

FROM FARM TO FORK TO PHYSICIAN

Assessing the Long-term Sequelae of Foodborne Illness

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A GLOBAL ISSUE



21 billion food animals raised to feed world's **6.5 billion people**.

26% of land surface used for grazing.

33% of arable land used to grow feed.

70% of emerging infectious diseases are zoonotic.

THE PUBLIC HEALTH IMPACT



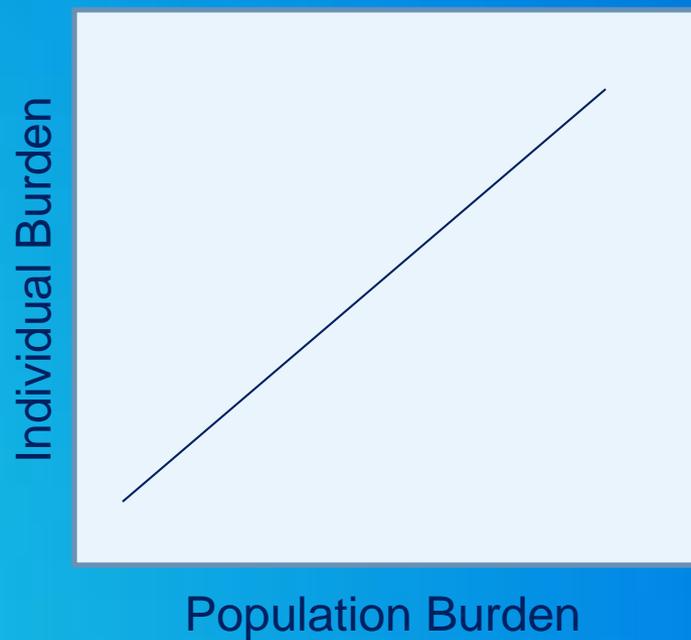
World Health
Organization

- **2 billion cases** of diarrheal disease worldwide.
- **1.8 million deaths**, predominantly children.
- Leading cause of child mortality and morbidity.
- Mostly results from contaminated food/water.
- Affects **up to 30%** in industrialized countries.

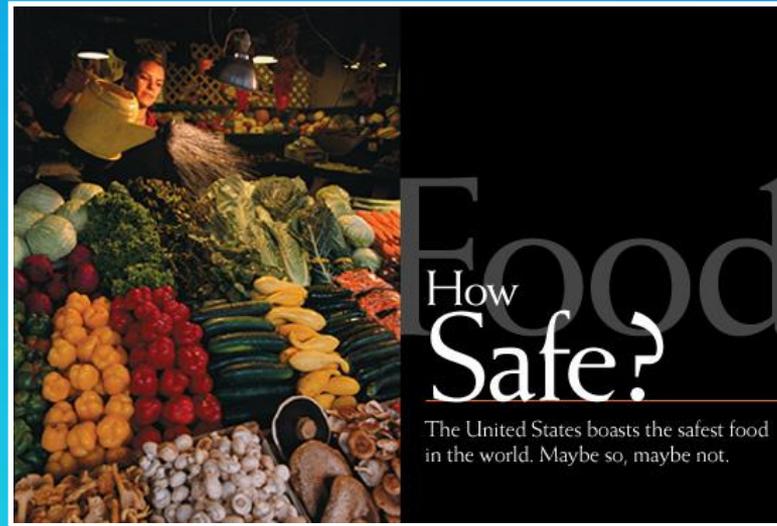
Source: WHO, <http://www.who.int/mediacentre/factsheets/fs330/en/>

UNDERSTANDING THE BURDEN

- Foundation for evidence-informed policy making
- Metrics: morbidity, mortality, severity, duration, disability, quality of life (DALY, QALY, etc)
- Two types of burden
 - Population burden
 - Individual burden
- Estimates inform
 - Attribution analyses
 - Economic assessments
 - Priority setting



