The Importance of Research

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Overview of talk

1. LOOKING BACK: Evidence that research (followed by action) has impacted on rates of healthcare-associated infection (HCAI) in the UK

1. TAKING STOCK: At what points in the care pathway could fresh research activities be undertaken that lead to further reductions in HCAI?

1. FUTURE RESEARCH: Description of an important emerging technology and its potential capabilities

LOOKING BACK:

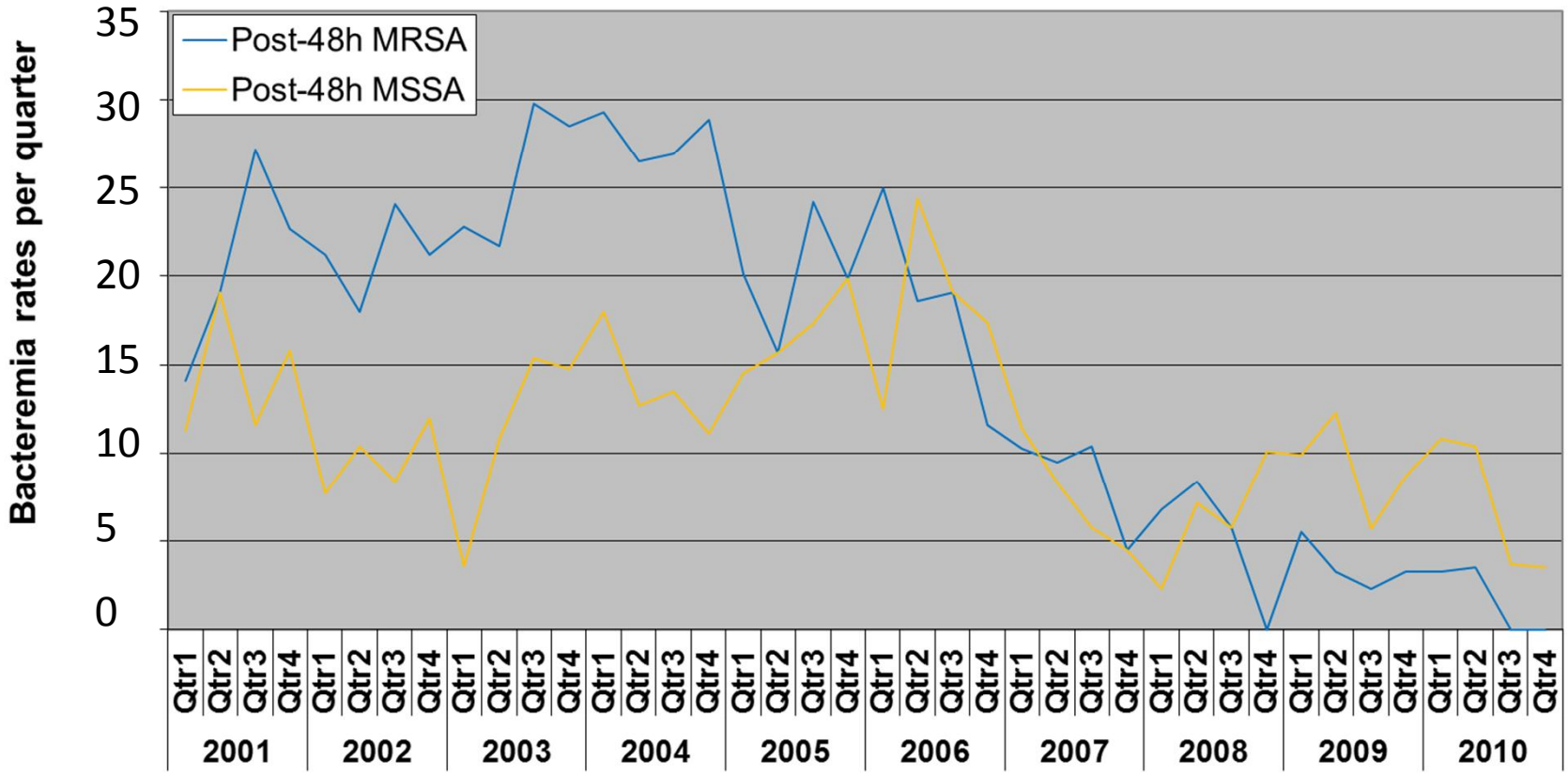
Impact of research
on MRSA bloodstream infections

LOOKING BACK:

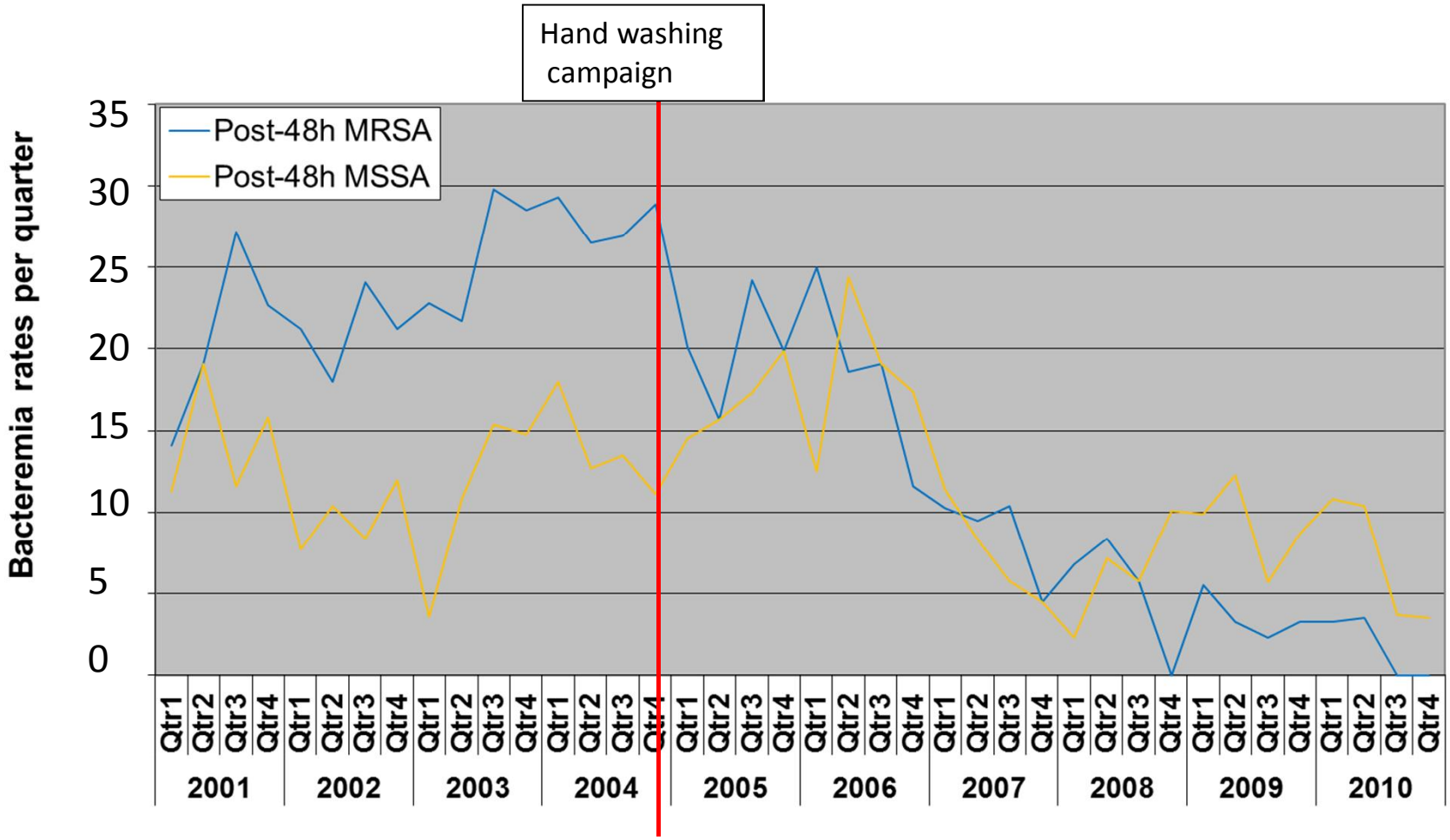
Impact of research, campaigns and legislation on MRSA bloodstream infections

Rates of healthcare-associated *S. aureus* bloodstream infections

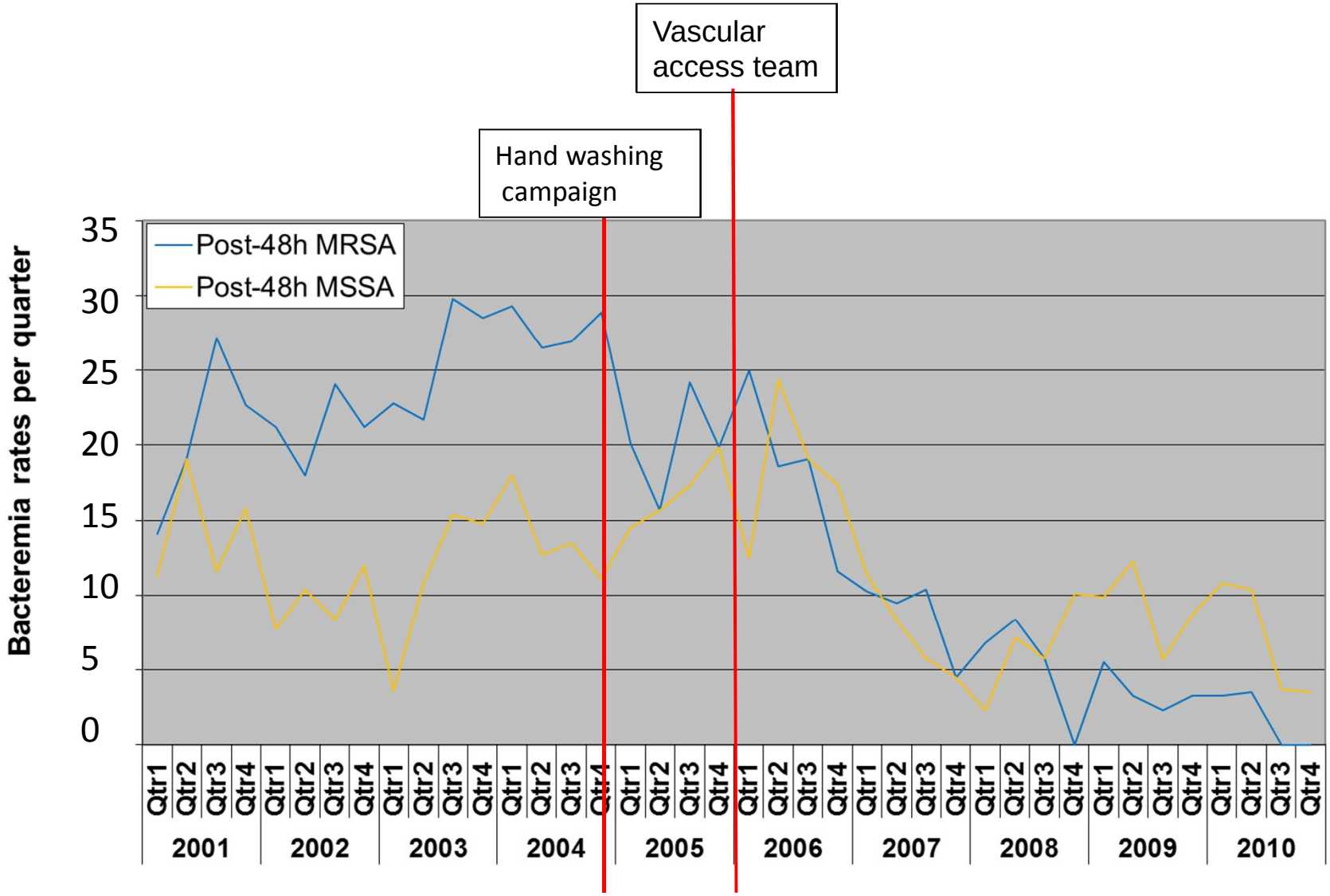
Cambridge University Hospitals NHS Foundation Trust



