Stochastic Modelling and Bayesian Inference for the Effect of Antimicrobial Treatments on Transmission and Carriage of Nosocomial Pathogens

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Abstract

Nosocomial pathogens are usually organisms such as fungi and bacteria that are associated with infections caused in a hospital environment. Examples include Clostridium difficile, Pseudomonas aeruginosa, Vancomycin-resistant enterococcus and Methicillin-resistant *Staphylococcus aureus* (MRSA). MRSA, like most of the nosocomial pathogens, is resistant to antibiotics and is one of the most serious causes of infections. In this thesis we assess the effects of antibiotics and antiseptics on carriage and transmission of MRSA. We use highly-detailed patient level data taken from two Intensive Care Unit (ICU) wards in St. Guys and Thomas's hospital in London, where patients were receiving daily antimicrobial treatment and a decolonisation protocol was used. We work in discrete time and employ three different patient-level stochastic models in a Bayesian framework to explore the effectiveness of antimicrobial treatment on MRSA in discrete time. We also develop suitable methods of model assessment.

The first two models assume that there is no transmission between patients in the ICU wards. Initially a Markov model is used, assuming perfect swab test specificity and sensitivity, to describe the colonisation status of an individual on a daily basis. Results are obtained using Gaussian random walk Metropolis-Hastings algorithms. We find some evidence that decolonisation treatment and Oxazolidinone have a positive effect in clearing MRSA carriage.

The second model is a hidden Markov model and assumes perfect swab test specificity but imperfect sensitivity. We obtain the results using data- augmented Markov Chain Monte Carlo (MCMC) algorithms to make inference for the unobserved patient colonisation states. We find evidence that the Antiseptic treatment used during the decolonisation period is effective in the clearance of MRSA carriage.

In the third case we assume that there is MRSA transmission between the pa-

tients in the ICUs. We use three different stochastic transmission models which overcome many of the unrealistic assumptions of other models. A data- augmented MCMC algorithm is employed in order to estimate the transmission rates of MRSA between the patients assuming imperfect swab test sensitivity. We found no or limited evidence that antibiotic use affects the transmission process, whereas antiseptic treatment was found to have an effect.

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CHAPTER 1

Introduction

The research presented in this thesis considers the effects of antimicrobial treatment on carriage and transmission of methicillin-resistant *Staphylococcus aureus* (MRSA) in an intensive care unit (ICU) environment. MRSA is a bacterium that is resistant to many classes of antimicrobials and is a common cause of nosocomial infections. Using stochastic modelling and Bayesian analysis, our aim in this thesis is to discover whether antimicrobial treatment can have an effect on MRSA colonisation.

1.1 Motivation

Nosocomial pathogens are pathogens typically found in a hospital setting and are responsible for nosocomial acquired infections. Nosocomial acquired infections usually occur in patients who have been hospitalised for a different reason than the infection. Such infections add to functional disability and emotional stress of the patient and may, in some cases, lead to disabling conditions that reduce the quality of life, [Ducel et al., 2002], or even death.

Most nosocomial acquired infections are caused by bacteria, but viruses and fungi can also be involved. Most of nosocomial pathogens are resistant to some classes of antibiotics. This raises the possibility of infections against which none of the current antimicrobial agents are effective, [Sébille et al., 1997]. Antibiotic resistance increases the morbidity and mortality associated with infections and contributes to rising costs of care resulting from prolonged hospital stays and

the need for more expensive antimicrobials, [Struelens, 1998]. One of the common antimicrobial resistant infections is caused by *Staphylococcus aureus* with most cases due to MRSA.

Mathematical models are important tools in analysing the spread and control of infectious diseases, [Grundmann and Hellriegel, 2006]. Over the recent years, many models have been introduced in the literature trying to explain the transmission dynamics of nosocomial pathogens in hospitals. Mathematical modelling offers a way to explore the relations between several factors that influence the acquisition and transmissibility of a nosocomial pathogen. Deciding which factors and how they should be quantified is where clinical medicine meets mathematics, [Weinstein et al., 2001].

The motivation behind this thesis is to explore the role of antimicrobial treatment on transmission and carriage of MRSA in two intensive care unit wards of a London hospital. Stochastic mathematical modelling is going to be used for this purpose with the help Bayesian inference and Markov chain Monte Carlo techniques.

1.2 *Staphylococcus aureus* - MRSA

Staphylococcus aureus is a bacterium that can be found in the nose or on the skin of about one third of humans, [Kluytmans et al., 1997]. It can usually be found in the nares but throat, perineum and axillae are also carriage sites. Studies have shown that in a healthy population, about 20% of individuals are persistent *Staphylococcus aureus* nasal carriers, approximately 30% are intermittent carriers, and about 50% non-carriers, [Wertheim et al., 2005]. Once *Staphylococcus aureus* enters the blood stream, it can be harmful and cause from mild infections such as skin and soft-tissue infections to more serious ones like sepsis that can sometimes be fatal, [Weber, 2005]. Factors that can lead to the development of antimicrobial resistant pathogens such as *Staphylococcus aureus* in hospitals, include transmission via health care workers and the use of antimicrobial treatment for infections, [Tenover and McGowan Jr, 1996].

MRSA belongs to a *Staphylococcus aureus* group of strains which is resistant to methicillin and other antibiotics. It is one of the most widespread nosocomial

pathogens and it can cause serious infections. Since it is resistant to many antimicrobials, it is difficult and expensive to be treated effectively. MRSA first appeared in the UK in 1961, [Enright et al., 2002], and since then it has been an endemic problem in hospitals, especially in ICU wards and nursing homes in many countries around the world. Without treatment, MRSA can stay in the body for large periods ranging from several months to more than three years, [Robicsek et al., 2009; Scanvic et al., 2001; Vriens et al., 2005].

To fight MRSA in ICU wards, several control measures and rational use of antibiotics need to be taken into account. There have been great efforts to design proper control strategies that can be used for the detection and eradication of MRSA, although it is still under debate which approaches could improve its control and reduce its clinical impact. These strategies include early detection of asymptomatic MRSA carriers which may lead to rapid isolation and minimise the possibility of transmission, improvement of the hand hygiene protocol for health-care workers, decolonisation strategies using antiseptic as well as thorough environmental cleaning and careful antimicrobial treatments, [Harbarth, 2006].

Several mathematical models have been used to predict the impact of different control measures in order to eradicate MRSA transmission. Most of them suggest that improving the health worker hand hygiene is the most effective control strategy, [Austin and Anderson, 1999; McBryde et al., 2007; Raboud et al., 2005] along with the reduction of colonised patients admitted in the ward, [Cooper et al., 1999]. There are also a number of models that relate antibiotic consumption with MRSA colonisation, [Tacconelli et al., 2008].

1.2.1 The role of antimicrobial treatment

As an attempt to limit the spread of MRSA, many hospitals use either topical or oral antimicrobial treatment in order to eradicate MRSA from individuals who are colonized. Antibiotics that are not effective against MRSA encourage acquisitions, [Dancer, 2008]. Thus, many studies have focused on the investigation of the relationship between antibiotic treatments and MRSA resistance. Most of them have underlined that antimicrobial use can increase the risk of MRSA colonisation or infection, [Loeb et al., 2003; Muller et al., 2006; Tacconelli

et al., 2008]. Others on the other hand, have found little change to the spread of MRSA when antibiotic control strategies were used, [Carling et al., 2003].

In [Lodise et al., 2003] a prediction model showed that 80% of the nosocomial and 60% of the community-acquired *Staphylococcus aureus* bacteremia will be methicillin resistant. This model indicated that there are no differences between the use of antimicrobial treatment and MRSA prediction. Other studies however, have shown that the use of control practices was related with a decrease of MRSA, while some antibiotics were found to help its spread. More specifically, the use of Fluoroquinolones, third-generation Cephalosporins, Macrolides and Amoxicillin were related to increased MRSA incidents, [Aldeyab et al., 2008; Dancer, 2001; Mahamat et al., 2007; Monnet et al., 2004; Muller et al., 2006; Weber et al., 2003]. Nevertheless, there is a lot of uncertainty about the kind and amount of antimicrobial treatment which can be a threat to MRSA transmission. This is due to heterogeneity between the studies that differ in the length of time each antimicrobial treatment was prescribed as well as the lack of data on the duration of antimicrobial use and dosages, [Tacconelli et al., 2008].

Antimicrobial treatment using Linezolid and Vancomycin is considered to be MRSA targeting. There are many surveys in the literature that try to find which one eradicates MRSA more efficiently. Many of them have shown that Linezolid is as effective as Vancomycin for the treatment of MRSA, [Dennis et al., 2002] and that Linezolid is related to shorter hospital stays, [Itani et al., 2010]. Others claim that Linezolid can be more effective than Vancomycin in surgical sited infections, [Stevens et al., 2002; Weigelt et al., 2004] but can be equivalent to Vancomycin in the treatment of complicated skin and soft tissue infections, [Weigelt et al., 2005].

1.2.2 Decolonisation strategies

Decolonisation is considered an important part of infection control strategies. Decolonisation policies can help control MRSA in ICU wards. Previous studies have shown that the introduction of a Chlorhexidine based decolonisation protocol in an ICU can dramatically reduce the transmission of susceptible MRSA strains, [Batra et al., 2010; Kypraios et al., 2010]. There are also studies outside the ICU ward i.e. in Macfarlane et al. [Macfarlane et al., 2007], which report

successful decolonisation using a protocol for MRSA. Other studies however, found that such policies were not that effective, [Kurup et al., 2010], or other practices such as hand hygiene were more efficient, [McBryde et al., 2007]. These differences might be due to variability in the use of protocols or other control strategies, [Edgeworth, 2011].

In the next section we present the data we are going to use, which form the basis for the development of the stochastic models described in the following chapters in this thesis.

1.3 Data

The dataset we are going to use in this thesis was provided by Guy's and St. Thomas' Hospital Trust (GSTT), London where a four-year study was carried out in two ICU wards, located on adjacent floors. The data are very detailed and include three main tables which contain:

1. Information about each patient's condition and the antimicrobial and antiseptic treatment they were receiving daily in the ICU ward.
2. Each patient's hospital and ICU admission and discharge dates (these dates can be different as a patient can be admitted in a general ward and then, after some days, enter the ICU ward).
3. Information about the dates MRSA tests were taken as well as their results for each patient in the ICU ward.

It is the daily treatment information that makes this data set especially unusual, and which also leads to much of our novelty in our modelling.

All patients were admitted to the two 15-bed general ICU wards between 1 January 2002 and 20 April 2006. MRSA screening swab samples (from anterior nares, axillae, groin) were taken from all patients on day of admission and every Monday morning. When there was a clinically suspected infection, swab samples from different parts of the body were also taken. A surface antiseptic protocol was introduced from 26 April 2004 where MRSA colonised patients had

1% (w/v) Chlorhexidine gluconate (Hibitane; Derma, Stotfold, Bedfordshire, UK) applied to the nostrils, around the mouth, and at tracheostomy sites four times daily; 1% Chlorhexidine acetate powder (CX Antiseptic Dusting Powder, Adams Health, UK) applied to groin, axillae, and skinfolds daily and were washed daily with 4% Chlorhexidine (Hibiscrub, SSL International, UK) applied by a wet cloth. Patients with negative MRSA tests had the same protocol apart from Hibitane use twice daily and 2% (w/v) triclosan (Aquasept, Medlock Medical) instead of Hibiscrub, [Batra et al., 2010].

MRSA was identified from pooled screening swabs using mannitol salt agar plates (Baird Parker) until July 2004 when a selective mannitol broth method was introduced, [Batra et al., 2008; Edgeworth et al., 2007]. Isolates were confirmed to be MRSA by tube coagulase and disc diffusion testing methods using methicillin discs, [Batra et al., 2010; Kypraios et al., 2011].

In this thesis we are going to use three groups of data which are subsets of the dataset provided by Guy's and St. Thomas' Hospital Trust. These are the following:

- MRSA Data Set which includes the MRSA swab tests taken from anterior nares, axillae, groin as mentioned above.
- Wounds Data Set which includes the MRSA swab tests taken from any wound on patient's body.
- Respiratory Data Set which includes the MRSA swab tests taken from respiratory site on the body (sputum, nasopharyngeal aspirates, bronchial washings or via bronchoalveolar lavage).

It is important to note that these three datasets are not comparable. Their main difference is that the tests they include come from different part of the body for each dataset. They also differ in the number of patients as well as they do not include the same patients.

1.3.1 Assumptions

- We assume that each test can have only two outcomes; a positive "$+$" and a negative "$-$".

- We assume that all patients have at least one test during their stay in the ICU.
- We account for only one screening per test day per patient. However, some patients had more than one screening tests on the same day. In this case, since positive tests were considered more reliable that the negatives, we kept the positive one if there was any, otherwise one of the negative tests.
- We assume that there are no patients in isolation in the ICU wards.
- We ignore any information given about patient bed or ward changes.
- We consider each patient who is readmitted to the ICU ward as a new patient. We make this assumption also for patients who might changed ward.

1.3.2 Summary Statistics

Tables 1.1, 1.2 and 1.3 show some basic statistics for the three datasets; MRSA, Wounds and Respiratory respectively, in total and in each ward separately.

MRSA Data Set			
Statistic	**Ward 1**	**Ward 2**	**Both Wards**
no. of patients	1855	1998	3853
average stay/patient (days)	11.24	10.91	11.07
median stay/patient (days)	6	6	6
average no. of tests/patient	2.12	2.12	2.12
no. of tests	3946	4244	8190
no. of positive tests	463	447	910
proportion of positive tests	0.1104	0.1053	0.1111
days of study	1581	1580	1581
total no. of days in ICU	20856	21813	42669
total no. of days antimicrobials prescribed	27712	28022	55734

Table 1.1: Summary statistics for the MRSA Data Set for Ward 1 (second column), Ward 2 (third column) and both (fourth column).

Wounds Data Set			
Statistic	**Ward 1**	**Ward 2**	**Both Wards**
no. of patients	1298	1389	2687
average stay/patient (days)	14.5631	14.1547	14.3520
median stay/patient (days)	10	9	10
average no. of tests/patient	3.6494	3.3707	3.5053
no. of tests	4737	4682	9419
no. of positive tests	325	411	736
proportion of positive tests	0.0686	0.0877	0.0781
days of study	1581	1579	1581
total no. of days in ICU	18903	19661	38564
total no. of days antimicrobials prescribed	25854	25645	51499

Table 1.2: Summary statistics for the Wounds Data Set for Ward 1 (second column), Ward 2 (third column) and both (fourth column).

Respiratory Data Set			
Statistic	**Ward 1**	**Ward 2**	**Both Wards**
no. of patients	863	876	1739
average stay/patient (days)	16.1726	16.3835	16.2789
median stay/patient (days)	10	11	10
average no. of tests/patient	1.8609	1.8047	1.8326
no. of tests	1606	1581	3187
no. of positive tests	255	225	480
proportion of positive tests	0.1587	0.1423	0.1506
days of study	1569	1578	1581
total no. of days in ICU	13957	14352	28309
total no. of days antimicrobials prescribed	18624	18088	36712

Table 1.3: Summary statistics for the Respiratory Data Set for Ward 1 (second column), Ward 2 (third column) and both (fourth column).

Figures 1.1, 1.2 and 1.3 display the number of tests taken in each ward during the study period as well as the number of positive tests found for the MRSA, Wounds and Respiratory Data Set respectively. It can be seen that the number of positive tests becomes smaller at the second half of the study period. This is due to the decolonisation protocol that began at around the second half of the study period.

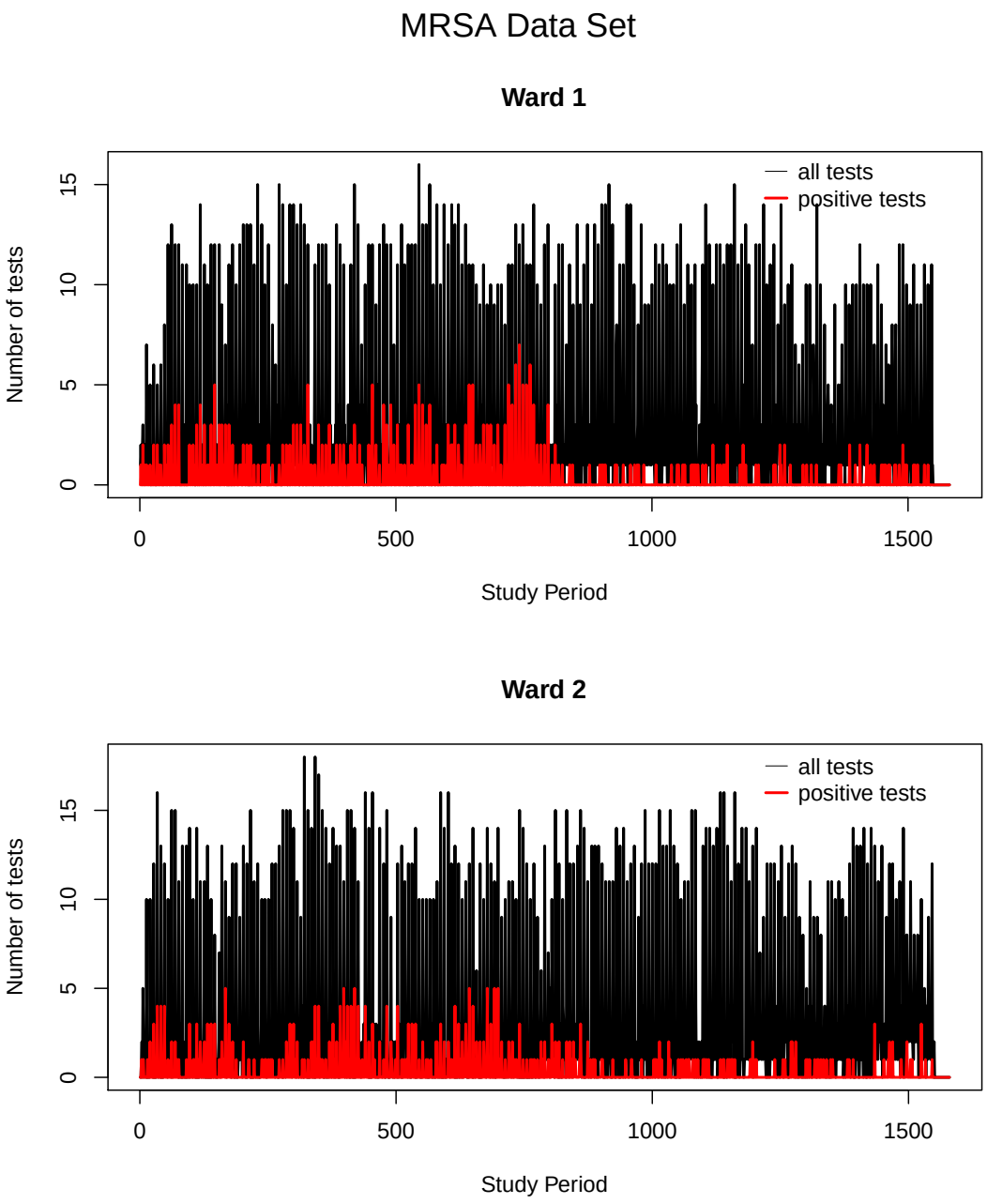


Figure 1.1: Graph displaying the number of tests taken during the study period (black line) and the number of positive tests for the same period (red line) for each ward for the MRSA Data Set.

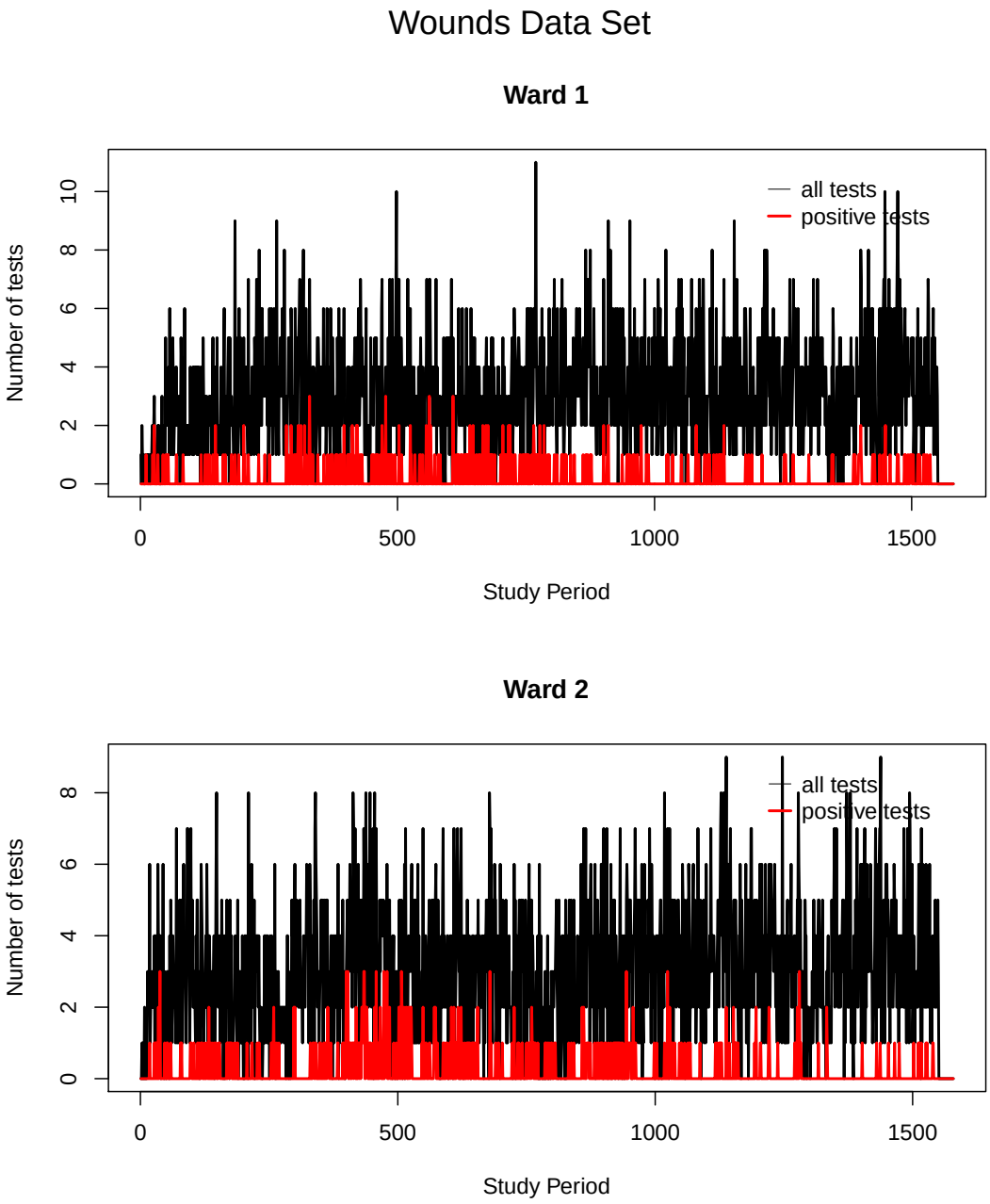


Figure 1.2: Graph displaying the number of tests (black line) taken during the study period (black line) and the number of positive tests (red line) for the same period (red line) for each ward for the Wounds Data Set.

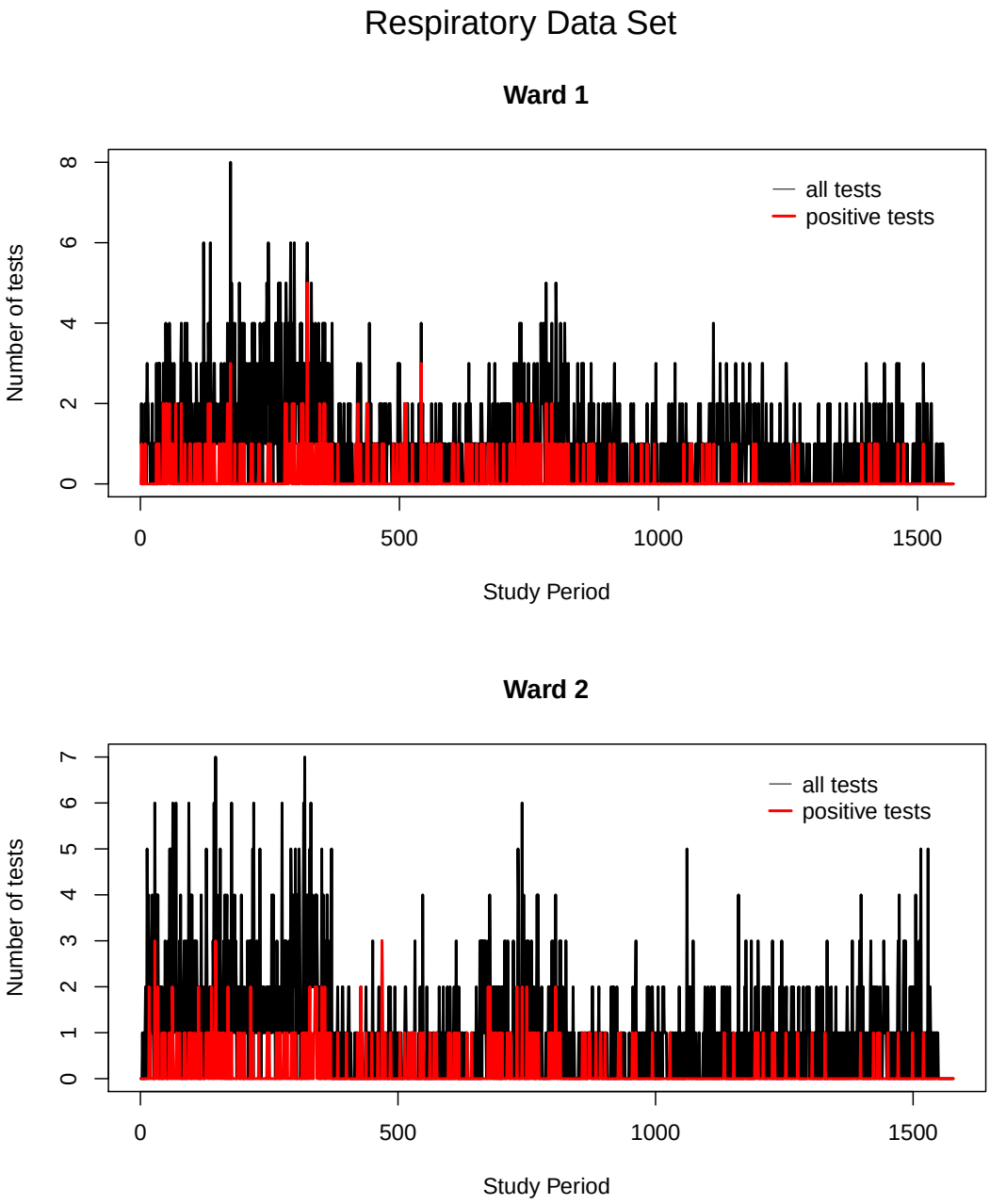


Figure 1.3: Graph displaying the number of tests (black line) taken during the study period (black line) and the number of positive tests (red line) for the same period (red line) for each ward for the Respiratory Data Set.

1.3.3 Antimicrobial Treatment

During the study, 77 different antimicrobials were prescribed to patients in the two ICU wards depending on their clinical condition. However, only 18 of these, classified in 11 antimicrobial groups, may have an effect against MRSA and thus will be considered in this thesis. Table 1.4 contains these 18 antimicrobials as well as the antimicrobial group they belong to. Antimicrobials belonging to the same antimicrobial group have similar effects.

Antimicrobial Group	**Antimicrobial**
Aminoglycoside	Amikacin Gentamicin
Antiseptic	Chlorhexidine
Cephalosporin	Ceftazidime Cefuroxime
Glycopeptide	Teicoplanin Vancomycin
Macrolide	Clarithromycin Erythromycin
Nitroimidazole	Metronidazole
Oxazolidinone	Linezolid
Penicillin	Amoxicillin Co-amoxiclav Flucloxacillin Pip Taz Tazocin
Polymyxin	Colistin
Quinolone	Ciprofloxacin
Rifamycin	Rifampicin

Table 1.4: Table showing all the antimicrobial treatment that was MRSA targeting and was used during the study (first column), classified in antimicrobial groups (second column) .

Tables 1.5, 1.6 and 1.7 contain details about the number of days each of the antimicrobial treatment was used in each ward and in both wards for the MRSA Data Set, Wounds Data Set and the Respiratory Data Set respectively.

GROUP	Ward 1	Ward 2	Both Wards
Aminoglycoside	2588	2600	5188
Antiseptic	8690	9049	17739
Cephalosporin	3690	3686	7376
Glycopeptide	4733	4599	9332
Macrolide	2782	2556	5338
Nitroimidazole	2491	2694	5185
Oxazolidinone	204	139	343
Penicillin	1297	1125	2422
Polymyxin	191	228	419
Quinolone	828	938	1766
Rifamycin	528	98	626

Table 1.5: Number of days each antimicrobial treatment was received in ward 1, ward 2 and both wards, for the MRSA Data Set.

GROUP	Ward 1	Ward 2	Both Wards
Aminoglycoside	2472	2477	4949
Antiseptic	8186	8515	16701
Cephalosporin	3167	3164	6331
Glycopeptide	4557	4420	8977
Macrolide	2548	2340	4888
Nitroimidazole	2143	2386	4529
Oxazolidinone	190	139	329
Penicillin	1137	1003	2140
Polymyxin	191	221	412
Quinolone	764	884	1648
Rifamycin	499	96	595

Table 1.6: Number of days each antimicrobial treatment was received in ward 1, ward 2 and both wards, for the Wounds Data Set.

GROUP	Ward 1	Ward 2	Both Wards
Aminoglycoside	1842	1862	3704
Antiseptic	5420	5624	8044
Cephalosporin	2279	2130	4409
Glycopeptide	3389	3241	5530
Macrolide	2036	1891	3927
Nitroimidazole	1404	1558	2962
Oxazolidinone	146	106	252
Penicillin	824	661	1485
Polymyxin	174	210	384
Quinolone	677	742	1419
Rifamycin	433	63	496

Table 1.7: Number of days each antimicrobial treatment was received in ward 1, ward 2 and both wards, for the Respiratory Data Set.

Figures 1.4, 1.5, 1.6, 1.7, 1.8 and 1.9 show the number of patients who were receiving each antimicrobial treatment each day during the study period for wards 1 and 2 for the three datasets. It can be seen in all three datasets that the use of the Antiseptic increases dramatically after the second half of the study period. This is because of the antiseptic protocol which was commenced that period.

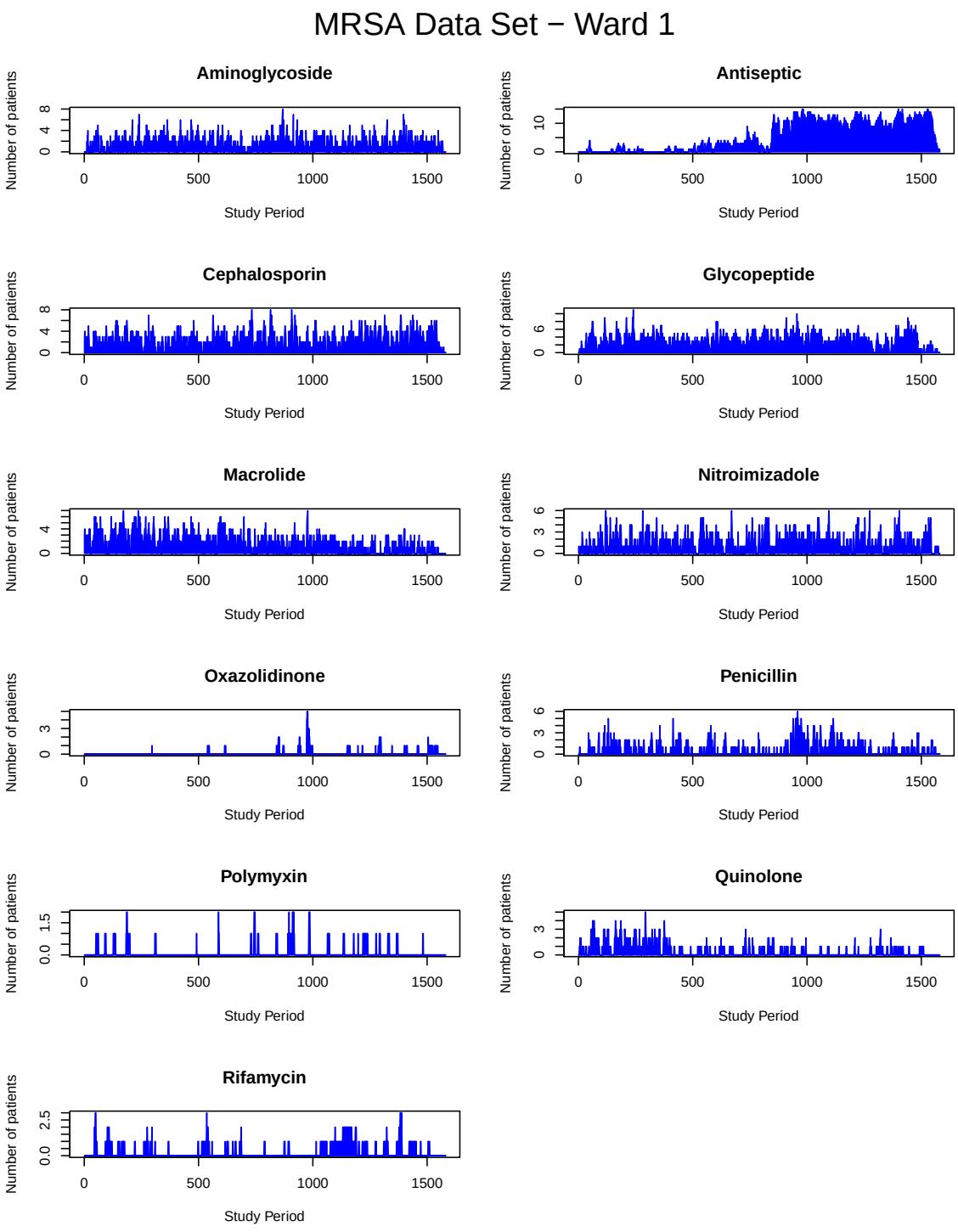


Figure 1.4: Antimicrobial treatment use over the study period. The plots present the number of patients receiving each antimicrobial treatment each day over the study period for the MRSA Data Set, ward 1.

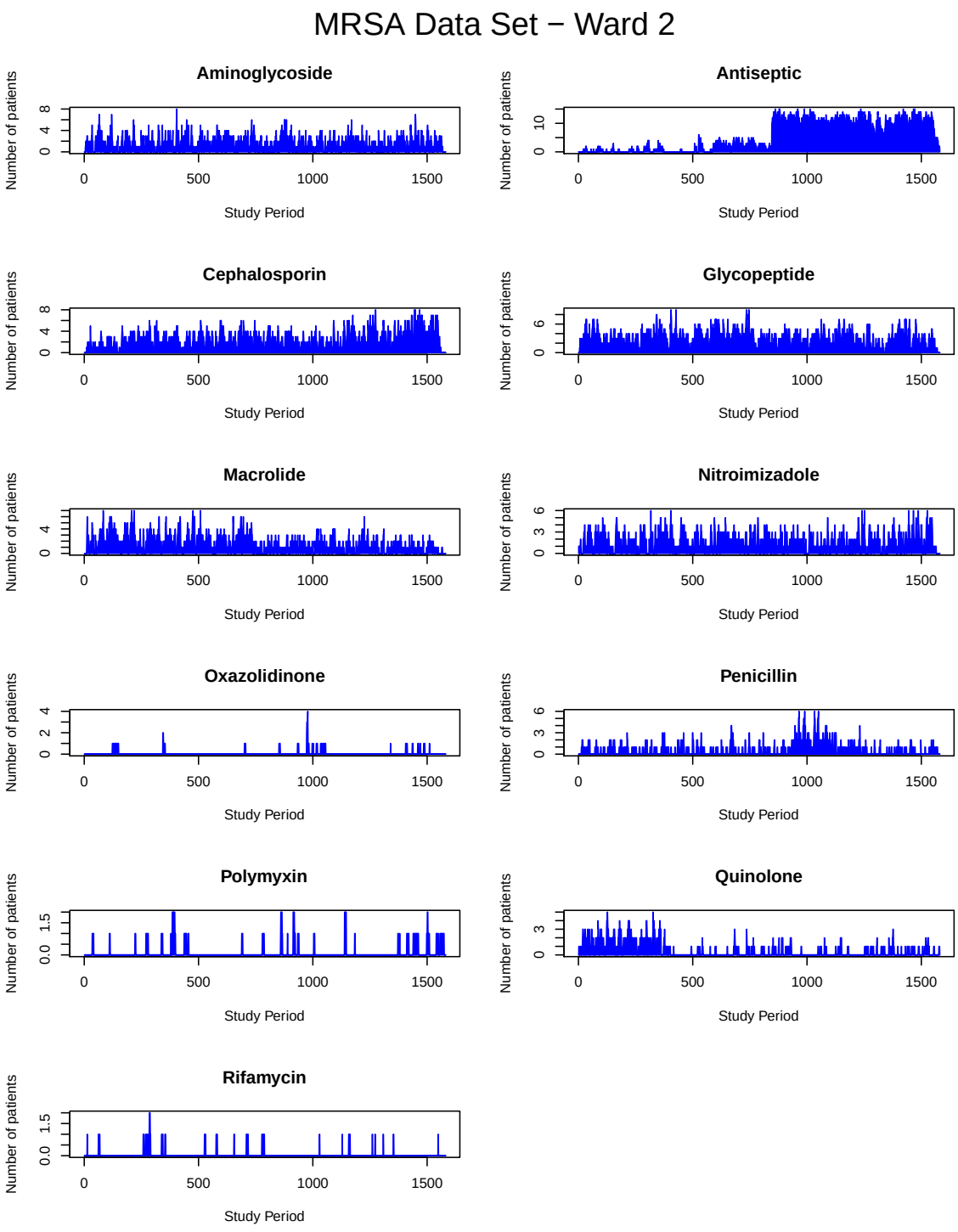


Figure 1.5: Antimicrobial treatment use over the study period. The plots present the number of patients receiving each antimicrobial treatment each day over the study period for the MRSA Data Set, ward 2.

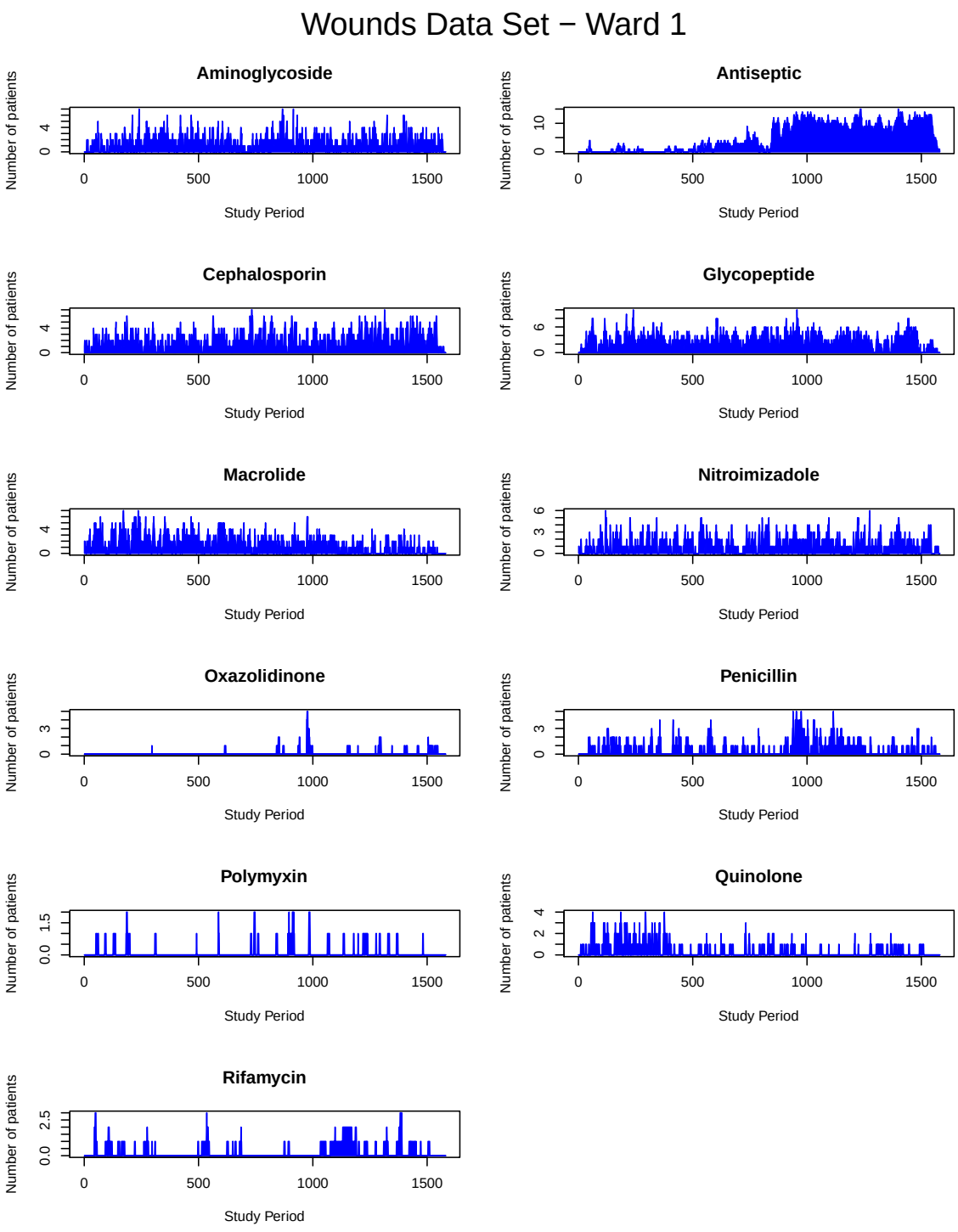


Figure 1.6: Antimicrobial treatment use over the study period. The plots present the number of patients receiving each antimicrobial treatment each day over the study period for the Wounds Data Set, ward 1.

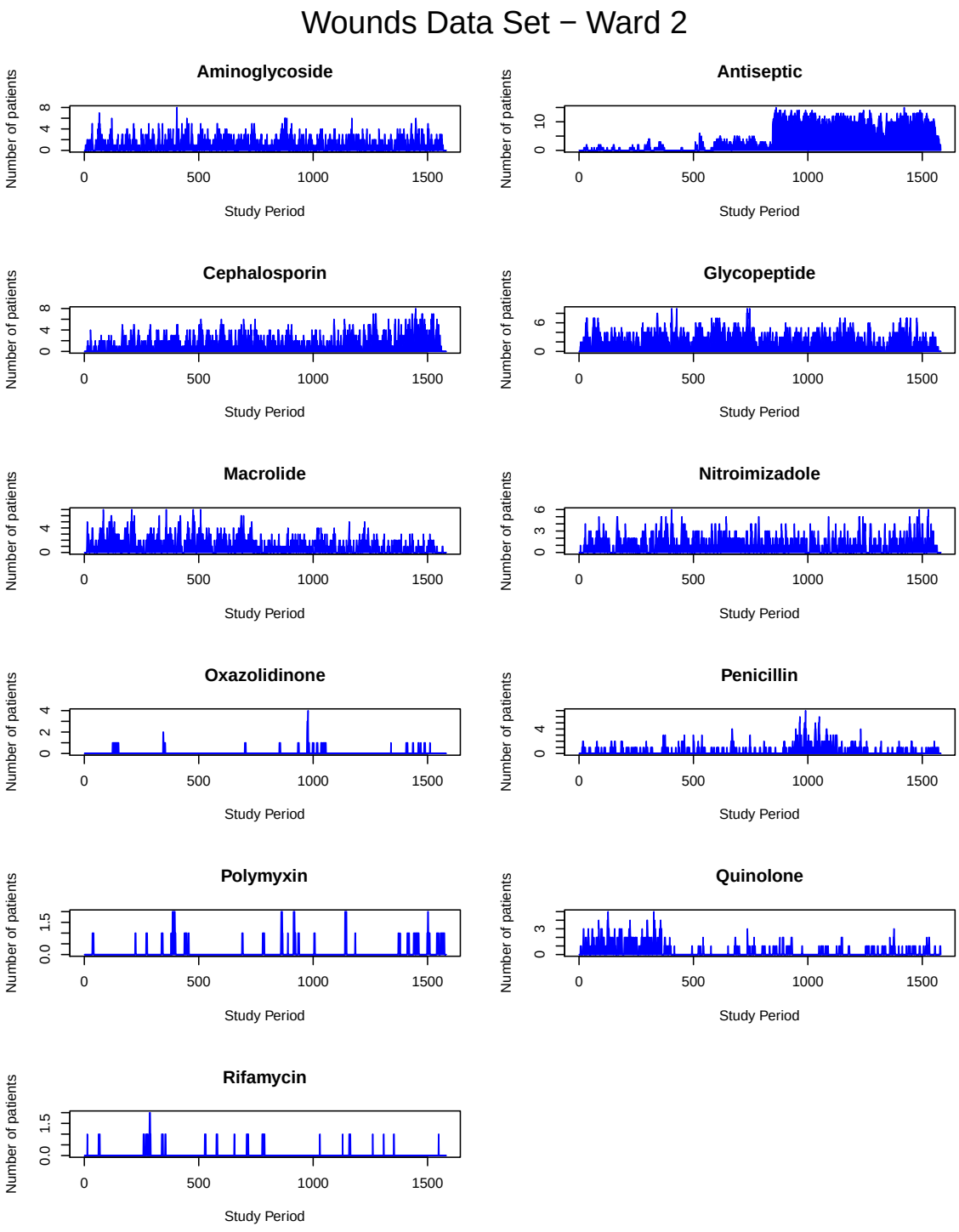


Figure 1.7: Antimicrobial treatment use over the study period. The plots present the number of patients receiving each antimicrobial treatment each day over the study period for the Wounds Data Set, ward 2.

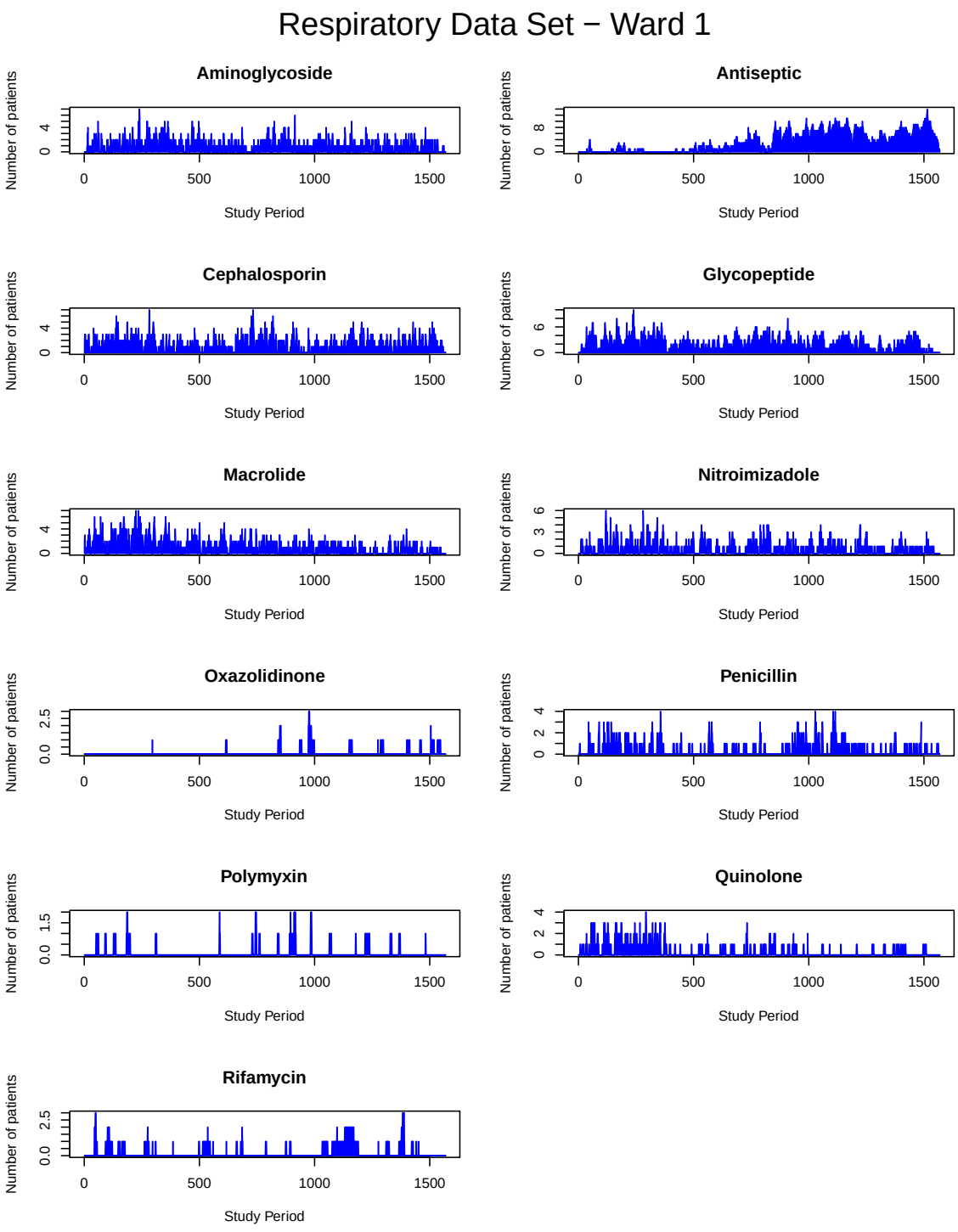


Figure 1.8: Antimicrobial treatment use over the study period. The plots present the number of patients receiving each antimicrobial treatment each day over the study period for the Respiratory Data Set, ward 1.

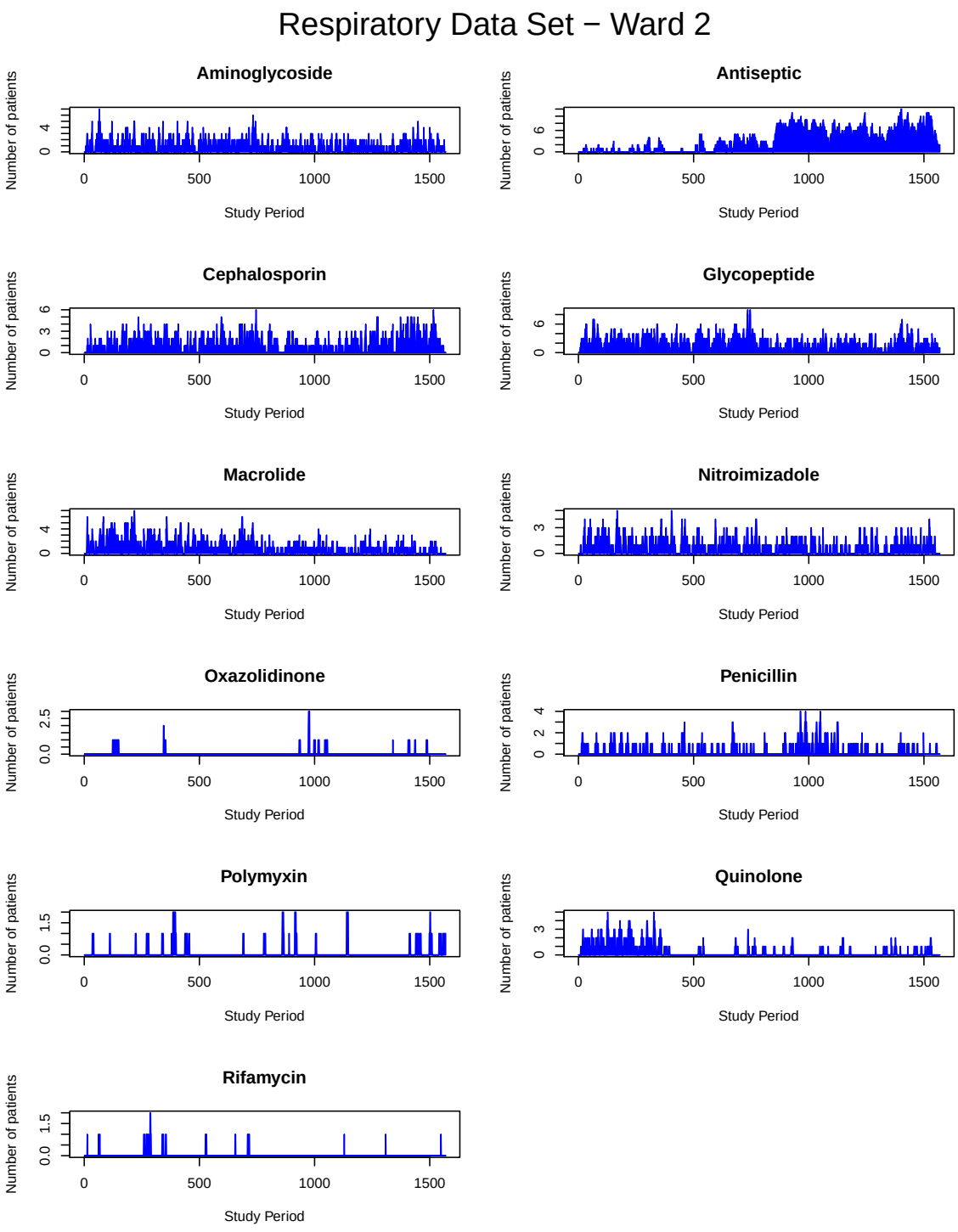


Figure 1.9: Antimicrobial treatment use over the study period. The plots present the number of patients receiving each antimicrobial treatment each day over the study period for the Respiratory Data Set, ward 2.

1.4 Statistical Inference

Mathematical models have been widely used to describe the spread of antimicrobial -resistant bacteria. They can be divided into two categories; deterministic models and stochastic models. Deterministic models are simple to analyse and thus were used to describe the transmission of nosocomial pathogens between patients in single wards, [Austin et al., 1999; Haber et al., 2010; Lipsitch et al., 2000; Sébille et al., 1997]. However, stochastic models are more preferable especially when small populations such as intensive care units are concerned, [Grundmann and Hellriegel, 2006; Pelupessy et al., 2002]. They are more realistic and it is a natural way to describe disease transmission, [Andersson and Britton, 2000; O'Neill, 2010]. In this thesis only stochastic models are going to be considered.

Data that come from infectious diseases are usually partially observed and can make their analysis more complicated, [O'Neill, 2010]. Patients infected by nosocomial pathogens are often asymptomatic so their colonisation status can only be partially observed by swab tests. Such data are usually analysed using Bayesian inference with the help of Markov Chain Monte Carlo (MCMC) algorithms, [Gibson and Renshaw, 1998; O'Neill, 2002; O'Neill and Roberts, 1999; Streftaris and Gibson, 2004].

In the following section we are going to present some general information about Bayesian inference and MCMC algorithms that is required in the next three chapters; 2, 3 and 4. A more extensive literature review as well as more information about the methodology used is given in each chapter separately.

1.5 Bayesian Inference - MCMC

Over the last two decades the use of Bayesian methods in applied statistics problems has greatly increased. Bayesian inference is the process of fitting a probability model to data and summarising the result using a probability distribution on the model parameters and unobserved quantities, [Gelman et al., 2004].

1.5.1 Bayes' Theorem

Here we are going to review the fundamentals of the Bayesian theory. A more detailed approach can be found in [Bernardo et al., 1994].

The Bayesian approach begins specifying a model for the observed data $\mathbf{Y}$ given the model's unknown parameters denoted by $\boldsymbol{\theta}$. The model then can be given in the form of a *likelihood* function $\pi(\mathbf{Y}|\boldsymbol{\theta})$. Since the parameter vector $\boldsymbol{\theta}$ is unknown, all the initial information (i.e. before seeing the data) about $\boldsymbol{\theta}$ can be summarised in the form of a probability distribution, $\pi(\boldsymbol{\theta})$, called the *prior* distribution. Inference concerning $\boldsymbol{\theta}$ requires the combination of the *likelihood* and the *prior* to determine the *posterior* distribution, $\pi(\boldsymbol{\theta}|\mathbf{Y})$, using *Bayes' theorem* as follows:

$$\pi(\boldsymbol{\theta}|\mathbf{Y}) = \frac{\pi(\mathbf{Y}|\boldsymbol{\theta})\,\pi(\boldsymbol{\theta})}{\pi(\mathbf{Y})} \propto \pi(\mathbf{Y}|\boldsymbol{\theta})\,\pi(\boldsymbol{\theta}), \tag{1.5.1}$$

where $\pi(\mathbf{Y}) = \sum_{\boldsymbol{\theta}} \pi(\mathbf{Y}|\boldsymbol{\theta})\,\pi(\boldsymbol{\theta})$ for the discrete case, where the sum is all over possible values of $\boldsymbol{\theta}$ or $\pi(\mathbf{Y}) = \int \pi(\mathbf{Y}|\boldsymbol{\theta})\,\pi(\boldsymbol{\theta})\,d\boldsymbol{\theta}$ in the case of continuous $\boldsymbol{\theta}$. The latter integral is a normalising constant so that $\pi(\boldsymbol{\theta}|\mathbf{Y})$ defines a valid probability distribution. Its computation has been the source of most of the practical difficulties in Bayesian inference, mainly because in high dimensions the resulting distribution cannot always be written in closed form. This difficulty can be overcome with the use of MCMC methods.

Prior Distributions

In this section we present the most popular approaches for choosing a prior distribution.

Informative Priors
Informative priors are usually used when some information is known about the parameter $\boldsymbol{\theta}$ before the data are obtained.

Conjugate priors
Conjugate priors are distributions that lead the posterior to have the same distributional family as the prior. Their choice can be more computationally convenient than others.

Non-informative priors

Non-informative priors contain very little or no information about parameter $\boldsymbol{\theta}$ so allow the information from the likelihood to be interpreted probabilistically.

1.5.2 Markov Chain Monte Carlo

MCMC is the most popular method for Bayesian computation as it can handle complex problems and it is easy to program,[Berger, 2000]. MCMC is based on drawing values of parameter vector $\boldsymbol{\theta}$ from approximate distributions and then correcting those draws to better approximate the target posterior distribution $\pi(\boldsymbol{\theta}|\mathbf{Y})$. The samples are drawn sequentially from a Markov chain whose stationary distribution is the desired joint posterior distribution of interest.

In this section we are going to present the main idea of MCMC and its basic well known algorithms. More information about the theory and applications can be found in [Gilks and Spiegelhalter, 1996], [Tanner, 1996], [Robert and Casella, 2004] and [Brooks et al., 2011].

The idea of MCMC comes from Metropolis et al., [Metropolis et al., 1953] and was then generalised by Hastings, [Hastings, 1970]. Simulations following this scheme are said to use the Metropolis-Hastings algorithm, [Chib and Greenberg, 1995].

The Metropolis-Hastings algorithm

In a Bayesian setting, the main aim of the Metropolis-Hastings (MH) algorithm is to generate samples from a posterior density $\pi(\boldsymbol{\theta}|\mathbf{Y})$ known up to a normalising constant. For the MH algorithm, at each time t, the next state $\boldsymbol{\theta}_{t+1}$ is chosen by first sampling a candidate point $\boldsymbol{\theta}^*$ from a proposal density $q(\cdot|\boldsymbol{\theta}_t)$. The proposal distribution might depend on the current point $\boldsymbol{\theta}_t$. The candidate point $\boldsymbol{\theta}^*$ is then accepted with probability $a(\boldsymbol{\theta}_t, \boldsymbol{\theta}^*)$ where

$$a(\boldsymbol{\theta}_t, \boldsymbol{\theta}^*) = \min\left(1, \frac{\pi(\boldsymbol{\theta}^*|\mathbf{Y})\, q(\boldsymbol{\theta}_t|\boldsymbol{\theta}^*)}{\pi(\boldsymbol{\theta}_t|\mathbf{Y})\, q(\boldsymbol{\theta}^*|\boldsymbol{\theta}_t)}\right). \tag{1.5.2}$$

If the candidate point is accepted, the next state becomes $\boldsymbol{\theta}_{t+1} = \boldsymbol{\theta}^*$, otherwise the chain does not move i.e. $\boldsymbol{\theta}_{t+1} = \boldsymbol{\theta}_t$.

Pseudocode for this algorithm is as follows:

Metropolis-Hastings Algorithm

1. Give initial values to $\boldsymbol{\theta}_0$.
2. $t = 0$
3. Repeat the following steps:

   Sample $\boldsymbol{\theta}^* \sim q(\cdot|\boldsymbol{\theta}_t)$

   Draw a uniform $(0, 1)$ random variable U

   If $U \leq a(\boldsymbol{\theta}_t, \boldsymbol{\theta}^*)$
   set $\boldsymbol{\theta}_{t+1} = \boldsymbol{\theta}^*$

   Else
   set $\boldsymbol{\theta}_{t+1} = \boldsymbol{\theta}_t$

   $t = t + 1$

The parameters of the vector $\boldsymbol{\theta}$ in the MH algorithm can be updated in many ways. Firstly, they can be updated all together, as a block, so they can be either all accepted or rejected. Secondly, they can be updated separately so that in each iteration t there will be an update of each of the parameters in $\boldsymbol{\theta}$. Lastly, there can be a combination of updates where some of the parameters in $\boldsymbol{\theta}$ are updated separately and others as a block.

Gibbs Sampler

The Gibbs sampler was introduced by Geman and Geman, [Geman and Geman, 1984] and is a special case of the Metropolis-Hastings algorithm where the probability of accepting the candidate is always unity, [Casella and George, 1992; Gelfand and Smith, 1990].

Suppose we have the parameter vector $\boldsymbol{\theta}$ which consists of n parameters, $\boldsymbol{\theta} = (\theta_1, \theta_2, ..., \theta_n)$. In each iteration of the Gibbs sampler, each subvector θ_i, $i = 1, ..., n$ of $\boldsymbol{\theta}$ is drawn conditional on the value of all the others. More specifically,

let $\boldsymbol{\theta}_{-i}$ be the vector $\boldsymbol{\theta}$ with subvector θ_i removed. The functions $\pi_i\left(\theta_i|\boldsymbol{\theta}_{-i}, \mathbf{Y}\right)$ are called the full conditional distributions of $\pi\left(\boldsymbol{\theta}|\mathbf{Y}\right)$. So in the Gibbs sampler, in each iteration t, we sample from the joint posterior distribution $\pi\left(\theta_1, \theta_2, ..., \theta_n\right)$ using the full conditional distributions. So each of the parameters θ_i is conditional on the latest values of the components of $\boldsymbol{\theta}$.

Pseudocode for this algorithm is as follows:

Gibbs Sampler Algorithm

For each iteration $t = 1, ...T$, repeat:
Draw θ_1^{t+1} from $\pi\left(\theta_1|\theta_2^t, \theta_3^t, \ldots, \theta_n^t\right)$
Draw θ_2^{t+1} from $\pi\left(\theta_2|\theta_1^{t+1}, \theta_3^t, \ldots, \theta_n^t\right)$
.
.
.
Draw θ_n^{t+1} from $\pi\left(\theta_n|\theta_1^{t+1}, \theta_2^{t+1}, \ldots, \theta_{n-1}^{t+1}\right)$
$t = t + 1$

Proposal Distributions

In the Metropolis-Hastings algorithm, a proposal distribution is required to simulate the next parameter values. The proposal distribution may depend on the latest previous value of the parameter, but it is independent of all earlier values of the parameters so that the Markov property holds. A common choice for a proposal distribution is to use Gaussian proposals. This proposal distribution is normal centered at the current parameter value and the only thing that needs to be specified is the variance σ for each parameter. This approach is called random walk Metropolis. If σ is too low, the Metropolis steps are too short so the chain moves too slowly to the target distribution. On the other hand, if σ is too high, the algorithm almost always rejects the new candidate value and does not move, [Gelman et al., 1996]. A quite general rule is to choose σ in a way such that the acceptance rate for each candidate parameter is around 0.25, [Roberts et al., 1997], although others suggest that acceptance rated around 0.5 is also optimal, [Carlin and Louis, 2009]. However, these results usually vary with the

dimension and true posterior correlation structure of parameter vector $\boldsymbol{\theta}$. More information on this can be found in the references mentioned in this section.

The Gaussian proposal distribution is symmetric and this can simplify the computation of the parameter updates in the Metropols-Hastings algorithm. Assume we have the probability in (1.5.2),

$$a\left(\boldsymbol{\theta}_t, \boldsymbol{\theta}^*\right) = \min\left(1, \frac{\pi\left(\boldsymbol{\theta}^*|\mathbf{Y}\right) q\left(\boldsymbol{\theta}_t|\boldsymbol{\theta}^*\right)}{\pi\left(\boldsymbol{\theta}_t|\mathbf{Y}\right) q\left(\boldsymbol{\theta}^*|\boldsymbol{\theta}_t\right)}\right).$$

To calculate the ratio of proposal distribution using Gaussian random walk we will have,

$$\frac{q\left(\boldsymbol{\theta}_t|\boldsymbol{\theta}^*\right)}{q\left(\boldsymbol{\theta}^*|\boldsymbol{\theta}_t\right)} = \frac{N\left(\boldsymbol{\theta}^*, \sigma^2\right)}{N\left(\boldsymbol{\theta}_t, \sigma^2\right)} = \frac{\frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{1}{2\sigma^2}\left(\boldsymbol{\theta}_t - \boldsymbol{\theta}^*\right)^2}}{\frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{1}{2\sigma^2}\left(\boldsymbol{\theta}^* - \boldsymbol{\theta}_t\right)^2}} = 1. \tag{1.5.3}$$

thus, the Metropolis-Hastings update probability becomes,

$$a\left(\boldsymbol{\theta}_t, \boldsymbol{\theta}^*\right) = \min\left(1, \frac{\pi\left(\boldsymbol{\theta}^*|\mathbf{Y}\right)}{\pi\left(\boldsymbol{\theta}_t|\mathbf{Y}\right)}\right).$$

Burn-in

With the term *burn-in* we refer to the practice of discarding the early iterations of MCMC to diminish the effect of the starting distribution [Gelman et al., 2004]. The length of the burn-in usually depends on the starting values and how fast the MCMC chain converges to the target distribution. Burn-in can be determined from MCMC trace plots, [Gilks and Spiegelhalter, 1996]. However, Gelman et al., [Gelman et al., 2004], suggest discarding the first half of the MCMC iterations as a burn-in.

Thinning

When computer storage is a problem, we can keep only every kth simulation draw from each sequence and discard the rest of them. This practice is called *thinning*. k can be set to some value high enough that successive draws of parameter $\boldsymbol{\theta}$ are approximately independent, [Gilks and Spiegelhalter, 1996]. Furthermore, the amount of thinning should be chosen in a way so that the full sample will have more information than the amount that is discarded.

1.6 Thesis Outline

In this chapter we presented some information about *Staphylococcus aureus* and MRSA and some background information about the previous work that has been done considering the control strategies and the use of antimicrobial treatment for this pathogen. We also gave a description of the data analysed in this thesis and gave the fundamentals of Bayesian inference and MCMC that are going to be used in the following chapters.

The remaining chapters of this thesis are organised as follows:

In Chapter 2 we use a discrete time Markov Model to look at the effects of antimicrobial treatment on carriage levels of MRSA, ignoring patient-to-patient transmission. Swab test sensitivity and specificity are assumed to be perfect. Maximum likelihood and MCMC techniques are used to obtain the parameter estimates followed by an investigation of model assessment. Lastly, we present some simulation results as well as the results obtained form the three datasets used.

In Chapter 3 a discrete time hidden Markov model is used to investigate the effect of antimicrobials on MRSA carriage, again without taking into account patient-to-patient transmission. We still assume perfect swab test specificity but imperfect sensitivity. Thus, to obtain our parameter estimates we use a data augmentation MCMC algorithm. We then discuss model assessment and display the results from the simulations and from the three datasets used.

In Chapter 4 we use three discrete time stochastic transmission models to explore the effect of antimicrobial treatment on MRSA transmission. We assume imperfect swab test sensitivity and perfect specificity. Results are obtained using a data-augmented MCMC algorithm to infer the unobserved patient colonisation times. Then we describe the model assessment and lastly we present the results from simulations and the GSTT datasets for the three models.

In Chapter 5 we conclude discussing the main results drawn for this research and any model limitations. We also present possible future work.

All results and graphics for this thesis have been obtained using the C programming language and the R statistical software.

CHAPTER 2

Modelling the effect of antimicrobial treatment on carriage levels of MRSA using Markov models

2.1 Introduction

In this chapter we look at the effects of antibiotics and antiseptic treatment on MRSA carriage levels of colonised patients. Throughout this chapter we assume that there is perfect swab test sensitivity and specificity. Moreover, we make the assumption that there is no person-to-person transmission so we use only a within-patient modelling approach. We will include only the patients who have at least one positive test. The reason we do this is because we have ignored patient-to-patient transmission and thus we cannot draw any conclusions about the effect of antimicrobial treatment when a patient has only negative tests.

We will use a discrete-time Markov chain to model the colonisation status of an individual on a daily basis taking into account daily antimicrobial treatment. The data we are going to use come from the two 15-bed ICUs from St. Guy's and Thomas' hospital in London as described in section 1.3.

Earlier work using Markov Models to analyse whether antimicrobial treatment

can influence carriage levels of MRSA has been done by Kypraios et al. in [Kypraios et al., 2011]. In their work they use discrete time Markov models to assess the effects of antimicrobial treatment considering three models: one using a 1-day timescale, and two using a 1-week timescale considering either one antimicrobial at a time or multiple antimicrobial use. For the weekly transition models, they included only tests that took place at weekly intervals and assumed that an antimicrobial had been received that week only if the patient was receiving it for four or more days that week. There was strong evidence that antiseptic treatment had an effect on reducing MRSA carriage while antibiotic treatment was not associated with changes in MRSA carriage. One limitation of this work is that there is no discussion about assessing model fit.

The work in this chapter uses a similar model as the model for daily transitions used in [Kypraios et al., 2011]. The MRSA Data Set that includes only the patients with at least one positive test is also the same as the one used in [Kypraios et al., 2011]. However, here we will obtain results from two more data sets: the Wounds Data Set and the Respiratory Data Set for which we will also consider only patients with at least on positive test. Furthermore, this chapter includes a detailed analysis of model assessment which has not been done in any previous works.

For the model's parameter estimation, a Frequentist and a Bayesian approach are used utilising maximum likelihood estimation and Markov Chain Monte Carlo (MCMC) methods respectively. We initially validate our methods using simulated data and then, using the GSTT data, we obtain results making several different assumptions for the three different data sets; MRSA Data Set, Wounds Data Set and Respiratory Data Set. We then assess the model fit using two different methods discussed in Section 2.6.

We find that antiseptic treatment has an effect on the clearance of MRSA carriage for the MRSA Data Set. Moreover, Oxazolidinone seems to be effective in reducing MRSA carriage for all the three data sets while Macrolide and Cephalosporin seem to have the opposite effect. These results are in agreement with the findings in [Kypraios et al., 2011]. Finally, it was not always clear that the model fit was adequate.

In Section 2.2 we present some summary statistics of the data we are going to use in this chapter. In Section 2.3 we describe the model, in Section 2.4 the

Likelihood, in Section 2.5 we discuss the inference methods and in Section 2.6 the model assessment methods. In Sections 2.7 and 2.8 we validate our methods using simulated data and present the results from the three data sets (MRSA Data Set, Wounds Data Set and Respiratory Data Set). Finally, Section 2.9 gives an overview of the methods and the results discussed in the previous sections as well as model's limitations and suggestions for possible improvements.

2.2 Data

In this chapter we perform our analysis by including only patients that have at least one positive test. The reason we do this is that, since we are interested in the effects of antimicrobial treatment on MRSA carriage levels, it is better to include in our study those patients who had acquired the infection. Another reason is that including all patients is computationally demanding. However, for comparison, in Section 2.8 we have a case where we include the results for patients with no positive tests, to show that these results do not differ much from the those that include only the positive patients.

The data sets we use for our main study in this chapter will be subsets of the MRSA, Wounds and Respiratory Data Sets described in the previous chapter 1. We are going to refer to them as p-MRSA Data Set, p-Wounds Data Set and p-Respiratory Data Set to distinguish them from the original and complete data sets.

Tables 2.1 and 2.2 give some basic statistics of the three data sets.

Statistic	p-MRSA	p-Wounds	p-Respiratory
number of patients	545	351	302
average stay/patient (days)	18.510	26.603	26.473
median stay/patient (days)	12	17	19
average no. of tests/patient	3.121	6.752	2.884
no. of tests	1701	2370	871
no. of positive tests	910	736	480
proportion of positive tests	0.5349	0.3105	0.5510
days of study	1574	1566	1547
total no. of days in ICU	10088	9338	7995
total no. of days antimicrobials prescribed	7322	6773	5863

Table 2.1: Summary statistics for the p-MRSA, p-Wounds and p-Respiratory Data Sets.

Antimicrobial	p-MRSA	p-Wounds	p-Respiratory
Aminoglycoside	1119	1058	908
Antiseptic	3715	3752	2902
Cephalosporin	1327	1014	892
Glycopeptide	2900	2691	2404
Macrolide	1278	1096	1099
Nitroimidazole	1136	941	760
Oxazolidinone	118	129	89
Penicillin	639	625	450
Polymyxin	161	173	136
Quinolone	549	397	468
Rifamycin	128	80	108

Table 2.2: Number of days each antimicrobial group was prescribed for the p-MRSA, p-Wounds and p-Respiratory Data Sets.

2.3 Model

We are modelling the effects of antimicrobial treatment on carriage levels of MRSA in patients in the two 15-bed ICU wards. We extract information from the swab tests results from each patient, their antimicrobial treatment they had during their stay as well as the length of their stay in the ICU. We also consider that the colonisation status of each patient is independent of the others. This means that every patient has the same probability of becoming colonised with MRSA and in particular this probability does not depend on the colonisation status of any other patient. Moreover, we assume that the swab tests have perfect sensitivity and specificity. Sensitivity denotes the proportion of actual positive tests which are observed correctly and specificity denotes the proportion of negative tests which are observed correctly.

We will use a two-state discrete time Markov chain to model the colonisation status of an individual. We assume that each day a given patient can be in either one of the following states: colonised (C) or not colonised (N).

Let $\{X_n : n \geq 0\}$ be a stochastic process, where n denotes the number of days patient has stayed in the ICU ($n = 0$ is the first day) and X_n denotes the colonisation status of the individual. So, $X_n \in \{C, N\}$.

Furthermore, a patient each day can be either "on" or "off" antimicrobial treatment, meaning that they are given antimicrobials or not on that day. In this study we consider only one antimicrobial treatment at a time. If a patient receives antimicrobial treatment on day n then we assume they are "on" antimicrobial treatment otherwise they are "off" antimicrobial treatment. So, for each patient we define $\Delta(n) \in \{ON, OFF\}$, where $\Delta(n)$ is the antimicrobial state on day n . We have made the assumption that antimicrobials have an immediate effect on patients.

Moreover, we suppose that the process $\{X_n : n \geq 0\}$ is a Markov chain and that it satisfies the Markov property,

$$P\left(X_{n+1} = j | X_n = i, X_{n-1} = i_{n-1}, \ldots, X_1 = i_1, X_0 = i_0\right) = P\left(X_{n+1} = j | X_n = i\right),$$

where $i_0, i_1, ..., i_{n-1}, i, j \in \{C, N\}$.

The Markov chain is not time-homogeneous, since the one-step transition matrix depends on whether the individual is "on" or "off" antibiotics. We assume that the daily transition probabilities are independent of which particular patient is being considered.

Then the one-day transition matrix, for a patient whose current antimicrobial state is Δ is

$$P_{\Delta(n-1)} = \begin{array}{c} \\ N \\ C \end{array} \begin{array}{c} \begin{array}{cc} N & C \end{array} \\ \begin{pmatrix} p_\Delta & 1-p_\Delta \\ q_\Delta & 1-q_\Delta \end{pmatrix} \end{array},$$

where

$$p_\Delta = Pr(X_n = N | X_{n-1} = N, \Delta\,(n-1) = \Delta),$$
$$q_\Delta = Pr(X_n = N | X_{n-1} = C, \Delta\,(n-1) = \Delta),$$

and

$$0 \leq p_\Delta = p_0 + \alpha \mathbb{1}_{\{\Delta = ON\}} \leq 1,$$
$$0 \leq q_\Delta = q_0 + \beta \mathbb{1}_{\{\Delta = ON\}} \leq 1.$$

Here, $p_\Delta = p_0 + \alpha \mathbb{1}_{\{\Delta=ON\}}$ is the transition probability that a patient remains in a non-colonised state where p_0 is the baseline probability when a patient is "off" antimicrobial treatment and α is the antimicrobial contribution to the patient on that day. This means that when a patient is "off" antimicrobial treatment we have the transition probability p_0 and when a patient is "on" we have the transition probability $p_0 + \alpha$. Similarly, $q_\Delta = q_0 + \beta \mathbb{1}_{\{\Delta=ON\}}$ is the transition probability that a patient goes from a colonised state to a non-colonised state, where q_0 is the baseline probability when a patient is "off" antimicrobial treatment and β is the antimicrobial contribution to the patient on that day. So, when a patient is "off" antimicrobial treatment we have the transition probability q_0 and when a patient is "on" antimicrobial treatment we have the transition probability $q_0 + \beta$.

More explicitly, when a patient is "off" antimicrobial treatment then the transition matrix is

$$P_{OFF} = \begin{array}{c} \\ N \\ C \end{array} \begin{array}{c} \begin{array}{cc} N & C \end{array} \\ \begin{pmatrix} p_0 & 1-p_0 \\ q_0 & 1-q_0 \end{pmatrix} \end{array},$$

and when a patient is "on" antimicrobial treatment the transition matrix becomes

$$P_{ON} = \begin{array}{c} \\ N \\ C \end{array} \begin{array}{c} \begin{array}{cc} N & C \end{array} \\ \begin{pmatrix} p_0+\alpha & 1-p_0-\alpha \\ q_0+\beta & 1-q_0-\beta \end{pmatrix} \end{array},$$

2.4 Likelihood

Patient i's data, $i = 1, ..., N_p$, where N_p is the number of patients with at least one positive test, consist of a sequence of observations each of which is defined by the quantity $(n_0, t; j, k)^{(i)}$, where $n_0 > 0$ is the observation day, $t > 0$ is the number of days until the next swab test and j and k denote the state that the patient is on day n_0 and on day $n_0 + t$ respectively, $j, k \in \{C, N\}$. Moreover, suppose that the colonisation status of a patient i is observed on day n_0 and on day $n_0 + t$ but not in between. We define as $\Gamma_{jk}^{(i)}(n_0, t)$ the probability that patient i who is observed on day n_0 and then on day $n_0 + t$ goes from colonisation state j to colonisation state k. Then,

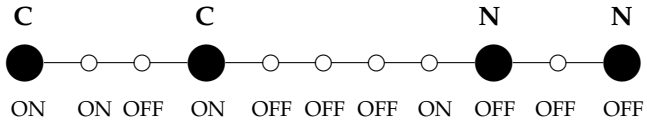
$$\Gamma_{jk}^{(i)}(n_0, t) = \left(\prod_{l=n_0}^{n_0+t-1} P_{\Delta(l)} \right)_{jk}, \; j, k \in \{C, N\}.$$

Furthermore, denote by $\mathcal{S}_i = \{(n_0, t; j, k)\}^{(i)}$ the set of all the observations for patient i, i.e. and let $\mathcal{S} = \bigcup_i \mathcal{S}_i$. Then, the likelihood when all patient information is taken into account is given by

$$L(p_0, q_0, \alpha, \beta; \mathcal{S}) = \prod_{i=1}^{N_p} \prod_{(n_0,t;j,k)^{(i)} \in \mathcal{S}_i} \Gamma_{jk}^{(i)}(n_0, t) \mathbb{1}_{\{0 \le p_0+\alpha \le 1, 0 \le q_0+\beta \le 1\}}. \quad (2.4.1)$$

2.4.1 Example

Suppose that patient i's data can be described by the diagram below:



Each bullet denotes one day of patient i's stay in the ICU ward. We assume the first day is day 1. The black bullets denote that the patient had a test on that day. Moreover, we have information about what antimicrobial treatment was given to the patient each day.

Then, in order to find the probability that the patient goes from state C to state C in three days, $\Gamma^{(i)}_{CC}(1,3)$, considering that the patient was receiving antimicrobial treatment the first two days but not the third one, we multiply two times the transition matrix when the patient is "on" antimicrobial treatment by the transition matrix that corresponds to "off" antimicrobial treatment. From the derived matrix we only need the probability in the cell of the CC transition.

$$\Gamma^{(i)}_{CC}(1,3) = \left(P_{\Delta(1)=ON} \times P_{\Delta(2)=ON} \times P_{\Delta(3)=OFF}\right)_{CC} =$$

$$\left(\begin{pmatrix} p_0+\alpha & 1-p_0-\alpha \\ q_0+\beta & 1-q_0-\beta \end{pmatrix}^2 \times \begin{pmatrix} p_0 & 1-p_0 \\ q_0 & 1-q_0 \end{pmatrix}\right)_{CC}.$$

Similarly we compute the probabilities $\Gamma^{(i)}_{CN}(4,5)$ and $\Gamma^{(i)}_{NN}(9,2)$ as shown below.

$$\Gamma^{(i)}_{CN}(4,5) = \left(P_{\Delta(4)=ON} \times P_{\Delta(5)=OFF} \times P_{\Delta(6)=OFF} \times P_{\Delta(7)=OFF} \times P_{\Delta(8)=ON}\right)_{CN} =$$

$$\left(\begin{pmatrix} p_0+\alpha & 1-p_0-\alpha \\ q_0+\beta & 1-q_0-\beta \end{pmatrix}^2 \times \begin{pmatrix} p_0 & 1-p_0 \\ q_0 & 1-q_0 \end{pmatrix}^3\right)_{CN}.$$

$$\Gamma^{(i)}_{NN}(9,2) = \left(P_{\Delta(9)=OFF} \times P_{\Delta(10)=OFF}\right)_{NN} = \left(\begin{pmatrix} p_0 & 1-p_0 \\ q_0 & 1-q_0 \end{pmatrix}^2\right)_{NN}.$$

So, the likelihood for patient i can then be computed as follows,

$$L\left(p_0, q_0, \alpha, \beta; \mathcal{S}_i\right) = \Gamma^{(i)}_{CC}(1,3) \times \Gamma^{(i)}_{CN}(4,5) \times \Gamma^{(i)}_{NN}(9,2).$$

Next section shows the methods we used to obtain the estimates for the model's parameters.

2.5 Inference

We are interested in finding estimates for all the parameters of the model. We used two different methods to achieve this, Maximum Likelihood Estimation (MLE) and Bayesian inference using MCMC algorithms. We have data $\mathcal{S}$, as described above, and we wish to estimate the parameters p_0, q_0, α and β.

For MLEs we used `optim` in R using the Nelder-Mead algorithm to perform optimisation.

For MCMC we used a Gaussian random walk Metropolis scheme [Gilks and Spiegelhalter, 1996].

2.5.1 Prior distributions

We assume non-informative prior distributions for all the model parameters so, we use independent Uniform $\mathrm{U}(0,1)$ distributions for each one.

Combining the prior information for each parameter and the likelihood given in (2.4.1) we get the following posterior density function,

$$\pi\left(p_0, q_0, \alpha, \beta \mid \mathcal{S}\right) \propto L\left(p_0, q_0, \alpha, \beta; \mathcal{S}\right) \pi(p_0)\pi(q_0)\pi(\alpha)\pi(\beta),$$

where from (2.4.1) we have $0 \leq p_0 + \alpha \leq 1$, $0 \leq q_0 + \beta \leq 1$ and we assume that p_0, q_0, α and β are a priori independent.

2.5.2 Updating the parameters

We update each of the parameters p_0, q_0, α and β using a Gaussian random walk Metropolis scheme. We cannot use Gibbs sampling because (2.4.1) gives us intractable full conditional distributions.

Let $\omega^{(t)}$ denote the set of current model parameters at iteration t and ω^* be the proposed new set of these parameters. We use a multivariate normal pro-

posal distribution $N(\omega^*, \sigma^2_{\omega^*})$ to propose the parameters, where $N(\mu, \sigma^2)$ is the normal distribution with mean μ and standard deviation σ.

Standard deviation σ_{ω^*} is chosen so that the acceptance rate is around 0.25 [Roberts et al., 1997].

We sample a candidate point ω^* from a gaussian density $g\left(\omega^*|\omega^t\right) \sim N\left(\omega^t, \sigma^2_{\omega^*}\right)$. Then, the probability that the candidate point ω^* is accepted is:

$$\alpha\left(\omega^t, \omega^*\right) = \min\left(1, \frac{L\left(\omega^*; \mathcal{S}\right)\pi\left(\omega^*\right) g\left(\omega^t|\omega^*\right)}{L\left(\omega^t; \mathcal{S}\right)\pi\left(\omega^t\right) g\left(\omega^*|\omega^t\right)}\right).$$

where $\pi(\omega^*)$ is the prior distribution of parameter ω^* and $\frac{g\left(\omega^t|\omega^*\right)}{g(\omega^*|\omega^t)} = 1$ as shown in 1.5.3.

If the candidate ω^* is accepted then the next step becomes $\omega^{t+1} = \omega^*$, otherwise, the chain does not move, i.e. $\omega^{t+1} = \omega^t$. In order to allow the chain to reach stationarity, we discard the first l values as a burn-in period. Burn-in period formalities are discussed in [Gilks and Spiegelhalter, 1996].

A Pseudocode for this algorithm is as follows:

Gaussian Random Walk MCMC Algorithm

1 Assign initial values to the parameters of interest ω

2 For $t = 1 \ldots N_{iter}$, N_{iter} is the number of iterations

- Propose $\omega^* \sim N\left(\omega^t, \sigma^2_{\omega^t}\right)$
- Draw a uniform $\mathrm{U}(0,1)$ random variable u
- If $u \leq \alpha\left(\omega^t, \omega^*\right)$
  - set $\omega^{t+1} = \omega^*$
- Else
  - set $\omega^{t+1} = \omega^t$

3 End For loop

4 Return values $\{\omega^1, \omega^2, ..., \omega^n\}$

2.6 Model Assessment for Markov Models

In this section we discuss how to assess the model fit.

Initially we present some previous work on goodness-of-fit tests for Markov models. Then, we consider model assessment of a Markov model without taking into account the information about antimicrobial treatment. Later, we discuss how we can include antimicrobial treatment and point out limitations that might arise and finally, we explain how we obtained the model fit for our model.

2.6.1 Background Information

Kalbfleisch and Lawless in [Kalbfleisch and Lawless, 1985] proposed a goodness-of-fit statistic for equally spaced longitudinal data for a continuous time Markov model. The patients were observed at the same time and the Markov model was time homogeneous. They found the contingency tables of the observed and expected transition counts for each time interval. They used the matrix of the estimated transition probabilities to find the expected transition counts. Then for each contingency table a Pearson chi-squared statistic was calculated to test the fit of the Markov model. This goodness-of-fit test was also proposed by Stavola, [De Stavola, 1988].

Gentleman et al. in [Gentleman et al., 1994] applied the estimation methods of Kalbfleisch and Lawless presented in [Kalbfleisch and Lawless, 1985] to longitudinal partially observed data using continuous-time, time-homogeneous Markov models. For the model fit, they compared the observed to the expected values based on the model. In order to do this, the authors calculated the observed and expected counts using either the number of people in each time state or transition counts. To calculate the observed counts, they assumed that the time of the disease onset was known and that a patient who had not been observed at time t_u remained at the same state as at their earlier inspection time. It is suggested that these assumptions might not have a considerable effect if the observations are frequent. Expected times were obtained by summing the probability an individual is at state u at time t_u for example, given their initial state, over all individuals who were being observed at time t_u. Then, to assess

the goodness-of-fit, the observed transition counts, say for state u to v, O_{uv} were compared to the expected transition counts E_{uv} either looking at the matrix of observed minus expected values or through

$$M_{uv} = \frac{(O_{uv} - E_{uv})^2}{E_{uv}}.$$

However, they do not give a formal way of assessing whether the difference between observed and expected values is statistically significant.

On the other hand, Aguirre-Hernandez and Farewell (AH/F) [Aguirre- Hernández and Farewell, 2002] proposed a Pearson-type statistic to examine the goodness -of-fit of stationary and time homogeneous Markov regression models of order one. They grouped the observations in H categories according to their type and the time intervals between the transitions. Then, they propose the statistic

$$T = \sum_{H} \frac{(n_h - e_h)^2}{e_h},$$

where n_h denotes the total number of observed transitions in cell h and e_h is the expected number of transitions in cell h. The estimated transition probabilities are obtained by generating independent bootstrap samples from the model specified by the null hypothesis and calculating the goodness-of-fit for each statistic. They simulated the observed states based each time on the existing observed states and then refitted the model and calculated the statistic for each simulation. Then, the value of the statistic of the observed data is compared with the simulated values to compute the significance level.

Later, Titman and Sharples [Titman and Sharples, 2008] proposed a modification of this test that includes processes with an absorbing state in the case of Markov models and then an extension for misclassification-type hidden Markov models. Moreover, Titman in [Titman, 2009] proposed an approximation of the asymptotic null distribution of the goodness-of-fit tests for panel, observed, continuous time multi-state Markov models and hidden Markov models. This work had the potential to improve applicability of the goodness-of-fit tests described in [Aguirre- Hernández and Farewell, 2002] and [Titman and Sharples, 2008] as bootstrapping in many cases can be computationally expensive.

All the methods described above refer to continuous-time Markov models that

are time-homogeneous. Only Kalbfleisch and Lawless in [Kalbfleisch and Lawless, 1985] investigated briefly the case of a Markov model being non- homogeneous but only for certain cases. Later in this section we analyse how we assess the model fit for the time-homogeneous case i.e when antimicrobial treatment is not included and then for the non-homogeneous case including the antimicrobial information.

2.6.2 Model assessment of the Markov model: theoretical considerations

Here we are going to discuss about how feasibly we can perform model assessment and discuss any difficulties and limitations we meet when we include the information about antimicrobial treatment.

We classify the number of observed transitions in groups according to each day interval. Let us focus on a given k-day interval and assume that we have $n = n(k)$ patients who have such an observed transition. If we sum up the numbers of transitions of each day interval we have a summary matrix

$$\text{observed} = \begin{pmatrix} X_{NN} & X_{NC} \\ X_{CN} & X_{CC} \end{pmatrix},$$

where $X_{jk}, j, k \in \{C, N\}$ denotes the number of transitions from state j to state k. Moreover, suppose that $X_{NN} + X_{NC} = n_N$ and $X_{CN} + X_{CC} = n_C$.

The corresponding model for X_{NN} for example, is

$$X_{NN} = \sum_{j=1}^{n_N} Y_j, \tag{2.6.1}$$

where $Y_j \sim Bernoulli(p_j)$, Y_j independent, $p_j = p_j(p_0, q_0, \alpha, \beta, \tilde{z}_j)$ and $\tilde{z}_j$ is the antimicrobial treatment information for each day during the k-day interval. More explicitly, $\tilde{z}_j$ indicates whether patient j is "on"/"off" antimicrobial treatment on each of the k days. Similar representation holds for X_{NC}, X_{CN} and X_{CC}.

No information about antimicrobial treatment

In the following we consider the asymptotic behaviour of X_{NN} via equation (2.6.1).

In the case where we ignore any data on the antimicrobial treatment in our model, $Y_j \sim Bernoulli(p)$, $p = p(p_0, q_0)$, Y_j independent. Then from the Central Limit Theorem,

$$\frac{\sum_{j=1}^{n_N} \left(Y_j - E[Y_j]\right)}{\sqrt{Var\left(\sum_{j=1}^{n_N} Y_j\right)}} \xrightarrow{D} N(0,1) \text{ as } n_N \to \infty,$$

where $\xrightarrow{D}$ means convergence in distribution.

Then,

$$\frac{\sum_{j=1}^{n_N} \left(Y_j - p\right)}{\sqrt{n_N p\left(1-p\right)}} = \frac{\sum_{j=1}^{n_N} Y_j - n_N p}{\sqrt{n_N p\left(1-p\right)}} \xrightarrow{D} N(0,1).$$

Now for the standard χ^2 approach consider the quantity

$$K := \frac{(X_{NN} - E(X_{NN}))^2}{E(X_{NN})} + \frac{(X_{NC} - E(X_{NC}))^2}{E(X_{NC})}. \tag{2.6.2}$$

Recall the standard argument that K is χ^2 distributed with 1 degree of freedom, as follows. Since $E[X_{NN}] = n_N p$ we have

$$E[X_{NC}] = E[n_N - X_{NN}] = n_N - E[X_{NN}] = n_N\left(1-p\right)$$

and

$$\left(X_{NC} - E\left(X_{NC}\right)\right)^2 = \left(n_N - X_{NN} - n_N + E\left(X_{NN}\right)\right)^2 = \left(X_{NN} - E\left(X_{NN}\right)\right)^2.$$

So, from (2.6.2) we have

$$
\begin{aligned}
&(X_{NN} - E(X_{NN}))^2 \left\{ \frac{1}{E(X_{NN})} + \frac{1}{n_N - E(X_{NN})} \right\} \\
&\quad = (X_{NN} - E(X_{NN}))^2 \left\{ \frac{1}{n_N p} + \frac{1}{n_N (1-p)} \right\} = \frac{(X_{NN} - E(X_{NN}))^2}{n_N p (1-p)} \\
&\quad = \left(\frac{X_{NN} - E(X_{NN})}{\sqrt{n_N p (1-p)}} \right)^2 \xrightarrow{D} \chi_1^2.
\end{aligned}
$$

Similarly we can show that the quantity

$$
\frac{(X_{CN} - E(X_{CN}))^2}{E(X_{CN})} + \frac{(X_{CC} - E(X_{CC}))^2}{E(X_{CC})}
$$

is also χ^2 distributed with 1 degree of freedom.

Including information about antimicrobial treatment

We now see if it is possible to extend the above approach to the case where we have antimicrobial treatment data. In this case we still consider the model (2.6.1) but now we have $Y_j \sim Bernoulli(p_j)$, $p_j = p_j(p_0, q_0, \alpha, \beta, \tilde{z}_j)$, Y_j independent and where $\tilde{z}_j$ is the antimicrobial information for each day during the k-day interval. Now, $\tilde{z}_j$ only has finitely many options (at most 2^k, but in actual data we typically see less than 2^k different antimicrobial treatment patterns), and so it follows that p_j can only take finitely many values for given p_0, q_0, α and β.

Thus, from (2.6.1),

$$
\begin{aligned}
E(X_{NN}) &= \sum_{j=1}^{n_N} p_j, \\
Var(X_{NN}) &= \sum_{j=1}^{n_N} p_j (1 - p_j).
\end{aligned}
$$

In both cases we condition on knowing n_N.

Recall Liapounov's Theorem ([Loève, 1963], p.275):

Lemma 2.6.1. *If $X_1, X_2, ..., X_n$ are independent with zero means and variances σ_1^2, σ_2^2, $\ldots$, σ_n^2 and $s_n^2 = \sigma_1^2 + ... + \sigma_n^2$ and there exists $\delta > 0$ with*

$$\frac{\sum_{i=1}^{n} E|X_i|^{2+\delta}}{s_n^{2+\delta}} \to 0, \ \ as \ \ n \to \infty$$

then $s_n^{-1} \sum_{i=1}^{n} X_i \xrightarrow{D} N(0,1)$.

We will use Lemma 2.6.1 to establish the following result.

Lemma 2.6.2. *If the p_js are uniformly bounded away from 0 and 1 (i.e. there exists $\delta_1 > 0$, $\delta_2 < 1$ such that $\delta_1 < p_j < \delta_2$ for all j), then,*

$$\frac{X_{NN} - \sum_{j=1}^{n_N} p_j}{\sqrt{\sum_{j=1}^{n_N} p_j \left(1 - p_j\right)}} \xrightarrow{D} N(0,1) \quad as \ \ n_N \to \infty.$$

Proof. We have that $X_{NN} = \sum_{j=1}^{n_N} Y_j$ so

$w_j = Y_j - p_j$ has $E[w_j] = 0$ and $Var[w_j] = Var[Y_j] = p_j(1-p_j) = \sigma_j^2$, say.

Now,

$$w_j = \begin{cases} 1 - p_j & \text{with prob } \ p_j, \\ 0 - p_j & \text{with prob } \ 1 - p_j, \end{cases}$$

so

$$|w_j| = \begin{cases} 1 - p_j & \text{with prob } \ p_j, \\ p_j & \text{with prob } \ 1 - p_j, \end{cases}$$

and

$$|w_j|^{2+\delta} = \begin{cases} (1-p_j)^{2+\delta} & \text{with prob } \ p_j, \\ p_j^{2+\delta} & \text{with prob } \ 1 - p_j. \end{cases}$$

Thus,

$E|w_j|^{2+\delta} = p_j(1-p_j)^{2+\delta} + p_j^{2+\delta}(1-p_j)$ and $s_n^2 = \sigma_1^2 + ... + \sigma_n^2 = \sum_{j=1}^{n} p_j(1-p_j)$.

So, the condition $\frac{\sum_{i=1}^{n} E|X_i|^{2+\delta}}{s_n^{2+\delta}} \to 0$ in Lemma 2.6.1, as $n \to \infty$ is equivalent to

$$\frac{\sum_{j=1}^{n} \{p_j \left(1 - p_j\right)^{2+\delta} + p_j^{2+\delta} \left(1 - p_j\right)\}}{\left(\sum_{j=1}^{n} p_j \left(1 - p_j\right)\right)^{\frac{2+\delta}{2}}} \to 0 \ \text{ as } \ n \to \infty. \tag{2.6.3}$$

To show that (2.6.3) holds, let $\delta = 2$. Recall that the p_j's are bounded away from 0 and 1. Then, there exists $\epsilon > 0$ such that $0 < \epsilon < p_j\left(1 - p_j\right)$,

so that

$$\left(\sum_{j=1}^{n} p_j\left(1 - p_j\right)\right)^2 > n^2\epsilon^2. \tag{2.6.4}$$

Also, $p_j\left(1 - p_j\right)^4 + p_j^4\left(1 - p_j\right)$ is maximised at $p_j = \frac{1}{2}$, so

$$0 < p_j\left(1 - p_j\right)^4 + p_j^4\left(1 - p_j\right) \leq \left(\frac{1}{2}\right)^4,$$

so,

$$\sum_{j=1}^{n}\left(p_j\left(1 - p_j\right)^4 + p_j^4\left(1 - p_j\right)\right) \leq n\left(\frac{1}{2}\right)^4. \tag{2.6.5}$$

(2.6.4) and (2.6.5) imply that

$$\frac{\sum_{j=1}^{n}\left(p_j\left(1 - p_j\right)^4 + p_j^4\left(1 - p_j\right)\right)}{\left(\sum_{j=1}^{n} p_j\left(1 - p_j\right)\right)^2} \leq \frac{n\left(\frac{1}{2}\right)^4}{n^2\epsilon^2} \to 0 \quad \text{as} \quad n \to \infty,$$

as required. □

The standard χ^2 approach invites us to consider again the quantity in (2.6.2)

$$K := \frac{\left(X_{NN} - E\left(X_{NN}\right)\right)^2}{E\left(X_{NN}\right)} + \frac{\left(X_{NC} - E\left(X_{NC}\right)\right)^2}{E\left(X_{NC}\right)}.$$

We next show that the latter sum is not generally asymptotically a χ^2-distribution.

Again, we have

$$E\left(X_{NC}\right) = E\left(n_N - X_{NN}\right) = n_N - E\left(X_{NN}\right),$$

so

$$\left(X_{NC} - E\left(X_{NC}\right)\right)^2 = \left(n_N - X_{NN} - n_N + E\left(X_{NN}\right)\right)^2 = \left(X_{NN} - E\left(X_{NN}\right)\right)^2.$$

Then (2.6.2) simplifies to

$$(X_{NN} - E(X_{NN}))^2 \left\{ \frac{1}{E(X_{NN})} + \frac{1}{n_N - E(X_{NN})} \right\} = \frac{n_N (X_{NN} - E(X_{NN}))^2}{E(X_{NN})(n_N - E(X_{NN}))}$$
$$= \frac{n_N \left(X_{NN} - \sum_{j=1}^{n_N} p_j \right)^2}{\left(\sum_{j=1}^{n_N} p_j \right) \left(\sum_{j=1}^{n_N} (1 - p_j) \right)}.$$

We require that, as $n_N \to \infty$,

$$\frac{n_N}{\left(\sum_{j=1}^{n_N} p_j \right) \left(\sum_{j=1}^{n_N} (1 - p_j) \right)} \sim \frac{1}{\sum_{j=1}^{n_N} p_j (1 - p_j)},$$

in order to use the Central Limit Theorem result. In the case where $p_j = p$, for all j, this is true since then

$$\left(\sum_{j=1}^{n_N} p_j \right) \left(\sum_{j=1}^{n_N} (1 - p_j) \right) = (np)(n(1-p)) = n^2 p(1-p).$$

Specifically,

$$\frac{n_N \left(X_{NN} - \sum_{j=1}^{n_N} p_j \right)^2}{\left(\sum_{j=1}^{n_N} p_j \right) \left(\sum_{j=1}^{n_N} (1 - p_j) \right)} = \frac{\left(X_{NN} - \sum_{j=1}^{n_N} p_j \right)^2}{\left(\sum_{j=1}^{n_N} p_j (1 - p_j) \right)} \cdot \frac{n_N \sum_{j=1}^{n_N} p_j (1 - p_j)}{\left(\sum_{j=1}^{n_N} p_j \right) \left(\sum_{j=1}^{n_N} (1 - p_j) \right)}$$

so by Slutsky's Theorem ([Fisz, 1963], p.238), if

$$\frac{n_N \sum_{j=1}^{n_N} p_j (1 - p_j)}{\left(\sum_{j=1}^{n_N} p_j \right) \left(\sum_{j=1}^{n_N} (1 - p_j) \right)} \xrightarrow{P} L \text{ as } n_N \to \infty,$$

where $\xrightarrow{P}$ means convergence in probability and L is a non-zero constant, then

$$\frac{K}{L} = \frac{n_N \left(X_{NN} - \sum_{j=1}^{n_N} p_j \right)^2}{L \left(\sum_{j=1}^{n_N} p_j \right) \left(\sum_{j=1}^{n_N} (1 - p_j) \right)} \xrightarrow{D} \chi^2_{(1)}.$$

One case of practical interest is that each p_j is chosen at random from m alternatives $\tilde{p}_1, ..., \tilde{p}_m$ with probabilities $\alpha_1, ..., \alpha_m$ respectively. Then by the Strong Law

of Large Numbers, as $n_N \to \infty$ we have

$$\frac{1}{n_N}\sum_{j=1}^{n_N} p_j\left(1-p_j\right) \xrightarrow{\text{a.s}} \sum_{i=1}^{m} \alpha_i \tilde{p}_i\left(1-\tilde{p}_i\right)$$

$$\frac{1}{n_N}\sum_{j=1}^{n_N} p_j \xrightarrow{\text{a.s}} \sum_{i=1}^{m} \alpha_i \tilde{p}_i$$

$$\frac{1}{n_N}\sum_{j=1}^{n_N} \left(1-p_j\right) \xrightarrow{\text{a.s}} \sum_{i=1}^{m} \alpha_i \left(1-\tilde{p}_i\right),$$

where $\xrightarrow{\text{a.s}}$ means almost surely.

