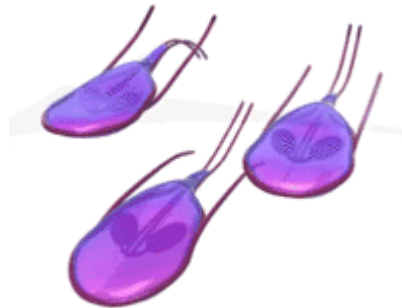




Enteric pathogens and infections; what's new and what's to do?

Colin Hill



(Enteric) Infection



Infection occurs when a microbe grows on/in a body, causing damage to the host (disease)

Usually infection is restricted to microbes which can overcome body defences and cause damage

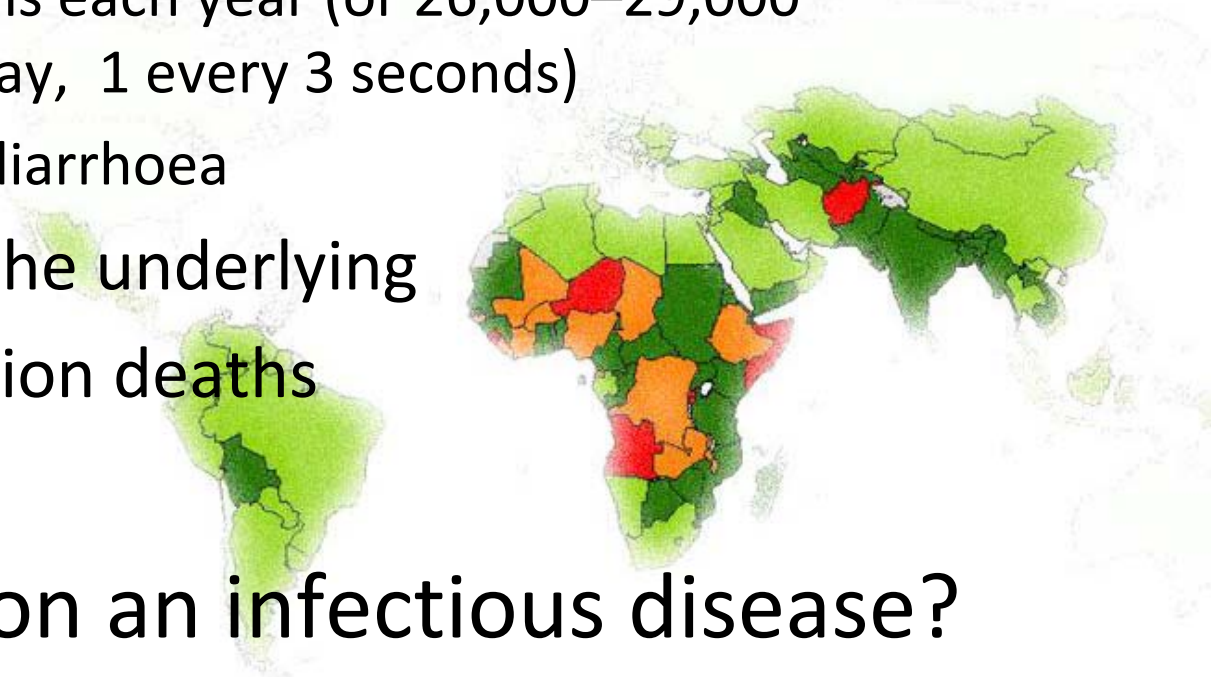
Sometimes microbes can cause disease if body defences are weakened.

Infection can occur at almost any site on/in the body and can range from mild to fatal

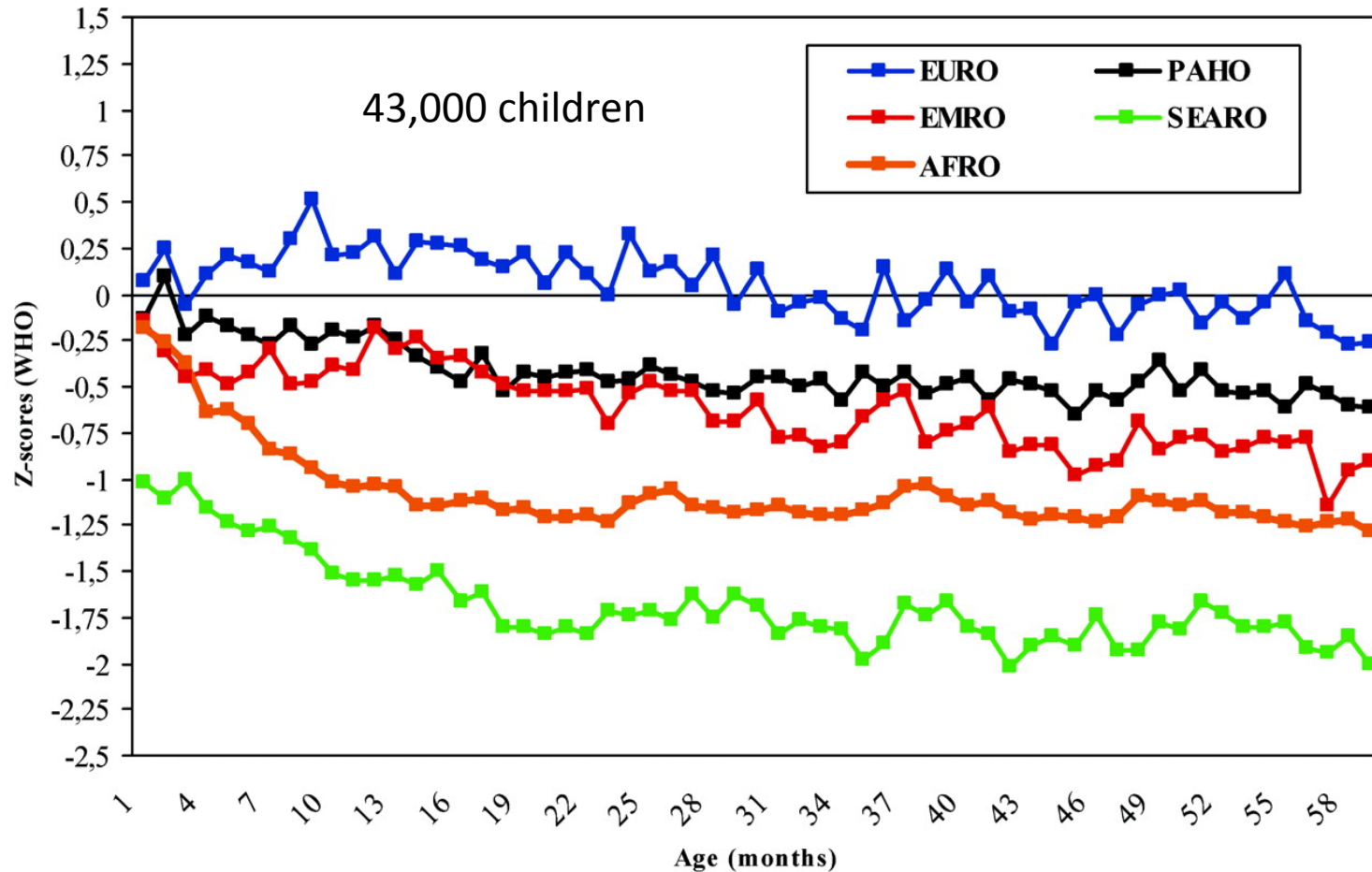
Enteric infections occur in the GI tract

