

# Analysis of hospital infection data: dynamics, inference, policy, and future directions.

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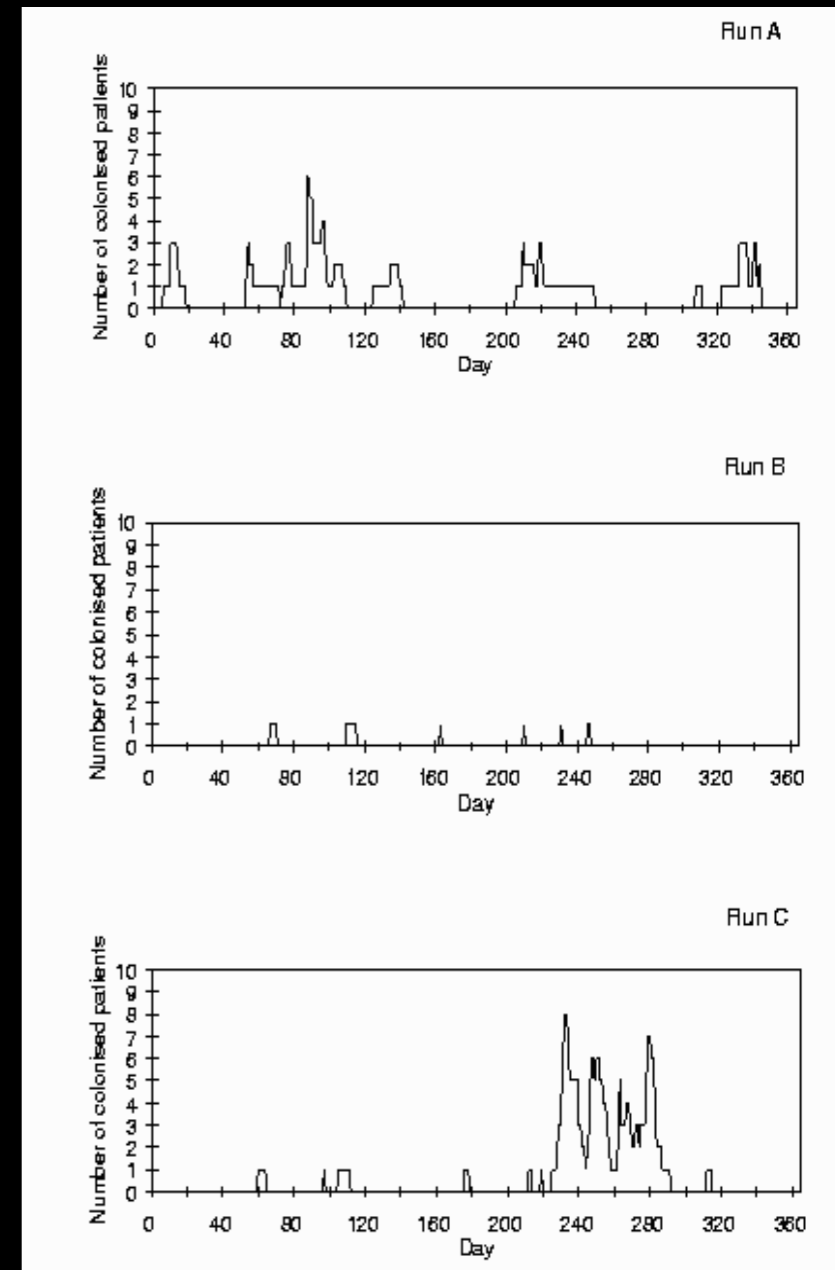
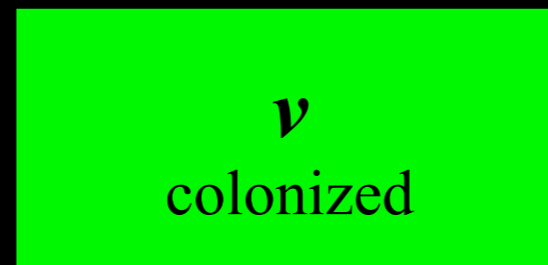
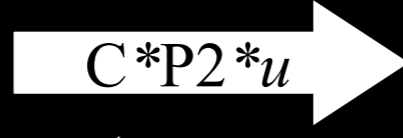
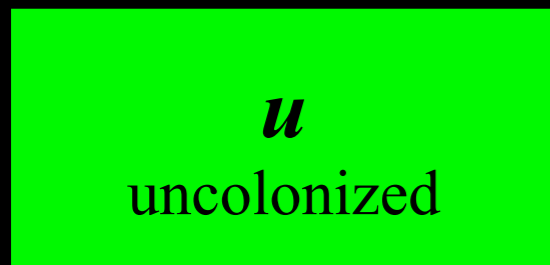
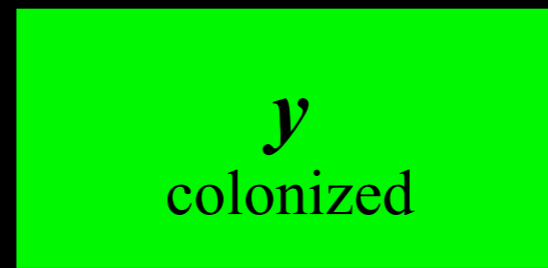
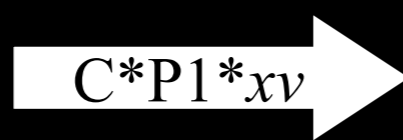
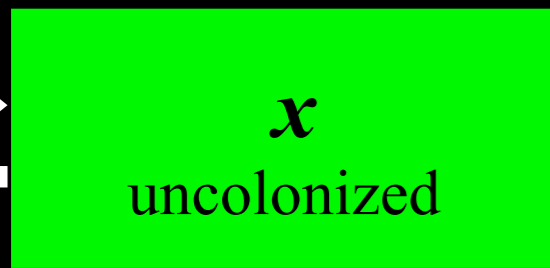
1. Dynamics of healthcare associated infections (HCAIs)
2. Inference for models of HCAIs
3. Policy evaluation
4. The future

Dynamics

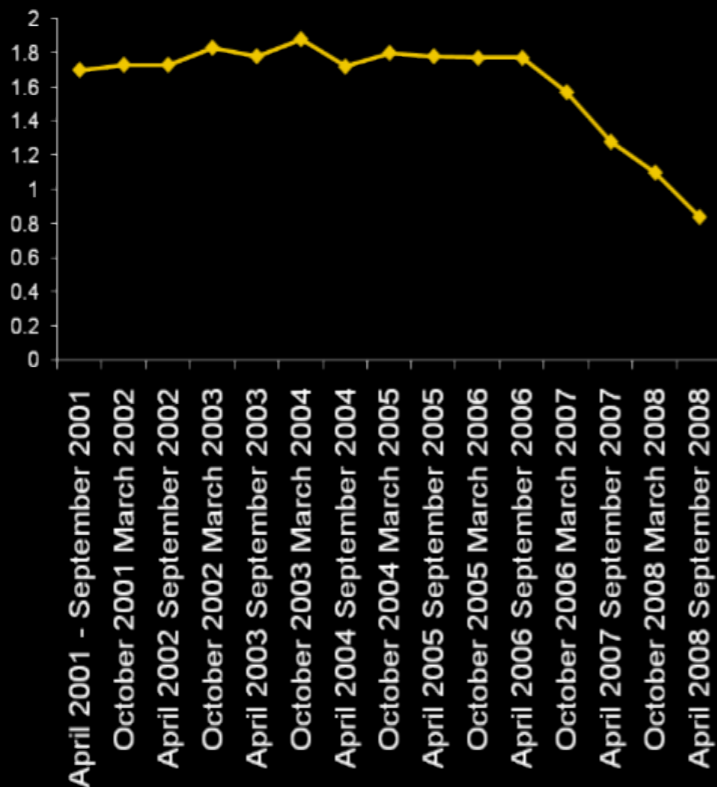
Inference

Policy

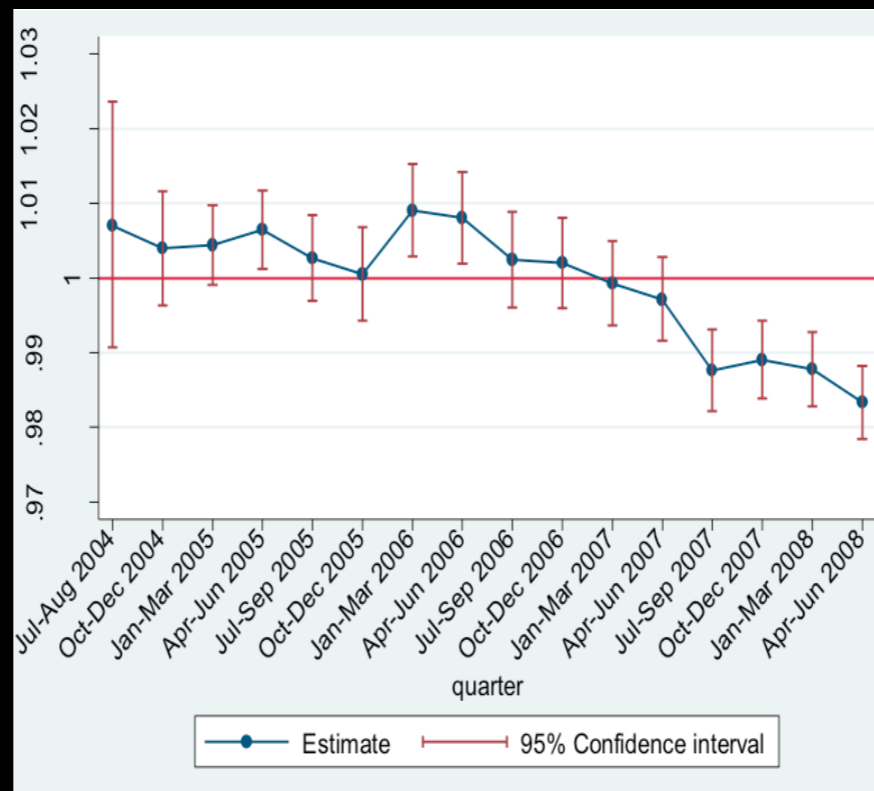
Future



MRSA bacteraemia rate per 10,000 bed days



Estimated IRR for MRSA bacteraemia for a 1 ml per bed day increase in alcohol hand rub by quarter

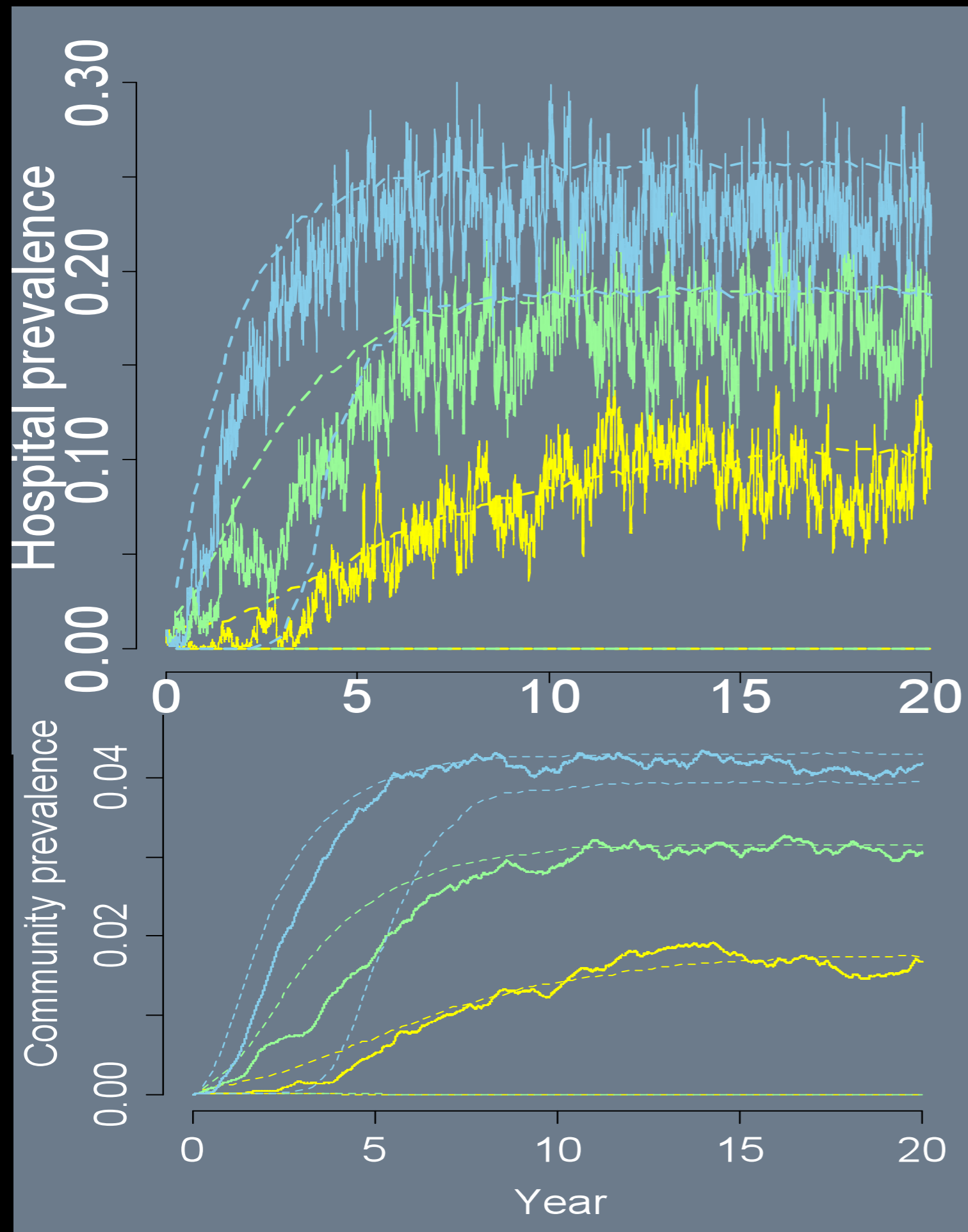


Cooper et al. J Hosp Infect 1999

Austin et al. PNAS 1999

Séville et al. ICHE 1997

Ross Proc R Soc Lon 1916



Cooper *et al.* PNAS 2004

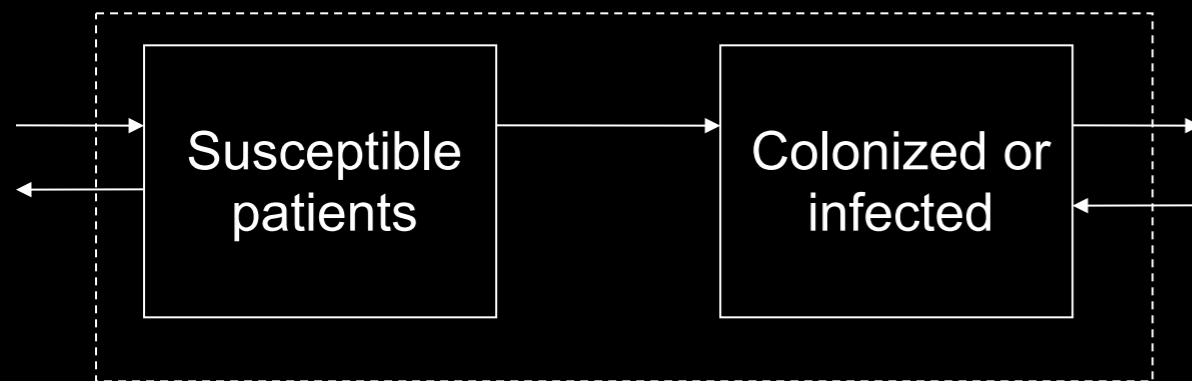
Smith *et al.* PNAS 2004

Bootsma *et al.* PNAS 2006

## Insights from “data free” models

1. Stochastic effects dominant
2. Resistance levels change quickly in response to changes in drug use and resistance can disappear quickly after a drug is discontinued or in response to other interventions (if resistance is rare in the community).
3. Non-specific control (e.g. hand hygiene) disproportionately reduces resistance (if resistance is rare in the community).
4. Long-term dynamics can be driven by a build-up of resistance in the community reservoir.
5. Long-term control failure is possible, even when all outbreaks are controlled successfully in the short-term.

# Maximum likelihood estimation of parameters for a simple transmission model for a hospital ward



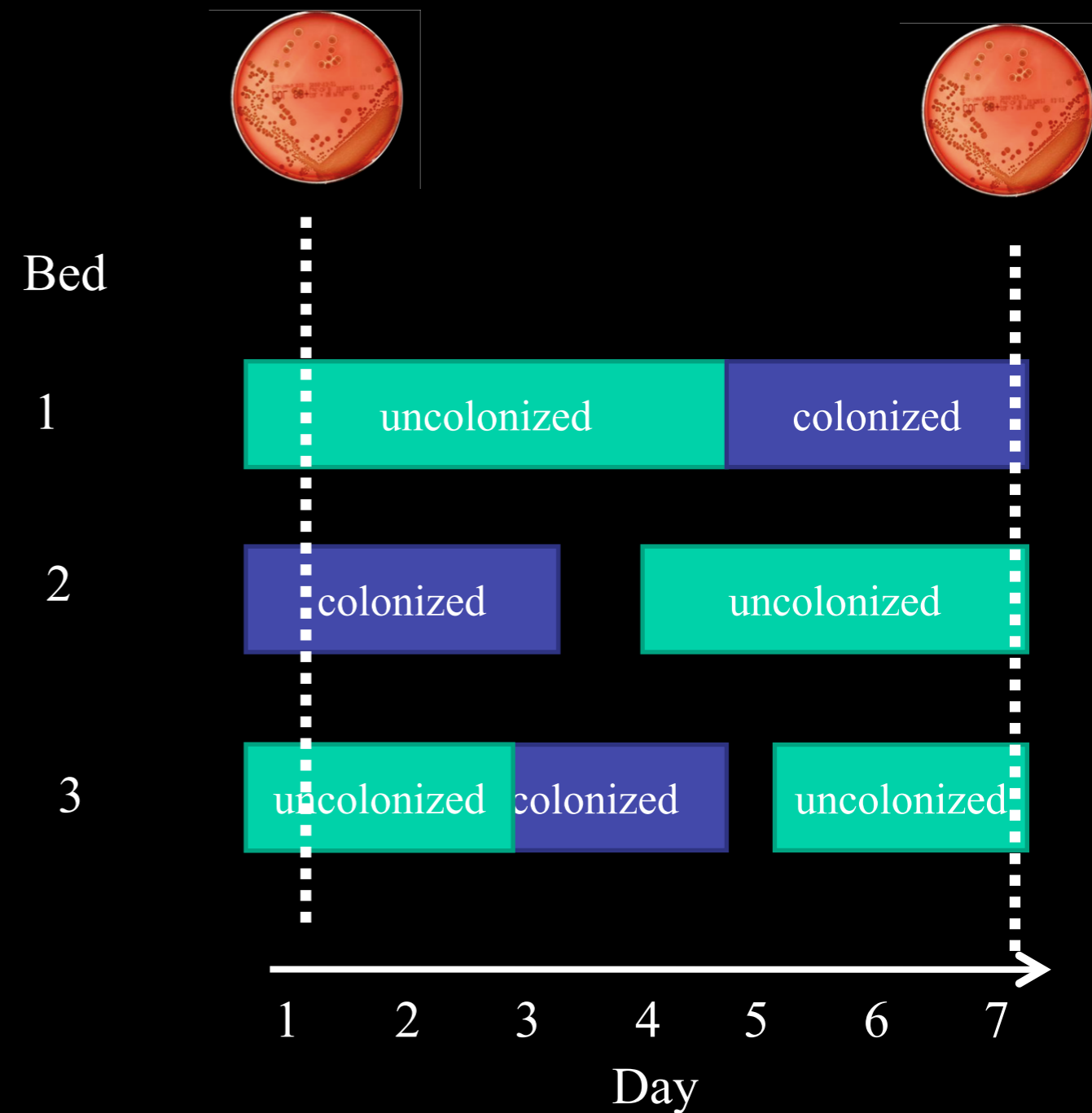
## Assumptions:

- Susceptible patients become colonized faster as the number of colonized patients on the ward increases (colonization pressure).
- Colonization assumed to last a long time compared to length of stay
- The *Markov* assumption (what happens next depends only on the current state of the system, not on history).

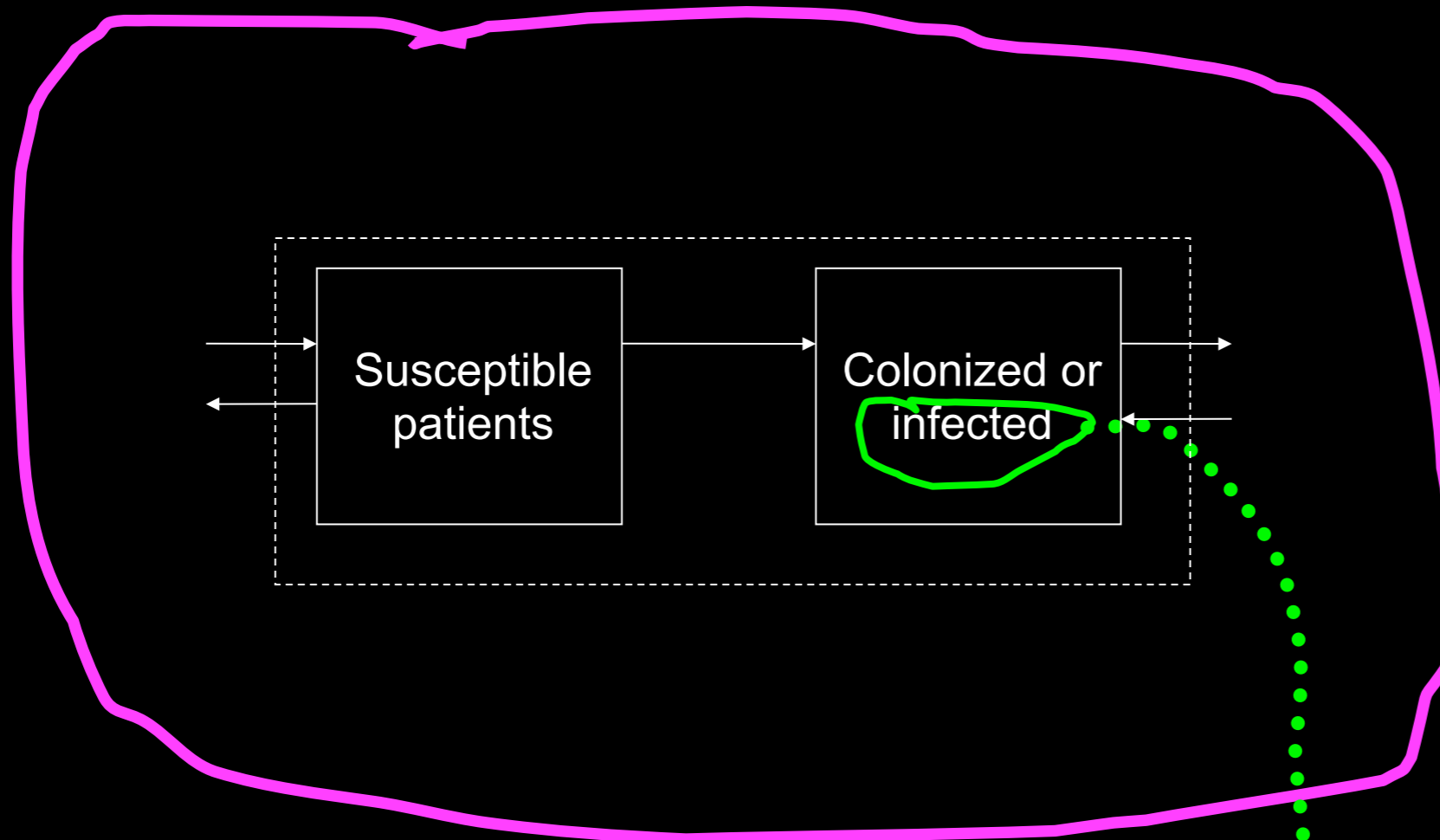
## Parameters

- rate of replacement of colonized by non-colonized patients Transmission rate ( $c$ )
- spontaneous colonization rate ( $a$ )
- transmission rate ( $\theta$ )

Proposed by Pelupessy *et al.* (PNAS 2002) for analysing hospital infection data.



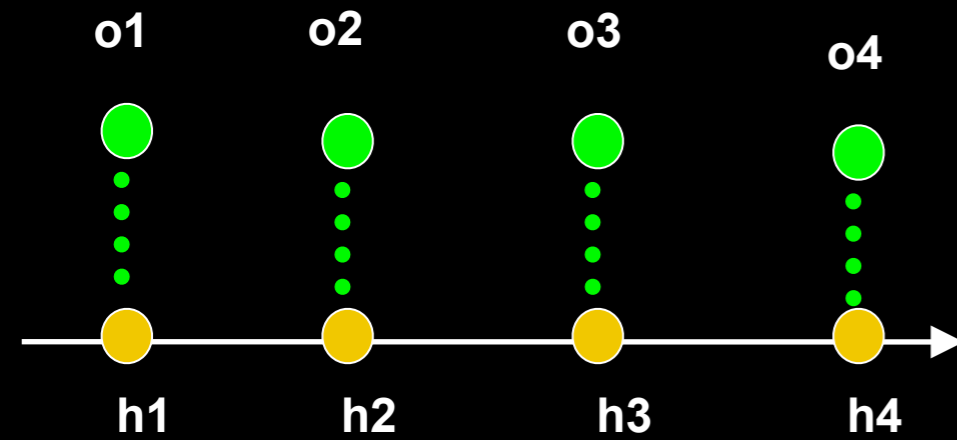
If only those patients who develop infections are observed :



Markov assumption violated.  
Structured *Hidden* Markov Models are required.



## Structured Hidden Markov Models



- Hidden (unobserved) state
- Observation.

## Transmission model

$$\Pr(H_{t+h} = i+1 | H_t = i) = \beta i(N-i)h + \nu(N-i)\mu h + o(h)$$

If  $i < N$  (0 otherwise).

$$\Pr(H_{t+h} = i-1 | H_t = i) = (1-\nu)i\mu h + o(h)$$

If  $i > 0$  (0 otherwise).

$N$  is number of patients or beds,  
 $\mu$  is discharge rate

$\nu$  is probability patient is +ve on admission

$\beta$  is transmission parameter

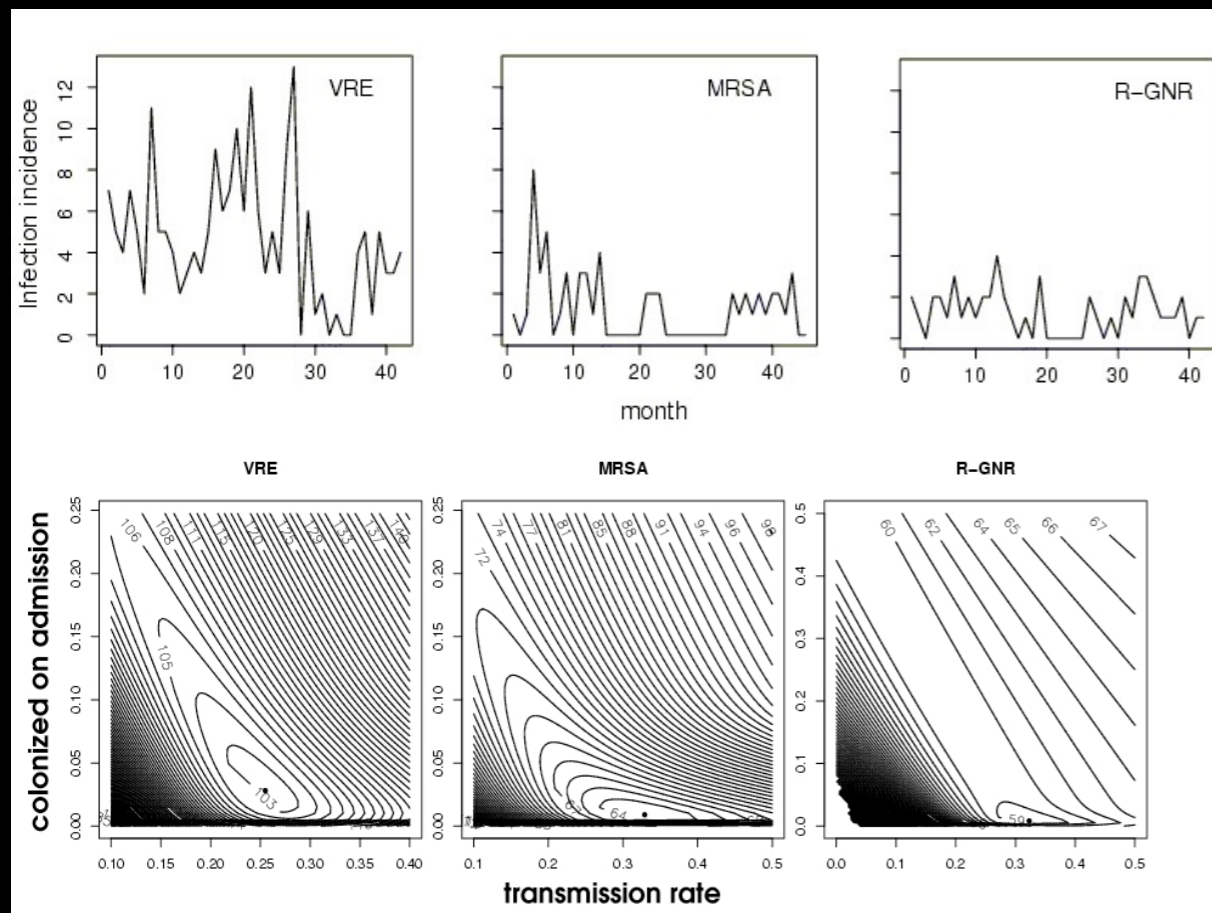
$h$  is a short time interval

$i$  can be interpreted as the number of colonized

## Observation model

$$\Pr(Y_t = y | H_t = i) = \exp(-\lambda i) (\lambda i)^y / y!$$

i.e. Poisson with mean  $\lambda i$



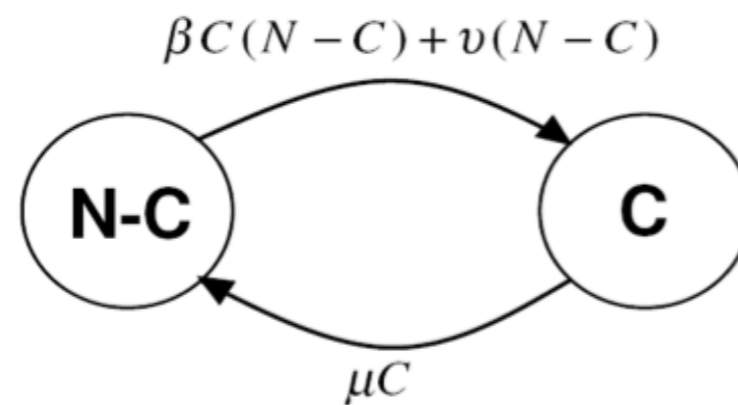
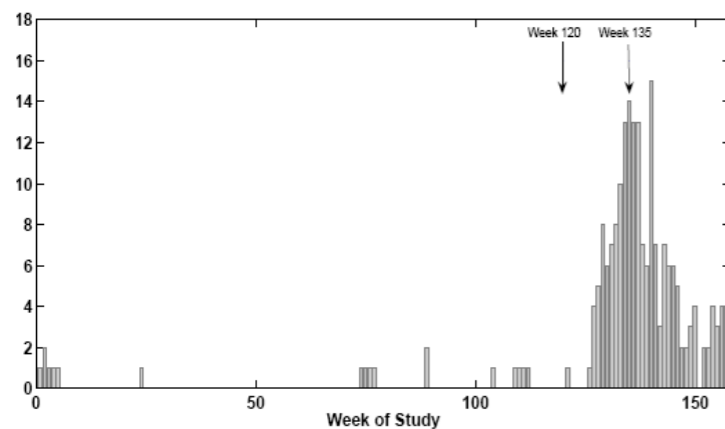


