Dynamics of MRSA carriage in the Dutch population

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Voorwoord

In het kader van mijn afstudeerproject voor de master *Mathematics with Lifesciences* heb ik gekozen voor een afstudeerstage in een onderzoeksinstituut buiten de VU. Dit is het RIVM (Rijksinstituut voor Volksgezondheid en Milieu) geworden op de afdeling Centrum voor Infectieziekten Epidemiologie, bij de projectgroep wiskundige modellering. Naast mijn afstudeerproject heb ik ook deelgenomen aan de literatuurdiscussies in de projectgroep.

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Abstract

Increasing prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in countries that so far had successful control (such as the Netherlands and Scandinavian countries) is cause for concern. Recently, asymptomatic MRSA carriage has been identified as an important contributor to this increase. Mathematical modelling can help to interpret the contribution of this feature and to evaluate additional intervention measures.

In this paper we investigate the contribution of asymptomatic MRSA carriers to the prevalence in the hospital and in the community and to the number of outbreaks of hospital-acquired MRSA. The dynamics of MRSA carriage in the Netherlands is characterised by a system of interference at detected high prevalence of MRSA in the hospital. These dynamics of MRSA carriage are modelled with a linear matrix model concerning a system of density regulation, i.e. a "flip-flop" system. Thereafter, intervention measures such as screening in and outgoing patients and HCW measures are investigated.

Surprisingly, if hygiene measures are not performed well enough the prevalence of MRSA in the hospital and the community increase. This is in contrast with models found in the literature, which are claiming that hygiene measures are effective interventions. Screening all outgoing patients reduces the prevalence of MRSA in both the hospital and the community more than screening all incoming patients. Furthermore, we show that screening only a part of the population (the 65^+) when leaving the hospital is also effective to reduce the prevalence of MRSA in the hospital and in the community. Moreover, the age group of the elderly of 65 and older contribute 1.76 times more to the spread of MRSA than the non-elderly, because on average they stay longer in the hospital and they visit the hospital more frequently then younger individuals. We conclude that to reduce the prevalence of MRSA in the hospital and in the community one should start with screening outgoing elderly or patients who stay the longest in the hospital and who visit most frequently the hospital.

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1 Introduction

1.1 History of MRSA

Methicillin-resistant *Staphylococcus aureus* (MRSA) was discovered in 1961 one year after the introduction of the antibiotic methicillin [1]. Soon epidemics of MRSA in hospitals were reported all over the world. Therefore MRSA is often referred as 'the hospital *Staphylococcus*'. The mortality rate in patients with invasive MRSA infection is twice as high compared to patients with an invasive methicillin-susceptible *S. aureus* infection [2].

There are two different types of strains of MRSA: hospital-acquired (HA) and community-acquired (CA) MRSA. The distinction between HA- and CA-MRSA is: hospital-acquired MRSA is almost only transmitted in hospitals, while community-acquired MRSA also is transmitted in the community. Community-acquired MRSA is most often found in groups with high intensity physical contacts, such as football players, which might help with transmission [3].

An MRSA positive individual can either be an asymptomatic carrier or have a symptomatic infection [4]. In both cases the individual is colonised with MRSA and infectious. Those asymptomatic carriers can serve as reservoirs, because they are not easily detected.

1.2 MRSA in the Netherlands

Nowadays the prevalence of MRSA in hospitals in most countries is higher than 20% [5] which is reported by the European Antimicrobial Resistance Surveillance System (EARSS). The Netherlands and Scandinavia are exceptions, because in those countries the prevalence among clinical *S.aureus* was less than 1% until 2003 [6, 2]. This is due to the "search and destroy" (S&D) policy in combination with restrictive antibiotic use in those countries [2]. In this S&D policy every potential MRSA-patient is immediately isolated [7] after admission to a hospital until they are proved to be clean of MRSA. In the Netherlands a potential MRSA-patient is defined by [6]:

1. All patients that are known to be positive for MRSA.

2. All patients transferred from a foreign hospital or nursing home, who had been admitted there for at least 24h or had undergone surgery there or have a drain or catheter in place at the time of transfer or are intubated or have open wounds or infections such as abscesses or furuncles.

3. All patients that had known contact with an MRSA carrier.

4. (Since July 2006) All patients who professionally have intensive contact with pigs.

The prevalence of MRSA upon hospital admission among patients without risk factors is very low: 0.03% [2]. Among patients, admitted to Dutch hospitals, repatriated from

foreign countries the prevalence of MRSA is 10-17% [2, 8]. In the Netherlands we speak of an epidemic in a hospital, when 2 or more patients or health-care-workers (HCWs) are found with an MRSA colonisation [6]. At the time an epidemic is noticed a team is formed which has to prevent further transmission. This can be done by isolation, cohorting (a few patients per nurse) or more hygiene measures [6].

Unfortunately, the S&D policy does not seem to be enough to prevent the spread of MRSA, because in the past years, an increase in the number of outbreaks is noted in Dutch hospitals [5]. In 2003 the prevalence was circa 1% [9], however in 2004 the prevalence has increased to 1.5% [10]. This rise is alarming, because if the prevalence rises further the isolation-beds will all be occupied and then the control of preventing transmission is lost. Recently, asymptomatic MRSA carriage has been identified as an important contributor to this increase.

1.3   Research question

In this paper we investigate the contribution of asymptomatic MRSA carriers to the prevalence and number of outbreaks of hospital-acquired MRSA. To investigate this, the dynamics of MRSA carriage will be modelled in a setting between a hospital and a community. These dynamics of MRSA carriage in the Netherlands is characterised by a system of interference at detected high prevalence of MRSA in the hospital. Therefore two situations are possible in the Netherlands: no interference thus transmission can continue or interference to prevent further transmission. This gives rise to a "flip-flop" system in which periods of high and low levels of interventions alternate, depending on the prevalence of MRSA in the hospital. Therefore we will specifically investigate such a system with density regulation. Thereafter, we will investigate which control measures are effective to reduce the number of outbreaks and the prevalence of MRSA carriage in the community and the hospital. These interventions include enhanced hand-washing and other hygiene measures of HCWs, screening incoming and/or outgoing patients for MRSA in a hospital. Furthermore, we will investigate the effect of an age group, that contributes more to the spread of MRSA than other groups in the population. If this is true, we will investigate if interventions aimed at specific age groups will be enough to reduce the prevalence of MRSA in the hospital and in the community and the number of outbreaks of MRSA.

In chapter 2 of this paper an overview is given of mathematical models of MRSA transmission found in the literature. In the subsequent chapter a model with a single hospital and a community has been made. This model is used to investigate which intervention measure is most effective to reduce the number of outbreaks and the prevalence of MRSA in the hospital and in the community. Furthermore, to investigate the influence of an age group on the transmission of MRSA in the hospital in chapter 4 the population is divided into two age groups. In chapter 5 the model is extended with 5-year age groups to investigate which specific age groups contribute the most to the spread of MRSA. Finally in chapter 6 we will discuss the overall results.

2   Models in the literature

Several compartmental transmission models have been developed in the literature to describe the dynamics of MRSA colonisation. These models are often used to understand nosocomial transmission and to investigate the effectiveness of interventions against MRSA. Unfortunately mathematical models are not capable to give detailed forecasting of patterns of transmission, because of stochastic variation in small populations. However, models will have potential benefits [11]. First, they can suggest explanations for observations, that are not yet understood. Second, models can illustrate the range of stochastic variation in incidence and prevalence of colonisation. Finally, population models can identify key parameters of the transmission process to suggest and evaluate alternative intervention measures.

Grundmann and Hellriegel (2006) [4] point out three different kind of models in the literature:

- Single ward models

- Single hospital and the community

- Multiple hospitals and health-institutions and the community

We will discuss these three categories briefly.

2.1   Single ward models

Single ward models in the literature often describe the transmission in an Intensive Care Unit (ICU). The transmission takes place through contacts with contaminated HCWs. To simulate the stochastic effects which are important in small populations Cooper et al. (1999) [12], Austin et al. (1999) [13] and Grundmann et al. (2002) [14] use the Ross-Macdonald model, which originally was made for the transmission of malaria. In the transmission model for malaria the mosquito is the vector. While in the transmission model for MRSA the HCW is the vector. HCWs bring MRSA from one patient to another with a certain probability of losing MRSA before having contact with the next patient. They all conclude that hand washing of HCWs is the best control measure to prevent the spread of MRSA. Reducing the contact rate of patients with HCWs decreases the transmission rate too.

Austin and Anderson (1999) [15] describe the transmission dynamics with ordinary differential equations (ODEs) of indirect transmission by HCWs within a hospital. They conclude that hand washing alone is not sufficient to eradicate the colonisation. Cohorting the HCWs, i.e. decreasing HCW-patient ratios, is more effective. Moreover, a combination of cohorting and hand washing is the most effective control measure.

Bonten et al. (2001) [11] divide the patients in an ICU in three groups: colonised with resistant bacteria, colonised with sensitive bacteria and without colonisation. Besides cohorting

and hand disinfection compliance they also investigate antibiotic strategies. Treatment with antibiotic 1 is assumed to eradicate colonisation with sensitive bacteria. While treatment with antibiotic 2 is assumed to clear carriage of both sensitive and resistant bacteria. Cohorting and hand washing together is an effective control measure, antibiotic strategies are positive for the unit, but negative for the treated individual.

2.2   Single hospital and the community models

Cooper et al.(2004) [16] use a deterministic model with ODEs to describe the dynamics of MRSA colonisation in a single hospital and the community divided in a population with high readmission rates and a population with lower readmission rates. They simulate the model starting at low prevalence in the hospital and in the community and let the model run until the prevalence in the hospital and in the community reach the stable equilibria. When equilibrium is reached an isolation unit is opened to decrease the prevalence level. These simulations are done for different basic reproduction rates (R_0), i.e. the average number of secondary cases caused by one primary case over all admissions of the primary case until carriage is cleared, assuming that all other patients are susceptible. For low values of R_0 (< 1.3) isolation eradicates MRSA.

Bootsma et al. (2006) [17] made an analytical one-hospital model to quantify the effectiveness of different infection control measures and to predict the effects of rapid diagnostic testing on isolation needs. The patient dynamics and MRSA dynamics within and between different wards is taken into account. They conclude that only isolation of identified MRSA carriers is not sufficient to eradicate MRSA completely, but combining isolation with other measures from the Dutch S&D program, such as screening known MRSA carriers at admittance will eradicate MRSA, even when started at high prevalence.
They introduce the critical basic reproduction ratio (R_A^c) of a single outbreak of MRSA in the hospital that leads to an effective R_0 value of 1 when readmission is taken into account. Below this value ($R_A < R_A^c \Rightarrow R_0 < 1$) transmission is insufficient to generate a large outbreak. However, above this level ($R_A > R_A^c \Rightarrow R_0 > 1$) transmission control will fail and prevalence levels will rise. The critical reproduction ratio will be used to investigate control measures besides different combinations of the interventions of the S&D program. Hand hygiene increases R_A^c, however increasing the detection rate increases R_A^c much faster. They also investigated the effect of a core group who visits the hospital more often. Changing the core group size hardly affects the efficacy of the infection control measures of the S&D program. This may sound surprising, because a larger core group size corresponds to more readmission and, therefore, a higher R_0. However, they claim that the R_0 of a disease is not much influenced by the core group size. Moreover, for the same R_0 value, the transmissibility of the disease should be lower if the core group is larger. Therefore, the core group size does not influence the effects of intervention measures very much.

Heijne and Wallinga (2006) [18] made a simple linear matrix model to describe the dynamics of MRSA carriage in a single hospital with its corresponding community. They tried to model the situation in the Netherlands: as long as no epidemic is detected, it is unnecessary to take more hygiene and isolation measures and immediately after detecting an epidemic, interventions are taken to lower the transmission rate in the hospital. Furthermore Heijne and Wallinga used their model to investigate some interventions and concluded that screening every incoming patient lowers the number of MRSA carriers in the hospital and the community equally, however the number of epidemics stays the same. Moreover, screening every outgoing patient lowers the number of MRSA carriers in the community more than in the hospital. It also lowers the number of outbreaks detected. In contrast to other models, staff interventions have a very small effect on the number of MRSA carriers and the number of epidemics in the hospital.

2.3 Multiple hospitals and health-institutions and the community

Smith et al.(2004) [19] use structured population models with ODEs to model the population dynamics of antibiotic-resistant bacteria (ARB) like MRSA. They divide the population into subpopulations (e.g., hospitals, community and Long-term care facilities (LTCF)) and groups (e.g. elderly and non-elderly). The transmission rates differ among subpopulations and the length of stay (LOS) differs among groups and subpopulations. They conclude that a longer LOS of the elderly in the hospital increases the prevalence of MRSA in the hospital and in the community compared to the homogeneous model. Moreover, introducing an LTCF, like a nursing home, in the model increases the prevalence in the hospital and in the community even more.

3 A single hospital and a homogeneous community

3.1 The Transmission Model

In this paper the model of Heijne and Wallinga [18] will be expanded to understand the effects of different lengths of stay (LOS), the mean carriage time of MRSA and the transmission rate. In this chapter the dynamics of undetected HA-MRSA carriage of the whole population together in the hospital and in the community will be simulated, using discrete time steps. We use a probabilistic model, because then it is easier to evaluate different parameter values and their influences to the model than in stochastic models. Therefore we assume that an outbreak will be detected when the number of MRSA carriers in the hospital is higher than a certain detection threshold k. When the prevalence in the hospital is higher than the threshold, interventions will be taken to lower the prevalence. Thus at every time point t the number of individuals colonised with MRSA in the hospital determines in which situation the model is. There are two situations possible:

1. No MRSA carriers are detected in the hospital and transmission can continue.

2. MRSA carriers are detected in the hospital and intervention measures to prevent further transmission are taken.

In matrix notation the discrete model becomes:

$$v(t+1) = \begin{cases} A \cdot v(t) & \text{if } 0 \leq x_h(t) < k; \\ B \cdot v(t) & \text{if } x_h(t) \geq k. \end{cases}$$

$$v(t) = \begin{pmatrix} x_h(t) \\ x_c(t) \end{pmatrix}$$

With x_h the number of undetected MRSA carriers in the hospital and x_c the number of undetected MRSA carriers in the community.

The matrix A (no intervention) and its elements are defined as:

$$A = \begin{pmatrix} a & b \\ c & d \end{pmatrix}$$

a = the relative growth of MRSA in the hospital,
b = the probability of MRSA carriage at admittance to the hospital,
c = the probability of MRSA carriage at discharge from the hospital,
d = the relative growth of MRSA in the community.

And the matrix B (intervention) becomes:

$$B = \begin{pmatrix} a_1 & b \\ c_1 & d \end{pmatrix}$$

In the matrix B the elements represent the same process, but for the situation when an outbreak is discovered and interventions are taken in the hospital. Therefore the elements b and d will not change, but the elements a and c do. Both matrices A and B are positive, thus they are irreducible and primitive, see appendix B.1.

Transmission in the hospital is proportional to the fraction of carriers and the fraction of non-carriers: $x_h(1 - x_h)$. However, because of the intervention measures the prevalence of MRSA in the hospital can be kept very low. Therefore, and because immediately after clearance of MRSA an individual is susceptible again, we assume the fraction of non-carriers in the hospital stays close to 1. Therefore, the transmission in the hospital is only proportional to the carriers. Furthermore transmission takes place through HCWs who can travel from room to room and ward to ward. These conditions allow us to use a linear model to describe the dynamics of HA-MRSA.

