Modeling Antibiotic Resistant Bacterial Epidemics in Hospitals

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Antibiotic Resistant Bacteria
(□□□□□□□□□)

The development of drug-resistant strains of bacteria (□□□□□) is an increasing threat to society, *especially in hospital settings*. Many antibiotics that were formerly effective in combating bacterial infections are no longer effective due to the evolution of resistant strains. The evolution of these strains compromises medical care worldwide.

Nosocomial infections (□□□□□)

- are those that originate or occur in a hospital or hospital-like setting.
- may involve patients, visitors and hospital personnel.
- estimated 18,650 deaths in patients with invasive methicillin-resistant *Staphylococcus aureus (MRSA)* in the US in 2005, exceeding the total number of deaths due to HIV/AIDS in the same year (Klevens et al. 2007; Bancroft 2007)
- *More than 70 percent of the bacteria that cause nosocomial infections are resistant to at least one of the drugs most commonly used to treat them*

Main Types of Infections

- Urinary tract (□□□)(44%)
- Lower respiratory tract (□□□□) (18%)
- Surgical wound sites (11%)
- Bloodstream (8%)

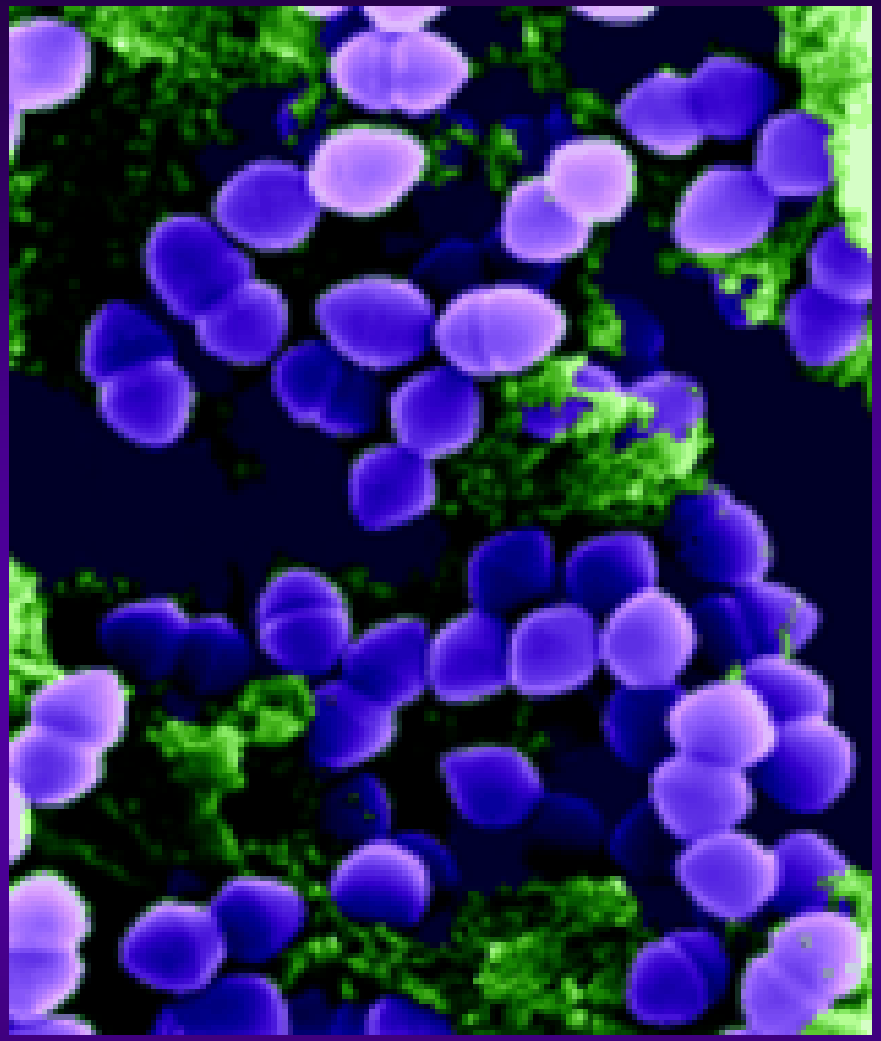
Intensive Care Units (ICU □□□□□) and long-term care patients are at greatest risk

Examples of Resistant Nosocomial Pathogens

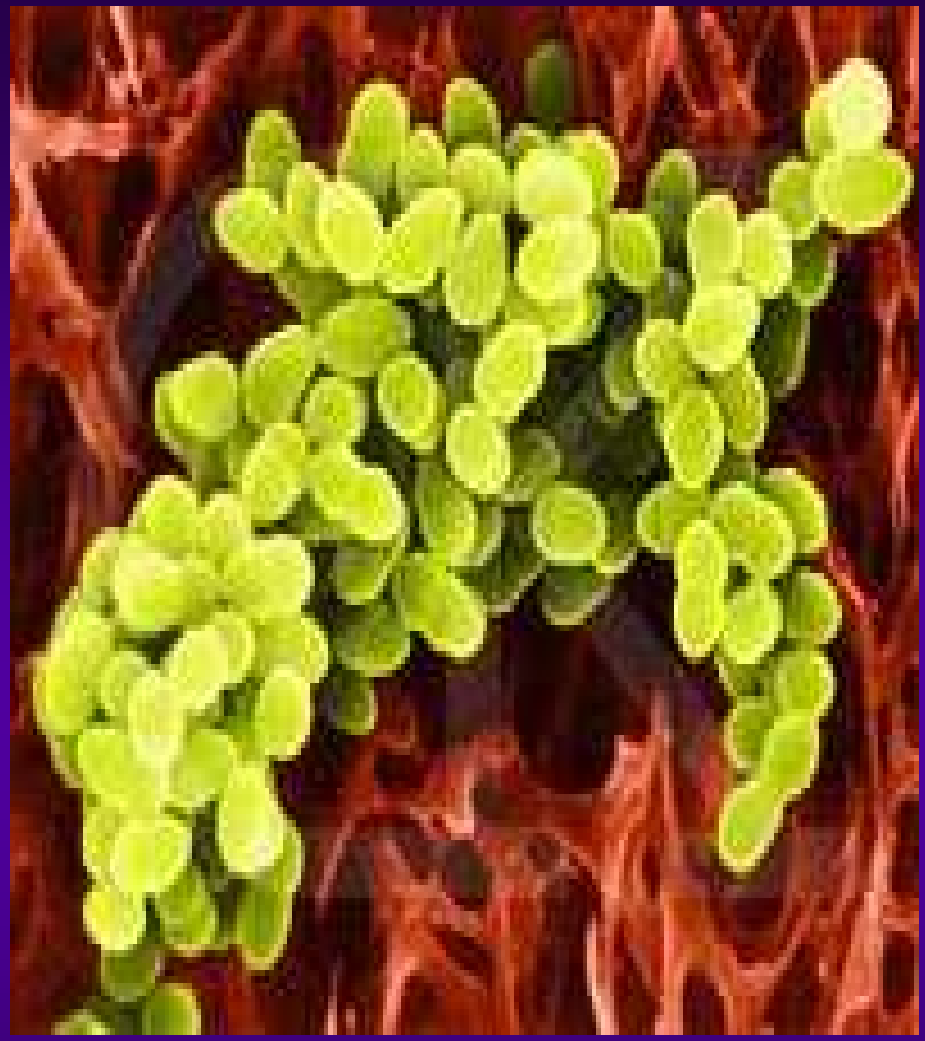
Vancomycin (□□□□)-resistant *Enterococci* (□□□) (VRE)

Methicillin (□□□□)-resistant *Staphylococcus aureus* (□□□□□□□) (MRSA)

Methicillin-resistant *S. epidermidis* (□□□□□□) (MRSE)

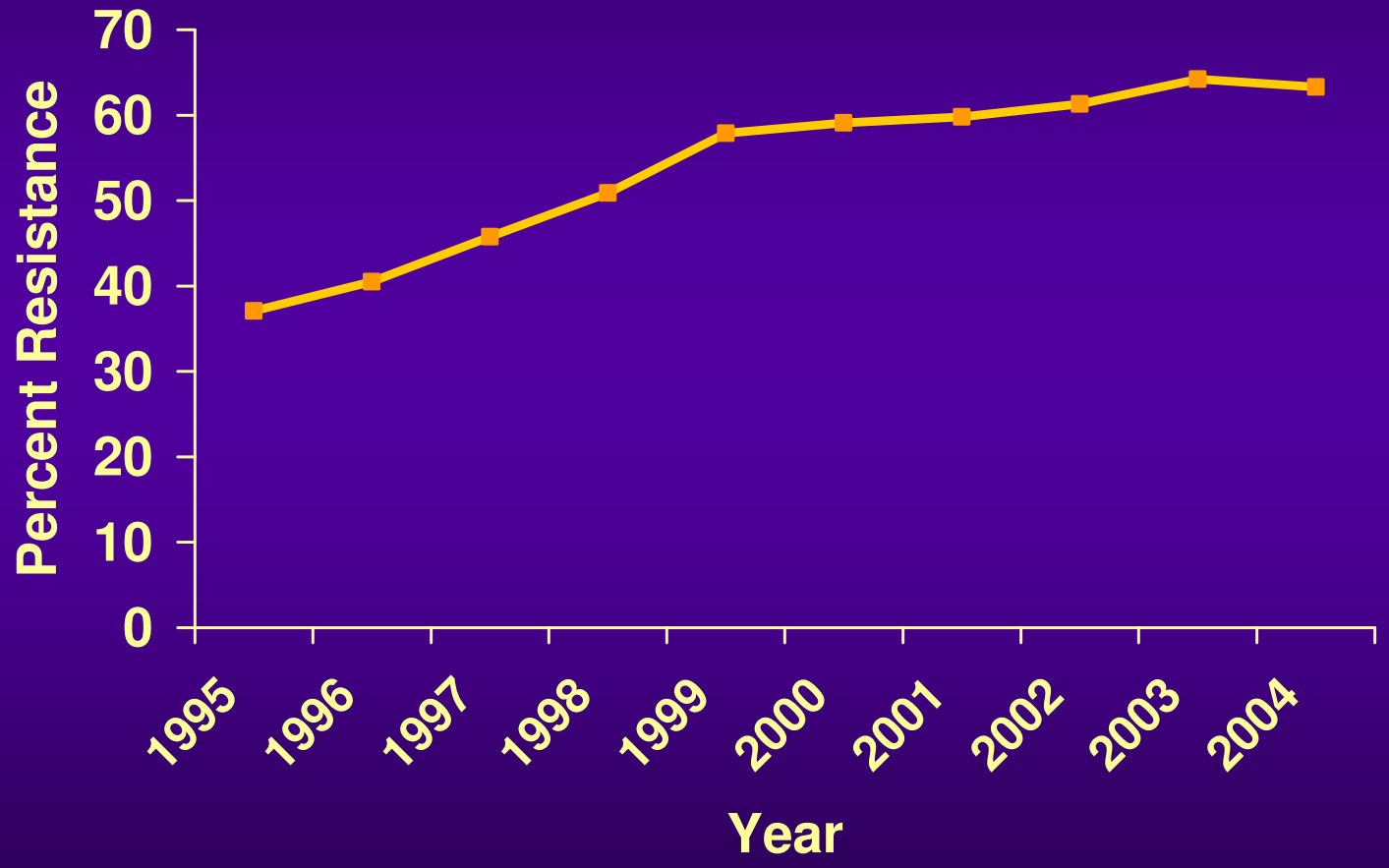


Vancomycin-resistant
Enterococci (VRE)
(□□□)



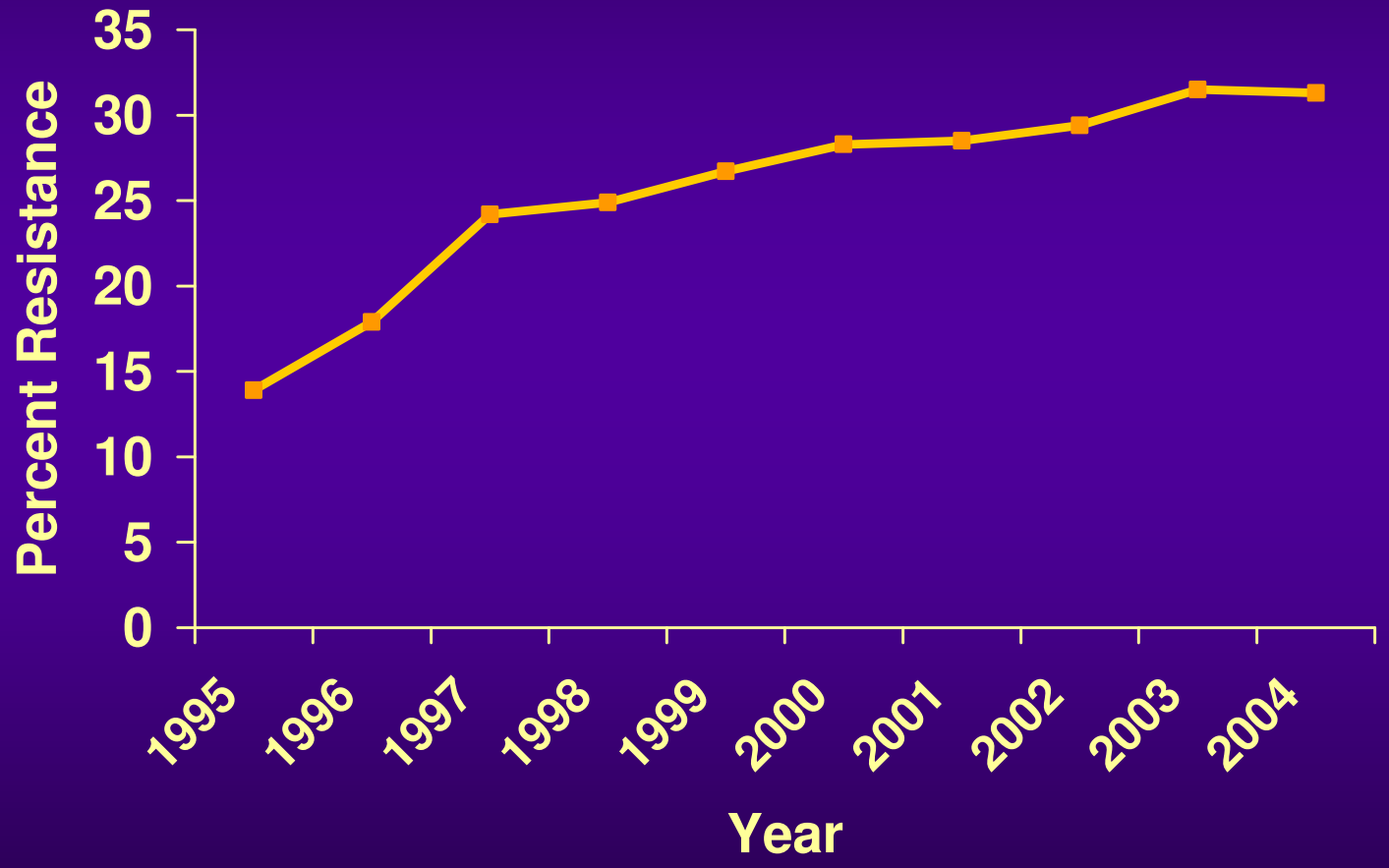
Methicillin-resistant
Staphylococcus aureus (MRSA)
(□□□□□□□)

Methicillin (oxacillin)-resistant *Staphylococcus aureus* (MRSA) Among ICU Patients, 1995-2004



Source: National Nosocomial Infections Surveillance (NNIS) System

Vancomycin-resistant *Enterococci* Among ICU Patients, 1995-2004



Source: National Nosocomial Infections Surveillance (NNIS) System

Why Now?

