School of Pharmacy and Biomedical Sciences

Antibiotic Stewardship in Residential Aged Care Facilities

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Declaration

To the best of my knowledge and belief, this thesis contains no material previously published by any other person except where due acknowledgment has been made. This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

The research presented and reported in this thesis was conducted in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007) – updated March 2014. The proposed research study received human research ethics approval from the Curtin University Human Research Ethics Committee (EC00262), Approval Number: HR26/2016, HRE2018-0610

Signature:

Date:

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List of abbreviations

AACQA	Australian Aged Care Quality Agency
ACEI	Angiotensin Converting Enzyme Inhibitor
ADEs	Adverse Drug Events
aHR	Adjusted Hazard Ratio
aOR	Adjusted Odds Ratio
AMS	Antimicrobial Stewardship
AIIRA	Angiotensin II Receptor Antagonist
CI	Confidence Interval
CYP	Cytochrome P450
CYP3A4	Cytochrome P450 3A4
DAA	Dosage Administration Aid
DDIs	Drug-Drug Interactions
ESBL	Extended Spectrum Beta- Lactamase
GFR	Glomerular Filtration Rate
GPs	General Practitioners
HR	Hazard Ratio
INR	International Normalised Ratio
IRR	Incidence Rate Ratio
LRTI	Lower Respiratory Tract Infection
MCQs	Multiple-Choice Questions
MDR	Multi Drug Resistant
NPs	Nurse Practitioners
NRMC	National Residential Medication Chart

OR	Odds Ratio
PDDIs	Potential Drug-Drug Interactions
P-gP	P-Glycoprotein
PIM	Potentially Inappropriate Medication
PPIs	Proton Pump Inhibitors
QUM	Quality Use of Medicines
RACF	Residential Aged Care Facilities
RR	Relative Risk
RTI	Respiratory Tract Infection
SD	Standard Deviation
SSTI	Skin and Soft Tissue Infection
TCA	Tricyclic Antidepressants
TdP	Torsade de Pointes
UI	Urinary Incontinence
UK	United Kingdom
UTI	Urinary Tract Infection
URTI	Upper Respiratory Tract Infection
WA	Western Australia

Glossary

Antibiotic	A medicinal agent that kills or prevents the growth of bacteria.
Antimicrobial	Used broadly to refer to any agent used to treat or inhibit infections caused by microorganisms (bacteria, viruses, fungi, and parasites). This term covers antibiotics, antifungals, antivirals and antiparasitic agents.
Data custodian	Organisation with overall responsibility for the data.
Resident' vs 'Patient' vs 'Individual'	Used interchangeably; individuals who are residing in an aged care facility.
Third level category	A third heading level of a therapeutic chapter in AMH, such as Anti-infectives is the first heading, antibacterial is a second heading under anti-infectives, and then each category of anti-infectives such as macrolides, aminoglycosides are third-level categories.

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Abstract

Background: Residents of aged care facilities are susceptible to infections for a variety of reasons, and hence are high consumers of antibiotics. They also live with multiple chronic diseases and use multiple medications. Taking multiple medications for complex multiple conditions further increases the risk of infection and antibiotic-related drug interactions. Although there is ample evidence of drug-associated infections in the elderly, available antimicrobial stewardship initiatives focus on appropriate selection and use of antimicrobial agents, taking into consideration the infection, prescribing formulary, and current prescribing guidelines. Research related to drugs that increase the risk of infections, thus resulting in increased prescribing of antibiotics, and interactions between these antibiotics and chronic medications of the residents, is lacking.

Aim and objectives: This study aimed to reduce the risk of antibiotic-related medication misadventure in residents of aged care facilities. The specific objectives were to: determine the prevalence of use of medicines that potentially contribute to the infection burden amongst residents of aged care facilities; assess the risk of drug interactions associated with co-prescribing of antibiotics and other medicines for residents of aged care facilities; develop an educational intervention, based on findings from Objectives 1 and 2 and supported by current literature for healthcare professionals providing care to residents of aged care facilities, aimed at minimising drug misadventure related to infectious diseases; and implement and evaluate the educational intervention.

Hypotheses: This research was based on three null hypotheses: residents' chronic medications do not contribute to increased risk of infection and antibiotic use in aged care facilities; the prescribing of antibiotics in RACFs presents a minimal risk of (serious) drug interactions; and a tailored education intervention will not influence the use of antibiotics in RACFs.

Method: The research involved analysis of data from two sources: individual residents' electronic medical records from The Bethanie Group Inc. ('Bethanie') aged care facilities in Western Australia; and dispensing data from Webstercare®. To determine the association between medication use and infection risk in elderly nursing home residents, a retrospective case-control study was conducted using Bethanie data. Cases (n=375 residents) were all residents who had at least one infection in 2015; controls (n=351 residents) were those who had no infection in 2015. Further regression analysis was conducted by utilising the Webstercare dataset to determine the association between antibiotic prescriptions and the use of medicines identified in the Bethanie analysis as a risk medicine for infection. The analysis was also undertaken in the Bethanie dataset to determine the prevalence of potential interactions between the antibiotics prescribed and residents' chronic medications. Pilot implementation of an educational program for nurses about the risk of medication associated infections and antibiotic-drug interactions was deployed through the Bethanie continuing education platform. Stages of development of the intervention included rounds of content review internally and with Bethanie educational staff as end-users, and consultation with Bethanie staff regarding the intervention design and deployment.

Results: This analysis found that the use of benzodiazepines (odds ratio (OR): 1.78, 95% confidence interval (CI): 1.1-2.7), other antiepileptics (pregabalin, valproate, carbamazepine, lamotrigine, gabapentin, phenytoin, levetiracetam, lacosamide, levetiracetam) (OR: 1.62, 95%CI: 1.0-2.5), other antidepressants (mirtazapine, moclobemide, agomelatine) (OR: 2.21, 95%CI: 1.3-3.5) and tricyclic antidepressants (OR: 2.98, 95%CI: 1.6-5.5) were independently associated with a significant increase in the risk of infection ($p<0.05$).

Further regression analysis utilising Webstercare data of 4,332 residents (with 188,394 dispensed histories from May 2001 to March 2016) revealed that exposure to proton pump inhibitors, other antiepileptics, other antidepressants (mirtazapine, moclobemide, agomelatine), tricyclic antidepressants, benzodiazepines, and beta-blockers were independently associated with an increased the prescription of antibiotics ($p<0.05$). The highest likelihood of increasing antibiotic use was observed within seven days after initiating the PPIs (OR: 27.7, 95% CI: 6.6-116.2, $p<0.05$), benzodiazepines (OR: 16.2, 95% CI: 3.7-69.8, $p<0.05$), other antidepressants (OR: 23.8, 95% CI: 3.0-185.0) and other antiepileptics (OR:11.6, 95% CI: 1.4-93.1).

Risks associated with co-prescribing of antibiotics and other medicines in the Bethanie data revealed that 64 of the 351 residents who had an infection were prescribed an antibiotic that could potentially interact with medicines they were already taking. These 64 residents had a total of 96 potential drug interactions between antibiotics and co-prescribed medication. The most frequent antibiotics involved in the potential drug-drug interactions (PDDI) were macrolides (29/96 PDDIs) and trimethoprim (26/96 PDDIs).

These findings highlighted the need to educate aged care staff members about the risk of infection from the use of particular medicines, as well as potential interactions between antibiotics and other medicines. Pilot implementation of the educational intervention, successfully deployed through the Bethanie continuing education platform, provided preliminary results and feedback from nursing staff, demonstrating generally positive engagement and feedback.

Conclusion: The current study provides evidence that residents' chronic medications can contribute to increased risk of infection and antibiotic use in aged care facilities. The prescribing of antibiotics within RACFs was not considered theoretically safe. This study also suggests that online education for nurses on medicine-associated infections and antibiotic-related drug interactions is useful for their practice.

The outcomes of this research suggest the need to expand the scope of antimicrobial stewardship in RACFs by addressing two issues of medication misadventure, namely, the potential medication-associated infection that may lead to the increased use of antibiotics, and antibiotic-related drug interactions that may contribute to increased adverse drug reactions. This is the first-known investigation to explore these facets of antimicrobial stewardship and adds to an increasingly important body of knowledge that will improve the care of vulnerable elderly in RACFs.

Further research is recommended to evaluate the effectiveness of educational interventions targeting nurses versus other health professionals. Further research has been suggested to confirm this finding in terms of how the PDDIs had manifested clinically in this cohort. Future research is also required to evaluate and adopt appropriate deprescribing strategies in aged care facilities to reduce the overprescribing of medicines that are associated with infections and lead to over-prescribing of antibiotics.

Chapter 1 Introduction

The population of Australia aged 65 years and over is expected to increase from 2.6 million in 2004 to 6.5 million by 2051.[1] It is anticipated that by 2031, 6% of those aged 65 years and 30% of those aged 85 years will live in Residential Aged Care Facilities (RACFs), and this demand will continue to rise.[2] RACFs in Australia can be broadly divided into high-level care (nursing homes) and low-level care (hostels).[3, 4] Nursing homes provide 24-hour nursing care and related medical and/or psychosocial services for a population with a high degree of dependency and a high burden of illness.[4] Hostels, on the other hand, allow residents to live more independently without intensive nursing care, while still receiving assistance with personal care and accommodation support.[4]

Elderly people living in RACFs are vulnerable to infection due to factors such as multiple chronic diseases, use of medicines that may increase the risk of infection, age-related physiological changes, decline in immunological function, and their institutionalisation.[5, 6] Taking multiple medications for complex multiple conditions further increases the risk of adverse drug events.[7] Such institutions are also becoming a reservoir for multidrug-resistant (MDR) organisms due to the irrational use of broad-spectrum antibiotics.[5] To reduce the emergence of multidrug-resistant organisms, antimicrobial stewardship programs have been implemented to enhance the appropriate use of antibiotics in this population.[5]

Residents of RACFs are among the highest medication consumers, but research specific to this setting is minimal.[7] Only 2% of research studies are related to aged care residents as a subset of the overall elderly population.[7, 8] RACF-specific research is needed in medication use due to the unique institutionalised structure of RACFs compared to community-dwelling health consumers, as well as the relative frailty of aged care residents.[7] Therefore, adopting clinical evidence from community settings, where residents are more robust and independent, may be inappropriate.[7]

The following section discusses the bodily changes with ageing. Risk factors for infection, as a result of these bodily changes, are discussed later.

1.1 Anatomical, physiological and immunological changes in the elderly

1.1.1 Anatomical changes

In the elderly, myocytes are lost from the myocardium, with consequent hypertrophy of the remaining cells.[9] Loss of myocytes also leads to the formation of collagen from fibroblasts, which results in a stiffer ventricle.[10] The cardiac conduction system[11] and valvular apparatus[12] also undergo changes with ageing. Development of fibrosis, fatty infiltration, and loss of pacemaker cells occur in the sinoatrial node with ageing.[10] In conjunction with atrial amyloid deposits and calcification, these changes in the conduction system may predispose an elderly person to rhythm disturbances.[10]

Several changes occur in the respiratory system with age. Structural deformities in the chest wall and thoracic spine diminish respiratory compliance, leading to increased effort in breathing.[13] Dilation of airspaces occur due to the loss of supporting structure of the lung parenchyma, which leads to the decreased static elastic recoil of the lung and increased residual volume and functional residual capacity.[14] Clearance of airway secretions and ventilation can be impaired due to the decrease of strength of respiratory muscle.[15]

Kidney mass decreases gradually with age, and the reduction is much prominent in the renal cortex than in the medulla.[16, 17] In elderly subjects, the total number of glomeruli diminishes in each kidney.[18] Hyalinisation of the vascular tuft reduces the blood flow in the afferent arterioles in the cortex.[17] Renal plasma flow is also reduced in the elderly.[17] Glomerular filtration rate (GFR) declines without a concomitant increase in serum creatinine.[17] In the elderly, bladder capacity can also change and may lead to urinary incontinence (UI) or urinary retention.[18]

Gastric secretion of hydrochloric acid and pepsin decrease with age under basal conditions, due to changes in enzyme-secreting cells and organs and alterations in hormonal and neuronal activity.[17] The colon becomes hypotonic, which leads to increased storage capacity, longer stool transit time, and greater stool dehydration.[18] Sphincter control is reduced with age, due to the loss of tone of the external rectal sphincter, which leads to faecal incontinence.[18]

In elderly people, the size of the liver and blood flow to the liver are reduced,[19] the endoplasmic reticulum is diminished, the hepatic extracellular space is increased and bile flow is decreased.[17]

1.1.2 Physiological changes in the elderly

In the elderly, gastrointestinal acid secretion and blood flow are reduced.[20] The surface area of the gut epithelium is decreased.[20] Gastrointestinal motility can be retarded in the elderly, which affects gastric emptying.[20]

Water and fat content of the body change with advancing age. In the elderly, body fat tends to increase, and lean body mass tends to decrease, along with total body water.[21] In the elderly, plasma albumin level decreases.[20] In contrast to albumin, the level of alpha-1 acid glycoprotein (AAG) is frequently increased in old age due to age-associated inflammatory diseases.[20]

Hepatic metabolism alters with age, in line with functional and structural changes in the liver (see above). Decreased hepatic blood flow and the size of the liver may impair the cytochrome P450-mediated phase I reactions to a great extent than the phase II conjugation reactions of hepatic clearance.[22] For example, a 20% decrease in the metabolism of cytochrome P450 2D6 substrates has been reported.[23]

Renal function declines with advancing age due to a decrease in kidney mass, GFR, tubular secretion, and renal blood flow.[16, 24] The decrease in GFR is considered the most significant age-related change in pharmacokinetics in the elderly.[20]

1.1.3 Immunological changes

Advanced age is not only associated with the decline in anatomical or physiological functions but is also associated with a decline in immunological function. This deterioration in age-related immune function is collectively known as immunosenescence.[25] Humoral, cellular, and innate immunity change with age.[26] The principal changes in cellular immunity due to ageing involve a decrease in T-cell function, such as a decrease in T-cell lymphopoiesis, the proportion of naïve T cells, and signal transduction.[26] The decline in T-cell function is considered a result of thymic involution.[26] Modifications in humoral immunity due to ageing include a decline in the number of B-cells,[27] decline in immunoglobulin production,[25] production of lower affinity antibodies,[25] and defect in B-cell receptor signaling.[25] The changes in innate immunity in the elderly include decreased functional ability, with the diminished cytotoxic activity of Natural Killer cells;[28] decline in phagocytic activity of macrophages;[29, 30] increase in production of proinflammatory cytokines by mononuclear cells; and functional alteration in neutrophils.[26]

1.2 Risk factors for infection in RACFs

This section discusses the different risk factors for infections in the elderly in RACFs, as well as how anatomical, physiological, and immunological changes predispose an older person to infection. Residents of aged care facilities are susceptible to infections for a variety of reasons, including age-related changes in physiological functions, comorbidities, functional disabilities, immunosenescence (age-related decline of the immune system), and the use of invasive devices (e.g. urinary tract catheterisation).[31] Residents live in a communal environment and have close interaction with potentially infected or colonised residents and/or staff.[31]

Epithelia from the skin, bladder, the bronchi, and the digestive system form a physical barrier to infection, and thereby play a key part in preventing bacteria from invading the human body.[32] Efficient removal of bacteria from apparently sterile body compartments is crucial for the prevention of infection.[32] Examples are mucociliary clearance from the lungs and rapid urine flow from the bladder.[32] Valve-like mechanisms, such as larynx closure during swallowing, also contribute to the exclusion of bacteria from sterile compartments.[32] High acidity in the stomach protects not only the small bowel from pathogens, but also decreases the risk of lung colonisation resulting in reflux.[33] Older people, in general, have a less cardiac reserve, stiffer lungs, diminished clearance mechanisms for pulmonary secretions,

incomplete emptying of their bladders, decreased gastric acidity, poor wound healing, and some degree of renal dysfunction, and therefore are at greater risk of infection.[34]

With increasing age, there is increased interstitial fibrosis in the myocardium, which causes myocardial stiffness.[18] Consequently, in older adults, cardiac output decreases by 50% compared to younger adults.[18] Degenerative calcification occurs in the aortic valve with increasing age.[35] This calcification causes functional stenosis of the valve leading to limited mobility of its cusps.[35] The resulting turbulence predisposes elderly patients to infective endocarditis (IE).[35] Elderly persons with mitral valve prolapse and mitral regurgitation are more susceptible to IE.[36] Streptococci and staphylococci are the predominant organisms responsible for approximately 80% of cases in the elderly population.[37]

Ageing is associated with declined immunity, which increases susceptibility to infections. Age-related changes in humoral, cellular, and innate immunity in the elderly play a role in increasing the incidence of infectious diseases.[25, 26] This predisposes the elderly to viral infections such as reactivation of herpes zoster and influenza virus, and bacterial infections such as pneumonia and urinary tract infection, skin and soft-tissue infections.[26] Impaired humoral and cellular immunity also leads to reduced vaccine responses in the elderly.[38]

Older people are more likely to present with chronic medical conditions such as heart failure, arthritis, diabetes mellitus, chronic lung conditions, and disturbances of bladder function, which place them at increased risk of site-specific infections.[32] Frequently, these people require medication including acid-lowering drugs (such as proton pump inhibitors), immunosuppressive, sedative, and antipsychotic agents.[34] Benzodiazepines,[39-41] antipsychotics,[42-44] corticosteroids[45, 46] and opioid analgesics[47, 48] increases the risk of pneumonia. PPIs increase the risk of *Clostridium difficile* infection,[49, 50] pneumonia,[33, 51] and tuberculosis.[52] Antipsychotics may also increase the risk of urinary tract infections.[53, 54]

Invasive procedures such as urinary catheters, percutaneous feeding tubes, or tracheostomies increase the risk of infection.[34] Increasing use of bioprosthetic valves, intravascular catheters, and urinary catheters are additional risk factors for IE.[36]

The environment of RACFs can also contribute to infection amongst residents.[55] Elderly people live in these institutions in close proximity and may participate in group activities, where they come in close contact with other residents as well as caregivers.[34] According to an Australian survey involving 19 RACFs in the Australian Capital Territory in 2002, despite local and national guidelines on immunisation and infection control, only 28% of staff had received the influenza vaccine; this was considered insufficient to provide protection for residents.[56] A more recent study involving seven facilities of a multisite aged care provider in Sydney reported 48.1% uptake of vaccination (n= 135 staffs) in 2018.[57] Although this was 20% higher than the previous study conducted in the Australian Capital Territory (28%), it still represents suboptimal coverage recommended by the Communicable Diseases Network of Australia (CDNA).[58] According to Garibaldi, the combination of inadequate programs in infection control and poor compliance with routine infection control practices contribute to the spread of infections in this environment.[34]

1.3 Common infections in the elderly

Infectious diseases are among the major causes of mortality in older adults (one-third of all deaths in people 65 years and older), in spite of advanced antimicrobial therapy.[59] The most common infections are urinary tract infections (UTI), pneumonia, endocarditis, bacteraemia, influenza, and skin and soft tissue infection (SSTI).[32] According to an infection surveillance of the proportion and incidence of major types of healthcare-associated infections in four Melbourne RACFs (January 2006 to December 2010), the four most common infections in these facilities were UTI (36.8%), lower and upper respiratory infection (26.9%), SSTI (14.7%) and eye, ear and mouth infection (17.1%); others such as gastroenteritis and systemic infection constituted less than 5%.[60] According to a review by Mouton et al.[59] in people 65 years and older, pneumonia and influenza are the leading cause of death in the USA. These authors also reported that in older adults, the most common reason for bacteraemia is UTI.[59]

1.4 Antimicrobial prescribing patterns in RACFs

According to two Australian studies, cefalexin, trimethoprim, amoxicillin-clavulanic acid, doxycycline, flucloxacillin and roxithromycin collectively comprised 60-62% of all antibiotic courses prescribed in nine RACFs of Melbourne.[60, 61] Other commonly used antibiotics were amoxicillin, ceftriaxone, norfloxacin, erythromycin, chloramphenicol, minocycline and nitrofurantoin.[60, 61] UTIs and respiratory tract infections (RTIs) were the most common indications for antimicrobial use.[60, 61] In UTI, around 11% of antimicrobials prescribed were broad-spectrum antibiotics.[60] However, both studies reported that in the RACFs, up to 40% of antibiotic prescriptions were not clinically indicated.[60, 61] A similar scenario of inappropriate antibiotic use was also found in Northern Ireland and North Carolina, USA.[62, 63] A qualitative study reported Australian healthcare providers perceived antibiotics as over-prescribed in RACFs.[64] Thus, inappropriate and extensive use of antimicrobials may be associated with a rise of antimicrobial-resistant infections in RACFs.[65] The use of antimicrobials may predispose individuals to drug interactions, as elderly persons with multiple diseases use multiple medications.[66]

1.5 Interaction of antimicrobials with other medicines

Drug-drug interactions are more prevalent in the elderly compared to young adults.[66] Older people commonly have multiple chronic diseases, which leads to the concurrent use of multiple drugs (polypharmacy).[1] In Australian RACFs, In Australian RACFs, the number of medicines per resident has increased from, on average, seven medicines[67, 68] to 11.5 medicines[69] from 1999 - 2018. This high prevalence of concurrent medication use increases the risk of drug-drug interactions, and consequently, drug toxicity.[20] According to a European study in elderly outpatients, 46% of patients had at least one potential drug-drug interaction.[70] Other than polypharmacy, with increasing age, changes in body composition and pharmacokinetics (drug absorption, distribution, metabolism and clearance) are also evident in elderly people, necessitating special attention in drug selection and dosing.[20]

1.6 Antimicrobial stewardship

Irrational use of antimicrobials affects patient safety and treatment outcomes and significantly impacts the cost of therapy. This can be reduced by optimising antimicrobial use through antimicrobial stewardship (AMS).[2] Stuart et al. defined AMS as "the limitation of inappropriate antimicrobial use while optimising antimicrobial drug selection, dosing, route and duration of therapy in order to maximise clinical cure and to limit unintended consequences, such as adverse drug reactions and the emergence and selection of pathogenic organisms."[61] AMS is important to control the occurrence and extent of MDR organisms.[2] According to a review by Fishman, strategies adopted in such programs include education, formulary restriction, pre-approval, streamlining, antibiotic cycling, and computerised programs.[71] Educational intervention is the process whereby educational information is provided to physicians, pharmacists, or nurses, or multiple health professionals.[71] However, one study included patients in an educational intervention group with a physician, which had little effect on treatment outcome.[72] Formulary restriction is the process where a committee decides which drugs should be in the formulary of the institution.[73] In prior approval programs, prescribers notify a member of the infectious disease unit of the institute before ordering for the patients.[71] A streamlining program of AMS was described by Fishman as, "modification of an initial empiric antibiotic regimen, frequently in response to results from the microbiologic laboratory."[71] In computer-assisted programs, drug selection decisions are supported by software on the basis of patient history and drug-related side effects.[74] Effective and viable AMS programs should be developed and implemented on the basis of the resource strengths of the institution.[2] AMS is a relatively new concept in RACFs compared to acute care hospital settings.[75] Hospital-derived AMS programs may not be directly applicable in RACFs, due to differences in their resources and organisational structures.[2]

1.7 Significance

Present AMS initiatives focus on the appropriate selection and use of antimicrobial agents, taking into consideration the infection, prescribing formulary, and current prescribing guidelines. However, two other areas of concern have been identified: the use of medications that may predispose individuals to infection, e.g., cytotoxic and immunosuppressant medicines, thus resulting in increased prescribing of antibiotics; and medication misadventure as a result of interactions between prescribed antibiotics and individuals' ongoing chronic medications. This is the first-known study to investigate drugs as a potential risk factor for the development of infections amongst aged care residents, and hence, their contribution to antibiotic use. Furthermore, it addresses the issue of medication misadventure as a consequence of the prescribing of antibiotics to aged care residents. The findings related to these two issues will inform the development of an educational intervention aimed at minimising identified medication misadventure. This is important due to the prescribing of multiple medications ('polypharmacy') for residents of aged care facilities and the complexities of managing medications in older people. Thus, this study is significant in investigating both drug-associated infections and drug interactions between residents' chronic medication and prescribed antibiotics, describing their prevalence and associated risks, and developing and evaluating an educational intervention to minimise the risk of such drug misadventure.

Chapter 2 Literature review

A RACF is a residential healthcare site that delivers extended care to the elderly who are incapable of managing independently in the community.[5, 76] The term RACF is also known as Long Term Care Facility or nursing home used interchangeably according to geographical areas. The term RACF is more commonly used in Australia, whereas nursing homes or long-term care facilities are used in the USA.[5]

Aged care services are run by government organisations, not-for-profit organisations, and private organisations in Australia. On 30 June 2018, 2,695 services were operated by 886 organisations in Australia, and there were 207,142 operational places with an average occupancy rate of 90% in residential aged care. Seventy-nine percent of these places were in the states of New South Wales, Victoria, and Queensland.[77]

2.1 Medicine management in Australian RACFs

Medicine management in Australian RACFs is a complex multidisciplinary process requiring coordination between general practitioners (GPs), nurses, community pharmacies.

2.1.1 Prescribers in RACFs

Medicines are generally prescribed for aged care residents by off-site GPs, who visit periodically. Australian aged care providers do not hire full-time GPs, though some have onsite full-time nurse practitioners (NPs) who have prescribing rights.[7] NPs in Australian RACFs deliver advanced clinical assessments, prescribe treatments and medicines, and refer for diagnosis (e.g. pathology and radiology).[78, 79] Medical practitioners in RACFs prescribe medicines either by traditional prescription or by *National Residential Medication Chart* (NRMC).[80] The NRMC is a medication chart developed by the Australian Commission on Safety and Quality in Health Care for RACFs in Australia.[80] The purpose of the NRMC is to increase medication safety for residents, and to reduce the administrative liability of prescribers, aged care staff, and pharmacists when ordering, managing, and delivering prescription or non-prescription medicines and nutritional suppliments.[80]

2.1.2 Dispensing and supply of medicines

Medicines are dispensed by a pharmacy located in the community, independent of the RACF, based on traditional prescriptions or the *National Residential Medication Chart*.[7] The pharmacist is often requested to pack oral medications into dose administration aids to facilitate administration of the medicines by RACF staff.[7] Dose administration aids are also known as medication organisers, blister packs, Webster-Paks® or unit-dose sachets. Inhalers, injections, topical products, are delivered separately.[7] The community pharmacy usually supplies medications directly to the RACFs.[7]

2.1.3 Administration

By virtue of their age and frailty, most aged care residents are dependent on the healthcare staff of RACFs for medicine administration.[7] Residents can self-administer medicines if they have been evaluated as capable to do so; however, this is not common in practice.[81] In some RACFs, medicines are administered by competent care workers with proper training to administer them. Nursing staffs have more medication training than care workers.[82] Staff verify the resident's medicines chart and dose administration aids, prior to administering the medicine.[82] Multiple medicines, complex medication regimens, and residents not willing to take medication can all make medicine administration a challenging process.[83] Healthcare staff may need to crush or request alternative dosage forms of certain medicines for residents with swallowing difficulties.[7, 84] Administration of medicines prescribed "when required" or prn (*pro re nata*) depends on the assessment of the resident by nurses and care workers.[83] Due to limited resources in RACFs, administration of regular parenteral medications (such as intravenous antibiotics) may need hospitalisation of residents.[7]

2.2 Prevalence of infection in RACFs

Infections in aged care residents correlate to high rates of hospitalisation, prolonged hospital stay, significant healthcare costs, and death.[85] UTIs, lower respiratory tract infections, and skin and soft tissue infections (SSTI) are the most prevalent endemic infections among residents of RACFs.[76] In addition to endemic infections, the outbreak of epidemic infections most commonly reported include gastrointestinal infections (such as gastroenteritis), respiratory infections (such as influenza), and skin infections.[76]

A survey in the United Kingdom (UK) of 15 RACFs in 2006 found an incidence rate of 6.04 infections/1000 bed-days.[86] The most common infections were RTI, UTI, SSTI, and gastrointestinal infections; incidence rates were 2.52, 1.87, 1.57, 0.41/1000 bed-days, respectively.[86] According to an infection surveillance of the proportion and incidence of major types of healthcare-associated infections in four Melbourne RACFs (January 2006 to December 2010), the average rate of healthcare-associated infection was 4.16 episodes/1000 occupied bed day (OBD) annually (95% CI: 3.92-4.41) and the four most common infections in these facilities were UTI (36.8%), lower and upper respiratory infection (26.9%), SSTI (14.7%) and eye, ear and mouth infection (17.1%); others such as gastroenteritis and systemic infection constituted less than 5%.[60]

2.2.1 Urinary tract infections

UTIs are the most reported common infections in RACFs.[85] In residents of RACFs, bacteriuria is very common.[85] Increased functional impairment (incontinence of urine or faeces) and the existence of an inserted urinary catheter are associated with an increased incidence of UTI and bacteriuria.[85] Seven to 10% of aged care residents have an indwelling urethral catheter, which predisposes them to UTIs and bacteriuria.[76] The incidence rate of symptomatic UTIs is 7-11 episodes/1000 days in prolonged catheter users.[34] In addition, residents who have indwelling urinary catheters for 76% or more of their resident-days in RACFs are three times more likely to die than non-catheterised residents within a year.[87] The prevalence of asymptomatic bacteriuria in aged care residents is estimated at 15-50%.[34] The incidence of symptomatic UTI in residents without indwelling catheter ranges between 0.2-2.2 episodes/1000 days.[34] Residents with urinary catheters have an incidence rate of 9.1 UTIs/1000 resident-days, significantly higher than 2.8 UTIs/1000 resident-days in the non-catheterised group.[88] In an Australian retrospective study in two Victorian RACFs, 119 UTIs were diagnosed in 57 residents over a 16-month period. However, only 5.9% (7/119) met the standard criteria of UTIs.[89]

2.2.2 Respiratory tract infection

Residents of RACFs are highly vulnerable to upper and lower RTIs.[90] Pneumonia is one of the most common causes of mortality in RACFs, and a key reason for transferring residents to a hospital.[85] Aged care residents in the USA account for 10-18% of hospitalisations due to pneumonia, which incurred an approximate average cost of US$10,000 per admission.[85, 91] The estimated prevalence of RACF-related pneumonia varies between 48.6% and 61.2%.[90, 92, 93] A database analysis of 5,160 patients with community-acquired pneumonia from the USA, Canada, and Europe reported that *Streptococcus pneumoniae* (31%), Staphylococcus species (31%), and *Pseudomonas aeruginosa* (7%) were the most common pathogens identified in "nursing home-associated pneumonia".[94] Residents of RACFs are more likely to have severe pneumonia than community-dwelling elderly people,[94] due to multi-morbidities such as neurological diseases, cerebrovascular diseases, and diabetes mellitus, and other factors such as poor functional status, the presence of a feeding tube, swallowing difficulties, aspiration, and poor oral hygiene.[76, 92, 93] Aspiration pneumonia in residents of RACF is often associated with dysphagia.[90, 95]

2.2.3 Skin and soft tissue infections

SSTIs are the third most prevalent infection identified in the residents of RACFs.[96] According to point prevalence surveys in RACFs of Europe[97] and the USA,[98] about 22-23% of infections are SSTIs.[96] In a European survey, 87.4% of SSTIs were related to bacterial infections (such as cellulitis, soft tissue, and wound infections), and the remainder were fungal infections (8.3%), herpes simplex or herpes zoster infections (2.4%), and scabies (1.9%).[97] In a national survey conducted in Australia in 2016 in RACFs, 3.1% of residents were reported to have infections, of which 26.4% were suspected to be SSTIs.

2.2.4 Antibiotic-resistant infection

The emergence of infections by multi-drug-resistant (MDR) organisms, e.g. vancomycin-resistant-enterococci, penicillin-resistant Pneumococci, methicillin-resistant *Staphylococcus aureus*, MDR Gram-negative bacilli, in residents of aged care facilities is becoming a global concern.[5, 99-101] According to a study in metropolitan Melbourne in four RACFs in 2011, up to 49% of 115 residents were colonised with MDR organisms. Amongst this group, MDR GNB colonisation (21%), specifically extended-spectrum beta-lactamase (ESBL) *E. coli* and carbapenem-resistant *Acinetobacter baumannii*, was more prevalent than colonisation with

MRSA and VRE.[99] A similar increasing trend of ESBL producing *E. coli* (overall 12%) had been reported by a previous study in 2010 in another geographical location in Melbourne.[102] Apart from beta-lactam resistance, this strain of *E. coli* was also resistant to ciprofloxacin, norfloxacin, and sulfamethoxazole and trimethoprim, medicines that are commonly used in older populations.[102] The inappropriate use of broad-spectrum oral antimicrobials is one of the major factors for the rise of MDR organisms in RACFs.[102]

2.3 Prevalence of common antibiotics used in RACFs

It has been reported that 50-75% of residents of RACFs are exposed to at least one course of antimicrobials annually,[103-105] and at any given time, more than 10% of residents take an antibiotic.[106] In the USA, almost 40% of all the prescribed systemic medications in RACFs are antibiotics.[107] It is plausible that antibiotic use may have decreased since these audits, due to clinical initiatives to ensure their appropriate use.

In Australia, according to the Aged Care National Antimicrobial Prescribing Survey conducted by the *National Centre for Antimicrobial Stewardship* in partnership with the Victorian Healthcare Associated Infection Surveillance System in 2017, the three most common antimicrobials were clotrimazole (20.8%), cefalexin (19.4%) and amoxicillin (6.1%) (Table 1). On the survey day in 2017, at least one antimicrobial was prescribed in 8.8% of residents, compared with 9.9% in 2016 ($p<0.01$).[108]

Table 1. Prevalence of the most common antimicrobials prescribed in RACFs from 2015-2017

Year	Prevalence of the most common antimicrobials (percentage of total antimicrobial prescriptions)
2017[108]	Clotrimazole (20.8%), cefalexin (19.4%) and amoxicillin (6.1%), amoxicillin-clavulanate (5.8%), trimethoprim (5.8%)
2016[109]	Cefalexin (21.7%), clotrimazole (13.3%), amoxicillin-clavulanate (7.2%), trimethoprim (6.7%) and chloramphenicol (5.8%)
2015[110]	Cefalexin (16.7%), clotrimazole (16.5%), amoxicillin-clavulanate (6.5%), trimethoprim (6.5%) and chloramphenicol (6.4%)

According to two independent studies in Australia, cefalexin, trimethoprim, amoxicillin-clavulanic acid, doxycycline, flucloxacillin, and roxithromycin collectively comprised 60-62% of all antibiotic courses prescribed in nine RACFs of Melbourne.[60, 61] Other commonly used antibiotics were amoxicillin, ceftriaxone, norfloxacin, erythromycin, chloramphenicol, minocycline, and nitrofurantoin.[60, 61] UTIs and RTIs were the most common indications for antimicrobial use.[60, 61] In UTIs, around 11% of antimicrobials prescribed were broad-spectrum antibiotics.[60] Another Australian study in 29 RACFs in Victoria found that the most commonly prescribed antimicrobial was cefalexin (32.5%), followed by amoxicillin, trimethoprim, and nitrofurantoin (each comprising 10.4% of all prescriptions).[31]

Prescribing patterns of antibiotics in RACFs differ by country.[5] National and regional antibiotic guidelines influence prescribing practice.[5] However, patterns of the most commonly used antibiotics are more similar in studies performed in the same country (Table 2). For example, quinolones are used significantly in RACFs in the USA and Canada, whereas in Australia their use is low.[5, 103, 106]

Table 2. Antibiotic use patterns in RACFs of Australia vs other countries

Australia		Worldwide	
Studies	**Most commonly used antibiotics**	**Studies**	**Most commonly used antibiotics**
Pringle et al.[111] 2015 (23 RACFs)	Cefalexin, followed by amoxicillin-clavulanate, trimethoprim and amoxicillin	Sloane et al.,[63] 2010-2011 (USA, four RACFs)	Ciprofloxacin (25%), levofloxacin (14%), trimethoprim-sulfamethoxazole (13%), cefalexin (8%), nitrofurantoin and azithromycin (7% each)
Stuart et al.[61] 2011 (five RACFs)	Doxycycline (26%), cefalexin (17%) and flucloxacillin (13%), or trimethoprim (13%)	Latour et al.[112] (21 European countries, 2009, 323 RACFs)	β-lactam penicillins (29%), quinolones (14%), other beta-lactam antibiotics (11%)
Smith et al.[31] 2011 (29 RACFs)	Cefalexin (33%), amoxicillin, trimethoprim, and nitrofurantoin (10% each)	Daneman et al.[113] (Canada, 2009, 363 RACFs)	Nitrofurantoin (15%), trimethoprim/sulfamethoxazole (14%), and ciprofloxacin (13%)
Lim et al.[60] 2010 (four RACFs)	Cefalexin (25%), trimethoprim (14%), amoxycillin–clavulanate (13%)	Rummukainen et al.[114] (Finland, 2009, nine RACFs)	Methenamine (41%), trimethoprim (14%), and pivmecillinam (11%)
		McClean et al.[6] (15 European countries, 2009, 85 RACFs)	Methenamine (18%), trimethoprim (11%), and co-amoxiclav (11%) in April and co-amoxiclav (12%), nitrofurantoin (12%) and methenamine (12%) in November
		Moro et al.[115] (Italy, 2010, 92 RACFs)	Quinolones (24%), penicillin plus beta-lactamase inhibitor (22%), and third-generation cephalosporins (21%)
		McClean et al.[62] (Ireland, 2010–2011, 30 RACFs)	Trimethoprim, cefalexin, and nitrofurantoin were the most commonly prescribed
		Heudorf et al.[116] (German, 2011, 40 RACFs)	Quinolones, cephalosporins, penicillins, and co-trimethoprim/sulfamethoxazole were the most commonly prescribed
		Blix et al.[117] (Norway, 2003, 133 RACFs)	Penicillins with extended spectrum, followed by trimethoprim and sulfonamides
		Pettersson et al.[118] (Sweden, 2003, 58 RACFs)	Penicillins (38%), followed by quinolones (23%) and trimethoprim (18%)

Australia	Worldwide	
	Daneman et al.[103] (Canada, 2010, 630 RACFs)	Second-generation fluoroquinolones (19%), penicillins (17%), third-generation fluoroquinolones (17%)
	Pakyz and Dwyer,[106] (US, 2004, 1174 RACFs)	Nitrofurantoin (12%), levofloxacin (12%), and ciprofloxacin (7%)

2.4 Inappropriate prescribing

A retrospective study in four RACFs in Melbourne, Australia, reported that 37% of antibiotic prescriptions were for the episodes which did not satisfy the McGeer Criteria of Infection.[60] Another Australian study in five RACFs also utilised the McGeer criteria and reported 39.7% of prescribed antibiotics were inappropriate.[61] 2017 The *Aged Care National Antimicrobial Prescribing Survey* report stated that "over one-half of the antimicrobial prescriptions (55.2%) were for residents with no signs and/or symptoms of a suspected infection in the week prior to the start date".[108] Inappropriate antibiotic use was found in Northern Ireland[62] and North Carolina, USA.[63] A qualitative study reported Australian healthcare providers perceived antibiotics as over-prescribed in RACFs.[64]

Thus, inappropriate and extensive use of antimicrobials may be associated with a rise of antimicrobial-resistant infections in RACFs.[65] Further, the use of antimicrobials may predispose individuals to drug interactions, as elderly persons with multiple diseases use multiple medications.[66]

2.5 Risk factors for infection in RACFs

RACFs are at increased risk of infection burden due to the emergence of antimicrobial-resistant organisms.[60] Residents live in a communal environment and have close interaction with potentially infected or colonised residents and/or staff.[31] Residents of aged care facilities are particularly susceptible to infections due to their age-related changes in physiological functions, comorbidities, functional disabilities, immunosenescence (age-related decline of the immune system), and the use of invasive devices (e.g. urinary tract catheterisation).[31] These factors have been described in Section 1.2. The following section provides an overview of medicine-associated infections (in more detail in Section 4.1.2).

