Antibiotic resistant Gram-negative bacteria in long-term care facilities, an epidemiological and dynamic modelling study

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I, Alicia Roselló Gilchrist confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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"*Everyone is my teacher. Some I seek. Some I subconsciously attract. Often I learn simply by observing others. Some may be completely unaware that I'm learning from them, yet I bow deeply in gratitude.*" Eric Allen

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Abstract

Tackling antimicrobial resistance (AMR) is a national and global priority. Despite this, much of our understanding of the epidemiology and transmission of AMR outside the hospital, and thus, how we might control it, remains limited. Long term care facilities (LTCFs) play an important role in the care of older people. However, there have been few studies of the epidemiology and transmission of AMR in this setting. LTCF residents present with frequent co-morbidities which increase their risk of hospitalisation and of AMR infection. LTCFs also offer opportunities for transmission of AMR strains due to the long lengths of stay of residents and the lack of strictly applied infection control measures. This thesis focuses on urinary tract infections (UTIs), one of the most common bacterial infections in LTCFs, hospitals and the community. I first present a systematic review of mathematical models of infectious disease transmission set in LTCFs and a critical review of mathematical models evaluating interventions against AMR bacteria in LTCFs. A checklist for good quality models in this area is proposed. Next, using data from routinely collected microbiology samples, the frequency of AMR in urinary tract *E. coli* and *Klebsiella* was compared in LTCF residents with that in older people living in their own homes. Residents of LTCFs had more than four times the rate of *E. coli* and *Klebsiella* UTI caused by antibiotic-resistant bacteria compared with those living in the community. The seasonality of UTI consultations was also assessed. A September to November peak in UTI consultation incidence was observed for ages 14-69. This seasonality progressively faded in older age groups and no seasonality was found in individuals aged 85 and over. Finally, a stochastic compartmental mathematical model was developed to explore the transmission of trimethoprim-resistant *E. coli* in LTCFs. Different treatment, importation and transmission scenarios were addressed.

Impact statement

First, this work contributes towards improving our understanding of the dynamics of UTI (Chapter 6). Due to increases in temperature during the summer, which can make individuals prone to dehydration, UTIs could be expected to peak during this time. These changes could be particularly pronounced in the elderly population, as aging is a risk factor for water homeostasis impairments and inadequate water intake. However, GP consultations for UTI in older people in the UK were not found to be seasonal. This contrasts with the autumnal peak observed for individuals aged 14 to 69. As UTIs in older people are common year round, UTI prevention in this population should warrant attention throughout the year. The autumnal peak in UTI consultation incidence observed in younger age groups could also be helpful in interpreting the results of interventions and surveillance reports. This work was published in the journal *Epidemiology and Infection*. [1]

Second, UTIs caused by AMR *E. coli* and *Klebsiella* were shown to be more common in LTCFs in the West Midlands than in older people residing in their own homes, even after adjusting for confounders. This highlights that LTCFs should be a focus of antibiotic stewardship and infection prevention and control interventions aiming to prevent the spread of AMR bacteria, as well as of increased surveillance of AMR and antimicrobial prescribing. Findings from this thesis also support the recent switch in the national primary care treatment guidelines for uncomplicated UTI from recommending trimethoprim to nitrofurantoin, as trimethoprim was shown to be ineffective to treat a large proportion of the UTIs in LTCF residents due to the high prevalence of resistance in this population. This work was published in the *Journal of Antimicrobial Chemotherapy*.[2]

Third, antibiotic-resistant Gram-negative bacteria are currently organisms of high public health importance and, as shown in the systematic review of the literature (Chapter 2), an increasing number of studies modelling the transmission of infectious diseases in LTCFs are being published. Therefore, the conclusions of mathematical models that simulate the transmission of Gram-negative bacteria in LTCFs could be important for policy making. A

checklist was developed to guide policy makers in assessing the quality of such models. This work was published in *Infection Control and Hospital Epidemiology*.[3]

Finally, the output from the mathematical model developed to simulate the transmission of *E. coli* resistant to trimethoprim in the LTCF (in Chapter 7) suggested that LTCFs with a high prevalence of resistance could contribute towards the prevalence of resistance in hospitals, highlighting the importance of reducing avoidable hospital admissions by enhancing support for LTCF residents and the potential of screening strategies. In addition, the transmission of *E. coli* resistant to trimethoprim was found to have a greater impact on the prevalence of *E. coli* resistant to trimethoprim in the LTCF than trimethoprim treatment, at least in LTCFs with a high incidence of trimethoprim-resistant urinary *E. coli* submitted for laboratory testing. These findings suggest that reducing transmission may be key to diminishing the prevalence of carriage of trimethoprim-resistant *E. coli* in LTCFs.

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Abbreviations

AIC: Akaike information criterion

AMR: antimicrobial resistance

aORs : adjusted odds ratios

BSAC: The British Society for Antimicrobial Chemotherapy

BSI: bloodstream infection

CE-pc: communal establishment postcodes

CLSI: Clinical Laboratory and Standards Institute

CPRD: Clinical Practice Research Datalink

CQC: Care Quality Commission

EUCAST: The European Committee on Antimicrobial Susceptibility Testing

GP: general practitioner

HES: Hospital Episode Statistics

IBM: individual-based model

LTACH: long-term acute care hospital

LTCF: long-term care facility

LTCF CE-pc: LTCF postcodes classified by the ONS as “communal establishment only”

MRSA: methicillin-resistant *Staphylococcus aureus*

MSSA: methicillin-sensitive *Staphylococcus aureus*

NEQAS: National External Quality Assurance Scheme

ONS: Office for National Statistics

RR: rate ratio

THIN: The Health Improvement Network

UTI: urinary tract infection

Ethics

This work was conducted as a PHE employee, on a PhD programme funded by PHE with the aim of this informing PHE strategy for control of antimicrobial resistance. On the 11th of November 2013, I became a PHE employee in the position of PhD student and I continue to be employed by PHE after the PhD position. PHE has National Information Governance Board for Health and Social Care approval for the collation and analysis of this surveillance data in accordance with section 251 of the NHS Act 2006. This thesis included a secondary analysis of routinely collected AmSurv data. Patient postcode, NHS number, age and sex were included in the AmSurv database extract provided by PHE, as well as GP name and hospital name. This thesis also included a secondary analysis of The Health Improvement Network (THIN) data. THIN is a primary care electronic database that contains anonymised patient, prescribing practice, and consultation data. The data collection scheme for THIN is approved by the UK Multicentre Research Ethics Committee (reference number: 07H1102103). In accordance with this approval, the study protocol was reviewed and approved by an independent Scientific Review Committee (reference number 17THIN017). All of this analysis was carried out on PHE servers with appropriate information governance approvals.

Chapter 1 Introduction

This thesis focuses on the problem of antimicrobial resistance (AMR) in long-term care facilities (LTCF) for older people, with a particular focus on the antibiotic resistance of bacteria that cause urinary tract infections. Previous research on antibiotic resistance has mostly focused either on primary care or secondary care, and relatively little research has been carried out within LTCFs. LTCFs are a critical part of the healthcare system, housing residents whose needs do not warrant acute care in hospitals, but cannot be met in their own homes. Demographic shifts mean that an increasing proportion of our population are elderly.[4] In addition, increases in life expectancy have outpaced improvements in disability-free life expectancy, meaning that a greater proportion of the population lives with disability later in life.[5] The combination of these factors is driving an increasing demand for LTCF residence in older people, which is struggling to be met due to reductions in local authority budgets.[5,6] Residents of LTCFs have high levels of co-morbidity, predisposing them to a wide range of infections, which are an important cause of hospital admissions.[7–10] High levels of antibiotic exposure are, therefore, likely, and infections, including those caused by resistant bacteria, will likely spread readily in these congregate settings. It is, therefore, likely that AMR is a significant problem in the LTCF setting and that this setting makes an important contribution to the overall problem of antimicrobial resistance. This thesis uses statistical and mathematical modelling tools to shed light on the epidemiology of AMR in LTCFs using routinely available data.

The problem of antibiotic resistance

Bacteria can easily spread between humans, animals and the environment. We carry approximately 38 trillion of these organisms in our bodies, mostly in our gut and on our skin.[11] Although most bacteria are not harmful, and in fact play an important role in our good health, they also cause infection.[12] Bacteria that are commonly carried asymptomatically (without any symptoms) are problematic to survey, as their spread goes mostly undetected.[13]

Antimicrobials are therapeutic agents used to kill or slow the growth of organisms that cause infection such as bacteria, fungi, viruses or parasites. The first antimicrobial was discovered by Paul Ehrlich in 1909.[14,15] This was a synthetic arsenic-based compound that was highly effective at treating syphilis. Nineteen years later, in 1928, Alexander Fleming discovered penicillin, the first antimicrobial of clinical relevance derived from microorganisms, which was introduced as a therapeutic in 1941.[16–18] Sulfonamides were discovered soon after penicillin, in 1932.[18] The discovery of these agents triggered the subsequent discovery of most of the antimicrobials used to date, in what is known as the "golden age" of antimicrobial discovery (1940s-1960s).[16,18] Antimicrobials have been instrumental in healthcare, enabling the treatment and prevention of infections. Surgical procedures and treatments that suppress immunity, such as chemotherapy, have become much safer in the knowledge that infections may be prevented or treated by antimicrobials.[19] Antimicrobials are also widely used in veterinary medicine and in agriculture for the treatment and prevention of infections in animals and plants.[19] However, tied hand in hand with antimicrobial use, is the development of AMR.

AMR arises when organisms develop mechanisms to counteract the effect of antimicrobials, enabling them to survive and grow despite the presence of the antimicrobial.[16] Antibiotics are a type of antimicrobials that target bacteria. Bacteria are able to develop and spread antibiotic resistant traits at a high rate due to their elevated growth rate and their ability to transfer genes between individuals, strains and even families.[16] In many cases, genes encoding antibiotic resistant traits precede the use of antibiotics in human beings. They have been found in bacteria isolated in extreme environments that are unlikely to have been contaminated with antibiotics manufactured by humans.[16,20] However, resistant traits are favoured by antibiotic use. Antibiotic treatment confers an evolutionary selective advantage for the acquisition of antibiotic resistant traits, allowing bacteria with these traits to resist antibiotic treatment, survive and proliferate.[16] A famous evolutionary hypothesis is the Red Queen effect, which proposes that organisms constantly evolve and adapt in response to their ever-changing environment.[21] This metaphor of an evolutionary arms race was coined by Leigh Van Valen in 1973[21] and was derived from a passage

of *Through the Looking-Glass* by Lewis Carroll (1871): “Now, *here*, you see, it takes all the running you can do, to keep in the same place”. This plight for adaption and survival is not unlike that of bacteria in the presence of antibiotic drug development.[22]

Although the lack of access to antibiotics is still a problem in many countries, particularly in the developing world[23], antibiotic use has been increasing, thus providing a selection pressure for resistant strains of bacteria to prevail.[16] Antibiotics are frequently misused in the treatment and prevention of infection in humans.[23] The four conditions which contributed most to inappropriate prescribing in primary care were sore throat (23.0% of identified inappropriate prescriptions), cough (22.2%), sinusitis (7.6%) and acute otitis media (5.7%).[24] Antibiotics are also prescribed in even larger quantities in animal husbandry. Although important, this was beyond the scope of this thesis.[25,26]

Due to the paucity of new antibiotics being developed, a rise in antibiotic resistance limits treatment options and increases the risk of treatment failure, leading to increases in morbidity and mortality.[19,27] The spread of antibiotic resistance is a major healthcare concern nationally and worldwide.[19,28,29] In particular, antibiotic-resistant Gram-negative bacteria have been highlighted as organisms of concern.[30–32] Gram-negative bacteria are a group of bacteria that contain small levels of peptidoglycan in their cell wall and possess an outer membrane, which confers them protection against several antibiotics. Two Gram-negative bacteria, *Escherichia coli* and *Klebsiella* have recently been highlighted as critical priority pathogens for research and development of new antibiotics by the World Health Organization.[30] *E. coli* and *Klebsiella* have also been highlighted as bacteria to monitor for resistance in the five year AMR strategy for the UK (2013-2018).[31]

Urinary tract infections- why do they matter?

Gram-negative bacteria such as *E. coli* are part of the natural microflora of the gut; however, they are also the primary cause of urinary tract infections (UTIs).

UTIs comprise both infections of the upper and lower urinary tract. Common symptoms of UTI include dysuria (painful or difficult urination), a high frequency of urination, suprapubic tenderness, urgency in urination, polyuria (abnormally large passage of urine), new incontinence, fever and haematuria (blood in the urine).

UTIs impact quality of life and are the most common cause of acute emergency admissions to hospitals amongst conditions that could be effectively treated and managed in the community[10,33]. Age and sex adjusted admissions for UTI per 100,000 population increased from 102 in 2001/2002 to 229 in 2012/2013[34]. In 2015, UTIs were the second most common cause for antibiotic prescribing in primary care and prescribing for UTI has been increasing from 2010 to 2015[35]. As such, antibiotic treatment for UTI is an important driver of antibiotic resistance.

UTI sequelae include recurrences, pyelonephritis, complications associated with antibiotic use, such as antibiotic resistance and *Clostridium difficile* colitis, and bloodstream infection (BSI).[36] BSIs are severe infections associated with high mortality, in particular if they are caused by antibiotic resistant bacteria.[37] Studies performed in English hospitals during the winter of 2012/2013, between April 2012 and March 2014 and between July 2011 and June 2012 found that 51.2%, 41.1% and 52.4% of BSIs caused by *E. coli*, respectively, had a urogenital tract focus of infection.[37–39] One of these studies showed that 98.4% of BSIs that had their origin in the urogenital tract were UTIs.[39] In England, the Department of Health and NHS England demands the mandatory surveillance of the incidence of *E. coli* BSI by NHS Acute Trusts. From 2012 to 2016, the cases reported increased by 24.3%, with 40,272 cases reported in 2016.[40] A steady increase was also observed from 2002 to 2008 in the BSIs reported to EARS-Net from laboratories across Europe.[41] The rate of laboratory reports of *Klebsiella* BSI have increased steadily since 2013.[42] The incidence of MRSA BSI, in contrast, has been decreasing since 2007.[43] Given this increase in *E. coli* BSI, the Secretary of State for Health has set an ambition of reducing healthcare-associated Gram-negative BSIs by 50% by 2020.[32] NHS England has developed the Quality Premium Scheme to reward clinical commissioning

groups for quality improvements in the aim of meeting this goal. The inappropriate prescribing of antibiotics for UTI may result in recurrences or treatment failure which may lead to BSI. Therefore, one of the targets in reducing BSIs is the reduction of inappropriate antibiotic prescribing for UTIs in primary care.[44]

Urine has long been thought to be sterile; however, recent evidence suggests that bacteria are present in small concentrations in the healthy human bladder, and certain bacteria may in fact have a protective effect for UTI. [45] Particularly in the elderly, where catheterisation and asymptomatic bacteriuria (the presence of bacteria in the urine in the absence of clinical UTI symptoms) are common[46–48], the presence of Gram-negative bacteria in the urine, even in high concentrations, does not necessarily equate to a UTI. It is, therefore, important that symptoms are accounted for in UTI diagnoses. Accordingly, English national guidelines do not recommend sending urines from elderly people with a suspected lower UTI for laboratory culture unless two or more signs of infection are present or in case of treatment failure, and this is not recommended if patients are catheterised. Dipsticks with nitrite are recommended only in women under 65 years of age with cloudy urine and either mild symptoms, or two or fewer symptoms of UTI.[49] The guidelines also recommend that suspected lower UTIs in elderly people should be treated empirically only when fever and one other symptom is present. [49,50] Due to the high frequency of co-morbidities such as dementia, which may hinder the ability to verbalise symptoms, and other comorbidities such as incontinence, diagnosis is complex. The distinction between colonisation and infection is, therefore, problematic when interpreting electronic health records capturing consultation for UTIs or surveillance databases capturing antibiotic susceptibility results and attempting to derive from this the rate or incidence of infection. Empiric treatment for UTI is frequent and may also complicate the interpretation of susceptibility data, as cultures may only be taken after treatment failure.

UTIs are most frequent in the elderly**.** As mentioned above, the clinical management of UTI in this population is complex due to the high frequency of co-morbidities. Residence in a LTCF is a known risk factor for UTI.[47]

Long-term care facilities

LTCFs are defined in different ways in the literature, comprising, for example, acute-care hospitals with long lengths of stay, residential facilities, and facilities that provide care to people of all ages including those with learning disabilities. However, for the purpose of this thesis, LTCFs are defined as facilities that provide accommodation for elderly people and support them in their daily activities such as washing, dressing and eating.[51] They are otherwise known as care homes. Some LTCFs additionally provide nursing services. In 2011, 291,000 people in England over 65 years of age (3.2% of the total population aged 65 and over) were recorded in the census as living in LTCFs[52]. This is predicted to increase in the coming years as the population in Europe ages and healthcare systems strive for cost optimisation, which frequently results in shorter hospital stays.[53]

LTCF residents are at an increased their risk of being hospitalised compared to elderly individuals residing in their own homes.[9] It has been shown that the ratio of emergency admissions and A&E attendances to elective attendances is 40-50% higher in residents of a postcode containing a LTCF than in individuals aged >75 that did not live in a postcode containing a LTCF.[9] The five year forward view suggested that many of these admissions to hospital could be avoidable[54], which has resulted in the "enhanced health in care home" vanguards pioneered by NHS England.[55]

Immunosenescence, the progressive decline in immune function that occurs during aging, increases the risk of infection in older people.[7,56–58] Frailty, which is common in the old, increases individuals' vulnerability to stresses such as infection and worsens their prognosis.[59] LTCF residents additionally present with functional impairment, such as faecal and urinary incontinence; malnutrition; frequent co-morbidities, which often require the use of invasive devices such as catheters; and are potentially dehydrated.[7,8,60]

Infection control can be challenging in LTCFs due to frequent opportunities for transmission through group activities; sharing of living space, objects and bathroom facilities; poor coordination of medical care; as well as a lack of staff

adequately trained in infection control.[61,62] Infection control is also challenged by the fact that LTCFs are residents' homes, and, as such, it is neither possible nor desirable to implement infection control measures similar to those in hospitals.

In a point-prevalence survey carried out in LTCFs across Europe, UTIs were found to be the joint most common healthcare-associated infection together with respiratory tract infections (31%).[63] In England, UTIs in LTCFs were the second most common healthcare-associated infection after respiratory tract infections (35.7%).[63]

AMR in Gram-negative bacteria in LTCFs

Point prevalence studies have also shown that a high proportion of residents were prescribed an antibiotic at any one time in LTCFs in Europe and Canada.[63–66] In 2011, a literature review found that, any one time in Europe, between 4.8% and 15.2% of LTCF residents are being treated with antibiotics, and between 47% and 79% of LTCF residents in Canada, USA, and Italy receive at least one course of antibiotics per year.[66] A point-prevalence survey co-ordinated by the European Centre for Disease Prevention and Control conducted between April and May 2013 in LTCFs across Europe found that 4.4% of residents were being treated with at least one antibiotic on the day of the survey (N=3,367/77,264). Amongst the 16 English LTCFs included in this study, the prevalence of antibiotic treatment was higher, at 9% (N=37/409). In this subset of facilities, 86.8% of prescriptions made were aimed at treating infections (13.2% were prophylaxis prescriptions), and 45.5% of these were prescribed for UTIs. [63] However, antibiotic prescription is likely to vary significantly between LTCFs. [67]

Antibiotic treatment in LTCF residents and in elderly individuals living in their own homes was compared in the literature. A study of the national prescribing records in Sweden in 2008 found a higher usage of antibiotics for UTI in LTCF residents compared to elderly individuals living in their own homes.[68] In England, a study of the electronic health records routinely collected by GPs in Hampshire showed that care home residents aged 75 or older had an unadjusted odd's ratio of 2.66 (95% CI 2.51-2.82) of being prescribed a UTI

antibiotic when compared to individuals aged 75 or older residing in their own homes, and 2.12 (95% CI 1.99-2.26) after adjusting for gender, age, co-morbidities and presence of a urinary catheter.[69] With this exception, antibiotic usage in England has not yet been linked to LTCF data and is not routinely surveyed.

The prevalence of colonisation with AMR Gram-negative bacteria has been shown to be high in several studies of individual LTCFs.[70–72] Larger carriage surveys of AMR in Gram-negative bacteria have also been carried out in LTCFs. For example, a point-prevalence set in 107 LTCFs in the Netherlands between October 2012 and July 2014 found that 25% (95% CI 23-27%) of *E. coli* isolated from urine screening samples were resistant to trimethoprim, 1% (95% CI 0.6-1.6%) to nitrofurantoin, and 20% (95% CI 18-23%) to ciprofloxacin.[73] Another study surveyed 20 LTCFs in Belfast (Northern Ireland) between July 2005 and May 2006 and found a large variability between LTCFs in the prevalence of colonisation by Extended spectrum beta-lactamase-producing *E. coli*, ranging from 0% to 75%.[74]

Several small studies have aimed to compare the prevalence of resistance in urinary isolates from LTCFs and from elderly individuals living in their own homes using GP data in Dublin (Ireland)[75] and in Vestfold County (Norway)[76]; and using hospital data in Melbourne (Australia)[77] and Dundee (Scotland)[78]. In Dublin, Dundee and Australia there was a higher prevalence of resistant Gram-negative bacteria in the LTCF population compared to elderly individuals living in their own homes. The Norwegian study found no significant differences between the two groups.

Only one study analysed the prevalence of carriage of antibiotic resistant Gram-negative bacteria in English LTCFs. This study was set in Cambridgeshire in a LTCF of 105 beds during 2014. Stool and urine specimens were collected weekly from 45 participants, and 17 patients (38%) were found to be carriers of ESBL-producing *E. coli* at some point during the six months of the study.[79] This study additionally showed that the strains isolated from several residents in the LTCF were highly related, suggesting that either transmission or acquisition

from a common source was occurring. In addition, the lineages of these isolated strains were highly related to that of strains associated with BSI in a local hospital. Another study found LTCFs to be a driver of hospital outbreaks of carbapenem-resistant *Klebsiella pneumoniae*.[80] A prospective study set in three LTCFs in Philadelphia (USA) also found a high acquisition rate for fluoroquinolone-resistant *E. coli*, as detected through serial faecal sampling, with 47.5% of 120 residents newly acquiring this colonisation during a year of follow up.[81]

In summary, although the combined evidence from the literature suggests that antibiotic usage and antibiotic resistance in Gram-negative bacteria are high in the LTCF setting; antibiotic prescribing and susceptibility data is not routinely collected and surveyed in LTCFs. Very few studies have investigated this problem in England.

How can mathematical modelling can help?

By definition, infectious diseases are different from non-communicable diseases in that they can be transmitted from one organism to another. Therefore, transmission often needs to be considered to fully understand the natural history of an infectious disease, or the impact of any intervention to control it.[82] Dynamic mathematical models incorporate transmission, and as a result, have become important tools in epidemiology and public health. They are used to understand the epidemiology of infectious diseases, to target interventions appropriately and to evaluate their health and economic impact.[82–85]

Infectious disease transmission has been simulated extensively in the hospital setting using dynamic mathematical models.[86] These are useful tools to simulate different “what if” scenarios under different sets of assumptions. They have been used to predict the impact of infection control interventions such as hand hygiene, antibiotic stewardship, isolation, healthcare worker cohorting, screening, decolonisation, patient cohorting, barrier precautions, environmental cleaning, vaccination and prophylaxis in hospitals.[86–93] In addition, dynamic models have been used to analyse the impact of changes in antibiotic exposure and screening upon hospital admission on the prevalence of vancomycin-

resistant enterococci (VRE).[94] Mathematical models have also been used to propose novel strategies to reduce antibiotic resistance in hospitals such as informed switching between antibiotics.[95] Furthermore, findings from mathematical models have been used to make policy decisions for hospitals. For example, a model used to analyse the cost-effectiveness of screening of all patients admitted to hospitals in England for MRSA has helped to shape the current national MRSA screening policy.[87] Because of their mechanistic nature, mathematical models can also help us understand how a particular infection control strategy in a hospital can affect the epidemiology of an infection. For example, modelling the long-term impact of different mupirocin usage strategies for MRSA decolonisation in hospitals has helped identify the fitness cost of mupirocin resistance in MRSA.[88]

Likewise, mathematical modelling has the potential to provide insight into the transmission of infections in LTCFs. Like in hospitals, LTCF residents live in close proximity to one another, and are more likely than the general population to be older and frailer individuals with chronic conditions which may warrant invasive devices such as catheters, or surgical operations, which increase their risk of contracting infections.[7,9,96] However, LTCFs offer greater opportunities for infectious disease transmission than hospitals through many more shared objects and spaces, higher contact between residents, and longer lengths of stay, which favour prolonged exposure to the organisms residents may be carrying.[97–99] Hence, existing insights from mathematical models of infectious disease transmission in the hospital may not apply in LTCFs.

In addition, dynamic transmission models can incorporate patient movement dynamics between different institutions, which may be important for the spread of infectious diseases. Elderly residents in LTCFs are frequently admitted directly from their LTCF into a hospital and then discharged from the hospital back to the LTCF[9]. This process may occur repeatedly and is known as the "revolving door syndrome". [96] Patients might acquire infections or become carriers of infectious diseases present in hospitals or in LTCFs, and may then transmit them to hospitalised patients during their visit or to other residents upon their return to the LTCF. In this scenario, infection control measures in

LTCFs alone may fail to decrease the prevalence of infection due to the constant re-admission of infected or carrier residents to hospital, coupled with high rates of transmission within LTCFs. Infection control measures in hospitals could also be hampered by this amplification of transmission through LTCFs.

Thesis objectives

The objectives of this thesis were four-fold:

- First, to review the literature of dynamic transmission modelling of infectious diseases in LTCFs; to critically compare the mathematical models evaluating interventions against AMR bacteria in the LTCF; and to establish a checklist for policy makers to review the quality of mathematical models of interventions against AMR bacteria in LTCFs.
- Second, to link antibiotic susceptibility data to the LTCF registry in England in order to determine if patients from which the samples were taken were LTCF residents, and use this dataset to compare the prevalence of AMR in LTCF samples and in older people living in their own homes.
- Third, to determine the seasonality of UTIs in the UK, in order to understand whether this needed to be accounted for in transmission models.
- Fourth, to develop a mathematical model to simulate the transmission of *E. coli* resistant to trimethoprim in the LTCF.

Thesis outline

Chapter 1: Introduction

Chapter 2: Systematic review of published peer-reviewed dynamic transmission models of infectious disease transmission set in LTCFs.

Chapter 3: Critical review of mathematical models of interventions against antimicrobial resistant bacteria in LTCFs and checklist of good quality models for policy making.

Chapter 4: AMR in LTCFs: linking the AmSurv dataset to the CQC dataset

Chapter 5: Impact of LTCF residence on the antibiotic resistance of urinary tract *E. coli* and *Klebsiella*

Chapter 6: Seasonality of UTIs in the United Kingdom in different age groups: longitudinal analysis of THIN data

Chapter 7: Mathematical modelling of the transmission of *E. coli* resistant trimethoprim in the LTCF

Chapter 8: Discussion

Chapter 2 Systematic review of published peer-reviewed dynamic mathematical models of infectious disease transmission set in long-term care facilities

Published in Infection Control and Hospital Epidemiology.[3]

Aim

To review the published peer reviewed literature that described any dynamic mathematical models relating to infectious disease transmission in LTCFs, and summarise their methods and research themes.

Introduction

Chapter 1 introduced the use of mathematical models in explaining infectious disease dynamics. One of their main features is that they can explicitly simulate the transmission infectious diseases between individuals. Infectious disease population dynamic models generally represent changes in infection states (e.g. being susceptible to infection, being infected or being infectious).[82] Changes between these states depend on parameters that can vary according to the proportion of the population in each infection state and, therefore, can vary over time.

Table 2-1 defines the main terminology relating to mathematical models. Broadly, mathematical models used in infectious disease epidemiology can be divided into deterministic and stochastic models. In a deterministic model, the output of the model is simply determined by its parameters and, as such, the model output remains the same every time the model is run. Stochastic models, however, take into account randomness or variations which may occur by chance, producing different model outputs every time they are run.[82,84]

Table 2-1. Modelling terms definitions.

Static model	Model in which transmission does not change with the number of infected or colonised individuals in the population. Therefore, the infectious process does not vary over time. This type of model has been applied, for example, to the progression of varicella to herpes zoster.[100]
Dynamic model	Model representing a process (infection) that changes over time in such a way that the transmission to susceptible individuals is dependent on the number of infected or colonised individuals in the population. This type of model has been used to study most infectious diseases, for example measles.[101]
Deterministic model	Model in which the output of the model is simply determined by its parameters and, as such, the model output remains the same every time the model is run. Deterministic models have been used to describe infections in large populations, for example pertussis resurgence in England and Wales.[102]
Stochastic model	Model that takes into account randomness or variations which occur by chance, producing different model outputs every time they are run. Stochastic models are more appropriate to simulate diseases transmitted within small confined environments, for example, in hospital wards[103], where the effect of randomness becomes more important.
Compartmental model	Model that groups individuals into categories (e.g. infectious individuals). All individuals in one category are assigned the same set of parameter values. Individuals then transition through infectious states as groups. Compartmental models have been used, for example, to simulate the transmission dynamics of Ebola.[104]
Individual-based model (IBM)	Model that follows individuals as separate entities and infection states are recorded for each individual.[82,83] Amongst others, IBMs have been used to understand sexually transmitted infections such as HPV.[105]
Model fitting	The inference of unknown model parameters.[86] In frequentist theory, this is achieved by obtaining the set of parameters that are most likely given the data observed.
Model validation	Comparing the model predictions to a second dataset that has not been used for model fitting. [86]

Dynamic transmission models can also be divided into those that are individual-based and those that are compartmental. Compartmental models group individuals into categories (e.g. infectious individuals). All individuals in one category are assigned the same set of parameter values. Individuals then transition through infectious states as groups. Individual-based models (IBMs), however, model individuals as separate entities and infection states are recorded for each individual.[82,83]

The choice of mathematical model type should be based on the question the researcher is aiming to answer.[82] Stochasticity is important when modelling processes in small populations in which chance events might interrupt transmission but are less important in larger populations. Stochasticity also becomes important when attempting to understand the persistence of infection. IBMs are more complex and computationally intensive than compartmental models. They are appropriate when individual patient characteristics such as demographics, medical history, or contact patterns are relevant to the question addressed, and where the corresponding data is available to inform them.

A variety of techniques are available to improve the quality of a mathematical model. Ideally, models should be fit against empirical data to make them more realistic. This empirical data can include, for example, data concerning the incidence or the duration of infection. Model fitting can be achieved through the statistical calibration of model parameters.[86] In frequentist theory, this is achieved by obtaining the set of parameters that are most likely given the data observed[106]. Sensitivity analyses explore the impact of varying parameter values on model outputs. This could also encompass the sensitivity of the model outputs to assumptions surrounding the biology of the infection and transmission, which may impact the model structure. Sensitivity analyses are important in order to check for errors in models, to test their robustness, to increase our understanding of the underlying dynamics and to determine uncertainty in model parameters, structure and, therefore, in the outputs.[86] Validation involves comparing the model output to a second dataset.[86]

Chapter 1 highlighted the potential of mathematical models in studying infectious disease dynamics in the LTCF setting. To our knowledge, no systematic review of mathematical models of infectious disease transmission in LTCFs has been conducted. This chapter describes the peer reviewed dynamic mathematical models relating to infectious disease transmission in LTCFs and summarises their methods and research themes. This was carried out in order to identify research gaps, which in turn helped guide the direction of this thesis, and was published in Infection Control and Hospital Epidemiology.[3] This search was then updated for the thesis submission.

Methods

Database search and abstract screening

The CINAHL, EMBASE, Global Health, MEDLINE and Scopus databases were systematically searched on the 27/12/13 for abstracts and titles that included terms relating to "model" AND "long-term care facility" AND "mathematical" (see Appendix Chapter 2). An outline of the review process can be found in Figure 2-1. The Scopus search alone bore 5,971 results and, therefore, had to be limited thematically to immunology and microbiology, computer science and mathematics, which yielded 450 results. Under these criteria, the search generated 1,562 results (164 CINAHL, 523 EMBASE, 1 Global Health, 424 MEDLINE, 450 Scopus). Upon de-duplication, these were reduced to 1,067 records (88 CINAHL, 481 EMBASE, 1 Global Health, 76 MEDLINE, 421 Scopus). The abstracts of these 1,067 papers were read. All peer reviewed dynamic mathematical models describing infectious disease transmission in LTCFs written in English were included. Those describing animal work, statistical models and within-host models were discarded. This left 21 papers for full text assessment.

This search was performed again on the 19/02/16. Using the same search strategy, the EMBASE search yielded 729 new results, MEDLINE 630, Scopus 133, CINAHL 13 and Global Health zero. Of these, two further studies were included for full text assessment.

Full-text assessment

Twenty three papers were read in full text. Studies that did not report mathematical models of infectious disease transmission in LTCFs were excluded. Studies were only considered to be set in LTCFs if they provided accommodation and support for elderly people in their daily activities such as washing, dressing and eating. LTCFs included facilities with and without nursing care. Rehabilitation centres, long-term acute care facilities and facilities for younger users did not meet the eligibility criteria for this study.

Only one paper was excluded due to access restrictions[107]. Two papers were excluded because they didn't include mathematical models[108,109], two because they were congress abstracts and there was no full text available[110,111] and two because they didn't include dynamic transmission models but statistical models analysing cost-effectiveness[112,113]. This left 16 papers[114–129]. From the references of the selected 16 papers, two additional papers were identified that fulfilled our criteria[130,131] giving a total of 18 papers to review. These were categorised according to organism, date, setting, theme and methodology.

Update of review for thesis submission

The EMBASE and MEDLINE searches were kept active since the completion of this review until thesis submission (October 2017). Nine new papers describing infectious disease transmission in LTCFs through mathematical modelling were published. [132–140] These are also included in the description below.

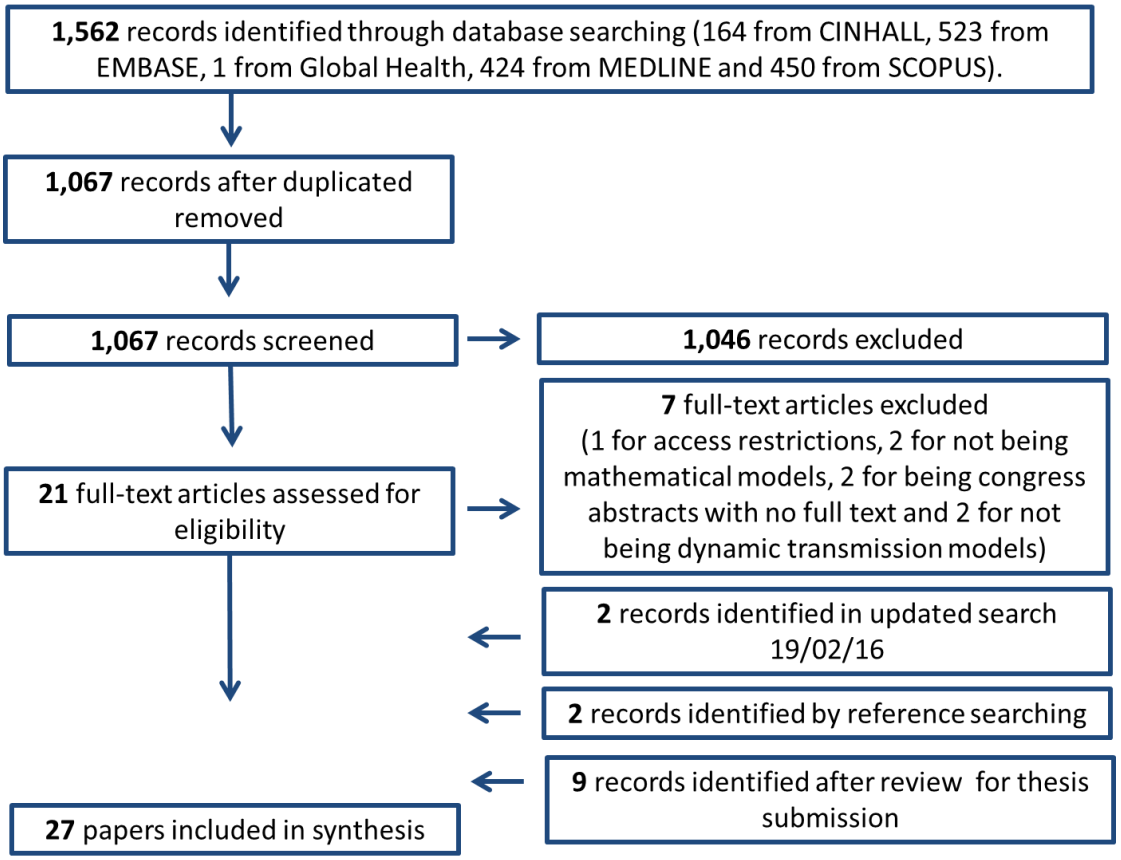

Figure 2-1. Flow chart of the review process. One thousand five hundred and sixty two records were identified through the CINAHL, EMBASE, Global Health, MEDLINE and Scopus

databases. After all duplicates were removed, 1,046 records were excluded through abstract screening, seven full-text articles were excluded through full-text assessment, two additional papers were identified through reference searching and two more through in an updated search on the 19/02/16. Nine papers were identified after the review for thesis submission. Twenty-seven papers were selected for review.

Results

Twenty-seven papers describing 22 different models were selected for review.[114–127,130–140] In the original review carried out in February 2016, 1067 abstracts were identified for screening and 18 papers that examined 15 different dynamic models of infectious disease transmission in LTCFs were selected for review. In October 2017, nine further papers had been published on this subject. In total, therefore, 27 papers were reviewed.

Organism

The most commonly studied micro-organisms were influenza viruses (nine papers: five seasonal[120,123,125,128,131], three pandemic[118,124,130] and one both[121]) and methicillin-resistant *Staphylococcus aureus* (MRSA) (seven papers[114–117,127,138,139]). One of the latter studied both MRSA and methicillin-sensitive *Staphylococcus aureus* (MSSA).[139] Of the remaining studies, three focused on the transmission of Gram-negative bacteria (two of carbapenem-resistant *Enterobacteriaceae* [132,133] and one of *E. coli* ST131[134]), three on norovirus[126,129,137], two on *Clostridium difficile.*[135,136], and in three cases the authors did not specify a bacterial species (two generic non-species-specific AMR bacteria[119,140] and one generic non-species-specific bacteria in healthcare[122]) (see Figure 2-2).

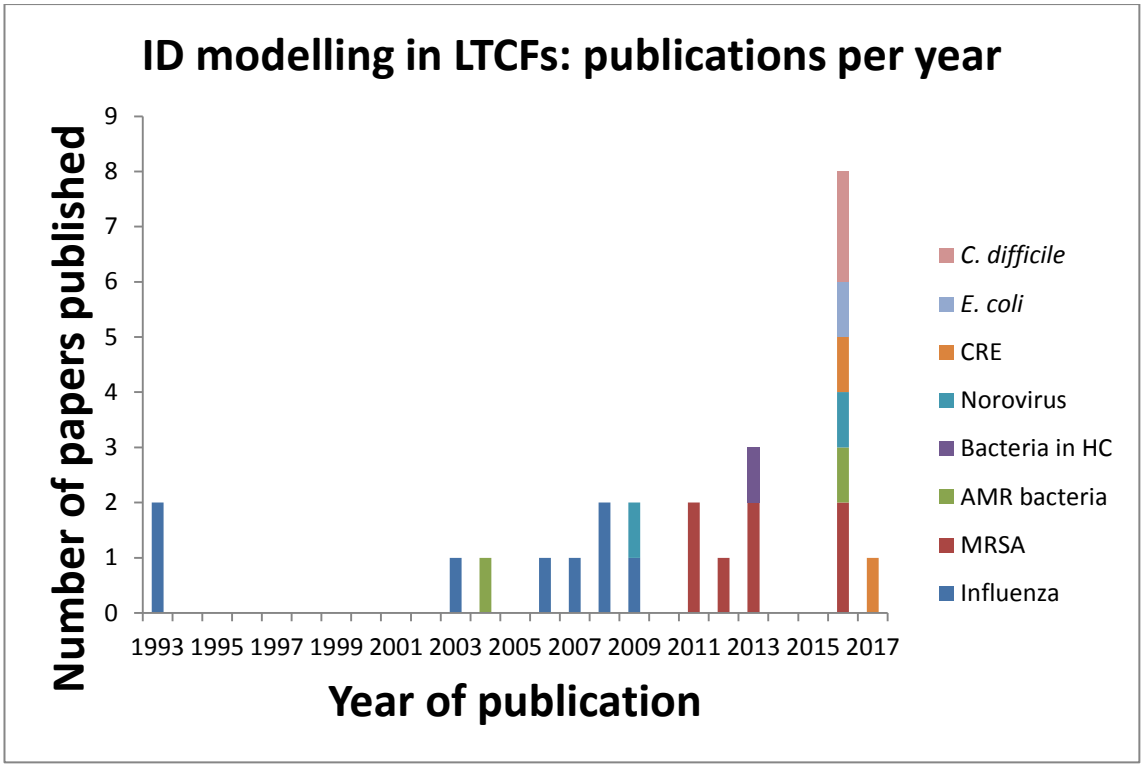

Figure 2-2. Infectious disease modelling in LTCFs: publications per year. CRE, carbapenem-resistant *Enterobacteriaceae*; Bacteria in HC, Bacteria in healthcare; AMR bacteria, antimicrobial-resistant bacteria; MRSA, methicillin-resistant *Staphylococcus aureus*.

Chronology

The first models studying infectious disease transmission in LTCFs were published in 1993[125,131]. These were two papers describing the same model. For the ten subsequent years there were no publications in this field. Since 2003 there has been a resurgence of publication in this area. From 2003 until 2016, the number of papers published remained small, averaging at 1.5 publications per year. In 2016, eight papers were published on this subject.

Setting

Eight papers modelled transmission within LTCFs[114,118,120,125,126,137,138,141], nine in both LTCFs and hospitals[115–117,122,127,129,132,139,140], one in the community, hospital and LTCFs (stratified into 5 demographic groups)[135], one in the community, ICU and LTCFs[136], one in the community, LTCFs, long-term acute care hospitals and acute care hospitals[133], one in a small population (a small urban US community)[124], one in a medium size population of 800,000 with

3,000 individuals in hospital and 7,000 in LTCFs[134], two in larger populations (a country-size population and a USA state-sized population)[123,128] and three did not define their population size[119,130,131]. Most papers were either explicitly or implicitly (though their choice of parameters) set in the USA (N=11 [115,116,119,124,127,128,132,133,135,138,139]) or did not indicate a national setting (N=5 [114,118,122,125,131]). Three other studies were set in the Netherlands[120,121,140], two in France[130,137], two in England[129,136], one in Belgium[126], one in Spain[134], and one in an unspecified developed country[123]. One was an international study that utilised data from both Canada and the USA[117].

Theme

Twenty-two papers assessed one or several interventions[114,116–118,120–124,126–128,130,132–140]. The most common intervention (evaluated in nine papers[114,118,122,124,126,130,132,133,135]) was the isolation of residents. Other commonly studied interventions included decolonisation[114,122,127,139], screening[114,118,127], different types of surveillance systems[132,133,135,139], contact precautions[116,122,132,139], hand hygiene measures[137], and prophylactic treatment[120,123,128,130]. Two papers researched the impact of altering patterns and rates of patient transfer and lengths of stay[114,117] and three others investigated vaccination[121,128,130]. Altering staff to patient ratios and increasing staff shifts were each researched in one paper[114,118]. One study assessed the impact of reducing community and LTCF transmission, although the precise methods of how this would be achieved were not discussed.[135] Other themes researched included the role of LTCFs in infectious disease prevalence and transmission (in seven papers[114–116,119,127,132,133]), the impact of patient transfers among institutions (in three papers[117,127,139]), the spread of AMR overall (in two papers[119,140]), theoretical concepts about a particular model (in two papers[125,131]) and modelling methodology for small outbreaks[129].

Methodology

The majority of these papers (N=19[115–118,120–122,124,125,128–133,135–137,139,140]) described stochastic models whilst four papers described deterministic models[119,123,126,127], one described a deterministic model with a stochastic

component for transmission[128] and three described both types[114,134,138]. Thirteen papers described compartmental models[114,118,119,122,123,126–129,134,135,137,138] and thirteen IBMs[115–117,120,121,124,125,130–133,136,139]. The three models that were repeated in two different papers each were stochastic IBMs. One was a network model[140].

Various model structures were described in the papers. One was a modification of a susceptible-infectious-recovered (SIR) model[127]; ten were based on a susceptible-infectious-susceptible (SIS) model[114–117,119,132,133,138–140]; one on a susceptible-exposed-infectious (SEI) model[124]; ten on variants of a susceptible-exposed-infectious-recovered (SEIR) model[118,120,121,123,125,126,128–131], one on a SEIS variant[134], one on a variation of a PSCIC structure (protected, susceptible, colonised, infected, colonised) which included colonised individuals that were immune and not immune, one on two different structures: susceptible-colonised (SC) and susceptible-colonised-infected-isolated (SCII)[122], and one on a UCIRc structure (uncolonised, asymptomatically colonised, infected and colonised subject to recurrence) that was then modified to include treatment.

Five models were fit to data using formal statistical inference or emulation methods.[128,129,134,135,137] One used a chi-squared goodness-of-fit test[128], two using the least-square criterion [134,137], one used Markov Chain Monte Carlo[135], and one used a gradient-based optimisation code to find the maximum-likelihood estimate[129]. Only four studies validated their findings[128,129,134,136]. Two papers described simple fitting processes for some parameters used in the models[117,126] and 17 of the 27 papers did carry out sensitivity analyses of the parameter sets[114,116,120,121,123–125,128–131,133,134,136–139]. Of these, five were carried out through Latin hypercube sampling[120,121,125,136,137].

Discussion

From 2003 until 2015, the number of papers publishing dynamic models of infectious disease transmission in LTCFs remained small, averaging at 1.5 publications per year. However, in 2016, eight papers were published on this subject, which could indicate a potential increase in interest in studying infectious diseases in this setting.

Up until February 2016, the scope of the organisms studied in the literature was limited to three organisms (norovirus, MRSA and the influenza virus) in addition to two more generic organism categories which were not sub-specified further (bacteria in healthcare and AMR bacteria). Norovirus, MRSA and the influenza virus are organisms that frequently cause infections in LTCFs; however, the transmission of other organisms such as Gram-negative bacteria, which also very commonly cause infection in this setting, were not studied. UTIs (together with respiratory tract infections) are in fact the most common infections in LTCFs and they are in their majority caused by Gram-negative bacteria. As discussed in Chapter 1, infections caused by Gram-negative bacteria are increasingly becoming problematic in hospitals as they are now the most frequent cause of bloodstream infections (BSIs), and have been highlighted as critical priority pathogens for research and development of new antibiotics by the World Health Organization.[30] Interventions to prevent their spread are being trialled[28,142–145]. For these reasons policy makers are likely to be interested in models of Gram-negative bacteria transmission in LTCFs. The transmission of other infections such as *Clostridum difficile* infection and scabies, common in older people, had also not been modelled. From February 2016 to October 2017, nine new papers describing infectious disease transmission in LTCFs through mathematical modelling had been published. [132–140] Three papers described the transmission of Gram-negative bacteria (two of carbapenem-resistant *Enterobacteriaceae* [132,133] and one of *E. coli* ST131[134]) and two of *Clostridium difficile.*[135,136] These studies begin to address the abovementioned gap in the type of organisms modelled in this setting; however, they focus on infections caused by particularly pathogenic Gram-negative bacteria, which may not be representative of most infections caused by Gram-negative bacteria

observed in LTCFs. The dynamics of *Klebsiella* colonisation and infection have also not been studied to date.

The means of transmission, the time between infection and infectiousness and the duration of infectiousness vary greatly between organisms. As such, the infection processes of different organisms may warrant different types of mathematical models. The conclusions obtained from modelling the spread of one specific organism in the LTCF cannot be meaningfully extrapolated beyond this to other organisms without the necessary model adaptations, which could range from adjusting the model parameters to a completely new model structure and model type.

Either explicitly or through their choice of parameter set, most studies were set in the USA and none were set in developing countries. This distribution may be reflective both of the mathematical modelling groups worldwide and of the countries in which LTCFs are most common. Eight studies modelled the transmission of infectious disease in LTCFs without taking into account other facilities such as hospitals or the community. Due to their frailty, LTCF residents are known to frequently visit hospitals[9] and hospitals may act as an amplifier for some infections, particularly for healthcare-associated infections. Therefore, including patient hospitalisation may be important to accurately reflect the dynamics of transmission of infectious diseases in LTCFs.

Several interventions were rarely addressed or not studied at all in the studies reviewed. Vaccination against influenza was explored; however, vaccination against bacterial infections was only explored in one study published in 2016[136], which sought to quantify the impact of vaccination against *C. difficile*. This was perhaps due to the lack of licenced vaccines to this effect. However, as vaccines for infections which are common in LTCFs become closer to being licenced and are undergoing phase III clinical trials[146–148], and in the face of growing antibiotic resistance, it becomes important to analyse the effect of vaccines on transmission dynamics in this setting.

Other important interventions to model in LTCFs relate to antibiotic treatment and include antibiotic switching and antibiotic stewardship. The effect of these

interventions would have on transmission in the LTCF setting is still not well understood. Four studies published in 2016/2017 have aimed to address some of these questions. One study assessed the impact of switching between antimicrobial drug classes on *C. difficile* infection[135]. The authors additionally assessed the impact of improving hospital hygiene which had also not been previously assessed. [135] Another study investigated the effect of reducing the exposure to fluoroquinolones and cephalosporins in the population colonised by *E. coli* ST131 from 5% to 0%[134]. However, this was considered implausible. A further study assessed the impact of antibiotic use in the previous 3 months on the epidemic potential of MRSA USA-300 and MRSA non-USA-300. The authors did not model the reduction of antibiotic use as an intervention but rather compared the epidemic potential with and without previous antibiotic use.[138]

The majority of these papers (N=19[115–118,120–122,124,125,128–133,135–137,139,140]) described stochastic models. The choice of model type, as mentioned in the introduction, should be dependent on the question posed. In the LTCF setting, stochasticity is important as these are generally small enclosed environments where chance events may become critical. Deterministic models would therefore not simulate the infection process accurately. Formal fitting techniques improve the reliability of model parameters and therefore, of the conclusions drawn from the model. However, only seven of the studies reviewed fit their models to data in some form[117,126,128,129,134,135,137]. In absence of formal model fitting, the full uncertainty surrounding the parameters should be presented. Sensitivity analyses of the parameter sets were carried out in 17 of the 27 papers [114,116,120,121,123–125,128–131,133,134,136–139]. If possible, models should be validated through the use of other available data to allow the generalisability of their findings to be ascertained. Only four studies validated their findings[128,129,134,136].

The range of organisms studied (and therefore, the range of interventions and models developed) complicated an in-depth comparison of the methods. Chapter 3 aims to address this by focusing on the models of interventions

against AMR bacteria identified in the original review of the literature carried out in February 2016.

Conclusions

Few (27) mathematical models have characterised the spread of infectious diseases in LTCFs, nine of which were published during the last year. Eight of the studies reviewed did not account for the movement of individuals between LTCFs and hospitals, which are frequent and may act as an amplifier for some infections. The scope of the microorganisms studied is also limited. The transmission of Gram-negative bacteria is particularly understudied given the commonality of the infections they cause and their increasing public health importance.[30,31] Future models require more robust methodology. Authors should carry out extensive sensitivity analyses and, when possible, employ formal fitting techniques to ensure the model accurately represents the data and is sufficiently robust to produce sound conclusions. In addition, the effect of interventions relating to antibiotic treatment such as antibiotic stewardship on the transmission of infections caused by antibiotic-resistant bacteria in the LTCF has not been investigated rigorously to date and could provide a valuable solution for reducing antibiotic resistance in this setting.

Chapter 3 Critical review of mathematical models of interventions against antimicrobial resistant bacteria in LTCFs and checklist of good quality models for policy making.

Published in Infection Control and Hospital Epidemiology.[3]

Aims

1. To critically evaluate models of interventions against antimicrobial resistant bacteria in LTCFs.
2. To develop a checklist for epidemiologists and policy makers to distinguish good quality models of AMR in LTCFs.

Introduction

As described in Chapter 2, dynamic mathematical models have been useful to evaluate the impact of a variety of infection control interventions in hospitals.[86] In particular, many of these models have been used to evaluate interventions against AMR bacteria. Dynamic mathematical models allow better interpretation of the long-term impact of any intervention that aims to prevent infection by resistant bacteria than static models, as transmission and patient movement dynamics are complex and their impact on control measures are not intuitive.

Although mathematical models can be useful in evaluating the impact of interventions, conclusions from these models will only be as good as the quality of the model from which they are drawn. For example, a mathematical model that underestimates the importation of AMR bacteria to the LTCF will likely conclude that screening upon admission to the LTCF is an ineffective strategy. Similarly, a model parameterised with outdated estimates could lead to conclusions that are not relevant to current LTCFs. Therefore, it is important to assess the quality of mathematical models published prior to their use in policy-making.

When using mathematical models to inform policy at a local or national level there is a growing consensus as to what is desirable in model design, parameterisation and reporting.[82,149–151] Despite this, there is no practical guide summarising best practice for mathematical modelling of interventions against AMR bacteria in LTCFs. Infection control specialists and policy makers making decisions about infection prevention and control in LTCFs may wish to interpret the validity of findings from mathematical models in this setting to guide their decision-making. For example, they may wish to implement interventions that have been shown to be effective in mathematical modelling studies. In order for this type of decisions to be successful, they should be based on high quality mathematical models that accurately represent the infection dynamics.

This chapter will evaluate the quality of the existing models that quantify the impact of interventions against AMR in LTCFs and create a practical checklist to assess the quality of these models. It is important to develop a particular checklist for the LTCF setting. Firstly, LTCFs vary greatly in characteristics such as their size, the services they provide, and their case mix.[152] Therefore, it becomes important to define precisely the type of facility being modelled and ensure that all the parameters in the model align with the type of facility being studied. In addition, LTCFs have strong links with other institutions such as hospitals, such that epidemics in one institution may drive epidemics in another or one institution may act as a reservoir for another; hence, it is important to model the flow of patients between them. LTCFs are also generally small institutions where chance events become important and stochasticity should also be included.

This best practice checklist would also be useful in this thesis to aid the development of a mathematical model of transmission of *E. coli* resistant to trimethoprim (presented in Chapter 7).

Methods

In order to facilitate the critical evaluation of models of interventions against infectious diseases in LTCFs, this analysis focused on models that assessed interventions against similar organisms, in this case AMR bacterial infections as these were closer to the subject of this thesis. In Chapter 2, 22 papers were identified that assessed one or several interventions against infectious diseases in the LTCF setting.[114,116–118,120–124,126–128,130] Four of these evaluated interventions targeted at resistant bacterial infections.[114,116,117,127] One of these studies was excluded as it evaluated altering transfer rates between hospital and LTCFs. This study was not included in the critical review because altering transfer rates between hospital and LTCFs was not considered an intervention that could realistically be introduced as hospital transfers from LTCFs may not be able to be safely reduced. All three remaining studies assessed interventions against MRSA.[114,116,127]

These studies were critically evaluated. As criteria to evaluate these types of model have not yet been developed, these had to be determined in light of growing consensus in the literature to what is desirable in model design, parameterisation and reporting[82,149–151], as well as expert opinion from AMR modellers. The following criteria were applied: Firstly, the reporting itself was considered important to enable replicability and the understanding of the study. The design should be justified, the aims clearly stated, the importance of the question studied made clear, the methodology appropriately described, and the assumptions made explicit. Secondly, the research question should determine the model structure and model type. This is so that the model is able to answer the question posed. Thirdly, the outcome measures used to answer the study question should be relevant and measured and valued appropriately to facilitate the decisions made by policy makers. Ideally, these should permit the comparison between studies; therefore, numerical reporting was considered preferable. Finally, the model parameterisation is key. Parameters should be taken from current sources and be relevant to the setting so that the model yields pertinent results to the setting evaluated, and sensitivity analyses should be carried out to determine uncertainty and, therefore, the robustness of the

model outputs to the parameter values. Preferably, data should be used for formal model fitting or validation.

Using the criteria obtained from this critical evaluation; a checklist was developed that will enable clinicians and other decision-makers to appraise mathematical models of AMR in LTCFs.

Comparison of model results

Together, the three studies selected for critical review[114,116,127] found four interventions to be effective in reducing MRSA prevalence in the LTCF setting: screening and decolonisation, hand hygiene, contact precautions and increasing the staff to patient ratio. Figure 3-1 describes the interventions assessed, how their action was simulated in the model and the results observed. A detailed description of each model is provided in Appendix Chapter 3. Barnes et al.[127], aimed to evaluate the impact of screening and decolonisation on the equilibrium prevalence of MRSA in the LTCF. Chamchod and Ruan[114], assessed the conditions under which screening and decolonisation, hand hygiene, and increasing the staff to patient ratio eliminated the probability of invasion of MRSA. Lee et al.[116], sought to assess the impact of contact precautions for different sub-groups of LTCF residents on the number of acquisitions adverted within six months.

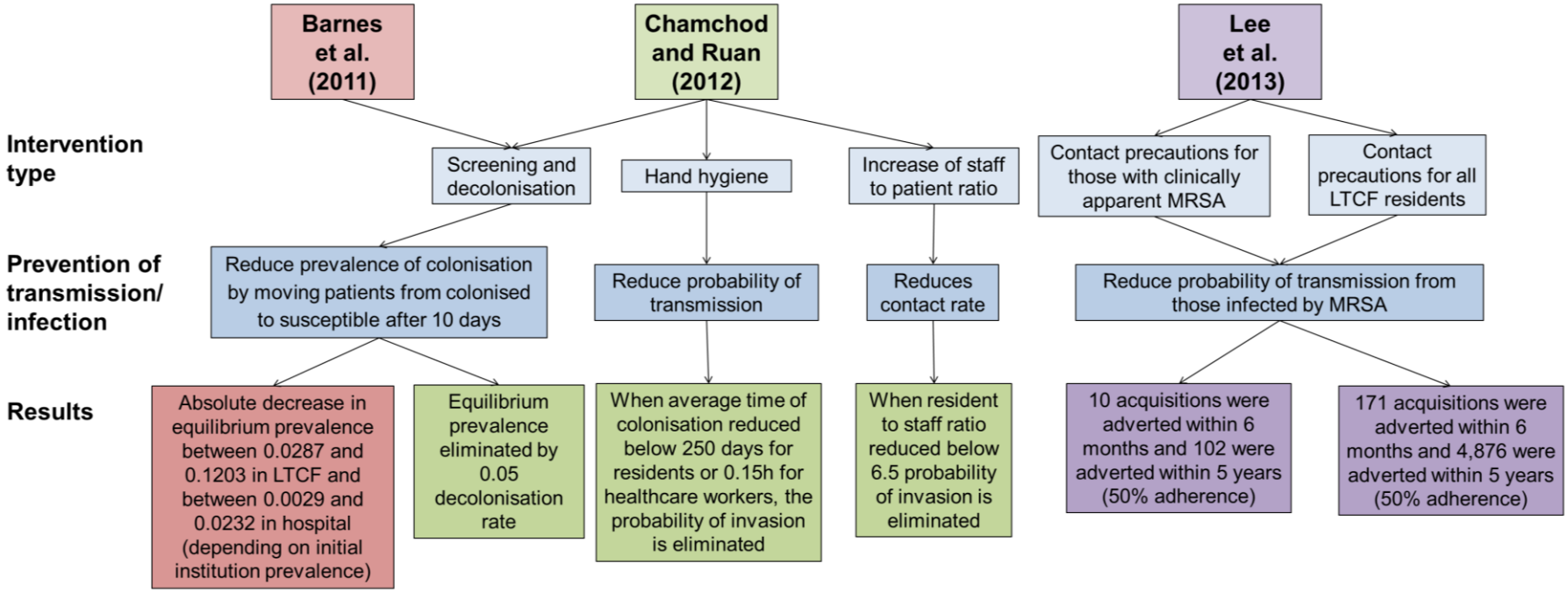

Figure 3-1. Assessing the effects of interventions against MRSA in LTCFs through modelling. Three papers have published models of interventions against *methicillin-resistant Staphyloccocus aureus* (MRSA) in long-term care facilities (LTCFs). The models have assessed five types of interventions in this setting. Two reduced the probability of transmission, one reduced the prevalence of colonisation and one reduced the contact rate. The results from the interventions modelled are shown on the right.

The likely outcome of an intervention is determined by the model pathways that are targeted by an intervention, the parameters associated with it and the assumptions behind it. Screening and decolonisation reduces the prevalence of colonisation by moving patients from a colonised state (for Barnes et al.[127], both persistently colonised and transiently colonised) to a susceptible state (uncolonised). The opportunities for transmission are also reduced as the pool of infectious individuals is decreased. The other three interventions only prevent or decrease the rate of colonisation. In this case, interventions will take longer to reduce the prevalence of colonisation if there are frequently patients admitted to the LTCF who are colonised on admission. The impact of MRSA interventions on a generic susceptible-infected-susceptible (SIS) model structure is depicted in Figure 3-2.

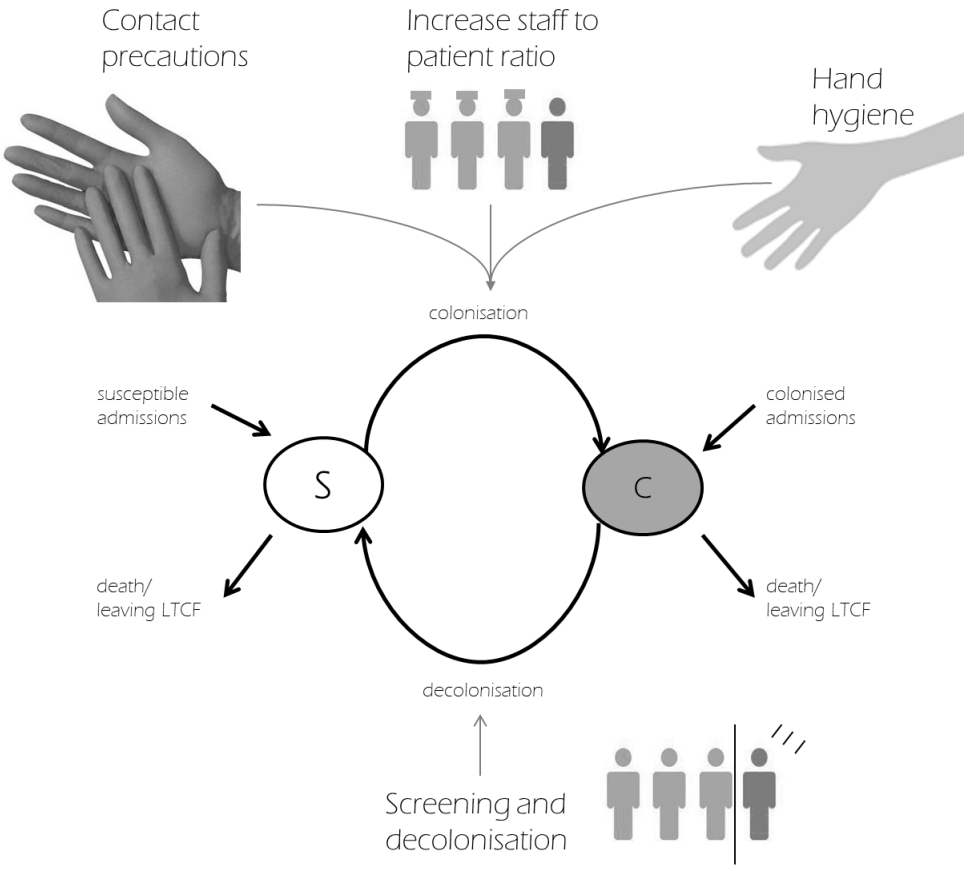

Figure 3-2. Impact of MRSA interventions on a generic susceptible (S) –colonised (C)-susceptible (S) model structure in the long-term care facility (LTCF). Whilst hand hygiene, increase of staff to patient ratio and contact precaution decrease the rate of colonisation, screening and decolonisation interventions reduce the prevalence of colonisation, therefore increasing the rate of decolonisation.

Were the model structures and parameters used realistic?

Chronology

The main characteristics of the papers reviewed are summarised in Table 3-1. The three models[114,116,127] were recently published (2011-2013), however, some parameters used by Barnes et al.[127] and Chamchod and Ruan[114] were based on older estimates that may be out-dated. Barnes et al.[127] (published in 2011) based their parameter estimates on literature from 2004 to 2010 and Chamchod and Ruan[114] (published in 2012) from 1999 to 2010. Lee et al.[116] (published in

2013) based their estimates on current sources, using data published from 2010-2011, with the exception of length of stay, which was the only parameter they based on data published before 2010 (2007).

Table 3-1. Characterisation of the papers that modelled MRSA transmission in LTCFs and assessed the impact of one or more interventions.

	Barnes et al.	Chamchod and Ruan	Lee et al.
Year	2011	2012	2013
Deterministic/ Stochastic	Deterministic	Both	Stochastic
Compartmental/IBM	Compartmental	Compartmental	IBM
Formally fit to data?	No	No	No
Sensitivity analysis?	No	Yes	Yes, but only adherence to intervention
Type		Univariate	Univariate
Formally validated?	No	No	No
Population setting	LTCFs and hospitals	LTCF	LTCFs, hospital and community
Country setting	USA	Not stated	Orange County, CA, USA

IBM: individual-based model

Model structure and model type

Chamchod and Ruan's[114] model only involved one LTCF and didn't take into account the "revolving door syndrome" of patient transfer between hospital and LTCFs which might be important in driving transmission. Lee et al.'s IBM model[116] was the most complex, incorporating LTCF, hospital and community settings and accounting for stochasticity. Barnes et al.'s model[127] was the simplest, a deterministic compartmental model.

The patient flow and transmission structures for the models are represented in Figure 3-3 and Figure 3-4, respectively. Patients were assumed to mix homogeneously within LTCFs across all models. A particular strength of the model developed by Lee et al., was that it used data to parameterise patient flow between healthcare facilities, where the other models did not. Barnes et al.

differentiated between persistently and transiently colonised individuals. Evidence for these different types of colonisation by *S. aureus* is mixed[153]. Chamchod and Ruan[114] and Lee et al.[116] distinguished between healthcare workers and residents and between residents taking contact precautions and residents that did not, respectively, adapting the disease states in their model to fit the questions addressed.

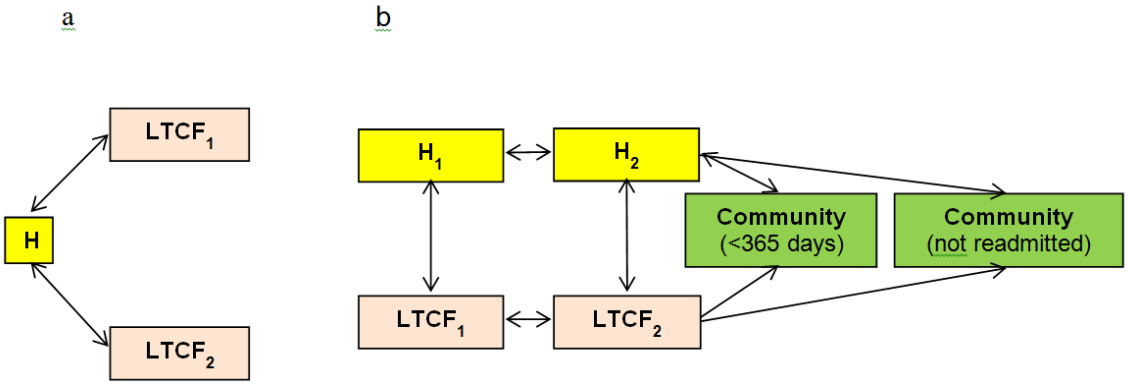

Figure 3-3. Structures of patient flow. 3a: Patient flow between hospitals (H) and example long-term care facilities 1 and 2 (LTCF1 and LTCF2) in the compartmental model of Barnes et al.[127]. 3b: Patient flow between example hospital 1 (H_1), example hospital 2 (H_2), example LTCF 1 ($LTCF_1$), example LTCF 2 ($LTCF_2$) and the community (sub-classified into those that remain for more and less than 365 days) in a representation of Lee et al.'s individual-based model. [116]

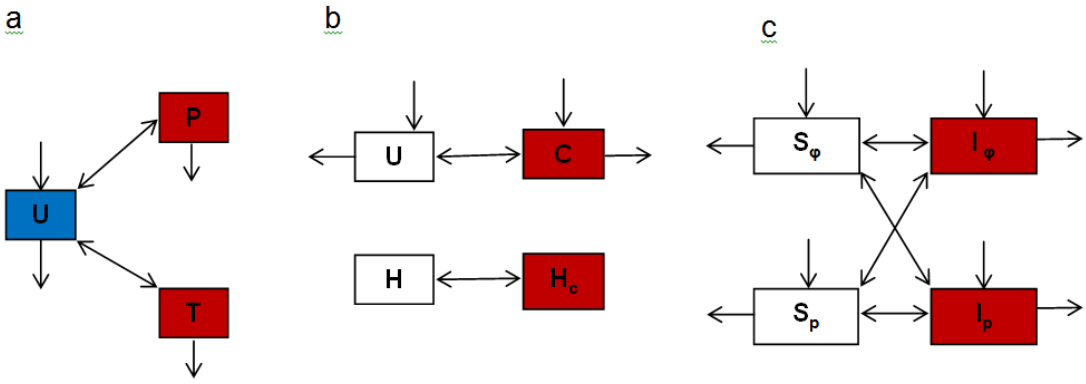

Figure 3-4. Model transmission structures. 4a: Transitions between uncolonised (U), persistently colonised (P) and transiently colonised (T) disease states in Barnes et al.'s compartmental model[127]. 4b: Transitions between the uncolonised (U) and colonised (C) disease states (for residents) and between the uncontaminated (H) and contaminated (H_c) disease states (for healthcare workers) in Chamchod and Ruan's compartmental model[114]. 4c: Representation of transitions between the susceptible with precautions (S_p), susceptible without precautions (S_φ), infectious with precautions (I_p) and the infectious without precautions (I_φ) disease states in Lee et al.'s individual-based model. [116]

Parameter validity, estimation and uncertainty

Table 3-2 summarises the key parameters used by Barnes et al.[127], Chamchod and Ruan[114] and Lee et al.[116]. The parameters used by the models, including the LTCF size, the transmission rates, the prevalence of colonisation and the

duration of colonisation, were very different in different models and often involved different units of measurement that did not allow for comparison across models (for example, the transmission rates). In addition, many parameter estimates were based on expert opinion instead of data. None of the models were formally fit to data. Chamchod and Ruan[114] carried out univariate sensitivity analyses, which added credibility to their findings, whilst Barnes et al. did not.[127] Lee et al.[116] only carried out a sensitivity analysis on the adherence to the intervention.

Table 3-2. Comparison of key parameters used by Barnes et al. (2011)[154], Chamchod and Ruan (2012)[114] and Lee et al. (2013)[116].

	Barnes et al. (2011)	Chamchod and Ruan.(2012)	Lee et al. (2013)
Size of institution (number of beds)	300 for hospitals, 100 for LTCFs and 20 for hospital units	2000 (LTCF)	mean for hospital 228.6 (SD=120.2) and mean for LTCF 108.6 (SD=58)
Rate(s) of transmission of MRSA (per day)	0.15 (low), 0.25 (medium), 0.35 (high) for hospitals and hospital units. 0.05 (low), 0.075 (medium) and 0.1 (high) for LTCFs.	0.015 (resident to resident), 0.12 (healthcare worker to resident) and 0.12 (resident to healthcare worker)	mean for hospital 0.0099[a] (SD=0.0402) and mean for LTCFs 0.000082[a] (SD=0.000056)
MRSA colonisation prevalence on admission	10% for both facilities	10%	mean for hospital 6.1% (SD=5.4) and mean for LTCF 26.1% (SD=8.6)
Duration of colonisation (days)	5 for transiently colonised and 50 for persistently colonised across all institution types	60 and 80 (two scenarios)	1/3 of those colonised with MRSA had indefinite carriage. The remaining 2/3 lost their carriage linearly with a half-life of 6 months.

[a]rate of transmission per person per day (vs. effective contact resulting in transmission, rate averaged per day)

The three studies chose different sizes of LTCFs, ranging from 100[127] to 2000 beds[114]. However, the average number of beds in care homes registered in England by the Care Quality commission (the regulator of health and social care in England) on the 01/04/2014 was 37 beds[152]. Only 1.3% (116) of care homes were able to cater for over 100 residents and the largest registered LTCF had 215 residents. In the USA, the average nursing home size was 106 beds (ranging from 2 to 1,389) and the average capacity of residential care communities was 38 beds (ranging from 4 to 582)[155]. A LTCF with 2000

residents[114] is, therefore, highly implausible in the English and American settings. A large LTCF size is likely to reduce the effect of stochasticity, diluting the importance of a chance event. For example, an additional infected individual entering the LTCF won't be very important in a large population; however, in a small population this could greatly increase the infection prevalence in the LTCF. Therefore, a large LTCF size will reduce the probability of a "die out" (in this case, the AMR bacteria not being dominant in any individual within the LTCF) or rapidly increasing due to a chance event.

Lee et al.[116] referenced their transmission parameter for MRSA in LTCFs as belonging from a study of MRSA transmission in LTCFs.[156] The origin of the transmission parameters in the models published by Barnes et al.[127] and Chamchod and Ruan[114] was unclear. Barnes et al.[127] modelled three different levels of transmission rates for LTCFs (0.05 (low), 0.075 (medium) and 0.1 (high)) but did not report the source of these estimates. Chamchod and Ruan[114] reported different transmission rates for resident to resident, healthcare worker to resident, and resident to healthcare worker. These were derived from their respective probabilities of colonisation, which were referenced as originating from two studies[157,158], multiplied by the average number of contacts between residents and between residents and healthcare workers (estimated as 1 and 8, respectively). The two studies referenced were a study of MRSA transmission carried out in a hospital[158] and a modelling study set in a tertiary care hospital[157]. The later, in turn, based their transmission estimates on the literature. Chamchod and Ruan[114] assumed the probability of colonisation between residents, healthcare worker to resident, and resident to healthcare worker was the same (0.015). However, as the average number of contacts between residents and healthcare workers was eight times higher than between residents, the resulting transmission rates were also eight times higher between residents and healthcare workers than between residents. It was unclear how the average number of contacts between residents and between residents and healthcare workers was estimated.

Lee et al.[116] and Barnes et al.[127] assumed that transmission rates for hospitals were much higher than those for LTCFs, which is not necessarily the case[159].

As described above, Lee et al.[116] parameterised the transmission rate in LTCFs using the results of a study of MRSA transmission in LTCFs.[156] They then parameterised the hospital transmission coefficient using estimates from a previous study that calibrated this parameter so as to obtain 1%, 2% and 3% incidence of MRSA in general wards, long-term acute care wards and ICUs, respectively. [160] Barnes et al.[127], in the same way as for LTCFs, modelled three different levels of transmission rates for hospitals and did not report the source of these estimates. Barnes et al.[127] did not provide a justification for the transmission rates in hospitals being higher than in LTCFs.

Other assumptions, such as that the prevalence of MRSA on admission being broadly equal to the population prevalence of MRSA in the USA[114,127], 10%[161], may be incorrect as age is a risk factor for MRSA infection[162–165]. Older studies carried out in USA LTCFs (in 2005 and 2003-2004, respectively) have shown double this prevalence (59% and 40%, respectively)[166,167]. It also may not be generalisable across settings. Lee et al. estimated MRSA prevalence in LTCFs at 26.1%, which is in line with most of the published literature (21% in Leeds (England), 23% in Northern Ireland, 17% in Spain and 22% in Hong Kong [168–170]). The population-weighted mean MRSA percentage in the EU/EEA has decreased significantly over the recent years.[171] Evidence of this decline in the USA is conflicting.[172] Timely prevalence estimates of MRSA on admission may impact the best interventions to implement in the LTCF. For example, underestimating prevalence on admission will underestimate the effectiveness of interventions relating to screening on admission.

Antibiotic prescription was not simulated by any of these models; however, it is a main driver of resistance. It increases the risk of colonisation and subsequent infection by resistant bacteria.[28] Antibiotic treatment in the LTCF setting has been shown to be high and associated with MRSA carriage. [173–176] Antibiotic stewardship is, therefore, a very important strategy to reduce antibiotic resistance and should be one of the main interventions modelled.

Were the interventions modelled appropriately?

Barnes et al.[127] and Chamchod and Ruan[114] did not clearly report their intervention outcomes and their relevance for clinical practice was not easy to interpret. Barnes et al.[127] reported prevalence at equilibrium (a theoretical state of model stability) in numerical and graphical form whilst Chamchod and Ruan[114] reported prevalence at equilibrium only in graphical form. For this reason, it was only possible to derive the threshold at which an intervention would eliminate MRSA at equilibrium prevalence or eliminate the probability of invasion. Lee et al.[116] reported the median percentage decrease in MRSA prevalence at equilibrium and, in addition, calculated the acquisitions of MRSA adverted under certain adherence conditions, which facilitated the interpretation of their findings.

Overall, Barnes et al.[127] and Chamchod and Ruan[114] described the assumptions related to the interventions they modelled in very little detail. Barnes et al.[127] assumed that, on average, two cycles of five-day "decolonisation" treatments were necessary for patients to be successfully decolonised (10 days). After these 10 days, therefore, the intervention was assumed to be 100% effective. Neither the adherence to this protocol, nor the impact of this assumption on the results were reported. Chamchod and Ruan[114] merely reported the thresholds of decolonisation rate, duration of colonisation and resident to staff ratio reduction that were necessary to eliminate the equilibrium of prevalence and the probability of invasion. They did not report the effectiveness, adherence or time necessary for the interventions to be successful in achieving these thresholds; therefore, their validity cannot be judged.

In contrast, Lee et al.[116] assessed the effect of contact precautions in LTCFs under three different levels of adherence (25%, 50% and 75%). This allowed comparison across a spectrum of scenarios that were realistically parameterised when compared to the literature[177,178]. Their findings were also comparable to those from hospital models, suggesting that focusing interventions on the small minority of clinically apparent MRSA cases will be ineffective[179]. Therefore, the findings from this study are more robust compared to the two other papers.