- Increased use of antimicrobials(□□□) in hospitals and long-term care facilities in the 1970s-1990s created many bacterial strains resistant to antibiotics
- Hospital personnel fail to follow basic infection control. In ICUs, asepsis (□□□) is overlooked in the rush of crisis care
- Patients in hospitals are increasingly immunocompromised (□□□□)

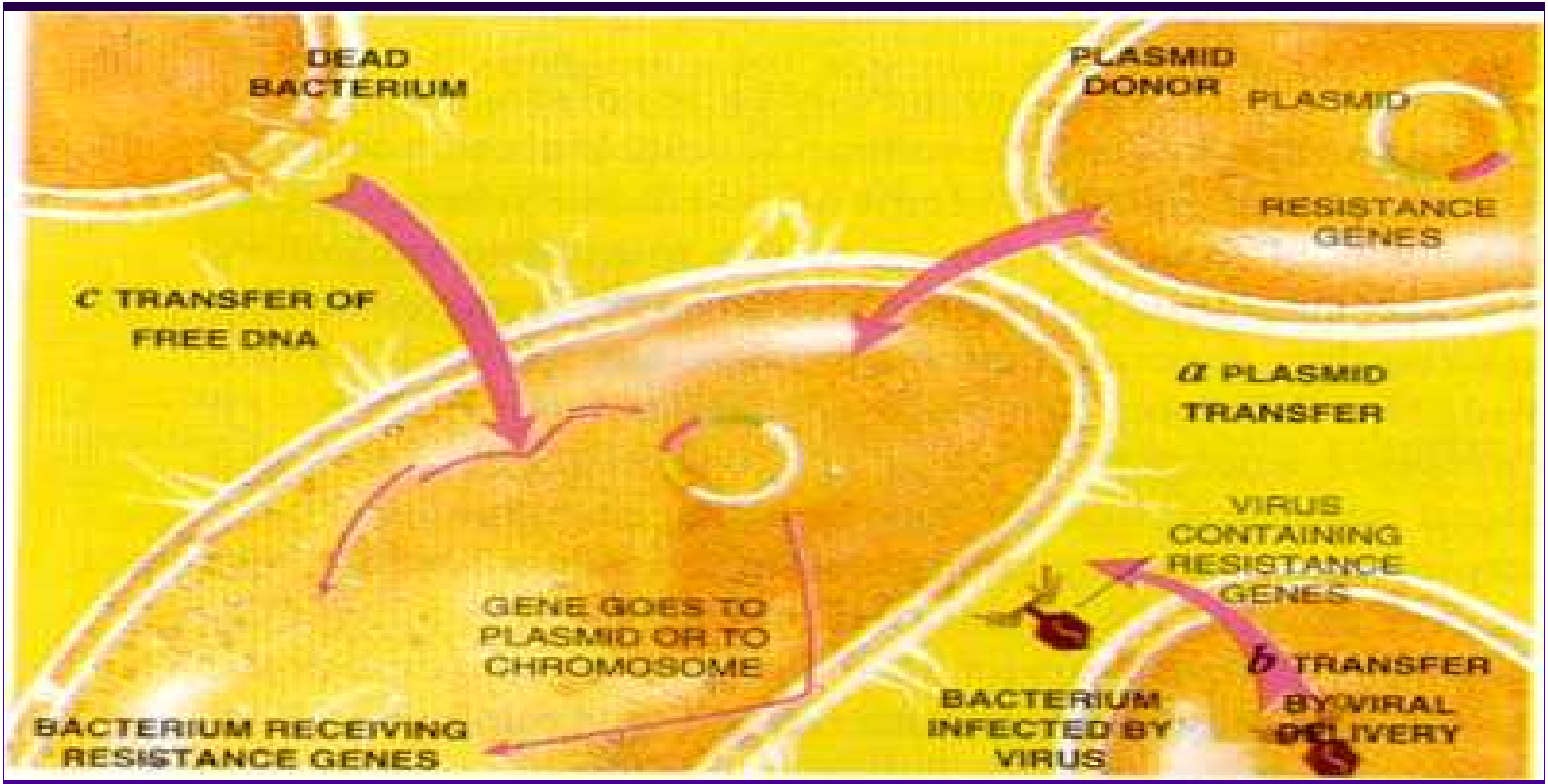
How Bacteria Develop Antibiotic Resistance?

Antibiotics are derived from microorganisms which are resistant to their own antibiotics

- ***Inherent*** (□□□□□) - microorganisms may be resistant to antibiotics because of the physical and biochemical differences.
- ***Acquired*** (□□□□□) - bacteria can develop resistance to antibiotics driven by two genetic processes in bacteria:

  (a) mutation (□□) and selection (□□) *(vertical evolution)*

  (b) exchange of genes between strains and species *(horizontal evolution).*



Bacteria pick up resistance genes from other bacterial cells in three way. (a)They receive whole plasmids(□□) bearing one or more such genes from a donor cell. (b)A virus picks up a resistance gene from one bacterium and inject it into a different bacterial cell. (c)Bacteria scavenge (□□) gene-bearing snippets (□□) of DNA from dead cells in the vicinity.

A plasmid bearing cell (top) transferring the plasmid genome to a plasmid free bacteria (bottom). Paul Turner (http://www.eeb.yale.edu/faculty/turner/)

References

Bacteria Level:

C. R. Bergstrom, M. Lipsitch and B. R. Levin (2000), *Genetics*, 155 : 1505-1519.

B. R. Levin and C. T. Bergstrom (2000), *Proc. Natl., Acad. Sci.*, 97: 6981-6985.

B. R. Levin & F. M. Stewart (1980), *Genetics* 94: 425-443.

F. M. Stewart & B. R. Levin (1977), *Genetics* 87: 209-228.

Patient Level:

D. J. Austin et al. (1999), *Proc. Natl., Acad. Sci.*, 96: 6908-6913.

B. S. Cooper et al. (2004), *Proc. Natl., Acad. Sci.*, 101: 10223-10228.

E. D'Agata, M. A. Horn and G. F. Webb (2002), *J. Infect. Dis.* 185: 766-773.

M. C. Lipsitch et al. (2000), *Proc. Natl., Acad. Sci.*, 97: 1938-1943.

Community Level:

D. L.Smith, J. Dushoff, E. N. Perencevich, A. D. Harris & S. A. Levin (2004), *Proc. Natl., Acad. Sci.* 101: 3709-3714.

D. L. Smith, S. A. Levin & R. Laxminarayan (2005), *Proc. Natl., Acad. Sci.* 101: 3153-3158.

Survey:

H Grundmann and B Hellriegel, Mathematical modelling: a tool for hospital infection control, ***Lancet – ID* Vol 6 (2006), 39-45.**

Ross-Macdonald Malaria Model

Sir Ronald Ross
1857-1932

$$\frac{dx}{dt} = -rx(t) + abm[1 - x(t)]y(t),$$
$$\frac{dy}{dt} = -\mu y(t) + acx(t)[1 - y(t)].$$

- $x(t)$ and $y(t)$ - the proportion of infected humans and vectors, resp., at time t
- r - the per capita rate of recovery in humans such that $1/r$ is the duration of the disease in humans
- μ - the per capita rate of mortality in vectors such that $1/\mu$ is the life expectancy of vectors
- m - the number of mosquitoes per human host
- a - the rate of biting on man by a single mosquito (# of bites per unit time)
- b - the proportion of infected bites on man that produce an infection
- c – infected human to mosquito transmission efficiency

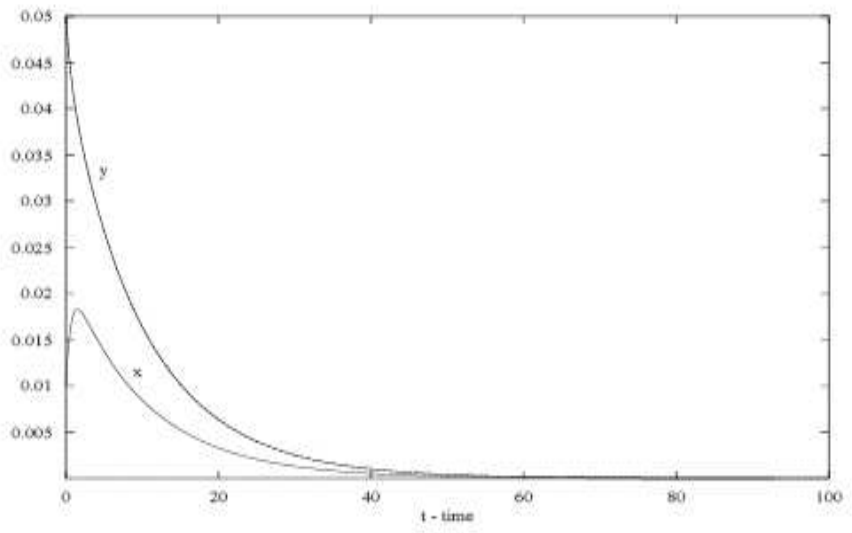
Ross (1911): introduced the concept of a threshold density and concluded that

"*... in order to counteract malaria anywhere we need not banish Anopheles there entirely -- we need only to reduce their numbers below a certain figure.*" (Nobel Prize in 1902)

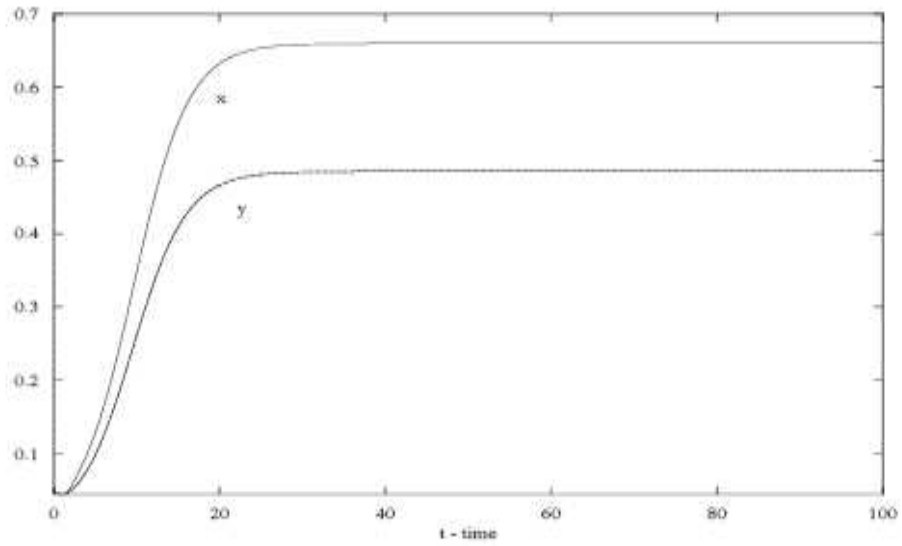
Macdonald (1957): extended Ross' basic model, analyzed several factors contributing to malaria transmission, and *introduced the basic reproduction number* (□□□□□) as the average number of secondary cases produced by an index case during its infectiousness period.

The basic reproduction number $R_0 = a^2bcm/r\mu$

***Conclusion**: If $R_0 < 1$, then the Ross-Macdonald model has a unique equilibrium, the trivial equilibrium $(0; 0)$, which is stable. If $R_0 > 1$, then the Ross-Macdonald model has two equilibria, the trivial equilibrium $(0; 0)$ which is unstable, and a positive equilibrium (x_1, y_1); which is stable.*



$R_0 < 1$



$R_0 > 1$

Ross' Claim: m=M/H=mosquito/man, $R_0 = a^2bcM/r\mu H<1$ implies that $M<r\mu H/a^2bc$