2.5.1 Medicine-associated infections

Studies have demonstrated the increased risk of diarrhoea caused by C. difficile in patients taking acid-lowering drug proton pump inhibitors (PPIs).[119, 120] Use of corticosteroids and narcotics double the risk of pneumonia in patients with inflammatory bowel disease.[45]

Benzodiazepine exposure has been associated with an increased risk of developing pneumonia and dying from pneumonia.[39] Benzodiazepines are widely used for anxiety, epilepsy, muscle spasm, alcohol withdrawal, palliation, insomnia and to provide sedation.[39] Animal studies suggest that diazepam (a benzodiazepine) increases susceptibility to infection, including pneumonia, by the stimulation of gamma-aminobutyric-acid-A receptors suppressing macrophage and monocyte function.[121]

The use of antipsychotics is also a risk factor for the occurrence of pneumonia in elderly people.[42] Antipsychotics are indicated in the treatment of acute and chronic psychiatric disorders and are generally divided into atypical and typical antipsychotics.[43] In residents of aged care facilities, antipsychotics are often used to treat behavioural symptoms associated with dementia. Atypical antipsychotics are widely used due to their reported reduced incidence of extrapyramidal adverse effects in the elderly.[122] Knol et al. reported the risk of infection as higher than the use of atypical antipsychotics compared to typical antipsychotics in the initial stage of treatment.[42] However, another study found no difference in the risk of pneumonia between the two groups of antipsychotic agents.[122] It is likely that antipsychotics induce aspiration pneumonia in frail elderly through multiple mechanisms.[43]

Antithyroid drugs may induce agranulocytosis, which increases the incidence of life-threatening infection.[55, 123]

Thus, the occurrence of infections leads to additional use of antibiotics that may interact with other medicines taken by the elderly.

2.6 Interaction of antibiotics with other medicines

Drug-drug interactions are more prevalent in the elderly compared to young adults.[66] Older people commonly have multiple chronic diseases, which leads to the concurrent use of multiple drugs (polypharmacy).[1] Residents of RACFs use multiple medications concurrently.[124] Polypharmacy is common in Australian RACFs.[124] Research spanning 36 RACFs in Western Australia found that 91.2% of residents were taking an average of 9.75 medications.[124] Other studies in Australia suggest 39-63% of residents are taking nine or more medications on a regular basis. In Australian RACFs, on average, seven medications are prescribed for each resident.[67, 68] This high prevalence of concurrent medication use increases the risk of drug-drug interactions, and consequently, drug toxicity.[20]

Population-based retrospective case-control studies in patients aged 66 and older reported that simultaneous use of angiotensin II receptor antagonist (AIIRA) or an angiotensin converting enzyme inhibitor (ACEI) (adjusted odds ratio, aOR: 6.7; 95% CI: 4.5 -10.0),[125] beta-blockers (aOR: 5.1; 95% CI: 2.8 – 9.4),[126] or spironolactone (aOR: 12.4; 95% CI: 7.1 – 21.6)[127] with co-trimoxazole (trimethoprim with sulfamethoxazole) increased the risk of hyperkalaemia requiring hospital admission (Table 3). Sudden death due to arrhythmia also reported by another population based case-control study in Canada within seven days of the concurrent use of co-trimoxazole and ACEI or AIIRA (aOR: 1.3; 95% CI: 1.0 – 1.7).[128] Several case reports also described hyperkalaemia attributed to the combined use of co-trimoxazole together with an ACEI, AIIRA or spironolactone.[129, 130] The development of methotrexate associated toxicity in patients taking simultaneous trimethoprim or co-trimoxazole also reported by some case reports.[131, 132] Interaction of erythromycin, clarithromycin or azithromycin with calcium channel blockers (CCB) can increase the risk of hypotension[133] and acute kidney injury.[134]

In a retrospective, population-based cohort study of adults older than 65 years taking a statin (atorvastatin, simvastatin, and lovastatin), concomitant administration with macrolide antibiotics (clarithromycin or erythromycin) was associated an increased rate of hospitalisation for rhabdomyolysis and acute kidney injury.[135] According to a nested case-control study in a cohort of 38,762 patients aged 65 years and older who were continuous warfarin users, macrolides (azithromycin, clarithromycin, dirithromycin, erythromycin, telithromycin, troleandomycin) were associated with a 1.86-fold (95% CI, 1.08-3.21) increased risk of bleeding that required hospitalisation within 60 days of antibiotic exposure compared with non-exposure.[136] Baillargeon et al.[136] also reported the other antibiotics which can increase the risk of bleeding with the concomitant use of warfarin in the elderly were azole antifungals (aOR: 4.57; 95% CI: 1.9-11.03), cotrimoxazole (aOR: 2.7; 95% CI: 1.46-5.05), penicillins (aOR: 1.92; 95% CI: 1.21-2.07), cephalosporins (aOR: 2.45; 95% CI: 1.52-3.95), and quinolones (aOR: 1.69; 95% CI, 1.09-2.62). There is significant reporting of roxithromycin interaction with warfarin compared with other macrolides and other roxithromycin interactions. Of the reports for roxithromycin in the *Australian Adverse Drug Reactions Advisory Committee* database, more than 10% were for interactions, predominantly with warfarin.[137] According to population-based studies, concurrent use of digoxin and macrolides (azithromycin, erythromycin, clarithromycin) were associated with increased risk of digoxin toxicity.[138, 139] Concomitant use of clarithromycin (aOR: 14.8; 95% CI: 7.9-27.9) poses a four-fold higher risk compared to erythromycin and azithromycin (aOR: 3.7; 95% CI: 1.7-7.9; and aOR: 3.7; 95% CI: 1.1-12.5, respectively).[138]

Above drug interactions between antibiotic and other medicines are not a comprehensive list of antibiotic-related drug interactions. Drug interaction databases such as *Micromedex*®,[140] *Lexicomp*®,[141] and *MIMS*®[142] contain comprehensive list of drugs that have potential for interaction with antibiotics. The prevalence of potential antibiotic-drug interactions is described in Section 4.2.1.

Table 3. Interactions between antibiotics and commonly-used drugs

Antibiotic	Drug	Setting	Method	Interaction
Macrolides[143]	Warfarin	Primary care	Retrospective, electronic data source	Risk of bleeding
Erythromycin, clarithromycin[133]	CCB	Ontario Drug Benefit Claim Database, and hospital records	Population-based cohort study, retrospective, 66 y and older	Risk of hypotension
Azithromycin[134]	CCB	Health care database, Ontario	Population-based retrospective cohort study, 66 y and older	Risk of acute kidney injury
Erythromycin, clarithromycin[135]	Statins	Health care database, Ontario, 2003 to 2019	Population-based cohort study, retrospective, 66 y and older	Rhabdomyolysis due to increased concentration of statins
Ciprofloxacin[144]	Theophylline	Ontario, Canada, 1992-2009	Population-based cohort study, retrospective, 66 y and older	Theophylline toxicity
TMP-SMX[126]	Beta-blocker	Ontario, Canada, database, 1994 to 2008	Retrospective, nested case control study, 73-84 y	Hyperkalaemia
TMP-SMX[125]	ACEI or AIIRB	Ontario, Canada, database, April 1994 to March 2008	Population-based retrospective nested case control study, 66 y and older	Hyperkalaemia
Co-trimoxazole[128] (TMP-SMX)	ACEI or AIIRB	Ontario Drug Benefit Claim Database, and hospital records, April 1994 to January 2012	Population-based retrospective nested case control study, 66 y and older	Sudden death due to arrhythmias
TMP-SMX[127]	Spironolactone	Ontario, Canada, April 1992 to March 2010	Population-based nested case control study	Hyperkalaemia

CCB: Calcium channel blocker; ACEI: Angiotensin converting enzyme inhibitor; AIIRB: Angiotensin II receptor blocker; TMP-SMX: Trimethoprim-Sulfamethoxazole

2.6.1 Age-related changes in drug pharmacokinetics predisposing the elderly to drug-drug interactions

Apart from polypharmacy, with increasing age changes in body composition and pharmacokinetics (drug absorption, distribution, metabolism, and clearance) are also evident in elderly people, necessitating special attention in drug selection and dosing.[20] Ageing can result in changes in all phases of the pharmacokinetics of a drug – absorption, distribution, metabolism, and excretion – due to changes in the body's physiological functions. As discussed below, these changes can lead to clinically significant drug-drug interactions between antibiotics and other co-administered drugs.

2.6.1.1 Changes in absorption

Age-related delayed stomach emptying and reduced gastrointestinal motility, gastrointestinal blood flow, and bowel surface area can decrease the bioavailability of amoxicillin and clavulanic acid.[145] Decrease in acid secretion in the elderly (which can also be caused by long-term use of acid suppressants), can change the chemical stability and solubility of macrolides, β-lactams, and azoles.[146] Thus, the bioavailability of these drugs is reduced.[146] However, decreased oesophageal motility and increased gastric pH have less effect on oral antibiotic absorption.[23] Active transport processes may also be reduced in the elderly, leading to clinically significant drug interactions; these are of specific importance in elder patients treated with multiple medicines.[147, 148] for example, macrolide antibiotics may increase blood concentrations of digoxin by inhibiting intestinal P-glycoprotein (P-gp), which leads to digoxin toxicity.[149]

2.6.1.2 Changes in distribution

Age-related modifications in body composition may affect drug distribution in several ways. The volume of distribution for lipophilic drugs may increase with a prolonged half-life due to the increase in body fat content and the decrease in total body water,[150] whereas an alternate effect occurs in water-soluble drugs, with a subsequent increase in blood concentration.[151] Thus, the elimination of lipophilic antimicrobial agents, such as fluoroquinolones, rifampin, amphotericin B, macrolides, tetracyclines, and most of the imidazole antifungals, is decreased.[152] Age-related reduction in total body water reduces the volume of distribution of hydrophilic antimicrobial drugs such as β-lactams, aminoglycosides, and glycopeptides.[152] In the elderly, blood albumin level may remain unchanged or may

decline by 15-20%, which may affect the pharmacokinetics of protein-bound drugs.[24] Thus, co-administration of co-trimoxazole with methotrexate or sulfonylureas may require attention. Co-trimoxazole can displace methotrexate and sulfonylureas from plasma protein, resulting in a clinically relevant increased risk of severe bone marrow suppression and hypoglycaemia, respectively.[149]

2.6.1.3 Changes in metabolism

In the elderly, the bioavailability of drugs undergoing the first-pass metabolism tends to increase, whereas the bioavailability of drugs that need to be activated in the liver is decreased.[23, 153] Therefore, serum concentrations of antimicrobials such as macrolides, tetracyclines, clindamycin, rifampin, fluoroquinolones (except levofloxacin) and co-trimoxazole may increase.[152, 154] With advancing age, the hepatic clearance of drugs with flow-limited metabolism may be reduced up to 40%.[155] Due to the decrease in hepatic blood flow and overall liver size, hepatic clearance by cytochrome P450 (CYP)-mediated phase I oxidisation, reduction, and hydrolysis reactions is impaired to a greater extent with respect to clearance mediated by phase II conjugation reactions.[155, 156] Thus, co-administration of warfarin, statins, and antiarrhythmics with an antimicrobial agent (e.g. macrolides) needs monitoring and may require a change of therapy.[23]

2.6.1.4 Changes in excretion

Age-related decrease in the glomerular filtration rate and tubular secretion may affect the renal excretion of antimicrobials, leading to drug toxicity.[23] Blood concentrations of β-lactam antibiotics can be increased by drugs affecting their renal tubular secretion, such as probenecid, methotrexate, aspirin, and indomethacin.[149] Renal excretion and tubular secretion of methotrexate may be reduced by ciprofloxacin, leading to severe methotrexate toxicity.[157, 158]

2.7 Antimicrobial stewardship

As established in Chapter 1, residents of aged care facilities are vulnerable to infections due to their old age, multiple diseases, reduced functional ability, reduced immunity, and use of invasive devices such as urinary catheters.[34] Living in close proximity to other infected residents or staff, and recent hospitalisation, present other risks for infection in aged care residents.[159, 160] Due to inappropriate and overuse of antimicrobials, aged care residents may act as hosts for MDR organisms.[64, 100, 161] Development of new antibiotics to fight these resistant microorganisms is not promising; therefore, sensible use of antibiotics in RACFs is a prime concern to control antimicrobial resistance.[64] Aged care providers can integrate infection control and prevention initiatives to protect vulnerable residents by implementing evidence-based strategies to significantly reduce infections.[108]

As a part of infection prevention and control programs, AMS aims to monitor inappropriate use of antibiotics and to avoid adverse effects of antibiotic use, including resistance to antibiotics, toxicity, and economic burden from unnecessary costs.[108] AMS programs are well recognised in hospital settings but remain relatively uncommon in RACFs.[75] However, the emphasis on AMS is increasing in this sector. The *Aged Care Quality Standards* produced by the *Aged Care Quality and Safety Commission* propose that RACFs should take initiatives to measure the risk of, and to prevent, identify and control the extent of, infections. RACFs should implement proper antibiotic prescribing and consumption to provide ideal care and reduce the risk of increasing antibiotic resistance.[162]

The need for AMS in RACFs is evident and supported in Australia and internationally.[76] However, useful models for AMS in RACFs are still poorly outlined.[64] Implementing hospital models of AMS in the RACF setting may be impractical, due to differences in institutional resources and prescribing patterns of antibiotics between these two settings.[64] Therefore, a successful AMS program needs to be designed on the basis of existing infection prevalence, antibiotic use, and pattern of antibiotic resistance, and needs to be evidence-based with comprehensive RACF surveillance data.[64] For example, in Australian RACFs, the most common prescribed antimicrobials were clotrimazole, cefalexin, and amoxicillin, and less frequently, fluoroquinolone,[60, 108] whereas fluoroquinolone was extensively used in the USA.[106]

The current study searched for recent studies of AMS in RACFs in *PubMed®* and *Embase®* from 2011-2019 (Table 4). The majority of the studies implemented educational interventions[63, 163-166] as their AMS program. Other initiatives were the implementation of an antibiogram created using clinical culture data from a six-month period,[167] guideline development and implementation,[167-170] a Resident Antimicrobial Management Plan,[171] a decision-making aid for UTI management, and an educational session followed by letters to GPs, detailing findings of the baseline audit and reminders on appropriate prescribing.[172]

Reducing antibiotic prescribing was the main aim of the studies. Most studies aimed to reduce antibiotic prescribing in UTIs.[163, 164, 166, 168, 172] The reason for targeting UTI for intervention was the rate of inappropriate use of antibiotics for suspected UTI, which comprised 30-50% of all antibiotic use in RACFs.[173] One study aimed to reduce antibiotic use for lower UTI in women.[163] UTI is the main indication for antibiotic use in RACFs.[174] One study aimed to evaluate the rate of urine culture testing for UTI.[164] Uncertainty in identifying the difference between UTI and asymptomatic bacteriuria, and a liberal prescribing culture, contribute to the overprescribing of antibiotics and over-utilisation of urine testing for infection.[107, 175, 176]

Zimmerman developed the guideline for their AMS program, which indicates the minimum criteria for initiation of antibiotics suggested by Loeb et al. and the 12 common conditions where antibiotics are usually not prescribed.[170, 177, 178] These 12 conditions in where systemic antibiotics are not usually prescribed are: asymptomatic residents with positive urine culture; urine-culture indicated only because of alteration in appearance of urine; nonspecific symptoms or signs not referable to the urinary tract (with or without a positive urine culture); common cold; bronchitis or asthma in an resident without chronic obstructive pulmonary disease; infiltrate on chest X-ray in the absence of clinically significant symptoms; influenza (suspected or proven) without a secondary infection; respiratory problems in resident receiving palliative care or at the end of life with advanced dementia; skin wound lacking evidence of cellulitis, osteomyelitis, or sepsis (irrespective of culture result); small (<5 cm) localised abscess without significant surrounding cellulitis; decubitus ulcer in an individual at the end of life; and acute vomiting or diarrhoeal symptoms without a positive toxin assay for *C. difficile* or a positive culture for salmonella or shigella.[170]

Ensuring proper antibiotic use and good antibiotic stewardship can be achieved through the implementation of peer-reviewed clinical guidelines for the management of particular infections.[71, 73] However, guidelines need to be frequently revised to reflect the most current information.[71]

Table 4. Antimicrobial stewardship trials in Residential Aged Care Facilities

Author	Objective	Design	Intervention	Participants	Measurement	Effectiveness
Pasay, 2019 [164]	Prevention of unnecessary urine testing, and reduction of antibiotic use for UTI	Cluster RCT	Educational	Physician, nurse, families, caregivers	Rate of urine culture testing, antimicrobial prescribing for UTIs, hospital admissions, mortality rate	Rate of urine culture testing and antimicrobial prescriptions for UTI decreased, no increase in hospital admissions or mortality.
Lee , 2018 [166]	Unnecessary urine testing prevention, antibiotic use reduction, and prescribing appropriateness evaluation in UTI	Prospective chart audit	Educational	Aged-care staff	Rate of urine culture testing, cost associated with inappropriate treatments, appropriateness of prescribing	Inappropriate antibiotic treatment of asymptomatic bacteriuria decreased
McMaughan, 2016 [168]	Reducing antibiotic prescriptions in UTI	Controlled, pre/post intervention	Guideline implementation	Residents	Number of prescriptions for suspected UTI with no symptoms	Number of prescriptions decreased
Stuart, 2015 [165]	Antibiotic use reduction	Pilot study pre/post intervention	Educational	Nurse consultant	Antibiotic consumption	Significant changes in prescribing in UTI, SSTI
Doernberg, 2015[172]	Reducing antibiotic prescriptions in UTI	Quasi-experimental study, pre/post intervention	Audit and feedback	The ASP team (infectious diseases (ID) pharmacist and ID physician)	Rates of antibiotic prescribing and antibiotic resistance	Antibiotic utilization decreased

Author	Objective	Design	Intervention	Participants	Measurement	Effectiveness
Buul, 2015[169]	antibiotic prescriptions reduction, guideline-adherence in antibiotic selection in UTI	Controlled, pre/post intervention	Guideline implementation	Physician	Appropriateness of prescribing, total antibiotic consumption	Was not effective in improving antibiotic prescribing behaviour
Furuno JP,2014[167]	Improving antibiotic prescribing.	Cross-sectional, pre/post intervention	Guideline implementation	Resident	Prevalence of appropriate antibiotic prescribing	Implementation of antibiograms may be effective in improving empirical antibiotic prescribing
Fleet, 2014[171]	Reduction in antibiotic prescribing	Cluster RCT	"Resident antimicrobial management plan" tool	Residents	Total antibiotic consumption	Total antibiotic consumption decreased
Zimmerman, 2014[170]	Reduction in antibiotic prescribing	Controlled, pre/post intervention	Guideline implementation	Residents	Rates of antibiotic prescribing for infections	Rates of antibiotic prescribing decreased
Sloane, 2014[63]	Reducing inappropriate prescribing	Pre/post intervention	Educational	Prescribers, staff who communicate with prescribers, and residents	Antibiotic prescribing rate, rate of appropriate prescribing	Reduce inappropriate prescribing.
Pettersson, 2011[163]	Reduction in antibiotic prescribing	Cluster RCT	Educational	Nurses	Proportion of quinolones and nitrofurantoin prescribed, UTI per resident, antibiotic prescribing rate in lower UTI	Modest effect

2.7.1 Educational interventions

Educational interventions may involve either one-to-one discussion with health professionals or a less personalised interventions such as staff conference or information dissemination by posters, leaflets, newsletters, or mailing of instructional materials.[71]

A comprehensive, multidimensional educational intervention for treating infections (such as UTI and RTI) in the elderly has been reported as a safe and effective method to achieve a significant change in prescribing.[179] Educating both physicians and nurses has been found more effective than educating the physician alone.[180]

A cluster randomised study of an educational intervention to reduce the rate of urine culture testing and antibiotic prescribing for UTIs in 42 Canadian nursing homes demonstrated a significant decrease in urine culture test by 2.1 tests/1000 resident-days and prescribing of antibiotics for UTIs by 0.7 prescriptions/1000 resident-days.[164] Intervention nursing homes received on-site face-to-face staff education and academic detailing session with physicians conducted by an antibiotic stewardship pharmacist.[164]

A 15-minute educational session for 212 clinical nurses was associated with a statistically significant decrease from 90% to 62.9% (p=0.003) in inappropriate antibiotic treatment in asymptomatic bacteriuria in the residents of RACF in Canada.[166] The session consisted of evidence-based guideline of asymptomatic bacteriuria, presentation of pre-intervention findings, and criteria of diagnosis of asymptomatic bacteriuria.[166]

In RACFs in Australia, up to 40% of antibiotics have been inappropriately prescribed.[60, 61] Another Australian qualitative study in RACFs reported that the over-prescribing of antibiotics had been identified by the GPs and pharmacists servicing those facilities.[64] Inappropriate and over-prescribed antibiotics are related to the increase of MDR organisms.[102] However, “there are limited to negligible antimicrobial stewardship (AMS) programs in Australian RACFs despite evidence suggesting an urgent need for AMS interventions to optimise antimicrobial use”- as noted by Kong et al.[2] in their report to express the present situation in AMS initiatives in Australian RACFs.

2.8 Deprescribing: a process of reducing inappropriate medicine use

The current research had not been designed to implement a deprescribing strategy for intervention, but this concept is discussed here to introduce the reader to this term, as it has been used several times in the forthcoming chapters.

Reeve et al. defined deprescribing as "the process of withdrawal of an inappropriate medication under supervision by a healthcare professional with the goal of managing polypharmacy and improving health outcomes".[181] Scott et al. defined deprescribing more elaborately as "the systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individual patient's care goal".[182] Thus, deprescribing is a pathway of tapering or ceasing medicines, aimed at reducing the use of multiple medicines simultaneously for a longer period of time and improving a patient's outcome.[182] Inappropriate use of multiple medicines in elderly people causes a considerable burden of drug-related adverse outcomes.[183] Deprescribing does not mean denying a patient effective management; it follows the same prescribing principles when the therapy was initiated.[182] This means deprescribing follows the patient-centred interventions (dose titration, changing or adding drugs, substituting or stopping drug therapies), shared decision making, informed patient consent, and close monitoring of the therapy.[182]

Instances in the elderly where deprescribing should be considered include any new presenting symptom or clinical syndrome, any new complaint indicating an adverse drug outcome, advanced or end-stage disease, incurable illness, dementia, extreme frailty or full dependence on others for all care, use of high-risk medicines or combinations, and use of preventive medicines for situations related with no increased risk in spite of drug termination.[182]

Many deprescribing protocols are available for research investigators and health practitioners as decision support in their practice. The deprescribing protocols by Scott et al.[182] and Reeve et al.[184] consists of a five-step process commencing with gathering an inclusive medication history to identify potentially inappropriate medications and to developed patient-centred deprescribing protocols utilising knowledge of patients' understanding of medicine cessation and consideration of patient preferences and needs throughout the process, with the aim of improving long-term health benefit.

2.9 Summary

Elderly people living in RACFs are vulnerable to infection due to their frailty, multiple chronic diseases, and use of medicines that may increase the risk of infection, but also on account of the close living quarters and prevalence of multidrug-resistant organisms in these facilities.

UTIs, RTIs, gastroenteritis, and SSTIs are the most prevalent infections among aged care residents.

Benzodiazepines, PPIs, antipsychotics, corticosteroids, and opioid analgesics are the most commonly used drugs for multi-morbidities. These drugs may increase the risk of infection in this vulnerable population. This in turn increases the prescribing of antibiotics. The inappropriate use of broad-spectrum oral antimicrobials is one of the major factors contributing to the rise of multidrug-resistant organisms in RACFs, as well as other unwanted drug events such as the interaction of antibiotics with other co-administered drugs.

Thus, a practical approach (such as AMS and/or deprescribing) is a pressing need in RACFs to reduce the unnecessary use of antibiotics. These can be achieved through rationalising the prescribing of medications that contribute to an increased risk of infection and to minimise medication misadventure through reducing the potential interaction of antibiotics with other drugs.

To date, AMS initiatives in RACFs reported in the literature have focussed on improving the treatment of infection, and initiatives to reduce antibiotic resistance by reducing the inappropriate use of antibiotics and inappropriate laboratory testing and improving diagnosis. Aged care residents are at increased risk of infection for various reasons including from the medicines they take, yet none of the published initiatives had focussed on the drug-associated risk of infection. Furthermore, antibiotics, whether appropriately or inappropriately used for the treatment of infections, can interact with other co-administered medicines in the elderly, which may include lipid-lowering agents, antihypertensives, antiarrhythmics, antidiabetics, and anticoagulants. These interactions can lead to serious adverse effects including severe liver toxicity, muscle destruction, risk of bleeding, and hyperkalaemia. Importantly, present studies had not measured the outcomes from the point of view of drug interactions and related adverse effects.

Therefore, effective AMS should consider medicines that may increase the risk of infection, which may inadvertently contribute to over-prescribing and inappropriate prescribing of antibiotics, and potentially leads to unwanted consequences such as antibiotic resistance and antibiotic-drug interactions. Thus, research is required to identify the prevalence of use of medicines that potentially contribute to infection burden in residents of RACFs, as a means of reducing infection risk and associated antibiotic use, together with the prevalence of antibiotic-associated drug interactions as a means of minimising the risk of preventable drug misadventure.

Chapter 3 Thesis overview

The review of the literature (Chapters 1 and 2) identified that infections are a significant problem in aged care facilities, both in Australia and internationally. UTIs, RTIs, and SSTIs are the most common infections in RACFs. Risk factors for these infections in the elderly include structural and physiological changes in organ function, a decline in immunity, and the presence of multiple diseases, which leads to taking multiple medicines that may increase the risk of infections.

The most commonly used antibiotic groups are cephalosporins, macrolides, and other antibiotics such as trimethoprim. These antibiotics can cause adverse toxicity to the elderly by interacting with other medicines used to treat comorbidities.

Effective AMS should be designed and implemented on the basis of the need and resources of residential aged care. Research into antibiotic stewardship in RACFs (Table 4) has ascertained the need for AMS and attempted to reduce the inappropriate use of antibiotics. Despite this, there remains a need for designing an AMS program to address the issue of medicine-associated increased risk of infection, as well as antibiotic-related drug interactions.

3.1 Aim and objectives

The aim of this study is to reduce the risk of medication misadventure, specifically relating to antibiotics, in residents in aged care facilities. The specific objectives were to:

1. Determine the prevalence of use of medicines that potentially contribute to the infection burden amongst residents of aged care facilities.
2. Assess the risk of drug interactions associated with the co-prescribing of antibiotics and other medicines for residents of aged care facilities.
3. Develop an educational intervention, based on findings from Objectives 1 and 2 and supported by current literature for healthcare professionals providing care to residents of aged care facilities, aimed at minimising drug misadventure related to infectious diseases.
4. Implement and evaluate the educational intervention.

3.2 Null hypotheses

This research was based on three null hypotheses:

1. Residents' chronic medications do not contribute to an increased risk of infection and antibiotic use in aged care facilities.
2. The prescribing of antibiotics in RACFs presents a minimal risk of (serious) drug interactions.
3. A tailored education intervention will not influence the use of antibiotics in RACFs.

3.3 Method

This research utilised two unrelated databases. One source of data was the aged care provider Bethanie, which provided medication utilisation data and remote access to the residents' profile through *iCare*®. Bethanie is one of the leading aged care providers in Western Australia; further details are provided in Section 4.1.4.1. The other source was Webstercare, which provides medication dispensing services to aged care residents; further details are provided in Section 4.1.6.2. Data were collected from the Bethanie aged care through remote access to residents' profiles. Webstercare data were received from the data custodian. A retrospective case-control study was utilised in the analysis of the Bethanie data set to identify the risk drugs. Another retrospective observational study was utilised to analyse the Webstercare dataset to identify the association of increased use of antibiotics with the risk drugs which identified in the Bethanie dataset. The first two studies were non-interventional. The Bethanie dataset was also utilised to investigate the potential drug interactions between antibiotics and other concurrent medicines. In the subsequent research stage, an educational module was developed by utilising the findings obtained from the analysis of the Bethanie dataset for the nursing staff in Bethanie.

3.4 Overview of chapters

Chapter 4 addresses Objectives 1 and 2. This chapter consists of two parts. Part One (*Do drugs increase the risk of infection?*) addresses Objective 1 by utilising both data sources. Part Two (*Does the use of antimicrobials increase the risk of drug interaction?*) addresses objective 2 by utilising Bethanie aged care data.

Chapter 5 (development and implementation of an educational intervention) addresses Objectives 3 and 4. The development of the educational intervention was based on the findings from Objective 1 and 2 and expert advice.

Each of Chapters 4 and 5 comprises a brief introduction with a more detailed literature review specific to that chapter, methodology, results, and discussion of the respective study.

Chapter 6 provides the overall thesis discussion containing recommendations for stakeholders and direction for future research. An overall discussion, with a critique of the methods and findings, is also presented in this chapter.

Chapter 7 provides the conclusion of the thesis, with a reflection on the overall achievements of this research in relation to the objectives of this study.

Chapter 4 Drug-associated infection and antibiotic-drug interactions

This chapter describes the first study of this thesis: analysis of data sourced from an aged care provider network in Western Australia and a national service provider, Webstercare.

The initial research stage was a retrospective study to evaluate a) medication-related factors that may be influencing antibiotic use, and b) medication misadventure as a consequence of antibiotic use, thus addressing Objective 1 (determine the prevalence of use of medicines that potentially contribute to infection burden) and Objective 2 (assess risks associated with co-prescribing of antibiotics and other medicines).

The specific focus of the analysis was the prevalence of risks in the target population, the specific 'signals' being:

1. *Drug-associated infection*: this was determined via the co-prescribing of antibiotics with medicines (identified from the scientific literature) associated with an increased risk of infections in older people. The association between chronic medication and the development of infection was estimated using multivariate regression analysis and expressed as odds ratios with 95% confidence intervals. Further regression analysis was conducted by utilising the Webstercare dataset to determine the association between antibiotic prescriptions and the use of medicines identified in the Bethanie analysis as a risk medicine for infection.

   The research involved analysis of data from two sources: individual residents' electronic medical records from Bethanie aged care facilities in Western Australia; and dispensing data from Webstercare.
2. *Interactions between antibiotics and other medicines*: the prevalence of a range of antibiotic-drug interactions is reported using descriptive statistics.

4.1 Part One: Do certain medicines increase the risk of infection in RACFs?

4.1.1 Introduction

The elderly Australian population aged 65 years and over have an increased burden of illness and disability due to chronic diseases.[1] Chronic disease commonly results in deterioration of quality of life,[185] functional ability, and mobility.[186] It also increases hospitalisations,[187] mortality,[185] mental distress,[188] and the use of healthcare resources.[1] Examples are diabetes mellitus increasing the risk of diabetic foot ulcers and other associated infections,[189] and atherosclerosis enhancing the risk of stroke, which in turn increases the risk of pneumonia.[190] Decline in functional status (e.g. activities of daily living) in the elderly further increases the risk and severity of infections.[191] A prospective cohort study involving six metropolitan and regional residential aged care services in South Australia reported infections (25.5%) was one of the common reason for hospitalisation.[192]

The use of multiple medications is common in the elderly to manage their multiple chronic diseases. Almost 88% of Australians aged 65 years and over who live in the community use at least one prescription medication,[193] while in RACFs, on average 11.1 (SD 5.3) medicines are reportedly used per resident.[69] According to a cross-sectional study of pharmacy dispensing data for all prescription and non-prescription medications used in 2009 by 1,560 residents of 26 Australian RACFs, among the psychotropic medication users (70% of residents), approximately 38% of residents used an antipsychotic, 33% used a hypnotic or sedative, and 35% used an antidepressant.[69] Opioids were used by 43% of residents, and PPIs by 46% of residents in RACFs.[69] Another cross-sectional study of 446 residents with dementia from 53 Australian RACFs found that 58% of residents were prescribed psychotropic medications, where antipsychotics were used by 36%, benzodiazepines by 31%, and antidepressants used by 26% of residents.[194] A cross-sectional study of Westbury et al.[195] of residents from 150 residential aged care facilities of six states of Australia from April 2014 to October 2015, found that antidepressants were the most commonly used medication class, followed by antipsychotics (21.8%), and benzodiazepines (21.6%).[195] Mirtazapine (12.3%), citalopram/escitalopram (10.8%), sertraline (6.9%), and tricyclic antidepressants (4.4%) were the most commonly prescribed antidepressants.

Prescribing patterns of such medicines in RACFs are often not appropriate. According to a systematic review of prevalence studies, the overall prevalence of potentially inappropriate medication use in nursing homes was 43%.[196] Long-acting benzodiazepines, tricyclic antidepressants, fluoxetine, medicines with anticholinergic properties, non-steroidal anti-inflammatory drugs, PPIs, iron supplements, ferrous sulfates, digoxin, and nitrofurantoin were the most prevalent inappropriate medications.[196] An average of two medicine-related problems were present per resident of four RACFs in Victoria, Australia. One-third of these problems were due to overprescribing.[67] A study of 2,345 residents of Australian RACFs reported that 43.8% of all residents were prescribed at least one potentially inappropriate medication (PIM) determined by two tools (Beer's criteria and McLeod's criteria); the residents who were prescribed more than six medicines, and had five or more medical conditions, were at higher risk of PIM use.[197] Psychotropic medicines were the most commonly prescribed PIMs.[197] Overprescribing of antipsychotics, benzodiazepines, and drugs with moderate to strong anticholinergic properties has also been observed in Australian RACFs.[198] A cross-sectional study of 17 RACFs in Australia identified that PPIs (42% of residents had been exposed to a PPI for longer than eight weeks), benzodiazepines (38%), antidepressants (6%), and antipsychotics (31%) were the most common medicine groups involved in potential inappropriate prescribing.[199]

Overprescribing has also been recognised internationally. A cross-sectional study of 29 RACFs in Quebec City, Canada, found that nearly 23% of the residents were inappropriately prescribed (for more than one month) intermediate- and short-acting benzodiazepines. Long-acting benzodiazepines were given inappropriately to almost 6% of residents. A considerable number of residents were receiving dual prescriptions of antipsychotics (17%) or benzodiazepines (15%). Haloperidol was given to 5.2% of residents at a potentially inappropriate dosage.[200]

As established above, inappropriate prescribing of medications is a common problem in RACFs in Australia and other developed countries. Consequences include drug-related adverse outcomes in the elderly. Over the past 20 years, an increasing incidence of these adverse outcomes had been noted in elderly Australians.[68] According to a retrospective study of 62 RACFs in Australia, a total of 1,433 potential drug-related problems were identified in 480 of the 500 residents and were associated with antipsychotics, antidepressants, anxiolytics, hypnotics, opioid analgesics, antiepileptics, PPIs and drugs acting on the renin-angiotensin system.[201] Excess exposure to antipsychotics, benzodiazepines, and

antidepressants increased the risk of falls in aged care residents with dementia.[202] Although PPIs are considered to be safe,[203] adverse outcomes such as bone loss and fractures[204] and nutritional deficiencies[205, 206] have been reported.

Inappropriate use of medicines also increases healthcare costs. In Australia in 2018-2019, the government spent around AU$13.3 billion annually on RACFs.[207] Gnanamanickam et al.[208] reported that a high proportion of all direct health costs are due to medication. The aforementioned cross-sectional study of 17 Australian RACFs reported that the medication cost for each resident exposed to inappropriate prescribing in one year was AU$411±$479.[199] The major portion of the cost was incurred due to the inappropriate use of PPIs, antipsychotics, and benzodiazepines.[199]

As established in Section 1.2, the elderly are vulnerable to infection due to anatomical and physiological changes. Such changes include reduced cough reflex, thinning of the skin, and impaired bladder emptying and capacity. These changes, along with widespread and chronic use of medicines, deteriorate the capacity of the body to prevent infection and make the elderly prone to infections.[209] Particular medicines that increase the risk of infection in the elderly are identified in the following section.

