Connecting the dots: Norovirus, Gut Microbiota and Post-infectious IBS

Ching Man Chan, Jenny
Mphil student
Supervisor: Dr. Martin Chan
Joint Graduate Seminar
Department of Microbiology, Faculty of Medicine, CUHK
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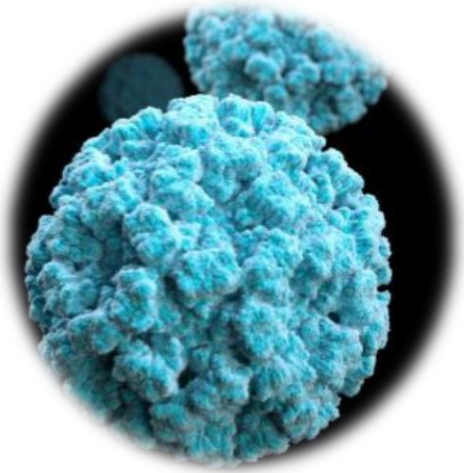
Outline

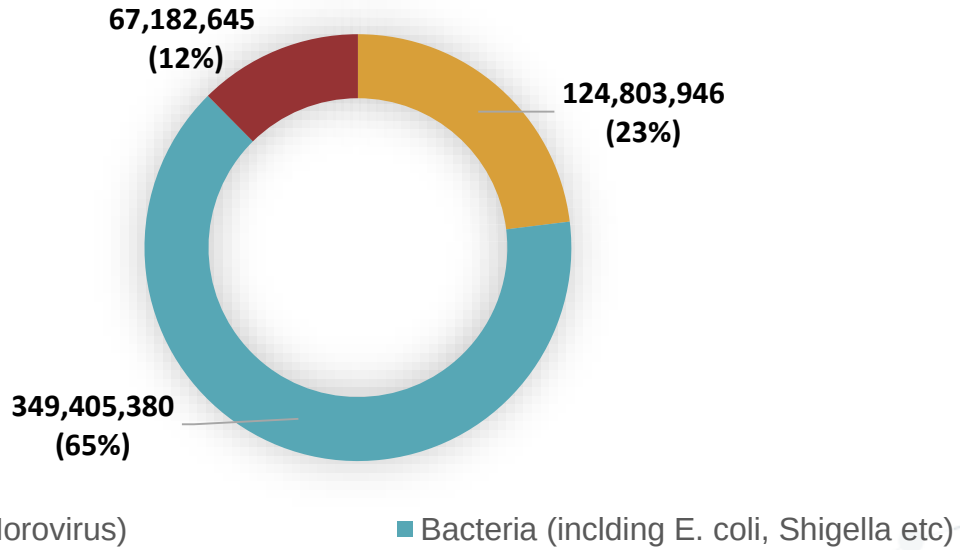
1. Background information on norovirus and post-infectious irritable bowel syndrome (PI-IBS)
2. Linkage with gut microbiota
3. Proposed mechanism
4. Observation based on literature review
5. Future work



1.1

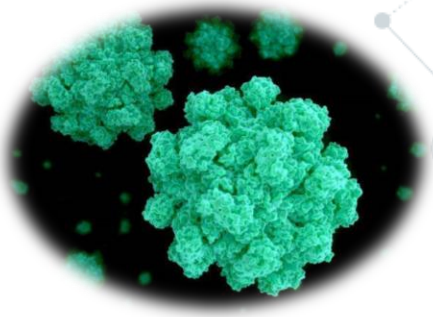
Norovirus

- The leading cause of viral acute gastroenteritis (18% in norovirus metanalysis)

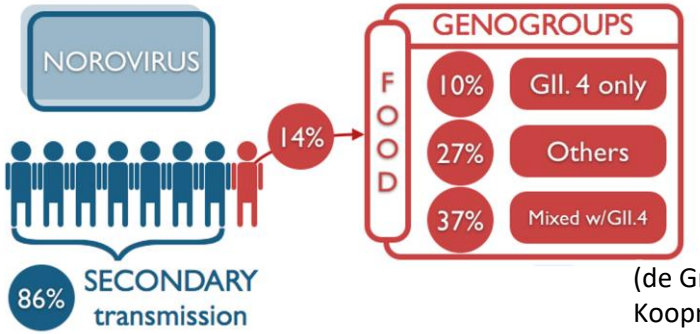


(Ahmed *et al.*, Lancet ID, 2014;
Havelaar *et al.*, PLOS Medicine, 2010)

What are noroviruses?



- A member of the *Caliciviridae* family
- Faecal-oral route and affect all age groups
- Low infectious dose, 12-48 hours incubation period and self-limiting
- Bind to histo-blood group antigens (HBGAs) as functional receptors/co-receptors on host cells
- No licensed vaccine available



(de Graaf, van Beek and Koopmans, Nature Reviews Microbiology, 2016)

1.2

Post-infectious Irritable Bowel Syndrome

What is Post-infectious IBS?