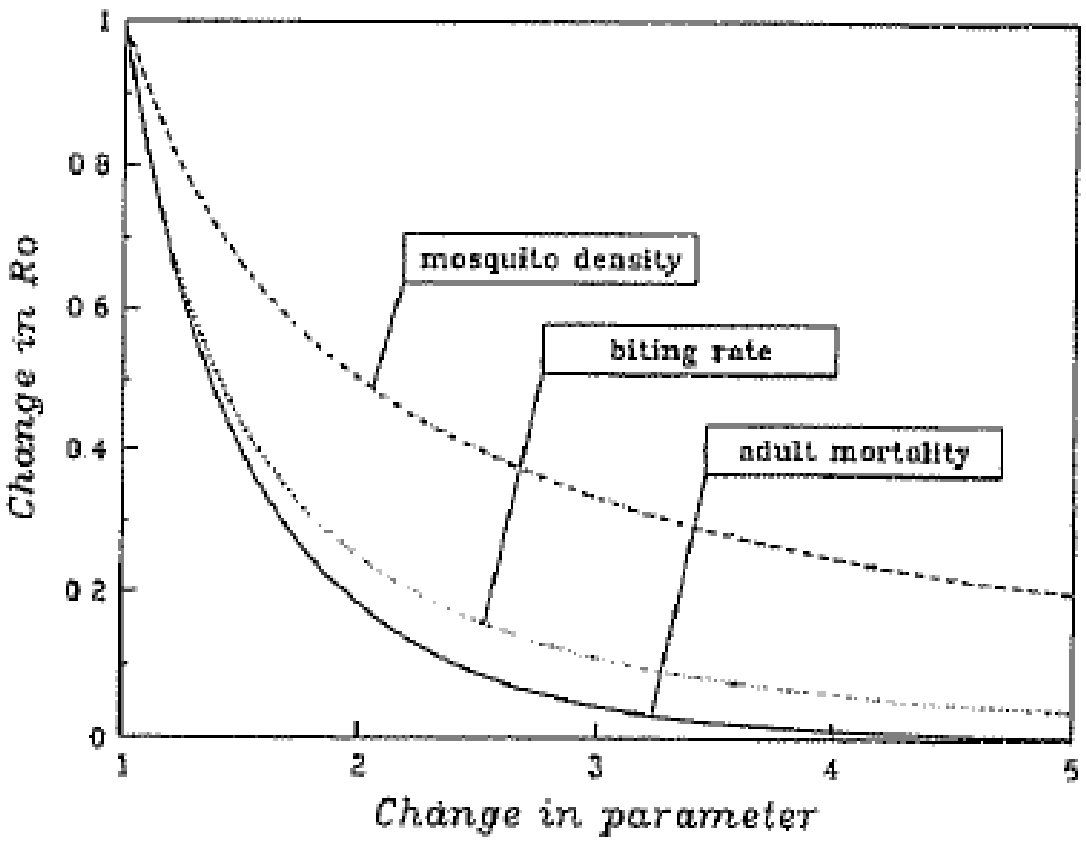


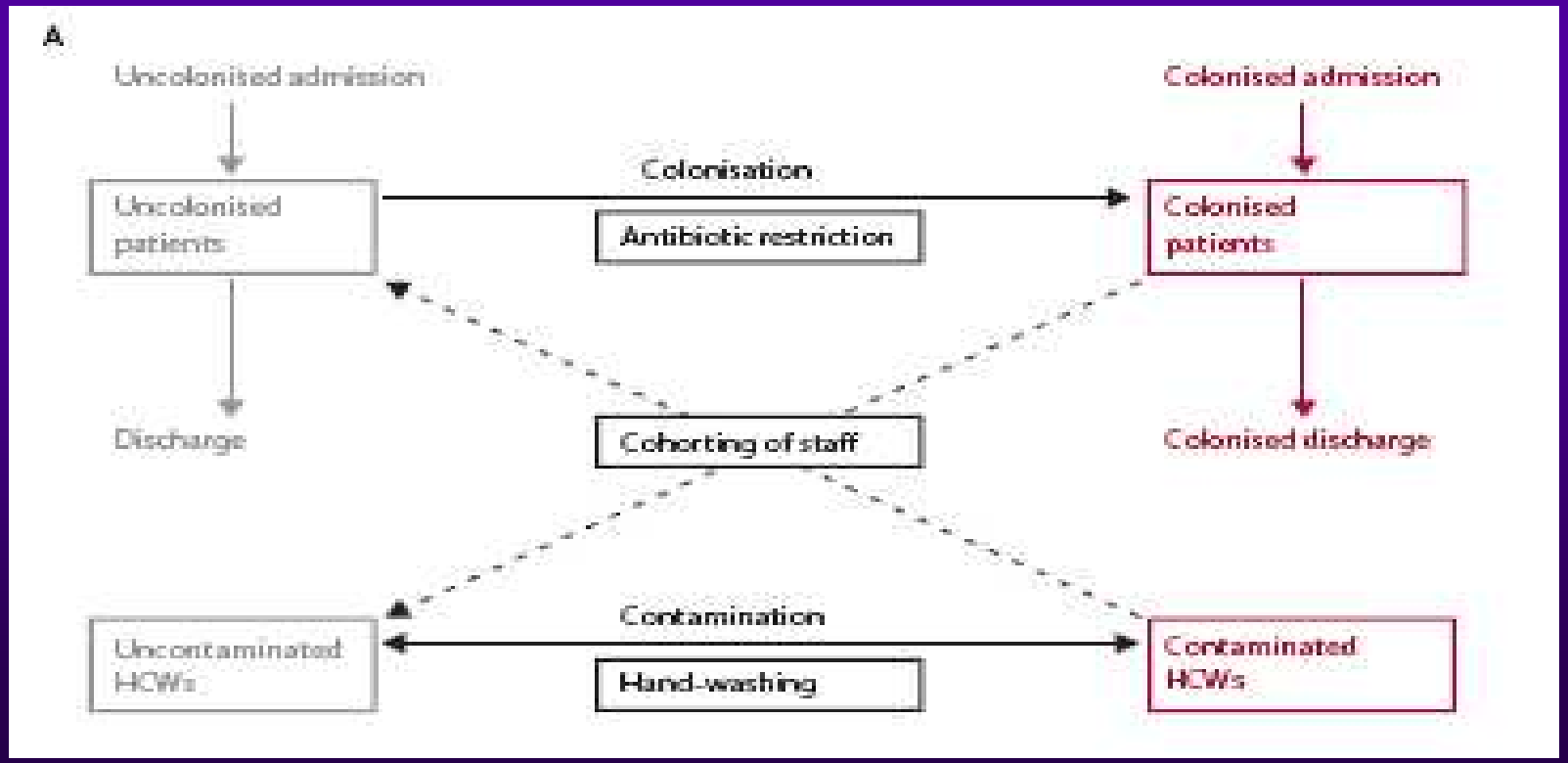
Fig. 5. Sensitivity of basic reproductive number as calculated for the Ross-Macdonald model on mosquito density, biting rate, and mosquito survival. A given endemic setting is given with the values one for each parameter and for R_0. Changes in parameter values are shown as factors relating to the original setting, e g , a value of 2 for mosquito density denotes that density decreased two-fold. Mosquito density enters the equation for the basic reproductive number linearly. Therefore a two-fold decrease in mosquito density leads to a two-fold decrease in reproductive number. Biting rate enters the reproductive number quadratically, so that a two-fold decrease leads to a four-fold decrease in reproductive number. Survival of adult mosquitoes enters reproductive number exponentially, and decreases lead to the largest changes

Macdonald's sensitivity analysis of the basic reproduction number on the parameters indicated that:

- Halving (□□) the mosquito population (e.g. by larvicides □□□□) reduces R_0 by a factor of two whilst halving biting rate (e.g. with bed nets) reduces R_0 by a factor of four.
- The largest reduction of R_0 is expected for increase in adult mosquito mortality (e.g. by imagicides □□□□) because of their exponential relationship.
- An important conclusion is thus that imagicides are more effective for controlling malaria than larvicides.

The work of Macdonald (1957) had a very beneficial impact on the collection, analysis, and interpretation of epidemic data on malaria infection (Molineaux and Gramiccia, The Garki Project, WHO, Geneva, 1980) and guided the enormous global malaria-eradication campaign of his era.

(A)Single Ward Models: Model of "vector-mediated" transmission between patient–HCW–patient exploring the effects of hand washing, staff cohorting, and antibiotic restriction. Patients (colonized or uncolonized) are admitted to a hospital where they interact with HCW (contaminated or uncontaminated).
Austin, Bonten, Weinstain, Slaughter & Anderson, *Proc Natl Acad Sci* (1999)



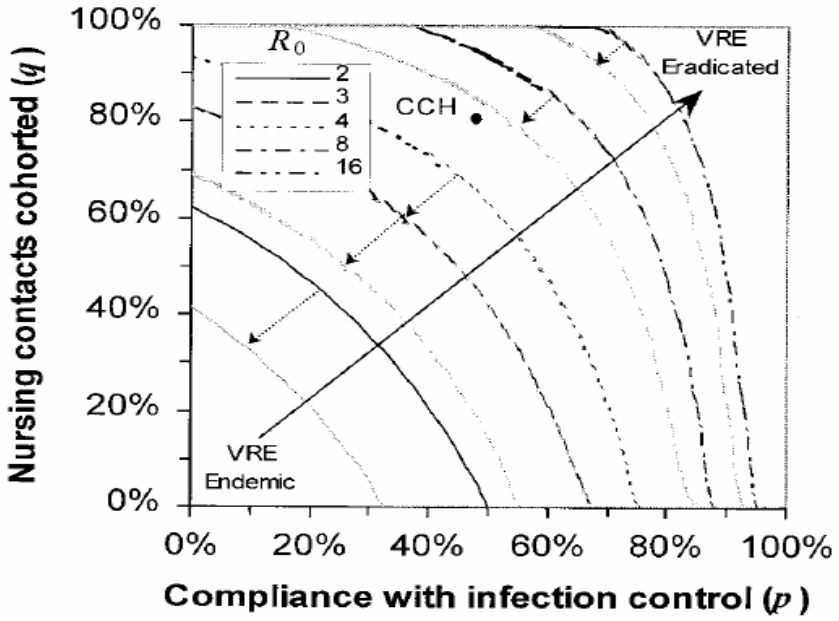
X_p -- uncolonized patients
Y_p -- colonized patients
X_h -- VRE-free HCWs
Y_h -- contaminated HCWs

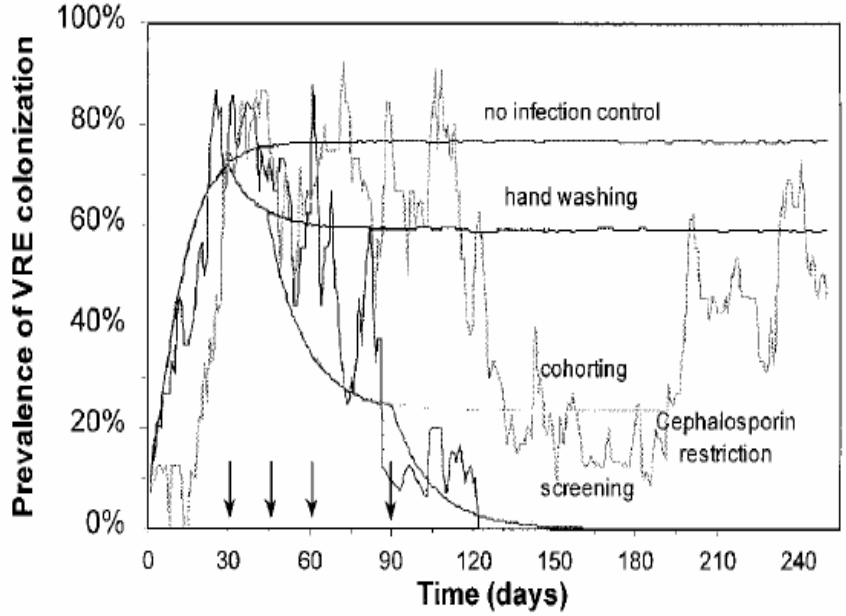
$$\frac{dX_p}{dt} = \Lambda(1-\phi) - \gamma X_p - ab_p X_p Y_h$$

$$\frac{dY_p}{dt} = \Lambda\phi - \gamma' Y_p + ab_p X_p Y_h$$

$$\frac{dX_h}{dt} = -ab_h X_h Y_p + \mu Y_h$$

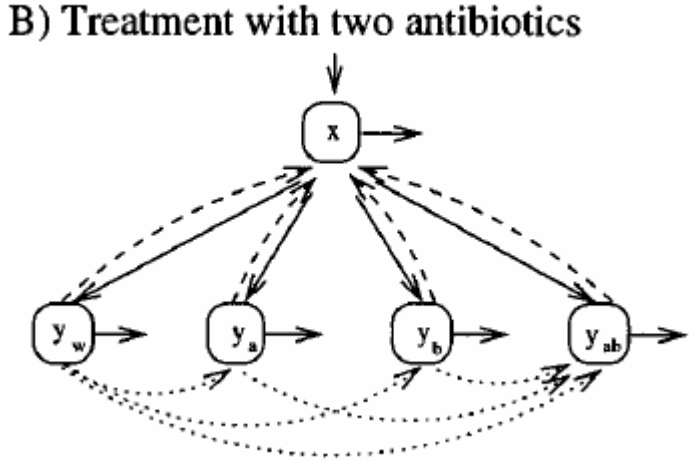
$$\frac{dY_h}{dt} = -\frac{dX_h}{dt}.$$





Analyses suggest that compliance for hand washing significantly in excess of reported levels, or the cohorting of nursing staff, are needed to prevent nosocomial transmission of VRE in endemic settings.

Evaluating treatment protocols: Bonhoeffer, Lipsitch & Levin *Proc Natl Acad Sci* 1997) proposed two mathematical models to evaluate the population-wide effects of treatment protocols for directly transmitted bacterial infections and discuss different usage patterns for single and multiple antibiotic therapy.



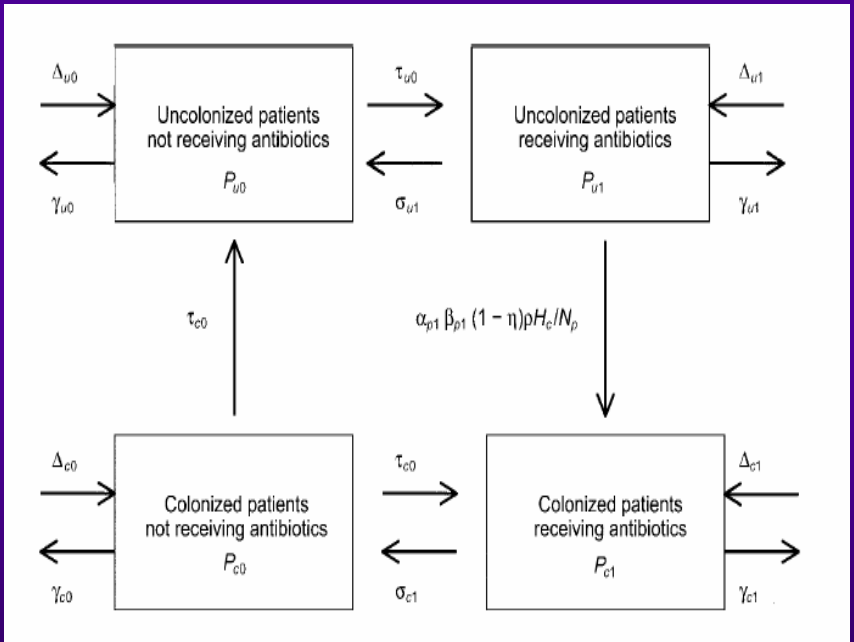
$$
\begin{cases}
\frac{dx}{dt} = \Lambda - dx - bx(y_w + y_a + y_b + y_{ab}) + r_w y_w + r_a y_a + r_b y_b + r_{ab} y_{ab} \\
\qquad +h(1-q)f_{ab} y_w + h(1-s)((f_a + f_b)y_w + f_a y_b + f_b y_a + f_{ab}(y_a + y_b)), \\
\frac{dy_w}{dt} = (bx - c - r_w - h(f_a + f_b + f_{ab}))y_w, \\
\frac{dy_a}{dt} = (bx - c - r_a - h(f_b + f_{ab}))y_a + hsf_a y_w, \\
\frac{dy_b}{dt} = (bx - c - r_b - h(f_a + f_{ab}))y_b + hsf_b y_w, \\
\frac{dy_{ab}}{dt} = (bx - c - r_{ab})y_{ab} + hs(f_{ab}(y_a + y_b) + f_a y_b + f_b y_a) + qhf_{ab} y_w,
\end{cases}
$$

Different treatments (cycling, 50-50, combination) were examined. Sequential use of different antibiotics in the population (cycling) is inferior to treatment strategies where equal fractions of the population receive different antibiotics. Treatment of all patients with a combination of antibiotics is the optimal treatment strategy.

Bergstrom, Lo & Lipsitch, Ecological theory suggests that antimicrobial cycling will not reduce antimicrobial resistance in hospitals, *Proc Natl Acad Sci* (2004)

Reluga, Simple models of antibiotic cycling, *Math. Med. Biol.* (2005)

D'Agata,Webb & Horn (*J Infect Dis* 2005) developed a model to quantify the contribution of antibiotic exposure and of other modifiable factors to the dissemination of VRE in the hospital setting. The model consists of 4 compartments: patients colonized with VRE receiving and not receiving antibiotics, and uncolonized patients receiving and not receiving antibiotics.



Conclusions.

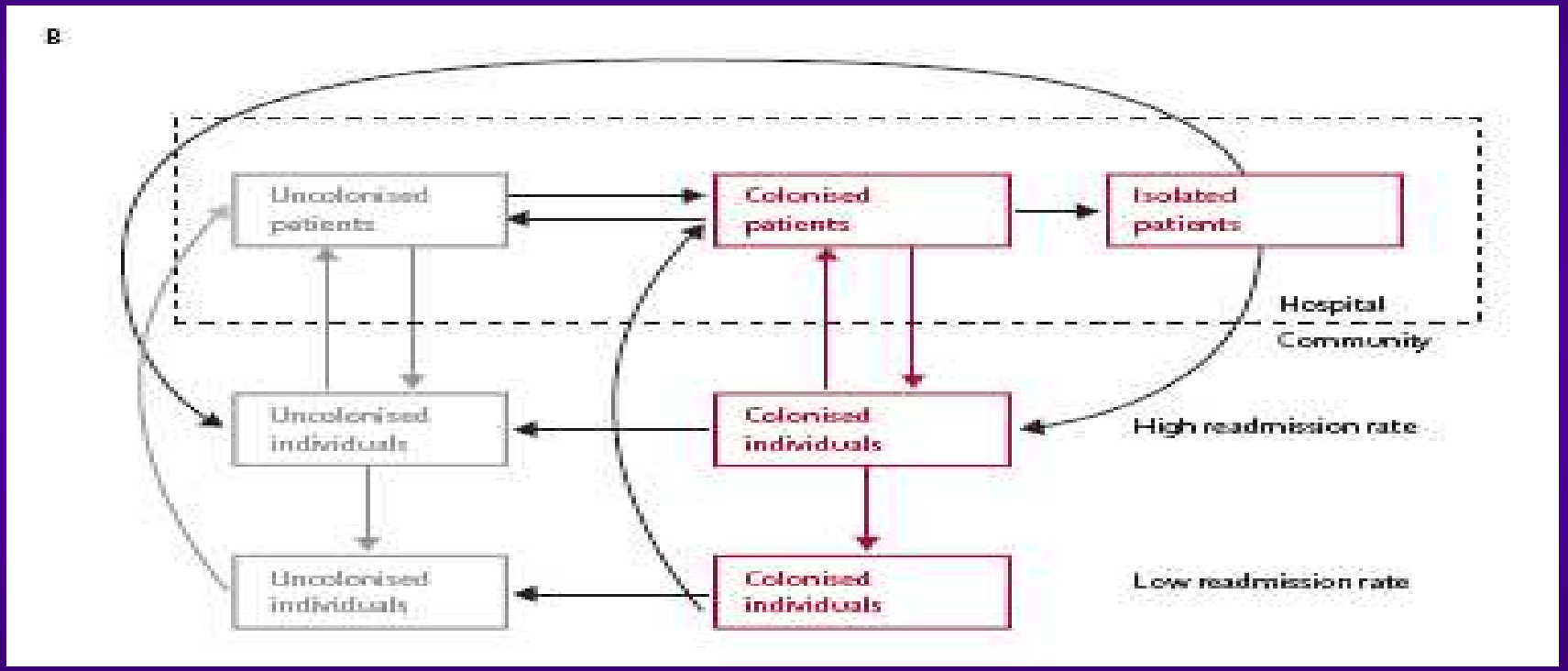
(1) Preventing the initiation or enhancing the discontinuation of unnecessary antimicrobial therapy will have a greater impact if it is targeted to patients who are not colonized with VRE;

(2) Increasing the number of patients harboring VRE at the time of hospital admission substantially increases the endemic prevalence of VRE;

(3) Eliminating the influx of VRE results in the eradication of this pathogen from the hospital.

