Australian National University

Understanding Gastroenteritis in Middle-aged and Older Australians

by

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Declaration

I hereby declare that the work contained in this thesis is the result of original research and has not been submitted to any other University or Institution.

All information in this thesis has been obtained and presented in accordance with academic rules and ethical conduct.

The content of this thesis is the result of my own work, except where indicated by references or acknowledgement in the text. I have clearly stated the contribution of others to my thesis as a whole, including study design, data analysis, statistical assistance, technical procedures, and any other original work used or reported in this thesis. I have clearly stated the contribution of others who co-authored published works that I have included in this thesis. I certify that all information sources and literature used are appropriately acknowledged.

Signed: _____

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Finally, I dedicate this thesis to the memory of my beloved mother, Zhao Huanyi, who had been an outstanding inspiration to me. I miss you.

Abstract

Background: Gastroenteritis is an important cause of morbidity in older adults, resulting in a significant health burden globally. The aims of this thesis were to describe the epidemiology of gastroenteritis in older adults, and to investigate factors associated with hospitalisation with all-cause and cause-specific gastroenteritis in a cohort of middle-aged and older Australians.

Methods: I used design-based logistic regression and proportional hazards regression to analyse two datasets: (1) a national survey of gastroenteritis in the Australian community conducted in 2008–2009; and (2) a large-scale population-based cohort of middle-aged and older Australians with data linkage to hospitalisations, pharmaceuticals, notifiable diseases and deaths data. Additionally, I conducted a systematic review and meta-analysis of *Clostridium difficile* infection among people with inflammatory bowel disease.

Results: I estimated that 78,356 people aged ≥65 years old visited a doctor due to gastroenteritis in Australia annually, with 157,317 million courses of medication use in one year period from 2008–2009. From population-based cohort data, I demonstrated that the incidence of hospitalisation with gastroenteritis increased with older age; from 2.4 per 1,000 person-years in adults aged 45-54 years old to 9.5 per 1,000 in those aged ≥65 years. Compared to adults aged 45-54 years old, older persons had a higher incidence of hospitalisation with *Salmonella* infection and *C. difficile* infection. After adjustment, the risk of hospitalisation with gastroenteritis differed

depending on sex and region of residence. Poor self-rated health and use of proton pump inhibitors (PPI) were significantly associated with gastroenteritis hospitalisation. Hospitalisation with *C. difficile* infection was associated with longer hospital stays, greater in-hospital costs and higher in-hospital deaths compared to hospitalisation without *C. difficile* infection. In a meta-analysis of six international studies included in the systematic review, *C. difficile* infection was a significant risk factor for colectomy among patients with inflammatory bowel disease (Odds Ratio: 1.90; 95%CI 1.23-2.93).

Conclusions: This thesis demonstrates a significant burden of gastroenteritis in older Australians. Incidence of hospitalisation with all-cause and cause-specific gastroenteritis increases significantly with age. Future efforts should focus on defining and improving preventive measures for gastroenteritis hospitalisation among the elderly. The risk of hospitalisation varies by sex and region of residence, which reflects differences in exposure. PPI use is significantly associated with gastroenteritis hospitalisation. Given the widespread of PPI use, particularly among older people, clinicians should be aware of this potential association when considering PPI therapy. In addition, early recognition and supportive treatment of diarrhoea in older patients with poor self-rated health may prevent subsequent hospitalisation and improve their health outcomes.

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Chapter 1

General introduction and outline

1.1 Rationale and aims

Acute gastroenteritis causes significant morbidity and occasional mortality in Australia. In 2010, there were 15.9 million episodes of gastroenteritis in the country, resulting in 94,000 hospital admissions [1]. The economic costs of gastroenteritis are substantial from healthcare visits, medication usage and days of work lost, which are largely preventable.

Agents causing gastroenteritis can be transmitted by contaminated food or water, contact with infected animals or the environment, or person to person transmission [2]. Previous data suggested that approximately 25% of cases of gastroenteritis in Australia were transmitted by contaminated food [3]. Norovirus and non-typhoidal *Salmonella* were amongst the most commonly known causes of foodborne gastroenteritis [3]. In addition, the emergence and continued rise of *Clostridium difficile* as a leading cause of gastroenteritis and deaths has led to concern worldwide [4, 5].

Older adults (aged 65 years and older) are potentially at higher risk of gastroenteritis due to age-related changes in their gastrointestinal system and immune competence [6, 7]. Despite this, the incidence of gastroenteritis in the elderly living in the community is lower than other age groups [8]. However, gastroenteritis-associated hospitalisations are more common in elderly individuals than in other age groups in high income countries [9, 10].

While hospitalisation due to gastroenteritis imposes a significant burden on society, particularly in an aging population, the epidemiology and clinical outcomes of gastroenteritis among the elderly have not been well characterised. In most studies of gastroenteritis, data for older study participants are too sparse to provide meaningful results. Therefore, the aims of this thesis were to describe the epidemiology of gastroenteritis, and to investigate factors associated with gastroenteritis in older adults. The focus was on plausible factors for which there is limited evidence, or where the literature shows contradictory results.

In this thesis, I firstly assessed the healthcare utilisation and loss of productivity due to acute gastroenteritis in the Australian community using data collected from a nation-wide cross-sectional survey. Building upon this, I then estimated the incidence of, and risk factors for hospitalisation with gastrointestinal infections among middle-aged and older adults (aged 45 years and older) using data collected from a large-scale population-based cohort with data linkage to multiple administrative databases. I constructed a series of research questions and conducted several research studies that are detailed in Chapter 3 on 'Research design'.

1.2 Outline of thesis

This thesis is a collection of eight published scientific papers that address research questions related to acute gastroenteritis in middle-aged and older adults, along with chapters providing background, research questions and methods, discussion and conclusion that are unpublished. At the beginning of

each chapter, I have documented the publication status, co-authors and the contribution of the paper to this thesis.

Chapter 1 describes the rationale and aims of this thesis, and outlines the thesis structure and my role as author of the thesis.

Chapter 2 provides a general overview of the epidemiology of acute gastroenteritis in middle-aged and older adults. This section highlights important pathogens causing gastroenteritis that are of international importance as well as the main risk factors investigated within this thesis.

Chapter 3 documents the research questions and methods used to address each question. This chapter also discusses data sources used for this thesis, and general methods for data analysis.

Chapter 4 describes the healthcare utilisation and loss of productivity related to gastroenteritis in the Australian community. This chapter has been published as: Chen Y, Ford L, Hall G, Dobbins T, Kirk M. Healthcare utilization and lost productivity due to infectious gastroenteritis, results from a national cross-sectional survey Australia 2008-2009. *Epidemiol Infect*. 2016;144:241-6. Cambridge University Press.

Chapter 5 reports the incidence of, and risk factors for all-cause gastroenteritis hospitalisation in middle-aged and older adults. This chapter has been published as: Chen Y, Liu B, Glass K, Kirk M. High incidence of

hospitalisation due to infectious gastroenteritis in older people associated with poor self-rated health. *BMJ Open.* 2015;5:e010161. BMJ Publishing Group Ltd.

Chapter 6 investigates the association between proton pump inhibitor (PPI) use and gastroenteritis, and examines the effect of different dose and type of PPIs. This chapter has been published as: Chen Y, Liu B, Glass, Du W, Banks E, Kirk M. Use of proton pump inhibitors and the risk of hospitalization for infectious gastroenteritis. *Plos One.* 2016;20;11:e0168618. Public Library of Science.

Chapter 7 summarises the literature on norovirus infection in long-term care facilities, and proposes strategies for disease management in those settings. This chapter has been published as: Chen Y, Hall A, Kirk M. Norovirus disease in older adults living in long-term care facilities: strategies for management. *Current Geriatrics Reports.* 2017;6:26–33. Springer Publishing.

Chapter 8 describes the epidemiology of *Salmonella* infection and infection-associated hospitalisation in middle-aged and older adults. This chapter has been published as: Chen Y, Glass K, Liu B, Hope K, Kirk M. *Salmonella* infection in middle-aged and older adults: incidence and risk factors from the 45 and Up Study. *Foodborne Pathog Dis.* 2016;13:689-694. Mary Ann Liebert, Inc., Publishers.

Chapter 9 describes the epidemiology of hospital identified *Clostridium difficile* infection in middle-aged and older adults. This chapter has been published as: Chen Y, Glass K, Liu B, Riley T, Korda R, Kirk M. A population-

based longitudinal study of *Clostridium difficile* infection-related hospitalization in mid-age and older Australians. *Epidemiol Infect.* 2017;145:575-582. Cambridge University Press.

Chapter 10 describes the cost, length of hospital stay and in-hospital mortality related to *Clostridium difficile* infection in middle-aged and older adults. This chapter has been published as: Chen Y, Glass K, Liu B, Korda R, Riley T, Kirk M. Burden of *Clostridium difficile* infection: associated hospitalization in a cohort of middle-aged and older adults. *Am J Infect Control.* 2017;45:508-511. Association for Professionals in Infection Control and Epidemiology, Inc.

Chapter 11 documents a systematic review and meta-analysis of the risk of colectomy related to *Clostridium difficile* infection among patients with inflammatory bowel disease. This chapter has been published as: Chen Y, Furuya-Kanamori L, Doi S, Ananthakrishnan A, Kirk M. *Clostridium difficile* infection and risk of colectomy in patients with inflammatory bowel disease: A bias adjusted meta-analysis. *Inflamm Bowel Dis.* 2017;23:200-207. Lippincott Williams & Wilkins.

Chapter 12 summarises the main findings from this thesis, and provides general discussion and conclusion in arising from the papers presented in this thesis.

1.3 My role as author of this thesis

The initial idea of identifying risk factors for infectious colitis related to *Clostridium difficile* infection in older adults was conceived by my primary supervisor Associate Professor Martyn Kirk. The evolution of this thesis to focus on gastroenteritis in older adults occurred following preliminary analyses that I conducted using data from a larger program of research—"Identifying predisposing factors for, and the consequences of, common and emerging infectious diseases"—led by my co-supervisor Associate Professor Bette Liu.

This program of research utilises data collected in the 45 and Up Study, managed by the Sax Institute in collaboration with major partners. When I started this PhD, the linked data from the 45 and Up Study to administrative databases were already obtained as part of Associate Professor Liu's research project. Ethics approval for the research project was obtained from the NSW Population and Health Services Research Ethics Committee, before I began my PhD. For this thesis, I applied for and obtained ethics approval from the Australian National University Human Research Ethics Committee.

To describe gastroenteritis-related healthcare utilisation and loss of productivity in the Australian community, I analysed data collected in 2008–2009 from a national cross-sectional survey—National Gastroenteritis Survey II (NGSII). The data were weighted to the 2008 resident population for age, sex and state by the Australian Bureau of Statistics (www.abs.gov.au). I then incorporated

post-stratification in the analysis to adjust for known differences between the survey sample and the target population.

The concept for each of the chapters in this thesis including each of the papers was initiated by myself in association with my supervisors, Associate Professors Martyn Kirk, Bette Liu and Kathryn Glass. I wrote all of the chapters in this thesis, including the first draft of all papers. I conducted all of the analyses presented in this thesis. My co-authors for the various papers included in this thesis (Ashwin Ananthakrishnan, Emily Banks, Suhail Doi, Timothy Dobbins, Wei Du, Laura Ford, Luis Furuya-Kanamori, Aron Hall, Gillian Hall, Kirsty Hope, Rosemary Korda, Thomas Riley) read and provided advice on the content and/or methods and/or the statistical analysis for each paper that they were involved in.

Table 1.1 shows my estimated contribution to each paper. The criteria include (1) concept and drafting, (2) analysis and interpretation, and (3) drafting and revising. For each paper, I approved and submitted the final version of the manuscript and responded to comments from journal editors and reviewers.

Table 1.1. Estimate of my (Yingxi Chen) contribution to different aspects of publications included in this thesis as discrete chapters.

Chapter Number	Article title	Journal	Status	Student contribution (%)		
				Concept & design	Analysis & interpretation	Drafting & revising
4	Healthcare utilization and lost productivity due to infectious gastroenteritis, results from a national cross-sectional survey Australia 2008–2009	*Epidemiol Infect*	Published	40%	90%	70%
5	High incidence of hospitalisation due to infectious gastroenteritis in older people associated with poor self-rated health	*BMJ Open*	Published	80%	95%	70%
6	Use of proton pump inhibitors and the risk of hospitalisation for infectious gastroenteritis: a population-based cohort study	*Plos One*	Published	85%	95%	75%
7	Norovirus disease in older adults living in long-term care facilities: strategies for management	*Current Geriatrics Reports*	Published	30%	75%	70%
8	*Salmonella* infection in middle-aged and older adults: incidence and risk factors from the 45 and Up Study	*Foodborne Pathog Dis*	Published	80%	95%	70%
9	A population-based longitudinal study of *Clostridium difficile* infection-related hospitalisation in mid-age and older Australians	*Epidemiol Infect*	Published	80%	95%	70%
10	Burden of *Clostridium difficile* infection: associated hospitalisation in a cohort of middle-aged and older adults	*Am J Infect Control*	Published	70%	90%	75%
11	*Clostridium difficile* infection and risk of colectomy in patients with inflammatory bowel disease: A bias adjusted meta-analysis	*Inflamm Bowel Dis*	Published	95%	85%	80%

References

1. Kirk M, Ford L, Glass K, Hall G. Foodborne illness, Australia, circa 2000 and circa 2010. Emerg Infect Dis. 2014;20(11):1857-64.

2. Tauxe RV, Doyle MP, Kuchenmuller T, Schlundt J, Stein CE. Evolving public health approaches to the global challenge of foodborne infections. Int J Food Microbiol. 2010;139 Suppl 1:S16-28.

3. Kirk M, Glass K, Ford L, Brown K, Hall G. Foodborne illness in Australia: Annual incidence circa 2010. Canberra, ACT: National Centre for Epidemiology and Population Health, Australian National University. 2014.

4. Mitchell BG, Gardner A, Hiller JE. Mortality and Clostridium difficile infection in an Australian setting. J Adv Nurs. 2013;69(10):2162-70.

5. Redelings MD, Sorvillo F, Mascola L. Increase in Clostridium difficile-related mortality rates, United States, 1999-2004. Emerg Infect Dis. 2007;13:1417-9.

6. Gavazzi G, Krause K-H. Ageing and infection. Lancet Infect Dis. 2002;2(11):659-66.

7. Castle SC. Clinical relevance of age-related immune dysfunction. Clin Infect Dis. 2000;31(2):578-85.

8. Hall G, Kirk M, Ashbolt R, Stafford R, Lalor K. Frequency of infectious gastrointestinal illness in Australia, 2002: regional, seasonal and demographic variation. Epidemiol Infect. 2006;134(01):111-8.

9. Kirk MD, Hall GV, Becker N. Gastroenteritis in older people living in the community: results of two Australian surveys. Epidemiol Infect. 2012;140:2028-36.

10. Lopman BA, Hall AJ, Curns AT, Parashar UD. Increasing Rates of Gastroenteritis Hospital Discharges in US Adults and the Contribution of Norovirus, 1996–2007. Clin Infect Dis. 2011;52(4):466-74.

Chapter 2

Background

Aging and infections

Aging population in Australia

Australia's population today is much older than a hundred years ago. At the beginning of the 20th century, the median age was 22 years and only 4% of the total Australian population was aged 65 years and older [1]. With low fertility, reduced mortality and the aging of the large baby boomer generation, the elderly (aged 65 years and older) accounted for approximately 14% of the entire Australian population in 2011 [1]. This is anticipated to increase to 22% in 2061, with a rapid growth of the older elderly (people aged 85 years and over) throughout the projection period [2].

Common infections in the elderly

Theoretically, older people are at higher risk for acquiring infections due to declining immune competence that occurs with aging. However there is little evidence to suggest that older age is related to increased risks from all infections. Previous data have indicated that some infections, including lower respiratory infections, bacterial pneumonia, urinary tract infections, skin and soft tissue infections, sepsis, bacterial meningitis and herpes zoster, are more common in older people, and are often associated with greater morbidity and mortality [3].

Gastrointestinal infections are a leading cause of morbidity in all age groups, resulting in a substantial burden worldwide. Older people are potentially at higher risk of some enteric infections due to decreased gastric acidity,

intestinal motility disorders, and a compromised immune system [4, 5], although many bacterial and parasitic enteric pathogens are preventable.

Acute gastroenteritis

Burden of gastroenteritis

Acute gastroenteritis is the most common clinical manifestation of gastrointestinal infections. Pathogens, such as viruses, bacteria, and other microbes can cause gastroenteritis. Despite a large burden of disease, the aetiology of most gastroenteritis cases and outbreaks remain unknown. The majority episodes are thought to be associated with viral infection. In addition, consumption of contaminated food or water is another common cause of illness.

Acute gastroenteritis is a major cause of mortality internationally, particularly among children aged <5 years in low and middle income countries[6]. In high income countries, viral and bacterial gastroenteritis are associated with considerable morbidity in all age groups. In one international study estimating prevalence of diarrhoeal disease in the community, diarrhoea was commonly reported in Australia, Canada, Ireland and the United States [7].

In Australia in 2010, there were an estimated 15.9 million episodes of gastroenteritis and 94,000 associated admissions to hospital [8]. This was based on a nationally representative cross-sectional survey undertaken to estimate the population burden of gastroenteritis in the Australian community in 2008–2009, that was modelled on a similar survey in 2001–2002 [9]. Pooled data from the surveys showed that the incidence of self-reported gastroenteritis among people

in the community declined markedly with age, with participants aged >85 years having the lowest incidence at 0.12 episodes per person-year [10]. However, compared to other adults, elderly people had a longer duration of illness and were more likely to receive health care [10].

The impact of gastroenteritis in elderly patients is particularly noteworthy. While people aged ≥65 years old have the lowest prevalence in the community, the elderly account for the highest proportion of health professional visits [7]. Older adults are also at higher risk of gastroenteritis-related hospitalisations [11, 12] due to the decrease in immune function, intestinal motility disorders, poor nutrition, altered diet, living environment and comorbid conditions [11-15]. Kirk *et al*'s analysis of pooled data from the two large national surveys to examine outcomes of gastroenteritis in older Australians showed that elderly cases reported less stomach cramps, fever and myalgia than younger cases, but were more likely to be hospitalised [10].

In Australia, the incidence of gastroenteritis-related hospitalisations increased from 15.0 per 1,000 population per year in 2005–2006 to 20.2 per 1,000 population per year in 2009–2010 among people aged ≥65 years, despite a marked decrease in gastroenteritis hospitalisation among children <5 years old [16]. In the US, hospitalisation due to all-cause gastroenteritis increased by over 50% in all adults and elderly age groups between 1996–2007 [11].

While gastroenteritis hospitalisation imposes a significant burden on society, particularly in an aging population, the epidemiology of gastroenteritis

among the elderly has not been well described. In most studies of gastroenteritis, data for older study participants are too sparse to provide meaningful results.

Main causes of gastroenteritis

Acute gastroenteritis can be caused by viral, bacterial and parasitic infections. Viruses, such as rotavirus and norovirus, are common causes of viral gastroenteritis. While rotavirus is the most common cause of gastrointestinal infections presenting in infants and young children [17], norovirus has emerged as a key pathogen worldwide, causing approximately 10–20% of gastroenteritis hospitalisations, 10–15% of gastroenteritis deaths, and ≥0.2% of all-cause mortality among older adults in upper-middle income and high income countries [18-21]. Older adults are at higher risk of norovirus-associated hospitalisation, contributing to lengthy hospital stays and greater costs compared to young adults[22].

Notably, norovirus is the most common cause of gastroenteritis outbreaks in healthcare settings and nursing homes [23], which are often associated with high attack rates [24]. Outbreaks of norovirus infection have a significant impact on the institutionalised elderly and cause severe and prolonged illness [25]. The highly contagious nature of norovirus and the individual susceptibility of older residents pose significant challenges to address norovirus infection in healthcare settings.

Bacterial infection is another important cause of acute gastroenteritis. Many pathogens, including *Campylobacter* spp., *Escherichia coli* O157, *Salmonella*

spp., *Shigella* spp., *Bacillus cereus* and *Clostridium difficile* can cause bacterial gastroenteritis. While *Campylobacter* spp. is associated with the largest number of cases of foodborne bacterial infections, diarrhoeal and invasive infections due to non-typhoidal *Salmonella* infections resulted in the highest burden worldwide (4.07 million DALYs in 2010; 95% UI 2.49–6.27 million DALYs) [26].

Non-typhoidal *Salmonella* is a globally important cause of infection, contributing to an estimated 153 million illnesses and 57 thousand deaths worldwide in 2010 [26]. In Australia, *Salmonella* Typhimurium is one of the most common serotypes of *Salmonella*, and frequently causes sporadic infections and foodborne outbreaks, of which the majority are related to the consumption of dishes containing raw or undercooked eggs [27].

Non-typhoidal *Salmonella* infections in older adults can cause invasive disease, resulting in severe complications [28] and death [29-31]. Kirk *et al* found that rates of salmonellosis in elderly people rose dramatically over 2000-2009 in Australia [32]. The cause of this increase is unknown, although has been hypothesised to be associated with consumption of chicken meat and eggs which were identified as the common source of outbreaks through public health surveillance [33].

The emergence and continued rise of *C. difficile* as a leading cause of gastroenteritis and deaths has been documented worldwide [34, 35]. Since the first identification of *C. difficile* as a cause of pseudomembranous colitis in the 1970s [36, 37], the burden of disease due to *C. difficile* has been increasing in the

past decades, along with a marked rise in disease severity [38]. With regard to all pathogens causing gastrointestinal infections, *C. difficile* infection has been documented as the leading cause of death listed on death certificates in Australia (unpublished data).

C. difficile is the principal cause of infectious diarrhoea in hospitalised patients [39]. While *C. difficile* is generally thought of as a hospital problem, data from high income countries have suggested that community-acquired infections are on the rise and comprise approximately 27%–41% of all cases of *C. difficile* infection (CDI) in those countries [40, 41]. Internationally, CDI incidence has increased significantly over the last decade, resulting in a considerable burden on healthcare systems.

In Australia, national surveillance for hospital-identified CDI has demonstrated increasing incidence since 2011 [42], although data on the burden of CDI-associated hospitalisation are incomplete. A cross-sectional study conducted in Sydney, Australia, reported that *C. difficile* is one of the most frequently detected pathogens in hospital patients with gastrointestinal illness[43]. This study also found that 69% of people infected with *C. difficile* were aged ≥50 years [43].

Transmission of gastrointestinal infections

Transmission of gastrointestinal infections may occur through person to person contact, contaminated food or water, environmental sources (often water-associated), or exposure to animals. Although the transmission of infection is

complex and not all gastroenteritis is foodborne, food represents an important vehicle for pathogens causing gastroenteritis [44].

Foodborne diseases result in a substantial burden globally. A recent estimate of the global and regional disease burden of 22 foodborne pathogens reported that 582 million illnesses were transmitted by contaminated food worldwide in 2010, accounting for 25.2 million DALYs [26]. In Australia, there were an estimated annual 4.1 million cases of foodborne gastroenteritis, accounting for 25% of all gastroenteritis cases circa 2010 [45]. Similar studies have been conducted in the US [29], Canada [46], and the Netherlands [47]. Scallan *et al* estimated that contaminated food was related to 26% of domestically acquired infections caused by known pathogens in the US [29]. The proportion was higher (39%) in the Netherlands [47], although the overall estimates of foodborne gastroenteritis depend on the investigated pathogens and the incidence of common foodborne pathogens in the study areas.

Of all foodborne pathogens, norovirus is the leading cause of illness, and contributed to 125 million cases internationally in 2010 [26]. Diarrhoea due to non-typhoidal *Salmonella* infections resulted in the highest burden, causing 4.07 million DALYs worldwide in 2010 [26]. Regionally, norovirus and non-typhoidal *Salmonella* spp. are among the most common known causes of foodborne gastroenteritis in Australia [45], the Netherlands [47], Canada [46], and the US [29].

Person-to-person transmission is another important pathway for infection transmission resulting in acute gastroenteritis, in particular for norovirus. Direct person-to-person transmission is responsible for >90% of the norovirus outbreaks in healthcare settings, where close living arrangements, shared facilities and contact with visitors and staff increase the risk of norovirus spread from one person to another [48, 49].

Infection can also be transmitted through contaminated environments. Aerosolisation of norovirus via vomitus can be particularly problematic in healthcare settings, as virus particles can settle on surfaces and survive for long periods of time, leading to environmental contamination for future exposure [50]. Whereas *C. difficile* is transmitted by spores that are resistant to heat, acid and antibiotics. The spores can persist in the environment for several months, causing colonisation and infection in healthcare settings as well as community [51].

Risk factors for gastroenteritis

Socio-demographic factors

It is not clear if gender differences have been reported for gastrointestinal illness. *Zarling et al* reviewed computerised data relating to all hospitalisations in the US over one year period, and found that the gender distribution for all gastrointestinal illness was highly significant, with females having a higher hospitalisation rate for gastroenteritis [52]. These differences may reflect a gender-based treatment bias, could reflect differences in disease severity among

males and females, or could indicate a difference in the true prevalence of enteric infections between the sexes [52].

The association between socioeconomic status and gastroenteritis has been found to differ between studies according to study design, target population and case definition [53-56]. Ecological studies have reported higher rates of foodborne illness from low income areas [57], which may be related to poorer quality of food or greater exposure to high-risk foods [58]. Similarly, Kirk *et al* reported significantly less gastroenteritis among elderly people with a higher household income compared to those with an annual income of < Australian dollar (AUD) 25,000 [10].

A prospective cohort study conducted in the Netherlands in the late 1990s detected an increasing trend of incidence of diarrhoea with increasing education level [59]. However, a register study conducted in England showed a significant association between low socioeconomic status and risk of hospital admission with gastroenteritis [60]. In addition, associations with socioeconomic variables varied by type of bacteria. A nation-wide Danish study reported that people with high-income had increased risks of infection with *Campylobacter*, *Shigella*, and *Salmonella* Enteritidis, and higher education was associated with increased risk of *Campylobacter* and *Shigella* infection [61].

Contributory factors across different socio-economic groups may be related to differences in diet and travel activity. It could also reflect differential probabilities of diagnostic reporting across groups [61]. High risks of certain

enteric infections in low-income areas could be associated with environmental exposure, poor hygiene and food handling practices, and increased person-to-person transmission due to overcrowding.

General health

Immunocompromised patients due to immunosuppressive therapy, cancer chemotherapy, or infection with the human immunodeficiency virus are prone to gastrointestinal infections. Impairment of host immunity and alteration of gut microbiota that favours intestinal domination of invasive pathogens, lead to bacterial overgrowth and increase individual's susceptibility to systemic infection[62].

In addition, comorbid illness and the severity of underlying conditions have been reported as important risk factors for gastrointestinal infections, including *C. difficile, Salmonella,* and *Campylobacter* infection [63-66]. Self-rated health has also previously been reported as a significant predictor of severe health outcomes, such as mortality [67].

Dietary factors

While acute gastroenteritis is often foodborne, reservoirs and risk factors differ for different types of pathogens. In Australia, poultry and eggs are the most common vehicle for *Salmonella* infection in reported outbreaks [68, 69]. International data from outbreak investigations have identified poultry, egg, beef, and milk as important sources of infection [69-72]. A meta-analysis of case-control studies to investigate source attribution of human salmonellosis found

chicken consumption in restaurants as an important source of infection [63]. Similarly, Glass *et al* adopted a Bayesian source attribution model to estimate the contribution of different reservoirs to *Salmonella* infection in South Australia, and found that eggs were a common source of infection for different serotypes of *Salmonella* [73].

Consumption of fresh fruit and vegetables is commonly viewed as a potential risk factor for enteric infections, with outbreaks frequently linked to contaminated fruit and vegetables [74, 75]. However, a study examining the risks of foodborne illness by food types reported a low risk ratio for salad vegetables and fruit [76]. Domingues *et al* conducted two systematic reviews of case-control studies examining source attribution of campylobacteriosis and salmonellosis, and found that fruit and vegetables were protective factors for human infection, although reasons for the association are unknown [63, 64]. Beneficial health effects from a high fruit and/or vegetable diet may protect individuals against enteric infections, although selection bias in the control group with particularly healthy lifestyle may also be an explanation.

Proton pump inhibitors

Proton pump inhibitors (PPIs), introduced in 1989, are the most potent gastric acid suppressants available [77]. They are widely used by clinicians in the effective treatment of gastric acid-related disorders. PPIs are one of the most commonly prescribed medications worldwide [78]. In Australia in the 2013–2014

financial year, physicians issued over 19 million prescriptions for PPIs, with the most commonly prescribed type of PPIs costing over $200 million [79].

Although PPIs are considered safe and have been approved for long-term use [80], concerns have been raised regarding associated adverse effects. Diarrhoea is a common adverse event of treatment with PPIs for patients with gastric acid-related disorders. It is believed that PPI therapy may potentially impair host defence due to their effects on gastric acid [81]. Significant hypochlorhydria, particularly among the elderly population who may have decreased clearance of PPIs, could result in bacterial overgrowth [82] and increase an individual's susceptibility to infection. Other effects of PPIs include impairment of neutrophil function [83] and reduced bactericidal killing of microbes [84].

Observational studies have found increased risks of bacterial gastroenteritis with PPI use [85, 86]. A systematic review of gastric acid suppressants reported a significant association between these drugs and enteric infections [87]. Case-control studies have suggested associations between gastroenteritis caused by acid sensitive pathogens and the use of PPIs [88, 89]. In addition, a study that compared the effect of PPIs and histamine receptor antagonists observed a trend toward a higher risk with PPIs, suggesting the degree of acid suppression is correlated with the degree of elevated risk [90].

As with all observational studies, it is possible that the reported associations between PPIs and enteric infections could be a result of residual

confounding. Few epidemiological studies have considered pre-existing conditions and severity of illness when investigating the risk of PPI use, and the effect of different types and doses of PPIs remain unknown. Further studies are needed to address this knowledge gap.

Conclusion

In conclusion, acute gastroenteritis imposes a significant burden on society, particularly among the elderly. Prospective studies investigating the risk factors and incidence of infection-associated hospitalisation are uncommon in Australia. Identifying risk factors of all-cause and cause-specific gastroenteritis is an important step towards a more complete understanding of gastroenteritis epidemiology to adequately inform policy-makers and allocate appropriate resources for infection prevention and intervention efforts.

References

1. 3105.0.65.001 - Australian Historical Population Statistics, 2014. [Internet]. 2014 [cited August 2016]. Available from: http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/3105.0.65.001Main+Features12014?OpenDocument.

2. Population Projections, Australia, 2012 (base) to 2101 [Internet]. 2013 [cited August 2016]. Available from: http://www.abs.gov.au/ausstats/abs@.nsf/Latestproducts/3222.0Main%20Features32012%20%28base%29%20to%202101?opendocument&tabname=Summary&prodno=3222.0&issue=2012%20%28base%29%20to%202101&num=&view=.

3. Yoshikawa T, Norman D. Infectious disease in the aging: a clinical handbook. 2nd. New York, NY: Springer Science & Business Media; 2009.

4. Gavazzi G, Krause K-H. Ageing and infection. Lancet Infect Dis. 2002;2(11):659-66.

5. Castle SC. Clinical relevance of age-related immune dysfunction. Clin Infect Dis. 2000;31(2):578-85.

6. Black RE, Cousens S, Johnson HL, et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. Lancet. 2010;375:1969-87.

7. Scallan E, Majowicz SE, Hall G, Banerjee A, Bowman CL, Daly L, et al. Prevalence of diarrhoea in the community in Australia, Canada, Ireland, and the United States. Int J Epidemiol. 2005;34(2):454-60.

8. Kirk M, Ford L, Glass K, Hall G. Foodborne illness, Australia, circa 2000 and circa 2010. Emerg Infect Dis. 2014;20(11):1857-64.

9. Hall GV, Kirk MD, Ashbolt R, Stafford R, Lalor K. Frequency of infectious gastrointestinal illness in Australia, 2002: regional, seasonal and demographic variation. Epidemiol Infect. 2006;134(1):111-8.

10. Kirk MD, Hall GV, Becker N. Gastroenteritis in older people living in the community: results of two Australian surveys. Epidemiol Infect. 2012;140:2028-36.

11. Lopman BA, Hall AJ, Curns AT, Parashar UD. Increasing Rates of Gastroenteritis Hospital Discharges in US Adults and the Contribution of Norovirus, 1996–2007. Clin Infect Dis. 2011;52(4):466-74.

12. Hall AJ, Curns AT, McDonald LC, Parashar UD, Lopman BA. The Roles of Clostridium difficile and Norovirus Among Gastroenteritis-Associated Deaths in the United States, 1999–2007. Clin Infect Dis. 2012;55(2):216-23.

13. Iturriza-Gomara M, Lopman B. Norovirus in healthcare settings. Curr Opin Infect Dis. 2014;27(5):437-43.

14. Trinh C, Prabhakar K. Diarrheal diseases in the elderly. Clin Geriatr Med. 2007;23(4):833-56.

15. Blackman DK, Kamimoto LA, Smith SM. Overview: surveillance for selected public health indicators affecting older adults-United States. MMWR. 1999;48:1-6.

16. Dey A, Wang H, Menzies R, Macartney K. Changes in hospitalisations for acute gastroenteritis in Australia after the national rotavirus vaccination program. Med J Aust. 2012;197(8):453.

17. World Health Organization. Rotavirus infections. [Internet]. 2010 [cited April 2016]. Available from: http://www.who.int/topics/rotavirus_infections/en/.

18. van Asten L, Siebenga J, van den Wijngaard C, Verheij R, van Vliet H, Kretzschmar M, et al. Unspecified Gastroenteritis Illness and Deaths in the Elderly Associated With Norovirus Epidemics. Epidemiol. 2011;22(3):336-43.

19. Haustein T, Harris JP, Pebody R, Lopman BA. Hospital admissions due to norovirus in adult and elderly patients in England. Clin Infect Dis. 2009;49(12):1890-2.

20. Hall AJ, Curns AT, McDonald LC, Parashar UD, Lopman BA. The roles of Clostridium difficile and norovirus among gastroenteritis-associated deaths in the United States, 1999-2007. Clin Infect Dis. 2012;55(2):216-23.

21. Schmid D, Kuo HW, Simons E, Kanitz EE, Wenisch J, Allerberger F, et al. All-cause mortality in hospitalized patients with infectious diarrhea: Clostridium difficile versus other enteric pathogens in Austria from 2008 to 2010. J Infect Public Health. 2014;7(2):133-44.

22. Lindsay L, Wolter J, De Coster I, Van Damme P, Verstraeten T. A decade of norovirus disease risk among older adults in upper-middle and high income countries: a systematic review. BMC Infect Dis. 2015;15:425.

23. Greig JD, Lee MB. Enteric outbreaks in long-term care facilities and recommendations for prevention: a review. Epidemiol Infect. 2009;137(2):145-55. Epub 2008/05/14. doi: 10.1017/s0950268808000757. PubMed PMID: 18474129.

24. Matthews J, Dickey B, Miller R, Felzer J, Dawson B, Lee A, et al. The epidemiology of published norovirus outbreaks: a review of risk factors associated with attack rate and genogroup. Epidemiol Infect. 2012;140(07):1161-72.

25. Trivedi TK, Desai R, Hall AJ, Patel M, Parashar UD, Lopman BA. Clinical characteristics of norovirus-associated deaths: a systematic literature review. Am J Infect Control. 2013;41(7):654-7.

26. Kirk MD, Pires SM, Black RE, Caipo M, Crump JA, Devleesschauwer B, et al. World Health Organization Estimates of the Global and Regional Disease Burden of 22 Foodborne Bacterial, Protozoal, and Viral Diseases, 2010: A Data Synthesis. PLoS Med. 2015;12(12):e1001921.

27. Moffatt CR, Musto J, Pingault N, Miller M, Stafford R, Gregory J, et al. Salmonella Typhimurium and Outbreaks of Egg-Associated Disease in Australia, 2001 to 2011. Foodborne pathog dis. 2016. In press. doi: 10.1089/fpd.2015.2110.

28. Parry CM, Thomas S, Aspinall EJ, Cooke RP, Rogerson SJ, Harries AD, et al. A retrospective study of secondary bacteraemia in hospitalised adults with community acquired non-typhoidal Salmonella gastroenteritis. BMC Infect Dis. 2013;13(1):107.

29. Scallan E, Hoekstra RM, Angulo FJ, Tauxe RV, Widdowson MA, Roy SL, et al. Foodborne illness acquired in the United States--major pathogens. Emerg Infect Dis. 2011;17(1):7-15.

30. Kendall PA, Val Hillers V, Medeiros LC. Food Safety Guidance for Older Adults. Clin Infect Dis. 2006;42(9):1298-304.

31. Kennedy M, Villar R, Vugia DJ, Rabatsky-Ehr T, Farley MM, Pass M, et al. Hospitalizations and deaths due to Salmonella infections, FoodNet, 1996–1999. Clin Infect Dis. 2004;38(Supplement 3):S142-S8.

32. Kirk MD, Gregory J, Lalor K, Hall GV, Becker N. Foodborne and waterborne infections in elderly community and long-term care facility residents, Victoria, Autralia. Emerg Infect Dis. 2012;18(3):377.

33. OzFoodNet Working Group. Monitoring the incidence and causes of diseases potentially transmitted by food in Australia: Annual report of the OzFoodNet network, 2011. Commun Dis Intell Q Rep. 2015;39(2):E236.

34. Redelings MD, Sorvillo F, Mascola L. Increase in Clostridium difficile-related mortality rates, United States, 1999-2004. Emerg Infect Dis. 2007;13:1417-9.

35. Mitchell BG, Gardner A, Hiller JE. Mortality and Clostridium difficile infection in an Australian setting. J Adv Nurs. 2013;69(10):2162-70.

36. Tedesco FJ, Barton RW, ALPERS DH. Clindamycin-associated colitis: a prospective study. Ann Intern Med. 1974;81(4):429-33.

37. Bartlett JG, Chang TW, Gurwith M, Gorbach SL, Onderdonk AB. Antibiotic-associated pseudomembranous colitis due to toxin-producing clostridia. New Engl J Med. 1978;298(10):531-4.

38. Lessa FC, Gould CV, McDonald LC. Current status of Clostridium difficile infection epidemiology. Clin Infect Dis. 2012;55(suppl 2):S65-S70.

39. Leffler DA, Lamont JT. Clostridium difficile Infection. New Engl J Med. 2015;372(16):1539-48.

40. Khanna S, Pardi DS, Aronson SL, Kammer PP, Orenstein R, St Sauver JL, et al. The epidemiology of community-acquired Clostridium difficile infection: a population-based study. Am J Gastroenterol. 2012;107(1):89-95.

41. Lambert PJ, Dyck M, Thompson LH, Hammond GW. Population-based surveillance of Clostridium difficile infection in Manitoba, Canada, by using interim surveillance definitions. Infect Control Hosp Epidemiol. 2009;30(10):945-51.

42. Slimings C, Armstrong P, Beckingham W, Bull AL, Hall L, Kennedy KJ, et al. Increasing incidence of Clostridium difficile infection, Australia, 2011–2012. Med J Aust. 2014;200:272-6.

43. Fletcher S, Sibbritt D, Stark D, Harkness J, Rawlinson W, Andresen D, et al. Descriptive epidemiology of infectious gastrointestinal illnesses in Sydney, Australia, 2007–2010. Western Pacific Surveillance and Response. 2015; 6(4).

44. Flint JA, et al. Estimating the burden of acute gastroenteritis, foodborne disease, and pathgens commonly transmitted by food: an international review. Clin Infect Dis. 2005;41:698-704.

45. Kirk M, Glass K, Ford L, Brown K, Hall G. Foodborne illness in Australia: Annual incidence circa 2010. Canberra, ACT: National Centre for Epidemiology and Population Health, Australian National University. 2014.

46. Thomas MK, Murray R, Flockhart L, Pintar K, Pollari F, Fazil A, et al. Estimates of the burden of foodborne illness in Canada for 30 specified pathogens and unspecified agents, circa 2006. Foodborne Pathog Dis. 2013;10(7):639-48.

47. Havelaar AH, Haagsma JA, Mangen M-JJ, Kemmeren JM, Verhoef LP, Vijgen SM, et al. Disease burden of foodborne pathogens in the Netherlands, 2009. Int J Food Microbiol. 2012;156(3):231-8.

48. Vega E, Barclay L, Gregoricus N, Shirley SH, Lee D, Vinje J. Genotypic and epidemiologic trends of norovirus outbreaks in the United States, 2009 to 2013. J Clin Microbiol. 2014;52(1):147-55.

49. Kroneman A, Verhoef L, Harris J, Vennema H, Duizer E, van Duynhoven Y, et al. Analysis of integrated virological and epidemiological reports of norovirus outbreaks collected within the Foodborne Viruses in Europe network from 1 July 2001 to 30 June 2006. J Clin Microbiol. 2008;46(9):2959-65.

50. Repp KK, Keene WE. A point-source norovirus outbreak caused by exposure to fomites. J Infect Dis. 2012;205(11):1639-41.

51. Martin JS, Monaghan TM, Wilcox MH. Clostridium difficile infection: epidemiology, diagnosis and understanding transmission. Nat Rev Gastroenterol Hepatol. 2016;13(4):206-16.

52. Zarling EJ, Bernsen MB. The effect of gender on the rates of hospitalization for gastrointestinal illnesses. Am J Gastroenterol. 1997;92(4):621-3.

53. Hall G, Kirk M, Ashbolt R, Stafford R, Lalor K. Frequency of infectious gastrointestinal illness in Australia, 2002: regional, seasonal and demographic variation. Epidemiol Infect. 2006;134(01):111-8.

54. Herikstad H, Yang S, Van Gilder T, Vugia D, Hadler J, Blake P, et al. A population-based estimate of the burden of diarrhoeal illness in the United States: FoodNet, 1996–7. Epidemiol Infect. 2002;129(01):9-17.

55. Majowicz S, Dore K, Flint J, Edge V, Read S, Buffett M, et al. Magnitude and distribution of acute, self-reported gastrointestinal illness in a Canadian community. Epidemiol Infect. 2004;132(04):607-17.

56. Bytzer P, Howell S, Leemon M, Young LJ, Jones MP, Talley NJ. Low socioeconomic class is a risk factor for upper and lower gastrointestinal symptoms: a population based study in 15 000 Australian adults. Gut. 2001;49(1):66-72.

57. Varga C, Pearl DL, McEwen SA, Sargeant JM, Pollari F, Guerin MT. Evaluating area-level spatial clustering of Salmonella Enteritidis infections and their socioeconomic determinants in the greater Toronto area, Ontario, Canada (2007–2009): a retrospective population-based ecological study. BMC Public Health. 2013;13(1):1078.

58. Koro ME, Anandan S, Quinlan JJ. Microbial quality of food available to populations of differing socioeconomic status. Am J Prev Med. 2010;38(5):478-81.

59. De Wit M, Koopmans M, Kortbeek L, Wannet W, Vinje J, Van Leusden F, et al. Sensor, a population-based cohort study on gastroenteritis in the Netherlands: incidence and etiology. Am J Epidemiol. 2001;154(7):666-74.

60. Olowokure B, Hawker J, Weinberg J, Gill N, Sufi F. Deprivation and hospital admission for infectious intestinal diseases. Lancet. 1999;353(9155):807-8.

61. Simonsen J, Frisch M, Ethelberg S. Socioeconomic risk factors for bacterial gastrointestinal infections. Epidemiol. 2008;19(2):282-90.

62. Taur Y, Pamer EG. The intestinal microbiota and susceptibility to infection in immunocompromised patients. Curr Opin Infect Dis. 2013;26(4):332-7.

63. Domingues AR, Pires SM, Halasa T, Hald T. Source attribution of human salmonellosis using a meta-analysis of case-control studies of sporadic infections. Epidemiol Infect. 2012;140(6):959-69.

64. Domingues AR, Pires SM, Halasa T, Hald T. Source attribution of human campylobacteriosis using a meta-analysis of case-control studies of sporadic infections. Epidemiol Infect. 2012;140(6):970-81.

65. Kyne L, Sougioultzis S, McFarland LV, Kelly CP. Underlying disease severity as a major risk factor for nosocomial Clostridium difficile diarrhea. Infect Control Hosp Epidemiol. 2002;23(11):653-9.

66. Ananthakrishnan AN. Clostridium difficile infection: epidemiology, risk factors and management. Nat Rev Gastroentero. 2011;8(1):17-26.

67. DeSalvo KB, Bloser N, Reynolds K, He J, Muntner P. Mortality Prediction with a Single General Self - Rated Health Question. J Gen Intern Med. 2006;21(3):267-75.

68. NSW OzFoodNet. OzFoodNet—Enhancing Foodborne Disease Surveillance Across Australia [Internet]. 2015 [cited April 2016]. Available from: http://www.health.nsw.gov.au/Infectious/foodborne/Documents/NSW-2nd-quarterly-report-2015.pdf.

69. The OzFoodNet Working Group. Monitoring the incidence and causes of diseases potentially transmitted by food in Australia: annual report of the OzFoodNet network, 2010. CDI. 2012;36:E213-41.

70. Centers for Disease Control and Prevention. Surveillance for foodborne disease outbreaks--United States, 2009-2010. MMWR Morb Mortal Wkly Rep. 2013;62(3):41-7.

71. Hedberg CW, David MJ, White KE, et al. Role of egg consumption in sporadic Salmonella enteritidis and Salmonella typhimurium infections in Minnesota. J Infect Dis. 1993;167(1):107-11.

72. Parry SM, Palmer SR, Slader J, et al. Risk facotrs for salmonella food poisoning in the domestic kitchen: A case control study. Epidemiol Infect. 2002;129(2):277-85.

73. Glass K, Fearnley E, Hocking H, Raupach J, Veitch M, Ford L, et al. Bayesian Source Attribution of Salmonellosis in South Australia. Risk Anal. 2016;36(3):561-70.

74. Munnoch S, Ward K, Sheridan S, Fitzsimmons G, Shadbolt C, Piispanen J, et al. A multi-state outbreak of Salmonella Saintpaul in Australia associated with cantaloupe consumption. Epidemiol Infect. 2009;137(03):367-74.

75. Taormina PJ, Beuchat LR, Slutsker L. Infections associated with eating seed sprouts: an international concern. Emerg Infect Dis. 1999;5(5):626-34.

76. Adak GK, Meakins SM, Yip H, Lopman BA, O'Brien SJ. Disease risks from foods, England and Wales, 1996–2000. Emerg Infect Dis. 2005;11(3):365-72.

77. Wolfe MM, Sachs G. Acid suppression: optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. Gastroenterol. 2000;118(2 Suppl 1):S9-31.

78. Forgacs I, Loganayagam A. Overprescribing proton pump inhibitors. BMJ. 2008;336(7634):2-3.

79. The Pharmaceutical Benefits Scheme, PBS Statistics [Internet]. Australian Government Department of Health. [cited 15 November 2015]. Available from: http://www.pbs.gov.au/info/browse/statistics#ASM.

80. Garnett WR. Considerations for long-term use of proton-pump inhibitors. Am J Health Syst Pharm. 1998;55(21):2268-79.

81. Dial MS. Proton pump inhibitor use and enteric infections. Am J Gastroenterol. 2009;104:S10-S6.

82. Lombardo L, Foti M, Ruggia O, Chiecchio A. Increased incidence of small intestinal bacterial overgrowth during proton pump inhibitor therapy. Clin Gastroenterol Hepatol. 2010;8(6):504-8.

83. Yoshida N, Yoshikawa T, Tanaka Y, Fujita N, Kassai K, Naito Y, et al. A new mechanism for anti - inflammatory actions of proton pump inhibitors – inhibitory effects on neutrophil – endothelial cell interactions. Aliment Pharmacol Ther. 2000;14(s1):74-81.

84. Zedtwitz-Liebenstein K, Wenisch C, Patruta S, Parschalk B, Daxböck F, Graninger W. Omeprazole treatment diminishes intra-and extracellular neutrophil reactive oxygen production and bactericidal activity. Crit Care Med. 2002;30(5):1118-22.

85. Hassing RJ, Verbon A, de Visser H, Hofman A, Stricker BH. Proton pump inhibitors and gastroenteritis. Eur J Epidemiol. 2016;31(10):1057-63.

86. Kwok CS, Arthur AK, Anibueze CI, Singh S, Cavallazzi R, Loke YK. Risk of Clostridium difficile infection with acid suppressing drugs and antibiotics: meta-analysis. Am J Gastroenterol. 2012;107(7):1011-9.

87. Leonard J, Marshall JK, Moayyedi P. Systematic review of the risk of enteric infection in patients taking acid suppression. Am J Gastroenterol. 2007;102(9):2047-56.

88. Doorduyn Y, Van Pelt W, Siezen C, Van Der Horst F, Van Duynhoven Y, Hoebee B, et al. Novel insight in the association between salmonellosis or campylobacteriosis and chronic illness, and the role of host genetics in susceptibility to these diseases. Epidemiol Infect. 2008;136(09):1225-34.

89. Neal KR, Scott HM, Slack RC, Logan RF. Omeprazole as a risk factor for campylobacter gastroenteritis: case-control study. BMJ. 1996;312(7028):414-5.

90. Neal K, Slack R. Diabetes mellitus, anti-secretory drugs and other risk factors for campylobacter gastro-enteritis in adults: a case-control study. Epidemiol Infect. 1997;119(03):307-11.

Chapter 3

Research questions and methods

Research questions

In this thesis, I address four research questions:

1. What is the healthcare burden of gastroenteritis in Australia?
2. What is the epidemiology of gastroenteritis in middle-aged and older adults?
3. What is the incidence of and risk factors for *Salmonella* and *Clostridium difficile* infection in middle-aged and older adults?
4. What are the complications of *Clostridium difficile* infection among people with inflammatory bowel diseases?

I address these research questions specifically through published studies that are reproduced as chapters in this thesis, as outlined below.

Research question 1: What is the healthcare burden of gastroenteritis in Australia?

To answer this research question, I analysed data collected from a national cross-sectional survey—the National Gastroenteritis Survey II (NGSII). The NGSII is a retrospective survey conducted across all Australian states and territories over a one year period of 2008–2009 to estimate the population burden of gastroenteritis in Australia. This dataset allowed me to produce nationally representative estimates of the healthcare utilisation and lost productivity due to gastroenteritis in Australia (Chapter 4).

Research question 2: What is the epidemiology of gastroenteritis in middle-aged and older adults?

To answer this research question, I analysed data collected from a large-scale population-based cohort study—the 45 and Up Study—with record linkage to multiple administrative databases. This allowed me to estimate the incidence of, and identify important risk factors for gastroenteritis hospitalisation in middle-aged and older adults living in the community (Chapter 5). In Chapter 6, I specifically examined the association between proton pump inhibitor (PPI) use and risk of all-cause infectious gastroenteritis and bacterial gastroenteritis hospitalisation within an Australian population-based sample, and investigated whether this association varied by different types and doses of PPI. In Chapter 7, I reviewed the literature regarding norovirus infection among residents of long-term care facilities (LTCFs) to identify potential strategies for infection management in LTCFs.

