THE DYNAMICS OF MULTI-DRUG RESISTANT ORGANISMS: MODELLING NOSOCOMIAL INFECTION CONTROL MEASURES

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Abstract

It has long been a challenge to try and understand how nosocomial infections develops in order to find the most efficient methods to combat it. Though drugs do exist to treat them, they are known to be highly resistant and have proven to be a reoccuring problem in hospitals, posing an increasing medical burden. Infection control measures have been implemented in order to reduce their impact and spread with various degrees of completeness and efficiency.

A multi-drug resistant ODE model, featuring three types of infection status and two groupings of patient history classes, is created to model the transmission dynamics of Vancomycin-Resistant Enterococcus and Methicillin-Resistant Staphylococcus Aureus. Analysis of the model is supported with numerical simulations. It is shown that infection control procedures, including the identification of high-risk patient groupings, have a strong effect on the transmission dynamics.

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Introduction

1.1 Overview

Mathematical models are becoming valuable tools with which to explain transmission mechanisms and predict infection trends for nosocomial infection, infection that takes place primarily within a health care setting such as a hospital or a hospital intensive care unit. In particular, modelling and analysis are playing a crucial role in informing decision and practice for the effort to control the growing threat to public health posed by antibiotic-resistant bacteria.

A mathematical model has been created and analyzed with the intention of being able to inform the impact of control strategies on efforts to effectively control the burden of multidrug resistant organisms. Due to the resurgence of Methicillin-Resistant Staphylococcus Aureus (MRSA) and Vancomycin-Resistant Enterococcus (VRE) among hospital acquired infections [25], the focus is on the mathematical modelling of the dynamics of these multi-drug resistant organisms.

1.1.1 Objectives

The model is used to, first of all, understand the transmission dynamics of antimicrobial resistance. Infection control measures have been put in place in order to better control antibiotic-resistant nosocomial infections [14,19,21,25,26]. However, these measures have had varying degrees of completeness and efficiency, and infections continue to increase due to the highly resistant nature as well as the ease at which they spread [10,17]. This study aims to highlight the effectiveness of each measure alone and the integrated program consisting of a variety of mitigation strategies. Looking in depth into these aspects together will bring light as to why exactly nosocomial infections pose a more serious medical and societal burden than current studies suggest.

Though it is known that hospitals provide host to a wide variety of resistant organisms, particular attention is drawn on the interaction one resistant organism can have on another, in the analysis. The model will analyse the effects of control strategies such as barrier procedures, screening methods, and the compliance of health care workers in adhering to such methods. Due to the large amount of nosocomial infections that require the isolation of patients, combined with the small amount of space available for either isolation procedures or patient cohorting, the model will not consider isolation protocols. When dealing with VRE or MRSA, isolation is not an infection control method that can be widely implemented in practice.

A deterministic approach is used, based on the compartmental model framework, where the patients under consideration are stratified into the disjoint groups of Uncolonized, Colonized, and Infected patients, and where there is a separate set of groups for those at higher risk of acquiring an infection [6,12].

Focusing primarily on those with past exposure to antimicrobials, the model illustrates how the identification of high-risk groups can aid in infection control. Due to the nature of the organisms spread and transmission, the model structure will in particular include both colonized and uncolonized health care workers.

The model's analysis is focused on the effects of control strategies such as barrier procedures, screening methods, and the compliance of workers in adhering to such methods upon the transmission dynamics and spread of these organisms.

1.1.2 Motivation

It has long been a challenge to try and understand how antimicrobial resistance develops and spreads in order to find the most cost efficient methods to combat it [24]. One of the main problems is that there is no universal set of standard guidelines regarding treatment, and no legislation regulating the quality and use of antimicrobials, let alone a set of guidelines optimized for the highest rate of effectiveness [1,2,3,4,29]. Even simple training and education of health care personnel is lacking in certain areas, despite efforts to improve it. This study will provide useful information to providers and consumers of health care, as well as raise awareness and encourage action by public policy makers. A study such as this one is able to help in providing a better understanding of the burden Antimicrobial Resistance has on the both society and the health sector in particular, and bring suggestions on how to reduce these types of infections, leading to significant health benefits [29].

In this study Vancomycin-Resistant Enterococcus and Methicillin-Resistant Staphylococcus Aureus, two of the most easily spread resistant pathogens, are used. In fact, Staphylococcus Aureus is the most common cause of hospital-associated infections. Though drugs do exist to treat them, they are known to be highly resistant and have proven to be a reoccurring problem in hospitals. Studying both the financial cost (medical costs to the healthcare system), the societal impact (duration of hospital stay, inability to work), and the impacts of death (emotional and financial burden on society and healthcare systems) is crucial as most analysis are done from only the institutional point of view, without taking into account the society costs and impacts [12,16,17,26,28,32]. Generally, most studies will consider the impact of a longer hospital stay, more expensive drugs, higher personnel costs, more specialized laboratory services, more stringent infection control practices, and inappropriate prescribing of antibiotics [2].

VRE and MRSA are associated with both community and hospital acquired infections. The problem is that they have acquired resistance genes to counter antibiotics that were once effective in treatment. This is why Vancomycin-Resistant Enterococcus and Methicillin-Resistant Staphylococcus Aureus pose such a problem when treating them. Doctors face not only the challenge of dealing with the limited range of antibiotics available for treatment, or the delay in treatment time due to the waiting period for laboratory results, but with these particular infections, specifically VRE, the choice of antibiotics depends upon the particular strain and what it is resistant to.

1.1.3 Historical Motivation

The World Health Organization has long since recognized Antimicrobial Resistant Infections as one of the most serious health threats to the treatment of disease worldwide. In fact, in June 2000, the WHO released a report, 'Overcoming Antimicrobial Resistance', which included recommendations on use of antibiotics in both humans and agriculture, with the intent of preserving the efficacy of available drugs through limiting their use in health care as well as in food production [1]. In 2005, there was a World Health Assembly resolution on antimicrobial resistance that called for rational use of Antimicrobials. Despite the fact that the strategic interventions needed to control Antimicrobial Resistance have been known, few actual policy changes have been made nationally and globally.

In May 1997, there was a Health Canada Consensus Conference on Antimicrobial

Resistance which generated an 'Integrated Action Plan for Canadians on Controlling Antimicrobial Resistance'[4]. This plan was comprised of twenty-seven key recommendations (i.e. formation of a national committee, establishment of a national surveillance system, reduction in antibiotic use) and parts of it have been implemented, but the issues of implementation are now considered a provincial responsibility. In fact, following this, a B.C. 'Antimicrobial Resistance Action Plan'steering committee was convened in order to meet the need for development of an effective provincial strategy [3].

In more recent years, the Public Health Ontario (PHO) Principle Infectious Diseases Advisory Committee on Infection Prevention and Control (PIDAC-IPC) published an Evidence Based Review in December of 2012 that reviewed in detail the published literature available on the control of Vancomycin-resistant Enterococci (up to July 2012) [5]. Based on the evidence reviewed, PIDAC-IPC continues to recommend screening, surveillance and control measures as outlined in 'Screening, Testing and Surveillance for Antibiotic-resistant Organisms (AROs)'. In fact, both Ontario and many other health care jurisdictions currently recommend surveillance and control measures for VRE (Public Health Agency of Canada, Centres for Disease Control and Prevention, British Columbia's Provincial Infection Control Network (PICNet)). The main recommended components of major VRE control programs are: control of vancomycin use; early detection of VRE colonization and infection in patients; surveillance cultures (stool, rectal swabs) to detect patients colonized with VRE; and single room accommodation, gloves, and gown for contact with the VRE patient or the patients environment.

In June 2012 four Ontario tertiary-care teaching hospitals implemented a change in IPAC practices related to VRE surveillance in their facilities [10]. The practice changes included cessation of screening patients for VRE, additional precautions for patients with VRE, and declaration of VRE outbreaks. Each of the centres experienced increasing rates of VRE colonization of patients despite intensive VRE control measures. The four centres cited their arguments for changing practice: there had been few clinical infections and no known significant adverse outcomes related to VRE despite increasing rates of colonization; there are adverse events associated with the use of antimicrobial prescribing (AP); patient flow and access to care were compromised by the use of AP for the control of VRE; the cost associated with surveillance and containment of VRE was significant; concerns that vancomycin resistance would be transferred to other pathogens, such as MRSA and would become clinically significant, have not been realized; there are antibiotics currently available to treat VRE (previously not available); while current VRE control measures are effective in controlling transmission of VRE, the costs and resources required for VRE control measures were not sustainable (also no evidence that patient safety and outcomes are improved through implementation of these measures); the standard of routine IPAC practice (hand hygiene, environmental cleaning) is higher in Ontario today than it was in the past. It should be noted that a cost-benefit analysis was not carried out by any of the four hospitals prior to cessation of control efforts.

1.2 Background on Antimicrobial Resistance

1.2.1 Antibiotic Resistance

Hospitals provide not only medical treatment, they host many pathogens that can often pose a serious risk of infection, most particularly to those individuals with compromised immune systems such as the elderly or the young. Antimicrobial resistance is the ability of micro-organisms to resist the effects of the antimicrobials used to treat such pathogens. It occurs when organisms are exposed to antimicrobial drugs and develop genetic mutations that make the drugs ineffective. Antimicrobial Resistance increases length of hospital stay, morbidity, and mortality, as well as using a significantly larger amount of time, resources, and money to treat [29].

Most hospital acquired infections are caused by antibiotic resistant pathogens such as Vancomycin-Resistant Enterococcus (VRE) and Methicillin-Resistant Staphylococcus Aureus (MRSA). More than seventy percent of the bacteria that cause hospital-acquired infections are resistant [27]. In the past decade, there has been an increasing focus on the costs of medical care and it has also become clear that prolonged hospital stay and higher costs result from infections caused by antibiotic-resistant pathogens as compared to infections due to antibiotic-susceptible strains of the same species [27].

Antibiotic use has a strong effect upon antibiotic resistance i.e. when isoniazid (INH) is used alone to treat TB, more than seventy percent of patients infecting strains develop resistance to INH[18]. Likewise, before the use of Vancomycin in the U.S. there were no known Enterococcus faecalis or Enterococcus faecium (the two types of Enterococci) isolates with vancomycin resistance. It is also clear that some part of this problem has been due to the spread of resistant strains from patient to patient via contaminated health care workers. Spread beyond the boundaries of a hospital is also frequent. The risk itself of VRE colonization has been associated with the use of multiple antimicrobial classes, and there have been two studies reporting that greatly reducing or stopping the use of certain antibiotics will give a two-thirds relative reduction in the prevelance of VRE [27,33].

1.2.2 Vancomycin-Resistant Enterococcus

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Enterococci are bacteria found naturally in the faeces and gastrointestinal tract of most humans and animals. Vancomycin-resistant Enterococcus occurs when Enterococcus faecium and Enterococcus faecalis strains have become resistant to Vancomycin

[4]. In the United States VRE is found almost exclusively in patients exposed to health-care settings. The situation is different in Europe, where VRE has been identified in the gastrointestinal tract of healthy individuals and farm animals and on processed meat products in grocery stores [27].VRE can be found in the digestive tract, urinary-tracts, surgical-incision, and blood stream. There is little to no evidence to suggest that VRE is associated with greater mortality than infection with vancomycin-sensitive enterococci.

The main factors that pose individuals at high risk include previous colonization or infection, greater than 12 hours in any health care facility in the past 12 months, recent exposure to a unit/area of a health care facility having an outbreak, health care in another country. Other factors that pose individuals at high-risk of colonization are those that have a compromised immune system, the use of catheters, co-morbidities (diabetes, cancer, those on dialysis), length of stay in the hospital, infection control practices among health care workers, and prolonged antibiotic use. VRE can be transmitted through either direct or indirect contact with colonized or infected individuals.

VRE colonized individuals means that the pathogen is present in the body but is not causing illness. The importance of this is that when screening both VRE colonized individuals and VRE infected individuals, the VRE colony counts are similar. This has important implications, as it means that the overall burden of VRE will usually be underestimated, if it is based on cultures taken solely from those individuals that are infected. Also, the duration of colonization can last from weeks to months (4-709 days).

1.2.3 Methicillin-Resistant Staphylococcus Aureus

Staphylococcus Aureus and Enterococcus are gram-positive bacteria that live on the skin (S. Aureus) and inside the gastrointestinal tract (Enterococcus) of most healthy adults (60% or more) [4]. Methicillin-resistant Staphylococcus Aureus develops when Staphylococcus Aureus develops resistance to the beta lactam class of antibiotics. Though there is little evidence to suggest it is more infectious than Methicillin-sensitive Staphylococcus Aureus (MSSA), due to the delay in treatment resulting from infection with MRSA, there is a strong association with a higher case fatality rate than MSSA. MRSA can be either a health care-associated infection (HA-MRSA) or a community-associated infection (CA-MRSA).

The main factors that pose individuals at high risk include invasive procedures, stay in an intensive care or burn unit, surgical wound infection, and close proximity to a colonized patient, or infection of a child through the mothers breast milk [4]. Other factors that pose individuals at high-risk of colonization are those that have a compromised immune system, prolonged length of stay in the hospital, infection control practices among health care workers, and prolonged or prior antibiotic use [4]. MRSA can be transmitted through either direct or indirect contact with colonized or infected individuals. It is most commonly spread through the hands of colonized health care workers who have acquired it through either direct contact with patients or indirect contact after handling contaminated equipment. There is some evidence that suggests when some individuals are co-infected with a respiratory virus they are able to spread MRSA through respiratory droplets [4].

1.2.4 Methicillin-resistant Staphylococcus Aureus and Vancomycin-resistant Enterococcus Co-Colonization and Co-Infection

In the United States, a study was done by Furuno et. al. in an ICU of a tertiary-care facility, and it was found that 3% of patients were co-colonized with VRE and MRSA. It was also found that co-colonized patients are at an increased risk for colonization or infection by Vancomycin-resistant Staphylococcus Aureus (VRSA). Risk factors for co-colonization include admission to a medical ICU and other critically ill patients, being male, having a previous positive culture of either MRSA or VRE, and receiving antimicrobial drugs on a previous admission within 1 year.

1.3 Background on Infection Control Measures

Due to the direct nature of these types of infections, transmission prevention precautions can be instituted through a series of practices and procedures that limit contact and exposure. These practices can help to limit the burden of infection upon the health care system and limit infection rates among patients. Note that when considering infection control procedures, we must take into account the average compliance with such procedures by health care workers, as well as the staff-patient contact rate, and average length of stay for a given patient.

1.3.1 Patient Screening for Multi-resistant Organisms

For most guidelines, this means active screening of high-risk patients including those who have previously been colonized or infected, those transferred between health care facilities, those who have recently be exposed to a unit/area with a VRE outbreak, other high-risk client/patient populations as identified by Public Health (i.e. ICU). Screening itself is not an infection control method, but with the proper identification of colonized or infected patients health care workers may apply further control measures in order to limit the spread. A number of studies have shown that up to 50% of MRSA cases may be identified through admission screening of high risk patients, though the definition of what is considered 'high risk' varies among guidelines [45].

Those considered to be at high risk of acquiring both MRSA and VRE include those who have been colonized or infected previously, those who have spent time in a health care facility outside of Canada in the last 12 months, those who have spent more than 12 continuous hours in a health care facility in the past 12 months, those transferred between health care facilities, those who have been exposed to an area with an outbreak. Additionally, those who are at high risk of acquiring MRSA include those receiving home health care services in the past 12 months, those with an indwelling medical device, those in ICUs/transplant units/burn units, those living in a communal setting (shelter, halfway home, correctional facility), those with a history of injection drug use, those who are household contacts of people infected, those who are immunocompromised, individuals from populations where CA-MRSA is a problem. Additionally, those who are at high risk of becoming infected with VRE are those who have been recently exposed to second and third-generation cephalosporins.

It is to be noted that specimens may be falsely negative if the patient is on an antibiotic to which the micro-organism is sensitive. Also, the risk of staff colonization with VRE is extremely low and there is no evidence to support the need to screen staff for VRE. Though the model does not account for the time lag between when specimens are taken, and results are received, or false negatives, it does stratify the patients into patient groupings consisting of those considered ‘high-risk’ and those considered ‘non high-risk’.

1.3.2 Antimicrobial Stewardship Programs

It appears likely that antibiotic exposure facilitates VRE transmission by increasing susceptibility to VRE acquisition by suppressing normal flora and providing selective advantage for survival to VRE acquired through cross-transmission, and increasing the likelihood of transmission from colonized patients by increasing the concentration of

VRE in the stool (increasing the probability of environmental of HCW contamination) [29].

VRE and MRSA have been associated with the use of antibiotics. Antibiotic Stewardship helps to create policies and procedures that should be implemented to promote judicious antibiotic use, in order to limit the increase and spread of antibiotic resistant organisms. Health care settings should institute formulary control of antibiotics and should conduct regular reviews of antibiotic utilization.

Antimicrobial Stewardship Programs help to facilitate the education of staff on the epidemiology, prevention and control of VRE. Education may improve compliance with routine practices and additional precautions. Education of patients and visitors is also important to ensure compliance with established practices.

1.3.3 Environmental Cleaning Procedures

Multiple studies have demonstrated that portable healthcare equipment can serve as a potential vector for antibiotic-resistant pathogens to patients, either via direct contact or by contamination of clinicians hands. VRE has been recovered from experimentally inoculated hands of HCWs (with or without gloves) for sixty minutes. Multi-drug resistant organisms may survive for weeks to several months on various surfaces including faucets, bed rails, wheelchairs, thermometers, and portable equipment (i.e. stethoscopes, tourniquets, cuffs, pagers etc.) [33]. In one study, forty-two percent of nurses gloves became contaminated with MRSA when they touched surfaces in the room of a patient with MRSA without actually touching the patient [12,33]. For this reason, the model takes into consideration the sixty minute 'recovery period' for colonized HCWs.

Good hand hygiene practices involve the use of alcohol based hand run and running water for at least 15 seconds. Hand Hygiene should occur before patient or environment contact, before performing aseptic procedures, after care involving body fluids, after client or environment contact. Dedicated equipment or adequate cleaning and disinfecting of shared equipment, including transport equipment is also recommended.

Also, special discharge cleaning protocol is vital for VRE and MRSA. The intensity of cleaning is important though, Falk et. al., reported control of a VRE outbreak only after an increase in the intensity of environmental disinfections (decrease in proportion of environmental cultures positive from twenty-nine to one percent) [33].

1.3.4 Isolation Procedures and Contact Precautions

It is strongly recommended that clients/patients known to be colonized or infected with VRE or MRSA be placed in a single room with individual toileting facilities. When single rooms for Contact Precautions are limited, priority should be given to patients who are at increased risk of disseminating micro-organisms into the environment. If a single room is not available, as is commonly the case, patients known to be colonized or infected with VRE may be cohorted with other patients. In fact, patient cohorting was analyzed in the paper by Austin et. al. [10]. The likelihood for isolation procedures to be included into the model is common among existing models, but does not take into account the multitude of other nosocomial infections requiring more urgent attention and use of the limited existing space available for such precautions to be implemented.

1.3.5 Active Surveillance Methods

If contact precautions are important in the prevention of spread from colonized patients, then active surveillance cultures are necessary to identify colonized patients. Active surveillance cultures and isolation have also been used to successfully control

MRSA and VRE throughout the province of Ontario, Canada [33]. In another study, a public health initiative used active surveillance cultures in all 32 healthcare facilities in a health district and showed the VRE could be controlled in all facilities in a region (3 years), even while rates of VRE infection continued to increase during those three years at most other facilities in the U.S. [33]. It is important to note that though interventions in a single ward usually can have significant impact, when transmission is occurring on multiple other wards and between wards, or in the case where only one facility in an area employs an intervention, the impact is lessened.

1.3.6 Barrier Procedures (Personal Protective Equipment)

VRE is most commonly spread via the transiently colonized hands of health care workers who acquire it from contact with colonized or infected clients/patients/residents, or after handling contaminated material or equipment. Zachary et. al. found thirty-seven percent of HCWs gowns to be contaminated with VRE after care of a patient with VRE (higher number for MRSA) [24,32]. Four of five studies have shown significantly lower rates of patients becoming VRE culture positive when HCWs used gowns and gloves as compared with gloves alone (or gloves and handwashing) [33,11,38,40,45,46].

It is generally recommended that gloves be used for all activities in the patients room or bed space, or for direct care of clients in long-term care and ambulatory/clinic settings. It is important to note that hand contamination may still occur due to leaks in the gloves or improper removal, so the use of gloves cannot be considered a substitute for hand hygiene.

Long sleeved gown for activities where skin or clothing will come in contact with the patient or their environment in acute care, or for direct care of clients in long-term care and ambulatory setting, as well as the use of a protective mask are also recommended.

It is clear that the usage of barrier procedures is an efficient method of infection control, the question lies herein whether and what proportion of HCWs will actually use them as recommended. For this reason, the model does not taken into consideration the failure rate, but the compliance of HCWs in implementing barrier procedures. For more detail on this issue see Chapter 2.

Several studies have shown that gloves can dramatically reduce hand contamination and transmission of pathogens. There was a study that concluded that gloves prevented hand contamination seventy-seven percent of the time [24]. Non compliance rates of twenty-one to thirty-eight percent and lack of similar precautions throughout other hospitals make evaluation of the time and place of transmission difficult though [33, 45].

There has been one study that demonstrated that at least one particular brand of disposable isolation gown reliably prevented contamination of the HCWs clothing beneath the gown [13].