D'Agata,Horn & Webb, The impact of persistent gastrointestinal colonization on the transmission dynamics of Vancomycin-Resistant Enterococci, *J Infect Dis* (2002)

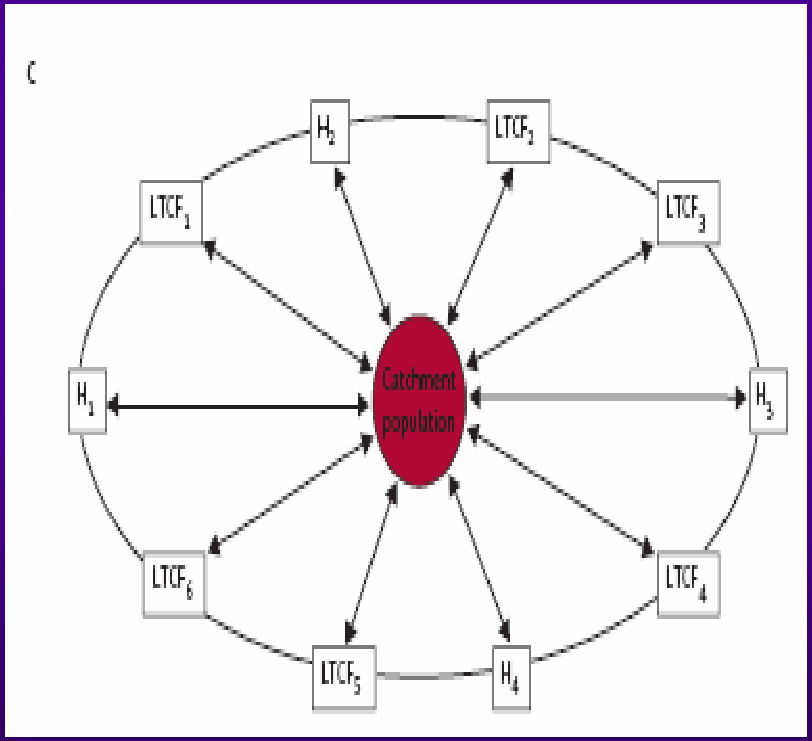
(B) Single Hospital and Community Models: Model with patient–patient transmission between randomly mixing individuals investigating the effect of an isolation unit. Individuals (colonised or uncolonised) are admitted to a hospital, discharged, and readmitted at a high or low rate.
Cooper et al., *Proc Natl Acad Sci* (2004)



Showed how the timing of the intervention, the level of resource provision, and chance combine to determine whether control measures succeed or fail. If resources do not scale with MRSA prevalence, isolation policies can fail ‘‘catastrophically.’’

(C) Multiple Hospitals and Communities Models: Metapopulation model for a multi-institutional setting with hospitals (H), long-term care facilities(LTCFs), and their catchment population (community). Individuals (colonised or uncolonised) migrate between the different institutions and the community due to admissions, discharges, and referrals.

Smith, Dushoff, Perencevich, Harris & Levin, *Proc. Natl. Acad. Sci*. (2004)



Applied structured population models to explore the dynamics of ARB, addressing
(i) What is the relationship between the proportion of carriers admitted to a hospital, transmission, and the risk of infection with ARB?
(ii) How do frequently hospitalized patients contribute to epidemics of ARB?
(iii) How do transmission in the community, long-term care facilities, and hospitals interact to determine the proportion of the population that is carrying ARB?

Smith,Levin & Laxminarayan, *Proc. Natl. Acad. Sci*. (2005)

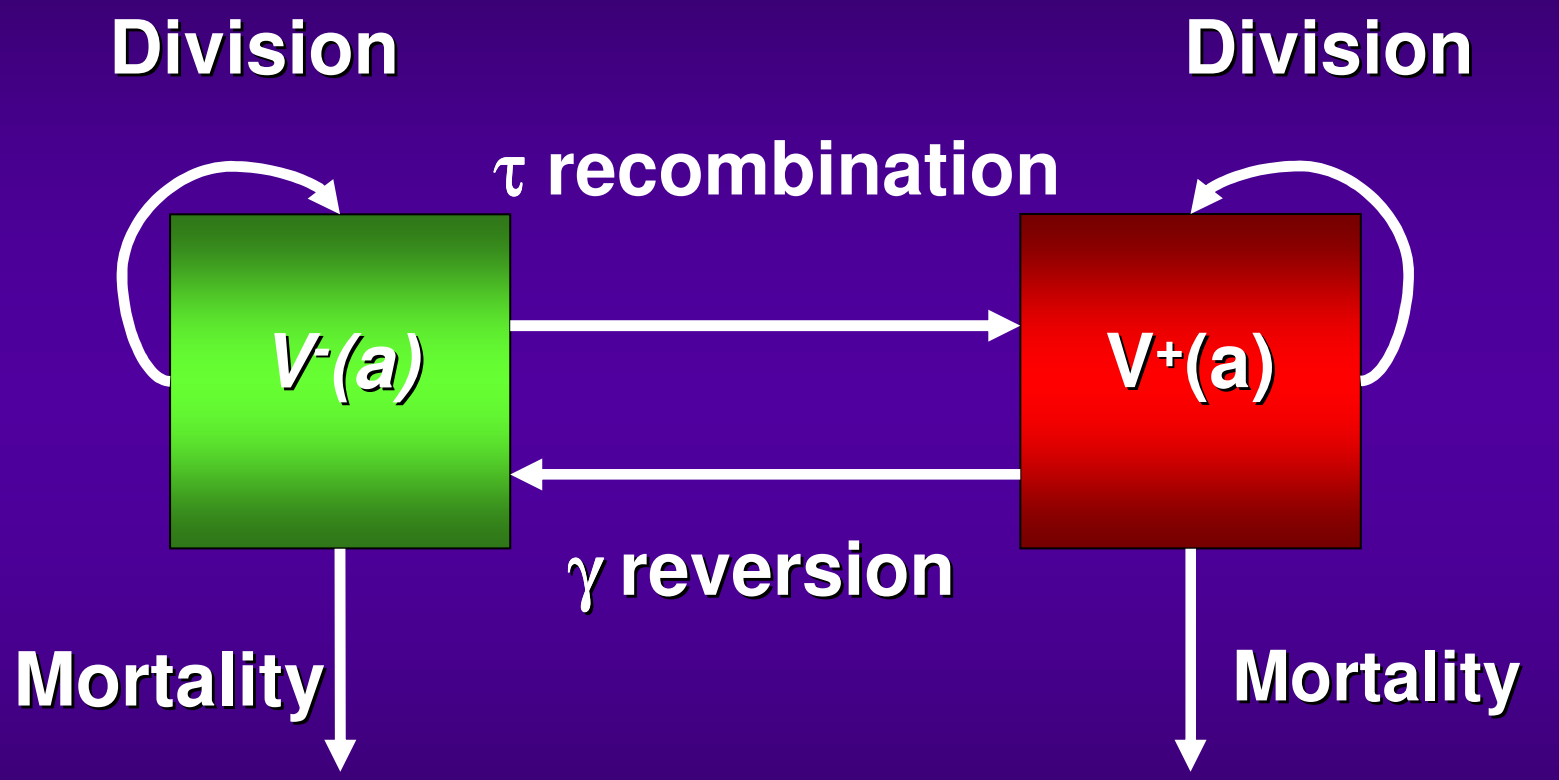
(D) Two Level Nosocomial Models: Models that incorporate both the bacteria population level in a single infected host and the patient level in the hospital.

Webb, D'Agata, Magal & Ruan, *Proc. Natl. Acad. Sci.* (2005)

The bacteria population level in a single infected host
- (i) hosts infected with the nonresistant strain (plasmid free)
- (ii) hosts infected with the resistant strain (plasmid bearing)

Patient level in the hospital
- (i) uninfected patients susceptible to infection
- (ii) patients infected with the nonresistant strain
- (iii) patients infected with the resistant strain

Diagram Flux for Bacteria

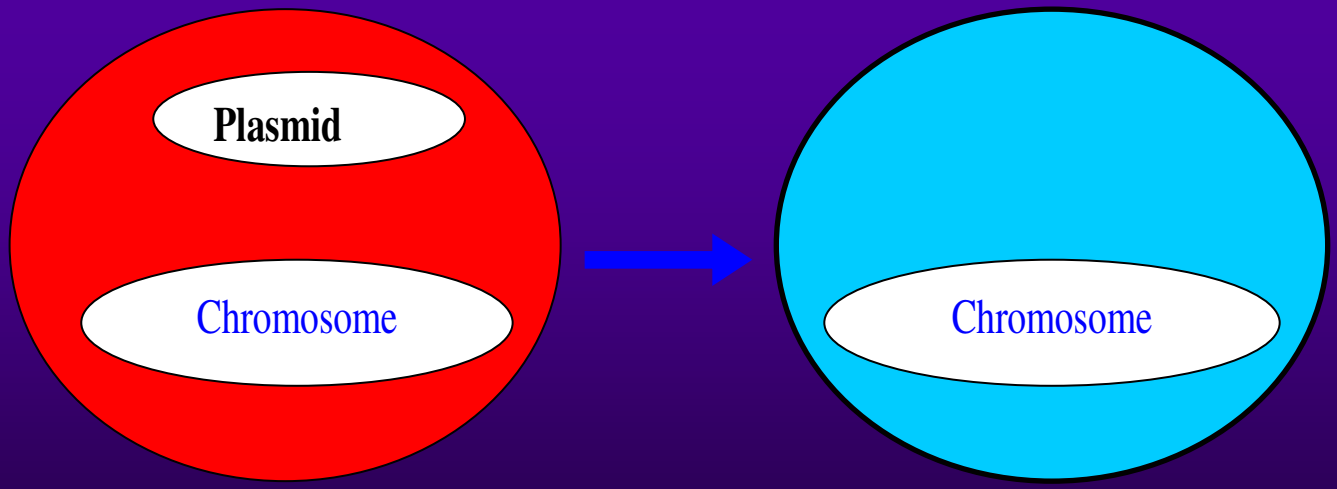


V-(a)= non-resistant strain

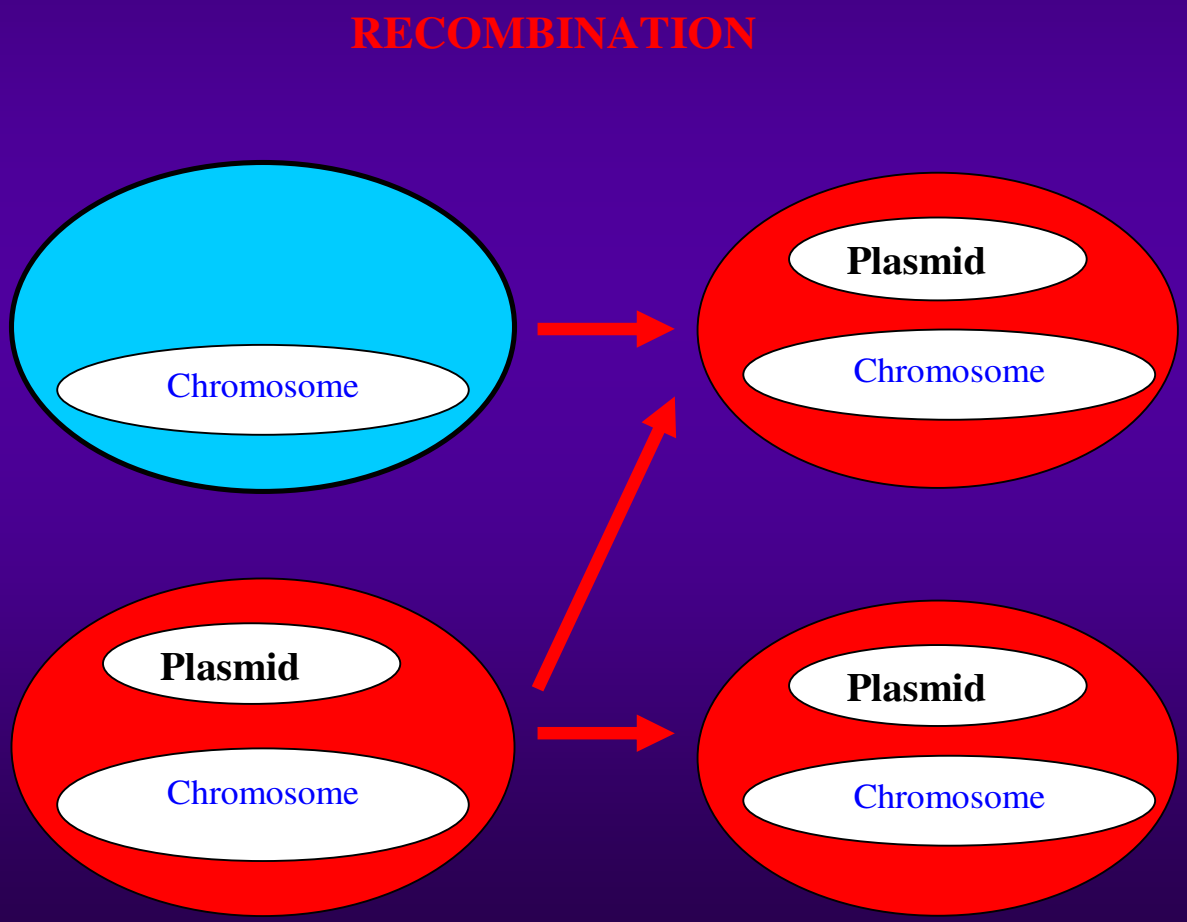
V+(a)= resistant strain

Plasmid is extra-chromosomal DNA in the bacteria cell whose genes may confer resistance to antibiotics. A bacterium containing plasmid may revert to a bacterium without plasmid.

REVERSION



A bacterium with plasmid may recombine with a bacterium not containing plasmid to yield two bacteria with plasmid



Model equations of plasmid free and plasmid bearing bacteria in a single infected host

$$\begin{cases} \dfrac{dV^-(a)}{da} = \left(-\dfrac{\tau V^+(a)}{V^-(a) + V^+(a)} \right. \\ \qquad \left. + \beta_- - \dfrac{V^-(a) + V^+(a)}{\kappa_F} \right) V^-(a) + \gamma V^+(a), \\ \dfrac{dV^+(a)}{da} = \left(\dfrac{\tau V^-(a)}{V^-(a) + V^+(a)} \right. \\ \qquad \left. + \beta_+ - \dfrac{V^-(a) + V^+(a)}{\kappa_F} - \gamma \right) V^+(a), \end{cases} \qquad [2]$$

with $V^-(0) = V_0^- > 0$ and $V^+(0) = V_0^+$ as the number of bacteria initially.