Research question 3: What is the incidence of and risk factors for Salmonella and Clostridium difficile infection in middle-aged and older adults?

In Chapter 8, I analysed data collected from the 45 and Up Study to estimate incidence and risk factors for laboratory-confirmed *Salmonella* infection and infection-related hospitalisation in middle-aged and older Australians. In this study, I also conducted supplementary analyses to estimate the incidence and examine risk factors of infection notification and hospitalisation by *Salmonella* Typhimurium and other *Salmonella* serotype.

In Chapter 9, I analysed data from the 45 and Up Study to estimate the incidence of *C. difficile*-related hospitalisation, quantify its association with

potential risk factors, and calculate the median length of hospital stay and in-hospital costs per admission with *C. difficile* infection (CDI) in middle-aged and older adults. Building upon this, I further described the burden of CDI in this cohort (Chapter 10). Specifically, I calculated the average length of hospital stay and cost per hospitalisation, as well as in-hospital death for CDI-associated hospitalisation.

Research question 3: What are the complications of Clostridium difficile infection among people with inflammatory bowel diseases?

To answer this research question, I conducted a systematic review and meta-analysis of studies examining the effect of CDI on the risk of colectomy among patients with inflammatory bowel diseases (Chapter 11).

Data sources

The National Gastroenteritis Survey II (NGSII)

In Chapter 4, I used data collected from the NGSII. The NGSII was a representative retrospective cross sectional survey of the Australian community, across all states and territories. NGSII was conducted by the OzFoodNet network in partnership with the Australian National University and the New South Wales Food Authority in 2008–2009. The primary aim of this survey was to estimate the burden of gastroenteritis in the Australian community.

The sample size for the NGSII was 7,578 respondents. As there are eight states and territories in Australia, it collected a sample that was representative at the state level. A stratified sample of respondents in each state and territory was

collected (Victoria, Northern Territory, Queensland, Western Australia, Southern Australia, Tasmania). New South Wales (NSW) and the Australian Capital Territory were grouped together and over-sampled to accommodate the NSW authority's interest in precise estimates of foodborne gastroenteritis.

Participants were recruited using random digit dialling of landline phone numbers over a twelve month period in 2008–2009. Specifically, the interviewers administered the computer-assisted telephone interview questionnaire to the person with the next birthday in the household to ensure randomisation. The person answering the telephone was asked about the age of household members, and permission to continue with the questionnaire was sought. If the selected respondent was under 15 years old, the parent/guardian was asked to answer on their behalf. If an adolescent was between 15 and 18 years old, permission was sought from the parent/guardian to ask the adolescent the questions. If the selected respondent was not at home, nine attempts were made to contact the person before moving on to the next selected household.

The NGSII questionnaire was similar to a survey conducted by OzFoodNet during 2001–2002, which was modelled on population surveys carried out by the Centers for Disease Control and Prevention in the USA [1]. The questions captured symptoms of diarrhoea/vomiting, symptom of respiratory illness, chronic illness, basic demographics, travel exposure, health care seeking behaviour, investigation and treatment practices, effect on work, reporting of outbreaks of gastroenteritis, and perceptions of outbreaks of gastroenteritis in nursing homes. The questionnaire was kept to 10–15 minutes duration, which has

been shown to increase completion rates for telephone-based surveys [2]. The completion rate for the NGSII was 49.1% (7,590/15,456).

The 45 and Up Study

Several papers in this thesis (Chapter 5, 6, 8, 9 and 10) used data collected from a large-scale Australian cohort study of middle-aged and older Australians—the 45 and Up Study. The primary aim of the 45 and Up Study was to provide timely and reliable information on a wide range of exposures and outcomes of public health importance for the aging population.

Individuals aged 45 and over who lived in NSW, Australia between January 2006 and December 2008 were randomly sampled from the Medicare Australian enrolment database. This database captures address information of all citizens and permanent residents of Australia, some temporary residents and refugees. There was oversampling of individuals living in rural regions and those aged over 80 years. Individuals could also volunteer to participate in the study by calling the study helpline and requesting an invitation pack.

Eligible individuals were mailed an invitation to participate, an information leaflet, the study questionnaire and consent form and a reply paid envelope during 2006–2008. Individuals participated in the study by completing the questionnaire and consent form, and mailing the completed documents to the study coordinating centre. Data from the completed questionnaires were scanned electronically and stored as images.

The baseline questionnaire for the study broadly includes: measures of health status, such as past medical and surgical history; known risk factors for major causes of morbidity and mortality; likely confounding factors; potential mediators of risk and some novel factors, such as dietary preference (Appendix 1).

The final sample size of the 45 and Up study was over 270,000 persons, comprising approximately 10% of the general population in the target age range in NSW. The overall response rate to the mailed invitations was estimated to be 17.9% (95% CI 17.8–18.1), although the exact response rate is difficult to determine as some people may not have received the invitation if their address was incorrect in the Medicare Australia database. About 1.3% of people entered the study by contacting the helpline without receiving an invitation. Details of the study methods are published elsewhere [3].

The sample size of the 45 and Up Study in this thesis included participants who had not withdrawn at the time of data extraction. Table 3.1 summarises the baseline characteristics of the 45 and Up Study participants analysed in this thesis. Overall, 53.6% of participants were women. Participants ranged in age from 45 to 106.2 years old, with a mean age of 61.8 years (standard deviation (SD): 11.1 years) for women and 63.8 years (SD: 11.1 years) for men.

There was considerable diversity in terms of location of residence and income. About 44.1% of women and 46.2% of men were resident in major cities, 35.8% of women and 34.3% of men were resident in regional areas, and 20.1% of women and 19.5% of men were resident in outer regional/remote areas. Around

29.3% of participants reported a gross household income less than AUD 30,000 per year, which was ≤60% of the median gross household income in NSW [4]. Overall, 7.2% participants were current smokers and 67.6% reported drinking alcohol at least weekly; 14.6% participants reported having excellent health and 2.1% reported poor health (Table 3.1).

Table 3.1. Baseline characteristics of the participants, 2006-2008, the 45 and Up Study, New South Wales, Australia

Characteristic	Women N=143,201 (%)	Men N=123,928 (%)	Total N=267,129 (%)
Age group (years)			
45-54	32.4	25.4	29.2
55-64	32.7	31.5	32.2
65-74	20.0	23.9	21.8
75-84	11.7	16.3	13.8
≥85	3.2	2.9	3.1
Household income (AUD/year)			
<20,000	20.6	18.7	19.7
$20,000-29,999	9.2	9.9	9.6
$30,000-39,999	7.5	8.4	7.9
$40,000-49,999	6.7	7.8	7.2
$50,000-69,999	9.7	11.3	10.4
$70,000 or more	19.9	27.7	23.5
Prefer not to answer	20.1	12.2	16.5
Missing/invalid	6.3	4.0	5.2
Region of residence			
Cities	44.1	46.2	45.0
Inner regional	35.8	34.3	35.1
Outer regional/remote/very remote	20.1	19.5	19.9
Tobacco smoking			
Never	64.4	48.4	57.0
Current	6.9	7.6	7.2
Past	28.2	43.4	35.2
Missing/invalid	0.5	0.6	0.2
Alcohol drinks per week			
None	40.4	23.2	32.4
≤14	51.1	51.8	51.4
>14	6.0	23.4	14.1
Missing/invalid	2.5	1.6	2.1
Body mass index (kgm^{-2})			
<18.5	1.7	0.7	1.2
18.5-24.9	39.0	28.9	34.3
25-29.9	29.7	43.9	36.3
≥30	28.6	25.6	27.3
Missing/invalid	1.0	0.9	0.9
Self-rated health			
Excellent	16.1	12.8	14.6
Very good	36.3	34.8	35.6
Good	30.9	34.5	32.6
Fair	10.8	12.5	11.6
Poor	2.0	2.3	2.1
Missing/invalid	3.9	3.1	3.5

Administrative health data

Administrative databases generally originate from systems that are either mandated by law for social or public health reasons, such as disease registers, or those that finance health care to patients, such as claims data. Using linked population health data can provide an efficient method to capture important

events of interest on a large number of study participants, and to assess risk factors and associations between outcomes that are independently collected. The following administrative databases were linked to the 45 and Up Study and used in this thesis.

Hospital records

The NSW Admitted Patient Data Collection (APDC), formerly named the Inpatient Statistics Collection, is a clinical and administrative database documenting episode-related information for all patient admissions to NSW hospitals [5]. The database was initially created in 1981 by the NSW Health Department to monitor the utilisation of NSW hospital services under the *Health Administration Act 1982* for public hospitals, and the *Private Hospitals and Day Procedures Centres Act 1988* and *Health Insurance Act 1973* for private hospitals [5]. This database covers information on patient demographics, source of referral to the service, location referred to on separation, diagnoses, procedures, external causes, activities when injured, places of occurrence and morphologies.

Clinical information is coded using the International Classification of Disease version 10 Australian modification (ICD-10-AM) [6] and the Australian Classification of Health Interventions (ACHI) [7]. For each coded episode of care, there is a principal diagnosis and up to 54 additional diagnoses contributing to the episode of care. All separations are allocated to a diagnosis code based on the principle diagnosis.

Hospital admissions may be coded with more than one episode within the database. The episodes of care end with the discharge, transfer, or death of a patient. Therefore if a patient is transferred to another service due to a change in on-going clinical requirements during the stay in hospital, then this patient will have another entry in the database. Patients who have multiple admissions, and within this have multiple episodes of care, may have a large number of individual records within the database [5].

For the purpose of follow-up of the 45 and Up Study participants for disease outcomes, the data of particular interest in the APDC database include basic demographics, the admission date, discharge date, episode number, modes of separation, length of stay, all the diagnosis codes and codes of diagnosis related groups.

Disease registers

The NSW Notifiable Conditions Information Management System (NCIMS) is a confidential application used to manage the surveillance and reporting of notifiable diseases and conditions under the NSW *Public Health Act 2010* [8]. Under the *Public Health Act 2010*, laboratories, hospitals, medical practitioners, schools, and child care centres must notify NSW Health or their local public health unit of diagnoses of certain infectious diseases. These notifications are compiled into the NCIMS.

The NCIMS database contains a record of all notifiable diseases in NSW. Commonly notified enteric diseases include salmonellosis, outbreaks of probable

foodborne disease, outbreaks of probable viral gastroenteritis and listeriosis. Notably, campylobacteriosis is currently notifiable in all Australian states and territories, except NSW. Sporadic, or non-outbreak cases of norovirus infection are not notifiable in Australia. Notification data provided include disease code, date of onset, confirmation methods, the type of specimen used for confirmation, date of notification to the relevant health authority, basic demographics, and postcode of residence [8]. In 2009, there were 6,575 enteric disease notifications to the NCIMS [9].

The NSW Cancer Registry databases documents records of cancer patients in NSW. This database contains demographic, clinical and death details for people diagnosed or treated with cancer in NSW. It also includes these details for residents of NSW diagnosed with cancer in other Australian states and territories since 1972. Notification of new cancer cases and cancer deaths is required under the *Public Health Act 2010* [10].

The Births, Deaths and Marriages

In Australia, these records are held by the registrar generals of births, deaths and marriages. The NSW Register of Births, Deaths, and Marriages (RBDM) includes a record of all births, marriages and deaths in NSW and the date of the event. For the purpose of follow-up of the 45 and Up Study participants to identify deaths, only death records were requested. Death records are based on medical certificates of cause of death and death information

documents. Cause of death information was only available for a small period of follow-up at the time of this thesis, and therefore was not used.

Claims data

In Australia, claims data are generated by the Pharmaceutical Benefits Scheme (PBS), one of the largest systems run by Medicare Australia. It is a national government system that subsidises the cost of medicines, most of which are dispensed by pharmacists. The PBS database documents information about subsided dispensed prescription drugs for the Australian population [11]. For medications listed on the PBS, consumers contribute a co-payment towards the cost, and the Australian Government pays the remainder. People with concession cards pay a smaller copayment (AUD 6 in 2014) than the general population. Concession card holders include people with a Pensioner Concession Card, a Commonwealth Senior Health Card or a Health Care Card [12].

Before July 2012, the PBS database did not capture dispensed medications that were below the consumer copayment level. Since no medication cost less than the concessional copayment, the PBS dataset captured all medications dispensed to concession card holders in the time period covered by this thesis.

Record linkage

In 1946, the term 'record linkage' was introduced by Dr Halbert Dunn to designate the linking of various records of an individual's life [13]. In Australia, data linkage has been used for health and medical research in Western Australia since the 1970s. In 1995, the first Australian data linkage system—the Western

Australian Data Linkage System—was established by Professor D'Arcy Holman and colleagues. Ten years later, the Centre for Health Record Linkage (CHeReL) was established to facilitate the linkage of routinely collected health and administrative databases in NSW in order to conduct health based research [14].

Probabilistic record linkage

Currently, pervasive unique individual identifiers are not available for routine data linkage of administrative databases in Australia. Partial identifiers, such as name, date of birth, address and postcode are subject to error, truncation and incompleteness. Therefore, probabilistic methods have been widely used to conduct linkage of survey data to multiple administrative databases. Probabilistic linkage is a process of linking records through the calculation of a linkage likelihood or probability weights, adjusting for data entry errors, and incomplete and missing data. These methods attempt to simulate human reasoning by comparing multiple elements within the records [15].

The basic steps in probabilistic linkage include pre-processing, blocking, field comparison, classification of weights and grouping, and post processing [16, 17]. Prior to matching, records are assembled into common forms that allow comparisons of fields. Standardisation, parsing and phonetic coding are commonly used to facilitate matching in pre-processing. Theoretically, the idea of record comparison would be to compare each record from one database against each record from another database. In practice, this is impossible as for two databases X and Y, the product space X×Y will be too large to process,

especially for large-scale datasets. Therefore, blocking is useful to reduce the size of record pairs through in-block comparisons. After blocking, each field comparison returns a match weight, which is used to classify record pairs into matches, non-matches and possible matches. After the resolution of possible matches, record pairs are assigned a status of link or non-link, and incorporated into the record linkage system.

Data linkage of the 45 and Up Study

The NSW Centre for Health Record Linkage (CHeReL) links participants' information from the 45 and Up Study to multiple administrative databases using a privacy preserving model [18]. Under this model, CHeReL only holds the personal identifying information used to create a unique number (linkage key) for linkage, in most cases involving name, date of birth, sex and address. Other personal information and health data stay with the original database. CHeReL provides this linkage key back to the relevant data custodians. The data custodian then provides the approved health information with the linkage key for researchers to link records in order to conduct research. The process of record linkage, which requires access to personally identifying information, is completely separate from the data analysis.

Before starting this thesis, the data had been obtained from data custodians and linkage were completed by CHeReL as part of my co-supervisor Associate Professor Bette Liu's research project—identifying predisposing factors for, and the consequences of, common and emerging infectious diseases. This

project is funded by by National Health and Medical Research Council grant (Grant number: 1048180).

Figure 3.1 illustrates the timing and data sources of data linkage in the 45 and Up study. CHeReL used personally identifying information to create a linkage key that identifies where records for the same participant can be found in different databases. In this thesis, I used the linkage key—provided by CHeReL—to link the health data for each participant from the different databases before conducting analysis. With linked data, I was able to investigate the relationships between exposures measured in the baseline questionnaire and outcomes occurring over a period of time. Figure 3.2 shows the study period of linked data for analysis in this thesis.

Figure 3.1 Data sources and timing for data linkage of participants in the 45 and Up Study, New South Wales, Australia

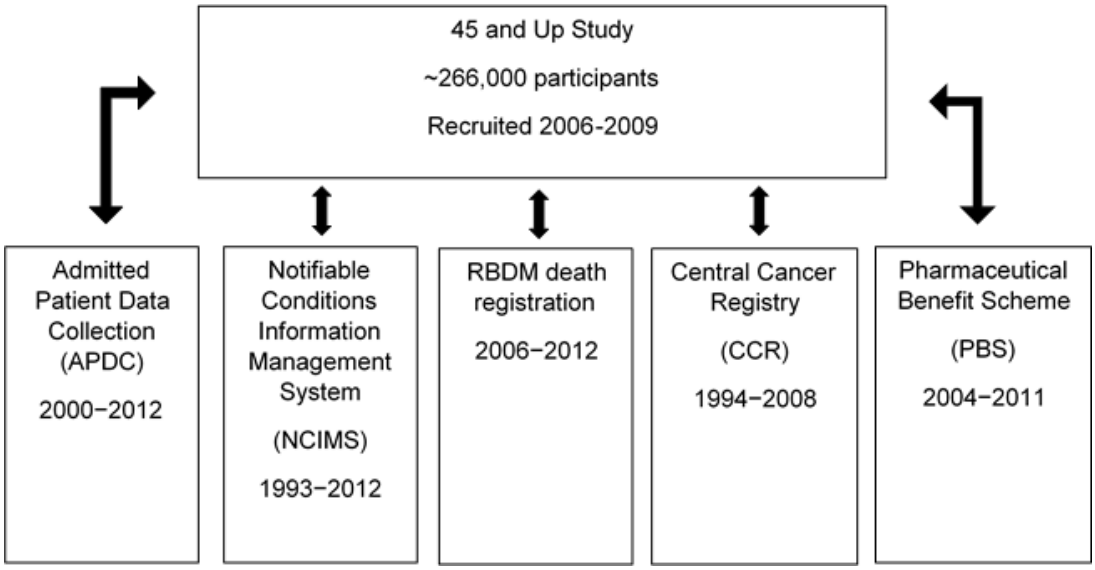
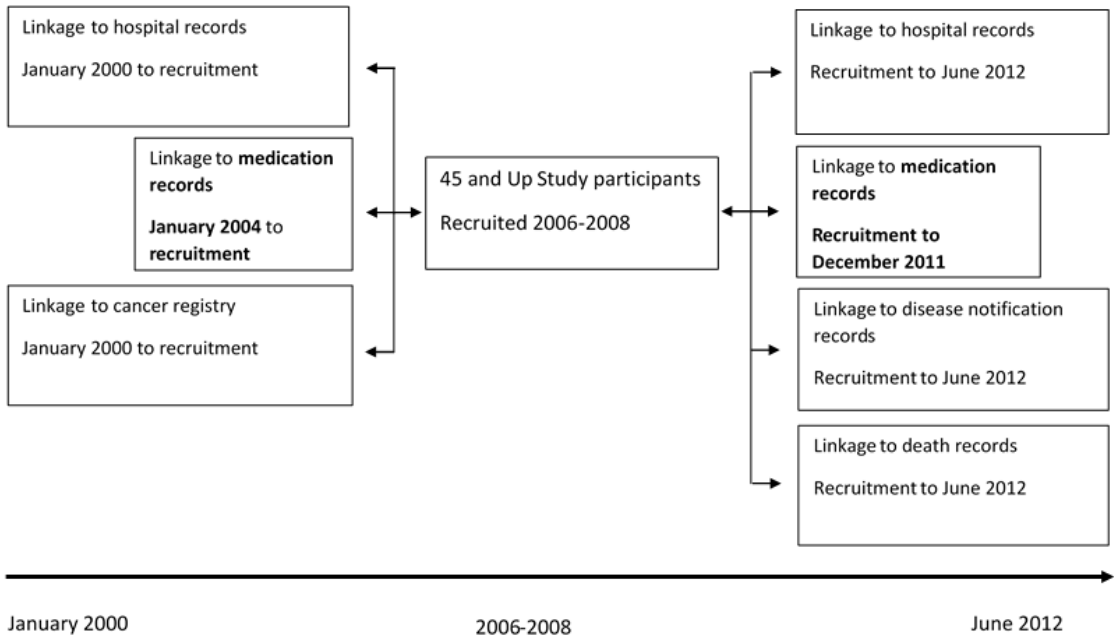


Figure 3.2 The study period of linked data for analysis in this thesis, the 45 and Up Study, New South Wales, Australia, 2000-2012



Data quality

For record linkage studies, the major technical issues are the proportion of incorrect links and missed links, and any biases in these errors. The implications of linkage errors on outcome measurements have been described previously [19]. At CHeReL, the quality of record linkage is assessed through detailed clerical review of a sample of record groups to calculate false positive rates. Error rates for the master linkage key are also estimated regularly, with false positive and false negative rates of <0.5% and <0.1%, respectively [14].

Although linked administrative data are an important source of outcome measurements, concerns have been raised regarding the quality of these datasets. Administrative data are primarily collected for funding and other administrative

purposes rather than health research. Therefore, residual confounding related to the nature of secondary analysis is a particular concern of administrative data. The limitations and challenges discussed below provide a general background for the datasets used in this thesis. Details of the quality of each dataset used in this thesis has been discussed in each chapter accordingly.

Measurement error is an important concern of studies using hospital data. In Australia, clinical coders currently use two classifications, ICD-10-AM and the Australian Classification of Health Interventions (ACHI), to record clinical documentation for each episode of care. The quality of coding is subject to the coder's knowledge of medical science and medical terminology, and the coding standards. While hospital records are generally considered accurate on operation coding, there are little data available regarding the accuracy of diagnosis coding in the APDC database. Internal audits are not publicly available, although studies assessing the quality of hospital discharge data have showed a generally high level of reporting specificities, indicating that population health datasets can be a reliable information source [20, 21].

Disease registers, such as the NCIMS data, which is based on laboratory testing, are reliable in general, although may have testing artefacts related to different types of laboratory testing methods. In addition, the notification database only included cases for which health care was sought, a test conducted and a diagnosis made followed by a notification to health authorities. Therefore it only represents a proportion of the total cases occurring in the community. Analysis using NCIMS data may lead to underestimates of disease burden.

Additionally, changes in reporting and testing practices could result in improved detection of notifications.

The PBS dataset provides detailed information about prescription and dispensing of government subsidised medications. However, like other administrative datasets, there are challenges in using PBS data for epidemiological research. These include incomplete data capture during the study period of this thesis, changes in medications listed on the PBS and changes in beneficiary status. These challenges need to be carefully considered and addressed when conducting research using PBS data.

In this thesis, most of the exposure variables were collected from the 45 and Up Study, which were based on self-report. Self-reported data are prone to information bias. Additionally, the 45 and Up Study was not designed specifically to examine risk factors for enteric infections. Consequently, this may lead to missing information on confounders or important risk factors.

Data analysis

Throughout this thesis, I used standard statistical methods, including descriptive analysis, logistic regression, survival analysis using traditional Cox regression and time varying analysis, and systematic review and meta-analysis. The methodology and statistical analysis discussed here provides a general background for the thesis. Details of more specific analyses are explained in the methods section of each of the following chapters.

General statistical consideration

In this thesis, most investigations involve quantifying the associations between exposures measured at the study recruitment and events occurring over a period of follow-up. Therefore, I used Cox proportional hazards regression models to conduct time to event analysis. Cox regression methods allowed me to model survival data and estimate the regression coefficients [22].

There are several methodological considerations when conducting analyses using Cox regression. The first is related to the choice of time-scale. Korn *et al* discussed the appropriate methods of analysing time-to-event data, in particular the choice of the time-scale in a proportional hazards regression of large-scale population data [23]. They found that compared to using time-to-event as the time-scale with baseline age as a covariate, using age as the time-scale provided more meaningful and less biased results [23]. Similarly, Thiébaut *et al* performed a simulation study to investigate the existence and magnitude of bias for different degrees of association between age and the covariate of interest, and confirmed that using age as the time-scale provided less biased estimates [24].

Model adequacy should be considered when conducting Cox regression. In applied settings, a fitted model must provide a valid summary of the analysed data. Therefore, a thorough assessment of model adequacy is essential to the interpretation and use of a fitted model. The common methods for assessing the adequacy of a proportional hazards model include: 1) examining residuals; and 2) testing the proportional hazards assumption [25].

In 1982, Schoenfeld proposed the first set of residuals for use with a fitted proportional hazards model, which later became known as 'Schoenfeld residuals' [26]. These are obtained by summing the residuals at a particular time point over individuals. Ten years later, Grambsh *et al* found that scaling the Schoenfeld residuals by their variance yielded residuals with greater diagnostic power than unscaled residuals [27]. Currently, most statistical software has implemented the scaled Schoenfeld residuals to check model fit. In this thesis, I used Stata to plot Schoenfeld residuals against time to evaluate model adequacy. A significant non-zero slope may indicate a poor model fit.

Examining the proportional hazards assumption is vital in analysis of survival data using Cox regression. One of the main assumptions of the proportional hazards model is proportionality, which means that the ratio of the hazard functions for two individuals with different sets of covariates is independent of the time scale. Violation of this assumption can lead to incorrect inferences. Therefore, it is essential to examine the proportional hazards assumption when considering Cox regression. There have been several methods proposed to test the assumption, including numerical goodness-of-fit statistics and graphical methods. Due to the limited statistical power of numerical statistics, researchers suggested graphical methods as a useful means to assess the proportional hazards assumption [28].

Last but not the least, it is important to incorporate risk adjustment when conducting observational studies. Risk adjustment is a statistical tool that adjusts for the association between one or more exposure variables and outcomes. In

most of my analyses, I used multivariate regression models to adjust simultaneously for a number of confounders. The most common confounders are sociodemographic variables, severity of illness and comorbid conditions. Failure to account for these variables can lead to confounding by indication that may obscure the true estimate.

References

1. Jones TF, Mcmillian MB, Scallan E, Frenzen PD, Cronquist AB, Thomas S, et al. A population-based estimate of the sunstantial burden of diarrhoeal disease in the United States; Food-Net,1996-2003. Epidemiol Infect. 2007;135(2):293-301.

2. Hall G, group tOw. Results from the national gastroenteritis survey 2001-2002. In: Australian National University NCEPH, editor. Canberra 2004.

3. Collaborators, 45andUpStudy. Cohort profile: the 45 and up study. Int J Epidemiol. 2008;37(5):941-7.

4. Australian Bureau of Statistics. Year Book Australia 2007. Canberra: Australian Bureau of Statistics; 2007.

5. NSW Health Department, Admitted Patient Data Collection [Internet]. 2008 [cited May 2014]. Available from: http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/1368.1Explanatory%20Notes1452007.

6. Roberts RF, Innes KC, Walker SM. Introducing ICD-10-AM in Australian hospitals. Med J Aust. 1998;169:S32-5.

7. Australian Classification of Health Interventions (ACHI) 8th edition [Internet]. [cited May 2014]. Available from: http://meteor.aihw.gov.au/content/index.phtml/itemId/514008.

8. National Notifiable Disease Surveillance System. [Internet]. 2015 [cited May 2016]. Available from: http://www.health.nsw.gov.au/epidemiology/Pages/notifiable-diseases.aspx.

9. Communicable Diseases Branch, NSW Department of Health. Year in review: communicable disease surveillance, NSW, 2009. NSW Public Health Bulletin. 2010;21:1-10.

10. NSW Cancer Registry [Internet]. 2016 [cited Aug 2016]. Available from: https://www.cancerinstitute.org.au/data-and-statistics/cancer-registries/nsw-cancer-registry.

11. Duckett SJ. Drug policy down under: Australia's pharmaceutical benefits scheme. Health Care Financ Rev. 2003;25(3):55-67.

12. Department of Health. About the PBS. Canberra: Commonwealth of Australia; 2015.

13. Dunn HL. Record linkage. Am J Public Health Nations Health. 1946;36(12):1412-6.

14. Centre for Health Record Linkage. [Internet]. 2014 [cited Aug 2014]. Available from: www.cherel.org.au.

15. Clark DE. Practical introduction to record linkage for injury research. Inj Prev. 2004;10(3):186-91.

16. Herzog TN, Scheuren FJ, Winkler WE. Data quality and record linkage techniques. New York, NY: Springer Science & Business Media; 2007.

17. Newcombe HB. Handbook of record linkage: methods for health and statistical studies, administration, and business. Oxford University Press, Inc.; 1988.

18. Kelman CW, Bass AJ, Holman CD. Research use of linked health data--a best practice protocol. Aust N Z J Public Health. 2002;26(3):251-5.

19. Blakely T, Salmond C. Probabilistic record linkage and a method to calculate the positive predictive value. Int J Epidemiol. 2002;31(6):1246-52.

20. Lain SJ, Roberts CL, Hadfield RM, Bell JC, Morris JM. How accurate is the reporting of obstetric haemorrhage in hospital discharge data? A validation study. Aust N Z J Obstet Gynaecol. 2008;48(5):481-4.

21. Henderson T, Shepheard J, Sundararajan V. Quality of diagnosis and procedure coding in ICD-10 administrative data. Med Care. 2006;44(11):1011-9.

22. Cox DR, Oakes D. Analysis of survival data: CRC Press; 1984.

23. Korn EL, Graubard BI, Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. Am J Epidemiol. 1997;145(1):72-80.

24. Thiebaut AC, Benichou J. Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. Stat Med. 2004;23(24):3803-20.

25. Hosmer DW, May S, Lemeshow S. Applied survival analysis. 2nd ed. Hoboken New Jersey: A John Wiley & Sons, Inc; 2008.

26. Schoenfeld D. Partial residuals for the proportional hazards regression model. Biometrika. 1982;69(1):239-41.

27. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika. 1994;81(3):515-26.

28. Hess KR. Graphical methods for assessing violations of the proportional hazards assumption in Cox regression. Stat Med. 1995;14(15):1707-23.

Chapter 4

Paper one: Healthcare utilization and lost productivity due to infectious gastroenteritis, results from a national cross-sectional survey Australia 2008–2009

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About This Chapter

This chapter sets the scene for the thesis. It emphasises the burden of gastroenteritis in Australia, providing estimates of the healthcare usage and loss of productivity due to gastroenteritis in the Australian community. Prior to publication of this paper, there had been limited estimates of the healthcare burden related to gastroenteritis in Australia. In this paper, I found that gastroenteritis resulted in a substantial burden on society, with in excess of 8.7 million days of lost productivity, and 5.5 million courses of medication used each year in Australia. While not all cases of gastroenteritis will present to a doctor or hospital due to the mild symptoms, gastroenteritis-associated healthcare utilisation and lost productivity can result in considerable costs to society. This chapter contributes to answering the research question: 'What is the healthcare burden of gastroenteritis in Australia?'. This paper has been published and is reproduced here with permission from Cambridge University Press.

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Healthcare utilization and lost productivity due to infectious gastroenteritis, results from a national cross-sectional survey Australia 2008–2009

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SUMMARY

The aim of this study was to estimate the healthcare usage and loss of productivity due to gastroenteritis in Australia using the National Gastroenteritis Survey II. In 2008–2009, 7578 participants across Australia were surveyed about infectious gastroenteritis by telephone interview. A gastroenteritis case was defined as a person experiencing $\geqslant 3$ loose stools and/or $\geqslant 2$ vomits in a 24-h period, excluding cases with a non-infectious cause for their symptoms, such as pregnancy or consumption of alcohol. Lost productivity was considered any lost time from full- or part-time paid work due to having gastroenteritis or caring for someone with the illness. Interference with other daily activities was also examined along with predictors of healthcare-seeking practices using multivariable regression. Results were weighted to obtain nationally representative estimates using Stata v. 13·1. Of the 341 cases, 52 visited a doctor due to gastroenteritis, 126 reported taking at least one medication for their symptoms and 79 cases reported missing $\geqslant 1$ days' paid work due to gastroenteritis. Gastroenteritis results in a total of 13·1 million (95% confidence interval 6·7–19·5) days of missed paid work each year in Australia. The indirect costs of gastroenteritis are significant, particularly from lost productivity.

Key words: Australia, healthcare utilization, infectious gastroenteritis, lost productivity.

INTRODUCTION

Gastroenteritis is a common illness, resulting in an estimated 15·9 million cases in Australia in 2010 [1]. While not all cases of gastroenteritis will present to a doctor or hospital due to the mild nature of symptoms for the majority of episodes, gastroenteritis-associated healthcare utilization and lost productivity can result in considerable costs to society [2, 3].

Gastroenteritis often interferes with daily activities, such as working, school attendance, and recreational activities. In particular, examining how much time is taken off from paid work to recover from gastroenteritis or care for someone else who is ill highlights the effect of gastroenteritis on lost productivity. This productivity loss can be very expensive and has been identified as the largest contributor to total costs for all gastroenteritis [3–6]. Lost productivity attributable to gastroenteritis can have a substantial burden on society due to its commonness.

In 2001, a nationally representative cross-sectional survey, the National Gastroenteritis Survey I (NGSI 2001), was undertaken to determine the population burden of infectious gastroenteritis in Australia [7]. The NGSI found that about 20% of people with gastroenteritis attended a medical practitioner and,

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of these, 20% submitted faecal specimens for testing [8]. In addition, gastroenteritis resulted in around 0·9 million prescriptions for antibiotics [8]. Robust estimates of healthcare-seeking behaviour can improve the understanding of the number of cases reported to public health surveillance systems and highlight the impact of gastroenteritis on the healthcare system.

In 2008–2009, we conducted the National Gastroenteritis Survey II (NGSII 2008) – a retrospective cross-sectional survey to identify the population burden of infectious gastroenteritis in Australia in that year. The methodology applied in NGSII was a repeat of NGSI to assess changes in the prevalence of gastroenteritis in Australia. In this paper we analyse healthcare system utilization, medication usage, and lost productivity for cases reporting gastroenteritis during NGSII.

METHODS

The NGSII was a retrospective cross-sectional computer-assisted telephone survey across all States and Territories of Australia during a 1-year period from February 2008 to January 2009 with a sample of 7578 individuals. The full methods for NGSII are described elsewhere [9]. Information on demographic characteristics, gastrointestinal and respiratory symptoms, duration of illness, illness risk factors, healthcare-seeking behaviour, medication usage, and interference of illness with daily life were included in the survey questionnaire. This paper is concerned with the data collected from cases on questions of healthcare-seeking behaviour, medication usage, and lost productivity due to gastroenteritis.

Case definition

The case definition for gastroenteritis used in our study was a respondent experiencing $\geqslant 3$ episodes of diarrhoea and/or $\geqslant 2$ episodes of vomiting in a 24-h period over the previous 4 weeks, excluding cases who identified a non-infectious cause for their symptoms, such as pregnancy or consumption of alcohol. As respiratory infections can result in gastrointestinal symptoms, an adjustment was made by applying a stricter definition if the person had concomitant respiratory symptoms, requiring $\geqslant 4$ loose stools and/or $\geqslant 3$ vomits in a 24-h period [10]. The number and duration of gastrointestinal symptoms were evaluated. Duration was calculated from the first to the last day of experiencing either diarrhoea or vomiting. Lost productivity was defined as any time lost from full- or part-time paid work due to having gastroenteritis, or caring for someone with the illness.

Analysis

To provide nationally representative results, post-stratification was applied to all analyses to adjust for known differences between the survey sample and the Australian population by weighting to the 2008 resident population age, sex and State from the Australian Bureau of Statistics. All estimates were based on the Australian population in 2008 (21·4 million persons). The method is described in detail elsewhere [9].

We calculated weighted proportions and estimated the number of cases nationally that sought health advice, took medications or submitted a stool for culture. Time lost from work and daily activities due to infectious gastroenteritis were examined in relation to demographic characteristics of survey respondents and the severity of their illness. Daily activities was defined as 'working, attending school, or recreational activities'.

To examine whether symptoms and duration of illness were associated with the likelihood of cases visiting a doctor, design-based logistic regression was used to calculate crude odds ratios of explanatory variables of all individual symptoms, duration of illness, age group, sex, income, and Indigenous status [11]. Those explanatory variables that were statistically significant were then entered into a backwards stepwise multivariable logistic regression process and those that significantly improved the fit of the model formed the final model. Statistical significance was taken at $P < 0{\cdot}05$. The Hosmer–Lemeshow test was used to check model fit [12].

Survival analysis was used to estimate the mean duration of illness to account for respondents with ongoing illness at the time of interview. Analyses were undertaken with Stata statistical package, version 13·1. The 'svyset' commands in Stata was used to account for survey design and post-stratification to the Australian population [13].

Ethical considerations

Verbal consent was obtained from all participants and from parents and guardians on behalf of children during the interview. Where the respondent was a child aged <15 years, questions were answered by their carer. Adolescents aged 15–17 years answered questions themselves following consent from their parents or guardians. The study and consent procedures were approved by the ethics committees of the Australian Government Department of Health, the Australian National University and the NSW Cancer Council.

Table 1. *Age and sex distribution of survey respondents and cases with gastroenteritis, Australia, 2008–2009*

Variables	No. of respondents (weighted %) ($n = 7578$)	No. of respondents with gastroenteritis (weighted %)	Weighted proportion of cases by groups (%)
Age group (years)			
0–4	249 (6·4)	42 (6·3)	12·1
5–9	249 (6·3)	16 (4·4)	6·4
10–19	497 (13·4)	20 (12·8)	5·6
20–29	507 (14·1)	47 (15·6)	9·1
30–39	802 (14·3)	53 (15·4)	6·1
40–49	1064 (14·3)	54 (16·0)	6·1
50–59	1374 (12·6)	52 (12·4)	3·5
60–64	755 (5·3)	25 (4·3)	2·7
⩾65	2081 (13·3)	32 (12·9)	1·2
Sex			
Male	3024 (49·7)	142 (47·6)	6·2
Female	4554 (50·3)	199 (52·4)	5·2

RESULTS

Of 7578 respondents in the NGSII survey, 555 respondents reported experiencing diarrhoea or vomiting in the 4 weeks prior to interview, with 341 meeting the case definition for infectious gastroenteritis. Reporting of recent gastroenteritis episodes was highest in children aged <5 years (Table 1).

Health-seeking behaviour

Overall, 123 cases presented their illness to a health professional, of which doctors and pharmacists were the health professionals most frequently seen. There were 52 cases visiting a doctor, of these, 11 cases submitted a stool sample for testing. When weighted to the Australian population by age, sex, and State, there were an estimated 2·7 million [95% confidence interval (CI) 1·8–3·6] people visiting health professional due to gastroenteritis in Australia annually, with 517 219 (95% CI 119816–914621) stool tests submitted in one year (2008–2009).

Factors associated with cases visiting a doctor

In univariate analysis, age, sex, household income, Indigenous status, diarrhoea, blood in stool, nausea, loss of appetite, aches, headache, stiff neck and vomiting were not found to be statistically significantly associated with visiting a doctor. Earache, stomach cramps, respiratory symptoms, fever, and the duration of illness were significantly associated with cases visiting a doctor for gastroenteritis, and were therefore entered into the backward stepwise regression building. In the final model, having stomach cramps, fever, respiratory symptoms, and duration of illness were significantly associated with cases visiting a doctor (Table 2). Cases with stomach cramps were less likely to seek medical consultation [adjusted and weighted odds ratio (aOR) 0·3, $P = 0·001$], while cases with fever were more likely to visit a doctor for their illness (aOR 2·5, $P = 0·01$). Cases symptomatic for 3 or 4 days were more likely to see a doctor compared to those who were ill for 1 or 2 days (aOR4·2, $P < 0·001$, as were those ill for ⩾5 days (aOR 6·1, $P < 0·001$).

Overall, 12 of the cases that visited a doctor were asked to submit a stool specimen. Of those who were asked, 11 out of 12 cases submitted a specimen. Duration of ⩾5 days was associated with higher likelihood of a case submitting a specimen (OR 4·6, $P = 0·08$).

The Hosmer-Lemeshow goodness-of-fit test showed a good fit for the final logistic model ($P = 0·8$)

Medications for gastroenteritis

Of the 341 cases, 126 (weighted 32·2%) reported taking at least one medication to treat or relieve symptoms and of these, 19 (21·0%) received a prescription from a doctor, 28 (18·6%) chose medication based on a chemist's advice, 41 (29·3%) chose medication without professional advice, and 19 (9·2%) used left-over medication or received it from a friend. Half of cases reporting medication usage for gastroenteritis reported taking only one medication, while 16 cases reported taking at least three types of medication.

Overall, 64 (15·5%) cases took antidiarrhoeal medication for their conditions. Sixty respondents reported the generic or brand name of the antidiarrhoeal medication, among which the main type reported was loperamide. Additionally, 68 (15·6%) respondents with gastroenteritis used a painkiller for their conditions, and the main types reported were paracetamol and non-steroidal anti-inflammatory drugs (NSAIDS). Of all cases, eight (1·8%) reported antibiotic usage and five of those provided the specific brand name, including four courses of penicillin usage and one course of augmentin.

Extrapolating data to the Australian population, there were an estimated 5·5 million (95% CI 4·4–6·6) courses of medication usage for gastroenteritis each year, including 2·1 million (95% CI 1·4–2·8) courses of antidiarrhoeals (Table 3).

Table 2. *Unadjusted and adjusted odds ratios and 95% confidence intervals for 341 cases to visit a doctor by symptoms of gastroenteritis and duration of illness (weighted to the Australian population by age, sex, and State), Australia, 2008–2009*

Variable	Cases reporting ($n = 341$)	No. visiting a doctor ($n = 52$)	Univariate OR (95% CI)	Adjusted OR (95% CI)*
Symptoms				
Diarrhoea	298	46	1·1 (0·4–3·0)	
Blood in stool	12	2	1·4 (0·3–7·2)	
Stomach cramps	216	28	0·5 (0·2–0·8)	0·3 (0·1–0·6)
Nausea	225	37	2·2 (1·0–4·9)	
Loss of appetite	256	43	3·4 (1·0–10·7)	
Fever or chills	151	34	3·2 (1·7–6·2)	2·5 (1·5–5·2)
Muscle/body aches	135	24	1·9 (1·0–3·6)	
Headache	142	23	0·8 (0·4–1·6)	
Stiff neck	51	10	0·9 (0·4–2·3)	
Respiratory symptoms	87	26	3·6 (1·8–7·0)	2·3 (1·0–5·4)
Earache	22	10	3·2 (1·2–8·1)	2·7 (0·7–9·8)
Vomiting	161	32	1·6 (0·9–2·9)	
Gastroenteritis duration				
1–2 days	215	18	Reference	
3–4 days	75	19	5·3 (2·6–10·8)	4·2 (1·9–9·2)
$\geqslant 5$ days	51	15	5·2 (2·0–13·5)	6·1 (2·3–16·4)

OR, Odds ratio; CI, confidence interval.
* Final model after backward stepwise logistic regression for significant variables, with stomach cramps, fever or chills, respiratory symptoms, earache, and duration of illness remaining in final model.

Table 3. *Number and proportion of cases taking medication for symptoms of gastroenteritis and median duration of treatment, Australia, 2008–2009*

Medication type	Number taking medication (weighted %) ($n = 341$)	Median duration of treatment (days)	Weighted number of medication taken/year in Australia (million) (95% CI)
Antidiarrhoeal	64 (15·5)	2	2·1 (1·4–2·8)
Painkiller	68 (15·6)	2	3·4 (2·5–4·3)
Anti-nausea	29 (7·1)	2	1·3 (0·7–1·9)
Anti-cramps	11 (2·1)	3	0·4 (0·05–6·5)
Antibiotics	8 (1·8)	8	0·5 (0·06–1·0)

CI, Confidence interval.

Missed work or activities

In the 4 weeks prior to the survey, 189 (56·7%) of cases were in full- or part-time employment, 103 (33·5%) of cases either being retired, students or on home duties, 38 (11·1%) of cases were too young to attend school, and the rest were either unemployed or unable to work. Gastroenteritis had a considerable impact on cases' work, school and recreational activities in the survey, with 230 (68·9%) reporting that their illness interfered with daily activities for a median of 1 day. Forty-seven of the 230 respondents were answering on behalf of their child. Seventy-nine (23·3%) cases reported missing at least 1 day of paid work in the 4 weeks prior to the interview, the median being 2 days (range 1–28 days) missed for their own illness. Twenty-nine (7·1%) cases reported that someone else cared for them (13 respondents) or their child (16 respondents), and missed a median of 2 days (range 1–21 days) paid employment of the carers.

Based on these results, gastroenteritis results in an estimated 13·1 million (95% CI 6·7–19·5) missed days of productivity in Australia annually. This comprised 8·7 million (95% CI 5·2–12·2) missed days of employment for people with their own illness, and 4·4 million (95% CI 1·5–7·4) missed days of employment for people who cared for someone else experiencing gastroenteritis.

DISCUSSION

Gastroenteritis results in a substantial burden in Australia with over a million days of lost productivity each month, either for people suffering from gastroenteritis or caring for someone who was ill.

Additionally, there were an estimated 2·7 million gastroenteritis-related medical consultations each year in Australia. Disease-associated medication usage, consultation of doctors and lost daily activities are considerable.

The BEACH dataset on General Practice consultations (Bettering the Evaluation of Care of Health) shows that gastroenteritis is one of the most frequently managed problems in general practice during 2008/2009 in Australia [14]. The proportion of cases who visited health professionals (36·1%) found in this study was similar to the proportion reported in New Zealand and France [15, 16], but lower than the proportion observed in a Chinese study [17]. These differences may reflect important differences in the healthcare system in the studied countries.

We found that approximately 13·4% of people experiencing gastroenteritis visited a doctor for their illness, suggesting that most cases are mild. Of all the respondents with gastroenteritis, only 3·1% provided a stool sample, which is similar to what was reported in the NGSI study, and these results are within the range for other high-income countries (2–8%) [8, 18, 19]. Our study also highlights that increasing duration of gastrointestinal illness was associated with cases presenting to a doctor. However, the small number of cases with some characteristics, such as blood in stool, meant we were unable to detect significant associations between these variables and cases visiting a doctor for gastroenteritis.

The percentage of cases taking medication for gastroenteritis in Australia (37·0%) is similar to New Zealand, but lower than that reported from France, Canada, and China [16, 17, 20]. Additionally, only 2·3% cases reported antibiotic usage for their illness, which is lower than reported from the NGSI study where about 5% of cases were prescribed antibiotics for gastroenteritis [21]. However, as the confidence intervals of these results overlap with the small numbers of cases reporting antibiotic usage, comparisons between the results are uncertain. The relatively low proportion of cases using antibiotics in our study may suggest a decrease in systemic antibacterial prescribing rates in Australia. It is appropriate that there is a low rate of empirical treatment of gastroenteritis with antibiotics in this country. People with gastroenteritis rarely benefit from antibiotic treatment [22], but antimicrobial therapies are still recommended for severe bacterial infections causing gastroenteritis.

In this study, we estimated that there are 13·1 million days of lost employment due to gastroenteritis annually. Our estimate is much higher than reported in the NGSI study, which estimated six million days of lost paid work due to gastroenteritis in Australia in 2001 [8]. This may be due to a change to questions to try to improve this variable, which probably influenced the results. While gastroenteritis is often mild, it leads to substantial lost productivity in terms of days off work for illness or caring for others. In Australia, estimated cost of lost productivity of foodborne illness due to gastroenteritis was responsible for 68% of all costs in 2004 [23]. Internationally, cost-of-illness studies have reported that lost productivity, including missed paid employment by sick individuals and employment missed by caregivers, accounted for the majority of indirect costs of gastroenteritis [5, 24].

Our study has several limitations, including the self-reported nature of the survey. However, similar symptom-based case definitions have been used previously, and therefore, comparison between studies is possible. The participation rate for the survey (49%) was less than the previous survey in Australia in 2001, but comparable to that obtained in other recent cross-sectional surveys [20, 25, 26]. Elderly females comprised the largest proportion of the respondents in our study, but we tried to minimize the impact of the skewed sample by weighting data to the Australian population to adjust for known difference between the sample and the target population. Based on the weighted data, we estimated that there were approximately 10·5 million employed persons (data not shown) in Australia during 2008/2009, which is similar to what was reported in the census data (10·6 million employed people) [27]. Therefore, post-stratification weighting by age/sex/State in our study should provide comparable estimates to the Australian population.

CONCLUSION

Gastroenteritis incurs considerable resource usage, and substantial costs for employers in Australia. The indirect costs of gastroenteritis are significant, particularly from lost productivity. It is important that we better understand the determinants of healthcare-seeking behaviour, medication usage for people with gastroenteritis, and submission of specimens for testing to address the costs of gastroenteritis. These estimates for Australia have important implications for addressing the burden of this illness and the impact on the healthcare system.

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DECLARATION OF INTEREST

None.

REFERENCES

1. **Kirk M, *et al.*** Foodborne illness in Australia: annual incidence circa 2010. Canberra: Australian Government Department of Health, 2014.
2. **Doorduyn Y, W Van PeltAH Havelaar.** The burden of infectious intestinal disease (IID) in the community: a survey of self-reported IID in The Netherlands. *Epidemiology and Infection* 2012; **140**: 1185–1192.
3. **Abelson P, Potter-Forbes M, Hall G.** The annual cost of foodborne illness in Australia. Canberra, Department of Health & Ageing, 2006.
4. **Friesema IH, Lugner AK, van Duynhoven YT.** Costs of gastroenteritis in the Netherlands, with special attention for severe cases. *European Journal of Clinical Microbiology & Infectious Disease* 2012; **31**: 1895–1900.
5. **Henson SJ, *et al.*** Estimation of the costs of acute gastrointestinal illness in British Columbia, Canada. *International Journal of Food Microbiology*; **127**: 43–52.
6. **Majowicz SE, *et al.*** Burden and cost of gastroenteritis in a Canadian community. *Journal of Food Protection* 2006; **69**: 651–659.
7. **Hall GV, *et al.*** Frequency of infectious gastrointestinal illness in Australia, 2002: regional, seasonal and demographic variation. *Epidemiology and Infection* 2006; **134**: 111–118.
8. **Hall G.** Results from the national gastroenteritis survey 2001–2002, Australian National University, NCEPH Working Paper Number 50, Canberra, 2004.
9. **Chen Y, Kirk M.** Incidence of acute respiratory infections in Australia. *Epidemiology and Infection* 2014; **142**: 1355–1361.
10. **Hall G, *et al.*** Estimating foodborne gastroenteritis, Australia. *Emerging Infectious Diseases* 2005; **11**: 1257–1264.
11. **Hosmer Jr. DW, Lemeshow S.** *Applied Logistic Regression*. John Wiley & Sons, 2004.
12. **Archer KJ, Lemeshow S, Hosmer DW.** Goodness-of-fit tests for logistic regression models when data are collected using a complex sampling design. *Computational Statistics & Data Analysis* 2007; **51**: 4450–4464.
13. **StataCorp LP.** *Stata Survey Data Reference Manual*, release 9, College Station, Texas: Stata Press Publication, 2005.
14. **Britt H, *et al.*** General practice activity in Australia, 2008–2009. Canberra: AIHW 2009; General practice series no. 25. Cat. no. GEP 25.
15. **Adlam S, *et al.*** Acute gastrointestinal illness in New Zealand: a community study. *Epidemiology and Infection* 2011; **139**: 302–308.
16. **Van Cauteren D, *et al.*** Burden of acute gastroenteritis and healthcare-seeking behaviour in France: a population-based study. *Epidemiology and Infection* 2012; **140**: 697–705.
17. **Chen Y, *et al.*** Burden of self-reported acute gastrointestinal illness in China: a population-based survey. *BMC Public Health* 2013; **13**: 456.
18. **Scallan E, *et al.*** Acute gastroenteritis in northern Ireland and the Republic of Ireland: a telephone survey. *Communicable Disease and Public Health* 2004; **7**: 61–67.
19. **Kuusi M, *et al.*** Incidence of gastroenteritis in Norway – a population-based survey. *Epidemiology and Infection* 2003; **131**: 591–597.
20. **Scallan E, *et al.*** Prevalence of diarrhoea in the community in Australia, Canada, Ireland, and the United States. *International Journal of Epidemiology* 2005; **34**: 454–460.
21. **Hall G, *et al.*** Estimating foodborne gastroenteritis, Australia. *Emerging Infectious Disease* 2005; **11**: 1257–1264.
22. **Murphy M.** Guidelines for managing acute gastroenteritis based on a systematic review of published research. *Archives of Disease in Childhood* 1998; **79**: 279–284.
23. **Abelson P, *et al.*** The annual cost of foodborne illness in Australia. Canberra: Department of Health & Ageing, 2006.
24. **Van Den Brandhof W, *et al.*** Costs of gastroenteritis in The Netherlands. *Epidemiology and Infection* 2004; **132**: 211–221.
25. **Majowicz SE, *et al.*** Magnitude and distribution of acute, self-reported gastrointestinal illness in a Canadian community. *Epidemiology and Infection* 2004; **132**: 607–617.
26. **Imhoff B, *et al.*** Burden of self-reported acute diarrheal illness in FoodNet Surveillance areas, 1998–1999. *Clinical Infectious Diseases* 2004; **38**: S219–S226.
27. **Anon.** 2·07 Employment status including CDEP participation. AIHW (http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=10737420026). Accessed 10 July 2014.

