Three aspects of the spread of antibiotic resistance: hospital re-entry, multiple acquisition routes, multiple colonization sites.

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Data driven multi level models of infectious diseases

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Background

- Antibiotic resistance of micro organisms is emerging worldwide
- driven by the spread of micro organisms and resistance genes
- fuelled by the use of antibiotics.

- Data on prevalence and incidence are abundant.
- But how to base sound conclusions,
  -e.g. effectiveness of various control measures, on these data ?

Traditional multivariate risk factor analyses neglect that
cross transmission creates dependence among individuals.

We focus on a mechanistic description of pathogen transmission
 - i.e., explicit model for the spread

People involved

- Prof. Odo Diekmann MI
- Prof. Marc Bonten UMCU
- Barbara Boldin MI (PhD-student)
- Slavik Koval MI (PhD-student)

-Website: http://www.math.uu.nl/people/boldin/nwo/

Outline of the talk

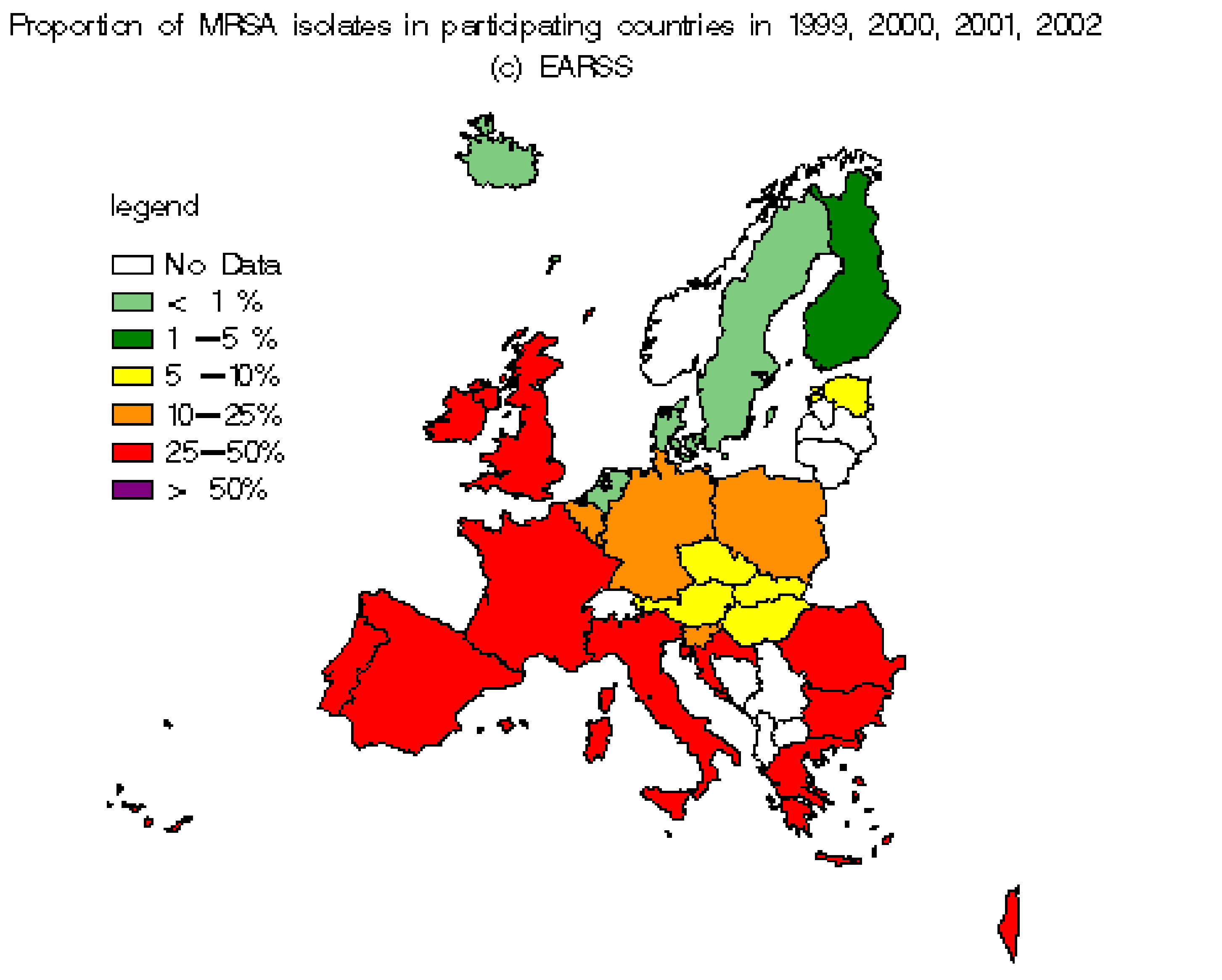
- Part 1: hospital re-entry
- Part 2: multiple acquisition routes
- Part 3: multiple colonization sites

Part 1: hospital re-entry

- Aim: Determine the effect of various control measures
- Species in mind: MRSA (Methicillin-resistant *Staphylococcus aureus*)
- Colonization vs. Infection

Publication: Controlling MRSA: Quantifying the effects of interventions and rapid diagnostic testing. M. Bootsma, O. Diekmann, M. Bonten. Proceedings of the National Academy of Sciences USA 2006;103;5620-5

MRSA in Europe



The Dutch Search & Destroy policy

I Identified carriers are isolated

II High-risk patients are screened on admission and precautiously isolated

III Unexpected case of MRSA -> screening of contact patients

IV Evidence of MRSA-transmission -> ward closed

V Unexpected case of MRSA -> screening of health care workers

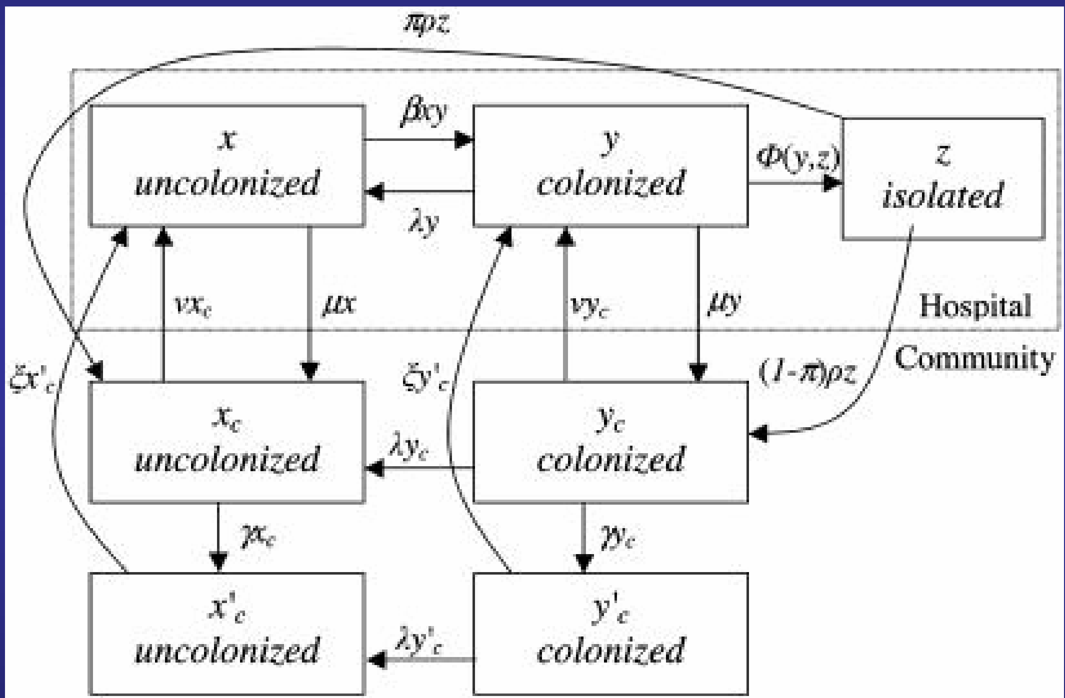
VI Decolonization of carriers

Disadvantages of search and destroy

- Costly
  - Materials
  - Admission capacity
- Possibly reducing quality of patient care

So, how effective are the individual components?

