

# Understanding the spread of antibiotic resistant pathogens in hospitals

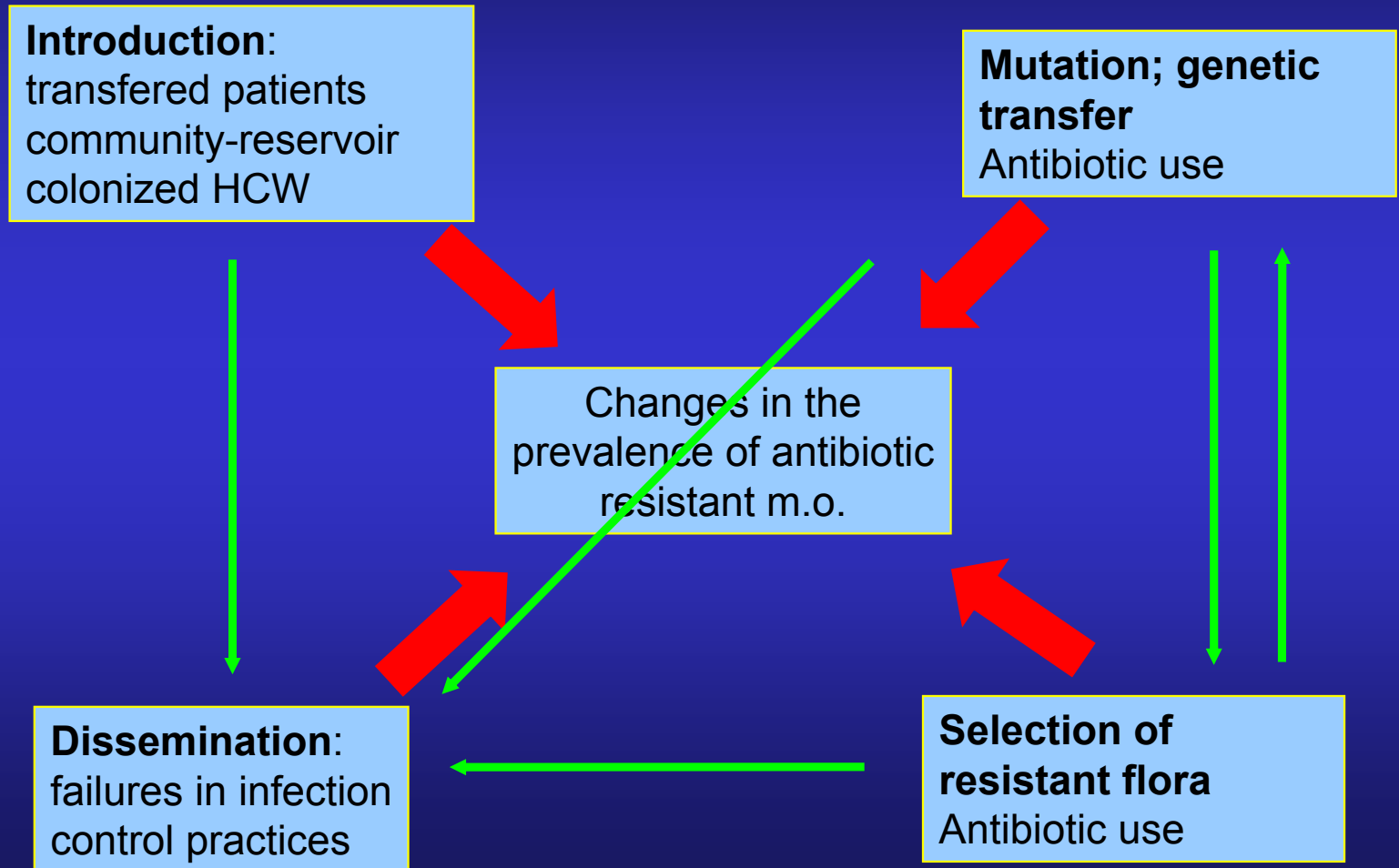
Marc Bonten

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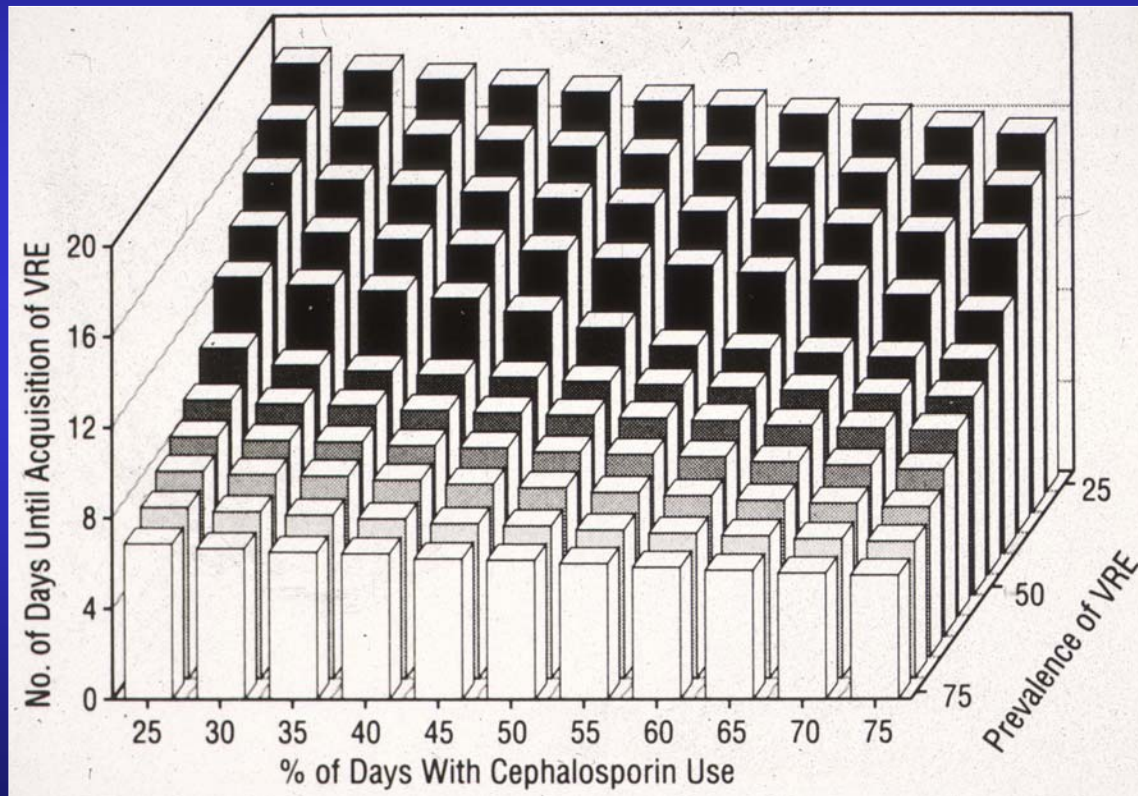


# Pathways of spread and appearance of antibiotic resistant microorganisms



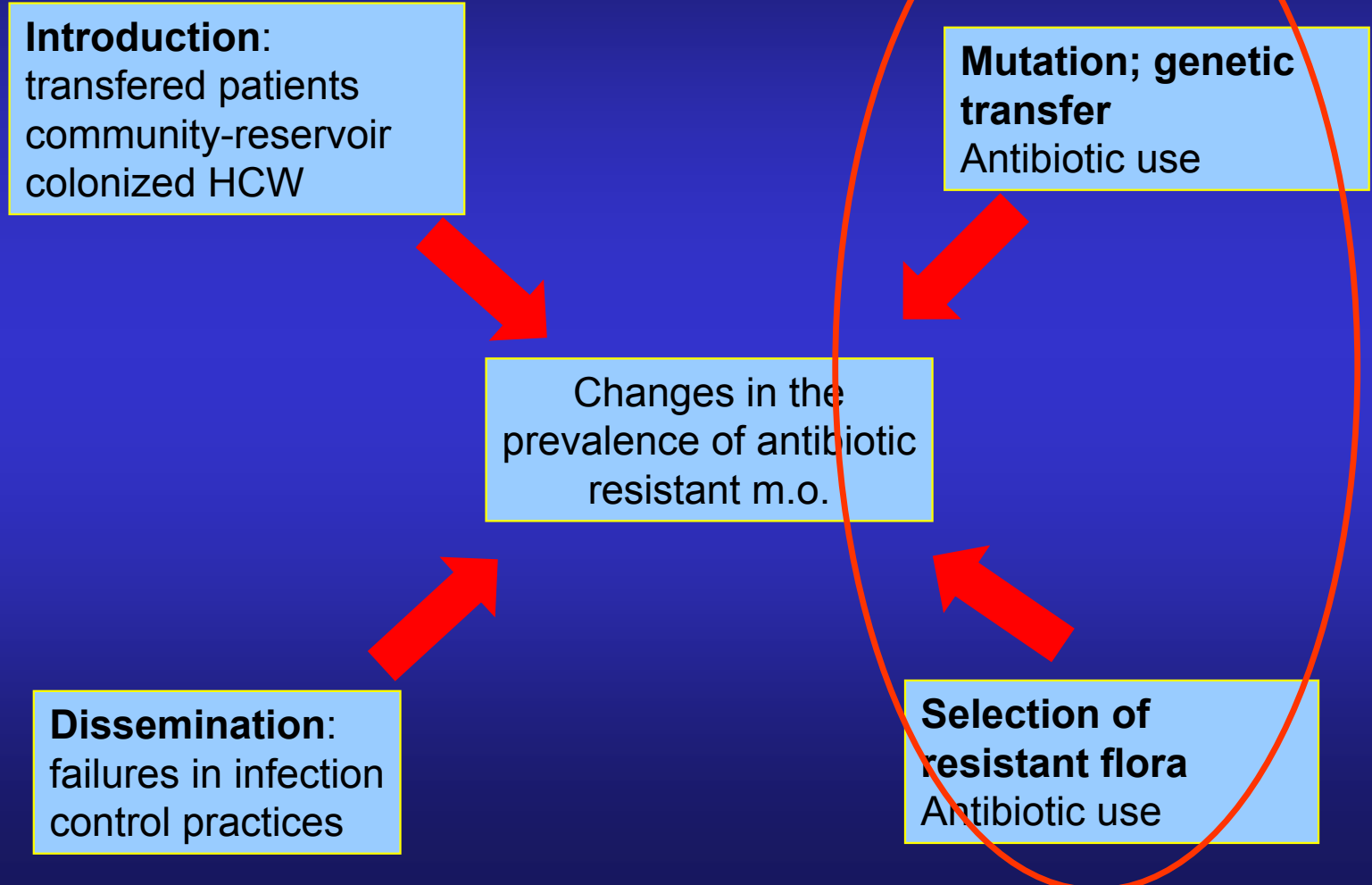
# The Role of “Colonization pressure” in the Spread of Vancomycin-Resistant Enterococci.

## An Important Infection Control Variable

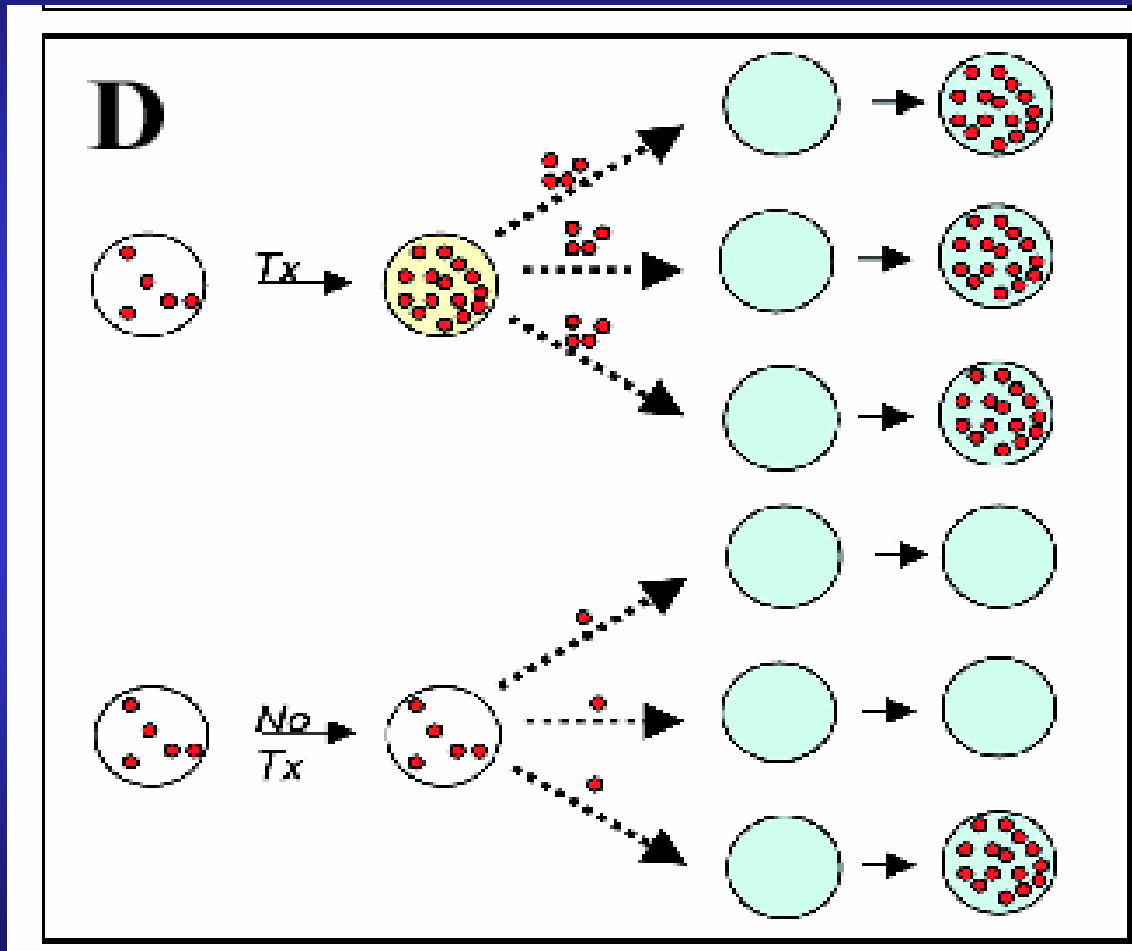


Bonten et al, *Arch Int Med* 1998; 158:1127-32.