System 2 has at most three equilibria: the trivial equilibrium $E_0 = (0,0)$ (no infection), the semitrivial equilibrium $E_F = (\kappa_F \beta_-, 0)$ (infected only by plasmid-free bacteria), and the positive equilibrium

$$E^* = \left(\frac{\gamma \kappa_F}{\gamma + \sigma} \left(\beta_- + \sigma - \frac{\tau \sigma}{\gamma + \sigma} \right), \frac{\sigma \kappa_F}{\gamma + \sigma} \left(\beta_- + \sigma - \frac{\tau \sigma}{\gamma + \sigma} \right) \right)$$

(infected by both plasmid-free and plasmid-bearing bacteria) if

$$\sigma = \tau - \gamma + \beta_+ - \beta_- > 0,$$

Theorem. *For the original system [2], the topological structure of the trivial equilibrium E_0 in the interior of the first quadrant consists of a parabolic sector and a hyperbolic sector; the semi-trivial equilibrium E_F is stable if $\sigma<0$ and unstable if $\sigma>0$; the positive equilibrium E^* is a global attractor if $\sigma>0$.*

Patient Population Level

S(t) = number of patients susceptible at time t
$i_N(a,t)$ = infection age density of antibiotic nonresistant infectives at time t
$i_R(a,t)$ = infection age density of antibiotic resistant infectives at time t

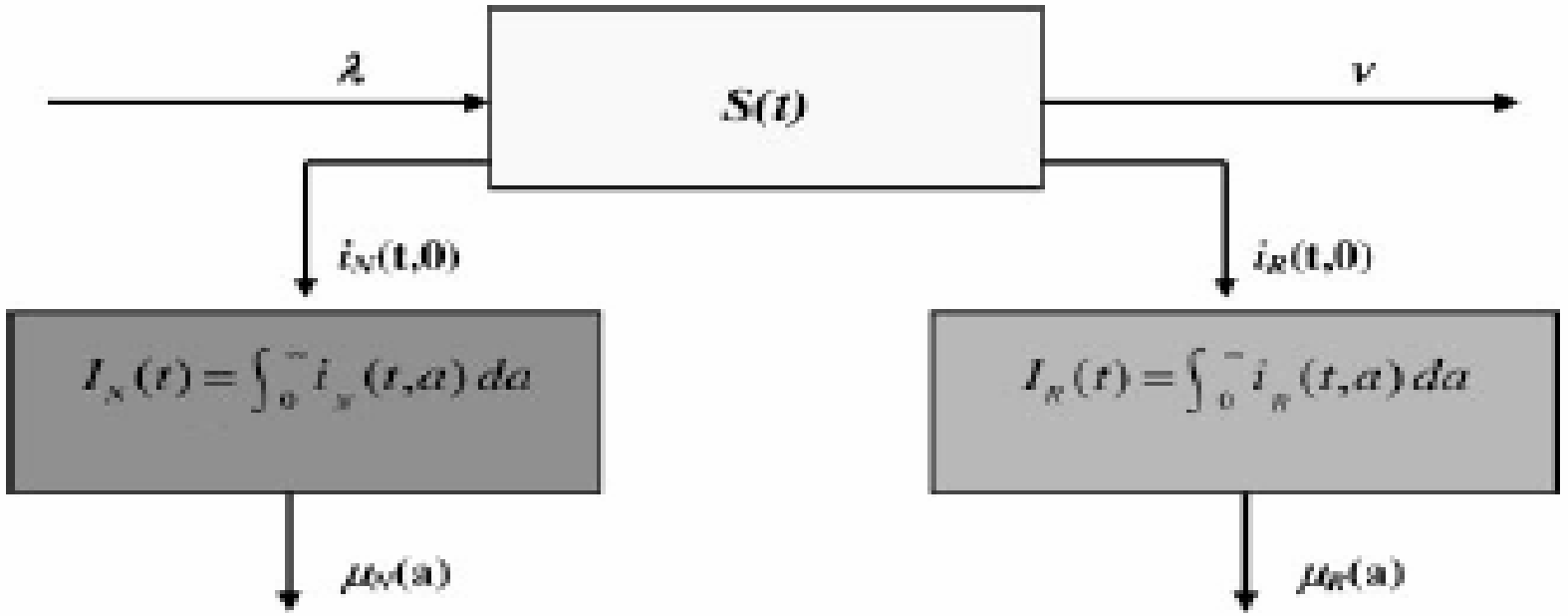


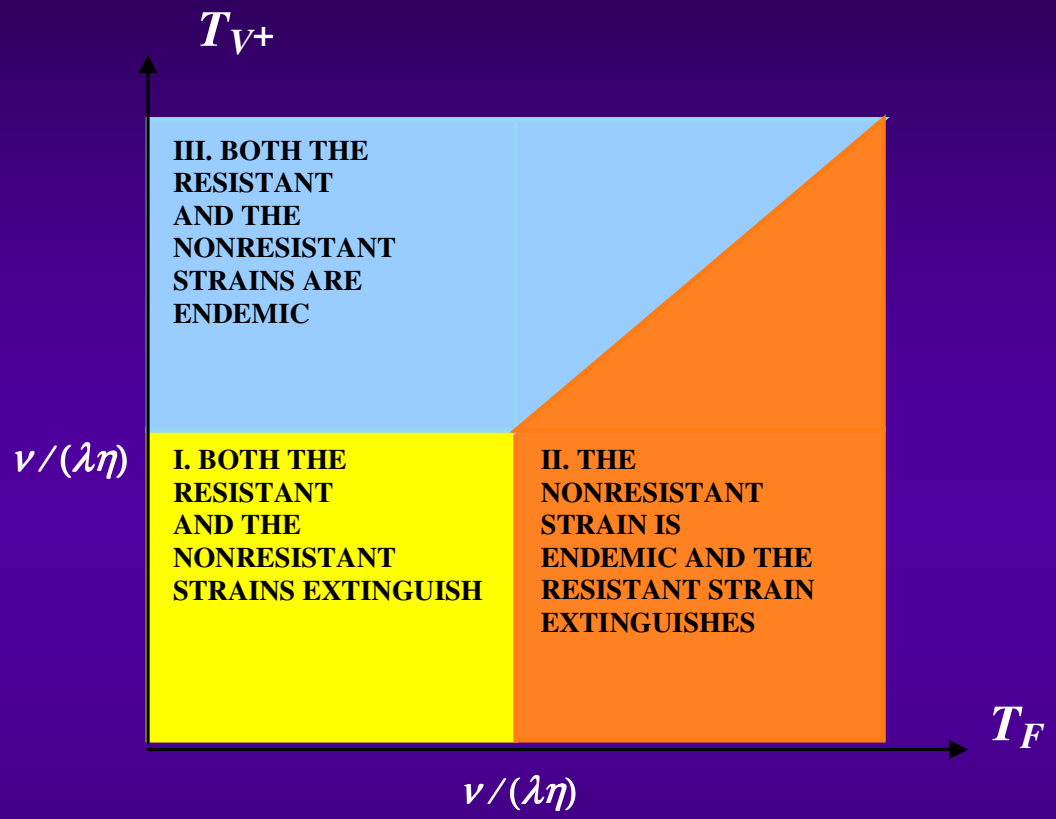
Fig. 5. Flow diagram of epidemic populations in the hospital. Susceptible patients acquire nonresistant or resistant bacteria at infection age 0 at time t.

Equations of the Epidemic Model

$$
\begin{cases}
\dfrac{dS(t)}{dt} = \lambda - \nu S(t) - \eta \left[\Phi_{V_F}(i_N(t)) + \Phi_{V^- + V^+}(i_R(t)) \right] S(t), \\
\dfrac{\partial}{\partial t} i_N(t, a) + \dfrac{\partial}{\partial a} i_N(t, a) = -\mu_N(a) i_N(t, a), \; a \in (0, \infty), \\
\dfrac{\partial}{\partial t} i_R(t, a) + \dfrac{\partial}{\partial a} i_R(t, a) = -\mu_R(a) i_R(t, a), \; a \in (0, \infty), \\
i_N(t, 0) = \eta \left[\Phi_{V_F}(i_N(t)) + \Phi_{V^-}(i_R(t)) \right] S(t), \\
i_R(t, 0) = \eta \Phi_{V^+}(i_R(t)) S(t), \\
(S(0), i_N(0, a), i_N(0, a)) = (S_0, \varphi_N(a), \varphi_R(a)),
\end{cases}
\qquad [3]
$$

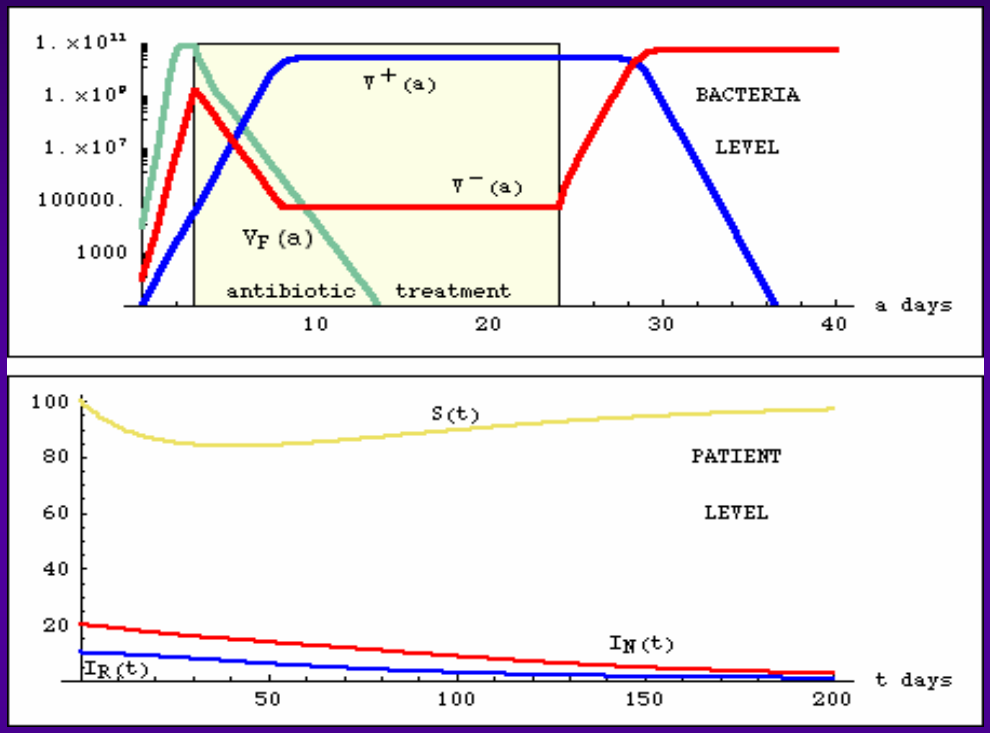
where $(S_0, \varphi_N, \varphi_R) \in [0, \infty) \times L^1(0, \infty) \times L^1(0, \infty)$.

Basic Reproduction Number $R_0 = (\lambda\eta/\nu)\ \max(T_F, T_V^+)$



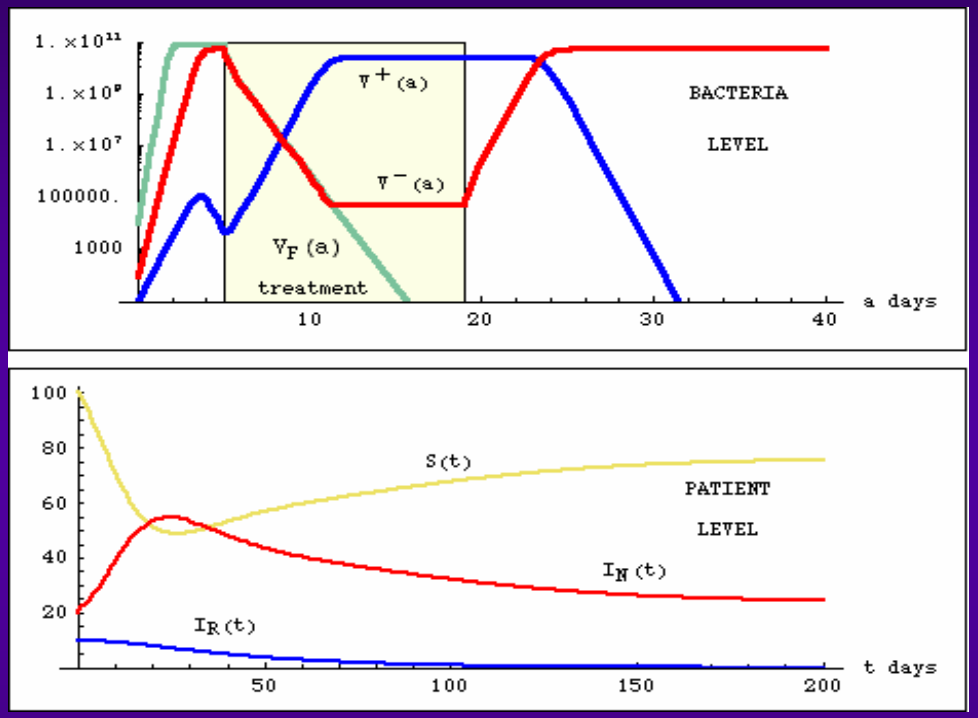
If $R_0 < 1$, then both strains extinguish. If $R_0 > 1$ and $T_F > T_V^+$, then the nonresistant strain becomes endemic and the resistant strain extinguishes. If $R_0 > 1$ and $T_V^+ > T_F$, then both strains become endemic.

Region I. $R_0 = \lambda\,\eta/\nu\ \ max(T_F, T_V+) < 1$



When the parameters lie in Region I, the only nontrivial steady state is given by $S = \lambda/\nu$, $I_N = 0$, $I_R = 0$.

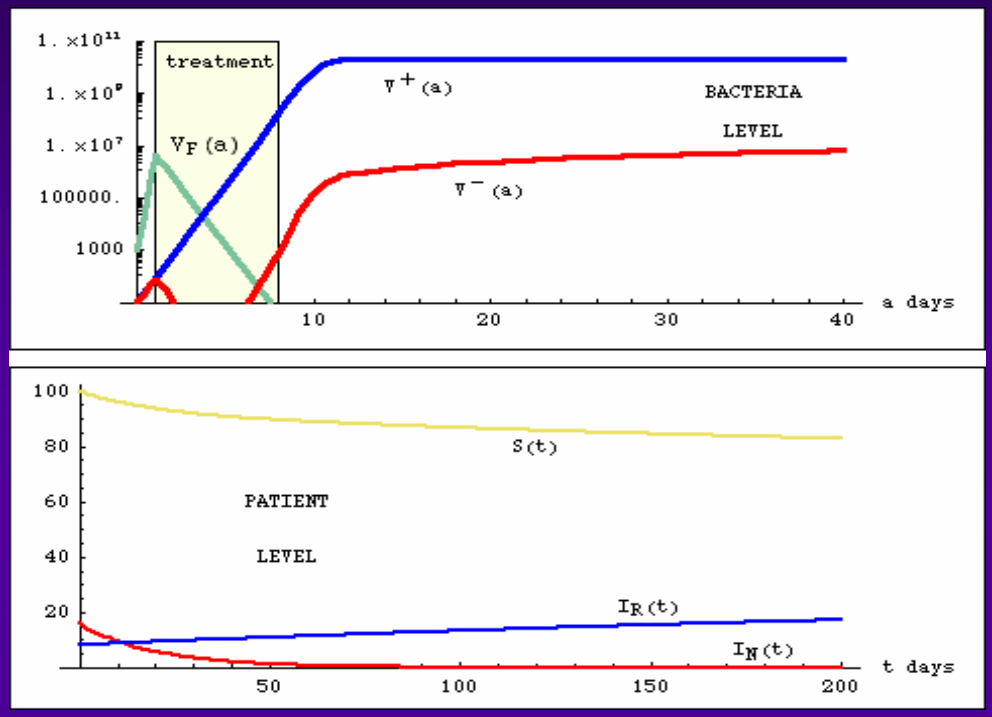
Region II. $R_0 = \lambda\,\eta/\nu\ max(T_F, T_V+) < 1$



When the parameters lie in Region **II**, there is a nontrivial steady state

$$S = 1/(\eta T_F), i_N(a) = \left(\lambda - \nu/(\eta T_F)\right)\exp\left[-\int_0^a \mu_N(s)ds\right], i_R(a) = 0$$

Region III. $R_0 = \lambda\eta/\nu \ max(T_F, T_V+) = \lambda\eta/\nu \, T_V+ > 1$



When the parameters lie in Region **III**, there is a nontrivial steady state

$$S = \frac{1}{\eta T_{V^+}}, i_N(a) = \frac{\left(\lambda - \nu/(\eta T_{V^+})\right) T_{V^-}}{T_{V^+} + T_{V^-} - T_F} \exp\left[-\int_0^a \mu_N(s)ds\right]$$

$$i_R(a) = \frac{\left(\lambda - \nu/(\eta T_{V^+})\right)(T_{V^+} - T_F)}{T_{V^+} + T_{V^-} - T_F} \exp\left[-\int_0^a \mu_R(s)ds\right]$$

D'Agata, Magal, **Ruan & Webb** (2006), Asymptotic behavior in bacterial infection models with antibiotic resistance. *Differential Integral Equations* **19**: 573-600.