1.3.7 Compliance with Infection Control Procedures

Hand Hygiene is often said to be the single most important measure for controlling transmission of multi-drug-resistant organisms (CDC recommendation). One study (there are others with similar results) suggested that extremely high compliance with hand hygiene (i.e. after eighty percent of contacts) could reduce VRE transmission in an ICU by only approximately a quarter because of the relatively high rate of transmission when HCWs hands were not being cleaned following the remaining twenty percent of contacts [33]. The authors concluded that strict isolation measures and surveillance cultures for identifying colonized patients should be considered by those trying to control these pathogens.

It seems unlikely then, that hand hygiene by itself will result in control of antibiotic-resistant pathogens such as MRSA, VRE and VRSA. Supporting factors include poor compliance with hand hygiene contamination of clothing and equipment (which occurs frequently when patients are not identified and cared for using contact precautions and furthermore, contributes to transmission) [33].

One of the problems we currently face is the hand hygiene compliance of HCWs. Most studies that access such compliance before and after the implementation have shown low compliance rates, averaging ten to forty percent [33]. Compliance rates often remain low despite efforts to improve them. For example, one hospital increased its overall compliance rate from forty-eight to sixty-six percent following the implementation of a multi-year hand hygiene campaign involving posters, among other methods of education exposure [33].

Risk factors for poor compliance with hand hygiene include being a physician or nurse assistant, working in an ICU, working during weekdays, performing activities with a high risk for transmission, having many opportunities for hand hygiene per hour of patient care, under-staffing and overcrowding, HCWs perception that they are at low risk for acquiring infection from patients, and assumptions that glove use precludes the need for hand hygiene, and skin irritation cause by frequent exposure to soap and water [34]. Mathematical modelling suggested that a twelve percent increase in cohorting of staff with colonized patients or a twelve percent increase in compliance with hand hygiene during periods of overcrowding and high workload could compensate for staff shortage and prevent transmission [34].

1.4 Population Structure: basic ODEs

In this thesis, the infection status of various patient populations colonized or co-colonized with VRE and MRSA will be discussed. As with the vast majority of vector-host studies, we are concerned with the changes in population size and structure over time. Thus, it is appropriate to work with the derivative with respect to time.

Let $N(t)$ represent the size of a particular patient sub-population status at time t, and let N_0 represent its size at some initial point in time.

We can split the derivative $N'(t)$ into three parts,

$$N'(t) = L(t) + S(t) \tag{1.1}$$

where

L = changes due to life processes (admissions and discharges or deaths), and

S = changes due to structural changes (non-'life' processes).

Characterizing the population structure as either spatial or non-spatial, we decompose S:

$$N'(t) = L(t) + M(t) + C(t) \tag{1.2}$$

where

M = net changes of a spatial nature (interal movement within the hospital departments).

C = net changes in category (not due to life processes).

Can be indexed for either space or category as appropriate.

Further decomposition is possible, offering an increasing and decreasing term for each original term. It is to be noted that these additional terms may be decomposed into additional terms depending on the amount of detail or simplicity needed in the model.

$$\begin{cases} L(t) = B(t) - D(t) \\ M(t) = I(t) - E(t) \\ C(t) = C_{in}(t) - C_{out}(t) \end{cases} \tag{1.3}$$

where

B = the increase due to birth processes, in this case we are referring to new hospital admissions.

D = the decrease due to death processes,

I = the increase due to internal movement into the given area,

E = the decrease due to internal movement away from the given area,

C_{in} = the increase due to movement into a category, and

C_{out} = the decrease due to movement out of a category.

In this thesis, rather than consider the spatial structure, it is assumed that patient populations are within a single geographical area of interest within the hospital, such as an Intensive Care Unit. Thus, the internal movement terms have been eliminated, but the category change terms have been retained. Since all patient populations in this thesis are adults, the birth processes can be simplified to merely consider new hospital admission, instead of new births, in addition to merely considering disease related deaths as opposed to both disease and natural deaths.

One particularly useful further decomposition is the death term - due to cause of death or movement away from the hospital environment. Ommiting the migration term, splitting the category term, and rearranging the death term, we obtain,

$$N'(t) = B_a(t) + C_{in}(t) - C_{out}(t) - D_d(t) - D_i(t) \tag{1.4}$$

where

N = the total number of individuals in the population,

B_a = the increase due to new hospital admissions,

C_{in} = the increase due to movement into a category,

C_{out} = the decrease due to movement out of a category,

D_d is the decrease due to hospital discharges, and

D_i is infection related death.

Equation (1.4) is the general form for the ODEs of this model, the principle variation being that in some cases, the movement in and out of a particular category may include additional terms that may or may not necessarily depend on time.

1.5 Compartmental Models

It is common for epidemiologists and epidemiological modellers to compartmentalize a population N according to disease state. These compartments are a form of the population structure covered by C_{in} and C_{out}, described above. Some commonly used compartments include

S - suceptible (otherwise known as uncolonized)

C - carrier (otherwise known as colonized)

E - exposed

I - infective (sometimes known infected, or infectious)

Q - quarantined

R - recovered (sometimes known as resistant, or removed)

T - treated

The mutually exclusive compartments account for all of the individuals of a particular population. Somewhat arbitrary thresholds are used to mark passage from one compartment to the next. 'Membership' is permitted in only one compartment at any given time, so for an SEIR model, for instance, all living individuals would be classified as either susceptible, exposed, infective, or recovered.

$$N = N_S + N_E + N_I + N_R \tag{1.5}$$

SEIR is the building block of the model presented in this document, so a few words of explanation are in order. Also, please see the glossary in Appendix G.

A susceptible (S) individual has the potential to develop an infection, but has not yet been exposed to the virus at any point.

An exposed (E) individual has undergone some contact, transformation, or behaviour, such that it is reasonable to assume that an infection might result. In this model, we consider the exposed class to be those that are colonized. Simply being in close proximity to an infective individual does not necessarily constitute exposure, but either direct or indirect contact with surfaces they have touched would count as such.

An infective (I) individual has built up a level of pathogen (e.g. virus) such that it is possible, under the right conditions, for it to be spread to other individuals. The term *infected* is also applicable in most cases, as the individual has received the virus and developed an infection. *Infectious* is treated as a synonym for *infective* by some authors, but others use it only in restricted contexts, such as "infectious agent" or "infectious disease."

A recovered (R) individual has previously had an infection, but currently lacks the pathogen (virus) level necessary to be infective or symptomatic. The term *resistant* is also sometimes used in this case, as the reduction in virus level is often due to immune response, which may convey immunity after the infection passes. *Removed* is another term sometimes used, as the individual cannot be infected again in such cases, i.e. it no longer participates in the cycle. In other cases, the given recovered individual may be considered doubly susceptible for another infection. In most cases, patients in this model, upon recovery, move to the class of people with past antibiotic exposure.

In general, compartmental models may allow for both forward and backward transitions between states.

1.6 Existing Mathematical Transmission Models of Nosocomial Infectious Disease

It is important to consider some published models with which the one here can be compared. Most models in the literature use the structure of models for basic vector-borne diseases, using the health care workers as the vectors and the patients as the hosts. A good starting point for models specifically designed to model the transmission dynamics of Vancomycin-resistant Enterococcus or Methicillin-resistant Staphylococcus Aureus is the model by Austin et. al.[10] This model is intended to analyze the impact of infection control programs for Vancomycin-resistant Enterococci in an intensive care nosocomial setting. The model is described as well by Chamchod and Ruan [12], and is commonly used as the basic format with which to describe the dynamics of Vanocmycin-resistant Enterococcus and/or Methicillin Resistant Enterococcus. This model is similarly described by Banks and Castillo-Chavez [34] but with the addition of a stochastic term to account for the variability of hospital disease transission. This model is designed as a cross-acquisition model (i.e. patient-HCW-patient VRE acquisition). We have patients N_p and health care workers (HCW) N_w,uncolonized patients U_p, colonized patients C_p, VRE-free HCWs U_w, and contaminated HCWs C_w.

$$\frac{dU_p}{dt} = \delta(1-\theta) + \tau C_p - \gamma U_p - ab_p U_p C_w \tag{1.6}$$

$$\frac{dC_p}{dt} = \delta\theta - \tau C_p - \gamma' C_p + ab_p(1-\epsilon_w) U_p C_w \tag{1.7}$$

$$\frac{dU_w}{dt} = -ab_h U_w C_p + \tau C_w + \mu C_w \tag{1.8}$$

$$\frac{dC_w}{dt} = -\frac{dU_w}{dt} \tag{1.9}$$

where,

Parameter	Description
N_p	Number of patients/beds
N_w	Number of health care workers
U_p	Number of uncolonized patients
C_p	Number of colonized patients
δ	Rate patients are admitted
θ	Fraction of patients admitted that are already colonized with VRE
γ	Uncolonized Discharge rate
γ'	Colonized Discharge rate
bp	Colonization probability
b_h	Contamination probability
a	Per-capita contact rate health care worker encounteres patient
aN_p	HCW-patient contact rate
$1/\mu$	Average length of time contaminted HCWs can transmit VRE
τ	Rate of infection clearance for a given individual

Table 1.1: Parameter Values, Austin et. al.

Patients are admitted to the hospital at a rate of δ per day, are colonized with a probability of λ_c, are infected with a probability of λ_i, and are uncolonized with a probability of $(1 - \lambda_c - \lambda_i)$. γ_u,γ_c, and γ_i are the respective discharge rates of each class. Colonized patients become infected at a rate of β per day. Decolonization occurs at a rate of ω per day. It is important to note that in this type of model patients that have cleared the infection are considered to be colonized, in other words, complete clearance of the infection cannot occur without passing through the colonized state. Uncolonized patients can become infected through contact with a colonized health care worker. Health care workers do not become infected as both types of bacteria generally target those with a lower immune system.

Though most models of this type tend to combine colonized and infected individuals, A. Banks and C. Castillo-Chavez [34,35] take a similar approach to the proposed model in the separation of patients into those that are uncolonized, colonized upon admission, colonized during the hospital stay, and those that are infected. The problem lies in the accountability for the compliance of health care workers in adhering to the implemented infection control procedures, which has been shown to be surprisingly low despite best efforts to increase it. The proposed model will look in depth into this issue.

What models of this type also do not take into account explicitly is the potential for either a successful or unsuccessful treatment with antibiotics. Models such as the one by Perencevich and Fisman [17], include an additional term $\rho\lambda$ which takes the place of the decolonization term in the traditional models. This term is a reflection of the probability of a successful treatment, and allows for better usage of the data available in order to gain a better indication of how the infection spreads and what the effects of particular control strategies have on the spread. It is important to note that this model holds much similarity to the one by Chamchod and Ruan [12], with the exception of their sole usages of MRSA data.

This model will differ from this set-up. It will differentiate between those infected patients that have been treated unsuccessfully or successfully by considering the potential of those who have been treated previously to be at a higher risk of infection, due to their recent exposure to antibiotics. This model also differs from currently available literature through the consideration of more than one method of infection control. The majority of current models [6,12,13,15,24], analyze one particularly useful or common method, such as barrier control or screening. This is true for cost analysis studies as well [7,17], and increases the difficulty of conducting a comparison between the different methods. It is to be noted that the studies depth, breadth, magnitude, and setting impact the results of such an analysis. The model also differs from previously available literature through the incorporation of VRE, MRSA, co-colonized, and co-infected individuals all in the same model. As merely the existence of studies and information on co-colonized and co-infected individuals is rare [18,48], this is a major step forward in approaching the transmission dynamics of multi-drug resistant organisms in ICUs.

It is in this respect that the model presented in the following chapter differs significantly from the work published to date.

Chapter 2

Modelling

Modellers seek to reduce a real-world or hypothetical situation down to a manageable set of equations, rules, or algorithms. Generally the model will represent a compromise between the conflicting goals of completeness and practicality.

2.1 Model Paramaters

A parametric model such as this one can be evaluated for a wide variety of situations. This model is parametrized with disease-related transition rates between compartments and with both disease and non-disease-related admission and discharge rates.

A survey of the literature reveals that there is little consistency with regard to the symbols used for these parameters. Therefore, the choices for this document were somewhat arbitrary, relying on consensus where there seemed to be one.

There is a set of paramaters for each of the three infection types in this model. An english or greek letter identifies each paramater, and the three sets are distinguished by the use of subscripts, as follows:

1 - Vancomycin-resistant Enterococcus (patient infection of type 1)

2 - Methicillin-resistant Staphylococcus Aureus (patient infection of type 2)

3 - Co-infection or Co-colonization (patient infection of type 3)

E.g. β_1 is the transmission rate for VRE.

Certain paramaters can be further distinguished by their infection status:

U - Uncolonized

C - Colonized

I - Infected

Ua - Uncolonized with past antibiotic exposure

Ca - Colonized with past antibiotic exposure

Ia - Infected with past antibiotic exposure

E.g. θ_{C1} is the admission rate for patients colonized with VRE.

θ is the admission rate. This rate is per unit time, and per individual in the population.

γ is the death rate for infected patients and the discharge rate for uncolonized and colonized patients. It is the reciprocal of the amount of time spent in the given class, for the discharge rate, and for the death rate this reciprocal is multiplied by the probability of a treatment failure.

β is the transmission rate. In this, we are assuming that any individual who become colonized will eventually transition to infectivity, where they may be treated with a success rate of $\lambda\rho^s$ and a failure rate of $\lambda\rho^u$. λ represents the maximum rate that antibiotics can be given to patients, and ρ^s or ρ^u represents the probability of either success or failure. Note that the incorporation of transmission success at this stage is prospective; we are therefore assuming that any uncolonized individual who becomes colonized, makes the transition to the infective class, unless they die, get discharged, or become decolonized first.

ω is the decolonization rate, the rate of transition from C to U. $\frac{1}{\omega}$ represents the recovery period.

μ is the rate at which health care workers transmit the disease. This rate is the reciprocal of the average amount of time health-care workers can transmit MRSA or VRE.

ab_p is the contact rate between patients and health-care workers. Contact is modelled as a patient-HCW mass-action term. More of either will tend to cause more contact, fewer of either will tend to cause less contact. (Please see Appendix A for more details).

ϵ is the rate of compliance that health-care workers employ barrier precautions when interacting with patients. The effectiveness of such barrier precautions is e. If precautions are 100 percent effective in removing VRE contamination, then HCWs have a reduced probability of transmitting VRE to their next patient. Where efficacy is less that 100 percent, compliance should include the measured efficacy accordingly.

As mentioned above, in the models most general case, there is one set of these parameters for each category / species.

2.2 The Basic Equations of this Model

This model is designed as a cross-acquisition model (i.e. patient-HCW-patient VRE acquisition). We begin with the basic transmission model, but with the addition of barrier procedures, including the use and change of gowns, gloves, and hand washing by health care workers before and after contact with patients. These barrier precautions serve to reduce the likelihood that HCWs will become contaminated with VRE. Precautions reduce both acquisition and transmission of VRE by HCWs (as we should expect for hand washing before and after patient contact).

It is known that one of the main risk factors of becoming colonized with VRE or MRSA is a past history of antibiotic exposure. This is specifically due to their vulnerability to skin infections, as well as to the emergence of resistant bacteria promoted by antibiotic usage. The importance of the history of antibiotic exposure in the transmission and acquisition of these bacteria is also due to the fact that antibiotic resistance can persist for a year after taking them. This factor is incorporated into the model below. In the model, treated patients either become colonized or remain infected with antibiotic exposure.

All three infections in this model behave according to a variation on the following basic theme:

$$\frac{dU}{dt} = \delta\theta_u - \gamma_u U - ab_p(1-\epsilon_w)UC_w + (\tau+\omega)C \tag{2.1}$$

$$\frac{dC}{dt} = \delta\theta_c + ab_p(1-\epsilon_w)UC_w - (\tau + \omega + \beta + \gamma_c)C \tag{2.2}$$

$$\frac{dI}{dt} = \delta\theta_i + \beta C - (\lambda\rho^u + \gamma_i + \lambda\rho^s)I \tag{2.3}$$

$$\frac{dU_A}{dt} = \delta\theta_{uA} - ab_{pA}(1-\epsilon_w)U_A C_w - \gamma_{uA}U_A + \omega_A C_A \tag{2.4}$$

$$\frac{dC_A}{dt} = \delta\theta_{cA} + ab_{pa}(1-\epsilon_w)U_A C_w + \rho^s\lambda I + \rho_A\lambda_A I_A - (\omega_A + \beta_A + \gamma_{cA})C_A \tag{2.5}$$

$$\frac{dI_A}{dt} = \delta\theta_{iA} + \beta_A C_A + \rho^u\lambda I - (\gamma_{iA} + \rho_A\lambda_A)I_A \tag{2.6}$$

$$\frac{dU_w}{dt} = -a(1-\epsilon_w)(b_{hc}C + b_{hi}I + b_{hcA}C_A + b_{hiA}I_A)U_w + \mu U_w \tag{2.7}$$

$$\frac{dC_w}{dt} = -\frac{dU_w}{dt} \tag{2.8}$$

There is one ODE for each compartment (disease state) and for each type of infection. U(t), C(t), and I(t) represent patients that are uncolonized, colonized, or infected with the disease; $U_a(t)$,$C_a(t)$, and $I_a(t)$ represent patients with exposure to antibiotics in the past year that are either uncolonized, colonized, or infected with the disease; and $U_w(t)$,$C_w(t)$ represent uncolonized and colonized health care workers. Each ODE features a way for the compartment population to increase, and a way for it to decrease - increasing by admittance or movement into the compartment, and decreasing by death/discharge or movement out of the compartment. Spatial movement within the hospital is not considered in this particular model.

2.3 Model Basics and Assumptions

A mathematical model is unable to capture all the intricate detail of real-world interactions. As is done here, it is common practice for assumptions to be made in order to make the problem more manageable, and some assumptions are made because of the difficulty of obtaining accurate information. This section identifies some key simplifications or assumptions and their ramifications.

The model is only concerned with a single ICU, and does not incorporate internal movement within the hospital by patients.

Uncolonized and colonized patients, due to the length of their stay in the ICU and the severity of these particular infections, do not have a death rate. Once patients become infected, they are not released from the hospital until properly treated. This means that infected patients only have a death rate due to complication associated with infection, and not a discharge rate.

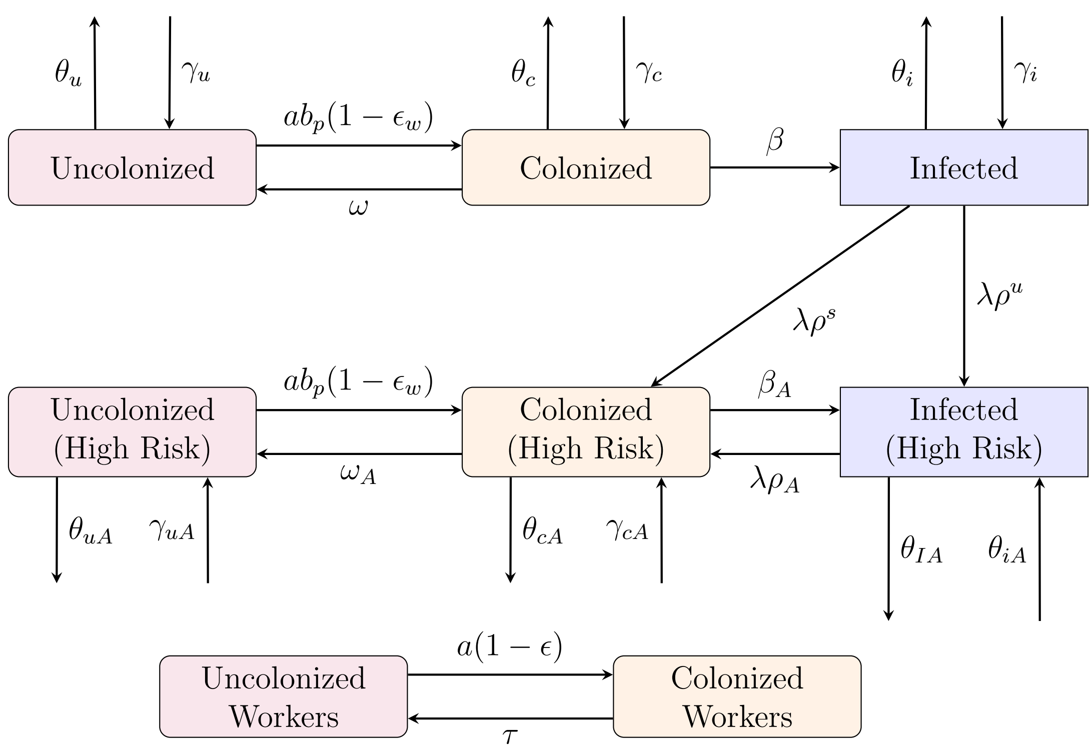

Figure 2.1: Basic Model Transmission Dynamics Diagram

HCWs mix homogeneously with patients at a per-capita rate a/patient per HCW per day. Due to the frequency at which health-care workers interact with each other, and the likelihood of them transmitting the bacteria to one another, it is assumed that the infection is only transmitted from health-care worker to patient and vise-versa. Transmission of the disease does not occur through patient-patient interactions, given the low or non-existent rate at which patients in an ICU interact with each other.

Barrier procedures are 100% effective when implemented.

Admission screening is 100% effective.

Patients colonized with MRSA or VRE are more likely than uncolonized patients to develop infection. Therefore, it is assumed that there is no direct infection of uncolonized patients by the hands of contaminated health care workers.

There is no movement of ICU patients within the hospital.

2.4 Suitability of the parameters, and the values used

The choice of parameter values is crucial to any transmission model. Please see Appendix E for a more in-depth discussion on the suitability of the parameter values used.

2.4.1 Admittance Rate

For simplicity of the model, constant linear admittance rates were used. The admittance rates θ were assumed to be uniformly distributed with respect to time.

2.4.2 Death and discharge rates

Two types of 'death' rates are used. For uncolonized and colonized patients this rate represents the rate at which they are discharged from the ICU, and for infected patients this rate represents the disease-related death rate.

