Quantitative and Qualitative Aspects of the Spread of Methicillin Resistant *Staphylococcus aureus* (MRSA)

The Austin-Kakehashi-Anderson Model Revisited

Invitation by Bernhelm Booss-Bavnbek

RUC, 26 Oct. 2006

Thanks to
Jing Guo, Qian He, Jing Lu, Yang Wang, and Manyu Yue
of the Roskilde International Science Bachelor Program

Outline

Geographic Differences

Noteworthy puzzles:

- Differences by country
  - High prevalence countries (UK, Japan ...)
  - Low prevalence countries (DK, NL ...)
- Regional and local differences
  - Geographic distribution of clone ST80-IV in DK
  - Differences between hospitals

Changes In Time

Noteworthy puzzles:

- National level
  - Steady levelling off in Britain (on high level)
  - Exponential rise in Denmark (on low level)
- Level of institution (e.g., single hospital)
  - Internal spread of clones
  - Imported infections

New microbiological evidence

[Fa05] Detailed epidemiological and molecular analysis of the 81 MRSA infections identified in Denmark in 2001

- Smaller number and greater genetic portrait variability of HA-MRSA compared with CO-MRSA
- Of the HA-MRSA variety of 28 clones of different profile, only one popped up 5 times and four twice. All other clones were single events

[Hu06] Amoeba promote persistence of epidemic trains of MRSA

[Li05] Biological cost of single and multiple resistance mutations

[Mu06] First direct documentation of (rapid) conjugal transfer between gram-negative donor and gram-positive recipient bacteria in situ

Aims of Mathematical Modeling

What mathematical models can be good for:

- Description
  - Point to parameters (influences)
  - Estimate parameters
  - Describe typical developments
- Prediction
  - Saturation level
  - Slope of development
- Prescription
  - Focus on infection control measures
    - Antibiotic consumption
    - Best hospital practice
    - Other measures to be taken
  - Comparative evaluation of control measures
  - Dimensioning and timing of control measures

Character of Models

Mathematical models are different:

- Ad-hoc models
  - Predictive power when tuned properly
  - No theoretical basis
- Theoretically based models
  - Strong explanational power
  - In science: exceptional
- Metaphors
  - Imaginative power
  - Totally misleading when taken literally
  - Only applicable for excluding erroneous perceptions

Susceptible and Sensitive 1

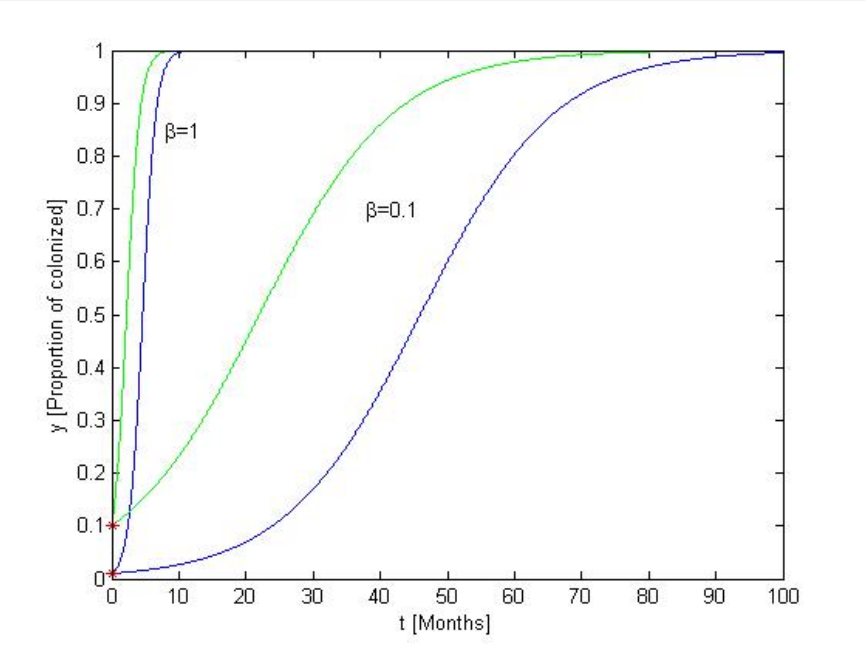
No recovery, no treatment, neither in- nor outflow