- **IBS**

  → gastrointestinal tract disorder, characterised by abdominal discomfort and chronically disturbed bowel habit

- **PI-IBS**

  → *de novo* development of IBS after acute gastroenteritis, despite the clearance of the inciting pathogen

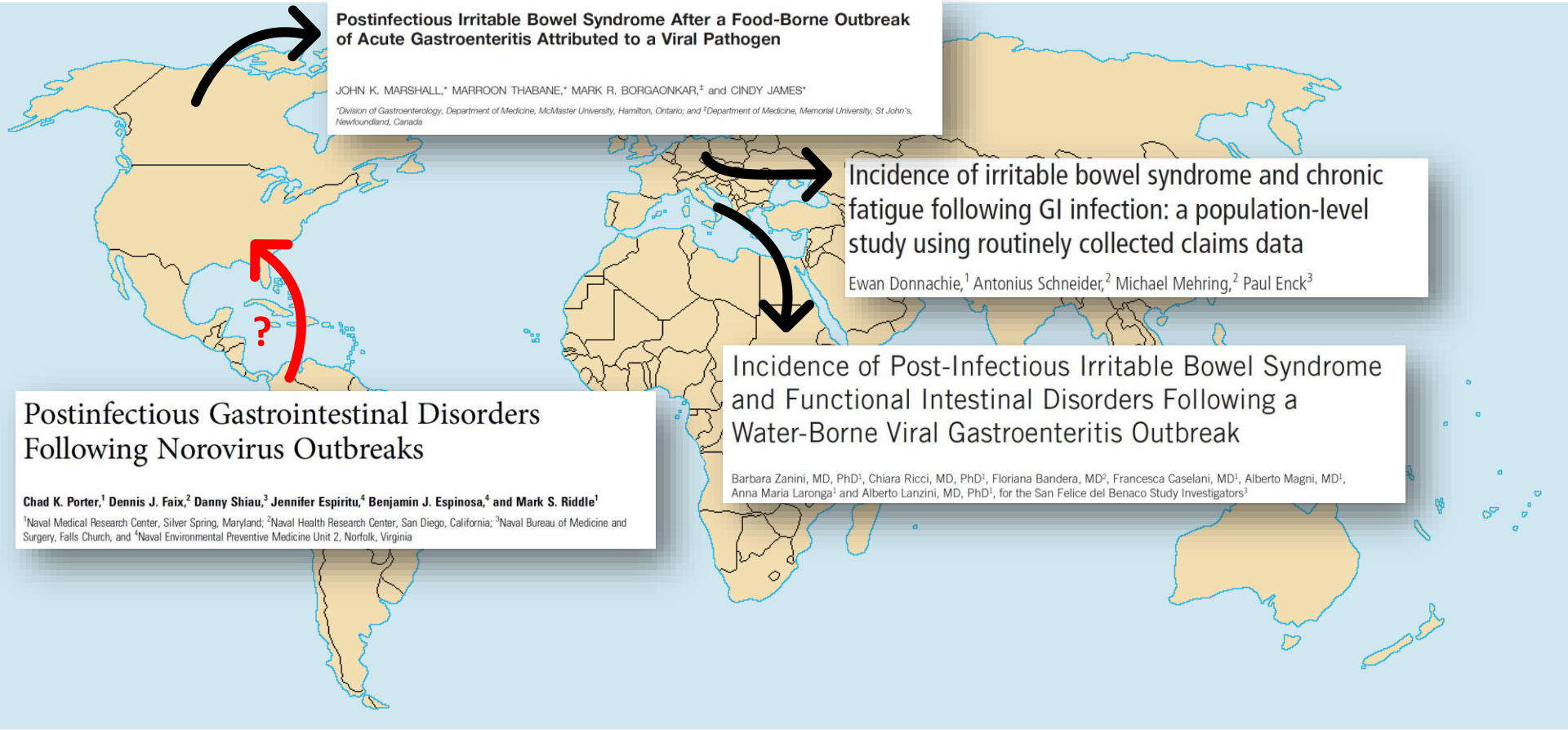
  → involved persistent subclinical inflammation, changes in intestinal permeability and alteration of gut microbiota

(Marshall *et al.*, CGH, 2007)

BUT

How are they related to each other?

Epidemiological evidence



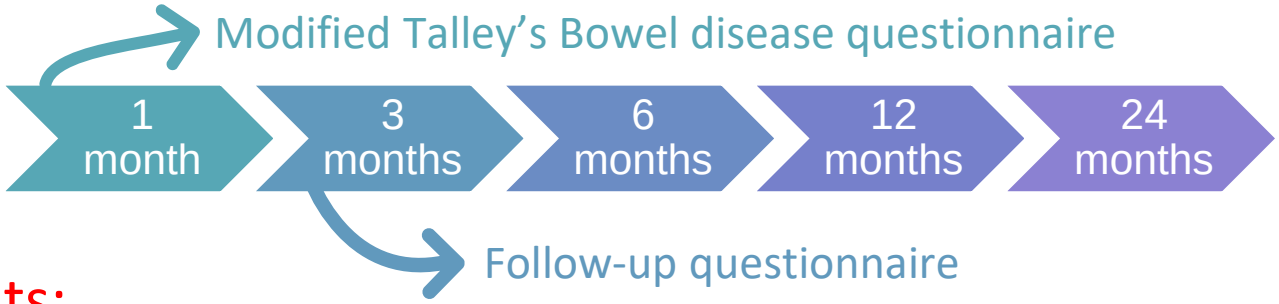
Epidemiological evidence- Canada

Postinfectious Irritable Bowel Syndrome After a Food-Borne Outbreak of Acute Gastroenteritis Attributed to a Viral Pathogen

JOHN K. MARSHALL,* MARROON THABANE,* MARK R. BORGAONKAR,‡ and CINDY JAMES*

*Division of Gastroenterology, Department of Medicine, McMaster University, Hamilton, Ontario; and ‡Department of Medicine, Memorial University, St John's, Newfoundland, Canada

Methods:



Results:

Time point	All subjects	Cases exposed to gastroenteritis	Unexposed controls	*P* value	OR (95% CI)
3 Mo	22/118 (18.6)	21/89 (23.6)	1/29 (3.4)	.014	6.9 (1.0–48.7)
6 Mo	14/116 (12.1)	11/87 (12.5)	3/29 (10.3)	1.000	1.2 (0.4–4.1)
12 Mo	15/112 (13.4)	13/86 (15.1)	2/26 (7.8)	.514	1.9 (0.5–8.15)
24 Mo	17/101 (19.0)	15/77 (19.5)	2/24 (8.3)	.348	2.3 (0.6–9.5)