2.4.3 Transmission Rates

The disease transmission term β characterizes the transition from colonized to infected individual.

2.5 Comments about individual ODEs

Each ODE in the general models system is based upon Equation (4). The overall ODE system comprises three subsystems - one for each type of infection. Further, each subsystem is similar to the one illustrated by Equations (10)-(17). In this section, the particular variations upon Equations (10)-(17) are discussed.

2.5.1 Uncolonized (U) Patients of Category 1

Patients are admitted into the uncolonized compartment at a rate equal to the sum of all admittance rates of all other compartments in a given category, subtracted from one. Specifically, we have $(1-\theta_c-\theta_i-\theta_{ua}-\theta_{ca}-\theta_{ia})$, the fraction of patients admitted to each compartment, and δ the rate at which patients are admitted to the hospital

ICU each day. Patients exit the uncolonized compartment by way of exposure or discharge, and enter by way of admittance or decolonization.

The change from the C to the U compartment is modelled by the ωC terms, one for each category. The general model accounts for multiple species, giving three different sets of equations for Colonized, Infected, Colonized with Antibiotic Exposure, and Infected with Antibiotic Exposure patients. In the case of Uncolonzied patients, there is a single equation, giving three different decolonization terms, $\omega_1 C_1$,$\omega_2 C_2$, and $\omega_3 C_3$.

The change from the U to the C compartment is modelled by the transmission term, $ab_p(1-\epsilon)UC_w$, which is adjusted to account for the compliance of health care workers in donning gloves and gowns, as well as the likelihood of transmission. The term is weighted with a per capita contact rate to account for the number of contacts between health care workers colonized with either VRE or MRSA and patients.

There is no disease-related death term in patients that are not infected or colonized, so, the death rate represents only the normal discharge term in this compartment. Therefore, we have $\gamma_u U$, and, adding all terms with the applicable category 1 subscripts,

$$\dot{U}_1 = \delta(1 - \sum_{j \in \Omega} \theta_j) - e_0 U_3 C_w - \gamma U + \sum_{j=1}^{3} \omega_j C_j \tag{2.9}$$

using the abbreviations, $e_0 = ab_p(1-\epsilon)$. Ω is the set of all admittance rate subscripts, and $C_w = C_{w1} + C_{w2}$.

2.5.2 Colonized (C) Patients of Category 1

Patients enter the colonized compartment through either admittance to the hospital $\delta\theta_c$, or from the uncolonized compartment through interaction with colonized health care workers. The interaction term complements that of the $\dot{U}_1$ equation (described above). The admittance term is weighted with a fraction θ_c representing the fraction of patients that are admitted to the hospital already colonized.

They leave the compartment through either natural progression of the disease to infected status (the β term), by being discharged (the γ_{c1} term), through decolonization (the ω_1 term) or by becoming co-colonized. An additional term is added to account for those that become co-colonized through interaction with a colonized health care worker. In this case, a VRE-colonized patient interacting with a MRSA-colonized health care worker becomes co-colonized with both at a rate $ab_p(1-\epsilon)C_1C_{2w}$. There is no disease related death rate in this compartment due to the low or non-existence of death due to patients being colonized with VRE.

$$\dot{C}_1 = \delta\theta_{c1} + e_0 C_1 C_{w2} - (\omega_1 + \beta_1 + \gamma_{c1})C_1 \tag{2.10}$$

2.5.3 Infected (I) Patients of Category 1

Patients enter the infected compartment by being admitted to the hospital already in possession of such an infection status, or through natural progression of the disease from colonized to infected.

It is assumed that once patients are known to be infected they are not discharged form the hospital until proper treatment procedures have occurred. Patients leave the compartment through death γ_i, or by either successful $\lambda\rho^s$ or unsuccessful treatment $\lambda\rho^u$ to the I_{a1} compartment in the case of failure, or the C_{a1} compartment in the case of success. The treatment term is a combination of the probability of a treatment being either a success ρ^s or a failure ρ^u, weighted by the maximum rate that antibiotics can be given to patients λ.

Adding all the terms and applying all the applicable category 1 subscripts,

$$\dot{I}_1 = \delta\theta_{i1} + \beta_1 C_1 - (\lambda\rho^{u1} + \lambda^{s1} + \gamma_{i1})I_1 \tag{2.11}$$

2.5.4 Uncolonized (U_a) Patients with Past Antibiotic Exposure of Category 1

Patients enter the uncolonized with past antibiotic exposure category through either admittance or through decolonization. The decolonization term, $\sum_{j=1}^{3} \omega_{aj} C_a$ complements that of the uncolonized compartment, U_1. The change from the U_a to the C_a compartment is modelled by the transmission term, which also complements that of the uncolonized compartment (described above). Patients exit the compartment by being discharged from the ICU. There is no disease-related death term in patients that are not infected or colonized, so, the death rate represents only the normal discharge term in this compartment. Therefore, we have $\gamma_{ua} U_a$, and, adding all terms with the applicable category 1 subscripts,

$$\dot{U}_a = \delta\theta_a - \gamma_a U_a - e_a U_a (C_{w2} + C_{w1}) + \sum_{j=1}^{3} \omega_{aj} C_{aj} \tag{2.12}$$

2.5.5 Colonized (C_a) Patients with Past Antibiotic Exposure of Category 1

Patients enter the colonized compartment through either admittance to the hospital $\delta\theta_{ca}$, from the uncolonized compartment through interaction with colonized health care workers, or through successful treatment. The interaction term complements that of the $\dot{U}_1$ equation (described above). The treatment term $\lambda_a \rho_a I_a$ is a combination of the maximum rate that patients are able to recieve antibiotics (λ), and the probability that a patient in compartment I_a will be treated successfully. They leave the compartment through either natural progression of the disease to infected status (the β_a term), by being discharged (the γ_{ca} term), through decolonization (the ω_{a1} term) or by becoming co-colonized. The co-colonization interaction term complements that of the $\dot{U}_1$ equation (described above).

Adding all terms with the applicable category 1 subscripts,

$$\frac{dC_{a1}}{dt} = \delta\theta_{ca1} + e_a U_a C_{w1} + \lambda \rho^{s1} I_1 + \lambda_a \rho_{a1} I_{a1} - (\omega_{a1} + \beta_{a1} + \gamma_{ca1}) C_{a1} \tag{2.13}$$

2.5.6 Infected (I_a) Patients with Past Antibiotic Exposure of Category 1

Patients enter the infected compartment by being admitted to the hospital already in possession of such an infection status, through natural progression of the disease from colonized to infected β_a, through unsuccessful treatment of infected patients $\lambda\rho^u$, or through successful treatment of co-infected patients $\lambda\rho^s$.

It is assumed that once patients are known to be infected they are not discharged form the hospital until proper treatment procedures have occurred. Patients leave the compartment through either death γ_{ia}, or through successful treatment. The treatment term $\lambda_a \rho_a I_a$ complements that of compartment C_a.

Adding all terms with the applicable category 1 subscripts,

$$\dot{I_{a1}} = \delta\theta_{ia1} + \beta_{a1}C_{a1} + \lambda\rho^{u1}I_1 + \lambda\rho^{s(4)}I_3 - (\gamma_{ia1} + \lambda_a\rho_{a1})I_{a1} \tag{2.14}$$

2.5.7 Uncolonized Health Care Workers of Category 1

Health care workers enter the uncolonized compartment at a rate μ reflective of the reciprocal of the amount of time that a given worker will remain colonized. They become colonized and leave the compartment through interaction with VRE colonized or infected patients of any type. The interaction term complements that of $\dot{U}_1$.

Adding all terms with the applicable category 1 subscripts,

$$\dot{U_{w1}} = -a(1-\epsilon)(b_{hc1}C_1 + b_{hi1}I_1 + b_{hca1}C_{a1} + b_{hia1}I_{a1})C_{w1} + \mu C_{w1} \tag{2.15}$$

2.5.8 Colonized Health Care Workers of Category 1

Health care workers enter the colonized compartment, become colonized, through interaction with VRE colonized or infected patients of any type. The interaction term complements that of $\dot{U}_1$. Health care workers enter the uncolonized compartment at a rate μ reflective of the amount of time that a given worker will remain colonized.

Adding all terms with the applicable category 1 subscripts,

$$\dot{C_{w1}} = a(1-\epsilon)(b_{hc}C_1 + b_{hi}I_1 + b_{hca}C_{a1} + b_{hia}I_{a1})C_{w1} - \mu C_{w1} \tag{2.16}$$

2.5.9 Patients of Category 2

Patients of category 2 (MRSA) are treated identically to patients of category 1 (VRE), with the exception for the specific paramater values.

2.5.10 Colonized (C) Patients of Category 3

Patients enter the colonized compartment for category 3 through admittance, or through co-colonization. The co-colonization interaction term is reflective of those who were originally colonized with only VRE and through interaction with a colonized health care worker, acquired MRSA, or vise-versa. The co-colonized interaction term complements that of the $\dot{U_1}$ equation (described above). Patients leave the compartment through either natural progression to infected status, decolonization, or discharge.

Adding all terms with the applicable category 3 subscripts,

$$\dot{C_3} = \delta\theta_{c3} + e_0(C_1C_{w2} + C_2C_{w1}) - (\omega_3 + \beta_3 + \gamma_{c3})C_3 \tag{2.17}$$

2.5.11 Infected (I) Patients of Category 3

It is assumed that once patients are known to be infected they are not discharged form the hospital until proper treatment procedures have occurred. Patients enter the infected compartment by being admitted to the hospital already in possession of such an infection status, or through natural progression of the disease from colonized to infected. Patients leave the compartment through death γ_i, or by either successful $\lambda\rho^s$

or unsuccessful treatment $\lambda\rho^u$ to the I_{a3} compartment in the case of failure, or the C_{a3} compartment in the case of success. The treatment term complements that of the $\dot{I}_1$ equation (described above).

Adding all terms with the applicable category 3 subscripts,

$$\dot{I}_3 = \delta\theta_{i3} + \beta_3 C_3 - (\lambda\rho^{s3} + \lambda\rho^{u3} + \gamma_{i3}) I_3 \tag{2.18}$$

2.5.12 Colonized (C_a) Patients with Past Antibiotic Exposure of Category 3

Patients enter the colonized compartment through either admittance to the hospital $\delta\theta_{ca}$, through successful treatment, or through co-colonization. The interaction and treatment terms complement that of the $\dot{C}_3$ and $\dot{C}_{a1}$ equations respectively (described above).

They leave the compartment through either natural progression of the disease to infected status (the β_a term), by being discharged (the γ_{ca} term), or through decolonization (the ω_{a3} term).

Adding all terms with the applicable category 3 subscripts,

$$\dot{C}_{a3} = \delta\theta_{ca3} + e_a(C_{a1}C_{w2} + C_{a2}C_{w1}) + \lambda_{a3}\rho_{a3}I_{a3} + \lambda\rho^{s3}I_3 - (\beta_{a3} + \omega_{a3} + \gamma_{a3})C_{a3} \tag{2.19}$$

2.5.13 Infected (I_a) Patients with Past Antibiotic Exposure of Category 3

Patients enter the infected compartment by being admitted to the hospital already in possession of such an infection status, through natural progression of the disease β_a, or through unsuccessful treatment of infected patients $\lambda\rho^u$.

It is assumed that once patients are known to be infected they are not discharged form the hospital until proper treatment procedures have occurred. Patients leave the compartment through either death γ_{ia}, or through successful treatment. The treatment term $\lambda_a \rho_a I_a$ complements that of compartment C_a.

Adding all terms with the applicable category 3 subscripts,

$$\dot{I_{a3}} = \delta\theta_{ia3} + \beta_{a3} C_{a3} + \lambda \rho^{u3} I_3 - \lambda_{a3} \rho_{a3} I_{a3} - \gamma_{ia3} I_{a3} \tag{2.20}$$

2.5.14 The model, most general format

We begin with a nonautonomous system of ODEs:

$$\frac{dU}{dt} = \delta(1 - \sum_{j \in \Omega} \theta_j) - e_0 U_3 (C_{w1} + C_{w2}) - \gamma U + \sum_{j=1}^{3} \omega_j C_j \tag{2.21}$$

$$\frac{dU_a}{dt} = \delta\theta_a - \gamma_a U_a - e_a U_a (C_{w2} + C_{w1}) + \sum_{j=1}^{3} \omega_{aj} C_{aj} \tag{2.22}$$

$$\frac{dC_k}{dt} = \delta\theta_{ck} + e_0 C_k C_{w,j \neq k} - (\omega_k + \beta_k + \gamma_{ck}) C_k \tag{2.23}$$

$$\frac{dI_k}{dt} = \delta\theta_{ik} + \beta_k C_k - (\lambda \rho^{uk} + \lambda^{sk} + \gamma_{ik}) I_k \tag{2.24}$$

$$\frac{dC_{ak}}{dt} = \delta\theta_{cak} + e_a U_{a3} C_{wk} + \lambda \rho^{sk} I_k + \lambda_a \rho_{ak} I_{ak} - (\omega_{ak} + \beta_{ak} + \gamma_{cak}) C_{ak} \tag{2.25}$$

$$\frac{dI_{ak}}{dt} = \delta\theta_{iak} + \beta_{ak} C_{ak} + \lambda \rho^{uk} I_k + \lambda \rho^{s(k+3)} I_3 - (\gamma_{iak} + \lambda_a \rho_{ak}) I_{ak} \tag{2.26}$$

$$\frac{dC_3}{dt} = \delta\theta_{c3} + e_0 (C_1 C_{w2} + C_2 C_{w1}) - (\omega_3 + \beta_3 + \gamma_{c3}) C_3 \tag{2.27}$$

$$\frac{dI_3}{dt} = \delta\theta_{i3} + \beta_3 C_3 - (\lambda\rho^{s3} + \lambda\rho^{u3} + \gamma_{i3})I_3 \tag{2.28}$$

$$\frac{dC_{a3}}{dt} = \delta\theta_{ca3} + e_a(C_{a1}C_{w2} + C_{a2}C_{w1}) + \lambda_{a3}\rho_{a3}I_{a3} + \lambda\rho^{s3}I_3 - (\beta_{a3} + \omega_{a3} + \gamma_{a3})C_{a3} \tag{2.29}$$

$$\frac{dI_{a3}}{dt} = \delta\theta_{ia3} + \beta_{a3}C_{a3} + \lambda\rho^{u3}I_3 - \lambda_{a3}\rho_{a3} - \gamma_{ia3}I_{a3} \tag{2.30}$$

$$\frac{dU_{w1}}{dt} = -a(1-\epsilon)(b_{hc1}C_1 + b_{hi1}I_1 + b_{hca1}C_{a1} + b_{hia1}I_{a1})C_{w1} + \mu C_{w1} \tag{2.31}$$

$$\frac{dC_{w1}}{dt} = a(1-\epsilon)(b_{hc}C_1 + b_{hi}I_1 + b_{hca}C_{a1} + b_{hia}I_{a1})C_{w1} - \mu C_{w1} \tag{2.32}$$

$$\frac{dU_{w2}}{dt} = -a(1-\epsilon)(b_{hc}C_2 + b_{hi}I_2 + b_{hca}C_{a2} + b_{hia}I_{a2})C_{w2} + \mu C_{w2} \tag{2.33}$$

$$\frac{dC_{w2}}{dt} = a(1-\epsilon)(b_{hc}C_2 + b_{hi}I_2 + b_{hca}C_{a2} + b_{hia}I_{a2})C_{w1} - \mu C_{w2} \tag{2.34}$$

For k = 1,2 and where $e_j = ab_{pj}(1-\epsilon)$, j = 0,a. Ω is the set of all admittance rate subscripts.

It is nonautonomous because in the most general case, the paramaters can vary with time, e.g. $\theta = \theta(t)$. This has not been indicated explicitly above due to space limitations.

Note that all the patient sub-population figures are non-negative.

U is the number of uncolonized patients

C_j is the number of colonized patients

I_j is the number of infected patients

U_a is the number of uncolonized patients with exposure to antibiotics in the past year

C_{aj} is the number of colonized patients with exposure to antibiotics in the past year

I_{aj} is the number of infected patients with exposure to antibiotics in the past year

U_{wk} is the number of uncolonized health care workers, k = 1,2

C_{wk} is the number of colonized health-care workers k = 1,2

where j = 1,2,3 represents the colonization or infection with VRE, MRSA, and co-colonization respectively, and k = 1,2 represents the colonization status of health-care workers colonized with either VRE or MRSA, respectively.

θ is the admission prevalence of each respective class.

δ is the admission rate.

a is the contact rate between health care workers and patients.

b_p is the colonization probability.

ϵ is the probability a health care worker will comply with barrier precautions.

γ is the discharge or death rate.

β is the transmission rate.

λ is the maximum rate antibiotics can be given to patients.

ρ^s is the probability of a patient receiving a successful treatment.

ω is the decolonization rate for each bacterium.

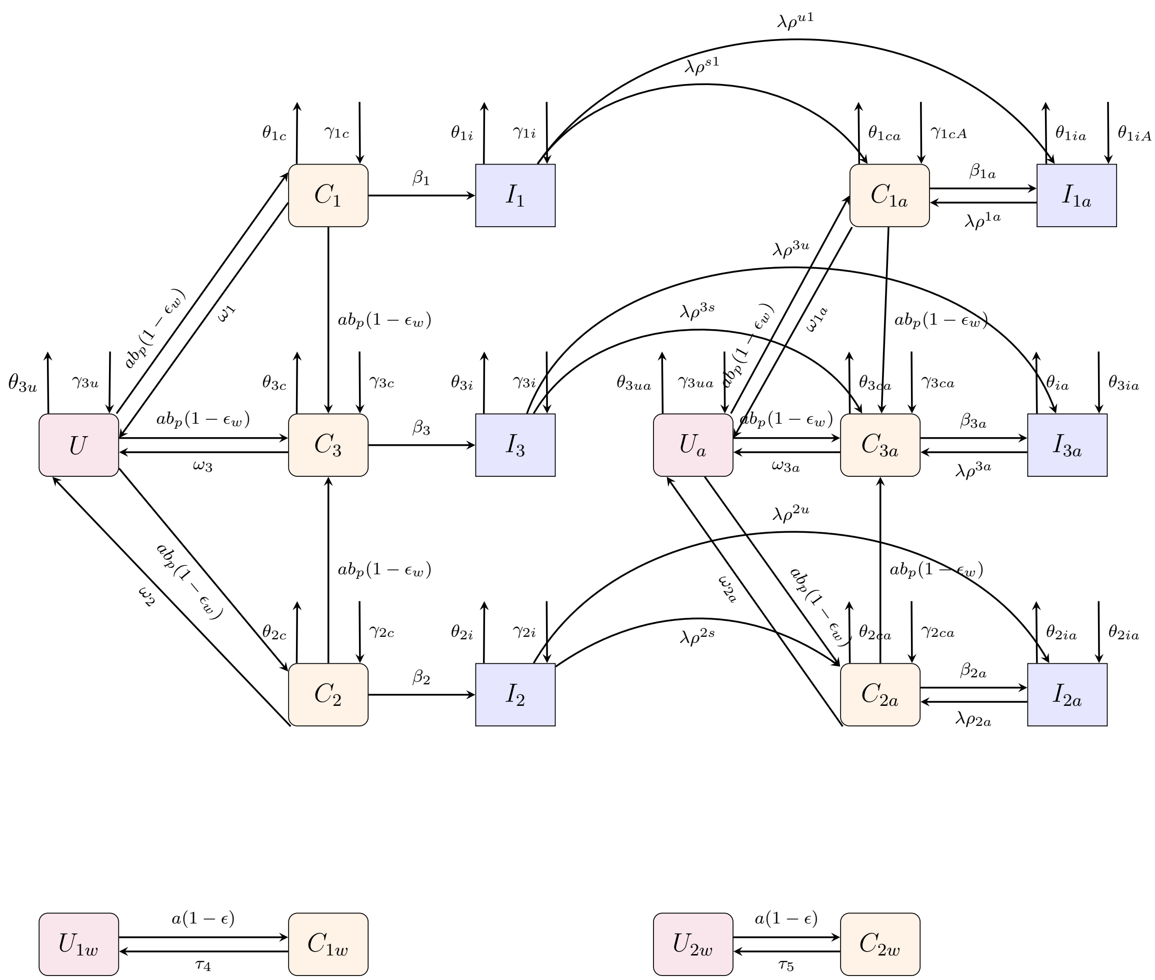

Figure 2.2: General Model Transmission Dynamics Diagram

2.5.15 Model Equilibria

The model's equilibria can be found by setting all of the ODEs to zero. These equilibria are not necessarily stable.

Two equilibria are of special interest, the disease-free equilibrium (DFE), and the endemic equilibrium (EE).

2.5.16 Disease-Free Equilibrium (DFE)

In the case of the DFE, as the name implies, there are no new infections, and existing infections die off:

$$\mathrm{C} = \mathrm{I} = C_a = I_a = 0.$$

There is a trivial DFE for U $= U_a = 0$, but that one is not of great interest. Instead, we shall be concerned with the DFE consisting of only susceptible individuals:

$$\begin{pmatrix} U^* \\ C^* \\ I^* \\ U_A^* \\ C_A^* \\ I_A^* \\ U_w^* \\ C_w^* \end{pmatrix} = \begin{pmatrix} \frac{\delta(1-theta_u)}{1-\gamma_{ua}} \\ 0 \\ 0 \\ \frac{\delta\theta_{ua}}{\gamma_{ua}} \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \tag{2.35}$$

In this case we have, $C = I = 0$ and $C_a = I_a = 0$ which gives us that $C_w = U_w = 0$ as well.

