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

Technical Appendix 1

Sequelae Incidence after Bacterial Gastroenteritis: The Sequelae Multiplier

For each sequel, a multiplier was used that estimated the proportion of bacterial gastroenteritis cases that developed into chronic sequelae. This appendix summarizes the relevant studies published during 1995–2012, which we selected for review, as well as the sequelae multipliers that were estimated for Guillain-Barré syndrome (GBS), hemolytic uremic syndrome (HUS), irritable bowel syndrome (IBS), and reactive arthritis (ReA).

GBS

A few studies have quantified the incidence of GBS illness following *Campylobacter* spp. infection by using large cohorts of patients or the literature (online Technical Appendix 1 Table 1). In a population-based cohort study in the United Kingdom, including 2 months of follow-up, 3 cases of GBS occurred among 15,587 *Campylobacter* spp. cases. This yielded a rate of 19.2 cases of GBS per 100,000 cases of campylobacteriosis (*1*). In Sweden, 0.03% of a cohort of 29,567 persons with laboratory-confirmed *C. jejuni* infection developed GBS illness after 2 months of follow-up, yielding an annual incidence of 30.4 cases of GBS per 100,000 cases (95% CI 13.9–57.8) of *C. jejuni* infection (*2*). In a literature review, Allos (*3*) estimated that in the United States, GBS develops in 1 of every 1,058 cases, or 94.5 per 100,000 cases, of *C. jejuni* infection. Baker et al. (*4*) performed a study of hospital records in New Zealand, which found a rate of 414 cases of GBS per 100,000 *Campylobacter* spp. hospitalizations.

For the sequelae multiplier, a midpoint of 30.4 cases of GBS per 1000,000 cases of campylobacteriosis was taken from the study by McCarthy and Gieseke (*2*) using a minimum value of 19.2 per 100,000 from the UK study and a maximum value of 94.5 per 100,000 from the study by Allos (*3*). Although the study by Baker et al. (*4*) is a valuable one, we excluded it from

the calculation of our sequelae multiplier because persons hospitalized with *Campylobacter* spp. infection may not be representative of *Campylobacter* spp. cases in the community.

Technical Appendix 1 Table 1. Incidence of GBS after infection with *Campylobacter* spp.*

Reference	Study years	Type of study	Country	No. GBS cases/*Campylobacter* spp. patients	Incidence per 100,000 (95% CI)
Baker et al. (*4*)	1995–2008	Cohort	New Zealand	35/8,448 hospitalizations	414 (373–459)
Tam et al. (*1*)	1991–2001	Cohort	UK	3/15,587 cases	19.2 (17.1–21.5)
McCarthy and Giesecke (*2*)	1987–1995	Cohort	Sweden	9/29,563 cases	30.4 (13.9–57.8)
Allos (*3*)	1964–1996†	Review and estimation	Global/USA	1/1058 cases	94.5 (2.4–525)

*GBS, Guillain-Barré syndrome.
†Years of reviewed studies.

HUS

A variety of organisms, drugs and conditions can initiate the symptoms of HUS, but the majority of HUS cases are post-diarrheal—usually caused by Shiga toxin–producing *Escherichia coli* (STEC) (*5*). In developed communities, STEC is the most commonly implicated organism in HUS (*6*), and in children, 90% of HUS cases are due to STEC (*5*). HUS is also associated with *Shigella dysenteria* serotype 1, particularly in less developed communities (*6*); however, a recent systematic review was unable to find an adequate number of studies to quantify the association between *S. dysenteria* serotype 1 and HUS (*7*). In addition, in a few studies, HUS has been associated with *Clostridium difficile* and *Salmonella enterica* serotype Typhi, but the evidence is limited (*8–10*). Therefore we estimated food-related HUS cases as a sequel to STEC, which may create an underestimation of HUS if there are food-related HUS cases in Australia from other organisms.

Several sources have reported that 3%-7% of sporadic STEC infections develop into HUS (*11–14*). Australian studies support this estimate range. Vally et al. (*15*) examined South Australian surveillance data and identified 14 HUS cases and 460 STEC cases, resulting in an estimate of 3% of STEC cases developing into HUS. Sixty percent of HUS case-patients were ≤15 years of age. In addition, in a case–control study in 6 Australian jurisdictions, 113 STEC case-patients were identified, 44 of whom were infected with O157 and 66 who were infected with non-O157 (*14*). Eight (7%) of all the STEC cases, 1 (2%) case-patient with O157, and 7 (10%) case-patients infected with non-O157 developed HUS (*14*). Although STEC O157 is more commonly associated with HUS worldwide (*6*), data on geographic differences in STEC serotypes suggest that in Australia, "non-O157:H7 STEC strains predominate," and STEC O157:H7 is not as frequently implicated in "diarrhea-associated HUS" (*16*).