$x(t)$ Susceptible

$\beta xy \downarrow$

$y(t)$ Sensitive

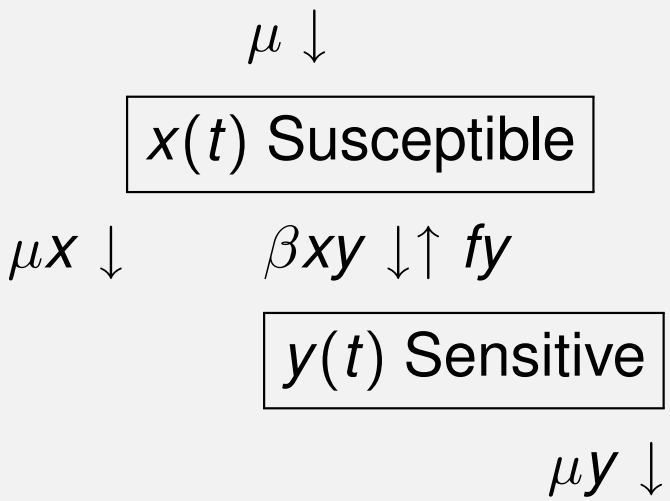
β Transmission rate

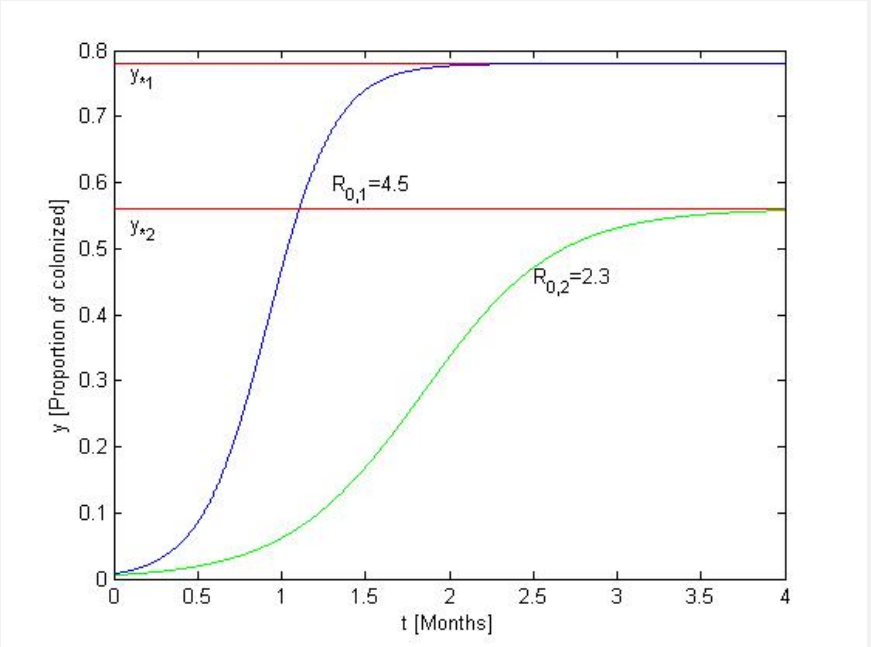


1. $\Delta y \propto y$, i.e., unlimited capacity
2. No separate compartment for amoeba hosts and implants
3. No distinction between active and less active propagators
4. No distinction between clones nor colonization vs. outbreak

Susceptible and Sensitive 2

No treatment, but recovery and in- and outflow





f Recovering rate, $R_0 = \frac{\beta}{f+\mu}$ Reproductive ratio,
$y_* = 1 - 1/R_0$ Prevalence (if $R_0 > 1$)