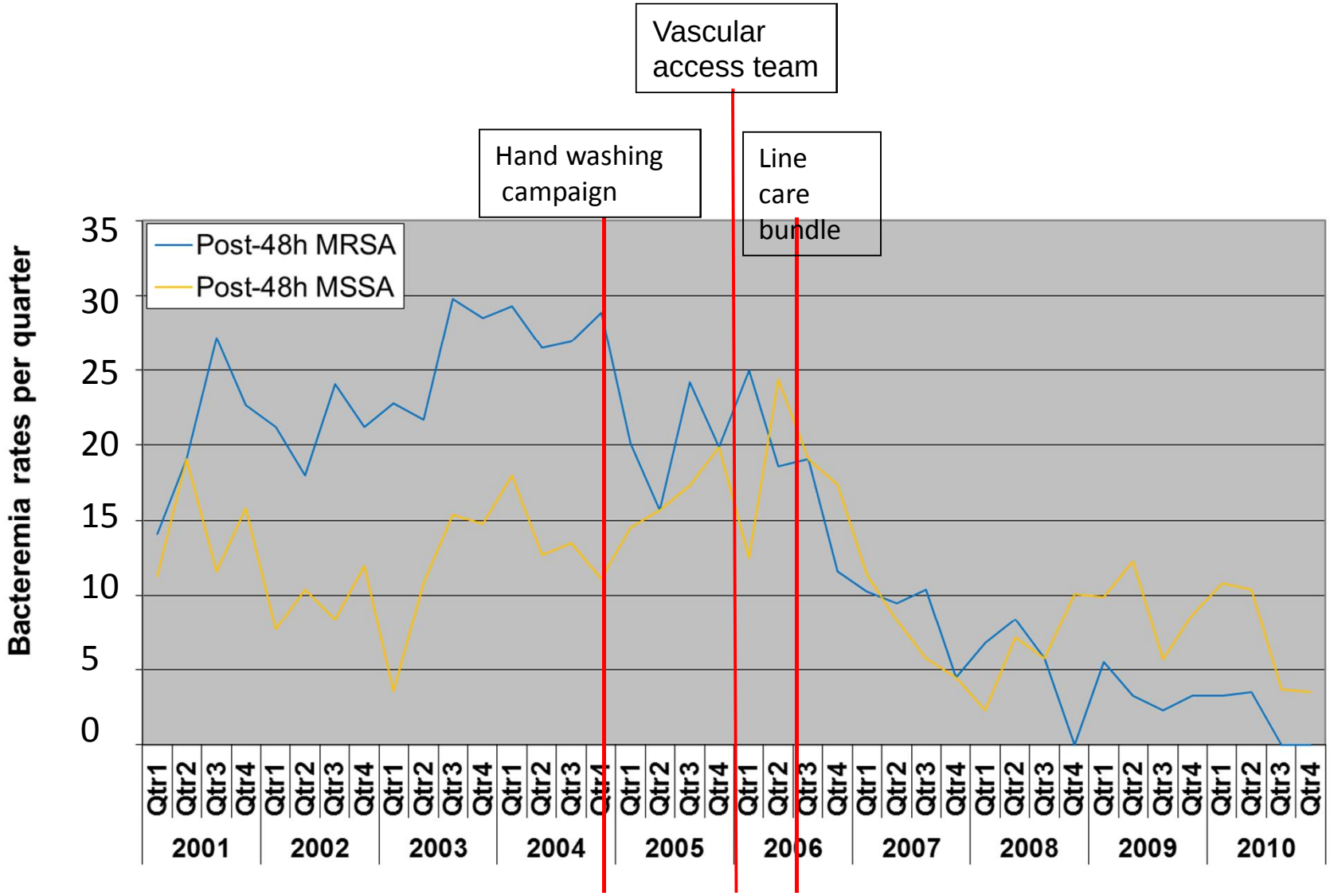
Rates of healthcare-associated *S. aureus* bloodstream infections



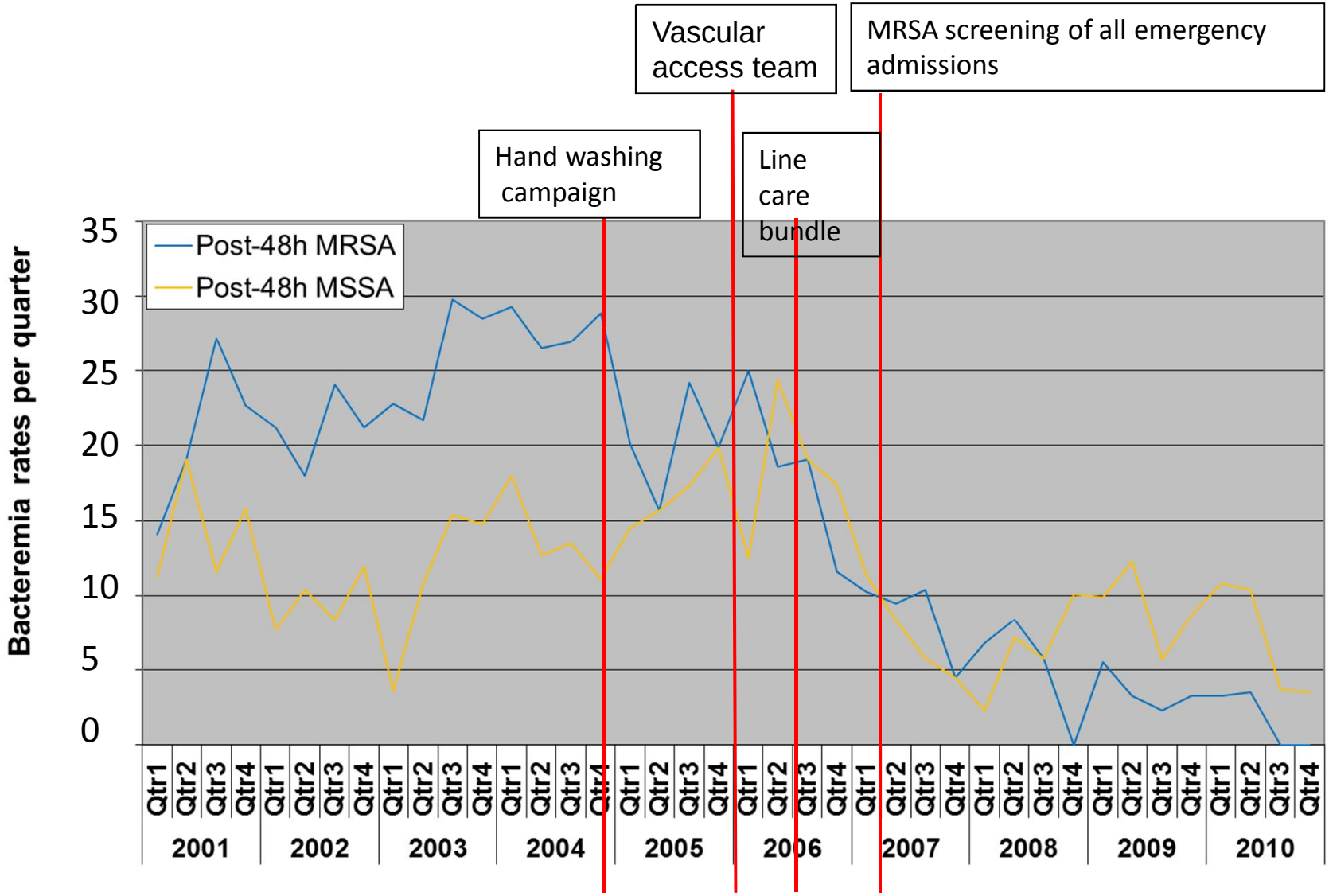
Rates of healthcare-associated *S. aureus* bloodstream infections



Rates of healthcare-associated *S. aureus* bloodstream infections



Rates of healthcare-associated *S. aureus* bloodstream infections



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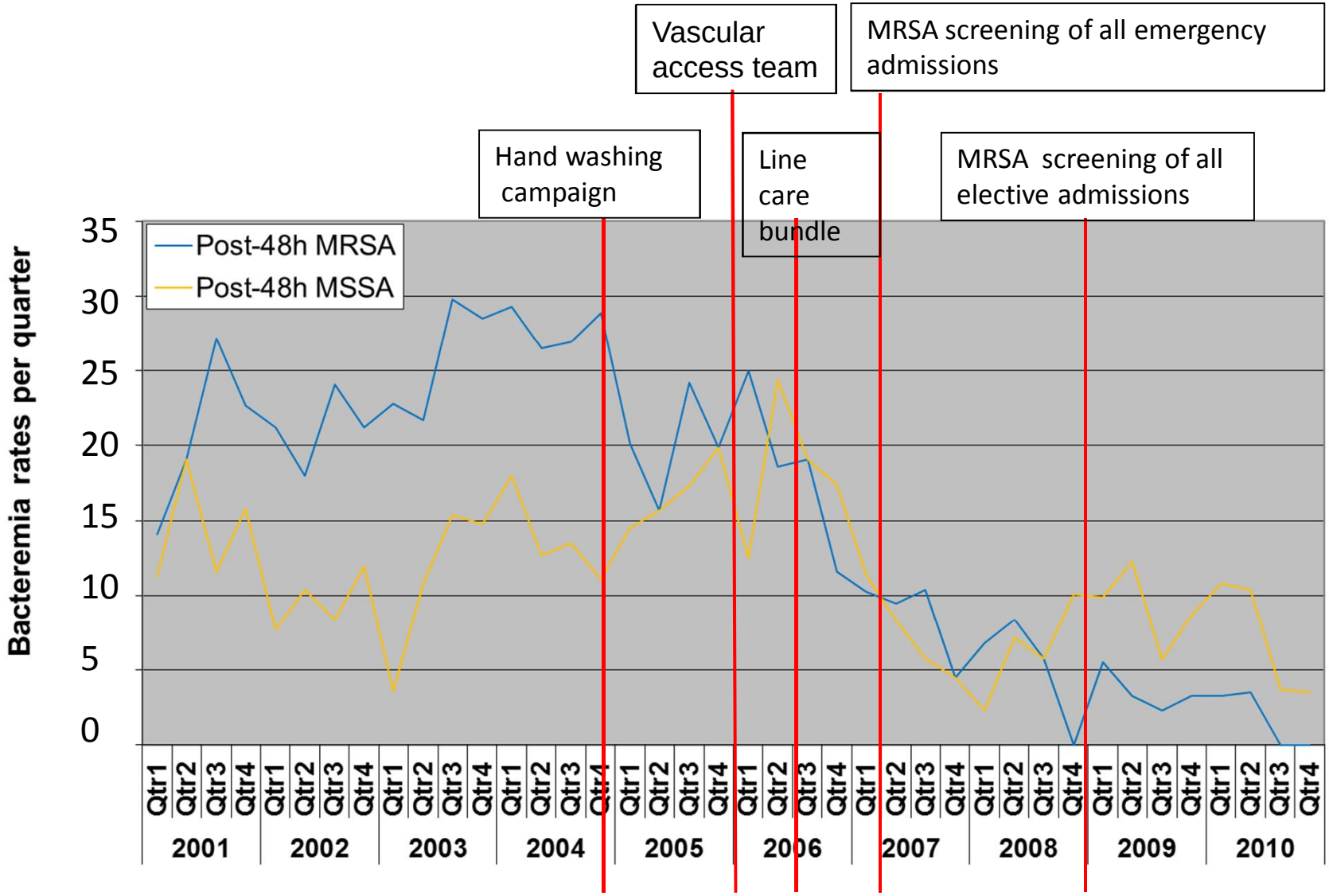