Thus

$$L = \frac{\sum_{i=1}^{m} \alpha_i \tilde{p}_i\left(1-\tilde{p}_i\right)}{\left(\sum_{i=1}^{m} \alpha_i \tilde{p}_i\right)\left(\sum_{i=1}^{m} \alpha_i\left(1-\tilde{p}_i\right)\right)}.$$

In practice we could estimate $\hat{p}_1, \ldots, \hat{p}_m$ and $\hat{\alpha}_1, \ldots, \hat{\alpha}_m$ from the antimicrobial treatment data and model parameters, and thus find L. However, in practice n_N may not be that large which makes this approach less appealing.

Later in this section we will show a simulation based method in order to perform model fit.

2.6.3 Model assessment for the Markov model

Here we discuss how we assess the model fit for the Markov model in this thesis.

Model Fit when antimicrobial information is not included

As shown at the beginning of this section, when antimicrobial treatment is not included, we can use the standard chi-squared goodness-of-fit procedure to assess how well the model fits the data.

For each day interval we have the observed transition counts $X_{NN}, X_{NC}, X_{CN}, X_{CC}$ and we use the MLE results $\hat{p}_0, \hat{q}_0, \hat{\alpha}, \hat{\beta}$ to find the $E[X_{NN}], E[X_{NC}], E[X_{CN}], E[X_{CC}]$ under the model. Then we calculate the test-statistic

$$\chi^2 = \sum_{i,j \in \{C,N\}} \frac{\left(X_{ij} - E[X_{ij}]\right)^2}{E[X_{ij}]}. \tag{2.6.6}$$

For example, to calculate the χ^2 for the k-day interval we do the following: assume that we have obtained the ML Estimates to be $\hat{p}_0, \hat{q}_0, \hat{\alpha}$ and $\hat{\beta}$. Then the transition matrix when the patient is "off" antimicrobial treatment will be,

$$P_{OFF} = \begin{pmatrix} \hat{p}_0 & 1-\hat{p}_0 \\ \hat{q}_0 & 1-\hat{q}_0 \end{pmatrix}.$$

Since we are interested in the k-day interval we raise the matrix P_{OFF} to the power of k.

$$(P_{OFF})^k = \begin{pmatrix} \hat{p}_0 & 1-\hat{p}_0 \\ \hat{q}_0 & 1-\hat{q}_0 \end{pmatrix}^k = \begin{pmatrix} p' & 1-p' \\ q' & 1-q' \end{pmatrix}$$

where

$$p' = p'\left(\hat{p}_0, \hat{q}_0\right) \text{ and } q' = q'\left(\hat{p}_0, \hat{q}_0\right).$$

Then we use (2.6.6) to find the χ^2 statistic using $E[X_{NN}] = n_N p'$, $E[X_{NC}] = n_N(1-p')$, $E[X_{CN}] = n_C q'$ and $E[X_{CC}] = n_C(1-q')$. The asymptotic distribution of (2.6.6) is χ^2_2, as discussed in [Kullback et al., 1962] and [Anderson and Goodman, 1957].

We assume that for all the k-day intervals, the χ^2_2 statistics are independent, so if say, there are m k-day intervals, their sum will also be chi-squared distributed with $2m$ degrees of freedom, [Lindgren, 1993], i.e. $\sum_{i=1}^{m} \chi^2_{2(i)} \sim \chi^2_{2m}$, where $\chi^2_{2(i)}$ is the χ^2_2 statistic for the i-day interval.

Model Fit when antimicrobial information is included

When antimicrobial information is included, we cannot easily compare the test statistic result with the χ^2 distribution. We followed the idea of (AH/F), [Aguirre-Hernández and Farewell, 2002].

We simulate 500 independent samples from the model using the posterior means of the parameters p_0, q_0, α and β.

For each one of the samples we find the transition counts for each day interval. We find the transition counts as follows: For each patient i we condition on each observed state and we simulate a Markov chain until the next state, using the observed daily antimicrobial treatment to specify each transition probability. In this way the counts n_N and n_C remain the same as in the observed data.

Then, we group the transitions according to the day intervals they refer to. So, for each day interval we have counts for the transitions $N \to N$, $N \to C$, $C \to N$ and $C \to C$.

Thus, at the end we have 500 counts for each transition, for each day interval.

The model fits when each of the observed counts for each transition for each day interval, lie within the relevant equal-tailed 95% quantile formed from the 500 samples.

Another way to do this is by simulating a Markov chain conditioning only on each patient's first state. This method gives us slightly different results with the model fit to be a little bit worse than the previous method. In the Appendix we have table (A.4) which shows the model fit using both methods for the antiseptic treatment for the p-MRSA data set.

In the next sections we present the results obtained from the methods above, firstly using simulated data and then using the GSTT data.

2.7 Simulation

In order to validate our Frequentist and Bayesian approaches described in Section 2.5 we first consider estimation based on simulated data. In this section we obtain the estimates of the model parameters ignoring data about patient antimicrobial use so, as a consequence we have $\alpha = \beta = 0$.

We simulated 10000 daily transitions with probabilities $p_0 = 0.8697$ and $q_0 = 0.1283$, where p_0 and q_0 are the baseline probabilities for remaining to a non-colonised state and going from a colonised state to a non-colonised state respectively. We used these particular values since they are the MLEs of the real data without including any information about antimicrobial treatment. Once we simulated the data set, we estimated the parameters of interest using MLEs

and MCMC. We initially assumed that we have a fully observed Markov chain with one day intervals between the tests and then having a partially observed Markov Chain with two-day intervals, three-day and so on up to an interval of one week.

Calculations of Standard Errors

Once we obtained the MLEs for the model parameters we calculated the standard errors for each parameter. In order to do that we needed to find the Hessian matrix derived from the second derivatives of the likelihood with respect to the parameters. Let ω denote the set of model parameters. Then the Hessian matrix is given by

$$H(\omega) = \frac{\partial^2 lnL(\omega; \mathcal{S})}{\partial\omega\partial\omega'}.$$

Taking the negative expectation of this matrix we get the *Fisher information matrix*,

$$I(\omega) = -E(H(\omega)).$$

The inverse of the *information matrix* $I(\omega)$ gives us the variance-covariance matrix $var(\omega)$ whose off diagonal elements are the asymptotic covariances of the parameters and the diagonal elements are the variances of the parameters. The standard errors are the square roots of the diagonal elements of this variance-covariance matrix.

In practice, we use `optim` in the R statistical package to find the MLEs. `Optim` can also give us the hessian matrix H.

Calculation of Standard Deviation

To get the standard deviations from the MCMC posterior distributions, we used the following formula

$$s = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N}(x_i - \bar{x})^2},$$

where N is the length of the sample size, $x_i, i = 1, 2, ..., N$ is the estimate of the

parameter x in each MCMC iteration and $\bar{x} = N^{-1} \sum_{i=1}^{N} x_i$.

2.7.1 Results

For the MCMC algorithm, we used independent uniform $\mathrm{U}(0,1)$ prior distributions for p_0 and q_0. We ran the algorithm for 50000 iterations and discarded the first 1000 as a burn in period. Figure 2.1 gives an example of the trace plots given by the MCMC algorithm.

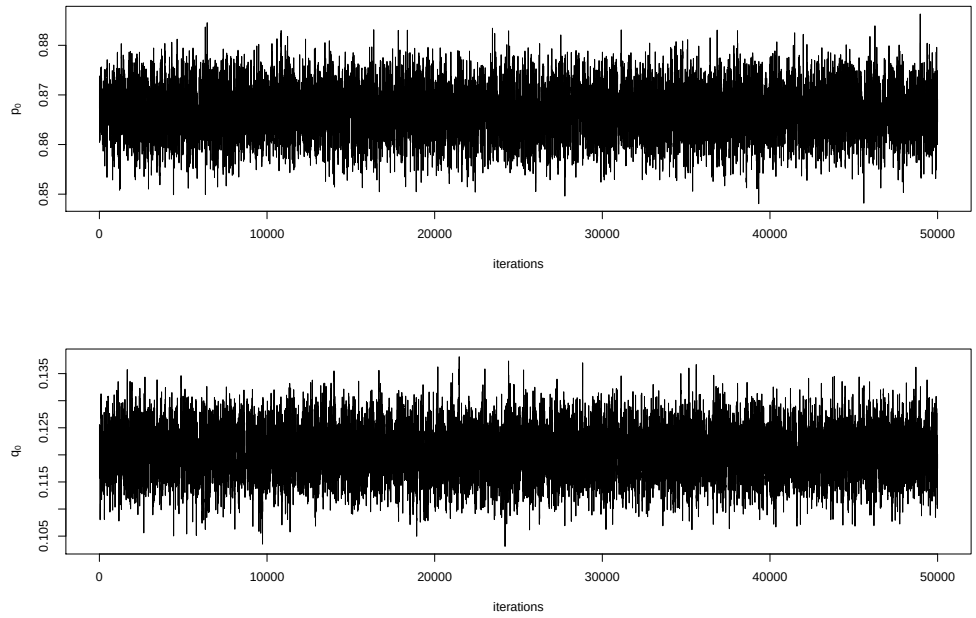


Figure 2.1: Trace plots for p_0 and q_0 using simulated data and assuming that we have daily transitions.

Table 2.3 shows the results from the MLEs, the summary statistics of the posterior distributions for one-day intervals, 3-day intervals, and 7-day intervals, and the posterior correlation between p_0 and q_0. It can be clearly seen that the parameter estimates are consistent with the values set. Furthermore, we notice that as day intervals increase, the posterior correlation between p_0 and q_0 also increases. Density plots in Figure 2.2 show the results of MCMC in each case. We can see that MLEs and MCMC output are in agreement and that estimation improves when the observations are more frequent.

We also performed the chi-squared goodness-of-fit test to the model. In order to obtain the expected frequencies for the 3-day interval transitions and 7-day in-

1-day Interval		
parameters	**MLE(st.error)**	$\mathbf{E}[\cdot\|\mathcal{S}]$
p_0	0.8703 (0.0047)	0.8701 (0.0047)
q_0	0.1247 (0.0046)	0.1249 (0.0046)
p_0, q_0 **posterior correlation**		-0.0010
3-day Interval		
parameters	**MLE(st.error)**	$\mathbf{E}[\cdot\|\mathcal{S}]$
p_0	0.8700 (0.0059)	0.8699 (0.0059)
q_0	0.1215 (0.0056)	0.1219 (0.0056)
p_0, q_0 **posterior correlation**		-0.3048
7-day Interval		
parameters	**MLE(st.error)**	$\mathbf{E}[\cdot\|\mathcal{S}]$
p_0	0.8627 (0.0131)	0.8556 (0.0275)
q_0	0.1316 (0.0126)	0.1384 (0.0263)
p_0, q_0 **posterior correlation**		-0.9520

Table 2.3: MLEs, summary statistics and posterior correlation for p_0 and q_0 using the simulated transitions for intervals of 1-day, 3-days and 7-days without antimicrobial treatment. The true values are $p_0 = 0.8697$ and $q_0 = 0.1283$.

terval transitions we raise the obtained transition matrix P_Δ (as defined above) to the power of 3 and 7 respectively. Results are shown in Table 2.4. It can be seen that the chi-squared statistic in all cases is close to zero and thus the model fits reasonably well using the critical value $\chi^2_2 = 13.82$ at the 0.001 significance level.

Goodness of fit			
	Day Intervals		
	1	**3**	**7**
χ^2_2	0.0010	0.0028	0.00001

Table 2.4: Chi-squared statistic for the simulated data for day intervals of 1-day, 3-days and 7-days without antimicrobial treatment.

Chi-squared statistic should be zero for the 1-day intervals. Next we show that when there are only daily transitions the χ^2 statistic is 0, as follows.

Suppose we have the matrix with the counts of observed transitions X_{NN}, X_{NC}, X_{CN} and X_{CC} in each cell,

$$\text{observed} = \begin{pmatrix} X_{NN} & X_{NC} \\ X_{CN} & X_{CC} \end{pmatrix},$$

and that $X_{NN} + X_{NC} = n_N$ and $X_{CN} + X_{CC} = n_C$.

The transition matrix is

$$P_{OFF} = \begin{pmatrix} p_0 & 1-p_0 \\ q_0 & 1-q_0 \end{pmatrix}.$$

So, the likelihood will be,

$$L(p_0, q_0) = p_0^{X_{NN}} (1-p_0)^{X_{NC}} q_0^{X_{CN}} (1-q_0)^{X_{CC}}. \tag{2.7.1}$$

The MLEs for (2.7.1) are:

$$\hat{p}_0 = \frac{X_{NN}}{n_N}, \tag{2.7.2}$$

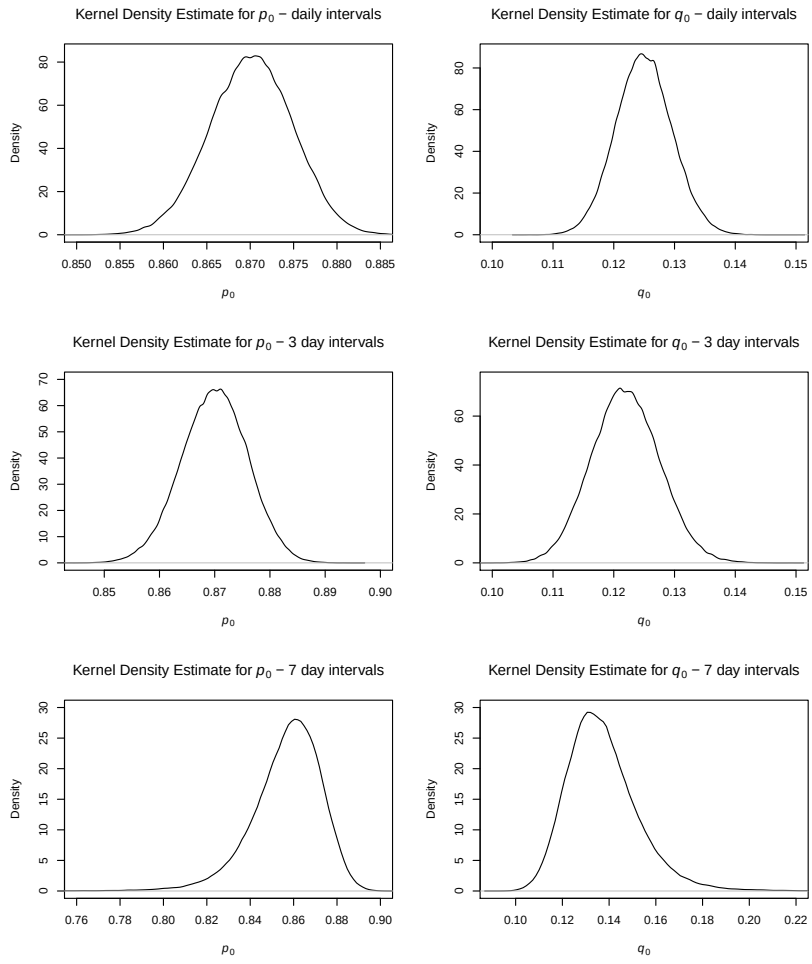


Figure 2.2: Kernel density plots for p_0 and q_0 from the simulated data and for simulated 1-day, 3-day and 7-day transition intervals without antimicrobial treatment. The true values are $p_0 = 0.8697$ and $q_0 = 0.1283$.

and

$$\hat{q}_0 = \frac{X_{CN}}{n_C}. \tag{2.7.3}$$

Now for the χ^2 statistic we need to calculate

$$\chi^2 = \frac{(X_{NN} - e_{NN})^2}{e_{NN}} + \frac{(X_{NC} - e_{NC})^2}{e_{NC}} + \frac{(X_{CN} - e_{CN})^2}{e_{CN}} + \frac{(X_{CC} - e_{CC})^2}{e_{CC}}, \tag{2.7.4}$$

where e_{NN}, e_{CN}, e_{NC} and e_{CC} are the expected transitions.

However, $e_{NN} = \hat{p}_0 n_N = \frac{X_{NN}}{n_N} n_N = X_{NN}$ and similarly we can show that $e_{NC} = X_{NC}$, $e_{CN} = X_{CN}$ and $e_{CC} = X_{CC}$. So (2.7.4) becomes

$$\chi^2 = \frac{(X_{NN} - X_{NN})^2}{X_{NN}} + \frac{(X_{NC} - X_{NC})^2}{X_{NC}} + \frac{(X_{CN} - X_{CN})^2}{X_{CN}} + \frac{(X_{CC} - X_{CC})^2}{X_{CC}} = 0.$$

For k-day intervals, where $k \geq 2$, the likelihood becomes too complicated to be maximised in a general way. The following example shows that the chi-squared statistic cannot be zero in all cases.

Example

Let us assume that we have the following summary matrix for the 2-day between test intervals,

$$\begin{pmatrix} X_{NN} & X_{NC} \\ X_{CN} & X_{CC} \end{pmatrix} = \begin{pmatrix} 1 & 9 \\ 9 & 1 \end{pmatrix}. \tag{2.7.5}$$

Also assume that $X_{NN} + X_{NC} = n_N = 10$ and $X_{CN} + X_{CC} = n_C = 10$.

The transition matrix for the 2-day intervals in general is

$$\begin{pmatrix} p_0 & 1-p_0 \\ q_0 & 1-q_0 \end{pmatrix} \cdot \begin{pmatrix} p_0 & 1-p_0 \\ q_0 & 1-q_0 \end{pmatrix} = \begin{pmatrix} p_0^2 + q_0(1-p_0) & (1-p_0)(1-q_0+p_0) \\ p_0 q_0 + q_0(1-q_0+p_0) & q_0(1-p_0) + (1-q_0)^2 \end{pmatrix}. \tag{2.7.6}$$

Let $\hat{p}_0$ and $\hat{q}_0$ be the model's ML estimates for the 1-day intervals. In order to

have $\chi^2 = 0$ we need for example for the first cell of matrix (2.7.6), to have a similar form as in (2.7.2), i.e.

$$\hat{p}_0^2 + \hat{q}_0(1 - \hat{p}_0) = \frac{X_{NN}}{n_N} = \frac{1}{10}. \tag{2.7.7}$$

However, maximising the likelihood for the matrix (2.7.5) we find that $\hat{p}_0 = \hat{q}_0 \approx 0.5$. So

$$\hat{p}_0^2 + \hat{q}_0(1 - \hat{p}_0) \approx \frac{1}{2} \neq \frac{1}{10}.$$

So the chi-squared statistic cannot generally be zero for test intervals of more than one day.

We also assessed the model fit using simulations. Table 2.5 shows the equal-tailed 95% quantiles. The same table contains the observed counts for each day interval and transition. We can see that the model fits very well for every day interval, as all the observed counts lie in the equal-tailed 95% quantiles and that the model fit agrees with the fit using chi-squared goodness-of-fit test.

	Day Intervals		
	1	**3**	**7**
obs. counts $N \to N$	**4250** (4065, 4569)	**1165** (1077, 1263)	**395** (349, 440)
obs. counts $N \to C$	**657** (615, 682)	**491** (470, 519)	**312** (297, 333)
obs. counts $C \to N$	**658** (615, 683)	**502** (475, 531)	**292** (276, 330)
obs. counts $C \to C$	**4398** (4126, 4623)	**1158** (1093, 1268)	**393** (359, 451)

Table 2.5: Model fit for the model using simulated data with 1-day, 3-day and 7-day interval transitions. The intervals in red color show that the equal-tailed 95% quantiles include the number of the observed transition counts.

2.7.2 Using the day intervals from the p-MRSA Data Set

Next we derive the parameter estimates for the simulated data using the between-test intervals from the p-MRSA Data Set. So now we do not use a sequence of fixed day-intervals between the tests but the sequence of day-intervals found in the p-MRSA Data Set where tests are taken in irregular day-intervals. Table 2.6 shows the results of MLEs, the summary statistics of the posterior density,

and the posterior correlation between p_0 and q_0 . Figure 2.3 shows the marginal posterior density estimates from the MCMC output while from the scatterplot in Figure 2.4 we can see that p_0 and q_0 are highly correlated.

The reason why mean numbers of the posterior distributions of the model's parameters are different from the MLE values is that the posterior distribution might be left skewed or right skewed. This will have an effect on the mean making it smaller or bigger than the mode of the distribution.

Finally, Table 2.7 shows the results of the related chi-squared goodness-of-fit test. It can be seen that the model fits quite well using the critical value $\chi^2_2 = 13.82$ at the 0.001 significance level. The sum is $\sum_{i=1}^{7} \chi^2_{2\,(i)} = 10.8912$ which means that the model fits well using the critical value $\chi^2_{14} = 36.12$ at the 0.001 significance level. Table 2.8 present the results for the model fit using simulations. The model also fits very well for this case.

no antimicrobial treatment		
parameters	**MLE (st. error)**	**E** $[\cdot \mid \mathcal{S}]$ **(s.d.)**
$\mathbf{p_0}$	0.8542 (0.0148)	0.8716 (0.0134)
$\mathbf{q_0}$	0.1366 (0.0139)	0.1412 (0.0147)
$\mathbf{p_0}$**,** $\mathbf{q_0}$ **posterior correlation**	-0.7806	

Table 2.6: MLEs, summary statistics for p_0 and q_0 and posterior correlation between p_0 and q_0 using the simulated transitions and the day intervals from the p-MRSA Data Set without antimicrobial treatment. The true values are $p_0 = 0.8697$ and $q_0 = 0.1283$.

Goodness of fit							
	Day Intervals						
	1	**2**	**3**	**4**	**5**	**6**	**7**
χ^2_2	0.1166	0.0105	1.8898	0.1228	3.5211	3.6979	1.5325

Table 2.7: Chi-squared statistic for the simulated transitions using the day intervals from the p-MRSA Data Set assuming no antimicrobial treatment.

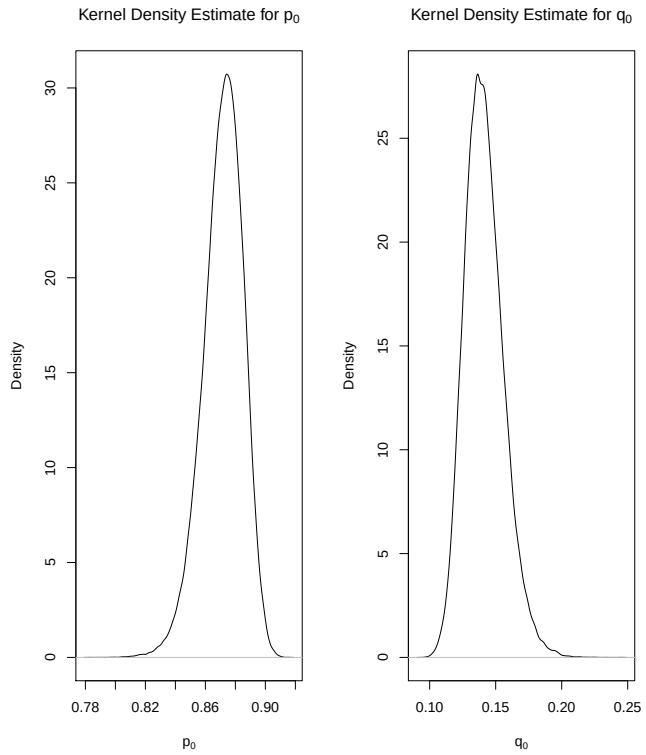


Figure 2.3: Kernel density plots for p_0 and q_0 for the simulated transitions using the day intervals from the p-MRSA Data Set without antimicrobial treatment. The true values are $p_0 = 0.8697$ and $q_0 = 0.1283$.

	Day Intervals						
	1	**2**	**3**	**4**	**5**	**6**	**7**
obs. counts	**23**	**31**	**14**	**22**	**19**	**29**	**190**
$N \to N$	(16, 25)	(22, 32)	(9, 17)	(14, 24)	(13, 23)	(21, 34)	(168, 204)
obs. counts	**0**	**3**	**5**	**7**	**10**	**20**	**124**
$N \to C$	(0, 6)	(2, 12)	(2, 10)	(5, 15)	(6, 16)	(15, 28)	(122, 160)
obs. counts	**1**	**4**	**9**	**11**	**9**	**18**	**126**
$C \to N$	(0, 6)	(2, 10)	(5, 14)	(6, 16)	(7, 17)	(17, 32)	(112, 144)
obs. counts	**19**	**23**	**23**	**20**	**23**	**40**	**168**
$C \to C$	(13, 21)	(16, 25)	(18, 27)	(15, 25)	(14, 25)	(26, 41)	(150, 181)

Table 2.8: Model fit for the model using simulated data but with the day intervals from the p-MRSA Data Set. The intervals in red color show that the equal-tailed 95% quantiles include the number of the observed transition counts.

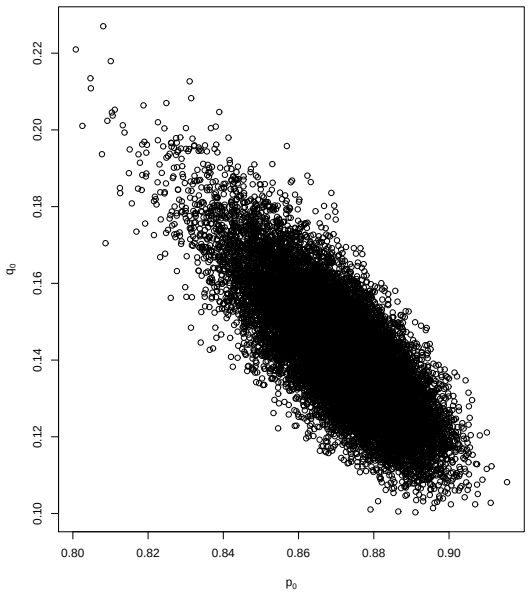


Figure 2.4: Scatterplot showing the correlation between p_0 and q_0 for the simulated transitions using the day intervals from the p-MRSA Data Set without antimicrobial treatment.

2.8 Results using GSTT Data

In this section we fit the model described in Section 2.3 to the GSTT data. Since we are interested in patient test transitions, only those patients who had at least two swab tests were included. The summary statistics for the three data sets are given in Tables 2.9 and 2.10.

We initially find the estimates for p_0 and q_0 from the p-MRSA Data Set ignoring information about the antimicrobial treatment. Then, we fit the model considering all antimicrobial different treatments that were used as one group. Due to model fit inadequacy in some cases, we will make the following different assumptions in order to achieve a better fit.

Firstly, we will use the data excluding information before each patient's first positive test and considering again all antimicrobial different treatments that were used as one group. The reason we do this is that throughout this chapter we do not consider any patient-to-patient MRSA transmission. However, we notice that some of the patients become colonised after staying for some time in the ICU ward. Take for example a patient with tests $-$, $+$, $+$. The $- \to +$ transition is (under the assumption of perfect sensitivity and specificity) due to

Statistic	p-MRSA	p-Wounds	p-Respiratory
number of patients	382	304	185
average stay/patient (days)	24.633	29.601	34.535
median stay/patient (days)	17	21	26
average no. of tests/patient	4.026	7.641	4.075
no. of tests	1538	2323	754
no. of positive tests	747	689	363
proportion of positive tests	0.485	0.296	0.481
days of study	1574	1566	1547
total no. of days in ICU	9410	9090	6389
total no. of days antimicrobials prescribed	6878	6622	4751

Table 2.9: Summary statistics for the p-MRSA, p-Wounds and p-Respiratory Data Sets for patients who were included in the analysis.

colonisation. We assume that the probability of colonisation is independent of other patient colonisation states. However, this might be unrealistic, so if we ignore the $- \rightarrow +$ transition, we try to minimise the impact of this assumption.

Secondly, we will take Chlorhexidine, Linezolid and Vancomycin as one group because Chlorhexidine was used for the antiseptic treatment during the decolonisation period and has been used before for this purpose, [Batra et al., 2010; Kypraios et al., 2010], and Linezolid and Vancomycin are considered as an effective treatment for MRSA, [Stevens et al., 2002; Weigelt et al., 2004]).

Thirdly, we will consider each antimicrobial treatment separately and we will also present the results using the MRSA Data Sets that includes all patients initially without antimicrobial treatment and then including the antiseptic treatment.

Finally, we will also find the parameter estimates for each antimicrobial treatment for the p-Wounds Data Set and the p-Respiratory Data Set as well as for the data that start from the patients first positive test. In each case we will perform simulated goodness-of-fit tests to assess the model fit as described in section 2.6.2.

Antimicrobial	p-MRSA	p-Wounds	p-Respiratory
Aminoglycoside	1048	1035	719
Antiseptic	3564	3711	2393
Cephalosporin	1175	965	649
Glycopeptide	2745	2635	1910
Macrolide	1188	1055	847
Nitroimidazole	1020	910	590
Oxazolidinone	116	129	82
Penicillin	577	606	333
Polymyxin	161	173	125
Quinolone	511	374	407
Rifamycin	126	80	98

Table 2.10: Number of days each antimicrobial group was prescribed for the p-MRSA, p-Wounds and p-Respiratory Data Sets for patients who were included in the analysis.

2.8.1 p-MRSA Data Set

For the analysis of the p-MRSA Data Set, 382 patients were considered whose summary statistics are shown in Tables 2.9 and 2.10.

Results excluding antimicrobial treatment

We fitted the model assuming that there was no information about antimicrobial treatment. The results using MLE, the summary statistics of the posterior distributions and the posterior correlation between p_0 and q_0 are given in Table 2.11. The density plots in Figure 2.5 show the results from MCMC.

no antimicrobial treatment		
parameters	MLE (st. error)	$E[\cdot \mid \mathcal{S}]$ (s.d.)
$\mathbf{p_0}$	0.8697 (0.0147)	0.8537 (0.0403)
$\mathbf{q_0}$	0.1284 (0.0158)	0.1455 (0.0426)
$\mathbf{p_0}$, $\mathbf{q_0}$ **posterior correlation**	-0.9702	

Table 2.11: MLEs, summary statistics for parameters p_0 and q_0 and posterior correlation between p_0 and q_0 for the p-MRSA Data Set ignoring antimicrobial treatment.

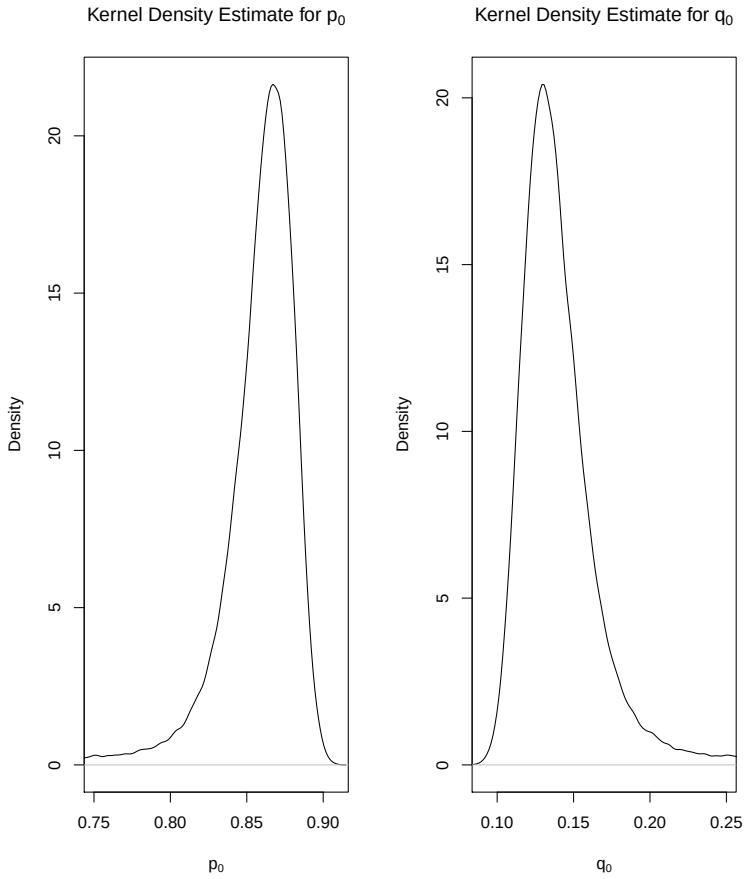


Figure 2.5: Kernel density plots for p_0 and q_0 from the p-MRSA Data Set assuming no antimicrobial treatment.

We perform the chi-squared goodness-of-fit test using the p-MRSA Data Set using the transitions of one day, two days, three days etc. up to one week day intervals. The results are displayed in Table 2.12. We can see that the model does not fit very well as some of the values of χ^2_2 are much bigger than the critical value $\chi^2_2 = 13.82$ at the 0.001 significance level. The sum of $\chi^2_{2\,(i)}$, $i = 1, ...7$, $\sum_{i=1}^{7} \chi^2_{2\,(i)} = 102.6351$ also shows that the model does not fit well using the critical value $\chi^2_{14} = 36.12$ at the 0.001 significance level. Table 2.13 presents the results from the simulations. It can be seen that the results are in agreement with the results from the chi-squared goodness-of-fit tests. A plausible reason for this is that the model is too simplistic, ignoring antimicrobial use.

Goodness of fit							
	Day Intervals						
	1	**2**	**3**	**4**	**5**	**6**	**7**
χ^2_2	35.6432	6.4387	5.9308	13.677	0.9297	2.5234	37.4817

Table 2.12: Chi-squared statistic for the model using the p-MRSA Data Set ignoring antimicrobial treatment.

Day Intervals							
	1	**2**	**3**	**4**	**5**	**6**	**7**
obs. counts $N \to N$	**17** (19, 16)	**19** (18, 28)	**19** (18, 29)	**8** (12, 22)	**17** (13, 24)	**31** (26, 40)	**243** (189, 228)
obs. counts $N \to C$	**10** (1, 8)	**11** (2, 12)	**15** (5, 15)	**18** (5, 15)	**14** (7, 17)	**26** (17, 31)	**132** (146, 186)
obs. counts $C \to N$	**8** (0, 4)	**11** (3, 12)	**8** (2, 9)	**12** (6, 17)	**10** (6, 17)	**26** (14, 28)	**72** (95, 126)
obs. counts $C \to C$	**7** (10, 15)	**20** (19, 28)	**9** (8, 15)	**21** (16, 27)	**20** (13, 24)	**24** (22, 36)	**185** (130, 161)

Table 2.13: Model fit for the model of the p-MRSA Data Set without antimicrobial treatment. The intervals in red color show that the equal-tailed 95% quantiles include the number of the observed transition counts.

Including antimicrobial treatment

We also obtain estimates from the model including the information about antimicrobial treatment. The results from the MLEs and the summary statistics of the posterior distributions are given in Table 2.14. The posterior correlations between p_0, q_0, α and β are shown in Figure 2.6. It can be seen that all the parameters are highly correlated. Figure 2.7 shows the posterior density plots of $p_0 + \alpha$ and $q_0 + \beta$ which are the probabilities that a patient remains in a non-colonised state and goes from a colonised state to a non-colonised state respectively when they are "on" antimicrobial treatment, along with the density plots of p_0 and q_0 which are the same probabilities but when patients are "off" antimicrobial treatment. In broad terms, it appears that there is some effect on the transition matrix from receiving antimicrobials.

Table 2.15 shows the equal-tailed 95% quantiles from the model fit simulations. In the same table there are also the observed counts for each day interval and transition. We can see that the model does not fit very well as many of the observed counts are outside the equal-tailed 95% quantiles.

A reason for this is that the model including antimicrobial treatment is probably

still not detailed enough to give a good fit to the data. After the classification of the antimicrobials, it is possible to get better answers since each antimicrobial's contribution to the model is different.

Antimicrobial treatment		
parameters	MLE (st. error)	$E[\cdot \mid \mathcal{S}]$ (s.d.)
$\mathbf{p_0}$	0.7142 (0.0743)	0.6893 (0.1373)
$\mathbf{q_0}$	0.2416 (0.0669)	0.2721 (0.1266)
$\boldsymbol{\alpha}$	0.1825 (0.0759)	0.1591 (0.1104)
$\boldsymbol{\beta}$	−0.1313 (0.0682)	−0.1109 (0.0971)

Table 2.14: MLEs and summary statistics for p_0, q_0, α and β using the p-MRSA Data Set including antimicrobial treatment.

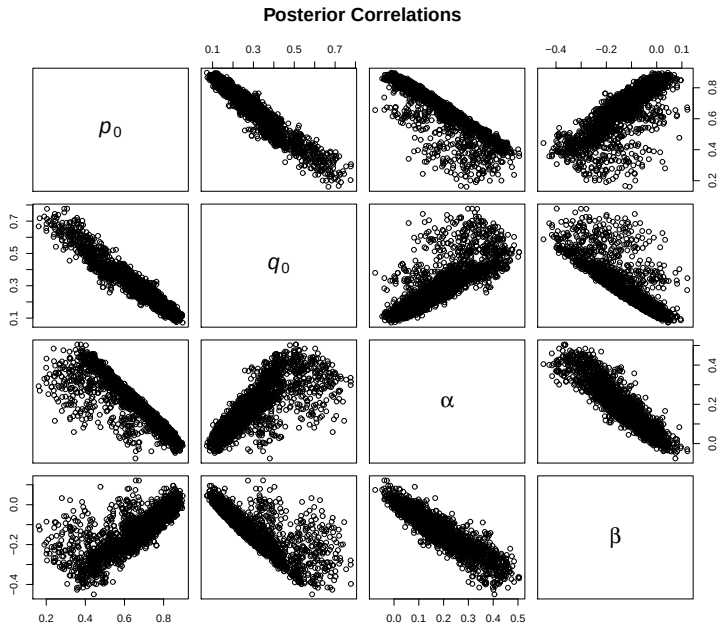


Figure 2.6: Posterior correlations between p_0, q_0, α and β using the p-MRSA Data Set including antimicrobial treatment.

	Day Intervals						
	1	**2**	**3**	**4**	**5**	**6**	**7**
obs. counts	**17**	**19**	**19**	**8**	**17**	**31**	**243**
$N \to N$	(17, 25)	(16, 25)	(16, 25)	(10, 20)	(12, 23)	(23, 38)	(178, 216)
obs. counts	**10**	**11**	**15**	**18**	**14**	**26**	**132**
$N \to C$	(2, 10)	(4, 14)	(8, 18)	(6, 15)	(8, 18)	(19, 33)	(159, 196)
obs. counts	**8**	**11**	**8**	**12**	**10**	**26**	**72**
$C \to N$	(1, 6)	(4, 14)	(3, 10)	(9, 19)	(8, 18)	(16, 30)	(106, 138)
obs. counts	**7**	**20**	**9**	**21**	**20**	**24**	**185**
$C \to C$	(9, 14)	(16, 27)	(7, 14)	(14, 24)	(12, 22)	(19, 34)	(118, 151)

Table 2.15: Model fit for the model using the p-MRSA Data Set including antimicrobial treatment. The intervals in red color show that the equal-tailed 95% quantiles include the number of the observed transition counts.

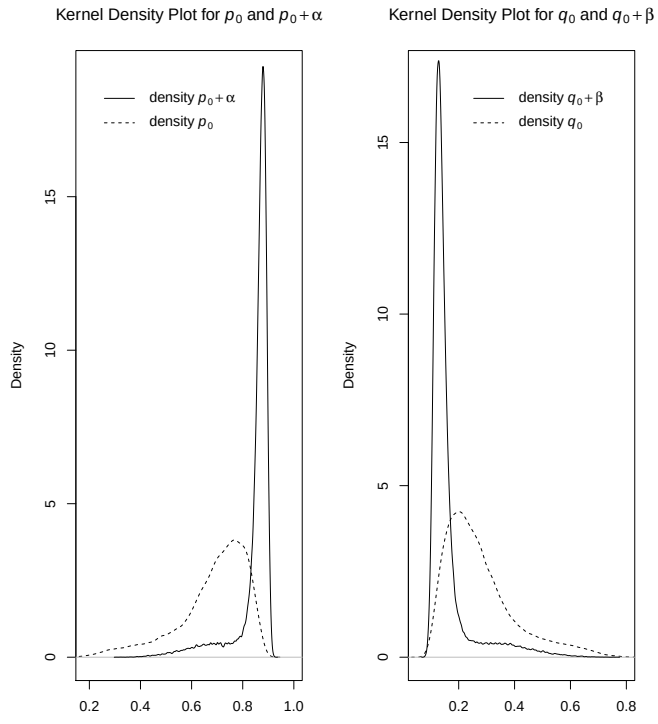


Figure 2.7: Kernel density plots for p_0 and $p_0 + \alpha$, q_0 and $q_0 + \beta$ for the p-MRSA Data Set including antimicrobial treatment.

Starting from first positive test

Here we obtain the parameter estimates from the model including antimicrobial treatment starting from the date that a patient was first found colonised. The reason is that in this chapter we only look at the MRSA carriage levels on each patient separately. We do not take into account that there is MRSA transmission between the patients which is unrealistic in some sense. So, starting from a patient's first positive test is one way to overcome this restriction.

The number of patients with at least one transition was 290. The results from the MLEs and the MCMC are given in Table 2.16. The density plots of $p_0 + \alpha$ and $q_0 + \beta$ along with the density plots of p_0 and q_0 are given in Figure 2.8.

The results of the equal-tailed 95% quantiles of the simulations for the model fit are given in Table 2.17 along with the transition counts from the observed data. We can see that the model does not fit well as some of the observed transitions counts are again outside the equal-tailed 95% intervals.

starting from first positive test		
parameters	MLE (st. error)	$E[\cdot \mid \mathcal{S}]$ (s.d.)
p_0	0.8823 (0.0378)	0.8685 (0.0496)
q_0	0.0877 (0.0206)	0.1113 (0.0301)
α	0.0791 (0.0393)	0.0892 (0.0506)
β	0.0003 (0.0223)	−0.0240 (0.0313)

Table 2.16: MLEs and summary statistics for p_0, q_0, α and β using the p-MRSA Data Set including antimicrobial treatment and starting from patients' first positive test.

	Day Intervals						
	1	**2**	**3**	**4**	**5**	**6**	**7**
obs. counts $N \to N$	**3** (3, 4)	**2** (1, 2)	**1** (1, 2)	**1** (0, 1)	**2** (1, 3)	**12** (9, 16)	**134** (117, 139)
obs. counts $N \to C$	**1** (0, 1)	**0** (0, 1)	**1** (0, 1)	**0** (0, 1)	**1** (0, 2)	**5** (1, 8)	**37** (32, 54)
obs. counts $C \to N$	**8** (0, 4)	**11** (2, 10)	**8** (1, 7)	**12** (5, 15)	**10** (5, 15)	**26** (13, 25)	**72** (90, 122)
obs. counts $C \to C$	**7** (11, 15)	**20** (21, 29)	**9** (10, 16)	**21** (18, 28)	**20** (14, 25)	**24** (25, 37)	**185** (135, 166)

Table 2.17: Model fit for the model using the p-MRSA Data Set including antimicrobial treatment and starting from patients' first positive test. The intervals in red indicate that the observed transition counts are included in the equal-tailed 95% quantiles.

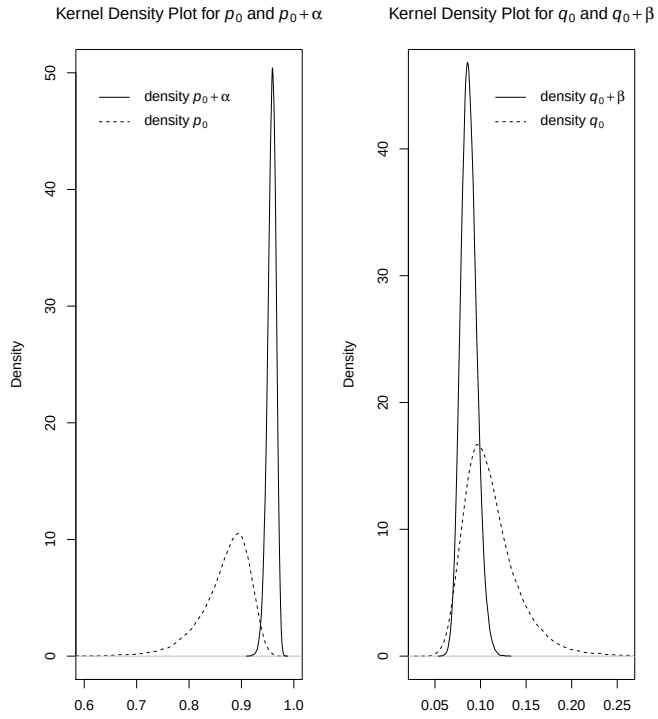


Figure 2.8: Kernel density plots for p_0 and $p_0 + \alpha$, q_0 and $q_0 + \beta$ for the p-MRSA Data Set including antimicrobial treatment and starting from patients' first positive test.

Classification of the antimicrobial treatment

So far, we have considered the antimicrobial treatment as a whole. However, only a few antimicrobials were actually MRSA-targeting. These include Chlorhexidine, which is an antiseptic and was mostly used during the decolonisation period. Other antimicrobials were Vancomycin and Linezolid which are known to be MRSA targeting (Section 1.2.1). The MLEs and the MCMC results considering Chlorhexidine, Linezolid and Vancomycin as one group, are given in table 2.18. Figure 2.9 shows the posterior density plots of $p_0 + \alpha$ and $q_0 + \beta$ along with the density plots of p_0 and q_0. Comparing this plot with the one in Figure 2.7, we can see that MRSA targeting antimicrobial treatment may have an effect in clearing MRSA carriage.

The results from the equal-tailed 95% quantiles from the simulations for the model fit are shown in Table 2.19. Again, we can see that the model fit is not adequate.

MRSA targeting antimicrobials		
parameters	MLE (st. error)	$E[\cdot \mid \mathcal{S}]$ (s.d.)
p_0	0.8560 (0.0218)	0.8167 (0.0624)
q_0	0.1010 (0.0206)	0.1375 (0.0576)
α	0.037 (0.0292)	0.0460 (0.0691)
β	0.0347 (0.0292)	0.0344 (0.0797)

Table 2.18: MLEs and summary statistics for p_0, q_0, α and β using the MRSA targeting antimicrobials from p-MRSA Data Set.

Day Intervals							
	1	**2**	**3**	**4**	**5**	**6**	**7**
obs. counts $N \to N$	**17** (19, 26)	**19** (17, 26)	**19** (17, 27)	**8** (10, 19)	**17** (12, 22)	**31** (24, 38)	**243** (180, 218)
obs. counts $N \to C$	**10** (1, 8)	**11** (3, 13)	**15** (6, 17)	**18** (6, 16)	**14** (9, 19)	**26** (19, 33)	**132** (157, 194)
obs. counts $C \to N$	**8** (0, 6)	**11** (3, 13)	**8** (2, 10)	**12** (8, 18)	**10** (7, 17)	**26** (16, 28)	**72** (105, 136)
obs. counts $C \to C$	**7** (9, 15)	**20** (18, 28)	**9** (7, 15)	**21** (15, 25)	**20** (12, 23)	**24** (21, 34)	**185** (120, 151)

Table 2.19: Model Fit for the model using MRSA targeting antimicrobials of the p-MRSA Data Set. The intervals in red indicate that the observed transition counts are included in the equal-tailed 95% quantiles.

Considering each antimicrobial separately

In this section we are presenting only the MCMC results. The reason is that for some of the antimicrobials we were not able to get estimates via MLE due to the fact that the likelihood is very flat, causing numerical problems for the optimisation methods.

It is known that some of the antimicrobials are more effective than others in treating MRSA. For this reason we fit the model to data which consist of one antimicrobial treatment only . This means that for each group we assume that a patient is "on" a antimicrobial treatment the day they take this particular antimicrobial, otherwise they are considered "off" antimicrobial treatment meaning that they are not receiving any antimicrobial treatment.

Tables A.1, A.2 and Figures A.1, A.2 show the results from the MCMC for the parameters for each antimicrobial group when all patients' tests are included. It can be seen that patients on Oxazolidinone and Penicillin are more likely to be protected against MRSA carriage. Moreover, patients on Oxazolidinone, Rifamycin and Polymyxin have a higher probability to be cleared while Macrolide

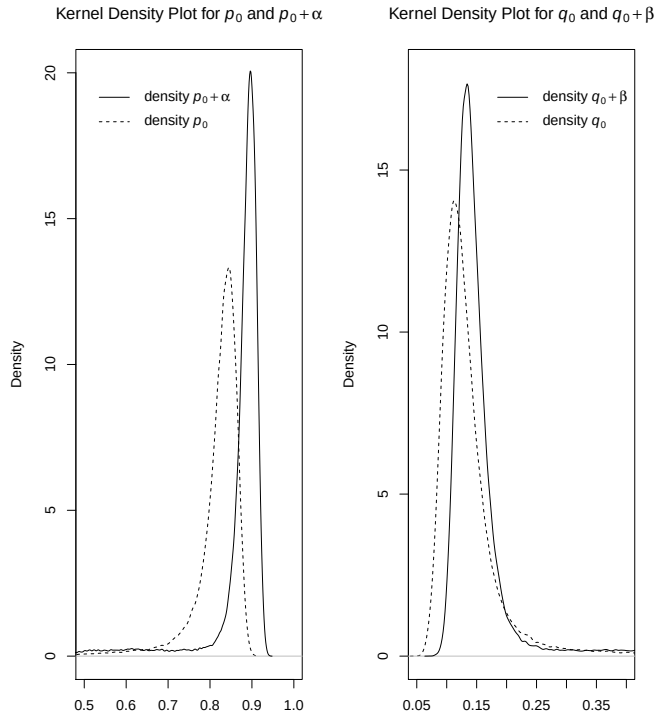


Figure 2.9: Kernel density plots for p_0 and $p_0 + \alpha$, q_0 and $q_0 + \beta$ for the MRSA targeting antimicrobials from p-MRSA Data Set.

has a smaller probability to protect a patient against MRSA. It is also noted that decolonisation treatment using Chlorhexidine (Antiseptic) seems to be effective.

The results of the equal-tailed 95% quantiles from the simulations for the model fit are shown on Table A.3. The equal-tailed 95% quantiles for each antimicrobial group are compared with the number of observed counts for each day interval and each transition . It can be seen that the model does not fit very well as some of the equal-tailed 95% intervals do not include the observed transition counts.

Next, we obtained the parameter estimates for all antimicrobial groups starting from the date that a patient was first found colonised. Tables A.5, A.6 and Figures A.3, A.4 show the results from the MCMC for the parameters p_0, q_0, α and β for each antimicrobial group. The results show that patients on Aminoglycoside, Penicillin, Glycopeptide and Nitroimidazole can prevent against colonisation. On the other hand, colonised patients on Oxazolidinone are more likely to become non-colonised while Quinolone has the opposite effect.

The equal-tailed 95% quantiles from the simulations for the model fit in Table A.7 show that there has been some improvement but again some of the observed transitions counts are outside the equal-tailed 95% intervals.

2.8.2 Results from the MRSA Data Set without antimicrobial treatment

In this section we present the results from the MRSA Data Set, as presented in Section 1.3, without taking into account any of the antimicrobial treatment. Table 2.20 shows the summary statistics of the posterior density for parameters p_0 and q_0. Figures 2.10 and 2.11 present the density plots and the posterior correlation between parameters p_0 and q_0. It can be seen that p_0 has a larger value for this data set compared to the p-MRSA Data Set, This is reasonable considering that in the MRSA Data Set there are a lot more non-colonised to non-colonised transitions, since there are a lot more negative tests in this data set. We also notice that p_0 and q_0 are moderately correlated comparing to the strong correlation between them on the p-MRSA Data Set. The reason for this difference is that p-MRSA Data Set contains only patients with at least one positive test which causes more dependencies in the data.

Table 2.21 shows the results of the related chi-squared goodness-of-fit test. It can be seen that the model does not fit well using the critical value $\chi^2_2 = 13.82$ at the 0.001 significance level. The sum $\sum_{i=1}^{7} \chi^2_{2\,(i)} = 357.5058$ also shows that the model does not fit well using the critical value $\chi^2_{14} = 36.12$ at the 0.001 significance level.

no antimicrobial treatment	
parameters	$E[\cdot \mid \mathcal{S}]$ (s.d.)
p_0	0.9853 (0.0009)
q_0	0.0750 (0.0055)
p_0, q_0 **posterior correlation**	-0.3034

Table 2.20: Summary statistics for p_0 and q_0 using the MRSA Data Set without antimicrobial treatment.

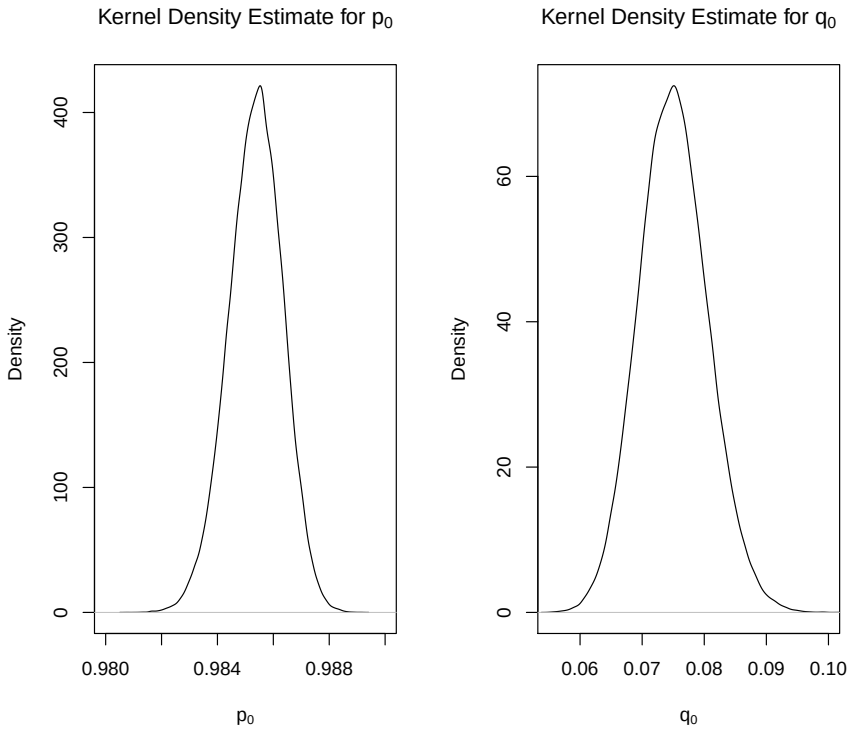


Figure 2.10: Kernel density plots for p_0 and q_0 using the MRSA Data Set without antimicrobial treatment.

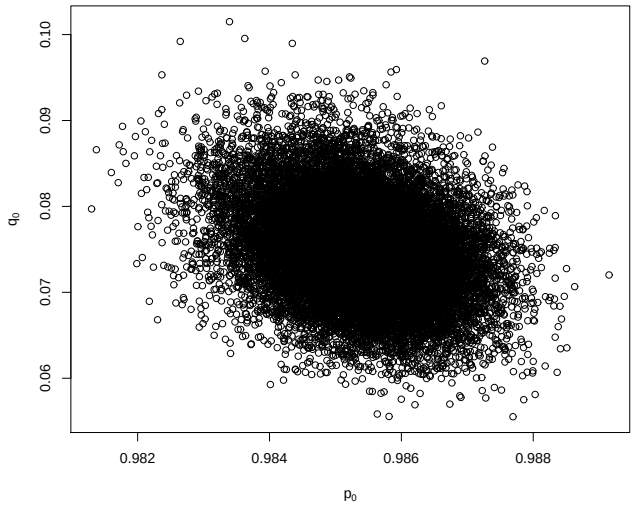


Figure 2.11: Scatterplot presenting the posterior correlation between p_0 and q_0 using the MRSA Data Set without antimicrobial treatment.

Goodness of fit							
	Day Intervals						
	1	**2**	**3**	**4**	**5**	**6**	**7**
χ^2_2	182.1831	85.5282	33.1261	23.6780	5.0990	5.4498	22.4416

Table 2.21: Chi-squared statistic for the model using the MRSA Data Set without antimicrobial treatment.

2.8.3 Results from the MRSA Data Set including the antiseptic treatment

We also derive the parameter estimates for the MRSA Data Set including the antiseptic treatment. Table 2.22 shows the summary statistics of the posterior densities for the parameters p_0, q_0, α and β, while Figures 2.12 and 2.13 show the density plots of $p_0 + \alpha$ and $q_0 + \beta$ and posterior correlations between the model parameters respectively. It can be seen that the antimicrobial treatment seems to have an effect both on clearing and protecting against MRSA colonisation comparing to the relevant results from the p-MRSA Data Set. We also notice that parameters are correlated but not as much as in the p-MRSA data set.

Finally, Table 2.23 shows the results of the model assessment. We can see that the model does not fit well as some of the observed counts are outside the equal-tailed 95% quantiles.

Antiseptic		
parameters	$E[\cdot \mid \mathcal{S}]$ (s.d.)	95% CI
p_0	0.9801 (0.0014)	(0.0977, 0.9830)
q_0	0.0565 (0.0064)	(0.0445, 0.0696)
α	0.0112 (0.0019)	(0.0074, 0.0151)
β	0.0499 (0.0132)	(0.0247, 0.0769)

Table 2.22: Summary statistics for p_0, q_0, α and β using the MRSA Data Set including antiseptic treatment.

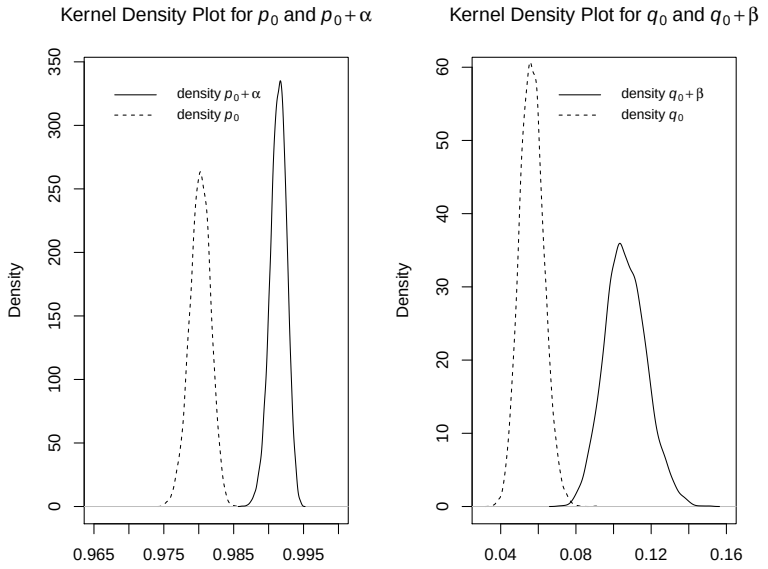


Figure 2.12: Kernel density plots for p_0 and $p_0 + \alpha$, q_0 and $q_0 + \beta$ using the MRSA Data Set including antiseptic treatment.

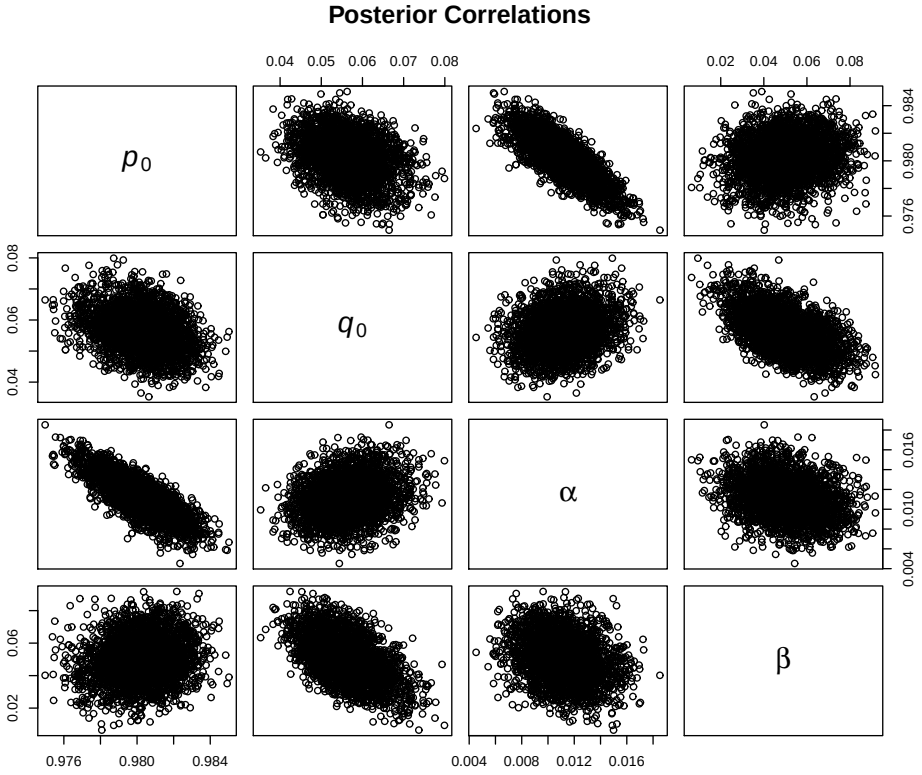


Figure 2.13: Scatterplot illustrating correlations between p_0, q_0 , α and β for the MRSA Data Set including antiseptic treatment.

	Day Intervals						
	1	**2**	**3**	**4**	**5**	**6**	**7**
obs. counts $N \to N$	**155** (159, 165)	**298** (294, 305)	**301** (295, 309)	**242** (239, 253)	**228** (218, 233)	**357** (346, 365)	**1643** (1615, 1659)
obs. counts $N \to C$	**10** (0, 6)	**11** (4, 15)	**15** (6, 21)	**18** (6, 21)	**14** (9, 24)	**26** (17, 36)	**132** (115, 159)
obs. counts $C \to N$	**8** (0, 3)	**11** (1, 8)	**8** (1, 7)	**12** (3, 13)	**10** (4, 14)	**26** (11, 26)	**72** (88, 119)
obs. counts $C \to C$	**7** (12, 15)	**20** (23, 30)	**9** (10, 16)	**21** (19, 29)	**20** (16, 25)	**24** (24, 38)	**185** (137, 168)

Table 2.23: Model fit for the model using the MRSA Data Set including the antiseptic treatment. The intervals in red indicate that the observed transition counts are included in the equal-tailed 95% quantiles.

2.8.4 p-Wounds Data Set

In this section we present the results coming from the p-Wounds Data Set. Initially we look at the whole data set, and then only starting from the first positive test.

Tables A.8, A.9 and Figures A.5, A.6 show the parameters estimates from the p-Wounds Data Set. We can see that Oxazolidinone has the greatest effect in preventing a non-colonised patient from becoming colonised, followed by Penicillin and Polymyxin. Moreover, it can be seen that Macrolide, Rifamycin, Aminoglycoside and Oxazolidinone have higher probability to clear detectable MRSA carriage.

The results from the simulations to check the model fit are shown in Table A.10. We can see that the model does not fit well as again some of the observed transition counts are outside the equal-tailed 95% quantiles.

The parameter estimates for the p-Wounds Data Set starting from patients' first positive test are shown in Tables A.11, A.12 and Figures A.7, A.8. The number of patients with at least two tests was 259. We notice that Oxazolidinone and Penicillin have the greatest effect in the prevention of MRSA carriage. In addition, Macrolide, Oxazolidinone, Rifamycin and Aminoglycoside are the most effective in the clearance of detectable MRSA carriage levels.

Table A.13 shows the equal-tailed 95% quantiles for the model fit simulations. It can be seen there has been some improvement to the model fit but still some of the observed transition counts are outside the equal-tailed 95% quantiles.

2.8.5 p-Respiratory Data Set

Here, we estimate the parameters p_0, q_0, α and β from the p-Respiratory Data Set.

The results are shown in Tables A.14, A.15 and Figures A.9, A.10. It can be seen that almost none of the antimicrobials have a great effect on the prevention of MRSA carriage. On the other hand, we can see that only colonised patients on Oxazolidinone, are more likely to become non-colonised.

Table A.16 shows the results from the model fit simulations. Again it is obvious that the model does not fit well.

Finally, Tables A.17, A.18 and Figures A.11, A.12 show the parameter estimates for the p-Respiratory Data Set starting from patients' first positive test. The number of patients included in the analysis was 135. We conclude that no antimicrobial group has any significant effect in protecting against colonisation. However, Oxazolidinone is again the most effective in the clearance of detectable MRSA carriage.

The equal-tailed 95% quantiles from the model fit simulations on Table A.19 show that the model fits very well.

2.9 Summary

In this chapter we investigated the effects of the antimicrobial treatment on MRSA carriage. A discrete time Markov chain model was used for the modelling of the colonisation status of individual patients. We also assumed that the colonisation status of each patient does not depend on the status of other patients and that the swab test is perfectly accurate. Finally, we showed that decolonisation treatment was effective in most of the cases in clearing MRSA carriage.

We used two different methods to find the estimates for the model parameters, MLE and MCMC algorithm. We found that the results using these two methods are in agreement, but in some cases MLE failed to produce any results probably because of the limited information we had for some of the antimicrobial groups. The MCMC converges to valid parameter estimates since some

numerical issues with the MLEs were overcome by the MCMC approach. To assess how well the model fit the data, typical chi-squared test was used with 2 degrees of freedom for each day interval when no antimicrobial treatment was assumed. When antimicrobial treatment was present, a simulation based model fit was used.

For the method validation we initially used simulated data ignoring any information about the antimicrobial treatment. The results were in agreement using the two different methods and the model fit was very good. Similar answers derived when simulated data was used along with the day intervals taken from the p-MRSA Data Set.

When the GSTT data was used we found that antimicrobial treatment can have a preventing role against MRSA carriage but cannot help in its clearance. Similar results were obtained when only the data starting from each patient's first positive test were used. In both cases the proposed model did not fit well.

The results for each antimicrobial separately for the three different data sets showed that Oxazolidinone and Penicillin are significantly the most effective in protecting against colonisation in the p-Wounds Data Set. Oxazolidinone was also found to help in the clearance of MRSA carriage in both p-MRSA Data Set and p-Respiratory Data Set. We also found that in the p-MRSA Data Set, Nitroimidazole and Cephalosporin can clear MRSA carriage while Macrolide and Cephalosporin were found to have the opposite effect. The findings for Macrolide and Cephalosporin agree with the literature, [Dancer, 2001; Monnet et al., 2004; Tacconelli et al., 2008]. In the p-Wounds Data Set we found evidence that Macrolide has an effect in the clearance of MRSA carriage. In addition, decolonisation treatment appears to be effective only in the p-MRSA Data Set. However, we detected a poor model fit for all three data sets.

Results for the p-MRSA data set are also in agreement with the study in [Kypraios et al., 2011], where antiseptic treatment seemed to have an effect in reducing MRSA carriage levels. However, limited evidence was found that any antibiotic treatment has an effect. It was also found that Oxazolidinone has an effect on the clearance of MRSA carriage while Cephalosporin was found to increase non-colonised to colonised transitions.

In the case where the patients with no positive tests from the MRSA Data Set

were included, we found that when we ignored antimicrobial treatment the model fit was very poor as in the relevant p-MRSA Data Set case. When antiseptic treatment was included we also found that decolonisation was effective but the model fit was still poor.

When the data starting from first positive test were used for all the three different data sets, we found the same answers with the difference that in the p-MRSA Data Set along with Oxazolidinone, Rifamycin, Cephalosporin were found to be effective in the MRSA clearance. On the other hand, Quinolone was found to have the opposite results. The latter result is consistent with the findings in [Tacconelli et al., 2008], [Weber et al., 2003] and [Monnet et al., 2004]. For all the three Data Sets the model fit improved but again it was not acceptable apart from the p-Respiratory Data Set when only the tests starting from the first positive are considered.

Our results about the effectiveness of Oxazolidinone are in agreement with the literature, [Dennis et al., 2002; Itani et al., 2010]. Furthermore, results that antiseptic treatment can clear MRSA carriage are consistent with previous findings in [Batra et al., 2010], [Kypraios et al., 2010] and [Macfarlane et al., 2007].

Overall, there is some evidence that antibiotics have an effect against MRSA carriage. Antiseptic treatment was also found to be effective in some cases. However, in most cases the proposed model did not fit well. A possible explanation is that the assumption of perfect accuracy for the swab test might be flawed. In the next chapter we relax this assumption and look at the effect of antibiotics on MRSA carriage assuming imperfect swab test sensitivity.

CHAPTER 3

Modelling the effect of antimicrobial treatment on carriage levels of MRSA using hidden Markov models

3.1 Introduction

In this chapter as also in the previous one we are interested in the effects of antimicrobial treatment on MRSA carriage levels. In Chapter 2 we used a discrete time Markov model to describe the colonisation status of an individual patient on a daily basis assuming perfect swab test specificity and sensitivity. We obtained the results from the three data sets, p-MRSA Data Set, p-Wounds Data Set and p-Respiratory Data Set, that were also used in Chapter 2, using a Gaussian random walk Metropolis-Hastings algorithm in a Bayesian framework. However, we found that the model did not provide an entirely adequate fit to the data. A possible reason for this might be the assumption we made that swab test specificity and sensitivity are perfect.

In this chapter we will assume that the swab test has imperfect sensitivity while we will still consider perfect specificity. In other words, we make the assumption that some negative tests might actually be false-negatives while we consider positive tests as accurate. We are going to use a discrete-time hidden

Markov model (HMM) to explore the daily colonisation status of an individual and the outcomes of the swab tests.

A hidden Markov model is a Markov process $\{X_n : n \geq 0\}$ in which the states are unobserved (hidden). However, another stochastic process is observable, $\{Y_n : n \geq 0\}$, where $Y_n = Y_n(X_n)$. HMMs have been used in the literature before to describe disease progression considering screening measurement error. Satten and Longini in [Satten and Longini Jr, 1996] and Jackson et al. in [Jackson et al., 2003] used a HMM to study HIV and chronic diseases respectively via Maximum likelihood estimation methods. Moreover, Guihenneuc-Jouyaux et al. [Guihenneuc-Jouyaux et al., 2000] proposed a hierarchical model in a Bayesian framework to analyse a hidden Markov process with application to HIV progression with measurement error. The authors used MCMC methods to obtain the parameter estimates of interest, specifically using a Gibbs sampler. Parameter estimation of HMMs in a Bayesian framework is also discussed by Robert et al. in [Robert et al., 1993]. The authors use a Gibbs sampler to obtain the parameters estimates of a hidden Markov model.

Data Augmentation was introduced in 1987 by Tanner and Wong [Tanner and Wong, 1987] and is a way to augment the observed data so that it is easier to analyse by having more information about the data. This method was firstly used by Dempster et al. [Dempster et al., 1977] to handle missing data and solve maximum likelihood problems via the EM algorithm.

Here we will use data augmentation to deal with the unobserved states and estimate the model parameters. We are going to validate our methodology using simulated data and then apply it to the three data sets, p-MRSA Data Set, p-Wounds Data Set and p-Respiratory Data Set. Similarly to the previous chapter, we will use a subset of each of the three data sets that contains only the patients with at least one positive swab test. We then assess the model fit discussed in section 3.5.

Results show that Oxazolidinone can help in MRSA clearance in all three data Sets while Antiseptic treatment can protect against MRSA as well as reduce its carriage for the p-MRSA Data Set. On the other hand, we find that some antimicrobials such as the Macrolide or Cephalosporin do not offer any protection against MRSA colonisation. The model assessment shows that the model fit was not acceptable in some cases.

The chapter plan is the following. In Section 3.2 we introduce the model we are going to use. Section 3.3 describes the likelihood and Section 3.4 how we make the inference. Section 3.5 contains information about the model assessment and Section 3.6 presents the results from the simulations for the validation of our methods. The results from the three data sets are shown in Section 3.7 and finally Section 3.8 contains a summary of the all the methods and results discussed in the chapter.

3.2 Model

We will use the same basic Markov model for the evolution of patient carriage status introduced in Chapter 2. There, we made the assumption that swab tests results had perfect sensitivity and specificity. In this chapter we assume that sensitivity is imperfect but specificity is still 100%. More explicitly we consider that positive tests are observed correctly but some of the negative tests might be false negatives. We will use a discrete time hidden Markov model to model the colonisation status of an individual.

Consider the Markov process $\{X_n : n \geq 0\}$ as described in Chapter 2, section 2.3, with state space $\{C, N\}$ where n denotes the number of days patient has stayed in the ICU, C is the colonised state and N the non-colonised state. However, we do not observe this process but the process $\{Y_n : n \geq 0\}$, $Y_n \in \{C, N\}$. We assume that Y_n is related to X_n by the following relationship,

$$Y_n = \begin{cases} N & & & \text{if} \quad X_n = N \\ N & \text{w. p.} & (1-\phi) & \text{if} \quad X_n = C \\ C & \text{w. p.} & \phi & \end{cases}, \tag{3.2.1}$$

where ϕ is the swab test's sensitivity i.e. the probability that a colonised patient is observed as being colonised when tested.

Next, as in Chapter 2, we assume that $\Delta(n)$ denotes the antimicrobial state on day n, so $\Delta(n) \in \{ON, OFF\}$. We also assume that antimicrobial treatment acts immediately. The transition matrix for the Markov chain $\{X_n : n \geq 0\}$ is,

$$P_{\Delta(n-1)} = \begin{array}{c} \\ N \\ C \end{array} \begin{array}{c} \begin{array}{cc} N & C \end{array} \\ \begin{pmatrix} p_\Delta & 1-p_\Delta \\ q_\Delta & 1-q_\Delta \end{pmatrix} \end{array},$$

where

$$p_\Delta = Pr(X_n = N | X_{n-1} = N, \Delta\,(n-1) = \Delta),$$

$$q_\Delta = Pr(X_n = N | X_{n-1} = C, \Delta\,(n-1) = \Delta),$$

and

$$0 \leq p_\Delta = p_0 + \alpha \mathbb{1}_{\{\Delta = ON\}} \leq 1,$$

$$0 \leq q_\Delta = q_0 + \beta \mathbb{1}_{\{\Delta = ON\}} \leq 1.$$

Here $p_\Delta = p_0 + \alpha \mathbb{1}_{\{\Delta=ON\}}$ is the transition probability that a patient remains in a non-colonised state where $p_0 / p_0 + \alpha$ is the baseline probability when a patient is "off"/"on" antimicrobial treatment that day. Similarly, $q_\Delta = q_0 + \beta \mathbb{1}_{\{\Delta=ON\}}$ is the transition probability that a patient goes from a colonised state to a non-colonised state, where q_0 / $q_0 + \beta$ is the baseline probability when a patient is "off"/"on" antimicrobial treatment that day. So, when a patient is "off" antimicrobial treatment then the transition matrix is

$$P_{OFF} = \begin{array}{c} \\ N \\ C \end{array} \begin{array}{c} \begin{array}{cc} N & C \end{array} \\ \begin{pmatrix} p_0 & 1-p_0 \\ q_0 & 1-q_0 \end{pmatrix} \end{array},$$

and when a patient is "on" antimicrobial treatment the transition matrix becomes

$$P_{ON} = \begin{array}{c} \\ N \\ C \end{array} \begin{array}{c} \begin{array}{cc} N & C \end{array} \\ \begin{pmatrix} p_0 + \alpha & 1-p_0-\alpha \\ q_0 + \beta & 1-q_0-\beta \end{pmatrix} \end{array},$$

3.3 Likelihood

Consider patient i, $i = 1, ..., N_p$, where N_p is the number of patients with at least one positive test, who is observed on day $n_0 > 0$ and then after t days goes from state j to state k, where $j, k \in \{C, N\}$. If we know the true states j and k then, as defined in (2.4) the probability that patient i who is observed on day n_0 goes from colonisation state j to colonisation state k in t days is

$$\Gamma_{jk}^{(i)}(n_0, t) = \left(\prod_{l=n_0}^{n_0+t-1} P_{\Delta(l)} \right)_{jk}, \; j, k \in \{C, N\}. \tag{3.3.1}$$

In a hidden Markov model, however, it is not simple to work out one transition at a time because we also need to take into account all the possible true colonisation states. So, for hidden Markov models one can proceed via the formula

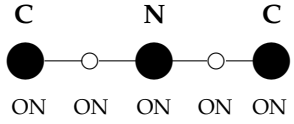
$$P(Y|\theta) = \sum_X P(X|\theta) P(Y|X, \theta), \tag{3.3.2}$$

where, X is the unobserved true process, Y is the observed process and θ is the parameter vector, i.e. $\theta = (p, q, \alpha, \beta, \phi)$. Probability $P(X|\theta)$ can be obtained from (3.3.1) and

$$P(Y|X, \theta) = \phi^{\delta_1} (1 - \phi)^{\delta_2} \times \delta_3, \tag{3.3.3}$$

where, δ_1 is the number of true positive test results, i.e. the total number of positive test results, δ_2 is the number of false negative test results, i.e. the total number of times that the X process is in state C but the observed process Y is in state N, and $\delta_3 = 1$ if and only if there are no false positive test results, otherwise $\delta_3 = 0$, i.e. there is no possibility that process X is in state N while process Y is in state C.

For example, let us assume that patient i's data are given by the following diagram:



where each bullet denotes one day of patient i's stay in the ICU ward. The black bullets denote that patient i had a test on that day. We assume that the first day

is day 1.

The observed transitions $C \to N \to C$ may come from either the true transitions $C \to C \to C$ or $C \to N \to C$. So, using (3.3.2) we have

$$\begin{aligned} P(Y = C \to N \to C|\theta) = \\ P(Y = C \to N \to C|X = C \to C \to C, \theta)P(X = C \to C \to C|\theta) + \\ P(Y = C \to N \to C|X = C \to N \to C, \theta)P(X = C \to N \to C|\theta), \end{aligned}$$

where,

$P(Y = C \to N \to C|X = C \to C \to C, \theta) = \phi^2(1-\phi)$,
$P(X = C \to C \to C|\theta) = \Gamma^{(i)}_{CC}(1,2) + \Gamma^{(i)}_{CC}(3,4)$,
$P(Y = C \to N \to C|X = C \to N \to C, \theta) = \phi^2$ and
$P(X = C \to N \to C|\theta) = \Gamma^{(i)}_{CN}(1,2) + \Gamma^{(i)}_{NC}(3,4)$

However, one complication for X is that, if for example a patient has k negative results, then there are 2^k possible values for X, and so the numerical evaluation of this formula is not trivial. An alternative is to use data-augmented MCMC algorithms, which can naturally take account of the unobserved X values by including them as latent variables.

In the next Section we will describe the data-augmented MCMC algorithm we used for the parameter estimation.

3.4 Inference

In this section we will describe how we make the inference for the model. We used a data-augmentation MCMC algorithm to obtain the model parameters from the data. In this way, we could incorporate the true colonisation states for each patient.

The basic idea of the Data Augmentation algorithm is the following. Assume that we have the observed data y with a parameter vector θ and that we are interested in sampling from the posterior $\pi(\theta|y) \propto \pi(y|\theta)\pi(\theta)$, where $\pi(y|\theta)$ is a probability density function and $\pi(\theta)$ is the prior density of the parameter θ. However, $\pi(\theta|y)$ might be intractable. To overcome this problem we can

construct augmented data x such that it is easier to sample from the posterior density $\pi(\theta|y,x) \propto \pi(y|\theta,x)\pi(x|\theta)\pi(\theta)$. The Data Augmentation algorithm has two steps. The Imputation-step (I-step) where we sample from $\pi(x|y,\theta)$, and the Posterior-step (P-step) where we sample from $\pi(\theta|y,x)$. Steps I and P are then iterated until the algorithm reach convergence.

The data augmentation algorithm can be simulated using MCMC methods. That is because inference for x is actually based on a sequence of random draws from a Markov chain having stationary distribution $\pi(\theta,x|y)$. Thus, the I-step and P-step of the data augmentation algorithm can be considered as a two-step Gibbs sampler. Furthermore, if any of the two steps of the Data Augmentation algorithm is difficult to do directly, they can be replaced by a sequence of Gibbs or Metropolis steps assuming that they have $\pi(\theta,x|y)$ as a target distribution. A discussion of the recent work on Data Augmentation algorithm as well as some applications using MCMC methods can be found in [van Dyk and Meng, 2001]. More information about MCMC methods for HMMs can be found in [Cappé et al., 2005].

In the rest of this section we will describe the MCMC algorithm we used for the inference, giving pseudocode at the end.

3.4.1 Prior distributions

We need to sample from the posterior distributions for the model parameters p_0, q_0, α, β and ϕ. Initially, we set the prior distributions for these parameters as follows,

$$\phi \sim \text{Beta}(\kappa,\lambda),$$
$$p_0,q_0,\alpha,\beta \sim \text{U}(0,1),$$

where $\text{U}(0,1)$ is the uniform distribution and $\text{Beta}(\kappa,\lambda)$ is the beta distribution with shape parameters κ and λ, i.e. with probability density function $f(x) \propto x^{\kappa-1}(1-x)^{\lambda-1}$ for $0<x<1$. We will use uninformative priors so $\kappa=\lambda=1$, but this can be easily relaxed.

We are going to augment the observed data Y. We set $\theta=(p_0,q_0,\alpha,\beta,\phi)$ as the parameter vector and X the "unobserved" true data. Then, using Bayes

theorem we can derive the posterior density function assuming a priori independence between the parameters:

$$\pi(X, \theta \mid Y) \propto \pi(Y \mid X, \theta)\pi(X, \theta) = \pi(Y \mid X, \theta)\pi(X \mid \theta)\pi(\theta),$$

where $\pi(Y \mid X, \theta)$ can be obtained from equation in (3.3.3), $\pi(X \mid \theta)$ can be obtained from equation in (3.3.1), and $\pi(\theta)$ is the prior density of the model parameters θ.

3.4.2 Updating the parameters

We update parameters p_0, q_0, α and β using a random walk Metropolis scheme and parameter ϕ using a Gibbs step. The parameters are updated one at a time and then we update the augmented data.

To update ϕ, we draw samples from the beta distribution

$$\pi\left(\phi \mid p_0, q_0, \alpha, \beta, X, Y\right) \propto Beta\left(n_{TP} + 1, n_{FN} + 1\right),$$

where n_{TP} is the number of true positive tests and is known from the data, and n_{FN} is the number of false negative tests and is unknown.

We update parameters p_0, q_0, α and β using a Gaussian random walk Metropolis scheme. This is similar to the scheme we followed in Chapter 2. Let $\omega^{(t)}$ denote the set of current model parameters at iteration t and ω^* be the proposed new set of these parameters. We use a multivariate normal proposal distribution $N(\omega^*, \sigma^2_{\omega^*})$ to propose the parameters, where $N(\mu, \sigma^2)$ is the normal distribution with mean μ and standard deviation σ.

Standard deviation σ_{ω^*} is chosen so that the acceptance rate is around 0.25 [Roberts et al., 1997].

We sample a candidate point ω^* from a gaussian density $g\left(\omega^* | \omega^t\right) \sim N\left(\omega^t, \sigma^2_{\omega^*}\right)$. Then, the probability that the candidate point ω^* is accepted is:

$$a\left(\omega^t, \omega^*\right) = \min\left(1, \frac{\pi\left(\omega^* | \phi, X, Y\right) \pi\left(\omega^*\right) g\left(\omega^t | \omega^*\right)}{\pi\left(\omega^t | \phi, X, Y\right) \pi\left(\omega^t\right) g\left(\omega^* | \omega^t\right)}\right).$$

where $\pi(\omega^*)$ is the prior distribution of parameter ω^*, $g\left(\omega^t|\omega^*\right)$ and $g\left(\omega^*|\omega^t\right)$ are the proposal densities for a move from ω^t to ω^* and vice versa, and $\frac{g\left(\omega^t|\omega^*\right)}{g(\omega^*|\omega^t)} = 1$ as shown in 1.5.3,

so the acceptance probability is

$$a\left(\omega^t, \omega^*\right) = \min\left(1, \frac{\pi\left(\omega^*|\phi, X, Y\right)\pi\left(\omega^*\right)}{\pi\left(\omega^t|\phi, X, Y\right)\pi\left(\omega^t\right)}\right).$$

Next, we update the augmented data X. Let X^* be the proposed augmented data and X the current augmented data. We generate X^* as follows: first, we assume that each negative test is a false negative. Then, with a constant probability z, each test result becomes positive independently of all the other negative tests. Then, X^* is accepted with probability

$$a(X, X^*) = \min\left(1, \frac{\pi(X^* \mid Y, \omega, \phi)\pi(Y \mid X^*, \omega, \phi)g(X \mid X^*)}{\pi(X \mid Y, \omega, \phi)\pi(Y \mid X, \omega, \phi)g(X^* \mid X)}\right),$$

where $g(X \mid X^*)$ and $g(X^* \mid X)$ are the proposal densities for a move from X to X^* and X^* to X respectively and $\frac{g(X|X^*)}{g(X^*|X)} = z^{n_{FN}-n^*_{FN}}\left(1-z\right)^{n^*_{FN}-n_{FN}}$, where n^*_{FN} is the proposed number of false negative tests.

Pseudocode for this algorithm is as follows:

Data Augmented MCMC Algorithm

1 Give initial values to the parameters of interest ω, ϕ

2 For $t = 1 \ldots N_{iter}$, N_{iter} is the number of iterations

a. Update ϕ using Gibbs Sampler

b. Update parameters ω

Propose $\omega^* \sim N\left(\omega^t, \sigma_{\omega^t}\right)$

Draw a uniform $(0, 1)$ random variable U

If $\mathrm{U} \leq \alpha\left(\omega^t, \omega^*\right)$

· set $\omega^{t+1} = \omega^*$

Else

· set $\omega^{t+1} = \omega^t$

c. Update Data X

– If a test is negative

Draw a uniform $(0, 1)$ random variable U

If $\mathrm{U} \leq z$

· the test remains negative

Else

· the test is a false negative

Draw a uniform $(0, 1)$ random variable U

If $\mathrm{U} \leq \alpha\left(X^t, X^*\right)$

· set $X^{t+1} = X^*$

Else

· set $X^{t+1} = X^t$

3 End For loop

4 Return values $\{\omega^1, \phi^1, \omega^2, \phi^2, ..., \omega^{N_{iter}}, \phi^{N_{iter}}\}$

3.5 Model Assessment

In this section we are going to discuss about the methods we used to assess model fit. We are going to give some information about the goodness-of-fit for HMMs found in the literature and then we will describe the methods we used.

3.5.1 Background Information

MacKay Altman in [MacKay Altman, 2004] proposed a graphical method to assess the goodness-of-fit of stationary HMMs. In this study, an estimated cumulative distribution function (CDF) based on HMMs estimates is calculated and then, this estimated CDF is compared graphically to the observed empirical CDF. This approach however, is applied to time-series data.

Bureau et al. in [Bureau et al., 2003] applied a continuous-time hidden Markov model to longitudinal data of a binary disease outcome. Parameter estimation is carried out using maximum likelihood methods via the EM algorithm. For model assessment, the authors proposed the use of the Kaplan-Meier estimator to the transitions between specified pairs of observed subsequent states. Then, these empirical estimates are plotted along with estimates using simulated data. However, it is stated that dependencies in the observed data can result in a bad fit between the observed and expected plots. Another approach presented in the same work, was constructing contingency tables in which the observed and expected counts were grouped by taking into account the last two observed states. Then, they computed a χ^2 statistic to assess the fit using these counts. It is stated that although this χ^2 statistic does not follow a known distribution, it provides a useful method for comparing models.

Satten and Longini in [Satten and Longini Jr, 1996] suggested a method to predict an observation Y_k conditional on the previous observations by calculating the distribution

$$P(Y_k = y_k \mid Y_j = y_j,\ j = 1, 2, .., k-1) = \frac{P(Y_j = y_j,\ j = 1, 2, ..., k)}{P(Y_j = y_j,\ j = 1, 2, ..., k-1)}.$$

Then, all these probabilities are grouped in contingency tables according to the time period and compared to the observed probabilities.

Titman and Sharples in [Titman and Sharples, 2008] proposed a modification of the Pearson-type goodness -of-fit test proposed by Aguirre-Hernandez and Farewell (AH/F) in [Aguirre- Hernández and Farewell, 2002]. This modification applies to misclassification-type hidden Markov models. The authors followed the method in [Aguirre- Hernández and Farewell, 2002] to group observations, but since the observed states are not coming from a Markov process, they conditioned on all previous observations up to the current time in order to estimate an expected state at that time. A drawback of this method is that the derived statistic cannot be compared to a known null distribution. The authors, as also in [Aguirre- Hernández and Farewell, 2002], suggest bootstrapping the distribution and then refitting the model and calculating the statistic as a possible solution, but they also state that this can be computationally expensive.

All the models discussed above take into account continuous-time, time- homogeneous hidden Markov models. However, we are using a discrete-time non-homogeneous HMM and we also have extra covariate data in the form of the daily treatment information, so the methods described above cannot be applied directly.

3.5.2 Model assessment of a HMM model: theoretical considerations

In this section we are going to investigate whether a similar approach to model assessment discussed to that discussed in 2.6.2 is also possible for hidden Markov models.

Suppose we have the observation process introduced in (3.2.1), $\{Y_n : n \geq 0\}$ where,

$$Y_n = \begin{cases} N & & & \text{if} \quad X_n = N \\ N & \text{w. p.} & (1-\phi) & \text{if} \quad X_n = C \\ C & \text{w. p.} & \phi & \end{cases},$$

Suppose that we focus on the observations for a k-day interval, so the summary matrix is

$$\text{observed} = \begin{pmatrix} Y_{NN} & Y_{NC} \\ Y_{CN} & Y_{CC} \end{pmatrix}.$$

Suppose in addition that for patient i we have the k-day transition matrix for process $\{X_n : n \geq 0\}$,

$$P_\Delta = \begin{array}{c} \\ N \\ C \end{array} \begin{array}{c} \begin{array}{cc} N & C \end{array} \\ \begin{pmatrix} p_i & 1-p_i \\ q_i & 1-q_i \end{pmatrix} \end{array},$$

so that p_i, q_i are functions of p_0, q_0, α, β, and $\tilde{z}_i$, where $\tilde{z}_i$ is patient i's antimicrobial information for each day during the k-day interval.

Consider now that observations arise from the true process $\{X_n : n \geq 0\}$ starting at state C and assume that we have n_C such transitions. Then we have,

$$\xi_i^C = \begin{cases} 1 & \text{observe : } CC \quad w.p. \ (1-q_i)\phi^2 \\ 2 & \text{observe : } CN \quad w.p. \ (1-q_i)\phi(1-\phi) + q_i\phi \\ 3 & \text{observe : } NC \quad w.p. \ (1-q_i)\phi(1-\phi) \\ 4 & \text{observe : } NN \quad w.p. \ (1-q_i)(1-\phi)^2 + q_i(1-\phi) \end{cases},$$

where ξ_i^C, $i = 1, 2, 3, 4$ is a vector indicating the observed transition assuming that the true process $\{X_n : n \geq 0\}$ starts at state C.

Similarly for the observations when the true process starts in state N, so that we have n_N such transitions

$$\xi_i^N = \begin{cases} 1 & \text{observe : } CC \quad w.p. \ 0 \\ 2 & \text{observe : } CN \quad w.p. \ 0 \\ 3 & \text{observe : } NC \quad w.p. \ (1-p_i)\phi \\ 4 & \text{observe : } NN \quad w.p. \ p_i + (1-p_i)(1-\phi) \end{cases}.$$

where ξ_i^N, $i = 1, 2, 3, 4$ is a vector indicating the observed transition assuming that the true process $\{X_n : n \geq 0\}$ starts at state N.

Thus, each of the observed transition counts $(Y_{NN}, Y_{CN}, Y_{NC}, Y_{CC})$ can be expressed as a sum of a number of ξ_i^Cs and ξ_i^Ns. So, for example, for Y_{NN} we will have

$$Y_{NN} = \sum_{j=1}^{n_C} \mathbb{1}_{\{\xi_i^C = 4\}} + \sum_{j=1}^{n_N} \mathbb{1}_{\{\xi_i^N = 4\}}. \tag{3.5.1}$$

Consider now the special case where $n_C = n_N = n$. We are going to prove that Liapounov's theorem holds for Y_{NN}. Similar results hold for Y_{CN}, Y_{NC} and Y_{CC}.

Consider the model in (3.5.1), then we have

$$Y_{NN} = \sum_{j=1}^{n} Z_j, \tag{3.5.2}$$

where $Z_j = Z_j^C + Z_j^N$ and $Z_j^C \sim$ Bernoulli(r_1^j) and $Z_j^N \sim$ Bernoulli(r_2^j), where $r_1^j = (1-q_j)(1-\phi)^2 + q_j(1-\phi)$ and $r_2^j = p_j + (1-p_j)(1-\phi)$.

Then,

$$Z_j = \begin{cases} 0 & w.p. \quad 1 - p_1^j - p_2^j \\ 1 & w.p. \quad p_1^j \\ 2 & w.p. \quad p_2^j \end{cases},$$

where $p_1^j = r_1^j(1-r_2^j) + r_2^j(1-r_1^j)$ and $p_2^j = r_1^j r_2^j$.

So,

$$E[Y_{NN}] = \sum_{j=1}^{n} Z_j = \sum_{j=1}^{n} \left(p_1^j + 2p_2^j \right)$$

and

$$Var(Y_{NN}) = \sum_{j=1}^{n} \left(p_1^j(1-p_1^j) + 4p_2^j(1-p_1^j-p_2^j) \right)$$

Lemma 3.5.1. *If the p_j^1's and p_j^2's are uniformly bounded away from 0 and 1, then as in Lemma 2.6.2*

$$\frac{Y_{NN} - E[Y_{NN}]}{\sqrt{Var(Y_{NN})}} \xrightarrow{D} N(0,1), \quad as\ n \to \infty.$$

Proof. We have that $Y_{NN} = \sum_{j=1}^{n} Z_j$ so $w_j = Z_j - E[Z_j]$ has $E[w_j] = 0$ and $Var[w_j] = Var[Z_j] = p_1^j \left(1 - p_1^j\right) + 4p_2^j \left(1 - p_1^j - p_2^j\right) = \sigma_j^2$.

So we have

$$w_j = \begin{cases} 0 - (p_1^j + 2p_2^j) & \text{with prob } \ 1 - p_1^j - p_2^j, \\ 1 - (p_1^j + 2p_2^j) & \text{with prob } \ p_1^j, \\ 2 - (p_1^j + 2p_2^j) & \text{with prob } \ p_2^j, \end{cases}$$

so,

$$|w_j| = \begin{cases} p_1^j + 2p_2^j & \text{with prob } 1 - p_1^j - p_2^j, \\ |1 - (p_1^j + 2p_2^j)| & \text{with prob } p_1^j, \\ |2 - (p_1^j + 2p_2^j)| & \text{with prob } p_2^j, \end{cases}$$

and

$$|w_j|^{2+\delta} = \begin{cases} (p_1^j + 2p_2^j)^{2+\delta} & \text{with prob } 1 - p_1^j - p_2^j, \\ |1 - (p_1^j + 2p_2^j)|^{2+\delta} & \text{with prob } p_1^j, \\ |2 - (p_1^j + 2p_2^j)|^{2+\delta} & \text{with prob } p_2^j, \end{cases}$$

thus,

$$E[|w_j|^{2+\delta}] = \left(1 - p_1^j - p_2^j\right) | \left(p_1^j + 2p_2^j\right) |^{2+\delta} + p_1^j |1 - \left(p_1^j + 2p_2^j\right) |^{2+\delta} + p_2^j |2 - \left(p_1^j + 2p_2^j\right) |^{2+\delta}$$

and

$$s_n^2 = \sigma_1^2 + ... + \sigma_n^2 = \sum_{j=1}^{n} \left(p_1^j \left(1 - p_1^j\right) + 4p_2^j \left(1 - p_1^j - p_2^j\right)\right).$$

So, the condition $\frac{\sum_{i=1}^{n} E|X_i|^{2+\delta}}{s_n^{2+\delta}} \to 0$ in Lemma 2.6.1, as $n \to \infty$ is equivalent to

$$\frac{\sum_{j=1}^{n} E[|w_j|^{2+\delta}]}{\left(\sum_{j=1}^{n} \left(p_1^j \left(1 - p_1^j\right) + 4p_2^j \left(1 - p_1^j - p_2^j\right)\right)\right)^{\frac{2+\delta}{2}}} \to 0 \quad \text{as } n \to \infty. \tag{3.5.3}$$

To show that (3.5.3) holds, let $\delta = 2$. Recall that the p_i^j's, $i = 1, 2$, are bounded away from 0 and 1. Then, there exists $\epsilon > 0$ such that $0 < \epsilon < p_1^j \left(1 - p_1^j\right) + 4p_2^j \left(1 - p_1^j - p_2^j\right)$,

so that

$$\left(\sum_{j=1}^{n} \left(p_1^j \left(1 - p_1^j\right) + 4p_2^j \left(1 - p_1^j - p_2^j\right)\right)\right)^2 > n^2\epsilon^2. \tag{3.5.4}$$

Also let

$$c = \left(1 - p_1^j - p_2^j\right) \mid \left(p_1^j + 2p_2^j\right) \mid^4 + p_1^j \mid 1 - \left(p_1^j + 2p_2^j\right) \mid^4 + p_2^j \mid 2 - \left(p_1^j + 2p_2^j\right) \mid^4,$$

and let $\left(1 - p_1^j - p_2^j\right) \leq 1$, $\left(p_1^j + 2p_2^j\right) \leq 3$, $1 - \left(p_1^j + 2p_2^j\right) \leq 4$ and $2 - \left(p_1^j + 2p_2^j\right) \leq 5$.

Then,

$$0 < c \leq 962,$$

so

$$\sum_{j=1}^{n} c \leq 962n, \tag{3.5.5}$$

(3.5.4) and (3.5.5) imply that

$$(3.5.3) \leq \frac{962n}{n^2\epsilon^2} \to 0 \text{ as } n \to \infty.$$

□

Thus, in the special case where for the model in 3.5.1 when $n_C = n_N = n$,

$$\frac{Y_{NN} - E[Y_{NN}]}{\sqrt{Var(Y_{NN})}} \xrightarrow{D} N(0,1), \text{ as } n \to \infty.$$

We are not going to consider other possibilities for $n_C \to \infty$, $n_N \to \infty$ although in principle these could also be considered along similar lines.

In the following section we present another way to assess the model fit.

3.5.3 Model assessment using simulations

To assess the model fit of the hidden Markov model described in this chapter, we will use simulations similar to those described in the previous chapter. We simulate 500 data sets using the posterior means of the model parameters and find the transition counts for each day interval. So, for each of the patients we

simulate a Markov chain using the parameters p_0, q_0, α and β, which correspond to the simulated true process, $\{X_n : n \geq 0\}$. Then, in order to create the observed process $\{Y_n : n \geq 0\}$ we assume that each one of the positive tests of process $\{X_n : n \geq 0\}$ might be observed with error. One complication here is that, due to imperfect sensitivity, we cannot condition on each observed state and simulate the Markov chain until the next state because non-colonised states might be observed with error.

A possible solution to this problem is to use the *negative predictive value* as a way to determine whether an observed non-colonised state is observed correctly. The *negative predictive value* is the probability that a patient with a negative test is not colonised. The *negative predictive value* can be found using Bayes theorem as follows: Define ψ to be the *negative predictive value* then,

$$\begin{aligned}\psi &= P(X = N \mid Y = N) \\ &= \frac{P(Y = N \mid X = N)P(X = N)}{P(Y = N \mid X = N)P(X = N) + P(Y = N \mid X = C)P(X = C)}. \end{aligned} \tag{3.5.6}$$

Now, since specificity is 100%, it will be $P(Y = N \mid X = N) = 1$ and we also have $P(Y = N \mid X = C) = 1 - \phi$.

So from (3.5.6)

$$\psi = \frac{P(X = N)}{P(X = N) + (1 - \phi)P(X = C)}. \tag{3.5.7}$$

We can obtain estimates for $P(X = N)$ and $P(X = C)$ from our MCMC algorithm and thus estimate ψ. For each iteration, k, we obtain the number of false negative tests n_{FN}^k. The number of true positive tests n_{TP} is known from the data so it is fixed. Let N_{tests} be the number of all tests, then $P(X = N) = N_{tests} - n_{TP} - n_{FN}^k$ and $P(X = C) = n_{TP} + n_{FN}^k$. Thus, 3.5.7 can be easily calculated.

Then, for the model assessment, we use the posterior mean of ψ to adjust the proportion of times we start in an N (non-colonised) state for each simulated transition. That is, if an observed transition starts in an N state, we assume with probability equal to ψ that this observed N state is a true N state. Once this is done we follow the same process described in Section 2.6.3.

In the next section we will validate our method using simulated data.

3.6 Simulation

In this section we validate the methodology described above using simulated data. Initially, we use simulated transitions and day intervals for each patient but keeping the same number of patients and patient length of stay in the ICU from the p-MRSA data set without considering any information about the antimicrobial treatment. Then, we are going to use the day intervals from the p-MRSA Data Set again without the information about antimicrobial treatment.

3.6.1 Simulated Data

Initially we simulated data sets using daily, 2-day, 3-day intervals and so on up to an interval of one week. We used the values of p_0, q_0 and ϕ that obtained from the p-MRSA Data Set without taking into account the antimicrobial treatment (the results for this data set are presented later in this chapter). So, we set $p_0 = 0.8859$, $q_0 = 0.0800$ and $\phi = 0.8568$. The summary statistics for the daily, 3-day and 7-day intervals are shown in Table 3.2. It can be seen that the simulated values obtained for these three data sets are very close to the values set. Moreover we can see that as day intervals increase, the posterior correlation between p_0 and q_0 also increases. Figures 3.1 and 3.2 show the posterior density estimates from the MCMC output for p_0 and q_0, and ϕ respectively. The negative predictive value for the three data sets was $\psi = 0.8586$ for the daily interval, $\psi = 0.8395$ for the 3-day interval and $\psi = 0.7925$ for the 7-day interval transitions.

Table 3.1 shows the equal-tailed 95% quantiles from the model fit simulations. In the same table there are also the observed counts for each day interval and transition. We can see that the model fits very well for every day interval, as all the observed counts lie in the equal-tailed 95% quantiles.

3.6.2 Using the day intervals from the p-MRSA Data Set

To verify that our method works using irregular day-intervals, we simulated data using the day-intervals from the p-MRSA Data Set. To simulate the data we set $p_0 = 0.8859$, $q_0 = 0.0800$ and $\phi = 0.8568$. We used these values because

	Day Intervals		
	1	**3**	**7**
obs. counts $N \to N$	**2761** (2700, 2787)	**744** (706, 768)	**249** (224, 265)
obs. counts $N \to C$	**644** (617, 704)	**329** (303, 365)	**187** (169, 211)
obs. counts $C \to N$	**612** (576, 663)	**283** (260, 315)	**154** (138, 177)
obs. counts $C \to C$	**2285** (2231, 2320)	**598** (565, 621)	**184** (161, 199)

Table 3.1: Model fit for the model using simulated data with 1-day, 3-day and 7-day interval transitions. The intervals in red color show that the equal-tailed 95% quantiles include the number of the observed transition counts.

1-day Interval		
parameters	$E[\cdot \mid Y]$ (s.d.)	95% CI
p_0	0.8887 (0.0065)	(0.8760, 0.9014)
q_0	0.0835 (0.0063)	(0.0712, 0.0958)
p_0, q_0 **posterior correlation**		-0.2906
ϕ	0.8580 (0.0083)	(0.8411, 0.8746)
3-day Interval		
parameters	$E[\cdot \mid Y]$ (s.d.)	95% CI
p_0	0.8826 (0.0090)	(0.8640, 0.8998)
q_0	0.0828 (0.0112)	(0.0624, 0.1065)
p_0, q_0 **posterior correlation**		-0.5104
ϕ	0.8425 (0.0271)	(0.7904, 0.8968)
7-day Interval		
parameters	$E[\cdot \mid Y]$ (s.d.)	95% CI
p_0	0.8561 (0.0231)	(0.8037, 0.8923)
q_0	0.0938 (0.0235)	(0.0539, 0.1437)
p_0, q_0 **posterior correlation**		-0.9549
ϕ	0.8050 (0.0532)	(0.7083, 0.9125)

Table 3.2: Summary statistics and posterior correlation for p_0, q_0 and ϕ using the simulated transitions for intervals of 1-day, 3-days and 7-days without antimicrobial treatment. The true values are $p_0 = 0.8859$, $q_0 = 0.0800$ and $\phi = 0.8568$.

these are the parameter estimations for the p-MRSA Data Set excluding the antimicrobial treatment information.