Summary and critical evaluation

The results from the critical appraisal are summarised below in Table 3-3. The choice of design was justified in all three papers and the importance of the question was made clear in the introductions. Barnes et al.[127] and Lee et al.[116] set clearly focused questions and aims for their paper. Barnes et al.[127] aimed to determine the effect of patient movement between hospitals and LTCFs on steady-state prevalence. As a secondary question they studied the effectiveness of screening and decolonisation. Lee et al.[116] aimed to understand if contact precautions in LTCFs reduced MRSA prevalence in LTCFs and hospitals. In contrast, Chamchod and Ruan[114] set broad objectives, to understand the persistence and prevalence of MRSA and possible means of control in LTCFs. The evaluation of interventions was purely theoretical and derived from the model behaviour a-posteriori.

Chamchod and Ruan[114] did not model the transfer of patients between LTCFs and hospitals, failing to include the dynamics of the “revolving door syndrome”. Barnes et al.[127] did not address stochasticity in their model which could be important in in LTCFs as these are generally small contained environments, heavily influenced by chance events.

Chamchod and Ruan[114] only presented their outcomes in graphical form which made comparison with other studies challenging. Model assumptions governing structure and transmission were made explicit but the assumptions behind interventions were often not explained nor tested. None of the models were formally fit to data, and only Chamchod and Ruan and Lee et al. carried out any univariate sensitivity analyses[114,116]. Most of the parameters in these three studies were chosen from the literature. Only Lee et al. [116] used data to parameterise their model. Parameters chosen from older literature may be out-dated. Chamchod and Ruan[114] chose an unrealistically large LTCF size[114] and both Barnes et al.[127] and Chamchod and Ruan[114] based the prevalence of MRSA on admission on the population prevalence of MRSA in the USA. This did not take into account that the population likely to be admitted to LTCFs is at a higher risk of MRSA carriage due to older age and frailty. Antibiotic treatment was also not considered in any of the models.

In their current state, none of the models reviewed were deemed of sufficient quality to inform policy concerning interventions in LTCFs. Although Lee et al.[116] explicitly described the assumptions behind their intervention and considered different levels of adherence; used data to parameterise their model and adopted a very complete model structure; they did not formally fit their model nor, in absence of this, test the robustness of their parameter estimates through sensitivity analyses for anything other than the intervention adherence. In addition, the authors did not consider antibiotic treatment and how this could impact their predictions.

Table 3-3. Critical appraisal of Barnes et al. (2011)[127], Chamchod and Ruan (2012)[114] and Lee et al. (2013)[116].

	Barnes et al. (2011)	Chamchod and Ruan (2012)	Lee et al. (2013)
Was the choice of design justified?	Authors chose deterministic compartmental model as an "introductory model" on the subject	Authors chose both stochastic and deterministic models model variations due to chance	Authors chose individual based model to simulate patient movement in complex Orange County facility network
Were the question and aims appropriately focused and clearly stated?	Specific goal: Determine the effect of patient movement between hospitals and LTCFs on steady-state prevalence Secondary question: Study screening and decolonisation effectiveness.	Broad goals: What is the persistence and prevalence of MRSA and possible means of control in LTCFs?	Specific goal: Can contact precautions in LTCFs reduce MRSA prevalence in LTCFs and hospitals?
Was the importance of the question made clear?	Yes, in introduction of paper.	Yes, in introduction of paper.	Yes, in introduction of paper.
Was the methodology appropriately described?	Some confusion about terms "hybrid" and "agency-based model"	Clearly described	Clearly described
Was the structure of the model appropriate to answer the research question?	Yes, authors included the transfer between hospital and LTCFs	No, authors did not include the transfer between hospital and LTCFs	Yes, authors included the transfer between hospital and LTCFs as well as the community.

Was the choice of model type appropriate to answer the research question?	No, stochasticity should be included.	Yes, stochasticity was included.	Yes, stochasticity was included and contact precautions were explicitly modelled as disease states to address research question.
Were the outcome measures used to answer the study question relevant and measured and valued appropriately?	Yes, steady-state prevalence reported. Resulting graphs included numbers which helped interpretation	Yes, prevalence and equilibrium prevalence are commonly used measures. Graphical outcomes only with no numerical reporting.	Yes, median % decrease in MRSA prevalence and MRSA acquisitions adverted (shown in tables) reported. Graphical example of change in prevalence over time provided a good additional explanation. Numerical values also reported.
Were any assumptions made explicit?	The adherence to the intervention was not addressed. Other assumptions were made explicit.	The effectiveness of the interventions and the adherence to these were not addressed. Other assumptions were made explicit.	Clearly outlined
Were data used for formal model fitting and/or validation?	No	No	Data from a national long-term care dataset, 2006-2008 hospital and LTCF surveys, 2007 California mandatory hospital dataset and patient screenings were used to parameterise the model but the model was not formally fit to data

Were the parameters appropriate?	Some parameters were chosen from the literature 2004 to 2010 and some by the authors. Prevalence on admission to the LTCF was too low. No sensitivity analysis. Antibiotic prescription was not considered	Parameters were chosen from literature 1999-2010 (some could be out-dated). LTCF size was unrealistic. Prevalence on admission to the LTCF was too low. Univariate sensitivity analysis. Antibiotic prescription was not considered	Parameters based on data published 2007-2011 (above). Univariate sensitivity analysis only on adherence to intervention. Antibiotic prescription was not considered

What makes a good mathematical model for the evaluation of interventions?

A practical guide in the form of checklist that can be used by infection control specialists and policy makers for the appraisal of mathematical models of AMR in LTCFs is presented in Table 3-4. Many desirable criteria were identified, however, not all of them were considered essential to guide policy making. They were divided accordingly into low, medium and high criteria.

In mathematical modelling studies for the evaluation of interventions where a high level of certainty is required from clinicians or policy makers, all high importance criteria should be met. Defining the LTCF setting clearly was considered a high importance criterion due to the extensive diversity between LTCFs in case-mix, size and the care provided.[152] Findings from one setting may, therefore, not be applicable to other types of LTCFs. To avoid this confusion, it was considered important to clearly outline the characteristics of the LTCF studied. Modelling the flow of patients between hospital and LTCFs was also considered to be of high importance. This is because the prevalence of colonisation may be different in these two settings. In this scenario, the flow of patients between hospitals and LTCFs could highly influence the prevalence of colonisation in the LTCF (and in the hospital), and infection control policies that target these flows could be very effective in decreasing the prevalence of colonisation. Following the same reasoning, it was also considered highly important to test whether the prevalence of colonisation in hospitals and the community was different, and if so, account for this in different prevalence of colonisation on admission to the LTCF from these two settings. The prevalence of colonisation on admission to the LTCF from the community also should be based on LTCF data or data for older people population. This is to avoid underestimating the prevalence of colonisation on admission to the LTCF, which could be higher in this population. Another important criterion was the transparency in describing the methodology, including the assumptions underlying the interventions, and the sources of the model parameters. This was considered essential in order to evaluate their quality. Stochasticity was also deemed highly important in LTCFs, as these are generally small institutions where chance events become important. Finally, sensitivity analyses were

considered essential for models of sufficient quality to test policy, as they provide an estimate of uncertainty in the model outputs.

Parameterisation using data and model fitting is preferable; however, data may not available for this purpose. In absence of these data, parameters may be sufficiently informed using estimates from current high quality studies which are relevant to the model setting, provided a full sensitivity analysis is conducted to test the robustness of the model to these parameters (a high importance criterion). Country specific data for LTCF size, structure and movement would best inform differences between LTCFs in different countries. In absence of this data, a clear description of these parameters (a high importance criterion) may help avoid the extrapolation of findings from LTCFs that are very different to the English setting. Antibiotic prescription is also considered desirable, as it is an important driver of AMR; however, data available to inform this are scarce. Ideally, the outputs of the study should permit the comparison between studies; therefore, numerical reporting was considered preferable, albeit not essential.

The transmission in hospital is likely to impact the prevalence of colonisation on admission to the LTCF. Both processes are dynamic, therefore, modelling both the transmission in hospital and LTCFs would be best practice. However, parameterising both hospital and LTCF transmission would require multiple data sources, which are rarely available. In their absence, numerous assumptions based on little evidence would have to be made, which would undermine the robustness of the conclusions drawn from the model. In absence of this data, parameterising the admission to the LTCF from hospital appropriately (a high importance criterion) may be sufficient. Validation is also considered best practice; however, secondary datasets in this setting are rare. Finally, when possible, novel organism-intervention combinations should be studied to expand the existing knowledge in this field.

Table 3-4. Checklist for the critical appraisal of mathematical models of AMR bacteria in LTCFs. Ideally all high importance criteria should be addressed in a high quality model to permit the evaluation of interventions, generate and test hypotheses, and explore long term scenarios of AMR transmission and control in LTCFs. For the evaluation of interventions where a high level of certainty is required from clinicians or policy makers, all high importance criteria should be present in models. In both cases, medium and low importance criteria increase the quality of the model.

Themes of appraisal	Importance	Checklist questions
Setting and methodology		
	High	Is the LTCF setting clearly defined?
	High	Is the flow of patients between hospitals and LTCFs modelled?
	High	Have sensitivity analyses been performed?
	High	Is the methodology employed fully described in publication including the assumptions underlying the interventions?
	High	Has stochasticity been addressed in the model?
	Medium	Has the model been fit to data?
	Medium	Have formal fitting techniques (e.g. least square criterion, maximum likelihood estimation, Markov Chain Monte Carlo) been used to fit the model to data?
	Low	Is hospital transmission included?
	Low	Have models been validated using an auxiliary dataset (if this is available)?
Parameters		
	High	Is the source of the model parameters described?
	High	Is the prevalence of colonisation on admission to the LTCF from the community based on data specific to LTCFs or, in its absence, to the elderly population?

	High	If the prevalence of colonisation in hospitals is different to that in the community, is the prevalence on admission to the LTCF from hospitals different to that from the community?
	Medium	Are any parameters based on data rather than the literature?
	Medium	If any parameters are based on data, are the data relevant to the setting?
	Medium	Have transmission parameters appropriate to each setting (e. g. healthcare facility, bacteria) been employed? OR has model fitting been used to estimate transmission parameters from available data? OR if none are available, has a full sensitivity analysis been conducted?
	Medium	If any parameters are based on data, are these recent data?
	Medium	Is antibiotic prescription included in the model?
	Medium	Has country-specific data been used to describe institution size, facility structure and patient movement?
Interventions		
	Medium	Have numeric results of the outcome of interventions been made available to permit comparison across studies?
	Low	Is the model exploring organism-intervention combinations that are novel (i.e. have not previously been evaluated in the LTCF context)?

Discussion

Dynamic mathematical models of AMR bacteria have been used extensively to evaluate the impact of infection control interventions in the hospital setting and have helped shape current infection control policy in hospitals. [86,87] Antibiotic resistance is common in LTCFs[66] and interventions for the control and prevention of AMR infections are being studied.[180–184] In addition, LTCFs and hospitals are tightly linked due to frail residents of LTCFs being frequently admitted to hospital.[9] These transfers could play an important role in the transmission of AMR bacteria in hospital (and vice-versa). Mathematical modelling has the potential to provide insight into the dynamics of AMR infections in LTCFs and the interventions that may be useful to control them. Robust models that will guide policymaking in this area are needed to this purpose.

It is challenging to parameterise mathematical models of AMR transmission in the LTCF setting. Firstly, these facilities vary considerably in their patient populations, number of beds, and in the type of care they provide.[152] As such, data gathered in one LTCF may not be representative of another.

In addition, there is little data available for fitting and validation purposes. The surveillance systems that have been established in hospitals are not in place in LTCFs. In England, LTCF residents are seen either by GPs or in hospital. Diagnoses and prescriptions made by GPs may be captured by surveillance systems such as The Health Improvement Network (THIN) and the Clinical Practice Research Datalink (CPRD). Hospitalisation data (treatment, diagnosis) are recorded in the Hospital Episode Statistics (HES) database. Susceptibility data from laboratories concerning pathogens extracted from samples obtained from LTCF residents by GPs or in hospitals are collected centrally by AmSurv. LTCF characteristics such as bed numbers and services provided are separately gathered by the Care Quality Commission (CQC). Currently, there is no unified database where the infection journey of patients residing in LTCFs can be analysed. This hinders the calculation of incidence and prevalence of colonisation and infection by AMR bacteria, the rate of antibiotic treatment, and the duration of treatment in LTCFs. Patient movement between hospital and

LTCFs is also difficult to parameterise. Most of the data quantifying these parameters are available from small scale studies which may not be representative of the national or regional picture.

Other parameters such as the antibiotic treatment and resistance in the community are more readily available as these can be captured by single data sources.

In addition to the problems specific to the LTCF setting, there are general problems with parameterising models of AMR bacteria. Firstly, their rapidly changing epidemiology results in parameters quickly becoming outdated. Secondly, there is a plethora of organism-antibiotic combinations to be studied and each of these will require different parameters to be estimated. Thirdly, the interactions between these organisms are poorly understood and may be relevant to many of the processes surrounding transmission, including the duration of colonisation, the progression of colonisation to infection and the rate of transmission. Finally, the interactions between antibiotic prescribing and AMR are complex and difficult to simplify in a way that still yields valuable insights. This often requires making numerous assumptions, the validity of which can be disputed.

The models assessed above are not considered robust enough to test policy; therefore, there is room for improvement in the mathematical modelling of interventions against MRSA in LTCFs through mathematical modelling. Since this review was conducted, several other publications developed models to this aim. Lee et al. (2016) expanded the same model explored in this chapter to study the impact of ICU screening for MRSA, contact precautions for MRSA carriers and decolonisation for all ICU patients, on the transmission of *Staphylococcus aureus* (MRSA and MSSA). [139] The authors stated fitting transmission rates in LTCFs to the target prevalence found in the literature; however, they did not describe the methods they used to achieve this. The effectiveness of contact precautions and decolonisation was varied in a univariate sensitivity analysis. No further model fitting nor sensitivity analyses were described. Another study assessed the impact of antibiotic use in the

previous 3 months on the epidemic potential of MRSA USA-300 and MRSA non-USA-300. However, the authors did not model the reduction of antibiotic use as an intervention but rather compared the epidemic potential with and without previous antibiotic use.[138] According to the checklist proposed above, these two models would, therefore, also not be considered appropriate for use in policy-making.

The prevalence of MRSA has been decreasing over the recent years in most countries of the EU/EEA.[171] In contrast, resistant percentages in gram-negative bacteria are now high and increasing and gram-negative bacteria are the most frequent cause of bloodstream infections (BSIs) in Europe.[171] Therefore, it is increasingly becoming important to model interventions against AMR gram-negative bacteria in LTCFs.

Since this review was conducted, Lee et al. developed a stochastic IBM of carbapenem-resistant *Enterobacteriaceae* transmission[132]. The authors used their existing stochastic IBM model of facilities in Orange County (California, USA) including LTCFs and hospitals [116,139]. They assessed the impact of active surveillance for CRE when patients arrived from another hospital or LTCF and contact precautions/isolation in two scenarios: (a) when a facility acted in isolation when it had reached a certain threshold number of CRE cases and (b) in a scenario of coordinated regional infection and control when CRE cases were observed in a certain threshold number of hospitals. The authors tested the sensitivity of their results to assumptions made about the intervention. They also calibrated their transmission coefficients to reach a target 25% prevalence in LTCFs; however, the target itself and the methods used to achieve this were not described further. No formal fitting or sensitivity analyses were described.

Talaminos et al. (2016) coded a model of ESBL and non-ESBL producing *E. coli* ST131 in a population consisting of households, hospitals, nursing homes and the general population. [134] They assessed the impact of two theoretical interventions, one that would reduce the acquisition rate by 10%, and one that would reduce the exposure to fluoroquinolones and cephalosporins from 5% to 0%. The authors built both stochastic (hospitals and nursing homes) and

deterministic (households and general population) processes into their compartmental model. They fit the mean probability of colonisation for each compartment of the model to clinical data collected using the least squares method. They carried out multivariate sensitivity analysis of the dominant parameters and univariate sensitivity analysis of the remaining parameters. The authors validated their model, although they did not mention what data was used for this.

Toth et al. (2017) developed a stochastic IBM of carbapenem-resistant *Enterobacteriaceae* transmission set in the community, LTCFs, long-term acute care hospitals (LTACHs) and acute care hospitals. [133] The authors assessed the impact of active surveillance and enhanced isolation in LTACHs. The authors fit the transmission rate and the clinical detection rate to data; however, their methods were not explained. The sensitivity of model outputs to starting interventions at different time points and to different assumptions regarding discharge from LTACHs was explored.

All three of these studies[132–134] modelled the flow of patients between hospital and LTCFs and performed some form of sensitivity analysis. Talaminos et al. (2016) [134] explored the uncertainty in their model in a more consistent way. They also fit two of their parameters to data formally and validated their model. Therefore, methodologically, this was the best model; however, the interventions assessed were theoretical. A 0% exposure to fluoroquinolones and cephalosporins is deemed extremely difficult to implement. The 10% reduction in acquisition rate could be achieved by result of an intervention. Further work would be needed to establish which intervention would produce this reduction and whether it would produce it consistently.

Future studies should aim to model the transmission of gram-negative bacteria in LTCFs using robust methodology. The checklist above has been developed to facilitate this task; however, further work is needed for its validation. Further research is also needed to gather the data necessary to parameterise these models. Chapter 4 describes the data obtained from linking AmSurv, an English AMR surveillance tool, to the CQC database of registered LTCFs in the West

Midlands, in the aim of parameterising a transmission model of *E. coli* resistance to trimethoprim in LTCFs (presented in Chapter 7).

Conclusions

Three dynamic mathematical models assessing interventions against AMR bacterial infections in LTCFs were identified through a systematic review of the literature and were critically reviewed in this chapter. All three of these models simulated the transmission of MRSA. These models were not considered robust enough to test policy. The first study, by Barnes et al.[127], aimed to evaluate the impact of screening and decolonisation on the equilibrium prevalence of MRSA in the LTCF. The authors did not address stochasticity, did not formally fit their model to data nor, in absence of this, perform a sensitivity analysis. This study also based the prevalence of MRSA on admission on the population prevalence of MRSA in the USA. By the authors' own admission, this was an "introductory model" on the subject.[127] The second study, by Chamchod and Ruan[114], addressed screening and decolonisation, hand hygiene, and increasing the staff to patient ratio. Chamchod and Ruan[114] did not model the transfer of patients between LTCFs and hospitals and based the prevalence of MRSA on admission on the population prevalence of MRSA in the USA. They did not formally fit to data, but carried out univariate sensitivity analyses. In addition, the authors also chose an unrealistically large LTCF size. The third model, developed by Lee et al.[116], sought to assess the impact of contact precautions for different sub-groups of LTCF residents on the number of acquisitions adverted within six months. The authors developed a mathematical model with a very complete model structure, explicitly described their assumptions, and considered different levels of adherence to their intervention; however, they did not formally fit their model nor test the robustness of their parameter estimates through sensitivity analyses for anything other than the intervention adherence. Antibiotic treatment was also not considered in any of the models.

A checklist was developed for the evaluation of mathematical models of interventions against antimicrobial resistant bacteria in LTCFs by clinicians or policy makers. When a high level of certainty is required, for example, for policy-making, the following minimum criteria should be met:

1. The LTCF setting should clearly defined.
2. The flow of patients between hospital and LTCFs should be modelled.

3. If the prevalence of colonisation in hospitals and the community is different, this should be accounted for in different prevalence of colonisation on admission to the LTCF from these two settings.
4. The prevalence of colonisation on admission to the LTCF from the community should be based on LTCF data or data for the elderly population.
5. There should be transparency in describing the methodology, including the assumptions underlying the interventions, and the sources of the model parameters.
6. Stochasticity should be considered.
7. Sensitivity analyses should be carried out to test the robustness of the model outputs to the parameters.

Chapter 4 AMR in LTCFs: linking the AmSurv dataset to the CQC dataset.

Aims

1. To introduce the datasets used for the analysis in subsequent chapters.
2. To describe the cleaning and linkage methods used.
3. To describe the main characteristics of the clean dataset.
4. To outline the key strengths and limitations of the dataset.

Introduction

This chapter will describe the characteristics of the dataset used to study the epidemiology of antibiotic resistance in urinary tract *E. coli* and *Klebsiella* from residents of LTCFs for older people and adults aged over 70 living in the community. Subsequent chapters will describe the results of the analysis of the dataset.

The previous chapter outlined the problems with parameterising mathematical models of AMR bacteria in LTCFs. One particular concern was the lack of data available for fitting and validation purposes. One important data source required is the incidence of infection by AMR bacteria in LTCFs. This chapter described how this need was addressed through the linkage of antibiotic susceptibility data with LTCF data.

Chapter 1 introduced the importance of the problem of AMR in Gram-negative bacteria, and the reasons why it is of particular concern in LTCFs. Despite the many risk factors for AMR infections present in LTCFs, data on AMR is not routinely collected from LTCFs. Therefore, the extent of any problem is unknown and there is a lack of coordinated action to address the issue. The importance of UTIs is also explained in Chapter 1. UTIs are commonly sampled in the LTCF population; therefore, routinely collected urine microbiology samples provide an available means to study AMR in Gram-negative urinary bacteria. *E. coli* and *Klebsiella*, which frequently cause UTIs, were selected for analysis because they have recently been highlighted as critical priority pathogens for research and development of new antibiotics by the World Health

Organization and have also been highlighted as bacteria to monitor for resistance in the five year AMR strategy for the UK (2013-2018).[30,31] In addition, the incidence of BSIs caused by both of these organisms has been increasing in England. [35,42,43,185]

AmSurv is an AMR surveillance tool established by the Health Protection Agency (now Public Health England) in 2009. It collects antibiotic susceptibility testing results from routine microbiology samples sent to participating diagnostic laboratories in England from both hospitals and GPs.[186] Since December 2012, all laboratories in the West Midlands report to AmSurv, making data from this region the most complete longitudinal source of AMR surveillance information in England, with more than 95% of laboratories currently participating. The West Midlands Region (England) comprises a population of 700,000 individuals over the age of 70.[4] Linking the AmSurv West Midlands susceptibility dataset to the registry of LTCFs in England enables the study of the epidemiology of antibiotic resistance in urinary tract *E. coli* and *Klebsiella* from residents of LTCFs.

Figure 4-1 illustrates the complexity of the AmSurv database. Specimens can be collected from any individual in the population independently of whether they reside in LTCFs. Specimens can be collected in a GP practice or in a hospital. One patient may have one or more specimens taken. The same patient may have a specimen taken at their GP practice and another in hospital, which may then be sent to different laboratories for antibiotic susceptibility testing. In these laboratories, one patient specimen may culture one or several organisms, which are then tested for susceptibility against a panel of antibiotics. Antibiotic panels for the same organism vary between laboratories. Figure 4-2 defines some terms used throughout this chapter.

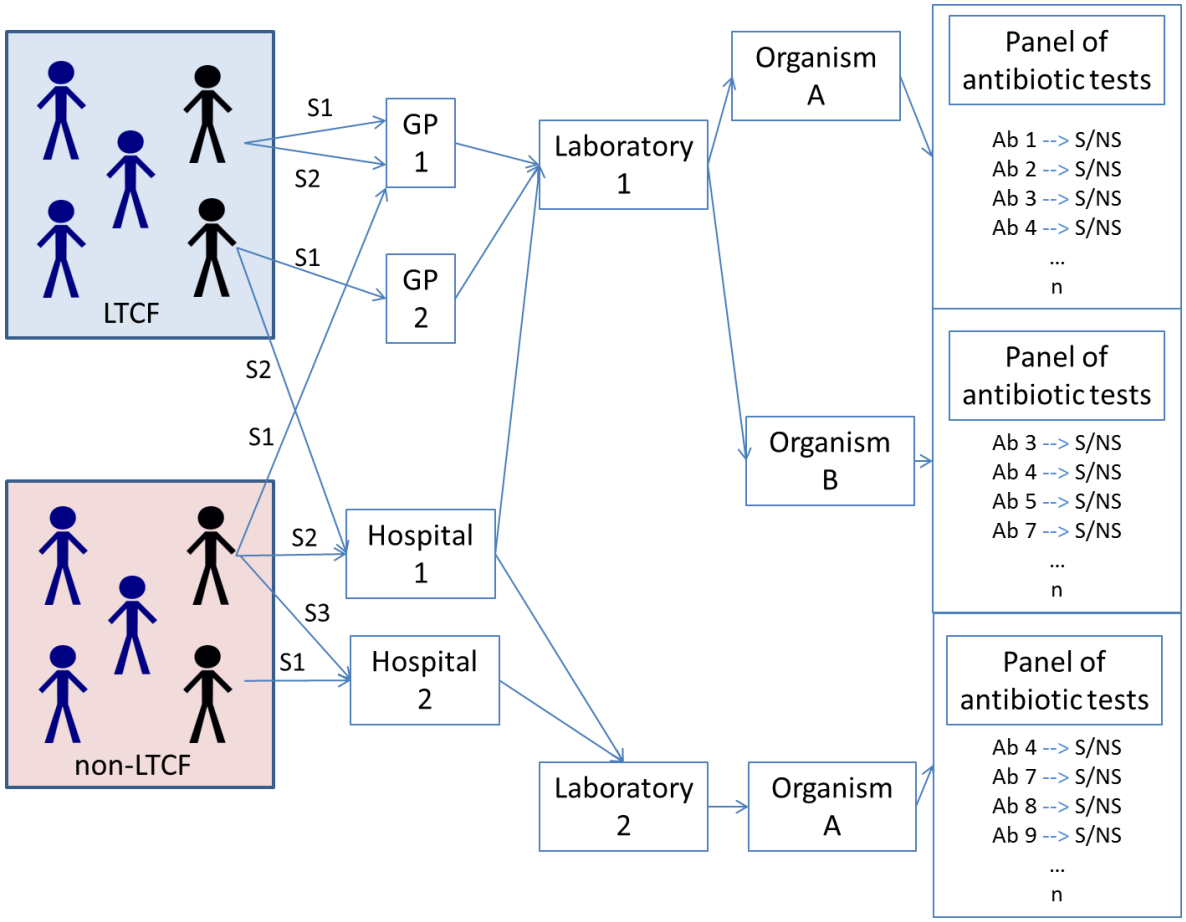

Figure 4-1. Flow diagram showing the complexity of the AmSurv dataset. The black characters are those presenting with symptoms that require a sample to be taken. LTCF, long-term care facility; S, sample; GP, general practitioner; Ab, antibiotic; S, susceptible; NS, non-susceptible.

Specimens: the sample of bodily fluid/material being collected (blood/urine/swab, etc.)

Specimen sites: the body location from which specimens are collected (e.g. blood/upper gastrointestinal tract/urine and kidneys)

Samples: a unique combination of organism, specimen site, patient, date, laboratory (i.e. one organism from a particular body site collected from one patient on a particular date and tested in one laboratory)

Tests: antibiotic tests carried out on the samples

Figure 4-2. Definition of specimens, specimen sites, samples and tests.

Methods

Data extraction from AmSurv

All antibiotic susceptibility results from all specimens collected from individuals over 70 years of age reported from the 15 microbiology laboratories in the West Midlands to AmSurv from 01/04/2010 to 31/03/2014 were extracted from the server.

Data linkage of the AmSurv and CQC datasets to determine LTCF residence

To determine which antibiotic susceptibility tests in the AmSurv dataset were from individuals that resided in LTCFs; the tests were linked with the Care Quality Commission registry of LTCFs. The Care Quality Commission, the national regulator of health and social care in England, holds a publicly available registry of LTCFs in England.[152] Only LTCFs in the West Midlands region classified as “care homes” for elderly residents and recorded as active in the register from 2011/2012 (797 LTCFs) were included. Care homes, as defined by the Care Quality Commission, “offer accommodation and personal care for people who may not be able to live independently”.[187] Care homes with 24-hour medical care from qualified nursing staff are referred to as nursing LTCFs and care homes without this service as residential LTCFs. LTCF status (nursing or residential), bed numbers for the entire LTCF, and LTCF postcodes were extracted from this registry.

Individuals’ full postcodes in the AmSurv database, collected on the request form for microbiological investigation, were matched against the full postcodes of LTCFs in the Care Quality Commission registry as of April 2014. Samples from individuals residing in a postcode that contained a LTCF (LTCF-pc) are subsequently referred to as LTCF samples and those with a postcode that did not (non-LTCF-pc) are referred to as non-LTCF samples.

Postcodes may cover several buildings; therefore, LTCF postcodes may also include some elderly people who are not LTCF residents. Patient postcodes in AmSurv were matched to the postcodes in a dataset obtained from open data

held by the ONS that described the number of households per postcodes [188]. Postcodes containing only communal establishments (CE-pc) in the West Midlands were identified.

Cleaning of the overall dataset

All cleaning was carried out in R 3·1.[189] Figure 4-3 depicts the data cleaning process of an example bacterium-antibiotic combination (*Klebsiella* samples tested against trimethoprim).

The first step involved eliminating spaces in the patient ID, NHS number, postcodes and AmSurv sender code fields. Tests with patient postcodes in incorrect format (172,999 tests), rows with “unknown” patient IDs (12 tests) and duplicated tests incorrectly generated in the data linkage from matching to LTCFs in the same LTCF postcode but with different names (36,330 tests) were eliminated.

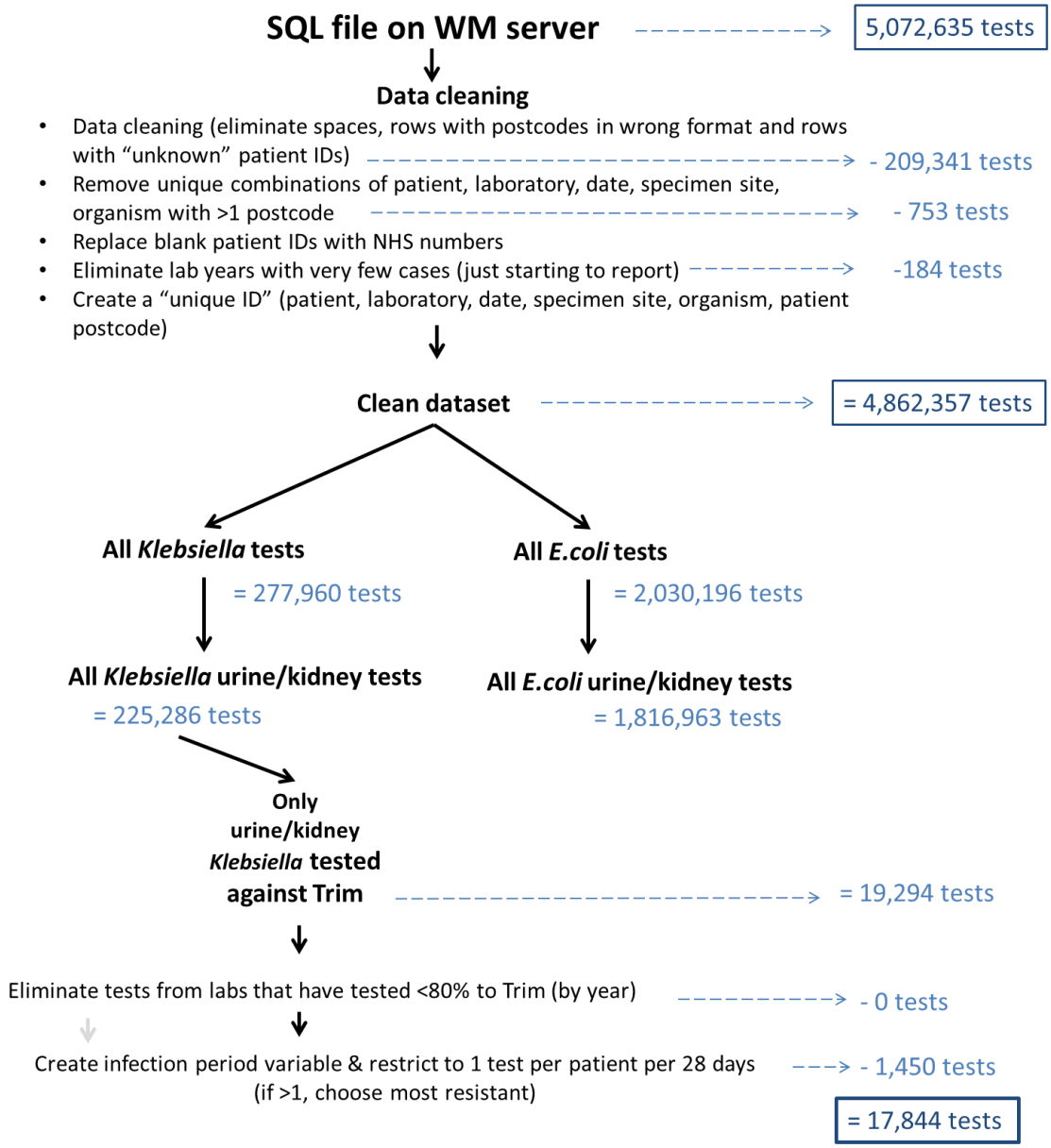

Figure 4-3. Flow diagram showing the data cleaning process of an example bacterium-antibiotic combination: *Klebsiella* samples tested against Trim (trimethoprim).

Patient IDs were a composite of NHS number and laboratory codes automatically created by AmSurv. Blank patient IDs were replaced with NHS numbers. Unique combinations of patient ID, laboratory, date, specimen site and organism with more than one postcode were eliminated (753 tests). Each sample was associated with a unique sample ID. Sample IDs were created with unique combinations of patient ID, laboratory, date, body site where the sample was taken, bacterium, and patient postcode. The number of samples per laboratory year is described in Table 4-1. Tests from laboratory years where

laboratories were just beginning to report were also eliminated (184 tests, 15 samples). The overall dataset comprised 4,862,357 antibiotic tests (96% of the full extract).

Table 4-1. Number of samples per year submitted to AmSurv by laboratories in the West Midlands. The numbers in bold depict samples eliminated during the data cleaning process. Laboratory 571200 closed during years 3 and 4. Laboratory 610710 received fewer samples as it did not receive community samples. Laboratory 591250 did not receive any samples in year 1.

Laboratory ID	N samples year 1	N samples year 2	N samples year 3	N samples year 4	Total N samples (all years)
571200	963	733	0	0	1696
573255	3992	4081	4487	4617	17177
579070	1833	11858	14818	16244	44753
587635	12026	9341	16613	17321	55301
591250	0	2030	2741	2887	7658
597840	1152	6973	6583	6606	21314
597955	12580	14061	12167	15065	53873
610660	4586	4252	6391	7194	22423
610710	71	62	79	69	281
610735	12080	11904	12128	12630	48742
610740	7791	7762	8004	8055	31612
611985	0	**15**	5968	14008	19991
612480	4571	5935	5899	7387	23792
618530	**1**	3681	3556	6169	13407
619000	0	1417	6177	6455	14049

Test results were grouped by susceptibility, where resistant tests were those where the bacterium was described by the laboratories as intermediately resistant or fully resistant to the antibiotic.

Microbiology

All the NHS clinical microbiology laboratories in the West Midland undertake UKAS external accreditation to verify competencies and assure conformity to standard methods.[190] Laboratory information systems are configured to only send significant bacteriuria to PHE and PHE, through the national Standard Methods for Investigation for urine specimens, which recommends specific cut-offs for clinical laboratory processing.[191]

These laboratories perform antibiotic susceptibility testing using a variety of methods: EUCAST (The European Committee on Antimicrobial Susceptibility Testing), BSAC (The British Society for Antimicrobial Chemotherapy) and CLSI (Clinical Laboratory and Standards Institute); with a mix of automated susceptibility testing (e.g. VITEK, Phoenix) and manual laboratory methods (e.g. disc and gradient strip MIC testing (E-test)). All laboratories contributing to this dataset participate in the UK National External Quality Assurance Scheme (NEQAS). Clinical laboratories most commonly use EUCAST breakpoints, and until recently BSAC methodology, but where EUCAST breakpoints are unavailable for key antibiotics, laboratories use alternative published breakpoints such as the National Committee for Clinical Laboratory Standards (NCCLS), and are asked to report their methods to NEQAS when reporting specific organism antibiotic susceptibility results. Specifically in the West Midlands, in 2012, out of 15 laboratories, seven laboratories used BSAC disc diffusion, four used Vitek 2, three used breakpoint methods and one used a combination of Vitek 2 and BSAC disc diffusion (depending on if tests were performed during normal working hours) to test antibiotic susceptibility.[192] Seven of the eight laboratories using the BSAC method reported using the latest breakpoints during the study period. The remaining laboratory used an earlier version (version 10). Vitek 2 software uses EUCAST v1.1 (2010) breakpoints. During the study, two laboratories switched from using the BSAC method to a breakpoint technique.

The CLSI breakpoints for ceftazidime (one of the four 3GC tested) changed in 2010 and this change was implemented in automated systems between 2012 and 2013. In 2012, no laboratories in the West Midlands reported using CLSI

breakpoints for this antibiotic. The methods used may have changed from 2012 to 2014, which is a limitation of the percentage of 3GC reported. However, in our dataset, ceftazidime resistance constituted a fraction of what is reported as third-generation cephalosporin resistance (33% of 3GCs tests for *Klebsiella* and 19% for *E. coli*) and there was no stepwise increase nor decrease in the percentage of urinary *E. coli* and *Klebsiella* resistant to cefazidime in any of the West Midlands laboratories. In addition, across all laboratories providing services to non-teaching hospitals in the region, 50% of urine samples come from the community with LTCFs sending samples to their closest laboratory rather than having a specific managed contract with one laboratory within the region. Bacteria that were either fully resistant or intermediately resistant to a particular antibiotic were considered resistant.

Cleaning of the organism-antibiotic combinations

Of the overall dataset, 249,567 tests were carried out on urine samples (from urine or kidney body sites). National guidelines from Public Health England state that urine specimens in older people (>65 years) should only be sent for culture if two or more signs of infection are present. Therefore, all urine samples were assumed to be submitted due to clinical need and, therefore, were indicative of a suspected UTI.[49,50] The dataset did not contain sufficient clinical information to identify urine samples from catheters or distinguish between UTIs and asymptomatic bacteriuria, common in the elderly population, and, in particular, amongst those residing in LTCFs.[193]

The tests carried out on urine samples were further subdivided by bacterium-antibiotic combinations. Following the Department of Health's Five Year Antimicrobial Resistance Strategy recommendations[31] and expert opinion, *E. coli* and *Klebsiella* that were tested against key antibiotics were selected for analysis (see Table 4-2 and Table 4-3). The resistance of *Klebsiella* and *E. coli* urine samples to key antibiotic treatments in the community (trimethoprim and nitrofurantoin) and markers for important resistance profiles (3GCs (ceftazidime, cefpodoxime, cefotaxime, or ceftriaxone), ciprofloxacin, and carbapenems (imipenem or meropenem)) were included for full analysis. Trimethoprim and nitrofurantoin are recommended as first-line treatments for UTI;[194] therefore,

resistance to these agents can result in treatment failure, hospitalisation, and the subsequent use of antibiotics such as ciprofloxacin or 3GCs that should be reserved for the treatment of more serious infections. Although they were not included in the drug-bug combinations highlighted by the Chief Medical Officer[31], the reduction of inappropriate antibiotic prescribing for UTIs in primary care is in fact one of the targets of the Quality Premium Scheme developed by NHS England for reducing gram-negative BSI[44]. This involves reducing the trimethoprim: nitrofurantoin prescribing ratio by 10% and reducing the number of trimethoprim prescriptions in patients aged 70 or older by 10% from 2015/2016 to 2017/2018.[44]

Table 4-2. Panel of antibiotic tests selected for *E. coli*. 1GC refers to first-generation cephalosporins, 2GC refers to second-generation cephalosporins, 3GC refers to third-generation cephalosporins.

Final antibiotic groups	Samples tested to any of the subcategory antibiotics (N)	Samples tested to any of the subcategory antibiotics (%)
Trimethoprim	171434	99.98
Nitrofurantoin	171130	99.80
3GC	148607	86.66
Co-amoxiclav	146833	85.63
1GC	141020	82.24
Amoxicillin/Ampicillin	138718	80.90
Ciprofloxacin	129206	75.35
Gentamicin	114707	66.89
Imipenem/Meropenem	69980	40.81
Piperacillin/Tazobactam	50857	29.66
2GC	57068	33.28
Temocillin	47023	27.42

Table 4-3. Panel of antibiotic tests selected for *Klebsiella*. 1GC refers to first-generation cephalosporins, 2GC refers to second-generation cephalosporins, 3GC refers to third-generation cephalosporins.

Final antibiotic groups	Samples tested to any of the subcategory antibiotics (N)	Samples tested to any of the subcategory antibiotics (%)
Trimethoprim	19267	99.96
1GC	16151	83.80
Ciprofloxacin	15950	82.75
Co-amoxiclav	15895	82.47
Gentamicin	15292	79.34
Nitrofurantoin	14052	72.91
3GC	13739	71.28
Imipenem/Meropenem	10624	55.12
Piperacillin/Tazobactam	9401	48.78
2GC	8488	44.04
Temocillin	6845	35.51

The percentage of samples that were tested against a particular antibiotic was calculated for each year in each laboratory in the West Midlands. Laboratory years in which fewer than 80% of samples were tested against a particular antibiotic were excluded from the analysis. This was in order to avoid biases surrounding rarely tested antibiotics (for example, temocillin). The final number of laboratories included for each bacterium-antibiotic combination are described below in Table 4-4.

Table 4-4. Number of laboratories included after cleaning per bacterium-antibiotic combination. 1GC refers to first-generation cephalosporins, 2GC refers to second-generation cephalosporins, 3GC refers to third-generation cephalosporins.

Organism	Antibiotic	Laboratories included (N)
Klebsiella	Trimethoprim	15
	Nitrofurantoin	14
	3GC	12
	Co-amoxiclav	14
	1GC	13
	Ciprofloxacin	11
	Gentamicin	12
	Imipenem/Meropenem	9
	Piperacillin/Tazobactam	9
	2GC	7
	Temocillin	5
E. coli	Trimethoprim	15
	Nitrofurantoin	15
	3GC	13
	Co-amoxiclav	13
	1GC	14
	Amoxicillin/Ampicillin	13
	Ciprofloxacin	9
	Gentamicin	11
	Imipenem/Meropenem	6
	Piperacillin/Tazobactam	5
	2GC	9
	Temocillin	4

Samples of the same bacterium-antibiotic combination from the same individual within a 28 day period were considered to be the same episode of infection. For

each bacterium-antibiotic combination, tests were de-duplicated to one per patient per infection period (28 day period) and the most resistant test from each individual was chosen from each infection period. When there was more than one resistant result from tests carried out on different dates, the first test date was selected.

Figure 4-3 shows the cleaning of the example bacterium-antibiotic combination *Klebsiella*-trimethoprim. In this example, more than 80% of samples were tested against trimethoprim in all laboratory years; therefore, no tests were eliminated. 1,450 *Klebsiella* tested against trimethoprim were considered duplicates and were eliminated.

Description of the overall dataset

There were 15 diagnostic laboratories in the West Midlands region testing routine microbiological samples, all of which reported to AmSurv during the study period (01/04/2010-31/03/2014). The overall dataset comprised 376,089 samples from 218,251 patients over 70 years of age. There were 8.6% of samples were from individuals residing in 750 LTCF-pc. Prior to de-duplication per infection period, the three most common tests were for *E. coli* (41.8%), *Staphylococcus* (28.7%) and *Klebsiella* (5.7%). Fifty seven percent of all tests were carried out on urine specimens. As shown in Figure 4-4, most *E. coli* and *Klebsiella* samples (91% and 85%, respectively) were urine samples (from urine or kidney body sites). 52% of samples were submitted by GPs and 48% by hospitals.

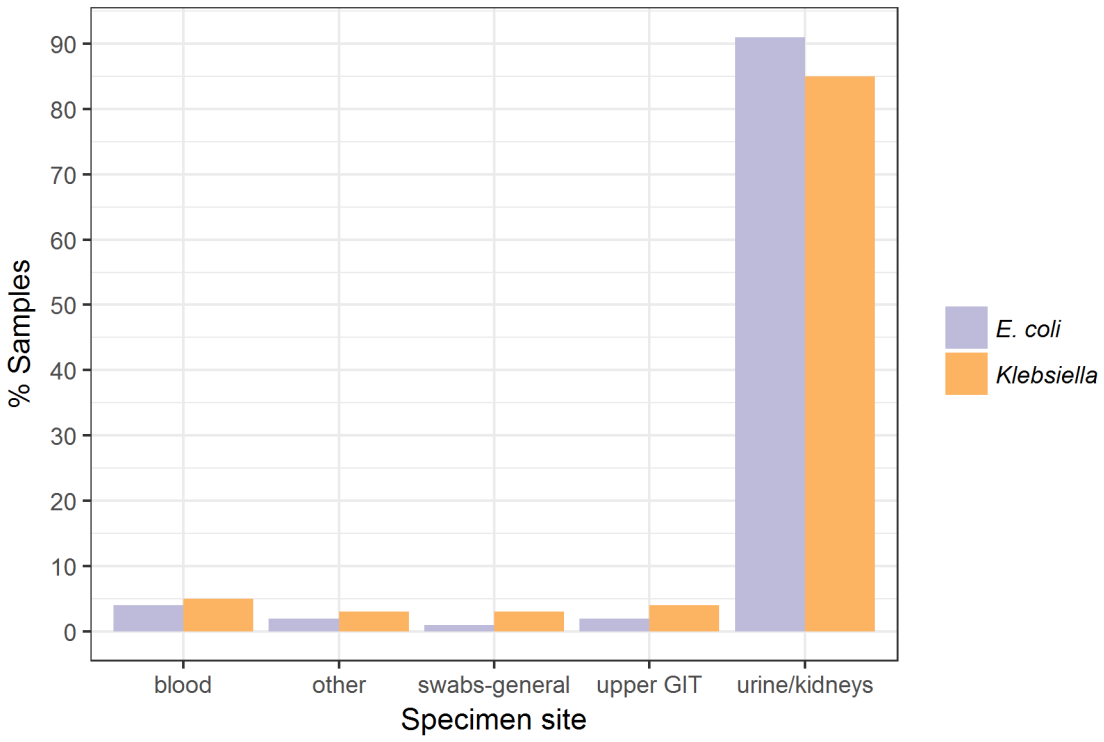

Figure 4-4. Distribution of samples per specimen site. Upper GIT refers to upper gastro-intestinal tract. The "other" specimen site category includes specimen sites labelled as bones and joints, brain and cerebral, cardiac, faeces and lower gut, fluids, genital, lower respiratory tract, tips and lines, tissue, upper respiratory tract/mouth/ear, unassigned class, and unknown class

Description of the urine dataset

There were 144,738 individuals over 70 years of age who had at least one positive urine specimen reported to the AmSurv database from any of the 15 diagnostic microbiology laboratories in the West Midlands region. 9.1% of samples were from individuals residing in 741 different LTCF-pc. 62% of samples were submitted to laboratories by GPs, whilst 38% were submitted by hospitals. As shown in Figure 4-5, the most commonly reported bacterium in the dataset was *E. coli* (57.2% samples). *Klebsiella* spp. accounted for 6.2% of the samples (of which 65% were *K. pneumoniae,* 19% *K. oxytoca,* and 15% other *Klebsiella* of undefined species).

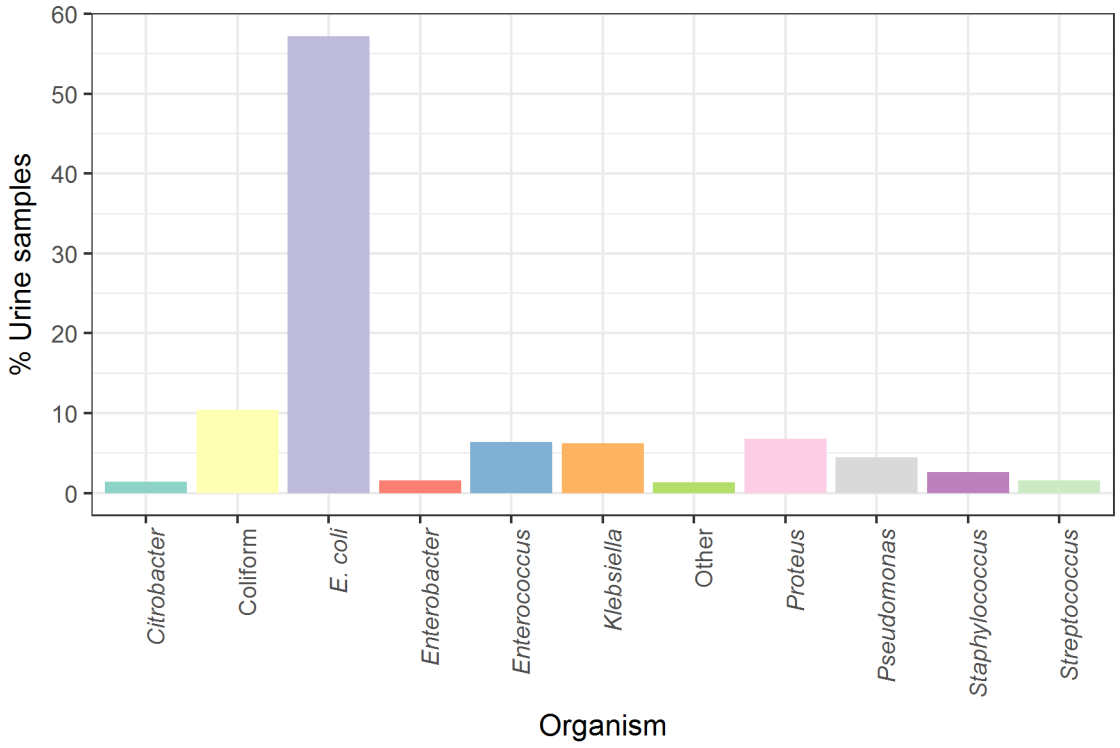

Figure 4-5. Distribution of urine samples by organism.

Description of urinary tract *E. coli* and *Klebsiella*

There were 171,475 urine *E. coli* samples and 19,279 urine *Klebsiella* samples (10% and 7%, respectively) from patients residing in LTCF-pc. The number of samples received per laboratory over the four years of the study is depicted in Figure 4-6 below.

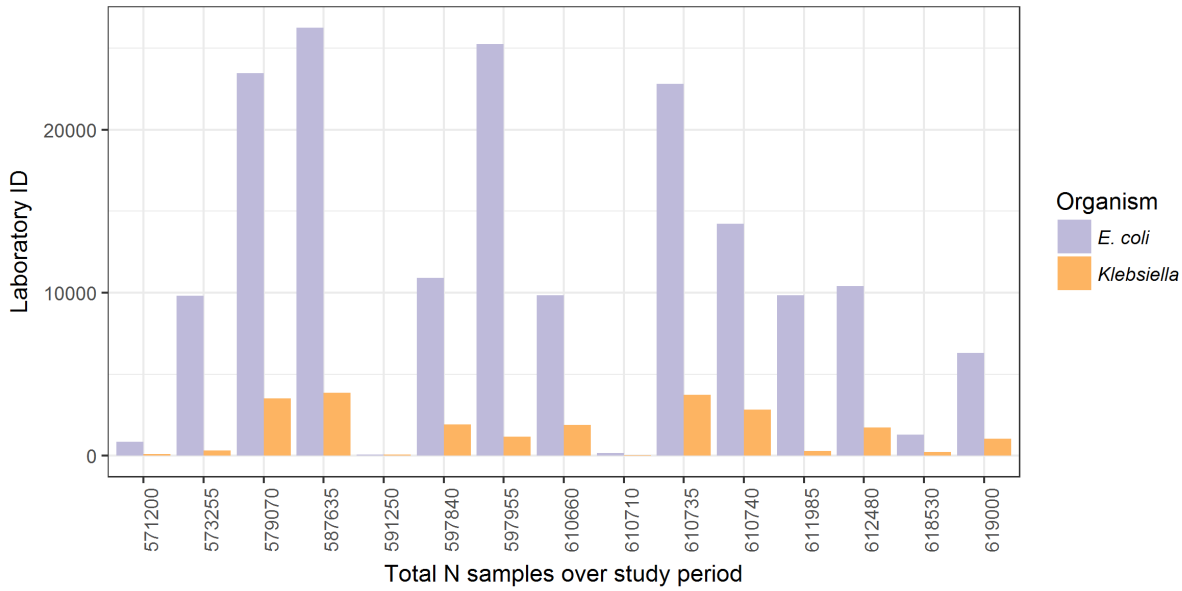

Figure 4-6. Total number of samples per laboratory over the four years of the study. Laboratory 571200 closed during years 3 and 4. Laboratory 610710 received fewer samples as it did not receive community samples. Laboratory 591250 did not receive any samples in year 1.

The size of the LTCFs that were matched to urine samples reported to AmSurv and the size of LTCFs in the Care Quality Commission registry overall (matched and unmatched) was similar (see Table 4-5 below).

Table 4-5. Number of beds in LTCFs in the Care Quality commission dataset compared to those that were matched to urine specimens in the AmSurv dataset.

	Care Quality Commission LTCFs	AmSurv LTCFs
Mean number of beds in LTCFs	34.47	36.66
Median number of beds in LTCFs	31	33
Range beds in LTCFs	1-171	1-214
% LTCFs under 20 beds	18 (146/797)	16.2 (120/741)
% LTCFs under 10 beds	4 (31/797)	2.16 (16/741)

The number of samples per patient, the age and the percentage of samples sent by GPs (vs. hospitals) did not vary greatly across different bacterium-antibiotic combinations (see Table 4-6 and Table 4-7). The percentage of samples from individuals residing in LTCF-pc varied from 5-10%. The number of samples per bed is shown in Table 4-8.

Table 4-6. Main characteristics of each bacterium-antibiotic combination. 1GC refers to first-generation cephalosporins, 2GC refers to second-generation cephalosporins, 3GC refers to third-generation cephalosporins.

Organism	Antibiotic	N samples/ tests	N patients	N samples per patient (mean, median, min, max)				Patient age (mean, median, min, max)				N postcodes
Klebsiella	Trimethoprim	17844	13245	1.35	1	1	16	81.23	81	70	106	10458
	Nitrofurantoin	12159	9002	1.35	1	1	16	81.31	81	70	105	7300
	3GC	11593	8777	1.32	1	1	13	81.12	81	70	106	7059
	Co-amoxiclav	14360	10755	1.34	1	1	16	81.25	81	70	106	8500
	1GC	14436	10844	1.33	1	1	16	81.26	81	70	106	8625
	Ciprofloxacin	13738	10262	1.34	1	1	16	81.18	81	70	106	8138
	Gentamicin	13003	9787	1.33	1	1	16	81.13	81	70	106	7852
	Imipenem/ Meropenem	8397	6368	1.32	1	1	12	81.09	81	70	106	5089
	Piperacillin/ Tazobactam	7542	5795	1.3	1	1	11	81.12	81	70	103	4685
	2GC	7384	5657	1.31	1	1	12	81.07	81	70	106	4528
	Temocillin	6314	4820	1.31	1	1	12	81	81	70	106	3806
E. coli	Trimethoprim	158764	96340	1.65	1	1	27	81.15	81	70	113	47742

Organism	Antibiotic	N samples/ tests	N patients	N samples per patient (mean, median, min, max)				Patient age (mean, median, min, max)				N postcodes
E. coli	Nitrofurantoin	158501	96211	1.65	1	1	27	81.15	81	70	113	47705
	3GC	134957	82146	1.64	1	1	27	81.2	81	70	113	41967
	Co-amoxiclav	128842	79307	1.62	1	1	27	81.14	81	70	113	39472
	1GC	126190	78984	1.6	1	1	27	81.15	81	70	113	40200
	Amoxicillin/ Ampicillin	126897	80365	1.58	1	1	27	81.13	81	70	113	40854
	Ciprofloxacin	111220	66540	1.67	1	1	27	81.06	81	70	113	32813
	Gentamicin	99410	63876	1.56	1	1	27	81.07	81	70	113	33754
	Imipenem/ Meropenem	50718	33240	1.53	1	1	27	80.94	80	70	113	17110
	Piperacillin/ Tazobactam	35648	24912	1.43	1	1	15	80.91	80	70	113	14211
	2GC	51386	33637	1.53	1	1	27	81.12	81	70	113	17981
	Temocillin	43348	28147	1.54	1	1	26	81	80	70	113	14155

Table 4-7. LTCF characteristics of each bacterium-antibiotic combination.

Organism	Antibiotic	N LTCFs	% samples/tests from LTCFs	% samples sent from GPs (vs. hospitals)	% LTCF samples sent from GPs (vs. hospitals)	% non-LTCF samples sent from GPs (vs. hospitals)
Klebsiella	Trimethoprim	383	7	63.8	77.1	62.8
	Nitrofurantoin	285	8	64.3	77.7	63.2
	3GC	257	7	61.6	74.3	60.7
	Co-amoxiclav	315	7	63.9	76.3	63
	1GC	335	7	64	76.1	63.1
	Ciprofloxacin	285	7	62.4	75.2	61.5
	Gentamicin	269	6	62.5	75.1	61.6
	Imipenem/ Meropenem	170	6	60.8	70.6	60.2
	Piperacillin/ Tazobactam	163	6	59.8	69.7	59.2
	2GC	150	6	61.6	71.8	60.9
	Temocillin	111	5	62.6	73.7	62
E. coli	Trimethoprim	715	10	67.3	75.2	66.4
	Nitrofurantoin	715	10	67.3	75.3	66.4
	3GC	673	10	67.3	74.9	66.4

Organism	Antibiotic	N LTCFs	% samples/tests from LTCFs	% samples sent from GPs (vs. hospitals)	% LTCF samples sent from GPs (vs. hospitals)	% non-LTCF samples sent from GPs (vs. hospitals)
E. coli	Co-amoxiclav	626	10	67.2	75.1	66.3
	1GC	670	10	67	75.7	66
	Amoxicillin/ Ampicillin	645	10	68.2	76.1	67.4
	Ciprofloxacin	464	9	66.3	74.2	65.5
	Gentamicin	548	9	66.9	72.7	66.3
	Imipenem/ Meropenem	273	8	66.8	72	66.4
	Piperacillin/ Tazobactam	237	8	66	70.9	65.6
	2GC	382	9	66.8	73	66.2
	Temocillin	185	8	67.9	73.7	67.4

Table 4-8. Number of samples per bed in LTCFs

Organism	Antibiotic	N LTCFs	Number of samples per bed in LTCFs (mean, median, min, max)			
Klebsiella	Trimethoprim	383	0.1	0.06	0.01	2
	Nitrofurantoin	285	0.1	0.06	0.01	2
	3GC	257	0.09	0.05	0.01	0.88
	Co-amoxiclav	315	0.1	0.06	0.01	2
	1GC	335	0.09	0.06	0.01	2
	Ciprofloxacin	285	0.09	0.06	0.01	0.88
	Gentamicin	269	0.09	0.06	0.01	0.88
	Imipenem/Meropenem	170	0.09	0.05	0.01	0.88
	Piperacillin/Tazobactam	163	0.08	0.05	0.01	0.88
	2GC	150	0.09	0.05	0.01	0.88
	Temocillin	111	0.09	0.05	0.01	0.88
E. coli	Trimethoprim	715	0.68	0.48	0.02	7.33
	Nitrofurantoin	715	0.68	0.48	0.02	7.33
	3GC	673	0.61	0.38	0.01	7.33
	Co-amoxiclav	626	0.64	0.43	0.01	7.33
	1GC	670	0.59	0.36	0.02	7.33

Organism	Antibiotic	N LTCFs	Number of samples per bed in LTCFs (mean, median, min, max)			
E. coli	Amoxicillin/Ampicillin	645	0.6	0.4	0.02	7.33
	Ciprofloxacin	464	0.68	0.5	0.01	6
	Gentamicin	548	0.48	0.3	0.01	6
	Imipenem/Meropenem	273	0.48	0.25	0.01	6
	Piperacillin/Tazobactam	237	0.39	0.25	0.01	6
	2GC	382	0.37	0.18	0.01	6
	Temocillin	185	0.59	0.35	0.01	6

The distribution of *Klebsiella* species per antibiotic tested is described in Table 4-9.

Table 4-9. Distribution of *Klebsiella* samples tested by species for each antibiotic selected. 1GC refers to first-generation cephalosporins, 2GC refers to second-generation cephalosporins, 3GC refers to third-generation cephalosporins.

Organism	Antibiotic	% *K. pneumoniae*	% *K. oxytoca*	% other *Klebsiella* spp.
Klebsiella	Trimethoprim	64.2	18.8	14
	Nitrofurantoin	58.5	18.6	20
	3GC	70	19.5	7.1
	Co-amoxiclav	66.4	18.7	12.4
	1GC	64.1	18.6	14.8
	Ciprofloxacin	62.1	17	17.8
	Gentamicin	64.1	17	15.9
	Imipenem/Meropenem	76.4	19.5	1.1
	Piperacillin/Tazobactam	76.3	19.8	1
	2GC	76.4	19.4	1.1
	Temocillin	76.8	19.2	1.2

Table 4-10 shows the distribution of 1GCs, 2GCs, 3GCs, imipenem/meropenem tested against *E. coli* and *Klebsiella* and amoxicillin/ampicillin tested against *E. coli.*

Table 4-10. Distribution of antibiotics tested against *E. coli* and *Klebsiella* where the precise antibiotic was not specified. 1GC refers to first-generation cephalosporins, 2GC refers to second-generation cephalosporins, 3GC refers to third-generation cephalosporins.

Organism	Antibiotic	Antibiotics tested
Klebsiella	1GC	Cephalexin (99.9%), Cephalothin (0.08%)
	3GC	Cefpodoxime (35.3%), Ceftazidime (32.8%), Cefotaxime (31.8%), Ceftriaxone (0.02%)
	2GC	Cefuroxime (100%)
	Imipenem/Meropenem	Meropenem (98.6%), Imipenem (1.4%)
E. coli	1GC	Cephalexin (99.96%), Cephalothin (0.04%)
	2GC	Cefuroxime (100%)
	3GC	Cefpodoxime (62.8%), Ceftazidime (18.7%), Cefotaxime (18.5%), Ceftriaxone (0.007%)
	Imipenem/Meropenem	Meropenem (99.99%), Imipenem (0.006%)
	Amoxicillin/Ampicillin	Amoxicillin (38.4%), Ampicillin (33%), Ampicillin/amoxicillin (28.5%)

Table 4-11 describes the characteristics of *E. coli* and *Klebsiella* in LTCF samples and non-LTCF samples. LTCF samples were more frequently reported from very elderly age groups (>85) than non-LTCF samples. Overall, most samples were from female residents. This difference in gender was greater for LTCF samples than for non-LTCF samples. Slightly more LTCF samples were from residential LTCFs than nursing LTCFs. The number of samples increased during the study period. LTCF samples (and non-LTCF samples) comprised samples both sent by GPs and hospitals (e.g. during a LTCF resident's hospital stay). LTCF samples were more frequently sent by GPs (versus hospitals) than non-LTCF samples.

Table 4-11. Characteristics of urine *E. coli* and *Klebsiella* positive samples.

		LTCF *E. coli* samples (N=17,022) N(%)	Non-LTCF *E. coli* samples (N=154,453) N(%)	LTCF *Klebsiella* samples (N=1,510) N(%)	Non-LTCF *Klebsiella* samples (N=21,262) N(%)
Age	Age 70-74	807 (4.7%)	34,984 (22.7%)	91 (6.0%)	4,621 (21.7%)
	Age 75-80	2,038 (12.0%)	45,300 (29.3%)	222 (14.7%)	6,445 (30.3%)
	Age 81-85	3,573 (21.0%)	35,178 (22.8%)	308 (20.4%)	5,034 (23.7%)
	Age >85	10,604 (62.3%)	38,991 (25.2%)	889 (58.9%)	5,162 (24.3%)
Gender	Female	14,406 (85.0%)	124,547 (80.7%)	1,080 (71.8%)	13,150 (61.9%)
	Male	2,545 (15.0%)	29,753 (19.3%)	425 (28.2%)	8,094 (38.1%)
LTCF type	Residential	10,139 (59.6%)	N/A	823 (54.5%)	N/A
	Nursing	6,883 (40.4%)	N/A	687 (45.5%)	N/A
Year of study	Year 1	2,541 (14.9%)	25,220 (16.3%)	247 (16.4%)	3,615 (17.0%)
	Year 2	3,958 (23.3%)	33,396 (21.6%)	337 (22.3%)	4,926 (23.2%)
	Year 3	4,911 (28.8%)	43,784 (28.4%)	414 (27.4%)	6,007 (28.3%)
	Year 4	5,612 (33.0%)	52,053 (33.7%)	512 (33.9%)	6,714 (31.6%)
Sender	GP	12,571 (74.1%)	99,727 (64.9%)	1,033 (68.5%)	11,369 (53.5%)
	Hospital	4,396 (25.9%)	54,011 (35.1%)	475 (31.5%)	9,872 (46.5%)

In order to assess the quality of LTCF matching by postcode, the household size per postcode using data from the Office for National Statistics (ONS) that

described the number of households per postcodes was analysed. Of the ONS postcodes that matched a LTCF in our dataset, the number of households in the postcode ranged from 0 to 91 (mean=19.2, median=16) (see Figure 4-7). Zero household postcodes were those classed by the ONS as “communal establishment only”. They are used in the subsequent chapter (Chapter 5) as a sensitivity analysis for inferring LTCF residence from patient postcodes.

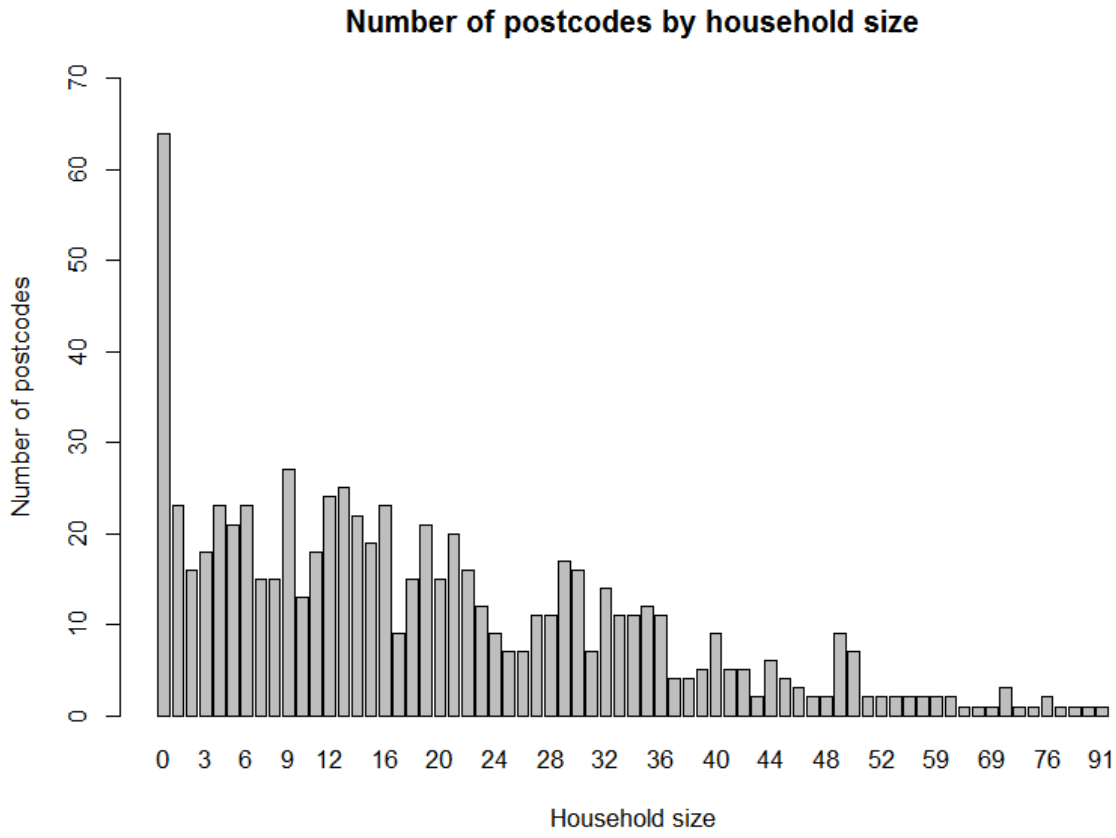

Figure 4-7. Distribution of household size of LTCF postcodes that matched ONS postcodes. Zero household postcodes were those that contained only communal establishments.

Discussion

AmSurv is a complex surveillance dataset comprising susceptibility tests carried out on specimens sent to participating laboratories in England. The subset of AmSurv analysed in this thesis includes only specimens taken from individuals aged 70 or older residing, and sent to laboratories, in the West Midlands. Most *E. coli* and *Klebsiella* samples (91% and 85%, respectively) were urine samples (from urine or kidney body sites). Conversely, of all urine samples, the most commonly reported bacterium was *E. coli* (57.2% samples, N=171,475), and *Klebsiella* accounted for 6.2% of samples (N=19,279).

The size of LTCFs for older people in the West Midlands registered in the CQC dataset varied greatly, ranging from 1 to 171 beds (mean=34.47 beds). These comprised both nursing and residential LTCFs.

The initial descriptive analysis of the AmSurv dataset revealed differences in age, sex, and sender (GP vs. hospital) when comparing LTCF to non-LTCF samples. Most samples were taken from females, which is in line with the literature which suggests that females are at a higher risk of developing UTIs[36]. In addition, a higher proportion of the female population over 65 years of age resides in LTCFs (4.2% in 2011) compared to males (1.9% in 2011).[195] This also explains that the difference in gender was greater for LTCF samples than for non-LTCF samples. LTCF samples were more frequently reported from very elderly age groups (>85) than non-LTCF samples. This could be due to a higher proportion of the eldest population being female, and a higher proportion of the eldest population living in LTCFs.[195]

LTCF samples (and non-LTCF samples) comprised samples both sent by GPs and hospitals (e.g. during a LTCF resident's hospital stay). LTCF samples were more frequently sent by GPs (versus hospitals) than non-LTCF samples. In addition, the number of samples increased during the study period, which was only to a small extent reflective of the increase in the 70+ population in the West Midlands during that period. Crudely, LTCF *E. coli* samples increased by 120.9%, non-LTCF *E. coli* samples increased by 106.4%, LTCF *Klebsiella* samples increased by 107.3%, and non-LTCF *Klebsiella* samples increased by

85.7% from the first year of the study (2010/2011) to the last year of the study (2013/2014). In contrast, the 70+ population in the West Midlands increased by 8.2% from 2010 to 2014.

This increase is analysed in more detail in Chapter 6. The differences in age, sex, year of study and sender were taken into account when determining differences in AMR for samples from LTCF/non-LTCF residents (Chapter 5).

The major strengths of this dataset are, firstly, that since 2012, all 15 laboratories in the West Midlands report to AmSurv, making data from this region the most complete source of AMR data and providing insight into the burden and temporal changes of AMR within a defined population. Secondly, matching patient postcodes to LTCF postcodes registered by the national regulator of health and social care in England has allowed the development of unprecedented knowledge of AMR in this setting over four years. Thirdly, the AmSurv surveillance system collects routine diagnostic samples from both community and hospital settings, permitting a fuller understanding of AMR in the population than other surveillance systems such as the mandatory surveillance for BSIs.

There were, however, a number of limitations associated with using a large surveillance dataset. Firstly, the dataset did not contain sufficient clinical information to identify urine samples from catheters or distinguish between UTIs and asymptomatic bacteriuria, common in the elderly population in particular amongst those residing in LTCFs.[193] However, clinical guidelines emphasise that only urinary samples from patients with a clinically suspected UTI, and either a risk factor for resistance or a history of UTIs should be sent for laboratory testing, and that catheter samples should not be sent.[196,197] This dataset only included urine specimens positive for bacterial growth. Separately, there is evidence for variation in the rate of submission of community samples from GPs to laboratories.[198] This is an unquantified potential confounder; however, this variation should be less pronounced in older populations, as English national guidance advocates sampling all patients over 65 years old

with two or more signs of UTI.[199] Sampling may be biased towards those failing to respond to treatment, which could increase the apparent risk of resistance.

Another limitation is that the threshold to diagnose UTIs might be lower in LTCFs as staff might notice UTI symptoms earlier than would otherwise be detected in individuals living in their own homes. Also, cognitive impairment was not recorded. Therefore, the analysis could not take into account differences in this condition in the two populations, which may lower the diagnosis threshold due to the inability of patients to verbalise symptoms. A recent report by the Alzheimer's society showed that the prevalence of dementia was 73% in nursing home residents and 57.9% in residential homes.[200] In the CQC dataset used for matching by postcode to the AmSurv dataset, 64.7% (516/797) LTCFs were classified as "Dementia service user band", indicating they provided care to patients suffering with dementia. These difficulties in diagnosing UTIs could lead to more samples being sent.

The study also is limited by the *in vitro* measurement of resistance, which does not always equate to clinical failure. It should also be noted that different breakpoints for ceftazidime (one of the four 3GC tested) and co-amoxiclav may have been used during the time period. This is described in more detail in the subsequent chapter.

In addition, susceptibility to carbapenems were only tested routinely in very few laboratories, giving a less precise estimate of resistance for the bacteria causing these infections (nine laboratories were included in the analysis of *Klebsiella* resistance to imipenem/meropenem and six in the analysis of *E. coli* resistance to imipenem/meropenem). A recent study found that carbapenemase-producing *Enterobacteriaceae* increased in the West Midlands from 2009 to 2014.[201]

A 28 day infection period was used to de-duplicate repeat specimens taken for the same infection. This was to prevent repeated samples from the same UTI period to be incorrectly interpreted as recurrences, whilst still capturing true UTI

recurrences. The 28 day estimate was based on expert opinion and could also be subject to error.

The prevalence of resistance to rarely tested antibiotics is likely to be high and not representative of the real prevalence of resistance, as these tests are likely to be carried out after treatment failure. In order to avoid this bias, the laboratory years in which less than 80% of samples were tested against a particular antibiotic were excluded from the analysis. This was also informed by expert opinion and subject to error.

We inferred LTCF residence from patient postcodes. While the methodology presented has been employed previously in other studies [9,69] , it does introduce a risk of bias. Whilst those living in non-LTCF postcodes are highly unlikely to be LTCF residents, a proportion of those living in LTCF postcodes will live in the community in neighbouring households. This means that the prevalence of resistance for LTCFs is likely to be slightly underestimated. To address this, as described in the subsequent chapter, a sensitivity analysis was carried out using the more specific postcodes that contained only communal establishments (the 64 postcodes that contained zero households in the first bar of Figure 4-7).

The CLSI breakpoints for ceftazidime (one of the four 3GC tested) changed in 2010 and this change was implemented in automated systems between 2012 and 2013, which could have influenced the trend in antibiotic resistance for 3GCs in this study. However, this did not appear to be the case. This is discussed in more detail in the methods section. In addition, some laboratories used the systemic rather than UTI breakpoint guidelines for co-amoxiclav, which resulted in an increase in the percentage of resistant samples between mid-2011 and early 2012.

Conclusions

This is the first study to link the West Midlands AmSurv dataset to the CQC register of LTCFs in England. The subset of AmSurv analysed included all antibiotic tests carried out in laboratories in the West Midlands on routinely collected microbiological specimens taken from individuals aged 70 or older by GPs or in hospitals from April 2010 to March 2014, providing susceptibility data from a population of 700,000 individuals over the age of 70. Of all urine samples, the most commonly reported bacterium was *E. coli* (57.2% samples, N=171,475), and *Klebsiella* accounted for 6.2% of samples (N=19,279). LTCF samples were more frequently reported from very elderly age groups (>85), from females, and were more frequently sent by GPs (versus hospitals) than non-LTCF samples. The number of samples reported also increased during the study period. There are a number of limitations of this dataset, such as a lack of clinical information available from patients from which samples were taken (for example, symptoms, catheterisation, and cognitive impairment were not recorded). LTCF residence was also inferred from patient postcode, which will have over-estimated the number of individuals assumed to reside in LTCFs. In addition, sampling may be biased towards those failing to respond to treatment, which could increase the apparent risk of resistance. However, this dataset also is the first to provide insight into the burden and temporal changes of AMR in LTCFs in England within a large population.

Chapter 5 Impact of LTCF residence on the antibiotic resistance of urinary tract *E. coli* and *Klebsiella*

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Aim

To compare the frequency of antibiotic resistance in urinary tract bacteria from residents of LTCFs for older people and adults aged over 70 or older living in the community.

Introduction

As explained in Chapter 1, the AMR of urinary tract bacteria is thought to be an important problem in the LTCF setting. Due to their frailty and frequent co-morbidities, LTCF residents are at increased risk of infection and hospitalisation compared to elderly individuals living in their own homes.[7–10] In addition, LTCFs provide opportunities for the transmission of infectious diseases through the sharing of objects and spaces. Infection control in these facilities is also challenging due to the poor coordination of medical care.[62] Due to the frequency of infection in LTCF residents, these individuals may be frequently exposed to antibiotics, which may select for antibiotic resistant strains. UTIs are common in older people, particularly in those residing in LTCFs, where they are the joint most common type of infection together with RTI. UTIs are frequently caused by Gram-negative bacteria such as *E. coli* and *Klebsiella*. AMR *E. coli* and *Klebsiella* have been identified as organisms of particular public health concern by the WHO and the Chief Medical Officer for England.[30,31]

In spite of this, AMR infections are not routinely surveyed in LTCFs. Little is known about the antibiotic susceptibility of bacterial isolates from LTCF residents in England due to the difficulty in identifying these individuals in healthcare data in general and in AMR data in particular. This chapter aims to compare the frequency of antibiotic resistance in urinary tract bacteria from residents of LTCFs for older people and elderly adults living in the community.

As highlighted in Chapter 1, only one study analysed the prevalence of carriage of antibiotic resistant Gram-negative bacteria in LTCFs in England. This study found a high prevalence of carriage of ESBL-producing *E. coli* in a LTCF of 105 beds in Cambridgeshire during 2014.[67] Other studies set in other countries have also found a high prevalence of colonisation with AMR Gram-negative bacteria in LTCFs. [70–74]

In addition, several small studies have aimed to compare the prevalence of AMR in urinary isolates in individuals residing in LTCFs and in older people living in their own homes in Ireland (2132 urine isolates), Norway (3786 urine isolates), Australia (4262 urine isolates) and Scotland (45 isolates), using either GP or hospital data, but not both.[75–78] This comparison has not been made using both types of samples, in a large population, nor in England, where resistance patterns in LTCFs could be different.