The transmission rate, i.e. the number of new cases caused by one individual during one time period in the jth subpopulation is noted by $\beta_j \in [0, N_j]$ for $j = h, c$ and N_j the number of individuals in subpopulation j. In this paper the focus is on hospital-acquired MRSA, therefore we assume transmission does not take place in the community: $\beta_c = 0$. The mean LOS per subpopulation is assumed to be $1/\sigma_j$. So σ_j is the fraction of individuals who leave subpopulation j. The mean carriage time, on the other hand, is assumed to be equal for all subpopulations: $1/\lambda$. Therefore, the fraction of individuals who lose MRSA without treatment will be λ.

The probability of being discharged or admitted to the hospital is independent of being carrier or not. Therefore the probability to still be an MRSA carrier while leaving subpopulation j during one time-period becomes:

$$b/c = \mathbb{P}(\text{leave } j \cap \text{carrier}) = \mathbb{P}(\text{leave } j) \cdot \mathbb{P}(\text{carrier}) = \sigma_j(1 - \lambda).$$

MRSA positive individuals in the community can either lose MRSA or leave the community by going to the hospital. Therefore, the probability that an individual in x_c, the group of MRSA carriers in the community, stays in x_c during one time-period is the probability of staying in the community while still being a carrier. In formula form the relative growth (or decay) in the community becomes:

$$d = \mathbb{P}(\text{stay in } c \cap \text{carrier}) = \mathbb{P}(\text{stay in } c) \cdot \mathbb{P}(\text{carrier}) = (1 - \sigma_c)(1 - \lambda).$$

An MRSA positive individual in the hospital stays in x_h in the same way with the probability: $(1 - \sigma_h)(1 - \lambda)$. Furthermore an individual in x_h infects β_h individuals in the hospital. Therefore the relative growth in the hospital becomes:

$$a = \beta_h + (1 - \sigma_h)(1 - \lambda).$$

At the moment that the number of MRSA carriers in the hospital passes the detection threshold a fraction α of x_h is assumed to be detected and removed to the known MRSA positives, who are put in isolation where they can not transmit MRSA to other patients anymore. The detected MRSA positives are labelled MRSA positive, which means when they are readmitted to the hospital they can not transmit MRSA, because they are immediately put into isolation until they are proved to be MRSA negative. Therefore a fraction $(1 - \alpha)$ of x_h stays undetected in the hospital and is still possible to transmit MRSA. This fraction consists of patients at whom for some reason no screening is performed or where the test turned out false negative [20].
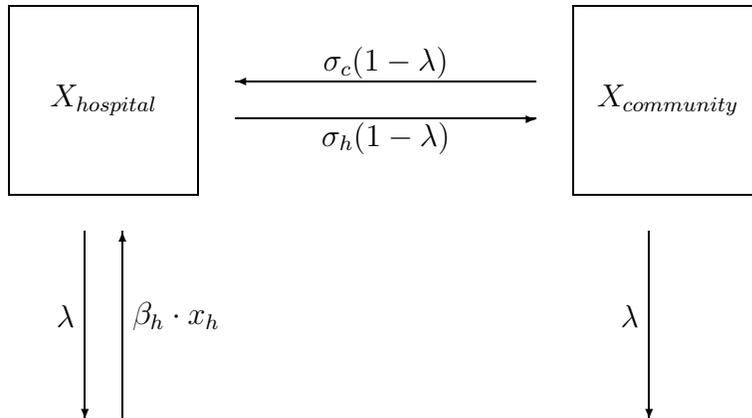
Figure 1: Situation 1: no outbreak detected. The life cycle graph of the homogeneous model when transmission can continue. With x_j the MRSA carriers, λ the rate of losing MRSA and σ_j the rate of leaving subpopulation j.
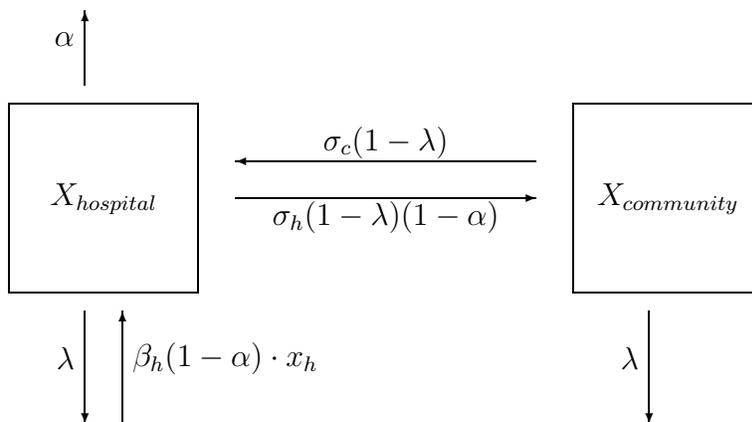

Figure 2: Situation 2: an outbreak detected. The life cycle graph of the homogeneous model when a fraction α of the MRSA carriers in the hospital is detected. With x_j the MRSA carriers, λ the rate of losing MRSA and σ_j the rate of leaving subpopulation j.

In figures 1 and 2 the life cycle graphs for the two situations are given. The population matrices A and B now become:

$$A = \begin{pmatrix} \beta_h + (1-\sigma_h)(1-\lambda) & \sigma_c(1-\lambda) \\ \sigma_h(1-\lambda) & (1-\sigma_c)(1-\lambda) \end{pmatrix}$$

$$B = \begin{pmatrix} (\beta_h + (1-\sigma_h)(1-\lambda))(1-\alpha) & \sigma_c(1-\lambda) \\ \sigma_h(1-\lambda)(1-\alpha) & (1-\sigma_c)(1-\lambda) \end{pmatrix}$$

3.2 Defining R_0 in structured population models

Frequently the transmission rate of a disease is unknown, but the number of new infectives caused by one infective is. Furthermore, to compare linear models and non-linear models consisting of ODEs, epidemiologists evaluate the *basic reproduction ratio* defined by Diekmann and Heesterbeek (2000) [21]:

R_0 := expected number of secondary cases per primary case in a 'virgin' population.

With a 'virgin' population they mean a population without immunity or infectives at introduction of the first case. When $R_0 > 1$ one infective makes more than one new infection on average, therefore an epidemic will occur. Contrary, when $R_0 < 1$ the disease dies out.

We found different ways to define and calculate R_0 for our model if no intervention measures are taken. Thus only for the situation where transmission can continue in the hospital. One way to define R_0 is as the product of the number of secondary cases in a single stay (R_A) and the mean number of stays per carrier ($1/(1-P)$) see Cooper et al. (2004) [16] or Bootsma (2005) [20]. Here, R_A is the product of the mean sojourn time of being a carrier in the hospital, which is a geometrical series, see appendix C, and the transmission rate:

$$R_A = \frac{1}{\lambda + \sigma_h - \lambda\sigma_h} \cdot \beta_h.$$

And P is the probability that an MRSA carrier leaves the hospital and will be readmitted at least once while still being a carrier:

$$P = \frac{\sigma_h(1-\lambda)}{\lambda + \sigma_h - \lambda\sigma_h} \frac{\sigma_c(1-\lambda)}{\lambda + \sigma_c - \lambda\sigma_c}.$$

Therefore the mean number of visits to the hospital while still being an MRSA carrier is:

$$1 + P + P^2 + P^3 + .. = \sum_{n=0}^{\infty} P^n = \frac{1}{1-P}.$$

Thus

$$R_0 = \frac{R_A}{1-P} = \frac{\beta_h(\lambda + \sigma_c - \lambda\sigma_c)}{\lambda(\lambda + \sigma_c - \lambda\sigma_c + \sigma_h - \lambda\sigma_h)}.$$

A second way to define R_0 is by taking the dominant eigenvalue of the next-generation matrix of Diekmann and Heesterbeek (2000) [21], see appendix D.1. The next-generation matrix projects the population from one generation to the next. Thus the dominant eigenvalue will give the growth rate from one generation to the next. This method can be used for homogeneous two-subpopulation models, see Smith et al. (2004) [19]. Our model gives the following next-generation matrix:

$$K = \begin{pmatrix} \frac{\beta_h}{\lambda+\sigma_h-\lambda\sigma_h} & \frac{\sigma_c(1-\lambda)}{\lambda+\sigma_c-\lambda\sigma_c} \\ \frac{\sigma_h(1-\lambda)}{\lambda+\sigma_h-\lambda\sigma_h} & 0 \end{pmatrix}$$

Interestingly, this next-generation matrix counts transitions from the hospital to the community and back, and new infections. Therefore, it is questionable whether this method is suited for subpopulation models with movement between the subpopulations. Furthermore, the dominant eigenvalue of the next-generation matrix is different from the R_0 found above:

$$R_0 = \frac{R_A + \sqrt{R_A^2 + 4P}}{2}.$$

Another method to calculate the next-generation matrix is proposed by Caswell (2001) [22]. See for a simple example, about the difference with the next-generation matrix above, appendix D.3. Caswell (2001) [22] uses the decomposition of the population matrix: $A = T + F$, see appendix D.2. The matrix T represents the transition matrix and the matrix F represents the transmission matrix. Moreover, this approach can also be used for larger matrices.

For the homogeneous two-subpopulation model of this paper T and F are:

$$T = \begin{pmatrix} (1-\lambda)(1-\sigma_h) & (1-\lambda)\sigma_c \\ (1-\lambda)\sigma_h & (1-\lambda)(1-\sigma_c) \end{pmatrix}$$

and

$$F = \begin{pmatrix} \beta_h & 0 \\ 0 & 0 \end{pmatrix}.$$

From the matrix T, which has determinant < 0, the fundamental matrix N can be formed, which gives the expected number of time steps spent in each state:

$$N = I + T + T^2 + .. = (I - T)^{-1} = \begin{pmatrix} 1 - (1-\lambda)(1-\sigma_h) & -(1-\lambda)\sigma_c \\ -(1-\lambda)\sigma_h & 1 - (1-\lambda)(1-\sigma_c) \end{pmatrix}^{-1}$$

$$= \frac{1}{\lambda^2 + \lambda\sigma_c - \lambda^2\sigma_c + \lambda\sigma_h - \lambda^2\sigma_h} \begin{pmatrix} 1 - (1-\lambda)(1-\sigma_c) & (1-\lambda)\sigma_c \\ (1-\lambda)\sigma_h & 1 - (1-\lambda)(1-\sigma_h) \end{pmatrix}$$

For instance $N_{1,1}$ is the total time spent in the hospital while being a carrier started as a carrier in the hospital at $t = 0$. Thus the fundamental matrix N gives the expected number

of time steps spent in each transient state [22]. Furthermore the reproduction matrix F gives the expected number of transmissions of MRSA per time step. Multiplying F with N gives the next-generation matrix according to Caswell:

$$R = FN = \frac{1}{\lambda^2 + \lambda\sigma_c - \lambda^2\sigma_c + \lambda\sigma_h - \lambda^2\sigma_h} \begin{pmatrix} \beta_h(1 - (1-\lambda)(1-\sigma_c)) & \beta_h(1-\lambda)\sigma_c \\ 0 & 0 \end{pmatrix}$$

The eigenvalues of R are zero and R_0, which will be:

$$R_0 = \beta_h \frac{1 - (1-\lambda)(1-\sigma_c)}{\lambda^2 + \lambda\sigma_c - \lambda^2\sigma_c + \lambda\sigma_h - \lambda^2\sigma_h} = \frac{\beta_h(\lambda + \sigma_c - \lambda\sigma_c)}{\lambda(\lambda + \sigma_c - \lambda\sigma_c + \sigma_h - \lambda\sigma_h)}.$$

This value is the same value as we found by using the definition of Cooper et al. (2004) [16] and Bootsma (2005) [20]! The difference with the next-generation matrix of Diekmann and Heesterbeek is the definition of a generation. Here a generation is the whole carriage time and in Diekmann and Heesterbeek a generation is the duration of one visit to either the hospital or the community. From this point on, the method of calculating R_0 by Caswell will be used in this paper, because of its suitability for more-dimensional matrix models.

3.3 Simulation

The parameters used to simulate our homogeneous two-subpopulation model can be found in table 5 in appendix F.1. To calculate β_h from R_0, the formula of Cooper [16], Bootsma [20] and Caswell [22] is used:

$$\beta_h = R_0 \frac{\lambda(\lambda + \sigma_c - \lambda\sigma_c + \sigma_h - \lambda\sigma_h)}{\lambda + \sigma_c - \lambda\sigma_c}.$$

When the parameters of appendix F.1 are filled in using $R_0 = 1.35$, then $\beta_h = 0.27$ and $R_A = 1.16$.

Simulating the dynamics of numbers of MRSA carriers with the numbers in $\mathbb{R}$ instead of in $\mathbb{N}$ is not very realistic. Furthermore prevalence or fractions will say more than numbers and are more comparable. Therefore, instead of simulating the numbers of carriers in the hospital and in the community the fraction of carriers will be simulated. In order to comply this, the dynamics of a closed population will be modelled, i.e. the number of individuals in the hospital (N_h) and the number of individuals in the community (N_c) do not change. Therefore the total inflow into the hospital and the total outflow out of the hospital are equal. In formula form this becomes:

$$\sigma_c \cdot N_c = \sigma_h \cdot N_h.$$

This will be used to determine the size of the community corresponding to the hospital. Furthermore the community is larger than the hospital and therefore one MRSA positive

individual will represent a larger fraction in the hospital than in the community. Thus if one MRSA positive individual leaves the hospital where it is a fraction x_h than it will be a fraction $x_h \cdot \frac{N_h}{N_c}$ in the community. And the other way around: one MRSA positive individual in the community representing a fraction x_c will be a fraction $x_c \cdot \frac{N_c}{N_h}$ in the hospital at the moment this individual is admitted to the hospital. Thus the inflow into the hospital will be multiplied with $\frac{N_c}{N_h}$ and the outflow out of the hospital will be multiplied with $\frac{N_h}{N_c}$.

We will investigate the following three results of the model. First the mean number of outbreaks per 100 days. The second and third model results are the mean fractions of MRSA carriers in the hospital and in the community respectively. The model is simulated for different initial conditions long enough such that the initial conditions do not influence the results anymore, i.e. "steady-state" is reached. In other words the finite sequences of symbols in an itinerary are independent of the initial conditions and therefore the mapping is ergodic [23], see also appendix E.

The model results are calculated from the moment that the fraction of MRSA carriers in the hospital is just after one outbreak until another outbreak for almost 1000 days (depends on the time between outbreaks). This is done after a simulation for 10,000 days and then for the last 1000 days, such that the initial conditions do not influence the results anymore. An example of the dynamics of the MRSA carriers in the hospital and in the community can be found in figures 3 and 4. The dynamics are 'quasi-periodic', i.e. it looks like it is periodic, but there is no value which will be reached twice.