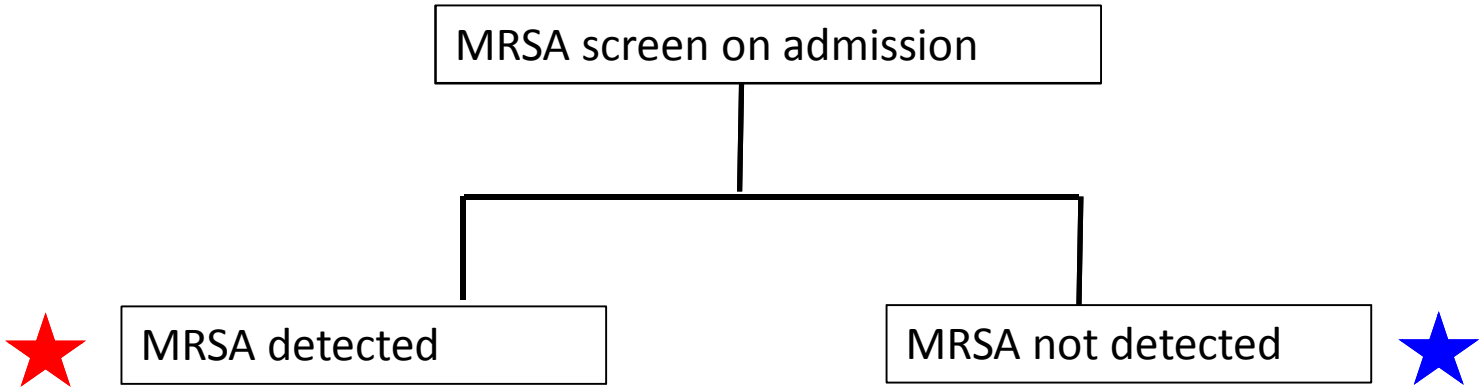
Department of Health Objectives, Jan 2012

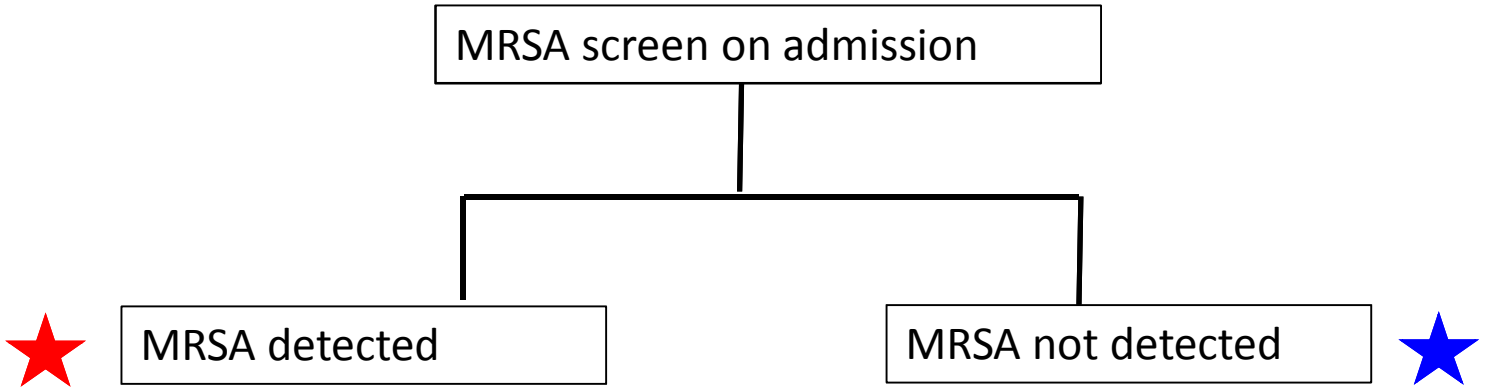
To collectively reduce the number of infections in 2012-13 caused by MRSA by a further 29% and *Clostridium difficile* by 17%

How to achieve further reductions?

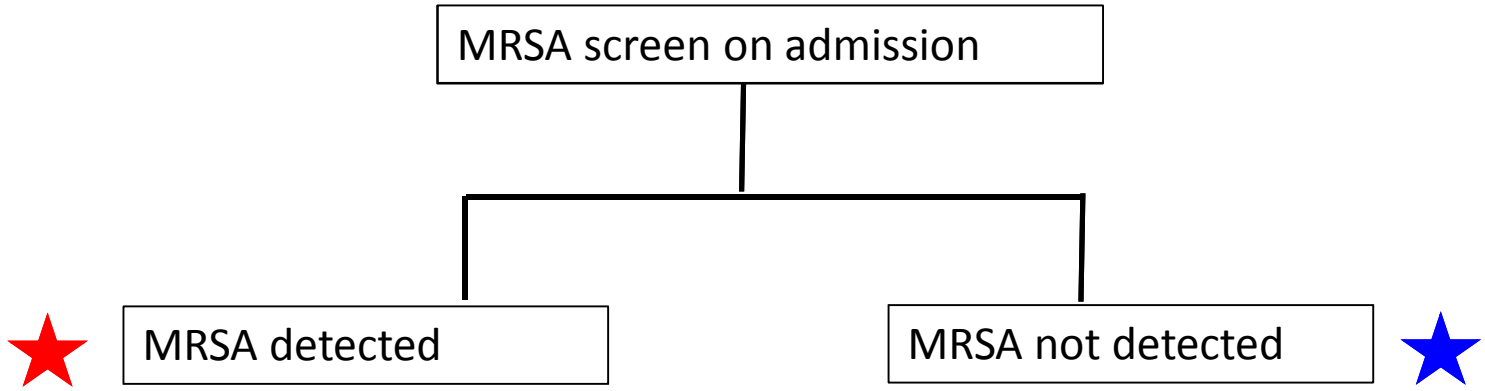
1. Holding ground by maintaining current standards