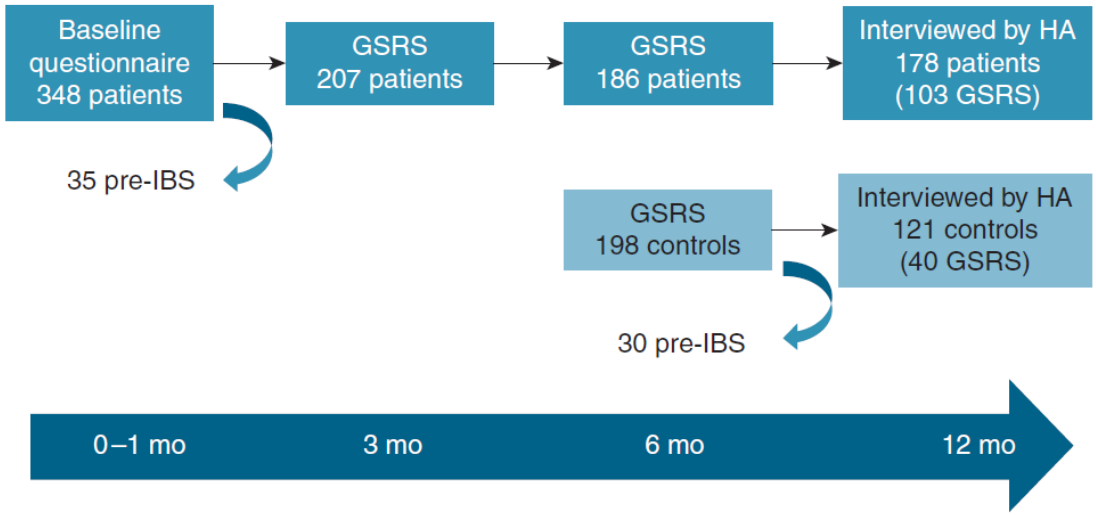
Mo, months.

(Marshall *et al.*, CGH, 2007)

Epidemiological evidence- Italy

Incidence of Post-Infectious Irritable Bowel Syndrome and Functional Intestinal Disorders Following a Water-Borne Viral Gastroenteritis Outbreak

Barbara Zanini, MD, PhD[1], Chiara Ricci, MD, PhD[1], Floriana Bandera, MD[2], Francesca Caselani, MD[1], Alberto Magni, MD[1], Anna Maria Laronga[1] and Alberto Lanzini, MD, PhD[1], for the San Felice del Benaco Study Investigators[3]



(Zanini *et al*., Am J Gastroenterol, 2012)

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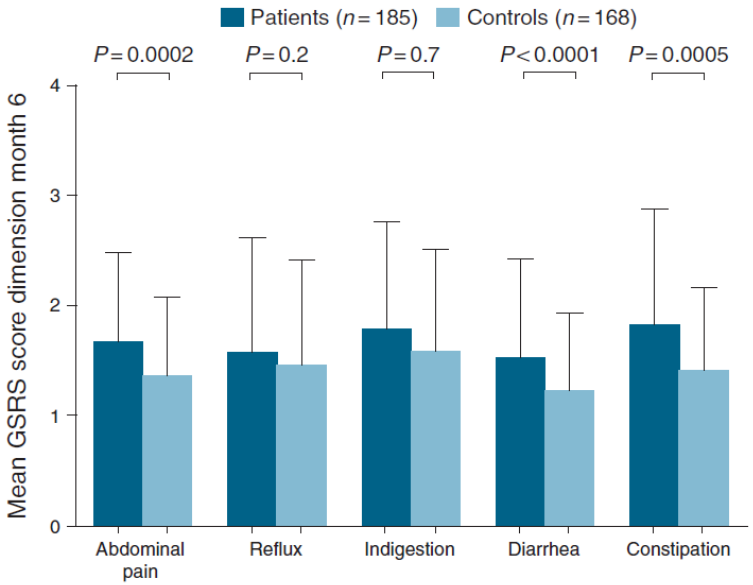
Month 6



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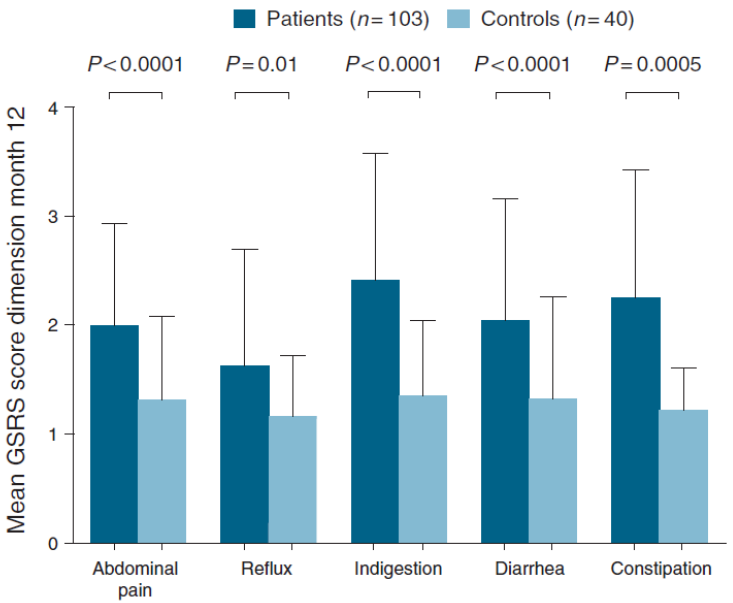

(Zanini *et al*., Am J Gastroenterol, 2012)

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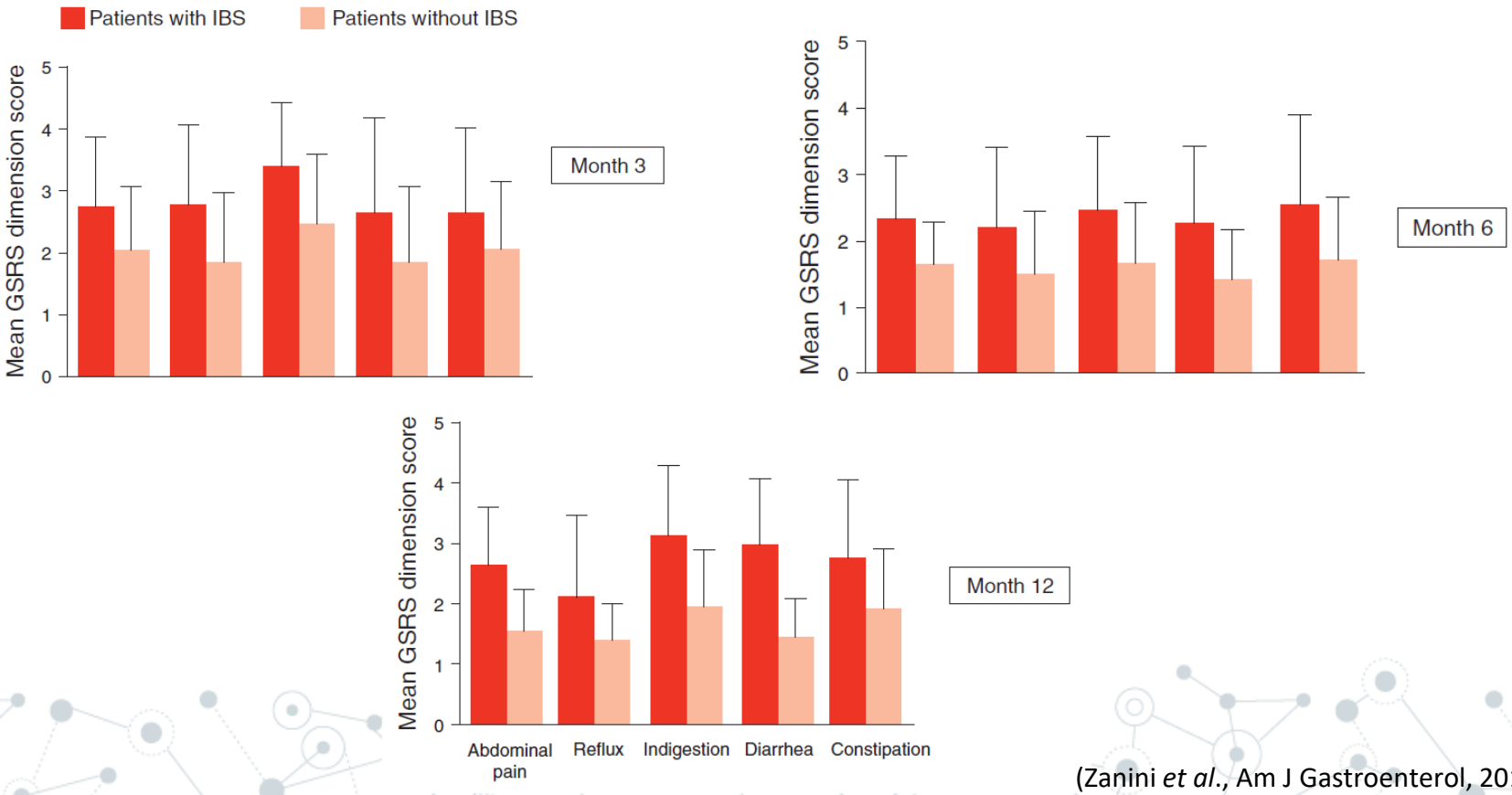


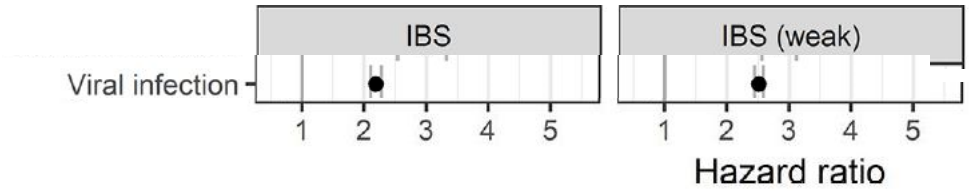
(Zanini *et al*., Am J Gastroenterol, 2012)

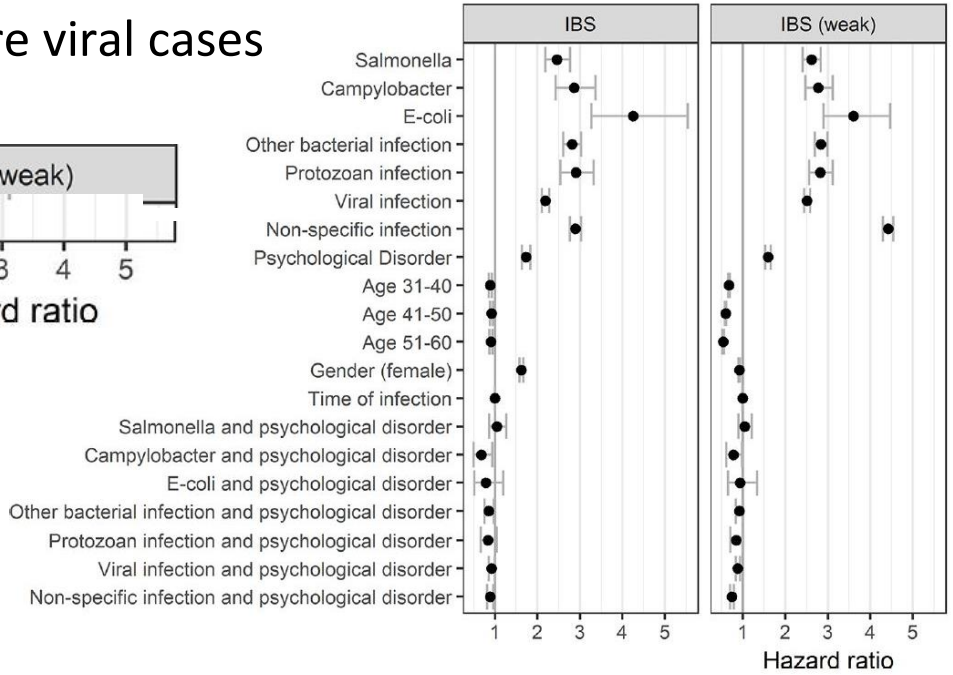
Epidemiological evidence- Germany

Incidence of irritable bowel syndrome and chronic fatigue following GI infection: a population-level study using routinely collected claims data

Ewan Donnachie,[1] Antonius Schneider,[2] Michael Mehring,[2] Paul Enck[3]

- Followed-up 508,287 patients up to 5 years after first episode of GI infection 305,697 were viral cases





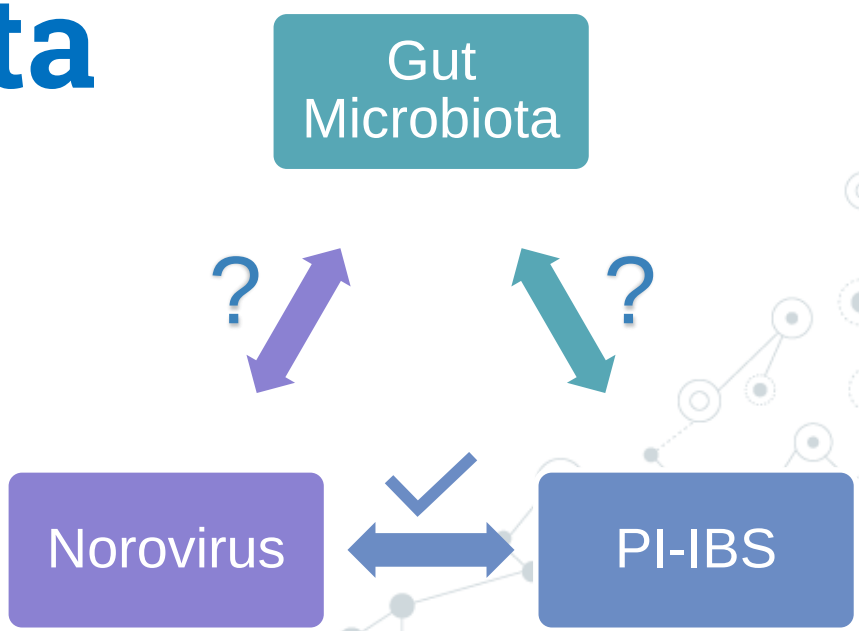
(Donnachine *et al*., Gut, 2017)

So…

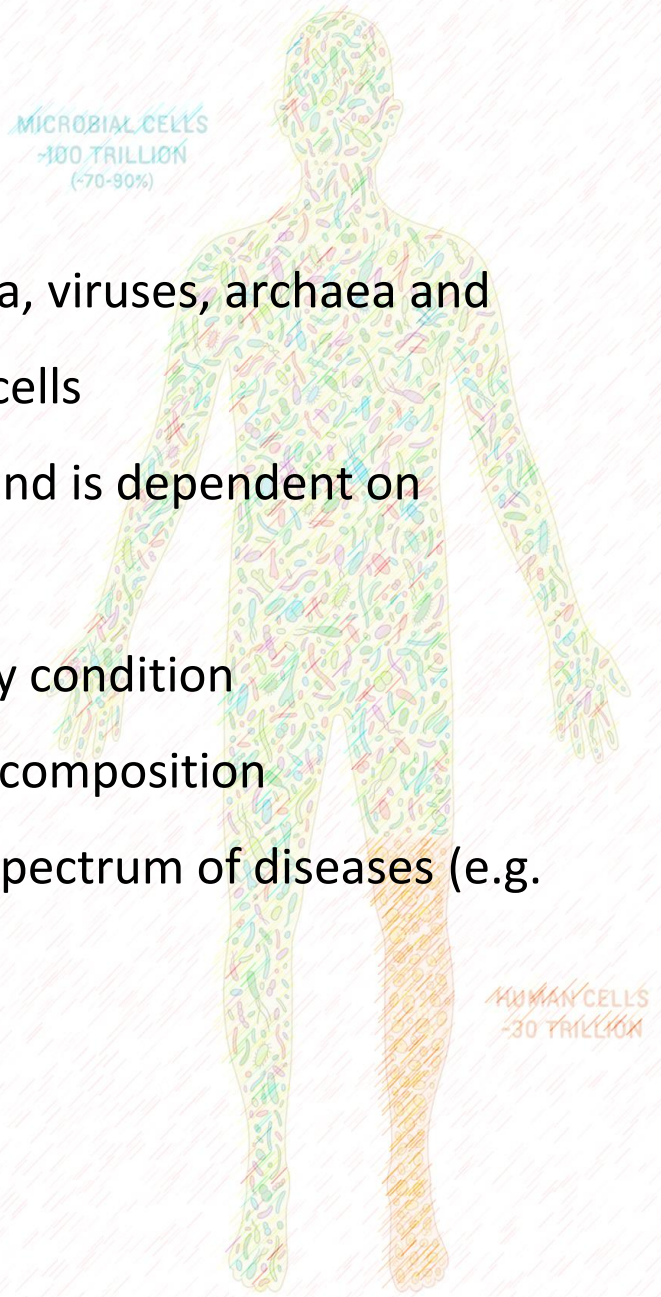
All the three researches demonstrated that PI-IBS frequently occurs after acute viral gastroenteritis

2.

Linkage with gut microbiota



Gut microbiota

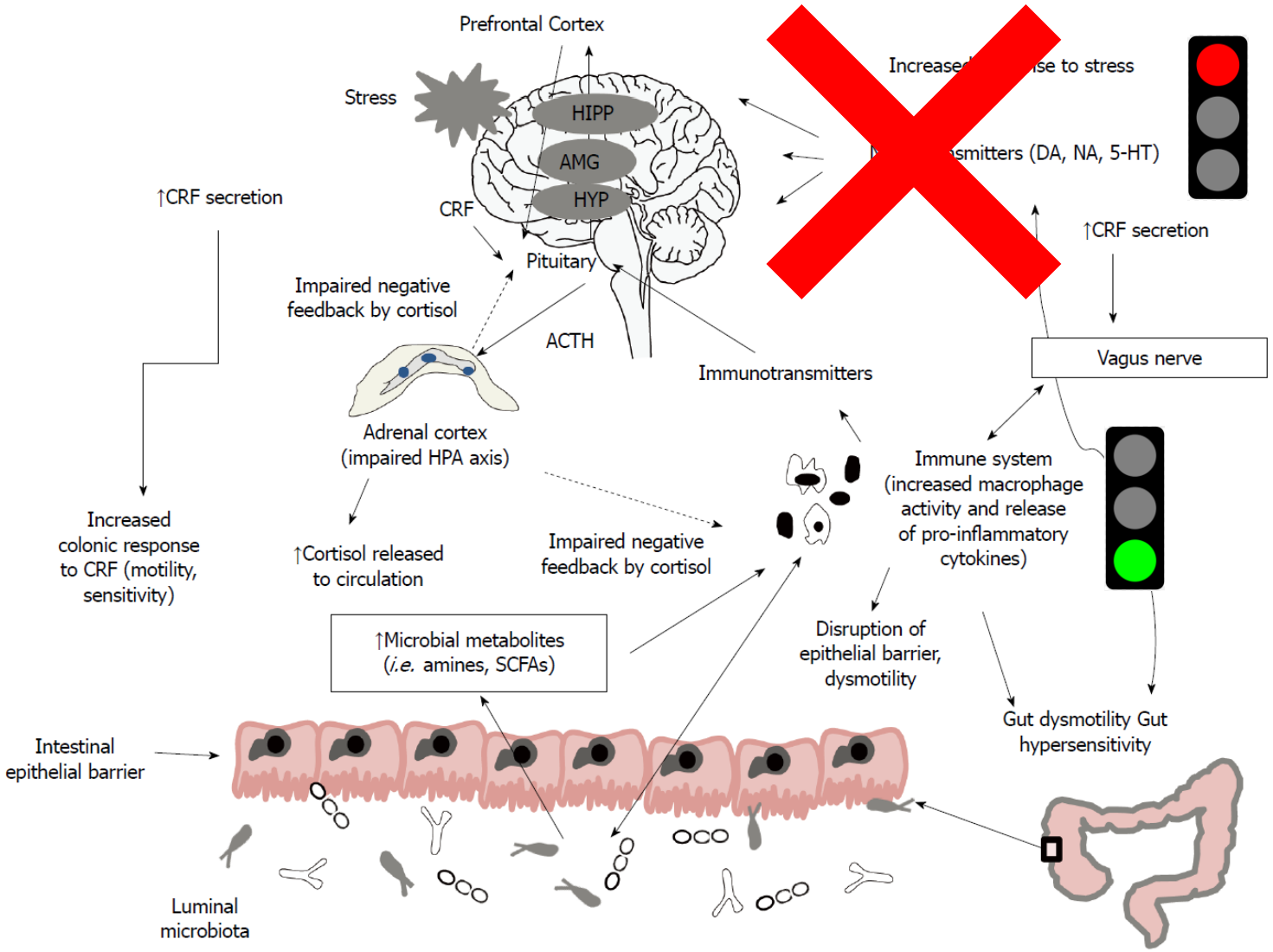


- Complex living ecosystem (✓ bacteria, viruses, archaea and eukaryotes) ☛ 10-fold of human cells
- Highly dynamic between individuals and is dependent on environmental factors
- Mutualistic relationship under healthy condition
- However → changes in numbers and composition

  → lead to appearance of a spectrum of diseases (e.g. Obesity, IBD etc)

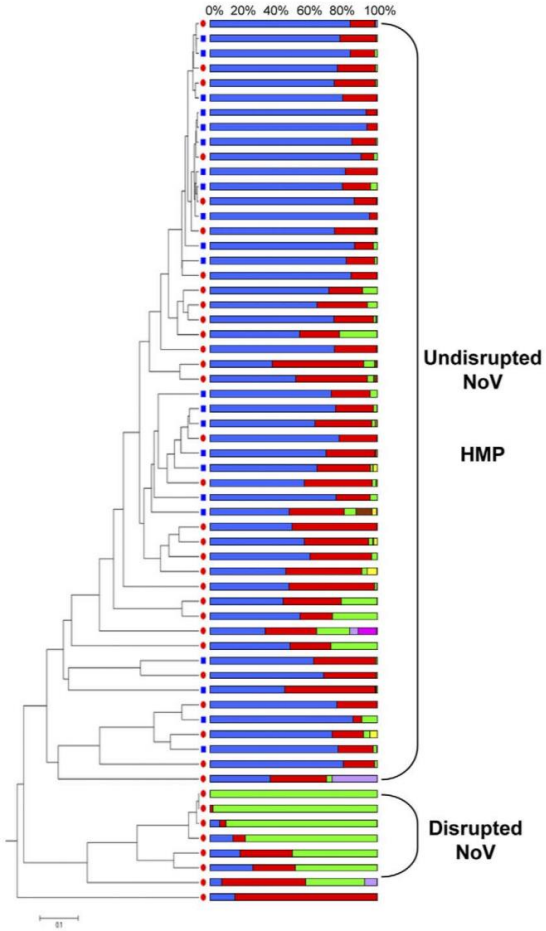
(Distrutti *et al*., WJG, 2012)

Gut microbiota and IBS



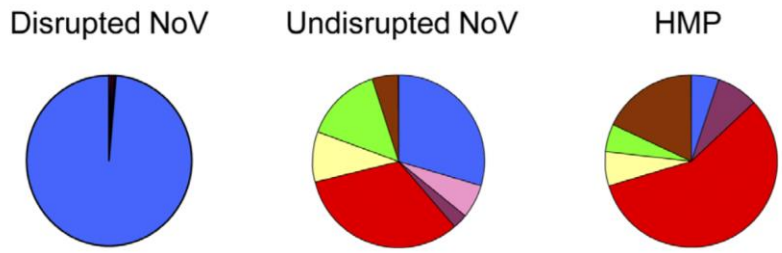
(Distrutti *et al.*, WJG, 2012)

Gut microbiota and norovirus



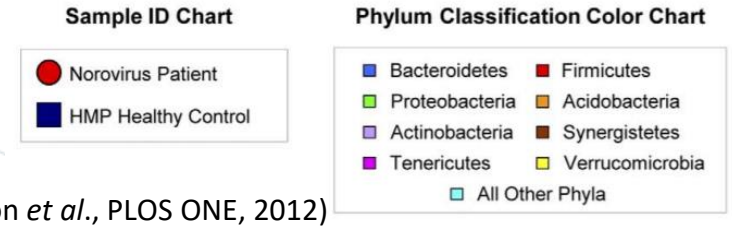
- Gut microbiota's diversity was highly disrupted after norovirus infection
- Significant increase in proteobacteria community (e.g. *E.coli*)

  → increase incidence in mucosal inflammation development



Family level assignments within Proteobacteria
Mean proportion of bacteria per treatment group

Enterobacteriaceae	98.65 %	±1.89	29.36 %	±35.29	5.64 %	±19.11
Pasteurellaceae	0.52 %	±1.22	2.72 %	±8.06	8.46 %	±21.99
Pseudomonadaceae	0.14 %	±0.32	6.52 %	±21.35	0.00 %	±0.00
Alcaligenaceae	0.56 %	±1.18	32.63 %	±36.04	56.08 %	±41.98
Neisseriaceae	0.03 %	±0.04	9.44 %	±24.28	6.99 %	±21.72
Desulfovibrionaceae	0.04 %	±0.06	14.40 %	±26.40	5.60 %	±11.65
All Other Families	0.05 %	±0.07	4.93 %	±11.86	17.24 %	±26.97

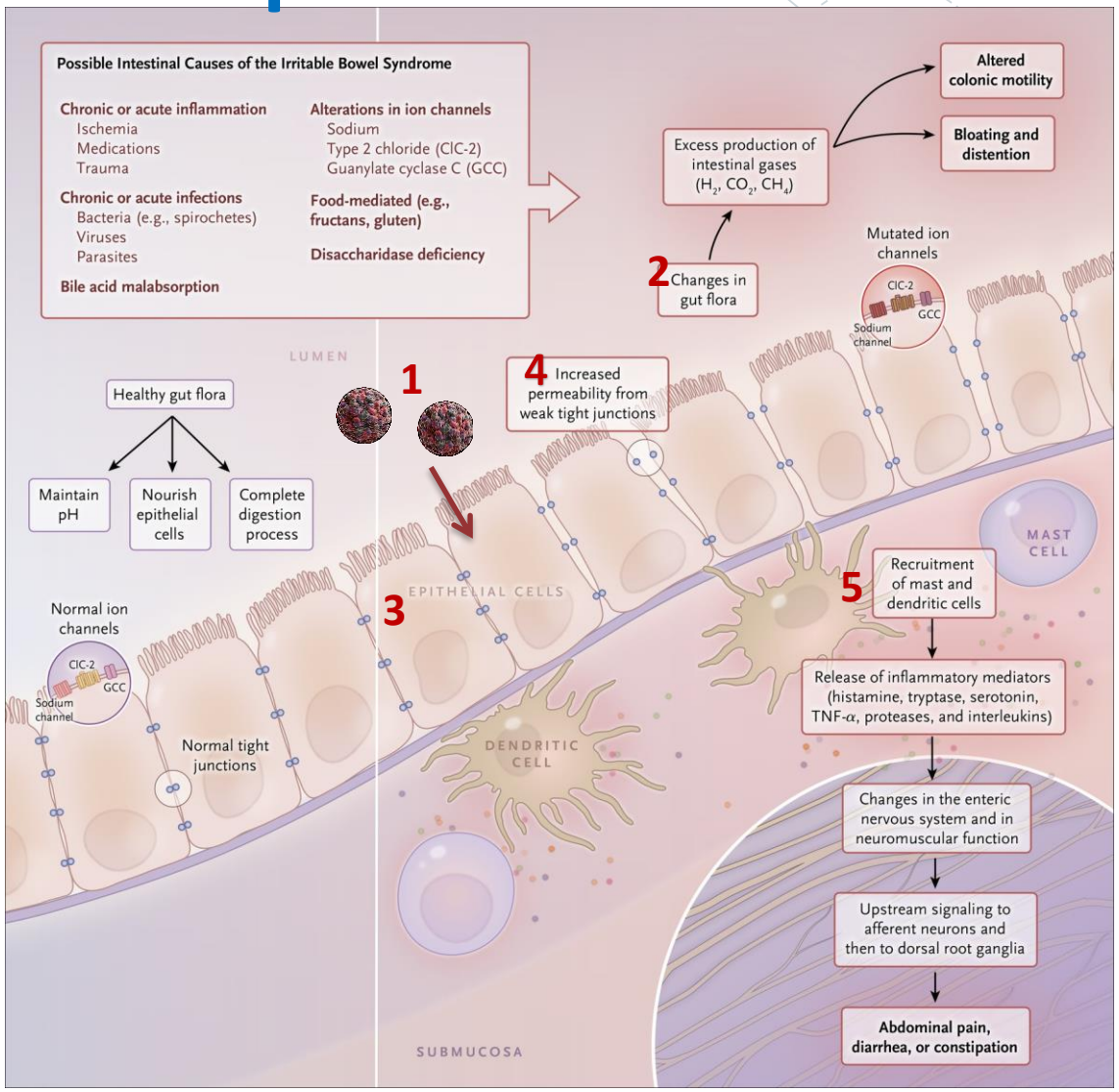


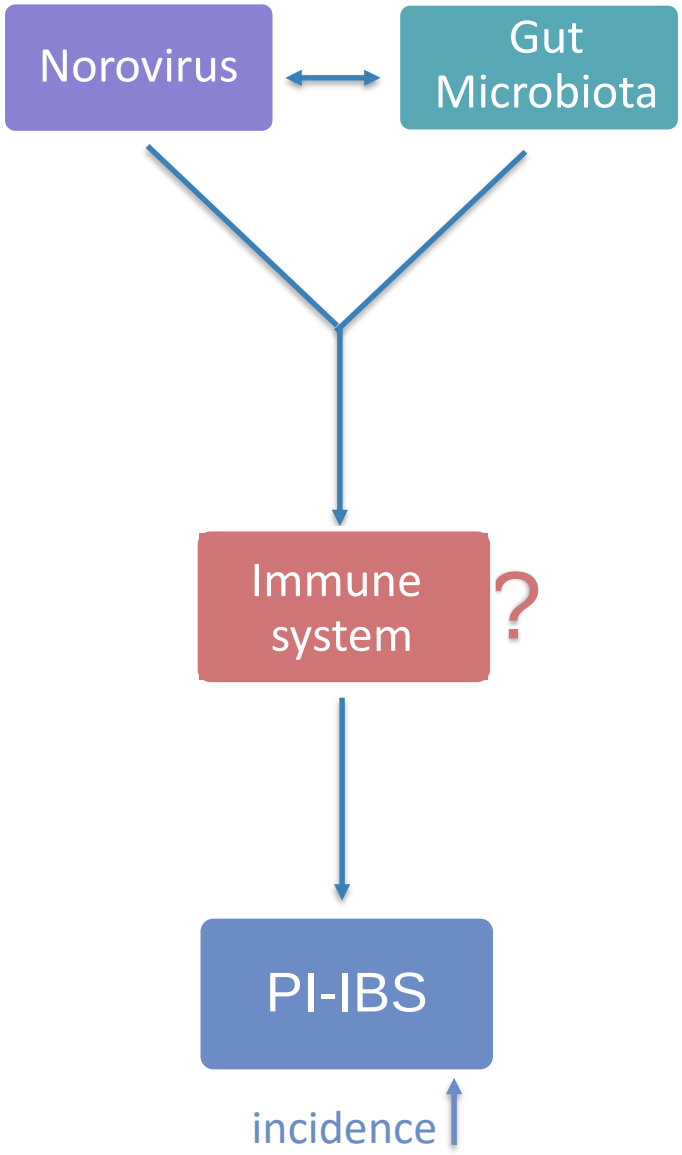
(Nelson *et al.*, PLOS ONE, 2012)

3.

Connecting the dots

Proposed mechanism

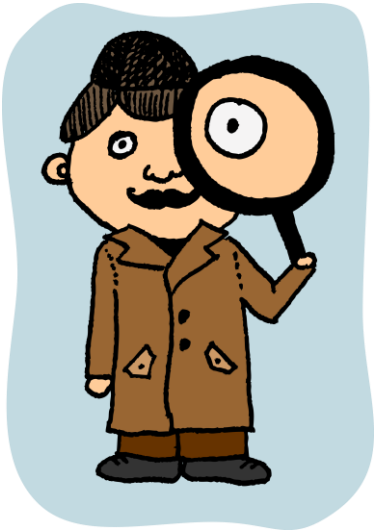




(Edited from Figure 3. Ford, Lacy and Talley, NEJM, 2017)

4.

Observation based on literature review



Observation

- An inverse proportion relationship between gastroenteritis occur time and PI-IBS development

Restoration of gut microbiota balance?

- Severity of gastroenteritis could be a chronic consequence of an acute mucosal injury

Less severity would lead to fewer long term sequelae? + further reduce the long term risk of PI-IBS development?

5.
Future work

- Porter *et al*, show that there is no significant increase in incidence of PI-IBS after AGE by measuring the inflammatory signal
- To evaluate long term sequelae of norovirus infection (is it really self-limiting?)
- To establish association studies→ should also collect patient's stool for microbiota analysis during longitudinal studies
- For norovirus vaccine studies

  → may need to consider the prevention of the potential outcomes

  → or is there any possibility of secondary benefits (e.g. alleviate PI-IBS) towards the general public?

(Porter *et al*., CID, 2012)

Any questions?

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