Like in the one-dimensional model of Wallinga et al. (1999) [24] about the control of weed, see also appendix E, the detection threshold k does not influence the number of outbreaks and the time between two outbreaks. However, it influences the mean fractions of MRSA carriage linearly. These observations are numerically tested for the 2-dimensional model of the population dynamics of MRSA carriage.

fraction MRSA carriers in the hospital ($\times 10^{-3}$)
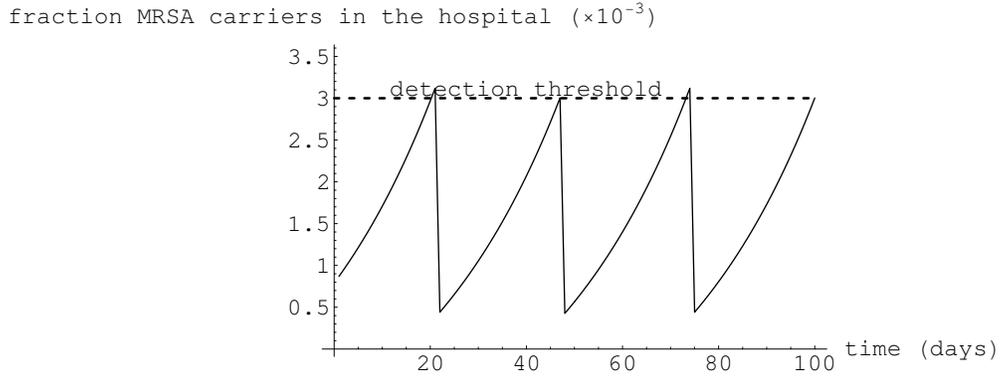
Figure 3: An example of the dynamics of the fraction of MRSA carriers in the hospital for 100 days.

fraction MRSA carriers in the community ($\times 10^{-4}$)
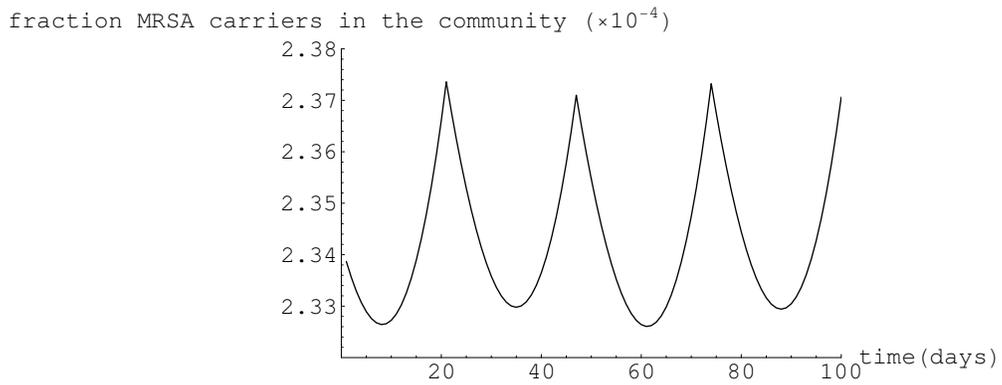

Figure 4: An example of the dynamics of the fraction of MRSA carriers in the community for 100 days.

3.4 Interventions

Heijne and Wallinga [18] suggested three intervention measures to lower the prevalence of MRSA carriers, see chapter 2: screening all incoming patients in the hospital for MRSA, screening all outgoing patients for MRSA and HCW measures to lower the transmission rate, e.g. hand washing or cohorting. The models with interventions are simulated like the model without interventions until 'steady-state' is reached. Then the four results of the adjusted homogeneous models are compared to the original homogeneous model.

3.4.1 Screening all incoming patients

When screening is performed all the time with efficacy α before patients are admitted to the hospital only a fraction $(1-\alpha)$ of the undetected carriers enter the hospital undetected and are able to transmit MRSA to other patients. Then the matrices A and B become:

$$A = \begin{pmatrix} \beta_h + (1-\sigma_h)(1-\lambda) & \sigma_c(1-\lambda)(1-\alpha)\frac{N_c}{N_h} \\ \sigma_h(1-\lambda)\frac{N_h}{N_c} & (1-\sigma_c)(1-\lambda) \end{pmatrix}$$

$$B = \begin{pmatrix} (\beta_h + (1-\sigma_h)(1-\lambda))(1-\alpha) & \sigma_c(1-\lambda)(1-\alpha)\frac{N_c}{N_h} \\ \sigma_h(1-\lambda)(1-\alpha)\frac{N_h}{N_c} & (1-\sigma_c)(1-\lambda) \end{pmatrix}$$

3.4.2 Screening all outgoing patients

When all patients who leave the hospital are screened all the time with efficacy α, a fraction $(1-\alpha)$ of the carriers comes into x_c and is able to transmit MRSA again when they re-enter the hospital while still being a carrier. The matrices A and B become:

$$A = \begin{pmatrix} \beta_h + (1-\sigma_h)(1-\lambda) & \sigma_c(1-\lambda)\frac{N_c}{N_h} \\ \sigma_h(1-\lambda)(1-\alpha)\frac{N_h}{N_c} & (1-\sigma_c)(1-\lambda) \end{pmatrix}$$

$$B = \begin{pmatrix} (\beta_h + (1-\sigma_h)(1-\lambda))(1-\alpha) & \sigma_c(1-\lambda)\frac{N_c}{N_h} \\ \sigma_h(1-\lambda)(1-\alpha)(1-\alpha)\frac{N_h}{N_c} & (1-\sigma_c)(1-\lambda) \end{pmatrix}$$

3.4.3 Screening both incoming and outgoing patients

A combination of screening all incoming and all outgoing patients both with efficacy α gives the next matrices:

$$A = \begin{pmatrix} \beta_h + (1-\sigma_h)(1-\lambda) & \sigma_c(1-\lambda)(1-\alpha)\frac{N_c}{N_h} \\ \sigma_h(1-\lambda)(1-\alpha)\frac{N_h}{N_c} & (1-\sigma_c)(1-\lambda) \end{pmatrix}$$

$$B = \begin{pmatrix} (\beta_h + (1-\sigma_h)(1-\lambda))(1-\alpha) & \sigma_c(1-\lambda)(1-\alpha)\frac{N_c}{N_h} \\ \sigma_h(1-\lambda)(1-\alpha)(1-\alpha)\frac{N_h}{N_c} & (1-\sigma_c)(1-\lambda) \end{pmatrix}$$

3.4.4 HCW measures

HCW measures are taken to lower the transmission rate. One can think of washing hands more often and/or more cohorting, i.e. less patients per HCW [14]. In this case the matrices are the same only β_h will decrease depending on how many measures are taken.

3.4.5 Comparing interventions

When transmission rate $\beta_h = 0.27$ and detection threshold $k = 0.003$, then the interventions will give the next differences in the model results expressed in percentages:

Table 1: Comparing intervention measures in the homogeneous model

Interventions	mean number of outbreaks	mean prevalence of MRSA in the hospital	mean prevalence of MRSA in the community
screening incoming	-54%	-15%	-12%
screening outgoing	-54%	-15%	-89%
screening in and out	-61%	-18%	-90%
10% reduction of β_h	-33%	6%	9%
20% reduction of β_h	-70%	30%	37%
30% reduction of β_h	-100%	-100%	-100%

When all incoming and/or outgoing patients are screened, the mean prevalence in the hospital and in the community always decrease. Screening incoming or outgoing patients for MRSA gives the same decrease in the number of outbreaks and the prevalence in the hospital, but the prevalence in the community decreases more when outgoing patients are screened. Screening both incoming and outgoing patients decreases the number of outbreaks and the prevalence in the hospital and in the community the most, but only with a slight difference relative to screening only outgoing patients.

If $\beta_h(new) < 0.74\beta_h(old)$ the dominant eigenvalue of A is less than 1, therefore also without interventions in situation one, the prevalence of MRSA carriers decreases and eventually the prevalence of MRSA will be eradicated. However, if $0.74\beta_h(old) < \beta_h(new) < \beta_h(old)$ the prevalence of MRSA in the hospital and in the community increase, while the number of outbreaks decreases.

The results of Heine and Wallinga (2006) [18] are different from ours. They reduced the detection threshold k to investigate the effect of screening the incoming patients. But this also has effect on the number of MRSA carriers in the hospital. Furthermore, we already concluded that the prevalence of MRSA carriers in the hospital and in the community depend on k linearly. Thus if k is reduced, the prevalence of MRSA is reduced by the same size. We also concluded that the number of outbreaks does not depend on k. Therefore, Heine and Wallinga (2006) [18] did not see any difference in the number of outbreaks.

Screening the outgoing patients gives different outcomes, because of the difference in the elements of the matrices A and B. However, the interpretation is the same: the mean prevalence of MRSA in the hospital and the community are reduced and the number of outbreaks too. Furthermore, Heine and Wallinga (2006) [18] did not see good results in taking HCW measures either.

3.5 Discussion

Our model suggests that screening all incoming or outgoing patients for MRSA can help to reduce the prevalence of MRSA in both the hospital and the community. Not surprisingly, combining both gives the best result. However, it is much more expensive and it cost a lot of effort to screen both incoming and outgoing patients, which has just a very small difference relative to a single screening. In this model with the detection threshold in the hospital, it is hard to lower the mean prevalence of MRSA carriage in the hospital. However, the growth of the prevalence of MRSA carriers in the community depends on the carriers who leave the hospital undetected, because we assumed that no transmission takes place in the community. Therefore, if the prevalence in the hospital decreases the prevalence in the community will decrease with roughly the same amount. Furthermore, if the patients who leave the hospital are screened the prevalence of undetected carriers in the community will decrease much faster. If all incoming or all outgoing patients are screened the eigenvalues of the matrix A are the same, consequently the growth rates are equal. Therefore the mean time between two outbreaks and the number of outbreaks per 100 days are also equal. Therefore, the best intervention measure investigated for this model will be screening all outgoing patients.

When comparing the intervention measures in table 1, the best intervention seems to be decreasing β_h, the transmission rate, such that the dominant eigenvalue of matrix A and R_0 are less than 1. But this is not always possible in practise. And the burden for the HCWs will be much higher compared to taking no interventions. And it is not known how long it will take from the initial conditions to eradicate the prevalence of MRSA. Surprisingly, if β_h is not decreased enough, the mean prevalence of MRSA in the hospital and in the community can even increase. This is because if the growth rate is decreasing, it will take longer to pass the detection threshold k, and the mean prevalence of MRSA can increase. Furthermore after a trough the prevalence in the hospital growths faster than just before a peak. This is not suggested by figure 3, when no intervention measures are taken. Therefore the mean prevalence in the hospital and the community are higher.

In the present model the rate of leaving the hospital is a continuing process, but in reality individuals do not stay the same amount of time in the hospital, one individual can stay one day in the hospital while another can stay there for a month or even longer. Therefore, including a core-group who stays longer in the hospital makes the model more realistic. This will be done in the next section.

4 A single hospital and a heterogeneous community: the elderly and non-elderly

4.1 The Transmission Model

To investigate the effect of longer LOS and more frequent admittances to the hospital of a specific group on MRSA carriage in the whole population, we divide the population into two groups. These groups are the elderly of 65 and older and the non-elderly, because information about LOS, admittance and group size in the community are available for age groups, and not for e.g. chronically ill people. The elderly have a longer LOS on average than the non-elderly. Therefore they have more time to transmit MRSA in the hospital, which results in an higher R_0 value, than the non-elderly.

For simplicity, we assume that age groups do not change in size during the simulation or due to birth and death and neither do the subpopulations. Therefore the fraction of an age group in a subpopulation does not change either. Like in the homogeneous model the prevalence of MRSA in the hospital in this model will be kept very low and after clearance of MRSA an individual is immediately susceptible again, therefore the fraction of non-carriers in a certain age group in the hospital is assumed to stay close to 1. Consequently transmission in the hospital is never reduced because of unavailable susceptibles and the model can be linearised. Furthermore the transmission rate is assumed to be equal between and within age groups because the transmission of MRSA goes through HCWs and individuals of different age groups can stay in the same room.

This model with two subpopulations (the hospital and the community) and two age groups (elderly and youth) becomes in matrix notation:

$$v(t+1) = \begin{cases} A \cdot v(t) & \text{if } 0 \le x_{e,h}(t) + x_{y,h}(t) < k; \\ B \cdot v(t) & \text{if } x_{e,h}(t) + x_{y,h}(t) \ge k. \end{cases}$$

$$v(t) = \begin{pmatrix} x_{e,h}(t) \\ x_{y,h}(t) \\ x_{e,c}(t) \\ x_{y,c}(t) \end{pmatrix}$$

With

$$
\begin{aligned}
x_{e,h} &= \text{the elderly MRSA carriers in the hospital,} \\
x_{y,h} &= \text{the non-elderly MRSA carriers in the hospital,} \\
x_{e,c} &= \text{the elderly MRSA carriers in the community,} \\
x_{y,c} &= \text{the non-elderly MRSA carriers in the community.}
\end{aligned}
$$

Because of the assumption that an individual stays in one age group:

$$\mathbb{P}(\text{individual goes from age group } f \text{ to age group } g) = 0,$$

and the assumption that no transmission takes place in the community, the matrices A and B and their elements are defined as:

$$A = \begin{pmatrix} a & b & c & 0 \\ d & e & 0 & f \\ g & 0 & h & 0 \\ 0 & i & 0 & j \end{pmatrix}$$

a = the relative growth of MRSA in the elderly in the hospital,
b = the probability of a non-elderly to infect an elderly in the hospital,
c = the probability of MRSA carriage at admittance to the hospital of an elderly,
d = the probability of an elderly to infect a non-elderly in the hospital,
e = the relative growth of MRSA in the non-elderly in the hospital,
f = the probability of MRSA carriage at admittance to the hospital of a non-elderly,
g = the probability of MRSA carriage at discharge from the hospital of an elderly,
h = the relative growth of MRSA in the elderly in the community,
i = the probability of MRSA carriage at discharge from the hospital of a non-elderly,
j = the relative growth of MRSA in the non-elderly in the community.

$$B = \begin{pmatrix} a_1 & b_1 & c & 0 \\ d_1 & e_1 & 0 & f \\ g_1 & 0 & h & 0 \\ 0 & i_1 & 0 & j \end{pmatrix}$$

In the matrix B the elements are the same only then for the situation when an outbreak is detected and interventions are taken in the hospital.

We assume that the transmission rate between age groups is the same as within age groups, because transmission takes place through HCWs who travel from room to room and most of the time elderly and non-elderly share wards. Therefore if an individual infects β_h new individuals, these new infected individuals are divided over the age groups like the age groups are divided over the hospital. Thus one individual infects $\beta_h q_{e,h}$ elderly and $\beta_h q_{y,h}$ non-elderly, with $q_{g,h}$ the fraction of individuals in age group g in the hospital.