4.1.2 Evidence relating to drug-associated infection in the elderly

4.1.2.1 Antipsychotics

Antipsychotics, mainly atypical antipsychotics, are widely used in RACFs for the treatment of behavioural and psychiatric disorders in the residents.[210] A review and a meta-analysis including 19 observational studies in the elderly (>65 years) have documented an association between antipsychotic drug use and the incidence of pneumonia.[44] Exposure to both typical (first-generation) antipsychotics and atypical (second-generation) antipsychotics is associated with an increased risk of pneumonia compared to non-exposure to these agents.[44]

A cohort study using linked Medicaid/Medicare data for 83,959 residents of nursing homes in the USA reported a 25% (hazard ratio, HR=1.25, 95% CI: 1.05-1.49) higher risk of bacterial infection in the residents exposed to first-generation antipsychotics than in similar residents exposed to second-generation antipsychotics.[211] The researchers used several approaches to manage confounding; however, residual confounding by indication, underestimation of the

outcomes, and misclassification of exposure status were noted.[211] Two studies contrasted this finding. Firstly, a retrospective cohort study in USA nursing home residents reported no significant difference in risk of pneumonia between first-generation (typical) versus second-generation (atypical) antipsychotic use in nursing home residents.[122] The unmatched and matched cohorts comprised 49,904 (46,293 atypical and 3,611 typical) and 7,218 (3,609 atypical and 3,609 typical) new antipsychotic users, respectively.[122] Secondly, Herzig et al. investigated the association between exposure to antipsychotics and the risk of aspiration pneumonia in 146,552 hospitalised patients (median age=56 years; 61% female).[212] Their retrospective cohort study found that exposure to an antipsychotic was significantly associated with aspiration pneumonia (adjusted OR: 1.5, 95% CI: 1.2-1.9), and the association of the risk of aspiration pneumonia was similar with typical (aOR: 1.4, 95% CI: 0.9-2.2) and atypical antipsychotics (aOR: 1.5, 95% CI: 1.1-2.0).[212] In two case-control studies, the strongest association for the risk of pneumonia was observed within the first seven days of antipsychotics therapy.[42, 213] Utilising the claims dataset of the Australian Government Department of Veterans' Affairs, Pratt et al. found that patients initiated on atypical antipsychotics (n=9,239) were less likely to have been hospitalised for pneumonia in the previous 12 months (relative risk: 0.85, 95% CI: 0.77–0.93, p <0.001).[214]

Two studies also reported an increased risk of UTI in the elderly.[53, 54] A Dutch study of 18,541 women (≥65 years) using dispensing data obtained from the PHARMO Database Network for the period of 1998-2008 demonstrated that current users of antipsychotics were 1.33-fold (95% CI 1.27-1.39) more likely to have experienced a UTI than past users.[54] The risk of occurrence of UTI was high in the first week following the start of the antipsychotics (adjusted hazard ratio, aHR: 3.03, 95% CI: 2.63-3.50) and declined after three months (adjusted HR: 1.22, 95% CI: 1.17-1.28). A similar effect was reported between typical and atypical antipsychotics.[54] However, a recent cohort study of 191,827 primary care patients of 65 years or older in the UK showed that the risk of UTI was slightly higher in males than females, and the risk also slightly higher in typical than the atypical antipsychotic users.[53] Similar to the previous Dutch study, current exposure to antipsychotics increased the risk of UTI compared to the past user (aHR: 1.31; 95% CI: 1.28-1.34). This association was highest in the first two weeks of use (aHR: 1.83; 95% CI: 1.73-1.95) and in patients with concurrent use of more than one antipsychotic (aHR: 1.64; 95% CI: 1.45-1.87).[53]

4.1.2.2 Benzodiazepines

According to a population-based study, benzodiazepine exposure increased the risk of developing pneumonia by 1.54 times (95% confidence interval, CI: 1.42-1.67).[39] Using short- and long-term mortality analysis, this study found that benzodiazepines were associated with the increased rate of mortality within 30 days (HR: 1.22, 95% CI: 1.06-1.39) and long term (HR: 1.32, 95% CI: 1.19-1.47) following initiation of benzodiazepines.[39] Therefore, benzodiazepine exposure was not only associated with the increased risk of pneumonia but also dying from pneumonia.[39] Another recent study reported that benzodiazepine exposure increased the relative risk of community-acquired pneumonia by 2.76 times (95% CI: 2.35-3.25).[215] Community-dwelling adults with a recent diagnosis of Alzheimer's disease were also at significant risk of developing pneumonia associated with benzodiazepines use (aHR: 1.28, 95% CI: 1.07-1.54), and the risk was highest within the first 30 days of benzodiazepine exposure (HR: 2.09, 95% CI: 1.26-3.48).[40] Exposure to benzodiazepines within 30 days prior to the "influenza-like-illness" was associated with increased occurrence of both "influenza-like-illness"-related pneumonia (aHR: 4.24, 95% CI: 2.27-7.95) and mortality (aHR: 20.69, 95% CI: 15.54-27.54).[216] In a large nested case-control study of more than 36,000 of chronic kidney disease patients, risks of pneumonia increased by 31% among the current (within 1-30 days) users of benzodiazepines (aOR: 1.31, 95% CI: 1.18-1.26) than the non-users. This increase in risk was independent of the daily dose. However, the risk was greater when benzodiazepines were newly initiated within 30 days (aOR: 2.47, 95% CI: 2.02-3.03) or administered parenterally (aOR: 2.88, 95% CI: 1.87-4.42).[41]

However, conflicting evidence also exists. Two population-based case-control studies observed decreased community-acquired pneumonia risk with benzodiazepine use compared to non-use, [47, 217] while one study reported no association.[218] The possible reason for this discrepancy (decreased risk) was proposed in a review as the burden of high comorbidity in the elderly, which is an independent factor increasing the risk of pneumonia greater than the risk of benzodiazepine exposure.[219] In the other study supporting no association, possible bias in case selection, younger participants (age >14 years), use of a self-reported questionnaire, and a specific geographical location in Spain (eastern coast, Mediterranean climate), may be the reason for this difference with other studies.

4.1.2.3 Proton pump inhibitors

PPIs are associated with an increased risk of diarrhoea caused by *C. difficile* infection and pneumonia in the elderly.[220] An approximately two-fold (OR: 1.99, CI: 1.73-2.30, p<0.001) increased risk of *C. difficile* infection was reported in patients with PPIs users than the non-users by a recent meta-analysis of 56 studies (40 case-control and 16 cohort) involving 356,683 patients.[220] A significant association of increased risk of *C. difficile* infection in PPIs users compared to non-users was also previously reported by several meta-analyses.[49, 50, 221, 222] Two to three-fold increased risk of *C. difficile* infection in PPIs users than in non-users also reported in a population (cross-national study)[223] and hospital-based studies.[120, 224-227] A study of 53 residents of RACFs (mean age: 82.2 years) by retrospective chart review reported PPI use was a risk factor for the *C. difficile*-associated disease (60% versus 32%, χ^2=4.137; p<.05).[228]

Another recent meta-analysis of 26 studies (which included 226,769 cases of community-acquired pneumonia among 6,351,656 participants) reported that PPI users were nearly 50% (OR: 1.49, 95% CI: 1.16-1.92) more likely to be associated with an increased risk of community-acquired pneumonia than non-users. The risk was highest within the first 30 days of PPI therapy (OR: 2.10, 95% CI: 1.39-3.16).[229] Arai et al.[230] conducted a retrospective observational study of 335 acute stroke patients who were admitted to a tertiary care hospital in Hiratsuka, Japan, from 1st January 2006 through 1st January 1, 2016. They reported the PPI-exposed group was at two-fold (95% CI: 1.12-3.57) increased risk of pneumonia in the first 14 days of hospital admission than the non-exposed group with acute stroke.[230]

4.1.2.4 Antiepileptics

A recent meta-analysis found a 4% higher risk of infection in topiramate users compared to non-users (95% CI: 0.01-0.06). Levetiracetam and brivaracetam were associated with a 3% increased risk of infection (95% CI: 0.01-0.05).[231] A systematic review reported that levetiracetam increased the risk of URTI and the common cold compared to those taking a placebo (13.4% versus 7.5%, p=0.005).[232] These results have not been confirmed by other reports.[232] In general, the rates of all types of infections (bacterial, viral, fungal, and parasitic) were higher in levetiracetam group than the placebo group (30.2% and 26.9%, respectively; statistical significance was not mentioned).[232]

4.1.2.5 Antidepressants

According to a case-control investigation of *C. difficile* infection amongst hospitalised adults (n=4,047), patients taking mirtazapine (OR: 2.14, 95% CI: 1.30-3.52) and fluoxetine (OR: 1.98, 95% CI: 1.16-3.17) were significantly more likely to develop a *C. difficile* infection.[233] A hospital-based retrospective cohort study of 14,719 patients also found antidepressants (as a group) were a significant predictor for *C. difficile* infection.[225] Including pharmacologically-diverse antidepressant agents as a single group may not be appropriate, if considering that acid secretion is reduced by tricyclic antidepressants (by antagonizing histamine and muscarinic receptors)[234] and stimulated by serotonin reuptake inhibitors (fluoxetine and sertraline).[235] Another limitation of their study was being unable to acquire and measure other co-morbidities that might have affected the outcome of their study.

A study in the USA of 30,998 elderly inpatients who were hospitalised for depression found that "hospitalisation for aspiration pneumonia was three times as likely to occur in the 90-day period following hospitalisation for depression, compared to the 90-day period preceding a hospitalisation for depression, leading to the hypothesis that antidepressant drugs may increase the risk of aspiration pneumonia".[236] However, another recent study suggests no increased risk of hospitalisation (OR: 0.63, 95% CI: 0.23-1.71) for pneumonia in elderly people taking antidepressants after adjusting for comorbidities (dysphagia, chronic obstructive pulmonary disease, senile dementia, past use of antipsychotics, past use of benzodiazepines, and current use of anti-Parkinsonian medicines).[237]

4.1.2.6 Opioid analgesics

The observational studies have assessed the association between the risk of serious infections and opioid analgesic use in the general population, all reporting a higher risk of infections associated with opioid analgesic use compared with no use.[47, 48, 238]

A self-controlled retrospective case series analysis of a cohort of 13,796 patients with rheumatoid arthritis enrolled in the Tennessee Medicaid program (1995-2009), USA, demonstrated that opioid analgesics were associated with an increased risk of hospitalisations for serious infection, such as pneumonia, meningitis, encephalitis, septicaemia, cellulitis, soft-tissue infections, endocarditis, pyelonephritis, infective arthritis and osteomyelitis.[48] Among patients with rheumatoid arthritis, the incidence of hospitalisations due to serious infection was higher during periods of new (incidence rate ratio, IRR: 2.38, 95% CI: 1.65-3.42) and current (IRR: 1.39, 95% CI: 1.19-1.62) opioid use in

comparison to periods of non-opioid use. Higher risks were associated with long-acting opioids (IRR: 2.01, 95% CI: 1.52-2.66), immunosuppressive opioid use (IRR: 1.72, 95% CI: 1.33–2.23), new opioid use (IRR: 2.38, 95% CI: 1.65-3.42), than non-use.[48] The study examined the association between opioid use and serious infection by controlling for both fixed and time-varying covariates, which increased the strength of the study. However, the probability of confounding by indication cannot be excluded. Rheumatoid arthritis is an autoimmune disease, which itself is a risk factor for increased risk for serious infections.[239-241]

A population-based case-control study also observed higher pneumonia risk (aOR: 1.38, 95% CI: 1.08-1.76) with current use (five to 60 days prior to pneumonia incidence) of prescription opioids in this study of community-dwelling older adults aged 65-94 years from 2000-2003. The risk was highest within 14 days of opioid use (OR: 3.24, 95% CI: 1.64-6.39) and with use of long-acting opioids (OR: 3.43, 95% CI: 1.44-8.21) or those classified as an "immunosuppressive opioid" (OR: 1.88, 95% CI: 1.26-1.79) compared to non-use.[47]

More recently, a nested case-control study reported that exposure to opioids was associated with an increased risk for invasive pneumococcal disease. A 1.62-fold (95% CI: 1.36-1.92) higher risk of infection was observed among the current users of opioids compared with past users. Associations were strongest for opioids that were long acting (aOR: 1.87, 95% CI: 1.24-2.82), of high potency (aOR: 1.72, 95% CI: 1.32-2.25), or were used at high dosages (aOR: 1.71, 95% CI: 1.22-2.39). That study included patients aged five years and older.[238]

4.1.2.7 Antithyroid medicines

According to a retrospective study using medical record review at National Taiwan University Hospital between January 1987 and December 1997, 5,653 patients were treated with antithyroid medicines (thionamides and propylthiouracil).[123] Among them, the prevalence of life-threatening infection related to antithyroid-induced agranulocytosis was 13 (0.23%), and the most common pathogen isolated in these infections was *Pseudomonas aeruginosa*.[123] Although that study reported most of the patients were female (10/13 cases of agranulocytosis induced by antithyroid drugs), agranulocytosis may occur irrespective of gender in any age group.[123]

4.1.2.8 Corticosteroids

Observational studies have reported that systemic exposure to corticosteroids were associated with the increased risk of tuberculosis,[242, 243] bacterial pneumonia,[45] *C. difficile* infection,[244] viral infections,[242] postoperative infections,[245] opportunistic infections (oral candidiasis, tuberculosis)[242] and sepsis.[242] Using provincial healthcare databases, a Canadian case-control study examined the risk of serious infections in patients with inflammatory bowel disease and explored a significantly higher risk of serious infections in oral corticosteroids user than the non-users at any time within the previous six months (adjusted relative risk, aRR 2.3; 95% CI: 1.8-2.9).[46] The risk of common bacterial infections was increased by four times in those exposed to oral corticosteroids during the 45 days prior to the incidence of infection (aRR: 4.0, 95% CI: 2.5-6.6).[46]

In a recent cohort study of the UK population, using The Health Improvement Network primary care database, 275,072 adults were identified as prescribed oral glucocorticoids between 2000 and 2012.[246] When comparing glucocorticoid-exposed and non-exposed groups with the same underlying disease, the adjusted hazard ratios for infections were significantly higher in the glucocorticoid-exposed group, ranging from 2.01 (95% CI: 1.83-2.19; p<0.001) for cutaneous cellulitis to 5.84 (95% CI: 5.61-6.08; p<0.001) for LRTI.[246] No difference was reported in the risk of dermatophytosis, scabies, and varicella.[246] The higher relative risk (RR) of local candidiasis and LRTI was observed in the glucocorticoid-exposed group during the first week of treatment with glucocorticoids.[246] Use of medical linkage data may have resulted in misclassification of infectious outcomes. The potential for reporting bias and lack of data regarding adherence to glucocorticoid treatment should also be noted.[246]

4.1.3 Summary of the evidence

Among the studies above, eight were case-control studies[39, 41, 42, 46, 47, 213, 233, 238] and six were observational cohort studies.[53, 122, 211, 212, 225, 246] One was a self-controlled retrospective case series analysis,[48] and two were based on retrospective chart review.[228, 230] Nine of the studies identified patients from administrative databases,[39, 41, 42, 46, 48, 54, 211, 213, 246] four from nursing homes,[47, 122, 228, 238] four from hospital records,[212, 225, 230, 233] and one from primary care records.[53]

The drug groups associated with increased risk of infections included antipsychotics, benzodiazepines, PPIs, antiepileptics (topiramate, levetiracetam and brivaracetam), antidepressants, opioid analgesics, antithyroid, and corticosteroids. Antipsychotics were associated with pneumonia,[44, 122, 212] bacterial infection[211] and UTI;[53, 54] benzodiazepines with pneumonia;[39-41, 216] PPIs with pneumonia[229, 230] and *C. difficile* infection;[49, 50, 220, 221, 223, 228] antiepileptics with URTI[232] and all types of infections (bacterial, viral, fungal, and parasitic);[231, 232] antidepressants with *C. difficile* infection[225, 233] and aspiration pneumonia;[236] opioid analgesics with pneumonia,[47, 48] pneumococcal infection[238] and other serious infections (meningitis, encephalitis, septicaemia, cellulitis, soft-tissue infections, endocarditis, pyelonephritis, infective arthritis and osteomyelitis);[48] antithyroid agents with *Pseudomonas aeruginosa* infection[123]; corticosteroids were associated with increased risk of tuberculosis,[242] pneumonia,[45] *C. difficile* infection,[244] oral candidiasis,[242] common bacterial infection[46] and other infections (dermatophytosis, scabies, and varicella).[246]

The highest risk of occurrence of infection was observed within seven days,[54, 246] 14-days,[47] 45 days,[46, 230] 30 days,[39-41, 229, 238] 60 days,[47] 90 days,[236] and 180 days[46] following the start of the risk drugs.

Most of the studies were population-based studies, with only four conducted in RACFs. The extant literature in this field is based on individual drug groups, rather than their relative impact on aged care residents subject to polypharmacy. Thus, the investigation into the residents of RACFs is warranted. Therefore, the aim of this study is to determine the prevalence of use of medicines that potentially contribute to the infection burden amongst residents of aged care facilities.

4.1.4 Methods (Bethanie data)

This method section was the first type of analysis of the Bethanie dataset. A retrospective case-control method was selected in the current study. Case-control studies are applied in health research to ascertain a variable that differs in frequency between the case and control groups, and which later may be predicted as a possible risk factor for the outcome.[247] Thus, retrospective case-control studies look back to identify the statistically significant difference in the rates of exposure to a defined risk factor between the case and control groups.[247] A number of retrospective case-control studies revealed a possible association of pneumonia,[41, 213, 248, 249] tuberculosis,[52] and gastroenteritis[119] with particular medicines in elderly people. Case-control methods have some advantages over other methods, such as being well suited for examining rare outcomes, outcomes with a long latency period, the ability to use existing records, and the ability to examine multiple risk factors.[247] However, limitations include susceptibility to recall or information bias, difficulty in the validation of retrospective data, the possibility of incomplete control of extraneous variables, and difficulty in the selection of an appropriate comparison group.[247]

4.1.4.1 Data access

Data for this study were accessed via The Bethanie Group Inc. ('Bethanie'). Bethanie is an aged care provider in Western Australia, established in 1954.[250] Bethanie has facilities across the Perth metropolitan area as well as regional centres in the south-west of Western Australia (WA). Their 12 sites are Bethanie Beachside, Bethanie Elanora, Bethanie Fields, Bethanie Peel, Bethanie Joondanna, Bethanie Kingsley, Bethanie at Wearne, Bethanie Waters, Bethanie Warwick, Bethanie at Riversea, Bethanie Illawong, and Bethanie Geneff Hostel. The total capacity is 2,030 beds. Bethanie also operates nine social centres throughout WA, where clients can connect with other members of the community for social activities, and care services are provided to 3,600 clients in their homes. The present research focused on the residents of RACFs, not the community-dwelling citizens.

Bethanie has a commitment to research as a part of continuous quality improvement and corporate social responsibility.[250] To uphold their mission and vision, Bethanie supports academic research that aims to improve services to, and the quality of life of, aged care clients. Bethanie's strategic research priorities and support of university research since 2010 have spanned quality of life, dementia, palliative care, wound management, falls, medication management, infection control, and workforce development. A letter of intent was supplied to indicate their endorsement of this research (Appendix 1).

Data sourced from Bethanie comprise clinical data in conjunction with medicine administration data and were accessed at the level of individual residents. This enabled the construction of relevant cohorts of residents to determine the relative risk of antibiotic prescribing amongst those receiving (versus not receiving) medicines known to increase the risk of infection while correcting for other risk factors. In the case of antibiotic-drug interactions, incidence and clinical outcomes were also examined. Access to residents' records enabled review of data relating to the residents' predisposing medical conditions and risk factors that may have contributed to the infection, indications for prescribed medicines (including antibiotics) and medical history. Bethanie residents' data were accessed remotely through *iCare*® manually; this platform and the available data are described in the following section.

4.1.4.2 *iCare*® Health software

iCare® is an electronic platform for real-time management of aged care residents' clinical and non-clinical data, accessed and managed by Bethanie staff via an intranet across the 12 Bethanie facilities. The Bethanie intranet is available through the secure *Netscaler*® gateway. *iCare*® *Health Live*® is then accessed via the intranet home screen.

The training was provided by Bethanie management to access and navigate *iCare*®. Following training, log-in details were provided, enabling access to relevant sections (tabs): *Home*, *Residents*, *Documentation*, *Medication, Reporting,* and *Funding*. Among these six sections or tabs, two (*Residents* and *Medication*) tabs were navigated to search required information for the research. The *Residents* tab reveals each resident's Profile, Progress Notes, Care Plan, Forms, Charts, Residential Details, Contacts, and Tasks. In the current research, data were commonly sourced from (i) the Progress Notes, which lists daily records of the resident's health, treatment provided, and other care given, and (ii) the Resident Details menu, which lists the resident's demography, family history, and past and current diagnoses.

The *Medication* tab is configured with sub-menus: Medication Profile, Missed Medication, Pharmacy Messages, Daily Drug Round, and Medication Report. Among these sub-menus, Medication Profile and Daily Drug Round were commonly used for data collection. The Medication Profile contains a single electronic medication chart of regular, PRN (as-required), and short-course medication. Data on daily administered medication, including the time of administration for a specific resident, were retrieved from the Daily Drug Round.

4.1.4.3 Case and control definitions

Cases were all residents who had at least one infection in 2015. Controls were defined as all residents who had no infection in 2015.

Inclusion criteria:

Only residents who were alive and stayed in the residence for the 12-month study period were included in the regression analysis.

Exclusion criteria:

In the case group, residents with hospital-acquired infection, surgical site infection, shingles infection or urinary catheter-related infection were excluded. These were identified and reported by the Bethanie staff member which were noted in the residents' Progress Note.

In the control group, residents who entered the RACF after 2015, and residents who were living in the community (a small subgroup under a different care arrangement), were excluded.

4.1.4.4 Sample size

The sample size was calculated using an online sample size calculator.[251] This calculator uses the following formula for the sample size: "n=(Zα/2+Zβ)2 * (p1(1-p1)+p2(1-p2)) / (p1-p2)2, where Zα/2 is the critical value of the Normal distribution at α/2 (e.g. for a confidence level of 95%, α is 0.05 and the critical value is 1.96), Zβ is the critical value of the Normal distribution at β (e.g. for a power of 80%, β is 0.2 and the critical value is 0.84) and p1 and p2 are the expected sample proportions of the two groups".

Proportion 1 is 9.9%, which indicates the annual incidence rate of pneumonia.[252] Proportion 2 is 16.8%, which has been calculated by multiplying proportion 1 by the average OR of 1.7 for drug-associated pneumonia reported for three common drug groups: PPIs, antipsychotics, and benzodiazepines (1.6,[42] 1.5,[39] and 2.2,[249] respectively). The sample size calculation indicated that data relating to 375 residents were required for each group (case and control) to achieve 80% power with a 95% (α is 0.05) confidence interval to detect a significant difference between the two groups. Pneumonia was chosen as the infection of interest because this was the most prevalent infection in RACFs,[60, 108, 252] and most of the identified drugs in the literature showed a strong association with the increased risk of pneumonia (Section 4.1.2).

4.1.4.5 Sample selection

4.1.4.5.1 Case group

Bethanie provided an *Excel*® data file of 640 residents with a total of 1,236 documented incidences of infection from January 2015 to December 2015. Among the 640 residents, 20 were community-based residents, who were subsequently excluded from the dataset. Residents were assigned a serial number from 1 to 620. An online randomiser[253] was used to select 375 residents to constitute the case group, in accordance with the calculated sample size (section 4.1.4.4) 4.1.4.4. Fifty-four residents whose information could not found in *iCare*® (records of deceased residents were not available) or who did not meet the inclusion criteria were replaced with the next resident on the list who had not been randomly assigned into the study.

4.1.4.5.2 Control group

Residents who had no infection or did not use an antimicrobial agent (excluding prophylactic use) during 2015 were selected as the control group. To identify the control group, lists of residents were printed from all Bethanie facilities; these totalled 2,030 residents, assuming full capacity of the 12 facilities, prior to the elimination of ineligible data and the 620 residents who had an infection in 2015.. The index dates for the control group were generated by an online date randomiser (https://random-date-generator.com/).

4.1.4.6 Coding

4.1.4.6.1 Coding of disease category

The *International Statistical Classification of Diseases and Related Health Problems 10th Revision* (ICD-10)[254] was used for classifying all medical histories. Diseases were classified by main class (I to XXI). Category I represents "Certain infectious and parasitic diseases", II "Neoplasms", III "Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism", IV "Endocrine, nutritional and metabolic diseases", V "Mental and behavioural disorders", VI "Diseases of the nervous system", VII "Diseases of the eye and adnexa", VIII "Diseases of the ear and mastoid process", IX "Diseases of the circulatory system", X "Diseases of the respiratory system", XI "Diseases of the digestive system", XII "Diseases of the skin and subcutaneous tissue", XIII "Diseases of the musculoskeletal system and connective tissue", XIV "Diseases of the genitourinary system", XV "Pregnancy, childbirth and the puerperium", XVI "Certain conditions originating in the perinatal period", XVII "Congenital malformations, deformations and chromosomal abnormalities", XVIII "Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified", XIX "Injury, poisoning and certain other consequences of external causes", XX "External causes of morbidity and mortality", and XXI "Factors influencing health status and contact with health services".

4.1.4.6.2 Coding of medicines

Medications were classified according to the third level category in the *Australian Medicines Handbook* (*AMH*), accessed through the Curtin University Library database,[255] to justify the use of the *AMH* classification system – presumably relevant to Australian medicine formularies. All vitamin and mineral supplements were classified as Vitamins and Minerals.

4.1.4.6.3 Coding of infections

All infections were classified according to the *Therapeutic Guidelines: Antibiotic*, Version 13, 2006.[256] Infections were classified under the broad categories of Eye infections, Gastrointestinal tract infections, Oral and dental infections, Respiratory tract infections, Skin and soft tissue infections, or Urinary tract infections.

4.1.4.7 Ethical issues

Ethical approval was granted by the Human Research Committee of Curtin University (approval number HR26/2016 (Appendix 2). The resident data accessed via *iCare*® were re-identifiable, as each person was allocated a code number. During all stages of data review, analysis and reporting, data were stored on a secure server at Curtin University.

The ethical approval included a Waiver of Consent, in accordance with section 2.3.10 of the *National Statement on Ethical Conduct in Human Research* (2007) (updated May 2015).[257] The Waiver of Consent was granted on the basis that: individual residents did not need to be contacted about this research for consent to access their data; there was no physical harm to the residents associated with not seeking consent throughout this data collection; the outcomes of this data collection were utilised to develop an educational intervention for better treatment outcome of the residents; and the only risk was to individuals' privacy (managed as described above).

4.1.4.8 Statistical analysis

The chi-square test was used to compare age groups (less than 60, 61-65, 66-70, 71-75, 76-80, 81-85, 86-90, 91-95, more than 96 years), gender, medical history (as described in Section 4.1.4.6) and current medicine use (as described in Section 4.1.4.6) between the case and control groups. The age groups were determined to represent the breadth of residents in these facilities and were presented categorically to facilitate descriptive analysis.

Univariate logistic regression, followed by multivariate logistic regression, was used to determine any association between medication and incidence of infection, within a 95% confidence interval and with significance determined at $p<0.05$. Residents' medication class and class of medical conditions were included as independent variable. The multivariate logistic regression model, with case/control (infection vs no infection) as the dependent variable, and all the medication and medical histories were included initially as independent variables. Through a process of backward elimination, the least significant variable was dropped from the model (one at a time), until all variables remaining in the final model were significantly associated with the outcome. All pairwise interaction terms between these final variables were then explored for statistical significance. The Akaike Information Criteria was obtained on the output of the analysis. For each model, the change in Akaike Information Criteria between the simple model, including only the intercept, and the full model, including the intercept plus independent variables, was obtained.

4.1.5 Results (Bethanie data)

4.1.5.1 Demographics of the resident sample

According to the sample size calculation (Section 4.1.4.4), a total of 750 residents (375 in each of the case and control groups) were required for the study. A total of 726 Bethanie residents were included in this research. Among them, 375 (who had a documented infection in 2015) were in the case group and 351 (who had no infection documented in 2015) were in the control group. The mean age of residents of the case group (85.4±7.8 years) was slightly higher than the control group (83.1±8.7 years), but the difference was not statistically significant. Among the residents in the case group, 105 (28.0%) were male and 270 (72.0%) were female, whereas in the control group, 123 (35.4%) were male and 228 (64.9%) were female. This distribution was significantly weighted towards females in the case group ($p=0.04$) (Table 5).

Table 5. Age and gender distribution of residents at enrolment

Gender	Case (N=375) n (%)	Control (N=351) n (%)
Female	270 (72.0)	228 (64.9)
Male	105 (28.0)	123 (35.4)
Age (years)	Case (N = 375) n (%)	Control (N = 351) n (%)
≤70	21 (5.6)	34 (9.6)
71 – 75	18 (4.8)	28 (7.9)
76 – 80	49 (13.0)	50 (14.2)
81 – 85	74 (19.7)	83 (23.6)
86 – 90	108 (28.8)	96 (27.3)
91 – 95	84 (22.4)	42 (11.9)
≥ 96	21 (5.6)	18 (5.1)

Gender distribution: chi-square = 4.1744, p = 0.04
Age distribution: chi-square = 19.94, p = 0.003

4.1.5.2 Medical history

Table 6 presents the differences in medical history between the case and control groups. In the control group, 71.7% (n=252) of residents had a history of disease of the circulatory system, whereas in the case group, this was 70.6% (n=265). Residents of the case group had a significantly higher prevalence of diseases of the genitourinary system (32.8%, n=123), digestive system (29.6%, n=111) and respiratory system (22.6%, n=85) than the control group (18.8%, n=66; 22.7%, n=80 and 14.2%, n=50 respectively). The prevalence of mental and behavioural disorders was significantly higher in the control group (82.9%, n=291) than the case group (68%, n=255).

Table 6. Medical history at enrolment

Medical history[#]	Case group (N=375) n (%)	Control group (N=351) n (%)	P value
Diseases of the circulatory system	265 (70.6)	252 (71.7)	0.73
Mental and behavioural disorders	255 (68)	291 (82.9)	<0.0001*
Diseases of the musculoskeletal system and connective tissue	231 (61.6)	215 (61.2)	0.92
Endocrine, nutritional and metabolic diseases	166 (44.2)	150 (42.7)	0.67
Diseases of the genitourinary system	123 (32.8)	66 (18.8)	<0.0001*
Diseases of the digestive system	111 (29.6)	80 (22.7)	0.03*
Diseases of the nervous system	104 (27.7)	103 (29.3)	0.63
Diseases of the respiratory system	85 (22.6)	50 (14.2)	0.00*
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	80 (21.3)	69 (19.6)	0.57
Diseases of the eye and adnexa	51 (13.6)	34 (9.6)	0.10

*p<0.05, significant difference

[#]Diseases classified according to *The International Statistical Classification of Diseases and Related Health Problems* 10th revision (ICD-10)[254]

4.1.5.3 Current medicines

Table 7 shows the use of medicines between the two groups. There were significant differences in the prevalence of use of PPIs (44.5% vs 34.4%), beta-blockers (27.25 vs 20.2%), benzodiazepines (24.2% vs 15.3%), tricyclic antidepressants (13.3% vs 5.4%), "other antiepileptics" (19.7% vs 13.3%), and "other antidepressants" (17.6% vs 11.1%) between residents of the case group and the control group. The prevalence of antipsychotics and selective serotonin reuptake inhibitors use were significantly high in the control group (17.9% and 18.2%, respectively) than the case group (11.4% and 12.5%, respectively).

Table 7. Current medicines at enrolment

Medicine groups#	Case (N=375) n (%)	Control (N=351) n (%)	P value
Vitamins and minerals	192 (51.2)	161 (45.9)	0.15
Non-opioid analgesics	207 (55.2)	195 (55.5)	0.92
Proton pump inhibitors	167 (44.5)	121 (34.4)	0.00*
Other antiplatelet drugs	107 (28.5)	99 (28.2)	0.92
Loop diuretics	99 (26.4)	91 (25.9)	0.88
Beta-blockers	102 (27.2)	71 (20.2)	0.02*
Statins	91 (24.2)	78 (22.2)	0.51
Benzodiazepines	91 (24.2)	54 (15.3)	0.00*
Other antiepileptics	74 (19.7)	47 (13.3)	0.02*
Selective serotonin reuptake inhibitors (SSRIs)	47 (12.5)	64 (18.2)	0.03*
Thyroid hormones	62 (16.5)	53 (15.1)	0.59
Sartans	53 (14.1)	50 (14.2)	0.96
Antipsychotics	43 (11.4)	63 (17.9)	0.01*
ACE inhibitors	67 (17.9)	62 (17.7)	0.94
Other antidepressants	66 (17.6)	39 (11.1)	0.01*
Calcium channel blockers	58 (15.4)	45 (12.8)	0.30
Antidiabetic agents	41 (10.9)	36 (10.3)	0.76
Laxatives combination	41(10.9)	33 (9.4)	0.49
Tricyclic antidepressants	50 (13.3)	19 (5.4)	<0.001*
Opioid analgesics	29 (7.7)	27 (7.6)	0.98
P2Y12 antagonists	33 (8.8)	26 (7.4)	0.49
Opioid agonist antagonists combination	23 (6.1)	20 (5.7)	0.80
Anticholinergics	24 (6.4)	14 (3.9)	0.14
Serotonin and noradrenaline reuptake inhibitors	20 (7.1)	25 (7.1)	0.31
Antiarrhythmics	19 (5.0)	20 (5.7)	0.70
Other anticoagulants	21 (5.6)	16 (4.5)	0.52
Nitrates	16 (4.2)	18 (5.1)	0.58
Corticosteroids	36 (9.6)	27 (7.7)	0.36

*p<0.05

#Medicines classified according to *Australian Medicines Handbook* (*AMH*)

4.1.5.4 Prevalence of infections

The types of infections among the residents of the case group has been documented in Table 8. The most common infection was UTI, affecting nearly half (45.9%, n=172) of the residents in 2015. The prevalence of RTI and SSTI were 38.9% (n=146) and 22.9% (n=86), respectively. Nearly two-thirds (63.7%, n=239) of residents had experienced one documented infection in 2015, whereas 22.1% (n=83) had two infections documented. Very few residents (4%, n=15) were hospitalised following the infection. From the available records, 2.9% (n=11) of residents had been infected with a MDR organism.

Table 8. Prevalence of infection and number of infection incidence at enrolment (case group only, N=375; Jan 2015 – Dec 2015)

Variable	Prevalence, n (%)
Types of infection	
Urinary tract infection	172 (45.9)
Respiratory tract infection	146 (38.9)
Skin and soft tissue infection	86 (22.9)
Eye infection	31 (8.3)
Gastrointestinal tract infection	16 (4.3)
Multidrug-resistant infection	11 (2.9)
Mixed infection	5 (1.3)
Oral and dental infection	3 (0.8)
Ear infection	1 (0.3)
Number of infections per residents	
1	239 (63.7)
2	83 (22.1)
3	33 (8.8)
4	10 (2.7)
5	6 (1.6)
6	3 (0.8)
7	1 (0.3)
Infection-associated hospitalisation	15 (4.0)

The most commonly prescribed antimicrobial agents for the documented infections were cephalosporins (33.8%), penicillins (25.3%), and other antibacterials (19.6%). Macrolides were used for 10.2% of the infections. Other prescribed antimicrobials for infections, totalling 10%, comprised quinolones (6%), tetracyclines (3%) and aminoglycosides (1%). Less than one percent of infections were treated with lincosamides (0.3%), nitroimidazoles (0.3%) and azoles (0.1%) (Table 9).

Table 9. Prevalence of antimicrobial use in 2015 (N =564[a] infection incidents)

Antimicrobial agents	Prevalence, n (%)
Cephalosporins	191 (33.8)
Penicillins	143 (25.3)
Other antibacterials[b]	111 (19.6)
Macrolides	57 (10.1)
Quinolones	34 (6.0)
Tetracyclines	17 (3.0)
Aminoglycosides	6 (1.0)
Lincosamides	2 (0.3)
Nitroimidazoles	2 (0.3)
Azoles	1 (0.1)

[a] This number represents the total number of infection incidences by considering the multiple infection incidents per residents in the case group. Thus, total number was higher than the resident number (375).
[b] Classified according to the *AMH.* This group consisted of chloramphenicol, hexamine hippurate, nitrofurantoin, trimethoprim, and trimethoprim with sulfamethoxazole.

Univariate OR, and their p-values and 95% CI, were calculated to determine the association between medication categories and the risk of infections (Table 10). These analyses were based on the people who were resident in the facility for the entire 12-month observation period in 2015; this period enabled review of the residents' progress, including those whose infection occurred later in the year. The analysis was restricted to residents who were alive in 2015, as the Bethanie aged care record system archives the records of deceased residents from its electronic patient care system, and as a result they were not available for review. This analysis identified that 372 of 375 residents in the case group and 318 of 351 residents of the control group were in the facility for the whole year. Attrition was primarily due to death and hospitalisation, the rates of which were unable to be estimated in the initial sample.

PPIs, beta-blockers, benzodiazepines, "other antiepileptics",[255] "other antidepressants,"[255] and tricyclic antidepressants showed statistically significant associations with increased risk of infection. On the contrary, SSRIs and antipsychotics were both significantly associated with decreased risk of infection, i.e., appeared to have a protective effect. These findings are explored in more detail below.

The incidence of any infection in the 12-month period among PPI users was 44.3%, whereas among non-users, it was 56.6%. This represents a significant difference ($p<0.05$, OR: 1.43, 95% CI: 1.05-1.94). The associated odds ratio reveals residents who used PPIs were 1.43 times more likely to have had an infection in 12-month period than the non-users.

In case of beta-blockers, 101 out of 164 users had a documented infection, whereas 271 out of 526 non-users had an infection. The incidence of any infection in past 12 months among beta-blocker users was 27.1%, compared to non-users at 72.8%. This represents a significant difference ($p<0.05$, OR: 1.51, 95% CI: 1.05-2.16). Residents who used beta-blockers were more likely (1.51 times) to have had an infection in the 12-month period of 2015 than the non-users.

Amongst residents taking benzodiazepines, the incidence of any infection in the past 12 months was 24.1%, whereas, among non-users, it was 75.8%. This represents a significant difference ($p<0.05$, OR: 1.71, 95% CI: 1.17-2.51). The associated odds ratio reveals residents who used benzodiazepines were 1.71 times more likely to have had an infection in a 12-month period than the non-users. The residents exposed to other antidepressants were 1.74 times more likely to have infection than the non-exposed group ($p<0.05$, OR: 1.74, 95% CI: 1.12-2.71) .

Use of “other antiepileptics” also demonstrated a significant association with increased risk of infection (OR: 1.60, 95% CI: 1.06-2.43).

Those taking tricyclic antidepressants were 2.86 times (95% CI: 1.59-5.14) more likely to have had an infection than the non-users.

However, SSRIs (OR: 0.58, 95% CI: 0.39-0.88, $p<0.05$) and antipsychotics (OR: 0.57, 95% CI: 0.38-0.88, $p<0.05$) were associated with a decreased risk of infection, which suggests SSRIs and antipsychotic users were less likely to have had an infection than non-users of these medicines.