2.5.17 Endemic Equilibria (EE)

In defining EE, we adopt a public health perspective, namely, that patients are the victims and health care workers are the vectors who carry and spread the disease from patient to patient. In other words, we mean to say the equilibria is 'Endemic' with respect to the total patient population.

There are two broad categories of EE: (1) a stable equilibrium, which always has a pool of infectives (I's) of one or more categories; and (2) an oscillating equilibrium, wherein the pool of infectives may be distributed over more than one category, or may even be missing at times, as long as there are C's.

For the stable EE, since the infective portion of the patient population is reduced by both recovery and death, it is necessary to have a non-zero I and C, and therefore, in fact, $U \geq 0$, $C \geq 0, I \geq 0, U_a \geq 0, C_a \geq 0, .I_a \geq 0$. We must also have $R_0 \geq 1$.

It is clear that in order to maintain C and I, we must have transmission in both directions (patient to HCW, HCW to patient). Otherwise, the Cs and Is (and the C_as and I_as) would eventually die off, leaving no supply of the virus.

We have,

$$
\begin{pmatrix} U^* \\ C^* \\ I^* \\ U_A^* \\ C_A^* \\ I_A^* \\ U_w^* \\ C_w^* \end{pmatrix} = \begin{pmatrix}
\frac{\delta\theta_u Q + \omega\delta\theta_c}{(eC_w-\gamma_u)(\beta+\gamma_c)-\gamma_u\omega} \\
\frac{\delta\theta_c}{Q} + \frac{eC_w\delta\theta_u}{(eC_w-\gamma_u)(\beta+\gamma_c)-\gamma_u\omega} + \frac{eC_w\delta\theta_c\omega}{Q((eC_w-\gamma_u)(\beta+\gamma_c)-\gamma_u\omega)} \\
\frac{1}{P}\left(\delta\theta_i + \beta\left(\frac{\delta\theta_c}{Q} + \frac{eC_w\delta\theta_u}{(eC_w-\gamma_u)(\beta+\gamma_c)-\gamma_u\omega} + \frac{eC_w\delta\theta_c\omega}{Q(eC_w-\gamma_u)(\beta+\gamma_c)-\gamma_u\omega}\right)\right) \\
\frac{\delta\theta_{ua}}{Y} + \frac{\omega_a}{A}\left(\delta(\theta_{ca}Z + \frac{e_1C_w\theta_{ua}Z}{Y} + \theta_{ia}\lambda_a\rho_a) + \frac{(\lambda\rho^s ZY + \lambda\lambda_a\rho^u\rho_a Y)I^*}{Y}\right) \\
\frac{1}{A}\left(\delta(\theta_{ca}YZ + e_1C_w\theta_{ua}Z + \theta_{ia}\lambda_a\rho_a Y) + (\lambda\rho^s ZY + \lambda\lambda_a\rho^u\rho_a Y)I^*\right) \\
\frac{\delta\theta_{ia}}{Z} + \frac{\beta_a\delta}{A}\left(\theta_{ca}Y + e_1C_w\theta_{ua} + \frac{\theta_{ia}\rho_a\lambda_a Y}{Z}\right) + \frac{1}{PZ}\left(\frac{(\lambda\rho^s ZY + \lambda\lambda_a\rho^u\rho_a Y)\beta_a}{A} + \lambda\rho^u\right) I^* \\
\frac{\mu C_w}{a(1-\epsilon)T} \\
C_w
\end{pmatrix} \tag{2.36}
$$

with $C_w^* \in R$ where $\theta_u = 1 - \sum_{j\in J}$, $J = c, i, ua, ca, ia$, $e = ab_p(1-\epsilon_w)$, $e_1 = ab_{pa}(1-\epsilon_w)$, $P = \lambda\rho^u + \lambda\rho^s + \gamma_i$, $Q = \omega + \beta + \gamma_c$, $X = \omega_a + \beta_a + \gamma_{ca}$, $Y = e_1C_w + \gamma_{ua}$, $Z = \lambda_a\rho_a + \gamma_{ia}$ and $A = XYZ - e_1C_w\omega_a Z - \lambda_a\rho_a\beta_a Y$, $T = \left(b_{hc} + \frac{\beta b_{hi}}{P} + \frac{\beta b_{hia}\lambda\rho^u}{PZ}\right)(PC^* - \delta\theta_i) + \frac{b_{hia}\delta\theta_{ia}}{Z} + \frac{\delta\theta_i}{P}\left(b_{hi} + \frac{b_{hia}\lambda\rho^u}{Z}\right) + \frac{b_{hca}Z + b_{hia}\beta_a}{A}\left(\delta(\theta_{ca}Y + e_1C_w\theta_{ua} + \frac{\theta_{ia}\rho_a\lambda_a Y}{Z}) + \frac{C^*B}{Z}\right)$.

2.5.18 R_0 The Basic Reproductive Number

In studying an outbreak, one may wish to look at the potential for growth of the outbreak. A negative derivative in the case of $\dot{C}_i$,$\dot{I}_i$,$\dot{C}_{ai}$,$\dot{I}_{ai}$, for i=1,2,3 would indicate that the disease was declining, as would a positive derivative indicate growth of the disease.

More common in analysis is to look at the value of the reproductive ratio R_0. The interpretation of R_0, is that if one organisms is infected, then R_0 more cases should develop, so long as there is a sufficiently large enough pool of uninfected individuals with the potential for infection. An empiric value of R_0 can be achieved through using the field data to look at the number of primary and secondary cases, namely, it is the number of original cases divided by the number of secondary cases.

The 'Next Generation Method ' by Diekmann was used to caluculate the reproductive ratio. It gives the mean number of new infectives per infective in any class, 'per generation '.

The following will show how R_0 was determined for this model:

Let F be the vector of new infections where each F_i is the rate of appearance of new infections in compartment i. Let V be the vector of transfer rates by all other means in which $V_i = V_i^- - V_i^+$ where V_i^+ represents the transfer of individuals into compartment i, and V_i^- represents the transfer of individuals out of compartment i. Rearrancing the order of equations and variables as, C,C_a,I,I_a,C_w, U, U_a, U_w, we have,

$$F = \begin{pmatrix} ab_p(1-\epsilon_w)UC_w \\ ab_{pa}(1-\epsilon_w)U_aC_w \\ 0 \\ 0 \\ a(1-\epsilon_w)(b_{hc}C + b_{hi}I + b_{hca}C_a + b_{hia}I_a)U_w \\ 0 \\ 0 \\ 0 \end{pmatrix} \tag{2.37}$$

and

$$
V = \begin{pmatrix}
(\omega + \beta + \gamma_c)C \\
(\omega_a + \beta_a + \gamma_{ca})C_a - (\lambda\rho^s I + \lambda_a \rho_a I_a) \\
(\lambda\rho^u + \lambda\rho^s + \gamma_i)I - \beta C \\
(\gamma_{ia} + \lambda_a \rho_a)I_a - (beta_a C_a + \lambda\rho^u I) \\
\mu C_w \\
ab_p(1-\epsilon_w)UC_w + \gamma_u U - \omega C \\
ab_{pa}(1-\epsilon_w)U_a C_w + gamma_{ua} U - \omega_a C_a \\
a(1-\epsilon_w)(b_{hc}C + b_{hi}I + b_{hca}C_a + b_{hia}I_a)U_w - \mu C_w
\end{pmatrix} \tag{2.38}
$$

Next, define F and V as partitioned matricies from the disease-related variables of the Jacobian maricies of F and V at the disease-free steady state, respectively. For simplicities sake, we let $e = a(1-\epsilon_w)$.

$$
F = \begin{pmatrix}
0 & 0 & 0 & 0 & eb_p U \\
0 & 0 & 0 & 0 & eb_{pa} U_a \\
0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 \\
eb_{hc} & eb_{hca} & eb_{hi} & eb_{hia} & 0
\end{pmatrix} \tag{2.39}
$$

and

$$
V = \begin{pmatrix}
(\omega + \beta + \gamma_c) & 0 & 0 & 0 & 0 \\
0 & (\omega_a + \beta_a + \gamma_{ca}) & -\lambda\rho^s & \lambda\rho_a & 0 \\
-\beta & 0 & (\lambda\rho^s + \lambda\rho^u + \gamma_i) & 0 & 0 \\
0 & -\beta_a & -\lambda\rho^u & \gamma_{ia} + \rho_a\lambda_a & 0 \\
0 & 0 & 0 & 0 & \mu
\end{pmatrix} \tag{2.40}
$$

Inverting V, we get,

$$V^{-1} = \begin{pmatrix} \frac{1}{A} & 0 & 0 & 0 & 0 \\ \frac{-\lambda_a\rho_a\beta F+G\beta\lambda\rho^s}{ABDG} & \frac{-\lambda_a\rho_a\beta_a DA+GDA}{ABDG} & \frac{-F\lambda_a\rho_a+G\lambda\rho^s}{BDG} & \frac{-\lambda_a\rho_a}{G} & 0 \\ \frac{\beta}{AD} & 0 & \frac{1}{D} & 0 & 0 \\ \frac{\beta F}{ADG} & \frac{\beta_a}{G} & \frac{F}{DG} & \frac{B}{G} & 0 \\ 0 & 0 & 0 & 0 & \frac{1}{\mu} \end{pmatrix} \tag{2.41}$$

where $A = \omega + \beta + \gamma_c$,$B = \omega_a + \beta_a + \gamma_{ca}$, $D = \lambda\rho^s + \lambda\rho^u + \gamma_i$, $E = \gamma_{ia} + \rho_a\lambda_a$, $F = \lambda\rho^u B + \beta_a\lambda\rho^s$, and $G = BE + \beta_a\lambda_a\rho_a$.

Calculating FV^{-1} we have,

$$FV^{-1} = e \begin{pmatrix} 0 & 0 & 0 & 0 & \frac{eb_pU}{\mu} \\ 0 & 0 & 0 & 0 & \frac{b_{pa}(N_p-U)}{\mu} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ J & \frac{-b_{hca}(\lambda_a\rho_a\beta_a DA+GDA)}{ABDG} + \frac{b_{hia}\beta_a}{G} & \frac{-b_{hca}H}{\beta BDG} + \frac{b_{hi}}{D} + \frac{b_{hia}F}{DG} & \frac{b_{hia}B-b_{hca}\lambda_a\rho_a}{G} & 0 \end{pmatrix} \tag{2.42}$$

where $J = \frac{b_{hc}}{A} - \frac{b_{hca}(\lambda_a\rho_a\beta F+G\beta\lambda\rho^s)}{ABDG} + \frac{\beta b_{hi}}{AD} + \frac{b_{hia}F\beta}{ADG}$

The eigenvalues of FV^{-1} are

0 (repeated 3 times), and

$$\pm\left(\frac{e^2 b_p N_p}{\mu}\left(\frac{b_{hc}}{A}-\frac{b_{hca}(\lambda_a\rho_a\beta F+G\beta\lambda\rho^s)}{ABDG}+\frac{\beta b_{hi}}{AD}+\frac{b_{hia}\beta F}{ADG}+\frac{b_{hca}\lambda_a\rho_a\beta_a}{BG}+\frac{b_{hca}}{B}+\frac{b_{hia}\beta_a}{G}\right)\right)^{1/2}$$

Taking the positive eigenvalue we obtain,

$$\left(\frac{e^2 b_p N_p}{\mu}\left(\frac{b_{hc}}{A}-\frac{b_{hca}(\lambda_a\rho_a\beta F+G\beta\lambda\rho^s)}{ABDG}+\frac{\beta b_{hi}}{AD}+\frac{b_{hia}\beta F}{ADG}+\frac{b_{hca}\lambda_a\rho_a\beta_a}{BG}+\frac{b_{hca}}{B}+\frac{b_{hia}\beta_a}{G}\right)\right)^{1/2}$$

Therefore, factoring, the Reproductive Ratio is,

$$R_0=\left(\frac{e^2 b_p N_p}{\mu}\left(\frac{b_{hc}}{A}+\frac{b_{hca}B(\gamma_{ia}\rho^s+\rho_a\lambda_a(\rho^s-\rho^u))+b_{hi}\beta F}{AD(BE+\beta_a\lambda_a\rho_a)}+\frac{b_{hi}\beta}{AD}+\frac{b_{hca}E}{BE+\beta_a\lambda_a\rho_a}+\frac{b_{hia}\beta_a}{BE+\beta_a\lambda_a\rho_a}\right)\right)^{1/2}$$

with $A=\omega+\beta+\gamma_c$, $B=\omega_a+\beta_a+\gamma_{ca}$, $D=\lambda\rho^s+\lambda\rho^u+\gamma_i$,$E=\gamma_{ia}+\rho_a\lambda_a$ and $F=\lambda\rho^u B+\beta_a\lambda\rho^s$.

Note:

- It is not a strictly dominant eigenvalue, as R_0 is also an eigenvalue.
- The ratio is independent of admission rates.
- In this specific instance, N_p represents the total number of uncolonized patients.

2.5.19 Control Strategies

Once one has an expression for R_0, one can pursue control strategy theories by seeking to reduce it to a value less than one.

Some possible simplifications include having $\lambda\approx 0$ and $\lambda_a\approx 0$. This makes intuitive sense as if the maximum rate patients are being given antibiotics is low, then there is less of a chance of them developing resistance. Also it is important to note that once a treatment failure has occurred, patients move to the class of people with past antibiotic exposure, where the infection is transmitted much faster and treatment is much more difficult.

2.5.20 Possible Simplifications

The general full-model results in a system of 18 equations, and it is desirable to consider reducing this through simplifications and rescaling. Unfortunately, in the case of the three-bacterium model this is complicated through the interaction between single and co-colonized individuals. Reducing the complicity of the model, in many cases, is not possible through the numerical differences in parameter values between the three different types of bacterium. Creating a universal value for the probability of successful or unsuccessful treatment is a possibility, though due to the lack of sufficient empirical data, it is not possible to ascertain whether this is an appropriately accurate assumption. It is possible to consider creating universal values for other parameter values such as the discharge or admittance rates, but doing so would not be appropriate given the differences in empirical data. It is to be noted though that in the case of the length of time that Health-care Workers can transmit infection μ, the empirical value is the same for all three bacterium, and so a single value is used in this case.

Elimination of negligible terms should also be considered. The death rate for uncolonized and colonized individuals, γ_u and γ_c is believed to be near zero due to the length of stay for patients in the ICU and the severity of the bacterium for colonized individuals, and so is disregarded. The lack of discharge rate for infected individuals is similarly disregarded, due to hospital procedures, it is only very few undiagnosed cases where patients having such an infection status are discharged without treatment. The fraction of patients that become co-colonized in a single interaction with a single health care worker is close enough to zero that one can eliminate this term. This simplification is both a realistic and useful one.

Any implementation of the above simplifications that have not already been done does not yield a good-pay off, as it does not reduce the complicity of the model greatly and does not allow for the elimination of any equations.

2.5.21 Model Variations

Omitting (I) or (I_a)

The model herein has been case as a model with (U), (C), and (I), but it can be reduced by possible elimination (I) and/or (I_a), for a total of six basic equations and twelve equations in the general model.

Elimination of the infected compartment is a common simplification seen in the literature. Unfortunately in the general model, treatment of infected individuals is a key aspect in the addition of individuals with past antibiotic exposure. This can be rectified by combining the C and I compartments, and having patients treated upon arrival in the colonized class. Though not reflective of the non-symptomatic reality of those in the colonized class, it is a good method with which to still retain the treatment aspect crucial to the involvement of past antibiotic exposure in the model. We would then have patients entering the 'colonized' compartment through acquisition of the bacteria (the interaction term), and leave through treatment (either unsuccessful or successful) or death. The β progression term is eliminated, in this case. These changes are the same in the case of the elimination of (I_a), with the exception of treatment, wherein patients who have been unsuccessfully treated enter the compartment. The decolonization term would be combined to account for the success of treatment.

$\theta(t)$ and $\gamma(t)$

Though not necessarily a simplification, one may consider the conversion of admittance and discharge rates to time-dependent functions. This is not particularly difficult in the numerical analysis, but program run-time would increase dramatically.

Chapter 3

Methods

3.1 Analysis of the ODE

Analysis of the ODE system was made difficult due to the presence of non-linear terms in over half of the model equations. This is why an attempt to find an explicit form for the solutions of the general system was not pursued with any major effort. This is illustrated in the complicity of the original models analytic solutions. Determination of equilibria, calculation of the reproductive ratio (R_0), and simulation of the transmission process were pursued to the fullest extent possible.

A set of parameter values (table 3.1) was chosen for general use. Please refer to Appendix E for a more in-depth discussion of the specifics on the choice of parameter values selected. Values for VRE, MRSA, and co-colonization are listed where applicable, in the cases where there is a single value for all three bacterium the value is listed under VRE. For more in-depth information on the co-colonized parameter values please refer to Appendix E.

Paramater	Description	VRE	MRSA
δ	Rate patients are admitted	1.36**	NA
γ_u	Uncolonized Discharge Rate	0.2*	NA
γ_{cj}	Colonized Discharge Rate	0.1**	0.142857*
γ_{ij}	Infected Death Rate	0.042857*	0.042857*
γ_{ua}	Uncolonized Discharge Rate	0.0714***	NA
γ_{caj}	Colonized Discharge Rate	0.03571***	0.09928*
γ_{iaj}	Infected Death Rate	0.02857*	0.02857*
θ_{cj}	Fraction of colonized patients admitted	0.1**	0.047*
θ_{ij}	Fraction of infected patients admitted	0.2****	0.001*
θ_u	Fraction of uncolonized patients admitted	0.142857**	NA
θ_{uA}	Fraction admitted that have had AB exposure	0.29411***	NA
θ_{caj}	Fraction of colonized patients admitted	0.013	0.03*
θ_{iaj}	Fraction of infected patients admitted	0.001*	0.001*
ω_j	Decolonization Rate / day	0.00142857*	0.00142857*
ω_{aj}	Decolonization Rate / day	0.000714*	0.000714*
λ	Maximum rate ABs given to infected patients	0.3***	NA
λ_a	Maximum rate ABs given to infected patients	0.1*	NA
ρ^{sj}	Probability of successful treatment	0.24	0.5*
ρ^{uj}	Probability of unsucessful treatment	0.76	0.15*
ρ_{aj}	Probability of successful treatment	.35*	0.35*
β_j	Rate colonized patients become infected	0.2795**	0.042857*
β_{aj}	Rate colonized patients become infected	0.2795**	0.0428*
b_p	Colonization probability	0.06*	NA
b_{pa}	Colonization probability	0.025*	NA
b_{hc}	Colonization probability	0.25*	NA
b_{hi}	Colonization probability	0.1*	NA
b_{hca}	Colonization probability	0.15*	NA
b_{hia}	Colonization probability	0.3*	NA
a	per capita HCW-patient contact rate	1.38*	NA
$1/\mu$	Time contaminated HCWs can transmit	24**	NA

Table 3.1: Parameter Values, general model

*Chamchod and Ruan [13]

**D.J.Austin et. al. [10]

***E.D'Agata et. al. [8]

****D.Fisman [17]

The value θ_{1ca} was taken from G. Papia [36]. The of ρ^{1s} and ρ^{1u} was taken from L.S. Chavers et. al. [44].

3.2 Simulate Progress of the Disease

Twelve basic cases were generated. These cases include four base-line cases where there are no infected individuals, as well as various situation where there is only 15% of a given patient class infected. Some of the cases serve as controls by omitting selected compartments.

For the most part, the cases were run with a total population of 600 patients and 150 health care workers, with a single ICU consisting of 16 beds and 5 health care workers. In some cases the total number of ICU patients in the hospital, in most cases around 60, is used. Unless otherwise specified, the initial starting population values used were $U_0 = 50$,$C(0) = 5$, $I(0) = 1$, $U_a(0) = 10$, $C_a(0) = 1$,$I_a(0) = 0$, $U_w(0) = 30$, $C_w(0) = 3$. These numbers were arrived at through consideration of the literature and data from multiple hospitals in Ontario.

The twelve cases, and the parameter values listed in the previous section were run on a suite of programs in MATLAB.

The program was written in MATLAB programming language. Patient population figures were reported as the program runs and were also saved in a file at the end of each run. Population values are not allowed to run into the negative territory. The program is a deterministic, discrete approximation of the continuous model, and the results are repeatable at will.

3.2.1 Other Programs and Tools

A MAPLE program was used for simplifying complicated expressions, particular with regards to the equilibria calculation, and R_0.

3.3 Software Quality and Testing

A variety of measures was used to avoid software bugs and similar problems. Defensive programming was used throughout, with modularity and testability being pursued at all times. The list of parameter values was centrally maintained so that all programs and documents were using the same values. All program outputs were checked for reasonableness, and they were validated against special cases and prior work where possible. The special cases included zero populations of certain patient classes, and there are found in the list of cases. This testing revealed certain problems, which is discussed in the next chapter.

Chapter 4

Results/Findings

4.1 Results of the Deterministic Model Simulation

Case A is a control case wherein there are no colonized or infected individuals in the starting population. There were 50 initial uncolonized patients, 10 initial uncolonized patients with past exposure, as well as 30 initial uncolonized health care workers. In this case, the final population numbers were the same as the starting ones. This is because there is no infection present, and the admittance and discharge rates were equal, providing a steady influx of patients. On the x-axis the time runs in most cases from 0 to 60, and on the y-axis the corresponding uncolonized, colonized, or colonized patient population was plotted.

Case B and C are single-patient runs, where in case B the colonized patient population is set at 10 percent of the uncolonized ($U(0) = 50$,$U_a(0) = 10$, $U_w(0) = 30$, $C(0) = 5$, $C_a(0) = 1$, $C_w(0) = 0$), and in case C a single infective patient is introduced ($U(0) = 50$,$U_a(0) = 10$, $U_w(0) = 30$, $I(0) = 1$, $I_a(0) = 1$, $C_w(0) = 0$). Note that in Case B there are no infected patients introduced initially, and in Case C there are no colonized patients introduced initially. Notice how the infection still managed to increase in severity. This shows that it is not necessarily the amount of infected or colonized patients or health care workers introduced into the population that plays a large role in whether there is an epidemic. This made clear in consideration of R_0 wherein there is a dependence on the total number of uncolonized patients. It should be noted that the presence of colonized workers in the initial population has no change on the dynamics.