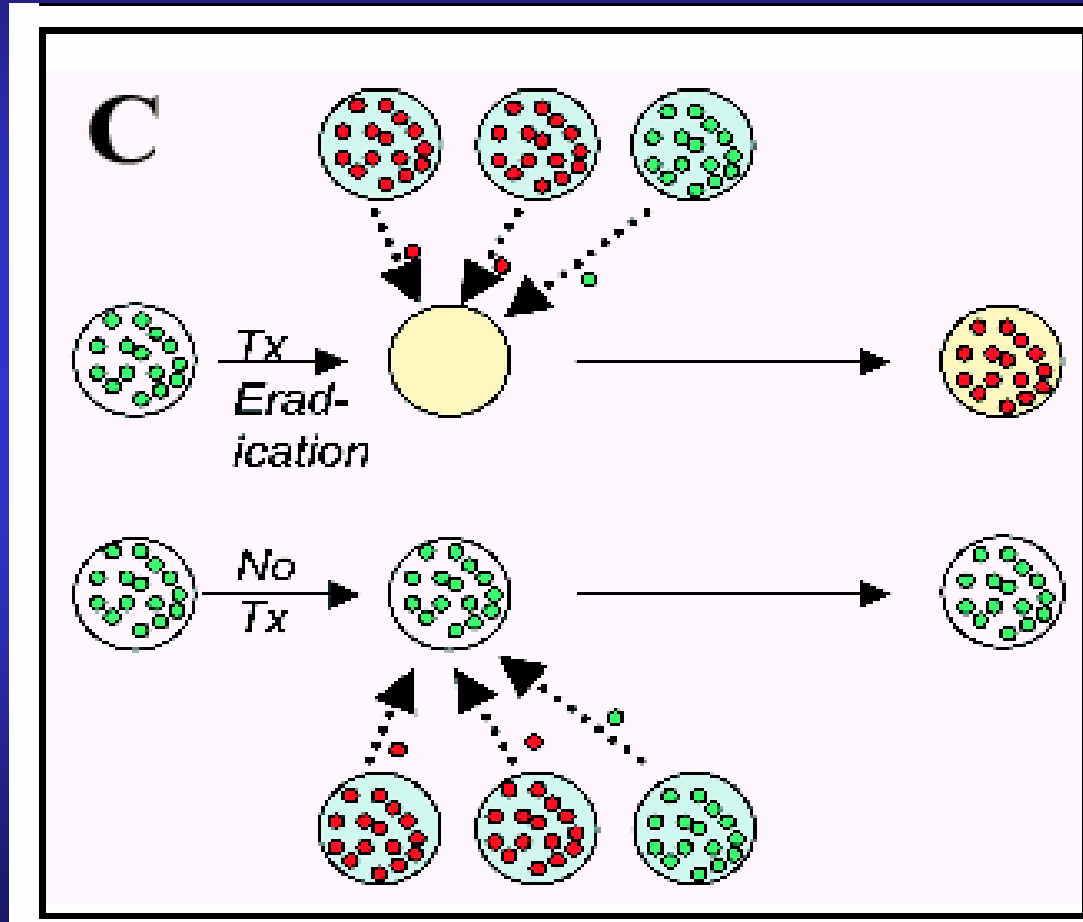
# Pathways of spread and appearance of antibiotic resistant microorganisms



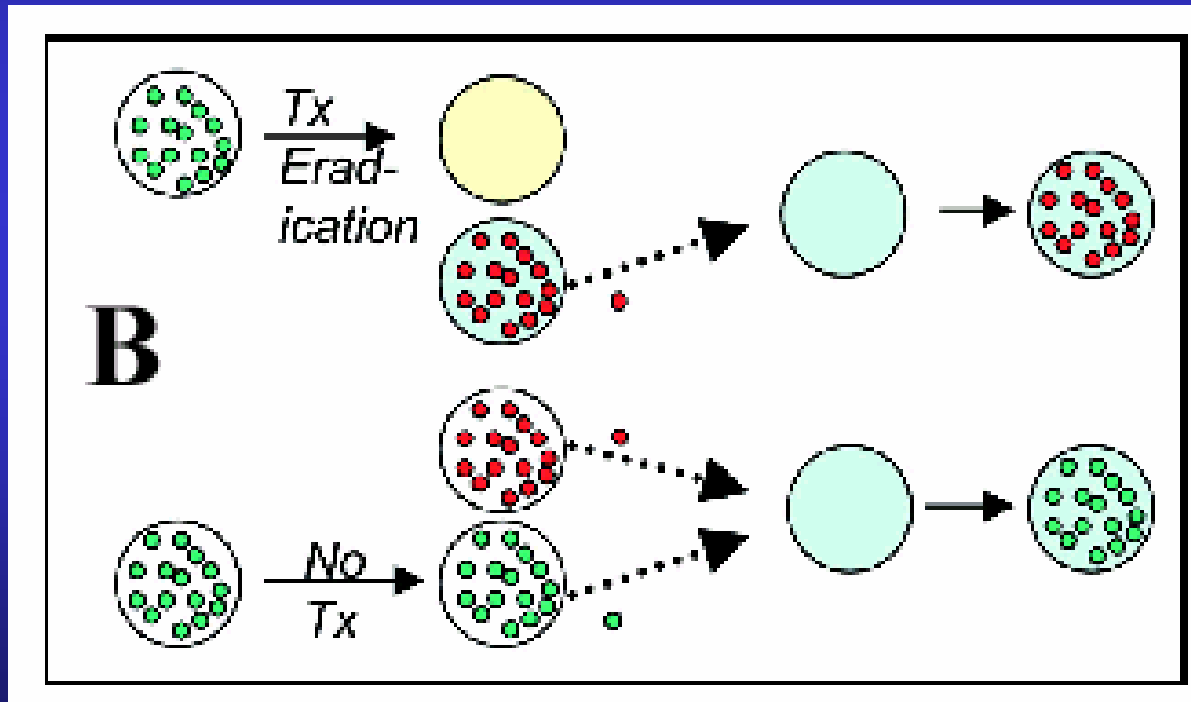
# Antibiotics directly select for pre-existing resistant flora



# Eradication of susceptible flora increases risk of acquisition of resistant flora



Eradication of susceptible flora increases risk of transmission of resistant flora to other patients



# Population size: Why randomness is important in ICUs

- Coefficient of variation =  $SD/Mean$  (%)
- Scales as  $1/\sqrt{N}$

ICU      Hospital      Town      City      Country

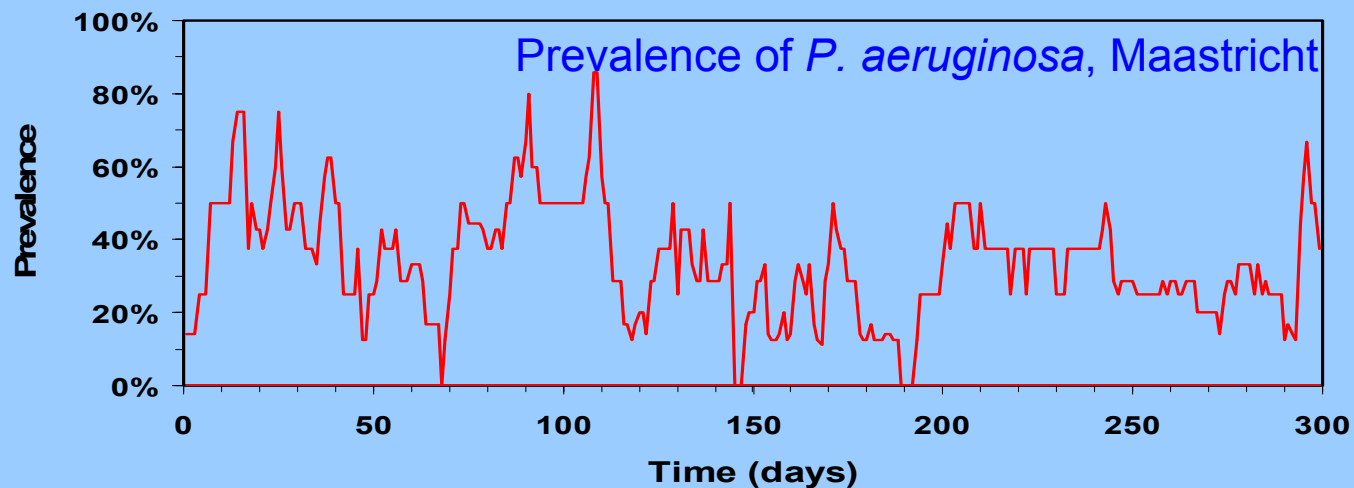
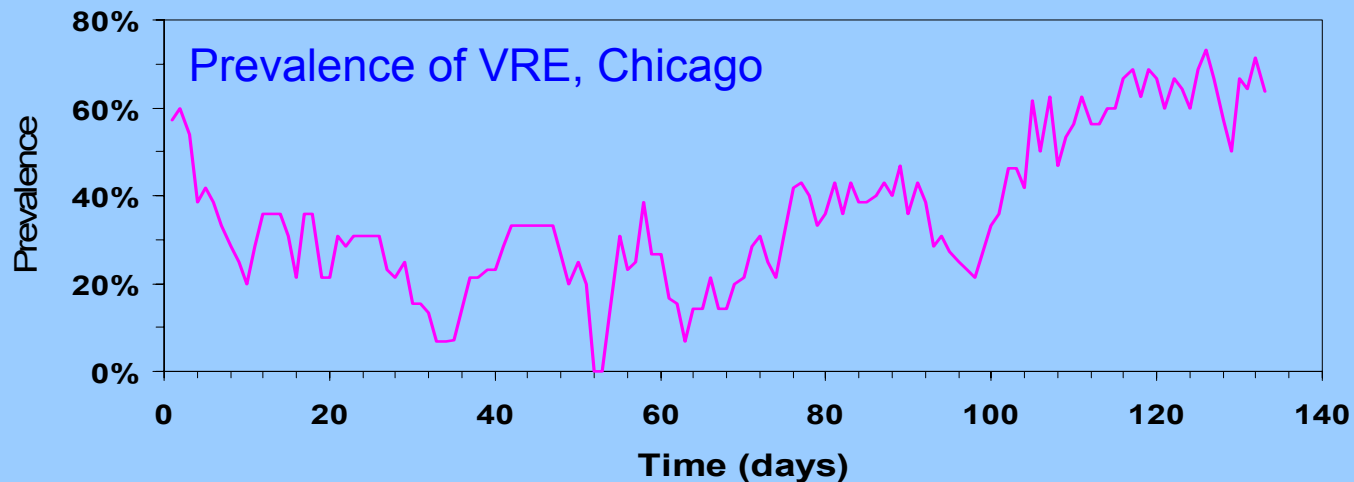


CV= $\sim$ 25%

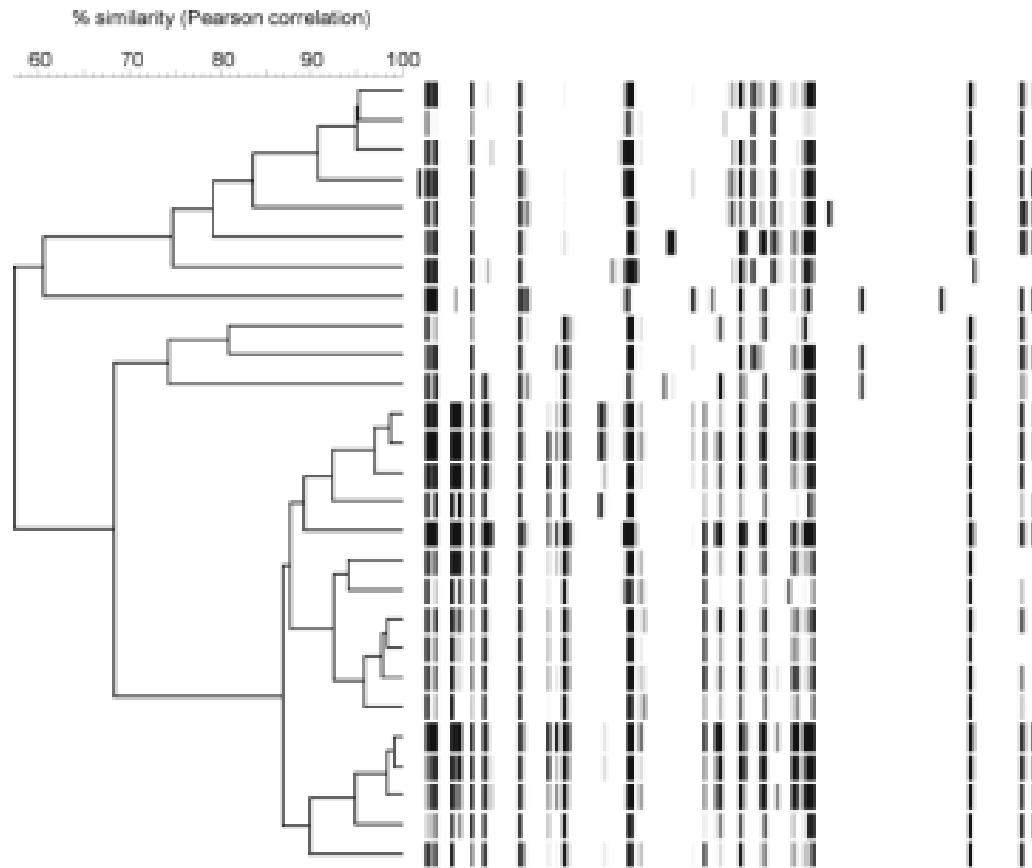
CV=0.1%



# Natural history of antibiotic resistance in ICUs

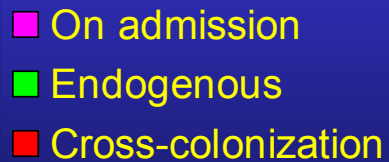
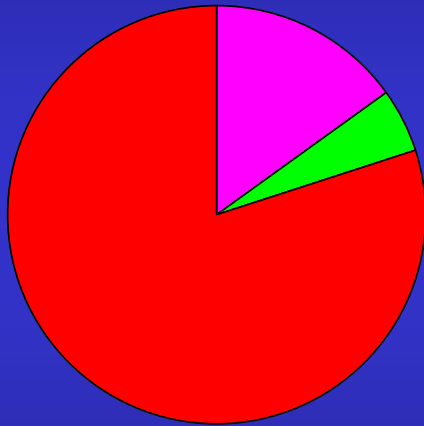


# Fingerprinting necessary to determine transmission routes

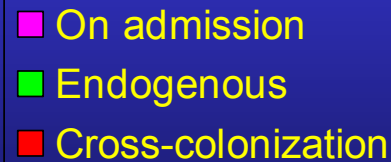
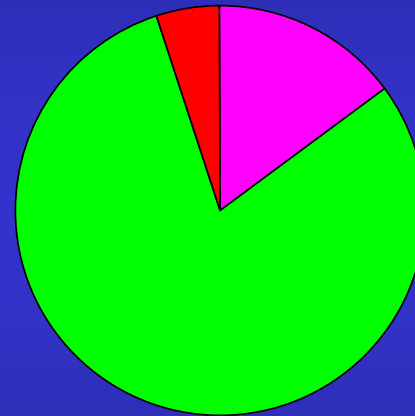


# Characteristics of endemicity

VRE, Chicago



*P. aeruginosa*, Maastricht



# Endogenous sources

- Patients are colonised/infected by their own host flora
- Patients may not show colonisation at admission
  - > 48 hr definition of nosocomial acquisition
- Antibiotic pressure may lead to overgrowth of resistant organisms
- Linear process: risk for acquisition increases with time

# Environmental Contamination

- Common source outbreak
  - Patients exposed to a similar risk
  - E.G. Food contamination
  - Self limiting once source identified
  - Linear process: risk for acquisition increases with time

# Cross-transmitted Cases

- New cases generated via either direct *patient-patient* contact, or *transiently* contaminated intermediate vectors
- Characterised by the basic reproductive number
  - $R_0$  = number of secondary cases generated by an index case
  - Infection control practices reduce  $R_0$  to *effective R*
- Self-limiting unless  $R_0 < 1$  or new cases are admitted
- Non-linear process: risk of acquisition increases in time and depends on “colonization pressure”

# Mathematical modeling of the spread of resistance - Why?

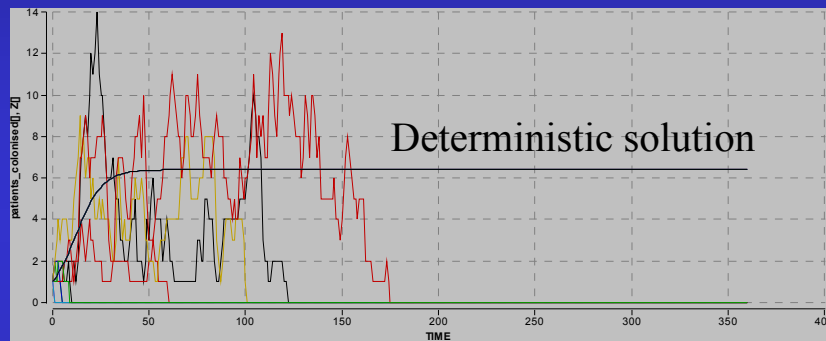
- to quantify the transmission process
- to identify key variables of the transmission process
- to make predictions of interventions that can be tested in clinical studies
- to determine relative effects of individual control measures