The age-structured model has been the inspiration of a series of studies:

Magal & Ruan (2007), On integrated semigroups and age structured models in Lp spaces, *Differential Integral Equations* **20**, 197-239.

Magal & Ruan (2009), On semilinear Cauchy problems with non-dense domain, *Advances in Differential Equations* **14,** 1041-1084.

Magal & Ruan (2009), Center Manifolds for Semilinear Equations with Non-dense Domain and Applications to Hopf Bifurcation in Age Structured Models, *Memoirs of the American Mathematical Society*, **Vol. 202**, No. 951.

Liu, Magal & Ruan, Hopf bifurcation for non-densely defined Cauchy problems, *Zeitschrift für angewandte Mathematik und Physik* (accepted)

Liu, Magal, Ruan & Wu, Normal Forms for Semilinear Equations with Non-dense Domain and Applications to Delay Differential Equations (submitted)

D'Agata, Dupont-Rouzeyrol, Magal, Olivier & Ruan, The impact of different antibiotic regimens on the emergence of antimicrobial-resistant bacteria, *PLoS ONE* (2008)

$$B'(t) = \underbrace{\lambda B(t)}_{\substack{\text{Division}\\ \text{and}\\ \text{Mortality}}} - \underbrace{B(t)^2 \Big/ \kappa}_{\substack{\text{Limitation}\\ \text{of}\\ \text{Ressources}}} - \underbrace{\gamma \frac{P}{P+B(t)} B(t)}_{\substack{\text{Immune}\\ \text{Response}}}, \qquad (1)$$

$$\begin{cases} B_S'(t) = -\tau \dfrac{B_S(t)B_R(t)}{B(t)} + (\delta_S - \mu_S)B_S(t) + \delta_R \dfrac{p}{2} B_R(t) - \\ \qquad \dfrac{B(t)}{\kappa} B_S(t) - \gamma \dfrac{P}{P+B(t)} B_S(t) \\ B_R'(t) = \tau \dfrac{B_S(t)B_R(t)}{B(t)} + \left(\delta_R\left(1-\dfrac{p}{2}\right) - \mu_R\right) B_R(t) - \\ \qquad \dfrac{B(t)}{\kappa} B_R(t) - \gamma \dfrac{P}{P+B(t)} B_R(t) \end{cases} \qquad (2)$$

$$\begin{cases} B_S'(t) = -\tau \dfrac{B_S(t)(B_A(t)+B_B(t)+B_{AB}(t))}{B(t)} + (\delta_S - \mu_S)B_S(t) \\ \quad + \delta_A \dfrac{p}{2} B_A(t) + \delta_B \dfrac{p}{2} B_B(t) + \delta_{AB} \dfrac{p^2}{2} B_{AB}(t) - \dfrac{B(t)}{\kappa} B_s(t) \\ \quad - \gamma \dfrac{P}{P+B(t)} B_S(t) \\ B_A'(t) = \tau \dfrac{B_S(t)B_A(t)}{B(t)} - \tau \dfrac{B_A(t)(B_B(t)+B_{AB}(t))}{B(t)} \\ \quad + \left(\delta_A\left(1-\dfrac{p}{2}\right) - \mu_A\right) B_A(t) + \delta_{AB} \dfrac{p}{4} B_{AB}(t) \\ \quad - \dfrac{B(t)}{\kappa} B_A(t) - \gamma \dfrac{P}{P+B(t)} B_A(t) \\ B_B'(t) = \tau \dfrac{B_S(t)B_B(t)}{B(t)} - \tau \dfrac{B_B(t)(B_A(t)+B_{AB}(t))}{B(t)} \\ \quad + \left(\delta_B\left(1-\dfrac{p}{2}\right) - \mu_B\right) B_B(t) + \delta_{AB} \dfrac{p}{4} B_{AB}(t) \\ \quad - \dfrac{B(t)}{\kappa} B_B(t) - \gamma \dfrac{P}{P+B(t)} B_B(t) \\ B_{AB}'(t) = \tau \dfrac{B_S(t)B_{AB}(t)}{B(t)} \\ \quad + \tau \dfrac{B_A(t)(B_B(t)+B_{AB}(t)) + B_B(t)(B_A(t)+B_{AB}(t))}{B(t)} + \\ \quad + \left(\delta_{AB}\left(1-\dfrac{p}{2}-\dfrac{p^2}{2}\right) - \mu_{AB}\right) B_{AB}(t) - \dfrac{B(t)}{\kappa} B_{AB}(t) - \gamma \dfrac{P}{P+B(t)} B_{AB}(t) \end{cases} \qquad (3)$$

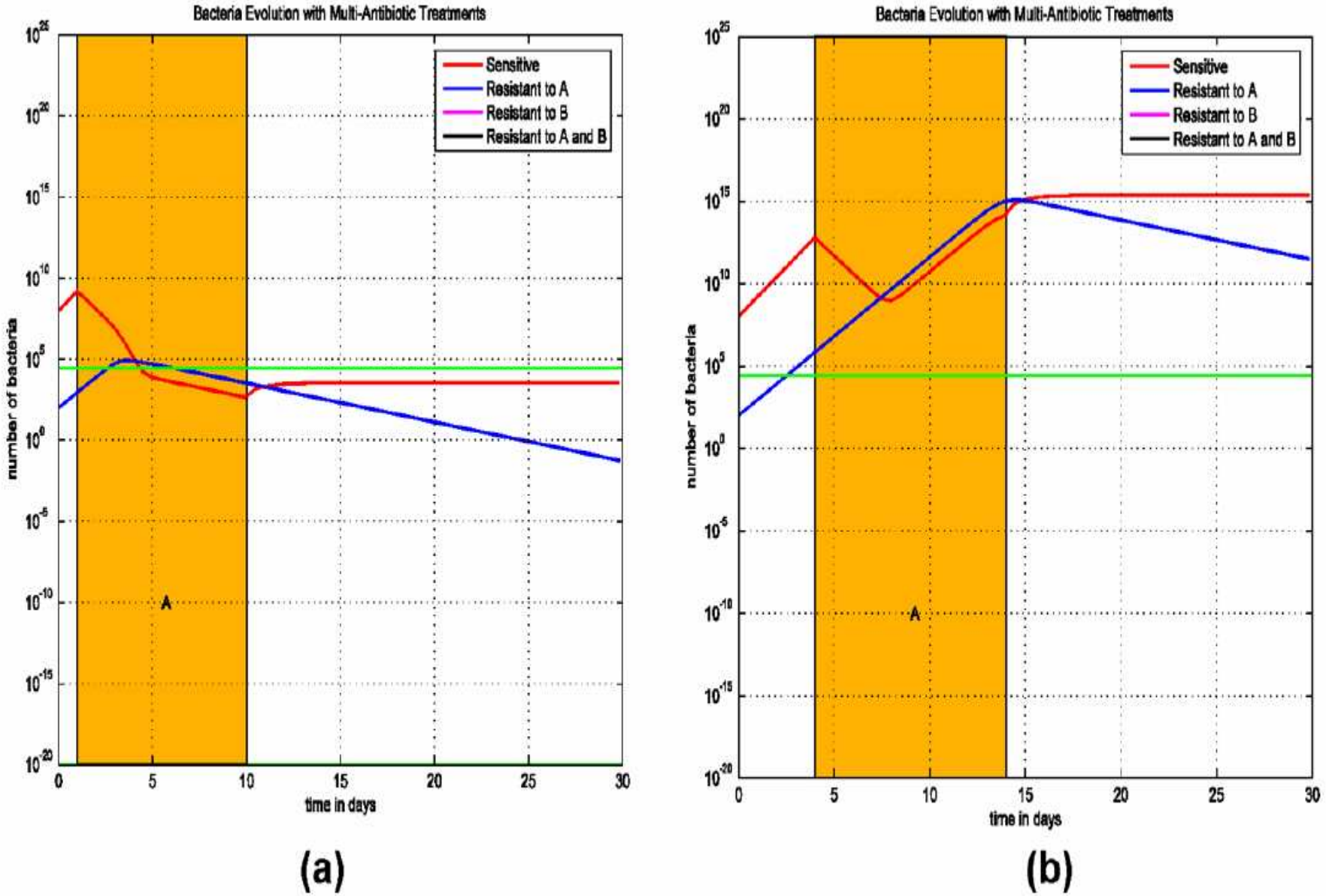
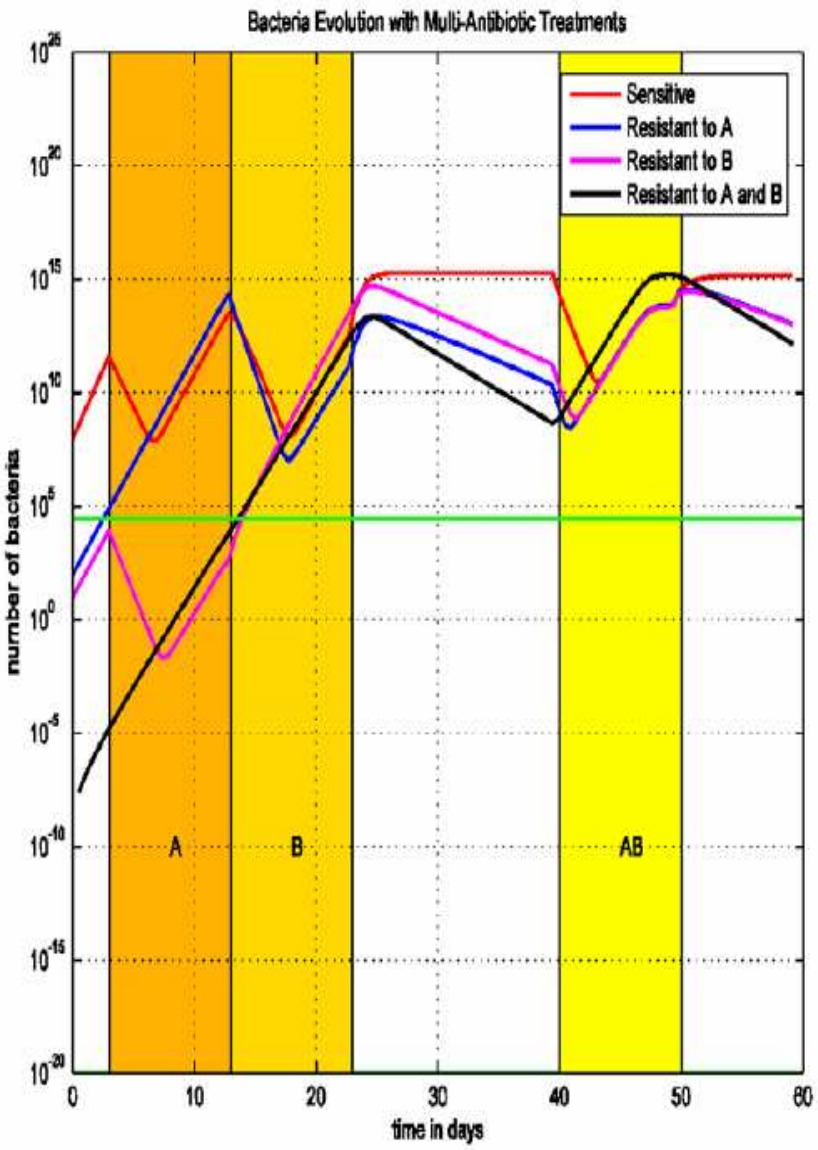
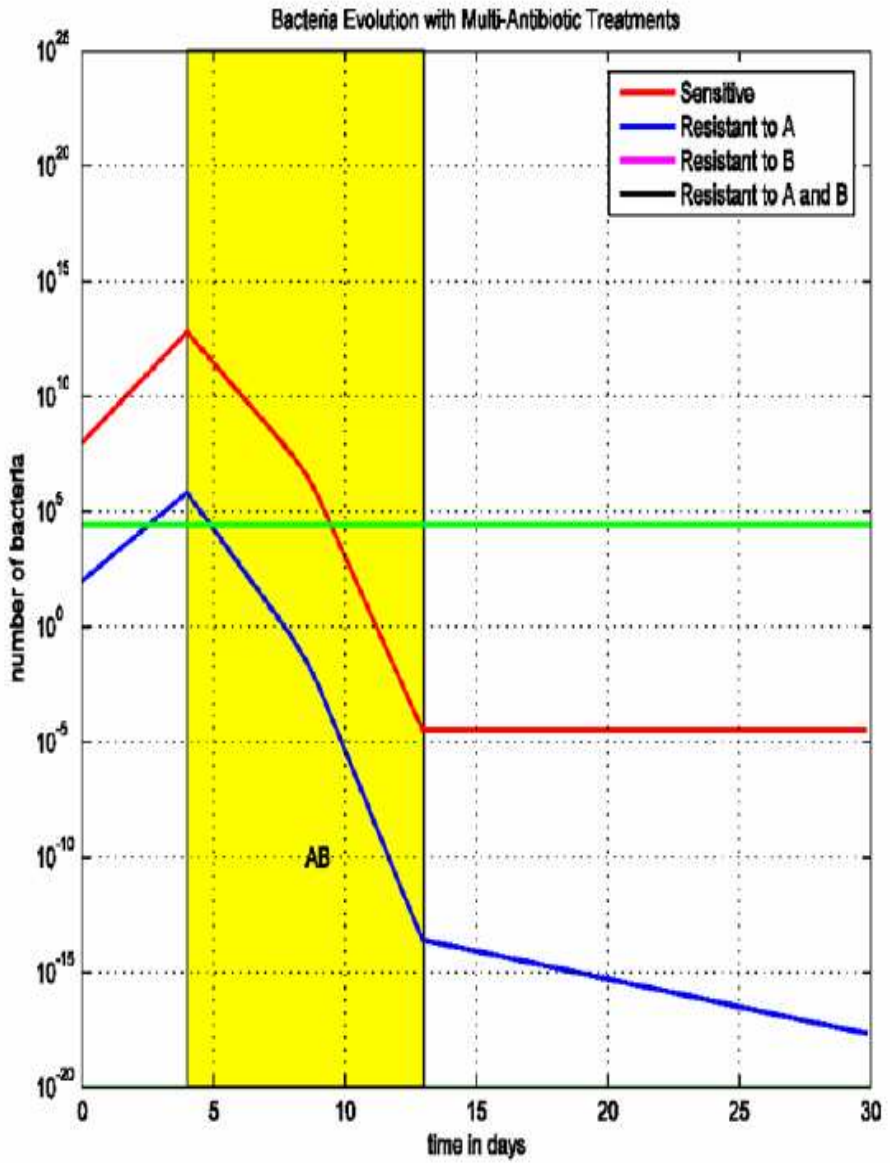


Figure 2. Simulations of Model (1) on the initiation of an antimicrobial therapy and infection progression. (a) Treatment starts at the 1st day after an infection and lasts for 9 days. The bacterial load decreases to below the threshold and the infection is prevented. (b) Treatment starts at the 3rd day after an infection and lasts for 9 days. The bacterial load decreases slightly, but stays above the threshold and increases even during the treatment.