U.S. BURDEN OF DISEASE ESTIMATES



48 million Americans are sickened,

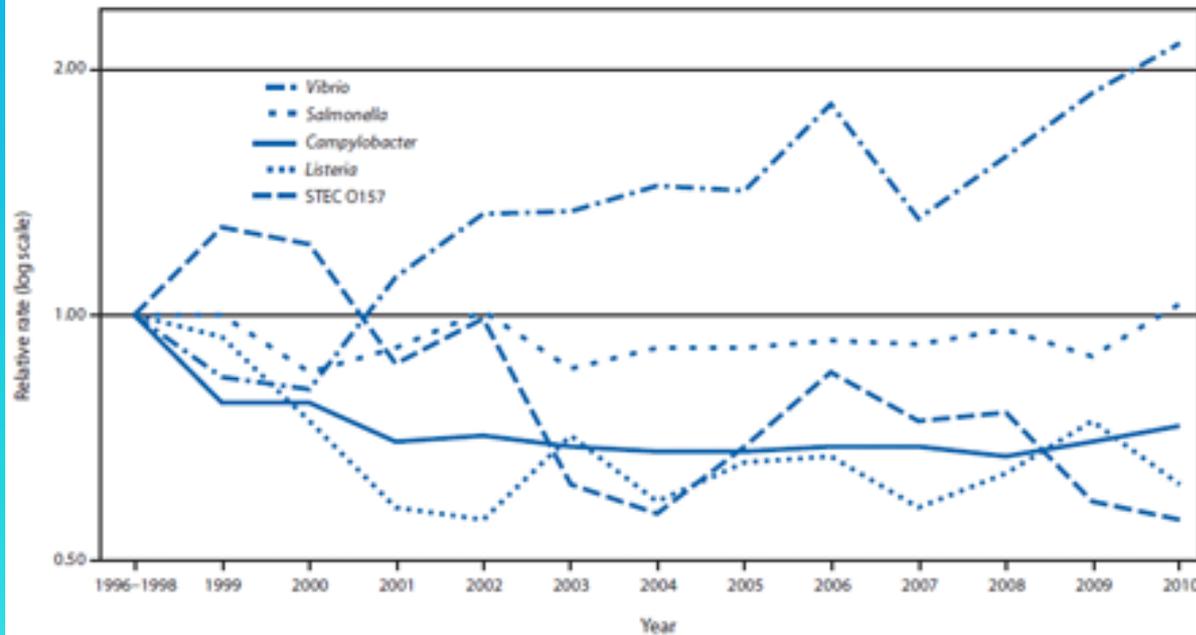
128,000 are hospitalized

and **3,000** die each year from food-borne illnesses.

Source: Centers for Disease Control and Prevention. <http://www.cdc.gov/foodborneburden>

TRENDS IN REPORTED CASES

FIGURE 1. Relative rates of laboratory-confirmed infections with *Campylobacter*, STEC O157, *Listeria*, *Salmonella*, and *Vibrio*, compared with 1996--1998 rates, by year --- Foodborne Diseases Active Surveillance Network, United States, 1996—2010



Source: Centers for Disease Control and Prevention. *Incidence and Trends of Infection with Pathogens Transmitted Commonly Through Food --- Foodborne Diseases Active Surveillance Network, 10 U.S. Sites, 1996--2010* MMWR 2011; 60(22);749-755

DISEASE BURDEN TOP 10

	Pathogen	QALY Loss	Cost	Illnesses	Deaths
1	<i>Salmonella</i>	16,782	3,309	1,027,561	378
2	<i>Toxoplasma gondii</i>	10,964	2,973	86,686	327
3	<i>Campylobacter</i>	13,256	1,747	845,024	76
4	<i>Listeria monocytogenes</i>	9,651	2,655	1,591	255
5	<i>Norovirus</i>	5,023	2,002	5,461,731	149
6	<i>E. coli</i> O157:H7	1,565	272	63,153	20
7	<i>Clostridium perfringens</i>	875	309	965,958	26
8	<i>Yersinia enterocolitica</i>	1,415	252	97,656	29
9	<i>Vibrio vulnificus</i>	557	291	96	36
10	<i>Shigella</i>	1,415	121	131,254	10

Source: Batz M, Hoffman S, Morris JG. *Ranking the risks: The 10 Pathogen-Food Combinations with the greatest burden on public health.* 2011

LONG-TERM SEQUELAE

- FDA estimates that 2% to 3% of all cases develop secondary long-term sequelae.
- Probability of consequences vary by
 - Pathogen
 - Age and health status of individual
- Convened group of medical experts to explore five pathogen-consequence pairs.
- Published a white paper summarizing current knowledge on long-term health outcomes.