Readmission essential



$$\frac{dy}{dt} = \beta xy - \lambda y + \nu y_c + \xi y'_c - \mu y - \Phi(y, z)$$

$$\frac{dx}{dt} = -\beta xy + \lambda y + \nu x_c + \xi x'_c$$

$$\frac{dz}{dt} = \Phi(y, z)y - \rho z$$

$$\frac{dy_c}{dt} = \mu y + \rho(1 - \pi)z - (\nu + \lambda + \gamma)y_c$$

$$\frac{dx_c}{dt} = \mu x + \lambda y_c + \rho \pi z - (\nu + \gamma)x_c$$

$$\frac{dy'_c}{dt} = \gamma y_c - (\xi + \lambda)y'_c$$

$$\frac{dx'_c}{dt} = \gamma x_c + \lambda y'_c - (\xi + \lambda)x'_c.$$

B. S. Cooper et al. (2004) PNAS 101, 10223-10228

Basic reproduction number

R_0 : the average number of infections by the first infectious case during the entire infectious period when s/he enters a totally susceptible population in the absence of interventions

$R_0>1$	$R_0<1$
Disease can spread	Disease cannot spread

R_A : the average number of secondary infectious cases directly infected by a single infectious case during a single hospitalization in the absence of interventions

$R_0>R_A$

MRSA: $R_A<1$, $R_0>1$

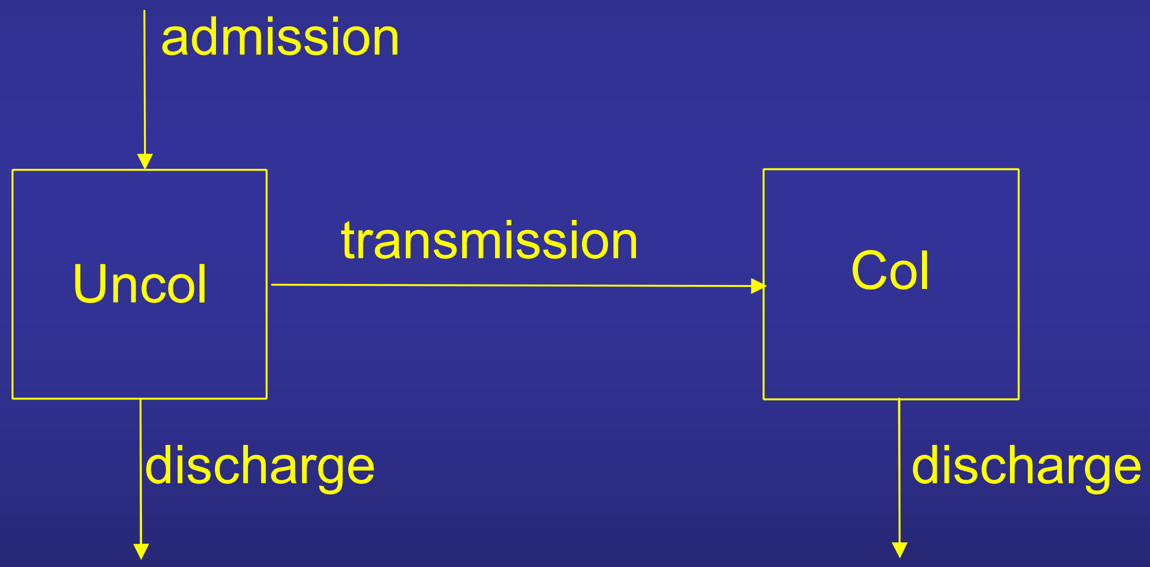
Aim of infection control: Reduce $R_0>1$ to $R_E<1$

Contents

- 2 Models :
  - -stochastic simulation model (see article for details)
  - -analytical model

Analytical model

Transmission within units (mass action)



Calculate the expected number of acquisitions within a unit
(depends on LOS, interventions,….)

Method of analysis

Calculate expected number of acquisitions outside the initial unit (depends on number of acquisitions within the unit)->
Expected outbreak size in hospital: T

Readmission

When $T < \infty$, readmission essential for persistence.

To persist (both extramural and intramural), $T > T_c$ (critical outbreak size), T_c depends on readmission rate.

T_c is related to a critical transmission parameter and a critical basic reproduction ratio R_0^c.

Analytical model

- Using multiple ward structure in hospital
- Effects of individual components of S&D are expressed as the critical basic reproduction ratio - R_0^c -, which represents the maximum value for R_0 for which an MRSA-epidemic can be prevented
- Efficacy of prevention measures increases with raising values of R_0^c
- In each graph, one parameter is gradually changed, to determine the relative effects of individual parameters
- Based on longitudinal nosocomial prevalence data of MRSA the basic reproduction number (R_0) has been estimated between 1.2 and 1.3 [1,2]

[1] Cooper B.S., Medley G.F., Stone S.P., Kibbler C.C., Cookson B.D., Roberts J.A., Duckworth G., Lai R., Ebrahim S. (2004) Proc Natl Acad Sci USA **101(27)**, 10223–10228.

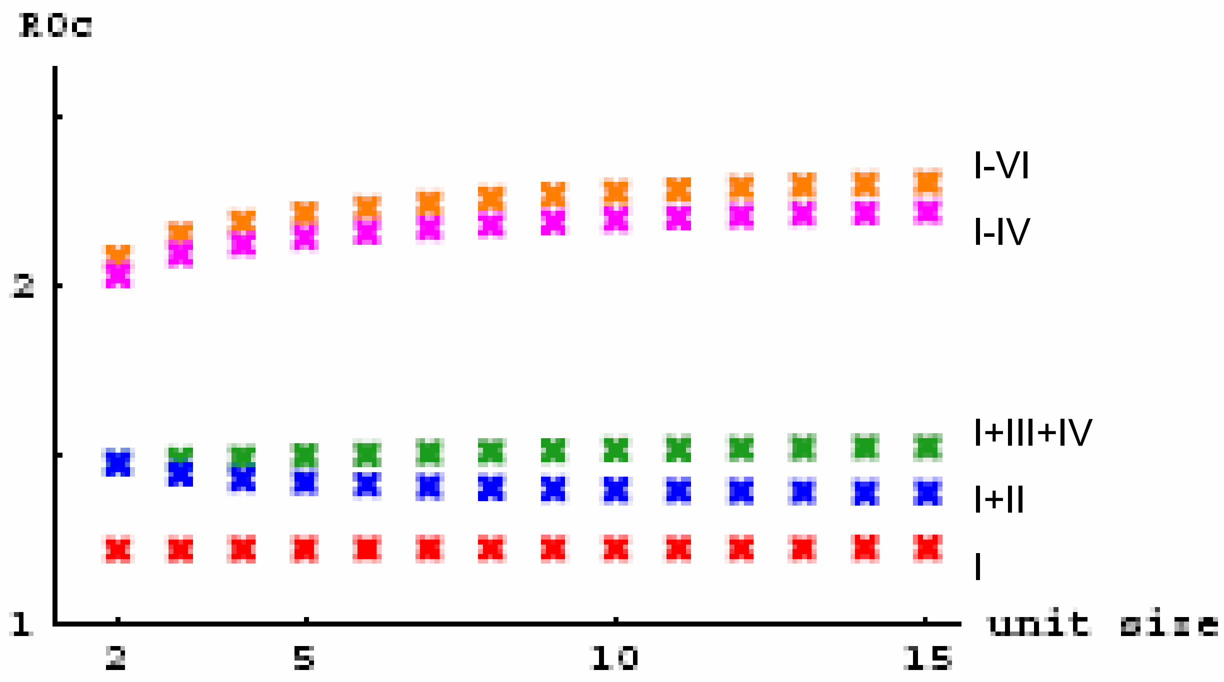
[2] Bootsma M.C.J.. (2005) Mathematical studies of the dynamics of antibiotic resistance, PhD thesis, Utrecht University, http://igiturarchive.library.uu.nl/dissertations/2005-0526-201427/.