Overseas studies have reported higher proportions of STEC infections developing into HUS. In a cohort study of Argentinian children, aged ≤15 years, 8 (8.6%) of 93 STEC patients developed HUS (*17*). Through enhanced surveillance in the Netherlands, Van Duynhoven et al. (*18*) found that HUS developed in 12 of 82 (14.6%) patients. Seventy-five percent of HUS case-patients were ≤15 years (*18*). With the highest proportion from all reviewed studies, a Swiss linkage study found that HUS developed in 13 (29.5%) of 44 STEC patients, all of whom were ≤15 years of age (*19*). Several studies on the incidence of HUS after STEC outbreaks have found that ≈20% of STEC cases develop into HUS (*20–23*). However, Sigmundsdottir et al. found no HUS cases among 9 STEC outbreak patients in Iceland (*24*) (Technical Appendix 1 Table 2).

A sequelae multiplier proportion of 3% (95% CI 1.7%–5.4%) was chosen, based on the South Australian study by Vally et al. (*15*). This study was chosen because STEC surveillance in South Australia is more complete than for other Australian states (*11*) and would therefore give a more representative estimate for Australia than the other available studies.

Technical Appendix 1 Table 2. Incidence of HUS after STEC*

Reference	Study years	Study type	Country	Age of HUS case-patients	No. HUS cases/no. STEC cases	STEC cases developing into HUS, %
Bradley et al. (*20*)	2008	Epidemiology investigation and case–control: after an outbreak	USA	Median: 46 y (range1–88 y), 60% adult	11/56	20
Lopez et al. (*17*)	2006	Prospective cohort	Argentina	≤15 y	8/93	8.6
Neil et al. (*21*)	2009	Case–control: after an outbreak	USA	Not stated	10/57	18
Vally et al. (*15*)	1997–2009	Surveillance	Australia	Range: <5–60+, 60% aged ≤15 y	14/460	3
Frank et al. (*22*)	2011	Surveillance: after an outbreak	Germany	Median: 42, 88% aged >15 y	845/3816	22
Kappelli et al. (*19*)	2000–2009	Linkage	Switzerland	Median: 3.5 y (range 0–15 y)	13/44	29.5
McPherson et al. (*14*)	2003–2007	Case–control	Australia	Median: 4 y (range 1–62)	8/113	7
Sigmundsdottir et al. (*24*)	2007	Cohort: after an outbreak	Iceland	Not stated	0/9	0
Rangel et al. (*25*)	1982–2002	Outbreak surveillance	USA	Not stated	354/8598	4.1
Jay et al. (*23*)	1999	Epidemiology investigation and case–control: after an outbreak	USA	Not stated	3/13	23
Van Duynhoven et al. (*18*)	1999–2001	Enhanced surveillance	The Netherlands	Range: 0–70 y, 75% aged ≤15 y	12/82	14.6

*HUS, hemolytic uremic syndrome; STEC, Shiga toxin–producing *Escherichia coli*.

IBS

There have been a few systematic reviews and/or meta-analyses on the association between intestinal infection and post-infectious IBS (PI-IBS). A recent review suggests the proportion of persons developing IBS following gastrointestinal infection is 4%–35% (*26*). In

2010, Haagsma et al. (*27*) found that 1 year after infection from nontyphoidal *S. enterica* serotypes (hereafter referred to as nontyphoidal *Salmonella* spp.), nontyphoidal *Salmonella* spp., *Shigella* spp., or *Campylobacter* spp., IBS developed in 9% (95% CI 7.2–10.7) of patients. Similarly, in a systematic review of 18 studies, Thabane et al. (*28*) found a pooled incidence of PI-IBS of 10% (95% CI 9.4–85.6). Comparably, Halvorson et al. (*29*) reviewed 8 studies on nontyphoidal *Salmonella* spp., *Shigella* spp., bacterial unspecified, or unspecified, and their association with IBS, and calculated a median prevalence of IBS of 9.8% (interquartile range 4.0–13.3) in the exposed group and 1.2% Interquartile rate range 0.04–1.8) in the control group. A review by Smith and Bayles (*30*) found a mean prevalence of PI-IBS of 15% from 15 studies, with species of *Campylobacter*, nontyphoidal *Salmonella* spp., and/or *Shigella* as the most common agents of infection.