Simulating data using the day-interval structure from the p-MRSA Data Set means that we will keep the same number of patients and number of transitions for each patient as in the p-MRSA Data Set. A problem that arises when simulating a data set of this kind (i.e. when including only patients with at

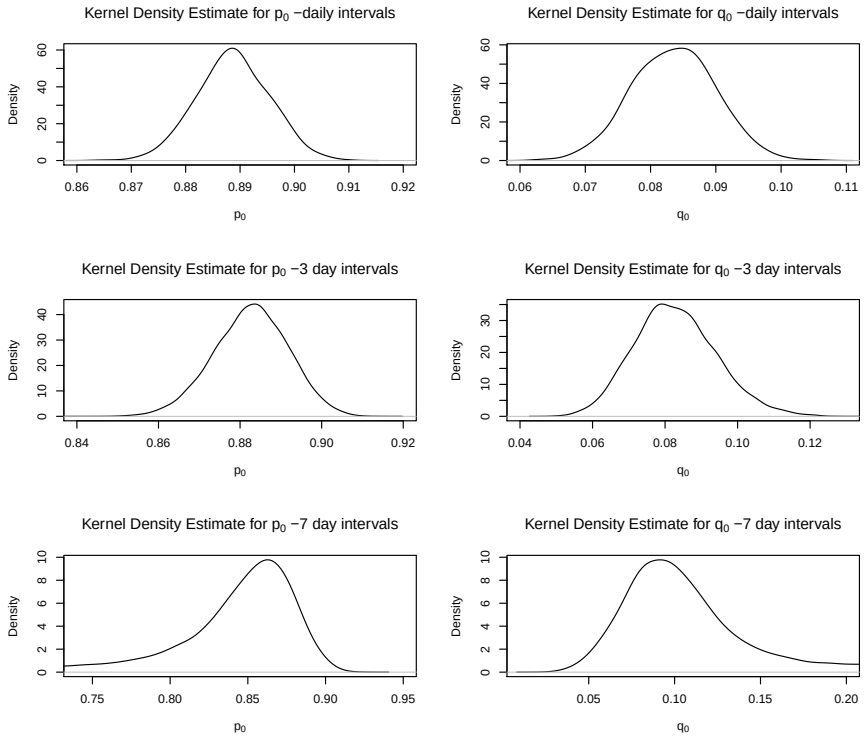


Figure 3.1: Kernel density plots for parameters p_0 and q_0 from the simulated data and for simulated 1-day, 3-day and 7-day transition intervals without antimicrobial treatment. The true values are $p_0 = 0.8859$ and $q_0 = 0.0800$.

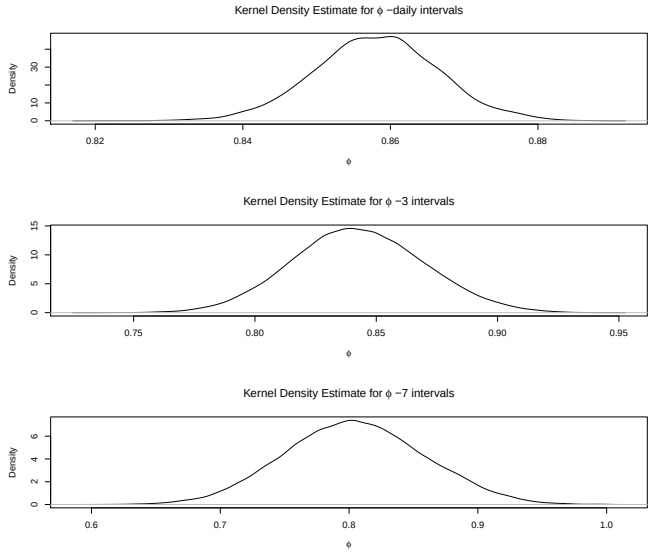


Figure 3.2: Kernel density plots for sensitivity ϕ from the simulated data and for simulated 1-day, 3-day and 7-day transition intervals without antimicrobial treatment. The true value is $\phi = 0.8568$.

least one positive test) is that the output will almost always also include patients with only negative tests. Here we will investigate two cases of simulated data. The first generates a data set that has the same structure as the p-MRSA Data Set. This means that it includes patients with no positive tests. The second case uses only the patients of the first case that have at least one positive test. We will show that in both cases the model fits equally well.

Case 1: Simulated data set with the p-MRSA day-interval structure

The simulated data set we are using here has the same structure as the p-MRSA data set as shown in Section 2.2. The summary statistics of the posterior density are shown in Table 3.3. It can be seen that the parameter estimates are very close to the values we set to construct the simulated data set. Figures 3.3 and 3.4 show the marginal posterior density estimates from the MCMC output for p_0 and q_0 and ϕ respectively. The posterior mean of the negative predictive value ψ was found equal to 0.8472. The correlation between p_0 and q_0 is shown in Figure 3.5. We notice that parameters p_0 and q_0 are strongly correlated.

no antimicrobial treatment		
parameters	$E[\cdot \mid Y]$ (s.d.)	95% CI
$\mathbf{p_0}$	0.8645 (0.0167)	(0.8275, 0.8935)
$\mathbf{q_0}$	0.0930 (0.0003)	(0.0590, 0.1323)
$\mathbf{p_0}$, $\mathbf{q_0}$ **posterior correlation**	-0.8009	
ϕ	0.8596 (0.0018)	(0.7735, 0.9444)

Table 3.3: Summary statistics for p_0, q_0 and ϕ for the simulated transitions using the day intervals from the p-MRSA Data Set without antimicrobial treatment. The true values are $p_0 = 0.8859$, $q_0 = 0.0800$ and $\phi = 0.8568$.

Finally, The results of the equal-tailed 95% quantiles as well as the transition counts from the observed data are shown in Table 3.4. We can see that the model fits very well.

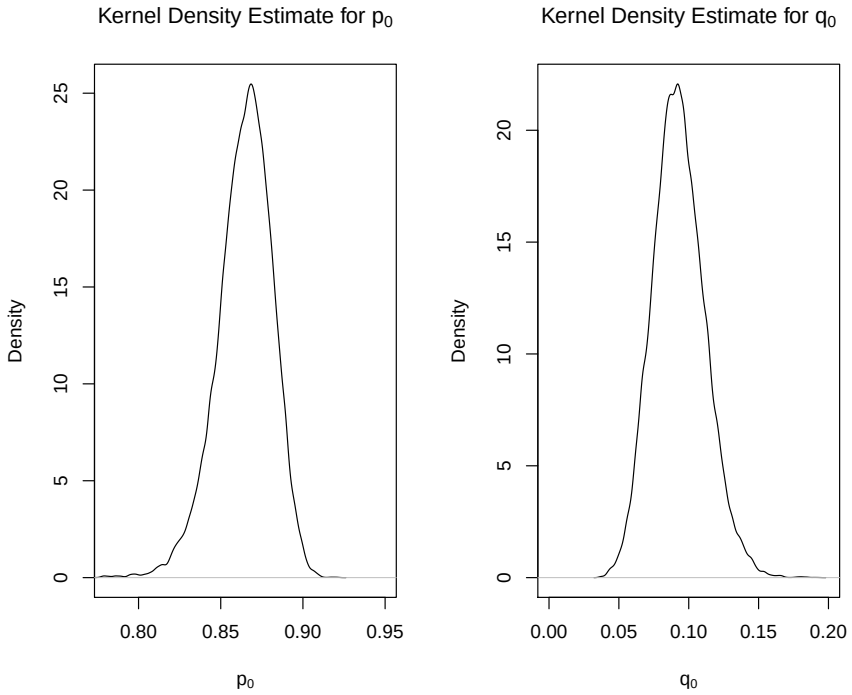


Figure 3.3: Kernel density plots for p_0 and q_0 for the simulated transitions using the day intervals from the p-MRSA Data Set without antimicrobial treatment. The true values are $p_0 = 0.8859$ and $q_0 = 0.0800$.

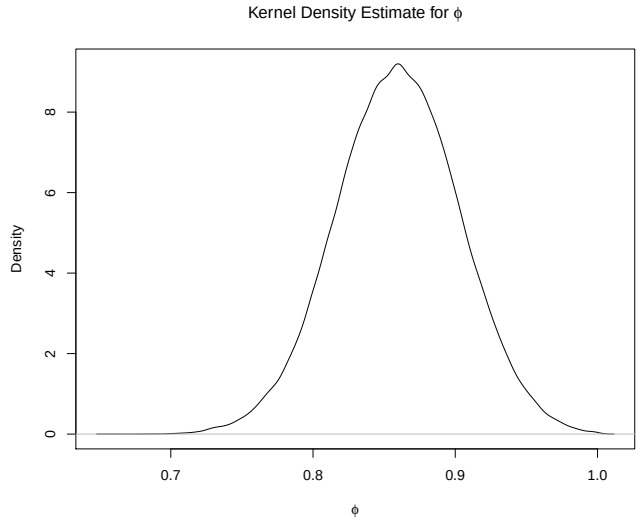


Figure 3.4: Kernel density plot for sensitivity ϕ for the simulated transitions using the day intervals from the p-MRSA Data Set without antimicrobial treatment. The true value is $\phi = 0.8568$.

	Day Intervals						
	1	**2**	**3**	**4**	**5**	**6**	**7**
obs. counts	**19**	**23**	**19**	**19**	**21**	**43**	**174**
$N \to N$	(17, 26)	(18, 28)	(13, 22)	(13, 24)	(14, 24)	(29, 45)	(157, 191)
obs. counts	**9**	**10**	**8**	**11**	**11**	**22**	**143**
$N \to C$	(2, 11)	(5, 15)	(4, 14)	(6, 16)	(8, 18)	(20, 36)	(125, 158)
obs. counts	**2**	**8**	**7**	**11**	**8**	**17**	**140**
$C \to N$	(0, 6)	(3, 12)	(4, 12)	(6, 16)	(7, 17)	(11, 24)	(119, 153)
obs. counts	**12**	**20**	**17**	**18**	**21**	**25**	**175**
$C \to C$	(8, 13)	(16, 25)	(12, 20)	(13, 23)	(12, 23)	(18, 31)	(161, 196)

Table 3.4: Model fit for the model using simulated data but with the day intervals from the p-MRSA Data Set. The intervals in red color show that the equal-tailed 95% quantiles include the number of the observed transition counts.

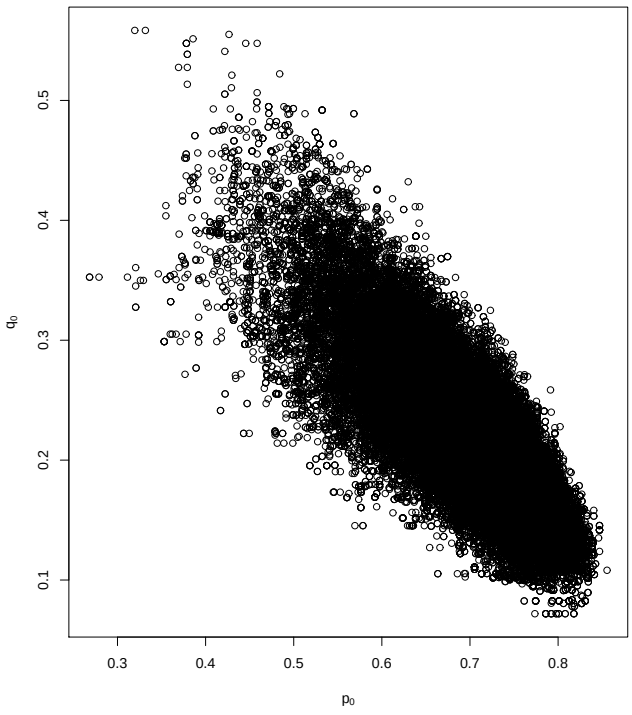


Figure 3.5: Scatterplot showing the correlation between p_0 and q_0 for the simulated transitions using the day intervals from the p-MRSA Data Set without antimicrobial treatment.

Case 2: Simulated data set having the p-MRSA Data Set day-interval structure but including only the patients with at least one positive test of Case 1.

In this section we use the same data set as in Case 1 but include only the patients with at least one positive test. So for this dataset we had to remove 79 patients who had only negative tests.

Table 3.5 shows the summary statistics of the posterior densities of the parameters. It can be seen that the parameter estimates are different to the values we set to construct the simulated data set. This is because in this case we have excluded some patients. Figures 3.6 and 3.7 show the marginal posterior density estimates from the MCMC output for p_0 and q_0 and ϕ respectively. Finally, Figure 3.8 shows the correlation between p_0 and q_0. The posterior mean of the negative predictive value was found equal to $\phi = 0.8272$.

Table 3.6 shows the 95% quantiles of the model fit. It can be seen that the model fit is quite satisfactory.

no antimicrobial treatment		
parameters	$E[\cdot \mid Y]$ (s.d.)	95% CI
$\mathbf{p_0}$	0.6527 (0.0876)	(0.4434, 0.7818)
$\mathbf{q_0}$	0.2569 (0.0043)	(0.1577, 0.4139)
$\mathbf{p_0}$, $\mathbf{q_0}$ **posterior correlation**	-0.8900	
ϕ	0.9789 (0.0190)	(0.9291, 0.9993)

Table 3.5: Summary statistics for p_0, q_0 and ϕ for the simulated transitions using the day intervals from the p-MRSA Data Set without antimicrobial treatment and including patients with at least one positive test.

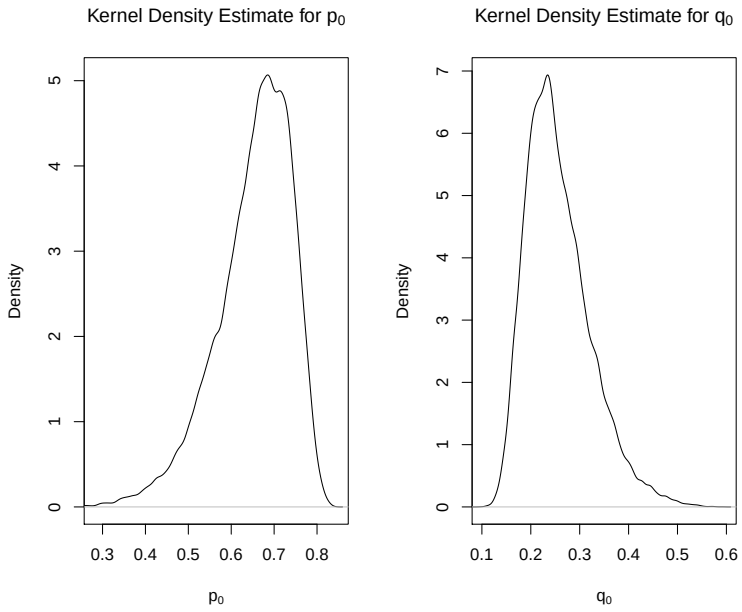


Figure 3.6: Kernel density plots for p_0 and q_0 for the simulated transitions using the day intervals from the p-MRSA Data Set without antimicrobial treatment and including patients with at least one positive test.

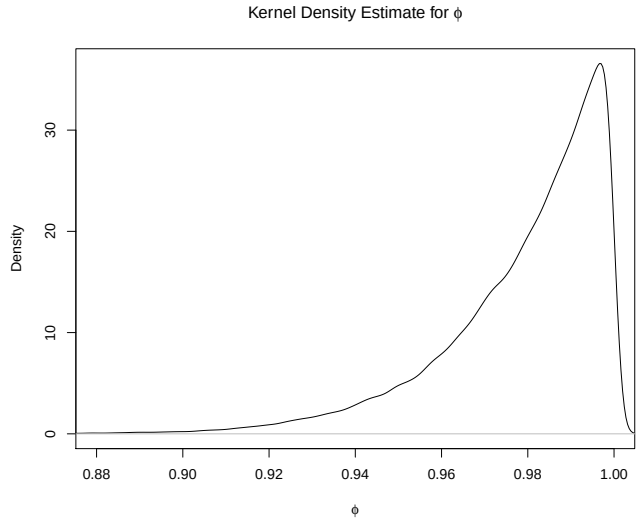


Figure 3.7: Kernel density plot for sensitivity ϕ for the simulated transitions using the day intervals from the p-MRSA Data Set without antimicrobial treatment and including patients with at least one positive test.

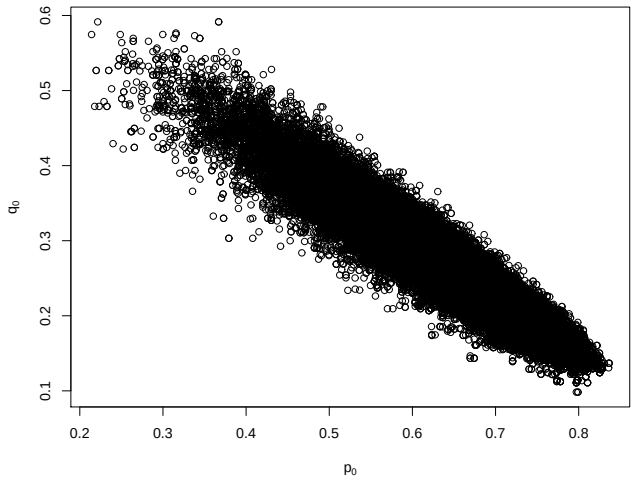


Figure 3.8: Scatterplot showing the correlation between p_0 and q_0 for the simulated transitions using the day intervals from the p-MRSA Data Set without antimicrobial treatment and including patients with at least one positive test.

	Day Intervals						
	1	**2**	**3**	**4**	**5**	**6**	**7**
obs. counts $N \to N$	**9** (8, 16)	**10** (6, 15)	**9** (4, 12)	**7** (4, 12)	**8** (4, 13)	**25** (14, 27)	**130** (102, 135)
obs. counts $N \to C$	**9** (2, 11)	**10** (5, 14)	**8** (5, 13)	**11** (6, 14)	**11** (6, 14)	**22** (20, 33)	**143** (137, 171)
obs. counts $C \to N$	**2** (1, 7)	**8** (5, 16)	**7** (5, 14)	**11** (7, 18)	**8** (7, 18)	**17** (13, 24)	**140** (120, 154)
obs. counts $C \to C$	**12** (7, 13)	**20** (12, 22)	**17** (10, 19)	**18** (11, 22)	**21** (11, 22)	**25** (18, 29)	**175** (160, 195)

Table 3.6: Model fit for the model using simulated data but with the day intervals from the p-MRSA Data Set and including patients with at least one positive test. The intervals in red color show that the equal-tailed 95% quantiles include the number of the observed transition counts.

3.7 Results using GSTT Data

In this section we fit the hidden Markov model to the GSTT data. Initially, we use only the p-MRSA Data Set and fit the model under various assumptions. Next, we obtain the parameter estimates for the p-Wounds and p-Respiratory Data Sets.

3.7.1 p-MRSA Data Set

Firstly, we will ignore the information about the antimicrobial treatment and find only the baseline probabilities p_0 and q_0 and sensitivity ϕ. Secondly, we will consider all antimicrobial treatment as one group both for the whole p-MRSA Data Set and starting from first positive test. We make the latter assumption because in this chapter we have ignored that there is patient-to-patient transmission in the ICU ward. Lastly, we will consider each antimicrobial treatment separately.

We also perform model assessment under all the assumptions listed above. We will see that the model fit is not always adequate.

Results assuming no antimicrobial treatment

Here we present the results of fitting the model without taking into account the information about antimicrobial treatment. From the MCMC output, we derived the posterior mean of probability p_0 of patients who remain in a non-colonised state equals to 0.8859, while the probability of MRSA clearance, q_0, is 0.0800. Moreover, the posterior mean of the swab test sensitivity, ϕ equals to 0.8568. Swab test sensitivity ranges between $66.7\% - 87\%$ according to the body site the swab is taken, [Hope et al., 2004; Keene et al., 2005]. The posterior mean of the negative predictive value ψ is 0.8453. Table 3.7 shows the summary statistics of the posterior distributions of p_0, q_0 and ϕ as well as the posterior correlation between p_0 and q_0. It can be seen that parameters p_0 and q_0 are highly correlated, possibly because here we consider only patients with at least one positive test and there might be some dependencies in the data.

Figure 3.9 presents the density plots for p_0 and q_0 and Figure 3.10 shows the

density plot for sensitivity ϕ.

no antimicrobial treatment		
parameters	$E[\cdot \mid Y]$ (s.d.)	95% CI
$\mathbf{p_0}$	0.8859 (0.0139)	(0.8549, 0.9100)
$\mathbf{q_0}$	0.0800 (0.0140)	(0.0559, 0.1114)
$\mathbf{p_0}$, $\mathbf{q_0}$ **posterior correlation**	-0.6821	
ϕ	0.8568 (0.0326)	(0.7931, 0.9218)

Table 3.7: Summary statistics for p_0, q_0 and ϕ for the p-MRSA Data Set without antimicrobial treatment.

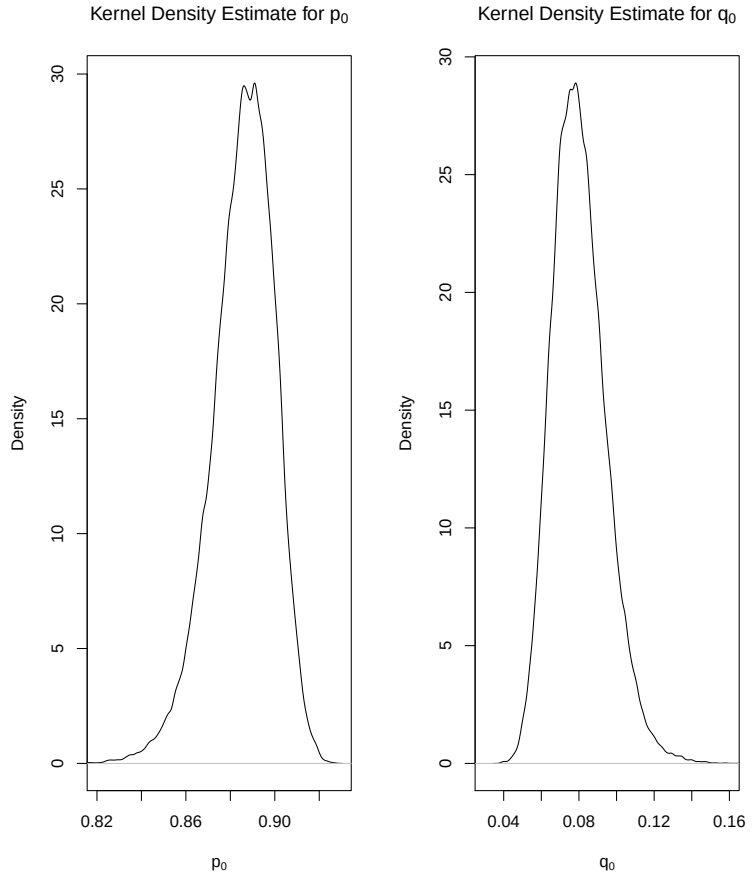


Figure 3.9: Kernel density plots for p_0 and q_0 from the p-MRSA Data Set assuming no antimicrobial treatment.

Table 3.8 shows the results of the 95% quantiles as well as the transition counts from the observed data. We can see that the model fit is not adequate as some of the observed transition counts are not in the 95% intervals.

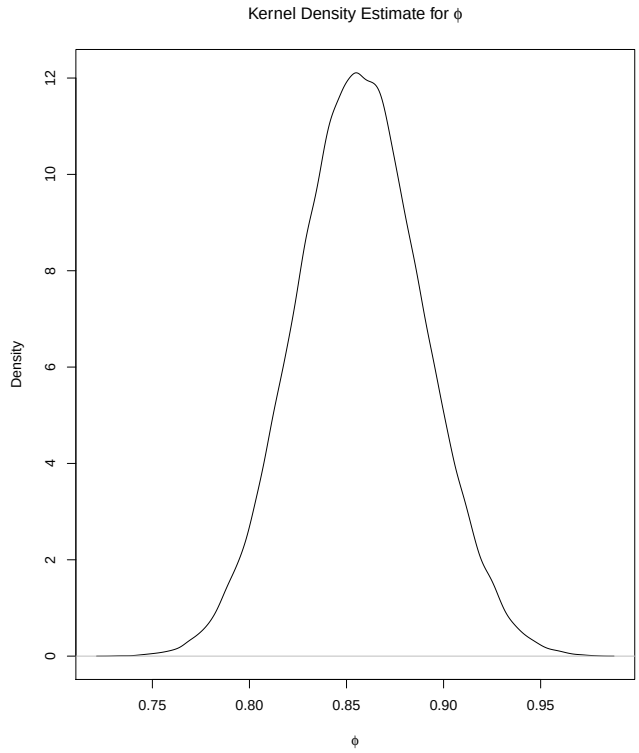


Figure 3.10: Kernel density plot for sensitivity ϕ from the p-MRSA Data Set assuming no antimicrobial treatment.

	Day Intervals						
	1	**2**	**3**	**4**	**5**	**6**	**7**
obs. counts $N \to N$	**17** (8, 19)	**19** (13, 25)	**19** (12, 24)	**8** (13, 25)	**17** (14, 28)	**31** (24, 41)	**243** (180, 234)
obs. counts $N \to C$	**10** (6, 14)	**11** (10, 19)	**15** (13, 23)	**18** (14, 24)	**14** (12, 22)	**26** (25, 39)	**132** (173, 207)
obs. counts $C \to N$	**8** (9, 18)	**11** (17, 29)	**8** (6, 15)	**12** (12, 22)	**10** (13, 25)	**26** (26, 40)	**72** (172, 203)
obs. counts $C \to C$	**7** (2, 9)	**20** (1, 8)	**9** (1, 8)	**21** (1, 9)	**20** (1, 8)	**24** (3, 14)	**185** (31, 62)

Table 3.8: Model fit for the model of the p-MRSA Data Set without antimicrobial treatment. The intervals in red color show that the equal-tailed 95% quantiles include the number of the observed transition counts.

3.7.2 Results from the MRSA Data Set

Excluding antimicrobial treatment

In order to see differences between the results from the p-MRSA Data Set and those from the MRSA Data Set, we will present here the results from the MRSA Data Set (this is the data set including patients with no positive tests as de-

scribed in 1.3). We will not take into account any of the antimicrobial treatment. Table 3.9 shows the summary statistics of the posterior density for parameters p_0 and q_0 and ϕ. Figures 3.11, 3.12 and 3.13 present the density plots of the parameters parameters p_0, q_0 and ϕ and the posterior correlation between parameters p_0 and q_0. It can be seen that probability p_0 is higher that the relevant probability of the p-MRSA Data Set. The reason for this is that MRSA Data Set includes also patients with no positive tests, thus there are a lot more transitions from a non-colonised to a non-colonised state and this has an impact on probability p_0. Here we can see that p_0 and q_0 are moderately correlated comparing to the relevant p-MRSA Data Set result. MRSA Data Set contains all the patients and thus there are less dependencies in the data.

no antimicrobial treatment	
parameters	$E[\cdot \mid \mathcal{S}]$ (s.d.)
p_0	0.9983 (0.0007)
q_0	0.0057 (0.0025)
p_0, q_0 **posterior correlation**	-0.3696
$\boldsymbol{\phi}$	0.3017 (0.0123)

Table 3.9: Summary statistics for p_0, q_0 and ϕ using the MRSA Data Set without antimicrobial treatment.

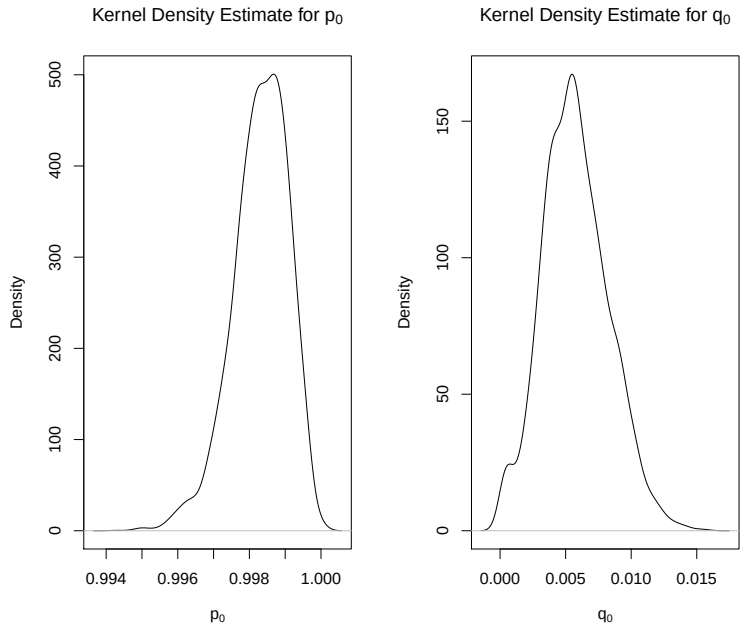


Figure 3.11: Kernel density plots for p_0 and q_0 for the MRSA Data Set without antimicrobial treatment.

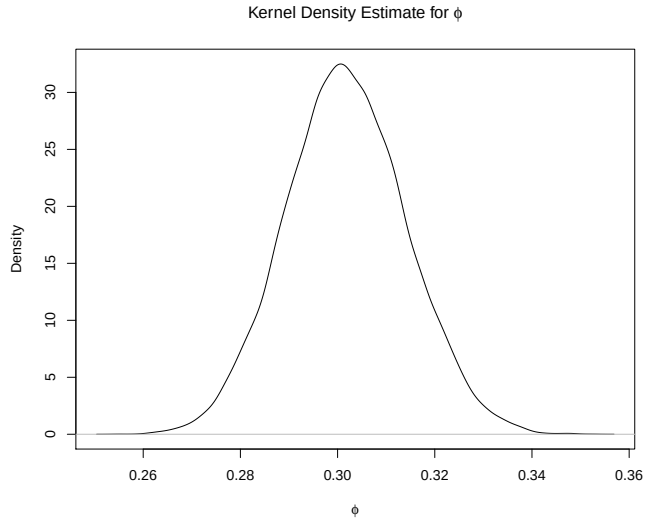


Figure 3.12: Kernel density plots for ϕ for the MRSA Data Set without antimicrobial treatment.

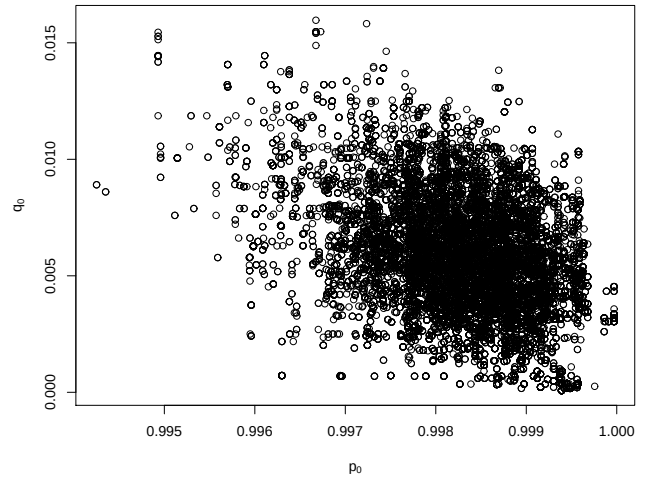


Figure 3.13: Scatterplot presenting the correlation between p_0 and q_0 for the MRSA Data Set without antimicrobial treatment.

Table 3.10 shows the results from the model fit. The posterior mean of the negative predictive value ψ was fount to be equal to $\psi = 0.6785$. It can be seen that the model does not fit well as some of the observed counts are outside the 95% quantiles.

The main complication in using the MRSA data set in our analysis is that the MCMC algorithm needs a lot of time to converge. The data augmentation algorithm we described in section 3.4 requires in every MCMC iteration the up-

	Day Intervals						
	1	**2**	**3**	**4**	**5**	**6**	**7**
obs. counts $N \to N$	**155** (142, 157)	**298** (268, 290)	**301** (276, 295)	**242** (227, 245)	**228** (209, 228)	**357** (336, 357)	**1643** (1683, 1631)
obs. counts $N \to C$	**10** (8, 23)	**11** (18, 39)	**15** (20, 40)	**18** (15, 33)	**14** (14, 32)	**26** (26, 47)	**132** (143, 192)
obs. counts $C \to N$	**8** (7, 14)	**11** (16, 26)	**8** (17, 27)	**11** (7, 18)	**10** (10, 25)	**26** (29, 41)	**72** (168, 195)
obs. counts $C \to C$	**7** (1, 8)	**20** (5, 15)	**9** (1, 9)	**21** (4, 15)	**20** (4, 14)	**24** (9, 21)	**185** (61, 88)

Table 3.10: Model fit for the MRSA Data Set excluding antimicrobial treatment. The intervals in red color show that the equal-tailed 95% quantiles include the number of the observed transition counts.

date of each of the negative tests, which makes it very time consuming especially when the number of parameters updated is also large. An example is that the MRSA Data Set including antimicrobial treatment needs 130 hours to run 100,000 iterations to reach convergence. For this the reason we have not displayed any results for this case.

3.7.3 Results from the p-MRSA Data Set including antimicrobial treatment

Next, we obtain the parameter estimates including information about antimicrobial treatment. We consider all antibiotics and the antiseptic as one group. This means that a patient receiving any of the antimicrobials or treated with the antiseptic is "on" antimicrobial treatment, otherwise they are "off". Table 3.11 presents the summary statistics of the posterior distributions for parameters p_0, q_0, α and β. We can see that antimicrobial treatment seems to have a protective effect when a patient is in a non-colonised state. On the other hand, there is no strong evidence antimicrobial treatment can clear MRSA from colonised patients. Sensitivity ϕ is again around 85%. Posterior correlations of the model parameters are shown in Figure 3.15 where we can see that all the parameters are strongly correlated, possibly because of the dependencies in the data as we only consider patients with at least one positive test. The density plots of the probability a patient remains in a non-colonised state, $p_0 + \alpha$, and the probability that a patient goes from a colonised state to an non-colonised one, $q_0 + \beta$, while they are "on" antimicrobial treatment are shown in Figure 3.14. The same Figure, also shows the density plots of p_0 and q_0 which are the respective probabilities when a patient is "off" antimicrobial treatment.

Antimicrobial treatment		
parameters	$E[\cdot\|Y]$ (s.d.)	95% CI
$\mathbf{p_0}$	0.7783 (0.0784)	(0.6056, 0.8924)
$\mathbf{q_0}$	0.1310 (0.0521)	(0.0543, 0.2526)
$\boldsymbol{\alpha}$	0.1197 (0.0810)	(−0.0044, 0.2953)
$\boldsymbol{\beta}$	−0.0525 (0.0517)	(−0.1697, 0.0269)
$\boldsymbol{\phi}$	0.8576 (0.0340)	(0.7913, 0.9251)

Table 3.11: Summary statistics for p_0, q_0, α, β and ϕ using the p-MRSA Data Set including antimicrobial treatment.

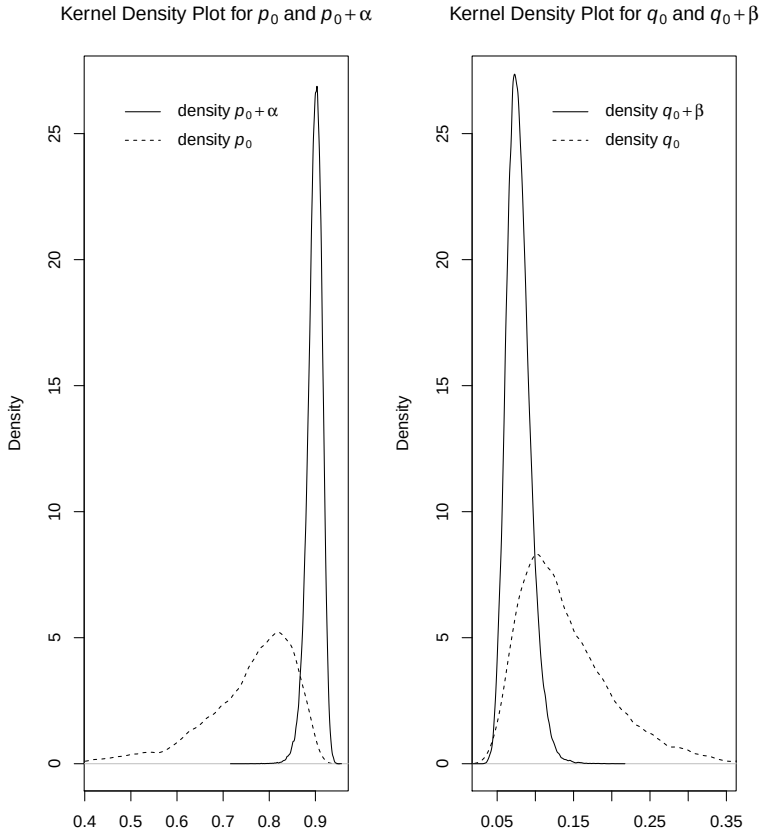


Figure 3.14: Kernel density plots for p_0 and $p_0 + \alpha$, q_0 and $q_0 + \beta$ for the p-MRSA Data Set including antimicrobial treatment.

Table 3.12 presents the equal-tailed 95% quantiles from the model fit simulations along with the observed transition counts for each day interval. The negative predictive value was estimated around 0.8389. It can be seen that the model does not fit well as some of the observed transition counts are outside the equal-tailed 95% quantiles.

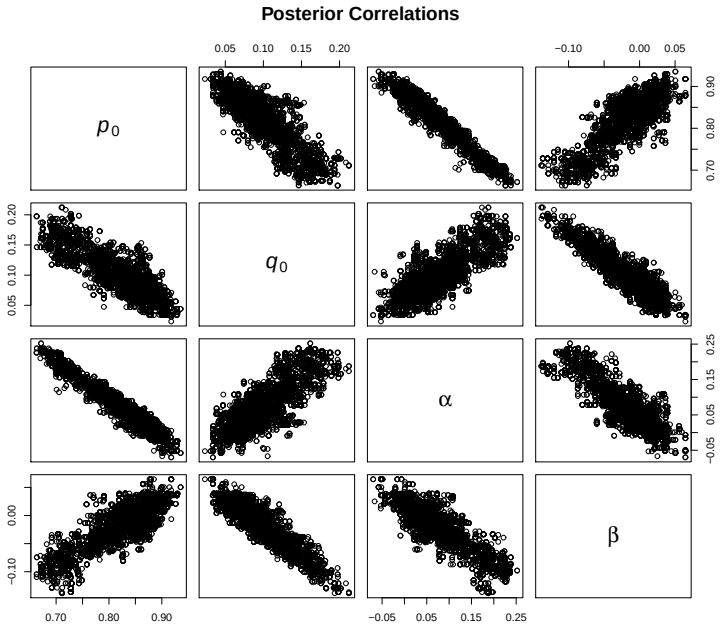


Figure 3.15: Posterior correlations between p_0, q_0, α and β using the p-MRSA Data Set including antimicrobial treatment.

	Day Intervals						
	1	**2**	**3**	**4**	**5**	**6**	**7**
obs. counts $N \to N$	**17** (4, 13)	**19** (6, 17)	**19** (6, 17)	**8** (6, 16)	**17** (6, 18)	**31** (11, 26)	**243** (100, 142)
obs. counts $N \to C$	**10** (3, 13)	**11** (7, 18)	**15** (6, 18)	**18** (8, 21)	**14** (8, 19)	**26** (15, 32)	**132** (124, 158)
obs. counts $C \to N$	**8** (5, 15)	**11** (8, 21)	**8** (5, 15)	**12** (7, 18)	**10** (8, 19)	**26** (16, 32)	**72** (123, 156)
obs. counts $C \to C$	**7** (11, 22)	**20** (16, 30)	**9** (12, 24)	**21** (14, 28)	**20** (15, 29)	**24** (32, 51)	**185** (206, 257)

Table 3.12: Model fit for the model of the p-MRSA Data Set including antimicrobial treatment. The intervals in red color show that the equal-tailed 95% quantiles include the number of the observed transition counts.

Next, we consider the model including antimicrobial treatment but starting from a patient's first positive test.

Starting from first positive test

In this chapter, as well as the previous one, we consider the MRSA carriage levels on each patient separately, so we assume that there is no transmission between the patients. One way to deal with this constraint is to make infer-

ence for the model parameters excluding the patients' information before they were found positive for the first time. The summary statistics of the model's parameter estimates is shown in Table 3.13, and Figure 3.16 presents the posterior density plots of parameters p_0, $p_0 + \alpha$, q_0 and $q_0 + \beta$. It can be seen that antimicrobial treatment has a positive effect on protecting non-colonised patients from MRSA carriage but it cannot help much on its clearance. We can also notice that sensitivity ϕ has a lower value comparing to the one when the whole p-MRSA Data Set was used. A possible reason for this is that our model assumes that if a patient has a negative test after a positive it is more likely that this test would be false negative. Finally, Table 3.14 presents the results from the 95% quantiles from the simulations for the model fit. Again, some of the observed transition counts are outside of the equal-tailed 95% quantiles which suggests a poor fit.

Antimicrobial treatment		
parameters	$E[\cdot \mid Y]$ (s.d.)	95% CI
$\mathbf{p_0}$	0.9079 (0.0472)	(0.7730, 0.9712)
$\mathbf{q_0}$	0.0482 (0.0188)	(0.0186, 0.0927)
$\boldsymbol{\alpha}$	0.0753 (0.0478)	(0.0103, 0.2107)
$\boldsymbol{\beta}$	−0.0085 (0.0182)	(−0.0518, 0.0208)
$\boldsymbol{\phi}$	0.7857 (0.0377)	(0.7123, 0.8594)

Table 3.13: Summary statistics for p_0, q_0, α, β and ϕ using the p-MRSA Data Set with antimicrobial treatment starting patients' first positive test.

Day Intervals							
	1	**2**	**3**	**4**	**5**	**6**	**7**
obs. counts $N \to N$	**3** (0,5)	**2** (1,8)	**1** (0,5)	**1** (1,8)	**2** (1,7)	**12** (4,14)	**134** (36,64)
obs. counts $N \to C$	**1** (1,7)	**0** (2,11)	**1** (1,8)	**0** (3,12)	**1** (3,11)	**5** (7,19)	**37** (78,104)
obs. counts $C \to N$	**8** (1,8)	**11** (3,13)	**8** (1,7)	**12** (3,12)	**10** (3,11)	**26** (8,21)	**72** (77,105)
obs. counts $C \to C$	**7** (4,12)	**20** (9,21)	**9** (4,13)	**21** (10,21)	**20** (9,20)	**24** (22,38)	**185** (170,217)

Table 3.14: Model fit for the model of the p-MRSA Data Set including antimicrobial treatment starting from first positive test. The intervals in red color show that the equal-tailed 95% quantiles include the number of the observed transition counts.

The above results make us consider each antimicrobial group separately. The results are presented in the following section.

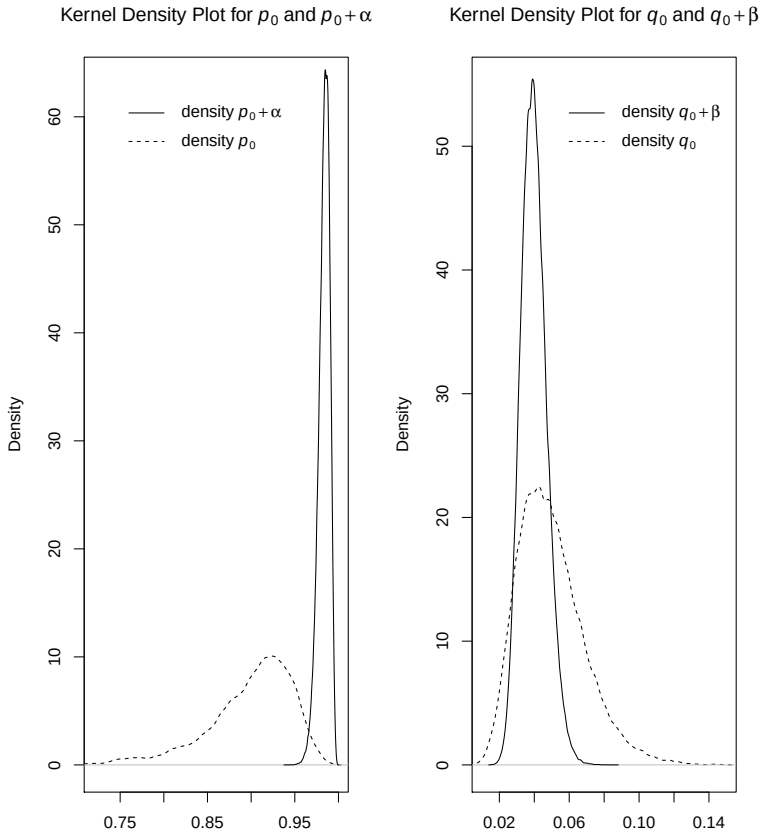


Figure 3.16: Kernel density plots for p_0 and $p_0 + \alpha$, q_0 and $q_0 + \beta$ for the p-MRSA Data Set with antimicrobial treatment starting from first positive test.

Considering each antimicrobial group separately

In this section we present the results of each antimicrobial group separately of the p-MRSA Data Set, p-Wounds Data Set and p-Respiratory Data Set. For each group, if a patient has received a particular antimicrobial treatment one day we assume that they are "on" this antimicrobial that day. Otherwise they are "off" that antimicrobial.

Parameter estimates are shown in Tables B.1, B.2 and B.3, and in Figures B.1 and B.2. It can be seen that swab test sensitivity (Table B.3), ϕ, is around 0.85. Results of the estimates for the negative predictive value ψ are also shown in Table B.3. Considering the antimicrobial groups (Tables B.1 and B.2) there is evidence that patients on Oxazolidinone, Nitroimidazole, Cephalosporin and Rifamycin groups have higher probability to clear MRSA carriage. Moreover,

there is little evidence that Oxazolidinone protects against MRSA, while on the other hand, Macrolide and Cephalosporin groups have the opposite effect. Finally, decolonisation treatment using Chlorhexidine seems to be effective on both protecting against MRSA recolonisation and on MRSA clearance.

Considering the model assessment, Table B.4 shows the equal-tailed 95% quantiles from the simulations for each antimicrobial treatment. It can be seen that the model fit is not so good as some of these quantiles do not include the observed transition counts.

Next, we obtain the parameter estimates from the p-MRSA Data Set starting from patients' first positive test. The results are shown in Tables B.5 and B.6 and Figures B.3 and B.4. Table B.7 shows the estimates of the swab test sensitivity, ϕ and negative predictive value ψ. In Table B.6, we notice that Oxazolidinone, Rifamycin and Cephalosporin have a positive effect on the clearance of MRSA carriage. Moreover, Glycopeptide may protect against MRSA colonisation but on the other hand, it can be seen that Rifamycin has the opposite effect. Lastly, Antiseptic use seems to help in the clearance of MRSA.

Table B.8 shows the equal-tailed 95% quantiles for the model fit simulations. It can be seen that some of the observed transition counts are outside the quantiles and as a result the model does not fit adequately.

3.7.4 p-Wounds Data Set

This section includes the results from the p-Wounds Data Set firstly considering all the data and later starting from patients' first positive test.

Parameters estimates are presented in Tables B.9 and B.10 and Figures B.5 and B.6. It can be seen that Oxazolidinone, Glycopeptide, Macrolide and Penicillin are effective in clearing MRSA carriage. In contrast, Macrolide has a negative effect on preventing MRSA colonisation. The results of swab test sensitivity, ϕ and the estimates for the negative predictive value ψ are shown in Table B.11.

The results for the model fit simulations are shown in Table B.12. Negative predictive value ψ was found to be around 0.64. It can be seen that the model fit is not adequate.

In the case of starting from patients' first positive test, the results can be seen in

Tables B.13 and B.14 and Figures B.7 and B.8. There is some evidence that Oxazolidinone, Rifamycin, Macrolide and Aminoglycoside can help in the clearance of MRSA carriage. Moreover, Aminoglycoside and Macrolide may not protect against MRSA. The estimates of sensitivity ϕ and the estimates for the negative predictive value ψ are shown in Table B.15.

Table B.16 shows the results from the model fit simulations. The negative predictive value was around 0.61. It can be seen that the model does not fit well as again some of the observed transition counts are outside the equal-tailed 95% quantiles.

3.7.5 p-Respiratory Data Set

Here we include the results from the p-Respiratory Data Set.

Tables B.17 and B.18 and Figures B.9 and B.10 present the results for the parameters p_0, q_0, α and β. It can be seen that Oxazolidinone is effective in the clearance of MRSA. On the other hand, Quinolone, Nitroimidazole and Macrolide may not prevent from MRSA colonisation. Swab test sensitivity results and the estimates for the negative predictive value ψ are shown in Table B.19.

Regarding the model fit, Table B.20 show the equal-tailed 95% quantiles obtained by the simulations. It can be seen that the model does not fit well.

Finally, Tables B.5 and B.22 and Figures B.11 and B.12 show the parameter estimates for Respiratory Data Set starting from patients' first positive test. We can see that Oxazolidinone can help in MRSA clearance, while Polymyxin and Quinolone might have a negative effect on protection against MRSA colonisation. Table B.23 show the estimates for sensitivity ϕ and the negative predictive value ψ.

The model assessment simulation results are shown in Table B.24. It can be seen that the model fit is acceptable.

3.8 Summary

In this chapter a discrete time hidden Markov model was used to model the colonisation status of individual patients and assess the effects of antibiotics

and antiseptics on carriage levels of MRSA. We assumed that there was imperfect swab test sensitivity so that some of the negative test results might be false negative. However, we considered perfect specificity. We found that Oxazolidinone and the Antiseptic treatment are effective in the clearance of MRSA carriage.

The parameter estimates for the HMM model were obtained using a data augmented MCMC algorithm in a Bayesian framework. This algorithm enabled us to estimate the true, unobserved, Markov process of patients' colonisation states. For the model assessment we used simulated data sets based on the parameters' estimates obtained by the MCMC and compared their distributions to the observed data.

To validate our methodology we used simulated data initially with fixed day-intervals and then using the day-intervals from the p-MRSA Data Set. In both cases we did not take into account information about the antimicrobial treatment. We found that the estimated values for the parameters were in agreement with the values set while constructing the simulated data set. We found that the model fitted adequately.

The results using the GSTT data showed that the antimicrobial treatment can protect against MRSA colonisation but it cannot help to its clearance. The same results were drawn when the data including only the information after patients' first positive test were used. In each case the model did not fit very well.

Looking at each antimicrobial group separately, all three data sets obtained that Oxazolidinone can be effective on MRSA clearance. This result is in agreement with previous reports and more specifically on the effectiveness of Linezolid which belongs to the Oxazolidinones, [Dennis et al., 2002; Itani et al., 2010]. In addition, Nitroimidazole, Cephalosporin and Rifamycin seem to have similar effects for the p-MRSA Data Set and Macrolide and Penicillin for the p-Wounds Data Set. However, in some cases, we found some evidence that Macrolide and Cephalosporin might not can be protective against MRSA. This result is consistent with the literature, [Dancer, 2001; Monnet et al., 2004; Tacconelli et al., 2008]. Lastly, decolonisation policy found to help clear MRSA only for the p-MRSA Data Set. The model fit was adequate in some cases.

Considering only the data starting from patient's first positive test, we derived

that Oxazolidinone can help on MRSA clearance in all the three data sets. Moreover, we obtained that the same effect holds for Rifamycin and Cephalosporin for the p-MRSA Data Set, Rifamycin, Macrolide and Aminoglycoside for the p-Wounds Data Set. On the other hand, no evidence was found that any antimicrobial can prevent MRSA colonisation apart from Glycopeptide on the p-MRSA Data Set. Antiseptic treatment can be effective on the MRSA clearance only for the p-MRSA Data Set. The model fitted better in this case.

In conclusion, some of the antimicrobial treatment seems to be effective against MRSA carriage. Decolonisation policy however seem to have an effect for the p-MRSA Data Set, result that is consistent with the literature, [Batra et al., 2010; Kypraios et al., 2010; Macfarlane et al., 2007]. Nonetheless, the model fit was not good enough in many cases. This suggests that the assumption we made that there is no MRSA transmission between the patients was not appropriate. In the following chapter we will overcome this constraint assuming that MRSA can be transmitted between patients.

CHAPTER 4

Assessing the effect of antimicrobial treatment on MRSA transmission

4.1 Introduction

In this chapter we are going to examine the effects of antimicrobial treatment on the transmission of MRSA. In Chapters 2 and 3 we investigated the effects of antibiotics and antiseptics on within-host carriage levels of MRSA using a Markov chain and a hidden Markov chain model respectively. Both models however, showed some evidence of lack of fit, at least using the criteria we adopted. One possible reason for this is our assumption that our models did not account for transmission between the patients. In this chapter we are going to relax this assumption using an individual-level discrete-time stochastic epidemic model that takes (indirect) person-to-person MRSA transmission into account. Thus, we will follow a different approach than in the previous chapters, assuming that MRSA is transmitted to patients either from the background or indirectly, for example via the hands of healthcare workers. We will investigate the impact of antimicrobial treatment on the transmission of MRSA.

Mathematical models have been used over the years to describe the spread of antimicrobial resistant nosocomial bacteria. Simulation studies using deterministic models have been proposed by Sébille et al., [Sébille et al., 1997], who used a model to describe person-to-person and person-healthworker transmission in an ICU ward. Results showed that staff member handwashing had an effect

in reducing their colonisation but there was only a slight decrease in patient colonisation. Austin et al. in [Austin et al., 1999] used a compartmental deterministic model to show how infective control measures and antibiotic reduction policies can have an effect on Vancomycin-resistant Enterococcus (VRE) transmission in an ICU. They found that not only measures such as handwashing and cohorting were effective but also careful antibiotic use. A similar model to [Austin et al., 1999] was proposed by Lipsitch et al. [Lipsitch et al., 2000]. In their work the cycling strategy is proposed, in which a first class of antibiotics is used for infection treatment, for a period of time, and when resistance is detected, this treatment is replaced by a second class of antibiotic treatment in which resistance is rare or absent. Results showed resistance was decreasing according to patient turnover within the ward. A similar study has been performed by Haber et al., [Haber et al., 2010], where a simulation study is proposed using a deterministic and a stochastic model that describe the transmission dynamics of drug-sensitive and drug-resistant bacteria. The authors assessed the effectiveness of switching from a first class of antibiotics, for which there were resistant bacteria, to a second class of antibiotics. Then, they explored how effective is the latter class to successfully treat the patients and reducing the frequency of resistance to other antimicrobials. Results showed that the proposed protocol can have an effect when there is an early switch to second class of antimicrobials.

Many studies have used stochastic models to analyse the spread of nosocomial pathogens. A stochastic Markov chain model was proposed by Pelupessy et al., [Pelupessy et al., 2002], for the transmission dynamics and importance of different colonisation routes of bacteria in a hospital ward using longitudinal data on the number of colonised patients. One of the basic assumptions was that surveillance swabs' sensitivity was perfect. They used maximum likelihood methods to obtain the transmission rates for two data sets of data, VRE and *Pseudomonas aeruginosa*, which were taken from different ICUs.

An extension to the Markov model in [Pelupessy et al., 2002] was introduced by Cooper et al. in [Cooper and Lipsitch, 2004], where hidden Markov models (HMM) were used to infer patients' unknown colonisation times. The data they used were time series with at least 40 continuous months of data having an average of at least on case per month, for MRSA, VRE and third generation

cephalosporin resistant Gram-negative rods (R-GNR), coming from a surveillance study over 40 months from ICU wards at 41 U.S hospitals. Three different models were fitted to these data, namely, a simple Poisson model, a standard HMM using a Poisson observation model, and a HMM model based on the SIS epidemic model. A Newton-type algorithm was used for likelihood maximisation. Model assessment was made using Akaike information criterion and a parametric bootstrap method.

Forrester and Pettit, [Forrester and Pettitt, 2005], used a stochastic epidemic model to estimate the transmission rates of patients with MRSA in an ICU ward. The swabs were taken at fixed intervals twice a week. The authors described the probability of colonisation as a function with three parameters, namely background pressure, pressure from non-isolated colonised patients and from isolated colonised patients. The model fit was assessed using a deviance information criterion. A limitation of this study is the assumption that colonisations within each swab-test interval were considered unrelated to each other and occurred by either a colonised patient in a previous interval or background.

A later work by Forrester et al. [Forrester et al., 2007], uses a stochastic epidemic model to estimate the transmission rate parameters of a nosocomial pathogen and is an extension of [Forrester and Pettitt, 2005]. The model, as in [Forrester and Pettitt, 2005], consisted of three colonisation rate parameters, namely background rate, non-isolated, and isolated colonised rate but it also accounted for the importation probability i.e. the probability that a patient was already colonised on admission, and that there was imperfect swab test sensitivity while specificity was assumed to be perfect. For the inference, MCMC algorithms were used in a Bayesian framework. This methodology was applied to MRSA data taken from an ICU ward.

Another study using the methodology in [Forrester et al., 2007] is described in Kypraios et al., [Kypraios et al., 2010]. A stochastic transmission model was used to estimate the importance of undetected MRSA carriage and the effect of barrier precautions in the prevention of MRSA transmission in eight ICU wards. The model was fitted to data in a Bayesian framework using data-augmentation MCMC algorithms.

To our knowledge there has not been any similar work considering the effect

of antimicrobial agents on MRSA using stochastic transmission models. In this chapter we are going to extend and adapt the methodology described in [Forrester et al., 2007] and [Kypraios et al., 2010] and apply it to the antimicrobial treatment data introduced in Chapter 1. We are going to fit three different models to the data and obtain estimates using MCMC methods. Finally we give information about the model adequacy.

The outline of the chapter is as follows: in Section 4.2 we describe the models we are going to use and Section 4.3 gives the likelihood. In Section 4.4 we give the MCMC methodology and in Section 4.5 we describe how we assess the model. In Section 4.6 we present results using simulated data and in Section 4.7 we present the results obtained from the three data sets, namely the MRSA Data Set, Wounds Data Set and Respiratory Data set. Finally we conclude this chapter discussing any limitations of the proposed models.

4.2 Model

In this chapter we assume that there is transmission between the patients in an ICU ward. Thus, we will divide the patients into two groups according to which ICU ward they were admitted into. The summary statistics as well as information about the antimicrobial treatment for each ICU ward and each data set is shown in 1.3.2 and 1.3.3.

We consider the two ICU wards, ward 1 and ward 2. In each ward, a patient i is admitted at time a_i and discharged at time d_i during the study period. There might be multiple admissions or discharges occurring at the same time, but we treat the patients as separate admission episodes. We will use an individual-level stochastic epidemic model to describe the transmission dynamics of MRSA within each ICU ward. We will work in discrete time so we will assume that events occur daily.

Patients who enter the ward can be either susceptible (S) or colonised (C) with MRSA bacteria. Susceptible patients can acquire MRSA indirectly via the hands of healthcare workers or by background transmission. Background transmission includes the nosocomial transmission coming from outside the ward such as transmission from colonised healthcare workers or contaminated hospital

equipment.

Moreover, some patients might be already colonised with MRSA before they enter the ICU ward. When a patient enters the ICU already colonised, we will refer to them as "colonised on admission" and when a patient is colonised during their stay in the ICU we will refer to them as "colonised on the ward".

We assume that once a patient becomes colonised, they remain in this state until they leave the ward. The reason for this is because of the duration of colonisation with MRSA bacteria that can last for several months [Robicsek et al., 2009].

Patients in the ICU ward undergo tests in order to determine whether they are colonised or not. We assume imperfect sensitivity ϕ and that specificity is 100%. Sensitivity ϕ denotes the probability that an observed positive test is actually positive, while specificity denotes the probability that a negative test is observed correctly.

Finally, a patient can be "on" or "off" antimicrobial treatment each day during their stay in the ICU, which means that they receive antimicrobials or not that day. We define $\Delta(n) \in \{ON, OFF\}$ be the antimicrobial state on day n.

We have also made the following assumptions:

1. All patients in the ICU have at least one test.
2. Patients are admitted at the start and discharged at the end of each day.
3. Antimicrobial treatment is received after admission and before discharge.
4. Swab tests were taken at the start of the day, after admission.
5. If a swab test is found positive on patient's admission date we assume that the patient has imported MRSA.
6. Colonised patients remain colonised until they leave the ward.
7. If a patient is colonised on their admission to the ward they can transmit MRSA the same day.
8. If a patient becomes colonised in the ward they can transmit the bacterium from the following day.

9. If a patient becomes colonised in the ward on their discharged day they are ignored as they leave the ward.

We define $q(n)$ as the colonisation pressure acting on a given susceptible on day n, where n refers to a day during the study period. The basic assumption of the model is that a susceptible patient on day n remains susceptible on day $n+1$ with probability $e^{(-q(n))}$, with all susceptibles behaving independently in this respect.

We will consider three different transmission models to describe the transmission process.

Susceptibily Model : This model assumes that a susceptible patient receives different colonisation pressure from background transmission and colonised patients according to whether or not they receive antimicrobial treatment. We do not take the antimicrobial state of colonised patients into account. Specifically, we have

$$q(n) = \beta_0 \mathbb{1}_{OFF} + \tilde{\beta}_0 \mathbb{1}_{ON} + \beta_1 C_n \mathbb{1}_{OFF} + \tilde{\beta}_1 C_n \mathbb{1}_{ON}, \tag{4.2.1}$$

where "$\sim$" means "on" antimicrobial treatment, $\mathbb{1}_{\Delta}$ denotes the indicator function of the event $\Delta(n) \in \{ON, OFF\}$, C_n denotes the number of colonised patients on day n, $\beta_0/\tilde{\beta}_0$ is the background transmission rate to susceptibles being "off"/"on" antimicrobial treatment respectively and $\beta_1/\tilde{\beta}_1$ is the transmission rate to susceptibles being "off"/"on" antimicrobial treatment from the number of colonised patients at day n.

Figure 4.1 represents the *Susceptibility Model* in (4.2.1).

Infectivity Model : In this model we do not take into account whether the susceptible is "on" antimicrobial treatment or not. However, we assume that colonisation pressure on a susceptible comes from the background rate and from colonised patients being "off"/"on" antimicrobials. Here, we do not take the antimicrobial state of susceptible patients into account. More specifically,

$$q(n) = \beta_0 + \beta_1 C_n + \beta_1^{'} \tilde{C}_n, \tag{4.2.2}$$

where "$\sim$" means "on" antimicrobial treatment, $C_n/\tilde{C}_n$ denotes the number of colonised individuals who are "off"/"on" antimicrobial treatment on day

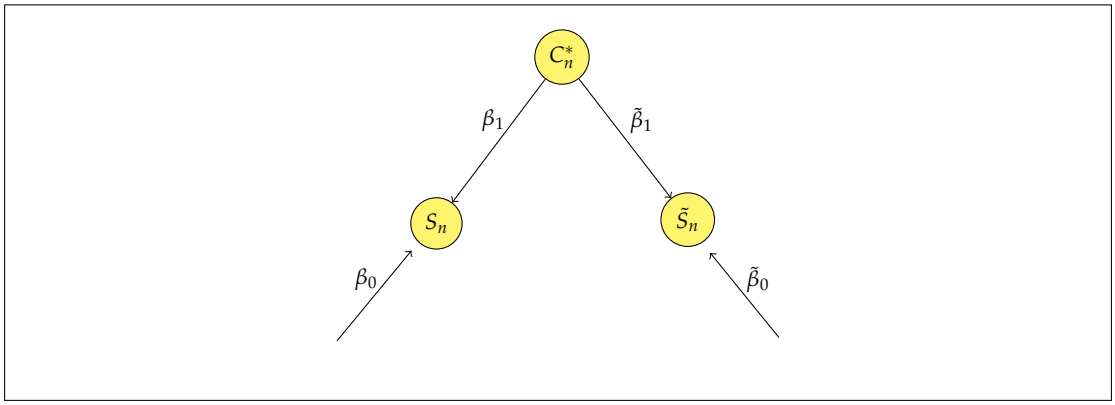


Figure 4.1: Graph representing the *Susceptibility Model* in (4.2.3) where "$\sim$" means "on" a given antimicrobial treatment. Susceptible patients who are "off"/"on" antimicrobial treatment, receive colonisation pressure from either the background, $\beta_0/\tilde{\beta}_0$, or by colonised patients, $\beta_1/\tilde{\beta}_1$. "$*$" denotes that antimicrobial treatment information has not been taken into account for that patient group.

n, β_0 is the background transmission and $\beta_1/\beta_1^{'}$ are the transmission rates to susceptible on day n from $C_n/\tilde{C}_n$ respectively.

Infectivity Model (4.2.2) is represented in Figure 4.2.

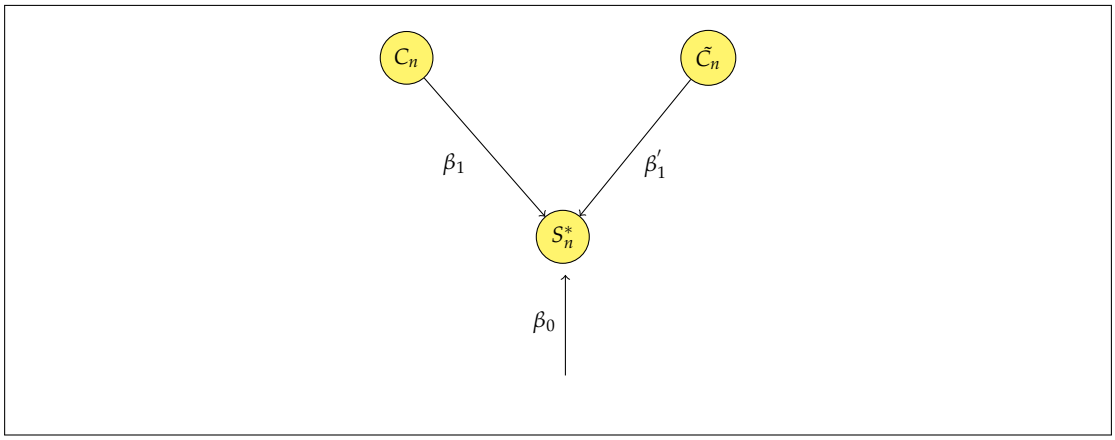


Figure 4.2: Graph representing the *Infectivity Model* in (4.2.3) where "$\sim$" means "on" a given antimicrobial treatment. Susceptible patients receive colonisation pressure from either the background, β_0, or by colonised patients, $\beta_1/\beta_1^{'}$ who are "off"/"on" antimicrobial treatment. "$*$" denotes that antimicrobial treatment information has not been taken into account for that patient group.

Full Model: This model assumes that both susceptible and colonised individuals can be "on" or "off" antimicrobial treatment receiving at the same time back-

ground pressure according to their antimicrobial state. Specifically we have

$$q(n) = \beta_0 \mathbb{1}_{OFF} + \tilde{\beta}_0 \mathbb{1}_{ON} + \beta_1 C_n \mathbb{1}_{OFF} + \beta_1^{'} \tilde{C}_n \mathbb{1}_{OFF} + \tilde{\beta}_1 C_n \mathbb{1}_{ON} + \tilde{\beta}_1^{'} \tilde{C}_n \mathbb{1}_{ON}, \tag{4.2.3}$$

where "$\sim$" means "on" antimicrobial treatment, $\mathbb{1}_{\Delta}$ denotes the indicator function of the event $\Delta(n) \in \{ON, OFF\}$, $C_n/\tilde{C}_n$ denotes the number of colonised individuals who are "off"/"on" antimicrobial treatment on day n, $\beta_0/\tilde{\beta}_0$ is the background transmission rate to susceptibles being "off"/"on" antimicrobial treatment respectively, $\beta_1/\beta_1^{'}$ is the transmission rate to S_n from $C_n/\tilde{C}_n$ and $\tilde{\beta}_1/\tilde{\beta}_1^{'}$ is the transmission rate to $\tilde{S_n}$ from $C_n/\tilde{C}_n$.

A representation of the *Full Model* (4.2.3) is presented in Figure 4.3.

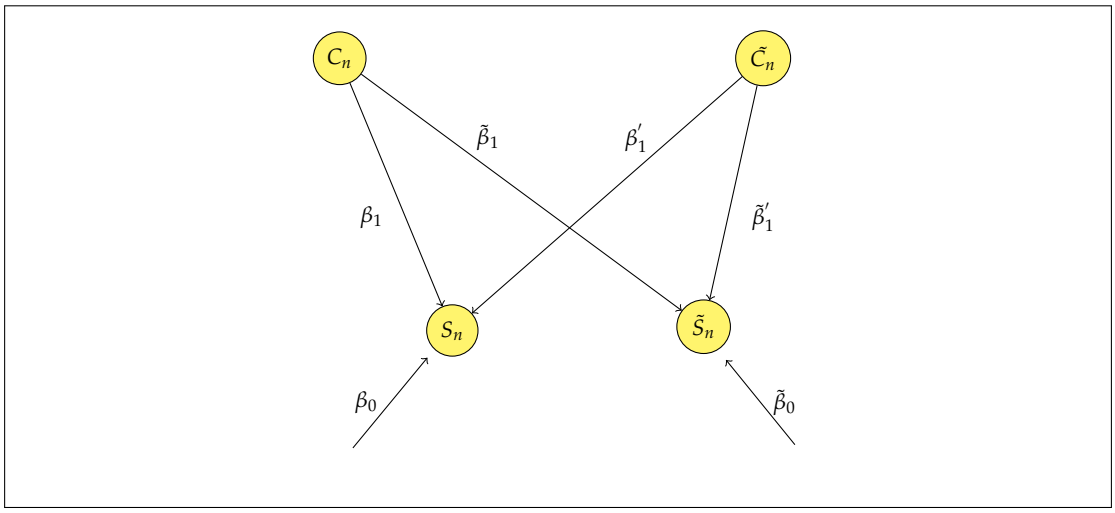


Figure 4.3: Graph representing the *Full Model* in (4.2.3) where "$\sim$" means "on" a given antimicrobial treatment. Susceptible patients depending on their antimicrobial state receive colonisation pressure from either the background, $\beta_0/\tilde{\beta}_0$, or by colonised patients, $\beta_1/\beta_1^{'}$ who are "off" ($\beta_1/\tilde{\beta}_1$) or "on" ($\beta_1^{'}/\tilde{\beta}_1^{'}$) antimicrobial treatment.

4.3 Likelihood

The data of patient i, $i = 1, ..., N$, where N is the total number of patients in the ward, consist of the following quantities,

- admission time a_i,
- discharge time d_i,

- test dates $\mathbf{t}_i = \left(t_i^{(1)}, t_i^{(2)}, ..., t_i^{(m_i)}\right)$, where m_i is the number of tests of patient i,
- test results $\mathbf{r}_i = \left(r_i^{(1)}, r_i^{(2)}, ..., r_i^{(m_i)}\right)$,
- information about the antimicrobial treatment they were receiving each day $\boldsymbol{\delta}_i = \left(\delta_i^{(1)}, \delta_i^{(2)}, ..., \delta_i^{(l_i)}\right)$, where l_i denotes the number of days in the ICU of patient i.

The probability that a patient acquires MRSA on day n is given by $1 - \exp(-q(n))$.

We define ψ_i, $i = 1, \ldots, N$, be the colonisation status of each patient i, i.e.

$$\psi_i = \begin{cases} 0 & \text{if colonised in the ward} \\ 1 & \text{if colonised on admission} \\ 2 & \text{if not colonised} \end{cases}, \tag{4.3.1}$$

We also assume that each patient i has a colonisation time c_i. If a patient was colonised in the ward, then $a_i \leq c_i \leq d_i$. However, when a patient enters the ward they might be already colonised with MRSA. In this case we set $c_i = a_i - 1$. If patient i was never colonised, $c_i = \infty$.

It is important to note that patient i with a colonisation time $c_i \leq \infty$, joins the number of colonised patients C_n the next day.

We define z as the probability that a patient is colonised on admission. Let n_c^a denote the number of patients in the ward who were admitted colonised. Then, $n_c^a = \sum_{i=1}^{N} \mathbb{1}_{\{\psi_i = 1\}}$.

We assume that colonisation times are not observed.

Let $\mathbf{a} = (a_1, a_2, ..., a_N)$, $\mathbf{d} = (d_1, d_2, ..., d_N)$, $\boldsymbol{\delta} = (\boldsymbol{\delta}_1, \boldsymbol{\delta}_2, ..., \boldsymbol{\delta}_N)$, $\mathbf{t} = (\mathbf{t}_1, \mathbf{t}_2, ..., \mathbf{t}_N)$ and $\mathbf{r} = (\mathbf{r}_1, \mathbf{r}_2, ..., \mathbf{r}_N)$ be the vectors of all the admission times, discharge times, antimicrobial information, test dates and test results respectively. These quantities are observed and thus they are assumed known.

Furthermore, we define n_{TP} and n_{FN} be the number of true positive and false negative tests in the ward. Since we have assumed that specificity is perfect, the number n_{TP} is known, while the assumption for imperfect sensitivity implies that n_{FN} is unknown.

Let admission times, **a**, discharge times, **d**, antimicrobial treatment δ and test dates **t** be defined by vector $\mathbf{y} = (\mathbf{a}, \mathbf{d}, \delta, \mathbf{t})$. Note that vector **y** does not have an underlying probability model while we have a model for test results **r** with parameters $\boldsymbol{\theta}$, where $\boldsymbol{\theta} = (\beta_0, \tilde{\beta_0}, \beta_1, \tilde{\beta_1})$ for the *Susceptibility Model*, $\boldsymbol{\theta} = \left(\beta_0, \beta_1, \beta_1^{'}\right)$ for the *Infectivity Model* and $\boldsymbol{\theta} = \left(\beta_0, \tilde{\beta_0}, \beta_1, \tilde{\beta_1}, \beta_1^{'}, \tilde{\beta_1^{'}}\right)$ for the *Full Model*.

We would like to estimate the parameters $\boldsymbol{\theta}$ given **y** and **r**. However, the likelihood $\pi(\mathbf{r}|\boldsymbol{\theta}, \mathbf{y})$ is intractable due to unknown colonisation times. Thus, we will need to augment the observed data **y** with the colonisation times **c** and therefore we have

$$\pi(\mathbf{c}, \mathbf{r}|\boldsymbol{\theta}, \mathbf{y}) = \pi(\mathbf{r}|\mathbf{c}, \boldsymbol{\theta}, \mathbf{y})\pi(\mathbf{c}|\boldsymbol{\theta}, \mathbf{y}), \tag{4.3.2}$$

where **c** contains all the c_i's and ψ_i's. The term $\pi(\mathbf{c}|\boldsymbol{\theta}, \mathbf{y})$ contains information for patients who are colonised on admission as well as colonised in the ward and can be expressed as

$$\pi\left(\mathbf{c} \mid \boldsymbol{\theta}, \mathbf{y}\right) = z^{n_c^a}\left(1-z\right)^{N-n_c^a} \times \left(\prod_{j:\psi_j=0}\left(1-\exp(-q(c_j))\right)\right)\prod_{i:\psi_i\neq 1}\exp\left(-\sum_{n=a_i}^{min(d_i,c_i-1)} q(n)\right), \tag{4.3.3}$$

where,

- $z^{n_c^a}\left(1-z\right)^{N-n_c^a}$ takes into account those individuals colonised on admission,
- $\left(\prod_{j:\psi_j=0}(1-\exp(-q(c_j)))\right)$ gives the pressure on the susceptible j just before they become colonised on day c_j, and
- $\prod_{i:\psi_i\neq 1}\exp\left(-\sum_{n=a_i}^{min(d_i,c_i-1)} q(n)\right)$ gives the total colonisation pressure to susceptible patients during their time in the ward.

The term $\pi(\mathbf{r}|\mathbf{c}, \boldsymbol{\theta}, \mathbf{y})$ in equation (4.3.2) gives the probability of the observed test results and is given by

$$\pi(\mathbf{r}|\mathbf{c}, \boldsymbol{\theta}, \mathbf{y}) = \phi^{n_{TP}}(1-\phi)^{n_{FN}}. \tag{4.3.4}$$

Taking into account equations (4.3.4) and (4.3.3) the likelihood can be written as follows

$$\pi(\mathbf{c},\mathbf{r}|\boldsymbol{\theta},\mathbf{y}) \propto \phi^{n_{TP}}(1-\phi)^{n_{FN}} z^{n_c^a}(1-z)^{N-n_c^a} \times \left(\prod_{j:\psi_j=0}(1-\exp(-q(c_j)))\right) \prod_{i:\psi_i\neq 1} \exp\left(-\sum_{n=a_i}^{min(d_i,c_i-1)} q(n)\right). \quad (4.3.5)$$

4.4 Inference

We are interested in finding the estimates for the parameters for each of the three models. For this purpose we will use a data-augmented Markov Chain Monte Carlo (MCMC) algorithm in a Bayesian framework. The methodology we are going to use was introduced by O'Neill and Roberts, [O'Neill and Roberts, 1999], where the authors used Bayesian inference for partially observed data using MCMC methods. We are going to follow the same methods presented by Kypraios et al., [Kypraios et al., 2010], and Forrester et al., [Forrester et al., 2007], for the estimation of the parameters of interest. The difference is that the aforementioned articles are in continuous time while we conduct our analysis in discrete time, and also we use different models to take account of the antimicrobial treatments.

4.4.1 Prior distributions

We would like to draw samples from the posterior density

$$\pi(\boldsymbol{\theta},\mathbf{c} \mid \mathbf{r},\mathbf{y}) \propto \pi(\mathbf{r},\mathbf{c} \mid \boldsymbol{\theta},\mathbf{y})\pi(\boldsymbol{\theta}),$$

where $\pi(\boldsymbol{\theta})$ is the prior density of $\boldsymbol{\theta}$. We assume that individual parameters in $\boldsymbol{\theta}$ are a priori independent.

We set non-informative prior distributions for the parameters ϕ and z as follows,

$$\phi,\, z \sim\ Beta(1,1),$$

where $Beta(1,1)$ is the beta distribution with parameters $\alpha = 1$ and $\beta = 1$

respectively, i.e. ϕ, $z \sim \mathrm{U}(0,1)$.

We also set non-informative priors for each of the model's remaining parameters. Specifically we have

Susceptibility Model:

$$\beta_0,\ \tilde{\beta}_0,\ \beta_1,\ \tilde{\beta}_1 \sim \mathrm{Exp}(10^{-3}),$$

Infectivity Model :

$$\beta_0,\ \beta_1,\ \beta_1^{'} \sim \mathrm{Exp}(10^{-3}),$$

Full Model:

$$\beta_0,\ \tilde{\beta}_0,\ \beta_1,\ \tilde{\beta}_1,\ \beta_1^{'},\ \tilde{\beta}_1^{'} \sim \mathrm{Exp}(10^{-3}),$$

where $\mathrm{Exp}(10^{-3})$ is the exponential distribution with mean and standard deviation 10^3.

4.4.2 Updating the parameters

We update the parameters z and ϕ using Gibbs steps from their full conditional distributions. Let $\boldsymbol{\theta}_{-z}$ be the vector $\boldsymbol{\theta}$ with parameter z removed. Then we have

$$z \mid \boldsymbol{\theta}_{-z}, \mathbf{y}, \mathbf{c}, \mathbf{r} \sim Beta(1 + n_{TP}, 1 + n_{FN}),$$
$$\phi \mid \boldsymbol{\theta}_{-\phi}, \mathbf{y}, \mathbf{c}, \mathbf{r} \sim Beta(1 + n_c^a, 1 + N - n_c^a).$$

We update the parameters β_i, $i = 1, 2, ..., m$, where m is the number of β parameters for each model, using a Gaussian random walk Metropolis algorithm. For each iteration k, let $\beta_i^{(k)}$ denote the current parameter and β_i^* be the candidate. Using a univariate normal proposal distribution $N(\beta_i^*, \sigma_i)$, $\beta_i^* > 0$, we draw the proposal value β_i^*, where σ_i is chosen in a way that the acceptance rate is around 0.25 [Roberts et al., 1997].

The probability that the candidate point β_i^* is accepted is:

$$\min\left(1, \frac{\pi\left(\beta_i^* | \boldsymbol{\theta}_{-\beta_i^{(k)}}, \mathbf{y}, \mathbf{c}, \mathbf{r}\right) g\left(\beta_i^{(k)} | \beta_i^*\right)}{\pi\left(\beta_i^{(k)} | \boldsymbol{\theta}_{-\beta_i^{(k)}}, \mathbf{y}, \mathbf{c}, \mathbf{r}\right) g\left(\beta_i^* | \beta_i^{(k)}\right)}\right),$$

where,

$\pi\left(\beta_i^*|\boldsymbol{\theta}_{-\beta_i^{(k)}}, \mathbf{y}, \mathbf{c}, \mathbf{r}\right)$ is the full conditional distribution of β_i^*, and $g\left(\beta_i^*|\beta_i^{(k)}\right)$ and $g\left(\beta_i^{(k)}|\beta_i^*\right)$ are the proposal densities for a move from $\beta_i^{(k)}$ to β_i^* and vice versa. It is shown in 1.5.3 that $\frac{g\left(\beta_i^{(k)}|\beta_i^*\right)}{g\left(\beta_i^*|\beta_i^{(k)}\right)} = 1$.

Then, we update the colonisation times. Let u_C^C denote the set of patients with a colonisation time $c_i \neq \infty$, $i = 1, \ldots, N$. This set includes both patients "colonised on admission" and "colonised on ward". Let also n^C be set u_C^C's number of patients. Let u_C^A be the set of patients whose colonisation time was added by the algorithm and n^A denote the number of patients in it, and u_C^N denote the set of patients with no positive tests and let n^N denote its number of patients. Vector u_C^N is fixed, while u_C^C and u_C^A are latent variables and are updated in each iteration. Also, $u_C^A = u_C^N \cap u_C^C$.

Vector ψ will be updated in each iteration along with the colonisation times.

Next, we update the colonisation times with Metropolis-Hastings steps. With equal probability we either

- Move an existing colonisation time.

  An existing patient i is chosen uniformly at random from the u_C^C set. If u_C^C is empty we skip this move. With probability w we propose that patient i is admitted positive and thus we set $c_i^* = a_i - 1$ and $\psi_i^* = 1$. Otherwise, $\psi_i^* = 0$ and we set a new colonisation time chosen uniformly at random from $[a_i, h]$, where $h = \min((f_i - 1), d_i)$ and f_i is the date of patient i's first positive test. We assume that once a patient is colonised they remain so until they leave the ward. A patient can be colonised on any day before their first positive test, if it exists. If patient i does not have any positive test then $f_i = \infty$.

  The proposed move is accepted with probability

$$\min\left(1, \frac{\pi(\mathbf{c}^*, \mathbf{r} \mid \boldsymbol{\theta}, \mathbf{y})}{\pi(\mathbf{c}, \mathbf{r} \mid \boldsymbol{\theta}, \mathbf{y})} \cdot q_{\mathbf{c},\mathbf{c}^*}\right) \tag{4.4.1}$$

  where $q_{\mathbf{c},\mathbf{c}^*}$ is given as follows,

– if $\psi_i^* = 1$ then,

$$\begin{cases} q_{\mathbf{c},\mathbf{c}^*} = 1 & \text{if } \psi_i = 1 \\ q_{\mathbf{c},\mathbf{c}^*} = (h - a_i + 1)^{-1} \frac{1-w}{w} & \text{if } \psi_i = 0 \end{cases},$$

– if $\psi_i^* = 0$ then,

$$\begin{cases} q_{\mathbf{c},\mathbf{c}^*} = 1 & \text{if } \psi_i = 0 \\ q_{\mathbf{c},\mathbf{c}^*} = (h - a_i + 1) \frac{w}{1-w} & \text{otherwise} \end{cases}.$$

- Add a new colonisation time.

  An individual i say, is chosen uniformly at random from the set of patients included in u_C^N but not in u_C^A. Thus, this set includes patients who have $c_i = \infty$, i.e. patients who are not colonised. If this set is empty we skip this move.

  As before, we assume with probability w that patient i is admitted positive, so $\psi_i^* = 1$. Otherwise, we choose a colonisation time uniformly at random from the interval $[a_i, d_i]$.

  The proposed move is accepted with probability

$$\min\left(1, \frac{\pi(\mathbf{c}^*, \mathbf{r} \mid \boldsymbol{\theta}, \mathbf{y})}{\pi(\mathbf{c}, \mathbf{r} \mid \boldsymbol{\theta}, \mathbf{y})} \cdot q_{\mathbf{c},\mathbf{c}^*}\right)$$

  where the proposal ratio $q_{\mathbf{c},\mathbf{c}^*}$ is

  – if $\psi_i^* = 1$ then,

$$q_{\mathbf{c},\mathbf{c}^*} = \frac{n^N - n^A}{w\,(n^A + 1)}$$

  – if $\psi_i^* = 0$ then,

$$q_{\mathbf{c},\mathbf{c}^*} = \frac{\left(n^N - n^A\right)(d_i - a_i + 1)}{(1 - w)\,(n^A + 1)}$$

  If this move is accepted then the chosen patient included in the u_C^A set.

- Remove (a previously added) colonisation time.

  We remove a colonisation time c_i for individual i who is chosen uniformly at random from the set u_C^A. If set u_C^A is empty we skip this move. The proposed move is accepted with probability

$$\min\left(1, \frac{\pi(\mathbf{c}^*, \mathbf{r} \mid \boldsymbol{\theta}, \mathbf{y})}{\pi(\mathbf{c}, \mathbf{r} \mid \boldsymbol{\theta}, \mathbf{y})} \cdot q_{\mathbf{c},\mathbf{c}^*}\right),$$

  where the proposal ratio $q_{\mathbf{c},\mathbf{c}^*}$ is

  - if $\psi_i = 1$ then,

$$q_{\mathbf{c},\mathbf{c}^*} = \frac{n^A w}{(n^N - n^A + 1)},$$

  - if $\psi_i = 0$ then,

$$q_{\mathbf{c},\mathbf{c}^*} = \frac{n^A(1-w)}{(d_i - a_i + 1)(n^N - n^A + 1)}.$$

Pseudocode for this algorithm is as follows:

Data Augmented MCMC Algorithm

1 Set initial values to the parameters of interest $\boldsymbol{\theta}$

2 Set initial colonisation times $\mathbf{c}$

3 For $k = 1 \ldots n_{iter}$, n_{iter} is the number of iterations

- Update ϕ , z using Gibbs Sampler
- Update parameters $\boldsymbol{\beta}$

  Propose $\beta_j^* \sim N\left(\beta_j^k, \sigma_j\right)$

  Draw a uniform $(0, 1)$ random variable U

  If $U \leq \alpha\left(\beta_j^k, \beta_j^*\right)$

  · set $\beta_j^{k+1} = \beta_j^*$

  Else

  · set $\beta_j^{k+1} = \beta_j^k$
- Update colonisation times $\mathbf{c}$
- With equal probability chose one of the following moves
  1. Move an existing colonisation time
  2. Add a new colonisation time
  3. Remove (a previously added) colonisation time
- Accept the new colonisation time c^* with probability:

$$\min\left(1, \frac{\pi(\mathbf{c}^*, \mathbf{r} \mid \boldsymbol{\theta}, \mathbf{y})}{\pi(\mathbf{c}, \mathbf{r} \mid \boldsymbol{\theta}, \mathbf{y})} \cdot q_{\mathbf{c},\mathbf{c}^*}\right).$$

5 End For loop

4 Return values $\boldsymbol{\theta}$

In the next section we will discuss about model assessment.

4.5 Model Assessment

Model assessment for transmission epidemic models is not a well established topic. The reason for this is that there are no standard methods one can follow to test the model adequacy, especially for complex models. Forrester et al. in [Forrester et al., 2007] use two methods to assess goodness-of-fit for epidemic models, namely the posterior predictive assessment method and a cross validation technique.

Posterior predictive checks are discussed in [Rubin, 1984] and [Gilks and Spiegelhalter, 1996] and more extensively in [Gelman et al., 2004]. This method compares replicated data generated under the model to the observed data. For an adequate model fit the replicated data should look similar to the observed data. Forrester et al. [Forrester et al., 2007] use posterior prediction to check whether the number of colonised patients in the observed data is similar to the number of colonised patients coming from the simulated data sets. The results showed that their model can predict adequately the number of observed colonised patients over the study period.

The authors in [Forrester et al., 2007] used a cross validation method to compare the observed data y_j to the expected data $Y_j|y_{-j}$ from the data y_{-j} with the j_{th} element missing. Then, they used two checking functions, the Freeman-Tukey residual and the tail-area probability to make the comparison between the observed and expected data. Results showed an acceptable fit in the first case but poor fit for the second case. This method is also discussed in [Gelfand et al., 1992].

Furthermore, the authors in [Forrester et al., 2007] suggest alternative methods for assessing the goodness-of-fit of an epidemic model without investigating them further. These include Bayesian p-values [Bayarri and Berger, 1999], a simulation based approach [Dey et al., 1998], use of Bayesian latent residuals [Aslanidou et al., 1998] and prequential approaches for model assessment [Arjas and Gasbarra, 1997].

In this project, we have daily data from the antimicrobial treatment information so it is difficult to use any of the methods mentioned above. We will therefore, adopt a different approach concerning the model assessment. For each of the three models, we will simulate 200 data sets using the posterior means from the

parameter estimates given by MCMC. Then we will compare the distribution of the number of colonised patients per day during the study period from the simulated data sets, to the number of colonised patients from the observed data.

In the following sections we will see how we assess the model using simulated and the GSTT's Data.

4.6 Simulation

In order to validate our methods which were described previously, we will use simulated data. Ignoring any antimicrobial treatment information we will use the model:

$$q(n) = \beta_0 + \beta_1 C_n. \tag{4.6.1}$$

We simulated data using the data structure of the MRSA Data Set ward 1, i.e. we used the admission times, discharge times and dates of tests to simulate a new data set. For the simulation we used the values we obtained from the MRSA Data Set so we set $\beta_0 = 0.0011$, $\beta_1 = 0.0021$, $\phi = 0.5522$ and $z = 0.1570$.

We ran the MCMC algorithm for 10,000,000 iterations with a thin of 10 iterations and we discarded the first $10,000$ as "burn in". The parameter trace plots of first 300,000 iterations are shown in Figure 4.4 and the relevant density plots in Figure 4.5. It can be seen that the model obtained correctly the values for the parameter set.

Table 4.1 shows the summary statistics of the parameter estimates obtained by the MCMC.

No antimicrobial treatment		
	Ward 1	
parameters	$E[\cdot \vert \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
$\boldsymbol{\beta_0}$	0.0012 (0.0010)	$(0.00003, 0.0039)$
$\boldsymbol{\beta_1}$	0.0024 (0.0005)	$(0.0013, 0.0034)$
$\boldsymbol{\beta_0}$, $\boldsymbol{\beta_1}$ **posterior correlation**	-0.5289	
$\boldsymbol{\phi}$	0.5561 (0.0253)	$(0.5062, 0.6057)$
$\mathbf{z}$	0.1577 (0.0135)	$(0.1322, 0.1852)$

Table 4.1: Summary statistics for the transition rates β_0, β_1 sensitivity ϕ and importation probability z from the simulated data using the data-structure of the MRSA Data Set, ward 1.

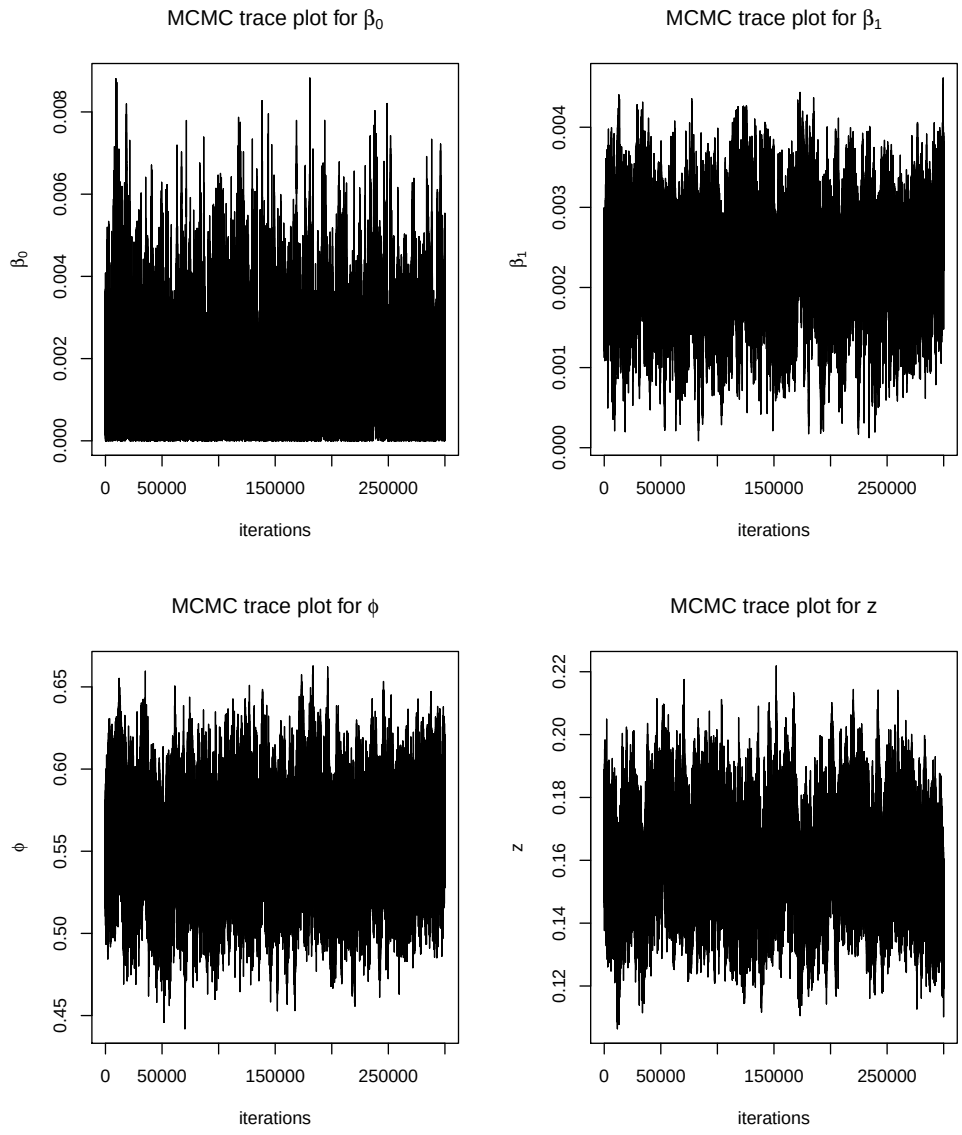


Figure 4.4: MCMC trace plots for each of the parameters of the simulated data using the data-structure of the MRSA Data Set ward 1.

Figure 4.6 shows the model assessment using the simulation method we described in Section 4.5. The Figure shows three plots. In the first, the observed data lie within the equal-tailed 95% quantile of the simulated values. The second one compares the number of colonised patients from the observed data to the mean number of colonised patients over the study period obtained by the simulations, and the third plot presents the number of colonised patients from the observed data along with the median of the colonised patients obtained by the simulations. In all cases we can see that the model fit is acceptable.

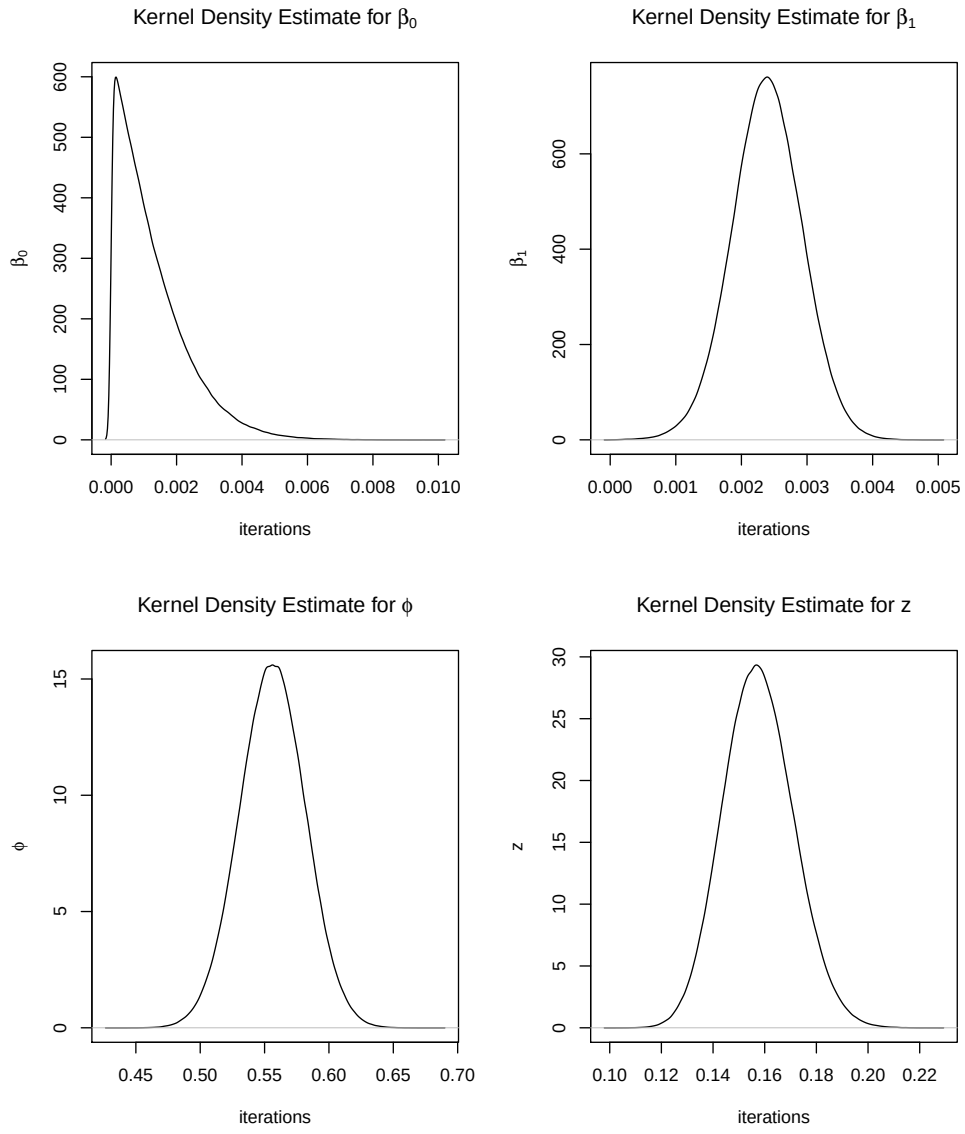


Figure 4.5: Kernel density plots for each of the parameters of the simulated data using the data-structure of the MRSA Data Set ward 1.

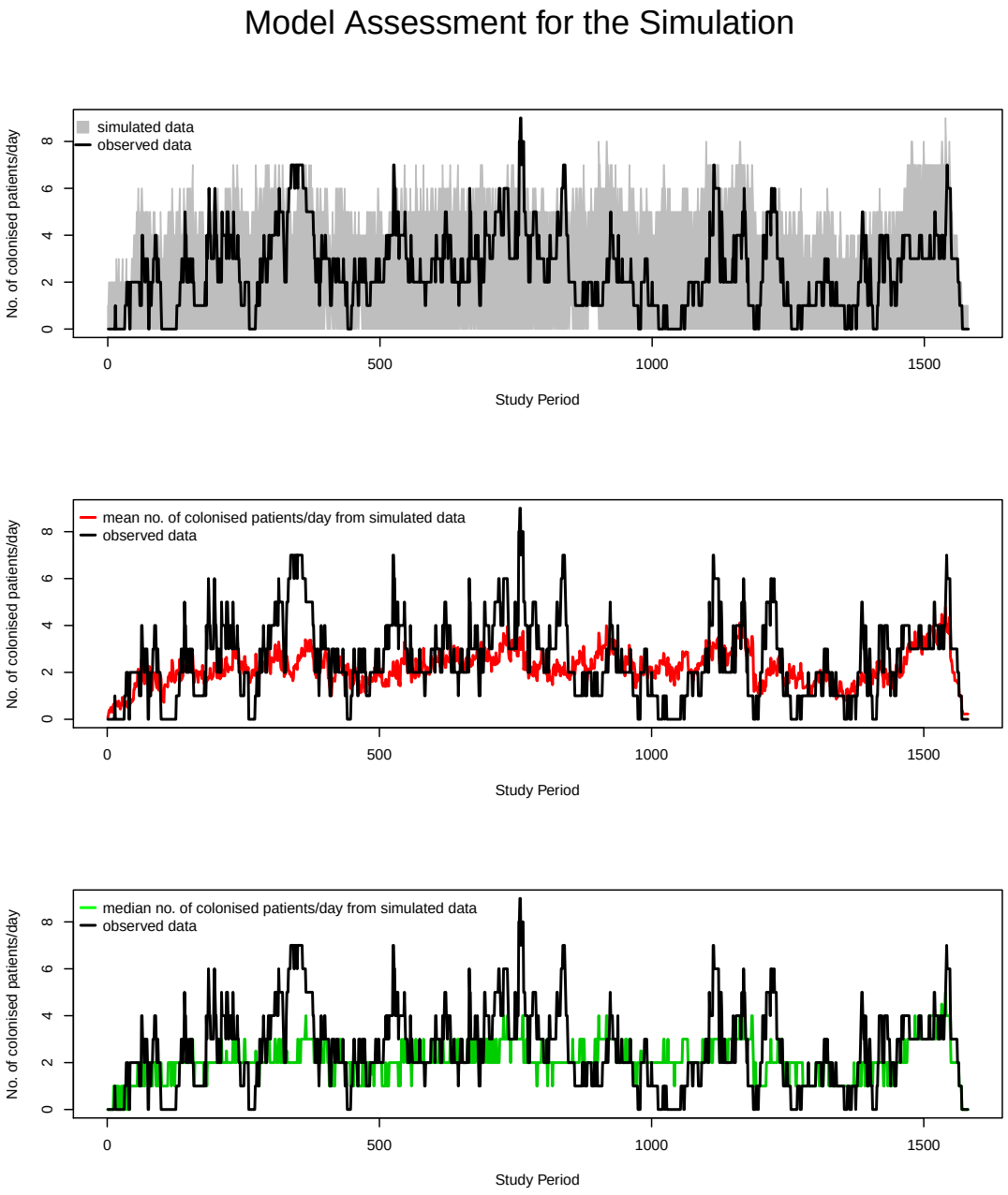


Figure 4.6: Assessment for the simulated data assuming no antimicrobial treatment. The first line shows the 95% quantile (grey area) of the number of colonised patients from the model fit simulations data compared to the observed number of colonised patients (black line). The Second line shows the mean number of colonised patients (red line) from the simulations compared to the observed number of colonised patients (black line). The third line shows the median of the number of colonised patients (green line) from the simulations compared to the observed number of colonised patients (black line).

In Appendix C, section C.1, there are also the results from another two simulations we performed along with the model assessment results. For both simulations we used the MRSA Data Set structure, i.e. MRSA Data Set's admission times, discharge times and dates of tests.

Table C.1 show the results from the simulation when we set the same values we obtained from the MRSA Data Set without taking into account antimicrobial treatment information, so we set $\beta_0 = 0.0011$, $\beta_1 = 0.0021$, $\phi = 0.5522$ and $z = 0.1570$. Figure C.1 presents the model fit results where we can see that the model fits adequately.

