Emerging Evidence on Causality for other Post-infectious Chronic GI Conditions

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The views expressed in this presentation are those of the author and do not reflect the official policy or position of the Department of the Navy, Department of Defense, or the U.S. Government .

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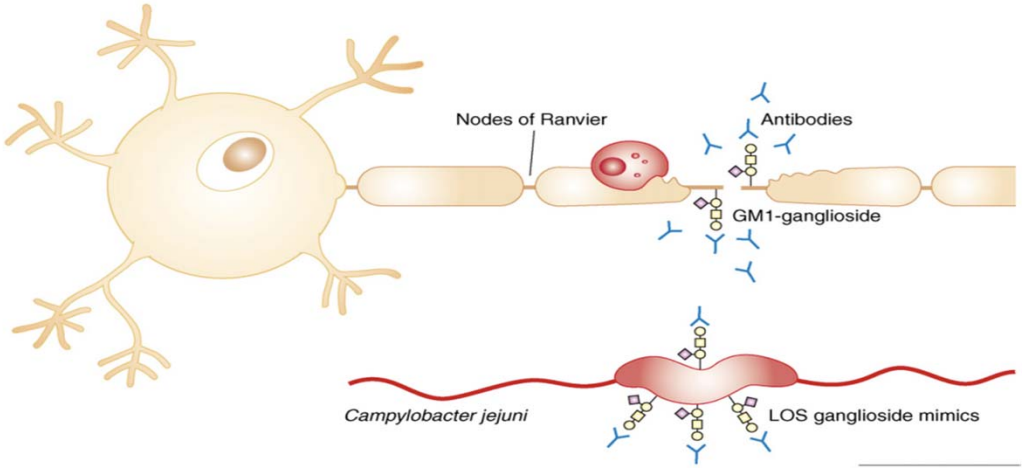
On the notion of causality…

Example: Campylobacter and Guillain-Barré Syndrome

- **Campy most common global bacterial food-borne infection**
- **GBS is leading cause of paralysis worldwide**
- **1 GBS case per 1,058 Campy infections**
- **Multiple epi studies**



Guerry P and Szymanski C, *Trends Microbiol* 2008;16:428

Bradford-Hill Criteria:

✓ Strength	✓ Temporality	✓ Coherence
✓ Consistency	✓ Biological gradient	✓ Experiment
✓ Specificity	✓ Plausibility	✓ Analogy

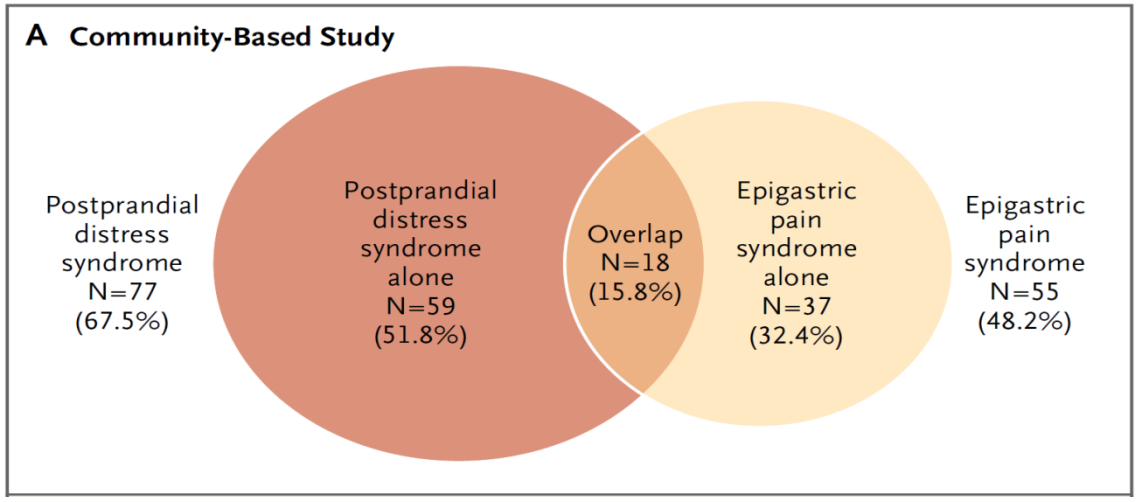
Functional Dyspepsia (FD)

FD Subtype*	Rome IV 2016	Rome III 2006
Post-prandial Syndrome (PDS)	Bothersome early satiety or postprandial fullness ≥ 3 days per week in the past 3 months.	Early satiety or postprandial fullness ≥ 1 day per week in the past 3 months.
Epigastric Pain Synd. (EPS)	Bothersome epigastric pain or epigastric burning ≥ 1 day per week in the past 3 months.	Epigastric pain or epigastric burning ≥ 1 day per week in the past 3 months.