Table 10. Univariate association between medication categories and risk of infections (N=690; Case=372, Control=318)[#]

Medication category	Cases (%), n=372	Control (%), n=318	OR (95% CI)	P value
Proton pump inhibitors				
Yes	165 (44.3)	114 (35.8)	1.43 (1.05-	**0.02***
No	207 (56.6)	204 (64.1)	1.94)	
Beta-blockers				
Yes	101 (27.1)	63 (19.8)	1.51 (1.05-	**0.02***
No	271 (72.8)	255 (80.1)	2.16)	
Benzodiazepines				
Yes	90 (24.1)	50 (15.7)	1.71 (1.17-	**0.00***
No	282 (75.8)	268 (84.2)	2.51)	
Other antiepileptics				
Yes	73 (19.6)	42 (13.2)	1.60 (1.06-	**0.02***
No	299 (80.3)	276 (86.7)	2.43)	
Selective serotonin reuptake inhibitors				
Yes	46 (12.3)	62 (19.4)	0.58 (0.39-	**0.01***
No	326 (87.6)	256 (80.5)	0.88)	
Other antidepressants				
Yes	66 (17.7)	35 (11.0)	1.74 (1.12-	**0.01***
No	306 (26.8)	283 (88.9)	2.71)	
Tricyclic antidepressants				
Yes	49 (13.1)	16 (5.0)	2.86 (1.59-	**0.00***
No	323 (86.8)	302 (94.9)	5.14)	
Antipsychotics				
Yes	43 (11.5)	59 (18.5)	0.57 (0.38-	**0.01***
No	329 (88..4)	259 (81.4)	0.88)	
Non-opioid analgesics				
Yes	206 (55.3)	182 (31.4)	0.93 (0.69-	0.62
No	166 (44.6)	136 (42.7)	1.25)	
Other antiplatelet drugs				
Yes	105 (28.2)	92 (28.9)	0.97 (0.69-	0.83
No	267 (71.7)	226 (71.0)	1.35)	
Loop diuretics				
Yes	99 (26.6)	82 (25.7)	1.04 (0.74-	0.80
No	273 (73.3)	236 (74.2)	1.47)	
Statins				
Yes	90 (24.1)	74 (23.2)	1.05 (0.74-	0.77
No	282 (75.8)	244 (76.7)	1.50)	
Thyroid hormones				
Yes	60 (16.1)	46 (14.4)	1.14 (0.75-	0.54
No	312 (83.8)	272 (85.5)	1.73)	
Sartans				
Yes	53 (14.2)	46 (14.4)	0.98 (0.64-	0.93
No	319 (85.7)	272 (85.5)	1.51)	
ACE inhibitors				
Yes	67 (18.0)	55 (17.2)	1.05 (0.71-	0.80
No	305 (81.9)	263 (82.7)	1.56)	

Medication category	Cases (%), n=372	Control (%), n=318	OR (95% CI)	P value
Calcium channel blockers				
Yes	58 (15.5)	40 (12.5)	1.28 (0.83-1.98)	0.25
No	314 (84.4)	278 (87.4)		
Antidiabetic drugs				
Yes	48 (12.9)	40 (12.5)	1.03 (0.66-1.61)	0.89
No	324 (87.0)	278 (87.4)		
Combination of laxatives				
Yes	41 (11.0)	31 (9.7)	1.15 (0.70-1.88)	0.58
No	331 (88.9)	287 (90.2)		
Opioid analgesics				
Yes	29 (7.7)	24 (7.5)	1.04 (0.59-1.82)	0.90
No	343 (92.2)	294 (92.4)		
P2Y12 antagonists				
Yes	33 (8.8)	17 (5.3)	1.72 (0.94-3.16)	0.07
No	339 (91.1)	301 (94.6)		
Opioid agonist antagonist combination				
Yes	23 (6.1)	18 (5.6)	1.10 (0.58-2.07)	0.77
No	349 (93.8)	300 (94.3)		
Anticholinergics				
Yes	24 (6.4)	14 (4.4)	1.50 (0.76 – 2.95)	0.24
No	348 (93.5)	304 (95.5)		
Serotonin and noradrenaline reuptake inhibitors				
Yes	20 (5.3)	24 (7.5)	0.70 (0.38 – 1.29)	0.24
No	352 (94.6)	294 (92.4)		
Antiarrhythmics				
Yes	19 (5.1)	17 (5.3)	0.95 (0.49 – 1.87)	0.88
No	353 (94.8)	301 (94.6)		
Other anticoagulants				
Yes	21 (5.6)	14 (4.4)	1.30 (0.65 – 2.60)	0.45
No	351 (94.3)	304 (95.5)		
Nitrates				
Yes	16 (4.3)	17 (5.3)	0.80 (0.40 – 1.60)	0.52
No	356 (95.6)	301 (94.6)		
Corticosteroids				
Yes	36 (9.6)	25 (7.8)	1.26 (0.74 – 2.14)	0.40
No	336 (90.3)	293 (92.1)		
Vitamins and minerals				
Yes	189 (50.8)	142 (44.6)	1.28 (0.95 – 1.73)	0.10
No	183 (49.1)	176 (55.3)		

*p<0.05, # Residents who resided in a Bethanie facility for the entire year of 2015, OR: Odds Ratio, CI: Confidence Interval

The disease of the genitourinary system and disease of the respiratory system were significantly associated with the increased risk of infection in the 12-month period in 2015. On the other hand, mental and behavioural disorders were both associated with decreased risk of infection in the residents in the same period ($p<0.05$, OR: 0.41, 95% CI: 0.28-0.59). Residents with the disease of the genitourinary system were 2.12-fold ($p<0.05$, 95% CI: 1.48-3.02) more likely to have an infection in the 12-month period in 2015 than residents who had not had such a condition. Residents with the disease of the respiratory system were 1.73 times ($p<0.05$, 95% CI: 1.16-2.56) more likely to have had an infection in the 12-month period in 2015 than residents who had not had such a condition (Table 11).

Table 11. Univariate association between medical history and incidence of infections (N=690; Case=372, Control=318)[#]

Medical history	Cases (%), n=372	Control (%), n=318	OR (95% CI)	P value
Circulatory system				
Yes	263 (70.6)	226 (71.0)	0.98 (0.71-	0.91
No	109 (29.3)	92 (28.9)	1.37)	
Mental Health				
Yes	252 (67.7)	266 (83.6)	0.41 (0.28-	**<0.0001***
No	120 (32.2)	52 (16.3)	0.59)	
Musculoskeletal system	228 (61.2)	191 (60.0)	1.05 (0.78-	0.74
Yes	144 (38.7)	127 (39.9)	1.43)	
No				
Endocrine/metabolic				
Yes	164 (44.0)	135 (42.4)	1.07 (0.79-	0.66
No	208 (55.9)	183 (57.5)	1.45)	
Genitourinary system	121 (32.5)	59 (18.5)	2.12 (1.48-	**<0.0001***
Yes	251 (67.4)	259 (81.4)	3.02)	
No				
Digestive system				
Yes	111 (29.8)	75 (23.5)	1.38 (0.98-	0.06
No	261 (70.1)	243 (76.4)	1.94)	
Nervous system				
Yes	104 (27.9)	91 (28.6)	0.97 (0.69-	0.84
No	268 (72.0)	227 (71.3)	1.35)	
Respiratory system				
Yes	84 (22.5)	46 (14.4)	1.73 (1.16-	**0.00***
No	288 (77.4)	272 (85.5)	2.56)	
Symptoms, signs				
Yes	79 (21.2)	63 (19.8)	1.09 (0.75-	0.64
No	293 (78.7)	255 (80.1)	1.58)	
Eyes and adnexa				
Yes	51 (13.7)	33 (10.3)	1.37 (0.86-	0.18
No	321 (86.2)	285 (89.6)	2.19)	
Other history				
Yes	129 (34.6)	67 (21.0)	1.63 (1.24-	**0.00***
No	243 (65.3)	251 (78.9)	2.15)	

Residents who resided in a Bethanie facility for the entire year of 2015, OR: Odds Ratio, CI: Confidence Interval

Multivariate logistic regression (regressing medication classes and medical history against the incidence of infection; using backward elimination) revealed benzodiazepines, "other antiepileptics", antidepressants (TCA and "other antidepressants), and disease of the genitourinary system were associated with the increased incidence of infection in the 12-month period in 2015. Antipsychotics and mental/behavioural disorders were associated with decreased incidence of infection in the 12-month period in 2015. Both variables appeared to be associated with a protective effect, confirming the univariate analysis. Benzodiazepine exposure increased the risk of infection by 1.78 times (95% CI: 1.16-2.73, $p<0.05$). "Other antiepileptics", "other antidepressants", and tricyclic antidepressants were associated with increased risk of infection by 1.62 (95% CI: 1.04-2.54, $p<0.05$), 2.21 (95% CI: 1.36-3.54, $p<0.05$), and 2.98 (95% CI: 1.60-5.54, $p<0.05$), respectively. Antipsychotics (OR: 0.57, 95% CI: 0.36-0.91, $p<0.05$) and mental and behavioural disorders (OR: 0.33, 95% CI: 0.22-0.49, $p<0.05$) were less likely associated with the risk of infection. Disease of the genitourinary system was 2.44 times (95% CI: 1.66-3.57, $p<0.05$) more likely to increase the risk of infection. There were no significant pairwise interaction effects, suggesting that these variables all act to influence the chance of being a case, regardless of the status of the other variables in the model (Table 12). Beta-blockers, SSRIs, and disease of the respiratory system, all of which showed significant association with infections in the univariate analysis, were not significant in the multivariate analysis.

Table 12. Association between medication category and medical history with incidence of infections in multivariate logistic regression model

Variables	Odds Ratio	95% CI	P value
Benzodiazepines	1.78	1.16 – 2.73	0.00
Other antiepileptics	1.62	1.04 – 2.54	0.03
Antipsychotics	0.57	0.36 – 0.91	0.01
Other antidepressants	2.21	1.36 – 3.57	0.00
Tricyclic antidepressants	2.98	1.60 – 5.54	0.00
Mental and behavioural disorder	0.33	0.22 – 0.49	<0.0001
Disease of the genitourinary system	2.44	1.66 – 3.57	<0.0001
Other medical history	1.63	1.22 – 2.18	0.00

4.1.6 Methods (Webstercare data)

4.1.6.1 Design overview

A retrospective case-control study was performed using Webstercare data. In this analysis, cases were people taking the 'risk' drug and not on an antibiotic. Controls were a subset of people not taking the 'risk' drug (and not taking an antibiotic at the start) who were matched to the cases by gender and year of birth

The current study analysed this second dataset to investigate the association of particular medicines, identified in the analysis of Bethanie data, with an increase in antibiotic use. This analysis further estimated the association of duration of medicine use with increased risk of infection, by measuring increased use of antibiotics. Here, antibiotic use was considered a surrogate of an occurrence of infection. The risk drug groups that demonstrated a significant association with infection either in univariate or multivariate regression in the Bethanie data analysis were selected for further analysis using this second dataset to validate their association with infection. These risk drugs were PPIs, benzodiazepines, beta-blockers, tricyclic antidepressants, other antidepressants, and other antiepileptics.

4.1.6.2 Data source

This analysis utilised Webstercare® data for medicines dispensed to residents of RACFs. The supplied dataset will hereafter be referred to as "the Webstercare data". Webstercare® is a company that provides medication management solutions to the end-users in the community and in RACFs to manage their medication safely and effectively.[258] This company has been providing this service with other innovative products for more than 30 years.[258] Webstercare "cater for residents of residential aged care facilities whose medications are arranged for them by the staff at their RACF via a local pharmacist".[258] Webster-pak® is a dosage administration aid (DAA) product of Webstercare® dispensed by a local community pharmacy to aged care residents.

Webstercare provided de-identified dispensing-level data for 4,332 residents of RACFs. The dataset comprised 188,394 rows of dispensed medicines from May 2001 to March 2016. If a patient received multiple medicines in one or more Webster-pak®, these were represented by multiple rows in the dataset. The dataset listed residents' date of birth, gender, brand, and generic prescribed drug names, prescribed directions, and medicine's prescribed start and cease date.

PRN (as-required) medicines which were used regularly, were included. All regular packed and non-packed medicines were included. Data relating to non-medicated items (e.g., body wash, oatmeal, blood sugar monitoring instruction, moisturising eye drops and body lotion), complementary medicines and prophylactic antibiotics (prior to dental procedures, as indicated by the data custodian in the Excel® data file) were excluded from the final dataset in the Excel® data file. Regular antibiotics, irrespective of dosage form were included. The final number of retained rows was 173,719. The final dataset was considered as master data file for the analysis.

4.1.6.3 Data extraction

The Webstercare file (after exclusion criteria were applied) was scanned to identify the first and last dates of any prescription of a particular resident. This was taken as a surrogate measure of the period during which each person was 'under the management' of the pharmacy. To explain further, PPIs was taken as an example of medicines increasing the risk of infection. The following steps were repeated for all risk medicines: The 'risk medicines' were scanned within the master data file, and a file named 'PPI' was compiled to contain anyone who was given a PPI during the time period (May 2001 to March 2016). The remaining cases following extraction of those receiving a PPI were named the 'No_PPI' file. The PPI records were reviewed to check if the person received an antibiotic at the time of starting a PPI. This was done by looking for an antibiotic start date which was within the seven days after the PPI start date. This implicitly meant that the antibiotic start date had to be at least seven days after the date of the person's first ever prescription. The PPI records were reviewed to identify anyone starting a course of antibiotics which was of less than 20 days' duration (indicating an acute infection rather than chronic), within the period (7/14/30/60/90/180 days) following the start of the PPI. To be included, the total time under study (last date minus first date) had to be longer than the 'window' period (up to 180 days). This meant that all cases included for study must have been alive and being given prescriptions for the minimum period required for study (which varied depending on the 'window' period). The models were run separately for each of the exposure windows to obtain the risk of infection separately for each exposure.

4.1.6.4 Statistical analysis

The age groups (less than 60, 61-65, 66-70, 71-75, 76-80, 81-85, 86-90, 91-95, more than 96 years, consistent with the Bethanie analysis) and gender were expressed as percentage and frequency. Logistic regression was performed to estimate the crude OR of increased antibiotic use (as surrogate of infection incidence) with a 95% confidence interval. Significance was again determined at $p<0.05$. Data were analysed using *SAS®* software version 9.2.

4.1.7 Results (Webstercare data)

4.1.7.1 Demographics of the resident sample

From the total of 4,332 residents, gender data were available for 3768. Of these, 65.0% (2,394) were female and 36.4% (1,374) were male. The mean age of the residents was 80.7 years (SD: 20.6 years). As described in Table 13, for those with available age data (n=4,103), 19.7% of residents (n=808) were aged 86-90 years, 21.3% (n=872) were aged 91-95 years, and 17.2% (n=706) were over 96 years.

Table 13. Resident' age distribution

Age group (years)	Frequency n (%)
Under 60	643 (15.7)
61-65	55 (1.3)
66-70	85 (2.1)
71-75	154 (3.8)
76-80	274 (6.7)
81-85	506 (12.3)
86-90	808 (19.7)
91-95	872 (21.3)
Over 96	706 (17.2)
Total	4,103* (100.0)

* Age not available for 229 residents and gender was not available for 564 residents in the Webstercare data-set

4.1.7.2 Association of particular medicines with increased antibiotic use

PPI users were more likely to be prescribed antibiotics than the non-users within 180 days of initiation of PPI therapy (Table 14). The highest likelihood was observed within seven days (OR: 27.7, 95% CI: 6.6-116.2, p<0.0001), and the lowest was within 180 days (OR: 5.8, 95% CI: 3.4-9.8, p<0.0001).

Table 14. Association of Proton pump inhibitors (PPIs) with increased antibiotic use

Duration (days)	PPIs Non-user		PPIs User		OR (95% CI)	P value
	Non-Antibiotic	Antibiotics	Non-Antibiotics	Antibiotics		
7	407 (99.5)	2 (0.4)	271 (87.9)	37 (12.0)	27.7 (6.6 – 116.2)	<0.0001
14	406 (99.2)	3 (0.7)	258 (86.8)	39 (13.1)	20.4 (6.2 – 66.8)	<0.0001
30	406 (99.2)	3 (0.7)	237 (83.4)	47 (16.5)	27.8 (8.2 – 87.1)	<0.0001
60	398 (97.1)	11 (2.6)	210 (81.4)	48 (18.6)	8.2 (4.2 – 16.2)	<0.0001
90	395 (96.5)	14 (3.4)	195 (79.5)	50 (20.4)	7.2 (3.9 – 13.4)	<0.0001
180	386 (94.3)	23 (5.6)	150 (74.2)	52 (25.7)	5.8 (3.4 – 9.8)	<0.0001

Residents taking benzodiazepines were 16.2 times more likely to be prescribed antibiotics than non-users (95% CI: 3.7-69.8, p<0.05) within seven days of the initiation of benzodiazepines. Association of increased antibiotic use was found in any time point within 180 days of initiation of Benzodiazepines. Decreasing association was observed after 30 days (Table 15).

Table 15. Association of benzodiazepines with antibiotic use

Duration (days)	Benzodiazepine Non-user		Benzodiazepine User		OR (95% CI)	P value
	Non-Antibiotic	Antibiotics	Non-Antibiotics	Antibiotics		
7	309 (99.3)	2 (0.6)	209 (90.4)	22 (9.5)	16.2 (3.7-69.8)	<0.0001*
14	307 (98.7)	4 (1.2)	193 (88.5)	25 (11.4)	9.9 (3.4-29.0)	<0.0001*
30	307 (98.7)	4 (1.2)	175 (85.7)	29 (14.2)	12.7 (4.3-36.7)	<0.0001*
60	303 (97.4)	8 (2.5)	149 (81.8)	33 (18.1)	8.3 (3.7-18.6)	<0.0001*
90	300 (96.4)	11 (3.5)	135 (78.9)	36 (21.0)	7.2 (3.5-14.7)	<0.0001*
180	290 (93.2)	21(6.7)	104 (71.7)	41 (28.2)	5.4 (3.0-9.6)	<0.0001*

In beta-blocker users (Table 16), the highest probability of co-prescribing of an antibiotic was observed within 14 days of initiation of the drugs (OR: 32.4, 95% CI: 4.3-243.5, p<0.0001). The likelihood of increasing the use of antibiotics was decreased with increasing duration. More than five-fold increased use of antibiotics was observed following 180 days of beta-blockers initiation (OR: 5.9, 95% CI: 3.0-11.8, p<0.0001), compared to a 32.4-fold increase in seven days.

Table 16. Association of beta-blockers (BB) with antibiotic use

Duration (days)	BB Non-user		BB User		OR (95% CI)	P value
	Non-Antibiotic	Antibiotics	Non-Antibiotics	Antibiotics		
7	283 (100.0)	0 (0.0)	183 (90.5)	19 (9.4)	>999.9 (<0.001->999.9)	0.944
14	282 (99.6)	1 (0.3)	174 (89.6)	20 (10.3)	32.4 (4.3-243.5)	<0.0001*
30	280 (98.9)	3 (1.0)	156 (87.6)	22 (12.3)	13.1 (3.8-44.6)	<0.0001*
60	280 (98.9)	3 (1.0)	139 (83.7)	27 (16.2)	18.1 (5.4-60.7)	<0.0001*
90	279 (98.5)	4 (1.4)	121 (80.6)	29 (19.3)	16.7 (5.7-48.5)	<0.0001*
180	269 (95.0)	14 (4.9)	93 (76.2)	29 (23.7)	5.9 (3.0-11.8)	<0.0001*

According to this cohort study, residents taking TCAs were 11.2 times more likely to be prescribed antibiotics within 90 days of the initiation of TCAs compared to non-users of TCAs (95% CI: 1.2-98.8, p=0.029). A 15-fold increased use of antibiotics was found at 180 days (OR: 15.0, 95% CI: 1.7-130.6, p=0.013) in TCAs users compared to non-users (Table 17).

Table 17. Association of tricyclic antidepressants (TCAs) with antibiotic use

Duration (days)[#]	TCA Non-user		TCA User		OR (95% CI)	P value
	Non-Antibiotic	Antibiotic	Non-Antibiotic	Antibiotic		
90	43 (97.7)	1 (2.2)	23 (79.3)	6 (20.6)	11.2 (1.2-98.8)	0.029*
180	43 (97.7)	1 (2.2)	20 (74.0)	7 (25.9)	15.0 (1.7-130.6)	0.013*

*p<0.05, significant.

[#]Insufficient data at 7, 14, 30 and 60 days

Antibiotic use was found to be more likely (OR=23.8, 95% CI: 3.0-185.0) in RACF residents who had used "other antidepressants" for 30 days than in residents who did had not (Table 18).

Table 18. Association of "other antidepressants" (OAs) with increased antibiotic use

Duration (days)	OA Non-user		OA User		OR (95% CI)	P value
	Non-Antibiotic	Antibiotics	Non-Antibiotics	Antibiotics		
7	204 (99.5)	1 (0.4)	136 (93.7)	9 (6.21)	13.5 (1.6-107.7)	0.014*
14	204 (99.5)	1 (0.4)	126 (93.3)	9 (6.6)	14.5 (1.8-116.3)	0.011*
30	204 (99.5)	1 (0.4)	111 (89.5)	13 (10.4)	23.8 (3.0-185.0)	0.002*
60	203 (99.0)	2 (0.9)	93 (86.92)	14 (13.0)	15.2 (3.4-68.5)	<0.0001*
90	201 (98.0)	4 (1.9)	80 (84.2)	15 (15.7)	9.4 (3.0-29.2)	<0.0001*
180	199 (97.0)	6 (2.9)	57 (76.0)	18 (24.0)	10.4 (3.9-27.6)	<0.0001*

Table 19 shows that residents taking “other antiepileptics” were more likely to be prescribed antibiotics than non-users in any time point within 180 days of initiation of “other antiepileptics”. A decreasing association was observed after seven days. Those exposed with “other antiepileptics” within seven days were at significant higher risk of antibiotic use (OR:11.6, 95% CI: 1.4-93.1) than the non-exposed.

Table 19. Association of “other antiepileptics” (OAe) with antibiotic use

Duration (days)	**OAe Non-user**		**OAe User**		**OR (95% CI)**	**P value**
	Non-Antibiotic	Antibiotics	Non-Antibiotics	Antibiotics		
7	184 (99.4)	1 (0.5)	142 (94.0)	9 (5.9)	11.6 (1.4-93.1)	0.020
14	183 (98.9)	2 (1.0)	136 (93.7)	9 (6.2)	6.0 (1.2-28.4)	0.022
30	180 (97.3)	5 (2.7)	122 (89.7)	14 (10.2)	4.1 (1.4-11.7)	0.007
60	177 (95.6)	8 (4.3)	105 (85.3)	18 (14.6)	3.7 (1.5-9.0)	0.002
90	177 (95.6)	8 (4.3)	94 (81.7)	21 (18.2)	4.9 (2.1-11.5)	0.000
180	171 (92.4)	14 (7.5)	67 (69.0)	30 (30.9)	5.4 (2.7-10.9)	<0.0001

4.1.8 Discussion

This stage of research of the current study had utilised two data sources. One was sourced from The Bethanie Group Inc. and the other from Webstercare®. Bethanie had provided records of the residents. Data supplied by Bethanie comprises clinical data in conjunction with drug administration data. This enabled determination of the relative risk of antibiotic prescribing in cohorts of patients on drugs known to increase the risk of infection but correcting for other risk factors. Residents' records were also accessed remotely through *iCare*® (software for aged care). The benefit of access to patient records (further to the medication supply data) was the additional detail relating to the residents' predisposing medical conditions and risk factors that may have contributed to the infection, indications for prescribed medicines (including antibiotics) and medical history.

Webstercare® also provided de-identified data reporting the medicines supplied to RACFs in Webster-Paks® prepared by pharmacies servicing those RACFs. These medicines supply data were used to identify the likelihood of increased use of antibiotics in the residents who were exposed to the risk drugs for infection identified in the Bethanie data. Specific analysis was conducted, identifying residents receiving particular medicines with versus without antibiotics. This enabled the identification of drug-associated infection. Here, an antibiotic prescription was utilised as a surrogate for an infection incidence. This dataset did not specify the diagnosis of each patient. Therefore, the analysis of the Webstercare dataset only focussed on medicine groups (not medical conditions) found in the Bethanie analysis to be associated with the incidence of infection.

There was a reasonable balance in numbers between the age groups except for the age group of 91-95 years. There were twice as many cases in the 91-95 age group compared to controls (n=84 vs 42). It was considered that if this age group had been included as a covariate in all subsequent analyses, the increase in the number of parameters may have led to instability (wider confidence intervals) in the results with respect to medications and medical history.

4.1.8.1 Prevalence of antimicrobial use

This study found that cephalosporins, penicillins, and trimethoprim were the most commonly used antibiotics for the residents in Bethanie in 2015 to treat infections. This finding differs from overseas studies that reported fluoroquinolones were the most frequently used medicines for infection treatment in the residents of aged care.[259, 260] A

Slovenian point-prevalence study reported that co-amoxiclav (41%) and fluoroquinolones (22.3%) were the most frequently prescribed antibiotics in the 251 residents of 80 RACFs.[261] The study was conducted between April and June 2016, through an online questionnaire sent to all Slovenian RACFs.[261] However, the present data are consistent with one Australian study in four Australian RACFs (of 1,114 episodes of an infectious syndrome over 267,684 occupied-bed-days) by Lim et al., 2012, reporting that cefalexin and trimethoprim were more commonly used than fluoroquinolones and other broad-spectrum antibiotics.[60]

On the other hand, another Australian study of five RACFs reported that doxycycline and cefalexin were the most commonly used antibiotics, followed by trimethoprim and flucloxacillin.[61] Norfloxacin use was limited.[61] However, these two studies used a different methodological approach to this current study to identify the prevalence of infection and antimicrobial use in RACFs. One study used retrospective data from an infection surveillance system from January 2006 to December 2010 in four RACFs comprising 150 residential care beds.[60] Another study utilised the point prevalence method in September 2011 to analyse data for all 257 residents in five RACFs. Both studies used McGeer criteria to identify inappropriate antimicrobial use. These criteria were developed to help in infection control surveillance,[262] rather than criteria for initiating antimicrobial prescribing. Also, these criteria had not indicated the risk of infection with particular medicines. Therefore, previous studies are not directly comparable with this current study, which was designed to investigate drug-associated infection by case-control analysis. In the present study, the case group (375 residents) were residents who had a documented infection in 2015 and were randomly selected from the cohort of 640 residents. Thus, the estimation of the prevalence of infection and antimicrobial use in all residents could have been different.

According to international studies, about 25-75% of antibiotics were inappropriately prescribed in RACFs.[97, 107, 262-264] Recent studies in Australian RACFs have indicated up to 40% inappropriate antimicrobial use.[60, 61] The Australian government restricted quinolone use through its national pharmaceutical subsidy scheme,[265] due to the emergence of quinolone-resistant Gram-negative organisms in RACFs with high quinolone use.[266] Thus, the lower use of fluoroquinolones in the current study may be a reflection of their restriction in the Australian Pharmaceutical Benefits Scheme. Prescribing of antimicrobials can be influenced by the national and local antimicrobial guidelines, institutional formularies, cost of antimicrobials, prescriber's preferences and experiences, and availability in the market.

It should be noted that the aim of the current study was not to identify the prevalence of inappropriate prescribing of antibiotics, only the association between particular medicines and infections (or use of antibiotics as a surrogate for a diagnosed infection) to indicate the potential for particular medicines to predispose a person to infection, which can then increase the use of antibiotics and contribute to antibiotic resistance.

4.1.8.2 Prevalence of infections

This current study found that UTIs, RTIs, SSTIs, eye infections, and gastrointestinal tract infections were the common infections among the residents of Bethanie facilities. No data describing the indication of the prescribed medicines and medical history of aged care residents receiving Webstercare® services were available. The Bethanie analysis is consistent with the study of Lim et al.,[60] who reported the four most common infections in RACFs were UTI (36.8%), LRTI and URTI (26.9%), SSTI (14.7%), and eye, ear, and mouth infection (17.1%); others, such as gastroenteritis and systemic infection, constituted less than 5%.

The current study found that UTI was the most prevalent (45.9%) infection in the Bethanie residents. This may be due to the high prevalence of female residents in the current study, with females more vulnerable to UTI than males.[267, 268] Women with a history of UI are more likely to have UTI, and *vice versa*.[269] UI may be precipitated by age-related conditions including structural changes in the genitourinary tract, such as prolapsed bladder (cystocele),[270] changes after hysterectomy,[271] hormone replacement therapy,[272] and/or imbalance in vaginal flora[269, 270] all of which may be associated with UTI. Medicines such as antidepressants, antihypertensives (e.g. alpha blockers, ACEIs, CCBs, diuretics), opioids, sedative-hypnotics, alcohol, antihistamines, antipsychotics and skeletal muscle relaxants, are also responsible for UI,[273] and therefore, may predispose elderly people, particularly females, to UTI. However, UTIs can also lead to further UI by stimulating bladder detrusor activity, inhibiting alpha adrenergic receptors in the urethra, and decreasing bladder sphincter pressure. Thus, residents with a history of UTI can experience UI, which in turn leads to further UTI.

The second most common infection was respiratory tract infection (38.9%). Aged care residents are more likely to have severe pneumonia than elderly who live in the community,[94] due to multiple morbidities such as neurological diseases, cerebrovascular diseases and diabetes mellitus, and other factors such as poor functional status, the presence of a feeding tube, swallowing difficulties, aspiration, and poor oral hygiene.[76, 92, 93]

4.1.8.3 Prevalence of medicine use

The current study using Bethanie data revealed that antihypertensives, antidepressants, non-opioid analgesics (paracetamol), PPIs, statins, benzodiazepines, antipsychotics, antiplatelet agents, and antiepileptics were commonly used among all the residents. This finding is consistent with an observational study of 16,126 veterans using pharmacy claims data of the Department of Veterans' Affairs in Australia.[274] A 2003 survey in 51 RACFs (3,093 residents) in Sydney, Australia, revealed that 24% of residents were prescribed antipsychotics, 20% were prescribed antidepressants, and 15% were prescribed benzodiazepines.[275] However, a more recent study reported a higher prevalence of antipsychotic (38%), antidepressants (35%), and PPIs (46%) use in the residents of 26 Australian RACFs.[69] This high prevalence of prescribing medications suggests reluctance in changing prescribing patterns in spite of ongoing national and international concerns about the safety and risks of these medications in aged care residents.[69]

Prescribing of such medicines in RACFs is often not appropriate. As mentioned in Section 4.1.1, 43.2% of prescribed medicines were potentially inappropriate in nursing homes.[196] A cross-sectional study of 17 RACFs in Australia also identified that PPIs (42% of residents exposed to a PPIs prescribed for longer than eight weeks), benzodiazepines (38%), antidepressants (6%), and antipsychotics (31%) were the most common drug group involved in potential inappropriate prescribing.[199] However, direct comparison with the current study and the previously-mentioned evidence should be considered within the context of methodological differences between the studies. The current study was designed as case-control study, and not designed for prevalence estimation of drug use among the residents. The current study also reported that there were significant differences in the prevalence of use of PPIs, beta-blockers, benzodiazepines, antipsychotics and different groups of antidepressants between the case group residents and control group residents.

4.1.8.4 Association of medicines with increased risk of infection

The univariate and multivariate analyses using the Bethanie dataset revealed a number of associations between medication groups and infections, and medical conditions and infections. Benzodiazepines, antidepressants and antiepileptics were associated with infection burden in RACFs. This study was not able to identify which infection was associated with the above medicine groups.

Published evidence has suggested that benzodiazepines increase the risk of pneumonia in the elderly.[41, 215] Although the mechanism has not been clearly depicted in any published evidence, it is speculated that benzodiazepines suppress peripheral immunity by stimulating GABAA receptors, thus weakening the immunity.[41] Activation of peripheral benzodiazepine receptors may also be the reason for suppressed immunity by benzodiazepines.[41] A study in mice reported an increased rate of pneumonia mortality due to diazepam use, which activates the alpha1 subunit of GABAA receptors.[276] On the other hand, benzodiazepines activate the Peripheral-type benzodiazepine receptor, which can impair the activity of macrophages and neutrophils.[277] The Peripheral-type benzodiazepine receptor signalling pathway for the development of pneumonia has not been well established.[41] Thus activation of GABAA and Peripheral-type benzodiazepine receptors can underline the cause of pneumonia by benzodiazepine.[41]

Benzodiazepine may also be the reason for UTIs. Evidence suggested that these medicines can cause UI by decreasing bladder contraction due to sedation and impaired cognition.[278-280] As discussed earlier, UI can be associated with UTIs, hence there is some evidence to speculate that benzodiazepines may be associated with UTIs. The analysis of the Webstercare dataset revealed that residents taking benzodiazepines were 16.2 times more likely to be prescribed antibiotics than non-users (95% CI: 3.7-69.8, $p<0.05$) within seven days of the initiation of benzodiazepines, and the risk of antibiotic use decreased with prolonged duration.

The Bethanie analysis also found that certain types of antidepressants can increase the risk of infection in older adults. Mirtazapine, moclobemide, agomelatine, and TCAs (e.g., amitriptyline, nortriptyline and dothiepin) were associated with infection, whereas SSRI antidepressants were negatively associated with infection. This finding differs from the study of Roger *et al*., who reported that people who had depression and were taking mirtazapine and fluoxetine (SSRI) antidepressants were at increased risk of *C. difficile* infection.[233] Those authors utilised mixed methods: a population-based longitudinal study (n=16,781) and a hospital-based (n=4,047) case-control study.[233] Another retrospective cohort study in hospitalised patients reported antidepressants were associated with *C. difficile* infection.[225] A guinea pig model using found that the TCA imipramine inhibited gastric acid secretion through antagonising anticholinergic and H2-antihistamine receptors in the stomach.[234] Mirtazapine works through the alteration of serotonin levels.[281] Evidence suggests that serotonin has a major role in the pathogenesis of inflammatory colitis.[282]

On the other hand, antidepressants that alter the function of serotonin or dopamine may be associated with aspiration pneumonia. In rats, it was found that both serotonergic[283, 284] and dopaminergic[285] activity can affect swallowing and lower oesophageal sphincter function.[286] Dopamine can inhibit oesophageal sphincter pressure and gastroduodenal motility, which leads to aspiration of stomach contents.[287] However, Rogers et al.[233] commented that "it cannot be ascertained from the population-based studies whether the antidepressant medicines or the depression itself was the major predictor for the association with infections". It is possible that the physiological episodes of depression itself are associated with *C. difficile* infection.[233]

Another finding from the Bethanie study was that certain antiepileptics were associated with increased risk of infection. "Other Antiepileptics", as classified in the *AMH*, were pregabalin, valproate, carbamazepine, lamotrigine, gabapentin, phenytoin, levetiracetam and lacosamide. A possible reason for the increased risk of infection by the antiepileptics is their modulation of the immune system.[288] Levetiracetam decreases the function of CD8+ T-lymphocytes, thus precipitating imbalance in the antiviral activity of the immune system.[289] This can be the possible mechanism of increased risk of URTIs by levetiracetam.[289] Carbamazepine may increase the risk of respiratory tract infection by inducing hypogammaglobulinaemia.[290] Carbamazepine can also cause leukopaenia, neutropaenia, and agranulocytosis, all of which contribute to increased infection risk.[291]

The current study using Bethanie data found that antipsychotics were not likely associated with the increased risk of infection in aged care residents. This finding is different from previous studies. In this study, residents were prescribed risperidone, olanzapine, and quetiapine, which are atypical or second-generation antipsychotics, and haloperidol, pericyazine and zuclopenthixol, which are typical or first-generation antipsychotics. Among antipsychotics, risperidone was the most commonly used medicine for the Bethanie residents in 2015. Previous study suggested that antipsychotics – both typical and atypical – were associated with the increased risk of pneumonia in the elderly,[42] and the risk was higher soon after the initiation of the treatment.[42] A study found that among the atypical antipsychotics, clozapine was highly associated with a greater risk of pneumonia than the others in this group.[292] Therefore, the possible explanation for this different outcome in the present study is the absence of clozapine amongst the prescribed medicines. Possible reasons for clozapine's underuse or non-use are safety concerns around agranulocytosis and myocarditis, and metabolic side effects.[293] Thus, clozapine prescribing requires extra

monitoring of haematological, metabolic and cardiac parameters.[294] Restriction in prescribing, dispensing, and monitoring of clozapine in Australia also limits the use of clozapine.[293] Noting that the time of initiation of the treatment is a likely predisposing factor for infection, the sequencing of commencement of the antipsychotic medication and the diagnosis of infection was not able to be determined in the current study. Moreover, findings of previous studies cannot be extrapolated to this population, because those studies sampled general populations, not specifically in residential aged care.

The Webstercare data analysis demonstrated that in the short-term following PPI initiation (seven days), there was an increased chance of antibiotic use. Similarly, at 30 days, a difference was still apparent. According to the studies, PPIs were associated with increased risk of pneumonia, gastroenteritis (such as *C. difficile* diarrhoea), and tuberculosis. Due to differences in research design, it is difficult to directly correlate the current finding with other studies. However, a recent meta-analysis found PPI use is associated with an increased risk of community-acquired pneumonia, and the highest risk was observed within the first 30 days of therapy.[229] Another meta-analysis of 55 studies (40 case-control and 16 cohorts) involving 356,683 patients showed an increased risk of diarrhoea caused by *C. difficile* in PPI users compared with non-users.[220] Since PPIs decrease gastric acidity, this decreases the gastric defence mechanism against ingested bacteria or the normal gut microbiome, which may increase susceptibility to infection. Intra-gastric acidity provides a major nonspecific defence mechanism of the stomach to ingested pathogens. In normal gastric juice with a pH below 4, most pathogens are promptly killed (except *H. pylori*), whereas they survive in hypochlorhydric (deficiency of hydrochloric acid in the stomach) to achlorhydric (absence of hydrochloric acid in the stomach) circumstances and increase the risk of enteric infections, including those caused by *Vibrio cholerae*, Shigella spp., *Salmonella* spp., *C. difficile*, and parasitic agents (e.g. giardiasis, amoebiasis).[295]

The association between PPIs and pneumonia appears multifactorial. Acid suppression induced by PPIs also leads to reduced gastrointestinal motility. This can increase intestinal content and bacterial load, which then increase pressure on the lower oesophageal sphincter. The increased pressure against the oesophageal sphincter may lead to back-flow of gastric contents and bacterial transfer up the oesophagus. This reflux of bacteria increases the risk of aspiration pneumonia.[33] Again, PPIs, through their inhibition of extra-gastric proton pump or H(+)/K(+)-ATPase enzymes, may reduce the acidity of the upper "aerodigestive tract", thus resulting in increased bacterial colonisation of the larynx, oesophagus and lungs. The increased bacterial colonisation may contribute to an increased incidence of pneumonia.[296, 297]

Beta-blockers were univariately associated with the increased risk of infection but did not show any association in multivariate analysis in the case-control study using Bethanie data. This indicated that beta-blockers were not independently associated with increased risk of infection in the residents of Bethanie. In the Webstercare cohort, beta-blocker users demonstrated increased use of antibiotics compared to non-users of beta-blockers. The highest likelihood of antibiotic use was involved within 14 days of initiation of the medicine. Some studies have reported protective effects of beta-blockers on the incidence of pneumonia,[298, 299] while others have reported neutral effects[300] or increased rates of infections.[301] A recent study in Germany found a non-significant increased risk for UTIs in stroke patients with beta-blocker therapy (OR: 3.12, 95% CI: 0.88-11.05, p=0.077), and no significant effect of beta-blocker therapy on the risk of pneumonia, sepsis or mortality.[302] However, their study was unable to explain the increased risk for UTIs associated with beta-blocker therapy in major stroke patients.[302] Rates of UTI might be overestimated due to difficulty in diagnosing UTI in major stroke patients. Stroke itself increases risk factors such as immobilisation and dysphagia, which may increase the incidence of infection.[303, 304]

Interestingly, the present study found that mental and behavioural disorders were associated with decreased risk of infection in the residents of Bethanie (this analysis involving medical history was only facilitated by the Bethanie data). Depression and dementia were the most prevalent amongst the mental health and behavioural disorders of the Bethanie residents. It is possible that individual mental health and behavioural disorders may be a risk factor for infection but grouping all disorders may have changed this phenomenon. Although a population-based study using linked data of Danish registries (976,398 individuals, 142,169 of whom had depression between 1995 and 2012) claimed an association between history of depression and risk of infections, unrelated to the onset of depression, the number of infections was observed to reduce with an increase in the number of depressive episodes.[305] This relationship remains unconfirmed and may be confounded by underreporting of depression in the control group, and inability to adjust for socioeconomic status, environmental factors, smoking, obesity, and other comorbidities.[305] Moreover, the mean age of the population of that study was 46.3 (SD=20.8 years),[305] which is not comparable to the present study.[305]

4.1.8.5 What could be done?

Residents of aged care facilities carry a burden of multiple chronic diseases due to age-related frailty. As established in Section 4.1.1, these underlying multiple diseases lead to the use of multiple medicines. Use of multiple medicines does not necessarily mean inappropriate medication; however, mounting evidence indicates the existence of potentially inappropriate prescribing in RACFs. Specifically, 19% to 83% (median 47%) of residents in aged care facilities are exposed to inappropriate medicine.[306]

Different types of interventions to optimise the medicine use in RACFs have been implemented; these include pharmacist or multidisciplinary team intervention, medication review, computer-assisted support, educational, and deprescribing strategies.[307] A systematic review demonstrated that medication reviews (prescription review, clinical review) conducted by pharmacists, either alone or in a multidisciplinary team with other health care professionals, may improve the quality of medication use in RACFs by reducing inappropriate prescribing.[307] A review article mentioned that physicians' acceptance of the recommendations made by the pharmacist or a multidisciplinary team after medication review is reportedly high.[307] However, in Australia, pharmacists' involvement in medication review in RACFs through the RMMR program is only periodic.