Table C.2 show the results from the MCMC for simulated data when random values were set for their generation and assuming no antimicrobial treatment information. We set $\beta_0 = 0.003$, $\beta_1 = 0.005$, $\phi = 0.75$ and $z = 0.08$. Figure C.2 presents the model assessment where we can see that the model fit is adequate.

4.7 Results using the GSTT Data

In this section we are going to fit the *Susceptibility Model*, *Infectivity Model* and the *Full Model* to the GSTT data set. We will start by fitting the MRSA Data Set to each model, initially without taking into account antimicrobial treatment and later presenting the results from each antimicrobial separately. We also present the results from the model assessment. Finally, we obtain the parameter estimates and present the model assessment for the Wounds and Respiratory Data Sets.

4.7.1 MRSA Data Set

Here we are going to present the results from the MRSA Data Set. At the beginning we will not take into account any information about the antimicrobial treatment and obtain only the baseline rates for each ICU ward i.e. the rates that are not related with antimicrobial use. Then, we will consider each antimicrobial treatment separately for each of the three models. In each case we will examine the model fit using the simulation-based method described earlier.

Ignoring antimicrobial treatment

We fit the model ignoring the antimicrobial treatment information. So, we use the model in (4.6.1).

Table 4.2 shows the summary statistics for the posterior distributions of β_0, β_1, ϕ and z. It can be seen that in both wards the background transmission rates are a lot smaller that the rate coming from the colonised patients. Furthermore, sensitivity ϕ is quite low in both wards. This probably has to do with the assumption that when a patient becomes colonised remains so until they leave the ward. So if a patient's test is found positive, then we assume that the rest of their negative tests, if any, are false negatives.

Importation probability z on the other hand, is large compared to other studies i.e. [Thompson, 2004], where importation probability in general ICUs is found to be around 10%. In our case, this might be due to the fact that throughout our study we made the assumption that any re-admitted patient is considered a new patient.

In the same table we give the posterior correlation between β_0 and β_1 for ICU wards 1 and 2. We can see that β_0 and β_1 are highly correlated. Figure 4.7 shows the density plots from posteriors β_0 and β_1 for each ICU ward while Figures 4.8, 4.9 and 4.10 present the density plots of the posteriors ϕ and z and the correlation between β_0 and β_1 for each of the ICU wards respectively.

No antimicrobial treatment		
	Ward 1	
parameters	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
$\boldsymbol{\beta_0}$	$0.0011\ (0.0009)$	$(0.00003, 0.0036)$
$\boldsymbol{\beta_1}$	$0.0021\ (0.0005)$	$(0.0010, 0.0032)$
$\boldsymbol{\beta_0}$, $\boldsymbol{\beta_1}$ **posterior correlation**	-0.4766	
$\boldsymbol{\phi}$	$0.5522\ (0.0249)$	$(0.5035, 0.6014)$
$\mathbf{z}$	$0.1570\ (0.0142)$	$(0.1304, 0.1863)$
	Ward 2	
parameters	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
$\boldsymbol{\beta_0}$	$0.0013\ (1.2693 \times 10^{-6})$	$(0.00004, 0.0042)$
$\boldsymbol{\beta_1}$	$0.0024\ (0.0005)$	$(0.0013, 0.0034)$
$\boldsymbol{\beta_0}$, $\boldsymbol{\beta_1}$ **posterior correlation**	-0.5763	
$\boldsymbol{\phi}$	$0.4779\ (0.0252)$	$(0.4292, 0.5282)$
$\mathbf{z}$	$0.1639\ (0.0147)$	$(0.1358, 0.1940)$

Table 4.2: Summary statistics for the transition rates β_0, β_1 sensitivity ϕ and importation probability z from the MRSA Data Set.

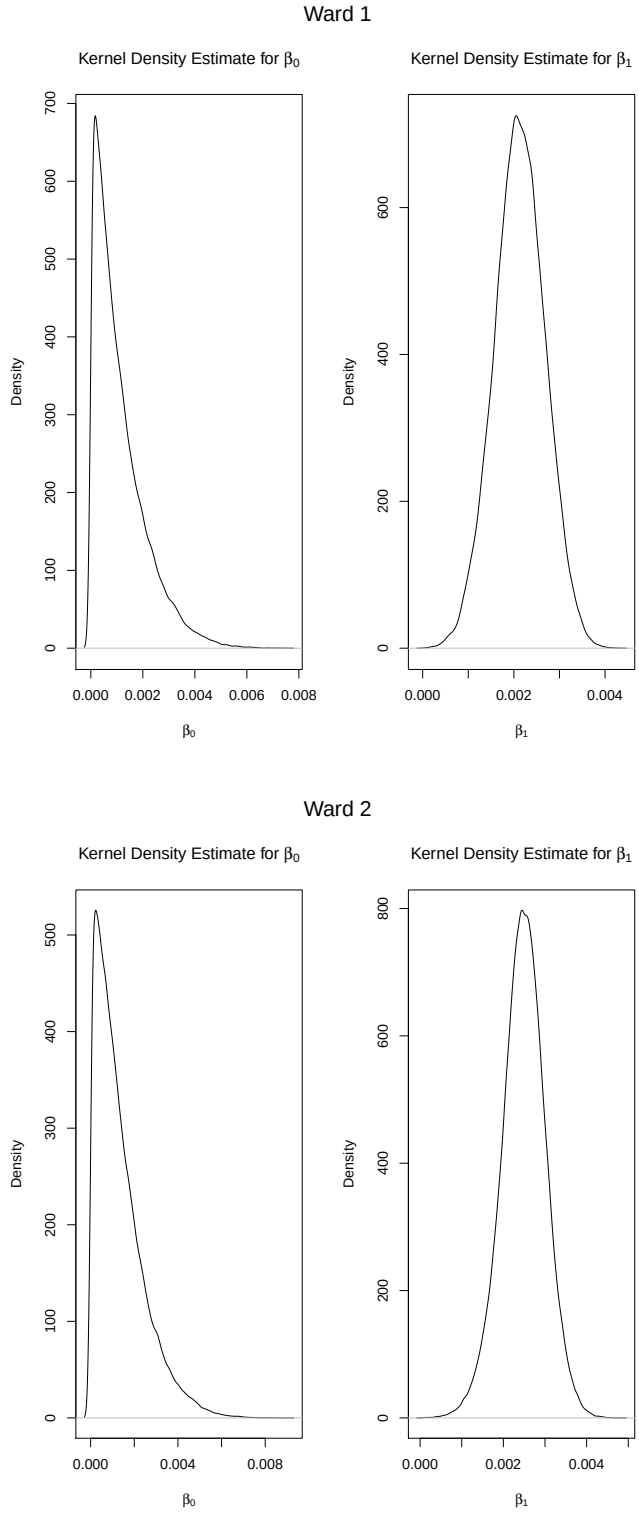


Figure 4.7: Kernel density plots for transmission rates β_0 and β_1 for ward 1 (first line) and ward 2 (second line).

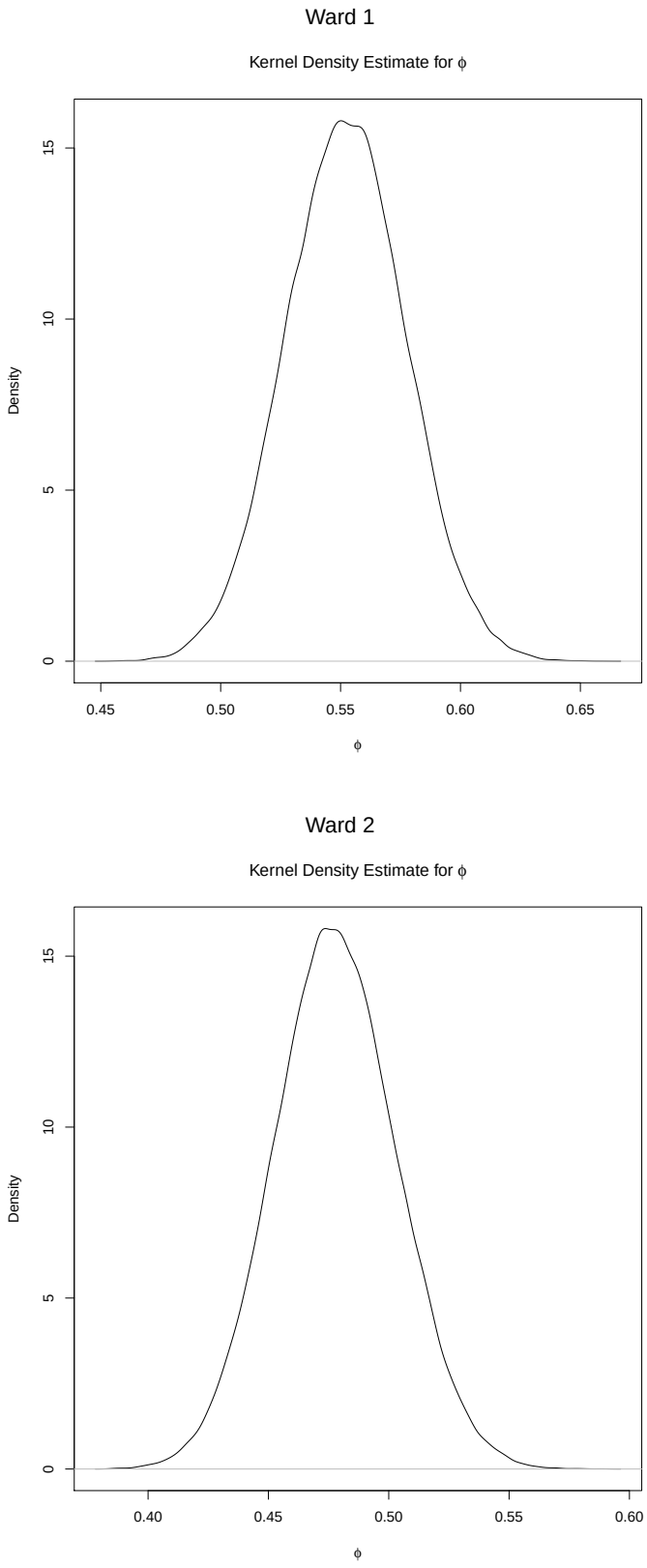


Figure 4.8: Kernel density plots for sensitivity ϕ for ward 1 (first line) and ward 2 (second line).

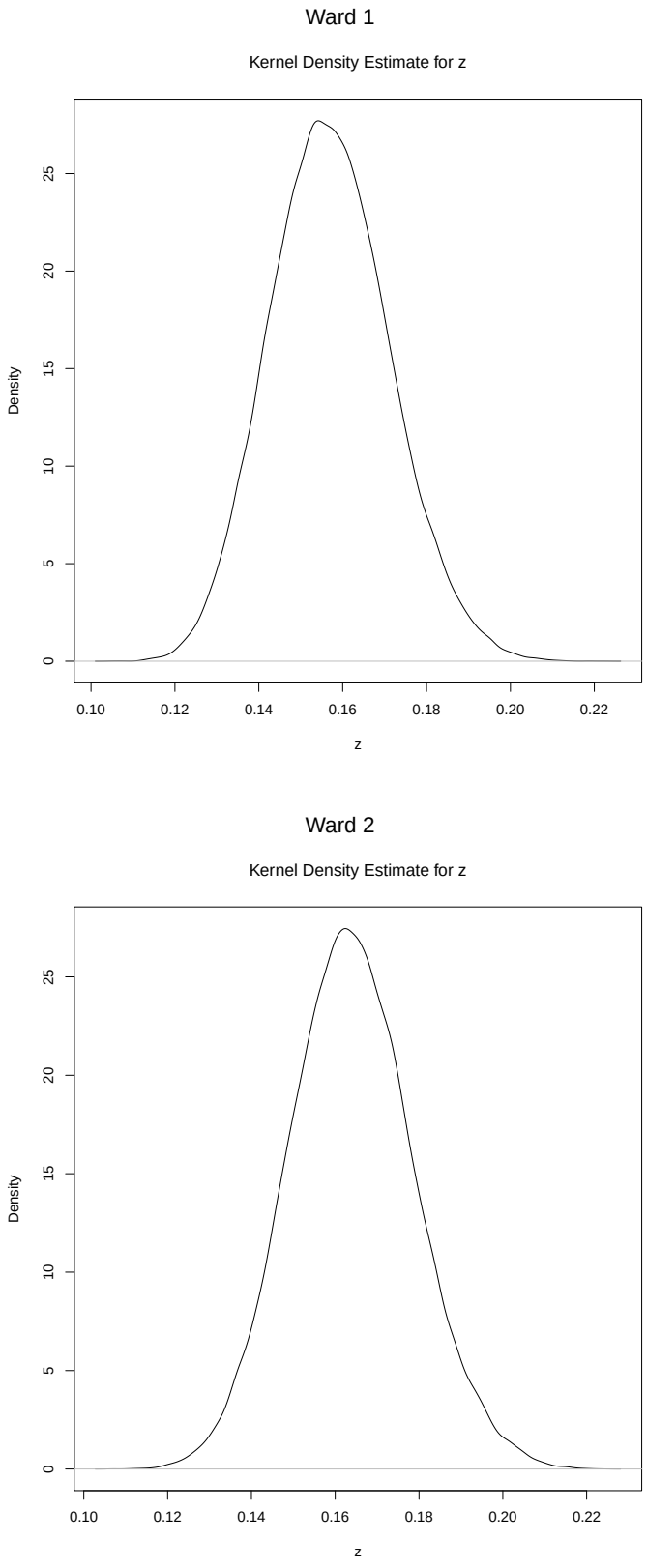


Figure 4.9: Kernel density plots for importation probability z for ward 1 (first line) and ward 2 (second line).

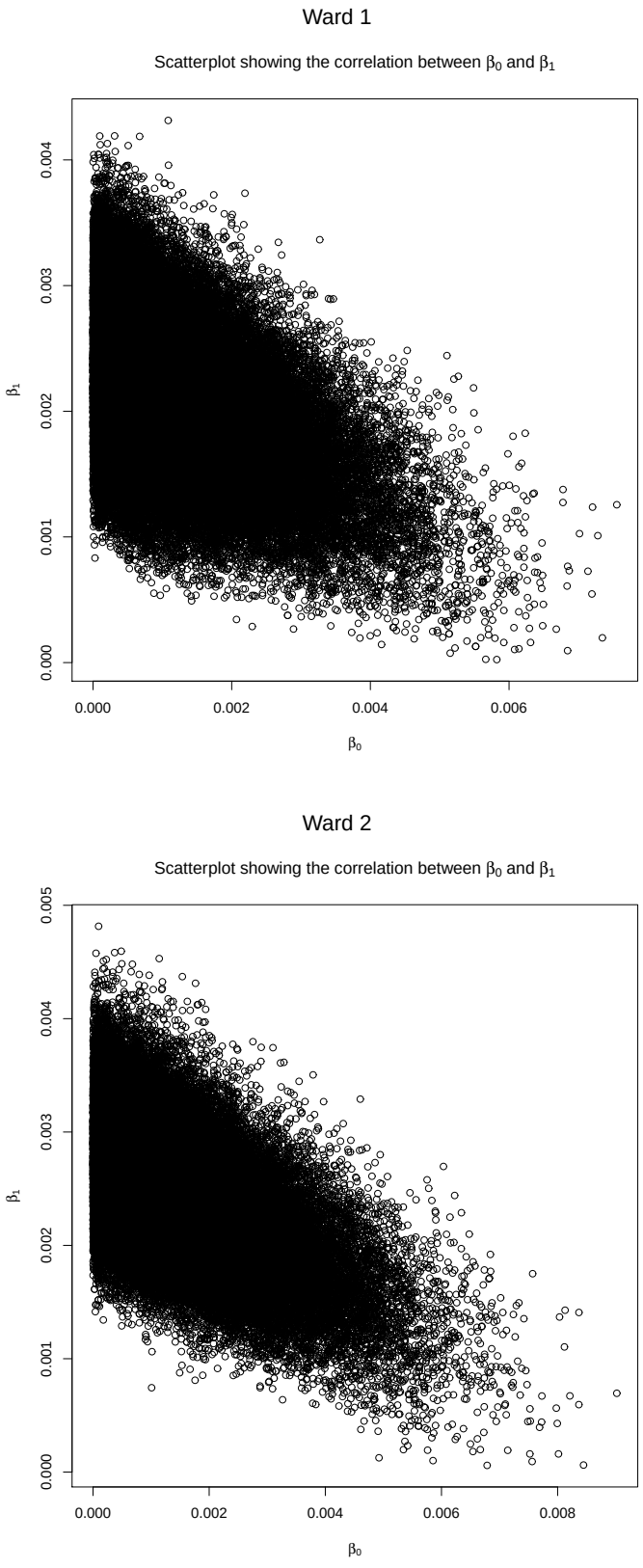


Figure 4.10: Scatterplots showing the correlation between parameters β_0 and β_1 for ward 1 (first line) and ward 2 (second line).

Figure 4.11 shows the model assessment. We simulated 200 data sets from model (4.6.1), obtained the number of colonised patients per day over the study period for each simulated data set and compared the equal tailed 95% quantile of these values to the number of colonised patients taken from the observed data. It can be seen in Figure 4.11 that the model fit is adequate.

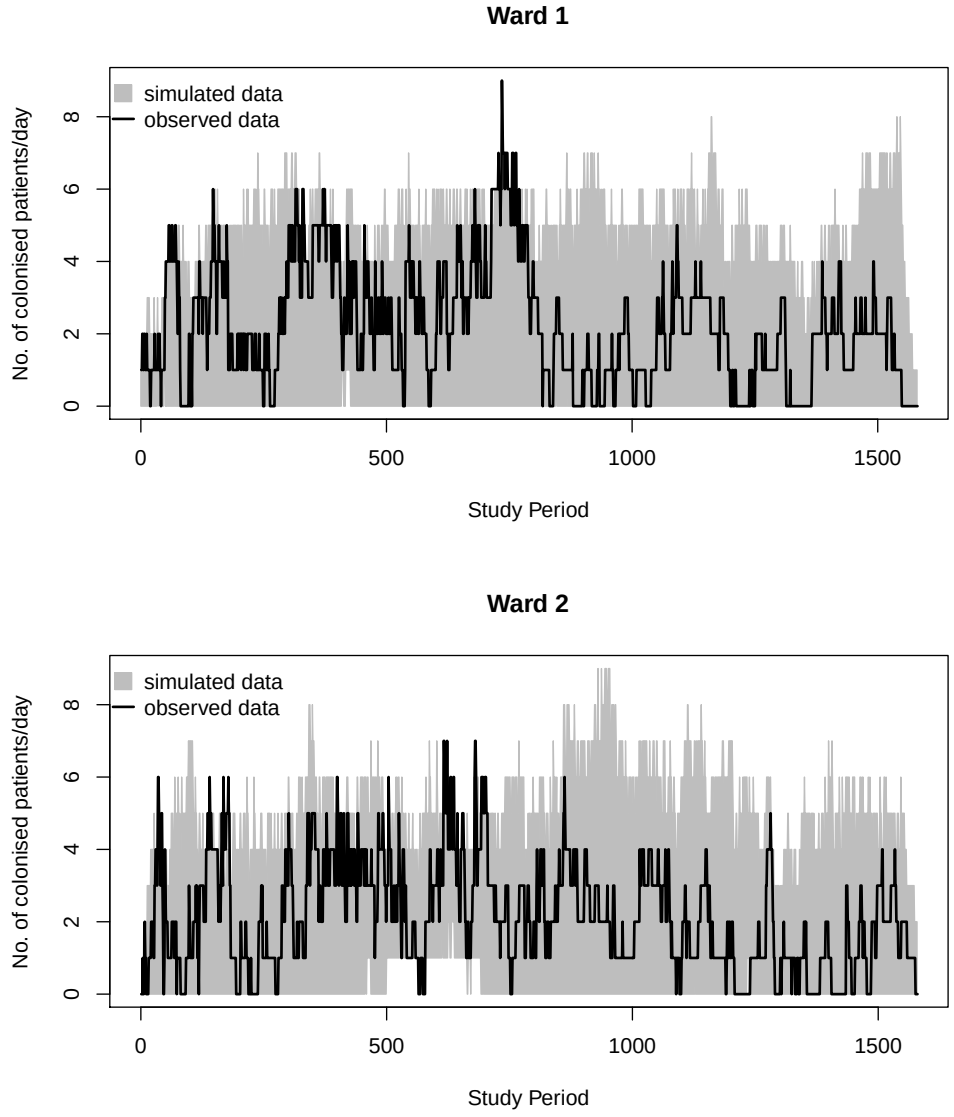


Figure 4.11: Assessment for the baseline model for ICU wards 1 and 2 where the black line shows the number of people colonised in the ward during the study period and the grey area is the equal=tailed 95% quantile from the simulated data.

Including antimicrobial treatment

Next, we are are going to examine whether the antimicrobial treatment has any effect on MRSA transmission. Thus we are going to present the results considering each antibiotic and the antiseptic separately. We assume that when a patient takes an antimicrobial one day they are "on" this antimicrobial that day, otherwise they are considered "off" antimicrobial treatment.

In all of our models we found that swab test sensitivity ϕ is around 0.55 for ward 1 and 0.47 for ward 2 while importation probability z is 0.15 for ward 1 and 0.16 for ward 2. We can see that sensitivity ϕ is quite low in both wards so, at the end of this section we will do the analysis for some of the antimicrobials using sensitivity estimated from the data.

Susceptibility Model

Results of the transmission rate parameters β_0, $\tilde{\beta}_0$, β_1 and $\tilde{\beta}_1$ are shown in Tables C.3 and C.4 where we can actually see the ratios $\log(\beta_0/\tilde{\beta}_0)$ an $\log(\beta_1/\tilde{\beta}_1)$ for wards 1 and 2 respectively. We use the log ratios because it is easier to determine whether an antimicrobial has an effect. If a log ratio is bigger that 0 then the antimicrobial treatment has an effect otherwise it does not. So, in Table C.3 it can be seen that Antiseptic may have a positive effect on reducing the background transmission of MRSA on ward 1 and a smaller effect for ward 2. Rifamycin seems also to have a positive effect on ward 1. On the other hand, Rifamycin and Oxazolidinone seem to have a negative effect on the MRSA transmission coming from the background in ward 2. A negative effect also seem to have Polymyxin and Quinolone in ward 1. Table C.4 shows the results from patient-to-patient transmission, where there is evidence that the Antiseptic is effective in reducing MRSA transmission among patients in both wards and Rifamycin in ward 1. The difference in the results in the two wards is because antimicrobial treatment was received for a different time period in each ward. We can see in Table 1.5 for example, that Rifamycin was received much fewer days in ward 2 (98) than in ward 1 (528). This can affect the parameter estimates as there is not much information to draw significant conclusions. Furthermore, Aminoglycoside, Macrolide and Penicillin may also to help reduce MRSA in both wards, although not significantly.

Tables C.5 and C.6 show the results from swab test sensitivity ϕ and importation

probability z respectively, for each antimicrobial group.

The results from model assessment are shown in Figures C.3 and C.4 for ward 1 and C.5 and C.6 for ward 2. It can be seen that the model fit is acceptable.

Infectivity Model

Tables C.7 and C.8 show the results from the background pressure β_0 and the transmission rates to the susceptible given by $\log(\beta_1/\beta_1^{'})$ for wards 1 and 2. It can be seen in Table C.7 that background transmission rate is between $0.0007 - 0.0010$ for ward 1 and between $0.0009 - 0.0016$ for ward 2 with Antiseptic having the lowest value in both wards.

In Table C.8 there is evidence that Antiseptic can reduce the transmission of MRSA in both wards. In contrast, Macrolide seems to have the opposite result in both wards.

The results from sensitivity ϕ and importation probability z are shown in Tables C.9 and C.10 respectively.

Finally, Figures C.7 and C.8 show the model fit for ward 1 and Figures C.9 and C.10 show the model fit for ward 2. We can see that the model fit is adequate.

Full Model

The results from the transmission parameters for the *Full Model* are shown in Tables C.11, C.12 and C.13. From Table C.11 we can see that there is some evidence that Antiseptic help in the reduction of background MRSA transmission in both wards. On the other hand, Oxazolidinone and Rifamycin may have a negative effect on the reduction of MRSA transmission.

Tables C.12 and C.13 show the results from the rates when colonised patients are "off" and "on" antimicrobial treatment respectively. It can be seen that Antiseptic is effective in reducing MRSA transmission in both cases for both wards, while there is some evidence that Penicillin might be effective when the susceptible is receiving antimicrobial treatment and the colonised not. Glycopeptide has the same effect but when both susceptible and colonised receive antimicrobial treatment. Moreover, Rifamycin may have a positive effect on the reduction of MRSA transmission for colonised "off" antimicrobial treatment in ward 1, but has the opposite effect in ward 2 when colonised patients are "on" antimicrobial treatment. This is probably because there is much more information

about Rifamycin in ward 1 than in ward 2. There is also some evidence that Quinolone may have the a negative effect against MRSA transmission when both susceptible and colonised receive the antibiotic. The NAs mean that we were not able to obtain the parameter estimates for these antimicrobial treatment groups for this model, possibly due to small number of data of that antimicrobial treatment available, and the large number of model parameters and thus the MCMC algorithm could not converge.

Tables C.14 and C.15 show the estimates for parameters ϕ and z respectively.

The model assessment results are presented in Figures C.11 and C.12 for ward 1 and C.13 and C.14 for ward 2. We have not displayed the model fit results for the parameters we could not obtain the parameter estimates. From the plots it can be seen that the model fit is acceptable.

Estimating ϕ from the data

Here we will check if our results remain the same when we estimate sensitivity from the data and use its value as fixed. Then we will obtain the parameter estimates for the Antiseptic and Glycopeptide.

To calculate the sensitivity in each ward from the data, we take the ratio of the number of positive swab tests over the number of all tests. To find the number of positive swab tests we assume that if a patient has negative tests after a positive has been found, then all those tests are considered false-negative. This has been also done in [Kypraios et al., 2010].

We found that $\phi = 0.7369$ for ward 1 and $\phi = 0.6937$ for ward 2. These values are higher than those estimated from the model because the model assumes that patients with no positive test might be also colonised in the ward, and thus all their negative tests after their colonisation time are considered as false-negative. This can have an effect on the ratio as there will be more positive swab tests.

The parameter estimates of the transmission rates obtained for the *Susceptibility Model* are presented in Tables C.16 and C.17, for the *Infectivity Model* in Tables C.18 and C.19 and for the *Full Model* in Tables C.20, C.21 and C.22. It can be seen that there are not any major differences to the parameters comparing to those when sensitivity ϕ is estimated by the model.

Importation probability z was found to be around $z = 0.116$ which is a little lower than previously. The estimates for z for the three models can be found in Table C.23.

Model assessment for all models in wards 1 and 2 is presented in Figures C.15 and C.16 for the Antiseptic and in Figures C.17 and C.18 for Glycopeptide. It can be seen that the model fit is adequate for the *Susceptibility Model*, but not so good for the other models.

4.7.2 Wounds Data Set

Here we will present the results obtained from the Wounds Data Set. In all three models test's sensitivity was found to be around 0.268 for ward 1 and 0.347 for ward 2. Importation probability was estimated around 0.17 in ward 1 and around 0.105 in ward 2.

Susceptibility Model

Table C.24 shows the MCMC estimates for the background parameters β_0 and $\tilde{\beta}_0$. We can see that Antiseptic may have an positive effect on the MRSA transmission in both wards. Results concerning person-to-person transmission are given in Table C.25. It can be seen that Antiseptic, Aminoglycoside, Glycopeptide and Cephalosporin can help in the reduction of MRSA transmission in both wards but not significantly.

The parameter estimates for sensitivity ϕ and importation probability z are shown in Tables C.26 and C.27 respectively. Figures C.19 and C.20 show the model assessment for ward 1 and Figures C.21 and C.22 show the model assessment for ward 2. It can be seen that in both wards the model fits well.

Infectivity Model

Infectivity Model's results for the background transmission are shown in Table C.28. It can be seen that for all antimicrobials the rates do not differ much with each other. Table C.29 shows the results from the rates on susceptibles coming from colonised individuals that are "off"/"on" antimicrobial treatment. We can see that there is strong evidence that Antiseptic has a positive effect in MRSA transmissibility when colonised patients receive antimicrobial treatment in both wards. On the other hand, Macrolide has the opposite effect. Rifamycin

seems also to have a negative effect on MRSA transmission in ward 1. This result cannot be compared to the result in ward 2 since in ward 2 Rifamycin was received for much fewer days. (Table 1.6)

Tables C.30 and C.31 present the parameter estimates for swab test sensitivity ϕ and importation probability z.

Finally, ward's 1 model assessment is displayed in Figures C.23 and C.24 and in Figures C.25 and C.26 for ward 2. The model seems to fit better in ward 1 than in ward 2.

Full Model

Considering the *Full Model* for the Wounds Data Set, Table C.32 gives the results from the rates on the susceptibles coming from the background. It can be seen that Antiseptic and Glycopeptide may have a positive effect against transmissibility of MRSA in both wards, but not significant.

Tables C.33 and C.34 display the results from the transmission rates from a colonised individual when they are "off" /"on" antimicrobial treatment. It can be seen that Aminoglycoside and Cephalosporin may have a positive effect against MRSA transmission when colonised patients are "off" antimicrobials. In Table C.34, there is some evidence, but not significant, that Aminoglycoside, Antiseptic and Glycopeptide may have a positive effect against MRSA transmission in ward 1. The NAs as above, mean that we were not able to obtain the parameter estimates for these particular antimicrobial groups due to MCMC convergence issues.

The parameter estimates for sensitivity ϕ for each antimicrobial group are shown in Table C.35 and importation probability's z results are given in Table C.36.

Finaly, Figures C.27 and C.28 show the model fit for ward 1 and Figures C.29 and C.30 the model fit for ward 2. It can be seen that the fit is not adequate especially for ward 2.

4.7.3 Respiratory Data Set

Here we are going to show the results given by the *Susceptibility Model*, *Infectivity Model* and *Full model* for the Respiratory Data Set. The swab test sensitivity and importation probability is the same for the three models. Sensitivity ϕ is

around 0.56 and 0.48 for wards 1 and 2 respectively, and importation probability z is around 0.14 for ward 1 and around 0.12 for ward 2.

Susceptibility Model

The results for the transmission rates from the *Susceptibility Model* are shown in Tables C.37 and C.38. Table C.37 presents the results from the background transmissibility. It can be seen that Antiseptic and Aminoglycoside may have an effect against MRSA transmission in both wards, while there is some evidence that Cephalosporin, Macrolide and Quinolone might have the opposite effect.

From the results in Table C.38 we can see that Antiseptic and Aminoglycoside may help in reducing the transmission of MRSA in both wards. On the other hand, Quinolone might have the opposite effect. Again, the NAs mean that we were not able to obtain the parameter estimates for these particular antimicrobial groups. Sensitivity ϕ and importation probability z results are shown in Tables C.39 and C.40 respectively.

The model assessment is shown in Figures C.31 and C.32 for ward 1 and in C.31 and C.32 for ward 2. It can be seen that the model fits adequately.

Infectivity Model

Tables C.41 and C.42 present the results from the transmission rates coming from the background and among patients respectively for the *Infectivity model*. In can be seen in Table C.41 that Antiseptic may have an effect against MRSA transmission, while in Table C.42 there is strong evidence that Antiseptic reduces MRSA transmissibility in both wards. On the other hand, Rifamycin seems to have the opposite effect. Tables C.43 and C.44 display the results from sensitivity ϕ and importation probability z respectively.

Model assessment for the *Infectivity Model* is shown in Figures C.35 and C.36 for ward 1 and in C.37 and C.38 for ward 2. We can conclude that the model fit is acceptable.

Full Model

Finally, for the *Full Model*, Table C.45 shows the results from the background transmission rate on the susceptibles when they are "off"/"on" antimicrobial treatment. There is some evidence that Antiseptic and Aminoglycoside may re-

duce the background transmission of MRSA in both wards, while Cephalosporin and Macrolide might have the opposite effect.

Tables C.46 and C.47 present the results from the rates when colonised individuals are "off" and "on" antimicrobial treatment respectively. We can see that Aminoglycoside and Antiseptic may protect from MRSA transmission when colonised patients have not received antimicrobial treatment.

Tables C.48 and C.49 present the parameter estimates for swab test sensitivity ϕ and importation probability z.

Finally, Figures C.35 and C.36 show the model fit for ward 1 and Figures C.37 and C.38 show the model fit for ward 2. We can see that the model does not fit very well.

In the next section we are going to discuss the methodology and results presented in this chapter.

4.8 Summary

In this chapter we looked at the effects of antimicrobial treatment on MRSA in the two ICU wards using three different stochastic transmission models. More specifically, a model that was taking into account only the antimicrobial treatment information received by the susceptible patients (*Susceptibility Model*); a model that was considering antimicrobial treatment received from the colonised patients (*Infectivity model*) and a model that was combining *Susceptibility Model* and *Infectivity Model* (*Full Model*). We also took into account the possibility that a patient might be already colonised when he/she enters the ward. Moreover, we assumed that there was imperfect swab test sensitivity but we assumed 100% specificity. Results showed that the Antiseptic treatment was the most effective almost in all cases.

We obtained the estimates of the parameters of interest for all three models using a data augmented MCMC algorithm in a Bayesian framework. Using this algorithm we were able to infer each patient's unknown colonisation time, if any. To assess the model adequacy we followed a simulation based approach. According to this approach, for each model, we used the parameter posterior means given by the MCMC to simulate several data sets and compute the num-

ber of colonised patients for each data set and for each model over the study period. We then compared these values to the observed data for each model.

Initially, we used simulated data to validate our methodology. To do that, we used the data structure from the MRSA Data Set ward 1 ignoring antimicrobial treatment information and simulated data using the same values for the parameters as those found when the MRSA Data Set was used. The estimated parameters from the simulated data set were in agreement with the values set and the model fit was adequate.

Next, we used the GSTT data ignoring the antimicrobial use and then we looked at each antimicrobial treatment separately for each model. For the MRSA Data Set, we found that Antiseptic can have a positive effect in reducing MRSA transmission coming from background in all the three models in both wards. Considering the transmission rate on susceptibles from the colonised patients in the ward, we saw that the Antiseptic was again the most effective for the reduction of MRSA transmissibility in all cases. Furthermore, the *Susceptibility Model* showed, although not significantly, that Aminoglycoside and Macrolide may help in reducing the MRSA transmission in both wards. Macrolide was found to have the opposite effect in the *Infectivity Model*. When colonised patients were "on" antimicrobial treatment, the *Full Model* showed Glycopeptide may help reduce MRSA in both wards and that Quinolone may increase transmissibility. The model fitted adequately in all cases.

In the case where sensitivity was estimated from the data we did not find any major differences in the parameter estimates in the results comparing to those where sensitivity was estimated from the model. However, the model fit was adequate only for the *Susceptibility Model*.

For the Wounds Data Set, we found evidence that Antiseptic is effective on reducing MRSA transmission coming from the background. *Susceptibility Model* and the *Full Model* also had the same results for Glycopeptide and Cephalosporin. Considering patient-to-patient transmission, *Susceptibility Model* and *Full Model* agreed that Aminoglycoside and Cephalosporin may have an effect on reducing transmission when colonised patients are "off" antimicrobial treatment in both wards. *Infectivity Model* showed opposite results for Macrolide. Furthermore, Antiseptic was found effective against MRSA transmissibility at the *Susceptibility Model* and *Infectivity Model*. The model fit was adequate only for the

Susceptibility Model.

Respiratory Data Set results showed that the *Susceptibility Model* and the *Full Model* almost agreed that Antiseptic and Aminoglycoside may have an effect on MRSA background transmission. The three models showed that Antiseptic is effective against person-to-person transmission. When a colonised person is "off" antimicrobial treatment the *Susceptibility Model* and the *Full Model* showed that in most cases Aminoglycoside might have a positive effect against MRSA transmissibility, while Cephalosporin and Macrolide have a negative effect. The *Infectivity Model* seemed to support that only for Rifamycin. In addition, the *Full Model* also showed that colonised patients who receive Aminoglycoside may not be able to transmit MRSA to patients who also receive these antimicrobials. The model fit was acceptable for the *Susceptibility* and *Infectivity* Models but not for the *Full Model*.

In all three data sets we found that sensitivity was quite low. This might has to do with our assumption that all negative tests after a patient's first positive are false-negative. In addition, importation probability was in some cases quite high which is probably due to the assumption that re-admitted patients are considered as new patients in the ward.

Some of our findings are consistent with the literature. In most of our cases we obtained that the decolonisation protocol using antiseptic treatment had an effect on MRSA transmission. This results are in agreement with the studies in [Batra et al., 2010], [Kypraios et al., 2010] and [Macfarlane et al., 2007]. We also found in some cases that Cephalosporin, Macrolide and Quinolone may have a negative effect against MRSA transmissibility. These results were also found in [Muller et al., 2006], [Weber et al., 2003], [Dancer, 2001], [Monnet et al., 2004], [Mahamat et al., 2007] and [Aldeyab et al., 2008].

To conclude, we found evidence that Antiseptic can reduce MRSA transmission from background and between patients. However we did not find any significant results which show that the antimicrobial treatment used has an effect against MRSA transmissibility. Maybe if more or different assumptions were made and if we had more information for some of the antibiotic treatment, we could be able to come to more certain conclusions.

CHAPTER 5

Conclusions and Future work

5.1 Conclusions

In this thesis we used stochastic modelling and Bayesian inference to investigate the effect of antimicrobial treatment on carriage and transmission of methicillin -resistant *Staphylococcus aureus* (MRSA). We considered a Markov model and a hidden Markov model to describe antimicrobial treatment effectiveness on carriage levels of MRSA and three different transmission models to look at MRSA transmission in two ICU wards.

The data we used to apply our methodology were provided from Guy's and St. Thomas' Hospital Trust in London. The data set came from a four-year study that was carried out in the two hospital's ICU wards and was very detailed, containing information about the decolonisation protocol that was followed and the daily antimicrobial prescription that each patient was receiving during that period. We used three groups of this data set, namely MRSA Data Set, Wounds Data Set and Respiratory Data. In Chapter 1 we gave information about these three data sets as well as details for the different antimicrobial groups that were used in this thesis.

In Chapter 2 we considered an individual level discrete-time Markov model to look at the effects of antimicrobials on carriage levels of MRSA. Two of our main assumptions in this chapter were perfect sensitivity and specificity, and ignoring MRSA transmission between patients. The latter assumption made us use only those patients who had at least on positive MRSA test. To ob-

tain the model's parameter estimates we used two methods; Maximum likelihood estimation methods and Metropolis-Hastings MCMC algorithms. We looked at several cases and the main results showed evidence that decolonisation treatment had an effect in clearing MRSA carriage. There was also some evidence that Oxazolidinone might have an effect on MRSA clearance, while Cephalosporin, Macrolide and Quinolone were found to have the opposite effect. To assess the model fit, we initially proved that the typical chi-squared goodness-of-fit test holds in the case where no antimicrobial treatment is taken into account but there might be some practical issues when antimicrobial information is included. To overcome this, we used a simulation method for model assessment. Nonetheless, the model did not fit adequately in some of the cases considered.

The lack of fit of some cases in Chapter 2, made us relax some of our assumptions in Chapter 3 and consider a model taking into account imperfect sensitivity. In this chapter we used an individual level discrete-time hidden Markov model to allow for the possibility of observing false negative swab tests in the data. We still assumed perfect specificity and ignored patient-to-patient transmission, as we did in Chapter 2. We used the same data as in the previous chapter, i.e. only the patients who had at least on positive test. The model's parameters were estimated using a data-augmented MCMC algorithm. This algorithm helped us infer the unobserved patients' transition states. Results showed little evidence that Oxazolidinone and antiseptic treatment may have a positive effect on the clearance of MRSA carriage while there were not any clear results about the effect of other antimicrobial treatment. To assess the model's fit we proved that a chi-squared goodness-of-fit test cannot be used under a hidden Markov model, so we followed a simulation approach. However, the model fit was not acceptable in some of the cases considered.

In Chapter 4, we considered imperfect sensitivity and perfect specificity. We also accounted for person-to-person transmission in order to look at the effects of antimicrobial treatment. We used a novel approach employing three different individual level discrete-time transmission models, namely the *Susceptibility Model* which took into account only antimicrobial treatment that is received from susceptible patients; the *Infectivity Model* which considered only colonised patients' prescribed antimicrobial treatment, and the *Full Model* which con-

tained the antimicrobial information from both susceptible and colonised patients. For the analysis we used the data sets that included all patients, even those who had never had a positive test. To obtain the parameter estimates we used data-augmented MCMC algorithms to infer patients' colonisation times which were not observed. Results showed evidence that Antiseptic treatment has a positive effect on MRSA transmission and that in most cases Macrolide, Cephalosporin and Quinolone have the opposite effect. We assessed each model's fit using a simulation method, and we found that in most cases the models fitted adequately.

Overall, the work in this thesis considered a variety of ways to investigate the effect of antimicrobial treatment on carriage and transmission of MRSA. To our knowledge, there are not any other studies in the literature that consider the effects of antimicrobial treatment on MRSA or other nosocomial pathogens in so much detail. However, there remain model limitations and assumptions that could be improved. In the next section we discuss some potential improvements.

5.2 Future Work

Modelling improvements should be taken into account. In Chapter 4 we have used three different models to account for MRSA transmission between the patients. A possible extension to this approach might be to investigate which of the three models can explain better the effects of antimicrobial treatment on MRSA. A possible way to do that is by using Bayesian model choice via reversible-jump Markov chain Monte Carlo algorithms. This method has been used for epidemic modelling by O'Neill and Marks in [O'Neill and Marks, 2005]. Another improvement for this chapter is to assume that there is some possibility that a patient can be decolonised once they are found MRSA positive. However, this approach would need also to take into account imperfect sensitivity and involve some extra parameters that may make the analysis more complicated.

There are also some assumptions we made in this project that might be relaxed to allow a more realistic approach of analysis of the data.

First of all, throughout this thesis we considered only one antimicrobial treatment at a time. Nevertheless, looking at the effects of multiple antimicrobial use might be a more realistic assumption. This approach has been examined for MRSA carriage levels by Kypraios et al., [Kypraios et al., 2011], where two models for weekly transitions were used. For the analysis, a multiple logistic regression model was employed using a Bayesian model averaging method.

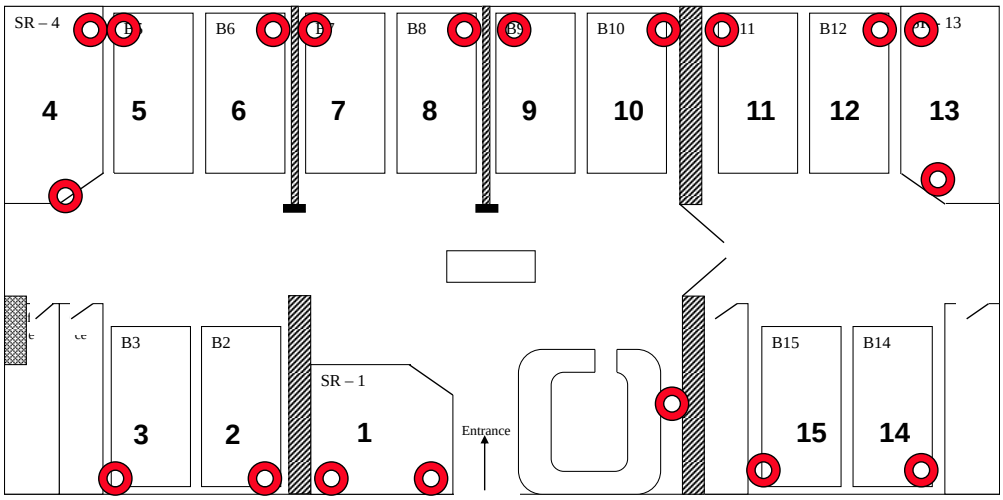
Another parameter we ignored in this work is information about isolated patients. In the data there is detailed information of which patients were isolated and when. It would be interesting to explore if antibiotics and antiseptic treatment have different effects when patients are in isolation. Similar studies have been done, for example in [Kypraios et al., 2010] and [Forrester et al., 2007], but only for the assessment of the effect of control policies. However, these studies are not conclusive as there was weak evidence that isolation has an effect on reducing MRSA transmissibility.

Moreover, in this study, we have accounted for only one test per patient per test day, the positive test where available, otherwise a negative test taken randomly from any body site that day. However, tests might have different results according to the body site the swab has been taken from. This can be included in the analysis allowing for more detailed and realistic outcomes.

Another assumption we made in this thesis is that patients who were re-admitted in the ICU wards were considered as new admissions, even those who had just changed ward. This is not quite realistic as some of these patients might have been already colonised with MRSA when they entered the ward for the second time. In addition, we could possibly use the information available about patient bed changes. Knowing each patient's bed position and whether or not they changed bed or ward can affect MRSA transmission. Figure 5.1 shows the plan of the two ICU wards, where we notice the position of each bed and beds in isolation. The red circles are the positions of hand-cleaning facilities used for healthcare workers' hand hygiene.

We have not also taken into account the fact that different MRSA strains react differently in antimicrobial treatment. This is mainly because some MRSA strains may be resistant to a class of antibiotics and others are not. However, this approach may require a much larger data set in order to obtain significant results.

Design of East Wing 1 - built 1999



Design of East Wing 2 - built 1959

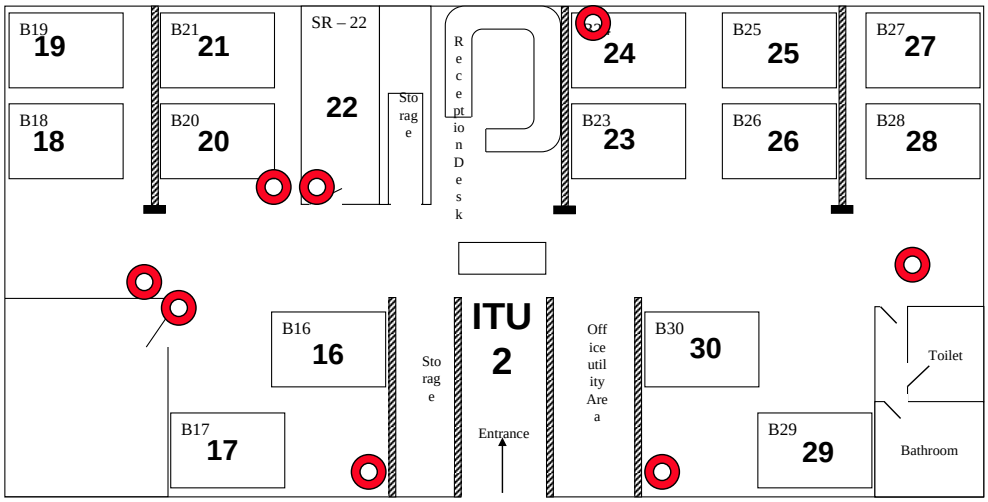


Figure 5.1: First graph: Plan for ward 1. **Second graph**: Plan for ward 2.

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APPENDIX A

Appendix for the Markov Model

A.1 p-MRSA Data Set

	p_0		q_0	
GROUP	$E[\cdot \mid \mathcal{S}]$ (s.d.)	95% CI	$E[\cdot \mid \mathcal{S}]$ (s.d.)	95% CI
Aminoglycoside	0.7597 (0.1264)	(0.4513, 0.8848)	0.2348 (0.1282)	(0.1072, 0.5477)
Antiseptic	0.8422 (0.02908)	(0.7739, 0.8801)	0.1100 (0.0252)	(0.0764, 0.1691)
Cephalosporin	0.8934 (0.0127)	(0.8652, 0.9146)	0.1055 (0.0138)	(0.0821, 0.1355)
Glycopeptide	0.7285 (0.1133)	(0.4356, 0.8811)	0.3008 (0.1481)	(0.1228, 0.6193)
Macrolide	0.8809 (0.0174)	(0.8413, 0.9072)	0.1294 (0.0195)	(0.0995, 0.1736)
Nitroimidazole	0.8726 (0.0197)	(0.8275, 0.9003)	0.1278 (0.0201)	(0.0979, 0.1753)
Oxazolidinone	0.8639 (0.0188)	(0.8180, 0.8922)	0.1296 (0.0198)	(0.0995, 0.1774)
Penicillin	0.7608 (0.1282)	(0.4488, 0.8811)	0.2367 (0.1318)	(0.1122, 0.5612)
Polymyxin	0.8302 (0.0804)	(0.5570, 0.8877)	0.1692 (0.0842)	(0.1087, 0.4545)
Quinolone	0.8245 (0.0910)	(0.5353, 0.8920)	0.1822 (0.0973)	(0.1089, 0.4883)
Rifamycin	0.8469 (0.0617)	(0.6186, 0.8903)	0.1506 (0.0649)	(0.1043, 0.3864)

Table A.1: Summary statistics for parameters p_0 and q_0 for each antimicrobial group for the p-MRSA Data Set.

	α		β	
GROUP	$E[\cdot \mid \mathcal{S}]$ (s.d.)	95% CI	$E[\cdot \mid \mathcal{S}]$ (s.d.)	95% CI
Aminoglycoside	-0.0959 (0.1546)	$(-0.4293, 0.1965)$	0.2132 (0.1869)	$(-0.0767, 0.6176)$
Antiseptic	-0.1703 (0.1273)	$(-0.3922, 0.0673)$	0.3860 (0.1742)	$(0.0572, 0.6929)$
Cephalosporin	-0.1903 (0.0792)	$(-0.3812, -0.0692)$	0.1618 (0.0812)	$(0.0361, 0.3576)$
Glycopeptide	-0.0171 (0.1217)	$(-0.3096, 0.2094)$	-0.0463 (0.1209)	$(-0.3009, 0.2216)$
Macrolide	-0.3089 (0.1221)	$(-0.5680, -0.0990)$	0.1606 (0.1030)	$(-0.0087, 0.3888)$
Nitroimidazole	-0.2448 (0.1187)	$(-0.4884, 0.0444)$	0.2151 (0.1214)	$(0.0140, 0.4715)$
Oxazolidinone	0.0806 (0.0628)	$(-0.0884, 0.1576)$	0.6358 (0.1742)	$(0.2388, 0.8680)$
Penicillin	0.0376 (0.1839)	$(-0.4188, 0.3778)$	0.0658 (0.2530)	$(-0.3347, 0.6950)$
Polymyxin	-0.2549 (0.2630)	$(-0.7758, 0.1451)$	0.3562 (0.2906)	$(-0.1311, 0.8283)$
Quinolone	-0.2406 (0.1728)	$(-0.6001, 0.0442)$	0.1022 (0.1552)	$(-0.1625, 0.4597)$
Rifamycin	-0.3084 (0.2519)	$(-0.7947, 0.1101)$	0.4733 (0.2626)	$(-0.0301, 0.8564)$

Table A.2: Summary statistics for parameters α and β for each antimicrobial group for the p-MRSA Data Set.

Model Fit							
Day Intervals	**1**	**2**	**3**	**4**	**5**	**6**	**7**
$N \to N$							
obs. counts	**17**	**19**	**19**	**8**	**17**	**31**	**243**
Aminoglycoside	(15, 25)	(13, 24)	(14, 25)	(9, 19)	(10, 22)	(22, 36)	(171, 209)
Antiseptic	(17, 25)	(16, 26)	(16, 26)	(10, 20)	(12, 22)	(23, 38)	(180, 218)
Cephalosporin	(20, 26)	(16, 26)	(17, 28)	(11, 20)	(13, 23)	(24, 40)	(195, 236)
Glycopeptide	(15, 24)	(13, 23)	(13, 25)	(9, 18)	(10, 21)	(22, 37)	(173, 211)
Macrolide	(20, 26)	(18, 27)	(16, 26)	(9, 19)	(13, 23)	(25, 39)	(192, 225)
Nitroimidazole	(18, 25)	(16, 26)	(17, 27)	(10, 20)	(13, 23)	(25, 40)	(189, 226)
Oxazolidinone	(19, 26)	(18, 27)	(18, 28)	(12, 21)	(13, 24)	(25, 40)	(188, 226)
Penicillin	(17, 25)	(14, 25)	(14, 26)	(9, 19)	(11, 22)	(21, 36)	(172, 210)
Polymyxin	(19, 26)	(17, 26)	(16, 27)	(10, 20)	(12, 23)	(24, 38)	(179, 216)
Quinolone	(18, 26)	(17, 26)	(16, 26)	(11, 20)	(12, 23)	(23, 39)	(180, 214)
Rifamycin	(20, 26)	(18, 27)	(17, 28)	(11, 20)	(12, 23)	(24, 38)	(181, 221)
$N \to C$							
obs. counts	**10**	**11**	**15**	**18**	**14**	**26**	**132**
Aminoglycoside	(2, 11)	(5, 16)	(9, 20)	(7, 17)	(9, 21)	(21, 35)	(165, 202)
Antiseptic	(2, 10)	(4, 14)	(8, 18)	(6, 16)	(8, 19)	(19, 34)	(156, 195)
Cephalosporin	(1, 7)	(4, 14)	(6, 17)	(6, 15)	(8, 18)	(17, 33)	(138, 178)
Glycopeptide	(3, 12)	(7, 17)	(9, 21)	(7, 17)	(10, 20)	(20, 35)	(164, 202)
Macrolide	(1, 7)	(3, 12)	(7, 18)	(7, 17)	(8, 18)	(17, 32)	(149, 183)
Nitroimidazole	(1, 9)	(4, 14)	(7, 17)	(5, 15)	(8, 18)	(17, 31)	(147, 186)
Oxazolidinone	(1, 8)	(2, 12)	(5, 16)	(5, 14)	(6, 18)	(17, 32)	(147, 186)
Penicillin	(2, 10)	(5, 16)	(8, 20)	(6, 16)	(9, 20)	(21, 35)	(165, 201)
Polymyxin	(1, 8)	(3, 13)	(7, 17)	(6, 16)	(8, 18)	(19, 33)	(158, 196)
Quinolone	(1, 8)	(4, 13)	(7, 18)	(5, 15)	(8, 19)	(18, 34)	(160, 195)
Rifamycin	(1, 7)	(3, 12)	(6, 17)	(5, 15)	(8, 19)	(19, 33)	(154, 193)
$C \to N$							
obs. counts	**8**	**11**	**8**	**12**	**10**	**26**	**72**
Aminoglycoside	(1, 7)	(6, 17)	(4, 11)	(10, 21)	(9, 19)	(17, 31)	(112, 144)
Antiseptic	(0, 5)	(6, 15)	(3, 10)	(9, 19)	(7, 18)	(17, 29)	(107, 138)
Cephalosporin	(0, 5)	(3, 12)	(3, 10)	(6, 17)	(7, 17)	(14, 27)	(91, 124)
Glycopeptide	(1, 7)	(7, 17)	(3, 12)	(10, 22)	(10, 20)	(18, 32)	(113, 144)
Macrolide	(0, 5)	(3, 12)	(2, 10)	(6, 18)	(7, 18)	(15, 29)	(101, 132)
Nitroimidazole	(0, 5)	(4, 13)	(3, 10)	(7, 18)	(7, 18)	(15, 29)	(100, 130)
Oxazolidinone	(0, 5)	(2, 12)	(2, 9)	(7, 18)	(8, 18)	(14, 28)	(96, 128)
Penicillin	(1, 7)	(7, 16)	(3, 11)	(9, 21)	(9, 20)	(17, 31)	(111, 143)
Polymyxin	(0, 6)	(4, 14)	(3, 10)	(8, 19)	(8, 18)	(16, 30)	(105, 137)
Quinolone	(0, 6)	(4, 14)	(2, 10)	(9, 19)	(8, 19)	(17, 30)	(106, 135)
Rifamycin	(0, 5)	(4, 13)	(2, 10)	(8, 18)	(7, 18)	(16, 29)	(101, 134)
$C \to C$							
obs. counts	**7**	**20**	**9**	**21**	**20**	**24**	**185**
Aminoglycoside	(8, 14)	(14, 24)	(6, 13)	(12, 23)	(11, 21)	(19, 32)	(113, 145)
Antiseptic	(10, 14)	(16, 25)	(7, 14)	(14, 24)	(12, 23)	(20, 33)	(118, 150)
Cephalosporin	(10, 15)	(19, 28)	(7, 14)	(16, 27)	(13, 23)	(23, 36)	(133, 166)
Glycopeptide	(8, 14)	(13, 24)	(5, 13)	(11, 23)	(10, 20)	(18, 32)	(112, 143)
Macrolide	(10, 15)	(19, 28)	(7, 15)	(15, 27)	(12, 23)	(21, 35)	(124, 156)
Nitroimidazole	(10, 15)	(18, 27)	(7, 14)	(15, 26)	(12, 23)	(21, 35)	(125, 157)
Oxazolidinone	(10, 15)	(19, 29)	(8, 15)	(15, 26)	(12, 22)	(22, 36)	(127, 160)
Penicillin	(8, 14)	(15, 24)	(5, 14)	(12, 24)	(10, 21)	(18, 32)	(113, 146)
Polymyxin	(9, 15)	(17, 27)	(7, 14)	(14, 25)	(11, 22)	(20, 34)	(119, 151)
Quinolone	(9, 15)	(17, 27)	(7, 15)	(14, 24)	(11, 22)	(19, 33)	(121, 150)
Rifamycin	(10, 15)	(18, 27)	(7, 15)	(15, 25)	(12, 23)	(20, 34)	(122, 155)

Table A.3: Model fit for each antimicrobial group for the p-MRSA Data Set. The intervals in red indicate that the observed transition counts are included in the equal-tailed 95% quantiles.

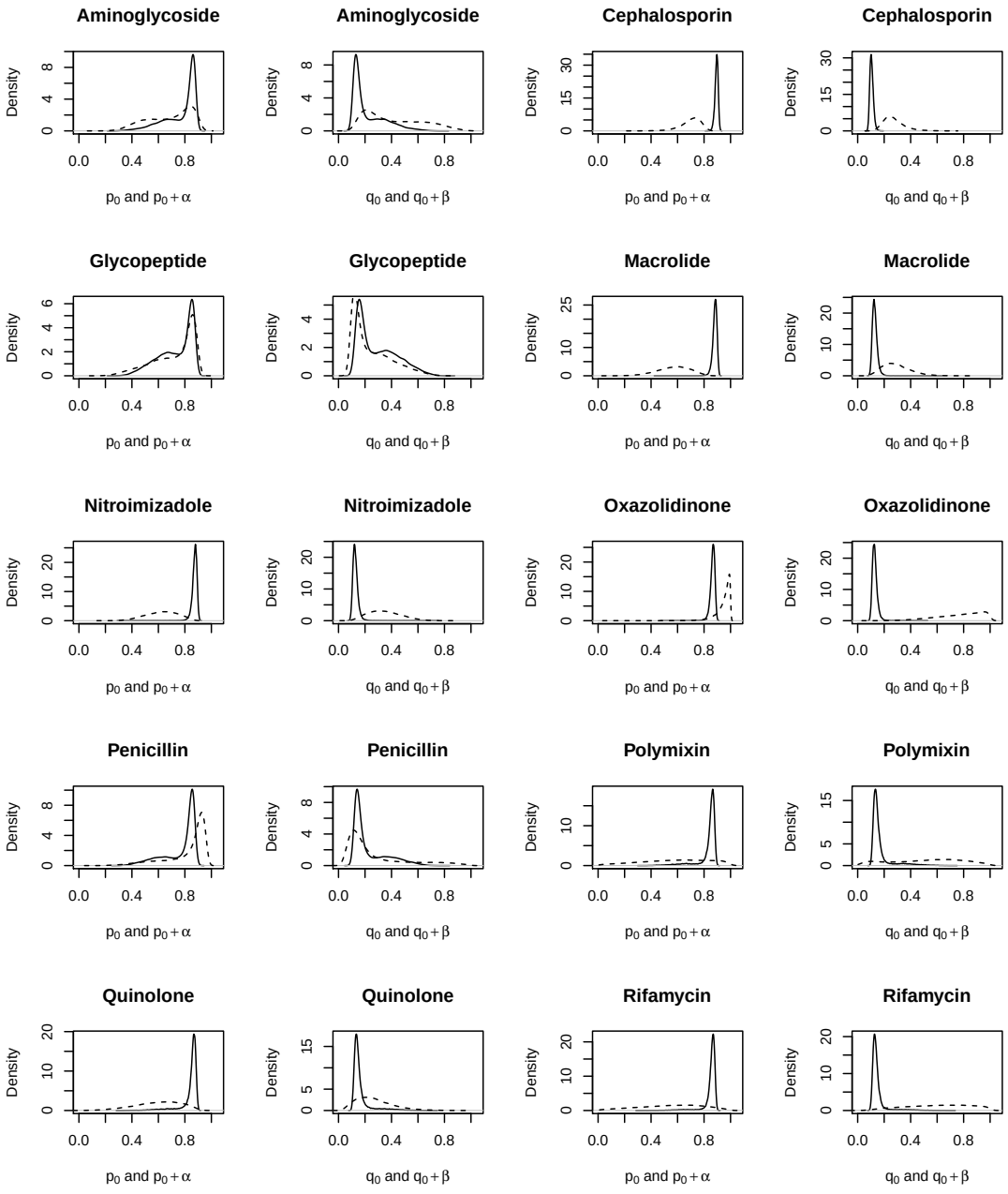

Figure A.1: Kernel density plots for p_0, $p_0 + \alpha$, q_0 and $q_0 + \beta$ for the antibiotics from the p-MRSA Data Set. The continuous line shows the probabilities p_0 and q_0 whereas the dashed line shows the probabilities $p_0 + \alpha$ and $q_0 + \beta$.

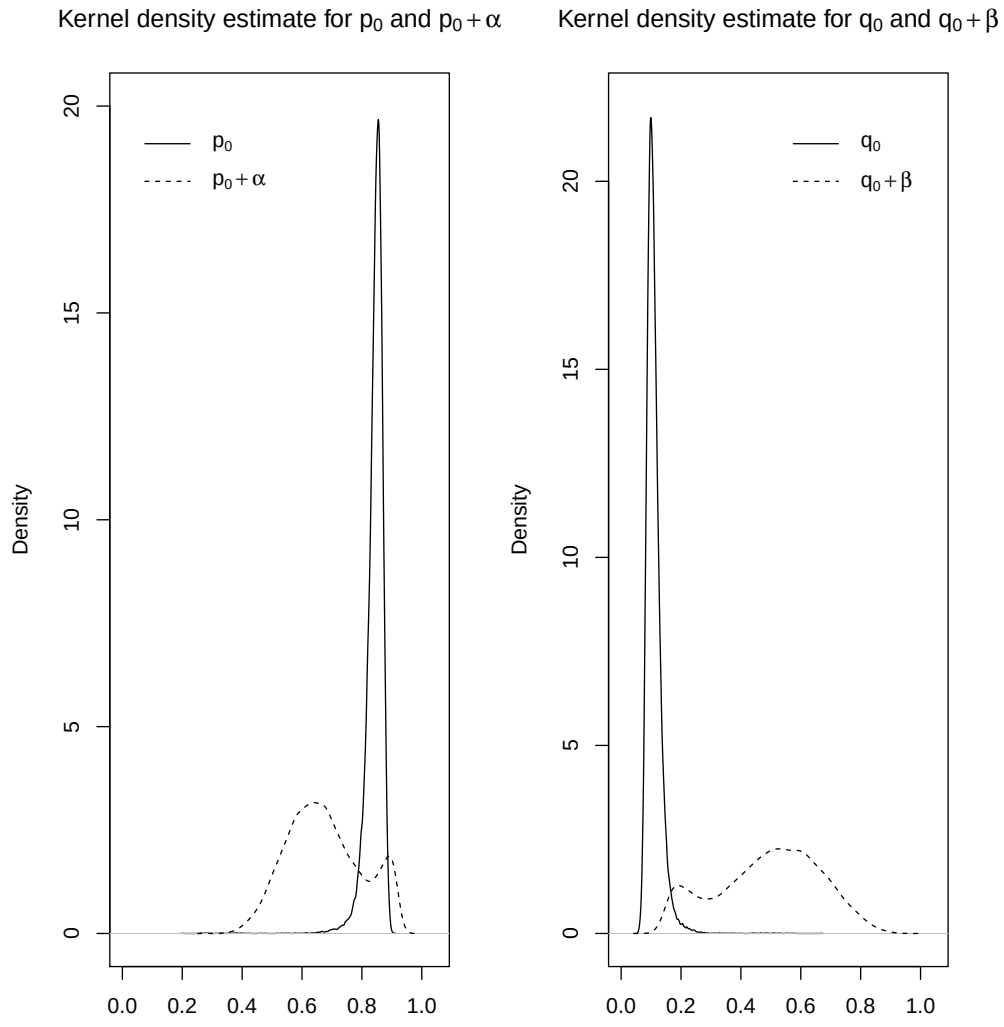

Figure A.2: Kernel density plots for p_0, $p_0 + \alpha$, q_0 and $q_0 + \beta$ for the antiseptic from the p-MRSA Data Set. The continuous line shows the probabilities p_0 and q_0 whereas the dashed line shows the probabilities $p_0 + \alpha$ and $q_0 + \beta$.

A.1.1 Model fit example

	Day Intervals						
	1	**2**	**3**	**4**	**5**	**6**	**7**
$N \to N$							
obs. counts	**17**	**19**	**19**	**8**	**17**	**31**	**243**
Condition on each state	(7, 16)	(10, 21)	(12, 22)	(11, 21)	(11, 23)	(22, 36)	(159, 205)
Condition on initial state	(17, 26)	(15, 25)	(15, 26)	(11, 22)	(11, 21)	(22, 38)	(149, 201)
$N \to C$							
obs. counts	**10**	**11**	**15**	**18**	**14**	**26**	**132**
Condition on each state	(4, 12)	(8, 19)	(7, 16)	(11, 22)	(12, 22)	(17, 32)	(133, 165)
Condition on initial state	(2, 10)	(4, 14)	(7, 17)	(7, 17)	(8, 18)	(17, 32)	(134, 164)
$C \to N$							
obs. counts	**8**	**11**	**8**	**12**	**10**	**26**	**72**
Condition on each state	(6, 15)	(10, 20)	(7, 16)	(7, 15)	(9, 18)	(17, 30)	(131, 160)
Condition on initial state	(0, 7)	(6, 15)	(3, 11)	(8, 18)	(9, 19)	(17, 31)	(128, 159)
$C \to C$							
obs. counts	**7**	**20**	**9**	**21**	**20**	**24**	**185**
Condition on each state	(8, 15)	(11, 21)	(6, 14)	(10, 20)	(8, 17)	(23, 37)	(136, 173)
Condition on initial state	(8, 15)	(17, 26)	(8, 16)	(12, 23)	(12, 23)	(20, 36)	(138, 188)

Table A.4: Model fit for the p-MRSA Data Set including only the antiseptic treatment. The intervals in red indicate that the observed transition counts are included in the equal-tailed 95% quantiles.

A.1.2 After first positive test

	p_0		q_0	
GROUP	$E[\cdot\|\mathcal{S}]$ (s.d.)	95% CI	$E[\cdot\|\mathcal{S}]$ (s.d.)	95% CI
Aminoglycoside	0.9430 (0.0094)	(0.9234, 0.9591)	0.0840 (0.0084)	(0.0686, 0.1015)
Antiseptic	0.9332 (0.0157)	(0.8976, 0.9595)	0.0662 (0.0157)	(0.0505, 0.0857)
Cephalosporin	0.9496 (0.0084)	(0.9319, 0.9643)	0.0789 (0.0080)	(0.0643, 0.0954)
Glycopeptide	0.9391 (0.0107)	(0.9153, 0.9573)	0.0915 (0.0107)	(0.0753, 0.1148)
Macrolide	0.9470 (0.0087)	(0.9282, 0.9623)	0.0892 (0.0084)	(0.0737, 0.1069)
Nitroimidazole	0.9445 (0.0088)	(0.9259, 0.9603)	0.0889 (0.0085)	(0.0733, 0.1069)
Oxazolidinone	0.9465 (0.0084)	(0.9286, 0.9613)	0.0844 (0.0075)	(0.0705, 0.0999)
Penicillin	0.9441 (0.0088)	(0.9252, 0.9597)	0.0884 (0.0080)	(0.0737, 0.1053)
Polymyxin	0.9475 (0.0082)	(0.9294, 0.9623)	0.0877 (0.0076)	(0.0735, 0.1037)
Quinolone	0.9482 (0.0083)	(0.9299, 0.9632)	0.0899 (0.0081)	(0.0747, 0.1068)
Rifamycin	0.9472 (0.0083)	(0.9290, 0.9618)	0.0850 (0.0076)	(0.0720, 0.1015)

Table A.5: Summary statistics for parameters p_0 and q_0 for each antimicrobial group for the p-MRSA Data Set starting from patients' first positive test.

	α		β	
GROUP	$E[\cdot\|\mathcal{S}]$ (s.d.)	95% CI	$E[\cdot\|\mathcal{S}]$ (s.d.)	95% CI
Aminoglycoside	0.0320 (0.0256)	(−0.0323, 0.0668)	0.0363 (0.0304)	(−0.0167, 0.1016)
Antiseptic	0.0111 (0.0210)	(−0.0299, 0.0528)	0.0716 (0.0215)	(0.0328, 0.1167)
Cephalosporin	−0.0521 (0.0636)	(−0.2025, 0.0399)	0.0832 (0.0444)	(0.0131, 0.1859)
Glycopeptide	0.0245 (0.0174)	(−0.0120, 0.0568)	−0.0096 (0.0175)	(−0.0437, 0.0249)
Macrolide	−0.2067 (0.2512)	(−0.8086, 0.0342)	0.1063 (0.1690)	(−0.0453, 0.5548)
Nitroimidazole	0.0074 (0.0727)	(−0.1579, 0.0628)	0.0020 (0.0410)	(−0.0491, 0.0876)
Oxazolidinone	−0.0107 (0.0701)	(−0.2028, 0.0580)	0.6866 (0.1708)	(0.2991, 0.9075)
Penicillin	0.0282 (0.0307)	(−0.0518, 0.0648)	0.0034 (0.0373)	(−0.0569, 0.0895)
Polymyxin	−0.3499 (0.2638)	(−0.8679, 0.0355)	0.4030 (0.2920)	(−0.0635, 0.8821)
Quinolone	−0.5445 (0.2351)	(−0.9149, −0.0403)	0.2221 (0.1481)	(−0.0204, 0.5483)
Rifamycin	−0.3889 (0.02622)	(−0.9027, 0.0345)	0.4753 (0.2576)	(0.0238, 0.8893)

Table A.6: Summary statistics for parameters α and β for each antimicrobial group for the p-MRSA Data Set starting from patients' first positive test.

Model Fit							
Day Intervals	**1**	**2**	**3**	**4**	**5**	**6**	**7**
$N \to N$							
obs. counts	**3**	**2**	**1**	**1**	**2**	**12**	**134**
Aminoglycoside	(3, 4)	(1, 2)	(1, 2)	(0, 1)	(1, 3)	(9, 16)	(117, 139)
Antiseptic	(2, 4)	(1, 2)	(1, 2)	(0, 1)	(1, 3)	(9, 16)	(115, 138)
Cephalosporin	(2, 4)	(1, 2)	(1, 2)	(0, 1)	(1, 3)	(10, 16)	(116, 138)
Glycopeptide	(3, 4)	(1, 2)	(1, 2)	(0, 1)	(1, 3)	(9, 16)	(117, 139)
Macrolide	(3, 4)	(0, 2)	(0, 2)	(0, 1)	(1, 3)	(10, 16)	(112, 134)
Nitroimidazole	(3, 4)	(1, 2)	(1, 2)	(0, 1)	(1, 3)	(10, 16)	(114, 136)
Oxazolidinone	(3, 4)	(1, 2)	(0, 2)	(0, 1)	(1, 3)	(10, 16)	(117, 139)
Penicillin	(3, 4)	(1, 2)	(1, 2)	(0, 1)	(1, 3)	(9, 16)	(117, 139)
Polymixin	(3, 4)	(1, 2)	(1, 2)	(0, 1)	(1, 3)	(9, 16)	(115, 139)
Quinolone	(3, 4)	(1, 2)	(1, 2)	(0, 1)	(0, 3)	(10, 16)	(115, 136)
Rifamycin	(3, 4)	(1, 2)	(0, 2)	(0, 1)	(1, 3)	(10, 16)	(115, 139)
$N \to C$							
obs. counts	**1**	**0**	**1**	**0**	**1**	**5**	**37**
Aminoglycoside	(0, 1)	(0, 1)	(0, 1)	(0, 1)	(0, 2)	(1, 7)	(31, 54)
Antiseptic	(0, 2)	(0, 1)	(0, 1)	(0, 1)	(0, 2)	(1, 8)	(33, 56)
Cephalosporin	(0, 1)	(0, 1)	(0, 1)	(0, 1)	(0, 2)	(1, 7)	(32, 55)
Glycopeptide	(0, 1)	(0, 1)	(0, 1)	(0, 1)	(0, 2)	(1, 7)	(31, 54)
Macrolide	(0, 1)	(0, 2)	(0, 2)	(0, 1)	(0, 2)	(1, 7)	(37, 58)
Nitroimidazole	(0, 1)	(0, 1)	(0, 1)	(0, 1)	(0, 2)	(1, 7)	(35, 56)
Oxazolidinone	(0, 1)	(0, 1)	(0, 1)	(0, 1)	(0, 2)	(1, 7)	(32, 54)
Penicillin	(0, 1)	(0, 1)	(0, 1)	(0, 1)	(0, 2)	(1, 7)	(32, 54)
Polymixin	(0, 1)	(0, 1)	(0, 1)	(0, 1)	(0, 2)	(1, 7)	(32, 55)
Quinolone	(0, 1)	(0, 1)	(0, 1)	(0, 1)	(0, 2)	(1, 7)	(35, 56)
Rifamycin	(0, 1)	(0, 1)	(0, 1)	(0, 1)	(0, 2)	(1, 7)	(32, 56)
$C \to N$							
obs. counts	**8**	**11**	**8**	**12**	**10**	**26**	**72**
Aminoglycoside	(0, 3)	(2, 10)	(1, 8)	(5, 15)	(5, 15)	(12, 25)	(90, 120)
Antiseptic	(0, 3)	(1, 9)	(1, 7)	(4, 15)	(5, 15)	(13, 26)	(91, 123)
Cephalosporin	(0, 4)	(2, 10)	(2, 9)	(5, 16)	(6, 16)	(12, 26)	(88, 117)
Glycopeptide	(0, 4)	(1, 9)	(1, 7)	(5, 14)	(5, 15)	(11, 26)	(90, 120)
Macrolide	(0, 4)	(2, 10)	(1, 8)	(5, 16)	(6, 16)	(13, 26)	(92, 124)
Nitroimidazole	(0, 4)	(2, 11)	(1, 8)	(5, 15)	(6, 16)	(14, 27)	(91, 125)
Oxazolidinone	(0, 4)	(1, 9)	(1, 8)	(4, 14)	(6, 16)	(11, 25)	(86, 117)
Penicillin	(0, 4)	(1, 9)	(1, 7)	(5, 15)	(5, 15)	(12, 25)	(88, 119)
Polymixin	(0, 4)	(1, 9)	(1, 7)	(4, 14)	(6, 16)	(12, 26)	(89, 121)
Quinolone	(0, 4)	(2, 11)	(1, 7)	(5, 15)	(5, 14)	(12, 26)	(92, 122)
Rifamycin	(0, 4)	(2, 9)	(1, 8)	(4, 14)	(5, 15)	(12, 25)	(90, 120)
$C \to C$							
obs. counts	**7**	**20**	**9**	**21**	**20**	**24**	**185**
Aminoglycoside	(11, 15)	(21, 29)	(9, 16)	(18, 28)	(15, 25)	(24, 38)	(136, 167)
Antiseptic	(11, 15)	(21, 29)	(10, 16)	(18, 28)	(15, 25)	(24, 37)	(134, 166)
Cephalosporin	(11, 15)	(21, 29)	(8, 15)	(17, 28)	(14, 24)	(24, 37)	(139, 169)
Glycopeptide	(11, 15)	(22, 30)	(10, 16)	(18, 28)	(15, 25)	(24, 39)	(136, 167)
Macrolide	(11, 15)	(21, 29)	(9, 16)	(17, 28)	(14, 24)	(24, 37)	(132, 164)
Nitroimidazole	(11, 15)	(20, 29)	(8, 16)	(18, 28)	(14, 24)	(23, 36)	(132, 165)
Oxazolidinone	(11, 15)	(22, 30)	(9, 16)	(19, 29)	(14, 24)	(25, 39)	(140, 170)
Penicillin	(11, 15)	(22, 30)	(10, 16)	(18, 28)	(15, 25)	(24, 38)	(137, 168)
Polymixin	(11, 15)	(22, 30)	(10, 16)	(18, 28)	(14, 24)	(24, 37)	(135, 167)
Quinolone	(11, 15)	(20, 29)	(10, 16)	(18, 28)	(15, 25)	(24, 37)	(135, 165)
Rifamycin	(11, 15)	(21, 29)	(9, 16)	(18, 29)	(15, 25)	(24, 38)	(137, 167)

Table A.7: Model fit for each antimicrobial treatment group of the p-MRSA Data Set starting from patients' first positive test. The intervals in red indicate that the observed transition counts are included in the equal-tailed 95% quantiles.

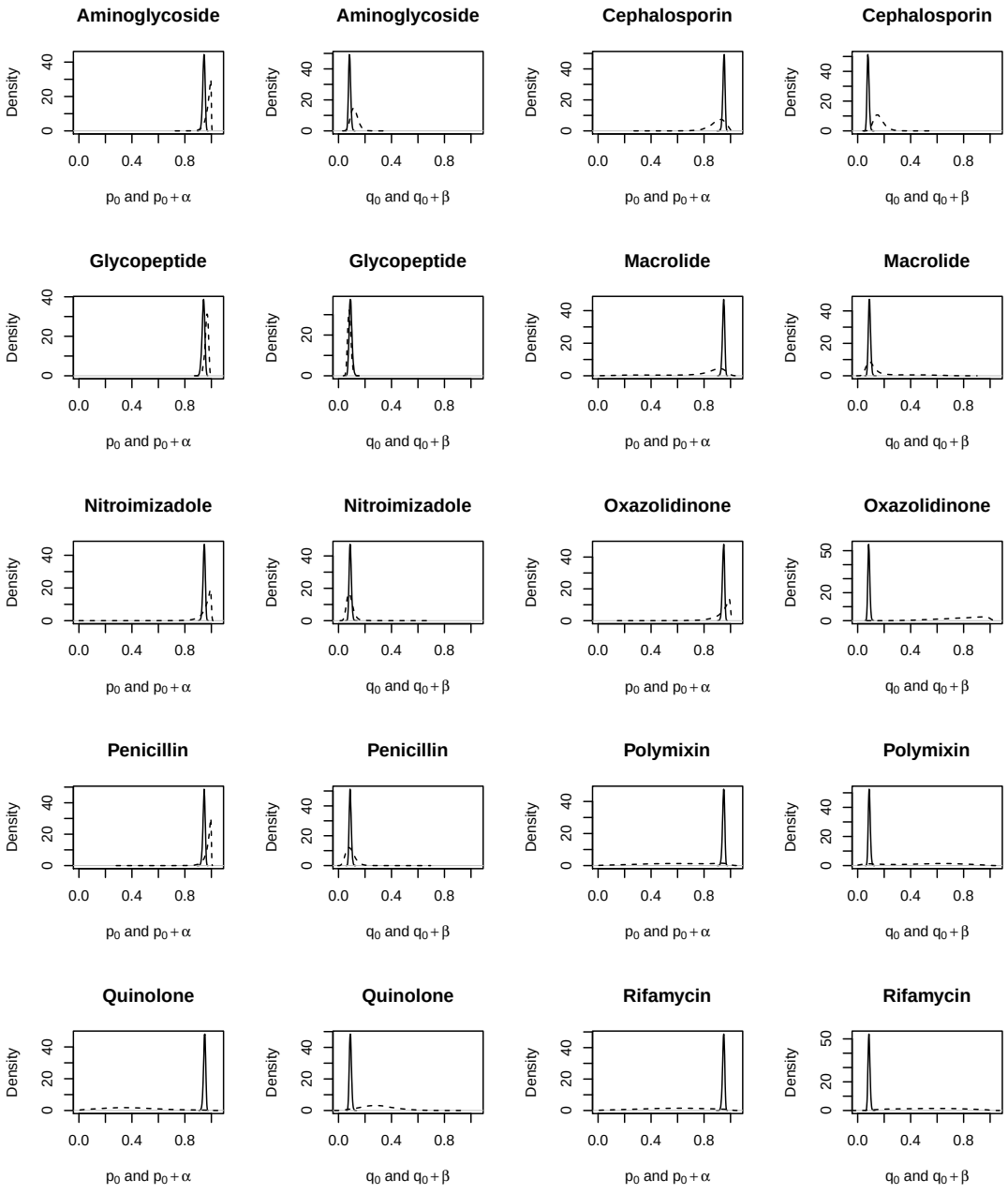

Figure A.3: Kernel density plots for p_0, $p_0 + \alpha$, q_0 and $q_0 + \beta$ for the antibiotics from the p-MRSA Data Set after first positive test. The continuous line shows the probabilities p_0 and q_0 whereas the dashed line shows the probabilities $p_0 + \alpha$ and $q_0 + \beta$.

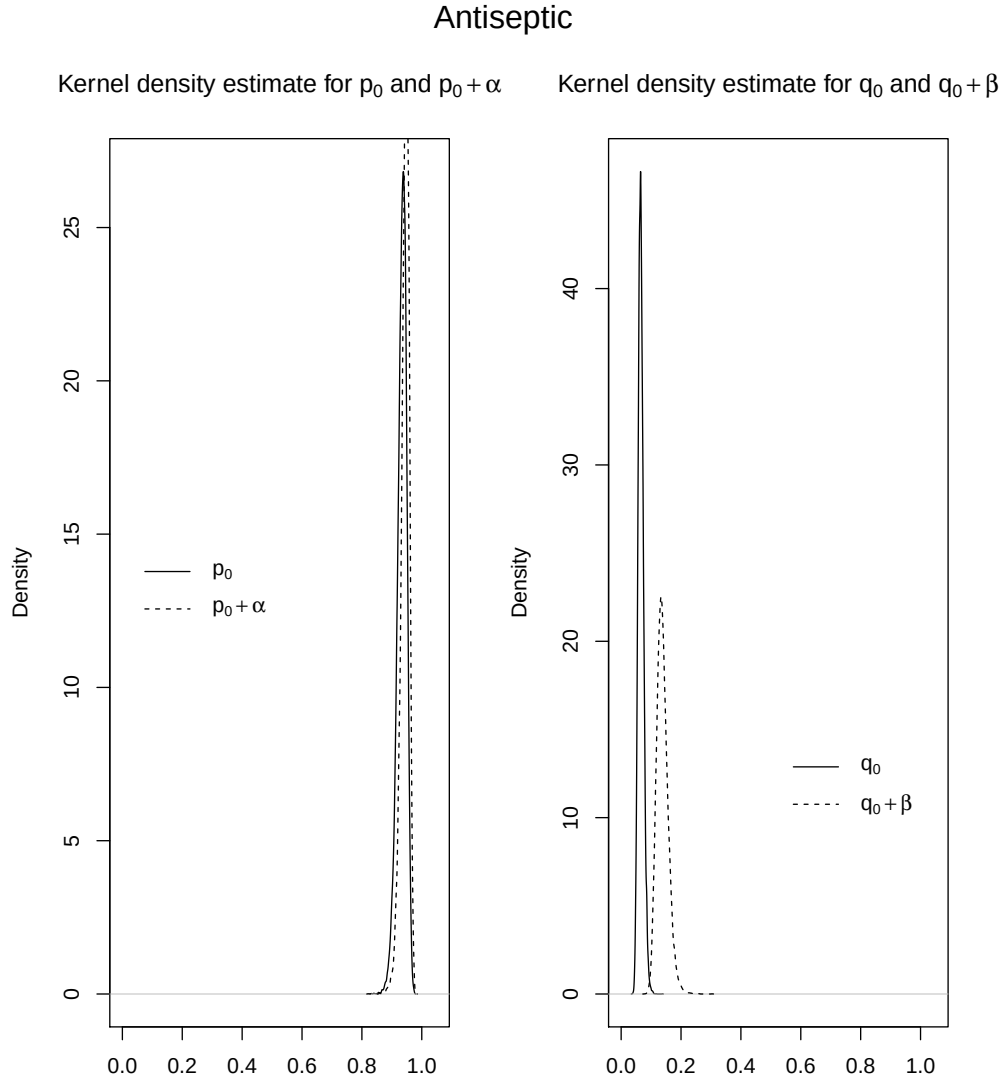

Figure A.4: Kernel density plots for p_0, $p_0 + \alpha$, q_0 and $q_0 + \beta$ for the antiseptic from the p-MRSA Data Set after first positive test. The continuous line shows the probabilities p_0 and q_0 whereas the dashed line shows the probabilities $p_0 + \alpha$ and $q_0 + \beta$.

A.2 p-Wounds Data Set

	p_0		q_0	
GROUP	$E[\cdot\|\mathcal{S}]$ (s.d.)	95% CI	$E[\cdot\|\mathcal{S}]$ (s.d.)	95% CI
Aminoglycoside	0.7977 (0.0149)	(0.7672, 0.8257)	0.5023 (0.0323)	(0.4402, 0.5677)
Antiseptic	0.7931 (0.0185)	(0.7546, 0.8281)	0.5087 (0.0418)	(0.4297, 0.5930)
Cephalosporin	0.7872 (0.0153)	(0.7554, 0.8165)	0.5164 (0.0331)	(0.4538, 0.5827)
Glycopeptide	0.7887 (0.0173)	(0.7534, 0.8212)	0.4923 (0.0380)	(0.4192, 0.5682)
Macrolide	0.8051 (0.0143)	(0.7759, 0.8323)	0.4801 (0.0313)	(0.4211, 0.5430)
Nitroimidazole	0.7876 (0.0151)	(0.7566, 0.8156)	0.5199 (0.0326)	(0.4575, 0.5860)
Oxazolidinone	0.7918 (0.0141)	(0.7627, 0.8183)	0.5137 (0.0304)	(0.4545, 0.5746)
Penicillin	0.7881 (0.0146)	(0.7591, 0.8154)	0.5124 (0.0315)	(0.4523, 0.5754)
Polymyxin	0.7926 (0.0138)	(0.7645, 0.8188)	0.5194 (0.0304)	(0.4615, 0.5815)
Quinolone	0.7967 (0.0141)	(0.7673, 0.8229)	0.5189 (0.0317)	(0.4584, 0.5826)
Rifamycin	0.7948 (0.0137)	(0.7668, 0.8205)	0.5131 (0.0306)	(0.4534, 0.5742)

Table A.8: Summary statistics for parameters p_0 and q_0 for each antimicrobial group for the p-Wounds Data Set.

	α		β	
GROUP	$E[\cdot\|\mathcal{S}]$ (s.d.)	95% CI	$E[\cdot\|\mathcal{S}]$ (s.d.)	95% CI
Aminoglycoside	−0.0412 (0.0479)	(−0.1389, 0.0488)	0.1661 (0.1076)	(−0.0482, 0.3661)
Antiseptic	0.0015 (0.0185)	(−0.0540, 0.0547)	0.0203 (0.0622)	(−0.0997, 0.1443)
Cephalosporin	0.0615 (0.0368)	(−0.0158, 0.1277)	0.0229 (0.0962)	(−0.1598, 0.2144)
Glycopeptide	0.0215 (0.0292)	(−0.0368, 0.0770)	0.0555 (0.0636)	(−0.0672, 0.1815)
Macrolide	−0.0719 (0.0408)	(−0.1547, 0.0058)	0.3013 (0.0841)	(0.1287, 0.4534)
Nitroimidazole	0.0578 (0.0384)	(−0.0227, 0.1270)	−0.0168 (0.1025)	(−0.2102, 0.1885)
Oxazolidinone	0.1629 (0.0482)	(0.0353, 0.2226)	0.1618 (0.2030)	(−0.2776, 0.4748)
Penicillin	0.0821 (0.0380)	(0.0032, 0.1494)	0.0939 (0.1113)	(−0.1213, 0.3117)
Polymyxin	0.0649 (0.1027)	(−0.2057, 0.1862)	−0.1123 (0.2652)	(−0.4670, 0.4548)
Quinolone	−0.0874 (0.0800)	(−0.2584, 0.0537)	−0.0119 (0.1211)	(−0.2472, 0.2220)
Rifamycin	−0.0136 (0.1335)	(−0.3411, 0.1716)	0.2336 (0.2083)	(−0.2263, 0.5032)

Table A.9: Summary statistics for parameters α and β for each antimicrobial group for the p-Wounds Data Set.

Model Fit							
Day Intervals	**1**	**2**	**3**	**4**	**5**	**6**	**7**
$N \to N$							
obs. counts	**316**	**213**	**179**	**125**	**96**	**59**	**35**
Aminoglycoside	(314, 345)	(206, 234)	(148, 173)	(99, 121)	(83, 102)	(49, 65)	(28, 41)
Antiseptic	(315, 346)	(205, 235)	(148, 174)	(98, 121)	(83, 102)	(49, 65)	(28, 40)
Cephalosporin	(316, 349)	(205, 234)	(147, 172)	(100, 120)	(83, 102)	(48, 65)	(28, 39)
Glycopeptide	(316, 348)	(206, 236)	(149, 173)	(99, 120)	(82, 101)	(49, 65)	(28, 40)
Macrolide	(316, 348)	(206, 237)	(150, 174)	(100, 121)	(83, 102)	(50, 65)	(28, 40)
Nitroimidazole	(315, 347)	(204, 235)	(149, 174)	(99, 122)	(81, 103)	(49, 64)	(28, 40)
Oxazolidinone	(314, 347)	(207, 234)	(147, 172)	(100, 121)	(82, 102)	(49, 65)	(27, 40)
Penicillin	(314, 348)	(206, 234)	(146, 173)	(99, 121)	(82, 101)	(49, 65)	(28, 40)
Polymyxin	(313, 347)	(203, 234)	(148, 173)	(99, 121)	(83, 101)	(49, 65)	(28, 40)
Quinolone	(314, 347)	(204, 235)	(146, 174)	(99, 121)	(82, 103)	(49, 64)	(28, 40)
Rifamycin	(314, 348)	(205, 234)	(149, 173)	(98, 121)	(82, 101)	(50, 65)	(27, 40)
$N \to C$							
obs. counts	**101**	**86**	**44**	**29**	**33**	**21**	**13**
Aminoglycoside	(71, 103)	(64, 92)	(50, 75)	(33, 55)	(27, 46)	(15, 30)	(7, 20)
Antiseptic	(71, 101)	(64, 93)	(48, 75)	(33, 55)	(27, 46)	(15, 31)	(8, 20)
Cephalosporin	(68, 100)	(64, 94)	(51, 75)	(34, 54)	(27, 46)	(15, 31)	(9, 20)
Glycopeptide	(69, 100)	(63, 92)	(49, 74)	(33, 55)	(27, 47)	(15, 31)	(8, 20)
Macrolide	(68, 100)	(62, 93)	(49, 73)	(33, 54)	(26, 45)	(15, 30)	(8, 20)
Nitroimidazole	(70, 102)	(64, 94)	(48, 74)	(32, 55)	(26, 48)	(16, 31)	(8, 20)
Oxazolidinone	(70, 103)	(64, 92)	(50, 75)	(32, 53)	(27, 47)	(14, 31)	(8, 20)
Penicillin	(69, 103)	(65, 92)	(50, 76)	(33, 55)	(27, 47)	(15, 30)	(8, 20)
Polymyxin	(69, 104)	(64, 96)	(50, 75)	(32, 55)	(27, 46)	(15, 31)	(8, 20)
Quinolone	(69, 102)	(63, 95)	(48, 76)	(32, 54)	(26, 46)	(15, 31)	(8, 20)
Rifamycin	(68, 102)	(65, 93)	(49, 73)	(33, 55)	(28, 47)	(15, 30)	(8, 20)
$C \to N$							
obs. counts	**100**	**65**	**48**	**40**	**30**	**16**	**11**
Aminoglycoside	(83, 110)	(72, 94)	(46, 61)	(37, 51)	(22, 33)	(14, 23)	(7, 14)
Antiseptic	(84, 109)	(71, 93)	(46, 61)	(36, 51)	(21, 33)	(13, 22)	(7, 14)
Cephalosporin	(84, 111)	(72, 92)	(47, 61)	(36, 51)	(23, 33)	(13, 22)	(7, 14)
Glycopeptide	(83, 110)	(73, 93)	(46, 61)	(37, 52)	(22, 33)	(14, 22)	(7, 14)
Macrolide	(83, 109)	(69, 90)	(46, 61)	(36, 51)	(22, 33)	(13, 22)	(7, 14)
Nitroimidazole	(84, 111)	(72, 93)	(46, 60)	(36, 50)	(21, 33)	(13, 22)	(7, 14)
Oxazolidinone	(82, 110)	(71, 92)	(45, 61)	(36, 50)	(22, 34)	(14, 22)	(7, 14)
Penicillin	(83, 111)	(71, 92)	(45, 61)	(36, 50)	(22, 33)	(13, 22)	(7, 14)
Polymyxin	(83, 111)	(71, 91)	(46, 61)	(37, 50)	(22, 33)	(14, 22)	(7, 14)
Quinolone	(83, 111)	(72, 93)	(47, 62)	(38, 50)	(22, 33)	(13, 22)	(7, 14)
Rifamycin	(83, 109)	(71, 93)	(47, 61)	(38, 51)	(22, 34)	(13, 22)	(7, 14)
$C \to C$							
obs. counts	**88**	**60**	**29**	**22**	**9**	**9**	**4**
Aminoglycoside	(78, 104)	(31, 53)	(16, 30)	(11, 25)	(6, 17)	(2, 11)	(1, 8)
Antiseptic	(78, 104)	(31, 53)	(15, 31)	(11, 25)	(6, 17)	(3, 12)	(1, 8)
Cephalosporin	(76, 104)	(33, 53)	(15, 30)	(10, 26)	(5, 16)	(2, 12)	(1, 8)
Glycopeptide	(78, 105)	(32, 52)	(16, 30)	(10, 25)	(5, 17)	(3, 11)	(1, 8)
Macrolide	(79, 105)	(35, 55)	(15, 31)	(11, 26)	(6, 17)	(3, 12)	(1, 7)
Nitroimidazole	(76, 104)	(31, 53)	(16, 31)	(12, 25)	(6, 18)	(3, 11)	(1, 8)
Oxazolidinone	(78, 105)	(32, 53)	(15, 31)	(12, 25)	(5, 17)	(3, 11)	(1, 8)
Penicillin	(76, 104)	(32, 53)	(16, 32)	(11, 26)	(6, 17)	(3, 12)	(1, 8)
Polymyxin	(76, 103)	(33, 53)	(15, 31)	(12, 25)	(6, 17)	(3, 11)	(1, 8)
Quinolone	(77, 104)	(32, 52)	(15, 30)	(11, 24)	(6, 17)	(3, 11)	(1, 7)
Rifamycin	(79, 105)	(31, 53)	(16, 30)	(11, 24)	(5, 17)	(3, 12)	(1, 8)

Table A.10: Model fit for each antimicrobial treatment group of the p-Wounds Data Set. The intervals in red indicate that the observed transition counts are included in the equal-tailed 95% quantiles.

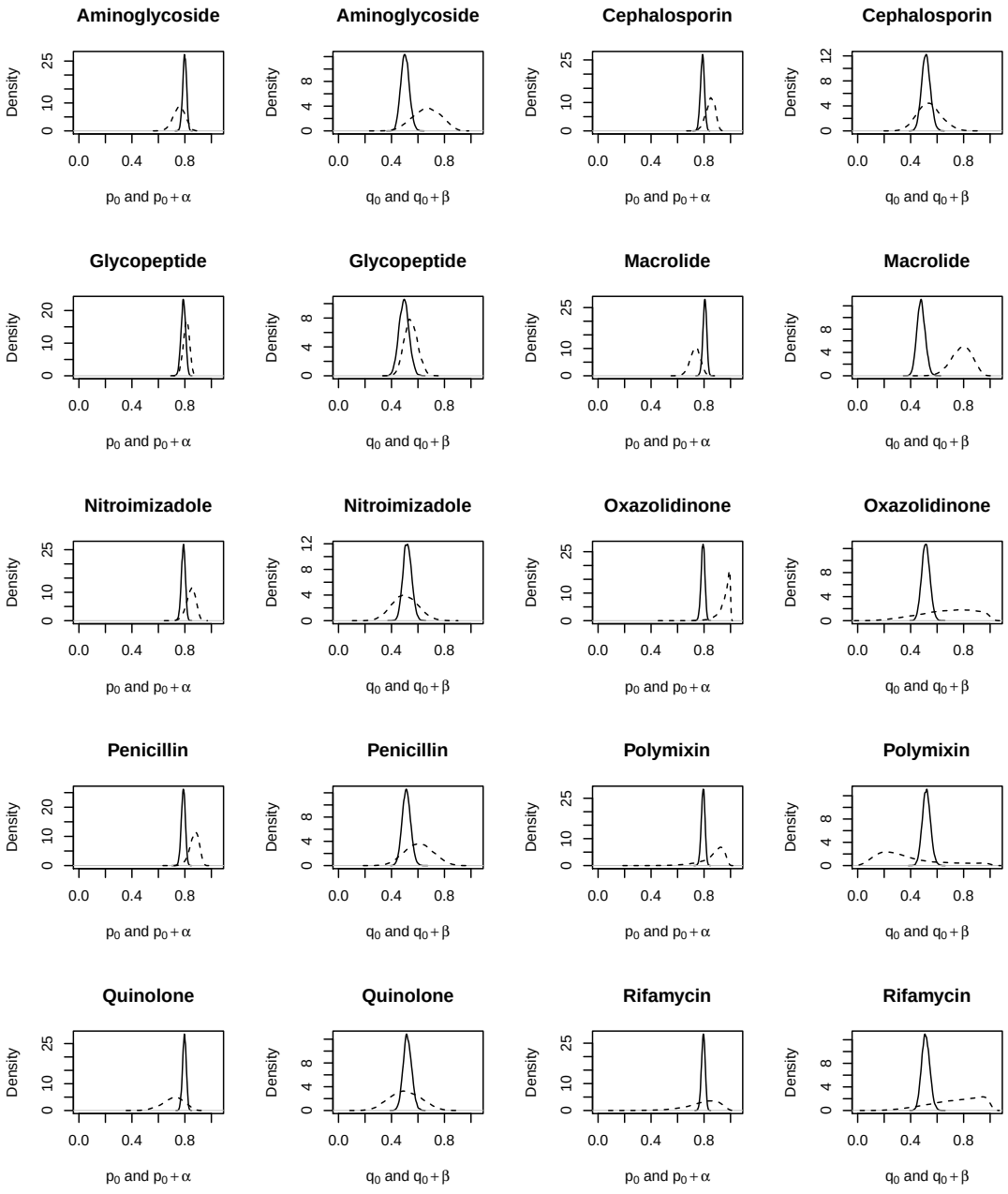

Figure A.5: Kernel density plots for p_0, $p_0 + \alpha$, q_0 and $q_0 + \beta$ for the antibiotics from the p-Wounds Data Set. The continuous line shows the probabilities p_0 and q_0 whereas the dashed line shows the probabilities $p_0 + \alpha$ and $q_0 + \beta$.

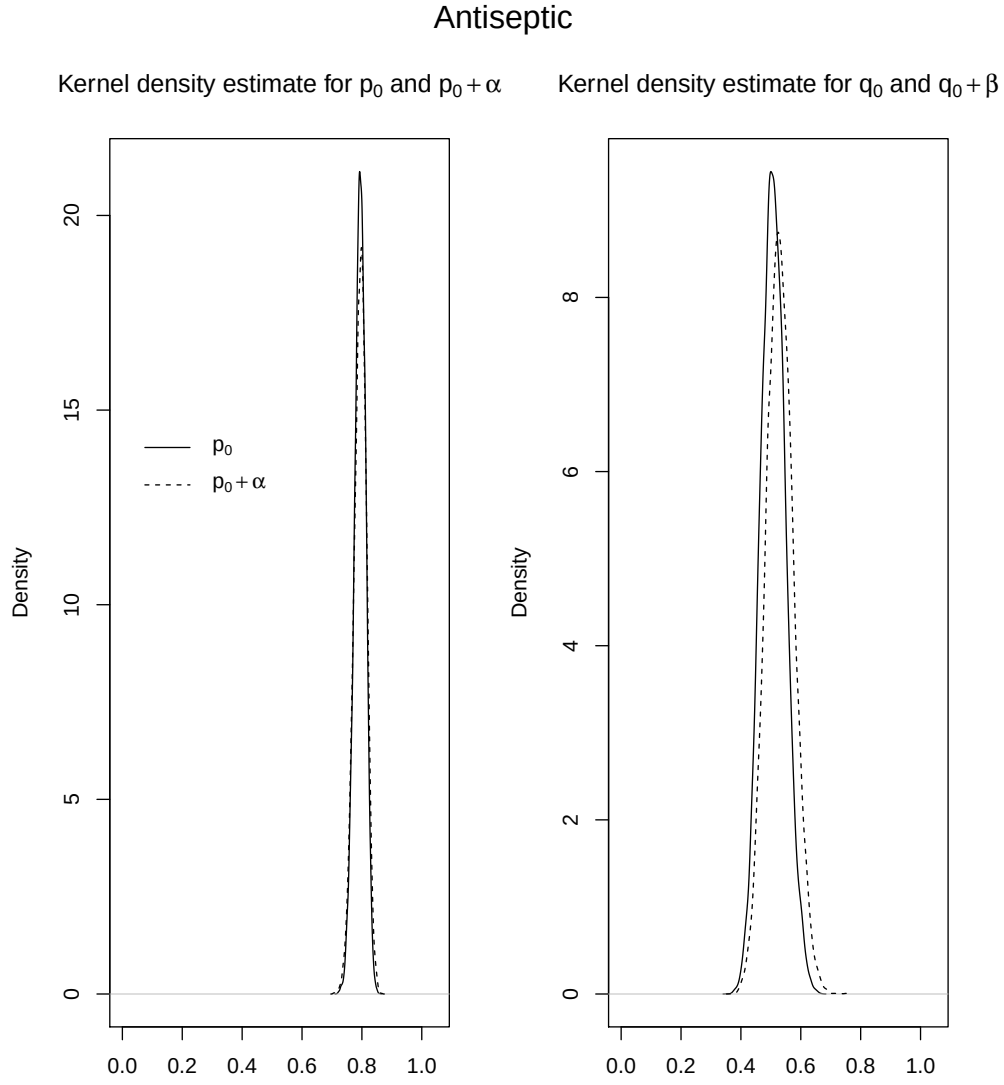

Figure A.6: Kernel density plots for p_0, $p_0 + \alpha$, q_0 and $q_0 + \beta$ for the antiseptic from the p-Wounds Data Set. The continuous line shows the probabilities p_0 and q_0 whereas the dashed line shows the probabilities $p_0 + \alpha$ and $q_0 + \beta$.