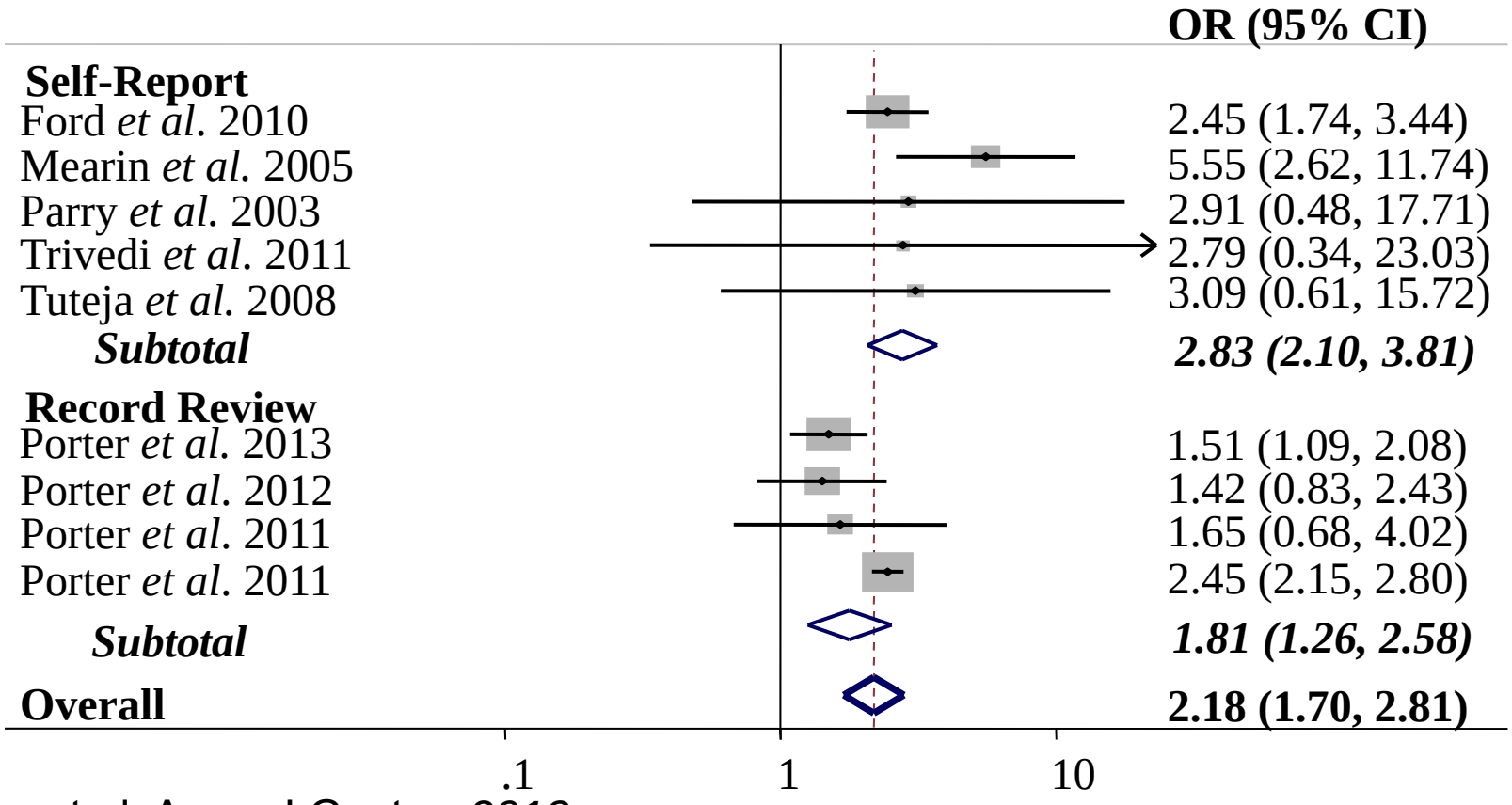
*All require symptoms for at least 6 months

- **Not a single disorder**
- **Prevalence: 10 – 20%**
- **East/West differences in epidemiology**
- **Association with anxiety is bidirectional**