# Deterministic versus Stochastic models

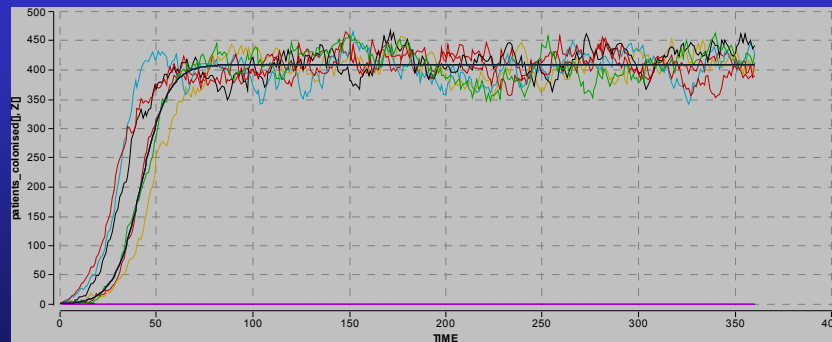
- Partition the population into “compartments” of epidemiological interest
- Events move individuals between compartments
- Models describe the rates with which events occur
  - Use differential equations ( $d/dt$ ) to measure net rates of change
- Deterministic:
  - Calculates mean behavior (e.g. 2.3 pts colonized)
  - Excludes fluctuations due to chance
  - Provides exact solutions
- Stochastic:
  - Calculates individual behavior (e.g. 80% of realisations >3 pts colonized)
  - Includes fluctuations due to chance
  - Provides numerical results based on Monte Carlo simulations

Example: 10 simulated outbreaks,  
1 index case,  $R_0 = 2$ , LOS = 1 week

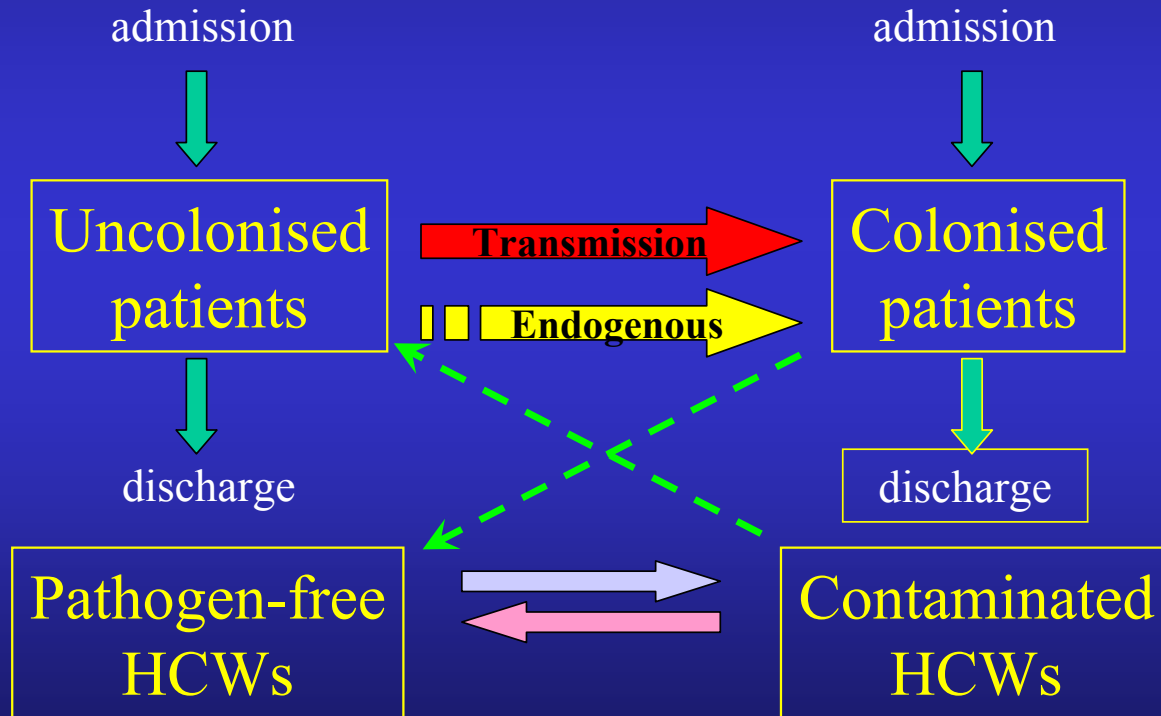
$N = 16$



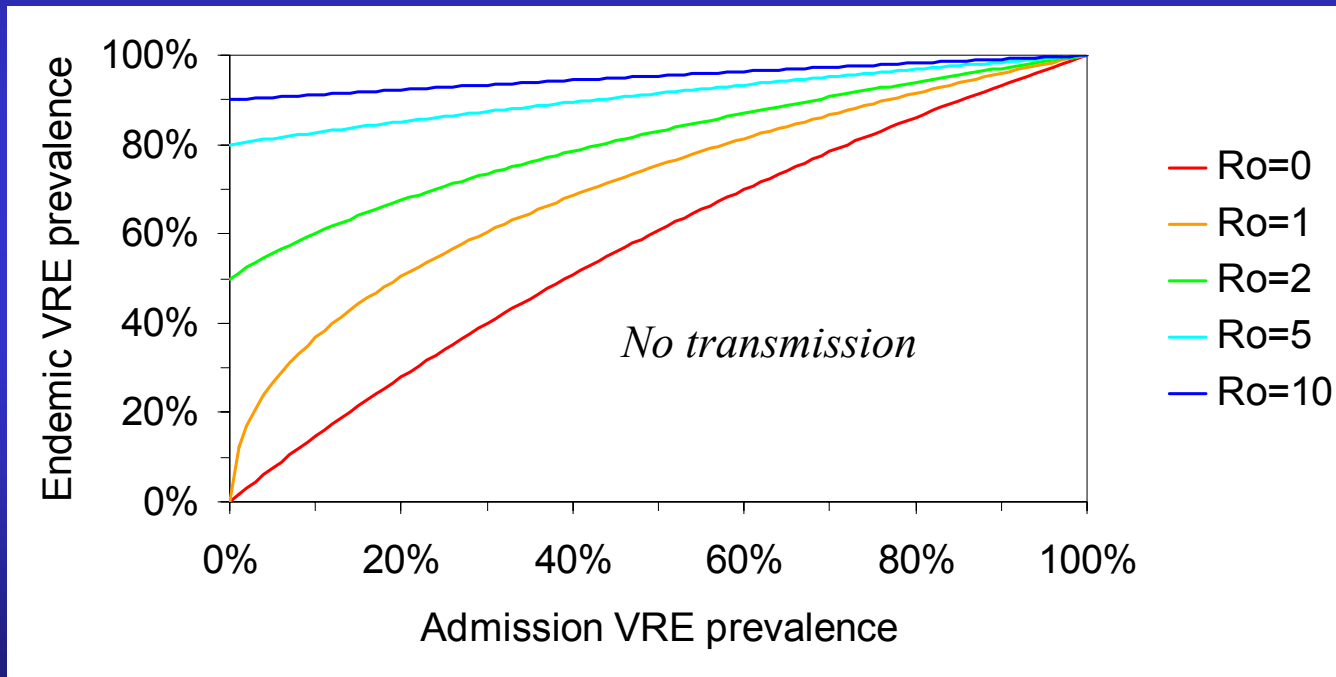
$N = 1024$



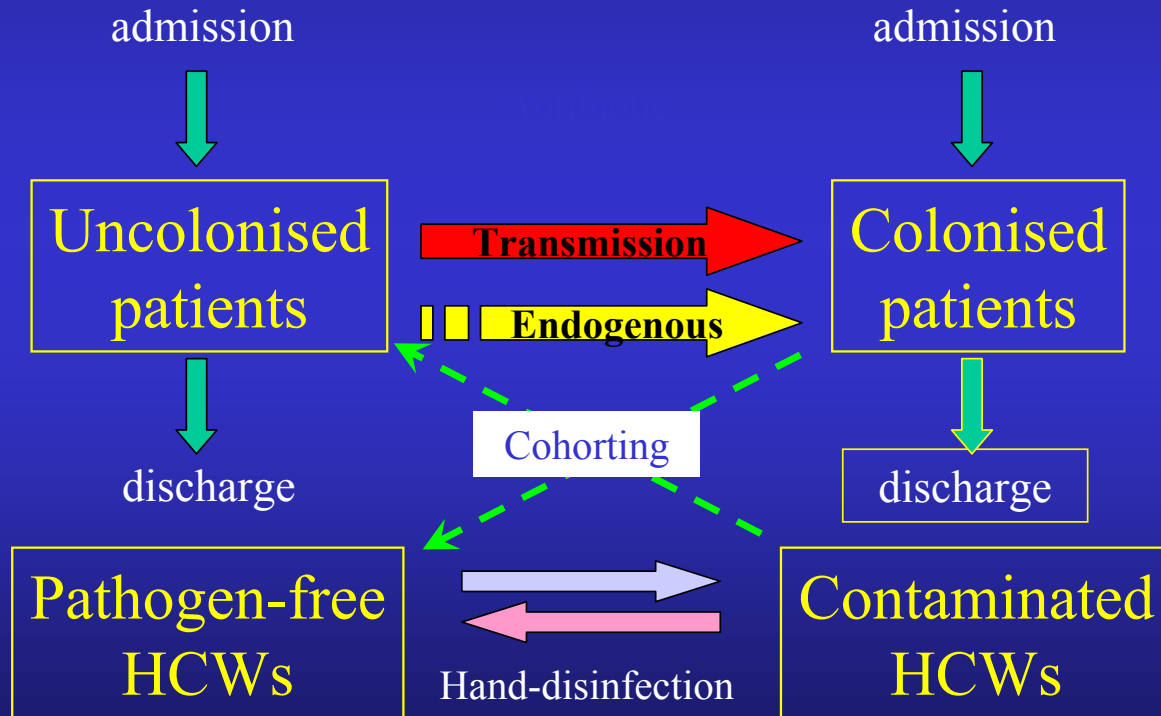
# Theoretical framework for pathogen acquisition and spread



# Equilibrium solutions: Colonised admissions stabilise transmission

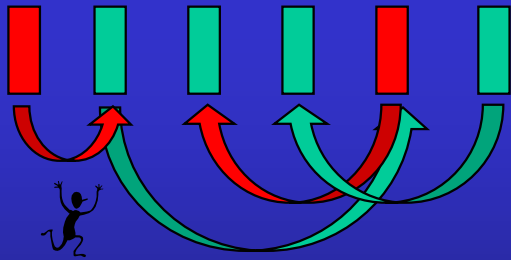


# Theoretical framework for pathogen acquisition and spread



# Cohorting strategies

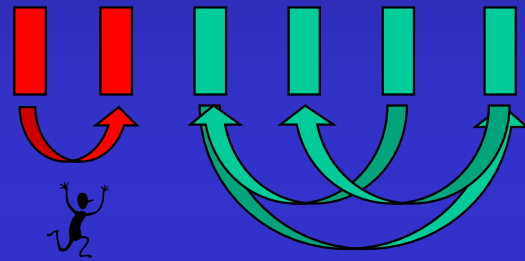
Random mixing



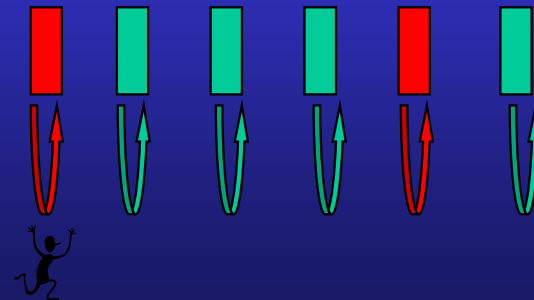
$q$  = probability of receiving  
a cohorted contact

Staff cohorting:  $R_0 (1 - q)$

Patient cohorting



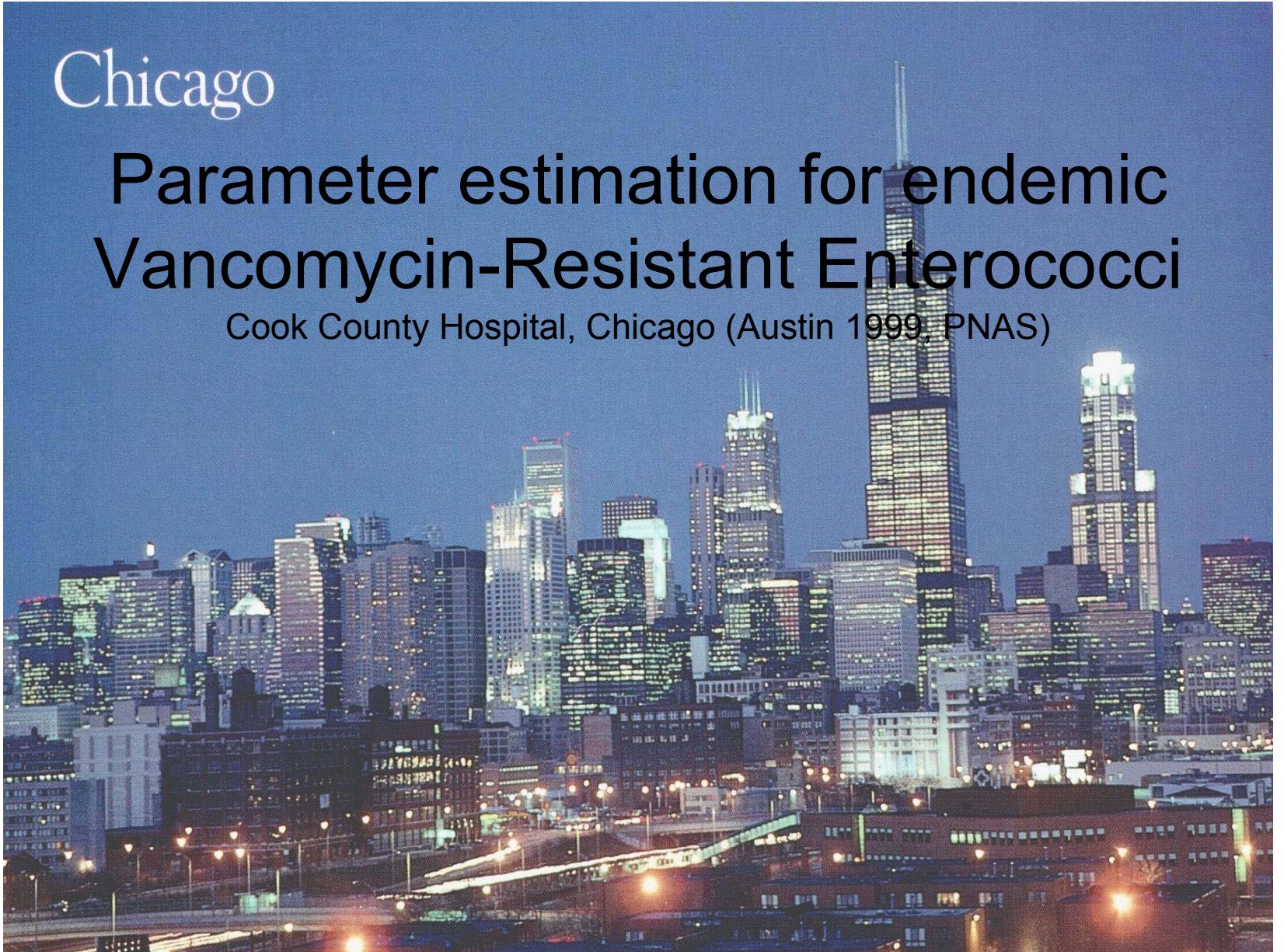
HCW cohorting



Chicago

# Parameter estimation for endemic Vancomycin-Resistant Enterococci

Cook County Hospital, Chicago (Austin 1999, PNAS)