# Bayesian formulation of the HMM

## Likelihood methods may fail due to:

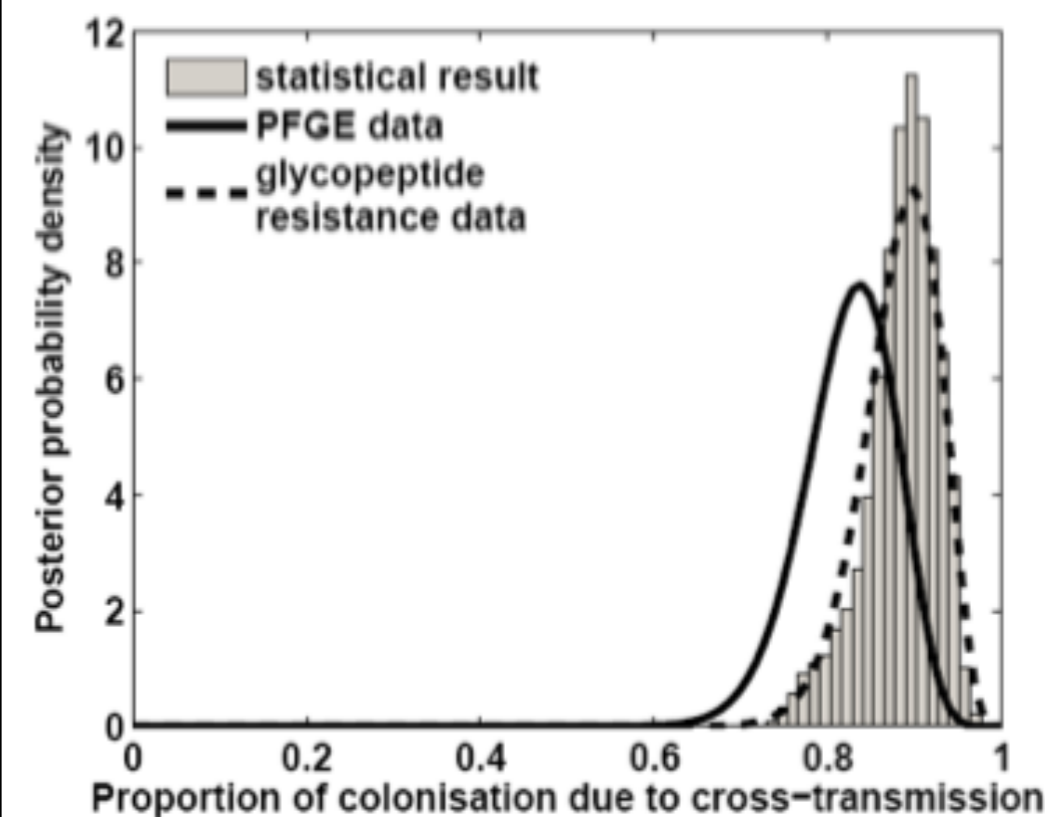
- sparse data (convergence failure)
- state space being too large (numerical problems)
- MLE may correspond to a biologically implausible region of parameter space

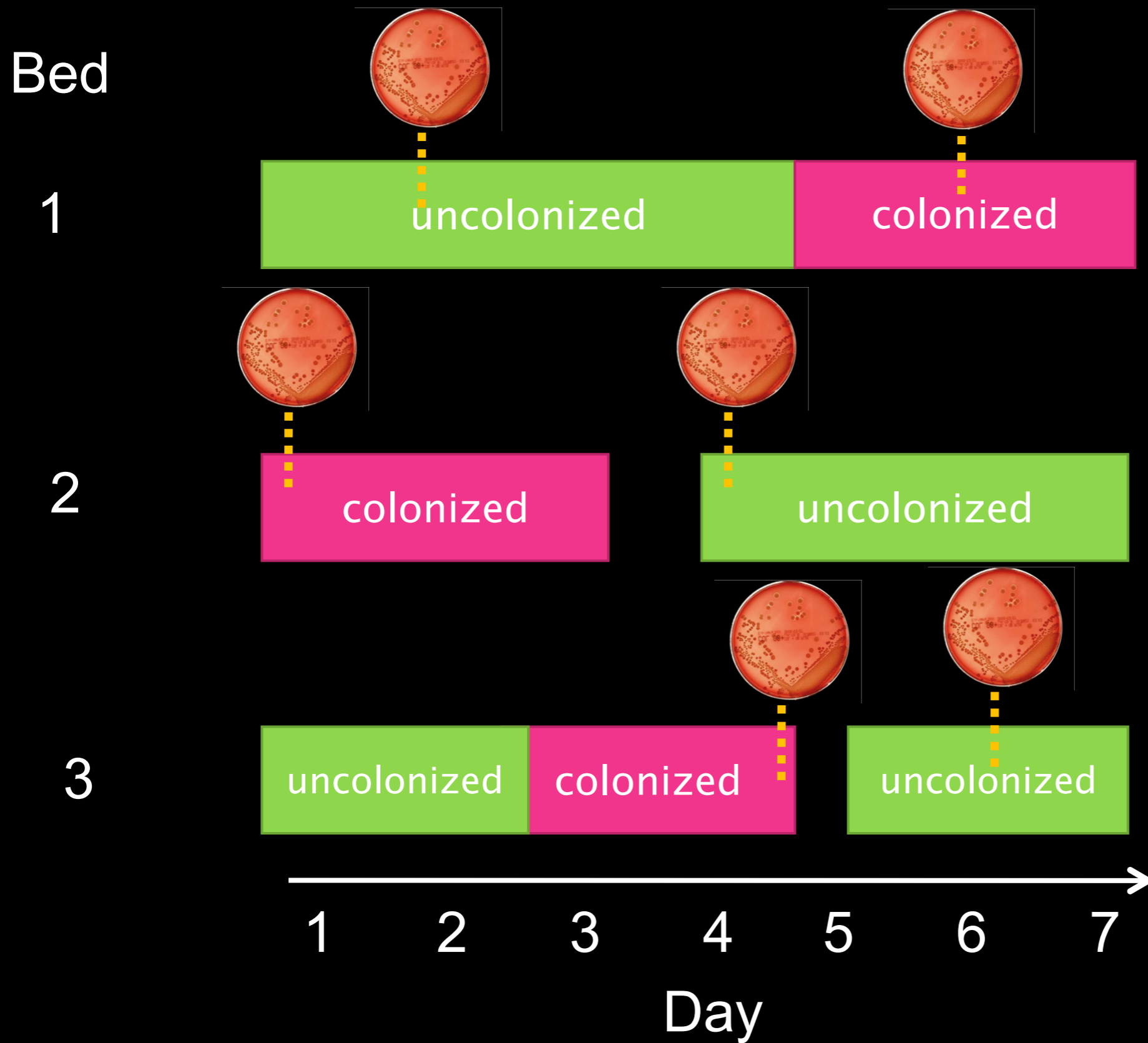
Problems may be overcome by adopting a Bayesian perspective, using prior information (e.g. for proportion colonized on admission).



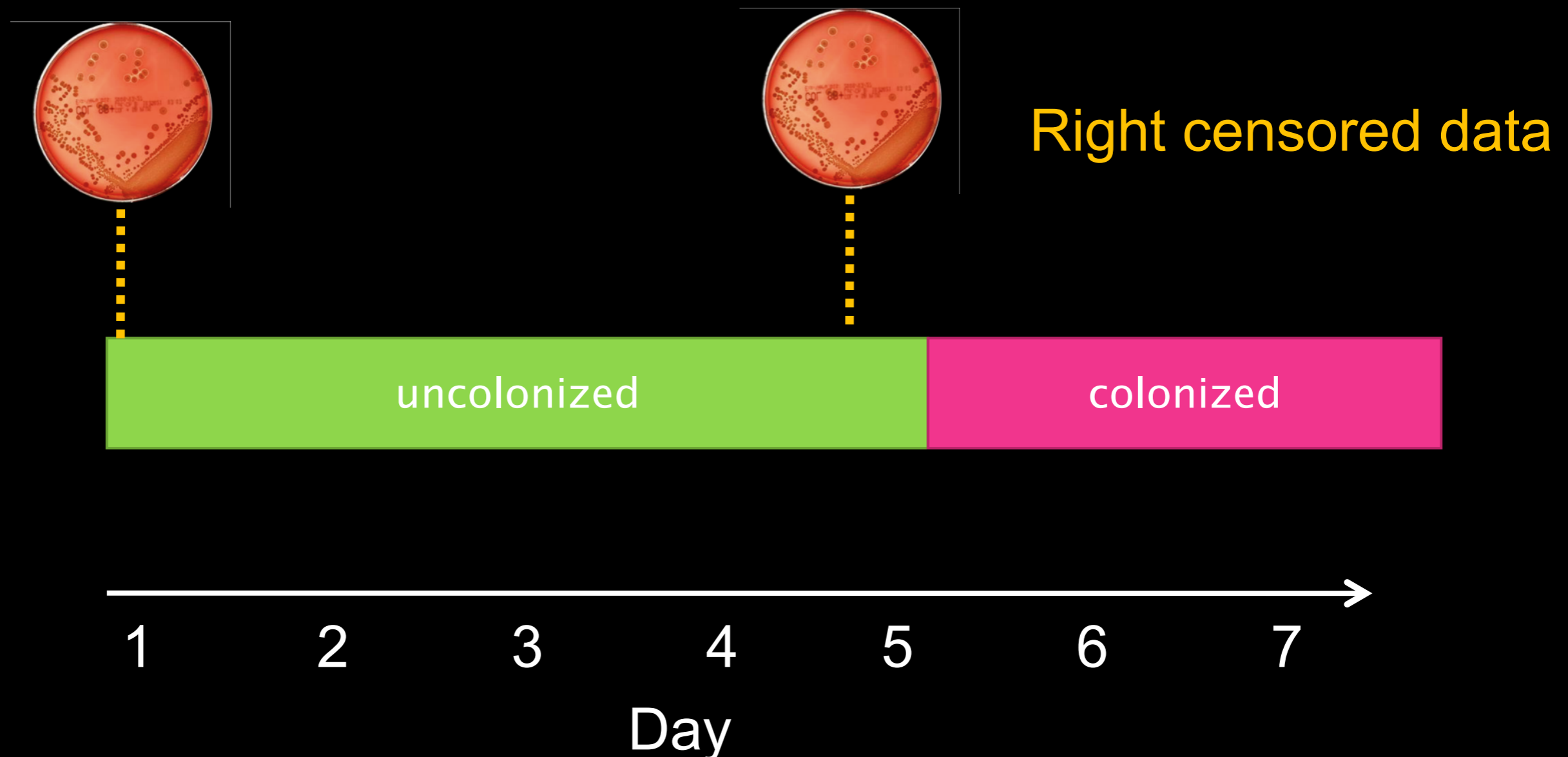
The probability of a change in the number of colonised patients,  $C$ , in a short time period,  $h$ , is given by

$$\begin{aligned} Pr[C(t+h) = i+1 | C(t) = i] &= \beta i(N-i)h + \nu(N-i)h + o(h), \\ Pr[C(t+h) = i-1 | C(t) = i] &= \mu i h + o(h), \\ Pr[C(t+h) = i | C(t) = i] &= 1 - \beta i(N-i)h - \nu(N-i)h - \mu i h + o(h), \end{aligned}$$

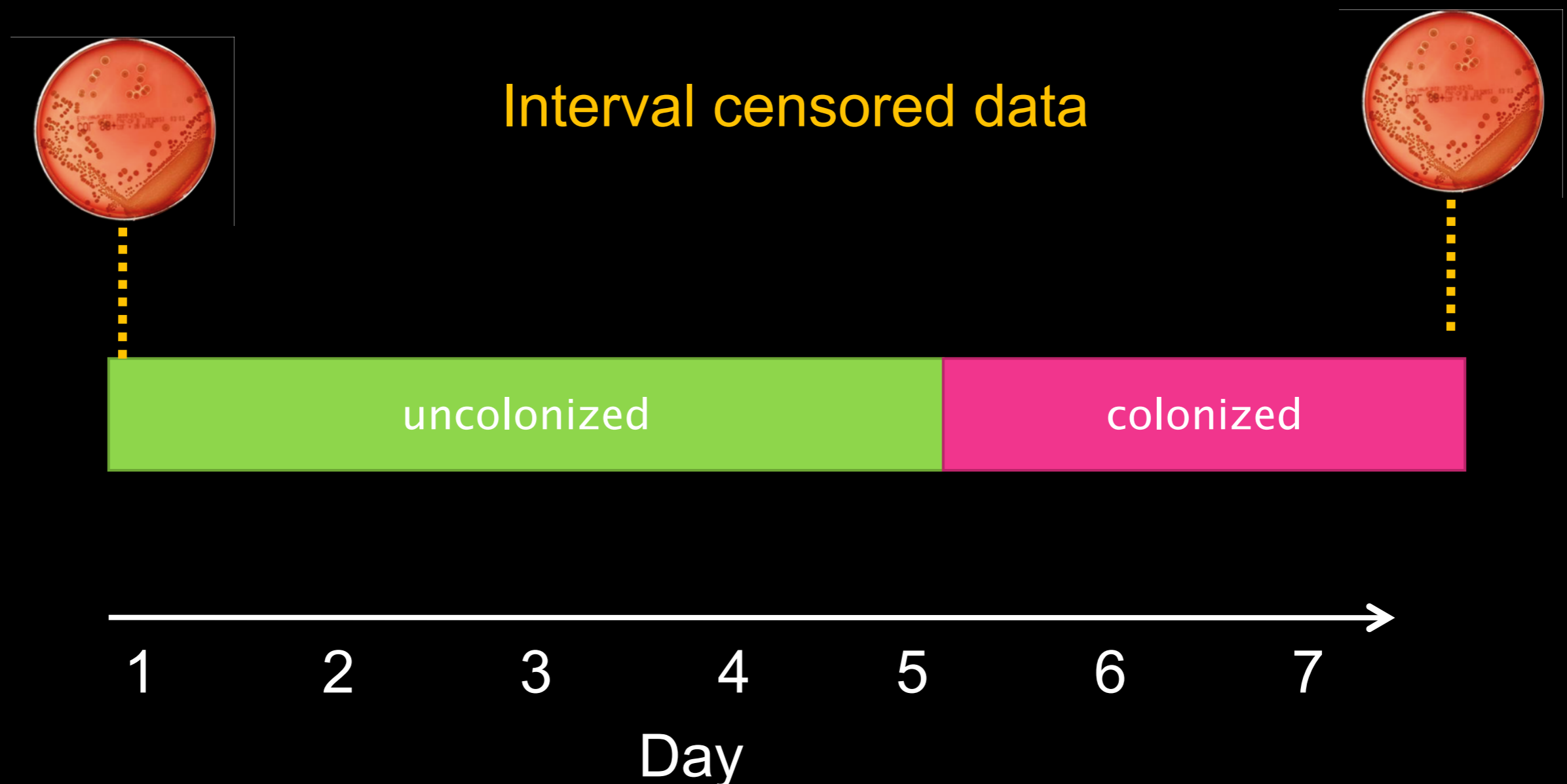




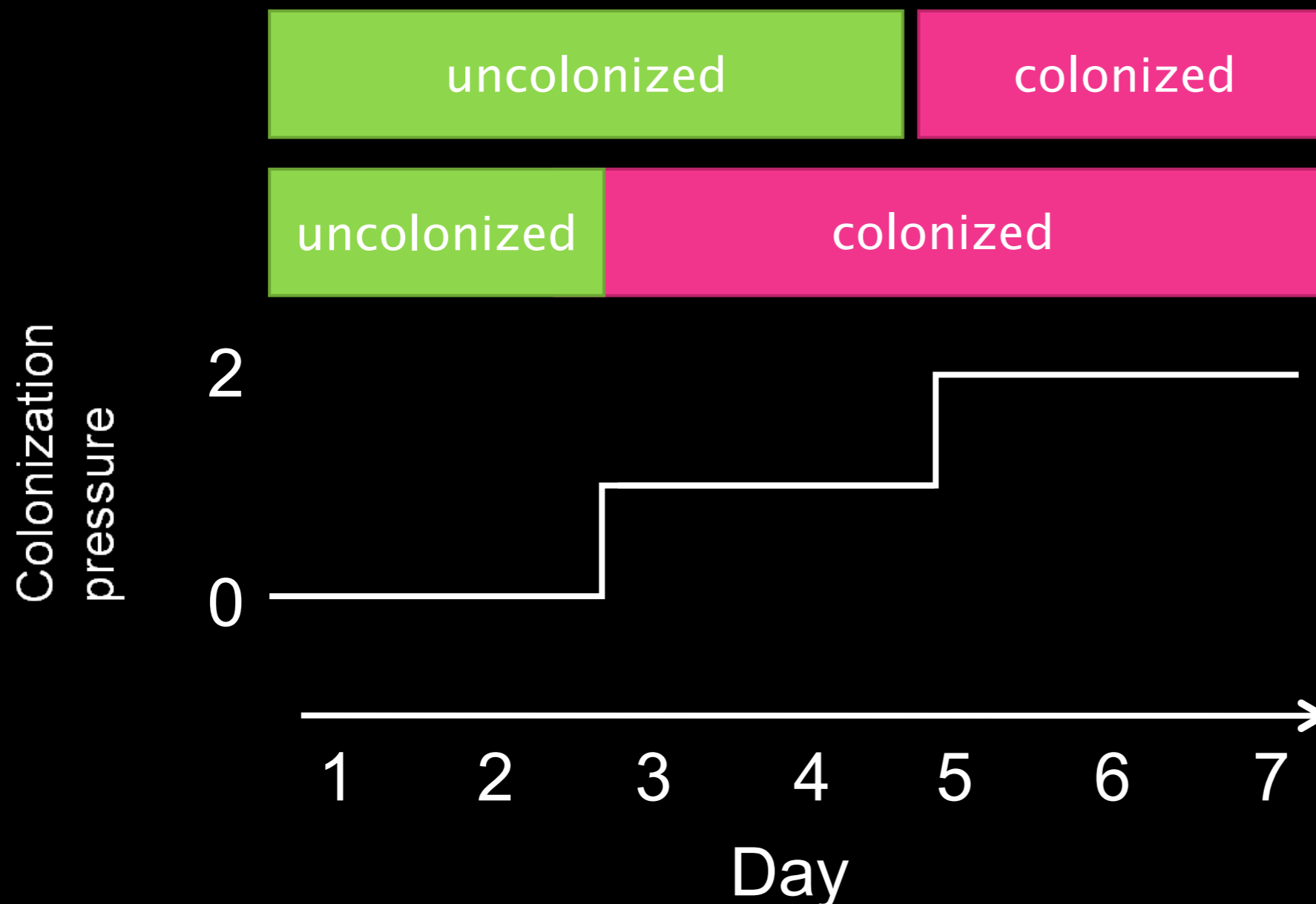
1. We observe an individual's "state" only at certain time points. This leads to censored data.



1. We may observe an individual's "state" only at certain time points. This leads to censored data.



2. The probability that a person's state changes at a particular time depends on the states that other patients are in



### 3. There may be ascertainment error:

false negative results: e.g. a negative MRSA screening swab when a patient is MRSA positive

false positive results: positive screening result when a patient is negative

# Solution: Bayesian data augmentation

$$\begin{aligned} p(\mathbf{D}, \mathbf{A}, \lambda_1, \lambda_2 \dots) &= p(\mathbf{D}, \mathbf{A} \mid \lambda_1, \lambda_2 \dots) p(\lambda_1, \lambda_2 \dots) \\ &= p(\mathbf{D} \mid \mathbf{A}) p(\mathbf{A} \mid \lambda_1, \lambda_2 \dots) p(\lambda_1, \lambda_2 \dots) \end{aligned}$$

Likelihood of data given augmented data  
(observation model)

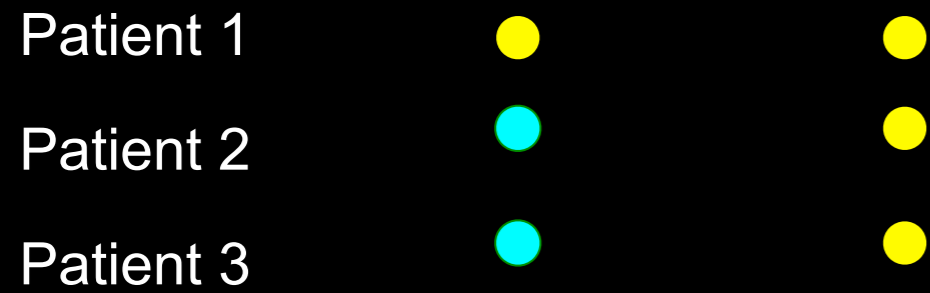


Likelihood of augmented data given parameters  
(transmission model)

Prior probabilities of parameters  
(prior model)

D=data. A=augmented data.

## Observed data



● = positive swab (observed data)

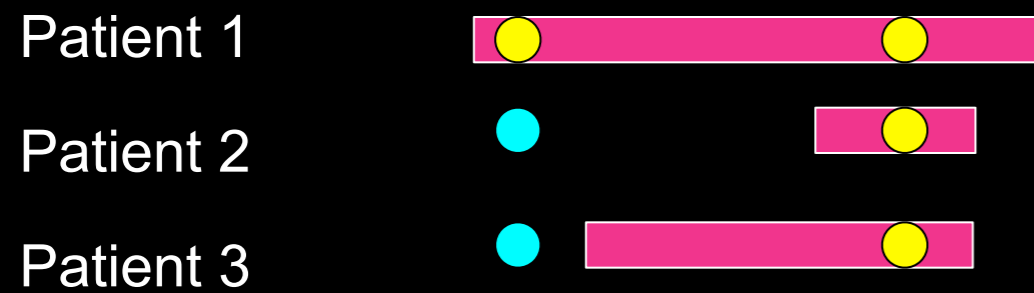
● = negative swab (observed data)


time





# Observed data & unobserved process



 = carriage episode (latent or unobserved process)

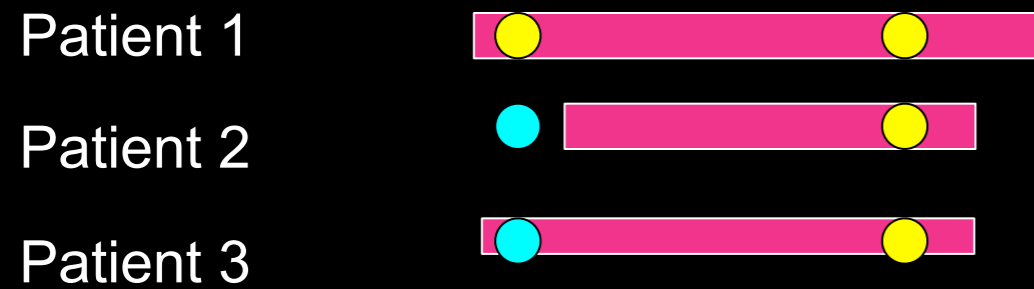
 = positive swab (observed data)


 = negative swab (observed data)

time



# Observed data & unobserved process



 = carriage episode (latent or unobserved process)

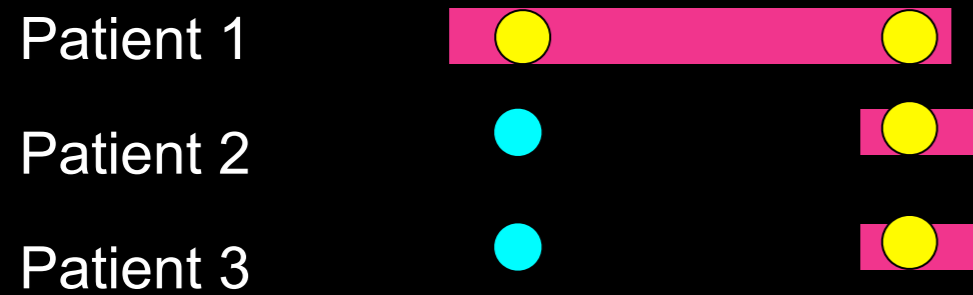
 = positive swab (observed data)


 = negative swab (observed data)

time



# Observed data & unobserved process



 = carriage episode (latent or unobserved process)

 = positive swab (observed data)

 = negative swab (observed data)

time



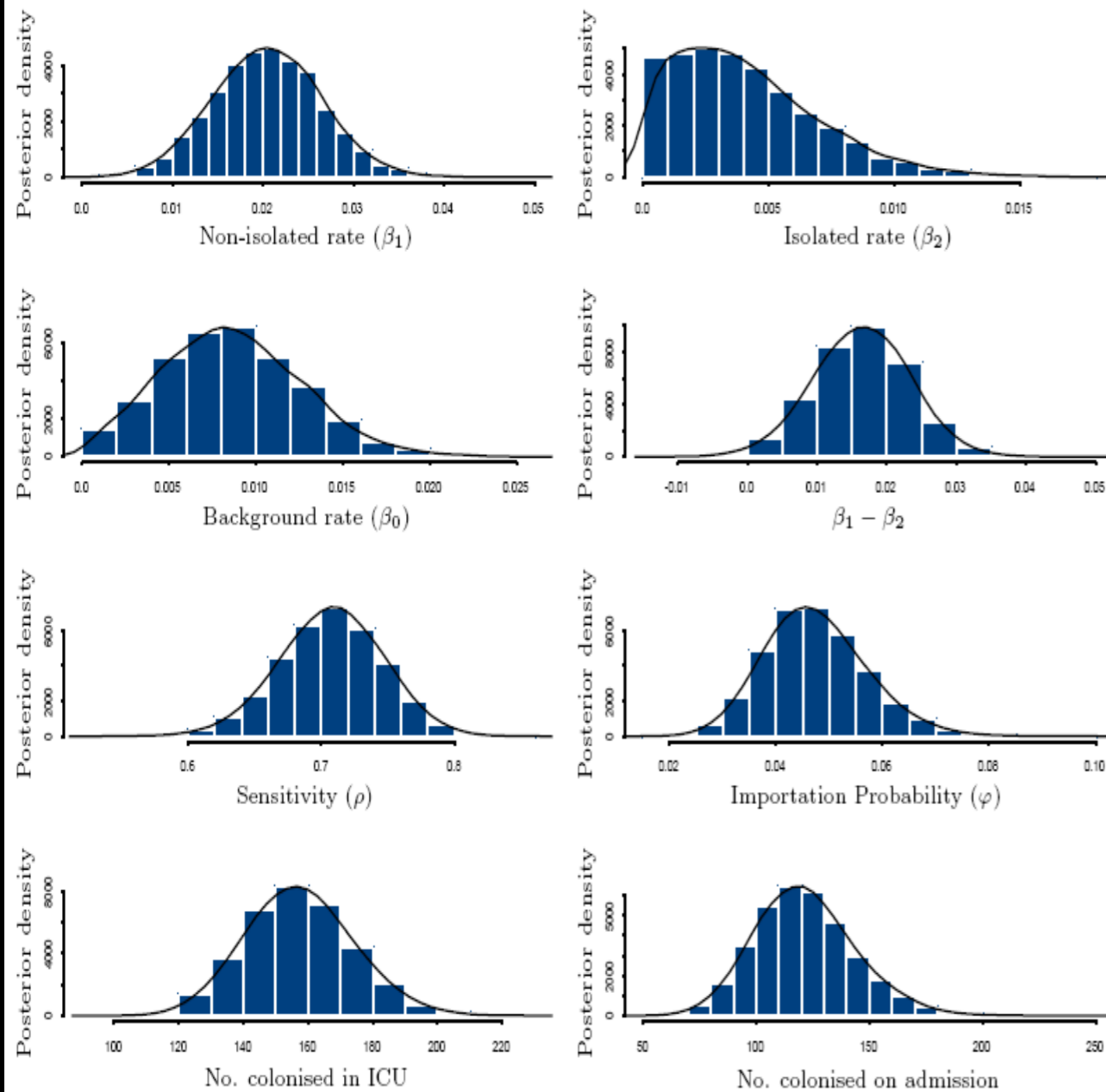
## Bayesian inference of hospital-acquired infectious diseases and control measures given imperfect surveillance data

M. L. FORRESTER, A. N. PETTITT\*

Queensland University of Technology, Brisbane QLD, Australia  
a.pettitt@qut.edu.au

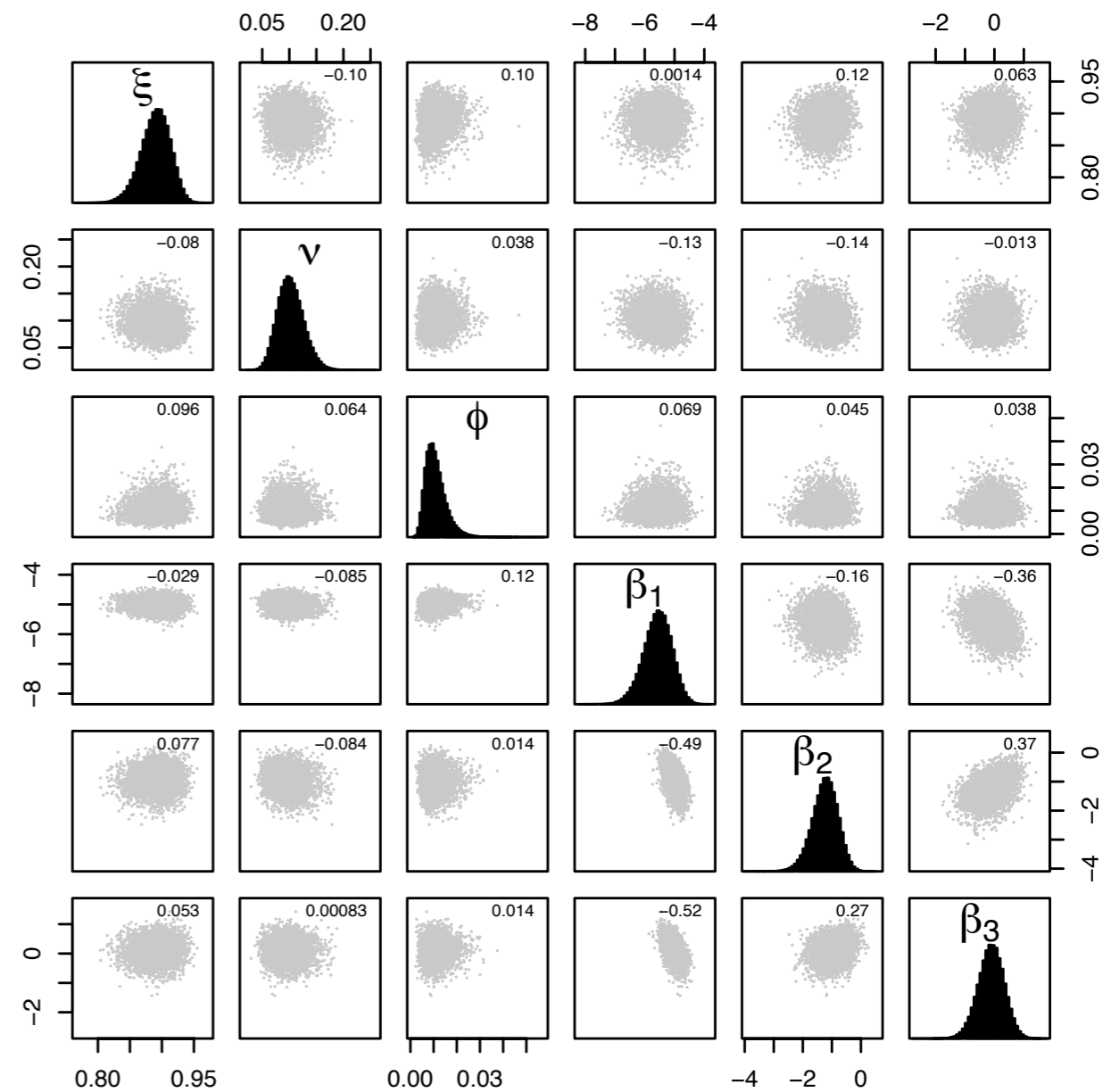
G. J. GIBSON

Heriot-Watt University, Edinburgh, United Kingdom



## An Augmented Data Method for the Analysis of Nosocomial Infection Data

Ben S. Cooper<sup>1</sup>, Graham F. Medley<sup>2</sup>, Susan J. Bradley<sup>3</sup>, and Geoffrey M. Scott<sup>4</sup>



$\xi$  - swab sensitivity;  $\nu$  - probability colonized on admission  
 $\phi$  - carriage clearance rate;  $\beta_1, \beta_2, \beta_3$  - transmission rates in phases 1-3

# Policy questions

Which screening technologies and screening strategies should be used for controlling MRSA when combined with isolation and decolonisation measures?

Is it worth investing in new molecular screening test that gives a result in a few hours instead of a few days (with higher sensitivity)? If so, who should we screen with a rapid test?

Benefits of a change a screening policy have to be weighed against costs. We have to ask, could the money have had greater health benefit if invested elsewhere in the health service?