Chapter 4 outlined the characteristics of the West Midlands AmSurv dataset that was linked to the CQC dataset to address this problem. LTCF samples were more commonly reported from older age groups and females, and more often sent by GPs (vs. hospitals) compared to non-LTCF samples. In addition, the number of *E. coli* and *Klebsiella* samples sent to AmSurv appeared to increase by year of the study. These variables were, therefore, included as co-variates when comparing AMR in LTCF and non-LTCF samples.

Methods

The dataset used for analysis in this chapter is introduced in Chapter 4. The West Midlands AmSurv dataset, which included all antibiotic tests carried out in laboratories in the West Midlands on routinely collected microbiological specimens taken from individuals aged 70 or older by GPs or in hospitals from April 2010 to March 2014, was linked to the CQC register of LTCFs in England in order to determine if patients from which the samples were taken were LTCF residents. Urine samples positive for *E. coli* and *Klebsiella* were selected for subsequent analysis in this chapter.

Crude rate comparisons

Positive urinary tract bacterial cultures with *E. coli* and *Klebsiella* reported to AmSurv were used as a surrogate for *E. coli* and *Klebsiella* UTI, as urinary tract specimens should only be sent to the microbiology laboratory when there is a clinical suspicion of a UTI.[49,50] *E. coli* and *Klebsiella* samples were grouped as these were the most common Gram-negative bacteria with similar antibiotic treatment. Samples containing *Proteus* species were not included as these bacteria are known to be intrinsically resistant to nitrofurantoin.[202] The rates of *E. coli* and *Klebsiella* UTI in LTCF-pc and in non-LTCF-pc were calculated as follows:

$$E.coli \text{ and } Klebsiella \text{ UTI rate in LTCF} - \text{pc} = \frac{\text{N } E.coli \text{ and } Klebsiella \text{ UTI in LTCF}-\text{pc per year in those aged } 70^{+} \text{ in the West Midlands}*}{\text{N beds in LTCFs per year}^{\wedge}}$$

$$E.coli \text{ and } Klebsiella \text{ UTI rate in non} - \text{LTCF} - \text{pc} = \frac{\text{N } E.coli \text{ and } Klebsiella \text{ UTI in non}-\text{LTCF}-\text{pc per year in those aged } 70^{+} \text{ in the West Midlands}*}{\text{N population aged } 70^{+} \text{ in the West Midlands per year}**-\text{N beds in LTCFs per year}^{\wedge}}$$

*Calculated for the year 2013/2014, de-duplicated to one sample per person per 28-day period

^Obtained from the national regulator of health and social care in England (Care Quality Commission) from April 2014 as described above.[152]

**Obtained from the population ONS estimate of mid-2014.[4]

The number of beds in each LTCF was used as an indicator of the number of person years in each LTCF, assuming full bed occupancy. Similarly, mid-year population estimates were used as an estimate of the number of person years in the population.

The denominator for the UTI rate in non-LTCF postcodes was calculated by subtracting the number of LTCF residents (using the number of beds in LTCFs per year as a proxy of the number of people in LTCFs) from the number of residents in the West Midlands that were aged 70+ (as per ONS data). This approximately equated to the number of 70+ individuals in the population that did not live in a LTCF.

The rates of UTI caused by resistant *E. coli* and *Klebsiella* were calculated using the same approach. Confidence intervals were calculated using the function epitab in the R package epitools which used normal approximation.[203]

Postcodes may cover several buildings; therefore, LTCF postcodes may also include some elderly people who are not LTCF residents. In the sensitivity analysis, the rates of *E. coli* and *Klebsiella* UTI in LTCFs were estimated using only data from LTCF postcodes that were classified by the ONS as "communal establishment only" postcodes (LTCF CE-pc) (see Chapter 4).

Comparison of resistance levels in culture confirmed samples

Logistic regression models coded in the rms package in R were used to calculate the odds of resistance for bacteria in LTCF samples compared to non-LTCF samples.[204] Further analyses compared nursing and residential LTCFs. Age group (70-74, 75-80, 81-85, and >85), sex, and sender (GP versus hospital) were included in the model as categorical covariates because they were shown to differ in LTCF samples compared to non-LTCF samples (see Chapter 4), and are plausible risk factors of antibiotic resistance in urinary tract bacteria. In Chapter 4, it was also noted that the number of samples increased each year of study. The year of the study was, therefore, also included as a categorical covariate in the model (2010/2011, 2011/2012, 2012/2013, and 2013/2014).

Both univariable and multivariable analyses were undertaken. No interactions between the model variables improved model fit, assessed using the Akaike information criterion (AIC); therefore, they were not included in the final model (see Table 5-1 and Table 5-2). The non-independence of samples in the same postcode (and, therefore, in the same LTCF) was accounted for by adjusting the standard errors using a clustering term in the robcov function. [205]

The robcov function of the rms package computes the Huber robust covariance matrix estimator with an adjustment for clustering:

$$H_c = I^{-1}(b)[\sum_{i=1}^{c}\{(\sum_{j=1}^{n_i} U_{ij})(\sum_{j=1}^{n_i} U_{ij})'\}]I^{-1}(b),$$

Where c is the number of clusters, n_i is the number of observations in the ith cluster, U_{ij} is the contribution of the jth observation within the ith cluster to the score vector and $I(b)$ is the observed information matrix, computed in the same way as without the clusters.[205]

Table 5-1. Multivariable model fit with interactions. The largest interaction seen was between age and sender when examining the odds of *E. coli* resistance to ciprofloxacin, which decreased the AIC from 92,338.01 to 92,278.54 (0.064%). In these models LTCF residence was considered as binary (LTCF samples vs. non-LTCF samples).

Organism	Antibiotic	Age * LTCF AIC	Sex * LTCF AIC	Sender * LTCF AIC	Year * LTCF AIC	Sex * Age AIC	Sex * Sender AIC	Sex * Year AIC	Age * Sender AIC	Age * Year AIC	Sender * Year AIC
E. coli	Ciprofloxacin	92358.2	92355.7	92334.5	92366	92372.1	92369.2	92370.2	92308.4	92372.4	92371.2
	Carbapenems^	241.1	237.1	237.1	241.1	237.6	237	237.7	232.3	242.2	239.2
	Nitrofurantoin	52229.2	52222.4	52218.8	52234.3	52231	52228.7	52233.3	52224.3	52232.7	52235.9
	3GCs~	62596.6	62593.3	62596.3	62601.5	62593.4	62579.6	62596.1	62578.4	62601.9	62598.5
	Trimethoprim	207364	207363.6	207370.4	207356	207347.4	207326.7	207375.2	207354.4	207374	207378.1
Klebsiella	Ciprofloxacin	7512.1	7506.9	7509.6	7511.1	7511.6	7509	7500.8	7507.4	7517.1	7508.6
	Carbapenems^	210.8	206.3	208.5	210.2	207.7	208.2	210.2	211.5	212.4	209.8
	Nitrofurantoin	15492	15484.51	15485.2	15484.6	15490.5	15485.8	15486.5	15491.4	15479	15490.1
	3GCs~	5901.3	5896.9	5897.2	5897.8	5898.3	5896.8	5891.1	5899.8	5897	5899.3
	Trimethoprim	20435	20443	20438.1	20446.4	20433	20441.3	20440	20443.5	20452.4	20442.7

* Interaction between the terms

^ Imipenem or Meropenem

~ 3GCs, third-generation cephalosporins. 3GC resistance was defined as resistance to ceftazidime, cefpodoxime, cefotaxime, or ceftriaxone.

Table 5-2. Comparing the multivariable model fit with and without interactions. The final column shows the difference between the AIC (Akaike information criterion) from the multivariable model without interactions and the model with the lowest AIC for that bacterium-antibiotic combination. In these models LTCF residence was considered as binary (LTCF samples vs. non-LTCF samples).

Organism	Antibiotic	Normal AIC	Min AIC with interactions	Normal AIC -Min AIC
E. coli	Ciprofloxacin	92368.2	92308.4	59.8
	Carbapenems^	235.1	232.3	2.8
	Nitrofurantoin	52230.6	52218.8	11.8
	3GCs~	62597.5	62578.4	19.1
	Trimethoprim	207375.9	207326.7	49.3
Klebsiella	Ciprofloxacin	7507.9	7500.8	7.1
	Carbapenems^	207.3	206.3	1.1
	Nitrofurantoin	15486.2	15479	7.1
	3GCs~	5895.9	5891.1	4.8
	Trimethoprim	20441.4	20433	8.4

* Interaction between the terms

^ Imipenem or Meropenem

~ 3GCs, third-generation cephalosporins. 3GC resistance was defined as resistance to ceftazidime, cefpodoxime, cefotaxime, or ceftriaxone.

Rate of *E. coli* and *Klebsiella* UTI caused by AMR bacteria in LTCF and non-LTCF samples

The rate of laboratory confirmed *E. coli* and *Klebsiella* UTI was 20.6 per 100 person years in LTCF residents and 7.8 per 100 person years in community dwelling older adults; giving a rate ratio (RR) of 2.66 (95% CI=2.58-2.73) (see Table 5-3). In the sensitivity analysis, the rate of *E. coli* and *Klebsiella* UTI in the LTCFs located in CE-pc was similar (21.5 per 100 person years) giving a similar RR of 2.77 (95% CI=2.57-2.98) (see Table 5-4).

Table 5-3. Rate of *E. coli* and *Klebsiella* UTI and *E. coli* and *Klebsiella* UTI caused by antibiotic-resistant bacteria for LTCF and non-LTCF residents per 100 person years.

	LTCF rate	non-LTCF rate	rate ratio	95% CI
UTI^	20.6	7.8	2.7	2.6-2.7
UTI^ caused by bacteria resistant to trimethoprim	12.7	2.9	4.4	4.3-4.6
UTI^ caused by bacteria resistant to nitrofurantoin	1.7	0.4	4.4	4.0-4.8
UTI^ caused by bacteria resistant to ciprofloxacin^	3.3	0.6	5.2	4.8-5.6
UTI^ caused by bacteria resistant to third-generation cephalosporins~	1.8	0.4	4.5	4.1-4.9

^ Urinary tract *E. coli* and *Klebsiella* reported to AmSurv.

~ Third-generation cephalosporins. 3GC resistance was defined as resistance to ceftazidime, cefpodoxime, cefotaxime, or ceftriaxone.

Table 5-4. Sensitivity analysis for the rate of *E. coli* and *Klebsiella* UTI and *E. coli* and *Klebsiella* UTI caused by antibiotic-resistant bacteria per 100 person years for LTCF and non-LTCF residents. The LTCF rate was calculated using only data from LTCF postcodes that were classified by the ONS as "communal establishment only" postcodes (LTCF CE-pc).

	LTCF rate	non-LTCF rate	Rate ratio	95% CI
UTI^	21.5	7.8	2.77	2.57-2.98
UTI^ caused by bacteria resistant to trimethoprim	12.8	2.9	4.44	4.04-4.89
UTI^ caused by bacteria resistant to nitrofurantoin	1.9	0.4	4.82	3.77-6.16
UTI^ caused by bacteria resistant to ciprofloxacin^	5.0	0.6	7.88	6.76-9.19
UTI^ caused by bacteria resistant to 3GCs~	1.7	0.4	4.09	3.14-5.33

^Urinary tract *E. coli* and *Klebsiella* reported to AmSurv.

~ 3GCs, third-generation cephalosporins. 3GC resistance was defined as resistance to ceftazidime, cefpodoxime, cefotaxime, or ceftriaxone.

The largest difference in the rate of *E. coli* and *Klebsiella* UTI caused by resistant bacteria between LTCF and non-LTCF samples was seen for ciprofloxacin (RR=5.18, 95% CI=4.82-5.57). Large differences were also seen for trimethoprim resistance (RR=4.41, 95% CI=4.25-4.57), nitrofurantoin (RR=4.38, 95% CI=3.98-4.83) and third-generation cephalosporins (RR=4.49, 95% CI=4.08-4.94).

The sensitivity analysis yielded very similar findings (see Table 5-4). In the sensitivity analysis, LTCF residents had a higher rate of *E. coli* and *Klebsiella* UTI caused by bacteria that were resistant to ciprofloxacin (RR=7.88, 95% CI=6.76-9.19).

Prevalence of AMR and odds ratio of AMR

The prevalence of antibiotic resistance was higher in bacteria from LTCF samples than in non-LTCF samples for all bacterium-antibiotic combinations (Table 5-5 and Table 5-6). *E. coli* resistance to trimethoprim was 60% versus 37% (adjusted odds ratios (aORs)=2.36, 95% CI=2.21-2.53); nitrofurantoin 7% versus 4% (aOR=1.74, 95% CI=1.53-1.97); ciprofloxacin 29% versus 14% (aOR=2.42, 95% CI=2.17-2.69); and 3GCs 10% versus 6% (aOR=1.89, 95% CI=1.64-2.17). The prevalence of *Klebsiella* resistant to: trimethoprim was 41% versus 26% (aOR=1.89, 95% CI=1.6-2.24); nitrofurantoin 41% versus 34% (aOR=1.31, 95% CI=1.09-1.59); ciprofloxacin 10% versus 8% (aOR=1.54, 95% CI=1.13-2.1); and 3GCs 8% versus 7% (aOR=1.24, 95% CI=0.85-1.83). Further results of the univariate and multivariate results are shown in Appendix Chapter 5.

Table 5-5 Prevalence of antibiotic resistance in LTCF, non-LTCF, residential LTCF, and nursing LTCF samples.

Organism	Antibiotic	% resistance overall n/N(%)	% resistance LTCF samples n/N(%)	% resistance Res LTCF samples n/N(%)	% resistance Ns LTCF samples n/N(%)	% resistance non-LTCF samples n/N(%)
E. coli	Trimethoprim	61879/158764 (39.0%)	9513/15914 (59.8%)	5491/9438 (58.2%)	4022/6476 (62.1%)	52366/142850 (36.7%)
	Nitrofurantoin	6322/158501 (4.0%)	1059/15889 (6.7%)	571/9425 (6.1%)	488/6464 (7.6%)	5263/14261 2 (3.7%)
	Ciprofloxacin	16937/111220 (15.2%)	3075/10564 (29.1%)	1625/6100 (26.6%)	1450/4464 (32.5%)	13862/100656 (13.8%)
	3GCs~	8581/134957 (6.4%)	1412/13482 (10.5%)	791/8084 (9.8%)	621/5398 (11.5%)	7169/121475 (5.9%)
Klebsiella	Trimethoprim	4759/17844 (26.7%)	513/1257 (40.8%)	282/707 (39.9%)	231/550 (42.0%)	4246/16587 (25.6%)
	Nitrofurantoin	4232/12159 (34.8%)	377/916 (41.2%)	213/517 (41.2%)	164/399 (41.1%)	3855/11243 (34.3%)
	Ciprofloxacin	1105/13738 (8.0%)	95/918 (10.4%)	48/510 (9.4%)	47/408 (11.5%)	1010/12820 (7.9%)
	3GCs~	846/11593 (7.3%)	60/754 (8.0%)	29/430 (6.7%)	31/324 (9.6%)	786/10839 (7.3%)

~ 3GCs, third-generation cephalosporins. 3GC resistance was defined as resistance to ceftazidime, cefpodoxime, cefotaxime, or ceftriaxone.

Table 5-6. Unadjusted and adjusted odds ratio of antibiotic resistance in bacteria from LTCF samples compared to non-LTCF samples.

Organism	Antibiotic	uOR LTCF[#]	Adjusted 95%CI uOR LTCF	aOR LTCF[^]	Adjusted 95% CI aOR LTCF
E. coli	Trimethoprim	2.56	2.4 - 2.7	2.4	2.2 - 2.5
	Nitrofurantoin	1.86	1.6 - 2.1	1.7	1.5 - 2.0
	Ciprofloxacin	2.57	2.3 - 2.9	2.4	2.2 - 2.7
	3GCs[~]	1.86	1.6 - 2.1	1.9	1.6 - 2.2
Klebsiella	Trimethoprim	2.01	1.7 - 2.4	1.9	1.6 - 2.2
	Nitrofurantoin	1.34	1.1 - 1.6	1.3	1.1 - 1.6
	Ciprofloxacin	1.36	1.0 - 1.9	1.5	1.1 - 2.1
	3GCs[~]	1.1	0.8 - 1.6	1.2	0.9 - 1.8

[#]uOR LTCF is the unadjusted odds ratio (univariable analysis) of antibiotic resistance in bacteria from LTCF samples compared to non-LTCF samples with 95% CIs adjusted for clustering at the postcode level

[^]aOR LTCF is the adjusted OR**,** adjusted for age group, sex, year of study, and sender as categorical covariates of antibiotic resistance in bacteria from LTCF samples compared to non-LTCF samples with 95% CIs adjusted for clustering at the postcode level. Interactions were not included in the model as they did not improve model fit (see Table 5-1).

[~] 3GCs, third-generation cephalosporins. 3GC resistance was defined as resistance to ceftazidime, cefpodoxime, cefotaxime, or ceftriaxone.

After accounting for LTCF residence, age, sender, and year of study, sex was a significant contributor to antibiotic resistance across multiple bacteria-antibiotic combinations. *E. coli* isolated from samples sent from males had significantly higher odds of nitrofurantoin, ciprofloxacin, and 3GC resistance than females (adjusted odds ratio (aOR) 1.48, 95% CI 1.36-1.61; aOR 1.69, 95% CI 1.58-1.81; aOR 1.47, 95% CI 1.35-1.6; respectively). *Klebsiella* from male samples had significantly higher odds of ciprofloxacin and 3GC resistance than females (aOR 1.34, 95% CI 1.11-1.62; aOR 1.42, 95% CI 1.15-1.75; respectively).

After accounting for LTCF residence, sex, sender, and year of study, age only contributed significantly to antibiotic resistance in a small number of bacterium-antibiotic groups. The odds of *E. coli* resistance to trimethoprim, nitrofurantoin, and ciprofloxacin were higher in those over 85 years of age than in those aged

70-74 (aOR 1.28, 95% CI 1.22-1.34; aOR 1.34, 95% CI 1.19-1.51; aOR 1.35, 95% 1.24-1.47).

The odds of antibiotic resistance were higher in bacteria sent from hospitals than in samples sent from GPs with the exception of the odds of *Klebsiella* resistance to nitrofurantoin, which was lower in samples sent from hospitals than in those sent by GPs (aOR 0.85, 95% CI 0.78-0.93). The odds of *E. coli* resistant to ciprofloxacin and 3GCs were higher in samples sent from hospitals than in samples sent by GPs (aOR 1.11, 95% CI 1.06-1.16; aOR 1.36, 95% CI 1.29-1.45). The odds of *Klebsiella* resistant to ciprofloxacin and 3GCs were also significantly higher in samples from hospital (aOR 1.45, 95% CI 1.25-1.69; aOR 1.83, 95% CI 1.54-2.17).

Bacteria isolated from individuals residing in LTCFs with nursing support had higher levels of resistance to most antibiotics than those isolated from individuals living in residential LTCFs (see Table 5-5 and Table 5-7). Levels of antibiotic resistance were also higher in urinary tract bacteria from LTCF residents (obtained both from GPs and hospitals) than from hospitals (including samples from residents of LTCF-pc and non-LTCF-pc) (Table 5-8). The prevalence of *E. coli* resistant to trimethoprim, nitrofurantoin, ciprofloxacin and 3GCs was higher in LTCF samples than in samples sent from hospitals (60% versus 40%, 7% versus 4%, 29% versus 16%, and 11% versus 8%). The prevalence of *Klebsiella* resistant to trimethoprim and nitrofurantoin was also higher in LTCFs (41% versus 27% and 41% versus 32) but ciprofloxacin resistance was similar (10% versus 10%) and 3GCs resistance was higher in hospitals (8% versus 10%).

Table 5-7. Unadjusted and adjusted odds ratio of antibiotic resistance in bacteria from residential LTCF samples compared to non-LTCF samples and from nursing LTCF samples compared to non-LTCF samples.

Organism	Antibiotic	uOR residential LTCF[#]	Adjusted 95%CI uOR residential LTCF	aOR residential LTCF[^]	Adjusted 95% CI aOR residential LTCF	uOR nursing LTCF[##]	Adjusted 95%CI uOR nursing LTCF	aOR nursing LTCF[^^]	Adjusted 95% CI aOR nursing LTCF
E. coli	Trimethoprim	2.39	2.2 - 2.61	2.2	2.02 - 2.4	2.82	2.55 - 3.13	2.63	2.37 - 2.92
	Nitrofurantoin	1.68	1.43 - 1.99	1.59	1.35 - 1.87	2.12	1.78 - 2.53	1.95	1.64 - 2.33
	Ciprofloxacin	2.28	2 - 2.59	2.17	1.9 - 2.47	3.01	2.58 - 3.51	2.78	2.38 - 3.24
	3GCs[~]	1.73	1.45 - 2.06	1.76	1.47 - 2.1	2.07	1.69 - 2.55	2.09	1.7 - 2.56
Klebsiella	Trimethoprim	1.94	1.52 - 2.46	1.82	1.43 - 2.31	2.11	1.7 - 2.62	1.98	1.59 - 2.46
	Nitrofurantoin	1.35	1.05 - 1.72	1.31	1.02 - 1.68	1.33	1.02 - 1.75	1.31	1 - 1.73
	Ciprofloxacin	1.21	0.79 - 1.87	1.41	0.9 - 2.19	1.56	1.03 - 2.37	1.7	1.13 - 2.56
	3GCs[~]	0.9	0.57 - 1.41	1.06	0.67 - 1.68	1.37	0.75 - 2.49	1.47	0.81 - 2.67

[#]uOR residential LTCF is the unadjusted odds ratio (univariable analysis) of antibiotic resistance in bacteria from residential LTCF samples compared to non-LTCF samples, with 95% confidence intervals adjusted for clustering at the postcode level

[##]uOR nursing LTCF is the unadjusted odds ratio (univariable analysis) of antibiotic resistance in bacteria from nursing LTCF samples compared to non-LTCF samples, with 95% confidence intervals adjusted for clustering at the postcode level

[^]aOR residential LTCF is the adjusted OR**,** adjusted for age group, sex, year of study, and sender as categorical covariates of antibiotic resistance in bacteria from residential LTCF samples compared to non-LTCF samples, with 95% confidence intervals adjusted for clustering at the postcode level. Interactions were not included in the model as they did not improve model fit (see Table 5-1).

[^^]aOR nursing LTCF is the adjusted OR**,** adjusted for age group, sex, year of study, and sender as categorical covariates of antibiotic resistance in bacteria from nursing LTCF samples compared to non-LTCF samples, with 95% confidence intervals adjusted for clustering at the postcode level. Interactions were not included in the model as they did not improve model fit (see Table 5-1).

[~] 3GCs, third-generation cephalosporins. 3GC resistance was defined as resistance to ceftazidime, cefpodoxime, cefotaxime, or ceftriaxone.

Table 5-8. Prevalence of antibiotic resistance in urinary tract bacteria present in LTCF samples, in non-LTCF samples, in samples sent by GPs, and in samples sent from hospitals. Samples sent by GPs and from hospitals included both LTCF and non-LTCF samples, and vice-versa.

Organism	Antibiotic	% resistance samples overall n/N(%)	% resistance LTCF sample n/N(%)	% resistance non-LTCF samples n/N(%)	% resistance GP samples n/N(%)	% resistance hospital samples n/N(%)
E. coli	Trimethoprim	61879/158764 (38.98%)	9513/15914 (59.78%)	52366/142850 (36.66%)	41338/106779 (38.71%)	20243/51258 (39.49%)
	Nitrofurantoin	6322/158501 (3.99%)	1059/15889 (6.66%)	5263/142612 (3.69%)	4184/106645 (3.92%)	2111/51130 (4.13%)
	Ciprofloxacin	16937/111220 (15.23%)	3075/10564 (29.11%)	13862/100656 (13.77%)	10852/73720 (14.72%)	6085/37500 (16.23%)
	Third-generation cephalosporins~	8581/134957 (6.36%)	1412/13482 (10.47%)	7169/121475 (5.9%)	5187/90769 (5.71%)	3325/43466 (7.65%)
Klebsiella	Trimethoprim	4759/17844 (26.67%)	513/1257 (40.81%)	4246/16587 (25.6%)	3019/11379 (26.53%)	1721/6445 (26.7%)
	Nitrofurantoin	4232/12159 (34.81%)	377/916 (41.16%)	3855/11243 (34.29%)	2821/7822 (36.06%)	1402/4317 (32.48%)
	Ciprofloxacin	1105/13738 (8.04%)	95/918 (10.35%)	1010/12820 (7.88%)	591/8579 (6.89%)	497/5139 (9.67%)
	Third-generation cephalosporins~	846/11593 (7.3%)	60/754 (7.96%)	786/10839 (7.25%)	398/7137 (5.58%)	439/4436 (9.9%)

~ 3GC resistance was defined as resistance to ceftazidime, cefpodoxime, cefotaxime, or ceftriaxone.

There were differences in resistance to trimethoprim, nitrofurantoin, ciprofloxacin, and 3GCs over the study period for bacteria from LTCF samples and non-LTCF samples. These patterns are plotted in Figure 5-1. Resistance to other antibiotics are plotted in Figure 5-2 and Figure 5-3.

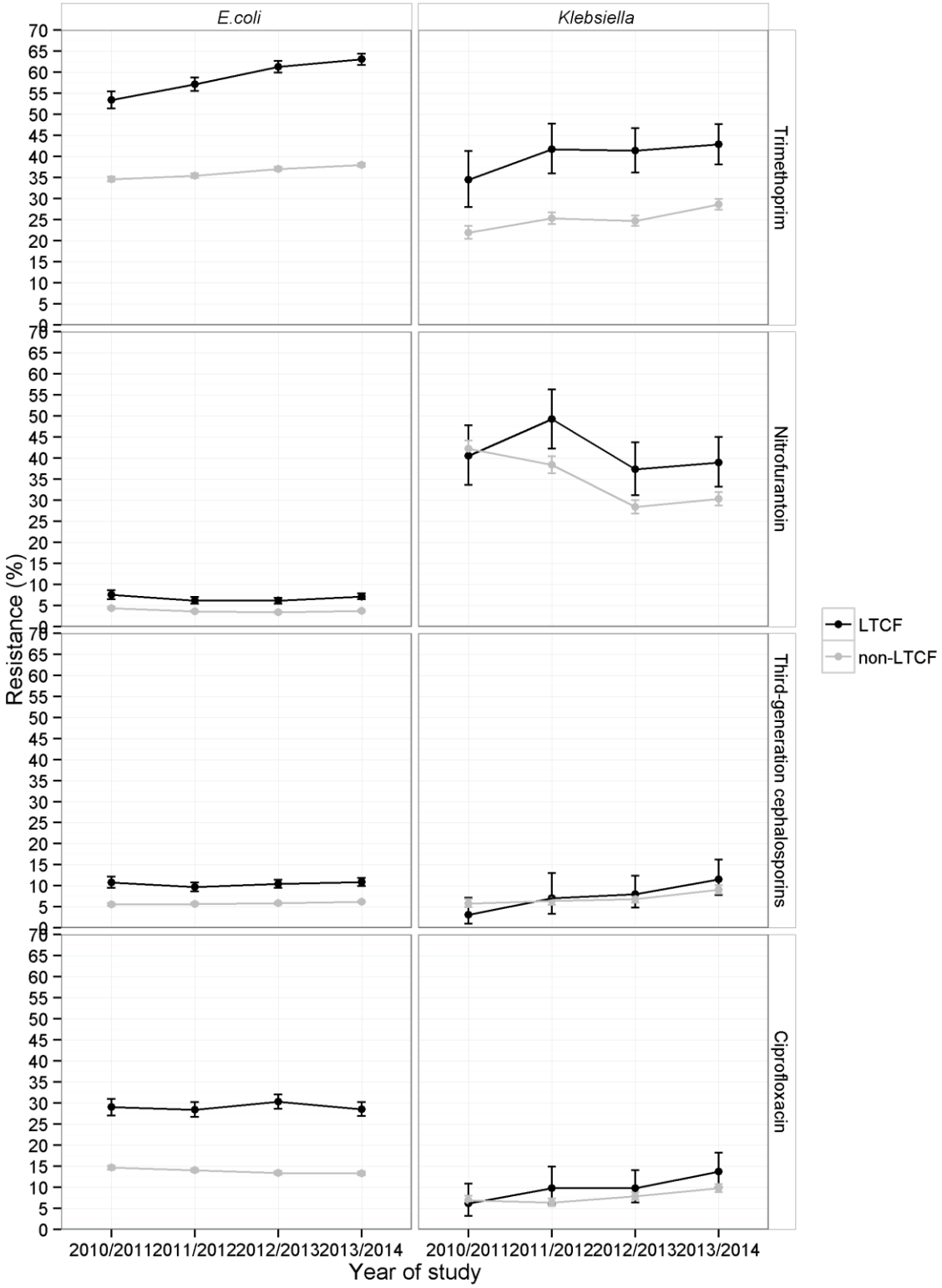

Figure 5-1. Percentage of *Klebsiella* and *E. coli* samples resistant to trimethoprim, nitrofurantoin, third-generation cephalosporins, and ciprofloxacin. The black line represents LTCF samples and the grey line represents non-LTCF samples. Yearly point estimates are presented with 95% binomial CIs. 3GC resistance was defined as resistance to ceftazidime, cefpodoxime, cefotaxime, or ceftriaxone.

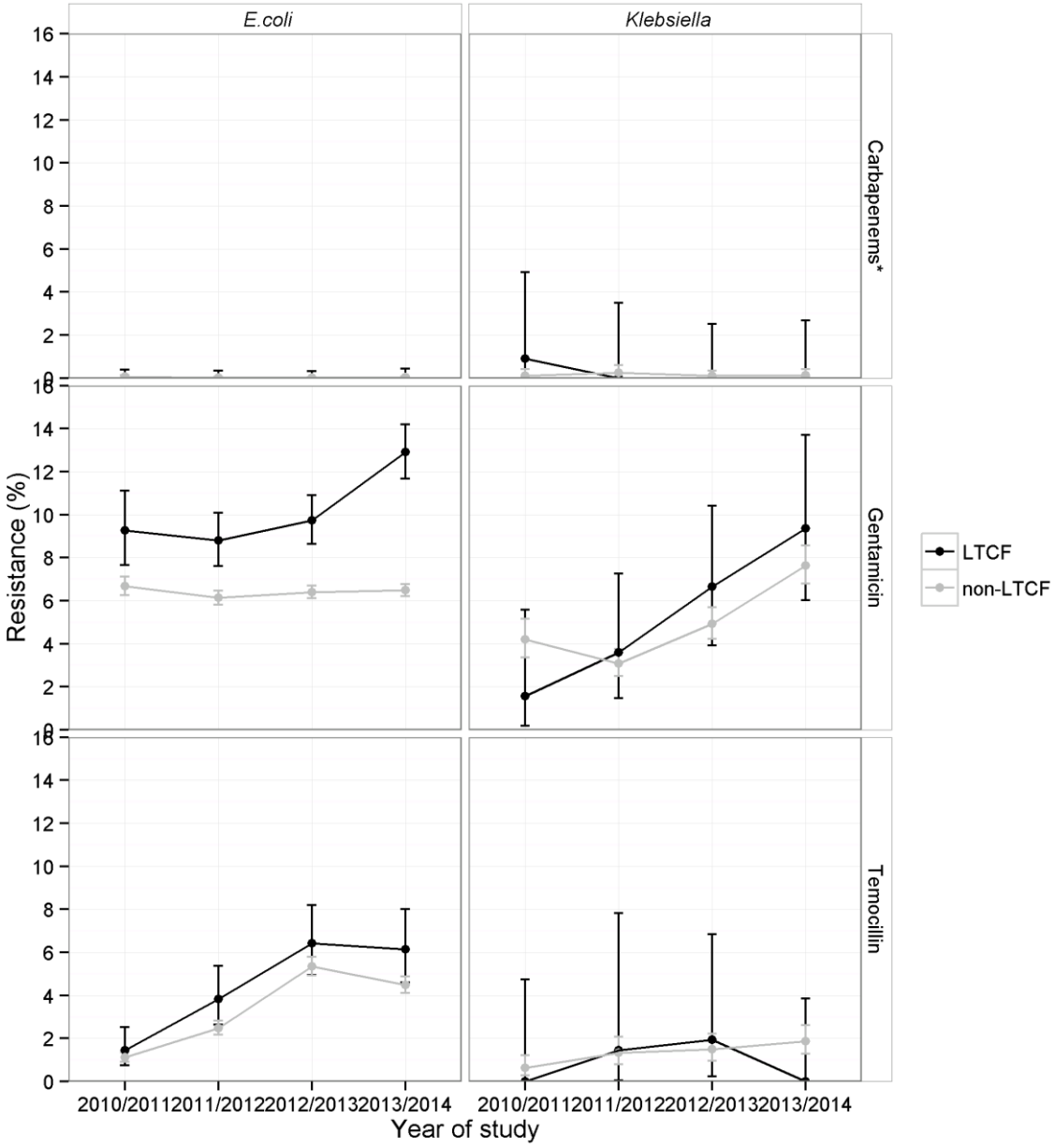

Figure 5-2 Percentage of *Klebsiella* and *E. coli* samples resistant to imipenem/meropenem, temocillin, and gentamicin. The black line represents LTCF samples and the grey line represents non-LTCF samples. Yearly point estimates are presented with 95% binomial confidence intervals. *The carbapenems included in this analysis were imipenem and meropenem.

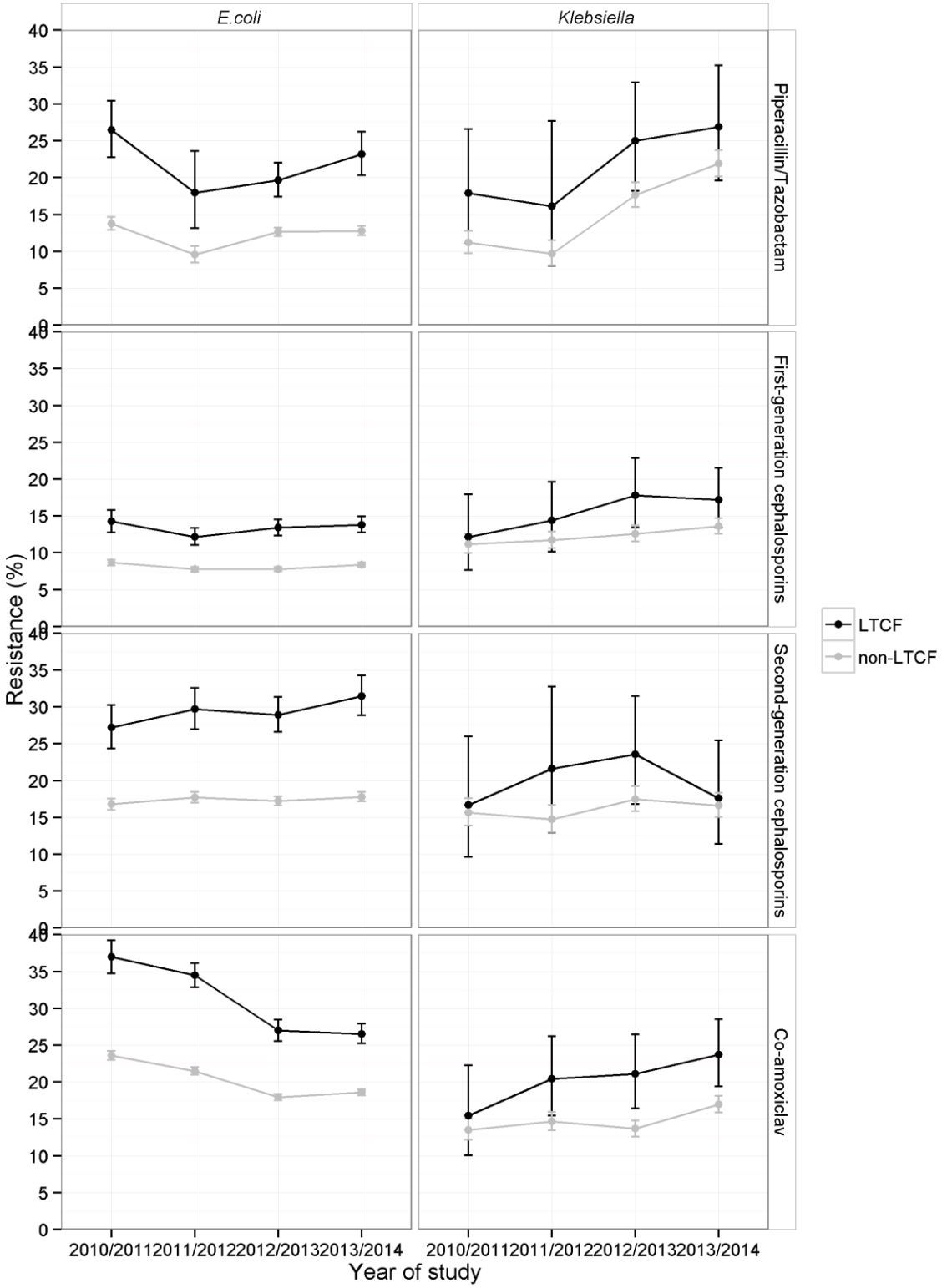

Figure 5-3. Percentage of *Klebsiella* and *E. coli* samples resistant to piperacillin/tazobactam, first-generation cephalosporins (1GC), second-generation cephalosporins (2GC), and co-amoxiclav[+]. The black and grey lines represent LTCF samples and non-LTCF samples (respectively). Yearly point estimates are presented with 95% binomial confidence intervals. [+]Note that some laboratories used the systemic rather than UTI breakpoint

guidelines for co-amoxiclav resulting in an increase in the percentage of resistant samples between mid-2011 and early 2012.

Discussion

Summary of main findings

Elderly residents of LTCFs are more than twice as likely as community dwelling adults of similar age to have a laboratory confirmed *E. coli* or *Klebsiella* UTI. UTIs are most commonly caused by *E. coli*. In LTCF residents, 60% of samples that grew *E. coli* were resistant to trimethoprim, 29% to ciprofloxacin, 10% to 3GC, and 7% to nitrofurantoin; 41% of samples that grew *Klebsiella* were resistant to trimethoprim, 41% to nitrofurantoin, 10% to ciprofloxacin, and 8% to 3GCs. LTCF residents were more than four times more likely than community dwelling older people to develop a laboratory confirmed *E. coli* or *Klebsiella* UTI caused by resistant bacteria. The increased risk of antibiotic resistance amongst bacteria causing culture confirmed *E. coli* and *Klebsiella* UTIs in older people residing in LTCFs is seen across different antibiotic classes.

Strengths

The linkage of the West Midlands AmSurv dataset, which included samples sent by both GPs and hospitals from a large population, with the CQC registry of LTCFs in England through patient postcode enabled unprecedented insight into the patterns of AMR in Gram-negative bacteria in LTCFs in England. The differences in resistance patterns between residential and nursing LTCFs were also analysed.

A multivariable regression model was developed to determine the odds of antibiotic resistance in LTCF and non-LTCF settings. This model accounted for variation in antibiotic resistance due to key risk factors (for example, samples being sent from hospitals versus from GPs), and the odds were adjusted for clustering at the postcode level. Interactions between the regression terms were also explored, although none were found to improve the model fit.

In addition, the sensitivity of the model findings to inferring LTCF residence from patient postcodes (explained in Chapter 4 in more detail) was explored by limiting the analysis to LTCFs in postcodes classed by the ONS as “communal establishment only”. The sensitivity analysis yielded very similar findings to the

main analysis, indicating the robustness of this methodology in the comparative analysis of resistance.

Limitations

Bias

The first limitations that could have biased these results are not knowing whether samples were from catheter or mid-stream urines and the fact that symptoms are not recorded in AmSurv. English national guidelines state that urine samples from catheterised patients should only be sent for susceptibility testing in the presence of systemic infection symptoms; and that samples from elderly individuals should only be sent in the presence of two or more signs of infection.[49] Therefore, the underlying presumption is that patients had samples sent appropriately. Bacteriuria is very common in older people, particularly in patients with indwelling catheters; therefore, if, despite the guidelines, some samples from these patients are sent for testing, the burden of UTI is likely to have been over-estimated. Asymptomatic bacteriuria is more prevalent amongst individuals residing in LTCFs than in those living in their own homes[47] (perhaps due to increased detection); therefore, the RR of laboratory confirmed *E. coli* and *Klebsiella* UTI in LTCF residents compared to community dwelling older adults could be lower than this analysis suggests.

Another limitation that could lead to bias is that the threshold to diagnose UTIs could be lower for LTCF residents than non-LTCF residents because their health is more frequently surveyed by staff and cognitive impairment could be more prevalent, which may make patients unable to verbalise symptoms. This would result in a greater number of samples overall being submitted for testing from LTCF residents compared to their community counterparts; which would result in an underestimation of the prevalence of resistance in LTCF residents.

Sampling may also be biased towards those failing to respond to treatment. This would lead to overestimating the prevalence of resistance in both populations[206]; however, it is unclear why this bias would be greater in LTCF samples.

Inferring LTCF residence from patient postcodes means that a proportion of those living in LTCF postcodes will live in the community in neighbouring households. This will tend to bias odds ratios toward the null hypothesis, potentially leading to underestimates of the impact of LTCF residence on antibiotic resistance. However, LTCF UTI rates were similar when using the more specific postcodes that contained only communal establishments, suggesting that this bias was minimal. In addition, this methodology has previously been employed in other studies.[9,69]

Laboratory years in which fewer than 80% of samples were tested against a particular antibiotic were excluded. This resulted in the exclusion of 1 laboratory for *Klebsiella* tested against nitrofurantoin, 3 for *Klebsiella* and 2 for *E. coli* tested against 3Gs, and 4 for *Klebsiella* and 6 for *E. coli* tested against ciprofloxacin from the 15 laboratories in the West Midlands. The analysis of antibiotic resistance may not be representative of the catchment areas of the laboratories excluded, which could have biased findings if these areas had lower or higher rates of antibiotic resistant UTI than those included.

Confounding

Antibiotic prescribing and clinical need are likely to be higher in the LTCF population and may be drivers of the patterns of resistance observed. However, no data was available to inform this.

The change in breakpoints for ceftazidime (one of the four 3GC tested) is deemed unlikely to have confounded the analysis of 3GC resistance. This is discussed in more detail in Chapter 4. The observed increase in the prevalence of resistance to co-amoxiclav between mid-2011 and early 2012 was an artefact caused by some laboratories using the systemic rather than UTI breakpoint guidelines for this antibiotic.

General

Urinary tract samples reported to AmSurv with confirmed culture results for *E. coli* and *Klebsiella* accounted for 63% of urinary tract bacteria samples. Caution

must also therefore be applied before extrapolating these results to UTIs caused by other bacterial species. In addition, resistance was measured *in vitro*, which does not always equate to clinical failure.

Finally, resistance to pivmecillinam and fosfomycin was not reported in this chapter. Pivmecillinam is recommended in the national guidelines if the first-line treatment for UTI is deemed unsuitable or if renal function is decreased (GFR is lower than 45mls/min). Fosfomycin is recommended in cases where there is a high risk of resistance. However, resistance to these antibiotics is not tested routinely. The most recent ESPAUR report reported that only 35% and 29% of isolates in England were tested against mecillinam and fosfomycin, respectively. [40]

Implications for clinical practice and policy

Our findings suggest that in older people a large proportion of *E. coli* and *Klebsiella* UTIs will not respond to trimethoprim treatment, and that this problem is heightened in LTCFs, where the prevalence of resistance is even higher. 39% of UTIs caused by *E. coli* and 27% of UTIs caused by *Klebsiella* (60% and 41%, respectively, in LTCFs) were resistant to trimethoprim. Resistance to trimethoprim is of particular concern because it may result in treatment failure, hospitalisation, and the subsequent use of antibiotics such as ciprofloxacin or 3GCs that should be reserved for the treatment of more serious infections. One explanation for these high levels of resistance could be the high consumption of trimethoprim in England. In 2014, national primary care prescribing guidelines have switched from recommending trimethoprim as first-line treatment for UTI to recommending nitrofurantoin (unless there is a low risk for resistance to trimethoprim, in which case trimethoprim is also recommended).[50] In line with these recommendations, trimethoprim prescription has decreased during 2014-2015; however, trimethoprim treatment and resistance remain high. Trimethoprim is still the most commonly prescribed antibiotic in the community for UTI. In 2015, 0.17 items were prescribed per 1000 population per day compared to 0.11 for nitrofurantoin.[35] Resistance to trimethoprim increased during the study period (2010/2011-2013/2014), faster for LTCF samples (*E. coli* from 53% to 63% and *Klebsiella* from 34% to 43%) than for non-LTCF

samples (*E. coli* from 35% to 38% and *Klebsiella* from 22% to 29%). These increases could partly be explained by trimethoprim consumption increasing in England by 4.2% between 2010 and 2013.[207]

The prevalence of resistance of *E. coli* and *Klebsiella* against nitrofurantoin was high for *Klebsiella* (35%) but much lower for *E. coli* (4%). This suggests nitrofurantoin might still remain very effective in treating UTIs caused by *E. coli* in older people, particularly in women, where the aOR of acquiring a UTI caused by nitrofurantoin-resistant *E. coli* are lower. Nitrofurantoin comprised 3.8% of all antibiotics consumed in England in 2013 in the community and was the second most frequently prescribed antibiotic agent of those recommended in empiric guidelines for lower UTI (20.8%).[207] In the West Midlands, the consumption of nitrofurantoin increased by 66% from 2010 to 2014.[43] As nitrofurantoin consumption continues to increase, resistance to this antibiotic, particularly in *Klebsiella*, may rise. The low resistance in *E. coli* in spite of the selective pressure exerted by the increased consumption of this antibiotic may be explained by a high fitness cost of resistance to nitrofurantoin in these bacteria.[208,209] However, *E. coli* might develop mechanisms to compensate for this, for example through second-site mutations that may increase fitness.[210] It is therefore, important to continue to monitor nitrofurantoin resistance in both *E. coli* and *Klebsiella* in the future.

Ciprofloxacin is a broad-spectrum antibiotic that can be used to treat infections caused by both Gram-negative and Gram-positive bacteria. Resistance to ciprofloxacin is of particular concern because it is often carried alongside resistance to beta-lactams, notably methicillin-resistance in *Staphylococci*.[211–214] Ciprofloxacin usage, therefore, selects for methicillin-resistance in *Staphylococcus aureus*. *Neisseria gonorrhoeae* also rapidly acquire resistance to ciprofloxacin, which is worrying given that resistance has emerged to all antibiotic classes that are used for treatment of gonorrhea.[40] In addition, fluoroquinolone usage has also been linked to the incidence to *C. difficile* infections.[215] In the primary care national guidelines, ciprofloxacin treatment is now only recommended for UTIs with acute prostatitis or acute pyelonephritis, or as second-line prophylaxis for recurrent UTIs.[50] It is also recommended for

lower respiratory tract infections under the premise of proven resistance to other antibiotics, and for epididymitis. Ciprofloxacin use has been declining in England since 2007.[40,215] From 2012 to 2016, quinolone usage (81% of which are ciprofloxacin prescriptions) declined by 5.8%.[40] In this context, the prevalence of resistance to ciprofloxacin in *E. coli* (15%), albeit stable, is concerning, in particular in LTCF samples (29%). The levels of resistance to ciprofloxacin in *Klebsiella* were lower (8% in non-LTCF samples and 10% in LTCF samples), although they increased from 2010/2011 to 2013/2014, faster for LTCF samples (from 6% to 14%) than for non-LTCF samples (7% to 10%). The drivers of this increasing prevalence of resistance, given the decrease observed in prescribing, warrants further study. The high levels of resistance in urinary *E. coli* isolated from LTCF residents once again highlight the benefit of nitrofurantoin treatment for UTI caused by *E. coli* in this population.

3GCs are antibiotics that are almost exclusively administered in hospitals for the treatment of severe infections. 3GCs are not recommended in the empiric treatment of UTIs but are needed to treat more severe infections such as bacterial meningitis.[194,207] The levels of resistance to 3GC in *E. coli* and *Klebsiella* were low (6%, and 7%, respectively). Similarly to ciprofloxacin resistance, the prevalence of *E. coli* resistant to 3GCs remained stable during the study period, whilst the prevalence of *Klebsiella* resistant to 3GC increased steadily (faster for LTCF samples, 3% to 12%, than for non-LTCF samples, 6% to 9%). This increase might be explained by the 21% increase in consumption of 3GCs during the study period.[43] This emphasises the need to ensure that 3GCs are prescribed only when it is strictly necessary.

Importantly, resistance to 3GC and ciprofloxacin do not only result in treatment failures but in the prescription of “last resort” antibiotics such as carbapenems that should be reserved for the treatment of severe infections in hospitals.[28] In the present study, the prevalence of resistance in urinary tract bacteria to carbapenems in the over 70s was similarly low in both *Klebsiella* and *E. coli* (0.2% and 0.02%, respectively) to what has been reported in the literature between 2010 and 2013 in the overall West Midlands population;[192] which prevented any formal statistical analysis but is reassuring.

Future work

Our findings highlight the very high levels of AMR bacteria in LTCF residents compared to their community counterparts and even to hospital patients; showing the importance of improving infection prevention and control; reducing antibiotic usage in LTCFs through antibiotic stewardship programmes; and the need for LTCF specific surveillance that can guide empiric treatment. There is also a need to understand if trimethoprim resistance is reversible through antimicrobial stewardship interventions, as evidence from the literature is conflicting[208,216], and how the mechanisms for the selection of resistances differ between species of urinary bacteria. In order to understand the causes of the high levels of antibiotic resistance observed in LTCFs, more information about antibiotic prescription, recent hospitalisations, and transmission of resistant bacteria is required. It is equally important that interventions are developed to reduce the risk of transmission of AMR bacteria between LTCF residents. The findings from this chapter were published in the Journal of Antimicrobial Chemotherapy.[2]

Conclusions

This was the first study to estimate the burden of antibiotic resistance in urinary *E. coli* and *Klebsiella* in England in a large number of LTCFs. It is also the first study to include both hospital and GP samples when comparing the frequency of antibiotic resistance in urinary tract bacteria from residents of LTCFs for older people and older people living in the community. Residents of LTCFs for older people had more than double the rate of *E. coli* and *Klebsiella* UTI and more than four times the rate of *E. coli* and *Klebsiella* UTI caused by antibiotic-resistant bacteria compared to those living in the community. The odds of resistance of *E. coli* and *Klebsiella* to trimethoprim, nitrofurantoin, ciprofloxacin and 3GCs were significantly higher in LTCF samples than non-LTCF samples, after adjusting for age, sex, sender (GP vs. hospital) and the year of the study. The prevalence of *E. coli* resistant to trimethoprim, nitrofurantoin, ciprofloxacin and 3GCs was higher in LTCF samples (obtained both from GPs and hospitals) than in samples sent from hospitals (including samples from residents of LTCF-pc and non-LTCF-pc). The prevalence of *Klebsiella* resistant to trimethoprim and nitrofurantoin was also higher in LTCFs but ciprofloxacin resistance was similar and 3GCs resistance was higher in hospitals. Together, these findings suggest that LTCFs are important reservoirs of urinary AMR bacteria, and that interventions to prevent and control these are warranted in this setting. A large proportion of *E. coli* and *Klebsiella* UTIs in older people living in LTCFs (60% and 41%, respectively) and a high proportion of those living in their own homes (37% and 26%, respectively) will not respond to trimethoprim treatment, which is the most commonly prescribed antibiotic for lower UTI. However, the prevalence of resistance of *E. coli* and *Klebsiella* against nitrofurantoin, another very commonly prescribed first-line antibiotic treatment for UTI, although high for *Klebsiella* (35%), was much lower for *E. coli* (4%). This suggests that nitrofurantoin might still remain very effective in treating UTIs caused by *E. coli* in older people. The prevalence of resistance of *E. coli* against ciprofloxacin, a second line treatment for UTI was very high in LTCFs (29% versus 14%), which is concerning given the high frequency of carriage of this resistance alongside resistance to beta-lactams such as methicillin. Resistance to 3GCs and carbapenems was low, which is reassuring. However, the prevalence of

Klebsiella resistant to 3GC increased steadily (faster for LTCF samples, 3% to 12%, than for non-LTCF samples, 6% to 9%), which highlights the need for antibiotic stewardship interventions targeting the use of this antibiotic. More information about antibiotic prescription, recent hospitalisations, and transmission of resistant bacteria is required to understand the drivers of the high levels of AMR observed in LTCFs.

Chapter 6 Seasonality of UTIs in the United Kingdom in different age groups: longitudinal analysis of THIN data

Accepted for publication in Epidemiology and Infection.[1]

Aim

To explore the seasonality and trends of UTI in the UK

Introduction

As highlighted in Chapter 1, UTIs are a common cause of BSI and the second most common cause for antibiotic prescribing in primary care, which is an important driver of antibiotic resistance. Chapter 5 found a high prevalence of antibiotic resistant *E. coli* and *Klebsiella* UTI in LTCF residents, reiterating the importance of improving our understanding of the dynamics of these infections. In addition, in view of developing a mathematical model of trimethoprim resistant *E. coli* (Chapter 7), it was important to determine whether these infections were seasonal.

Understanding the seasonality dynamics of UTI may provide a valuable insight into the determinants of infection, which can help clinicians and infection control specialists understand the risk factors for these infections and ultimately improve their prevention. Any seasonality should also be accounted for in the evaluation of interventions against UTI, as decreases in incidence due to seasonality could be misinterpreted as decreases caused by the intervention. Seasonality is also important when interpreting surveillance datasets and antibiotic prescription datasets, as increases in incidence or prescriptions could be misinterpreted as outbreaks or inappropriately high prescribing.

Whilst some bacterial infections seem to exhibit a winter seasonal pattern in temperate climates, such as bacterial meningitis[217,218], other infections such as Campylobacter and Salmonella infections are more common during the warmest months of the year[219,220]. Dehydration has been suggested to increase the risk of UTI, by causing lower rates of urine flow and voiding frequency, which may delay bacterial eradication from the urinary tract[221]. Due to

increases in temperature during summer time, which can make individuals prone to dehydration, UTIs could be expected to peak in summer. These changes could be particularly marked in the elderly population, who are prone to dehydration[60]. However, drinking more water in summer could also cause dehydration to be less common this period. Sexual activity is also a known risk factor for UTI and may also influence UTI dynamics[36].

Evidence regarding the seasonality of UTIs from the literature is conflicting (Table 6-1). One study showed UTI incidence was higher in the winter[222], 1 in autumn[223], and others in summer[224–228]. Additional studies suggested seasonality varied by causative organism[229,230] and by whether patients were seen by general practitioners (GPs) or in hospital[231]. These differences may be partly caused by the use of inadequate methodology (for example, comparing incidence without any formal statistical analysis[222,227,230,232]), the assessment of seasonality in different geographical areas (for example, in Norway[223] vs. in Greece[225]), different species (for example, *Escherichia coli* and *Staphylococcus saprophyticus*[230]), and different case-mix (for example, in children[222,227,232] vs. in all ages[223,226,228,230,233], in the community[223–225,227,229,230,232] vs. in hospital[222,228] or in females[224,229,231,233] vs. both sexes[222,223,225–228,230,232]).

Initially, the seasonality of UTI was investigated using the West Midlands AmSurv data described in Chapter 4 (see Appendix Chapter 6 PART A). The lack of seasonality found in these data drove the assessment of seasonality of UTI using other sources. In the first instance, the monthly GP prescriptions available per region from the Health & Social Care Information Centre website[234] were analysed; however, this data is only available for all ages. Trimethoprim and nitrofurantoin prescriptions in this dataset were found to be seasonal, with a clear autumnal peak (see Appendix Chapter 6 PART A). Many confounders such as age and sampling hindered the interpretation of these differences. In order to investigate the origin of this discrepancy, the UTI consultations and antibiotic prescriptions by GPs in the UK over 2008-2015 for different age groups were extracted from a nationally representative database of electronic health records from primary care, The Health Improvement

Network (THIN). The seasonality of UTI was investigated using this data and is presented subsequently in this chapter.

Table 6-1. Studies that analysed the seasonality of UTI

Author	Year	Country	Community/ hospital	Organism	Sex	Age	Seasonality	Methods
Stansfeld[222]	1966	England	Hospital	All	All	0-12	In cases >1 year age, 96 in winter and 58 in summer (significant at 1% level)	Unknown
Anderson[224]	1983	Canada	Community	All	Females	15 or older	August peak	Edward's test for cyclic variation
Pead et al.[229]	1985	England	Community	All	Females	15-25	*S. saprophyticus* UTI peak in mid-September. Coliform (all Gram-negative bacilli other than Proteus spp. and Pseudomonas spp.) UTI peak in mid-March	Chi-squared test
Vorland et al.[223]	1985	Norway	Community	*E. coli*	All	All	Higher incidence from September to December (10.2 per 1,000 inhabitants) than from January to April (8.6 per 1000 inhabitants) or May to August (6.2 per 1,000 inhabitants), but non-significant.	Chi-squared test

Author	Year	Country	Community/ hospital	Organism	Sex	Age	Seasonality	Methods
Ferry et al.[230]	1987	Sweden	Community	All	All	All	No seasonality in *E. coli* UTI but August peak in *S. saprophyticus* UTIs	Comparing incidence
Stamm et al.[233]	1991	USA	Outpatient recurrence clinic	All	Females	All	Decrease in incidence November to February	Wilcoxon's signed-rank test
Kwok et al.[232]	2006	Netherlands	Community	All	All	0-18	Decrease in the summer months mainly in children 0-12	Comparing incidence rates
Falagas et al.[225]	2009	Greece	Community (house call visits)	All	All	All	UTIs correlate with higher temperatures and decreased relative humidity	Spearman's rank correlation
Eriksson et al.[231]	2013	Sweden	Community and hospital	*E. coli*, *K. pneumoniae* and *P. mirabilis* aggregated and *S. saprophyticus*	Females	15-29	In GP samples, both peak in September, in hospital samples, both peak in August. Stronger seasonality in *S. saprophyticus*.	Chi-squared test

Author	Year	Country	Community/ hospital	Organism	Sex	Age	Seasonality	Methods
Rossignol et al.[226]	2013	France, Germany, USA, China Italy, Brazil and Australia	Community (online)	All	All	All	Increases of 8-19% in search trends for UTI-related terms in summer in France, Germany, USA, China and Italy, and peaks in the southern hemisphere austral summer in Brazil and Australia	Google trends analysis, Mann-Whitney test
Yolbas et al.[227]	2013	Turkey	Community	All	All	1 month-15 years	More UTIs in summer (53/150) than overall in winter (46/150), spring (35/150) or autumn (16/150) but difference in seasonality by sex	Comparing incidence
Melamed et al.[228]	2014	USA	Hospital	All	All	All	Summer peak	Lomb-Scargle periodograms in de-trended data

Methods

THIN is a validated database of primary care consultation data covering over 3.7 million active patients which are demographically representative of the UK.[235–237] The dataset contains individual pseudonymised patient ID, prescription details, consultation date and time, reason for consultation (recorded through diagnostic code), patient registration details and patient clinical and demographic information.

In order to obtain the monthly rate of de-duplicated UTI consultations, nitrofurantoin prescriptions and trimethoprim prescriptions by age and sex, for 2008-2015, diagnostic codes were extracted (listed in Appendix Chapter 6 PART B), Patient ID, trimethoprim and nitrofurantoin prescriptions (derived from the prescribing information in THIN), country, date of UTI consultation/prescription, date of registration at GP, date of de-registration at GP, patient age, patient sex, and patients registered on the 1st of July (mid-year) each year for 2008-2015 at each of the GP practices present in THIN during the whole duration of the study (for this, practice ID was required). UTI consultations and nitrofurantoin and trimethoprim prescriptions from UK practices meeting acceptable standard for research (as suggested by the THIN Data Guide for Researchers) were de-duplicated to one per patient per 30-day period in order to approximate episodes of infection (one nitrofurantoin or trimethoprim prescription during the 30-day period) and subsequently aggregated by age group, sex and moth of the study. The denominator population was the number of patients (of the corresponding age group and sex) registered at each of the GP practices on the 1st of July (mid-year) each year of the study.

Reasoning for analysing both GP consultations and antibiotic prescriptions

Consultation codes in THIN are known to be poorly recorded[238,239]. However, all prescriptions made by GP practices reporting to THIN are automatically included in the database and do not suffer from this reporting bias. Hence, the analysis of UTI consultations was repeated for trimethoprim and nitrofurantoin

prescriptions. Both trimethoprim and nitrofurantoin are almost exclusively prescribed for UTIs and account for the majority of antibiotics used for UTIs in primary care.

Only the rate of UTI consultations (and not antibiotic prescriptions) was used to assess the trend in UTIs over time, because nitrofurantoin and trimethoprim prescriptions for UTI as a proportion of all antibiotic prescriptions increased over the study period (Figure 6-1). Although coding for UTI consultations by GPs was poor, it remained stable over the study period (the percentage of trimethoprim and nitrofurantoin prescriptions that had a UTI consultation coded on the same day fluctuated between 35-41% during the study period), enabling the study of trend over time (Figure 6-2).

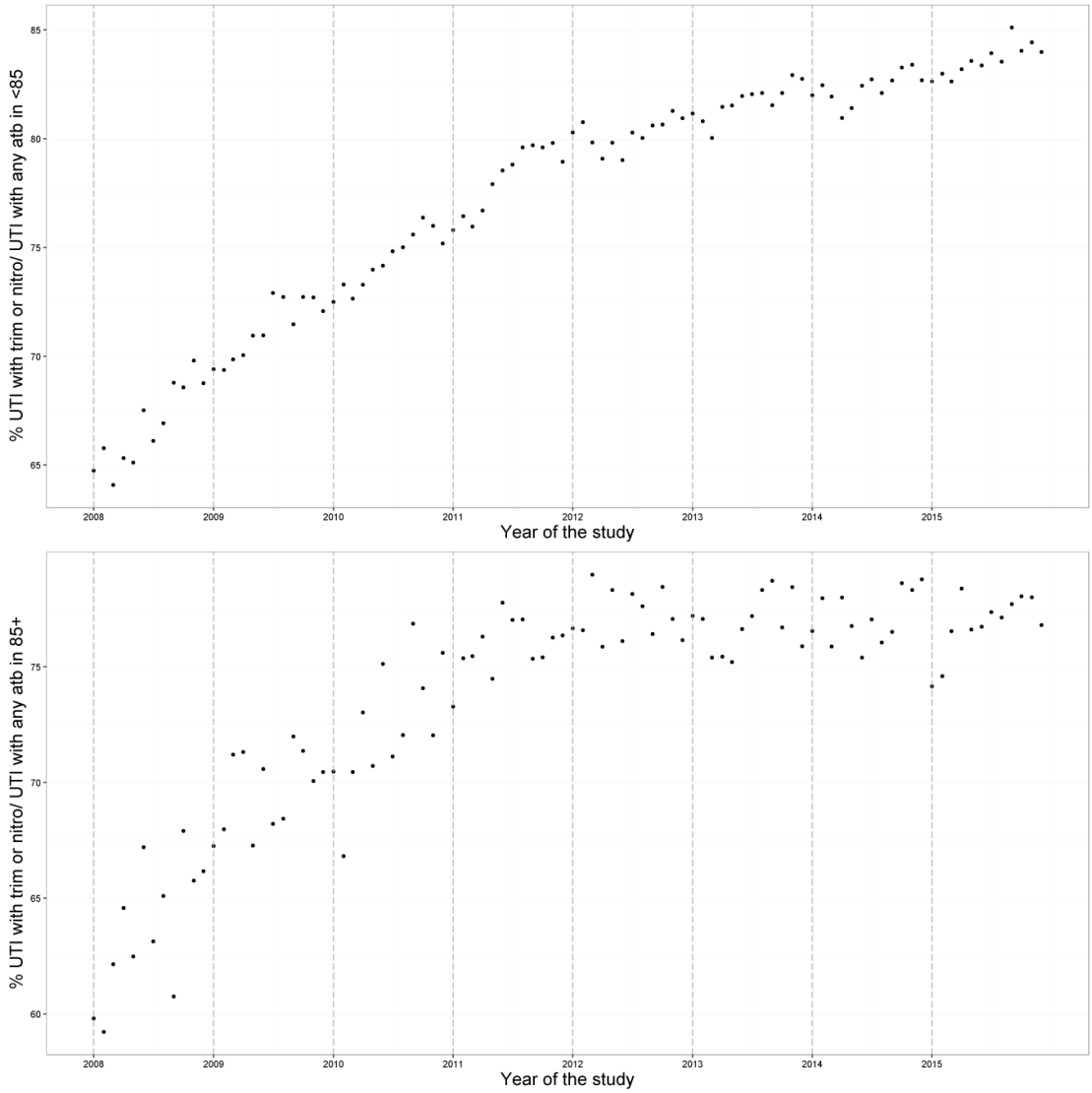

Figure 6-1. Percentage of monthly UTI consultation coded with any antibiotic prescription on the same day for which that antibiotic was trimethoprim or nitrofurantoin, by age group.

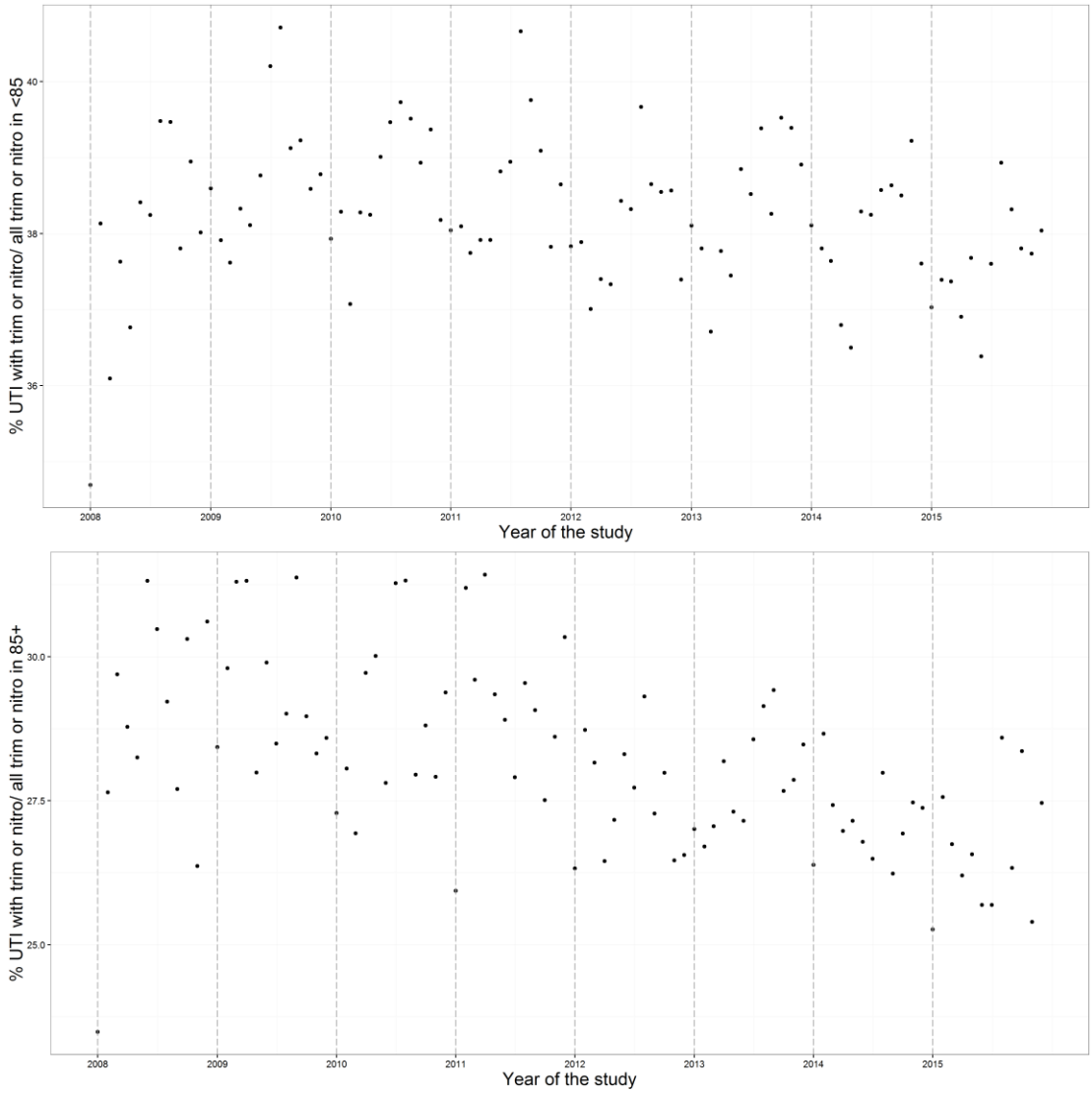

Figure 6-2. Percentage of monthly trimethoprim and nitrofurantoin prescriptions that had a UTI consultation coded on the same day for those aged under 85 and 85 or over. Nitrofurantoin and trimethoprim are almost exclusively prescribed for UTI; therefore this can be interpreted as a proxy for coding of UTI consultation.

Statistical methods

Separate negative binomial models were fit to the rate of UTI consultations and trimethoprim and nitrofurantoin prescriptions in order to assess trend and seasonality. Negative binomial models were best suited to model the rates of consultations and prescriptions due to the overdispersion in the data. These were repeated by age group (14-17, 18-24, 25-45, 46-69, 70-84, 85+) and by sex. All models included a trend term modelled as a quadratic function of time. This term explained the trend observed better than a linear term, as measured by the AIC. A seasonality term was then added. The dispersion parameter was fixed at the estimate derived for the seasonal model, which was more complex. This enabled the comparison of the fit of the models with and without the seasonality term using the AIC and the percentage of deviance explained by the model. In addition, a correlogram was plotted to explore the correlations between the residuals of the model and the lagged values of the residuals for lags 1-12 (over the course of a year).

The negative binomial model including seasonality can be defined by the following equation:

$$\log(\lambda_t) = \mathrm{a} + trend_t + seasonality_t + \log(population_t)$$

Where, t was the month of the study; λ_t was the number of consultations and prescriptions at month t; a was the intercept; $trend_t$ was a quadratic term defined as $trend_t = \mathrm{a} + \mathrm{b}t + ct^2$, used to account for the decreasing trend observed in the rates; $seasonality_t$ was a seasonality term defined as $seasonality_t = \cos\left(\frac{2\Pi t}{12}\right) + \sin\left(\frac{2\Pi t}{12}\right)$; and $\log(population_t)$ was an offset used to model the rates of consultations and prescriptions instead of the counts.

Adding an autoregressive term at lag of 1 month in the regression to test for local statistical dependence or autocorrelation was also explored, as it is common for infection time series data; however, it did not significantly improve the fit of the models.

All the analysis was carried out in R version 3.3.0[240] using the glm.nb function in the MASS package[241] to obtain the theta (the dispersion parameter) of the full model. Subsequently the glm function (stats package) was used to fit the model with the fixed theta.

Sensitivity analysis

In order to assess coding reliability for UTI consultations in THIN, the percentage of monthly trimethoprim and nitrofurantoin prescriptions that had a UTI consultation coded on the same day was calculated. These appeared to follow a cyclical pattern during the year; therefore, in order to account for any seasonality in coding, the monthly UTI consultations were scaled for each age group by dividing by a scaling factor. This scaling factor was the percentage of UTIs coded in each month (as described above) divided by the maximum percentage coded over the study period for that age group. As a sensitivity analysis, the seasonality was also assessed in these scaled UTIs. We also repeated the analysis for England.

Results

UTI consultations and trimethoprim and nitrofurantoin prescriptions

Between 1 January 2008 and 31 December 2015, there were 992,803 de-duplicated UTI consultations and 1719416 de-duplicated trimethoprim and nitrofurantoin prescriptions reported to THIN. The mean monthly rate of UTI consultations and trimethoprim and nitrofurantoin prescriptions per 100,000 population for all age groups and by sex is shown in Table 6-2. Both measures increased steeply with age, particularly in males.

Table 6-2. Descriptive table of the rates of UTI consultations and trimethoprim and nitrofurantoin prescriptions by age group and sex. These were de-duplicated to 1 per patient per 30-day period in order to approximate episodes of infection (1 nitrofurantoin or trimethoprim prescription during the 30-day period).

Age groups	Percentage of UTI consultations	Mean monthly rate of UTI consultations per 100,000 population	Mean monthly rate of UTI consultations in females per 100,000 population	Mean monthly rate of UTI consultations in males per 100,000 population	Percentage of trimethoprim and nitrofurantoin prescriptions	Mean monthly rate of trimethoprim and nitrofurantoin prescriptions per 100,000 population	Mean monthly rate of trimethoprim and nitrofurantoin prescriptions in females per 100,000 population	Mean monthly rate of trimethoprim and nitrofurantoin prescriptions in males per 100,000 population
0-13	6.3	144.3	232.0	51.5	6.0	238.3	360.3	123.7
14-17	2.6	195.4	377.4	19.4	2.4	302.1	581.9	55.4
18-24	10.1	394.0	736.7	25.8	7.9	529.4	1002.0	67.8
25-45	23.6	257.5	452.6	37.1	20.4	385.5	679.6	83.2
46-69	28.7	313.1	508.1	93.9	30.5	573.5	941.6	207.2
70-84	20.0	617.2	830.6	305.1	22.5	1200.2	1663.7	643.5
85+	8.7	738.1	845.3	471.2	10.3	1489.5	1793.6	958.3

Trend

Although coding for UTI consultations by GPs was poor, it remained stable over the study period (the percentage of trimethoprim and nitrofurantoin prescriptions that had a UTI consultation coded on the same day fluctuated between 35-41% during the study period), enabling the study of trend over time (Figure 6-3).

With the exception of males aged 70-84, the rate of UTI consultations for both males and females of all age groups decreased during the study period, as shown by the greatly improved AIC when adding a linear trend term to the model (see Figure 6-3, Table 6-3 and Table 6-4). This decrease was particularly pronounced for females aged 85 or older. The trend in the UK was very similar to the trend in England (Figure 6-4).

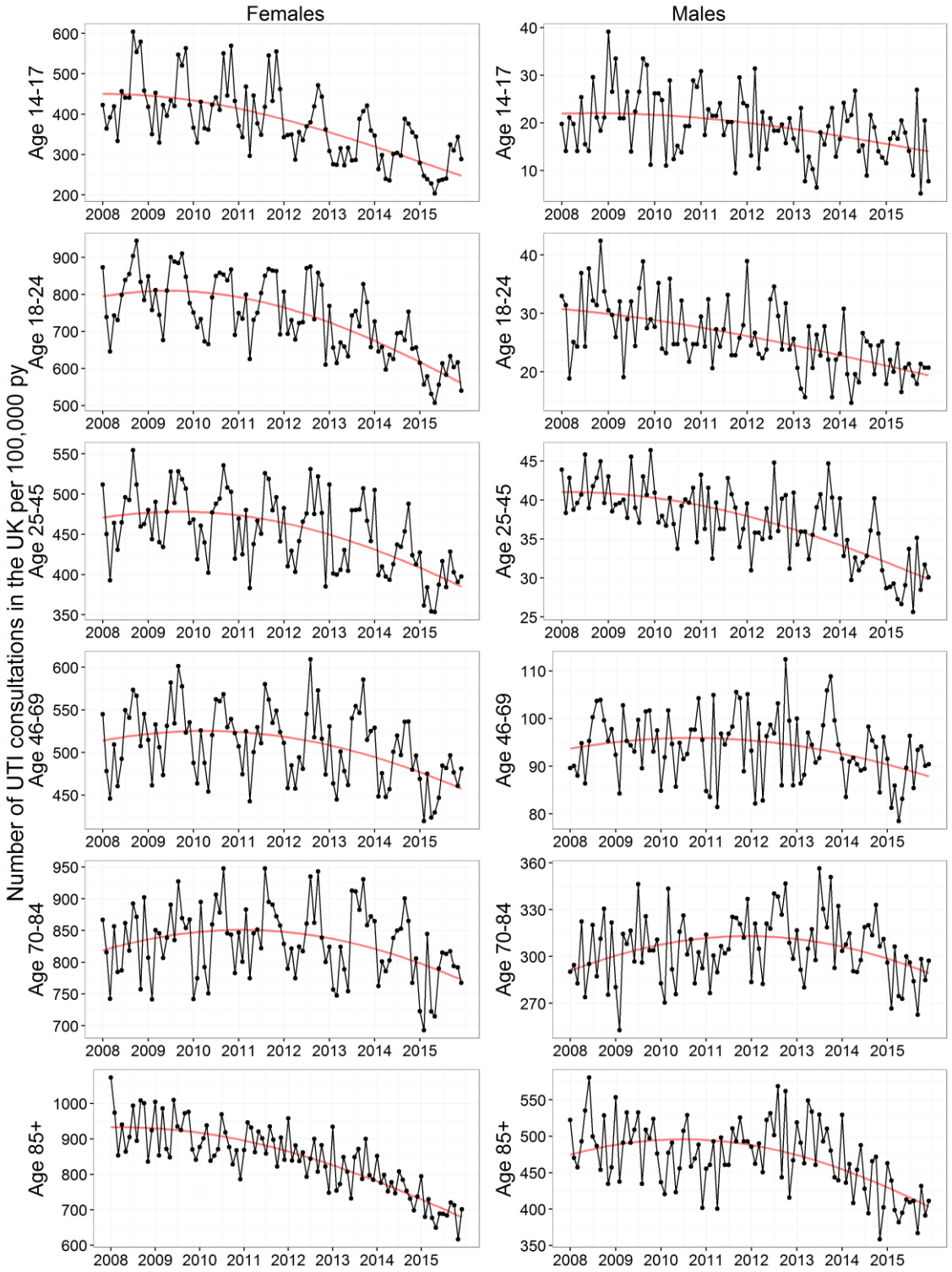

Figure 6-3. Monthly UTI consultations coded by GPs per 100,000 person years in the UK by age group and sex. The central red lines represent the fitted trend predictions from the seasonal regression model. This was a negative binomial polynomial regression model of degree two with the number of patients registered at each of the GP practices on the 1st of July (mid-year) each year of the study as offset. The UTI consultations were de-duplicated to one per 30-day period. The y axes differ between panels.