Bacteria Evolution with Multi-Antibiotic Treatments
Sensitive
Resistant to A
Resistant to B
Resistant to A and B
number of bacteria
time in days
A
B
AB

(a)


Bacteria Evolution with Multi-Antibiotic Treatments
Sensitive
Resistant to A
Resistant to B
Resistant to A and B
number of bacteria
time in days
AB

(b)

***Conclusions/Significance*:**

(i) Shorter lengths of antibiotic therapy and early interruption of antibiotic therapy provide an advantage for the resistant strains
(ii) Combination therapy with two antibiotics prevents the emergence of resistance strains in contrast to sequential antibiotic therapy
(iii) Early initiation of antibiotics is among the most important factors preventing the emergence of resistant strains.

(E) Individual Based Model (IBM):

D'Agata, Magal, Olivier, Ruan & Webb, *J. Theoret. Biol.* (2007)

- **Individuals**
  - Healthcare workers
  - Patients
- **Environment**
  - Hospital divided in departments
- **Spatial Structure**
  - Not explicit but implicit with the visit process
- **Time**
  - Discrete
  - Structured in shift
- **Contamination**
  - A patient transmits bacteria to a healthcare worker
- **Infection**
  - Healthcare worker transmits bacteria to a patient

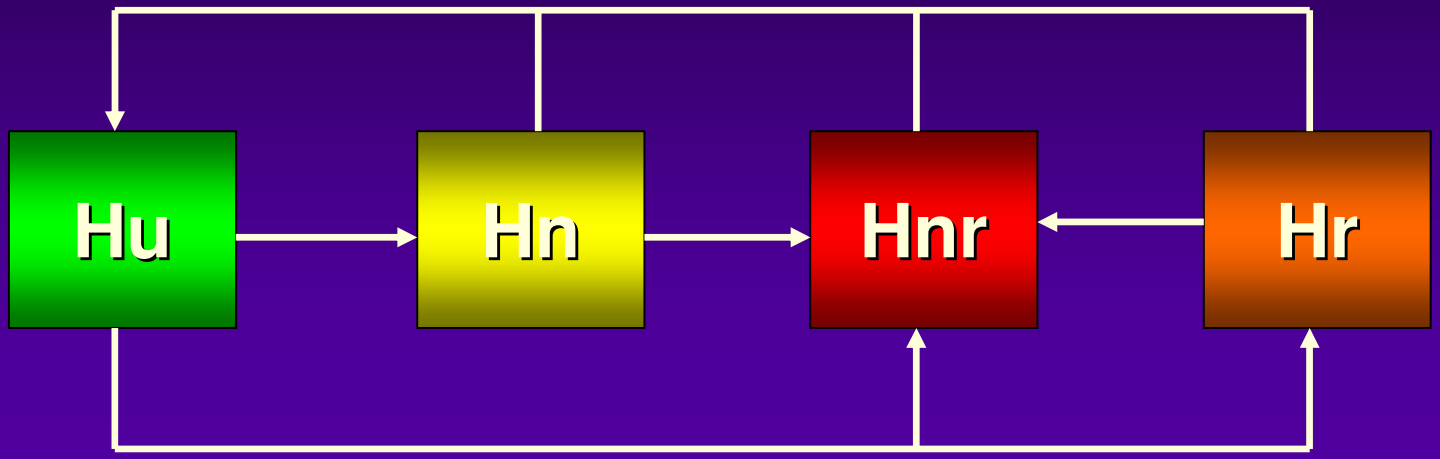
Time Scales

A shift = 8 Hours

The healthcare workers begin each shift uncontaminated

Each shift is also decomposed into time steps Δt = 5 minutes.

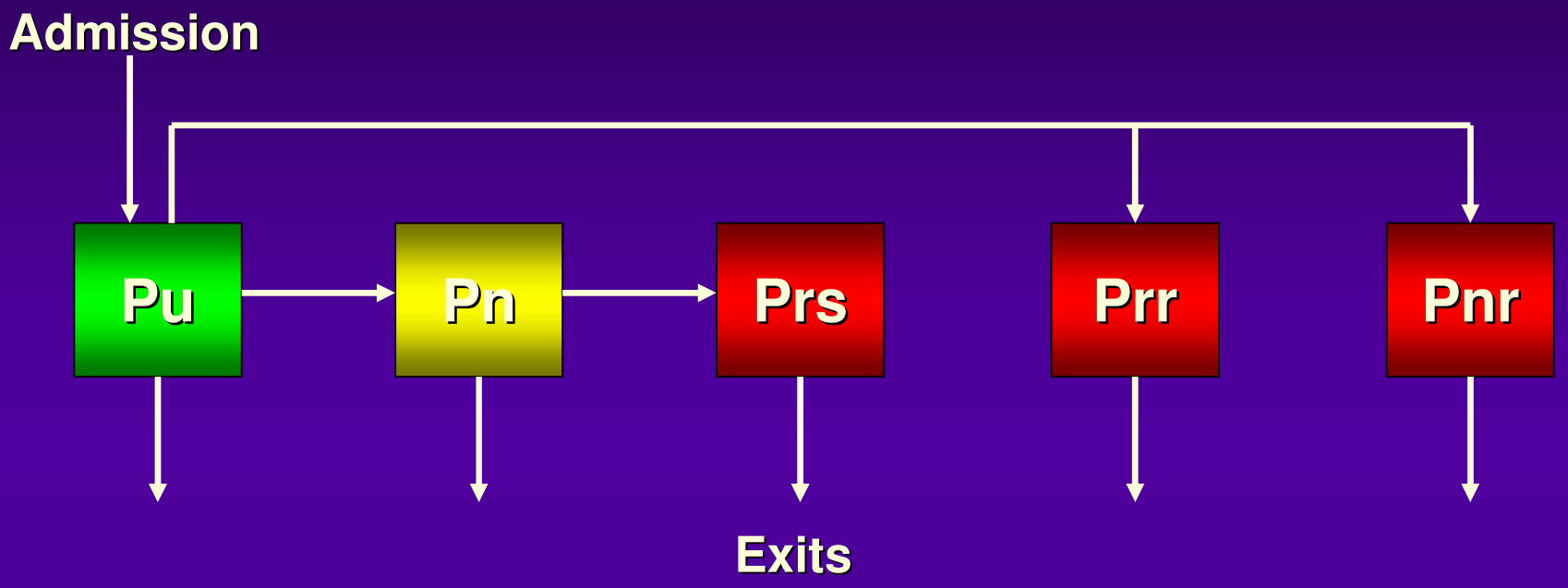
Healthcare workers



Four status for Healthcares workers

- **Hu** **Uncontaminated**
- **Hn** Contaminated only by **Non resistant bacteria.**
- **Hnr** Contaminated by both **Non resistant and Resistant strains**.
- **Hr** Contaminated only by **Resistant bacteria.**

Patients



Five status for patients

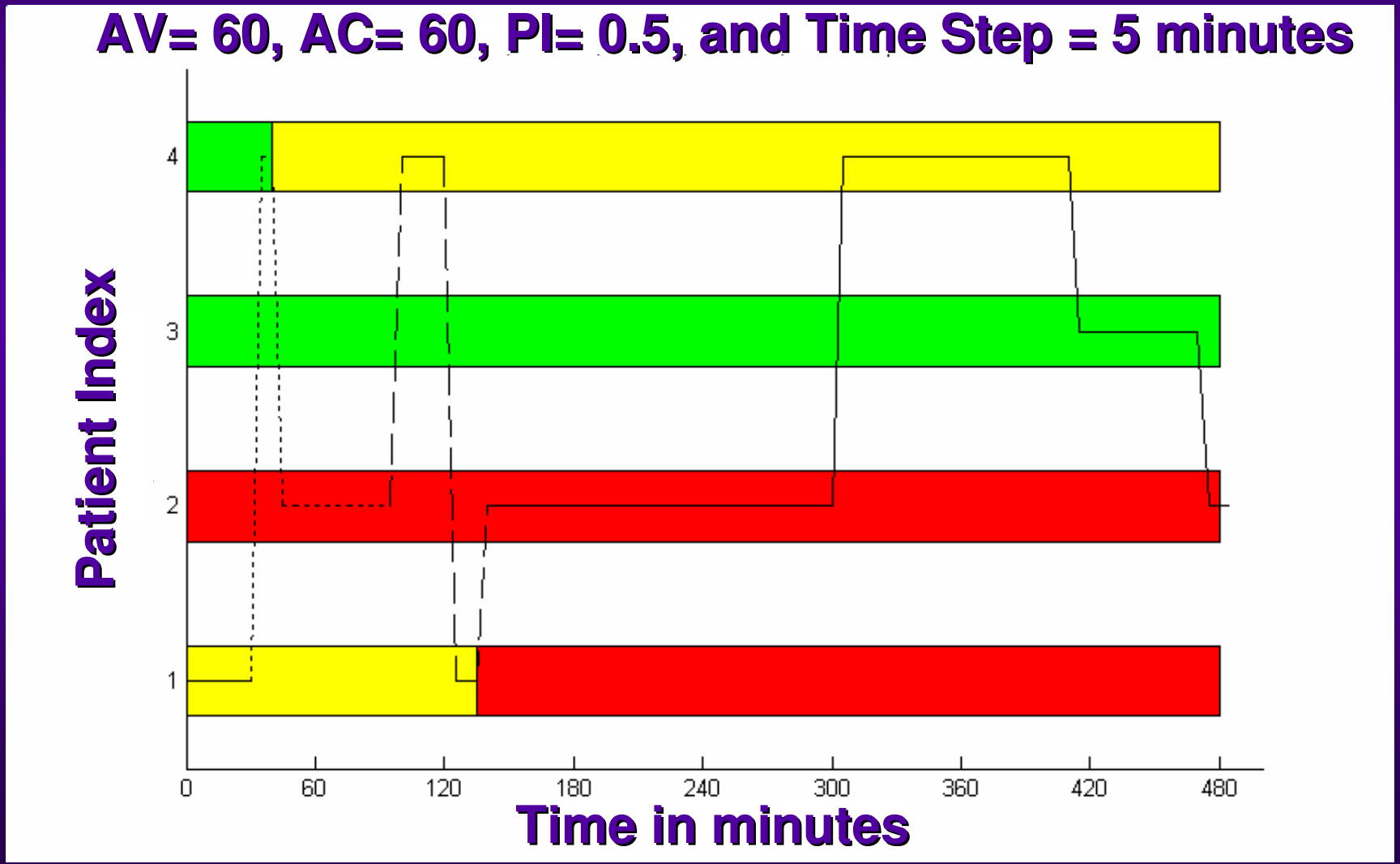
- **Pu** **Uninfected**
- **Pn** Infected only by a **Non resistant bacteria**
- **Prs** First Pn, and then infected by a **Resistant bacteria**
- **Prr** Infected only by a **Resistant bacteria**
- **Pnr** Infected by **Non resistant and Resistant bacteria**

Interactions Contamination and Infection Processes

- Healthcare workers transmit only what they have !
- The contamination of HCWs can only occur if the patient is infectious.
- Patients infectiousness depends on the time of infection
- The doses inoculated to patients are fixed, but depend on the status of the patient ‘n’ ‘rs’, ‘rr’, or ‘nr’.
- Each healthcare worker visits only one patient.
- The average time of visit is

$$A_V = 90 \text{ minutes}$$

Visits for 1 HCW and 4 patients



Parameters of the model

Number of patients	Nbp	400*
Number of healthcare workers	Nbh	100*
Average length of stay for patient ‘u’	A_U	5 days*
Average length of stay for patient ‘n’	A_N	14 days*
Average length of stay for patient ‘r’	A_R	28 days*
Average time of visit	A_V	90 mn
Probability of contamination	P_C	0.4**
Probability of infection	P_I	0.06**
Average time of contamination	A_C	60 mn**

* Beth Israel Deaconess Medical Center, Harvard, Boston, ** Cook County Hospital, Chicago

From The IBM to a PDE Model

To simplify the interpretation and application of the model's conclusions, a corresponding deterministic model was created, which describes the average behavior of the individual based model over a large number of simulations.

The integration of these two model systems provides a quantitative analysis of the emergence and spread of antibiotic-resistant bacteria, and demonstrates that early initiation of treatment and minimization of its duration mitigates antibiotic resistance epidemics in hospitals.

Basic Reproduction Numbers Derived from the PDE Model

We have

$$R_0^N = \frac{(\nu_V)^2 \beta_V P_I P_C}{\nu_C} \int_0^{+\infty} \gamma_N^N(a) \exp(-\nu_N a) da$$

$$R_0^R = \frac{(\nu_V)^2 \beta_V P_I P_C}{\nu_C} r(A)$$

where

$$A = \begin{pmatrix} \int_0^{+\infty} \gamma_R^{RR}(a) \exp(-\nu_R a) da & \int_0^{+\infty} \gamma_R^{NR}(a) \exp(-\nu_R a) da \\ \int_0^{+\infty} \gamma_{NR}^{RR}(a) \exp(-\nu_R a) da & \int_0^{+\infty} \gamma_{NR}^{NR}(a) \exp(-\nu_R a) da \end{pmatrix},$$

Comparison between the IBM and the PDE model

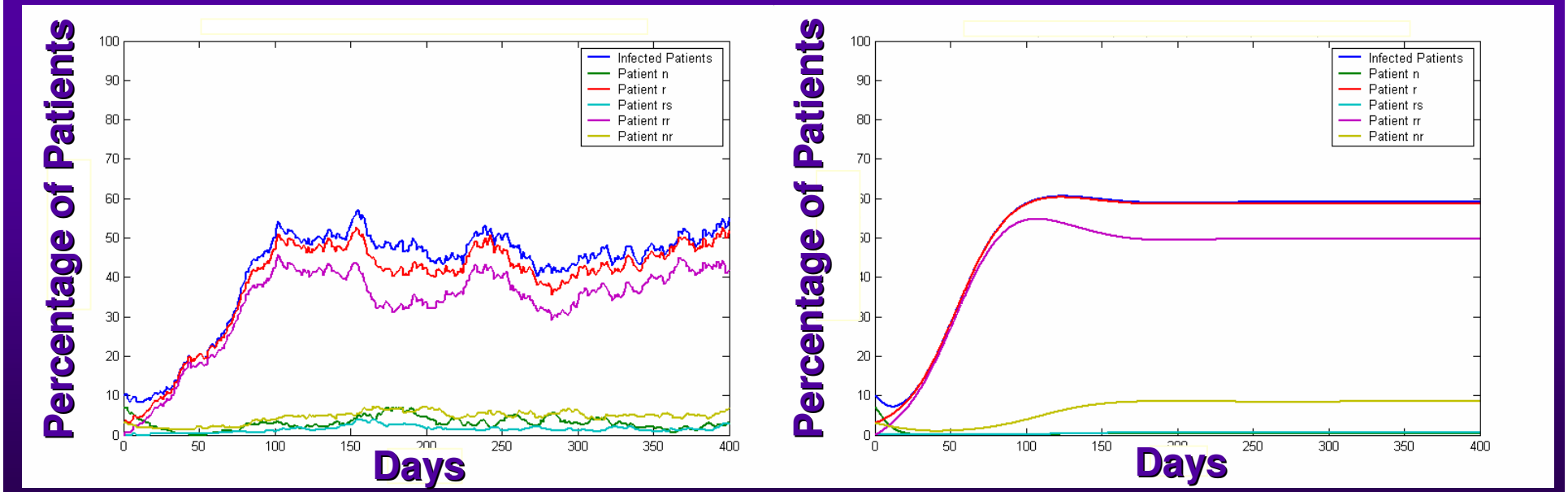
Treatment starts on day 3 and stops on day 21