LONG-TERM SEQUELAE

Pathogen	Sequelae
<i>Campylobacter</i>	GBS, ReA, carditis, cholecystitis, endocarditis, meningitis, pancreatitis, septicemia
<i>E. coli</i> O157:H7	HUS, neurological problems, diabetes, gallstones, hypertension, irritable bowel syndrome, intestinal strictures, pneumonia
<i>Listeria monocytogenes</i>	Meningitis, neurological dysfunction, sepsis
<i>Salmonella</i>	ReA, aortitis, cholecystitis, colitis, endocarditis, epididymo-orchitis, meningitis, osteomyelitis, pancreatitis, septicemia, splenic abscess
<i>Toxoplasma gondii</i>	Mental retardation, visual impairment, central nervous system disease, encephalitis, pancarditis, polymyositis, retinochoroiditis,

Source: Council for Agricultural Science and Technology (CAST). *Foodborne pathogens: risks and consequences*. CAST, Ames, IA 1994.

CAMPYLOBACTER

- One of most common causes of diarrheal illness in U.S.
- Causes about 2.5 million illnesses and 100 deaths each year.
- Almost 20% of reported cases occur in children under age 10.
- Incidence in infants under 1 year is twice that in general population.
- **Major source:** Undercooked meat/poultry.
- **Symptoms:** Fever, diarrhea, abdominal cramps.

Sources: Centers for Disease Control and Prevention, www.cdc.gov

Shea, Katherine, MD and the Committee on Environmental Health and Committee on Infectious Diseases. *Nontherapeutic Use of Antimicrobial Agents in Animal Agriculture: Implications for Pediatrics*. American Academy of Pediatrics, n.d., p. 8 of 24. <http://pediatrics.aappublications.org/cgi/content/full/114/3/862>

CAMPYLOBACTER & GBS

- Approximately 1 out of every 1,000 illnesses will result in Guillian-Barre Syndrome.
- GBS: an autoimmune reaction
 - GBS causes acquired paralysis & hospitalization
 - Permanent disability varies with age
 - 100 GBS patients die each year
- *Campylobacter* is the most common trigger
 - 40% of the 5,500 GBS cases in U.S. each year

E. COLI 0157:H7

- Causes an estimated 73,000 illnesses and 61 deaths/year.
- Very low infectious dose – less than 10 microbes.
- Most recover but consequences can be very serious.
- Nearly half of reported cases occur in children under age 5.
- 2% - 7% of cases result in Hemolytic Uremic Syndrome (HUS).
- **Major source:** Undercooked meat and raw produce; also petting zoos and contact with farm animals.
- **Symptoms:** Severe/bloody diarrhea, abdominal cramps.

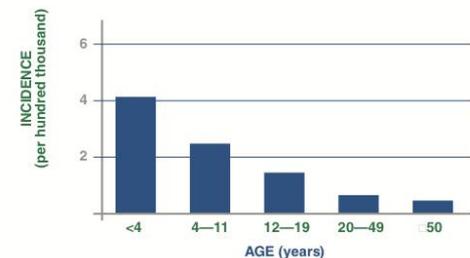
Sources: Centers for Disease Control and Prevention, www.cdc.gov

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E. COLI O157:H7 & HUS OUTCOMES

- Children have highest incidence of STEC infection and at greatest risk for developing HUS.
- ~15% develop Hemolytic Uremic Syndrome (HUS)
- Leading cause of acute kidney failure in children under age 5 in U.S.
- Most recover but consequences can be very serious:
 - Renal sequelae
 - Hypertension
 - Diabetes
 - Cardiovascular disease
- 3% - 5% of die.

FIGURE 3:
Incidence of *E. coli* O157:H7 Infections by Age, 2008



Source: Centers for Disease Control and Prevention (CDC). Preliminary FoodNet data on the incidence of infection with pathogens transmitted commonly through food—10 States, 2008. *MMWR*, 2009; 58 (13):333-7.

LISTERIA MONOCYTOGENES

- Causes an estimated 2,500 illnesses and 500 deaths/year.
- Most cases are foodborne.
- Pregnant women 20 times more likely to develop *listeriosis* and ~1/3 of reported cases occur in pregnant women.
- Kills more than 1/3 of its perinatal victims.
- Newborns frequently suffer from sepsis or meningitis.
- **Major source:** deli meat, hot dogs, soft cheeses
- **Symptoms:** Mild flu-like symptoms (fever, muscle aches).