5 Inflow not colonized

6 No groups of different duration of carriage $1/f$

Susceptible, Sensitive, and Treated

With antibiotics, but without resistant bacteria

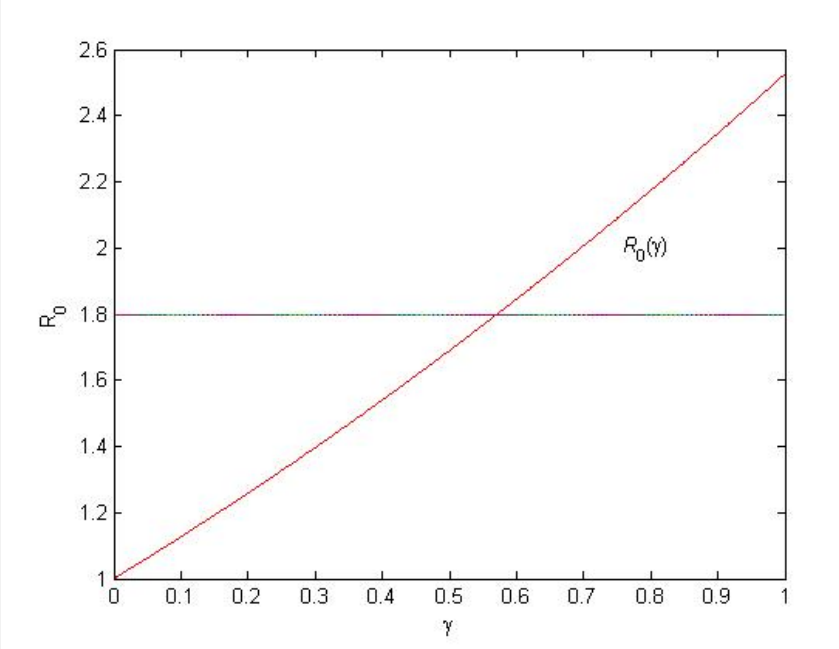
$\mu \downarrow$

$x(t)$ Susceptible $\underset{gX}{\overset{\gamma x}{\rightleftarrows}}$ $X(t)$ Treated

$\mu x \downarrow$ $\quad \beta xy \downarrow\uparrow fy \quad \gamma y \nearrow \quad \mu X \downarrow$

$y(t)$ Sensitive

$\mu y \downarrow$

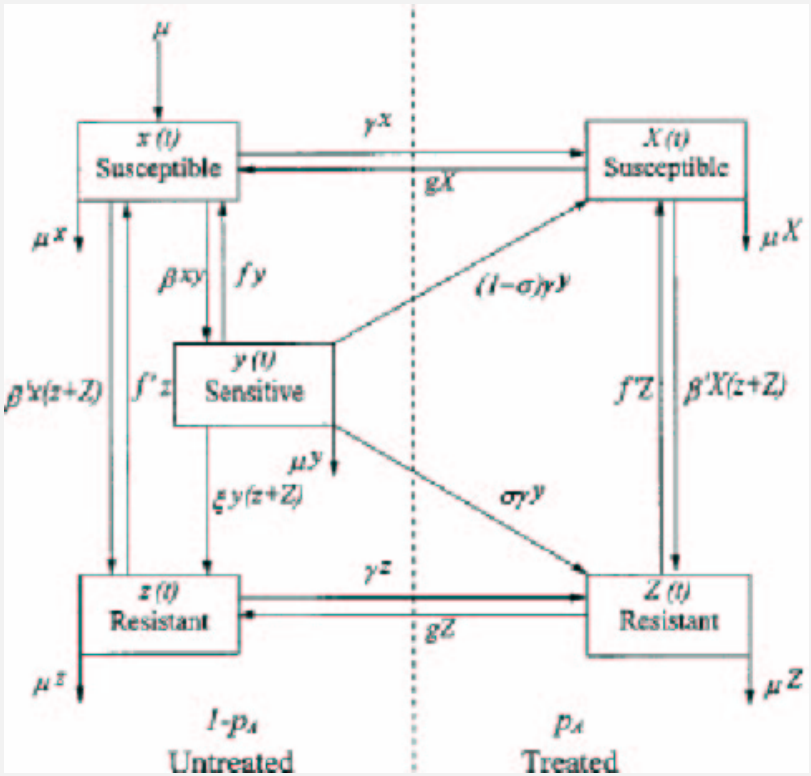


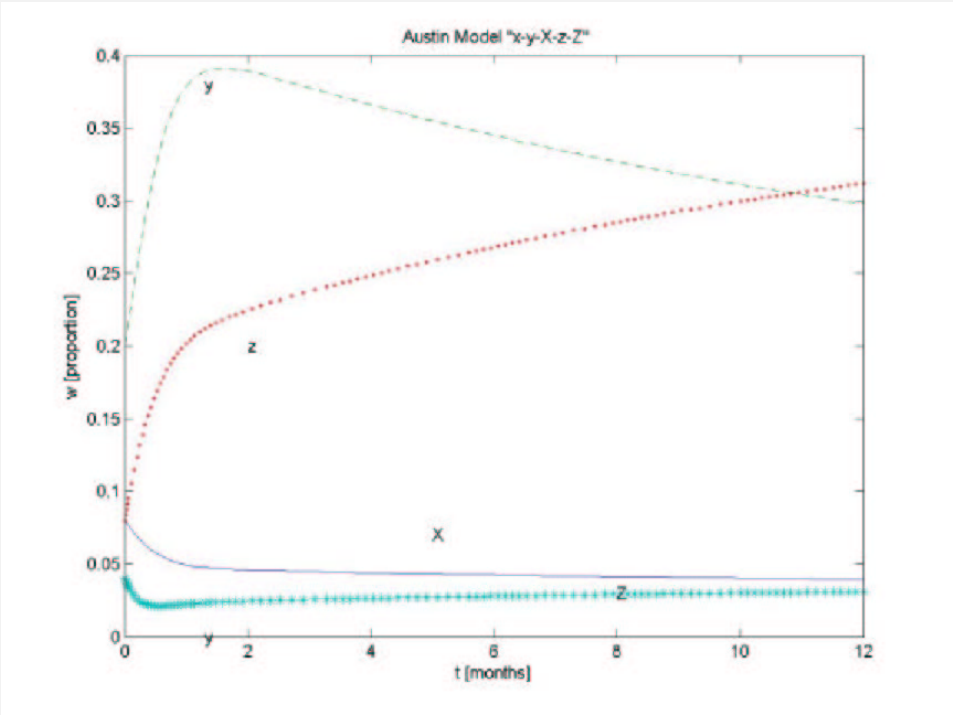
γ Prescribing rate, $1/g$ Treatment duration,