Deprescribing interventions have been demonstrated effective in the elderly population of both RACFs and non-RACF settings. A review of 31 trials of medicine withdrawal in people aged 65 years and over demonstrated that 20% to 100% of patients can be successfully withdrawn from excessively prescribed antihypertensives, psychotropics and benzodiazepines without adverse effects, with appropriate withdrawal and close monitoring.[308] An Australian study of a six-month controlled trial of pharmacist-led multi-faceted intervention conducted in 25 Tasmanian RACFs in 2008-2009 reported that antipsychotic prescribing declined by 2% (20.3% to 18.6%, $p<0.05$) and benzodiazepine by 5% (31.8% to 26.9%, $p<0.005$) in the intervention facilities.[309] While a 12-month follow-up of that Tasmanian study reported a 25% decrease in benzodiazepine use in the intervention RACFs, the reduction in antipsychotic utilisation was not sustained and returned to baseline.[310] The Australian National Blood Pressure study in 169 general practices (503 patients, aged 65-84 years) in Victoria found that 37% of patients remained normotensive after 12 months of the drug withdrawal.[311] The likelihood of sustained normal blood pressure at one year was higher among younger patients (65-74 years), and also patients on single antihypertensive treatment, with a higher waist: hip ratio, and with lower "on-treatment" systolic blood pressure.[311] Thus, by careful withdrawal of inappropriate medicines to reduce the total number of regular medicines might increase health benefits in older people. However, fear of prescribers and residents around adverse consequences of deprescribing sometimes limit the initiation of this process.[312]

Intervention through education of RACF care staff is another beneficial approach in reducing inappropriate medicine use and adverse outcome in RACFs. A recent prospective study in 150 Australian RACFs reduced the prevalence of regular antipsychotic prescribing by 13% and benzodiazepines by 21%. The study was multi-faceted and interdisciplinary, comprising a baseline audit and feedback about use of psychotropic medicines, staff education, and interdisciplinary case review.[313] A study by Juola et al.[314] showed that educating nurses by providing four-hour session on harmful drugs for the elderly, reduced the prevalence of inappropriate drug use and incidences of falls in RACFs.

Overall, studies have demonstrated that pharmacists can effectively contribute to improvement in medication use by providing residents medication management review. However, RACFs do not have regular on-site pharmacists in their health care team due to funding constraint. Nurses are the only available on-site health care professional to provide medication and medical support to the residents. Therefore, interventions focussing on nursing staff can be beneficial.

4.1.8.6 Limitations

The current study investigated the association of medications and medical conditions with infection in residents of Bethanie aged care facilities in Western Australia. Findings from this research may not be generalisable to the elderly who are not living in RACFs, as well as to the residents of other aged care in Australia. However, further analysis was undertaken using data provided by Webstercare, at a national level. While the Webstercare data were limited in terms of resident-level data (clinical history), this analysis confirmed the likelihood of increased use of antibiotics by residents who were exposed to certain medications.

The sample size was calculated using the annual incidence of pneumonia from an international reference of 1998. More recent and local data may have generated a different result, as the incidence of pneumonia can vary from country to country and with jurisdictional immunisation policies or practices.

Another limitation of the Bethanie data analysis was that the exposure duration of the co-prescribed medicines was not undertaken into considerations in relation to the infection. This raise the question that if a drug was initiated just a day before the infection occurrence, should this be considered a possible association?

Furthermore, the indication for medicine use was not recorded, as a result assumption had to be made. In the Bethanie dataset, it was assumed that all infections were diagnosed, and diagnosed accurately. The pathology reports were not available in the residents' electronic profile accessed through *iCare*®, although it is acknowledged that in many cases therapy is likely to be empirical.

In the Webstercare® dataset, it was assumed that the dispensing of an antibiotic was for an infection that had been diagnosed within seven, 14, 30, 60, 90 or 180 days of initial dispensing of medicines of interest, and that the resident then received the dispensed antibiotics. Cumulative exposure to at-risk medications could not be assessed as part of the

study, its impact on infection risk was not able to be evaluated. The point estimates (ORs) presented in section 4.1.7 are very high, which might be due to the low cell size. This study was not designed to manage missing data. The representativeness of the sample can be reduced by the missing data.

Despite the age and gender of the Webstercare® sample being broadly representative of the aged care population, this research did not explore potential differences between the demographic characteristics of cases and controls in this dataset. Such differences may have some bearing on the association of medicines with increased antibiotic use.

The current study reported the association of infection (or dispensing of an antibiotic, as a surrogate indicator of an active infection) with medicine groups rather than single medicines. Therefore, it cannot be confirmed which individual medicine within a 'class' was the determinant of infection risk.

. The present study used the *AMH* classification system to categorise medicines, and the *Australian Therapeutic Guidelines: Antibiotic* to categorise infectious disease. The use of these coding systems, unique to Australia, restricts the relevance of the study findings internationally.

The 'other' categories (classified in the *AMH*) are particularly susceptible to comprising medicines with different modes of action. The current research found some significant results with the "other antiepileptics" and "other antidepressant" groups, and as such, these require further exploration using a larger national database (this may require linkage of multiple datasets).

Some residents in the Bethanie case group had been identified as meeting the inclusion criteria of a diagnosed infection, but not been prescribed any antibiotics for that infection. Due to the lack of data around the diagnosis of each infection in the *iCare®* records, it was difficult to ascertain the relevant details. Facility outbreaks of URTI and diarrhoea might have increased the infection incidence among the residents. Therefore, incorporating these residents into the case group might have led to an overestimation of association with the risk of infection and medicines.

When examining associations between medicine use and infection or antibiotic initiation in residents of aged care facilities, pharmacoepidemiological studies can be difficult because there are often many frequent users of medicines, which can introduce bias when examining associations between medicine use and infection or antibiotic initiation. To address this, Ray proposed to implement "new-user design" to avoid biases by excluding prevalent users from a study.[315] However, this design has some limitations. One of the limitations is the logistical difficulty of identifying the time when the medicines were started and collecting data on potential confounders at the time of therapy initiation.[315] This requires tracking both drug use and potential confounders daily.[315] It is mainly feasible to assess the effectiveness of a new drug[316] and restricting a study to a new user may reduce sample size and power of the study.[315] This approach was not feasible for our study.

4.1.8.7 Strengths of the study

This is the first known study to investigate the association between medicine use and increased risk of infection in RACFs irrespective of their comorbidities. One of the strengths of this study was that unlike other previous studies, residents with any kind of morbidity were included. This enabled multivariate analysis to determine relative contributions of risk factors. In the Bethanie data, the risk factors were medicine groups and medical history. In the Webstercare® data, the risk groups were the medicine groups with positive association from the Bethanie analysis. Inclusion criteria of previous studies focussed on specific conditions, such as patients with dementia.

4.2 Part two: Does the use of antibiotics increase the risk of drug interactions?

As established in Chapter 1, residents of RACFs are at increased risk of infection due to comorbidity, anatomical and physiological changes, the environment of the RACF, and their medicines. Analysis reported in Section 4.1 demonstrated that some medicines may increase the risk of infection, as evidenced by concomitant prescribing of antimicrobials. The current chapter advances the argument for antimicrobial stewardship in aged care by proposing that antimicrobials may further increase the risk of adverse drug events such as drug-drug interactions. The aim of this part of Chapter 4 is to identify potential antibiotic-related drug-drug interactions using existing medication profiles.

4.2.1 Introduction

In RACFs, definitive diagnosis of an infection is sometimes difficult due to lack of routine microbial culture and susceptibility testing, and lack of microbial resistance data, in many facilities. These issues may manifest as non-specific diagnosis of infection, overprescribing and/or inappropriate use of antimicrobials among residents of RACFs.[107, 317] Residents of RACFs are already under clinical burden from multiple medications and comorbidities. Thus, residents taking antimicrobials may also be at increased risk of adverse drug effects due to drug-drug interactions (DDIs).[318]

A DDI occurs when a drug alters the effect of another drug.[319] "When two drugs interact with each other and this leads to adverse outcome to the patients", this is known as an "actual DDI".[320] On the contrary, potential drug-drug interactions (PDDIs) are defined as "simultaneous use of two interacting drugs, irrespective of occurrence of an adverse effect to the patient."[320, 321] PDDIs are among the most important avoidable causes of adverse drug events (ADEs). A review reported that 17% of all preventable ADEs in hospitalised patients were caused by DDIs.[322] Similarly, in a hospital-based prospective observational study in the UK, 16.6% of hospital admission were due to DDI-related ADEs.[323] Unintended outcomes of DDI are morbidity, treatment failures, and increased healthcare utilisation and associated costs.[324] A review of 23 studies reported that DDIs were responsible for 4.8% of the hospital admissions in the elderly (65 years and older).[325]

Multiple factors are associated with DDIs in the elderly. Most notable is multi-morbidity, necessitating prescribing of multiple medications and increased healthcare needs.[326] Residents of RACFs are older, frailer, and with more co-morbidity than at the time of entry to RACFs.[326] It has been estimated that 12.8% to 74.4% of residents use of nine or more medicines.[327] Recent Australian data suggest that over 90% of residents use five or more medicines.[328] Thus the complex nature of drug regimens and age-related physiological changes predisposes the elderly to drug-related problems including PDDIs.[329]

4.2.1.1 Prevalence of potential drug-drug interactions in the elderly

DDI-related ADEs are a considerable health burden in the elderly worldwide, regardless of the type of healthcare service and aged care facility.[324] Investigation of actual DDIs is feasible in settings where data on clinical information are available.[320] However, evaluating and estimating the prevalence of actual DDIs is complicated by incomplete clinical data.[320] Instead of actual DDIs, a number of studies have assessed the prevalence of PDDIs, and logical interpretation of the prevalence of PDDIs provides an indication of the magnitude of the problem.[320] Although not all PDDIs lead to actual DDIs, prevalence of PDDIs is used as an indicator of the quality and safety of prescribing, to alert health practitioners of possible adverse effects from DDIs.[330, 331] Subject to the types of study population and setting, only 0.25% to 25% of the PDDIs have been reported as leading to actual DDIs.[332-336]

The prevalence of PDDIs in the elderly differs widely between studies. According to a clinical review of population-based studies by Gnjidic and Johnell, 1.5% to 47.4% of elderly people were exposed to potential DDIs.[337] The prevalence of PDDIs in RACFs was reported as up to 55%, while a higher prevalence (up to 80%) of PDDIs was reported in hospital settings in the same review.[337] In a study in Denmark of 26,337 elderly patients, 4.4% used “severely interacting” drug combinations.[338] A cross-sectional study conducted in 140 elderly inpatients (aged 60 years and above) admitted to the medical ward of a Northern Ethiopian hospital estimated that 62.2% of the elderly patients were exposed to at least one PDDI.[339] Similarly, the prevalence of clinically important PDDIs was 47.4% in elderly patients attending the primary health care system in Brazil.[340] That study also reported the drug groups most frequently implicated in PDDIs were thiazide diuretics (72.9%), ACEIs (63.0%), digitalis glycosides (44.3%), antiplatelet drugs (44.0%) and loop diuretics (31.0%).[340]

In RACFs in Central Taiwan, 25.1% of residents experienced PDDIs, among which, 65.0% were of moderate and 7.2% of major severity.[341] According to a cross sectional study in a Finnish nursing home, 4.8% of residents were exposed to PDDIs.[342] The most prevalent PDDIs were related to the use of carbamazepine, potassium-sparing diuretics, and codeine.[342] The prevalence of potentially inappropriate prescribing with interacting drugs was 37.0% among the residents of a nursing home in Macao, identified using two drug interaction compendia (*Drug-Reax* and *Lexi-Interact*),[343] and 33.9% in Quebec, Canada.[200] Roughead et al.[344] identified the prevalence of PDDIs in the 287,074 older (average age 78.1±10.8 years) Australian veterans and stated that potentially interacting drug-pairs were dispensed to 1.5% of veterans. Among them, potentially interacting drug-pairs related to warfarin, digoxin, and methotrexate were dispensed to 13.1%, 14.0%, and 35.2% of veterans, respectively.[344] Dolton et al.[345] using dispensing data, reported the prevalence of harmful PDDIs was 6.1% amongst the 3,876 residents from 26 RACFs in Sydney from July 2008 to June 2010. Four international databases were used to determine the severity level in both studies: *Vidal*, *Drug-Reax*, *British National Formulary*, and *Drug Interaction Facts*.[344, 345] Interactions involving methotrexate (52.0%), spironolactone (34.2%), warfarin (22.9%), and amiodarone (35.8%) had the highest prevalence among the residents.[345]

Very few studies have investigated PDDIs specifically between antimicrobials and other drugs. An observational, point-prevalence study conducted in 2016 reported PDDIs with antimicrobials comprised 26.4% of all potential interactions in five hospitals in Turkey.[346] That study utilised the *Micromedex*® online drug reference to determine the severity level of PDDIs. Among the 12 contraindicated and 220 major severity PDDIs, antimicrobials accounted for 42.0% (5/12) and 27.7% (61/220) respectively.[346] Quinolones, triazoles, metronidazole, linezolid and clarithromycin were responsible for 92.1% of the potential interactions.[346] That study also reported that among all PDDIs, 34 (56%) of 61 major, 35 (45%) of 78 moderate, and all of the minor PDDIs were due to macrolides and quinolones.[346] Ciprofloxacin and clarithromycin were the only drugs responsible for contraindicated PDDIs.[346] Similar outcomes were also reported by a cross-sectional study conducted from February to May 2014 in elderly (mean age 68±7 years) patients of a hospital in Ethiopia, utilising the same online drug reference (*Micromedex*®), where all contraindicated PDDIs (3.6% of patients) involved clarithromycin with either simvastatin or ciprofloxacin. Overall, 62.2% of patients were exposed to at least one PDDI.[339]

Studies of PDDIs with antimicrobials in RACFs are limited. Only one study in Singapore involving nursing home residents reported the prevalence of PDDIs involving antimicrobials was 46% (32 of the 70 residents). Among these, 81% of residents had "clinically significant" PDDI that required either therapy modification or avoid combination of the drugs. Similarly, to previous hospital-based studies, ciprofloxacin (35%), and clarithromycin (21%) were the most commonly implicated drugs among the residents involving clinically significant PDDIs.[318]

4.2.1.2 Drug-drug interaction tools

PDDIs can be detected by DDI screening tools. These tools help clinicians in identifying and managing of DDIs.[347] A DDI screening tool should have the high sensitivity to identify clinically significant interactions and have high specificity to ignore clinically insignificant interactions.[347] With high sensitivity and specificity, a DDI tool should have high positive predictive value.[347] A low positive predictive value might confuse clinicians with many irrelevant warnings and chances of missing significant interactions.[348, 349] Clinicians should be vigilant of the benefits and drawbacks of these tools.

Kheshti et al.[347] evaluated *Lexi-Interact®*, *Micromedex®*, *iFacts®*, *Medscape®* and *Epocrates®*, common DDI tools to identify clinically significant DDIs. It has been reported that *Lexi-Interact®* has the highest sensitivity and *Micromedex* has the highest specificity.[347, 350-352] In several studies, *Lexi-Interact®*,[353] *Micromedex®*,[350] and *iFacts®*[350] received the highest score for accuracy. On the other hand, Vonbach et al.[353] who assessed four DDI screening tools (*iFacts®*, *Micromedex®*, *Lexi-Interact®* and *Pharmavista®*), reported that *Pharmavista®* showed the highest sensitivity among the tools and an acceptable positive predictive value. *Stockley's Drug Interactions®* was used in their study as the 'gold standard' to identify clinically important interactions.[353]

Drugs implicated in PDDIs are influenced by prescribing formularies and practices in different countries and settings. Most of the reported studies were conducted in hospital settings. Due to lack of information regarding PDDIs between antibiotics and other medicines in RACFs, the aim of the present study was to investigate the frequency and type of PDDIs with antibiotics in residents of RACFs.

4.2.2 Method

4.2.2.1 Study design and setting

This was a retrospective observational study conducted using remotely accessed electronic data from the residents of Bethanie facilities of WA, Australia. This analysis required access to medicine administration data, which were only available in the Bethanie dataset, and not the Webstercare dataset.

4.2.2.2 Sample selection

This analysis used the sample of residents who had a documented infection or infections in 2015 (the case group), as reported in Section 4.1.4.5.1. Their data were used to identify potential interactions between antibiotics and other medicines in their medication profiles. In Section 4.1.4.5.1, 375 (out of 620) residents were randomly selected from the residents who had at least one infection incidence in 2015. Among these 375 residents, 351 residents were selected for the PDDI analysis. Others (24 residents) were excluded because although they had a documented infection, there was no evidence in their medication profile of antibiotic therapy was given for that infection. This was a convenience sample that was not intended to be representative of aged care residents nationally but was expected to produce useful insights for the Bethanie group of aged care facilities.

4.2.2.3 Data collection

Data were collected retrospectively for each eligible resident by accessing the medication profile of each resident through Bethanie's clinical and care management system, *iCare*®. Details were described in Section 4.1.4.2. The following variables were included for this stage of the current study: age and gender of the residents, orally administered antibiotics and other drugs.

4.2.2.4 Definition of PDDI

Here, a PDDI was defined as the occurrence of a potentially harmful combination of an antibiotic and another drug in a given to a resident on the same day, rather than the occurrence of a documented adverse event from that combination for a resident.

4.2.2.5 Identification of DDI

The antibiotics prescribed for these residents were searched in *Micromedex®*[140] for drugs with which they theoretically interact. A list of drugs interacting with each antibiotic was prepared. The presence of these drugs was then searched manually in residents' medication profiles. Each identified interacting drug pair in a resident's profile was assessed according to its severity and reliability rating using three interaction checker databases: *Micromedex®, Lexicomp® Lexi-interact™,* and *MIMS®*. As roxithromycin and flucloxacillin were not available in *Micromedex®*, *Stockley's Interaction Checker®*[354] was used to identify drugs that interact with roxithromycin and flucloxacillin.

4.2.2.6 Classification of medicines

Medications were classified according to therapeutic groups used by the *AMH*, accessed through the Curtin University Library database.[255]

4.2.2.7 Risk rating

Risk rating is an indicator of how to respond to an interaction and was classified according to the *Lexicomp® Lexi-interact™* drug interaction tool. Using this tool, each interacting drug pair is assigned a risk rating of A, B, C, D, or X. The progression from A to X is accompanied by increased urgency to respond to the interaction. Category A means "No known interaction", B means "No action needed", C means "Monitor therapy", D means "Modify regimen", and X means "Avoid combination". Detailed definitions of the risk ratings are given in Table 20.

Table 20. Risk rating of potential drug-drug interactions[141]

Risk rating	Definition
A: No known interaction	"Pharmacodynamics or pharmacokinetic interactions have not been reported between the specified agents."
B: No action needed	"Data demonstrate that the specified agents may interact with each other, but there is little to no evidence of clinical concern resulting from their concomitant use."
C: Monitor therapy	"Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The benefits of concomitant use of these two medications usually outweigh the risks. An appropriate monitoring plan should be implemented to identify potential negative effects. Dosage adjustments of one or both agents may be needed in a minority of patients."
D: Modify regimen	"Data demonstrate that the two medications may interact with each other in a clinically significant manner. A patient-specific assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risks. Specific actions must be taken in order to realise the benefits and/or minimize the toxicity resulting from concomitant use of the agents. These actions may include aggressive monitoring, empiric dosage changes, choosing alternative agents."
X: Avoid combination	"Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The risks associated with concomitant use of these agents usually outweigh the benefits. These agents are generally considered contraindicated."

4.2.2.8 Reliability rating of evidence

The reliability of documentation or evidence supporting the PDDI is rated by *Micromedex*® as excellent, good, fair, or unknown; *Lexicomp® Lexi-interact™* as excellent, good, fair, or poor, and *MIMS*® as well established, good, limited, or not established. Details are provided in Table 21.

4.2.2.9 Severity rating

Micromedex® uses the severity ratings contraindicated, major, moderate, minor and unknown; while *Lexicomp*® *Lexi-interact*™ refers to major, moderate, and minor, and *MIMS*® lists severity as severe, moderate, minor, caution, not clinically significant, and not established. Table 22 provides more detail.

4.2.2.10 Potential outcome of the DDI

The potential outcome of the DDI means the unintended effect of that DDI that might have occurred due to the interaction between antibiotics and other drugs. These were reported according to *Micromedex®*. The potential outcome of the DDI related to roxithromycin and flucloxacillin were reported according to *Stockley's Interaction Checker®*.

4.2.2.11 Ethical issues

As described in Section 4.1.4.7, ethical approval was granted by the Human Research Committee of Curtin University (approval number HR26/2016) (Appendix 2). A letter of support from the data custodian for the approval of data collection from the records of Bethanie residents (Appendix 1) was supplied to the Human Research Ethics Committee by the Research and Report Coordinator. The resident data accessed via *iCare®* were re-identifiable. During all stages of data review, analysis and reporting, data were stored on a secured server at Curtin University.

The ethical approval included a Waiver of Consent; individual residents did not need to be contacted about this research for consent to access their data. This was in accordance with Section 2.3.10 of the *National Statement on Ethical Conduct in Human Research* (2007) (Updated May 2015).[257] Justifications for the Waiver of Consent were: the retrospective observational nature of this study; remote data collection from current records of Bethanie residents; impracticality of obtaining consent from each individual; the absence of physical harm to the residents associated with not seeking consent throughout this data collection; and utilisation of the outcomes of this data collection for ultimate benefit of the residents. The only risk was to individuals' privacy; this was managed as described above.

4.2.2.12 Statistical analysis

Descriptive statistics were used to report prevalence of PDDIs in this cohort. Frequencies, expressed as percentages, were used to summarise gender. Age was presented as mean ± standard deviation together with the range. Descriptive analysis was performed to assess the frequency of categorical variables such as severity, onset of effect, documentation rating, risk rating, and outcome of PDDIs. *IBM SPSS®* statistics version 24.0 (SPSS for Windows, Chicago, IL, USA) software was used to analyse the data.

Table 21. Reliability rating of documentation of the three databases[140-142]

Micromedex®	Lexicomp® Lexi-interact™	MIMS®
Excellent: "Controlled studies have clearly established the existence of the interaction." Good: "Documentation strongly suggests the interaction exists, but well-controlled studies are lacking." Fair: "Available documentation is poor, but pharmacologic considerations lead clinicians to suspect the interaction exists; or documentation is good for a pharmacologically similar drug." Unknown: "Unknown".	Excellent: "Documented in multiple well-controlled investigations. Contradictory evidence is anecdotal or non-existent." Good: "Documented in at least one well-controlled investigation (e.g., RCT) or a plausible interaction with significant supporting evidence from non-RCTs. Evidence of an interaction greatly outweighs evidence of no interaction." Fair: "Plausible interaction based on the known pharmacology of the agents which meets one or more of the following criteria: 1) Not formally studied but reported in one or more case studies/series, retrospective reviews, pilot investigations with low sample size or control of extraneous variables, safety monitoring data, drug labelling, or other similar scientifically non-definitive sources; 2) Studied and/or documented but only described in drug labelling; 3) Plausible interaction where studies or cases have yielded inconsistent results; 4) Predicted interaction based on known pharmacodynamics or pharmacokinetic properties and/or animal or in-vitro data." Poor: "Potential interaction meets one or more of the following criteria: 1) A single case report with questionable mechanistic base; 2) Theoretical without sound mechanistic or clinical support; 3) Evidence of no interaction greatly outweighs evidence supporting an interaction."	Well established: "There have been several reports of this interaction. The pharmacological explanation of why the interaction occurs is well documented and understood. There are usually controlled studies that have established that the interaction exists." Good: "Although controlled studies may not have been performed, several case reports have been documented and other data strongly suggests this interaction exists." Limited: "Few reports of this interaction exist. These few reports usually consist of limited case reports where clinically sound justification of the interaction is found." Not established: "The interaction may have occurred with other medicines within the same class, or there is a theoretical possibility that the interaction exists."

Table 22. Severity rating of the three databases[140-142]

Micromedex®	Lexicomp® Lexi-interact™	MIMS®
Contraindicated: "The drugs are contraindicated for concurrent use." Major: "The interaction may be life-threatening and/or require medical intervention to minimise or prevent serious adverse effects." Moderate: "The interaction may result in exacerbation of the patient's condition and/or require an alteration in therapy." Minor: "The interaction would have limited clinical effects. Manifestations may include an increase in the frequency or severity of the side effects but generally would not require a major alteration in therapy." Unknown: "Unknown".	Major: "Effects may result in death, hospitalisation, permanent injury, or therapeutic failure." Moderate: "Effects of interaction may need medical intervention." Minor: "Effects would be considered tolerable in most cases and medical intervention are not required."	Severe: "The interaction between these medications may be life-threatening or may cause permanent damage. These medications are not usually used concurrently; medical intervention may be required." Moderate: "These medications may interact resulting in the potential deterioration of the patient's condition. The patient should be monitored for the possible manifestations of the interaction. Medical intervention or a change in therapy may be required." Minor: "Clinical effects of the interaction are limited and may be bothersome but would not usually require a major change to therapy. The patient should be monitored for the possible manifestations of the interaction." Caution: "The interaction may occur based on the mechanism of action of the co-administered medicines. Be alert for increased or decreased effect, depending on the combination of medicines." Not clinically significant: "The interaction may occur, but the outcome is not clinically significant." Not established: "Theoretical, no established report."

4.2.3 Results

4.2.3.1 Characteristics of the residents

Overall, 64 (18.2%) residents among the 351 residents who received antibiotic therapy in the year 2015 were also prescribed and administered at least one medicine associated with a PDDI. Among the 64 residents, 48 (75%) were female and 16 (25%) were male. The mean age of the residents with PDDIs was 85.9±6.8 (range 66-98) years.

4.2.3.2 Characteristics of PDDIs

A total of 96 PDDIs were identified, comprising 56 types of interacting combinations. Among the 64 residents, 44 (68.8%) had experienced one PDDI, 15 (23.4%) experienced two, two (3.1%) experienced three PDDIs, one (1.6%) experienced four PDDIs, one (1.6%) experienced six PDDIs, and one (1.6%) experienced seven PDDIs.

In terms of severity, 78 out of 96 PPDIs (81.3%) were classified by *Micromedex®* as either contraindicated (n=1) or major (n=77). Only 2.1% of PDDIs (2/96 PDDIs) were identified as moderate. *Lexicomp®Lexi-interact™* and *MIMS®* identified most of the PDDIs as moderate: 58.3% (56/96 PDDIs) and 45.8% (44/96 PDDIs), respectively. *Lexicomp® Lexi-interact™* identified 13.5% (13/96 PDDIs) of PDDIs as major. *MIMS®* identified 9.4% (9/96 PDDIs) of PDDIs as severe (Table 23).

Table 23. Severity of potential drug-drug interaction according to the three databases

Database	Severity	Prevalence (N = 96 PDDIs), n (%)
Micromedex®	Contraindicated	1 (1.0)
	Major	77 (80.2)
	Moderate	2 (2.1)
	No information	16 (16.7)
Lexicomp® Lexi-interact™	Major	13 (13.5)
	Moderate	56 (58.3)
	Minor	8 (8.3)
	No known interaction	4 (4.2)
	No information	4 (4.2)
MIMS®	Severe	9 (9.4)
	Moderate	44 (45.8)
	No information	43 (44.8)

Most of the scientific evidence supporting possible interactions was good (30.2%) or fair (48.9%), while only 6.2% was rated as excellent by *Micromedex®*. *Lexicomp®Lexi-interact™* identified three interactions (3.1%) with excellent evidence and 33 (34.4%) interactions with good evidence. *MIMS®* identified three interactions (3.1%) with well-established evidence and 34 (35.4%) with good evidence (Table 24).

Table 24. Reliability rating of documentation of the evidence of PDDI according to three databases

Database	Reliability rating	Prevalence (N = 96 PDDIs), n (%)
Micromedex®	Excellent	6 (6.25)
	Good	29 (30.2)
	Fair	45 (48.9)
	No information	16 (16.7)
Lexicomp® Lexi-interact™	Excellent	3 (3.1)
	Good	33 (34.4)
	Fair	38 (39.6)
	Poor	3 (3.1)
	No known interaction	4 (4.2)
	No information	4 (4.2)
MIMS®	Well established	3 (3.1)
	Good	34 (35.4)
	Limited	13 (13.5)
	Not established	3 (3.1)
	No information	17 (17.7)

4.2.3.3 Classes of drugs involved in PDDIs

Among the antibiotics involved in total PDDIs (96), 29 (30.2%) belonged to the macrolide group of antibacterials. Other antibacterials, as classified in the *AMH* [255], were implicated in 26 drug interactions (27.1%). Quinolones were involved in 16 PDDIs (16.7%). Penicillins and cephalosporins were each involved in 12 (12.5%) of the PDDIs. Of all PDDIs, the most common antimicrobials involved in DDIs were trimethoprim (n=24, 25.0%), cefalexin (n=12, 12.5%), roxithromycin (n=12, 12.5%), and clarithromycin (n=10, 10.4%). Norfloxcin, ciprofloxacin, amoxicillin with clavulanic acid, and erythromycin were each involved in less than 10% of PDDIs (Table 25).

Table 25. Prevalence of potential drug-drug interaction according to the antimicrobial class

Antibiotic class	Antibiotic	Prevalence (N=96 PDDIs), n (%)
Macrolides		29 (30.2)
	Roxithromycin	*12 (12.5)*
	Clarithromycin	*10 (10.4)*
	Erythromycin	*6 (6.3)*
	Azithromycin	*1 (1.0)*
Other antibacterials*		26 (27.1)
	Trimethoprim	*24 (25.0)*
	Co-trimoxazole	*2 (2.1)*
Quinolones		16 (16.7)
	Norfloxacin	*9 (9.4)*
	Ciprofloxacin	*7 (7.3)*
Penicillins		12 (12.5)
	Amoxicillin with clavulanic acid	*6 (6.3)*
	Flucloxacillin	*4 (4.2)*
	Amoxicillin	*1 (1.0)*
	Dicloxacillin	*1 (1.0)*
Cephalosporins		12 (12.5)
	Cefalexin	12 (12.5)
Nitroimidazoles		1 (1.0)
	Metronidazole	*1 (1.0)*
Total		96 (100.0)

*Other antibacterial: classified by the *AMH*[255]. This class includes nitrofurantoin, trimethoprim, trimethoprim with sulfamethoxazole (co-trimoxazole), chloramphenicol, hexamine hippurate, linezolid.

The most common class of drugs involved in PDDIs with these antibiotics were "other anticoagulants" (as classified by the *AMH* (2015), namely warfarin) (n=18, 18.8%), tricyclic antidepressants (n=12, 12.5%), and statins (n=11, 11.5%). ACEIs were involved in 9.4% (n=9) of the PDDIs, while antiarrhythmic drugs were involved in 9.4% (n=9) and sartans 8.3% (n=8) (Table 26).

Table 26. Prevalence of potential drug-drug interaction according to drug class

Drug class	Prevalence (N = 96 PDDIs), n(%)
Other anticoagulants (warfarin)*	18 (18.8)
Tricyclic antidepressants	12 (12.5)
Statins	11 (11.5)
ACEI	9 (9.4)
Antiarrhythmics (digoxin, sotalol)	9 (9.4)
Sartans	8 (8.3)
Opioid analgesics	5 (5.2)
SSRIs	5 (5.2)
Serotonin and noradrenaline reuptake inhibitors	4 (4.2)
Non-opioid analgesics	4 (4.2)
Antipsychotics	2 (2.1)
Other drugs for diabetes*	2 (2.1)
Others#	7 (7.0)
Total	96 (100.0)

*As classified in the *AMH*. ACEI: Angiotensin converting enzyme inhibitor, SSRIs: Selective serotonin re-uptake inhibitors, sartans: also known as angiotensin II antagonists or angiotensin receptor blocker (*AMH*). # Others consist of Anticholinergics (genitourinary), Anticholinestearases in Alzheimer's disease, Antimetabolites, Dopamine antagonists, Alpha reductase inhibitors, Aldosterone antagonists, Other antiepileptics*

In terms of risk rating, *Lexicomp® Lexi-interact*™ identified 60 (62.5%) of the PDDIs as requiring therapy monitoring, and seven (7.3%) as requiring therapy modification, while two (2.1%) were contraindicated (Table 27).

Table 27. Risk rating of PDDI and their prevalence according to *Lexicomp® Lexi-interact*™

Rating	Prevalence (N = 96 PDDIs), n (%)
Avoid combination	2 (2.1)
Consider therapy modification	7 (7.3)
Monitor therapy	60 (62.5)
No action needed	8 (8.3)
No known interaction	19(19.8)
Total	96 (100.0)

Among the 96 PDDIs, when classified according to their consequence reported by *Micromedex*®, 25 (26.0%) may lead to QT interval prolongation, 18 (18.8%) hyperkalaemia, 17 (17.7%) increased risk of bleeding, 11 (11.4%) rhabdomyolysis, six (6.3%) digoxin toxicity, four (4.2%) increased risk of serotonin syndrome, and four (4.2%) metabolic acidosis. Other potential adverse effects were hypoglycaemia or hyperglycaemia, risk of respiratory depression, decreased clarithromycin plasma concentrations, decreased international normalised ratio (INR)/prothrombin time and anticoagulant effectiveness, increased dutasteride plasma concentrations, and methotrexate toxicity, which collectively constituted just over 11% (Table 28).

Table 28. Potential adverse effects related to potential drug-drug interaction according to *Micromedex*®

Potential adverse effect	Antibiotic class*	Drug class*	Prevalence (N = 96 PDDIs), n (%)
QT interval prolongation	Quinolones, macrolides, trimethoprim, metronidazole	Antiarrhythmics, solifenacin, donepezil, antipsychotics, prochlorperazine, escitalopram, TCAs	25 (26.0)
Hyperkalaemia	Trimethoprim	ACEIs, spironolactone, sartans	18 (18.8)
Risk of bleeding	Cefalexin, macrolide, penicillin	Warfarin	17 (17.7)
Myopathy or rhabdomyolysis	Macrolides	Statins	11 (11.4)
Digoxin toxicity	Macrolides	Digoxin	6 (6.3)
Serotonin syndrome	Penicillin	Venlafaxine	4 (4.2)
Increased risk for high anion gap metabolic acidosis	Flucloxacillin	Paracetamol	4 (4.2)
Increased oxycodone concentration	Macrolides, ciprofloxacin	Oxycodone	3 (3.1)
Hypoglycaemia or hyperglycaemia	Quinolones	Antidiabetic drugs	2 (2.1)
Increased tramadol exposure and increased risk of respiratory depression	Clarithromycin, ciprofloxacin	Tramadol	2 (2.1)
Decreased clarithromycin plasma concentrations	Clarithromycin	Phenytoin	1 (1.0)
Decreased INR/prothrombin time and anticoagulant effectiveness	Dicloxacillin	Warfarin	1 (1.0)
Increase in dutasteride plasma concentrations	Ciprofloxacin	Dutasteride	1 (1.0)
Increased risk of methotrexate toxicity (myelotoxicity, pancytopenia, megaloblastic anaemia)	Trimethoprim	Methotrexate	1 (1.0)
Total			96 (100.0)

*Drug name presented when a single drug is involved in the drug class, TCA: tricyclic antidepressants, ACEI: angiotensin converting enzyme inhibitor

Statins (n=11, 11.5%) and digoxin (n=6, 6.3%) were the most frequently involved in PDDIs with macrolides. ACEIs (n=9, 9.4%) and sartans (n=8, 8.3%) were frequently implicated with trimethoprim. Tricyclic antidepressants (n=6, 6.3%) were commonly identified as potential interacting drugs with quinolones (Table 29).

Table 29. Prevalence of drug classes interacting with antibiotic classes

Antimicrobial class	Drug class*	Prevalence (N = 96 PDDIs), n (%)
Macrolides	Statins	11 (11.5)
	Digoxin	6 (6.3)
	TCA	3 (3.1)
	Opioid analgesics	3 (3.1)
	Escitalopram	3 (3.1)
	Warfarin	1 (1.0)
	Antipsychotics	1 (1.0)
	Phenytoin	1 (1.0)
Other antibacterials	ACEI	9 (9.4)
	Sartans	8 (8.3)
	Sotalol	3 (3.1)
	TCAs	3 (3.1)
	Spironolactone	1 (1.0)
	Methotrexate	1 (1.0)
	Antipsychotics	1 (1.0)
Quinolones	TCAs	6 (6.3)
	Opioid analgesic	2 (2.1)
	Escitalopram	2 (2.1)
	Other drugs for diabetes	2 (2.1)
	Prochlorperazine	1 (1.0)
	Solifenacin	1 (1.0)
	Warfarin	1 (1.0)
Penicillins	Paracetamol	4 (4.2)
	Warfarin	4 (4.2)
	Venlafaxine	4 (4.2)
Cephalosporins	Warfarin	12 (12.5)
Metronidazole	Donepezil	1 (1.0)
Total		96 (100.0)

*Drug name presented when a single drug is involved in the drug class, TCA: tricyclic antidepressants, ACEI: angiotensin converting enzyme inhibitor, Other antibacterials: trimethoprim, co-trimoxazole

Ten PDDIs were related to the use of clarithromycin; among these, only one incidence of PDDI between clarithromycin and digoxin was of major severity according to *Micromedex®*, and moderate according to *Lexicomp® Lexi-interact™* and *MIMS®*, supported by excellent evidence (*Micromedex®*, and *Lexicomp® Lexi-interact™*) or well-established evidence by *MIMS®*. For erythromycin, one potential interaction was with digoxin (1%), one with warfarin (1%), and one with simvastatin (1%) (Table 30). The most frequent drug interaction with trimethoprim was with perindopril (7.3% of PDDIs, 7.8% of the residents), followed by with candesartan (4.2% of PDDIs, 3.1% of the residents) (Table 31).

The most frequent PDDIs involving quinolones were interactions with norfloxacin and amitriptyline (5.2% of PDDIs, 3.1% of the residents), which were supported with fair evidence, and were of major severity according to *Micromedex®* and minor severity by *Lexicomp® Lexi-interact™*. Only the norfloxacin and warfarin interaction (1% of PDDIs, 1.5% of the residents) was supported by a good level of evidence and rated as major in terms of severity by *Micromedex®* while moderate by other two databases (Table 32).

Among cephalosporins, the only PDDI identified was between cefalexin and warfarin, comprising 12.5% (12/96) of all PDDIs and involving 12.5% (8/64) of the residents. The most frequent interaction involving penicillins was flucloxacillin with paracetamol (4.5% of PDDI, 6.2% of the residents) according to *MIMS®*; however, the existence of this interaction was not supported by the other two databases (Table 33).