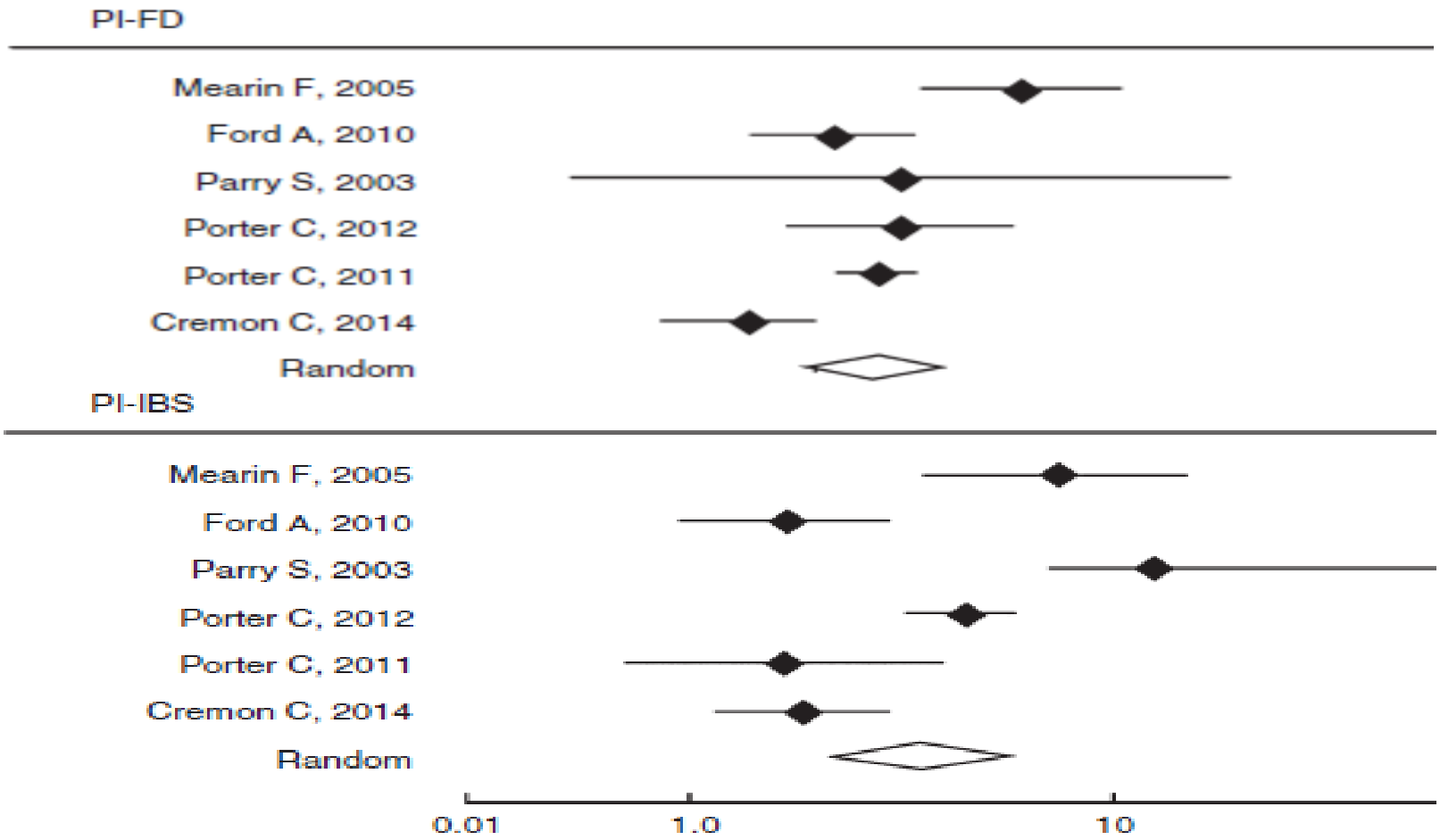
Talley & Ford, NEJM, 2015



Dyspepsia – the PI link



Pike et al. Amer J Gastro. *2013*



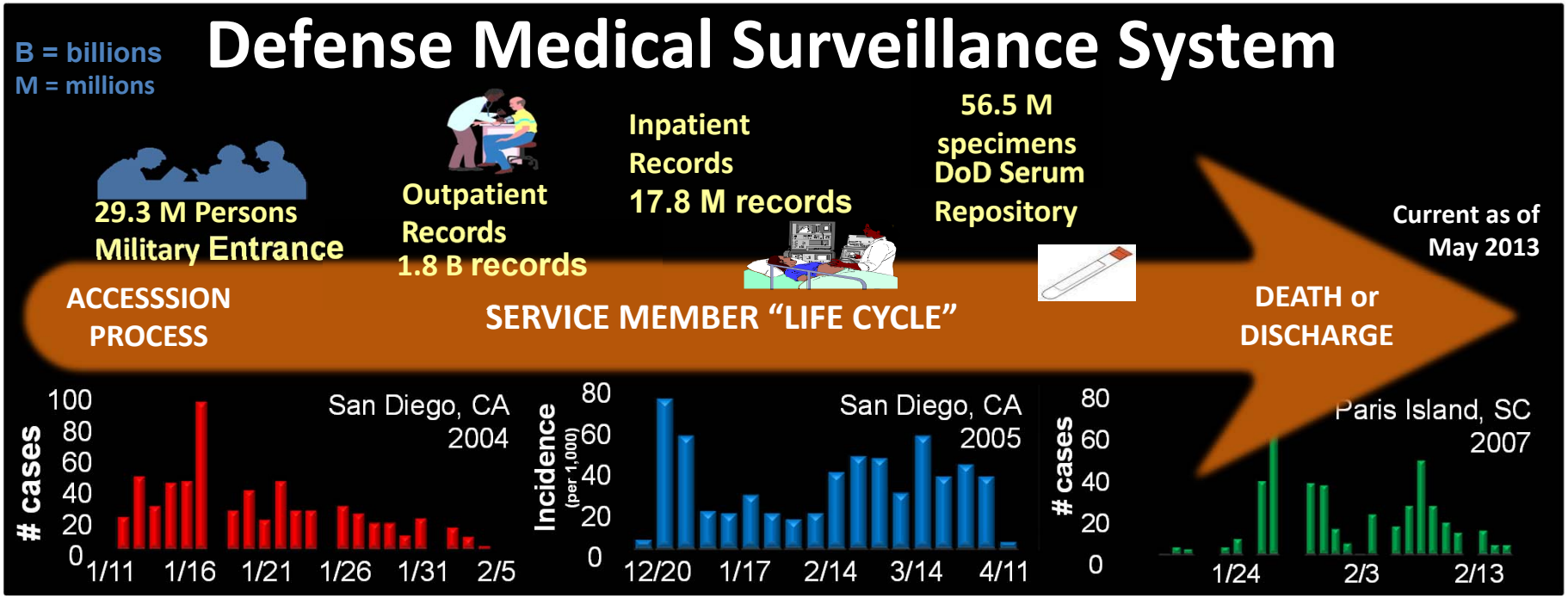
Futugami et al. Aliment Pharmacol Ther **2015**; 41: 177–188