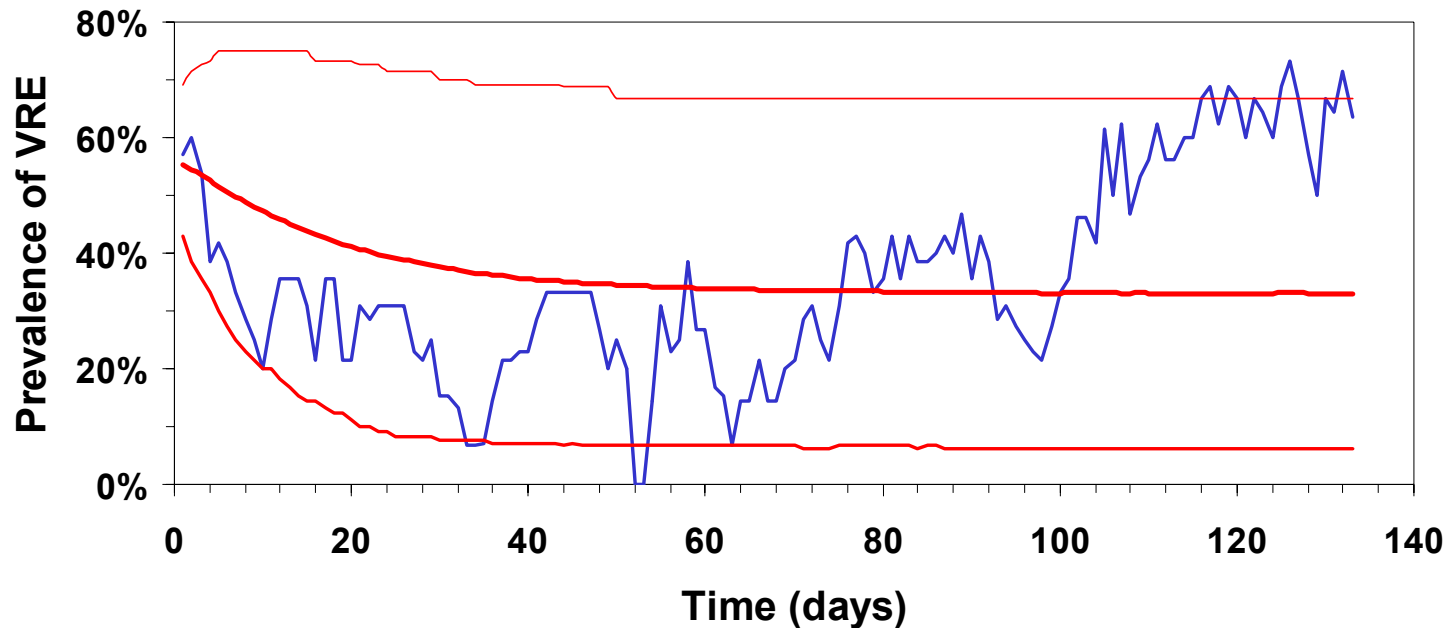
# Parameter estimation for endemic VRE

Cook County Hospital, Chicago (Austin et al 1999, PNAS)

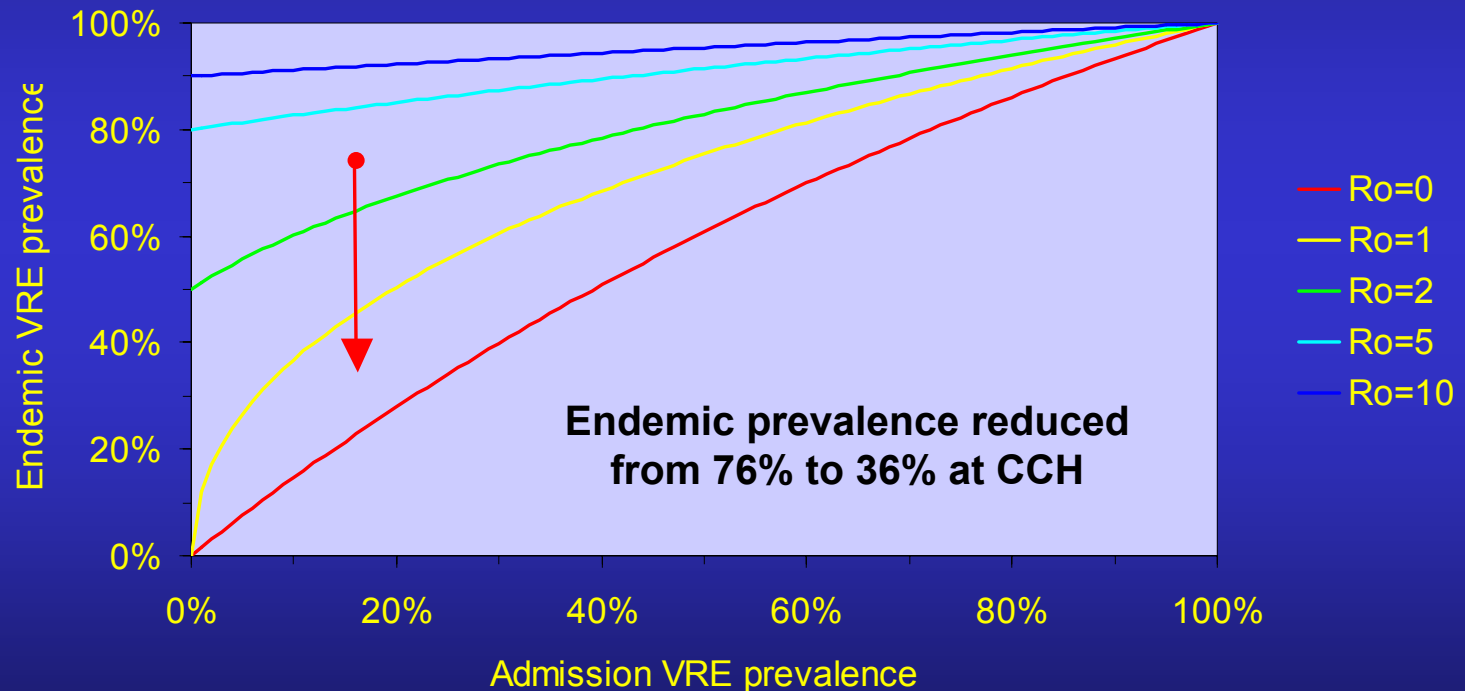
- 16 bed ICU with 1:1 staff-patient ratio
- Prevalence of VRE
  - 15% mean admission prevalence
  - 36% mean endemic prevalence
- Infection control
  - 50% hand-washing compliance
  - 80% of nursing staff cohorted?
- $R_0 = 3.8$ ,  $R = 0.7$

# Comparison of model with data

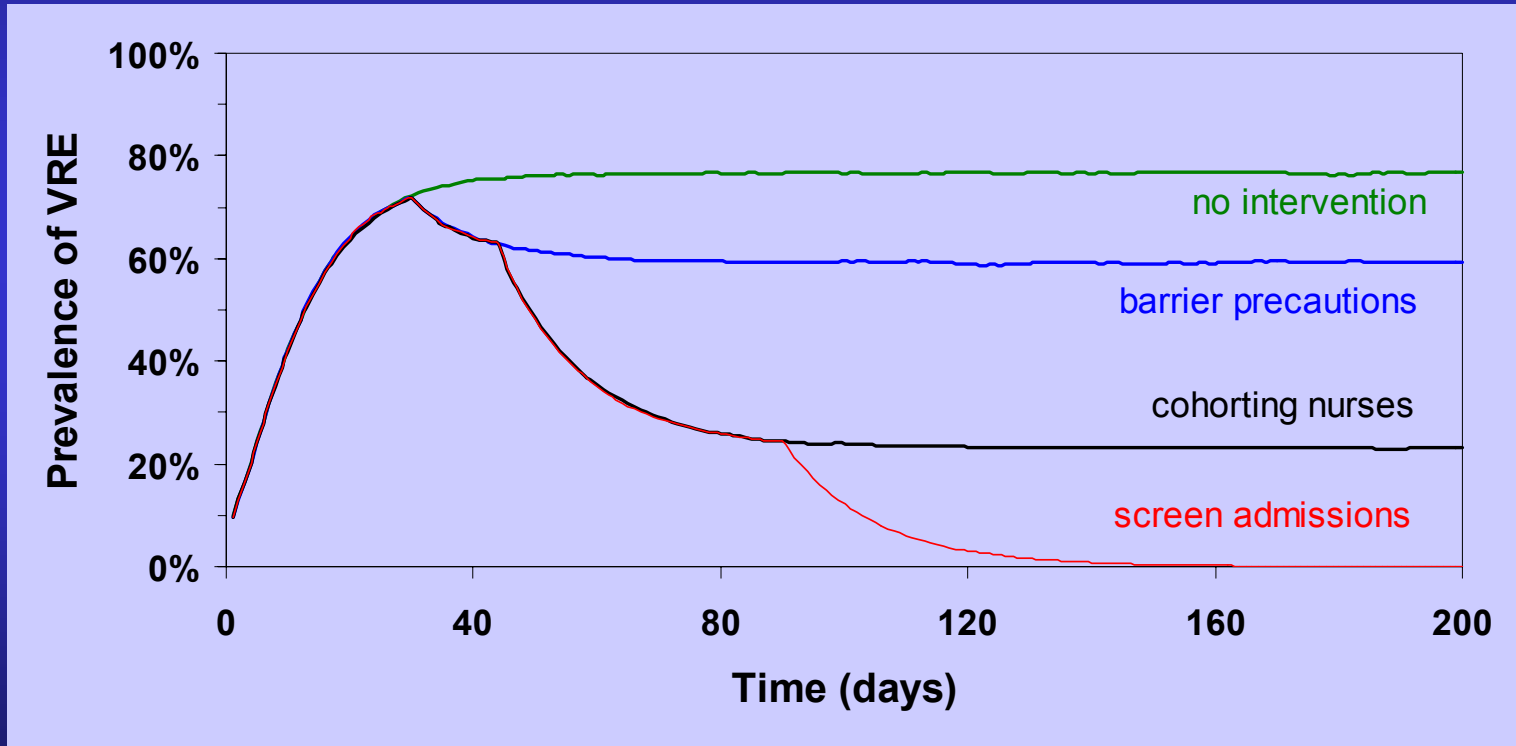
$10^5$  realisations of model predicts endemic prevalence (36%),  
fluctuations ( $\pm 34\%$ ) and number of patients treated (189)



# Estimating the impact of infection control practices at CCH



# Cumulative infection control of a VRE outbreak

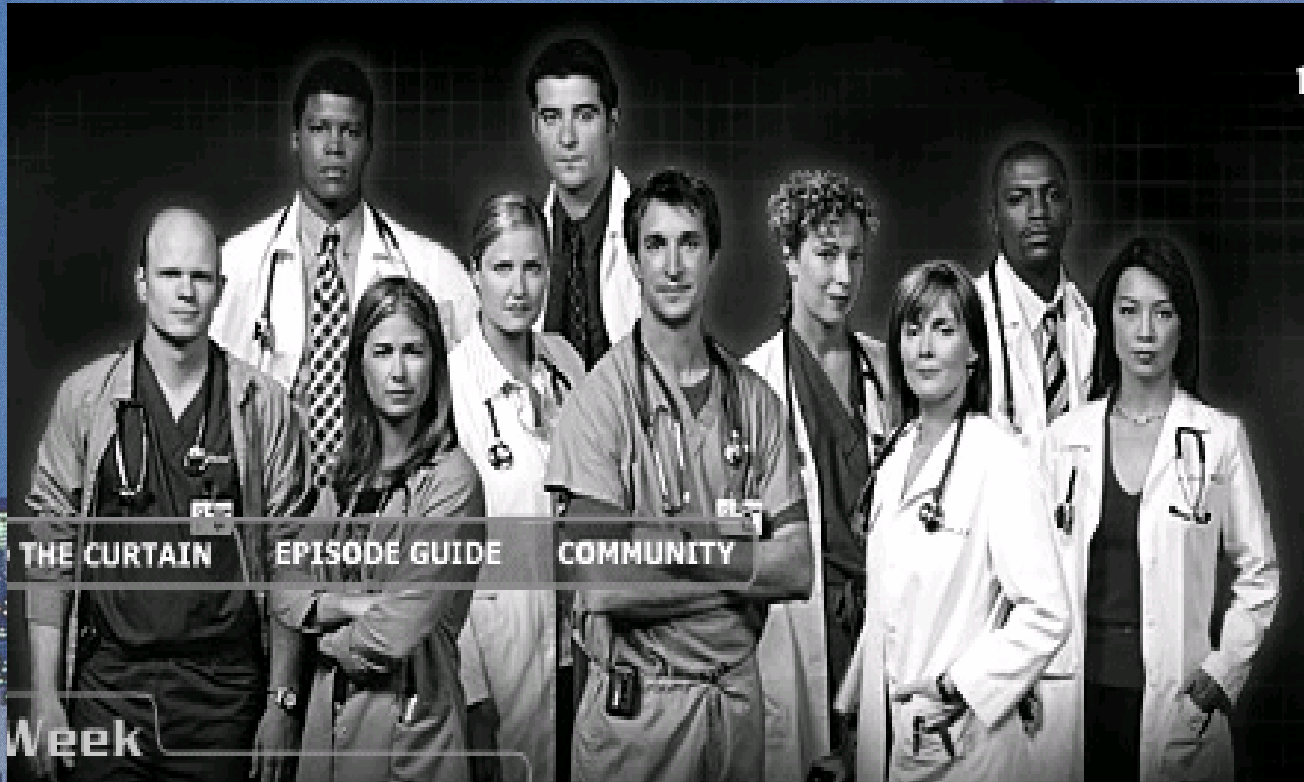


# Conclusions from the model

- A mathematical model provides a representation of nosocomial transmission with insights into
  - why hand-disinfection may not afford complete protection
  - why outbreaks may persist even when infection control is very good
  - how admissions can stabilise outbreaks in endemic settings
  - importance of cohorting level of staff (= staff deficit?)