2. Re-iteration of care pathway to identify possible targets for innovative new research FOCUS = MRSA TRANSMISSION


MRSA screen on admission
MRSA detected
MRSA not detected

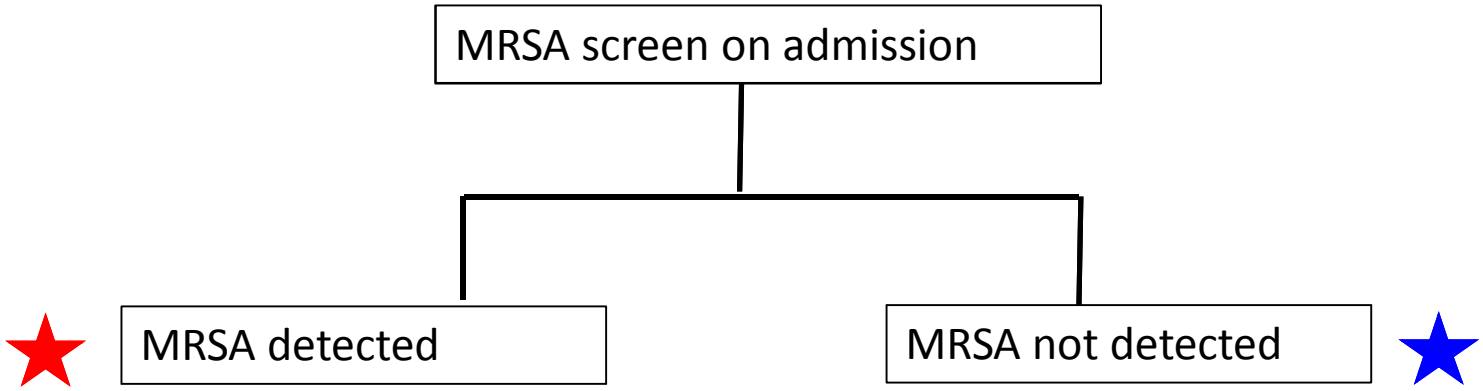


Å Isolate/cohort nurse
Å Barrier precautions
Å Decolonize



ÅIsolate/cohort nurse
ÅBarrier precautions
ÅDecolonize

DETECTION: Speed and accuracy
DECOLONIZATION: Speed and efficacy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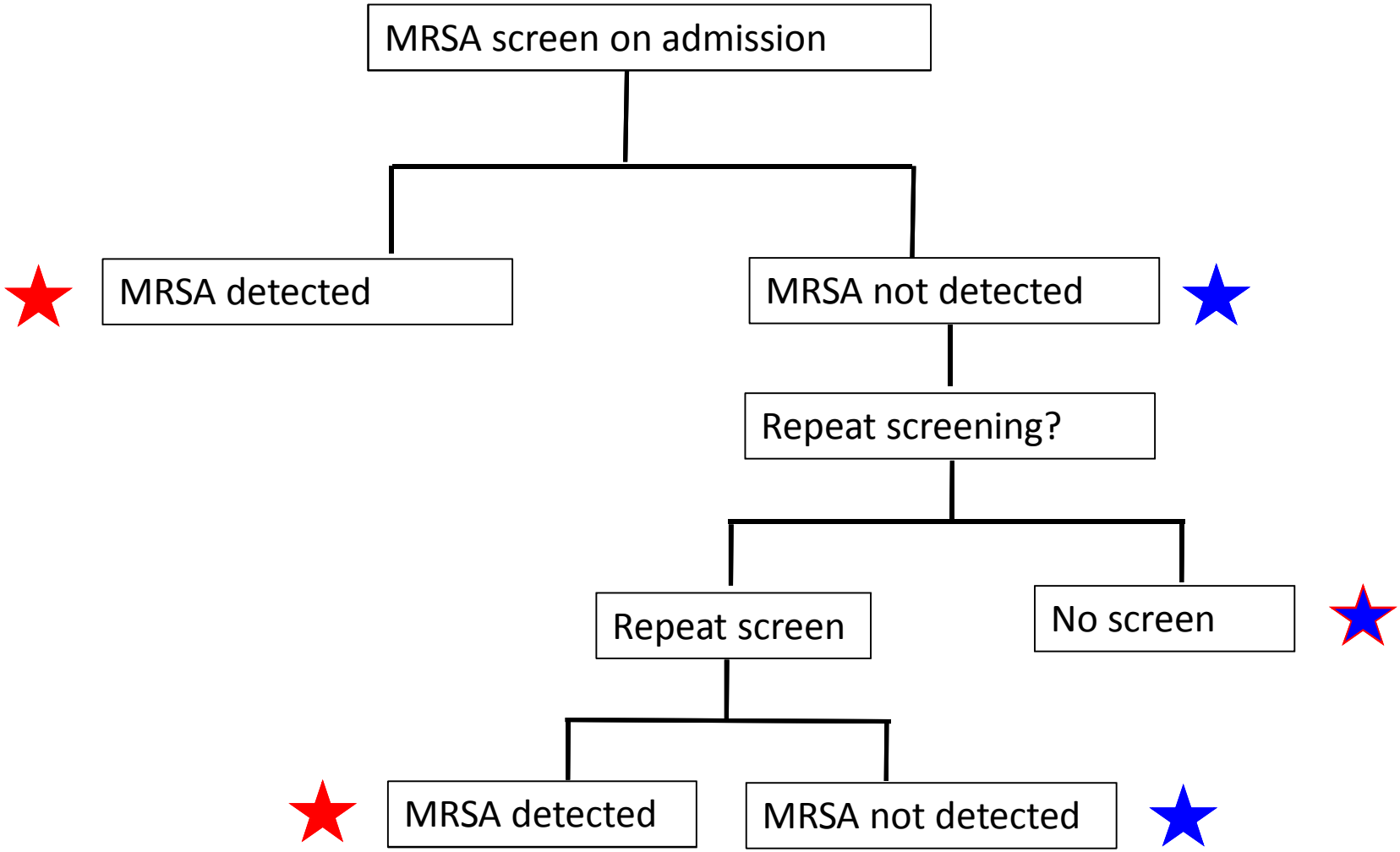
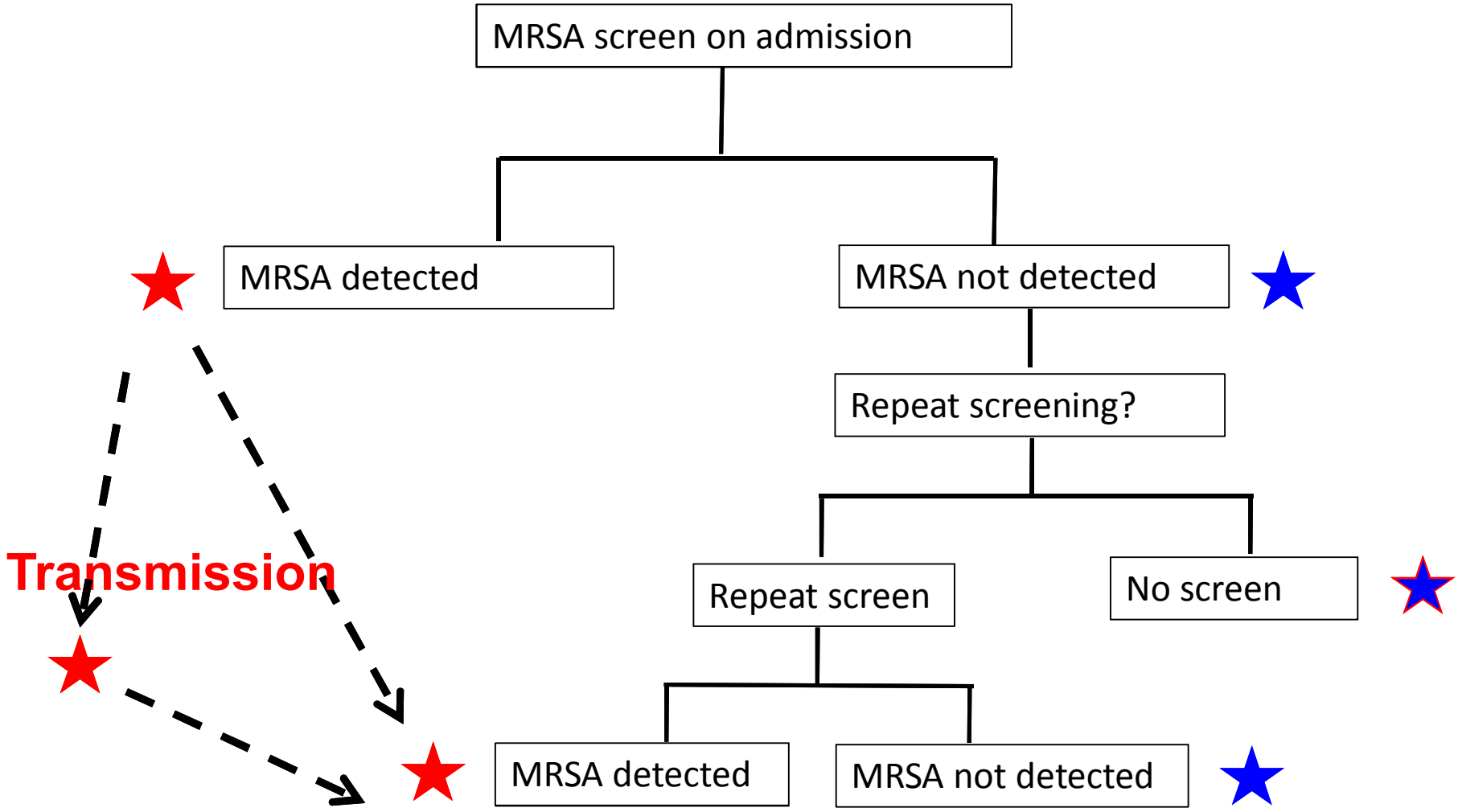
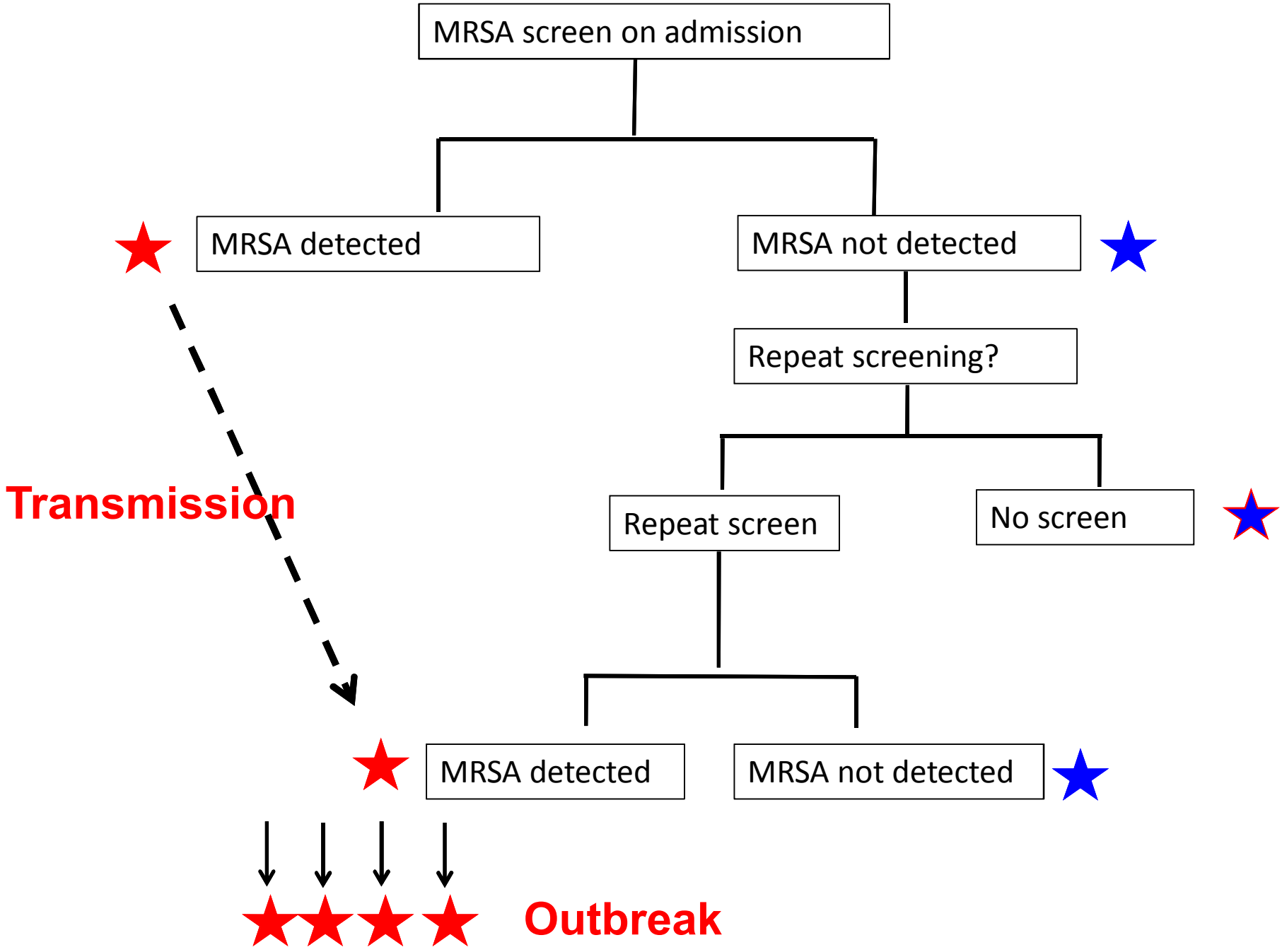
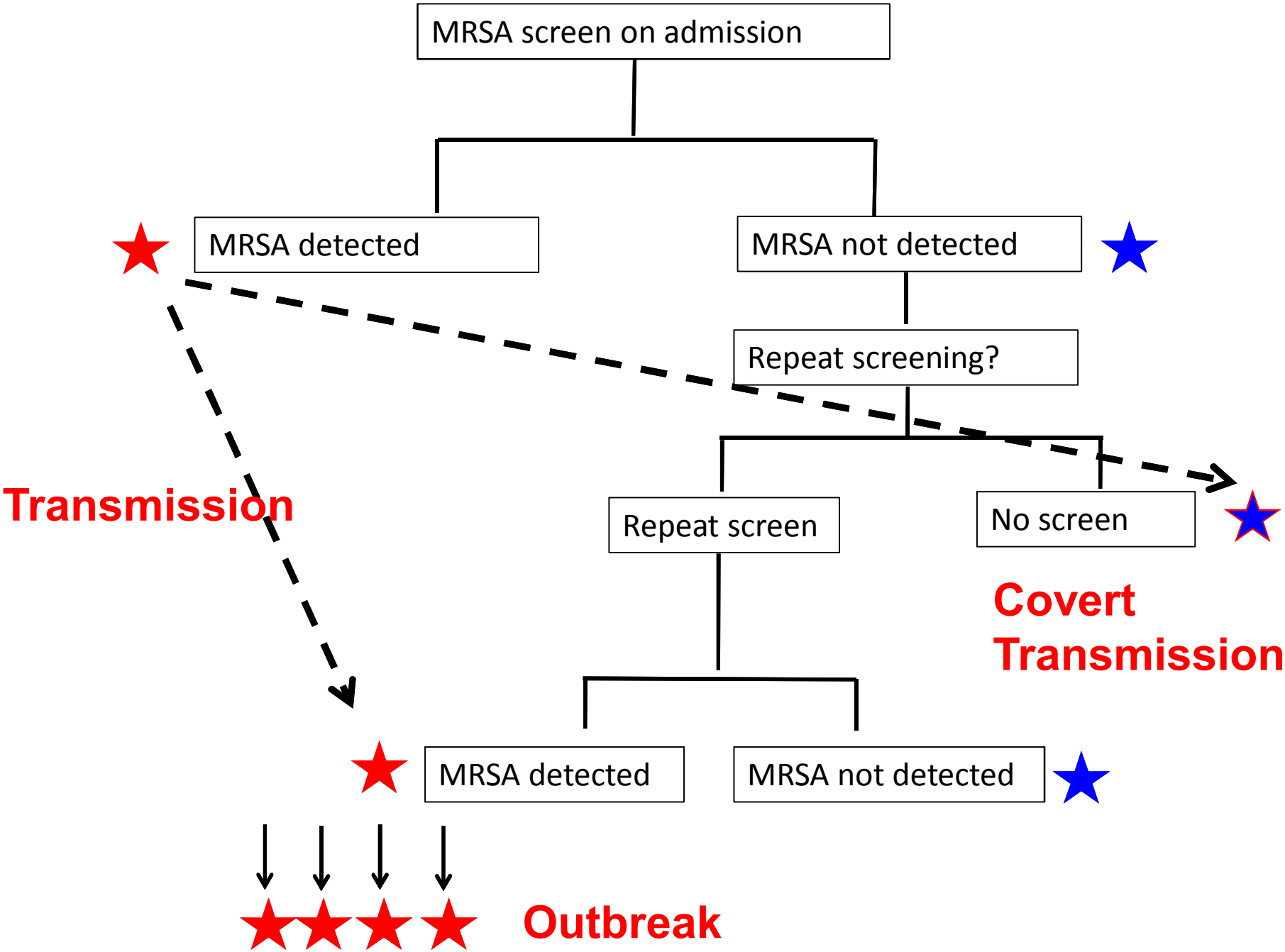
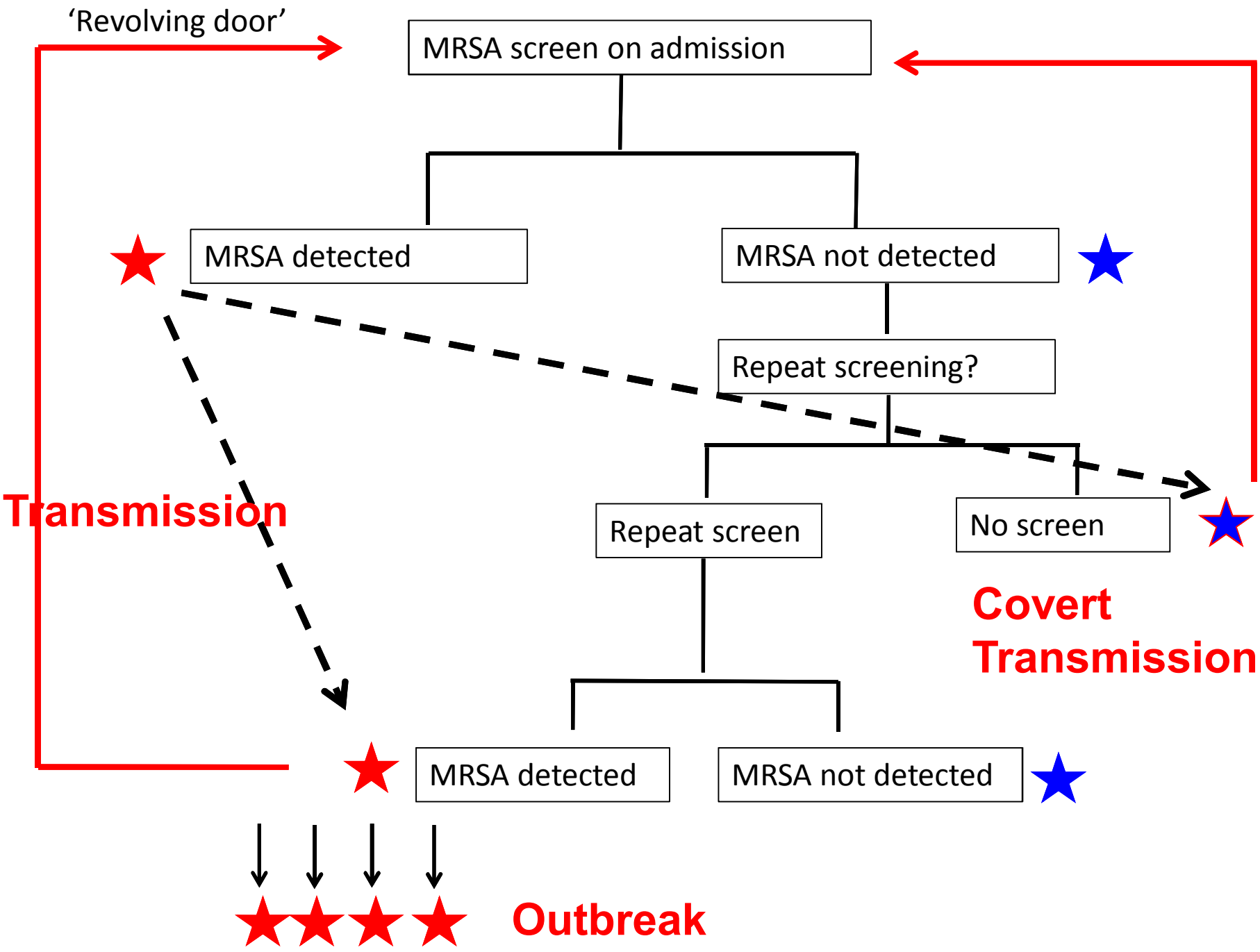