Table 6-3. Akaike information criteria (AIC) for the models of UTI consultations in the UK including a seasonal component with no trend term, a linear trend term and a quadratic trend term, by sex and age group. *In order to calculate the AIC, the dispersion parameter (theta) was fixed at the estimate derived for the most complex model (the seasonal model with a quadratic trend term). The trend term was given by $t + t^2$ and the seasonality term by $\cos\left(\frac{2\Pi t}{12}\right) + \sin\left(\frac{2\Pi t}{12}\right)$, where t was the month of the study (1 to 96).

Sex	Age group	AIC of the regression model with no trend term*	AIC of the regression model with a linear trend term (t)*	AIC of the regression model with a quadratic trend term $(t + t^2)$
All UTIs	14-17	1131.302	936.8906	925.5975
All UTIs	18-24	1375.33	1119.663	1083.569
All UTIs	25-45	1330.703	1249.725	1234.055
All UTIs	46-69	1281.198	1244.596	1231.499
All UTIs	70-84	1193.373	1181.468	1168.383
All UTIs	85+	1298.537	1054.343	1036.552
Female UTIs	14-17	1170.251	930.8574	917.3008
Female UTIs	18-24	1360.837	1117.974	1078.937
Female UTIs	25-45	1327.862	1237.177	1221.477
Female UTIs	46-69	1262.241	1218.761	1205.818
Female UTIs	70-84	1143.959	1134.796	1123.924
Female UTIs	85+	1241.139	1015.206	1001.247
Male UTIs	14-17	582.4998	568.1808	570.5024
Male UTIs	18-24	678.9267	624.9811	627.5591
Male UTIs	25-45	918.8692	802.7613	797.7937
Male UTIs	46-69	930.2015	922.5998	920.3444
Male UTIs	70-84	929.6153	931.4508	920.3366
Male UTIs	85+	861.6667	830.0555	819.1208

Table 6-4. Coefficients and 95% confidence intervals (CI) of the models of UTI consultations in the UK by sex and age group. The trend term was given by $t + t^2$ and the seasonality term by $\cos\left(\frac{2\Pi t}{12}\right) + \sin\left(\frac{2\Pi t}{12}\right)$, where t was the month of the study (1 to 96). The confidence intervals were calculated using the confint function in R.

Sex	ages	$intercept$ (95% CI)	t (95% CI)	t^2 (95% CI)	$\cos\left(\frac{2\Pi t}{12}\right)$ (95% CI)	$\sin\left(\frac{2\Pi t}{12}\right)$ (95% CI)
All UTIs	14-17	-6.08	0.000415	-6.2e-05	0.0994	-0.154
		(-6.15, -0.00268)	(-6.15, -0.00268)	(-6.15, -0.00268)	(-6.15, -0.00268)	(-6.15, -0.00268)
All UTIs	18-24	-5.46	0.00193	-5.85e-05	0.0241	-0.1
		(-5.49, 0.00013)	(-5.49, 0.00013)	(-5.49, 0.00013)	(-5.49, 0.00013)	(-5.49, 0.00013)
All UTIs	25-45	-5.93	0.00173	-3.83e-05	0.0205	-0.0818
		(-5.97, 4.64e-05)	(-5.97, 4.64e-05)	(-5.97, 4.64e-05)	(-5.97, 4.64e-05)	(-5.97, 4.64e-05)
All UTIs	46-69	-5.76	0.00172	-2.9e-05	0.0102	-0.0763
		(-5.79, 0.000349)	(-5.79, 0.000349)	(-5.79, 0.000349)	(-5.79, 0.000349)	(-5.79, 0.000349)
All UTIs	70-84	-5.1	0.00222	-2.98e-05	-0.00302	-0.0524
		(-5.13, 0.000806)	(-5.13, 0.000806)	(-5.13, 0.000806)	(-5.13, 0.000806)	(-5.13, 0.000806)
All UTIs	85+	-5.1	0.00222	-2.98e-05	-0.00302	-0.0524
		(-5.13, 0.000806)	(-5.13, 0.000806)	(-5.13, 0.000806)	(-5.13, 0.000806)	(-5.13, 0.000806)
Female UTIs	14-17	-5.4	0.000229	-6.72e-05	0.101	-0.167
		(-5.47, -0.0029)	(-5.47, -0.0029)	(-5.47, -0.0029)	(-5.47, -0.0029)	(-5.47, -0.0029)
Female UTIs	18-24	-4.84	0.00225	-6.12e-05	0.0236	-0.101
		(-4.87, 0.000431)	(-4.87, 0.000431)	(-4.87, 0.000431)	(-4.87, 0.000431)	(-4.87, 0.000431)
Female UTIs	25-45	-5.36	0.00164	-3.87e-05	0.0201	-0.0852
		(-5.4, -6.22e-05)	(-5.4, -6.22e-05)	(-5.4, -6.22e-05)	(-5.4, -6.22e-05)	(-5.4, -6.22e-05)

Sex	ages	$intercept$ (95% CI)	t (95% CI)	t^2 (95% CI)	$\cos\left(\frac{2\Pi t}{12}\right)$ (95% CI)	$\sin\left(\frac{2\Pi t}{12}\right)$ (95% CI)
Female UTIs	46-69	-5.27 (-5.3, 0.000253)	0.00168 (-5.3, 0.000253)	-2.98e-05 (-5.3, 0.000253)	0.0114 (-5.3, 0.000253)	-0.0812 (-5.3, 0.000253)
Female UTIs	70-84	-4.81 (-4.84, 0.000701)	0.00216 (-4.84, 0.000701)	-2.85e-05 (-4.84, 0.000701)	-0.00206 (-4.84, 0.000701)	-0.0564 (-4.84, 0.000701)
Female UTIs	85+	-4.81 (-4.84, 0.000701)	0.00216 (-4.84, 0.000701)	-2.85e-05 (-4.84, 0.000701)	-0.00206 (-4.84, 0.000701)	-0.0564 (-4.84, 0.000701)
Male UTIs	14-17	-8.43 (-8.61, -0.00787)	0.00113 (-8.61, -0.00787)	-6.03e-05 (-8.61, -0.00787)	0.0924 (-8.61, -0.00787)	0.0412 (-8.61, -0.00787)
Male UTIs	18-24	-8.08 (-8.19, -0.00684)	-0.00185 (-8.19, -0.00684)	-3.08e-05 (-8.19, -0.00684)	0.0383 (-8.19, -0.00684)	-0.0673 (-8.19, -0.00684)
Male UTIs	25-45	-7.8 (-7.85, -0.00216)	0.000213 (-7.85, -0.00216)	-3.67e-05 (-7.85, -0.00216)	0.028 (-7.85, -0.00216)	-0.0499 (-7.85, -0.00216)
Male UTIs	46-69	-6.97 (-7.01, -0.000274)	0.0015 (-7.01, -0.000274)	-2.24e-05 (-7.01, -0.000274)	0.00462 (-7.01, -0.000274)	-0.0508 (-7.01, -0.000274)
Male UTIs	70-84	-5.84 (-5.88, 0.00151)	0.00323 (-5.88, 0.00151)	-3.39e-05 (-5.88, 0.00151)	-0.0071 (-5.88, 0.00151)	-0.036 (-5.88, 0.00151)
Male UTIs	85+	-5.84 (-5.88, 0.00151)	0.00323 (-5.88, 0.00151)	-3.39e-05 (-5.88, 0.00151)	-0.0071 (-5.88, 0.00151)	-0.036 (-5.88, 0.00151)

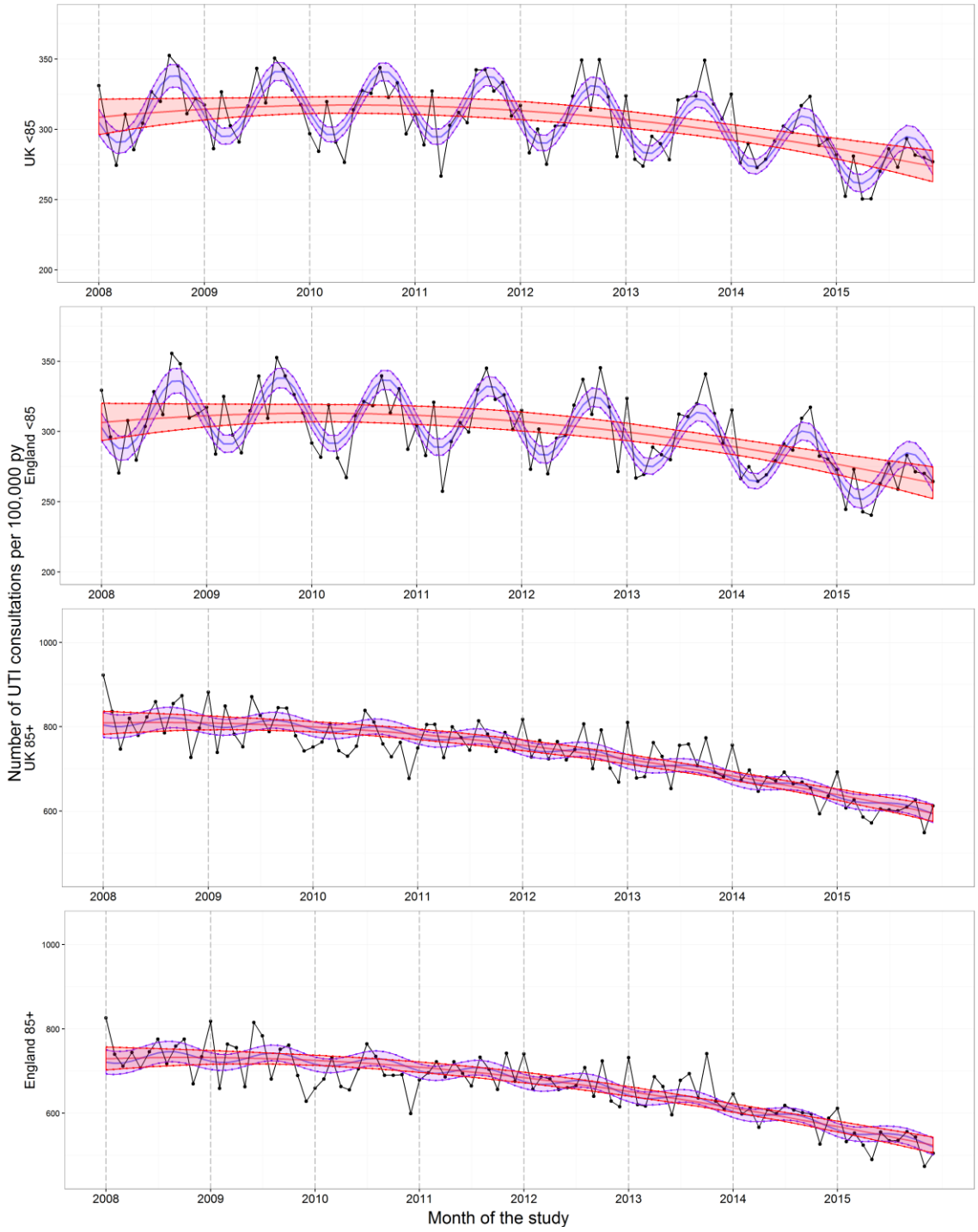

Figure 6-4. Monthly UTI consultations coded by GPs per 100,000 person years in England and in the UK by age group. The central red lines represent the fitted predictions of the negative binomial polynomial regression model of degree two with the number of patients registered at each of the GP practices on the 1st of July (mid-year) each year of the study as offset. The central blue lines represent the fitted predictions of the same model but with a seasonal component included. The shaded areas represent the 95% confidence intervals for their respective models. These were calculated using the standard errors from the predict function, which calculates the confidence intervals around the mean. The UTI consultations were de-duplicated to one per 30-day period. The y axes differ between panels.

Seasonality by age

Adding a seasonal component to the negative binomial regression greatly improved the model fit to the data for ages 14-17, 18-24, 25-45 and 46-69, as measured by the AIC and the percentage of deviance explained by the model (see Table 6-5), showing UTI consultations in these age groups follow a cyclic yearly pattern. For ages 70-84, there was also a notable improvement in model fit; however, in those aged 85 or older, the improvement was minimal (73.62% of the deviance explained by the seasonal model, 72.91% by the non-seasonal model). In younger ages there is no overlap between the 95% CIs of the models with and without seasonality during the September to November period for most years (Figure 6-5), which meant the difference was statistically significant.

Table 6-5. Akaike information criteria (AIC) and the percentage deviance explained by the models of UTI consultations in the UK including a seasonal component and models that did not by age group.

Age group	AIC seasonal model	AIC non-seasonal model*	% deviance explained by the seasonal model	% deviance explained by the non-seasonal model
14-17	925.60	1063.98	77.46	43.25
18-24	1083.57	1210.22	80.65	53.94
25-45	1234.05	1329.14	66.19	30.61
46-69	1231.50	1353.64	64.17	16.43
70-84	1168.38	1218.51	46.24	14.95
85+	1036.55	1033.14	73.62	72.91

*In order to calculate the AIC and percentage deviance explained for the non-seasonal model, the dispersion parameter (theta) was fixed at the estimate derived for the seasonal model.

The correlograms in Figure 6-5 show the autocorrelation functions for the residuals of the regression models without seasonality at lags of 0-12 months. For ages 14-17, 18-24, 25-45 and 46-69, the correlograms show oscillatory patterns consistent with seasonality. This pattern is less pronounced in the 70-84 year olds and disappears in those aged 85+. With 1 exception (January 2014), the month of the year with the highest number of UTI consultations in

those aged under 85 every year from 2008 to 2015 were between September and November (Table 6-6).

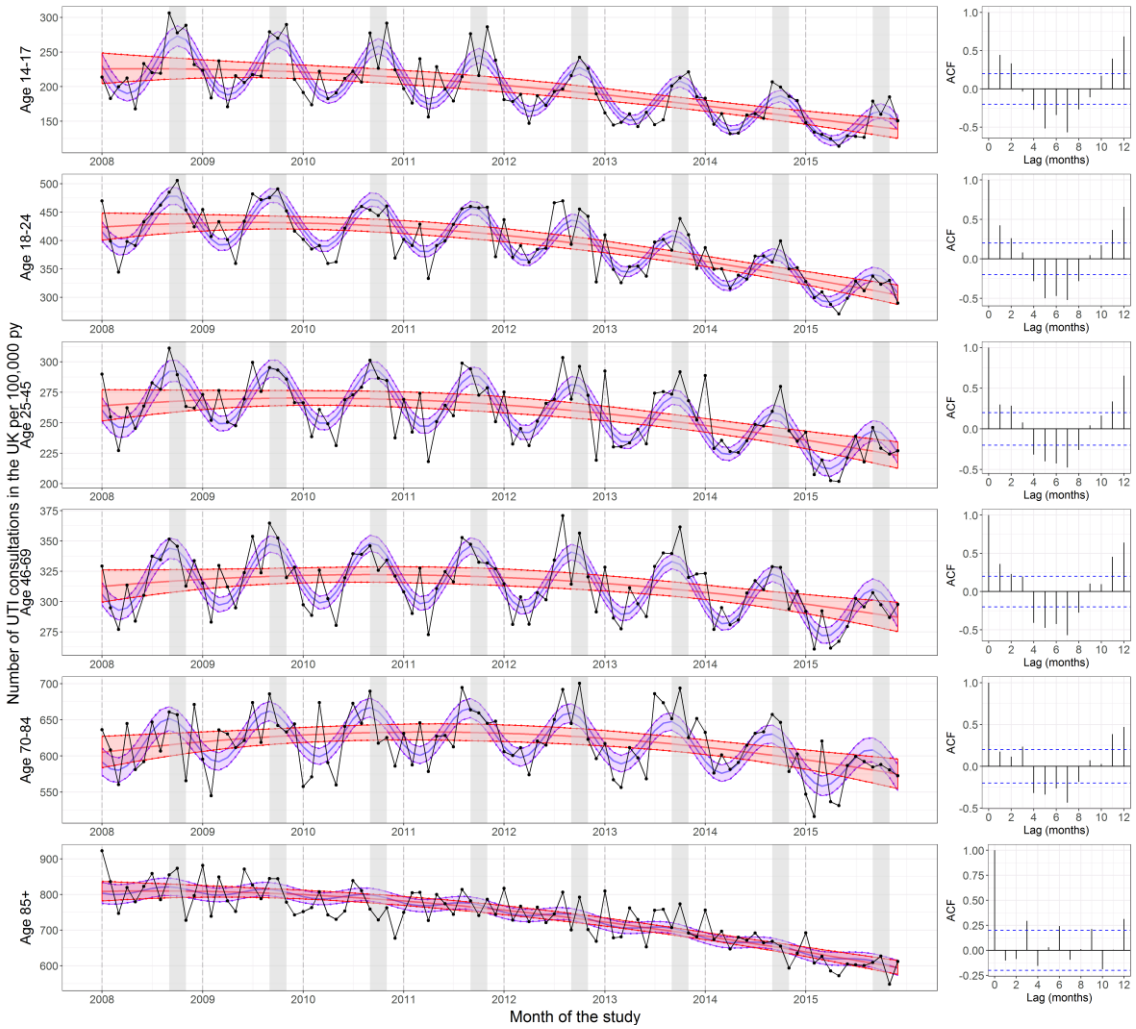

Figure 6-5. Seasonality in UTI consultations coded in the UK per 100,000 person years by age. The left panels show the rate of UTI consultations by age group. The central red lines represent the fitted predictions of the negative binomial polynomial regression model of degree 2 with the number of patients registered at each of the GP practices on the 1st of July (mid-year) each year of the study as offset. The central blue lines represent the fitted predictions of the same model but with a seasonal component included. The shaded areas represent the 95% confidence intervals for their respective models. These were calculated using the standard errors from the predict function, which calculates the confidence intervals around the mean. The right panels show the correlograms for the residuals of the regression models without seasonality at lags of 0-12 months for each age group. The September to November period is shaded in grey. The UTI consultations were de-duplicated to 1 per 30-day period. The y axes differ between panels.

Table 6-6. Month of the year with the highest number of UTI consultations or trimethoprim and nitrofurantoin prescriptions by age group. In brackets, the rate of UTI consultations or trimethoprim and nitrofurantoin prescriptions per 100,000 person years for that month.

Date	Trimethoprim and nitrofurantoin prescriptions in the UK <85	Trimethoprim and nitrofurantoin prescriptions in the UK 85+	UTI consultations in the UK <85	UTI consultations in the UK 85+	UTI consultations in England <85	UTI consultations in England 85+
2008	Oct (515.08)	Jan (1886.24)	Sep (352.52)	Jan (922.37)	Sep (355.56)	Jan (826.19)
2009	Sep (535.13)	Oct (1622.4)	Sep (350.65)	Jan (881.78)	Sep (352.6)	Jan (817.95)
2010	Sep (554.32)	Mar (1612.09)	Sep (344.01)	Jul (838.79)	Sep (339.61)	Jul (764.2)
2011	Nov (587.15)	Mar (1653.98)	Sep (342.48)	Aug (814)	Sep (345.05)	Nov (742.15)
2012	Oct (621.67)	Jan (1799.42)	Oct (349.52)	Jan (817.35)	Oct (345.29)	Jan (740.61)
2013	Oct (622.2)	Jan (1768.77)	Oct (349.18)	Jan (809.73)	Oct (340.93)	Oct (741.06)
2014	Oct (597.12)	Jan (1687.91)	Jan (325.01)	Jan (756.34)	Oct (317.27)	Jan (645.86)
2015	Sep (556.59)	Jan (1517.94)	Sep (293.28)	Jan (692.45)	Sep (282.98)	Jan (611.35)

The same seasonal pattern was observed for the scaled monthly UTI consultations (Figure 6-6 and Table 6-7), for trimethoprim and nitrofurantoin prescriptions (Figure 6-7), when restricting the analysis to England (Figure 6-8), and when analysing the seasonality of urine samples submitted to the AmSurv database[186] in the West Midlands (Appendix Chapter 6 PART A).

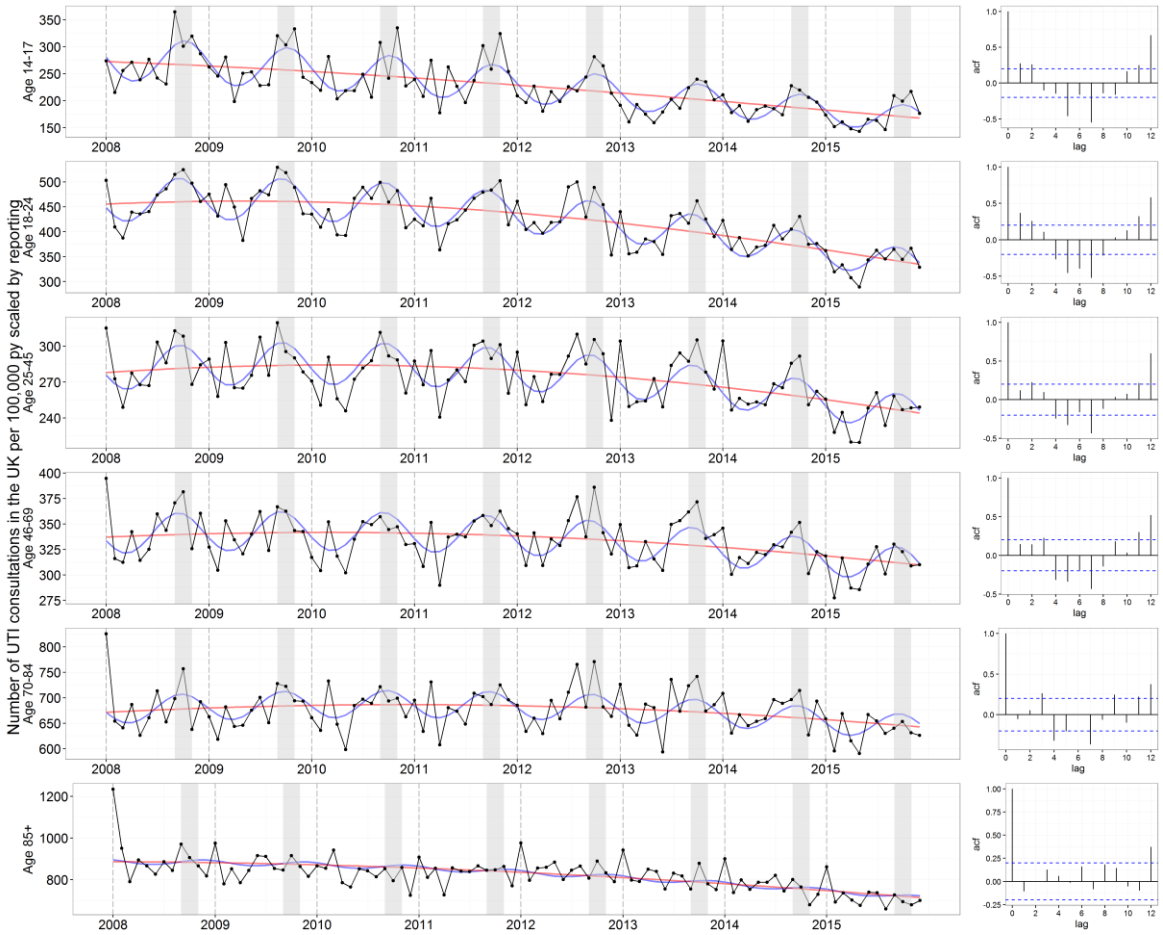

Figure 6-6. Scaled monthly UTI consultations coded per 100,000 person years in the UK by age group. The UTI consultations were de-duplicated to one per 30-day period. The red lines represent the fitted predictions of the negative binomial polynomial regression model of degree two with the number of patients registered at each of the GP practices on the 1st of July (mid-year) each year of the study as offset. The blue lines represent the fitted predictions of the same model but with a seasonal component included. No confidence intervals are presented as these were scaled predictions. The monthly UTI consultations were scaled for each age group by dividing by a scaling factor. This scaling factor was the percentage of UTIs coded in each month (the percentage of monthly trimethoprim and nitrofurantoin prescriptions that had a UTI consultation coded on the same day) divided by the maximum percentage coded over the study period for that age group. The right panels show the correlograms for the residuals of the regression models without seasonality at lags of 0-12 months for each age group. The y axes differ between panels.

Table 6-7. Akaike information criteria (AIC) for models of the scaled UTI consultations in the UK which included a seasonal component and models that did not by age group. *In order to calculate the AIC for the non-seasonal model, the dispersion parameter (theta) was fixed at the estimate derived for the seasonal model.

Age group	AIC seasonal model	AIC non-seasonal model*	% deviance explained by the seasonal model	% deviance explained by the non-seasonal model
14-17	960.78	1041.58	72.21	46.84
18-24	1096.01	1196.45	77.92	53.5
25-45	1242.65	1293.55	54.06	26.85
46-69	1254.36	1309.21	48.88	16.55
70-84	1196.56	1217.86	28.74	8.51
85+	1108.25	1103.92	44.43	43.47

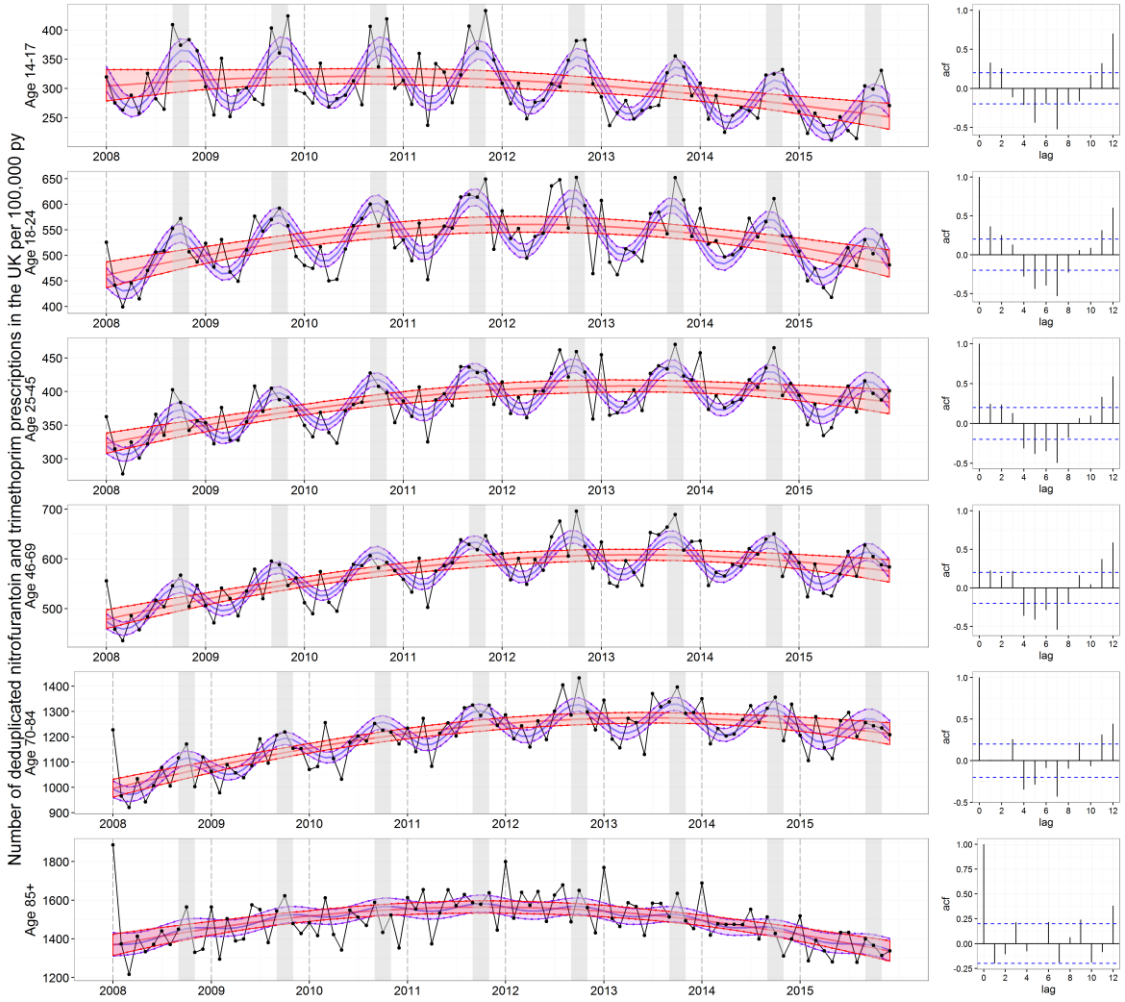

Figure 6-7. Monthly nitrofurantoin and trimethoprim prescriptions administered by GPs per 100,000 person years in the UK by age group. The nitrofurantoin and trimethoprim prescriptions were de-duplicated to one per 30-day period. The central red lines represent the fitted predictions of the negative binomial polynomial regression model of degree two with the number of patients registered at each of the GP practices on the 1st of July (mid-year) each year of the study as offset. The central blue lines represent the fitted predictions of the same model but with a seasonal component included. The shaded areas represent the 95% confidence intervals for their respective models. These were calculated using the standard errors from the predict function, which calculates the confidence intervals around the mean. The right panels show the correlograms for the residuals of the regression models without seasonality at lags of 0-12 months for each age group. The y axes differ between panels.

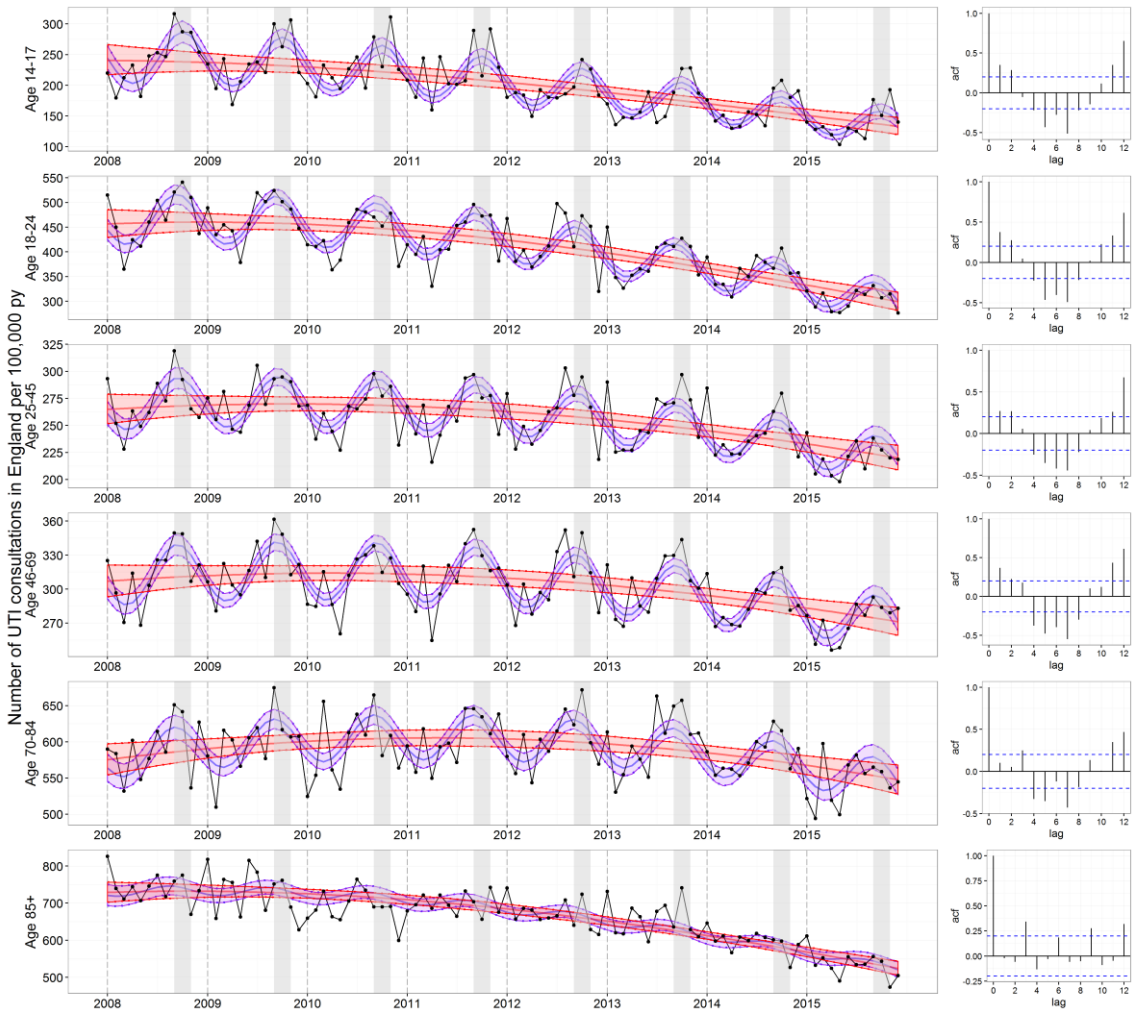

Figure 6-8. Monthly UTI consultations coded per 100,000 person years in England by age group. The UTI consultations were de-duplicated to one per 30-day period. The central red lines represent the fitted predictions of the negative binomial polynomial regression model of degree two with the number of patients registered at each of the GP practices on the 1st of July (mid-year) each year of the study as offset. The central blue lines represent the fitted predictions of the same model but with a seasonal component included. The shaded areas represent the 95% confidence intervals for their respective models. These were calculated using the standard errors from the predict function, which calculates the confidence intervals around the mean. The right panels show the correlograms for the residuals of the regression models without seasonality at lags of 0-12 months for each age group. The y axes differ between panels.

Seasonality by sex

Figure 6-9 shows the seasonality of the rate of UTI consultations by sex and large groupings of age for which seasonality varies (<85 and 85+). UTIs in males followed a similar pattern to females; however, they were rare, which reduced statistical power to detect seasonality. Including a seasonal component into the regression model of the younger age group improved the model fit (the AIC decreased from 1092.5 to 1066.3 and the percentage deviance explained by the model more than doubled from 12.9 to 34.8). There was also an oscillatory pattern visible in the correlogram, although few correlations were significant. This contrasted with a clear lack of oscillatory shape in the correlogram for UTI consultations in males aged 85 and older and a lack of improvement in model fit when adding a seasonal term (the AIC increased from 816.5 to 819.1 and the percentage deviance explained by the model only increased very slightly from 32.9 to 35.3). This is similar to what is observed for trimethoprim and nitrofurantoin prescriptions (Figure 6-10).

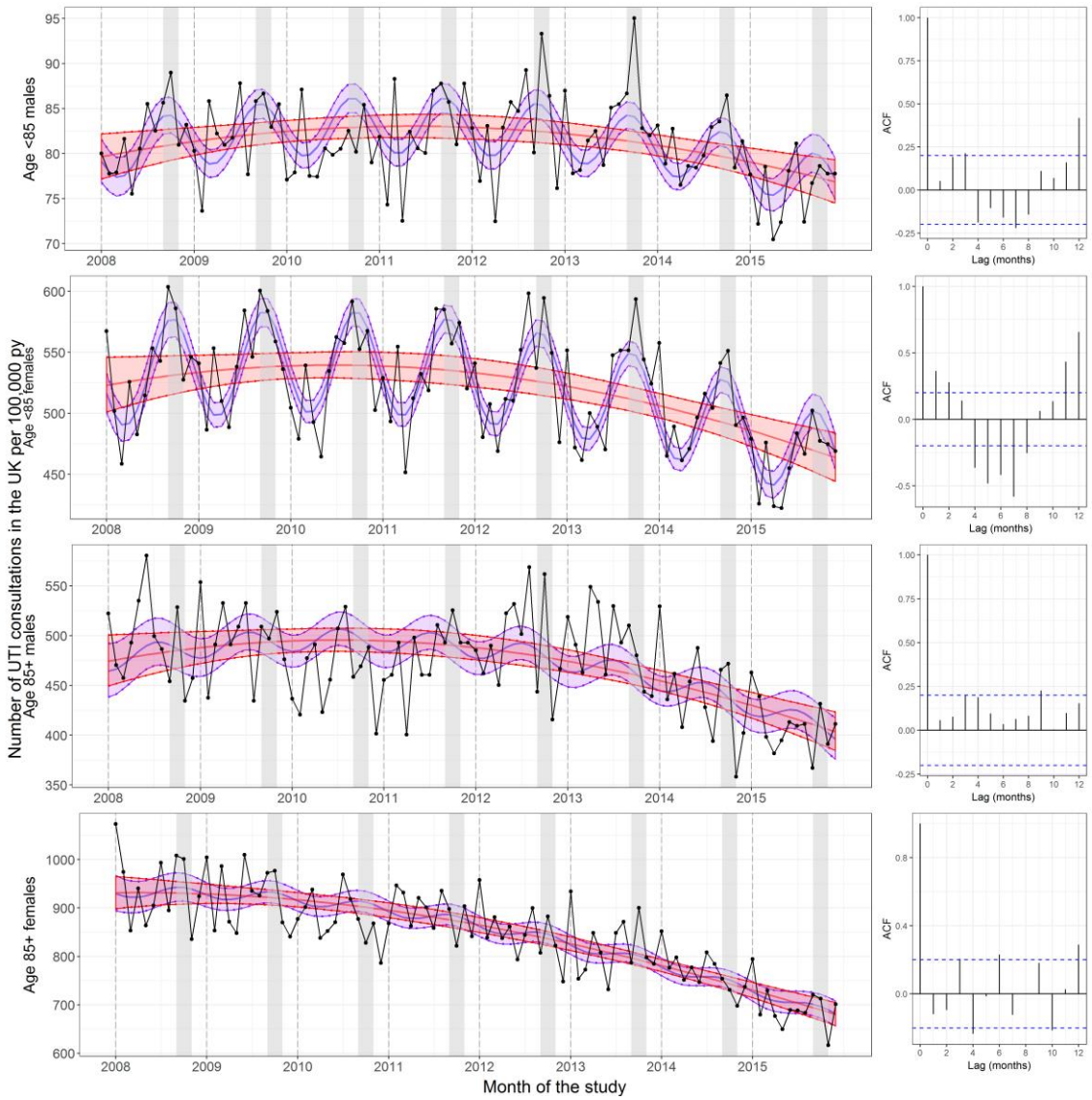

Figure 6-9. Seasonality in UTI consultations coded in the UK per 100,000 person years by age group and sex. The left panels show the rate of UTI consultations by age group and sex. The central red lines represent the fitted predictions of the negative binomial polynomial regression model of degree 2 with the number of patients registered at each of the GP practices on the 1st of July (mid-year) each year of the study as offset. The central blue lines represent the fitted predictions of the same model but with a seasonal component included. The shaded areas represent the 95% confidence intervals for their respective models. These were calculated using the standard errors from the predict function, which calculates the confidence intervals around the mean. The right panels show the correlograms for the residuals of the regression models without seasonality at lags of 0-12 months for each age group. The September to November period is shaded in grey. The UTI consultations were de-duplicated to 1 per 30-day period. The y axes differ between panels.

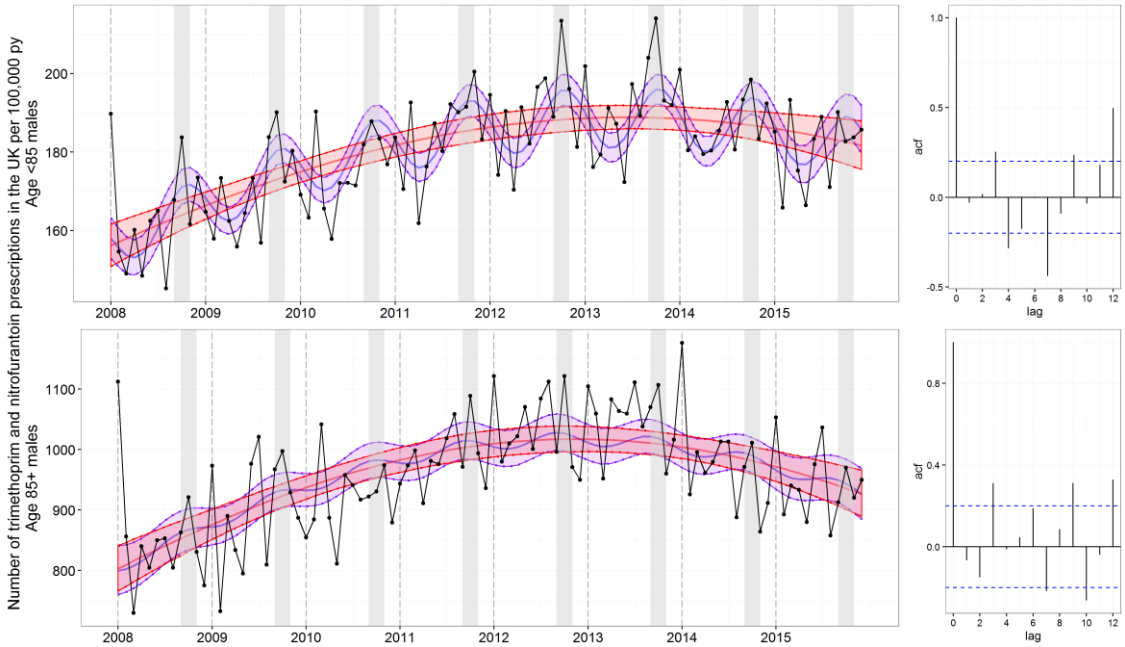

Figure 6-10. Monthly nitrofurantoin and trimethoprim prescriptions administered by GPs to males per 100,000 person years in the UK by age group. The nitrofurantoin and trimethoprim prescriptions were de-duplicated to one per 30-day period. The central red lines represent the fitted predictions of the negative binomial polynomial regression model of degree two with the number of patients registered at each of the GP practices on the 1st of July (mid-year) each year of the study as offset. The central blue lines represent the fitted predictions of the same model but with a seasonal component included. The shaded areas represent the 95% confidence intervals for their respective models. These were calculated using the standard errors from the predict function, which calculates the confidence intervals around the mean. The right panels show the correlograms for the residuals of the regression models without seasonality at lags of 0-12 months for each age group. The AIC of the model in those aged under 85 decreases (from 1262.5 to 1237.4) by including seasonality in older people, but remains similar in those aged 85+ (928.0 in the model without seasonality and 932.9 in the model with seasonality). The y axes differ between panels.

Discussion

Summary

There was a September to November peak in UTI consultations and in trimethoprim and nitrofurantoin prescriptions for UTI in those aged 14-69 in the UK; however, this seasonality gradually disappeared with age and was not apparent in those aged 85 or older. Similar patterns were observed for males and females, although male UTIs were rare, which reduced statistical power.

Mechanism

The exact mechanism surrounding the seasonality of UTI consultations observed is likely to be complex, involving interactions between real UTI incidence, healthcare seeking behaviour, access to care and severity. A full analysis of the mechanisms underlying the autumnal seasonality observed in younger age groups is beyond the scope of this study and warrants further research. However, these could be influenced by sexual behaviour patterns, as recent sexual intercourse is an important risk factor for UTI in young women[242]. Given that the seasonal peak was not in high summer, when one might expect more dehydration, the influence of dehydration and temperature on UTI incidence in younger age groups remains unclear.

Risk factors for UTI in older people include recurrent UTIs, incontinence, catheter use, disruptions to the normal vaginal flora, diabetes mellitus, prostatic hypertrophy (in men), and cognitive impairment or other comorbidities that may impede adequate self-hygiene[47]. These risk factors are less likely to be influenced by seasonal variation. UTIs in the very old can be considered a symptom of general frailty and poor care, such as consistent dehydration throughout the year, poor hygiene or inadequate catheter care. Our findings do not suggest a different seasonality in men and women; therefore, it is unlikely that the lack of seasonality detected in the very old is driven by the increase in the proportion of UTIs that are in males in this age group.

The decrease in GP consultations for UTI contrasts with the steady increase in admissions to hospital for UTIs in England (which did not include A&E

attendances)[10,34]. While these are not truly comparable datasets, this difference between the GP and hospital data could indicate an increase in severity of UTIs or treatment failure due to antibiotic resistance, which means UTIs could more frequently warrant hospitalisation. Increases in hospital admissions for UTI could also denote shortfalls in the management of UTI in the community, for example in social care and community nursing[5], as well as correct antibiotic treatment in primary care, which are important in preventing admissions to hospital. Antibiotic prescriptions were not used to assess the trend in UTIs over time, because nitrofurantoin and trimethoprim prescriptions for UTI as a proportion of all antibiotic prescriptions increased over the study period.

Findings in context

Many studies that addressed seasonality in the literature simply reported differences in incidence[222,227,230,232]. One of the studies set in the UK reported a peak in *S. saprophyticus* UTI in mid-September and a peak in all Gram-negative bacilli other than Proteus spp. and Pseudomonas spp. (aggregated) in March[229]. Gram-negative bacteria comprise the majority of the organisms that cause UTI; therefore, their findings are not in agreement with ours. That study assessed the seasonality of urine specimens from 1978-1983 and the epidemiology and sampling of UTIs could have changed greatly since then. The other study from the UK found a higher number of UTIs during the winter months in children seen in hospital in Durham[222]. As only adults in this study were studied and the authors did not report their methods, a comparison is not possible.

The seasonality of UTIs has been studied in other countries; however, the findings from these studies are also conflicting (Table 6-1). Two studies reported autumnal peaks in incidence[223,231]. However, neither employed appropriate methods to assess seasonality. Eriksson et al. (2012) only reported the monthly total of samples received for 1 year and Vorland et al. (1985) studied seasonality in large aggregated time periods, which resulted in loss of information.

In England, the seasonality of *E. coli* BSIs varied by region[243]. As the urinary tract has been reported to be a primary source of infection for bloodstream infections, the seasonality of UTIs could also vary by region.

Strengths and limitations

This study is the first to formally assess the trend and seasonality of UTI consultations in the UK. This was a large study carried out in THIN, which is a validated database of primary care consultation data covering over 3.7 million active patients which are demographically representative of the UK[235–237]. It was carried out over a period of 8 years (January 2008 to December 2015), which should help minimize the bias of detecting patterns that only occurred sporadically. In addition, the UTI consultations analysis was repeated for trimethoprim and nitrofurantoin prescriptions, which confirmed these findings.

The percentage of trimethoprim or nitrofurantoin prescriptions that had a UTI consultation coded on the same day (a proxy for UTI consultation coding) was low; however, it remained relatively stable during the study period, at between 35-41%. As this study focused on patients with UTIs that presented to primary care, these conclusions may not extend to complicated UTIs seen in hospital, nor to UTIs that resolved with over-the-counter medication such as alkalinising agents and didn't warrant a GP visit. In addition, although the analysis of seasonality in trimethoprim and nitrofurantoin prescriptions was used as a sensitivity analysis, there are also limitations in using these antibiotics as a proxy for UTI consultation as they do not make up the entirety of prescriptions for UTIs in secondary care.

Two alterations could have also been made to the model. Firstly, seasonality could have been modelled using alternative shapes. For example, a harmonic could have been added; however, although this model may have fit the data better, it would not change the findings of the study. Secondly, an alternative to separately modelling each age group and sex would be to combine these in a model and use interaction terms to estimate age-specific parameters of trend and seasonality.

Finally, care must be taken when extrapolating these findings beyond the UK setting, where the range of temperatures throughout the year is relatively small.

Clinical implications

Our findings highlight that UTI prevention in older people should warrant attention throughout the year, as UTIs in this population are common year round and can be regarded as a symptom of general frailty. We also provide helpful information for the interpretation of the results of interventions and surveillance reports. For example, a decrease in UTI incidence in spring could be due to the effectiveness of a trialled intervention against UTIs, the seasonal pattern in UTIs, which yearly decrease during this period, or a combination of both, and their effect should be disentangled in order to correctly interpret the intervention effectiveness. Oppositely, an increase in incidence or antibiotic prescription during the autumn should be interpreted in the context of the yearly peak observed during this time.

Further research

Further research should focus on the prevention of UTI in older people, as this was the population with the highest burden of UTI. This study did not identify an impact of season on the incidence of UTI in this population; therefore, further research on the impact of patient and clinical factors is needed to identify areas that could be targeted for quality improvement. In addition, understanding the causes of the peak in UTI incidence during the autumn in those aged 14-69 could then help select strategies for their avoidance and treatment. It would also be interesting to determine the susceptibility of samples taken during GP UTI consultations. This would help give more precise estimates of the prevalence of resistance, as the proportion of UTIs sampled would be recorded, and identify the comorbidity and prescribing practices associated with antibiotic resistance, which would help target interventions appropriately. However, there is no routinely collected dataset in England that captures both GP consultations and susceptibility data.

The contrast between the decrease in GP consultations for UTI in this analysis and the steady increase in admissions to hospital for UTIs in England (which did

not include A&E attendances)[10,34] also warrants further study. The Clinical Practice Research Datalink (CPRD) database, which is a similar dataset to THIN, comprising GP consultation data from practices representative of the UK, has been linked to the Hospital Episode Statistics (HES) database. This dataset may be useful to track the most commonly occurring UTI pathways in older people and identify the main adverse outcomes resulting from UTI (e.g. recurrent UTI, hospital admission, progression to blood stream infection). The association between antibiotic prescribing practice and UTI progression to adverse outcomes could also be quantified using these data. This will be important in order to improve the community management of UTIs and prevent unnecessary admissions to hospital in the future.

LTCF residence is poorly recorded in GP and hospital records. Identifying LTCF residents within the CPRD-HES database would enable the comparison of these patient pathways for LTCF residents and older people living in the community. In addition, this would provide the first large source of data of antibiotic prescribing data for this population in England.

Conclusions

This study is the first to formally assess the trend and seasonality of UTI consultations in the UK. This was a large study comprising UTI consultations from January 2008 to December 2015. Two distinct age-dependent patterns of seasonality were found in the UK. UTI consultations in those aged 14-69 peaked from September to November. This seasonality gradually disappeared with age and was not apparent in those aged 85 or older. Similar patterns were observed for males and females, although male UTIs were rare. This analysis was repeated for trimethoprim and nitrofurantoin prescriptions, in England, confirming these findings. These results suggest that, unlike in those ages 14-69, UTIs in older people are not associated with seasonal factors, suggesting that UTI prevention in this population should warrant attention throughout the year. In addition, the autumnal peak observed in those aged 14-69 provides helpful information for the interpretation of the results of interventions and surveillance reports. Further research should focus on the prevention of UTI in older people, and on understanding the causes of the peak in UTI incidence during the autumn in those aged 14-69. In addition, GP data provides exciting opportunities for linkage with hospital, susceptibility and LTCF data, which could yield interesting insights into the pathways of UTI progression in older people. Insight from these studies could help identify key factors that could be targeted to prevent hospitalisations.

Chapter 7 Mathematical modelling of the transmission of *E. coli* resistant trimethoprim in the LTCF

Aims

1. To develop a mathematical model which describes the movement of patients in and out of a LTCF and describes the transmission dynamics of trimethoprim resistance
2. To parameterise this model using the best available data and literature sources.
3. To carry out sensitivity analyses on this parameter set.

Introduction

In Chapter 5, it was shown that LTCF residents were more than four times more likely than community dwelling older people to develop a laboratory confirmed *E. coli* UTI caused by resistant bacteria; and that 60% of *E. coli* from urine specimens taken from LTCF residents were resistant to trimethoprim. These figures highlight the need for understanding the dynamics of trimethoprim resistance in this setting.

Resistance to first-line treatments for UTI such as trimethoprim and nitrofurantoin can result in treatment failure, hospitalisation, and the subsequent use of antibiotics such as ciprofloxacin or 3GCs that should be reserved for the treatment of more serious infections. The reduction of inappropriate antibiotic prescribing for UTIs in primary care is precisely one of the targets of the Quality Premium Scheme developed by NHS England for reducing gram-negative BSIs.[244] As explained in Chapter 5, in 2014, national primary care prescribing guidelines have switched from recommending trimethoprim as first-line treatment for UTI to recommending nitrofurantoin (unless there is a low risk for resistance to trimethoprim, in which case trimethoprim is also recommended).[50] Although in line with these recommendations, trimethoprim prescription has decreased during 2014-2015; trimethoprim is still the most commonly prescribed antibiotic in the community for UTI.[35] In addition, 86% of CCGs in

England found that 25% of their community urine specimens were resistant to trimethoprim.

As described in Chapters 2 and 3, dynamic mathematical models are important tools in epidemiology and public health which have been used to understand the epidemiology of infectious diseases, including AMR infections, to target interventions appropriately and to evaluate their health and economic impact.[82–85] Although infectious disease transmission has been modelled extensively in the hospital setting, few mathematical models have characterised the spread of infectious diseases in the LTCF setting (27 studies). Only three studies have modelled the transmission of AMR Gram-negative bacteria in LTCFs (two of carbapenem-resistant *Enterobacteriaceae* [132,133] and one of *E. coli* ST131[134]).

This is an important gap in the literature for multiple reasons. Firstly, understanding the dynamics of AMR Gram-negative bacteria in LTCFs is vital. Gram-negative bacteria are now the most common cause of hospital-acquired infection in England, Wales, and Northern Ireland, including very severe infections such as BSIs[28]. As shown in Chapter 5, AMR Gram-negative bacteria are of particular concern in the LTCF setting, where the prevalence of UTI caused by AMR bacteria is higher than in hospitals and the rate of acquiring a UTI caused by *E. coli* and *Klebsiella* resistant to antibiotics is more than four times this rate in the remaining community. Understanding the epidemiology of infections caused by AMR *E. coli* is particularly important, as these bacteria are ubiquitous in the human gut.

Secondly, the dynamics of infections caused by AMR *E. coli* are poorly understood through regression models, as shown in Chapter 6, where a negative binomial model including a seasonality component was fit to *E. coli* UTI incidence data and was unable to account for all the residual variance observed in the data. A dynamic mathematical model should help elucidate the additional variance in the data that has not been accounted for in the negative binomial regression.

Thirdly, mathematical models can incorporate patient movement dynamics between different institutions such as between LTCFs and hospitals, which may be important for the spread of AMR.

The three studies that modelled the transmission of AMR Gram-negative bacteria in LTCFs published since the initial review focused on infections caused by particularly pathogenic Gram-negative bacteria, such as *E. coli* ST131, or bacteria resistant to third-line antibiotics such as carbapenems. These may not be representative of most Gram-negative bacteria transmitted in LTCFs. As shown in Chapter 5, in the LTCF setting, the most prevalent resistance in UTIs caused by *E. coli* was the resistance to trimethoprim.

Antibiotic treatment increases the risk of colonisation and subsequent infection by resistant bacteria, and therefore, is an important factor to capture when modelling the transmission of AMR bacteria.[28] One of these three studies explored the effect of antibiotic treatment (fluoroquinolones and cephalosporins) on resistance. However, no study to date has explored the dynamics of the transmission of trimethoprim resistant *E. coli* in the LTCF setting.

The incidence of urinary *E. coli* resistant to trimethoprim used for model fitting was derived from the West Midlands AmSurv dataset (described in Chapters 4 and 5). Consequently, the model was set in the West Midlands and all other parameters were, when possible, adjusted to represent the dynamics of transmission of *E. coli* resistant to trimethoprim in LTCFs within this region.

Methods

Modelling approach

Modelling the dynamics of trimethoprim resistant *E. coli* in a LTCF involved a number of processes. First, a compartmental stochastic dynamic transmission model was developed. This was then parameterised with data from a variety of sources. CQC registry data, microbiology samples from hospitals and GPs, and electronic health records were used. Where suitable data was not available, parameters were informed by the literature. Where possible, data from the West Midlands were used. As there were no suitable transmission parameters in the literature, the model was fit to incidence data, adjusted for case reporting, using maximum likelihood estimation.

The baseline scenario involved fitting the model to incidence data from a LTCF in the highest incidence quartile to determine the values of the transmission parameters. All remaining parameters were kept at their most plausible values, as estimated from data or the literature.

Sensitivity analyses were then carried out to test the influence of varying the model parameters within plausible ranges to the model outputs. This included varying the LTCF selected for model fitting.

In addition, three scenarios were simulated: one in which the transmission rate was varied, one in which the proportion of residents discharged to the LTCF from hospital (vs. the community) was varied, and one in which the rate of trimethoprim prescription was increased.

Model structure and description

A compartmental stochastic dynamic transmission model was developed to simulate the transmission of trimethoprim-resistant *E. coli* in a LTCF in the West Midlands and the movement of patients in and out of the LTCF.

All patients were assumed to be colonised with *E. coli*. This is because *E. coli*, although also sometimes a pathogen, is a common constituent of the healthy gut microbiota.[12,245] Therefore, this model assumed no uncolonised individuals

were present in the LTCF. Due to the lack of data available to parameterise a mathematical model of co-colonisation with sensitive and resistant bacteria, a simple model was developed in which individuals could either be dominantly colonised with *E. coli* susceptible to trimethoprim or dominantly colonised with *E. coli* resistant to trimethoprim. In this model structure, those colonised with *E. coli* sensitive to trimethoprim are equivalent to 'susceptible' individuals in a traditional SIS model. Only the transmission of *E. coli* resistant to trimethoprim, which displaced the 'normal' *E. coli* gut flora (*E. coli* sensitive to trimethoprim), was simulated. It was assumed that residents, if untreated with trimethoprim, reverted to being colonised by *E. coli* sensitive bacteria at rate γ.

LTCF residents could be either treated with trimethoprim or not. Treatment with other antibiotics was not modelled. LTCF residents were divided into four compartments according to whether they were colonised with *E. coli* sensitive to trimethoprim or resistant to trimethoprim, and whether they were being treated with trimethoprim or not.

Individuals could leave the LTCF by either dying or being hospitalised, and could either enter the LTCF directly from hospital or from the community. Transfer between LTCFs and discharges of LTCF residents to the community were not accounted for because they were considered to be comparatively rare events.

This model can be subdivided in three distinct types of processes: transmission, treatment and movement of patients in and out of the LTCF. A schematic of the compartmental model can be found in Figure 7-1.

In the LTCF, patients were divided into four compartments according to whether they were being treated with trimethoprim (T, treated) or not (U, untreated) and whether they were colonised with *E. coli* sensitive to trimethoprim (Us and Ts) or resistant to trimethoprim (Ur and Tr). The size of the LTCF, N, was the sum of the number of individuals in compartments Us, Ur, Ts and Tr. This was kept constant through the study.

Individuals left the LTCF by either dying (D) or by going to hospital (H). Individuals were not assumed to re-enter the community. Individuals could either enter the LTCF directly from hospital or from the community.

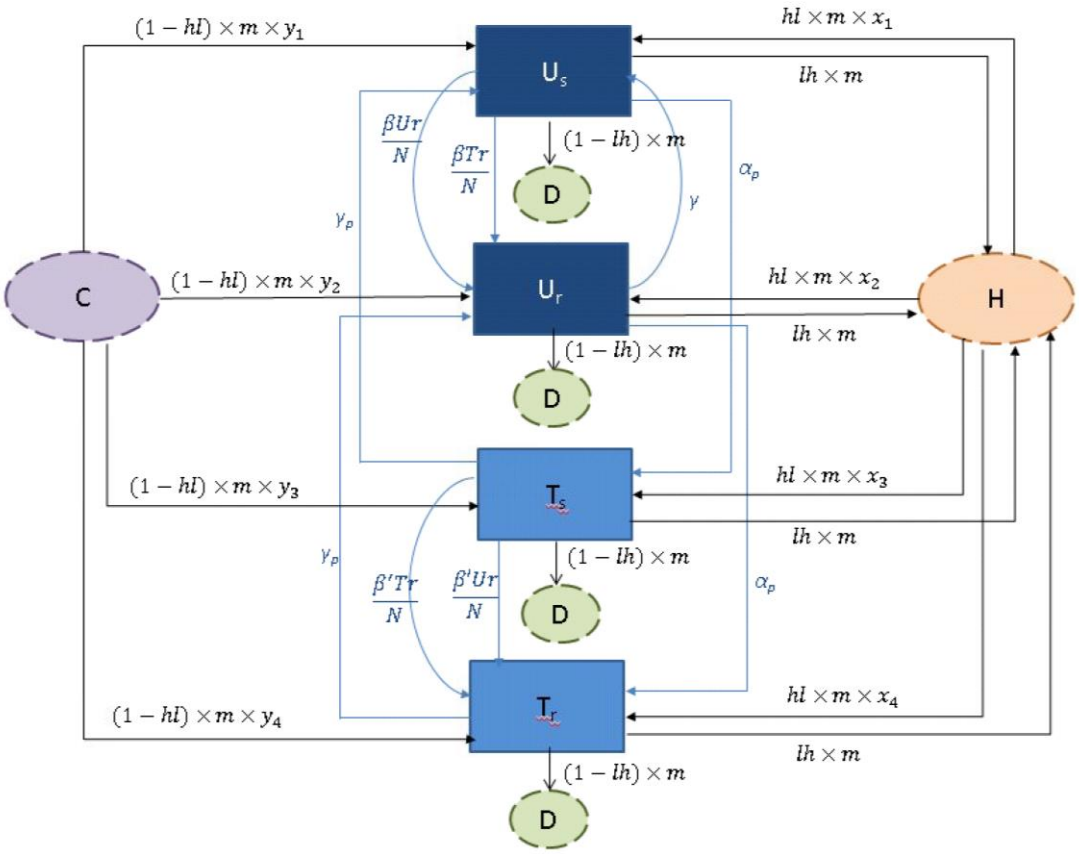

Figure 7-1. Model structure. In purple (C), the community; in blue (Us, Ur, Ts, and Tr), the LTCF; in orange (H), the hospital; and in green (D), the dead. Us were individuals untreated with trimethoprim colonised with *E. coli* susceptible to trimethoprim, Ur were individuals untreated with trimethoprim colonised with *E. coli* resistant to trimethoprim, Ts were individuals treated with trimethoprim colonised with *E. coli* susceptible to trimethoprim, and Tr were individuals treated with trimethoprim colonised with *E. coli* resistant to trimethoprim. N was the total population of the LTCF ($Us + Ur + Ts + Tr$). β was the rate of transmission of resistance to untreated individuals in the LTCF, β' was the rate of transmission of resistance to treated individuals in the LTCF, γ was the rate of recovery from colonisation by *E. coli* resistant to trimethoprim in the LTCF, α_p was the rate of trimethoprim treatment in the LTCF, γ_p was 1/average duration of trimethoprim treatment in the LTCF, m was the rate of exit or entrance into the LTCF (the rate of deaths from the LTCF + hospitalisations from the LTCF, or the rate of admissions to the LTCF from hospital and the community), hl was the proportion of admissions to the LTCF from hospital (vs. community), and lh was the proportion of residents who leave the LTCF and go to hospital (vs. die). x_1, x_2, x_3, and x_4 were the proportions of Us, Ur, Ts and Tr (respectively) out of the total population discharged to the LTCF from hospital ($x_1 + x_2 + x_3 + x_4 = 1$). y_1, y_2, y_3, and y_4 were the proportions of Us, Ur, Ts and Tr (respectively) out of the total population admitted to the LTCF from the community ($y_1 + y_2 + y_3 + y_4 = 1$).

Model equations

$$\frac{dUs}{dt} = -\frac{\beta\ Us\ Ur}{N} - \frac{\beta\ Us\ Tr}{N} - (\alpha_p\ Us) - [(1-lh)\ m\ Us] - (lh\ m\ Us) + (\gamma Ur) + (\gamma_p\ Ts) + (N\ m\ hl\ x_1) + (\mathrm{N}\ m\ (1-hl)\ y_1)$$

$$\frac{dUr}{dt} = -(\gamma\ Ur) - (\alpha_p Ur) - [(1-lh)\ m\ Ur] - (lh\ m\ Ur) + \frac{\beta\ Us\ Ur}{N} + \frac{\beta\ Us\ Tr}{N} + (\gamma_p Tr) + (N\ m\ hl\ x_2) + (\mathrm{N}\ m\ (1-hl)\ y_2)$$

$$\frac{dTs}{dt} = -\frac{\beta'\ Ts\ Tr}{N} - \frac{\beta'\ Ts\ Ur}{N} - (\gamma_p Ts) - [(1-lh)\ m\ Ts] - (lh\ m\ Ts) + (\alpha_p\ Us) + (N\ m\ hl\ x_3) + (\mathrm{N}\ m\ (1-hl)\ y_3)$$

$$\frac{dTr}{dt} = -(\gamma_p Tr) - [(1-lh)\ m\ Tr] - (lh\ m\ Tr) + \frac{\beta'\ Ts\ Tr}{N} + \frac{\beta'\ Ts\ Ur}{N} + (\alpha_p Ur) + (N\ m\ hl\ x_4) + (\mathrm{N}\ m\ (1-hl)\ y_4)$$

In red, the equation terms relating to transmission; in blue, the equation terms relating to antibiotic treatment; in green the equation terms relating to movement in and out of the LTCF. This model was coded and simulated using the pomp package in R.[246,247]

Assumptions

General

1. All individuals are colonised with *E. coli*.
2. There is dominance of a single strain of *E. coli* in a colonised individual, and this strain is either resistant or susceptible to trimethoprim. This binary process means that:
    a. Between strain competition is not modelled, and
    b. Colonisation with other bacteria is assumed to not affect the colonisation with *E. coli*.
3. The time between events is exponential.
4. The model is run per 0.1 day and the reporting period is weekly.
5. The proportion of individuals predominantly colonised with *E. coli* resistant to trimethoprim (vs. susceptible) is the same as the proportion of individuals presenting with a UTI caused by *E. coli* resistant to trimethoprim (vs. susceptible).

6. A separate analysis of the seasonality of uncomplicated UTIs (described in Chapter 6) found that UTIs in older people were not seasonal; therefore, seasonality was not included in this model.

Transmission

7. Only person-to-person transmission is considered. The rate of acquiring dominance by an *E. coli* strain resistant to trimethoprim through endogenous factors (for example, spontaneous mutation) is not modelled explicitly, as these were considered comparatively rare events and data was not available to parameterise this.
8. Transmission of *E. coli* resistant to trimethoprim is only modelled between LTCF residents (including, implicitly, via healthcare workers). The transmission of resistance from the remaining population, including from healthcare workers and visitors, was not modelled.
9. Transmission is frequency dependent (vs. density dependent). This means that the contact rate between individuals does not depend on the population density.
10. Patients mix homogenously within the LTCF. This is a simplifying assumption but unlikely to be true, as there may be little mixing between floors of a LTCF and some highly dependent residents may leave their rooms infrequently compared to other more mobile residents.
11. Control measures in place for colonised individuals are not modelled explicitly.

Treatment

12. Colonisation with *E. coli* resistant to trimethoprim cannot be lost during trimethoprim treatment. The fitness cost is assumed smaller than the selection pressure for the duration of treatment.
13. Co-selection is assumed not to take place; meaning the effect of other antibiotic treatment is minimal in acquiring trimethoprim resistance.
14. All individuals independently of their carriage status were exposed to antibiotic treatment at the same rate.

15. Both individuals treated and untreated who are predominantly colonised by *E. coli* resistant to trimethoprim (Tr and Ur, respectively) are able to transmit resistant *E. coli* to individuals treated and untreated who are predominantly colonised by *E. coli* sensitive to trimethoprim (Ts and Us, respectively).
16. Treated individuals who are predominantly colonised by *E. coli* resistant to trimethoprim (Tr) and untreated individuals who are predominantly colonised by *E. coli* resistant to trimethoprim Ur are able to transmit resistance at the same rate.
17. During the acquisition of resistance by treated individuals predominantly colonised by *E. coli* sensitive to trimethoprim (Ts), the transmission rate is higher than during the acquisition of resistance by untreated individuals predominantly colonised by *E. coli* sensitive to trimethoprim (Us), by a factor of tr. A successful transmission in the treatment scenario is benefited by the removal of other competing bacteria susceptible to trimethoprim.
18. Endogenous acquisition of resistance by treated individuals predominantly colonised by *E. coli* sensitive to trimethoprim (Ts) within one individual is not explicitly simulated.

LTCF

19. In the baseline scenario, the LTCF simulated was selected from the LTCFs in the quartile with the highest incidence of urine *E. coli* samples sent to AmSurv, which were resistant to trimethoprim per bed day. This was to ensure that sufficient samples were present to enable model fitting and to ensure that transmission (if present at all in the LTCF setting) was detected. LTCFs from the other three quartiles of incidence were simulated in sensitivity analyses.
20. Full bed occupancy in LTCFs. Therefore, the size of the LTCF was kept constant during the study.
21. Being colonised with *E. coli* resistant to trimethoprim does not impact the length of stay.

22. Individuals can be admitted to the LTCF either from hospital or from the community, and can be discharged from the LTCF to be hospitalised or due to death. Residents cannot transfer between LTCFs.
23. Transfers from the LTCF to hospital and deaths (respectively) are equally probable for residents colonised *E. coli* sensitive and resistant to trimethoprim.
24. The proportion of individuals admitted to the LTCF treated (vs. untreated) and colonised with *E. coli* resistant (vs. sensitive) to trimethoprim from hospital and from the community depend on the proportion of individuals within these categories in hospital and the community (respectively).

Many of these assumptions were simplifications that were driven by a lack of data available to inform a more complex model. The validity of these assumptions is considered further in the discussion.

Data

The model was parameterised using four sources of data: susceptibility data from urinary *E. coli* samples submitted to AmSurv in the West Midlands (linked to CQC data, as described in Chapter 4), CQC data on LTCF characteristics, a point-prevalence survey of antimicrobial use in acute care hospitals in England[40], THIN data on trimethoprim prescribing, as well as values from the literature.

The first source of data was the publicly available registry of LTCFs in England held by the CQC.[152] Only LTCFs in the West Midlands region classified as "care homes" for elderly residents and recorded as active in the register from 2011/2012 (797 LTCFs) were selected for analysis. LTCFs in this registry were classified according to the number of beds in each facility and nursing status (nursing LTCFs were LTCFs with 24-hour medical care from qualified nursing staff and residential LTCFs were those without this service). The length of stay in LTCFs (used to parameterise m), the rate of hospital admission of LTCF patients (used to parameterise lh), and the rate of discharge of hospitalised patients to LTCFs (used to parameterise hl) were all derived from studies which estimated these parameters by LTCF nursing status. The CQC dataset was

used to scale the parameters from the literature to represent the distribution of nursing LTCFs registered in the West Midlands.[9,248,249]

The second source of data used for parameterisation was the AmSurv dataset, which was linked to CQC data and is described in detail in Chapter 4. Briefly, AmSurv is an AMR surveillance tool established by the Health Protection Agency (now Public Health England) in 2009 which collects antibiotic susceptibility testing results from routine microbiology samples sent to participating diagnostic laboratories in England from both hospitals and GPs.[186] Since December 2012, all laboratories in the West Midlands report to AmSurv, making data from this region the most complete longitudinal source of AMR surveillance information in England, with more than 95% of laboratories currently participating. Following national guidelines from Public Health England, all urine samples were assumed to be submitted due to clinical need and, therefore, were indicative of a suspected UTI.[196] The AmSurv dataset used for parameterisation in this chapter includes the trimethoprim susceptibility results from all urine specimens collected from individuals aged 70 or older, which were reported from the 15 microbiology laboratories in the West Midlands to AmSurv from 01/04/2010 to 31/03/2014. The AmSurv dataset was linked to CQC data to determine which antibiotic susceptibility tests in the AmSurv dataset were from individuals that resided in LTCFs. This combined dataset was used to derive (1) the weekly incidence of UTIs caused by *E. coli* resistant to trimethoprim for each LTCF, which was used to fit the model; (2) the number of beds in each LTCF selected for model fitting; (3) the proportion of individuals colonised by *E. coli* resistant to trimethoprim (vs. susceptible to trimethoprim) in the community, calculated from samples submitted by GPs from individuals residing outside of LTCFs (used to parameterise prc); and (4) the proportion of individuals colonised by *E. coli* resistant to trimethoprim (vs. susceptible to trimethoprim) in hospitals, calculated from samples submitted by hospitals from individuals residing outside of LTCFs (used to parameterise prc).

A point-prevalence survey of antimicrobial use in acute hospitals in England performed in 2016 was used to parameterise the proportion of patients treated with trimethoprim in hospitals.[40] A personalised extract of the West Midlands

hospital data was extracted for the purposes of this model. Only three NHS Trusts from the West Midlands were included in this dataset. This point-prevalence survey was carried out in patients of all ages.

Finally, data from THIN (described in more detail in Chapter 6) was used to derive the proportion of registered days in which individuals aged 70 or over in the community in the West Midlands were exposed to trimethoprim (ptc). Only data from April 2010 to March 2014 was analysed in order to match the AmSurv study period. The rate of trimethoprim prescription in the community was also calculated from THIN prescription data from this period and scaled using values from the literature to derive the rate of trimethoprim treatment in the LTCF (α_p). Finally, THIN was also used to calculate the duration of trimethoprim treatment (used to derive γ_p). THIN is a validated database of primary care consultation data covering over 3.7 million active patients which are demographically representative of the UK[235–237].

Parameter sources and values

A summary of the parameter sources and values is presented in Table 7-1. Parameters relating to the movement in and out of the LTCF were derived from the literature and were adjusted using CQC data to match the characteristics of the LTCFs in the dataset used for model fitting.[152] Parameters relating to antibiotic resistance and the incidence data used to fit the model were derived from AmSurv data. Parameters relating to treatment were estimated from the hospital point-prevalence survey and THIN data (scaled by values from the literature when appropriate). Finally, parameters relating to transmission were both derived from the literature and were estimated by fitting the model to AmSurv data.

Table 7-1. Parameters in the model

Parameter		Source type	Value
β	Rate of transmission of resistance to untreated individuals in the LTCF	Estimated	0.0062 per person per day
β'	Rate of transmission of resistance to treated individuals in the LTCF	Estimated	1.5 per person per day
γ	Rate of recovery from colonisation by *E. coli* resistant to trimethoprim in the LTCF or 1/average duration of colonisation with *E. coli* resistant to trimethoprim in the LTCF	Literature[250–254]	0.0035 per person per day (sensitivity analysis 0.0025-0.0055)
α_p	Rate of trimethoprim treatment in the LTCF	Unpublished data from THIN scaled using literature. [69]	0.001 per person per day (varied in sensitivity analyses)
γ_p	1/average duration of trimethoprim treatment in the LTCF	Unpublished data from THIN and the national guidelines[50]	0.2 (sensitivity analysis 0.16-0.3, 3-6 days duration)
m	Entry/exit rate into/out of the LTCF or 1/average LOS in LTCF	Literature[248] adjusted using CQC data.	0.002 per person per day
lh	Proportion of residents who leave the LTCF that go to hospital (vs. die)	Literature[9,249] adjusted using CQC data.	0.8 (sensitivity analysis 0.77-0.9)
hl	Proportion of admissions to the LTCF from hospital (vs. community)	Literature[248] adjusted using CQC data.	0.6057 (sensitivity analysis 0.4057)
prc	Proportion of residents admitted to the LTCF from the community colonised with *E. coli* resistant to trimethoprim $(Ur + Tr)/N$	Unpublished data from AmSurv)	0.3602 (fitted linear regression model in sensitivity analysis)
ptc	Proportion of residents admitted to the LTCF from the community on trimethoprim treatment $(Ts + Tr)/N$	Unpublished data from THIN	0.0049 (fitted linear regression model in sensitivity analysis)
pth	Proportion of treated $(Ts + Tr)/N$ discharged to the LTCF from hospital	Data from a point-prevalence survey in hospitals.[40]	0.0248 (sensitivity analysis 0.017-0.032)
prh	Proportion of residents discharged to the LTCF from hospital colonised with *E. coli* resistant to trimethoprim $(Ur + Tr)/N$	Unpublished data from AmSurv)	0.3792 (fitted linear regression model in sensitivity analysis)
rho	Probability of a patient colonised with a resistant *E. coli* developing a UTI for which a sample is taken and the results are reported to AmSurv	Estimated	0.55

Parameters describing the movement in/out of LTCFs

Parameters in this section relate to the movement of patients in and out of the LTCF. m describes the rate of entering or exiting the LTCF (which were assumed to be the same), lh and hl describe the proportion of residents admitted to hospital from the LTCF (vs. dying) and discharged to the LTCF from hospital (vs. the community), respectively. pth, ptc, prh and pth describe the proportion of individuals treated (vs. untreated) and colonised by *E. coli* resistant to trimethoprim (vs. susceptible) in the community and in hospital. Together, these parameters define the flow in and out of the LTCF for each of the four types of individuals in this compartmental model (Us, Ur, Ts and Tr).

- $\boldsymbol{m}$: rate of entry or exit into the LTCF- i.e. rate of (deaths from the LTCF + hospitalisations from the LTCF) or rate of (admissions to the LTCF from hospital + admissions to the LTCF from the community)

The length of stay in LTCFs was obtained from the literature, and, in the absence of specific data for the West Midlands population, it was scaled to represent the LTCFs registered in the West Midlands. Using CQC data (described above), values taken from Steventon et al.[248] were scaled as follows: Steventon et al. estimated the number of days spent in permanent LTCFs (544.5 days), and in nursing LTCFs (283 days) using data from three local authorities in England (a seaside town, a rural area and a London suburb). In the West Midlands CQC dataset, 35.38% of LTCFs were nursing LTCFs and 64.62% were residential LTCFs. Therefore, the estimated length of stay overall was (544.5 * 0.6462) + (283 * 0.3538) = 451.98. m, and the birth or death rate into the LTCF was, therefore, 1/451.98=0.002 per person per day.

- $\boldsymbol{lh}$: the proportion of residents who leave the LTCF that go to hospital (vs. die)

The proportion of residents who leave the LTCF and go to hospital (vs. die), lh, was estimated using published values for the rate of hospitalisation of LTCF

residents, scaled to represent the LTCFs registered in the West Midlands using CQC data (described above), and in combination with parameter m.