Case D-F show increasing the decolonization rate, ω, by a factor of 10. This does have some effect in reducing the spread of transmission, but not in such a way for it to be useful in practical applications. It is to be noted that increasing the decolonization rate for patients with past exposure has a similar effect, but stronger. This case was not shown as it is not a realistic method with which to control infection, as infected patients still increase in this instance.

Case G-I show increasing the probability of compliance, ϵ, from 0.3 to 0.9. We see that the upper limit that the number of infected patients reaches a much lower level. Though the infection is quite efficiently controlled through increasing of the compliance rate, generally compliance rates will be at around 0.2 to 0.4 in most hospitals. Other means of encouraging mandatory use of barrier precautions must be devised for this to be an adequate strategy in reducing the spread of infection.

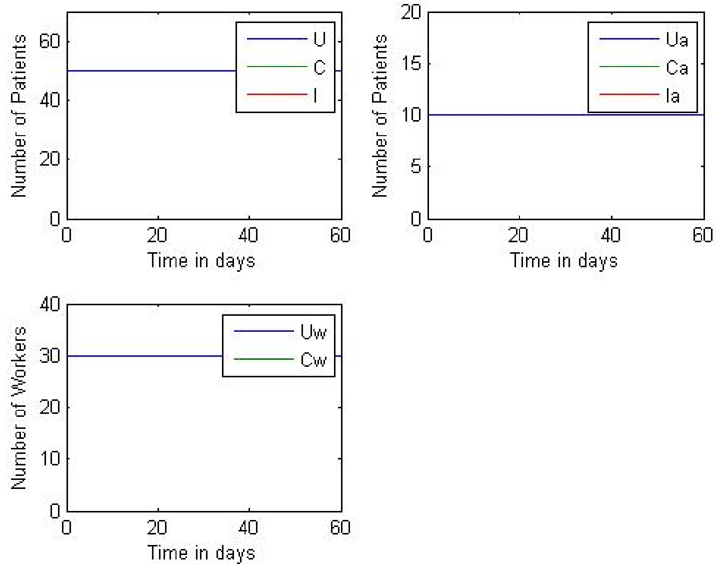

Figure 4.1: Case A: Control case, population dynamics with no initial infected or colonized patients, using the basic model.

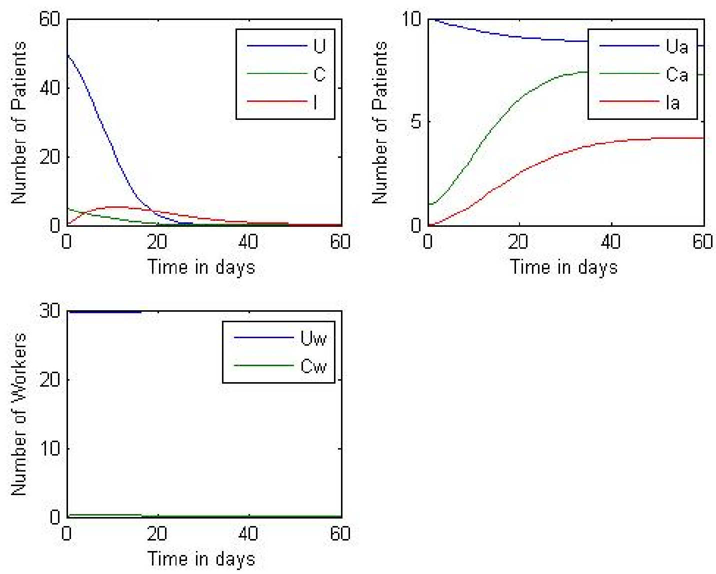

Figure 4.2: Case B: Population dynamics with initial colonized populations set at 10% of uncolonized patient populations for those with and without past antibiotic exposure, respectively, using the basic model.

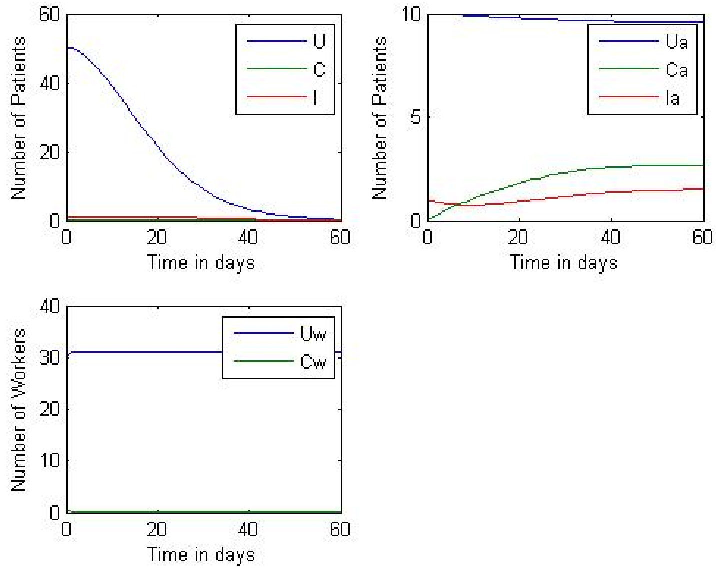

Figure 4.3: Case C: Population dynamics with a single initial infected patient introduced for those with and without past antibiotic exposure, respectively, using the basic model.

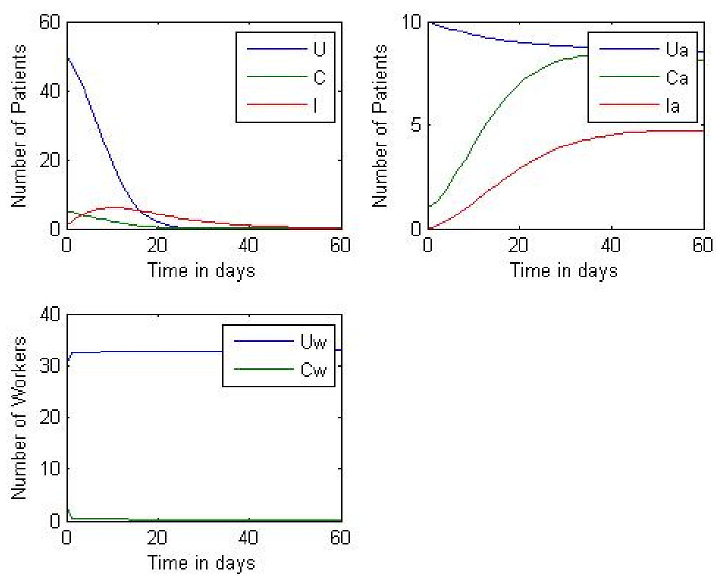

Figure 4.4: Case D: Population dynamics as the decolonization rate (ω) varies using the basic model. This is a control case where there is no change in ω.

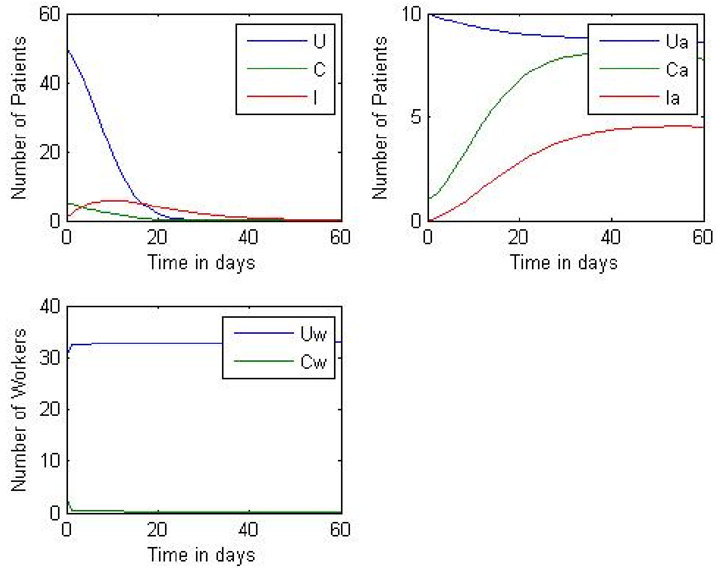

Figure 4.5: Case E: Population dynamics as the decolonization rate (ω) varies using the basic model. In this case ω is increased by a factor of 10.

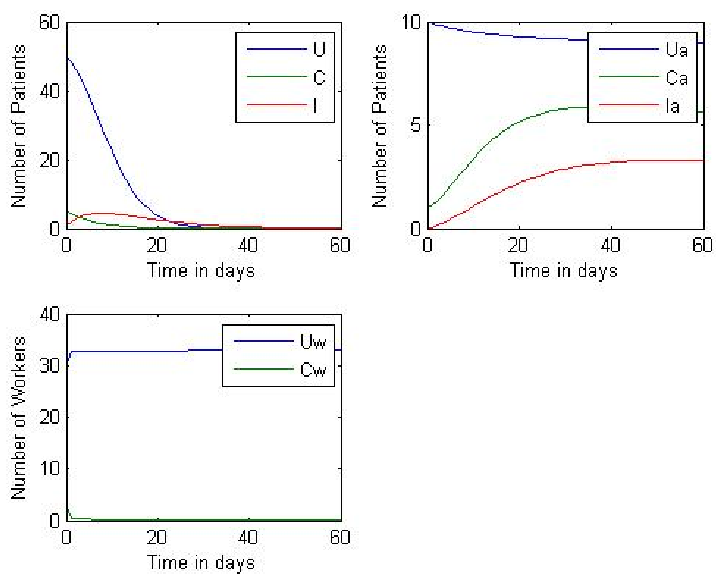

Figure 4.6: Case F: Population dynamics as the decolonization rate (ω) varies using the basic model. In this case ω is increased by a factor of 100.

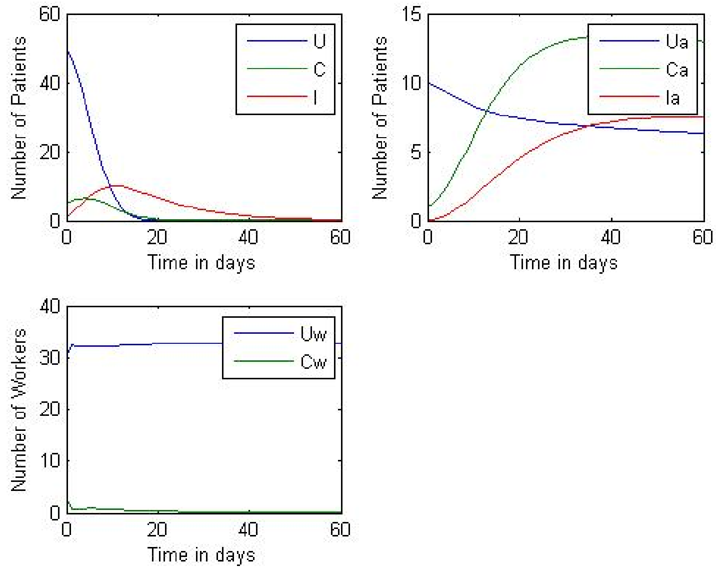

Figure 4.7: Case G: Population dynamics as the compliance probability (ϵ) is varied, using the basic model. In this case $\epsilon = 0.3$

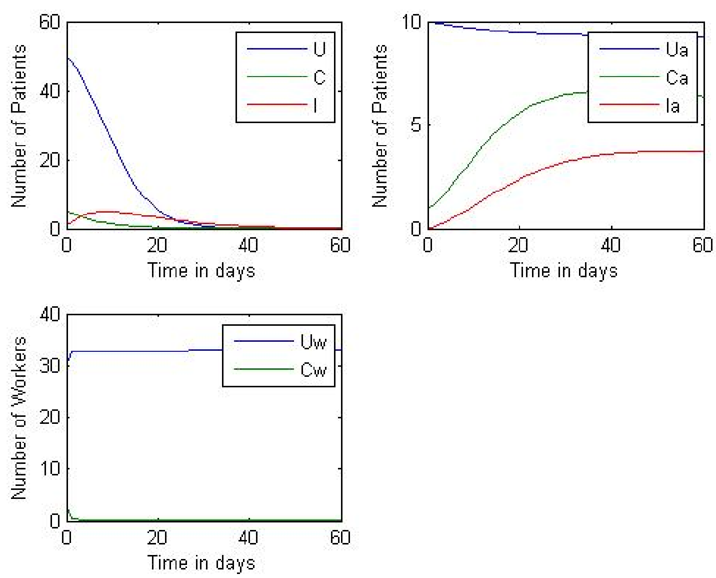

Figure 4.8: Case H: Population dynamics as the compliance probability (ϵ) is varied, using the basic model. In this case $\epsilon = 0.6$

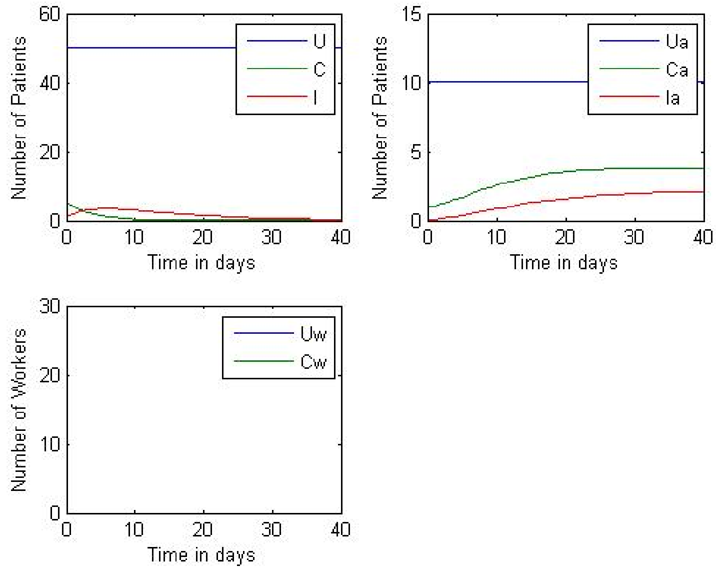

Figure 4.9: Case I:Population dynamics as the compliance probability (ϵ) is varied, using the basic model. In this case $\epsilon = 0.9$

4.2 Results of the Deterministic General Model Simulation

In the limited cases where data was not available for the co-colonized parameters, the value for MRSA was used. Perusal of the literature shows this to be an adequate estimate until such a time as more realistic data becomes available. On the x-axis the time runs in most cases from 0 to 60, and on the y-axis the corresponding uncolonized, colonized, or colonized patient population was plotted.

Case J shows the simulation when run with real data. Case K-M shows the simulation with varying compliance probability *epsilon* from 0.3 to 0.9 in 0.3 intervals. Notice how there is much less of an effect on controlling the spread of infection. That said, the effect of increasing the compliance rate is still an effective method of reducing the potential pool of infectives. It is also to be noted that varying the probability of a successful treatment, ρ, has no effect on controlling the outbreak. Case N-O shows increasing decolonization rate ω. We see a similar result as with the basic model, in that both the colonized and infected patients are seen to decline with increasing ω.

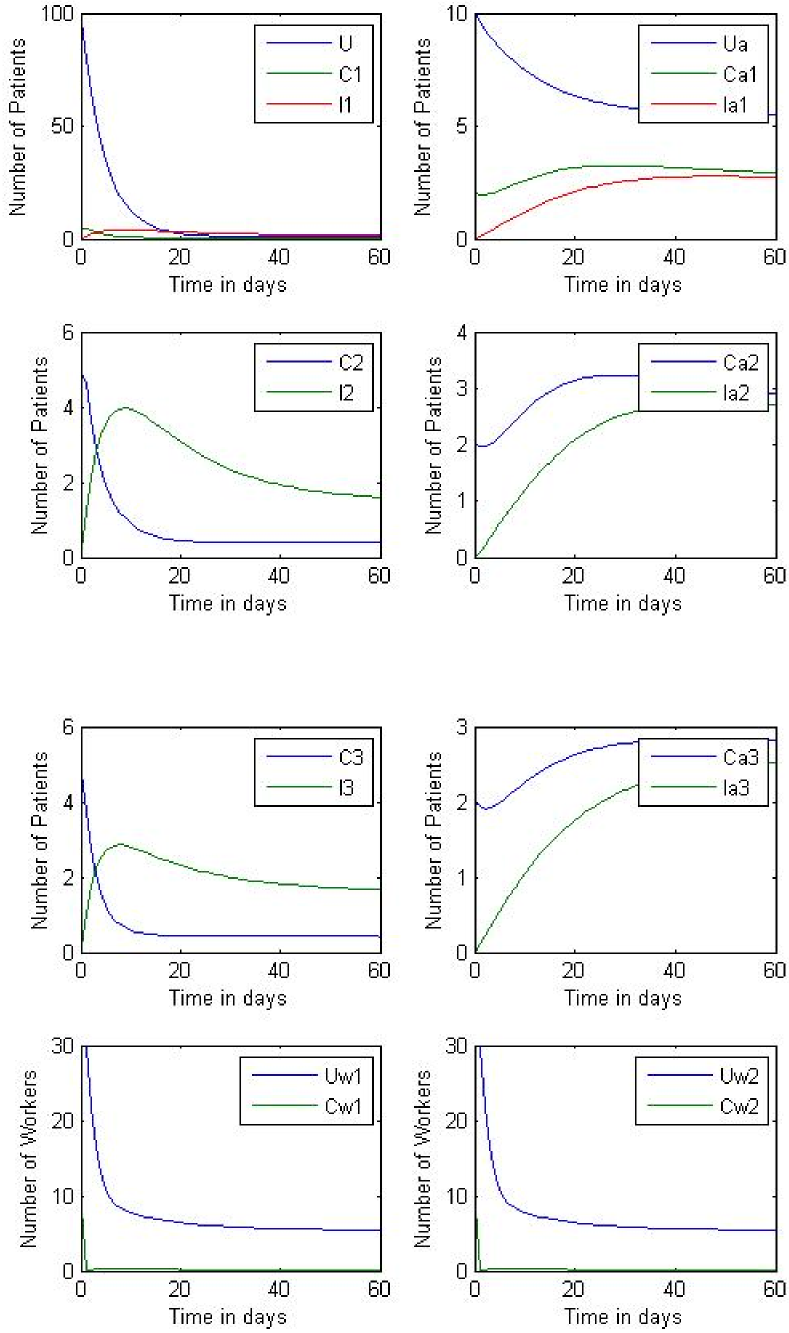

Figure 4.10: Case J: This is a control case where the patient population dynamics are simulated using the general model. Parameter values and initial population numbers are taken from the literature.