Table 30. Macrolide-related potential drug-drug interactions

Interacting drug pairs	Prevalence		*Micromedex®*		*Lexicomp® Lexi-interact™*		*MIMS®*	
	N = 96 (total PDDIs) n (%)	N = 64 (Residents with PDDI) n (%)	Severity	Reliability	Severity	Reliability	Severity	Reliability
Azithromycin, simvastatin	1 (1.0)	1 (1.5)	Major	Good	Moderate	Fair	Moderate	Limited
Clarithromycin, amitriptyline	1 (1.0)	1 (1.5)	Major	Fair	Moderate	Fair	NI	NI
Clarithromycin, atorvastatin	1 (1.0)	1 (1.5)	Major	Good	Major	Good	Severe	Good
Clarithromycin, digoxin	1 (1.0)	1 (1.5)	Major	Excellent	Moderate	Excellent	Moderate	Well estab
Clarithromycin, escitalopram	1 (1.0)	1 (1.5)	Major	Fair	Major	Fair	Severe	Not estab
Clarithromycin, oxycodone	1 (1.0)	1 (1.5)	Major	Fair	Major	Good	Moderate	Limited
Clarithromycin, phenytoin	1 (1.0)	1 (1.5)	Major	Fair	Major	Good	Moderate	Limited
Clarithromycin, pravastatin	1 (1.0)	1 (1.5)	Moderate	Good	Major	Fair	Moderate	Limited
Clarithromycin, quetiapine	1 (1.0)	1 (1.5)	Major	Fair	Major	Fair	Moderate	Good
Clarithromycin, sertraline	1 (1.0)	1 (1.5)	Major	Fair	Moderate	Fair	NI	NI
Clarithromycin, tramadol	1 (1.0)	1 (1.5)	Major	Fair	Moderate	Fair	Moderate	Limited
Roxithromycin, atorvastatin	4 (4.2)	3 (4.6)	NI	NI	NNI	NNI	NI	NI
Roxithromycin, digoxin	4 (4.2)	4 (6.2)	NI	NI	Moderate	Fair	Moderate	Good
Erythromycin, amitriptyline	1 (1.0)	1 (1.5)	Major	Fair	Moderate	Fair	NI	NI
Erythromycin, atorvastatin	1 (1.0)	1 (1.5)	Major	Good	Moderate	Good	Moderate	limited
Erythromycin, digoxin	1 (1.0)	1 (1.5)	Major	Excellent	Moderate	Excellent	Moderate	Good
Erythromycin, oxycodone	1 (1.0)	1 (1.5)	Major	Fair	Moderate	Good	NI	NI
Erythromycin, simvastatin	1 (1.0)	1 (1.5)	Contra.	Excellent	Major	Good	Severe	Well estab
Erythromycin, warfarin	1 (1.0)	1 (1.5)	Major	Excellent	Moderate	Excellent	Severe	Good
Roxithromycin, escitalopram	2 (2.1)	2 (3.1)	NI	NI	Major	Fair	Severe	Not estab
Roxithromycin, simvastatin	2 (2.1)	2 (3.1)	NI	NI	Moderate	Poor	Moderate	Limited

Contra.: contraindicated, Not estab: not established, Well estab: well established, NNI: no known interaction, NI: no information

Table 31. Trimethoprim-related potential drug-drug interactions

Interacting drug pairs	Prevalence		*Micromedex®*		*Lexicomp® Lexi-interact™*		*MIMS®*	
	N = 96 (total PDDIs) n (%)	N = 64 (Residents with PDDI) n (%)	Severity	Reliability	Severity	Reliability	Severity	Reliability
Trimethoprim, perindopril	7 (7.3)	5 (7.8)	Major	Fair	Moderate	Good	Moderate	Good
TMP-SMX, amitriptyline	1 (1.0)	1 (1.5)	Major	Good	NNI	NNI	NI	NI
TMP-SMX, telmisartan	1 (1.0)	1 (1.5)	Major	Fair	Moderate	Good	Moderate	Good
Trimethoprim, methotrexate	1 (1.0)	1 (1.5)	Major	Excellent	Major	Fair	Severe	Well estab
Trimethoprim, risperidone	1 (1.0)	1 (1.5)	Major	Fair	NNI	NNI	NI	NI
Trimethoprim, spironolactone	1 (1.0)	1 (1.5)	Major	Fair	Moderate	Good	Moderate	Limited
Trimethoprim, telmisartan	1 (1.0)	1 (1.5)	Major	Fair	Moderate	Good	Moderate	Good
Trimethoprim, candesartan	4 (4.2)	2 (3.1)	Major	Fair	Moderate	Good	Moderate	Good
Trimethoprim, amitriptyline	2 (2.1)	2 (3.1)	Major	Good	NNI	NNI	Moderate	Limited
Trimethoprim, irbesartan	2 (2.1)	2 (3.1)	Major	Fair	Moderate	Good	Moderate	Good
Trimethoprim, Ramipril	2 (2.1)	1 (1.5)	Major	Fair	Moderate	Good	Moderate	Good
Trimethoprim, sotalol	3 (3.1)	1 (1.5)	Major	Fair	NNI	NNI	NI	NI

TMP-SMX: Trimethoprim-sulphamethoxazole, Well estab: well established, NNI: no known interaction, NI: no information

Table 32. Quinolone-related potential drug-drug interactions

Interacting drug pairs	Prevalence		*Micromedex®*		*Lexicomp® Lexi-interact™*		*MIMS®*	
	N = 96 (total PDDIs) n (%)	N = 64 (Residents with PDDI) n (%)	Severity	Reliability	Severity	Reliability	Severity	Reliability
Norfloxacin, warfarin	1 (1.0)	1 (1.5)	Major	Good	Moderate	Good	Moderate	Good
Ciprofloxacin, amitriptyline	1 (1.0)	1 (1.5)	Major	Fair	Moderate	Fair	Severe	Limited
Ciprofloxacin, dutasteride	1 (1.0)	1 (1.5)	Moderate	Good	NNI	NNI	NI	NI
Ciprofloxacin, escitalopram	1 (1.0)	1 (1.5)	Major	Fair	Major	Fair	Severe	Limited
Ciprofloxacin, metformin	1 (1.0)	1 (1.5)	Major	Fair	Moderate	Fair	NI	NI
Ciprofloxacin, oxycodone	1 (1.0)	1 (1.5)	Major	Fair	Moderate	Poor	NI	NI
Ciprofloxacin, prochlorperazine	1 (1.0)	1 (1.5)	Major	Fair	NNI	NNI	NI	NI
Ciprofloxacin, tramadol	1 (1.0)	1 (1.5)	Major	Fair	NNI	NNI	NI	NI
Norfloxacin, amitriptyline	5 (5.2)	2 (3.1)	Major	Fair	Minor	Fair	NI	NI
Norfloxacin, escitalopram	1 (1.0)	1 (1.5)	Major	Fair	Moderate	Fair	NI	NI
Norfloxacin, insulin	1 (1.0)	1 (1.5)	Major	Fair	Moderate	Fair	NI	NI
Norfloxacin, solifenacin	1 (1.0)	1 (1.5)	Major	Fair	Minor	Fair	NI	NI

NNI: no known interaction, NI: no information

Table 33. Cephalosporin-, penicillin- and nitroimidazole-related potential drug-drug interactions

Interacting drug pairs	Prevalence		*Micromedex®*		*Lexicomp® Lexi-interact™*		*MIMS®*	
	N = 96 (total PDDIs) n (%)	N = 64 (Residents with PDDI) n (%)	Severity	Reliability	Severity	Reliability	Severity	Reliability
Cefalexin warfarin	12 (12.5)	8 (12.5)	Major	Good	Moderate	Fair	NI	NI
Amox/clav, venlafaxine	3 (3.1)	3 (4.6)	Major	Good	NNI	NNI	NI	NI
Amox/clav, warfarin	3 (3.1)	3 (4.6)	Major	Good	Moderate	Good	Moderate	Good
Amoxicillin, venlafaxine	1 (1.0)	1 (1.5)	Major	Good	NNI	NNI	NI	NI
Flucloxacillin, paracetamol	4 (4.2)	4 (6.2)	NI	NI	NNI	NNI	Moderate	Good
Dicloxacillin, warfarin	1 (1.0)	1 (1.5)	Major	Excellent	Moderate	Good	Moderate	Good
Metronidazole, donepezil	1 (1.0)	1 (1.5)	Major	Good	NNI	NNI	NI	NI

NNI: no known interaction, NI: no information, Amox/clav : amoxicillin/clavulanate

4.2.4 Discussion

To the candidate's knowledge, this is the first study of potential antibiotic interactions with concurrent medicines in RACFs in Australia. Overall, 64 (18.2%) residents, among the 351 residents who were on antibiotic therapy in the year 2015, were susceptible to at least one PDDI. Antibiotics with higher incidences of interactions were macrolides and trimethoprim, followed by quinolones. Warfarin, amitriptyline, atorvastatin, perindopril, digoxin, and candesartan were frequently involved in the PDDIs with antibiotics. The common potential adverse effects due to these PDDIs were QT interval prolongation, hyperkalaemia, and increased risk of bleeding, followed by rhabdomyolysis and digoxin toxicity.

Among the 64 residents, 48 (75%) were female and 16 (25%) were male. The retrospective cross-sectional study in December 2008 in residents of Singaporean RACFs reported 32 (46%) of the 70 residents (female 48.4%) who used antimicrobials were identified with PDDIs. The multicentre, observational, point-prevalence study in five hospitals in Turkey reported that 22.7% of patients (female 44.3%) were exposed to at least one PDDI. As such, the prevalence of PDDIs in the current study is lower, but the proportion of female participants is higher. Association of gender with PDDIs seems questionable. Some studies have found gender, specifically female gender, as a potential risk factor for PDDIs,[340] whereas another study found no significant association with any specific gender.[355] However, females are more prone (1.5- to 1.7-fold) to increased risk of developing an adverse drug effect than males.[356] Gender-related immunological and hormonal differences influence pharmacodynamic and pharmacokinetic response to psychotropic and cardiac medicines.[357] The findings of this current study may not be comparable to other studies due to the limited sample. Also, differences in the populations, study design, settings, time periods, DDIs tools and the lack of consistent strategy for detecting DDIs challenge comparison of findings among studies.[318, 346, 358, 359] Notably, there was only one study that investigated PDDIs between antimicrobials and other co-prescribed medicines among residents of RACFs in Singapore,[318] and international differences in prescribing protocols and formularies may limit this comparison.

In the current study, *Micromedex*®, *Lexicomp® Lexi-interact*™ and *MIMS*® were utilised as clinical decision support tools. In previous studies, inconsistencies among DDI tools were observed.[353, 360, 361] Therefore, screening of PDDIs by more than one source is a common approach in clinical studies.[343] Both *Micromedex*® and *Lexicomp® Lexi-interact*™ have high reported sensitivity and specificity.[347] *MIMS*® is utilised in primary and tertiary heathcare systems in Australia. In this study, *Micromedex*® identified most of the PDDIs of major

severity, whereas *Lexicomp® Lexi-interact*™ and *MIMS®* identified most of the interactions as moderate severity. In a cross-sectional study in two intensive care units, Vanham et al. also found that *Micromedex®* identified the most PDDIs as major compared to two other DDIs tools, *Stockley's Interaction Checker®* and *Epocrates®*.[362] This highlights the need for using several compendia to detect and manage PDDIs in clinical practice. Again, the interaction between trimethoprim and risperidone was detected as major severity with fair level of evidence by *Micromedex®*, whereas this interaction was not identified by other two DDI tools. In the cross-sectional study in adult patients from two academic intensive care units, only 13% of PDDIs were concurrently detected by three prominent DDI tools (*Stockley's Interaction Checker® Micromedex®*, and *Epocrates®*).[362] This reconfirms the inconsistency between different DDI compendia, and justifies the approach to use multiple compendia as references. However, due to these discrepancies in the concordance of different DDI tools, the application of these tools remains questionable as to whether DDI compendia represent the most appropriate means of detecting DDIs in RACFs. Therefore, it is recommended to use more than one DDI compendia with the clinician's judgement to identify and differentiate between relevant PDDIs and irrelevant PDDIs by considering patient-related factors.[347]

Electronic databases are not free of limitations. One disadvantage is that these databases report a large number of PDDIs of low clinical importance, which leads to over-detection of PDDIs compared to the clinician's assessment.[363] According to a large study by Peng et al.[364] on 30 million prescriptions, clinical pharmacists' observation reduced the prevalence of DDIs to 5.7% of initially detected DDIs. The other key limitation of these DDI tools is that they are not specific to elderly populations, and do not consider elderly-related factors such as pharmacokinetic and pharmacodynamic changes, frailty, and reduced homoeostatic mechanisms.[320] DDI tools are also not specific to dose of the drugs in the evaluation of DDIs.[352, 365] These tools do not have the ability to identify and ignore a co-prescribed drug-pair if the drugs are given in a non-interacting dose.[366, 367] A drug that may interact in high doses may not lead to a significant interaction in a lower dose.[366, 367]

Therefore, sole dependence on electronic databases is cautioned due to differences in identification, severity rating, and concordance with clinical assessment. If managed effectively, many DDIs may not have any adverse outcome. Thus, studies that estimated PDDIs by reporting frequency and severity of interactions irrespective of their manageability may have overestimated the risk caused from PDDIs. A population based study in Germany

showed that 15% (132/882) of the identified DDIs were of major severity, among which 76.5% (101/132) were considered manageable.[367] The current study was focused on PDDIs, not actual DDIs. While only a limited proportion (0.25% to 25%) of PDDIs can lead to actual DDIs, the measurement of PDDIs is an indicator for actual DDI.

In the present study, the most commonly used antibiotics (see Section 4.1.5.4) amongst the Bethanie residents were cephalosporins, penicillins, trimethoprim, and macrolides, whilst the antibiotics with a higher incidence of potential interactions were macrolides and trimethoprim, followed by quinolones. According to the nationwide surveillance report of Australia (the 2019 Aged Care National Antimicrobial Prescribing Survey (AC NAPS)), the most frequently used antimicrobials in RACFs were cefalexin (n = 790, 21.2%), clotrimazole (n = 654, 17.5%), amoxicillin–clavulanic acid (n = 274, 7.3%), and trimethoprim (n = 236, 6.3%).[368] Macrolide (roxithromycin) and quinolone (ciprofloxacin) constituted less than 5%. The study in the residents of RACFs in Singapore reported the most common antimicrobials involved in PDDIs were ciprofloxacin, followed by clarithromycin and doxycycline.[318] In that study, the most commonly prescribed antimicrobials were amoxicillin-clavulanate, ciprofloxacin, and doxycycline. The differences between the two studies could be attributed to differences in geography, national regulatory policies, availability of medicines, and clinicians' practice.[114]

The current study reported that anticoagulants (warfarin), tricyclic antidepressants (amitriptyline), statins (atorvastatin), ACEIs (perindopril), antiarrhythmics (digoxin), and sartans (candesartan) were frequently involved in the PDDIs with antibiotics. This finding was somewhat different from the previous studies. The study in Singapore by Selcuk et al.[318] found that inorganic ions (calcium, iron, magnesium, sodium, zinc) were the most frequently used drugs in the residents exposed to PDDIs, followed by amlodipine, domperidone, and fluoxetine. The hospital-based study in Turkey by Kuscu et al.[346] reported that diclofenac, budesonide, methylprednisolone and tramadol were the commonly interacting drugs with antimicrobials. The study in the elderly patients who attended the public primary health care system in Brazil found that thiazide diuretics were the most commonly prescribed drugs in patients exposed to PDDIs, followed by ACEIs, digitalis glycosides, antiplatelet drugs and loop diuretics. [340] This suggests no clear consensus either in the published literature or between the current findings and any particular study. The logical explanation is the international differences in prescribing patterns.

4.2.4.1 Potential antibiotic-drug interactions and adverse effects

The current study demonstrated that macrolides and trimethoprim were the antibacterials most frequently involved in DDIs. Macrolides were frequently prescribed with statins, digoxin, and in one incidence, with warfarin; all of these combinations may result in adverse outcomes. Trimethoprim was frequently prescribed with ACEIs, sartans, and in one incidence, with spironolactone, combinations that may lead to hyperkalaemia. Furthermore, it was co-prescribed with methotrexate, which can lead to bone marrow suppression.[131] This study also reported the common potential adverse effects due to the PDDIs were QT interval prolongation, hyperkalaemia, and risk of bleeding, followed by rhabdomyolysis and digoxin toxicity.

4.2.4.1.1 Macrolide-related drug interactions

Macrolides with statins

Eleven instances of PDDIs between macrolides and statins were identified in 57 cases where macrolides were prescribed. These included co-prescription of azithromycin with simvastatin, clarithromycin with atorvastatin or pravastatin, roxithromycin with atorvastatin and simvastatin, and erythromycin with atorvastatin or simvastatin. Macrolides may increase the toxicity of statins, which lead to myopathy, with the symptoms of muscle aches or pains, weakness, renal dysfunction, and dark urine.[369-371] Studies have reported that patients treated with statins metabolised by CYP3A4 and macrolide antibiotics such as erythromycin[372, 373] or clarithromycin[374-376] have developed rhabdomyolysis and/or renal failure. A case report of two elderly patients, one who was co-prescribed erythromycin and the other clarithromycin with high dose simvastatin (80 mg/day), were hospitalised after one to two weeks of completing their short course of antibiotics, due to myalgias, inability to raise their arms and legs, muscle weakness, and higher (more than 60 times the upper limit of normal) serum creatine kinase levels.[371] This indicates the short-term use of macrolides may lead to adverse effects, and clinicians should be aware of the risks associated with this co-therapy.[371] A Canadian population-based retrospective cohort study using linked data from 721,277 elderly individuals (older than 65 years) reported that co-prescribing of clarithromycin or erythromycin with a statin (metabolised by CYP3A: atorvastatin, simvastatin, lovastatin) was associated with increased risk of rhabdomyolysis and hospitalisation with acute kidney failure compared to azithromycin.[135]

CYP3A4 is responsible for the metabolism of simvastatin, atorvastatin and lovastatin. Inhibition of CYP3A4 causes impaired metabolism of these statins.[377] Both erythromycin and clarithromycin are the most pronounced inhibitors of CYP3A4, whereas azithromycin is a weak inhibitor.[378] In addition, erythromycin, clarithromycin, roxithromycin, and to a lesser extent, azithromycin, inhibit P-glycoprotein (Pgp), which may lead to an increase in statin absorption or reduced biliary secretion.[378] Both erythromycin and clarithromycin also inhibit the uptake transporter OATP1B1, a member of organic anion transporting polypeptide, which plays a role in the disposition of certain statins, such as simvastatin.[379, 380] Thus residents with CYP3A4-mediated statins, such as simvastatin, lovastatin or atorvastatin, are at an increased risk of toxicity from co-prescribing of erythromycin or clarithromycin. Therefore, it is recommended to avoid co-administration of these statins with clarithromycin, erythromycin or roxithromycin, or to select an alternative antibiotic from another class.[378] If macrolide therapy is required, it is recommended to discontinue statin for the duration of macrolide treatment.[378]

Macrolides with warfarin

The current study reported a potential interaction between warfarin and erythromycin that may result in increased risk of bleeding. Several case reports have identified episodes of haematuria and bruising[381] and increased prothrombin time after initiation of erythromycin therapy while on warfarin.[381-383] According to a nested case-control study in a cohort of 38,762 patients aged 65 years and older who were continuous warfarin users, macrolides (azithromycin, clarithromycin, dirithromycin, erythromycin, telithromycin, troleandomycin) were associated with a 1.86-fold (95% CI, 1.08-3.21) increased risk of bleeding that required hospitalisation within 60 days of antibiotic exposure compared with non-exposure.[136] Nine drug interactions between erythromycin and warfarin were among the 423 reports for erythromycin submitted to the Therapeutic Goods Administration (TGA) from 2001 to 2021.[384]

Macrolides may increase the effects of warfarin via the inhibition of CYP450-mediated metabolism of warfarin and by the disruption of vitamin K synthesis.[385] If concomitant use of a macrolide and warfarin is required, more frequent monitoring of the patient's INR is recommended, especially during initiation and discontinuation of a macrolide.[386, 387] Where possible, macrolides should be substituted with an antibiotic with a low-risk profile for bleeding, such as clindamycin or cefalexin.[388]

Macrolides with digoxin

Six PDDIs between macrolides and digoxin were identified in 57 cases where macrolides were prescribed in this cohort. These included clarithromycin, erythromycin or roxithromycin with digoxin. Macrolide antibiotics may increase the serum concentration of digoxin, which can lead to digoxin toxicity.[389] Symptoms of digoxin toxicity include gastrointestinal distress,[389, 390] weakness,[389] dizziness,[389] arrhythmia,[389] loss of appetite,[389] and nausea.[390]

According to population-based studies, macrolides (azithromycin, erythromycin, clarithromycin) were associated with increased risk of digoxin toxicity.[138, 139] Concomitant use of clarithromycin (aOR: 14.8; 95% CI: 7.9-27.9) poses a four-fold higher risk compared to erythromycin and azithromycin (aOR: 3.7; 95% CI: 1.7-7.9; and aOR: 3.7; 95% CI: 1.1-12.5, respectively).[138] A randomised, placebo-controlled, double-blind cross-over study in 12 healthy volunteers found that co-administration of clarithromycin (250 mg, twice daily for three days) increased plasma concentration of digoxin (single oral 0.75 mg) by 1.7 times compared to placebo.[391]

Macrolides may increase the serum levels and toxicity of digoxin by the inhibition of Pgp-mediated transport of digoxin, which increases intestinal absorption and reduces renal excretion of digoxin.[392] According to an *in vitro* study, macrolides (azithromycin, clarithromycin, erythromycin and roxithromycin) increased digoxin concentration by inhibiting Pgp-mediated digoxin transport.[393] Roxithromycin was the most potent inhibitor of Pgp, whilst azithromycin was the least potent inhibitor.[393] Furthermore, it has been postulated that inhibition by macrolides (specifically erythromycin) of the growth of specific gut flora, namely *Eubacterium lentum*, which is responsible for intestinal metabolism of digoxin, increases the serum concentration of digoxin due to less degradation and more absorption of digoxin.[394]

Monitoring for signs of digoxin toxicity and serum levels of digoxin is advisable when treatment with a macrolide antibiotic is required.[393] It is also recommended to use the combination of macrolides and digoxin with caution. Azithromycin may be the safest macrolide in this group due to its lower inhibition of Pgp[393] and lack of effect on CYP450.[395]

4.2.4.1.2 Trimethoprim-related drug interactions

Trimethoprim or TMP-SMX with ACEIs, sartans or spironolactone

Eighteen incidences of PDDIs related to trimethoprim or co-trimoxazole co-prescribed with ACEIs, sartans or spironolactone were identified in 68 cases of use of these antibacterials. Trimethoprim interacts with ACEIs, sartans or spironolactone, which may cause hyperkalaemia. Malaise, palpitations, and muscle weakness can be symptoms of this adverse effect.[396] A nested case-control study in the UK found that concurrent use of spironolactone (OR: 3.01; 95% CI: 2.61-3.48), or ACEIs (OR: 1.70; 95% CI 1.41-2.04) with trimethoprim was associated with an increased risk of hyperkalaemia amongst a cohort of heart failure patients.[397] Two population-based retrospective case-control studies reported that in patients aged 66 and older, simultaneous use of inhibitors of renin-angiotensin systems (sartans or ACEI),[128] or a spironolactone[398] with co-trimoxazole increased the risk of sudden death due to hyperkalaemia compared to amoxicillin. A nested case-control study in patients treated with ACEIs or sartans with simultaneous use of co-trimoxazole aged 66 or older reported a more than six-fold increased risk of hospitalisation due to hyperkalaemia when compared with the concurrent use of amoxicillin.[125] Several case reports described hyperkalaemia due to the combined use of co-trimoxazole together with an ACEI, sartans or spironolactone.[129, 130, 399]

Trimethoprim increases the risk of hyperkalaemia by inhibiting the sodium channels in the luminal membrane of the distal tubule, which results in inhibition of renal excretion of potassium.[400] It is recommended to monitor patients for symptoms of hyperkalaemia when co-administered with trimethoprim or with sulfamethoxazole.[398] Dose adjustment or use an alternative antibiotic should be considered in elderly patients who are taking ACEIs, sartans or spironolactone, or are at risk of hyperkalaemia (such as renal insufficiency).[125, 398]

Trimethoprim or co-trimoxazole with methotrexate

One incidence of potential drug interaction between trimethoprim and methotrexate was identified in 68 infection cases for which trimethoprim or co-trimoxazole was prescribed in the Bethanie residents. Trimethoprim may increase the methotrexate toxicity.[401] Trimethoprim is also used in combination with sulfamethoxazole (known as co-trimoxazole) as synergistic antimicrobial combination to treat bacterial infections.[402] Several case reports describe the development of methotrexate-associated toxicity in patients taking concomitant co-trimoxazole.[131, 132] A recent nationwide study in Taiwan found an association

between concurrent methotrexate and co-trimoxazole use and the risk of hospitalisation (adjusted OR: 1.45, 95% CI: 1.33-1.58) in patients with rheumatoid arthritis compared to methotrexate alone.[403] Whether the presumed interaction is due to a single component (trimethoprim or sulfamethoxazole) of co-trimoxazole or the combination is unclear. This toxicity manifests as painful mucositis, [131],[132] leucopaenia,[132] renal insufficiency,[131, 132] diarrhoea,[131] and myelosuppression.[131] Both trimethoprim and methotrexate inhibit dihydrofolate reductase, which reduces folate metabolism, thus causing myelosuppression.[404, 405] Co-trimoxazole may increase the toxicity of methotrexate by a synergistic anti-folate mechanism,[404] reducing its renal clearance[406] and displacement from its protein binding sites.[407] It is recommended to avoid concomitant use of methotrexate and either trimethoprim or co-trimoxazole.[131] If used concomitantly, patients should be monitored for the development of signs and symptoms of methotrexate toxicity.[131]

4.2.4.2 Other outcomes of potential drug-drug interactions

QT interval prolongation is a severe event that may cause life-threatening cardiotoxicity with torsade de pointes (TdP).[408] TdP may present as sudden death, dizziness, syncope, ventricular tachycardia, seizures and/or palpitations.[409]

Antimicrobials that may precipitate QT prolongation include the macrolides (clarithromycin, erythromycin), certain fluoroquinolones, antimalarials, pentamidine, and the azole antifungals.[408] In the current study, macrolides, quinolones, trimethoprim and metronidazole were involved in PDDIs that may cause QT interval prolongation.

Multiple clinical risk factors are responsible for drug-associated QT prolongation. These include female gender,[410, 411] hypokalaemia,[412],[413] bradycardia,[414] congestive heart failure,[415] concurrent digoxin therapy,[414, 416] prolonged QT at baseline,[414] and severe hypomagnesaemia.[408, 417] Concurrent use of drugs that are substrates and/or inhibitors of CYP450 enzymes (CYP2C9, CYP2C19, CYP2D6 and CYP3A4) with an potassium channel blocking agent (such as quinidine, sotalol) increase the risk of TdP.[418]

These risk factors are useful in predicting the risk for an individual resident. Residents' medical and medication history should be checked for these risk factors before commencing any antibiotic that may increase the risk of QT prolongation.

4.2.5 Strengths of the study

This is the first-known study to identify antibiotic-related drug interactions in aged care residents in Western Australia. Despite not observing the clinical outcome of the PDDIs, which would require clinical consensus methods, this study presented preliminary data on the prevalence of PDDIs involving antibiotics in this population. The outcome of this study reinforces the significance of increasing knowledge about DDIs among nurses, pharmacists and physicians to prevent adverse drug effects due to DDI by avoiding the use of interacting drug combinations, or by monitoring the common toxicities of DDI (where the drug combination cannot be avoided). Hence, the findings support the development of an educational intervention, emphasising the identification and monitoring of antibiotic-drug interactions, for aged care staff.

4.2.6 Limitations

The findings of the present study should be considered with caution due to the study design. Retrospective observational methods may have inherent bias as a result of incomplete records of residents. This study was not designed to identify actual drug-drug interactions and related adverse effects, due to absence of clinical monitoring data. The limited sample size, compared to other published research, is also another limitation of this study. The current data were accessed from one aged care group in Western Australia, and while the sample was randomly selected, the results may not be generalisable at a state or national level. The study was not designed to identify the overall prevalence of PDDIs in this sample of residents; the focus on antibiotic-drug interactions should be recognised as only one facet of this larger clinical issue.

Residents of RACFs may also take herbal medicines and dietary supplements, which were not documented in the current study. Antimicrobials might have also interacted with these products. Further, a lack of clinical evidence about antimicrobial-supplement and herb interactions makes it difficult to consider them.[343]

The current study has recorded the drug co-administration data irrespective of the timing of when the two drugs were given. Therefore, drugs administered in the morning and the drugs administered at night were recorded as drug pairs and examined for PDDIs. Some pharmacokinetic or pharmacodynamic DDIs may occur only on simultaneous administration of the interacting drugs.[419] Thus, there is a possibility that the prevalence of the PDDIs may have been overestimated.

4.2.7 Action to be taken

4.2.7.1 Utilising information technology

Drug-related problems can be reduced by the application of health information technology such as electronic health records,[420] computerised physician order entry,[421] clinical decision support systems,[420] and drug interaction software for personal digital assistants[422] in healthcare settings.

Electronic health records provide patient information, improve documentation and interdisciplinary communication.[420] To improve patient safety, healthcare providers are implementing electronic health records with integrated clinical decision support.[423] Computerised alerts that notify clinicians regarding drug-drug interactions, drug-allergy warnings, and contraindication warnings, or give guidance for dosing, are commonly implemented in hospital settings.[423, 424] A review of hospital-based studies by Nuckols et al.[425] concluded that implementation of a computerised physician order entry can decrease potential adverse drug events by 50%. Outcomes research in ambulatory care on medicines alerts indicated that electronic prescribing alerts reduced drug-related problems including DDIs.[349] However, computerised order entries are also associated with inappropriate alerts, and following those alerts could cause harm to the patient.[426] Therefore, clinicians are advised to utilise patient record for proper history to evaluate the appropriateness of the alerts.

4.2.7.2 Pharmacy intervention

Martinez reported that intervention by pharmacists decreased the prevalence of clinically relevant DDIs and the number of residents with clinically relevant DDIs in nursing homes.[427] Similarly, Fog reported that medication reviews by a clinical pharmacist within a multidisciplinary team during November 2011 to February 2014 in 41 nursing homes in Norway demonstrated the reduction of medicines commonly associated with the incidence of DDI in the residents.[428] Accredited pharmacists who are responsible for RMMRs[429] in Australian RACFs should be vigilant to identify the PDDIs and can recommend appropriate measures to the prescribers and nurses.

4.2.7.3 Reporting and documentation

Reporting and documenting of DDIs and related adverse effects are key to preventing and managing DDIs.[430] Failure to document any incidences will increase the probability of re-exposure to the same DDI by the same patient.[430]

4.2.7.4 Monitoring residents

Residents who are at increased risk of DDIs can be identified and monitored by analysing predictive factors of the drug interaction.[320] Interactions are frequent among residents taking drugs that have a narrow therapeutic index, or are substrates, inducers, or inhibitors of CYP450 isoenzymes.[320] Residents with nine or more medicines and five or more diseases are commonly vulnerable to DDIs.[320] Symptoms such as lethargy, tiredness, dizziness, incontinence, falls and depression are all non-specific complaints that should prompt review of the residents' drug lists.[329] These symptoms can be monitored by nursing staff who are in daily contact with the residents.

4.2.7.5 Developing an educational program

Continuous professional development of health care professionals of RACFs is needed to increase their awareness and knowledge regarding potential life-threatening drug interactions between antibiotics and other medications. Multidisciplinary education related to the impact of ageing on physiology and its effect on drug handling and drug action is essential to reduce DDIs in the elderly.[329] The implementation of educational programs decreased clinically significant major DDIs by 18.2% in the cardiology department of hospitals in Kazakhstan.[431] Another multicentre controlled trial involving 629 residents of 159 nursing homes in South-Western France included an educational intervention delivered by 20 hospital geriatricians to the prescribers, the director of each nursing home and nurses, and demonstrated successful reduction in potentially inappropriate drug prescribing, including reduction in the rate of PDDIs.[432]

4.3 Conclusion

This is the first study in Australian RACFs to investigate drug-associated infection leading to the increasing use of antibiotics and antibiotic-related PDDIs. Australian and international studies have provided evidence about the successful role of pharmacists involved in medication review. As healthcare professionals with expertise in drug management, pharmacists can play a prominent role in optimising medication use in this setting. Minimisation of ADEs due to DDI should be ensured by improving appropriate prescribing in the elderly. Due to the fast growth of the elderly population and their polypharmacy burden, more attention should be given to safe and quality use of medicines for aged care residents. Thus, understanding the mechanism of antibiotic-related drug interactions can reduce adverse drug outcomes by ensuring the appropriate co-prescribing of antibiotics and other drugs. Online resources, along with consultation with pharmacists and education of nursing staff, may enhance the health outcomes of residents in aged care facilities.

Chapter 5 Development and implementation of an online educational intervention

5.1 Introduction

As discussed in Chapter 1, the increased susceptibility to infection of residents living in aged care stems from their age-related changes in physiological functions, multiple comorbidities, functional disabilities, use of invasive devices, and use of particular medicines. Evidence suggests that medicines such as benzodiazepines, PPIs, corticosteroids, opioid analgesics and antipsychotics can increase the risk of infection in the elderly. The current study found that use of benzodiazepines, antiepileptics, antidepressants, and tricyclic antidepressants all showed statistically significant associations with increased risk of infections, as indicated by the increased use of antimicrobials. Furthermore, it found antimicrobials prescribed for those infections may lead to serious interactions with the residents' other medications. Sixty-four of the 351 residents who had an infection were prescribed an antimicrobial that had the potential to interact with a medicine they were already taking. Those 64 residents had a total of 96 potential drug interactions between antimicrobials and their co-prescribed medicines. An example is the concurrent use of warfarin and macrolide antimicrobials, which may increase the risk of bleeding. These findings described in detail in Chapter 4 demonstrate the need for rational prescribing of both medicines that may contribute to an increased infection risk and antibiotics that have the potential to interact with other drugs.

Also as discussed in Chapter 1, off-site GPs prescribe for residents, and usually visit RACFs periodically and when required. Although Australian aged care providers do not employ full-time GPs, some have on-site full-time NPs who have prescribing rights.[7] NPs in Australian RACFs deliver advanced clinical assessments, prescribe treatments and medicines, and refer for diagnosis (e.g. pathology and radiology).[78] Pharmacists contribute either by dispensing medicines via an off-site community pharmacy or by conducting RMMRs on request by a GP, a government-funded periodic service for an individual resident. This means nurses are the only on-site healthcare professionals in RACFs. Therefore, aged care nursing staff are proposed to play an important role in identifying residents with particular medication profiles, informing doctors and pharmacists about these residents, and, where no changes can be made, monitoring the resident for any signs of infection or adverse outcome due to DDIs.

Educational programs aiming to improve knowledge have an important role in staff development.[433] Continuing educational programs increase productivity of staff and reduce the frequency of professional mistakes.[434] The focus of these programs is to upskill nurses to deliver safe and effective care.[435]

Constant developments in information technology offer prospects for continuing education for nurses via e-learning platforms to improve and develop the practical clinical knowledge and skills.[436] The advantages of e-learning include consistent delivery of education, less instruction time, and increased learners' motivation and satisfaction.[437-439] E-learning can be completed at a time and place of the learner's preference.[440]

Online (web-based) learning is one mode of e-learning.[441] Online delivery provides easy access to learning and can overcome some of the limitations of face-to-face teaching methods such as limited flexibility and resource requirements.[433, 437] Use of the Internet for delivery facilitates flexible and quality teaching.[442, 443] Khatony et al.[433] compared the usefulness of online and face-to-face education methods for improving nurses' knowledge about acquired immune deficiency syndrome and suggested there was no difference between the two methods in their effectiveness, although that study was unable to monitor the time taken to complete the course and post-test questions, and whether the nurses in the online group accessed extra resources. Other studies have also shown no differences in outcomes between online and face-to-face education.[444, 445] Furthermore, participants in online courses were more motivated and satisfied about their experience than those receiving traditional education.[444, 445]

5.1.1 The effectiveness of online learning for nurses

A pre-and-post knowledge testing study demonstrated that an e-learning course on delirium produced a significant increase in the knowledge of nurses with regard to the definition, symptoms, consequences and risk factors of delirium.[446] The course was introduced to 1,196 nursing staff of internal medicine and surgical wards of 17 Dutch hospitals, with a response rate of 86.4%. Baseline knowledge was tested with 24 multiple-choice, true/false, and matching questions. There was a significant difference in the test scores on the final knowledge test (mean score 87.4, 95% CI: 86.7-88.2) compared to baseline (mean score 79.3, 95% CI: 78.5-80.1). This hospital-based study could not preclude nurses' use of written notes or other resources while answering the test questions, or measure retention of knowledge, and lacked a control group.[446]

Wilson et al.[447] developed an educational intervention consisting of a free online course comprising six interactive modules (180 minutes total) regarding diagnosis of UTI, asymptomatic bacteriuria, URTI, bronchitis, and pneumonia. Pre- and post-course surveys were completed by the 103 registered or licensed practical nurses. The online course improved the mean knowledge score of nurses by 11% (mean knowledge score in pre-course: 75%, vs post-course: 86%, $p<0.001$) in the care of residents with infections. It also improved their confidence to be involved in antimicrobial stewardship programs. Nurses could claim 3.0 nursing contact hours upon completion of all six modules and the pre- and post-course surveys.[447]

Huckstadt et al.[448] evaluated case-based interactive online courses on back pain and dermatology for advanced practice nurses and indicated a significant improvement of knowledge after the completion of two online modules. Nurses reported satisfaction with the online course, and evaluated it as suitable, innovative and less time consuming than other methods.[448] Wilkinson et al.[440] reported nurses' satisfaction regarding the flexibility and self-paced manner of four newly developed online modules ("Diabetes in Primary Care", "Nurse Prescribing", "Dermatology for nurses", and "Mentorship for Professional Practice") for post-registration nurses. The effectiveness of online learning depends on participants' self-confidence in using a computer, validity and reliability of the instrument applied to assess the outcomes of learning, and quality of the learning contents.[441]

Nurses in Bethanie aged care can play important roles in providing safe healthcare. The outcome of Chapter 4 indicated the potential for an intervention to improve knowledge about antibiotic misadventure amongst nurses in Bethanie facilities. Online learning can be an attractive alternative to traditional educational methods in terms of labour, time management and other resources. It is also a useful tool to improve knowledge and/or dissemination of information to a large group of nurses in different locations. Therefore, the aim of this educational intervention is to improve knowledge about potential antibiotic misadventure amongst nurses in Bethanie facilities.