$Rate\ of\ hospitalisation\ of\ LTCF\ residents = lh \times m$. Therefore,

$$lh = \frac{Rate\ of\ hospitalisation\ of\ LTCF\ residents}{m}.$$

The rate of hospital admission of LTCF residents aged 75 or older estimated by Sherlaw-Johnson et al.[249] was 0.45 per available bed per year for nursing homes and 0.62 per available bed per year for residential homes. In the West Midlands CQC dataset, 35.38% of LTCFs were nursing LTCFs and 64.62% were residential LTCFs. Therefore, the estimated rate of hospitalisation per day was ((0.62 * 0.6462) + (0.45 * 0.3538))/365 = 0.00153. Substituting this value in the equation above,

$$lh = \frac{0.00153}{0.002} = 0.767.$$

The Quality Watch study by Smith et al.[9] reported 246,031 admission episodes to hospital for 374,191 maximum potential service users in a year. Therefore, the estimated rate of hospitalisation per day was 246,031/374,191/365=0.0018. Substituting this value in the equation above,

$$lh = \frac{0.0018}{0.002} = 0.9.$$

In absence of better estimates that would apply specifically to the LTCFs studied in the West Midlands, lh was set at a value between that of these two studies (0.8), and the range of these values (0.77-0.9) was explored in sensitivity analyses.

- $\boldsymbol{hl}$: the proportion of admissions to the LTCF from hospital (vs. community)

hl was derived from published values from the literature, scaled to represent the LTCFs registered in the West Midlands using CQC data (described above).

Steventon et al. 2012[248] reported that 55.9% permanent admissions to residential care were preceded by emergency admissions (45.1%) and elective admissions (10.8%) to hospital during the 3 months prior to admission, and that 69.1% admissions to nursing homes were preceded by emergency admissions (56.7%) and elective admissions (12.4%) to hospital during the 3 months prior to admission. In the West Midlands CQC dataset, 35.38% of LTCFs were nursing LTCFs and 64.62% were residential LTCFs. Using these data, the values obtained from Steventon et al. 2012[248] were scaled to derive the estimated proportion of admissions to the LTCF from hospital (vs. community) as follows: (55.9* 0.6462) + (69.1 * 0.3538) = 60.57%. This was likely to be an overestimate because not all patients that visited hospital within the previous 3 months will have been directly discharged to the LTCF from hospital. Therefore, the value of hl was decreased by 20% in a sensitivity analysis.

- $\boldsymbol{pth}$: the proportion of treated (Ts + Tr)/N discharged to the LTCF from hospital

pth was derived from a point prevalence study of hospitals in England carried out in patients of all ages (described above). Two West Midlands NHS trusts were included in this survey: the Burton Hospitals NHS foundation trust, in which 3.23% patients were being treated with trimethoprim, and The Royal Wolverhampton NHS Trust, in which 1.73% of patients were being treated with trimethoprim. The mean between these two NHS trusts, (3.23+1.73)/2=2.48% was taken as the estimate for pth. The range of values between these two trusts (1.73-3.23%) was considered in the sensitivity analyses.

- $\boldsymbol{prh}$: the proportion of residents discharged from the hospital to the LTCF colonised with *E. coli* resistant to trimethoprim (vs. susceptible): (Ur + Tr)/N

prh was obtained from West Midlands AmSurv data (described above). Over the study period 37.92% of urine *E. coli* samples sent by hospitals from individuals aged 70 or older that did not reside in a LTCF postcode were resistant to trimethoprim. This proportion of individuals with a resistant *E. coli*

urine sample submitted to AmSurv (vs. susceptible) was assumed to be the same as the proportion of individuals predominantly colonised with *E. coli* resistant to trimethoprim (vs. susceptible).

Trimethoprim resistance increased during the study period. Therefore, in a sensitivity analysis, a linear regression was fit to the weekly AmSurv data and prh was modelled as the function for this linear regression:

$$prh = 0.3424633 + (0.0003089331 * (\text{week of the study})).$$

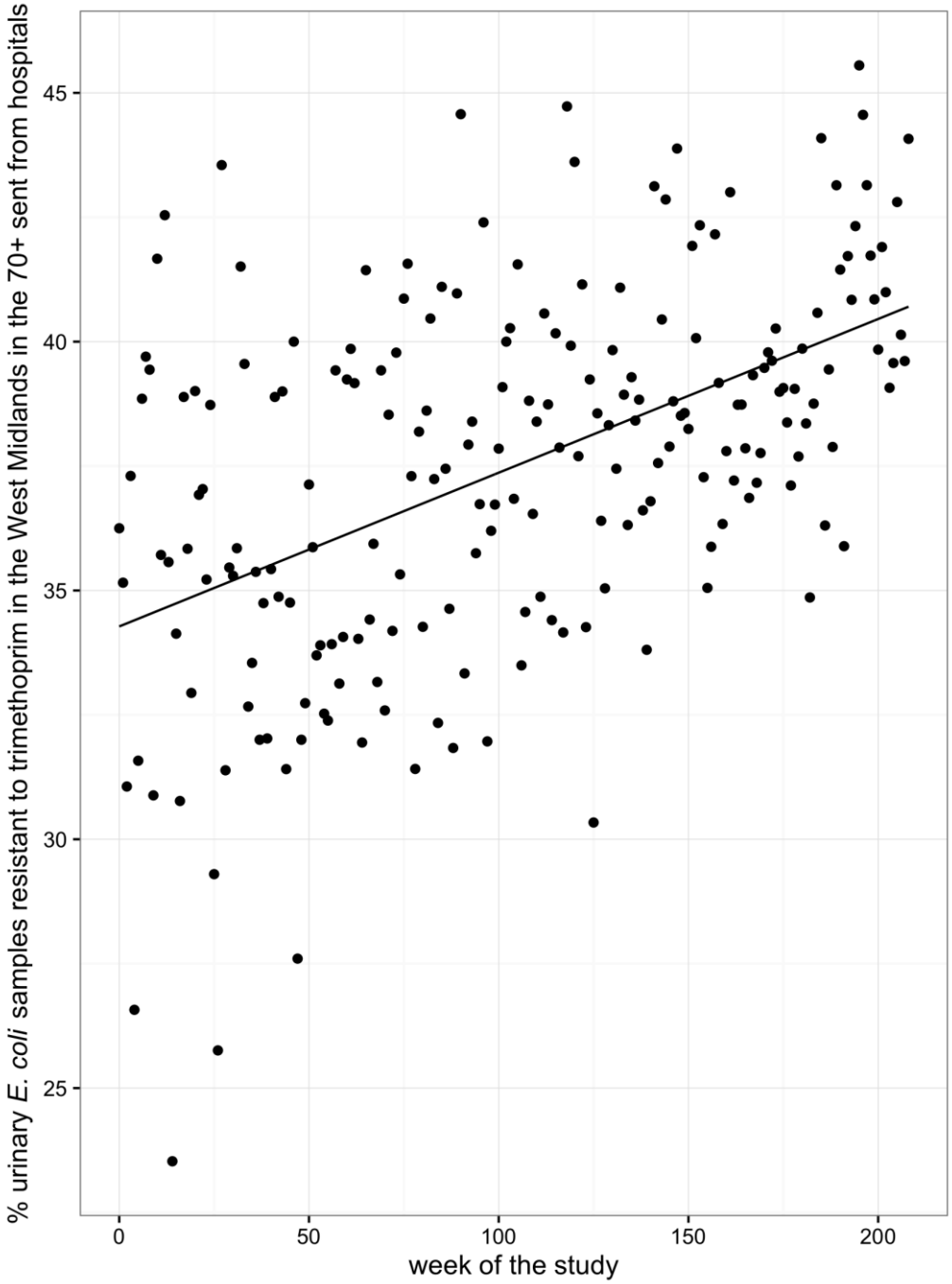

Figure 7-2. Percentage of urinary *E. coli* samples resistant to trimethoprim submitted to AmSurv by hospitals in the West Midlands from individuals aged 70 and over. April 2010 to March 2014.

- $\boldsymbol{x1}, \boldsymbol{x2}, \boldsymbol{x3}, \boldsymbol{x4}$: the proportion of admissions to the LTCF from hospital into the Us, Ur, Ts and Tr compartments (respectively)

$x1+ x2+ x3+ x4=1$

$x1$: the proportion of Us/N discharged to the LTCF from hospital

$$= (1 - prh) \times (1 - pth)$$

$x2$: the proportion of Ur/N discharged to the LTCF from hospital

$$= prh \times (1 - pth)$$

$x3$: the proportion of Ts/N discharged to the LTCF from hospital

$$= (1 - prh) \times pth$$

$x4$: the proportion of Tr/N discharged to the LTCF from hospital

$$= prh \times pth$$

- $\boldsymbol{prc}$: the proportion of residents admitted to the LTCF from the community colonised with *E. coli* resistant to trimethoprim ($Ur + Tr$)/N

prc was obtained from West Midlands AmSurv data (described above). Over the study period 36.66% of urine samples sent by GPs from individuals aged 70 or older residing in postcodes that did not contain LTCFs were resistant to trimethoprim (vs. sensitive). This proportion of individuals with a resistant *E. coli* urine sample submitted to AmSurv (vs. susceptible) was assumed to be the same as the proportion of individuals predominantly colonised with *E. coli* resistant to trimethoprim (vs. susceptible).

Trimethoprim resistance increased during the study period. Therefore, in a sensitivity analysis, a linear regression was fit to the weekly data and prc was modelled as the function for this linear regression:

$prc = 0.3350485 + (0.0002101702 * (\text{week of the study}))$.

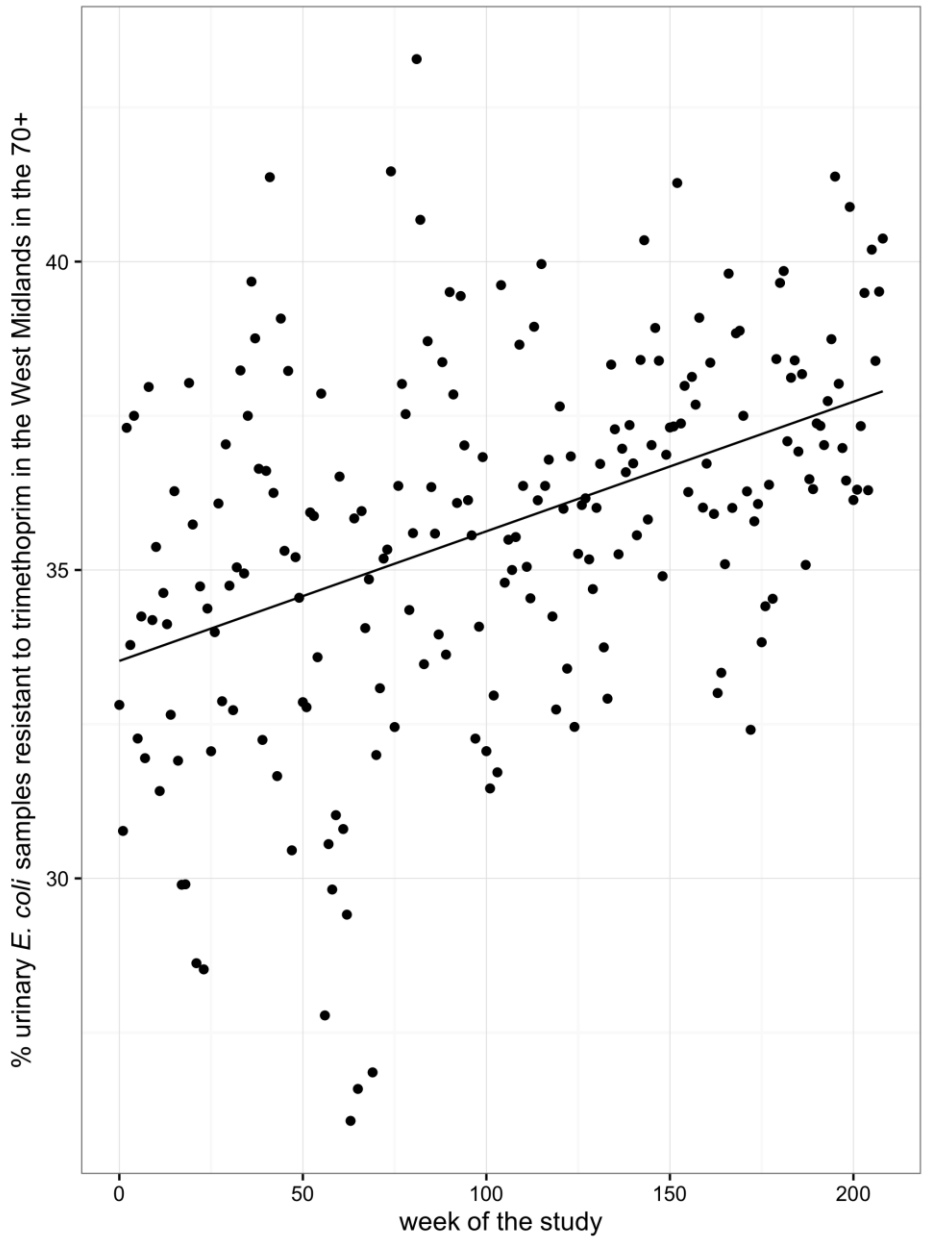

Figure 7-3. Percentage of urinary *E. coli* samples resistant to trimethoprim submitted to AmSurv by GPs in the West Midlands from individuals aged 70 and over. April 2010 to March 2014.

- $\boldsymbol{ptc}$

The proportion of residents admitted to the LTCF from the community on trimethoprim treatment $(Ts + Tr)/N$, ptc, was derived from West Midlands THIN data (described above). The proportion of the registered days in which individuals aged 70 or older in the West Midlands were exposed to trimethoprim was calculated per month of the study (April 2010 to March 2014). The mean

proportion was 0.49% over the study period; however, it increased linearly during this time (see Figure 7-4). Therefore, in a sensitivity analysis, a linear regression was fit to the THIN data and ptc was modelled as the function for this linear regression:

$$ptc = 0.004195201 + (6.732339\text{e} - 06 * (\text{week of the study})).$$

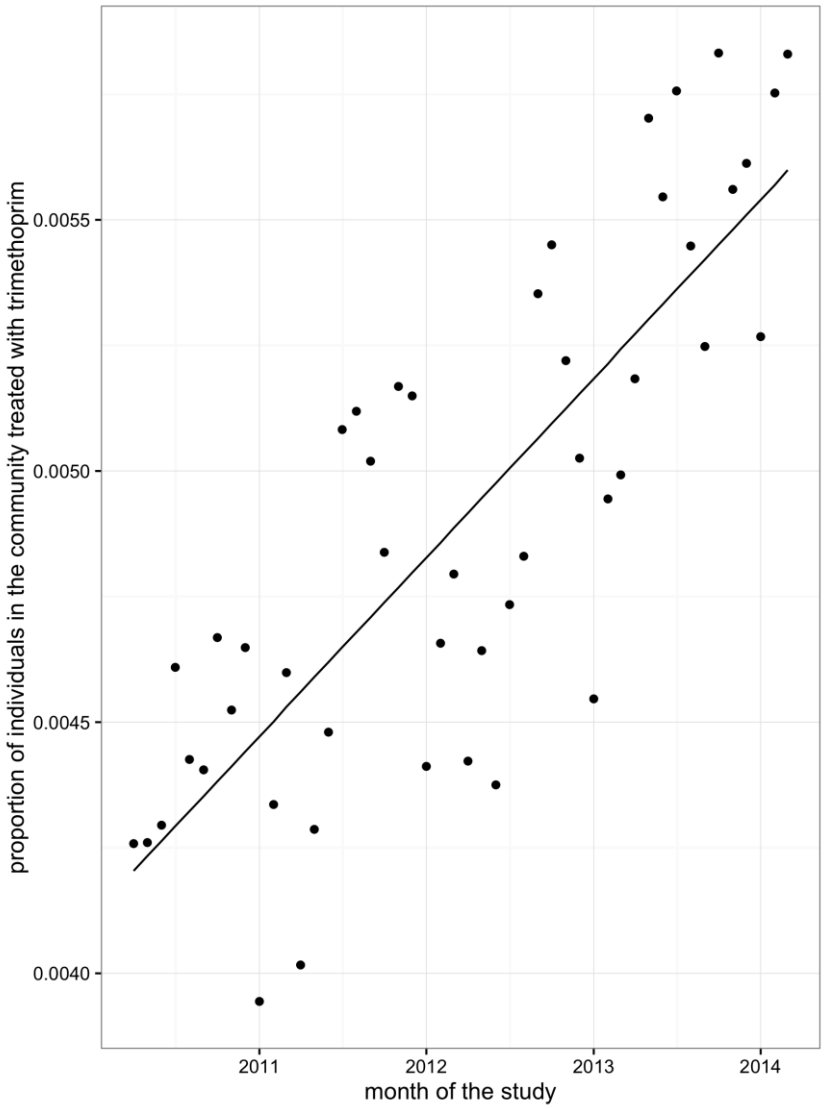

Figure 7-4. Proportion of individuals aged 70 or older in the community in the West Midlands treated with trimethoprim. THIN data, April 2010 to March 2014.

- $\boldsymbol{y1, y2, y3, y4}$: the proportion of admissions to the LTCF from the community that arrive into the $\boldsymbol{Us}$, $\boldsymbol{Ur}$, $\boldsymbol{Ts}$ and $\boldsymbol{Tr}$ compartments (respectively)

$y1+ y2+ y3+ y4=1$

$y1$: proportion Us admitted to the LTCF from the community $= (1 - prc) \times (1 - ptc)$

$y2$: proportion Ur admitted to the LTCF from the community $= prc \times (1 - ptc)$

$y3$: proportion Ts admitted to the LTCF from the community$= (1 - prc) \times ptc$

$y4$: proportion Tr admitted to the LTCF from the community$= prc \times ptc$

Treatment

Parameters in this section relate to the treatment of patients with trimethoprim. α_p describes the rate of trimethoprim treatment in the LTCF and γ_p describes the rate of stopping trimethoprim treatment.

- **α_p:** rate of trimethoprim treatment in the LTCF

The rate of trimethoprim treatment in the LTCF, α_p, was derived from West Midlands THIN data (described above) for individuals aged 70 for the community overall (including LTCF and non-LTCF residents). These values were then scaled to represent treatment in the LTCF by using estimates from the literature[69]. Sundvall et al. [69] showed that in Hampshire in those aged 75 and older, without adjustment, antibiotic prescription for UTIs in LTCFs was 0.69/0.24=2.875 times higher in LTCF residents than in elderly individuals that lived in their own homes. The mean monthly rate of trimethoprim prescription in the West Midlands from April 2010 to March 2014 per 100,000 population was calculated from THIN (=1172.889). Therefore, the rate of trimethoprim prescription in the overall community per person per day, α_p, was 1172.889/100,000/30= 0.0003909629. Since 4% of the population >65 lives in LTCFs[9] (and, therefore, 96% do not), this can be written as two equations:

$$0.00039 = (0.96 \times \mathrm{x}) + (0.04 \times \mathrm{y})$$

$$\mathrm{y} = 2.875 \times \mathrm{x} ,$$

where x is the rate of trimethoprim prescription in individuals that did not reside in LTCFs and y is the rate of trimethoprim prescription in LTCF residents.

Solving these equations gives $\mathrm{y} = 0.001$.

As shown in Figure 7-5 the rate of trimethoprim prescription in older people West Midlands community overall remained stable during the study period. It was therefore modelled as a constant.

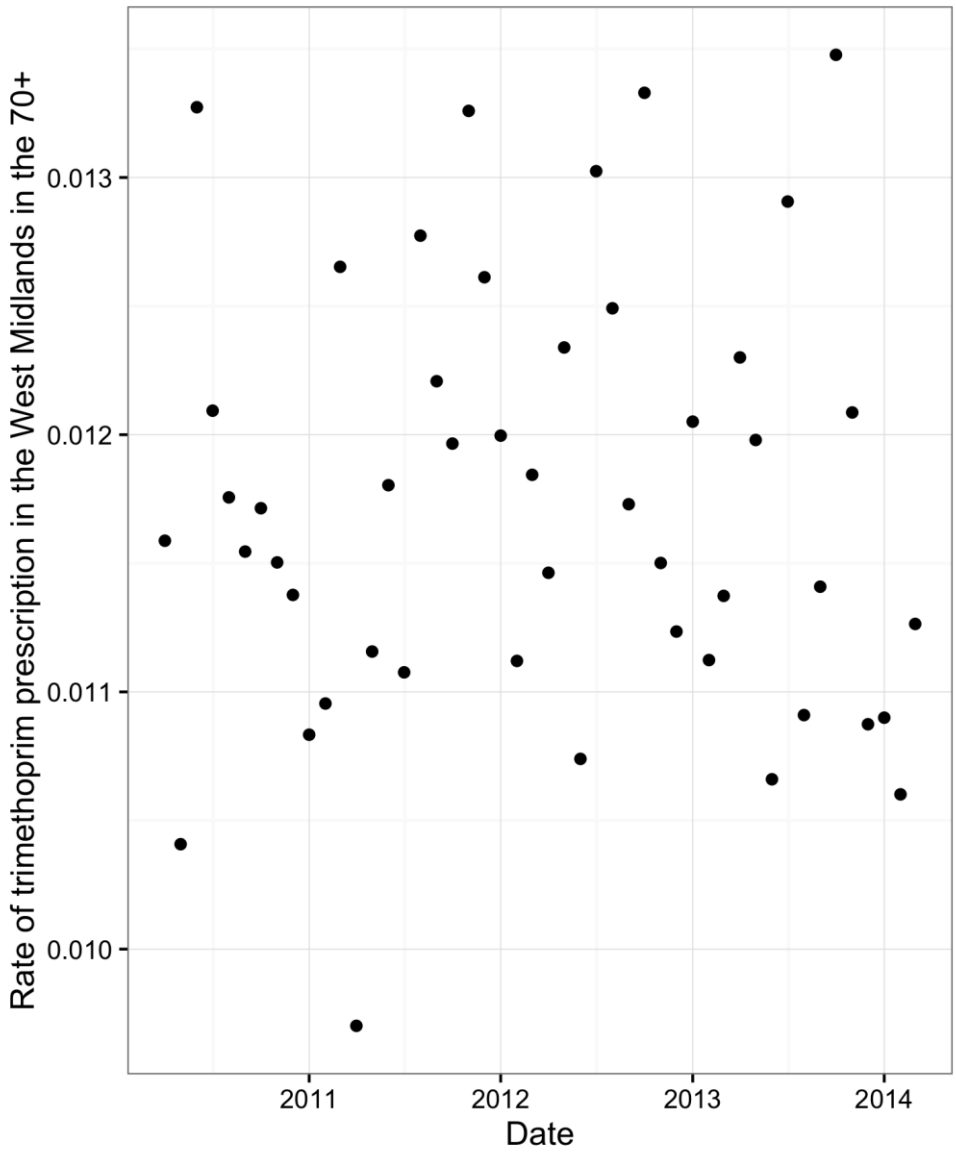

Figure 7-5. Rate of trimethoprim prescription in the West Midlands in individuals aged 70 and over. THIN data, April 2010 to March 2014.

- γ_p: 1/average duration of trimethoprim treatment in the LTCF

The trimethoprim prescription guidelines recommend 3 days of treatment for women and 7 days for men.[50] In THIN, in those aged 70 or over registered in practices in the West Midlands from January 2010 to December 2014, the median duration of trimethoprim treatment was 5 days. Therefore, γ_p, or 1/the average duration of trimethoprim treatment in the LTCF, was set at 1/5=0.2 per person per day. A sensitivity analysis explored durations of treatment from 3 to 6 days. (γ_p =0.16 to 0.3).

Transmission

Parameters in this section relate to transmission of trimethoprim-resistant *E. coli* in the LTCF. β and β' describe the rate of transmission of resistance in untreated and treated individuals (respectively) in the LTCF, and γ describes the rate of recovery from colonisation by *E. coli* resistant to trimethoprim in the LTCF.

- $\boldsymbol{\beta}$ and $\boldsymbol{\beta'}$: the rate of transmission of resistance in untreated and treated individuals (respectively) in the LTCF.

To our knowledge, the transmission rate of trimethoprim resistant *E. coli* has not been reported to date. In the literature, the transmission of *E. coli* resistant to expanded-spectrum cephalosporins in ICUs in various locations across Europe was estimated at 0.0078 (95%CIs=0.0029-0.016).[255] Haverkate et al. estimated the transmission rate of KPC-producing bacteria in LTACHs at 0.014 (95%CIs=0.0071-0.026).[256] Toth et al. assumed the transmission rate of CRE in LTCFs to be 0.1 in a low transmission scenario and 0.14 in a high transmission scenario.[133] Lee et al. modelled the transmission of CRE in LTCFs using a transmission parameter of 0.000057895 (range 0-0.00053513). [132] Talaminos et al. modelled the transmission of *E. coli* ST131 in LTCFs using a transmission parameter of 0.00008 for colonisation with *E. coli* ST131 that did not produce ESBLs and 0.00003 for colonisation by ESBL-producing *E. coli* ST131. Haverkate et al. (2017) estimated the within-household transmission rate of ESBL-producing *Enterobacteriaceae* (67% *E. coli*) at 0.0053 per person per day.[257] Due to the wide range of transmission parameters in the literature and the lack of studies that specifically reported the transmission of trimethoprim resistant *E. coli* in LTCFs, β and β' were estimated (procedure described below).

- $\boldsymbol{\gamma}$: rate of recovery from colonisation by *E. coli* resistant to trimethoprim in the LTCF, or 1/average duration of colonisation with *E. coli* resistant to trimethoprim in the LTCF

The duration of colonisation with *E. coli* resistant to trimethoprim in LTCF residents was not specifically assessed in the literature. Ismail et al. 2016[252] reported a mean duration of carriage of ciprofloxacin-resistant *E. coli* in nursing home residents of 6 months. Birgand et al. 2013[250] reported a median duration of colonisation after hospital discharge for ESBL-E of 6.6 months. Haverkate et al. 2015[253] calculated a mean duration of colonisation for *E. coli* OXA-48 of 225 days (7.5 months). Titelman et al. 2014[251] showed that colonisation with *E. coli* was still apparent 12 months after infection in 64% (n=9), and 40% (n=14) of those carrying *E. coli* ST131 or other STs, respectively (p=0.12). Overdevest et al.[254] showed that in a Dutch LTCF with high rectal colonisation rate, the half-life of ESBL-ST131 *E. coli* carriage was 13 months. We assumed a duration of colonisation of 9.5 months and carried out a sensitivity analysis in which this was varied between 6 and 13 months. Therefore, γ, the rate of recovery from colonisation by *E. coli* resistant to trimethoprim in the LTCF, was $\frac{1}{\frac{365}{12}\times 9.5 \text{ days}} = 0.0035$ per person per day (sensitivity analysis from $\frac{1}{\left(\left(\frac{365}{12}\right)\times 13\right)days} = 0.0025$ to $\frac{1}{\left(\left(\frac{365}{12}\right)\times 6\right)days} = 0.0055$).

Initial values

The distribution of individuals in compartments Us, Ur, Ts, Tr at time point zero, with which the model was initiated, was calculated as follows:

$$Us_{t0} = LTCF\ size \times (1 - prl) \times (1 - ptl)$$

$$Ur_{t0} = LTCF\ size \times prl \times (1 - ptl)$$

$$Ts_{t0} = LTCF\ size \times (1 - prl) \times ptl$$

$$Ts_{t0} = LTCF\ size \times prl \times ptl$$

where prl was the proportion of individuals initially colonised by *E. coli* resistant to trimethoprim in the LTCF, and ptl was the proportion of individuals initially treated with trimethoprim in the LTCF. These figures were then rounded to give whole numbers of individuals.

prl was derived from the proportion of urine *E. coli* samples sent to AmSurv that were resistant to trimethoprim. This proportion increased during the study period as can be seen in Figure 7-6 below.

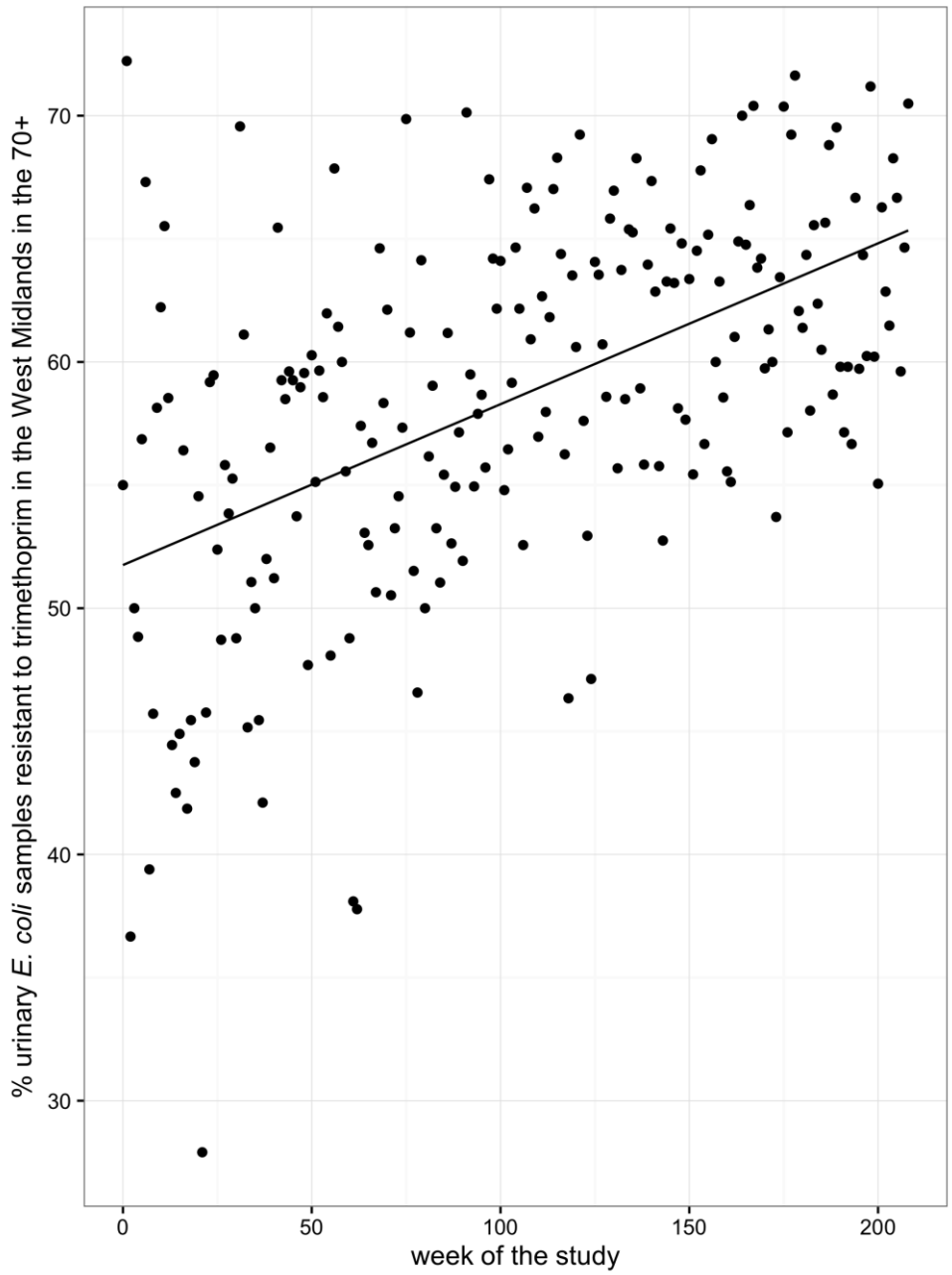

Figure 7-6. Percentage of urinary *E. coli* samples resistant to trimethoprim in the West Midlands in individuals aged 70 and over residing in LTCFs. April 2010 to March 2014.

The proportion of individuals colonised by *E. coli* resistant to trimethoprim in the LTCF in the first week of the study (51.75%) was calculated by fitting a linear regression to the weekly West Midlands AmSurv data (described above):

$$prl = 0.5168852 + (0.0006532183 \times (\text{week of the study})) = 0.5168852 + 0.0006532183 = 0.5175$$

The proportion of individuals with a resistant *E. coli* urine sample submitted to AmSurv (vs. susceptible) was assumed to be the same as the proportion of individuals predominantly colonised with *E. coli* resistant to trimethoprim (vs. susceptible).

ptl was informed by data from the HALT-2 study, which found that 2.69% (11/409) of English residents in the 16 LTCFs surveyed were being treated with trimethoprim/sulphonamides on the survey day[63]. According to THIN data (described above), 97% of trimethoprim/sulphonamides prescriptions to patients of all ages in England (2013-2015) were trimethoprim prescriptions.

LTCF size is described in the incidence section below.

Reporting: how does the incidence derived from the model relate to the incidence in the data?

The mathematical model presented describes the transmission of trimethoprim resistance amongst individuals colonised with *E. coli*. The incidence derived from the model (Inc) is, therefore, the cumulative number of individuals colonised with *E. coli* resistant to trimethoprim per week. However, the susceptibility data available for AmSurv captures UTIs reported to AmSurv. Therefore, in order to calculate the observations predicted by the model at each time point (obs), Inc was multiplied by rho. By multiplying by rho, Inc is adjusted to the level of cases reported.

$$obs = Inc \times rho$$

- $\boldsymbol{rho}$**:** the proportion of colonised patients with a resistant *E. coli* who develop a UTI for which a sample is taken and the results are reported to AmSurv.

Calculating rho would require knowledge of the proportion of individuals colonised with *E. coli* resistant to trimethoprim who go on to develop a UTI and the proportion of UTIs in individuals in LTCFs in the West Midlands that are then sampled and therefore reported to AmSurv. As these parameters were unknown, rho had to be estimated (procedure described below).

Incidence data and model fitting procedure: estimating β, β' and rho

Processing of incidence data to allow model fitting

To estimate the transmission parameters (β, β') and rho, the incidence of colonisation with *E. coli* resistant to trimethoprim in the model (Inc) was fitted to the incidence of urinary *E. coli* samples resistant to trimethoprim from a LTCF in the AmSurv dataset.

The incidence of colonisation with *E. coli* resistant to trimethoprim in the model (Inc) was the cumulative number of individuals that became dominantly colonised by *E. coli* resistant to trimethoprim (Ur and Tr) in the simulated LTCF in each week of the study. This model incidence included both individuals entering the LTCF from hospital or from the community already colonised by *E. coli* resistant to trimethoprim, and individuals acquiring this colonisation through transmission within the LTCF.

The incidence of urinary *E. coli* samples resistant to trimethoprim from a LTCF in the AmSurv dataset was the cumulative number of urine samples from residents of a LTCF submitted to AmSurv in each week of the study that grew *E. coli* resistant to trimethoprim. The choice of LTCF is described below. Assuming that the national guidelines were followed appropriately and urine samples were only sent for susceptibility testing for patients with UTIs, the incidence of urinary *E. coli* samples resistant to trimethoprim should capture the incidence of UTIs caused by *E. coli* resistant to trimethoprim.

The majority of people are colonised with *E. coli* without developing a UTI. Only a proportion of colonised individuals will develop a UTI, and a proportion of these will have a urine sample submitted for susceptibility testing. Therefore, the model incidence could not directly be fit to the incidence in the data. To account for this, the parameter rho was created, which is the 'case development and ascertainment proportion'. We multiplied Inc (the incidence in the model) by rho in order to adjust Inc to the level of cases reported in the AmSurv dataset.

Processing of incidence data to allow model fitting

The West Midlands AmSurv dataset (described above) included incidence data from 715 different LTCFs. This section describes the process of selecting the appropriate LTCF for model fitting. Four LTCFs were selected for model fitting (one for the baseline scenario and three for the sensitivity analyses).

As shown in Chapter 4, the median number of beds in LTCFs submitting at least one *E. coli* urine sample to AmSurv (N=715) was 33 (mean=36.9, range 1-214). 114 LTCFs were smaller than 20 beds, which were considered difficult to fit in isolation. Therefore, LTCFs smaller than 20 beds (N=114/715) were excluded. LTCFs submitting less than 10 urine samples per year to AmSurv growing *E. coli* resistant to trimethoprim (557/715) were also excluded as it was considered that transmission would be unlikely to occur in these facilities.

The LTCFs remaining (N=44) were sub-divided by quartiles according to the number of urine *E. coli* samples sent to AmSurv which were resistant to trimethoprim per bed per day (see Figure 7-7 below).

Figure 7-8 shows the number of beds in each of the 44 remaining LTCFs in the Amsurv dataset by incidence quartile. LTCFs with higher incidence had a lower mean number of beds. The weekly incidence of trimethoprim resistant *E. coli* samples submitted to AmSurv from each LTCF per bed day by incidence quartile is plotted in the Appendix Chapter 7.

One LTCF was selected from each of these quartiles for model fitting. The incidence of trimethoprim resistant urine *E. coli* samples submitted to AmSurv for each of the four selected LTCFs is shown in Figure 7-9 below.

In the baseline scenario, the model was fit to incidence data from a LTCF in the highest incidence quartile. This was to ensure that sufficient samples were present to enable model fitting and to ensure that transmission (if present at all in the LTCF setting) was detected. This was a LTCF of 30 beds. The LTCF size in this baseline scenario was therefore set to 30 beds. The prevalence of resistance in the LTCF selected for the baseline scenario was 74%, as derived

by dividing the urine samples growing *E. coli* resistant to trimethoprim sent to AmSurv by this facility by the total urine samples growing *E. coli* sent to AmSurv by this facility. The other three selected LTCFs were simulated in sensitivity analyses (one of 39 beds, one of 57 and another of 83).

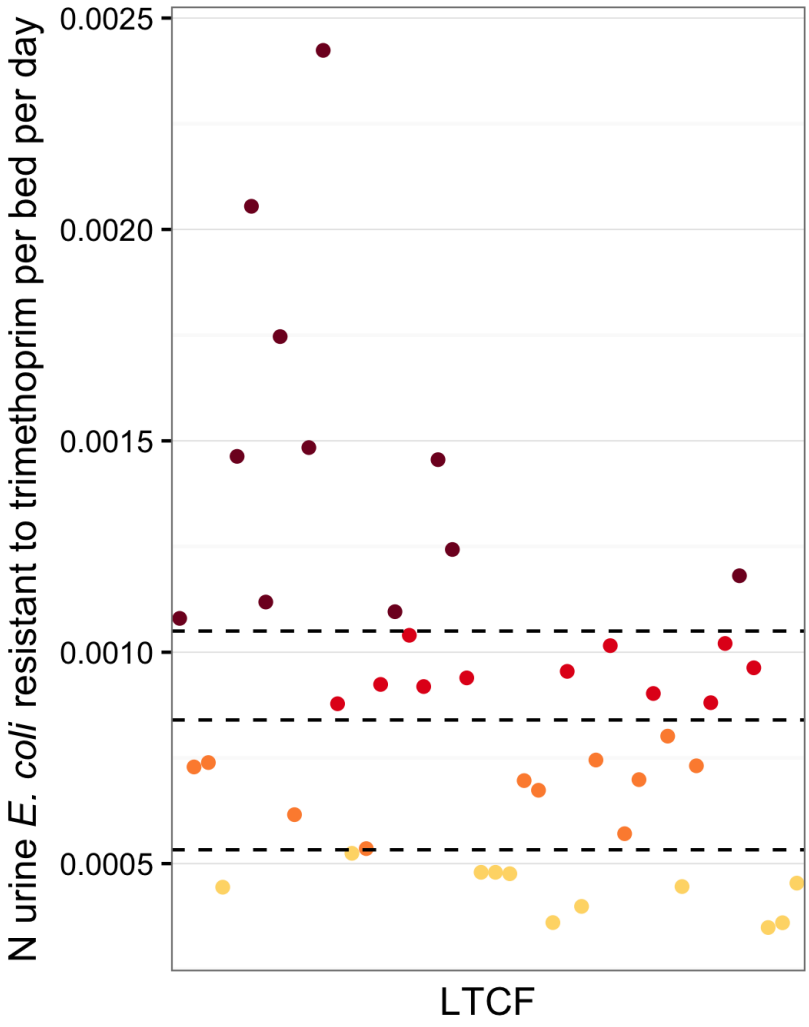

Figure 7-7 The number of urine *E. coli* samples resistant to trimethoprim submitted to AmSurv per bed day, by LTCF. Quartiles are denoted by the horizontal dotted lines. LTCFs within each quartile are coloured the same. LTCFs below 20 beds (N=114/715) and LTCFs submitting less than 10 urine samples to AmSurv growing *E. coli* resistant to trimethoprim (557/715) were excluded.

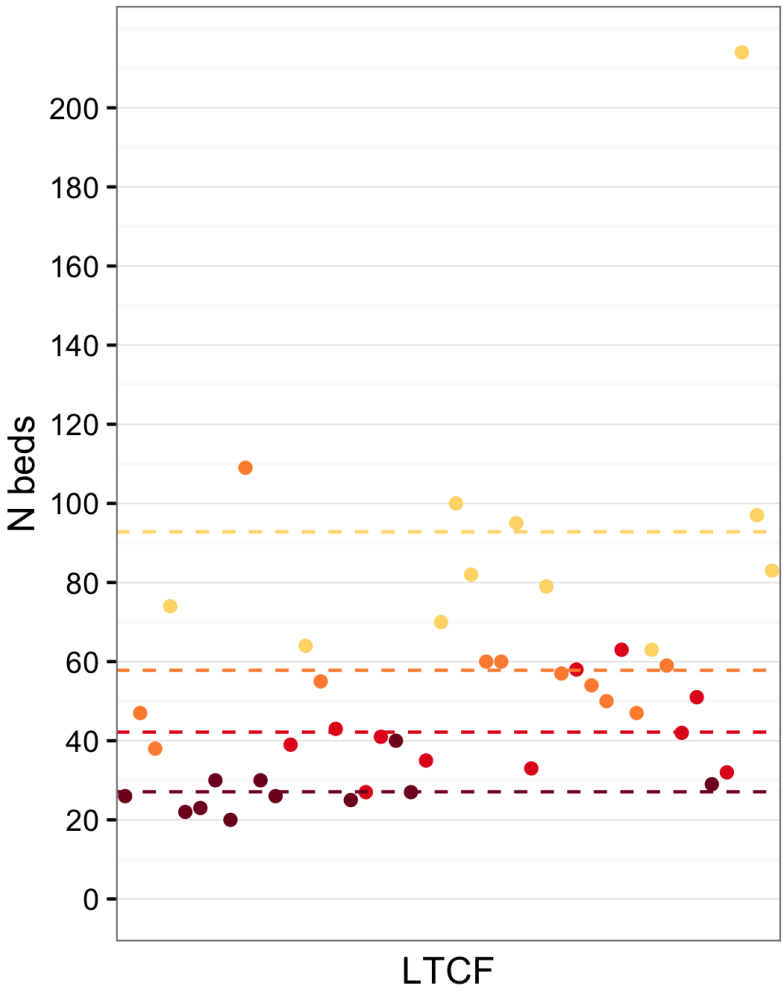

Figure 7-8. Number of beds per LTCF. LTCFs are subdivided by colour in quartiles according to the number of urine *E. coli* samples resistant to trimethoprim they sent to AmSurv. In dark red, LTCFs in the quartile with the highest incidence; in red, LTCFs in the quartile with the second highest incidence; in orange, LTCFs in the quartile with the second lowest incidence; in yellow, LTCFs in the quartile with the lowest incidence. The dashed lines represent the mean number of beds for the LTCFs in each incidence quartile (from high to low incidence: 27.1, 42.2, 57.8, 92.8). LTCFs below 20 beds (N=114/715) and LTCFs submitting less than 10 urine samples to AmSurv growing *E. coli* resistant to trimethoprim (557/715) were excluded.

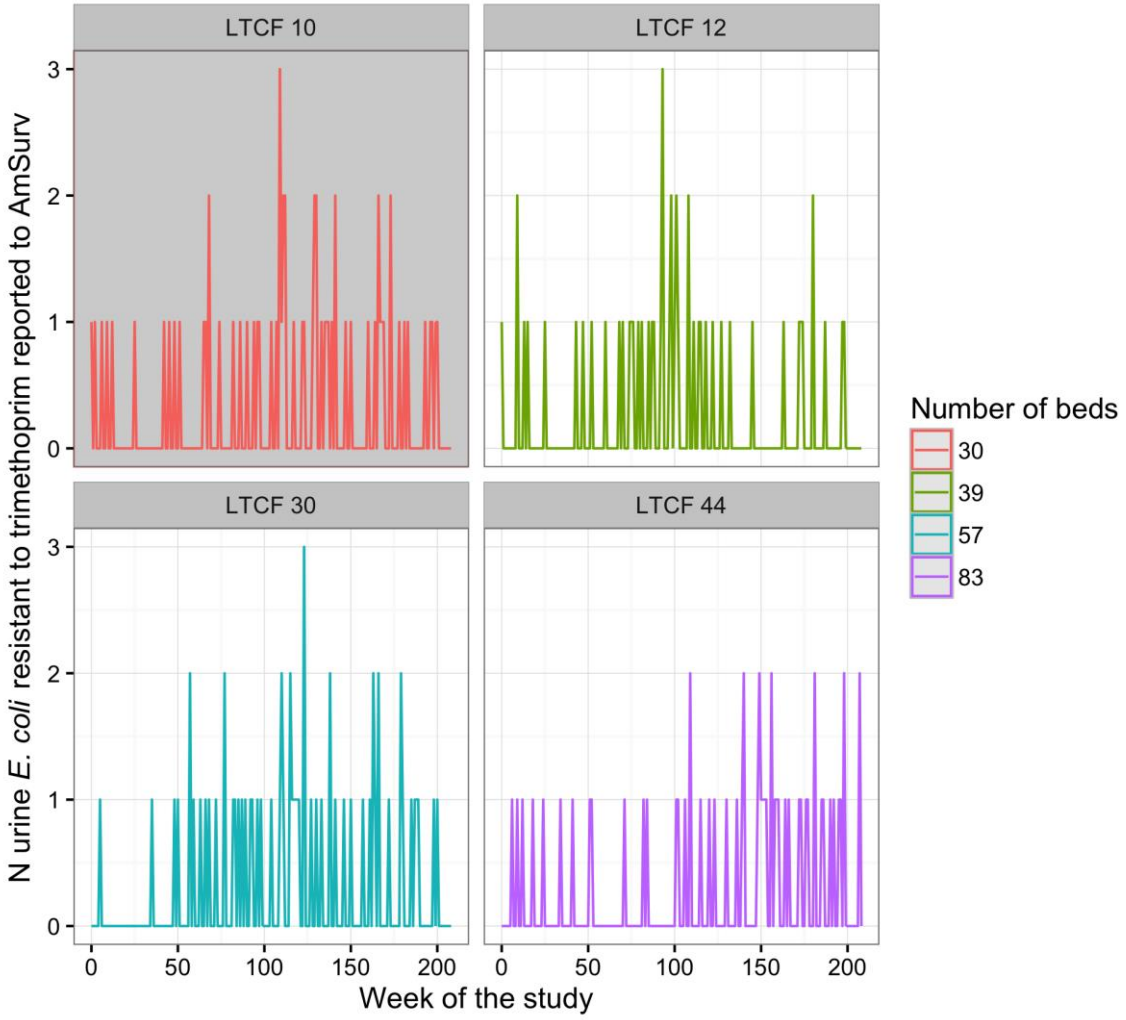

Figure 7-9. The weekly incidence of urine *E. coli* samples resistant to trimethoprim submitted to AmSurv for each of the LTCFs that were selected for simulation. The LTCF selected for the baseline simulation scenario (30 beds) is highlighted in grey.

Model fitting: estimating β, β' and rho

β, the rate of transmission of *E. coli* resistant to trimethoprim to untreated individuals in the LTCF, β', the rate of transmission of *E. coli* resistant to trimethoprim in individuals treated with trimethoprim in the LTCF, and rho, the proportion of patients colonised with a resistant *E. coli* who develop a UTI for which a sample is taken and the results are reported to AmSurv, were unknown and, therefore, had to be estimated through fitting the model to the incidence data described in the section above. β' was expressed as the product of β and tr:

$$\beta' = \beta * tr$$

where $tr > 1$. Therefore, β' was assumed to be greater than β.

β, tr and rho were fit to the incidence of urinary tract *E. coli* resistant to trimethoprim in the LTCF selected for the baseline scenario (described above) by maximum likelihood estimation using the function traj.match in the pomp package[246,247]. This function uses the deterministic version of the model for model fitting. It calls the optim function in R (using Nelder-Mead optimisation method) to maximise the likelihood of the data given the model trajectory, which is defined by a function that evaluates the probability density of point observations of the model incidence following a Poisson probability distribution with mean $rho \times Inc$, as defined by the following line of C code:

```
lik = dpois(obs, rho * Inc, give_log);
```

The model fitting was carried out in three stages.

First, the values of β and rho were estimated for different values of tr (see Table 7-2 below), with all remaining parameters kept as per the baseline scenario described above (see values in Table 7-1). The starting value of β was taken from published literature and set at 0.0053.[257] The starting value of rho was not available in published literature, and so was estimated as 0.7333 through the following assumption: number of tests per resident, per year. As the

length of stay in LTCFs was on average 451.98 days (calculated as described above for the m parameter), all patients were assumed to remain in the LTCF for at least a year. The LTCF simulated in the baseline scenario had 22 urine *E. coli* samples reported to AmSurv in 2013/2014 and 30 beds; therefore, the starting value for rho was $rho = \frac{22}{30} = 0.7333$. The cumulative number of cases predicted ($Inc \times rho$) over the study period, the prevalence of resistance predicted overall (for treated and untreated) and the prevalence of resistance in treated individuals compared to untreated individuals were derived from the deterministic model at equilibrium.

Table 7-2. Estimating β and rho for different values of tr.

tr (fixed)	Estimated β (per person per day)	Estimated rho	$Inc \times rho$ predicted by the model (vs. 65 in data)	Prevalence of resistance predicted by the model at equilibrium ($\frac{Ur+Tr}{N}$) (%)	Prevalence of resistance in treated individuals compared to untreated individuals: ($\frac{Tr}{Tr+Ts}$)/($\frac{Ur}{Ur+Us}$) at equilibrium
1	0.0083	0.53	65.2	51.4	1
1.5	0.0083	0.53	65.3	51.5	1
2	0.0082	0.53	64.9	51.1	1
10	0.0079	0.53	64.7	51	1.2
50	0.0071	0.54	64.9	50.3	1.5
70	0.0068	0.54	64.1	49.7	1.5
100	0.0066	0.55	65.1	49.6	1.6
140	0.0063	0.56	65.4	48.9	1.7
180	0.0061	0.56	64.8	48.5	1.8
200	0.006	0.56	64.5	48.2	1.8
210	0.006	0.56	64.6	48.3	1.8
220	0.0059	0.57	65.2	48	1.8
230	0.0059	0.57	65.3	48	1.8
250	0.0058	0.57	64.9	47.7	1.9
300	0.0057	0.57	64.6	47.6	1.9
350	0.0056	0.58	65.5	47.3	1.9
400	0.0055	0.58	65.1	47.1	1.9
500	0.0053	0.59	65.3	46.5	2

As shown in Table 7-2, as the value of tr was increased from 1 to 500, β decreased from 0.0083 to 0.0053 and rho increased from 0.53 to 0.59. The cumulative number of cases predicted by the model ($Inc \times rho$) over the study period agreed closely with the data (65), implying a reasonable model fit to the data. The prevalence of resistance at equilibrium predicted by the model, however, was lower for all cases explored (51.5%-46.5%) than that estimated from AmSurv data for the LTCF selected (74%).

As described above, $tr = \frac{\beta}{\beta'}$. Increasing tr, therefore, increased the prevalence of resistance in treated individuals compared to untreated individuals in the model. For values of tr between 250 and 400, the prevalence of resistance in treated individuals compared to untreated individuals was 1.9. This was similar

to the relative risk of resistance in treated individuals compared to untreated individuals observed in the literature (1.88).[258] Therefore, a value of tr between 250 and 400 was considered reasonable. rho was estimated at between 0.53 and 0.59.

Second, tr and rho were estimated for different values of β in order to explore if fixing β would condition and change the values of rho and tr that best fit the model (see Table 7-3). Having found more realistic values for these parameters to initiate the model fitting, the starting value for tr was increased to 250 and the starting value for rho was decreased to 0.6.

Table 7-3. Estimating rho and tr for different values of β. Note that β and β' are now estimated per person per 1/10 day.

β (fixed) (per person per 1/10 day)	Estimated rho	Estimated tr	$\beta' = \beta * tr$ (per person per 1/10 day)	$Inc \times rho$ predicted by the model (vs. 65 in data)	Prevalence of resistance predicted by the model at equilibrium (%)	Prevalence of resistance in treated individuals compared to untreated individuals: $(\frac{Tr}{Tr+Ts})/(\frac{Ur}{Ur+Us})$ at equilibrium
0.0002	0.8	16287940	3257.588			
0.0003	0.72	148806	44.6418			
0.0004	0.64	115238	46.0952			
0.0005	0.59	11049	5.5245	65.3	46.5	2.2
0.0006	0.56	282.2	0.16932	65.2	48.8	1.8
0.00065	0.55	134.6	0.08749	65.3	49.8	1.7
0.0007	0.54	69.7	0.04879	65.3	50.6	1.5
0.0008	0.52	19.8	0.01584	65.3	52.5	1.3
0.0009	0.5	0.09	0.000081	64.8	54.1	1

β was increased from 0.0002 per person per 1/10 day (0.002 per day) to 0.0009 per 1/10 day (0.009 per day). For values of β smaller or equal to 0.0004 per person per 1/10 day (0.004 per day), the fitting algorithm estimated values of tr that, although produced a similar cumulative number of cases as observed in the data; implied that $\beta' = \beta \times tr \geq 46.1$ per person per 1/10 day (4.61 per person per day), which was not considered biologically plausible as this would imply $R_0 = \beta \times \gamma^{-1} \times N = 4.61 \times \left(9.5 * \frac{365}{12}\right) \times 30 = 39962.94$ and there were only 30 individuals in the LTCF. Therefore, these values were not presented in Table 7-3. As β increased, the prevalence of resistance predicted by the model also increased, becoming closer to that estimated from AmSurv data (74%). However, increasing β also resulted in a progressive decrease in tr, which, in turn, decreased the prevalence of resistance in treated individuals compared to untreated individuals, lowering it below the estimates reported in the literature (1.88).[257] When β was fixed at 0.0009 per 1/10 day (0.009 per day), the relative risk of resistance was equal to 1.

Third, the value of tr and rho and β were estimated with starting values of 250, 0.55 and 0.0008 per person per 1/10 day (0.008 per day), respectively. tr was set to 250 because it was the lowest value of tr at which a relative risk of resistance in treated individuals compared to untreated individuals of 1.9 was achieved. β was set to a value that resulted in the highest prevalence of resistance for which the relative risk of resistance in treated individuals compared to untreated individuals was greater than 1. rho was set at 0.55 as a compromise between 0.52 (estimated for β=0.0008 per person per 1/10 day (0.008 per day)) and 0.58 (estimated for tr=250).

The combination of tr, rho and β that best fit the data was tr=250, rho=0.55 and β=0.00062 per person per 1/10 day (0.0062 per day), giving β'=0.155 per person per 1/10 day (1.55 per day). These values were subsequently used in the baseline scenario.

In the sensitivity analysis, the model was fit to incidence data from three different LTCFs. The LTCF size was modified accordingly. In this secondary

model fitting process, tr and rho were kept constant and only β was estimated. The starting values for this estimation were tr=250, rho=0.55 and β=0.00062, the fitted values for the baseline scenario. The maximum likelihood estimation optimisation method was changed to “SANN”, as this method was better suited to estimating one parameter value than the Nelder-Mead optimisation algorithm.

Sensitivity analyses

Several sensitivity analyses were carried out to test the sensitivity of the model output to the choice of parameter set. Firstly, ptc, prc and prh, which are fixed at the mean for the study period in the baseline scenario, were increased linearly with an intercept and slope defined by the regression models fit to the prescription and antibiotic resistance data for this period (described in the parameterisation section above). γ, γ_p, lh, and pth were varied according to plausible ranges (also described in the parameterisation section). The model was additionally fit to data from three different LTCFs with lower incidence and higher number of beds.

Scenarios

Four transmission scenarios were explored: (1) where the transmission rate was halved, (β=0.0031 per person per day); (2) where the transmission rate was increased by 20% (β=0.0074 per person per day), (3) where the transmission rate was doubled (β=0.0124 per person per day); and (4) where the rate of transmission of resistance to treated individuals was equal to the rate of transmission of resistance to untreated individuals ($\beta = \beta'$=0.0062 per person per day). Two movement scenarios were considered where hl were increased and decreased by 20%. Three treatment scenarios were explored where α_p was increased by 20% (to 0.0012), 50% (to 0.0015) and one scenario in which α_p was increased by 5.5 fold (to 0.0055). The effect of decreasing the rate of trimethoprim treatment was not modelled after a Swedish study demonstrated little evidence for reversibility of trimethoprim resistance after a drastic reduction in trimethoprim use.[208]

Modelling output

The following output was derived from 1,000 simulations of the stochastic model:

- The number of UTIs caused by *E. coli* resistant to trimethoprim in the LTCF in the last four weeks of the study as predicted by the model (median, mean, and 95th percentile for 1,000 simulations)

- The number of individuals discharged to hospital from the LTCF colonised by *E. coli* resistant to trimethoprim in the LTCF in the last four weeks of the study as predicted by the model (median, mean, and 95th percentile for 1,000 simulations)
- The number of individuals discharged to the LTCF from hospital colonised by *E. coli* resistant to trimethoprim in the LTCF in the last four weeks of the study as predicted by the model (median, mean, and 95th percentile for 1,000 simulations)
- The percentage of individuals in the LTCF colonised by *E. coli* resistant to trimethoprim (vs. sensitive to trimethoprim) in the last year of the study (median, mean, and 95th percentile for 1,000 simulations)
- The percentage of individuals in the LTCF treated with trimethoprim (vs. untreated) in the last year of the study (median, mean, and 95th percentile for 1,000 simulations)
- The percentage of individuals colonised by *E. coli* resistant to trimethoprim (vs. sensitive to trimethoprim) admitted to hospital from the LTCF in the last year of the study (median, mean, and 95th percentile for 1,000 simulations)
- The percentage of individuals colonised by *E. coli* resistant to trimethoprim (vs. sensitive to trimethoprim) discharged to the LTCF from hospital in the last year of the study (median, mean, and 95th percentile for 1,000 simulations)
- The relative importance of importation from hospital, transmission and prescription in increasing the proportion of individuals colonised with *E. coli* resistant to trimethoprim (vs. susceptible to trimethoprim) in the LTCF

These same outputs were derived for the baseline scenario, for the sensitivity analysis and for the scenarios.

Results

The deterministic model output was consistent with the median stochastic model output over 1,000 runs.

Baseline scenario

The median LTCF size was kept constant at 30 beds during the study period (see Figure 7-10).

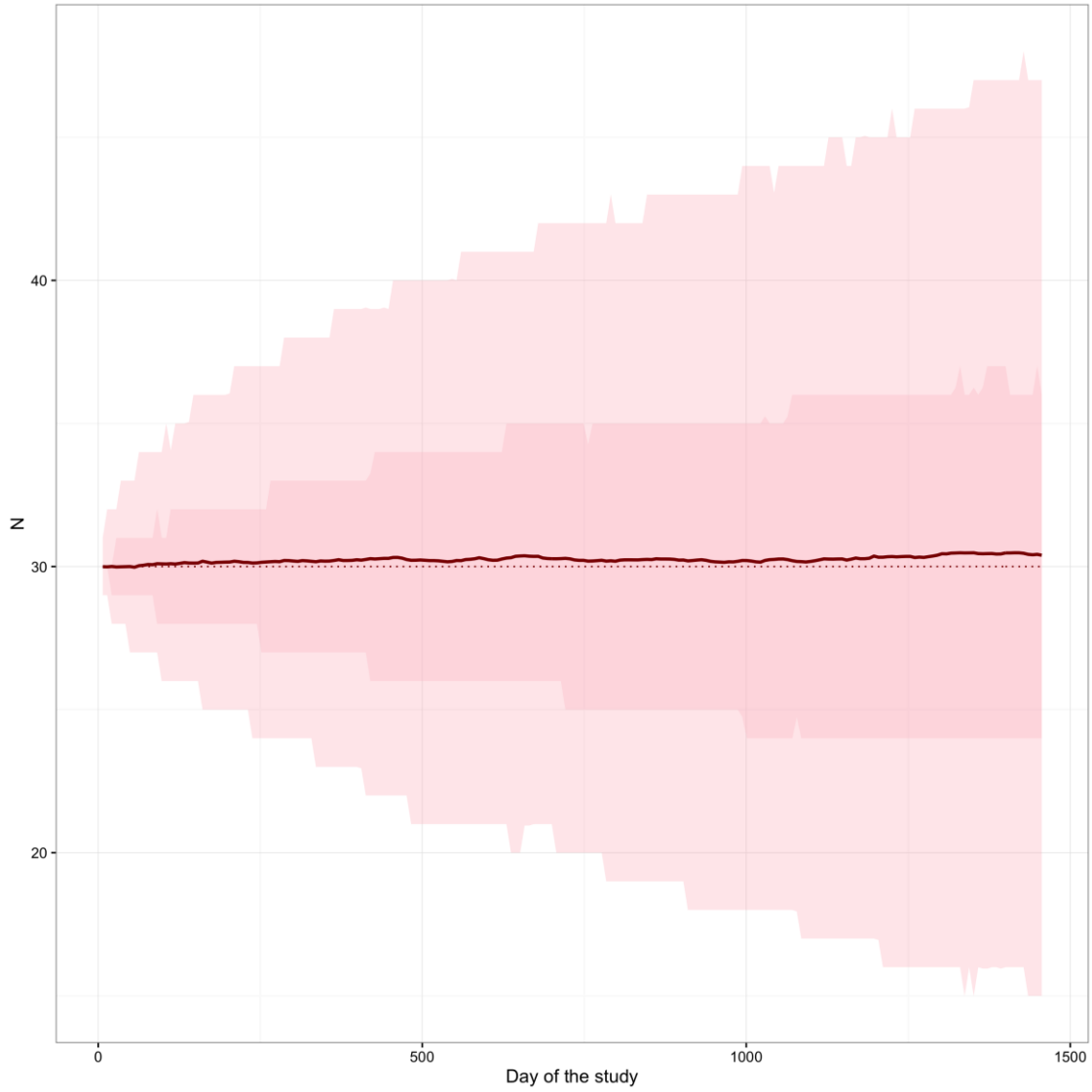

Figure 7-10. Total LTCF population size by week of the study period. N was the total number of residents in the LTCF. In light and dark pink, the 95th and 50th percentile of 1,000 stochastic runs (respectively). The solid and dotted dark red lines represent the mean and median of the 1,000 stochastic runs (respectively).

The number of entries and exits to each of the LTCF compartments are shown in Appendix Chapter 7. The exit rates from the LTCF were constant over time. Therefore, the number of individuals exiting each compartment depended on the number of individuals in each compartment at that time. The entry rates were also constant over time.

In the stochastic model, over the last year of the study, the median proportion of individuals discharged to the LTCF from hospital colonised by *E. coli* resistant to trimethoprim was 37.5% (95th percentile=13.33%-66.67%, mean=38.39%). The

median proportion of individuals admitted to hospital from the LTCF colonised by *E. coli* resistant to trimethoprim over 1,000 runs was 48.28% (95th percentile=25%-71.43%, mean=48.15%).

In the last four weeks of the study, the stochastic model predicted a median of one patient colonised by *E. coli* resistant to trimethoprim being discharged to the LTCF from hospital (95th percentile= 0-3, mean=0.91) and a median of one patient colonised by *E. coli* resistant to trimethoprim being admitted to hospital from the LTCF (95th percentile= 0-3, mean=1.35).

Figure 7-11 shows the number of individuals in the LTCF in compartments Us, Ur, Ts and Tr in the model over the study period (four years) for 1,000 stochastic model runs, against the deterministic output (black line). The 50th and 90th percentiles of the stochastic runs and their mean and median are plotted in Figure 7-12. There was a similar number of untreated individuals colonised with *E. coli* sensitive to trimethoprim and resistant to trimethoprim. The number of treated individuals was much lower. Over the last year of the study, the median prevalence of resistant colonisation amongst those untreated for 1,000 stochastic runs was 47.79% (95th percentiles=31.05%-61.08%, mean=47.30%). The median prevalence of resistance in treated residents was 90% (95th percentiles=50%-100%, mean=86.2%). Overall, the median prevalence of resistance over the last year of the study was 48.02% (95th percentiles=31.24%-61.24%, mean=47.51%).

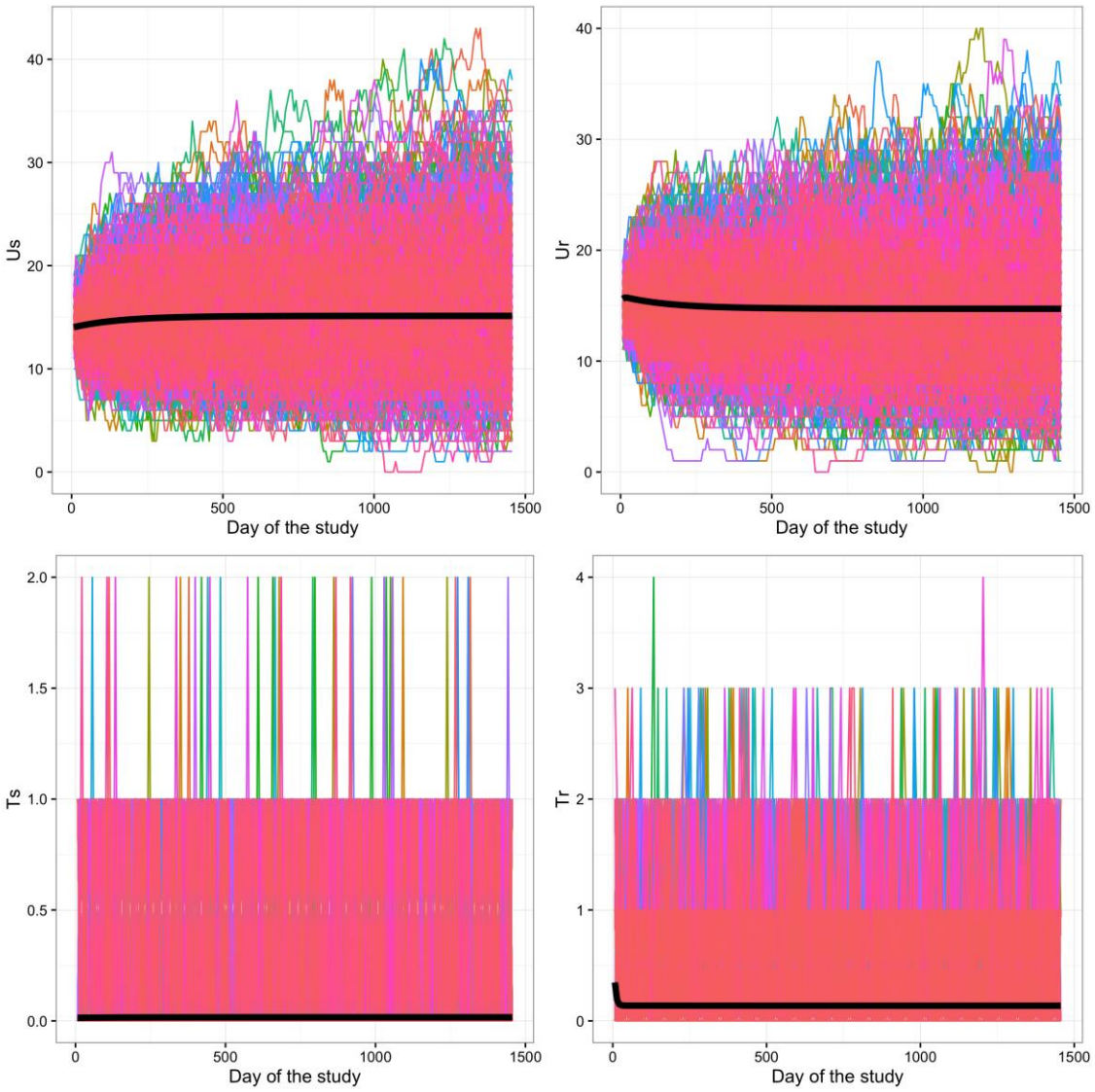

Figure 7-11. Distribution of individuals between the four compartments of the model during the study period. $\boldsymbol{Us}$ were individuals untreated with trimethoprim colonised with *E. coli* susceptible to trimethoprim, $\boldsymbol{Ur}$ were individuals untreated with trimethoprim colonised with *E. coli* resistant to trimethoprim, $\boldsymbol{Ts}$ were individuals treated with trimethoprim colonised with *E. coli* susceptible to trimethoprim and $\boldsymbol{Tr}$ were individuals treated with trimethoprim colonised with *E. coli* resistant to trimethoprim. The coloured lines represent the output of 1,000 stochastic simulations. The black line represents the output from the deterministic model.

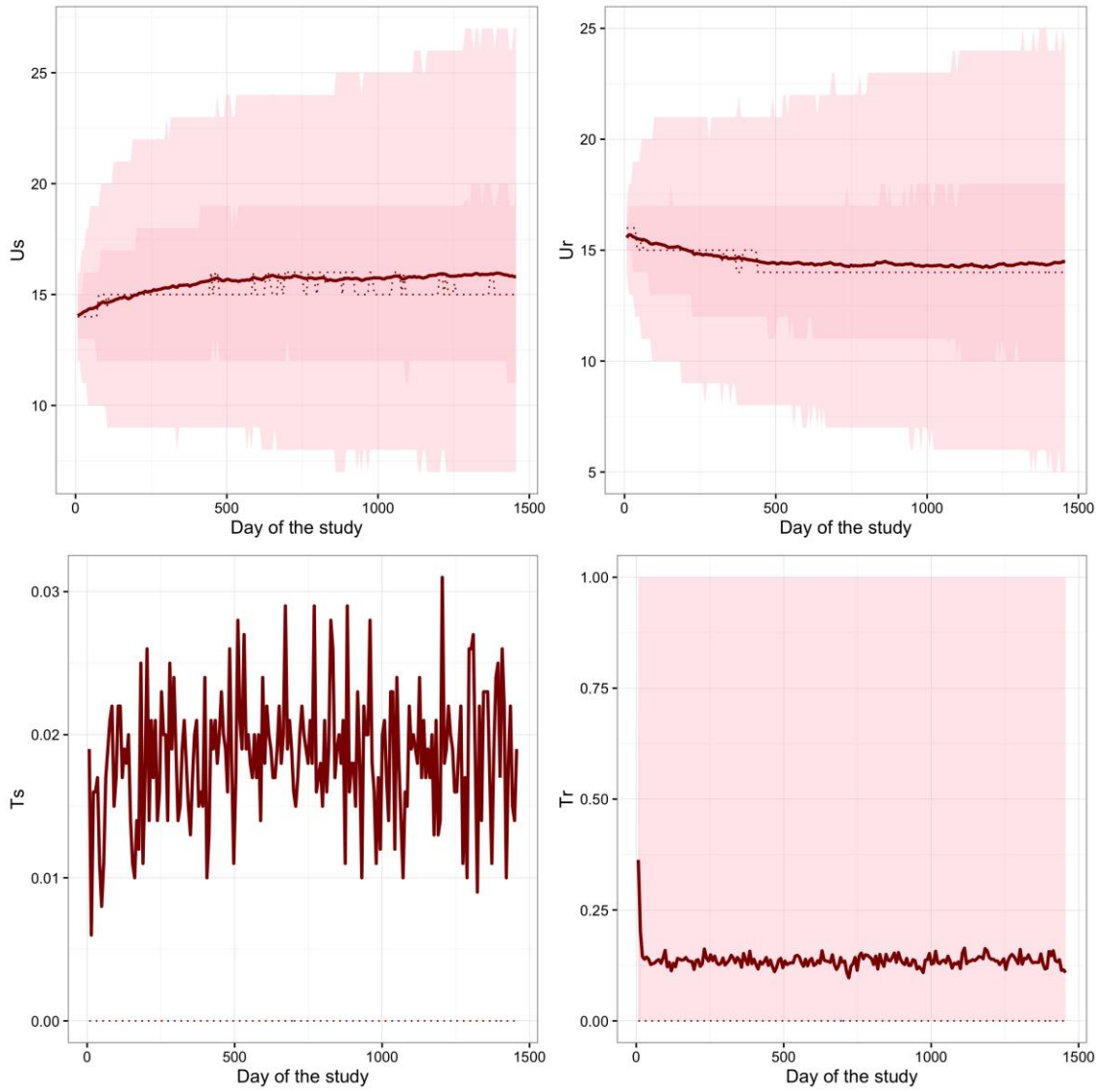

Figure 7-12. Distribution of individuals between the four compartments of the model by week of the study period. $\boldsymbol{Us}$ were individuals untreated with trimethoprim colonised with *E. coli* susceptible to trimethoprim, $\boldsymbol{Ur}$ were individuals untreated with trimethoprim colonised with *E. coli* resistant to trimethoprim, $\boldsymbol{Ts}$ were individuals treated with trimethoprim colonised with *E. coli* susceptible to trimethoprim and $\boldsymbol{Tr}$ were individuals treated with trimethoprim colonised with *E. coli* resistant to trimethoprim. In light and dark pink, the 95th and 50th percentile of 1,000 stochastic runs (respectively). The solid and dotted dark red lines represent the mean and median of the 1,000 stochastic runs (respectively). The median, 95th and 50th percentile of 1,000 stochastic runs (respectively) for the $\boldsymbol{Ts}$ compartment are equal to zero.

Figure 7-13 shows the weekly incidence of UTIs caused by *E. coli* resistant to trimethoprim in the LTCF reported in AmSurv (black points) compared to that predicted by the model. The median number of UTIs caused by *E. coli* resistant to trimethoprim in the LTCF for 1,000 runs of the stochastic model over the study period was zero (dotted dark red line, 95th percentiles= 0-2).

In the last four weeks of the study, the stochastic model predicted a median of one UTI caused by *E. coli* resistant to trimethoprim (95th percentiles= 0-4, mean=1.31). Over the study period, there were 65 UTIs caused by *E. coli* resistant to trimethoprim in the LTCF in the data. The stochastic model predicted a mean of 63.5 and a median of 63 (95th percentile=38-95) over the 1,000 simulations.

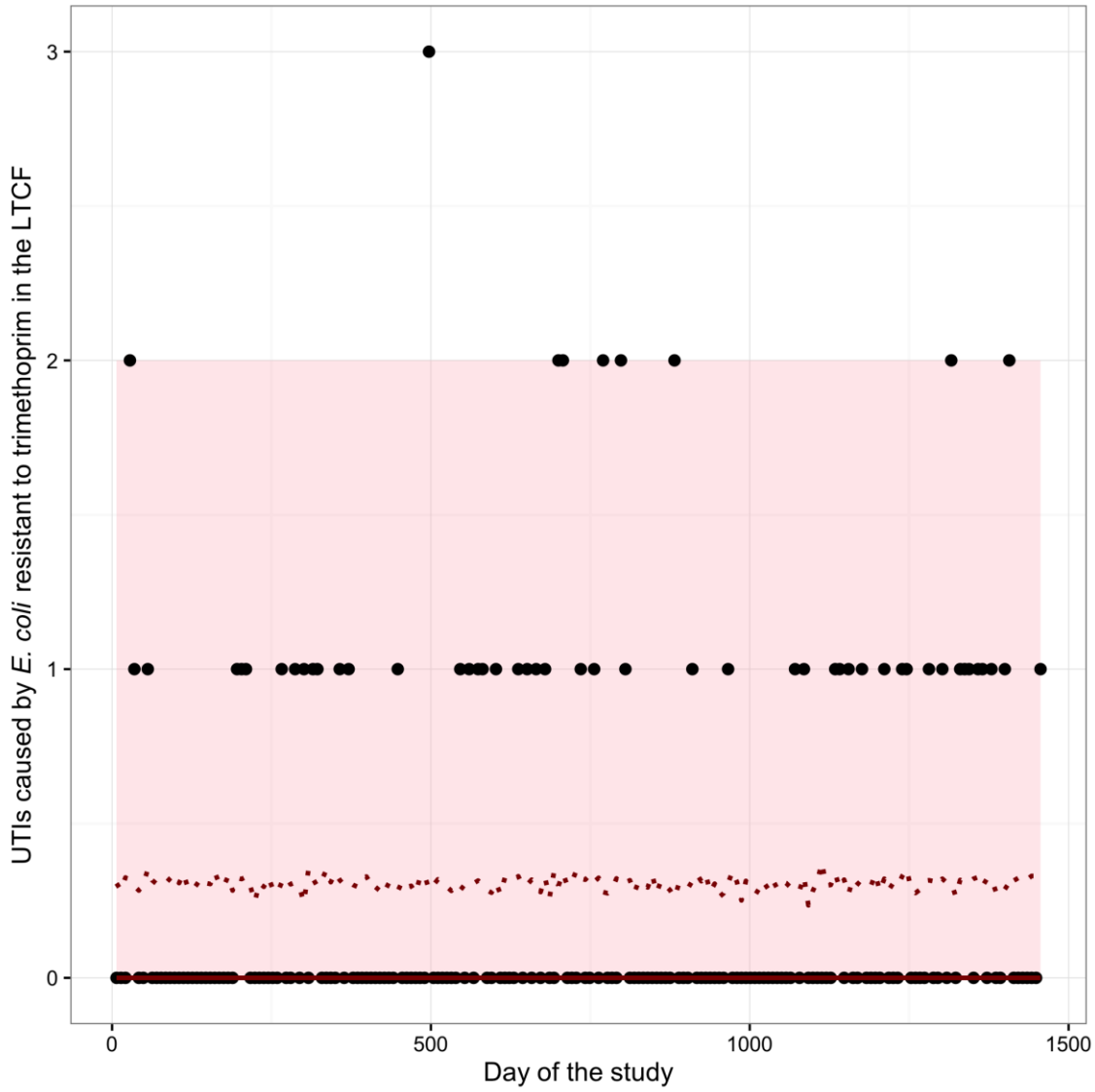

Figure 7-13. Weekly incidence of UTIs caused by *E. coli* resistant to trimethoprim in the data compared to the model. The black dots represent the incidence in the AmSurv West Midlands dataset for the LTCF selected for model fitting. The solid and dotted dark red lines represent the mean and median of the 1,000 stochastic runs (respectively).In light pink, the 95th percentile of 1,000 stochastic runs (the 50th percentile is not shown as both its limits were equal to zero).