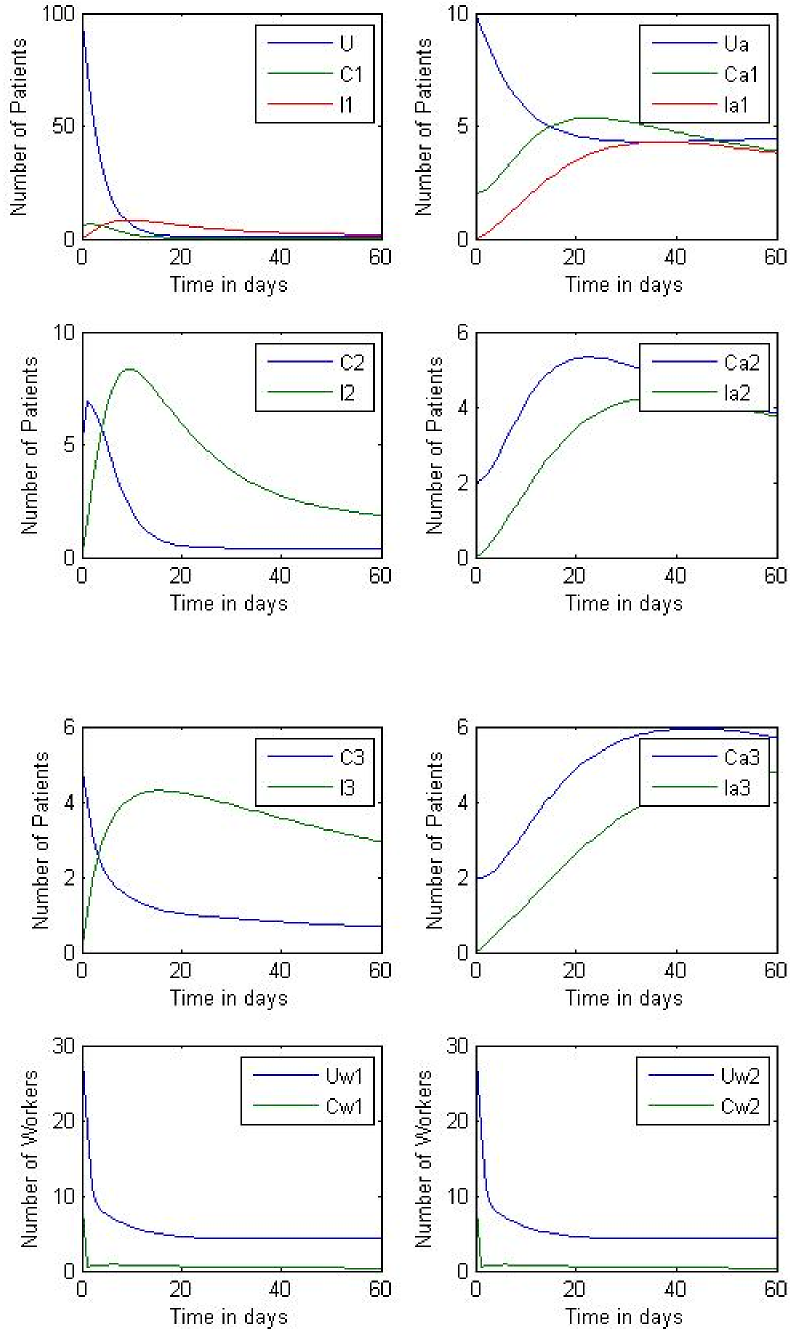

Figure 4.11: Case K: Population dynamics as the compliance probability (ϵ) is varied, using the general model. In this case $\epsilon = 0.3$

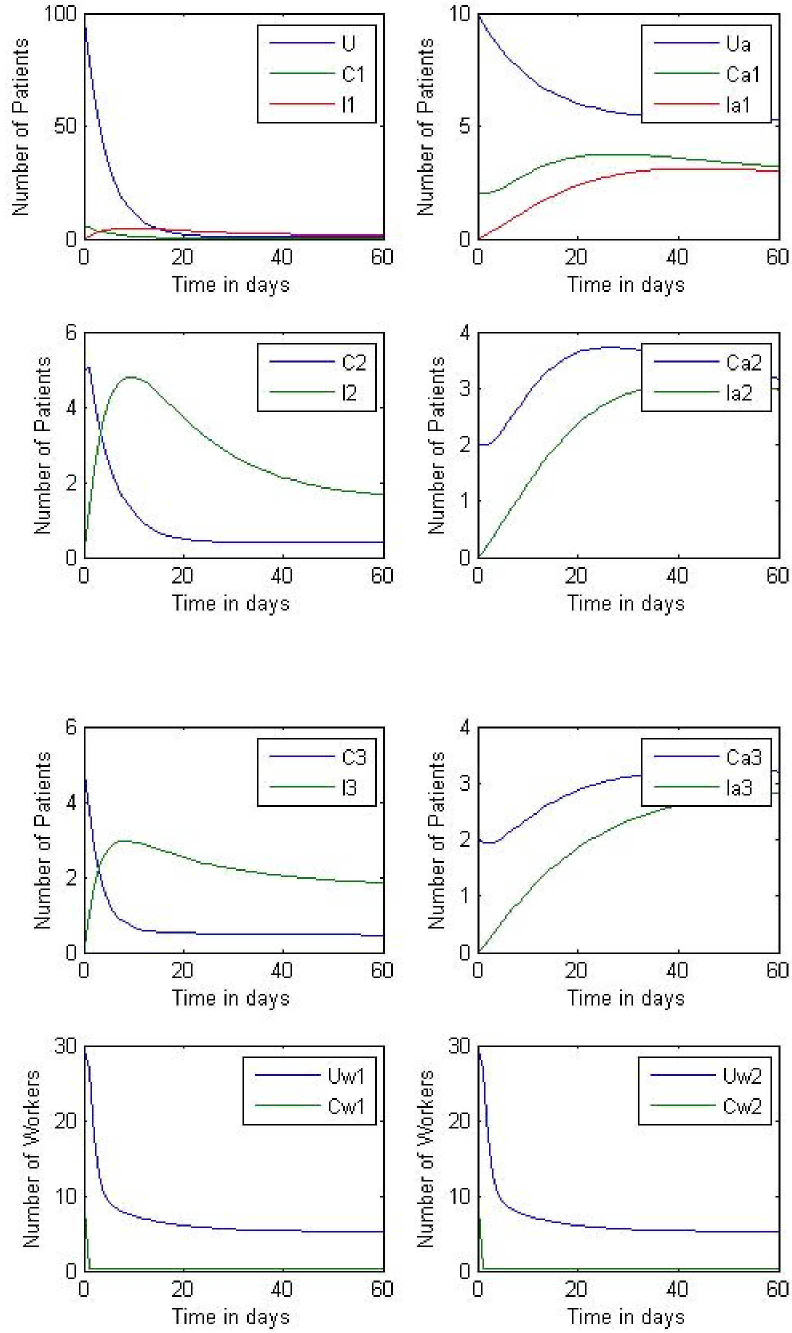

Figure 4.12: Case L: Population dynamics as the compliance probability (ϵ) is varied, using the general model. In this case $\epsilon = 0.6$

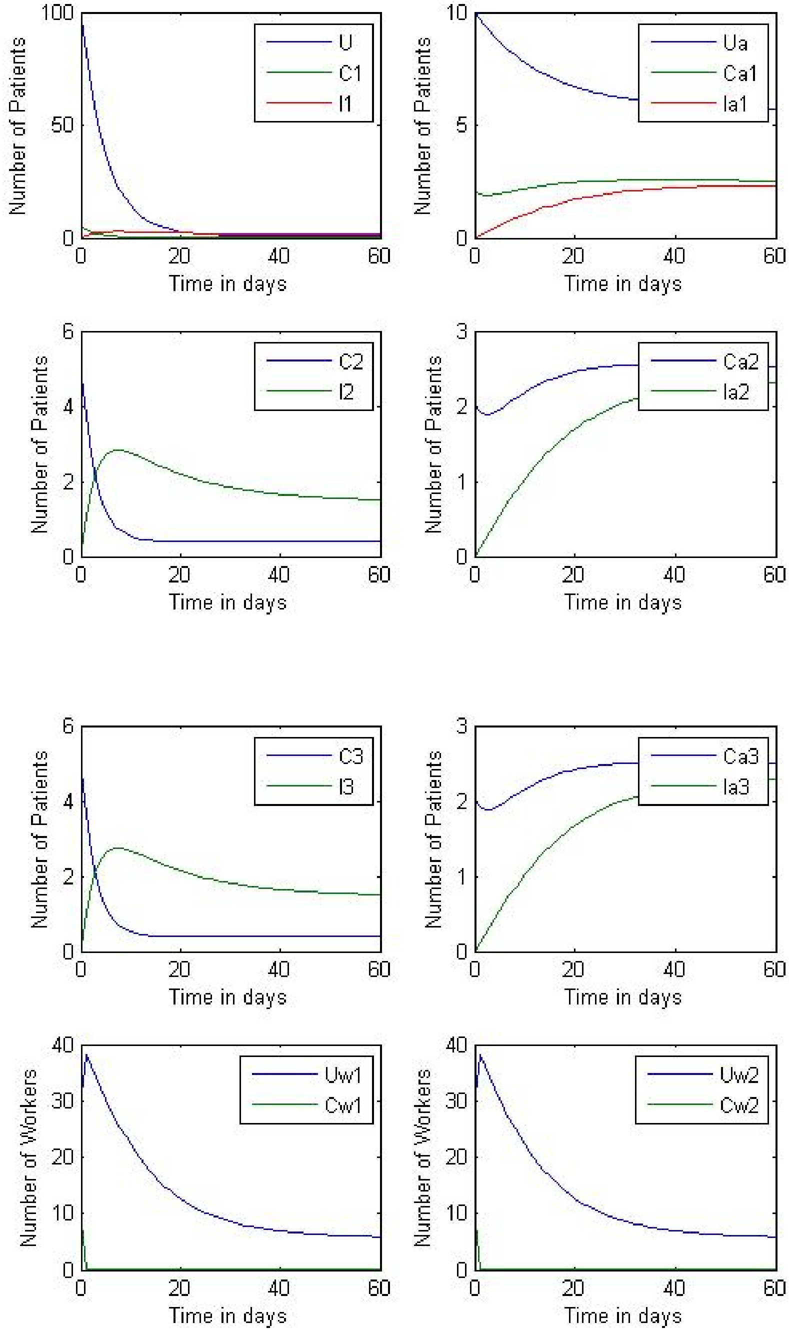

Figure 4.13: Case L: Population dynamics as the compliance probability (ϵ) is varied, using the general model. In this case $\epsilon = 0.9$

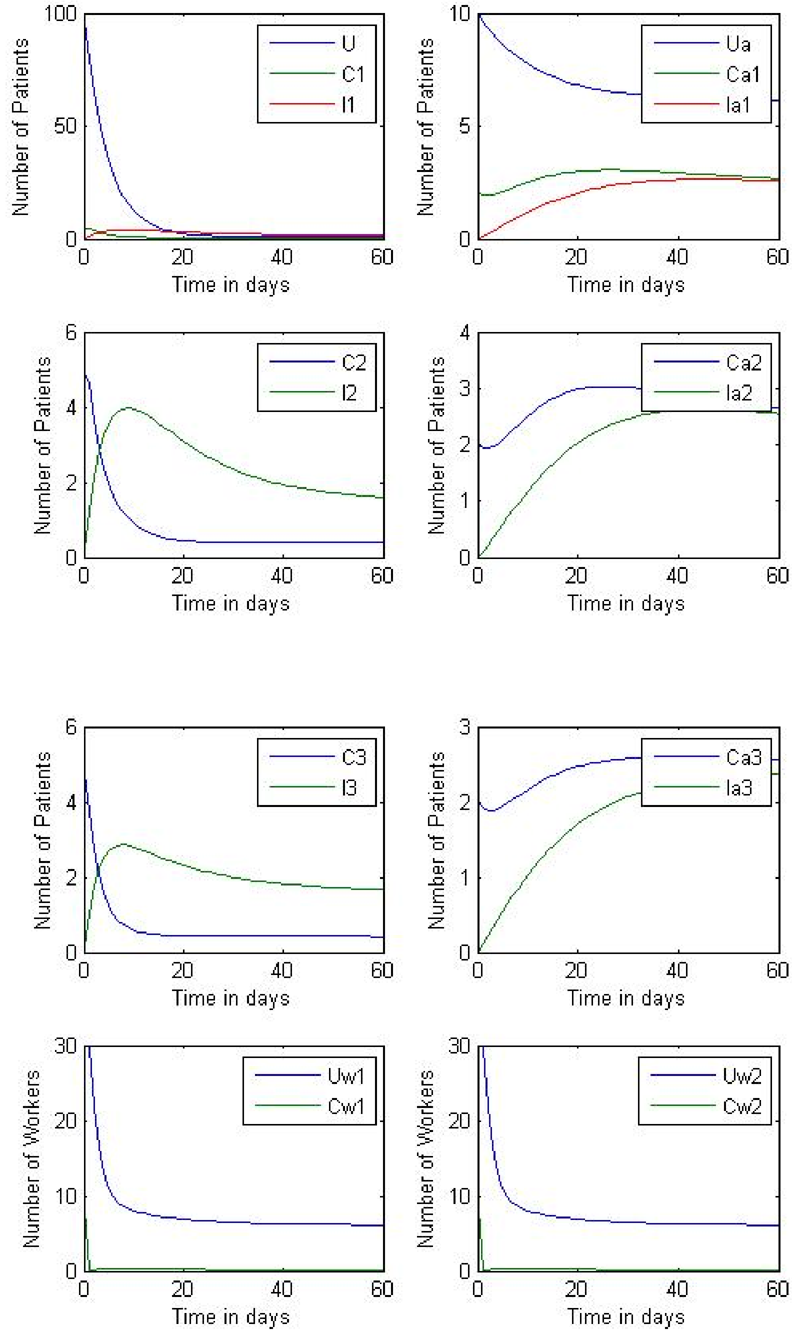

Figure 4.14: Case N: Population dynamics as the decolonization rate (ω) varies using the general model. In this case ω is increased by a factor of 10.

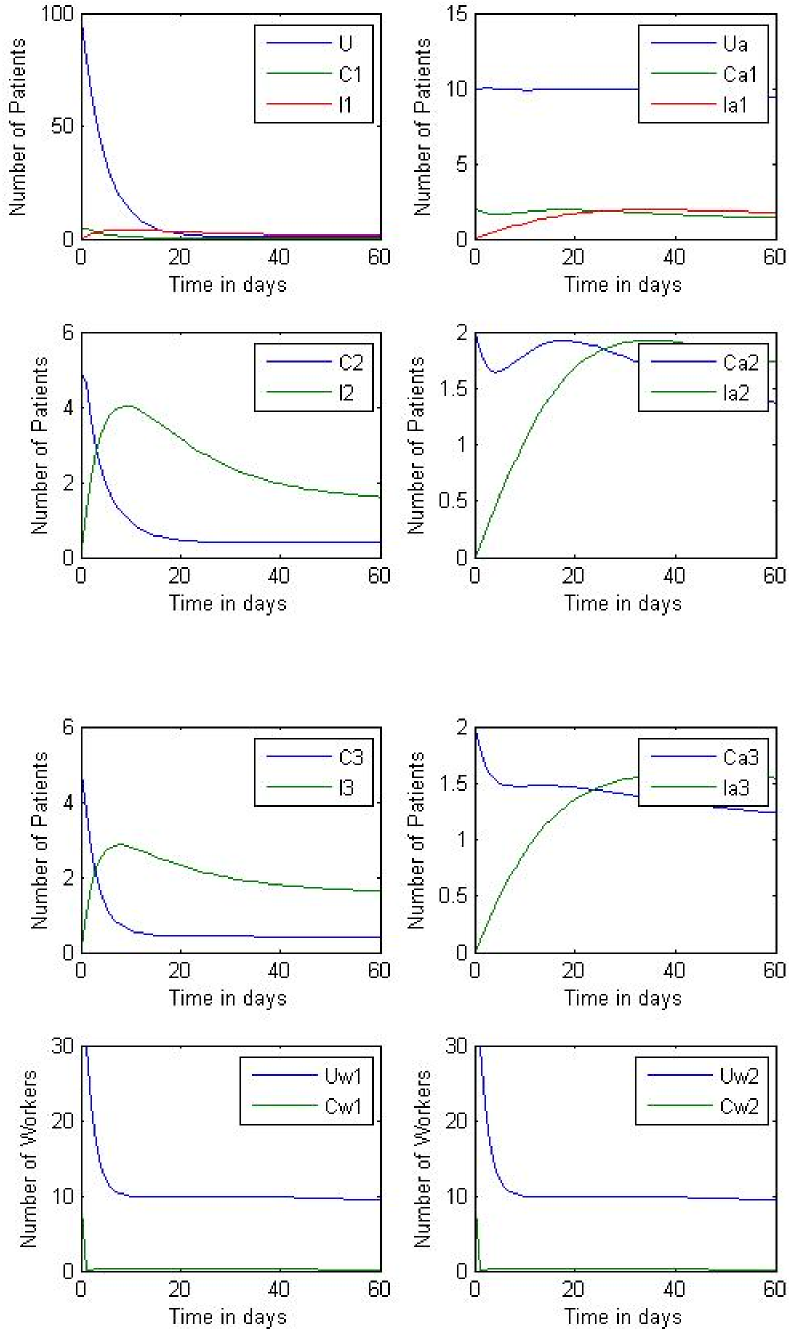

Figure 4.15: Case O: Population dynamics as the decolonization rate (ω) varies using the general model. In this case ω is increased by a factor of 100.

4.3 Basic Reproductive Ratio: R_0

The basic reproductive ratio for the basic model was calculated for 4 of the 12 cases (cases A-C and G-O result in the same value, as no parameters are varied). These ratios were calculated using a MATLAB program. A complete set of parameter values can be found in table 3.1. We also include case P-Q and S wherein the number of patients is increased starting from 10, by a factor of 10 (Case R has a total patient population of 500). Both the simulations involving R_0 and the deterministic model simulations are in agreement. Increasing the decolonization rate, ω, decreases R_0, but not by a significant amount. It is ϵ that has the strongest effect upon reducing R_0 to less than one, and thus inhibiting any sort of epidemic from occurring. It is also important to note that as the number of patients grows, it becomes increasingly difficult to contain an outbreak.

Case	Parameter varied	R_0
D	$\omega = 0.00132857$	1.1553
E	$\omega = 0.0132857$	1.1521
F	$\omega = 0.132857$	1.1296
G	$\epsilon = 0.3$	1.6174
H	$\epsilon = 0.6$	0.9242
I	$\epsilon = 0.9$	0.2311
P	$N_p = 10$	0.3653
Q	$N_p = 100$	1.1553
R	$N_p = 500$	2.5833
S	$N_p = 1000$	3.6533

Table 4.1: Basic Reproductive Ratio calculations with decolonization rate (ω) varied by a factor of 10, compliance probability (ϵ) increased at 0.3 intervals, and the total number of patients (N_p) increased by a factor of 10, respectively

4.4 Search for Equilibria

The equilibrium values were calculated and plotted using MRSA data, varying $C_w(t)$ from 0 to 10 in 0.05 intervals. The equilibrium values were not calculated for total health care worker population numbers of under 5. As the model was designed to consider an entire

ICU which has on average 15-20 patients, having populations numbers under 5 for health care workers is unrealistic and would require patient populations of under 10 (which the model is not designed to account for). On the x-axis is the value of C_w, and on the y-axis the corresponding equilibrium point was plotted. Notice how in some cases, the equilibrium points do not change, and in others (namely U_w, and I_a) there is a clear relationship with the value of C_w. Note that the number of colonized health care workers at equilibrium, can, by definition be expressed in terms of the number of uncolonized health care workers. Namely, looking at the equilibrium values in terms of the number of colonized health care workers can give an impression of the relationship between the equilibrium state of patients with varying infection status and the total number of health care workers.

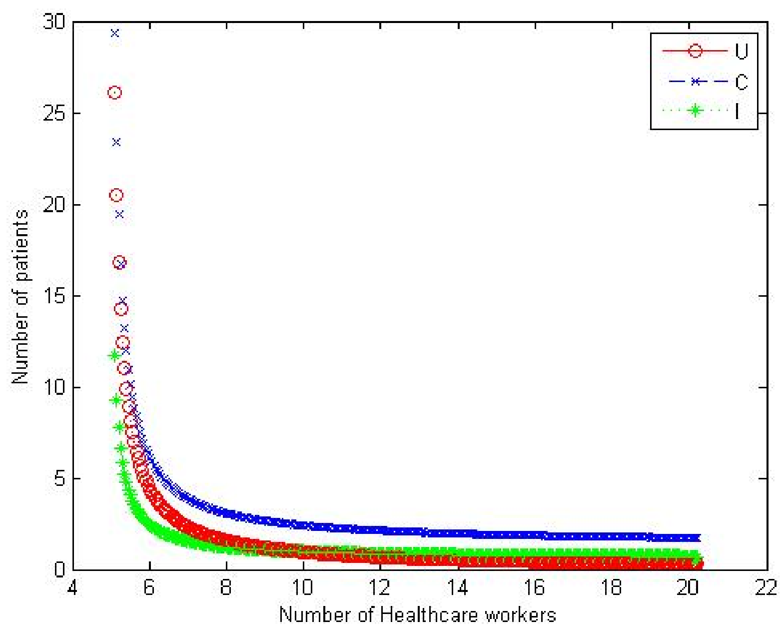

Figure 4.16: Equilibrium values for U(t), C(t), and I(t) with $C_w(t)$ from 5 to 20, MRSA

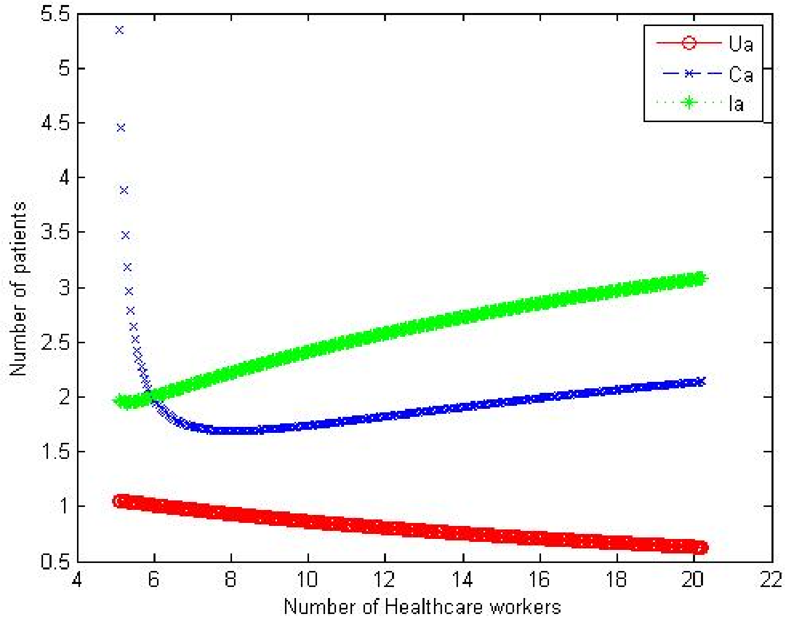

Figure 4.17: Equilibrium values for $U_a(t)$, $C_a(t)$, and $I_a(t)$ with $C_w(t)$ from 5 to 20, MRSA

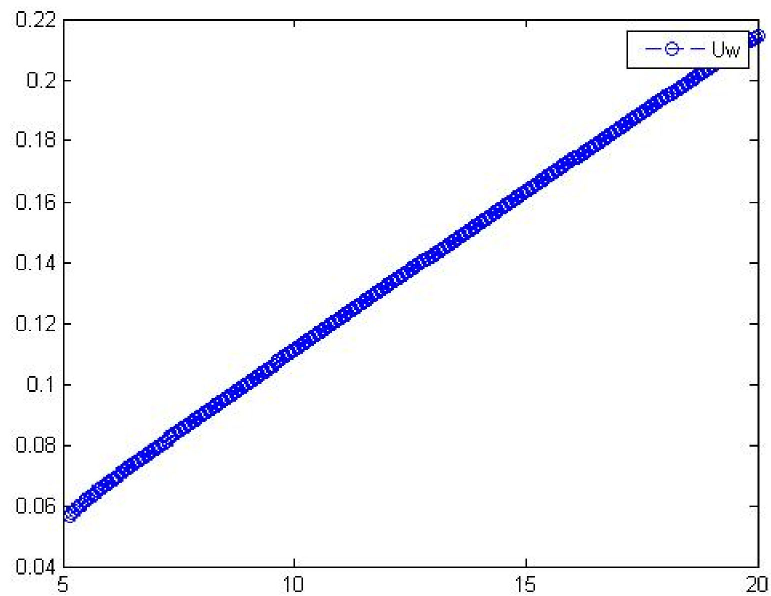

Figure 4.18: Equilibrium values for $U_w(t)$ with $C_w(t)$ from 5 to 20, MRSA

The simulation was run with VRE data as well, and minimal differences were found.