Results analytical model

- The critical basic reproduction number (R_0^c) for MRSA is:
  - 1.2 for I
  - 1.4 for I+II
  - 1.5 for I+III+IV
  - 2.2 for I+II+III+IV
  - 2.3 for I+II+III+IV+VI

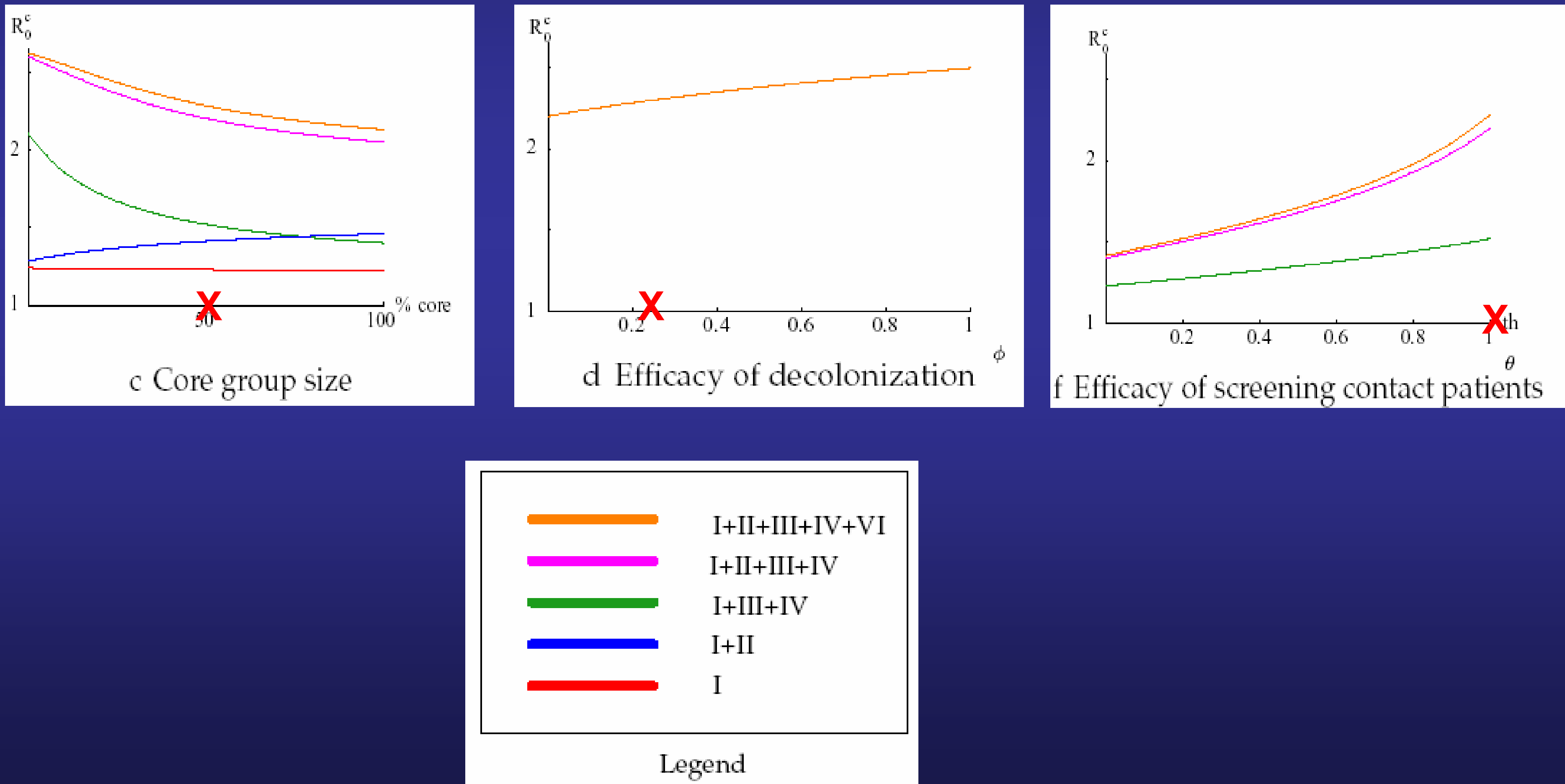
I	Identified carriers are isolated
II	High-risk patients screened on admission and preventively isolated
III	Unexpected case of MRSA -> screening of contact patients
IV	Evidence of MRSA-transmission -> ward closed
V	Unexpected case of MRSA -> screening of health care workers
VI	Decolonization of carriers

Sensitivity analysis

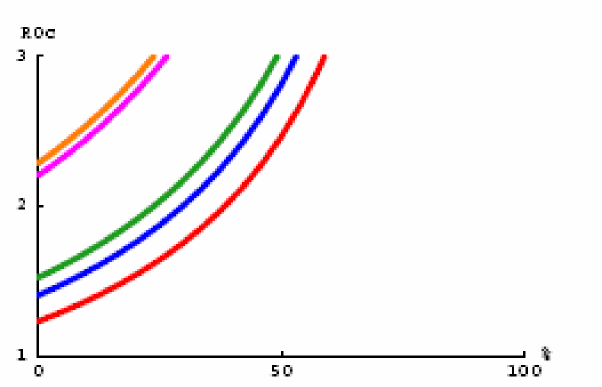


a Unit size

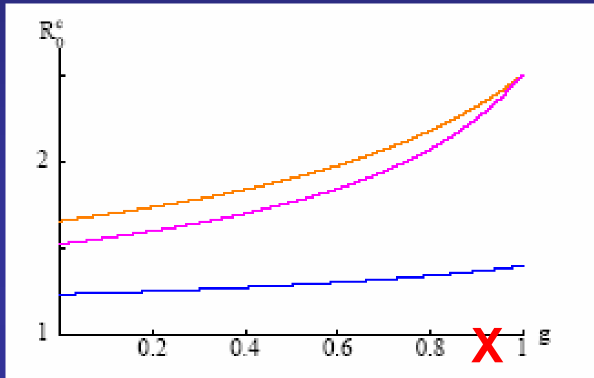
Sensitivity analysis of some other variables