MRSA screen on admission
MRSA detected
MRSA not detected
Repeat screening?
Repeat screen
No screen
MRSA detected
MRSA not detected

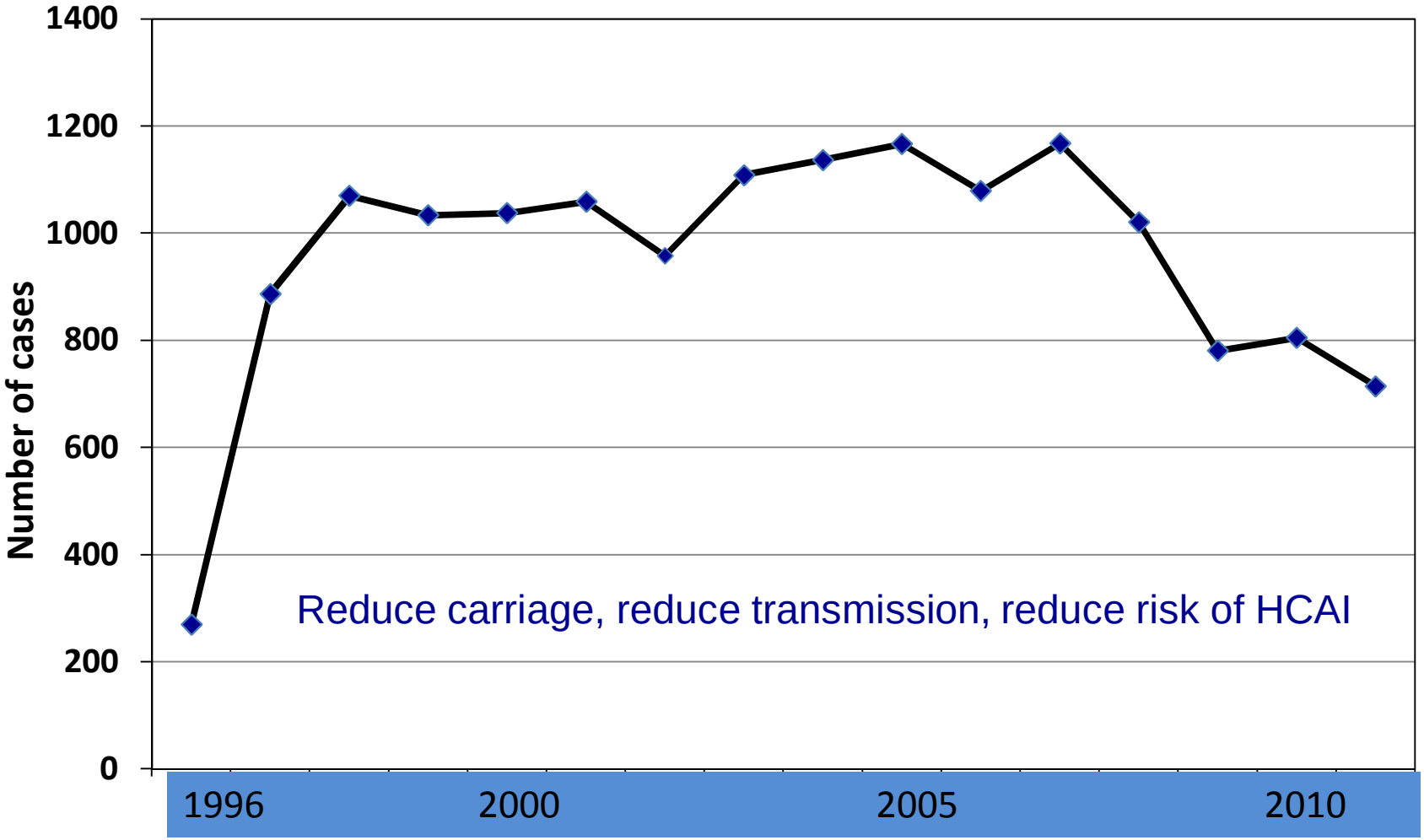

MRSA screen on admission
MRSA detected
MRSA not detected
Repeat screening?
Transmission
Repeat screen
No screen
MRSA detected
MRSA not detected


MRSA screen on admission
MRSA detected
MRSA not detected
Repeat screening?
Transmission
Repeat screen
No screen
MRSA detected
MRSA not detected
Outbreak


MRSA screen on admission
MRSA detected
MRSA not detected
Repeat screening?
Transmission
Repeat screen
No screen
Covert Transmission
MRSA detected
MRSA not detected
Outbreak


'Revolving door'
MRSA screen on admission
MRSA detected
MRSA not detected
Repeat screening?
Transmission
Repeat screen
No screen
Covert Transmission
MRSA detected
MRSA not detected
Outbreak

True burden of MRSA
MRSA positive samples, not BSI



3. Future research

Understanding transmission of MRSA using microbial whole genome sequencing

MRSA transmission

What we want to know:

Å When two or more patients are MRSA +ve in the same clinical area, has a transmission event occurred between these two cases, or not?

Å Where and when did it happen?

How we currently determine this:

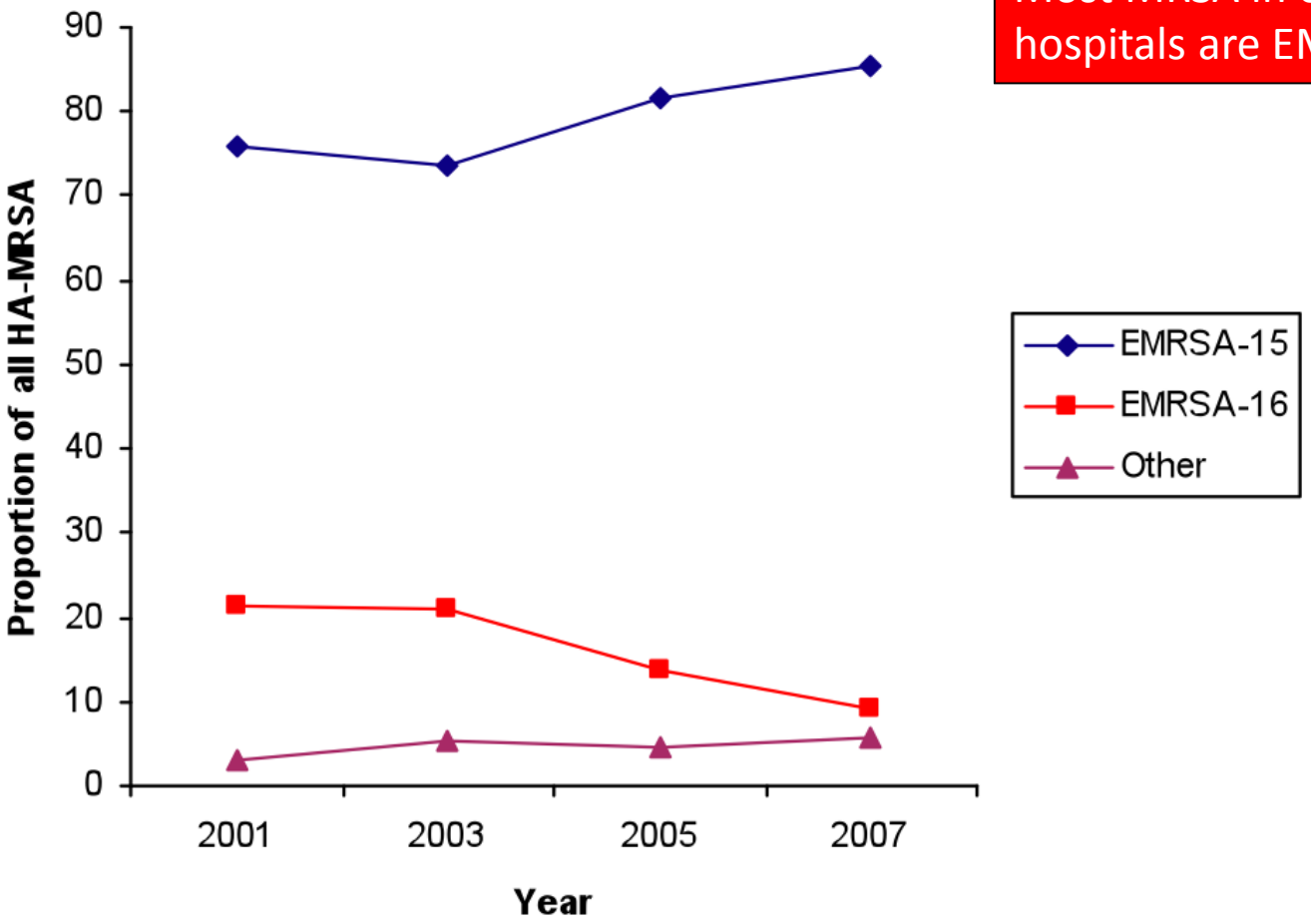
Å Assess the probability that the affected individuals came into contact (time, place)