Like in the homogeneous model the probability of being discharged or admitted to the hospital is independent of being carrier or not. Therefore the probability of an MRSA carrier in age group g to leave subpopulation j while still being a carrier becomes:

$$\mathbb{P}(\text{leave subpopulation } j \cap \text{carrier}) = \mathbb{P}(\text{leave subpopulation } j) \cdot \mathbb{P}(\text{carrier}) = \sigma_{g,j}(1-\lambda).$$

The probability of an MRSA positive individual in age group g and subpopulation j to leave $x_{g,j}$ without MRSA is:

$$\mathbb{P}(\text{leave } x_{g,j} \cap \text{MRSA lost}) =$$

$$\mathbb{P}(\text{leave subpop. } j \cap \text{MRSA lost}) + \mathbb{P}(\text{stay in subpop. } j \cap \text{MRSA lost}) =$$

$$\mathbb{P}(\text{leave subpop. } j) \cdot \mathbb{P}(\text{MRSA lost}) + \mathbb{P}(\text{stay in subpop. } j) \cdot \mathbb{P}(\text{MRSA lost}) =$$

$$\sigma_{g,j}\lambda + (1 - \sigma_{g,j})\lambda = \lambda.$$

The probability of an individual in age group g to stay in subpopulation j is 1 minus the probability to leave:

$$\mathbb{P}(\text{stay in } x_{g,j}) = 1 - \mathbb{P}(\text{leave } x_{g,j}) =$$

$$1 - (\mathbb{P}(\text{leave } x_{g,j} \cap \text{ MRSA lost}) + \mathbb{P}(\text{leave } x_{g,j} \cap \text{carrier})) =$$

$$1 - (\lambda + \sigma_{g,j}(1 - \lambda)) = 1 - \lambda - \sigma_{g,j} + \sigma_{g,j}\lambda = (1 - \lambda)(1 - \sigma_{g,j}).$$

Again we assume that at the moment the total fraction of MRSA carriers in the hospital is above the detection threshold a fraction α is detected and put into isolation where transmission can not take place anymore.

Putting all this information together the matrices A and B and their life-cycle graphs, see figures 5 and 6, become:

$$A = \begin{pmatrix} \beta_h q_{e,h} + (1 - \lambda)(1 - \sigma_{e,h}) & \beta_h q_{e,h} & \sigma_{e,c}(1 - \lambda) & 0 \\ \beta_h q_{y,h} & \beta_h q_{y,h} + (1 - \lambda)(1 - \sigma_{y,h}) & 0 & \sigma_{y,c}(1 - \lambda) \\ \sigma_{e,h}(1 - \lambda) & 0 & (1 - \lambda)(1 - \sigma_{e,c}) & 0 \\ 0 & \sigma_{y,h}(1 - \lambda) & 0 & (1 - \lambda)(1 - \sigma_{y,c}) \end{pmatrix}$$

$$B = \begin{pmatrix} (\beta_h q_{e,h} + (1 - \sigma_{e,h})(1 - \lambda))(1 - \alpha) & \beta_h q_{e,h}(1 - \alpha) & \sigma_{e,c}(1 - \lambda) & 0 \\ \beta_h q_{y,h}(1 - \alpha) & (\beta_h q_{y,h} + (1 - \sigma_{y,h})(1 - \lambda))(1 - \alpha) & 0 & \sigma_{y,c}(1 - \lambda) \\ \sigma_{e,h}(1 - \lambda)(1 - \alpha) & 0 & (1 - \sigma_{e,c})(1 - \lambda) & 0 \\ 0 & \sigma_{y,h}(1 - \lambda)(1 - \alpha) & 0 & (1 - \sigma_{y,c})(1 - \lambda) \end{pmatrix}$$
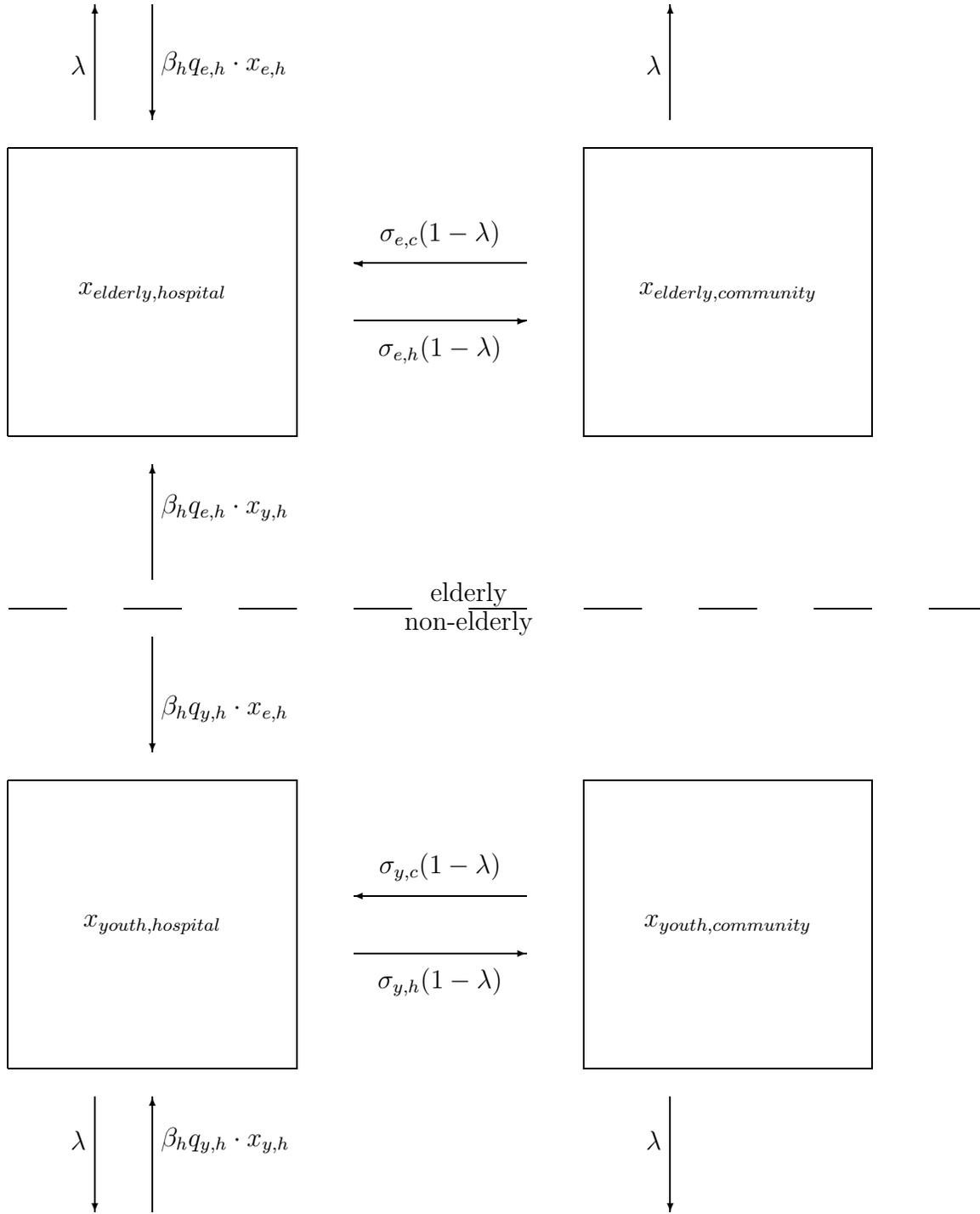
Figure 5: Situation 1: no outbreak detected. The life cycle graph of the heterogeneous model when transmission can continue. With $x_{g,j}$ the MRSA carriers per age group and per subpopulation, λ the rate of losing MRSA and $\sigma_{g,j}$ the rate of age group g to leave subpopulation j.
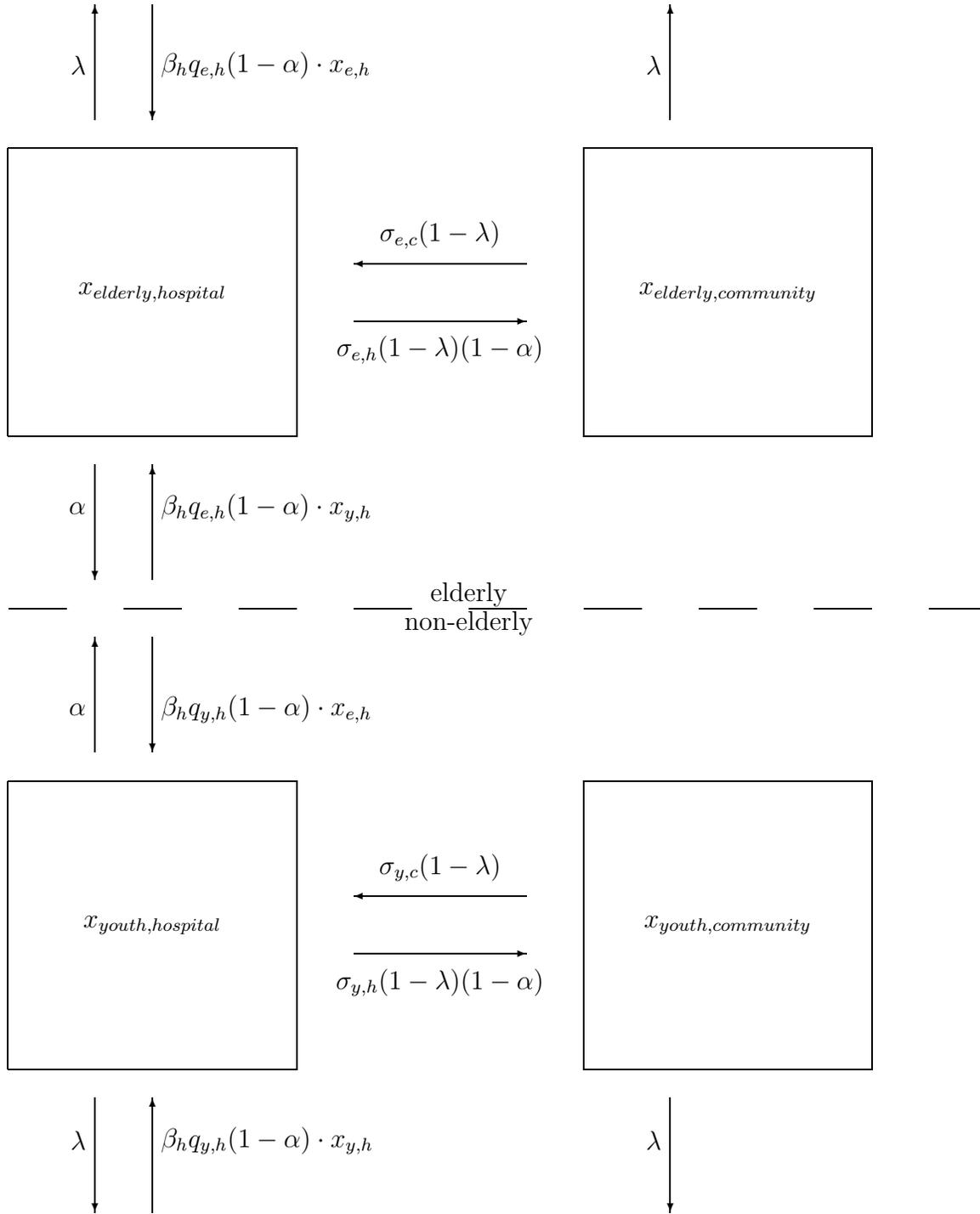
Figure 6: Situation 2: an outbreak detected. The life cycle graph of the heterogeneous model when a fraction α of the MRSA carriers in the hospital is detected. With $x_{g,j}$ the MRSA carriers per age group and per subpopulation, λ the rate of losing MRSA and $\sigma_{g,j}$ the rate of age group g to leave subpopulation j.

4.2 Simulation

In the Netherlands the age of retirement is 65 years. Therefore we chose, arbitrarily, to divide the population into 65 and older (the elderly) and younger than 65 (the non-elderly). The parameters used to simulate the heterogeneous two-subpopulation model are in table 6 in appendix F.2. The method of Caswell, see appendix D.2 and section 3.2, is used to define the relation between R_0 and β_h. We chose $R_0 = 1.35$ by expert opinion, this corresponds to $\beta_h = 0.22$. This is less than in the homogeneous model, because if a core group is introduced the transmissibility is less for the same R_0 value [17].

Like in the homogeneous model the prevalence of MRSA carriers in the hospital and in the community are simulated. We assume that the subpopulations and that the age groups in the subpopulations stay the same size. Therefore the outflow out of the hospital of an age group is equal to the inflow into the hospital of the same age group:

$$\sigma_{g,h} q_{g,h} N_h = \sigma_{g,c} q_{g,c} N_c.$$

With this formula the fractions of the age groups in the community and the community size, N_c, can be calculated. Then the outflows of the elderly and non-elderly out of the hospital will be multiplied with $\frac{N_h}{N_c}$ and the inflows into the hospital with $\frac{N_c}{N_h}$.

In this model we investigate the same model results as in the homogeneous model of chapter 3: the mean number of outbreaks per 100 days and the mean prevalence of MRSA carriers in the hospital and in the community, divided in elderly, non-elderly and total. These results are calculated from one time-step after an outbreak until another outbreak for almost 1000 days, which depends on the time between outbreaks. This for the last 1000 days of a simulation of 10,000 days, such that the starting conditions do not influence the model results anymore.

The effect of introducing a core group, represented by the elderly, to the model results compared to the homogeneous model without any core group is pointed out in table 2.

Table 2: Comparison of the heterogeneous model with the homogeneous model

$R_0 = 1.35$	mean number of outbreaks per 100 days	Mean MRSA prevalence in the hospital	Mean MRSA prevalence in the community
no groups	3.67	0.0016	0.00023
two groups	3.01	0.0017	0.00022
difference in %	-18%	6%	-7%

4.3 Differences between the elderly and the non-elderly

As stated before, we expect the elderly and the non-elderly to have differences in MRSA carriage and MRSA transmission. The difference in MRSA carriage can be represented by the right eigenvector and the difference in MRSA transmission can be represented by the left eigenvector or in the R_0 values per age group.

The heterogeneous model is, like the homogeneous model of chapter 3, most of the time in situation 1, where no outbreak is detected and transmission can continue. Therefore, we will evaluate the dominant right and left eigenvectors of matrix A belonging to the dominant eigenvalue, with matrix A working on numbers and not on fractions. The normalised right eigenvector represents the population distribution when matrix A will be multiplied with the initial population long enough, see appendix B.2. Filling in the parameters of appendix F.2 the following right eigenvector is calculated:

$$u_d = (0.05 \ 0.03 \ 0.40 \ 0.52)^T.$$

Thus, in a stable distribution, 5% of all MRSA carriers is an elderly in the hospital, 3% is a non-elderly in the hospital, 40% is an elderly in the community and 52% is a non-elderly in the community. Adding the elderly toghether gives 45%, this is equal to the total fraction of elderly in the hospital, see appendix F.2. This is logical, because we assumed that MRSA will be transmitted over the two age groups according to how they are divided over the hospital.

The mean distribution of the whole model, also with interventions, can be calculated by multiplying the mean prevalence of the elderly and the non-elderly in the hospital with N_h and the mean prevalence of both age groups in the community with N_c. Thereafter, these numbers are normalised to represent fractions of the total number of MRSA carriers:

$$x = (0.010 \ \ 0.007 \ \ 0.398 \ \ 0.585).$$

The left eigenvector represents the reproduction values, see appendix B.2. We choose to normalise the left eigenvector such that the second element equals one:

$$w_d = (1.76 \ 1 \ 0.11 \ 0.02).$$

Therefore, if we start with one elderly MRSA carrier in the hospital, then the population of MRSA carriers will be 1.76 times larger than if we start with one non-elderly MRSA carrier in the hospital, in the same length of time. Therefore, we expect taking intervention measures on the elderly will have a larger effect than on the non-elderly.