**Many hospitals screen patients for asymptomatic MRSA carriage (colonisation), but practices vary greatly and there is wide selection of screening technologies:**

**Conventional Culture**

**Chromogenic Agar:** CHROMagar; MRSA-ID; MRSA-Select

**PCR:** IDI-MRSA/gene-ohm; Genotype MRSA direct; Hyplex StaphyloResist; Easy-plex

**all with different characteristics:**

**Sensitivity**  
(prob. screen is +ve if patient has MRSA)

**Specificity**  
(1-prob. screen is +ve if patient does not have MRSA)

**Turn around time**  
(time from screen to action taken based on screen result)

**Throughput**

**Costs**

**Who and when to screen?**

Different combinations of admission, discharge, periodical (i.e. weekly or twice weekly) and targeted screening.

**What screening technology to use?**

**Combine with what control measures?**

Isolation (single rooms, isolation wards, patient and staff cohorting, and contact precautions)

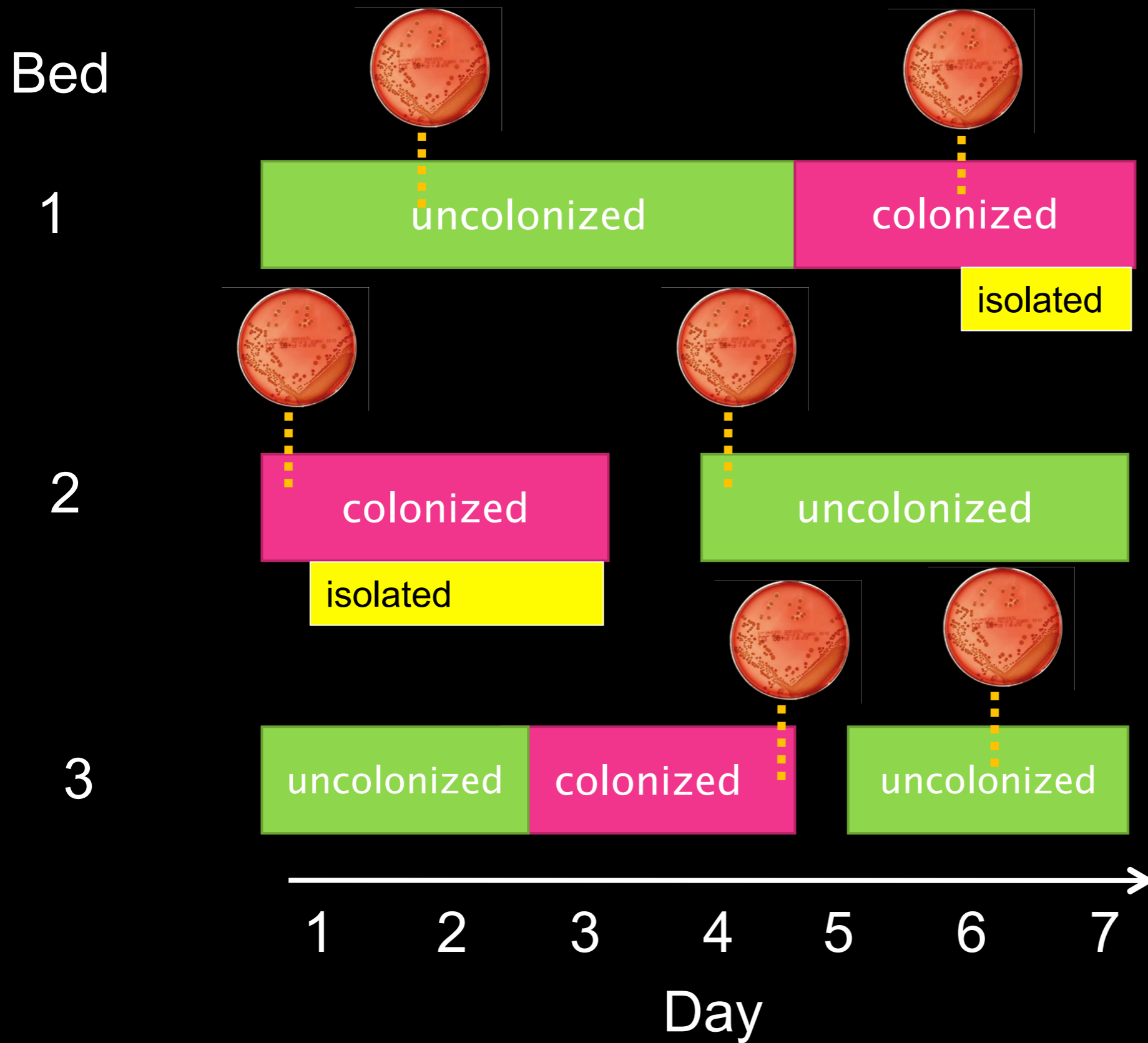
Therapy to suppress colonisation (e.g. chlorhexidine body washes, mupirocin)

# Isolation measures in the hospital management of methicillin resistant *Staphylococcus aureus* (MRSA): systematic review of the literature

B S Cooper, S P Stone, C C Kibbler, B D Cookson, J A Roberts, G F Medley, G Duckworth, R Lai and S Ebrahim

*BMJ* 2004;329:533

**Conclusion** Major methodological weaknesses and inadequate reporting in published research mean that many plausible alternative explanations for reductions in MRSA acquisition associated with interventions cannot be excluded. No well designed studies exist that allow the role of isolation measures alone to be assessed. None the less, there is evidence that concerted efforts that include isolation can reduce MRSA even in endemic settings. Current isolation measures recommended in national guidelines should continue to be applied until further research establishes otherwise.

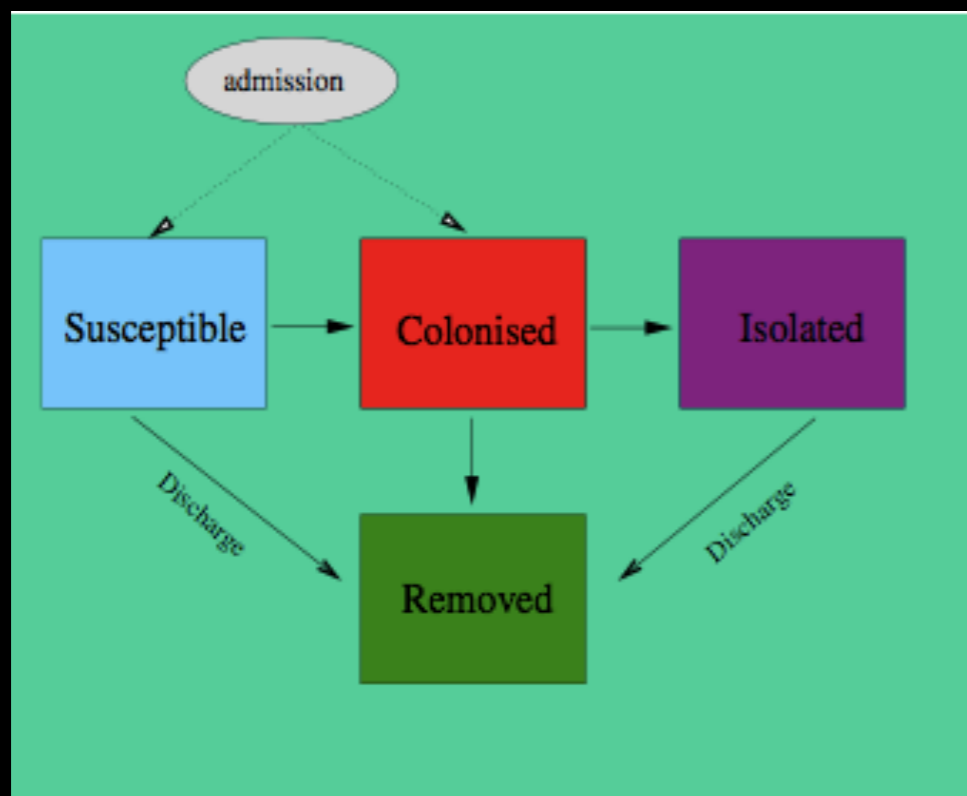




# Assessing the role of undetected colonization and isolation precautions in reducing Methicillin-Resistant *Staphylococcus aureus* transmission in intensive care units

Theodore Kypraios<sup>1,6</sup>, Philip D. O'Neill<sup>1</sup>, Susan S. Huang<sup>2,3</sup>, Sheryl L. Rifas-Shiman<sup>4</sup>, Ben S. Cooper<sup>5,6</sup>.

BMC Infectious Diseases 2010



Model fitted to data from 8 adult ICUs in Boston. Admission and weekly n nares screening for MRSA

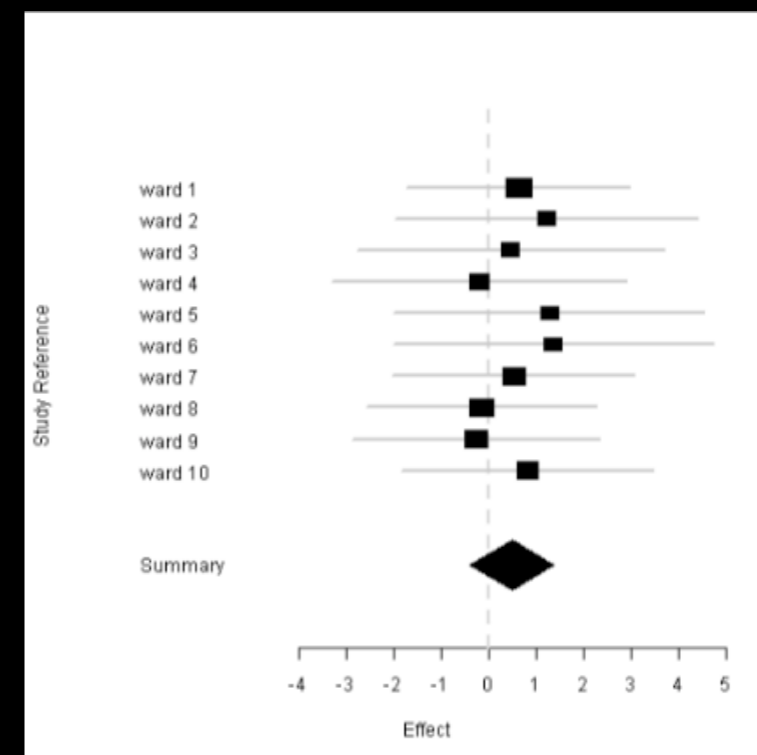
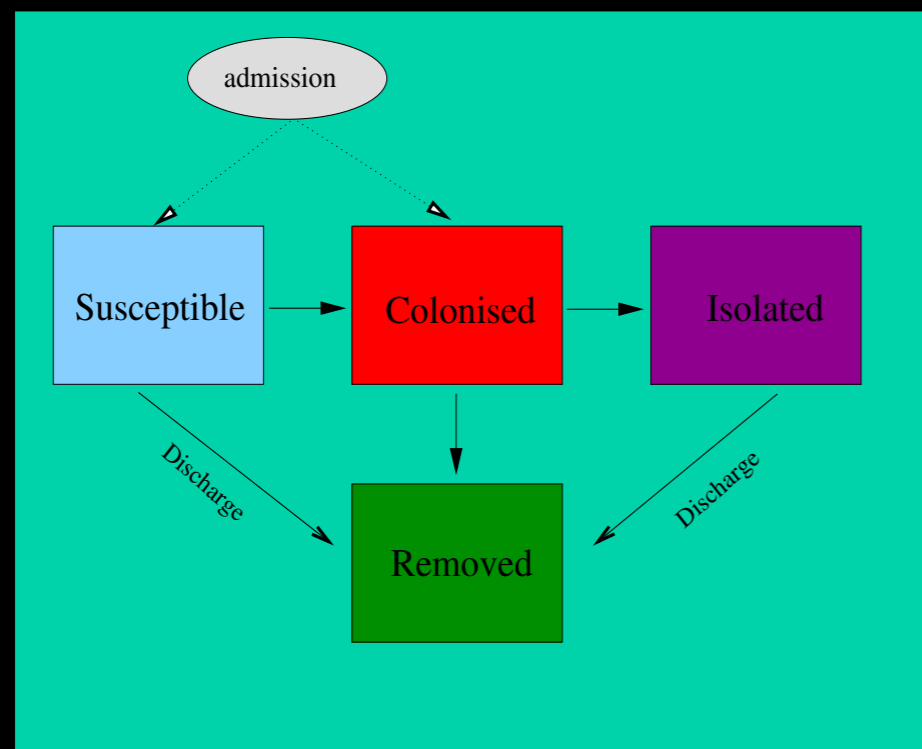
Newly-identified and previously known MRSA+ patients were placed under contact precautions (gloves+gowns).

# Isolation Effectiveness

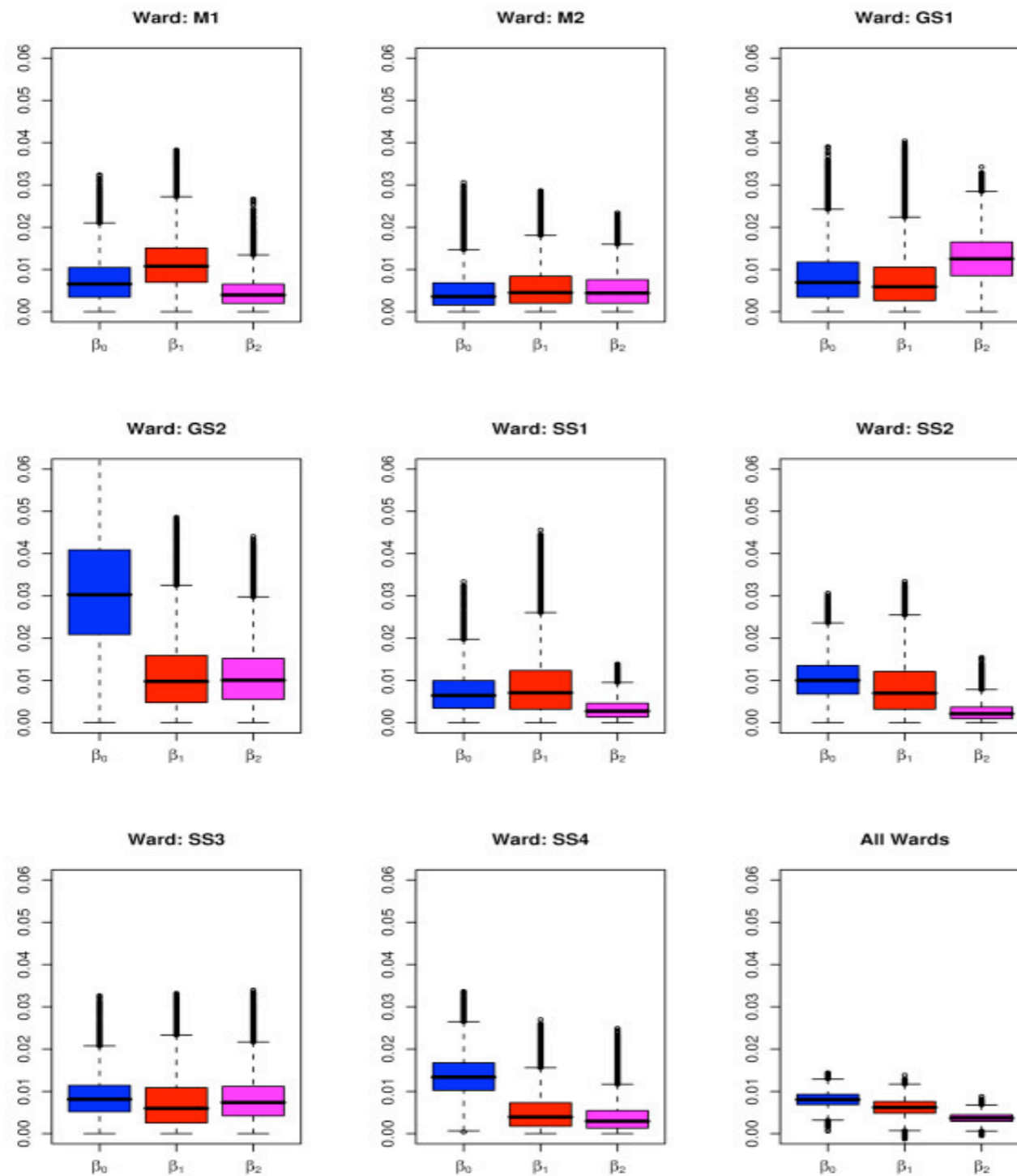
Effectiveness of isolation (gloves and gowns) in reducing transmission estimated by fitting a stochastic transmission model to 17 months of MRSA surveillance data from 10 ICUs.

Parameters estimated within a Bayesian data augmentation framework using MCMC.

Kypraios *et al.* BMC Infectious Dis 2010



Marginal posterior distributions of the colonization rates for each ward.



Background  
transmission rate

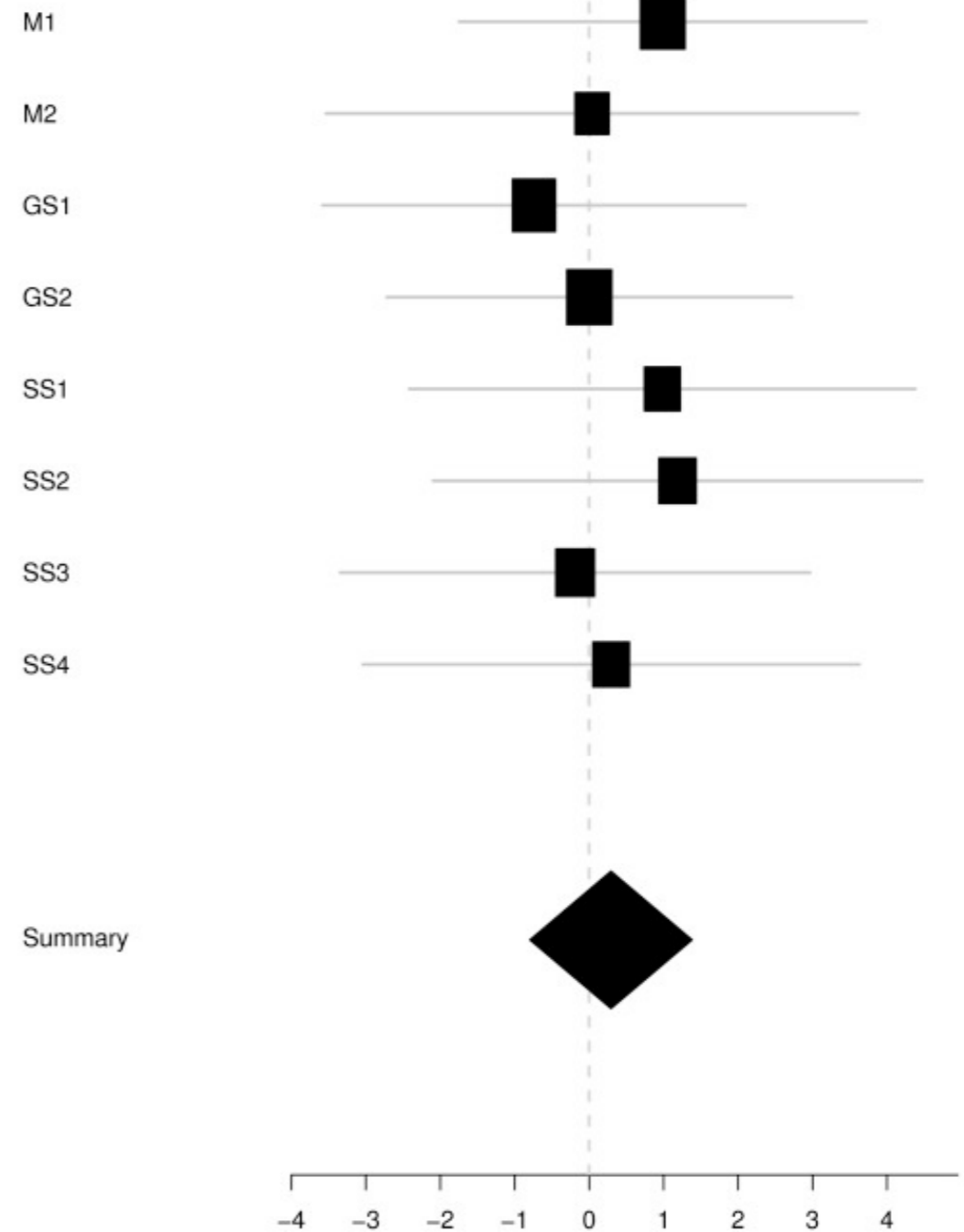
Transmission rate from  
unisolated MRSA  
patients

Transmission rate from  
isolated MRSA patients

Ward	Estimated probability isolation reduced transmission	Estimated probability isolation reduced transmission
	$P(\beta_1 > \beta_2)$	Median ( $\beta_1/\beta_2$ )
M1	0.82	2.7
M2	0.51	1.0
GS1	0.27	0.5
GS2	0.50	1.0
SS1	0.73	2.7
SS2	0.79	3.3
SS3	0.44	0.8
SS4	0.58	1.3

Ward

# Isolation effectiveness



effect -&gt;

Impact of rapid screening tests on acquisition of meticillin resistant *Staphylococcus aureus*: cluster randomised crossover trial

Dakshika Jeyaratnam, research fellow,<sup>1,2</sup> Christopher J M Whitty, professor,<sup>3</sup> Katie Phillips, medical laboratory assistant,<sup>1</sup> Dongmei Liu, medical statistician,<sup>3</sup> Christina Orezzi, information analyst,<sup>1</sup> Uchechukwu Ajoku, research assistant,<sup>1</sup> Gary L French, professor of microbiology<sup>1,2</sup>

Model 1

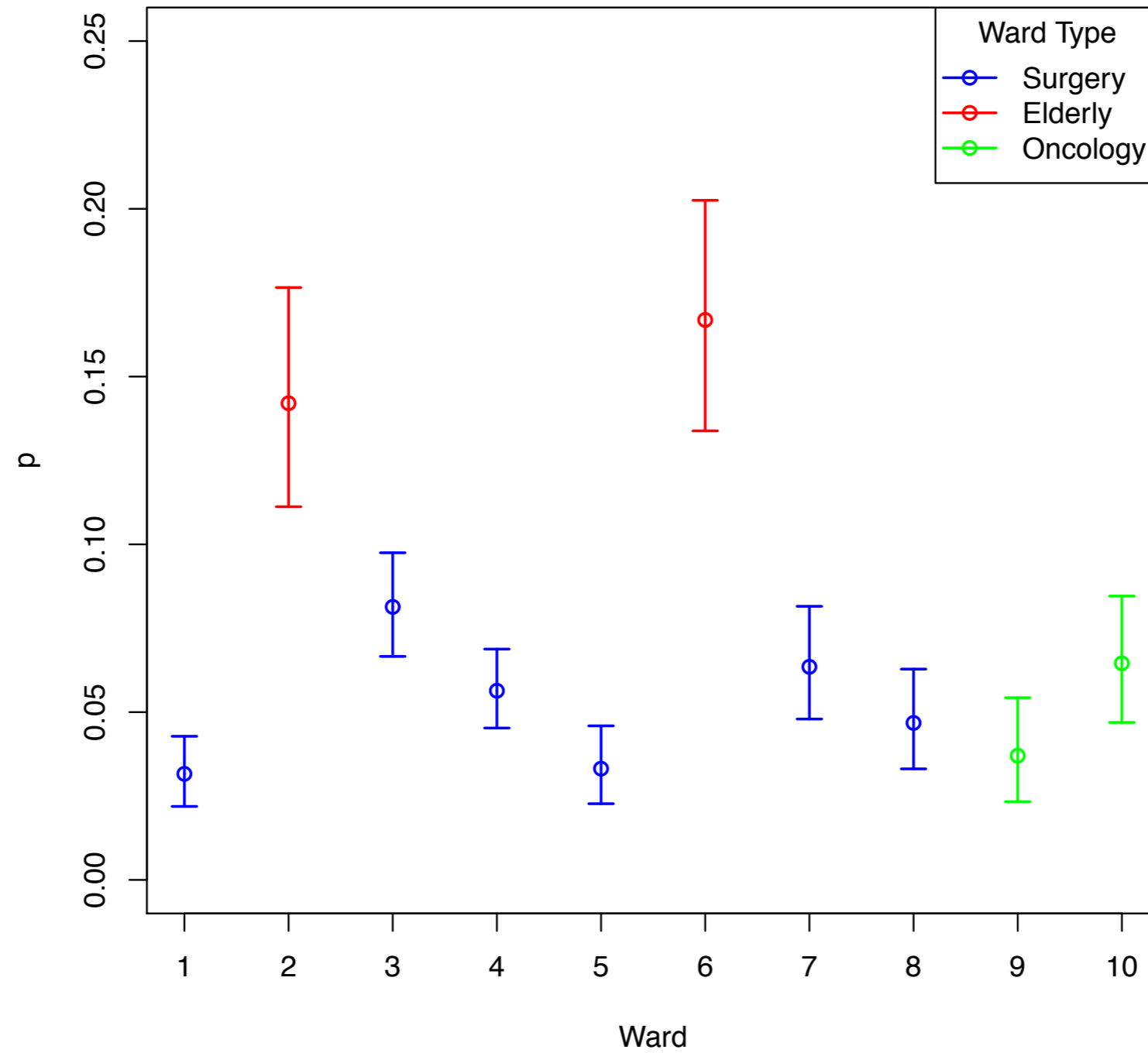
Rate of transmission from susceptible to colonized =  $a_0 + a_1 \times \text{number colonized} + a_2 \times \text{number colonized and isolated}$

$$E_{iso} = \frac{P(\text{MRSA acquisition given 1 colonized patient in isolation})}{P(\text{MRSA acquisition given 1 colonized not in isolation})} = \frac{1 - \exp(-a_0 - a_2)}{1 - \exp(-a_0 - a_1)}$$

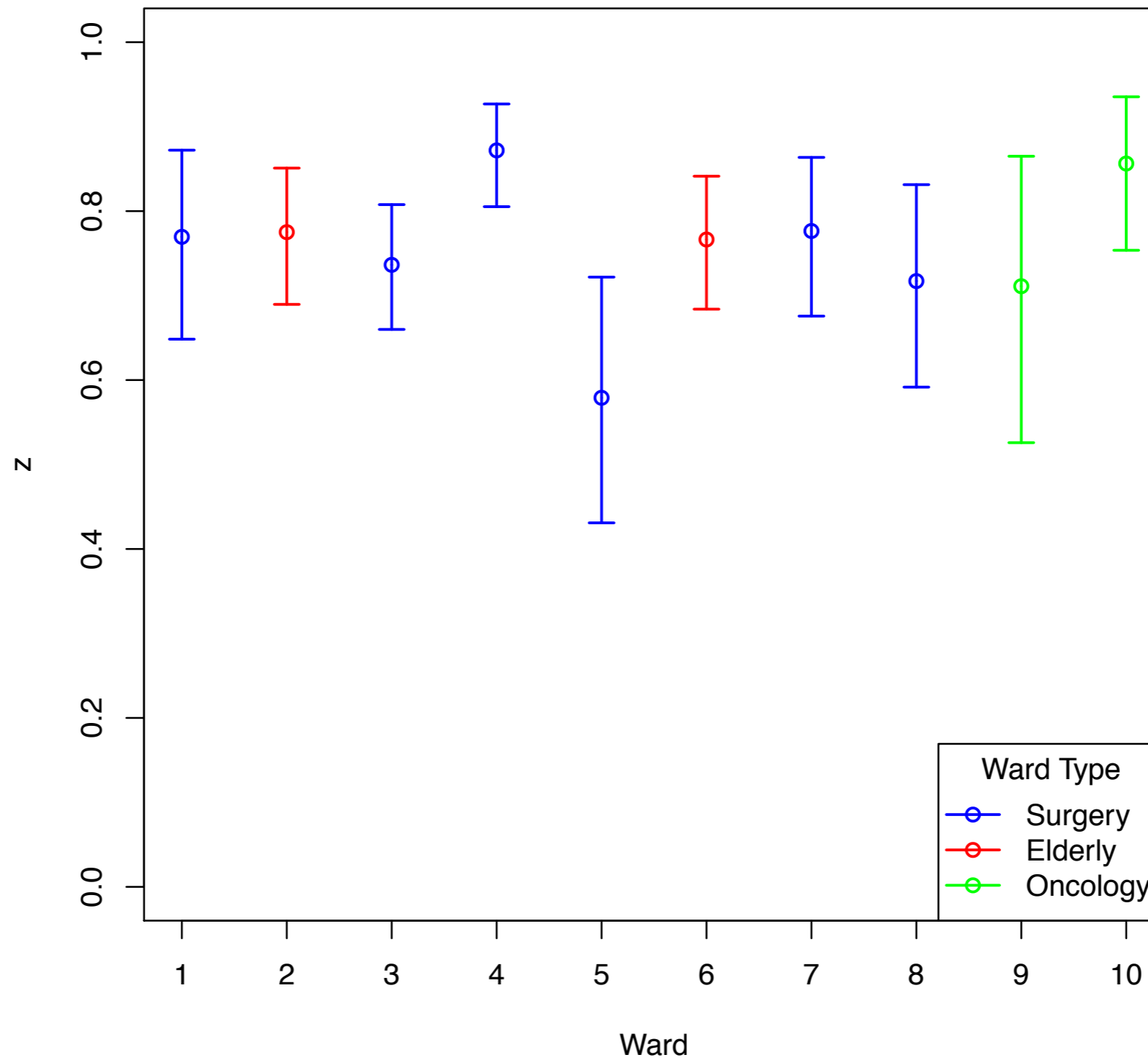
Model 2

Rate of transmission from susceptible to colonized =  $a_0 + a_1 \times \text{number colonized} + a_2 \times \text{number colonized \& isolated on open ward} + a_3 \times \text{number colonized \& isolated in a single room}$

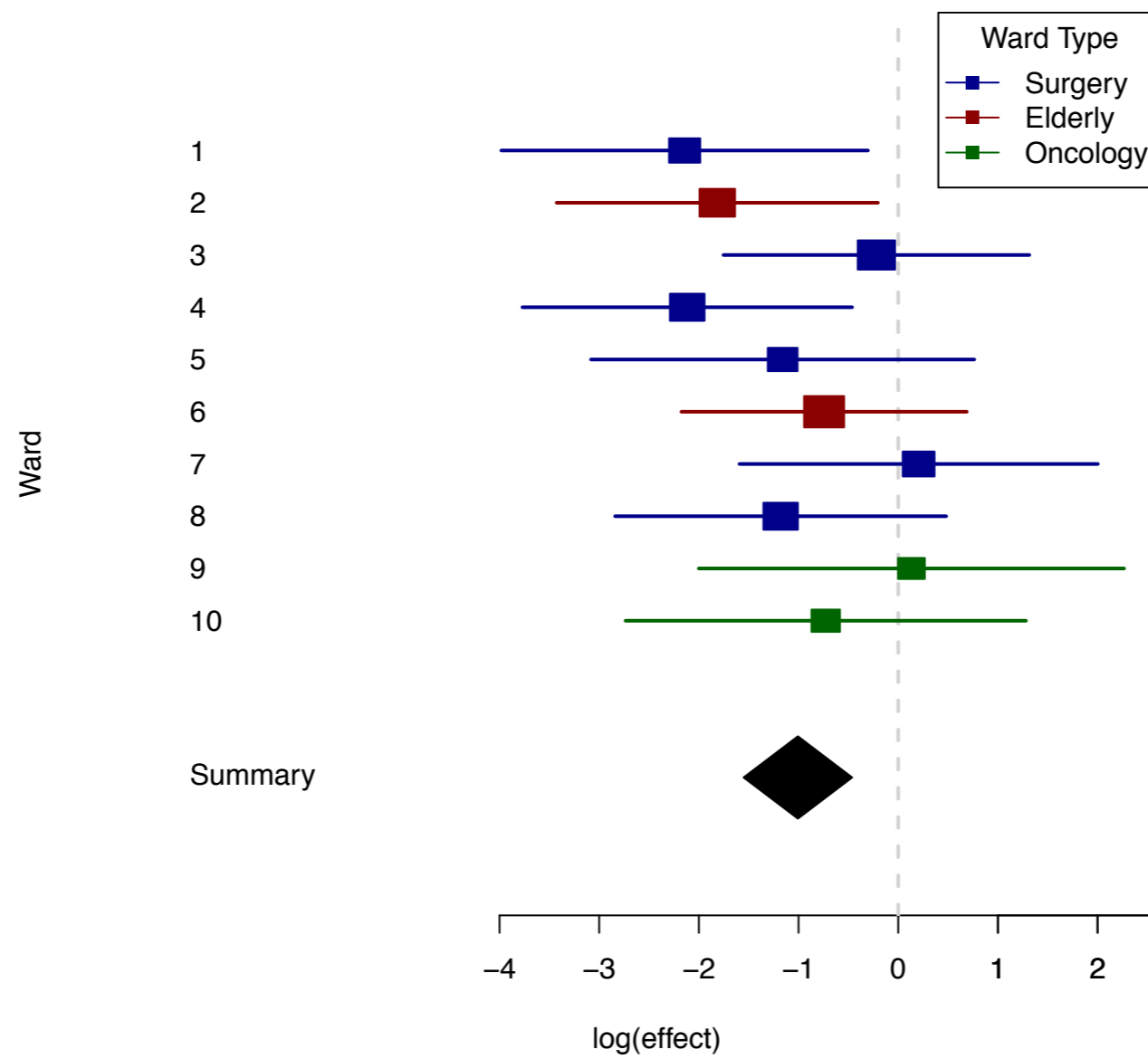
**P(colonised on admission)  
(estimates & 95% CI)**