"Don't Worry it's Just a Viral Gastroenteritis"

Postinfectious Gastrointestinal Disorders Following Norovirus Outbreaks

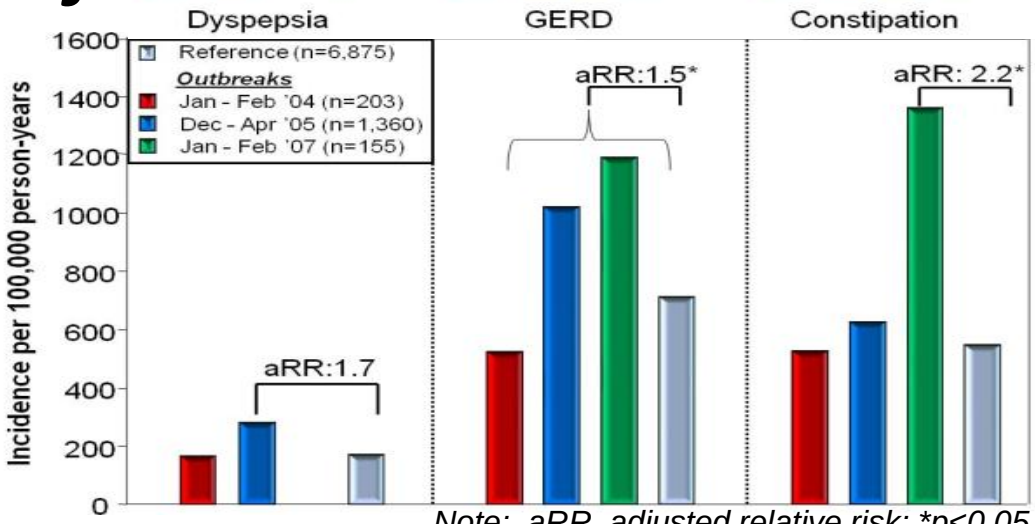
Chad K. Porter,[1] Dennis J. Faix,[2] Danny Shiau,[3] Jennifer Espiritu,[4] Benjamin J. Espinosa,[4] and Mark S. Riddle[1]

CID 2012:55 (1 October) • 915

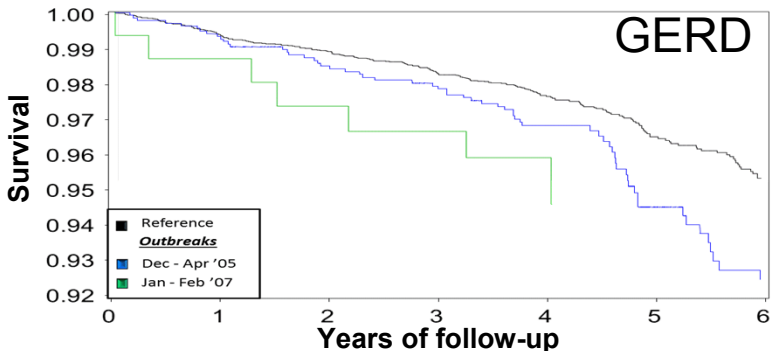


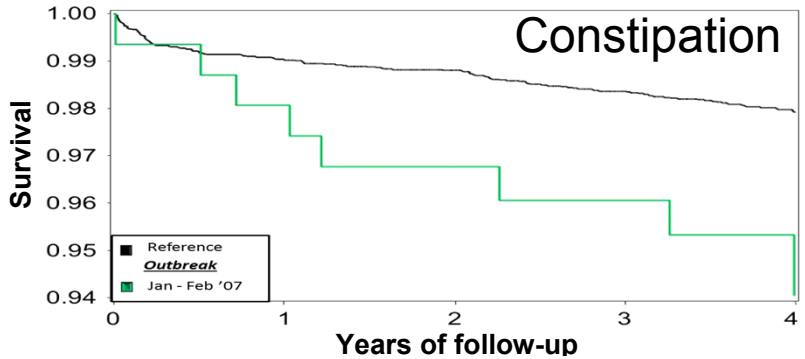
Reflux disease and constipation, but not IBS associated with confirmed NoV outbreaks