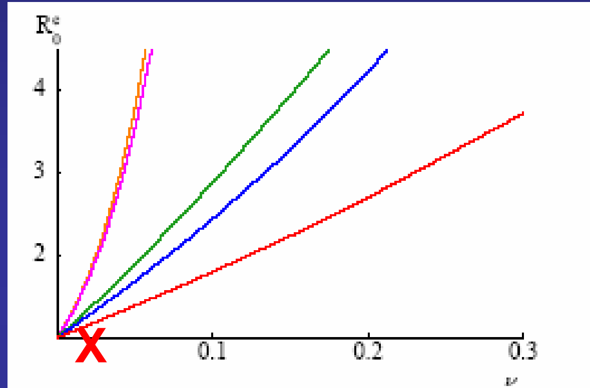
Improving hand hygiene and surveillance can markedly improve efficacy



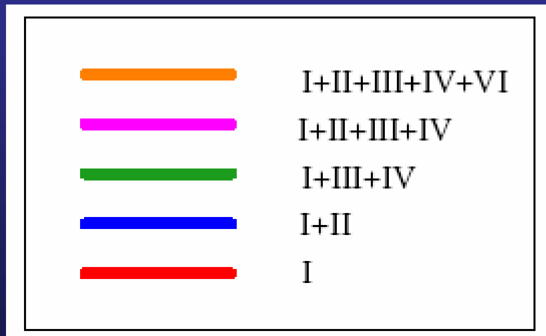
b Effect improvement hand hygiene



e Efficacy of screening high-risk patients on admission



h detection rate of hospitalized patients



Legend

Conclusions

- Isolation of MRSA-carriers as identified upon clinical cultures is insufficient to control MRSA
- Combined approach of measures necessary to control MRSA
- Results of interventions are most sensitive to detection of carriers (*e.g.*, active surveillance) and improved hand hygiene

Open problems and weakness

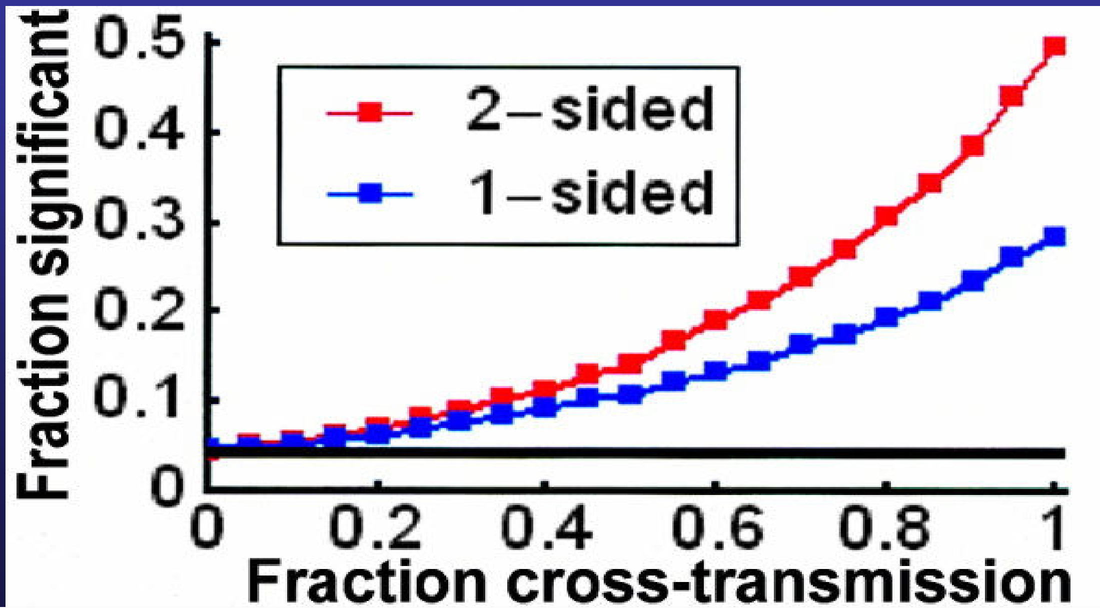
- How are the results affected by incorporating more detailed structure?
- Importance persistently colonized HCW?
- What if CA-MRSA becomes more important?
  - Effect interventions in hospitals
  - Effect contact tracing in extramural population
- Effect various rapid diagnostic tests (only partially discussed in article).

Part 2: Multiple acquisition routes

- Effective strategies to prevent spread required
- Efficacy depending on nature of spread
- Identification of the important of each route relevant
- Transmission
  - Improving hand hygiene
  - Gloves, gowns
  - Treatment of colonized patients in isolation rooms
- Outgrowth of pre-existing bacteria or de novo resistance
  - Change policy when to use antimicrobial agents

How to analyze effect of an intervention when cross-transmission is relevant?

- 100,000 simulations of an ICU during 1 year
- 5% colonized on admission
- Transmission parameters such that prevalence 20%
- After 6 months an intervention without any effect
- Perform before-after analysis with χ^2-test with p=0.05



Aim

On the basis of available data: determine the importance of each acquisition routes

Setting

- Typical small patient populations in ICU’s (<20)
- Rapid turnover of patients
- Large natural fluctuations

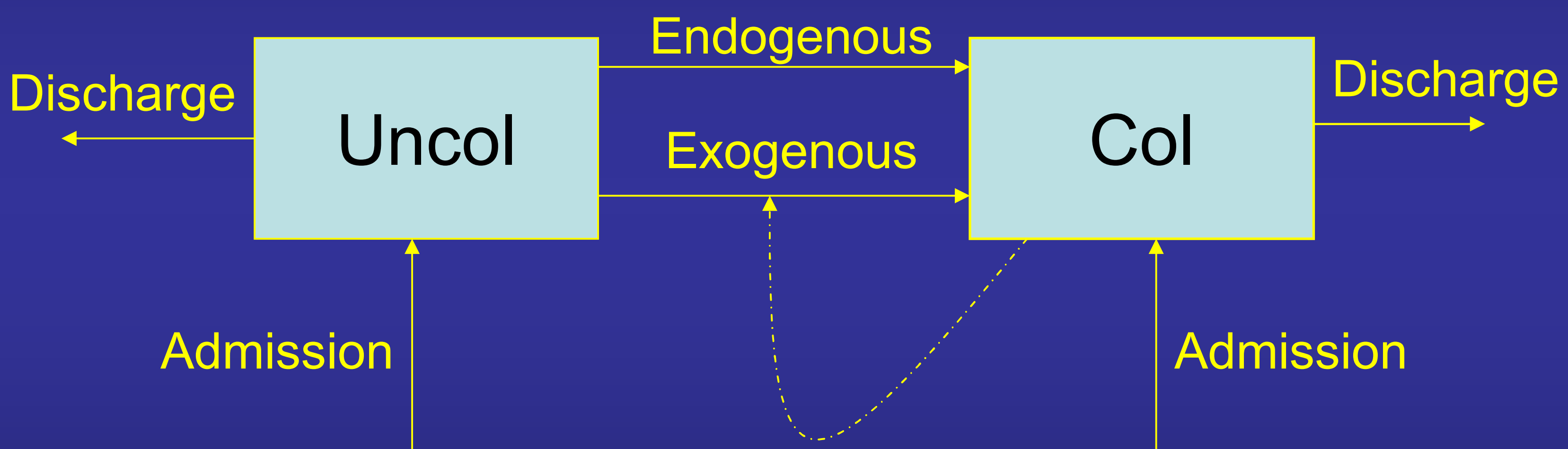
Standard way to differentiate between infection routes: Genotyping

- Time-consuming
- Expensive (not feasible in the developing world)
- Not routinely available
- How to define relatedness between strains?
- Are related strains the result of transmission within the unit or at another unit?
- and: How to calculate confidence intervals for the relative importance of each route?