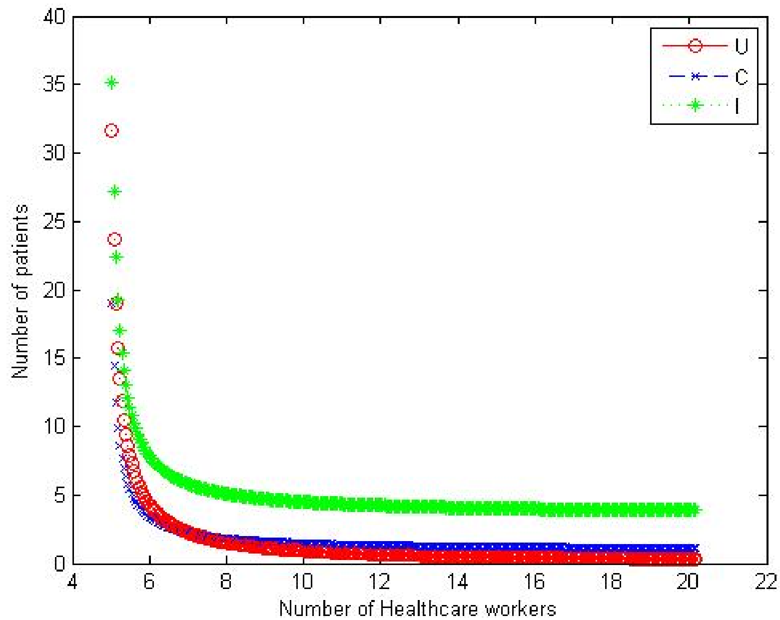

Figure 4.19: Equilibrium values for U(t), C(t), and I(t) with $C_w(t)$ from 5 to 20, VRE

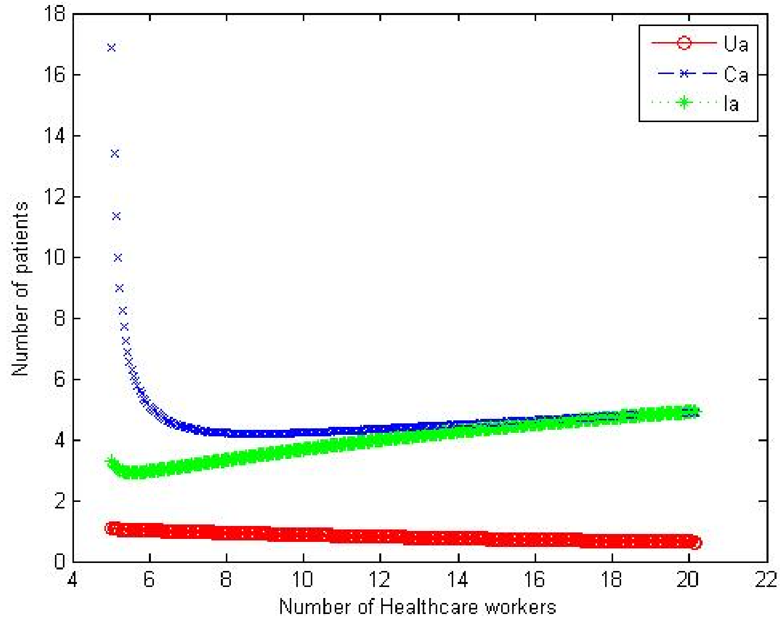

Figure 4.20: Equilibrium values for $U_a(t)$, $C_a(t)$, and $I_a(t)$ with $C_w(t)$ from 5 to 20, VRE

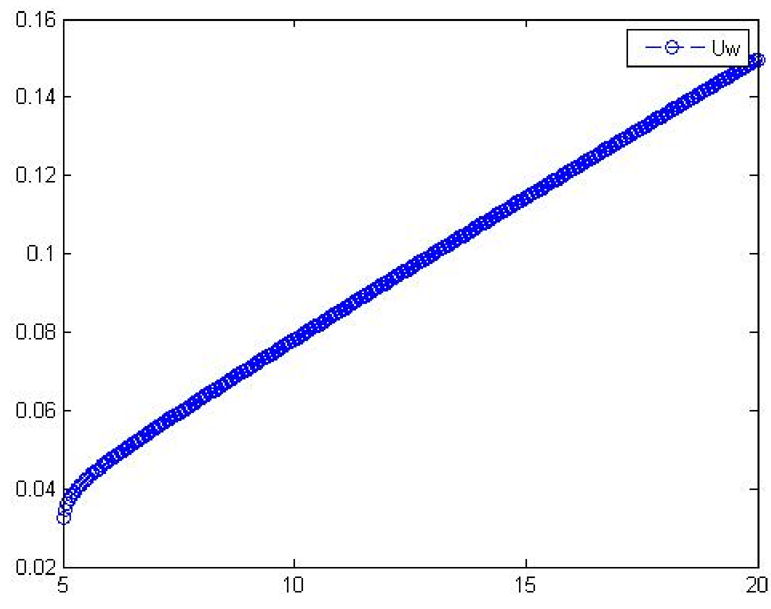

Figure 4.21: Equilibrium values for $U_w(t)$ with $C_w(t)$ from 5 to 20, VRE

4.5 Summary of Results

It was shown that there is a difference in efficiency or vulnerability between the species - e.g. that a single MRSA infection has a completely different effect upon the general population than a single VRE infection. Namely, that varying different parameters will have a different effect upon the colonized and infected VRE patient populations that that of the MRSA patient populations. The overall effect each parameter has on the different infection types is much the same though e.g. parameters that are effective in lowering the VRE infected patient population will do so to a similar degree with the corresponding MRSA infected patient population.

One significant finding of the early simulation studies for both models was that, over a wide range of parameter values, only one or two will have an effect upon the control of an outbreak. Most specifically, the parameters that represent infection control (i.e. compliance with barrier procedures) hold strong importance. The results of the calculations of the reproductive ratio support those of the numerical simulations, in this way.

Increasing the probability of compliance health care workers have with employing barrier procedures is an effective method of controlling an outbreak in both models, to varying degrees. Specifically, the increase has a stronger effect in the basic model. Due to the existence of only one type of infection in the basic model as opposed to three, the effect of different infection control procedures employed will have a stronger effect as there are significantly less factors influencing the spread (i.e. spread amoung co-colonized patients. and transference of patients moving from the VRE or MRSA class to that of the co-colonized class). This allows for a better grasp on which infection control measure is the most effective in controlling an outbreak. The general model still allows for such a grasp, but through it we are able to see how exactly the different infection types interact with each other in order to receive a more realistic picture of how infection will spread in an ICU.

Increasing the decolonization rate has some effect in reducing the spread of transmission, but not in such a way for it to be useful in practical applications. It is also crucial to note that as an infection control procedure that is to be widely implemented, this is quite difficult in implementation.

Chapter 5

Conclusions, Future Work

Certain things stand out in the results:

(1) Infection Control Procedures strongly impact the spread of infection.

(2) The results support most scientifically-based infection control strategy theory.

(3) The basic and general model are in agreement as to the parameters that most impact the spread of disease.

5.1 Conclusions

Using mathematical modelling to analyze the spread of antimicrobial resistant diseases is a fairly new approach. Its usefulness in aiding decision makers is something that should not be overlooked though. The work of this thesis, even will all its deficiencies, has shown that the transmission and spread of MRSA and VRE is strongly connected to the types of infection control procedures implemented. Specifically, that the type of screening method chosen (i.e. identifying those with past antibiotic exposure), as well as the implementation of barrier precautions is crucial in controlling the spread of infection. There are many other factors such as compliance with such procedures that must be taken into account.

Patients that have had past exposure to antibiotics are known to be at a higher risk of infection, and transmission to others is much stronger with them than with those that have not had past exposure. This is reflected in both models, as in all cases there was a much higher prevalence of patients with past exposure than there was of patients without. Identifying and separating those with past exposure and those without in both the general and basic models, first and foremost allowed for better identification of how exactly infection control measures differ in controlling the spread between the two groups, and will help policy makers in differentiating between how the two groups are treated, and how to best minimize the spread of infection to other patients.

The implementation of barrier procedures is a useful method in controlling the spread of infection. It is to what compliance that such procedures are implemented that is left to question. That is why both models incorporate such compliance. It is shown through numerical simulations that varying the compliance probability has a clear effect on the transmission dynamics in both models. This is particularly important to policy makers as attention must be paid to the actual implementation of such procedures and how many health care workers comply with them, or the effect they have on reducing the spread of infection will be much diminished and not at its full potential.

The results of the two models are in agreement with other studies done on MRSA and VRE. This is important as the general model is one of the first of its kind to look at the interaction and effect that MRSA, VRE, and co-colonization and infection have on each other and on infection control procedures implemented. The two models themselves are in agreement with which parameters have the strongest effect, but to varying degrees in each model. This is expected as the general model includes other factors that could potentially impact the implementation and spread, even simply with the inclusion of co-colonized patients.

Lastly, despite its size and complexity, the model is easy enough to use. It was not difficult to implement the eight ODEs using the MATLAB and MAPLE programming languages. That said, the general model represents a new step forward in the analysis of the spread of MRSA and VRE, and as such, should be given the time and work it needs. The model of this thesis represents a starting point for future work to build on.

5.2 Future Work

The model found in this thesis opens the door to a great deal of follow up work. In this section are listed a number of avenues that could be pursued. They are presented in no particular order.

It was apparent that the listing of parameter values could use some refinement. A more accurate representation of the circumstances could be acquired through use of data from a single hospital, in order to maintain a better sense of continuity. This would allow for follow-up and comparisons with the model results and the empirical data. There could also be extensions by using time-dependent parameters to support the concept of non-uniform resistance rates.

It is clear through perusal of the literature available that further analysis and refinement of the general model would provide many useful insights.

The spatial aspects of transmission should be explored further. In this thesis, a single ICU was considered. To envision the model setting within a whole hospital, and have consideration of intra-hospital movement of patients and health care workers would allow for a more realistic perspective on the spread of infection.

In order to provide additional insight into possible control strategies or simplifications of R_0 a sensitivity analysis must be conducted. Due to time constraints, this was not possible. Such an analysis would provide useful information as per which parameters are the most sensitive to change, though.

A useful method of infection control consists of patient cohorting. By arranging infected patients into designated areas and likewise having designated health care workers devoted to their care, it would greatly reduce the contamination probability. This unfortunately is not always a realistic course of action for hospitals to take, given the size and space constraints. Studies have shown that such cohorting does greatly reduce the spread of the infection though, so it would be prudent to look into more realistic methods of cohorting.

Alternative methods for calculating R_0 should be explored.

Chapter 6

Appendices

Appendix A

The transmission term

The transmission term is of great importance in many epidemiological models. The choice of transmission term is crucial in the creation of an accurate model which can then be properly analysed.

The term, $ab_p(1-\epsilon)$, appears in every equation except for the ones outlining the change in infected individuals of any type.

Appendix B

Derivations

The transmission terms feature a per-capita contact rate which warrants explanation. In this section, it is briefly explained how the terms were derived. For all derivations, it is assumed that the colonized population of health-care workers transmits the bacteria to uncolonized patients through touch.

In mathematical models for vector-borne diseases, each mosquito bites at a constant rate (irrespective of the number of humans), whereas the rate at which humans are bitten increases in proportion to the number of mosquitoes [12]. These assumptions are amended slightly in the construction of the per-capita contact rate.

It is not assumed that each health-care worker contacts the patients at a constant rate, but that each patient needs a constant number of contacts with health-care workers per day. Under this assumption, transmission is a frequency-dependent with respect to health-care workers, and the rate at which health-care workers contact residents increases in proportion to the number (or density) of residents.

A particular HCW contacts a particular patient at a rate of $a = a^*/N_h$, where a^* is the number of contacts required by each patient per day and N_h is the total number of health care workers.

The transmission term also possess the probability b_p which represents the probability that uncolonized patients will become colonized during contact with a contaminated HCW. In contrast, HCWs can become contaminated by contact with colonized patients with a probability b_{hc}, and by contact with infected patients with a probability b_{hi}.

Thus, in this appendix, it has been shown how the model's final transmission terms were derived.

Appendix C

Birth and Death Rates

C.1 Admittance rate Issues

Admittance rates differ between both hospitals and regions. This makes it difficult to acquire a realistic set of admittance rates for all compartments. It is common for a hospital to only publish admittance rates for patients of a specific infection status as well, and so this makes it difficult to acquire a realistic complete set of admittance rates from the same hospital.

Furthermore, a hospitals admittance rates will change depending on seasonality and outbreaks of other diseases. VRE and MRSA are usually acquired by patients with compromised immune system, those who are already infected with other diseases or have had surgery.

C.2 Death rate Issues

For normal discharge rates we have seasonality issues similar to the ones described above.

Appendix D

R_0, The reproductive ratio

Diekmann makes a fairly convincing argument for the choice of wording, 'reproductive ratio,' over the choice some sources make such as 'replacement rate' or 'replacement number.'

The subscript zero appears to be a notation without much significance, but Diekmann offers two possible interpretations: (1) that it refers to the 'virgin' environment; and (2) that it refers to zeroth moment.

The unit context for R_0 is *new cases per reference case*, and more specifically, this should be *new cases in bacteria X per reference case in bacteria X*. This suggests that it should be a valid concept only for transmissions from one individual infected or colonized with bacteria X, to another of the same infection status.

Unfortunately, in the case of a vector-borne diseases, specifically considering the patient-health care worker situation of this thesis, a reference case in a patient can lead next to a 'case' in a health care worker. Only after another transmission (health care worker to patient) do we get an additional infection. From a calculation point of view this is dealt with by taking the square root of the numbers for the two processes i.e. their geometric mean.

Appendix E

Symbols and abbreviations used in this document

Symbol	Description
E_0	Disease-free equilibrium (DFE)
E_E	Endemic equilibrium (EE)
N_p	Total number of patients admitted in the time interval studied
N_h	Total number of health care workers
θ	Admittance rate
δ	Admittance rate
θ	Fraction of patients admitted to a given infection status
ω	Decolonization rate
λ	Maximum rate ABs given to patients
ρ^s	Probability of successful treatment
ρ^u	Probability of unsuccessful treatment
β	Rate that colonized patients become infected
b	Contamination probability from infected or colonized patients
a	Per-capita contact-rate
a^*	Number of required contacts from health-care workers to patients per day
μ	Decolonization rate for colonized health-care workers

Table E.1: Symbols used in this document

Disease State Subscripts	Description
u	Uncolonized
c	Colonized
i	Infected
ua	Uncolonized with past antibiotic exposure in the past year
ca	Colonized with past antibiotic exposure
ia	Infected with past antibiotic exposure
1	Vancomycin-resistant enterococcus
2	Methicillin-resistant staphylococcus aureus
3	Co-colonized with both VRE and MRSA
p	Patients
h	Health-care worker

Table E.2: Disease state subscripts used in this document

Abbreviation	Description
AB	Antibiotics
HCW	Health-care worker
VRE	Vancomycin-resistant Enterococcus
MRSA	Methicillin-resistant Staphylococcus aureus
ODE	Ordinary differential equation
EE	Endemic equilibria
DFE	Disease-free equilibria
AP	Antimicrobial prescribing
VRSA	Vancomycin-resistant Staphylococcus Aureus
ICU	Intensive care unit
PHO	Public health ontario
AE	Antimicrobial exposure

Table E.3: Abbreviations used in this document

Appendix F

A brief discussion of the sources of parameter values

For this model, it was necessary to select a single value for each parameter. A number of resources were consulted in order to obtain suitable figures for use here, with great variation in their justification and perceived reliability.

$\delta = 1.36$ - Rate patients are admitted to the hospital

The model is constructed such that there is one general admission rate and twelve specific parameters that detail prevalence at admission of the different infection statuses.

$\gamma_u = 0.2$ - discharge Rate, uncolonized

Chamchod and Ruan [13] give discharge rate of 0.2 in their model on MRSA transmission.

$\gamma_{c1} = 0.1$, $\gamma_{c2} = 0.142857$, $\gamma_{c3} = 0.0833$ - discharge rate, colonized

D.J. Austin et. al [10] give an average length of stay for VRE colonized individuals of 10 days, which, taking the reciprocal, gives us a discharge rate of 0.1.
Chamchod and Ruan [13] give an average length of stay for MRSA colonized individuals of 7 days, which, taking the reciprocal, gives us a discharge rate of 0.142857.
Furuno et. al. gives an average length of stay of 12 days for co-colonized individuals, which, taking the reciprocal, gives us a discharge rate of 0.0833.

$\gamma_{i1} = 0.042857$, $\gamma_{i2} = 0.042857$, $\gamma_{i3} = 0.24615$ - death/discharge rate, infected

Chamchod and Ruan give an average length of stay of 14 days for individuals infected with MRSA. Taking the reciprocal and multiplying by the probability of an unsuccessful treatment gives us 0.042857. Due to the lack of data available for VRE, the same value is used as an estimate for the purpose of simulations. Furuno et. al. gives a death rate of 0.24615 for co-infected individuals.

$\gamma_{ua} = 0.0714$ - discharge rate, uncolonized with past AB exposure

E. D'Agata et. al [8] give an average length of stay for uncolonized individuals with past antibiotic exposure of 14 days, which, taking the reciprocal gives a value of 0.0714

$\gamma_{ca1} = 0.03571$, $\gamma_{ca2} = 0.09928$, $\gamma_{ca3} = 0.03571$ - discharge rate, colonized with past AB exposure

E. D'Agata et. al. [8] give an average length of stay for individuals with past antibiotic exposure colonized with VRE of 28 days, which, taking the reciprocal gives a value of 0.03571.

Chamchod and Ruan [13] give a discharge rate for patients with past antibiotic exposure colonized with MRSA of 0.09928. Due to the lack of data available for co-colonized individuals, the same value is used as VRE as a minimal estimate for the purpose of simulations.

$\gamma_{ia1} = 0.02857$, $\gamma_{ia2} = 0.02857$, $\gamma_{ia3} = 0.02857$ - discharge/death rate, infected

Chamchod and Ruan [13] give an average length of stay for individuals with past AB exposure infected with MRSA of 14 days. Taking the reciprocal and multiplying by the probability of treatment failure gives the death/discharge rate 0.02857. Due to the lack of data available for VRE and co-infected individuals, the same value is used as an estimate for the purpose of simulations.

$\theta_u = 0.85$ - fraction of patients admitted, uncolonized

Austin et. al. [10] give an admission prevalence of uncolonized patients of 0.85.

$\theta_{c1} = 0.1$, $\theta_{c2} = 0.047$, $\theta_{c3} = 0.56769$ - fraction of patients admitted, colonized

Austin et. al. [10] give an admission prevalence for patients colonized with VRE of 0.148. Chamchod and Ruan [13] give an admission prevalence for patients colonized with MRSA of 0.047. Furuno et. al. gives an admission prevalence for co-colonized patients of 0.56769.

$\theta_{i1} = 0.2$, $\theta_{i2} = 0.001$, $\theta_{i3} = 001$ - fraction of patients admitted, infected

D. Fisman [17] give an admission prevalence for patients infected with VRE of 0.2.
Chamchod and Ruan [13] give an admission prevalence for patients infected with MRSA of 0.001. Due to the lack of data available for co-infected individuals, the same value is used as an estimate for the purpose of simulations.

$\theta_{uA} = 0.29411$ - Fraction of patients admitted, uncolonized with past AB exposure

E. D'Agata et. al.[8] give an admission prevalence of 0.4 uncolonized patients with past AB exposure per day. Using our value for the admission rate and dividing, we get 0.29411.

$\theta_{ca1} = 0.013$, $\theta_{ca2} = 0.03$, $\theta_{ca3} = 0.013$ - fraction of patients admitted colonized with past AB exposure

G. Papia [36] gives an admission prevalence of 0.013 for patients with past AB exposure colonized with VRE.
Chamchod and Ruan [13] give an admission prevalence of 0.03 for patients with past AB exposure colonized with MRSA. Due to the lack of data available for co-colonized individuals, the same value is used as VRE as a minimal estimate for the purpose of simulations.

$\theta_{ia1} = 0.001$, $\theta_{ia2} = 0.001$, $\theta_{ia3} = 0.001$ - fraction of patients admitted, infected with past AB exposure

Chamchod and Ruan [13] give an admission prevalence for patients colonized with MRSA of 0.001. Due to the lack of data available for VRE and co-infected individuals, the same value is used as an estimate for the purpose of simulations.

$\omega_1 = 0.00142857$, $\omega_2 = 0.00142857$, $\theta_3 = 0.00142857$ - decolonization rate

Chamchod and Ruan [13] give a decolonization rate for patients colonized with MRSA of 0.00142857. Due to the lack of data available for VRE and co-infected individuals, the same value is used as an estimate for the purpose of simulations.

$\omega_{a1} = 0.000714$, $\omega_{a2} = 0.000714$, $\omega_{a3} = 0.000714$ - decolonization Rate

Chamchod and Ruan [13] give a decolonization rate for patients with past AB exposure colonized with MRSA of 0.000714. Due to the lack of data available for VRE and co-infected individuals, the same value is used as an estimate for the purpose of simulations.