Å Antibiotic resistance pattern of the bacteria involved

What we do not generally do:

Å Bacterial genotyping. It is slow, and lacks discrimination

Healthcare associated MRSA infection is clonal



Most MRSA in our hospitals are EMRSA-15

Ellington et al, JAC 2010;65:446-8

Transmission pathways

EMRSA-15

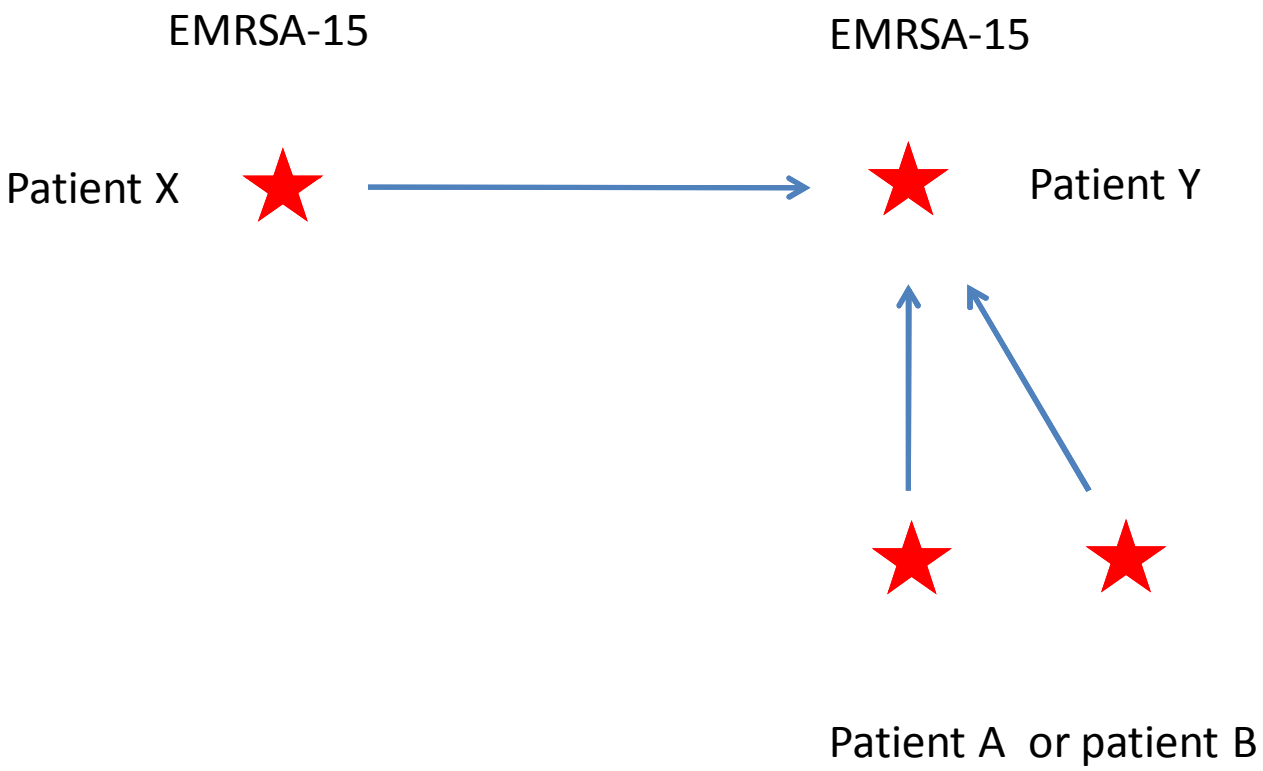
Patient X

EMRSA-15

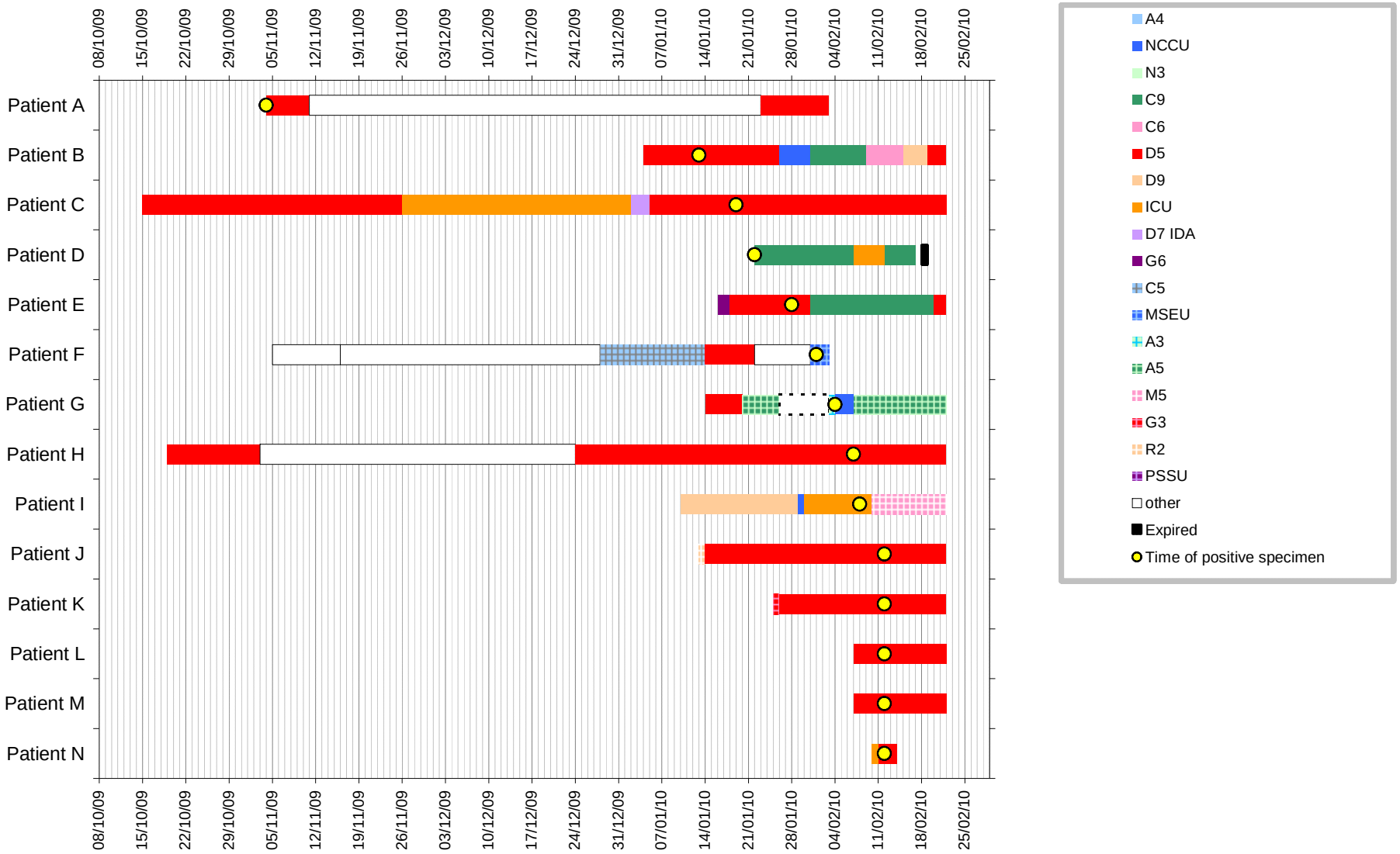
Patient Y

Transmission pathways

Transmission pathways



Complexity of transmission pathways



Case of need for new genotyping method

- Å Tracking MRSA transmission at a hospital level is complex
- Å Tracing the place of acquisition for óneweô MRSA carriers is not possible
- Å Typing MRSA could provide links between patients (no two MRSA are completely identical at the genome level) but current methods are not sufficiently discriminatory
- Å What is the evidence that microbial genome sequencing can contribute towards a greater understanding of HCAI?

MRSA transmission defined by genome sequencing

Global transmission

Local transmission

interaction with epithelial cells. We next asked if epithelial cell *mmp9* induction was dependent on MyD88 and TNF (tumor necrosis factor) signaling, as each can enhance mycobacterial induction of *mmp9* in cultured cells under certain conditions (*19*, *20*). ESAT-6 induced *mmp9* in *myd88* and *tnf-receptor 1* (*tr1*) morphants (Fig. 4D), suggesting a previously unknown pathway for this epithelial cell–specific interaction. Moreover, TNF-independent induction of *mmp9* is consistent with the finding that TNF does not mediate granuloma formation either in the presence or absence of bacterial RD1 (*13*).

Thus, ESAT-6 functions in virulence by promoting granuloma formation via interaction with epithelial cells, previously regarded as bystanders in the pathogenesis of tuberculosis (fig. S7). The cooption of epithelial cells may offer mycobacteria a means of amplifying MMP9 secretion in the vicinity of a single infected macrophage to establish the granuloma niche. In addition, the differential induction of inflammatory programs in macrophages and epithelial cells may generate a hospitable growth niche in macrophages while harnessing epithelial cells to facilitate the chemotaxis of additional macrophages for niche expansion (*6*) (fig. S7). Our work provides a mechanistic explanation for the implication of MMP9 in human susceptibility to tuberculosis (*9*, *11*, *12*) and suggests targeted inhibition of its expression as a host-directed antituberculous therapy. Because increased MMP9 is detrimental in both tuberculosis and a variety of noninfectious inflammatory conditions (*7*), interception of this pathway may have broad utility in treating a

48, 217 (2004).
23. D. R. Sherman *et al.*, *J. Infect. Dis.* **190**, 123 (2004).
24. I. C. Koo *et al.*, *Cell. Microbiol.* **10**, 1866 (2008).