Chapter 5

Paper two: High incidence of hospitalisation due to infectious gastroenteritis in older people associated with poor self-rated health

Chen Y, Liu B, Glass K, Kirk M. High incidence of hospitalisation due to infectious gastroenteritis in older people associated with poor self-rated health. *BMJ Open*. 2015;5:e010161. BMJ Publishing Group Ltd.

About This Chapter

In this chapter, I report the incidence and risk factors for hospitalisation related to gastroenteritis in middle-aged and older adults. Hospitalisation due to gastroenteritis imposes a significant burden on the health system in high income countries, particularly among the elderly. Prior to publication of this paper, Australian data on the incidence and risk factors of hospitalisation with all-cause infectious gastroenteritis were limited. There had been a nation-wide study estimating the changes in hospitalisations for acute gastroenteritis in Australia, with a focus on rotavirus. However, risk factors among older adults remained unknown. This chapter contributes to answering the research question: 'What is the epidemiology of gastroenteritis in middle-aged and older adults?'. This paper was published as an open access research article in *BMJ Open*.

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High incidence of hospitalisation due to infectious gastroenteritis in older people associated with poor self-rated health

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ABSTRACT

Objectives: To estimate the incidence and risk factors for gastroenteritis-related hospitalisations in older adults.

Design: Longitudinal cohort study.

Participants: The 45 and Up Study is a large-scale Australian prospective study of adults aged ≥45 years (mean 62.7 years) at recruitment in 2006–2009. Self-reported demographic, health and dietary information at recruitment from 265 440 participants were linked to infectious gastroenteritis hospitalisation data.

Outcome measures: We estimated the incidence of hospitalisation for infectious gastroenteritis, and calculated HRs using Cox regression, adjusting for sociodemographic, health and behavioural variables, with age as the underlying time variable.

Results: There were 6077 incident infectious gastroenteritis admissions over 1 111 000 person-years. Incidence increased exponentially with increasing age; from 2.4 per 1000 (95% CI 2.2 to 2.5) in individuals aged 45–54 years to 9.5 per 1000 (95% CI 9.2 to 9.8) in those aged 65+ years. After adjustment, hospitalisation due to infectious gastroenteritis was significantly more common in those reporting use of proton pump inhibitors (HR 1.6, 95% CI 1.5 to 1.7), and those with poorer self-rated health (HR 4.2, 95% CI 3.6 to 4.9).

Conclusions: Infectious gastroenteritis results in hospitalisation of approximately 1% of people ≥65 years old each year. Early recognition and supportive treatment of diarrhoea in older patients with poorer self-rated health may prevent subsequent hospitalisation.

Strengths and limitations of this study

- A large population-based cohort study examining risk factors for hospitalisation due to gastroenteritis, with record linkage to multiple databases.
- Prospectively collected data on a range of potential risk factors and confounders, allowing analysis of multiple variables.
- Self-reported exposure assessment at the recruitment.

INTRODUCTION

Gastroenteritis is one of the most common infectious diseases among humans and is a major cause of mortality in low-income and middle-income countries, particularly among children aged <5 years.[1] By contrast, the highest rates of mortality due to gastroenteritis in high-income countries occur in the elderly,[2] particularly people aged ≥75 years.[3]

The elderly are potentially at higher risk of some enteric infections, due to decreased gastric acidity, intestinal motility disorders, and a compromised immune system.[4 5] Despite this, the incidence of gastroenteritis in the elderly living in the community is lowest of any age group, with one Australian study estimating the incidence of people ≥65 years old at 0.33 (95% CI 0.24 to 0.42) episodes per person per year.[6]

However, older people may experience more severe symptoms and be more likely to require hospitalisation than younger people.[6] In Australia, people aged ≥65 years old were hospitalised with all-cause gastroenteritis at a rate of 20.2 per 1000 population annually between 2009 and 2010.[7] In the USA, hospitalisation due to all-cause gastroenteritis increased by ≥50% in all adults and elder age groups between 1996 and 2007, with norovirus estimated to be a significant contributor to the high rates among the elderly.[8] Furthermore, the total healthcare costs for gastroenteritis requiring hospitalisation are three times higher per adult patient compared with a child, due to increasing length of hospital stay and more common presentation with severe symptoms and complications.[9]

Hospitalisation due to infectious gastroenteritis imposes a significant burden on the

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health system in industrialised countries.[10] However, risk factors among older adults have not been well described. In this study, our objective was to estimate age-specific rates of hospitalisation due to infectious gastroenteritis, along with risk factors, in a large cohort of Australian adults.

METHOD

Study population

The Sax Institute's 45 and Up Study is a population-based cohort which recruited over 267 000 residents in the Australian state of New South Wales (NSW) who were aged 45 years and over between January 2006 and December 2008. Details of the study methods are published elsewhere.[11] Study participants were randomly selected from the national health insurance database (Medicare), and there was oversampling of those living in rural regions and those aged over 80 years. Participants completed a questionnaire at recruitment where they provided information on sociodemographics, lifestyle, dietary habits and their health (see https://www.saxinstitute.org.au/our-work/45-up-study/questionnaires/), and agreed to have their data linked to other administrative health records.

Questionnaire data from study participants were linked to the NSW Admitted Patient Data Collection (APDC) to identify hospitalisations due to infectious gastroenteritis, and the NSW Register of Births, Deaths and Marriages (RBDM) for deaths. The NSW APDC records demographic and episode-related information for all patient admissions to NSW hospitals, and includes the principal diagnosis responsible for the admission, up to 54 additional diagnoses contributing to the admission, and the date of admission. Clinical information is coded using the International Classification of Disease V.10 Australian modification (ICD-10-AM).[12] The NSW RBDM includes a record of all deaths in NSW and the date of death. Information on cause of death was not available at the time of analysis. We had complete APDC and RBDM records until 30 June 2012. The 45 and Up Study participant data, APDC and RBDM were linked independently of the study investigators by the NSW Centre for Health Record Linkage using personal information such as name, date of birth and sex, with false-positive and false-negative rates of <0.5% and <0.1%, respectively.[13]

Case definition

Participants were defined as having an incident hospitalisation with infectious gastroenteritis if they had a linked APDC record where the principal or a secondary diagnosis was coded with an ICD-10-AM code for either diarrhoea of determined aetiology-bacterial (A00-A05), parasitic (A06-A07), viral (A08) or undetermined aetiology-presumed infectious disease (A09), and the admission occurred following recruitment.

A gastroenteritis complication was defined if cases also had coded in their linked APDC record either fluid, electrolyte and acid–base disorders (ICD-10-AM E87 excluding fluid overload E87.7); shock (R57, excluding cardiogenic shock R57.0) or septicaemia (A41.9).

Statistical analysis

Participants who had a linked hospitalisation record for gastroenteritis in the 30 days prior to recruitment were excluded, as we wanted to exclude the possibility that any admissions due to gastroenteritis immediately following recruitment may be part of that same episode. To minimise the impact of pre-existing illness that may predispose individuals to infectious gastroenteritis, participants were also excluded if they had a linked hospitalisation record with a principal diagnosis code for any of the following: chronic bowel problems (non-infective enteritis and colitis K50-K52, irritable bowel syndrome K58), immunosuppressive disorders (D80-D89), or cancer (C00-C97) in the 5 years prior to study entry. Follow-up was calculated from the date of recruitment to the first date of admission for gastroenteritis, death or the end of database follow-up (30 June 2012), whichever came first. Incident gastroenteritis hospitalisation rates were calculated according to age (45–54, 55–64, 65–74, 75–84 or ≥85 years), sex, annual household income (<$A20 000, $A20 000–$A29 999, $A30 000–$A39 999, $A40 000–$A49 999, $A50 000–$A69 999, $A70 000 or more per year, or unknown), and region of residence (cities, inner regional or outer regional/remote/very remote) based on the Accessibility/Remoteness Index of Australia.[14]

HRs for hospitalisations due to gastroenteritis by sociodemographic, behavioural and health status variables were estimated using Cox proportional hazards models with age as the underlying time variable.[15] Regression models were adjusted for attained age (as this was the underlying time variable) and sex. Models were then adjusted for additional variables, including annual household income, region of residence, education (3 categories: university degree or higher, no university degree, or unknown), health status variables including self-rated health (excellent, very good, good, fair, poor or unknown), and body mass index (BMI: underweight (<18.5 kg/m^2), normal (18.5–24.99 kg/m^2), overweight (25–29.99 kg/m^2), obese (≥30 kg/m^2) or unknown), smoking (current, past, never or unknown), alcohol (none, 1–2 alcoholic drinks per day, >2 alcoholic drinks per day or unknown) and factors which have been previously identified as risk factors for gastroenteritis, including living in aged care facilities (yes, no or unknown), proton pump inhibitors (PPIs) usage (yes, no), frequency of chicken/poultry intake (none, at least once per week or unknown), frequency of seafood intake (none, at least once per week or unknown), egg consumption (ever, never), and fruit and vegetable intake (low, adequate or unknown). Fruit and vegetable intake was categorised as 'low' if fruit intake was less than two

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servings daily, or vegetable intake was less than five servings daily, and 'adequate' if fruit intake was at least two servings daily and vegetable intake at least five servings daily. Participants were classified as using PPIs if they answered yes to the question 'Have you taken any medications, vitamins or supplements for most of the last 4 weeks?', and crossed out either 'Nexium', 'Somac' or 'Losec, Acimax omeprazole' in the baseline questionnaire. Participants were classified as not using PPIs if they answered 'no' to the above question, or answered 'yes' to the above question but did not cross out any one of the above medications.

Missing values for variables were coded as separate categories in the model. The proportionality assumption was examined by plotting the Schoenfeld residuals against the time variable in each model.[16] Where this assumption was violated, we stratified exposure variables and compared findings under the two models. Sensitivity analyses were conducted by defining cases as only those with a principal hospital diagnosis of infectious gastroenteritis, and also including participants with a hospitalisation for chronic bowel problems, immunosuppressive disorders and cancer as a principal diagnosis, before recruitment. All analyses were carried out using STATA V.12.1.

RESULT

After excluding participants with a linked infectious gastroenteritis hospitalisation record 30 days prior to recruitment (n=45), participants with prior hospitalisations for specific illnesses associated with hospitalisations due to gastroenteritis (n=706), and confirmed linkage errors (n=44), there were 265 440 participants in the analysis, yielding a total of 1 111 223 years of follow-up (median 3.9 years per person). The mean age of study participants at recruitment was 62.7 years (SD 11.2), and 53.6% were women.

There were 6077 (2.3%) participants with at least one linked incident infectious gastroenteritis hospitalisation record during follow-up, of which 53.7% (3261/6077) had infectious gastroenteritis as the primary reason for admission (see online supplementary table S1). Among the 6077 participants with hospitalisation due to incident-infectious gastroenteritis, 58.6% (3560/6077) were referred to the hospital from the emergency department, and 26.8% (1631/6077) from a medical practitioner. The remaining cases were referred from a range of other sources, including community health, residential care and other hospitals. The mean length of hospital stay for the first hospitalisation among those 6077 participants admitted was 7.5 (SD 17.4) days; median length 3 days. Complications of gastroenteritis were reported in 11.0% (667/6077) of the hospitalisations due to gastroenteritis. Both the length of stay and the proportion with complications increased with increasing age (table 1). Among cases, 2.6% (160/6077) of the patients died within 30 days of hospital admission. Participants aged ≥65 years accounted for the majority of these deaths (90.6%, n=145) (table 1).

The crude incidence of hospitalisations due to gastroenteritis in the cohort was 5.5 per 1000 person-years (95% CI 5.3 to 5.6), which differed by age, sex, household income and region of residence. Incidence rose from 2.4 hospitalisations per 1000 (95% CI 2.2 to 2.5) person-years in individuals aged 45–54 years to 21.8 per 1000 (95% CI 20.2 to 23.6) in those aged 85+ years (p<0.001 for linear trend) (table 2). The rate of hospitalisations due to gastroenteritis was higher in women than in men (5.8 and 5.0 per 1000 person-years, respectively), but for both sexes, hospitalisation rates increased with decreasing household income (p<0.001). Rates were also greater among those living in cities than in other regions (6.1, 4.9 and 5.1 per 1000 person-years, respectively, in those living in cities, inner regional, outer regional; p=0.01) (table 2).

After full adjustment, participant sex, self-rated health, BMI and use of PPIs remained significantly associated with hospitalisation due to gastroenteritis (figure 1). The adjusted HRs (aHR) increased significantly with poorer self-reported health with risks >300% greater for those with poor versus those with excellent health (aHR 4.18, 95% CI 3.61 to 4.84). Hospitalisation due to infectious gastroenteritis was significantly more common in those reporting PPIs use (aHR 1.57, 95% CI 1.48 to 1.66). Compared with participants with a healthy BMI, the risk was significantly higher in the underweight (aHR 1.22, 95% CI 1.02 to 1.47) and the obese (aHR 1.08, 95% CI 1.01 to 1.15). We did not observe significant associations between hospitalisations due to gastroenteritis and food consumption, including fruit and vegetable intake, chicken/poultry intake, egg consumption and seafood consumption (figure 1).

Table 1 Proportion of total complications of gastroenteritis, and mean length of hospital stay by age group, 45 and Up Study

Age group (years)	Complications	Cases	Complications/ cases (%)	Mean length of hospital stay (days) (SD)	Death within 30 days of admission
45–54	56	785	7.1	4.0 (11.9)	4 (2.5)
55–64	118	1347	8.8	5.8 (15.3)	11 (6.9)
65–74	134	1484	9.1	6.2 (10.2)	25 (15.6)
75–84	260	1829	14.2	9.6 (15.8)	81 (50.6)
≥85	99	632	15.7	12.5 (34.5)	39 (24.4)
Total	667	6077	11.0	7.5 (17.4)	160

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Examining PPIs usage, we identified potential concerns with the proportionality assumption, however, a comparison of findings with a stratified version of the variable reassured us that PPIs usage could be included in the final Cox model unaltered (data not shown).

There were 3261 hospitalisations due to gastroenteritis, where a gastrointestinal infection code occurred in the principal hospital diagnosis field (see online supplementary table S1). Overall results were generally similar to the broader definition, with the rates of hospitalisations due to gastroenteritis increasing with increasing age (p<0.001 for linear trend). Male sex was significantly related to a reduced risk (aHR 0.75, 95% CI 0.69 to 0.81). Poorer self-rated health (aHR 3.45, 95% CI 2.80 to 4.26), obesity (1.12, 95% CI 1.02 to 1.22) and PPIs use (1.74, 95% CI 1.61 to 1.89) were all related to an increased risk of hospitalisations due to gastroenteritis. The sensitivity analysis, including cases with a linked record of hospital admission with pre-existing illness, showed little change in the HRs (n=266 146; 6783 incident hospitalisations due to gastroenteritis since baseline; see online supplementary table S2).

DISCUSSION

In this large population-based prospective study, hospitalisation due to infectious gastroenteritis was extremely common. We estimate that 1% of people aged ≥65 years old were hospitalised annually with gastroenteritis, and accounted for more than two-thirds of gastroenteritis-related complications. The incidence and length of hospital stay increased dramatically with increasing age. After adjustment, females, adults with poor general health, and those taking PPIs had a greater risk of being hospitalised with gastroenteritis.

The high rate of hospitalisations due to gastroenteritis in the elderly is consistent with increased rates of hospitalisation for infectious disease in this age group,[7 17] although the rate in people aged ≥65 years old was lower than a previous study examining hospitalisations due to gastroenteritis nationally due to all causes.[7] This may reflect differences in study design and case definitions. In particular, the national study included admission codes for conditions that were not necessarily infectious in nature, whereas, we attempted to include only infectious causes. The trend of increasing hospitalisations with age in our study is likely to be due to greater severity of illness in older patients,[18] and the increasing likelihood of severe consequences, such as dehydration, electrolyte imbalance and exacerbation of chronic conditions.[19]

Differences by sex were noted for hospitalisations due to gastroenteritis in all age groups. The pattern was previously reported in a US study, which used nationally representative data to investigate the trend of hospitalisations due to infectious disease for all ages.[20] One possible explanation for the higher rate in females may be inadequate family support and social care for older women, possibly resulting in greater use of hospital services. In this study, we observed a higher proportion of

Table 2 Crude incidence of hospitalisations due to gastroenteritis by characteristics in mid-age and older adults, the 45 and Up Study

Characteristics	Population	Cases/person-years	Incidence (95% CI)/1000 person-years	p Value
Age group (years)				<0.001
45–54	77 669	785/332 330	2.4 (2.2 to 2.5)	
55–64	85 487	1347/363 217	3.7 (3.5 to 3.9)	
65–74	57 678	1484/241 404	6.1 (5.8 to 6.5)	
75–84	36 470	1829/145 330	12.6 (12.0 to 13.2)	
≥85	8136	632/28 941	21.8 (20.2 to 23.6)	
Sex				<0.001
Female	142 313	3479/596 317	5.8 (5.6 to 6.0)	
Male	123 127	2598/514 905	5.0 (4.9 to 5.2)	
Household income ($A/year)				<0.001
<$A20 000	52 051	1855/214 088	8.7 (8.3 to 9.1)	
$A20 000–$A29 999	25 403	655/106 717	6.1 (5.7 to 6.6)	
$A30 000–$A39 999	21 005	433/88 693	4.9 (4.4 to 5.4)	
$A40 000–$A49 999	19 156	324/80 931	4.0 (3.6 to 4.5)	
$A50 000–$A69 999	27 751	397/117 755	3.4 (3.1 to 3.7)	
$A70 000 or more	62 605	655/263 829	2.5 (2.3 to 2.7)	
Unknown	57 469	1758/239 205	7.4 (7.0 to 7.7)	
Region of residence				0.01
Cities	119 449	3012/497 142	6.1 (5.8 to 6.3)	
Inner regional	93 299	1932/392 057	4.9 (4.7 to 5.2)	
Outer regional/remote/very remote	52 692	1133/222 023	5.1 (4.8 to 5.4)	
Total	265 440	6077/1 111 223	5.5 (5.3 to 5.6)	

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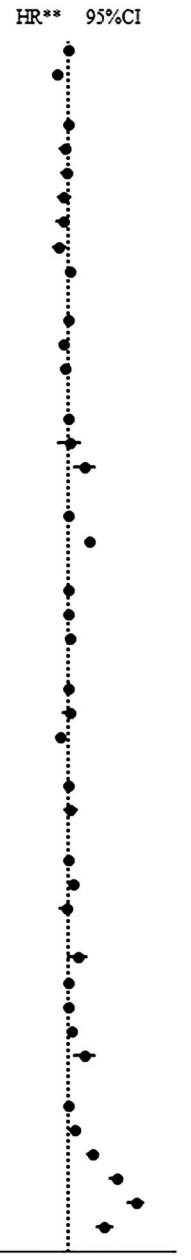
	Variables	Cases/ Population	HR*	95%CI		HR**	95%CI	
Sex	Female	3,479/142,313	1.00			1.00		
	Male	2,598/123,127	0.78	0.74	0.82	0.81	0.77	0.86
Household income	<$20000	1,855/52,051	1.00			1.00		
	$20000-29999	655/25,403	0.83	0.76	0.91	0.94	0.86	1.03
	$30000-39999	433/21,005	0.79	0.71	0.88	0.97	0.87	1.08
	$40000-49999	324/19,156	0.73	0.64	0.82	0.92	0.81	1.03
	$50000-69999	397/27,751	0.69	0.62	0.77	0.90	0.80	1.00
	+$70,000	655/62,605	0.60	0.54	0.66	0.83	0.75	0.92
	Unknown	1,758/57,469	1.96	0.90	1.03	1.05	0.99	1.13
Region of residence	Cities	3012/119,449	1.00			1.00		
	Inner regional	1,932/93,299	0.91	0.86	0.96	0.90	0.85	0.95
	Outer regional	1,133/52,692	0.97	0.91	1.04	0.94	0.88	1.01
Living in aged care facilities	No	5,903/261,770	1.00			1.00		
	Yes	78/1,221	1.31	1.04	1.65	1.01	0.81	1.28
	Unknown	96/2,449	1.54	1.26	1.89	1.42	1.16	1.74
Proton pump inhibitor usage	No	4,398/229,211	1.00			1.00		
	Yes	1,679/36,223	1.86	1.75	1.97	1.57	1.48	1.66
Fruit and vegetable intake	Low	3,792/175,551	1.00			1.00		
	Adequate	1,318/57,225	0.97	0.91	1.03	1.01	0.96	1.09
	Unknown	967/32,664	1.13	1.06	1.22	1.03	0.96	1.16
Chicken/poultry intake	None	4,395/207,044	1.00			1.00		
	≥1/week	294/11,087	1.12	0.99	1.26	1.05	0.93	1.19
	Unknown	1,388/47,309	0.86	0.81	0.92	0.84	0.79	0.89
Egg consumption	Ever	5,825/257,108	1.00			1.00		
	Never	251/8,325	1.21	1.07	1.38	1.06	0.94	1.21
Seafood intake	None	5,497/244,270	1.00			1.00		
	≥1/week	178/6,599	1.27	1.09	1.48	1.17	0.99	1.38
	Unknown	402/14,571	1.08	0.98	1.20	0.95	0.85	1.06
BMI	Underweight	127/3,222	1.45	1.21	1.74	1.22	1.02	1.47
	Normal	1,997/91,103	1.00			1.00		
	Overweight	2,034/96,430	1.06	1.00	1.13	1.00	0.94	1.07
	Obese	1,830/72,240	1.34	1.26	1.43	1.08	1.01	1.15
	Unknown	89/2,442	1.68	1.36	2.08	1.43	1.16	1.77
Self-rated health	Excellent	399/38,810	1.00			1.00		
	Very good	1,333/94,716	1.21	1.09	1.35	1.15	1.03	1.29
	Good	2,137/86,459	1.85	1.67	2.05	1.68	1.50	1.87
	Fair	1,459/30,552	3.25	2.92	3.62	2.78	2.47	3.12
	Poor	383/5,547	5.26	4.59	6.02	4.18	3.61	4.84
	Unknown	366/9,356	2.39	2.08	2.75	2.29	1.97	2.67



HR* Adjusted for age and sex
HR** Adjusted for age, sex, household income, university degree, region of residence, living in aged care facilities, proton pump inhibitor usage, fruit and vegetable , chicken/poultry, egg and seafood intake, alcohol use, smoking, BMI, and self-rated health

Figure 1 Associations between various baseline characteristics and incident infectious gastroenteritis hospitalisations, the 45 and Up Study (BMI, body mass index).

female cases (62%) having an additional diagnosis coded with an ICD-10-AM for living alone (Z60.2), inadequate family support (Z63.2) and absence of a family member (Z63.3), than male cases (38%) at the time of admission, which may indicate an inadequate care of female patients in our study.

Self-rated health has previously been reported as a significant predictor of severe health outcomes, such as mortality.[21] Although mortality remains the strongest biological indicator of ill-health, disease-related hospitalisation captures the direct burden of illness. In our study, participants' responses to questions about self-rated health demonstrated a strong association with hospitalisations due to gastroenteritis. Consequently, poor self-rated health may serve as a useful marker for people at higher risk of hospitalisation who present to family physicians with gastroenteritis. Similarly, people with a very high or very low BMI were at higher risk of hospitalisation with gastroenteritis. These findings highlight the importance of general health in affecting hospitalisation with gastrointestinal infection in older adults.

We identified an association between PPIs use and hospitalisation with gastroenteritis, which has been consistently shown in previous studies investigating risk

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factors for gastrointestinal infections.[22 23] Treatment with PPIs lowers gastric acidity, which is a first line of defence against ingested pathogens, leading to bacterial colonisation, thus increasing an individual's susceptibility to enteric infection.[24] A recent study examining the incidence of *Salmonella* and *Campylobacter* infection in patients prescribed PPIs argued that such people were already at higher underlying risk of enteric infection before prescription.[25] In our study, PPIs use was self-reported at recruitment, and was significantly associated with later hospitalisation for gastroenteritis even after adjusting for self-rated health at baseline. Although our study was insufficient to establish a causal relationship, this adds to the evidence that PPIs are associated with hospitalisation involving enteric infection.

We investigated the possible association between food consumption history and the risk of gastroenteritis, but did not observe any association between frequency of fruit and vegetable intake, chicken and poultry, seafood or eggs, and risk of hospitalisations due to infectious gastroenteritis. This may be due to the nature of the baseline questionnaire that did not collect detailed dietary information of participants. For example, in the questionnaire, participants were only asked if they ever eat eggs, and did not collect information on frequency of egg consumption. Additionally, our study captures cases of gastroenteritis due to a range of aetiological agents, so it is not surprising that foods were not important risk factors. *Campylobacter* spp and *Salmonella* spp are commonly found in adult patients hospitalised with infectious gastroenteritis,[26] although viral enteritis has also been identified as a key cause of seasonal increases in hospitalisation among the elderly.[27]

Our study has several limitations that may influence the interpretation of results. First, risk factors were reported at the time of recruitment, and may have changed between recruitment and hospitalisation. Second, exposure assessment was based on self-report. Dietary intake can be difficult to measure, despite self-report being reasonably reliable for some factors.[28 29] However, a validation study involving the short questions related to diet used in the 45 and Up Study questionnaire has shown them to be reproducible over time.[30] Third, the 45 and Up study cohort, while including about 1 in 10 adults in the age range in NSW, is likely to be more health conscious than the general NSW population, hence, the rates of hospitalisations due to gastroenteritis may be underestimated, although this would be unlikely to affect within-cohort comparisons, such as the estimates of HRs.[31]

CONCLUSION

Our results highlight a substantial burden to the healthcare system from gastroenteritis in an aging population. Future efforts should focus on defining and improving preventive measures for hospitalisations due to gastroenteritis among the elderly. Early recognition and supportive treatment of diarrhoea in older patients with poorer self-rated health may prevent subsequent hospitalisation. Additionally, further research is required to examine if PPIs use results in excess hospitalisations due to gastroenteritis and specific enteric infections, as it is a potentially modifiable risk factor.

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Contributors YC performed the analyses and wrote the first draft of the manuscript. BCL, KG and MDK provided input to the design of the study and interpretation of results, and provided advice on the drafting of the manuscript. All the authors read and approved the final manuscript.

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Competing interests None declared.

Ethics approval The conduct of the 45 and Up Study was approved by the University of New South Wales Human Research Ethics Committee. Ethics approval for this study was obtained from the NSW Population and Health Services Research Ethics Committee, the NSW Cancer Institute Human Research Ethics Committee, and the Australian National University Human Research Ethics Committee.

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Data sharing statement No additional data are available.

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REFERENCES

1. Black RE, Cousens S, Johnson HL, *et al*. Global, regional, and national causes of child mortality in 2008: a systematic analysis. *Lancet* 2010;375:1969–87.
2. Gangarosa RE, Glass RI, Lew JF, *et al*. Hospitalizations involving gastroenteritis in the United States, 1985: the special burden of the disease among the elderly. *Am J Epidemiol* 1992;135:281–90.
3. Jagai JS, Smith GS, Schmid JE, *et al*. Trends in gastroenteritis-associated mortality in the United States, 1985–2005: variations by ICD-9 and ICD-10 codes. *BMC Gastroenterol* 2014;14:211.
4. Gavazzi G, Krause K-H. Ageing and infection. *Lancet Infect Dis* 2002;2:659–66.
5. Castle SC. Clinical relevance of age-related immune dysfunction. *Clin Infect Dis* 2000;31:578–85.
6. Kirk MD, Hall GV, Becker N. Gastroenteritis in older people living in the community: results of two Australian surveys. *Epidemiol Infect* 2012;140:2028–36.
7. Dey A, Wang H, Menzies R, *et al*. Changes in hospitalisations for acute gastroenteritis in Australia after the national rotavirus vaccination program. *Med J Aus* 2012;197:453.
8. Lopman BA, Hall AJ, Curns AT, *et al*. Increasing rates of gastroenteritis hospital discharges in US adults and the contribution of norovirus, 1996–2007. *Clin Infect Dis* 2011;52:466–74.
9. Friesema I, Lugnér A, Van Duynhoven Y, *et al*. Costs of gastroenteritis in the Netherlands, with special attention for severe cases. *Eur J Clin Microbiol Infect Dis* 2012;31:1895–900.

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10. Gibney KB, O'Toole J, Sinclair M, *et al*. Disease burden of selected gastrointestinal pathogens in Australia, 2010. *Int J Infect Dis* 2014;28:176–85.
11. Collaborators, the 45 and Up Study. Cohort profile: the 45 and up study. *Int J Epidemiol* 2008;37:941.
12. Roberts RF, Innes KC, Walker SM. Introducing ICD-10-AM in Australian hospitals. *Med J Aus* 1998;169:S32–5.
13. Centre for Health Record Linkage. http://www.cherel.org.au (accessed Aug 2014).
14. Anon. ARIA and Accessibility 2014 (cited 1 October 2014). https://www.adelaide.edu.au/apmrc/research/projects/category/aria.html
15. Thiébaut A, Bénichou J. Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. *Stat Med* 2004;23:3803–20.
16. Pettitt A, Daud IB. Investigating time dependence in Cox's proportional hazards model. *Appl Stat* 1990:39: 313–29.
17. Yorita Christensen KL, Holman RC, Steiner CA, *et al*. Infections disease hospitalizations in the United States. *Clin Infect Dis* 2009;49:1025–35.
18. Fleury MD, Stratton J, Tinga C, *et al*. A descriptive analysis of hospitalization due to acute gastrointestinal illness in Canada, 1995–2004. *Can J Public Health* 2008;99:489–93.
19. Yoshikawa T, Norman D. *Infectious disease in the aging: a clinical handbook*. Springer Science & Business Media, 2009.
20. Christensen KLY, Holman RC, Steiner CA, *et al*. Infectious disease hospitalizations in the United States. *Clin Infect Dis* 2009;49:1025–35.
21. DeSalvo KB, Bloser N, Reynolds K, *et al*. Mortality prediction with a single general self-rated health question. *J Gen Intern Med* 2006;21:267–75.
22. Pilotto A, Franceschi M, Vitale D, *et al*. The prevalence of diarrhea and its association with drug use in elderly outpatients: a multicenter study. *Am J Gastroenterol* 2008;103:2816–23.
23. Garcia Rodriguez LA, Ruigomez A, Panes J. Use of acid-suppressing drugs and the risk of bacterial gastroenteritis. *Clin Gastroenterol Hepatol* 2007;5:1418–23.
24. Bavishi C, Dupont H. Systematic review: the use of proton pump inhibitors and increased susceptibility to enteric infection. *Aliment Pharmacol Ther* 2011;34:1269–81.
25. Brophy S, Jones KH, Rahman MA, *et al*. Incidence of Campylobacter and Salmonella infections following first prescription for PPI: a cohort study using routine data. *Am J Gastroenterol* 2013;108:1094–100.
26. Jansen A, Stark K, Kunkel J, *et al*. Aetiology of community-acquired, acute gastroenteritis in hospitalised adults: a prospective cohort study. *BMC Infect Dis* 2008;8:143.
27. Chui KK, Jagai JS, Griffiths JK, *et al*. Hospitalization of the elderly in the United States for nonspecific gastrointestinal diseases: a search for etiological clues. *Am J Public Health* 2011;101:2082–6.
28. Comino EJ, Tran DT, Haas M, *et al*. Validating self-report of diabetes use by participants in the 45 and Up Study: a record linkage study. *BMC Health Serv Res* 2013;13:481.
29. Ng SP, Korda R, Clements M, *et al*. Validity of self-reported height and weight and derived body mass index in middle-aged and elderly individuals in Australia. *Aust N Z J Public Health* 2011;35:557–63.
30. Roddam AW, Spencer E, Banks E, *et al*. Reproducibility of a short semi-quantitative food group questionnaire and its performance in estimating nutrient intake compared with a 7-day diet diary in the Million Women Study. *Public Health Nutr* 2005;8:201–13.
31. Mealing NM, Banks E, Jorm LR, *et al*. Investigation of relative risk estimates from studies of the same population with contrasting response rates and designs. *BMC Med Res Methodol* 2010;10:26.

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High incidence of hospitalisation due to infectious gastroenteritis in older people associated with poor self-rated health

Yingxi Chen, Bette C Liu, Kathryn Glass and Martyn D Kirk

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Chapter 6

Paper three: Use of proton pump inhibitors and the risk of hospitalization for infectious gastroenteritis: a population-based cohort study

Chen Y, Liu B, Glass, Du W, Banks E, Kirk M. Use of proton pump inhibitors and the risk of hospitalization for infectious gastroenteritis. Plos One. 2016;20;11:e0168618. Public Library of Science.

About This Chapter

In this chapter, I investigate the association between proton pump inhibitor (PPI) use and infectious gastroenteritis, and examine the effect of different dose and type of PPIs. Previous data have suggested a significant association between PPI use and bacterial gastroenteritis, although the effect of dose and type of PPIs remained unknown. The main reason for conducting this analysis was to contribute to answering the research question: 'What is the epidemiology of gastroenteritis in middle-aged and older adults?'. This paper was published in *Plos One*.

PLOS ONE

RESEARCH ARTICLE

Use of Proton Pump Inhibitors and the Risk of Hospitalization for Infectious Gastroenteritis

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Data Availability Statement: The 45 and Up Study is a cohort study of over 260,000 participants aged 45 years and above living in New South Wales (NSW), Australia. The study is managed by the Sax Institute, and it is an open research resource to help facilitate research on health, ageing and quality-of-life. The data set for the present study was created by linkage of 45 and Up Study baseline survey data to Australian Government and NSW state data sources with support of the Centre for Health Record Linkage (CHeReL) and permission from the custodians of each of the datasets under specific ethics approval managed by the Sax

Abstract

Introduction

To quantify the association between PPI use, type and dose and infectious gastroenteritis hospitalization in a population-based cohort of middle-aged and older adults.

Methods

Prospective study of 38,019 concession card holders followed up over 6 years in the Sax Institute's 45 and Up Study. Data from the baseline questionnaire were linked to prescription medication, hospitalization, notifiable disease, cancer registry and death datasets from 2006–2012. Associations between PPI use and gastroenteritis hospitalization were examined using Cox regressions with age as the underlying time variable.

Results

Among 38,019 participants, the median age was 69.7 years, and 57.3% were women. Compared to non-users, current PPI users were more likely to be older, and have a higher BMI. During follow-up there were 1,982 incident gastroenteritis hospitalizations (crude rate: 12.9 per 1000 person-years, 95% CI: 12.3–13.5). PPI use was significantly associated with infectious gastroenteritis hospitalization (aHR 1.4, 95% CI: 1.2–1.5). Among current users, a dose-response relationship was observed between the average daily dose (DDD) dispensed per day and infectious gastroenteritis hospitalization (P_{trend}<0.001). We also observed higher rates of infectious gastroenteritis hospitalization and greater PPI use among participants with a history of chronic bowel problems (aHR 2.2, 95% CI: 1.9–2.5). There was no difference in risk by type of PPI. Recent use of H_2 receptors was not associated with gastroenteritis hospitalization.

Conclusion

PPI use is associated with an increased risk of infectious gastroenteritis hospitalization. Clinicians should be aware of this risk when considering PPI therapy.

Institute. The Sax Institute retains a copy of the resultant dataset. Interested researchers should contact the Sax Institute (45andUp.research@saxinstitute.org.au) and CHeReL (cherel.mail@moh.health.nsw.gov.au) for data access approval procedures.

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Competing Interests: The authors have declared that no competing interests exist.

Introduction

Proton pump inhibitors (PPIs), introduced in 1989, are the most potent gastric acid suppressants available [1]. They are widely used by both gastroenterologists and primary care physicians in the effective treatment of acid-related disorders. PPIs are one of the most commonly prescribed medications worldwide [2], although it has been suggested that 25–70% of patients taking PPIs lack appropriate indications [2]. In Australia, there are five PPIs listed on the Pharmaceutical Benefits Scheme (PBS)—a national government system that subsidizes the cost of medicines, most of which are dispensed by pharmacists. Omeprazole and lansoprazole were first introduced onto the PBS in 1994, followed by pantoprazole in 1995, rabeprazole in 2001 and esomeprazole in 2002. Since their introduction, PPI use in Australia has grown dramatically [3]. In the 2013–14 financial year, physicians issued over 19 million prescriptions for PPIs with the most commonly prescribed type of PPI costing the PBS over $200 million [4].

Many patients take PPIs on a continuous or long-term basis [5]. Although this class of drug is considered safe and has been approved for long-term use [6], concerns have been raised regarding associated adverse effects [7]. Studies have reported that PPIs are associated with serious adverse events, including kidney diseases, hip fracture, community-acquired pneumonia, and *Clostridium difficile* infection [8–11]. PPIs irreversibly inactivate the gastric H^+/K^+-ATPase pump and cause a profound inhibition of gastric acid secretion [12, 13]. Significant hypochlorhydria, particularly among the elderly population who may have decreased clearance of PPIs, could result in bacterial overgrowth [14] and potentially increase susceptibility to infection. PPI use has also been shown to reduce gut commensal load and microbial density [15].

Although PPIs can potentially impair gastrointestinal host defenses, the association between PPI use and enteric infections has only recently been explored systematically [16, 17]. Observational studies have found increased risks of *Campylobacter*, *Salmonella* and *C. difficile* infection [9, 18]. However, the effects of different types and doses of PPIs remain unknown. Additionally, to our knowledge, no population-based studies have evaluated the effect of different PPI dosage and infectious gastroenteritis hospitalization among patients with chronic bowel problems. Given that older adults constitute the majority of PPI users [3, 19], the aim of this study was to investigate the association between PPI use and hospitalization for infectious gastroenteritis, considering both dose and type of PPIs, in a large prospective study of adults aged 45 years and older with and without a history of chronic bowel problems.

Methods

Data sources and study population

The Sax Institute's 45 and Up Study is an Australian cohort of 267,153 men and women aged 45 years and over from New South Wales (NSW), the most populous state in Australia. The 45 and Up Study cohort were randomly selected from the Medicare Australia (now the Department of Human Services) enrolment database. Baseline questionnaires were distributed from 1 January 2006 to 31 December 2008. Participants joined the study by completing the baseline questionnaire and giving consent for follow-up through repeated data collection and linkage of their data to multiple population health databases. Baseline questionnaire data include information on socio-demographics, general health and behavior. The study is described in detail elsewhere [20], and questionnaires can be accessed at http://www.45andup.org.au.

For this report we linked individual participant baseline data to prescription medication, hospitalization, notifiable disease, cancer registrations and death datasets. Specifically, the 45 and Up Study baseline questionnaire data were linked to medication data from the PBS

records to obtain medication use at baseline and during follow-up. Questionnaire data were linked to hospitalization data from the NSW Admitted Patient Data Collection (APDC) to identify cases of infectious gastroenteritis and to capture participants with previous hospitalizations. In order to identify cases of *Salmonella* infection, which is a notifiable disease in NSW, baseline data were linked to the Notifiable Conditions Information Management System (NCIMS). Data were then linked to death data to ascertain fact and date of death for censoring purposes. Baseline data were also retrospectively linked to cancer registry data from the NSW Central Cancer Registry (CCR) to identify participants who had a cancer diagnosis before recruitment. The NSW Centre for Health Record Linkage performed the data linkage independent of the study investigators and report false positive and false negative linkages of $<0.5\%$ and $<0.1\%$, respectively [21].

The PBS dataset is an administrative dataset documenting information about subsided dispensed prescription drugs including PPIs for the Australian population [22]. For medicines listed on the PBS, consumers contribute a copayment towards the cost, and the Australian Government pays the remainder. People with a concession card pay a smaller copayment (AUD 6 in 2014) than the general population. Concession card holders are people with a Pensioner Concession Card, a Commonwealth Seniors Health Card or a Health Care Card. The PBS captured all medicines dispensed to concession card holders in the time period covered by these analyses.

The NSW APDC dataset is a complete census of all hospital admissions in NSW. The principal diagnosis for each admission, and up to 54 additional diagnoses contributing to the admission were coded using the International Classification of Diseases, 10^{th} revision, Australian Modification (ICD-10-AM) [23]. The NCIMS database contains a record of *Salmonella* infections in NSW, including the estimated onset date and the type of laboratory specimen used for confirmation. The NSW CCR is a population-based registry that records all new diagnoses of cancer in NSW residents and all deaths from cancer.

Measurements

Case definition. The primary outcome of interest was hospitalization with infectious gastroenteritis, which was defined as a participant with an index linked hospitalization record where the principal or a secondary diagnosis was coded with an ICD-10-AM code for intestinal infectious diseases (A00-A09) following study recruitment.

Secondary outcomes included *Salmonella*-, *Campylobacter*- and *C. difficile* infection. A case of *Salmonella* infection was defined as a participant who had a linked notification record of non-typhoidal *Salmonella* infection during follow up. A case of *Campylobacter*-, or *C. difficile* infection was defined as a participant who had a linked hospitalization record with diagnosis of *Campylobacter* enteritis (ICD-10-AM code A04.5), or *C. difficile* colitis (A04.7) during follow up, respectively.

Definition of PPI use. PPI use was identified using linked records on dispensing from the PBS dataset with Anatomical Therapeutic Chemical (ATC) classification codes beginning with A02BC, proton pump inhibitors (World Health Organization Collaborating Centre for Drug Statistics Methodology, 2013) [24]. Study participants were categorized as current PPI users, former users and non-users. Current users were defined as those who had at least one PPI dispensing record within the 3 months prior to recruitment. Former users were defined as participants who had at least one PPI dispensing record in a period of 3–12 months prior to recruitment. Non-users were defined as participants who were not dispensed any PPIs over the period prior to recruitment that we had PBS records for, or who had a PPI dispensed $\geq$12 months prior to recruitment.

Current users were further categorized by type of PPI and dose. Types of PPIs used included omeprazole (ATC codes: A02BC01), pantoprazole (A02BC02), lansoprazole (A02BC03), rabeprazole (A02BC04), esomeprazole (A02BC05) or more than one type. Dose was described as the average number of dispensed DDD per day during the 3 months prior to recruitment [25]. DDD is a World Health Organization classification system which is defined as '*the assumed average maintenance dose per day for a drug used for its main indication in adults*' [26]. To obtain the average number of dispensed DDD per day, we firstly calculated the total number of dispensed DDD for each PPI, which was calculated as the strength (mg) of the dispensed PPI multiplied by the pack size and the number of dispensed packs, and then divided by the DDD of that PPI. This dispensed DDD was then summed for each participant and divided by the duration of use (3 months) to obtain the average dispensed DDD per day during the 3 months prior to the recruitment.

Definition of covariates. Socio-demographic factors and health status characteristics obtained from the baseline questionnaire included: age (grouped as 45–54, 55–64, 65–74 or ≥75 years), sex, body mass index (BMI: <18.5, 18.5–24.9, 25–29.9 or ≥30 kg/m^2), self-rated health (excellent, good, fair or poor), smoking (current, past or never) and alcohol intake (none, 1–2 alcohol drinks per day or >2 alcohol drinks per day). Region of residence was obtained from Medicare Australia using address at time of recruitment, grouped as cities, inner regional or outer regional/remote based on the Accessibility/Remoteness Index of Australia [27].

History of cancer diagnosis, excluding non-melanoma skin cancer, in the 5 years prior to recruitment (yes, no) was ascertained by linkage to the CCR. History of chronic bowel problems (yes, no), was ascertained by linkage to an APDC record with an ICD-10-AM diagnosis code of K50 to K52 (non-infective enteritis and colitis) and K58 (irritable bowel syndrome) in any of the 55 diagnostic fields in the 6 years prior to recruitment. Recent H_2 receptor antagonist and antibiotic use were defined based on the PBS dispensing records (ATC codes: A02BA01, A02BA02, A02BA03, A02BA04 for H_2 receptors and J01 for antibiotics) in the 3 months before recruitment.

Statistical methods

In this study, complete records of dispensed PPIs were only available for people with a valid healthcare concession-card [25]. Therefore, analyses were restricted to 45 and Up Study participants who were concession-card holders. Additionally, participants were excluded from the analyses if they had missing data on date of entry into the study, or missing PBS data on dispensing. Follow-up was calculated from the date of recruitment to the index date of admission for infectious gastroenteritis, death, or the last date for which database records were available (30 June 2012), whichever came first. Rates of infectious gastroenteritis hospitalizations since baseline and 95% confidence intervals (CIs) were calculated for PPI current users, former users and non-users at baseline.

Characteristics of PPI current users, former users and non-users were firstly compared using chi-squared tests. For the main analysis to examine the risk of PPI use and infectious gastroenteritis, Kaplan-Meier analysis with the log-rank test was first used to determine the probability of hospitalization with infectious gastroenteritis for current users, former users and non-users. Cox proportional hazards regression with age as the underlying time variable was then used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs). Regression models were initially adjusted only for age (as this was the underlying time variable) and sex, and then further adjusted for region of residence, self-rated health, BMI, cancer in previous 5 years, history of chronic bowel problems, recent H_2 receptor antagonist use, and recent antibiotic use. Finally, smoking and alcohol intake were also added to the model.

In current users, the risk of infectious gastroenteritis hospitalization was further evaluated according to type and dose of PPIs. To examine the potential impact of chronic bowel problems on the association between PPI use and infectious gastroenteritis, models were then stratified by history of chronic bowel problems. Similar analyses were performed for the secondary outcomes of *Salmonella*-, *Campylobacter*-, and *C. difficile* infection, respectively.

The proportionality assumption of the Cox regression models were verified by plotting the Schoenfeld residuals against the time variable in each model, with the time-dependent form of the model used where covariates displayed non-proportionality of hazards. No violations were detected for PPI use. Significant violation was observed for recent antibiotic use, and this covariate was included as a time-dependent form in the models.

Sensitivity analysis was conducted by restricting cases to only those with a principal hospital diagnosis of infectious gastroenteritis. To examine the effects of changes in PPI use over time a second sensitivity analysis was conducted by restricting the study population to participants who remained in the same PPI use category during follow-up. We then conducted a third sensitivity analysis using a time-dependent Cox model with time-varying PPI ever-use. All analyses were carried out using STATA 12.1.

Ethics approval

The conduct of the 45 and Up Study was approved by the University of New South Wales Human Research Ethics Committee. Ethics approval for this study was obtained from the NSW Population and Health Services Research Ethics Committee, and the Australian National University Human Research Ethics Committee. All participants provided written informed consent.

Results

After restricting participants to those with concessional-only PBS records during the study period (n = 38,074), and excluding those who had missing data on date of entry into the study (n = 10), or missing PBS data on dispensing (n = 45), there were 38,019 participants, who were followed from baseline for a median of 3.9 years, yielding a total of 153,997 person-years of follow-up. The median age of study participants at recruitment was 69.7 years (interquartile range: 63.3–77.4), and 57.3% were women.

Table 1 summarizes the characteristics of the study population. Overall, 52.1% (n = 19,787) of participants had been dispensed at least one PPI in the 3 months prior to recruitment (categorized as PPI current users), 38.8% (n = 14,762) were defined as non-users, of which 18.8% (n = 2,771) had a record of PPI use $\geq$12 months before recruitment. PPI current users were more likely to be older and have a higher BMI compared to non-users. Participants taking H_2 receptor antagonists had similar characteristics to participants taking PPIs (Table 1).

Among users, esomeprazole was the most frequently dispensed PPI (n = 5,950; 30.1%), followed by omeprazole (n = 4,983; 25.2%) and pantoprazole (n = 4,235; 21.4%). Most users had used only one type of PPI (n = 19,096; 96.1%).

There were 1,982 cases of incident infectious gastroenteritis hospitalization during follow-up. The crude incidence of gastroenteritis hospitalization in the cohort was 12.9 per 1,000 person years (95% CI, 12.3–13.5). Compared to non-users, the adjusted relative risk of hospitalization was significantly higher in current PPI users (aHR 1.4, 95% CI: 1.2–1.5) and former users (aHR 1.2, 95% CI: 1.1–1.5) (Fig 1). Recent use of prescribed H_2 receptors was not associated with hospitalization for infectious gastroenteritis (aHR 0.9, 95% CI: 0.7–1.1). Participants with a history of cancer or chronic bowel problems were more likely to be hospitalized with infectious gastroenteritis (aHR 1.5, 95% CI: 1.3–1.7; and 2.2, 95% CI: 1.9–2.5, respectively).

Table 1. Baseline characteristics of the study population, the 45 and Up Study, according to use of Proton Pump Inhibitors (PPI) and H_2 receptor antagonists.