Global impact of diarrhoea/malnutrition

- Global mortality among children under 5
 - 10 million deaths each year (or 26,000–29,000 children each day, 1 every 3 seconds)
 - 2 million from diarrhoea
- Malnutrition is the underlying cause of 3.5 million deaths
- Is malnutrition an infectious disease?

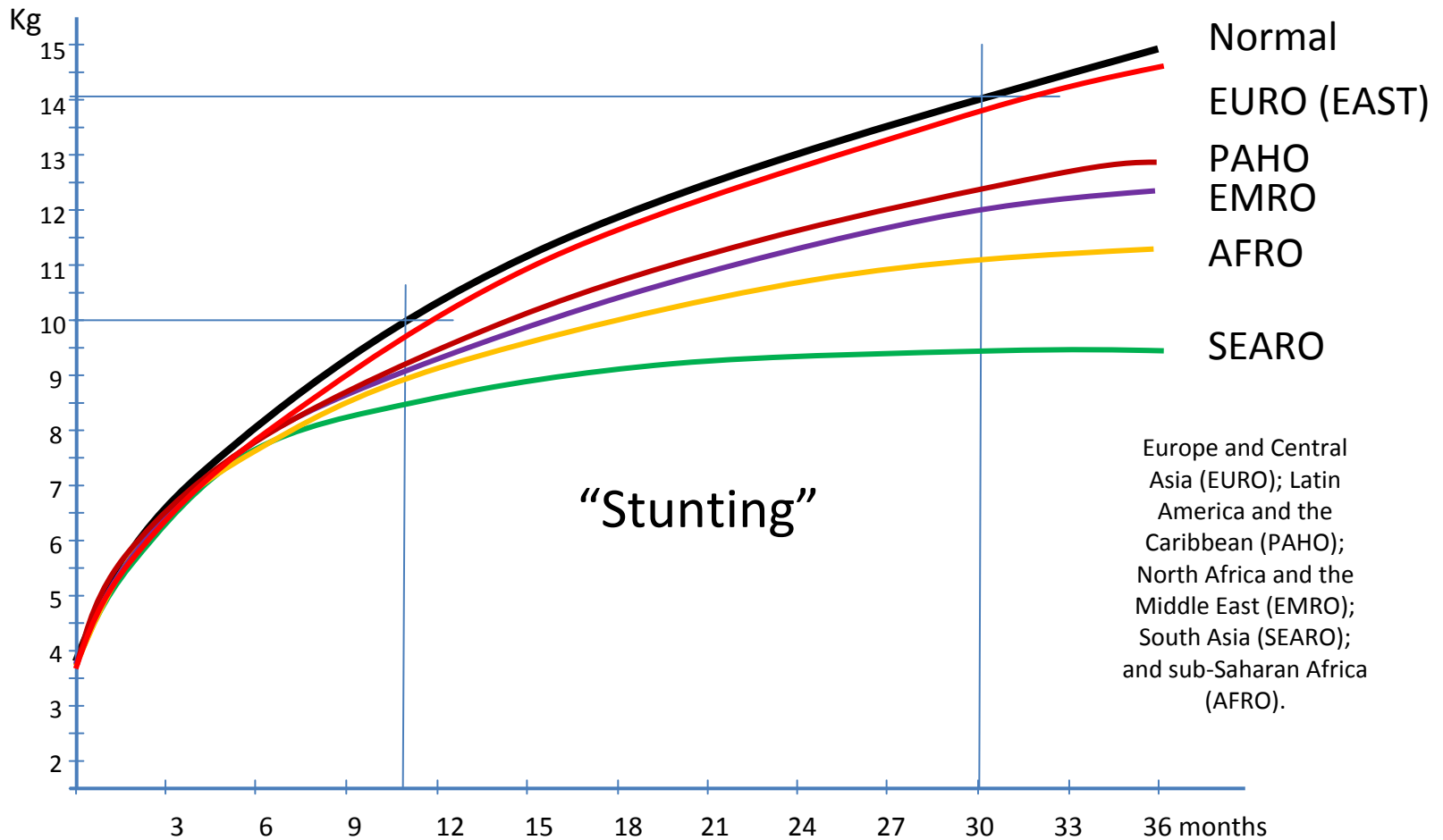


Weight for age Z scores (WAZ)