In the United Kingdom, Neal et al. (*31*) performed a postal survey and found that 25% of subjects had persistently altered bowel habits after bacterial gastroenteritis from nontyphoidal *Salmonella* spp., *Shigella* spp., or *Campylobacter* spp.; however, only 7% met the Rome criteria for new IBS. Also in the United Kingdom, Parry et al. (*32*) looked at the relationship between IBS and bacterial gastroenteritis from *Campylobacter* spp., nontyphoidal *Salmonella* spp., *Shigella* spp., *E. coli* O157, and *Aeromonas sobria*, and calculated an incidence of new IBS of 16.7% in the exposed group and 1.9% in the control group.

Studies looking at singular pathogens have also found an association between infectious gastroenteritis outbreaks and IBS. After an outbreak in 2002 in Spain, Mearin et al. (*33*) noted that before the outbreak, the prevalence of IBS was similar in case-patients and controls (2.9% vs. 2.3%); however, 3 months after the outbreak, IBS prevalence in case-patients had increased (9.2% vs. 1.7%), and 12 months after the outbreak, prevalence in case-patients remained higher (10.2% vs. 0.7%). The cumulative incidence was 7.4% at 3 months, 10.9% at 6 months, and 11.6% at 12 months. In Korea, 12 months after a *Shigella* spp. outbreak, Ji et al. (*34*) found that IBS had developed in 15 (14.9%) of 101 case-patients and 6 of 102 (5.9%) controls. In Canada, 2–3 years after an outbreak of *E. coli* O157:H7 and *Campylobacter* spp., 27.5% of 904 subjects with self-reported gastroenteritis reported IBS, and 36.2% of 464 subjects with clinically suspected gastroenteritis reported IBS (*35*). In a pediatric cohort from the Canadian outbreak, the cumulative incidence of PI-IBS for exposed subjects was 10.5% vs. a cumulative incidence in controls of 2.5% (*36*).

There have been studies on the association of *G. lamblia* with IBS; however, these have produced inconsistent results. While Wensaas et al. (*37*) found a high prevalence of IBS in exposed patients 2 years after acute giardiasis, Penrose et al. (*38*) found no linear association between *G. lamblia* and IBS, and a study by D'Anchino et al. (*39*) concluded that *G. lamblia* infection is a trigger for exacerbating preexisting IBS but could not conclude that *G. lamblia* causes IBS. PI-IBS has also been shown to develop after norovirus. Marshall et al. (*40*) performed a 2-year study after a norovirus outbreak; of the 89 respondents who reported an acute enteric illness during the outbreak and did not have preexisting IBS, 23.6% reported symptoms consistent with PI-IBS at 3 months versus 3.4% who reported symptoms but remained well during the outbreak. However, at 6, 12, and 24 months, the prevalence of IBS did not differ statistically among exposed and unexposed individuals, suggesting that PI-IBS might be more transient after viral gastroenteritis than it is after bacterial dysentery (*40*) (Technical Appendix 1 Table 3).

The meta-analysis by Haagsma et al. (*27*), which suggests that IBS develops in ≈9% (95% CI 7.2%–10.7%) of *Campylobacter* spp., nontyphoidal *Salmonella* spp., and *Shigella* spp. case-patients at 10–12 months of follow-up was chosen as the sequelae multiplier to simulate the plausible proportion of these bacterial pathogens that cause IBS using an alternate PERT distribution. While studies of multiple pathogens have found different rates of PI-IBS depending on etiology, this proportion was chosen for all 3 pathogens because it is a pooled rate that comes from a recent meta-analysis and is similar to PI-IBS rates after bacterial gastroenteritis that were reported in other studies (*28*,*29*,*41*).

Technical Appendix 1 Table 3. Incidence of IBS after infection with enteric pathogens, Australia, circa 2010*

Reference	Year of publication	Study years	Country	Study type	Foodborne pathogen	IBS patients after infectious gastroenteritis, %
Koh et al. (*41*)	2012	2008–2010	Korea	Prospective cohort	Nontyphoidal *Salmonella* spp., *Shigella* spp., STEC O157, *Vibrio cholerae*	9.2% at 3 mo†, 12.3% at 6 mo†
Wensaas et al. (*37*)	2012	2007–2008	Norway	Historic cohort	*Giardia lamblia*	46.1% at 3 y
Schwille-Kiuntke et al. (*26*)	2011	-	Global	Systematic review	*Campylobacter* spp., E*scherichia coli*, *G. lamblia*, norovirus, nontyphoidal *Salmonella* spp, *Shigella* sp., *Trichinella britovi*; bacterial, viral, and parasitic gastroenteritis and travelers' diarrhea	4%–36% Incidence range
Thabane et al. (*36*)	2010	2002–2008	Canada	Outbreak study	*E. coli* O157:H7, *Campylobacter* spp.	10.5%†
Haagsma et al. (*26*)	2010	-	The Netherlands	Meta-analysis	*Campylobacter* spp., nontyphoidal *Salmonella* spp.,	9% (95% CI 7.2–10.7)