A.2.1 After first positive test

	p_0		q_0	
GROUP	$E[\cdot\|\mathcal{S}]$ (s.d.)	95% CI	$E[\cdot\|\mathcal{S}]$ (s.d.)	95% CI
Aminoglycoside	0.8050 (0.0191)	(0.7656, 0.8403)	0.4795 (0.0330)	(0.4176, 0.5460)
Antiseptic	0.7831 (0.0296)	(0.7205, 0.8371)	0.4887 (0.0456)	(0.4027, 0.5820)
Cephalosporin	0.8003 (0.0196)	(0.7598, 0.8363)	0.4877 (0.0339)	(0.4243, 0.5569)
Glycopeptide	0.7804 (0.0259)	(0.7263, 0.8283)	0.4702 (0.0408)	(0.3939, 0.5540)
Macrolide	0.8101 (0.0188)	(0.7716, 0.8454)	0.4557 (0.0317)	(0.3950, 0.5196)
Nitroimidazole	0.7908 (0.0206)	(0.7478, 0.8282)	0.5042 (0.0348)	(0.4382, 0.5756)
Oxazolidinone	0.7952 (0.0194)	(0.7554, 0.8314)	0.4917 (0.0324)	(0.4298, 0.5574)
Penicillin	0.7915 (0.0201)	(0.7498, 0.8291)	0.4883 (0.0334)	(0.4254, 0.5560)
Polymyxin	0.7984 (0.0188)	(0.7606, 0.8338)	0.4954 (0.0318)	(0.4334, 0.5590)
Quinolone	0.8026 (0.0190)	(0.7635, 0.8380)	0.4963 (0.0335)	(0.4318, 0.5646)
Rifamycin	0.7976 (0.1929)	(0.7580, 0.8335)	0.4918 (0.0324)	(0.4313, 0.5563)

Table A.11: Summary statistics for parameters p_0 and q_0 for each antimicrobial group for the p-Wounds Data Set starting from patients' first positive test.

	α		β	
GROUP	$E[\cdot\|\mathcal{S}]$ (s.d.)	95% CI	$E[\cdot\|\mathcal{S}]$ (s.d.)	95% CI
Aminoglycoside	−0.0799 (0.0767)	(−0.2388, 0.0581)	0.1854 (0.1257)	(−0.0648, 0.4046)
Antiseptic	0.0259 (0.0400)	(−0.0528, 0.1048)	0.0193 (0.0707)	(−0.1191, 0.1580)
Cephalosporin	−0.0139 (0.0793)	(−0.1891, 0.1172)	0.0683 (0.1215)	(−0.1575, 0.3044)
Glycopeptide	0.0455 (0.0391)	(−0.0321, 0.1208)	0.0584 (0.0709)	(−0.0782, 0.1998)
Macrolide	−0.0754 (0.0654)	(−0.2129, 0.0417)	0.3486 (0.0950)	(0.1399, 0.5063)
Nitroimidazole	0.0803 (0.0554)	(−0.0427, 0.1732)	−0.0904 (0.1126)	(−0.2932, 0.1441)
Oxazolidinone	0.1572 (0.0566)	(0.0098, 0.2275)	0.2599 (0.2180)	(−0.2391, 0.5283)
Penicillin	0.1227 (0.0479)	(0.0144, 0.2020)	0.1185 (0.1265)	(−0.1232, 0.3580)
Polymyxin	0.0137 (0.1410)	(−0.3473, 0.1845)	−0.0377 (0.2830)	(−0.4372, 0.4900)
Quinolone	−0.1743 (0.1300)	(−0.4476, 0.0574)	−0.0026 (0.1350)	(−0.2524, 0.2558)
Rifamycin	0.0618 (0.1123)	(−0.2220, 0.2053)	0.1969 (0.2282)	(−0.2637, 0.5182)

Table A.12: Summary statistics for parameters α and β for each antimicrobial group for the p-Wounds Data Set starting from patients' first positive test.

Model Fit							
Day Intervals	**1**	**2**	**3**	**4**	**5**	**6**	**7**
$N \to N$							
obs. counts	**140**	**91**	**83**	**57**	**46**	**32**	**14**
Aminoglycoside	(138, 159)	(80, 98)	(62, 81)	(42, 57)	(39, 53)	(23, 33)	(10, 18)
Antiseptic	(138, 159)	(80, 99)	(64, 81)	(43, 57)	(39, 53)	(22, 34)	(10, 18)
Cephalosporin	(138, 160)	(80, 98)	(63, 80)	(43, 57)	(39, 53)	(23, 34)	(11, 19)
Glycopeptide	(139, 161)	(80, 99)	(64, 81)	(43, 57)	(38, 53)	(23, 33)	(10, 18)
Macrolide	(140, 161)	(81, 100)	(64, 81)	(43, 58)	(39, 52)	(23, 34)	(11, 18)
Nitroimidazole	(136, 158)	(78, 96)	(61, 79)	(41, 56)	(37, 52)	(21, 33)	(10, 18)
Oxazolidinone	(138, 159)	(81, 99)	(62, 81)	(43, 58)	(39, 53)	(23, 34)	(10, 19)
Penicillin	(140, 160)	(80, 99)	(64, 81)	(43, 57)	(39, 52)	(23, 33)	(10, 19)
Polymyxin	(139, 160)	(80, 99)	(63, 81)	(42, 57)	(38, 53)	(22, 34)	(10, 19)
Quinolone	(137, 159)	(81, 100)	(63, 81)	(43, 58)	(39, 53)	(22, 34)	(11, 19)
Rifamycin	(138, 160)	(79, 100)	(63, 81)	(42, 57)	(39, 53)	(23, 34)	(11, 19)
$N \to C$							
obs. counts	**47**	**31**	**18**	**13**	**19**	**8**	**7**
Aminoglycoside	(28, 49)	(24, 42)	(19, 38)	(12, 28)	(12, 26)	(7, 17)	(3, 11)
Antiseptic	(27, 49)	(23, 41)	(20, 37)	(12, 27)	(12, 26)	(6, 18)	(3, 11)
Cephalosporin	(27, 49)	(24, 42)	(20, 37)	(13, 27)	(12, 26)	(6, 17)	(2, 10)
Glycopeptide	(25, 48)	(23, 41)	(19, 37)	(13, 27)	(11, 26)	(7, 17)	(3, 11)
Macrolide	(26, 47)	(21, 40)	(19, 37)	(12, 27)	(12, 26)	(6, 17)	(2, 10)
Nitroimidazole	(29, 51)	(25, 43)	(21, 39)	(14, 29)	(13, 28)	(7, 18)	(2, 11)
Oxazolidinone	(27, 49)	(22, 40)	(19, 39)	(12, 27)	(12, 26)	(6, 17)	(2, 11)
Penicillin	(27, 47)	(22, 42)	(19, 37)	(12, 27)	(13, 26)	(6, 17)	(2, 11)
Polymyxin	(27, 48)	(23, 42)	(20, 38)	(13, 27)	(12, 26)	(6, 18)	(2, 10)
Quinolone	(27, 50)	(21, 41)	(20, 38)	(12, 27)	(11, 26)	(6, 18)	(2, 10)
Rifamycin	(26, 49)	(22, 43)	(20, 38)	(13, 28)	(12, 26)	(6, 17)	(2, 10)
$C \to N$							
obs. counts	**100**	**65**	**48**	**40**	**30**	**16**	**11**
Aminoglycoside	(79, 106)	(70, 91)	(46, 60)	(37, 51)	(22, 33)	(13, 22)	(7, 14)
Antiseptic	(80, 106)	(70, 92)	(45, 61)	(37, 50)	(22, 33)	(13, 22)	(7, 14)
Cephalosporin	(78, 105)	(70, 90)	(46, 60)	(37, 50)	(22, 33)	(13, 22)	(7, 13)
Glycopeptide	(76, 106)	(70, 91)	(45, 61)	(36, 51)	(22, 34)	(13, 22)	(7, 14)
Macrolide	(78, 106)	(68, 89)	(44, 61)	(36, 50)	(22, 33)	(13, 22)	(7, 14)
Nitroimidazole	(77, 101)	(67, 89)	(43, 58)	(34, 49)	(20, 32)	(12, 21)	(7, 14)
Oxazolidinone	(78, 105)	(68, 91)	(45, 60)	(37, 50)	(22, 33)	(13, 22)	(7, 14)
Penicillin	(79, 106)	(72, 91)	(46, 61)	(37, 50)	(21, 33)	(13, 22)	(7, 13)
Polymyxin	(80, 107)	(69, 92)	(45, 61)	(36, 50)	(22, 33)	(12, 22)	(7, 14)
Quinolone	(81, 107)	(69, 91)	(45, 61)	(36, 50)	(22, 33)	(13, 22)	(7, 14)
Rifamycin	(79, 107)	(69, 91)	(45, 61)	(36, 49)	(22, 33)	(13, 22)	(7, 14)
$C \to C$							
obs. counts	**88**	**60**	**29**	**22**	**9**	**9**	**4**
Aminoglycoside	(82, 109)	(34, 55)	(16, 31)	(11, 25)	(6, 17)	(3, 12)	(1, 8)
Antiseptic	(82, 106)	(32, 54)	(16, 32)	(11, 25)	(5, 16)	(3, 12)	(1, 8)
Cephalosporin	(83, 108)	(34, 54)	(16, 31)	(12, 24)	(6, 17)	(3, 11)	(1, 8)
Glycopeptide	(81, 111)	(34, 54)	(16, 32)	(11, 25)	(5, 17)	(3, 12)	(1, 8)
Macrolide	(82, 110)	(36, 57)	(15, 32)	(12, 25)	(6, 17)	(3, 11)	(1, 8)
Nitroimidazole	(86, 111)	(36, 58)	(18, 34)	(12, 27)	(7, 18)	(4, 13)	(1, 8)
Oxazolidinone	(83, 109)	(34, 57)	(17, 32)	(11, 25)	(6, 17)	(3, 12)	(1, 8)
Penicillin	(82, 109)	(34, 53)	(16, 31)	(12, 24)	(6, 18)	(3, 12)	(2, 8)
Polymyxin	(81, 107)	(32, 56)	(16, 32)	(12, 26)	(6, 17)	(3, 12)	(1, 7)
Quinolone	(81, 107)	(33, 56)	(16, 32)	(11, 26)	(6, 17)	(3, 11)	(1, 8)
Rifamycin	(80, 108)	(34, 56)	(16, 32)	(12, 26)	(6, 17)	(3, 12)	(1, 8)

Table A.13: Model fit for each antimicrobial treatment group of the p-Wounds Data Set starting from patients' first positive test. The intervals in red indicate that the observed transition counts are included in the equal-tailed 95% quantiles.

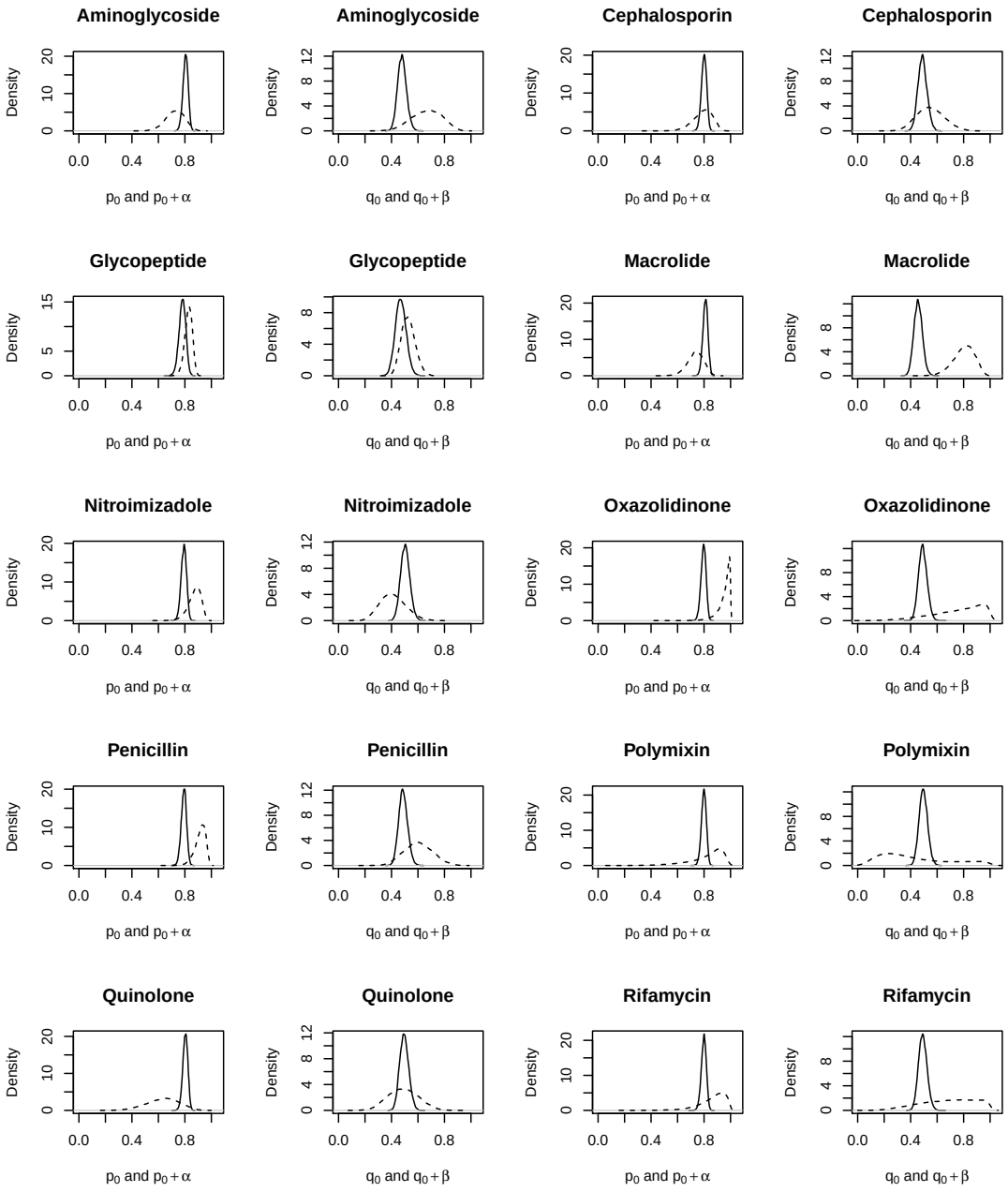

Figure A.7: Kernel density plots for p_0, $p_0 + \alpha$, q_0 and $q_0 + \beta$ for the antibiotics from the p-Wounds Data Set after first positive test. The continuous line shows the probabilities p_0 and q_0 whereas the dashed line shows the probabilities $p_0 + \alpha$ and $q_0 + \beta$.

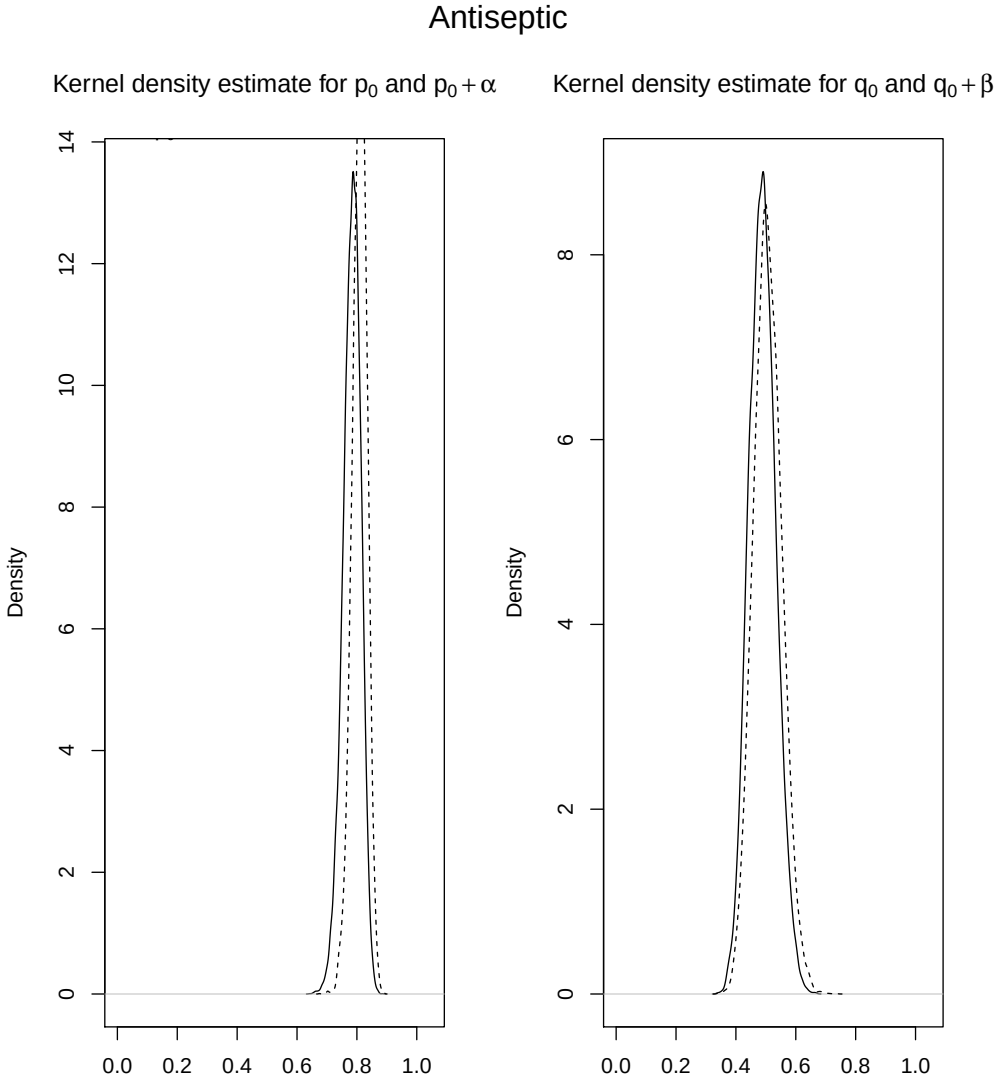

Figure A.8: Kernel density plots for p_0, $p_0 + \alpha$, q_0 and $q_0 + \beta$ for the antiseptic from the p-Wounds Data Set after first positive test. The continuous line shows the probabilities p_0 and q_0 whereas the dashed line shows the probabilities $p_0 + \alpha$ and $q_0 + \beta$.

A.3 p-Respiratory Data Set

	p_0		q_0	
GROUP	$E[\cdot\|\mathcal{S}]$ (s.d.)	95% CI	$E[\cdot\|\mathcal{S}]$ (s.d.)	95% CI
Aminoglycoside	0.7871 (0.0312)	(0.7193, 0.8422)	0.1961 (0.0311)	(0.1413, 0.2631)
Antiseptic	0.8115 (0.0271)	(0.7523, 0.8584)	0.1620 (0.0274)	(0.1143, 0.2212)
Glycopeptide	0.7884 (0.0324)	(0.7175, 0.8457)	0.1788 (0.0320)	(0.1219, 0.2480)
Cephalosporin	0.8102 (0.0274)	(0.7506, 0.8578)	0.1716 (0.0261)	(0.1265, 0.2287)
Macrolide	0.8012 (0.0297)	(0.7376, 0.8538)	0.1846 (0.0297)	(0.1325, 0.2480)
Nitroimidazole	0.8020 (0.0276)	(0.7421, 0.8501)	0.1743 (0.0267)	(0.1280, 0.2332)
Oxazolidinone	0.8080 (0.0256)	(0.7519, 0.8526)	0.1736 (0.0251)	(0.1293, 0.2277)
Penicillin	0.7973 (0.0273)	(0.7371, 0.8452)	0.1823 (0.0269)	(0.1351, 0.2401)
Polymyxin	0.8144 (0.0253)	(0.7593, 0.8586)	0.1713 (0.0250)	(0.1268, 0.2251)
Quinolone	0.8274 (0.0255)	(0.7712, 0.8708)	0.1707 (0.0259)	(0.1255, 0.2281)
Rifamycin	0.8049 (0.0267)	(0.7469, 0.8521)	0.1766 (0.0263)	(0.1304, 0.2337)

Table A.14: Summary statistics for parameters p_0 and q_0 for each antimicrobial group for the p-Respiratory Data Set.

	α		β	
GROUP	$E[\cdot\|\mathcal{S}]$ (s.d.)	95% CI	$E[\cdot\|\mathcal{S}]$ (s.d.)	95% CI
Aminoglycoside	0.0876 (0.0730)	(−0.0756, 0.2098)	−0.0761 (0.0687)	(−0.1968, 0.0783)
Antiseptic	−0.0445 (0.0846)	(−0.2428, 0.0900)	0.0828 (0.0753)	(−0.0393, 0.2579)
Cephalosporin	−0.1247 (0.1325)	(−0.4314, 0.0774)	0.2531 (0.1900)	(−0.0679, 0.6612)
Glycopeptide	0.0598 (0.0521)	(−0.0515, 0.1564)	−0.0047 (0.0489)	(−0.0975, 0.0961)
Macrolide	0.0002 (0.0701)	(−0.1630, 0.1175)	−0.0031 (0.0893)	(−0.1468, 0.2064)
Nitroimidazole	−0.0053 (0.0976)	(−0.2430, 0.1429)	0.1416 (0.1406)	(−0.0701, 0.4788)
Oxazolidinone	−0.0416 (0.2320)	(−0.6764, 0.2026)	0.5032 (0.2289)	(0.0043, 0.8222)
Penicillin	−0.0038 (0.2010)	(−0.5281, 0.2062)	0.1456 (0.2627)	(−0.1485, 0.7742)
Polymyxin	−0.4056 (0.2513)	(−0.7968, 0.0641)	0.3140 (0.2300)	(−0.0711, 0.7475)
Quinolone	−0.2309 (0.1182)	(−0.4929, −0.0328)	0.0611 (0.0919)	(−0.0878, 0.2695)
Rifamycin	−0.0091 (0.1852)	(−0.5018, 0.2077)	0.1822 (0.1925)	(−0.0952, 0.6403)

Table A.15: Summary statistics for parameters α and β for each antimicrobial group for the p-Respiratory Data Set.

Model Fit							
Day Intervals	**1**	**2**	**3**	**4**	**5**	**6**	**7**
$N \to N$							
obs. counts	**33**	**28**	**23**	**12**	**15**	**13**	**11**
Aminoglycoside	(29, 39)	(22, 34)	(16, 28)	(13, 23)	(8, 17)	(9, 19)	(5, 14)
Antiseptic	(29, 39)	(23, 35)	(17, 29)	(12, 24)	(8, 17)	(9, 19)	(5, 13)
Cephalosporin	(29, 39)	(22, 34)	(17, 28)	(13, 24)	(8, 17)	(9, 19)	(5, 14)
Glycopeptide	(30, 40)	(22, 35)	(17, 29)	(11, 24)	(8, 18)	(9, 18)	(5, 14)
Macrolide	(29, 39)	(22, 34)	(17, 29)	(13, 24)	(8, 17)	(9, 19)	(5, 14)
Nitroimidazole	(29, 40)	(22, 35)	(17, 28)	(13, 24)	(8, 17)	(9, 19)	(5, 14)
Oxazolidinone	(30, 39)	(23, 34)	(17, 29)	(12, 24)	(8, 18)	(9, 19)	(5, 14)
Penicillin	(28, 39)	(22, 34)	(17, 29)	(12, 23)	(8, 17)	(9, 19)	(5, 14)
Polymyxin	(30, 40)	(23, 35)	(17, 29)	(13, 24)	(8, 17)	(8, 19)	(6, 14)
Quinolone	(29, 39)	(22, 34)	(17, 29)	(13, 24)	(8, 17)	(9, 19)	(6, 14)
Rifamycin	(29, 40)	(22, 34)	(18, 29)	(12, 24)	(8, 17)	(9, 19)	(5, 13)
$N \to C$							
obs. counts	**10**	**14**	**15**	**21**	**9**	**14**	**8**
Aminoglycoside	(4, 14)	(7, 19)	(10, 21)	(10, 20)	(6, 16)	(8, 18)	(5, 13)
Antiseptic	(4, 14)	(7, 19)	(9, 21)	(9, 20)	(7, 16)	(8, 18)	(6, 14)
Cephalosporin	(4, 14)	(8, 20)	(10, 21)	(9, 20)	(7, 16)	(8, 18)	(5, 14)
Glycopeptide	(3, 13)	(7, 20)	(9, 21)	(9, 21)	(6, 16)	(9, 18)	(5, 14)
Macrolide	(4, 14)	(7, 20)	(9, 21)	(9, 20)	(7, 16)	(8, 18)	(5, 14)
Nitroimidazole	(3, 14)	(7, 19)	(10, 21)	(9, 20)	(6, 16)	(7, 18)	(5, 13)
Oxazolidinone	(4, 13)	(8, 19)	(9, 21)	(9, 21)	(6, 16)	(8, 18)	(5, 14)
Penicillin	(3, 14)	(8, 20)	(9, 21)	(10, 21)	(7, 16)	(8, 18)	(5, 14)
Polymyxin	(3, 13)	(7, 19)	(9, 21)	(9, 19)	(7, 16)	(7, 18)	(5, 13)
Quinolone	(4, 14)	(8, 20)	(9, 20)	(9, 20)	(7, 16)	(8, 18)	(4, 13)
Rifamycin	(3, 13)	(7, 20)	(9, 20)	(9, 20)	(6, 16)	(8, 18)	(6, 13)
$C \to N$							
obs. counts	**5**	**3**	**10**	**12**	**4**	**6**	**7**
Aminoglycoside	(3, 11)	(4, 14)	(5, 14)	(6, 16)	(2, 10)	(4, 12)	(3, 10)
Antiseptic	(2, 12)	(4, 13)	(4, 14)	(6, 15)	(2, 10)	(4, 13)	(3, 10)
Cephalosporin	(3, 11)	(5, 13)	(5, 14)	(6, 15)	(3, 10)	(4, 12)	(3, 10)
Glycopeptide	(2, 11)	(4, 13)	(4, 14)	(6, 15)	(3, 10)	(4, 12)	(3, 10)
Macrolide	(3, 12)	(3, 13)	(5, 14)	(6, 16)	(2, 10)	(4, 13)	(3, 10)
Nitroimidazole	(2, 11)	(4, 13)	(5, 14)	(6, 16)	(3, 10)	(4, 12)	(3, 10)
Oxazolidinone	(2, 12)	(4, 12)	(4, 14)	(5, 15)	(3, 9)	(4, 12)	(3, 10)
Penicillin	(3, 12)	(5, 13)	(5, 14)	(6, 16)	(3, 10)	(4, 12)	(3, 10)
Polymyxin	(2, 12)	(4, 13)	(5, 15)	(5, 16)	(3, 9)	(4, 12)	(3, 10)
Quinolone	(2, 12)	(3, 13)	(4, 14)	(6, 16)	(3, 9)	(4, 13)	(3, 10)
Rifamycin	(3, 12)	(4, 13)	(5, 15)	(6, 15)	(2, 10)	(4, 12)	(3, 10)
$C \to C$							
obs. counts	**33**	**26**	**16**	**14**	**10**	**12**	**7**
Aminoglycoside	(27, 35)	(15, 25)	(12, 21)	(10, 20)	(4, 12)	(6, 14)	(4, 11)
Antiseptic	(26, 36)	(16, 25)	(12, 22)	(11, 20)	(4, 12)	(5, 14)	(4, 11)
Cephalosporin	(27, 35)	(16, 24)	(11, 21)	(10, 20)	(4, 11)	(6, 14)	(4, 11)
Glycopeptide	(26, 35)	(16, 25)	(12, 21)	(11, 20)	(4, 11)	(6, 13)	(3, 11)
Macrolide	(26, 35)	(15, 25)	(12, 21)	(10, 20)	(4, 11)	(5, 14)	(4, 11)
Nitroimidazole	(26, 36)	(15, 25)	(12, 21)	(10, 20)	(4, 11)	(6, 14)	(4, 11)
Oxazolidinone	(26, 35)	(17, 25)	(11, 21)	(10, 20)	(5, 11)	(6, 14)	(4, 11)
Penicillin	(26, 35)	(16, 24)	(11, 21)	(10, 20)	(4, 11)	(6, 14)	(4, 11)
Polymyxin	(26, 36)	(16, 25)	(11, 21)	(10, 20)	(4, 11)	(6, 14)	(4, 11)
Quinolone	(26, 36)	(16, 26)	(12, 22)	(10, 20)	(4, 11)	(5, 14)	(4, 11)
Rifamycin	(26, 35)	(16, 25)	(11, 21)	(11, 20)	(4, 12)	(6, 14)	(4, 11)

Table A.16: Model fit for each antimicrobial treatment group of the p-Respiratory Data Set. The intervals in red indicate that the observed transition counts are included in the equal-tailed 95% quantiles.

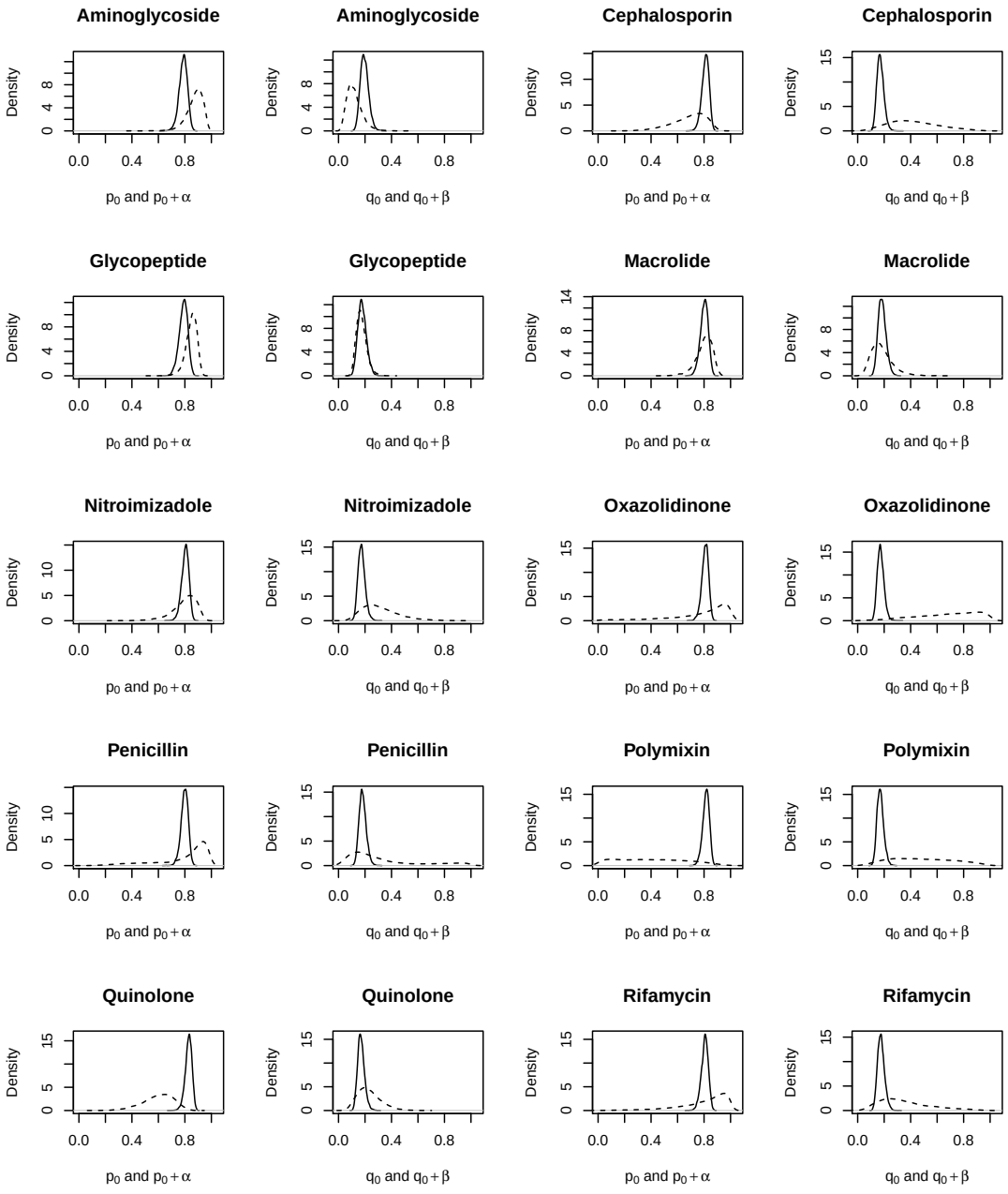

Figure A.9: Kernel density plots for p_0, $p_0 + \alpha$, q_0 and $q_0 + \beta$ for the antibiotics from the p-Respiratory Data Set. The continuous line shows the probabilities p_0 and q_0 whereas the dashed line shows the probabilities $p_0 + \alpha$ and $q_0 + \beta$.

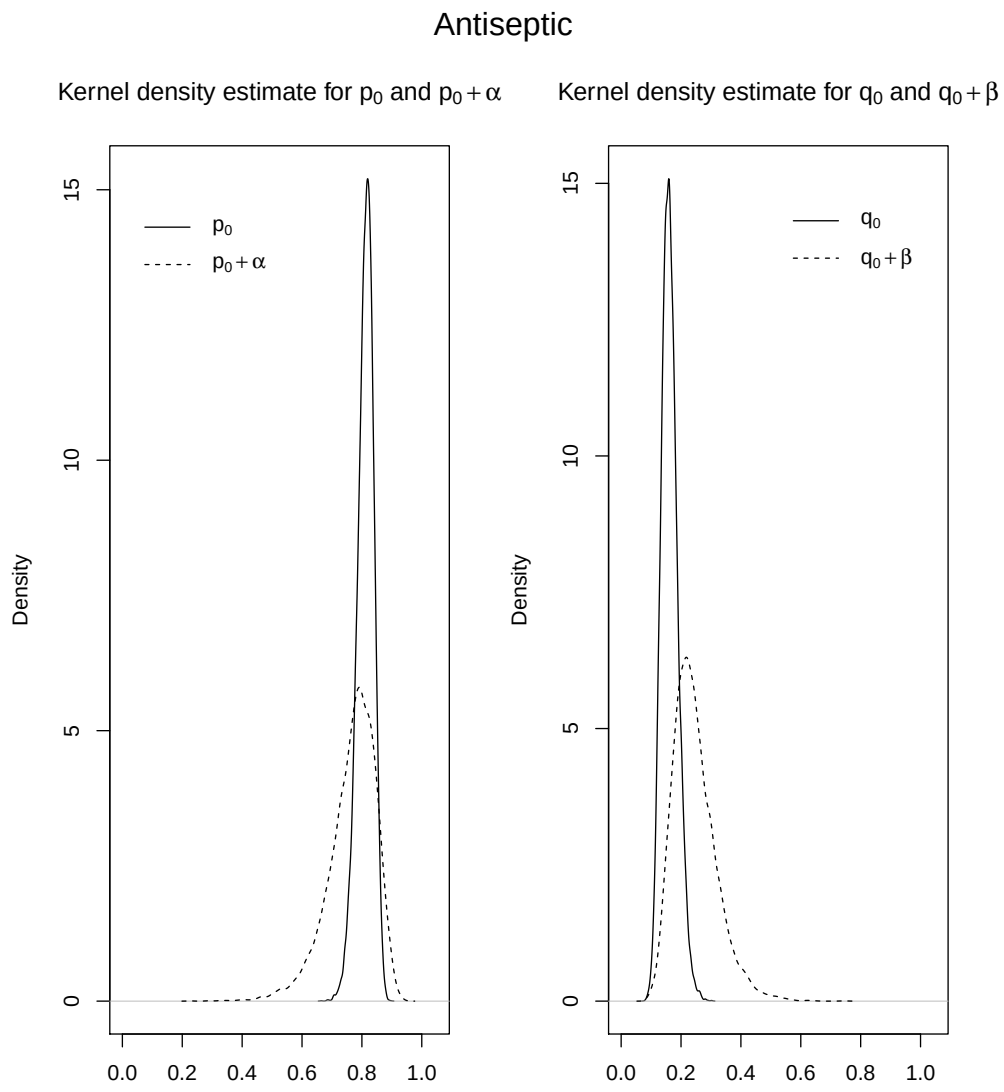

Figure A.10: Kernel density plots for p_0, $p_0 + \alpha$, q_0 and $q_0 + \beta$ for the antiseptic from the p-Respiratory Data Set. The continuous line shows the probabilities p_0 and q_0 whereas the dashed line shows the probabilities $p_0 + \alpha$ and $q_0 + \beta$.

A.3.1 After first positive test

	p_0		q_0	
GROUP	$E[\cdot\|\mathcal{S}]$ (s.d.)	95% CI	$E[\cdot\|\mathcal{S}]$ (s.d.)	95% CI
Aminoglycoside	0.9094 (0.0250)	(0.8503, 0.9498)	0.1307 (0.0236)	(0.0910, 0.1835)
Antiseptic	0.8938 (0.0305)	(0.8221, 0.9432)	0.1266 (0.0231)	(0.0880, 0.1792)
Glycopeptide	0.8843 (0.0332)	(0.8082, 0.9379)	0.1335 (0.0282)	(0.0855, 0.1972)
Cephalosporin	0.8893 (0.0282)	(0.8242, 0.9349)	0.1400 (0.0237)	(0.1001, 0.1923)
Macrolide	0.9000 (0.0279)	(0.8358, 0.9444)	0.1340 (0.0249)	(0.0932, 0.1905)
Nitroimidazole	0.9009 (0.0247)	(0.8446, 0.9407)	0.1301 (0.0219)	(0.0930, 0.1779)
Oxazolidinone	0.8974 (0.02421)	(0.8434, 0.9377)	0.1335 (0.0210)	(0.0974, 0.1798)
Penicillin	0.8956 (0.0255)	(0.8396, 0.9373)	0.1375 (0.0224)	(0.0990, 0.1877)
Polymyxin	0.9086 (0.0224)	(0.8585, 0.8453)	0.1264 (0.0200)	(0.0938, 0.1730)
Quinolone	0.9154 (0.0219)	(0.8659, 0.9517)	0.1285 (0.0204)	(0.0934, 0.1733)
Rifamycin	0.8996 (0.0254)	(0.8410, 0.9407)	0.1320 (0.0220)	(0.0948, 0.1805)

Table A.17: Summary statistics for parameters p_0 and q_0 for each antimicrobial group for the p-Respiratory Data Set starting from patients' first positive test.

	α		β	
GROUP	$E[\cdot\|\mathcal{S}]$ (s.d.)	95% CI	$E[\cdot\|\mathcal{S}]$ (s.d.)	95% CI
Aminoglycoside	−0.1283 (0.1172)	(−0.4061, 0.0476)	0.0559 (0.0861)	(−0.0858, 0.2507)
Antiseptic	−0.0243 (0.0753)	(−0.2000, 0.0938)	0.0647 (0.0681)	(−0.0407, 0.2232)
Cephalosporin	−0.0080 (0.1662)	(−0.5613, 0.1381)	0.1042 (0.1811)	(−0.1167, 0.5943)
Glycopeptide	0.0318 (0.0472)	(−0.0649, 0.1233)	0.0097 (0.0400)	(−0.0689, 0.0905)
Macrolide	−0.0375 (0.0833)	(−0.2417, 0.0898)	0.0468 (0.0969)	(−0.1006, 0.2838)
Nitroimidazole	−0.0744 (0.1090)	(−0.3447, 0.0817)	0.1396 (0.1226)	(−0.0445, 0.4246)
Oxazolidinone	−0.1266 (0.2258)	(−0.7439, 0.1128)	0.5308 (0.2368)	(0.0150, 0.8572)
Penicillin	−0.3619 (0.3088)	(−0.8636, 0.09614)	0.3396 (0.3374)	(−0.1147, 0.0861)
Polymyxin	−0.4823 (0.2635)	(−0.8934, 0.0142)	0.3311 (0.2129)	(−0.0233, 0.7556)
Quinolone	−0.4180 (0.1944)	(−0.8155, −0.0798)	0.1289 (0.1052)	(−0.0397, 0.3667)
Rifamycin	−0.0875 (0.1702)	(−0.5419, 0.1120)	0.1938 (0.1734)	(−0.0543, 0.6161)

Table A.18: Summary statistics for parameters p_0 and q_0 for each antimicrobial group for the p-Respiratory Data Set starting from patients' first positive test.

Model Fit							
Day Intervals	**1**	**2**	**3**	**4**	**5**	**6**	**7**
$N \to N$							
obs. counts	**15**	**7**	**9**	**5**	**4**	**5**	**2**
Aminoglycoside	(13, 18)	(7, 12)	(4, 11)	(4, 9)	(2, 7)	(1, 5)	(1, 4)
Antiseptic	(13, 18)	(6, 12)	(5, 11)	(4, 9)	(2, 7)	(1, 5)	(1, 4)
Cephalosporin	(13, 18)	(7, 12)	(5, 11)	(3, 9)	(2, 7)	(1, 5)	(1, 4)
Glycopeptide	(13, 18)	(7, 12)	(6, 11)	(4, 9)	(2, 7)	(1, 5)	(1, 4)
Macrolide	(13, 18)	(7, 12)	(5, 11)	(4, 9)	(2, 7)	(1, 5)	(1, 4)
Nitroimidazole	(13, 18)	(7, 12)	(5, 11)	(3, 9)	(2, 7)	(1, 5)	(1, 4)
Oxazolidinone	(13, 18)	(6, 12)	(5, 11)	(4, 8)	(2, 7)	(1, 5)	(1, 4)
Penicillin	(13, 18)	(7, 12)	(5, 11)	(4, 9)	(2, 7)	(1, 5)	(1, 4)
Polymyxin	(13, 18)	(7, 12)	(6, 11)	(3, 9)	(3, 7)	(1, 5)	(1, 4)
Quinolone	(13, 18)	(7, 12)	(5, 10)	(3, 9)	(2, 7)	(0, 5)	(1, 4)
Rifamycin	(13, 18)	(7, 12)	(5, 11)	(4, 9)	(2, 7)	(1, 5)	(1, 4)
$N \to C$							
obs. counts	**3**	**5**	**2**	**4**	**3**	**0**	**2**
Aminoglycoside	(0, 5)	(0, 5)	(0, 7)	(0, 5)	(0, 5)	(0, 4)	(0, 3)
Antiseptic	(0, 5)	(0, 5)	(0, 6)	(0, 5)	(0, 5)	(0, 4)	(0, 3)
Cephalosporin	(0, 5)	(0, 5)	(0, 5)	(0, 5)	(0, 5)	(0, 4)	(0, 3)
Glycopeptide	(0, 5)	(0, 5)	(0, 5)	(0, 5)	(0, 5)	(0, 4)	(0, 3)
Macrolide	(0, 5)	(0, 5)	(0, 6)	(0, 5)	(0, 5)	(0, 4)	(0, 3)
Nitroimidazole	(0, 5)	(0, 5)	(0, 6)	(0, 5)	(0, 5)	(0, 4)	(0, 3)
Oxazolidinone	(0, 5)	(0, 5)	(0, 5)	(0, 5)	(0, 5)	(0, 4)	(0, 3)
Penicillin	(0, 4)	(0, 5)	(0, 6)	(0, 5)	(0, 5)	(0, 4)	(0, 3)
Polymyxin	(0, 4)	(0, 5)	(0, 5)	(0, 6)	(0, 4)	(0, 4)	(0, 3)
Quinolone	(0, 5)	(0, 5)	(0, 5)	(0, 5)	(0, 5)	(0, 4)	(0, 3)
Rifamycin	(0, 5)	(0, 5)	(0, 5)	(0, 5)	(0, 5)	(0, 4)	(0, 3)
$C \to N$							
obs. counts	**5**	**3**	**10**	**12**	**4**	**6**	**7**
Aminoglycoside	(1, 9)	(3, 12)	(4, 13)	(5, 15)	(2, 10)	(4, 12)	(3, 10)
Antiseptic	(2, 10)	(3, 11)	(4, 13)	(5, 15)	(2, 10)	(4, 12)	(3, 10)
Cephalosporin	(2, 10)	(3, 12)	(4, 13)	(5, 15)	(3, 10)	(4, 13)	(3, 10)
Glycopeptide	(2, 10)	(3, 12)	(4, 13)	(5, 15)	(2, 10)	(4, 13)	(3, 11)
Macrolide	(1, 10)	(3, 12)	(4, 13)	(5, 15)	(3, 10)	(4, 12)	(3, 11)
Nitroimidazole	(2, 10)	(3, 11)	(4, 13)	(6, 15)	(2, 10)	(4, 12)	(3, 11)
Oxazolidinone	(1, 9)	(3, 11)	(4, 12)	(5, 14)	(2, 10)	(4, 12)	(3, 11)
Penicillin	(1, 10)	(3, 12)	(4, 13)	(6, 15)	(3, 9)	(4, 12)	(3, 11)
Polymyxin	(2, 9)	(3, 11)	(4, 13)	(5, 14)	(2, 9)	(4, 12)	(3, 11)
Quinolone	(2, 10)	(3, 12)	(4, 12)	(5, 14)	(2, 9)	(4, 12)	(3, 10)
Rifamycin	(1, 10)	(3, 12)	(4, 13)	(5, 15)	(3, 10)	(5, 12)	(3, 10)
$C \to C$							
obs. counts	**33**	**26**	**16**	**14**	**10**	**12**	**7**
Aminoglycoside	(29, 36)	(17, 26)	(12, 22)	(11, 20)	(4, 11)	(6, 14)	(4, 11)
Antiseptic	(28, 36)	(18, 26)	(13, 22)	(11, 21)	(4, 12)	(6, 14)	(3, 11)
Cephalosporin	(28, 36)	(17, 26)	(13, 22)	(11, 21)	(4, 11)	(5, 14)	(4, 11)
Glycopeptide	(28, 36)	(17, 26)	(12, 22)	(11, 21)	(4, 11)	(5, 14)	(3, 11)
Macrolide	(28, 37)	(17, 26)	(12, 22)	(11, 21)	(4, 11)	(6, 14)	(3, 11)
Nitroimidazole	(28, 36)	(18, 26)	(13, 22)	(11, 20)	(4, 11)	(6, 14)	(3, 11)
Oxazolidinone	(29, 37)	(17, 26)	(14, 22)	(12, 21)	(4, 11)	(6, 14)	(3, 11)
Penicillin	(28, 36)	(17, 26)	(13, 22)	(11, 20)	(4, 11)	(6, 13)	(3, 11)
Polymyxin	(29, 36)	(18, 26)	(13, 22)	(12, 21)	(5, 12)	(6, 14)	(3, 11)
Quinolone	(28, 36)	(17, 26)	(14, 22)	(12, 21)	(5, 12)	(6, 14)	(4, 11)
Rifamycin	(28, 37)	(17, 26)	(12, 22)	(11, 21)	(4, 11)	(6, 13)	(4, 11)

Table A.19: Model fit for each antimicrobial treatment group of the p-Respiratory Data Set starting from patients' first positive test. The intervals in red indicate that the observed transition counts are included in the equal-tailed 95% quantiles.

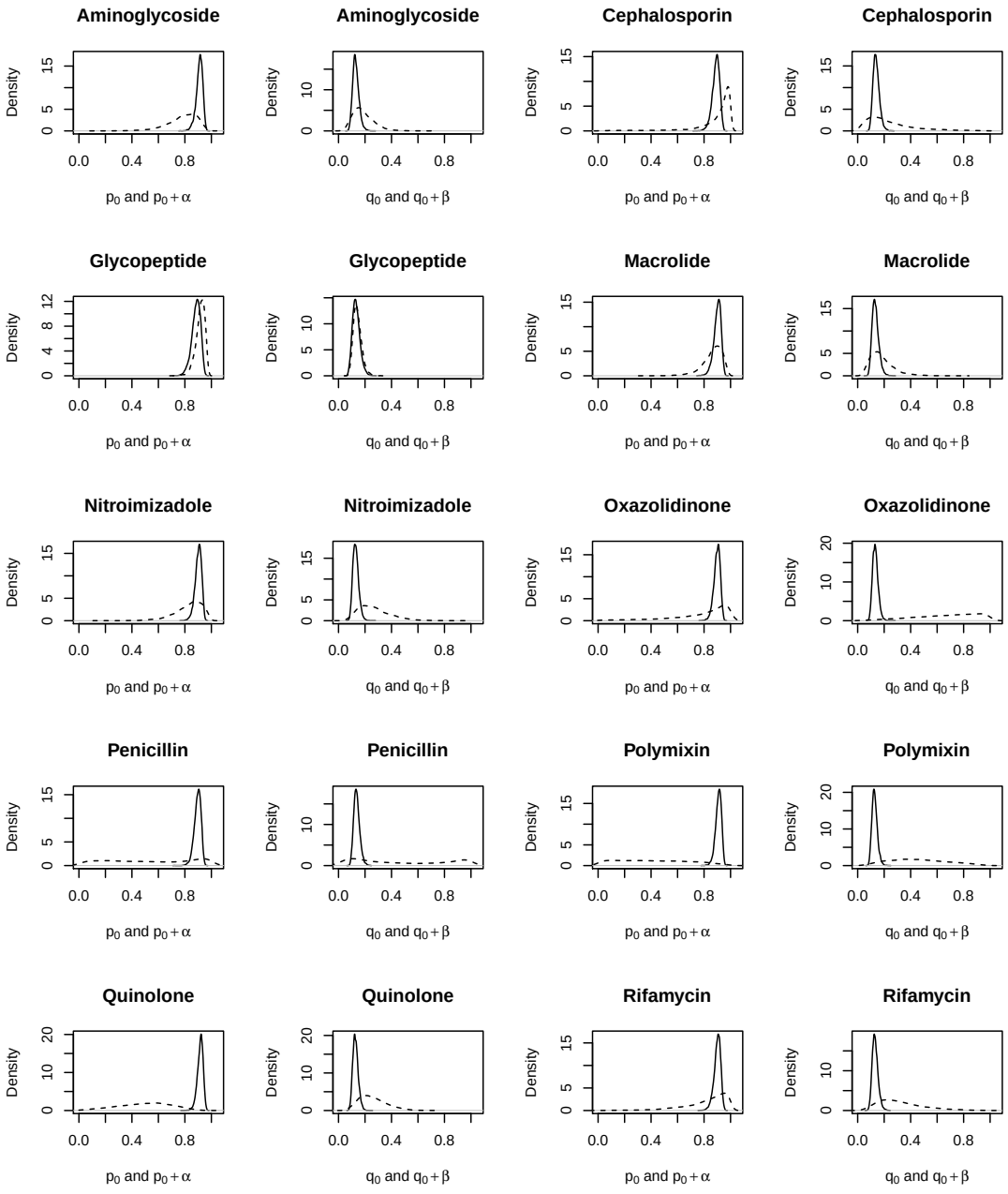

Figure A.11: Kernel density plots for p_0, $p_0 + \alpha$, q_0 and $q_0 + \beta$ for the antibiotics from the p-Respiratory Data Set after first positive test. The continuous line shows the probabilities p_0 and q_0 whereas the dashed line shows the probabilities $p_0 + \alpha$ and $q_0 + \beta$.

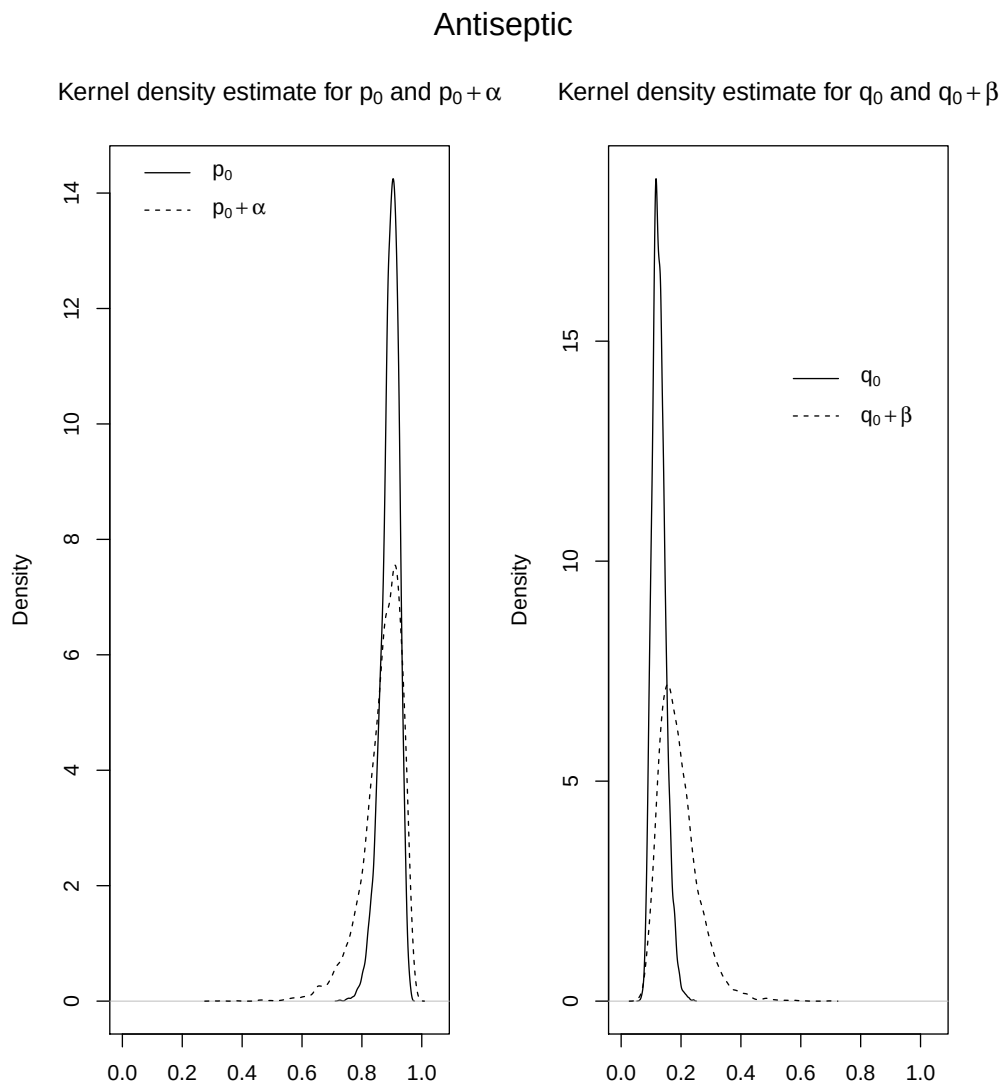

Figure A.12: Kernel density plots for p_0, $p_0 + \alpha$, q_0 and $q_0 + \beta$ for the antiseptic from the p-Respiratory Data Set after first positive test. The continuous line shows the probabilities p_0 and q_0 whereas the dashed line shows the probabilities $p_0 + \alpha$ and $q_0 + \beta$.

APPENDIX B

Appendix for the Hidden Markov Model

B.1 p-MRSA Data Set

	p_0		q_0	
GROUP	$E[\cdot \mid \tilde{\mathcal{S}}]$ (s.d.)	95% CI	$E[\cdot \mid \tilde{\mathcal{S}}]$ (s.d.)	95% CI
Aminoglycoside	0.8821 (0.03704)	(0.8421, 0.9127)	0.0793 (0.0330)	(0.0486, 0.1200)
Antiseptic	0.8617 (0.0210)	(0.8134, 0.8956)	0.0582 (0.0155)	(0.0331, 0.0924)
Cephalosporin	0.9187 (0.0109)	(0.8950, 0.9381)	0.0538 (0.0110)	(0.0344, 0.0773)
Glycopeptide	0.8779 (0.0222)	(0.8265, 0.9136)	0.0939 (0.0221)	(0.0580, 0.1447)
Macrolide	0.9080 (0.0134)	(0.8787, 0.9310)	0.0713 (0.0141)	(0.0471, 0.1022)
Nitroimidazole	0.8967 (0.0142)	(0.8648, 0.9204)	0.0725 (0.0143)	(0.0481, 0.1044)
Oxazolidinone	0.8879 (0.0134)	(0.8583, 0.9105)	0.0728 (0.0133)	(0.0497, 0.1021)
Penicillin	0.8777 (0.0170)	(0.8395, 0.9054)	0.0828 (0.0167)	(0.0551, 0.1198)
Polymyxin	0.8827 (0.0150)	(0.8490, 0.9080)	0.0816 (0.0149)	(0.0560, 0.1146)
Quinolone	0.8904 (0.0148)	(0.8566, 0.9155)	0.0809 (0.0147)	(0.0559, 0.1139)
Rifamycin	0.8860 (0.0144)	(0.8539, 0.9100)	0.0787 (0.0141)	(0.0548, 0.1099)

Table B.1: Summary statistics for parameters p_0 and q_0 for each antimicrobial group for the p-MRSA Data Set.

	α		β	
GROUP	$E[\cdot\|\tilde{\mathcal{S}}]$ (s.d.)	95% CI	$E[\cdot\|\tilde{\mathcal{S}}]$ (s.d.)	95% CI
Aminoglycoside	-0.0635 (0.0952)	$(-0.3236, 0.0571)$	0.0958 (0.0866)	$(-0.0128, 0.3385)$
Antiseptic	0.0552 (0.0368)	$(-0.0185, 0.1180)$	0.0628 (0.0358)	$(0.0114, 0.1385)$
Cephalosporin	-0.2983 (0.1138)	$(-0.5728, -0.1245)$	0.1733 (0.0773)	$(0.0538, 0.3593)$
Glycopeptide	-0.0052 (0.0439)	$(-0.1004, 0.0750)$	-0.0186 (0.0316)	$(-0.0815, 0.0454)$
Macrolide	-0.3924 (0.1552)	$(-0.7199, -0.1226)$	0.1352 (0.0906)	$(-0.0100, 0.3392)$
Nitroimidazole	-0.3511 (0.1689)	$(-0.6903, -0.0587)$	0.2078 (0.1145)	$(0.0146, 0.4467)$
Oxazolidinone	0.0511 (0.0683)	$(-0.1328, 0.1252)$	0.6942 (0.1727)	$(0.3042, 0.9214)$
Penicillin	-0.0269 (0.1592)	$(-0.5359, 0.1150)$	0.0882 (0.1619)	$(-0.0638, 0.5999)$
Polymyxin	-0.3068 (0.2567)	$(-0.8124, 0.0878)$	0.3585 (0.2497)	$(-0.0560, 0.8085)$
Quinolone	-0.2475 (0.1823)	$(-0.6752, 0.0098)$	0.0559 (0.0989)	$(-0.0745, 0.3051)$
Rifamycin	-0.4063 (0.2493)	$(-0.7954, 0.9211)$	0.4531 (0.2368)	$(0.0322, 0.8770)$

Table B.2: Summary statistics for parameters α and β for each antimicrobial group for the p-MRSA Data Set.

	ϕ		ψ	
GROUP	$E[\cdot\|\tilde{\mathcal{S}}]$ (s.d.)	95% CI	$E[\cdot\|\tilde{\mathcal{S}}]$ (s.d.)	95% CI
Aminoglycoside	0.8593 (0.0346)	$(0.7921, 0.9276)$	0.8321 (0.0125)	$(0.8042, 0.9158)$
Antiseptic	0.8562 (0.0210)	$(0.8134, 0.8956)$	0.8310 (0.0125)	$(0.8048, 0.9133)$
Cephalosporin	0.8400 (0.0317)	$(0.7787, 0.9028)$	0.8244 (0.0126)	$(0.7993, 0.9078)$
Glycopeptide	0.8583 (0.0340)	$(0.7926, 0.9257)$	0.8318 (0.0126)	$(0.8057, 0.8951)$
Macrolide	0.8452 (0.0337)	$(0.7798, 0.9115)$	0.8266 (0.0130)	$(0.7994, 0.8708)$
Nitroimidazole	0.8518 (0.0341)	$(0.7847, 0.9185)$	0.8297 (0.0132)	$(0.7814, 0.8828)$
Oxazolidinone	0.8511 (0.0321)	$(0.7876, 0.9142)$	0.8290 (0.0128)	$(0.7932, 0.8915)$
Penicillin	0.8569 (0.0341)	$(0.7909, 0.9248)$	0.8312 (0.0125)	$(0.8047, 0.8747)$
Polymyxin	0.8564 (0.0326)	$(0.7926, 0.9206)$	0.8313 (0.0122)	$(0.7879, 0.8736)$
Quinolone	0.8532 (0.0324)	$(0.7910, 0.9176)$	0.8299 (0.0123)	$(0.7839, 0.8725)$
Rifamycin	0.8575 (0.0320)	$(0.7954, 0.9211)$	0.8319 (0.0121)	$(0.7969, 0.8836)$

Table B.3: Summary statistics for parameters ϕ and ψ for each antimicrobial group for the p-MRSA Data Set.

Model Fit							
Day Intervals	**1**	**2**	**3**	**4**	**5**	**6**	**7**
$N \to N$							
obs. counts	**17**	**19**	**19**	**8**	**17**	**31**	**243**
Aminoglycoside	(17, 25)	(17, 26)	(18, 29)	(12, 21)	(14, 24)	(26, 40)	(196, 233)
Antiseptic	(17, 25)	(16, 26)	(17, 28)	(11, 21)	(12, 23)	(26, 40)	(197, 236)
Cephalosporin	(16, 25)	(15, 24)	(17, 27)	(10, 20)	(14, 24)	(26, 41)	(205, 243)
Glycopeptide	(17, 25)	(16, 26)	(18, 28)	(12, 21)	(13, 24)	(25, 41)	(195, 231)
Macrolide	(17, 25)	(17, 26)	(16, 26)	(10, 19)	(13, 23)	(27, 41)	(199, 238)
Nitroimidazole	(15, 25)	(15, 25)	(17, 27)	(10, 20)	(13, 24)	(26, 40)	(198, 234)
Oxazolidinone	(17, 25)	(17, 27)	(17, 28)	(12, 22)	(14, 25)	(27, 41)	(198, 235)
Penicillin	(17, 25)	(16, 26)	(18, 28)	(12, 21)	(14, 24)	(25, 40)	(195, 230)
Polymyxin	(16, 25)	(17, 27)	(17, 28)	(12, 21)	(14, 24)	(26, 40)	(197, 233)
Quinolone	(17, 25)	(18, 27)	(18, 27)	(12, 21)	(13, 24)	(26, 42)	(195, 232)
Rifamycin	(16, 25)	(17, 27)	(18, 28)	(12, 21)	(14, 24)	(26, 41)	(195, 232)
$N \to C$							
obs. counts	**10**	**11**	**15**	**18**	**14**	**26**	**132**
Aminoglycoside	(2, 10)	(3, 13)	(5, 16)	(5, 14)	(7, 17)	(17, 30)	(142, 178)
Antiseptic	(2, 10)	(4, 14)	(6, 17)	(5, 15)	(8, 19)	(17, 31)	(138, 177)
Cephalosporin	(2, 10)	(5, 15)	(7, 17)	(6, 15)	(7, 17)	(16, 30)	(131, 170)
Glycopeptide	(2, 10)	(4, 14)	(6, 16)	(5, 14)	(7, 18)	(15, 31)	(144, 179)
Macrolide	(2, 10)	(4, 13)	(8, 18)	(7, 16)	(7, 18)	(15, 30)	(136, 175)
Nitroimidazole	(2, 12)	(5, 15)	(7, 17)	(6, 15)	(7, 18)	(17, 31)	(141, 176)
Oxazolidinone	(2, 10)	(3, 13)	(6, 16)	(4, 14)	(6, 17)	(16, 30)	(140, 175)
Penicillin	(2, 10)	(4, 14)	(5, 16)	(5, 14)	(7, 17)	(16, 32)	(144, 179)
Polymyxin	(2, 10)	(3, 13)	(6, 16)	(5, 14)	(7, 16)	(16, 31)	(142, 178)
Quinolone	(2, 10)	(3, 12)	(6, 16)	(5, 14)	(6, 17)	(15, 31)	(142, 178)
Rifamycin	(2, 10)	(3, 13)	(5, 16)	(5, 14)	(7, 16)	(15, 31)	(143, 179)
$C \to N$							
obs. counts	**8**	**11**	**8**	**12**	**10**	**26**	**72**
Aminoglycoside	(1, 7)	(4, 14)	(2, 9)	(7, 18)	(6, 16)	(13, 27)	(94, 125)
Antiseptic	(0, 6)	(4, 13)	(2, 9)	(6, 17)	(6, 17)	(14, 28)	(96, 127)
Cephalosporin	(0, 7)	(5, 14)	(3, 11)	(6, 18)	(7, 17)	(13, 26)	(87, 116)
Glycopeptide	(1, 6)	(4, 14)	(2, 9)	(6, 17)	(7, 17)	(14, 27)	(92, 125)
Macrolide	(0, 7)	(4, 14)	(2, 10)	(6, 18)	(7, 17)	(13, 26)	(93, 125)
Nitroimidazole	(1, 6)	(5, 15)	(2, 10)	(7, 17)	(7, 17)	(14, 27)	(93, 122)
Oxazolidinone	(0, 6)	(4, 13)	(2, 9)	(6, 16)	(7, 17)	(12, 25)	(91, 121)
Penicillin	(0, 7)	(4, 14)	(2, 10)	(7, 17)	(7, 18)	(14, 27)	(94, 125)
Polymyxin	(1, 7)	(4, 13)	(2, 10)	(7, 17)	(6, 17)	(14, 26)	(92, 126)
Quinolone	(1, 7)	(4, 13)	(2, 9)	(7, 17)	(6, 16)	(13, 28)	(93, 125)
Rifamycin	(0, 7)	(4, 13)	(2, 9)	(7, 16)	(6, 17)	(13, 27)	(93, 124)
$C \to C$							
obs. counts	**7**	**20**	**9**	**21**	**20**	**24**	**185**
Aminoglycoside	(8, 14)	(17, 27)	(8, 15)	(15, 26)	(14, 24)	(22, 37)	(132, 162)
Antiseptic	(8, 15)	(17, 27)	(8, 15)	(16, 27)	(13, 23)	(22, 36)	(129, 159)
Cephalosporin	(8, 14)	(16, 26)	(6, 14)	(15, 26)	(13, 23)	(24, 37)	(141, 170)
Glycopeptide	(8, 14)	(17, 27)	(8, 15)	(16, 27)	(13, 23)	(23, 36)	(132, 165)
Macrolide	(8, 15)	(17, 27)	(7, 15)	(15, 26)	(12, 23)	(24, 37)	(132, 163)
Nitroimidazole	(9, 14)	(16, 26)	(7, 15)	(16, 26)	(13, 23)	(23, 36)	(135, 163)
Oxazolidinone	(9, 15)	(18, 27)	(7, 15)	(17, 27)	(13, 23)	(25, 37)	(136, 165)
Penicillin	(8, 15)	(17, 27)	(7, 15)	(16, 26)	(12, 23)	(23, 36)	(131, 162)
Polymyxin	(8, 14)	(18, 27)	(7, 15)	(16, 26)	(13, 24)	(23, 36)	(131, 165)
Quinolone	(8, 14)	(17, 27)	(8, 15)	(16, 26)	(13, 24)	(22, 37)	(132, 163)
Rifamycin	(8, 14)	(18, 27)	(8, 15)	(16, 26)	(13, 24)	(23, 36)	(133, 163)

Table B.4: Model fit for each antimicrobial treatment group of the p-MRSA Data Set. The intervals in red indicate that the observed transition counts are included in the equal-tailed 95% quantiles.

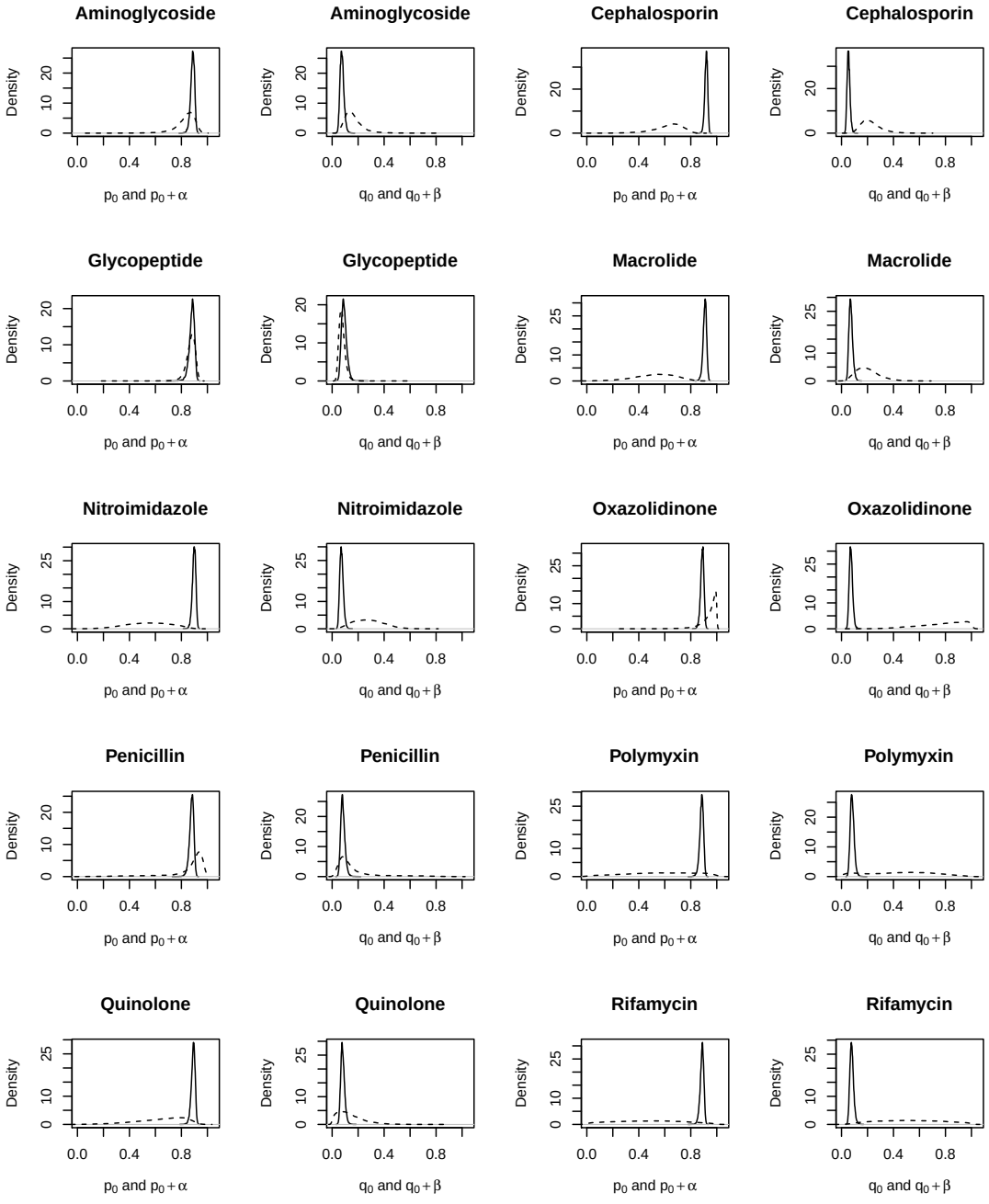

Figure B.1: Kernel density plots for p_0, $p_0 + \alpha$, q_0 and $q_0 + \beta$ for the antibiotics for the p-MRSA Data Set. The continuous line shows the probabilities p_0 and q_0 whereas the dashed line shows the probabilities $p_0 + \alpha$ and $q_0 + \beta$.

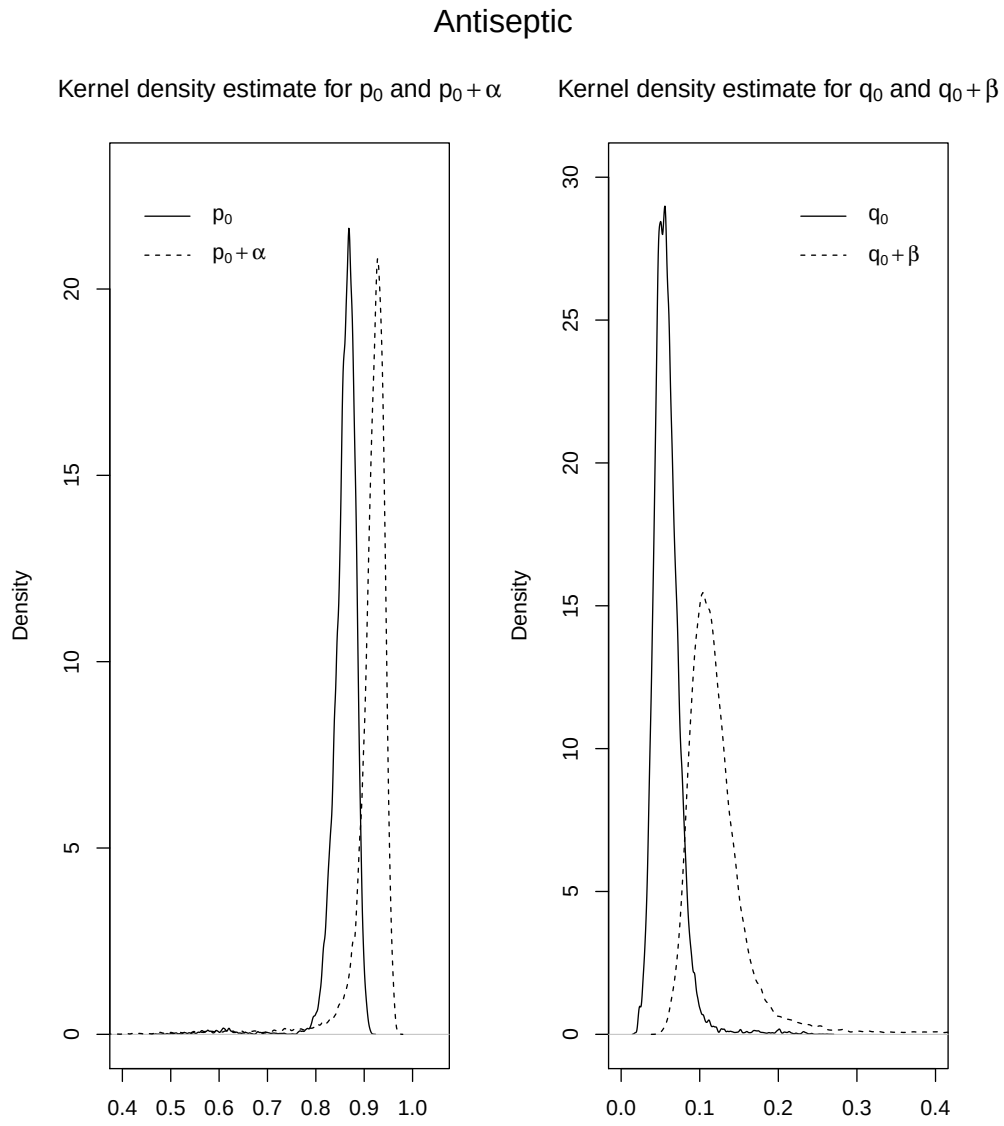

Figure B.2: Kernel density plots for p_0, $p_0 + \alpha$, q_0 and $q_0 + \beta$ for the antiseptic for the p-MRSA Data Set. The continuous line shows the probabilities p_0 and q_0 whereas the dashed line shows the probabilities $p_0 + \alpha$ and $q_0 + \beta$.

B.1.1 After first positive test

	p_0		q_0	
GROUP	$E[\cdot\|\tilde{\mathcal{S}}]$ (s.d.)	95% CI	$E[\cdot\|\tilde{\mathcal{S}}]$ (s.d.)	95% CI
Aminoglycoside	0.9747 (0.0080)	(0.9572, 0.9884)	0.0337 (0.0074)	(0.0206, 0.0495)
Antiseptic	0.9704 (0.0134)	(0.9396, 0.9913)	0.0242 (0.0069)	(0.0126, 0.0397)
Cephalosporin	0.9798 (0.0065)	(0.9400, 0.9908	0.0238 (0.0063)	(0.0189, 0.0438)
Glycopeptide	0.9661 (0.0098)	(0.9447, 0.9833)	0.0422 (0.0093)	(0.0256, 0.0625)
Macrolide	0.9777 (0.0074)	(0.9612, 0.9902)	0.0365 (0.0075)	(0.0232, 0.0527)
Nitroimidazole	0.9755 (0.0078)	(0.9576, 0.9885)	0.0367 (0.0076)	(0.0235, 0.0538)
Oxazolidinone	0.9766 (0.0072)	(0.9607, 0.9890)	0.0330 (0.0069)	(0.0210, 0.0481)
Penicillin	0.9761 (0.0077)	(0.9589, 0.9892)	0.0353 (0.0076)	(0.0221, 0.0519)
Polymyxin	0.9751 (0.0076)	(0.9583, 0.9881)	0.0384 (0.0076)	(0.0250, 0.0547)
Quinolone	0.9768 (0.0075)	(0.9599, 0.9896)	0.0388 (0.0077)	(0.0251, 0.0557)
Rifamycin	0.9763 (0.0073)	(0.9602, 0.9890)	0.0363 (0.0071)	(0.0235, 0.0517)

Table B.5: Summary statistics for parameters p_0 and q_0 for each antimicrobial group for the p-MRSA Data Set starting from patients' first positive test.

	α		β	
GROUP	$E[\cdot\|\tilde{\mathcal{S}}]$ (s.d.)	95% CI	$E[\cdot\|\tilde{\mathcal{S}}]$ (s.d.)	95% CI
Aminoglycoside	−0.0007 (0.0272)	(−0.0716, 0.0343)	0.0418 (0.0258)	(−0.0035, 0.0978)
Antiseptic	−0.0030 (0.0179)	(−0.0376, 0.0339)	0.0483 (0.0151)	(0.0218, 0.0811)
Cephalosporin	−0.1095 (0.1075)	(−0.3860, 0.0140)	0.0921 (0.0451)	(0.0271, 0.2012)
Glycopeptide	0.0266 (0.0121)	(0.0015, 0.0499)	−0.0062 (0.0124)	(−0.0312, 0.0179)
Macrolide	−0.0879 (0.1542)	(−0.6661, 0.0199)	0.0184 (0.0552)	(−0.0309, 0.1918)
Nitroimidazole	−0.0181 (0.0674)	(−0.1555, 0.0317)	0.0013 (0.0274)	(−0.0269, 0.0684)
Oxazolidinone	−0.0671 (0.0956)	(−0.3290, 0.0252)	0.7330 (0.1754)	(0.3302, 0.9588)
Penicillin	−0.0174 (0.0581)	(−0.1469, 0.0311)	0.0398 (0.0405)	(−0.0205, 0.1251)
Polymyxin	−0.2249 (0.2639)	(−0.8700, 0.0213)	0.1689 (0.2257)	(−0.0372, 0.7235)
Quinolone	−0.3335 (0.3046)	(−0.9364, 0.0148)	0.0513 (0.0847)	(−0.0380, 0.2763)
Rifamycin	−0.5153 (0.2733)	(−0.9494, −0.0069)	0.3270 (0.0142)	(0.2703, 0.3260)

Table B.6: Summary statistics for parameters α and β for each antimicrobial group for the p-MRSA Data Set starting from patients' first positive test.

	ϕ		ψ	
GROUP	$E[\cdot \mid \tilde{\mathcal{S}}]$ (s.d.)	95% CI	$E[\cdot \mid \tilde{\mathcal{S}}]$ (s.d.)	95% CI
Aminoglycoside	0.7786 (0.0374)	(0.7052, 0.8516)	0.6013 (0.0134)	(0.5787, 0.6264)
Antiseptic	0.7932 (0.0380)	(0.7190, 0.8680)	0.6025 (0.0136)	(0.5742, 0.3307)
Cephalosporin	0.7826 (0.0346)	(0.7138, 0.8498)	0.6087 (0.0130)	(0.5772, 0.3268)
Glycopeptide	0.7875 (0.0365)	(0.7161, 0.8589)	0.6045 (0.0123)	(0.5743, 0.3249)
Macrolide	0.7708 (0.0372)	(0.6982, 0.8444)	0.5934 (0.0139)	(0.5750, 0.3241)
Nitroimidazole	0.7765 (0.0374)	(0.7036, 0.8501)	0.6100 (0.0139)	(0.5713, 0.6451)
Oxazolidinone	0.7690 (0.0374)	(0.6965, 0.8429)	0.5957 (0.0145)	(0.5675, 0.6239)
Penicillin	0.7721 (0.0376)	(0.6990, 0.8471)	0.5990 (0.0137)	(0.5611, 0.6249)
Polymyxin	0.7792 (0.0385)	(0.7046, 0.8552)	0.6098 (0.0132)	(0.5716, 0.6274)
Quinolone	0.7771 (0.0382)	(0.7027, 0.8522)	0.6110 (0.0178)	(0.5711, 0.6365)
Rifamycin	0.7761 (0.0379)	(0.7018, 0.8507)	0.6016 (0.0165)	(0.5702, 0.6253)

Table B.7: Summary statistics for parameters ϕ and ψ for each antimicrobial group for the p-MRSA Data Set starting from patients' first positive test.

Model Fit							
Day Intervals	**1**	**2**	**3**	**4**	**5**	**6**	**7**
$N \to N$							
obs. counts	**3**	**2**	**1**	**1**	**2**	**12**	**134**
Aminoglycoside	(1, 4)	(0, 2)	(0, 2)	(0, 1)	(0, 3)	(8, 15)	(105, 130)
Antiseptic	(1, 4)	(0, 2)	(0, 2)	(0, 1)	(0, 3)	(8, 15)	(104, 129)
Cephalosporin	(1, 4)	(0, 2)	(0, 2)	(0, 1)	(0, 3)	(8, 15)	(106, 129)
Glycopeptide	(1, 4)	(0, 2)	(0, 2)	(0, 1)	(0, 3)	(8, 15)	(106, 130)
Macrolide	(1, 4)	(0, 2)	(0, 2)	(0, 1)	(0, 3)	(8, 15)	(104, 127)
Nitroimidazole	(1, 4)	(0, 2)	(0, 2)	(0, 1)	(0, 3)	(8, 15)	(106, 129)
Oxazolidinone	(1, 4)	(0, 2)	(0, 2)	(0, 1)	(0, 3)	(8, 15)	(107, 130)
Penicillin	(1, 4)	(0, 2)	(0, 2)	(0, 1)	(0, 3)	(8, 15)	(106, 128)
Polymyxin	(1, 4)	(0, 2)	(0, 2)	(0, 1)	(0, 3)	(8, 15)	(105, 129)
Quinolone	(1, 4)	(0, 2)	(0, 2)	(0, 1)	(0, 3)	(8, 15)	(105, 129)
Rifamycin	(1, 4)	(0, 2)	(0, 2)	(0, 1)	(0, 3)	(8, 15)	(107, 128)
$N \to C$							
obs. counts	**1**	**0**	**1**	**0**	**1**	**5**	**37**
Aminoglycoside	(0, 3)	(0, 2)	(0, 2)	(0, 1)	(0, 2)	(2, 9)	(41, 65)
Antiseptic	(0, 3)	(0, 2)	(0, 2)	(0, 1)	(0, 3)	(2, 9)	(42, 66)
Cephalosporin	(0, 3)	(0, 2)	(0, 2)	(0, 1)	(0, 2)	(2, 9)	(41, 65)
Glycopeptide	(0, 3)	(0, 2)	(0, 2)	(0, 1)	(0, 3)	(1, 9)	(40, 65)
Macrolide	(0, 3)	(0, 2)	(0, 2)	(0, 1)	(0, 2)	(2, 9)	(44, 66)
Nitroimidazole	(0, 3)	(0, 2)	(0, 2)	(0, 1)	(0, 2)	(2, 9)	(41, 64)
Oxazolidinone	(0, 3)	(0, 2)	(0, 2)	(0, 1)	(0, 2)	(2, 9)	(41, 64)
Penicillin	(0, 3)	(0, 2)	(0, 2)	(0, 1)	(0, 2)	(2, 9)	(43, 65)
Polymyxin	(0, 3)	(0, 2)	(0, 2)	(0, 1)	(0, 3)	(2, 9)	(42, 65)
Quinolone	(0, 3)	(0, 2)	(0, 2)	(0, 1)	(0, 3)	(2, 9)	(41, 66)
Rifamycin	(0, 3)	(0, 2)	(0, 2)	(0, 1)	(0, 3)	(2, 9)	(41, 64)
$C \to N$							
obs. counts	**8**	**11**	**8**	**12**	**10**	**26**	**72**
Aminoglycoside	(1, 8)	(4, 14)	(2, 9)	(7, 17)	(5, 16)	(12, 26)	(85, 117)
Antiseptic	(1, 7)	(4, 14)	(2, 9)	(5, 16)	(6, 16)	(13, 26)	(86, 118)
Cephalosporin	(0, 7)	(4, 14)	(2, 10)	(7, 17)	(6, 17)	(12, 26)	(82, 114)
Glycopeptide	(1, 7)	(4, 13)	(2, 9)	(6, 16)	(6, 15)	(12, 25)	(84, 115)
Macrolide	(1, 7)	(5, 14)	(2, 9)	(6, 16)	(6, 16)	(12, 26)	(86, 118)
Nitroimidazole	(1, 8)	(4, 14)	(2, 9)	(6, 17)	(6, 15)	(13, 26)	(85, 116)
Oxazolidinone	(1, 7)	(4, 14)	(2, 9)	(5, 17)	(7, 17)	(11, 25)	(82, 114)
Penicillin	(1, 7)	(4, 15)	(2, 9)	(6, 16)	(6, 16)	(13, 24)	(85, 117)
Polymyxin	(1, 7)	(4, 14)	(2, 9)	(5, 16)	(6, 16)	(12, 26)	(86, 119)
Quinolone	(1, 8)	(4, 15)	(2, 9)	(6, 16)	(6, 16)	(12, 26)	(88, 117)
Rifamycin	(1, 7)	(4, 13)	(2, 9)	(5, 16)	(6, 16)	(12, 26)	(88, 117)
$C \to C$							
obs. counts	**7**	**20**	**9**	**21**	**20**	**24**	**185**
Aminoglycoside	(7, 14)	(17, 27)	(8, 15)	(16, 26)	(14, 24)	(24, 37)	(140, 171)
Antiseptic	(8, 14)	(17, 27)	(8, 15)	(17, 27)	(14, 24)	(24, 37)	(138, 169)
Cephalosporin	(7, 14)	(17, 27)	(7, 14)	(16, 26)	(13, 23)	(24, 37)	(143, 174)
Glycopeptide	(8, 14)	(18, 27)	(8, 15)	(17, 27)	(15, 24)	(25, 38)	(141, 172)
Macrolide	(8, 14)	(17, 26)	(8, 15)	(17, 27)	(14, 24)	(24, 38)	(138, 171)
Nitroimidazole	(7, 14)	(17, 27)	(8, 15)	(16, 27)	(15, 24)	(24, 37)	(140, 172)
Oxazolidinone	(8, 14)	(17, 27)	(8, 15)	(16, 27)	(13, 23)	(24, 39)	(142, 173)
Penicillin	(8, 14)	(16, 27)	(8, 15)	(17, 27)	(13, 24)	(25, 37)	(140, 171)
Polymyxin	(8, 14)	(17, 27)	(8, 15)	(17, 27)	(14, 24)	(23, 37)	(138, 170)
Quinolone	(7, 14)	(16, 27)	(8, 15)	(17, 27)	(13, 24)	(24, 38)	(140, 169)
Rifamycin	(7, 14)	(18, 27)	(8, 15)	(17, 28)	(14, 24)	(24, 38)	(140, 169)

Table B.8: Model fit for each antimicrobial group for the p-MRSA Data Set starting from patients' first positive test. The intervals in red indicate that the observed transition counts are included in the equal-tailed 95% quantiles.

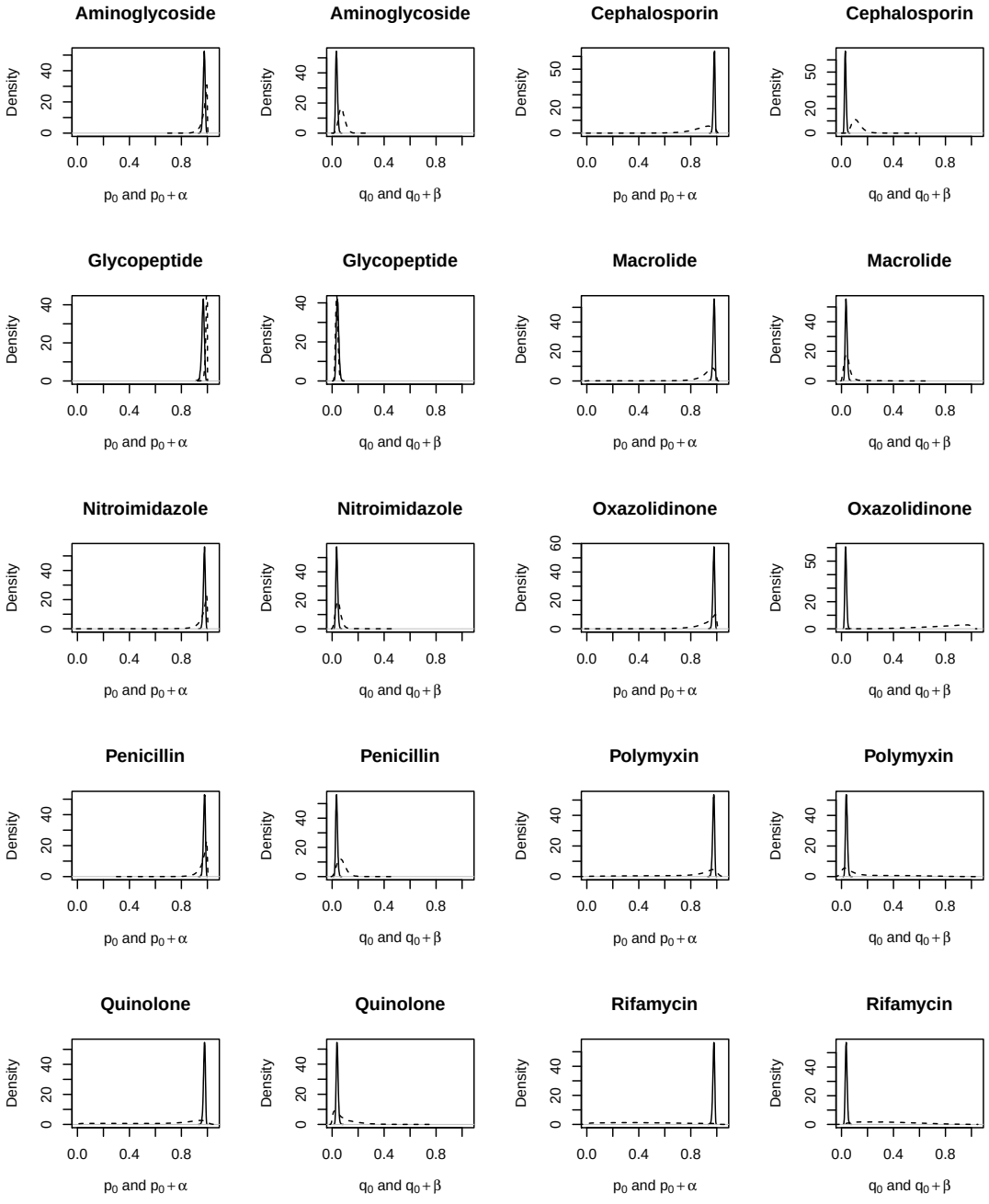

Figure B.3: Kernel density plots for p_0, $p_0 + \alpha$, q_0 and $q_0 + \beta$ for the antibiotics for the p-MRSA Data Set starting from patients' first positive test. The continuous line shows the probabilities p_0 and q_0 whereas the dashed line shows the probabilities $p_0 + \alpha$ and $q_0 + \beta$.

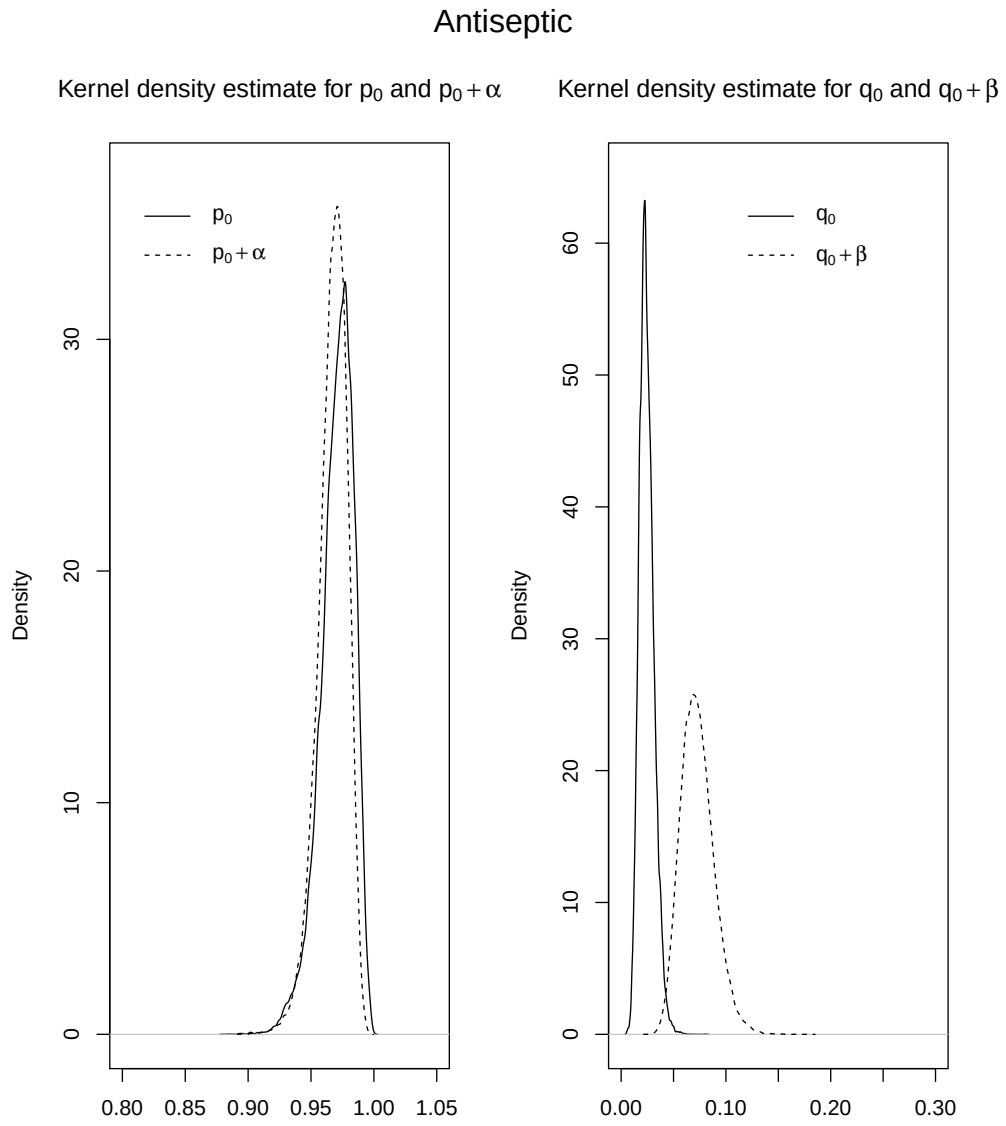

Figure B.4: Kernel density plots for p_0, $p_0 + \alpha$, q_0 and $q_0 + \beta$ for the antiseptic for the p-MRSA Data Set starting from patients' first positive test. The continuous line shows the probabilities p_0 and q_0 whereas the dashed line shows the probabilities $p_0 + \alpha$ and $q_0 + \beta$.

B.2 p-Wounds Data Set

	p_0		q_0	
GROUP	$E[\cdot\|\tilde{\mathcal{S}}]$ (s.d.)	95% CI	$E[\cdot\|\tilde{\mathcal{S}}]$ (s.d.)	95% CI
Aminoglycoside	0.8370 (0.0224)	(0.7892, 0.8766)	0.1978 (0.0426)	(0.1223, 0.2902)
Antiseptic	0.8350 (0.0273)	(0.7742, 0.8816)	0.1930 (0.0484)	(0.1109, 0.3013)
Cephalosporin	0.8133 (0.0244)	(0.7607, 0.8564)	0.2253 (0.0438)	(0.1460, 0.3175)
Glycopeptide	0.8123 (0.0303)	(0.7458, 0.8650)	0.1816 (0.0460)	(0.1038, 0.2816)
Macrolide	0.8497 (90.0201)	(0.8073, 0.8857)	0.1831 (0.0377)	(0.1151, 0.2648)
Nitroimidazole	0.8122 (0.0238)	(0.7605, 0.8545)	0.2279 (0.0437)	(0.1490, 0.3205)
Oxazolidinone	0.8281 (0.0215)	(0.7815, 0.8659)	0.2065 (0.0427)	(0.1323, 0.2995)
Penicillin	0.8315 (0.0223)	(0.7839, 0.8710)	0.1897 (0.0423)	(0.1159, 0.2821)
Polymyxin	0.8266 (0.0218)	(0.7797, 0.8659)	0.2168 (0.0433)	(0.1401, 0.3126)
Quinolone	0.8325 (0.0229)	(0.7843, 0.8729)	0.2112 (0.0466)	(0.1307, 0.3125)
Rifamycin	0.8315 (0.0214)	(0.7860, 0.8704)	0.2053 (0.0422)	(0.1309, 0.2944)

Table B.9: Summary statistics for parameters p_0 and q_0 for each antimicrobial group for the p-Wounds Data Set.

	α		β	
GROUP	$E[\cdot\|\tilde{\mathcal{S}}]$ (s.d.)	95% CI	$E[\cdot\|\tilde{\mathcal{S}}]$ (s.d.)	95% CI
Aminoglycoside	−0.1378 (0.1078)	(−0.3767, 0.0395)	0.2459 (0.1411)	(−0.0001, 0.5329)
Antiseptic	−0.0242 (0.0474)	(−0.1223, 0.0657)	0.0598 (0.0630)	(−0.0616, 0.1884)
Cephalosporin	0.0870 (0.0604)	(−0.0508, 0.1864)	−0.0086 (0.1099)	(−0.1934, 0.2394)
Glycopeptide	0.0734 (0.0464)	(−0.0216, 0.1626)	0.0247 (0.0581)	(−0.0866, 0.1440)
Macrolide	−0.2312 (0.0858)	(−0.4128, −0.0805)	0.3875 (0.1092)	(0.1720, 0.5958)
Nitroimidazole	0.1018 (0.0508)	(−0.0136, 0.1889)	−0.0727 (0.0910)	(−0.2270, 0.1345)
Oxazolidinone	0.1012 (0.0863)	(−0.1271, 0.1947)	0.4502 (0.2047)	(0.0329, 0.7827)
Penicillin	0.0079 (0.0696)	(−0.1471, 0.1221)	0.2669 (0.1293)	(0.0280, 0.5319)
Polymyxin	−0.1004 (0.2066)	(−0.6009, 0.1557)	0.2218 (0.2868)	(−0.1990, 0.7532)
Quinolone	−0.1551 (0.1494)	(−0.5181, 0.0646)	0.0433 (0.1300)	(−0.1670, 0.3371)
Rifamycin	−0.2648 (0.2511)	(−0.7742, 0.1114)	0.4524 (0.2259)	(−0.0048, 0.7940)

Table B.10: Summary statistics for parameters α and β for each antimicrobial group for the p-Wounds Data Set.

	ϕ		ψ	
GROUP	$E[\cdot \mid \tilde{\mathcal{S}}]$ (s.d.)	95% CI	$E[\cdot \mid \tilde{\mathcal{S}}]$ (s.d.)	95% CI
Aminoglycoside	0.6371 (0.0410)	(0.5611, 0.7213)	0.6421 (0.0133)	(0.6145, 0.6663)
Antiseptic	0.6361 (0.0413)	(0.5589, 0.7206)	0.6418 (0.0134)	(0.6134, 0.6662)
Cephalosporin	0.6398 (0.0401)	(0.5636, 0.7204)	0.6431 (0.0130)	(0.6155, 0.6662)
Glycopeptide	0.6174 (0.0385)	(0.5463, 0.6972)	0.6357 (0.0136)	(0.6074, 0.6607)
Macrolide	0.6385 (0.0395)	(0.5642, 0.7198)	0.6427 (0.0130)	(0.6160, 0.6661)
Nitroimidazole	0.6380 (0.0407)	(0.5611, 0.7206)	0.6424 (0.0132)	(0.6144, 0.6661)
Oxazolidinone	0.6326 (0.0423)	(0.5542, 0.7205)	0.6406 (0.0139)	(0.6113, 0.6658)
Penicillin	0.6255 (0.0415)	(0.5479, 0.7110)	0.6383 (0.0142)	(0.6080, 0.6639)
Polymyxin	0.6367 (0.0413)	(0.5601, 0.7227)	0.6420 (0.0134)	(0.6138, 0.6665)
Quinolone	0.6322 (0.0431)	(0.5520, 0.7207)	0.6404 (0.0143)	(0.6101, 0.6661)
Rifamycin	0.6305 (0.0415)	(0.5521, 0.7141)	0.6399 (0.0139)	(0.6104, 0.6647)

Table B.11: Summary statistics for parameters ϕ and ψ for each antimicrobial group for the p-Wounds Data Set.