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Include this information when citing this paper.

Evolution of MRSA During Hospital Transmission and Intercontinental Spread

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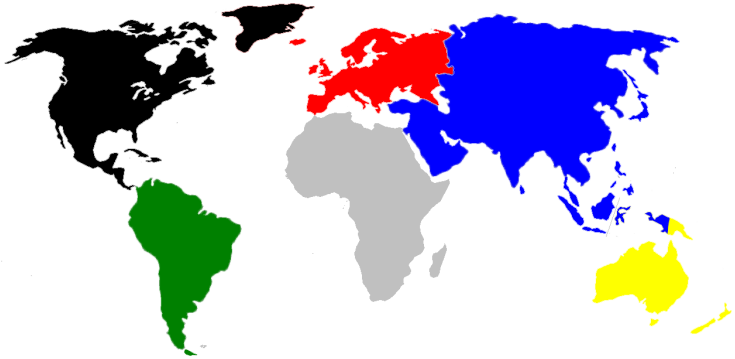
Current methods for differentiating isolates of predominant lineages of pathogenic bacteria often do not provide sufficient resolution to define precise relationships. Here, we describe a high-throughput genomics approach that provides a high-resolution view of the epidemiology and microevolution of a dominant strain of methicillin-resistant *Staphylococcus aureus* (MRSA). This approach reveals the global geographic structure within the lineage, its intercontinental transmission through four decades, and the potential to trace person-to-person transmission within a hospital environment. The ability to interrogate and resolve bacterial populations is applicable to a range of infectious diseases, as well as microbial ecology.

The development of molecular typing techniques has been instrumental in studying the population structure and evolution of bacterial pathogens. Sequence-based approaches, such as multilocus sequence typing (MLST) (*1*), have resulted in large searchable databases of the most clinically important species. However, MLST defines variation within a very small sample of the genome and cannot distinguish between closely related isolates. Full-genome sequencing provides a complete inventory of microevolutionary changes, but this approach is impractical for large population samples. The use of next-generation sequencing technologies, such as Illumina Genome Analyzer, bridges this gap by mapping genome-wide single-nucleotide poly-

Whole genome sequencing of a single clone of MRSA

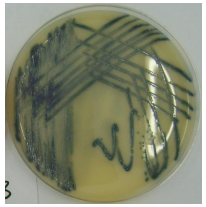


MLST sequence type 239
EMRSA 1, -4 and -11

62 isolate collection

Time: 1982-2007, including 20 isolates from single hospital over 7 months

Space: 15 countries, 5 continents



Extract DNA

Sequence DNA

Compare genetic code between strains

Whole genome sequencing as a typing tool

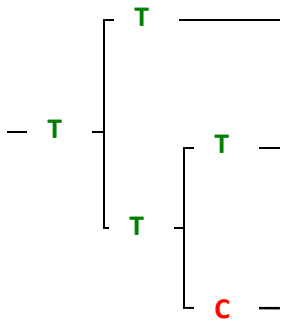
Illumina reads mapped to a reference genome