Sources: Centers for Disease Control and Prevention, www.cdc.gov

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LISTERIA HEALTH OUTCOMES

- **Infants with acute listeriosis**
 - 80% recover
 - 20% have long-term health outcomes
 - 20% mild disability & often need education assistance
 - 60% moderate to severe disability
 - 20% total impairment with life-long residential care
- **Adult cases in Netherlands study**
 - Acute illness seizures, cardio-respiratory failure
 - 60% recover, 40% die or seriously disabled

SALMONELLA

- Causes about 1.5 million illnesses and 600 deaths/year.
- Causes many serious acute disease, like meningitis.
- Incidence of antibiotic-resistant strains is increasing.
- More than 1/3 of all reported cases occur in children < 10.
- Children < 1 year are 10 times more likely to be sickened.
- Children are at increased risk of infection with antibiotic-resistant strains and great risk of severe complications.
- **Major source:** Various foods; contact with reptiles.
- **Symptoms:** Fever, diarrhea, abdominal cramps.

Sources: Centers for Disease Control and Prevention, www.cdc.gov

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SALMONELLA & REACTIVE ARTHRITIS

- Leading predictor for reactive arthritis (ReA).
- ReA causes painful and swollen joints and can greatly affect quality of life.
- Rates vary from 2.3% to 15%.
- Raybourne et al.
 - 40% recover
 - 60% develop progressive or recurrent arthritis

TABLE 2:

Pathogens associated with self-reported ReA symptoms

Pathogen	Percent with Symptoms
<i>Salmonella</i>	15
<i>Yersinia</i>	14.3
<i>Campylobacter</i>	12.7
<i>Shigella</i>	9.7
<i>E. Coli</i> O157:H7	8.9

Source: Townes, J.M., A.A. Deodhar, E.S. Laine et al. Reactive arthritis following culture-confirmed infections with bacterial enteric pathogens in Minnesota and Oregon: a population-based study. *Ann Rheum Dis*, 2008; 67:1689-96.

TOXOPLASMA GONDII

- **Acute toxoplasmosis, 50% foodborne**
 - 112,500 illnesses, 2,500 hospitalizations, 375 deaths
 - **Affects pregnant women and unborn children.**
 - **Major source:** Cat feces, soil and undercooked meat.
 - **Symptoms:** Few flu-like symptoms.
- **80% of newborns impaired by 17th year**
 - 33% have severe mental retardation
 - 17% moderate mental retardation
 - 8% blind in both eyes
 - 53% moderate visual impairment

CONCLUSIONS

- **Most foodborne pathogens have both acute illness outcomes & long-term outcomes.**
- **Few guidelines for medical care of long-term outcomes.**
- **Need follow-up studies to assess the connections between acute foodborne illness & long-term outcomes.**
- **Population-based studies, improved public health surveillance, and increased data sharing to improve knowledge.**
- **Long-term health outcome studies will help prioritize foodborne pathogen control goals.**

FILLING IN THE GAPS

- Received grant to examine feasibility (and benefit) of systematically studying long-term health sequelae of foodborne illness.
- Framework for assessing feasibility
 1. Evaluation of stated purpose
 2. Review of function, duration and scope
 3. Consideration of existing alternative data sources
 4. Assessment of practical feasibility
 5. Likelihood of sufficient start-up, long-term funding
 6. Evaluation of cost-effectiveness

Source: Solomon et al. Evaluation and Implementation of Public Health Registries. *Public Health Reports*. 1991; 106(2):142-150.

RESEARCH IN PROGRESS: ACUTE GE & IBS

- Acute gastroenteritis has been associated with the development of post-infectious irritable bowel syndrome.
- Pilot study will explore the association between acute GE and IBS in the Netherlands.
- Cohort study using electronic medical database.
- Estimate relative risk of developing IBS one year post acute GE and identify potential risk factors.
- Results will provide preliminary data for larger prospective study of IBS in the Netherlands.

IRRITABLE BOWEL SYNDROME

- **Chronic gastrointestinal disorder with no structural cause**
- **Characterized by episodic abdominal pain and altered bowel habits**
- **Affects ~ 12% of global population; 10% to 20% of Western populations**
- **Causes significant morbidity, places substantial burden on healthcare systems, greatly affects quality of life**
 - **Accounts for 2.4 to 3.5 million physician visits in U.S.**
- **Etiology, pathogenesis, prognosis not well understood**

POST-INFECTIOUS IBS

- Acute gastroenteritis (GE) can increase risk of IBS.
 - Two studies estimated 10% and 17% of IBS patients had previous GE.
 - Case-control study found significant association between IBS and GE (OR 3.72).
 - Meta-analysis of 18 studies found excess relative risk of 4.86 (95% CI: 2.6-8.54) for IBS in patients with GE.
- Disease burden in NL estimated to be 2,300 DALYs.
- Risk Factors: Severity of GE, antibiotic use, younger age, female gender, smoking, education level, psychosocial factors, health care seeking behaviors.

STUDY DESIGN

- **Prospective cohort study in Dutch population**
- **Primary Care Network Utrecht (PCNU)**
 - **Routine primary care data on cohort of patients**
 - **38 general practitioners in 6 primary care centers**
 - **Approximately 60,000 patients consult annually**
 - **ICPC coded diagnosis, ATC coded prescriptions/referrals entered into centralized database**

STUDY HYPOTHESIS AND AIMS

Hypothesis

IBS is frequent long-term sequelae of GE in Netherlands.

Aim 1: Determine annual incidence of GE consultations in PCNU by age and sex.

Aim 2: Estimate relative risk of IBS one year post-GE in patients compared to unexposed individuals.

Aim 3: Identify risk factors associated with IBS in patients with history of GE.

INCLUSION/EXCLUSION CRITERIA

- Patients aged 18 to 70 years
- PCNU consultation between 1998 and 2009
- At least one year of data in PCNU database
- Patients with Hx of cancer, alcohol abuse, GE symptoms in prior 12 months, IBD, prior IBS diagnosis, abdominal surgery, 5+ prescriptions associated with IBS/IBD excluded.
- Patients with ICPC codes for GE identified as exposed cohort.
- Patients without GE seen for unrelated medical reason randomly selected for comparison cohort.
 - Matched by age, sex, PCNU practice, time of visit

EXPOSURE/OUTCOME DEFINITIONS

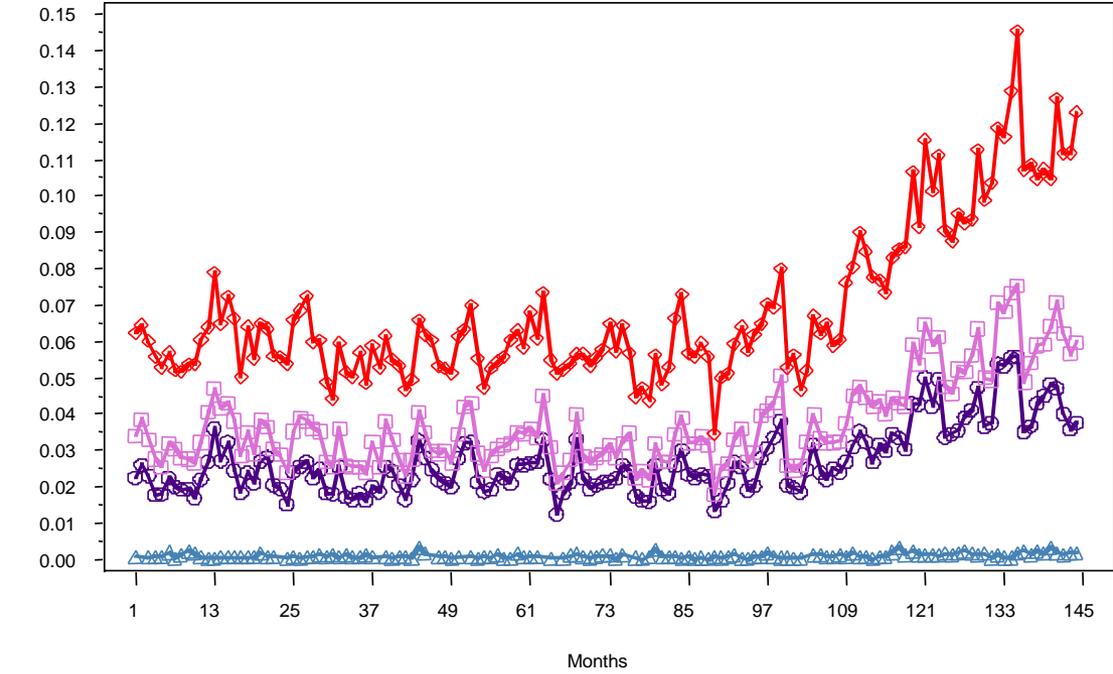
Exposures	
GE Confirmed	Gastrointestinal infection (D70)
GE Presumed	Gastrointestinal infection (D70), Gastroenteritis presumed infection (D73), Diarrhea (D11)
GE Symptomatic	Gastrointestinal infection (D70), Gastroenteritis presumed infection (D73), Diarrhea (D11), Nausea (D09), Vomiting (D10)
GE Broad	Gastrointestinal infection (D70), Gastroenteritis presumed infection (D73), Diarrhea (D11), Nausea (D09), Vomiting (D10), Abdominal pain (D06), Flatulence/gas/belching (D08)
Outcomes	
IBS	Irritable bowel syndrome (D93)
FBD	Irritable bowel syndrome (D93), Diverticular disease (D92), Chronic enteritis/ulcerative colitis (D94)