- Risk may vary by outbreak (genotype/strain variation?)
- Dysfunction in gastric accommodation / delayed gastric emptying identified in PI-dyspepsia (Tack, 2002; Futagami, 2010)



*Note: aRR, adjusted relative risk; *p<0.05*





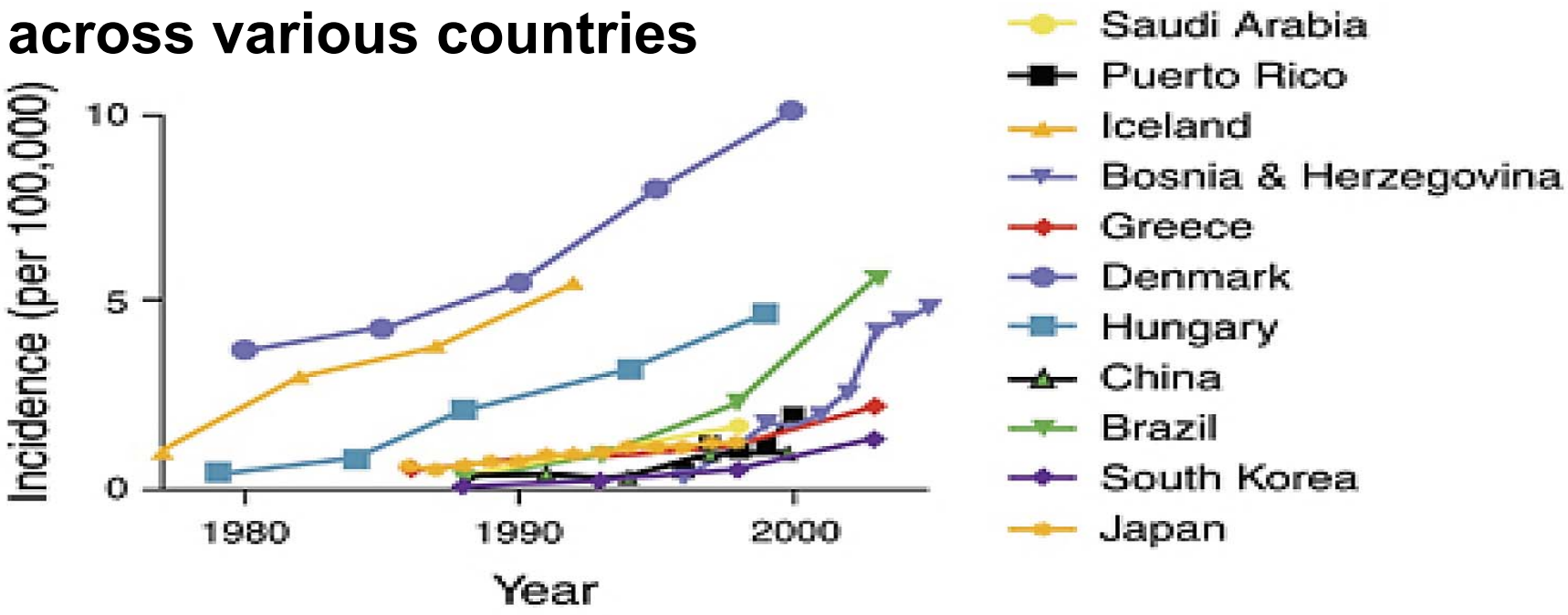
Understanding disease mechanisms

References	Subjects	Inflammatory cells in GI tract
Walker *et al.*[62]	PDS patients	Duodenal eosinophilia
Futagami *et al.*[5]	PI-FD	Duodenal eosinophilia
		Increased duodenal macrophages
		Increased CCR2-/CD68-double positive cells
Li *et al.*[28]	PI-FD	Increased mast cells, increased EC cells in the gastric mucosa
Kindt *et al.*[6]	PI-FD	Decreased $CD4^+$ cells
		Increased macrophages
		Surrounding the duodenal crypts
Dizdar *et al.*[7]	Giardia-induced PI-FD	Increased CCK producing EC cells
Talley *et al.*[32]	Unspecified FD	Duodenal eosinophilia

Futugami et al. Aliment Pharmacol Ther **2015**; 41: 177–188

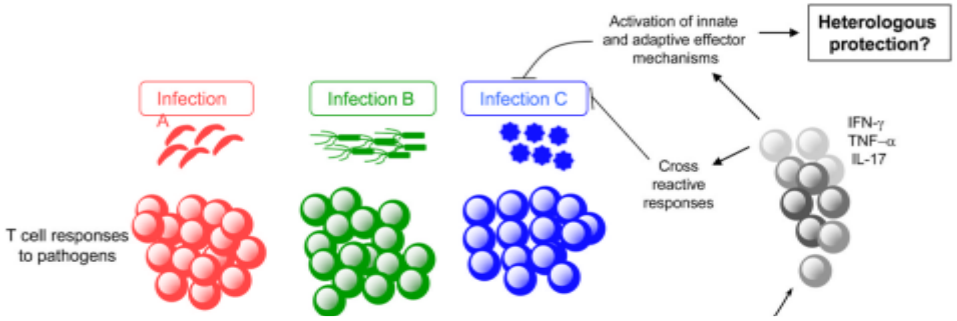
Inflammatory Bowel Disease

Crohn's disease incidence trends across various countries



Segal AW. **Making sense of the cause of Crohn's – a new look at an old disease** *F1000Research* 2016, **5**:2510

Potential Consequences of Commensal-Specific Memory T Cells



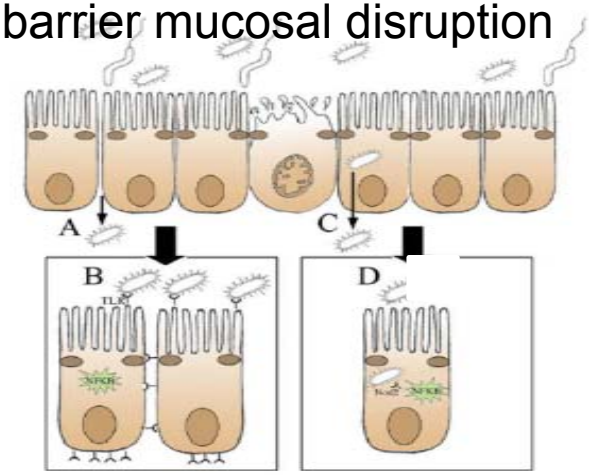
- Each infection at barrier surfaces represents an additional opportunity for the reactivation of commensal-specific T cells
- May be beneficial through promoting innate and adaptive effect mechanisms
- May be harmful if results in dysregulation of microbiome and/or altered barrier function

Belkaid Y. *Trends Immunol*. 2013.

Putative Pathogen-specific Trigger Mechanisms

Campylobacter jejuni

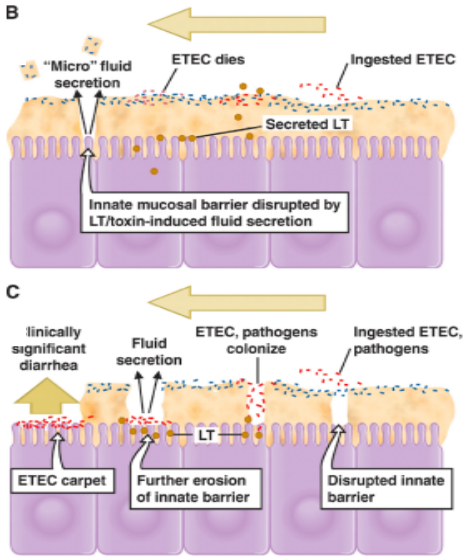
- Invasive organism and intestinal barrier mucosal disruption



A. Epithelial tight junctions disruption
B. Δ cellular polarity/receptor relocation
C. internalization of non-invasive *E. coli*
D. *Defective NOD2 interaction/regulation*

Enterotoxigenic *E. coli* (ETEC)

- Toxin-mediated effects on barrier disruption via lipid raft sloughing
- tight junction disruption
- "adjuvanted" response to commensals?



Kalischuk. 2009; Glenn. 2009.

Evidence linking IBD as a post-infectious sequela continues to accumulate, but is controversial

- Hermens DJ. *Gastroenterology* **1991**;101(1):254-62
  - Acute enteric Infections appear to be associated with relapses of IBD
- Schumacher G. *Scand J Gastroenterol Suppl* **1993**;198:1-24
  - 62% with first attack of IBD associated with diarrhea during travel/antibiotics
- Garcia Rodriguez LA. *Gastroenterol* **2006**;130(6):1588-94
  - IGE associated with 2.4X ▲ risk for IBD, greatest in first year (4.1X)
  - Risk of developing Crohn's disease in first year greatest (6.6X)
- Ternhag A. *Emerg Infect Dis* **2008**;14(1):143-8
  - 3X ▲ risk of IBD with 1 year after Campylobacter or Salmonella infection
- Porter CK. Gastroenterology **2008**
  - 2X ▲ risk of IBD in active duty members following IGE
- Gradel KO. *Gastroenterol* **2009**; doi: 10.1053
  - 2 – 3 X ▲ risk after Campylobacter or Salmonella infection
  - increased risk observed throughout the 15-year observation period

Gut The Controversy

Enteric *Salmonella* or *Campylobacter* infections and the risk of inflammatory bowel disease

Tine Jess et al. *Gut 2010*

"By finding risk associations that were consistently stronger for patients with negative stool tests than for those with positive stool tests, our study is the first to indicate that it is not the bacterial pathogens per se, but rather the testing activity as such that is associated with IBD risk."

"This strongly argues in favour of a non-causal association between Salmonella and Campylobacter infections and risk of IBD."

Gut 2011

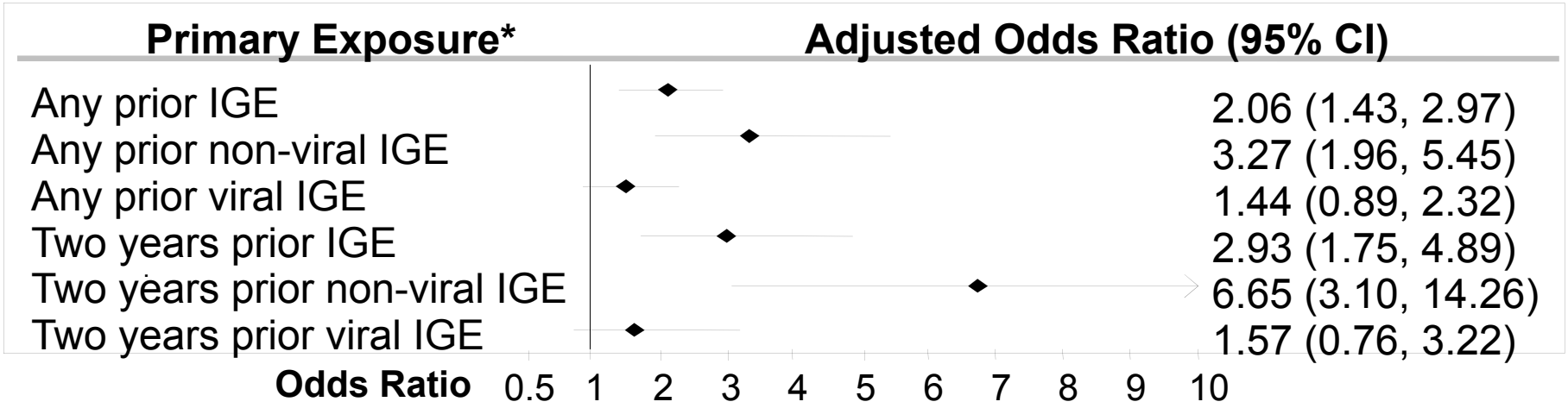
LETTER

Detection bias and the association between inflammatory bowel disease and *Salmonella* and *Campylobacter* infection **Mark S Riddle, Chad K Porter**

"…differential outcome surveillance between stool-culture-positive and -negative study groups may also explain the findings and should be considered in context of the results."

"…epidemiological studies should be interpreted within the context of additional emerging data on IBD pathogenesis, which suggests that IBD involves an inappropriate host response to intestinal microbes."

What about celiac disease?



Riddle et al. Am J Gastro 2012

Campylobacter-associated medical encounter had a 3.5-fold higher (0.15 per 100,000 person-years) rate of CD compared to unexposed individuals (p = 0.13). In contrast, no cases of CD were identified following infection with the other studied pathogens.

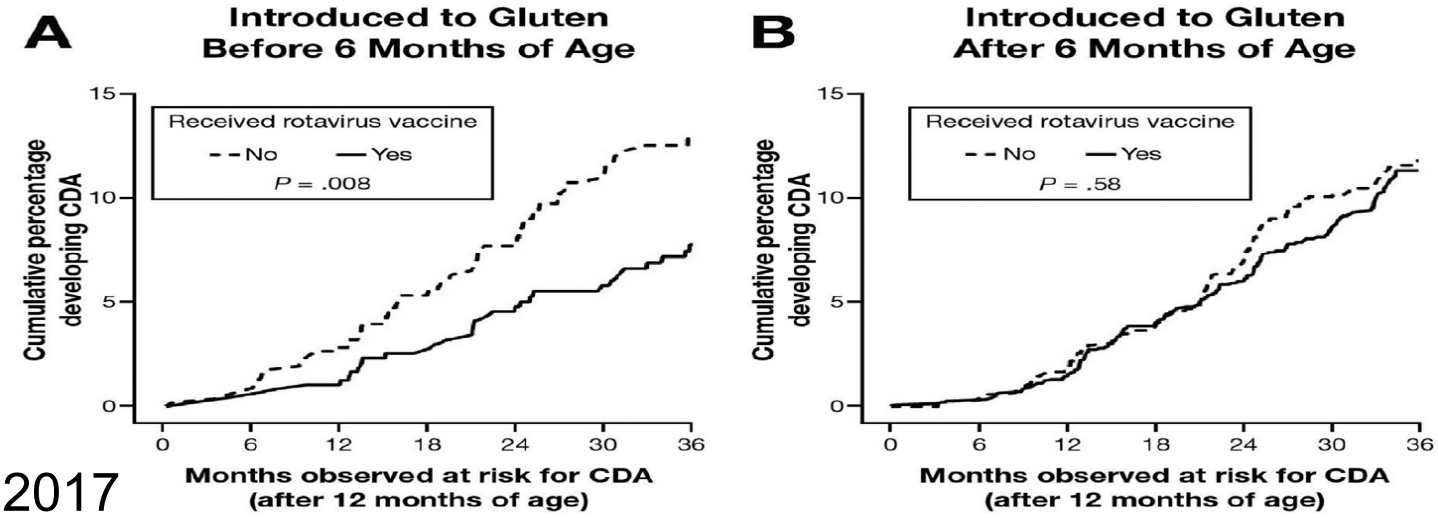
Riddle et al. Dig Dis Sci. 2013

Factors That Increase Risk of Celiac Disease Autoimmunity After a Gastrointestinal Infection in Early Life