The elderly have a larger LOS, thus they have more time to transmit MRSA than the non-elderly. Therefore the elderly are expected to transmit MRSA to more individuals than the non-elderly and thus the elderly have a larger R_0 than the non-elderly. These R_0 values can be calculated with the formula of Cooper et al. (2004) [16] and Bootsma (2005)[20], see also section 3.2:

$$R_{0_g} = \frac{\beta_h(\lambda + \sigma_{g,c} - \lambda\sigma_{g,c})}{\lambda(\lambda + \sigma_{g,c} - \lambda\sigma_{g,c} + \sigma_{g,h} - \lambda\sigma_{g,c})}.$$

Using the parameters from appendix F.2 and $\beta_h = 0.22$, calculated according to Caswell, the reproduction values can be calculated, see table 3. Multiplying the R_0 values with the fractions of carriers gives the mean R_0 value of 1.35: $R_{0_e}q_{e,h} + R_{0_y}q_{y,h} = 1.35$.

Table 3: The basic reproduction values per age group

Group	R_0
elderly	1.92
non-elderly	0.88
Mean	1.35

Thus an elderly is expected to transmit MRSA 2.2 times more often than a non-elderly until they lose MRSA. Furthermore, a non-elderly can not maintain an epidemic, because $R_{0_y} < 1$. The difference with the value found above in the left eigenvector is because the left eigenvector works on time and the R_0 values on a generation of carriage time.

4.4 Interventions

In chapter 3 we concluded that screening all outgoing patients was an effective intervention measure. Therefore we will only investigate that intervention here. Because it is very expensive and hard to comply to screen all patients we will also investigate screening only the elderly or only the non-elderly. When only the outgoing elderly are screened the elements g and g_1 in the matrices A and B respectively are multiplied with $(1 - \alpha)$. If only the outgoing non-elderly are screened, then the elements i and i_1 of the matrices A and B respectively are multiplied with $(1 - \alpha)$. Furthermore, if the outgoing elderly and non-elderly are screened, both the elements g and i of matrix A and both the elements g_1 and i_1 of matrix B are multiplied with $(1 - \alpha)$. The results of the simulations are in table 4.

Table 4: Screening outgoing patients for MRSA in the heterogeneous model

	Mean number of outbreaks	Mean prev. of MRSA of the elderly (65^+)		Mean prev. of MRSA of the non-elderly		Mean prev. of MRSA of all patients	
		hosp.	com.	hosp.	com.	hosp.	com.
Screen all	-82%	-14%	-89%	-10%	-89%	-12%	-89%
Screen elderly	-60%	-11%	-89%	7%	10%	-4%	-30%
Screen non-elderly	-16%	5%	6%	-8%	-89%	0%	-50%
hosp. = in the hospital, com. = in the community, prev.=prevalence.							

If all outgoing patients are screened for MRSA, the prevalence of all MRSA carriers in the hospital and in the community decreases with roughly the same amount as in the homogeneous model, see table 1. If only the outgoing elderly are screened the prevalence of the non-elderly MRSA carriers in the hospital and in the community increase. However, the prevalence of the elderly and of all MRSA carriers in the hospital and in the community decrease. This is the other way around when screening the non-elderly.

4.5   Discussion

In order to compare the models of this paper we have chosen the basic reproduction value, R_0, to be equal for the homogeneous and the heterogeneous model. To achieve this the transmission rate in the heterogeneous model is less than in the homogeneous model. Also the dominant eigenvalue of matrix A is lower. Therefore the prevalence of MRSA carriers grows slower than in the homogeneous model and less outbreaks occur. Thus less interventions are taken in the hospital in the same time-period. Consequently the mean prevalence in the hospital is a little higher, see table 2. However it does not differ very much, therefore the homogeneous model of chapter 3 already gives a good indication of how MRSA is transmitted and detected in the hospital.

Furthermore, the homogeneous model also gives a good indication for which intervention measure will be effective to decrease the prevalence of MRSA carriers in the hospital and in the community and to decrease the number of outbreaks. This effective intervention measure was screening outgoing patients, therefore we chose to investigate only the screening for MRSA of outgoing patients for the heterogeneous model in this paper. If all outgoing patients are screened for MRSA exactly the same decrease of the prevalence of MRSA in the community is noticed for the heterogeneous model as for the homogeneous model, see tables 1 and 4.

The heterogeneous model is often in the situation that no outbreak is detected, and transmission of MRSA in the hospital can continue. Therefore we choose to calculate the basic reproduction value, R_0, only for the situation when transmission can continue and no intervention measures are taken in the hospital. For the whole model R_0 is circa 1, because the prevalence of MRSA in the hospital and in the community fluctuates in a certain interval. Furthermore, we also use only the matrix A (no intervention) to calculate the right and left eigenvectors. With these eigenvectors we are able to understand the distribution of the undetected MRSA carriers and the contribution of each age group to the transmission. We compare the right eigenvector of matrix A with the mean prevalence of MRSA in the hospital and in the community of our simulation to see if the right eigenvector is a good indication. The difference between the right eigenvector and the simulation is that in the simulation 98% of the MRSA carriers is in the community, while the right eigenvector states 92%. However, this difference is not much and in both is a ratio of circa 1.5 between the number of elderly carriers in the hospital and the number of non-elderly carriers in the hospital. Therefore the right and left eigenvectors of matrix A give good indications for

the distribution of MRSA carriers and the contribution per age group to the transmission of MRSA.

When screening just one age group of the outgoing patients, the prevalence of MRSA in the community of this age group decreases the same as for screening all outgoing patients. If just one age group is screened both the prevalence of MRSA in the hospital and in the community of that age group decreases. However, the prevalence of MRSA in the hospital and in the community of the other age group are increasing. This can be explained by the fact that if the prevalence of one age group decreases, it takes longer for the total prevalence in the hospital to exceed the detection threshold thus the number of outbreaks also decreases. Therefore less interventions are taken in the hospital and thus the prevalence of the age group without screening increases.

When the outgoing elderly are screened the prevalence of MRSA of the non-elderly in the community and in the hospital increase slightly more than of the elderly when the outgoing non-elderly are screened. Furthermore, the total prevalence in the community decreases more when the non-elderly are screened. This can be explained by looking at the right eigenvector of matrix A without interventions. This right eigenvector says that the largest fraction of the number of MRSA carriers will be the non-elderly in the community. Thus the total prevalence of MRSA carriers in the community will decrease more when the largest fraction decreases with the same factor as the smallest fraction would. However, the number of outbreaks decreases much more if the elderly are screened than if the non-elderly are screened, see table 4. Therefore less interventions have to be taken in the hospital. Furthermore, the total prevalence of MRSA carriers in the hospital only decreases when the elderly are screened. Moreover, the age group of elderly in the hospital is smaller than the age group of non-elderly. Thus it is less expensive to screen only the elderly compared to screening only the non-elderly when leaving the hospital. Furthermore, the R_0 value of the elderly is 2.2 times higher than the R_0 value of the non-elderly. Thus one elderly is expected to transmit MRSA 2.2 times more often than one non-elderly. Therefore we would advise to screen all outgoing patients, but for economic reasons it is also possible to only screen the outgoing elderly.

The choice of definition of the elderly is arbitrary. However, Bootsma et al. (2006) [17] proved that the size of the core group does not influence the effect of the intervention measures of the S&D program. To investigate which groups of elderly are responsible for most of the transmissions the next chapter will divide the population into 5-year age groups.

5   5-year age groups

5.1   Introduction

In chapter 3 we concluded that screening outgoing patients is a good intervention strategy to reduce the prevalence of MRSA in the hospital and in the community. In chapter 4 we showed that the elderly contribute more to the transmission of MRSA than the non-elderly. However, it is not so evident how to divide the population in elderly and non-elderly. In this chapter detailed data allows us to divide the population into 5-year age groups, to determine which age groups contribute to the transmissions of MRSA. We will only investigate the situation when no outbreak is detected and transmission of MRSA can continue in the hospital.

Like for the heterogeneous model of chapter 4 the following assumptions are made: age groups do not change in size and neither do the subpopulations, therefore the fraction of an age group in a subpopulation does not change either. This is a closed population with movement between the subpopulations, but without movement between the groups. Furthermore, the fraction of non-carriers of MRSA in every age group is assumed to stay close to 1. Therefore enough susceptibles are available in every age group and the model can be linearised. Furthermore, the transmission rate in the hospital is assumed to be equal between and within the age groups and in the community no transmission takes place. Like in chapter 4 if one patient infects β_h other patients, these patients are divided over the age groups like the age groups are divided over the hospital. Furthermore, the next probabilities are also the same as in chapter 4:

$$\mathbb{P}(\text{Leave } x_{g,j} \ \cap \ \text{MRSA carrier}) = \sigma_{g,j}(1 - \lambda),$$

$$\mathbb{P}(\text{Leave } x_{g,j} \ \cap \ \text{MRSA lost}) = \lambda,$$

$$\mathbb{P}(\text{Stay in } x_{g,j}) = (1 - \sigma_{g,j})(1 - \lambda).$$

The matrix A (no intervention) can be made in the same way as in chapter 4 only then with dimension 36 instead of 4.

5.2   Results and discussion

As said above, in this heterogeneous model with the population divided into 5-year age groups, we only investigate the situation when no outbreak is detected and transmission of MRSA can continue in the hospital. The reproduction values per unit of time are represented in the left eigenvector of matrix A, see appendix B.2. To calculate the left eigenvectors, the parameters of table 7 in appendix F.3 are used. The reproduction values for the MRSA carriers in the hospital are normalised such that the reproduction value of age group 15-19 years equals 1 and can be found in figure 7. We chose this age group to have a reproduction value of 1, because this age group is approximately the mean of the age groups younger

than 55, which do not differ very much. The high value of the 0-4 age group is mainly caused by the newborns. However, they are most of the time already in isolation and they have their own ward with more hygiene measures than other wards. Moreover the ones who have a high LOS in the hospital are most of the time lying in incubators. Therefore, in reality this high reproduction value of the 0-4 age groups should be less than we calculated. The increase of reproduction values begins at the age of 55, however the choice of taking the 65 and older to be the age group of elderly is not such a bad choice. Because the age group 65-69 has a 1.5 higher reproduction value than the age group 15-19. Thus if one would start with one MRSA carrier in the age group 65-69 the number of MRSA carriers will grow 1.5 times faster than if one would start with one MRSA carrier in the age group 15-19. Furthermore the older age groups have even a higher reproduction value.

To compare the reproduction values represented by the left eigenvector in figure 7 with the length of stay in the hospital per age group, the LOS values are normalised such that the LOS of the 15-19 age group equals 1, see figure 8. In this way the reproduction values and the LOS values are both in ratios and we see almost the same values. Therefore we can conclude that the LOS in the hospital is primarily responsible for the fact that the elderly of 65 and older transmit MRSA to more patients than the non-elderly.

The larger LOS and the higher rate of admittance to the hospital of the elderly gives them more time to transmit MRSA before they lose MRSA. Therefore they will transmit MRSA to more patients during their carriage time than the younger MRSA carriers and thus have higher R_0 values. Like in chapter 4, these R_0 values are calculated according to the formula of Cooper et al. [16] and Bootsma [20]:

$$R_{0_g} = \frac{\beta_h(\lambda + \sigma_{g,c} - \lambda\sigma_{g,c})}{\lambda(\lambda + \sigma_{g,c} - \lambda\sigma_{g,c} + \sigma_{g,h} - \lambda\sigma_{g,c})}.$$

The R_0 values are also normalised to represent ratios in the same way as the LOS and the reproduction values, see figure 9. The R_0 ratios are higher for the age groups above 65 years than the LOS ratios or reproduction ratios. This can be explained by the fact that the reproduction values are based on generation time, which is the whole carriage time and thus includes readmission to the hospital besides mainly the LOS. Conversely, the reproduction values represent differences in growth rate of the MRSA carriers between initial conditions, see appendix B.2. Furthermore, the R_0 values represent both the age groups in the hospital and in the community, while the reproduction values and LOS values only represent the age groups in the hospital. However, the three graphs show the same shape and consequently they can be used to decide on which age groups intervention measures can be taken to have the most effective results.
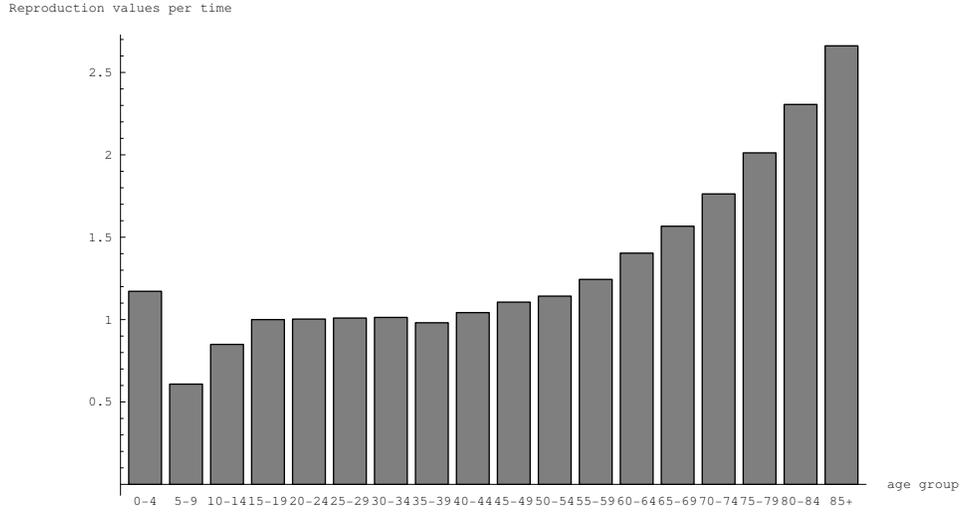
Figure 7: The reproduction values per time unit represented by the left eigenvector age group in the hospital. The reproduction values are normalised to represent ratios to the 15-19 age group. The age groups older than 65 show a clear increase to the contribution to transmission of MRSA.
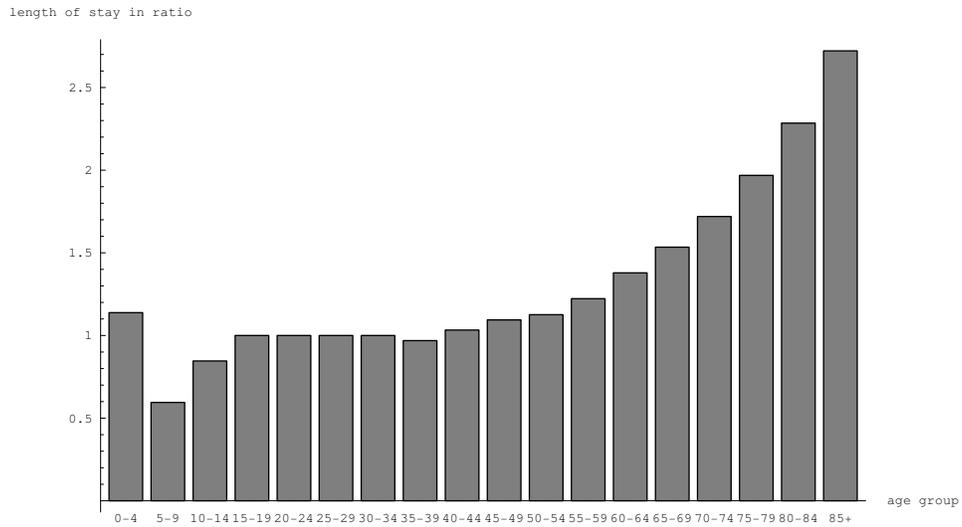
Figure 8: The lengths of stay in the hospital per age group. The LOS values are normalised to represent ratios to the 15-19 age group. The age groups older than 65 show the same increase in LOS as in reproduction values.