# Chicago

# Who's to blame?



THE CURTAIN

EPISODE GUIDE

COMMUNITY

Week

# Number of potentially contaminated contacts for nurses and physicians

S. Nijssen et al. Arch Intern Med 2003

## Potential number of contaminated contacts per hour

$$CR \times N_{\text{hcw}} \times (1 - q) \times (1 - p)$$

CR = contact rate

q = cohort level

p = compliance level

### Nurses (as a group)

$$2.6 \times 9.6 \times (1 - 0.77) \times (1 - 0.59) = 2.4 \text{ per hour}$$

### Physicians (as a group)

$$1.2 \times 6 \times (1 - 0.08) \times (1 - 0.43) = 3.8 \text{ per hour}$$

Relative Risk for contaminated contact =  $3.8/2.4 = 1.6$

# Risk factors for the transmission of methicillin-resistant *S. aureus* in an adult ICU: Fitting a model to the data.

Grundmann et al. J Infect Dis 2002; 185: 481-8

Cohort study on colonization with MRSA in ICU

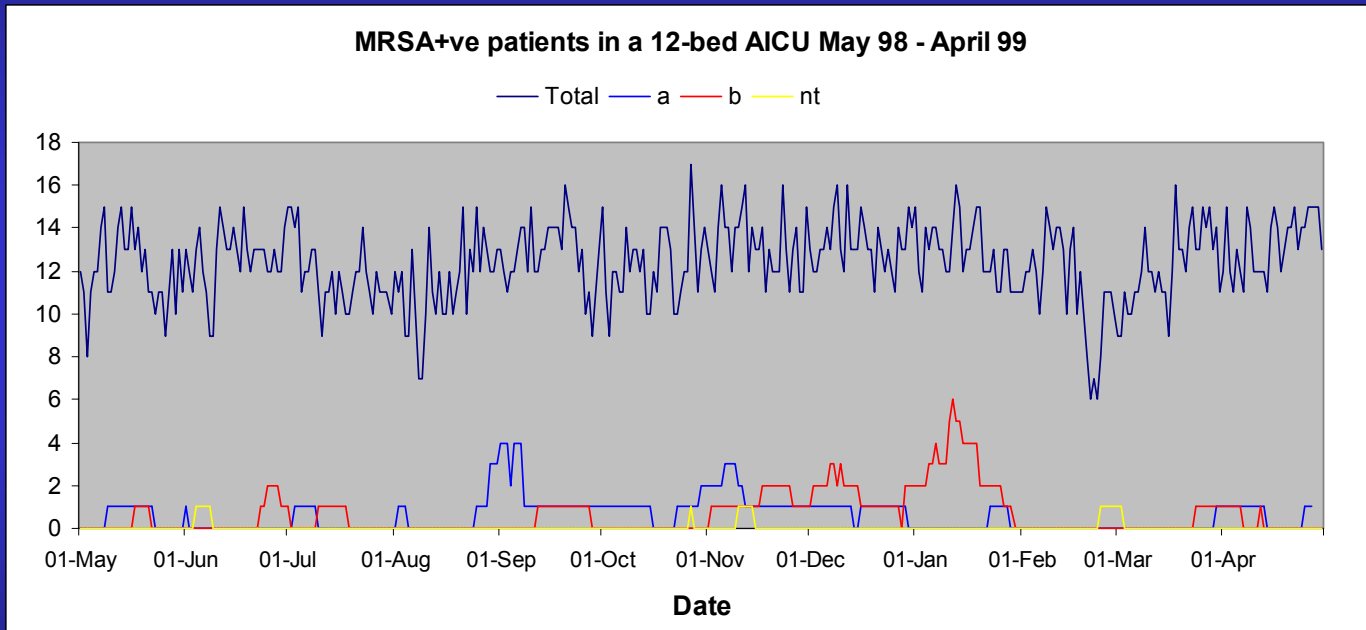
2 clusters of acquisition identified: cross-transmission (genotyping)

bimonthly analysis of colonization and average staff numbers

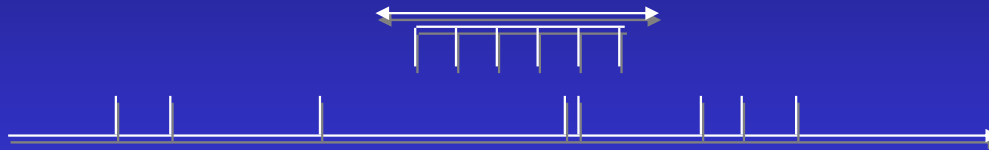
one-time measurement of infection control variables:

contact-rate:	3 pt/hr
hand-wash compliance:	59%
cohorting probability:	70
ratio nurses-patient:	0.78

# Endemicity with different genotypes of MRSA



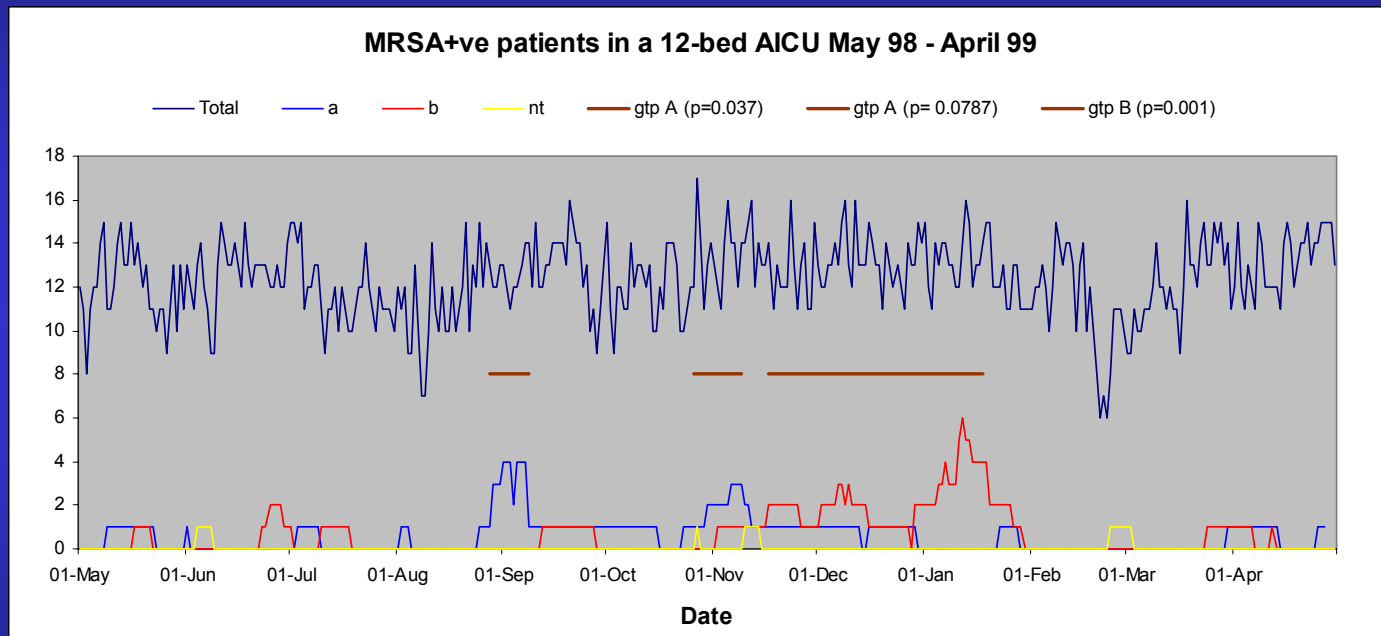
# Detection of clustered cases

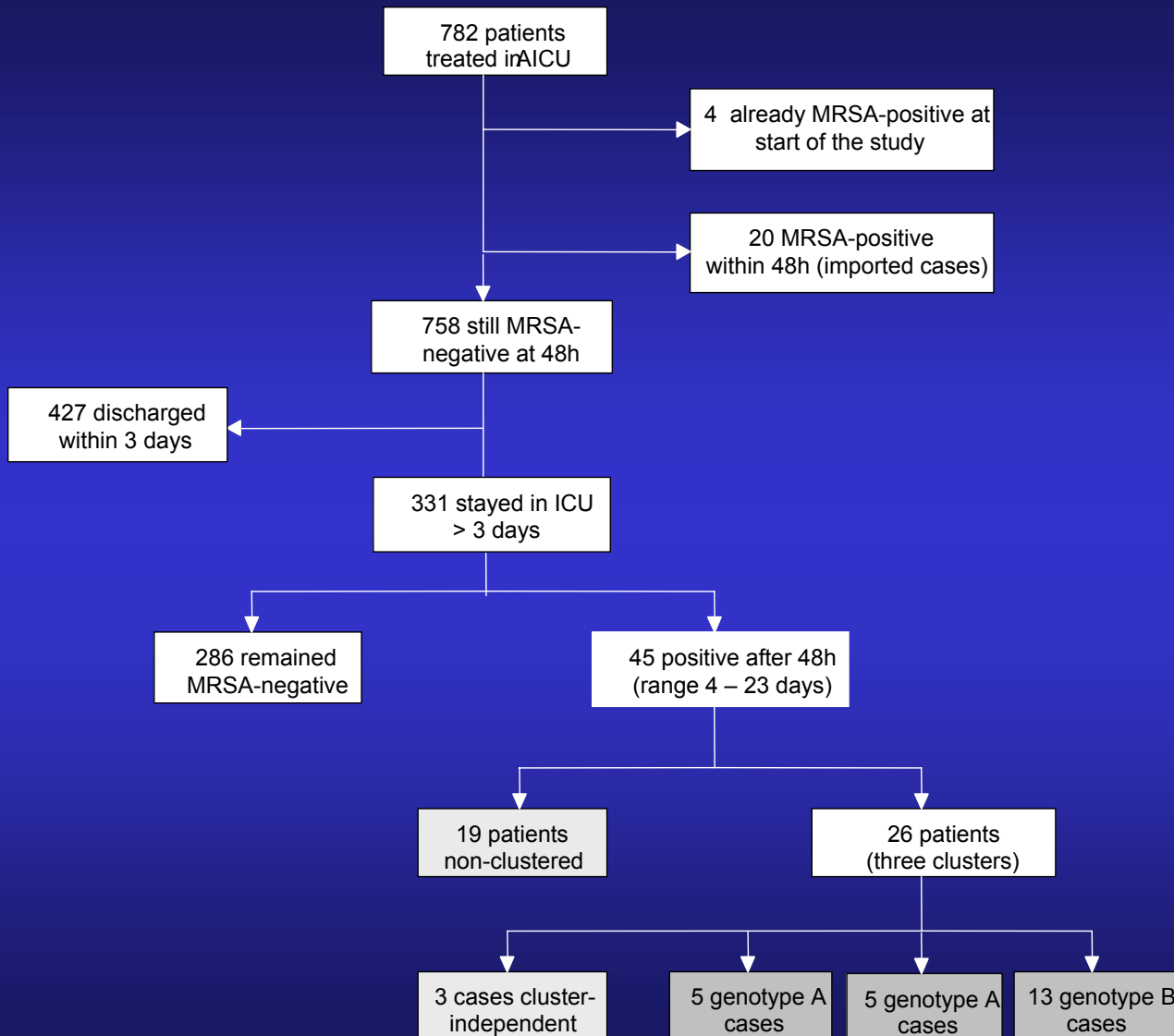


"sliding window or scan method"

- Test statistic  $S_w$  is the maximum number of cases when a predefined window is moved along a time series.
- The p value gives the probability for this number under the assumption of random distribution (null hypothesis)

# Three clusters of genotypes of MRSA





# Case-case comparison

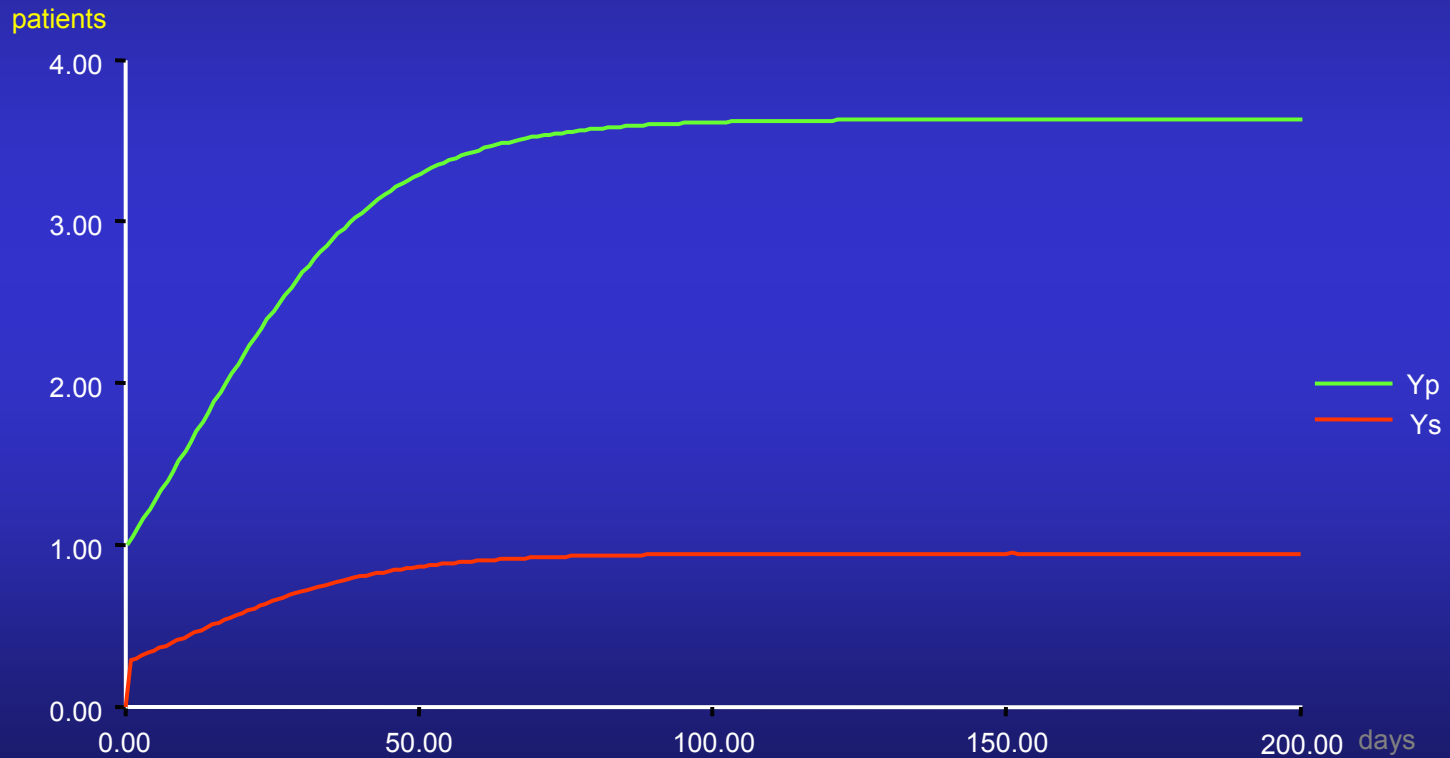
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Comparing clustered with non-clustered cases:

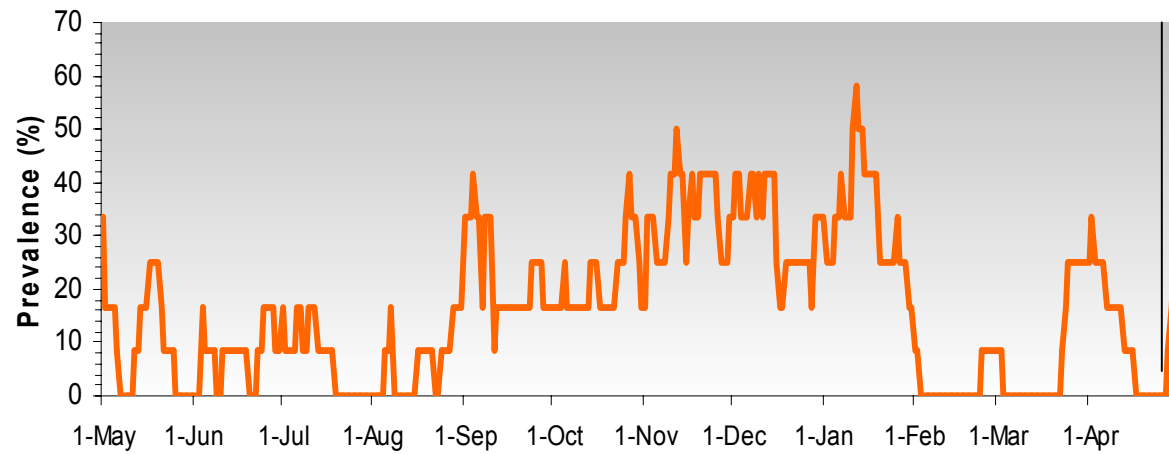
- Understaffing > 10 days OR 5.7, p=0.01
- Admission from a different hospital OR 0.16, p=0.01