### Sensitivity (estimates & 95% CI)

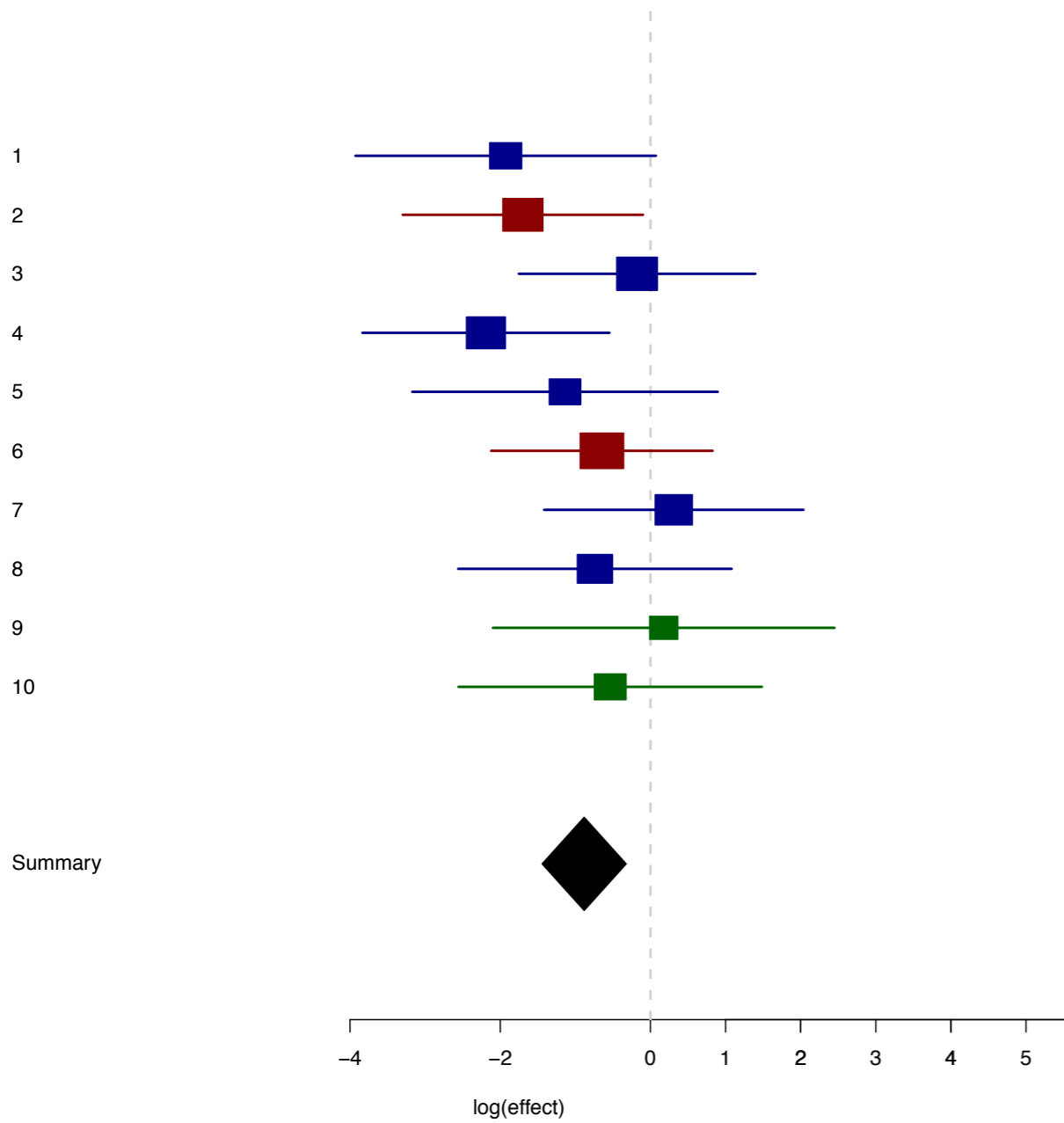


# Log-effect of isolation RR (95% CI)

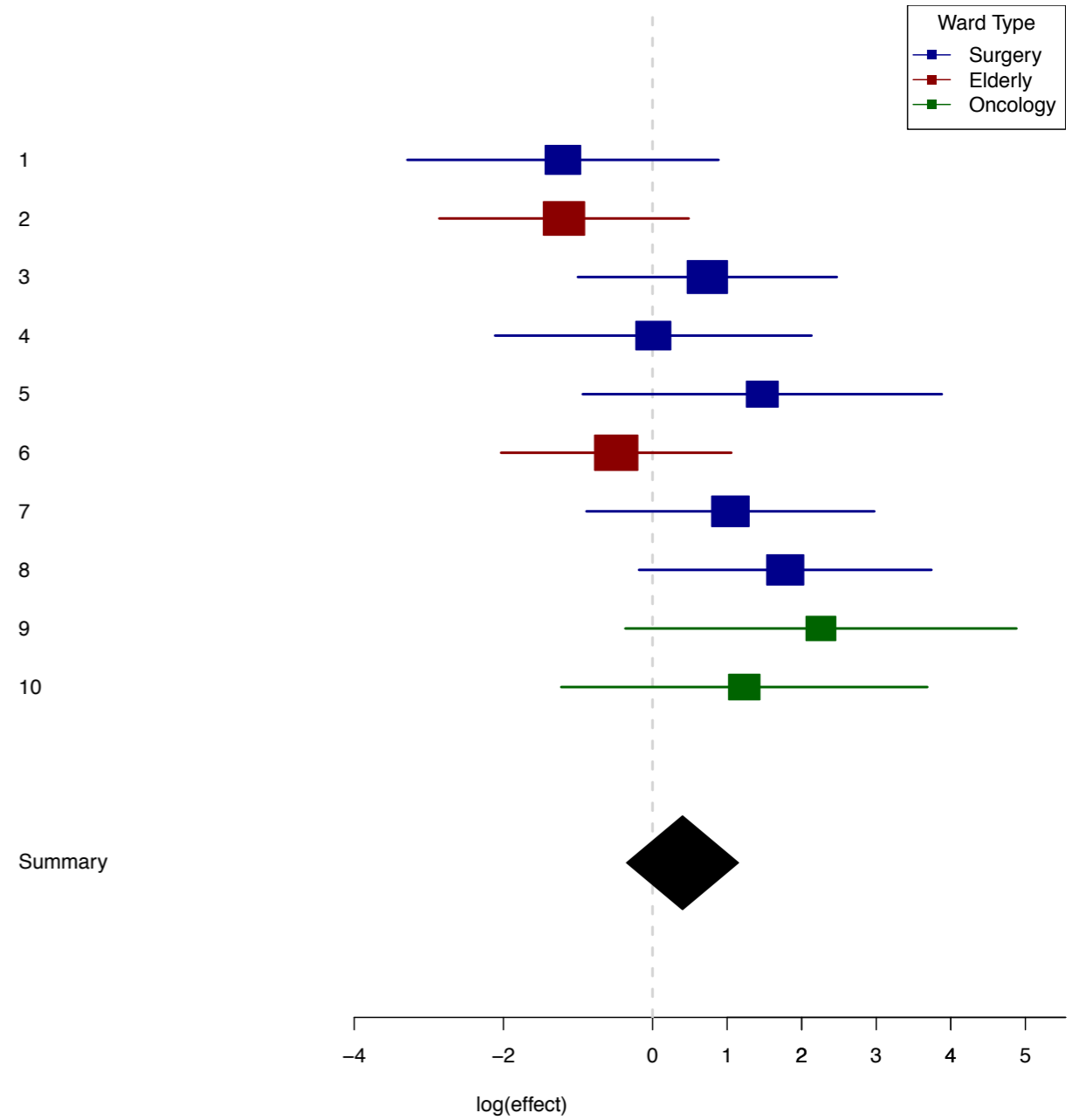




# Log-effect of side-room isolation RR (95% CI)



# Log-effect of open-ward isolation RR (95% CI)



**Effectiveness of interventions:**

- Screening
- Eradication therapy
- Isolation

Transmission parameters

**Health Economic parameters:**

- Cost of interventions
- QALY loss due to MRSA
- Attributable mortality
- Additional length of stay

**Transmission model**  
(individual-based, microsimulation model)

MRSA deaths, infections, admissions, ...

Assessment of effectiveness and cost effectiveness of interventions

# Inputs: Evidence Synthesis

Dynamics

Inference

**Policy**

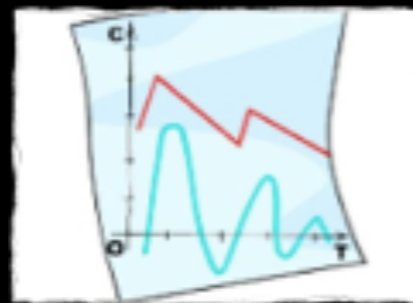
Future

## Literature



Few good studies on effectiveness of interventions but methodological quality of research is getting better

## Data

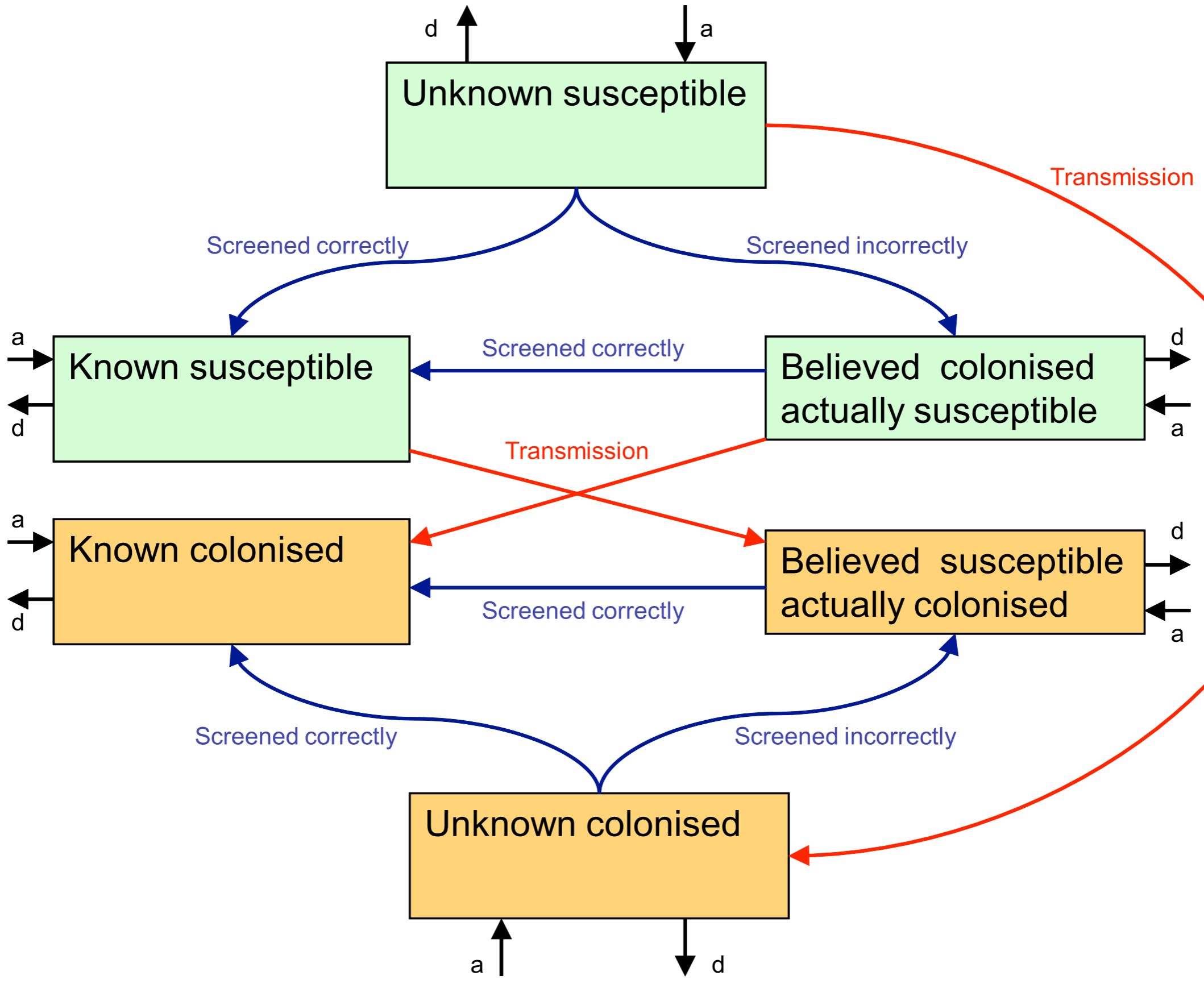


Analysis or reanalysis of original data sources required in the absence of reliable published estimates

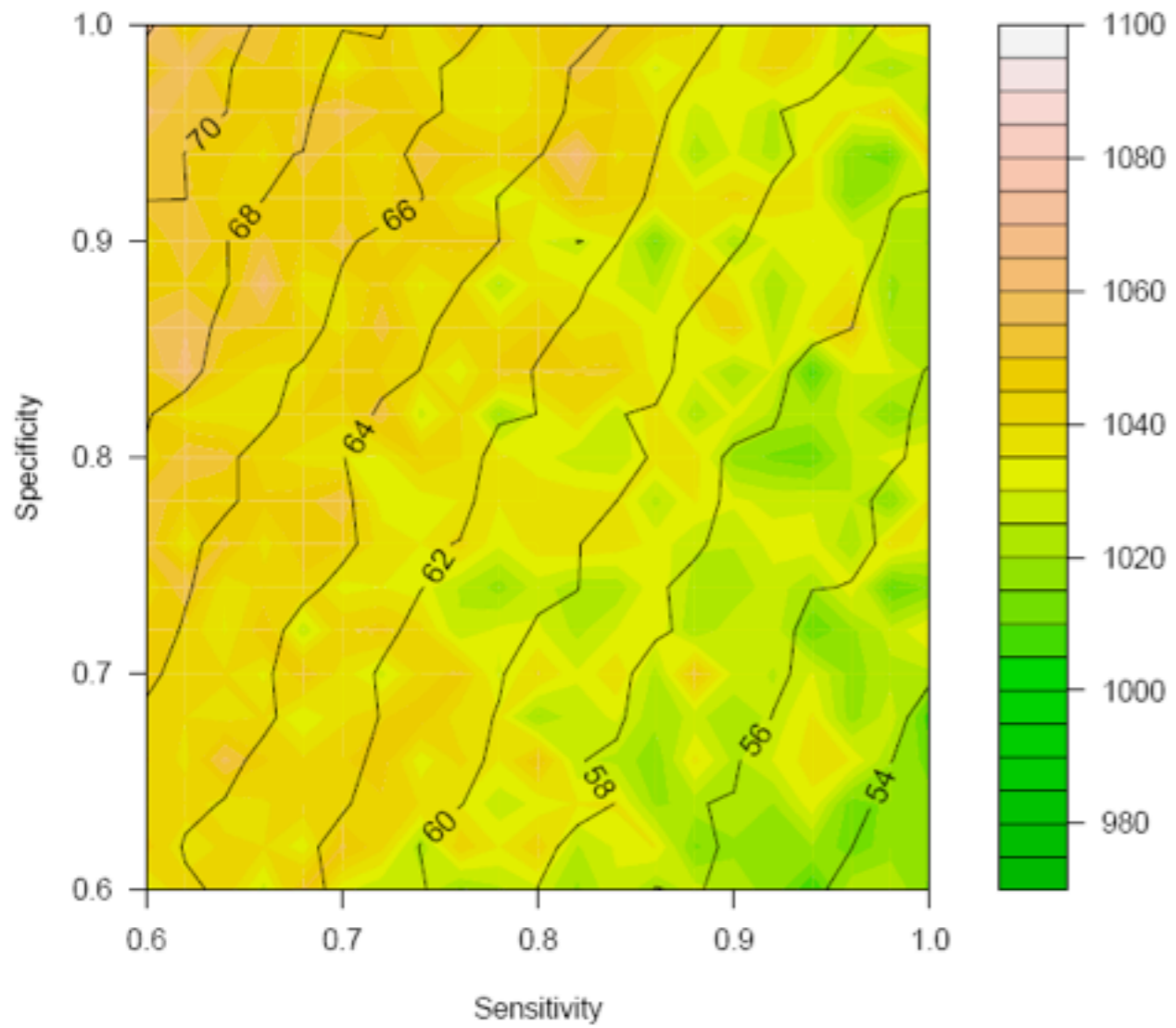
## Expert opinion



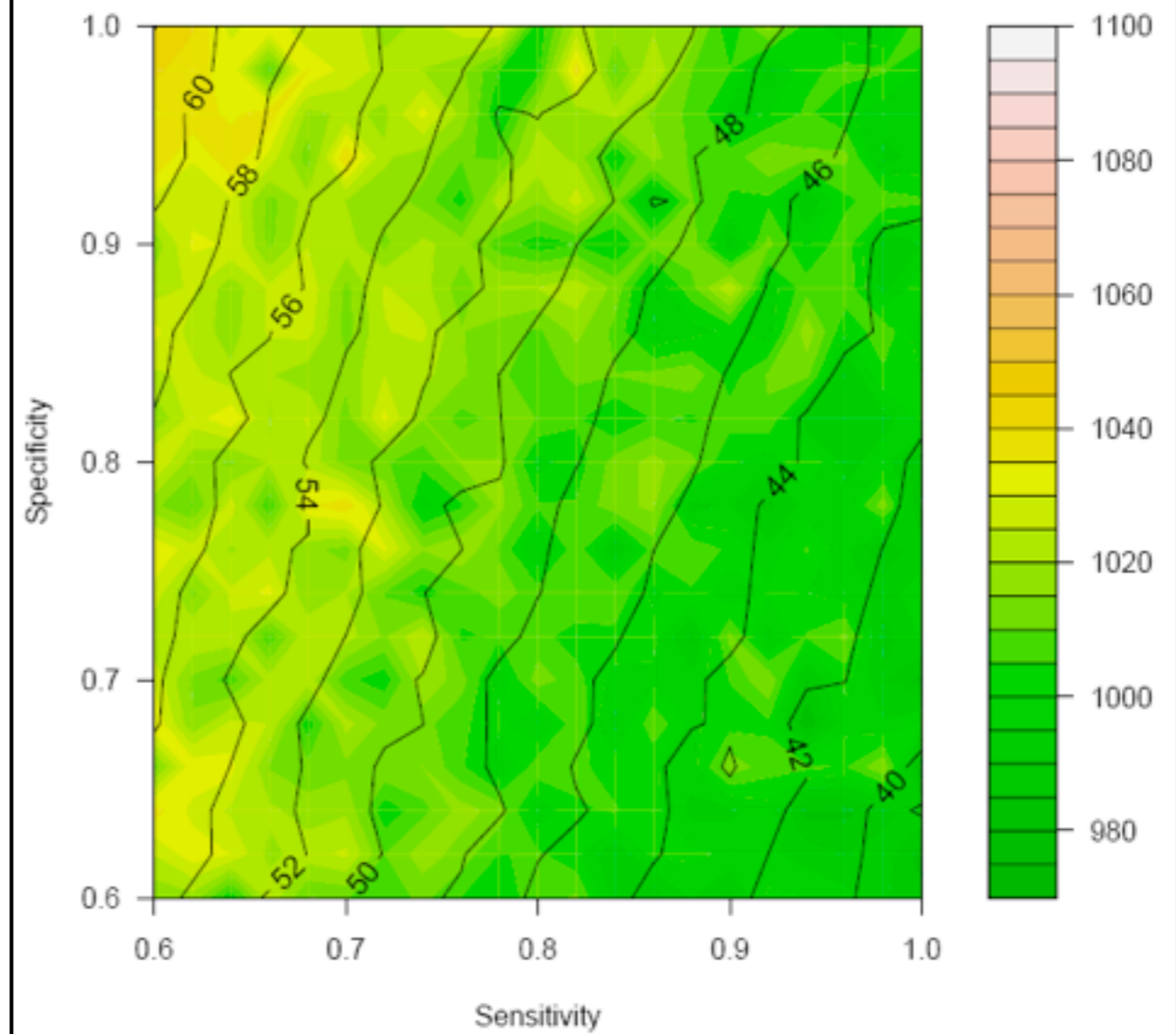
Where there were knowledge gaps formal elicitation techniques used to produce subjective prior distributions



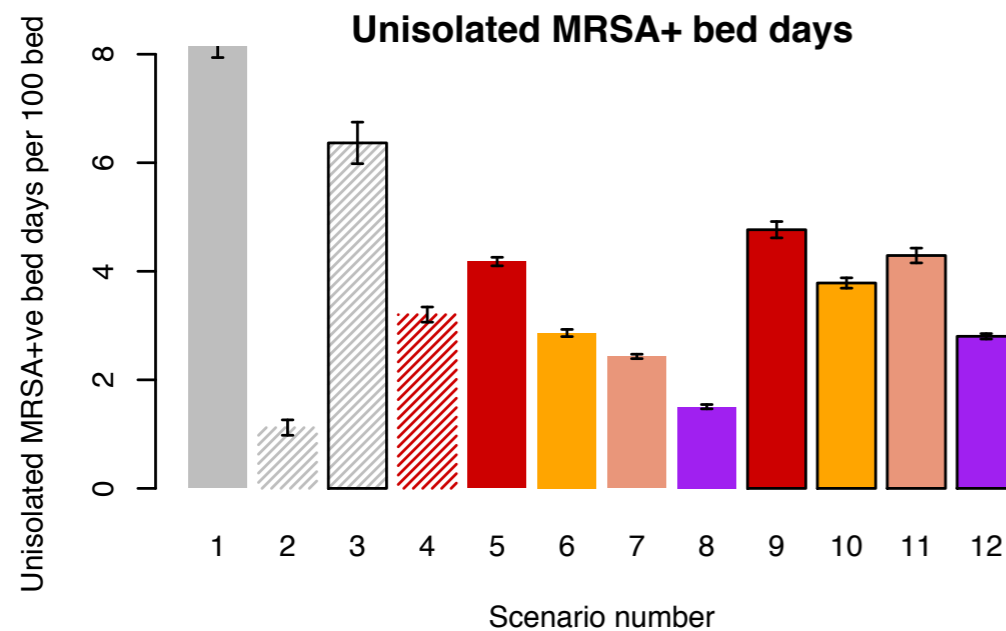
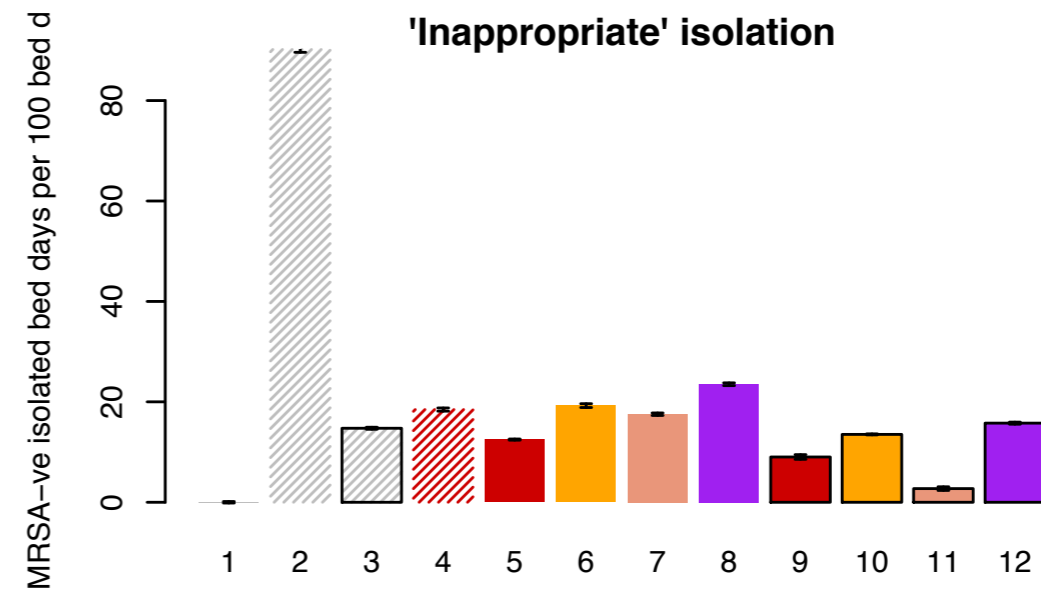
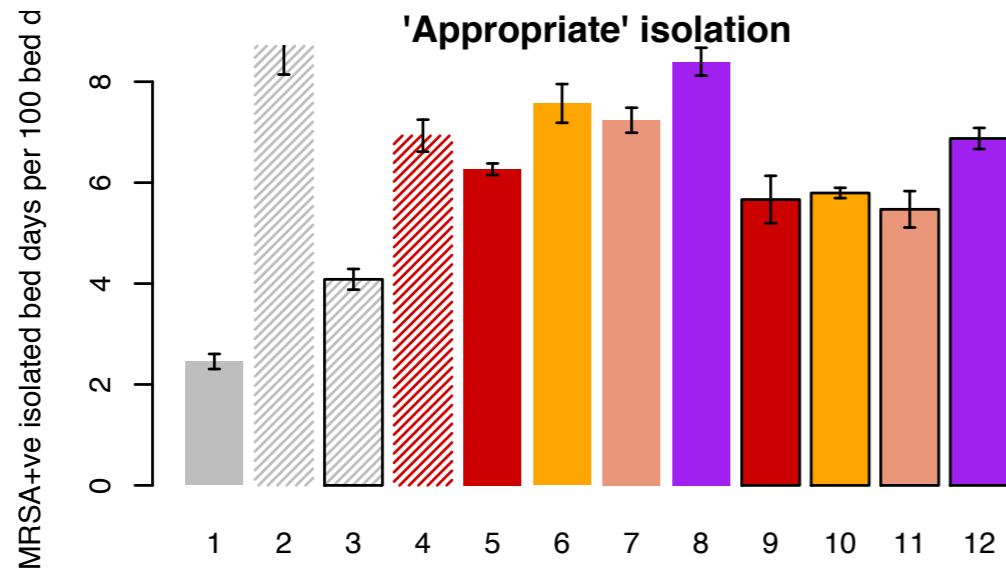
**MRSA+ Bed Days, TAT=4**  
(Black contours: % Unisolated)



**MRSA+ Bed Days, TAT=1**  
(Black contours: % Unisolated)



# Model outputs: effectiveness



Clinical cultures only

**Conventional Culture**

**Chromogenic Agar**

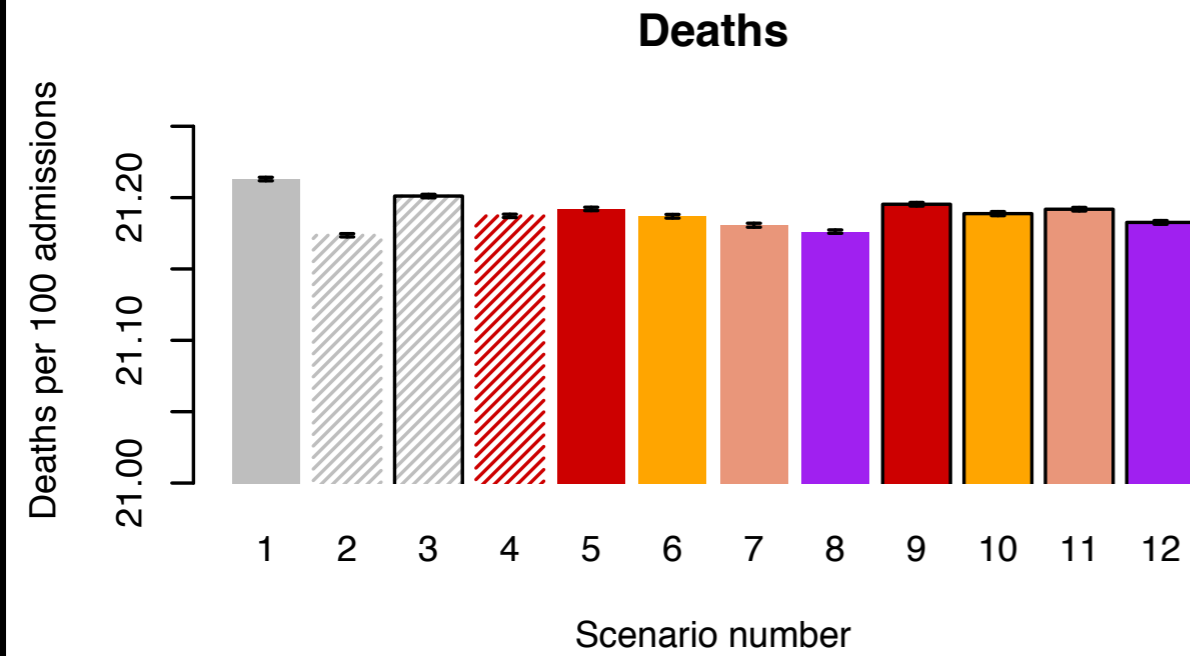
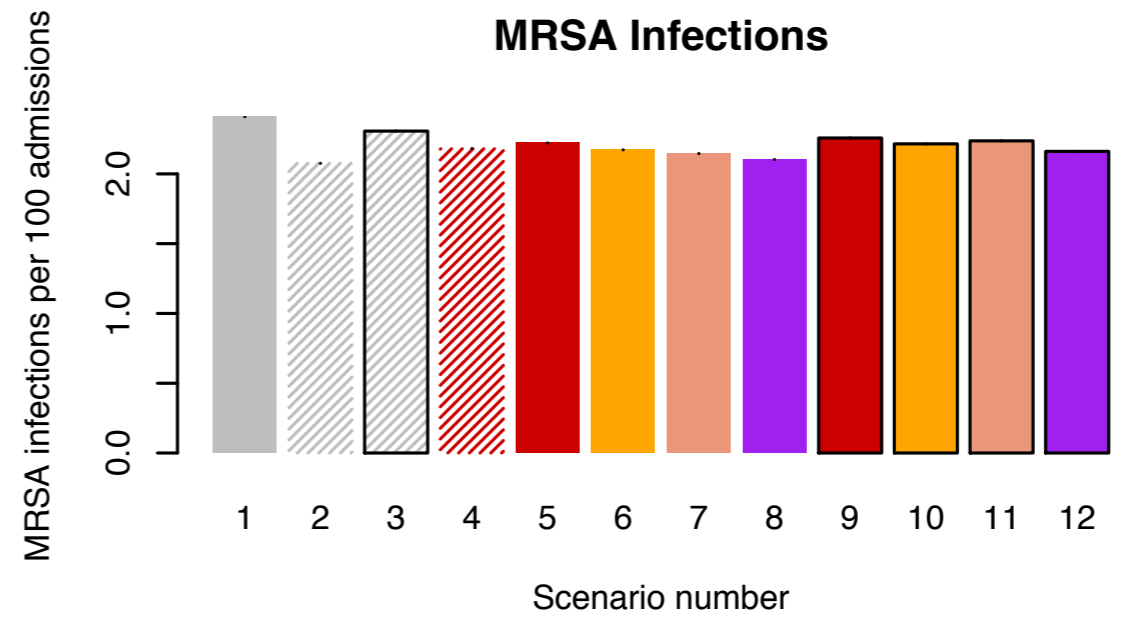
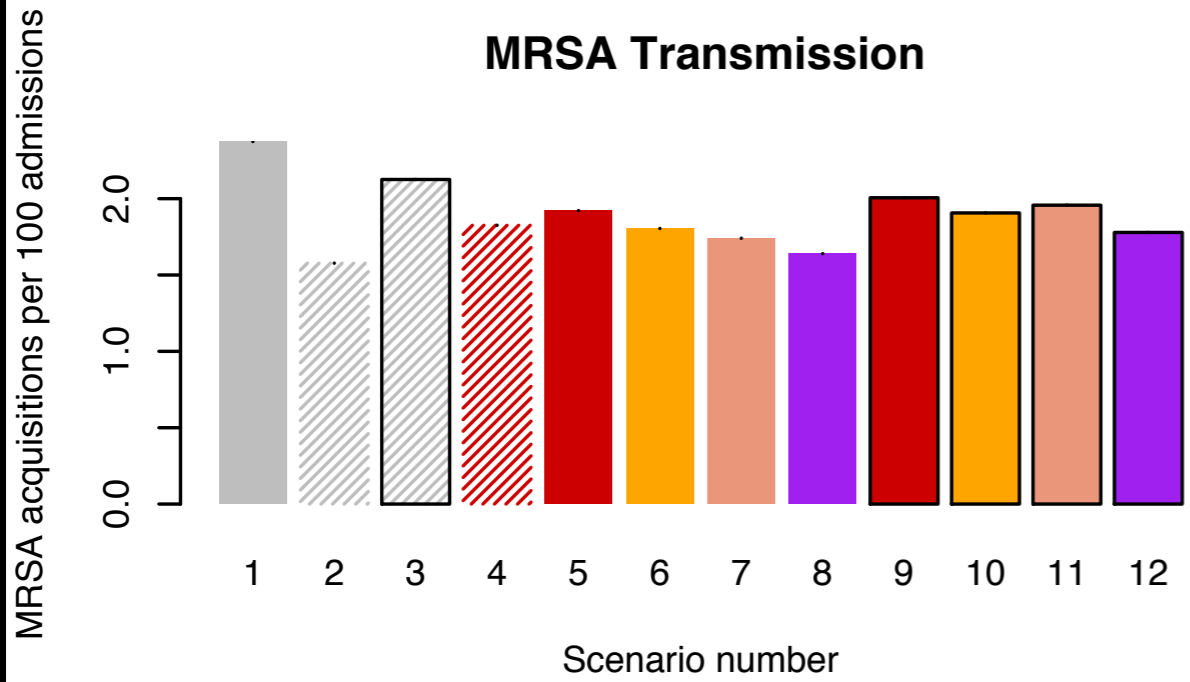
**Chromogenic Agar (early result)**