Can a mathematical model help?

- Low number of patients in hospital settings → Markov chain
- hosts are either colonised or ”free of colonization” (In Part 3, multiple colonization sites)

Mechanistic model:



•Transmission (exogenous): force of infection ~ $\beta I/N$
  -via temporarily colonized health care workers
•Endogenous: constant force of infection ~ α
  -mutations, i.e., de novo resistance
  -selection of resistant flora
•Colonization persistent during stay

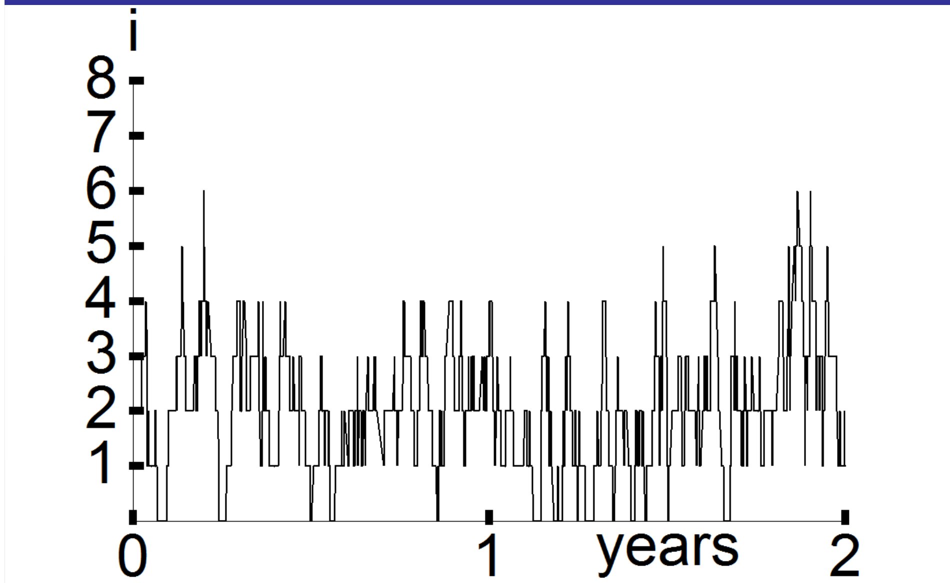
Aim: Estimate parameters α and β

- Advantage: If model is an accurate description, analysis can be done while taking dependency in the correct way into account
- Disadvantage: If mechanistic model is incorrect, fitting the data to the model is useless.
- Goodness of fit testing

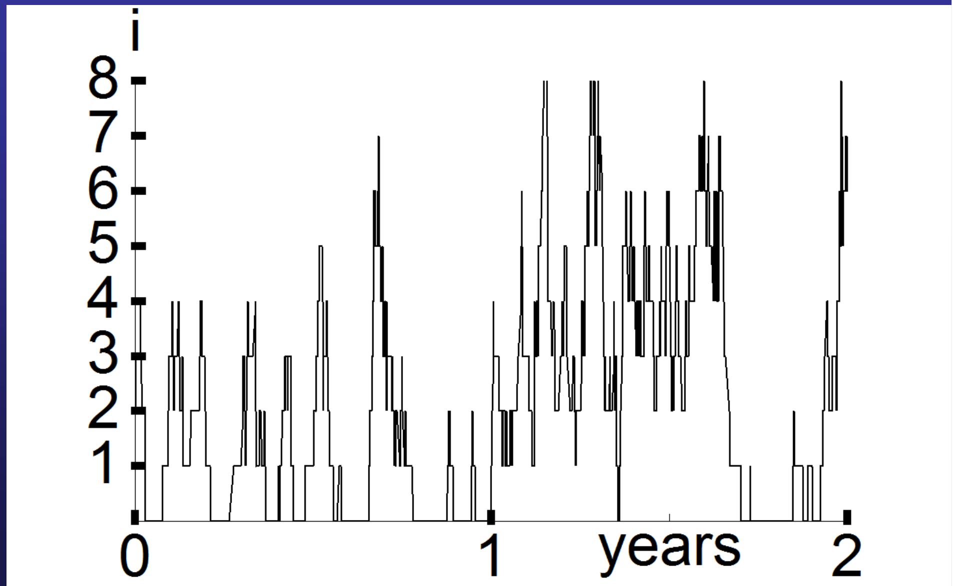
Based on fluctuations in the prevalence

- 2 simulations:
- Prevalence 20%
- 5% positive on admission
- Mean duration of stay: 8 days
- 10 beds (always occupied)

Only endogenous selection



Only cross transmission



Basic Idea: Model of Pelupessy et al.

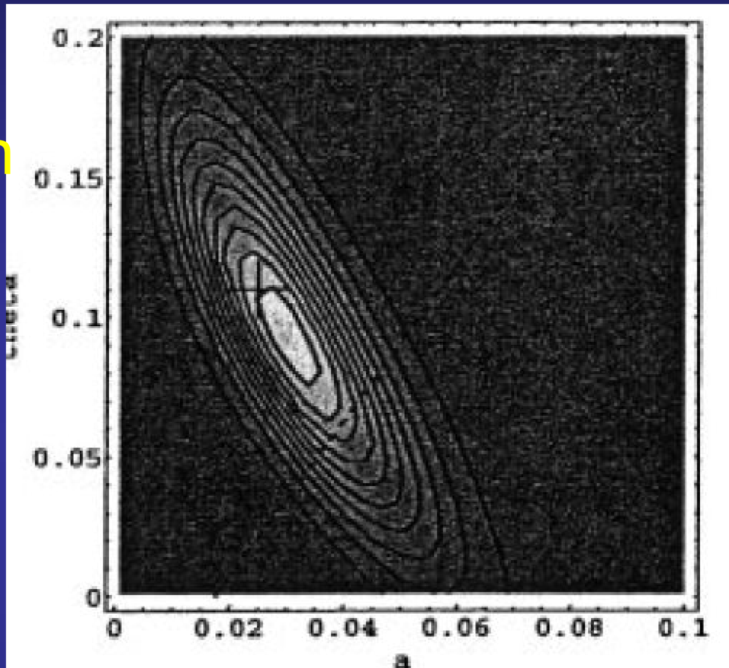
- Data: Number of colonized patients per day
- Calculate Likelihood transition from x colonized patients at day t to y colonized patients at day $t+1$.
- Likelihood period is product of relevant 1-day likelihoods.
- Maximum likelihood parameters:
  Those parameters for which the observed data are most likely

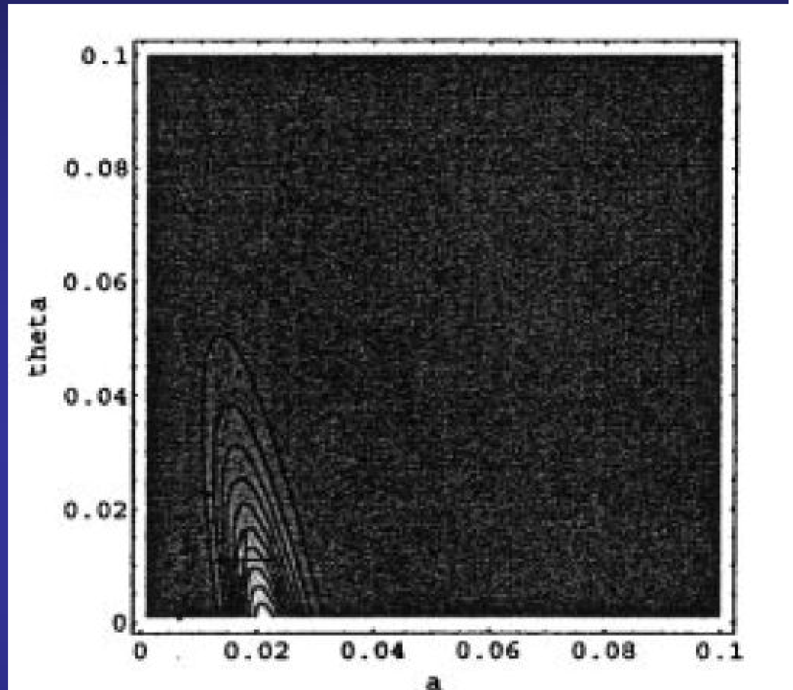
VRE

Pseudomonas aer.