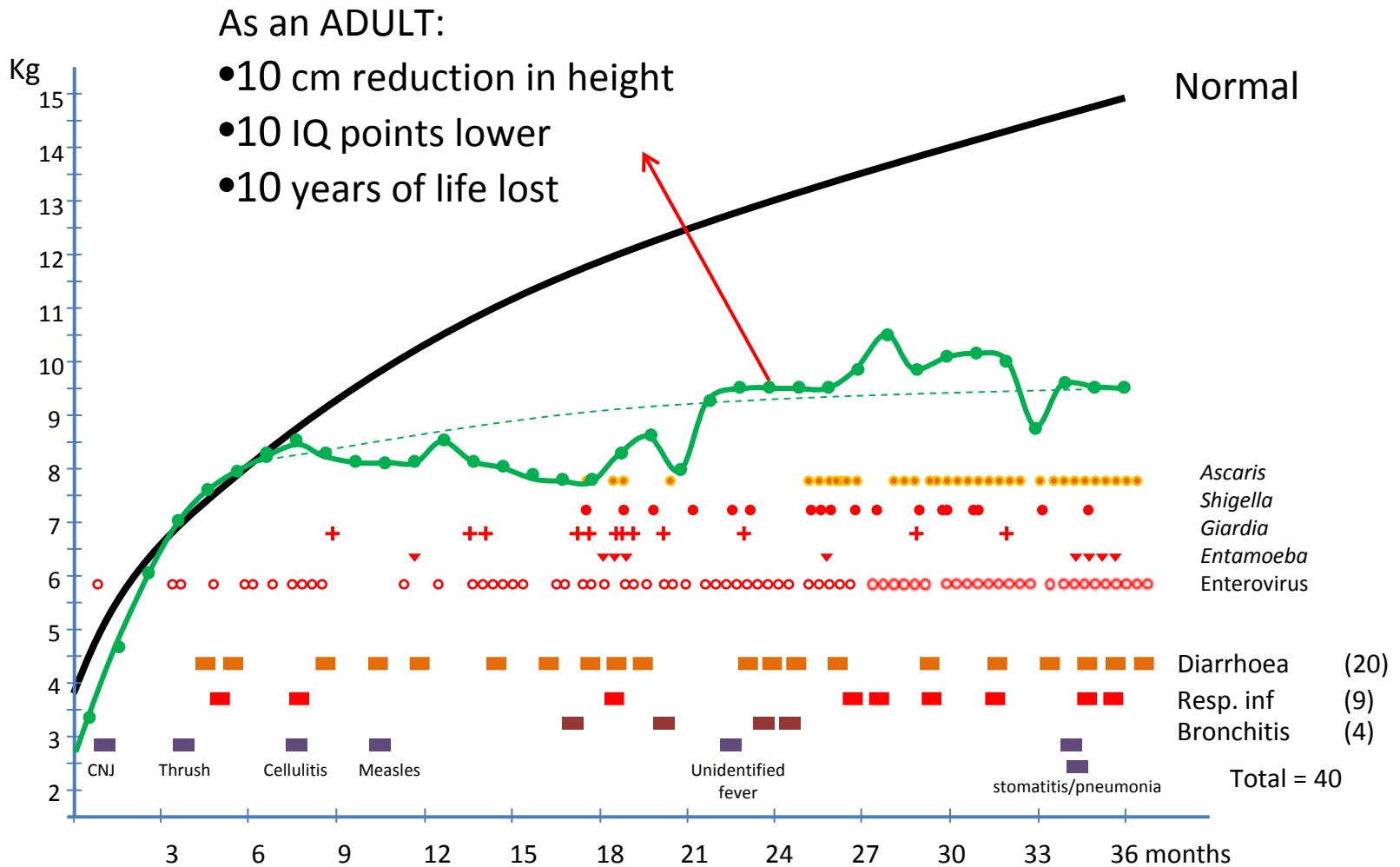
Europe and Central Asia (EURO); Latin America and the Caribbean (PAHO); North Africa and the Middle East (EMRO); South Asia (SEARO); and sub-Saharan Africa (AFRO).

Infant growth rates (45,000 children)



— Weight for age for a healthy infant

Malnutrition as an enteric infection



Disability

Growth shortfalls (8.2 cm by 7 y)

Cryptosporidial infections increase diarrhea, morbidity and nutritional shortfalls
Cryptosporidial infections ± diarrhea → decreased weight gain at 1 month
Cryptosporidial infections <6 m or stunting → 0.95–1.05 cm deficits at 1 y
EAEC infections + inflammation → growth shortfall
Diarrhea <2 y → 3.6 cm stunted at 7 y (8.2 cm with helminths)

Fitness impairment (=17% decreased work productivity)

Albendazole → 7% increased HST at 4 months
Diarrhea <2 y → 4–8% decreased HST at 4–7 y
4.3% increase HST → 16.6% increased work productivity

Cognitive impairment (10 IQ points)

Diarrhea <2 y decreased WISC coding/digit at 5–9 y
Diarrhea <2 y decreased TONI at 6–10 y
Giardia or stunting decreased WISC-R at 9 y by 4–10 points

School performance (circa 1 y)

Diarrhea <2 y → increased AASS; AFG

Reference

Molbak et al. (1997)
Checkley et al. (1997)
Checkley et al. (1998)
Steiner et al. (1998)
Moore et al. (1998)

Stephenson et al. (1993)
Guerrant (1999)
Ndamba (1993)

Guerrant et al. (1999)
Niehaus et al. (2002)
Berkman et al. (2002)

Lorntz et al. (2006)

AASS, age at starting school; AFG, age for grade; EAEC, enteroaggregative *E. coli*; HAZ-2, height for age Z score at 2 years; HST, Harvard Step Test scores; TONI, Test of Nonverbal Intelligence; WISC, Wechsler Intelligence Scale for Children; →, predisposes to.

Quality of life

1–2 year old male children given nutrient-dense atole in Guatemala between 1962 and 1977 now **earn 46% more** at ages 25–42 years.

Women who had been supplemented as children had **gains in schooling** and reading comprehension



(cornstarch, rice, oatmeal)

“Stunting” cannot be fully reversed (especially if infections continue).