Sensitivity analysis

Table 7-4 below shows the number of UTIs caused by *E. coli* resistant to trimethoprim in the LTCF, the number of individuals colonised by *E. coli* resistant to trimethoprim that were admitted to hospital from the LTCF and discharged to the LTCF from hospital, the percentage of individuals in the LTCF colonised by *E. coli* resistant to trimethoprim (vs. sensitive to trimethoprim), the percentage of individuals in the LTCF treated with trimethoprim (vs. untreated), and the percentage of individuals colonised by *E. coli* resistant to trimethoprim (vs. sensitive to trimethoprim) admitted to hospital from the LTCF and discharged to the LTCF from hospital in the baseline scenario and in several sensitivity analyses. These included increasing ptc, prc and prh linearly with an intercept and slope defined by the regression models fit to the prescription and antibiotic resistance data for this period, as well as varying γ, γ_p, lh, and pth according to plausible ranges (described in the parameterisation section).

The deterministic model output in the baseline scenario compared to when prc, ptc, and prh increase linearly (as derived from the data and explained in the parameterisation section above) is shown in Figure 7-14.

The model was additionally fit to data from three different LTCFs with lower incidence and higher number of beds (see Table 7-5).

Table 7-4. Sensitivity analysis part 1.

	Baseline scenario	prc, ptc, and prh increase linearly	γ=0.0025	γ=0.0055	γ_p=0.16	γ_p=0.3	lh=0.77	lh=0.9	pth=0.017	pth=0.032
N UTIs caused by *E. coli* resistant to trimethoprim in the LTCF in the last month of the study* (median, mean, and 95th percentile for 1,000 simulations)	1, 1.31, 0-4	1, 1.18, 0-4	1, 1.2, 0-4	1, 1.17, 0-4	1, 1.27, 0-4	1, 1.22, 0-4	1, 1.17, 0-4	1, 1.16, 0-4	1, 1.26, 0-4	1, 1.2, 0-4
N individuals admitted to hospital from the LTCF colonised by *E. coli* resistant to trimethoprim in the last month of the study* (median, mean, and 95th percentile for 1,000 simulations)	1, 1.35, 0-3	1, 1.36, 0-3	1, 1.36, 0-4	1, 1.39, 0-4	1, 1.36, 0-4	1, 1.28, 0-4	1, 1.28, 0-4	1, 1.53, 0-4	1, 1.3, 0-4	1, 1.32, 0-3
N individuals discharged to the LTCF from hospital colonised by *E. coli* resistant to trimethoprim in the last month of the study* (median, mean, and 95th percentile for 1,000 simulations)	1, 0.91, 0-3	0, 0.95, 0-4	1, 1.03, 0-4	1, 1.01, 0-4	1, 1.01, 0-4	1, 0.98, 0-3	0, 0.98, 0-4	1, 0.99, 0-3	1, 0.98, 0-4	1, 0.92, 0-3
Percentage of individuals in the LTCF colonised by *E. coli* resistant to trimethoprim (vs. sensitive to trimethoprim) in the last year of the study (median, mean, and 95th percentile for 1,000 simulations)	48.02, 47.51, 31.24-61.24	48.51, 48.01, 32.54-62.54	57.25, 56.69, 42.39-70.13	34.25, 33.7, 18.08-47.60	48.22, 48.09, 32.3-62.54	47.94, 47.17, 31.84-60.9	49.02, 48.49, 33.84-62.17	47.97, 47.79, 32.91-61.89	48.24, 47.77, 32.68-62.16	48.21, 48.13, 32.47-62.44

	Baseline scenario	prc, ptc, and prh increase linearly	γ=0.0025	γ=0.0055	γ_p=0.16	γ_p=0.3	lh=0.77	lh=0.9	pth=0.017	pth=0.032
Percentage of individuals in the LTCF treated with trimethoprim (vs. untreated) in the last year of the study (median, mean, and 95th percentile for 1,000 simulations)	0.49, 0.52, 0.12-0.96	0.49, 0.52, 0.17-0.94	0.5, 0.52, 0.19-0.91	0.49, 0.51, 0.14-0.94	0.6, 0.63, 0.21-1.16	0.32, 0.34, 0.09-0.65	0.49, 0.51, 0.18-0.93	0.49, 0.52, 0.17-0.95	0.49, 0.52, 0.17-0.95	0.48, 0.51, 0.18-0.94
Percentage of individuals colonised by *E. coli* resistant to trimethoprim (vs. sensitive to trimethoprim) admitted to hospital from the LTCF in the last year of the study (median, mean, and 95th percentile for 1,000 simulations)	48.28, 48.15, 25-71.43	47.62, 48.22, 27.27-70	57.14, 57.39, 33.33-80	33.33, 33.04, 11.99-54.55	47.62, 47.81, 26.67-70	47.62, 47.47, 25-70	50, 48.46, 23.77-71.43	48, 47.98, 26.67-70	50, 48.17, 25-68.77	50, 48.06, 23.51-70.59
Percentage of individuals colonised by *E. coli* resistant to trimethoprim (vs. sensitive to trimethoprim) discharged to the LTCF from hospital in the last year of the study (median, mean, and 95th percentile for 1,000 simulations)	37.5, 38.39, 13.33-66.67	40, 40.23, 16.67-66.67	36.84, 37.23,14.24-62.5	37.5, 38.07, 16.67-62.5	37.5, 37.59, 13.33-62.5	36.84, 37.15, 11.11-63.67	37.5, 37.42, 12.43-61.54	37.5, 36.95, 14.29-62.5	37.5, 37.63 13.29-64.29	36.84, 37.15, 12.5-62.5

* Four weeks, as the data was weekly. The last 4 weeks of the study were selected for analysis as this was representative of the equilibrium state.

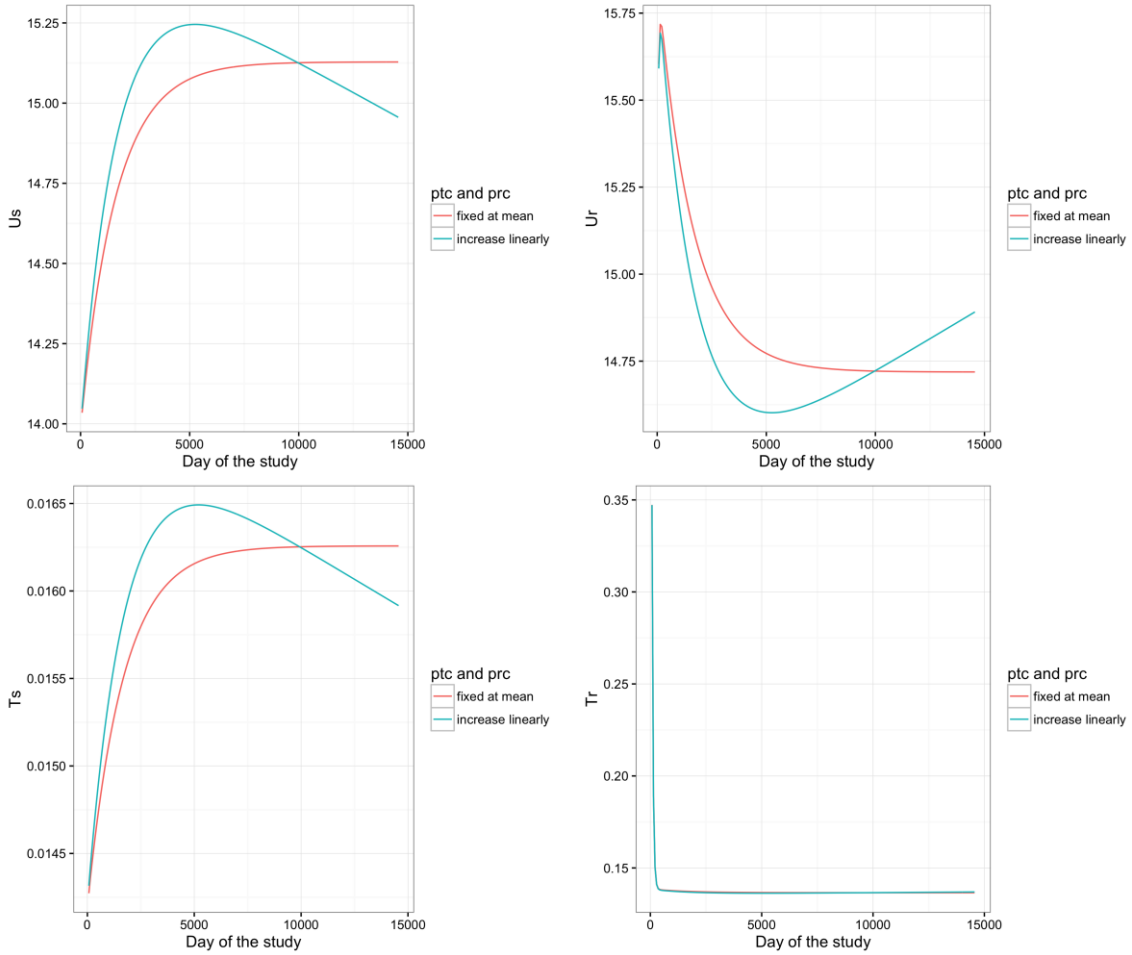

Figure 7-14. Outputs from the deterministic model in which prc, ptc, and prh were fixed at the mean (in red) compared to the scenario in which they were made to increase linearly in agreement with the data (in blue). Us were individuals untreated with trimethoprim colonised with *E. coli* susceptible to trimethoprim, Ur were individuals untreated with trimethoprim colonised with *E. coli* resistant to trimethoprim, Ts were individuals treated with trimethoprim colonised with *E. coli* susceptible to trimethoprim and Tr were individuals treated with trimethoprim colonised with *E. coli* resistant to trimethoprim.

Table 7-5. Sensitivity analysis part 2.

	Baseline scenario (LTCF with 30 beds, incidence of trimethoprim resistant urinary *E. coli*=0.0015 per bed day, β=0.0062 per person per day	LTCF with 39 beds, incidence of trimethoprim resistant urinary *E. coli*=0.00088 per bed day, β=0.0024 per person per day	LTCF with 57 beds, incidence of trimethoprim resistant urinary *E. coli*= 0.00075 per bed day, β=0.0016 per person per day	LTCF with 83 beds, incidence of trimethoprim resistant urinary *E. coli*= 0.00045 per bed day, β=0.000052 per person per day
N UTIs caused by *E. coli* resistant to trimethoprim in the LTCF in the last month of the study* (median, mean, and 95th percentile for 1,000 simulations)	1, 1.31, 0-4	1, 1.01, 0-4	1, 1.08, 0-4	0, 0.92, 0-4
N individuals admitted to hospital from the LTCF colonised by *E. coli* resistant to trimethoprim in the last month of the study* (median, mean, and 95th percentile for 1,000 simulations)	1, 1.35, 0-3	2, 1.78, 0-5	2, 2.49, 0-5	3, 3.63, 1-7
N individuals discharged to the LTCF from hospital colonised by *E. coli* resistant to trimethoprim in the last month of the study* (median, mean, and 95th percentile for 1,000 simulations)	1, 0.91, 0-3	1, 1.38, 0-5	1, 1.86, 0-5	2, 2.67, 0-6
Percentage of individuals in the LTCF colonised by *E. coli* resistant to trimethoprim (vs. sensitive to trimethoprim) in the last year of the study (median, mean, and 95th percentile for 1,000 simulations)	48.02, 47.51, 31.24-61.24	27.79, 27.97, 16.17-39.62	23.19, 23.20, 14.18-32.18	13.75, 13.82, 8.79-18.75

	Baseline scenario (LTCF with 30 beds, incidence of trimethoprim resistant urinary *E. coli*=0.0015 per bed day, β=0.0062 per person per day	LTCF with 39 beds, incidence of trimethoprim resistant urinary *E. coli*=0.00088 per bed day, β=0.0024 per person per day	LTCF with 57 beds, incidence of trimethoprim resistant urinary *E. coli*= 0.00075 per bed day, β=0.0016 per person per day	LTCF with 83 beds, incidence of trimethoprim resistant urinary *E. coli*= 0.00045 per bed day, β=0.000052 per person per day
Percentage of individuals in the LTCF treated with trimethoprim (vs. untreated) in the last year of the study (median, mean, and 95th percentile for 1,000 simulations)	0.49, 0.52, 0.12-0.96	0.49, 0.51, 0.23-0.86	0.49, 0.51, 0.26-0.81	0.50, 0.51, 0.3-0.75
Percentage of individuals colonised by *E. coli* resistant to trimethoprim (vs. sensitive to trimethoprim) admitted to hospital from the LTCF in the last year of the study (median, mean, and 95th percentile for 1,000 simulations)	48.28, 48.15, 25-71.43	28.57, 28.35, 11.09-45.83	23.08, 23.12, 9.99-36.67	13.6, 13.8, 5.99-22.22
Percentage of individuals colonised by *E. coli* resistant to trimethoprim (vs. sensitive to trimethoprim) discharged to the LTCF from hospital in the last year of the study (median, mean, and 95th percentile for 1,000 simulations)	37.5, 38.39, 13.33-66.67	37.5, 37.95, 18.18-60	38.24, 38.18, 22.22-55.56	37.5, 37.76, 24.13-51.72

* Four weeks, as the data was weekly. The last 4 weeks of the study were selected for analysis as this was representative of the equilibrium

Scenario analysis

Table 7-6 compares the output of 1,000 stochastic runs of the model in the baseline scenario; in two scenarios assuming different proportion of patients entering the LTCF from hospital (vs. from the community); in three different transmission scenarios; and in four scenarios in which the rate of treatment was progressively increased.

The impact of increasing the proportion of admissions from hospital (hl) by 20%, increasing the rate of treatment (α_p) by 20% and increasing the rate of transmission (β) by 20% on the percentage of individuals in the LTCF colonised by *E. coli* resistant to trimethoprim (vs. sensitive to trimethoprim) in the last year of the study was compared. Note that only increases of 20% in the rates of treatment and transmission are strictly comparable, as the admissions from hospitals are a proportion. Increasing the transmission rate resulted in a median 5.42% (mean 5.32%) percentage increase in the number of individuals in the LTCF colonised by *E. coli* resistant to trimethoprim. Increasing hl and α_p resulted in lower increases in resistance (median increases of 0.77% and 1.54%, respectively, and mean increases of 0.83% and 1.91%, respectively).

Table 7-6. Movement, transmission and treatment scenarios.

	Baseline scenario	hl=0.4057 (20% reduction)	hl=0.8057 (20% increase)	β=0.0031 (halved)	β=0.0074 (20% increase)	β=0.0124 (doubled)	β'= β=0.0062 (tr =1)	α_p=0.0012 (20% increase)	α_p=0.0015 (50% increase)	α_p=0.0055 (5.5 fold increase)
N UTIs caused by *E. coli* resistant to trimethoprim in the LTCF in the last month of the study* (median, mean, and 95th percentile for 1,000 simulations)	1, 1.31, 0-4	1, 1.19, 0-4	1, 1.24, 0-4	0, 0.79, 0-3	1, 1.37, 0-4	1, 1.63, 0-5	1, 1.01, 0-4	1, 1.24, 0-4	1, 1.3, 0-4	1, 1.68, 0-5
N individuals admitted to hospital from the LTCF colonised by *E. coli* resistant to trimethoprim in the last month of the study* (median, mean, and 95th percentile for 1,000 simulations)	1, 1.35, 0-3	1, 1.36, 0-3	1, 1.35, 0-4	1, 1.32, 0-4	1, 1.33, 0-4	1, 1.31, 0-4	1, 1.37, 0-4	1, 1.3, 0-3	1, 1.4, 0-4	1, 1.32, 0-3
N individuals discharged to the LTCF from hospital colonised by *E. coli* resistant to trimethoprim in the last month of the study* (median, mean, and 95th percentile for 1,000 simulations)	1, 0.91, 0-3	0, 0.65, 0-3	1, 1.24, 0-4	1, 0.98, 0-4	1, 1, 0-4	1, 1, 0-4	1, 0.98, 0-4	1, 0.98, 0-3	1, 1.09, 0-4	1, 0.97, 0-3

	Baseline scenario	hl=0.4057 (20% reduction)	hl=0.8057 (20% increase)	β=0.0031 (halved)	β=0.0074 (20% increase)	β=0.0124 (doubled)	β'= β=0.0062 (tr =1)	α_p=0.0012 (20% increase)	α_p=0.0015 (50% increase)	α_p=0.0055 (5.5 fold increase)
Percentage of individuals in the LTCF colonised by *E. coli* resistant to trimethoprim (vs. sensitive to trimethoprim) in the last year of the study (median, mean, and 95th percentile for 1,000 simulations)	48.02, 47.51, 31.24-61.24	48.29, 48.17, 33.25-62.28	48.79, 48.34, 34.42-61.92	31.76, 31.21, 15.39-45.7	53.44, 52.83, 37.82-66.18	67.85, 67.45, 56.47-77.62	39, 38.61, 21.78-53.93	49.56, 49.42, 34.14-63.35	51.5, 51.14, 36.12-64.41	67.21, 66.94, 56.95-76.09
Percentage of individuals in the LTCF treated with trimethoprim (vs. untreated) in the last year of the study (median, mean, and 95th percentile for 1,000 simulations)	0.49, 0.52, 0.12-0.96	0.47, 0.51, 0.18-0.99	0.49, 0.52, 0.17-0.96	0.48, 0.51, 0.16-0.95	0.48, 0.51, 0.17-0.96	0.47, 0.5, 0.17-0.93	0.48, 0.5, 0.16-0.93	0.58, 0.6, 0.22-1.07	0.72, 0.75, 0.33-1.28	2.62, 2.66, 1.84-3.6

	Baseline scenario	hl=0.4057 (20% reduction)	hl=0.8057 (20% increase)	β=0.0031 (halved)	β=0.0074 (20% increase)	β=0.0124 (doubled)	β'= β=0.0062 (tr =1)	α_p=0.0012 (20% increase)	α_p=0.0015 (50% increase)	α_p=0.0055 (5.5 fold increase)
Percentage of individuals colonised by *E. coli* resistant to trimethoprim (vs. sensitive to trimethoprim) admitted to hospital from the LTCF in the last year of the study (median, mean, and 95th percentile for 1,000 simulations)	48.28, 48.15, 25-71.43	48, 48.1, 25-70.63	47.37, 47.84, 25-70	31.14, 31.65, 9.5-54.55	53.85, 53.09, 28.57-75	66.67, 67.2, 46.67-87.5	38.46, 38.7, 16.67-61.56	50, 49.1, 25-71.43	50, 51.19, 27.27-73.33	68, 67.36, 46.64-87.5
Percentage of individuals colonised by *E. coli* resistant to trimethoprim (vs. sensitive to trimethoprim) discharged to the LTCF from hospital in the last year of the study (median, mean, and 95th percentile for 1,000 simulations)	37.5, 38.39, 13.33-66.67	37.5, 37.13, 0-66.67	37.5, 37.97, 16.67-60	38.1, 37.96, 12.5-62.5	37.5, 37.63, 12.5-63.64	37.5, 37.46, 14.29-63.64	37.5, 37.33, 13.62-60.9	38.68, 38.54, 12.5-62.5	36.36, 36.87, 13.29-61.54	36.36, 36.88, 12.5-63.64

* Four weeks, as the data was weekly. The last 4 weeks of the study were selected for analysis as this was representative of the equilibrium state

Discussion

Baseline scenario findings: incidence and prevalence of resistance

In the baseline scenario, a median of one UTI caused by *E. coli* resistant to trimethoprim was predicted to be reported during the last month of the study from a 30-bed LTCF over 1,000 stochastic runs (95th percentile range=0-4, mean=1.31 for the LTCF, or 0.04 per resident). The model predicted that even in scenarios where the prevalence of resistant colonisation neared 70% in the LTCF, the number of UTIs caused by *E. coli* resistant to trimethoprim reported would remain at a mean of 1.6-1.7 per month (0.05-0.06 per resident per month). This was in agreement with the dataset used for model fitting (range=0-8, 0.06 per resident per month). The total number of UTIs caused by *E. coli* resistant to trimethoprim in the LTCF over the study period was also similar in the data (65) and in the model (mean over 1,000 simulations=63.5, median=63, 95th percentile=38-95). The LTCF selected for model fitting in the baseline scenario had a higher incidence of trimethoprim resistant *E. coli* urine samples submitted to AmSurv than the mean observed for all LTCF residents surveyed in the West Midlands AmSurv dataset (from Chapter 5), which was 0.011 per resident per month. It should be noted that the incidence predicted by the model and the incidence in the West Midlands AmSurv dataset reflected the number of sampled and reported urinary *E. coli* resistant to trimethoprim, and that the number of residents developing UTIs caused by *E. coli* resistant to trimethoprim may be higher (as these are not always sampled and reported).

The median prevalence of colonisation with *E. coli* resistant to trimethoprim (vs. susceptible to trimethoprim) in the baseline scenario was predicted to be 48.02% (95th percentile range=31.24-61.24). This was lower than the prevalence of resistance in urinary *E. coli* samples reported to AmSurv from residents of this same LTCF (77.3%), calculated as the number of *E. coli* urinary samples resistant to trimethoprim divided by the total number of *E. coli* urine samples sent from residents in this facility. However, the prevalence of colonisation with *E. coli* resistant to trimethoprim in this simulated LTCF was still higher than that calculated for West Midlands AmSurv samples sent from elderly patients in hospitals (mean over 2010-2014=37.92%), which were used

to parameterise prh (the proportion of individuals colonised by *E. coli* resistant to trimethoprim discharged from hospital to the LTCF). Since it was additionally assumed that transfers from the LTCF to hospital were equally probable for residents colonised by *E. coli* sensitive and resistant to trimethoprim (both at rate m), and the rate of patient transfer from the LTCF to hospital was higher ($N \times m \times lh = 30 \times 0.002 \times 0.8$) than the rate of patient transfer from the hospital to the LTCF ($N \times m \times hl = 30 \times 0.002 \times 0.6057$), this meant there was a net transfer of individuals colonised with *E. coli* resistant to trimethoprim towards the hospital.

During the process of selecting the LTCF for model fitting, it transpired that larger LTCFs had a lower incidence of urinary *E. coli* resistant to trimethoprim per bed day than smaller LTCFs. This requires further study. LTCFs were sub-divided by quartiles according to the number of urine *E. coli* samples sent to AmSurv which were resistant to trimethoprim per bed per day. One LTCF was selected from each of these quartiles. The LTCF selected from the highest incidence quartile was used to fit the model in the baseline scenario and the remaining three LTCFs from the lower incidence quartiles were used to fit the model in sensitivity analyses. The prevalence of resistant colonisation was lower in the three LTCFs selected for sensitivity analyses. This was to be expected as the incidence of urine *E. coli* samples in these facilities was lower and the transmission parameter was estimated by fitting the model to this incidence data (all remaining parameters were kept the same). In all three LTCFs in the sensitivity analyses, the prevalence of resistant colonisation was lower in the LTCF than in the hospital, therefore, contrasting with the baseline scenario, there was a net transfer of individuals colonised with trimethoprim resistant *E. coli* from the hospital to the LTCF. The median prevalence of resistance in the LTCF selected amongst those in the lowest incidence quartile was 13.75% (8.79%-18.75%). LTCFs submitting fewer than 10 urinary *E. coli* samples resistant to trimethoprim to AmSurv per year were excluded from this analysis. Therefore, the prevalence of resistance in some LTCFs may be even lower.

Movement in and out of the LTCF

Increasing prc (the proportion of residents admitted to the LTCF from the community colonised with *E. coli* resistant to trimethoprim), ptc (the proportion of residents admitted to the LTCF from the community on trimethoprim treatment) and prh (the proportion of residents discharged to the LTCF from hospital colonised with *E. coli* resistant to trimethoprim) resulted in similar model outputs than when these proportions were fixed at the mean for the study period (as in the baseline scenario).

The model outputs were also robust to varying lh, the proportion of residents who leave the LTCF that go to hospital (vs. die), between 0.77 and 0.9, to reflect different hospital admission rates for LTCF residents reported in the literature[9,249]; and to varying pth, the proportion of admissions to the LTCF from hospital (vs. community), between 0.0173 and 0.0323, in line with the range of prevalence of trimethoprim treatment found in different hospitals in the West Midlands in the point-prevalence survey data.[40] Increasing and decreasing hl (the proportion of patients entering the LTCF from hospital (vs. the community)) by 20% increased and decreased the mean monthly number of individuals colonised by *E. coli* resistant to trimethoprim discharged to the LTCF from hospital from 0.91 to 1.24 and 0.65, respectively. However, this change did not alter the prevalence of resistant colonisation in the LTCF. This indicates that, in a LTCF similar to that used for model fitting in the baseline scenario, the prevalence of resistant colonisation would still be high even when fewer patients were admitted to the LTCF from hospital. For example, in a situation where hospitals were encouraged to discharge patients to the community with supported care in their own homes. The prevalence of trimethoprim resistant colonisation was higher in the LTCF than in hospital. This would, however, be different for other types of antibiotic resistance which are more prevalent in hospital.

Treatment

The proportion of LTCF residents treated with trimethoprim at equilibrium was lower than that reported in other studies (median=0.49%, mean=0.52%, 95th

percentile range=0.12%-0.96%). In HALT-2, 2.69% (11/409) of residents surveyed in 16 English LTCFs were being treated with trimethoprim or sulphonamides on the day of the study.[63] In Ireland, a point-prevalence survey carried out in 2011[259] showed 1.717% of residents being treated with trimethoprim on the survey day. Varying the duration of trimethoprim treatment between 3 and 6 days moderately decreased and increased (respectively) the proportion of residents treated with trimethoprim (increase of 0.11% and decrease of 0.18% in the median); however, this did not affect the prevalence of resistance in the LTCF. Only the scenario in which the treatment rate (α_p) was increased by 5.5 fold (to 0.0055 per person per day) was able to approximate (median=2.62%) the proportion of residents treated with trimethoprim found in HALT-2.[63] This high treatment rate resulted in an increase in the prevalence of resistance from a median of 48.02% to a median of 67.21%, which was closer to that observed in AmSurv for this LTCF (77.3%). In this scenario, the mean monthly number of UTIs reported caused by *E. coli* resistant to trimethoprim predicted by the model also increased, from 1.31 to 1.68. The monthly number of UTIs reported caused by *E. coli* resistant to trimethoprim was not altered by smaller increases in α_p.

Transmission

Doubling the transmission rate also resulted in a similar increase in the median prevalence of resistance in the LTCF (from 48.02% to 67.85%) and a similar increase in the mean monthly number of predicted UTIs reported caused by *E. coli* resistant to trimethoprim (from 1.31 to 1.63). Changes in the monthly number of UTIs reported caused by *E. coli* resistant to trimethoprim were not evident for smaller increases in transmission (20%). However, a 20% increase in the transmission rate still increased the median prevalence of resistance in the LTCF from 48.02% to 53.44%. Similarly, varying the duration of colonisation between 6 and 13 months altered the prevalence of resistance in the LTCF but didn't result in a significant difference in the number of UTIs reported caused by *E. coli* resistant to trimethoprim predicted by the model. Increasing the duration of colonisation to 13 months (instead of 9.5 as per the baseline scenario) increased the median prevalence of resistant colonisation in the LTCF by

9.23%. Decreasing the duration of colonisation to 6 months caused a 13.77% decrease. Setting the transmission rate in treated individuals equal to the transmission rate in untreated individuals reduced the median prevalence of resistance in the LTCF to 39%. The mean number of predicted UTIs reported caused by *E. coli* resistant to trimethoprim per month dropped slightly from 1.31 to 1.01.

What are the main drivers of trimethoprim resistance and what does this mean?

Of the scenarios explored, only doubling the transmission and increasing the rate of trimethoprim prescription by 5.5 fold per person per day caused a visible increase in the number of monthly UTIs reported caused by *E. coli* resistant to trimethoprim. However, the monthly number of predicted UTIs reported caused by *E. coli* resistant to trimethoprim was low, complicating the comparison of this output between different scenarios. The mean number of predicted UTIs reported caused by *E. coli* resistant to trimethoprim over 1,000 simulations had to be used for comparison, as the median in every scenario was equal to either 0 or 1, which was uninformative. Transmission appeared to be the most important driver of the prevalence of resistant colonisation in the LTCF. The transmission rate was doubled to yield a prevalence of resistance nearing 70%. In comparison, the treatment rate had to be increased by 5.5 fold to achieve the same prevalence of resistance. In addition, when increasing the transmission rate, the treatment rate and the proportion of admissions to the LTCF from hospital (vs. from the community) by 20%, the 20% increase in transmission resulted in the highest change in the prevalence of resistance within the LTCF. These findings were based on the model at equilibrium; therefore, increasing the time horizon of the model would have not changed these results. However, parameters will change over time; thus, the model outputs are reflective of the current model parameterisation and of the structure and assumptions made. The high levels of resistance to trimethoprim already present in this population mean that the number of transmission events will be higher under the same transmission rate than in a scenario where the prevalence of resistance is low (as there are more individuals dominantly colonised by *E. coli* resistant to

trimethoprim in the population), provided that there are still sufficient individuals dominantly colonised with *E. coli* susceptible to trimethoprim. It is worth noting, therefore, that these conclusions might change in a scenario with low prevalence of resistance and the main driver of the prevalence of resistance for other organism-antibiotic combinations such as *E. coli* resistant to nitrofurantoin may be different.

The relative importance of importation from hospital, transmission, and prescription in increasing the prevalence of resistant colonisation, coupled with the high levels of resistance to trimethoprim in the LTCF compared to hospitals and the community in the baseline scenario, suggest that interventions that target transmission such as hand washing, contact precautions and isolation would be more effective in reducing colonisation by resistant strains in LTCFs than interventions that target importations of resistance from hospitals or the community (for example, screening on admission to the LTCF). Importations from hospital could become more important in LTCFs where the prevalence of resistance is low (for example, the LTCFs in the sensitivity analysis). In these facilities, the prevalence of resistance was lower than that estimated from AmSurv data for hospitals (38%) and the community overall (36%), which seems implausible.

The difference between the prevalence of trimethoprim resistance predicted from the model (in the baseline scenario 48.02%) and the prevalence of resistance predicted by the AmSurv dataset (for the baseline scenario LTCF 77.3%) could be explained by a number of alternatives: (1) transmission is approximately double than in the baseline scenario, (2) the duration of treatment is substantially longer than 6 days, (3) antibiotic prescription is 5.5 fold higher than in the baseline scenario, (4) the duration of colonisation is much longer than 13 months, (5) there is a bias for antibiotic susceptibility testing of resistant strains, or (6) a combination of all these factors.

Strengths

This was the first study to model the dynamics of trimethoprim resistant Gram-negative bacteria in LTCFs. The model was informed by data from AmSurv

linked to CQC data, THIN data, a point-prevalence survey conducted in hospitals, and various studies from the literature. A range of parameter values was explored and the model was formally fit to four separate LTCFs with different number of beds and prevalence rates. All the high importance criteria for good quality mathematical models of AMR bacteria in LTCFs identified in Chapter 3 were met.

In addition, the datasets used to parameterise this model were well matched. Although some parameters were obtained from the literature and were not specific to the West Midlands, these were adjusted using CQC data to match the proportion of nursing LTCFs in the West Midlands. Moreover, the same susceptibility data from the West Midlands AmSurv dataset was used for model fitting, and informed the proportion of individuals entering the LTCF colonised with *E. coli* resistant to trimethoprim from hospital and from the community, which were specifically derived for individuals aged 70 or older. The trimethoprim prescription information from THIN was also obtained for the same period (April 2010 to March 2014) and for the same population (individuals aged 70 or older in the West Midlands). The trimethoprim prescription point-prevalence data from hospitals was also restricted to hospitals in the West Midlands.

Limitations of the assumptions

The LTCF was assumed to be at full bed occupancy during the duration of the study, which simplified the model. This may not have been the case; however, no data was available to inform this. In addition, recent reports have highlighted the shortage of available beds in care homes in the UK, making this scenario not completely implausible.[260,261] Residents were also assumed not to transfer between LTCFs. Van den Dool et al. (2016)[140] similarly did not model transfers between LTCFs as these were considered negligible. Residents were also assumed not to return to the community.

Dominance of a single strain in a colonised individual was assumed and competition between strains was not modelled as there was not sufficient data

available on multi-strain colonisation and infection to parameterise a model structure which would allow for co-colonisation.

In this model the rate of acquiring dominance by an *E. coli* strain resistant to trimethoprim was dependent on the number of individuals colonised with *E. coli* resistant to trimethoprim in the LTCF (and the number of individuals colonised with *E. coli* susceptible to trimethoprim). This model did not explicitly simulate neither the acquisition of dominant colonisation by *E. coli* resistant to trimethoprim through endogenous factors such as spontaneous mutation, which is assumed to be comparatively rare, nor the transfer of mobile genetic elements between bacteria within an individual. Endogenous acquisition of resistance was also not explicitly modelled during trimethoprim treatment. Therefore, the model did not explicitly account for the possibility that, in an individual colonised both by strains of *E. coli* resistant and susceptible to trimethoprim, but in which the susceptible strains dominate; trimethoprim treatment might confer a selective advantage for resistant strains, which may result in *E. coli* resistant to trimethoprim dominating within this individual. However, the rate of acquisition of resistance endogenously and through transmission are grouped into parameter β (under no treatment) and β' (under treatment). $\beta' = tr \times \beta$; therefore, tr is the magnitude by which the rate of acquisition of resistance is greater under treatment. tr will capture this selection of resistance under treatment within an individual as well as the increased susceptibility of individuals dominantly colonised by *E. coli* susceptible to trimethoprim to transmission of resistance from other individuals. The limitation of this approach is that β and β' are dependent on the number of people colonised with resistant bacteria in the LTCF (and susceptible to acquiring dominant resistant colonisation). Whilst this is accurate for the transmission of resistance from one individual to another, the endogenous acquisition of resistance does not depend on the number of people colonised with resistant bacteria in the LTCF. In order to parameterise this endogenous transmission, a separate parameter would need to be created; however, data to this effect is lacking. The endogenous acquisition of dominant colonisation by *E. coli* resistant to trimethoprim has been shown to be comparatively rare with respect to exogenous transmission (dominant colonisation by *E. coli* resistant to

trimethoprim acquired through person-person transmission) for KPC-producing bacteria and for *E. coli* resistant to expanded-spectrum cephalosporins. Haverkate et al.[256] estimated endogenous acquisition of KPC-producing bacteria in LTACH at 0.0026 per person per day (95%CI=0.0015–0.0043), compared to exogenous transmission at 0.014 (95%CIs=0.0071-0.026).[256] Gurieva et al. also found a lower endogenous acquisition of *E. coli* resistant to expanded-spectrum cephalosporins (0.0024, 95%CI=0.0013-0.0039 compared to 0.0078, 95%CI=0.0029-0.016, respectively).[255] These studies estimated endogenous acquisition of resistance through an algorithm developed by Bootsma et al.[262] which requires extensively detailed data on the patient trajectory and screening results.

Transmission of resistance was only modelled between residents and included transmission through direct contact or via healthcare workers. The transmission of resistance from the remaining population, including from healthcare workers and visitors, was not modelled. This was due to the lack of available data to parameterise these modes of transmission.

Only trimethoprim treatment was modelled. However, trimethoprim resistance has been correlated with a number of antibiotic resistances, including ampicillin and amoxicillin.[263,264] Co-selection of trimethoprim resistance by ampicillin/amoxicillin treatment has been shown to be an important predictor of geographical variation in trimethoprim resistance in urinary samples[263] and ampicillin and trimethoprim resistance genes are often linked on the same mobile genetic elements[264–266]. Given that amoxicillin and ampicillin are commonly prescribed antibiotics in primary care in England[267], these antibiotics may be an important driver of trimethoprim resistance.

Limitations of the parameterisation

The evidence from the literature used to parameterise the rate of exit and entry to the LTCF (m) and the proportion of residents leaving the LTCF to be hospitalised (vs. dying) (lh) was scaled to represent the distribution of nursing LTCFs in the West Midlands using CQC data; however, it was not specific to LTCFs in the West Midlands. The proportion of residents entering the LTCF

from hospital (vs. from the community) (hl), which was also taken from the literature and scaled using CQC data in the same way, was also not specific to the West Midlands. In addition, it was likely to be an overestimate because not all patients that visited hospital within the previous 3 months would have directly been discharged to the LTCF from hospital. Therefore, the prevalence of resistance and the proportion of individuals treated in some individuals in this population may have been more similar to the community than to hospital. This was explored in sensitivity analyses.

When parameterising prc and prh, the proportion of individuals colonised with *E. coli* resistant to trimethoprim was assumed to be the same as the proportion of individuals for which a urinary *E. coli* sample resistant to trimethoprim was reported to AmSurv. However, sampling could be biased towards resistance due to treatment failure. This would imply that the proportion of individuals admitted to the LTCF from the community and from hospital colonised with *E. coli* resistant to trimethoprim could be over-estimated in the model. In addition, the assumption that the prevalence of resistance is similar in carriage and infection may not be correct. A study characterising the *E. coli* faecal flora in patients with UTI compared to healthy individuals who had never had a UTI found that isolates from UTI patients were more frequently associated with multidrug resistance compared to healthy individuals.[268] However, this was a small-scale study (50 patients and 53 controls) set in Denmark in all ages which did not specifically study trimethoprim resistance and is subject to many possible confounders; therefore, further work is needed to test this assumption.

The proportion of treated individuals in hospitals, pth, was derived from a point-prevalence survey carried out in hospital in all ages. Only the two NHS trusts (five hospitals) in the West Midlands were selected to inform pth. There is, therefore, a need for point-prevalence surveys that capture antibiotic treatment stratified by age for a more representative number of hospitals in the West Midlands. In addition, patients were not followed through their hospital journey and return to the LTCF, and transmission was not modelled within the hospital setting. Due to this lack of history in the model structure, the model was unable to fully capture the “revolving door” syndrome.

The rate of trimethoprim treatment in the community was derived from THIN data for individuals aged 70 and older attending GP practices in the West Midlands, adjusted using findings from a study carried out in Hampshire in individuals aged 75 and older. In this study antibiotic prescribing for UTIs was 2.9 times higher in LTCFs than in the community.[69] This study was set in Hampshire, in which LTCFs could be different to those in the West Midlands. In addition, the difference between prescribing in the community and in the LTCF could vary by antibiotic used to treat UTI. Another limitation of this parameterisation was that it did not address that the rate of antibiotic treatment will be different in different LTCFs. The LTCF selected for model fitting in the baseline scenario was amongst the LTCFs in the highest quartile of incidence of urinary *E. coli* resistant to trimethoprim; therefore, it stands that this LTCF could also have had a higher trimethoprim treatment rate than average. Consequently, the treatment rate for the baseline scenario could have been underestimated. The lack of linked susceptibility and prescribing data also prevented the analysis of the patient journey through treatment and resistance.

There were no data available in the literature to inform the transmission of trimethoprim resistant *E. coli* in the LTCF, therefore, the transmission parameters in this model had to be estimated by fitting the model to incidence data. As such, the value of β was dependent on the LTCF selected for model fitting. This was shown in the sensitivity analyses, in which the estimates for β were smaller than the one derived for the baseline scenario when fitting to the LTCFs with lower incidence.

The baseline scenario transmission parameters were estimated by fitting the model to a LTCF with a high incidence of UTIs caused by *E. coli* resistant to trimethoprim per year reported to AmSurv. This was to ensure that sufficient samples were present to enable model fitting and to ensure that transmission (if present at all in the LTCF setting) was detected. This restricted the interpretation of the findings from the baseline scenario to facilities with a high incidence. The LTCF selected for model fitting was varied in sensitivity analyses to account for this. However, only three LTCFs amongst those with 20 beds or more and submitting 10 or more urine samples per year to AmSurv growing *E.*

coli resistant to trimethoprim were selected for model fitting in sensitivity analyses; therefore, the full spectrum of incidence in these facilities was not explored. It should be noted, therefore, that the conclusions drawn may be different for LTCFs smaller than 20 beds or LTCFs submitting fewer than 10 urine samples per year to AmSurv growing *E. coli* resistant to trimethoprim.

It would also be preferable to fit to the incidence of colonisation by *E. coli* resistant to trimethoprim in the LTCF as this is closer to what was estimated in the model; however, this data was not available. As a result, the rho parameter was created and grouped the proportion of residents colonised with *E. coli* resistant to trimethoprim that would develop a UTI, and the proportion of these UTIs that would be reported to AmSurv.

Maximum likelihood estimation is a formal model fitting procedure that takes a frequentist approach, estimating the set of parameters that are most likely given the data observed. Several other methods have been developed for model fitting in pomp, for example particle Markov-Chain Monte Carlo. This method takes a Bayesian approach, taking into account the prior knowledge about the distribution of each of the parameters estimated (the priors). One of the limitations of using maximum likelihood estimation is that the uncertainty around the parameter values estimated cannot be obtained. Maximum likelihood estimation also potentially ignores the volume of parameter space where the model fits the data well. This is a problem if the likelihood is “flat”, meaning that a large number of parameters give estimations consistent with the observed data, and less of a problem if the likelihood has a strong “peak”. Hence, maximum likelihood estimation can give a false sense of accuracy whilst selecting a more or less random value from a vast region of the parameter space which is more or less equally consistent with the data.

The duration of colonisation with *E. coli* resistant to trimethoprim has not been reported in the literature. Therefore, the range of values for this parameter (6-13 months) was obtained from the literature for *E. coli* resistant to other antibiotics. The duration of colonisation with *E. coli* resistant to trimethoprim could

potentially be longer since this resistance may not have a high fitness cost associated with it.[208]

Future work

A simple expansion of this mathematical model would involve parameterising the model to reflect the transmission of *E. coli* resistant to nitrofurantoin. These dynamics could then be compared to those of trimethoprim resistance. This would be particularly relevant to current English national policy, as the national guidelines recently recommended a switch from trimethoprim treatment to nitrofurantoin and nitrofurantoin prescriptions in England have been increasing accordingly.[35]

The model could also be fit to all the data available from all LTCFs or to a distribution of the incidence observed in all LTCFs using more complex methods such as particle Markov-Chain Monte Carlo, which would strengthen the robustness of the estimated parameters for transmission.

However, in general, the transmission of *E. coli* resistant to trimethoprim is poorly understood. A better understanding and quantification of transmission parameters is needed. Endogenous and exogenous acquisition of dominant carriage by *E. coli* resistant to trimethoprim could be derived by using the algorithm developed by Bootsma et al. (2007)[262] which requires extensively detailed data on the day of admission, day of discharge, day at which sample is taken, culture results and colonisation at admission, which has not been collected in England to date and was not within the remit of this PhD. With this information, transmission would ideally be modelled as four parameters: endogenous acquisition of resistance under treatment and under no treatment, and exogenous acquisition of resistance under treatment and under no treatment. Exogenous acquisition of resistance could also be informed by whole genome sequencing studies. This would avoid this parameter having to be estimated entirely through model fitting. In addition, the relationship between the rate of transmission of trimethoprim resistance in treated individuals compared to untreated individuals deserves further study.

Should incidence data of colonisation by *E. coli* resistant to trimethoprim in the LTCF become available, it would be preferable to fit the model to these data instead of to the incidence of urinary *E. coli* samples resistant to trimethoprim reported to AmSurv, as the model reproduces the dynamics of colonisation and not of infection. This would then eliminate the need for the rho parameter. Alternatively, rho could be better understood through the quantification of the relationship between an individual being colonised with *E. coli* developing a UTI and this UTI being reported to AmSurv.

Another extension of the model could involve simulating the transmission of resistance in the hospital. This could help understand how the dynamics of transmission of trimethoprim resistance in these two types of institutions are linked. Additional data specific to the hospital would be needed to parameterise this type of model.

Other extensions of this model would involve relaxing some of the assumptions made. In particular, a co-colonisation model would be interesting albeit currently very difficult to parameterise.

The conflicting evidence on the reversibility of trimethoprim resistance observed in the literature[208,216] suggests that the impact of antibiotic stewardship would be best studied through this type of model that accounts for competition between strains and co-selection, as the effect of decreasing the rate of treatment on resistance is likely complex and fitness cost and selection dynamics are likely to be important.

Conclusions

This was the first study to model the dynamics of trimethoprim resistant Gram-negative bacteria in LTCFs. A median of one UTI caused by *E. coli* resistant to trimethoprim was predicted to be reported monthly from a 30-bed LTCF (over 1,000 stochastic runs mean=1.31, 95th percentile range=0-4). The model predicted that even in scenarios where the prevalence of resistant colonisation neared 70% in the LTCF, the number of UTIs caused by *E. coli* resistant to trimethoprim would remain at 1.6-1.7 per month. The number of residents in LTCFs developing UTIs caused by *E. coli* resistant to trimethoprim is likely to be higher, as not all UTIs are sampled. In a LTCF with a high incidence of urinary *E. coli* resistant to trimethoprim reported to AmSurv, transmission appeared to be the most important driver of the prevalence of resistant colonisation in the LTCF. Therefore, in this type of LTCF where the prevalence of trimethoprim resistance is higher than that in hospitals and the community, interventions that target transmission such as hand washing, contact precautions and isolation would be more effective in reducing colonisation by resistant strains than interventions that target importations of resistance from hospitals or the community (for example, screening on admission to the LTCF) or antibiotic stewardship. These considerations are reflective of the current model parameterisation and of the structure and assumptions made. The main driver of the prevalence of resistance for other organism-antibiotic combinations such as *E. coli* resistant to nitrofurantoin may be different. A better understanding and quantification of the endogenous and exogenous acquisition of resistance; as well as antibiotic prescription data specific to the LTCF setting are needed to parameterise more informative models of AMR bacteria in the LTCF in the future.

Chapter 8 Discussion

Summary of findings

The objective of this thesis was to improve the current understanding of the epidemiology of antibiotic resistant Gram-negative bacteria in LTCFs. The focus was particularly set on bacteria causing UTIs.

Prior to this thesis, the burden of AMR in Gram-negative bacteria in LTCFs in England was unknown. This is an important gap in the literature due to the public health importance of these organisms.[19,28–31] It is also essential information to guide interventions aiming to tackle infections caused by AMR Gram-negative bacteria in LTCFs, such as antibiotic stewardship, or changes in the primary care prescribing guidelines. In addition, by February 2016, no mathematical models had simulated the transmission of Gram-negative bacteria in LTCFs, and only three had done so by the time of submission of this thesis. The latter simulated the transmission of carbapenem-resistant *Enterobacteriaceae* and *E. coli* ST131. No mathematical models to date have studied the transmission of *E. coli* resistant to more commonly prescribed antibiotics, such as trimethoprim. Mathematical models may provide helpful insights into the dynamics of colonisation and infection by these bacteria, and the effectiveness of potential interventions against them in LTCFs. Another gap in the literature was that the seasonality of UTIs in England had not been studied rigorously. These infections are a frequent cause of BSIs and antibiotic treatment, and an improved understanding of their dynamics may aid their prevention.

The systematic review presented in Chapter 2 highlighted the paucity of mathematical models published in the literature simulating the transmission of infectious diseases (27 papers). In February 2016, when the original literature search was conducted, no studies had modelled the transmission of Gram-negative bacteria in LTCFs. Since this review, however, three papers have described the transmission of Gram-negative bacteria: two of carbapenem-resistant *Enterobacteriaceae*[132,133] and one of *E. coli* ST131[134]. These studies begin to address the gap in the type of organisms modelled in this setting;

however, carbapenem-resistant *Enterobacteriaceae* are not currently a common cause of infections in LTCFs. In Chapter 5, the prevalence of resistance in urinary tract bacteria to carbapenems in the over 70s was found to be low in both *Klebsiella* and *E. coli* (0.2% and 0.02%, respectively). *E. coli* ST131 are highly virulent bacteria that have been associated with resistance to 3GCs, fluoroquinolones and aminoglycosides. [269–272] They are a common cause of UTIs and BSIs in England. Only two studies modelled the effect of antibiotic treatment on resistance in the LTCF. One study investigated the effect of reducing the exposure to fluoroquinolones and cephalosporins in the population colonised by *E. coli* ST131 from 5% to 0%[134]. A further study assessed the impact of antibiotic use in the previous 3 months on the epidemic potential of MRSA USA-300 and MRSA non-USA-300.[138] Antibiotic treatment increases the risk of colonisation and subsequent infection by resistant bacteria, and therefore, is an important factor to capture when modelling the transmission of AMR bacteria.[28,273]

In Chapter 3, the models of interventions against AMR bacteria in LTCFs were critically evaluated. At the time of review, these were three models of MRSA transmission that were not considered robust enough to test policy. A checklist was developed for epidemiologists and policy makers to distinguish good quality models of AMR in LTCFs as this field begins to expand.

Chapter 4 described the West Midlands AmSurv dataset, an AMR surveillance data comprising the antibiotic susceptibility tests carried out in the West Midlands on routinely collected microbiological specimens from individuals aged 70 or older sent by both GPs and hospitals. This dataset was linked to the CQC register of LTCFs in England to determine which samples were taken from individuals residing in LTCFs. This linked dataset was used to inform the prevalence of resistance in individuals entering the LTCF from hospital and the community and estimate the transmission parameters in the mathematical model described in Chapter 7.

Chapter 5 highlighted the burden of AMR in LTCFs, showing that residents of LTCFs had more than four times the rate of *E. coli* and *Klebsiella* UTI caused by

antibiotic-resistant bacteria compared to those living in the community. The odds of resistance of *E. coli* and *Klebsiella* to trimethoprim, nitrofurantoin, ciprofloxacin and 3GCs were significantly higher in LTCF samples than non-LTCF samples, after adjusting for age, sex, sender (GP vs. hospital) and the year of the study. In addition, 39% of UTIs caused by *E. coli* and 27% of UTIs caused by *Klebsiella* (60% and 41%, respectively, in LTCFs) were found to be resistant to trimethoprim, the most prescribed antibiotic for UTI.[35]

In Chapter 6, the seasonality of consultations for uncomplicated UTIs was explored, as evidence from the literature on this subject was conflicting and had not been rigorously assessed in the UK. A September to November peak in UTI consultation incidence was observed for ages 14-69. This seasonality progressively faded in older age groups and no seasonality was found in individuals aged 85 and over, in whom UTIs were most common.

Finally, in Chapter 7, a stochastic compartmental mathematical model was developed to simulate the transmission of trimethoprim resistant *E. coli* in LTCFs. In a LTCF amongst those in the highest quartile of incidence of urinary *E. coli* resistant to trimethoprim reported to AmSurv, there was a net transfer of individuals colonised with *E. coli* resistant to trimethoprim towards the hospital. Transmission appeared to be the most important driver of the prevalence of resistant colonisation in this LTCF.

Implications for clinical practice and public health policy

The implications of this work for clinical practice are the following:

Firstly, this work contributes towards improving our understanding of the dynamics of UTI (Chapter 6). Due to increases in temperature during the summer, which can make individuals prone to dehydration, UTIs could be expected to peak during this time. These changes could be particularly pronounced in the elderly population, as aging is a risk factor for water homeostasis impairments.[274] Older people are also more prone to dehydration due to inadequate water intake caused by impairments in the mechanisms controlling thirst, and this risk is potentiated in patients with dementia. [275,276]

However, GP consultations for UTI in older people in the UK were not found to be seasonal. This contrasts with the autumnal peak observed for individuals aged 14 to 69. Seasonal differences could be less important in older people due to mobility issues, which frequently confine them to indoor environments. Older people could then be equally prone to dehydration throughout the year. Other risk factors associated with UTI in older people are high postvoid residual urine and urinary retention, catheter use, urinary incontinence, as well as co-morbidities such as stroke and dementia, which may cause symptoms such as bladder and bowel incontinence.[47] As UTIs in older people are common year round, UTI prevention in this population should warrant attention throughout the year.

The autumnal peak in UTI consultation incidence in younger age groups could also be helpful in interpreting the results of interventions and surveillance reports. For example, if an intervention study were to show a decrease in UTI incidence in spring, this could be due to the effectiveness of a trialled intervention against UTIs, the seasonal pattern in UTIs, which yearly decrease during this period, or a combination of both, and their effect should be disentangled in order to correctly interpret the intervention effectiveness. Conversely, an increase in the incidence of UTI or antibiotic prescription during the autumn should be interpreted in the context of the yearly UTI peak observed during this time.

Secondly, the burden of AMR in urinary tract bacteria in English LTCFs was investigated (Chapter 5). UTIs caused by AMR *E. coli* and *Klebsiella* were shown to be more common in this population than in older people residing in their own homes, even after adjusting for confounders. The very high levels of AMR bacteria in LTCF residents compared to their community counterparts and even to hospital patients highlight that LTCFs should be a focus of antibiotic stewardship and infection prevention and control interventions aiming to prevent the spread of AMR bacteria. In order to target these interventions appropriately, there is a need for a better understanding of the causes of these high levels of AMR in LTCFs. Transmission of resistant organisms, antibiotic prescribing and high transfer rates between LTCFs and hospitals are key drivers of AMR in

LTCFs[62]; however, their relative importance is unknown for many organism-antibiotic combinations.

The high burden of AMR in English LTCFs also suggests that surveillance of AMR and antimicrobial prescribing in these facilities is warranted. The routine linkage of LTCF and susceptibility data could help LTCF staff become aware of the prevalence of AMR in their LTCF. If, additionally, prescribing data could be linked to these data, this would give LTCF staff a complete picture of the problem of AMR and prescribing in their LTCF, which has been identified as a key barrier to successful antimicrobial stewardship interventions in LTCFs.[277,278] Currently, information governance issues make the linkage of susceptibility and prescribing data challenging. However, the first pilot study exploring the linkage of the NHS Business Services Authority electronic records for antibiotic dispensing to Public Health England laboratory surveillance antibiotic susceptibility data over three months is currently under way, which suggests progress in this area.[279] This work should be a priority for AMR research in England. In LTCFs this linked data could also help infection prevention and control personnel identify the organism-antibiotic combinations of particular concern in order to target interventions to their control appropriately. In addition, at a CCG, regional, and national level, this information may help increase the awareness of the problem of AMR in LTCFs, which may facilitate future funding of interventions. It could also inform guidelines on antibiotic prescribing practice specifically for this setting. Finally, this information could help hospitals screen patients for organism-antibiotic combinations of particular concern in LTCFs from which they frequently receive admissions. Patients screening positive could be isolated and contact precautions for these individuals could be implemented.

Findings from this thesis also support the recent switch in the national primary care treatment guidelines for UTI from recommending trimethoprim to nitrofurantoin, as trimethoprim was shown to be ineffective to treat a large proportion of the UTIs in LTCF residents due to the high prevalence of resistance. Trimethoprim resistance in bacteria causing UTIs can result in treatment failure, hospitalisation, and the subsequent use of antibiotics such as

ciprofloxacin or 3GCs that should be reserved for the treatment of more serious infections. Ciprofloxacin usage, in turn, selects for ciprofloxacin resistance, which is often carried alongside resistance to beta-lactams, notably methicillin-resistance in *Staphylococci*.[211–214] Fluoroquinolone usage (mainly ciprofloxacin in England) has also been linked to the incidence to *C. difficile* infections.[215]

Antibiotic-resistant Gram-negative bacteria are currently organisms of high public health importance[19,28–31] and interventions to prevent their spread are being trialled in hospitals.[142–145] As highlighted in Chapter 5, LTCFs are also an important reservoir of antibiotic-resistant Gram-negative bacteria. In LTCFs, most studies have focused on the prevention of infections and on antimicrobial stewardship[173,280–283]. The systematic review of the literature (Chapter 2) showed that an increasing number of studies modelling the transmission of infectious diseases in LTCFs are being published. Therefore, the conclusions of mathematical models that simulate the transmission of Gram-negative bacteria in LTCFs could be important for policy making. Modelling the transmission of AMR in LTCFs is different to in hospitals, as LTCFs vary greatly in their characteristics such as their size, the services they provide to residents (e.g. nursing care and dementia care), the staff to patient ratio, and the acuity of patients. LTCFs also have strong links with other facilities such as hospitals and they are generally small institutions (mean=34.5 beds, median=31 beds, see Chapter 4). These models are also difficult to parameterise due to the paucity of data available. To this aim, a checklist was developed to guide policy makers in assessing the quality of such models.

The output from the mathematical model developed to simulate the transmission of *E. coli* resistant to trimethoprim in the LTCF (in Chapter 7) suggested that in LTCFs with high prevalence, there was a net output of individuals colonised with *E. coli* resistant to trimethoprim from the LTCF to hospital. The transfers between LTCFs and hospitals were frequent. These findings suggest that LTCFs with a high prevalence of resistant colonisation could contribute towards the prevalence of resistance in hospitals. As mentioned above, better surveillance in LTCFs could permit hospitals to implement screening strategies targeting individuals being transferred from

particular LTCFs with high prevalence of resistance. In addition, enhanced support for LTCF residents may prevent avoidable hospital admissions. An intervention designed by the Health Foundation in partnership with NHS England, as part of the NHS Five year forward view New Care Models programme in the Principia vanguard site saw a 28% reduction in potentially avoidable admissions to hospital.[284] This intervention included the alignment of LTCFs with general practices and the encouragement of residents to change to these general practices through advocacy; rapid review and comprehensive geriatric assessments upon residents' admission to the LTCF; weekly or fortnightly visits by named GPs; increased detection of dementia; improvement of nursing support through peer-to-peer support, training in infection prevention and control, and involvement in GP resident review rounds; as well as a programme to engage care home managers. [284]

Finally, using currently available parameter sources, the transmission of *E. coli* resistant to trimethoprim was shown to have a greater impact on the prevalence of *E. coli* resistant to trimethoprim in the LTCF than trimethoprim treatment, at least in LTCFs with a high incidence of trimethoprim-resistant urinary *E. coli* submitted to AmSurv. This suggests that reducing transmission may be key to diminishing the prevalence of carriage of trimethoprim-resistant *E. coli* in LTCF. In addition, reducing trimethoprim prescription might not greatly reduce the prevalence of resistance, although the evidence from the literature on this subject is scarce and conflicting.[208,216] Transmission events could be reduced by limiting the opportunities for transmission. In practice, limiting the opportunities for transmission in LTCFs may be challenging, as these are residents homes. High standards of environmental cleaning, patient hygiene and care, as well as hand hygiene interventions may be viable options. However, evidence on their effectiveness from the literature is limited. Multimodal interventions and national campaigns have been shown to be able to improve hand hygiene in LTCFs effectively.[285–289] However, these interventions carried out in Norway, USA, and China depend greatly on behavioural and cultural elements and may not be effective in LTCFs in England. Transmission of *E. coli* resistant to trimethoprim in the LTCF could also be reduced by decreasing the number of individuals colonised with *E. coli*

resistant to trimethoprim already present in the LTCF. This would involve measures such as intestinal decolonisation with colistin.[290] However, this may cause more harm than good as colistin is a “last-resort” antibiotic treatment and increasing its use might contribute to the spread and development of colistin resistance. Faecal microbiota transplantation that have been effective to treat *Clostridium difficile* infection[291,292] are being trialled and could be effective for the treatment of persistent colonisation with resistant Gram-negative bacteria. However, evidence for this is yet anecdotal.[293,294] Finally, the transmission of *E. coli* resistant to trimethoprim in the LTCF could also be decreased by reducing the susceptibility of individuals colonised with *E. coli* susceptible to trimethoprim to dominance by a resistant strain. However, no current therapies are available that decrease the susceptibility to resistant colonisation. It is worth highlighting that another way to counter the prevalence of *E. coli* resistant to trimethoprim in the LTCF is to prevent UTIs in the first place, which is discussed in the future work section below. It is also important to note that transmission might not be the main driver of the prevalence of resistance for other organism-antibiotic combinations such as *E. coli* resistant to nitrofurantoin.

Strengths

The first strength of this thesis was the West Midlands AmSurv dataset for those aged 70 or older, which was linked to CQC data. The AmSurv surveillance system captures the susceptibility results from all routine microbiology samples sent by hospitals and GPs to reporting laboratories for testing. The West Midlands was the first region in England to have all laboratories reporting to AmSurv. Therefore, this is the most complete source of AMR data within a defined population. This data was linked for the first time to the CQC registry of LTCFs. This enabled the formal comparison of AMR in LTCF residents to that in older people living in the community combining hospital and GP surveillance data (Chapter 5). Other studies were too small to yield statistically robust conclusions for several resistances, did not include GP or hospital samples, or did not carry out a formal statistical comparison. [75,76,78,295–297] This was also the first large scale study to quantify the burden of

AMR in English LTCFs. In England, resistance levels and the LTCFs themselves could be different to LTCFs in other countries.

Another key strength of this work was the eight year UTI consultation, trimethoprim prescription and nitrofurantoin prescription data extracted from THIN. THIN is a validated database of primary care consultation data covering over 3.7 million active patients which are demographically representative of the UK[235–237]. All three sources of data (UTI consultations, trimethoprim prescriptions and nitrofurantoin prescriptions) were used to study the trend and seasonality of UTI consultation, which had not formally been assessed to date in the UK (Chapter 6). The confirmation of our findings through these three sources of data strengthened the analysis. This analysis included fitting a negative binomial regression model to the data in which seasonality was modelled as cos(x)+sin(x) term. The correlations between the residuals of the model and the lagged values of the residuals for lags 1 to 12 months were also explored. This approach can be used to model the seasonality of UTIs or other infections in other countries.

Finally, this was the first study to model the transmission of trimethoprim resistant *E. coli* in LTCFs (Chapter 7). The model developed included trimethoprim treatment and the transfer of residents to and from hospital, as well as admissions from the community. Most parameters were informed by data from the same population (individuals aged 70 or older in the West Midlands) and over the same period (April 2010 to March 2014). When estimates were taken from the literature, these were adjusted to reflect the distribution of nursing LTCFs in the West Midlands. The transmission parameters were estimated through formal model fitting to incidence data from AmSurv by maximum likelihood estimation. Sensitivity analyses were carried out to determine the robustness of model outputs. This model provides an initial framework that may be expanded upon to examine the role of different resistances in the LTCF.

Limitations

One limitation of this thesis is the lack of antibiotic prescription data in the LTCF setting. Although antibiotic prescription data for the community overall is available from databases such as THIN and CPRD, this has not yet been linked to CQC LTCF data.

In order to parameterise the treatment rate in the mathematical model (Chapter 7), antibiotic prescription data from THIN was adjusted using a study that found that antibiotic prescribing for UTIs was 2.9 times higher in LTCFs than in the community.[69] However, this approach did not address the fact that different LTCFs will have different treatment rates. There could be a correlation between the incidence of urinary *E. coli* resistant to trimethoprim reported to AmSurv from a LTCF and the rate of trimethoprim prescription in the same facility. Antibiotic treatment could also help explain the higher levels of AMR observed in LTCFs in the West Midlands AmSurv data, and could have been included as an explanatory variable in the logistic regression (Chapter 5). This would have enabled the study of the effect of prescription on the risk of resistance. The effect of co-selection of resistance from different antibiotics could have also been explored. These findings, in turn, would have been beneficial to inform the mathematical model (Chapter 7).

Other important limitations of this work are those related to consultation and sampling. Prescription and UTI consultation data captured by THIN are limited by biases surrounding the frequency of consultation. The data also only include electronic health records from GP practices. Therefore, these data are only representative of treatment and consultation for uncomplicated UTIs. Consequently, the patterns in seasonality observed for UTI consultations (Chapter 6) cannot be extrapolated to all UTIs. AmSurv data includes both GP and hospital data but is limited by biases surrounding both consultation and sampling. Two conditions are required for a sample to be sent to a laboratory for testing, (1) a consultation (2) a urine sample is sent for testing. Sampling may be biased towards those failing to respond to treatment, which could increase the apparent risk of resistance. This is a limitation that applies both to the analysis of the burden of AMR in LTCFs (Chapter 5), and to the modelling

study (Chapter 7), in which the prevalence of resistant carriage in hospital and in the community were parameterised using these estimates. In addition, due to the unavailability of incidence data of colonisation by *E. coli* resistant to trimethoprim in LTCFs, the incidence of colonisation with *E. coli* resistant to trimethoprim in the model was fit to the incidence of urinary *E. coli* samples resistant to trimethoprim from a LTCF in the AmSurv dataset. To this aim, parameter rho was created, which was the 'case development and ascertainment proportion'. This parameter aimed to capture both the proportion of individuals colonised with *E. coli* resistant to trimethoprim who develop a UTI and the proportion of these who consult a physician and have a urinary sample sent for susceptibility testing. This was a crude method that did not capture the dynamics of consultation and sampling (as well as UTI development), which are likely to be complex and interact with trimethoprim treatment.

In addition, the difference in acquisition of dominant colonisation by *E. coli* resistant to trimethoprim under trimethoprim treatment and under no treatment is poorly understood. In the mathematical model developed (Chapter 7), this is assumed to occur through the transmission of trimethoprim resistance from individuals colonised with *E. coli* resistant to trimethoprim in the LTCF. As such, it depends on the number of these individuals present in the population and the number of individuals colonised with *E. coli* susceptible to trimethoprim ($\frac{\beta * Us * Ur}{N}$). Under trimethoprim treatment, it is assumed that (1) the colonisation with *E. coli* resistant to trimethoprim cannot be lost and (2) the rate of transmission β is greater than in the untreated scenario by a factor of tr. tr was adjusted so that the prevalence of resistance in treated individuals was approximately that reported in the literature.[257] However, data is needed to inform this parameter. In addition, part of the increase in transmission captured by tr during treatment is likely driven by the selection of resistance in an individual. This endogenous acquisition of dominant colonisation by *E. coli* resistant to trimethoprim may not be dependent on the number of individuals colonised with *E. coli* resistant to trimethoprim in the LTCF and the number of individuals colonised with *E. coli* susceptible to trimethoprim but may be driven by other factors such as fitness cost and selection pressure.

Finally, the mathematical model developed simplified many processes, mainly due to the lack of available data to inform them. For example, it assumed the dominance of a single strain in a colonised individual. However, competition between strains is known to be an important element in driving the resistance patterns observed in the population.[298] The effect of other antibiotic treatment such as ampicillin/amoxicillin on trimethoprim resistance was also not included in the model, although it has been shown to be an important predictor of geographical variation in trimethoprim resistance in urinary samples[263] and ampicillin and trimethoprim resistance genes are often linked on the same mobile genetic elements[264–266]. The model fitting process by maximum likelihood estimation could also be improved, using, for example, the particle Markov-Chain Monte Carlo method, which is implemented in pomp and takes a Bayesian approach to model fitting.

Further work

Further work is required to validate the checklist developed to assess the quality of mathematical models simulating transmission in the LTCF setting.

Prevention of UTIs could help avoid antibiotic treatment in the first place, which would help prevent antibiotic resistance. In older people residing in LTCFs, where these infections are most common, it is known that catheter use, co-morbidities such as stroke and dementia associated with bowel and bladder incontinence, bladder incontinence and impaired self-care are significant risk factors for UTI.[47] Effective interventions targeting good quality of care, involving appropriate hygiene, fluid intake and catheter care are therefore required and important. Various vaccines for UTI are currently being developed that target virulence determinants essential for attachment and disease.[299] A vaccine targeting FimH, which mediates the adherence to the gut epithelium, is currently in Phase I clinical trials and has been shown not to alter the gut microbiota.[299–301] Although currently far from licensure, a vaccine could provide an excellent option for reducing UTIs without impacting the ecosystem of the gut and, therefore, reduce antibiotic prescribing and antibiotic resistance.[302] Cranberry extracts and probiotics also show potential in the prevention of UTI, although they are not yet deemed effective.[303–305] In addition, further work is needed to

understand the causes of the autumn seasonality of UTI observed for ages 14 to 69 so as to enable more targeted prevention programmes.

Several expansions of the mathematical model would enable more robust conclusions to be drawn. As mentioned above, antibiotic prescription data specific to LTCFs would improve the parameterisation of the treatment rate in the model. Co-selection could also be simulated. In addition, LTCFs vary substantially in their size and the services they provide. Therefore, antibiotic treatment and the flow of patients in and out of the LTCF may also differ between facilities, and, therefore, different types of LTCFs may warrant different infection control recommendations. Antibiotic treatment data specific to each LTCF and detailed information on the flow of patients in and out of the LTCF would enable the characterisation of different categories of LTCFs. The mathematical model could then be parameterised for these distinct LTCF types. Another approach would be to develop an individual-based network model of LTCF and hospitals in a local patch area. In addition, whole genome sequencing could help quantify the acquisition of dominant resistance by endogenous and exogenous mechanisms and, therefore, help parameterise transmission in the LTCF setting. The model developed could then be fit to colonisation incidence data.

Another simple expansion of the model would be to parameterise it to reflect the transmission of *E. coli* resistant to nitrofurantoin. Although urinary *E. coli* resistance to nitrofurantoin is still low (7% in LTCFs for 2010-2015, see Chapter 5), the change in guidelines recommending nitrofurantoin treatment instead of trimethoprim for UTI may change this.[306] The dynamics of resistance to trimethoprim and nitrofurantoin could then be compared and the conditions for a high prevalence of *E. coli* resistant to nitrofurantoin in the LTCF could then be predicted.

Another area requiring further study is the effect of antibiotic stewardship interventions on trimethoprim resistance. The reversal of antibiotic resistance is not a straightforward process.[307,308] The outcome of antibiotic stewardship interventions is most frequently antibiotic prescription and the final effect on

resistance is not often studied. Further work is needed to understand if resistance to trimethoprim can be reversed by antibiotic stewardship, as evidence from the literature is conflicting.[208,216] The outcome of such studies may depend on whether other antibiotics with which trimethoprim has a strong co-selection are being prescribed during the intervention[309] and may also need long time frames to see an effect.

Finally, more research is needed to understand how *E. coli* strains resistant and sensitive to trimethoprim interact; how dominance of *E. coli* resistant to trimethoprim is achieved and, ultimately, how this is influenced by the interaction with different bacterial species. Bacteria do not grow in isolation and, therefore, other bacteria surrounding it may play an important role in the acquisition or suppression of resistance.

Conclusions

This thesis served to (1) review the literature of dynamic transmission modelling of infectious diseases in LTCFs; (2) establish a checklist for policy makers to review the quality of mathematical models of interventions against AMR bacteria in LTCFs; (3) link antibiotic susceptibility data covering a large population to the LTCF registry and highlight the burden of AMR in LTCFs; (4) rigorously address the seasonality of consultations for uncomplicated UTIs; and (5) develop the first mathematical model to quantify the transmission of *E. coli* resistant to trimethoprim in the LTCF setting. The lack of antibiotic prescription data for LTCFs is an important limitation of this work. The availability of this data, together with an improved knowledge about the acquisition of dominant colonisation by AMR bacteria, could enable a better understanding of the drivers of AMR in the LTCF setting.

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Appendix

Appendix Chapter 2

Search terms used in the literature review by database:

Medline (only)

model$.ti,ab.

model?ing.ti,ab.

framework$.ti,ab.

long-term care.ti,ab.

long term care.ti,ab.

residential facilit$.ti,ab

residential home$.ti,ab.

residential care.ti,ab.

nursing home$.ti,ab.

old age home$.ti,ab.

old-age home$.ti,ab.

mathematic$.ti,ab.

compartment$.ti,ab.

stochastic.ti,ab.

deterministic.ti,ab

transmiss$.ti,ab.

epidemi$.ti,ab.

individual-based.ti,ab.

population-based.ti,ab.

dynamic.ti,ab.

comput$.ti,ab.

reproduction number.ti,ab.

simulation.ti,ab.

markov chain$.ti,ab.

Monte Carlo.ti,ab.

Bayes.ti,ab.

patient flow.ti,ab.

readmission.ti,ab.

EMBASE

model$.ti,ab.

model?ing.ti,ab.

framework$.ti,ab.

long-term care.ti,ab.

long term care.ti,ab.

residential facilit$.ti,ab

residential home$.ti,ab.

residential care.ti,ab.

nursing home$.ti,ab.

old age home$.ti,ab.

old-age home$.ti,ab.

mathematic$.ti,ab.

compartment$.ti,ab.

stochastic.ti,ab.

deterministic.ti,ab

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individual-based.ti,ab.

population-based.ti,ab.

dynamic.ti,ab.

comput$.ti,ab.

reproduction number.ti,ab.

simulation.ti,ab.

markov chain$.ti,ab.

Monte Carlo.ti,ab.

Bayes.ti,ab.

patient flow.ti,ab.

readmission.ti,ab.

SCOPUS

Restricted by subject to immunology and microbiology, computer science and mathematics

Restricted by type to article or review

Title, abstract, keywords:

model (plural did not make a difference)

modelling (one or two “l” in spelling did not make a difference)

framework

long-term care

long term care

residential facility

residential home

residential care

nursing home

old age home

old age homes

old-age home

mathematic

mathematical

compartment

stochastic

deterministic

transmission

transmissible

epidemiology

epidemiological

individual-based

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Global Health

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patient flow.ti,ab.

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CINHAL

Searches in abstract:

Model

Models

Modelling

modeling

framework

frameworks

long-term care

long term care

residential facility

residential facilities

residential home

residential homes

residential care

nursing home

nursing homes

old age home

old age homes

old-age home

old-age homes

mathematic

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patient flow

readmission

readmissions

Appendix Chapter 3

Dates, settings and methodologies

These three models were built within the last five years (2011, 2012 and 2013). Lee et al.[116] based their estimates on current sources, using data published from 2007-2011. Length of stay was the only parameter based on data published before 2010. Barnes et al.[127], however, based their parameter estimates on literature from 2004 to 2010 and Chamchod and Ruan[114] from 1999 to 2010.

Chamchod and Ruan's model [114] was set within a LTCF; however, the nationality of the setting was not stated. Barnes et al.[127] modelled patient movement between hospitals and LTCFs in the USA. Lee et al [116] additionally included the non-LTFC community into their model. They made a distinction between those discharged for a short period of time (less than 30 days) and those discharged into the community for longer (patients who were not readmitted). Their model represented Orange County, California (USA).

Barnes et al.[127] built a compartmental deterministic model, Lee et al.[116] an individual-based stochastic model and Camchod and Ruan[114] built two compartmental models: one stochastic and one deterministic. None of these models were formally fit to data or validated. Barnes et al.[127] did not carry out a sensitivity analysis. Chamchod and Ruan[114] and Lee et al.[116] carried out univariate sensitivity analyses, varying key parameters one at a time and noting the effect of these changes on model outcomes.

Model structure

a. Patient flow

The three models varied in the complexity of their institutional structures: Chamchod and Ruan[114] modelled transmission of MRSA within a LTCF only with patients mixing homogenously within it. Barnes et al.[127] and Lee et al.[116] modelled patient flow between two types of facility: LTCFs and hospitals (see Figure 3).

Barnes et al.[127] modelled each LFCF and hospital as agents in a network of facilities (Figure 3a). Links between each pair of facilities in the network were assigned a specific weight, which, together with the facility size, determined the probability of transfer between the facilities. Various network configurations with different weights associated to the links were compared. In their model, patients at each facility type were admitted and discharged at the same rate (μ). Barnes et al.[127] did not define any finer grain compartments within each LTCF and hospital, therefore, patients were assumed to mix homogeneously within facilities.

Lee et al. [116] also included movement between the facilities and the community (Figure 3b). The authors modelled bidirectional patient flow between the 100 inpatient facilities present in Orange County (71 LTCFs and 29 hospitals) as well as discharge into the community (permanent or temporary, where patients were readmitted within a year of discharge). Their IBM used a 2007 California mandatory hospital dataset where patients were tracked between facilities to inform hospitalisation and rehospitalisation and data from 2006-2008 surveys to inform transfers between hospitals and LTCFs. Patient flow was also determined by the number of licensed beds, the average daily census and the length of stay in LTCFs obtained from a national long-term care dataset. Length of stay distributions for ICU and non-ICU patients in each hospital were used to inform transfers from hospitals. MRSA carriers had longer lengths of stay. LTCF residents with a length of stay of two or more weeks were assigned a daily probability of being transferred to a hospital for a short stay during which their LTCF bed was kept free. The authors assumed each hospital comprised 20-bed general hospital wards, 12-bed intensive care units and 10-bed long-term acute care facilities. Each LTCF contained one ‘ward’ within which patients mixed homogenously.

b. MRSA transmission

A schematic of the transmission structures of the models can be found in Figure 4. Each model considered two basic individual states; colonised with MRSA or uncolonised with MRSA. Infection was not considered in any model.

In Barnes et al.'s model[127] (see Figure 4a), individuals could transition between three states: U (uncolonised), P (persistently colonised) and T (transiently colonised). U individuals could become P or T and vice-versa through transmission and recovery, but they could not transition between P and T states of colonisation. Transition from P to U was slower than from T to U. The proportion of transferred patients in each disease state was established according to the proportions of U, P and T in the facility they were transferred from.

Chamchod and Ruan[114] modelled MRSA transmission between residents, between healthcare workers and between healthcare workers and residents as distinct processes (see Figure 4b). The disease states in residents were U (uncolonised) and C (colonised). The disease states in healthcare workers were H (uncontaminated) and Hc (contaminated). Patients and residents could transition between the uncolonised (U) and colonised (C) states through transmission and recovery. No distinction was made between the P and T colonisation states. Colonised and uncolonised residents had different probabilities of admission (λ and $1-\lambda$, respectively) and discharge (γ_c and γ_u, respectively). Transmission rates were different between residents (β_r), from healthcare workers to residents (β_h) and from residents to healthcare workers (α_h). Colonisation of an uncolonised resident depended on both β_r and β_h whilst contamination of an uncontaminated healthcare worker depended on α_h. Decolonisation rates in residents (ω) differed from decontamination rates in healthcare workers (μ).

Lee et al.'s IBM[116] distinguished two patient states: S (susceptible) and I (infectious) (see Figure 4c) which were analogous to uncolonised and colonised. As the authors were analysing the impact of contact precautions on transmission, they differentiated between residents in a scenario where contact precautions were in use (S_p and I_p) and residents in a scenario where they were not (S_φ and I_φ). The number of new cases of MRSA per unit per day was calculated using the equation described below:

$$\beta S_\varphi I_\varphi+\beta(1-\theta)S_p I_\varphi+\beta(1-\theta)S_\varphi I_p+\beta(1-\theta)^2 S_p I_p$$

where p= precautions, φ= no precautions, θ=efficacy of contact precautions.