Reference	Year of publication	Study years	Country	Study type	Foodborne pathogen	IBS patients after infectious gastroenteritis, %
					Shigella spp.	at 1 y
Marshall et al. (*35*)	2009	2002–2008	Canada	Outbreak study	*E. coli* O157:H7, *Campylobacter* spp.	27.5% (self-reported), 36.2% (clinically suspected)
Thabane et al. (*28*)	2007	-	Canada, China, Israel, Korea, New Zealand, UK, USA	Systematic review and meta-analysis	*Campylobacter* spp., nontyphoidal *Salmonella* spp., *Shigella* spp., confirmed bacterial gastroenteritis, and self-reported illness	10% (95% CI 9.4–85.6), 4%–32% incidence range
Marshall et al. (*40*)	2007	2002–2004	Canada	Outbreak study	Norovirus	23.6% at 3 mo
Smith and Bayles (*30*)	2007	-	Canada, China, Korea, Spain, UK, USA	Systematic review	*Campylobacter* spp., Cryptosporidium spp., E.*coli*, *G. lamblia*, nontyphoidal *Salmonella* spp., *Shigella* spp.	15% (range 3.4–31.6)‡
Halvorson et al. (*29*)	2006	-	Canada, China, Korea, Spain, UK, USA	Systematic review and meta-analysis	Nontyphoidal *Salmonella* spp., *Shigella* spp., bacterial, and unspecified	9.8% (IQR 4.0–13.3)‡
Ji et al. (*34*)	2005	2001–2002	Korea	Outbreak study	*Shigella* spp.	14.9% at 1 y
Mearin et al. (*33*)	2005	2002–2003	Spain	Cohort study after an outbreak	Nontyphoidal *Salmonella* spp.	7.4% at 3 mo†, 10.9% at 6 mo†, 11.6% at 1 y†
Parry et al. (*32*)	2003	2000–2001	UK	Prospective case–control study	*Campylobacter* spp., nontyphoidal *Salmonella* spp., *Shigella* spp., STEC O157, *Aeromonas sobria*	16.7% at 6 mo
Neal et al. (*31*)	1997	1994	UK	Cross-sectional	*Campylobacter* spp., nontyphoidal *Salmonella* spp., and *Shigella* spp.	7% at 6 mo

*IBS, irritable bowel syndrome; IQR, interquartile range; nontyphoidal *Salmonella* spp., nontyphoidal *S. enterica* serotypes; STEC, Shiga toxin–producing *E. coli*.
†Cumulative incidence.
‡Median prevalence.

ReA

The causes of ReA are ambiguous because no formal definition or agreed-upon diagnostic criteria exist (*42*,*43*). Although the primary focus of the infection is usually through the gut or urogenital track, ReA has also been associated with respiratory pathogens (*42*). The classical gastrointestinal microbes resulting in ReA are *Yersinia enterocolitica,* nontyphoidal *Salmonella* spp., *Shigella* spp., and *Campylobacter* spp (*43*). and most agree that the term "ReA" should be applied only to infection caused by these gastrointestinal pathogens and *Chlamydia* spp (*43*); however, nonclassical ReA forms have been associated by a variety of other bacteria, including *Brucella* and *Staphylococcus*, and many authors have applied the term ReA for arthritis after infection with *C. difficile*, *Cryptosporidium*, *Giardia lamblia*, *E. coli*, and *Strongyloides* spp (*43*,*44*). With the majority of the literature focusing on the 4 classical gastrointestinal pathogens as triggers for ReA, we chose to use these to estimate the incidence of ReA due to contaminated food. If other enteric pathogens are in fact associated with ReA, our estimates of foodborne ReA may be conservative.