Figure 9: The basic reproduction values per generation of MRSA carriage per age group. The R_0 values are normalised to represent ratios to the 15-19 age group. The age groups older than 65 have even a larger increase in R_0 values than in LOS values. One patient of 65 years old is expected to transmit MRSA 2 times more often during his whole carriage time than one patient of 15 years old.

6 Discussion/Conclusion

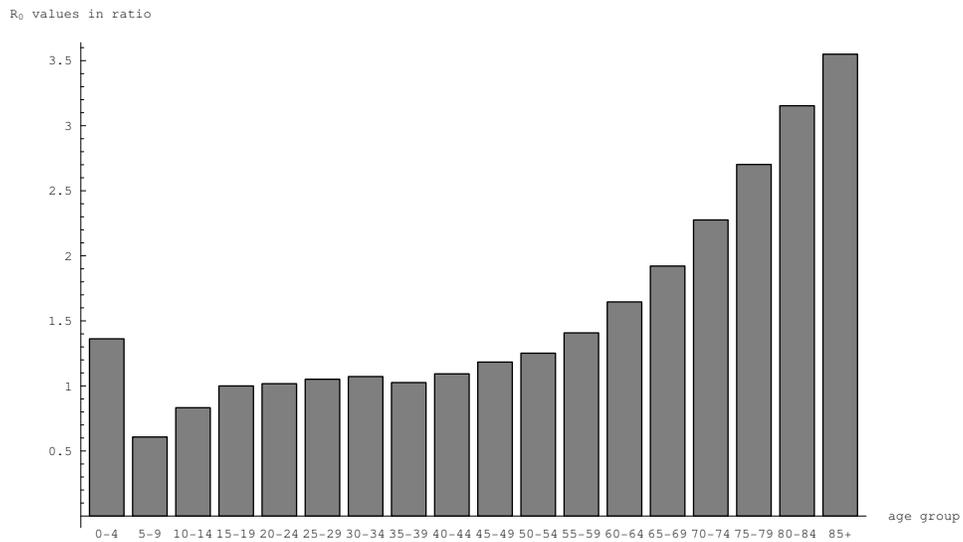In this paper we investigated the potential contribution of asymptomatic undetected MRSA carriers to the prevalence and number of outbreaks of hospital-acquired MRSA. We did this we the help of linear matrix models. Subsequently we investigated which control measures are effective to reduce the prevalence of MRSA in the hospital and in the community and to reduce the number of outbreaks in the hospital. Furthermore, we investigated if there is an age group which has a higher prevalence of MRSA and transmits MRSA more than other age groups in the population. We expected that the elderly will be this group, because they have a longer mean length of stay in the hospital and thus more time to transmit hospital-acquired MRSA. Thereafter, we investigated to what extent taking control measures on only one age group reduces the prevalence of MRSA carriers in the hospital and in the community and the number of outbreaks of MRSA.

In modelling the dynamics of hospital-acquired MRSA one should be aware of how to define the basic reproduction value R_0. In mathematical models of infectious diseases in which movement between subpopulations is important for the transmission of the disease one should be aware of how to construct the next-generation matrix, which is used to calculate R_0. For this next-generation matrix a generation has to be defined. Diekmann and Heesterbeek (2000) [21] define a generation to be the mean time spent in the hospital per visit, while Caswell (2001) [22] defines a generation to be the whole carriage time including readmission to the hospital. Therefore we used the method of Caswell for our models to find a formula for R_0 from which the transmission rate is calculated.

Our choice for the basic reproduction value, $R_0 = 1.35$, is based on expert opinion. This is in accordance with Cooper et al. (2004) [16], who investigated the values 1.1-1.3 for R_0. We assumed R_0 to be equal for all models discussed in this paper, allowing us to compare the different models to each other. If we would have chosen $R_0 > 1.35$ the growth rate is higher and thus more outbreaks will occur. For $1 < R_0 < 1.35$ the growth rate is lower and consequently less outbreaks occur. However, screening all in and outgoing patients will give roughly the same decrease in the prevalence of MRSA carriers in the hospital and in the community for different values of R_0. Therefore the value of R_0 has little influence on investigating which intervention measure will be effective.

After applying different intervention measures to the model to reduce the number of outbreaks and the prevalence of MRSA in the hospital and in the community, we found screening the outgoing patients for MRSA is an effective intervention. However, screening *all* outgoing patients may be very expensive and hard to apply in practise. Therefore we investigated if the elderly of 65 and older contribute more to the transmission of MRSA than the non-elderly. Even though the fraction of elderly in the hospital is smaller than the fraction of the non-elderly, we found that the elderly together do transmit MRSA 1.76 times more. Furthermore, we estimate that the R_0 value for one elderly is even 2.2 times higher than for one non-elderly. Therefore, screening only the outgoing elderly is a better intervention measure than screening only the outgoing non-elderly. Thus, if resources are

scarce for screening all outgoing patients, one should start with screening the outgoing elderly.

The models presented in this paper are two- and more-dimensional matrix models with different subpopulations and age groups. Unfortunately, little is known about these models of piecewise linear mapping. However, about one-dimensional models with a detection threshold, like our models, enough literature is available, see also appendix E. In the one-dimensional models one can find the interval, in which the population size eventually will fluctuate, depending on the parameters of the model [25]. Moreover, one can find what the pseudo cyclic behaviour of the model will be [26]; if these cycles are of finite period or that they are aperiodic [23]. Furthermore, one can find the detection frequency and the mean time between two subsequent outbreaks [25]. These do not depend on the detection threshold k, while the population size interval does depend on k, in one dimensional models [25]. When simulating our two- and more-dimensional models for different values of the detection threshold k, the mean prevalence of MRSA carriers in the hospital and in the community depends on k. Furthermore, the mean time between two outbreaks and the detection frequency do not depend on k. However, we were not able to find the relation between this model results and the parameters of our models.

In mathematical modelling assumptions have to be made to make the models more understandable and simple to work with. We also made a couple of simplifying assumptions. First, in the models discussed in this paper we assume a closed population. However, in reality it is possible to enter or leave the population with or without MRSA carriage. Patients who are admitted from foreign hospitals, are the largest part of MRSA carriers from outside the population [10], and are already screened and labelled. Therefore they will not enter the group with unknown MRSA carriers. Thus the probability that an undetected MRSA carrier from outside the population enters the studied population is very low and will not have great influence on the models presented here.

Second, in the Netherlands the search and destroy policy is used, in which detected MRSA carriers are labelled and put into isolation until clearance of MRSA. These detected MRSA carriers are not able to transmit MRSA to other patients. We assume that undetected asymptomatic carriers are responsible for continued MRSA transmission. Therefore, in our models we only investigated the prevalence of undetected MRSA carriers. However, the total MRSA prevalence as reported in hospital surveys also includes the detected patients.

Third, in the models discussed in this paper we assume for simplicity that no transmission takes place in the community. However, MRSA can be transmitted in the community too [3]. Most of the time this is community-acquired MRSA, which are different strains than the hospital-acquired MRSA we investigated. Furthermore, the prevalence of MRSA among patients without risk factors is very low at admittance to the hospital [2]. Therefore transmission in the community will probably not influence our models much. Moreover, we concluded that screening the outgoing patients is an effective intervention measure and this will still be true if transmission in the community would influence the dynamics of undetected MRSA carriage.

Fourth, because little is known about the clearance of undetected MRSA without treatment we assume that this is the same for the hospital and for the community. If the probability of clearing MRSA would be less in the hospital than we assumed in our models, because of antibiotic pressure, it takes less time to reach the detection threshold. Therefore more interventions are taken and thus the mean prevalence in the hospital and in the community will be less than in our simulations. To investigate this more precisely, data about clearance of undetected MRSA without treatment in the hospital and in the community is needed.

Furthermore, in the heterogeneous models we assumed that the transmission rate between age groups is the same as within age groups. However, in practise elderly and non-elderly do not all share the same HCWs and wards. Especially children and newborns who most of the time have their own ward. Unfortunately, we did not have data about contact between different age groups through the HCWs. This should be further investigated.

Finally, in the deterministic models of this paper we assumed the detection threshold to be constant. However, in reality an outbreak in hospitals will be detected when different numbers of undetected MRSA carriers are in the hospital. This would make the model stochastic, but the stochastic distribution of the detection threshold k is unknown. To have data to estimate the distribution of k, one would have to screen all the patients in the hospital at every outbreak for a long time. This distribution would probably be different per hospital. Therefore, a stochastic framework would require additional assumptions or data. Furthermore, in a stochastic model one should make the LOS and admission rate also stochastic, because they are actually exponentially distributed. However, the influence of the LOS can be better investigated in a deterministic or probabilistic model with use of the mean LOS.

Recently, it is noticed that HA-MRSA is not a problem in hospitals alone, but also in nursing homes. The mean age of residents in nursing homes is very high. Therefore they visit the hospitals more often than younger people, and they tend to stay longer in the hospitals, thus the residents have a higher probability of becoming colonised in the hospital. Moreover, in nursing homes the search-and-destroy policy is much harder to comply, because the length of stay is very long, which makes isolation problematic [8]. It is not ethical to put people in isolation for the rest of their lives. Also in nursing homes the staff-patient ratio is very low: sometimes only one nurse for a whole ward. This makes prevention of transmission of MRSA in nursing homes more difficult. And therefore nursing homes tend to become a reservoir for MRSA [8]. Smith et al. (2004) [19] investigated the influence of a nursing home as a third subpopulation on the prevalence of MRSA in the hospital and in the community. They concluded that the prevalence of MRSA in the hospital and in the community will be higher with a nursing home. To include a nursing home in our models, the admission rates from the nursing home to the hospital and back are needed. Furthermore to complete the model the lengths of stay in the nursing home per age group are and the admission rate from the community to the nursing home are needed. Moreover, other control measures such as screening only patients from or to the nursing home can be investigated.

Screening outgoing patients is a policy which hospitals probably do not want to pursue, because this is an intervention outside the hospital. However, in our models we saw no difference between screening outgoing or incoming patients for the prevalence of MRSA in the hospital and for the number of outbreaks in the hospital. Furthermore, if transmission takes place in the community or in nursing homes it will be more effective to reduce the prevalence in the community as much as possible.

We conclude that undetected MRSA carriers play a crucial role in the transmission of HA-MRSA. Furthermore, health care utilisation patterns suggest that some (age) groups may play a larger role in the transmission of MRSA than others, because of their increased number of visits and LOS. Mathematical models allow us to translate these data into age group based estimates of relative transmissibility and to evaluate potential age group based interventions. In the model with the population divided into 5-year age groups we concluded that it is effective to take interventions on the age groups who have a high mean LOS value and visit the hospital most frequently. However, in these age groups are also individuals who almost never visit the hospital. For these individuals it would be unnecessary to screen them when leaving the hospital. It might be more effective to use the history of hospital visits for every individual: if their LOS and frequency of visits are high, for instance chronically ill patients, then screen them for MRSA when leaving the hospital. Therefore we conclude that an effective intervention measure to reduce the prevalence of MRSA in the hospital and in the community and to reduce the number of outbreaks is screening outgoing patients, who have a history of long and frequent visits to the hospital.

A   Abbreviations

ARB: Antibiotic-Resistant Bacteria

CA: Community-Acquired

EARSS: European Antimicrobial Resistance Surveillance System

HA: Hospital-Acquired

HCW: Health Care Worker

ICU: Intensive Care Unit

LOS: Length Of Stay

LTCF: Long-Term Care Facility

MRSA: Methicillin-resistant *Staphylococcus aureus*

ODE: Ordinary Differential Equation

S&D: Search and Destroy

B   Linear population models

B.1   Construction of linear population models

To construct a population model Diekmann and Heesterbeek (2000)[21] divide the population into groups of individuals with the same i-state, which is divided in a d-state (*disease*-state: Susceptible or Infective) and an h-state (*heterogeneity*-state: age group g and subpopulation j). The characteristics, on which the h-states are based on, can be *static* (like sex) or *dynamic* (like being in the hospital or not) and they can take *discrete* or *continuous* values. These i-states and the rates to go from one i-state to another can be put into a life cycle graph like in figure 1 and the life cycle graph can be transformed into a population projection matrix A in the equation:

$$v(t+1) = Av(t) \tag{1}$$

where $v(t)$ is a vector of the population distribution. The matrix A is *non-negative*, i.e. all elements $a_{ij} \geq 0$, because populations can not become negative. A non-negative matrix is called a *positive* matrix if all elements $a_{ij} > 0$ and can be divided into *irreducible* and *reducible* matrices. Furthermore, an irreducible matrix, which belongs to a life cycle graph with a path from every node to every other node [22], can be divided into *primitive* and *imprimitive* matrices. The definitions of irreducible and primitive matrices are given by Diekmann and Heesterbeek (2000) in Definition 5.4 on page 76 [21]:

Definition B.1 *If for every pair $\{i, j\}$ $\exists n > 0$ such that $(A^n)_{ij} > 0$ then A is called* irreducible. *And if $\exists n > 0$ such that A^n is positive then A is called* primitive.

Also primitivism can be evaluated from the life cycle graph, when it is irreducible and the greatest common divisor (gcd) of the lengths of its loops is 1 [22]. When $gcd > 1$ the matrix is imprimitive and its *index of imprimitivism* is equal to gcd.

To investigate the model $v(t+1) = Av(t)$ the effects of the eigenvalues λ_i and its right and left eigenvectors u_i and w_i of A are evaluated, which satisfy:

$$Au_i = \lambda_i u_i \tag{2}$$

$$w_i^* A = \lambda_i w_i^* \tag{3}$$

where w_i^* is the complex conjugate transpose of w_i and the λ_i are solutions of the *characteristic equation*:

$$det(A - \lambda I) = 0. \tag{4}$$

Now suppose that $Au_i = \lambda_i u_i$ and write the initial population v_0 as a linear combination of the right eigenvectors u_i of A:

$$v_0 = c_1 u_1 + c_2 u_2 + \cdots + c_m u_m \tag{5}$$

where m is the dimension of A. To find the coefficients c_i of (5) write (5) as:

$$v_0 = (u_1 \cdots u_m) \begin{pmatrix} c_1 \\ \vdots \\ c_m \end{pmatrix} = Uc. \tag{6}$$

Thus

$$c = U^{-1}v_0. \tag{7}$$

Now applying (1) and (2) to find $v(1)$ and $v(2)$:

$$v(1) = Av_0 = \sum_{i=1}^{m} c_i Au_i = \sum_{i=1}^{m} c_i \lambda_i u_i \tag{8}$$

$$v(2) = Av(1) = \sum_{i=1}^{m} c_i \lambda_i Au_i = \sum_{i=1}^{m} c_i \lambda_i^2 u_i$$

Iterating this principle t times gives:

$$v(t) = \sum_{i=1}^{m} c_i \lambda_i^t u_i. \tag{9}$$

Thus the long-term behaviour of $v(t)$ depends on the eigenvalues, for instance if λ_i is positive, λ_i^t produces exponential growth if $\lambda_i > 1$ and exponential decay if $\lambda_i < 1$.