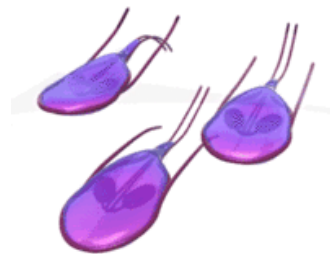
Enteric agents of disease

Acute diarrhoea

- enterotoxigenic *Escherichia coli*, rotaviruses, and noroviruses

Persistent diarrhoea

- enteroaggregative *E. coli*, *Cryptosporidium* and *Giardia*

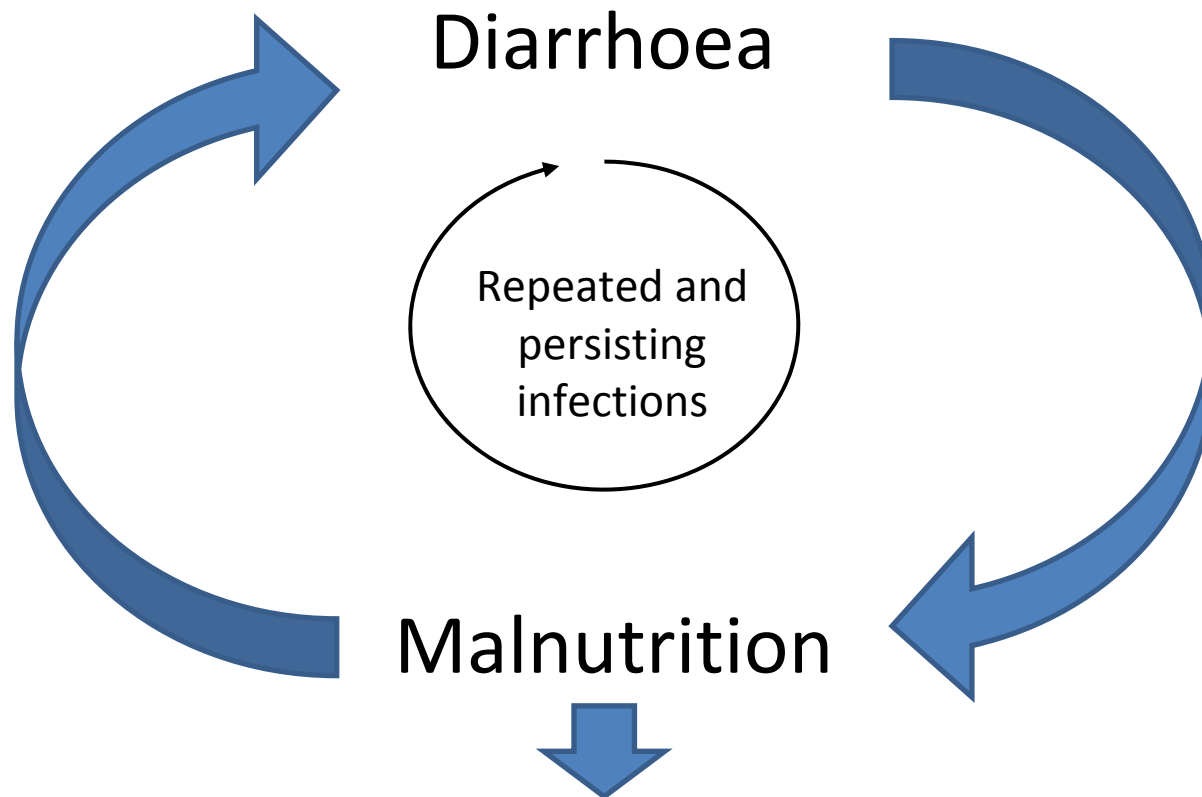


Giardia lamblia

Malnutrition and infection - a deadly cycle

Children with malnutrition have more severe diarrhoea

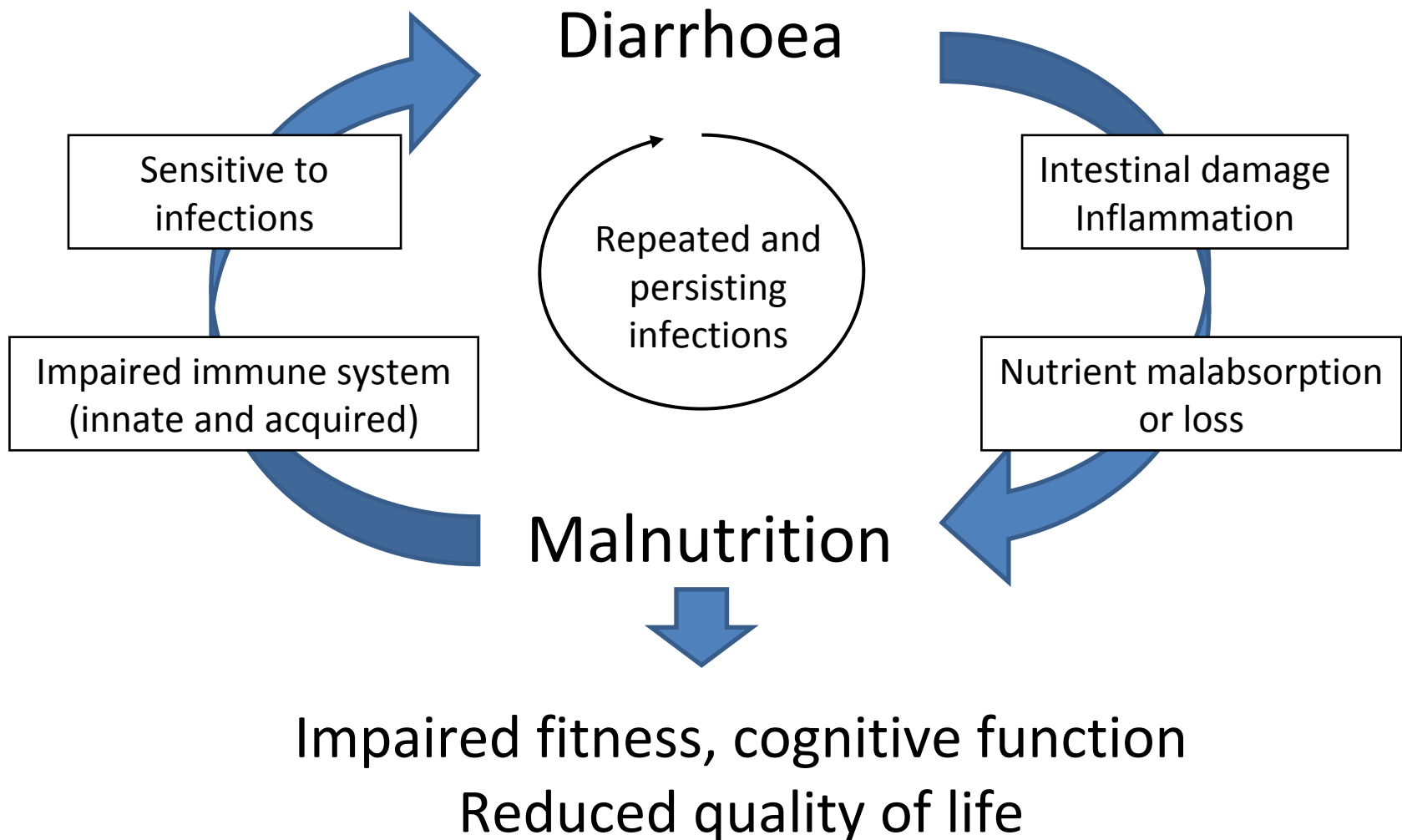
Children with diarrhoea are more likely to be malnourished