Characteristics	PPI non-users (n = 14,762)(%)	PPI former users (n = 3,470) (%)	PPI current users (n = 19,787) (%)	H_2 receptor users (n = 1,951) (%)	*P*-value*
Age (years)					*P* < .001
45–54	1,564 (10.6)	366 (10.6)	1,376 (6.9)	152 (7.8)	
55–64	3,440 (23.3)	728 (21.0)	4,102 (20.8)	384 (19.6)	
65–74	5,503 (37.3)	1,354 (39.0)	7,517 (38.0)	729 (37.4)	
≥75	4,255 (28.8)	1,022 (29.4)	6,792 (34.3)	686 (35.2)	
Female sex	8,336 (56.5)	2,043 (58.9)	11,408 (57.6)	1,136 (58.2)	*P* = .3
Region of residence					*P* = .03
Cities	5,898 (39.9)	1,488 (42.8)	7,898 (39.9)	881 (45.1)	
Inner regional	5,467 (37.1)	1,245 (35.9)	7,568 (38.3)	646 (33.1)	
Outer regional/remote	3,397 (23.0)	737 (21.3)	4,321 (21.8)	424 (21.7)	
History of chronic bowel problems	692 (4.7)	249 (7.2)	1,752 (8.9)	158 (8.1)	*P* < .001
Self-rated health					*P* < .001
Excellent	4,919 (33.3)	1,053 (30.4)	4,670 (23.6)	422 (21.6)	
Good	5,484 (37.2)	1,258 (36.3)	7,569 (38.3)	698 (35.7)	
Fair	2,961 (20.1)	765 (22.1)	5,108 (25.8)	531 (27.2)	
Poor	656 (4.4)	192 (5.5)	1,436 (7.3)	177 (9.1)	
Cancer in previous 5 years	1,184 (8.0)	299 (8.6)	1,760 (8.9)	155 (7.9)	*P* = .03
BMI (kg/m^2)					*P* < .001
<18.5	233 (1.7)	63 (1.9)	288 (1.6)	25 (1.4)	
18.5–24.9	4,682 (34.5)	1,127 (35.5)	5,252 (28.9)	601 (33.5)	
25–29.9	5,125 (37.7)	1,164 (36.7)	6,999 (38.6)	633 (35.3)	
>30	3,550 (26.1)	818 (25.9)	5,576 (30.8)	535 (29.8)	
Smoking					*P* < .001
Never	7,610 (51.9)	1,829 (53.0)	10,195 (51.8)	1,021 (52.9)	
Current	1,457 (9.9)	311 (9.1)	1,375 (7.0)	158 (8.2)	
Past	5,599 (38.2)	1,308 (37.9)	8,079 (41.2)	751 (38.9)	
Alcohol intake					*P* < .001
None	6,349 (43.0)	1,534 (44.2)	9,053 (45.7)	955 (48.9)	
≤2 units/day	6,211 (42.1)	1,431 (41.2)	7,951 (40.2)	718 (36.8)	
> 2 units/day	1,644 (11.1)	354 (10.2)	2,104 (10.6)	186 (9.5)	

P-value*: Chi-squared test for PPI category. Missing: self-rated health = 1,948 (5.1%); BMI = 3,142 (8.2%); smoking = 256 (0.6%); alcohol intake = 1,388 (3.6%)

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Among current users, a dose-response relationship was observed between the average number of DDD dispensed per day and risk of infectious gastroenteritis hospitalization (P_{trend}<0.001), with a 60% increase in risk among those dispensed >1 DDD/day versus non-use (aHR 1.6, 95% CI: 1.3–1.8). The risk did not differ significantly by PPI type (Table 2). The dose response effect was consistent when analyses were restricted to participants with a history of chronic bowel problems; compared to non-users, aHRs of infectious gastroenteritis hospitalization were 1.2 (95% CI: 0.8–1.9) in participants with a dose ≤0.5DDD/day, 1.7 (95% CI: 1.2–2.2) with a dose of 0.5-1DDD/day, and 2.0 (95% CI: 1.4–2.8) with a dose >1DDD/day (P_{trend}<0.001) (Table 2).

The broad relationships between PPI use and the risk of specific types of infectious gastroenteritis—*C. difficile*, *Salmonella* and *Campylobacter* infection—did not differ materially from that observed for infectious gastroenteritis hospitalization overall. Risks were significantly

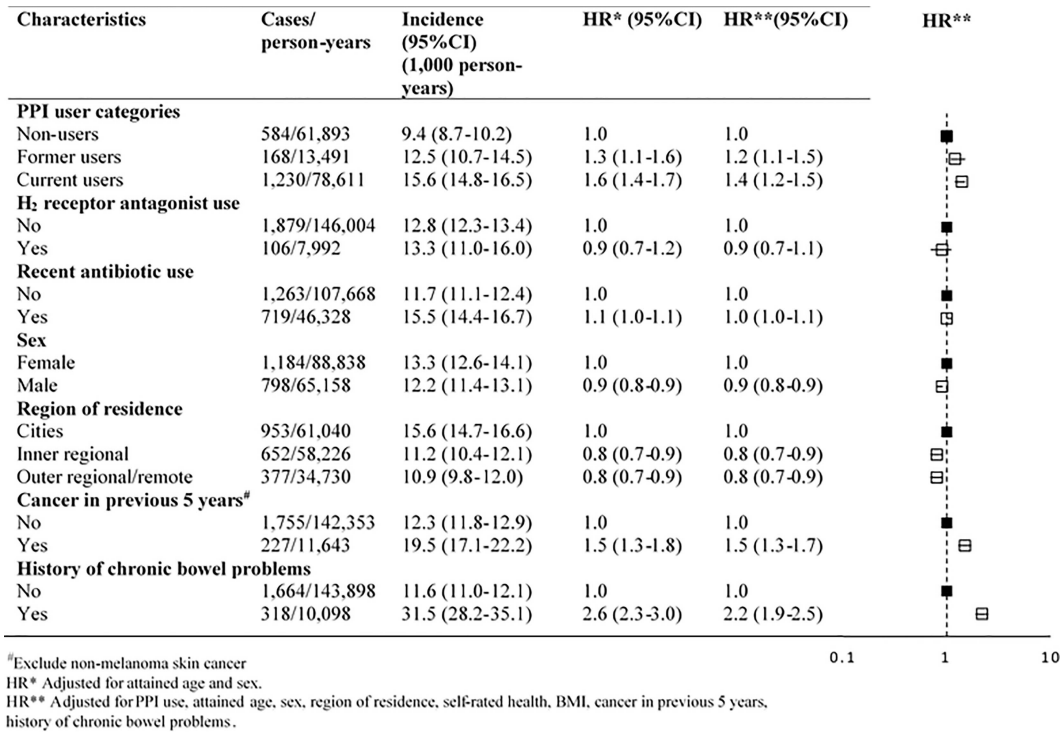

Fig 1. Crude incidence and hazard ratios of participants admitted to hospital with infectious gastroenteritis according to Proton Pump Inhibitor (PPI) user categories and other characteristics.

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elevated for *C. difficile* infection among PPI current users (aHR: 1.5, 95% CI: 1.1–2.1). Compared to non-users, participants dispensed >1 DDD/day were 120% more likely to have *C. difficile* infection (aHR: 2.2, 95% CI: 1.4–3.4), and 100% more likely to have *Salmonella* infection

Table 2. Hazard ratios of participants hospitalized with infectious gastroenteritis among current Proton Pump Inhibitor (PPI) users compared to non-users according to dose and type of PPI.

Characteristics	HR* (95%CI)	P_{trend}	Participants with chronic bowel problems			Participants without chronic bowel problems		
			Rate#	HR** (95%CI)	P_{trend}	Rate#	HR** (95%CI)	P_{trend}
Average daily dose (DDD)		<0.001			<0.001			<0.001
Non-users	1.0		22.1	1.0		9.4	1.0	
≤0.5	1.1 (0.9–1.3)		25.2	1.2 (0.8–1.9)		10.8	1.1 (0.9–1.3)	
0.5–1	1.4 (1.3–1.6)		37.5	1.7 (1.2–2.2)		14.3	1.4 (1.3–1.6)	
>1	1.6 (1.3–1.8)		45.1	2.0 (1.4–2.8)		15.9	1.5 (1.3–1.8)	
Type of PPI		0.2			0.3			0.4
Omeprazole	1.0		36.7	1.0		14.9	1.0	
Pantoprazole	0.9 (0.8–1.1)		38.8	1.1 (0.7–1.6)		12.7	0.9 (0.7–1.1)	
Lansoprazole	0.9 (0.6–1.2)		21.6	0.7 (0.3–1.7)		12.7	0.9 (0.6–1.2)	
Rabeprazole	1.1 (0.9–1.3)		44.8	1.3 (0.8–2.0)		14.4	1.1 (0.8–1.3)	
Esomeprazole	0.9 (0.8–1.1)		33.1	0.9 (0.6–1.4)		13.0	1.0 (0.8–1.1)	

Rate# /1,000 person-years. HR* Adjusted for age, sex, region of residence, self-rated health, BMI, cancer in previous 5 years, history of chronic bowel problems, H_2 receptor antagonist use, recent antibiotic use, smoking and alcohol consumption. HR** Adjusted for age, sex, region of residence, self-rated health, BMI, cancer in previous 5 years, recent H_2 receptor antagonist use, recent antibiotic use, smoking and alcohol consumption.

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Table 3. Proton Pump Inhibitor (PPI) use and the risk of *Salmonella*-, *Campylobacter*-, and *Clostridium difficile*-infection.

Characteristics	*Salmonella* infection (n = 84)	*Campylobacter* infection (n = 71)	*C. difficile* infection (n = 147)
	No. of events	No. of events	No. of events
PPI Non-users	30	21	43
PPI former users	3	5	7
PPI current users	51	45	97
Association between medication use and infections	**HR* (95%CI)**	**HR* (95%CI)**	**HR** (95%CI)**
PPI use			
Non-users	1.0	1.0	1.0
Former users	0.5 (0.2–1.6)	1.1 (0.4–2.9)	0.7 (0.3–1.6)
Current users	1.2 (0.7–1.8)	1.6 (1.0–2.7)	1.5 (1.1–2.1)
H_2 receptor antagonist use			
No	1.0	1.0	1.0
Yes	1.1 (0.3–3.3)	2.3 (0.9–5.9)	0.6 (0.2–1.7)
Antibiotic use			
No	1.0	1.0	1.0
Yes	1.4 (0.9–2.3)	1.0 (0.6–1.6)	1.1 (0.8–1.5)
Average daily dose (DDD)			
Non-users	1.0	1.0	1.0
Current users: $\leq$0.5	0.8 (0.3–1.9)	1.4 (0.6–3.1)	1.2 (0.6–2.1)
Current users: 0.5–1	1.3 (0.8–2.1)	1.8 (1.1–3.0)	1.3 (0.9–2.0)
Current users: >1	2.0 (1.1–3.8)	1.1 (0.4–2.7)	2.2 (1.4–3.4)

HR* Adjusted for age, sex, region of residence, self-rated health, recent H_2 receptor antagonist use, recent antibiotic use, cancer in previous 5 years, history of chronic bowel problems, and alcohol consumption. BMI and smoking status were not included in the model due to missing values in certain categories. HR** Adjusted for age, sex, region of residence, self-rated health, BMI, recent H_2 receptor antagonist use, recent antibiotic use, cancer in previous 5 years, history of chronic bowel problems, smoking and alcohol consumption.

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(aHR: 2.0, 95% CI: 1.1–3.8). While not statistically significant in all cases, there was a pattern of increased risk of these outcomes with increasing PPI dose, and this pattern was not generally observed for H_2 receptor antagonists (Table 3).

Sensitivity Analyses

The results remained similar when restricting cases to only those with a principal hospital diagnosis of infectious gastroenteritis; compared to non-users, aHRs were 1.7 (95% CI: 1.4–1.9) for current users and 1.5 (95% CI: 1.2–2.0) for former users. A significant dose-response relationship was also observed; compared to non-users, aHRs were 1.1 (95% CI: 0.9–1.4), 1.4 (95% CI: 1.2–1.7) and 2.1 (95% CI: 1.8–2.5) in participants with a dose $\leq$0.5, 0.5–1 and >1DDD/day, respectively ($P_{trend}<0.001$). In the second sensitivity analysis with PPI use as a time-varying covariate, PPI use was also associated with infectious gastroenteritis hospitalization (aHR: 1.9, 95% CI: 1.6–2.1). Associations remained similar when further restricting the study population to participants who did not change PPI use category during follow-up. A similar dose-response relationship was retained in this analysis ($P_{trend}<0.001$).

Discussion

In this study, we found a significantly increased risk of infectious gastroenteritis hospitalization associated with PPI use, and a significant dose-response relationship among current

users. This risk was specific to PPI users, as use of H_2 receptor antagonists, which are used for the same indication as PPIs, was not associated with hospitalization due to infectious gastroenteritis. This study confirms that the risk of infectious gastroenteritis hospitalization is elevated in people who have used PPIs, and also provides new and reliable information about the effects of different types of PPIs and dosages.

We found that former and current PPI users had significantly increased risks of infectious gastroenteritis hospitalization compared to those never using or using PPIs $\geq$12 months prior to baseline. Previous studies have reported current PPI therapy as a significant risk factor for bacterial gastroenteritis [18, 28]. Howell *et al* reported increasing rates of nosocomial *C. difficile* infection with increasing level of PPI therapy [29]. In this study, we observed a significant dose-response relationship between PPI exposure and all-cause infectious gastroenteritis hospitalization, which has not been demonstrated previously. This dose-response relationship, and the fact that it is specific to PPIs and was not seen in users of H_2 receptor antagonists, supports a causal association. In this study, we found a small elevation in risk of gastroenteritis hospitalization among former users, which has not been investigated previously; it may be due to long-term effects of PPI use, but requires confirmation.

The reason for the association between PPI use and infectious gastroenteritis is not known definitively, although colonization and proliferation of pathogens secondary to acid suppressive treatment is one potential explanation. Gastric acid plays an important role in preventing human gastrointestinal infections [30] and an acidic environment in the upper gastrointestinal tract constitutes one of the major non-specific defenses to protect against ingested microorganisms [31]. Acid suppression induced by PPIs also affects gastrointestinal motility and can indirectly alter gut microbiota [32]. In patients with functional bowel disorders, such as irritable bowel syndrome, such changes could be more pronounced [33, 34]. Our study found that PPI use resulted in elevated risk of infectious gastroenteritis hospitalization in people with and without a history of chronic bowel problems. We also observed higher rates of infectious gastroenteritis hospitalization and greater PPI use among participants with a history of chronic bowel problems, indicating greater absolute risks of PPI-attributable hospitalization in this group. This suggests that the necessity for PPI use may need to be evaluated more carefully in this group of patients.

Previous studies have reported associations between PPI use and enteric infections, such as *Campylobacter*, *Salmonella* [18] and *C. difficile* infection [35]. We found a broad association between PPI use and *Campylobacter*-, *Salmonella*- and *C. difficile* infection. While the association was not statistically significant in all cases, which could be due to smaller number of events, there was a pattern of increased risk of infections in PPI users and potential dose-response relationships. In addition, our prior work using the full 45 and Up Study dataset showed a significant risk of *Salmonella* infection among people who self-reported PPI use at baseline (aHR 1.87, 95%CI 1.43–2.40) [36]. Our findings regarding *C. difficile* infection were consistent with published data. A recent systematic review of 39 studies showed PPI users at higher risk of *C. difficile* infection compared to non-users (odds ratio: 1.74, 95%CI 1.47–2.85) [9]. Based on latest evidence, the FDA have published safety alerts warning of the association between *C. difficile* diarrhea and PPIs [37]. In Europe, PPI use for more than 8 weeks at the maximal dose without clear indication has been listed on the European list (EU [7)-PIM list) of potentially inappropriate medications for older people due to the association between PPI use and *C. difficile* infection [38].

To ensure that the study focused on the likely causal effect of PPI use on infectious gastroenteritis hospitalization, comorbidity status was controlled through adjustments of cancer history, general health and BMI. Participants with digestive disorders may be more likely to be prescribed acid suppressive medications. These patients also may be more likely to experience

infectious gastroenteritis and be hospitalized. It was not possible to account for all possible digestive disorders, although we identified participants with chronic bowel problems at baseline and adjusted for them in the regression models. We also stratified results by the status of chronic bowel problems. To examine the effect of confounding by indication of acid suppressive therapy, we considered recent H_2 receptor antagonist use in the analysis. Similar to PPIs, H_2 antagonists are a class of acid suppressants used to treat acid-related disorders such as peptic ulcers. We did not observe any increased risk of infection among H_2 receptor antagonist users, indicating that confounding by indication was unlikely to be a major source of bias in this study.

The large number of cases in the study enhanced the precision of the estimates, and allowed adequate assessment of the effects of potential confounders. However, we were only able to classify based on medication usage from dispensing data rather than directly observed therapy, meaning we were unable to confirm actual PPI use in this study. Misclassification relating to non-use among those with records of having been dispensed PPIs would tend to lead to an overestimation of the potential risk of PPIs. However, this bias would be unlikely to affect the assessment of dose, as it is less likely that patients with multiple dispensing records of PPIs did not take the medication. In addition, a recent systematic review suggested that the majority of patients with GERD are relatively adherent to PPIs, and adherence increases with severe symptoms [39]. Secondly, as with most observational studies, residual confounding by unmeasured factors is a potential concern. In this study, we controlled for several important confounders, although we were unable to assess other factors, such as use of over-the-counter antacids. During the study period, low-dose PPIs were available from pharmacies without a prescription in Australia, which could lead to misclassification of PPI exposure. Thirdly, inpatient hospitalization data can be subject to misclassification. However, sensitivity analysis restricting cases only to principal diagnosis of infectious gastroenteritis showed similar results to the main findings. Finally, the study population was restricted to concession-card-holders. Therefore, participants were likely to be older, with lower socio-economic status, when compared to the broader cohort, although risk factor estimates are considered broadly generalizable from within-cohort comparisons [40].

In summary, PPI use is associated with an increased risk of infectious gastroenteritis hospitalization in the 45 and Up Study participants, with higher risks with increasing doses. Given the widespread use of PPIs, particularly among the elderly, clinicians should be aware of this risk when considering PPI therapy, and use the lowest effective dose for patients with appropriate indications. For patients with chronic bowel problems, it may be worth considering an alternative dosage or switching to H_2 receptor antagonists.

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Funding acquisition: BL.

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Supervision: BL MK.

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Visualization: YC BL MK.

Writing – original draft: YC.

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References

1. Wolfe MM, Sachs G. Acid suppression: optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. Gastroenterol. 2000; 118(2 Suppl 1): S9–31.
2. Forgacs I, Loganayagam A. Overprescribing proton pump inhibitors. BMJ. 2008; 336(7634):2–3. doi: 10.1136/bmj.39406.449456.BE PMID: 18174564
3. Hollingworth S, Duncan EL, Martin JH. Marked increase in proton pump inhibitors use in Australia. Pharmacoepidemiol Drug Saf. 2010; 19:1019–24. doi: 10.1002/pds.1969 PMID: 20623646
4. The Pharmaceutical Benefits Scheme, PBS Statistics [Internet]. Australian Government Department of Health,. [cited 15 November 2015]. Available from: http://www.pbs.gov.au/info/browse/statistics#ASM.
5. Jacobson BC, Ferris TG, Shea TL, Mahlis EM, Lee TH, Wang TC. Who is Using Chronic Acid Suppression Therapy and Why. Am J Gastroenterol. 2003; 98:51–8. doi: 10.1111/j.1572-0241.2003.07186.x PMID: 12526936
6. Garnett WR. Considerations for long-term use of proton-pump inhibitors. AJHP. 1998; 55:2268–79. PMID: 9825878
7. Schoenfeld AJ, Grady D. Adverse Effects Associated With Proton Pump Inhibitors. JAMA Intern Med. 2016; 176:172–174. doi: 10.1001/jamainternmed.2015.7927 PMID: 26751904
8. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA. 2006; 296:2947–53. doi: 10.1001/jama.296.24.2947 PMID: 17190895
9. Kwok CS, Arthur AK, Anibueze CI, Singh S, Cavallazzi R, Loke YK. Risk of Clostridium difficile infection with acid suppressing drugs and antibiotics: meta-analysis. Am J Gastroenterol. 2012; 107:1011–9. doi: 10.1038/ajg.2012.108 PMID: 22525304
10. Filion KB, Chateau D, Targownik LE, Gershon A, Durand M, Tamim H et al. Proton pump inhibitors and the risk of hospitalisation for community-acquired pneumonia: replicated cohort studies with meta-analysis. Gut. 2014; 63:552–8. doi: 10.1136/gutjnl-2013-304738 PMID: 23856153
11. Lazarus B, Chen Y, Wilson FP, Sang Y, Chang AR, Coresh J et al. Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease. JAMA Intern Med. 2016; 176.
12. Shin JM, Kim N. Pharmacokinetics and pharmacodynamics of the proton pump inhibitors. J neurogastroenterol Motil. 2013; 19:25. doi: 10.5056/jnm.2013.19.1.25 PMID: 23350044
13. Sharma BK, Walt RP, Pounder RE, Gomes MD, Wood EC, Logan LH. Optimal dose of oral omeprazole for maximal 24 hour decrease of intragastric acidity. Gut. 1984; 25:957–64. PMID: 6469081
14. Lombardo L, Foti M, Ruggia O, Chiecchio A. Increased incidence of small intestinal bacterial overgrowth during proton pump inhibitor therapy. Clin Gastroenterol Hepatol. 2010; 8:504–8. doi: 10.1016/j.cgh.2009.12.022 PMID: 20060064

15. Jackson MA, Goodrich JK, Maxan ME, Freedberg DE, Abrams JA, Poole AC. Proton pump inhibitors alter the composition of the gut microbiota. Gut.
16. Martinsen TC, Bergh K, Waldum HL. Gastric juice: a barrier against infectious diseases. Basic Clin Pharmacol Toxicol. 2005; 96:94–102. doi: 10.1111/j.1742-7843.2005.pto960202.x PMID: 15679471
17. Dial MS. Proton pump inhibitor use and enteric infections. Am J Gastroenterol. 2009; 104:S10–S6. doi: 10.1038/ajg.2009.46 PMID: 19262540
18. Garcia Rodriguez LA, Ruigomez A, Panes J. Use of acid-suppressing drugs and the risk of bacterial gastroenteritis. Clin Gastroenterol Hepatol. 2007; 5:1418–23. doi: 10.1016/j.cgh.2007.09.010 PMID: 18054750
19. Ryder SD, O'Reilly S, Miller RJ, Ross J, Jacyna MR, Levi AJ. Long term acid suppressing treatment in general practice. BMJ. 1994; 308:827–30. PMID: 8167491
20. 45 and Up Study Collaborators, Banks E, Redman S, Jorm L, Armstrong B, Bauman A. Cohort profile: the 45 and Up Study. Int J Epidemiol. 2008; 37:941–7. doi: 10.1093/ije/dym184 PMID: 17881411
21. Centre for Health Record Linkage. Available from: www.cherel.org.au. Accessed Aug 2014.
22. Duckett SJ. Drug policy down under: Australia's pharmaceutical benefits scheme. Health Care Financing Review. 2003; 25:55–67.
23. National Centre for Classification in Health. Internationl statistical classification of diseases and related health problems, 10th revision, Australian Modification (ICD-10-AM). 5th edn. In: National Centre for Classification in Health: Sydney N, Australia, editor.: National Centre for Classification in Health: Sydney, NSW, Australia; 2006.
24. ATC/DDD index [Internet]. WHO Collaborating Centre for Drug Statistics Methodology. 2013. Available from: http://www.whocc.no/atc_ddd_index/?showdescription=yes&code=A02BC.
25. Page E, Kemp-Casey A, Korda R, Banks E. Using Australian Pharmaceutical Benefits Scheme data for pharmacoepidemiological research: challenges and approaches. Public Health Research & Practice. 2015; 25:e2541546.
26. Organization WH. World Health Organization Collaborating Centre for Drug Statistics Methodology. ATC index with DDDs. 2005.
27. Anon. ARIA and Accessibility 2014 [cited 2014 01 Oct]. Available from: https://www.adelaide.edu.au/apmrc/research/projects/category/aria.html.
28. Hassing RJ, Verbon A, de Visser H, Hofman A, Stricker BH. Proton pump inhibitors and gastroenteritis. Eur J Epidemiol. 2016; 31:1057–63. doi: 10.1007/s10654-016-0136-8 PMID: 26960438
29. Howell MD, Novack V, Grgurich P, Soulliard D, Novack L, Pencina M. Iatrogenic gastric acid suppression and the risk of nosocomial Clostridium difficile infection. Arch Intern Med. 2010; 170:784–90. doi: 10.1001/archinternmed.2010.89 PMID: 20458086
30. Williams C, McColl KE. Review article: proton pump inhibitors and bacterial overgrowth. Aliment Pharmacol Ther. 2006; 23:3–10.
31. Howden C, Hunt R. Relationship between gastric secretion and infection. Gut. 1987; 28:96–107. PMID: 3546004
32. Vesper BJ, Jawdi A, Altman KW, Haines GK 3rd, Tao L, Radosevich JA. The effect of proton pump inhibitors on the human microbiota. Current drug metabolism. 2009; 10:84–9. PMID: 19149516
33. Compare D, Pica L, Rocco A, De Giorgi F, Cuomo R, Sarnelli G. Effects of long-term PPI treatment on producing bowel symptoms and SIBO. Eur J Clin Invest. 2011; 41:380–6. doi: 10.1111/j.1365-2362.2010.02419.x PMID: 21128930
34. Simren M, Barbara G, Flint HJ, Spiegel BM, Spiller RC, Vanner S. Intestinal microbiota in functional bowel disorders: a Rome foundation report. Gut. 2013; 62:159–76. doi: 10.1136/gutjnl-2012-302167 PMID: 22730468
35. Cunningham R, Dale B, Undy B, Gaunt N. Proton pump inhibitors as a risk factor for Clostridium difficile diarrhoea. J Hosp Infect. 2003; 54:243–5. PMID: 12855243
36. Chen Y, Glass K, Liu B, Hope K, Kirk M. Salmonella Infection in Middle-Aged and Older Adults: Incidence and Risk Factors from the 45 and Up Study. Foodborne Pathog Dis. In press.
37. Proton Pump Inhibitors Information [Internet]. 2015 [cited February 02, 2016]. Available from: http://www.fda.gov/drugs/drugSafety/InformationbyDrugClass/ucm213259.
38. Renom-Guiteras A, Meyer G, Thürmann PA. The EU (7)-PIM list: a list of potentially inappropriate medications for older people consented by experts from seven European countries. Eur J Clin Pharmacol. 2015:1–15.
39. Hungin APS, Hill C, Molloy–Bland M, Raghunath A. Systematic review: patterns of proton pump inhibitor use and adherence in gastroesophageal reflux disease. Clin Gastroenterol Hepatol. 2012; 10:109–16. doi: 10.1016/j.cgh.2011.07.008 PMID: 21782770

40. Mealing NM, Banks E, Jorm LR, Steel DG, Clements MS, Rogers KD. Investigation of relative risk estimates from studies of the same population with contrasting response rates and designs. BMC Med Res Methodol. 2010; 10:26. doi: 10.1186/1471-2288-10-26 PMID: 20356408

Chapter 7

Paper four: Norovirus disease in older adults living in long-term care facilities: strategies for management

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About This Chapter

This chapter synthesises the literature regarding norovirus infection in elderly people living in long-term care facilities (LTCFs). The literature review highlights the significant burden of norovirus infection in LTCFs, and that outbreak-associated infection is a major problem for those facilities. This paper also proposes several strategies for disease management in LTCFs. It is an invited review from the journal *Current Geriatrics Reports*, and contributes to answering the research question: 'What is the epidemiology of gastroenteritis in middle-aged and older adults?'.

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Norovirus Disease in Older Adults Living in Long-Term Care Facilities: Strategies for Management

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Abstract
Purpose of Review Noroviruses are the most common cause of gastroenteritis outbreaks in long-term care facility (LTCFs). This review summarizes the most up-to-date knowledge on norovirus infection in LTCFs with the aim of identifying potential strategies for management.
Recent Findings LTCF residents are at greater risk of norovirus infection. Early identification of norovirus infection and prompt initiation of appropriate supportive therapy are required to reduce morbidity and mortality. Measures to prevent outbreaks and reduce the risk of norovirus infection in LTCFs include timely diagnosis and implementation of infection control interventions to limit virus transmission.
Summary Current guidelines for prevention and control are based on generic principles of infection control. Real-time reverse transcription-quantitative polymerase chain reaction assays have been the gold standard for the rapid and sensitive detection of noroviruses. With the recent breakthroughs of human norovirus in vitro culture, doors are now opened to evaluate the efficacy of environmental disinfectants and hand hygiene options. Additionally, development of licensed vaccines against noroviruses may provide another important tool for infection prevention among high-risk individuals.

Keywords Norovirus · Older adults · Long-term care facilities · Management

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Introduction

Human noroviruses are globally important pathogens, contributing substantially to the burden of acute gastroenteritis across all age groups. The World Health Organization recently estimated that noroviruses caused 684 million illnesses and over 200,000 deaths globally in 2010 [1••]. Ahmed et al. conducted a systematic review of the scientific literature published from January 1, 2008, to March 8, 2014, and found that noroviruses were associated with almost one fifth of all cases of acute gastroenteritis, and the prevalence was higher in high income countries compared to low- and middle-income countries [2••].

Long-term care facilities (LTCFs) are common settings for outbreaks of norovirus infection, where they are responsible for 30–80% of acute gastroenteritis outbreaks [3, 4, 5, 6•]. While noroviruses can cause both sporadic infections and outbreaks in all age groups, older people are at higher risks of hospitalization and death [3], owing to intrinsic factors, such as age-related immunosenescence or the presence of comorbid conditions, which result in more extended symptoms [7]. Additionally, elderly residents of LTCFs are at elevated risks of infection as a result of institutionalized confinement that promotes transmission by sharing rooms and touching common surfaces [8]. This review summarizes the most up-to-date knowledge on norovirus infection in LTCF residents with the aim of identifying potential strategies for management.

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Infection in Older Adults and in LTCFs

Norovirus infection generally manifests as a relatively brief, self-limited illness in healthy immunocompetent individuals, although it can cause significant morbidity and mortality in frail elderly adults. Lindasay et al. reviewed 39 studies on risk estimates of norovirus infection and found a high burden of the infection in all ages with the highest rates of hospitalization and death among the elderly [3]. Older people are at higher risk of norovirus-associated hospitalization, resulting in excess hospital stays and greater costs compared to young adults [3]. The overall estimates of disease burden suggest that noroviruses are responsible for approximately 10–20% of gastroenteritis hospitalizations, 10–15% of gastroenteritis deaths, and ≥0.2% of all-cause mortality among older adults in upper-middle-income and high-income countries [9, 10, 11•, 12, 13]. Additional data also suggest that noroviruses may trigger severe clinical complications, including acute renal failure, arrhythmia, chronic diarrhea, and severe enteropathy [14, 15].

Noroviruses are the most common cause of gastroenteritis outbreaks in LTCFs [16]. Review of US outbreak surveillance data show that over 60% of all norovirus outbreaks occur in LTCFs [17], while in other high-income countries norovirus outbreaks occur with roughly equal frequency in both acute-care hospitals and LTCFs. The definition of LTCFs differs between studies, but LTCFs generally refer to facilities that provide prolonged care for individuals who required daily living and/or nursing care support. Whereas most community cases of norovirus are self-limiting within 12–60 h, outbreaks of norovirus can significantly impact the institutionalized elderly and cause more severe or prolonged illness [18•, 19, 20]. Several factors contribute to the enhanced risk of severe norovirus infection among older adults living in LTCFs, including nutritional status, immunodeficiency or senescence, chronic inflammation, microbiome alterations, and the use of certain medications [21]. Decreased ability to maintain adequate personal hygiene may also increase individual risk among LTCF residents. Environmental factors, such as residence in close, shared quarters, use of shared facilities, and limited ability to isolate infected residents, may contribute to virus transmission in LTCFs. Shared dining facilities may also increase risk for foodborne exposures.

Infection Transmission

Transmission of human noroviruses can occur directly through person-to-person contact, or indirectly through consumption of contaminated food or water, or through contact with contaminated environmental surfaces (Fig. 1). Person-to-person transmission is responsible for >90% of the norovirus outbreaks in healthcare settings, where close living arrangements, shared facilities and contact with visitors and staff increase the risk of norovirus spread from one person to another [17, 22]. Foodborne transmission is another important route for the spread of noroviruses [1••] and can occur when food handlers contaminate food on site or during the earlier steps of food production [23]. An analysis of surveillance data on norovirus outbreaks in the USA, Europe, and New Zealand estimated that about 14% of norovirus outbreaks were attributed to foodborne transmission [24]. Noroviruses can also be transmitted through contaminated environment surfaces and aerosolized particles. Aerosolization of norovirus via vomitus can be particularly problematic in LTCFs, as virus particles can settle on surfaces and survive for long periods of time, leading to environmental contamination for future exposure [25].

The high shedding titers in feces and vomit [26], low level of infectious dose [27], and environmental stability [28] enable the virus to efficiently transmit via multiple modes. Transmission has also been reported to occur before the onset of symptoms [29], in the postsymptomatic period, and during subclinical infections [30]. Investigations of norovirus outbreaks in LTCFs confirmed that infected persons can asymptomatically shed virus at high levels for at least 3 weeks [31••], although reports from nosocomial norovirus outbreaks have shown that symptomatic patients contribute primarily to transmission of infection [32].

Importance of Genetic Diversity and Evolution

Noroviruses, divided into at least six genogroups (GI–GVI) and more than 40 different genotypes (e.g., GII.4), are a genetically diverse group of non-enveloped single-stranded positive-sense RNA viruses [33]. The prevalence of infecting genogroups and genotypes differ between populations and route of transmission [22]. Genogroup I viruses are generally associated with foodborne or waterborne outbreaks [24, 34], while GII.4 viruses are strongly associated with person-to-person transmission and occur predominantly in healthcare and institutional settings [5, 6•, 35, 36]. Infections with GII.4 viruses are more likely to cause severe infections, leading to more hospitalization and deaths than those caused by other GII or GI viruses [37]. Multiple strains of noroviruses can cause human reinfection. Protective immunity to specific types of noroviruses has been reported, but with a limited duration [38].

Despite the extensive genetic diversity, previous data suggest that GII.4 viruses are responsible for the majority of norovirus outbreaks worldwide [39], with a new GII.4 variant strain emerging every 2–4 years [40]. Several mechanisms may enhance GII.4 evolution, including the host herd immunity that drives antigenic drift in the hypervariable P2 domain [41••]. This domain of the viral capsid binds with human histo-blood group antigens (HBGAs), which serve as a point

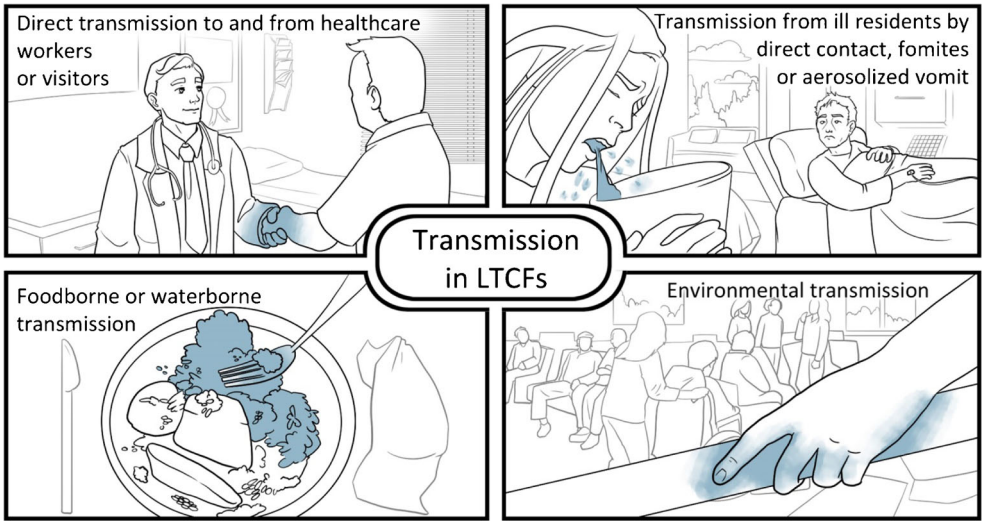

Fig. 1 Norovirus transmission in long-term care facilities

for initial viral attachment [42]. GII.4 viruses can bind a wider range of HBGAs than other genotypes, causing infections to a larger susceptible population [33]. Another explanation for the emergence of novel GII.4 variants is related to homologous recombination, which contributes to the emergence of the recent pandemic GII.4 variants, such as GII.4 New Orleans 2009, and GII.4 Sydney 2012 [43]. The emergence of epidemic strains of noroviruses has contributed to the changing epidemiology of norovirus infection worldwide [44, 45].

Clinical Features and Diagnosis

Noroviruses are highly contagious. Ingestion of a small number of viral particles can lead to infection [27]. The onset of norovirus infection occurs after an average incubation period of 1.2 (range 1–2) days [46]. Vomiting is a cardinal sign of norovirus infection, along with acute onset of other gastrointestinal symptoms including nausea, watery and non-bloody diarrhea, and abdominal cramps. Symptoms often last for 24–72 h with complete recovery in immunocompetent individuals [19], although older frail people may present with prolonged symptoms and develop complications. One study describing the clinical characteristics of nosocomial outbreaks found that elderly hospitalized patients had prolonged symptoms with norovirus infection, and almost one third of the patients experienced dehydration [47]. Notably, the majority of those study participants (83.9%) had underlying chronic conditions, suggesting that the impact of norovirus infection is more pronounced among older adults with comorbid conditions.

It is difficult to diagnose norovirus gastroenteritis in individual patients on the basis of clinical features alone. The definition for norovirus infection in LTCFs requires the presence of both a compatible clinical presentation and a laboratory confirmation [48]. Historically, human noroviruses could not be cultured in vitro. However, Jones et al. recently published a protocol describing methods for culturing the GII.4-Sydney human norovirus strain directly in human B lymphocytes [49••]. This is a breakthrough research, as for the first time, a human norovirus can be grown in a culture dish. It enables research into the development of antiviral drugs, as well as opens a door to definitively evaluate the efficacy of infection control and prevention options.

Diagnostic methods of norovirus infection have focused on detecting viral RNA or antigen. In recent years, real-time reverse transcription-quantitative polymerase chain reaction (RT-qPCR) assays have become the gold standard for the rapid and sensitive detection of noroviruses in stool, vomitus, foods, water, and environmental specimens [33]. However, virus detection by RT-qPCR does not always correlate with the disease. Infected persons can shed virus for weeks after recovery from clinical symptoms, and noroviruses are also frequently detected in stool samples from asymptomatic patients. Chan et al. analyzed data collected from sporadic cases and speculated a correlation between viral load and virus transmission from infected persons to susceptible hosts through fecal-oral route [50]. This finding indicates that assessment of a possible difference in viral load in samples may be a useful tool to aid clinical interpretation and to assess causal relationship.

Given the rapid spread of noroviruses, especially during outbreaks, timely diagnosis is essential to assist management and implementation of appropriate control measures. Rapid commercial assays, such as enzyme immunoassays (EIAs) have been cleared by the US Food and Drug Administration to detect norovirus antigen in stool samples during outbreaks. However, due to the poor sensitivity of EIAs [51], samples with negative results should be confirmed by a second technique, such as RT-qPCR [52]. Consequently, EIA kits should not replace molecular methods during outbreak investigations, and caution should be used when interpreting test results from sporadic cases [52].

In the absence of laboratory diagnostic tests or delays in obtaining laboratory results, outbreaks of norovirus infection can be identified according to Kaplan criteria [53]. These criteria are based on the clinical and epidemiological profile of illness, which include (1) vomiting in >50% of patients, (2) a mean incubation period of 24–48 h, (3) a mean duration of illness of 12–60 h, and (4) lack of bacterial pathogens in stool culture. The set of Kaplan criteria is highly specific (99%), although with moderate sensitivity (68%) in discriminating outbreaks due to bacteria from those due to norovirus [54]. In LTCF, outbreaks satisfying Kaplan's criteria may justify rapid institution of control measures to limit spread of infection.

Treatment

Currently, there is no specific antiviral therapy available to treat norovirus infection. The management of patients is primarily supportive and focuses on treatment of dehydration and infection control measures to prevent further spread. Dehydration is the most common complication that requires medical care and is especially of concern among LTCF residents with underlying chronic conditions [55]. Patients with comorbidities are often prescribed multiple medications, some of which may have a potential for drug interactions. Therefore, the effect of fluid and electrolyte disturbance on medications should be closely monitored among elderly patients.

Despite recent progress in the development of norovirus vaccines, licensed products are not yet available. Clinical trials have demonstrated safety, immunogenicity, and efficacy of some products [56, 57], although the development of norovirus vaccines is challenging due to the high degree of virus genetic diversity, rapidly evolving new variant strains, and an incomplete understanding of immune correlates of protection [41••, 58••]. The future efficacy of norovirus vaccines may rely on the development of products eliciting a broad cross-protective immune response against heterologous virus [41••]. It is clear that older adults living in LTCFs are at higher risks of norovirus infection and are more likely to have worse outcomes. Therefore, vaccinating LTCFs residents would be beneficial to directly prevent infection transmission and reduce disease burden [59•].

Prevention and Control of Norovirus Outbreaks in LTCFs

The highly infectious nature of noroviruses and their environmental persistence pose multiple challenges to infection management in LTCFs. In 2011, the Centers for Disease Control and Prevention published guidelines providing recommendations for the prevention and control of norovirus gastroenteritis outbreaks in healthcare facilities [60]. Table 1 summarizes the risk-based approach for norovirus infection prevention and management in LTCFs, based on these guidelines and other published recommendations [52, 60, 62, 63, 73•]. The major strategies have included measures for timely diagnosis and implementation of infection control interventions to limit virus transmission.

Cohorting and Exclusion

Social distancing measures, such as isolation or cohorting of symptomatic patients, have been successful in limiting norovirus transmission in large outbreaks [61]; however, the appropriate duration of isolation and use of contact precautions are uncertain. Patients may continue to shed norovirus in

Table 1 Measures recommended to manage norovirus infection in long-term care facilities

Surveillance and diagnosis
• Surveillance for infectious gastroenteritis
• Access to laboratory facilities capable of timely and accurate diagnosis of infection;
• Rapid testing of stool specimens for norovirus
• Outbreak notifications to appropriate health departments if norovirus gastroenteritis is suspected
Disease control and prevention practices
Interruption of person-to-person transmission
• Isolation and cohorting of infected persons, if feasible
• Minimizing resident transfers
• Adherence to personal protective equipment use for persons entering the patient care areas or caring for ill residents
• Hand hygiene with soap and water after contact with infected residents, their body substances, or potentially contaminated environment
• Informing visitors and residents about importance of hand hygiene to prevent infection spread
• Training staff about the transmission, clinical features, diagnosis, management, and prevention of norovirus infection
• Minimizing staff working at multiple facilities
• Ill staff exclusion until ≥48 h after symptoms resolve
Interruption of transmission via contaminated environment
• Disinfection and clean areas of any organic material
• Disinfection and sterilization using EPA approved products
• Restriction of staff working in contaminated areas
• Increasing the frequency of cleaning and disinfection of patient care areas and frequently touched surfaces during outbreaks
Interruption of transmission via contaminated food and water
• Avoiding bare-hand contact with ready-to-eat foods and appropriately hand hygiene practice before preparing foods
• Washing fresh foods and cooking shellfish thoroughly
• Enhancing cleaning in food facilities and contaminated areas
• Exclusion of ill food handlers until ≥48 h after symptoms resolve

their stool after resolution of symptoms, and recommendations have been made to minimize contact with patients during the acute phase of illness, and 24–72 h following recovery while patients still shed virus at high levels [52]. This is particularly important during outbreaks in LTCFs to help break the transmission cycle, prevent the amount of secondary transmission, and also decrease the outbreak duration. Most guidelines recommend cohorting patients into groups according to symptomatic, exposed asymptomatic, and unexposed asymptomatic status, with dedicated healthcare staff providing care for infected patients [52, 62, 63]. To minimize the risk of transmission from incubating or asymptomatic cases, such patients should not be transferred to unaffected areas, typically within 48 h after exposure [52].

Environmental Disinfection

Noroviruses are stable and persistent in the environment [64]. Current evidence suggests that environmental contamination with norovirus is common both within and outside outbreak settings [28]. Therefore, environmental cleaning and chemical disinfection are essential to interrupt the chain of virus transmission. To maximize penetration and efficacy, initial cleaning to remove gross organic matter should precede chemical disinfection. CDC recommends sodium hypochlorite at concentration of ≥1000 ppm for disinfection of hard and nonporous environmental surfaces if feasible [52, 65]. The US Environmental Protection Agency (EPA) has published a list of registered disinfectants for use in healthcare settings against noroviruses (https://www.epa.gov/sites/production/files/2016-06/documents/list_g_norovirus.pdf).

Hand Hygiene

Hand hygiene is another key part of interrupting the norovirus transmission cycle, including environmentally mediated transmission as contaminated hands can transfer virus to touched surfaces, or vice versa [66]. Actively promoting adherence to hand hygiene among staff and residents is strongly recommended and should be implemented [52]. Handwashing with soap and water have been reported as preferred means to prevent infection, especially during an outbreak or if there is gross fecal soiling of the hands [8, 52]. The efficacy of alcohol-based sanitizers against noroviruses remains controversial, and further research is required to evaluate the efficacy of alcohol-based hand sanitizers against the virus [67, 68]. As an additional preventive strategy during outbreaks, use of gloves is recommended.

Staff Members

Staff of LTCFs plays an important role in infection transmission. A recent meta-analysis summarizing risk factors of norovirus spread in nursing homes found a positive association between bedside care and the infection [69]. Training staff on the relevant guidelines and personal hygiene practices is important to prevent transmission in LTCFs. Exposure to vomit is another infectious risk [69]. Use of personal protective equipment, including gowns and facial masks, is recommended for staff entering the patient care area or caring for patients with gastroenteritis symptoms to reduce the likelihood of exposure [60]. Ill staff members should not return to work until ≥48 h after symptoms resolve [52, 70]. During outbreaks of norovirus, staff working in multiple facilities may facilitate spread of infection to other LTCF.

Food Safety

While food may become contaminated during production, most norovirus contamination occurs during preparation [71•]. Bare-hand contact by contagious workers with ready-to-eat foods has been frequently identified in the majority of reported foodborne norovirus outbreaks [71•]. Highly infectious noroviruses may be transmitted through contaminated food by ill catering or food service staff in LTCFs. Therefore, food handlers are recommended to adherence to appropriate recommendations for hand washing and avoiding bare-hand contact with ready-to-eat foods (e.g., through use of gloves or utensils). Ill food handlers should not return to work until ≥48 h after symptom resolve [71•]. For asymptomatic food service staff who have tested positive for norovirus, exclusion is recommended [52]. CDC also recommends washing fresh product and thoroughly cooking shellfish as additional specific measures for preventing foodborne norovirus transmission (http://www.cdc.gov/norovirus/preventing-infection.html).

Surveillance and Outbreak Management

Surveillance for norovirus infection is recommended in LTCFs to determine infection rates and outbreaks using the standard case definition [48]. Outbreaks of norovirus infection should be reported to health departments in accordance with local regulations. Outbreak management is a multistage process, including preparedness, identification, response, and evaluation [72]. Guidelines for managing norovirus outbreaks have been published by public health agencies in several high-income countries [60, 62, 63]. Generally, LTCFs should develop outbreak plans outlining management arrangements for outbreaks, which may require involvement of public health agencies. A facility outbreak control team, including physicians, nurses, facility managers, and domestic staff should aim to minimize the early spread of infection. The main approaches to infection control and prevention include implementing policies concerning hand hygiene, patient isolation and cohorting, ill staff exclusion from work, visitor

restrictions, food safety, and environmental cleaning and disinfection [52, 60, 62, 63, 73•]. Early detection and isolation of sporadic cases are also recommended to reduce the impact of noroviruses introduced into LTCFs [69].

Conclusions

The key means of managing norovirus infection in LTCFs are well-functioning infection control programs. Current guidelines for prevention and control are generally based on infection control principles, although the efficacy of those control measures is poorly quantified due to the inability to culture the virus. With the recent breakthroughs of human norovirus in vitro culture, doors are now opened to, for example, definitively evaluate the efficacy of environmental disinfectants and hand hygiene options. In addition, there is no specific antiviral therapy available to treat norovirus infection. Therefore, development of licensed vaccines against noroviruses may provide another important tool for infection prevention among high-risk individuals.

Compliance with Ethical Standards

Conflict of Interest Yingxi Chen, Aron Hall and Martyn Kirk declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Human and Animal Rights All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

Disclaimer The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.•• Kirk MD, Pires SM, Black RE, Caipo M, Crump JA, Devleesschauwer B, et al. World Health Organization estimates of the global and regional disease burden of 22 foodborne bacterial, protozoal, and viral diseases, 2010: a data synthesis. PLoS Med. 2015;12:e1001921. **Most recent estimates of the global burden of 22 foodborne bacterial, protozoal, and viral infections.**

2.•• Ahmed SM, Hall AJ, Robinson AE, Verhoef L, Premkumar P, Parashar UD, et al. Global prevalence of norovirus in cases of gastroenteritis: a systematic review and meta-analysis. Lancet Infect Dis. 2014;14:725–30. **Reviews the global prevalence of norovirus gastroenteritis.**

3. Lindsay L, Wolter J, De Coster I, Van Damme P, Verstraeten T. A decade of norovirus disease risk among older adults in upper-middle and high income countries: a systematic review. BMC Infect Dis. 2015;15:425.

4. Kirk MD, Fullerton KE, Hall GV, Gregory J, Stafford R, Veitch MG, et al. Surveillance for outbreaks of gastroenteritis in long-term care facilities, Australia, 2002–2008. Clin Infect Dis. 2010;51:907–14.

5. Rosenthal NA, Lee LE, Vermeulen BA, Hedberg K, Keene WE, Widdowson MA, et al. Epidemiological and genetic characteristics of norovirus outbreaks in long-term care facilities, 2003-2006. Epidemiol Infect. 2011;139:286–94.

6.• Hall AJ, Wikswo ME, Manikonda K, Roberts VA, Yoder JS, Gould LH. Acute gastroenteritis surveillance through the National Outbreak Reporting System, United States. Emerg Infect Dis. 2013;19:1305–9. **Demonstrates a more complete characterization of acute gastroenteritis outbreaks, particularly the relative importance of specific transmission modes and settings for norovirus.**

7. Payne R, Forde D, Vedio A, Cope A, Pratt G, Tunbridge A. 'It's just a virus'—viral illness in older people: prevention and management. Rev Clin Gerontol. 2013;23:131–41.

8. Rajagopalan S, Yoshikawa TT. Norovirus infections in long-term care facilities. J Am Geriatr Soc. 2016;64:1097–103.

9. Haustein T, Harris JP, Pebody R, Lopman BA. Hospital admissions due to norovirus in adult and elderly patients in England. Clin Infect Dis. 2009;49:1890–2.