Cross transmission

↑





→Endogenous route

Limitations

- Fixed number of beds
- Beds always occupied
- Constant discharge rate (calculated from data)
- Moment of culturing = moment of acquisition

probabilistic consideration of unobservable events (transmission) should not thwart the deterministic bookkeeping of known facts

- Incorporate known information:
  - duration of stay per patient
  - exact moments of culturing
  - results of the culturing
- Use a probabilistic description between culturing moments
- Individual patient characteristics can be used (e.g., antibiotic use)

Division period of stay

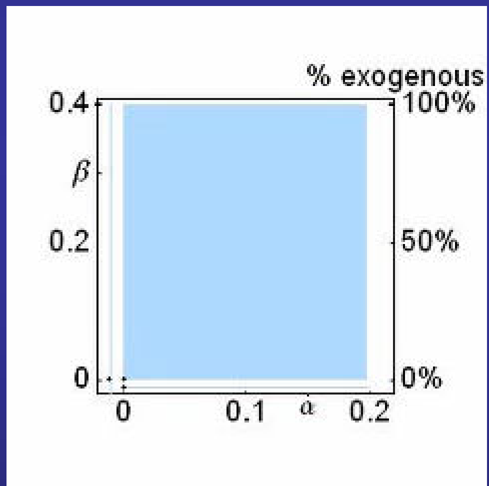
1. Patient is certainly uncolonized $[t_0, t_1]$
2. Patient may or may not be colonized $[t_1, t_2]$
3. Patient is certainly colonized $[t_2, t_e]$

'Average' over all moments of acquisition between t_1 and t_2 with weight depending on the parameters α and β.

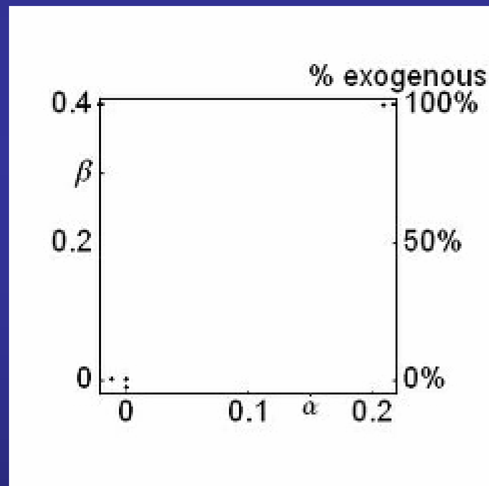
Reference: An Algorithm to Estimate the Importance of Bacterial Acquisition Routes in Hospital Settings. MCJ Bootsma, MJM Bonten, S Nijssen, AC Fluit, O. Diekmann. American Journal of Epidemiology. Accepted

Enterobacteriaceae resistant to 3rd generation cephalosporins in UMCU

8 month period



ICU-1



ICU-2

Relevant epidemiological quantities: relative importance of each route can be calculated with confidence interval

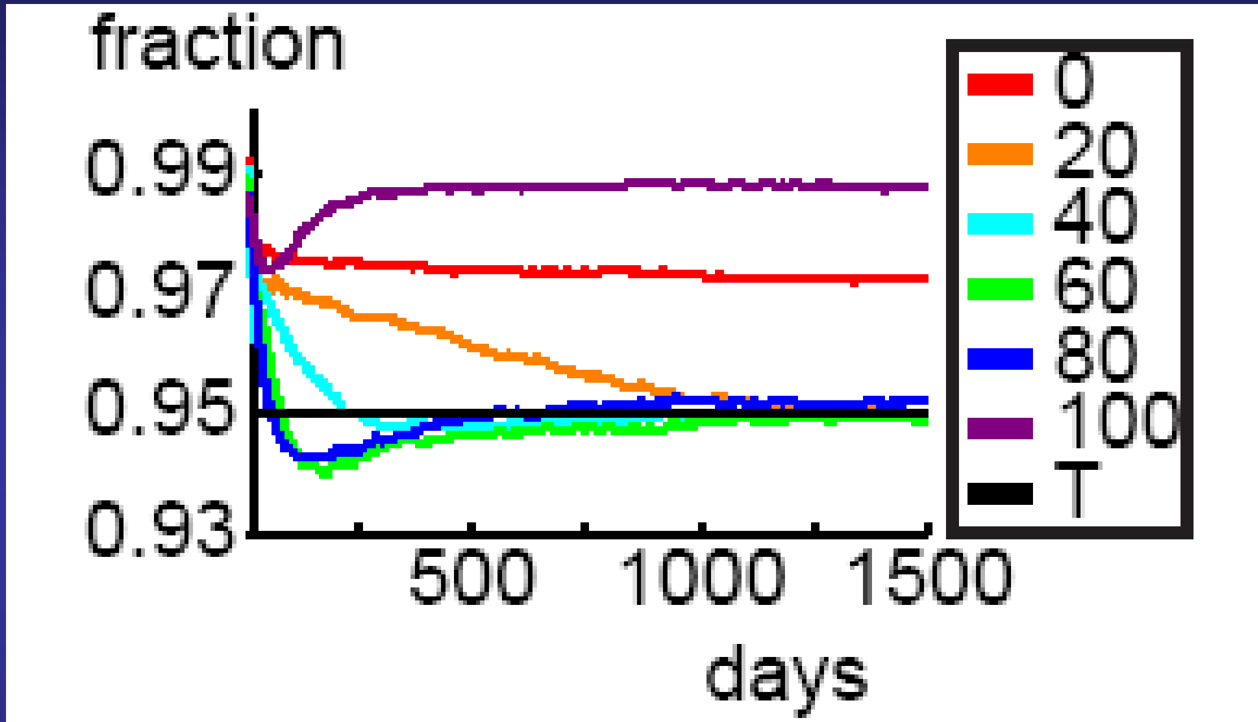
Likelihood ratio test

Be careful!

The method to calculate confidence sets

1. is only asymptotically correct (when the length of the study period approaches infinity)
2. breaks down when the true parameter values are on the boundary of the parameter domain.
3. Not aware of formal prove when dependency between patients is relevant

Fraction of simulations for which the true parameters are contained in the 95% confidence set obtained by our algorithm.