Impaired fitness, cognitive function
Reduced quality of life

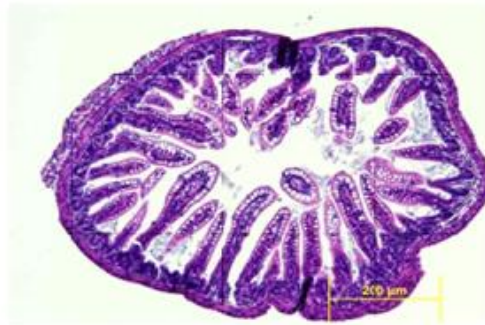
Malnutrition and infection - a deadly cycle

Children with malnutrition have more severe (and extended) diarrhoea
Children with diarrhoea are more likely to be malnourished

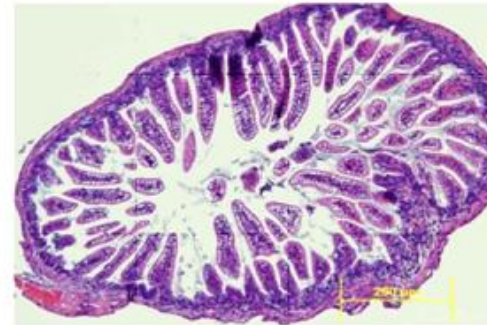


Malnutrition and infection - a deadly cycle

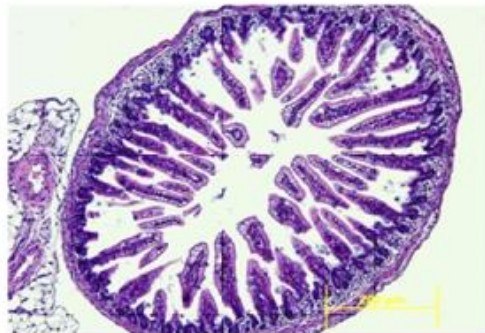
Cryptosporidium infection at 14 days (infected at 6 days)