# MRSA spread in ICUs:

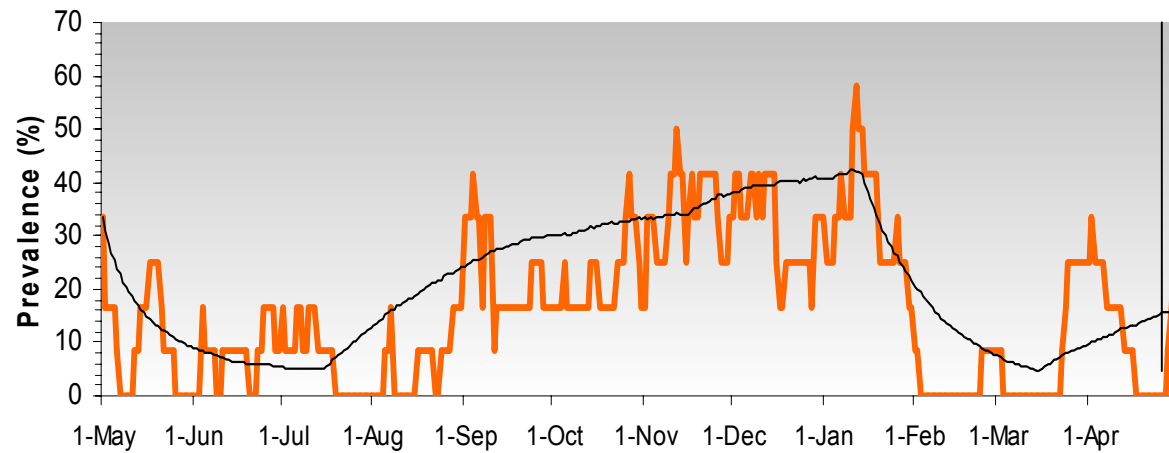
## Predictions from a Deterministic Model



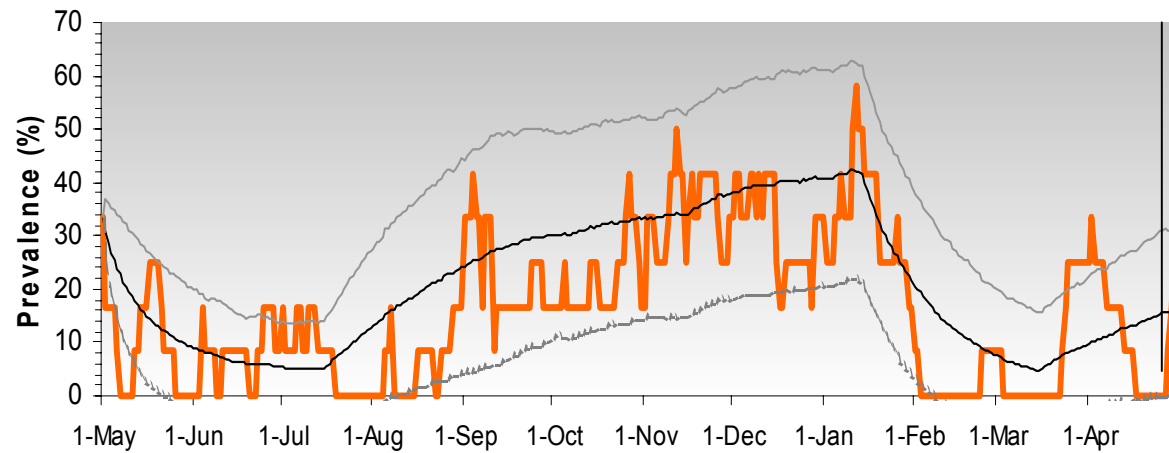
## Observed Prevalence



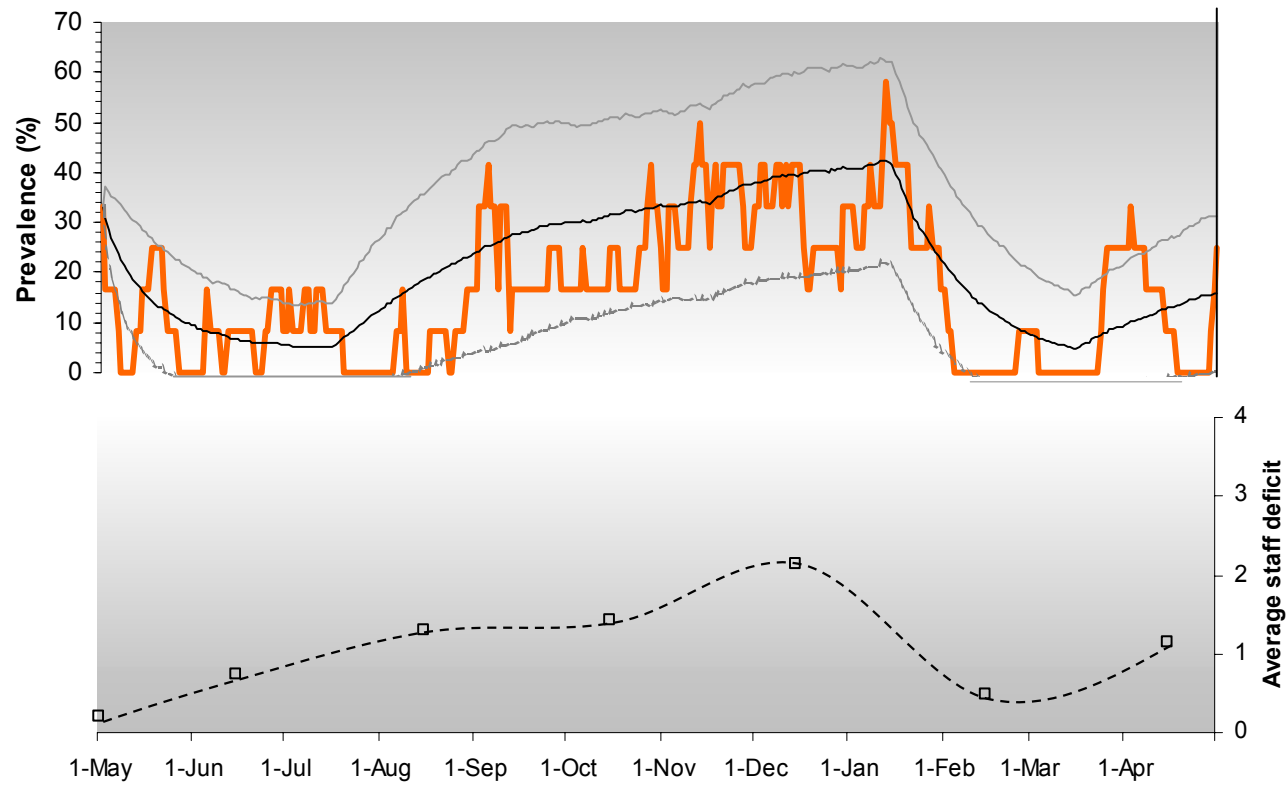
## Observed Prevalence with Model Predictions



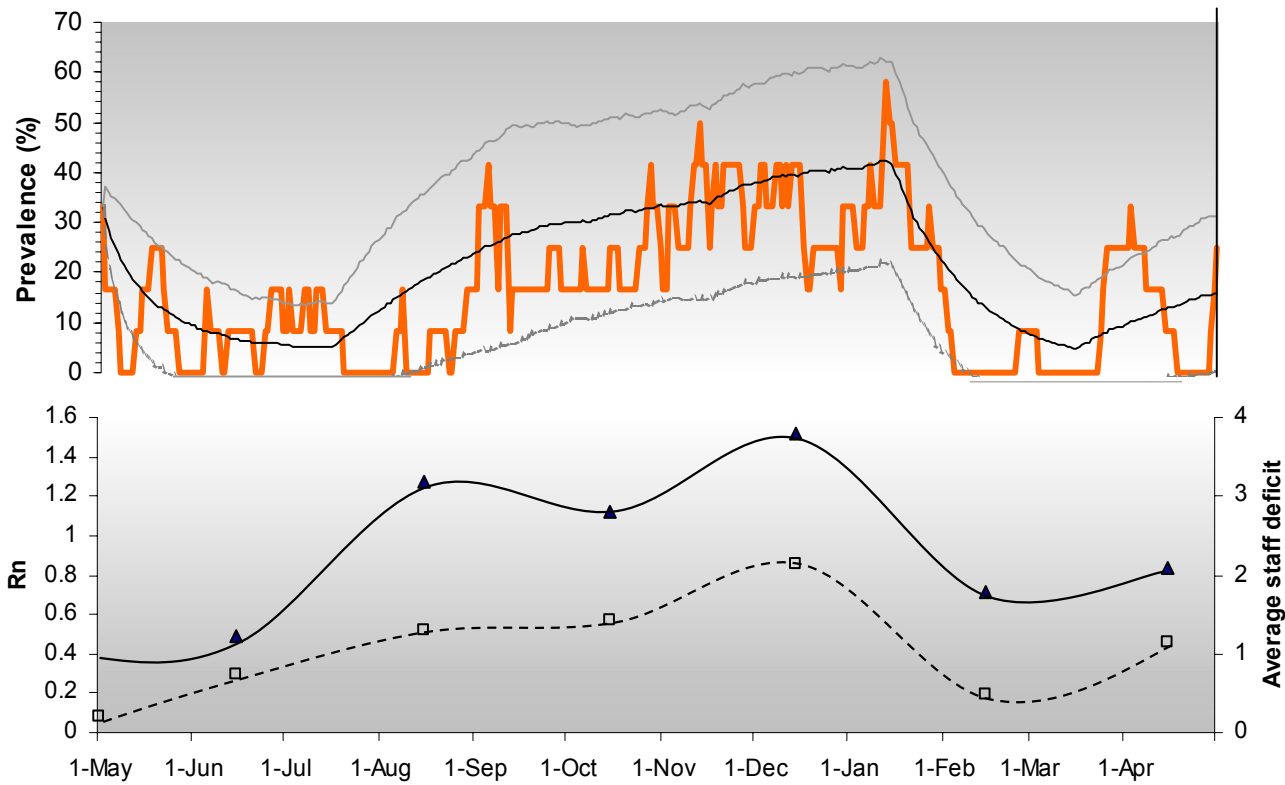
## Observed Prevalence with Model Predictions



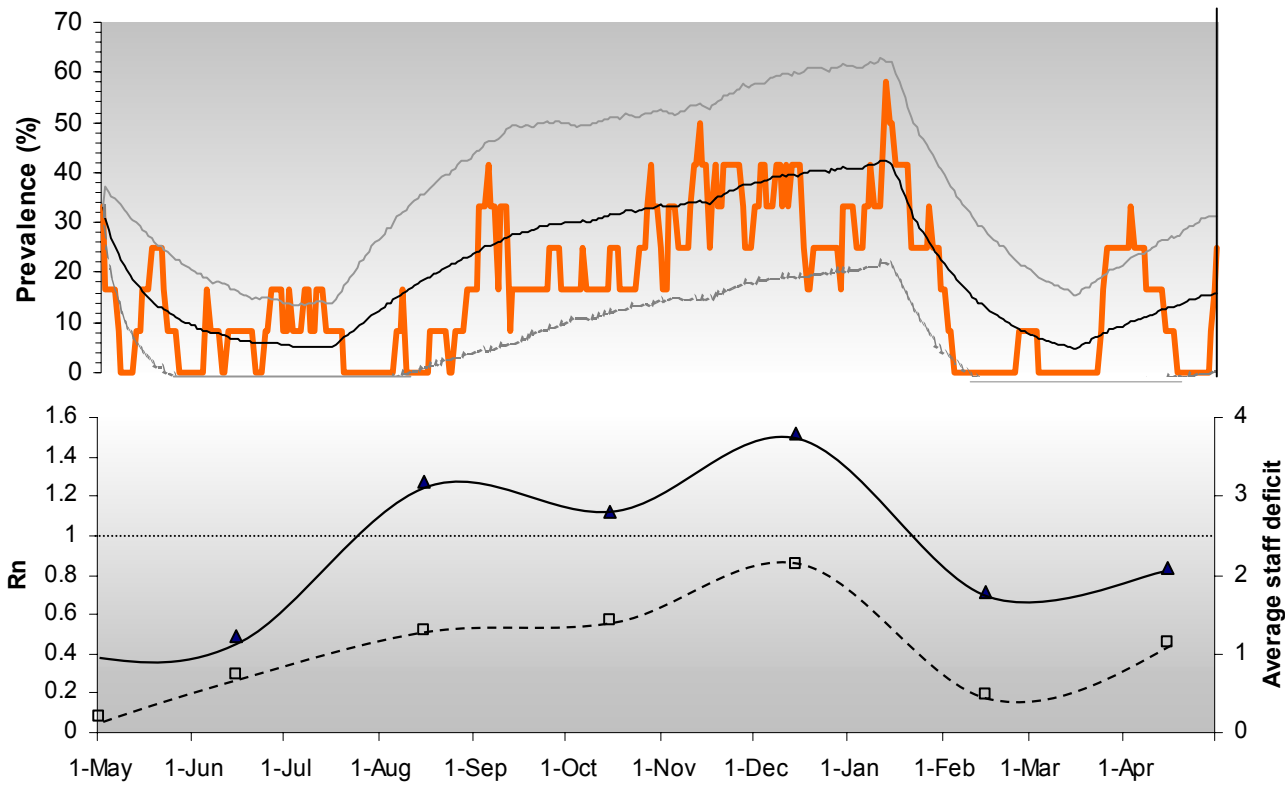
## Observed Prevalence with Model Predictions



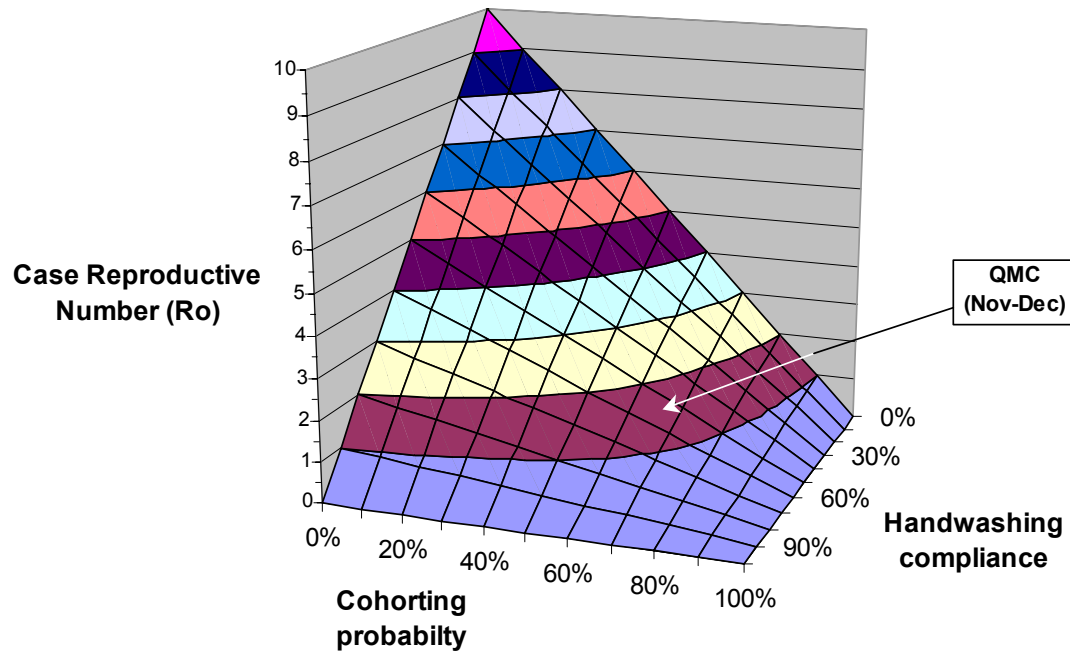
## Observed Prevalence with Model Predictions