We were unable to find any published systematic reviews that report a global incidence rate for ReA after infection with the bacterial pathogens *Campylobacter* spp., nontyphoidal *Salmonella* spp., *Shigella* spp., and *Y. enterocolitica*. Because there are no diagnostic criteria for ReA, the case definition and the resulting incidences vary (*42*). The literature suggests that the incidence of ReA as a sequel to bacterial gastroenteritis varies by the enteric pathogen. For each of the bacterial enteric pathogens that precede ReA, we compiled papers that reported the proportion of cases that developed into ReA published in 2000 or later where all enteric cases were confirmed by a laboratory (Technical Appendix 1 Table 4). Because there is still quite a bit of variation in incidence in studies by pathogen, the median and range for *Campylobacter* spp., nontyphoidal *Salmonella* spp., *Shigella* spp., and *Y. enterocolitica* from the studies in Technical Appendix 1 Table 4 were calculated for the sequelae multiplier and used to simulate a distribution of the plausible proportion of cases that result in this sequel using an alternate PERT or PERT distribution, respectively. From the literature, we assume that 7% (range 2.8%-16%) of foodborne *Campylobacter* spp., 8.5% (range 0%-26%) of foodborne nontyphoidal *Salmonella* spp., 9.7% (range 1.2%-9.8%) of foodborne *Shigella* spp., and 12% (range 0%-23.1%) of foodborne *Y. enterocolitica* result in ReA. These distributions were then applied to the estimates of domestically acquired foodborne cases for each of the preceding bacterial pathogens.

Technical Appendix 1 Table 4. ReA incidence* by foodborne pathogen, Australia, 2010

Reference	Study years	Study type	Country	ReA cases/gastroenteritis cases
				ReA cases/*Campylobacter* spp. cases
Schonberg-Norio et al. (*45*)	2002	Cross sectional	Finland	8/201 (4.0%)
Doorduyn et al. (*46*)	2005	Case–control	The Netherlands	20/434 (4.6%)
Townes et al. (*47*)	2002–2004	Cohort	USA	302/2384 (12.7%)
Schiellerup et al. (*48*)	2002–2003	Case–case comparison	Denmark	131/1003 (13.1%)
Pope et al. (*49*)	1966–2006	Review	Europe	1%–5%
Rees et al. (*50*)	1998–1999	Cohort	USA	9/324 (2.8%)
Hannu (*51*)	1997–1998	Cohort	Finland	45/609 (7.4%)
Locht and Krogfelt (*52*)	1997–1999	Cohort	Denmark	27/173 (15.6%)
				ReA cases/nontyphoidal *Salmonella* spp. cases
Arnedo-Pena et al. (*53*)	2005	Outbreak study	Spain	6/67 (9%)
Doorduyn et al. (*46*)	2005	Case–control	The Netherlands	8/181 (4.4%)
Townes et al. (47)	2002–2004	Cohort	USA	204/1356 (15.0%)
Schiellerup et al. (*48*)	2002–2003	Case–case comparison	Denmark	104/619 (16.8%)
Lee et al. (*54*)	1999	Outbreak study	Australia	38/261 (14.6%)
Rees et al. (*50*)	1998–1999	Cohort	USA	2/100 (2.0%)
Buxton et al. (*55*)	1999–2000	Case–control	Canada	17/66 (25.7%)
Hannu et al. (*56*)	1999	Outbreak study	Finland	5/63 (7.9%)
Rudwaleit et al. (*57*)	1998	Outbreak study	Germany	0/286 (0%) (children only)
Urfer et al. (*58*)	1993	Outbreak study	Switzerland	1/156 (0.6%)
				ReA cases/*Shigella* spp. cases
Townes et al. (*47*)	2002–2004	Cohort	USA	29/298 (9.7%)
Schiellerup et al. (*48*)	2002–2003	Case–case comparison	Denmark	10/102 (9.8%)
Rees et al. (*50*)	1998–1999	Cohort	USA	1/81 (1.2%)

Reference	Study years	Study type	Country	ReA cases/gastroenteritis cases
				ReA cases/*Yersinia enterocolitica* cases
Huovinen et al. (*59*)	2006	Case–control	Finland	11/248 (4.4%)
Townes et al. (*47*)	2002–2004	Cohort	USA	5/35 (14.3%)
Schiellerup et al. (*48*)	2002–2003	Case–case comparison	Denmark	21/91 (23.1%)
Rees et al. (*50*)	1998–1999	Cohort	USA	0/8 (0%)
Hannu et al. (*60*)	1998	Outbreak study	Finland	4/33 (12.1%)

*Incidence of ReA after *Campylobacter* spp. infection: median 7%, range 2.8%–16%; after *Salmonella* spp. infection: median 8.5%, range 0%–26%; after *Shigella* spp. infection: median 9.7%, range 1.2%–9.8%; after *Yersinia enterocolitica* infection: median 12%, range 0%–23.1%. ReA, reactive arthritis. Nontyphoidal *Salmonella* spp., nontyphoidal *S. enterica* serotypes.

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