$\mathcal{R}_0(\gamma) = (1 + \frac{\gamma}{\mu+f})(1 + \frac{\gamma}{\mu+g})$ Critical reproductive ratio

Susceptible, Sensitive, Treated, and Resistant 1

With antibiotics and resistant bacteria, see [AuKaAn97]

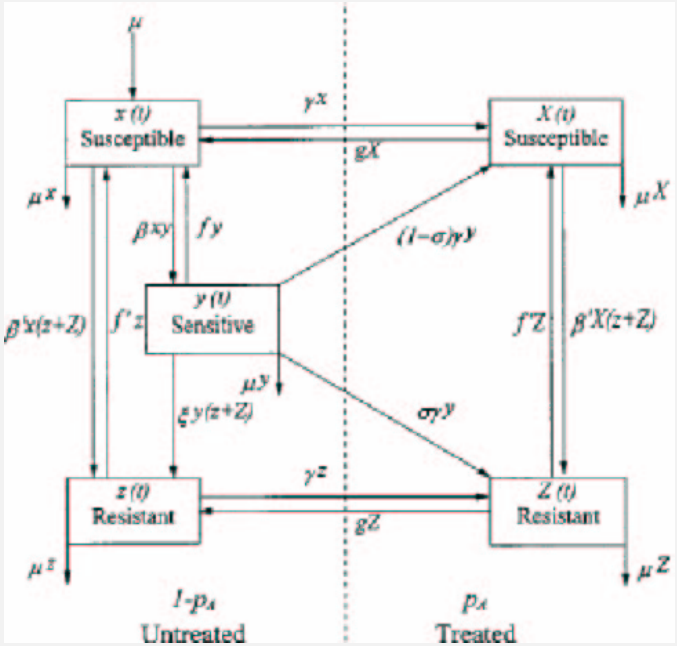


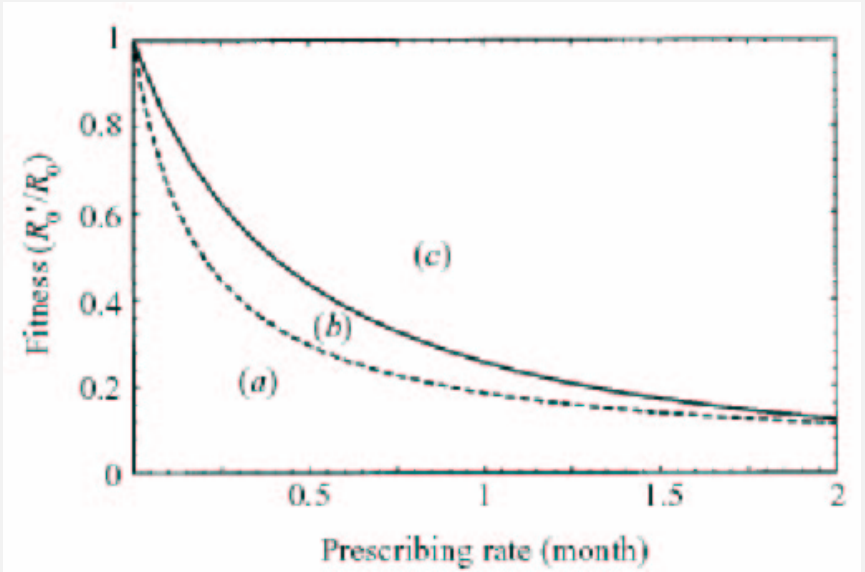


σ Plasmid transfer rate from natural environment under antibiotic selection pressure,
β', ξ Transmission rates, f' Recovering rate