## Observed Prevalence with Model Predictions



## MRSA in Adult Intensive Care Unit

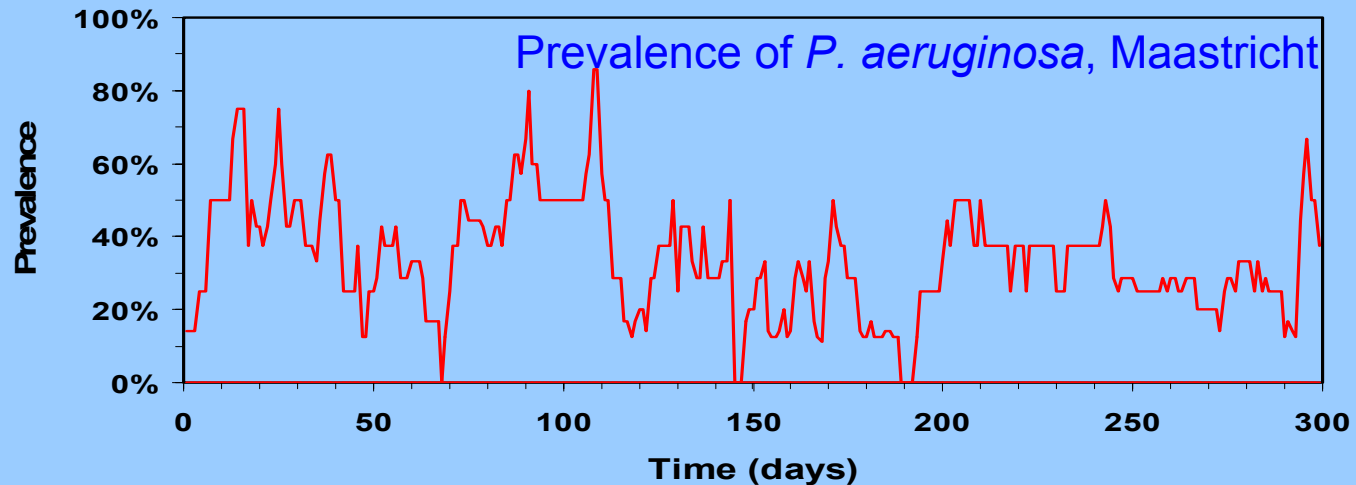
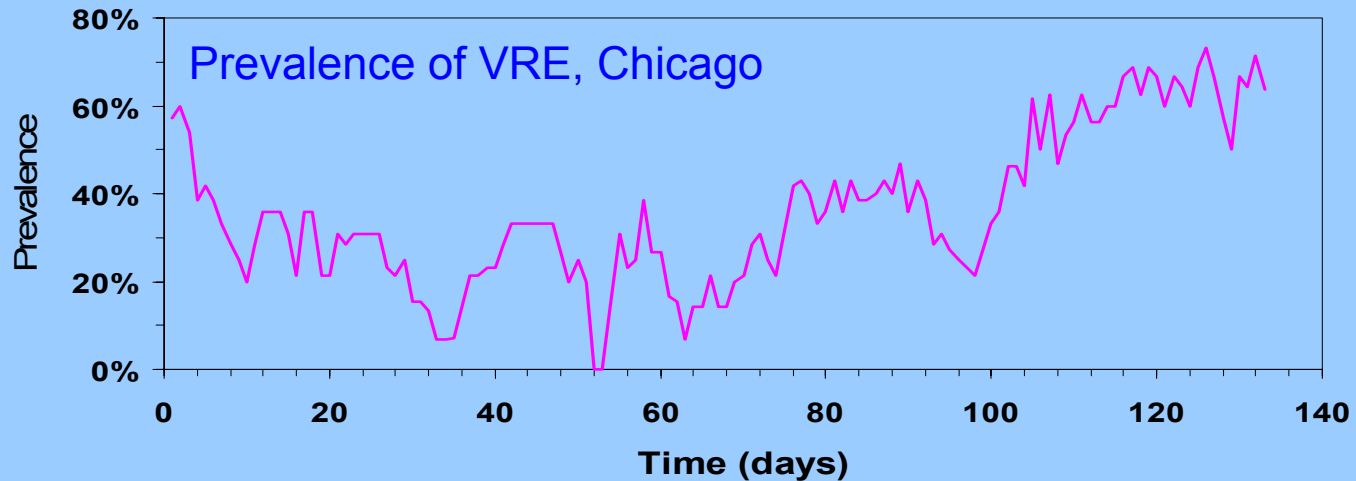


Can we predict the relative importance of endogenous and exogenous colonization routes without the need of genotyping?

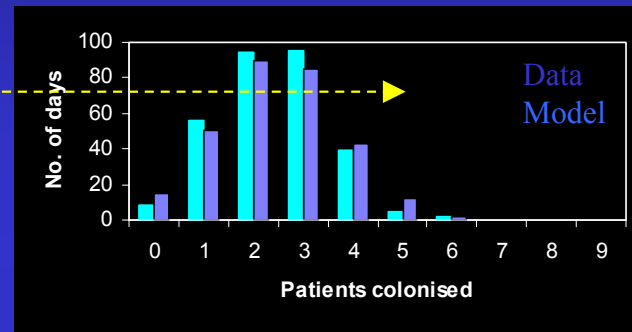
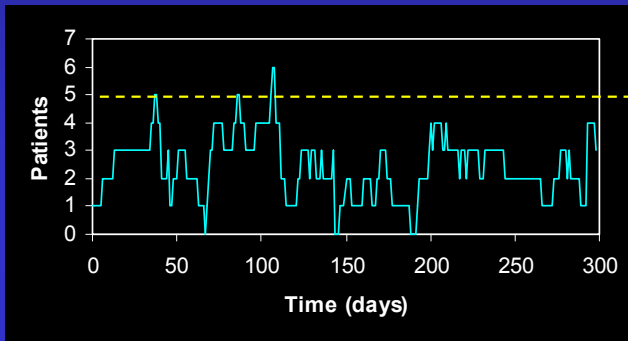
# Characteristic dynamics of endemic nosocomial colonisation

- Fluctuations are determined by the size of the ICU
- How does pathogen acquisition route influence fluctuations?
- Can any epidemiologically important information be gained from the magnitude of the fluctuations?

# Natural history of antibiotic resistance in ICUs



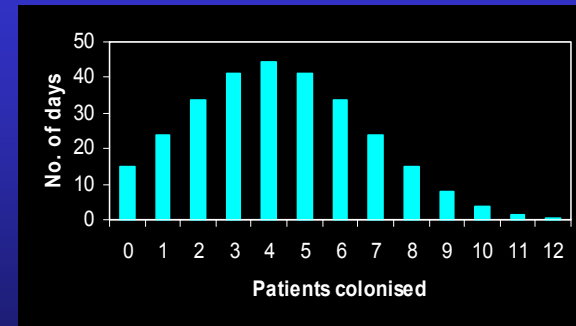
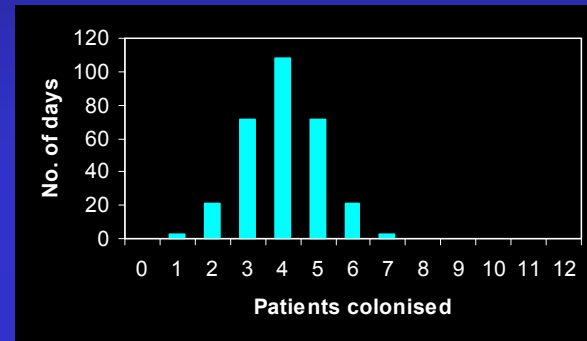
# Histogram of patients colonised



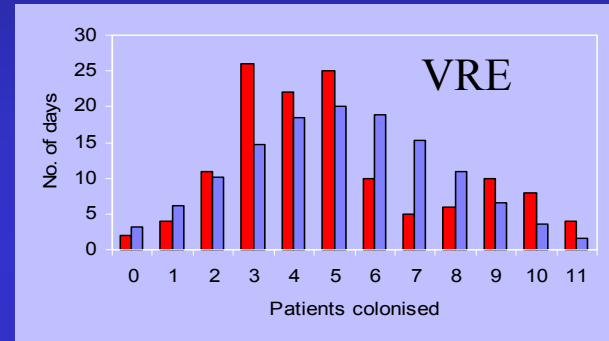
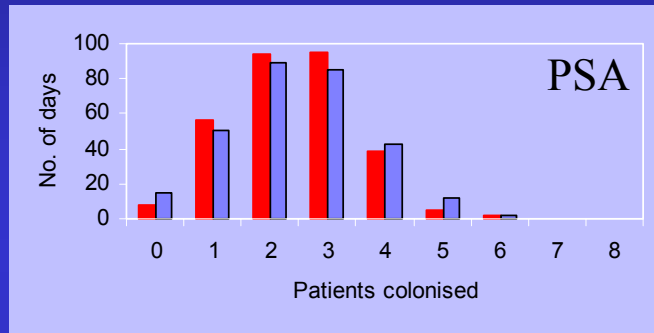
- Number of days with  $n$  patients colonised
- Simplified theory provides prediction of both mean AND variance

# Dispersion is a measure of fluctuations

- Random fluctuations  
Variance = Mean
- *Under-dispersed*  
Variance < Mean
- *Over-dispersed*  
Variance > Mean



# Dispersion characterises pathogen acquisition route

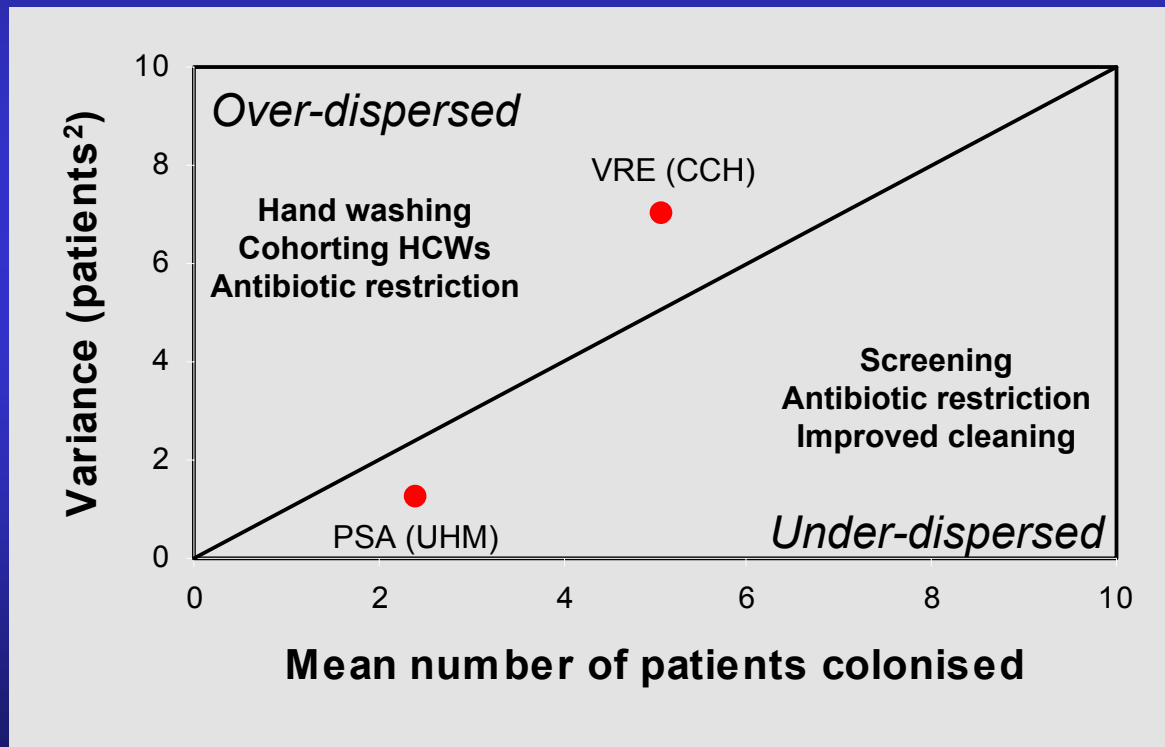


- *Under-dispersion* results from endogenous or environmental acquisition and colonised admissions (=linear processes)
- *Over-dispersion* is ALWAYS characteristic of nosocomial cross-transmission (=non-linear process)

## Characteristics of endemic colonization in 2 ICUs

	Maastricht <i>P. aeruginosa</i>	Chicago VRE
No. of beds in ICU	8	16
Mean endemic prevalence	35%	36%
Mean no of patients in ICU	7.2	14
Mean no of patients colonized	2.4	5.1
Variance	1.2	7.0
Coefficient of variance (SE/mean)	0.46	0.52
Variance / mean	0.5	1.37

# Infection control practices can be targeted using routine surveillance data



# Markov chain description to determine relative importance of different transmission routes

I.Pelupessy et al. PNAS 2002

- Non-colonized patient replaced by colonized patient
  - Colonized patient replaced by non-colonized
  - Non-colonized patient acquires colonization spontaneously
  - Non-colonized patient acquires colonization via cross-transmission
- 
- spontaneous colonization rate
  - “de-colonization” rate
  - transmission rate

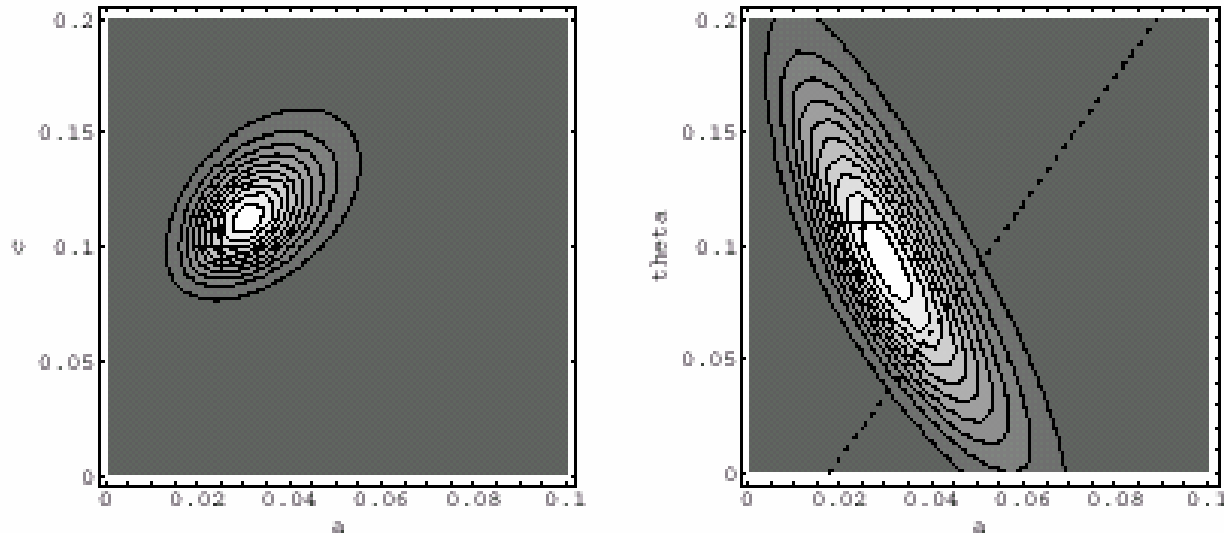
## Input

number of beds in ICU  
number of patients admitted  
number of patients colonized on admission  
number of patients with acquired colonization  
day of acquisition  
length of stay colonized patients  
length of stay non-colonized patients