**PCR**

Hashed = pre-emptive

Outlined = Intervention applies to high risk group only

# Model outputs: effectiveness



Clinical cultures only

**Conventional Culture** Chromogenic Agar

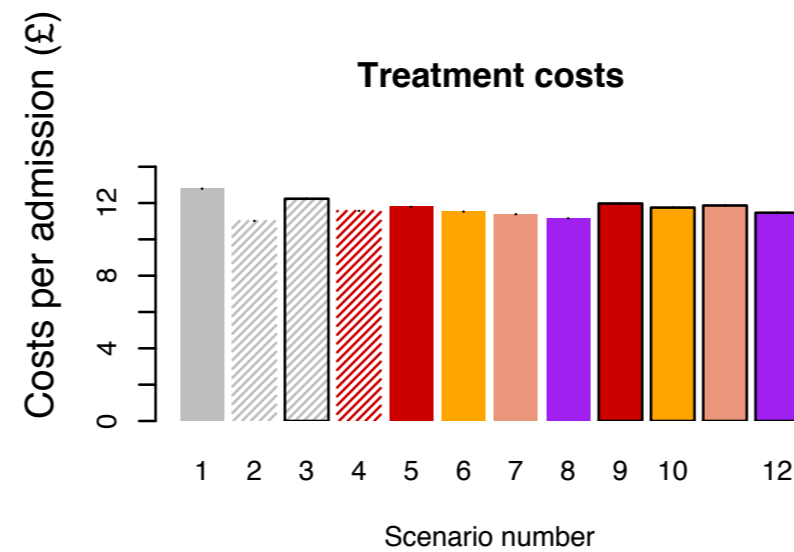
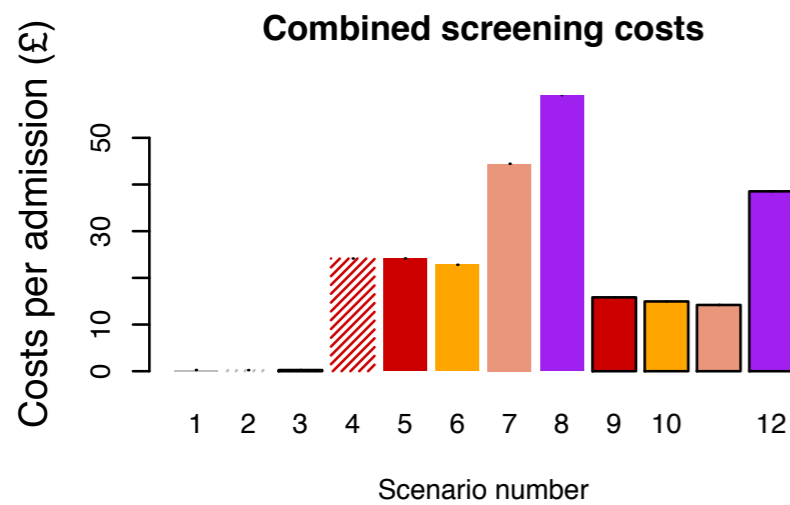
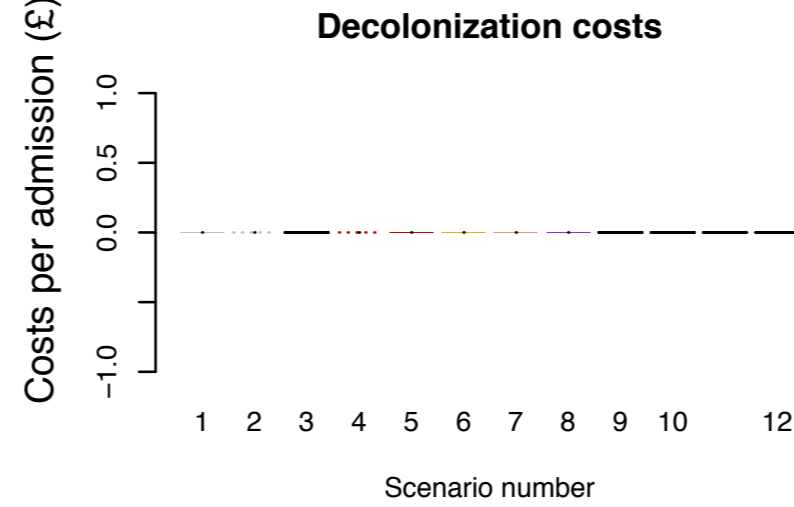
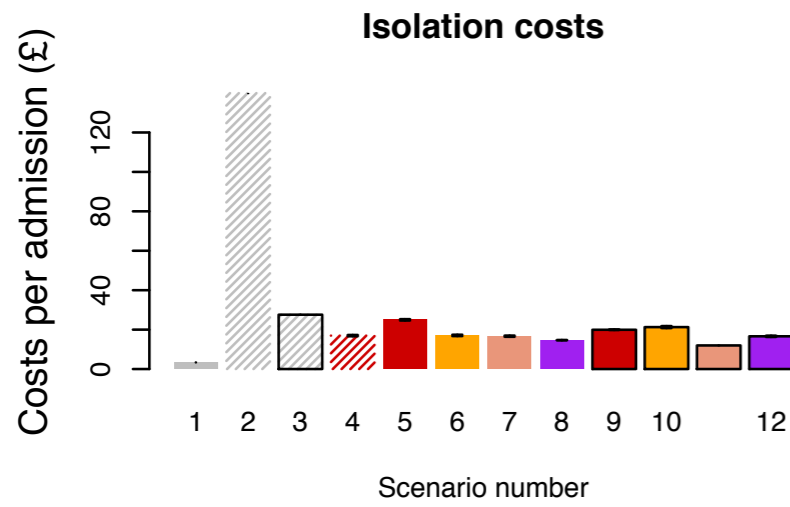
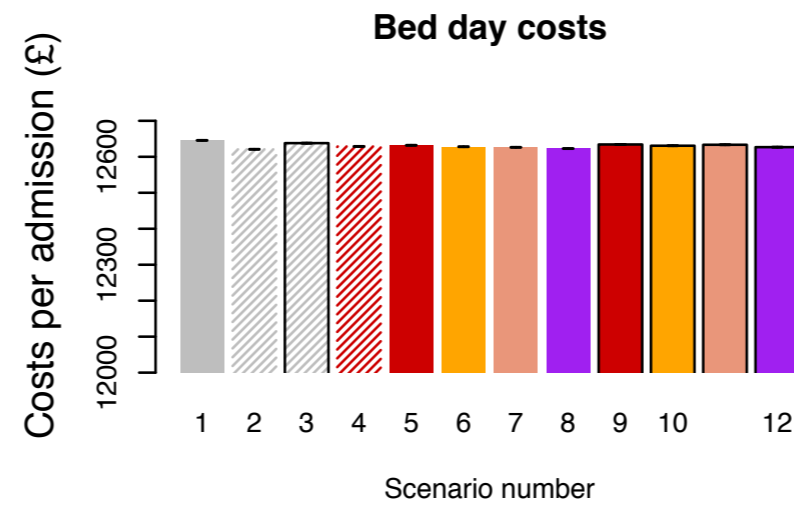
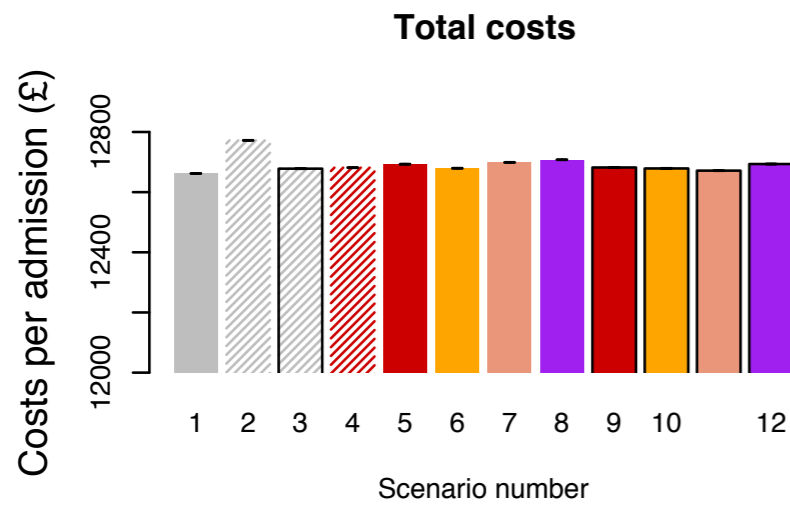
Chromogenic Agar (early result)

PCR

Hashed = pre-emptive

Outlined = Intervention applies to high risk group only

# Model Outputs: Costs

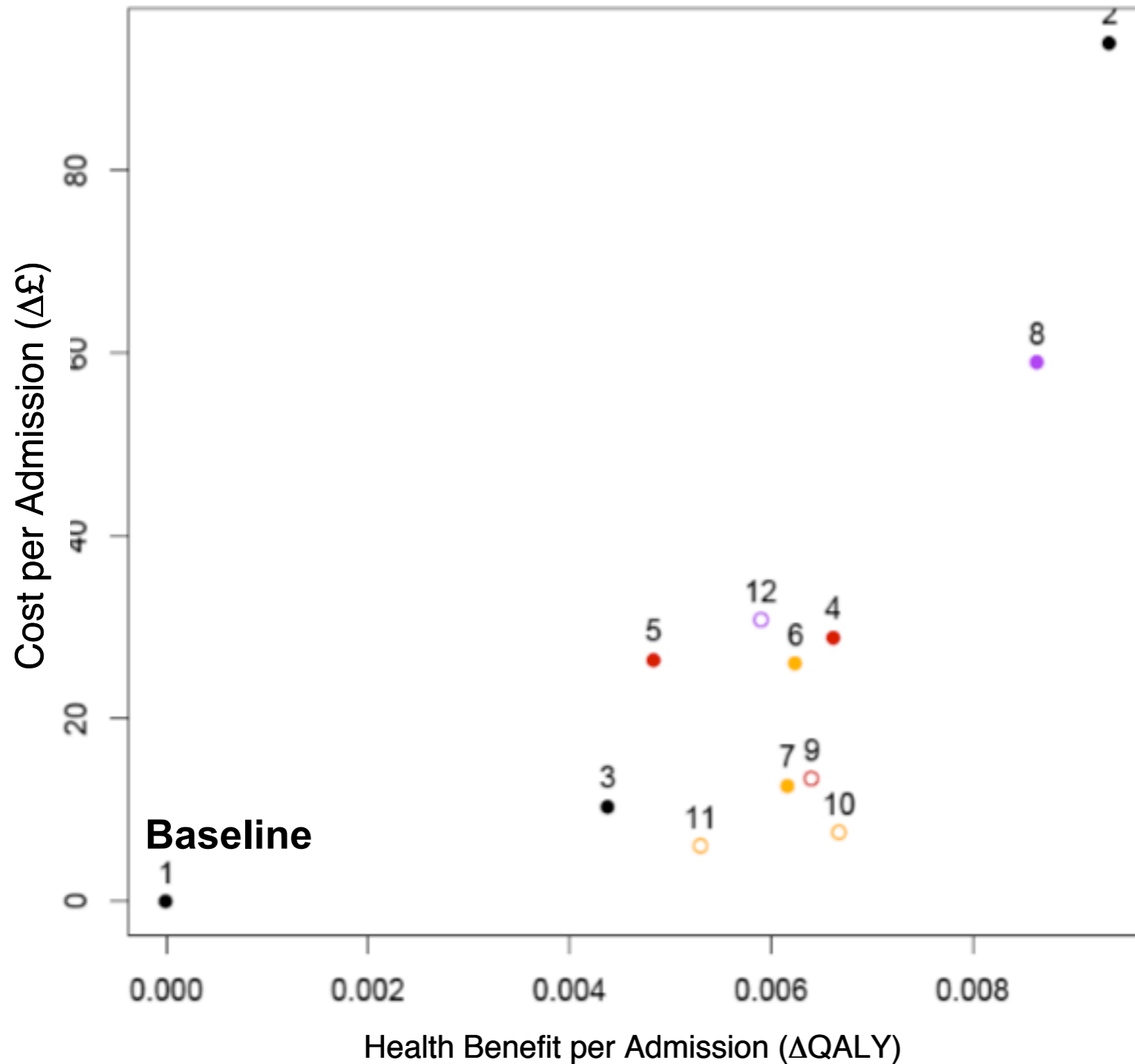


Clinical cultures only  
 Conventional Culture Chromogenic Agar  
 Chromogenic Agar (early result)  
 PCR

Hashed = pre-emptive  
 Outlined = Intervention applies to high risk group only

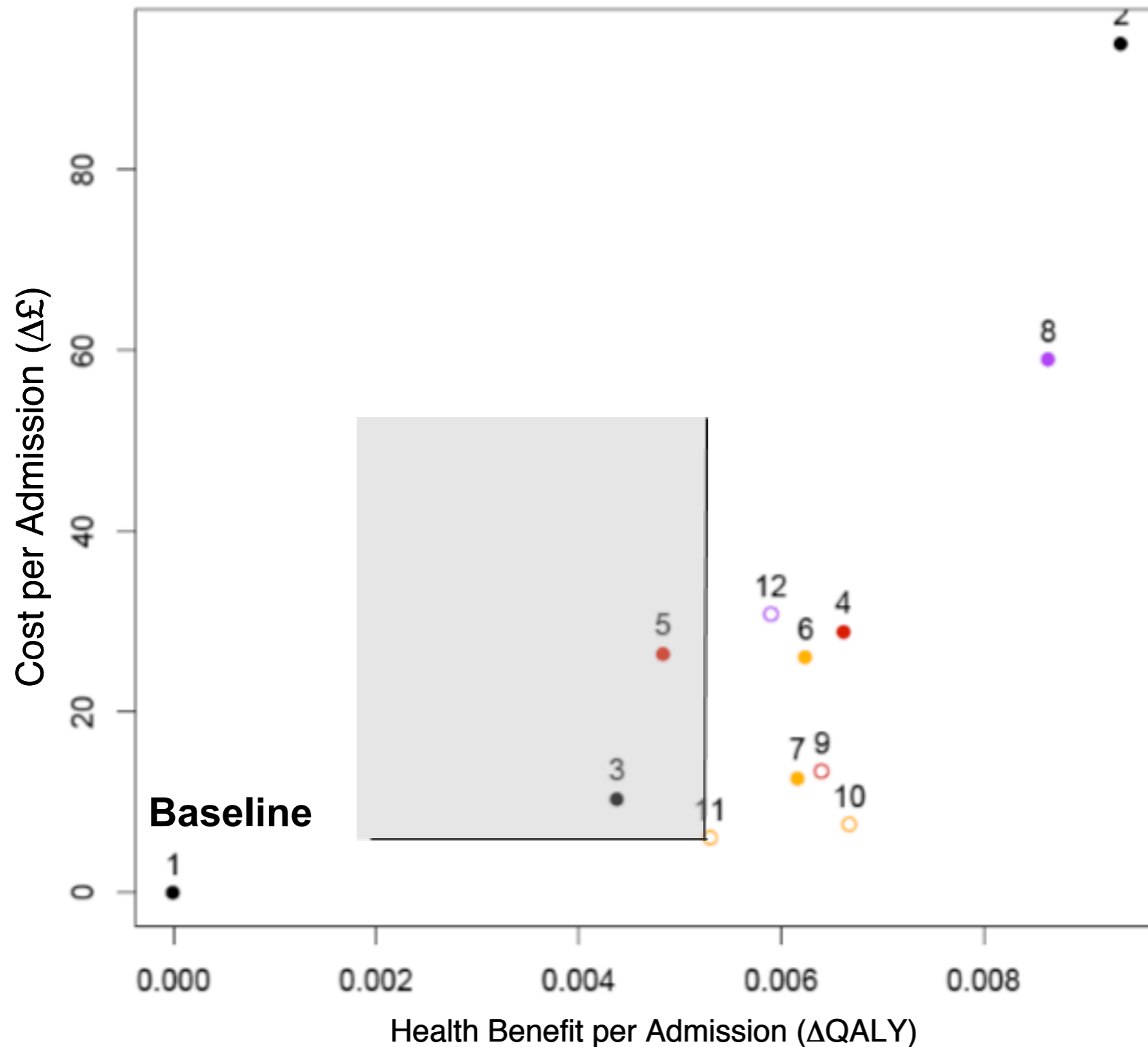


# Cost-Effectiveness Results: Isolation



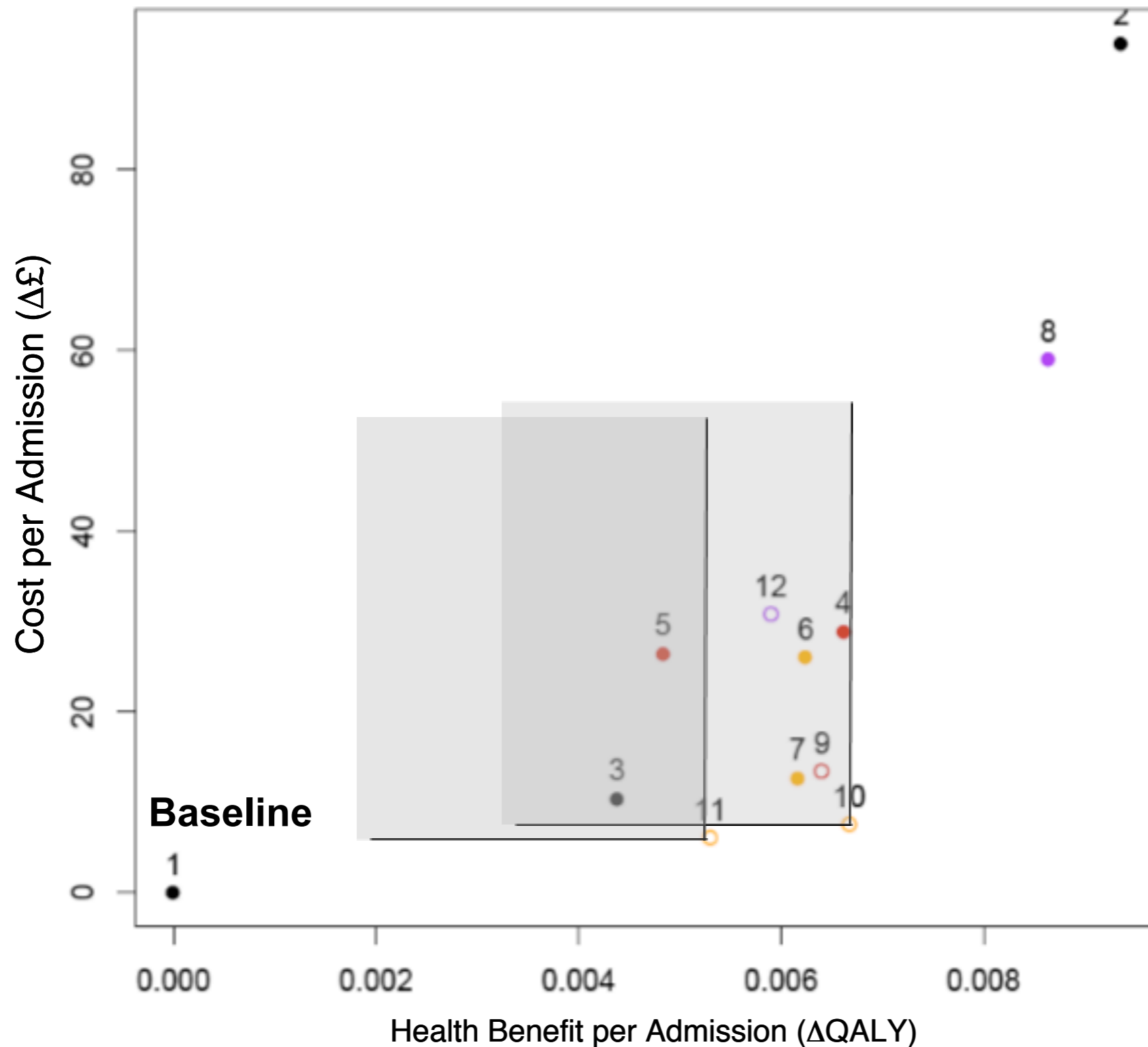
1. Isolate clinical cases only
2. Preemptive isolation of all
3. Preemptive isolation of high risk
4. Preemptive isolation of high risk (amended following CC screen result)
5. Screen all admissions (+wkly screens) with CC (isolate known +ves)
6. Screen all with CA
7. Screen all with CA\_early
8. Screen all with PCR
9. Screen high risk with CC
10. Screen high risk with CA
11. Screen high risk with CA\_early
12. Screen high risk with PCR

# Step 1 - exclude dominated options



1. isolate clinical cases only
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3. preemptive isolation of high risk
4. preemptive isolation of high risk (amended following CC screen result)
5. Screen all admissions (+wkly screens) with CC (isolate known +ves)
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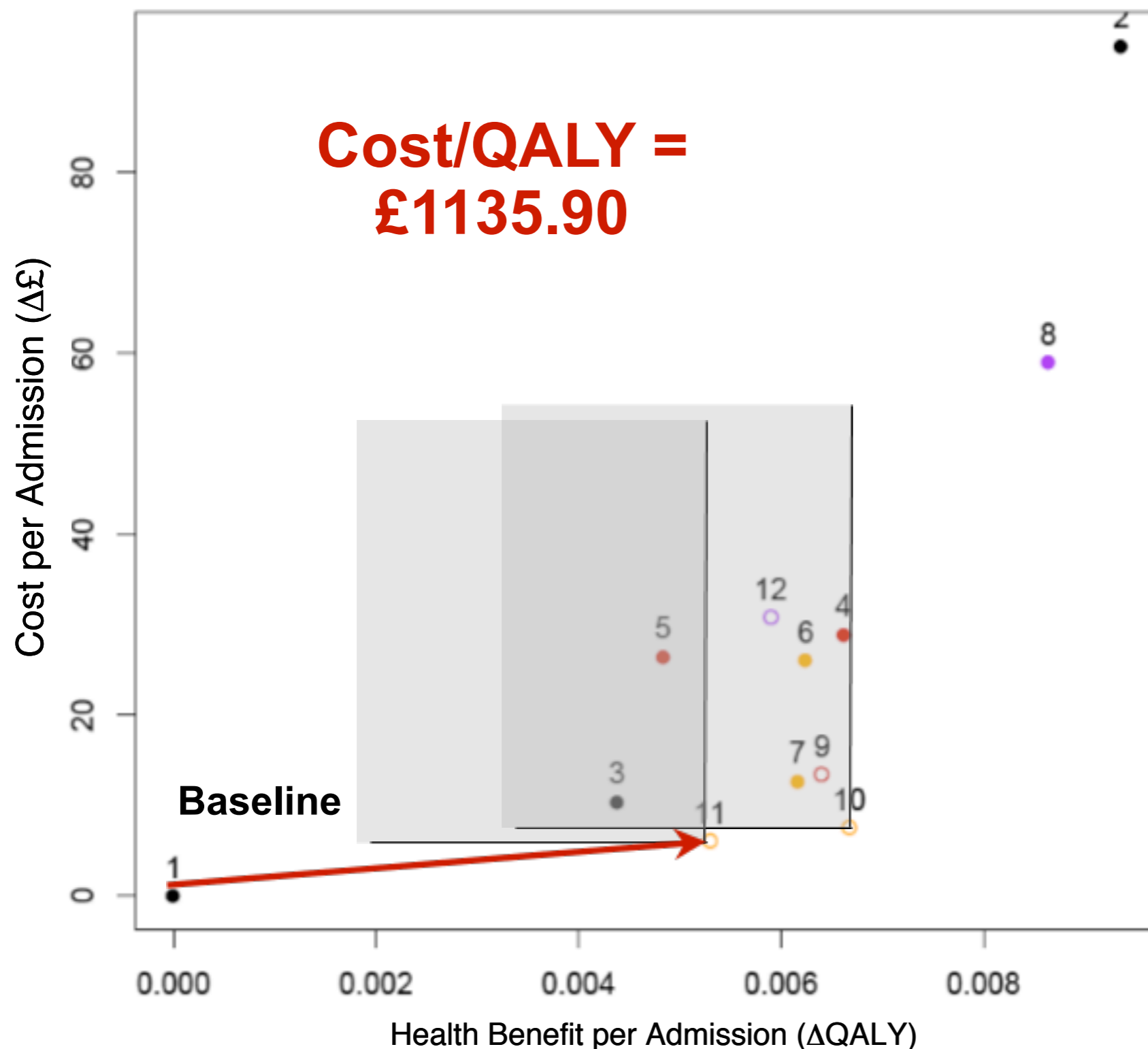
# Step 2 - evaluate remaining options

Dynamics

Inference

**Policy**

Future



1. isolate clinical cases only
2. preemptive isolation of all
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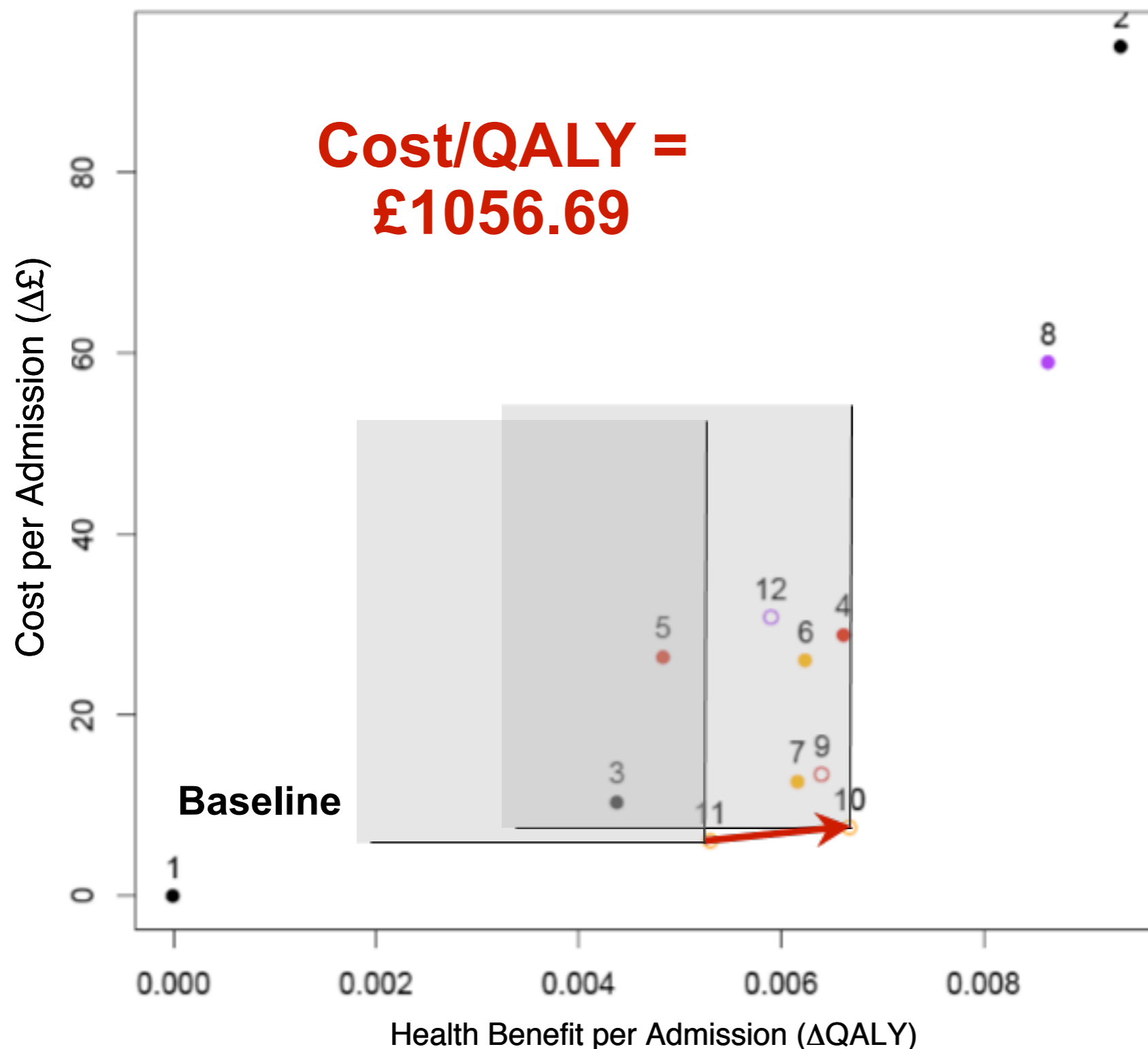
# Step 2 - evaluate remaining options

Dynamics

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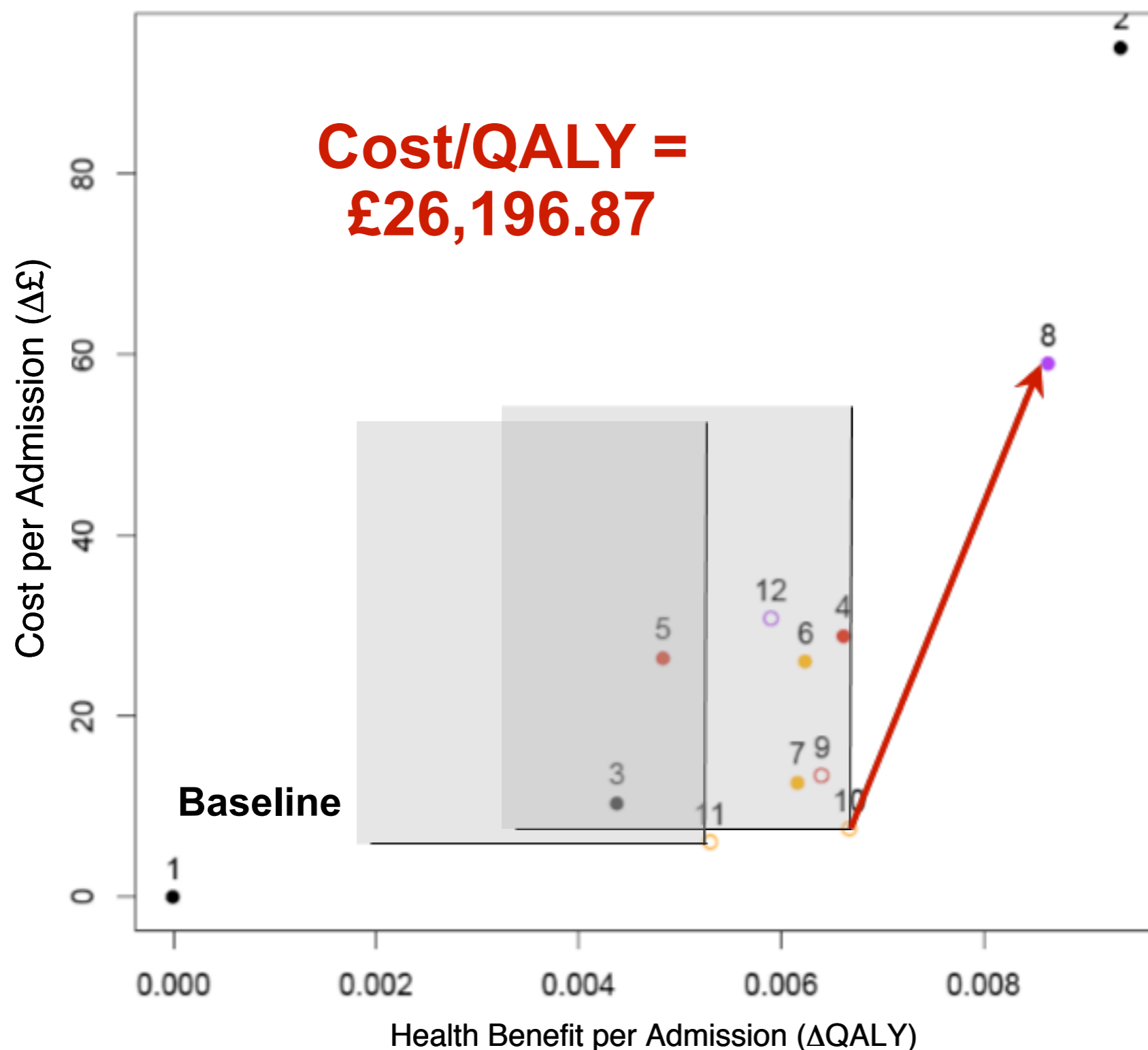
# Step 2 - evaluate remaining options