Single Nucleotide Polymorphisms identified

Gather SNPs from other isolates

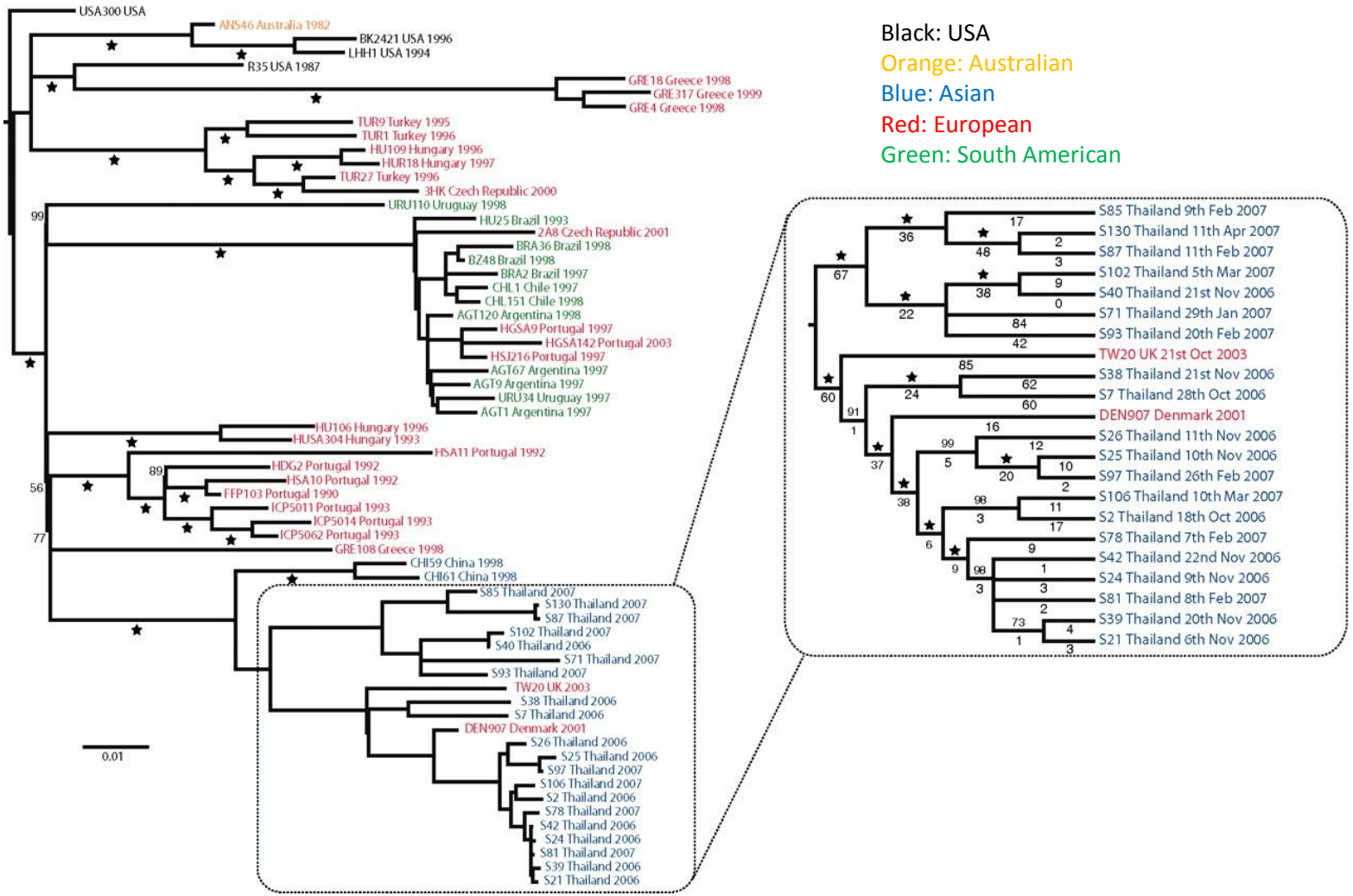
Phylogenetic tree

All SNPs used to construct a tree



A single SNP can distinguish closely related isolates

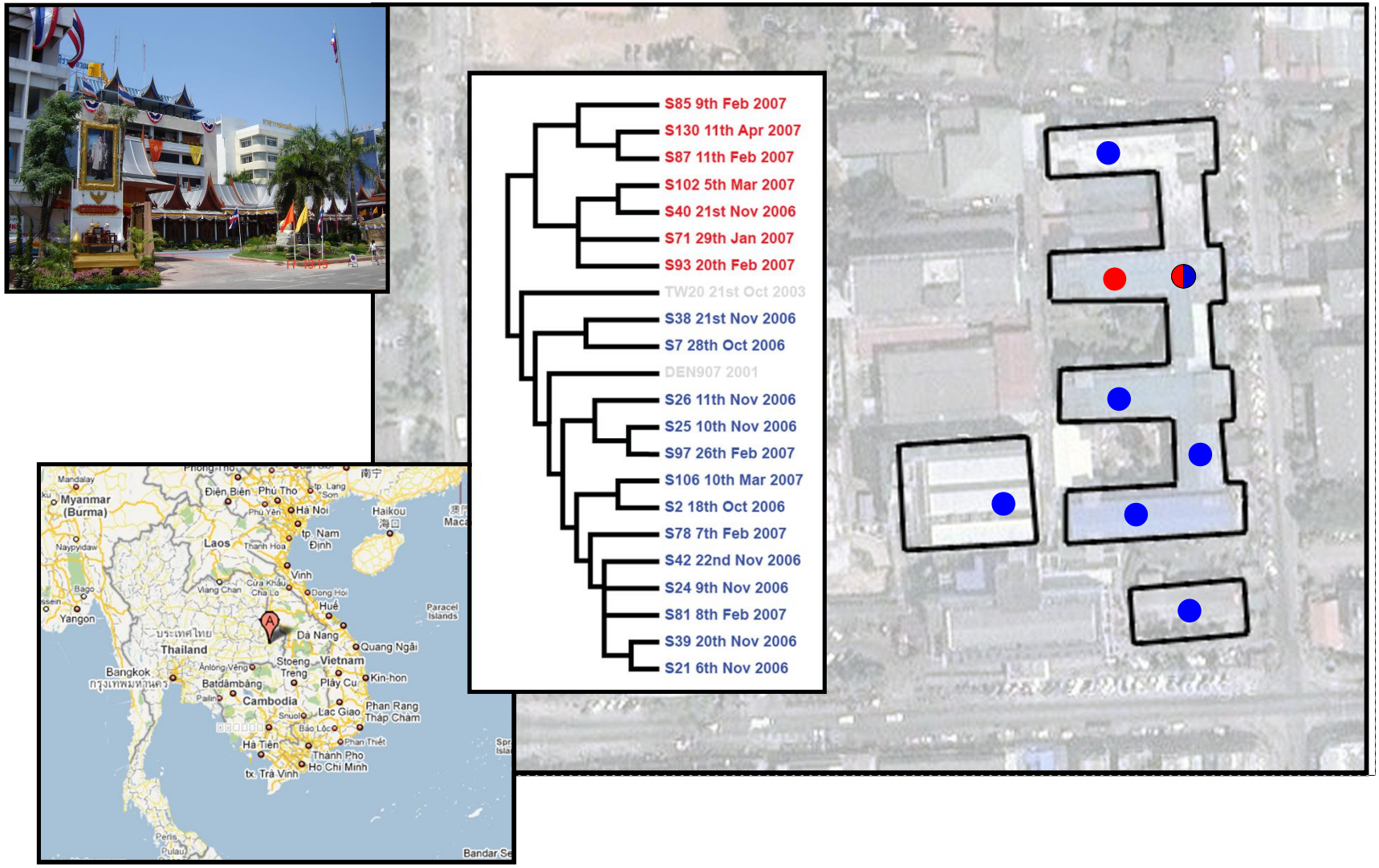
Geographic structure within ST239



4,310 core genome SNPs

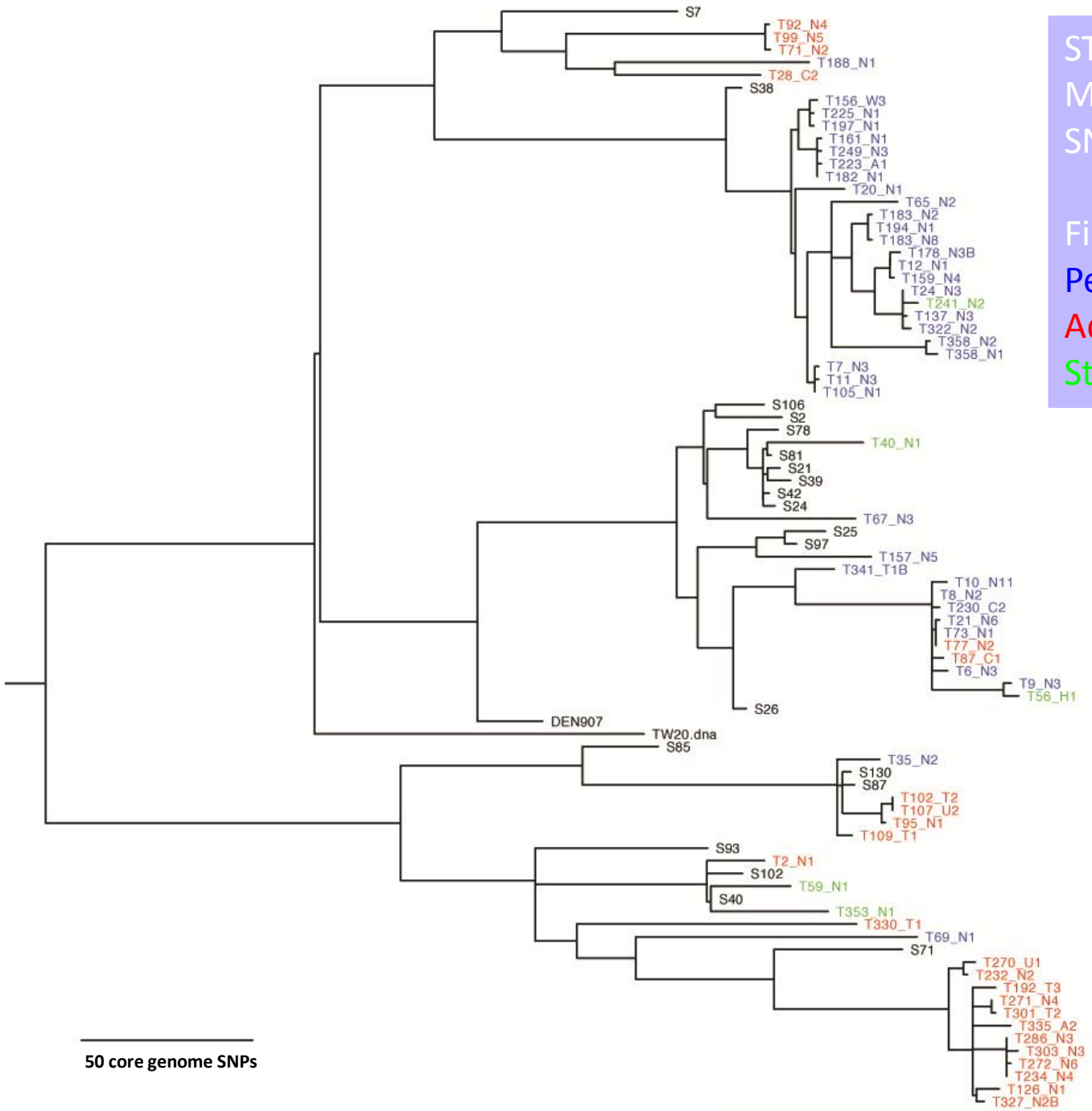
Harris et al. *Science* **327**, 469-474 (2010)

Local level structure of MRSA



Using sequencing to study hospital MRSA transmission

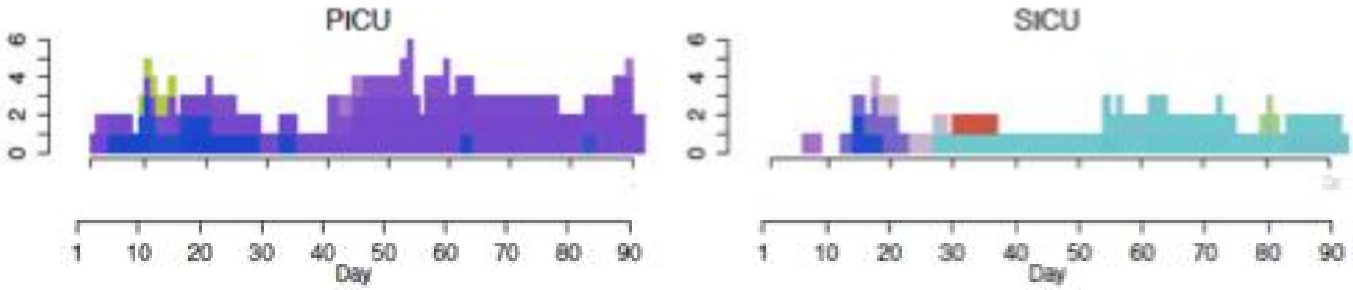
- Two ICUs (adult and paediatric)
- Twice weekly MRSA swabs over 3 month period
- Recruitment: 169 patients on the adult ICU and 98 patients on the paediatric ICU
- MRSA isolated from one or more screens from 27 patients (16%) on the adult ICU, and 33 patients (31%) on the paediatric ICU
- Staff swabbed on up to 3 occasions



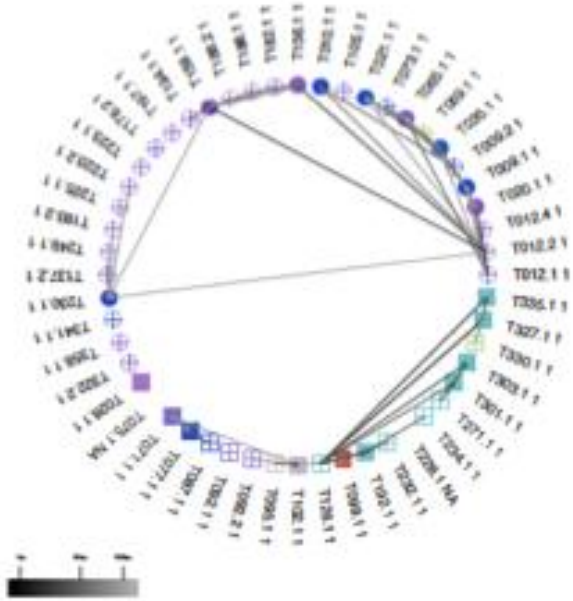
ST239 Thai isolates
ML tree based on core SNPs

First isolates from
Pediatric isolates
Adult isolates
Staff isolates

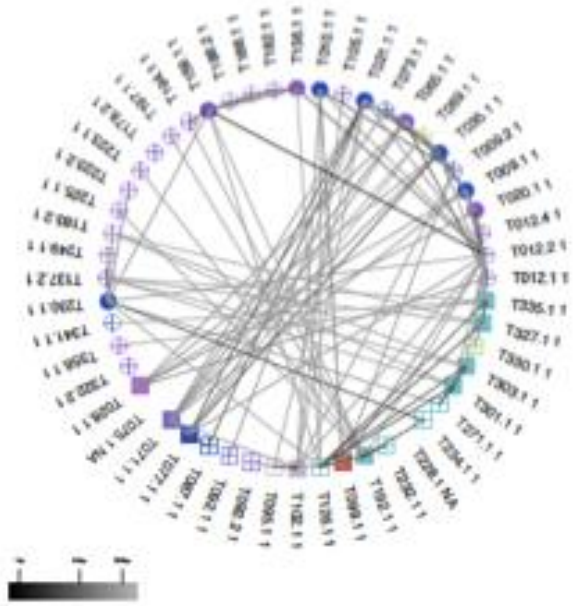
Skyline plot of genetic clusters



Networks: who transmitted to who, epi data



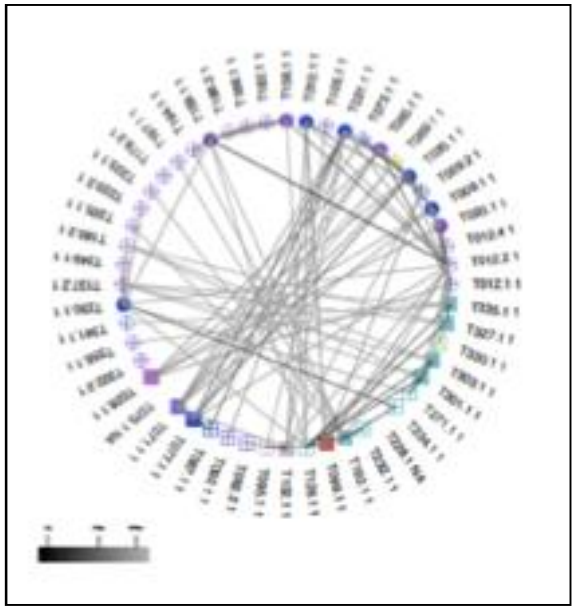
Transmission on same ward

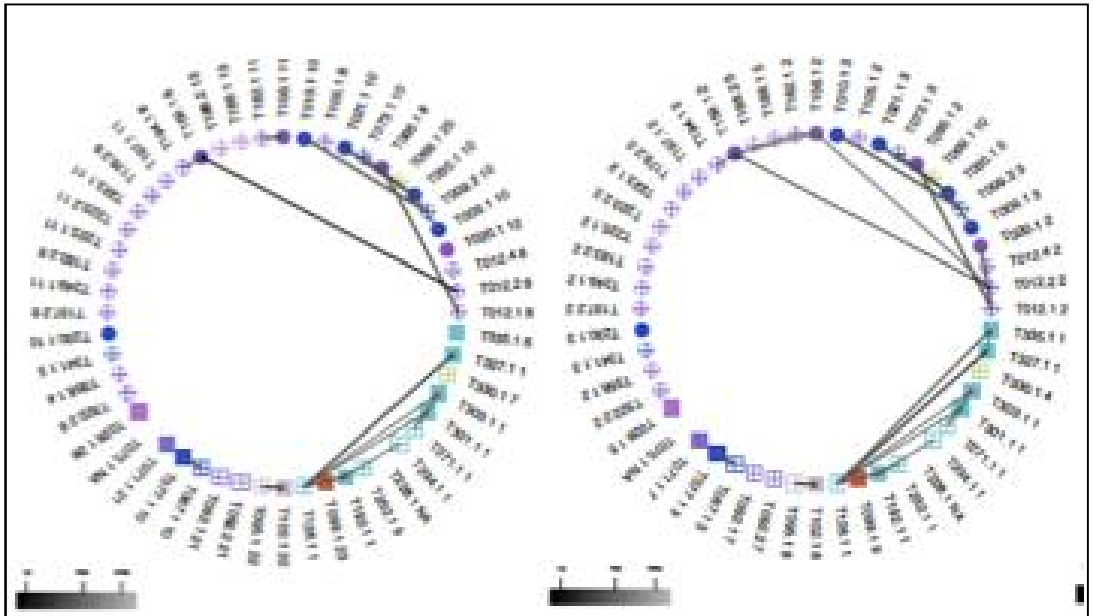


Transmission on same ward or between wards is equally likely

Networks: who transmitted to who, epi data versus epi plus genomic data

Transmission on same ward or between wards is equally likely





Cut off`: 25 SNPs different 100 SNPs different

Epi data only

Epi data plus genomic data

Microbial whole genome sequencing

- An emerging technology with major implications for infection control and public health
- Could become an instrument of infection control to pin-point where transmission is occurring and to confirm the presence of an outbreak
- This could lead to a much greater understanding of where transmission is occurring
- Turnaround time?
- Cost?
- Technological developments to support rapid interpretation required

The importance of research

- An essential partner to the actions and interventions required to control HCAI
- Has underpinned the major interventions to date
- The UK is a world leader in genomic research, and microbial whole genome sequencing is likely to play an important role in public health

Thanks for listening