5.2 Method

5.2.1 Development of the online educational intervention

The online educational intervention was developed for the nurses of Bethanie facilities. The module and survey instruments were developed using the findings of Chapter 4, with the advice of research supervisors and the Clinical Nurse Educator and the Learning and Development Manager of Bethanie. This online educational intervention contained three parts: a pre-module survey, the educational module, and a post-module survey. The pre-module survey comprised a short introduction about the module, consent statements and a pre-module knowledge quiz, and collected demographic information from participating nurses. All three parts of the module had been developed by the research candidate informed by a review of published literature to incorporate evidence-based information. The educational module provided information about medicines that increase the risk of infection and interactions between antibiotics and other medicines. The post-module survey consisted of a post-module knowledge quiz and satisfaction survey. These are described in following sections.

5.2.2 Development of the educational module

5.2.2.1 Content selection

The topics to be covered in the module were identified with reference to the outcomes of Chapter 4 and the clinical experience of investigators and Clinical Nurse Educator.

According to the multivariate analysis reported in Section 4.1.5.4, benzodiazepines and certain groups of antiepileptics and antidepressants were independently associated with increased risk of infection in the residents of Bethanie aged care facilities. PPIs were associated with increased risk of infection in univariate analysis, but not in multivariate analysis. Despite published evidence that antipsychotics are associated with increased risk of infection (Section 4.1.2.1),[44, 212] the present analysis found that antipsychotics were not associated with increased risk of infection, either independently or non-independently. Therefore, benzodiazepines, PPIs, antiepileptics and antidepressants were the focus in this educational module.

Groups of antibiotics were selected on the basis of the finding in Chapter 4 and expert advice. Trimethoprim and macrolides were the commonly used antibiotics in Bethanie (Section 4.1.5.4), and highly prevalent in PDDIs (Section 4.2.3.3). The antibiotic-drug interaction pairs were incorporated on the basis of a) if the specific interaction was found in Bethanie practice, and b) if the PDDI severity was reported as at least 'major' by one database and 'moderate' by the other two databases, and minimum reliability was rated 'good' by all three databases (Table 30 and 31). Where possible, this current study discussed the drug class pairs instead of individual drugs; an example is macrolides with statins.

5.2.2.2 Platform

Articulate Rise 360®[449] was used to develop the module. The research candidate completed training in Articulate Rise 360® with the Bethanie Clinical Nurse Educator. The module was developed by using a desktop computer with Windows® 7 and Microsoft Internet Explorer® web browser. The advantages of Articulate Rise 360® are user friendliness for both the developer and end user, adaptability for any web browser, and transportability across mobile and desktop devices.[449]

5.2.2.3 Description of the module

Content of the education module was divided into two sections. Section One was "Drugs and Infection Risk", which included four lessons: Benzodiazepines and risk of infection; Proton pump inhibitors and risk of infection; Antiepileptics and risk of infection; and Antidepressants and risk of infection. Section Two was titled "Antibiotics and the risk of Drug Interactions" and included five lessons: Trimethoprim/trimethoprim-sulfamethoxazole with ACEIs, AIIRAs (angiotensin II receptor antagonists) or spironolactone; Trimethoprim/trimethoprim-sulfamethoxazole with methotrexate; Macrolides with statins; Macrolides with warfarin; and Macrolides with digoxin. Presenting the module in two sections with component lessons aimed to maintain participants' focus and establish a routine for progressing through the module.

At the beginning of each section, a brief introduction was provided (Figure 1). Case scenarios were included at the beginning of lessons to encourage nurses to recognise common clinical challenges in their practice (Figure 2). These case scenarios were inspired by actual residents whose profiles were reviewed. Interactive quizzes were included after each lesson to self-verify learning before progressing to next lesson.

Each lesson of Section One discussed the indication of the drug class, drug examples, and their mode of pharmacological action, how the drugs may increase infection risk, risk of infection, and findings from the present study.

In Section Two, each lesson consisted of a case scenario, adverse effects of antibiotic-drug interactions, literature evidence, and mechanism of antibiotic-drug interaction, symptoms of the effect of antibiotic-drug interaction, action to be taken, and findings from the present study (Table 34). Adverse effects, symptoms, cause and action to be taken were presented as expandable text upon clicking the relevant option (Figure 3).

All clinical content was developed according to published references. A fully referenced version of the module was prepared for the purposes of ethical approval; the unreferenced version was implemented in the study.

Table 34. Contents of each lesson in Section Two

Contents	Description
Case scenario	A case with questions.
Adverse effect	The effect of interaction with antibiotics and other drugs.
Symptoms	Any subjective evidence relating to the adverse outcome of the interaction, with copyright free images where possible.
Cause	The mechanism of interaction with antibiotics and other drugs. Probable pathways of interaction.
What the literature tells us	Published evidence.
Drug interactions in Bethanie practice	PDDIs between the antibiotics and other drugs in Bethanie practice during the year 2015, to demonstrate relevance of the content to the nurses' practice.
Action to be taken	Steps that can be taken by nursing staff to monitor and/or manage the interaction.

PDDIs: Potential drug-drug interactions

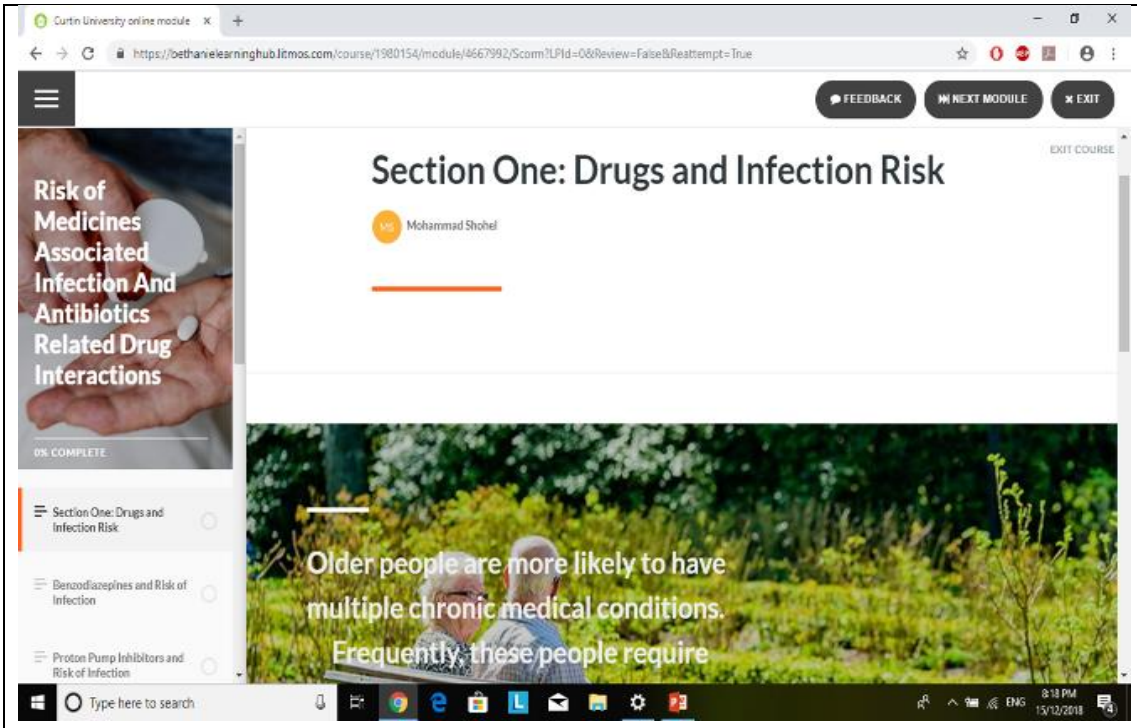

Figure 1 Introduction of Section One

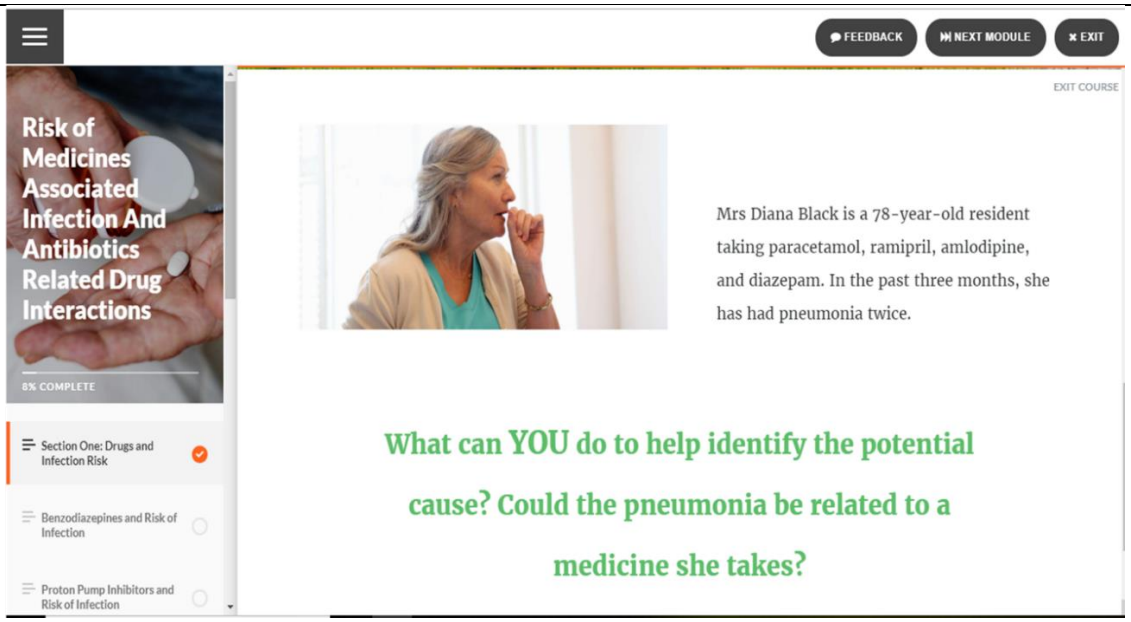

Figure 2 A case study

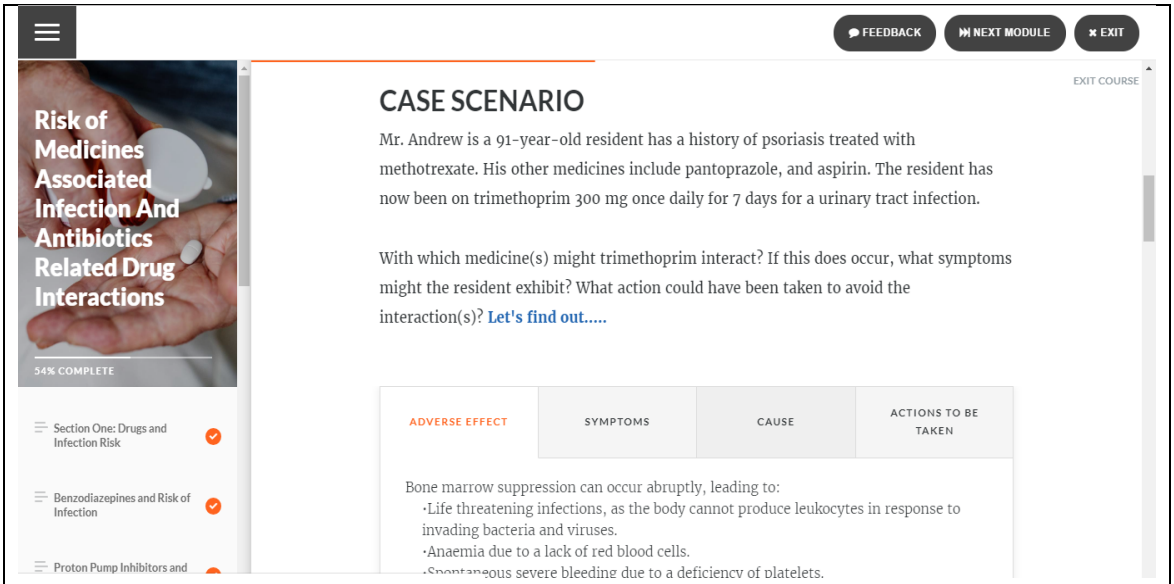

Figure 3 Expandable option in Section Two

5.2.3 Development of survey instruments

A study by Sahlqvist et al.[450] on the effect of questionnaire length in a postal survey reported that a shorter questionnaire significantly increased the response rate. Evidence suggests that response rates were increased by monetary incentives in both postal and online surveys.[451-454] However, it was not considered appropriate to offer monetary incentives for the Bethanie nurses for this trial, due to the perception that this might de-incentivise their compulsory continuing professional development. A brief questionnaire was developed relating to a selection of commonly used medicines in Bethanie.

5.2.3.1 Pre-module demographic survey

Demographic data requested of participants were gender (male, female or unwilling to say); age (less than 25 years, 25-34 years, 35-44 years, 45-54 years, 55-64 years or 65 years or older); highest level of education (Diploma, Bachelor or Master); present role (registered nurse, enrolled nurse or clinical nurse); and years of experience with elderly patients in aged care (less than one year, one to five years, six to 10 years, and more than 10 years). The provided categories were determined in consultation with the research supervisors.

5.2.3.2 Pre- and post-module knowledge quiz

No suitable questionnaire assessing the knowledge on medicine-associated infection and PDDIs between antibiotics and other co-administered drugs was found in the literature. Therefore, a new tool was required. For knowledge assessment, a questionnaire consisting of five multiple-choice questions (MCQs), each with four answer options (three wrong and one correct), was developed. MCQ style was selected for the design of the survey tool because it is the most applicable and efficient way for evaluating cognitive knowledge.[455] The first two questions were related to drug-associated infection risks, followed by three questions relating to PDDIs (Table 35). Responses to the pre-module questions were not accessible when answering the same questions post-completion of the education module. Questions could be skipped within the survey to avoid forced guesses.

Table 35. Pre- and post-survey knowledge quiz questions

Questions with options
Q1. Mrs Peterson, a 78-year-old resident is taking paracetamol, ramipril, amlodipine, and diazepam. In the past three months, she has had pneumonia twice. Which ONE of his medications is most likely to increase the risk of pneumonia? Paracetamol, Ramipril, Amlodipine, Diazepam*
Q2. Mr Jackson is an 83-year-old resident is taking ibuprofen, atorvastatin, valsartan, and pantoprazole. In the past six months, he has had diarrhoea numerous times. Which ONE of his medications is most likely to increase the risk of developing infectious diarrhoea? Ibuprofen, Atorvastatin, Valsartan, Pantoprazole*
Q3. Which of the following drugs does not increase serum potassium levels by interacting with trimethoprim? Perindopril, Irbesartan, Spironolactone, Methotrexate*
Q4. Which of the following drug pairs increases the risk of rhabdomyolysis ("a condition in which skeletal muscle is broken down, releasing muscle enzymes and electrolytes from inside the muscle cells")? Amoxycillin and atorvastatin, Trimethoprim and fluvastatin, Clarithromycin and simvastatin*, Norfloxacin and pravastatin
Q5. Which one of the following drug pairs is most likely to increase the risk of bleeding? Aspirin and trimethoprim-sulfamethoxazole, Clopidogrel and cefalexin, Dipyridamole and ciprofloxacin, Warfarin and erythromycin*

*Correct answer

5.2.3.3 Confidence in answering the five MCQs

A confidence scale was attached to each of the five MCQs in the pre- and post-education module quizzes (Figure 4). The question "How confident are you that your answer is correct?" was asked with four-point Likert-type scale that consisted of 0 (not at all confident, I guessed the answer), 1 (somewhat confident), 2 (quite confident), or 3 (very confident), modified from the study of Chan and Matter.[456]

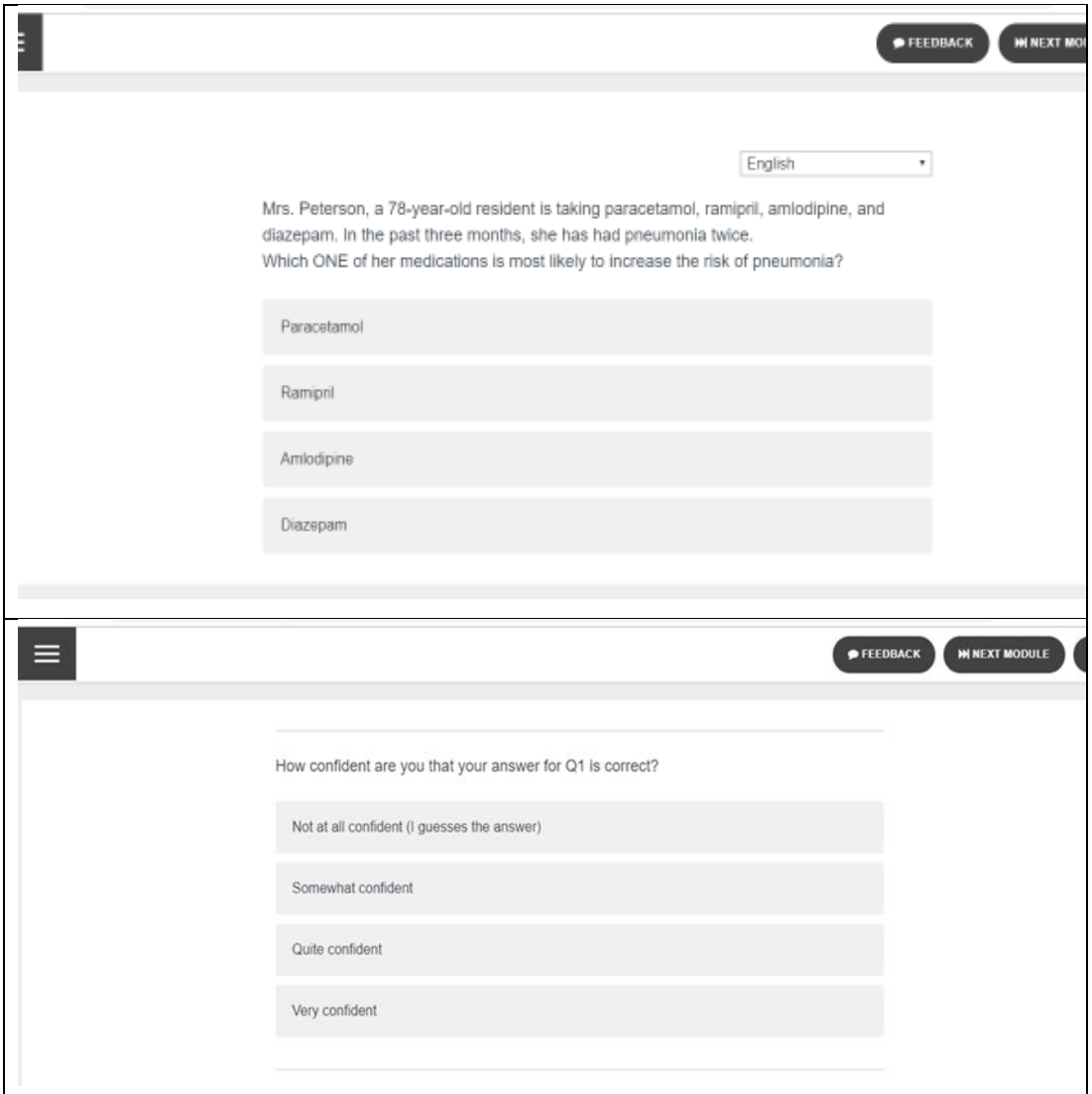

Figure 4 Knowledge quiz question and confidence scale

5.2.3.4 Post-module satisfaction survey

A brief questionnaire consisting of five questions was developed with reference to published literature[457] and feedback from the academic reviewers. The five questions were "The module was relevant to my practice", "The module held my interest", "The module was easy to understand", "The module was appealing in presentation", and "The module took an appropriate amount of time to complete". These questions examined the nurses' attitude towards the online module using a five-point Likert scale with 1=Strongly Disagree, 2=Disagree, 3=Neutral, 4=Agree, and 5=Strongly Agree.[457]

The survey was transferred to the *Qualtrics*® survey platform.

5.2.4 Validation

Face validity was achieved through expert advice and review by the Clinical Nurse Educator of Bethanie and research collaborators, followed by numerous rounds of testing of its functionality. The content of the module was reviewed by the two academic reviewers (supervisors of this thesis) who have extensive experience in adult learning design, content delivery and assessment. One of the academic reviewers is a clinical pharmacist, with expertise in infectious diseases, who has co-edited and contributed chapters to several textbooks dealing with infectious disease; was also the Secretary/Convenor of the Western Australian Antibiotic Guidelines Review Committee from 1990-1995 (https://research.curtin.edu.au/supervisor/prof-jeff-hughes/). Also, two experts from Bethanie (Learning and Training Manager and a Clinical Nurse Educator) reviewed the content of the module and suggested necessary amendments to improve the functionality of the educational module. Access to end users to engage them in the design was not forthcoming from Bethanie. As such, this trial intervention was considered a pilot test of the module to obtain insights and feedback for its further revision and broader deployment. The module was designed for self-directed learning, and to be suitable for nursing staff of varying qualifications and experience. The material was evaluated in terms of applicability, usability and navigation through the module. Items were revised according to reviewers' comments to improve the format, style, and answer options.

The final educational intervention was tested to check the display and functionality in a range of browsers (*Google Chrome®, Mozilla Firefox®*) and compatibly with iOS and Android devices.

5.2.5 Implementation of the module

5.2.5.1 Design, setting and sample

This study was designed as a quality improvement program. The data was collected over a four-week period to explore nurses' knowledge about medication-associated infection and antibiotic-drug interactions, before and after completing the module. Bethanie nursing staff were invited to trial the module, due to the relevance of data in the educational module to Bethanie residents and the established relationship with Bethanie management from earlier stages of the research. All nurses (n=227) with varying qualifications and employed either full-time or part-time by Bethanie were invited to participate in the study. No data were available to guide the expected completion rate. Facility managers and carers were not included in this study.

5.2.5.2 Implementation

The pre-module and post-module survey links to the *Qualtrics*® platform, and a link to the module within the *Articulate Rise 360*® platform, were sent to the Bethanie Learning and

Development Manager, who integrated the links into their "Learning Hub" and advertised the study to Bethanie nurses. Advertisement of the study was via email, with the subject line "Risk of medicines associated infection and antibiotic-related drug interactions" and a link to the educational module. Nurses were also able to start the module by direct log-in to their Learning Hub. This educational intervention was presented to the nurses as a "Course". Figure 5 shows the online course consisted of the course title, a short introduction, and three module links (pre-module survey, Curtin University online module (i.e., the educational module), and post-module survey), to be completed in order. The online course was made available for the nurses as of the 20th October, 2018. An email was sent to the facility managers to encourage nurses to participate in this online course. A second email was sent after two weeks to the nurses to remind and encourage them to participate in this online course. No deadline was given to the nurses. Participants were required to complete the pre-module survey to access the education module. All the sections of the education module had to be completed before participants could access the post-module survey (Figure 5).

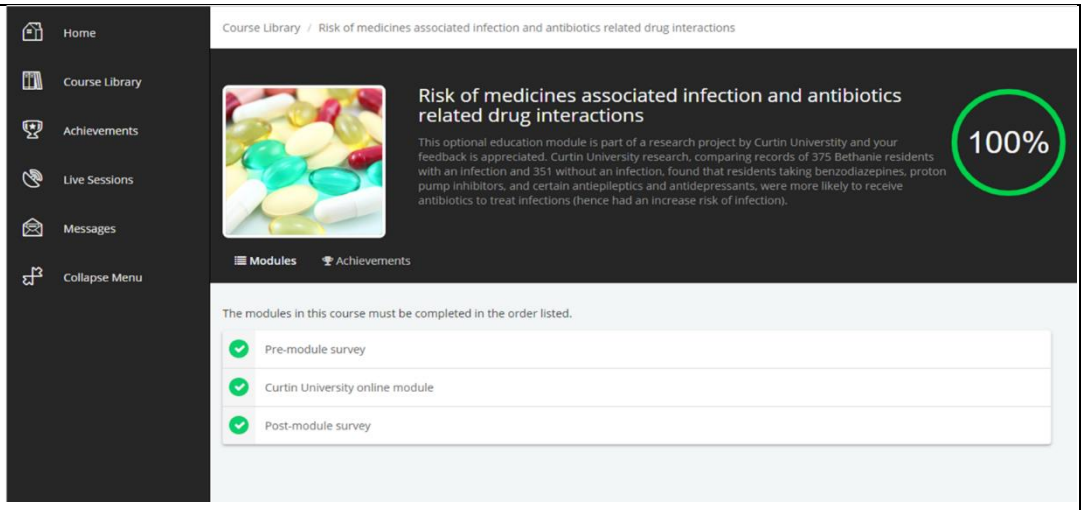

Figure 5 The landing page for the educational intervention in the Bethanie Learning Hub

5.2.5.3 Data retrieval and analysis

The data retrieval process was performed after four weeks of implementation, when no further responses were forthcoming. Responses were downloaded electronically through *Qualtrics*®. The demographic data were descriptively analysed to report the frequency and percentage of participants by gender, age, experience in aged care and educational level. Pre- and post-module knowledge improvement, confidence level in answering the questions, and satisfaction with the module were summarised descriptively. Each response was described to observe the response pattern in respect of missing data, and any tendency towards guessing answers amongst the respondents. Due to the limited number of responses from the nurses, inferential statistics were not appropriate. Individuals' pre- and post-module quiz responses were unable to be matched at that level due to the anonymity of the surveys; instead, patterns of responses were reported at a group level.

5.2.5.4 Ethical approval

This study was approved by the Human Research Ethics Committee, Curtin University (approval number HRE2018-0610, Appendix 4). Nurses completed the module and survey anonymously. Participation in the study was voluntary. The first page of the online module was a consent form that required that required the participant to provided informed consent before proceeding to the pre-module quiz, and then the module content. The consent page included Participant Information, namely an introduction to the study, what was expected of participants, the risks and benefits of participation, confidentiality issues, the fact that participation was voluntary, and the researchers' contact information.

5.3 Results

Of 220 eligible nurses, eight participated in this online educational module. The results are presented in the following sections, firstly as case studies at the respondent level for the pre-module and post-module surveys. Then the findings are summarised and presented quantitatively as frequency and percentage of respondents.

5.3.1 Pre-module survey

Eight nurses participated in the pre-module survey. Five completed the quiz questions, while three submitted partial responses. Each respondent case is presented below.

Respondent 1 was an enrolled nurse aged 45-54 years with a Bachelor degree and more than 10 years of work experience. This participant answered two quiz questions correctly. Among these two correct answers, one (Q2) was apparently guessed (“not confident at all”). For the other correct answer (Q3), the respondent was “somewhat confident”. However, the respondent was also “somewhat confident” in all incorrect answers.

Respondent 2 was an enrolled nurse aged 45-54 years with a Diploma and one to five years of aged care experience. This participant answered all five quiz questions incorrectly. Four questions were apparently guessed (“not confident at all”). The respondent was “somewhat confident” for the other incorrect answer. The respondent selected the third option in answering three of the questions.

Respondent 3 was a clinical nurse aged 35-44 years with a Master degree. This participant answered four quiz questions correctly and one incorrectly. The participant was “very confident” for all answers. This respondent had chosen the fourth option in all quiz questions. The incorrect answer given by the participant was related to an antibiotic-drug interaction. The respondent’s aged care experience was missing.

Respondent 4 was an enrolled nurse aged 45-54 years with a Diploma and more than 10 years of aged care experience, and answered the three quiz questions (Q1, 4, and 5) correctly. Among the correct answers, one (Q1) was apparently guessed (“not confident at all”), another (Q5) was answered “quite” confidently, and the confidence in answering Q4 was missing. This respondent did not answer Q3.

Respondent 5 was again an enrolled nurse aged 45-54 years with a Diploma and more than 10 years of aged care experience. This respondent answered two questions correctly. For these two correct answers, the respondent was “quite confident” for Q2 and “somewhat confident” for Q5. However, the respondent was “somewhat confident” in two incorrect answers (Q1, 4). One incorrect answer was apparently guessed (“not confident at all”). There was no trend observed in selecting an option in all questions.

Respondent 6 was a registered nurse aged 55-64 years with a Bachelor degree and five to 10 years of aged care experience, but did not completed the pre-module quiz.

The other two of the eight participants were unable to answer the pre-module quiz. Due to a technical error, these questions were not displayed to these respondents. This was observed through the “View response” option from the side menu for each respondent in *Qualtrics*®. The specific error message was “This question was not displayed to the respondent”. One respondent was a registered nurse with a Bachelor degree aged 35-44 years with five to 10 years of aged care experience, and the other had a Bachelor degree and more than 10 years of aged care experience.

5.3.2 Post-module survey

Six nurses completed the post-module survey. It is unclear whether the additional respondent was either one who did not see the pre-module quiz questions, or Respondent 6 who provided demographics but didn't attempt the pre-module quiz. The respondents are not numbered below, as their responses are unable to be matched to the pre-module survey responses.

One respondent answered four quiz questions incorrectly, and one correctly. The respondent answered Q5 correctly and was "somewhat confident" in that answer. However, the respondent was also "somewhat confident" in all incorrect answers. This respondent strongly agreed that the module was relevant to their practice, and agreed that the module was easy to understand, appealing in presentation, took an appropriate amount of time to complete, and held their interest.

Another respondent answered two quiz questions correctly. Within these correct answers, the respondent was "somewhat confident" for Q2 and "quite confident" for Q5. This respondent was also "somewhat confident" for two incorrect answers (Q1 and Q3) and apparently guessed ("not confident at all") one incorrect answer (Q4). Again, despite the unsatisfactory performance, this respondent agreed that the module was relevant to practice, easy to understand, appealing in presentation, took an appropriate amount of time to complete, and held their interest.

Another respondent answered four quiz questions correctly. Among these correct answers, the respondent was "somewhat confident" for Q1, Q2 and Q3, "quite confident" for Q5, and "quite confident" for one incorrect answer (Q4). This respondent strongly agreed that the module was relevant to practice and held their interest. The respondent also agreed that the module was easy to understand, was appealing in presentation and took an appropriate amount of time to complete.

Another respondent answered three quiz questions correctly. Among these correct answers, the respondent was "quite confident" for Q1 and Q5, and "somewhat confident" for Q3. However, this respondent was also "somewhat confident" for incorrect answers. This respondent strongly agreed that the module was relevant to practice, easy to understand, appealing in presentation, took an appropriate amount of time to complete, and held their interest.

Another respondent answered four quiz questions correctly. Among these correct answers, the respondent was “very confident” for Q1 and Q2, and “quite confident” for Q3 and Q5. This respondent was also “quite confident” for one incorrect answer (Q4). They also strongly agreed that the module held their interest, and agreed that the module was relevant to practice, easy to understand, appealing in presentation, and took an appropriate amount of time to complete.

The final respondent answered four quiz questions correctly. Among these correct answers, the respondent was “very confident” for Q1, Q2 and Q5, and “somewhat confident” for Q4. This respondent was “quite confident” for one incorrect answer (Q3). Feedback about the module was negative; the respondent strongly disagreed that the module was relevant to practice, easy to understand, appealing in presentation, and held their interest, and disagreed that the module took an appropriate amount of time to complete.

5.3.3 Quantitative results

5.3.3.1 Demographic characteristics of the participants

The demographic data of the respondents are presented in Table 36. The majority of respondents were female. All of the respondents were aged 35 years or older. Half of the respondents (4/8) had more than 10 years of aged care experience.

Table 36. Demographic details of the sample (N=8)

Characteristics		Number of participants n (%)
Gender	Male	1 (12.5)
	Female	6 (75.0)
	Unwilling to say	1 (12.5)
Age (years)	35-44	3 (37.5)
	45-54	4 (50.0)
	55-64	1 (12.5)
Highest level of education	Diploma	3 (37.5)
	Bachelor	4 (50.0)
	Master	1 (12.5)
Role	Clinical nurse	1 (12.5)
	Registered nurse	2 (25.0)
	Enrolled nurse	4 (50.0)
Experience (years)	1-5	1 (12.5)
	5-10	2 (25.0)
	More than 10	4 (50.0)

5.3.3.2 Assessment of knowledge

Table 37 shows the correct and incorrect responses to the five MCQs before and after the module. The total correct responses increased from 11 (in the pre-module quiz) to 18 (post-module quiz).

Table 37. Knowledge questions answered correctly before and after the module

Quiz questions	Pre-module quiz (N=5) n (%)	Post-module quiz (N=6) n (%)
Q1	2 (40.0)	4 (66.6)
Q2	3 (60.0)	4 (66.6)
Q3	2 (40.0)	3 (50.0)
Q4	1 (20.0)	1 (16.6)
Q5	3 (60.0)	6 (100.0)

N: total respondents, n: number of responses

5.3.3.3 Confidence in answering the quiz questions

The total responses for “Not at all confident” in the pre-module quiz were 7 and in the post-module quiz were 2 (Table 38).

Table 38. Pre- and post-module confidence in answering each question

Quiz question	Confidence in answering each quiz question							
	Pre-module quiz (N=5) n (%)				Post-module quiz (N=6) n (%)			
	Not at all	Some-what	Quite	Very	Not at all	Some-what	Quite	Very
Q1	2 (40.0)	2 (40.0)	0 (0.0)	1 (20.0)	0 (0.0)	3 (50.0)	1 (16.6)	2 (33.3)
Q2	1 (20.0)	1 (20.0)	1 (20.0)	1 (20.0)	0 (0.0)	4 (66.6)	0 (0.0)	2 (33.3)
Q3	2 (40.0)	1 (20.0)	0 (0.0)	1 (20.0)	1 (16.6)	3 (50.0)	2 (33.3)	0 (0.0)
Q4	1 (20.0)	2 (40.0)	0 (0.0)	1 (20.0)	1 (16.6)	3 (50.0)	2 (33.3)	0 (0.0)
Q5	1 (20.0)	2 (40.0)	1 (20.0)	1 (20.0)	0 (0.0)	1 (16.6)	4 (66.6)	1 (16.6)

N: total respondents, n: number of responses

5.3.3.4 Evaluation of the module

Table 39 illustrates the responses from the six respondents who evaluated the online module. The low number of responses meant calculation of median ratings was not warranted; instead, the raw data are presented. The majority of the participants agreed that the online educational module was relevant to their practice, held their interest, and was easy to understand. They also agreed that the presentation of the module was appealing and it took an appropriate amount of time to complete. However, as reported earlier, one respondent had a very negative opinion of the education module. No additional information was able to be collected as to why they held that view.

Table 39. Evaluation of the module

Questions	Number of responses (N=6) n (%)				
	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
The module was relevant to my practice	1 (16.6)	0 (0.0)	0 (0.0)	2 (33.3)	3 (50.0)
The module held my interest	1 (16.6)	0 (0.0)	0 (0.0)	2 (33.3)	3 (50.0)
The module was easy to understand	1 (16.6)	0 (0.0)	0 (0.0)	4 (66.6)	1 (16.6)
The module was appealing in presentation	1 (16.6)	0 (0.0)	0 (0.0)	4 (66.6)	1 (16.6)
The module took an appropriate amount of time to complete	0 (0.0)	1 (16.6)	0 (0.0)	4 (66.6)	1 (16.6)

N: total respondents, n: number of responses

5.4 Discussion

The focus of this current research was the development and trial deployment of an educational intervention. The educational module was developed with reference to educational literature and current research findings to ensure its effectiveness and relevance to the practice of nurses working for Bethanie aged care. The literature was searched and reviewed for the current evidence relating to medicines-associated infections and antibiotic-related drug interactions. According to previous studies, medicines such as benzodiazepines, antipsychotics, antidepressants and PPIs are inappropriately prescribed (in terms of dose and indication) in the elderly.[196-198] Evidence suggests that these medicines may be associated with increased risk of infection in the elderly.[39, 122, 220, 233] The first study of this PhD thesis explored and identified the medicines associated with risk of infection, as evidenced by increased use of antibiotics. The prevalence of potential antibiotic-drug interactions that may lead to adverse outcomes for Bethanie residents were also explored. Therefore, this educational module was designed on the basis of research outcomes from Bethanie aged care data and addressed these two avenues for medicine misadventure: medicine-associated infection and antibiotics-related drug interactions. The case scenarios presented at the start of each lesson within the education module were fabricated from the medication and medical profiles of actual residents. Along with the self-assessment quizzes throughout the module, these features aimed to increase the engagement of the nurses with the module and enhance learning.

The educational intervention (which was introduced as a "Course" by Bethanie) was deployed through the Bethanie "Learning Hub" with the expectation of spontaneous participation of the nurses. However, only a modest number of nurses participated in the pilot, which limited the insights into the effectiveness of the module. However, broad analysis demonstrated that nurses who participated in the online module increased their knowledge of concepts related to drug-associated infection and antibiotic-related drug interaction. The course content was generally found to be relevant to their practice, easy to understand, and of appropriate length and duration. The self-instructed module format was found to be satisfactory by the nurses. The potential for response bias, and further reflections on the strengths and limitations of this research stage, are discussed below.

Nurses generally conduct preliminary assessments of residents' health.[458, 459] In all RACFs, nurses are the only professionals (among the nurse, pharmacist and GP) who are available full-time.[171] Therefore, aged care providers must depend on their nursing staff to evaluate changes in a resident's clinical status and to contact their doctor.[460] Nurses play an important role in evaluating potential infections, administering and monitoring the effect of antibiotics in the elderly people.[461] With a view to the substantial role of nurses in the evaluation of residents' health status, nurses have been an important target for educational interventions.

While previous educational interventions in RACFs were based on appropriateness in diagnosis, evaluation, management of infections with the use of appropriate antibiotics,[164, 166, 169] the current study was designed with the aim of improving nurses' knowledge in identifying medicines that may increase the risk of infections and identifying potential antibiotic-related drug interactions in RACFs. Use of an online platform for delivery of an education module and surveys has some advantages over traditional methods, including shorter communicating time, lower distribution cost, more design choices, and less data recording time.[441, 448, 462]

It is difficult to claim that nurses in Bethanie aged care need additional knowledge on these topics, due to limited participation in the pre-module quiz. However, this study raises the issue that nurses may benefit from improved knowledge around medicine-associated infections and antibiotic-drug interactions. Nurses should have the knowledge to build their capability in recognising and analysing the adverse outcome due to drug-related problems, and the confidence to do so. Self-perceived confidence in answering the five quiz questions increased after working through the module. However, the correct answers were not

revealed to participants to reassure or correct them, and sustainability of their knowledge was not measured.

The overall response rate (eight of the 220 employed nurses) in this study is low, and inadequate to accurately compare knowledge before and after the module. An online survey on medical practitioners in Australia also found very poor response in their survey.[463] Even though their research method was sound and an incentive was offered, the overall response rate was 8.7% (52/600).[463] A meta-analysis reported 11% lower response rates for web surveys than the other modes of survey.[464] However, higher response rates were observed in other studies of nurses in hospitals or RACFs.[446, 465] High (978/1196 nursing staff) participation was observed in an online course on delirium offered to all nursing staff of 17 Dutch hospitals.[446] In that study, nurses were encouraged and reminded through their team leaders, which might have increased participation.[446] In the current study, an email had been sent to all facility managers to remind and encourage the nurses to complete the course. However, it was not confirmed whether this was actioned. While encouraging individuals to take part in any online education is a challenge,[457] a higher response rate was expected, because the module was designed on the basis of research outcomes using Bethanie data.