Dynamics

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**Policy**

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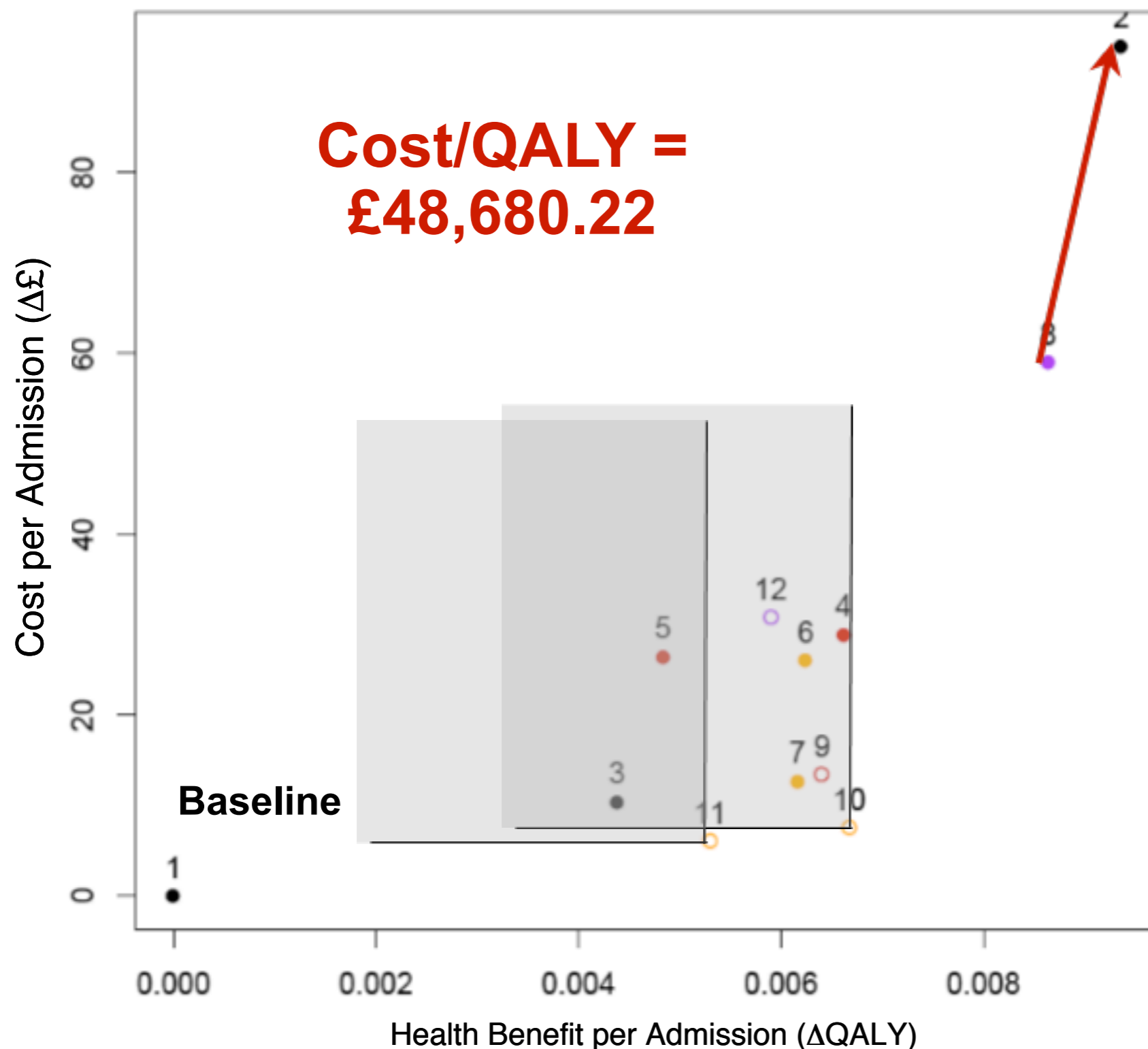
# Step 2 - evaluate remaining options

Dynamics

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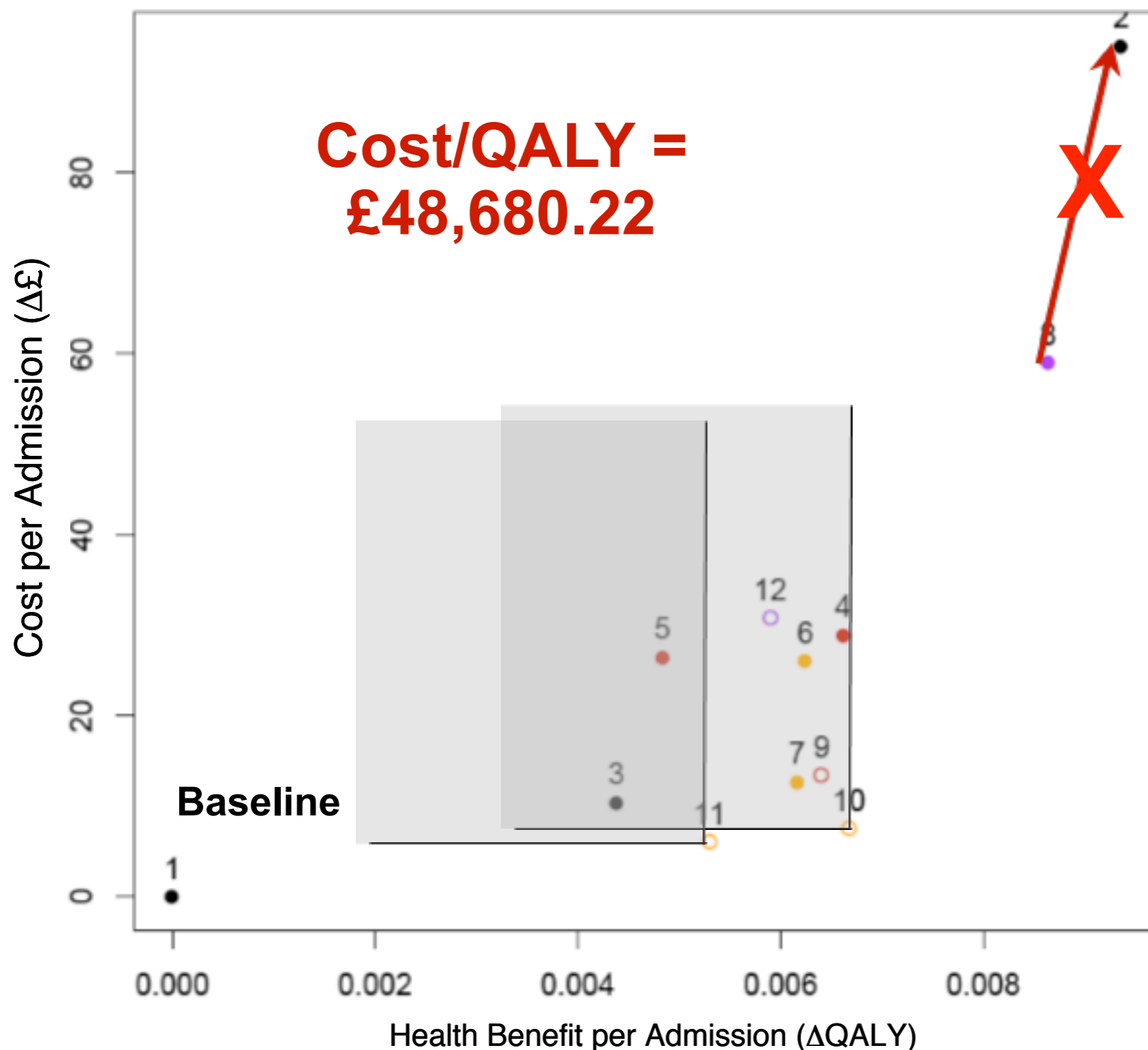
# Step 2 - evaluate remaining options

Dynamics

Inference

**Policy**

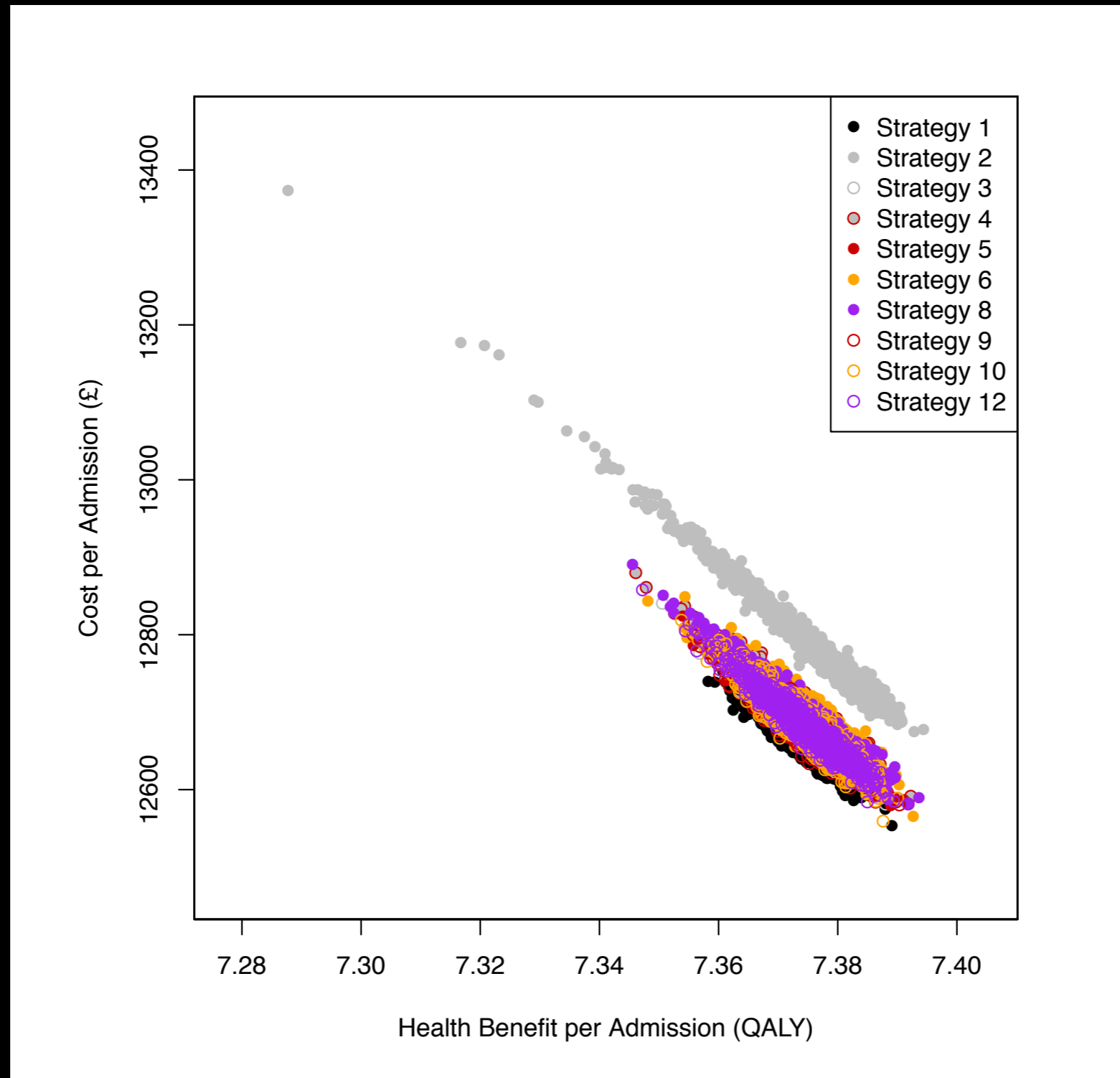
Future



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# Accounting for parameter uncertainty



# NMB, CEAC, CEAF

Net Monetary Benefit (NMB) =  $\Delta E \times \lambda - \Delta C$

$\Delta E$  is change in health outcomes (QALYs)

$\Delta C$  is change in costs

$\lambda$  is willingness to pay per QALY gain

Cost-effectiveness acceptability curves (CEACs) show the probability that each strategy has the highest NMB as  $\lambda$  varies.

Cost-effectiveness acceptability frontiers (CEAFs) show the probability that the strategy with the highest expected NMB has the highest NMB as  $\lambda$  varies.

# Screening & isolation in the ICU

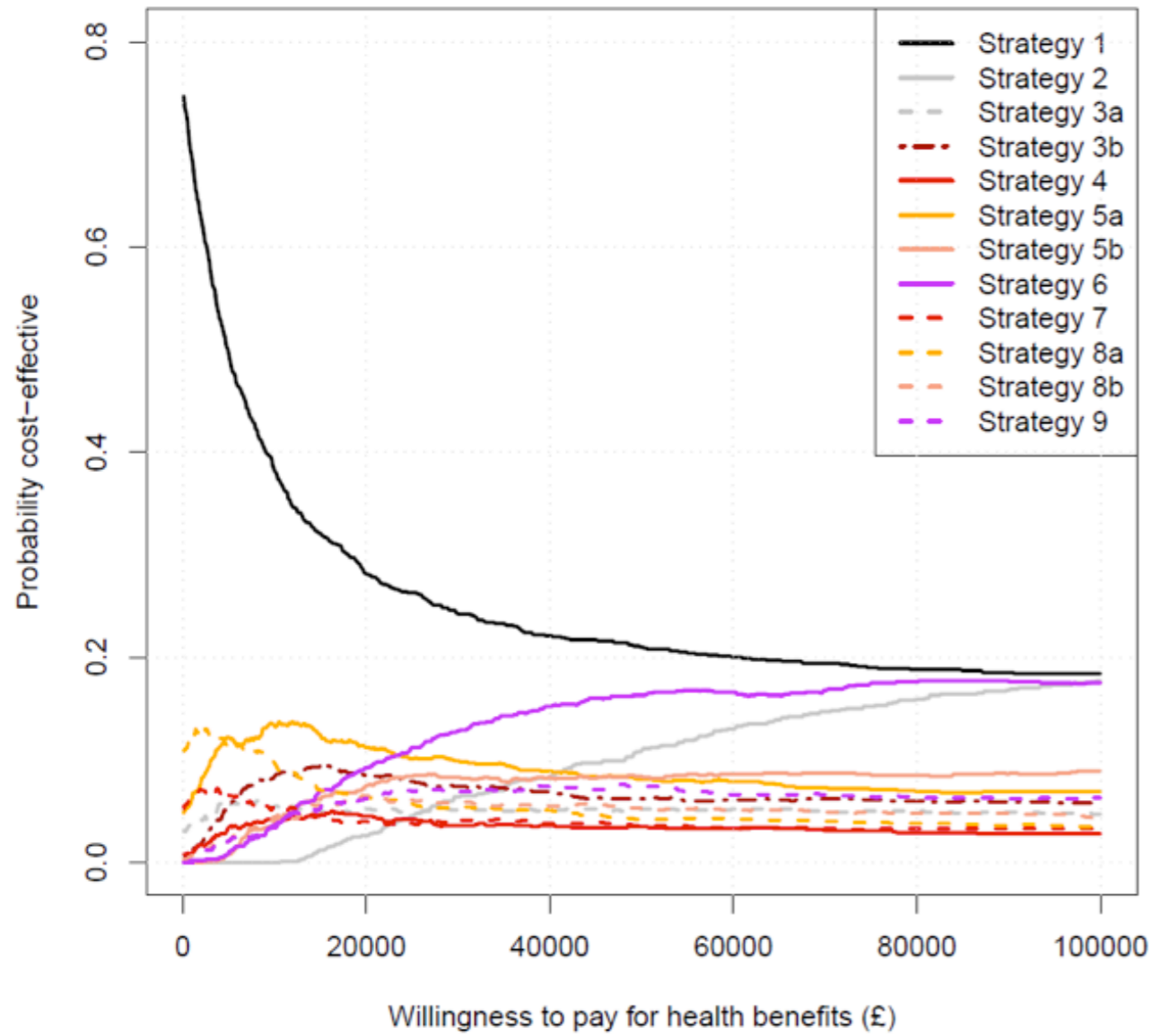
Dynamics

Inference

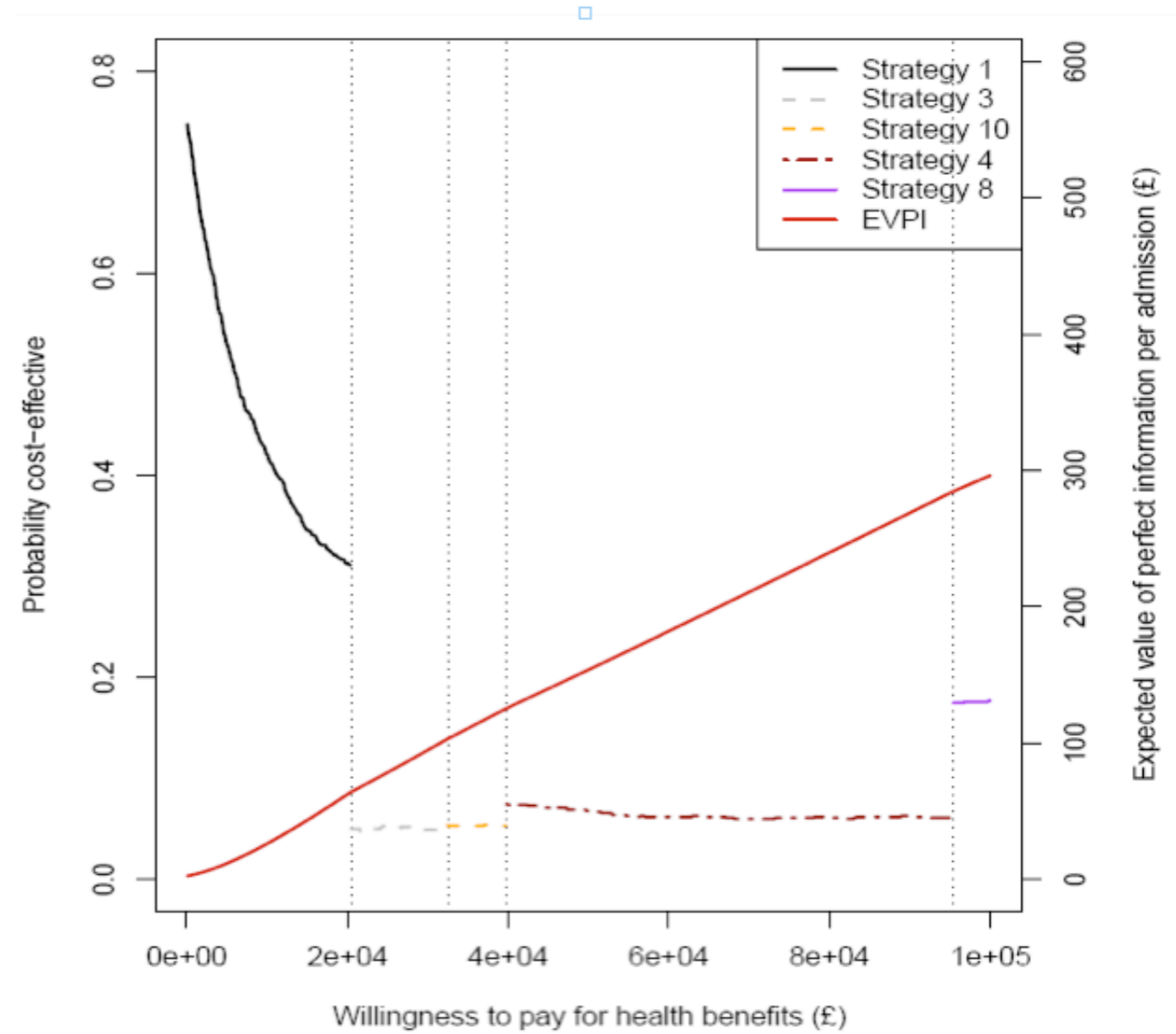
**Policy**

Future

## CEACs



## CEAF



# Screening & isolation in the ICU

Dynamics

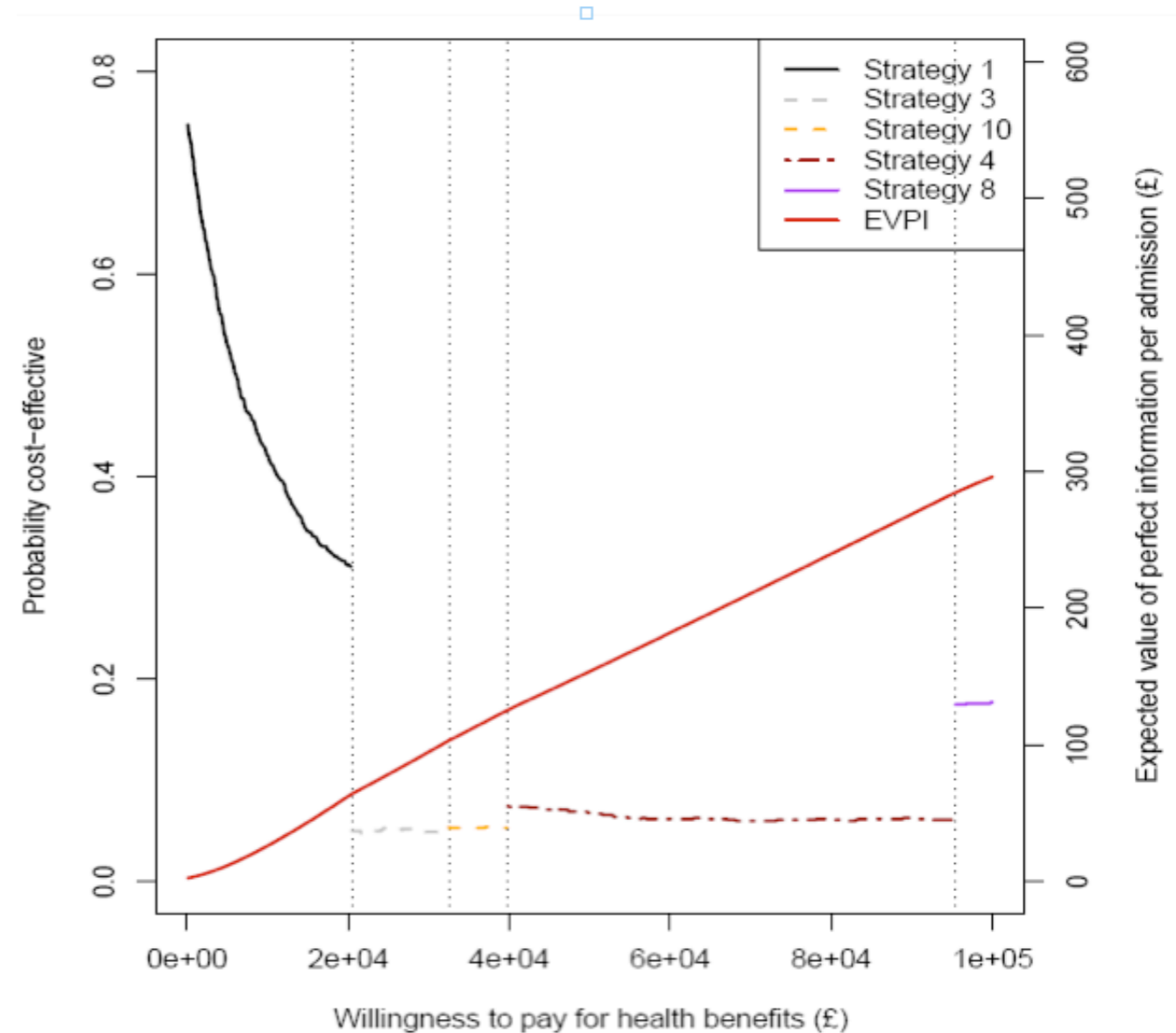
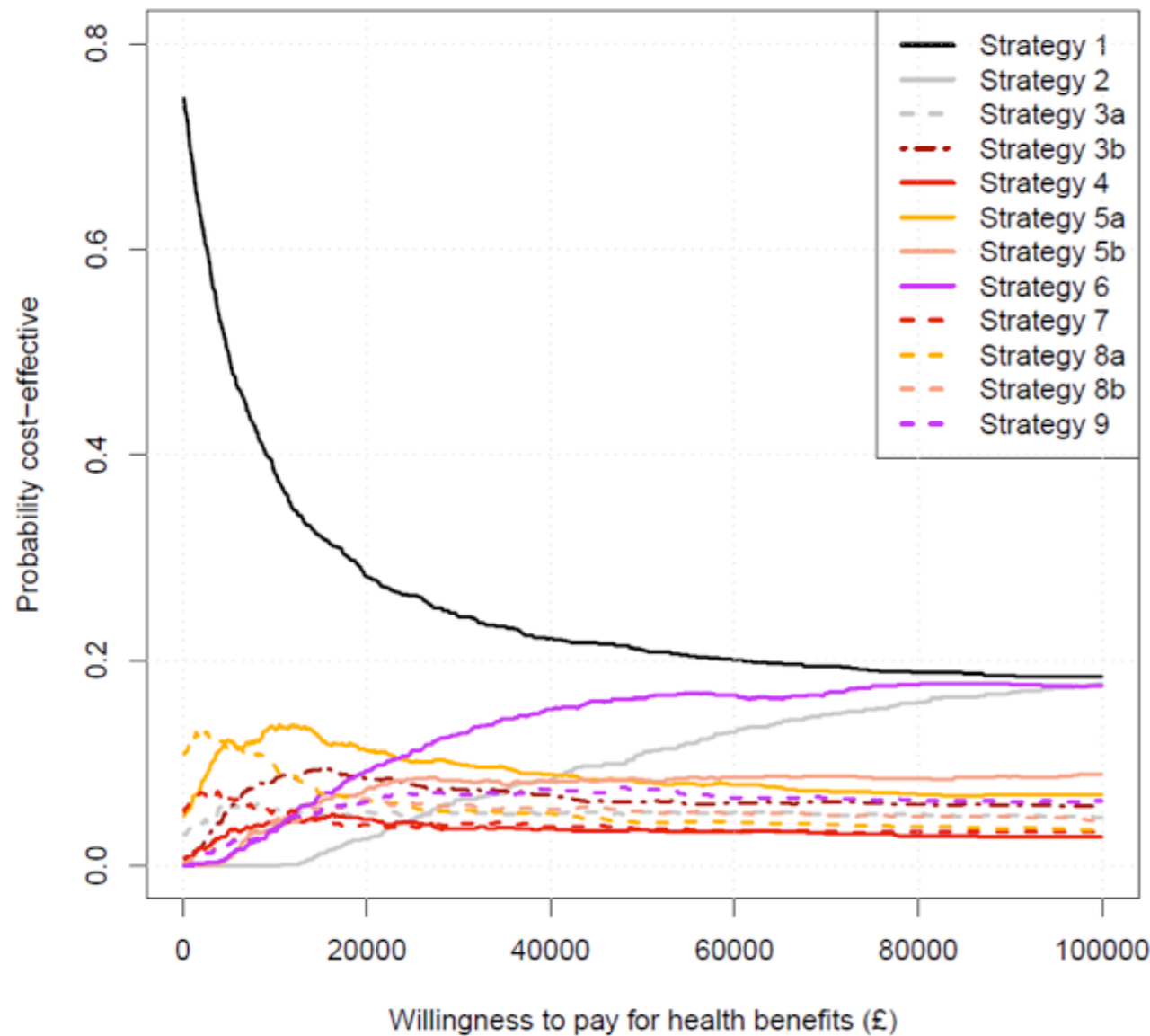
Inference

**Policy**

Future

## CEACs

## CEAF

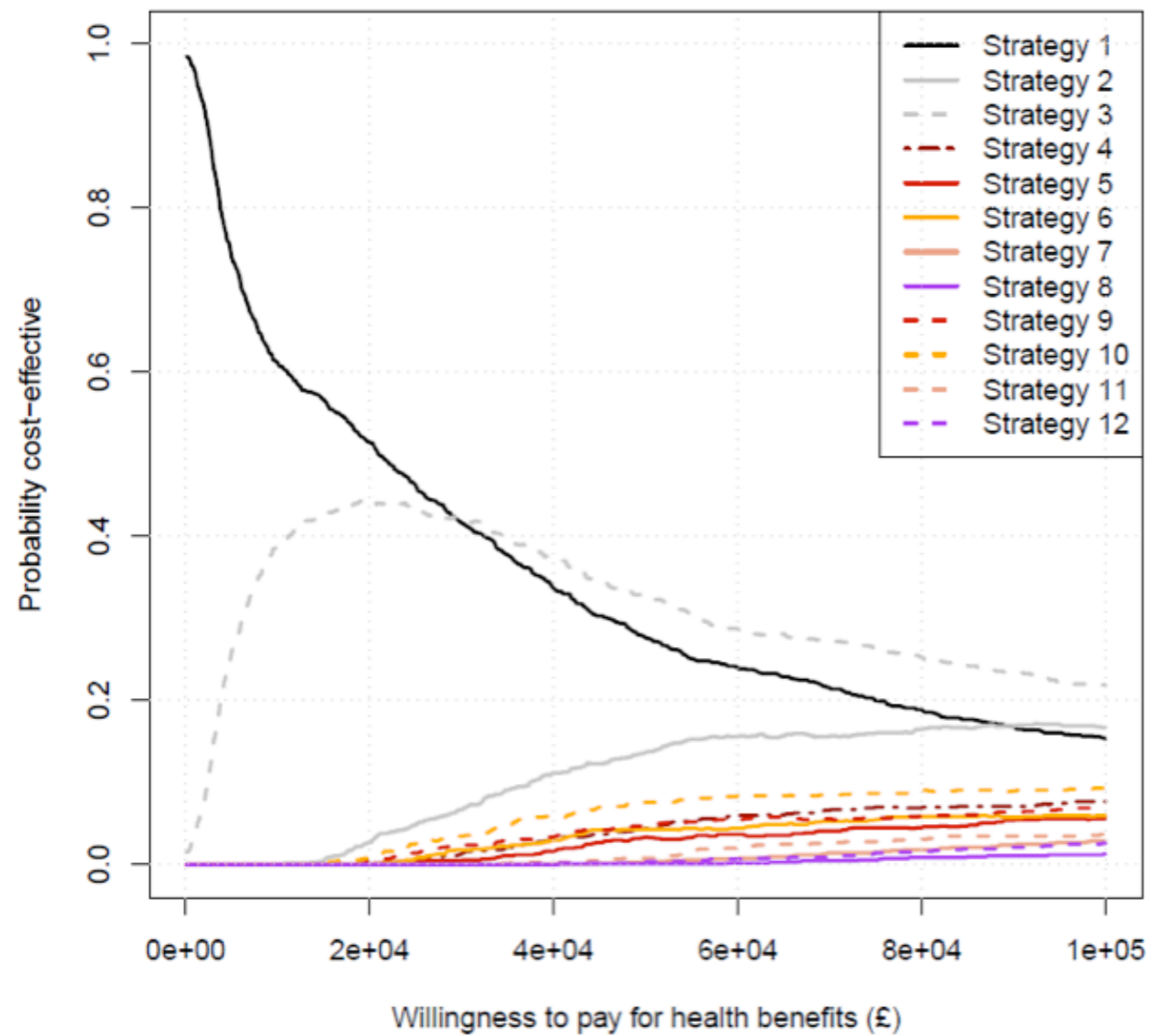


Expected value of perfect information (EVPI) tells us how much we would benefit if we knew all parameters perfectly