10. van Asten L, Siebenga J, van den Wijngaard C, Verheij R, van Vliet H, Kretzschmar M, et al. Unspecified gastroenteritis illness and deaths in the elderly associated with norovirus epidemics. Epidemiol. 2011;22:336–43. doi:10.1097/EDE.0b013e31821179af.

11.• Gastanaduy PA, Hall AJ, Curns AT, Parashar UD, Lopman BA. Burden of norovirus gastroenteritis in the ambulatory setting–United States, 2001-2009. J Infect Dis. 2013;207:1058–65. **Estimates the burden of norovirus gastroenteritis in ambulatory US patients.**

12. Schmid D, Kuo HW, Simons E, Kanitz EE, Wenisch J, Allerberger F, et al. All-cause mortality in hospitalized patients with infectious diarrhea: Clostridium difficile versus other enteric pathogens in Austria from 2008 to 2010. J Infect Public Health. 2014;7:133–44.

13. Hall AJ, Curns AT, McDonald LC, Parashar UD, Lopman BA. The roles of Clostridium Difficile and norovirus among gastroenteritis-associated deaths in the United States, 1999-2007. Clin Infect Dis. 2012;55:216–23.

14. Mattner F, Sohr D, Heim A, Gastmeier P, Vennema H, Koopmans M. Risk groups for clinical complications of norovirus infections: an outbreak investigation. Clin Microbiol Infect. 2006;12:69–74.

15. Woodward JM, Gkrania-Klotsas E, Cordero-Ng AY, Aravinthan A, Bandoh BN, Liu H, et al. The role of chronic norovirus infection in the enteropathy associated with common variable immunodeficiency. Am J Gastroenterol. 2015;110:320–7.

16. Greig JD, Lee MB. Enteric outbreaks in long-term care facilities and recommendations for prevention: a review. Epidemiol Infect. 2009;137:145–55.

17. Vega E, Barclay L, Gregoricus N, Shirley SH, Lee D, Vinje J. Genotypic and epidemiologic trends of norovirus outbreaks in the United States, 2009 to 2013. J Clin Microbiol. 2014;52:147–55.

18.• Trivedi TK, Desai R, Hall AJ, Patel M, Parashar UD, Lopman BA. Clinical characteristics of norovirus-associated deaths: a systematic literature review. Am J Infect Control. 2013;41:654–7. **Reviews of**

clinical and epidemiologic characteristics of deaths assocaited with norovirus infection.

19. Lopman BA, Reacher MH, Vipond IB, Sarangi J, Brown DW. Clinical manifestation of norovirus gastroenteritis in health care settings. Clin Infect Dis. 2004;39:318–24.
20. Kaufman SS, Green KY, Korba BE. Treatment of norovirus infections: moving antivirals from the bench to the bedside. Antivir Res. 2014;105:80–91.
21. Iturriza-Gomara M, Lopman B. Norovirus in healthcare settings. Curr Opin Infect Dis. 2014;27:437–43.
22. Kroneman A, Verhoef L, Harris J, Vennema H, Duizer E, van Duynhoven Y, et al. Analysis of integrated virological and epidemiological reports of norovirus outbreaks collected within the foodborne viruses in Europe network from 1 July 2001 to 30 June 2006. J Clin Microbiol. 2008;46:2959–65.
23. Rodriguez-Lazaro D, Cook N, Ruggeri FM, Sellwood J, Nasser A, Nascimento MS, et al. Virus hazards from food, water and other contaminated environments. FEMS Microbiol Rev. 2012;36:786–814.
24. Verhoef L, Hewitt J, Barclay L, Ahmed SM, Lake R, Hall AJ, et al. Norovirus genotype profiles associated with foodborne transmission, 1999-2012. Emerg Infect Dis. 2015;21:592–9.
25. Repp KK, Keene WE. A point-source norovirus outbreak caused by exposure to fomites. J Infect Dis. 2012;205:1639–41.
26. Atmar RL, Opekun AR, Gilger MA, Estes MK, Crawford SE, Neill FH, et al. Norwalk virus shedding after experimental human infection. Emerg Infect Dis. 2008;14:1553–7.
27. Teunis PFM, Moe CL, Liu P, Miller S, Lindesmith L, Baric RS, et al. Norwalk virus: how infectious is it? J Med Virol. 2008;80:1468–76.
28. Lopman B, Gastañaduy P, Park GW, Hall AJ, Parashar UD, Vinje J. Environmental transmission of norovirus gastroenteritis. Curr Opin Virol. 2012;2:96–102.
29. Ozawa K, Oka T, Takeda N, Hansman GS. Norovirus infections in symptomatic and asymptomatic food handlers in Japan. J Clin Microbiol. 2007;45:3996–4005.
30. Sukhrie FA, Teunis P, Vennema H, Copra C, Thijs Beersma MFC, Bogerman J, et al. Nosocomial transmission of norovirus is mainly caused by symptomatic cases. Clin Infect Dis. 2012;54:931–7.
31.•• Costantini VP, Cooper EM, Hardaker HL, Lee LE, Bierhoff M, Biggs C, et al. Epidemiologic, virologic, and host genetic factors of norovirus outbreaks in long-term care facilities. Clin Infect Dis. 2016;62:1–10. **Demostrates the epidemiology, virology, and genetic host factors of naturally occurring norovirus outbreaks in LTCF.**
32. Teunis PF, Sukhrie FH, Vennema H, Bogerman J, Beersma MF, Koopmans MP. Shedding of norovirus in symptomatic and asymptomatic infections. Epidemiol Infect. 2015;143:1710–7.
33. Vinje J. Advances in laboratory methods for detection and typing of norovirus. J Clin Microbiol. 2015;53:373–81.
34. Lysen M, Thorhagen M, Brytting M, Hjertqvist M, Andersson Y, Hedlund KO. Genetic diversity among food-borne and waterborne norovirus strains causing outbreaks in Sweden. J Clin Microbiol. 2009;47:2411–8.
35. Hall AJ, Eisenbart VG, Etingue AL, Gould LH, Lopman BA, Parashar UD. Epidemiology of foodborne norovirus outbreaks, United States, 2001-2008. Emerg Infect Dis. 2012;18:1566–73.
36. Bruggink LD, Oluwatoyin O, Sameer R, Witlox KJ, Marshall JA. Molecular and epidemiological features of gastroenteritis outbreaks involving genogroup I norovirus in Victoria, Australia, 2002-2010. J Med Virol. 2012;84:1437–48.
37. Desai R, Hembree CD, Handel A, Matthews JE, Dickey BW, McDonald S, et al. Severe outcomes are associated with genogroup 2 genotype 4 norovirus outbreaks: a systematic literature review. Clin Infect Dis. 2012;55:189–93.
38. Ayukekbong JA, Fobisong C, Tah F, Lindh M, Nkuo-Akenji T, Bergstrom T. Pattern of circulation of norovirus GII strains during natural infection. J Clin Microbiol. 2014;52:4253–9.
39. Siebenga JJ, Vennema H, Zheng DP, Vinje J, Lee BE, Pang XL, et al. Norovirus illness is a global problem: emergence and spread of norovirus GII.4 variants, 2001-2007. J Infect Dis. 2009;200:802–12.
40. Zheng DP, Widdowson MA, Glass RI, Vinje J. Molecular epidemiology of genogroup II-genotype 4 noroviruses in the United States between 1994 and 2006. J Clin Microbiol. 2010;48:168–77.
41.•• de Graaf M, van Beek J, Koopmans MP. Human norovirus transmission and evolution in a changing world. Nat Rev Microbiol. 2016;14:421–33. **Most recent review describing the transmission, pathogenesis and evolution of human noroviruses, and considering the ongoing risk of norovirus outbreaks, along with the future prospects for treatment.**
42. Lindesmith LC, Beltramello M, Donaldson EF, Corti D, Swanstrom J, Debbink K, et al. Immunogenetic mechanisms driving norovirus GII.4 antigenic variation. PLoS Pathog. 2012;8:e1002705.
43. Eden JS, Tanaka MM, Boni MF, Rawlinson WD, White PA. Recombination within the pandemic norovirus GII.4 lineage. J Virol. 2013;87:6270–82.
44. Hasing ME, Lee BE, Preiksaitis JK, Tellier R, Honish L, Senthilselvan A, et al. Emergence of a new norovirus GII.4 variant and changes in the historical biennial pattern of norovirus outbreak activity in Alberta, Canada, from 2008 to 2013. J Clin Microbiol. 2013;51:2204–11.
45. Allen DJ, Adams NL, Aladin F, Harris JP, Brown DW. Emergence of the GII-4 Norovirus Sydney 2012 strain in England, winter 2012-2013. PLoS One. 2014;9:e88978.
46. Lee RM, Lessler J, Lee RA, Rudolph KE, Reich NG, Perl TM, et al. Incubation period of viral gastroenteritis: a systematic review. BMC Infect Dis. 2013;13:446.
47. Tsang OTY, Wong ATY, Chow CB, Yung RWH, Lim WWL, Liu SH. Clinical characteristics of nosocomial norovirus outbreaks in Hong Kong. J Hosp Infect. 2008;69:135–40.
48. Stone ND, Ashraf MS, Calder J, Crnich CJ, Crossley K, Drinka PJ, et al. Surveillance definitions of infections in long-term care facilities: revisiting the McGeer criteria. Infect Control Hosp Epidemiol. 2012;33:965–77.
49.•• Jones MK, Grau KR, Costantini V, Kolawole AO, de Graaf M, Freiden P, et al. Human norovirus culture in B cells. Nat Protoc. 2015;10:1939–47. **Describes the first cell culture system for a human norovirus.**
50. Chan MC, Sung JJ, Lam RK, Chan PK, Lee NL, Lai RW, et al. Fecal viral load and norovirus-associated gastroenteritis. Emerg Infect Dis. 2006;12:1278–80.
51. Wilhelmi de Cal I, Revilla A, del Alamo JM, Roman E, Moreno S, Sanchez-Fauquier A. Evaluation of two commercial enzyme immunoassays for the detection of norovirus in faecal samples from hospitalised children with sporadic acute gastroenteritis. Clin Microbiol Infect. 2007;13:341–3.
52. Updated norovirus outbreak management and disease prevention guidelines. MMWR Recomm Rep. 2011;60: 1–18.
53. Kaplan JE, Gary GW, Baron RC, Singh N, Schonberger LB, Feldman R, et al. Epidemiology of Norwalk gastroenteritis and the role of Norwalk virus in outbreaks of acute nonbacterial gastroenteritis. Ann Intern Med. 1982;96:756–61.
54. Turcios RM, Widdowson MA, Sulka AC, Mead PS, Glass RI. Reevaluation of epidemiological criteria for identifying outbreaks of acute gastroenteritis due to norovirus: United States, 1998-2000. Clin Infect Dis. 2006;42:964–9.
55. Goller JL, Dimitriadis A, Tan A, Kelly H, Marshall JA. Long-term features of norovirus gastroenteritis in the elderly. J Hosp Infect. 2004;58:286–91.

56. Lindesmith LC, Ferris MT, Mullan CW, Ferreira J, Debbink K, Swanstrom J, et al. Broad blockade antibody responses in human volunteers after immunization with a multivalent norovirus VLP candidate vaccine: immunological analyses from a phase I clinical trial. PLoS Med. 2015;12:e1001807.
57. Atmar RL, Baehner F, Cramer JP, Song E, Borkowski A, and Mendelman PM. Rapid Responses to Two Virus-Like Particle Norovirus Vaccine Candidate Formulations in Healthy Adults: A Randomized Controlled Trial. J Infect Dis. 2016;In press.
58.•• Lopman BA, Steele D, Kirkwood CD, Parashar UD. The vast and varied global burden of norovirus: prospects for prevention and control. PLoS Med. 2016;13:e1001999. **Reviews the evidence for the global burden of norovirus and discusses the prospects for norovirus vaccine development.**
59.• Aliabadi N, Lopman BA, Parashar UD, Hall AJ. Progress toward norovirus vaccines: considerations for further development and implementation in potential target populations. Expert Rev Vaccines. 2015;14:1241–53. **Discusses recent data on human norovirus vaccine development and potential targets for implementation.**
60. MacCannell T, Umscheid CA, Agarwal RK, Lee I, Kuntz G, Stevenson KB. Guideline for the prevention and control of norovirus gastroenteritis outbreaks in healthcare settings. Infect Control Hosp Epidemiol. 2011;32:939–69.
61. Hansen S, Stamm-Balderjahn S, Zuschneid I, Behnke M, Ruden H, Vonberg RP, et al. Closure of medical departments during nosocomial outbreaks: data from a systematic analysis of the literature. J Hosp Infect. 2007;65:348–53.
62. Communicable Diseases Network Australia, Guidelines for the public health management of gastroenteritis outbreaks due to norovirus or suspected viral agents in Australia. 2010.
63. Party NW. Guidelines for the management of norovirus outbreaks in acute and community health and social care settings. London: Health Protection Agency; 2012.
64. D'Souza DH, Sair A, Williams K, Papafragkou E, Jean J, Moore C, et al. Persistence of caliciviruses on environmental surfaces and their transfer to food. Int J Food Microbiol. 2006;108:84–91.
65. Park GW, Sobsey MD. Simultaneous comparison of murine norovirus, feline calicivirus, coliphage MS2, and GII.4 norovirus to evaluate the efficacy of sodium hypochlorite against human norovirus on a fecally soiled stainless steel surface. Foodborne Pathog Dis. 2011;8:1005–10.
66. Otter JA, Yezli S, French GL. The role played by contaminated surfaces in the transmission of nosocomial pathogens. Infect Control Hosp Epidemiol. 2011;32:687–99.
67. Park GW, Barclay L, Macinga D, Charbonneau D, Pettigrew CA, Vinje J. Comparative efficacy of seven hand sanitizers against murine norovirus, feline calicivirus, and GII.4 norovirus. J Food Prot. 2010;73:2232–8.
68. Liu P, Yuen Y, Hsiao HM, Jaykus LA, Moe C. Effectiveness of liquid soap and hand sanitizer against Norwalk virus on contaminated hands. Appl Environ Microbiol. 2010;76:394–9.
69. Petrignani M, van Beek J, Borsboom G, Richardus JH, Koopmans M. Norovirus introduction routes into nursing homes and risk factors for spread: a systematic review and meta-analysis of observational studies. J Hosp Infect. 2015;89:163–78.
70. Friesema IH, Vennema H, Heijne JC, de Jager CM, Morroy G, van den Kerkhof JH, et al. Norovirus outbreaks in nursing homes: the evaluation of infection control measures. Epidemiol Infect. 2009;137:1722–33.
71.• Hall AJ, Wikswo ME, Pringle K, Gould LH, Parashar UD. Vital signs: foodborne norovirus outbreaks - United States, 2009-2012. MMWR Morb Mortal Wkly Rep. 2014;63:491–5. **Analysis of surveillance data suggests that food workers were associated with 70% of foodborne norovirus outbreaks reported to the National Outbreak Reporting System in the US.**
72. Connolly MA, Communicable disease control in emergencies: a field manual. 2005: World Health Organization.
73.• Barclay L, Park GW, Vega E, Hall AJ, Parashar U, Vinjé J, et al. Infection control for norovirus. Clin Microb Infect. 2014;20:731–40. **Reviews of infection prevention and control for norovirus.**

Chapter 8

Paper five: *Salmonella* infection in middle-aged and older adults: incidence and risk factors from the 45 and Up Study

Chen Y, Glass K, Liu B, Hope K, Kirk M. *Salmonella* infection in middle-aged and older adults: incidence and risk factors from the 45 and Up Study. *Foodborne Pathog Dis*. 2016 Oct 6. In press. Mary Ann Liebert, Inc., Publishers.

About This Chapter

In this chapter, I analysed data collected from a population based cohort study that had been linked to routinely collected laboratory data and hospital separation data to estimate the incidence of, and identify risk factors for *Salmonella* infection and infection-related hospitalisation among middle-aged and older adults. Foodborne *Salmonella* infection results in a substantial burden globally, and studies examining the burden in older people are rare. In this paper, I report that approximately one-third of participants with *Salmonella* infection were hospitalised. Importantly, there was a different risk profile for human salmonellosis and infection-related hospitalisation in older adults. This paper contributes to answering the research question: 'What is the incidence of and risk factors for *Salmonella* infection in middle-aged and older adults?'. This paper was published in *Foodborne Pathogens and Disease*.

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Original Article

Salmonella Infection in Middle-Aged and Older Adults: Incidence and Risk Factors from the 45 and Up Study

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Abstract

Background: *Salmonella* infection is one of the most common foodborne bacterial pathogens, and causes a significant health burden globally. We investigated the incidence and risk factors for notification and hospitalization due to *Salmonella* infection in older adults.

Materials and Methods: We used the 45 and Up Study, a large-scale Australian prospective study of adults aged ≥45 years, with record linkage to multiple databases for the years 2006–2012 to estimate the incidence of notification and hospitalization for *Salmonella* infection and estimate hazard ratios using Cox regression.

Results: Over a total follow-up of 1,120,242 person-years, 333 adults had laboratory-confirmed *Salmonella* infection and 101 were hospitalized; the notification and hospitalization incidence were 29.7 (95% confidence interval [CI]: 26.9–33.3) and 9.0 (95% CI: 7.4–10.9) per 100,000 person-years, respectively. The risk of *Salmonella* infection notification did not differ by age, but risk of hospitalization increased with age. Elderly males had the highest risk of infection-related hospitalization. The risk of notification was higher for those living in rural or remote areas (adjusted hazard ratio [aHR] 1.7, 95% CI 1.3–2.2), those taking proton pump inhibitors (aHR 1.9, 95% CI 1.4–2.4), and those reporting chicken/poultry intake at least seven times per week (aHR 3.2, 95% CI 1.3–7.9).

Conclusions: Chicken consumption remains a significant risk factor for *Salmonella* infection, highlighting the importance of reducing contamination of poultry and improving food safety advice for older people.

Keywords: *Salmonella* infection, hospitalization, older adults

Introduction

Salmonella infection is a globally important cause of foodborne disease, causing an estimated 153 million cases and 56 thousand deaths globally in 2010 (Kirk *et al.*, 2015). *Salmonella* spp. are widely distributed in domestic and wild animals (World Health Organization, 2013) and most infections are transmitted through contaminated food of animal origin (Pires *et al.*, 2014). Transmission through contact with infected persons or animals and consumption of contaminated water are less common in industrialized countries (Sanchez-Vargas *et al.*, 2011). Surveillance for salmonellosis relies on molecular testing to identify common-source outbreaks. In Australia, *Salmonella* Typhimurium is one of the most common serotypes, causing sporadic infections and foodborne outbreaks, of which the majority are associated with the consumption of raw or undercooked eggs (Moffatt *et al.*, 2016).

The elderly are particularly vulnerable to *Salmonella* infection, although few studies have specifically examined risk factors for infection in this population. *Salmonella* infection in older people can cause invasive disease, resulting in severe complications (Parry *et al.*, 2013) and higher mortality (Scallan *et al.*, 2015). In one study in Victoria, Australia, examining *Salmonella* infection in people over 65 years old, the case fatality rate of people infected with *Salmonella* Typhimurium was 1.6%, compared to 1.2% for all other serotypes (Kirk *et al.*, 2012). In addition, the study found that rates of salmonellosis in elderly people rose dramatically over 2000–2009 (Kirk *et al.*, 2012). The cause of the increase in rates is unknown, although could be linked to consumption of chicken meat and eggs which were identified as the common source of outbreaks through surveillance (Ozfoodnet Working Group, 2015).

Understanding the epidemiology of *Salmonella* infection is important to guide interventions to reduce its health burden, particularly among high-risk groups. In this study,

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we estimate the incidence and risk factors for laboratory-confirmed *Salmonella* infection and hospitalization in a large prospective study of adults aged 45 years and older in the Australian state of New South Wales (NSW).

Materials and Methods

The Sax Institute's 45 and Up Study is a prospective cohort study of Australian adults aged 45 years and older, randomly sampled from the general population of the Australian state of NSW (population 6.8 million persons, 2006) (Australian Bureau of Statistics, 2007) (45 and up Study Collaborators *et al.*, 2008). Eligible individuals received a mailed invitation to participate, with an information leaflet, a consent form and the study questionnaire. Participants were recruited by completing the postal questionnaire between 2006 and 2008. The final study cohort includes ~10% of the whole population aged 45 years and older in NSW.

Self-reported data from the 45 and Up Study participants were linked to the NSW Notifiable Conditions Information Management System (NCIMS) (to June 30, 2012), the NSW Admitted Patient Data Collection (APDC) (to June 30, 2012), and the NSW Register of Births, Deaths and Marriages (RBDM) (to June 30, 2012). In NSW, health practitioners and laboratories are required to report confirmed *Salmonella* infection under the Public Health Act 2010 (NSW Ministry of Health, 2010). *Salmonella* infection is confirmed based on isolation or detection of non-typhoidal *Salmonella* (NTS) species, and only confirmed cases are entered into NCIMS (Department of Health).

The NCIMS database contains a record of all *Salmonella* infection notifications in NSW, including the estimated onset date, the type of laboratory specimen used for confirmation, and the serotype of *Salmonella*. The APDC records details of all hospital separations for NSW residents admitted to hospitals, the principal diagnosis responsible for the admission coded using the International Classification of Diseases 10th revision-Australian Modification (ICD-10-AM) and up to 54 additional diagnoses contributing to the hospitalization. The RBDM database provides information on all deaths in NSW and the date of death.

The Centre for Health Record Linkage conducted the data linkage independently using identifiers such as name and date of birth in each of the records. Audits demonstrated false positive and false negative linkage rates of respectively <0.5% and <0.1% (Centre for Health Record Linkage).

Case definitions

We defined participants as having a *Salmonella* infection notification if they had a linked NCIMS record of NTS infection and categorized them into two groups: *Salmonella* Typhimurium and all other *Salmonella* serotypes (other *Salmonella* serotypes). We defined participants as having a *Salmonella*-related hospitalization if they had a linked NCIMS record of a NTS infection and a hospital admission date within a period of 1 week before and up to 4 weeks following the date of the notification where the hospital diagnosis was coded with an ICD-10-AM code prefixed with A02 (other *Salmonella* infections), or A09 (other gastroenteritis and colitis of infectious and unspecified origin).

Statistical analysis

Participants who had a linked notification record for *Salmonella* infection in the 30 days before recruitment to the 45 and Up Study were excluded from the analysis. To estimate incidence of *Salmonella* infection notification, follow-up time was calculated from the date of study entry to the 45 and Up Study to the first notification of NTS infection, death, or the last date which we had complete linked follow-up data (June 30, 2012), whichever came first.

Incidence was calculated by age (45–54, 55–64, 65–74, 75–84, or ≥85 years), sex, annual household income (six categories from less than $20,000 to $70,000 or more per year), region of residence (cities, suburban, and rural/remote) based on the Accessibility/Remoteness Index of Australia (Department of Health, 2001), health status variables including self-rated health (excellent, very good, good, fair, poor) and body mass index (BMI: <18.5, 18.5–24.9, 25–29.9, ≥30 kg/m^2). *Salmonella*-related hospitalization incidence was estimated using the admission date for first hospitalization with *Salmonella* infection.

In the analyses, missing values were categorized as missing for each variable. We then estimated the risk factors of *Salmonella* infection notification according to various sociodemographic and other characteristics that had either been reported to be associated with *Salmonella* infection previously, or were associated with the notification incidence in the cohort: age, sex, annual household income, region of residence, self-rated health and BMI, frequency of seafood consumption (None, <7 times/week, ≥7 times/week), frequency of chicken/poultry consumption (None, <7 times/week, ≥7 times/week), egg consumption (ever, never), fruit and raw vegetable consumption (low, adequate), proton pump inhibitor (PPI) use (yes, no), smoking (ever, never) and alcohol consumption (none, 1–2 drinks/day, >2 drinks/day).

Continuous variables were grouped into categories and treated as categorical. Firstly, Kaplan-Meier survival curves were produced for all study variables. Cox proportional hazards regressions were then used to calculate hazard ratios (HR) for *Salmonella* infection notification. Regression models were firstly adjusted for age and sex. Models were then adjusted for additional variables that were associated with the notification incidence in the cohort (log-rank test, $p < 0.3$).

We reviewed all APDC records where a participant was hospitalized with *Salmonella* infection to obtain data on comorbidities and characteristics of the hospitalization. We again used Cox proportional hazards regression to examine the HRs for *Salmonella*-related hospitalization, with the same model-building strategy as for the risk factor analysis for *Salmonella* infection notification.

We conducted supplementary analyses to calculate the incidence and examine risk factors of infection notification and hospitalization by *Salmonella* serotypes. Serotypes were grouped as *Salmonella* Typhimurium and other *Salmonella* serotypes, respectively. The proportionality assumptions for the model were assessed graphically. All analyses were carried out using STATA 12.1.

Ethics approval

The conduct of the 45 and Up Study was approved by the University of New South Wales Human Research Ethics

Committee. Ethics approval for this study was obtained from the NSW Population and Health Services Research Ethics Committee, and the Australian National University Human Research Ethics Committee. All participants provided written informed consent.

Result

Overall, 265,074 adults were included in the analyses, yielding a total of 1,120,242 years of follow-up (median 3.9 years per person). The median age of study participants at recruitment was 62.7 years (standard deviation 11.2) and 53.6% were women. There were 333 adults with a linked notification of *Salmonella* infection during follow-up, with 45.4% (151/333) due to *Salmonella* Typhimurium.

Salmonella infection

The incidence of *Salmonella* infection notification in the cohort was 29.7 per 100,000 person-years (95% confidence interval [CI], 26.9–33.3) (Table 1).

Incidence did not differ by sex ($p = 0.9$) or household income ($p = 0.3$), but did by age group ($p = 0.03$) and region of residence ($p = 0.002$). After adjustment, region of residence, PPI use and chicken/poultry intake remained significant risk factors for *Salmonella* infection notification; see Table 2. Participants reporting chicken/poultry intake at least seven times per week had a significant risk of notification (adjusted hazard ratio [aHR] 3.2, 95% CI 1.3–7.9). Participants living in rural/remote areas were 70% more likely to have *Salmonella* infection notification as those living in cities (aHR 1.7, 95% CI 1.3–2.2), while for those taking PPIs, the risk was 1.9 times higher than for those not taking PPI (aHR 1.9, 95% CI 1.4–2.4) (Table 2).

A total of 101 participants with *Salmonella* infection had a hospitalization related to their condition. Of these, 76.2% (77/101) had an ICD-10-AM diagnosis code on their hospitalization record indicating a *Salmonella* infection (A02), and 23.8% (24/101) had a hospitalization coded as infectious gastroenteritis (A09) and an adjacent notification of *Salmonella* infection. One participant died within 30 days of admission, and six participants died within 60 days of admission. Participants aged ≥65 years old accounted for all the deaths. The hospitalization incidence was found to increase with increasing age ($P_{trend} < 0.001$), and in univariate analysis, men were more likely to be hospitalized than women ($p = 0.02$). After adjustment, men were 70% more likely to be hospitalized with *Salmonella* infection (aHR 1.7, 95% CI 1.1–2.6). Compared to participants living in cities, the risk was significantly higher in participants from suburban areas (aHR 1.6, 95% CI 1.1–2.6) and rural/remote areas (aHR 1.9, 95% CI 1.1–3.2) (Table 2).

Subgroup analysis

The incidence of infection notification with *Salmonella* Typhimurium was 13.5 per 100,000 person-years (95% CI, 11.5–15.8), and for all other *Salmonella* serotypes was 16.2 per 100,000 person-years (95% CI, 14.1–18.8). The notification incidence of each serotype within the population did not differ by age and sex. The incidence of hospitalization with *Salmonella* Typhimurium was 5.1 per 100,000 person-years (95% CI, 3.9–6.6), and that of other *Salmonella* serotypes was 3.9 per 100,000 person-years (95% CI: 2.9–5.2) (Supplementary Table S1; Supplementary Data are available online at www.liebertpub.com/fpd).

Overall results of the risk factor analysis for other *Salmonella* serotypes were generally similar to the results of the main analysis, with region of residence, PPI use and chicken/poultry intake remaining significant risk factors. While none of the variables were significantly associated with notification for *Salmonella* Typhimurium infection, the direction of association was consistent with the main findings (Supplementary Table S2).

Discussion

We found that approximately one-third of the participants with *Salmonella* infection notification were hospitalized. This proportion increased with age, and was particularly high

Table 1. Incidence of *Salmonella* Infection Notification and Infection-Related Hospitalization in Adults by Age and Sex, 45 and Up Study

	Notification		*Hospitalization*[a]		*Hospitalization/ notification*
Characteristics	N	*Incidence (95%CI)/100,000 person years*	n	*Incidence (95% CI)/100,000 person years*	n/N *(%)*
Age (years)					
45–54	93	28.0 (22.8–34.3)	20	6.0 (3.9–9.3)	21.5
55–64	104	28.5 (23.5–34.5)	27	7.4 (5.0–10.7)	26.0
65–74	62	25.4 (19.8–32.6)	21	8.6 (5.6–13.1)	33.9
75–84	63	42.3 (33.1–54.2)	25	16.7 (11.3–24.7)	39.7
+85	11	36.6 (20.2–66.0)	8	26.4 (13.2–52.8)	72.7
Sex					
Female	178	29.6 (25.5–34.3)	43	7.1 (5.3–9.6)	24.2
Male	155	29.9 (25.5–35.0)	58	11.1 (8.6–14.4)	37.4
Total	333	29.7 (26.9–33.3)	101	9.0 (7.4–10.9)	30.3

[a]Diagnoses of other *Salmonella* infections (A02) and other gastrointestinal infections (A09).
CI, confidence interval.

Table 2. Association Between Sociodemographic and Health Characteristics and *Salmonella* Infection Notification and Hospitalization, 45 and Up Study

	Notification			*Hospitalization*		
Variables	N	*Adjusted Hazard Ratio*[a] *(95% CI)*[a]	p	N	*Adjusted Hazard Ratio*[#] *(95% CI)*[#]	p
Age groups (years)						
45–54	93	1		20	1	
55–64	104	0.9 (0.7–1.2)	0.7	27	1.1 (0.6–1.9)	0.8
65–74	62	0.7 (0.5–1.1)	0.1	21	1.0 (0.5–1.9)	0.9
75–84	63	1.2 (0.8–1.7)	0.2	25	1.7 (0.9–3.2)	0.1
+85	11	1.0 (0.5–1.9)	0.8	8	2.8 (1.2–6.6)	0.02
Sex						
Female	178	1		43	1	
Male	155	1.0 (0.8–1.2)	0.7	58	1.7 (1.1–2.7)	0.01
Region of residence						
Cities	121	1		34	1	
Suburban	124	1.4 (1.0–1.7)	0.02	40	1.6 (1.1–2.6)	0.3
Rural/remote	88	1.7 (1.3–2.2)	<0.001	27	1.9 (1.2–3.2)	0.1
Proton pump inhibitor usage						
No	251	1		77	1	
Yes	82	1.9 (1.4–2.4)	<0.001	24	1.4 (0.9–2.3)	0.1
Chicken/poultry intake						
None	8	1		4	1	
<7/week	245	1.6 (0.8–3.2)	0.2	74	1.3 (0.5–3.8)	0.6
≥7/week	11	3.2 (1.3–7.9)	0.01	2	1.4 (0.3–8.1)	0.7
Self-rated health						
Excellent	35	1		6	1	
Very good	95	1.1 (0.7–1.6)	0.7	22	1.3 (0.5–3.2)	0.6
Good	126	1.5 (1.0–2.2)	0.04	42	2.2 (0.9–5.3)	0.08
Fair	55	1.8 (1.1–2.8)	0.01	18	2.3 (0.9–5.9)	0.1
Poor	11	2.1 (1.1–4.2)	0.04	7	4.5 (1.4–14.1)	0.01

[a]Adjusted for age, sex, household income, region of residence, living in aged care facilities, proton pump inhibitor usage, fruit and vegetable intake, chicken/poultry intake, seafood intake, egg consumption, BMI, Self-rated health, smoking, alcohol consumption.
BMI, body mass index; CI, confidence interval.

among those aged ≥85 years, where almost three-quarters were admitted for their illness. While the incidence of *Salmonella* infection notification was similar across age groups, infection-related hospitalization increased significantly with age. Importantly, older people consuming poultry more than seven times per week were at the highest risk of infection.

Our estimates are similar to the findings from a number of industrialized countries. One US study using surveillance data to determine the rates of hospitalization and death associated with laboratory-confirmed *Salmonella* infection reported that people aged ≥60 years had the highest rate of hospitalization, with 47% of infected persons hospitalized (Kennedy *et al.*, 2004). We used linked notification data in our study and would expect our estimate of *Salmonella* incidence to be similar to that for routinely collected surveillance data. The incidence of the notification of *Salmonella* infection among people aged ≥60 years in our study (31.5 per 100,000 person-years) was comparable with the reported notification incidence in the same age group in NSW (36.4 per 100,000 person-years)—the state where the cohort study was conducted (NSW Ozfoodnet, 2011).

We identified that males aged ≥85 years were at the highest risk of hospitalization, despite having similar incidence of infection notification to other cohort participants. This may be because of an increased susceptibility of developing severe complications from infection with aging (Cummings *et al.*, 2012) which may lead to hospitalization. Other factors, such as sex differences in the incidence of invasive *Salmonella* infection (Vugia *et al.*, 2004) may explain the higher risk of *Salmonella*-related hospitalization in males.

We found that people living in rural areas had an elevated risk of *Salmonella* infection and hospitalization. In Australia, the rate of poverty in regional and rural areas is higher than in major cities. Ecological studies have reported higher rates of *Salmonella* infection from low income areas (Varga *et al.*, 2013), which may be explained by poorer microbial quality of food or greater exposure to high-risk foods (Koro *et al.*, 2010). One study reported that human contact with cattle might pose higher risks than food consumption for bovine strains of *Salmonella* (Hoelzer *et al.*, 2011).

Environmental exposures related to rural living may be important determinants of *Salmonella* infection. Additionally, we found that people living in remote areas were more likely to have infection notification from *Salmonella* serotypes other than Typhimurium, which is consistent with the geographical clustering of infection observed in notification data (Ashbolt and Kirk, 2006).

Participants with *Salmonella* Typhimurium infection were more likely to be hospitalized than people with infection of other *Salmonella* serotypes, and this was consistent across all age groups. In participants aged ≥85, all cases with *Salmonella* Typhimurium infection were hospitalized for their condition, while only half of the cases with infection of other *Salmonella* serotypes were admitted to hospital. *Salmonella* serotypes are closely related genetically, and yet differ significantly in pathogenicity. Further studies are needed to investigate the pathophysiology of human *Salmonella* infection. Understanding the mechanisms responsible for *Salmonella* pathogenesis is important to understand invasiveness of *Salmonella* infection, and thus prevent hospitalization.

Among all the food exposures analyzed in our study, chicken/poultry consumption was significantly associated with *Salmonella* infection; this was not true of *Salmonella* Typhimurium but could be due to the smaller number of events. A meta-analysis of case-control studies to investigate source attribution of human salmonellosis identified consumption of chicken in the restaurant as an important risk factor for infection (Domingues *et al.*, 2012). Sub-analyses of the systematic review also showed a different risk profile for infection by serotypes (Domingues *et al.*, 2012). Similarly, Glass *et al.* adopted a Bayesian source attribution model to estimate the contribution of different animal reservoirs to *Salmonella* infection and found that sources vary for different serotypes, with eggs more commonly indicated for *Salmonella* Typhimurium than non-Typhimurium serotypes (Glass *et al.*, 2016).

We did not observe any significant association between egg consumption and *Salmonella* infection, but this may be due to the fact that the baseline questionnaire used in this study only asked participants if they ever eat eggs, and did not collect information on frequency of egg consumption.

PPI use is another common risk factor for *Salmonella* infection (Wu *et al.*, 2014). In this study, we found that PPI use was significantly associated with *Salmonella* infection. Although we are not able to assess whether this increased risk is owing to host factors that are associated with PPI prescription (Brophy *et al.*, 2013), or if the increasing risk is due to the use of PPIs, our result adds to the body of evidence that PPI use is associated with *Salmonella* infection.

The strengths of our study are: the large study population, prospective independent ascertainment of notification and hospitalization with *Salmonella* infection in relation to risk factors, and the use of laboratory-confirmed cases. However, there were some limitations to this study. First, the use of passive notification data underestimates true incidence in the community (Hall *et al.,* 2008; Mytton *et al.*, 2015). Moreover, notifications which are mainly dependent on access to health services may under-represent deprived populations. Such biases may lead to an underestimation of incidence in those populations.

Second, data on exposures were based on self-report and collected at the time of recruitment. Although dietary intake is difficult to assess, a validation study involving the short questions related to diet used in the 45 and Up Study questionnaire has shown them to be reproducible over time (Roddam *et al.*, 2005). Third, the 45 and Up study cohort, while including about 1 in 10 adults in the age range in NSW, may not be exactly representative of the general NSW population and participants are likely to be more health conscious than the general NSW population.

Despite this, we found that the incidence of *Salmonella* infection from this study were generally comparable with the reported notification incidence in the same age group in NSW. Furthermore, risk factor estimates are still generalizable from within-cohort comparisons (Mealing *et al.*, 2010).

Conclusions

One-third of participants with laboratory-confirmed *Salmonella* infection were hospitalized and the risk of hospitalization increased significantly with age. Understanding factors contributing to hospitalization in this group can assist public health agencies in shaping effective risk reduction efforts and effective care management. Previous data have suggested *Salmonella* contamination of poultry meat (Fearnley *et al.*, 2011). Despite public health efforts to reduce foodborne infections, chicken consumption remains a significant risk factor for *Salmonella* infection, highlighting the importance of reducing contamination of poultry and ensuring education about safe cooking practices reach older people.

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Disclosure Statement

No competing financial interests exist.

References

45 and Up Study Collaborators Cohort profile: The 45 and Up Study. Int J Epidemiol 2008;37:941–947.

Ashbolt R, Kirk MD. Salmonella Mississippi infections in Tasmania: The role of native Australian animals and untreated drinking water. Epidemiol Infect 2006;134:1257–1265.

Australian Bureau of Statistics. *Population by age and sex, Australia, 2006*. Australia, Australian Bureau of Statistics, 2007.

Brophy S, Jones KH, Rahman MA, Zhou SM, John A, Atkinson MD, Francis N, Lyons RA, Dunstan F. Incidence of Campylobacter and Salmonella infections following first prescription for PPI: A cohort study using routine data. Am J Gastroenterol 2013;108:1094–1100.

Centre for Health Record Linkage 2012. Available at: http://www.cherel.org.au/quality-assurance, accessed August 1, 2014.

Cummings PL, Sorvillo F, Kuo T. *The Burden of Salmonellosis in the United States*. InTech 2012. DOI: 10.5772/28019. Available at: http://www.intechopen.com/books/salmonella-a-

dangerous-foodborne-pathogen/the-burden-of-salmonellosis-in-the-united-states, accessed August 1, 2014.

Department of Health. Public Health Laboratory Network case definitions. 2005. Available at: http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-phlncd-salmonella.htm/$FILE/salmo.pdf, accessed June 1, 2014.

Department of Health. Measuring Remoteness: Accessibility/Remoteness Index of Australia (ARIA) Revised Edition. 2001. Available at: http://www.health.gov.au/internet/main/publishing.nsf/Content/health-historicpubs-hfsocc-ocpanew14a.htm, accessed June 1, 2014.

Domingues AR, Pires SM, Halasa T, Hald T. Source attribution of human salmonellosis using a meta-analysis of case-control studies of sporadic infections. Epidemiol Infect 2012;140:959–969.

Fearnley E, Raupach J, Lagala F, Cameron S. *Salmonella* in chicken meat, eggs and humans; Adelaide, South Australia, 2008. Int J Food Microbiol 2011; 146:219–227.

Glass K, Fearnley E, Hocking H, Raupach J, Veitch M, Ford L, Kirk MD. Bayesian source attribution of Salmonellosis in South Australia. Risk Anal 2016;36:561–570.

Hall G, Yohannes K, Raupach J, Becker N, Kirk MD. Estimating community incidence of *Salmonella, Campylobacter*, and Shiga Toxin–producing *Escherichia coli* Infections, Australia. Emerg Infect Dis 2008;14:1601–1609.

Hoelzer K, Switt AM, Wiedmann M. Animal contact as a source of human non-typhoidal salmonellosis. Vet Res 2011; 42:34.

Kennedy M, Villar R, Vugia DJ, Rabatsky-Ehr T, Farley MM, Pass M, Smith K, Smith P, Cieslak PR, Imhoff B. Hospitalizations and deaths due to Salmonella infections, FoodNet, 1996–1999. Clin Infect Dis 2004;38(Supplement 3):S142–S148.

Kirk MD, Pires SM, Black RE, Caipo M, Crump JA, Devleesschauwer B, Döpfer D, Fazil A, Fischer-Walker CL, Hald T, Hall A, Keddy KH, Lake RJ, Lanata CF, Torgerson PR, Havelaar AH, Angulo FJ. World Health Organization Estimates of the Global and Regional Disease Burden of 22 Foodborne Bacterial, Protozoal, and Viral Diseases, 2010: A Data Synthesis. PLoS Med 2015;12:e1001940.

Kirk MD, Gregory J, Lalor K, Hall GV, Becker N. Foodborne and waterborne infections in elderly community and long-term care facility residents, Victoria, Autralia. Emerg Infect Dis 2012;18:377.

Koro ME, Anandan S, Quinlan JJ. Microbial quality of food available to populations of differing socioeconomic status. Am J Prev Med 2010;38:478–481.

Mealing NM, Banks E, Jorm LR, Steel DG, Clements MS, Rogers KD. Investigation of relative risk estimates from studies of the same population with contrasting response rates and designs. BMC Med Res Methodol 2010;10:26.

Moffatt CR, Musto J, Pingault N, Miller M, Stafford R, Gregory J, Polkinghorne BG, Kirk MD. Salmonella Typhimurium and outbreaks of egg-associated disease in Australia, 2001 to 2011. Foodborne Pathog Dis 2016; 13:379–385.

Mytton OT, Mccarthy N, Mannes T. Variation in incidence and notification of Campylobacter and Salmonella by general practice in the Thames Valley area. Public Health 2015;129:258–265.

NSW Ministry of Health. NSW legislation. Public Health Act 2010.

NSW Ozfoodnet. OzFoodNet—Enhancing Foodborne Disease Surveillance Across Australia. 2011. Available at: http://www.health.nsw.gov.au/Infectious/diseases/Documents/NSW-ofn-annual-report-2011.pdf, accessed August 1, 2015.

Ozfoodnet Working Group. Monitoring the incidence and causes of diseases potentially transmitted by food in Australia: Annual report of the OzFoodNet network, 2011. Commun Dis Intell Q Rep 2015;39:E236.

Parry CM, Thomas S, Aspinall EJ, Cooke RP, Rogerson SJ, Harries AD, Beeching NJ. A retrospective study of secondary bacteraemia in hospitalised adults with community acquired non-typhoidal Salmonella gastroenteritis. BMC Infect Dis 2013;13:107.

Pires SM, Vieira AR, Hald T, Cole D. Source attribution of human salmonellosis: An overview of methods and estimates. Foodborne Pathog Dis 2014;11:667–676.

Roddam AW, Spencer E, Banks E, Beral V, Reeves G, Appleby P, Barnes I, Whiteman DC, Key TJ. Reproducibility of a short semi-quantitative food group questionnaire and its performance in estimating nutrient intake compared with a 7-day diet diary in the Million Women Study. Public Health Nutr 2005;8:201–213.

Sanchez-Vargas FM, Abu-El-Haija MA, Gomez-Duarte OG. Salmonella infections: An update on epidemiology, management, and prevention. Travel Med Infect Dis 2011;9:263–277.

Scallan E, Crim SM, Runkle A, Henao OL, Mahon BE, Hoekstra RM, Griffin PM. Bacterial enteric infections among older adults in the united states: Foodborne diseases active surveillance network, 1996–2012. Foodborne Pathog Dis 2015;12:492–499.

Varga C, Pearl DL, Mcewen SA, Sargeant JM, Pollari F, Guerin MT. Evaluating area-level spatial clustering of Salmonella Enteritidis infections and their socioeconomic determinants in the greater Toronto area, Ontario, Canada (2007–2009): A retrospective population-based ecological study. BMC public health 2013;13:1078.

Vugia DJ, Samuel M, Farley MM, Marcus R, Shiferaw B, Shallow S, Smith K, Angulo FJ. Invasive Salmonella infections in the United States, FoodNet, 1996–1999: Incidence, serotype distribution, and outcome. Clin Infect Dis 2004;38 (Supplement 3):S149–S156.

World Health Organization. *Salmonella (non-typhoidal)*. Geneva: World Health Organization, 2013.

Wu HH, Chen YT, Shih CJ, Lee YT, Kuo SC, Chen TL. Association between recent use of proton pump inhibitors and nontyphoid Salmonellosis: A nested case-control study. Clin Infect Dis 2014; ciu628.

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Chapter 9

Paper six: A population-based longitudinal study of *Clostridium difficile* infection-related hospitalisation in mid-age and older Australians

Chen Y, Glass K, Liu B, Riley T, Korda R, Kirk M. A population-based longitudinal study of Clostridium difficile infection-related hospitalization in mid-age and older Australians. Epidemiol Infect. 2017;145:575-582. Cambridge University Press.

About This Chapter

This chapter documents the incidence of and risk factors for hospitalisation with *Clostridium difficile* infection (CDI) in a large population-based cohort of middle-aged and older adults. There was a 3-fold increase in incidence of CDI hospitalisation over 2009–2012, and approximately one third of these patients did not have recent hospital exposure. This paper contributes to answering the research question: 'What is the incidence of and risk factors for *Clostridium difficile* infection in middle-aged and older adults?'. This paper was published in *Epidemiology and Infection.*

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A population-based longitudinal study of *Clostridium difficile* infection-related hospitalization in mid-age and older Australians

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SUMMARY

Clostridium difficile is the principal cause of infectious diarrhoea in hospitalized patients. We investigated the incidence and risk factors for hospitalization due to *C. difficile* infection (CDI) in older Australians. We linked data from a population-based prospective cohort study (the 45 and Up Study) of 266 922 adults aged ⩾45 years recruited in New South Wales, Australia to hospitalization and death records for 2006–2012. We estimated the incidence of CDI hospitalization and calculated days in hospital and costs per hospitalization. We also estimated hazard ratios (HR) for CDI hospitalization using Cox regression with age as the underlying time variable. Over a total follow-up of 1 126 708 person-years, 187 adults had an incident CDI hospitalization. The crude incidence of CDI hospitalization was 16·6/100 000 person-years, with a median hospital stay of 6 days, and a median cost of AUD 6102 per admission. Incidence increased with age and year of follow-up, with a threefold increase for 2009–2012. After adjustment, CDI hospitalization rates were significantly lower in males than females (adjusted HR 0·6, 95% confidence interval 0·4–0·7). CDI hospitalization rates increased significantly over 2009–2012. There is a need to better understand the increasing risk of CDI hospitalization in women.

Key words: *Clostridium difficile*, epidemiology.

INTRODUCTION

Clostridium difficile is the principal cause of infectious diarrhoea in hospitalized patients [1]. The burden of disease due to *C. difficile* infection (CDI) has been increasing in the past decade with marked increases in severe cases and deaths related to CDI [2, 3]. A systematic review investigating the economic impact of CDI found that attributable mean CDI costs per admission ranged from AUD 8911 to AUD 30 049 for hospitalized patients globally [4]. A cross-sectional study conducted in Sydney, Australia, reported that *C. difficile* was one of the most frequently detected pathogens in patients who visited public hospitals for gastrointestinal illnesses, and that 69% of people infected with *C. difficile* were aged ⩾50 years [5]. Australian national surveillance for hospital-identified CDI has demonstrated increasing incidence since 2011, highlighting a need to further characterize the epidemiology of these infections [6].

Environmental contamination and frequent antibiotic use are the most important determinants of hospital-acquired CDI internationally [7]. In addition,

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advanced age is strongly associated with infection and severe clinical presentation [8]. While *C. difficile* is generally thought of as a hospital problem, data from industrialized countries suggest that community-acquired infections are on the rise and comprise about 27–41% of all cases of CDI in such countries [8, 9]. Patients with community-acquired CDI tend to be younger compared to those infected in the hospital setting and they often lack exposure to antibiotics [10], suggesting the existence of other important risk factors for infection. Recently, *C. difficile* has been isolated from various foods such as red meat and minimally processed fruit and vegetables [11, 12], although further studies are necessary to confirm food as an infection source.

There have not been any previous population-based cohort studies describing the epidemiology of CDI hospitalization in Australia. The aim of this study was to describe the epidemiology of hospital-identified CDI in mid-age and older Australians. Specifically, we analysed data from a large population-based longitudinal cohort to estimate the incidence of CDI hospitalization, quantify its association with potential risk factors, and calculate the median length of hospital stay and in-hospital costs per admission with CDI.

METHODS

Data sources

The Sax Institute's 45 and Up Study is a prospective cohort study of Australian adults aged ⩾45 years, randomly sampled from the general population of the Australian state of New South Wales (NSW; population 6·8 million persons, 2006) [13]. Participants were recruited by completing a postal questionnaire, distributed from 2006 to 2009. The final cohort includes ~10% of all NSW adults aged ⩾45 years. The detailed methodology is described elsewhere [14].

Questionnaire data from the 45 and Up Study participants were linked to the NSW Admitted Patient Data Collection (APDC) (to 30 June 2012), and the NSW Register of Births, Deaths and Marriages (RBDM) (to 30 June 2012). The APDC records details of all hospital separations for NSW residents admitted to hospitals. The principal diagnosis for each hospitalization, which is the main reason for hospitalization and up to 54 additional diagnoses contributing to the hospitalization, were coded using the International Classification of Diseases, 10th revision, Australian Modification (ICD-10-AM). These data also included the Australian Refined Diagnosis Related Group (DRG) code for each hospitalization. Each DRG represents a class of patients with similar clinical conditions requiring similar hospital resources [15]. Data were linked to the RBDM to ascertain fact of death for censoring purposes. The NSW Centre for Health Record Linkage performed the data linkage independent of the study investigators and report false-positive and false-negative linkages of < 0·5% and <0·1%, respectively [16].

Case definition

We defined participants as having a CDI hospitalization if they had a linked hospitalization record where the principal diagnosis field was coded for *C. difficile* colitis (ICD-10-AM code A04·7) following recruitment into the study. In a sensitivity analysis, we broadened the case definition to include patients where either the principal or a secondary diagnosis field was coded with *C. difficile* colitis.