- only one transmission routes present: confidence sets are conservative
- otherwise 95% confidence sets cover the true parameter in 95% of the simulations when $t \to \infty$
- Finite study periods: Errors small

Other articles with same aim:

- I. Pelupessy, M.J.M. Bonten, O. Diekmann. How to assess the relative importance of different colonization routes of pathogens within hospital settings. Proc Natl Acad Sci USA 2002;99:5601–5.
- B. Cooper, M. Lipsitch. The analysis of hospital infection data using hidden markov models. Biostatistics 2004;5:223–37.
- M. Forrester, A.N. Pettitt. Use of stochastic epidemic modeling to quantify rates of colonization with methicillin-resistant Staphylococcus aureus in an intensive care unit. Infect Control Hosp Epidemiol 2005;26:598–606.
- M.L. Forrester, A.N. Pettitt, G.J. Gibson. Bayesian inference of hospital-acquired infectious diseases and control measures given imperfect surveillance data. Biostatistics (2006) doi:10.1093/biostatistics/kxl017.
- R.T. Mikolajczyk, U. Sagel, R. Bornemann et al. A statistical method for estimating the proportion of cases resulting from cross-transmission of multi-resistant pathogens in an intensive care unit. J Hosp Infect. 2007;65:149–155

Conclusions and remarks

- Method can distinguish between colonization routes purely on longitudinal data
- Results confirmed by genotyping in several studies
- Determining key epidemiological quantities, by taking different routes into account:
  e.g., number of acquisitions per infection route

Weaknesses

- Data should be of high quality, not routinely available
- colonization is assumed to remain until discharge,
- only a limited number of acquisition routes can be incorporated in the model
- Number of patient with unknown colonization status should not be <<10
- Sensitivity and Specificity of cultures 100%

Open problems

- How to incorporate antibiotic use?
  - How does it affect infectivity/susceptibility?
  - Is assumption about persistence of colonization valid when antibiotics are prescribed?
- What is the best way to incorporate variation in susceptibility and infectivity? Score of severity illness?
- Delay between acquisition of colonization and spread of colonization? (Slavik Koval)
- Formal proof of correctness likelihood ratio method

Part 3: Multiple colonization sites

- Based on:
  Relative Effects of Barrier Precautions and Topical Antibiotics on Nosocomial Bacterial Transmission: Results of Multi-Compartment Models.
  B Boldin, MJM Bonten, O. Diekmann.
  To appear in Bulletin of Mathematical Biology
- (e-mail boldin@math.uu.nl for preprints)

Multiple colonization sites:

- For many pathogens multiple colonization sites exists
  -skin, respiratory tract, intestines,blood….
- Internal and external compartments
- In ICUs: -Small number
  -High patient turnover
- Aim: What is effect of intervention measures e.g., SDD?

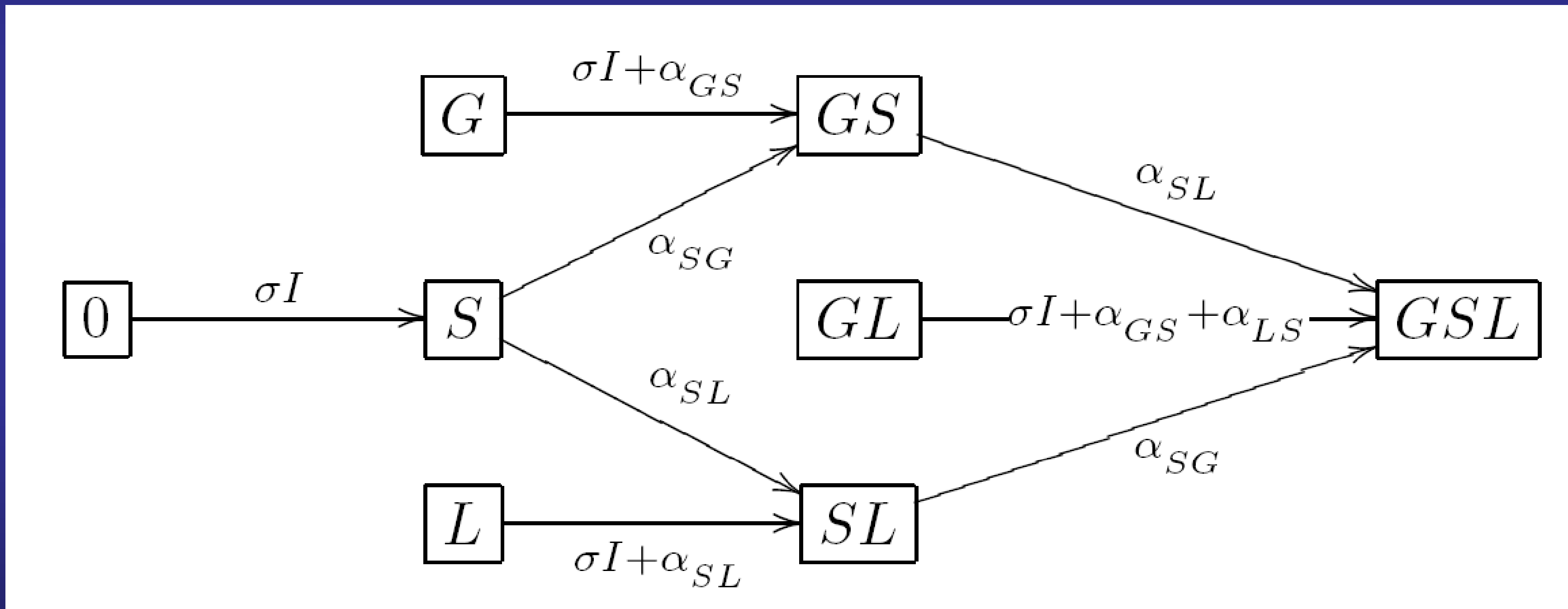
Selective Digestive Decontamination (SDD)

- Topical intestinal application of non-absorbable antibiotics
- To ICU-patients
- Kills potentially pathogenic microorganisms
- Selects for resistant microorganisms
- When Useful, when not?

Model

- 3 compartments
  - Lungs (L)
  - Gut (G)
  - Skin (S)
- Microorganism present or absent in each compartment
- 8 states for a patient:
  0, G, S, L, GS, GL, SL, GSL
- Transmission between patients:
  Skin colonization → hands HCW → skin other patient
- I=number of patients colonized on the skin
- Internal transmission: Between any compartment
  (Simplifying assumption: Only one transmission per day)
- Admission and discharge of patients at a fixed rate

Dynamics of an individual's infection status



Infection control measures

Topical, non-absorbable antibiotics

- do not affect the skin or lungs
- Either 1: Colonization in G eradicated
  2: G remains colonized but internal route G $\rightarrow$ S reduced

- Outcomes both models similar
  (Here only 2 presented)