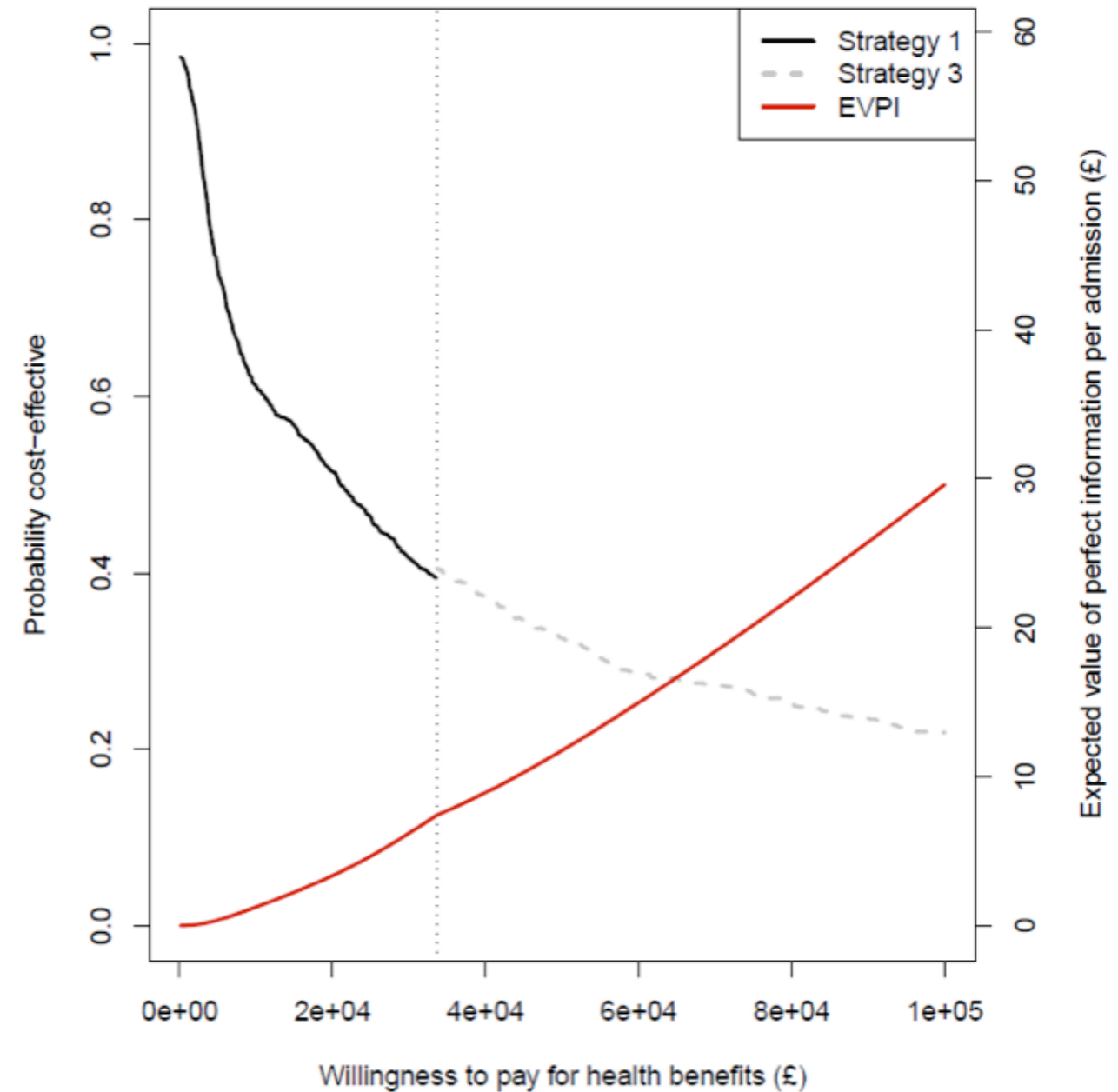
$$EVPI = E_{\theta}[\max_j \{NMB(j, \theta)\}] - \max_j \{E_{\theta}[NMB(j, \theta)]\}$$

# Screening & isolation in General Medical Wards

## CEACs

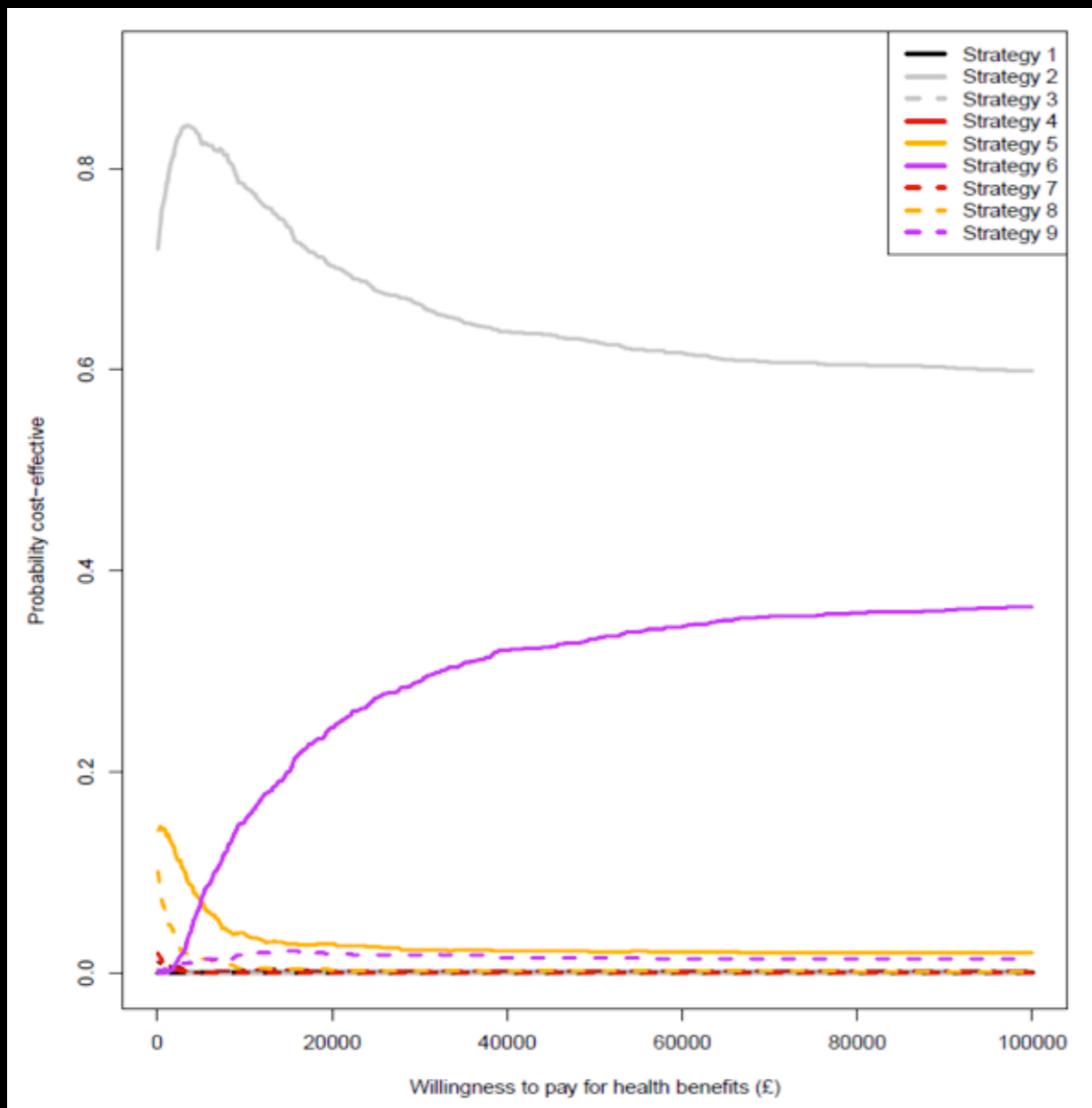


## CEAF

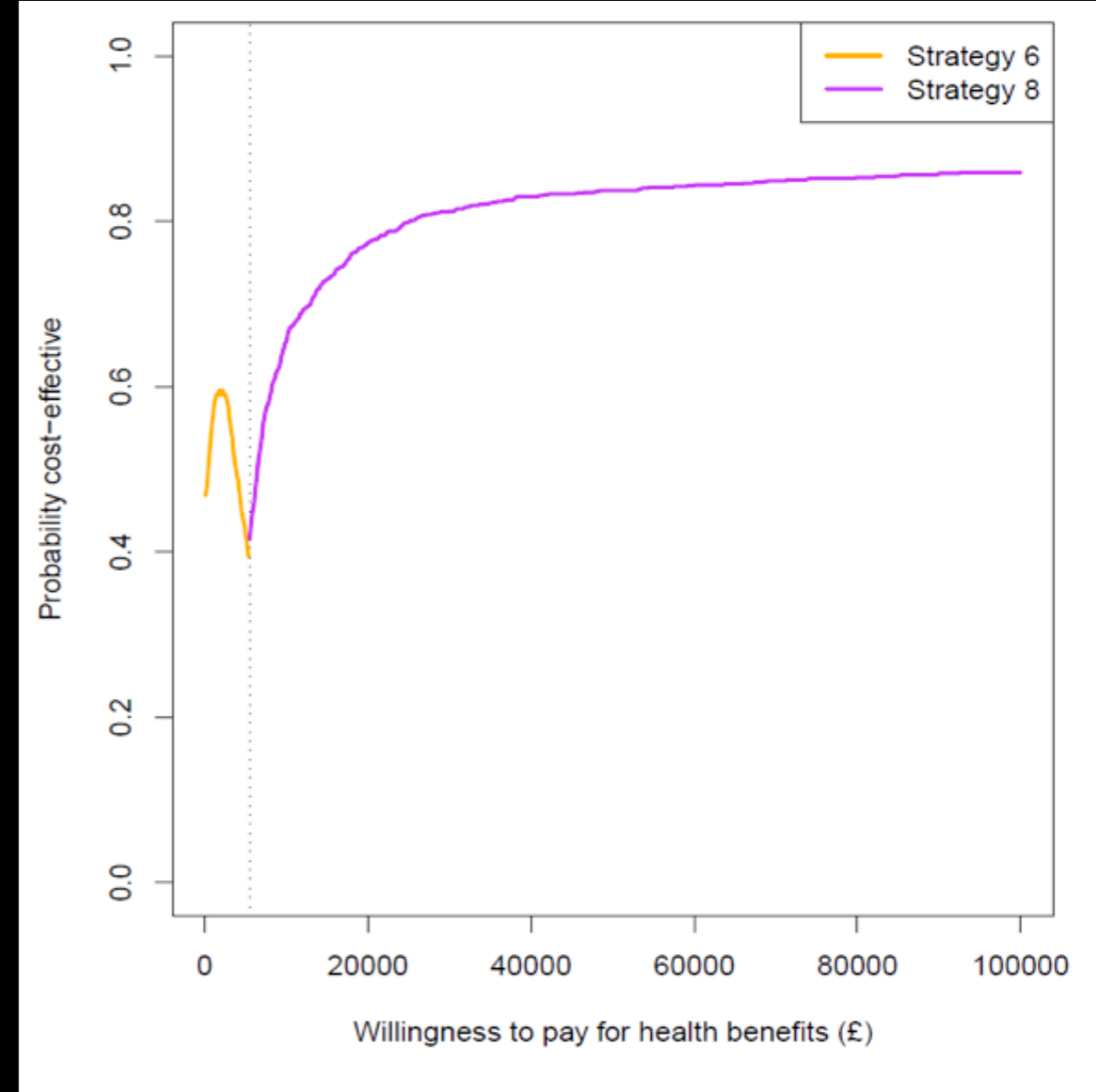


# Screening & decolonization in ICUs

## CEACs

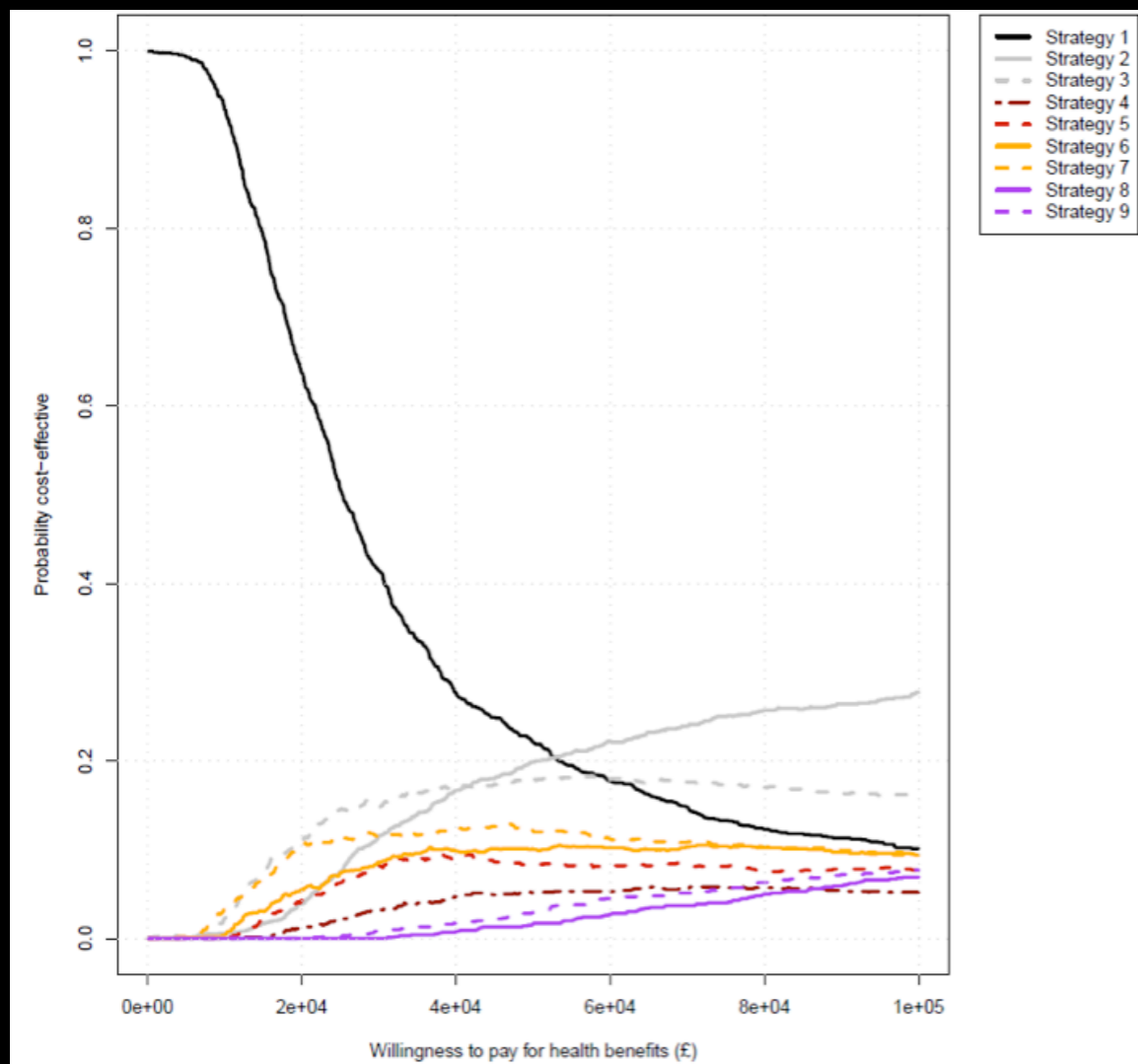


## CEAF

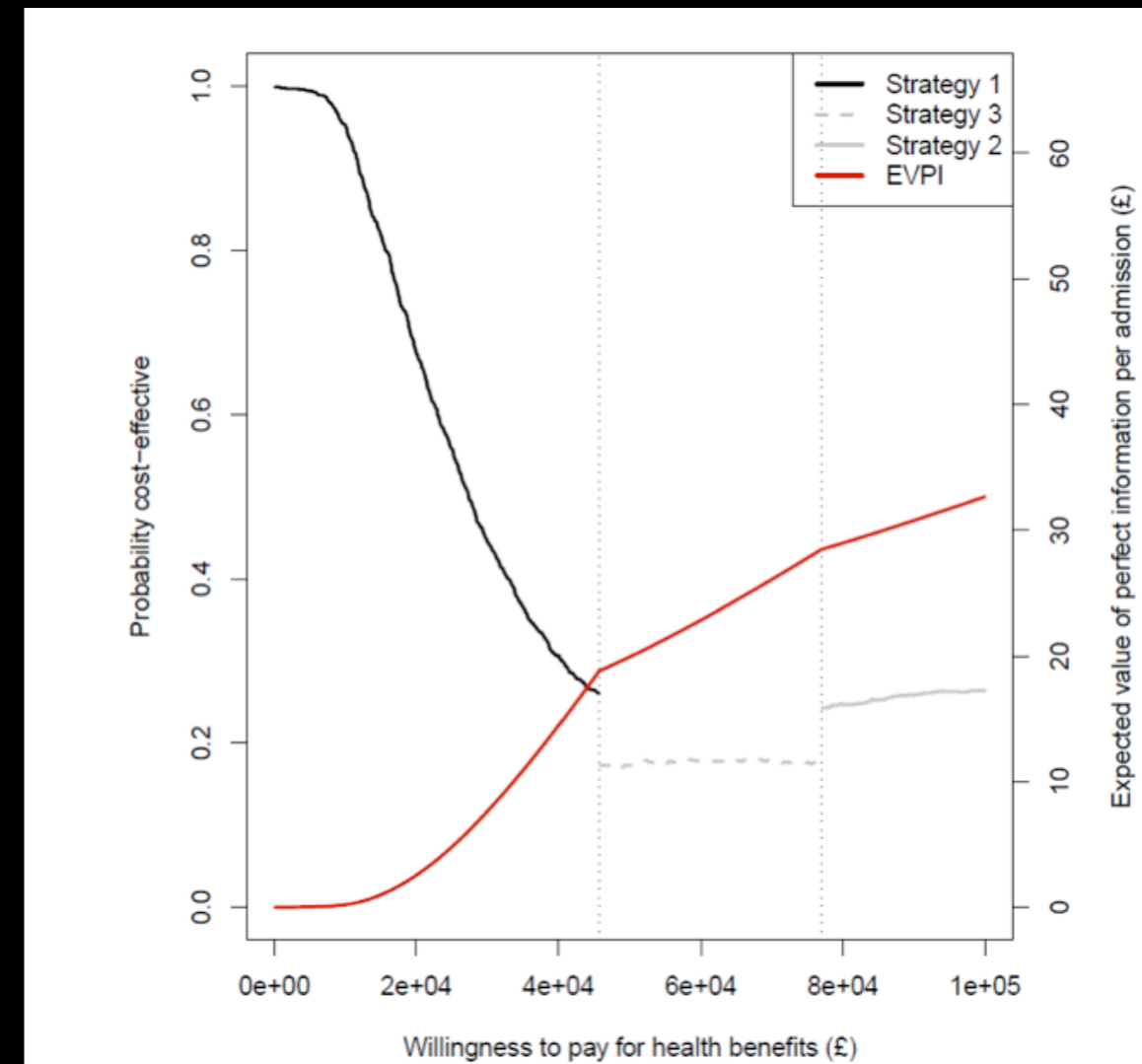


# Screening & decolonization in General Medical Wards

## CEACs



## CEAF



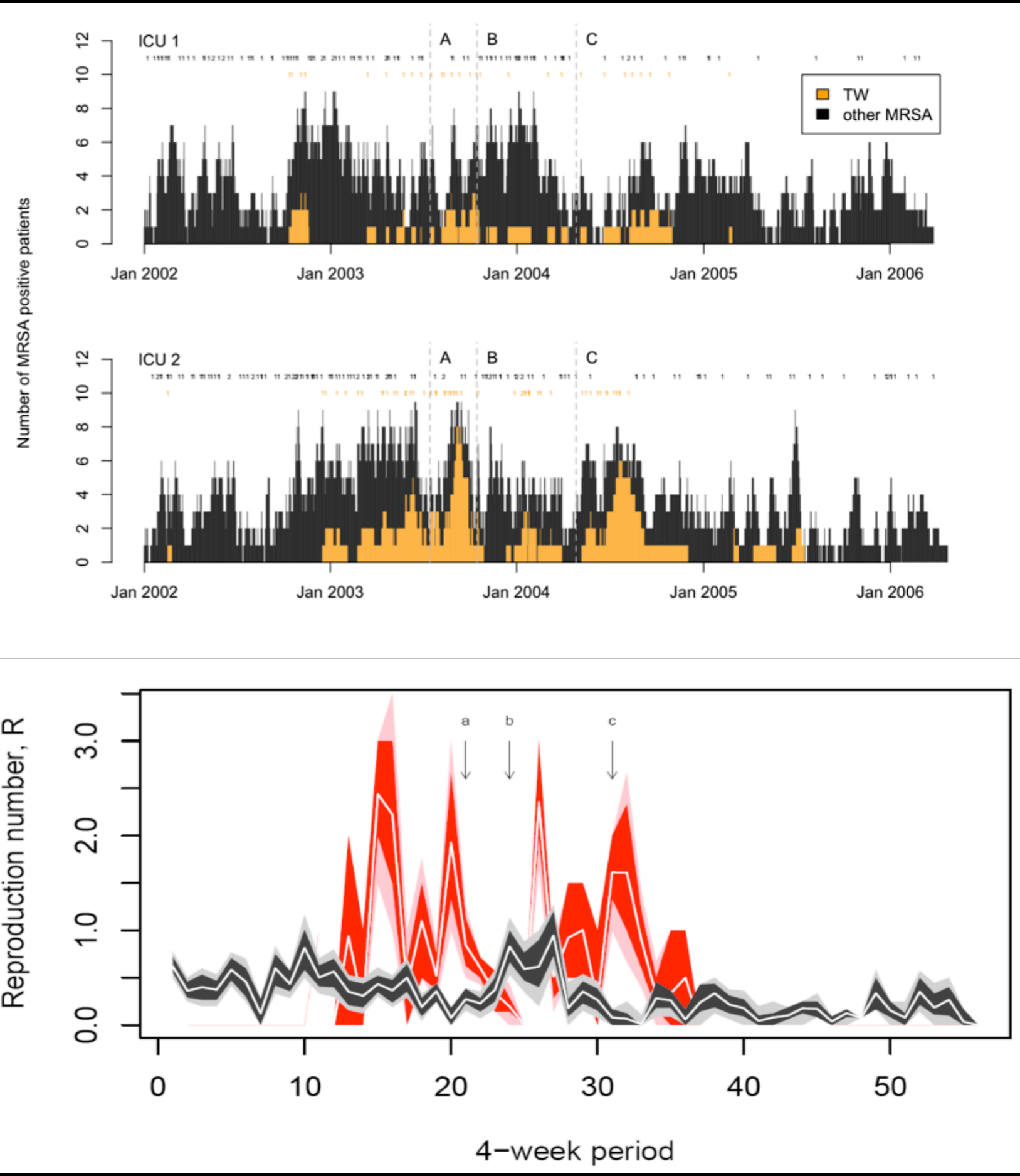
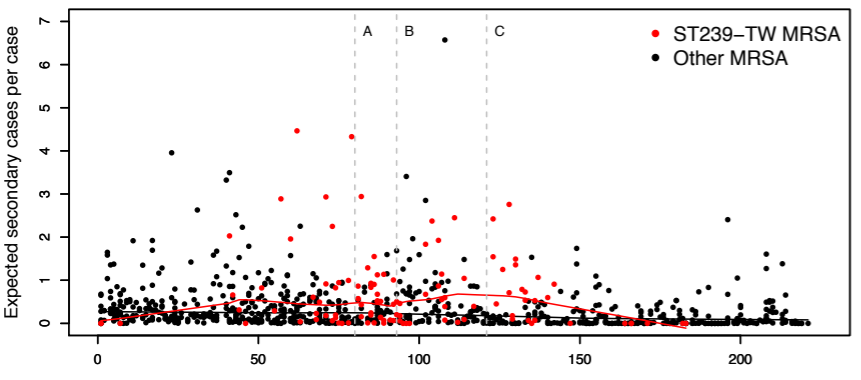
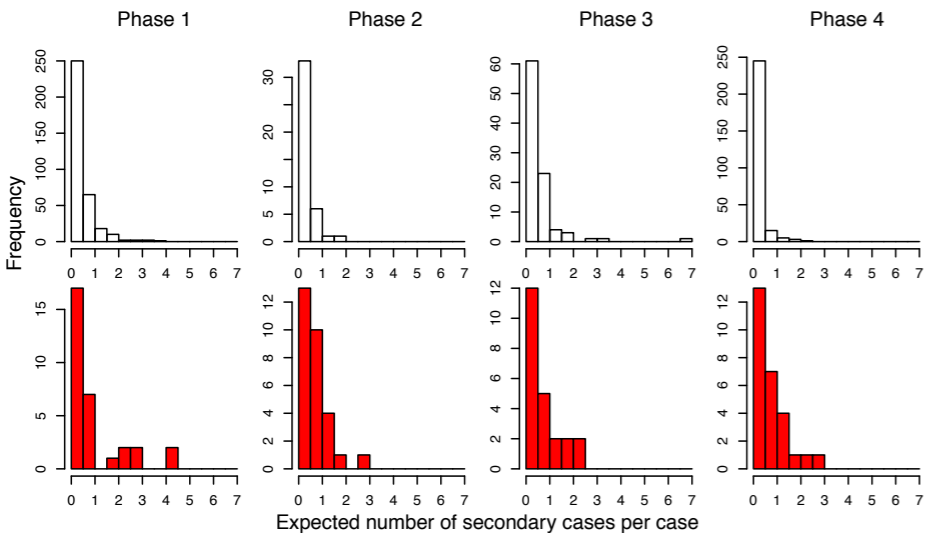
# Future challenges

- How to account for resistance selection in health economic models of antibiotic use?
- How to account for strain diversity?
- How to evaluate control strategies in low and middle income countries?
- EVPPI, EVSI...
- How to make use of sequencing data?



Concurrent outbreak of ST239 MRSA (TW clone) and endemic UK clones of MRSA at St Thomas's Hospital London.

Epidemic trees probabilistically reconstructed using hazards (as proposed by Kenah et al.. Math Biosciences 2008).



Genome Sequence of a Recently Emerged, Highly Transmissible, Multi-Antibiotic- and Antiseptic-Resistant Variant of Methicillin-Resistant *Staphylococcus aureus*, Sequence Type 239 (TW)<sup>†</sup>

Matthew T. G. Holden,<sup>1\*</sup> Jodi A. Lindsay,<sup>2</sup> Craig Corton,<sup>1</sup> Michael A. Quail,<sup>1</sup> Joshua D. Cockfield,<sup>2</sup> Smriti Pathak,<sup>3</sup> Rahul Batra,<sup>4</sup> Julian Parkhill,<sup>1</sup> Stephen D. Bentley,<sup>1</sup> and Jonathan D. Edgeworth<sup>3,4</sup>

J Bacteriology, 2010

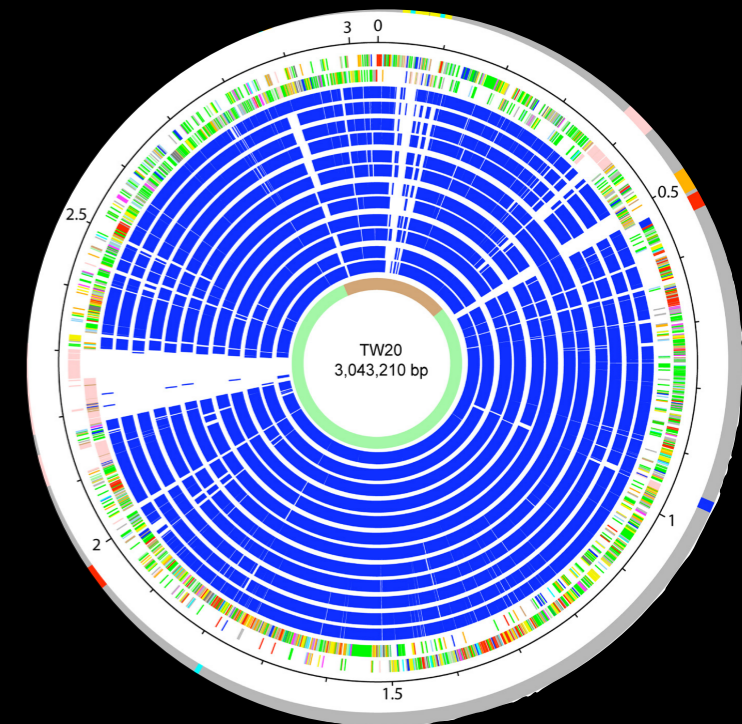
“...genomic analysis of TW20 provides evidence of its adaptation to survive in a health care setting through acquisition of drug and antiseptic resistance genes carried on MGEs, large chromosomal insertions, and point mutations in housekeeping genes. The large size of the TW20 genome reflects the ability of the ST239 lineage to undergo prolonged and continuing evolution to adapt to the hospital environment.