Model Fit							
Day Intervals	**1**	**2**	**3**	**4**	**5**	**6**	**7**
$N \to N$							
obs. counts	**316**	**213**	**179**	**125**	**96**	**59**	**35**
Aminoglycoside	(314, 345)	(213, 242)	(153, 178)	(102, 124)	(84, 104)	(50, 65)	(28, 40)
Antiseptic	(315, 348)	(214, 243)	(152, 178)	(102, 124)	(84, 104)	(49, 65)	(27, 40)
Cephalosporin	(314, 348)	(214, 241)	(154, 179)	(102, 123)	(83, 103)	(49, 66)	(28, 40)
Glycopeptide	(317, 347)	(214, 244)	(154, 179)	(103, 123)	(83, 103)	(49, 66)	(27, 40)
Macrolide	(316, 347)	(215, 243)	(153, 180)	(103, 124)	(85, 104)	(50, 65)	(28, 40)
Nitroimidazole	(312, 348)	(213, 242)	(153, 179)	(102, 124)	(84, 103)	(50, 65)	(29, 40)
Oxazolidinone	(315, 349)	(215, 243)	(153, 179)	(103, 124)	(84, 104)	(49, 65)	(28, 40)
Penicillin	(318, 348)	(215, 242)	(154, 179)	(102, 124)	(85, 105)	(50, 64)	(28, 40)
Polymyxin	(317, 348)	(216, 244)	(153, 180)	(103, 123)	(84, 104)	(50, 65)	(28, 41)
Quinolone	(315, 345)	(215, 244)	(153, 176)	(103, 124)	(84, 104)	(49, 65)	(28, 41)
Rifamycin	(315, 347)	(214, 243)	(155, 179)	(102, 124)	(84, 104)	(50, 65)	(29, 40)
$N \to C$							
obs. counts	**101**	**86**	**44**	**29**	**33**	**21**	**13**
Aminoglycoside	(71, 103)	(56, 85)	(44, 69)	(30, 52)	(25, 45)	(15, 30)	(7, 20)
Antiseptic	(69, 102)	(55, 85)	(44, 71)	(30, 51)	(25, 45)	(15, 31)	(8, 20)
Cephalosporin	(68, 103)	(57, 84)	(43, 69)	(30, 52)	(25, 46)	(14, 30)	(7, 19)
Glycopeptide	(69, 100)	(55, 85)	(44, 69)	(31, 51)	(25, 46)	(14, 30)	(8, 21)
Macrolide	(69, 100)	(55, 84)	(43, 69)	(29, 50)	(25, 44)	(15, 30)	(7, 19)
Nitroimidazole	(68, 104)	(56, 85)	(44, 69)	(29, 51)	(26, 45)	(15, 30)	(8, 19)
Oxazolidinone	(67, 101)	(56, 83)	(43, 70)	(30, 50)	(25, 45)	(14, 31)	(8, 20)
Penicillin	(69, 99)	(56, 84)	(44, 69)	(30, 52)	(24, 44)	(15, 30)	(8, 20)
Polymyxin	(68, 99)	(55, 83)	(42, 69)	(30, 51)	(25, 45)	(15, 30)	(7, 19)
Quinolone	(71, 101)	(55, 84)	(46, 69)	(30, 51)	(25, 45)	(15, 30)	(7, 20)
Rifamycin	(69, 101)	(56, 84)	(44, 68)	(29, 52)	(25, 45)	(15, 29)	(8, 19)
$C \to N$							
obs. counts	**100**	**65**	**48**	**40**	**30**	**16**	**11**
Aminoglycoside	(82, 107)	(62, 85)	(41, 58)	(35, 49)	(21, 32)	(13, 21)	(7, 14)
Antiseptic	(81, 106)	(63, 84)	(41, 58)	(35, 48)	(21, 32)	(13, 21)	(7, 14)
Cephalosporin	(82, 108)	(62, 84)	(41, 56)	(35, 49)	(22, 32)	(13, 21)	(7, 14)
Glycopeptide	(81, 108)	(60, 83)	(41, 57)	(34, 49)	(21, 32)	(13, 22)	(7, 14)
Macrolide	(82, 108)	(61, 82)	(41, 57)	(32, 49)	(21, 32)	(13, 22)	(7, 14)
Nitroimidazole	(80, 108)	(62, 84)	(42, 57)	(34, 48)	(21, 32)	(13, 22)	(7, 14)
Oxazolidinone	(79, 107)	(62, 83)	(40, 57)	(33, 49)	(21, 32)	(13, 22)	(7, 13)
Penicillin	(81, 107)	(63, 85)	(40, 56)	(33, 47)	(20, 32)	(13, 22)	(7, 14)
Polymyxin	(80, 107)	(62, 84)	(41, 58)	(34, 48)	(21, 32)	(13, 22)	(7, 14)
Quinolone	(81, 107)	(62, 84)	(41, 57)	(34, 49)	(20, 32)	(13, 22)	(8, 14)
Rifamycin	(81, 108)	(62, 84)	(40, 57)	(33, 49)	(22, 32)	(13, 22)	(7, 13)
$C \to C$							
obs. counts	**88**	**60**	**29**	**22**	**9**	**9**	**4**
Aminoglycoside	(80, 106)	(40, 62)	(19, 36)	(13, 27)	(6, 18)	(3, 12)	(1, 8)
Antiseptic	(82, 107)	(41, 61)	(19, 36)	(14, 27)	(6, 18)	(3, 12)	(1, 8)
Cephalosporin	(79, 105)	(41, 63)	(21, 36)	(13, 27)	(7, 17)	(4, 12)	(1, 8)
Glycopeptide	(80, 107)	(41, 64)	(20, 36)	(13, 28)	(6, 18)	(3, 12)	(1, 8)
Macrolide	(80, 105)	(42, 64)	(19, 36)	(13, 29)	(7, 18)	(3, 12)	(1, 8)
Nitroimidazole	(80, 108)	(41, 63)	(20, 35)	(14, 27)	(7, 18)	(3, 12)	(1, 8)
Oxazolidinone	(81, 108)	(42, 63)	(20, 37)	(12, 29)	(7, 18)	(3, 12)	(2, 8)
Penicillin	(81, 107)	(39, 62)	(20, 37)	(14, 28)	(7, 18)	(3, 12)	(1, 8)
Polymyxin	(81, 107)	(40, 62)	(19, 36)	(13, 27)	(6, 18)	(3, 12)	(1, 7)
Quinolone	(80, 107)	(40, 63)	(20, 36)	(13, 28)	(7, 19)	(3, 12)	(1, 7)
Rifamycin	(79, 106)	(41, 63)	(20, 36)	(13, 29)	(7, 17)	(3, 12)	(1, 8)

Table B.12: Model fit for each antimicrobial treatment group of the p-Wounds Data Set. The intervals in red indicate that the observed transition counts are included in the equal-tailed 95% quantiles.

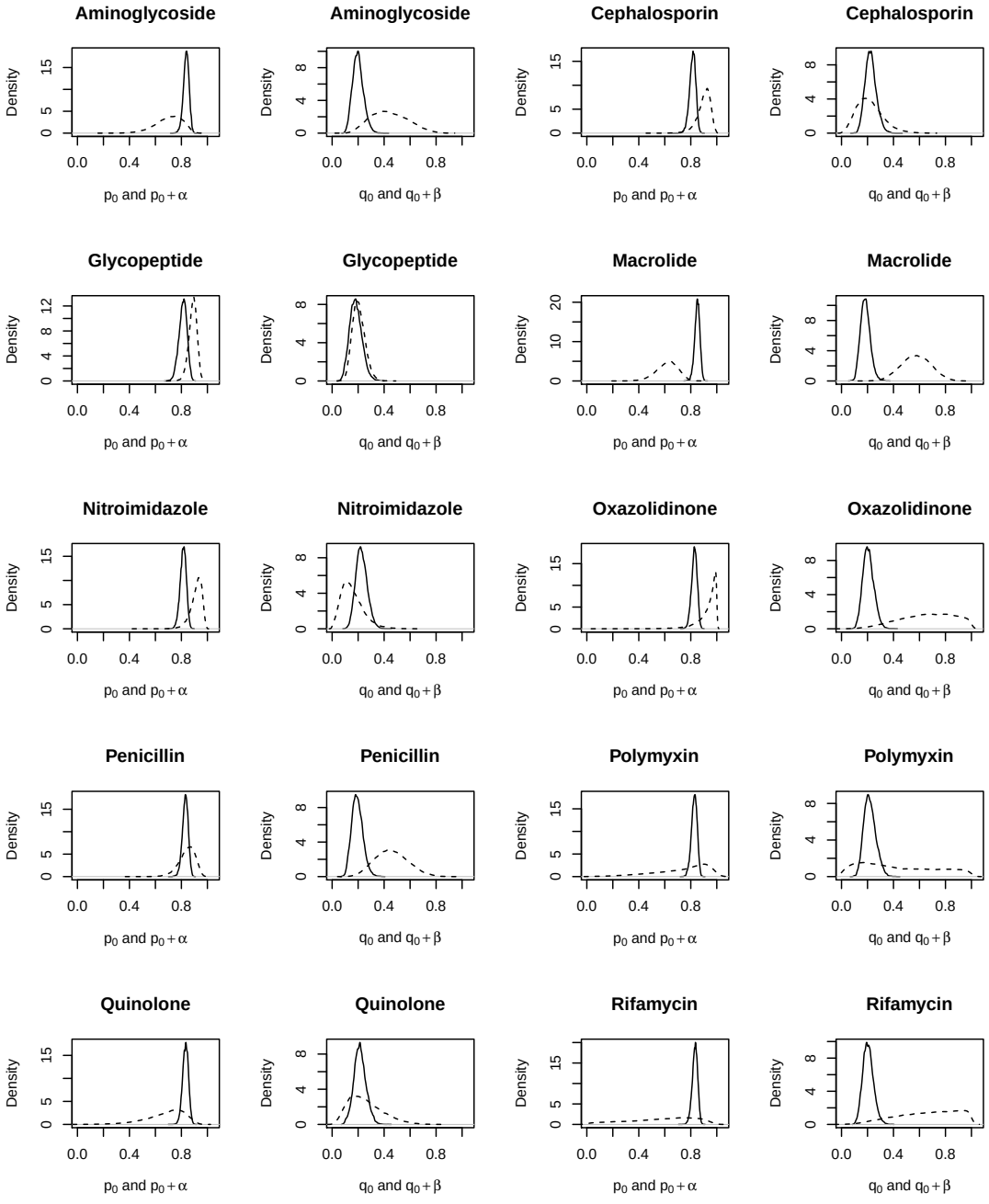

Figure B.5: Kernel density plots for p_0, $p_0 + \alpha$, q_0 and $q_0 + \beta$ for the antibiotics for the p-Wounds Data Set. The continuous line shows the probabilities p_0 and q_0 whereas the dashed line shows the probabilities $p_0 + \alpha$ and $q_0 + \beta$.

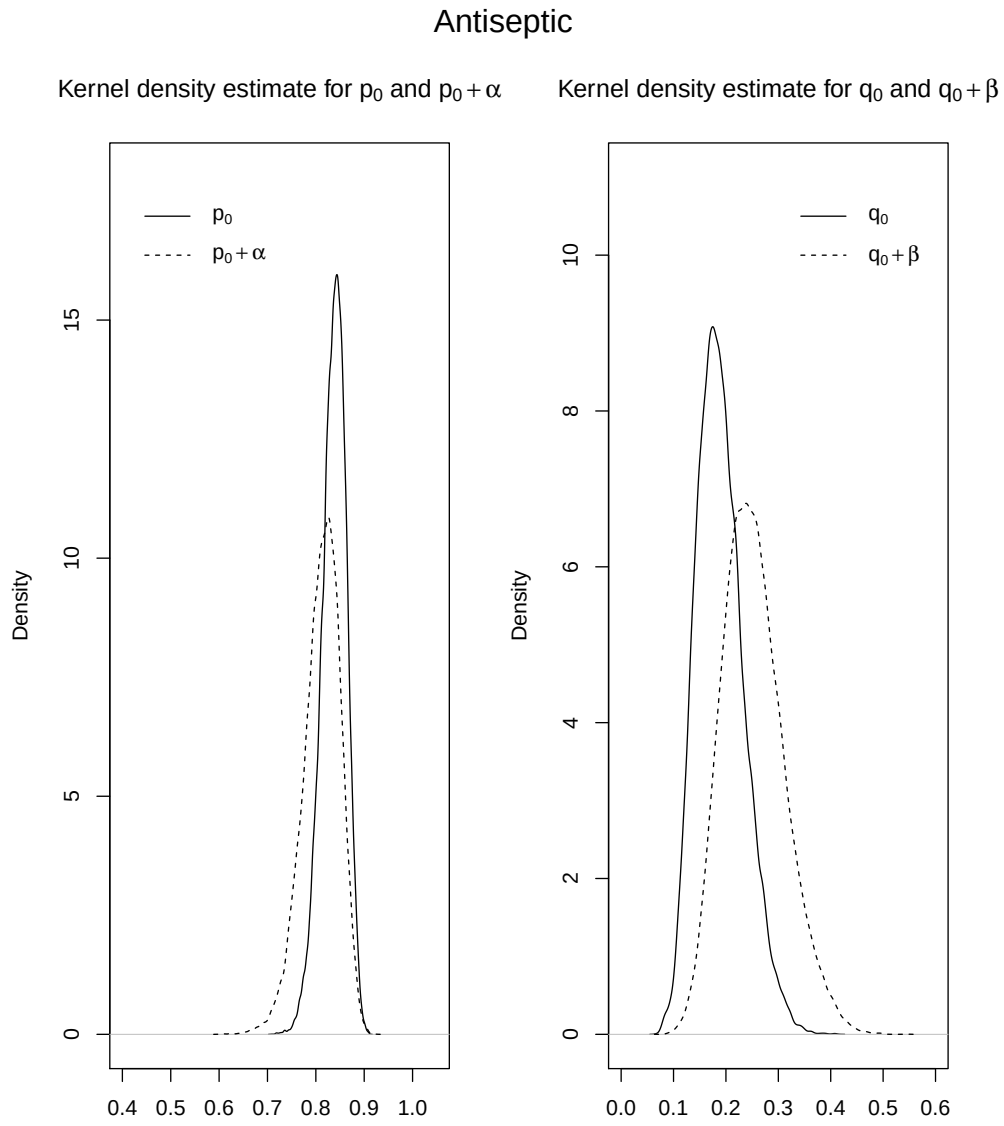

Figure B.6: Kernel density plots for p_0, $p_0 + \alpha$, q_0 and $q_0 + \beta$ for the antiseptic for the p-Wounds Data Set. The continuous line shows the probabilities p_0 and q_0 whereas the dashed line shows the probabilities $p_0 + \alpha$ and $q_0 + \beta$.

B.2.1 After first positive test

	p_0		q_0	
GROUP	$E[\cdot\|\tilde{\mathcal{S}}]$ (s.d.)	95% CI	$E[\cdot\|\tilde{\mathcal{S}}]$ (s.d.)	95% CI
Aminoglycoside	0.9150 (0.0271)	(0.8572, 0.9627)	0.0938 (0.0355)	(0.0374, 0.1748)
Antiseptic	0.8870 (0.0421)	(0.7907, 0.9544)	0.1129 (0.0431)	(0.0429, 0.2103)
Cephalosporin	0.8855 (0.0293)	(0.8231, 0.9372)	0.1253 (0.0413)	(0.0592, 0.2189)
Glycopeptide	0.8724 (0.0387)	(0.7853, 0.9351)	0.0852 (0.0368)	(0.0306, 0.1723)
Macrolide	0.8968 (0.0248)	(0.8442, 0.9413)	0.1169 (0.0358)	(0.0582, 0.1977)
Nitroimidazole	0.8720 (0.0304)	(0.8070, 0.9265)	0.1427 (0.0432)	(0.0725, 0.2397)
Oxazolidinone	0.8961 (0.0269)	(0.8382, 0.9438)	0.1064 (0.0348)	(0.0503, 0.1853)
Penicillin	0.8981 (0.0257)	(0.8427, 0.9436)	0.0982 (0.0319)	(0.0455, 0.1704)
Polymyxin	0.8951 (0.0267)	(0.8375, 0.9415)	0.1156 (0.0366)	(0.0596, 0.2005)
Quinolone	0.9008 (0.0283)	(0.8402, 0.9497)	0.1107 (0.0389)	(0.0504, 0.2002)
Rifamycin	0.9009 (0.0263)	(0.8446, 0.9470)	0.1047 (0.0343)	(0.0501, 0.1826)

Table B.13: Summary statistics for parameters p_0 and q_0 for each antimicrobial group for the p-Wounds Data Set starting from patients' first positive test.

	α		β	
GROUP	$E[\cdot\|\tilde{\mathcal{S}}]$ (s.d.)	95% CI	$E[\cdot\|\tilde{\mathcal{S}}]$ (s.d.)	95% CI
Aminoglycoside	−0.3027 (0.1994)	(−0.7586, −0.0034)	0.2516 (0.1377)	(0.0277, 0.5398)
Antiseptic	−0.0018 (0.0550)	(−0.1085, 0.1102)	0.0279 (0.0465)	(−0.0644, 0.1227)
Cephalosporin	0.0198 (0.1405)	(−0.4258, 0.1512)	0.0331 (0.1107)	(−0.1290, 0.3323)
Glycopeptide	0.0820 (0.0464)	(−0.0069, 0.1789)	0.0377 (0.0381)	(−0.0390, 0.1160)
Macrolide	−0.2447 (0.1369)	(−0.5623, −0.0268)	0.3650 (0.1200)	(0.1336, 0.5999)
Nitroimidazole	0.0844 (0.0522)	(−0.0368, 0.1674)	−0.0369 (0.0657)	(−0.1556, 0.1053)
Oxazolidinone	0.0015 (0.1223)	(−0.3400, 0.1325)	0.6236 (0.2038)	(0.1633, 0.9016)
Penicillin	0.0267 (0.0708)	(−0.1500, 0.1267)	0.2889 (0.1188)	(0.0837, 0.5479)
Polymyxin	−0.3106 (0.2675)	(−0.8434, 0.0754)	0.2910 (0.2699)	(−0.0987, 0.8195)
Quinolone	−0.2628 (0.2351)	(−0.7938, 0.0757)	0.0862 (0.1117)	(−0.0876, 0.3468)
Rifamycin	−0.2201 (0.2601)	(−0.8272, 0.0981)	0.4634 (0.2346)	(0.0486, 0.8687)

Table B.14: Summary statistics for parameters α and β for each antimicrobial group for the p-Wounds Data Set starting from patients' first positive test.

	ϕ		ψ	
GROUP	$E[\cdot \mid \tilde{\mathcal{S}}]$ (s.d.)	95% CI	$E[\cdot \mid \tilde{\mathcal{S}}]$ (s.d.)	95% CI
Aminoglycoside	0.6372 (0.0410)	(0.5612, 0.7214)	0.6422 (0.0133)	(0.6145, 0.6664)
Antiseptic	0.6362 (0.0413)	(0.5589, 0.7206)	0.6419 (0.0134)	(0.6135, 0.6662)
Cephalosporin	0.6399 (0.0401)	(0.5637, 0.7205)	0.6431 (0.0131)	(0.6156, 0.6662)
Glycopeptide	0.6174 (0.0385)	(0.5464, 0.6972)	0.6357 (0.0137)	(0.6074, 0.6608)
Macrolide	0.6386 (0.0395)	(0.5643, 0.7198)	0.6428 (0.0130)	(0.6160, 0.6661)
Nitroimidazole	0.6380 (0.0407)	(0.5611, 0.7207)	0.6424 (0.0132)	(0.6145, 0.6662)
Oxazolidinone	0.6326 (0.0424)	(0.5542, 0.7205)	0.6406 (0.0139)	(0.6113, 0.6659)
Penicillin	0.6256 (0.0416)	(0.5480, 0.7110)	0.6383 (0.0142)	(0.6081, 0.6639)
Polymyxin	0.6368 (0.0413)	(0.5601, 0.7228)	0.6420 (0.0134)	(0.6139, 0.6665)
Quinolone	0.6323 (0.0431)	(0.5521, 0.7207)	0.6404 (0.0144)	(0.6102, 0.6661)
Rifamycin	0.6305 (0.0416)	(0.5522, 0.7141)	0.6400 (0.0139)	(0.6105, 0.6648)

Table B.15: Summary statistics for parameters ϕ and ψ for each antimicrobial group for the p-Wounds Data Set starting from patients' first positive test.

Model Fit							
Day Intervals	**1**	**2**	**3**	**4**	**5**	**6**	**7**
$N \to N$							
obs. counts	**140**	**91**	**83**	**57**	**46**	**32**	**14**
Aminoglycoside	(126, 149)	(80, 99)	(66, 83)	(44, 59)	(40, 55)	(24, 34)	(11, 19)
Antiseptic	(128, 150)	(81, 99)	(66, 83)	(44, 59)	(41, 55)	(24, 35)	(11, 19)
Cephalosporin	(127, 150)	(80, 100)	(66, 83)	(44, 59)	(42, 55)	(24, 35)	(12, 19)
Glycopeptide	(127, 150)	(81, 99)	(67, 84)	(44, 59)	(41, 54)	(26, 35)	(11, 19)
Macrolide	(129, 152)	(82, 100)	(66, 84)	(45, 60)	(42, 55)	(23, 35)	(11, 19)
Nitroimidazole	(129, 151)	(81, 101)	(65, 83)	(45, 60)	(42, 55)	(24, 35)	(12, 19)
Oxazolidinone	(127, 150)	(82, 100)	(65, 83)	(45, 59)	(40, 54)	(24, 34)	(11, 19)
Penicillin	(128, 152)	(82, 100)	(66, 83)	(46, 59)	(40, 55)	(24, 35)	(11, 19)
Polymyxin	(127, 151)	(80, 100)	(65, 83)	(44, 59)	(42, 55)	(24, 35)	(12, 19)
Quinolone	(127, 149)	(81, 100)	(65, 83)	(44, 60)	(42, 55)	(24, 35)	(11, 19)
Rifamycin	(127, 151)	(81, 99)	(66, 84)	(45, 59)	(41, 55)	(25, 35)	(12, 19)
$N \to C$							
obs. counts	**47**	**31**	**18**	**13**	**19**	**8**	**7**
Aminoglycoside	(37, 61)	(22, 41)	(18, 35)	(11, 25)	(10, 25)	(5, 16)	(2, 10)
Antiseptic	(36, 59)	(23, 40)	(17, 35)	(11, 25)	(10, 24)	(5, 15)	(2, 10)
Cephalosporin	(36, 60)	(22, 42)	(18, 35)	(11, 25)	(10, 23)	(5, 16)	(2, 9)
Glycopeptide	(36, 60)	(23, 41)	(16, 34)	(11, 26)	(11, 24)	(5, 14)	(2, 9)
Macrolide	(34, 57)	(21, 40)	(17, 35)	(10, 25)	(9, 23)	(5, 16)	(1, 10)
Nitroimidazole	(35, 58)	(21, 41)	(18, 35)	(10, 25)	(10, 23)	(4, 16)	(2, 9)
Oxazolidinone	(37, 60)	(22, 40)	(18, 35)	(10, 24)	(10, 24)	(6, 15)	(2, 10)
Penicillin	(35, 58)	(22, 40)	(18, 34)	(11, 24)	(10, 24)	(5, 16)	(2, 10)
Polymyxin	(35, 60)	(22, 41)	(18, 35)	(10, 26)	(10, 23)	(5, 16)	(2, 9)
Quinolone	(38, 59)	(22, 41)	(18, 36)	(10, 25)	(10, 23)	(5, 15)	(1, 9)
Rifamycin	(36, 60)	(23, 41)	(16, 34)	(11, 25)	(10, 24)	(5, 15)	(2, 9)
$C \to N$							
obs. counts	**100**	**65**	**48**	**40**	**30**	**16**	**11**
Aminoglycoside	(87, 114)	(62, 84)	(40, 56)	(33, 47)	(20, 32)	(12, 21)	(7, 14)
Antiseptic	(87, 113)	(62, 83)	(39, 56)	(33, 48)	(20, 32)	(12, 22)	(7, 14)
Cephalosporin	(86, 113)	(62, 83)	(38, 55)	(33, 48)	(20, 32)	(13, 22)	(7, 14)
Glycopeptide	(87, 115)	(60, 84)	(40, 56)	(33, 48)	(20, 31)	(12, 21)	(7, 14)
Macrolide	(84, 112)	(61, 82)	(40, 56)	(33, 47)	(20, 32)	(13, 22)	(7, 13)
Nitroimidazole	(85, 112)	(62, 83)	(40, 56)	(33, 48)	(20, 31)	(13, 21)	(7, 14)
Oxazolidinone	(87, 115)	(61, 84)	(39, 55)	(33, 47)	(20, 31)	(13, 21)	(7, 14)
Penicillin	(87, 114)	(63, 84)	(39, 56)	(33, 47)	(20, 31)	(13, 21)	(7, 14)
Polymyxin	(86, 113)	(61, 83)	(39, 56)	(32, 47)	(20, 32)	(13, 21)	(7, 14)
Quinolone	(87, 112)	(61, 83)	(40, 55)	(33, 47)	(20, 32)	(12, 21)	(7, 14)
Rifamycin	(86, 113)	(62, 83)	(38, 55)	(32, 48)	(20, 31)	(12, 21)	(7, 14)
$C \to C$							
obs. counts	**88**	**60**	**29**	**22**	**9**	**9**	**4**
Aminoglycoside	(74, 101)	(41, 63)	(21, 37)	(15, 29)	(7, 19)	(4, 12)	(1, 8)
Antiseptic	(73, 101)	(41, 63)	(21, 38)	(14, 29)	(7, 19)	(3, 13)	(1, 8)
Cephalosporin	(74, 102)	(41, 63)	(22, 39)	(14, 29)	(7, 18)	(3, 12)	(1, 8)
Glycopeptide	(72, 100)	(40, 65)	(21, 37)	(14, 29)	(8, 19)	(4, 12)	(1, 8)
Macrolide	(76, 103)	(42, 64)	(21, 37)	(15, 29)	(7, 19)	(3, 12)	(1, 8)
Nitroimidazole	(75, 102)	(42, 63)	(21, 37)	(13, 29)	(7, 19)	(3, 12)	(1, 8)
Oxazolidinone	(73, 100)	(41, 64)	(22, 37)	(14, 29)	(8, 19)	(4, 12)	(1, 8)
Penicillin	(73, 101)	(40, 62)	(21, 38)	(14, 29)	(7, 19)	(3, 12)	(1, 8)
Polymyxin	(75, 101)	(42, 64)	(21, 37)	(15, 29)	(7, 19)	(4, 12)	(1, 8)
Quinolone	(75, 101)	(41, 64)	(21, 37)	(15, 29)	(7, 19)	(3, 13)	(1, 8)
Rifamycin	(75, 102)	(42, 63)	(22, 38)	(14, 30)	(8, 19)	(4, 13)	(1, 8)

Table B.16: Model fit for each antimicrobial treatment group of the p-Wounds Data Set starting from patients' first positive test. The intervals in red indicate that the observed transition counts are included in the equal-tailed 95% quantiles.

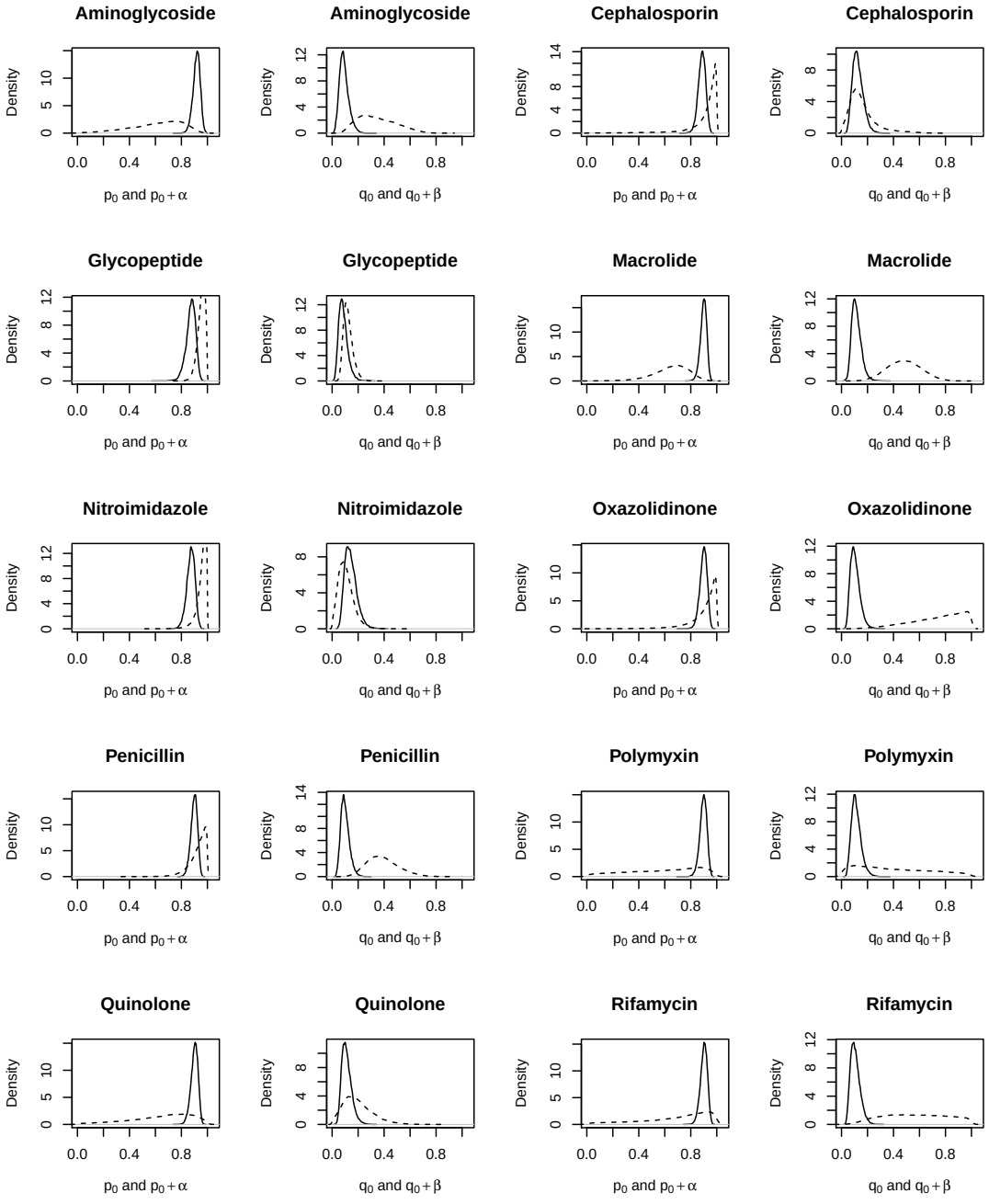

Figure B.7: Kernel density plots for p_0, $p_0 + \alpha$, q_0 and $q_0 + \beta$ for the antibiotics for the p-Wounds Data Set starting from patients' first positive test. The continuous line shows the probabilities p_0 and q_0 whereas the dashed line shows the probabilities $p_0 + \alpha$ and $q_0 + \beta$.

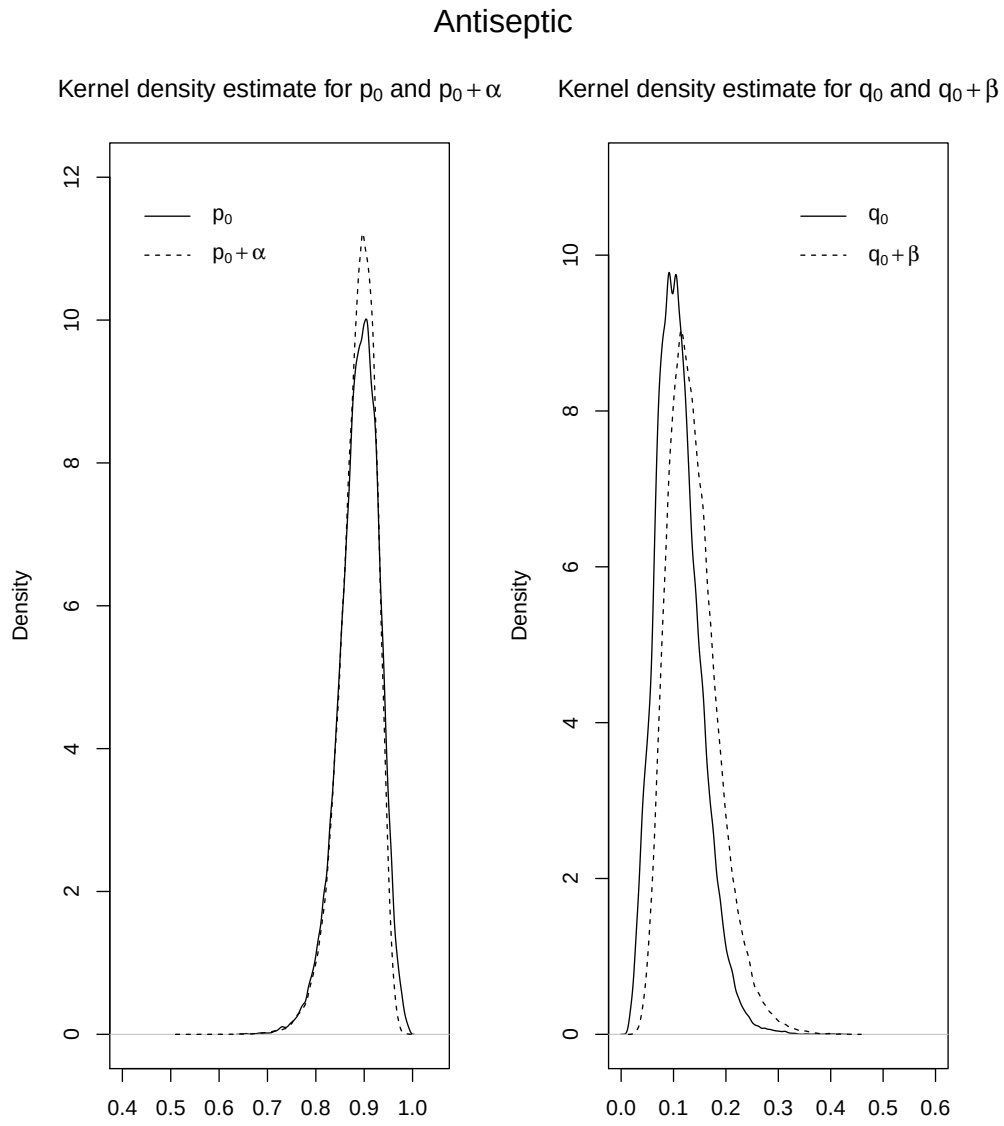

Figure B.8: Kernel density plots for p_0, $p_0 + \alpha$, q_0 and $q_0 + \beta$ for the antiseptic for the p-Wounds Data Set starting from patients' first positive test. The continuous line shows the probabilities p_0 and q_0 whereas the dashed line shows the probabilities $p_0 + \alpha$ and $q_0 + \beta$.

B.3 p-Respiratory Data Set

	p_0		q_0	
GROUP	$E[\cdot\|\tilde{\mathcal{S}}]$ (s.d.)	95% CI	$E[\cdot\|\tilde{\mathcal{S}}]$ (s.d.)	95% CI
Aminoglycoside	0.7921 (0.0362)	(0.7122, 0.8550)	0.1403 (0.0339)	(0.0801, 0.0211)
Antiseptic	0.8267 (0.0298)	(0.7615, 0.8760)	0.1038 (0.0299)	(0.0529, 0.1694)
Cephalosporin	0.8253 (0.0323)	(0.7548, 0.8806)	0.1161 (0.0316)	(0.0613, 0.1843)
Glycopeptide	0.7963 (0.0378)	(0.7135, 0.8607)	0.1154 (0.0354)	(0.0551, 0.1935)
Macrolide	0.8140 (0.0346)	(0.7367, 0.8735)	0.1272 (0.0347)	(0.0683, 0.2032)
Nitroimidazole	0.8115 (0.0320)	(0.7406, 0.8656)	0.1222 (0.0309)	(0.0692, 0.1907)
Oxazolidinone	0.8205 (0.0281)	(0.7590, 0.8688)	0.1172 (0.0291)	(0.0665, 0.1809)
Penicillin	0.8089 (0.0319)	(0.7395, 0.8639)	0.1286 (0.0324)	(0.0714, 0.1971)
Polymyxin	0.8269 (0.0272)	(0.7671, 0.8739)	0.1189 (0.0285)	(0.0688, 0.1799)
Quinolone	0.8371 (0.0278)	(0.7771, 0.8855)	0.1226 (0.0291)	(0.0699, 0.1844)
Rifamycin	0.8172 (0.0295)	(0.7520, 0.8683)	0.1208 (0.0306)	(0.0679, 0.1875)

Table B.17: Summary statistics for parameters p_0 and q_0 for each antimicrobial group for the p-Respiratory Data Set.

	α		β	
GROUP	$E[\cdot\|\tilde{\mathcal{S}}]$ (s.d.)	95% CI	$E[\cdot\|\tilde{\mathcal{S}}]$ (s.d.)	95% CI
Aminoglycoside	0.1129 (0.0834)	(−0.0784, 0.2473)	−0.0707 (0.0613)	(−0.1725, 0.0693)
Antiseptic	−0.0737 (0.1127)	(−0.3483, 0.0910)	0.0923 (0.0729)	(−0.0212, 0.2683)
Cephalosporin	−0.2280 (0.2020)	(−0.6918, 0.0745)	0.2715 (0.2028)	(−0.0563, 0.7016)
Glycopeptide	0.0773 (0.0583)	(−0.0416, 0.1884)	0.0072 (0.0434)	(−0.0763, 0.0945)
Macrolide	−0.0148 (0.0946)	(−0.2417, −0.1333)	0.0201 (0.0919)	(−0.1259, 0.2427)
Nitroimidazole	−0.0246 (0.1291)	(−0.3412, −0.1660)	0.1376 (0.1401)	(−0.0665, 0.4805)
Oxazolidinone	−0.0825 (0.2443)	(−0.7108, 0.1881)	0.5499 (0.2338)	(0.0447, 0.8814)
Penicillin	−0.1449 (0.2849)	(−0.7386, 0.1952)	0.2645 (0.3008)	(−0.1064, 0.8498)
Polymyxin	−0.4273 (0.2446)	(−0.8142, 0.0366)	0.2974 (0.2082)	(−0.0390, 0.07369)
Quinolone	−0.2530 (0.1460)	(−0.5857, −0.0188)	0.0350 (0.0890)	(−0.1003, 0.2438)
Rifamycin	−0.0751 (0.2255)	(−0.6542, 0.1921)	0.2222 (0.1950)	(−0.0581, 0.6868)

Table B.18: Summary statistics for parameters α and β for each antimicrobial group for the p-Respiratory Data Set.

	ϕ		ψ	
GROUP	$E[\cdot\|\tilde{\mathcal{S}}]$ (s.d.)	95% CI	$E[\cdot\|\tilde{\mathcal{S}}]$ (s.d.)	95% CI
Aminoglycoside	0.8751 (0.0498)	(0.7756, 0.9701)	0.8027 (0.0175)	(0.7440, 0.8525)
Antiseptic	0.8710 (0.0506)	(0.7705, 0.9687)	0.8112 (0.0181)	(0.7413, 0.8622)
Cephalosporin	0.8720 (0.0528)	(0.7672, 0.9741)	0.8013 (0.0189)	(0.7396, 0.8434)
Glycopeptide	0.8672 (0.0505)	(0.7678, 0.9677)	0.7998 (0.0182)	(0.7400, 0.8318)
Macrolide	0.8773 (0.0516)	(0.7750, 0.9764)	0.8034 (0.0181)	(0.7440, 0.8642)
Nitroimidazole	0.8775 (0.0515)	(0.7765, 0.9765)	0.8236 (0.0179)	(0.7444, 0.8639)
Oxazolidinone	0.8714 (0.0512)	(0.7710, 0.9699)	0.8013 (0.0183)	(0.7415, 0.8524)
Penicillin	0.8803 (0.0529)	(0.7750, 0.9804)	0.8043 (0.0185)	(0.7435, 0.8550)
Polymyxin	0.8789 (0.0498)	(0.7799, 0.9744)	0.80411 (0.0173)	(0.7461, 0.8435)
Quinolone	0.8807 (0.0508)	(0.7787, 0.9758)	0.7946 (0.0177)	(0.7455, 0.8639)
Rifamycin	0.8750 (0.0516)	(0.7728, 0.9732)	0.8125 (0.0182)	(0.7425, 0.8633)

Table B.19: Summary statistics for parameters ϕ and ψ for each antimicrobial group for the p-Respiratory Data Set.

Model Fit							
Day Intervals	**1**	**2**	**3**	**4**	**5**	**6**	**7**
$N \to N$							
obs. counts	**33**	**28**	**23**	**12**	**15**	**13**	**11**
Aminoglycoside	(27, 38)	(21, 33)	(17, 28)	(12, 24)	(9, 18)	(9, 19)	(5, 13)
Antiseptic	(26, 38)	(22, 33)	(17, 28)	(13, 24)	(8, 18)	(9, 19)	(5, 14)
Cephalosporin	(26, 37)	(22, 33)	(17, 29)	(13, 24)	(9, 18)	(9, 19)	(6, 14)
Glycopeptide	(27, 38)	(22, 34)	(18, 29)	(12, 24)	(9, 18)	(8, 19)	(6, 14)
Macrolide	(26, 37)	(22, 33)	(17, 29)	(13, 24)	(9, 18)	(9, 19)	(5, 14)
Nitroimidazole	(26, 38)	(22, 34)	(17, 29)	(13, 24)	(8, 18)	(9, 19)	(5, 14)
Oxazolidinone	(26, 38)	(22, 34)	(17, 29)	(13, 24)	(8, 17)	(9, 19)	(5, 14)
Penicillin	(27, 38)	(22, 34)	(17, 28)	(13, 24)	(8, 17)	(9, 19)	(5, 14)
Polymyxin	(27, 38)	(23, 35)	(17, 29)	(13, 24)	(8, 17)	(10, 18)	(5, 14)
Quinolone	(26, 38)	(22, 33)	(17, 29)	(13, 25)	(8, 17)	(8, 19)	(6, 14)
Rifamycin	(27, 37)	(22, 34)	(17, 29)	(13, 25)	(8, 17)	(8, 19)	(5, 14)
$N \to C$							
obs. counts	**10**	**14**	**15**	**21**	**9**	**14**	**8**
Aminoglycoside	(5, 16)	(8, 20)	(10, 21)	(9, 20)	(6, 15)	(7, 18)	(6, 14)
Antiseptic	(5, 17)	(8, 20)	(9, 21)	(9, 20)	(6, 16)	(8, 18)	(5, 14)
Cephalosporin	(6, 17)	(9, 20)	(9, 21)	(9, 20)	(6, 15)	(8, 18)	(5, 13)
Glycopeptide	(4, 16)	(8, 19)	(9, 20)	(8, 20)	(6, 15)	(8, 18)	(5, 13)
Macrolide	(5, 17)	(8, 20)	(9, 21)	(9, 20)	(6, 15)	(8, 18)	(5, 13)
Nitroimidazole	(5, 17)	(8, 20)	(9, 20)	(8, 20)	(6, 16)	(7, 17)	(5, 14)
Oxazolidinone	(5, 17)	(8, 19)	(9, 21)	(9, 20)	(6, 16)	(8, 18)	(5, 14)
Penicillin	(5, 16)	(8, 20)	(10, 21)	(9, 20)	(7, 16)	(8, 18)	(5, 13)
Polymyxin	(5, 16)	(7, 19)	(9, 21)	(9, 19)	(6, 16)	(8, 17)	(5, 14)
Quinolone	(5, 16)	(9, 20)	(9, 21)	(8, 20)	(6, 16)	(8, 19)	(5, 13)
Rifamycin	(5, 16)	(8, 20)	(9, 21)	(8, 20)	(7, 16)	(8, 18)	(5, 13)
$C \to N$							
obs. counts	**5**	**3**	**10**	**12**	**4**	**6**	**7**
Aminoglycoside	(4, 14)	(5, 14)	(5, 14)	(6, 15)	(3, 9)	(4, 12)	(3, 10)
Antiseptic	(3, 14)	(5, 13)	(5, 14)	(6, 15)	(2, 10)	(4, 12)	(3, 10)
Cephalosporin	(4, 15)	(5, 14)	(5, 14)	(6, 15)	(2, 9)	(4, 13)	(3, 10)
Glycopeptide	(4, 14)	(4, 14)	(5, 14)	(6, 15)	(2, 10)	(4, 12)	(3, 10)
Macrolide	(4, 14)	(4, 14)	(5, 14)	(5, 15)	(3, 10)	(4, 12)	(3, 10)
Nitroimidazole	(4, 15)	(4, 14)	(5, 14)	(6, 16)	(3, 10)	(4, 12)	(3, 10)
Oxazolidinone	(4, 14)	(4, 14)	(4, 14)	(5, 15)	(2, 9)	(4, 12)	(2, 10)
Penicillin	(4, 14)	(5, 14)	(5, 15)	(6, 15)	(3, 10)	(4, 12)	(3, 10)
Polymyxin	(4, 14)	(4, 14)	(5, 14)	(6, 15)	(2, 9)	(4, 12)	(2, 10)
Quinolone	(4, 14)	(4, 13)	(5, 14)	(5, 15)	(2, 9)	(4, 12)	(3, 10)
Rifamycin	(4, 14)	(4, 14)	(5, 15)	(6, 15)	(2, 9)	(4, 12)	(3, 10)
$C \to C$							
obs. counts	**33**	**26**	**16**	**14**	**10**	**12**	**7**
Aminoglycoside	(24, 34)	(15, 24)	(12, 21)	(11, 20)	(4, 11)	(6, 14)	(4, 11)
Antiseptic	(24, 34)	(15, 24)	(12, 21)	(11, 20)	(4, 11)	(6, 14)	(4, 11)
Cephalosporin	(23, 34)	(15, 24)	(12, 21)	(11, 20)	(5, 11)	(5, 14)	(4, 11)
Glycopeptide	(24, 34)	(15, 24)	(12, 21)	(11, 20)	(4, 12)	(6, 14)	(4, 11)
Macrolide	(24, 34)	(15, 25)	(12, 21)	(11, 20)	(4, 11)	(6, 14)	(4, 11)
Nitroimidazole	(23, 34)	(15, 25)	(12, 21)	(10, 20)	(4, 11)	(6, 14)	(4, 11)
Oxazolidinone	(24, 34)	(15, 25)	(12, 21)	(11, 21)	(5, 12)	(6, 14)	(4, 12)
Penicillin	(24, 34)	(15, 24)	(11, 21)	(11, 20)	(4, 11)	(5, 14)	(4, 11)
Polymyxin	(24, 34)	(15, 25)	(12, 21)	(11, 20)	(5, 12)	(6, 14)	(4, 12)
Quinolone	(24, 34)	(15, 24)	(12, 21)	(11, 21)	(5, 11)	(6, 14)	(4, 11)
Rifamycin	(24, 34)	(15, 24)	(11, 21)	(11, 20)	(5, 12)	(6, 14)	(4, 11)

Table B.20: Model fit for each antimicrobial treatment group of the p-Respiratory Data Set. The intervals in red indicate that the observed transition counts are included in the equal-tailed 95% quantiles.

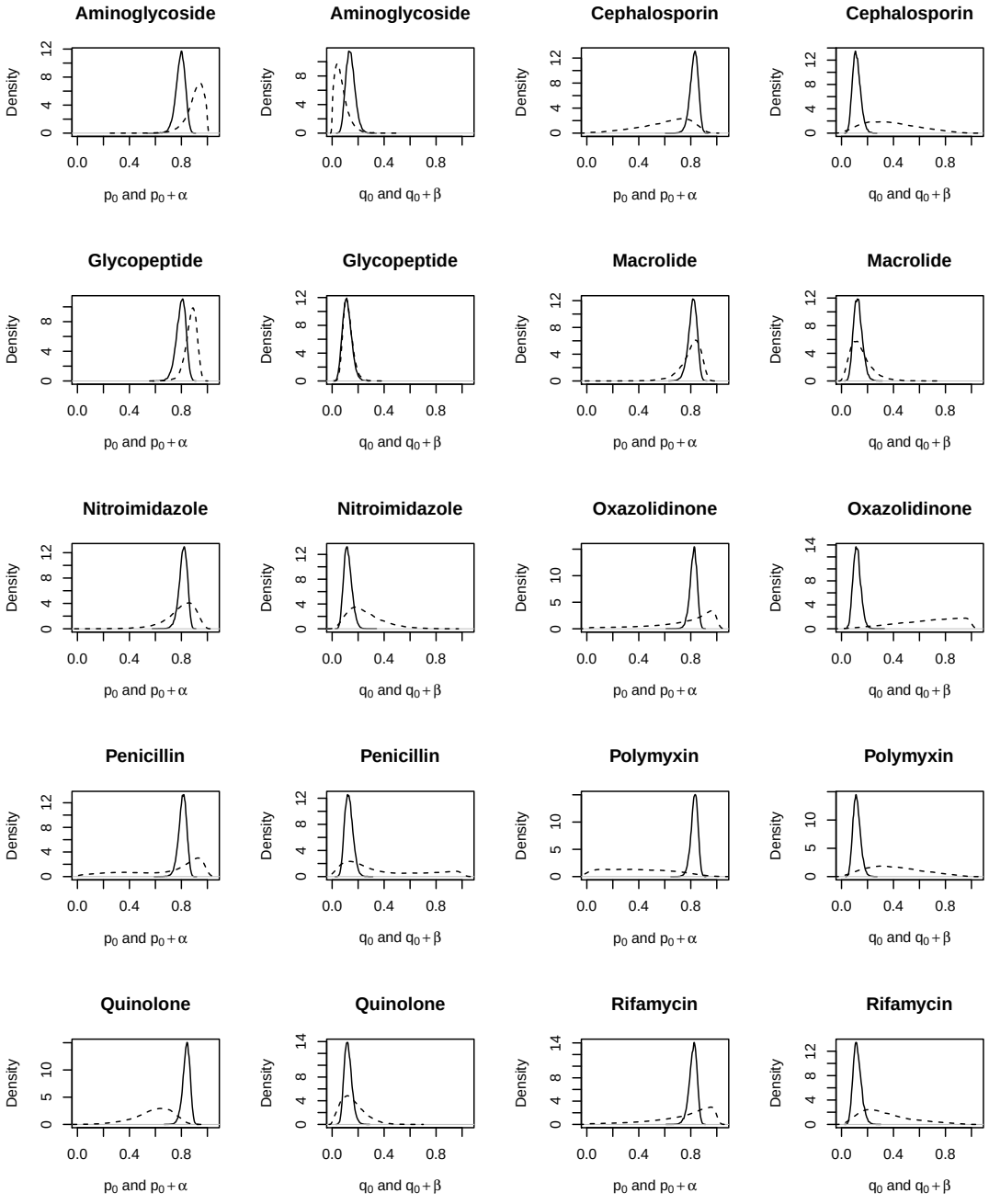

Figure B.9: Kernel density plots for p_0, $p_0 + \alpha$, q_0 and $q_0 + \beta$ for the antibiotics for the p-Respiratory Data Set. The continuous line shows the probabilities p_0 and q_0 whereas the dashed line shows the probabilities $p_0 + \alpha$ and $q_0 + \beta$.

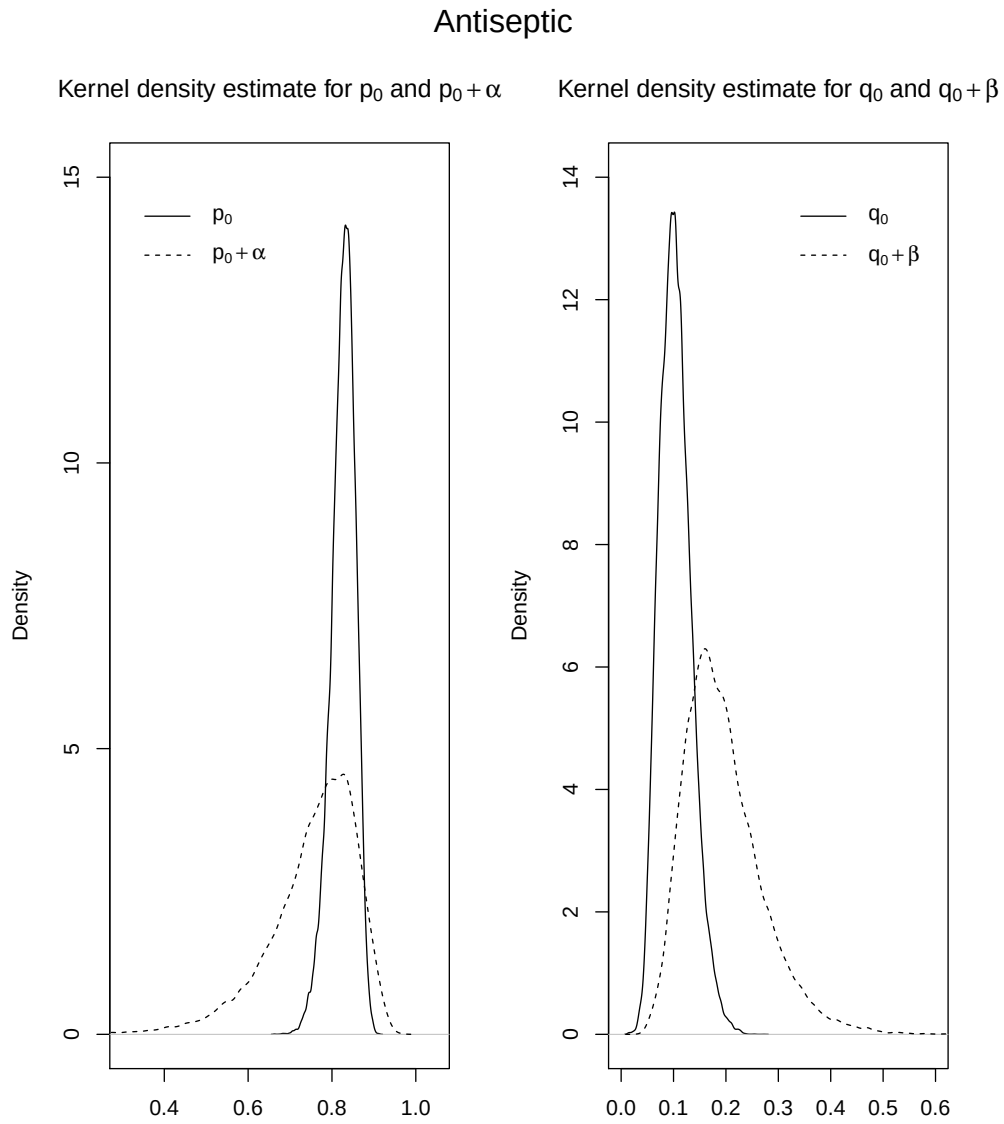

Figure B.10: Kernel density plots for p_0, $p_0 + \alpha$, q_0 and $q_0 + \beta$ for the antiseptic for the p-Respiratory Data Set. The continuous line shows the probabilities p_0 and q_0 whereas the dashed line shows the probabilities $p_0 + \alpha$ and $q_0 + \beta$.

B.3.1 After first positive test

	p_0		q_0	
GROUP	$E[\cdot\|\tilde{\mathcal{S}}]$ (s.d.)	95% CI	$E[\cdot\|\tilde{\mathcal{S}}]$ (s.d.)	95% CI
Aminoglycoside	0.9339 (0.0252)	(0.8755, 0.9747)	0.0904 (0.0272)	(0.0442, 0.1501)
Antiseptic	0.9232 (0.0335)	(0.8494, 0.9812)	0.0852 (0.0285)	(0.0329, 0.1449)
Cephalosporin	0.9111 (0.0293)	(0.8449, 0.9597)	0.1042 (0.0283)	(0.0521, 0.1639)
Glycopeptide	0.9123 (0.0331)	(0.8368, 0.9646)	0.0906 (0.0301)	(0.0412, 0.1575)
Macrolide	0.9255 (0.0266)	(0.8643, 0.9681)	0.0932 (0.0272)	(0.0462, 0.1527)
Nitroimidazole	0.9221 (0.0261)	(0.8624, 0.9651)	0.0921 (0.0268)	(0.0445, 0.1496)
Oxazolidinone	0.9206 (0.0257)	(0.8630, 0.9638)	0.0951 (0.0260)	(0.0485, 0.1502)
Penicillin	0.9172 (0.0267)	(0.8578, 0.9615)	0.1012 (0.0269)	(0.0533, 0.1586)
Polymyxin	0.9310 (0.0232)	(0.8776, 0.9694)	0.0904 (0.0249)	(0.0462, 0.1437)
Quinolone	0.9277 (0.0234)	(0.8756, 0.9672)	0.1030 (0.0256)	(0.0541, 0.1548)
Rifamycin	0.9248 (0.0259)	(0.8657, 0.9670)	0.0922 (0.0262)	(0.0459, 0.1494)

Table B.21: Summary statistics for parameters p_0 and q_0 for each antimicrobial group for the p-Respiratory Data Set starting from patients' first positive test.

	α		β	
GROUP	$E[\cdot\|\tilde{\mathcal{S}}]$ (s.d.)	95% CI	$E[\cdot\|\tilde{\mathcal{S}}]$ (s.d.)	95% CI
Aminoglycoside	−0.1689 (0.1483)	(−0.5276, 0.0450)	0.0544 (0.0802)	(−0.0740, 0.2395)
Antiseptic	−0.0445 (0.0813)	(−0.2412, 0.0780)	0.0687 (0.0627)	(−0.0251, 0.2206)
Cephalosporin	−0.0451 (0.1866)	(−0.6855, 0.1241)	0.1067 (0.1749)	(−0.0980, 0.6046)
Glycopeptide	0.0187 (0.0444)	(−0.0734, 0.1046)	0.0226 (0.0347)	(−0.0448, 0.0922)
Macrolide	−0.0570 (0.0958)	(−0.3011, 0.0740)	0.0612 (0.0916)	(−0.0690, 0.2939)
Nitroimidazole	−0.0610 (0.1167)	(−0.3551, 0.0877)	0.1159 (0.1096)	(−0.0408, 0.3838)
Oxazolidinone	−0.1751 (0.2405)	(−0.8020, 0.0898)	0.5592 (0.2400)	(0.0492, 0.8966)
Penicillin	−0.3873 (0.3137)	(−0.8942, 0.0760)	0.3067 (0.3211)	(−0.0836, 0.8796)
Polymyxin	−0.5003 (0.2648)	(−0.9127, −0.0022)	0.3606 (0.2170)	(−0.0050, 0.7909)
Quinolone	−0.4246 (0.2192)	(−0.8604, −0.0523)	0.1106 (0.1046)	(−0.0512, 0.3540)
Rifamycin	−0.1538 (0.2007)	(−0.6759, 0.0820)	0.2092 (0.1666)	(−0.0299, 0.6179)

Table B.22: Summary statistics for parameters α and β for each antimicrobial group for the p-Respiratory Data Set starting from patients' first positive test.

	ϕ		ψ	
GROUP	$E[\cdot \mid \tilde{\mathcal{S}}]$ (s.d.)	95% CI	$E[\cdot \mid \tilde{\mathcal{S}}]$ (s.d.)	95% CI
Aminoglycoside	0.8979 (0.0252)	(0.8755, 0.9747)	0.8904 (0.0265)	(0.8442, 0.9501)
Antiseptic	0.9023 (0.0599)	(0.7645, 0.9919)	0.8115 (0.0135)	(0.7767, 0.9396)
Cephalosporin	0.9174 (0.0534)	(0.7947, 0.9950)	0.8233 (0.0185)	(0.7894, 0.9403)
Glycopeptide	0.9111 (0.0524)	(0.7945, 0.9927)	0.8286 (0.0137)	(0.7896, 0.9398)
Macrolide	0.9072 (0.0556)	(0.7836, 0.9930)	0.8208 (0.0151)	(0.7853, 0.9398)
Nitroimidazole	0.9055 (0.0573)	(0.7770, 0.9931)	0.8287 (0.0123)	(0.7823, 0.9397)
Oxazolidinone	0.9065 (0.0561)	(0.7817, 0.9927)	0.8254 (0.0153)	(0.7846, 0.9397)
Penicillin	0.9120 (0.0538)	(0.7923, 0.9938)	0.8220 (0.0164)	(0.7884, 0.9399)
Polymyxin	0.9047 (0.0560)	(0.7798, 0.9919)	0.8201 (0.0126)	(0.7838, 0.9396)
Quinolone	0.9290 (0.0522)	(0.8051, 0.9969)	0.8259 (0.0154)	(0.7932, 0.9409)
Rifamycin	0.9038 (0.0572)	(0.7744, 0.9922)	0.8196 (0.0134)	(0.7815, 0.9396)

Table B.23: Summary statistics for parameters ϕ and ψ for each antimicrobial group for the p-Respiratory Data Set starting from patients' first positive test.

Model Fit							
Day Intervals	**1**	**2**	**3**	**4**	**5**	**6**	**7**
$N \to N$							
obs. counts	**15**	**7**	**9**	**5**	**4**	**5**	**2**
Aminoglycoside	(11, 17)	(6, 12)	(4, 10)	(4, 9)	(2, 7)	(1, 5)	(1, 4)
Antiseptic	(10, 17)	(6, 11)	(5, 10)	(3, 8)	(2, 7)	(1, 5)	(1, 4)
Cephalosporin	(11, 17)	(6, 12)	(5, 10)	(3, 9)	(2, 7)	(1, 5)	(1, 4)
Glycopeptide	(10, 17)	(6, 12)	(5, 11)	(4, 9)	(2, 7)	(1, 5)	(1, 4)
Macrolide	(10, 17)	(6, 12)	(4, 10)	(4, 9)	(2, 7)	(1, 5)	(1, 4)
Nitroimidazole	(11, 17)	(6, 11)	(5, 10)	(3, 9)	(2, 7)	(1, 5)	(1, 4)
Oxazolidinone	(11, 17)	(6, 12)	(5, 11)	(3, 9)	(3, 7)	(1, 5)	(0, 4)
Penicillin	(10, 17)	(6, 12)	(5, 10)	(3, 9)	(2, 7)	(1, 5)	(1, 4)
Polymyxin	(11, 17)	(6, 12)	(5, 11)	(3, 9)	(2, 7)	(1, 5)	(1, 4)
Quinolone	(11, 18)	(6, 11)	(5, 10)	(3, 8)	(2, 7)	(1, 5)	(1, 4)
Rifamycin	(11, 17)	(6, 12)	(5, 11)	(3, 9)	(2, 7)	(1, 5)	(0, 4)
$N \to C$							
obs. counts	**3**	**5**	**2**	**4**	**3**	**0**	**2**
Aminoglycoside	(1, 7)	(0, 6)	(1, 6)	(0, 5)	(0, 5)	(0, 4)	(0, 3)
Antiseptic	(1, 7)	(1, 6)	(1, 6)	(1, 5)	(0, 5)	(0, 4)	(0, 3)
Cephalosporin	(1, 7)	(0, 6)	(1, 6)	(0, 5)	(0, 5)	(0, 4)	(0, 3)
Glycopeptide	(1, 7)	(0, 5)	(0, 6)	(0, 5)	(0, 5)	(0, 4)	(0, 3)
Macrolide	(1, 8)	(0, 6)	(1, 6)	(0, 5)	(0, 5)	(0, 4)	(0, 3)
Nitroimidazole	(1, 7)	(1, 6)	(0, 6)	(0, 5)	(0, 5)	(0, 4)	(0, 3)
Oxazolidinone	(1, 7)	(0, 6)	(0, 6)	(0, 5)	(0, 4)	(0, 4)	(0, 4)
Penicillin	(1, 7)	(0, 6)	(0, 6)	(0, 5)	(0, 5)	(0, 4)	(0, 3)
Polymyxin	(1, 7)	(0, 6)	(0, 6)	(0, 6)	(0, 5)	(0, 4)	(0, 3)
Quinolone	(0, 7)	(0, 5)	(1, 6)	(1, 6)	(0, 5)	(0, 4)	(0, 3)
Rifamycin	(1, 7)	(0, 6)	(0, 6)	(0, 5)	(0, 5)	(0, 4)	(0, 3)
$C \to N$							
obs. counts	**5**	**3**	**10**	**12**	**4**	**6**	**7**
Aminoglycoside	(3, 12)	(3, 12)	(3, 13)	(5, 14)	(3, 10)	(4, 12)	(3, 10)
Antiseptic	(3, 12)	(3, 13)	(4, 13)	(5, 15)	(2, 10)	(4, 12)	(3, 10)
Cephalosporin	(2, 12)	(4, 12)	(4, 13)	(5, 15)	(3, 9)	(4, 12)	(3, 10)
Glycopeptide	(3, 11)	(3, 12)	(4, 13)	(5, 15)	(2, 9)	(4, 12)	(3, 10)
Macrolide	(3, 12)	(3, 12)	(4, 13)	(4, 14)	(2, 9)	(4, 12)	(3, 10)
Nitroimidazole	(2, 11)	(4, 12)	(5, 13)	(5, 15)	(3, 10)	(3, 12)	(3, 10)
Oxazolidinone	(3, 12)	(3, 12)	(4, 13)	(4, 14)	(2, 10)	(3, 12)	(3, 10)
Penicillin	(2, 12)	(4, 13)	(5, 13)	(5, 14)	(2, 9)	(4, 12)	(3, 10)
Polymyxin	(3, 12)	(3, 12)	(4, 12)	(5, 14)	(2, 9)	(4, 12)	(3, 10)
Quinolone	(2, 12)	(3, 12)	(3, 13)	(4, 14)	(2, 9)	(3, 12)	(3, 10)
Rifamycin	(2, 12)	(3, 13)	(4, 13)	(5, 14)	(2, 9)	(4, 12)	(3, 10)
$C \to C$							
obs. counts	**33**	**26**	**16**	**14**	**10**	**12**	**7**
Aminoglycoside	(26, 35)	(17, 26)	(13, 22)	(12, 21)	(4, 11)	(5, 13)	(3, 11)
Antiseptic	(25, 35)	(16, 26)	(13, 22)	(11, 21)	(4, 12)	(6, 14)	(4, 11)
Cephalosporin	(25, 35)	(16, 25)	(13, 22)	(11, 21)	(4, 11)	(6, 14)	(4, 11)
Glycopeptide	(27, 35)	(17, 26)	(12, 22)	(11, 21)	(5, 12)	(6, 14)	(4, 11)
Macrolide	(26, 35)	(17, 26)	(13, 22)	(12, 21)	(5, 11)	(6, 14)	(4, 11)
Nitroimidazole	(26, 35)	(17, 25)	(12, 21)	(11, 21)	(4, 11)	(6, 14)	(3, 11)
Oxazolidinone	(26, 35)	(17, 26)	(13, 22)	(12, 22)	(4, 12)	(6, 15)	(4, 11)
Penicillin	(26, 35)	(16, 25)	(13, 21)	(11, 21)	(5, 12)	(6, 14)	(4, 11)
Polymyxin	(26, 35)	(17, 26)	(13, 22)	(12, 21)	(5, 12)	(6, 14)	(4, 11)
Quinolone	(26, 36)	(17, 26)	(12, 22)	(12, 22)	(5, 12)	(6, 15)	(4, 11)
Rifamycin	(26, 35)	(16, 26)	(13, 22)	(12, 20)	(5, 12)	(5, 14)	(4, 11)

Table B.24: Model fit for each antimicrobial treatment group of the p-Respiratory Data Set starting from patients' first positive test. The intervals in red indicate that the observed transition counts are included in the equal-tailed 95% quantiles.

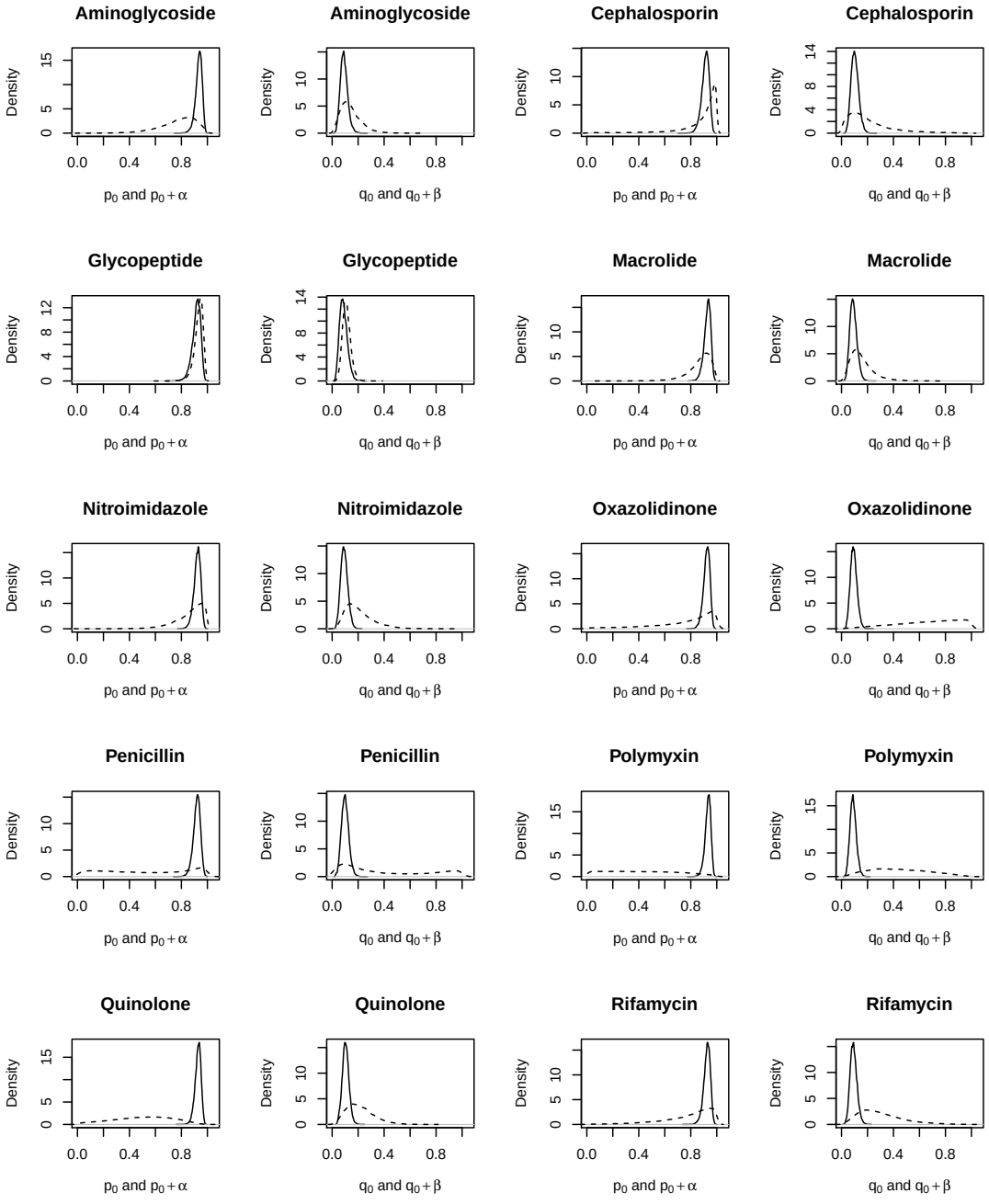

Figure B.11: Kernel density plots for p_0, $p_0 + \alpha$, q_0 and $q_0 + \beta$ for the antibiotics for the p-Respiratory Data Set starting from patients' first positive test. The continuous line shows the probabilities p_0 and q_0 whereas the dashed line shows the probabilities $p_0 + \alpha$ and $q_0 + \beta$.

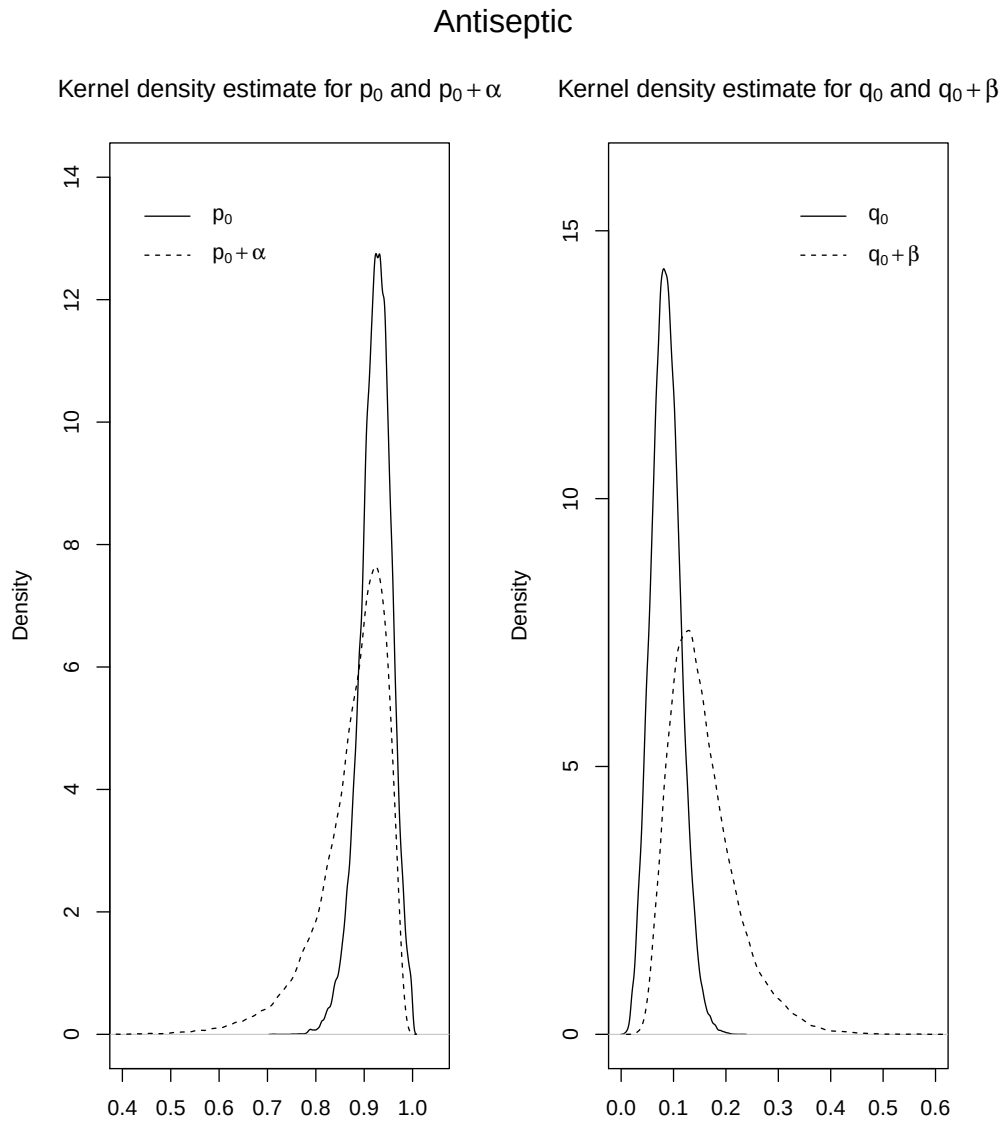

Figure B.12: Kernel density plots for p_0, $p_0 + \alpha$, q_0 and $q_0 + \beta$ for the antiseptic for the p-Respiratory Data Set starting from patients' first positive test. The continuous line shows the probabilities p_0 and q_0 whereas the dashed line shows the probabilities $p_0 + \alpha$ and $q_0 + \beta$.

APPENDIX C

Appendix Transmission Models

C.1 Simulation

Simulation results using the values obtained from the MRSA Data Set without taking into account antimicrobial treatment information, i.e. $\beta_0 = 0.0011$, $\beta_1 = 0.0021$, $\phi = 0.5522$ and $z = 0.1570$.

No antimicrobial treatment		
	Ward 1	
parameters	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
$\boldsymbol{\beta_0}$	0.0025 (0.0015)	(0.0001, 0.0059)
$\boldsymbol{\beta_1}$	0.0009 (0.0005)	(0.00008, 0.0020)
$\boldsymbol{\beta_0}$, $\boldsymbol{\beta_1}$ **posterior correlation**	-0.6081	
$\boldsymbol{\phi}$	0.5009 (0.0277)	(0.4473, 0.5551)
$\mathbf{z}$	0.1732 (0.0142)	(0.1471, 0.2025)

Table C.1: Summary statistics for the transition rates β_0, β_1 sensitivity ϕ and importation probability z from the simulated data using the data-structure of the MRSA Data Set, ward 1.

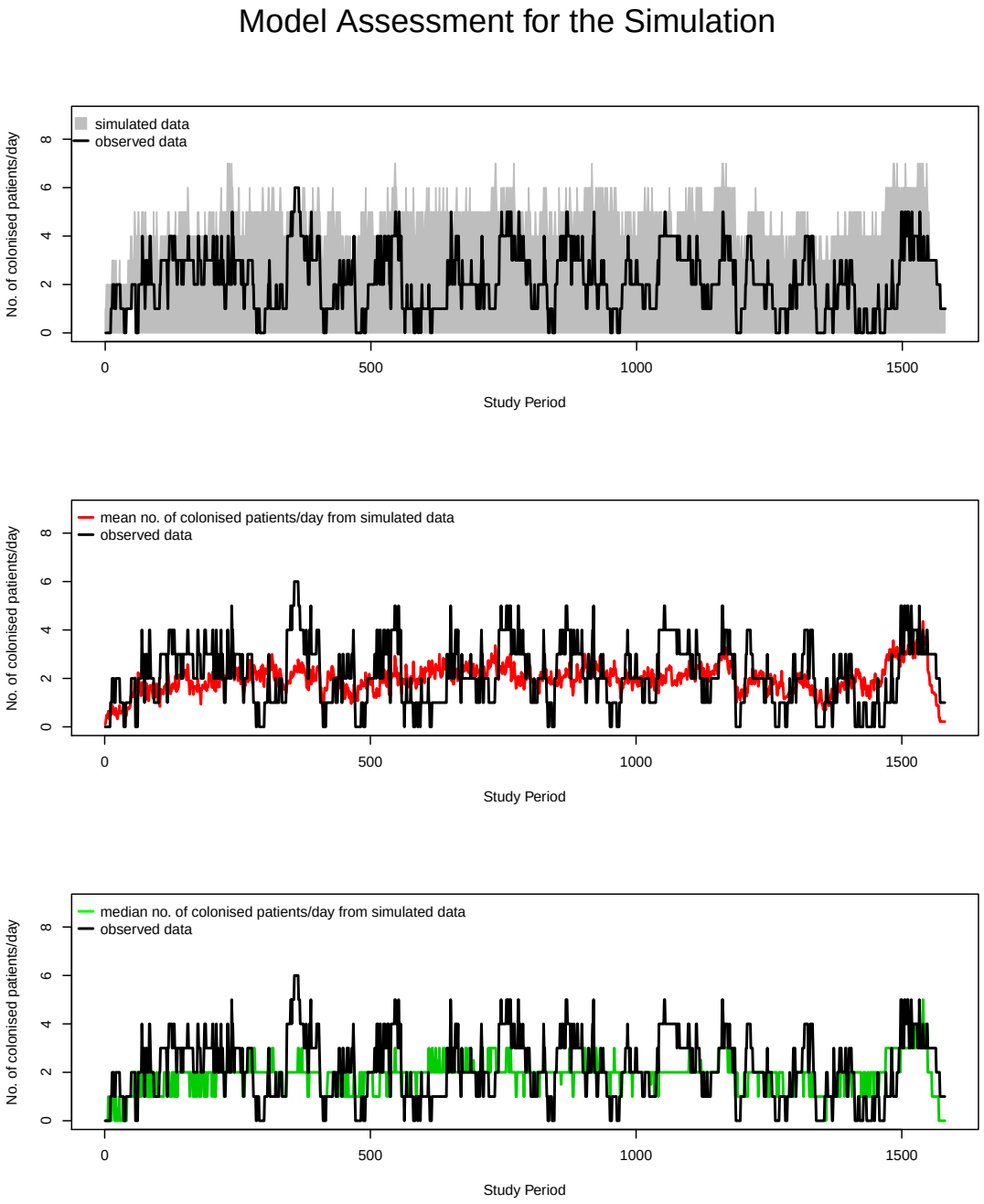

Figure C.1: Assessment for the simulated data assuming no antimicrobial treatment. The first line shows the 95% quantile (grey area) of the number of colonised patients from the model fit simulations data compared to the observed number of colonised patients (black line). The Second line shows the mean number of colonised patients (red line) from the simulations compared to the observed number of colonised patients (black line). The third line shows the median of the number of colonised patients (green line) from the simulations compared to the observed number of colonised patients (black line).

Simulation generated by the values $\beta_0 = 0.003$, $\beta_1 = 0.005$, $\phi = 0.75$ and $z = 0.008$.

No antimicrobial treatment		
	Ward 1	
parameters	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
$\boldsymbol{\beta_0}$	0.0039 (0.0021)	(0.0004, 0.0086)
$\boldsymbol{\beta_1}$	0.0051 (0.0007)	(0.0036, 0.0066)
$\boldsymbol{\beta_0}$, $\boldsymbol{\beta_1}$ **posterior correlation**	-0.5289	
$\boldsymbol{\phi}$	0.7568 (0.0195)	(0.7170, 0.7938)
$\mathbf{z}$	0.0791 (0.0089)	(0.0630, 0.0984)

Table C.2: Summary statistics for the transition rates β_0, β_1 sensitivity ϕ and importation probability z from the simulated data using the data-structure of the MRSA Data Set, ward 1 , when random values were set for their generation.

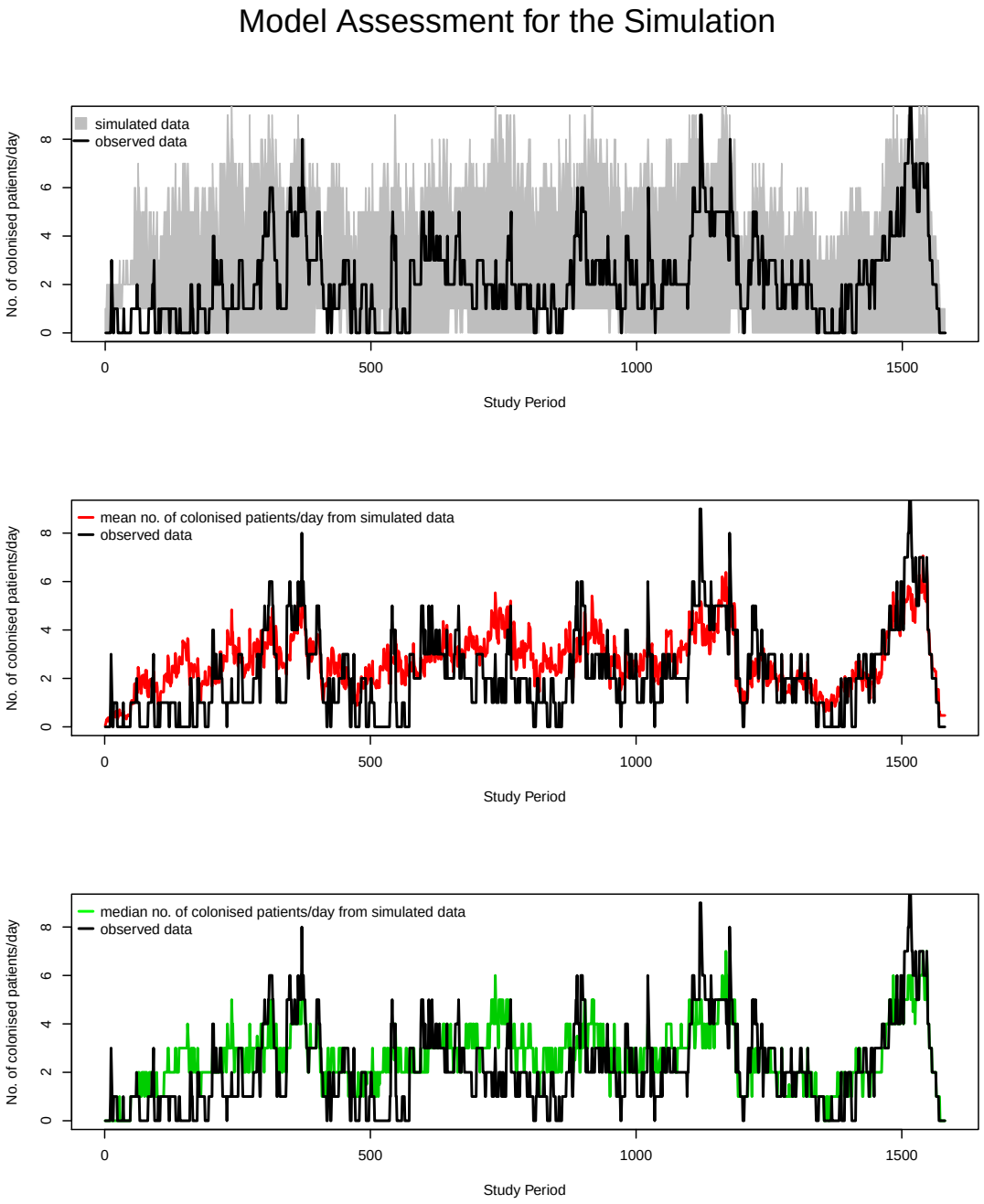

Figure C.2: Assessment for the simulated data, when random values were set for their generation, assuming no antimicrobial treatment. The first line shows the 95% quantile (grey area) of the number of colonised patients from the model fit simulations data compared to the observed number of colonised patients (black line). The Second line shows the mean number of colonised patients (red line) from the simulations compared to the observed number of colonised patients (black line). The third line shows the median of the number of colonised patients (green line) from the simulations compared to the observed number of colonised patients (black line).

C.2 MRSA Data Set

C.2.1 *Susceptibility Model*

$\log(\beta_0/\tilde{\beta}_0)$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	$-1.0223(1.7685)$	$(-4.6066, 2.6180)$	$-0.7048(1.6999)$	$(-4.1818, 2.8038)$
Antiseptic	$2.7374(1.4937)$	$(-0.0329, 6.0085)$	$1.0417(1.5666)$	$(-2.1879, 4.2422)$
Cephalosporin	$-1.1123(1.7399)$	$(-4.6668, 2.4146)$	$-0.5699(1.7293)$	$(-4.0103, 3.0019)$
Glycopeptide	$-0.6703(1.7253)$	$(-4.1736, 2.8758)$	$-0.5955(1.7527)$	$(-4.1113, 3.0290)$
Macrolide	$-2.4592(1.5603)$	$(-5.7615, 0.6429)$	$-1.5807(1.6830)$	$(-5.0326, 1.8396)$
Nitroimidazole	$-1.3739(1.7160)$	$(-4.8726, 2.1354)$	$-1.3633(1.7586)$	$(-4.9209, 2.2115)$
Oxazolidinone	$-2.8535(1.7760)$	$(-6.4361, 0.7522)$	$-4.1455(1.7958)$	$(-7.8527, -0.4902)$
Penicillin	$-0.9387(1.7322)$	$(-4.4394, 2.6367)$	$-1.5177(1.6913)$	$(-4.9756, 1.9068)$
Polymyxin	$-3.5102(1.7374)$	$(-7.0696, -0.0108)$	$-3.1431(1.6909)$	$(-6.6249, 0.3094)$
Quinolone	$-3.3249(1.6085)$	$(-6.7084, -0.0948)$	$-3.2701(1.6641)$	$(-6.7472, 0.0763)$
Rifamycin	$2.5372(1.5539)$	$(-0.4612, 5.8957)$	$-4.1743(1.7701)$	$(-7.7350, -0.5409)$

Table C.3: Summary statistics for parameters β_0 and $\tilde{\beta}_0$ for each antimicrobial group for the *Susceptibility Model*, for the MRSA Data Set.

$\log(\beta_1/\tilde{\beta}_1)$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	$0.7564(1.1885)$	$(-0.9583, 3.6654)$	$0.6781(1.0924)$	$(-0.9004, 3.3893)$
Antiseptic	$2.4933(1.3532)$	$(0.1208, 5.5835)$	$1.9721(1.0558)$	$(0.3371, 4.5754)$
Cephalosporin	$-0.1836(1.0215)$	$(-1.7420, 2.3219)$	$-0.4977(0.8640)$	$(-2.0564, 1.3743)$
Glycopeptide	$-0.5722(0.8471)$	$(-2.0607, 1.2679)$	$-0.1817(0.9083)$	$(-1.7691, 1.8375)$
Macrolide	$0.0467(1.0940)$	$(-1.5047, 2.7608)$	$0.5136(1.1291)$	$(-1.0936, 3.3158)$
Nitroimidazole	$-0.4479(0.9419)$	$(-1.8228, 1.9404)$	$-1.1419(0.7878)$	$(-2.6009, 0.5820)$
Oxazolidinone	$-0.5770(1.3166)$	$(-2.5745, 2.5845)$	$-1.2130(1.4568)$	$(-3.4707, 2.1570)$
Penicillin	$0.5330(1.2238)$	$(-1.2938, 3.4977)$	$0.3640(1.1970)$	$(-1.3688, 3.3182)$
Polymyxin	$-0.7566(1.2422)$	$(-2.6162, 2.2614)$	$-0.8705(1.2076)$	$(-2.6102, 2.1074)$
Quinolone	$-0.8154(1.1422)$	$(-2.4757, 1.9935)$	$-1.5553(1.0048)$	$(-3.0316, 0.9460)$
Rifamycin	$2.6411(1.3277)$	$(0.4789, 5.7057)$	$-1.5424(1.2867)$	$(-3.5111, 1.5170)$

Table C.4: Summary statistics for parameters β_1 and $\tilde{\beta}_1$ for each antimicrobial group for the *Susceptibility Model*, for the MRSA Data Set.

ϕ				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	0.5512(0.0253)	(0.5016, 0.6008)	0.4784(0.0245)	(0.4314, 0.5263)
Antiseptic	0.5585(0.0251)	(0.5093, 0.6073)	0.4785(0.0255)	(0.4295, 0.5288)
Cephalosporin	0.5553(0.0239)	(0.5084, 0.6018)	0.4816(0.0253)	(0.4325, 0.5315)
Glycopeptide	0.5549(0.0260)	(0.5049, 0.6064)	0.4806(0.0283)	(0.4200, 0.5321)
Macrolide	0.5565(0.0260)	(0.5032, 0.6059)	0.4802(0.0253)	(0.4317, 0.5294)
Nitroimidazole	0.5567(0.0247)	(0.5075, 0.6044)	0.4730(0.0272)	(0.4176, 0.5246)
Oxazolidinone	0.5558(0.0250)	(0.5070, 0.6053)	0.4645(0.0243)	(0.4149, 0.5100)
Penicillin	0.5562(0.0251)	(0.5077, 0.6060)	0.4733(0.0258)	(0.4249, 0.5254)
Polymyxin	0.5546(0.0257)	(0.5035, 0.6045)	0.4811(0.0234)	(0.4357, 0.5276)
Quinolone	0.5534(0.0265)	(0.5014, 0.6059)	0.4785(0.0241)	(0.4307, 0.5250)
Rifamycin	0.5581(0.0234)	(0.5129, 0.6043)	0.4763(0.0241)	(0.4298, 0.5245)

Table C.5: Summary statistics for parameter ϕ for each antimicrobial group for the *Susceptibility Model*, for the MRSA Data Set.

$\mathbf{z}$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	0.1580(0.0141)	(0.1316, 0.1871)	0.1647(0.0134)	(0.1396, 0.1915)
Antiseptic	0.1470(0.0127)	(0.1235, 0.1728)	0.1559(0.0143)	(0.1291, 0.1852)
Cephalosporin	0.1542(0.0127)	(0.1307, 0.1805)	0.1607(0.0155)	(0.1303, 0.1912)
Glycopeptide	0.1562(0.0139)	(0.1294, 0.1836)	0.1631(0.0174)	(0.1345, 0.2050)
Macrolide	0.1539(0.0140)	(0.1289, 0.1850)	0.1635(0.0150)	(0.1357, 0.1937)
Nitroimidazole	0.1534(0.0133)	(0.1293, 0.1813)	0.1636(0.0164)	(0.1353, 0.1996)
Oxazolidinone	0.1542(0.0130)	(0.1295, 0.1800)	0.1728(0.0145)	(0.1471, 0.2048)
Penicillin	0.1535(0.0133)	(0.1276, 0.1793)	0.1675(0.0151)	(0.1394, 0.1982)
Polymyxin	0.1560(0.0137)	(0.1311, 0.1849)	0.1630(0.0134)	(0.1364, 0.1894)
Quinolone	0.1557(0.0148)	(0.128, 0.1863)	0.1654(0.0138)	(0.1401, 0.1945)
Rifamycin	0.1471(0.0125)	(0.123, 0.172)	0.1663(0.0140)	(0.1388, 0.1934)

Table C.6: Summary statistics for parameter z for each antimicrobial group for the *Susceptibility Model*, for the MRSA Data Set.

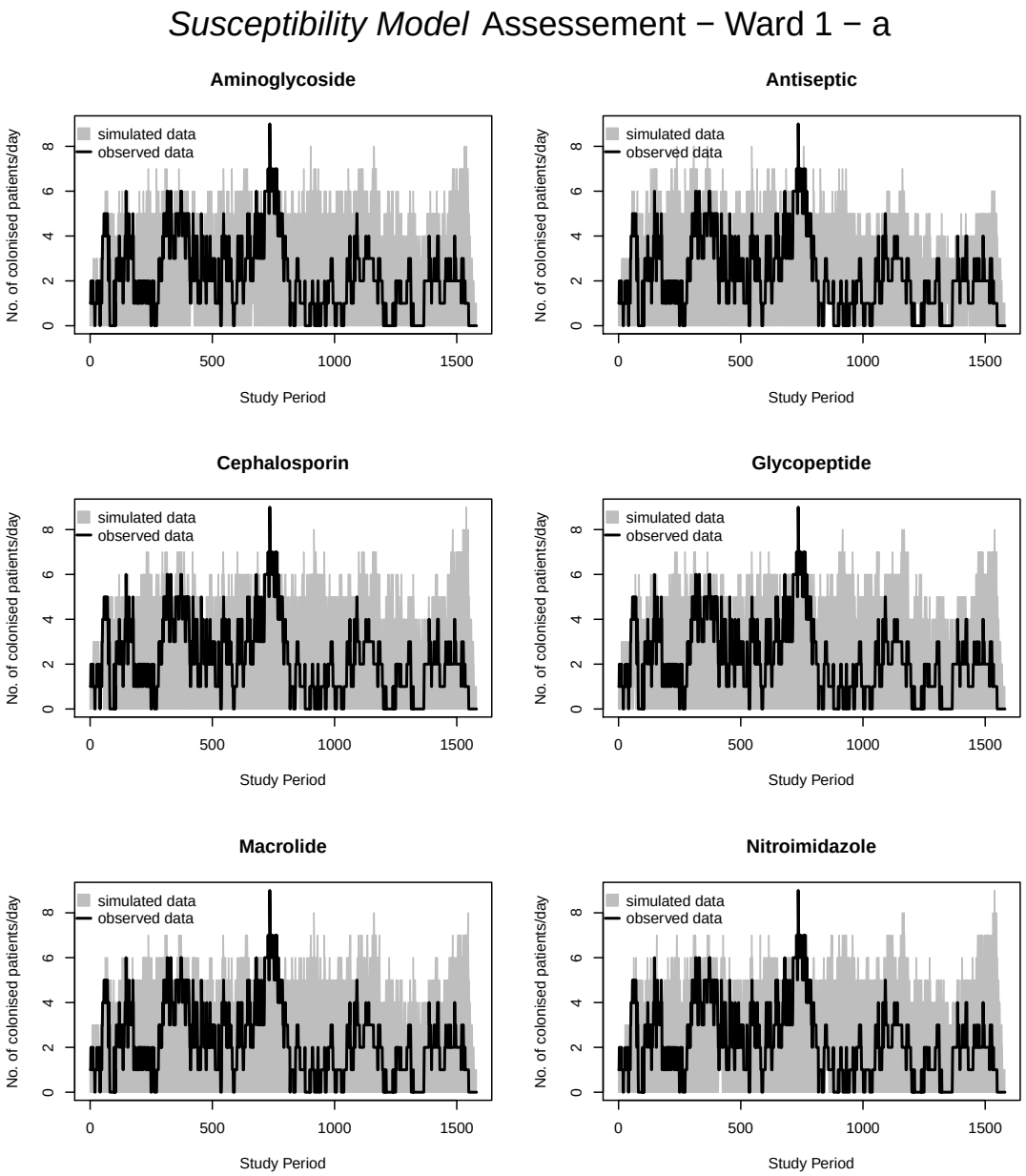

Figure C.3: Plots showing the *Susceptibility Model* assessement for the first 6 of the antimicrobials of ward 1, for the MRSA Data Set.

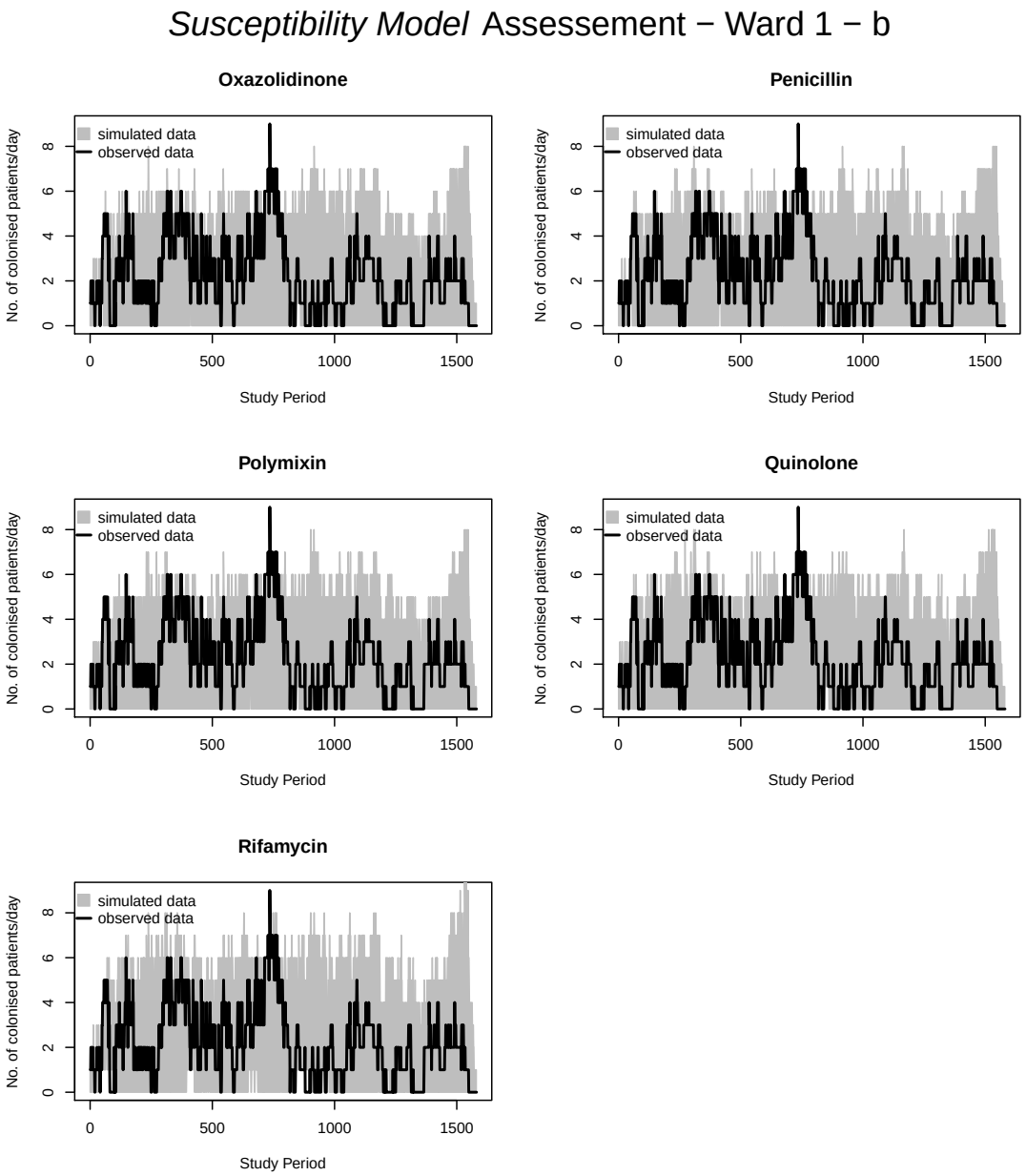

Figure C.4: Plots showing the *Susceptibility Model* assessement for the next 5 of the antimicrobials of ward 1, for the MRSA Data Set.

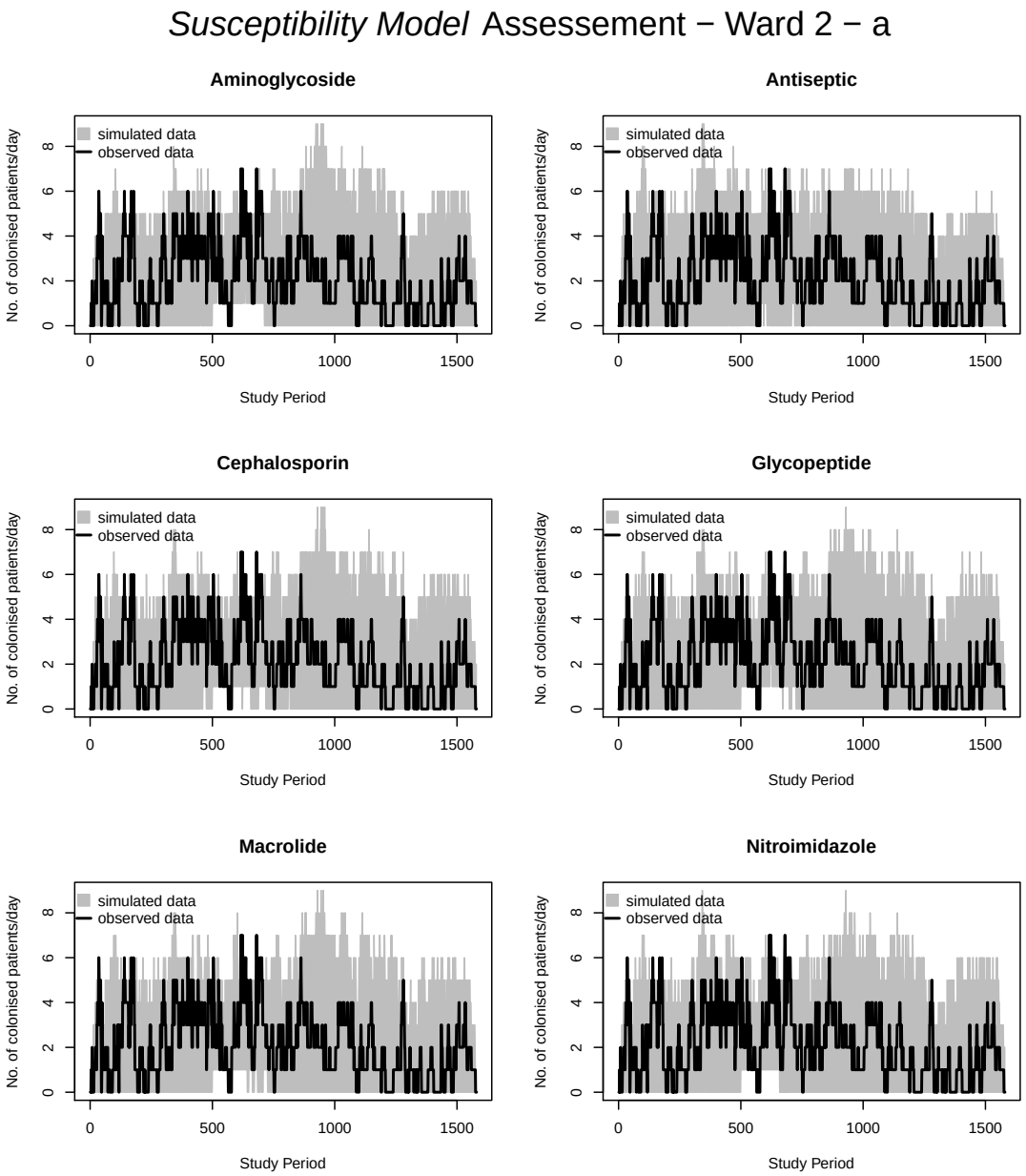

Figure C.5: Plots showing the *Susceptibility Model* assessement for the first 6 of the antimicrobials of ward 2, for the MRSA Data Set.

