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Disease burden of selected gastrointestinal pathogens in Australia, 2010

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SUMMARY

Objective: To estimate and compare disease burden attributable to six gastrointestinal pathogens (norovirus, rotavirus, Campylobacter, non-typhoidal Salmonella, Giardia, and Cryptosporidium) in Australia, 2010.

Methods: We estimated the number of acute gastroenteritis (AGE) cases and deaths, disability-adjusted life years (DALYs), and DALY/case for each pathogen. We included AGE cases that did not require medical care. Sequelae were included for Campylobacter (Guillain–Barré syndrome, reactive arthritis (ReA), irritable bowel syndrome (IBS)) and Salmonella (ReA, IBS).

Results: We estimated 16 626 069 AGE cases in Australia in 2010 (population 22 million). Of the pathogens studied, most AGE cases were attributed to norovirus (2 180 145), Campylobacter (774 003), and Giardia (614 740). Salmonella caused the fewest AGE cases (71 255) but the most AGE deaths (90). The DALY burden was greatest for Campylobacter (18 222 DALYs) and Salmonella (3856 DALYs), followed by the viral and protozoal pathogens. The average DALY/case was greatest for Salmonella (54.1 DALY/1000 cases), followed by Campylobacter (23.5 DALY/1000 cases).

Conclusions: The pathogen causing the greatest disease burden varied according to the metric used, however DALYs are considered most useful given the incorporation of morbidity, mortality, and sequelae. These results can be used to prioritize public health interventions toward Salmonella and Campylobacter infections and to measure the impact of these interventions.

1. Introduction

Acute gastroenteritis (AGE) results in significant morbidity and mortality in Australia and worldwide.[1,2] Estimating AGE disease burden is an important element of estimating food-borne disease burden, a worldwide public health priority.[1,3] Disease burden can be measured in multiple ways, including number of cases, number of deaths, and more sophisticated metrics such as disability-adjusted life years (DALYs). The DALY takes into account disease mortality (years of life lost, YLL) and morbidity (years lost due to disability, YLD), where DALY = YLL + YLD. Specifically, DALYs incorporate information on the incident number of disease cases, illness duration, disease severity (disability weight), incident number of deaths, and life expectancy at age of death. Differing health outcomes can be incorporated into DALY disease models, including disease sequelae. In high-income countries where case fatality rates of AGE are low, sequelae to Campylobacter and Salmonella infection have been reported to cause greater DALY burden than the AGE itself.[4,5] One DALY equates to one lost year of 'healthy' life and the metric quantifies the gap between a population's current health status and an ideal where everyone lives to advanced age in perfect health. In addition to using the DALY to quantify the population disease burden, the average DALY/case can indicate the relative severity of disease caused by different pathogens.

We estimated the disease burden of six common gastrointestinal pathogens in Australia for the year 2010 and compared the number of cases, number of deaths, DALYs, and average DALY/case for each pathogen. We examined the two most common pathogens for high-income countries in each of the three major AGE pathogen groups:[4,6,7] viruses (rotavirus and norovirus), protozoa (Cryptosporidium and Giardia), and bacteria (Salmonella and Campylobacter). Comparing our results to international studies highlights the impact of environmental conditions, risk factors, and preventive measures on disease burden, with differences in disease burden estimates from specific AGE pathogens even between high-income countries; for example the incidence of Campylobacter

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AGE is approximately nine-times higher in Australia than in the USA.[8] Therefore, there is the need for country-specific disease burden estimates. These results can be used to assess the burden of AGE illnesses caused by different pathogens and pathogen groups, to inform appropriate public health responses to specific pathogens and pathogen groups, and to rationalize optimal targets for disease prevention.

2. Methods

2.1. Overview

We first estimated the total number of all-cause AGE cases in Australia in 2010 and then the number of all-cause AGE cases in four severity categories based on the requirement for medical care: fatal, hospitalized (inpatient medical care), outpatient (outpatient medical care), and mild (no medical care). Next we estimated the number of AGE cases attributable to each study pathogen (norovirus, rotavirus, Campylobacter, non-typhoidal Salmonella, Giardia, and Cryptosporidium) in terms of total AGE cases as well as fatal, hospitalized, outpatient, and mild AGE cases (Figure 1). We then estimated the number of cases of sequelae attributable to the two bacterial pathogens and the proportion in each severity category. Sequelae were included for Campylobacter (Guillain–Barré syndrome, reactive arthritis (ReA), irritable bowel syndrome (IBS)) and Salmonella (ReA, IBS). Finally we estimated disease duration, disability weight, and average life expectancy at age of death in order to calculate the DALYs and DALY/case (Figure 2).

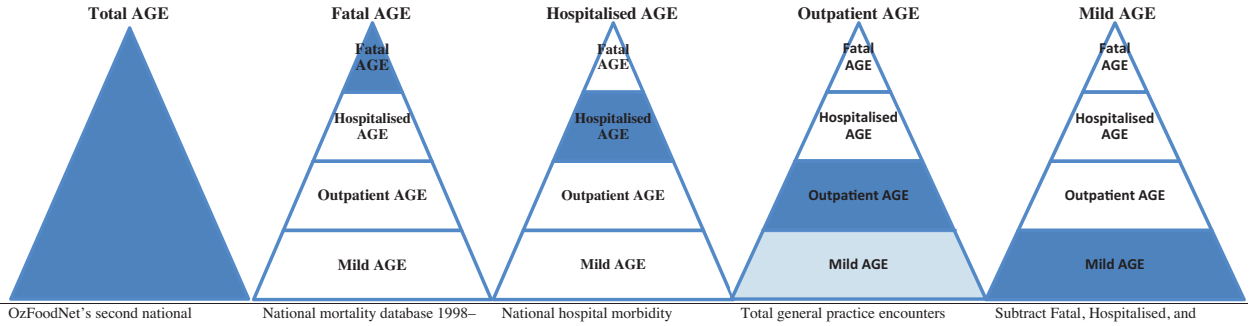
2.2. Population included

Our estimates were for all AGE cases, including those not requiring medical care, for the entire Australian population. For rotavirus, some previous DALY estimates have used a population of unvaccinated children <5 years of age.[9] However, because rotavirus cases are not confined to young children and rotavirus vaccine was added to Australia's National Immunisation Programme in July 2007,[10,11] we calculated the rotavirus burden in three Australian populations: (1) entire population, unvaccinated; (2) <5 years of age, unvaccinated; and (3) <5 years of age, vaccinated. Due to incomplete data on the impact of a partially vaccinated population, when comparing disease burden caused by the six AGE pathogens we used our estimates of rotavirus in the entire (unvaccinated) population.

2.3. Selecting data sources used in these DALY models

We used a combination of Australian administrative data (e.g., Australian notification/hospitalization/mortality data) and published and unpublished studies in our disease burden calculations. We obtained Australian administrative data through the websites of the relevant agencies and through formal data requests made to these agencies. Additionally, we submitted data requests to access unpublished data from OzFoodNet (a federally funded health network to enhance the surveillance of food-borne diseases in Australia) and the University of Sydney's 'Bettering the Evaluation And Care of Health' (BEACH) program, which collects information from Australian general practitioners (GPs).

To identify the published studies used in this report, we performed a literature review in PubMed using a combination of the following terms: 'gastroenteritis', 'community', 'hospital', 'deaths', 'epidemiology', 'Australia', 'norovirus', 'rotavirus', 'Campylobacter', 'Salmonella', 'Giardia', and 'Cryptosporidium'. We reviewed the titles of articles identified, and then based on perceived relevance we reviewed the abstracts before sourcing the full article. We reviewed the reference lists of articles to identify further relevant publications and reports. Only publications available in English were considered. The main literature review was performed in 2012; this was supplemented by targeted literature reviews until models were finalized. We selected data sources and studies based on certain criteria, including: (1) Study quality – size, duration, scientific rigor. These were the most important criteria for selecting studies to include in our DALY models. (2) Location – where possible we used Australian data, but if necessary we used data from other high-income countries (e.g., New Zealand, Europe, North America, and Japan). (3) Recency. (4) Internal consistency – where possible we used the same data sources for multiple pathogens. However, if the estimates for a particular pathogen deviated from other published estimates, we used judgement to choose an alternate data source to determine the most likely estimate. (5) Disease severity information, e.g., outpatient medical care, hospitalized, etc. (6) Age-group specific information – where available we included age-group specific data in our models.



All cause estimate	OzFoodNet's second national gastroenteritis survey (NGSII-2008)[65], 2008–2009	National mortality database 1998–2007, underlying cause A00–A09 (ICD 10)	National hospital morbidity database 1998/99–2007/08, principle diagnosis A00–A09 + 0.5 x total emergency department encounters x proportion due to AGE (Federal and State Health Departments)	Total general practice encounters (Medicare 2010) x proportion due to AGE (BEACH 2006–11)[18] + 0.5 x total emergency department encounters x proportion due to AGE (Federal and State Health Departments)	Subtract Fatal, Hospitalised, and Outpatient AGE from Total AGE
Pathogen specific estimate	Pathogen fraction (proportion of all-causes cases attributable to that pathogen)	Multiple methods: National Mortality Database data; National Notifiable Diseases Surveillance System data with case fatality rates; population mortality rates	Pathogen fraction	Pathogen fraction	Subtract Fatal, Hospitalised, and Outpatient AGE from Total AGE

Figure 1. Outline of methods used to estimate all-cause and pathogen-specific number of acute gastroenteritis (AGE) cases for each severity category.

DALY =	No. AGE deaths x average life expectancy at age of death	
	+	
	No. AGE cases x duration of illness x disability weight (for **mild** AGE)	
	+	
	No. AGE cases x duration of illness x disability weight (for **outpatient** AGE)	All study pathogens
	+	
	No. AGE cases x duration of illness x disability weight (for **hospitalized** AGE)	
	+	
	No. Reactive Arthritis (ReA) cases x duration of illness x disability weight (for **mild** disease)	
	+	
	No. ReA cases x duration of illness x disability weight (**outpatient** disease)	*Salmonella* and
	+	*Campylobacter* only
	No. ReA cases x duration of illness x disability weight (**hospitalised** disease)	
	+	
	No. Irritable Bowel Syndrome cases x duration of illness x disability weight	
	+	
	No. Guillain-Barré Syndrome (GBS) deaths x average life expectancy at age of death	
	+	
	No. GBS cases x duration of illness x disability weight (for **mild** disease)	
	+	*Campylobacter* only
	No. GBS cases x duration of illness x disability weight (for **severe** disease, <50 years of age)	
	+	
	No. GBS cases x duration of illness x disability weight (for **severe** disease, ≥50 years of age)	

Figure 2. Data points required to calculate disability-adjusted life years (DALY) for acute gastroenteritis (AGE) pathogens (ReA, reactive arthritis; GBS, Guillain–Barré syndrome).

2.4. Estimating AGE case numbers

2.4.1. Total all-cause infectious AGE cases

We applied age-weighted AGE rates from the national gastroenteritis survey NGSII-2008 study to the 2010 Australian population.[12] The NGSII-2008 study was a national cross-sectional telephone survey of 7578 participants conducted over 12 months in 2008–2009 in which infectious gastroenteritis was defined as at least three loose stools or two vomits in 24 h, in the absence of an identified non-infectious cause.[13] The full methodology of that study is a repeat of the earlier national gastroenteritis survey.[2]

2.4.2. All-cause AGE cases in each severity level

For each severity category we applied the estimated annual incidence of disease or death to the 2010 Australian population.[12]

For fatal AGE cases (all-cause), we determined average annual deaths with AGE as an underlying cause (International Classification of Diseases, 10th revision (ICD-10) codes A00–09) from the National Mortality Database (NMD, 1998–2007).[14]

For hospitalized AGE cases (all-cause), we combined the estimated number of AGE hospitalizations with half the estimated number of non-admitted emergency department (ED) encounters for AGE. Age-group specific hospitalization rates with a principal diagnosis of AGE (ICD-10 codes A00–A09) were obtained from the National Hospital Morbidity Database (1998/99–2007/08).[15] Total ED visits in 2010 was reported by the Australian Institute of Health and Welfare;[16] the proportion that were non-admitted ED encounters for AGE was obtained from state health departments (Queensland 2001/02–2009/10, New South Wales 1996/97–2009/10, Victoria 1999/2000–2009/10, and South Australia 2007/08–2009/10). We split the non-admitted ED encounters for AGE equally between the outpatient and hospitalized AGE categories, as we judged that some people attend ED with AGE because illness occurs when GP practices are closed (i.e., more like outpatient cases), while others go to the ED because they have severe symptoms (i.e., require intravenous fluid).

For outpatient AGE cases (all-cause), we combined GP visits for AGE with half the non-admitted ED encounters for AGE (see above). Total GP encounters for 2010 were obtained from Medicare, and the age-specific proportions attributable to AGE were derived from BEACH study data (2006–2011).[17,18] The BEACH study has been run by the University of Sydney since 1998. Each year, a random sample of 1000 GPs across Australia is surveyed with each recording details of 100 consecutive consultations.

With regard to mild AGE cases (all-cause), to account for AGE cases not requiring medical care and to ensure internal consistency in our disease models, mild AGE cases were estimated by subtracting fatal, hospitalized, and outpatient AGE cases from total AGE cases.

2.4.3. Pathogen-specific estimates of AGE cases and deaths

For total, hospitalized, and outpatient AGE cases (pathogen-specific), the proportions of all-cause AGE cases attributable to each pathogen (the pathogen fractions) were derived from studies listed in Table 1 and applied to the all-cause AGE estimate of each severity category. For total AGE cases we used the pathogen fraction from a population-based study from the Netherlands (the Sensor study) for all study pathogens other than Campylobacter,[19] for which we used the pathogen fraction from a British study (the IID2 study),[20] as this result was more consistent with other studies reviewed.[21–23] Similarly, for outpatient AGE cases we used the pathogen fraction from a GP-based study from the Netherlands (the NIVEL study) for the rotavirus, Cryptosporidium, Salmonella, and Campylobacter AGE estimates,[24] but the norovirus fraction from the IID2 study and the Giardia fraction from an Icelandic study (Hilmarsdóttir 2012),[20,25] as these were more consistent with the pathogen fraction reported in other studies reviewed.[26–31] As hospital-based studies were generally restrictive in terms of pathogens studied and age-groups included (paediatric vs. adult), a number of studies were used to estimate hospitalized AGE cases for each pathogen.[70–79]

With regard to fatal AGE cases (pathogen-specific), because of concerns about significant under-reporting of AGE deaths in the NMD, we used a combination of approaches to estimate AGE fatalities by different pathogens. For the protozoal study pathogens (Cryptosporidium and Giardia) we used vital registration data directly from the NMD (ICD-10 codes A00–A09, 1998–2007).[14] This is because, consistent with NMD data, published studies

Table 1
Data sources used to calculate number of cases and duration of illness for acute gastroenteritis and sequelae—Australia, 2010

Acute gastroenteritis	Number of cases			Duration		
	Total	Outpatient	Hospitalized[a]	Mild	Outpatient	Hospitalized
Norovirus	de Wit 2001[19]	Tam 2011[20]	Jansen 2008[70] Lorrot 2011[71] Patel 2008[72]	Sinclair 2005[23]	OzFoodNet outbreak registry[45]	Kemmeren 2006[49]
Rotavirus	de Wit 2001[19]	de Wit 2001[24]	Jansen 2008[70] Lopman 2011[73] Carlin 1998[74]	Kemmeren 2006[49]	Kemmeren 2006[49]	de Wit 2000[47]
Cryptosporidium	de Wit 2001[19]	de Wit 2001[24]	Tzipori 1983[75]	Sinclair 2005[23]	Sinclair 2005[23]	Robertson 2001[46]
Giardia	de Wit 2001[19]	Hilmarsdóttir 2012[25]	Jansen 2008[70] Essers 2000[76]	Nash 1987[77]	Homan 2012[50]	Nygård 2006[78]
Campylobacter	Tam 2011[20]	de Wit 2001[24]	Jansen 2008[70] Barnes 1998[79]	Kemmeren 2006[49]	Kemmeren 2006[49]	Kemmeren 2006[49]
Salmonella	de Wit 2001[19]	de Wit 2001[24]	Jansen 2008[70] Barnes 1998[79]	Sinclair 2005[23]	Food Standards Agency 2011[21]	McPherson 2006[48]

Sequelae (pathogen)	Number of cases		Duration
	Total	In each severity group	
GBS (Campylobacter)	Poropatich 2010[40] Hankey 1987[39]	Mangen 2004[41]	Havelaar 2000[22]
ReA (Campylobacter)	Hannu 2002[42]	Hannu 2002[42]	Mangen 2004[41]
ReA (Salmonella)	Tuompo 2013[43]	Tuompo 2013[43]	Mangen 2004[41]
IBS (Campylobacter, Salmonella)	Haagsma 2010[44]	-	Haagsma 2010[44]

GBS, Guillain–Barré syndrome; ReA, reactive arthritis; IBS, irritable bowel syndrome.

indicate that fatalities attributable to these pathogens are rare.[32,33] However, for the other pathogens we chose alternate methods, as the number of registered deaths in the NMD was much lower than reported in the published literature. We used data from the Australian National Notifiable Disease Surveillance System (NNDSS, 2001–10)[34] to estimate the number of notified cases of Campylobacter and Salmonella in 2010, and multiplied this by the case fatality rates for these pathogens used in a study of the burden of food-borne diseases in the USA.[6] The viral study pathogens are not nationally notifiable in Australia, and so we applied population mortality rates for rotavirus and norovirus reported in two German studies to the 2010 Australian population.[35,36]

For mild AGE cases (pathogen-specific), we subtracted the sum of outpatient, hospitalized, and fatal AGE cases from total AGE cases for each pathogen. This ensured internal consistency in our pathogen-specific estimates.

For rotavirus cases and deaths in a vaccinated population <5 years old, the estimated percentage reduction in rotavirus cases of each severity as a result of vaccination[37,38] was applied to the estimated number of rotavirus cases among unvaccinated children.

2.5. Disease sequelae

We estimated the sequela fraction (proportion of Campylobacter or Salmonella AGE cases that develop relevant sequelae) and the proportion of sequelae cases in each severity category from the studies listed in Table 1. We estimated the number of all-cause GBS cases based on a study reporting GBS incidence in Australia,[39] and the number of all-cause GBS deaths from the NMD (ICD-10 code G61.0, 2000–2010), and multiplied these by the pathogen-fraction derived from a systematic review of Campylobacter-associated GBS.[40] For non-fatal GBS, the severity groupings (mild, severe <50 years, and severe ≥50 years) and proportion of non-fatal GBS cases in each severity group were derived from Dutch studies of the burden of Campylobacter-associated disease.[22,41] We estimated the ReA fraction (proportion of Campylobacter or Salmonella AGE cases that develop ReA) and severity of ReA from two Finnish population-based studies.[42,43] As these studies followed laboratory-confirmed AGE cases, we applied this ReA fraction to outpatient and hospitalized Campylobacter and Salmonella AGE cases. Finally, we applied the IBS fraction from a meta-analysis of post-infectious IBS studies to our total estimated Campylobacter or Salmonella AGE cases.[44]

2.6. Disease duration

Average disease duration was estimated for each pathogen for mild, outpatient, and hospitalized AGE and sequelae using the studies listed in Table 1. Because many studies do not record duration of AGE according to disease severity, we used a combination of data sources, including raw data from Australian registries and studies (e.g., the OzFoodNet national outbreak register and the community-based Water Quality Study),[23,45,46] estimates from published studies from Australia and Europe,[21,47,48] and estimates used in other studies examining the burden of food-borne disease.[49,50] Disease durations for sequelae were derived from Dutch studies of the burden of food-borne diseases.[22,41,44] We chose data sources to include in our models based on the criteria listed above.

2.7. Other DALY model input

Disability weights for mild, outpatient, and hospitalized diarrhoea from the Global Burden of Disease 2010 study (GBD2010) were used for all six AGE pathogens.[51] Disability weights for sequelae were derived from Dutch studies of the burden of food-borne diseases.[22,41,44] Average YLL for deaths due to each pathogen were calculated from the NMD (1997–1998 to 2007–2008) using Australian cohort life expectancies for 1996 without discounting.[52] To determine the average DALY/case, we divided the DALY burden by the number of AGE cases for each pathogen.

2.8. Age-specific inputs into DALY models

Rates of AGE are known to differ by age. Some data used to estimate all-cause AGE cases were available for specific age-groups (e.g., total AGE cases from the NGSII and hospitalizations), while other data only had whole-population estimates available

(e.g., emergency department encounters and deaths). Likewise, pathogen fractions were often available for specific age-groups, however the age-groups used varied by study. Where available, age-group specific data were used in our calculations and data stratified by age and then aggregated up to a total. However, we have reported our results for the whole population and not for specific age-groups.

2.9. Statistical analysis

Single input values were used to obtain the point estimate for the number of cases and deaths, DALY, and DALY/case estimates. These single input values were considered the 'most likely' values, based on assessment of the quality and recency of the study from which the values were derived and generalizability of results to the Australian population. In addition, Monte Carlo analyses (10 000 iterations) using PERT (Project Evaluation and Review Techniques) distributions were used to calculate 95% credible intervals (95% CrI) for DALY/case estimates. Minimum, mode, and maximum values used in the PERT distributions, along with the data sources and approaches to calculate these, are included in the **Supplementary Material**.

3. Results

We estimated 16 626 069 cases of AGE in Australia in 2010 (total population 22 million persons[12]), of which 26.6% were attributed to one of norovirus, rotavirus, Cryptosporidium, Giardia, Salmonella, and Campylobacter. The greatest numbers of cases were caused by norovirus (2 180 145, 13.1% of all-cause AGE cases), Campylobacter (774 003 cases, 4.7%), and Giardia (614 740 cases, 3.7%) (Table 2). Rotavirus was estimated to cause 592 745 AGE cases in the total population (unvaccinated), of which 223 370 (37.7%) cases were among unvaccinated children <5 years old.

The proportion of all-cause AGE cases that were mild was 91.4%, outpatient was 8.1%, and hospitalized was 0.6%, but the proportion of cases in each severity category varied between pathogens (Table 2). The proportion of total AGE cases that were mild ranged from 20.6% (Salmonella) to 92.2% (norovirus). Salmonella had the highest proportion of outpatient (65.6%), hospitalized (13.7%), and fatal AGE (case fatality rate 126/100 000 AGE cases); therefore, Salmonella caused the fewest AGE cases (71 255) but the most AGE fatalities (90). Conversely, Giardia and Cryptosporidium were estimated to cause no deaths in Australia in 2010.

For sequelae, it was estimated that IBS was most common (68 112 Campylobacter-associated and 6270 Salmonella-associated cases), followed by ReA (11 252 and 2505 cases, respectively) and GBS (102 Campylobacter-associated cases). Of these sequelae, only GBS was estimated to cause fatalities (three deaths). The average duration of AGE was shortest for the viral and longest for the protozoal pathogens studied (Table 2). The average duration of sequelae was shortest for ReA (0.6 years), followed by IBS (5 years), while symptoms of GBS were estimated to persist lifelong. Average YLL per AGE death ranged from 7.1 years (norovirus) to 31.9 years (rotavirus, total population) and 82.6 years (rotavirus, children <5 years).

The DALY burden was greatest for the bacterial pathogens, followed by viral and then protozoal pathogens (Figure 3). Campylobacter was estimated to cause 18 222 DALYs at an average of 23.5 DALY/1000 cases and Salmonella caused 3856 DALYs at an average of 54.1 DALY/1000 cases (Table 3). Rotavirus was more severe among children than adults (average 4.2 DALY/1000 cases among unvaccinated children vs. 2.5 DALY/1000 cases among the total unvaccinated population), and rotavirus vaccine not only reduced the number of cases among children (223 370 to 78 180), but also the average burden of each rotavirus AGE case (4.2 to 1.6 DALY/1000 cases). Approximately half the pathogen-specific DALY was due to mild AGE for norovirus and Giardia, outpatient AGE for Cryptosporidium, and fatal AGE for Salmonella (Figure 4). The combined DALY for the six pathogens studied was 25 952, of which 70% was attributable to Campylobacter (including 55% attributed to Campylobacter-associated IBS) and 12% to deaths following Campylobacter or Salmonella AGE. Ranking of the six gastrointestinal pathogens by different burden of disease metrics is shown in Table 4.

Table 2
Estimating the burden of acute gastroenteritis (AGE) in Australia, 2010—number of cases and deaths, illness duration, and years of life lost (YLL)

AGE (population)	Number of cases								Deaths		Illness duration			YLL
	Total		Mild		Outpatient		Hospitalized		(Number per 100 000cases)		Mild	Outpatient	Hospitalized	
	No. (% of all-cause)		No. (% of total)		No. (% of total)		No. (% of total)							
All-cause AGE	16 626 069	(100)	15 192 016	(91.4)	1 339 866	(8.1)	94 128	(0.6)	61[a]	(0.4)				14.1
Norovirus AGE	2 180 145	(13.1)	2 010 290	(92.2)	157 081	(7.2)	12 757	(0.6)	17	(0.8)	2.1 days	2.4 days	7.2 days	7.1
Rotavirus AGE														
All ages, no vaccine	592 745	(3.6)	502 808	(84.8)	60 396	(10.2)	29 521	(5.0)	20	(3.4)	4.9 days	7.1 days	7.7 days	31.9
<5 years, no vaccine	223 370	-	169 149	(75.7)	34 557	(15.5)	19 657	(8.8)	7	(3.0)	4.9 days	7.1 days	7.7 days	82.6
<5 years, vaccinated	78 180	-	61 367	(78.5)	12 095	(15.5)	4 718	(6.0)	0	(0.0)	4.9 days	7.1 days	7.7 days	-
Cryptosporidium AGE	195 495	(1.2)	168 107	(86.0)	24 105	(12.3)	3 283	(1.7)	0	(0.0)	4.0 days	12.5 days	21.4 days	-
Giardia AGE	614 740	(3.7)	556 642	(90.5)	56 981	(9.3)	1 117	(0.2)	0	(0.0)	5 days	15 days	33 days	-
Campylobacter AGE	774 003	(4.7)	621 676	(80.3)	140 047	(18.1)	12 228	(1.6)	52	(6.7)	3.5 days	9.7days	14.4 days	19.2
Salmonella	71 255	(0.4)	14 697	(20.6)	46 726	(65.6)	9 742	(13.7)	90	(126.3)	2.5 days	6 days	12 days	22.6

Sequelae (pathogen)	Total (% AGE cases)		Mild		Outpatient		Hospitalized		Deaths		All cases	YLL
IBS (Campylobacter)	68 112	(8.8)	-	-	-	-	-	-	0	(0.0)	5 years	-
IBS (Salmonella)	6 270	(8.8)	-	-	-	-	-	-	0	(0.0)	5 years	-
ReA (Campylobacter)	11 252	(1.5)	8 751	(77.8)	2 250	(20.0)	250	(2.2)	0	(0.0)	0.6 years	-
ReA (Salmonella)	2 505	(3.5)	1 592	(63.6)	763	(30.5)	149	(6.0)	0	(0.0)	0.6 years	-

	Total		Mild		Severe, <50 years		Severe, ≥50 years		Deaths		Acute (clinical) phase	Chronic phase	YLL
GBS (Campylobacter)	102	(0.01)	17	(16.7)	39	(39.0)	44	44.1	3	(0.4)	1 year		
37.1 years		14.2											

IBS, irritable bowel syndrome; ReA, reactive arthritis; GBS, Guillain–Barré syndrome.

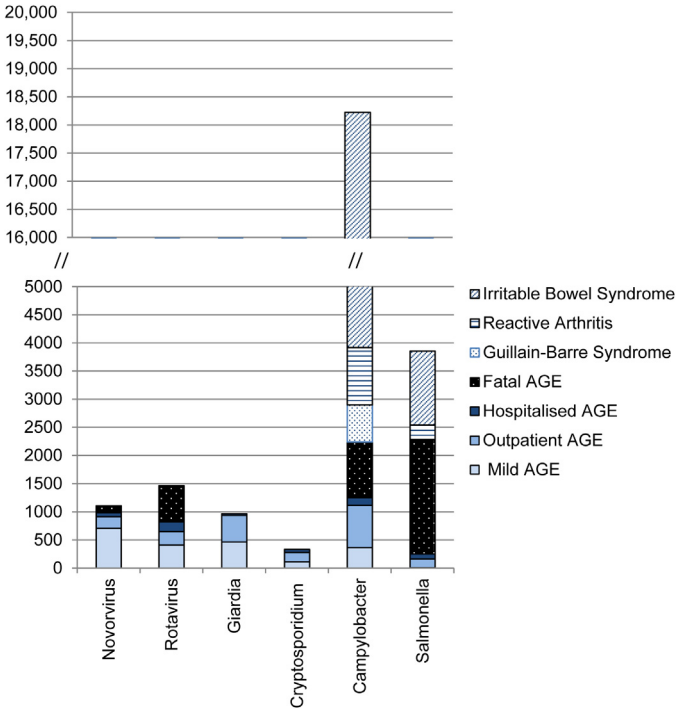


Figure 3. Disability adjusted life years (DALY) burden of six pathogens causing acute gastroenteritis (AGE), including contribution of different disease severity states and sequelae—Australia, 2010.

4. Discussion

We have documented the estimated disease burden in Australia 2010 attributable to six gastrointestinal pathogens using a number of metrics, including number of AGE cases, number of AGE fatalities, and DALYs. The pathogen with the greatest disease burden varied according to the metric used: norovirus caused the most cases (2 180 145), Salmonella the most fatalities (90), and Campylobacter with sequelae the most DALYs (18 222). Salmonella- and Campylobacter-associated sequelae, particularly Campylobacter-associated IBS, dominated the combined DALY estimates for the selected pathogens, while deaths associated with these two bacterial pathogens also had a significant impact. Therefore, preventing cases of Campylobacter and Salmonella would have a significant public health impact in Australia, and as food-borne transmission is significant for both,[4,6,53] optimizing food safety could significantly reduce the overall gastrointestinal disease burden. Additionally, these results support the need for further research into the pathogenesis, prevention, and management of post-infectious IBS to reduce the burden of AGE-associated disease in developed countries.

DALY models provide information that is lacking in estimates of disease cases and deaths. Using AGE case numbers to determine disease burden ignores differences in disease severity between pathogens. For example, although norovirus AGE cases are common, disease was often mild, fatalities were rare and occurred among the elderly, and illness duration was short, so the average DALY/case for norovirus was low. Using the number of deaths to demonstrate disease burden provides information about the most severe AGE cases, however information about morbidity is lacking. We estimated no deaths due to Giardia or Cryptosporidium, so their burden would be overlooked if only deaths were considered. In addition to number of AGE cases and deaths, DALY models incorporate information on different disease outcomes including sequelae, disease duration, disease severity (disability weights), and age at death. Furthermore, DALY/case estimates provide information about the severity of an average case of disease caused by each pathogen. Our disease models additionally demonstrate the contribution of different disease outcomes to the overall disease burden for each pathogen.

The six study pathogens were chosen as the most important in the three major pathogen groups (viral, protozoal, and bacterial) in high-income countries. Although the six study pathogens cause significant disease burden in developing countries, there are differences in AGE aetiology between high- and low-income countries. For example, in a prospective study of children in Africa and Asia, the four pathogens causing the most moderate-to-severe AGE cases were rotavirus, Cryptosporidium, enterotoxigenic *Escherichia coli* producing heat-stable toxin (ST-ETEC), and Shigella.[54] Therefore, the relative contribution of different pathogens to the overall AGE disease burden may differ substantially between high- and low-income countries. This highlights the need for country- or region-specific data when estimating pathogen-specific disease burden. Similarly, this study addresses the disease burden of study pathogens within the total Australian population and does not examine the burden among subpopulations. It would be interesting, but beyond the scope of the current study, to compare the burden of the study pathogens between indigenous and non-indigenous Australians; these results could be used to tailor public health interventions to the indigenous context. For

Table 3
Annual burden of selected pathogens causing acute gastroenteritis (AGE), Australia, 2010—number of cases and deaths, DALY, and DALY/case

Pathogen	Sequelae/population	AGE cases (Number per 1000 population)		AGE deaths (Number per million population)		DALY (Number per 100 000 population)		DALY/1000 cases Point estimate	DALY/1000 cases PERT distribution Mean	DALY/1000 cases PERT distribution 95% CrI
Campylobacter	Nil	774 003	(34.7)	52	(2.3)	2 242	(10.0)	2.9	3.0	2.0–4.2
	GBS, ReA					3 918	(17.5)	5.1	5.3	4.1–6.7
	GBS, ReA, IBS					18 222	(81.6)	23.5	25.9	10.7–43.6
Salmonella	Nil	71 255	(3.2)	90	(4.0)	2 285	(10.2)	32.1	34.9	13.8–57.4
	ReA					2 539	(11.4)	35.6	39.5	18.3–62.4
	ReA, IBS					3 856	(17.3)	54.1	59.8	32.2–88.0
Rotavirus	Nil									
	All, unvaccinated	592 745	(26.5)	20	(0.9)	1 465	(6.6)	2.5	2.2	1.8–2.5
	<5 years of age, unvaccinated	223 370	(152.9)	7	(4.5)	936	(64.1)	4.2	4.0	3.2–4.5
	<5 years of age, vaccinated	78 180	(53.5)	0	(0.0)	126	(8.6)	1.6	1.5	1.3–1.7
Norovirus	Nil	2 180 145	(97.6)	17	(0.8)	1 109	(5.0)	0.5	0.6	0.4–0.8
Giardia	Nil	614 740	(27.5)	0	(0.00)	967	(4.3)	1.6	1.7	1.1–2.8
Cryptosporidium	Nil	195 495	(8.8)	0	(0.0)	333	(1.5)	1.7	2.0	1.5–3.0

DALY, disability-adjusted life years; CrI, credible interval; GBS, Guillain–Barré syndrome; ReA, reactive arthritis; IBS, irritable bowel syndrome.

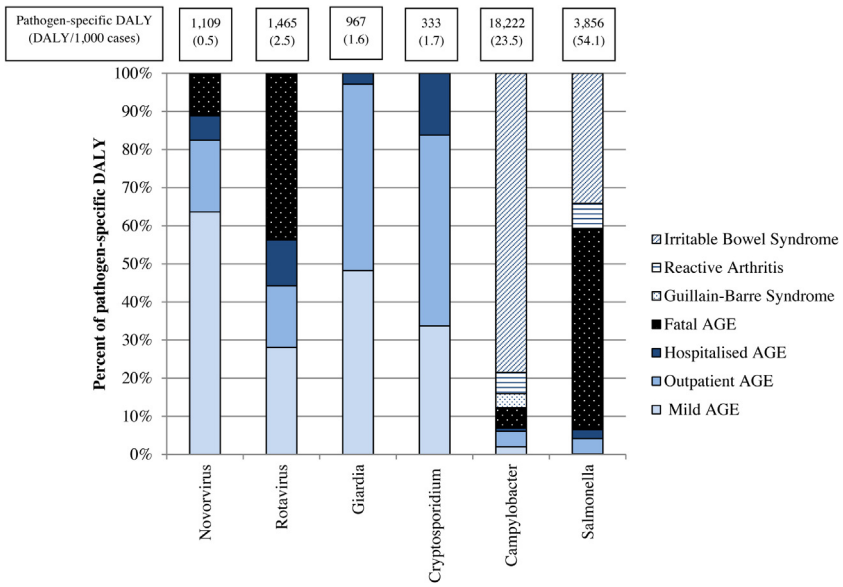


Figure 4. Relative contribution of disease severity states and sequelae to disability-adjusted life years (DALY) for six pathogens causing acute gastroenteritis (AGE)—Australia, 2010.

example, the burden of rotavirus disease in the pre-vaccine era was higher among indigenous compared to non-indigenous Australians and this gap has widened following vaccine introduction in 2007, possibly due to lower vaccine coverage among indigenous children and lower vaccine effectiveness against circulating rotavirus genotypes.[55]

Consistent with other studies that have failed to identify a pathogen for a majority of AGE cases, our six study pathogens accounted for 27% of the estimated number of all-cause infectious AGE cases in Australia in 2010. In a recent UK study, no pathogen was identified among 64% of mild AGE cases and 52% of outpatient AGE cases >5 years of age despite extensive testing.[20] Likewise, only 21% of AGE cases in the USA could be attributed to 24 known gastrointestinal pathogens.[56] Therefore, it is currently not possible to account for all AGE cases in pathogen-specific disease models.

The choice of AGE sequelae in disease models has the potential to dramatically impact DALY estimates. Based on our interpretation of available data, we incorporated GBS, ReA, and IBS into our Campylobacter disease model and ReA and IBS into our Salmonella disease model; however, other burden-of-disease studies have included different sequelae.[4,57,58] To facilitate comparison with other disease burden studies, we have clarified the contribution of each sequela to our DALY estimates and have provided results for Salmonella and Campylobacter with and without sequelae.

Comparing DALY results between studies is also affected by the inconsistent use of YLL discounting, disability weights, disease incidence, and duration estimates. For example, we used disability weights for AGE from the recently published GBD2010 study,[51] although the GBD2010 study defined AGE categories in terms of symptoms rather than healthcare-seeking behaviours as used in our study and most prior DALY studies of AGE.[4,9,58,59] Available data necessitated the use of healthcare-seeking behaviours rather than symptoms to classify mild, outpatient, and hospitalized AGE cases, however we believe that these criteria would roughly approximate the symptom-based categories of mild, moderate, and severe diarrhoea used in the GBD2010 study. The Burden of Disease and Injury in Australia 2003 study estimated the overall burden of diarrhoeal disease at 1858 DALYs,[59] much lower than our AGE DALY estimates. This is partly because they applied a discount rate of 3% to YLL estimates, did not include sequelae, and had different estimates for the proportion of cases requiring hospitalization and disease duration. Our DALY/1000 cases estimate for Salmonella was similar to a recent Dutch food-borne disease study (54.1 vs. 49), but our DALY/1000 cases estimate for Campylobacter was lower (23.5 vs. 41).[4] Conversely, our annual DALY/100 000 population estimate was higher for both Salmonella (17.3 vs. 7.7) and Campylobacter (81.6 vs. 20) than the Dutch study due to our higher estimated incidence of these diseases. Interestingly, the relative ranking of pathogens according to burden also differed between studies, with norovirus causing a greater DALY burden than Salmonella in Dutch and New Zealand food-borne disease studies, and Salmonella a greater quality-adjusted life years (QALY) loss than both Campylobacter and norovirus in a food-borne disease study in the USA.[57] Finally, our DALY/1000 cases estimate for rotavirus among unvaccinated children was much lower than a previous Australian estimate (4.2 vs. 13/1000 cases),[9] largely due to the reduction in estimated deaths when using data from Australia and other developed countries compared to estimates including developing countries with worse health outcomes. This highlights the benefits of using targeted, region-specific data sources.

Rotavirus vaccination has been available free of charge as part of Australia's National Immunisation Program since July 2007.[10] By the start of 2010, Australian children up to the age of 2.5 years would have been eligible for vaccination. Because data post-vaccination are limited, we presented our estimates for rotavirus burden among unvaccinated Australians but acknowledge this

Table 4
Ranking of gastrointestinal pathogens using different burden of disease metrics, Australia 2010[a]

Rank	No. AGE cases	No. deaths	DALY	DALY/case
1	Norovirus	Salmonella	Campylobacter	Salmonella
2	Campylobacter	Campylobacter	Salmonella	Campylobacter
3	Giardia	Rotavirus	Rotavirus	Rotavirus
4	Rotavirus	Norovirus	Norovirus	Cryptosporidium
5	Cryptosporidium	Giardia/ Cryptosporidium	Giardia	Giardia
6	Salmonella		Cryptosporidium	Norovirus

AGE, acute gastroenteritis; DALY, disability-adjusted life years.
[a] Rotavirus burden calculated using the non-vaccinated Australian population; however rotavirus vaccine was introduced for Australian infants in mid-2007.

overestimates the actual rotavirus burden in 2010 given vaccination reduces AGE cases, severity, and fatalities.[10] As further data become available, our rotavirus disease models could be used to quantify the reduction in DALY burden attributable to rotavirus vaccination in Australia.

Among our included pathogens, Salmonella stood out for having a high DALY/case. We estimated the incidence of Salmonella AGE to be 3.2/1000 person-years, which is similar to some previous estimates for Australasia and North America (2.5–6.9),[60–62] and our estimate of 71 255 Salmonella AGE cases in Australia in 2010 is in keeping with previous Australian estimates (49 843–92 000).[7,53] Our estimate that 65.6% of Salmonella AGE cases were outpatient cases exceeds studies from the USA and the Netherlands (12.3–15.4%),[49,62] however is similar to a UK study of food-borne disease (71.4%),[63] while our estimate that 13.7% of Salmonella AGE cases were hospitalized cases exceeds the other studies mentioned (1.1–3.6%), possibly due to our inclusion of half the non-admitted ED presentations in the hospitalized AGE category. Finally, although our case fatality rate for Salmonella (126/100 000 AGE cases) exceeds our estimates for the other pathogens studied (0–6.7/100 000), it is similar to recent estimates from Australasia and the Netherlands (114–152/100 000).[4,60]

The reliance on multiple datasets for our estimates is an acknowledged limitation. As highlighted by our Salmonella model, using multiple data sources to estimate numbers of AGE cases and deaths can result in apparent discrepancies within and between disease models. For fatal AGE cases we used different approaches as well as different data sources, resulting in our estimated number of fatal AGE cases caused by Campylobacter and Salmonella exceeding our estimated number of all-cause fatal AGE cases. NMD figures were used to estimate all-cause AGE mortality and these likely significantly underestimate deaths attributable to AGE due to under-diagnosis and under-reporting. Australian notification data have recently been used to estimate the number of food-borne Salmonella and Campylobacter AGE cases and these estimates were lower than ours.[64]

While an attempt has been made to include the most relevant high-quality data in the DALY/case models, inevitably the quality of input data varied across the models. We used results from the NGSII-2008 study to estimate the number of all-cause AGE in Australia.[65] Potential problems with the NGSII-2008 study include an unrepresentative sample of respondents (only those with a landline telephone were called, and of those contacted only 49% participated in the survey) and poor recall over a 4-week period. AGE rates estimated from retrospective surveys tend to be lower when the recall period is 4 weeks compared to 1 week,[20,66,67] while in a UK study, AGE rates calculated using a prospective cohort study design were lower than those obtained using a retrospective telephone survey design.[20] Although study design can impact estimated AGE rates, the NGSII-2008 study was designed to mirror the earlier national gastroenteritis survey and the estimated AGE rates were similar to international estimates.[2,68,69] Heterogeneity in data sources used could account for some of the apparent differences in pathogen-specific estimates presented in this study. However, we attempted to identify the most credible data source for each data point, which resulted in the use of different data sources within and between pathogen disease models. Differences in study design, including inconsistencies in laboratory techniques used to detect faecal pathogens, made pooling or meta-analysis of the results from different studies inappropriate. Monte Carlo simulations were performed to indicate the precision of the DALY/case point estimates.

In conclusion, we have estimated the burden of disease due to selected gastrointestinal pathogens using a number of metrics, including number of AGE cases, number of AGE fatalities, and DALYs. The pathogen with the greatest disease burden varied according to the metric used: norovirus caused the most cases, Salmonella the most fatalities, and Campylobacter with sequelae the greatest DALY burden. We believe DALYs provide the most meaningful measure of disease burden as they incorporate information about both morbidity and mortality. We have built disease models that can easily be updated as new data become available, including changes in case numbers and deaths due to public health interventions. These results can help prioritize and measure the impact of public health interventions and can be translated to other, similar, populations.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijid.2014.08.006.

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