Definition of outcomes

The study outcomes included incident hospitalization with CDI and, in those hospitalized with incident CDI, days in hospital and costs per admission (AUD). For transfer patients, the relevant admission records were first merged together. Days in hospital per hospitalization was calculated by subtracting the discharge date from the admission date, except for same day admissions where the length of stay was assigned to be a single day. To estimate *C. difficile*-associated hospital costs per hospitalization, we used the DRG codes of the index hospitalization due to CDI and assigned an average cost based on DRG cost data from the National Hospital Cost Data Collection Public Sector Estimated Cost Weights Reports (NHCDC) [17]. The NHCDC documents average costs per DRG, based on patient-costed and cost-modelled information. Average DRG-specific total cost per admission in Round 14 (2009–10) NHCDC was used (version 5.2 for admissions from January 2006 to December 2009 and version 6.0x from admissions from January 2010 to June 2012).

Definition of potential risk factors

Sociodemographic information was obtained from the baseline questionnaire and included: age (grouped as 45–54, 55–64, 65–74, 75–84, ⩾85years), sex, annual household income (seven categories from <AUD

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20 000 to ⩾AUD 70 000 per year), and region of residence (cities, inner regional, outer regional/remote) based on the Accessibility/Remoteness Index of Australia (ARIA) [18]. Health status and health-behaviour variables included: self-rated health (excellent, very good, good, fair, poor), body mass index (BMI: <18·5, 18·5–24·9, 25–29·9, ⩾30 kg/m^2), smoking (current, past, never), alcohol (0, 1–2, >2 alcohol drinks per day), proton pump inhibitor (PPI) use (yes, no), red meat intake (0, 1–7, ⩾7 times per week), and fruit and vegetable intake (low, adequate). Fruit and vegetable intake was grouped as 'low' if participants reported <2 servings of fruit and/or <5 servings of vegetables per day.

In addition, the Charlson comorbidity index was used to describe comorbid illness of the participants hospitalized with CDI. This index is a well-validated measure of comorbidity burden, and has been modified to produce reliable estimates using ICD-10 codes [19]. The 19 Charlson conditions were selected and weighted according to their potential influence on mortality (scores were categorized as 0, 1, 2, 3). Baseline data from the 45 and Up Study participants were also linked to the APDC retrospectively to obtain hospitalization records before recruitment.

Statistical analysis

Participants were excluded from the analyses if they had missing data on date of entry into the study, an invalid death date or confirmed linkage errors. Participants with a discharge diagnosis of CDI within 8 weeks prior to recruitment were excluded to remove recurrent cases.

Follow-up was calculated from the date of completing the baseline survey to the first date of admission for CDI, death, or 30 June 2012, whichever came first. The crude rate of incident CDI hospitalization in the cohort, and median days in hospital and costs per admission for those hospitalized for CDI, were calculated. Rates were also reported separately by quarter and calendar year (2009, 2010, 2011, 2012), and by the various sociodemographic factors, health characteristics and behaviors.

To identify the risk factors for CDI hospitalization, Kaplan–Meier analysis with the log-rank test was first used to determine the probability of hospitalization with CDI for all potential risk factor variables. Cox proportional hazards regressions were then used to estimate hazard ratios for each of these variables with age as the underlying time variable [20]. Regression models were initially adjusted for attained age (the underlying time variable) and sex. Models were then adjusted for additional variables that were associated with CDI hospitalization (log-rank test, $P < 0{\cdot}3$), including annual household income, region of residence, health status variables (self-rated health and body mass index), PPI use and dietary variables (red meat intake and fruit and vegetable intake).

A sensitivity analysis was conducted by repeating the analysis with the case definition modified to include patients where either the principal or additional diagnosis field was coded for CDI. We tested for violation of the proportionality assumptions for the model by inspecting the log-log plots. All analyses were performed using Stata v. 12.1 (StataCorp., USA).

Ethical approval

The conduct of the 45 and Up Study was approved by the University of New South Wales Human Research Ethics Committee. Ethics approval for this study was obtained from the NSW Population and Health Services Research Ethics Committee, and the Australian National University Human Research Ethics Committee. All participants provided written informed consent.

RESULTS

After excluding participants with invalid death records (death before recruitment, $n = 12$), confirmed linkage errors ($n = 192$), and those with a CDI hospitalization in the 8 weeks prior to recruitment ($n = 3$), there were 266 922 participants included in the analysis, yielding 1 126 708 years of follow-up (median 3·9 years per person). The median age of study participants at recruitment was 61·1 years (range 45·0–106·2 years), and 53·6% were women. Table 1 shows a summary of the characteristics of all study participants and those hospitalized with CDI.

There were 187 participants with an incident CDI hospitalization, and 5·4% (10/187) died within 30 days of admission. Overall, 25·1% (47/187) of cases had a Charlson index of ⩾1, although this proportion increased with increasing age (respectively, 9·1% and 47·6% in those aged 45–54 years and ⩾85 years). We found that 37·4% (70/187) of cases had a history of hospitalization in the previous 2 weeks and 67·9% (127/187) of cases had a hospital admission in the previous 3 months.

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Table 1. *Characteristics of all participants and those hospitalized with* C. difficile *infection, 45 and Up Study*

Variables	Population ($N = 266\,922$) *n* (%)	*C. difficile* infection ($n = 187$) *n* (%)
Age group (years)		
45–54	77 874 (29·2)	22 (11·8)
55–64	85 855 (32·2)	32 (17·1)
65–74	58 060 (21·7)	49 (26·2)
75–84	36 873 (13·8)	63 (33·7)
⩾85	8260 (3·1)	21 (11·2)
Sex		
Female	143 101 (53·6)	120 (64·2)
Male	123 821 (46·4)	67 (35·8)
Region of residence		
Cities	120 200 (45·0)	105 (56·2)
Inner regional	93 779 (35·1)	60 (32·1)
Outer regional	52 943 (19·8)	22 (11·7)

During follow-up, the incidence of CDI hospitalization was 16·6/100 000 person-years [95% confidence interval (CI) 14·4–19·2], with a median of 6 days [interquartile range (IQR) 4–10] spent in hospital per admission, and a median hospital cost of AUD 6102 (IQR 1909–6182) per admission.

The crude incidence of CDI hospitalization increased with age as: 6·6 (95% CI 4·3–9·9), 8·7 (95% CI 6·1–12·3), 19·9 (95% CI 15·1–26·4), 41·2 (95% CI 32·9–53·9) and 69·4 (95% CI 45·3–106·4) per 100 000 person-years in those aged 45–54 years, 55–64 years, 65–74 years, 75–84 years and ⩾85 years, respectively (P <0·001). Rates also increased with year of follow-up, with a threefold increase over the study period from 10·2/100 000 person-years in 2009 to 32·0/100 000 person-years in 2012 ($P <$ 0·001). Crude CDI hospitalization rates were higher in females ($P < 0·001$), in those living in cities compared to regional/remote regions ($P = 0·002$), in those taking PPIs ($P = 0·002$), and in those with poorer self-rated health ($P < 0·001$). Crude incidence did not differ significantly by BMI, smoking, alcohol, or food consumption.

After adjustment for age and other factors (as listed in Fig. 1), sex and self-rated health remained significant variables of CDI hospitalization. Males were 40% less likely to be hospitalized with CDI than females [adjusted hazard ratios (aHR) 0·6, 95% CI 0·4–0·7], while the aHRs increased significantly with poorer self-reported health with risks over five times greater for those with poor *vs.* those with excellent health (aHR 5·7, 95% CI 2·1–15·5). No statistically significant associations between other exposures and incident CDI hospitalization were observed.

Sensitivity analysis

A total of 461 participants had a linked incident hospitalization record with a diagnosis of CDI in either the principal ($n = 187$) or a secondary ($n = 274$) diagnosis field. Compared to patients with CDI as a principal diagnosis, patients with a secondary diagnosis of CDI had higher comorbidity with 39·7% (183/461) patients having a Charlson index of ⩾1, and longer hospital stays (median of 11 days compared to 6 days).

The rate of CDI hospitalization using this alternate case definition was higher, at 39·9 (95% CI 36·5–43·8)/100 000 person-years. The rates increased significantly with calendar year from 30·7/100 000 person-years (95% CI 24·8–38·1) in 2009 to 72·0/100 000 person-years (95% CI 58·6–88·4) in 2012. We observed a similar trend of incidence in hospitalization with CDI as a principal diagnosis and hospitalization with CDI as either a principal or secondary diagnosis (Fig. 2). The quarterly incidence rates rose significantly during 2011 to 2012, with a peak in October–December 2011. The risk factor analysis yielded similar results to our main analyses, except that use of PPIs was significantly associated with CDI hospitalization (aHR 1·3, 95% CI 1·1–1·5) (Supplementary Table S1).

DISCUSSION

In this large study of middle-aged and older adults, we found a significant increase in the incidence of CDI hospitalization over 2009–2012, and an increase in CDI hospitalization with increasing age. In industrialized countries, *C. difficile* is one of the most frequently reported nosocomial pathogens. The elevated rates in older adults, combined with the longer duration of CDI-associated hospital stay and high hospital costs in the elderly indicate a substantial burden and excess hospital costs due to CDI in an ageing population.

Since mandatory reporting was introduced in Australia, there has been a significant increase in incidence of hospital-identified CDI [6]. In our study, there is a similar trend of incidence between hospitalization with CDI as a principal diagnosis and hospitalization with CDI as either a principal or secondary diagnosis. Mandatory reporting began in 2010 while the rate increased markedly during 2011 and peaked by October–December 2011. Compared to previous years, there is a significant increase

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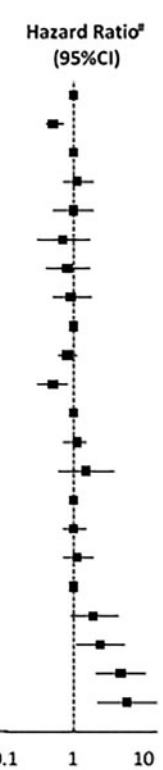
	Variables	Cases/ Population	Crude rate /100,000 person-years	Hazard Ratio*	Hazard Ratio# (95%CI)	*P*-value
Sex	Female	120/142,981	19.8	1.0	1.0	*P*<.001
	Male	67/123,754	12.8	0.6	0.6 (0.4-0.7)	
Household income	<$20000	60/52,444	27.4	1.0	1.0	*P*=.3
	$20000-29999	24/25,543	22.1	0.9	1.2 (0.7-1.9)	
	$30000-39999	12/19,250	13.4	0.7	0.9 (0.5-1.8)	
	$40000-49999	8/27,848	9.8	0.6	0.8 (0.4-1.8)	
	$50000-69999	9/62,780	7.6	0.6	0.8 (0.4-1.6)	
	+$70,000	17/57,780	6.4	0.6	0.9 (0.5-1.6)	
Region of residence	Cities	105/120,095	20.8	1.0	1.0	*P*=.05
	Inner regional	60/93,719	15.1	0.8	0.8 (0.6-1.1)	
	Outer/remote	22/52,921	9.8	0.6	0.5 (0.3-0.9)	
PPI use	No	145/230,126	14.9	1.0	1.0	*P*=.2
	Yes	42/36,603	27.8	1.3	1.1 (0.7-1.5)	
BMI (kg/m²)	<18.5	5/3,254	38.3	1.9	1.4 (0.6-3.6)	*P*=.07
	18.5-24.99	59/91,562	15.3	1.0	1.0	
	25-29.99	62/96,848	15.1	1.1	1.1 (0.8-1.6)	
	>30	38/57,410	15.7	1.3	1.1 (0.7-1.6)	
Self-rated health	Excellent	7/38,895	4.2	1.0	1.0	*P*<.001
	Very good	42/95,006	10.3	2.1	2.0 (0.9-4.5)	
	Good	63/86,910	17.1	2.9	2.7 (1.2-6.0)	
	Fair	53/30,865	42.1	6.1	5.3 (2.4-12.1)	
	Poor	10/5,642	47.9	7.1	5.7 (2.1-15.5)	



HR* Adjusted for age and sex only.
HR# Adjusted for age, sex, household income, region of residence, living in aged care facilities, proton pump inhibitor usage, fruit and vegetable, red meat, smoking, alcohol use, BMI, and self-rated health.
P-value shows overall associations for each variable.

Fig. 1. Associations between baseline characteristics and incident CDI hospitalization, 45 and Up Study.

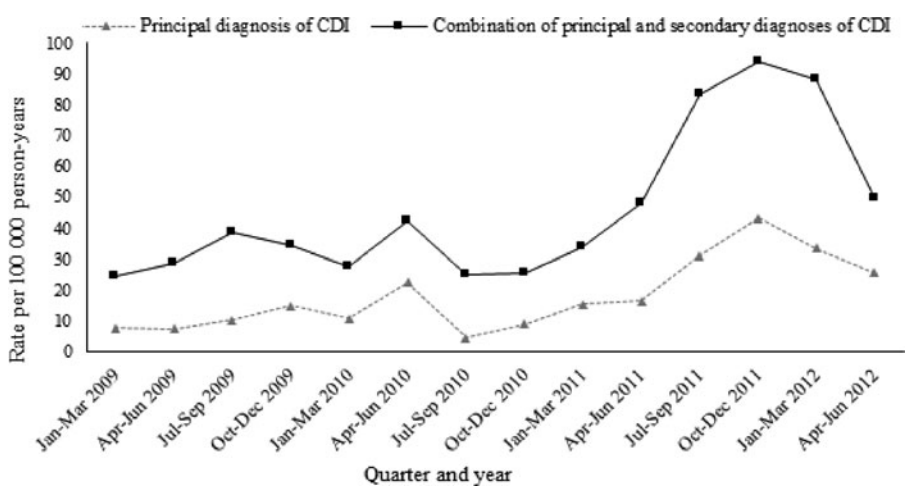


Fig. 2. Quarterly incidence of participants hospitalized with *C. difficile* infection in the 45 and Up Study, 2009–2012.

in incidence of CDI hospitalization during 2011–2012, which is unlikely to be due to changes in reporting but could be due to changes in testing practices. Changes in testing practices from enzyme immunoassay to nucleic acid amplification could result in improved detection of cases [21]. In addition, an Australian study using whole genome sequencing to describe the secular trends in the prevalence of hospital-identified CDI found that the introduction of new *C. difficile* strains, alongside rises in the incidence of established strains, may explain the observed increase in CDI [22]. Although we were not able to identify the specific *C. difficile* strains contributing to the hospitalizations in this study, our results are in line with published Australian data [6].

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Notwithstanding the fact that CDI hospitalization does not exclude patients that acquire CDI during the hospitalization, nearly a third of CDI cases did not appear to be exposed to a hospital environment during the 3 months prior to their hospitalization, suggesting a community-acquired infection. Community-acquired CDI is defined as symptom onset in the community over 12 weeks after the last discharge from a healthcare facility (HCF), while HCF-acquired CDI is defined as symptom onset >48 h after admission to a HCF [23]. The recommendations for surveillance of *C. difficile*-associated disease are to report community-onset HCF-associated CDI (defined as a patient with symptom onset in the community or $\leqslant$48 h after admission to an HCF) in addition to HCF-onset HCF-associated CDI (defined as a patient with symptom onset >48 h after admission to an HCF) due to the delayed onset of infection in the HCF [23]. In this study, we found a relatively high proportion of cases without inpatient hospital exposure in the previous 3 months. However, we were unable to assess whether these cases had contact with the healthcare environment as outpatients, although the risk of acquiring CDI in these settings has been considered low due to limited contact time [24].

The rate of CDI hospitalization increased with age, with the highest incidence observed in persons aged $\geqslant$85 years. This trend was in line with previous studies reporting that older people are at higher risk of experiencing severe CDI than younger people [1, 8]. We found that poorer self-rated health was also significantly associated with CDI hospitalization after adjustment for age, suggesting a significant impact of underlying health status. Comorbid illness and severity of underlying conditions have been reported as risk factors for CDI, partially through their association with greater healthcare contact [25, 26]. In addition, people with poor general health may be more likely to develop severe CDI, and therefore require hospitalization.

In our study, females were at higher risk of CDI hospitalization and the magnitude of relative risk was more extreme than published data [8]. There are contradictory reports concerning sex-specific differences in CDI [27, 28], although the overwhelming majority suggest a greater risk in females [29, 30]. The reason for a higher risk in female observed in this study is unknown. One hypothesis relates to females being prescribed antibiotics more often than males [31], and more likely to be associated with inappropriate antibiotic prescribing [32]; therefore increasing risk of CDI. Sex-specific differences in the gut microbiota may also explain these findings [33]. Animal studies have shown that androgen levels mediate gut microbiota [34]. Sex differences in the diversity and abundance of bacterial colonization in humans' gastrointestinal tracts may influence an individual's susceptibility to infection [35]. Further research is needed to confirm the sex-specific differences in CDI and to better understand the mechanisms of this association.

We found that people living in remote or rural areas had a lower risk of CDI hospitalization and the risk decreased with increasing remoteness. This may be associated with different health services models in cities, regional/outer regional and rural areas. People living in remote areas may have less access to HCFs and therefore, are less likely to experience HCF-acquired CDI.

PPIs are associated with an increasing risk of CDI [36], while other studies have not confirmed this relationship [25]. In our main analysis, PPI use was not associated with hospitalization with CDI as principal diagnosis (aHR 1·1, 95% CI 0·7–1·5), but was a significant risk factor for CDI hospitalization when expanding the case definition to combine principal CDI diagnosis with secondary CDI diagnoses (aHR 1·3, 95% CI 1·1–1·5). While this difference in results may in part reflect a lack of power in the main analysis, notably the combined CDI cases had longer hospital stays and more severe comorbidity than patients hospitalized with CDI as a principal diagnosis.

This is the first prospective population-based cohort study we are aware of to estimate the incidence of hospital-identified CDI and examine potential risk factors in Australia. The strengths of this study include a large sample size with linkage to hospitalization and death records, and prospectively collected data on a range of potential risk factors and confounders. The limitations include the relatively small number of cases which provide limited power to detect significant associations between certain risk factors and CDI hospitalization. The use of inpatient hospitalization data may underestimate the burden of CDI imposed on the community as cases not requiring hospitalization were not included in the analysis. Moreover, all the CDI cases were identified using coded diagnoses. The accuracy of ICD-10 codes for CDI has been assessed with 99·9% specificity and 35·6% sensitivity [37]. The trends in CDI rates for ICD-10 codes identified cases and laboratory-confirmed cases strongly correlated, although concordance was moderate. This may lead to an

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underestimate of the true population rates of CDI compared with active surveillance [37]. Finally, the 45 and Up Study cohort tend to be healthier and have a healthier lifestyle than the general NSW population; therefore, our results may underestimate the true incidence of CDI hospitalization in the general population. However, risk factor estimates are considered broadly generalizable from within-cohort comparisons [38].

Despite concerted efforts in disease prevention, the incidence of CDI hospitalization increased significantly between 2009 and 2012 in our study. Further analysis of trends over time is needed to characterize the possible seasonality of CDI in Australia. In addition, studies are required to better understand the mechanisms underlying the increased risk of CDI hospitalization in women.

SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0950268816002260.

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DECLARATION OF INTEREST

None.

REFERENCES

1. **Leffler DA, Lamont JT.** Clostridium difficile infection. *New England Journal Medicine* 2015; **372**: 1539–1548.
2. **Muto CA, *et al.*** A large outbreak of *Clostridium difficile*-associated disease with an unexpected proportion of deaths and colectomies at a teaching hospital following increased fluoroquinolone use. *Infection Control Hospital Epidemiology* 2005; **26**: 273–280.
3. **Oake N, *et al.*** The effect of hospital-acquired *Clostridium difficile* infection on in-hospital mortality. *Archives of Internal Medicine* 2010; **170**: 1804–1810.
4. **Nanwa N, *et al.*** The economic impact of *Clostridium difficile* infection: a systematic review. *American Journal of Gastroenterology* 2015; **110**: 511–519.
5. **Fletcher S, *et al.*** Descriptive epidemiology of infectious gastrointestinal illnesses in Sydney, Australia, 2007–2010. *Western Pacific Surveillance and Response* 2015; **6**: 7–16.
6. **Slimings C, *et al.*** Increasing incidence of *Clostridium difficile* infection, Australia, 2011–2012. *Medical Journal of Australia* 2014; **200**: 272–276.
7. **Badger VO, *et al.*** *Clostridium difficile* epidemiology, pathogenesis, management, and prevention of a recalcitrant healthcare-associated pathogen. *Journal of Parenteral Enteral Nutrition* 2012; **36**: 645–662.
8. **Khanna S, *et al.*** The epidemiology of community-acquired *Clostridium difficile* infection: a population-based study. *American Journal Gastroenterology* 2012; **107**: 89–95.
9. **Lambert PJ, *et al.*** Population-based surveillance of *Clostridium difficile* infection in Manitoba, Canada, by using interim surveillance definitions. *Infection Control and Hospital Epidemiology* 2009; **30**: 945–951.
10. **Delate T, *et al.*** Ambulatory-treated *Clostridium difficile* infection: a comparison of community-acquired vs. nosocomial infection. *Epidemiology and Infection* 2015; **143**: 1225–1235.
11. **Songer JG, *et al.*** *Clostridium difficile* in retail meat products, USA, 2007. *Emerging Infectious Diseases* 2009; **15**: 819.
12. **Bakri MM, *et al.*** *Clostridium difficile* in ready-to-eat salads, Scotland. *Emerging Infectious Diseases* 2009; **15**: 817–818.
13. **Australian Bureau of Statistics. Population by age and sex, Australia,** 2006, Australian Bureau of Statistics 2007 (http://www.abs.gov.au/ausstats/abs@.nsf/Products/3235.0~2006~Main+Features~New+South+Wales?OpenDocument). Accessed 2 November 2014.
14. **45 and Up Study Collaborators, *et al.*** Cohort profile: the 45 and Up Study. *International Journal of Epidemiology* 2008; **37**: 941–947.
15. National Casemix and Classification Centre. Australian refined diagnosis related groups, version 6.x, Addendum 2012.
16. **Centre for Health Record Linkage.** (www.cherel.org.au). Accessed Aug 2014.
17. **Australian Government Department of Health.** Round 14 (2009–2010) National Public Cost Weight Tables-version 6.0x and version 5.2., Canberra: Australian Government Department of Health and Aging (http://www.health.gov.au/internet/main/publishing.nsf/Content/Round_14-cost-reports). Accesed 10 April 2015.
18. **Anon.** ARIA and Accessibility (https://www.adelaide.edu.au/apmrc/research/projects/category/aria.html). Accesed October 10, 2014.

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19. **Sundararajan V, *et al.*** New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. *Journal of Clinical Epidemiology* 2004; **57**: 1288–1294.
20. **Thiébaut A, Bénichou J.** Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. *Statistics in Medicine* 2004; **23**: 3803–3820.
21. **Planche TD, *et al.*** Differences in outcome according to *Clostridium difficile* testing method: a prospective multicentre diagnostic validation study of *C. difficile* infection. *Lancet Infectious Diseases* 2013; **13**: 936–945.
22. **Eyre DW, *et al.*** Emergence and spread of predominantly community-onset *Clostridium difficile* PCR ribotype 244 infection in Australia, 2010 to 2012. *Eurosurveillance* 2015; **20**: 21059.
23. **McDonald LC, *et al.*** Recommendations for surveillance of *Clostridium difficile*-associated disease. *Infection Control and Hospital Epidemiology* 2007; **28**: 140–145.
24. **Tschudin-Sutter S, *et al.*** Distinguishing community-associated from hospital-associated *Clostridium difficile* infections in children: implications for public health surveillance. *Clinical Infectious Diseases* 2013; **57**: 1665–1672.
25. **Kyne L S, *et al.*** Underlying disease severity as a major risk factor for nosocomial *Clostridium difficile* diarrhea. *Infection Control and Hospital Epidemiology* 2002; **23**: 653–659.
26. **Ananthakrishnan AN.** Clostridium difficile infection: epidemiology, risk factors and management. *Nature Reviews Gastroenterology and Hepatology* 2011; **8**: 17–26.
27. **Foster NF, *et al.*** Epidemiology of *Clostridium difficile* infection in two tertiary-care hospitals in Perth, Western Australia: a cross-sectional study. *New Microbes and New Infections* 2014; **2**: 64–71.
28. **Fellmeth G, Yarlagadda S, Iyer S.** Epidemiology of community-onset *Clostridium difficile* infection in a community in the South of England. *Journal of Infection and Public Health* 2010; **3**: 118–123.
29. **Wozniak TM, Rubin G , MacIntyre CR.** The emergence of community-acquired Clostridium difficile in an Australian hospital. *Healthcare Infection* 2015; **20**: 72–77.
30. **Chitnis AS, *et al.*** Epidemiology of community-associated *Clostridium difficile* infection, 2009 through 2011. *JAMA Internal Medicine* 2013; **173**: 1359–1367.
31. **Sun C, Jew S, Dasta SL.** Osteopathic physicians in the United States: antibiotic prescribing practices for patients with nonspecific upper respiratory tract infections. *Journal of American Osteopathic Association* 2006; **106**: 450–455.
32. **Barlam TF, *et al.*** Antibiotics for respiratory tract infections: a comparison of prescribing in an outpatient setting. *Infection Control and Hospital Epidemiology* 2015; **36**: 153–159.
33. **Markle JG, *et al.*** Sex differences in the gut microbiome drive hormone-dependent regulation of autoimmunity. *Science* 2013; **339**: 1084–1088.
34. **Yurkovetskiy L, *et al.*** Gender bias in autoimmunity is influenced by microbiota. *Immunity* 2013; **39**: 400–412.
35. **Mueller S, *et al.*** Differences in fecal microbiota in different European study populations in relation to age, gender, and country: a cross-sectional study. *Applied Environmental Microbiology* 2006; **72**: 1027–1033.
36. **Lin YC, *et al.*** Characteristics of patients with *Clostridium difficile* infection in Taiwan. *Epidemiology and Infection* 2013; **141**: 2031–2038.
37. **Jones G, *et al.*** Accuracy of ICD-10 codes for surveillance of *Clostridium difficile* infections, France. *Emerging Infectious Diseases* 2012; **18**: 979–981.
38. **Mealing NM, *et al.*** Investigation of relative risk estimates from studies of the same population with contrasting response rates and designs. *BMC Medical Research Methodologhy* 2010; **10**: 26.

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Chapter 10

Paper seven: Burden of *Clostridium difficile* infection: associated hospitalisation in a cohort of middle-aged and older adults

Chen Y, Glass K, Liu B, Korda R, Riley T, Kirk M. Burden of Clostridium difficile infection: associated hospitalization in a cohort of middle-aged and older adults. Am J Infect Control. 2017;45:508-511. Association for Professionals in Infection Control and Epidemiology, Inc.

About This Chapter

This chapter describes the burden of hospitalisation related to *Clostridium difficile* infection (CDI) in middle-aged and older adults. Specifically, it documents the average length of hospital stay and cost per hospitalisation, as well as proportion of in-hospital deaths for CDI and non-CDI hospitalisation. Prior to this paper, Australian data on CDI associated healthcare burden were limited. This paper contributes to answering the research question: 'What is the incidence of and risk factors for *Clostridium difficile* infection in middle-aged and older adults?'. This paper was published in *American Journal of Infection Control.*

Burden of *Clostridium difficile* infection: associated hospitalization in a cohort of middle-aged and older adults

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Summary

Aim: To describe and compare length of stay (LOS), costs, and in-hospital deaths for *Clostridium difficile* infection (CDI) and non-CDI hospitalizations, in a cohort of middle-aged and older Australians.

Methods: We used survey data from the 45 and Up Study, linked to hospitalization and death data. We calculated the average LOS and costs per hospitalization, and the proportion of in-hospital deaths, separately for CDI and non-CDI hospitalizations. We compared hospitalizations with CDI as a secondary diagnosis to hospitalizations without a diagnosis of CDI by first stratifying hospitalizations into one of four major disease groups based on principal diagnosis and then using generalized linear models to compare LOS and in-hospital costs, and logistic regression for in-hospital deaths, adjusting for age and sex.

Results: There were 641CDI hospitalizations during 2006-2012. The average LOS was 17 days; the average costs per hospitalization was AUD 12,704; and in 7.3% (47/641) of admissions the patient died. In 64.9% (416/641) of the CDI hospitalizations, CDI was a secondary diagnosis, with digestive, cardiovascular, neoplastic and respiratory diseases constituting half (48%) of principal diagnoses for these hospitalizations. After adjusting for age and sex, hospitalizations with CDI were associated with longer LOS, higher costs and a greater proportion of in-hospital deaths compared to hospitalizations with similar principal diagnosis but without CDI.

Conclusions: CDI places additional burden on the hospital system, with CDI patients having relatively lengthy hospital stays and high costs. An appreciation of the burden of CDI hospitalization is important to ensure proper allocation of healthcare resources of CDI prevention and treatment efforts.

Introduction

Clostridium difficile is the principal cause of infectious diarrhoea in hospitalized patients [1]. Globally, the incidence of *C. difficile* infection (CDI) has increased significantly during the last decade, resulting in a considerable burden on healthcare systems. A recent systematic review of 45 CDI cost-of-illness studies confirmed a significant economic impact of CDI, and reported excess CDI costs ranging from USD 8,911 to 30,049 per admission for hospitalized patients [2]. Most (84%) of the selected studies were from the United States and all focused on direct costs [2]. Another review focusing on the burden of CDI on the US healthcare system estimated that CDI has resulted in USD 4.8 billion in healthcare costs in acute-care facilities alone in 2008 [3]

In Australia, national surveillance for hospital-identified CDI has demonstrated increasing incidence since 2011 [4], although data on the burden of CDI-associated hospitalization are limited. One Australian study estimated that hospital-acquired *C. difficile*-associated enterocolitis added AUD 19,745 to the cost of each hospital episode, making it one of the most costly hospital-acquired conditions in public hospitals in 2007-2008 [5]. However, this study focused on costs associated with hospital-acquired CDI, and the burden of all CDI hospitalizations was not reported. Our recent study found that the incidence of CDI hospitalization was 16.6 per 100,000 person-years in middle-aged and older Australians [6]. The aim of this study was to describe and compare length of stay (LOS), costs and in-hospital deaths for CDI and non-CDI hospitalizations, in a cohort of middle-aged and older Australians.

Methods

Study population and data sources

We used data from the Sax Institute's 45 and Up Study, a prospective cohort study of healthy aging involving 267,153 males and females aged 45 years and over from the general population of the Australian state of New South Wales (NSW) (population 6.8 million persons, 2006) [7]. Participants were randomly selected from the Medicare Australia database which includes all citizens and permanent residents of Australia, and some temporary residents and refugees. Approximately 10% of the population of NSW 45 years and over were included in the final cohort. More details of the 45 and Up Study can be found elsewhere [8].

In this study, self-reported questionnaire data collected from 45 and Up Study participants at recruitment from 2006-2009 were linked to the NSW Admitted Patient Data Collection (APDC) (date of recruitment to 30 June 2012), and the NSW Register of Births, Deaths and Marriages (RBDM) (date of recruitment to 30 June 2012). The APDC includes records of principal diagnosis for each admission, and up to 54 additional diagnoses contributing to the admission, coded using the International Classification of Diseases, 10th revision, Australian Modification (ICD-10-AM) [9, 10]. These data also include the Australian Refined Diagnosis Related Group (DRG) code for each admission. Each DRG represents a class of patients with similar clinical conditions requiring similar hospital resources [11]. The NSW Centre for Health Record Linkage performed the data linkage independent of the study investigators and report false positive and false negative linkages of <0.5% and <0.1%, respectively [12].

Case definition

Cases were defined as hospitalizations following the recruitment into the 45 and Up study with either the principal diagnosis or a secondary diagnosis of *C. difficile* colitis (ICD-10-AM code A04.7).

Hospitalization outcomes

Outcomes included in-hospital deaths, LOS (discharge date minus admission date, plus 1 day for same day admission), and costs of hospitalization. For patients who had been transferred between hospitals, relevant hospitalization records were merged together to avoid double counting of unique hospitalizations. To estimate the costs of each hospitalization, we matched DRG codes of each hospitalization to DRG-based cost data from the National Hospital Cost Data Collection Public Sector Estimated Cost Weights Reports (NHCDC) [13]. The NHCDC documents average costs per DRG, based on patient-costed and cost-modelled information. We used the average DRG-specific total costs per admission in the Round 14 (2009-10) NHCDC (version 5.2 for admissions from January 2006 to December 2009 and version 6.0x from admissions from January 2010 to June 2012). Costs are reported in Australian dollars (AUD).

Patient characteristic variables

Sociodemographic information was obtained from the baseline questionnaire and included: age (grouped as 45-54, 55-64, 65-74, 75-84 or ≥85years), sex, annual household income (7 categories from less than $20,000 to $70,000 or more per year), and region of residence (cities, inner regional or outer

regional/remote) based on the Accessibility/Remoteness Index of Australia (ARIA).

Analysis

Participants were followed from the date of recruitment to 30 June 2012, the last date for which hospital data were available. Participants were excluded from the analyses if they had missing data on date of entry into study, or if they had any DRG code/cost information missing.

We first summarized the sociodemographic characteristics of the patients for all hospitalizations in the study period, separately for CDI and non-CDI hospitalizations. We calculated the average LOS and costs per hospitalization, as well as the proportion of hospitalizations in which a patient died, separately for CDI and non-CDI hospitalizations, by age group. To compare outcomes of hospitalizations with CDI as a secondary diagnosis to hospitalizations without a secondary diagnosis of CDI, we further stratified hospitalizations into one of four major disease groups based on principal diagnosis (digestive disease, cardiovascular disease, neoplasm and respiratory disease), and calculated the age-adjusted average LOS and costs, and the proportion with in-hospital deaths. To compare the results, we used generalized linear model assuming a negative binomial distribution for LOS and a gamma distribution for in-hospital costs, and logistic regression for in-hospital deaths. Exact logistic regression was used when sample size was less than five. All models were adjusted for age and sex. All analyses were carried out using Stata 14.1.

Ethics approval

Ethics approvals for this study were obtained from the University of New South Wales Human Research Ethics Committee, the NSW Population and Health Services Research Ethics Committee, and the Australian National University Human Research Ethics Committee. All participants provided written informed consent.

Results

There were 641 hospitalizations with CDI during the study period. The average age of hospitalization was 76.7 years (standard deviation (SD): 11.2), and 45% of the patients were male. There were 712,178 hospitalizations without CDI and the average age of these patients was 70.4 years (SD: 11.4), 53% male. Table 1 summarizes the demographic characteristics of patients hospitalized with and without CDI during the study period.

Table 1. Characteristics of patients hospitalized with and without CDI, the 45 and Up Study.

Characteristics	Hospitalization with CDI (%) N=641	Hospitalization without CDI (%) N=712,178
Age (years)		
45-54	26 (4.1)	74,039 (10.4)
55-64	99 (15.4)	166,661 (23.4)
65-74	130 (20.3)	199,904 (28.1)
75-84	221 (34.5)	194,184 (27.3)
≥85	165 (25.7)	77,326 (10.9)
Sex		
Female	351 (54.8)	335,691 (47.1)
Male	290 (45.2)	376,440 (52.9)
Household income (AUD)		
20,000	224 (34.9)	188,703 (26.5)
20,000-29,999	61 (9.5)	82,112 (11.5)
30,000-49,999	47 (7.3)	53,602 (7.5)
50,000-59,999	34 (5.3)	44,481 (6.3)
60,000-69,999	24 (3.8))	54,001 (7.6)
≥70,000	52 (8.1)	105,601 (14.8)
Unknown	199 (31.1)	183,678 (25.8)
Region of residence		
Cities	402 (62.7)	359,295 (50.5)
Inner regional	175 (27.3)	232,954 (32.7)
Out regional/remote	64 (10.0)	119,882 (16.8)

Of those patients hospitalized with CDI, 7.3% (47/641) died during hospitalization. The average number of days in hospital was 17 (interquartile range (IQR): 5–22 days), and the average costs per hospitalization was $12,704 (IQR: $4,998–13,356). In 35% (225/641), CDI was classified as the principal diagnosis.

Table 2 compares the outcomes of hospitalization among patients hospitalized with CDI and those hospitalized without CDI during the study period, by age group. Compared to non-CDI hospitalizations, CDI-

hospitalizations had greater average LOS, costs, and proportion with in-hospital deaths. This pattern was consistent across all age groups (Table 2).

Table 2. Comparison of hospitalization burden for CDI and non-CDI hospitalizations, by age group, the 45 and Up Study.

	Death in hospital, % of hospitalizations		**Mean length of stay (days) (IQR)**		**Mean cost, AUD (IQR)**	
Age categories (years)	CDI	Non-CDI	CDI	Non-CDI	CDI	Non- CDI
45-54	0.0%	0.4%	12.6 (3-18)	2.2 (1-1)	12,439 (1,909-7,054)	3,816 (1,334-4,257)
55-64	4.0%	0.5%	18.5 (5-22)	2.4 (1-1)	14,602 (2,012-13,649)	4,021 (1,150-4,362)
65-74	6.2%	0.8%	15.7 (5-20)	2.7 (1-2)	14,479 (6,102-13,356)	4,314 (1,146-4,714)
75-84	9.1%	1.5%	17.7 (6-24)	3.7 (1-3)	13,272 (5,536-13,533)	4,539 (982-5,500)
≥85	9.1%	3.0%	16.8 (5-22)	5.3 (1-6)	9,449 (5,677-12,835)	5,070 (1,430-6,598)

CDI was a secondary diagnosis in 64.9% (416/641) of the CDI hospitalizations. Digestive, cardiovascular, neoplastic and respiratory diseases constituted nearly half (48%) of principal diagnoses for which CDI was a secondary diagnosis. Table 3 shows hospital outcomes stratified by these principal diagnosis for hospitalizations with CDI as a secondary diagnosis and for non CDI-related hospitalizations. After adjusting for age and sex, hospitalizations with CDI were associated with longer LOS, higher costs and a greater proportion of in-hospital deaths compared to hospitalizations with similar principal diagnosis but without CDI. For example, hospitalizations with a principal diagnosis of neoplasm and CDI as a secondary diagnosis were on average 25 days longer and cost $14,000 more, and the probability of in-hospital deaths was more than triple, compared to hospitalization with a principal diagnosis of neoplasm and no secondary diagnosis of CDI (Table 3).

Table 3. Comparison of hospitalization burden among patients with a secondary diagnosis of CDI and those without any diagnosis of CDI, by principal diagnosis group, the 45 and Up Study.

Principal diagnosis, variable	Hospitalization with CDI as a secondary diagnosis	Hospitalization without CDI	*P*-value*
Digestive disease			
No. of hospitalizations	51	74,539	
Mean age (years) (SD)	77.4 (11.3)	77.3 (10.9)	
Age-adjusted death in hospital, % of hospitalizations	1.4	0.5	0.8
Age-adjusted mean number of days in hospital (SE)	20.1 (2.4)	2.1 (0.02)	<0.001
Age-adjusted mean costs, AUD (SE)	19,900 (3,585)	3,671 (21.7)	<0.001
Cardiovascular disease			
No. of hospitalizations	63	60,234	
Mean age (years) (SD)	77.4 (10.3)	72.9 (11.2)	
Age-adjusted death in hospital, % of hospitalizations	4.0	2.7	0.4
Age-adjusted mean number of days in hospital (SE)	19.6 (3.1)	4.3 (0.03)	<0.001
Age-adjusted mean costs, AUD (SE)	17,947 (2,611)	7,825 (46.7)	<0.001
Neoplasm			
No. of hospitalizations	44	44,328	
Mean age (years) (SD)	76.2 (8.9)	70.9 (11.0)	
Age-adjusted death in hospital, % of hospitalizations	20.0	6.4	0.01
Age-adjusted mean number of days in hospital (SE)	29.9 (3.5)	4.5 (0.04)	<0.001
Age-adjusted mean costs, AUD (SE)	21,685 (2,097)	7,520 (45.2)	<0.001
Respiratory diseases			
No. of hospitalizations	42	23,804	
Mean age (years) (SD)	77.9 (9.0)	72.9 (11.8)	
Age-adjusted death in hospital, % of hospitalizations	11.0	4.3	0.3
Age-adjusted mean number of days in hospital (SE)	15.0 (1.6)	5.8 (0.05)	<0.001
Age-adjusted mean costs, AUD (SE)	13,389 (3,244)	6,945 (66.8)	<0.001
Overall#			
No. of hospitalizations	416	712,178	
Mean age (years) (SD)	77.3 (11.0)	70.4 (11.4)	
Age-adjusted death in hospital, % of hospitalizations	10.0	1.1	<0.001
Age-adjusted mean number of days in hospital (SE)	21.2 (1.0)	3.0 (0.009)	<0.001
Age-adjusted mean costs, AUD (SE)	16,920 (1,164)	4,317 (8.6)	<0.001

*Generalized linear models with negative binomial distribution for LOS, generalized linear model assuming a gamma distribution for in-hospital costs, and logistic regression for in-hospital death. All analyses were adjusted for age and sex.
#Including hospitalizations due to digestive, cardiovascular, neoplasm and respiratory diseases.
SD: standard deviation; SE: standard error

Discussion

Hospitalizations with CDI as a secondary diagnosis are longer, more costly and have a higher proportion of in-hospital deaths compared to hospitalization with similar principal diagnosis but without CDI in middle-aged and older Australians. While this may not translate to a large total burden on the health care system given they constitute only a small proportion of total hospital admissions (12,683 cases of hospital-identified CDI in public hospitals in Australia in 2011-12 [4] and 0.2% of all public hospital admissions [14]), the burden on individual patients is substantial.

There are few studies with which we can compare our findings, and different study settings, designs and case definitions preclude direct comparisons of estimates across studies. Nevertheless, the finding of increased LOS in CDI hospitalizations is broadly consistent with a study by Riley *et al,* conducted in one Australian hospital over 20 years ago, who found that, on average, CDI patients stayed in the hospital 18 days longer than non-CDI patients [15]. International studies (mostly form the US) have reported high costs and long LOS for both CDI requiring admission and for hospital-acquired CDI [16].

Our finding that hospitalizations with CDI as a secondary diagnosis had a greater probability of in-hospital deaths compared to hospitalization with a similar principal diagnosis but without CDI is also consistent with previous international evidence. Although we did not attempt to estimate CDI-attributable deaths in this study due to lack of clinical data, previous studies have found that CDI had a significant negative impact on patient survival. Oake *et al,*

using used data collected from 136,877 admissions with mean age at 63 years in the Ottawa Hospital, reported that hospital-acquired CDI significantly increased the absolute risk of in-hospital deaths by 11%, with a 3-fold increase in the relative risk [17]. Similarly, one US study found a higher proportion of deaths within 180 days of hospital admission among CDI patients compared to non-CDI patients [18].

There are several possible explanations for the higher burden associated with CDI hospitalization compared to non-CDI hospitalization. First, CDI may be associated with a decline in patient function and overall illness during hospitalization, ultimately leading to worse outcomes. Second, there may be confounding by overall health status. Patients with comorbid conditions may have higher risks of CDI, and these patients are also likely to have excess healthcare burden. Therefore, the higher burden of CDI hospitalization described in our study cannot necessarily be attributed to CDI. Previous studies have determined the CDI attributable costs using administrative datasets, although many of those are limited by inadequately controlling for such confounding; without this adjustment, CDI-associated burden may be over-estimated.

Our study has several limitations. The 45 and Up study cohort, while a population-based cohort including about 1 in 10 adults in the age range in the state of New South Wales (NSW), may not be representative of the general NSW population—participants are likely to be healthier. This may lead to an underestimation of the absolute burden of CDI hospitalization, although internal comparisons between CDI and non-CDI hospitalization are still valid [19].

Another limitation is the lack of clinical data in the database, which limits our ability to attribute worse outcomes of hospitalization to CDI. For example, we were unable to adjust for differences in severity of underlying conditions when comparing outcomes among different patient groups. There may also be institutional level variation that could account for some of the variation between those patients hospitalized with and without CDI.

We used the DRG-specific average costs to estimate in-hospital costs due to illness. While each DRG represents a class of patients with similar clinical conditions requiring similar hospital services, they are not sensitive to individual variations in resources use within DRG categories. Therefore, the costs assigned to each individual are indicative only. The use of DRG is likely to underestimate CDI costs as patients with CDI were likely to have longer length of stay, and costs associated with excess hospital stays for a given DRG are not captured in data. In addition, all CDI cases were identified using coded diagnoses, the sensitivity and specificity of which remain largely unknown. A recent French study found that the International Classification of Diseases-10 coding for CDI had 99.9% specificity and 35.6% sensitivity [20]. The trends in CDI rates for ICD-10 codes identified cases and laboratory-confirmed cases strongly correlated, but concordance was moderate, which may lead to an underestimation of true population rates [20]. Whether Jones's findings translate to Australia remains unclear. Nevertheless, given the lack of information on the burden of CDI in Australia, we believe that our estimates provide a useful addition to our understanding of the magnitude of the burden of CDI hospitalization.

In conclusion, we found that patients hospitalized with CDI have relatively lengthy hospital stays and high costs, and are more likely to die in hospital then those with non-CDI hospitalizations. The increased length of stay, costs and in-hospital deaths associated with CDI is found across patients with a range of diagnoses. An appreciation of the burden of CDI hospitalization is important to ensure proper allocation of healthcare resources for CDI prevention and treatment efforts.

References

1. Leffler DA, Lamont JT. Clostridium difficile Infection. New Engl J Med. 2015;372(16):1539-48.

2. Nanwa N, Kendzerska T, Krahn M, Kwong JC, Daneman N, Witteman W, et al. The economic impact of Clostridium difficile infection: a systematic review. Am J Gastroenterol. 2015;110(4):511-9.

3. Dubberke ER, Olsen MA. Burden of Clostridium difficile on the healthcare system. Clin Infect Dis. 2012;55(suppl 2):S88-S92.

4. Slimings C, Armstrong P, Beckingham W, Bull AL, Hall L, Kennedy KJ, et al. Increasing incidence of Clostridium difficile infection, Australia, 2011–2012. Med J Aust. 2014;200(5):272-6.

5. Jackson T, Nghiem HS, Rowell D, Jorm C, Wakefield J. Marginal costs of hospital-acquired conditions: information for priority-setting for patient safety programmes and research. J Health Serv Res Policy. 2011;16(3):141-6.

6. Chen Y, Glass K, Liu B, Riley T, Korda R, Kirk M. A population-based longitudinal study of Clostridium difficile infection-related hospitalization in mid-age and older Australians. Epidemiol Infect (In press). 2016. Doi:10.1017/S0950268816002260.

7. Population by age and sex, Australia, 2006 [Internet]. Australian Bureau of Statistics. 2007 [cited 2 November 2015]. Available from: http://www.abs.gov.au/ausstats/abs@.nsf/Products/3235.0~2006~Main+Features~New+South+Wales?OpenDocument

8. 45 and Up Study Collaborators, Banks E, Redman S, et al. Cohort profile: the 45 and Up Study. Int J Epidemiol. 2008;37(5):941-7.

9. National Centre for Classification in Health. Internationl statistical classification of diseases and related health problems, 10th revision, Australian Modification (ICD-10-AM). 5th edn. . In: National Centre for Classification in Health: Sydney N, Australia, editor.: National Centre for Classification in Health: Sydney, NSW, Australia; 2006.

10. NSW Health Department, Admitted Patient Data Collection [Internet]. 2008. Available from: http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/1368.1Explanatory%20Notes1452007. Accesed on 10 August 2014.

11. National Casemix and Classification Centre. Australian Refined Diagnosis Related Groups Version 6.x Addendum. 2012.

12. Centre for Health Record Linkage. Available from: www.cherel.org.au. Accessed Aug 2014.

13. Round 14 (2009-2010) National Public Cost Weight Tables-version 6.0x and version 5.2. [Internet]. Canberra: Australian Government Department of Health and Aging. Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/Round_14-cost-reports.

14. Australian Institute of Health and Welfare 2014. Australia's health 2014. Australia's health series no. 14. Cat. no. AUS 178. Canberra: AIHW.

15. Riley TV, Codde JP, Rouse IL. Increased length of hospital stay due to Clostridium difficile associated diarrhoea. Lancet. 1995;345(8947):455-6.

16. Gabriel L, Beriot-Mathiot A. Hospitalization stay and costs attributable to Clostridium difficile infection: a critical review. J Hosp Infect. 2014;88(1):12-21.

17. Oake N, Taljaard M, van Walraven C, Wilson K, Roth V, Forster AJ. The effect of hospital-acquired Clostridium difficile infection on in-hospital mortality. Arch Intern Med. 2010;170(20):1804-10.

18. Dubberke E, Butler A, Reske K, Agniel D, Olsen M, D'Angelo G, et al. Attributable outcomes of endemic Clostridium difficile-associated disease in nonsurgical patients. Emerg Infect Dis. 2008;14:1031-8.

19. Mealing NM, Banks E, Jorm LR, Steel DG, Clements MS, Rogers KD. Investigation of relative risk estimates from studies of the same population with contrasting response rates and designs. BMC Med Res Methodol. 2010;10(1):26.

20. Jones G, Tarright N, Boelle PY, Marty J, Lalande V, Eckert C, et al. Accuracy of ICD-10 codes for surveillance of Clostridium difficile infections, France. Emerg Infect Dis. 2012;18(6):979-81.

Chapter 11

Paper eight: *Clostridium difficile* infection and risk of colectomy in patients with inflammatory bowel disease: A bias adjusted meta-analysis

Chen Y, Furuya-Kanamori L, Doi S, Ananthakrishnan A, Kirk M. Clostridium difficile infection and risk of colectomy in patients with inflammatory bowel disease: A bias adjusted meta-analysis. Inflamm Bowel Dis. 2017;23:200-207. Lippincott Williams & Wilkins.

About This Chapter

In this chapter, I systematically reviewed the literature regarding the risk of colectomy associated with *Clostridium difficile* infection (CDI) among patients with inflammatory bowel diseases (IBD). CDI is a common complication of IBD and is associated with worse clinical outcomes. Previous studies that examined the association between CDI and colectomy among IBD patients reported variable surgical rates. I conducted a systematic review and a bias adjusted meta-analysis to summarise the literature and quantify the risk of colectomy in CDI-IBD patients. Pooled results showed that CDI-IBD patients had a near-doubling of the likelihood of colectomy compared to IBD patients alone. This paper contributes to answering the research question: 'What are the complications of *Clostridium difficile* infection among people with chronic bowel problem?'. This paper was published in *Inflammatory Bowel Diseases*.

Clostridium difficile infection and risk of colectomy in patients with inflammatory bowel disease: A bias adjusted meta-analysis

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Abstract

Background: *Clostridium difficile* infection (CDI) is a common complication of inflammatory bowel diseases (IBD) and is associated with worse outcome. Variable rates of colectomy have been reported among IBD complicated by CDI. We conducted a systematic review and meta-analysis of studies to assess the association between CDI and colectomy among IBD patients.