$\lambda = 0.3$ - maximum rate ABs given to infected patients

E. D'Agata et. al.[8] give a 0.3 maximum rate antibiotics are given to infected patients.

$\lambda_a = 0.1$ - maximum rate ABs given to infected patients

Chamchod and Ruan [13] give a 0.1 maximum rate antibiotics are given to infected patients with past AB exposure

$\rho^{s1} = 0.24$, $\rho^{s2} = 0.5$, $\rho^{s3} = 0.24$ - probability of successful treatment

L.S. Chavers et. al. [44] give a probability of successful treatment for patients infected with VRE of 0.24. Chamchod and Ruan [12] give a 0.5 probability of successful treatment for patients infected with MRSA. Due to the lack of data available for co-infected individuals, the same value as VRE is used as a minimal estimate for the purpose of simulations.

$\rho^{u1} = 0.76$, $\rho^{u2} = 0.15$, $\rho^{u3} = 0.76$ - probability of unsuccessful treatment

L.S. Chavers et. al. [14] give a probability of unsuccessful treatment for patients infected with VRE of 0.76. Chamchod and Ruan [13] give a 0.15 probability of successful treatment for patients infected with MRSA. Due to the lack of data available for co-infected individuals, the same value is used as VRE an estimate for the purpose of simulations.

$\rho_{a1} = 0.035$, $\rho_{a2} = 0.035$, $\rho_{a3} = 0.035$ - probability of successful treatment

Chamchod and Ruan [13] give a probability of unsuccessful treatment for patients with past AB exposure of 0.35. Due to lack of available data for co-infected individuals and VRE infected individuals, the same value is used as with MRSA as an estimate for the purpose of simulations.

$\beta_1 = 0.2795$, $\beta_2 = 0.042857$, $\beta_3 = 0.042857$ - rate patients become infected, colonized

The transmission rate for patients colonized with VRE is given by Austin et. al. [10] as 0.2795. The transmission rate for patients colonized with MRSA is given by Chamchod and Ruan as 0.042857 [13]. Due to the lack of data available for co-infected individuals, the same value is used as an estimate for the purpose of simulations.

$\beta_{a1} = 0.2795$, $\beta_{a2} = 0.0428$, $\beta_{a3} = 0.0428$ - rate colonized patients become infected

The transmission rate for patients colonized with VRE is given by Austin et. al. [10] as 0.2795. The transmission rate for patients colonized with MRSA is given by Chamchod and Ruan as 0.042857 [13]. Due to the lack of data available for co-infected individuals, the same value is used as an estimate for the purpose of simulations.

$\rho^{s4} = 0.2769$, $\rho^{u4} = 0.72307$ - probability of successful treatment of MRSA in co-infected patients

Furuno et. al. give a probability of success of 0.2769, and a probability of failure of 0.72307.

$\rho^{s5} = 0.4769$, $\rho^{u4} = 0.52307692$ - probability of successful treatment of VRE in co-infected patients

Furuno et. al. give a probability of success of 0.4769, and a probability of failure of 0.52307692.

$b_p 0.06$- colonization probability

The model is constructed such that there is one general colonization probability used for each infection status, as opposed to one for each bacterium. Chamchod and Ruan [13] give a probability of 0.06 for patients in their model on MRSA.

$b_{pa} = 0.025$ - colonization probability

Chamchod and Ruan [13] give a probability of 0.025 for patients with past AB exposure in their model on MRSA.

$b_{hc} = 0.25$ - colonization probability

Chamchod and Ruan [13] give a probability of 0.25 for health care workers interacting with colonized patients in their model on MRSA.

$b_{hi} = 0.1$ - colonization probability

Chamchod and Ruan [13] give a probability of 0.1 for health care workers interacting with colonized patients in their model on MRSA.

$b_{hca} = 0.15$ - colonization probability

Chamchod and Ruan [13] give a probability of 0.15 for health care workers interacting with colonized patients who have had past AB exposure in their model on MRSA.

$b_{hia} = 0.3$ - colonization probability

Chamchod and Ruan [13] give a probability of 0.3 for health care workers interacting with infected patients who have had past AB exposure in their model on MRSA.

$a = 1.38$ - per capita HCW-patient contact rate

The per-capita contact rate is given by Austin et. al. [10] as 1.38.

$1/\mu = 1/24$ - Time contaminated HCWs can transmit

Multiple sources (including Austin et. al. [10] and Chamchod and Ruan [13]) give the amount of time HCWs can transmit infection (either MRSA or VRE or both) as one hour. This translates to a value of 1/24 days.

Appendix G

Glossary of Terms

basic reproductive ratio R_0 - a ratio of new cases of a disease to old cases, serving as an answer to the hypothetical question: "If one case of the subject disease is introducted into an environment with no other cases of the disease, how many new cases can we expect to result *directly* for the single introductory case?" Please see Appendix C for further discussions.

category 1 - used in this document to refer to VRE.

category 2 - used in this document to refer to MRSA.

category 3 - used in this document to refer to co-colonized patients.

endemic - present more or less all of the time.

epidemic - the occurrence in a community or region of cases of an illness (or an outbreak) with a frequency clearly in excess of normal expectancy [52, p. 19].

host - an organism that harbours a virus.

incidence - the number of individuals falling ill with a particular disease during a defined time period, divided by the total population [52, p. 8]

infected - having been affected or contaminated by a disease-causing agent; used with respect to the receiving side/end of an infection, and having to do with the development or more germs; should not be confused with 'colonized' or 'exposed.' [53, p. 8] Note two classifications: clinical infections, with symptoms or signs making the disease apparent; and sub-clinical infections, with symptoms not apparent or mild enough to escape diagnosis other than by special testing.

infectious - having to do with an infection, as in 'infectious disease' or 'infectious agent' (alternatively, capable of producing an infection; used as a synonym of 'infective').

infective - capable of infecting, especially with respect to the propagating side of an infection. Abbreviation 'I' - the I also sometimes is said to stand for 'infected' or 'infectious.' Note that this term is very similar to one of the definitions of 'infectious.'

latent - not apparent; in a latent infection the virus is in a nonreproducive phase but there is some sort of virus-host equilibrium.

outbreak - a small, localized epidemic, perhaps confined to a municipality or hospital.

prevalence - the number of individuals who have a particular disease at a particular time, divided by the total population. [52, p. 9]

vector - an animal that picks up a pathogen from an infective individual and transmits it to a susceptible individual; [52, p. 19] as used in this document, does not refer to an element of a vector space.

virulent - an infectious agent's relative ability to do damage to its host; can be defined as the host's virus-induced loss of fitness.

References

1. Public Health Agency of Canada. (2013, October 23). The Chief Public Health Officers Report on the State of Public Health in Canada. Retrieved from www.phac-aspc.gc.ca/cphorsphc-respcacsp/2013/resistance-eng.php/.

2. Centres for Disease Control and Prevention. (2013). Antimicrobial Threats in the United States, 2013." *U.S. Department for Health and Human Services.*

3. " British Colombia: Ministry of Health and Ministry Responsible for Seniors. (2000). Antimicrobial Resistance: A Recommended Action Plan for British Colombia. *Office of the Provincial Health Officer.*

4. Provincial Infectious Diseases Advisory Committee (PIDAC). (2007). Best Practices for Infection Prevention and Control of Resistant Staphylococcus aureus and Enterococci in All Health Care Settings. *Ministry of Health and Long-Term Care.*

5. Provincial Infectious Diseases Advisory Committee (PIDAC). (2012). Review of Literature for Evidenced-Based Best Practices for VRE Control. *Public Health Ontario.*

6. Provincial Infectious Diseases Advisory Committee (PIDAC). (2012). Companion Document to: Review of Literature for Evidence-based Best Practices for VRE Control. *Public Health Ontario.*

7. Centers for Disease Control and Prevention. (2002, April 19). Campaign to Prevent Antimicrobial Reistance in Healthcare Settings: Why a Campaign? Retrieved from www.cdc.gov/drugresistance/healthcare/problem.htm.

8. D'Agata, EM, Webb, G., & Horn, M. (2005). A Mathematical Model Quantifying the Impact of Antibiotic Exposure and Other Interventions on the Endemic Prevelence of Vancomycin-resistant Enterococci. *Journal of Infectious Diseases*, 192(11), 2004-2011. Retrieved from PubMed.

9. Armstrong-Evans, M. (1999). Control of Transmission of Vancomycin-Resistant enterococcus faecium in a Long Term Care Facility. *Infection Control and Hospital Epidemiology*, 20(5), 312-317. Retrieved from PubMed.

10. Austin, D., Bonten, M., Weinstein, R., Slaughter, S., & Anderson, R. (1999). Vancomycin-resistant Enterococcus in Intensive-care Hospital Settings. *National Academy of Science*, 96(12), 6908-13. Retrieved from PubMed.

11. J.M. Boyce, et al. "Outbreak of multi-drug resistant Enterococcus faecium with transferable vanB class vancomycin resistance". J clin Microbial 1994;32:1148-1153.

12. Boyce, J., Potter-Bynoe, G., Chenevert, C., & King, T. (1997). Environmental Contamination Due To Methicillin-Resistant Staphylococcus Aureus: Possible Infection Control Implications. *Infection Control and Hospital Epidemiology*, 18(9), 622-627. Retrieved from Pubmed.

13. Chamchod, F., & Ruan, S. (2012). Modeling methicillin-resistant Staphylococcus aureus in hospitals: Transmission dynamics, antibiotic usage and its history. *Theoretical Biology and Medical Modelling*, 9(25). doi: 10.1186/1742-4682-9-25.

14. Chavers, L., Moser, S., Benjamin, W., Banks, S., Steinhauer, J., Smith, A., ... Waites, K. (2003). Vancomycin-resistant enterococci: 15 years and counting. *Journal of Hospital Infection*, 53(3), 159-171. doi: http://dx.doi.org/10.1053/jhin.2002.1375.

15. Day, T., & Gandon, S. (2012). The Evolutionary Epidemiology Of Multilocus Drug Resistance. *Evolution*, 66(5), 1582-97. doi: 10.1111/j.1558-5646.2011.01533.x.

16. Drees, M., Snydman, D., Schmid, C., Barefoot, L., Hansjosten, K., Vue, P., ... Golan, Y. (2008). Antibiotic Exposure and Room Contamination Among Patients Colonized With Vancomycin-Resistant Enterococci. *Infection Control and Hospital Epidemiology*, 29(8), 709-715. doi: 10.1086/589582.

17. Fisman, D., Perencevich, E., Lipsitch, M., Harris, A., Morris, J., & Smith, D. (2004). Projected Benefits of Active Surveillance for VancomycinResistant Enterococci in Intensive Care Units. *Clinical Infectious Diseases*, 38(8), 1108-1115. doi: 10.1086/382886.

18. Furuno, J.P., Perencevich, E.N., Johnson, J.A., Wright, M., McGregor, J.C., Strauss, S.M.,...Haris, A.D. Methicillin-resistant Staphylococcus aureus and Vancomycin-resistant Enterococci Co-colonization. *Emerging Infectious Diseases*, 11(10), 1539-1544. doi: 10.3201/eid1110.050508.

19. Gammaitoni, L. (1997). Using a Mathematical Model to Evaluate the Efficacy of TB Control Measures. *Emerging Infectious Diseases*, 3(3), 335-342. doi: 10.3201/eid0303.970310.

20. Giesecke, J. (2002). Modern infectious disease epidemiology (2nd ed.). London: Arnold.

21. Giesecke, J. (1991). Some remarks on definition and validity of terms used in models for infectious disease spread. *Mathematical Biosciences*, 107(2), 149-153. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1806110.

22. Hayakawa, K, Marchain, D., Bathina, P., Martin, E.T., Pogue, J.M.,...Kaye, K.S. Independent risk factors for the co-colonization of vancomycin-resistant Enterococcus faecalis and methicillin-resistant Staphylococcus aureus in the region most endemic for

vancomycin-resistant Staphylococcus aureus isolation. *European Journal of Clinical Microbiology and Infectious Diseases*, 32(6),815-820. doi: 10.1007/s10096-013-1814-z.

23. Hiramatsu, K. (2001). Vancomycin-resistant : A New Model Of Antibiotic Resistance. The Lancet Infectious Diseases, 1(3), 147-155. doi: http://dx.doi.org/10.1016/S1473-3099(01)00091-3.

24. Hurford, A., Morris, A., Fisman, D., & Wu, J. (2012). Linking antimicrobial prescribing to antimicrobial resistance in the ICU: Before and after an antimicrobial stewardship program. *Epidemics*, 4(4), 203-210. doi: 10.1016/j.epidem.2012.12.001.

25. Kajita, E., Okano, J., Bodine, E., Layne, S., & Blower, S. (2007). Modelling an outbreak of an emerging pathogen. *Nature Reviews Microbiology*, 5(9), 700-709. doi:10.1038/nrmicro1660.

26. Kanchana, M., Deneer, H., & Blondeau, J. (2000). Cost-Effective Algorithm for Detection and Identification of Vancomycin-Resistant Enterococci in Surveillance Cultures. *European Journal of Clinical Microbiology & Infectious Diseases*, 19(5), 366-369. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10898139.

27. Kleinpell, R.M., Munro, C.L., & Giuliano, K.K. (2008). Targeting Health Care-Associated Infections: Evidence Based Strategies. *Agency for Healthcare Research and Quality (US)*, Chapter 42. Retrieved from http://www.ncbi.nlm.nih.gov/books/NBK2632/.

28. Kunori, T., Cookson, B., Roberts, J., Stone, S., & Kibbler, C. (2002). Cost-effectiveness of different MRSA screening methods. *Journal of Hospital Infection*, 51(3), 189-200. doi: http://dx.doi.org/10.1053/jhin.2002.1247.

29. Leung, E., Weil, D., Raviglione, M., & Nakatani, H. (2011). The WHO policy package to combat antimicrobial resistance. *Bulletin of the World Health Organization*, 89(5), 390-392. doi: 10.2471/BLT.11.088435.

30. McGeer, A., Simor, A., Willians, V., Raboud, J., Larios, O., Weiss, K., ... Gravel, D. (2013). Prevalence of colonization and infection with methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococcus and of Clostridium difficile infection in Canadian hospitals. *Infection Control and Hospital Epidemiology*, 34(7), 687-693. doi: 10.1086/670998.

31. Michelson, S. (1993). Mathematical models for multidrug resistance and its reversal. *Journal of Theoretical Medicine*, 12(1-3), 315-324. doi: 10.1007/BF00744670.

32. Montecalvo, M., Jarvis, W., Uman, J., Shay, D., Petrullo, C., Horowitz, H., & Wormser, G. (2001). Costs and Savings Associated With Infection Control Measures That Reduced Transmission of Vancomycin Resistant Enterococci in an Endemic Setting. *Infection Control and Hospital Epidemiology*, 22(7), 437-442. doi: 10.1086/501931.

33. Muto, C.A., Jernigan, J.A., Ostrowsky, B.E., Richet, H.M., Jarvis, W.R., Boyce, J.M., & Farr, B.M. (2003).SHEA Guideline for Preventing Nosocomial Transmission of Multidrug Resistant Strains of Staphylococcus aureus and Enterococcus. *Infection Control and Hospital Epidemiology*, 24(5), 362-386. doi: 10.1086/502213.

34. Ortiz, A., Banks, H., Castillo-Chavez, C., Chowell, G., & Wang, X. (2011). A discrete events delay differential system model for transmission of Vancomycin-resistant enterococcus (VRE) in hospitals. *Journal of Inverse and Ill-Posed Problems*, 18(7), 787-821. doi: 10.1515/jiip.2011.004.

35. Papia, G., Louie, M., Tralla, A. Johnson, C., Collins, V., & Simor, A.E. (1999). Screening High-Rish Patients for Methicillin-resistant Staphylococcus aureus on Admission to the Hospital: Is it Cost Effective? *Infection Control and Hospital Epidemiology*, 20(7), 473-477. doi: 10.1086/501655.

36. Perencevich, E., Fisman, D., Lipsitch, M., Harris, A., Morris, J., & Smith, D. (2004). Projected Benefits of Active Surveillance for VancomycinResistant Enterococci in Intensive Care Units. *Clinical Infectious Diseases*, 38(8), 1108-1115. doi: 10.1086/382886.

37. Puzniak, L.A., Gillespie, K.N., Leet, T., Kollef, M., & Mundy, L.M. (2004). A Cost Benefit Analysis of Gown Use in Controlling Vancomycin Resistant Enterococcus Transmission: Is it Worth the Price? *Infection Control and Hospital Epidemiology*, 25(5), 418-424. doi: 10.1086/502416.

38. Puzniak, L.A., Leet, T., Mayfield, J., Kollef, M., & Mundy, L.M. (2002). To gown or not to gown: the effect on acquisition of vancomycin-resistant enterococci. *Journal of Clinical Infections Diseases,* 35(1), 18-25. doi: 10.1086/340739.

39. Quale, J., Landman, D., Saurina, G., Atwood, E., Ditore, V., & Patel, K. (1996). Manipulation of a Hospital Antimicrobial Formulary to Control an Outbreak of Vancomycin-Resistant Enterococci. *Clinical Infectious Diseases*, 23(5), 1020-1025. Retrieved from cid.oxfordjournals.org/contents/23/5/1020.long.

40. Reyes, K., Malik, R., Moore, C., Donabedian, S., Perri, M., Johnson, L., & Zervos, M. (2010). Evaluation of Risk Factors for Coinfection or Cocolonization with Vancomycin-Resistant Enterococcus and Methicillin-Resistant Staphylococcus aureus. *Journal of Clinical Microbiology*, 48(2), 628-630. doi: 10.1128/JCM.02381-08.

41. Robinson, D., & Enright, M. (2003). Evolutionary Models of the Emergence of Methicillin-Resistant Staphylococcus aureus. *Antimicrobial Agents And Chemotherapy*, 47(12), 3926-3934. doi: 10.1128/AAC.47.12.3926-3934.2003.

42. Simor, A., Willians, V., McGeer, A., Raboud, J., Larios, O., Weiss, K., ... Gravel, D. (2013). Prevalence of colonization and infection with methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococcus and of Clostridium difficile infection in Canadian hospitals. *Infection Control and Hospital Epidemiology*, 34(7), 687-693. doi: 10.1086/670998.

43. Singh, N., Leger, M., Campbell, J., Short, B., & Campos, J. (2005). Control of VancomycinResistant Enterococci in the Neonatal Intensive Care Unit. *Infection Control and Hospital Epidemiology*, 26(7), 646-649. doi: 10.1086/502595.

44. Slaughter, S. (1996). A Comparison of the Effect of Universal Use of Gloves and Gowns with That of Glove Use Alone on Acquisition of Vancomycin-Resistant Enterococci in a Medical Intensive Care Unit. *Annals of Internal Medicine*, 125(6), 448-456. doi:10.7326/0003-4819-125-6-199609150-00004.

45. Srinivasan, A., Song, X., Ross, T., Merz, W., Brower, R., & Perl, T. (2002). A Prospective Study to Determine Whether Cover Gowns in Addition to Gloves Decrease Nosocomial Transmission of VancomycinResistant Enterococci in an Intensive Care Unit. *Infection Control and Hospital Epidemiology*, 23(8), 424-428. doi: 10.1086/502079.

46. Van Kleef, E., Robotham, J., Jit, M., Deeny, S., & Edmunds, W. (n.d.). Modelling the transmission of healthcare associated infections: A systematic review. *BMC Infectious Diseases*, 13, 294-294. doi:10.1186/1471-2334-13-294.

47. Warren, D.K., Nitin, A., Hill, C., Fraser, V.J., & Kollef, M. H. (2004). Occurrence of co-colonization or co-infection with vancomycin-resistant enterococci and methicillin-resistant Staphylococcus aureus in a medical intensive care unit. *Infection Control and Hospital Epidemiology*, 25(2), 99-104. doi: 10.1086/502357.

48. Weinstein, R. (Ed.). (2000). Insights into the Epidemiology and Control of Infection with Vancomycin Resistant Enterococci. Clinical Infectious Diseases, 31(4), 1058-1065. doi: 10.1086/318126.

49. Wolkewitz, M., Dettenkofer, M., Bertz, H., Schumacher, M.,& Huebner, J. (2008). Environmental Contamination as an Important Route for the Transmission of the Hospital Pathogen VRE: Modelling and Prediction of Classical Interventions. *Infectious Diseases: Research and Treatment*, 3-11. Retrieved from http://www.la-press.com/environmental-contamination-as-an-important-route-for-the-transmission-article-a896.

50. Zachary, K., Bayne, P., Morrison, V., Ford, D., Silver, L., & Hooper, D. (2011). Contamination of Gowns, Gloves, and Stethoscopes With Vancomycin Resistant Enterococci. *Infection Control and Hospital Epidemiology*, 22(9), 560-564. doi: 10.1086/501952.

51. Zoutman, D., Ford, B., Bryce, E., Gourdeau, M., Hbert, G., Henderson, E., & Paton, S. (2003). The state of infection surveillance and control in Canadian acute care hospitals. *American Journal of Infection Control*, 31(5), 266-273. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12888761.

52. Ziakas, P., Thapa, R., Rice, L., Mylonakis, E., & Ratner, A. (2013). Trends and Significance of VRE Colonization in the ICU: A Meta-Analysis of Published Studies. *PLoS ONE*, 8(9), E75658-E75658. doi:10.1371/journal.pone.0075658.

53. Zhanel, G., Decorby, M., Laing, N., Weshnoweski, B., Vashisht, R., Tailor, F., ... Hoban, D. (2008). Antimicrobial-Resistant Pathogens in Intensive Care Units in Canada: Results of the Canadian National Intensive Care Unit (CAN-ICU) Study, 2005-2006. *Antimicrobial Agents And Chemotherapy*, 52(4), 1430-1437. doi: 10.1128/AAC.01538-07.