STATISTICAL METHODS

- Sample size of 4,206 per cohort group will provide at least 90% power to detect relative risk of 2 for IBS at 0.05 significance level.
- GE and IBS incidence rates calculated as proportion of patients (person years) seen in PCNU in given year.
- Estimate relative risk using Poisson regression adjusting for age, sex, practice. Negative binomial used if over-dispersion.
- Risk factors tested using univariate and multivariate logistic regression using backward elimination.

RESULTS – TRENDS IN INCIDENCE

Incidence rate per personmonths



diagclass  GE (Confirmed)  GE (Presumed)
 GE (Symptomatic)  GE (Broad)

RESULTS – COHORT SUMMARY

	Patients	Number Events
Total	23,451	50,503
Included Patients	6,173	11,808
• Included events	6,173	11,316
• Excluded events	332	492
Excluded Patients	17,278	38,695
• Excluded Age	9,208	19,248
• Excluded ICPC	8,341	21,924
• Less than one year in PCNU	3,492	5,319
• Less than one year of follow-up	2,235	2,742
• GE in prior 12 months	5,889	14,679
• > 5 excluded medications	418	2,479

RESULTS – RELATIVE RISK OF IBS AND FBD

	FBD Relative Risk (95% CI)	IBS Relative Risk (95% CI)
GE Confirmed	0/132 (0%) 9/137 (6.6%) 18.31 (1.08, 311.5)	0/132 (0%) 6/137 (4.4%) 12.53 (0.71, 220.23)
GE Presumed	13/2386 (0.5%) 83/2424 (3.4%) 6.18 (3.45, 11.06)	9/2386 (0.4%) 66/2464 (2.7%) 7.10 (3.55, 14.22)
GE Symptom	15/3013 (0.5%) 102/3128 (3.3%) 6.55 (3.82, 11.24)	10/3013 (0.3%) 83/3128 (2.7%) 7.99 (4.16, 15.38)
GE Broad	29/5967 (0/5%) 252/6173 (4.1%) 8.40 (5.73, 12.32)	20/5967 (0.3%) 201/6173 (3.3%) 9.71 (6.14, 15.36)

RESULTS – RISK FACTORS (IBS)

Risk Factor	GE Confirmed RR (95% CI)	GE Presumed RR (95% CI)	GE Symptom RR (95% CI)	GE Broad RR (95% CI)
Gender		0.82 (0.68, 0.99)		
SES		0.77 (0.65, 0.91)	0.76 (0.64, 0.91)	0.87 (0.77, 0.97)
Consultation frequency		1.45 (1.02, 2.07)	1.44 (1.05, 1.96)	1.57 (1.27, 1.93)
Multiple GE		1.85 (1.04, 3.29)	1.96 (1.19, 2.21)	1.93 (1.44, 2.16)
Concomitant Cramps		7.73 (3.0, 19.93)	4.92 (1.79, 13.53)	2.90 (1.62, 5.19)

LIMITATIONS

- PCNU patients may not be representative of entire Dutch population.
- Many GE patients do not seek medical care.
- Healthcare seeking behaviors may be related to severity of disease.
- Criteria used to diagnose GE and IBS can greatly impact results.
- Due to lack of stool studies, cannot verify cause of GE.
- Absence of data on pre-morbid bowel habits precludes identifying undiagnosed IBS.
- Limited amount of electronic information

CONCLUSIONS

- **GE and IBS/FBD represent significant burden in the Netherlands.**
- **Increased risk of IBS and FBD following GE**
- **Female gender, SES, consultation frequency, multiple GE, abdominal cramps associated with increased risk of IBS.**
- **Due to study limitations, several questions remain about underlying biology of GE and IBS.**
- **Prospective studies are needed to assess the risk of IBS and FBD following foodborne disease.**

FUTURE DIRECTIONS

- Systematic literature reviews of long-term sequelae
 - *Campylobacter*
 - *Salmonella*
 - *Listeria monocytogenes*
 - Shiga-toxin producing *E. coli* (STEC)
- Workshop on disease burden and long-term sequelae
- Peer-reviewed publications and scientific white paper
- Targeted pilot project to assess long-term sequelae

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QUESTIONS?

Thank You!

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