Every non-negative matrix A has a real non-negative *dominant eigenvalue* $\lambda_d \geq |\lambda_i| \; \forall i \neq d$, which and its left and right eigenvectors w_d and u_d are described by the Perron-Frobenius theorem stated by Caswell (2001) [22]:

Theorem B.2 (Perron-Frobenius)
Primitive matrices: *$\lambda_d > 0$ is a simple root of the characteristic equation. $\forall i \neq d$ $\lambda_d > |\lambda_i|$. w_d and u_d are real and strictly positive. There may be other real eigenvectors but λ_d is the only eigenvalue with non-negative eigenvectors.*
Irreducible but imprimitive matrices: *$\lambda_d > 0$ is a simple root of the characteristic equation. w_d and u_d are positive. $\forall i \neq d$ $\lambda_d \geq |\lambda_i|$, but the spectrum of A contains gcd, the index of imprimitivism, eigenvalues equal in magnitude to λ_d. One is λ_d itself and the others are the $(gcd - 1)$ complex eigenvalues:*

$$\lambda_d e^{2k\pi i/gcd} \; for \; k = 1, 2, \ldots, (gcd - 1).$$

Reducible matrices: *$\lambda_d \geq 0$, $w_d \geq 0$ and $u_d \geq 0$ and $\forall i \neq d$ $\lambda_d \geq |\lambda_i|$.*

A population model is called *ergodic* if its eventual behaviour is independent of the initial conditions. The dominant eigenvalue λ_d determines the population growth rate as stated in the next theorem reported by Caswell (2001) [22]:

Theorem B.3 (The strong ergodic theorem)
Consider $v(t)$ from (9):

$$v(t) = c_1 \lambda_1^t u_1 + c_2 \lambda_2^t u_2 + c_3 \lambda_3^t u_3 + \cdots \tag{10}$$

where $|\lambda_1| \geq |\lambda_2| \geq |\lambda_3| \geq \cdots$. If $\lambda_1 > |\lambda_i| \; \forall i \geq 2$ it will dominate all other terms in (10):

$$\lim_{t \to \infty} \frac{v(t)}{\lambda_1^t} = \lim_{t \to \infty} \left[c_1 u_1 + c_2 \left(\frac{\lambda_2}{\lambda_1} \right)^t u_2 + c_3 \left(\frac{\lambda_3}{\lambda_1} \right)^t u_3 + \cdots \right] = c_1 u_1 \tag{11}$$

Thus

$$\lim_{t \to \infty} v(t) = c_1 \lambda_1^t u_1.$$

Therefore any initial population converges to a fixed stable stage structure.

B.2 Right- and Left eigenvectors

From the Perron-Frobenius theorem and the strong ergodic theorem of appendix B.1 it is concluded that if A is primitive, the long-term dynamics of the population are described by the population growth rate λ_d and the stable population structure u_d, which is the positive right eigenvector vector belonging to λ_d and can be normalised to represent fractions:

$$\sum_{i=1}^{m} u_{d_i} = 1.$$

The left eigenvector belonging to λ_d, w_d, is also real and positive and satisfies:

$$w_d^T A = \lambda_d w_d^T \Leftrightarrow (w_d^T A)^T = (\lambda_d w_d^T)^T \Leftrightarrow A^T w_d = \lambda_d w_d.$$

The left eigenvector w_d represents the reproduction value vector and can be normalised such that one of the elements equals one. The other elements are in ratio to the unit element and all the elements will give weights to the initial condition. The population will eventually grow according to:

$$v(t) = w_d^T v(0) \lambda_d^t u_d.$$

Furthermore, the size of the population will be asymptotically proportional to a weighted sum of the initial population, with the weights given by the elements of w_d [22].

The next example will clarify the meaning of the left eigenvector. The population is divided into two subpopulations. The stable population structure corresponds to the right eigenvector: $u_d = \begin{pmatrix} 0.8 \\ 0.2 \end{pmatrix}$. The belonging left eigenvector with one unit element is: $w_d = \begin{pmatrix} 4 \\ 1 \end{pmatrix}$. If the population starts with one individual in subpopulation 1 the population will grow t units of time according to:

$$v(t) = (4 \quad 1) \begin{pmatrix} 1 \\ 0 \end{pmatrix} \lambda_d^t \begin{pmatrix} 0.8 \\ 0.2 \end{pmatrix} = 4\lambda_d^t \begin{pmatrix} 0.8 \\ 0.2 \end{pmatrix}.$$

On the other hand, when the population starts with one individual in subpopulation 2 the population will grow t units of time according to:

$$v(t) = (4 \quad 1) \begin{pmatrix} 0 \\ 1 \end{pmatrix} \lambda_d^t \begin{pmatrix} 0.8 \\ 0.2 \end{pmatrix} = 1\lambda_d^t \begin{pmatrix} 0.8 \\ 0.2 \end{pmatrix}.$$

Thus one individual in subpopulation 1 reproduces a population which is four times larger than the population reproduced by one individual in subpopulation 2 in the same amount of time.

C   Mean sojourn time during one visit to state x_j

The mean sojourn time can be calculated by looking at the probability of staying in state x_j. Here x_j is the MRSA carriers in the hospital or in the community. If we start with I_0 individuals in state x_j at time $t = 0$, then at time $t + 1$ the number of individuals who are still in state x_j is:

$$I_{t+1} = (1 - \lambda)(1 - \sigma_j) \cdot I_t = [(1 - \lambda)(1 - \sigma_j)]^t \cdot I_0.$$

Thus at time $t = 1$, $[1 - (1 - \lambda)(1 - \sigma_j)] \cdot I_0$ individuals have left state j and stayed in j for one time period. In the period from $t = 1$ until $t = 2$, $[(1 - \lambda)(1 - \sigma_j) - ((1 - \lambda)(1 - \sigma_j))^2] \cdot I_0$ individuals have left state j and stayed in j for two time periods. Repeating this principle and taking the mean over all time periods, i.e. dividing by I_0, gives the mean sojourn time:

$$\text{mean sojourn time} = 1 \cdot [1 - (1 - \lambda)(1 - \sigma_j)] + 2 \cdot [(1 - \lambda)(1 - \sigma_j) - ((1 - \lambda)(1 - \sigma_j))^2]$$

$$+ 3 \cdot [((1 - \lambda)(1 - \sigma_j))^2 - ((1 - \lambda)(1 - \sigma_j))^3] + \cdots$$

$$= 1 + (1 - \lambda)(1 - \sigma_j) + [(1 - \lambda)(1 - \sigma_j)]^2 + [(1 - \lambda)(1 - \sigma_j)]^3 + \cdots$$

$$= \sum_{n=0}^{\infty} [(1 - \lambda)(1 - \sigma_j)]^n = \frac{1}{1 - (1 - \lambda)(1 - \sigma_j)} = \frac{1}{1 - (1 - \lambda - \sigma_j + \lambda\sigma_j)} = \frac{1}{\lambda + \sigma_j - \lambda\sigma_j}.$$

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D R_0 and the next-generation matrix

D.1   According to Diekmann and Heesterbeek

To compare linear models and non-linear models consisting of ODEs with each other, epidemiologists evaluate the *basic reproduction ratio* defined by Diekmann and Heesterbeek (2000) [21]:

$$R_0 \quad := \quad \text{expected number of secondary cases per primary case in a 'virgin' population.}$$

With a 'virgin' population they mean a population without the disease at starting time. To calculate R_0 the *next-generation matrix* K is formed by:

$$K_{ij} \quad := \quad \text{expected number of new cases that have } h\text{-state } i \text{ at moment they become}$$
$$\text{infected, caused by one individual infected while having } h\text{-state } j,$$
$$\text{during the whole period of infectiousness.} \tag{12}$$

Thus

$$v_i^{new} = \sum_{j=1}^{m} K_{ij} v_j^{old}$$

and

$$v^n = K v^{n-1} = \cdots = K^n v^0.$$

The next-generation matrix K is like the population projection matrix A of (1) a non-negative matrix (it is not possible to infect a negative amount of individuals). The difference between K and A is the timescale: K works on generation time and A on days or weeks.

In this paper the normal norm for vectors is used:

$$\|v\| = \sum_{j=1}^{m} |v_j|$$

which is the total number of cases in the generation described by v.
The norm for matrices will be:

$$\|K\| = \sup_{\|v\| \neq 0} \frac{\|Kv\|}{\|v\|} = \sup_{\|v\|=1} \|Kv\|$$

this can be interpreted as the maximum multiplication number for the total number of cases. However the initial state v^0 can be chosen at random, eventually the distribution of the generations will be determined by the dynamics. Therefore instead of looking at the

multiplication number for one generation it is necessary to look at the multiplication in n generations on a 'per generation' basis:

$$\|K^n\|^{1/n}.$$

Taking the limit for $n \to \infty$ is called the *spectral radius* of K and is by definition the long-term average per generation multiplication number which is R_0:

$$R_0 := \lim_{n\to\infty} \|K^n\|^{1/n}.$$

The next theorem, theorem 5.3 of Diekmann and Heesterbeek (2000) [21], shows how one can easily compute R_0:

Theorem D.1 *Let $K \geq 0$, then the spectral radius R_0 is the dominant eigenvalue of K since $|\lambda| \leq R_0$ for all other eigenvalues of K. The eigenvector u_d can be chosen in such a way that all its components are non-negative and their sum equals one, i.e. u_d is normalised.*

The dominant eigenvector u_d describes the stable distribution. Combining this theorem with the Perron-Frobenius theorem, see appendix B.1, the next theorem, theorem 5.6 of Diekmann and Heesterbeek (2000) [21], is formed:

Theorem D.2 *Let K be primitive. Then*

1. *R_0 is strictly dominant, i.e. $R_0 > |\lambda_i|$;*

2. *The left and right dominant eigenvectors w_d and u_d have strictly positive components;*

3. *R_0 is an algebraically simple eigenvalue, i.e. R_0 is a simple solution of the characteristic equation;*

4. *no other eigenvalue has a positive eigenvector.*

Thus it is needed to form the next-generation matrix from which it is not hard to calculate the basic reproduction number R_0.

D.2 According to Caswell

According to Caswell (2001) [22] the population projection matrix A can be decomposed:

$$A = T + F.$$

The matrix T describes the *transitions* and the matrix F describes the *reproduction*. Thus the element T_{ij} is the probability that an individual in state j at time t will be in state i at time $t + 1$. And the element F_{ij} is the expected number of new individuals in state i produced by an individual in state j. The movement through the life cycle of an individual can be described by a Markov chain where T describes a part of it. Therefore an extra state "dead" or is added to the existing s states, which results in an $s + 1$ dimensional Markov chain with transition matrix:

$$P = \left(\begin{array}{c|c} \mathbf{T} & \mathbf{0} \\ \hline \mathbf{m} & 1 \end{array} \right).$$

The probability that an individual in state j dies is:

$$m_j = 1 - \sum_{i=1}^{s} t_{ij}.$$

The state $s + 1$ (death) is an absorbing state, i.e. when an individual enters this state it is not possible to leave this state. The other states are transient states, i.e. when an individual enters an transient state it is possible to leave this state. Therefore the states in an absorbing Markov chain can be divided into two sets: a set $\mathcal{T}$ of transient states and a set $\mathcal{A}$ of absorbing states. In this model it is assumed that there is a pathway from each transient state in $\mathcal{T}$ to one of the absorbing states in $\mathcal{A}$. Thus absorption is certain, therefore the probability that an individual in state j at time 0 will be in state i at time t, i.e $(T^t)_{ij}$, will eventually decay to zero. Furthermore the dominant eigenvalue of T is < 1, because an individual in every state in $\mathcal{T}$ eventually leaves $\mathcal{T}$, thus

$$\lim_{t \to \infty} T^t = 0.$$

Before absorption occurs an individual will visit various transients states various number of times. Let μ_{ij} be the number of visits to transient state i before absorption, given that this individual starts in state j. The expected values of the μ_{ij} are given by the matrix

$$(\mathbb{E}(\mu_{ij})) = I + T + T^2 + \cdots = (I - T)^{-1} =: N.$$

The matrix N is called the *fundamental matrix* of the Markov chain and gives the expected number of time steps spent in each transient state. The matrix F gives the expected number of offspring of each type produced per time step. Therefore the elements r_{ij} of the matrix $R = FN$ give the expected lifetime production of type i offspring of an individual who starts in state j. Thus R projects the population from one generation to the next. The dominant eigenvalue of R will give the rate of growth of the population from one generation to the next generation. Therefore it can be concluded that:

$$R_0 = \text{the dominant eigenvalue of } R.$$

D.3 Comparing R_0

With the next simple example the difference between calculating R_0 according to Diekmann an Heesterbeek (2000) [21] and according to Caswell (2001) [22] will be clear. In malaria the mosquito is the vector and the human is the infected. For simplicity during one generation one mosquito infects b humans and one human infects a mosquitoes. Furthermore the mosquito and the human are cleared of malaria during one generation time.

$$\begin{cases} V_{t+1} &=& a \cdot M_t \\ M_{t+1} &=& b \cdot V_t \end{cases}$$

$$X_t = \begin{pmatrix} V_t \\ M_t \end{pmatrix}$$

$$X_{t+1} = A \cdot X_t$$

$$A = \begin{pmatrix} 0 & a \\ b & 0 \end{pmatrix}$$

According to Diekmann and Heesterbeek (2000) [21] the matrix A is the next-generation matrix with dominant eigenvalue $R_0 = \sqrt{ab}$.

On the other hand according to Caswell (2001) [22] A can be written as $A = T + F$, because the malaria parasite travels from mosquito to human and infects new mosquitoes, T and F become:

$$T = \begin{pmatrix} 0 & 0 \\ b & 0 \end{pmatrix}$$

$$F = \begin{pmatrix} 0 & a \\ 0 & 0 \end{pmatrix}.$$

$$N = (I - T)^{-1} = \begin{pmatrix} 1 & 0 \\ b & 1 \end{pmatrix}$$

$$R = FN = \begin{pmatrix} ab & a \\ 0 & 0 \end{pmatrix}$$

The dominant eigenvalue of R is $R_0 = ab$!

E   One-dimensional models

One-dimensional models are often much easier to work with than more dimensional models. This is also true for the models described in this paper. Enough literature on one-dimensional population models with a control or detection threshold is available, but there is only limited literature available in the study of more-dimensional dynamical systems with discontinuities [27]. Therefore we will only point out some properties for the one-dimensional model and we will try to use those methods for our two-dimensional model.

The one-dimensional model becomes:

$$v(t+1) = \begin{cases} a \cdot v(t) & \text{if } 0 \leq v(t) < k; \\ a_1 \cdot v(t) & \text{if } v(t) \geq k, \end{cases}$$

with $a, a_1 \in \mathbb{R}$, $a > 1$ and $a_1 \in (0,1)$. This model can give rise to chaotic dynamical behaviour [28]. Eventually all values of v will fall into the range $[a_1 k, ak)$ [25]. Furthermore, taking natural logarithms of the population gives the next equation:

$$ln(v(t+1)) - ln(v(t)) = \begin{cases} ln(a) & \text{if } v(t) < k; \\ ln(a_1) & \text{if } v(t) \geq k. \end{cases}$$

Here $ln(a) > 0 > ln(a_1)$. Furthermore the logarithm of the population densities, $ln(v)$ is uniformly distributed on $[ln(a_1 k), ln(ak))$ [26]. From this it can be found that the fraction of time in which detection occurs will be [25]:

$$\frac{ln(ak) - ln(k)}{ln(ak) - ln(a_1 k)} = \frac{ln(a)}{ln(a) - ln(a_1)}.$$

This implies that the detection frequency is independent of the threshold k.