Several factors might have influenced the response rate. The course was part of a research project, and staff might have been reluctant to participate as their performance was to be assessed, and they might have felt these results might have been shared with their managers and/or peers. Workload of nurses could be a reason for poor response to this module. A low response rate due to workload has previously been reported from a hospital-based study to evaluate an intervention for nurses in identifying drug-related problems.[466] Nurses of RACFs spend a substantial amount of time in communication, documentation, and giving care to residents.[84, 467, 468] The online offering of the current module was intended to offer flexibility to the nurses to complete the module whenever and wherever they wanted.

The length of a module may be another factor that may limit the number of participants. However, those who completed the module indicated satisfaction with the time required to complete it. This study did not offer any incentive upon completion. Bethanie had several online modules released concurrently, and these modules were formally recognised for continuing professional development are incentivised with a paid work time allocation. This may be a reason why nurses did not give this course priority. Better understanding of motivational factors is required to engage nurses in future initiatives. It was assumed that the more engaged nurses who made the effort to complete the module represents a form of positive response bias. However, it was interesting to note the one case where the respondent had completed the module but reported a negative experience in doing so. Perhaps the lack of incentive negatively influenced that nurse's attitude towards the length, presentation, and usefulness of the module.

Knowledge quiz questions in the pre-module survey were not displayed to two nurses. In another case, no answers to these questions were recorded, and it is unclear whether this was a further technical issue or if that nurse withdrew from the module. None of those three nurses contacted the researcher using the contact details provided in the consent information, and anonymity of the survey meant the participants were unable to be contacted about the issues they faced.

Visual presentation of the questionnaire on the website might have a direct or indirect effect on the response rate.[469] For example, a survey question with a technical fault might actively cause respondents to quit from the web survey process.[462] It is also essential that software for online questionnaire be compatible with popular browsers.[469] The same questionnaire might be presented in a different way to respondents in different web browsers and using different devices.[469] Due to these differences, some of the respondents may not be able to navigate the questionnaire properly, and can experience difficulty in submitting their answers effectively, which may eventually lead them to exit the survey.[469]

Some other barriers such as limited computer access,[470] inadequate computer skills,[470] computer problems,[440] and lack of dedicated time for learning[471] are frequently cited as barriers in implementation of online learning.

5.4.1 Evaluation of the module

Educational activities should be assessed through an evaluation process that might be integrated with the educational program provided by an organisation. The current study included a brief satisfaction questionnaire to evaluate the module, requesting feedback about its relevance to practice, ease of understanding, presentation, and appropriateness of the length and duration. Most of the respondents agreed that the module was satisfactorily designed and beneficial for them. Other studies also reported the satisfaction of nurses towards online interactive learning due to its convenience, usefulness, and flexibility.[470, 471] The current module included interactive quiz questions and case studies. An interactive mode was appreciated by the 73 registered and advanced practice nurses in the study by Huckstadt et al.[448] in an online learning module.

Nonetheless, the module of this current study warrants some critique. Other ongoing modules of Bethanie, as viewed by the candidate during the deployment phase, appeared more precise in design and information, and easy to navigate. Due to its incorporation of two clinical topics (drug-associated infection and antibiotics-drug interaction), the present module became lengthy and focussed on clinical evidence and information, and may not have been as easy to navigate as existing modules. Minimising participant fatigue was a consideration in its formatting and structure, although, as recognised above, fatigue (relative to completing other modules) might have been a reason for low numbers of completion attempts. The length of a survey and respondent fatigue directly influences participation.[472] Nurses' comments should be sought either online or face-to-face, and should be included in the evaluation and revision process to improve user acceptability before wider implementation and/or implementation for another aged care provider network. Their feedback should be sought in light of lessons learnt from the implementation of this research, such as how to increase the response rate, and measures that can be taken to improve participation.

5.4.2 Strengths of the study

The module has several strengths. To the best of the candidate's knowledge, this is the first study that has developed, implemented and evaluated an online educational intervention regarding medicine-associated infections and antibiotic-related drug interactions for aged care nurses. The contents of the module were evidence based, informed by published literature and findings from current analysis of Bethanie data. Interactive case scenarios and quizzes were included in each lesson, reflecting best-practice educational design. Case scenarios encourage learners to attain information and improve their analysis, application, and evaluation skills.[448]

5.4.3 Limitations

The prepared module was not reviewed by the end users before deployment. This was considered beyond the scope of the current feasibility trial, and the current findings are considered useful as a pilot trial of the module. Despite the absence of end-user review, the content and design of the module were evidence based, informed by published literature and findings from current analysis of Bethanie data. Other aged care facilities of Western Australia and elsewhere in Australia might experience different prescribing behaviours of their GPs, and their nurses may have had exposure to other clinical information relating to the topics of this module. Therefore, this module may require revision with the input of relevant staff if intended for deployment in other facilities. Face validity was achieved through expert advice and review by the clinical educator of Bethanie and research collaborators, and numerous rounds of testing of the module's functionality were undertaken. Another limitation was the lack of control over participants' access to the Internet and hard-copy resources while answering the quiz questions. In clinical practice, nurses would not be prevented from accessing resources to research answers. This level of control would have been ideal for a research trial but is not pragmatic.

This study used the same questionnaire for the pre- and post-module quiz, which might have resulted in subject sensitisation bias. The attention and performance of the respondents may have been affected by the environment in which they were working, or if they were multitasking at the time of completing the online module. Environmental distraction (such as background conversation) and multitasking are recognised concerns while participating in online learning and assessment.[473]

This study was unable to assess knowledge retention or – perhaps more importantly – change in practice following completion of the online educational module. The satisfaction survey did not invite free-text comments or suggestions; this may be addressed in further user acceptability testing. Written evaluation comments would have given more opportunity to develop the module and could have strengthened the educational intervention for future reference. Several studies have applied this written evaluation comment section and found it to be beneficial for the future development of their module.[448, 471]

5.5 Conclusion

Regardless of the limitations of this pilot trial, this current study suggests that online education for nurses on medicine-associated infections and antibiotics-related drug interactions is useful for their practice. The pre- and post-module quiz results suggested that the module may have led to improvement in both knowledge and confidence, however this cannot be substantiated based on the small sample size. Nurses expressed their satisfaction regarding the effectiveness of the module in their practice. Improved knowledge around MRPs, particularly those affecting the vulnerable elderly, will improve nursing practice and assist clinical monitoring of aged care residents.

Chapter 6 Overall thesis discussion

6.1 Overall reflection

Australia is facing the challenge of our fastest growing population cohort being aged 85 years or older,[3] many of whom reside in an aged care facility and face risks of infection. Several factors are responsible for the infection prevalence in residents of RACFs: multiple chronic diseases, use of medicines that may increase the risk of infection, age-related physiological changes, decline in immunological functions and institutionalisation. UTIs, RTIs, gastroenteritis, and skin and soft tissue infections are the most prevalent infections in this cohort.

This study aimed to reduce the risk of antibiotic-related medication misadventure in residents of aged care facilities. The specific objectives were to: determine the prevalence of the use of medicines that potentially contribute to the infection burden; assess risks associated with co-prescribing of antibiotics and other medicines; develop an educational intervention, based on findings from Objectives 1 and 2 and supported by current literature, for healthcare professionals providing care to the residents of aged care facilities, aimed at minimising drug misadventure related to infectious diseases; and implement and evaluate the educational intervention.

The research involved analysis of data from two sources: individual residents' electronic medical records from Bethanie aged care facilities in Western Australia; and national dispensing data from Webstercare. To determine the association between medication use and infection risk in elderly aged care residents, a retrospective case-control study was firstly conducted using Bethanie data. Cases (n=375 residents) were all residents who had at least one infection in 2015; controls (n=351 residents) were those who had no infection in 2015. Further regression analysis was conducted by utilising the Webstercare dataset to determine the association between antibiotic prescriptions and the use of medicines identified in the Bethanie analysis as a risk medicine for infection. Analysis was also undertaken in the Bethanie dataset to determine the prevalence of potential interactions between the antibiotics prescribed and residents' chronic medications.

This analysis found that the use of benzodiazepines, “other antiepileptics”, “other antidepressants” and tricyclic antidepressants were independently associated with a significant increase in the risk of an infection ($p<0.05$). Further regression analysis utilising national Webstercare data from 4,332 aged care residents (with 188,394 dispensed histories from May 2001 to March 2016) revealed that exposure to PPIs, “other antiepileptics”, “other antidepressants”, tricyclic antidepressants, benzodiazepines and beta-blockers were independently associated with increased prescribing of antibiotics ($p<0.05$).

Risks associated with co-prescribing of antibiotics and other medicines in the Bethanie data revealed that 64 (18.2%) of the 351 residents who had an infection were prescribed an antibiotic that could interact with medicines they were already taking. These 64 residents had a total of 96 potential interactions between antibiotics and co-prescribed medication. The most frequent antibiotics involved in the PDDIs were macrolides (29/96 PDDIs) and trimethoprim (26/96 PDDIs).

These findings highlighted the need to educate aged care staff members about the risk of infection from use of particular medicines, as well as potential interactions between antibiotics and other medicines. Pilot implementation of an educational program for nurses about the risk of medication associated infections and antibiotic-drug interactions was deployed through the Bethanie continuing education platform. Stages of development of the intervention included rounds of content review internally and with Bethanie educational staff as end users, and consultation with Bethanie staff regarding the intervention design and deployment. Pilot implementation of the educational intervention, deployed through the Bethanie continuing education platform, provided preliminary results and feedback from nursing staff, demonstrating generally positive engagement and feedback, coupled with suggestions for future development.

An Australian survey in 2011 of five RACFs recommended that antibiotic stewardship interventions are necessary and beneficial.[61] The researchers also proposed antibiotic stewardship interventions applicable to the RACFs in Australia, including aged-care specific antibiotic guidelines, systematic surveillance of antibiotics and nurse-based education.[61] However, barriers have been reported around the introduction of antibiotic stewardship in Australian RACFs: lack of training of nurses in antibiotic use, high workload, lack of institutional infection management guidelines, and inexperienced nursing staff.[65] Other factors related to workflow and prescribing culture that influence antibiotic prescribing in Australian RACFs include shortcomings in nurse-driven infection management, pharmacy support and diagnostic facilities, as well as demand for the prescribing of antibiotics from residents' families.[2, 65]

Previous AMS initiatives aimed to decrease antibiotic prescribing in infections,[163, 165, 167, 169-171] evaluation of appropriateness of antibiotic prescribing,[167, 169, 171] appropriateness of withholding antibiotics,[169] evaluation cost effectiveness,[166] evaluation guideline adherence,[169] and evaluation of the harm of AMS.[164] Aims of AMS initiatives specific to UTI were reducing antibiotic prescribing in UTI,[164, 166, 168, 172] evaluation of the appropriateness of antibiotic treatment in UTI[166] to prevent unnecessary urine testing, and reduction of antibiotic use in UTI in women.[163]

Thus, AMS programs in RACFs have focussed on appropriate management of infections in terms of identification, diagnosis of infection and appropriate use of antibiotics. The outcomes of the current research suggest the need to expand the scope of antibiotic stewardship in aged care facilities by addressing two types of medication misadventure, namely, potential medication-associated infection that may lead to the increased use of antibiotics, and antibiotic-related drug-drug interactions that may contribute to increased adverse drug reactions. Research in this field, published in the past 10 years, has been conducted in the general population (Section 4.1.3). Case-control and cohort studies have explored medicine-associated infection in the elderly living in the community (Section 4.1.3). Cross-sectional studies have explored the prevalence of PDDIs in hospitals and primary care settings (Section 4.2.1). None of these studies focussed specifically on the elderly in the RACFs, and this paucity of data provided a platform for the current research. This is the first-known investigation to explore these facets of antimicrobial stewardship and adds to an increasingly important body of knowledge that will improve the care of vulnerable elderly in RACFs.

Due to the relevance of these findings for RACFs, the following pages propose recommendations for consideration of these two issues, followed by a collated reflection on future directions for further research.

6.2 Recommendations

Before making any recommendation, it is important to understand the present approaches by the Australian government for Quality Use of Medicines (QUM) in aged care. Australian government agencies have developed policies and resources for different stakeholders (health professionals, organisations and consumers) for QUM to ensure the use of medicines in the best-possible way by reducing medicine-related harm to achieve optimum health outcomes.[474, 475]

Australia's *National Strategy for Quality Use of Medicines* provides a theoretical framework to describe the approach for implementing strategies to guide consumers, health professionals, government, industry and other stakeholders to work together to achieve QUM.[475] The National Strategy indicates that health and aged care facilities are accountable for providing facilities, systems, and training opportunities to support staff, health practitioners and consumers in using medicines sensibly and avoiding medication errors.[475]

The *Guiding Principles for Medication Management in RACFs* published by the Department of Health and Ageing, comprise 17 principles to support optimal medication use in RACFs, encouraging safe and effective management of medicines.[474] Its purpose is to support RACFs to prepare, implement, and assess local policies and procedures to support all stakeholders in the medication management process.[474] The principles cover all aspects of medicine management, information resources for staff and residents, and the need for a multidisciplinary Medication Advisory Committee in RACFs.[474]

A RMMR is a GP-triggered and government-funded medication review of an aged care resident by an accredited pharmacist.[429] In this process, an accredited pharmacist systematically and periodically evaluates a resident's complete medicine regimen in conjunction with clinical information and data relating to the resident's health outcomes. The goal of RMMR is to ensure positive health care outcomes by detecting, preventing and resolving actual or potential medication-related problems to optimise pharmacotherapy.[429]

The QUM Service is a government-funded *ad hoc* service provided by a registered pharmacist that focuses on improving practices and management related to medicine use in RACFs.[429] This service also includes education sessions for nursing staff, carers or residents on medication use, disease management or prescribing issues, as well as medicines information for medical practitioners, and provides a medicine advisory service by contributing to the Medication Advisory Committee.[429] Thus, this service helps the RACF to meet their residents' health care needs.

The *Australian Aged Care Quality Agency* (AACQA) regularly audits RACFs in Australia. AACQA is a national autonomous accreditation body that regulates the aged care industry on the basis of four standards – management systems, staffing, and organisational development; health and personal care; resident lifestyle; and physical environment and safe systems – with 44 anticipated outcomes.[162] However, from 1 July 2019, RACFs are being assessed against eight Quality Standards: "Consumer dignity and choice, Ongoing assessment and planning with consumers, Personal care and clinical care, Services and supports for daily living, Organisation's service environment, Feedback and complaints, Human resources, and Organisational governance".[162]

6.2.1 Recommendations to aged care providers

6.2.1.1 Education for prescribers

Prescribers are at the forefront of medicine choice. Medicines review by pharmacists occurs periodically, as such a resident may be taking an inappropriate medicine or combination for some time undetected – hence the need for awareness amongst prescribers. Continuing medical education for prescribers servicing RACFs should target medicines associated with risk of infection, as well as antibiotics and their interactions with other medicines, focussing on the mechanisms of these effects and clinical evidence. Timely feedback to the prescribers about their prescribing patterns in aged care facilities may be a motivational tool to change their practice.

6.2.1.2 Education for nurses

Nurses, as care givers to residents in RACFs, should receive regular training on recognising clinical signs and symptoms, identification and investigation of problems, monitoring and reporting health outcomes related to infection caused by medicines and interactions involving antibiotics. Nurses were the target group in the current research in developing online educational module, due to their extensive role in RACFs. Chapter-Five reported modest uptake of this educational intervention by Bethanie nurses and a multi-disciplinary approach is therefore recommended.

Continuing professional education in nursing is required due to the rapid growth and changes in required professional knowledge, the healthcare system and the subsequent changes in the roles of nurses.[476] Delivering continuing professional education through an online platform can be a good approach in dissemination of knowledge.[477] Thus, aged care authorities are responsible for providing and creating a professional environment for nurses to achieve appropriate knowledge that will empower nurses as competent healthcare staff to ensure quality health outcomes for their residents.

6.2.1.3 Guideline development

Aged care providers may develop a guideline focusing the appropriate use of medication that may increase the risk of infection or increase potential drug interactions with antibiotics. Medicine use guidelines should be developed on the basis of the facility formulary, which would be easily available to prescribers. This guideline needs to be a developing document. It should be constantly updated on the basis of reflection and amendment based on knowledge and experiment of all stakeholders related to RACFs.

6.2.1.4 Introduction of an antibiotic stewardship committee

Aged care providers may initiate an antimicrobial stewardship committee. The purpose of this team can be infection surveillance, where focus should be given to medicine-associated infections, as well as surveillance of antibiotic use in terms of observing adverse effects related to drug interactions with antibiotics. In any stewardship activity, the team should be formed by engaging higher administrative personnel, directors from medical and nursing services, infection control and prevention coordinator, medical and nursing staff, and a consultant pharmacist.

6.2.1.5 Post-prescription review

Pharmacists can review prescriptions at least once per month and can investigate rationale for medicine use in each resident's medication profile. Thus, inappropriate medicine use can be identified and required steps can be taken with the GP. A study in UK aged-care facilities found that review of medicines by a pharmacist with GPs was beneficial in reducing inappropriate medicines prescribed for residents.[478] This study also investigated the financial benefit of such medicine review and found that this approach can be potentially cost effective for government and for the residents.[478]

Residents of RACFs can be benefited from deprescribing of unnecessary medicines from their medication profile.[182] Regular medicine review is important in residents of RACFs who are the high risk group due to advanced age, multiple medications for multiple diseases, multiple prescribers, frailty, and impaired renal and hepatic function.[479] Multiple medicines may increase the risk of non-adherence of residents with their treatment plan, and result in poor treatment outcome.[480] Multiple medicines may also increase the risk of adverse drug events.[68] By initiating deprescribing principle of inappropriate medicines, such risks can be minimised.

Residents are the centre of deprescribing and should be involved throughout. Residents should be informed of the reason(s) for considering any changes in the overall medications, and their wilful participation in the process should be established. Residents' opinion should be valued to determine whether they need all their medications.[481] Many evidence-based tools (e.g. Beers criteria, STOPP/START, NO TEARS) are available to identify inappropriate use of medicines in polypharmacy and to assist in deprescribing.[184]

6.2.1.6 Provision of technology

Aged care organisations should improve their information exchange system between different internal and external health care professionals. A survey in four RACFs in New South Wales and Victoria, Australia, reported an inefficient method of communication and high volume of information interchange activities with external health care providers.[467] Thus, the findings of that survey strengthen the concept of implementing intra- and inter-operable information technology systems for efficient information exchange.

Drug-related problems can be reduced by the application of health information technology such as electronic health records,[420] computerised physician order entries,[421] clinical decision support systems,[420] and drug interaction software for personal digital assistants[422] in healthcare settings. An electronic health record provides patient information, and improves documentation and interdisciplinary communication.[420]

In computerised physician order entry systems, the medication order is completed online, whereas clinical decision support systems provide evidence-based advice during prescribing about drug allergies, drug-drug interactions, doses and routes.[430] To improve patient safety, healthcare providers are implementing electronic health records with integrated clinical decision support.[423] Computerised alerts that notify clinicians regarding drug-drug interactions, drug allergies, and contraindication warnings or dosing guidance are commonly implemented.[423] A review of hospital-based studies by Nuckols et al. concluded that implementation of a computerised physician order entry system can decrease potential adverse drug events by 50%.[425] Outcomes research in ambulatory care on medicines alerts indicated that electronic prescribing alerts reduced drug-related problems including DDIs.[349] Personal digital assistants have potential as a clinical decision support system for nurses by improving their awareness of drug–drug interactions, patient medical history, and potentially inappropriate medicines use.[482]

Despite such potential, implementation of clinical decision support have not reliably improved the quality of patient care and patient outcomes in different settings.[483-485] Burden of alert messages and a lack of fully integrated clinical and pathological information affect the efficacy of such health technologies.[483] The burden of alerts, either clinically significant or non-significant, can cause alert fatigue and intentional ignorance of the alert by clinicians.[486] Therefore, information technologies in health should improve the quality of health care of residents without compromising the workflow of a health provider.

6.2.1.7 Improving medication reconciliation at the point of transition

Medication misadventure can occur when the residents of RACFs are transferred between the hospital and the RACF, as a result of changes in medical and pharmaceutical care and the prescriber.[487] Changes in medicines are common during transfer of care between hospital and RACF.[487] A study by Boockvar et al.[487] showed that the mean number of medications altered during transfer from aged care to hospital and hospital to aged care were 3.1 and 1.4, respectively ($p<0.001$) during a total of 122 admissions. Medicine discontinuation, dose changes and drug substitution were the most common medication changes made while in transfer. The overall risk of adverse effects per drug change (n=320) was 4.4% (95% CI: 2.5%-7.4%).[487] Transfer-related medication errors have been reported in 13-31% of RACF residents.[488] Implicated medicines include warfarin, insulin, psychoactive agents and opioids.[488] Medication reconciliation by healthcare professionals (physicians, pharmacists and nurses) can reduce adverse drug effects related to patient transfers.[487, 489, 490] Therefore, aged care providers should improve medicine reconciliation by preparing a transfer summary of management of medicines from hospitals, which then can be reviewed by the physician and pharmacist.

6.2.1.8 Mode of delivery

Multifaceted delivery such as online, poster, face-to-face training, will be more useful than a single approach.[71] Multidisciplinary professionals should be involved. Education needs to be continuous and periodic. A longer period of time and repeated training increases adherence to the intervention and the number of health professionals to complete the module.[163]

6.2.2 Recommendations to physicians

Residents of RACFs are at high risk of drug-related problems when transferred from the hospital to the RACF due to the changes in the medical and pharmaceutical care plan. General physicians can play a vital role in medication reconciliation to reduce medication errors related to resident transfers among different settings.[489] Continuing medical education for prescribers servicing RACFs should target medicines associated with risk of infection, as well as antibiotics and their interactions with other medicines, focussing on the mechanisms of these effects and clinical evidence. Timely feedback to the prescribers about the prescribing patterns in the facility may be a motivational tool to change their practice. Aged care facilities have the capacity to organise such activities and professional associations that offer continuing education could provide clinical training on this topic partnering with the RACFs.

6.2.3 Recommendations to pharmacists

Currently, RACFs do not have full-time pharmacists for the care of residents. Without this employment, pharmacists only have the opportunity to review residents' medication profiles under the RMMR program, which facilitates annual review for a resident. During their review, pharmacists should monitor the history of medication and review the history of infection. If a resident is receiving medicines that increase the risk of infection, the pharmacist should consult with the physician for deprescribing of that risk drug where possible.

Pharmacist can be vigilant while reviewing the residents' medication and medical profiles to identify antibiotics and other co-prescribed drug with liability to interact, identify and document actual DDIs in the medication profile, along with an action plan, and suggest antibiotics with a low-risk profile for drug interaction. Pharmacists can educate the healthcare team about monitoring of DDIs and related adverse outcomes.

In Australia, community pharmacies provide most of the pharmacy services to aged care facilities.[7] Community pharmacists should establish good communication between the GPs, nurses, and managers of the RACFs to ensure appropriate use of antibiotics and other medicines. They can also lead the design of an appropriate prescribing policy or medicine formulary, review the medicines associated with the risk of infection and antibiotic-drug interactions and related adverse outcomes, and educate or counsel the residents, nurses, families of residents, and carers about the risk of infections with long-term use of medicines and about antibiotic-related drug interactions. Pharmacists who prepare dose administration aids to RACFs should also be vigilant to identify inappropriate use, such as long-term continuation of therapy and/or any antibiotic-drug interactions and can communicate with the prescriber.

Reconciliation of medications and care plan is essential when a resident is transferred from other settings of care to promote safe use of medicines and therapeutic outcome.

6.2.4 Recommendations to nurses

Australian aged care providers do not hire full-time GPs, although some have onsite full-time nurse practitioners who have prescribing rights.[7] Nurses therefore have a key role in assessing the medication and medical profile of a resident who is experiencing multiple incidences of infection. They should look for medicines that may increase the risk of infections. Nurses should always check a resident who is on antibiotic therapy for possible adverse outcomes from antibiotic-drug interactions. Residents' activities of daily living, nutritional status, mouth, dental, and bowel conditions should be assessed for any possible adverse outcome related to antibiotics. Nurses should document and report any falls, bleeding, muscle weakness, urine discolouration, and any acute changes of the residents. Before administration of any antibiotic, nurses should check for its appropriateness in regard to possibility of drug interactions. Nurses may monitor a resident for any unexplained acute changes of health status and should not hesitate to communicate with the prescriber. Nurses' participation in, and promotion of, antibiotic stewardship is therefore a key role in aged care. Nurses can reconcile the medication list while a resident is being transferred from hospital and consult with the prescriber if any discrepancies are observed.

6.2.5 Recommendations to government

The high volume of medicines used by aged care residents contributes to medication-related problems.[197] The current study showed that medicines were associated with increased risk of infection and increased use of antibiotics, and subsequently, the potential for antibiotic-related drug interactions and adverse effects. According to a retrospective cohort study in Western Australia in 2001, AU$12.1M of inpatient costs were incurred over two years due to infection-related hospitalisations of residents of aged care facilities.[491] The authors estimated this amounted to 7.5% of the hospital costs due to total bed days used by the residents of RACFs.[491] Infections caused by MDR organisms increase hospital and associated costs.[492] Furthermore, the repeated transfer of the residents of RACFs to hospitals is associated with unwanted clinical outcomes.[493] Collectively, this evidence suggests interventions to reduce the inappropriate use of medicines associated with infection risk should be promoted at a national level to reduce financial burden of government. A full-time on-site pharmacist is therefore recommended to reduce medication-related problems. Several previous studies showed that medication review by the pharmacists can improve drug-related problems and increased the quality and safe use of medicines.[494-497] However, current funding by the Commonwealth Government of Australia restricts the role of pharmacists in medication review in RACFs. The government is urged to increase funding support to aged care in Australia, so that pharmacists can be involved full-time or more frequently in medication review to reduce medication-related problems. A team from University of Canberra also proposed an on-site residential care pharmacist model, rather than a visitational role presently delivered by RMMR pharmacists.[498] These researchers also conducted a pilot study, reporting that on-site pharmacists in RACFs were helpful in reducing time on drug rounds by the nurses, inappropriate drug use and adverse drug effects, and improving documentation of drug allergies and drug-related problems.[499] Kong et al.[2] stated in their report *Case for Action Proposal: Antimicrobial Usage in Residential Aged-Care Facilities*, "although the Australian Aged Care Quality Agency recommends that all Australian RACFs should have an 'effective infection control program' (i.e. Standard 4.7) which includes an infection surveillance system, it does not delineate the specific nature of such a system. Furthermore, the accreditation requirements have mainly focussed on control of outbreaks, without reference to antimicrobial use, hence benchmarking of antimicrobial use across different Australian RACFs is impossible. Establishment of an effective surveillance system is fundamental to optimising antimicrobial use."

The current research recommends government to initiate nationwide investigation to evaluate the possibility of implementing a specific policy and guidelines to reduce or otherwise manage use of medicines that can increase the risk of infections and antibiotic-related drug interactions and adverse effects.

6.3 Future research

As reported from the Bethanie and Webstercare data analyses, specific classes of antidepressants and antiepileptics may be associated with increased risk of infection or increased risk of antibiotic use. Therefore, interventions should be designed and implemented with specific focus on these drug groups in RACFs.

Further research is required to clarify indication biases in risk drug prescribing, especially in residents of RACFs. Observational studies provide less certain estimates and may suffer from residual bias and confounding compared to a well-controlled clinical trial. However, including the elderly in clinical trials is challenging.[500] Therefore, observational estimates in large representative populations based on robust statistical methods are likely to provide valuable estimates for informing safe prescribing practice in the residents of RACFs.

As of today, the physiological mechanisms behind medicine-associated infections are only proposed. The clinical mechanism of increased infection by drugs such as benzodiazepines, antiepileptics, antidepressants, antipsychotics, and proton-pump inhibitors are required to be investigated.

The current study described the association of medicines with increased risk of infection and increased antibiotic use. Despite this, it could not describe the specific type of infection or antibiotic type. As such, further research is required to identify the risk of specific infection associated with medicines.Further research is required to estimate the increased risk of actual morbidity, such as hospitalisation and mortality with the potential drug-antibiotic interactions in frail or non-frail residents. Additional research could be conducted to investigate the use of electronic drug-drug interaction databases in detecting these issues. Outcome measures would be the reduction of PDDIs and DDIs and related adverse health outcomes. Future studies should also aim to investigate the prevalence of PDDIs by considering the frequency and dose of the interacting drugs.

Present DDI software or databases are not specific to the elderly in residential aged care. As discussed, hat residents in aged care homes are more vulnerable to DDIs due to age-related changes in pharmacokinetic and pharmacodynamics parameters, and presence of chronic co-morbidities leading to polypharmacy. Therefore, software could be developed where clinicians can specifically identify DDIs in elderly residents by incorporating residents' factors such as age, comorbidities, race, gender, pathological data, and clinical sign and symptoms.

The extent of awareness of Bethanie staff regarding PDDIs between antibiotics and other prescribed drugs, and whether any measures have been taken to prevent clinically significant DDI, remains unknown and should be further examined through a well-designed prospective study. Research could also be conducted to investigate the use of electronic DDI databases by nurses in RACFs. The appropriateness and benefit of nurses' use of electronic DDI databases could be measured by the reduction of potential and actual DDIs and related adverse health outcomes.

A larger randomised controlled trial is required to understand the effectiveness, in-terms of residents' health outcome and cost, of a full-time on-site pharmacist in RACFs.

Further research is required to estimate the prevalence and severity of actual DDIs by considering the frequency, dose, and route of the interacting drugs, as well as the increased risk of morbidity and mortality associated with PDDIs in aged care residents. How the severity of PDDIs and reliability varies among the different classes of antibiotics can be another future research perspective.Online learning is useful – as already stated in earlier sections – due to its convenience, self-paced manner, and capacity for interactive learning; however, further study should focus on the factors that can affect the effectiveness of online learning of nurses in RACFs. Further study is required to understand how the workload of nurses influences their learning intention and application of knowledge from continuous professional development. The current findings also call for further user acceptability testing with more detailed feedback from users, particularly if the module is to be tailored for, and implemented in, other aged care provider networks. The current study did not investigate knowledge retention from the module amongst the nurses, and the application of this knowledge in their practice as a result of this online intervention. This should be explored in future research involving a substantially large cohort. Future research is required by applying (or adapting or creating) an evidence-based conceptual framework, behavioural change theory while implementing the educational module to ensure its effectiveness and relevance to the practice of nurses working in RACFs.

Chapter 7 Conclusion

This is the first-known study to investigate non-antimicrobial drugs as a potential risk factor for the development of infections amongst aged care residents, and hence, their contribution to antibiotic use. Furthermore, it investigated the potential medication misadventure as a result of interactions between prescribed antibiotics and residents' chronic medicines. The findings related to these two issues were utilised to develop an educational intervention aimed at minimising the identified types of medication misadventure. As stated in Section 3.1, the specific objectives of the overall study were to: firstly, determine the prevalence of the use of medicines that potentially contribute to the infection burden; secondly, assess risks associated with co-prescribing of antibiotics and other medicines; thirdly, develop an educational intervention, based on findings related to Objectives 1 and 2, and supported by current literature, for healthcare professionals providing care to the residents of aged care facilities, aimed at minimising drug misadventure related to infectious diseases; and fourthly, implement and evaluate the educational intervention.

Thus, this study was unique in its approach to investigating both drug-associated infections and drug interactions between residents' chronic medication and prescribed antibiotics, describing their prevalence and associated risks, and developing and evaluating an educational intervention aimed at minimising the risk of such drug misadventure.

The following conclusions were drawn from the three null hypotheses.

Null hypothesis 1: Residents' chronic medications do not contribute to increased risk of infection and antibiotic use in aged care facilities.

The current research found in the case-control study of Bethanie dataset by multivariate regression analysis that benzodiazepines, other antiepileptics, other antidepressants, and tricyclic antidepressants were associated with increased risk of infection in the residents of RACFs. Further analysis of Webstercare dataset by logistic regression method demonstrated that benzodiazepines, other antiepileptics, other antidepressants, tricyclic antidepressants, beta-blockers and proton pump inhibitors were more likely to increase the use of antibiotics. Thus, based on these findings, the null hypothesis has been rejected, with two independent sets of evidence that residents' chronic medications can contribute to increased risk of infection and antibiotic use in aged care facilities.

Null hypothesis 2: The prescribing of antibiotics in RACFs presents a minimal risk of (serious) drug interactions.

This study reported that anticoagulants (warfarin), tricyclic antidepressants (amitriptyline), statins (atorvastatin), ACEIs (perindopril), antiarrhythmics (digoxin), and sartans (candesartan) were commonly involved in the PDDIs with antibiotics. The current study demonstrated that macrolides and trimethoprim were the most frequently involved antibiotics in the PDDIs. Macrolides most commonly interacted with statins and digoxin, and in one incidence, with warfarin. Trimethoprim commonly interacted with ACEIs and sartans, and in one incidence with spironolactone and methotrexate each. This study also reported the common potential adverse effects due to the PDDIs were QT-interval prolongation, hyperkalaemia, and risk of bleeding, followed by rhabdomyolysis and digoxin toxicity. Thus, the prescribing of antibiotics within residential aged care facilities were not considered theoretically safe, and the null hypothesis has been rejected. Further research has been suggested to confirm this finding in terms of how the PDDIs had manifested clinically in this cohort.

Null hypothesis 3: A tailored education intervention will not influence the use of antibiotics in RACFs.

The current study demonstrates that online education for nurses can improve their knowledge of medicine associated infections and antibiotics-related drug interactions, which, if applied in clinical practice, could result in improved medicines use. The educational module was successfully developed and trialled with a modest number of practising aged care nurses. Results of the pre- and post-module knowledge quizzes suggested that the module had led to (at least short-term) improvement in both knowledge and confidence of the two key topics covered. Nurses expressed their satisfaction regarding the effectiveness of the module in their practice. Improved knowledge around medication-related problems, particularly those affecting the vulnerable elderly, should improve the practice of the nurses in terms of better clinical monitoring of aged care residents.

Present AMS initiatives focus on appropriate selection and use of antibiotics, taking into consideration the infection, prescribing formulary and current prescribing guidelines. However, two other areas of concern have been identified by this study: the use of medications that may predispose individuals to infection, e.g., proton pump inhibitors, benzodiazepines, other antiepileptics, tricyclic antidepressants and other antidepressants, resulting in increased prescribing of antibiotics; and interactions between prescribed antibiotics and individuals' ongoing chronic medications. This study proposes that these two issues should be incorporated in antibiotic stewardship initiatives and interventions to reduce infection burden of aged care residents and overprescribing of antibiotics, and therefore to reduce antibiotic-related drug interactions and related adverse outcomes in the aged care facilities. Educational interventions through online education should continue to be an effective approach to identify and reduce antibiotic-related misadventure. Due to their availability, nurses are recommended as key participants in these interventions.

Further research is recommended to evaluate the effectiveness of educational interventions targeting nurses versus other health professionals. Future research is also required to evaluate and adopt appropriate deprescribing strategies in aged care facilities to reduce the overprescribing of medicines that are associated with infections and lead to over-prescribing of antibiotics.

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Appendix A. Letter of support from Bethanie

Bethanie

20th of October 2015

Committee Secretary
Human Research Ethics Committee
Curtin University
Kent St, Bentley
Western Australia 6102

RE: Support for the application by Mohammad Shohel to the Curtin University Human Research Ethics Committee

To whom it may concern,

I refer to the application to the Curtin University HREC by Mr Mohammad Shohel, PhD Candidate, to undertake the project "Antibiotic Stewardship in Residential Aged Care Facilities."

The Bethanie Group Inc has received a research project application from Mr Shohel to undertake analysis of the medication records of clients residing in Bethanie's 12 aged care facilities. Bethanie's Research Review Committee has signed off and approved the project. Bethanie is proud to provide research support and assistance to undertake the project and will provide Mr Shohel with the necessary training and support to access Bethanie's electronic health records management system. We will facilitate opportunities for Mohammad to deliver an educational intervention based on his findings to relevant staff.

I ask that you take Bethanie's support into consideration when assessing the application.

Yours Sincerely,

Amy Steer
Research and Report Coordinator
The Bethanie Group Inc

Appendix B. Ethics approval from the Curtin University

MEMORANDUM

Curtin University

To:	A/Prof Lynne Emmerton School of Pharmacy
CC:	Mr Mohammad Shohel
From	Professor Peter O'Leary, Chair HREC
Subject	Ethics approval Approval number: HR26/2016
Date	24-Feb-16

Office of Research and Development
Human Research Ethics Office

TELEPHONE 9266 2784
FACSIMILE 9266 3793
EMAIL hrec@curtin.edu.au

Thank you for your application submitted to the Human Research Ethics Office for the project: 6529
Antibiotic Stewardship in Residential Aged Care Facilities

Your application was reviewed by Human Research Ethics Committee at Curtin University at their meeting on the 04/08/2015

Thankyou for providing the additional information requested by the Human Research Ethics Committee. The information you provided was satisfactory and your proposal is now approved.

Please note the following conditions of approval:

1. Approval is granted for a period of four years fror **25-Feb-16** to **25-Feb-20**
2. Research must be conducted as stated in the approved protocol.
3. Any amendments to the approved protocol must be approved by the Ethics Office.
4. An annual progress report must be submitted to the Ethics Office annually, on the anniversary of approval.
5. All adverse events must be reported to the Ethics Office.
6. A completion report must be submitted to the Ethics Office on completion of the project.
7. Data must be stored in accordance with WAUSDA and Curtin University policy.
8. The Ethics Office may conduct a randomly identified audit of a proportion of research projects approved by the HREC.

Should you have any queries about the consideration of your project please contact the Ethics Support Officer for your faculty, or the Ethics Office at hrec@curtin.edu.au or on 9266 2784. All human research ethics forms and guidelines are available on the ethics website.

Yours sincerely

Professor Peter O'Leary
Chair, Human Research Ethics Committee

Appendix C. Ethics approval from the Curtin University for educational intervention

Office of Research and Development

GPO Box U1987
Perth Western Australia 6845

Telephone +61 8 9266 7863
Facsimile +61 8 9266 3793
Web research.curtin.edu.au

14-Sep-2018

Name: Lynne Emmerton
Department/School: School of Pharmacy
Email: Lynne.Emmerton@curtin.edu.au

Dear Lynne Emmerton

RE: Ethics Office approval
Approval number: HRE2018-0610

Thank you for submitting your application to the Human Research Ethics Office for the project **An Antibiotic Stewardship Online Educational Module for Nurses in Residential Aged Care Facilities**.

Your application was reviewed through the Curtin University Negligible risk review process.

The review outcome is: **Approved**.

Your proposal meets the requirements described in the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research (2007).*

Approval is granted for a period of one year from **14-Sep-2018** to **13-Sep-2019**. Continuation of approval will be granted on an annual basis following submission of an annual report.

Personnel authorised to work on this project:

Name	Role
Emmerton, Lynne	CI
Shohel, Mohammad	Student
Hughes, Jeff	Co-Inv

Approved documents:

Document

Standard conditions of approval

1. Research must be conducted according to the approved proposal
2. Report in a timely manner anything that might warrant review of ethical approval of the project including: