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Sequelae of Foodborne Illness Caused by 5 Pathogens, Australia, Circa 2010

Technical Appendix 4

Methods to Estimate Sequelae Hospitalizations and Deaths

To estimate hospitalizations due to irritable bowel syndrome (IBS) and reactive arthritis (ReA), we used hospitalization data for 2006–2010 from all Australian states and territories, using International Classification of Disease, Tenth Revision, Australian Modification (ICD-10-AM) codes. All estimated incident foodborne *Campylobacter*-associated Guillain-Barré syndrome (GBS) and Shiga toxin–producing *Escherichia coli* (STEC)–associated hemolytic uremic syndrome (HUS) cases were considered hospitalized, so were not modeled. The estimate for hospitalizations due to GBS and HUS is the estimate for GBS and HUS incidence. To estimate deaths for all 4 sequelae illnesses, we used national deaths data for 2001–2010 from the Australian Bureau of Statistics, using ICD-10 codes (Technical Appendix 4 Table 1). The final estimate included 2 multipliers, which are discussed below.

Technical Appendix 4 Table 1. Mortality and hospitalization codes for each sequel, Australia, 2010*

Sequelae	Mortality ICD-10 code and description	Hospitalization ICD-10-AM code and description
Guillain-Barré syndrome	G610: Guillain-Barré syndrome	–
Hemolytic uremic syndrome	D593: Hemolytic uremic syndrome	–
Irritable bowel syndrome	K58: Irritable bowel syndrome	K58.0: Irritable bowel syndrome with diarrhea K58.9: Irritable bowel syndrome without diarrhea
Reactive arthritis	M021: Postdysenteric arthropathy M028: Other reactive arthropathies	M02.1: Postdysenteric arthropathy M02.3: Reiter's disease M02.8: Other reactive arthropathies M03.2: Other postinfectious arthropathies in diseases classified elsewhere

*ICD-10-AM, International Classification of Diseases, Tenth Revision; AM, Australian Modification; –, all patients with incident cases are assumed to have been hospitalized so hospitalization data not used for this pathogen.

Domestically Acquired Multiplier

This multiplier adjusts for the proportion of case-patients who acquired infection in Australia with values for each sequelae in Technical Appendix 4 Table 2. For GBS, we adopted the domestically acquired multiplier for *Campylobacter* spp. (*1*). Given the relatively small numbers of notified cases of HUS, we adopted the domestically acquired multiplier for STEC (*1*). The domestically acquired multiplier for IBS was calculated as a weighted average of the

domestically acquired multipliers for *Campylobacter* spp., nontyphoidal *Salmonella enterica* serotypes (hereafter referred to as nontyphoidal *Salmonella* spp.), and *Shigella* spp., weighted by the total number of IBS cases for each pathogen. Similarly, the domestically acquired multiplier for ReA was calculated as a weighted average of the domestically acquired multipliers for *Campylobacter* spp., nontyphoidal *Salmonella* spp., *Shigella* spp., and *Yersinia enterocolitica*, weighted by the total number of ReA cases for each pathogen.

Technical Appendix 4 Table 2. Domestically acquired multipliers*

Sequelae	Domestically acquired multiplier
Guillain-Barré syndrome	0.97 (range 0.91–0.99)
Hemolytic uremic syndrome	0.99 (range 0.93–1.00)
Irritable bowel syndrome	0.91 (90% CrI 0.88–0.94)
Reactive arthritis	0.91 (90% CrI 0.86–0.95)

*CrI, credible interval.

Proportion Foodborne Multiplier

This multiplier adjusts for the proportion of illness that is acquired from food and was required only to estimate hospitalizations and deaths. Sequelae can arise from a source other than a bacterial pathogen, from a bacterial pathogen that was not foodborne, or from a foodborne pathogen. Only this latter category is considered a foodborne source. The proportion foodborne multiplier is the simulated product of the bacterial multiplier and the weighted foodborne multiplier and can be found in Technical Appendix 4 Table 3. The approach for calculating the proportion foodborne multiplier for each sequel is described as follows:

Technical Appendix 4 Table 3. Proportion foodborne multiplier*

Sequelae	Foodborne multiplier
Guillain-Barré syndrome	0.25 (90% CrI 0.1–0.43)
Hemolytic uremic syndrome	0.33 (90% CrI 0.17–0.53)
Irritable bowel syndrome	0.13 (90% CrI 0.08–0.20)
Reactive arthritis	0.48 (90% CrI 0.36–0.62)

*CrI, credible interval.

GBS

There have been several reviews, as well as many case–control and cross-sectional studies, that estimated the percentage of GBS cases attributable to *Campylobacter* spp. (Technical Appendix 4 Table 3). Poropatich et al. (*8*) performed a systematic review of 30 case–control studies and concluded that 31.0% of GBS cases might be attributable to a previous infection due to *Campylobacter* spp. (*8*). The other global systematic review of GBS incidence does not look at *Campylobacter* spp. specifically or perform a meta-analysis (*9*). Other (nonsystematic) reviews have found that 13%–72% (*10*) and 8%–50% (*11*) of GBS occurs as a sequel to campylobacteriosis. We assume that 31% (range 4.8%–72%) of cases of GBS arise

from *Campylobacter* spp. (*2*). Multiplied together with the *Campylobacter* spp. foodborne multiplier of 0.77 (90% CrI 0.62–0.89) (*1*) led to a foodborne multiplier for GBS of 0.25 (90% CrI 0.11–0.43).

Technical Appendix 4 Table 4. Proportion of Guillain-Barré syndrome attributable to *Campylobacter* spp.*

Reference	Study years	Country	Study type	No. GBS cases	No. *Campylobacter* spp. cases based on	GBS cases attributable to campylobacteriosis
Poropatich et al. (*8*)	**1982–2010**	**Global**	**Systematic review**	**2,502**	**Stool samples or serology**	**31% (range 4.8%–71.7%)**
McGrogan et al. (*9*)	1980–2008	Global	Systematic review	–	–	6%–26%
Islam et al. (*12*)	2006–2007	Bangladesh	Prospective case-control	100	Stool samples and serology	57%
Sivadon-Tardy et al. (*13*)	1999–2005	France	Cross sectional	237	Stool samples and serology	27%
Tam et al. (*14*)	1991–2001	UK	Nested case-control	553	Corrected community incidence estimate	20%
Sivadon-Tardy et al. (*15*)	1996–2001	France	Cross sectional	263	Serology	22%
Takahashi et al. (*16*)	1990–2003	Japan	Case-control	1049	Stool samples and serology	11%
Tam et al. (*17*)	2000–2001	UK	Estimation	1146	Community incidence estimate	13.7%
Hadden and Gregson (*10*)	–	Global	Review	–	Serology	13%–72%
Nachamkin et al. (*11*)	–	USA	Review	–	Stool samples or serology	Best estimate 30%–40% (range 8%–50%)

*Boldface indicates chosen proportion for foodborne multiplier calculation.

HUS

Technical Appendix 4 Table 5 presents the percentage of cases of HUS that arise from STEC estimated in 4 different papers, including a global systematic review. From this, we assumed that 61% (range 30%–85%) of HUS cases arise from STEC, modelled as a PERT distribution. Multiplied with the STEC foodborne multiplier of 0.56 (90% credible interval [CrI] 0.32–0.83) (*1*) led to a foodborne multiplier for HUS of 0.33 (90% CrI 0.18–0.54).

Technical Appendix 4 Table 5. Proportion of HUS attributable to STEC*

Reference	Study years	Study type	Country	No. STEC isolations/no. HUS cases	STEC cases that develop into HUS
Walker et al. (*18*)	**1980–2011**	**Systematic review**	**Global**	**–**	**60.8% (range 30%–85.2%)**
Askar et al. (*19*)	2011	Surveillance	Germany	273/470	58%
Elliot et al. (*20*)	1994–1998	Surveillance	Australia	36/70	51%
Van de Kar (*21*)	1989–1993	Case control	The Netherlands	88/113	77.8%

*HUS, hemolytic uremic syndrome; STEC, Shiga toxin–producing *Escherichia coli*. Boldface indicates chosen proportion for foodborne multiplier calculation.

IBS

We estimated the proportion of IBS cases from *Campylobacter* spp., nontyphoidal *Salmonella* spp., or *Shigella* spp. based on the proportion of IBS considered to be postinfectious in the literature. In 1962, Chaudhary and Truelove (*22*) reported IBS occurring from infective dysentery, with 34 (26.2%) of 130 patients dating symptoms back to an attack of gastroenteritis.

More recently, review studies have estimated that 6%-17% (*23*) and 7%–33% of IBS is postinfectious (*24*). In the meta-analysis and estimation by Haagsma et al. (*25*), the authors considered that 17% of IBS is due to campylobacteriosis, salmonellosis, or shigellosis from the top end of the range of 6%-17% by Spiller and Garsed (*23*). We assumed 17% of IBS to be triggered by a gastrointestinal infection (*25*), with a range of 7%–33% from the review by Schwille-Kiuntke et al. (*24*). Because more than just *Campylobacter* spp., nontyphoidal *Salmonella* spp. and *Shigella* spp. can cause postinfectious IBS, this may be an overestimate.

A foodborne multiplier for the combined 3 pathogens of 73% (90% CrI 64%–82%) was calculated as a weighted average of the foodborne multipliers for each pathogen, weighted by the total number of IBS cases for each pathogen. Multiplied by the above PERT distribution of 17% (range 6%–33%), gave a foodborne multiplier for IBS of 13% (90% CrI 8%–20%).

Technical Appendix 4 Table 6. Proportion of IBS attributable to infectious gastroenteritis*

Reference	Publication year	Study type	Country	No. postinfectious IBS cases/IBS cases	IBS that is postinfectious, %
Chaudhary and Truelove (*22*)	1962	Epidemiologic report	UK	34/130	26.2
Spiller and Garsed (*23*)	2009	Review	Global	–	6–17
Haagsma et al. (*25*)	**2010**	**Meta-analysis and estimation**	**The Netherlands**	**–**	**17**
Schwille-Kiuntke et al. (*24*)	**2013**	**Review**	**Global**	**–**	**7–33**

*IBS, irritable bowel syndrome. Boldface indicates chosen proportion for foodborne multiplier calculation.

ReA

In a review of ReA, Hannu et al. (*4*) compiled population-based studies on the annual incidence of ReA—both from enteric and urogenital infection. We used this compilation and calculated the proportion of ReA due to enteric infection by dividing the enteric incidence by the total incidence found in each study (Technical Appendix 4 Table 7). We used the midpoint and range of the proportions from these studies for the bacterial multiplier. We therefore assumed a median of 66.7% of ReA is due to an enteric infection, with a range of 50%–94.7%. If enteric infections preceding ReA are from other infections besides campylobacteriosis, salmonellosis, shigellosis, or yersiniosis, using this distribution to estimate ReA cases from these infections may cause an overestimation.

We adjusted for the proportion foodborne using a weighted average of the foodborne multipliers for *Campylobacter* spp., nontyphoidal *Salmonella* spp., *Shigella* spp., and *Y. enterocolitica*, weighted by the total number of ReA cases for each pathogen. This gave a foodborne multiplier of 72% (90% CrI 60%–82%). Multiplied by the above alternate PERT

distribution of median 66.7% (range 50%–94.7%), gave a foodborne multiplier for reactive arthritis of 48% (90% CrI 36%–61%).

Technical Appendix 3 Table 7. Proportion of ReA attributable to enteric infection*

Reference	Country	Year	Incidence per 100,000			No. ReA due to enteric infection/total no. enteric infections
			Enteric	Urogenital	Total	
Isomaki et al. (*26*)	Finland	1978	14	13	27	14/27 (51.9%)
Kvien et al. (*27*)	Norway	1994	5	5	10	5/10 (50%)
Savolainen et al. (*28*)	Finland	2000	7	3	10	7/10 (70%)
Soderlin et al. (*29*)	Sweden	2002	18	1	19	18/19 (94.7%)
Townes et al. (*30*)	USA	2008	0.6–3.1	NA	NA	NA
Hanova et al. (*31*)	Czech Republic	2010	6	3	≈9	6/9 (66.7%)

*Adapted from the table of annual incidence of reactive arthritis based on population studies in Hannu et al. (*4*). NA, not applicable.

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