Parameters used

The LTCF sizes chosen varied greatly between the three models, ranging from 100 [127] to 2000 beds [114]. The research groups also chose different ways of quantifying transmission. Barnes et al.[127] and Chamchod and Ruan[114] reported transmission rates as the effective contact (resulting in transmission) rate averaged per day whilst Lee et al.[116] quantified the rate of transmission per person per day, explaining why their figures are not of the same magnitude. In addition, Chamchod and Ruan[114] broke down their overall transmission rate into resident-resident, healthcare worker-resident and resident-healthcare worker transmission rates. Resident-resident transmission was assumed to be eight times lower than the other transmission types. Their overall transmission rate was a combination of these three rates. Barnes et al.[127] used three different rates that were in a similar range than those provided by Chamchod and Ruan[114]. Barnes et al.[127] and Lee et al.[116] both used transmission rates for hospitals that were much higher than those for LTCFs. Barnes et al.[127] and Chamchod and Ruan[114] assumed the same proportion of patients admitted colonised by MRSA (10%). Lee et al.[116], however, reported the prevalence of colonisation within the hospitals (6.1%) and LTCFs (26.1%) which was much higher than the overall prevalence of all patients that enter the facility from the general population. Lee et al.[116] did not report their assumed duration of colonisation. Camchod and Ruan[114] supposed a duration of colonisation similar to that of persistently colonised individuals in Barnes et al.'s model[127]. Barnes et al.[127] reported recovery rates for persistently and transiently colonised individuals of 0.02 and 0.2 respectively that equate to 5 and 50 days of colonisation. These estimates were decided by the authors. Chamchod and Ruan[114] chose a middle estimate from the average decolonisation time range published by Kajita et al. (2007)[310], which were themselves based on expert opinion. Neither of the duration of colonisation estimates were taken from literature based on data.

Interventions

Barnes et al. [127] assessed the impact of three screening and decolonisation interventions: decolonisation on admission (no screening); screening by conventional culture on admission and subsequent decolonisation of positive residents and screening by PCR on admission and subsequent decolonisation of positive residents. These interventions reduced the prevalence of MRSA by moving patients from a colonised state (for Barnes et al.[127], both P and T) to a susceptible state (uncolonised) where they cannot transmit disease after a duration of 10-13 days (depending on the type of screening carried out). Barnes et al.[127] found that all three interventions yielded the same approximate results because facility transfers were frequent, which meant screening at admission was also frequent. Decolonisation decreased equilibrium prevalence in LTCFs by 0.0287-0.1203 and in hospitals by 0.0029-0.0232 (depending on initial institution equilibrium MRSA prevalence). It was assumed that, on average, it would take two cycles of five-day treatments for patients to be successfully decolonised (10 days).

Chamchod and Ruan[114] considered the theoretical impact of reducing different importation and transmission parameters on MRSA prevalence. Chamchod and Ruan[114] reported that, increasing the recovery rate by more than 0.05 resulted in the elimination of MRSA under equilibrium.

Chamchod and Ruan[114] considered the impact of hand hygiene on MRSA prevalence. Hand hygiene measures that target residents aim to decrease the transmission of MRSA from C to U and H (β_r and α_h). Implementing improved hand hygiene decreases the probability of colonisation per contact of for residents (p_r) and the probability of contamination per contact for healthcare workers (q_h). The average number of contacts between residents (a) and the average number of required contacts from healthcare workers by residents (b) remains the same. Hand hygiene measures that target healthcare workers aim to alter the transmission of MRSA from Hc to U (β_h) by decreasing the probability of colonisation via contacts of healthcare workers (q_r) without altering the average number of required contacts from healthcare workers by residents (b). The authors found that when the average duration of colonisation was reduced below 250 days for residents or below 0.15 hours for healthcare

workers, the probability of invasion resulting from the introduction of a contaminated healthcare worker/ a contaminated resident was eliminated[114].

Chamchod and Ruan modelled the impact of increasing the staff to patient ratio to reduce the contact rate. Assuming that the average number of contacts a resident requires by a healthcare worker (b) is a constant and is distributed amongst the number of healthcare workers, reducing the resident to staff ratio (N_r/N_h) diminishes the frequency at which a particular healthcare worker contacts a resident (b/N_h). Lower N_r/N_h reduces the frequency of contacts between U and Hc and between C and H. When resident to staff ratio was reduced below 6.5, the probability of invasion resulting from the introduction of a contaminated healthcare worker/ a contaminated resident was eliminated[114].

Lee et al.[116] compared the effect of contact precautions in LTCFs for residents with clinically apparent MRSA infections and for all MRSA carriers. Both interventions reduced the probability of transmission. The first intervention replaced I_φ individuals in the population with I_p. The second intervention replaced individuals in S_φ with S_p in a similar fashion. In their model, contact precautions in residents with clinically apparent MRSA did not significantly decrease MRSA prevalence and the number of MRSA acquisitions averted in Orange County was minimal, even after five years and assuming 75% adherence. However, when contact precautions were taken in all MRSA carriers, a substantial number of MRSA acquisitions were adverted. Assuming 50% adherence, 171 acquisitions of MRSA were projected to be adverted within six months and 4,876 within five years. Even in situations where adherence was lower (25%), 81 acquisitions were to be adverted after six months and 2,442 after 5 years. With high adherence (75%), 7,291 acquisitions were to be adverted after five years[116].

Appendix Chapter 5

Table A- 1. Univariable logistic regression results- odds of resistance in bacteria from LTCF samples (vs. non-LTCF samples), residential LTCF samples (vs. non-LTCF samples), and nursing LTCFs samples (vs. non-LTCF samples) for all bacterium-antibiotic combinations. Confidence intervals are adjusted for clustering at the postcode level.

Organism	Antibiotic	N Samples	N NS Samples	OR LTCF	Adjusted 95% CI LTCF	OR Residential LTCF	Adjusted 95% CI Residential LTCF	OR Nursing LTCF	Adjusted 95% CI Nursing LTCF
E. coli	Amoxicillin/Ampicillin	125958	70128	2.4	2.24 - 2.58	2.21	2.03 - 2.4	2.75	2.43 - 3.11
	Ciprofloxacin	111053	16900	2.57	2.32 - 2.85	2.28	2 - 2.59	3.01	2.58 - 3.51
	Co-amoxiclav[+]	127910	26621	1.74	1.57 - 1.93	1.69	1.48 - 1.93	1.81	1.54 - 2.12
	First-generation cephalosporins	125254	10839	1.74	1.55 - 1.96	1.53	1.32 - 1.78	2.07	1.73 - 2.48
	Gentamicin	98512	6630	1.7	1.48 - 1.94	1.52	1.27 - 1.82	1.96	1.63 - 2.37
	Carbapenems[*]	50641	12	NA	NA	NA	NA	NA	NA
	Nitrofurantoin	157556	6277	1.86	1.64 - 2.11	1.68	1.43 - 1.99	2.12	1.78 - 2.53
	Piperacillin/ Tazobactam	35600	4756	1.93	1.68 - 2.22	1.79	1.5 - 2.13	2.21	1.77 - 2.77
	Second-generation cephalosporins	51307	9483	1.98	1.68 - 2.33	1.88	1.54 - 2.29	2.13	1.62 - 2.79
	Temocillin	43273	1549	1.31	0.93 - 1.85	1.37	0.9 - 2.1	1.21	0.69 - 2.11
	Third-generation cephalosporins[~]	134105	8507	1.86	1.63 - 2.14	1.73	1.45 - 2.06	2.07	1.69 - 2.55
	Trimethoprim	157818	61469	2.56	2.39 - 2.74	2.39	2.2 - 2.61	2.82	2.55 - 3.13
Klebsiella	Ciprofloxacin	13698	1087	1.36	1 - 1.85	1.21	0.79 - 1.87	1.56	1.03 - 2.37
	Co-amoxiclav[+]	14317	2181	1.53	1.22 - 1.91	1.36	1.01 - 1.82	1.75	1.26 - 2.43
	First-generation cephalosporins	14393	1824	1.33	1.04 - 1.71	1.15	0.82 - 1.62	1.56	1.09 - 2.23
	Gentamicin	12963	655	1.16	0.76 - 1.76	0.79	0.45 - 1.38	1.64	0.92 - 2.92

Organism	Antibiotic	N Samples	N NS Samples	OR LTCF	Adjusted 95% CI LTCF	OR Residential LTCF	Adjusted 95% CI Residential LTCF	OR Nursing LTCF	Adjusted 95% CI Nursing LTCF
	Carbapenems*	8364	13	1.33	0.17 - 10.55	2.28	0.29 - 17.84	0.01	0 - 0.02
	Nitrofurantoin	12125	4219	1.34	1.11 - 1.61	1.35	1.05 - 1.72	1.33	1.02 - 1.75
	Piperacillin/ Tazobactam	7513	1215	1.55	1.1 - 2.19	1.5	0.93 - 2.41	1.63	1 - 2.65
	Second-generation cephalosporins	7372	1218	1.29	0.91 - 1.83	1.37	0.85 - 2.19	1.19	0.73 - 1.95
	Temocillin	6302	85	0.63	0.15 - 2.62	1.13	0.29 - 4.43	0	0 - 0
	Third-generation cephalosporins~	11561	837	1.1	0.75 - 1.62	0.9	0.57 - 1.41	1.37	0.75 - 2.49
	Trimethoprim	17801	4737	2.01	1.7 - 2.38	1.94	1.52 - 2.46	2.11	1.7 - 2.62

Imipenem or Meropenem. Resistance to carbapenems was very low in both *Klebsiella* and *E. coli* which prevented any formal statistical analysis.

~ 3GC resistance was defined as resistance to ceftazidime, cefpodoxime, cefotaxime, or ceftriaxone.

+ Note that some laboratories used the systemic rather than UTI breakpoint guidelines for co-amoxiclav resulting in an increase in the percentage of resistant samples between mid-2011 and early 2012.

Table A- 2. Univariable logistic regression results- odds of resistance in bacteria from male samples (vs. females) for all bacterium-antibiotic combinations. Confidence intervals are adjusted for clustering at the postcode level.

Organism	Antibiotic	N Samples	N NS Samples	OR Male	Adjusted 95% CI Male
E. coli	Amoxicillin/Ampicillin	125958	70128	1.18	1.14 - 1.23
	Ciprofloxacin	111053	16900	1.62	1.52 - 1.73
	Co-amoxiclav[+]	127910	26621	1.33	1.27 - 1.39
	First-generation cephalosporins	125254	10839	1.47	1.37 - 1.58
	Gentamicin	98512	6630	1.55	1.42 - 1.7
	Carbapenems[*]	50641	12	NA	NA
	Nitrofurantoin	157556	6277	1.43	1.31 - 1.56
	Piperacillin/Tazobactam	35600	4756	1.46	1.33 - 1.61
	Second-generation cephalosporins	51307	9483	1.4	1.29 - 1.51
	Temocillin	43273	1549	1.39	1.2 - 1.61
	Third-generation cephalosporins[~]	134105	8507	1.47	1.35 - 1.6
	Trimethoprim	157818	61469	1.03	0.99 - 1.07
Klebsiella	Ciprofloxacin	13698	1087	1.38	1.14 - 1.66
	Co-amoxiclav[+]	14317	2181	1.24	1.1 - 1.41
	First-generation cephalosporins	14393	1824	1.4	1.23 - 1.61
	Gentamicin	12963	655	1.47	1.17 - 1.86
	Carbapenems[*]	8364	13	NA	NA
	Nitrofurantoin	12125	4219	0.87	0.79 - 0.96
	Piperacillin/Tazobactam	7513	1215	1.39	1.19 - 1.64
	Second-generation cephalosporins	7372	1218	1.41	1.18 - 1.67
	Temocillin	6302	85	1.72	1.03 - 2.86
	Third-generation cephalosporins[~]	11561	837	1.49	1.2 - 1.84
	Trimethoprim	17801	4737	0.94	0.85 - 1.03

[*] Imipenem or Meropenem. Resistance to carbapenems was very low in both *Klebsiella* and *E. coli* which prevented any formal statistical analysis.
[~] 3GC resistance was defined as resistance to ceftazidime, cefpodoxime, cefotaxime, or ceftriaxone.
[+] Note that some laboratories used systemic rather than UTI breakpoint guidelines for co-amoxiclav resulting in an increase in the % resistant samples between mid-2011 and early 2012.

Table A- 3. Univariable logistic regression results- odds of resistance in bacteria from samples from those aged 75 to 80 (vs. 70-74), 81-85 (vs. 70-74), and over 85 (vs.70-74) for all bacterium-antibiotic combinations. Confidence intervals are adjusted for clustering at the postcode level.

Organism	Antibiotic	N Samples	N NS Samples	OR 75-80	Adjusted 95% CI 75-80	OR 81-85	Adjusted 95% CI 81-85	OR >85	Adjusted 95% CI >85
E. coli	Amoxicillin/Ampicillin	125958	70128	1	0.96 - 1.04	1.09	1.04 - 1.14	1.35	1.29 - 1.42
	Ciprofloxacin	111053	16900	1.06	0.98 - 1.15	1.2	1.1 - 1.3	1.6	1.47 - 1.74
	Co-amoxiclav[+]	127910	26621	1.02	0.96 - 1.07	1.11	1.05 - 1.18	1.35	1.27 - 1.43
	First-generation cephalosporins	125254	10839	1.02	0.93 - 1.11	1.18	1.08 - 1.29	1.31	1.2 - 1.43
	Gentamicin	98512	6630	1.02	0.91 - 1.13	1.08	0.96 - 1.21	1.27	1.14 - 1.42
	Carbapenems[*]	50641	12	NA	NA	NA	NA	NA	NA
	Nitrofurantoin	157556	6277	1.07	0.95 - 1.21	1.29	1.14 - 1.45	1.49	1.33 - 1.67
	Piperacillin/Tazobactam	35600	4756	0.96	0.85 - 1.08	1.04	0.92 - 1.17	1.34	1.19 - 1.5
	Second-generation cephalosporins	51307	9483	1.06	0.96 - 1.16	1.29	1.17 - 1.43	1.51	1.36 - 1.67
	Temocillin	43273	1549	1.03	0.85 - 1.25	1.3	1.06 - 1.58	1.13	0.93 - 1.38
	Third-generation cephalosporins[~]	134105	8507	0.98	0.88 - 1.08	1.11	1 - 1.23	1.26	1.13 - 1.4
	Trimethoprim	157818	61469	1.03	0.98 - 1.07	1.17	1.12 - 1.22	1.51	1.45 - 1.58
Klebsiella	Ciprofloxacin	13698	1087	0.78	0.61 - 0.99	0.94	0.72 - 1.22	0.81	0.64 - 1.04
	Co-amoxiclav[+]	14317	2181	0.99	0.83 - 1.17	1.16	0.97 - 1.39	1.19	1 - 1.42
	First-generation cephalosporins	14393	1824	0.94	0.78 - 1.13	1.07	0.88 - 1.3	1.08	0.9 - 1.3
	Gentamicin	12963	655	0.92	0.65 - 1.29	1.31	0.92 - 1.87	1.11	0.8 - 1.55
	Carbapenems[*]	8364	13	NA	NA	NA	NA	NA	NA
	Nitrofurantoin	12125	4219	1.02	0.9 - 1.16	1.02	0.88 - 1.17	1.03	0.91 - 1.18
	Piperacillin/Tazobactam	7513	1215	0.86	0.68 - 1.09	1.02	0.8 - 1.3	1.06	0.84 - 1.33
	Second-generation	7372	1218	0.94	0.74 - 1.19	1.01	0.79 - 1.3	1.07	0.84 - 1.36

Organism	Antibiotic	N Samples	N NS Samples	OR 75-80	Adjusted 95% CI 75-80	OR 81-85	Adjusted 95% CI 81-85	OR >85	Adjusted 95% CI >85
	cephalosporins								
	Temocillin	6302	85	1.08	0.52 - 2.27	0.66	0.3 - 1.45	0.74	0.33 - 1.65
	Third-generation cephalosporins[~]	11561	837	0.91	0.69 - 1.22	1.09	0.8 - 1.5	0.96	0.72 - 1.28
	Trimethoprim	17801	4737	0.93	0.82 - 1.06	1.1	0.96 - 1.26	1.29	1.13 - 1.46

[*] Imipenem or Meropenem. Resistance to carbapenems was very low in both *Klebsiella* and *E. coli* which prevented any formal statistical analysis.
[~] 3GC resistance was defined as resistance to ceftazidime, cefpodoxime, cefotaxime, or ceftriaxone.
[+] Note that some laboratories used the systemic rather than UTI breakpoint guidelines for co-amoxiclav resulting in an increase in the percentage of resistant samples between mid-2011 and early 2012.

Table A- 4. Univariable logistic regression results- odds of resistance in bacteria from samples taken in hospital (vs. from GPs) for all bacterium-antibiotic combinations. Confidence intervals are adjusted for clustering at the postcode level.

Organism	Antibiotic	N Samples	N NS Samples	OR Hospital	Adjusted 95% CI Hospital
E. coli	Amoxicillin/Ampicillin	125958	70128	1.17	1.13 - 1.2
	Ciprofloxacin	111053	16900	1.12	1.07 - 1.18
	Co-amoxiclav[+]	127910	26621	1.36	1.31 - 1.41
	First-generation cephalosporins	125254	10839	1.34	1.27 - 1.41
	Gentamicin	98512	6630	1.43	1.35 - 1.53
	Carbapenems[*]	50641	12	NA	NA
	Nitrofurantoin	157556	6277	1.06	0.99 - 1.13
	Piperacillin/Tazobactam	35600	4756	1.32	1.23 - 1.43
	Second-generation cephalosporins	51307	9483	1.45	1.37 - 1.54
	Temocillin	43273	1549	1.41	1.24 - 1.59
	Third-generation cephalosporins[~]	134105	8507	1.37	1.29 - 1.45
	Trimethoprim	157818	61469	1.03	1.01 - 1.06
Klebsiella	Ciprofloxacin	13698	1087	1.45	1.24 - 1.68
	Co-amoxiclav[+]	14317	2181	1.53	1.38 - 1.7
	First-generation cephalosporins	14393	1824	1.55	1.39 - 1.74
	Gentamicin	12963	655	2.08	1.72 - 2.51
	Carbapenems[*]	8364	13	NA	NA
	Nitrofurantoin	12125	4219	0.85	0.78 - 0.93
	Piperacillin/Tazobactam	7513	1215	1.58	1.37 - 1.81
	Second-generation cephalosporins	7372	1218	1.54	1.33 - 1.79
	Temocillin	6302	85	1.64	1.02 - 2.65
	Third-generation cephalosporins[~]	11561	837	1.86	1.56 - 2.21
	Trimethoprim	17801	4737	1.01	0.93 - 1.09

[*] Imipenem or Meropenem. Resistance to carbapenems was very low in both *Klebsiella* and *E. coli* which prevented any formal statistical analysis.[~] 3GC resistance was defined as resistance to ceftazidime, cefpodoxime, cefotaxime, or ceftriaxone.[+] Note that some laboratories used the systemic rather than UTI breakpoint guidelines for co-amoxiclav resulting in an increase in the percentage of resistant samples between mid-2011 and early 2012.

Table A- 5. Univariable logistic regression results- odds of resistance in bacteria from samples from the second year of the study (vs. the first year), the third year of the study (vs. the first year), and the fourth year of the study (vs. the first year) for all bacterium-antibiotic combinations. Confidence intervals are adjusted for clustering at the postcode level.

Organism	Antibiotic	N Samples	N NS Samples	OR Y2	Adjusted 95% CI Y2	OR Y3	Adjusted 95% CI Y3	OR Y4	Adjusted 95% CI Y4
E. coli	Amoxicillin/Ampicillin	125958	70128	1.01	0.97 - 1.06	1.07	1.03 - 1.12	1.09	1.05 - 1.14
	Ciprofloxacin	111053	16900	0.96	0.91 - 1.03	0.93	0.87 - 0.99	0.9	0.85 - 0.97
	Co-amoxiclav[+]	127910	26621	0.9	0.86 - 0.95	0.71	0.67 - 0.74	0.71	0.67 - 0.75
	First-generation cephalosporins	125254	10839	0.89	0.82 - 0.96	0.9	0.83 - 0.97	0.96	0.89 - 1.04
	Gentamicin	98512	6630	0.93	0.84 - 1.02	0.98	0.88 - 1.08	1.02	0.92 - 1.12
	Carbapenems[*]	50641	12	NA	NA	NA	NA	NA	NA
	Nitrofurantoin	157556	6277	0.84	0.76 - 0.92	0.78	0.71 - 0.86	0.87	0.79 - 0.95
	Piperacillin/Tazobactam	35600	4756	0.66	0.56 - 0.77	0.88	0.8 - 0.97	0.9	0.82 - 1
	Second-generation cephalosporins	51307	9483	1.08	1 - 1.17	1.04	0.96 - 1.13	1.09	1 - 1.18
	Temocillin	43273	1549	2.29	1.79 - 2.92	4.95	3.94 - 6.22	4.15	3.28 - 5.24
	Third-generation cephalosporins[~]	134105	8507	1.01	0.92 - 1.1	1.04	0.95 - 1.14	1.1	1 - 1.2
	Trimethoprim	157818	61469	1.06	1.02 - 1.1	1.15	1.1 - 1.19	1.19	1.14 - 1.24
Klebsiella	Ciprofloxacin	13698	1087	0.95	0.73 - 1.24	1.18	0.91 - 1.54	1.46	1.14 - 1.87
	Co-amoxiclav[+]	14317	2181	1.11	0.94 - 1.33	1.04	0.87 - 1.24	1.31	1.11 - 1.55
	First-generation cephalosporins	14393	1824	1.06	0.87 - 1.3	1.17	0.96 - 1.43	1.25	1.03 - 1.52
	Gentamicin	12963	655	0.76	0.51 - 1.15	1.26	0.86 - 1.84	1.86	1.29 - 2.67
	Carbapenems[*]	8364	13	NA	NA	NA	NA	NA	NA
	Nitrofurantoin	12125	4219	0.89	0.79 - 1	0.56	0.5 - 0.63	0.61	0.55 - 0.69
	Piperacillin/Tazobactam	7513	1215	0.85	0.66 - 1.09	1.69	1.36 - 2.09	2.1	1.71 - 2.59
	Second-generation	7372	1218	0.95	0.75 - 1.2	1.17	0.93 - 1.46	1.07	0.86 - 1.34

Organism	Antibiotic	N Samples	N NS Samples	OR Y2	Adjusted 95% CI Y2	OR Y3	Adjusted 95% CI Y3	OR Y4	Adjusted 95% CI Y4
	cephalosporins								
	Temocillin	6302	85	2.28	0.68 - 7.59	2.62	0.81 - 8.5	3.03	0.95 - 9.71
	Third-generation cephalosporins~	11561	837	1.16	0.85 - 1.58	1.25	0.93 - 1.69	1.67	1.26 - 2.22
	Trimethoprim	17801	4737	1.22	1.07 - 1.38	1.18	1.04 - 1.34	1.42	1.25 - 1.6

* Imipenem or Meropenem. Resistance to carbapenems was very low in both *Klebsiella* and *E. coli* which prevented any formal statistical analysis.
~ 3GC resistance was defined as resistance to ceftazidime, cefpodoxime, cefotaxime, or ceftriaxone.
+ Note that some laboratories used the systemic rather than UTI breakpoint guidelines for co-amoxiclav resulting in an increase in the percentage of resistant samples between mid-2011 and early 2012.

Table A- 6. Multivariable logistic regression results for all bacterium-antibiotic combinations with LTCF residence included as a binary variable (LTCF samples vs. non-LTCF samples) PART A. 95% confidence intervals (aCI) are adjusted for clustering at the postcode level. Interactions were not included in the model as they did not improve model fit.*

Organism	Antibiotic	OR LTCF	95% aCI LTCF	OR Male	95% aCI Male
E. coli	Amoxicillin/ Ampicillin	2.33	2.16 - 2.5	1.2	1.15 - 1.25
	Ciprofloxacin	2.42	2.17 - 2.69	1.69	1.58 - 1.81
	Co-amoxiclav[+]	1.71	1.55 - 1.9	1.35	1.28 - 1.41
	First-generation cephalosporins	1.75	1.55 - 1.98	1.47	1.37 - 1.59
	Gentamicin	1.69	1.47 - 1.94	1.53	1.4 - 1.68
	Nitrofurantoin	1.74	1.53 - 1.97	1.48	1.36 - 1.61
	Piperacillin/ Tazobactam	1.87	1.62 - 2.17	1.47	1.33 - 1.62
	Second-generation cephalosporins	1.89	1.61 - 2.23	1.38	1.28 - 1.5
	Temocillin	1.39	0.98 - 1.96	1.32	1.14 - 1.53
	Third-generation cephalosporins[~]	1.89	1.64 - 2.17	1.47	1.35 - 1.6
	Trimethoprim	2.36	2.21 - 2.53	1.06	1.02 - 1.11
Klebsiella	Ciprofloxacin	1.54	1.13 - 2.1	1.34	1.11 - 1.62
	Co-amoxiclav[+]	1.59	1.27 - 1.99	1.23	1.08 - 1.39
	First-generation cephalosporinss	1.42	1.1 - 1.83	1.38	1.2 - 1.58
	Gentamicin	1.29	0.84 - 1.96	1.4	1.1 - 1.77
	Nitrofurantoin	1.31	1.09 - 1.59	0.9	0.81 - 0.99
	Piperacillin/ Tazobactam	1.63	1.14 - 2.32	1.34	1.14 - 1.58
	Second-generation cephalosporinss	1.36	0.95 - 1.94	1.39	1.17 - 1.65
	Temocillin	0.77	0.19 - 3.11	1.58	0.94 - 2.66
	Third-generation cephalosporins[~]	1.24	0.85 - 1.83	1.42	1.15 - 1.75
	Trimethoprim	1.89	1.6 - 2.24	0.97	0.88 - 1.06

[*] Resistance to carbapenems was very low in both *Klebsiella* and *E. coli* which prevented any formal statistical analysis.
[~] 3GC resistance was defined as resistance to ceftazidime, cefpodoxime, cefotaxime, or ceftriaxone.
[+] Note that some laboratories used the systemic rather than UTI breakpoint guidelines for co-amoxiclav resulting in an increase in the percentage of resistant samples between mid-2011 and early 2012.

Table A- 7. Multivariable logistic regression results for all bacterium-antibiotic combinations with LTCF residence included as a binary variable (LTCF samples vs. non-LTCF samples) PART B. 95% confidence intervals (aCI) are adjusted for clustering at the postcode level. Interactions were not included in the model as they did not improve model fit.*

Organism	Antibiotic	OR 75-80	95% aCI 75-80	OR 81-85	95% aCI 81-85	OR over 85	95% aCI over 85
E. coli	Amoxicillin/ Ampicillin	0.98	0.94 - 1.02	1.02	0.97 - 1.06	1.15	1.1 - 1.21
	Ciprofloxacin	1.04	0.96 - 1.13	1.11	1.02 - 1.21	1.35	1.24 - 1.47
	Co-amoxiclav^{+}	0.99	0.94 - 1.04	1.04	0.99 - 1.1	1.19	1.12 - 1.26
	First-generation cephalosporins	0.99	0.91 - 1.08	1.11	1.01 - 1.21	1.15	1.05 - 1.26
	Gentamicin	0.99	0.89 - 1.11	1.01	0.9 - 1.13	1.13	1.01 - 1.27
	Nitrofurantoin	1.06	0.94 - 1.19	1.23	1.09 - 1.39	1.34	1.19 - 1.51
	Piperacillin/ Tazobactam	0.94	0.83 - 1.05	0.97	0.86 - 1.1	1.18	1.05 - 1.33
	Second-generation cephalosporins	1.04	0.94 - 1.14	1.2	1.09 - 1.33	1.31	1.18 - 1.46
	Temocillin	1.03	0.85 - 1.25	1.24	1.01 - 1.51	1.07	0.87 - 1.31
	Third-generation cephalosporins$^{~}$	0.95	0.86 - 1.05	1.02	0.92 - 1.14	1.08	0.97 - 1.21
	Trimethoprim	1.01	0.96 - 1.05	1.09	1.04 - 1.14	1.28	1.22 - 1.34
Klebsiella	Ciprofloxacin	0.76	0.6 - 0.97	0.9	0.69 - 1.18	0.76	0.59 - 0.97
	Co-amoxiclav^{+}	0.97	0.81 - 1.15	1.12	0.93 - 1.35	1.11	0.93 - 1.32
	First-generation cephalosporinss	0.92	0.76 - 1.11	1.04	0.86 - 1.27	1.04	0.86 - 1.25
	Gentamicin	0.89	0.63 - 1.27	1.26	0.89 - 1.8	1.05	0.75 - 1.46
	Nitrofurantoin	1.01	0.89 - 1.15	1.01	0.88 - 1.16	1	0.87 - 1.14
	Piperacillin/ Tazobactam	0.84	0.66 - 1.07	0.98	0.77 - 1.26	0.99	0.78 - 1.25
	Second-generation cephalosporinss	0.93	0.73 - 1.18	0.99	0.77 - 1.28	1.05	0.83 - 1.34
	Temocillin	1.08	0.51 - 2.27	0.65	0.3 - 1.43	0.78	0.35 - 1.73
	Third-generation cephalosporins$^{~}$	0.89	0.66 - 1.2	1.06	0.77 - 1.45	0.91	0.68 - 1.22

Organism	Antibiotic	OR 75-80	95% aCI 75-80	OR 81-85	95% aCI 81-85	OR over 85	95% aCI over 85
	Trimethoprim	0.92	0.81 - 1.05	1.07	0.93 - 1.22	1.16	1.03 - 1.32

[*]Resistance to carbapenems was very low in both *Klebsiella* and *E. coli* which prevented any formal statistical analysis. [¯] 3GC resistance was defined as resistance to ceftazidime, cefpodoxime, cefotaxime, or ceftriaxone. [+]Note that some laboratories used the systemic rather than UTI breakpoint guidelines for co-amoxiclav resulting in an increase in the percentage of resistant samples between mid-2011 and early 2012.

Table A- 8. Multivariable logistic regression results for all bacterium-antibiotic combinations with LTCF residence included as a binary variable (LTCF samples vs. non-LTCF samples) PART C. 95% confidence intervals (aCI) are adjusted for clustering at the postcode level. OR H are the odds of resistance for bacteria from samples from hospitals compared to that of those from GPs. Interactions were not included in the model as they did not improve model fit.*

Organism	Antibiotic	OR H	95% aCI H	OR Y2	95% aCI Y2	OR Y3	95% aCI Y3	OR Y4	95% aCI Y4
E. coli	Amoxicillin/ Ampicillin	1.18	1.14 - 1.21	1	0.96 - 1.05	1.07	1.02 - 1.11	1.09	1.05 - 1.14
	Ciprofloxacin	1.11	1.06 - 1.16	0.95	0.9 - 1.01	0.92	0.86 - 0.98	0.9	0.84 - 0.96
	Co-amoxiclav^{+}	1.34	1.3 - 1.39	0.89	0.85 - 0.94	0.7	0.66 - 0.74	0.71	0.67 - 0.74
	First-generation cephalosporins	1.33	1.26 - 1.4	0.88	0.81 - 0.95	0.9	0.83 - 0.97	0.96	0.89 - 1.04
	Gentamicin	1.4	1.31 - 1.49	0.92	0.83 - 1.02	0.97	0.88 - 1.07	1.01	0.92 - 1.12
	Nitrofurantoin	1.03	0.97 - 1.1	0.82	0.75 - 0.9	0.77	0.7 - 0.85	0.86	0.78 - 0.94
	Piperacillin/ Tazobactam	1.3	1.21 - 1.41	0.64	0.55 - 0.75	0.88	0.8 - 0.97	0.92	0.83 - 1.02
	Second-generation cephalosporins	1.43	1.35 - 1.51	1.07	0.99 - 1.16	1.03	0.95 - 1.12	1.1	1.01 - 1.19
	Temocillin	1.41	1.25 - 1.59	2.29	1.79 - 2.93	4.97	3.96 - 6.25	4.21	3.34 - 5.32
	Third-generation cephalosporins$^{\sim}$	1.36	1.28 - 1.44	1	0.91 - 1.09	1.03	0.94 - 1.13	1.09	1 - 1.2
	Trimethoprim	1.05	1.02 - 1.08	1.05	1.01 - 1.09	1.14	1.09 - 1.18	1.19	1.14 - 1.24
Klebsiella	Ciprofloxacin	1.45	1.25 - 1.69	0.96	0.73 - 1.25	1.19	0.91 - 1.55	1.47	1.15 - 1.89
	Co-amoxiclav^{+}	1.54	1.39 - 1.71	1.13	0.95 - 1.35	1.05	0.88 - 1.25	1.31	1.11 - 1.56
	First-generation cephalosporins	1.54	1.37 - 1.73	1.07	0.88 - 1.31	1.18	0.96 - 1.44	1.26	1.03 - 1.53
	Gentamicin	2.06	1.71 - 2.48	0.77	0.51 - 1.17	1.28	0.87 - 1.87	1.91	1.33 - 2.75
	Nitrofurantoin	0.85	0.78 - 0.93	0.88	0.78 - 0.99	0.56	0.49 - 0.63	0.61	0.54 - 0.68
	Piperacillin/ Tazobactam	1.62	1.41 - 1.86	0.83	0.64 - 1.07	1.69	1.36 - 2.09	2.1	1.7 - 2.6
	Second-generation	1.51	1.31 - 1.76	0.94	0.74 - 1.19	1.16	0.93 - 1.45	1.07	0.85 - 1.34

Organism	Antibiotic	OR H	95% aCI H	OR Y2	95% aCI Y2	OR Y3	95% aCI Y3	OR Y4	95% aCI Y4
	cephalosporins								
	Temocillin	1.61	1 - 2.6	2.26	0.67 - 7.62	2.62	0.8 - 8.55	3.04	0.95 - 9.76
	Third-generation cephalosporins~	1.83	1.54 - 2.18	1.15	0.85 - 1.57	1.24	0.92 - 1.68	1.68	1.26 - 2.23
	Trimethoprim	1.04	0.96 - 1.13	1.22	1.08 - 1.39	1.19	1.04 - 1.35	1.41	1.25 - 1.6

*Resistance to carbapenems was very low in both *Klebsiella* and *E. coli* which prevented any formal statistical analysis.
~ 3GC resistance was defined as resistance to ceftazidime, cefpodoxime, cefotaxime, or ceftriaxone.
+ Note that some laboratories used the systemic rather than UTI breakpoint guidelines for co-amoxiclav resulting in an increase in the percentage of resistant samples between mid-2011 and early 2012.

Table A- 9. Multivariable logistic regression results for all bacterium-antibiotic combinations where the odds of resistance of bacteria from residential (Res) and nursing (Ns) LTCF samples are each compared to that of non-LTCF samples PART A. 95% confidence intervals (aCI) are adjusted for clustering at the postcode level. OR H is the odds of resistance for bacteria from samples from hospitals compared to that of samples from GPs. Interactions were not included in the model as they did not improve model fit. [*]

Organism	Antibiotic	OR Res LTCF	aCI Res LTCF	OR Ns LTCF	aCI Ns LTCF	OR Male	aCI Male
E. coli	Amoxicillin/ Ampicillin	2.13	1.95 - 2.32	2.67	2.36 - 3.02	1.2	1.15 - 1.25
	Ciprofloxacin	2.17	1.9 - 2.47	2.78	2.38 - 3.24	1.68	1.58 - 1.8
	Co-amoxiclav[+]	1.68	1.47 - 1.91	1.76	1.51 - 2.06	1.34	1.28 - 1.41
	First-generation cephalosporins	1.54	1.33 - 1.8	2.05	1.71 - 2.46	1.47	1.36 - 1.58
	Gentamicin	1.52	1.27 - 1.83	1.93	1.6 - 2.34	1.52	1.39 - 1.67
	Nitrofurantoin	1.59	1.35 - 1.87	1.95	1.64 - 2.33	1.47	1.35 - 1.6
	Piperacillin/ Tazobactam	1.76	1.47 - 2.11	2.09	1.66 - 2.63	1.46	1.33 - 1.62
	Second-generation cephalosporins	1.82	1.48 - 2.22	2.01	1.55 - 2.61	1.38	1.27 - 1.49
	Temocillin	1.43	0.94 - 2.18	1.32	0.76 - 2.28	1.32	1.14 - 1.53
	Third-generation cephalosporins[~]	1.76	1.47 - 2.1	2.09	1.7 - 2.56	1.47	1.35 - 1.6
	Trimethoprim	2.2	2.02 - 2.4	2.63	2.37 - 2.92	1.06	1.02 - 1.1
Klebsiella	Ciprofloxacin	1.41	0.9 - 2.19	1.7	1.13 - 2.56	1.34	1.11 - 1.62
	Co-amoxiclav[+]	1.42	1.06 - 1.92	1.81	1.3 - 2.51	1.22	1.08 - 1.39
	First-generation cephalosporins	1.24	0.88 - 1.76	1.64	1.15 - 2.34	1.38	1.2 - 1.58
	Gentamicin	0.91	0.52 - 1.62	1.72	0.97 - 3.05	1.39	1.1 - 1.76
	Nitrofurantoin	1.31	1.02 - 1.68	1.31	1 - 1.73	0.9	0.81 - 0.99
	Piperacillin/ Tazobactam	1.65	1.02 - 2.68	1.6	0.99 - 2.59	1.34	1.14 - 1.58
	Second-generation cephalosporins	1.49	0.92 - 2.4	1.21	0.74 - 1.97	1.39	1.17 - 1.65
	Temocillin	1.5	0.4 - 5.65	0	0 - 0	1.6	0.95 - 2.68
	Third-generation cephalosporins[~]	1.06	0.67 - 1.68	1.47	0.81 - 2.67	1.42	1.15 - 1.75
	Trimethoprim	1.82	1.43 - 2.31	1.98	1.59 - 2.46	0.97	0.88 - 1.06

[*]Resistance to carbapenems was very low in both *Klebsiella* and *E. coli* which prevented any formal statistical analysis.
[~] 3GC resistance was defined as resistance to ceftazidime, cefpodoxime, cefotaxime, or ceftriaxone.
[+] Note that some laboratories used the systemic rather than UTI breakpoint guidelines for co-amoxiclav resulting in an increase in the percentage of resistant samples between mid-2011 and early 2012.

Table A- 10. Multivariable logistic regression results for all bacterium-antibiotic combinations where the odds of resistance of bacteria from residential (Res) and nursing (Ns) LTCF samples are each compared to that of non-LTCF samples PART B. 95% confidence intervals (aCI) are adjusted for clustering at the postcode level. OR H is the odds of resistance for bacteria from samples from hospitals compared to that of samples from GPs. Interactions were not included in the model as they did not improve model fit. *

Organism	Antibiotic	OR 75-80	aCI 75-80	OR 81-85	aCI 81-85	OR over 85	aCI over 85
E. coli	Amoxicillin/ Ampicillin	0.98	0.94 - 1.02	1.02	0.97 - 1.06	1.16	1.1 - 1.21
	Ciprofloxacin	1.04	0.96 - 1.13	1.11	1.02 - 1.21	1.35	1.24 - 1.47
	Co-amoxiclav+	0.99	0.94 - 1.04	1.04	0.99 - 1.1	1.19	1.12 - 1.26
	First-generation cephalosporins	0.99	0.91 - 1.08	1.11	1.01 - 1.21	1.15	1.05 - 1.26
	Gentamicin	0.99	0.89 - 1.11	1.01	0.9 - 1.13	1.13	1.01 - 1.27
	Nitrofurantoin	1.06	0.94 - 1.19	1.23	1.09 - 1.39	1.34	1.2 - 1.51
	Piperacillin/ Tazobactam	0.94	0.83 - 1.05	0.97	0.86 - 1.1	1.18	1.05 - 1.33
	Second-generation cephalosporins	1.04	0.94 - 1.14	1.2	1.09 - 1.33	1.31	1.19 - 1.46
	Temocillin	1.03	0.85 - 1.25	1.24	1.01 - 1.51	1.07	0.87 - 1.3
	Third-generation cephalosporins~	0.95	0.86 - 1.05	1.02	0.92 - 1.14	1.08	0.97 - 1.21
	Trimethoprim	1.01	0.96 - 1.05	1.09	1.05 - 1.14	1.28	1.22 - 1.34
Klebsiella	Ciprofloxacin	0.76	0.6 - 0.97	0.9	0.69 - 1.17	0.76	0.59 - 0.97
	Co-amoxiclav+	0.97	0.81 - 1.16	1.12	0.93 - 1.34	1.11	0.93 - 1.32
	First-generation cephalosporins	0.92	0.76 - 1.11	1.04	0.85 - 1.27	1.04	0.86 - 1.26
	Gentamicin	0.89	0.63 - 1.27	1.26	0.89 - 1.8	1.05	0.75 - 1.46
	Nitrofurantoin	1.01	0.89 - 1.15	1.01	0.88 - 1.16	1	0.87 - 1.14
	Piperacillin/ Tazobactam	0.84	0.66 - 1.07	0.98	0.77 - 1.25	0.99	0.78 - 1.25
	Second-generation cephalosporins	0.93	0.73 - 1.18	0.99	0.77 - 1.28	1.05	0.83 - 1.34
	Temocillin	1.08	0.51 - 2.29	0.65	0.3 - 1.43	0.77	0.35 - 1.71

Organism	Antibiotic	OR 75-80	aCI 75-80	OR 81-85	aCI 81-85	OR over 85	aCI over 85
	Third-generation cephalosporins~	0.89	0.66 - 1.19	1.06	0.77 - 1.45	0.92	0.69 - 1.22
	Trimethoprim	0.92	0.81 - 1.05	1.07	0.93 - 1.22	1.16	1.03 - 1.32

*Resistance to carbapenems was very low in both *Klebsiella* and *E. coli* which prevented any formal statistical analysis.

~ 3GC resistance was defined as resistance to ceftazidime, cefpodoxime, cefotaxime, or ceftriaxone.

+ Note that some laboratories used the systemic rather than UTI breakpoint guidelines for co-amoxiclav resulting in an increase in the percentage of resistant samples between mid-2011 and early 2012.

Table A- 11. Multivariable logistic regression results for all bacterium-antibiotic combinations where the odds of resistance of bacteria from residential (Res) and nursing (Ns) LTCF samples are each compared to that of non-LTCF samples PART C. 95% confidence intervals (aCI) are adjusted for clustering at the postcode level. OR H is the odds of resistance for bacteria from samples from hospitals compared to that of samples from GPs. Interactions were not included in the model as they did not improve model fit. *

Organism	Antibiotic	OR H	aCI H	OR Y2	aCI Y2	OR Y3	aCI Y3	OR Y4	aCI Y4
E. coli	Amoxicillin/ Ampicillin	1.18	1.15 - 1.21	1	0.96 - 1.05	1.07	1.02 - 1.11	1.09	1.05 - 1.14
	Ciprofloxacin	1.11	1.06 - 1.16	0.95	0.89 - 1.01	0.92	0.86 - 0.98	0.9	0.84 - 0.96
	Co-amoxiclav+	1.34	1.3 - 1.39	0.89	0.85 - 0.94	0.7	0.66 - 0.74	0.71	0.67 - 0.74
	First-generation cephalosporins	1.33	1.26 - 1.4	0.88	0.81 - 0.95	0.9	0.83 - 0.97	0.97	0.9 - 1.04
	Gentamicin	1.4	1.31 - 1.5	0.92	0.83 - 1.02	0.97	0.88 - 1.07	1.02	0.92 - 1.12
	Nitrofurantoin	1.04	0.97 - 1.1	0.82	0.75 - 0.9	0.77	0.7 - 0.85	0.86	0.78 - 0.94
	Piperacillin/ Tazobactam	1.3	1.21 - 1.41	0.64	0.55 - 0.75	0.88	0.8 - 0.97	0.92	0.83 - 1.02
	Second-generation cephalosporins	1.43	1.34 - 1.51	1.07	0.99 - 1.16	1.03	0.95 - 1.12	1.1	1.01 - 1.19
	Temocillin	1.41	1.25 - 1.59	2.29	1.79 - 2.92	4.97	3.96 - 6.25	4.21	3.33 - 5.32
	Third-generation cephalosporins~	1.36	1.29 - 1.45	1	0.91 - 1.09	1.03	0.94 - 1.13	1.1	1 - 1.2
	Trimethoprim	1.05	1.02 - 1.08	1.05	1.01 - 1.09	1.14	1.09 - 1.18	1.19	1.14 - 1.24
Klebsiella	Ciprofloxacin	1.45	1.25 - 1.69	0.96	0.73 - 1.25	1.19	0.91 - 1.55	1.47	1.14 - 1.89
	Co-amoxiclav+	1.54	1.39 - 1.71	1.13	0.95 - 1.35	1.05	0.88 - 1.25	1.31	1.11 - 1.56
	First-generation	1.54	1.37 - 1.73	1.07	0.88 - 1.31	1.18	0.96 - 1.44	1.26	1.03 - 1.53

Organism	Antibiotic	OR H	aCI H	OR Y2	aCI Y2	OR Y3	aCI Y3	OR Y4	aCI Y4
	cephalosporins								
	Gentamicin	2.05	1.7 - 2.48	0.77	0.51 - 1.17	1.28	0.87 - 1.87	1.91	1.33 - 2.74
	Nitrofurantoin	0.85	0.78 - 0.93	0.88	0.78 - 0.99	0.56	0.49 - 0.63	0.61	0.54 - 0.68
	Piperacillin/ Tazobactam	1.62	1.41 - 1.86	0.83	0.64 - 1.07	1.69	1.36 - 2.09	2.11	1.7 - 2.6
	Second-generation cephalosporins	1.52	1.31 - 1.76	0.94	0.74 - 1.19	1.16	0.93 - 1.45	1.07	0.85 - 1.34
	Temocillin	1.63	1.01 - 2.64	2.26	0.67 - 7.63	2.62	0.8 - 8.55	3.05	0.95 - 9.8
	Third-generation cephalosporins[~]	1.83	1.54 - 2.17	1.16	0.85 - 1.57	1.24	0.92 - 1.68	1.68	1.26 - 2.23
	Trimethoprim	1.04	0.96 - 1.13	1.22	1.08 - 1.39	1.19	1.04 - 1.35	1.41	1.25 - 1.6

[*]Resistance to carbapenems was very low in both *Klebsiella* and *E. coli* which prevented any formal statistical analysis.

[~] 3GC resistance was defined as resistance to ceftazidime, cefpodoxime, cefotaxime, or ceftriaxone.

[+] Note that some laboratories used the systemic rather than UTI breakpoint guidelines for co-amoxiclav resulting in an increase in the percentage of resistant samples between mid-2011 and early 2012.

Appendix Chapter 6 PART A

Trends and seasonality of UTIs caused by *E. coli* and *Klebsiella* in older people and GP trimethoprim and nitrofurantoin prescriptions in all ages.

Methods

The data sources employed in this analysis were:

1. The susceptibility tests for *E. coli* and *Klebsiella* urinary samples from patients aged 70+ sent to AmSurv from April 2010 to March 2014. These included samples sent both by GPs and hospitals.
2. The Office for National Statistics yearly all ages and 70+ population estimates for the West Midlands. [4]
3. The monthly GP trimethoprim and nitrofurantoin prescriptions for UTIs in all ages in the West Midlands from August 2010 to March 2014 from the Health & Social Care Information Centre.[234]

Urine/kidney samples that grew *E. coli* and *Klebsiella* from older people submitted to AmSurv from laboratories in the West Midlands from 2010 to 2014 (data source 1) were cleaned as described in Chapter 4. They were then aggregated by month of the study and are referred to subsequently as the monthly *E. coli* and *Klebsiella* UTIs.

The same methodology was employed to describe the trend and (if present) the seasonality of *E. coli* and *Klebsiella* UTIs and of trimethoprim and nitrofurantoin prescriptions. A negative binomial regression model, a type of regression used to model over-dispersed count outcome variables, was used, as the data were highly over-dispersed.

As the all ages and 70+ population in the West Midlands increased during the study period (see Figure A- 1), an offset was incorporated into the regression. This offset accounted for this increase in the population in the regression model. The offset was a logged vector that contained the all ages (for the all ages prescription dataset) or the 70+ (all other datasets) West Midlands population in

each of the months in the UTI dataset. These were obtained from yearly ONS estimates of the West Midlands 70+ population which were repeated for the months in each year [4].

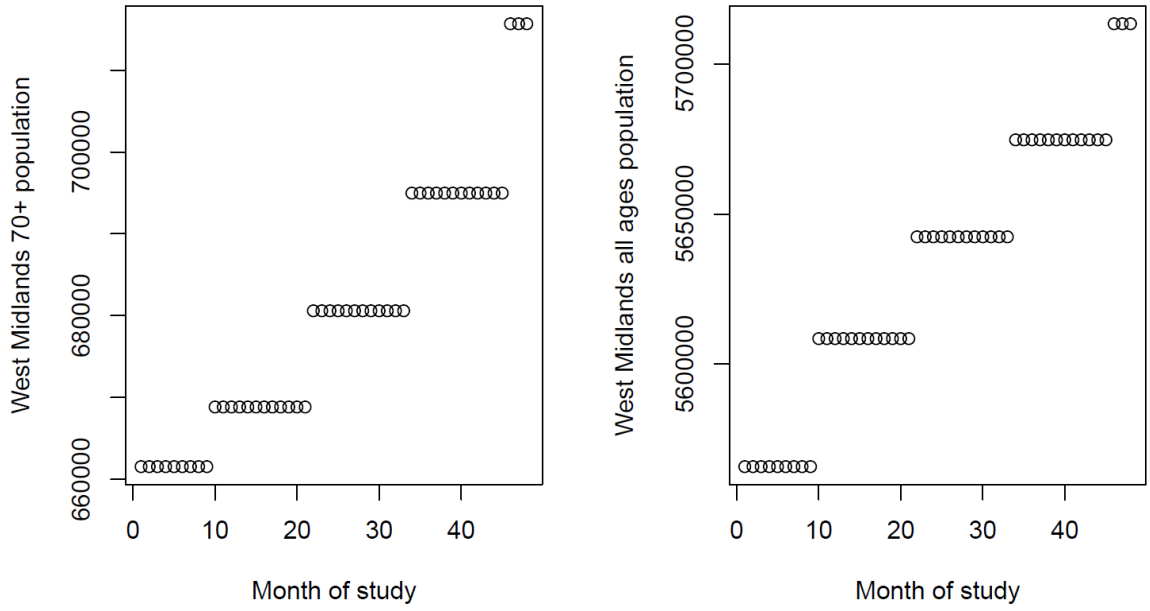

Figure A- 1. West Midlands yearly 70+ and all ages population.

The counts were de-trended by fitting a polynomial regression model of degree two to the time series:

$$f(x) = a + bx + cx^2$$

This allowed a better approximation to the data than achieved through a polynomial regression of degree one:

$$f(x) = a + bx$$

The negative binomial regression was coded in R using the glm.nb function in the MASS R package:

glm.nb(data~ times+I(times^2)+ offset(log(pop)))

where “times” was an integer 1:48 (as our data covered 48 months).

Seasonality was assessed, firstly, graphically by plotting the negative binomial model with and without seasonality. The model with seasonality included an additional term:

$$f(x) = \cos\left(\frac{2\Pi x}{12}\right) + \sin(\frac{2\Pi x}{12})$$

This regression was also coded in R using the glm.nb function in the MASS package:

```
c<-cos(2*pi*times/12)

s<-sin(2*pi*times/12)

glm.nb(data~ times+I(times^2)+ offset(log(pop.48))+c+s)
```

Secondly, a correlogram (or auto-correlation plot) was plotted to explore the correlations between the residuals of the model and the lagged values of the residuals for lags 1-12 (over the course of a year). The residuals are the difference between the estimated model values and the observed data. The residual values of the regression that modelled trend were the remaining variations in the data after trend was accounted for. The correlogram was used to investigate if these residual values were correlated in time. For example, a significantly positive correlation at a lag at one month would signify that, after accounting for trend, the residual values for one month were significantly correlated to the residual values for the next month.

The autocorrelation function (ACF) confidence intervals were calculated as follows:

$$\pm\frac{i}{\sqrt{N}}$$

where $i = qnorm(\frac{1+ci}{2})$, and $N = 48$.

qnorm is the normal quantile R function, ci is the confidence interval (which was set to 0.95), and N is the number of months used to calculate the ACF (48 in this case). Therefore:

$$\pm\frac{i}{\sqrt{N}} = \frac{1.96}{\sqrt{48}} = 0.28$$

The trends and seasonality of *E. coli* and *Klebsiella* UTIs were assessed for LTCF samples and non-LTCF samples, for *E. coli* and *Klebsiella* susceptible and resistant to trimethoprim as these could potentially be different. The *E. coli* and *Klebsiella* UTIs that were sent by GPs (vs. hospitals) were also analysed separately.

Trend in *E. coli* and *Klebsiella* UTI (in those aged 70 and over)

Negative binomial regression models with second degree polynomials were fit to the monthly UTIs caused by *E. coli* and *Klebsiella* in older people in the West Midlands during the study period in LTCFs and outside of LTCFs. The offset for these regressions was the elderly West Midlands population.

As can be seen in Figure A- 2, UTIs caused by *E. coli* and *Klebsiella* in older people increased in the West Midlands during the study period in LTCFs and outside of LTCFs. A similar increase was seen for UTIs caused by *E. coli* and *Klebsiella* susceptible and resistant to trimethoprim (see Figure A- 3 and Figure A- 4). In all cases, UTIs appeared to rapidly increase until early 2013. The rate of UTIs caused by *E. coli* in LTCFs and UTIs caused by *Klebsiella* outside of LTCFs very visibly stabilised from this moment and even dropped slightly in the last few months of the study. This tapering off, although present, was less apparent for UTIs caused by *E. coli* outside of LTCFs and UTIs caused by *Klebsiella* in LTCFs.

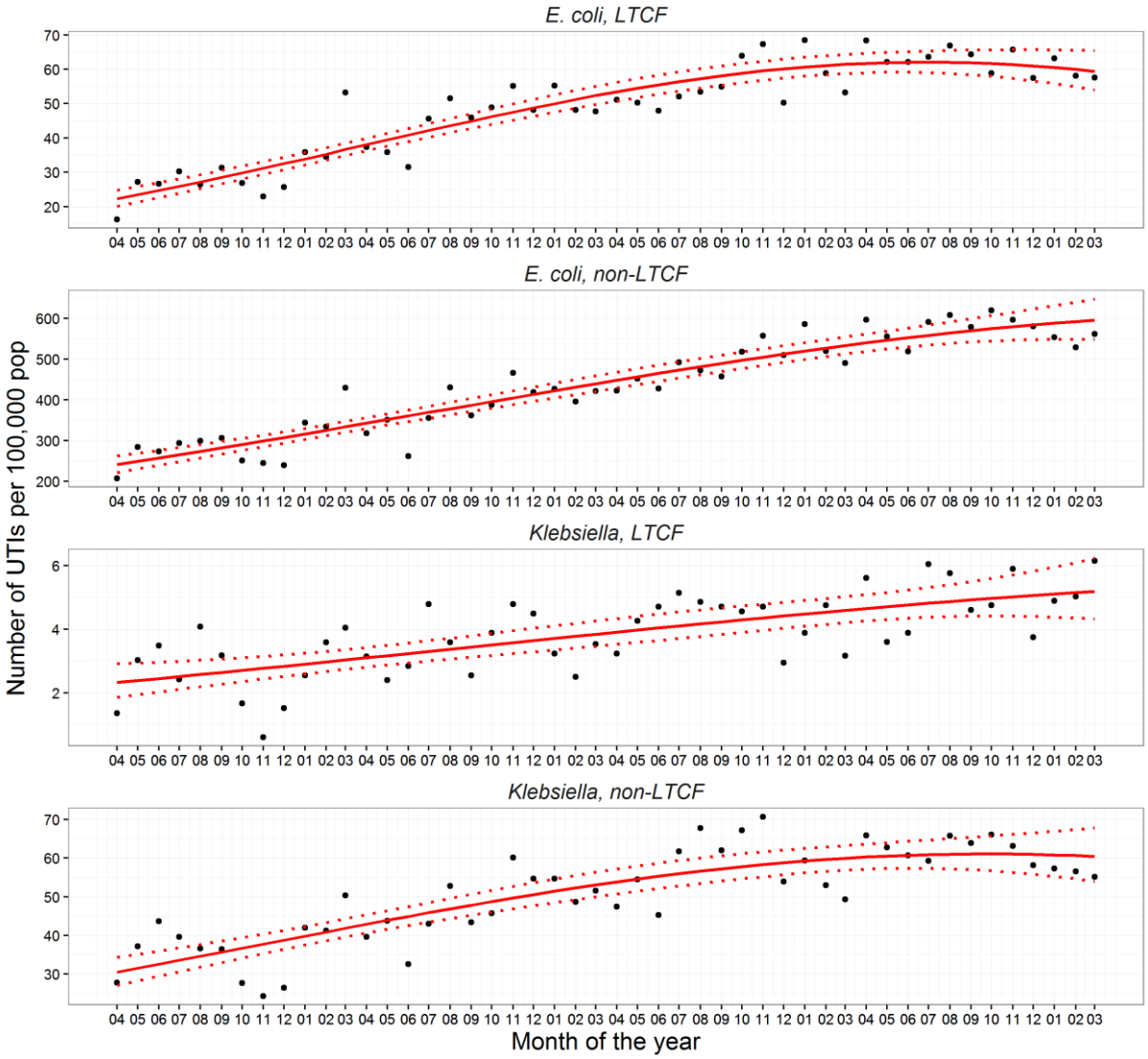

Figure A- 2. Monthly rate of UTIs caused by *E. coli* and *Klebsiella* in older people residing in and outside of long-term care facilities in the West Midlands from April 2010 to March 2014. In red, the fitted predictions of the negative binomial polynomial regression model of degree two with offset.

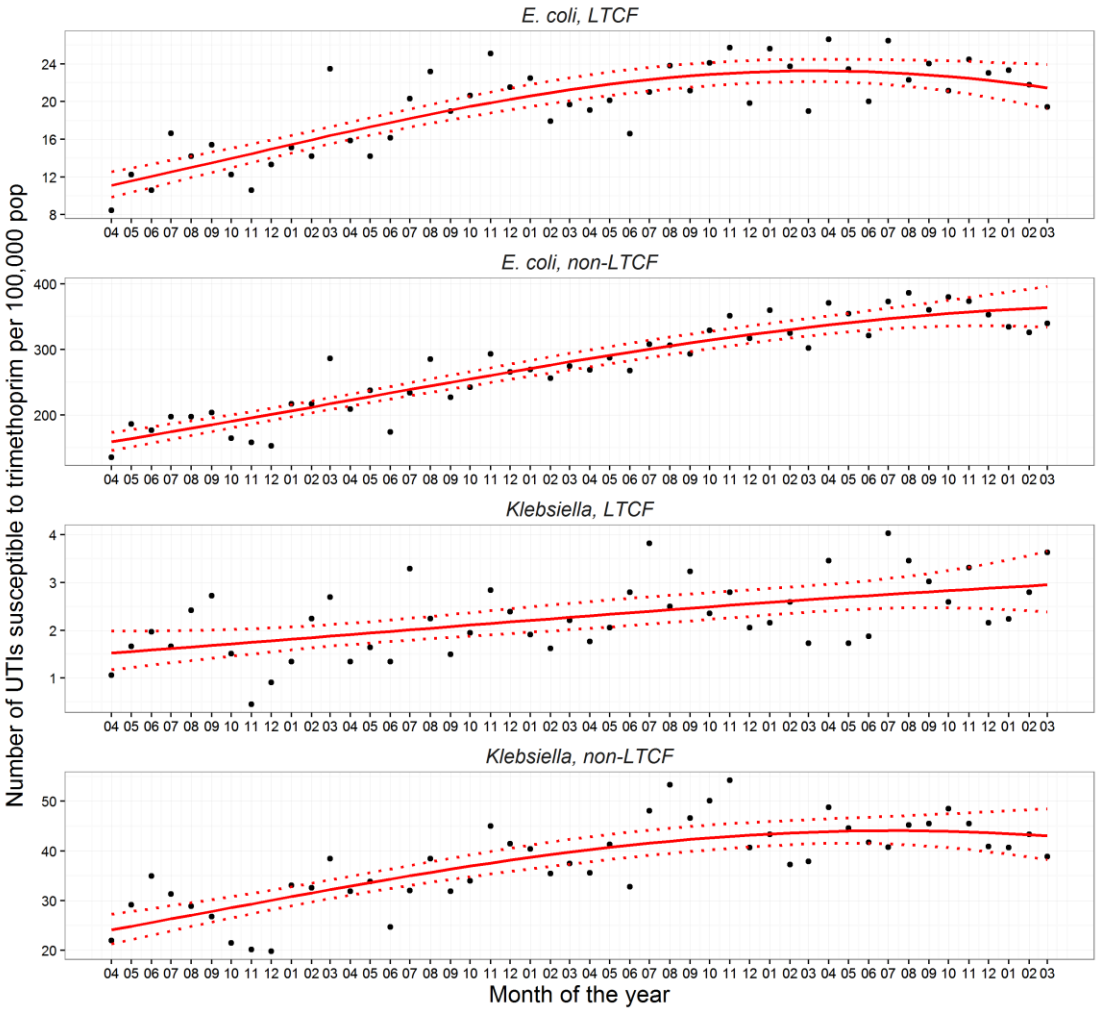

Figure A- 3. Monthly rate of UTIs caused by *E. coli* and *Klebsiella* that were susceptible to trimethoprim in older people residing in and outside of long-term care facilities in the West Midlands. In red, the fitted predictions of the negative binomial polynomial regression model of degree two with offset.

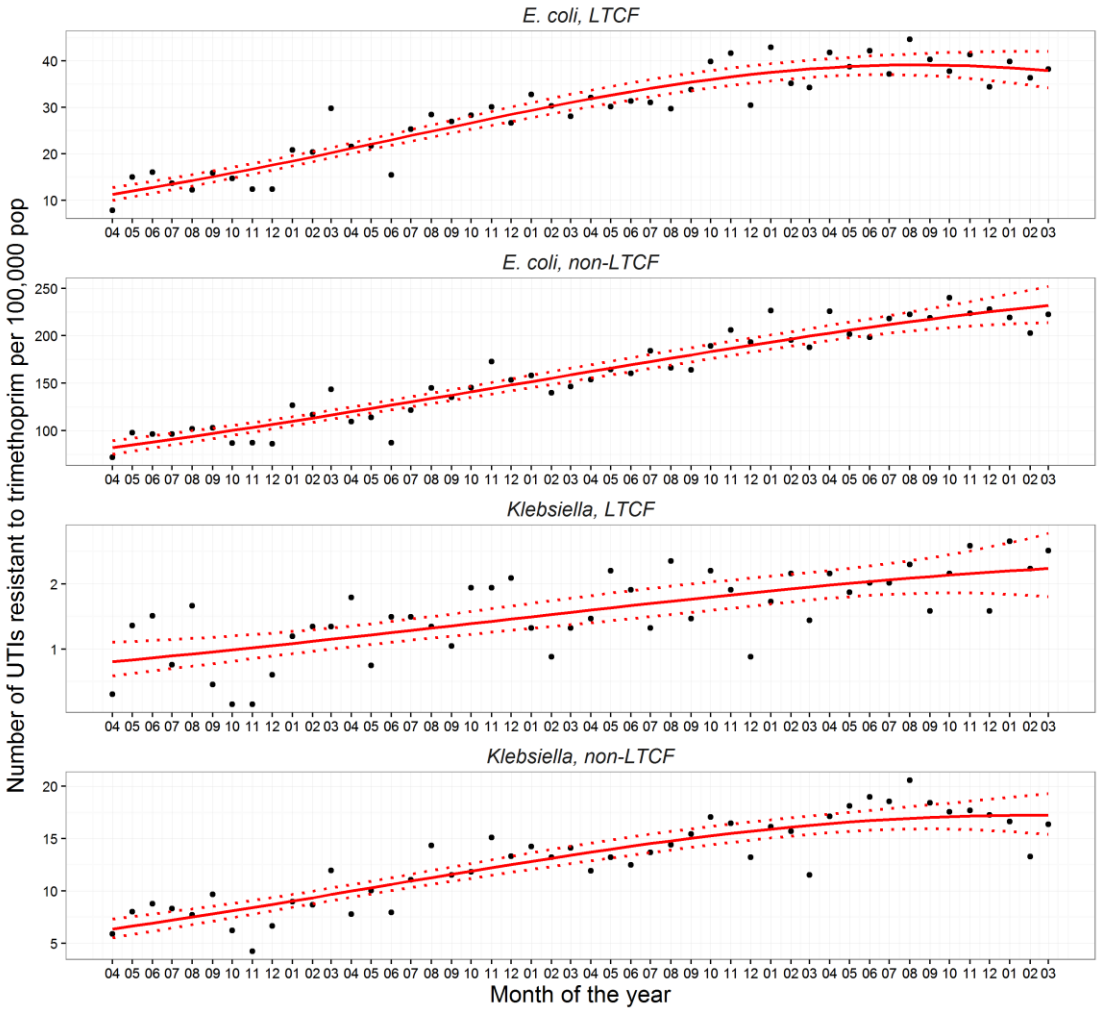

Figure A- 4. Monthly rate of UTIs caused by *E. coli* and *Klebsiella* that were resistant to trimethoprim in older people residing in and outside of long-term care facilities in the West Midlands. In red, the fitted predictions of the negative binomial polynomial regression model of degree two with offset.

The rate of UTIs increased by an average of:

- $y = 0.00021 * 1.056^{month} * 0.9993^{month^2} * 100{,}000$ per 100,000 individuals in the population for *E. coli* UTIs in LTCFs
- $y = 0.0023 * 1.034^{month} * 0.9997^{month^2} * 100{,}000$ per 100,000 individuals in the population for *E. coli* UTIs not in LTCFs
- $y = 0.00002 * 1.027^{month} * 0.9998^{month^2} * 100{,}000$ per 100,000 individuals in the population for *Klebsiella* UTIs in LTCFs
- $y = 0.00029 * 1.035^{month} * 0.9996^{month^2} * 100{,}000$ per 100,000 individuals in the population for *Klebsiella* UTIs in LTCFs

For example, this meant than in the first month of the study (April 2010), there were:

$0.00021 * 1.056^{1} * 0.9993^{1^2} * 100{,}000 = 22.16$ UTIs caused by *E. coli* in LTCFs per 100,000 individuals in the population (~22.29 in Table A- 12, as fewer decimals are reported above than are estimated in the model). The numeric solutions for eight time points are described in Table A- 12 below.

Table A- 12. UTIs caused by *E. coli* and *Klebsiella* in LTCF residents and in older people living in their own homes per 100,000 elderly individuals living in the West Midlands. Fitted values from the negative binomial regression model.

	April 2010	September 2010	March 2011	September 2011	March 2012	September 2012	March 2013	September 2013	March 2014
UTIs caused by *E. coli* in LTCFs per 100,000 pop	22.29	28.52	36.66	44.89	52.33	58.11	61.46	61.9	59.37
UTIs caused by *E. coli* outside LTCFs per 100,000 pop	241.21	282.06	333.93	387.27	439.94	489.57	533.67	569.86	596.06
UTIs caused by *Klebsiella* in LTCFs per 100,000 pop	2.32	2.64	3.03	3.44	3.84	4.23	4.59	4.92	5.19
UTIs caused by *Klebsiella* outside LTCFs per 100,000 pop	30.51	35.67	41.91	47.85	53.1	57.25	59.99	61.08	60.43

Seasonality in *E. coli* UTI (in those aged 70 and over)

There was no seasonal pattern observed in UTIs caused by *E. coli* in older people, neither in LTCF residents nor in patients that did not reside in LTCFs (see Figure A- 5 and Figure A- 6). Adding a $f(x) = \cos\left(\frac{2\Pi x}{12}\right) + \sin(\frac{2\Pi x}{12})$ wave to the regression model worsened the model fit for *E. coli* UTIs (from an AIC of 495.9 to 499.5 for LTCF residents, and from an AIC of 689.6 to 693.1 for those not residing in LTCFs). Graphically, the fit to the rates of *E. coli* UTI were very similar for the two models. The correlograms in Figure A- 6 show the autocorrelation functions for the residuals of the regression models without seasonality in *E. coli* UTIs from LTCFs and outside LTCFs (respectively) at lags of 0-12 months. Neither had an oscillatory shape consistent with seasonality. There was a borderline significant negative correlation at 11 months for UTIs caused by *E. coli* in LTCFs with no plausible biological explanation.

There was also a lack of clear seasonality in UTIs caused by *E. coli* susceptible and resistant to trimethoprim (Figure A- 7 and Figure A- 8).

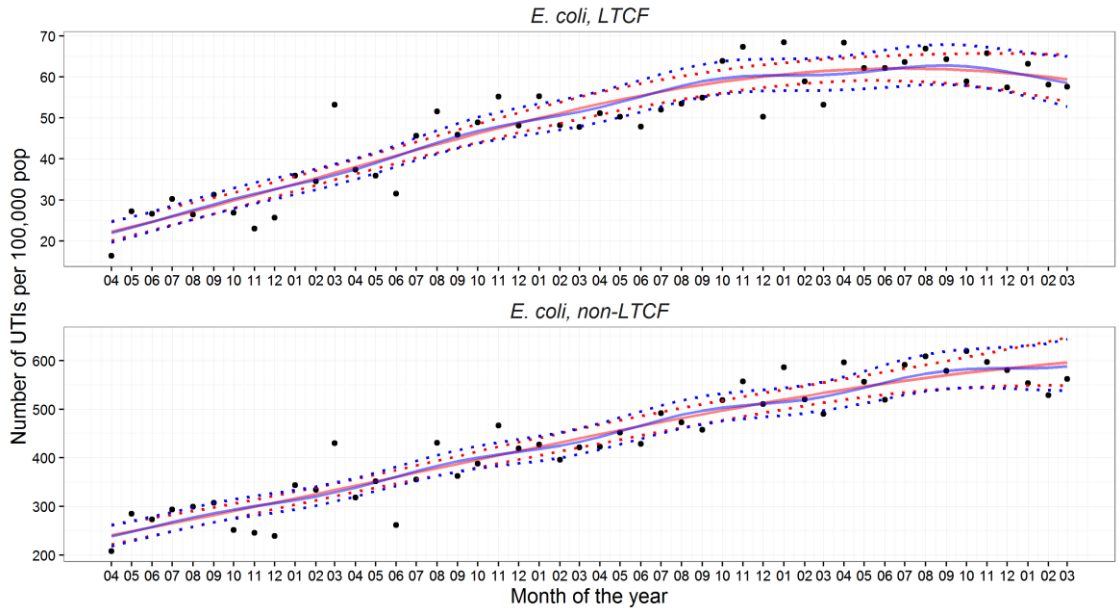

Figure A- 5. Seasonality in the monthly rate of UTIs caused by *E. coli* in elderly patients residing in and outside of long-term care facilities in the West Midlands from April 2010 to March 2014. In red, the fitted predictions of the negative binomial polynomial regression model of degree two with offset. In blue, the fitted predictions of the negative binomial polynomial regression model of degree two with offset and a seasonality component $f(x) = \cos\left(\frac{2\Pi x}{12}\right) + \sin(\frac{2\Pi x}{12})$.

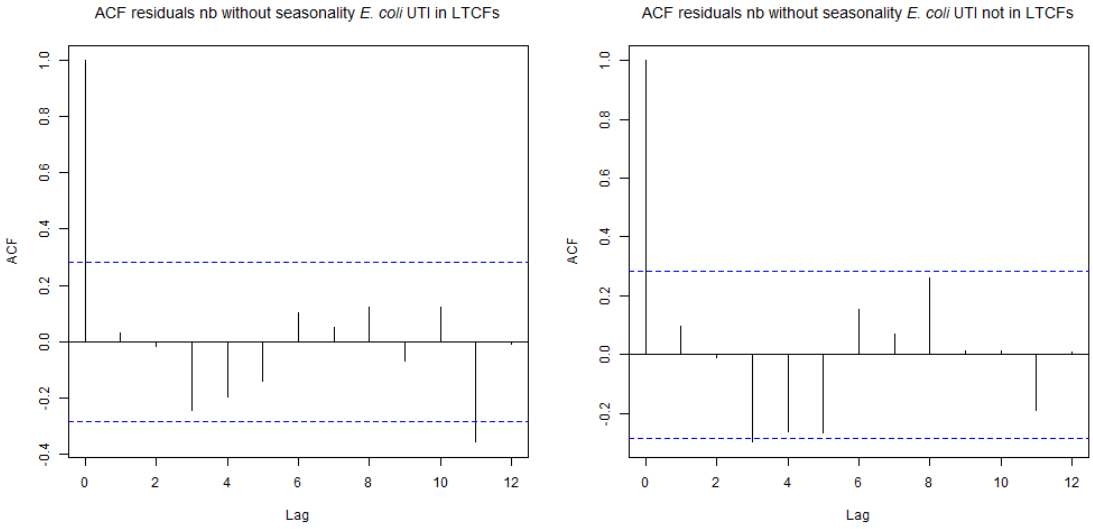

Figure A- 6. The autocorrelation function (ACF) for lags 0-12 of the residuals of the negative binomial regression without seasonality fit to the monthly UTIs caused by *E. coli* in elderly patients residing in LTCFs and outside LTCFs in the West Midlands. The 95% confidence intervals are marked with dashed horizontal blue lines.

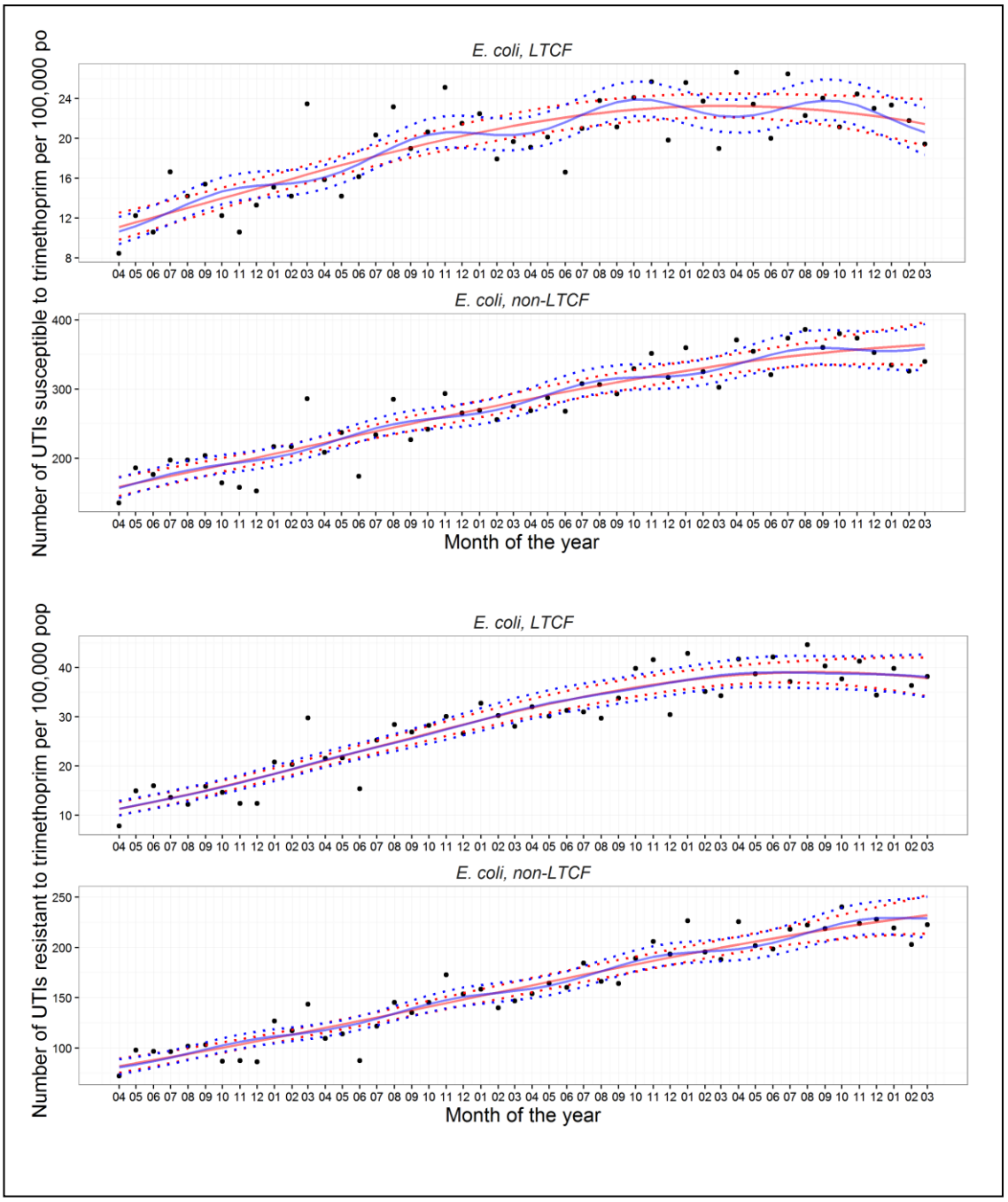

Figure A- 7. Seasonality in the monthly rate of UTIs caused by *E. coli* susceptible and resistant to trimethoprim in elderly patients residing in and outside of long-term care facilities in the West Midlands. In red, the fitted predictions of the negative binomial polynomial regression model of degree two with offset. In blue, the fitted predictions of the negative binomial polynomial regression model of degree two with offset and a seasonality component $\mathbf{f(x) = \cos\left(\frac{2\Pi x}{12}\right) + \sin(\frac{2\Pi x}{12})}$.