## Output

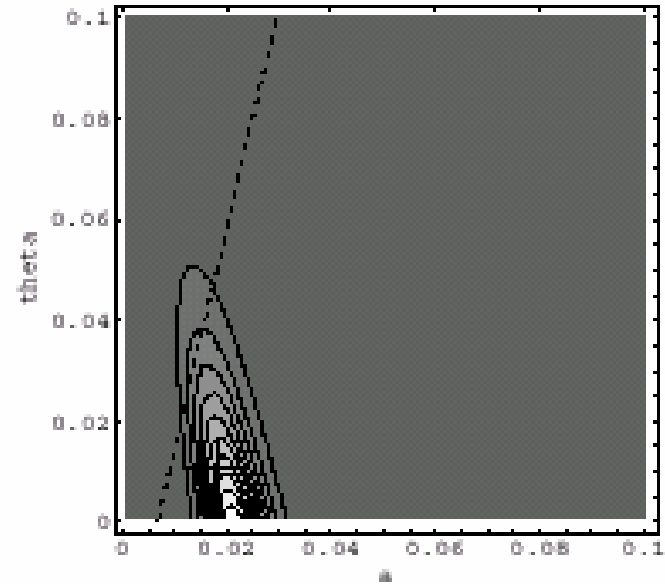
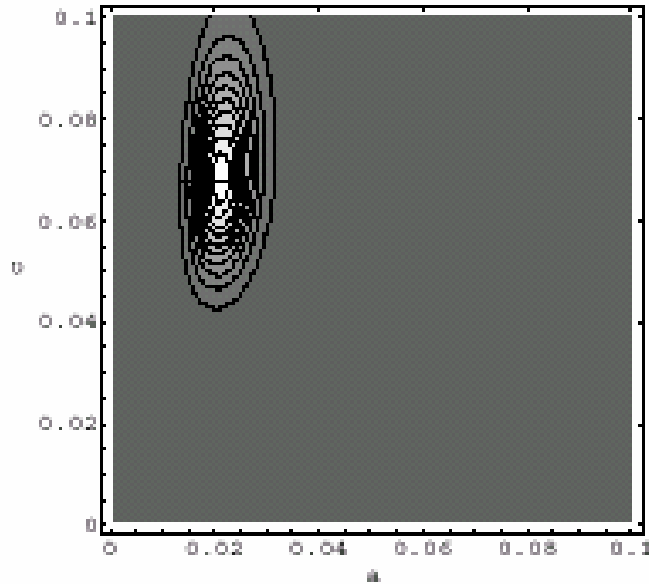
decolonization rate	$c$
endogenous colonization rate	$a$
exogenous colonization rate	$\theta$

## Endemicity of vancomycin-resistant enterococci



Contourplots of  $P_{\text{obs}}$  of  $a$ - $c$  and  $a$ - $\theta$  slices of parameter space at  $\theta=0.91$  and  $c=0.113$ , respectively. The dotted line indicates where spontaneous colonization and transmission are equally important

# Endemicity of *Pseudomonas aeruginosa*



Contourplots of  $P_{\text{obs}}$  of  $a$ - $c$  and  $a$ - $\theta$  slices of parameter space at  $\theta=0.001$  and  $c=0.069$ , respectively. The dotted line indicates where spontaneous colonization and transmission are equally important

# Colonization Dynamics of Third-Generation Cephalosporin-resistant Enterobacteriaceae (CRE) in two ICU settings



S. Nijssen<sup>1</sup>, M. Bootsma<sup>1,3</sup>, I.M. Hoepelman,<sup>1,2</sup> M. Bonten<sup>1,2</sup>

University Medical Center Utrecht

<sup>1</sup>Dept of Medicine, Div. Acute Internal Medicine & Infectious Diseases

<sup>2</sup>Eijkman Winkler Institute for Microbiology & Infectious Diseases

<sup>3</sup>Department of Mathematics Utrecht, The Netherlands

# Results: colonization CRE

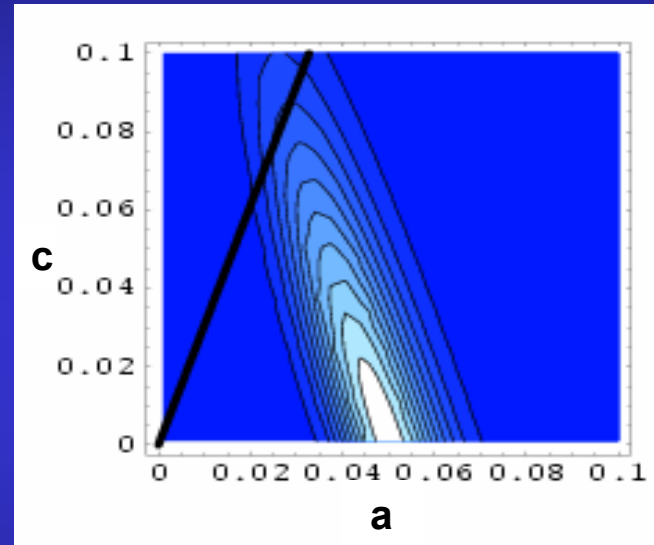
	<u>MICU</u>	<u>NSICU</u>	<i>P</i>
Patients with CRE colonization	25%	29%	ns
Colonization on admission	12%	13%	ns
Acquired colonization	13%	16%	ns
Acquisition rate/ 1000 patient -days	22	25	ns
Mean time to acquisition (days)	9	10	ns
Mean endemic prevalence (range) *	24% (0-67)	20% (0-60)	ns

\* Mean daily proportion of patients colonized with CRE

Therefore: ICUs were considered identical

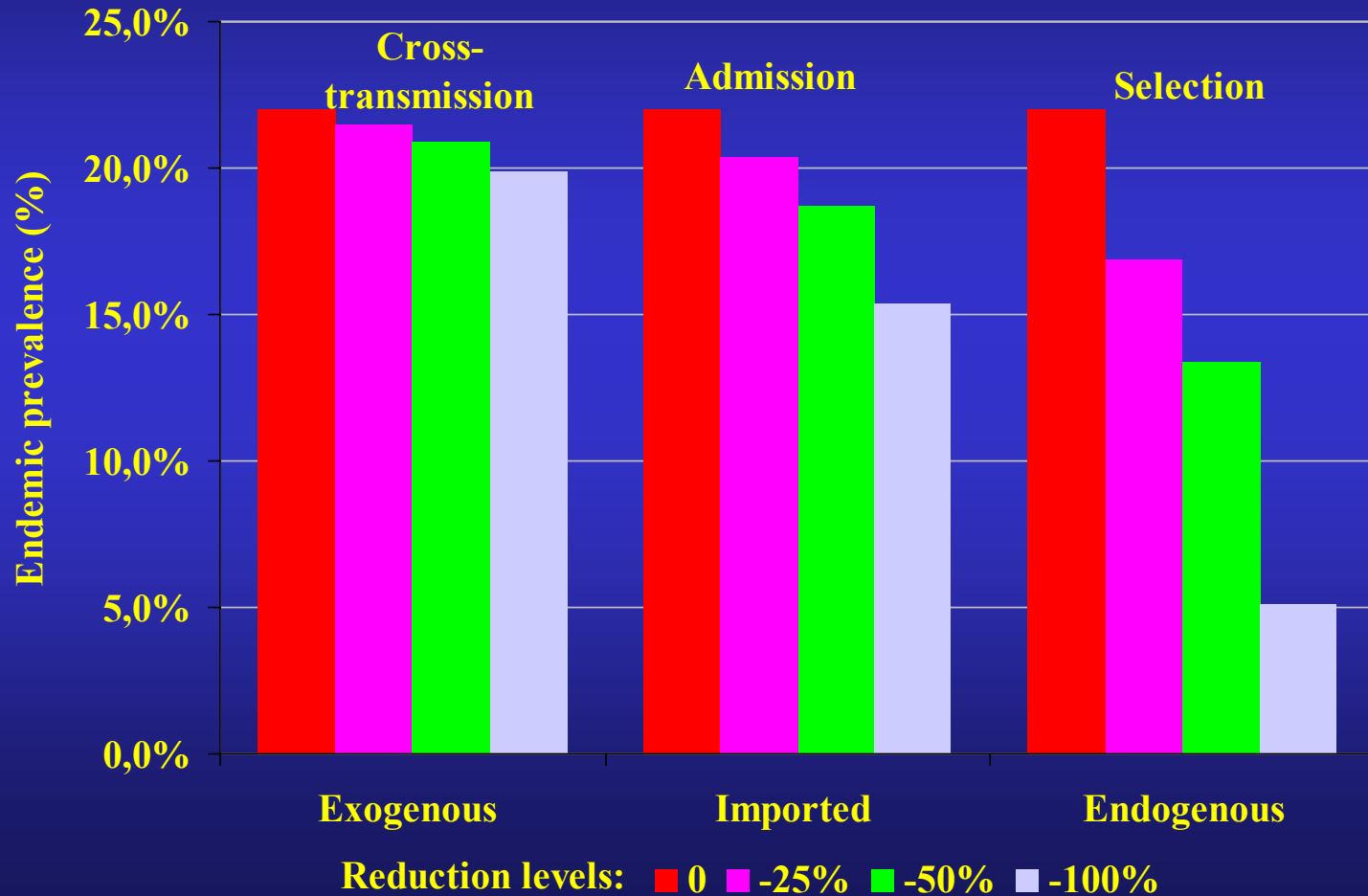
# Colonization routes of CRE

Model estimates of endogenous (a) and exogenous (c) colonization rates and determination of maximum likelihood estimate fits to the model



Interpretation: Colonization with CRE is predominantly acquired by the endogenous colonization route ( $\pm 80\%$  of acquisitions)

# Estimated changes in endemic prevalence according to model predictions



## The future of mathematical modeling of antibiotic resistance within hospital settings

- Provide a theoretical basis for interventions to control spread of microorganisms, which can be subjected to empirical testing
- Provide tools for analysis of large databases
- Develop models of within-host dynamics
- Develop statistical tools for analysis

# Acknowledgements

## UMC Utrecht

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Martin Bootsma

Inti Pelupessy

## RIVM, Bilthoven

Hajo Grundmann

## AZ Maastricht

Ellen Stobberingh

## Imperial College London

Daren Austin

Roy Anderson

# Inherent Variability of 10 ICU Outbreaks

ICU  
beds



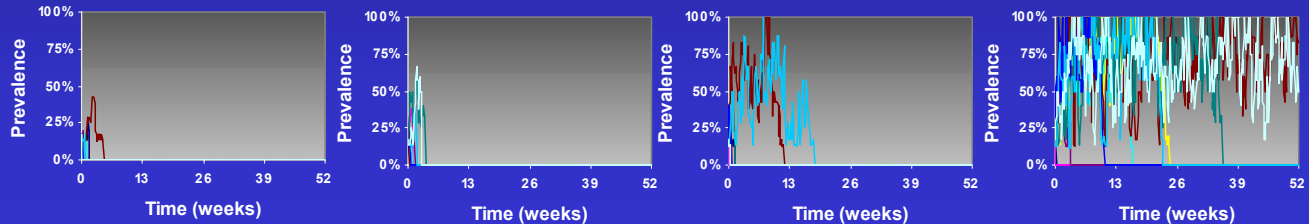
$R_0 = 0.5$

$R_0 = 1$

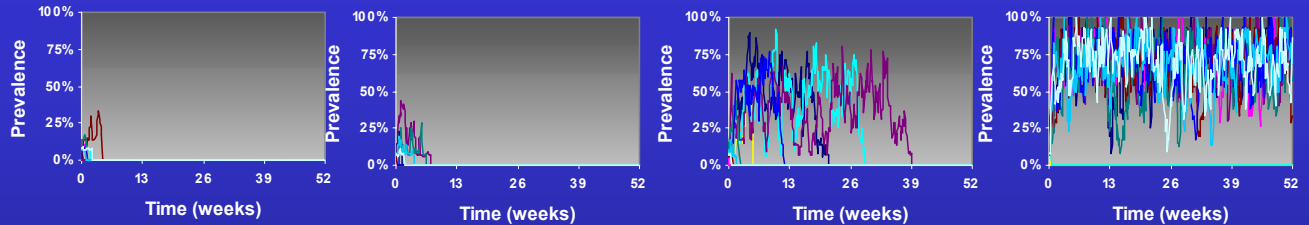
$R_0 = 2$

$R_0 = 4$

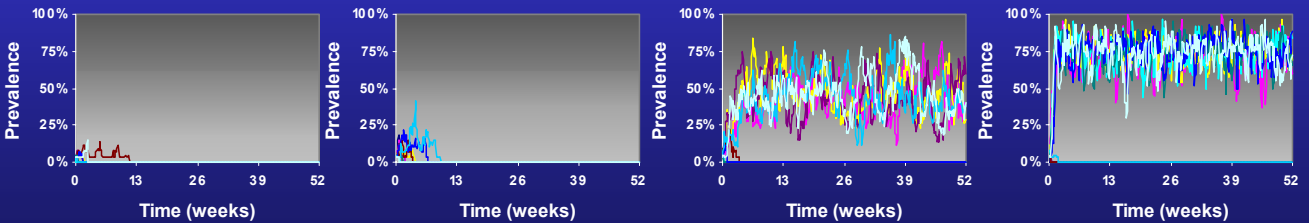
8



16



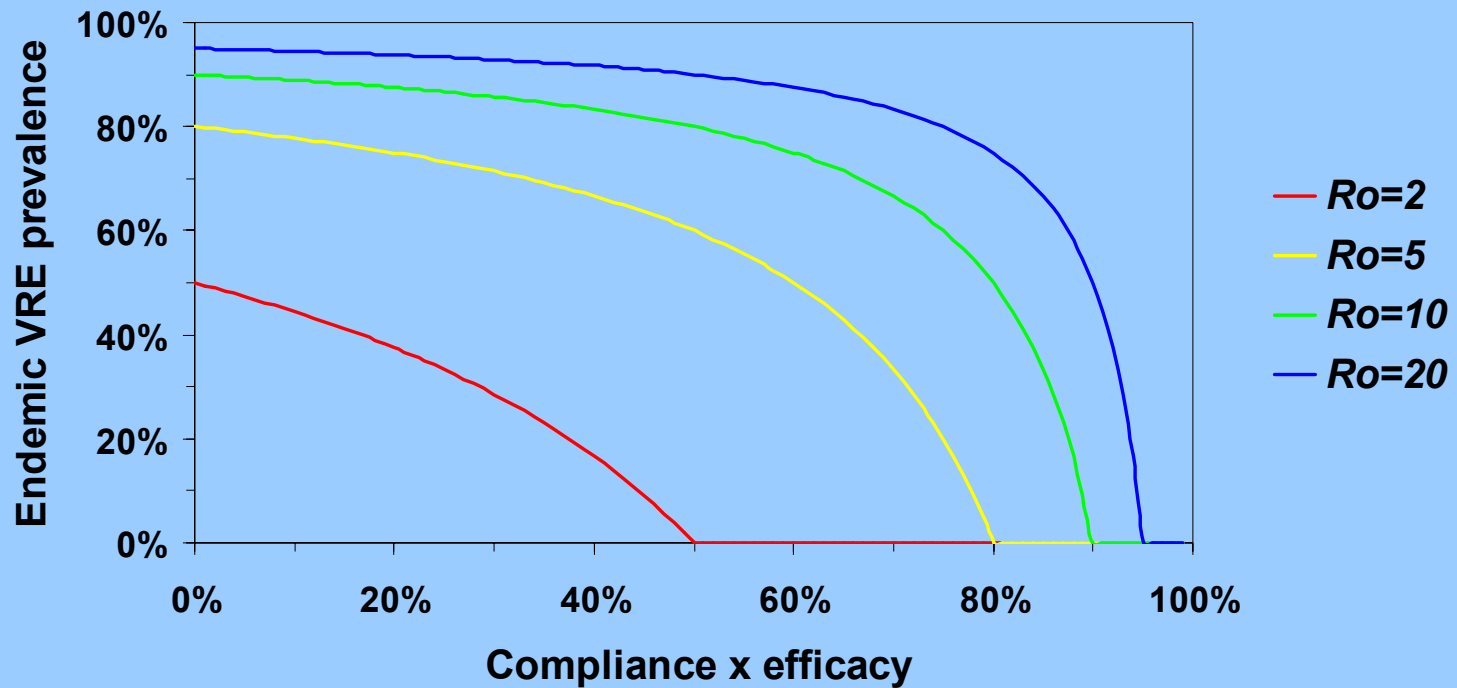
32



## Infection control replaces $R_0$ with and *effective* reproductive number $R$

- Changing staffing levels:  $\alpha R_0$  or  $R_0/\alpha$
- Hand-disinfection:  $R_0 (1-p)$
- Staff cohorting:  $R_0 (1 - q)$
- Antibiotic restriction  $R_0 (1-a + ar)$
- Control of transmission requires  $R < 1$

# Hand disinfection alone may not eradicate pathogens



### MRSA+ve patients in a 12-bed AICU May 98 - April 99