Nourished, noninfected



Malnourished, noninfected



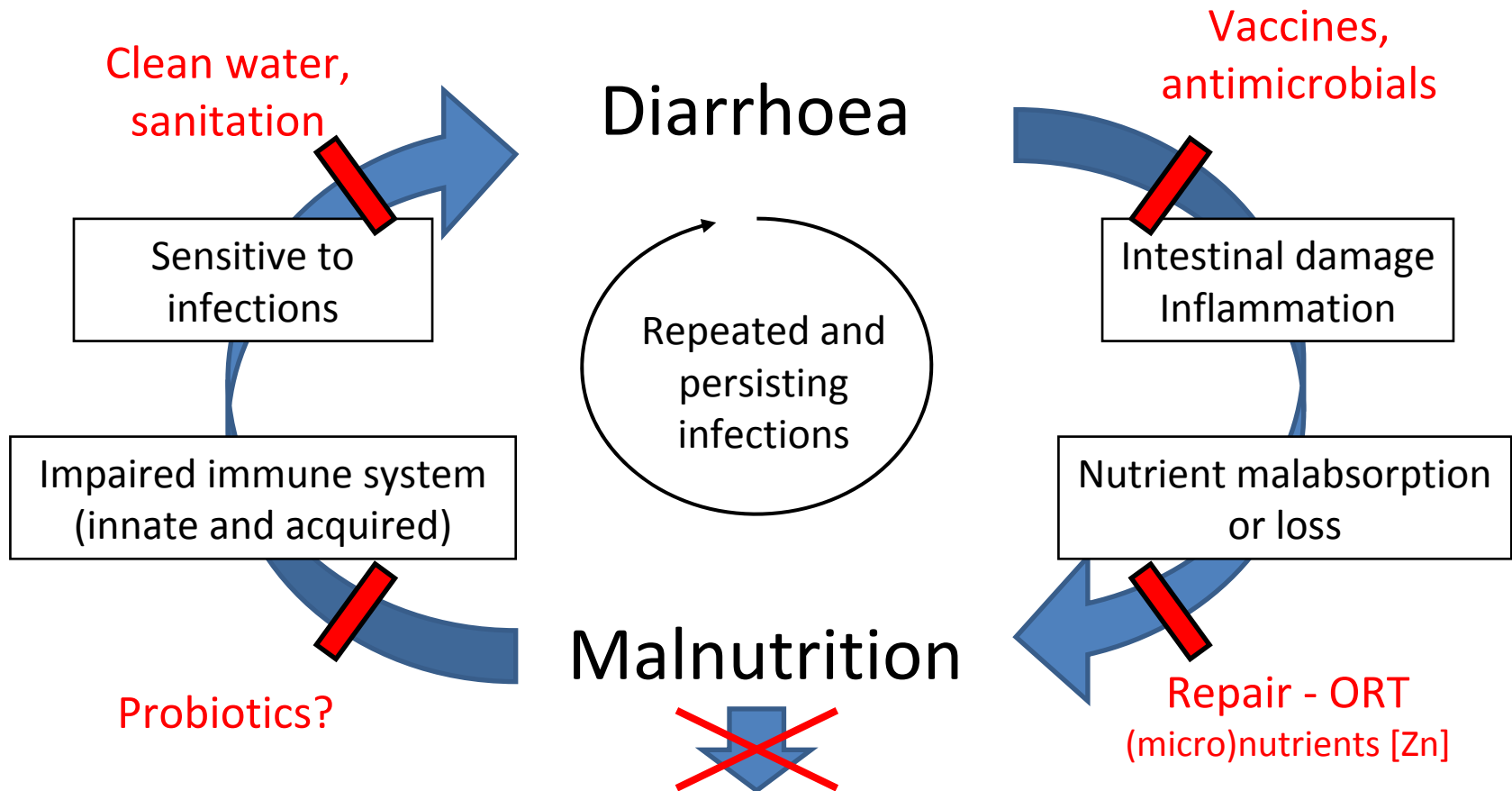
Nourished, infected



Malnourished, infected

Malnutrition and infection - a deadly cycle

What can be done?



Impaired fitness, cognitive function
Reduced quality of life

Probiotics



- Live microbes which, when ingested, have a beneficial effect on the host
- Have been shown to protect against infection, inflammation, atopic disease
- Can be delivered as capsules, or in foods



Could probiotics be used to reduce the burden of enteric infections?

- Can we use existing probiotics?
 - Commercial interests, patents, etc.
- Do we need new probiotics?
 - Which bacteria, where do we get them?
 - Do they really work (and how)?
 - What evidence is available?

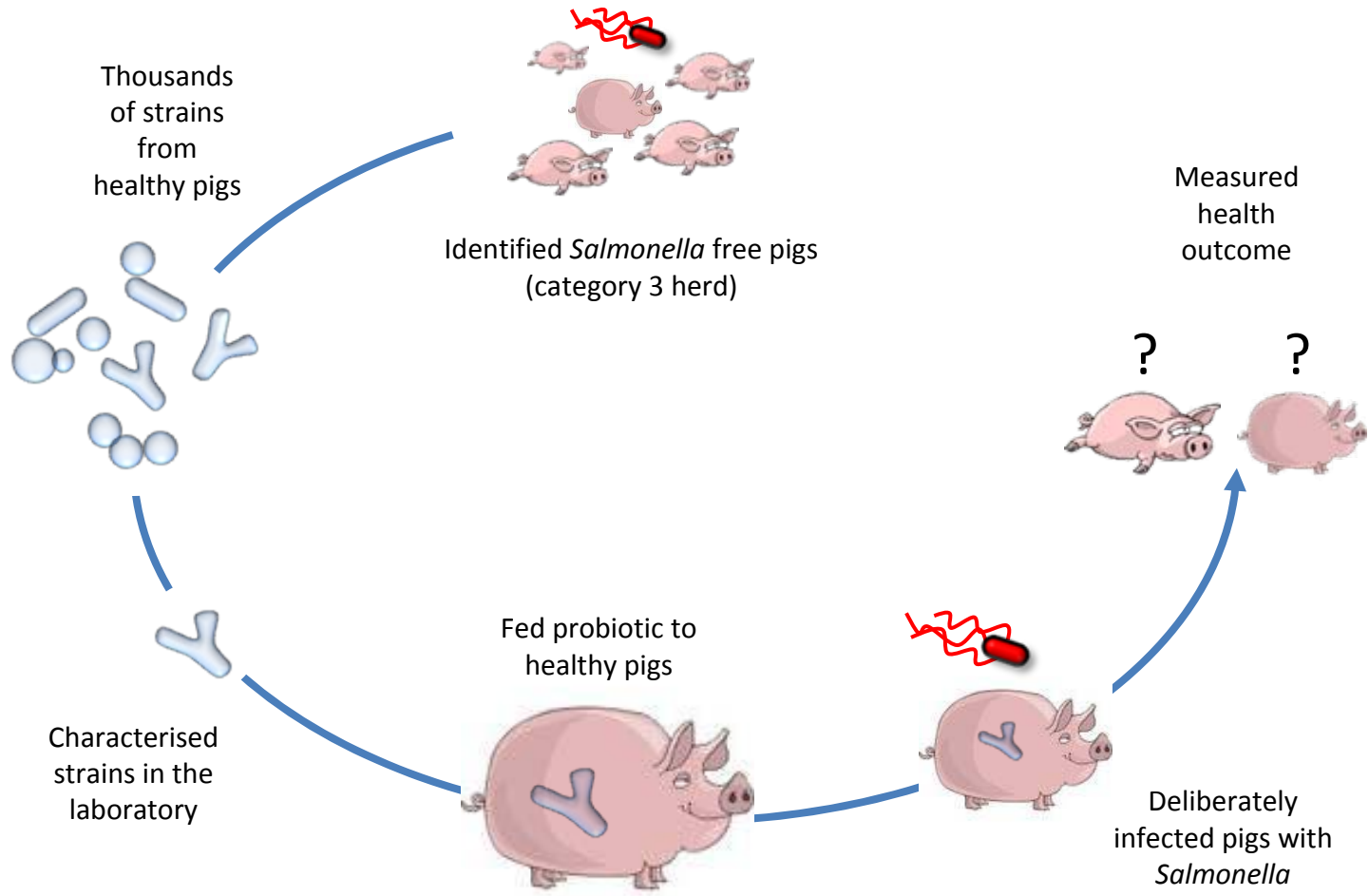


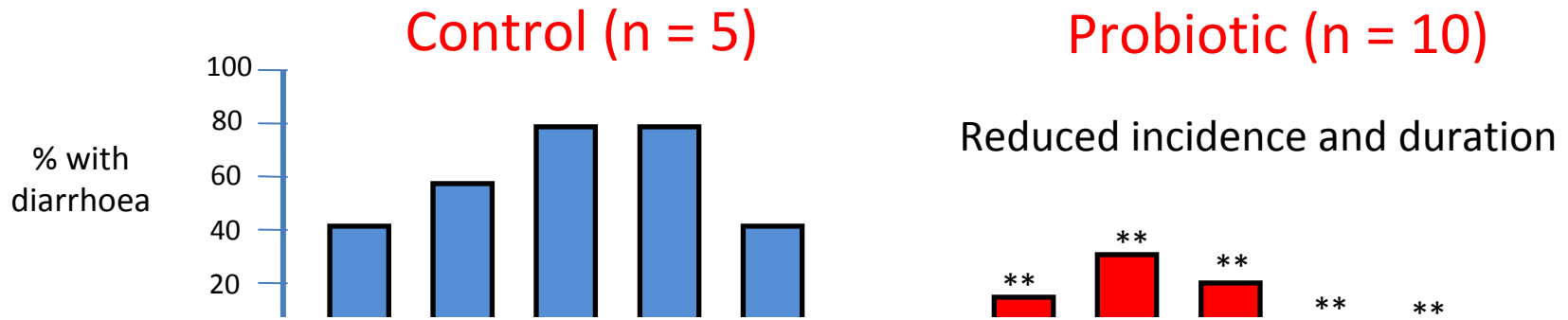
Porcine salmonellosis as a model for human enteric infection

- *Salmonella* is a leading cause of diarrhoea (millions of human cases every year)
- *Salmonella* can also infect pigs, and then be transmitted to humans
- Disease in pigs is very similar to disease in humans – a good model system of enteric infection



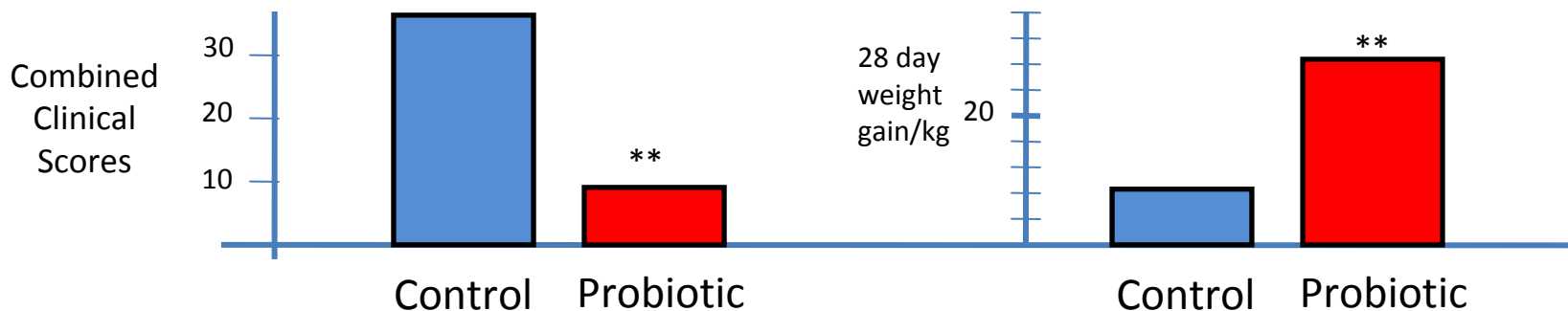
Porcine salmonellosis as a model for human enteric infection



