH-B as the likely conduit between LTACH-A and ACH-I



The power of WGS comes from its probing of single nucleotide variation

- Clock-like accumulation of single nucleotide variation allows for estimation of time-scale on which two isolates are related
- Mutational clock also facilitates dating of historic events (e.g. when outbreak began)
- Probing of single nucleotide variation allows for linking of variation to function (e.g. antibiotic resistance)