AV=60 mns

IBM

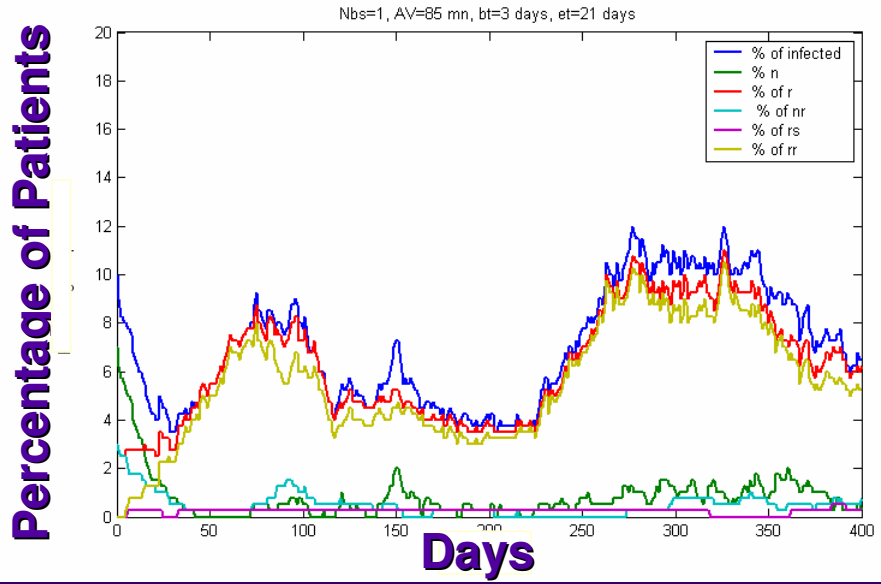
PDE

$R^N_0 = 0.21$, $R^R_0 = 2.8$

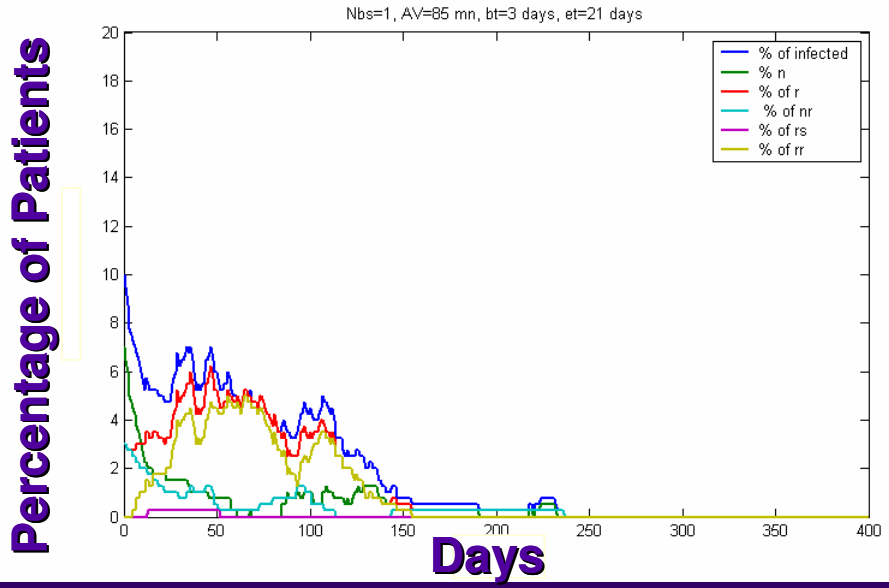


For the IBM

Beginning of treatment day 3
end of treatment day 21



Beginning of treatment day 1
end of treatment day 8

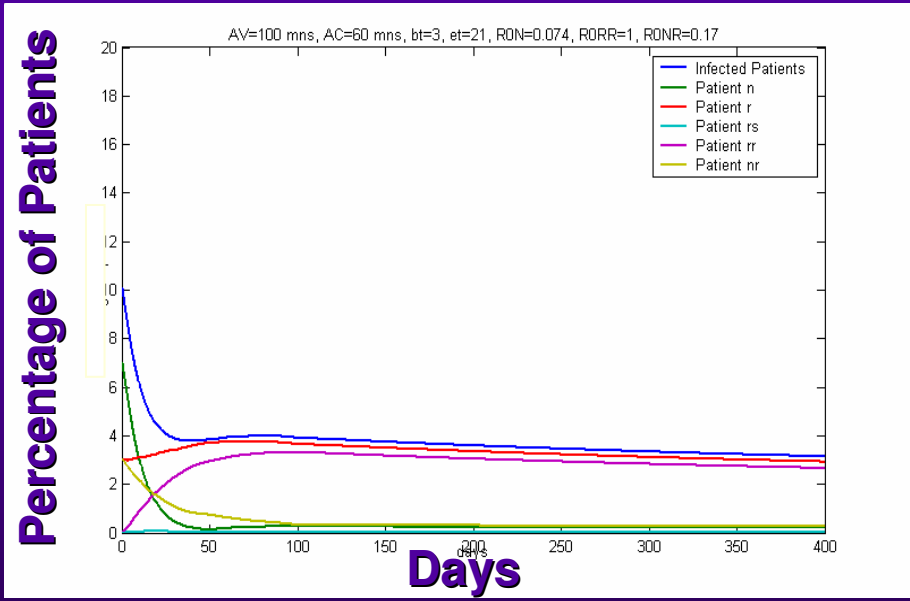


A_V=90 mn

Influence of the antibiotic treatment: an example

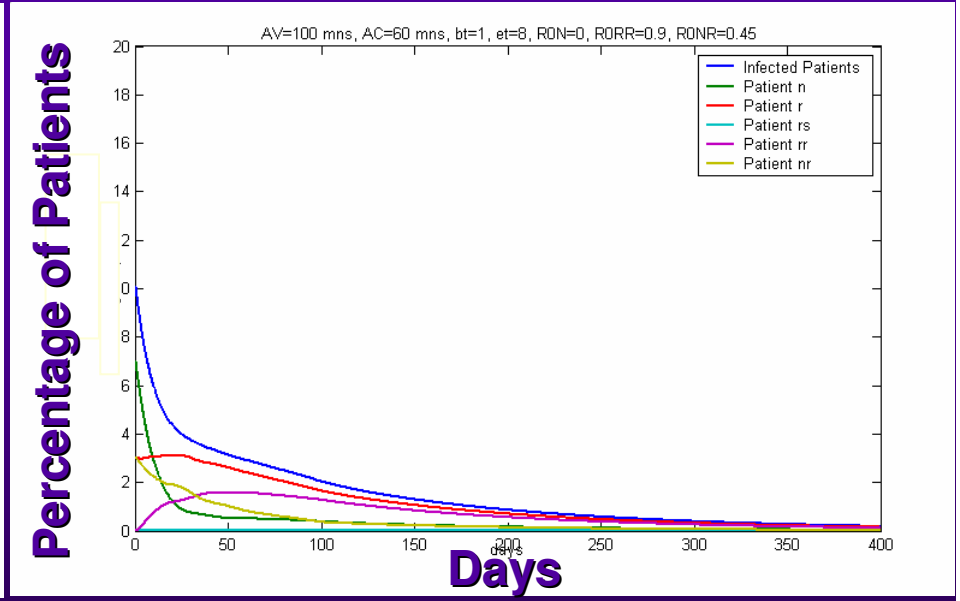
Beginning of treatment day 3
End of treatment day 21

$R^N_0=0.074$, $R^R_0=1.0218$



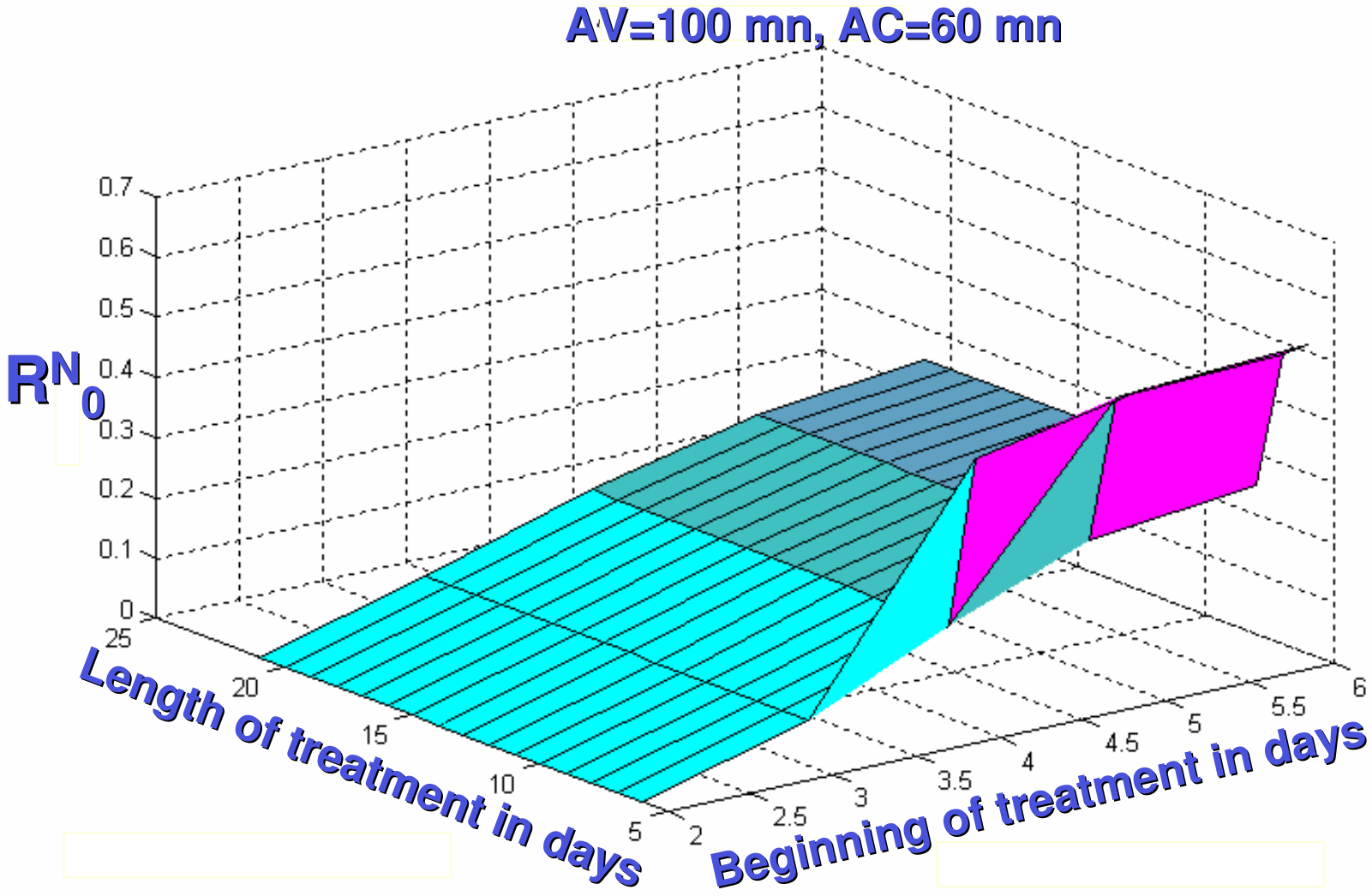
Beginning of treatment day 1
End of treatment day 8

$R^N_0=0$, $R^R_0=0.9$

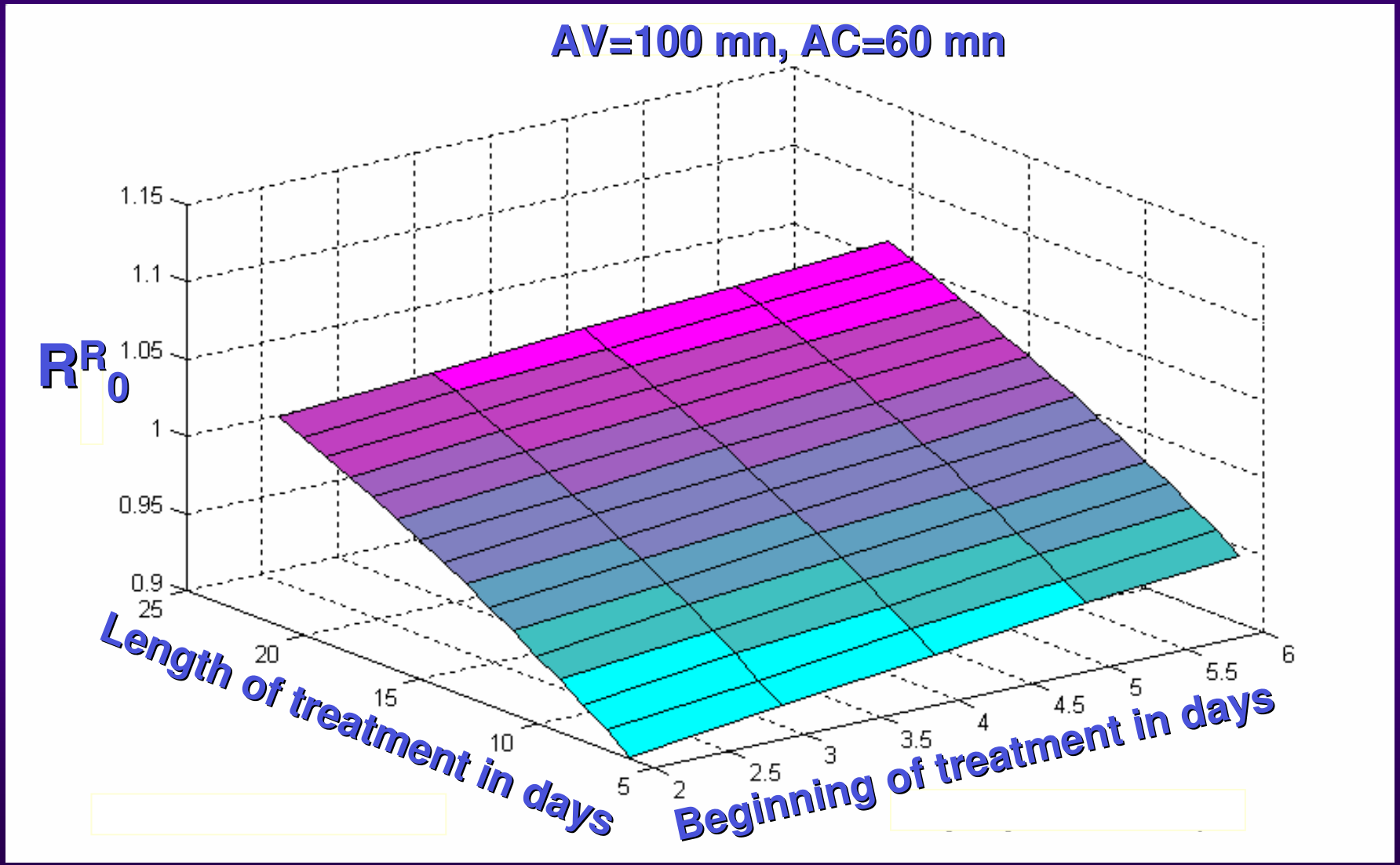


$A_V=100$ mn

Influence of the treatment on R^N_0



Influence of the treatment on R^R_0



CONCLUSIONS

- **Antibiotic therapy regimens should balance the care of individual patients and the general patient population welfare.**

- **Antibiotic treatment should start as soon as possible after infection is diagnosed and its duration should be minimized.**

- **Mathematical models can be used to design measures to control nosocomial epidemics in specific hospital environments.**