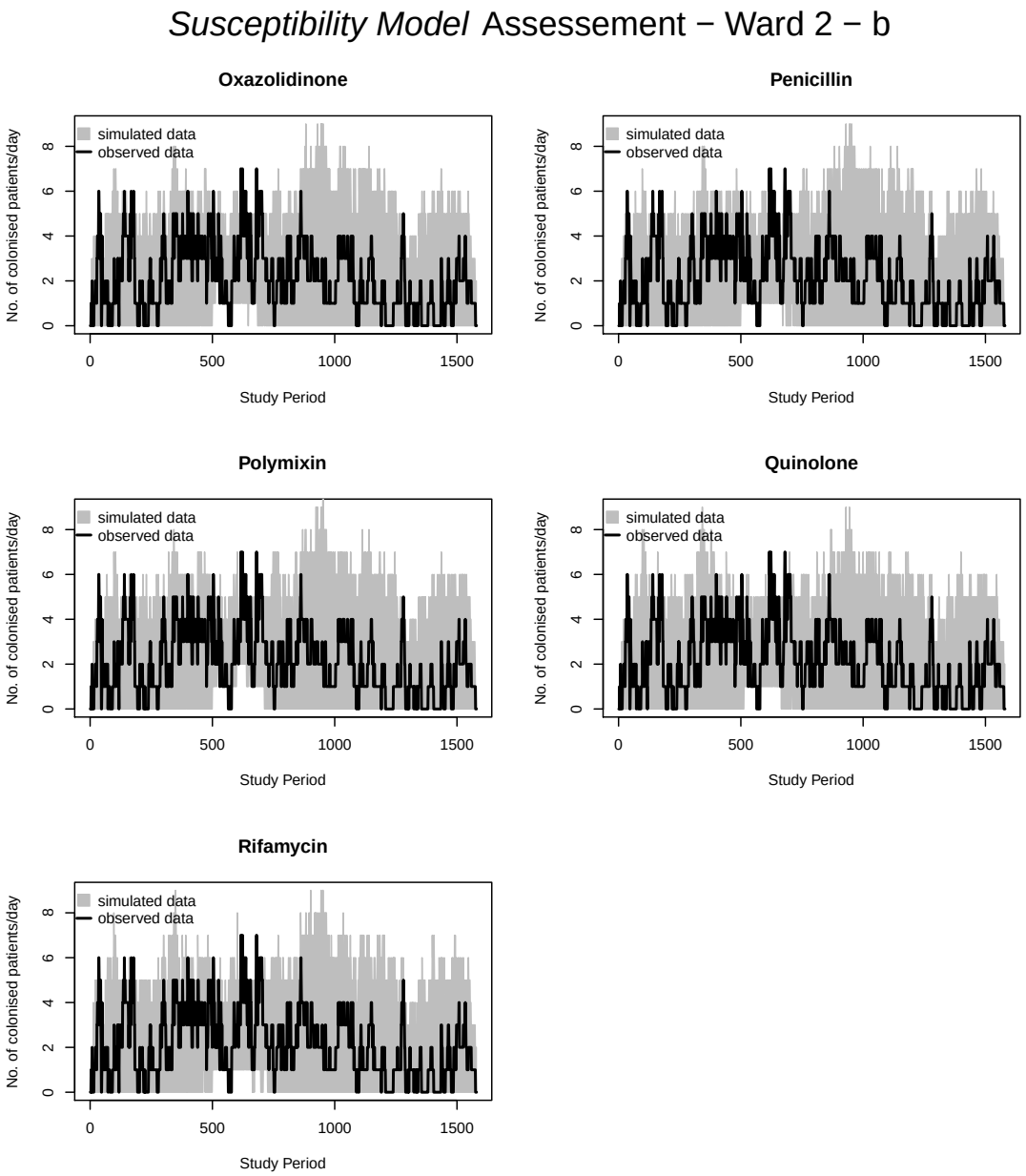

Figure C.6: Plots showing the *Susceptibility Model* assessement for the next 5 of the antimicrobials of ward 2, for the MRSA Data Set.

C.2.2 *Infectivity Model*

β_0				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	0.0009(0.0008)	(0.0000, 0.0030)	0.0014(0.0012)	(0.0000, 0.0046)
Antiseptic	0.0007(0.0006)	(0.0000, 0.0022)	0.0009(0.0007)	(0.0000, 0.0026)
Cephalosporin	0.0009(0.0008)	(0.0000, 0.0030)	0.0015(0.0013)	(0.0000, 0.0047)
Glycopeptide	0.0010(0.0009)	(0.0000, 0.0032)	0.0014(0.0011)	(0.0000, 0.0043)
Macrolide	0.0010(0.0008)	(0.0000, 0.0031)	0.0016(0.0012)	(0.0001, 0.0045)
Nitroimidazole	0.0010(0.0009)	(0.0000, 0.0033)	0.0013(0.0011)	(0.0000, 0.0042)
Oxazolidinone	0.0010(0.0009)	(0.0000, 0.0032)	0.0014(0.0012)	(0.0000, 0.0044)
Penicillin	0.0010(0.0009)	(0.0000, 0.0034)	0.0013(0.0011)	(0.0000, 0.0040)
Polymyxin	0.0009(0.0008)	(0.0000, 0.0031)	0.0012(0.0010)	(0.0000, 0.0038)
Quinolone	0.0010(0.0009)	(0.0000, 0.0034)	0.0013(0.0012)	(0.0000, 0.0043)
Rifamycin	0.0010(0.0009)	(0.0000, 0.0033)	0.0013(0.0012)	(0.0000, 0.0044)

Table C.7: Summary statistics for parameters β_0 for each antimicrobial group for the *Infectivity Model*, for the MRSA Data Set.

$\log(\beta_1/\beta_1^{'})$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	0.0043(1.2181)	$(-1.8166, 2.9772)$	$-0.7521(1.2489)$	$(-2.7962, 2.1884)$
Antiseptic	3.0329(1.2216)	(1.2548, 6.0426)	3.2235(1.1760)	(1.3791, 5.9960)
Cephalosporin	$-1.3987(1.0307)$	$(-3.1936, 0.8609)$	0.1598(1.2496)	$(-1.7460, 3.1932)$
Glycopeptide	$-1.8073(1.2085)$	$(-4.5946, 0.2988)$	$-1.7135(1.0505)$	$(-4.1153, 0.1089)$
Macrolide	$-1.8804(0.9369)$	$(-3.8726, -0.1676)$	$-2.8436(1.0470)$	$(-5.3755, -1.1979)$
Nitroimidazole	$-0.8276(1.2017)$	$(-2.7411, 1.9800)$	$-1.7093(1.0382)$	$(-3.8493, 0.3769)$
Oxazolidinone	0.4938(1.2955)	$(-1.4434, 3.6147)$	$-0.7399(1.2871)$	$(-2.7046, 2.3088)$
Penicillin	$-0.2430(1.2650)$	$(-2.1451, 2.7841)$	$-1.5024(0.9395)$	$(-2.9534, 0.7562)$
Polymyxin	$-1.2452(1.1885)$	$(-2.9589, 1.7023)$	$-2.1536(1.0140)$	$(-3.5907, 0.3943)$
Quinolone	$-1.4568(1.1042)$	$(-3.2547, 1.1724)$	$-0.5420(1.1830)$	$(-2.2883, 2.3641)$
Rifamycin	$-2.0195(1.0138)$	$(-3.6101, 0.3986)$	$-1.1696(1.2317)$	$(-2.9397, 1.8284)$

Table C.8: Summary statistics for parameters β_1 and $\beta_1^{'}$ for each antimicrobial group for the *Infectivity Model*, for the MRSA Data Set.

ϕ				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	0.5554(0.0249)	(0.5071, 0.6042)	0.4790(0.0245)	(0.4309, 0.5278)
Antiseptic	0.5584(0.0239)	(0.5108, 0.6043)	0.4808(0.0251)	(0.4317, 0.5296)
Cephalosporin	0.5583(0.0252)	(0.5083, 0.6067)	0.4766(0.0262)	(0.4264, 0.5287)
Glycopeptide	0.5556(0.0241)	(0.5087, 0.6028)	0.4771(0.0254)	(0.4253, 0.5253)
Macrolide	0.5488(0.0253)	(0.4960, 0.5971)	0.4763(0.0266)	(0.4237, 0.5274)
Nitroimidazole	0.5539(0.0256)	(0.5042, 0.6044)	0.4804(0.0247)	(0.4323, 0.5282)
Oxazolidinone	0.5508(0.0244)	(0.5023, 0.5985)	0.4793(0.0265)	(0.4255, 0.5290)
Penicillin	0.5528(0.0248)	(0.5032, 0.6004)	0.4768(0.0268)	(0.4220, 0.5280)
Polymyxin	0.5529(0.0250)	(0.5042, 0.6018)	0.4711(0.0230)	(0.4263, 0.5160)
Quinolone	0.5498(0.0234)	(0.5034, 0.5952)	0.4821(0.0255)	(0.4323, 0.5313)
Rifamycin	0.5488(0.0259)	(0.4988, 0.6000)	0.4797(0.0268)	(0.4253, 0.5301)

Table C.9: Summary statistics for parameter ϕ for each antimicrobial group for the *Infectivity Model*, for the MRSA Data Set.

$\mathbf{z}$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	0.1551(0.0137)	(0.1291, 0.1823)	0.1652(0.0150)	(0.1359, 0.1948)
Antiseptic	0.1504(0.0122)	(0.1273, 0.1755)	0.1551(0.0142)	(0.1289, 0.1840)
Cephalosporin	0.1536(0.0142)	(0.1281, 0.1832)	0.1662(0.0152)	(0.1380, 0.1961)
Glycopeptide	0.1556(0.0126)	(0.1317, 0.1811)	0.1660(0.0140)	(0.1400, 0.1949)
Macrolide	0.1586(0.0138)	(0.1338, 0.1896)	0.1647(0.0165)	(0.1359, 0.1987)
Nitroimidazole	0.1549(0.0133)	(0.1299, 0.1818)	0.1611(0.0141)	(0.1345, 0.1896)
Oxazolidinone	0.1574(0.0127)	(0.1337, 0.1837)	0.1638(0.0160)	(0.1349, 0.1973)
Penicillin	0.1565(0.0135)	(0.1316, 0.1851)	0.1667(0.0160)	(0.1390, 0.2034)
Polymyxin	0.1572(0.0140)	(0.1303, 0.1851)	0.1721(0.0134)	(0.1470, 0.1988)
Quinolone	0.1588(0.0118)	(0.1365, 0.1827)	0.1614(0.0151)	(0.1336, 0.1923)
Rifamycin	0.1592(0.0141)	(0.1323, 0.1871)	0.1644(0.0161)	(0.1359, 0.1992)

Table C.10: Summary statistics for parameter z for each antimicrobial group for the *Infectivity Model*, for the MRSA Data Set.

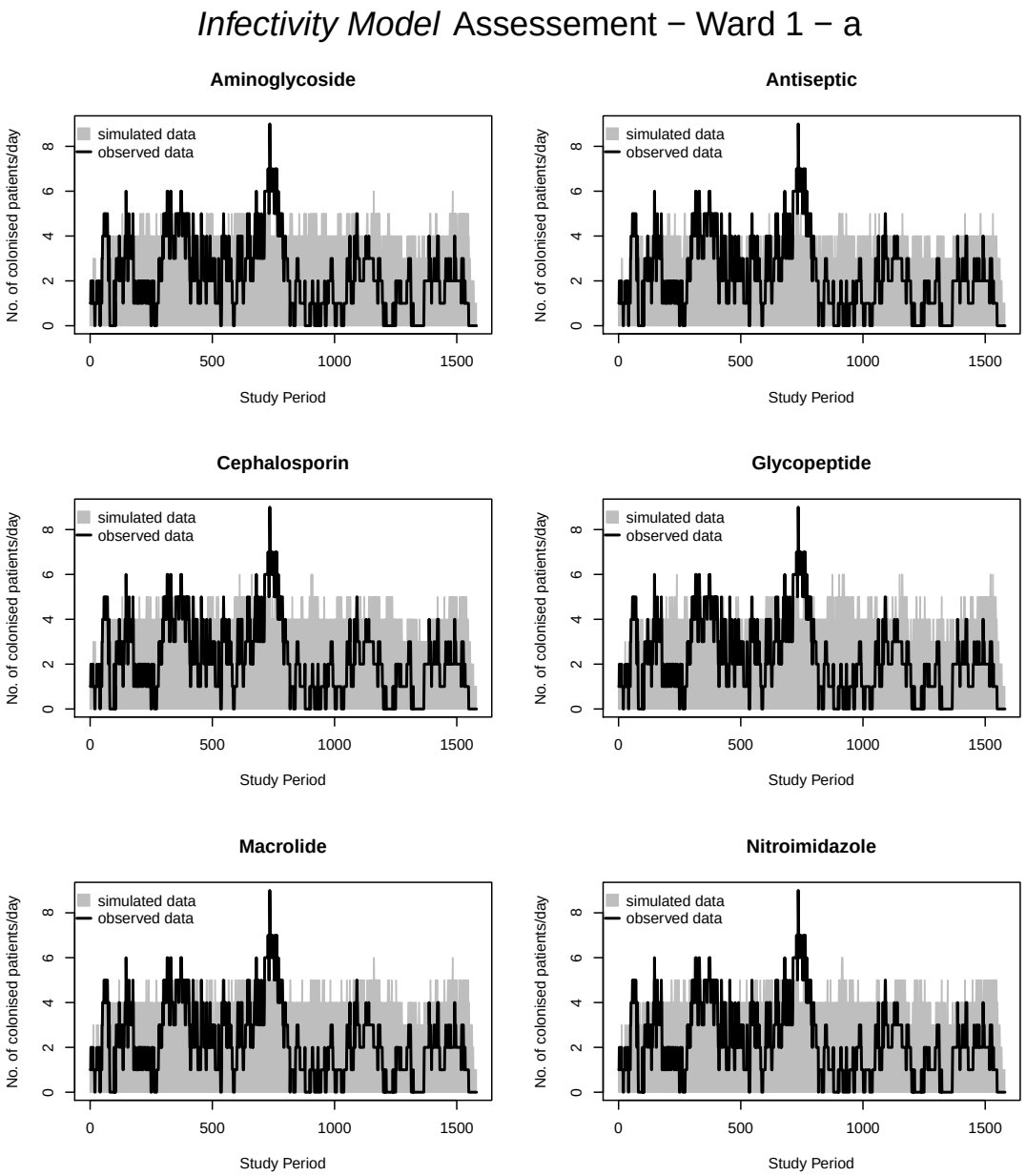

Figure C.7: Plots showing the *Infectivity Model* assessement for the first 6 of the antimicrobials of ward 1, for the MRSA Data Set.

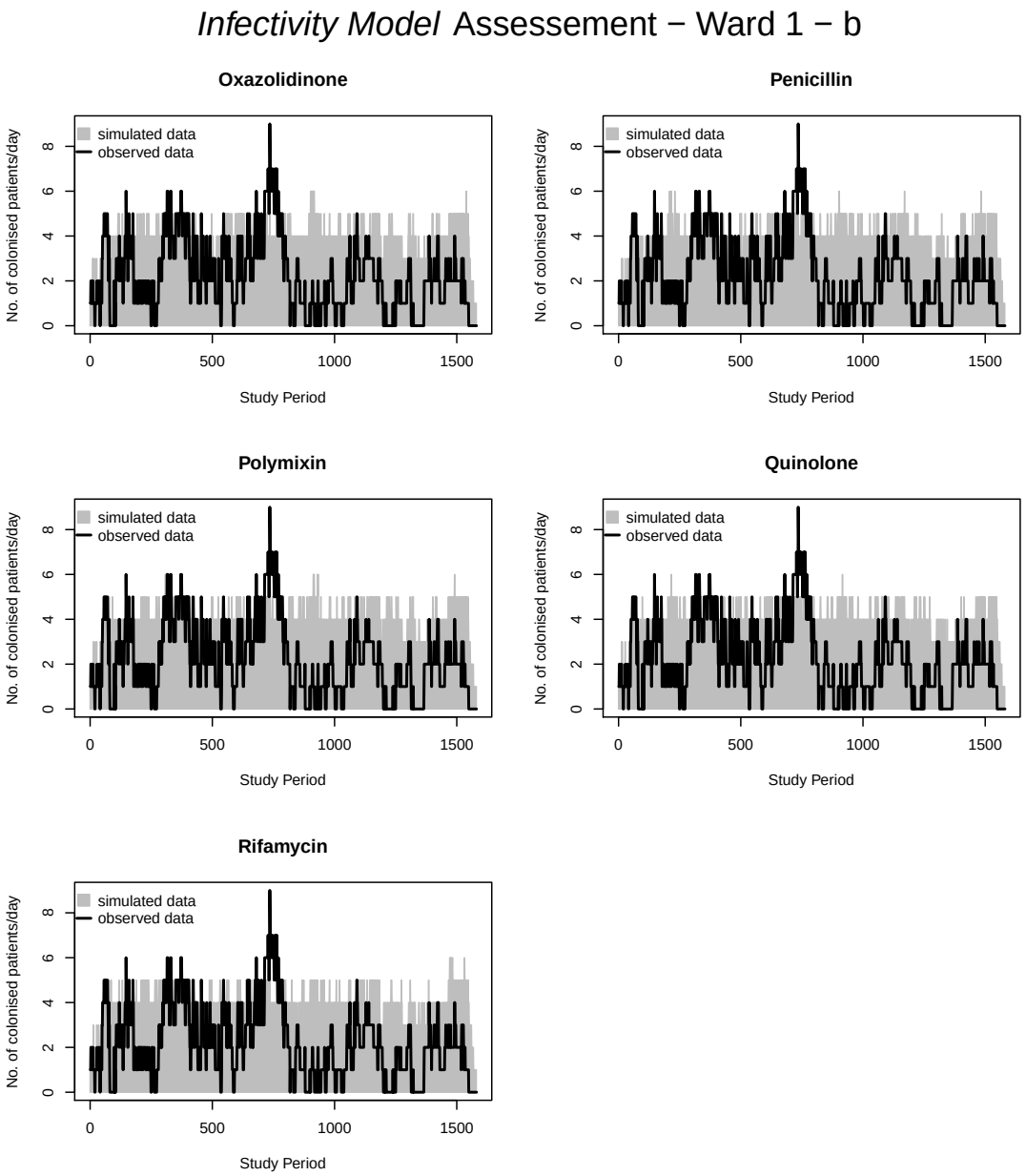

Figure C.8: Plots showing the *Infectivity Model* assessement for the next 5 of the antimicrobials of ward 1, for the MRSA Data Set.

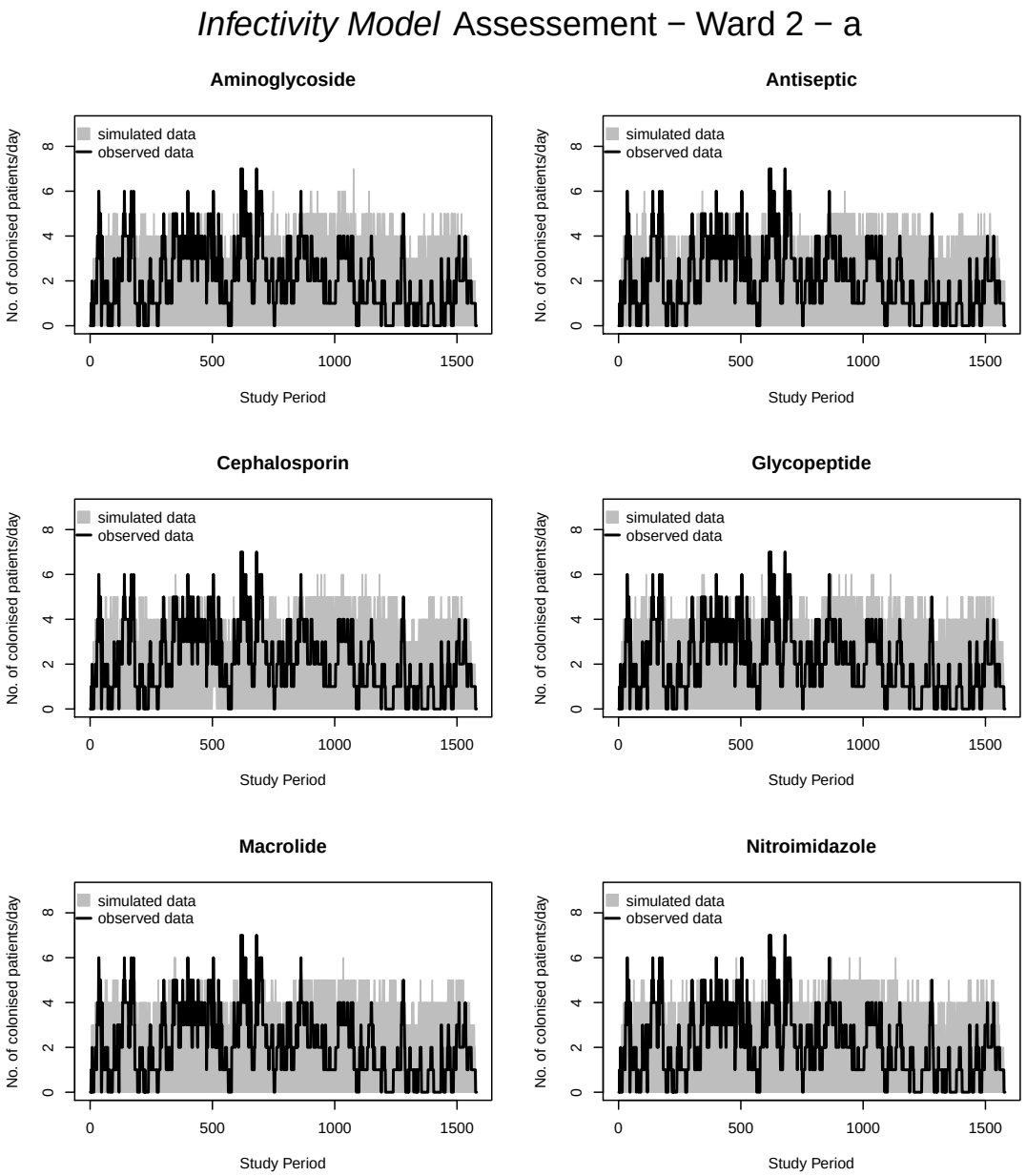

Figure C.9: Plots showing the *Infectivity Model* assessement for the first 6 of the antimicrobials of ward 2, for the MRSA Data Set.

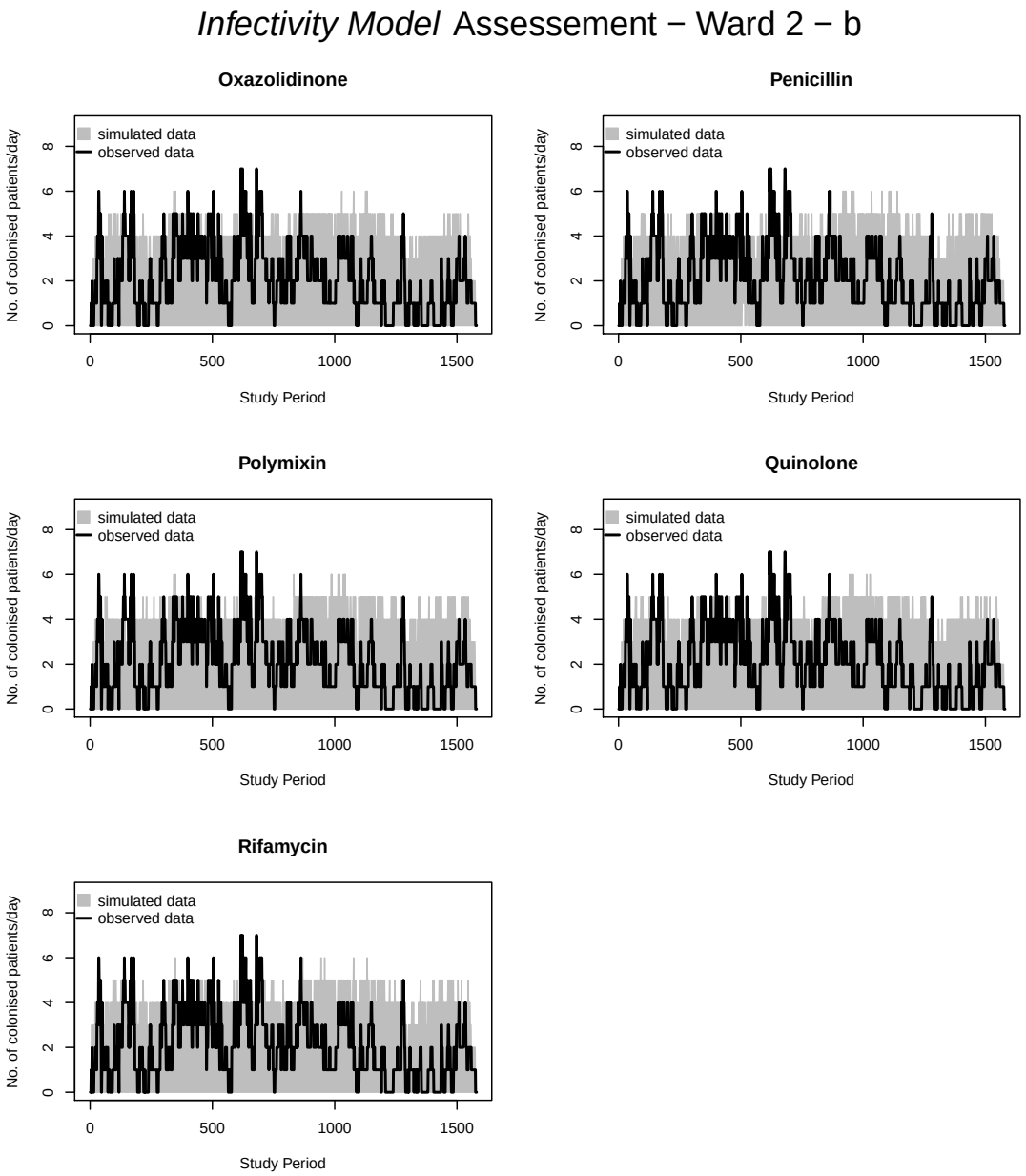

Figure C.10: Plots showing the *Infectivity Model* assessement for the next 5 of the antimicrobials of ward 2, for the MRSA Data Set.

C.2.3 *Full Model*

$\log(\beta_0/\tilde{\beta}_0)$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	$-0.7792(1.7416)$	$(-4.417, 2.7697)$	$-0.5499(1.7113)$	$(-4.0487, 2.9213)$
Antiseptic	$2.6298(1.5385)$	$(-0.3912, 5.921)$	$1.0744(1.6752)$	$(-2.3297, 4.5004)$
Cephalosporin	$-0.9576(1.7475)$	$(-4.5343, 2.5707)$	$-0.7503(1.7724)$	$(-4.3395, 2.8764)$
Glycopeptide	$-0.8868(1.7029)$	$(-4.3231, 2.5876)$	$-0.6914(1.6911)$	$(-4.114, 2.7895)$
Macrolide	$-1.8613(1.6682)$	$(-5.2379, 1.586)$	$-1.2212(1.6421)$	$(-4.5795, 2.1443)$
Nitroimidazole	$-1.3235(1.7456)$	$(-4.8716, 2.2326)$	$-1.0652(1.7474)$	$(-4.6824, 2.448)$
Oxazolidinone	$-2.8972(1.7463)$	$(-6.4499, 0.6855)$	$-4.0499(1.7932)$	$(-7.6348, -0.3714)$
Penicillin	$-1.0431(1.727)$	$(-4.5491, 2.4754)$	$-1.3088(1.7462)$	$(-4.8617, 2.2169)$
Polymyxin	$-3.095(1.664)$	$(-6.5095, 0.2822)$	$-3.1195(1.6855)$	$(-6.5949, 0.294)$
Quinolone	$-3.1181(1.6069)$	$(-6.4783, 0.1407)$	$-3.0392(1.6034)$	$(-6.3991, 0.1567)$
Rifamycin	$-1.2426(1.7637)$	$(-4.8122, 2.3232)$	$-3.9118(1.7549)$	$(-7.4789, -0.3436)$

Table C.11: Summary statistics for parameters β_0 and $\tilde{\beta}_0$ for each antimicrobial group for the *Full Model*, for the MRSA Data Set.

$\log(\beta_1/\tilde{\beta}_1)$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	$0.9022(1.2158)$	$(-0.9333, 3.8459)$	$0.4074(1.3104)$	$(-1.6835, 3.4682)$
Antiseptic	$1.1546(1.2838)$	$(-0.8277, 4.1935)$	$0.3399(0.8143)$	$(-0.8759, 2.2791)$
Cephalosporin	$0.4236(1.2525)$	$(-1.5334, 3.4256)$	$-0.2747(1.1814)$	$(-2.2599, 2.5284)$
Glycopeptide	$-1.1965(1.5384)$	$(-4.4351, 1.9369)$	$-1.1381(1.4069)$	$(-4.119, 1.6735)$
Macrolide	$0.0577(1.3386)$	$(-2.2113, 3.1799)$	$-0.207(1.5187)$	$(-3.1324, 3.1132)$
Nitroimidazole	$-0.5019(1.2557)$	$(-2.6884, 2.349)$	$-0.8137(1.2323)$	$(-3.3192, 1.8178)$
Oxazolidinone	$-0.8308(1.328)$	$(-2.8678, 2.3374)$	$-1.3037(1.4246)$	$(-3.6236, 1.9936)$
Penicillin	$0.5946(1.1998)$	$(-1.1649, 3.5361)$	$0.4466(1.214)$	$(-1.3537, 3.3553)$
Polymyxin	$-0.9356(1.2387)$	$(-2.8066, 2.0516)$	$-1.2994(1.1982)$	$(-3.0927, 1.6366)$
Quinolone	$-0.709(1.1609)$	$(-2.4109, 2.1784)$	$-0.9067(1.1333)$	$(-2.5209, 1.941)$
Rifamycin	$0.9297(1.3076)$	$(-1.106, 4.024)$	$-1.6862(1.3865)$	$(-3.9479, 1.5378)$

Table C.12: Summary statistics for parameters β_1 and $\tilde{\beta}_1$ for each antimicrobial group for the *Full Model*, for the MRSA Data Set.

$\log(\beta_1'/\tilde{\beta}_1')$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	$-0.19(1.6061)$	$(-3.3295, 3.1883)$	$-0.2774(1.5125)$	$(-3.3509, 2.8895)$
Antiseptic	$1.5804(1.6674)$	$(-1.8194, 5.0173)$	$1.1927(1.659)$	$(-2.2912, 4.4571)$
Cephalosporin	$-1.6491(1.2703)$	$(-4.4263, 0.7486)$	$-1.6279(1.6161)$	$(-5.0028, 1.5837)$
Glycopeptide	$0.2912(1.1815)$	$(-1.4769, 3.1992)$	$0.9081(1.3145)$	$(-1.2831, 3.9588)$
Macrolide	$-0.5239(1.2206)$	$(-2.8636, 2.1216)$	$-0.0528(0.9299)$	$(-1.3219, 2.3121)$
Nitroimidazole	$-0.5105(1.5383)$	$(-3.5453, 2.8123)$	$-1.5324(1.3927)$	$(-4.4367, 1.2502)$
Oxazolidinone	$-2.8655(1.8672)$	$(-6.6228, 0.8704)$	NA	NA
Penicillin	$-1.1707(1.7519)$	$(-4.6719, 2.4526)$	$-0.893(1.5551)$	$(-3.8856, 2.409)$
Polymyxin	NA	NA	$-1.0848(1.5164)$	$(-3.8402, 2.2467)$
Quinolone	$-2.4636(1.3419)$	$(-5.3758, 0.1607)$	$-4.8393(1.3892)$	$(-8.0766, -2.6002)$
Rifamycin	NA	NA	NA	NA

Table C.13: Summary statistics for parameters β_1' and $\tilde{\beta}_1'$ for each antimicrobial group for the *Full Model*, for the MRSA Data Set.

ϕ				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	$0.5566(0.0254)$	$(0.5054, 0.6054)$	$0.478(0.0239)$	$(0.4328, 0.5265)$
Antiseptic	$0.5627(0.0249)$	$(0.5119, 0.6101)$	$0.4815(0.0254)$	$(0.4315, 0.5309)$
Cephalosporin	$0.5539(0.0268)$	$(0.5021, 0.607)$	$0.4778(0.025)$	$(0.4288, 0.5258)$
Glycopeptide	$0.5618(0.0245)$	$(0.5141, 0.6103)$	$0.4838(0.0248)$	$(0.4347, 0.532)$
Macrolide	$0.5518(0.0259)$	$(0.5008, 0.6025)$	$0.4783(0.0253)$	$(0.4283, 0.5279)$
Nitroimidazole	$0.5532(0.0252)$	$(0.5034, 0.6016)$	$0.4782(0.0246)$	$(0.4297, 0.526)$
Oxazolidinone	$0.5532(0.0244)$	$(0.5053, 0.6007)$	$0.475(0.0253)$	$(0.4231, 0.5237)$
Penicillin	$0.5516(0.024)$	$(0.5039, 0.5982)$	$0.48(0.0238)$	$(0.434, 0.5267)$
Polymyxin	$0.5575(0.0243)$	$(0.5096, 0.6047)$	$0.4754(0.0254)$	$(0.4262, 0.5263)$
Quinolone	$0.5496(0.0235)$	$(0.5038, 0.596)$	$0.4775(0.0264)$	$(0.4254, 0.5281)$
Rifamycin	$0.5506(0.0257)$	$(0.5014, 0.6008)$	$0.4735(0.0236)$	$(0.428, 0.5204)$

Table C.14: Summary statistics for parameter ϕ for each antimicrobial group for the *Full Model*, for the MRSA Data Set.

z				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	0.1529(0.0131)	(0.1281, 0.1798)	0.1647(0.014)	(0.1369, 0.1917)
Antiseptic	0.1433(0.013)	(0.1193, 0.1706)	0.1543(0.0141)	(0.1277, 0.1838)
Cephalosporin	0.154(0.0146)	(0.125, 0.1826)	0.1623(0.0145)	(0.1358, 0.1923)
Glycopeptide	0.1507(0.0123)	(0.127, 0.1754)	0.1588(0.0133)	(0.1349, 0.1878)
Macrolide	0.155(0.0132)	(0.1304, 0.1818)	0.1619(0.0141)	(0.1357, 0.1915)
Nitroimidazole	0.1546(0.0132)	(0.1304, 0.1817)	0.1591(0.0136)	(0.1332, 0.186)
Oxazolidinone	0.1558(0.0135)	(0.1312, 0.1841)	0.1629(0.0163)	(0.1353, 0.2014)
Penicillin	0.1567(0.0121)	(0.1335, 0.1813)	0.1633(0.0129)	(0.1391, 0.1896)
Polymyxin	0.1508(0.0127)	(0.1275, 0.1771)	0.1678(0.0151)	(0.1386, 0.1985)
Quinolone	0.1587(0.0123)	(0.1353, 0.1834)	0.1595(0.016)	(0.1304, 0.1922)
Rifamycin	0.1559(0.0138)	(0.1289, 0.183)	0.1665(0.0139)	(0.1405, 0.1948)

Table C.15: Summary statistics for parameter z for each antimicrobial group for the *Full Model*, for the MRSA Data Set.

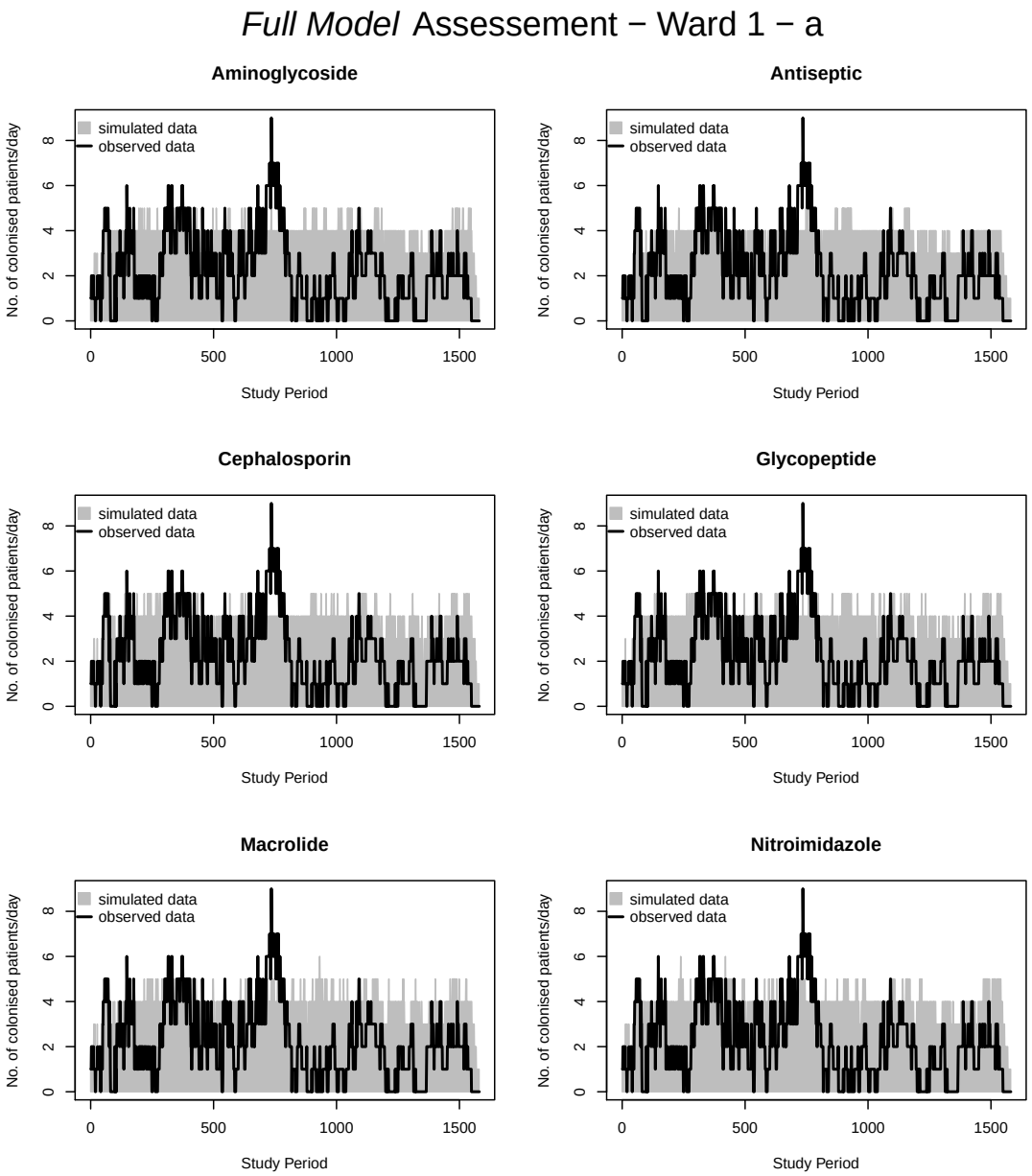

Figure C.11: Plots showing the *Full Model* assessement for the first 6 of the antimicrobials of ward 1, for the MRSA Data Set.

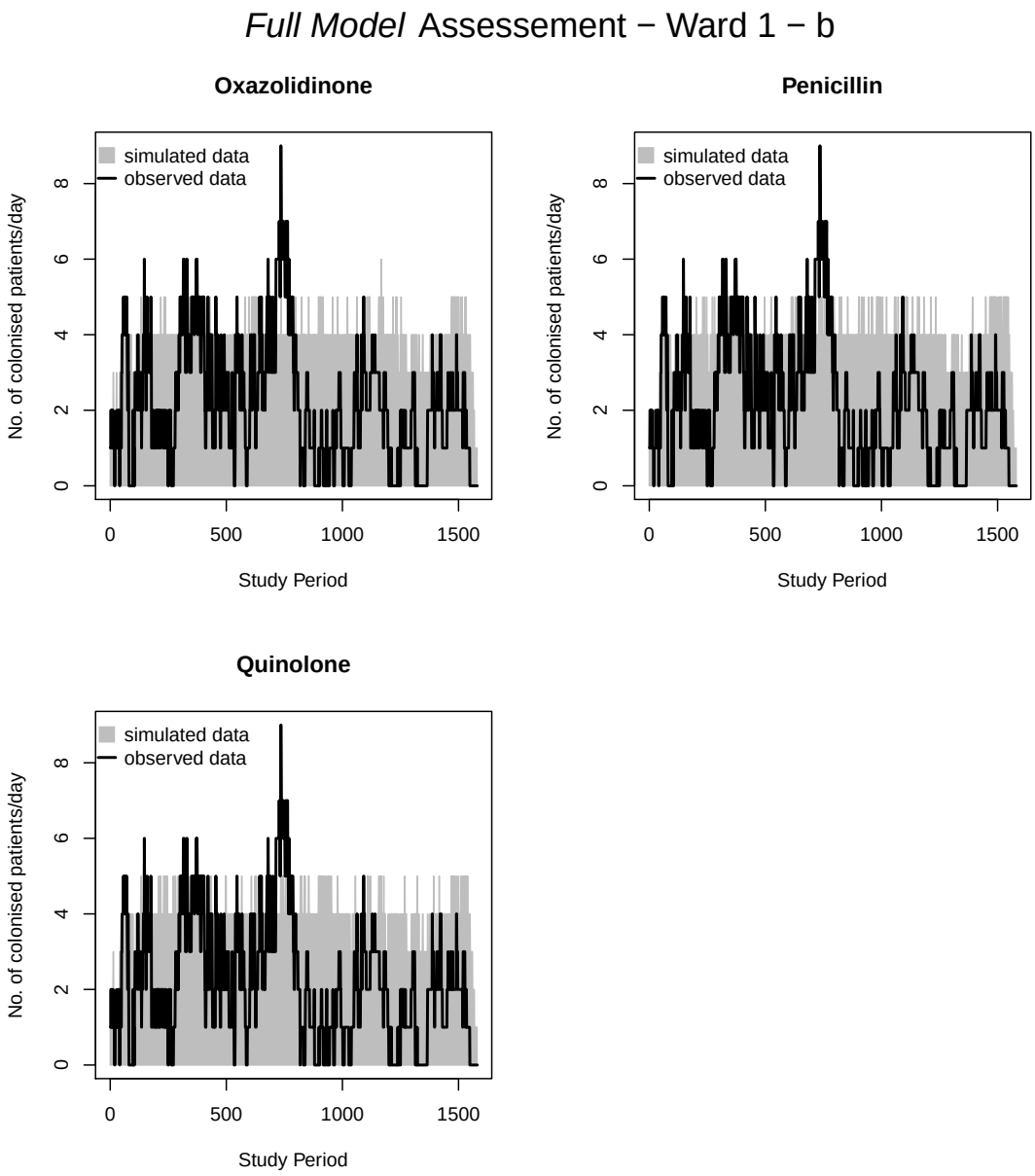

Figure C.12: Plots showing the *Full Model* assessement for the next 3 of the antimicrobials of ward 1, for the MRSA Data Set.

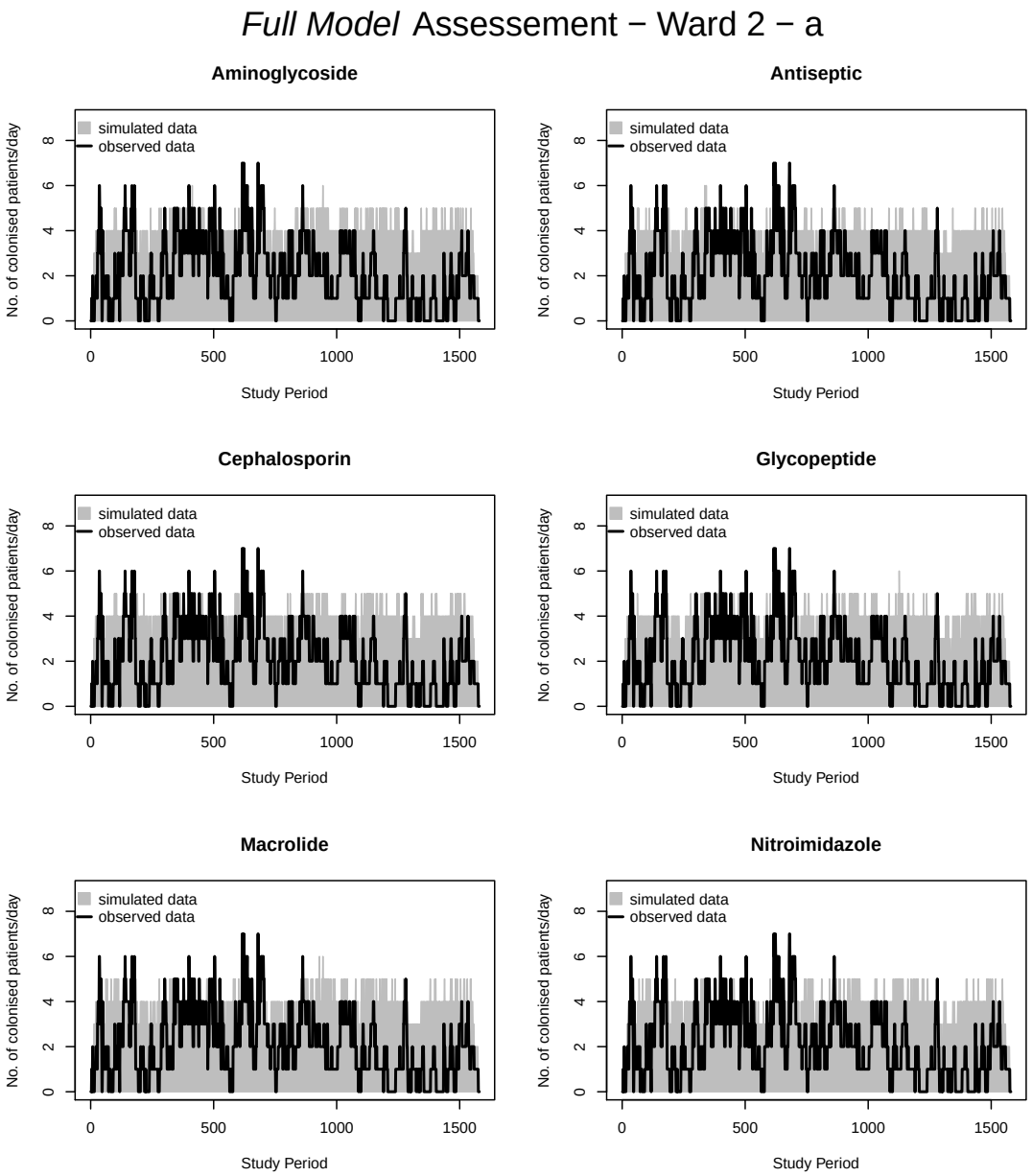

Figure C.13: Plots showing the *Full Model* assessement for the first 6 of the antimicrobials of ward 2, for the MRSA Data Set.

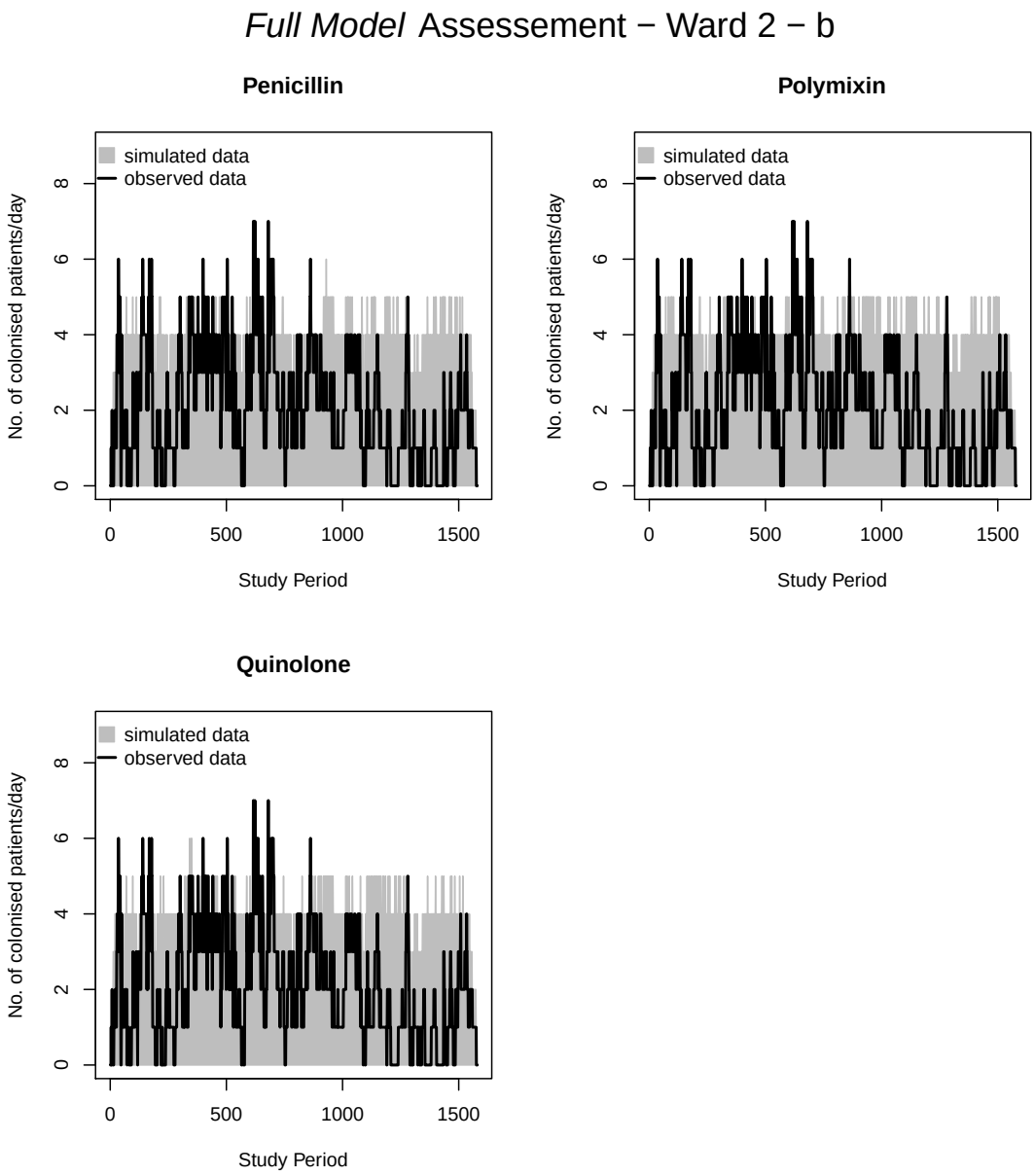

Figure C.14: Plots showing the *Full Model* assessement for the next 3 of the antimicrobials of ward 2, for the MRSA Data Set.

Sensitivity ϕ estimated from the data

Susceptibility Model

$\log(\beta_0/\tilde{\beta}_0)$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Antiseptic	$2.3079(1.2201)$	$(0.1728, 5.0678)$	$1.1339(1.2927)$	$(-1.4324, 3.9402)$
Glycopeptide	$-0.5936(1.5843)$	$(-3.7135, 2.7715)$	$-0.1737(1.5859)$	$(-3.3269, 3.1573)$

Table C.16: Summary statistics for parameters β_0 and $\tilde{\beta}_0$ for Antiseptic and Glycopeptide for the *Susceptibility Model* when sensitivity is estimated from the data, for the MRSA Data Set.

$\log(\beta_1/\tilde{\beta}_1)$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Antiseptic	$2.1525(1.2733)$	$(0.0638, 5.1601)$	$1.4539(0.9845)$	$(-0.1007, 3.8832)$
Glycopeptide	$-0.4577(0.6875)$	$(-1.5668, 1.1326)$	$-0.4963(0.7091)$	$(-1.7759, 1.0166)$

Table C.17: Summary statistics for parameters β_1 and $\tilde{\beta}_1$ for Antiseptic and Glycopeptide for the *Susceptibility Model* when sensitivity is estimated from the data, for the MRSA Data Set.

Infectivity Model

β_0				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Antiseptic	$0.0012(7.2596 \times 10^{-4})$	$(0.00001, 0.0032)$	$0.0019(0.0009)$	$(0.00002, 0.0040)$
Glycopeptide	$0.0016(0.0010)$	$(0.0001, 0.0041)$	$0.0021(0.0012)$	$(0.0002, 0.0049)$

Table C.18: Summary statistics for parameters β_0 for Antiseptic and Glycopeptide for the *Infectivity Model* when sensitivity is estimated from the data, for the MRSA Data Set.

$\log(\beta_1/\beta_1^{'})$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Antiseptic	$2.9339(1.2242)$	$(1.1539, 5.9499)$	$2.7606(1.3069)$	$(1.0639, 6.3529)$
Glycopeptide	$-1.3083(0.9550)$	$(-3.5830, 0.2078)$	$-1.2658(0.8712)$	$(-3.2071, 0.3390)$

Table C.19: Summary statistics for parameters β_1 and $\beta_1^{'}$ for Antiseptic and Glycopeptide for the *Infectivity Model* when sensitivity is estimated from the data, for the MRSA Data Set.

Full Model

$\log(\beta_0/\tilde{\beta}_0)$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Antiseptic	2.2946(1.8022)	$(-0.1058, 5.3179)$	1.0249(1.2515)	$(-1.4780, 3.6912)$
Glycopeptide	-0.5067(1.6147)	$(-3.7402, 2.9017)$	-0.2636(1.5738)	$(-3.4394, 3.0268)$

Table C.20: Summary statistics for parameters β_0 and $\tilde{\beta}_0$ for Antiseptic and Glycopeptide for the *Full Model* when sensitivity is estimated from the data, for the MRSA Data Set.

$\log(\beta_1/\tilde{\beta}_1)$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Antiseptic	1.0234(1.2197)	$(-0.8404, 4.0032)$	0.2754(0.8633)	$(-1.0696, 2.3274)$
Glycopeptide	-1.0305(1.3162)	$(-3.8075, 1.6908)$	-1.0256(1.2697)	$(-3.6744, 1.6367)$

Table C.21: Summary statistics for parameters β_1 and $\tilde{\beta}_1$ for Antiseptic and Glycopeptide for the *Full Model* when sensitivity is estimated from the data, for the MRSA Data Set.

$\log(\beta_1'/\tilde{\beta}_1')$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Antiseptic	1.3170(1.6323)	$(-2.0176, 4.6561)$	1.0315(1.7947)	$(-2.3802, 5.3356)$
Glycopeptide	0.0733(1.1005)	$(-1.6502, 2.7557)$	0.4656(1.3450)	$(-1.9131, 3.5059)$

Table C.22: Summary statistics for parameters β_1 and $\tilde{\beta}_1$ for Antiseptic and Glycopeptide for the *Full Model* when sensitivity is estimated from the data, for the MRSA Data Set.

$\mathbf{z}$				
	Ward 1		**Ward** 2	
Susceptibility Model				
Model	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Antiseptic	$0.1120(8.1549 \times 10^{-5})$	$(0.0947, 0.1301)$	$0.1102(8.0923 \times 10^{-5})$	$(0.0933, 0.1286)$
Glycopeptide	$0.1170(7.8102 \times 10^{-5})$	$(0.1002, 0.1350)$	$0.1161(8.0246 \times 10^{-5})$	$(0.0991, 0.1342)$
Infectivity Model				
Model	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Antiseptic	$0.1142(8.0646 \times 10^{-5})$	$(0.0972, 0.1325)$	$0.1123(8.3166 \times 10^{-5})$	$(0.0950, 0.1307)$
Glycopeptide	0.1177(0.0089)	$(0.1007, 0.1357)$	$0.1143(7.7655 \times 10^{-5})$	$(0.0976, 0.1321)$
Full Model				
Model	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Antiseptic	0.1121(0.0090)	$(0.0952, 0.1305)$	0.1093(0.0088)	$(0.0925, 0.1273)$
Glycopeptide	0.1241(0.0100)	$(0.1052, 0.1447)$	0.1144(0.0090)	$(0.0969, 0.1324)$

Table C.23: Summary statistics for parameter z for Antiseptic and Glycopeptide for all three models when sensitivity is estimated from the data, for the MRSA Data Set.

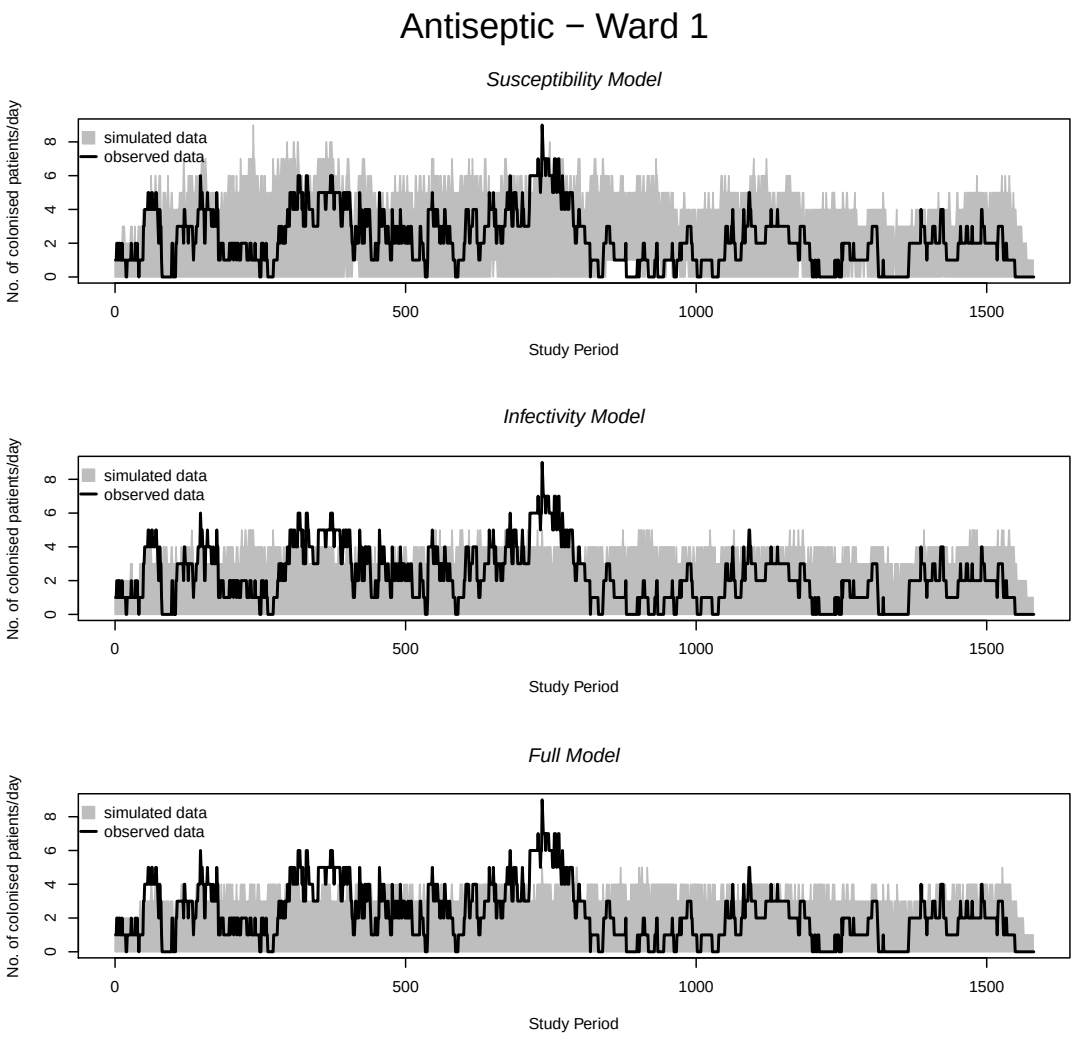

Figure C.15: Plots showing the assessment for the three models, for the MRSA Data Set: *Susceptibility Model* (first line), *Infectivity Model* (second line) and *Full Model* (third line) for the Antiseptic in ward 1 when the sensitivity is estimated from the data. The black line shows the number of colonised patients in the ward during the study period from the observed data and the grey area is the 95% quantile from the model fit simulations.

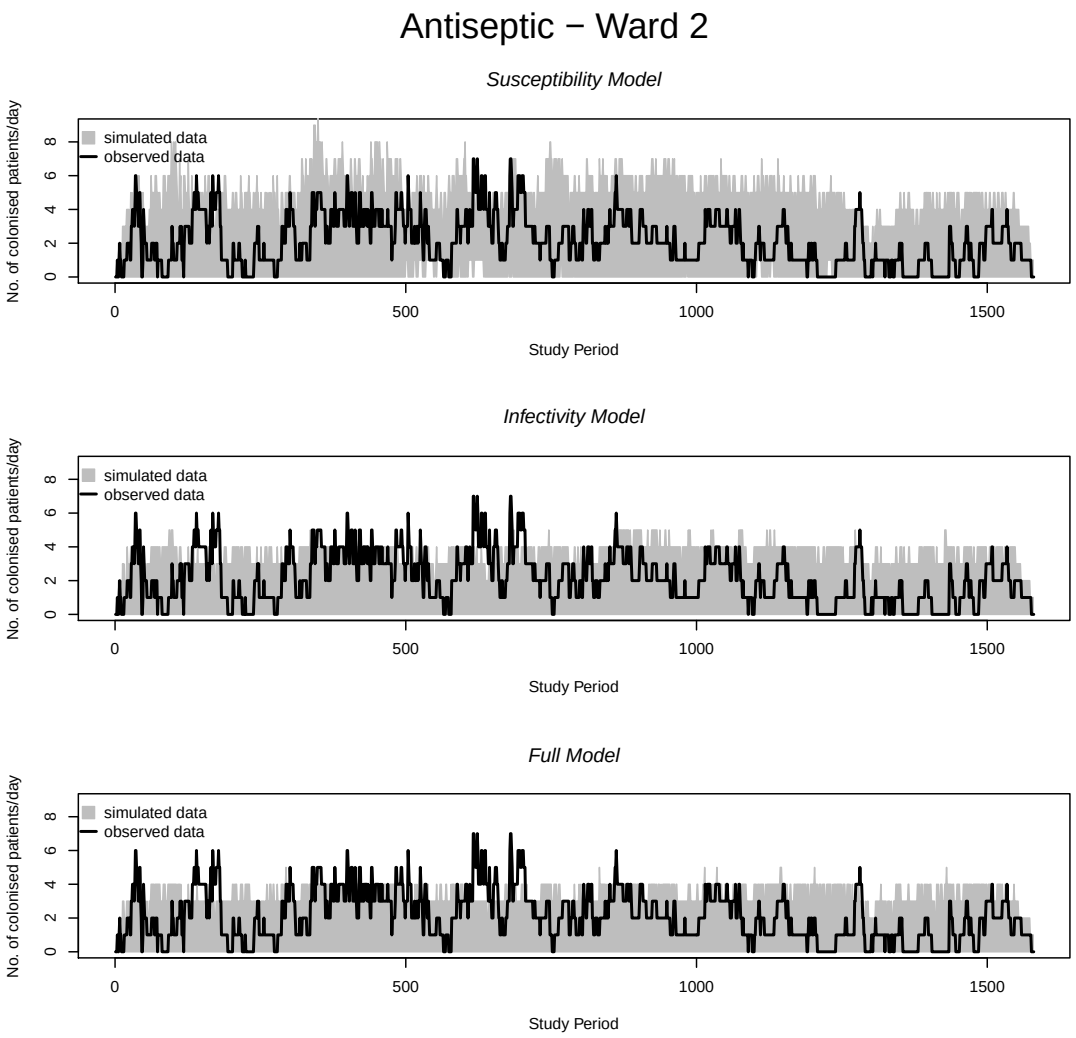

Figure C.16: Plots showing the assessment for the three models, for the MRSA Data Set: *Susceptibility Model* (first line), *Infectivity Model* (second line) and *Full Model* (third line) for the Antiseptic in ward 2 when the sensitivity is estimated from the data. The black line shows the number of colonised patients in the ward during the study period from the observed data and the grey area is the 95% quantile from the model fit simulations.

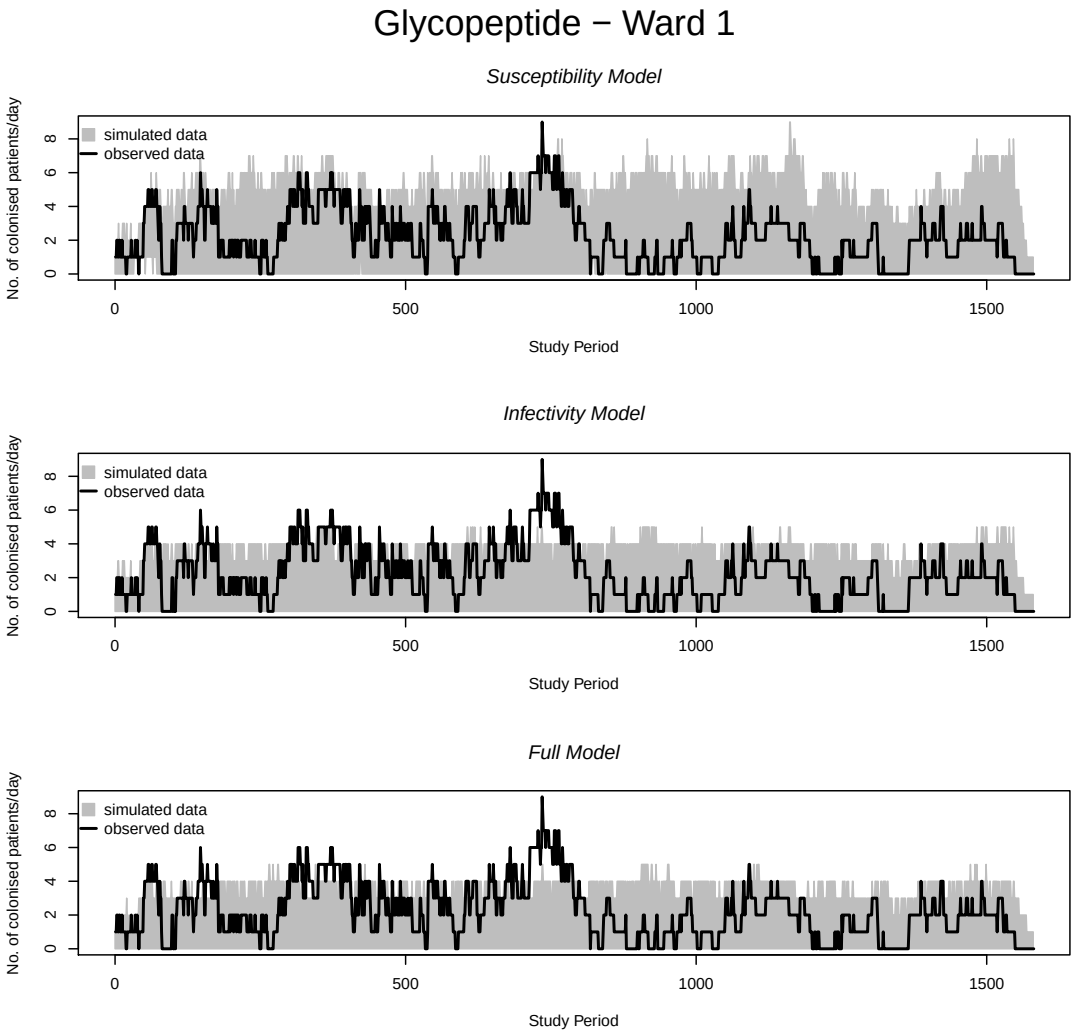

Figure C.17: Plots showing the assessment for the three models, for the MRSA Data Set: *Susceptibility Model* (first line), *Infectivity Model* (second line) and *Full Model* (third line) for the Glycopeptide in ward 1 when the sensitivity is estimated from the data. The black line shows the number of colonised patients in the ward during the study period from the observed data and the grey area is the 95% quantile from the model fit simulations.

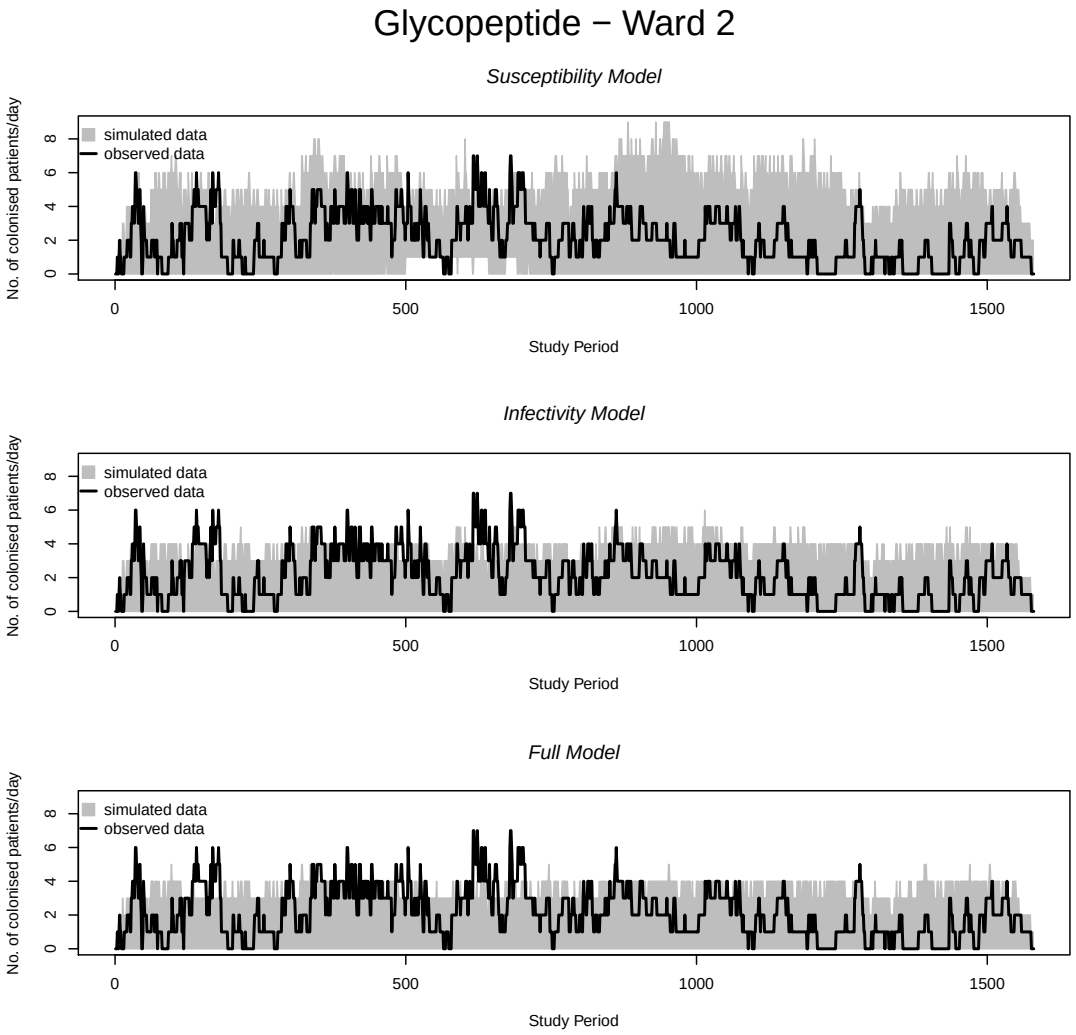

Figure C.18: Plots showing the assessment for the three models, for the MRSA Data Set: *Susceptibility Model* (first line), *Infectivity Model* (second line) and *Full Model* (third line) for the Glycopeptide in ward 2 when the sensitivity is estimated from the data. The black line shows the number of colonised patients in the ward during the study period from the observed data and the grey area is the 95% quantile from the model fit simulations.

C.3 Wounds Data Set

C.3.1 *Susceptibility Model*

$\log(\beta_0/\tilde{\beta}_0)$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	$-0.1195(1.6273)$	$(-3.2962, 3.3389)$	$-0.1552(1.567)$	$(-3.2036, 3.1887)$
Antiseptic	$1.7278(1.2211)$	$(-0.6153, 4.3613)$	$0.6293(1.2493)$	$(-1.9813, 3.1444)$
Cephalosporin	$0.22(1.5966)$	$(-2.7483, 3.6833)$	$-0.0356(1.6346)$	$(-3.2342, 3.428)$
Glycopeptide	$0.1556(1.5986)$	$(-2.995, 3.5272)$	$-0.1468(1.535)$	$(-3.1207, 3.1593)$
Macrolide	$-1.1919(1.4465)$	$(-4.0986, 1.8706)$	$-0.5878(1.4788)$	$(-3.3698, 2.5922)$
Nitroimidazole	$-0.2944(1.526)$	$(-3.2384, 3.0107)$	$-0.4767(1.5367)$	$(-3.4004, 2.8417)$
Oxazolidinone	$-2.2541(1.6932)$	$(-5.5636, 1.2774)$	$-2.2458(1.5766)$	$(-5.2404, 1.1535)$
Penicillin	$-0.6872(1.5605)$	$(-3.6942, 2.6574)$	$-0.0504(1.569)$	$(-3.0337, 3.3155)$
Polymyxin	$-2.0076(1.6175)$	$(-5.1579, 1.3918)$	$-3.0024(1.5477)$	$(-6.0707, 0.2404)$
Quinolone	$-1.9292(1.4428)$	$(-4.8314, 1.1273)$	$-1.8011(1.5432)$	$(-4.9242, 1.4577)$
Rifamycin	$-0.6814(1.6171)$	$(-3.8034, 2.7325)$	$-2.9838(1.6007)$	$(-6.1432, 0.3764)$

Table C.24: Summary statistics for parameters β_0 and $\tilde{\beta}_0$ for each antimicrobial group for the *Susceptibility Model*, for the Wounds Data Set.

$\log(\beta_1/\tilde{\beta}_1)$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	$0.5532(1.4294)$	$(-1.9839, 3.7955)$	$1.3999(1.1812)$	$(-0.3648, 4.3364)$
Antiseptic	$1.617(1.5118)$	$(-1.3035, 4.8722)$	$0.9875(0.8802)$	$(-0.439, 3.0379)$
Cephalosporin	$0.408(1.4565)$	$(-2.2726, 3.6343)$	$0.1888(0.8977)$	$(-1.0971, 2.449)$
Glycopeptide	$0.1095(1.4569)$	$(-2.6686, 3.2925)$	$1.0714(1.0631)$	$(-0.4039, 3.7405)$
Macrolide	$-0.5823(1.4388)$	$(-3.4751, 2.5281)$	$-0.1126(0.8806)$	$(-1.5318, 1.9794)$
Nitroimidazole	$-0.7323(1.442)$	$(-3.6563, 2.3056)$	$-0.2863(0.8263)$	$(-1.5722, 1.6592)$
Oxazolidinone	$-1.5849(1.465)$	$(-4.0875, 1.7026)$	$-0.4199(1.41)$	$(-2.7553, 2.8659)$
Penicillin	$-0.8668(1.3137)$	$(-3.2572, 2.0664)$	$1.0764(1.1732)$	$(-0.621, 4.0082)$
Polymyxin	$-1.386(1.4924)$	$(-4.143, 1.9137)$	$-0.6892(1.2941)$	$(-2.69, 2.4145)$
Quinolone	$-1.9092(1.3425)$	$(-4.6156, 0.9346)$	$-0.3942(1.0667)$	$(-1.8431, 2.3531)$
Rifamycin	$-0.1898(1.4853)$	$(-2.8128, 3.1334)$	$-1.6475(1.4212)$	$(-3.9447, 1.6831)$

Table C.25: Summary statistics for parameters β_1 and $\tilde{\beta}_1$ for each antimicrobial group for the *Susceptibility Model*, for the Wounds Data Set.

ϕ				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	0.2695(0.0179)	(0.2355, 0.3056)	0.3487(0.0182)	(0.3131, 0.3843)
Antiseptic	0.2726(0.0167)	(0.2411, 0.3064)	0.3466(0.0178)	(0.3121, 0.3817)
Cephalosporin	0.2711(0.0172)	(0.2378, 0.3055)	0.3486(0.0177)	(0.3145, 0.3837)
Glycopeptide	0.2671(0.017)	(0.2339, 0.3005)	0.3483(0.0183)	(0.3124, 0.3842)
Macrolide	0.2657(0.0176)	(0.2323, 0.3011)	0.3472(0.0179)	(0.3117, 0.3822)
Nitroimidazole	0.2698(0.0168)	(0.2377, 0.3032)	0.3469(0.0182)	(0.3124, 0.3838)
Oxazolidinone	0.2663(0.0175)	(0.2325, 0.3011)	0.3483(0.0186)	(0.3125, 0.3855)
Penicillin	0.271(0.0174)	(0.2374, 0.3056)	0.3495(0.0185)	(0.3133, 0.3857)
Polymyxin	0.2655(0.0176)	(0.2312, 0.3003)	0.3472(0.0177)	(0.3132, 0.3825)
Quinolone	0.2703(0.0171)	(0.2376, 0.3047)	0.3477(0.0179)	(0.3131, 0.3832)
Rifamycin	0.2676(0.018)	(0.2341, 0.3043)	0.3449(0.0188)	(0.3086, 0.3821)

Table C.26: Summary statistics for parameter ϕ for each antimicrobial group for the *Susceptibility Model*, for the Wounds Data Set.

z				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	0.1774(0.0242)	(0.1328, 0.2247)	0.1076(0.0162)	(0.0769, 0.1396)
Antiseptic	0.1607(0.0177)	(0.1266, 0.1964)	0.0965(0.0141)	(0.0704, 0.1257)
Cephalosporin	0.1775(0.0208)	(0.1367, 0.2212)	0.1041(0.0144)	(0.0769, 0.1328)
Glycopeptide	0.1854(0.0197)	(0.1509, 0.2321)	0.1037(0.017)	(0.0736, 0.1399)
Macrolide	0.1839(0.0231)	(0.1402, 0.2313)	0.1068(0.0138)	(0.0809, 0.1351)
Nitroimidazole	0.1755(0.0199)	(0.139, 0.2163)	0.1039(0.016)	(0.0716, 0.1346)
Oxazolidinone	0.1844(0.0219)	(0.143, 0.2303)	0.1034(0.016)	(0.074, 0.1373)
Penicillin	0.1744(0.0223)	(0.1349, 0.221)	0.1024(0.0157)	(0.0736, 0.1361)
Polymyxin	0.1854(0.0228)	(0.1424, 0.2294)	0.107(0.0156)	(0.0786, 0.1387)
Quinolone	0.1782(0.0192)	(0.1408, 0.216)	0.106(0.0152)	(0.077, 0.1367)
Rifamycin	0.1823(0.0227)	(0.1389, 0.2246)	0.1096(0.017)	(0.0792, 0.1444)

Table C.27: Summary statistics for parameter z for each antimicrobial group for the *Susceptibility Model*, for the Wounds Data Set.

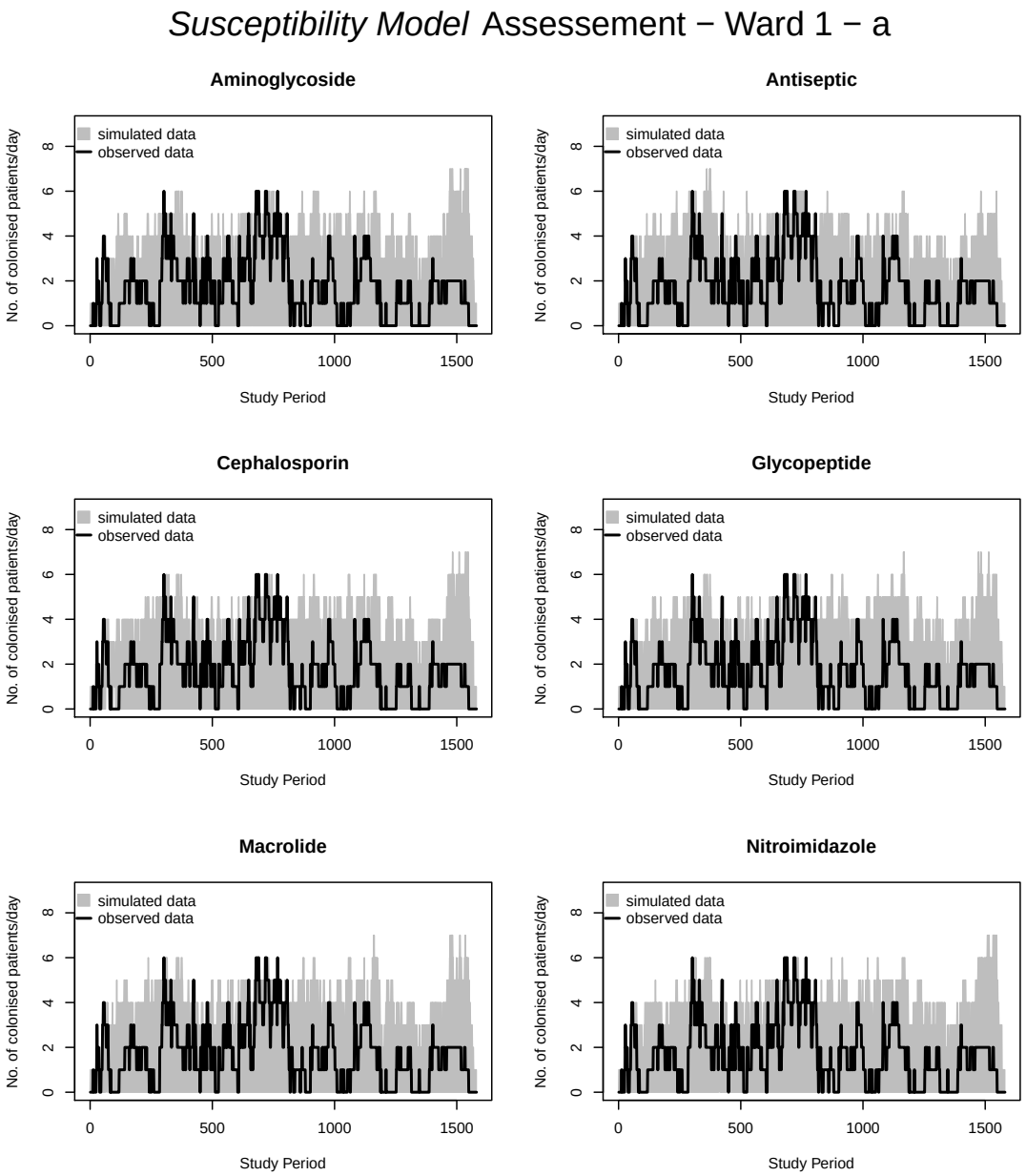

Figure C.19: Plots showing the *Susceptibility Model* assessement for the first 6 of the antimicrobials of ward 1, for the Wounds Data Set.

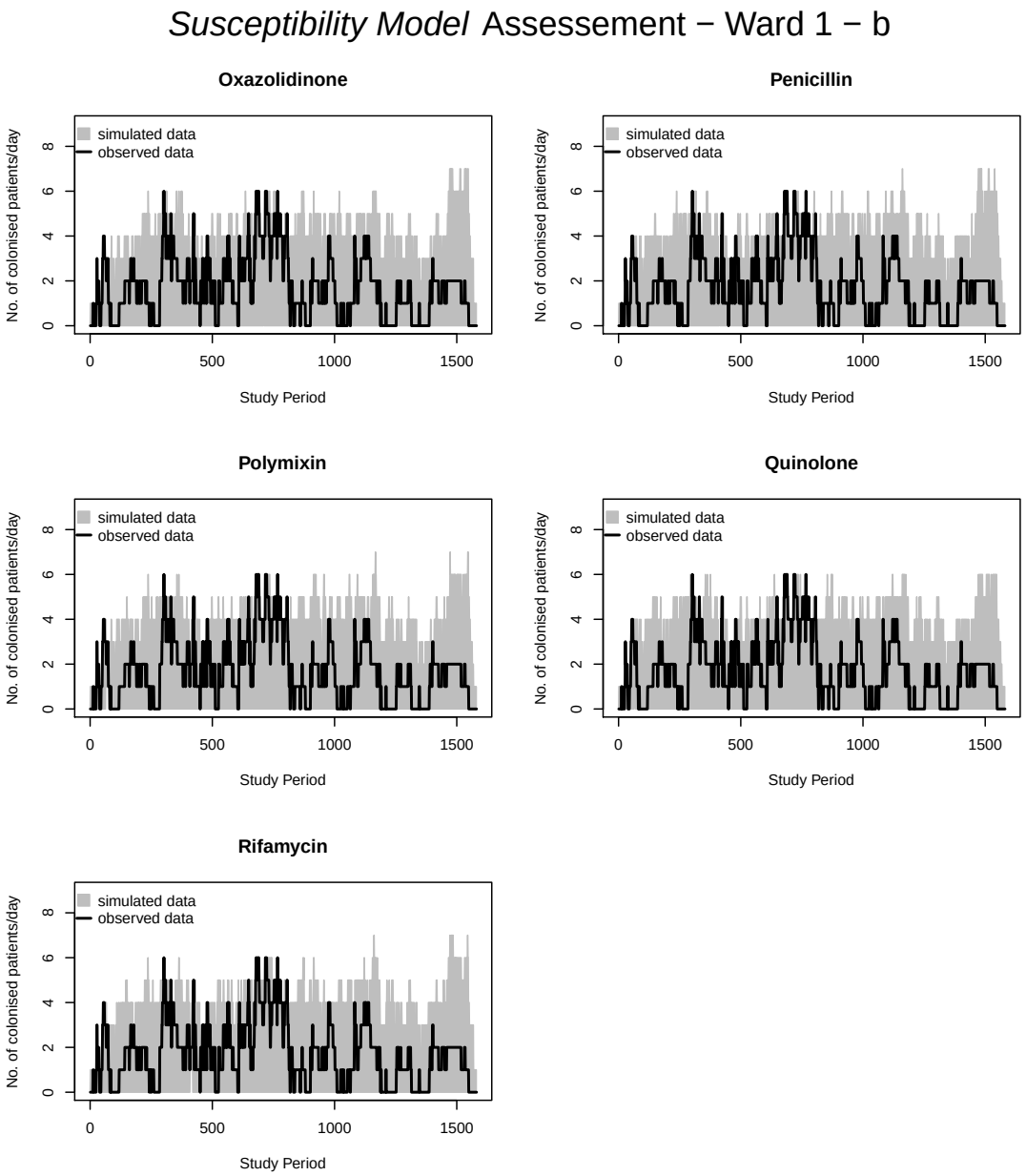

Figure C.20: Plots showing the *Susceptibility Model* assessement for the next 5 of the antimicrobials of ward 1, for the Wounds Data Set.

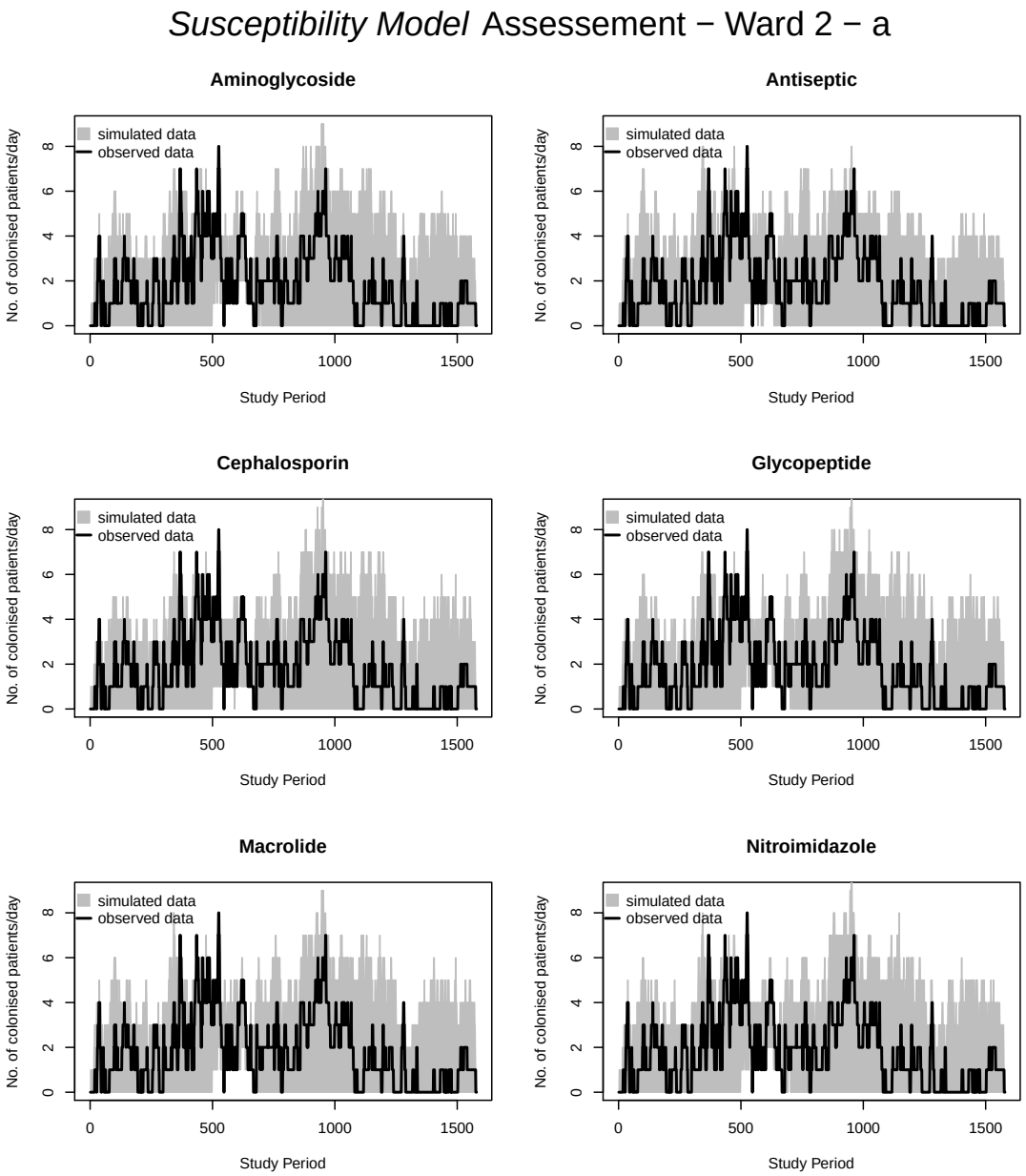

Figure C.21: Plots showing the *Susceptibility Model* assessement for the first 6 of the antimicrobials of ward 2, for the Wounds Data Set.

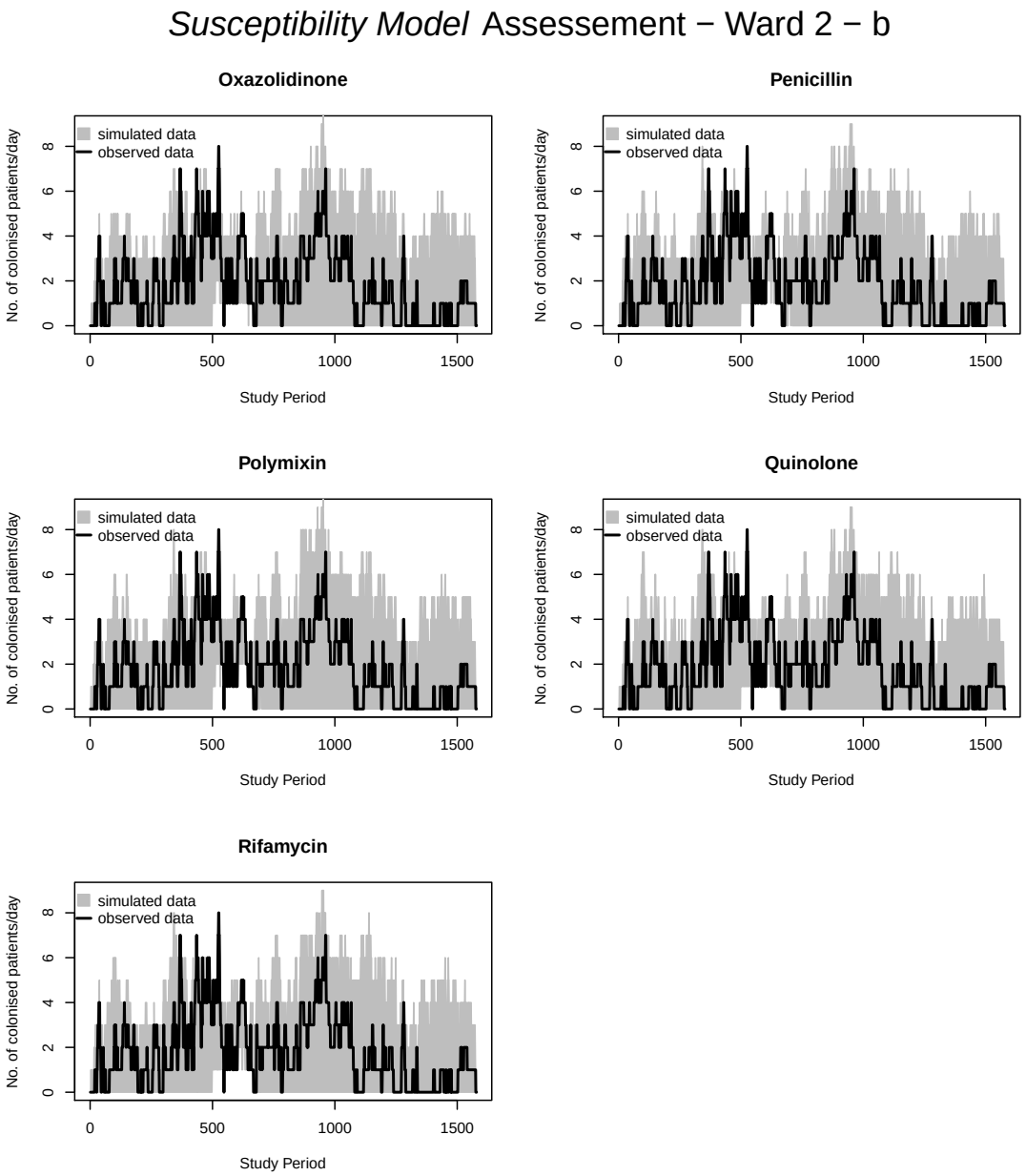

Figure C.22: Plots showing the *Susceptibility Model* assessement for the next 5 of the antimicrobials of ward 2, for the Wounds Data Set.

C.3.2 *Infectivity Model*

β_0				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	0.0024(0.0016)	(0.0001, 0.006)	0.003(0.002)	(0.0002, 0.0075)
Antiseptic	0.0017(0.0012)	(0.0001, 0.0046)	0.0032(0.0016)	(0.0004, 0.0068)
Cephalosporin	0.0022(0.0015)	(0.0001, 0.0057)	0.0026(0.0017)	(0.0002, 0.0067)
Glycopeptide	0.002(0.0014)	(0.0001, 0.0054)	0.003(0.0019)	(0.0002, 0.0073)
Macrolide	0.0023(0.0014)	(0.0002, 0.0054)	0.0037(0.0021)	(0.0004, 0.0084)
Nitroimidazole	0.0025(0.0017)	(0.0002, 0.0066)	0.0039(0.0022)	(0.0004, 0.0086)
Oxazolidinone	0.0025(0.0017)	(0.0001, 0.0065)	0.0028(0.0017)	(0.0002, 0.0068)
Penicillin	0.0027(0.0017)	(0.0002, 0.0067)	0.0032(0.0019)	(0.0003, 0.0077)
Polymyxin	0.0026(0.0017)	(0.0002, 0.0064)	0.0029(0.0019)	(0.0002, 0.0074)
Quinolone	0.0023(0.0015)	(0.0001, 0.0055)	0.0026(0.0018)	(0.0002, 0.0069)
Rifamycin	0.0024(0.0016)	(0.0001, 0.006)	0.0029(0.0018)	(0.0003, 0.0072)

Table C.28: Summary statistics for parameters β_0 for each antimicrobial group for the *Infectivity Model*, for the Wounds Data Set.

$\log(\beta_1/\beta_1^{'})$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	$-1.7316(1.5554)$	$(-4.8147, 1.5565)$	$-1.7397(1.0213)$	$(-3.823, 0.2327)$
Antiseptic	2.5656(1.3121)	(0.4782, 5.6818)	2.084(0.8791)	(0.8698, 4.3874)
Cephalosporin	$-1.3021(1.6051)$	$(-4.4191, 2.1924)$	$-0.6475(0.9752)$	$(-2.3305, 1.6188)$
Glycopeptide	$-2.3416(1.3885)$	$(-5.5298, -0.0116)$	$-0.7524(1.1861)$	$(-2.9912, 1.8358)$
Macrolide	$-2.7659(1.3899)$	$(-5.9071, -0.2675)$	$-2.1953(0.9775)$	$(-4.3663, -0.4494)$
Nitroimidazole	$-2.2434(1.3855)$	$(-5.2645, 0.382)$	$-2.0781(0.9108)$	$(-4.1474, -0.5022)$
Oxazolidinone	$-0.2825(1.4407)$	$(-2.7929, 2.9487)$	$-0.5989(1.248)$	$(-2.4362, 2.4184)$
Penicillin	$-0.8091(1.4986)$	$(-3.6784, 2.4587)$	0.4477(1.2977)	$(-1.4955, 3.5778)$
Polymyxin	$-2.1251(1.4748)$	$(-4.831, 1.1029)$	$-0.9401(1.0964)$	$(-2.557, 1.7851)$
Quinolone	$-2.4686(1.3035)$	$(-5.1828, 0.225)$	$-0.8074(1.0124)$	$(-2.1449, 1.8048)$
Rifamycin	$-3.1235(1.2313)$	$(-5.7381, -0.7031)$	$-1.3628(1.2335)$	$(-3.1924, 1.6189)$

Table C.29: Summary statistics for parameters β_1 and $\beta_1^{'}$ for each antimicrobial group for the *Infectivity Model*, for the Wounds Data Set.

ϕ				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	0.2673(0.0174)	(0.2337, 0.3015)	0.3439(0.0184)	(0.3084, 0.3803)
Antiseptic	0.2702(0.0178)	(0.2367, 0.3063)	0.346(0.018)	(0.3116, 0.3821)
Cephalosporin	0.2707(0.0179)	(0.2359, 0.3059)	0.3492(0.0184)	(0.3138, 0.3861)
Glycopeptide	0.2728(0.0172)	(0.2402, 0.3075)	0.3459(0.0186)	(0.31, 0.3828)
Macrolide	0.2689(0.0175)	(0.2349, 0.3034)	0.343(0.0194)	(0.3046, 0.3804)
Nitroimidazole	0.272(0.0178)	(0.2389, 0.3086)	0.3492(0.0187)	(0.3125, 0.3858)
Oxazolidinone	0.2699(0.0177)	(0.2362, 0.3055)	0.3487(0.0185)	(0.3124, 0.3852)
Penicillin	0.2707(0.0172)	(0.2376, 0.3054)	0.3511(0.0179)	(0.3169, 0.3868)
Polymyxin	0.2685(0.0164)	(0.2375, 0.3017)	0.346(0.0178)	(0.3114, 0.3812)
Quinolone	0.2669(0.0172)	(0.2339, 0.3011)	0.3462(0.0185)	(0.3094, 0.3821)
Rifamycin	0.27(0.0176)	(0.2359, 0.3053)	0.3472(0.0179)	(0.3127, 0.3829)

Table C.30: Summary statistics for parameter ϕ for each antimicrobial group for the *Infectivity Model*, for the Wounds Data Set.

$\mathbf{z}$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	0.1817(0.0209)	(0.1432, 0.2226)	0.1099(0.0157)	(0.08, 0.141)
Antiseptic	0.1672(0.0212)	(0.1289, 0.2132)	0.1015(0.0144)	(0.0751, 0.1312)
Cephalosporin	0.1772(0.0213)	(0.14, 0.2233)	0.1067(0.0162)	(0.0771, 0.1401)
Glycopeptide	0.1716(0.0191)	(0.135, 0.2097)	0.1098(0.0152)	(0.0812, 0.1403)
Macrolide	0.1768(0.0199)	(0.1352, 0.2134)	0.1097(0.0157)	(0.0805, 0.1416)
Nitroimidazole	0.1721(0.0224)	(0.1223, 0.2118)	0.1055(0.0164)	(0.078, 0.1434)
Oxazolidinone	0.1768(0.0232)	(0.1361, 0.2257)	0.107(0.017)	(0.0777, 0.1444)
Penicillin	0.1768(0.0199)	(0.1386, 0.2152)	0.1037(0.0154)	(0.0745, 0.135)
Polymyxin	0.1822(0.0188)	(0.1453, 0.2187)	0.1099(0.0161)	(0.0794, 0.143)
Quinolone	0.1814(0.0208)	(0.1431, 0.2239)	0.1082(0.0165)	(0.0765, 0.1419)
Rifamycin	0.1786(0.0227)	(0.1355, 0.2247)	0.1064(0.015)	(0.0788, 0.1381)

Table C.31: Summary statistics for parameter z for each antimicrobial group for the *Infectivity Model*, for the Wounds Data Set.

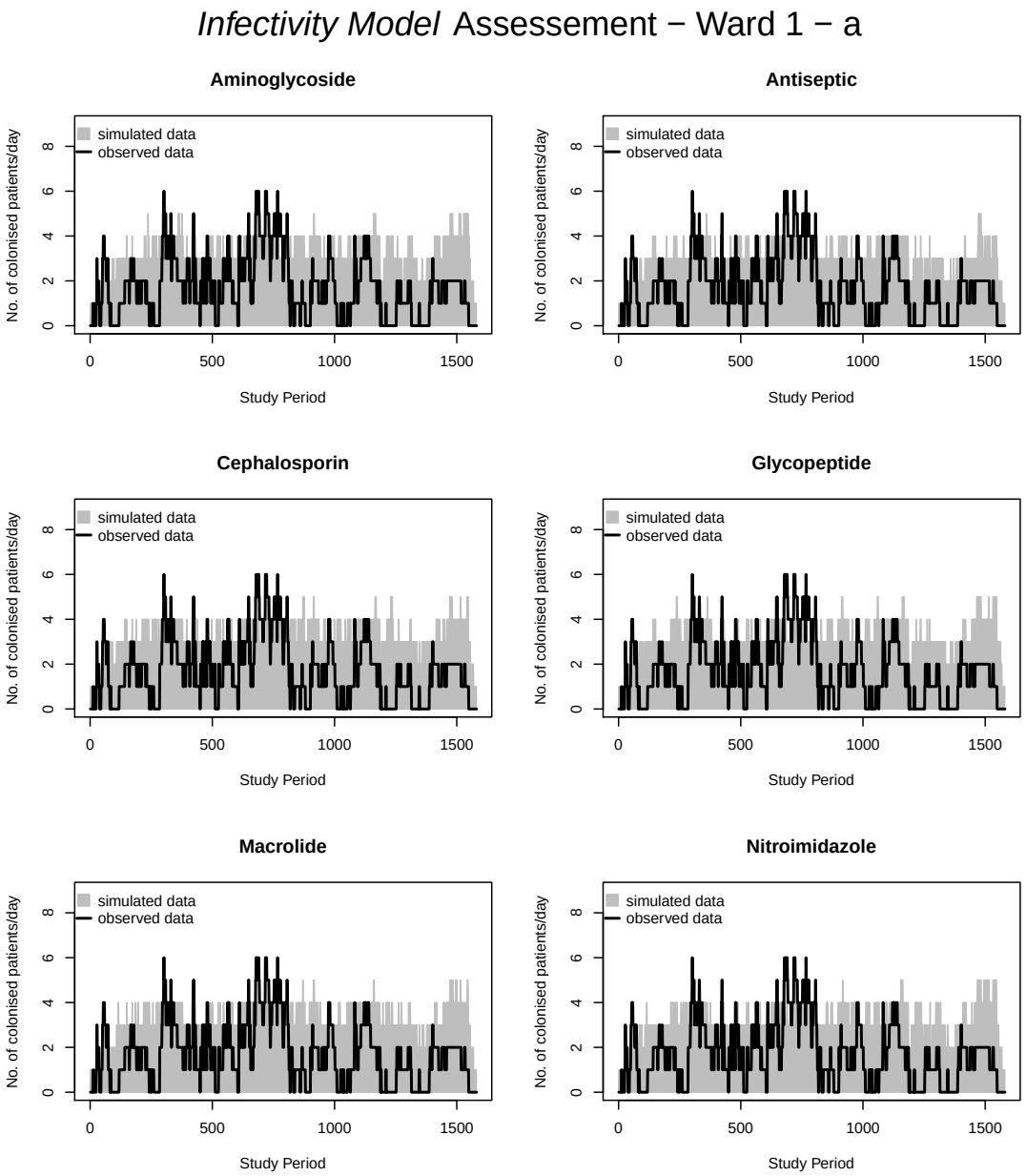

Figure C.23: Plots showing the *Infectivity Model* assessement for the first 6 of the antimicrobials of ward 1, for the Wounds Data Set.