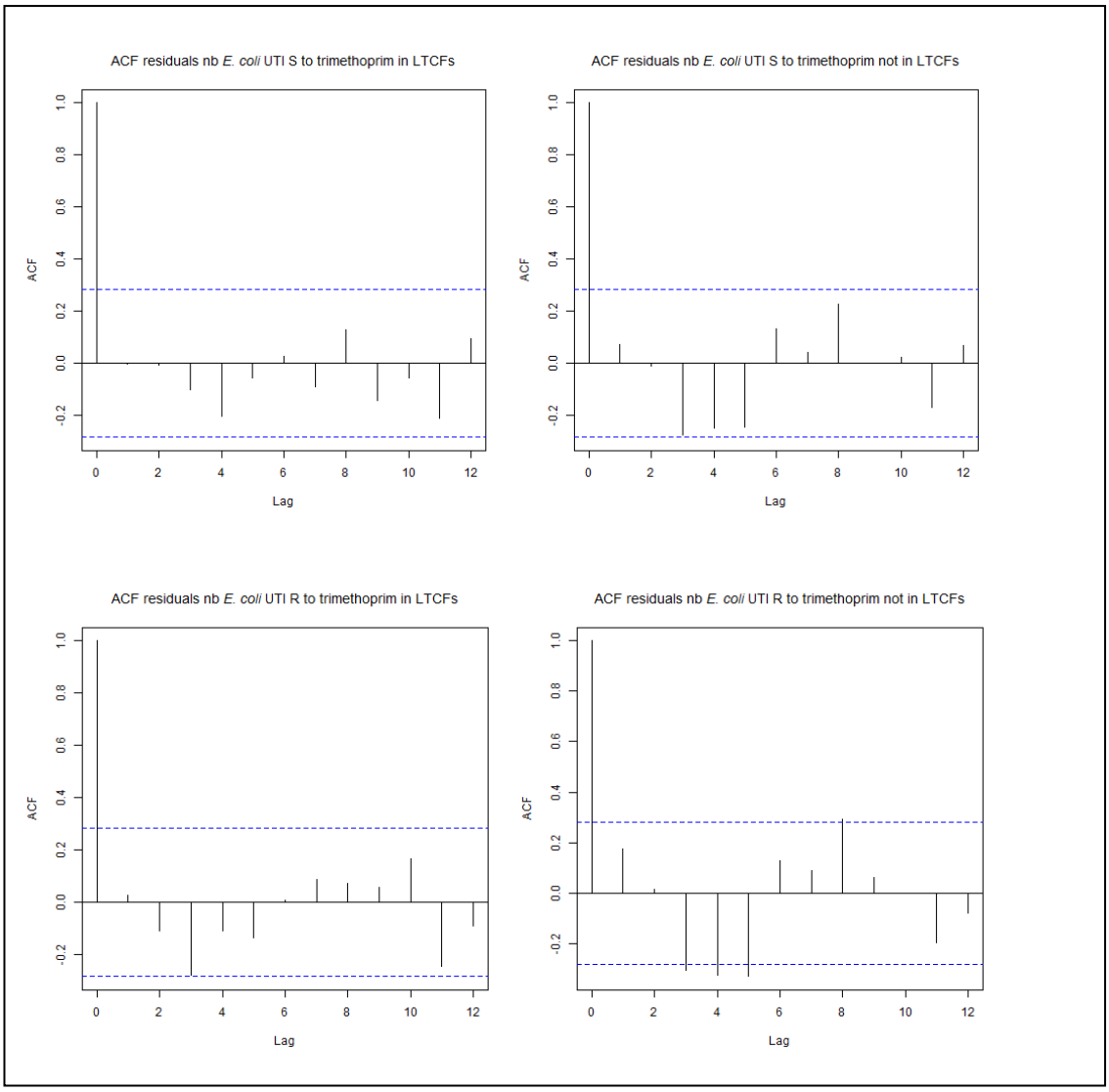

Figure A- 8. The autocorrelation function (ACF) for lags 0-12 of the residuals of the negative binomial regressions without seasonality fit to the monthly UTIs caused by *E. coli* sensitive (top plots) and sensitive (bottom plots) to trimethoprim in elderly patients residing in LTCFs (left plots) and outside of LTCFs (right plots) in the West Midlands. The 95% confidence intervals are marked with dashed horizontal blue lines.

Seasonality in *Klebsiella* UTI (in those aged 70 and over)

The number of UTIs caused by *Klebsiella* was lower than the number of UTIs caused by *E. coli*, and particularly low in the LTCF population, which increased stochasticity and hindered the analysis of seasonality.

There was no clear seasonal pattern observed in UTIs caused by *Klebsiella* in older people; neither in LTCF residents nor in patients that did not reside in LTCFs (see Figure A- 9 and Figure A- 10). Adding a $f(x) = \cos\left(\frac{2\Pi x}{12}\right) + \sin(\frac{2\Pi x}{12})$

wave to the regression model only improved the model fit very slightly for *Klebsiella* UTIs in LTCF residents (from an AIC of 326.3 to 323.5) and slightly worsened the fit for individuals that resided outside of LTCFs (from an AIC of 516.1 to 517.3). Figure A- 10 shows the correlograms for *Klebsiella* UTIs at lags of 0-12 months. The was a visible oscillation with a significant positive correlation at one month, a borderline significant negative correlation at four months and a significant negative correlation at five months for UTIs caused by *Klebsiella* outside LTCFs. The correlogram for UTIs caused by *Klebsiella* in LTCFs had a similar shape but none of the lags were significantly correlated. This could be due to the number of UTIs caused by *Klebsiella* in LTCFs being much smaller than outside LTCFs, thereby reducing statistical power.

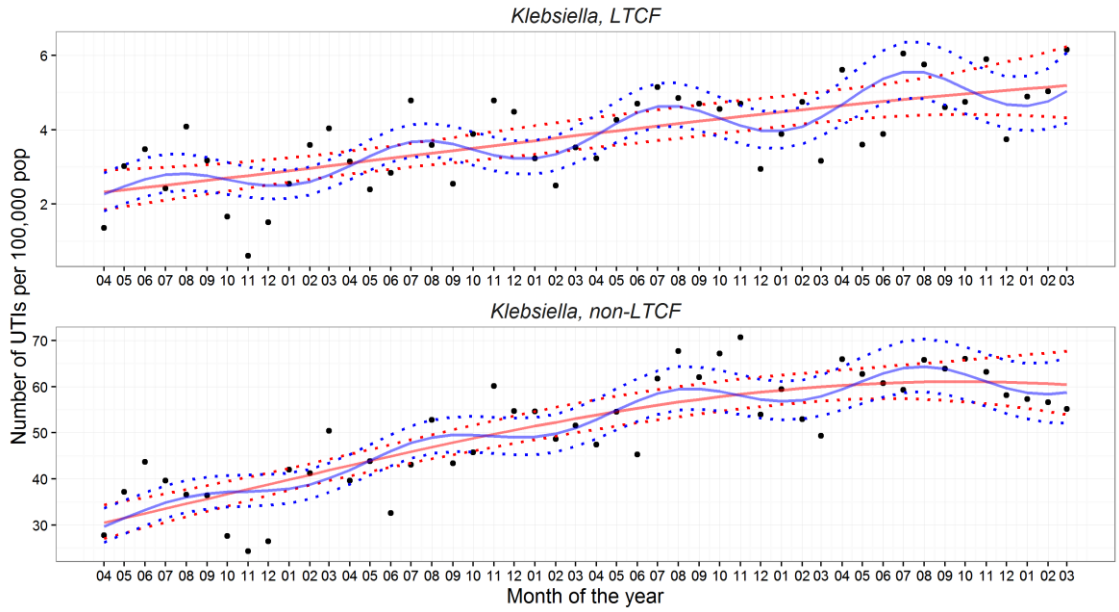

Figure A- 9. Seasonality in the monthly rate of UTIs caused by *Klebsiella* in elderly patients residing in and outside of long-term care facilities in the West Midlands from April 2010 to March 2014. In red, the fitted predictions of the negative binomial polynomial regression model of degree two with offset. In blue, the fitted predictions of the negative binomial polynomial regression model of degree two with offset and a seasonality component $f(x) = \cos\left(\frac{2\Pi x}{12}\right) + \sin(\frac{2\Pi x}{12})$.

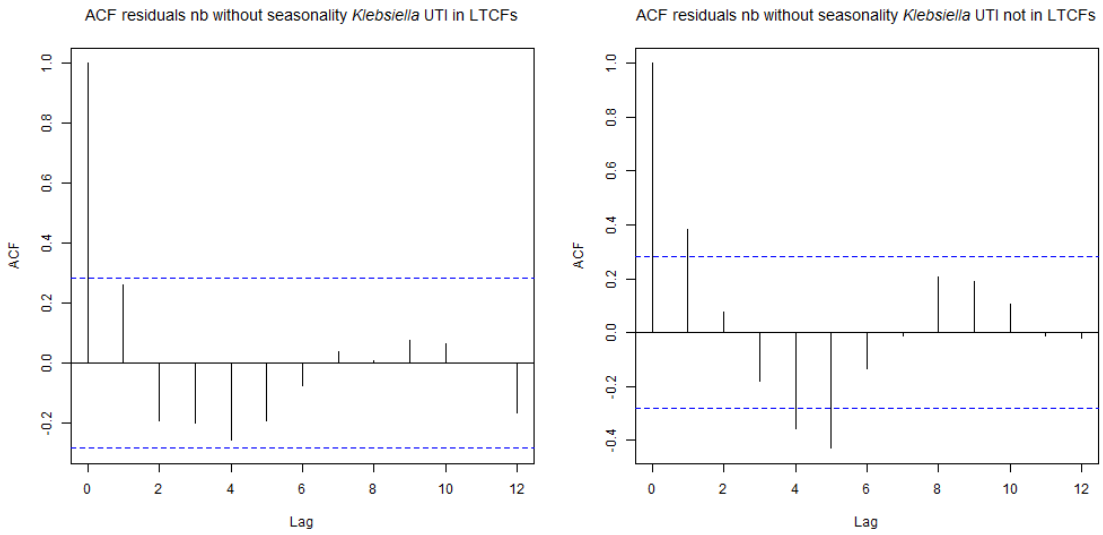

Figure A- 10. The autocorrelation function (ACF) for lags 0-12 of the residuals of the negative binomial regression without seasonality fit to the monthly UTIs caused by *Klebsiella* in elderly patients residing in LTCFs and outside LTCFs in the West Midlands. The 95% confidence intervals are marked with dashed horizontal blue lines.

Similar trends were observed in UTIs caused by *Klebsiella* that were susceptible and resistant to trimethoprim (see Figure A- 11 and Figure A- 12). A very similar oscillatory pattern was seen in the correlogram for UTIs caused by *Klebsiella* that were susceptible or resistant to trimethoprim outside LTCF residents and, to a lesser extent, in UTIs caused by *Klebsiella* that were susceptible to trimethoprim in LTCFs. There was no clear pattern in the correlogram for UTIs caused by *Klebsiella* that were resistant to trimethoprim in LTCFs.

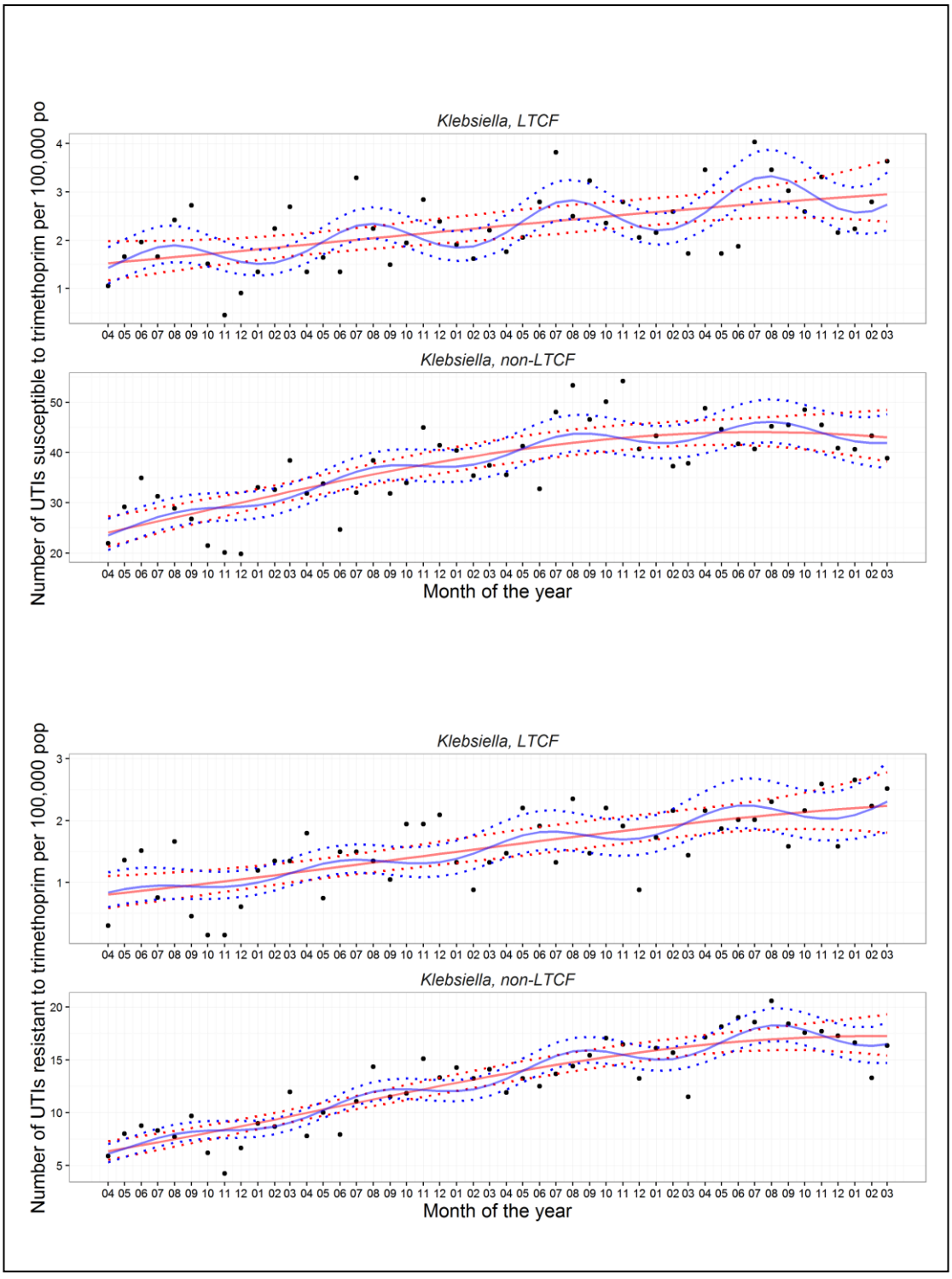

Figure A- 11. Seasonality in the monthly rate of UTIs caused by *Klebsiella* susceptible and resistant to trimethoprim in elderly patients residing in and outside of long-term care facilities in the West Midlands.

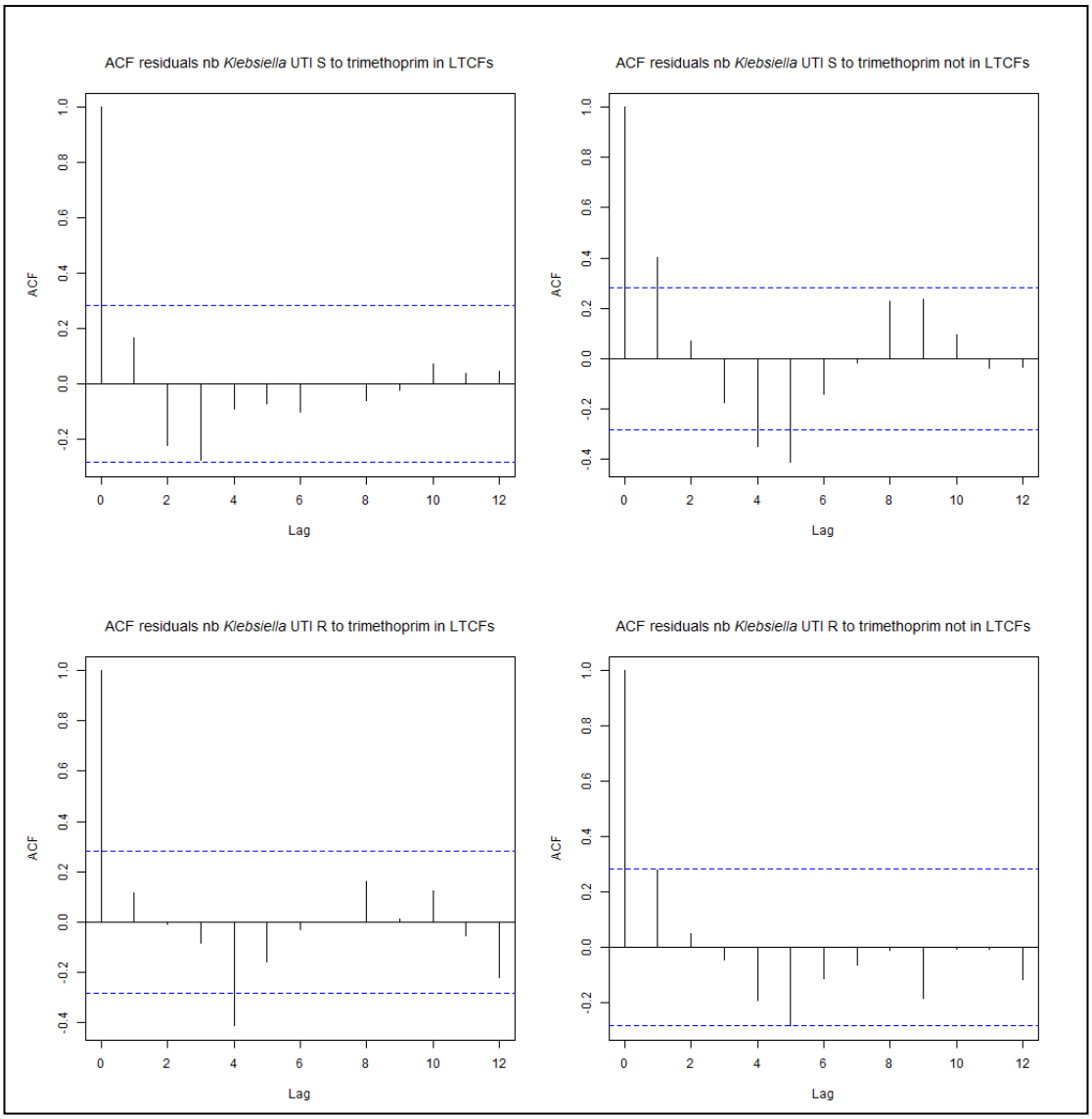

Figure A- 12. The autocorrelation function (ACF) for lags 0-12 of the residuals of the negative binomial regressions without seasonality fit to the monthly UTIs caused by *Klebsiella* sensitive (top plots) and sensitive (bottom plots) to trimethoprim in elderly patients residing in LTCFs (left plots) and outside of LTCFs (right plots) in the West Midlands. The 95% confidence intervals are marked with dashed horizontal blue lines.

Similar patterns were observed when excluding the samples submitted by hospitals and focusing exclusively on the samples submitted by GPs (Figure A- 13, Figure A- 14 and Figure A- 15).

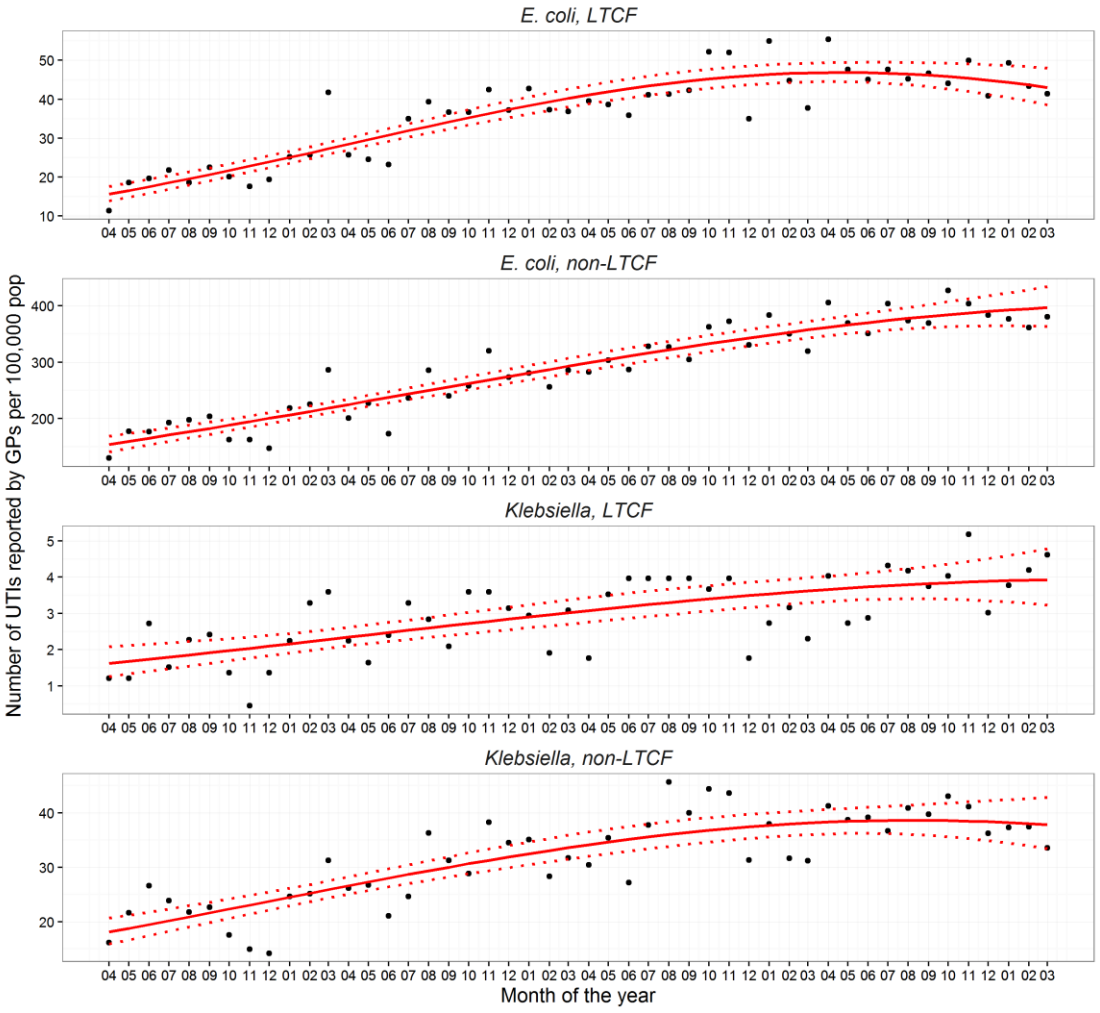

Figure A- 13. Monthly rate of UTIs caused by *E. coli* and *Klebsiella* in older people residing in and outside of long-term care facilities in the West Midlands reported by GPs. In red, the fitted predictions of the negative binomial polynomial regression model of degree two with offset.

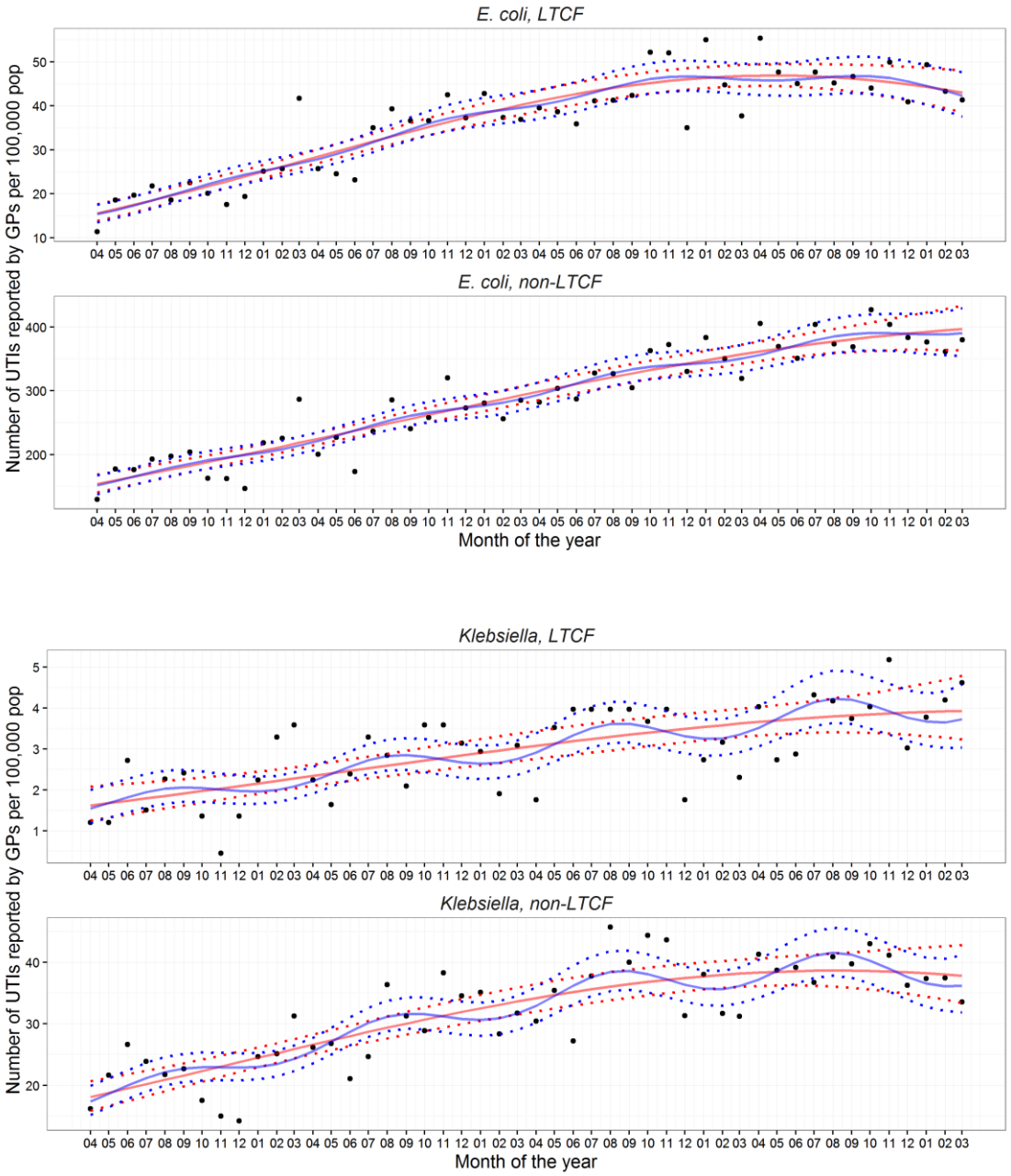

Figure A- 14. Seasonality in the monthly rate of UTIs caused by *E. coli* and *Klebsiella* in elderly patients residing in and outside of long-term care facilities in the West Midlands reported by GPs. In red, the fitted predictions of the negative binomial polynomial regression model of degree two with offset. In blue, the fitted predictions of the negative binomial polynomial regression model of degree two with offset and a seasonality component $f(x) = \cos\left(\frac{2\Pi x}{12}\right) + \sin(\frac{2\Pi x}{12})$.

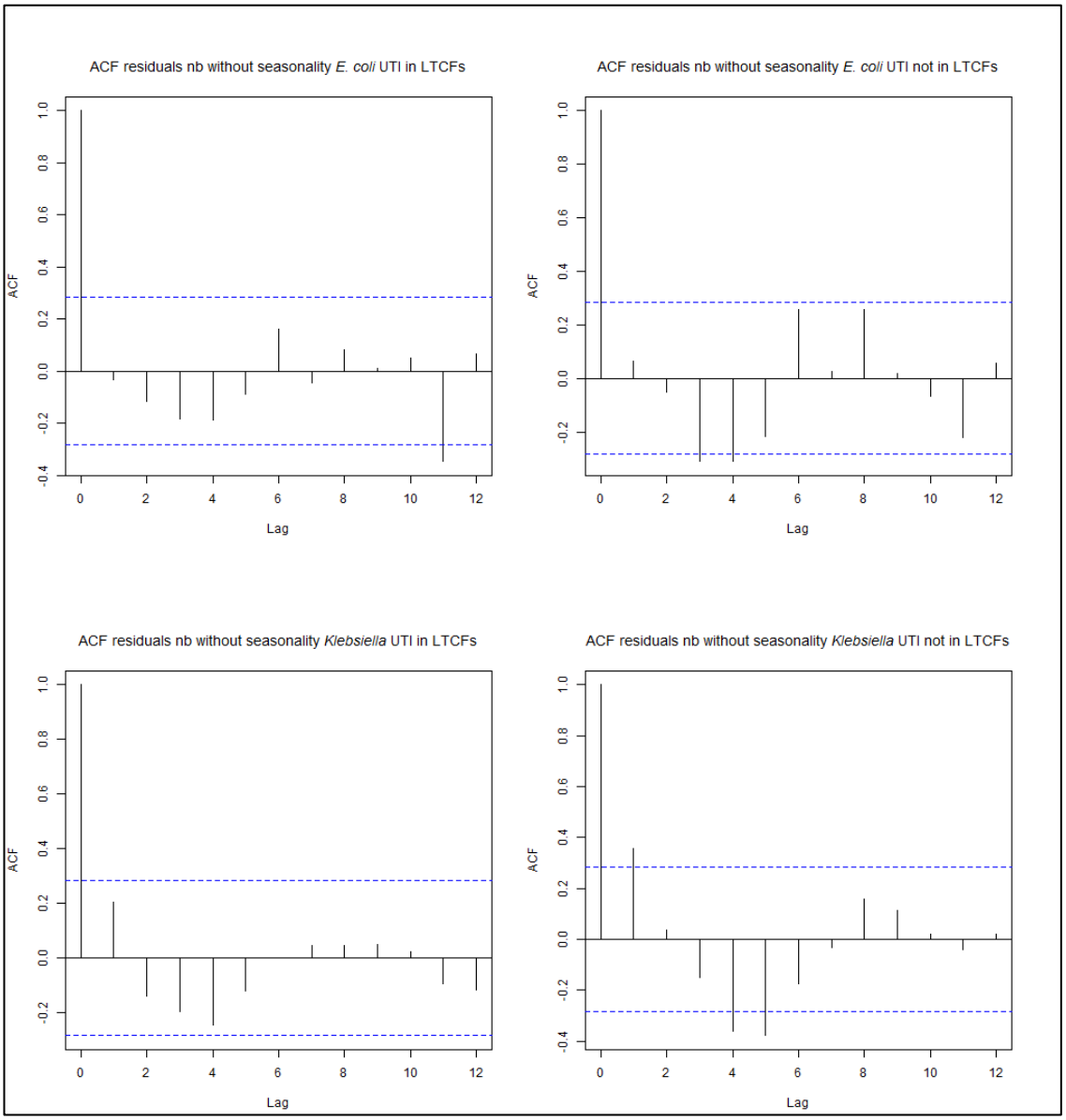

Figure A- 15. The autocorrelation function (ACF) for lags 0-12 of the residuals of the negative binomial regressions without seasonality fit to the monthly UTIs caused by *E. coli* (top plots) and *Klebsiella* (bottom plots) in elderly patients residing in LTCFs (left plots) and outside of LTCFs (right plots) in the West Midlands reported by GPs. The 95% confidence intervals are marked with dashed horizontal blue lines.

The monthly rate of UTIs caused by both *E. coli* and *Klebsiella* in older people in the West Midlands increased during the study period. There was no evidence for seasonality in *E. coli* UTIs; however, seasonality in UTIs caused by *Klebsiella* cannot be discarded due to the low monthly counts of these infections in the study population.

However, this could be due to biases in reporting. To this aim, these patterns were explored in a different dataset, the monthly trimethoprim and nitrofurantoin prescriptions in the West Midlands, which was only available for all ages.

Trend in trimethoprim and nitrofurantoin prescriptions (all ages)

A negative binomial model with offset and a second degree polynomial was fit to the monthly GP trimethoprim and nitrofurantoin prescriptions for all ages in the West Midlands, which were available for 44/48 months of this study. The offset in this regression was the all ages West Midlands population. Figure A-16 (below) shows that the rate of trimethoprim and nitrofurantoin prescriptions in the West Midlands increased by an average of:

$y = 0.0059 * 1.0084^{month} * 0.9999^{month^2} * 100{,}000$ per 100,000 individuals in the population.

This was determined using the equation of the regression model.

For example, this meant than in the first month of the study where prescription data was reported (August 2010), there were:

$y = 0.0059 * 1.0084^{1} * 0.9999^{1^2} * 100{,}000 = 594.9$ trimethoprim and nitrofurantoin prescriptions per 100,000 individuals in the population (~598.8, as fewer decimals are reported above than are estimated in the model).

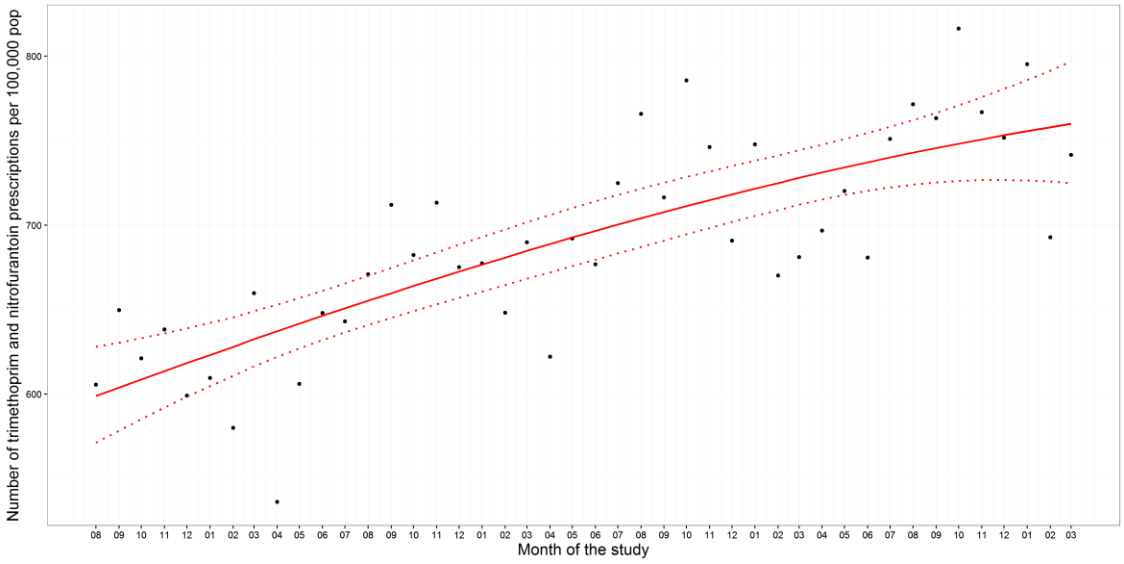

Figure A- 16. Increasing trend in the monthly rate of GP trimethoprim and nitrofurantoin prescriptions for all ages in the West Midlands from August 2010 to March 2014. In red, the fitted predictions of the negative binomial polynomial regression model of degree two with offset.

Seasonality of trimethoprim and nitrofurantoin prescriptions (all ages)

Adding a $f(x) = \cos\left(\frac{2\Pi x}{12}\right) + \sin(\frac{2\Pi x}{12})$ wave to the polynomial improved the fit of the regression model to the trimethoprim and nitrofurantoin prescription rates from an AIC of 808.8 to 781.1 (see Figure A- 17). The models with and without this seasonality term were significantly different as their confidence intervals did not overlap. Four waves were apparent with peaks in the autumn. Figure A- 18a and Figure A- 18b show the autocorrelation functions for the residuals of the regression models without and with seasonality (respectively) at lags of 0-12 months. The correlogram in Figure A- 18a had an oscillatory shape consistent with seasonality. There was a borderline significant positive correlation at a lag of two months and a strongly significant positive correlation at a lag of 12 months. There were also borderline significant negative correlations at four and six months and a significant negative correlation at five and seven months. After adding the seasonal term to the regression, the correlogram of the residual counts lost its oscillatory shape. There was a significant negative correlation at a lag of one month indicating large fluctuations and a borderline significant positive correlation at 12 months.

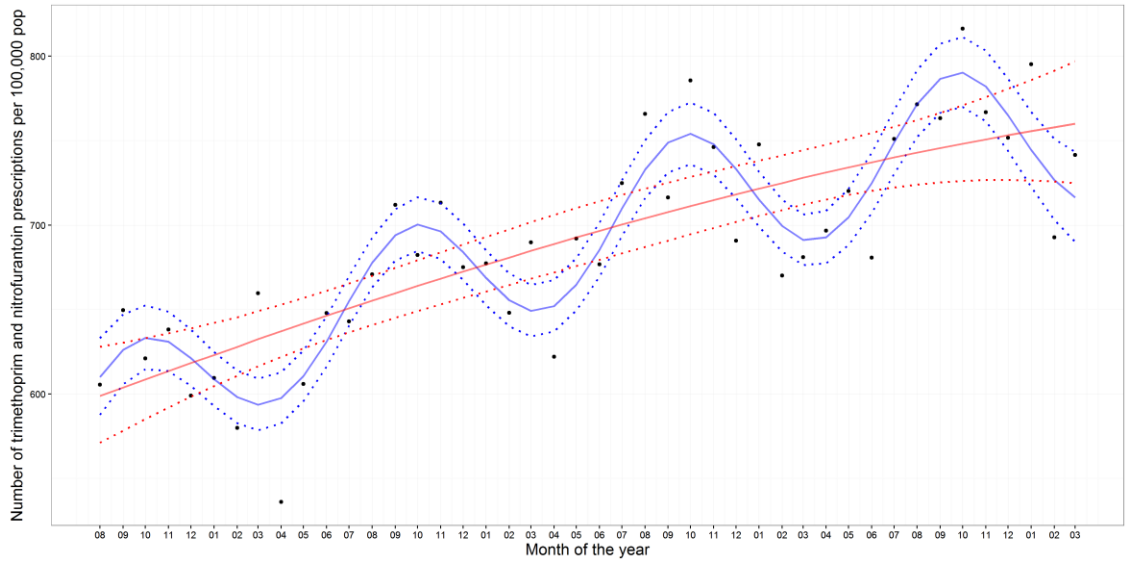

Figure A- 17. Seasonality in the monthly rate of GP trimethoprim and nitrofurantoin prescriptions for all ages in the West Midlands from August 2010 to March 2014. In red, the fitted predictions of the negative binomial polynomial regression model of degree two with offset. In blue the fitted predictions of the negative binomial polynomial regression model of degree two with offset and a seasonality component $\mathrm{f(x)} = \cos\left(\frac{2\Pi x}{12}\right) + \sin(\frac{2\Pi x}{12})$.

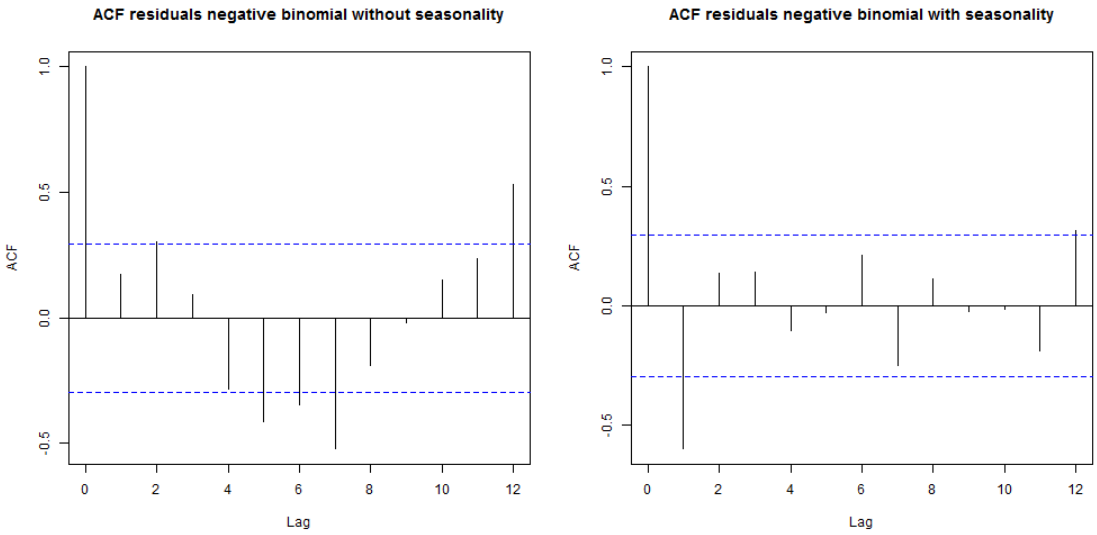

Figure A- 18. The autocorrelation function (ACF) for lags 0-12 of the residuals of the negative binomial regression without (5a) and with (5b) seasonality fit to the monthly GP trimethoprim and nitrofurantoin prescriptions for all ages in the West Midlands. The 95% confidence intervals are marked with dashed horizontal blue lines.

Discussion

AmSurv findings

The analysis of the AmSurv surveillance data showed that the rate of UTIs caused by *E. coli* and *Klebsiella* in older people living in the West Midlands increased dramatically from April 2010 to March 2014. The most rapid increase was seen in the rate of UTIs caused by *E. coli* in LTCFs, which tripled during the study period. The slowest increase was seen in the rate of UTIs caused by *Klebsiella* outside LTCFs, which doubled during the study. UTIs caused by *E. coli* and *Klebsiella* increased sharply from 2010 to 2013; however, in the last year of the study, UTIs increased at a much slower rate or even decreased slightly. UTIs caused by *E. coli* in LTCFs per 100,000 elderly in the West Midlands decreased from 61.46 in March 2013 to 59.37 in March 2014.

Whilst there is a clear lack of seasonality in UTIs caused by *E. coli* in older people during the study period, the oscillatory pattern observed for *Klebsiella* UTIs could be consistent with seasonality or with transmission. As, in addition, the monthly counts of *Klebsiella* UTI are low in this population, which decreased statistical power; the seasonality of *Klebsiella* UTIs cannot be discarded. The positive correlations at a lag of one month for *Klebsiella* UTIs in AmSurv are consistent with infectious disease transmission [311]. These correlations are not apparent in the correlograms for *E. coli* UTI, in agreement with the literature, which suggests that *E. coli* is less readily transmissible than *Klebsiella.* [255] This could be due to *E. coli* being ubiquitously present in the human gut whilst *Klebsiella* is not as often present.

The same trend and seasonality pattern was observed for UTIs caused by *E. coli* and *Klebsiella* that were resistant and susceptible to trimethoprim and for those UTIs that were reported only by GPs (vs. hospitals).

HSCIC findings

The Health & Social Care Information Centre all-ages GP trimethoprim and nitrofurantoin prescriptions in the West Midlands also increased during the study period, albeit at a slower rate.

These prescriptions were very markedly seasonal with yearly autumn peaks. Adding a seasonality component to the model significantly improved the model fit and the correlogram of the residuals of the negative binomial model that did not include seasonality showed an oscillatory shape consistent with seasonality which was not present in the model that included a seasonality component. There were no positive correlations at a lag of one month for trimethoprim and nitrofurantoin prescriptions.

Comparison between the two datasets and possible explanations

The increase in both datasets suggests there is a real increase in the rate of UTIs in older people in the West Midlands that was not driven by sampling. The clear autumn seasonality observed in the GP trimethoprim and nitrofurantoin prescriptions for all ages in the HSCIC dataset contrasts with the lack of clear seasonality in the UTIs caused by *E. coli* and (to a lesser extent) *Klebsiella* in older people in the AmSurv dataset. This suggests that:

1) UTIs are not seasonal in older people but are seasonal in the overall population, or
2) UTIs in older people are seasonal but the reporting of UTIs in AmSurv is not seasonal, or
3) UTIs caused by *E. coli* (76% of all urine samples reported in this age group) are not seasonal; however, UTIs caused by other bacteria (e.g. Proteus) are seasonal, or
4) Trimethoprim and nitrofurantoin are used to treat other infections which peak in the autumn, or
5) There is a seasonal pattern in the reporting of UTIs to AmSurv with a trough in autumn, or
6) A combination of the above

The first hypothesis would indicate that there are different dynamics of infection in the elderly population compared to younger age groups. Waning immunity in older people could make them more susceptible to these infections throughout the year. Older people are also less mobile and may not exhibit major lifestyle changes during the summer months. This contrasts with the younger age groups, which could exhibit greater behavioural changes according to the season (e.g. university and school terms).

The second hypothesis could be explained by a combination of seasonality in the less severe infections (treated by first-line antibiotics such as trimethoprim and nitrofurantoin), which are not sampled as frequently and therefore not registered in the AmSurv database, and a lack of seasonality in more severe infections (treated with more severe antibiotics such as ciprofloxacin or 3GCs), which would be reported to AmSurv.

The third hypothesis implies that UTIs caused by other organisms (e.g. UTIs caused by *Proteus*) are strongly seasonal. This hypothesis is not supported by the existing knowledge of UTIs and by the fact that most UTIs treated with trimethoprim and nitrofurantoin are caused by *E. coli*.

The fourth hypothesis is improbable because, although trimethoprim prescription is also indicated for acute and chronic bronchitis and pneumocystis pneumonia[312], which are known to be seasonal, these are conditions that usually peak in the winter months.[313] In addition, trimethoprim is primarily prescribed for UTI. Nitrofurantoin is not indicated for other infections.

Finally, the AmSurv dataset included only urines that were reported to laboratories for antibiotic susceptibility testing. However, other authors have proposed that large differences in reporting during the seasons are unlikely [224].

The two most plausible explanations are, therefore, the first two hypotheses.

Conclusion

Understanding the differences in seasonality observed requires the analysis of primary care electronic health records such as The Health Improvement Network (THIN) or the Clinical Practice Research Datalink (CPRD).

Appendix Chapter 6 PART B

Read codes for UTI

'K190300', 'K190400', '1AG..00', 'K190311', 'K190.11', '14D7.00', 'L166z11', 'L166800', 'K190.00', 'K190500', 'K190z00', 'K190000', 'K190100', 'K190200', 'K190600', 'K190X00', 'Q40y100', '1J4..00', '46U3.00', '4617.00', 'K190011', 'L166600',

'K15..00', 'K150.00', 'K15z.00', 'K152000', 'K154.00', 'K154000', 'K154300', 'K154400', 'K154600', 'K154800', 'K154z00', 'K15y.00', 'K15y200', 'K15y300', 'K15yz00', 'A32y300', 'K153.11', 'K151.00', 'K152y00', 'K152.00', 'K152z00', 'K155.00', '14D4.00',

'L166.11', 'L166500', 'K101.00', 'K101000', 'K101100', 'K101200', 'K101300', 'K101400', 'K101500', 'K101z00', 'K106.00', 'K100.00', 'K100000', 'K100100', 'K100200', 'K100300', 'K100400', 'K100500', 'K100600', 'K100z00', 'K10y000', 'A160200', 'K104.00',

'K10..00', 'K102.00', 'K102000', 'K102100', 'K102200', 'K102z00', 'K103.00', 'K105.00', 'K10y.00', 'K10y000', 'K10y100', 'K10y200', 'K10y300', 'K10y400', 'K10yz00','K10z.00', 'K10..11'.

Appendix Chapter 7

The weekly incidence of resistant urine *E. coli* samples submitted to AmSurv for each LTCF by incidence quartile is shown in Figure A- 19, Figure A- 20, Figure A- 21 and Figure A- 22.

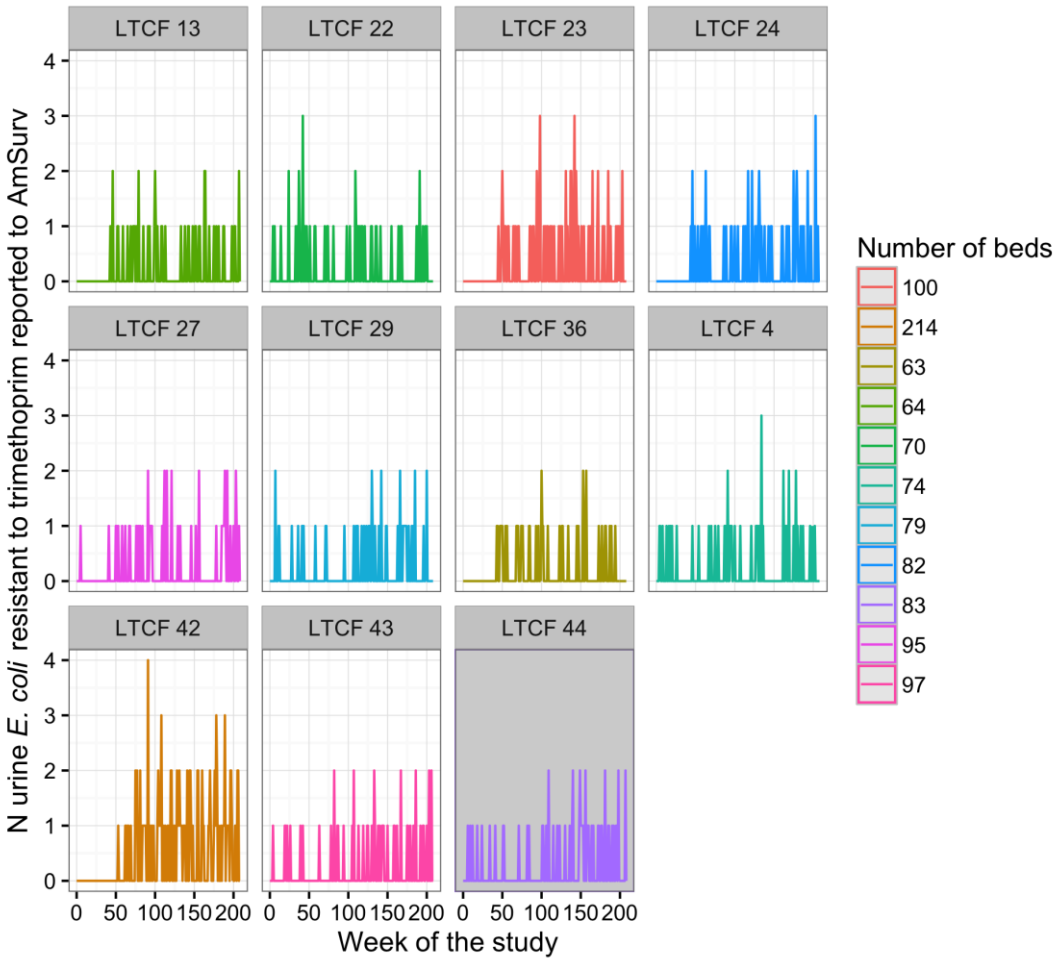

Figure A- 19. The weekly incidence of resistant urine *E. coli* samples submitted to AmSurv for each of the LTCFs in the highest incidence quartile. The LTCF selected for simulation is highlighted in grey.

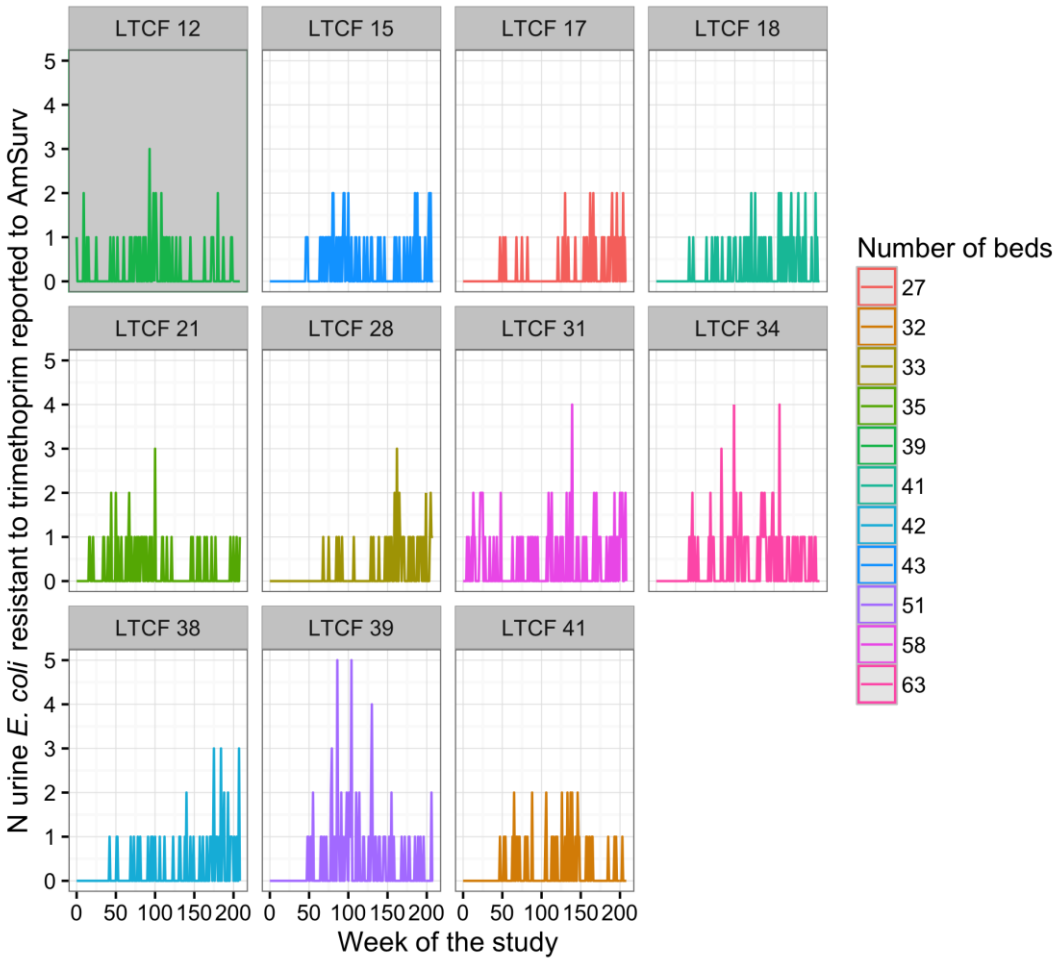

Figure A- 20. The weekly incidence of resistant urine *E. coli* samples submitted to AmSurv for each of the LTCFs in the second highest incidence quartile. The LTCF selected for simulation is highlighted in grey.

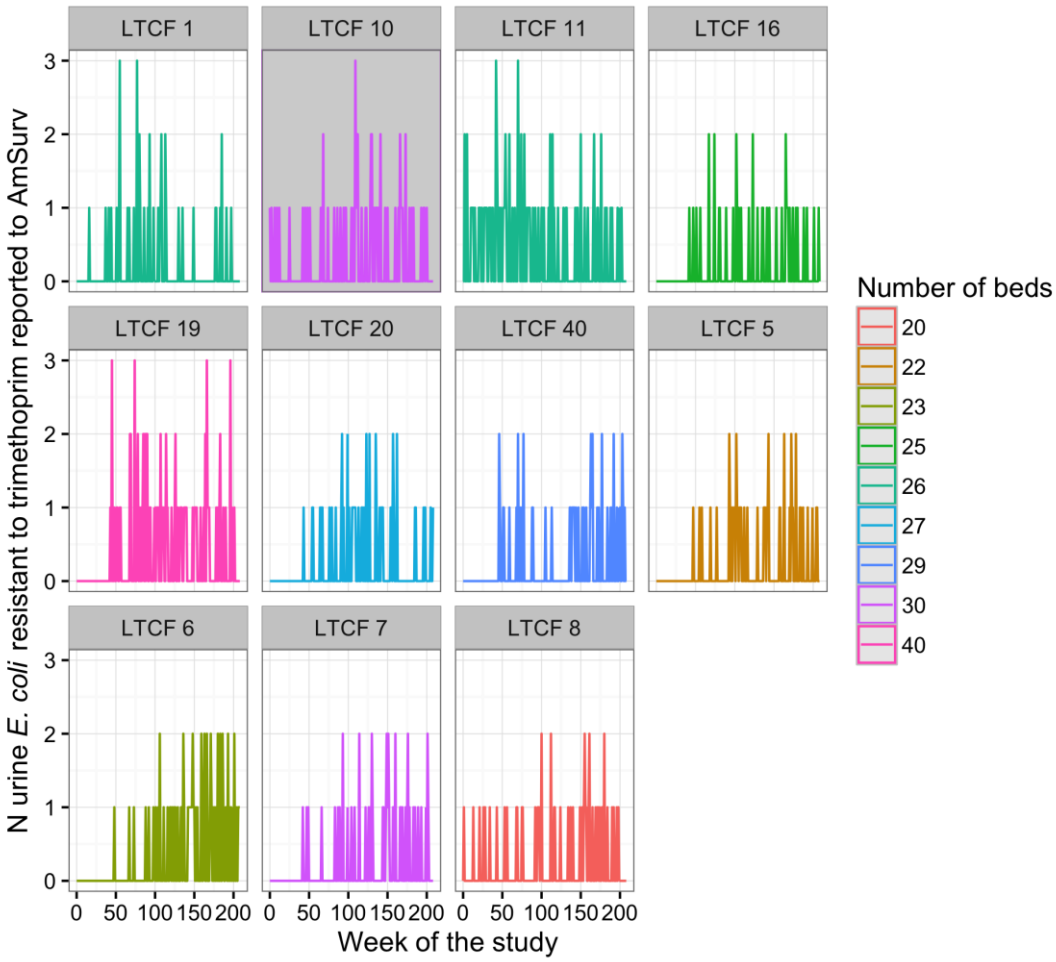

Figure A- 21. The weekly incidence of resistant urine *E. coli* samples submitted to AmSurv for each of the LTCFs in the second lowest incidence quartile. The LTCF selected for simulation is highlighted in grey.

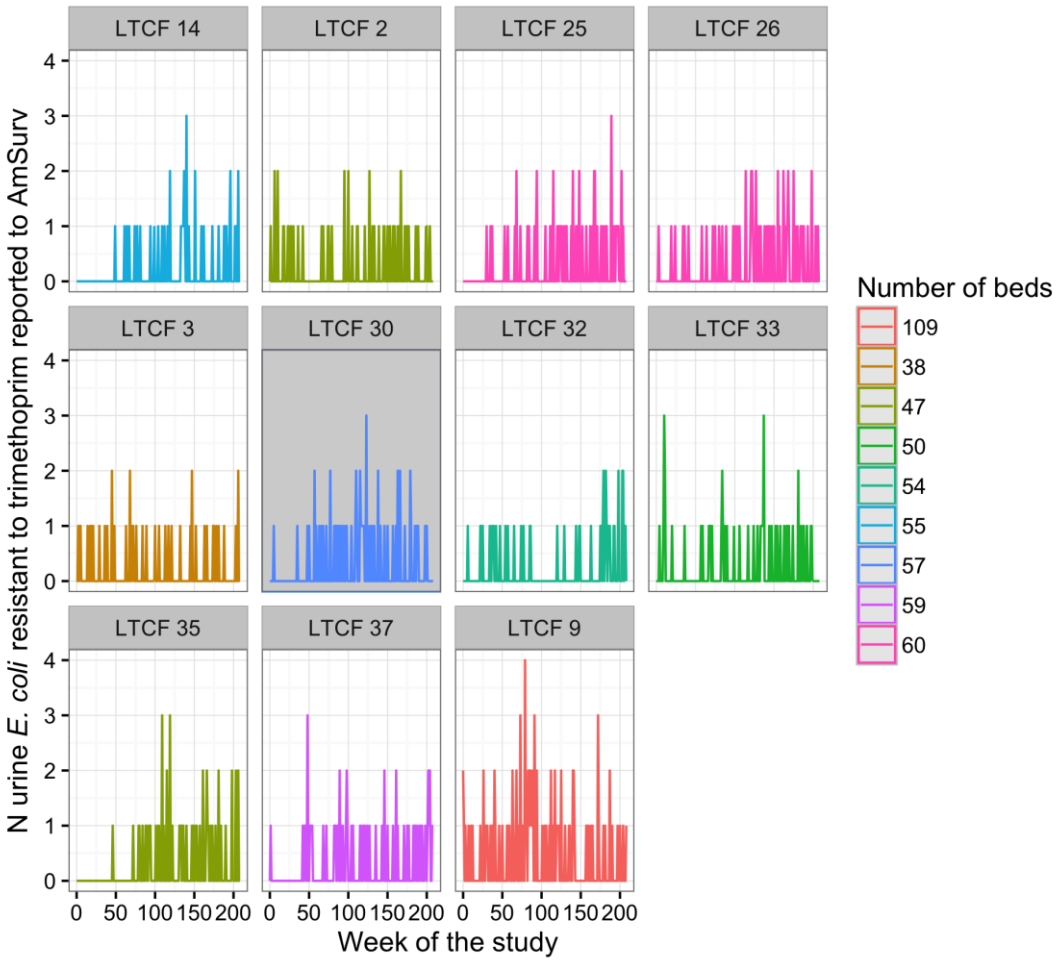

Figure A- 22. The weekly incidence of resistant urine *E. coli* samples submitted to AmSurv for each of the LTCFs in the lowest incidence quartile. The LTCF selected for simulation is highlighted in grey.

The number of entries and exits to each of the LTCF compartments are shown in Figure A- 23, Figure A- 24, Figure A- 25 and Figure A- 26. The deterministic model predicted every week 0.17 individuals were discharged from the 30-bed LTCF to hospital colonised by *E. coli* resistant to trimethoprim. Of all individuals discharged from the LTCF to hospital, 49.52% were colonised with resistant strains (vs. susceptible strains). Every week, 0.096 individuals were admitted into the LTCF from hospital. Of all individuals admitted into the LTCF from hospital, 37.92% were colonised with resistant strains (vs. susceptible strains).

The median number of patients colonised by *E. coli* resistant to trimethoprim admitted to hospital to the LTCF and discharged to the LTCF from hospital weekly in the stochastic model were both zero (95^{th} percentiles= 0-2 or 0-1 for both, depending on the week of the study). The mean number of admissions per week to the LTCF from hospital ranged from 0.19 to 0.31 and the mean number of discharges from the LTCF to hospital ranged from 0.29 to 0.39).

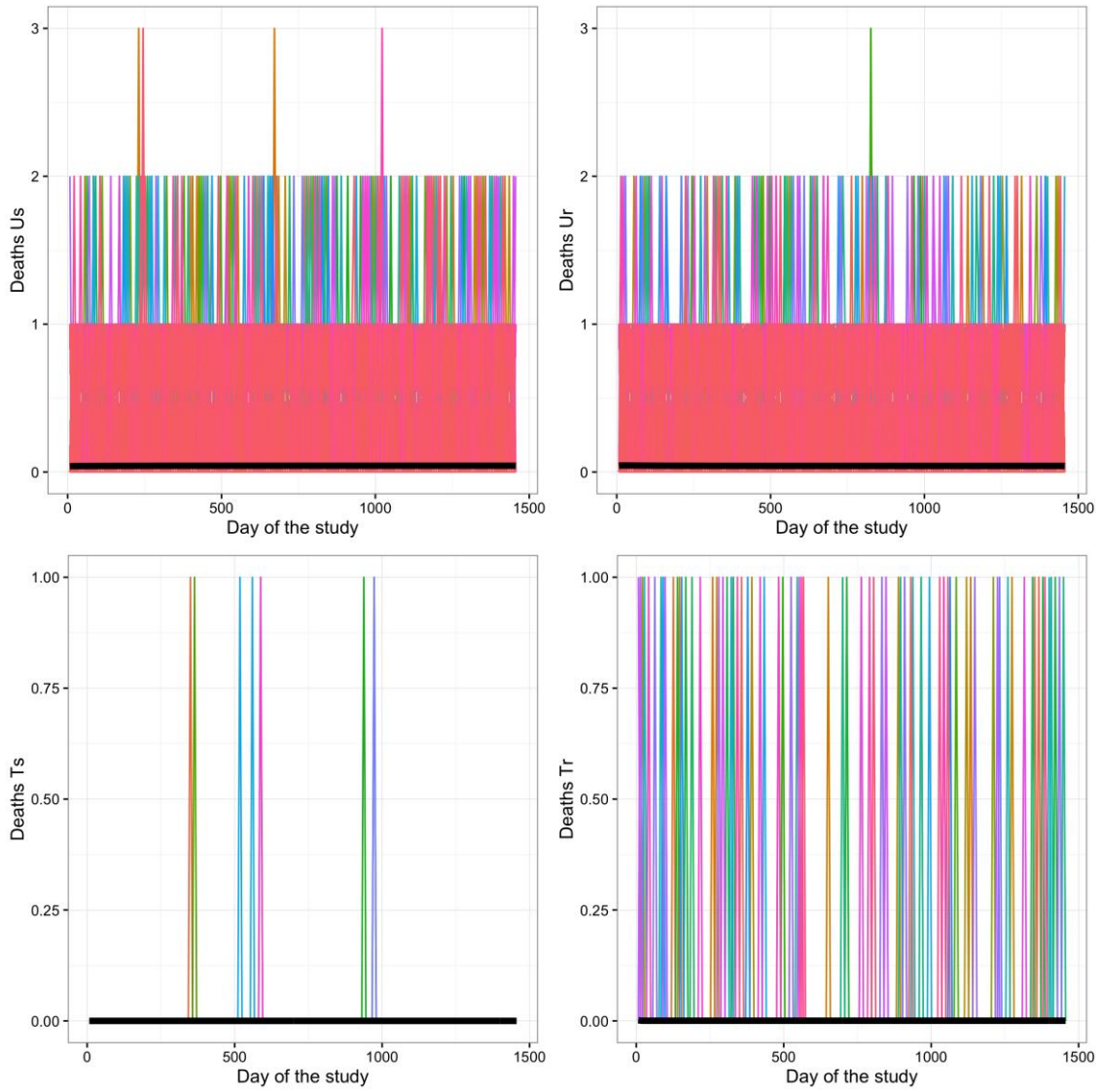

Figure A- 23. Number of deaths from each of the four compartments of the model by week of the study period. Us were individuals untreated with trimethoprim colonised with *E. coli* susceptible to trimethoprim, Ur were individuals untreated with trimethoprim colonised with *E. coli* resistant to trimethoprim, Ts were individuals treated with trimethoprim colonised with *E. coli* susceptible to trimethoprim and Tr were individuals treated with trimethoprim colonised with *E. coli* resistant to trimethoprim. The coloured lines represent the output of 1,000 stochastic simulations. The black line represents the output from the deterministic model.

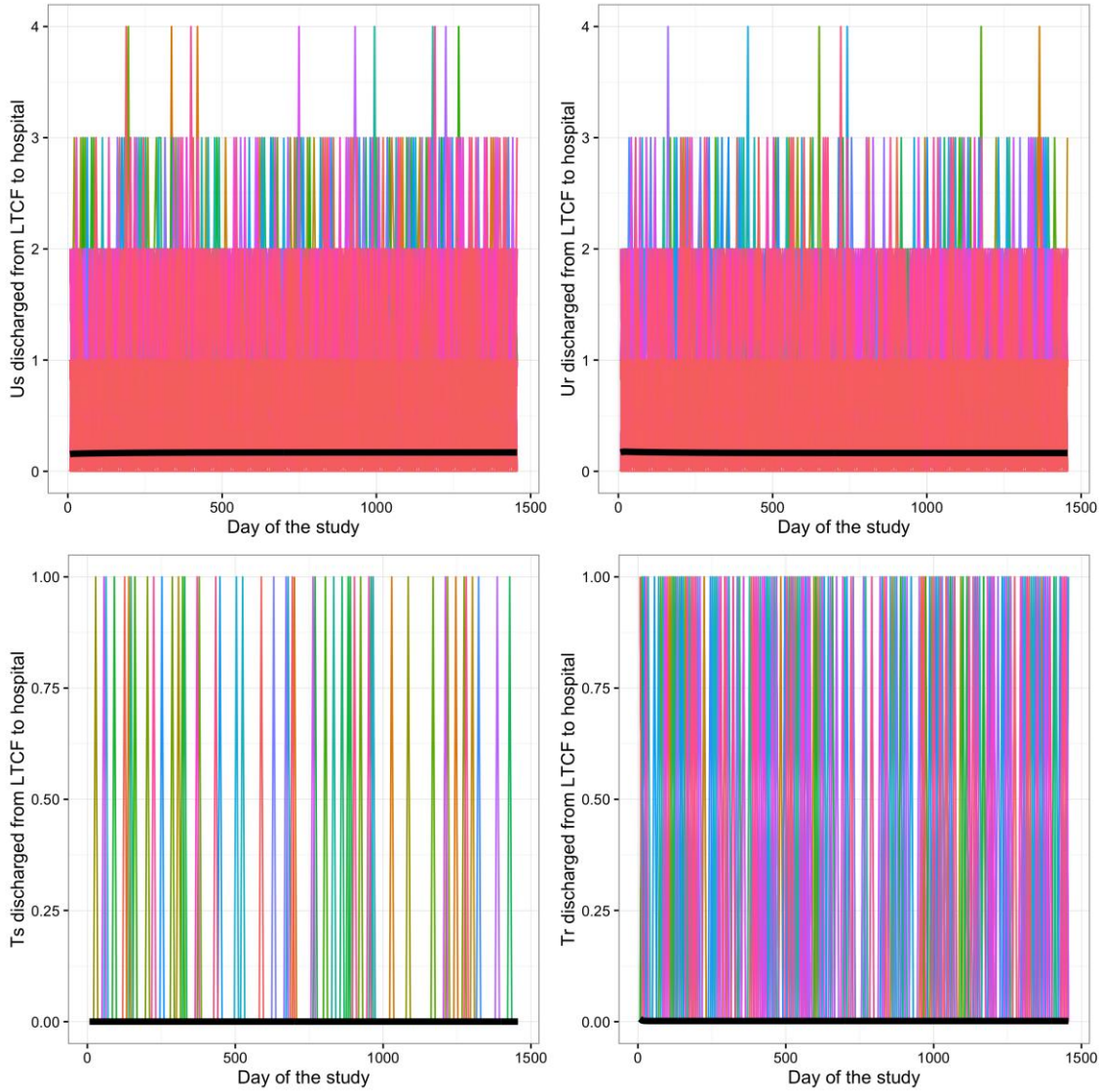

Figure A- 24. Number of individuals discharged from the LTCF to hospital from each of the four compartments in the model by week of the study period. Us were individuals untreated with trimethoprim colonised with *E. coli* susceptible to trimethoprim, Ur were individuals untreated with trimethoprim colonised with *E. coli* resistant to trimethoprim, Ts were individuals treated with trimethoprim colonised with *E. coli* susceptible to trimethoprim and Tr were individuals treated with trimethoprim colonised with *E. coli* resistant to trimethoprim. The coloured lines represent the output of 1,000 stochastic simulations. The black line represents the output from the deterministic model.

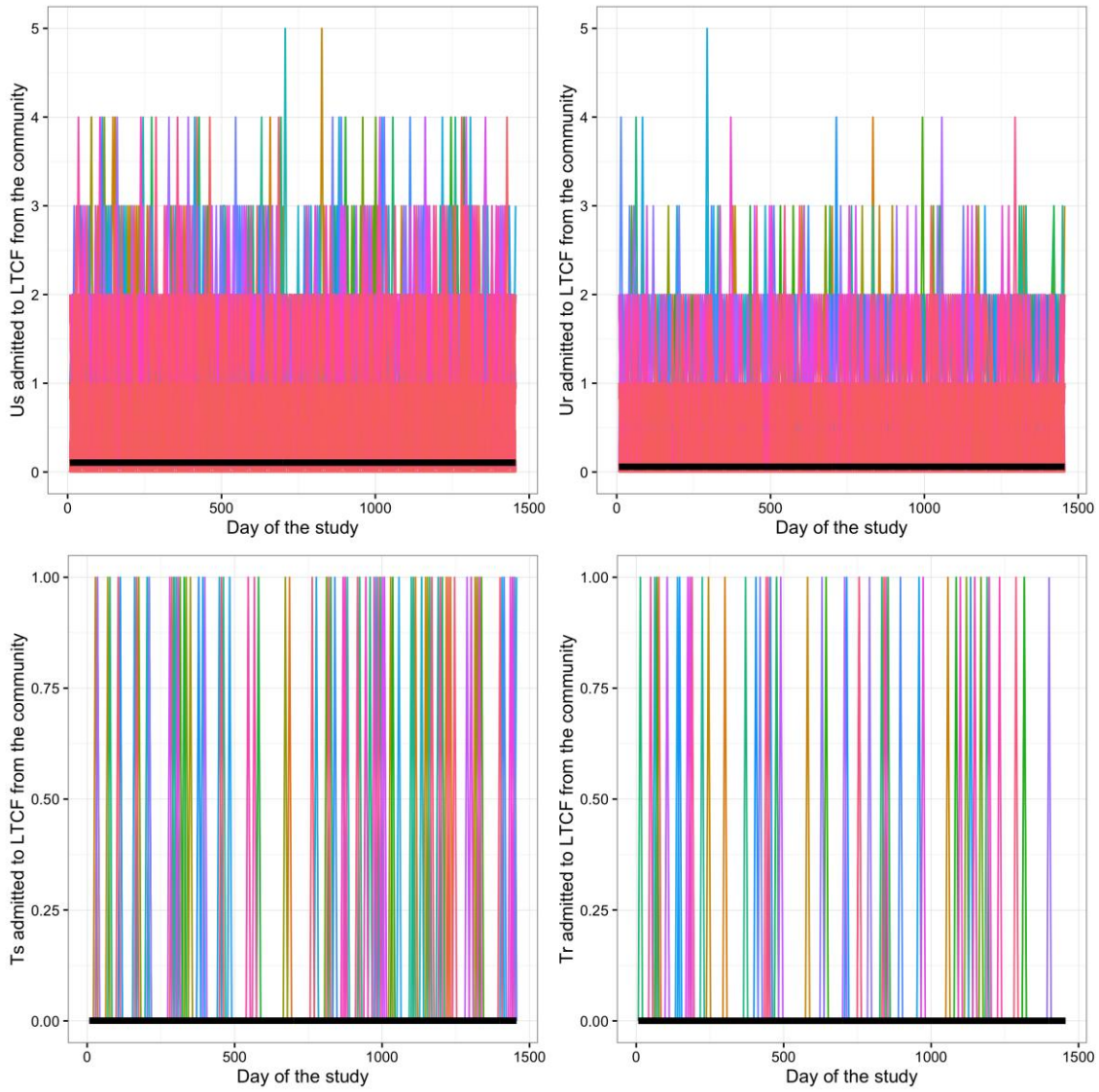

Figure A- 25. Number of individuals admitted to the LTCF from the community into each of the four model compartments by week of the study period. Us were individuals untreated with trimethoprim colonised with *E. coli* susceptible to trimethoprim, Ur were individuals untreated with trimethoprim colonised with *E. coli* resistant to trimethoprim, Ts were individuals treated with trimethoprim colonised with *E. coli* susceptible to trimethoprim and Tr were individuals treated with trimethoprim colonised with *E. coli* resistant to trimethoprim. The coloured lines represent the output of 1,000 stochastic simulations. The black line represents the output from the deterministic model.

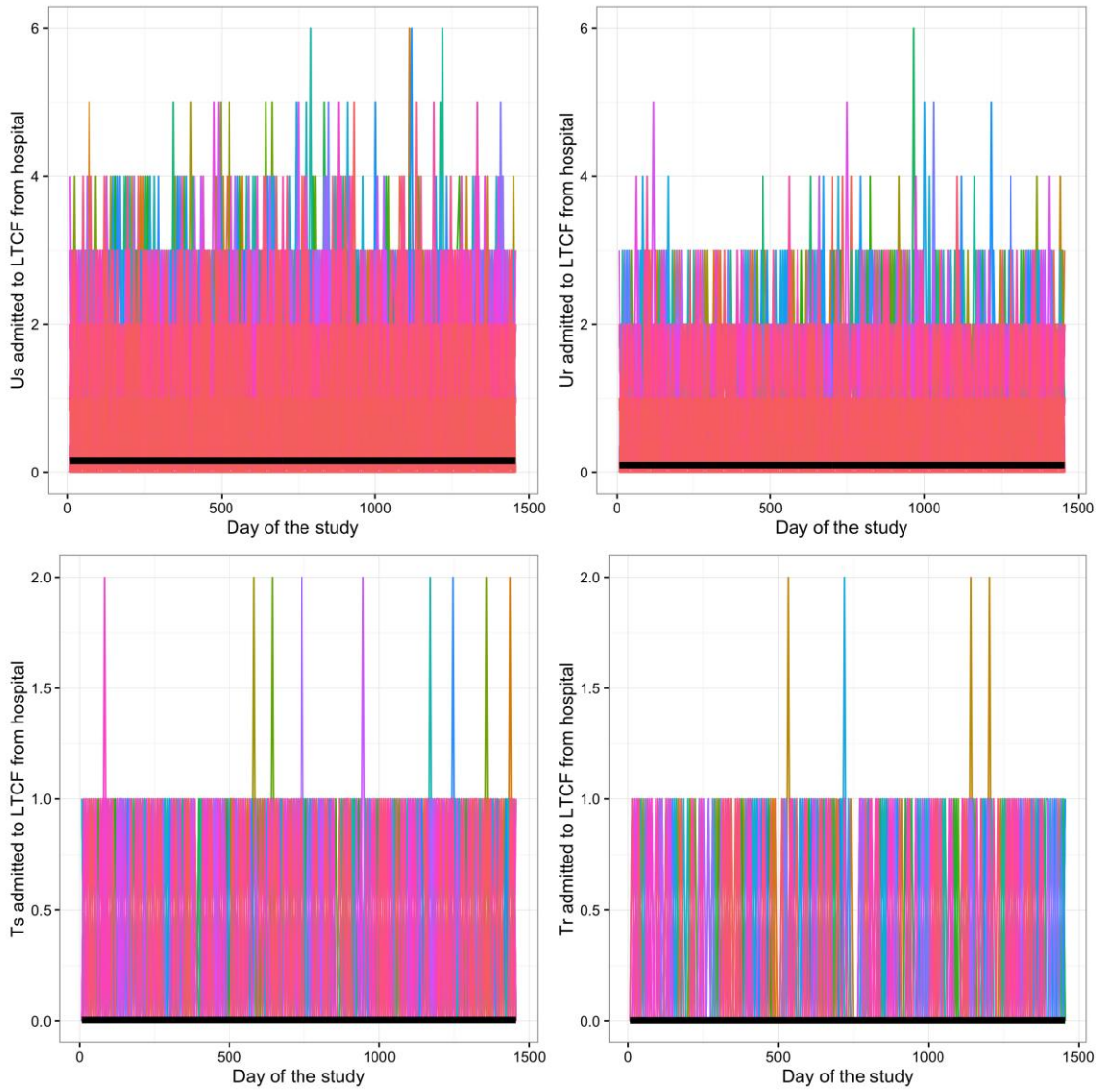

Figure A- 26. Number of individuals admitted to the LTCF from hosital into each of the four model compartments by week of the study period. Us were individuals untreated with trimethoprim colonised with *E. coli* susceptible to trimethoprim, Ur were individuals untreated with trimethoprim colonised with *E. coli* resistant to trimethoprim, Ts were individuals treated with trimethoprim colonised with *E. coli* susceptible to trimethoprim and Tr were individuals treated with trimethoprim colonised with *E. coli* resistant to trimethoprim. The coloured lines represent the output of 1,000 stochastic simulations. The black line represents the output from the deterministic model.