Susceptible, Sensitive, Treated, and Resistant 2

Endemic regions: (a) all-sensitive (b) coexisting (c) all-resistant





7 Fitness cost coded in $\beta - \beta'$, $\beta' - \xi$, $f - f'$, summarized partly in $\mathcal{R}_0'(\gamma)/\mathcal{R}_0(\gamma)$

8 No spontaneous back transfer from z to y

9 Plasmid transfer $\propto \gamma y$

The Austin-Kakehashi-Anderson Model, Revisited 1

Strength

1. Asymptotic results ($t \to \infty$)
   - Explains *S*-shaped (logistic) spread in observations
   - Indicates chances of eradicating MRSA due to fitness cost
   - Warns against all-resistant endemics
2. Explains differences by country and hospital due to best practice in hospital (β) and antibiotic prescription (γ) and opens for quantitative evaluation of health administration measures
3. Elaborates the decisive role of plasmid transfer
4. Predictive power depends on quality of data for estimating parameters and initial conditions

The Austin-Kakehashi-Anderson Model, Revisited 2

Weakness

1. $\Delta y \propto y$, i.e., unlimited capacity !!!!!!!!!!!!!!!!!!!!!
2. No separate compartment for amoeba hosts and implants
3. No distinction between active and less active propagators
4. No distinction between different clones
5. No distinction between colonization and outbreak
6. Inflow not colonized !!!!!!!!!!!!!!!!!!!!!!!!!
7. No groups of different duration of carriage $1/f$
8. Fitness cost coded in $\beta - \beta'$, $\beta' - \xi$, $f - f'$, summarized partly in $\mathcal{R}_0'(\gamma)/\mathcal{R}_0(\gamma)$
9. No spontaneous back transfer from z to y
10. Plasmid transfer $\propto \gamma y$

Summary

The AKA compartment model

- seems to be a useful ad-hoc model and versatile for analyzing MRSA spread in high prevalence situations;
- is less appropriate for analyzing geographic spread;
- is not applicable at all in low prevalence situations.

Outlook

- What Danish data do exist; are available; can be used for re-modeling the MRSA spread in DK?
- What discrete or stochastic models should replace the AKA compartment model in low-prevalence situations?

For Further Reading I


D. A. A. Ala'Aldeen og K. Hiramatsu (eds.).
Staphylococcus Aureus - Molecular and Clinical Aspects.
Horwood Publishing, Chichester, 2004, xiv + 267 pp.


Ch. Walsh.
Antibiotics - Actions, Origins, Resistance.
American Society for Microbiology - ASM Press, Washington D.C., 2003, x + 335 pp.


D. J. Austin, M. Kakehashi, R.M. Anderson.
Proc. R. Soc. Lond., B 264/1388 (November 1997): 1629–1638.


N. A. Faria et al.
J. Clin. Microbiol., 43/4 (April 2005): 1836–1842.

For Further Reading II


S.A. Huws et al.
Envir. Microbiol., 8/6 (June 2006): 1130–1133.


P.K. Lindgren et al.
Antimicrob. Agents Chemother., 49/6 (June 2005): 2343–2351.


S. Musovic et al.
Appl. Envir. Microbiol., 72/10 (October 2006): 6687–6692.

For Further Collaboration (First Ideas) I

Contacts, gathering, Danish or international workshop?

Molecular biologists and medical doctors:

- International
  - ...
  - ...
- Denmark
  - Rasmus Bugge Jensen <rbjensen@ruc.dk>
  - Niels Højby <hoiby@inet.uni2.dk>
  - Søren Molin <sm@biocentrum.dtu.dk>
  - Robert Leo Skov <RSK@ssi.dk>
  - Ole Skovgaard <olesk@ruc.dk>
  - Søren J. Sørensen <sjs@bi.ku.dk>
  - Frank M. Aarestrup via <dfvf@dfvf.dk>

For Further Collaboration (First Ideas) II

Contacts, gathering, Danish or international workshop?

Mathematicians:

- International
  - ...
  - ...
- Denmark
  - Viggo Andreasen <viggo@ruc.dk>
  - Bernhelm Booss-Bavnbek <booss@ruc.dk>
  - Klaus Skovbo Jensen <KLJ@ssi.dk>
  - Jørgen Larsen <jl@ruc.dk>
  - Johnny T. Ottesen <johnny@ruc.dk>
  - Michael Pedersen <M.Pedersen@mat.dtu.dk>