Kaisa M. Kemppainen,* Kristian F. Lynch,‡ Edwin Liu,§ Maria Lönnrot,‖ Ville Simell,¶

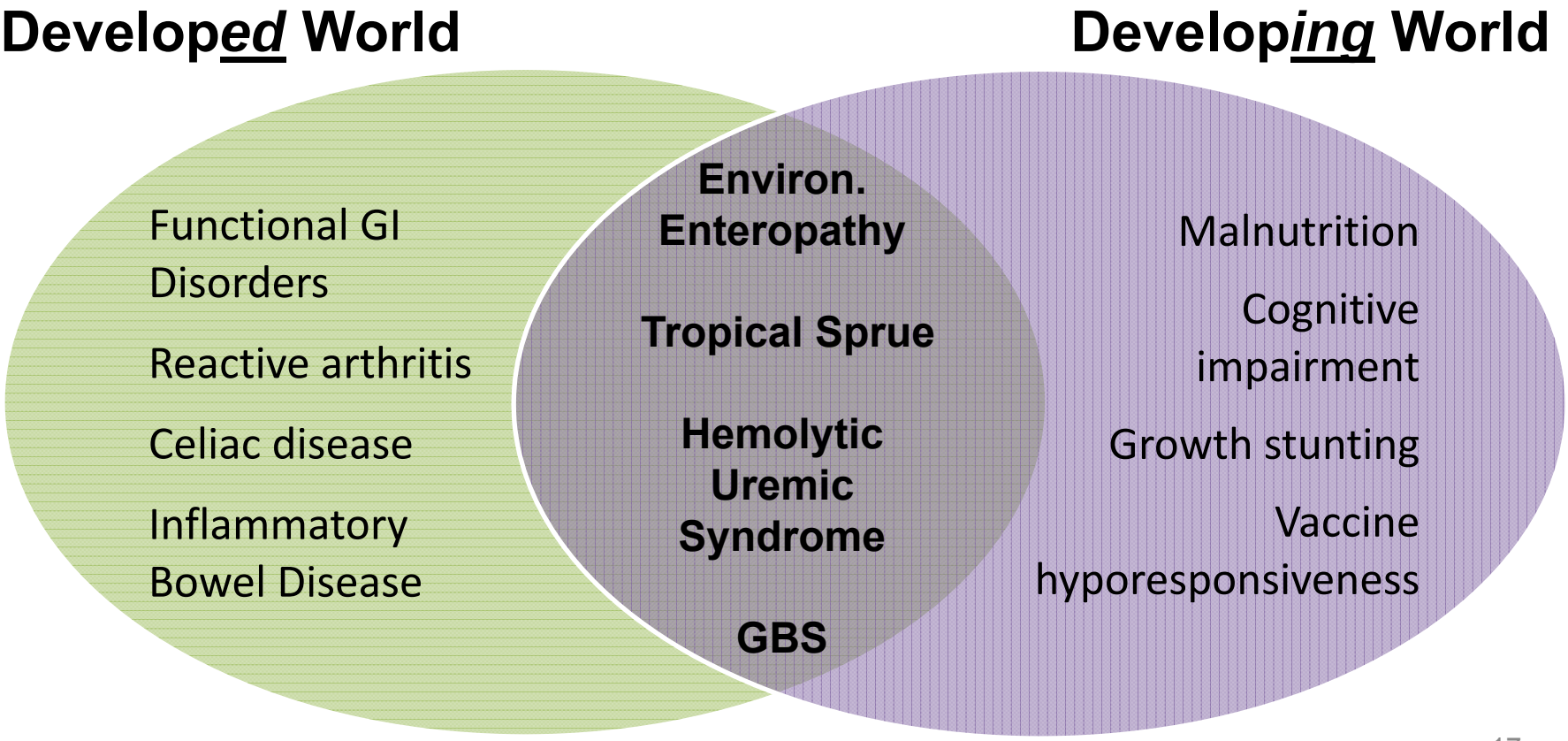
Clinical Gastroenterology and Hepatology

- 6327 children in the US and Europe carrying HLA risk genotypes for CD
- Monitored from 1-4 yrs of age for presence of tissue transglutaminase auto-Abs
- Parental reports of GI and resp infections collected q 3 months from birth.
- Time-varying covariates: infections, rotavirus vaccination, introduction of gluten, breastfeeding, and risk of celiac disease autoimmunity



In press, 2017

…and it's not just a Canadian problem



Causal association of post-enteric infectious sequelae: a summary of the evidence

	Strength / consistency	Specificity	Dose response	Temporality	Biol plaus
GBS					
Reactive arthritis					
IBS					
Dyspepsia					
GERD					
Constipation					
Func. Bloating					
Ulcerative colitis					
Crohns' Disease					
Celiac Disease					
Chronic fatigue					