The population size changes each time-step either a step $ln(a)$ upward on the log scale or a step $ln(a_1)$ downward. When $v(t)$ exceeds k it will decrease until it passes k and when $v(t)$ is below k it will increase again. Thus whatever the future behaviour of $v(t)$ in the region near k, its presence in that region is globally stable [26].

We will investigate two cases: $ln(a) > -ln(a_1)$ or $ln(a) < -ln(a_1)$. The case $ln(a) = -ln(a_1)$ is simple, because the steps upward are equal to the steps downward and therefore the model is periodic. In the first case when $ln(a_1 k) \leq ln(v(t)) < ln(k)$ the log population will increase only one step of size $ln(a)$ followed by a number of steps of size $ln(a_1)$ downward. This pseudo cyclic behaviour will be repeated indefinitely [26]. In the second case the behaviour is of the opposite sort; a number of time-steps of slow growth will be followed by only one time-step of decline.

These cycles are not of constant length. In the first case every step upward is followed by either n or $n+1$ steps downward, where $n = \lfloor -\frac{ln(a)}{ln(a_1)} \rfloor$ [23] [26]. ($\lfloor x \rfloor$ is defined as the greatest integer $\leq x$.) And in the second case the other way around; each step downward is followed by either m or $m+1$ steps upward, with $m = \lfloor -\frac{ln(a_1)}{ln(a)} \rfloor$.

If this model shows periodic behaviour, the population will be of the same size on two different time points, separated by i steps upward and j steps downward. Then

$$a^i a_1^j = (e^{ln(a)})^i (e^{ln(a_1)})^j = 1 \Rightarrow i \cdot ln(a) + j \cdot ln(a_1) = 0 \Rightarrow \frac{ln(a)}{-ln(a_1)} = \frac{j}{i}.$$

Thus if $-\frac{ln(a)}{ln(a_1)}$ is a rational number the model produces cycles of finite period, otherwise the dynamics are aperiodic [25] [26] [23]. Therefore, this model is almost always completely chaotic [26]. The average cycle length or mean time between two outbreaks can be simply computed. In the first case, $ln(a) > -ln(a_1)$, the mean time between two outbreaks is $-\frac{ln(a)}{ln(a_1)}$ [26]. Otherwise, in the second case the mean time between two outbreaks is $-\frac{ln(a_1)}{ln(a)}$. This is also independent of the detection threshold k.

The value $-\frac{ln(a)}{ln(a_1)}$ can also be used to find the itinerary of a point v_0. The itinerary of the point v_0 is defined to be the infinite sequence $\{s_i\}_{i=0}^{\infty}$ of the two symbols L and R according to [23]:

$$s_i = \begin{cases} L, & \text{if } v(t) < k; \\ R, & \text{if } v(t) \geq k. \end{cases}$$

When the mapping defined by this one-dimensional model is not periodic, it is ergodic [23], i.e. the model is independent of the initial conditions. Therefore, the itinerary of any starting point v_0 shares a truncated itinerary of any point in the interval $(a_1 k, ak)$. Thus the finite sequences of symbols in an itinerary are independent of the starting point. Successive blocks of the symbols L and R of increasing lengths are obtained by using the entries in the continued fraction expansion of $-\frac{ln(a)}{ln(a_1)}$ [23]:

$$-\frac{ln(a)}{ln(a_1)} = \alpha_0 + \cfrac{1}{\alpha_1 + \cfrac{1}{\alpha_2 + \cfrac{1}{\alpha_3 + \cdots}}}.$$

This is done by keeping at each step a current expansion which is derived from the expansion above. Thus the number of iterates between successive maxima differ by no more than 1. Furthermore the variations in the number of iterates between successive maxima are not random, but are determined by the continued fraction expansion.

Are the properties of the one-dimensional model discussed above also applicable for our models? In the two-dimensional homogeneous model of chapter 3 are the elements c and c_1 of matrix A and B respectively almost zero. Therefore we investigated what would happen if we put c and c_1 to be zero. This means that no MRSA carriers will leave the hospital undetected and the matrices become upper-triangle matrices:

$$A = \begin{pmatrix} a & b \\ 0 & d \end{pmatrix} \text{ and } B = \begin{pmatrix} a_1 & b \\ 0 & d \end{pmatrix}.$$

Furthermore, because $d < 1$ the prevalence of undetected MRSA carriers in the community will decay to zero. Therefore, this model becomes one-dimensional and can be investigated as such. In this appendix we found that, for the one-dimensional model, the mean time between two outbreaks is $-\frac{ln(a)}{ln(a_1)}$. This is also true for this model. Furthermore, because the eigenvalues of the matrix A are a and d and the eigenvalues of the matrix B are a_1 and d, the mean time between two outbreaks is also $-\frac{ln(\lambda_{d_A})}{ln(\lambda_{2_B})}$. This is not equal to $-\frac{ln(det(A))}{ln(det(B))}$, thus it is not necessary to investigate this value for two- and more-dimensional models. Unfortunately, in the 2-dimensional model with c and c_1 larger than zero, the values $-\frac{ln(\lambda_{d_A})}{ln(\lambda_{2_B})}$ and $-\frac{ln(a)}{ln(a_1)}$ are not the same values as we found in the simulations for the mean time between outbreaks. Furthermore, any combination of the elements and/or eigenvalues like multiplications, additions or subtractions do not give the simulation values either. Therefore it is not possible to predict what the mean time between two outbreaks will be, neither the number of outbreaks per 100 days or the detection frequency. Furthermore, if $c = c_1 = 0$ it is possible to find periodicity and if $c > 0$ this is not possible.

F Parameters

In this paper Dutch statistics from 2004 are used, available at the web pages from Prismant [29] and the CBS (Central Bureau for Statistics) [30]. Prismant delivered the hospital statistics as in number of admittances to the hospital and mean length of stay and the CBS delivered the number of citizens in the Netherlands.

F.1 Homogeneous model

For the homogeneous model the statistics for the whole community are used and some calculations are made:

$$\sigma_h = 1/LOS,$$

$$\sigma_c = \frac{\text{total admittances}}{\text{total citizens} \cdot 366}.$$

Table 5: Parameters for the homogeneous model

Parameter:	Value:	Source:
LOS	4.3	Prismant [29]
σ_h	0.2308	Prismant [29]
σ_c	0.00051	CBS [30] and Prismant [29]
λ	1/370	Cooper et al. [16]
β_h	0.265	calculated for $R_0 = 1.35$
α	0.88	Bootsma [20]

F.2 Heterogeneous model

For the heterogeneous model the statistics for the whole community, divided into the elderly, of 65 and older, and the non-elderly, are used and some calculations are made:

$$\sigma_{g,h} = 1/LOS_g,$$

$$\sigma_{g,c} = \frac{\text{total admittances of age group } g}{\text{total citizens in age group } g \cdot 366}.$$

Table 6: Parameters for the heterogeneous model

Parameter:	Elderly:	Non-elderly:	Source:
LOS	6.2	4.3	Prismant [29]
σ_h	0.162	0.288	Prismant [29]
σ_c	0.00116	0.0004	CBS [30] and Prismant [29]
q_h	0.45	0.55	Prismant [29]
q_c	0.14	0.86	CBS [30]
λ	1/370	1/370	Cooper et al. [16]
β_h	0.22	0.22	calculated for $R_0 = 1.35$
α	0.88	0.88	Bootsma [20]

F.3 5-year age groups

For the heterogeneous model with the population divided into 5-year age groups the statistics per 5-year age group are used.

Table 7: Parameters for the model with 5-year age groups

age in years	LOS in days	σ_h	% in hospital	σ_c $\cdot 10^{-4}$	% in community
0-4	3.6	0.275	7%	7.6	6%
5-9	1.9	0.526	1%	2.3	6%
10-14	2.7	0.370	1%	1.3	6%
15-19	3.2	0.313	2%	1.8	6%
20-24	3.2	0.313	2%	2.3	6%
25-29	3.2	0.313	3%	3.3	6%
30-34	3.2	0.313	4%	3.9	8%
35-39	3.1	0.323	4%	3.5	8%
40-44	3.3	0.303	4%	3.5	8%
45-49	3.5	0.286	5%	4.2	7%
50-54	3.6	0.278	6%	5.1	7%
55-59	3.9	0.256	7%	6.3	7%
60-64	4.4	0.227	8%	7.6	5%
65-69	4.9	0.204	9%	9.4	4%
70-74	5.5	0.182	10%	11.6	4%
75-79	6.3	0.159	11%	13.2	3%
80-84	7.3	0.137	9%	13.6	2%
85 and older	8.7	0.115	7%	11.5	1%
total	4.30	0.233	100%	5.1	100%

References

[1] M. Jevons. Celbenin resistant Staphylococci. *British Med. J.*, i:124–125, 1961.

[2] H.F.L. Wertheim, M.C. Vos, H.A.M.Boelens, A. Voss, C.M.J.E. Vandenbroucke-Grauls, M.H.M. Meester, J.A.J.W. Kluytmans, P.H.J. van Keulen, and H.A. Verburgh. Low prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) at hospital admission in the netherlands: the value of search and destroy and restrictive anitbiotic use. *J. Hospital. Infect.*, 56:321–325, 2004.

[3] H. Grundmann, M. Aires de Sousa, J. Boyce, and E. Tienersma. Emergence and resurgence of methicillin-resistant *Staphylococcus aureus* as a public-health threat. *Lancet*, online:1–12, 2006.

[4] H. Grundmann and B. Hellriegel. Mathematical modelling: a tool for hospital infection control. *Lancet Infect. Dis.*, 6(1):39–45, 2006.

[5] E.W. Tiemersma, S.L.A.M. Bronzwaer, O. Lyytikainen, J.E. Degener, P. Schrijnemakers, N. Bruinsma, J. Monen, W. Witte, and H. Grundmann. Methicillin-resistant *Staphylococcus aureus* in europe, 1999–2002. *Emerg. Infect. Dis.*, 10(9):1627–1634, 2004. Corporate name: European Antimicrobial Resistance Surveillance System Participants.

[6] W.I.P. Ziekenhuizen MRSA algemeen. *www.wip.nl*, 2006.

[7] W. Traa. Ziek van het ziekenhuis. *HP De tijd*, jan.:40–43, 2006.

[8] M.A. Bilkert. MRSA nationaal en internationaal. *Infectieziekten Bulletin*, 02:60–61, 2004.

[9] W.J.B. Wannet, A.J. de Neeling, M.E.O.C. Heck, G.N. Pluister, E. Spalburg, and E.W. Tienersma. MRSA in nederlandse ziekenhuizen: surveillanceresultaten 2003 en recente ontwikkelingen. *Infectieziekten Bulletin*, 15(05):167–170, 2004.

[10] W.J.B. Wannet, A.J. de Neeling, X.W. Huijsdens, M.E.O.C. Heck, G.N. Pluister, M.G. van Santen & E. Spalburg, D. Beaujean, and E.W. Tienersma. MRSA in nederlandse ziekenhuizen: surveillanceresultaten 2004 en recente ontwikkelingen. *Infectieziekten Bulletin*, 17(02):62–65, 2006.

[11] M.J.M. Bonten, D.J. Austin, and M. Lipsitch. Understanding the spread of antibiotic resistant pathogens in hospitals: mathematical models as tools for control. *Clin. Inf. Dis.*, 33:1739–46, 2001.

[12] B.S. Cooper, G.F. Medley, and G.M. Scott. Preliminary analysis of the transmission dynamics of nosocomial infections: stochastic and management effects. *J. Hospital. Infect.*, 43(2):131–147, 1999.

[13] D.J. Austin, M.J. Bonten, R.A. Weinstein, S. Slaughter, and R.M. Anderson. Vancomycin-resistant enterococci in intensive-care hospital settings: transmission dynamics, persistence, and the impact of infection control programs. *Proc. Natl. Acad. Sci. USA*, 96(12):6908–6913, 1999.

[14] H. Grundmann, S. Hori, B. Winter, A. Tami, and D.J. Austin. Risk factors for the transmission of methicillin-resistant *Staphylococcus aureus* in an adult intensive care unit: Fitting a model to the data. *J. Infect. Dis.*, 185(4):481–488, 2002.

[15] D.J. Austin and R.M. Anderson. Studies of antibiotic resistance within the patient, hospitals and the community using simple mathematical models. *Philos. T. R. Soc. Lond.* B, 345:721–738, 1999.

[16] B.S. Cooper, G.F. Medley, S.P. Stone, C.C. Kibbler, B.D. Cookson, J.A. Roberts, G. Duckworth, R. Lai, and S. Ebrahim. Methicillin-resistant *Staphylococcus aureus* in hospitals and the community: Stealth dynamics and control catastrophes. *Proc. Natl. Acad. Sci. USA*, 101(27):10223–10228, 2004.

[17] M.C.J. Bootsma, O. Diekmann, and M.J.M. Bonten. Controlling methicillin-resistant *Staphylococcus aureus*: Quantifying the effects of interventions and rapid diagnostic testing. *Proc. Natl. Acad. Sci. USA*, 103(14):5620–5625, 2006.

[18] J. Heijne and J. Wallinga. Verloop van aantal meticilline-resistente *Staphylococcus aureus* gevallen in ziekenhuis en bevolking bij verschillende interventie maatregelen. 2006.

[19] D.L. Smith, J. Dushoff, E.N. Perencevich, A.D. Harris, and S.A. Levin. Persistent colonization and the spread of antibiotic resistance in nosocomial pathogens: resistance is a regional problem. *Proc. Natl. Acad. Sci. USA*, 101(10):3709–3714, 2004.

[20] M.C.J. Bootsma. *Mathematical studies of the dynamics of antibiotic resistance.* http://igitur-archive.library.uu.nl/dissertations/2005-0526-201427/index.htm, 2005.

[21] O. Diekmann and J.A.P. Heesterbeek. *Mathematical Epidemiology of Infectious Diseases: Model Building, Analysis and Interpretation.* Mathematical and Computational Biology. John Wiley & Sons, Chicester, England, 2000.

[22] H. Caswell. *Matrix Population Models, construction, analysis, and interpretation.* Sinauer Associates, Inc., Sunderland, USA, 2001.

[23] J. Bélair and J.G. Milton. Itinerary of a discontinuous map from the continued fraction expansion. *Appl. Math. Lett.*, 1(4):339–342, 1988.

[24] J. Wallinga, J. Grasman, R.M.W. Groeneveld, M.J. Kropff, and L.A.P. Lotz. Prediction of weed density: the increase of error with prediction interval, and the use of long-term prediction for weed management. *J. Applied Ecology*, 36:307–316, 1999.

[25] J. Wallinga and M. van Oijen. Level of threshold weed ensity does not affect the long-term frequency of weed control. *Crop Protection*, 16(3):273–278, 1997.

[26] J. Felsenstein. r- and k-selection in a completely chaotic population model. *Am. Nat.*, 113(4):499–510, 1979.

[27] X. Fu and P. Ashwin. Symbolic analysis for some planar piecewise linear maps. *Discrete and Continuous Dynamical Systems*, 9:1533–1548, 2003.

[28] R.M. May and G.F. Oster. Bifurcations and dynamic complexity in simple ecological models. *Am. Nat.*, 110(974):573–599, 1976.

[29] prismant. *www.prismant.nl/informatieproducten/ziekenhuisstatistieken/*.

[30] CBS. *http://statline.cbs.nl/StatWeb/*.