Methods: The literature was systematically searched using PubMed from inception through April 2016. Studies were limited to cohort, case-control and cross-sectional studies reporting colectomy risk stratified by CDI in IBD patients. We estimated summary odds ratios (ORs) and 95% confidence intervals (CI) using the quality effects model. Study quality was assessed using an adaptation of the Newcastle-Ottawa scale.

Results: Six studies were included in the meta-analysis, comprising eight datasets. Results from meta-analysis showed that CDI was a significant risk factor for colectomy among IBD patients, mainly ulcerative colitis patients, almost doubling the odds (OR 1.90; 95%CI 1.23-2.93). There was significant heterogeneity across studies ($Q=22.02$, $P<0.001$; $I^2=68\%$). Funnel plots depict were grossly symmetrical. Results of sensitivity analysis restricting studies to those reporting ulcerative colitis only and studies using laboratory tests to confirm CDI were consistent with the result from the main analysis.

Conclusions: CDI is a significant risk factor for colectomy in IBD patients. Further research is needed to investigate the attributable risks of surgery due to CDI among patients with Crohn's disease.

Introduction

Inflammatory bowel disease (IBD), comprising ulcerative colitis and Crohn's disease, is a chronic relapsing disorder of genetically susceptible individuals exposed to environmental precipitants [1]. The initial management of IBD is medical therapy until treatment fails or a complication arises [2]. The majority of Crohn's patients and up to 35% of ulcerative colitis patients required intestinal resection during the course of their disease [3, 4]. However, improved medical therapy has resulted in decreased surgical interventions among IBD patients [5, 6]. Surgical treatment for IBD is associated with significant postoperative mortality and morbidity [7-9]. Identifying risk factors related to severe IBD flares that require surgery is a clinical priority.

Factors driving aggressive presentation in the early disease course of IBD are not known. *Clostridium difficile* infection (CDI) is considered an important risk factor in IBD exacerbations [10, 11], and is associated with worse clinical outcomes [12, 13]. The incidence of CDI has increased significantly among IBD patients, with recurrence in about one-third of both children and adults [14-16]. Individual studies have found that IBD patients with CDI have a higher rate of colectomy and a greater mortality than either non-CDI IBD or non-IBD CDI controls [14, 17, 18]. Peng *et al* conducted a meta-analysis using a fixed-effects model and found that ulcerative colitis patients with CDI had a significantly higher surgical rates than ulcerative colitis patients without CDI (odds ratio [OR]:1.76, 95%CI: 1.36-2.28) [19]. Interpreting

the results of this study is difficult due to the exclusion of studies using diagnostic codes to verify CDI.

Given that CDI is common in both active ulcerative colitis and Crohn's [20], it is important to have better evidence around the potential effect of CDI on the risk of colectomy in both groups. Most studies examining the association have used the International Classification of Diseases (ICD) codes to evaluate *C. difficile* diagnosis. Review papers excluding studies using diagnostic codes to identify CDI may lead to some degree of bias. Therefore, we conducted a systematic review and meta-analysis of studies using either laboratory methods or diagnostic codes to evaluate CDI to determine the association between CDI and colectomy among IBD patients.

Methods

Search strategy

A systematic review and meta-analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) guidelines [21].The literature was systematically searched using PubMed from inception through April 2016. Search terms included "inflammatory bowel disease", "Crohn's disease", "ulcerative colitis", and "*Clostridium difficile"*. No language restriction was used in the search filter. Eligible studies and relevant review articles were hand searched to identify any additional studies omitted by the database search.

Study selection

Inclusion criteria were studies that reported a comparison of colectomy rates in relation to CDI among IBD populations, studies that included a comparison group of non-CDI exposure, studies with a clear method for ascertainment of *C. difficile* diagnosis, and studies reporting colectomy as an outcome. Exclusion criteria were studies of patients without a known history of IBD, studies without CDI, and studies that did not report colectomy. Case reports, reviews, comments, news articles and editorial letters were also excluded from the search.

Two authors (Y.C. and L.FK.) independently reviewed all the studies by title and abstract. The full text of the remaining articles was obtained and reviewed including their bibliographic lists to see if there were additional missed publications on the subject. The reference lists of the studies that met the inclusion criteria, along with the reference list of a published systematic review [19] were then hand-searched.

Data extraction

Study references and citations were collected in Endnote version X7 (Thomson Reuters, New York, NY) and duplicate citations were removed. One author (Y.C.) extracted data from the included studies using a data collection form created in Microsoft Excel 2013 (Microsoft, Redmond, WA). Extracted data from each study included: first author's last name, year of publication, country of the population studied, study design and setting, number of IBD patients, age range, diagnosis method of CDI, and effect estimates (adjusted odds ratios [ORs]) and 95%

confidence intervals (CIs) for colectomy comparing those with and without the exposure. The disease exposure was defined as patients with CDI and the criteria for each study are listed in Table 1. Inter-extractor discrepancies were resolved by discussion. Extracted data were cross-checked by two authors (Y.C. and L.FK.), and discrepancies during the selection of studies or data extraction were resolved through discussion and consensus following independent evaluation by another author (S.A.D).

Table 1. Characteristics of studies included in the meta-analysis.

Author	Study period	Location/database	Design and setting	Patients	Median/mean Age (years)	*Clostridium difficile*		Outcome
				Disease N		Diagnosis method	n (n/N, %)	
Ananthakrishnan *et al.* 2011[29]	1998	Nationwide Inpatient Sample, USA	Case-control inpatient Population based from national administrative data	208,739 IBD 132,758 CD	56	ICD-9-CM codes	2,004 (0.96%)	In-hospital colectomy during index hospitalization
	2004	Nationwide Inpatient Sample, USA	Case-control inpatient Population based from national administrative data	208,739 IBD 132,758 CD	57	ICD-9-CM codes	4,801 (2.30%)	In-hospital colectomy during index hospitalization
	2007	Nationwide Inpatient Sample, USA	Case-control inpatient Population based from national administrative data	238,207 IBD 151,738 CD	60	ICD-9-CM codes	6,908 (2.90%)	In-hospital colectomy during index hospitalization
Jodorkovsky *et al.* 2010[31]	2004-2005	Mount Sinai Hospital in New York City, USA	Retrospective cohort inpatient Population based and non-national administrative data	99 UC	34/38[a]	Culture EIA	47 (47.48%)	30-day risk of colectomy
Kaneko *et al.* 2011[33]	2006-2009	Inflammatory Bowel Disease Centre in Yokohama, Japan	Prospective cohort out/inpatient Non-population based and non-national administrative data	137 UC	36	ELISA	55 (40.15%)	In-hospital colectomy during the index hospitalization
Murthy *et al.* 2012[32]	2002-2008	Acute care hospitals in Ontaria, Canada	Retrospective cohort inpatient Population based from national administrative data	2,016 UC	NR	ICD-10 codes	181 (9.0%)	In-hospital colectomy during index hospitalization
Navaneethan *et al.* 2012[26]	2002-2007	Cleveland Clinic's Digestive Disease Institute in Ohio, USA	Matched cohort out/inpatient Non-population based and non-national administrative data	153 UC	49/45[a]	ELISA	52 (33.97%)	1-year risk of colectomy
Negron *et al.* 2014[27]	2000-2009	Calgary Health Zone hospitals in Alberta, Canada	Case-control Inpatient Population based and non-national administrative data	278 UC	47/36[b]	EIA	17 (6.12%)	In-hospital emergent colectomy during index hospitalization

IBD, inflammatory bowel diseases; CD, Crohn's disease; UC ulcerative colitis; CDI, Clostridium difficile infection; NR, not reported
aMedian/mean age for patients with CDI/ patients without CDI
bMedian/mean age for patients with colectomy/patients without colectomy

Study quality assessment

This study quality assessment included screening for studies according to a modified version of the Newcastle–Ottawa quality assessment scale for observational studies. The modified scale was used to assess the possible sources of systematic error and potential bias of each study, which included: 1) definition of population and methods for IBD diagnosis, 2) representativeness of cohort/selection of cases and controls, 3) history of gastrointestinal surgery was not present at recruitment, 4) analysis adjusted for confounders, including age and sex, comorbid illness, antibiotic use, severity of IBD, and IBD treatment, 5) method used for ascertainment of CDI, 6) method used to ascertain CDI for cases and non-cases, and 7) assessment of outcome.

Statistical analysis

The outcome measure was the ORs of the association between CDI and colectomy among IBD patients. The ORs were pooled using the quality effects (QE) model to achieve bias adjustment [22]. Statistically significant heterogeneity was defined as a *P*-value for Cochran's Q <0.1, or the I^2 value >50%.

Sensitivity analyses were performed based on stratification of datasets by population. The categories were based on: a) restricting to non-population-based studies and non-national administrative datasets (subgroup A); b) population-based data excluding national administrative datasets (subgroup B); and c) restricting studies to population-based administrative datasets (subgroup C) (Table 1). A second

sensitivity analysis was conducted by restricting studies to those reporting ulcerative colitis only. A third sensitivity analysis was conducted by restricting studies to those using laboratory tests to confirm CDI. Finally, a sensitivity analysis was conducted by the two other statistical models [23, 24]. Funnel plots were created to detect potential asymmetry of the effect sizes. All statistical tests were two-tailed, and a significance level was set at $P < 0.05$. All analyses were conducted using MetaXL, version 5.1 (EpiGear Int. Pty Ltd).

Results

Literature search results

There were 590 studies identified in the initial search of which 483 studies were excluded after screening by title and abstract, and 101 further studies were excluded after discussion and full-text screening (Figure 1). These studies were excluded because the IBD population was not defined, colectomy was not evaluated and/or *C. difficile* exposure was not reported. There was overlap in subjects between three sets of studies. Two studies (Kariv *et al* 2011 [25] and Navaneethan *et al* 2012 [26]) used data from the Cleveland Clinic's Digestive Disease Institute between 2000 and 2007. Navaneethan *et al* 2012 [26] was included in this meta-analysis as it was the most recent study and had a larger sample size compared to the other study that used the same data. Two studies (Negron *et al* 2014 [27] and Negron *et al* 2016 [28]) used data of adults diagnosed with ulcerative colitis and living in Alberta, Canada. Negron *et al* 2016 [28] had a larger sample size, although this study reported hazard

ratios and odds ratios of associations were not available. Therefore this study was excluded from the meta-analysis. Additionally, two studies (Ananthakrishnan *et al* 2011 [29] and Nguyen *et al* 2008 [30]) used data from the United States Nationwide Inpatient Sample (NIS) between 1998 and 2007. Ananthakrishnan *et al* 2011 [29] was included in the analysis as it was the most recent study. Results of Ananthakrishnan *et al* 2011 [29] were entered as separate datasets by calendar year of 1998, 2004 and 2007 for meta-analysis as ORs were reported separately [29] (Figure 2).

Figure 1. Systematic reviews and meta-analysis flow-chart of the literature search

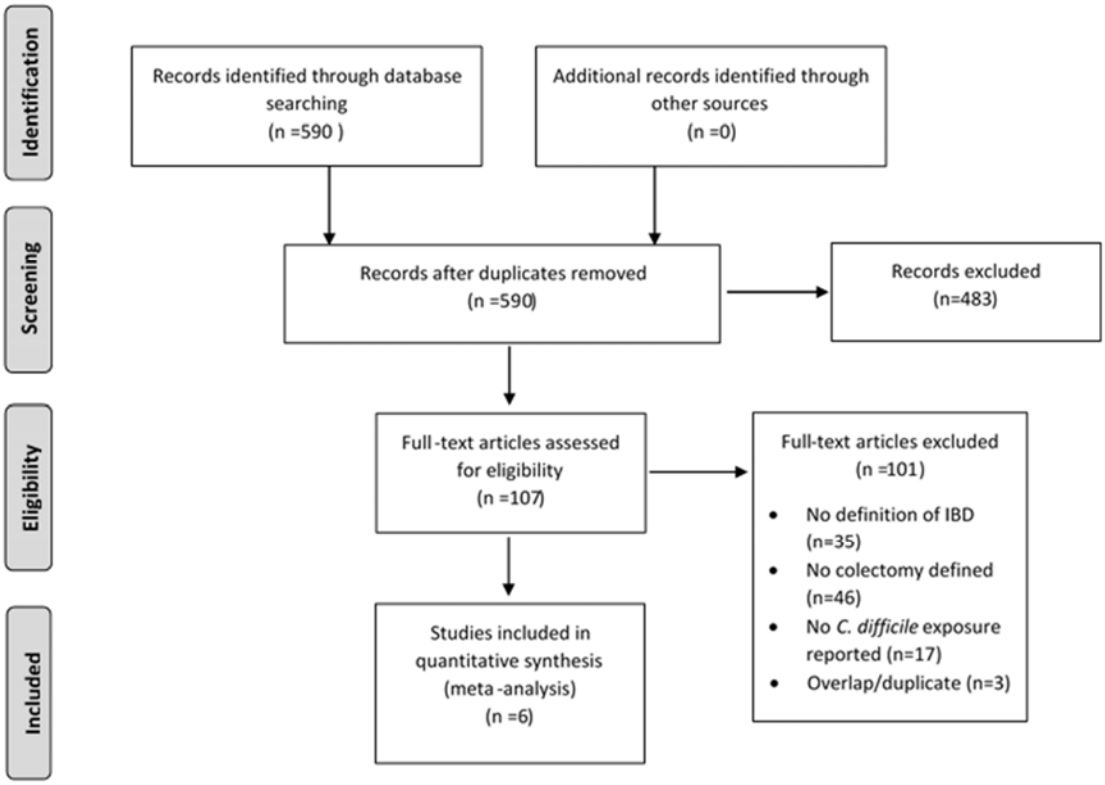
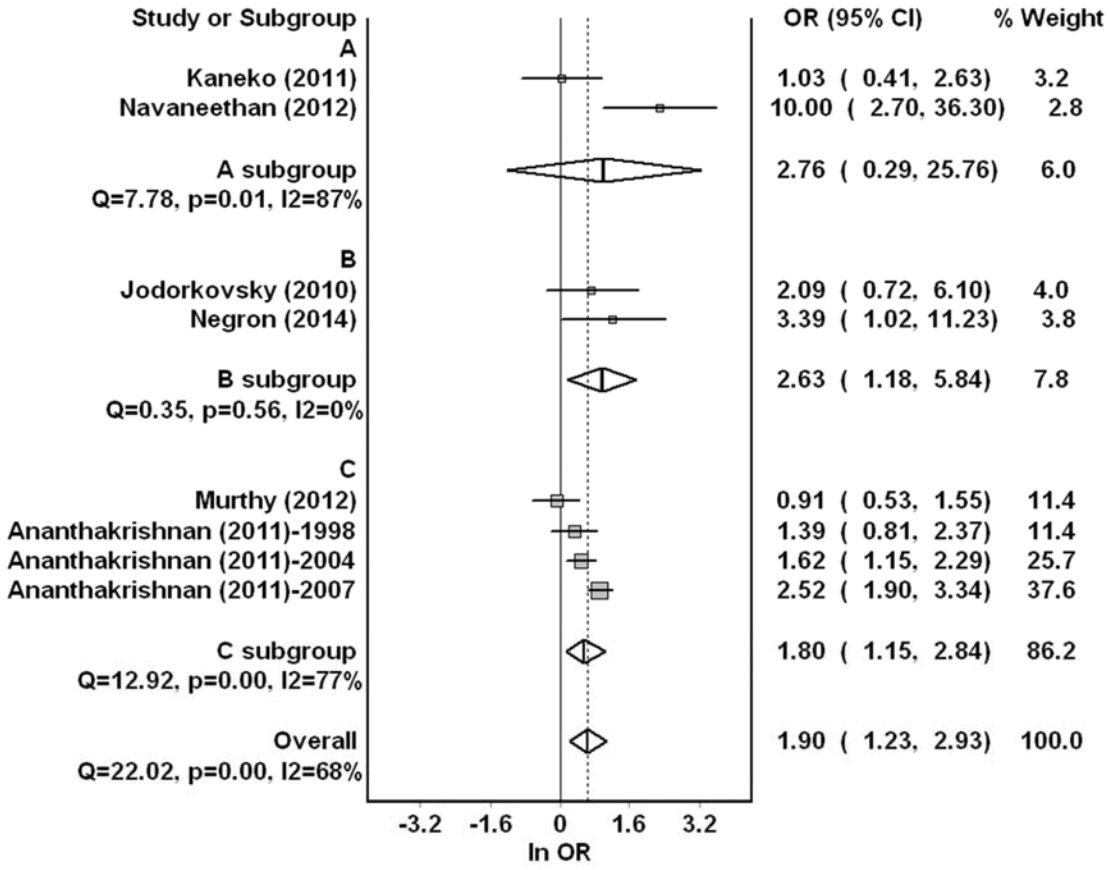


Figure 2. Forest plot depicting the association between CDI and colectomy among mainly ulcerative colitis patients (quality effects model). Horizontal lines represent 95% confidence intervals (CIs) for the study-specific effect size. The pooled odds ratio is shown as a diamond. The middle of the diamond corresponds to the odds ratio, and the width represents the 95%CI.



Subgroup A: studies of non-population-based and non-administrative datasets
Subgroup B: studies of population-based and non-national administrative datasets
Subgroup C: studies of population-based administrative datasets

Characteristics of the included studies for meta-analysis

There were six studies included in the meta-analysis (comprising eight datasets), of which one study had a prospective cohort design, and the remainder were retrospective observational studies. Of the five retrospective observational studies, two were case-control studies and three were cohort studies. The majority of the studies were from the United States, but there was one from Japan, and two studies from Canada. Four studies used laboratory methods to ascertain *C. difficile* diagnosis, through stool culture or toxin immunoassays, while the other two studies relied on a clinical diagnosis documented through electronic coding using the International Classification of Disease (ICD-9 or ICD-10) to identify *C. difficile* infection (ICD-9 of 8.45 or ICD-10 of A04.7). One study reported the effect of *C. difficile* on colectomy among IBD patients, and the remaining reported the results of ulcerative colitis patients only. (Table 1)

Five studies adjusted for potential confounders using multivariable models, although there was considerable diversity in the type of model and the selection of variables for adjustment. There may be confounding by indication which was not recorded such as severity of IBD and CDI. This remains a possible source of bias. Since systematic error that can be measured can have a huge impact, meticulous attention was given to the quality assessment. A univariate quality score of the studies created by empirically assigning a point to each safe guard present ranged between 6 and 10 out of a possible 12 (Table 2).

Table 2. Modified Newcastle-Ottawa Quality Assessment Scale for observational studies included in the meta-analysis.

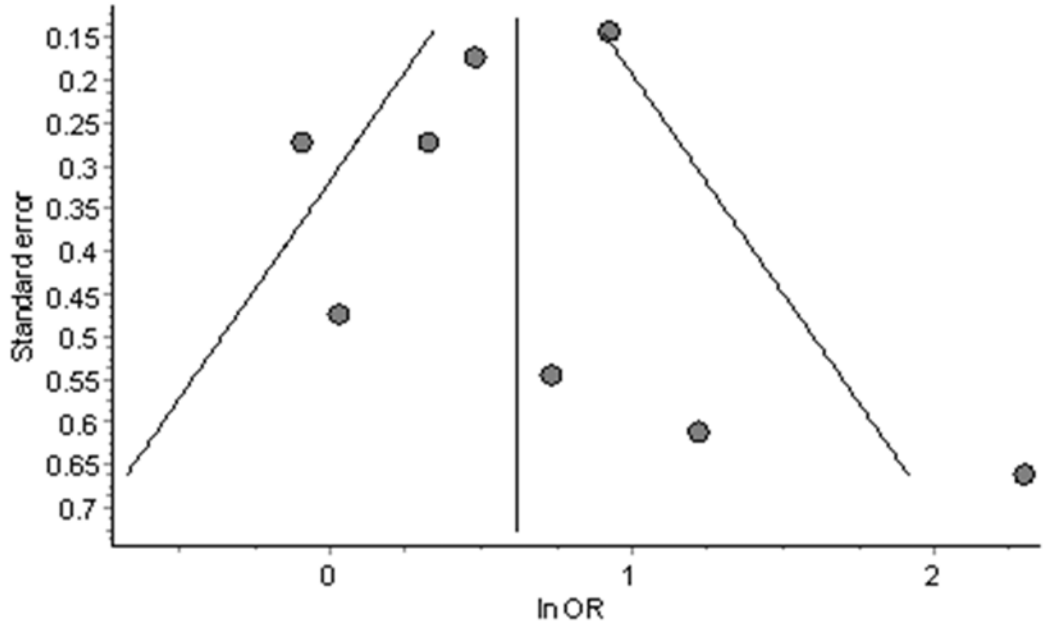
Author, publication year	Definition of population[a]	Settings of study population selected	History of gastrointestinal surgery was not present at recruitment	Analysis adjusted for confounders[d]	Ascertainment of exposures[e]	Same method used to ascertain CDI for cases and non-cases[f]	Assessment of outcome[g]	Total score (points)
Ananthakrishnan *et al.* 2011	2	2	0	2	1	1	1	9
Jodorkovsky*et al.*2010	2	2	1	1	2	1	0	9
Kaneko *et al.* 2011	2	1	0	0	2	1	0	6
Murthy *et al.* 2012	2	2	1	2	1	1	0	9
Navaneethan *et al.* 2012	2	1	0	2	2	1	0	8
Negron *et al.* 2014	2	2	0	2	2	1	1	10

[a]Definition of population: Method used for inflammatory bowel diseases including ulcerative colitis and Crohn's disease: clinical diagnosis or *International Classification of Disease* (ICD) code (2 points), based on self-reports (1 point), other or no description (0 points).
[b]Settings of study population selected: Representative of the IBD patients in the community/Community controls or drawn from the same community as the exposed cohort (2 points), Selected group of specialist centers (1 point), no description (0 points).
[c]History of gastrointestinal surgery was not present at recruitment: Exclusion of cases had gastrointestinal surgery at recruitment (1 point), no description (0 points).
[d]Analysis adjusted for confounders (age, sex, comorbid illness, antibiotic use, severity of IBD and IBD treatment. Adjusted for 6 factors (3 points), 3-5 factors (2 points), 1-2 factors (1 point), or non-adjusted (0 points).
[e]Ascertainment of exposures: method used for CDI diagnosis, stool culture or toxin detection (2 points), clinical diagnosis or *International Classification of Disease* (ICD) code (1 point), no description (0 points).
[f]Method of ascertainment of exposure for cases and non-cases: same method (1 point), no description (0 point).
[g]Assessment of outcome: clinical diagnosis or *International Classification of Disease* (ICD) code (1 point), no description (0 points).

Quantitative synthesis

Pooled results from six studies (eight data-sets) showed that CDI was a significant risk factor for colectomy among IBD patients (OR 1.90; 95%CI 1.23-2.93). There was significant heterogeneity across studies (Q=22.02, P<0.001; I^2=68%) (Figure 2). Funnel plots (Figure 3) suggested symmetry of study effects.

Figure 3. Funnel plots of studies examining the association between CDI and colectomy among mainly ulcerative colitis patients.



There were two studies that were not population-based and also did not use administrative data [26, 31], two studies used population-based data that were not from national administrative datasets [27, 32], and finally there were two studies (four datasets) that used population-based data derived from national administrative datasets [29, 33]. The sensitivity analysis by population subgroup had more or less consistent effect sizes across categories, but studies using administrative datasets were associated with weaker effects (Figure 2). Overall, there was significant heterogeneity, but this was mainly seen with non-population based and administrative datasets (Figure 2). Results of analysis restricting studies to those reporting ulcerative colitis only and studies using laboratory tests to confirm CDI

were similar to those of the main analysis (data not shown). The final sensitivity analysis based on statistical model was consistent across all three statistical models.

Discussion

This meta-analysis indicates that CDI is associated with a near-doubling in the odds of colectomy amongst a population consisting of mainly ulcerative colitis patients. Sensitivity analyses across different study populations showed similarly elevated risks. Despite statistical heterogeneity and differences in the actual point estimates, the elevated risk of colectomy with CDI was consistent when using different statistical models.

CDI is of concern when a patient with IBD symptoms is evaluated [34]. The dysbiotic gut microbiota observed among IBD patients provides an environment for *C. difficile* proliferation and potentially increase susceptibility to *C. difficile* induced mucosal damage, inflammation and mortality [35]. Infection with *C. difficile* alters the natural history of IBD by initiating an immune response to the organisms that may then activate acute flares. Despite growing evidence in the past decade with respect to worse outcomes among hospitalized IBD patients after exposure to CDI [36, 37], previous reviews evaluating disease-specific risk factors of CDI in IBD patients did not provide quantitative summaries of colectomy rates [20]. More recently, a meta-analysis has identified elevated surgical rates associated with CDI among ulcerative colitis patients [19]. This study used a fixed-effects model to generate a pooled estimate, which may not be the best analytical strategy for the

studies included. They also included studies using similar or the same datasets, which may have led to duplicate subjects in analyses.

Previous data have showed that hospitalized IBD patients experience higher rates of CDI than patients without IBD diagnoses [30]. This may be partly due to the immunomodulatory therapy, which has been reported as a risk factor for infection among IBD patients [36]. Nevertheless, despite patients with Crohn's having higher prevalence of immunomodulatory therapy, Crohn's patients have lower risks of CDI than ulcerative colitis patients [30, 38]. This may be explained by the differences between the two conditions. Ulcerative colitis is limited to the colon with continuous inflammation of the colon while Crohn's can occur anywhere in the gastrointestinal tract. As colonic disease is an independent risk factor for CDI [36], disproportionate rise in CDI co-infection has been reported in ulcerative colitis and Crohn's disease. Additionally, cytomegalovirus (CMV) which is another common comorbid intestinal infection in IBD does not interfere in the clinical course of Crohn's but is frequently reactivated in severe ulcerative colitis. Therefore, the clinical significance of intestinal infection such as CDI or CMV is different between Crohn's and ulcerative colitis, but the reason is not clear.

Previous data showed that patients with Crohn's have a higher surgical rate than patients with ulcerative colitis [39]. However, Ananthakrishnan *et al* found that patients with CDI-ulcerative colitis have a significantly higher surgical rate compared to CDI-Crohn's patients [18]. This could be because patients with

ulcerative colitis may experience more severe disease from *C. difficile* than those with Crohn's disease. Interestingly, this study also found that patients with CDI-IBD have significantly lower surgical rates compared to IBD patients alone [18]. One explanation is related to the limitation of using administrative datasets. For IBD patients admitted with CDI, surgical treatment may not occur during the index hospitalization, but occur during the subsequent hospitalization when the history of CDI may not be recorded in the datasets. This may falsely reduce the rates of surgery attributable to CDI. Another possibility is associated with clinical practice. If IBD patients, particularly Crohn's patients, found to be *C. difficile* positive before surgical therapy, the planned surgery that was unrelated to the infection would likely be deferred after the treatment of CDI. This may lead to a spurious inverse association in the study.

There were variable rates of colectomy reported among IBD complicated by CDI [30, 32]. The inconsistent data could emanate from systematic errors and other factors, such as the interests and experience of primary clinicians as well as different thresholds for colectomy, which have not been captured in our quality assessment. Studies conducted in specialist centers may have a higher index of suspicion for diagnosis of CDI in IBD patients due to the increasing attention, and lead to higher rates of testing for *C. difficile* [20]. These studies may be more likely to report significant adverse effect than studies using data associated with the practice of less specialist clinicians sampled from the Nationwide Inpatient Sample, although

sensitivity analysis excluding studies conducted in specialist centers confirmed CDI as a significant risk factor of colectomy. Despite that none of the studies reported the specific *C. difficile* ribotypes, the higher surgical rates observed in certain areas could be explained by the hyper-virulent strain that cause severe infection. In addition, surgical therapy is recommended for complicated CDI with failure to improve on medical treatment after 5 days [34]. Kaneko *et al* and Stange *et al* found a lower risk of gastrointestinal surgery among IBD patients with concomitant CDI due to the immediate treatment with antibiotics of infected patients [31, 40]. Therefore, higher surgical rates during the disease course of IBD may be confounded by treatment for CDI.

Results from sensitivity analyses using the RE model and IVhet model were consistent with the results from the QE model. Incorporation of univariate quality scores have long been a sticking point in the literature. Juni *et al* [41] suggested that the use of summary scores to identify trials of high quality is problematic and provide unreliable estimates of effect. However, Juni's analysis was limited by stratification of studies using quality and any difference in estimate would be dependent on the distribution of precision and effect sizes within quality strata, not on quality. Similarly, Greenland *et al* also suggested that univariate quality scores can be misleading but this was in the context of quantitative bias modeling [42]. The quality effects model does not model bias and in fact starts from the premise that the impact of the quality score on the direction and magnitude of a study effect is

unknown. What is assessed is the relative possibility of bias (relative to the best study in the list) and a synthetic bias variance is modeled using an intra-class correlation coefficient [43, 44]. Given this approach, subjectivity of quality scoring becomes irrelevant since any score that has some information value will improve the reliability of estimation. The only condition under which the QE model can be made to deteriorate in performance is when quality is deliberately inverted (the best study listed the worst) [43, 45].

There are several limitations in this meta-analysis. Firstly, although we performed a comprehensive systematic search for studies, publication bias could have resulted in positive associations between colectomy and CDI. The actual risks attributable to the infection could be less than what we found in the meta-analysis. Notwithstanding, heterogeneity across studies could also lead to effect size asymmetry, and this represents an alternative explanation to selective publication of positive results. Secondly, all selected studies were conducted in Northern Hemisphere countries, and the majority were from the US, including two of the larger studies using administrative databases. Sonnenberg *et al* reported geographic variations of CDI prevalence and mortality among IBD patients [46]. The epidemic patterns of CDI in IBD may differ between areas and countries, and therefore the generalizability of this study is limited. In addition, two studies used ICD diagnostic coding to identify cases, although the accuracy of ICD-10 coding for CDI has been assessed with 99.4% specificity and 82.1% sensitivity among ulcerative colitis

patients [28]. It may underestimate the prevalence of CDI among IBD patients as a result of miscoding and missed diagnoses. Finally, all studies reviewed were observational studies and the time order of exposure and outcome is not clear in most studies. Therefore, the results should be interpreted with caution.

In summary, this meta-analysis confirms that CDI is a significant risk factor for colectomy in IBD patients, particularly those with ulcerative colitis. Generalization to Crohn's disease is limited due to the nature of the data collected to date, and further research is needed to investigate the attributable risks of surgery due to CDI among patients with Crohn's disease.

References

1. Podolsky DK. Inflammatory bowel disease. N Engl J Med. 2002;347(6):417-29.

2. Carter MJ, Lobo AJ, Travis SP. Guidelines for the management of inflammatory bowel disease in adults. Gut. 2004;53 Suppl 5:V1-16.

3. de Groof EJ, Buskens CJ, Bemelman WA. Single-Port Surgery in Inflammatory Bowel Disease: A Review of Current Evidence. World J Surg. 2016. doi: 10.1007/s00268-016-3509-y.

4. Rungoe C, Langholz E, Andersson M, Basit S, Nielsen NM, Wohlfahrt J, et al. Changes in medical treatment and surgery rates in inflammatory bowel disease: a nationwide cohort study 1979-2011. Gut. 2014;63(10):1607-16.

5. Ramadas AV, Gunesh S, Thomas GA, Williams GT, Hawthorne AB. Natural history of Crohn's disease in a population-based cohort from Cardiff (1986-2003): a study of changes in medical treatment and surgical resection rates. Gut. 2010;59(9):1200-6.

6. Sandborn WJ, Rutgeerts P, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Colectomy rate comparison after treatment of ulcerative colitis with placebo or infliximab. Gastroenterol. 2009;137(4):1250-60; quiz 520.

7. Ricciardi R, Ogilvie JW, Jr., Roberts PL, Marcello PW, Concannon TW, Baxter NN. Epidemiology of Clostridium difficile colitis in hospitalized patients with inflammatory bowel diseases. Dis Colon Rectum. 2009;52(1):40-5.

8. Frolkis A, Kaplan GG, Patel AB, Faris P, Quan H, Jette N, et al. Postoperative complications and emergent readmission in children and adults with inflammatory

bowel disease who undergo intestinal resection: a population-based study. Inflamm Bowel Dis. 2014;20(8):1316-23.

9. Cosnes J, Gower–Rousseau C, Seksik P, Cortot A. Epidemiology and Natural History of Inflammatory Bowel Diseases. Gastroenterol. 2011;140(6):1785-94.e4.

10. Bolton RP, Sherriff RJ, Read AE. Clostridium difficile associated diarrhoea: a role in inflammatory bowel disease? Lancet. 1980;1(8165):383-4.

11. Trnka YM, LaMont JT. Association of Clostridium difficile toxin with symptomatic relapse of chronic inflammatory bowel disease. Gastroenterol. 1981;80(4):693-6.

12. Issa M, Vijayapal A, Graham MB, Beaulieu DB, Otterson MF, Lundeen S, et al. Impact of Clostridium difficile on Inflammatory Bowel Disease. Clin Gastroenterol Hepatol. 2007;5(3):345-51.

13. Rodemann JF, Dubberke ER, Reske KA, Seo DH, Stone CD. Incidence of Clostridium difficile infection in inflammatory bowel disease. Clin Gastroenterol Hepatol. 2007;5(3):339-44.

14. Razik R, Rumman A, Bahreini Z, McGeer A, Nguyen GC. Recurrence of Clostridium difficile Infection in Patients with Inflammatory Bowel Disease: The RECIDIVISM Study. Am J Gastroenterol. 2016. doi: 10.1038/ajg.2016.187.

15. Kelsen JR, Kim J, Latta D, Smathers S, McGowan KL, Zaoutis T, et al. Recurrence rate of clostridium difficile infection in hospitalized pediatric patients with inflammatory bowel disease. Inflamm Bowel Dis. 2011;17(1):50-5.

16. Rodemann JF, Dubberke ER, Reske KA, Seo da H, Stone CD. Incidence of Clostridium difficile infection in inflammatory bowel disease. Clin Gastroenterol Hepatol. 2007;5(3):339-44.

17. Jen MH, Saxena S, Bottle A, Aylin P, Pollok RC. Increased health burden associated with Clostridium difficile diarrhoea in patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2011;33(12):1322-31.

18. Ananthakrishnan AN, McGinley EL, Binion DG. Excess hospitalisation burden associated with Clostridium difficile in patients with inflammatory bowel disease. Gut. 2008;57(2):205-10.

19. Peng JC, Shen J, Zhu Q, Ran ZH. The impact of Clostridum difficile on surgical rate among ulcerative colitis patients: A systemic review and meta-analysis. Saudi J Gastroenterol. 2015;21(4):208-12.

20. Goodhand JR, Alazawi W, Rampton DS. Systematic review: Clostridium difficile and inflammatory bowel disease. Aliment Pharmacol Ther. 2011;33(4):428-41.

21. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of internal medicine. 2009;151(4):264-9.

22. Doi SAR, Thalib L. A Quality-Effects Model for Meta-Analysis. Epidemiology. 2008;19(1):94-100.

23. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177-88.

24. Doi SA, Barendregt JJ, Khan S, Thalib L, Williams GM. Advances in the meta-analysis of heterogeneous clinical trials I: The inverse variance heterogeneity model. Contemp Clin Trials. 2015. doi: 10.1016/j.cct.2015.05.009.

25. Kariv R, Navaneethan U, Venkatesh PG, Lopez R, Shen B. Impact of Clostridium difficile infection in patients with ulcerative colitis. J Crohns Colitis. 2011;5(1):34-40.

26. Navaneethan U, Mukewar S, Venkatesh PG, Lopez R, Shen B. Clostridium difficile infection is associated with worse long term outcome in patients with ulcerative colitis. J Crohns Colitis. 2012;6(3):330-6.

27. Negron ME, Barkema HW, Rioux K, De Buck J, Checkley S, Proulx MC, et al. Clostridium difficile infection worsens the prognosis of ulcerative colitis. Can J Gastroenterol Hepatol. 2014;28(7):373-80.

28. Negron ME, Rezaie A, Barkema HW, Rioux K, De Buck J, Checkley S, et al. Ulcerative Colitis Patients With Clostridium difficile are at Increased Risk of Death, Colectomy, and Postoperative Complications: A Population-Based Inception Cohort Study. Am J Gastroenterol. 2016. doi: 10.1038/ajg.2016.106.

29. Ananthakrishnan AN, McGinley EL, Saeian K, Binion DG. Temporal trends in disease outcomes related to Clostridium difficile infection in patients with inflammatory bowel disease. Inflamm Bowel Dis. 2011;17(4):976-83.

30. Nguyen GC, Kaplan GG, Harris ML, Brant SR. A national survey of the prevalence and impact of Clostridium difficile infection among hospitalized inflammatory bowel disease patients. Am J Gastroenterol. 2008;103(6):1443-50.

31. Kaneko T, Matsuda R, Taguri M, Inamori M, Ogura A, Miyajima E, et al. Clostridium difficile infection in patients with ulcerative colitis: investigations of risk factors and efficacy of antibiotics for steroid refractory patients. Clin Res Hepatol Gastroenterol. 2011;35(4):315-20.

32. Jodorkovsky D, Young Y, Abreu MT. Clinical outcomes of patients with ulcerative colitis and co-existing Clostridium difficile infection. Dig Dis Sci. 2010;55(2):415-20.

33. Murthy SK, Steinhart AH, Tinmouth J, Austin PC, Daneman N, Nguyen GC. Impact of Clostridium difficile colitis on 5-year health outcomes in patients with ulcerative colitis. Aliment Pharmacol Ther. 2012;36(11-12):1032-9.

34. Surawicz CM, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, et al. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. Am J Gastroenterol. 2013;108(4):478-98; quiz 99.

35. Buffie CG, Pamer EG. Microbiota-mediated colonization resistance against intestinal pathogens. Nat Rev Immunol. 2013;13(11):790-801. doi: 10.1038/nri3535.

36. Issa M, Vijayapal A, Graham MB, Beaulieu DB, Otterson MF, Lundeen S, et al. Impact of Clostridium difficile on inflammatory bowel disease. Clin Gastroenterol Hepatol. 2007;5(3):345-51.

37. Ananthakrishnan AN, McGinley EL. Infection-related hospitalizations are associated with increased mortality in patients with inflammatory bowel diseases. J Crohns Colitis. 2013;7(2):107-12.

38. Hourigan SK, Oliva-Hemker M, Hutfless S. The prevalence of Clostridium difficile infection in pediatric and adult patients with inflammatory bowel disease. Dig Dis Sci. 2014;59(9):2222-7.

39. Meregaglia M, Banks H, Fattore G. Hospital Burden and Gastrointestinal Surgery in Inflammatory Bowel Disease Patients in Italy: A Retrospective Observational Study. J Crohns Colitis. 2015;9(10):853-62.

40. Stange E, Travis S, Vermeire S, Reinisch W, Geboes K, Barakauskiene A, et al. European evidence-based consensus on the diagnosis and management of ulcerative colitis: definitions and diagnosis. J Crohns Colitis. 2008;2(1):1-23.

41. Juni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. Jama. 1999;282(11):1054-60.

42. Greenland S, O'Rourke K. On the bias produced by quality scores in meta-analysis, and a hierarchical view of proposed solutions. Biostatistics. 2001;2(4):463-71.

43. Doi SA, Barendregt JJ, Williams GM, Khan S, Thalib L. Simulation Comparison of the Quality Effects and Random Effects Methods of Meta-analysis. Epidemiol. 2015;26(4):e42-4.

44. Doi SAR, Thalib L. An Alternative Quality Adjustor for the Quality Effects Model For Meta-Analysis. Epidemiol. 2009;20(2):314.

45. Doi SA, Barendregt JJ, Khan S, Thalib L, Williams GM. Advances in the meta-analysis of heterogeneous clinical trials II: The quality effects model. Contemp Clin Trials. 2015;45(Pt A):123-9.

46. Sonnenberg A. Similar geographic variations of mortality and hospitalization associated with IBD and Clostridium difficile colitis. Inflamm Bowel Dis. 2010;16(3):487-93

Chapter 12

Discussion and conclusion

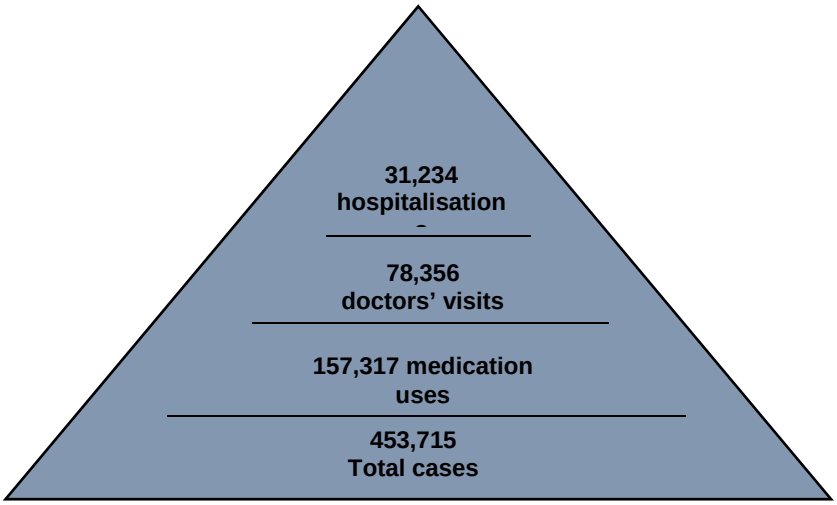
In this thesis, I have presented the results of eight studies describing the epidemiology of gastroenteritis in Australian adults, and highlighting a significant burden to the healthcare system from gastroenteritis-related hospitalisation in older people. In this chapter, I summarise key findings from these studies on the burden and risk factors for all-cause and cause-specific gastroenteritis in the elderly.

Summary of main findings

Gastroenteritis in the elderly

I estimated 453,715 episodes of gastroenteritis occurred among people aged ≥ 65 years old, resulting in about 78,356 doctor visits, and 157,317 courses of medication usage in Australia over a one year period in 2008–2009. From the population-based cohort study, I found approximately 1% of people aged ≥65 years old were hospitalised with gastroenteritis annually in Australia (Figure 12.1). Patients aged ≥65 years accounted for more than two thirds of gastroenteritis-related complications among gastroenteritis hospitalisations, and over 90% of gastroenteritis-related deaths within 30 days of hospital admission.

Figure 12.1. Estimates from this thesis of the annual numbers of episodes of acute gastroenteritis and the outcomes of these illnesses in older adults aged ≥65 years old, Australia.



The incidence of gastroenteritis hospitalisation increased with age: from 2.4 per 1,000 person-years in adults aged 45–54 years old to 9.5 per 1,000 in those aged ≥65 years. Incidence was also greater among those with poor self-rated health. Compared to adults aged 45–64 years old, people aged ≥65 years had a higher incidence of hospitalisation with *Salmonella* infection and *C. difficile* infection (CDI). Up to 80% of gastroenteritis hospitalisations were coded as unspecified gastroenteritis and colitis of infectious origin, and only 20% of hospitalisation had a pathogen identified. Table 12.1 summarises findings presented in this thesis that relate to incidence of all-cause and cause-specific gastroenteritis.

Table 12.1. Incidence of all-cause and cause-specific gastroenteritis presented as the number of episodes per 100,000 person-years from studies included in this thesis.

Characteristics	All-cause gastroenteritis hospitalisation	*Salmonella* infection		*Clostridium difficile* infection hospitalisation
		Notification	Hospitalisation	
Age group (years)				
45-54	2,400	28.0	6.0	6.6
55-64	3,700	28.5	7.4	8.7
65-74	6,100	25.4	8.6	19.9
75-84	12,600	42.3	16.7	41.2
≥85	21,800	36.6	26.4	69.4
Total	5,500	29.7	9.0	16.6

The high incidence of hospitalisation with all-cause and cause-specific gastroenteritis in the elderly is in line with increased hospitalisation rate for infectious diseases in this group [1, 2]. The trend of increasing hospitalisation rate with age is likely related to greater severity of illness in older patients [3] and the increasing risk of severe complications, such as dehydration, electrolyte imbalance and exacerbation of chronic conditions [4]. Cummings *et al* reported increased susceptibility of developing severe complications from *Salmonella* infection with aging [5]. Khanna *et al* also showed that compared to younger people, the elderly were at higher risk of experiencing severe CDI [6].

About one-third of participants with *Salmonella* infection went to hospital for their condition. This proportion increased with age, and was particularly high among those aged ≥85 years (72.7%). While the incidence of *Salmonella* infection was similar across age groups, infection-related hospitalisation increased significantly with old age.

I found that incidence of hospitalisation differed by *Salmonella* serotypes. Participants with *S.* Typhimurium infection were more likely to be hospitalised than people with infection due to other *Salmonella* serotypes, and this was consistent across all age groups. In participants aged ≥85 years, all cases with *S.* Typhimurium infection were hospitalised for their condition, while only half of the cases with infection due to other *Salmonella* serotypes were admitted to hospital.

Compared to hospitalisation with *Salmonella* infection, hospitalisation with incident CDI was more common among middle-aged and older adults, particularly among adults aged ≥65 years. I also observed a significant increase in the incidence of CDI hospitalisation over 2009–2012 in the 45 and Up Study cohort. Building upon this, I then further estimated the burden of all cases of CDI-related hospitalisation in the study cohort, and found that the average length of hospital stay was 17 days; the average cost was AUD 12,704 per hospitalisation; and 7.3% of CDI patients died in hospital. The elevated hospitalisation rates in older adults, combined with the longer duration of CDI-associated hospital stay and high hospital costs in the elderly indicate a substantial burden due to CDI in an aging population.

In the systematic review and meta-analysis of studies examining the effect of CDI on surgical outcomes of patients with inflammatory bowel disease (IBD), I found that CDI was significantly associated with colectomy among IBD patients, particularly among those with ulcerative colitis. Therefore, CDI needs to be

carefully assessed and managed in IBD patients to prevent worse clinical outcomes.

In the review of norovirus infection, I found that norovirus is a common cause of outbreaks in long-term care facilities, contributing 30–80% of acute gastroenteritis outbreaks in those settings [7-10]. While norovirus can cause both sporadic infections and outbreaks in all age groups, older people are at higher risk of hospitalisation and death. Current guidelines for prevention and control are generally based on infection control principles, although with the recent breakthroughs of human norovirus in-vitro culture [11], it is now possible to directly ascertain the efficacy of environmental disinfectants and hand hygiene options.

Risk factors related to gastroenteritis hospitalisation

The risk of hospitalisation with gastroenteritis differed by sex and region of residence. The association also differed by cause of infection, and I found that poor self-rated health and proton pump inhibitor use were significantly associated with gastroenteritis hospitalisation.

Compared to males, females were more likely to be hospitalised with all-cause gastroenteritis. This was previously reported in a US study using nationally representative data to investigate the trend of infectious disease hospitalisation across age groups [12]. Similarly, I found that females were at higher risk of CDI

hospitalisation. The reason for this is unclear, although could be related to different health-seeking behaviours changing risk of infection, or a difference in the true prevalence of infection between the sexes. Previous studies have reported a greater risk of CDI among females compared to males [29, 30].

Interestingly, while the risk of *Salmonella* infection was similar between both sexes, males were more likely to be hospitalised for infection. This may be associated with the higher incidence of invasive *Salmonella* infection among males, which leads to severe illness requiring hospitalisation [13].

Region of residence is another important factor related to gastroenteritis hospitalisation. While, participants living in major cities were more likely to be hospitalised with all-cause gastroenteritis and *C. difficile* infection, participants from rural or remote areas showed an elevated risk of *Salmonella* infection and infection-related hospitalisation. This may be due to differences in healthcare services in those areas. The higher incidence of CDI hospitalisation observed in major cities may be associated with testing and reporting practice, higher population density, or high healthcare usage and antibiotic use in metro areas. On the other hand, environmental exposures related to rural living may contribute to higher risk of *Salmonella* infection in certain areas.

I identified some risk factors for hospitalisation with all-cause and cause-specific gastroenteritis, including poor self-rated health and use of proton pump inhibitors (PPIs). Self-rated health has previously been reported as an important predictor of severe health outcomes, such as mortality [14]. In this thesis,

participants with poor self-rated health have consistently been found to be at higher risk of gastroenteritis hospitalisation. This highlights the importance of general health in affecting hospitalisation with gastrointestinal infection in older adults. Consequently, poor self-rated health may serve as a useful marker for people at higher risk of hospitalisation who present to doctors with diarrhoea or other gastrointestinal symptoms.

PPI use was another significant risk factor for gastroenteritis. Prior to this thesis, PPI use had been found to be associated with bacterial gastroenteritis and enteric infections [15-17], although the effect of different dose and type of PPIs remained unknown. In this thesis, I confirmed the association between PPI use and gastroenteritis in the Australian setting. Importantly, I observed a dose-response relationship. The reason for the detected association is not known definitively, although colonisation and proliferation of pathogens secondary to acid suppressive treatment is one potential explanation. Notably, use of a H_2-receptor antagonist—another type of acid suppressant—was not associated with gastroenteritis, indicating specificity in the association.

Potential future research

In this thesis, I have identified several key areas that would be important to address in any future research into gastroenteritis in the elderly, which I have listed below:

1. **Sex difference of enteric infections, particularly for CDI**: Contradictory data has been reported between sex-specific

difference and CDI, although the overwhelming majority suggested a greater risk of community-acquired infection among females. Given the increasing in incidence of community-acquired CDI, studies investigating the mechanisms underlying higher risk of CDI in females are important to better understand the epidemiology of CDI.

2. **CDI in patients with Crohn's disease**: Previous data have suggested that Crohn's patients had a higher surgical rate than patients with ulcerative colitis, although the effect of CDI among Crohn's patients has not been well examined. Studies are needed to investigate the attributable risks of surgery due to CDI among patients with Crohn's disease. In addition, management of CDI in IBD encounters diagnostic and therapeutic challenges because of the similar clinical presentations of CDI and IBD flare. A better understanding of the complex relationship between gut microbiota, CDI, and IBD is needed to guide clinical management.
3. **Genome-sequencing for *Salmonella* in Australia:** Consistent with previous studies, I found that chicken/poultry consumption was a significant risk factor for *Salmonella* infection, although due to the nature of the study design and data, I was not able to confirm the source of infection. Further studies of source attribution using whole genome-sequencing are needed to investigate sources of *Salmonella* and other bacterial pathogens in Australia.

4. **Living circumstances transition and risk of gastroenteritis**: In this thesis, exposure variables were collected at recruitment. Data on participants moving from community to a nursing home or residential care during the study period were unknown. Therefore, I did not intend to examine the effect of living circumstances transition and risk of gastroenteritis in the elderly. However, understanding this association is essential to provide targeted intervention to prevent gastroenteritis in vulnerable population.