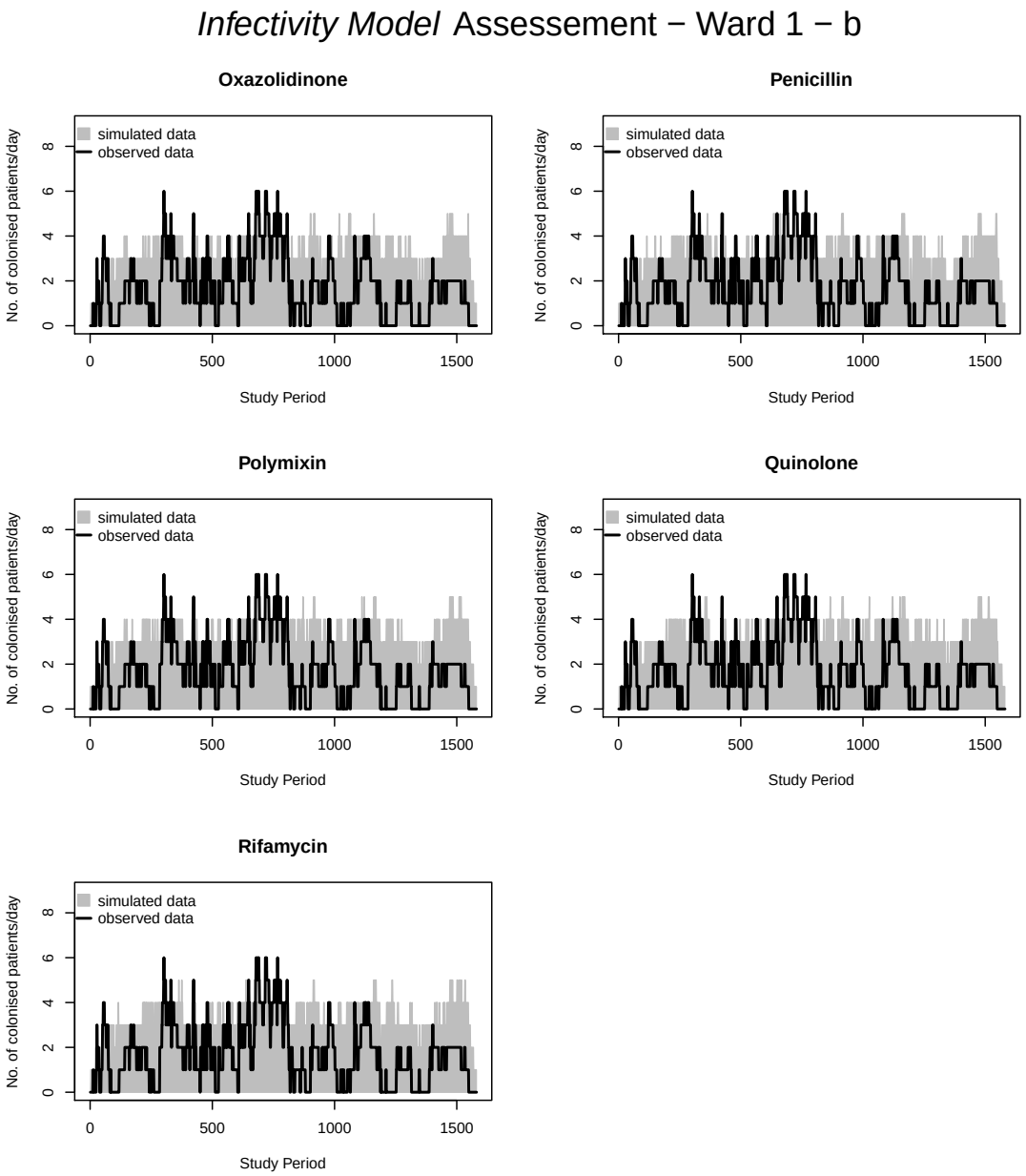

Figure C.24: Plots showing the *Infectivity Model* assessement for the next 5 of the antimicrobials of ward 1, for the Wounds Data Set.

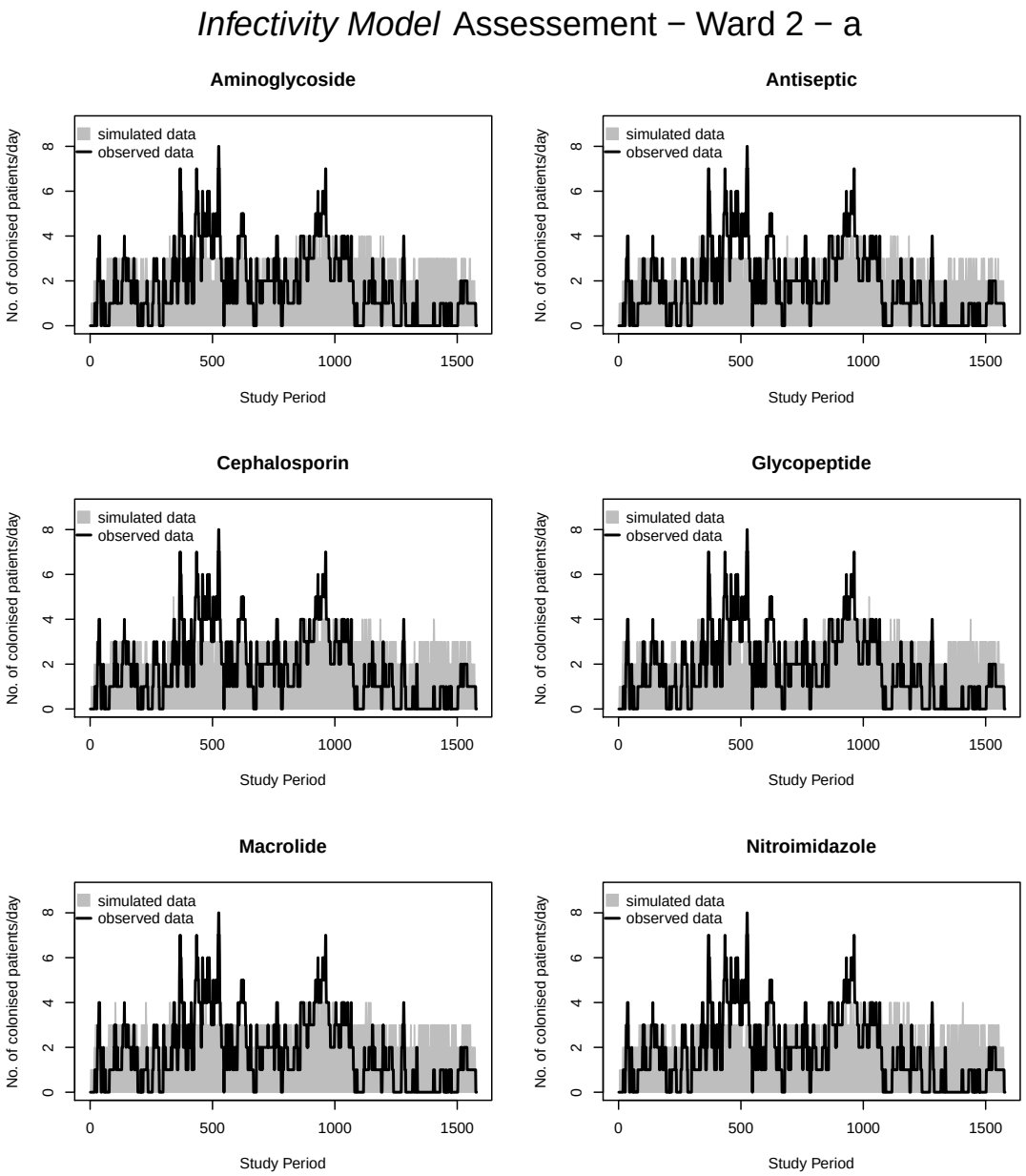

Figure C.25: Plots showing the *Infectivity Model* assessement for the first 6 of the antimicrobials of ward 2, for the Wounds Data Set.

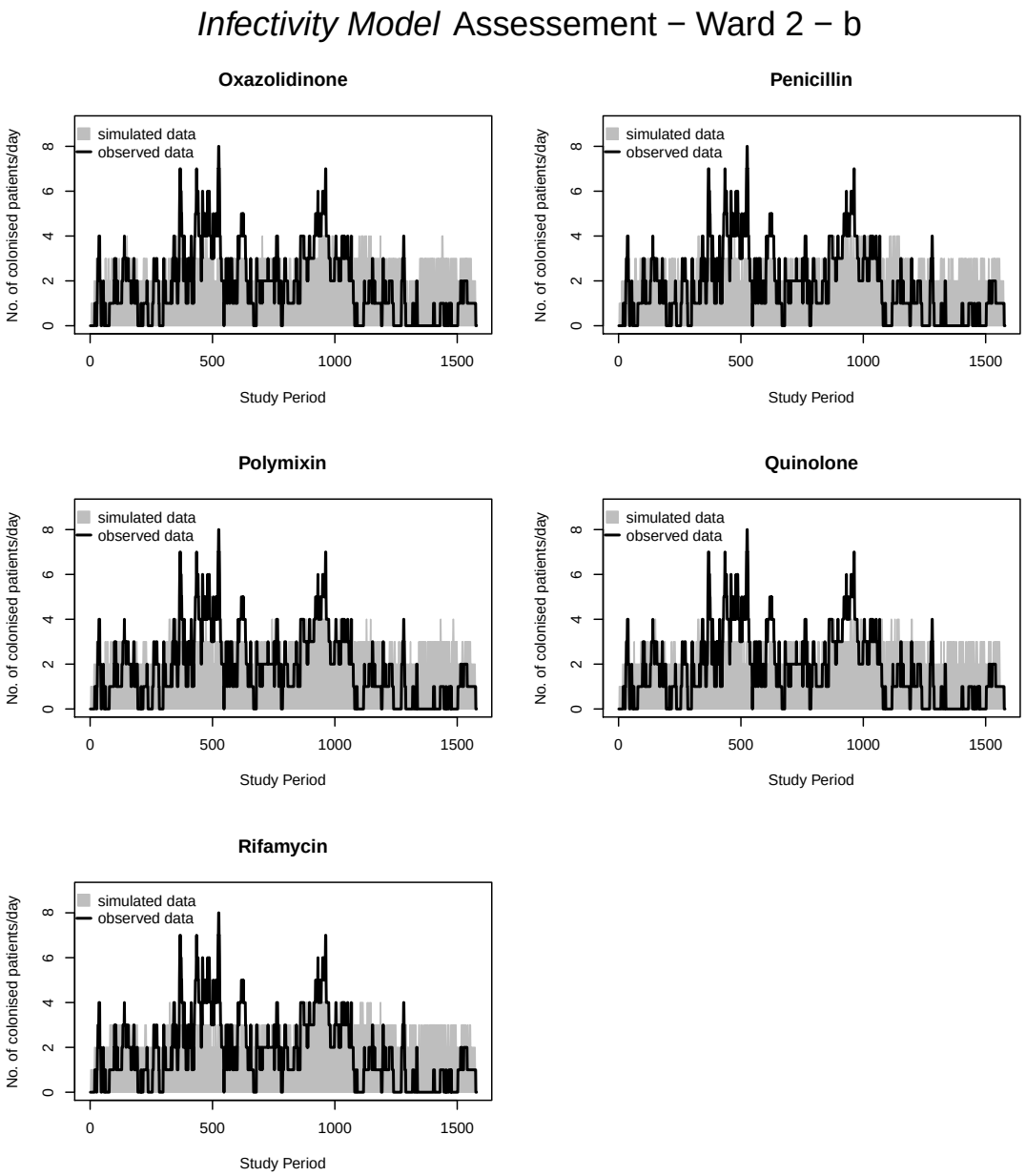

Figure C.26: Plots showing the *Infectivity Model* assessement for the next 5 of the antimicrobials of ward 2, for the Wounds Data Set.

C.3.3 *Full Model*

$\log(\beta_0/\tilde{\beta}_0)$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	$-0.1933(1.6715)$	$(-3.4953, 3.3009)$	$0.0339(1.5706)$	$(-2.9346, 3.4147)$
Antiseptic	$1.8676(1.3636)$	$(-0.7731, 4.8291)$	$0.6444(1.2722)$	$(-1.8564, 3.3998)$
Cephalosporin	$0.0859(1.6553)$	$(-3.1802, 3.5417)$	$-0.0138(1.5862)$	$(-3.1462, 3.3212)$
Glycopeptide	$0.1285(1.5976)$	$(-3.0051, 3.5201)$	$0.2373(1.6004)$	$(-2.9337, 3.6009)$
Macrolide	$-1.3135(1.5452)$	$(-4.4467, 1.9335)$	$-0.156(1.4879)$	$(-2.8622, 3.1253)$
Nitroimidazole	$-0.5251(1.6335)$	$(-3.7847, 2.8751)$	$-0.1668(1.5621)$	$(-3.187, 3.1947)$
Oxazolidinone	$-2.2404(1.71)$	$(-5.6461, 1.2973)$	$-2.7492(1.7187)$	$(-6.1866, 0.7765)$
Penicillin	$-0.4699(1.5567)$	$(-3.4803, 2.872)$	$-0.3744(1.6019)$	$(-3.5491, 3.0095)$
Polymyxin	$-2.0536(1.9533)$	$(-6.274, 1.6703)$	$-2.5157(1.5398)$	$(-5.5992, 0.7482)$
Quinolone	$-1.8953(1.3995)$	$(-4.5259, 1.1848)$	$-1.7156(1.5374)$	$(-4.7836, 1.512)$
Rifamycin	$0.2446(1.5406)$	$(-2.615, 3.5988)$	$-2.8798(1.4795)$	$(-5.5349, 0.4005)$

Table C.32: Summary statistics for parameters β_0 and $\tilde{\beta}_0$ for each antimicrobial group for the *Full Model*, for the Wounds Data Set.

$\log(\beta_1/\tilde{\beta}_1)$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	$0.055(1.603)$	$(-3.1504, 3.4116)$	$1.5159(1.3103)$	$(-0.5694, 4.5884)$
Antiseptic	$-0.0775(1.3531)$	$(-2.7647, 2.8571)$	$-0.2459(0.701)$	$(-1.3405, 1.3772)$
Cephalosporin	$0.6451(1.5733)$	$(-2.3527, 4.0277)$	$0.5681(1.1166)$	$(-1.1564, 3.3093)$
Glycopeptide	$-0.6035(1.7011)$	$(-4.0502, 2.9046)$	$1.4114(1.2519)$	$(-0.4862, 4.4192)$
Macrolide	$-1.3395(1.7029)$	$(-4.8145, 2.1904)$	$0.4355(1.4125)$	$(-2.104, 3.6258)$
Nitroimidazole	$-1.2825(1.6171)$	$(-4.6156, 2.022)$	$-0.554(1.4104)$	$(-3.4408, 2.423)$
Oxazolidinone	$-1.8541(1.4746)$	$(-4.4713, 1.403)$	$-0.5793(1.3937)$	$(-2.852, 2.6647)$
Penicillin	$-0.5749(1.4217)$	$(-3.2371, 2.5781)$	$1.1585(1.2216)$	$(-0.6501, 4.1468)$
Polymyxin	$-1.6311(1.7866)$	$(-5.3251, 1.9885)$	$-0.615(1.3083)$	$(-2.5957, 2.5143)$
Quinolone	$-2.1874(1.4346)$	$(-5.2024, 0.7954)$	$-0.3368(1.1119)$	$(-1.9069, 2.4369)$
Rifamycin	$0.6021(1.4317)$	$(-1.8956, 3.8473)$	$-1.7492(1.3428)$	$(-3.8267, 1.4044)$

Table C.33: Summary statistics for parameters β_1 and $\tilde{\beta}_1$ for each antimicrobial group for the *Full Model*, for the Wounds Data Set.

$\log(\beta_1'/\tilde{\beta}_1')$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	0.2591(1.5427)	$(-2.6723, 3.6029)$	$-0.5764(1.477)$	$(-3.567, 2.5105)$
Antiseptic	2.0286(1.6551)	$(-1.3521, 5.4513)$	$-0.4255(1.5153)$	$(-3.7075, 2.5071)$
Cephalosporin	$-0.8001(1.7382)$	$(-4.3047, 2.7423)$	$-1.1134(1.5127)$	$(-4.2267, 1.9806)$
Glycopeptide	0.8201(1.4012)	$(-1.5358, 4.0075)$	$-0.6249(1.332)$	$(-3.4341, 2.1044)$
Macrolide	0.6935(1.3164)	$(-1.5503, 3.7481)$	$-0.9584(1.1208)$	$(-3.169, 1.3745)$
Nitroimidazole	$-0.1571(1.4916)$	$(-3.0548, 3.0019)$	$-0.7387(1.0953)$	$(-2.671, 1.8219)$
Oxazolidinone	NA	NA	NA	NA
Penicillin	$-2.1817(1.7307)$	$(-5.7443, 1.2612)$	$-1.4207(1.7691)$	$(-5.0418, 2.1777)$
Polymyxin	NA	NA	NA	NA
Quinolone	$-1.4459(1.6485)$	$(-4.7982, 1.9319)$	$-1.1738(1.7175)$	$(-4.6296, 2.3399)$
Rifamycin	NA	NA	NA	NA

Table C.34: Summary statistics for parameters β_1' and $\tilde{\beta}_1'$ for each antimicrobial group for the *Full Model*, for the Wounds Data Set.

$\boldsymbol{\phi}$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	0.273(0.0174)	(0.2399, 0.3077)	0.348(0.0181)	(0.3131, 0.3839)
Antiseptic	0.2732(0.0177)	(0.2391, 0.3087)	0.3465(0.0184)	(0.3109, 0.383)
Cephalosporin	0.2699(0.0176)	(0.2367, 0.3055)	0.3502(0.0183)	(0.3146, 0.3863)
Glycopeptide	0.2716(0.0176)	(0.2382, 0.3072)	0.3493(0.0182)	(0.3138, 0.3851)
Macrolide	0.2697(0.0173)	(0.2368, 0.3047)	0.3456(0.0178)	(0.3112, 0.3809)
Nitroimidazole	0.2696(0.0184)	(0.2337, 0.3058)	0.3469(0.0182)	(0.3117, 0.3835)
Oxazolidinone	0.2653(0.0177)	(0.2311, 0.3005)	0.3461(0.0181)	(0.3111, 0.3821)
Penicillin	0.2688(0.0176)	(0.2354, 0.3042)	0.3472(0.0184)	(0.3116, 0.3838)
Polymyxin	0.2709(0.0185)	(0.2341, 0.3065)	0.3422(0.0178)	(0.3081, 0.3774)
Quinolone	0.2719(0.0172)	(0.2392, 0.3063)	0.3468(0.0179)	(0.3124, 0.3826)
Rifamycin	0.2779(0.019)	(0.2413, 0.3155)	0.3421(0.0179)	(0.3079, 0.378)

Table C.35: Summary statistics for parameter ϕ for each antimicrobial group for the *Full Model*, for the Wounds Data Set.

z				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	0.1686(0.0216)	(0.1285, 0.2124)	0.1023(0.0161)	(0.0745, 0.1391)
Antiseptic	0.1588(0.0192)	(0.1215, 0.1978)	0.0979(0.0153)	(0.0694, 0.1295)
Cephalosporin	0.1754(0.0217)	(0.1362, 0.2195)	0.1032(0.016)	(0.0748, 0.1366)
Glycopeptide	0.1695(0.0211)	(0.1323, 0.2147)	0.1011(0.0157)	(0.0712, 0.1328)
Macrolide	0.1695(0.0191)	(0.1332, 0.2088)	0.1034(0.0139)	(0.0765, 0.1309)
Nitroimidazole	0.1678(0.0229)	(0.1265, 0.2179)	0.1025(0.0156)	(0.0749, 0.1371)
Oxazolidinone	0.1842(0.0216)	(0.1434, 0.2283)	0.1035(0.0162)	(0.0736, 0.138)
Penicillin	0.1773(0.0211)	(0.1359, 0.2183)	0.1045(0.0166)	(0.0748, 0.1385)
Polymyxin	0.1698(0.0214)	(0.1332, 0.2157)	0.1061(0.0152)	(0.0786, 0.1382)
Quinolone	0.1723(0.0194)	(0.137, 0.2125)	0.1036(0.0145)	(0.0767, 0.1336)
Rifamycin	0.1605(0.0232)	(0.1185, 0.2088)	0.1106(0.0146)	(0.083, 0.1393)

Table C.36: Summary statistics for parameter z for each antimicrobial group for the *Full Model*, for the Wounds Data Set.

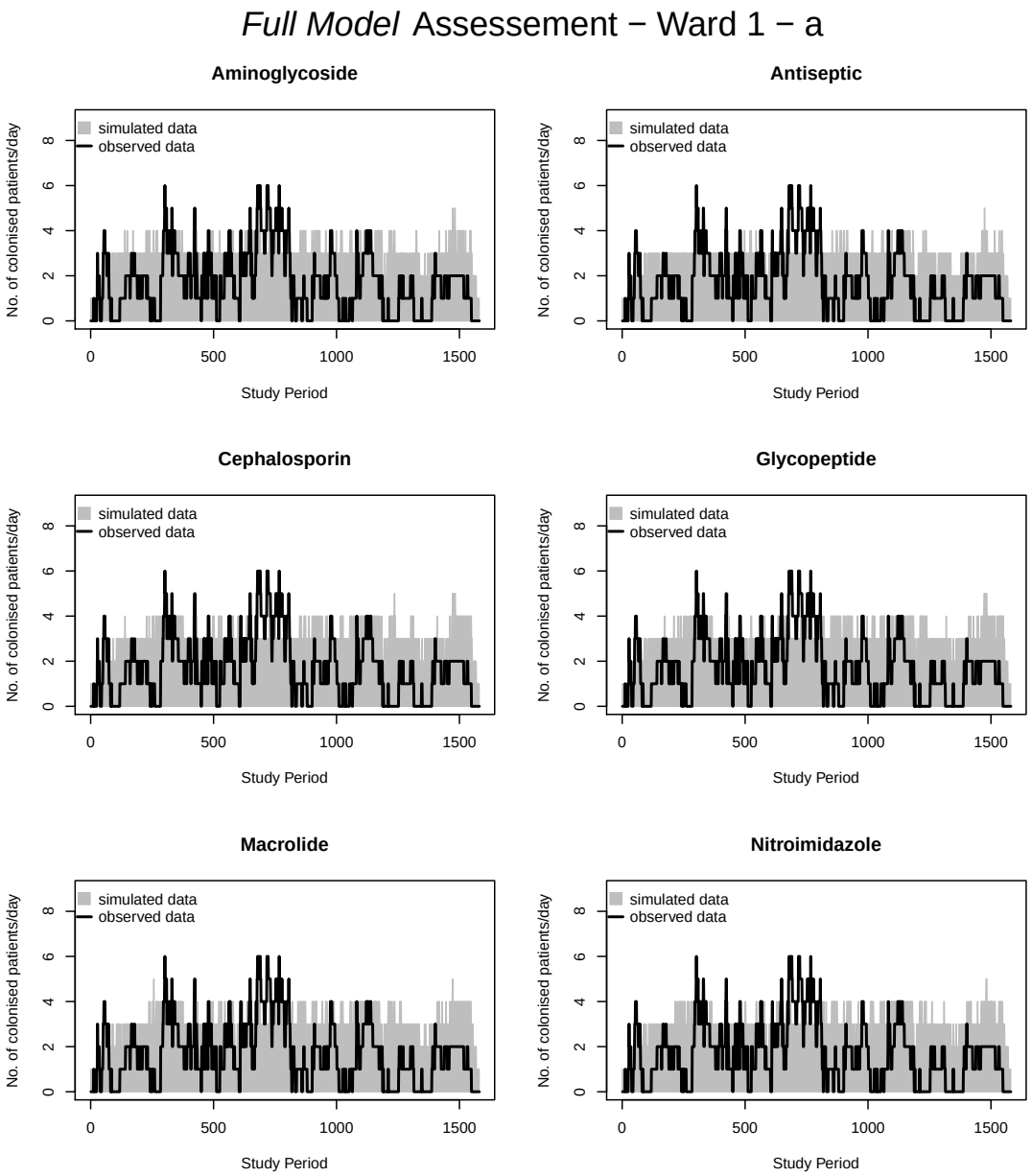

Figure C.27: Plots showing the *Full Model* assessement for the first 6 of the antimicrobials of ward 1, for the Wounds Data Set.

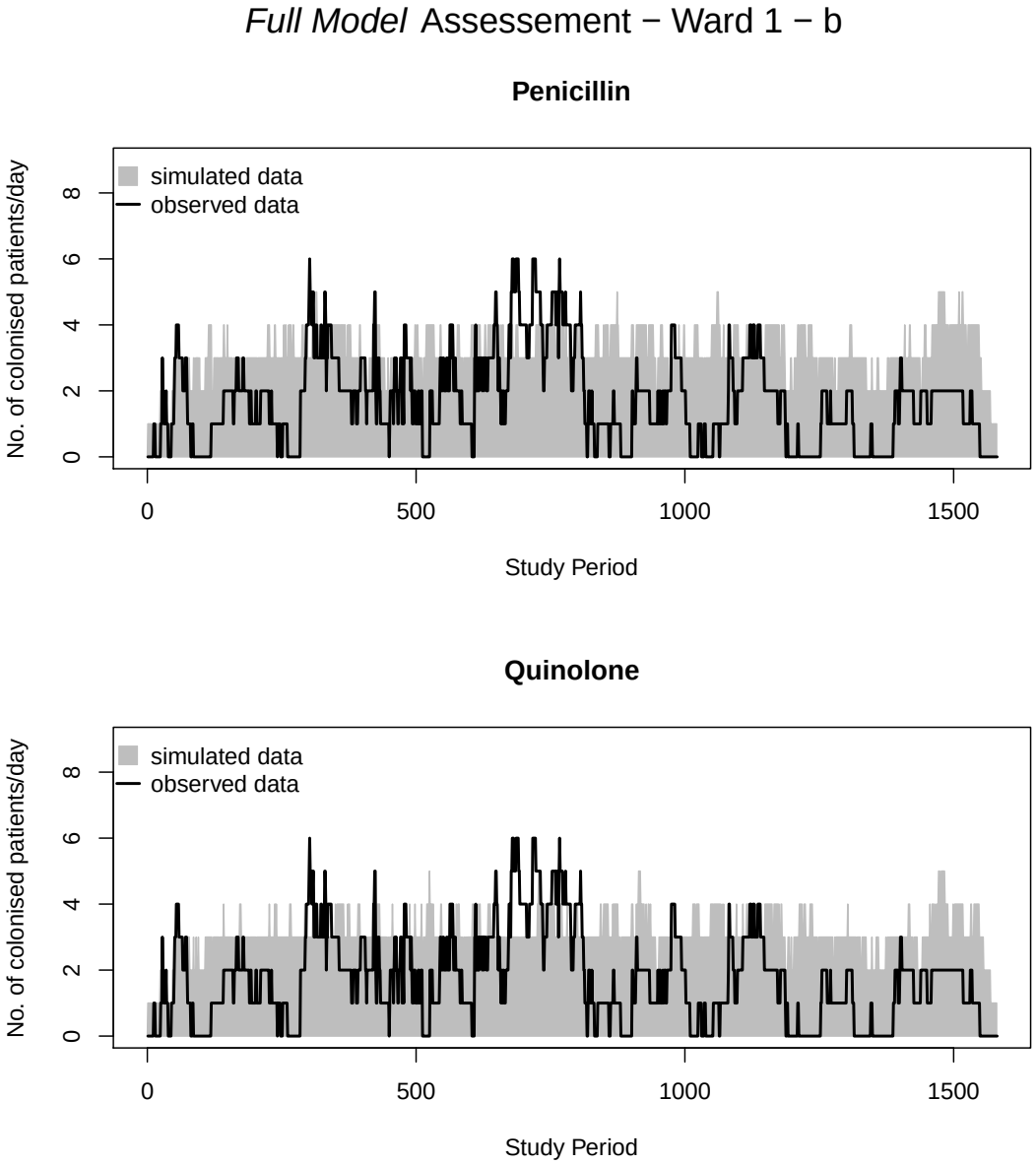

Figure C.28: Plots showing the *Full Model* assessement for the next 2 of the antimicrobials of ward 1, for the Wounds Data Set.

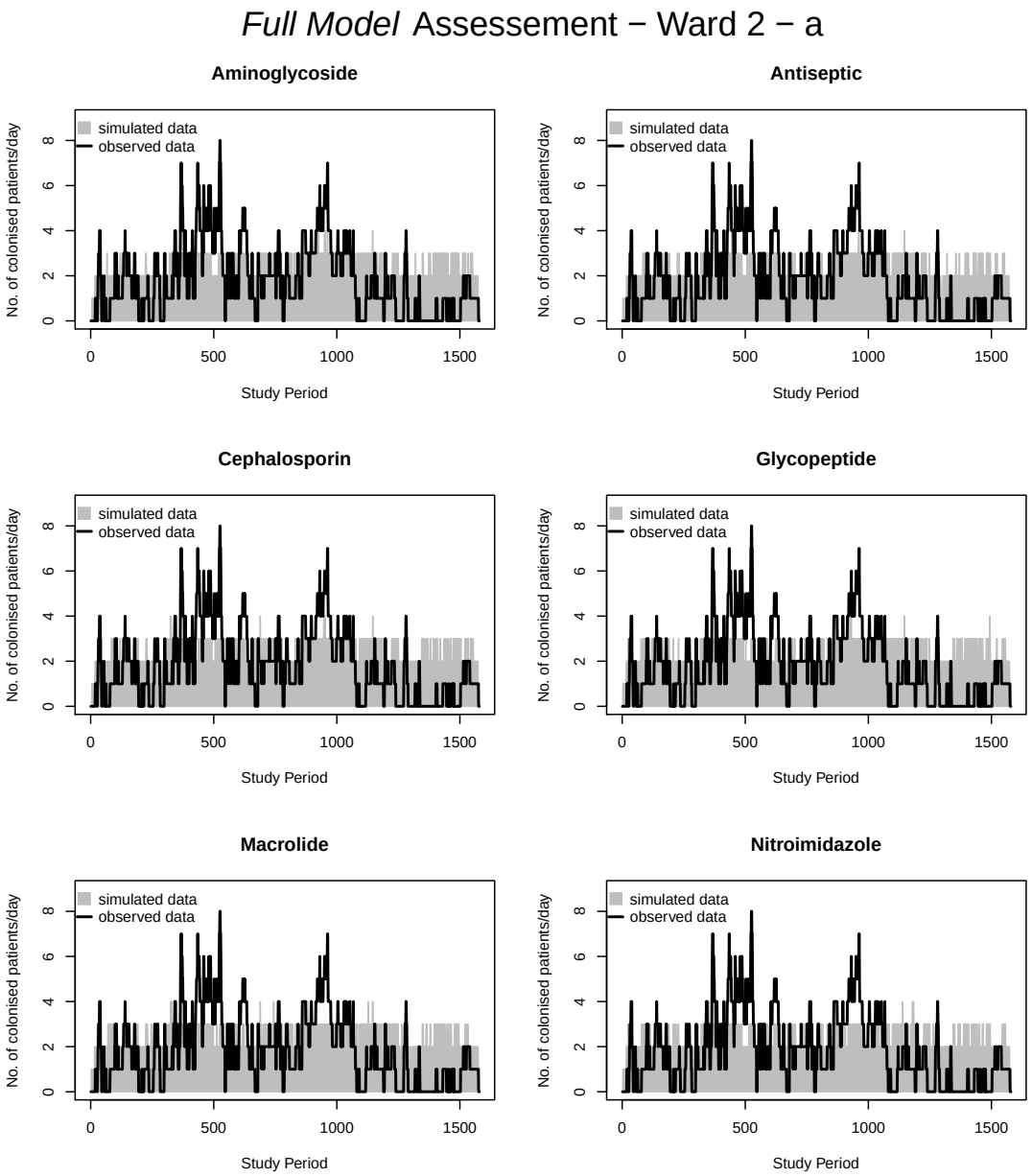

Figure C.29: Plots showing the *Full Model* assessement for the first 6 of the antimicrobials of ward 2, for the Wounds Data Set.

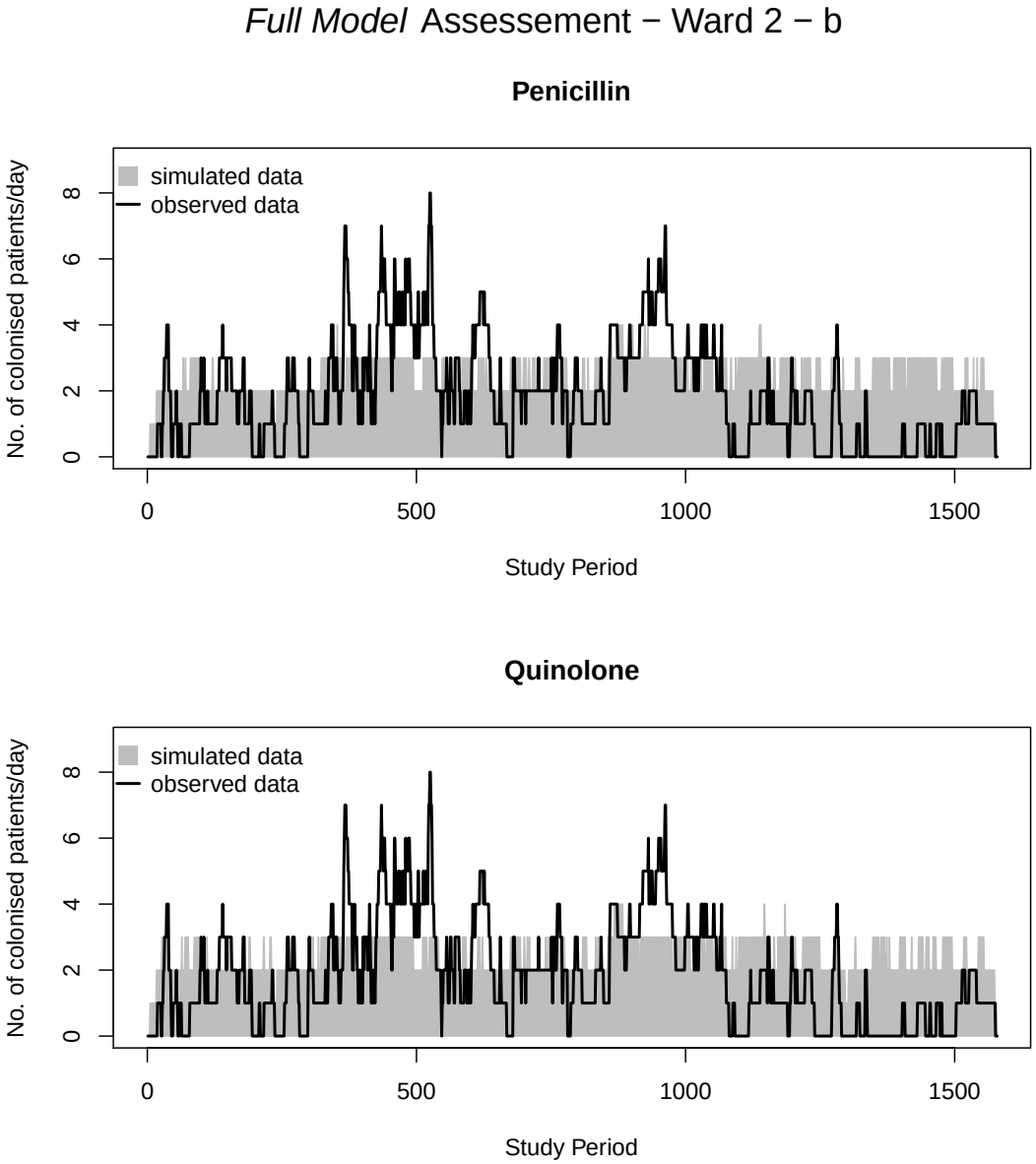

Figure C.30: Plots showing the *Full Model* assessement for the next 2 of the antimicrobials of ward 2, for the Wounds Data Set.

C.4 Respiratory Data Set

C.4.1 *Susceptibility Model*

$\log(\beta_0/\tilde{\beta}_0)$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	0.5925(1.5779)	$(-2.4947, 3.9999)$	0.1361(1.4214)	$(-2.4046, 3.3279)$
Antiseptic	1.3057(1.2706)	$(-0.9622, 4.1826)$	0.6792(1.1231)	$(-1.4418, 3.1491)$
Cephalosporin	$-1.9341(1.4933)$	$(-5.1088, 1.053)$	$-0.8131(1.5886)$	$(-4.0988, 2.4921)$
Glycopeptide	0.0159(1.554)	$(-2.9142, 3.363)$	$-0.2966(1.5347)$	$(-3.4441, 2.854)$
Macrolide	$-2.4275(1.4509)$	$(-5.6617, 0.1784)$	$-1.3954(1.3605)$	$(-4.3596, 1.2113)$
Nitroimidazole	$-0.4567(1.5176)$	$(-3.3843, 2.8352)$	$-1.3693(1.443)$	$(-4.4116, 1.5489)$
Oxazolidinone	NA	NA	NA	NA
Penicillin	$-0.5378(1.5937)$	$(-3.6955, 2.8135)$	$-0.9788(1.3973)$	$(-3.6084, 2.0908)$
Polymyxin	NA	NA	NA	NA
Quinolone	$-1.738(1.5806)$	$(-4.927, 1.5872)$	$-1.5261(1.4873)$	$(-4.4057, 1.6682)$
Rifamycin	0.0154(1.5842)	$(-3.0008, 3.4063)$	NA	NA

Table C.37: Summary statistics for parameters β_0 and $\tilde{\beta}_0$ for each antimicrobial group for the *Susceptibility Model*, for the Respiratory Data Set.

$\log(\beta_1/\tilde{\beta}_1)$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	1.1513(1.2838)	$(-0.8656, 4.2335)$	0.4444(1.2656)	$(-1.684, 3.3947)$
Antiseptic	1.0646(1.2607)	$(-1.1928, 3.9406)$	0.7875(1.2866)	$(-1.6777, 3.6505)$
Cephalosporin	$-0.0821(1.2131)$	$(-2.1294, 2.7834)$	0.4292(1.1728)	$(-1.4246, 3.238)$
Glycopeptide	$-0.2012(1.0207)$	$(-2.145, 2.0461)$	0.7376(1.2544)	$(-1.3565, 3.6597)$
Macrolide	1.157(1.2636)	$(-0.7238, 4.2388)$	0.2828(1.3108)	$(-2.0319, 3.2581)$
Nitroimidazole	$-0.2441(1.1066)$	$(-2.0446, 2.3534)$	0.0796(1.17)	$(-1.677, 2.9387)$
Oxazolidinone	NA	NA	NA	NA
Penicillin	0.3138(1.288)	$(-1.6856, 3.3732)$	$-0.1453(1.3321)$	$(-2.4959, 2.8897)$
Polymyxin	NA	NA	NA	NA
Quinolone	$-1.2023(1.0083)$	$(-2.9061, 1.1686)$	$-1.1535(1.1345)$	$(-3.0902, 1.4997)$
Rifamycin	1.0165(1.3501)	$(-1.144, 4.1833)$	NA	NA

Table C.38: Summary statistics for parameters β_1 and $\tilde{\beta}_1$ for each antimicrobial group for the *Susceptibility Model*, for the Respiratory Data Set.

ϕ				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	0.568(0.036)	(0.4961, 0.6375)	0.4907(0.0362)	(0.421, 0.5626)
Antiseptic	0.5702(0.035)	(0.4996, 0.6362)	0.4919(0.0359)	(0.4223, 0.5633)
Cephalosporin	0.5692(0.0356)	(0.4962, 0.6358)	0.488(0.0362)	(0.4182, 0.5595)
Glycopeptide	0.571(0.0357)	(0.5009, 0.6401)	0.4816(0.0375)	(0.4079, 0.5542)
Macrolide	0.5748(0.0363)	(0.5013, 0.6435)	0.4861(0.0373)	(0.4134, 0.5595)
Nitroimidazole	0.5705(0.0363)	(0.4995, 0.6409)	0.4797(0.0401)	(0.4016, 0.5579)
Oxazolidinone	0.5409(0.0353)	(0.4719, 0.6098)	0.4727(0.0382)	(0.396, 0.546)
Penicillin	0.5711(0.0342)	(0.5032, 0.6379)	0.4782(0.0377)	(0.4057, 0.5521)
Polymyxin	0.5531(0.0341)	(0.486, 0.6198)	0.4659(0.0334)	(0.4, 0.5309)
Quinolone	0.5591(0.035)	(0.4899, 0.6271)	0.4906(0.0375)	(0.4183, 0.5647)
Rifamycin	0.5719(0.0357)	(0.5017, 0.6416)	0.4681(0.0347)	(0.3997, 0.5362)

Table C.39: Summary statistics for parameter ϕ for each antimicrobial group for the *Susceptibility Model*, for the Respiratory Data Set.

$\mathbf{z}$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	0.1425(0.0211)	(0.1035, 0.1851)	0.1227(0.0234)	(0.0812, 0.1734)
Antiseptic	0.1416(0.0209)	(0.1022, 0.1852)	0.1175(0.0225)	(0.078, 0.1666)
Cephalosporin	0.1388(0.0216)	(0.0991, 0.1849)	0.1214(0.0217)	(0.0825, 0.1665)
Glycopeptide	0.1447(0.0213)	(0.1043, 0.1883)	0.1244(0.0224)	(0.0852, 0.1719)
Macrolide	0.1413(0.0219)	(0.1017, 0.1877)	0.1222(0.0238)	(0.079, 0.1699)
Nitroimidazole	0.1449(0.0239)	(0.1042, 0.1986)	0.1187(0.0242)	(0.0752, 0.1684)
Oxazolidinone	0.1615(0.0239)	(0.116, 0.2091)	0.1303(0.0274)	(0.0845, 0.1937)
Penicillin	0.1401(0.0206)	(0.1019, 0.1824)	0.1332(0.022)	(0.0929, 0.1794)
Polymyxin	0.1526(0.0226)	(0.109, 0.1974)	0.1379(0.0219)	(0.0963, 0.1823)
Quinolone	0.1519(0.0225)	(0.1105, 0.1981)	0.1237(0.0224)	(0.0831, 0.1711)
Rifamycin	0.1439(0.0214)	(0.1041, 0.189)	0.1281(0.0222)	(0.0862, 0.174)

Table C.40: Summary statistics for parameter z for each antimicrobial group for the *Susceptibility Model*, for the Respiratory Data Set.

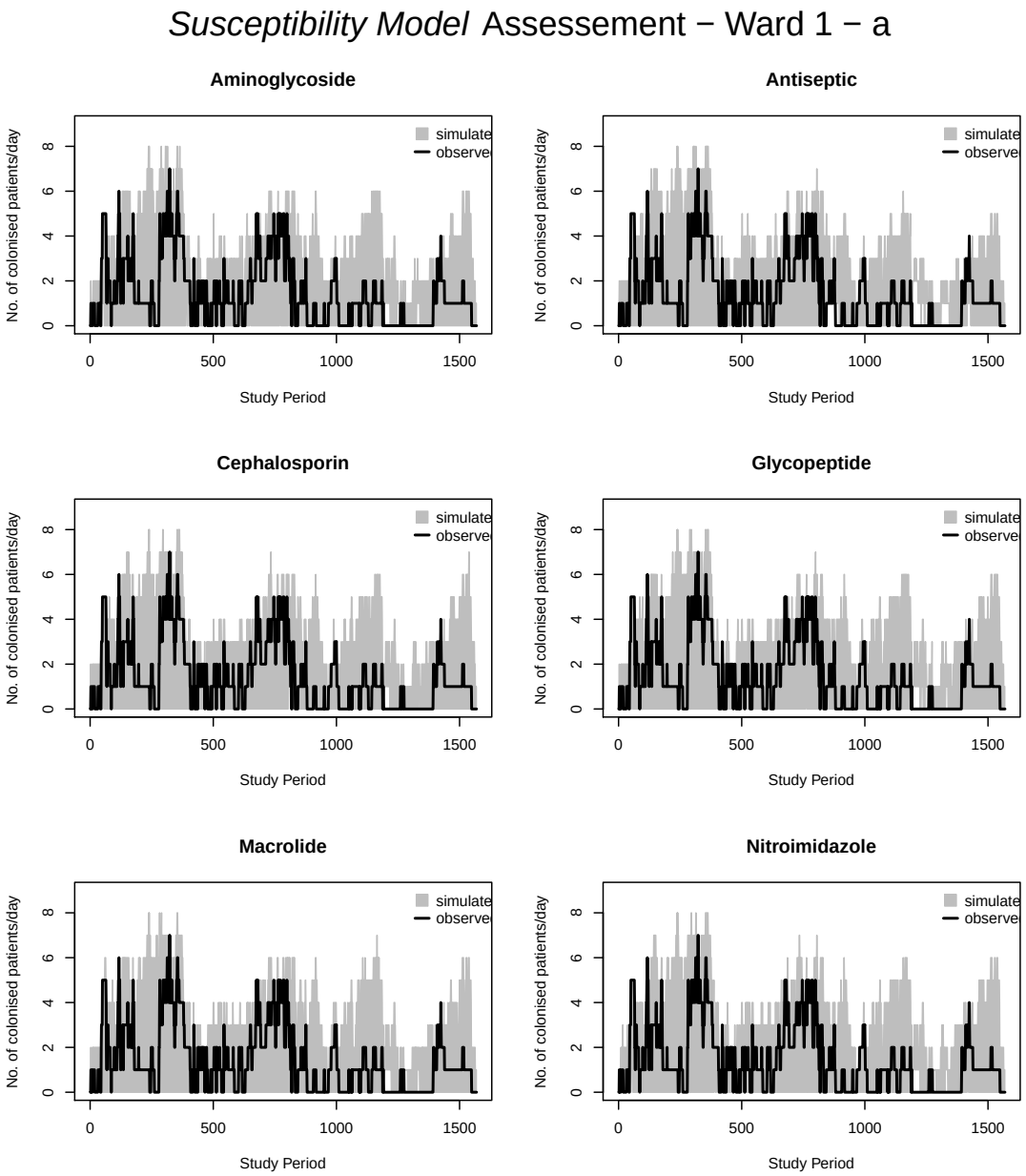

Figure C.31: Plots showing the *Susceptibility Model* assessement for the first 6 of the antimicrobials of ward 1, for the Respiratory Data Set.

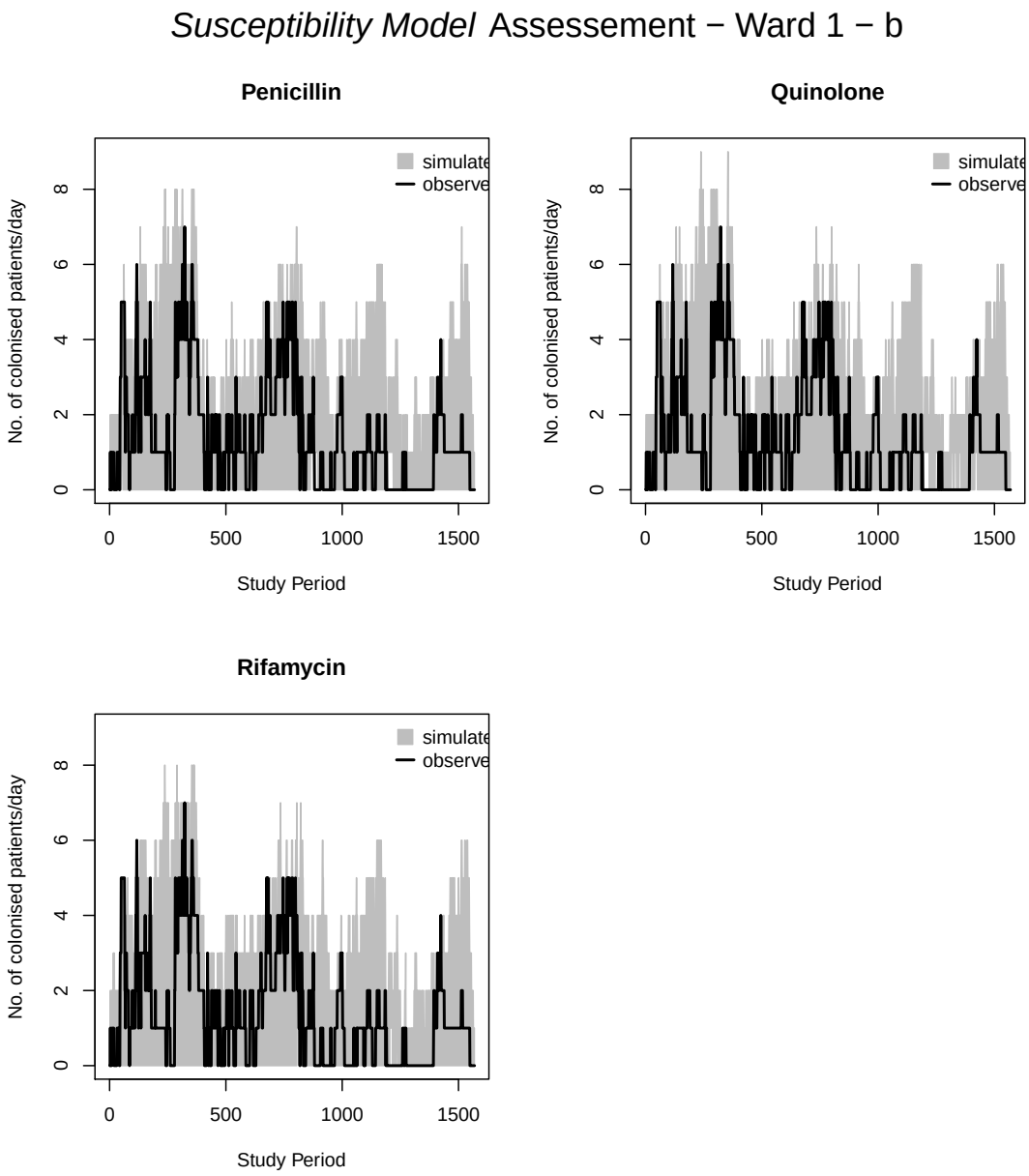

Figure C.32: Plots showing the *Susceptibility Model* assessement for the next 3 of the antimicrobials of ward 1, for the Respiratory Data Set.

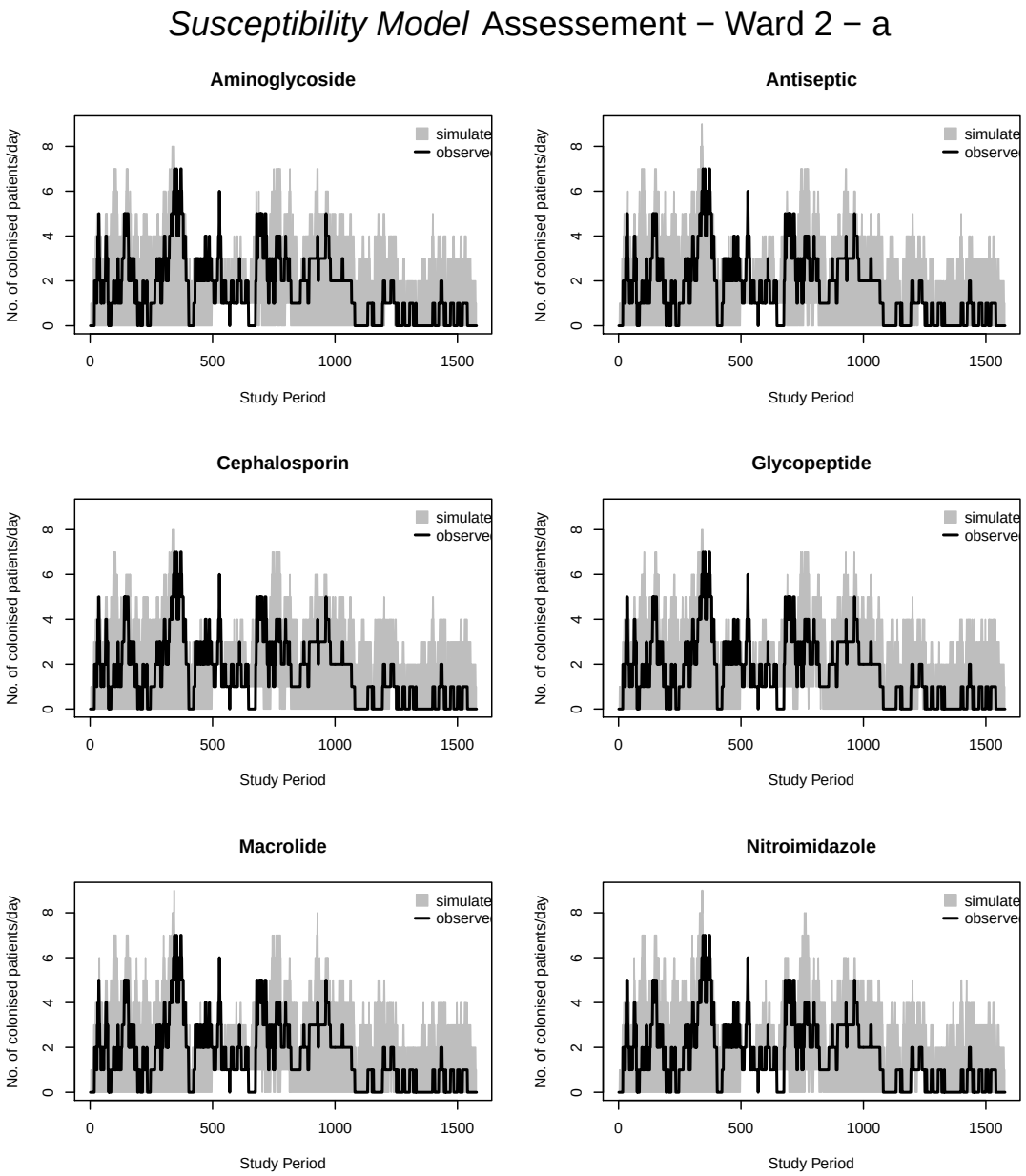

Figure C.33: Plots showing the *Susceptibility Model* assessement for the first 6 of the antimicrobials of ward 2, for the Respiratory Data Set.

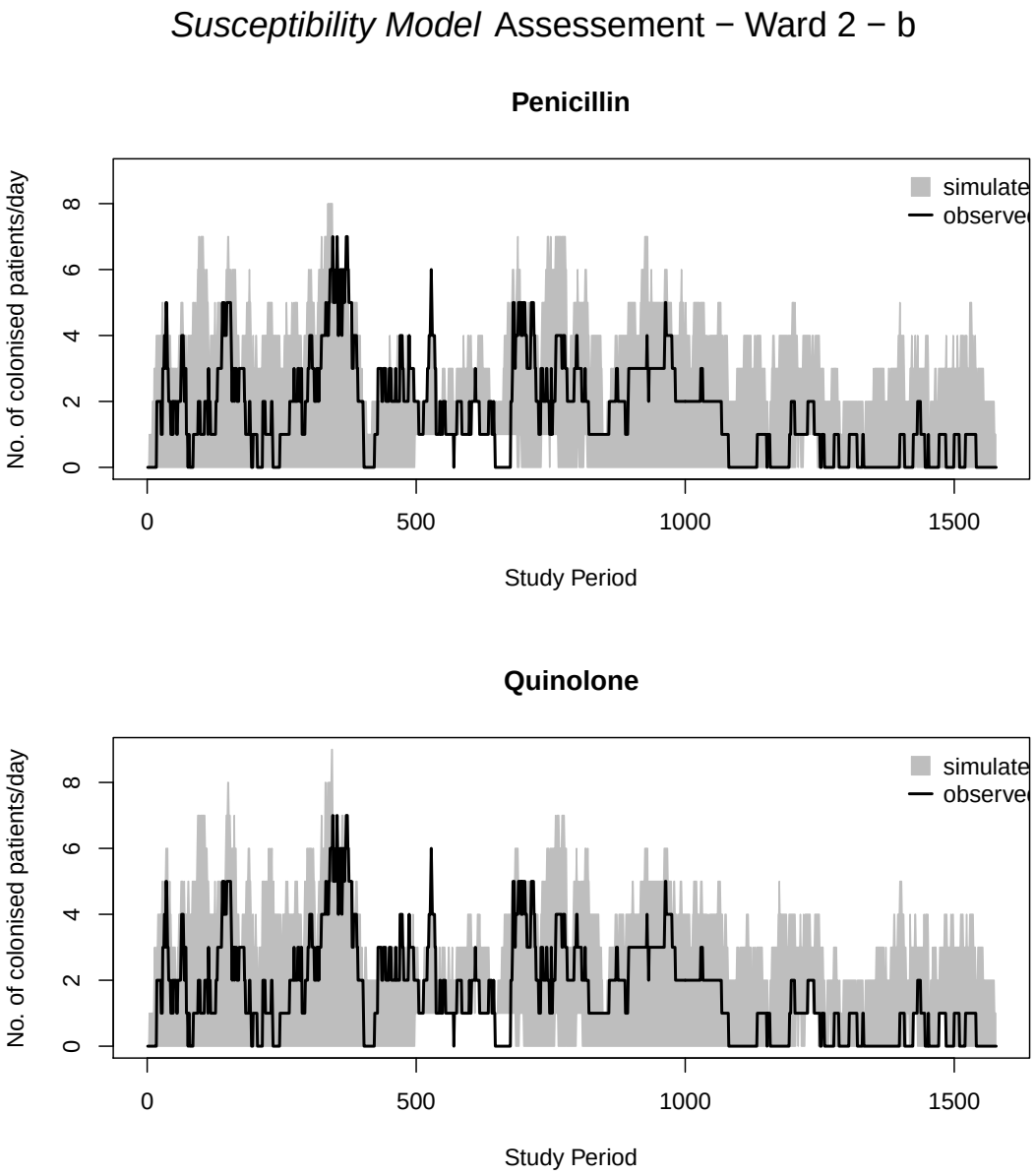

Figure C.34: Plots showing the *Susceptibility Model* assessement for the next 2 of the antimicrobials of ward 2, for the Respiratory Data Set.

C.4.2 *Infectivity Model*

β_0				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	0.0052(0.0034)	(0.0005, 0.0134)	0.0082(0.0052)	(0.0008, 0.0207)
Antiseptic	0.0055(0.003)	(0.0007, 0.0123)	0.0075(0.0042)	(0.0009, 0.0172)
Cephalosporin	0.0048(0.0031)	(0.0004, 0.0121)	0.009(0.0056)	(0.0008, 0.0214)
Glycopeptide	0.0057(0.0034)	(0.0005, 0.0133)	0.0099(0.0049)	(0.0017, 0.0207)
Macrolide	0.0051(0.0032)	(0.0005, 0.013)	0.0092(0.0051)	(0.0012, 0.0205)
Nitroimidazole	0.0046(0.0031)	(0.0003, 0.0118)	0.0113(0.0059)	(0.0015, 0.0239)
Oxazolidinone	0.005(0.0032)	(0.0004, 0.0127)	0.0108(0.0066)	(0.0015, 0.027)
Penicillin	0.0051(0.0032)	(0.0004, 0.0124)	0.0099(0.0054)	(0.0013, 0.0225)
Polymyxin	0.0059(0.0038)	(0.0004, 0.0146)	0.0094(0.0055)	(0.0009, 0.0216)
Quinolone	0.0065(0.0038)	(0.0007, 0.015)	0.0108(0.0056)	(0.0018, 0.0231)
Rifamycin	0.0056(0.0034)	(0.0004, 0.0133)	0.0107(0.0062)	(0.0012, 0.0253)

Table C.41: Summary statistics for parameters β_0 for each antimicrobial group for the *Infectivity Model*, for the Respiratory Data Set.

$\log(\beta_1/\beta_1^{'})$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	$-1.1584(1.0771)$	$(-3.0249, 1.2878)$	$-1.2731(1.2016)$	$(-3.395, 1.5184)$
Antiseptic	1.5381(1.1245)	(0.0017, 4.3725)	1.648(1.0089)	(0.2477, 4.2706)
Cephalosporin	$-1.1999(0.9962)$	$(-2.9637, 1.0306)$	$-0.2811(1.3737)$	$(-2.6257, 2.8908)$
Glycopeptide	$-0.3054(1.3764)$	$(-3.0855, 2.6008)$	$-2.1824(1.3083)$	$(-5.2109, 0.0625)$
Macrolide	$-1.0782(1.1749)$	$(-3.3232, 1.4962)$	$-2.2531(0.9604)$	$(-4.4896, -0.6459)$
Nitroimidazole	$-1.7077(1.0488)$	$(-3.8232, 0.3897)$	$-0.5324(1.333)$	$(-2.7936, 2.5714)$
Oxazolidinone	$-1.5461(1.3086)$	$(-3.6186, 1.5008)$	$-1.684(1.4728)$	$(-4.3702, 1.5571)$
Penicillin	$-0.1436(1.3253)$	$(-2.1841, 2.9802)$	$-0.9845(1.4092)$	$(-3.4915, 2.188)$
Polymyxin	$-1.4033(1.3358)$	$(-3.5725, 1.7129)$	$-1.4816(1.3243)$	$(-3.6376, 1.5207)$
Quinolone	$-1.8414(1.2572)$	$(-4.419, 0.7491)$	$-0.7486(1.3405)$	$(-3.2455, 2.2588)$
Rifamycin	$-2.7742(0.7591)$	$(-4.3896, -1.4035)$	$-3.1343(0.9462)$	$(-4.9181, -1.1638)$

Table C.42: Summary statistics for parameters β_1 and $\beta_1^{'}$ for each antimicrobial group for the *Infectivity Model*, for the Respiratory Data Set.

ϕ				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	0.57(0.0352)	(0.5007, 0.6395)	0.4853(0.0358)	(0.4169, 0.5569)
Antiseptic	0.57(0.0352)	(0.5016, 0.6391)	0.4938(0.0375)	(0.4218, 0.5675)
Cephalosporin	0.5745(0.0357)	(0.5044, 0.6434)	0.4886(0.0357)	(0.4178, 0.5575)
Glycopeptide	0.565(0.0354)	(0.4956, 0.6341)	0.489(0.0368)	(0.4185, 0.5622)
Macrolide	0.5714(0.0354)	(0.5014, 0.6399)	0.4935(0.0383)	(0.4185, 0.5685)
Nitroimidazole	0.5661(0.0355)	(0.4969, 0.6365)	0.484(0.0387)	(0.4092, 0.5604)
Oxazolidinone	0.5733(0.0355)	(0.5031, 0.6423)	0.4782(0.0396)	(0.4003, 0.5562)
Penicillin	0.5708(0.034)	(0.5037, 0.6371)	0.4924(0.0373)	(0.4197, 0.567)
Polymyxin	0.5627(0.0352)	(0.4934, 0.6302)	0.4867(0.0382)	(0.4137, 0.5618)
Quinolone	0.5685(0.035)	(0.5017, 0.6385)	0.4894(0.0375)	(0.4149, 0.5615)
Rifamycin	0.5659(0.0368)	(0.4937, 0.6365)	0.4843(0.0381)	(0.4108, 0.5605)

Table C.43: Summary statistics for parameter ϕ for each antimicrobial group for the *Infectivity Model*, for the Respiratory Data Set.

$\mathbf{z}$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot \mid \boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	0.1451(0.021)	(0.1051, 0.1872)	0.1262(0.0209)	(0.0877, 0.1699)
Antiseptic	0.1427(0.021)	(0.1029, 0.186)	0.1216(0.0219)	(0.0825, 0.1685)
Cephalosporin	0.1431(0.022)	(0.1047, 0.1912)	0.1257(0.0228)	(0.0849, 0.1735)
Glycopeptide	0.1496(0.0207)	(0.111, 0.1929)	0.1198(0.0227)	(0.0793, 0.1663)
Macrolide	0.1416(0.0207)	(0.1025, 0.1839)	0.1179(0.0238)	(0.0774, 0.1698)
Nitroimidazole	0.1502(0.0237)	(0.1062, 0.198)	0.1185(0.0232)	(0.0759, 0.1678)
Oxazolidinone	0.1433(0.0205)	(0.1048, 0.1849)	0.128(0.0223)	(0.0858, 0.1724)
Penicillin	0.1456(0.021)	(0.1076, 0.1904)	0.1243(0.0225)	(0.0825, 0.1695)
Polymyxin	0.1499(0.0232)	(0.1079, 0.1975)	0.1257(0.0209)	(0.0869, 0.1683)
Quinolone	0.1479(0.0236)	(0.1055, 0.1968)	0.1251(0.0213)	(0.086, 0.1702)
Rifamycin	0.1515(0.022)	(0.1118, 0.196)	0.1224(0.0222)	(0.0836, 0.1709)

Table C.44: Summary statistics for parameter z for each antimicrobial group for the *Infectivity Model*, for the Respiratory Data Set.

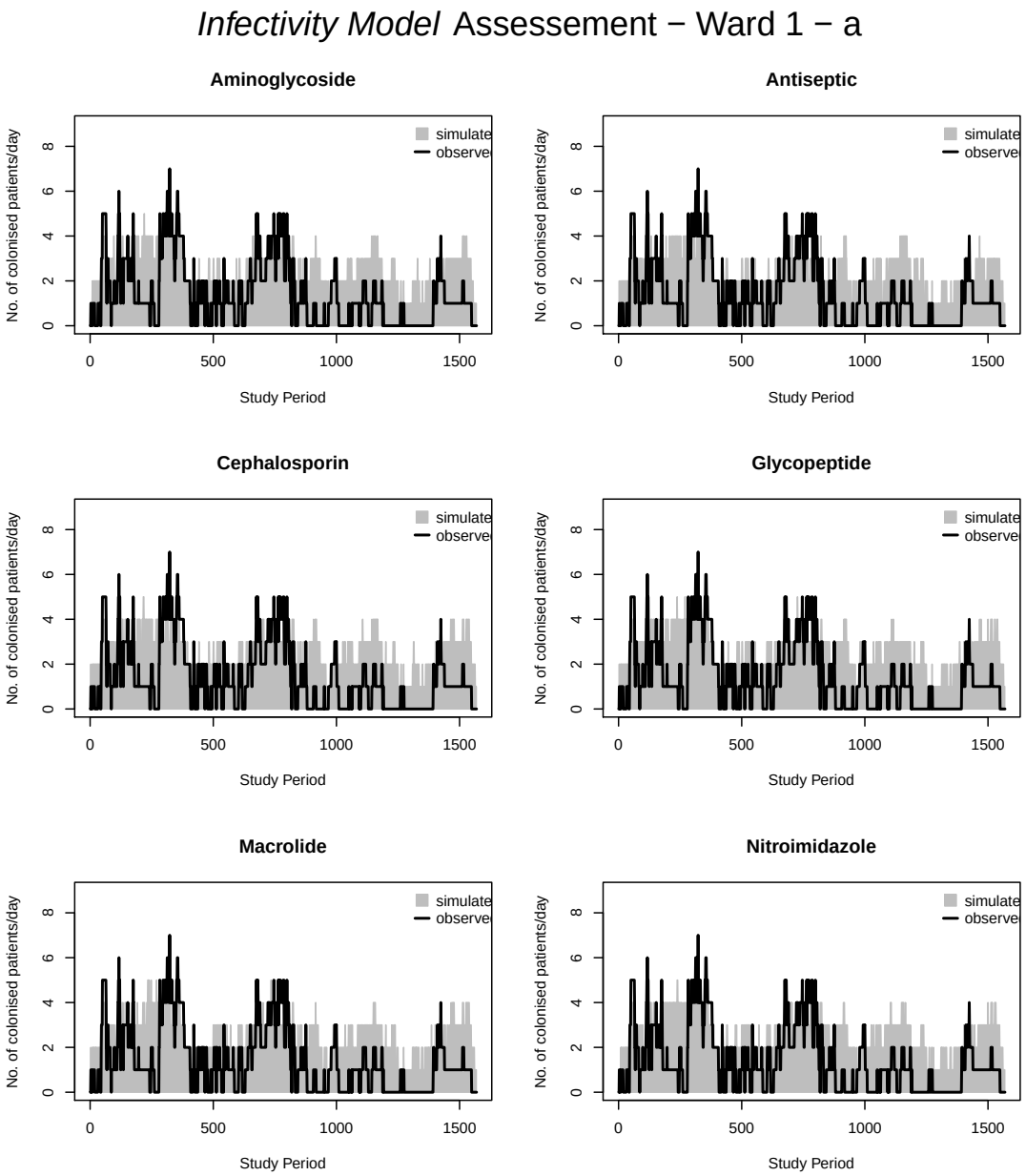

Figure C.35: Plots showing the *Infectivity Model* assessement for the first 6 of the antimicrobials of ward 1, for the Respiratory Data Set.

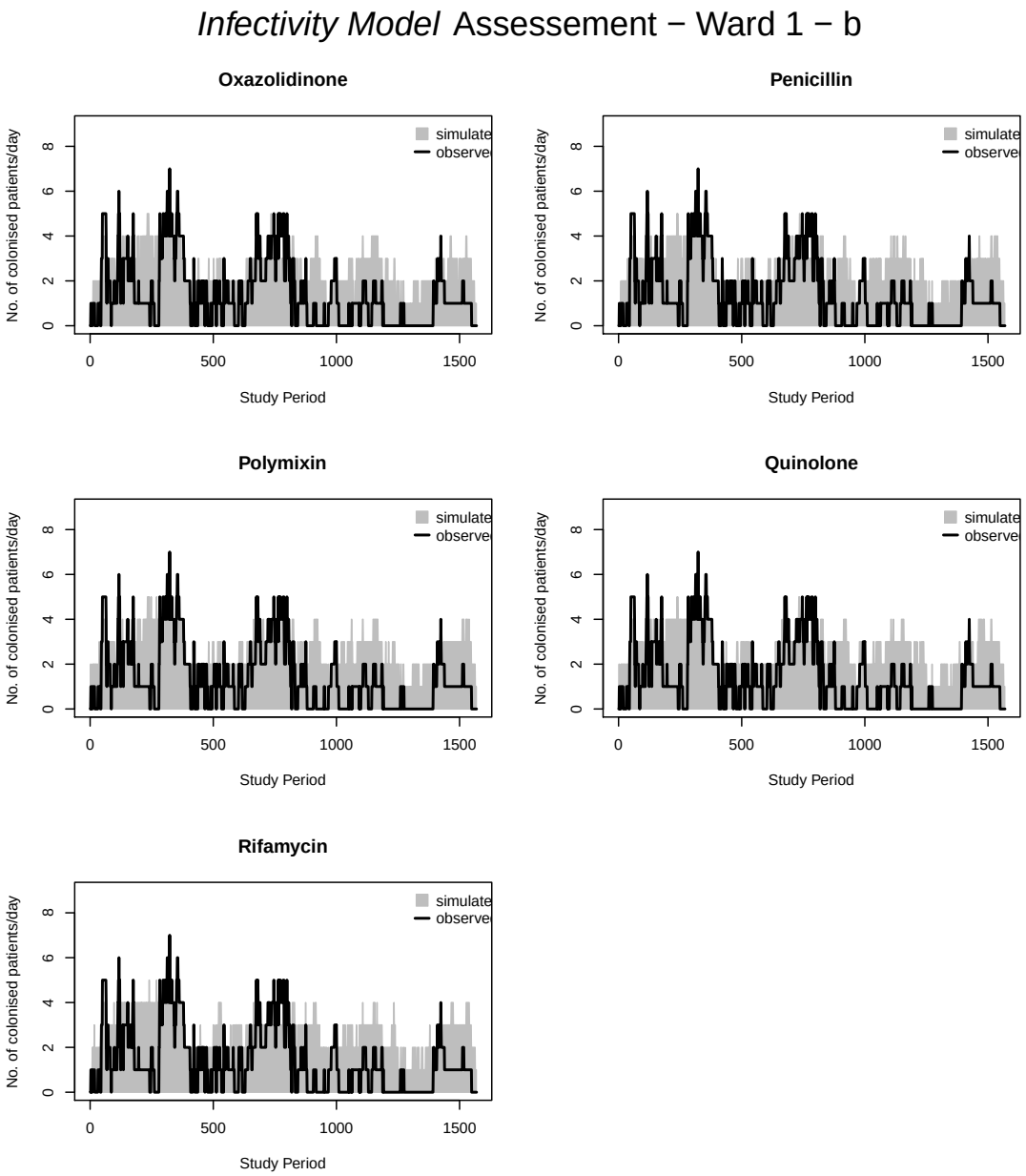

Figure C.36: Plots showing the *Infectivity Model* assessement for the next 5 of the antimicrobials of ward 1, for the Respiratory Data Set.

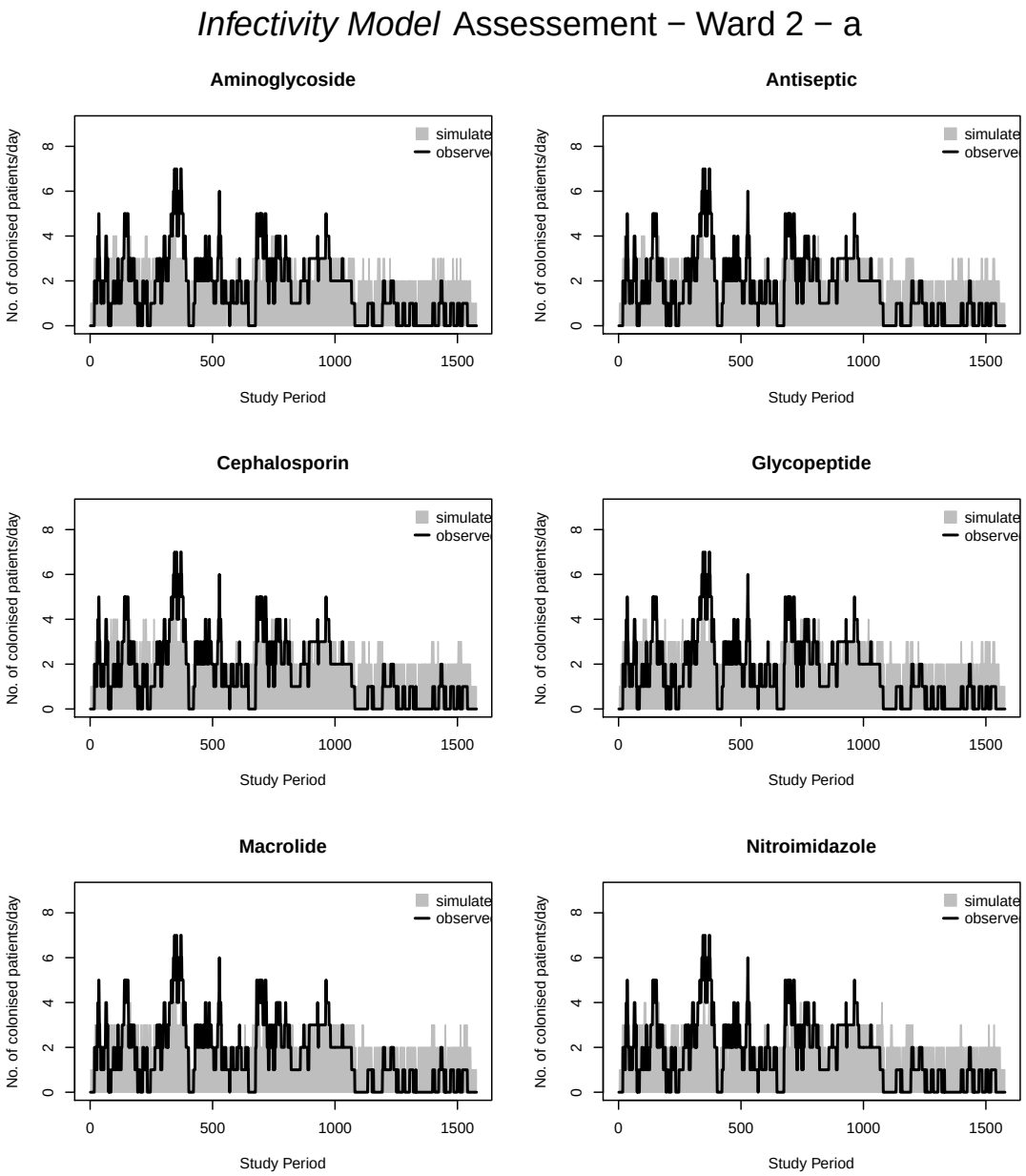

Figure C.37: Plots showing the *Infectivity Model* assessement for the first 6 of the antimicrobials of ward 2, for the Respiratory Data Set.

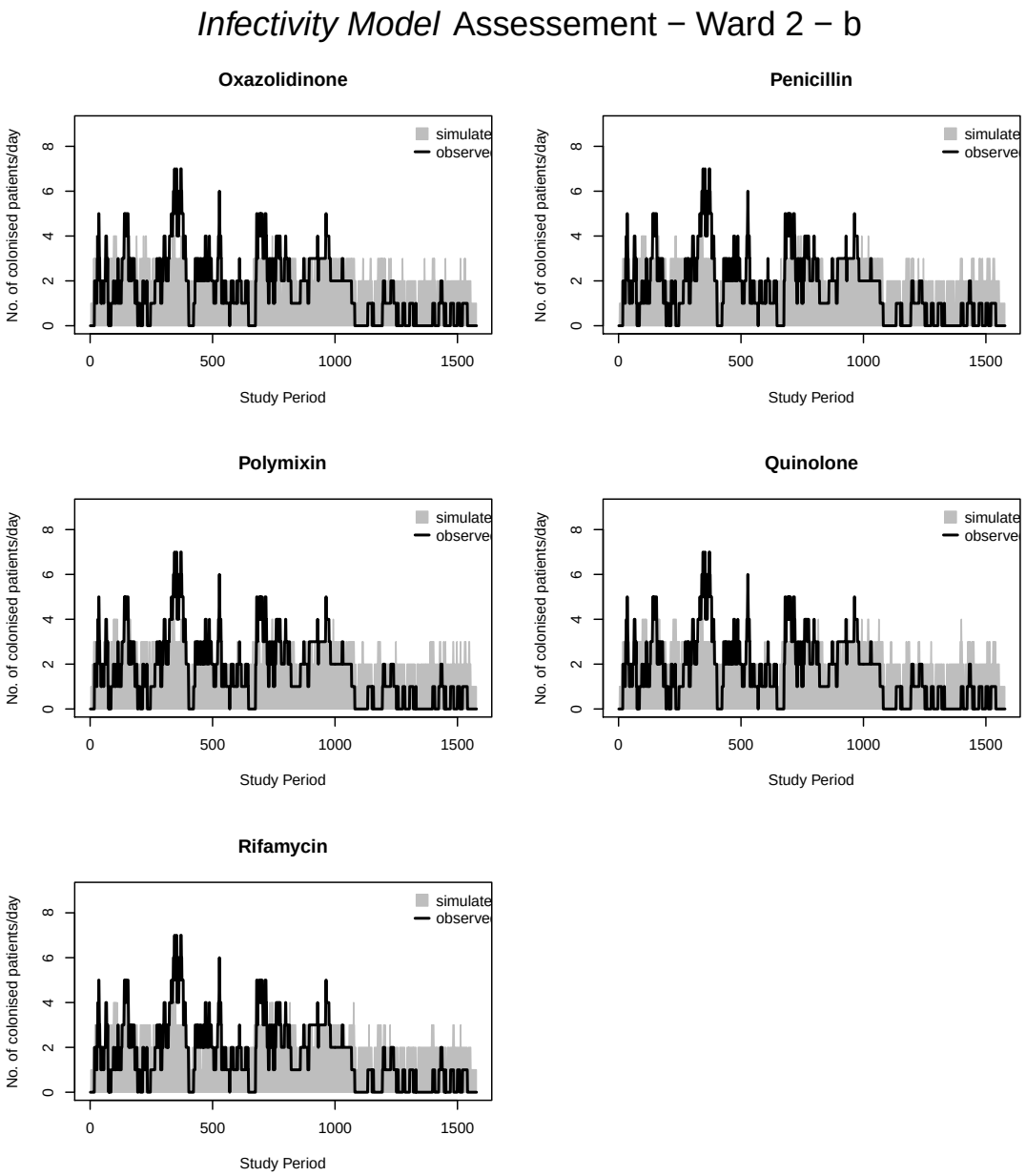

Figure C.38: Plots showing the *Infectivity Model* assessement for the next 5 of the antimicrobials of ward 2, for the Respiratory Data Set.

C.4.3 *Full Model*

$\log(\beta_0/\tilde{\beta}_0)$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	0.4279(1.5939)	$(-2.6437, 3.8377)$	0.1486(1.5246)	$(-2.7416, 3.4409)$
Antiseptic	1.34(1.3317)	$(-1.093, 4.3194)$	0.0959(1.3712)	$(-2.7502, 2.9367)$
Cephalosporin	-1.2785(1.5548)	$(-4.5354, 1.81)$	-0.693(1.5496)	$(-3.8885, 2.5314)$
Glycopeptide	0.1423(1.6194)	$(-3.0836, 3.5879)$	0.1106(1.363)	$(-2.3734, 3.1741)$
Macrolide	-2.3056(1.4535)	$(-5.5474, 0.3855)$	-1.426(1.3492)	$(-4.4194, 1.1858)$
Nitroimidazole	-0.3956(1.5045)	$(-3.3024, 2.85)$	-1.0732(1.3511)	$(-3.7033, 1.7899)$
Oxazolidinone	NA	NA	NA	NA
Penicillin	-0.408(1.5559)	$(-3.4661, 2.9013)$	-0.7777(1.3435)	$(-3.2405, 2.184)$
Polymyxin	NA	NA	NA	NA
Quinolone	-1.3651(1.5092)	$(-4.3812, 1.8398)$	-1.3633(1.4784)	$(-4.2409, 1.787)$
Rifamycin	0.8697(1.4955)	$(-1.792, 4.1704)$	NA	NA

Table C.45: Summary statistics for parameters β_0 and $\tilde{\beta}_0$ for each antimicrobial group for the *Full Model*, for the Respiratory Data Set.

$\log(\beta_1/\tilde{\beta}_1)$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	0.5005(1.42)	$(-2.054, 3.6426)$	0.671(1.2823)	$(-1.526, 3.6519)$
Antiseptic	0.6221(1.3327)	$(-1.5822, 3.6972)$	0.3789(1.1297)	$(-1.2848, 3.128)$
Cephalosporin	0.5196(1.2598)	$(-1.5188, 3.5024)$	0.1466(1.2368)	$(-2.0196, 3.0418)$
Glycopeptide	-0.8137(1.3748)	$(-3.7539, 2.0559)$	0.0699(1.5749)	$(-3.0706, 3.3742)$
Macrolide	1.0276(1.3193)	$(-1.0064, 4.1776)$	-0.4758(1.5254)	$(-3.488, 2.775)$
Nitroimidazole	-0.5441(1.326)	$(-3.0734, 2.3343)$	0.0032(1.3479)	$(-2.3411, 3.0816)$
Oxazolidinone	NA	NA	NA	NA
Penicillin	0.4941(1.3)	$(-1.5046, 3.5736)$	-0.342(1.3985)	$(-2.7818, 2.7925)$
Polymyxin	NA	NA	NA	NA
Quinolone	-1.5501(1.3476)	$(-4.1707, 1.3085)$	-0.8768(1.2465)	$(-3.0067, 2.0107)$
Rifamycin	1.2282(1.4034)	$(-1.1482, 4.4259)$	NA	NA

Table C.46: Summary statistics for parameters β_1 and $\tilde{\beta}_1$ for each antimicrobial group for the *Full Model*, for the Respiratory Data Set.

$\log(\beta_1'/\tilde{\beta}_1')$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	0.5414(1.568)	$(-2.556, 3.8976)$	$-0.6714(1.6795)$	$(-4.1312, 2.67)$
Antiseptic	0.5326(1.5246)	$(-2.6658, 3.607)$	$-0.1084(1.5638)$	$(-3.3335, 3.0917)$
Cephalosporin	$-2.2363(1.4735)$	$(-5.468, 0.3973)$	0.0119(1.6805)	$(-3.4129, 3.4656)$
Glycopeptide	0.346(1.5236)	$(-2.5822, 3.6357)$	0.3974(1.1723)	$(-1.4982, 3.2461)$
Macrolide	0.2352(1.5557)	$(-2.8414, 3.4995)$	0.8676(1.3822)	$(-1.4556, 3.9539)$
Nitroimidazole	$-0.3358(1.4912)$	$(-3.302, 2.8056)$	$-1.0312(1.6868)$	$(-4.4306, 2.4386)$
Oxazolidinone	NA	NA	NA	NA
Penicillin	$-2.1122(1.7563)$	$(-5.6594, 1.4264)$	$-2.1086(1.7939)$	$(-5.6063, 1.6051)$
Polymyxin	NA	NA	NA	NA
Quinolone	$-0.815(1.4621)$	$(-3.5721, 2.3824)$	$-2.0896(1.6479)$	$(-5.452, 1.314)$
Rifamycin	NA	NA	NA	NA

Table C.47: Summary statistics for parameters β_1' and $\tilde{\beta}_1'$ for each antimicrobial group for the *Full Model*, for the Respiratory Data Set.

$\boldsymbol{\phi}$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	0.5719(0.035)	(0.5039, 0.6399)	0.4834(0.0374)	(0.4116, 0.5568)
Antiseptic	0.566(0.0353)	(0.4967, 0.635)	0.4877(0.0366)	(0.4195, 0.5633)
Cephalosporin	0.5725(0.0336)	(0.5072, 0.6386)	0.4845(0.0379)	(0.4099, 0.5584)
Glycopeptide	0.5719(0.0353)	(0.5032, 0.6409)	0.4853(0.0361)	(0.4156, 0.5574)
Macrolide	0.5714(0.0344)	(0.5036, 0.6381)	0.4928(0.0361)	(0.4231, 0.5634)
Nitroimidazole	0.5641(0.0378)	(0.4908, 0.6381)	0.4802(0.0379)	(0.4047, 0.5527)
Oxazolidinone	0.552(0.0379)	(0.4769, 0.6249)	0.4679(0.0361)	(0.3975, 0.5385)
Penicillin	0.5649(0.0366)	(0.4917, 0.6355)	0.4727(0.0385)	(0.399, 0.5486)
Polymyxin	0.536(0.0352)	(0.4668, 0.604)	0.452(0.0364)	(0.3787, 0.5228)
Quinolone	0.5607(0.0365)	(0.4858, 0.6301)	0.4889(0.04)	(0.4085, 0.5657)
Rifamycin	0.5695(0.0355)	(0.4988, 0.6386)	0.4701(0.0365)	(0.4, 0.5428)

Table C.48: Summary statistics for parameter ϕ for each antimicrobial group for the *Full Model*, for the Respiratory Data Set.

$\mathbf{z}$				
	Ward 1		**Ward** 2	
GROUP	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI	$E[\cdot\|\boldsymbol{\theta}, \mathbf{y}, \mathbf{c}, \mathbf{r}]$ (s.d.)	95% CI
Aminoglycoside	0.1419(0.0209)	(0.1032, 0.1845)	0.1227(0.0208)	(0.0844, 0.1644)
Antiseptic	0.1366(0.0218)	(0.094, 0.1798)	0.1201(0.0215)	(0.0789, 0.163)
Cephalosporin	0.1354(0.0195)	(0.1, 0.1763)	0.1191(0.0223)	(0.0804, 0.1674)
Glycopeptide	0.1428(0.0221)	(0.104, 0.1902)	0.1151(0.0219)	(0.073, 0.1591)
Macrolide	0.1336(0.0188)	(0.0995, 0.1731)	0.1193(0.0201)	(0.0835, 0.162)
Nitroimidazole	0.1442(0.0222)	(0.1033, 0.1894)	0.1273(0.0241)	(0.0864, 0.1827)
Oxazolidinone	0.149(0.0221)	(0.1089, 0.1948)	0.1278(0.0245)	(0.0833, 0.1799)
Penicillin	0.1476(0.0234)	(0.106, 0.1971)	0.1255(0.0218)	(0.0866, 0.172)
Polymyxin	0.1595(0.0234)	(0.1187, 0.2113)	0.1356(0.0255)	(0.0908, 0.1892)
Quinolone	0.1502(0.0225)	(0.1109, 0.1994)	0.1238(0.026)	(0.0808, 0.1822)
Rifamycin	0.1409(0.0207)	(0.1036, 0.1851)	0.1275(0.0233)	(0.0862, 0.1762)

Table C.49: Summary statistics for parameter z for each antimicrobial group for the *Full Model*, for the Respiratory Data Set.

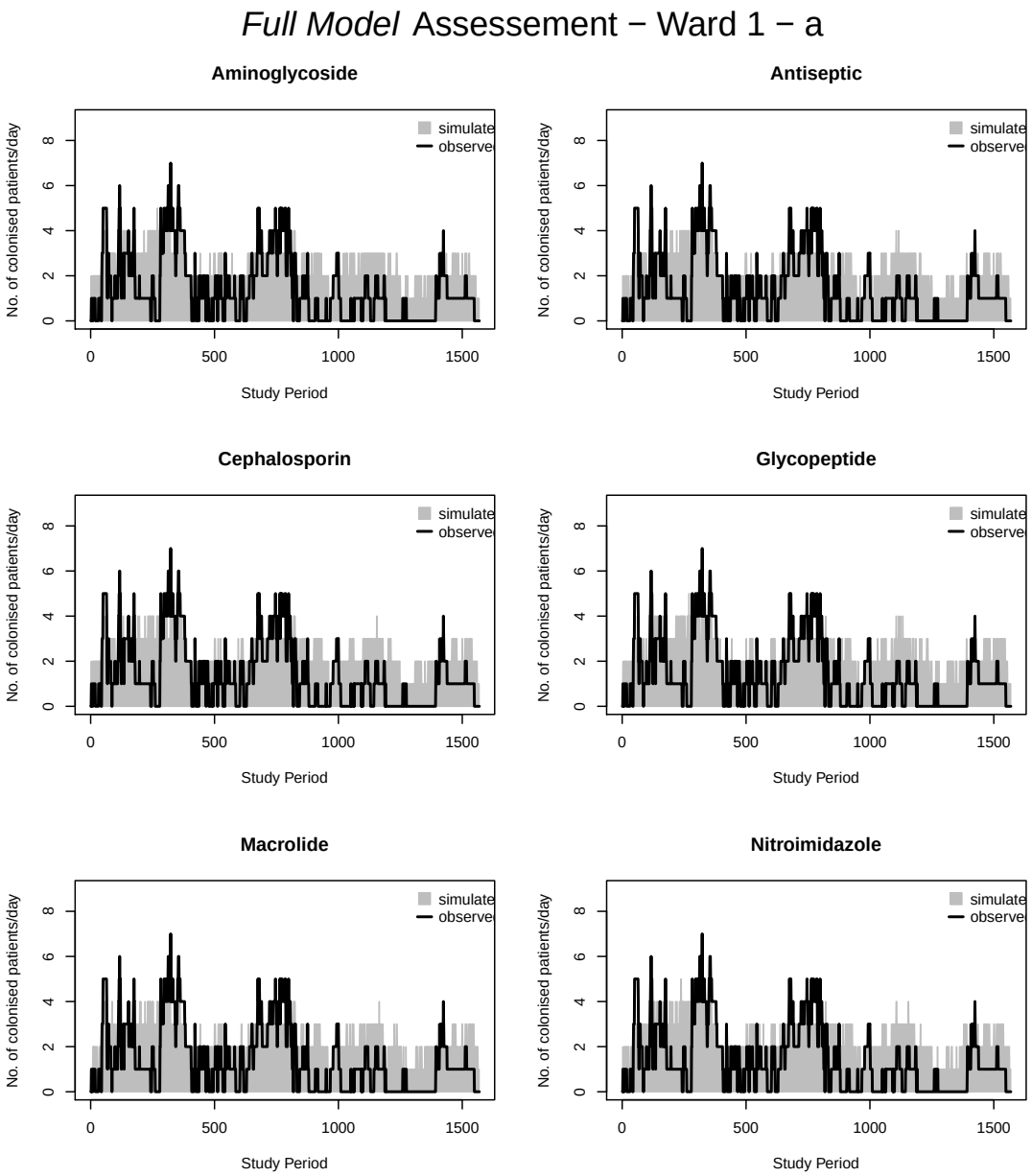

Figure C.39: Plots showing the *Full Model* assessement for the first 6 of the antimicrobials of ward 1, for the Respiratory Data Set.

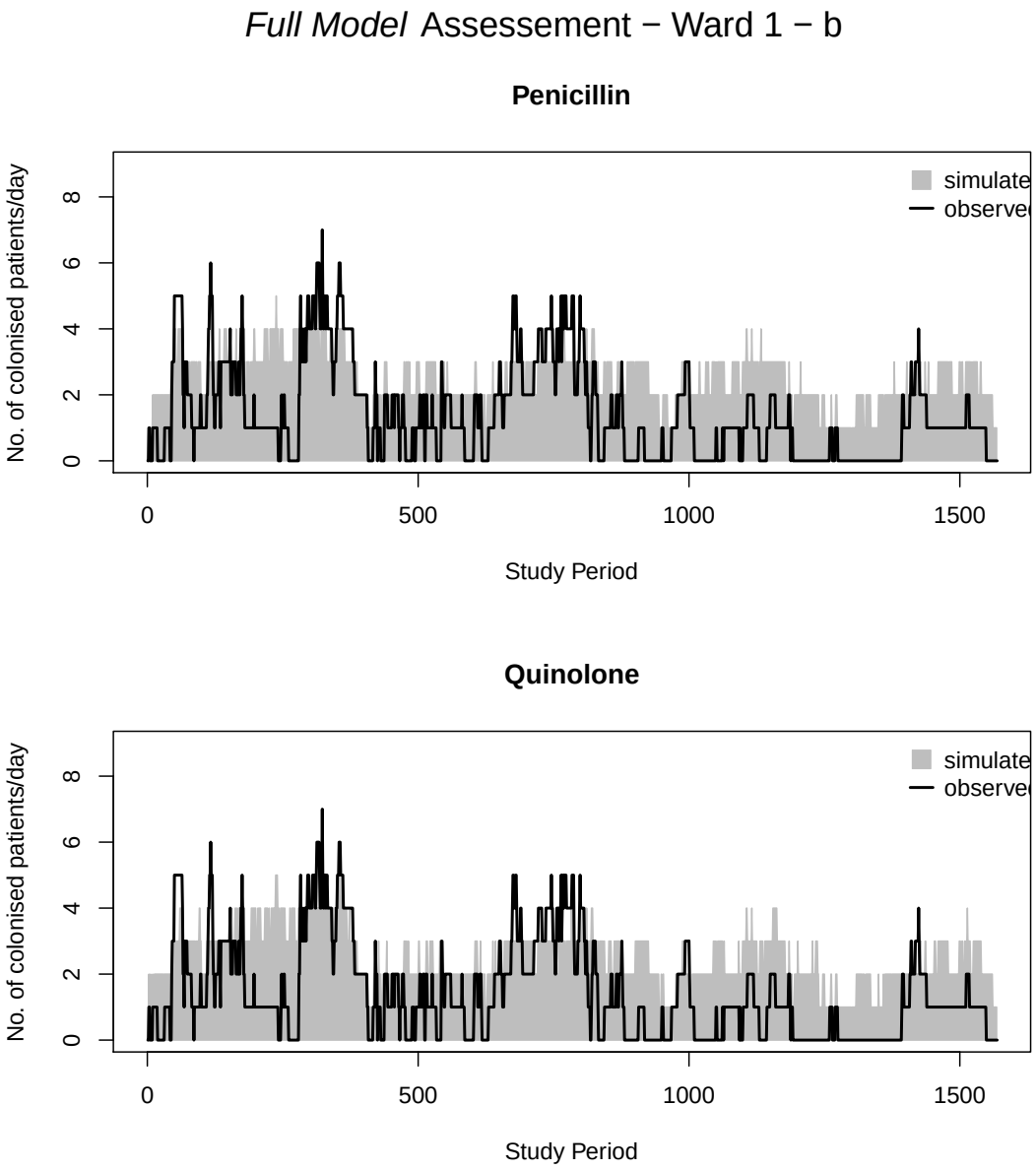

Figure C.40: Plots showing the *Full Model* assessement for the next 2 of the antimicrobials of ward 1, for the Respiratory Data Set.

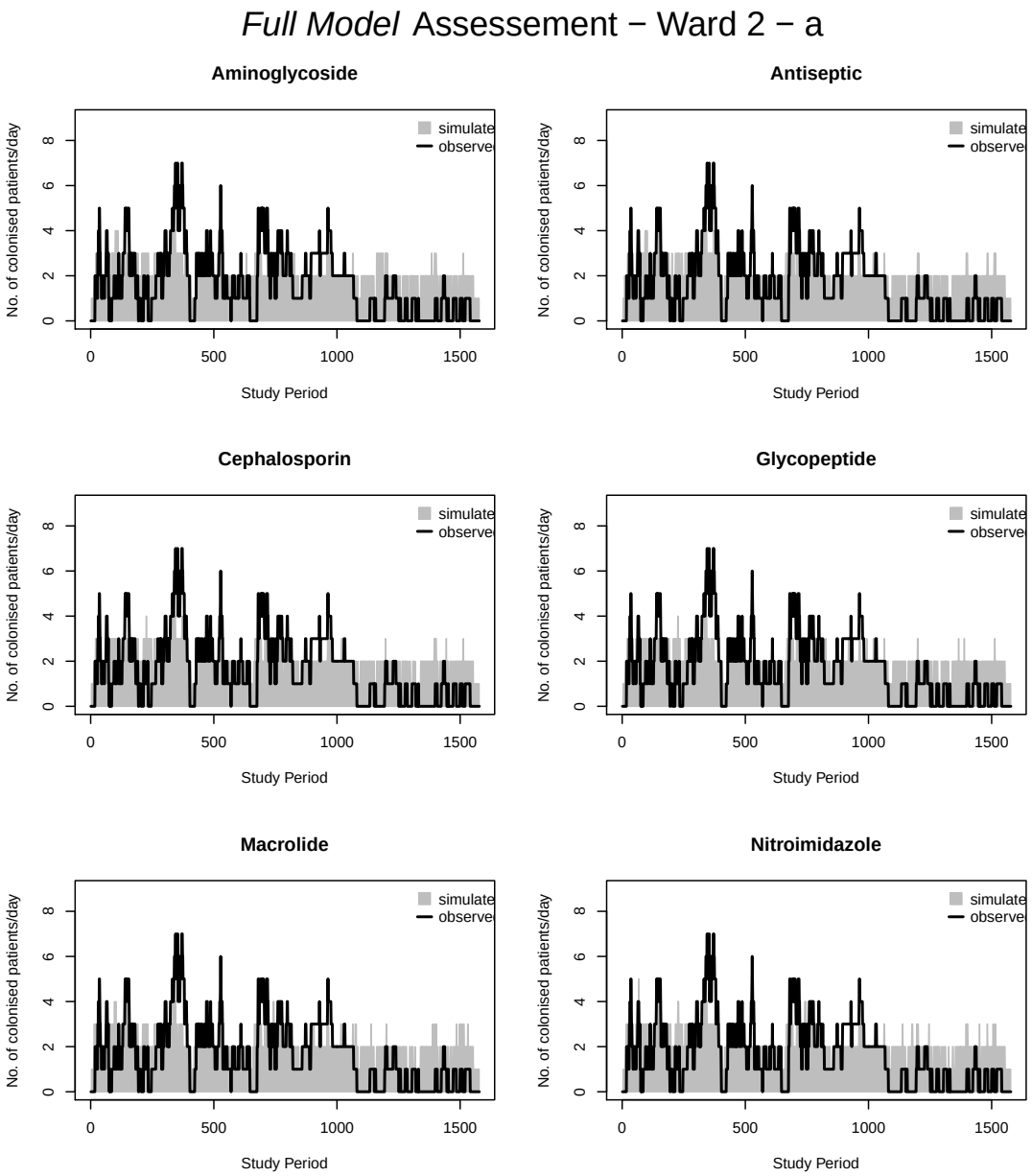

Figure C.41: Plots showing the *Full Model* assessement for the first 6 of the antimicrobials of ward 2, for the Respiratory Data Set.

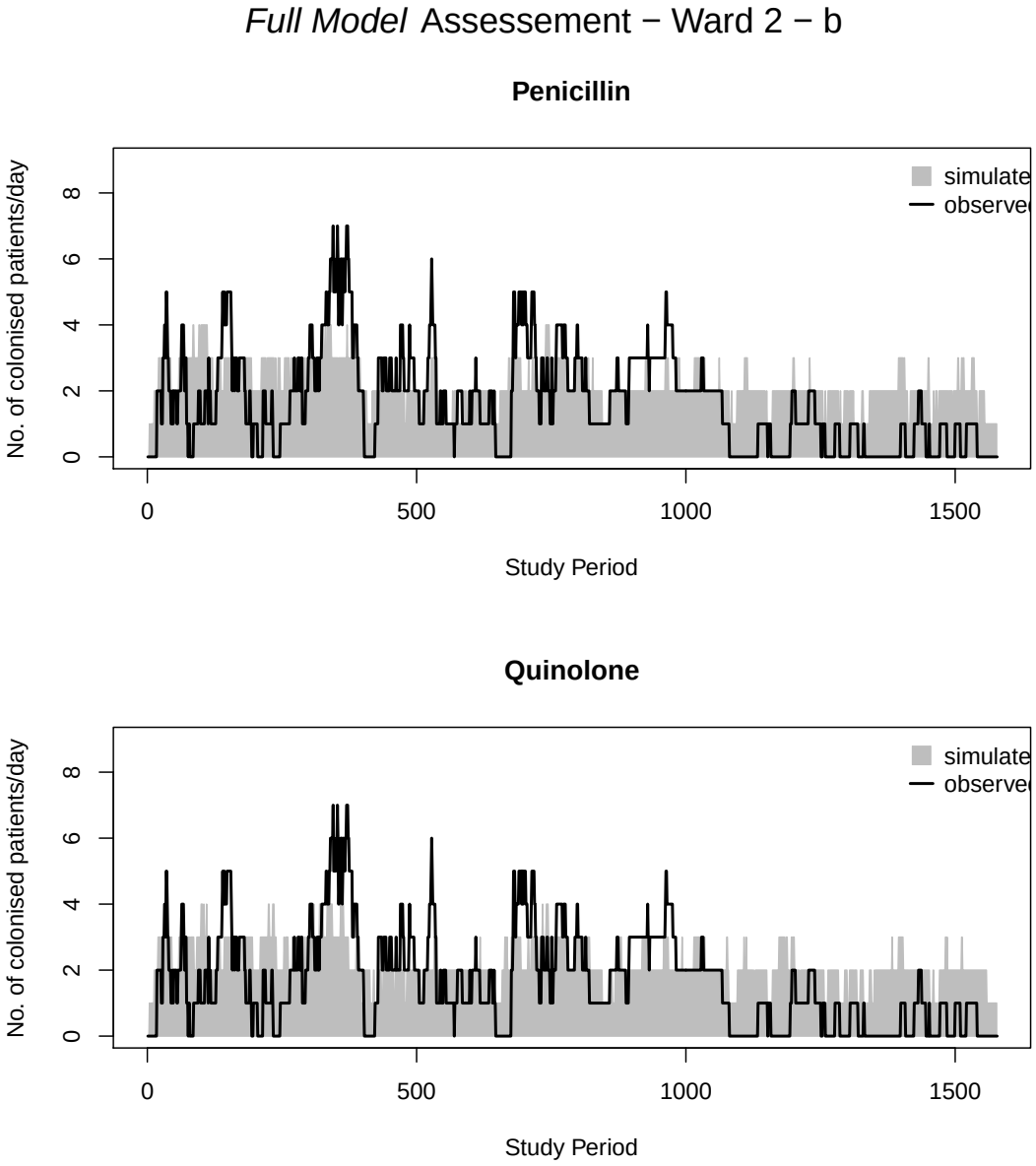

Figure C.42: Plots showing the *Full Model* assessement for the next 2 of the antimicrobials of ward 2, for the Respiratory Data Set.