Barrier precautions

- Reduce cross-transmission

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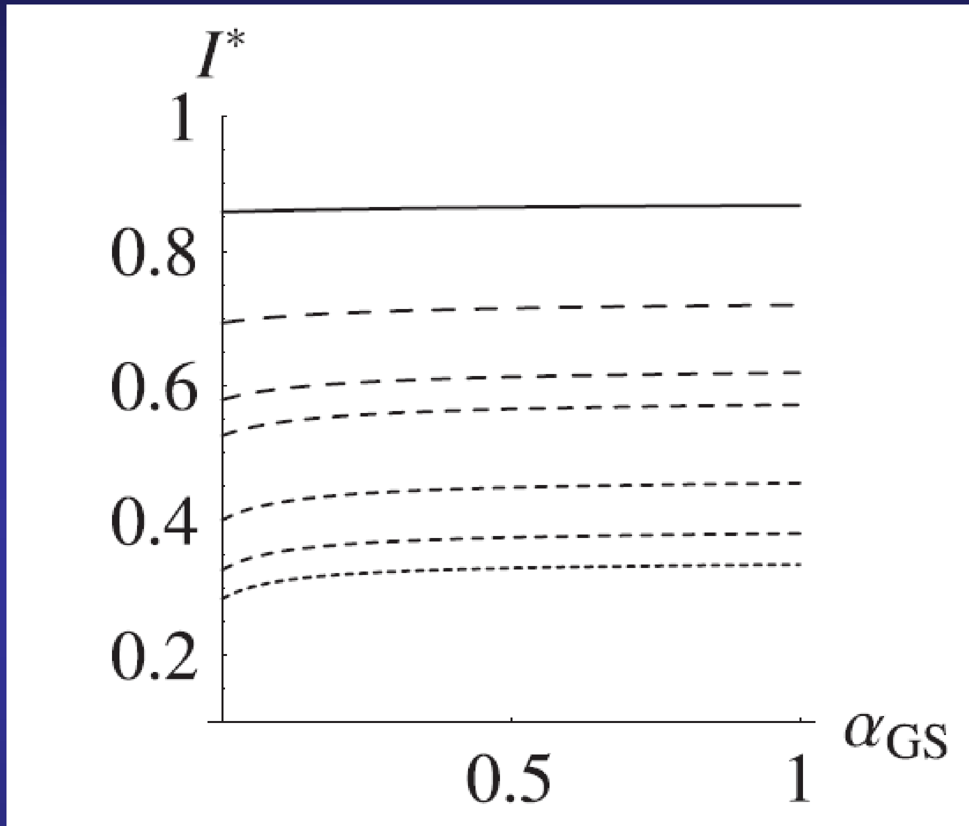
Deterministic Results

(Similar results of a stochastic simulation model of an ICU of 20 beds gives similar results, see preprint)

Mean length of stay:10 days

α_{LS}=1/2 (see preprint for α_{LS}=1/15)

Low level of intestinal colonization

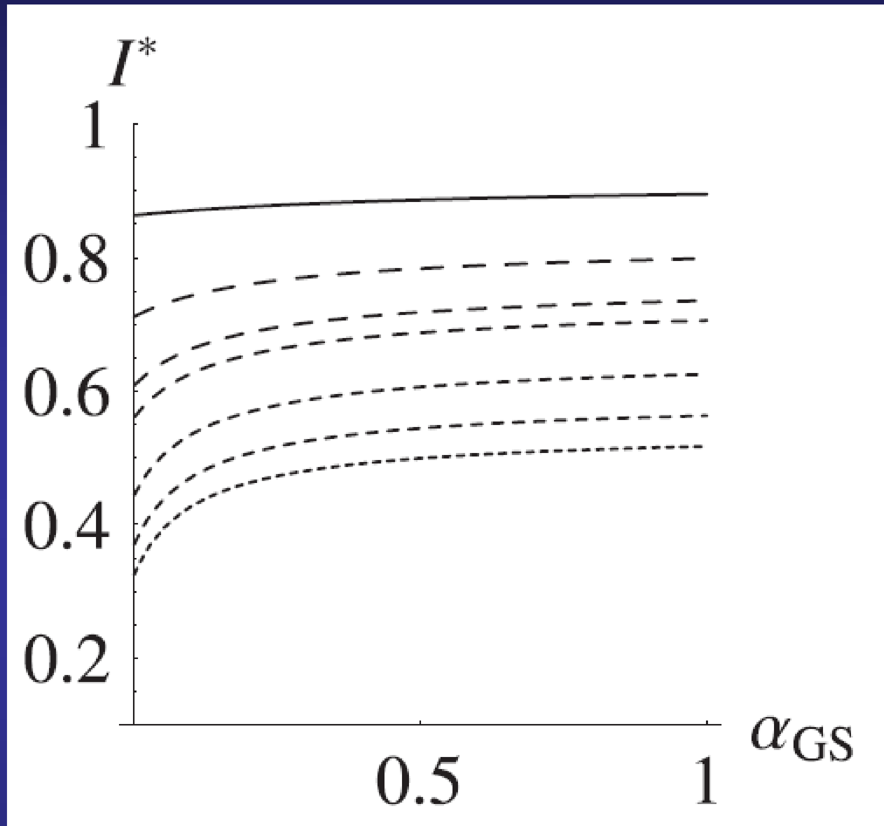


σ:
0.5
0.2
0.125
0.1
0.05
0.02
0

On admission, 15% colonized in gut, of which 5% also on skin

Conclusion:Effect SDD small

Medium level of intestinal colonization



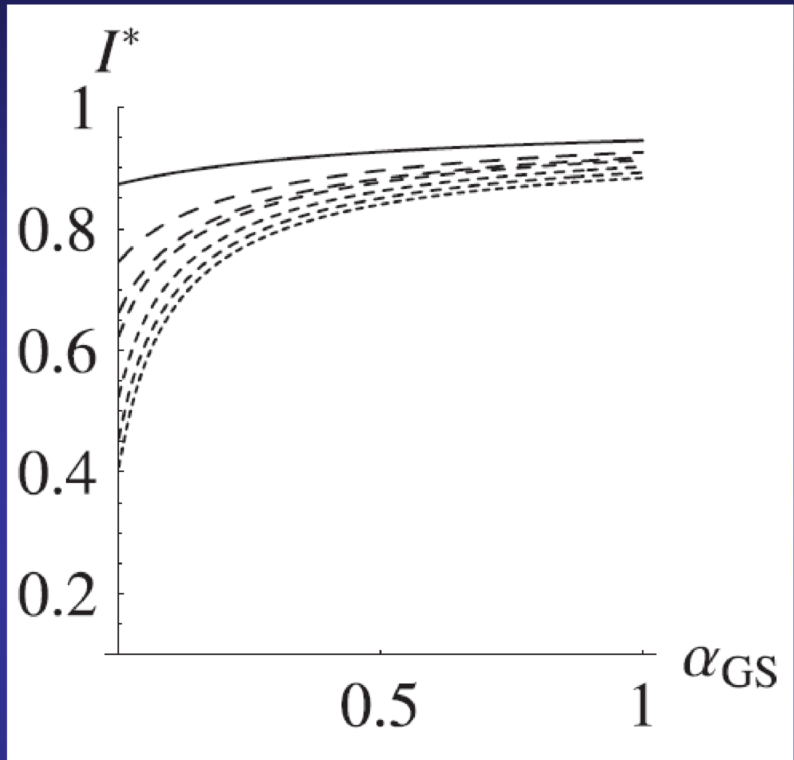
σ:
0.5
0.2
0.125
0.1
0.05
0.02
0

On admission, 35% colonized in gut, of which 5% also on skin

Conclusions: Effect SDD small

Maximum effect when no cross transmission: reduction from I=0.45 to I=0.35

High level of intestinal colonization



σ:
0.5
0.2
0.125
0.1
0.05
0.02
0

On admission, 70% colonized in gut, of which 0% also on skin

Conclusions: Cross transmission determines effect SDD.
Only when barrier precautions are sufficient (R_0<1), SDD can reduce *I**.

Conclusion/Remarks

- In clinical studies: SDD combined with additional barrier precautions
- SDD most useful
  - high occurrence of intestinal colonization on admission
  - low levels of cross transmission
- In real life, barrier precautions likely to be more effective than SDD

Weaknesses

- Simple model
- Colonization only absent or present
- No explicit modeling of strains resistant against the SDD-antibiotics
- No modeling of other antibiotics, HCW's..

All models are wrong,

but some are useful