Dynamics

Inference

Policy

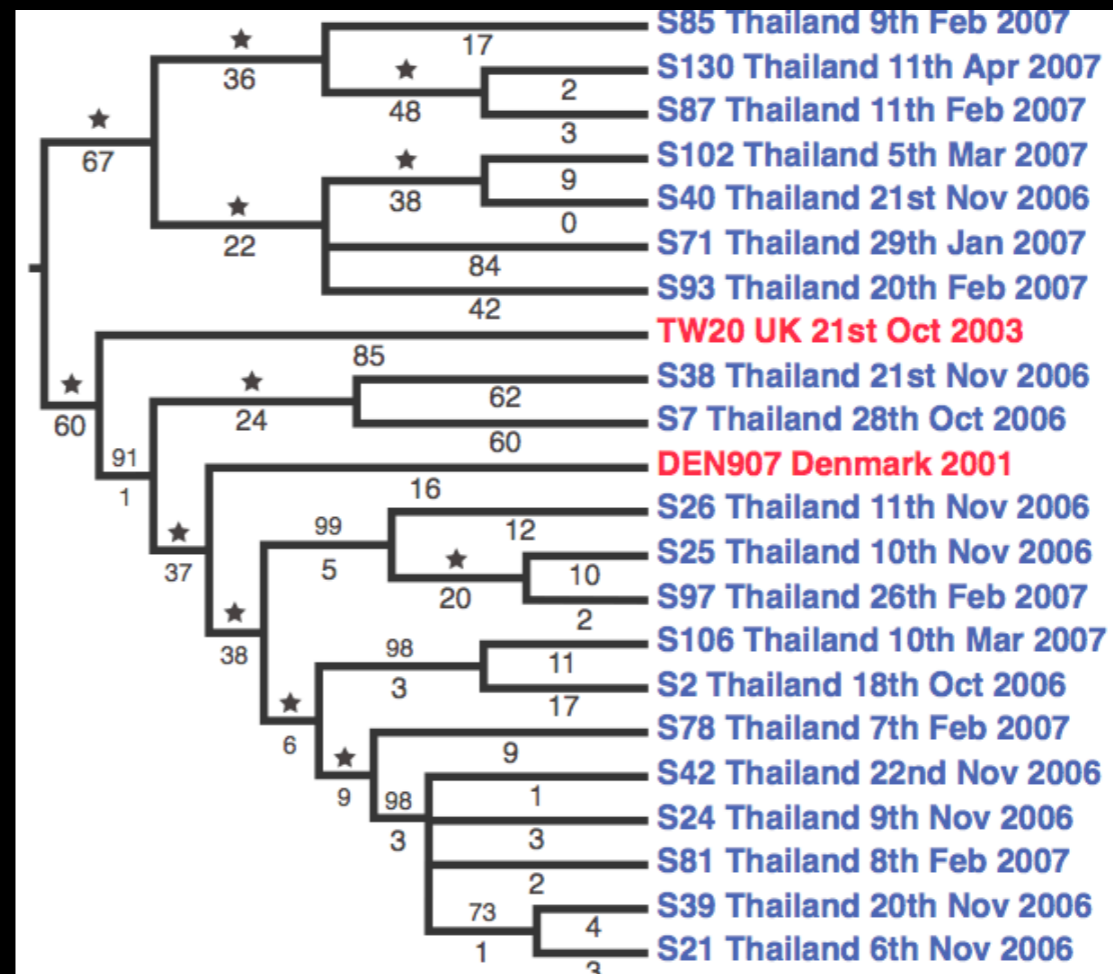
Future

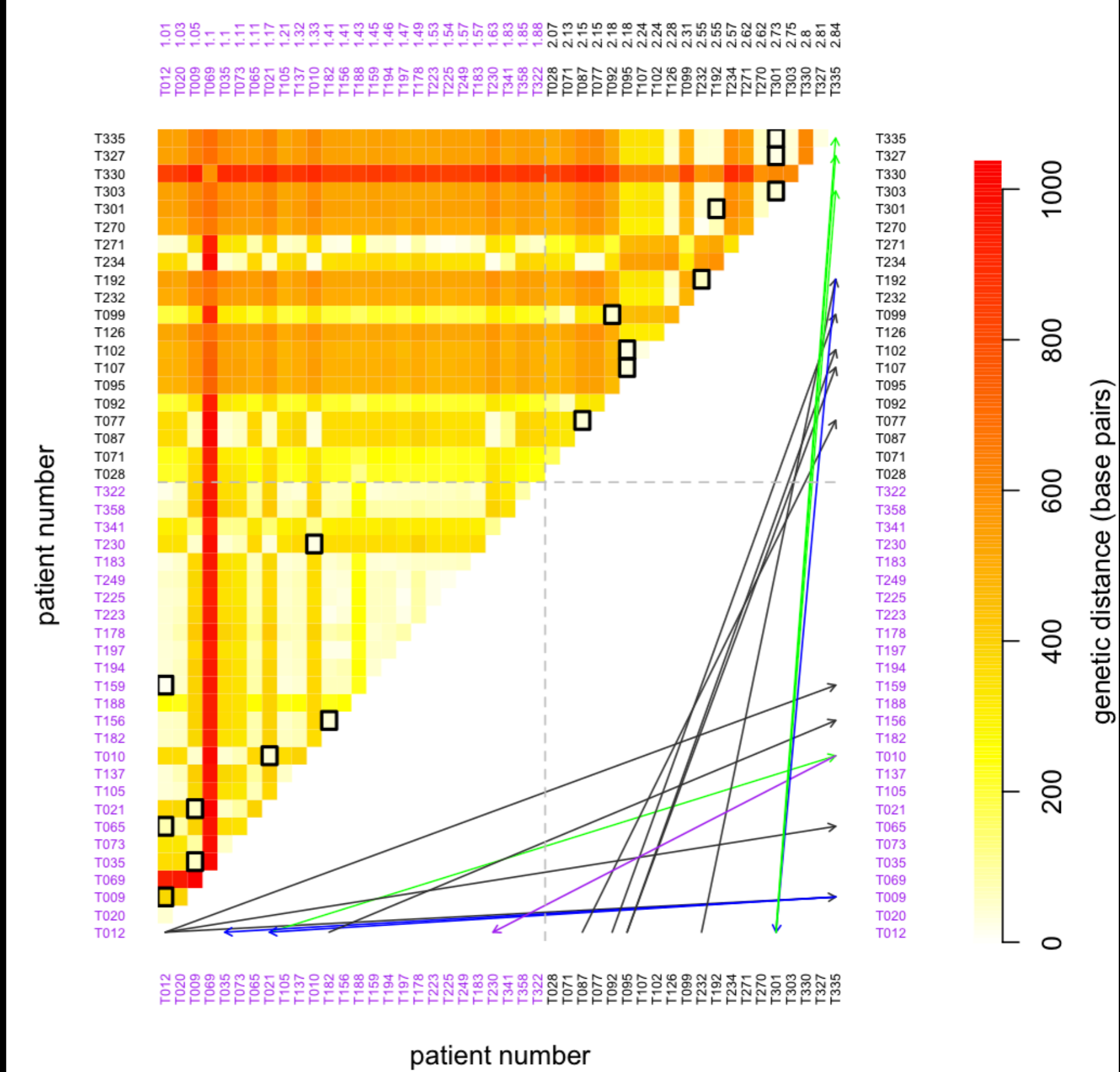
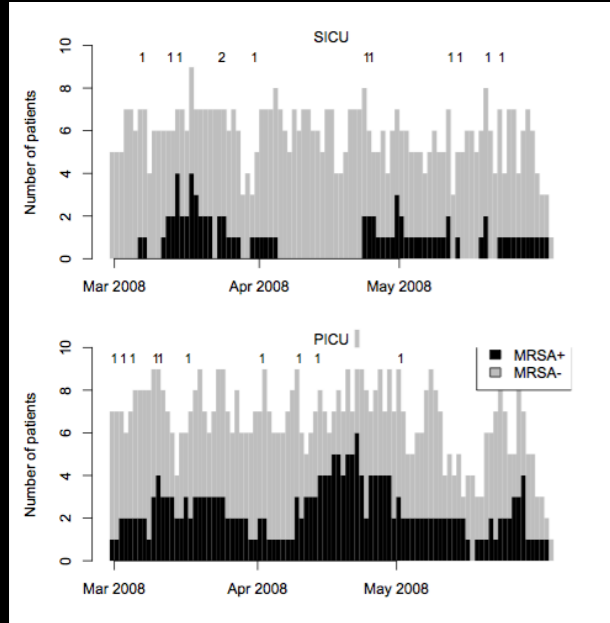


Evolution of MRSA During Hospital Transmission and Intercontinental Spread

Simon R. Harris,<sup>1\*</sup> Edward J. Feil,<sup>2\*</sup> Matthew T. G. Holden,<sup>2</sup> Michael A. Quail,<sup>1</sup> Emma K. Nickerson,<sup>3,4</sup> Narisara Chantratita,<sup>3</sup> Susana Gardete,<sup>5,6</sup> Ana Tavares,<sup>5</sup> Nick Day,<sup>3,7</sup> Jodi A. Lindsay,<sup>8</sup> Jonathan D. Edgeworth,<sup>9,10</sup> Hermínia de Lencastre,<sup>3,4</sup> Julian Parkhill,<sup>1</sup> Sharon J. Peacock,<sup>3,4</sup> Stephen D. Bentley<sup>1†</sup>

Science, 2010





## Acknowledgements

**Colin Worby**

**Theodore Kypraios**

**Julie Robotham**

**Graham Medley**

**Phil O'Neill**

**Nick Graves**

**Susan Huang**

**Dakshika Jeyaratnam**

**Jonathan Edgeworth**

**Rahul Batra**

**Barry Cookson**

**Jennie Wilson**

**Sharon Peacock**

**Emma Nickerson**

**Maliwan Hongsuwan**

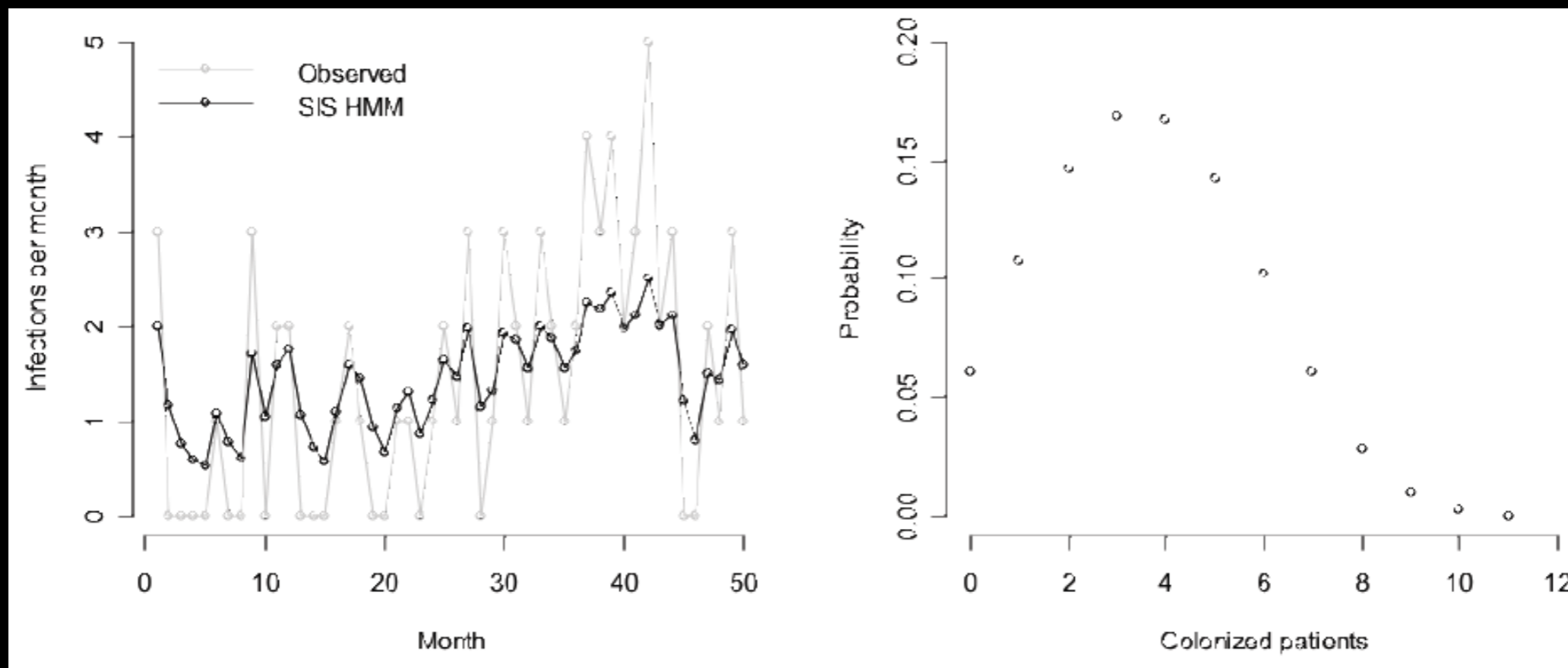
Funding: UK Dept of Health, Wellcome Trust, EU FP6 (MOSAR)



Data: 50 months MRSA infection data from an 11 bed MICU in Vellore, south India (no screening data).

Hidden Markov Model used to impute colonization data and estimate transmission parameters.

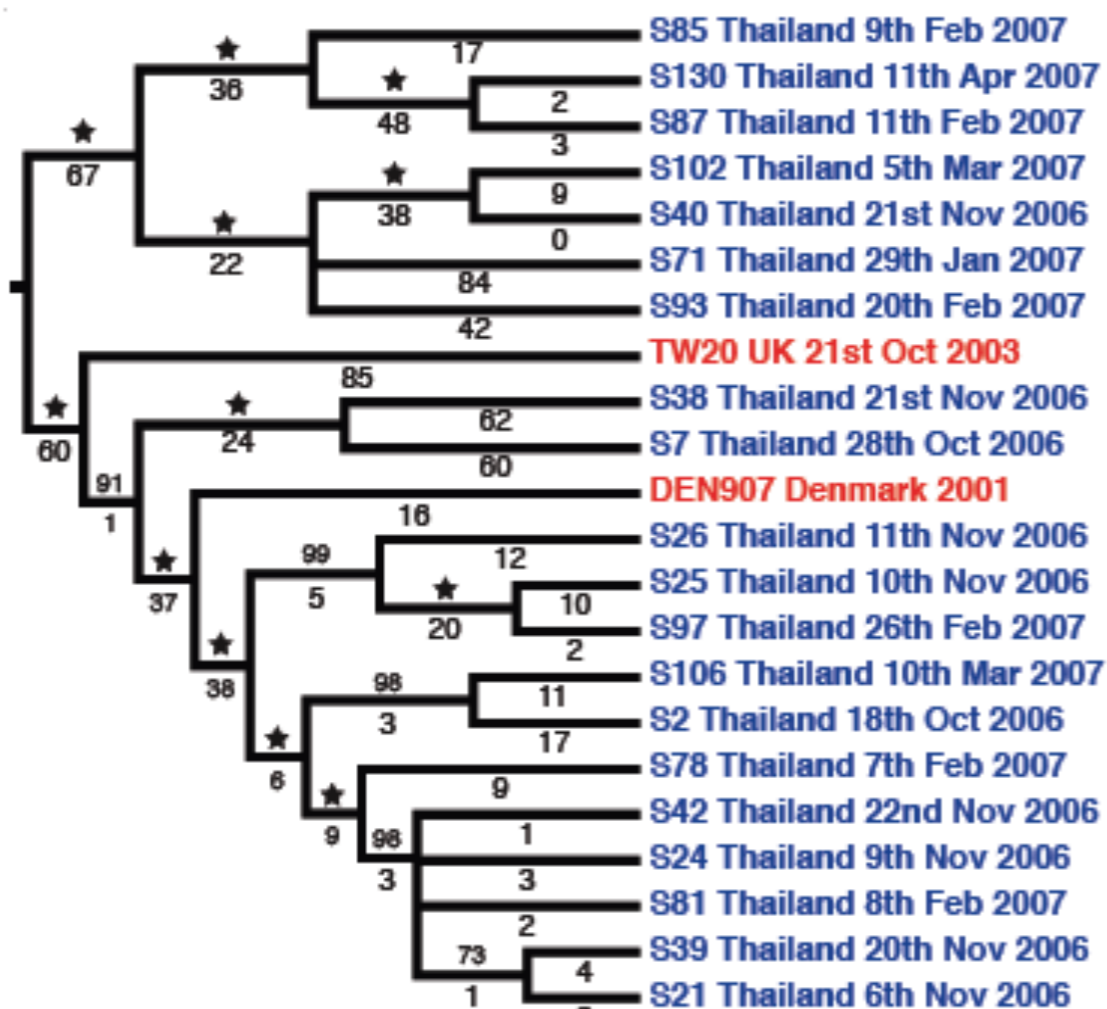
Estimated that 4% of patients were MRSA+ on admission, with a ward level reproduction number of 0.4 (indicating substantial transmission).



# Evolution of MRSA During Hospital Transmission and Intercontinental Spread

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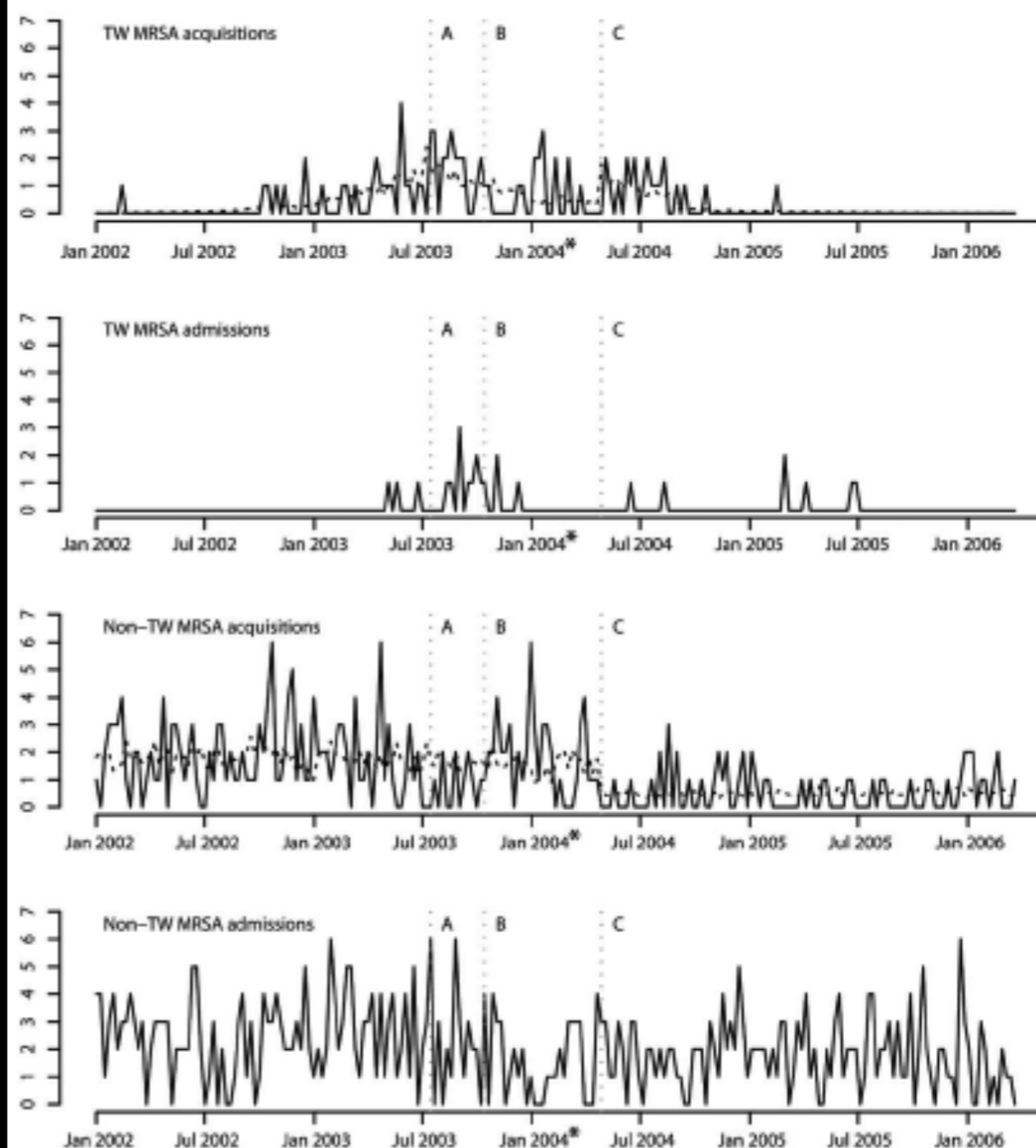
Science, January 2010



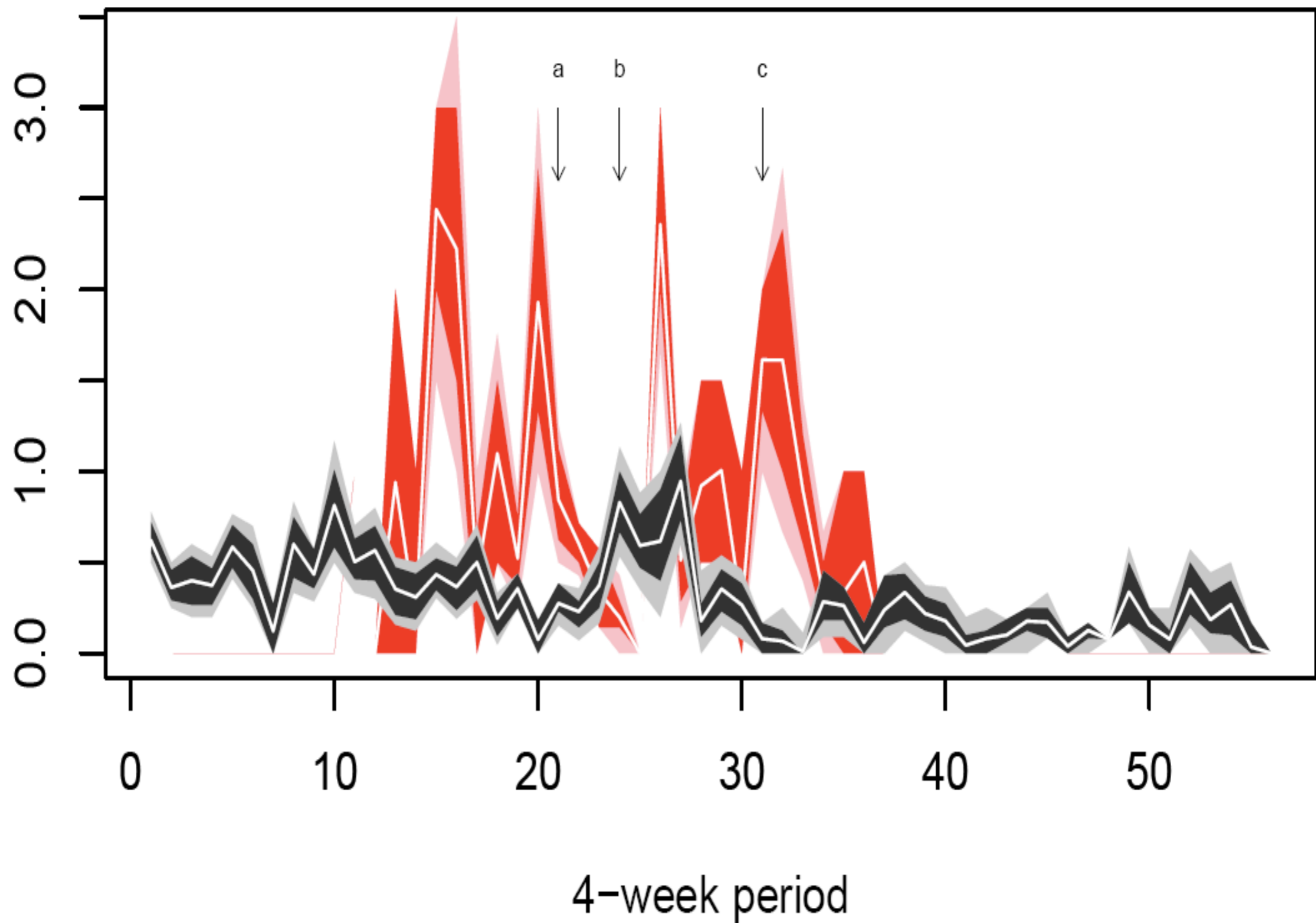
# Efficacy and Limitation of a Chlorhexidine-Based Decolonization Strategy in Preventing Transmission of Methicillin-Resistant *Staphylococcus aureus* in an Intensive Care Unit

Rahul Batra,<sup>1</sup> Ben S. Cooper,<sup>3</sup> Craig Whiteley,<sup>2</sup> Amita K. Patel,<sup>1</sup> Duncan Wyncoll,<sup>2</sup> and Jonathan D. Edgeworth<sup>1,4</sup>

CID January 2010



Reproduction number,  $R$

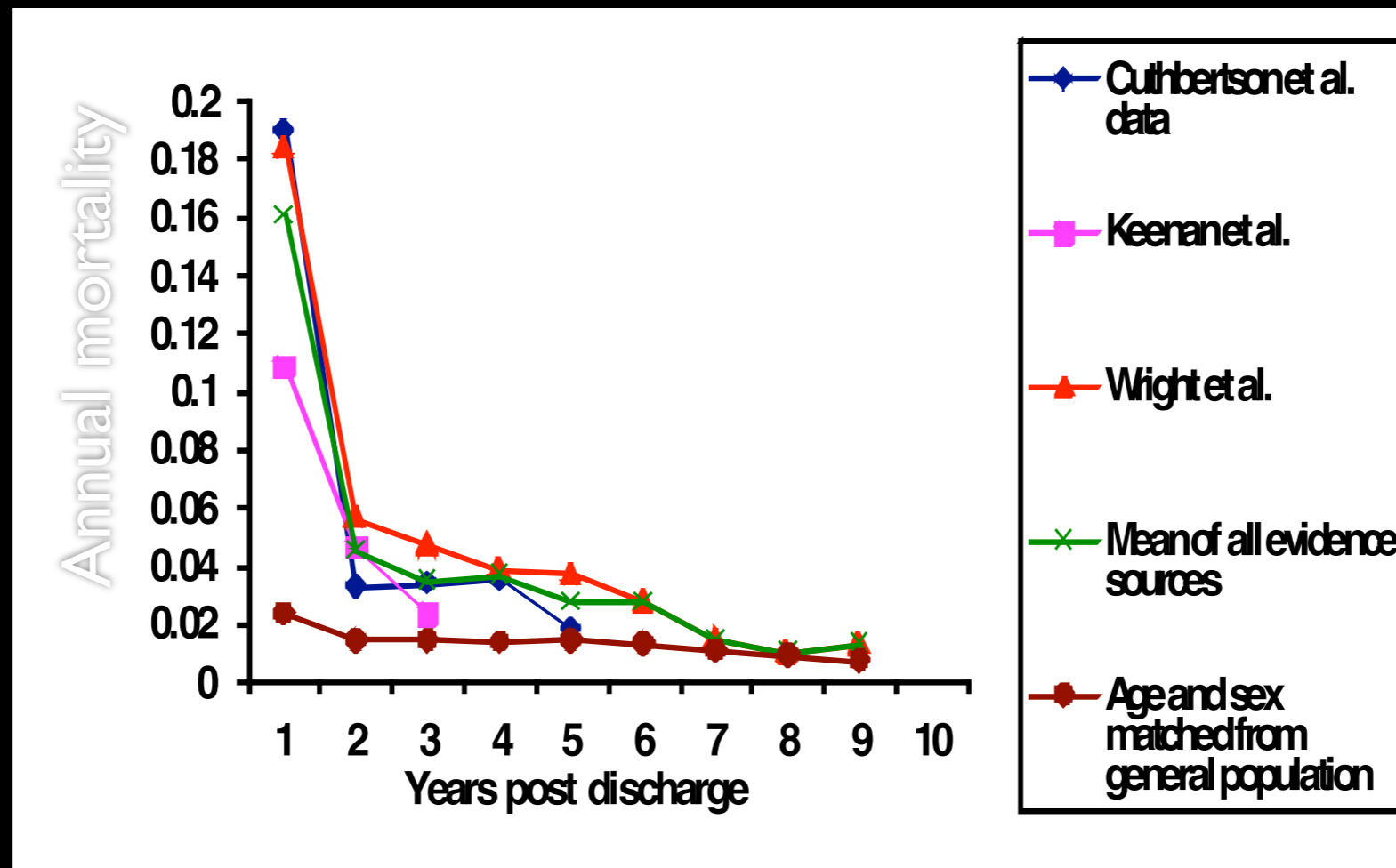






# Health Benefits (Quality Adjusted Life Years gained)

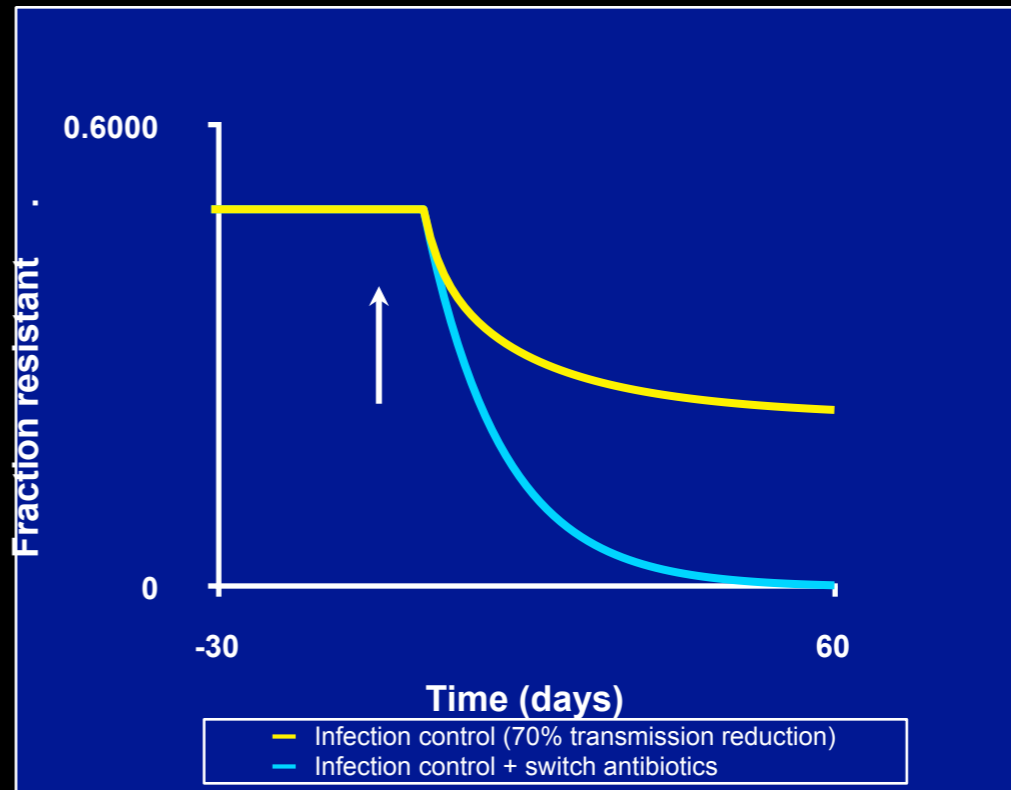
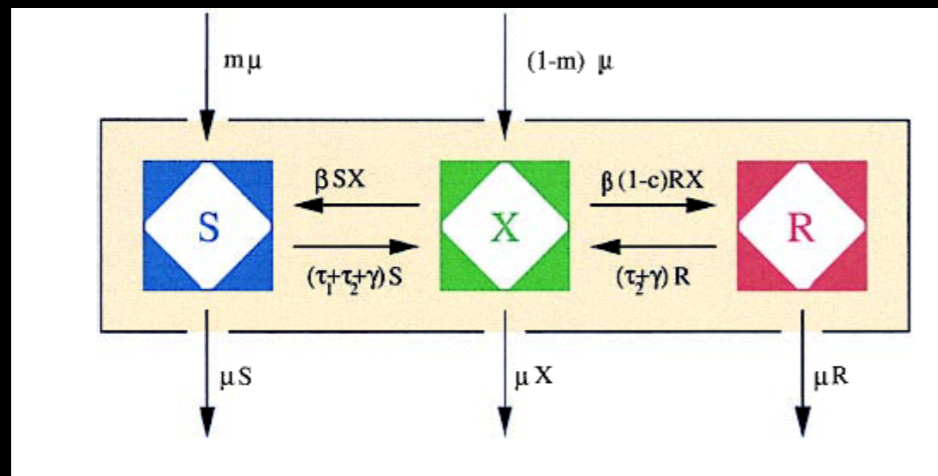
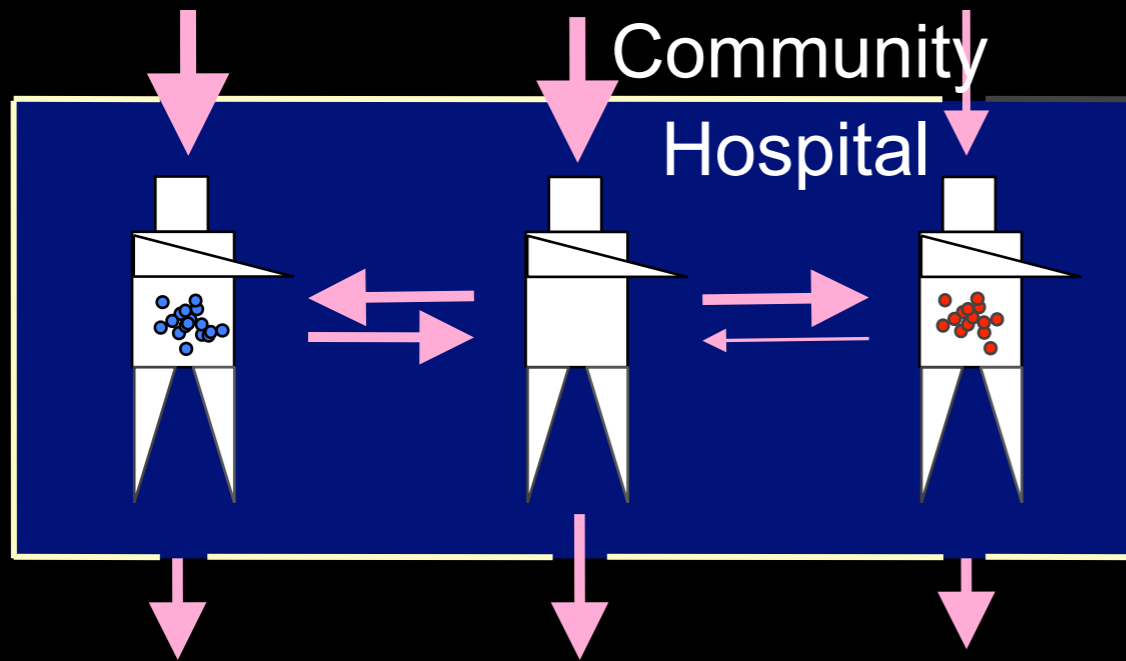
Differences in mortality between strategies will account for almost all differences in QALY gain

We estimated the expected quality adjusted life expectancy of someone discharged alive from an ICU is 9.34 years (calculated from quality weighted survival data)



 antibiotic-sensitive bacteria

 antibiotic-resistant bacteria



Resistance quickly increases in frequency in response to drug use, and quickly decreases in response to intervention.

Non-specific control does appreciably reduce resistance (when resistance is rare in the community).

Formulary changes can rapidly eradicate resistant bacteria.