Conclusions

This thesis demonstrates a significant burden of gastroenteritis in older Australians. Incidence of hospitalisation with all-cause and cause-specific gastroenteritis increases significantly with age. Future efforts should focus on defining and improving preventive measures for gastroenteritis hospitalisation among the elderly. The risk of hospitalisation varies by sex and region of residence, which reflects differences in exposure. PPI use is significantly associated with gastroenteritis hospitalisation. Given the widespread of PPI use, particularly among the elderly, clinicians should be aware of this potential association when considering PPI therapy. In addition, early recognition and supportive treatment of diarrhoea in older patients with poorer self-rated health or chronic bowel problems may prevent subsequent hospitalisation and improve their health outcomes.

The findings presented in this thesis will improve the understanding of gastroenteritis in middle-aged and older Australians. They provide clarity to some of the long-standing assumptions and quantify certain risk factors associated with hospitalisation related to gastroenteritis among older adults, thereby addressing the original aims of the thesis. To the best of my knowledge, the work in this thesis is the first time that a large prospective cohort study with data linkage to multiple administrative databases has been used to describe the epidemiology of gastroenteritis in older adults. Future prospective studies with more detailed information on diet, travel and living circumstances transition are important to better quantify risk factors of gastroenteritis among vulnerable population.

References

1. Yorita Christensen KL, Holman RC, Steiner CA, Sejvar JJ, Stoll BJ, Schonberger LB. Infections Disease Hospitalizations in the United States. Clin Infect Dise. 2009;49(7):1025-35.

2. Dey A, Wang H, Menzies R, Macartney K. Changes in hospitalisations for acute gastroenteritis in Australia after the national rotavirus vaccination program. Med J Aust. 2012;197(8):453.

3. Fleury MD, Stratton J, Tinga C, Charron DF, Aramini J. A descriptive analysis of hospitalization due to acute gastrointestinal illness in Canada, 1995-2004. Can J Public Health. 2008;99(6):489-93.

4. Yoshikawa T, Norman D. Infectious disease in the aging: a clinical handbook. New York, NY: Springer Science & Business Media; 2009.

5. Cummings PL, Sorvillo F, Kuo T. The Burden of Salmonellosis in the United States: INTECH Open Access Publisher; 2012.

6. Khanna S, Pardi DS, Aronson SL, Kammer PP, Orenstein R, St Sauver JL, et al. The epidemiology of community-acquired Clostridium difficile infection: a population-based study. Am J Gastroenterol. 2012;107(1):89-95.

7. Hall AJ, Wikswo ME, Manikonda K, Roberts VA, Yoder JS, Gould LH. Acute gastroenteritis surveillance through the National Outbreak Reporting System, United States. Emerg Infect Dis. 2013;19(8):1305-9.

8. Rosenthal NA, Lee LE, Vermeulen BA, Hedberg K, Keene WE, Widdowson MA, et al. Epidemiological and genetic characteristics of norovirus outbreaks in long-term care facilities, 2003-2006. Epidemiol Infect. 2011;139(2):286-94.

9. Kirk MD, Fullerton KE, Hall GV, Gregory J, Stafford R, Veitch MG, et al. Surveillance for outbreaks of gastroenteritis in long-term care facilities, Australia, 2002-2008. Clin Infect Dis. 2010;51(8):907-14.

10. Lindsay L, Wolter J, De Coster I, Van Damme P, Verstraeten T. A decade of norovirus disease risk among older adults in upper-middle and high income countries: a systematic review. BMC Infect Dis. 2015;15:425.

11. Jones MK, Grau KR, Costantini V, Kolawole AO, de Graaf M, Freiden P, et al. Human norovirus culture in B cells. Nat Protoc. 2015;10(12):1939-47.

12. Christensen KLY, Holman RC, Steiner CA, Sejvar JJ, Stoll BJ, Schonberger LB. Infectious disease hospitalizations in the United States. Clin Infect Dis. 2009;49(7):1025-35.

13. Vugia DJ, Samuel M, Farley MM, Marcus R, Shiferaw B, Shallow S, et al. Invasive Salmonella infections in the United States, FoodNet, 1996–1999: incidence, serotype distribution, and outcome. Clin Infect Dis. 2004;38(Supplement 3):S149-S56.

14. DeSalvo KB, Bloser N, Reynolds K, He J, Muntner P. Mortality Prediction with a Single General Self-Rated Health Question. J Gen Intern Med. 2006;21(3):267-75.

15. Kwok CS, Arthur AK, Anibueze CI, Singh S, Cavallazzi R, Loke YK. Risk of Clostridium difficile infection with acid suppressing drugs and antibiotics: meta-analysis. Am J Gastroenterol. 2012;107(7):1011-9.

16. Garcia Rodriguez LA, Ruigomez A, Panes J. Use of acid-suppressing drugs and the risk of bacterial gastroenteritis. Clin Gastroenterol Hepatol. 2007;5(12):1418-23.

17. Hassing RJ, Verbon A, de Visser H, Hofman A, Stricker BH. Proton pump inhibitors and gastroenteritis. Eur J Epidemiol. 2016. doi: 10.1007/s10654-016-0136-8.

Appendix 1

The 45 and Up Study questionnaire

SAX 45 and Up Study Female Scanning.qxd:Layout 1 20/6/08 2:26 PM Page 3

THE 45 AND UP STUDY

Research to improve health and wellbeing

45 and Up Study Questionnaire for Women

The *45 and Up Study* relies on the willingness of people in New South Wales to share information about their lives and experiences, to provide knowledge that will help people live healthy and fulfilling lives for as long as possible. Participation is completely voluntary, and you are free to withdraw from the Study at any time. To take part, please read the participant information leaflet, then complete the questionnaire and consent form and return them in the envelope provided. We very much hope you will be able to take part.

Any questions or comments? Please call the Study helpline: **1300 45 11 45** or go to **www.45andUp.org.au**

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RESEARCH PARTNERSHIPS FOR BETTER HEALTH

In collaboration with

The Cancer Council New South Wales

Heart Foundation

NSW HEALTH

beyondblue the national depression initiative

New South Wales Government

DADHC Department of Ageing, Disability & Home Care

SAMPLE ONLY

Your answers and experiences are important to us.

To help us read your answers, please write as clearly as possible using a **BLACK** or **BLUE** pen, and be sure to complete the questionnaire as shown:

Please put a cross in the appropriate box(es) ☒ Yes ☐ No

OR put numbers in the appropriate box, e.g. *21st June 1945*

2 1 / 0 6 / 1 9 4 5 age 6 2

General questions about you

1. **What is your date of birth?** day / month / year 1 9
2. **What is today's date?** day / month / year 2 0
3. **How tall are you without shoes?** (please give to the nearest cm or inch) ☐☐☐ cm **OR** ☐ feet ☐☐ inches
4. **About how much do you weigh?** ☐☐☐ kg **OR** ☐☐ stone ☐☐ lbs
5. **What is the highest qualification you have completed?** (please put a cross in the most appropriate box)
   - ☐ no school certificate or other qualifications
   - ☐ school or intermediate certificate (or equivalent)
   - ☐ higher school or leaving certificate (or equivalent)
   - ☐ trade/apprenticeship (e.g. hairdresser, chef)
   - ☐ certificate/diploma (e.g. child care, technician)
   - ☐ university degree or higher
6. **Are you of Aboriginal or Torres Strait Islander origin?** (you can cross more than one box)
   - ☐ No ☐ Yes, Aboriginal ☐ Yes, Torres Strait Islander
7. **In which country were you born?**
   - ☐ Australia ▶ please go to question 9
   - ☐ UK ☐ Ireland ☐ Italy ☐ China
   - ☐ Greece ☐ New Zealand ☐ Germany ☐ Lebanon
   - ☐ Philippines ☐ Netherlands ☐ Vietnam ☐ Malta
   - ☐ Poland ☐ other *(please specify)* _____
8. **What year did you first come to live in Australia for one year or more?** (e.g. 1970) ☐☐☐☐
9. **What is your ancestry?** (please cross up to 2 boxes)
   - ☐ Australian ☐ English ☐ Irish ☐ Chinese
   - ☐ Italian ☐ Greek ☐ Scottish ☐ German
   - ☐ Lebanese ☐ Dutch ☐ Maltese ☐ Polish
   - ☐ Filipino ☐ Indian ☐ Croatian ☐ Vietnamese
   - ☐ other *(please specify)* _____
10. **Do you speak a language other than English at home?**
    - ☐ Yes ☐ No
11. **Have you ever been a regular smoker?**
    - ☐ Yes ▼ ☐ No ▶ *If No – please go to question 12*

    How old were you when you started smoking regularly? ☐☐ years old

    Are you a regular smoker now? ☐ Yes ☐ No

    If No **– how old were you when you stopped smoking regularly?** ☐☐ years old

    About how much do you/did you smoke on average each day?
    (If you are an ex-smoker, how much did you smoke on average when you smoked?)

    ☐☐ cigarettes per day ☐☐ pipes and cigars per day
12. **About how many alcoholic drinks do you have each week?**
    one drink = a glass of wine, middy of beer or nip of spirits
    (put "0" if you do not drink, or have less than one drink each week)

    ☐☐ number of alcoholic drinks each week
13. **On how many days each week do you usually drink alcohol?** ☐ days each week

14. What best describes your current situation? (please cross one box)

☐ single ☐ married ☐ de facto/living with a partner
☐ widowed ☐ divorced ☐ separated

15. What best describes your current housing? (please cross one box)

☐ house ☐ flat, unit, apartment ☐ house on farm
☐ hostel for the aged ☐ mobile home ☐ other
☐ nursing home ☐ retirement village, self care unit

16. How many TIMES did you do each of these activities LAST WEEK?
(put "0" if you did not do this activity)

	times in the last week
Walking continuously, for at least 10 minutes *(for recreation or exercise or to get to or from places)*	☐☐
Vigorous physical activity *(that made you breathe harder or puff and pant, like jogging, cycling, aerobics, competitive tennis, but not household chores or gardening)*	☐☐
Moderate physical activity *(like gentle swimming, social tennis, vigorous gardening or work around the house)*	☐☐

17. If you add up all the time you spent doing each activity LAST WEEK, how much time did you spend ALTOGETHER doing each type of activity?
(put "0" if you did not do this activity)

	hours	minutes
Walking continuously, for at least 10 minutes *(for recreation or exercise or to get to or from places)*	☐☐ :	☐☐
Vigorous physical activity *(that made you breathe harder or puff and pant, like jogging, cycling, aerobics, competitive tennis, but not household chores or gardening)*	☐☐ :	☐☐
Moderate physical activity *(like gentle swimming, social tennis, vigorous gardening or work around the house)*	☐☐ :	☐☐

Questions about your family

18. Have your mother, father, brother(s) or sister(s) ever had:
(blood relatives only: please put a cross in the appropriate box(es))

	mother	father	brother/ sister		mother	father	brother/ sister
heart disease	☐	☐	☐	breast cancer	☐	☐	☐
high blood pressure	☐	☐	☐	bowel cancer	☐	☐	☐
stroke	☐	☐	☐	lung cancer	☐	☐	☐
diabetes	☐	☐	☐	melanoma	☐	☐	☐
dementia/Alzheimer's	☐	☐	☐	prostate cancer		☐	☐
Parkinson's disease	☐	☐	☐	ovarian cancer	☐		☐
severe depression	☐	☐	☐	osteoporosis	☐	☐	☐
severe arthritis	☐	☐	☐	hip fracture	☐	☐	☐
do not know	☐	☐	☐				

19. How many children have you given birth to?
(please include stillbirths but do not include miscarriages, please write "0" if you have not had any children)

☐☐ children

How old were you when you gave birth to your FIRST child? ☐☐ years old

How old were you when you gave birth to your LAST child? ☐☐ years old

For how many months, in total, have you breastfed?
(please add together all the time you spent breastfeeding all of your children; put "0" if you never breastfed)
☐☐ months

Questions about your health

20. About how many hours a week are you exposed to someone else's tobacco smoke?

hours per week ☐☐ at home
hours per week ☐☐ in other places *(e.g. work, going out, cars)*

21. Have you ever used the pill or other hormonal contraceptives?
(e.g. the combined pill, mini pill, contraceptive implant or injections)

☐ Yes ▼ ☐ No

If Yes, for how long altogether have you used hormonal contraceptives? ☐☐ years
(please write '0' if you used them for less than a year in total)

If Yes, how old were you when you LAST used hormonal contraceptives? ☐☐ age
(please write your current age if you are still using them)

Which type of pill or other hormonal contraceptive did you use MOST RECENTLY?

☐ "the pill", combined pill *(e.g. Microgynon, Levlen)*
☐ progesterone-only pill ("mini pill") *(e.g. Micronor, Noriday, Microval)*
☐ Depo Provera
☐ contraceptive implant *(e.g. Implanon, Norplant)*
☐ do not know

22. Have you ever used hormone replacement therapy (HRT)?

☐ Yes ▼ ☐ No

If Yes, for how long altogether have you used HRT? ☐☐ years
(please write '0' if you used HRT for less than a year in total)

Are you currently taking HRT? ☐ Yes ☐ No

If No, at what age did you stop? ☐☐ age

23. Have you taken any medications, vitamins or supplements for most of the last 4 weeks, including HRT and the pill?

☐ Yes ▼ ☐ No

If Yes, was it:		
☐ multivitamins + minerals	☐ multivitamins alone	☐ fish oil
☐ glucosamine	☐ omega 3	☐ paracetamol
☐ aspirin for the heart	☐ aspirin for other reasons	☐ Lipitor
☐ Avapro, Karvea	☐ warfarin, Coumadin	☐ Pravachol
☐ Coversyl, Coversyl Plus	☐ Lasix, frusemide	☐ Zocor, Lipex
☐ Cardizem, Vasocordol	☐ Micardis	☐ Nexium
☐ Norvasc	☐ Fosamax	☐ Somac
☐ Tritace	☐ Caltrate	☐ Losec, Acimax *omeprazole*
☐ Noten, Tenormin *atenolol*	☐ Oroxine *thyroxine*	☐ Ventolin *salbutamol*
☐ Zyloprim, Progout 300 *allopurinol*	☐ Diabex, Diaformin *metformin*	☐ Zoloft *sertraline*
☐ Cipramil *citaloprim*	☐ Efexor *venlafaxine*	

please list any other regular medications or supplements here

SAMPLE ONLY

24. Has a doctor EVER told you that you have:
(If YES, please cross the box and give your age when the condition was first found)

	Yes	Age when condition was first found
skin cancer (not melanoma)	☐	☐☐ age
melanoma	☐	☐☐ age
breast cancer	☐	☐☐ age
other cancer	☐	☐☐ age
type of cancer *(please describe)*		
heart disease	☐	☐☐ age
type of heart disease *(please describe)*		
high blood pressure – when pregnant	☐	☐☐ age
high blood pressure – when not pregnant	☐	☐☐ age
stroke	☐	☐☐ age
diabetes	☐	☐☐ age
blood clot (thrombosis)	☐	☐☐ age
asthma	☐	☐☐ age
hayfever	☐	☐☐ age
depression	☐	☐☐ age
anxiety	☐	☐☐ age
Parkinson's disease	☐	☐☐ age
none of these	☐	

25. In the last month have you been treated for:
(If YES, please cross the box and give your age when the treatment started)

	Yes	Age started treatment
cancer	☐	☐☐ age
heart attack or angina	☐	☐☐ age
other heart disease	☐	☐☐ age
high blood pressure	☐	☐☐ age
high blood cholesterol	☐	☐☐ age
blood clotting problems	☐	☐☐ age
asthma	☐	☐☐ age
osteoarthritis	☐	☐☐ age
thyroid problems	☐	☐☐ age
osteoporosis or low bone density	☐	☐☐ age
depression	☐	☐☐ age
anxiety	☐	☐☐ age
none of these	☐	

26. Are you NOW suffering from any other important illness?
☐ Yes ▼ ☐ No

Please describe this illness and its treatment

27. Do you regularly need help with daily tasks because of long-term illness or disability?
(e.g. personal care, getting around, preparing meals)
☐ Yes ☐ No

28. Does your health now LIMIT YOU in any of the following activities?

	yes, limited a lot	**yes**, limited a little	**no**, not limited at all
VIGOROUS activities *(e.g. running, strenuous sports)*	☐	☐	☐
MODERATE activities *(e.g. pushing a vacuum cleaner, playing golf)*	☐	☐	☐
lifting or carrying shopping	☐	☐	☐
climbing several flights of stairs	☐	☐	☐
climbing one flight of stairs	☐	☐	☐
walking one kilometre	☐	☐	☐
walking half a kilometre	☐	☐	☐
walking 100 metres	☐	☐	☐
bending, kneeling or stooping	☐	☐	☐
bathing or dressing yourself	☐	☐	☐

29. Have you ever had any of the following operations?
(If YES, please cross the box and give your age when you had the operation; give your age at the **most recent operation** if you have had more than one)

	Yes	Age when had operation
removal of skin cancer	☐	☐☐ age
hysterectomy	☐	☐☐ age
both ovaries removed	☐	☐☐ age
sterilisation (tubes tied)	☐	☐☐ age
repair of prolapsed womb, bladder or bowel	☐	☐☐ age
knee replacement	☐	☐☐ age
hip replacement	☐	☐☐ age
gallbladder removed	☐	☐☐ age
heart or coronary bypass surgery *(include stents and balloons)*	☐	☐☐ age

other *(please describe any other operations you have had in the last 10 years, with your age when you had them)*

SAMPLE ONLY

30. Do you regularly care for a sick or disabled family member or friend?

☐ Yes ▼ ☐ No

If Yes, about how much time each week do you usually spend caring for this person?

☐ full time OR ☐☐ hours/wk

31. In general, how would you rate your:

	excellent	very good	good	fair	poor
overall health?	☐	☐	☐	☐	☐
quality of life?	☐	☐	☐	☐	☐
eyesight? *(with glasses or contact lenses, if you wear them)*	☐	☐	☐	☐	☐
memory?	☐	☐	☐	☐	☐
teeth and gums?	☐	☐	☐	☐	☐

32. Do you feel you have a hearing loss? ☐ Yes ☐ No

33. How many of your own teeth do you have left?

☐ None – all of my teeth are missing ☐ 1-9 teeth left
☐ 10-19 teeth left ☐ 20 or more teeth left

34. During the past 12 months, how many times have you fallen to the floor or ground? (put "0" if you haven't fallen in this time)

☐☐ times

35. Have you had a broken/fractured bone in the last 5 years?

☐ Yes ▼ ☐ No

If Yes, which bones were broken?

☐ wrist ☐ arm ☐ hip ☐ ankle
☐ rib ☐ finger/toe ☐ other _____

How old were you when it happened? (give age at most recent fracture if more than one) ☐☐ years old

36. About how many times a week are you usually troubled by leaking urine?

☐ never ☐ once a week or less
☐ 2-3 times ☐ 4-6 times ☐ every day

37. Have you been through menopause?

☐ No
☐ Not sure *(because hysterectomy, taking HRT, etc.)*
☐ My periods have become irregular
☐ Yes – How old were you when you went through menopause? ☐☐ years old

38. Have you ever been for a breast screening mammogram?

☐ Yes ▼ ☐ No

If Yes, what year did you have your last mammogram? (e.g. 2005) ☐☐☐☐

How many times have you been for breast screening altogether? ☐☐ times

39. Have you ever been screened for colorectal (bowel) cancer?

☐ Yes ▼ ☐ No

If Yes, please indicate which test(s) you had:

☐ faecal occult blood test *(test for blood in the stool/faeces)*
☐ sigmoidoscopy *(a tube is used to examine the lower bowel: this is usually done in a doctor's office without pain relief)*
☐ colonoscopy *(a long tube is used to examine the whole large bowel; you would usually have to have an enema or drink large amounts of special liquid to prepare the bowel for this)*

What year did you have the most recent one of these tests? (e.g. 2005) ☐☐☐☐

Questions about your diet

40. About how many times each week do you eat: (please count all meals and snacks. put '0' if never eaten or eaten less than once a week)

	number of times eaten each week
beef, lamb or pork	☐☐
chicken, turkey or duck	☐☐
processed meat *(include bacon, sausages, salami, devon, burgers, etc)*	☐☐
fish or seafood	☐☐
cheese	☐☐

41. About how many of the following do you usually eat:

slices or pieces of brown/wholemeal bread each week *(also include multigrain, rye bread, etc.)* ☐☐

bowls of breakfast cereal each week ☐☐

If you eat breakfast cereal is it usually: (please cross)

☐ bran cereal *(allbran, branflakes, etc.)* ☐ muesli
☐ biscuit cereal *(weetbix, shredded wheat, etc.)* ☐ other *(cornflakes, rice bubbles,etc.)*
☐ oat cereal *(porridge, etc.)*

42. Which type of milk do you mostly have?

☐ whole milk ☐ reduced fat milk ☐ skim milk
☐ soy milk ☐ other milk ☐ I don't drink milk

43. About how many serves of vegetables do you usually eat each day? A serve is half a cup of cooked vegetables or one cup of salad (please include potatoes and put "0" if less than one a day)

☐☐ number of serves of cooked vegetables each day
☐☐ number of serves of raw vegetables each day (e.g. salad)
☐ I don't eat vegetables

44. About how many serves of fruit or glasses of fruit juice do you usually have each day? A serve is 1 medium piece or 2 small pieces or 1 cup of diced or canned fruit pieces (put "0" if you eat less than one serve a day)

☐☐ number of serves of fruit each day
☐☐ number of glasses of fruit juice each day
☐ I don't eat fruit

45. Please put a cross in the box if you NEVER eat:

☐ red meat ☐ chicken/poultry ☐ pork/ham ☐ dairy products
☐ any meat ☐ eggs ☐ sugar ☐ wheat products
☐ fish ☐ seafood ☐ cream ☐ cheese

Questions about time and work

46. What is your usual yearly HOUSEHOLD income before tax, from all sources? (please include benefits, pensions, superannuation, etc)

☐ less than $5,000 per year ☐ $30,000-$39,999 per year
☐ $5,000-$9,999 per year ☐ $40,000-$49,999 per year
☐ $10,000-$19,999 per year ☐ $50,000-$69,999 per year
☐ $20,000-$29,999 per year ☐ $70,000 or more per year
☐ I would rather not answer this question

SAMPLE ONLY

47. What is your current work status? (you can cross more than one box)

- ☐ in full time paid work
- ☐ in part time paid work
- ☐ completely retired/pensioner
- ☐ partially retired
- ☐ disabled/sick
- ☐ other
- ☐ self-employed
- ☐ doing unpaid work
- ☐ studying
- ☐ looking after home/family
- ☐ unemployed

48. If you are partially or completely retired, how old were you when you retired? ☐☐ years old

Why did you retire? (you can cross more than one box)

- ☐ reached usual retirement age
- ☐ to care for family member/friend
- ☐ made redundant
- ☐ other
- ☐ lifestyle reasons
- ☐ ill health
- ☐ could not find a job

49. About how many HOURS each WEEK do you usually spend doing the following? (please put "0" if you do not spend any time doing it)

hours per week ☐☐ paid work

hours per week ☐☐ voluntary/unpaid work

50. Which of the following do you have? (excluding Medicare)

- ☐ Private health insurance – with extras
- ☐ Private health insurance – without extras
- ☐ Department of Veterans' Affairs white or gold card
- ☐ Health care concession card
- ☐ none of these

51. What best describes the colour of the skin on the inside of your upper arm, that is your skin colour without any tanning?

- ☐ very fair
- ☐ fair
- ☐ light olive
- ☐ dark olive
- ☐ brown
- ☐ black

52. What would happen if your skin was repeatedly exposed to bright sunlight during summer without any protection? Would it:

- ☐ Get very tanned?
- ☐ Get moderately tanned?
- ☐ Get mildly or occasionally tanned?
- ☐ Never tan, or only get freckled?

53. About how many hours a DAY would you usually spend outdoors on a weekday and on the weekend?

hours per day ☐☐ weekday

hours per day ☐☐ weekend

54. About how many HOURS in each 24 hour DAY do you usually spend doing the following?
(please put "0" if you do not spend any time doing it)

hours per day		hours per day	
☐☐	sleeping (including at night & naps)	☐☐	sitting
☐☐	watching television or using a computer	☐☐	standing

55. How many TIMES in the LAST WEEK did you:
(please put "0" if you did not spend any time doing it)

	times in the last week
spend time with friends or family who do not live with you?	☐☐
talk to someone (friends, relatives or others) on the telephone?	☐☐
go to meetings of social clubs, religious groups or other groups you belong to?	☐☐

56. How many people outside your home, but within one hour of travel, do you feel you can depend on or feel very close to? ☐☐ people

57. During the past 4 weeks, about how often did you feel:

	none of the time	a little of the time	some of the time	most of the time	all of the time
tired out for no good reason?	☐	☐	☐	☐	☐
nervous?	☐	☐	☐	☐	☐
so nervous that nothing could calm you down?	☐	☐	☐	☐	☐
hopeless?	☐	☐	☐	☐	☐
restless or fidgety?	☐	☐	☐	☐	☐
so restless that you could not sit still?	☐	☐	☐	☐	☐
depressed?	☐	☐	☐	☐	☐
that everything was an effort?	☐	☐	☐	☐	☐
so sad that nothing could cheer you up?	☐	☐	☐	☐	☐
worthless?	☐	☐	☐	☐	☐

58. During the past 4 weeks, have you had any of the following problems with your work or daily activities because of any emotional problems (such as being depressed or anxious)?

cut down on the amount of time you spent on work or other activities	☐ Yes	☐ No
achieved less than you would have liked to	☐ Yes	☐ No
did work or other activities less carefully than usual	☐ Yes	☐ No

SAMPLE ONLY

Thank you very much for filling in the questionnaire

DON'T FORGET TO SIGN THE CONSENT FORM OVERLEAF

Are your name and address correct on the front of this questionnaire? ☐ Yes ☐ No

If INCORRECT, give details below.

Surname:

Given name(s):

Postal address:

Town or Suburb:

State or Territory: Postcode:

Consent form

THE 45 AND UP STUDY
Research to improve health and wellbeing

The *45 and Up Study* relies on the willingness of people in New South Wales to share information about their lives and experiences and to have their health followed over time. By signing this form you are agreeing to take part in the *45 and Up Study* and for the Study team to follow your health over time. Participation is completely voluntary, and you are free to ask questions or to withdraw from the Study at any time, by calling the Study helpline on 1300 45 11 45. More information on the Study can be found at www.45andup.org.au

I agree to have my health followed over time through:

the 45 and Up Study team following health and other records relating to me, including NSW hospital records, cancer records, death records and other health-related records, as outlined in the Study leaflet: *The 45 and Up Study: Information for participants*;

Medicare Australia releasing to the 45 and Up Study my enrolment details, including Medicare number, and information concerning services provided to me under Medicare, the Department of Veterans' Affairs, the Pharmaceutical Benefits Scheme and the Repatriation Pharmaceutical Benefits Scheme, including past information, until the end of the Study or for the duration of my involvement in the Study;

being contacted in the future to provide information on changes to my health and lifestyle. I may also be asked to provide further information including questionnaire responses or biological samples; my participation in any of these would be completely voluntary.

I give my consent on the understanding that:

my information will only be used for the purposes outlined in the Study leaflet entitled *The 45 and Up Study: Information for participants*, of which I have a copy;

my information will be kept strictly confidential and will be used for health research only;

reports and publications from the Study will be based on de-identified information and will not identify any individual taking part;

my participation in this Study is entirely voluntary and my consent will continue to be valid following death or disablement unless withdrawn by my next of kin or other person responsible. I am free to withdraw from the Study at any time by calling the **Study helpline on 1300 45 11 45;**

my decision on whether or not to take part in the Study or in any additional research will not disadvantage me or affect my future health care in any way.

I have been provided with information about the 45 and Up Study including how it will gather, store, use and disclose information about me, in the Study leaflet. I have been given an opportunity to ask questions and have been fully informed about the Study.

Name (Print): _____

Signature: _____ Date today: day ☐☐ / month ☐☐ / year 2 0 ☐☐

SAMPLE ONLY

Extra contact details

It would be very helpful and reduce Study costs if we could contact you in future by email. If you are happy for us to do this, please write your email address here:

Email address: _____

Sometimes we find that people have moved when we try to contact them again. It would be very helpful if you could give us your mobile phone number and/or the contact details of someone close to you (such as a relative or friend) who would be happy for us to contact them if we are unable to reach you. We would only get in touch with that person if we were unable to contact you directly and we would need to tell them our reason for contacting you. Please leave this section blank if you do not wish to provide these extra contact details.

Your home phone number: ( ) _____ Your mobile phone number: _____

Full name of contact person: _____

Phone number of contact person: ( ) _____

If you have any questions about the Study, please ring the Study helpline on **1300 45 11 45**.
You can also write to or send your questionnaire (no stamp required) directly to:

Associate Professor Emily Banks, Scientific Director,
The 45 and Up Study, Reply paid 5289, Sydney NSW 2001.

Thank you very much for taking part

SAX 45 and Up Study Male Scanning.qxd:Layout 1 20/6/08 2:27 PM Page 3

THE 45 AND UP STUDY

Research to improve health and wellbeing

45 and Up Study Questionnaire for Men

The *45 and Up Study* relies on the willingness of people in New South Wales to share information about their lives and experiences, to provide knowledge that will help people live healthy and fulfilling lives for as long as possible. Participation is completely voluntary, and you are free to withdraw from the Study at any time. To take part, please read the participant information leaflet, then complete the questionnaire and consent form and return them in the envelope provided. We very much hope you will be able to take part.

Any questions or comments? Please call the Study helpline: **1300 45 11 45** or go to **www.45andUp.org.au**

Auspiced by

the saxinstitute
RESEARCH PARTNERSHIPS FOR BETTER HEALTH

In collaboration with

The Cancer Council New South Wales

Heart Foundation

NSW HEALTH

beyondblue the national depression initiative

New South Wales Government

DADHC Department of Ageing, Disability & Home Care

SAMPLE ONLY

Your answers and experiences are important to us.
To help us read your answers, please write as clearly as possible using a **BLACK** or **BLUE** pen, and be sure to complete the questionnaire as shown:

Please put a cross in the appropriate box(es) [X] Yes [ ] No
OR put numbers in the appropriate box, e.g. *21st June 1945*
2 1 / 0 6 / 1 9 4 5 age 6 2

General questions about you

1. **What is your date of birth?** day / month / year 1 9
2. **What is today's date?** day / month / year 2 0
3. **How tall are you without shoes?** (please give to the nearest cm or inch) ____ cm **OR** ____ feet ____ inches
4. **About how much do you weigh?** ____ kg **OR** ____ stone ____ lbs
5. **What is the highest qualification you have completed?** (please put a cross in the most appropriate box)
   - [ ] no school certificate or other qualifications
   - [ ] school or intermediate certificate (or equivalent)
   - [ ] higher school or leaving certificate (or equivalent)
   - [ ] trade/apprenticeship (e.g. hairdresser, chef)
   - [ ] certificate/diploma (e.g. child care, technician)
   - [ ] university degree or higher
6. **Are you of Aboriginal or Torres Strait Islander origin?** (you can cross more than one box)
   - [ ] No [ ] Yes, Aboriginal [ ] Yes, Torres Strait Islander
7. **In which country were you born?**
   - [ ] Australia ▶ please go to question 9
   - [ ] UK [ ] Ireland [ ] Italy [ ] China
   - [ ] Greece [ ] New Zealand [ ] Germany [ ] Lebanon
   - [ ] Philippines [ ] Netherlands [ ] Vietnam [ ] Malta
   - [ ] Poland [ ] other *(please specify)*_____
8. **What year did you first come to live in Australia for one year or more?** (e.g. 1970) ____
9. **What is your ancestry?** (please cross up to 2 boxes)
   - [ ] Australian [ ] English [ ] Irish [ ] Chinese
   - [ ] Italian [ ] Greek [ ] Scottish [ ] German
   - [ ] Lebanese [ ] Dutch [ ] Maltese [ ] Polish
   - [ ] Filipino [ ] Indian [ ] Croatian [ ] Vietnamese
   - [ ] other *(please specify)* _____
10. **Do you speak a language other than English at home?**
    - [ ] Yes [ ] No
11. **Have you ever been a regular smoker?**
    - [ ] Yes ▼ [ ] No ▶ *If No – please go to question 12*

    How old were you when you started smoking regularly? ____ years old
    Are you a regular smoker now? [ ] Yes [ ] No
    If No – how old were you when you stopped smoking regularly? ____ years old
    About how much do you/did you smoke on average each day?
    (If you are an ex-smoker, how much did you smoke on average when you smoked?)
    ____ cigarettes per day ____ pipes and cigars per day
12. **About how many alcoholic drinks do you have each week?**
    one drink = a glass of wine, middy of beer or nip of spirits
    (put "0" if you do not drink, or have less than one drink each week)
    ____ number of alcoholic drinks each week
13. **On how many days each week do you usually drink alcohol?** ____ days each week

14. What best describes your current situation? (please cross one box)

☐ single ☐ married ☐ de facto/living with a partner
☐ widowed ☐ divorced ☐ separated

15. What best describes your current housing? (please cross one box)

☐ house ☐ flat, unit, apartment ☐ house on farm
☐ hostel for the aged ☐ mobile home ☐ other
☐ nursing home ☐ retirement village, self care unit

16. How many TIMES did you do each of these activities LAST WEEK?
(put "0" if you did not do this activity)

	times in the last week
Walking continuously, for at least 10 minutes *(for recreation or exercise or to get to or from places)*	☐☐
Vigorous physical activity *(that made you breathe harder or puff and pant, like jogging, cycling, aerobics, competitive tennis, but not household chores or gardening)*	☐☐
Moderate physical activity *(like gentle swimming, social tennis, vigorous gardening or work around the house)*	☐☐

17. If you add up all the time you spent doing each activity LAST WEEK, how much time did you spend ALTOGETHER doing each type of activity?
(put "0" if you did not do this activity)

	hours	minutes
Walking continuously, for at least 10 minutes *(for recreation or exercise or to get to or from places)*	☐☐ :	☐☐
Vigorous physical activity *(that made you breathe harder or puff and pant, like jogging, cycling, aerobics, competitive tennis, but not household chores or gardening)*	☐☐ :	☐☐
Moderate physical activity *(like gentle swimming, social tennis, vigorous gardening or work around the house)*	☐☐ :	☐☐

Questions about your family

18. Have your mother, father, brother(s) or sister(s) ever had:
(blood relatives only: please put a cross in the appropriate box(es))

	mother	father	brother/ sister		mother	father	brother/ sister
heart disease	☐	☐	☐	breast cancer	☐	☐	☐
high blood pressure	☐	☐	☐	bowel cancer	☐	☐	☐
stroke	☐	☐	☐	lung cancer	☐	☐	☐
diabetes	☐	☐	☐	melanoma	☐	☐	☐
dementia/Alzheimer's	☐	☐	☐	prostate cancer		☐	☐
Parkinson's disease	☐	☐	☐	ovarian cancer	☐		☐
severe depression	☐	☐	☐	osteoporosis	☐	☐	☐
severe arthritis	☐	☐	☐	hip fracture	☐	☐	☐
do not know	☐	☐	☐				

19. How many children have you fathered? ☐☐ children
(please include stillbirths but do not include miscarriages, please write "0" if you have not had any children)

How old were you when you fathered your FIRST child? ☐☐ years old

How old were you when you fathered your LAST child? ☐☐ years old

20. Have you ever tried for more than 1 year but have been unable to father children?

☐ Yes ☐ No

Questions about your health

21. About how many hours a week are you exposed to someone else's tobacco smoke?

hours per week ☐☐ at home
hours per week ☐☐ in other places *(e.g. work, going out, cars)*

22. Over the last month, how often have you:

	not at all	some times	often	almost always
found it difficult to postpone urination?	☐	☐	☐	☐
had to push or strain to start urination?	☐	☐	☐	☐
had a weak urinary stream?	☐	☐	☐	☐
stopped and started again several times when you urinated?	☐	☐	☐	☐
had to urinate again less than 2 hours after you finished urinating?	☐	☐	☐	☐
had the feeling that you had not emptied your bladder completely after urinating?	☐	☐	☐	☐

Over the past month, how many times did you usually get up from bed to urinate during the night?

☐ never ☐ some nights ☐☐ times each night

23. Have you taken any medications, vitamins or supplements for most of the last 4 weeks?

☐ Yes ▼ ☐ No

If Yes, was it:

☐ multivitamins + minerals	☐ multivitamins alone	
☐ fish oil	☐ glucosamine	☐ omega 3
☐ paracetamol	☐ aspirin for the heart	☐ aspirin for other reasons
☐ Lipitor	☐ Avapro, Karvea	☐ warfarin, Coumadin
☐ Pravachol	☐ Coversyl, Coversyl Plus	☐ Lasix, frusemide
☐ Zocor, Lipex	☐ Cardizem, Vasocordol	☐ Micardis
☐ Nexium	☐ Norvasc	☐ Fosamax
☐ Somac	☐ Tritace	☐ Caltrate
☐ Losec, Acimax *omeprazole*	☐ Noten, Tenormin *atenolol*	☐ Oroxine *thyroxine*
☐ Ventolin *salbutamol*	☐ Zyloprim, Progout 300 *allopurinol*	☐ Diabex, Diaformin *metformin*
☐ Zoloft *sertraline*	☐ Cipramil *citaloprim*	☐ Efexor *venlafaxine*

please list any other regular medications or supplements here

SAMPLE ONLY

24. Has a doctor EVER told you that you have:
(If YES, please cross the box and give your age when the condition was first found)

	Yes	Age when condition was first found
skin cancer (not melanoma)	☐	age
melanoma	☐	age
prostate cancer	☐	age
other cancer	☐	age
type of cancer *(please describe)*		
heart disease	☐	age
type of heart disease *(please describe)*		
high blood pressure	☐	age
stroke	☐	age
diabetes	☐	age
blood clot (thrombosis)	☐	age
enlarged prostate	☐	age
asthma	☐	age
hayfever	☐	age
depression	☐	age
anxiety	☐	age
Parkinson's disease	☐	age
none of these	☐	

25. In the last month have you been treated for:
(If YES, please cross the box and give your age when the treatment started)

	Yes	Age started treatment
cancer	☐	age
heart attack or angina	☐	age
other heart disease	☐	age
high blood pressure	☐	age
high blood cholesterol	☐	age
blood clotting problems	☐	age
asthma	☐	age
osteoarthritis	☐	age
thyroid problems	☐	age
osteoporosis or low bone density	☐	age
depression	☐	age
anxiety	☐	age
none of these	☐	

26. Are you NOW suffering from any other important illness?
☐ Yes ▼ ☐ No

Please describe this illness and its treatment

27. Do you regularly need help with daily tasks because of long-term illness or disability?
(e.g. personal care, getting around, preparing meals)
☐ Yes ☐ No

28. Does your health now LIMIT YOU in any of the following activities?

	yes, limited a lot	**yes**, limited a little	**no**, not limited at all
VIGOROUS activities *(e.g. running, strenuous sports)*	☐	☐	☐
MODERATE activities *(e.g. pushing a vacuum cleaner, playing golf)*	☐	☐	☐
lifting or carrying shopping	☐	☐	☐
climbing several flights of stairs	☐	☐	☐
climbing one flight of stairs	☐	☐	☐
walking one kilometre	☐	☐	☐
walking half a kilometre	☐	☐	☐
walking 100 metres	☐	☐	☐
bending, kneeling or stooping	☐	☐	☐
bathing or dressing yourself	☐	☐	☐

29. Have you ever had any of the following operations?
(If YES, please cross the box and give your age when you had the operation; give your age at the **most recent operation** if you have had more than one)

	Yes	Age when had operation
removal of skin cancer	☐	age
vasectomy	☐	age
part of prostate removed	☐	age
whole prostate removed	☐	age
knee replacement	☐	age
hip replacement	☐	age
gallbladder removed	☐	age
heart or coronary bypass surgery *(include stents and balloons)*	☐	age

other *(please describe any other operations you have had in the last 10 years, with your age when you had them)*

SAMPLE ONLY

30. Do you regularly care for a sick or disabled family member or friend?

☐ Yes ▼ ☐ No

If Yes, about how much time each week do you usually spend caring for this person?

☐ full time OR ☐☐ hours/wk

31. In general, how would you rate your:

	excellent	very good	good	fair	poor
overall health?	☐	☐	☐	☐	☐
quality of life?	☐	☐	☐	☐	☐
eyesight? *(with glasses or contact lenses, if you wear them)*	☐	☐	☐	☐	☐
memory?	☐	☐	☐	☐	☐
teeth and gums?	☐	☐	☐	☐	☐

32. Do you feel you have a hearing loss? ☐ Yes ☐ No

33. How many of your own teeth do you have left?

☐ None – all of my teeth are missing ☐ 1-9 teeth left
☐ 10-19 teeth left ☐ 20 or more teeth left

34. During the past 12 months, how many times have you fallen to the floor or ground? (put "0" if you haven't fallen in this time)

☐☐ times

35. Have you had a broken/fractured bone in the last 5 years?

☐ Yes ▼ ☐ No

If Yes, which bones were broken?

☐ wrist ☐ arm ☐ hip ☐ ankle
☐ rib ☐ finger/toe ☐ other _____

How old were you when it happened? (give age at most recent fracture if more than one) ☐☐ years old

36. About how many times a week are you usually troubled by leaking urine?

☐ never ☐ once a week or less
☐ 2-3 times ☐ 4-6 times ☐ every day

37. How often are you able to get and keep an erection that is firm enough for satisfactory sexual activity?

☐ always ☐ usually ☐ sometimes
☐ never ☐ I would rather not answer this question

38. Have you ever had a blood test ordered by your doctor to check for prostate disease? (PSA test)

☐ Yes ▼ ☐ No

If Yes, what year did you have your last PSA test? (e.g. 2005) ☐☐☐☐

How many times have you had a PSA test altogether? ☐☐ times

39. Have you ever been screened for colorectal (bowel) cancer?

☐ Yes ▼ ☐ No

If Yes, please indicate which test(s) you had:

☐ faecal occult blood test *(test for blood in the stool/faeces)*
☐ sigmoidoscopy *(a tube is used to examine the lower bowel: this is usually done in a doctor's office without pain relief)*
☐ colonoscopy *(a long tube is used to examine the whole large bowel; you would usually have to have an enema or drink large amounts of special liquid to prepare the bowel for this)*

What year did you have the most recent one of these tests? (e.g. 2005) ☐☐☐☐

Questions about your diet

40. About how many times each week do you eat: (please count all meals and snacks. put '0' if never eaten or eaten less than once a week)

	number of times eaten each week
beef, lamb or pork	☐☐
chicken, turkey or duck	☐☐
processed meat *(include bacon, sausages, salami, devon, burgers, etc)*	☐☐
fish or seafood	☐☐
cheese	☐☐

41. About how many of the following do you usually eat:

slices or pieces of brown/wholemeal bread each week *(also include multigrain, rye bread, etc.)* ☐☐

bowls of breakfast cereal each week ☐☐

If you eat breakfast cereal is it usually: (please cross)

☐ bran cereal *(allbran, branflakes, etc.)* ☐ muesli
☐ biscuit cereal *(weetbix, shredded wheat, etc.)* ☐ other *(cornflakes, rice bubbles,etc.)*
☐ oat cereal *(porridge, etc.)*

42. Which type of milk do you mostly have?

☐ whole milk ☐ reduced fat milk ☐ skim milk
☐ soy milk ☐ other milk ☐ I don't drink milk

43. About how many serves of vegetables do you usually eat each day? A serve is half a cup of cooked vegetables or one cup of salad (please include potatoes and put "0" if less than one a day)

☐☐ number of serves of cooked vegetables each day
☐☐ number of serves of raw vegetables each day (e.g. salad)
☐ I don't eat vegetables

44. About how many serves of fruit or glasses of fruit juice do you usually have each day? A serve is 1 medium piece or 2 small pieces or 1 cup of diced or canned fruit pieces (put "0" if you eat less than one serve a day)

☐☐ number of serves of fruit each day
☐☐ number of glasses of fruit juice each day
☐ I don't eat fruit

45. Please put a cross in the box if you NEVER eat:

☐ red meat ☐ chicken/poultry ☐ pork/ham ☐ dairy products
☐ any meat ☐ eggs ☐ sugar ☐ wheat products
☐ fish ☐ seafood ☐ cream ☐ cheese

Questions about time and work

46. What is your usual yearly HOUSEHOLD income before tax, from all sources? (please include benefits, pensions, superannuation, etc)

☐ less than $5,000 per year ☐ $30,000-$39,999 per year
☐ $5,000-$9,999 per year ☐ $40,000-$49,999 per year
☐ $10,000-$19,999 per year ☐ $50,000-$69,999 per year
☐ $20,000-$29,999 per year ☐ $70,000 or more per year
☐ I would rather not answer this question

SAMPLE ONLY

47. What is your current work status? (you can cross more than one box)

- ☐ in full time paid work
- ☐ in part time paid work
- ☐ completely retired/pensioner
- ☐ partially retired
- ☐ disabled/sick
- ☐ other
- ☐ self-employed
- ☐ doing unpaid work
- ☐ studying
- ☐ looking after home/family
- ☐ unemployed

48. If you are partially or completely retired, how old were you when you retired? ☐☐ years old

Why did you retire? (you can cross more than one box)

- ☐ reached usual retirement age
- ☐ to care for family member/friend
- ☐ made redundant
- ☐ other
- ☐ lifestyle reasons
- ☐ ill health
- ☐ could not find a job

49. About how many HOURS each WEEK do you usually spend doing the following? (please put "0" if you do not spend any time doing it)

hours per week ☐☐ paid work

hours per week ☐☐ voluntary/unpaid work

50. Which of the following do you have? (excluding Medicare)

- ☐ Private health insurance – with extras
- ☐ Private health insurance – without extras
- ☐ Department of Veterans' Affairs white or gold card
- ☐ Health care concession card
- ☐ none of these

51. What best describes the colour of the skin on the inside of your upper arm, that is your skin colour without any tanning?

- ☐ very fair
- ☐ fair
- ☐ light olive
- ☐ dark olive
- ☐ brown
- ☐ black

52. What would happen if your skin was repeatedly exposed to bright sunlight during summer without any protection? Would it:

- ☐ Get very tanned?
- ☐ Get moderately tanned?
- ☐ Get mildly or occasionally tanned?
- ☐ Never tan, or only get freckled?

53. About how many hours a DAY would you usually spend outdoors on a weekday and on the weekend?

hours per day ☐☐ weekday

hours per day ☐☐ weekend

54. About how many HOURS in each 24 hour DAY do you usually spend doing the following?
(please put "0" if you do not spend any time doing it)

hours per day		hours per day	
☐☐	sleeping (including at night & naps)	☐☐	sitting
☐☐	watching television or using a computer	☐☐	standing

55. How many TIMES in the LAST WEEK did you:
(please put "0" if you did not spend any time doing it)

	times in the last week
spend time with friends or family who do not live with you?	☐☐
talk to someone (friends, relatives or others) on the telephone?	☐☐
go to meetings of social clubs, religious groups or other groups you belong to?	☐☐

56. How many people outside your home, but within one hour of travel, do you feel you can depend on or feel very close to? ☐☐ people

57. During the past 4 weeks, about how often did you feel:

	none of the time	a little of the time	some of the time	most of the time	all of the time
tired out for no good reason?	☐	☐	☐	☐	☐
nervous?	☐	☐	☐	☐	☐
so nervous that nothing could calm you down?	☐	☐	☐	☐	☐
hopeless?	☐	☐	☐	☐	☐
restless or fidgety?	☐	☐	☐	☐	☐
so restless that you could not sit still?	☐	☐	☐	☐	☐
depressed?	☐	☐	☐	☐	☐
that everything was an effort?	☐	☐	☐	☐	☐
so sad that nothing could cheer you up?	☐	☐	☐	☐	☐
worthless?	☐	☐	☐	☐	☐

58. During the past 4 weeks, have you had any of the following problems with your work or daily activities because of any emotional problems (such as being depressed or anxious)?

cut down on the amount of time you spent on work or other activities	☐ Yes	☐ No
achieved less than you would have liked to	☐ Yes	☐ No
did work or other activities less carefully than usual	☐ Yes	☐ No

SAMPLE ONLY

Thank you very much for filling in the questionnaire

DON'T FORGET TO SIGN THE CONSENT FORM OVERLEAF

Are your name and address correct on the front of this questionnaire? ☐ Yes ☐ No

If INCORRECT, give details below.

Surname:

Given name(s):

Postal address:

Town or Suburb:

State or Territory: Postcode:

SAX 45 and Up Study Male Scanning.qxd:Layout 1 20/6/08 2:27 PM Page 2

Consent form

THE 45 AND UP STUDY
Research to improve health and wellbeing

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I agree to have my health followed over time through:

the 45 and Up Study team following health and other records relating to me, including NSW hospital records, cancer records, death records and other health-related records, as outlined in the Study leaflet: *The 45 and Up Study: Information for participants*;

Medicare Australia releasing to the 45 and Up Study my enrolment details, including Medicare number, and information concerning services provided to me under Medicare, the Department of Veterans' Affairs, the Pharmaceutical Benefits Scheme and the Repatriation Pharmaceutical Benefits Scheme, including past information, until the end of the Study or for the duration of my involvement in the Study;

being contacted in the future to provide information on changes to my health and lifestyle. I may also be asked to provide further information including questionnaire responses or biological samples; my participation in any of these would be completely voluntary.

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my information will be kept strictly confidential and will be used for health research only;

reports and publications from the Study will be based on de-identified information and will not identify any individual taking part;

my participation in this Study is entirely voluntary and my consent will continue to be valid following death or disablement unless withdrawn by my next of kin or other person responsible. I am free to withdraw from the Study at any time by calling the **Study helpline on 1300 45 11 45;**

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I have been provided with information about the 45 and Up Study including how it will gather, store, use and disclose information about me, in the Study leaflet. I have been given an opportunity to ask questions and have been fully informed about the Study.

Name (Print): _____

Signature: _____ Date today: day ☐☐ / month ☐☐ / year 2 0 ☐☐

SAMPLE ONLY

Extra contact details

It would be very helpful and reduce Study costs if we could contact you in future by email. If you are happy for us to do this, please write your email address here:

Email address: _____

Sometimes we find that people have moved when we try to contact them again. It would be very helpful if you could give us your mobile phone number and/or the contact details of someone close to you (such as a relative or friend) who would be happy for us to contact them if we are unable to reach you. We would only get in touch with that person if we were unable to contact you directly and we would need to tell them our reason for contacting you. Please leave this section blank if you do not wish to provide these extra contact details.

Your home phone number: ( ) _____ Your mobile phone number: _____

Full name of contact person: _____

Phone number of contact person: ( ) _____

If you have any questions about the Study, please ring the Study helpline on **1300 45 11 45**.
You can also write to or send your questionnaire (no stamp required) directly to:

Associate Professor Emily Banks, Scientific Director,
The 45 and Up Study, Reply paid 5289, Sydney NSW 2001.

Thank you very much for taking part