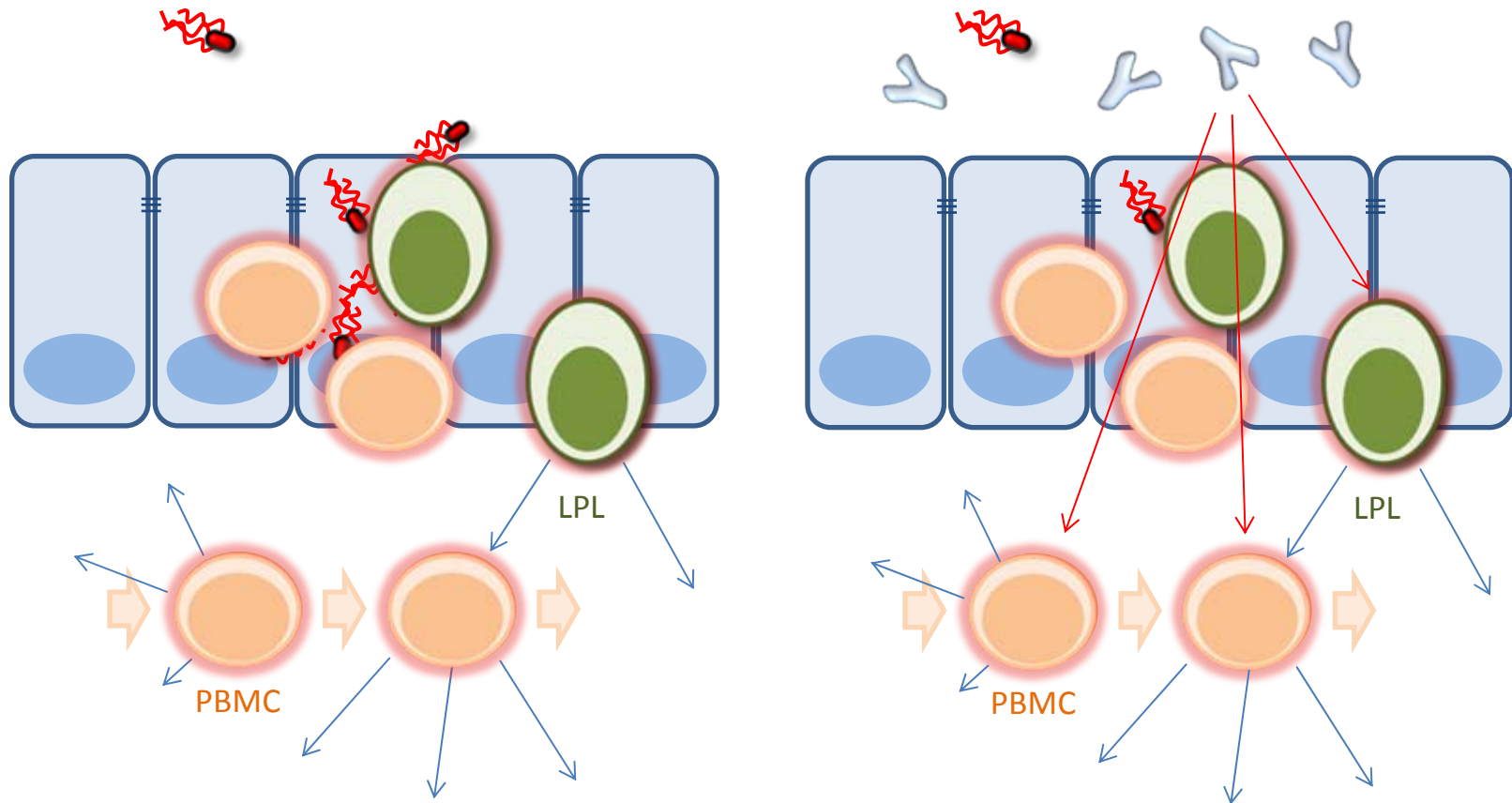


Probiotic strains provided significant protection against incidence and duration, resulted in reduced clinical scores and higher weight gain.

Salmonella /g faeces



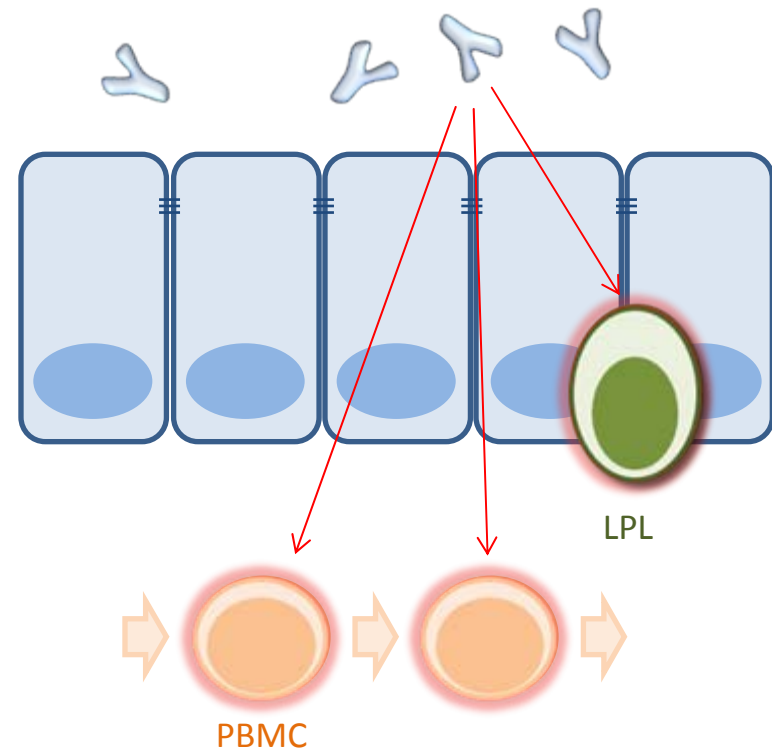
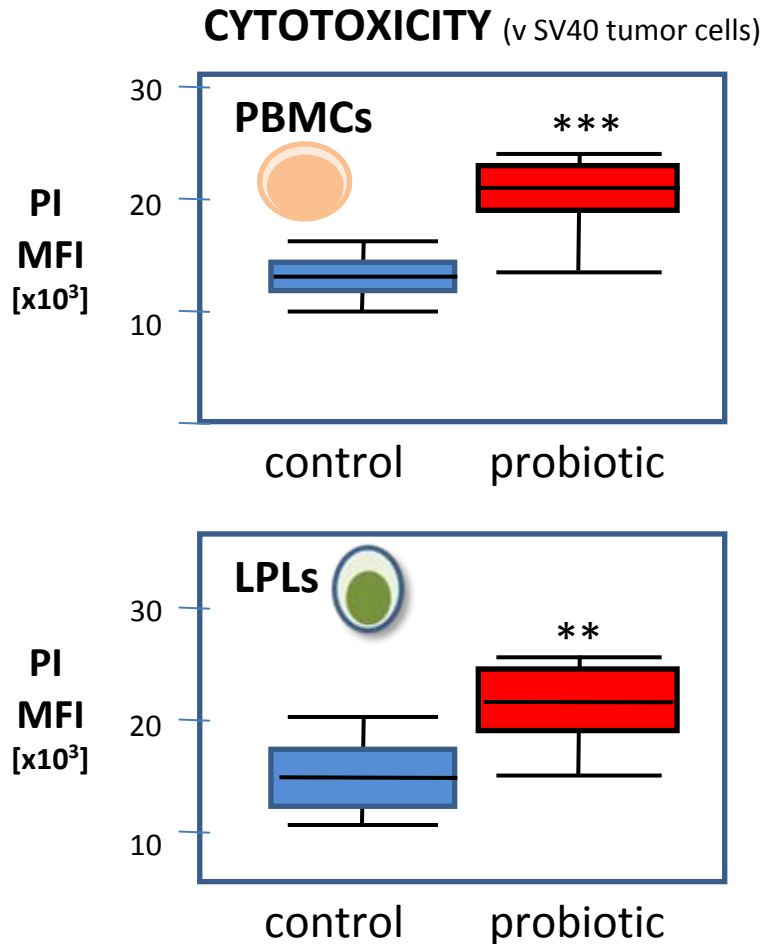
How? (Mechanism of action)



PBMC's: peripheral blood mononuclear cells; LPL's: lamina propria lymphocytes

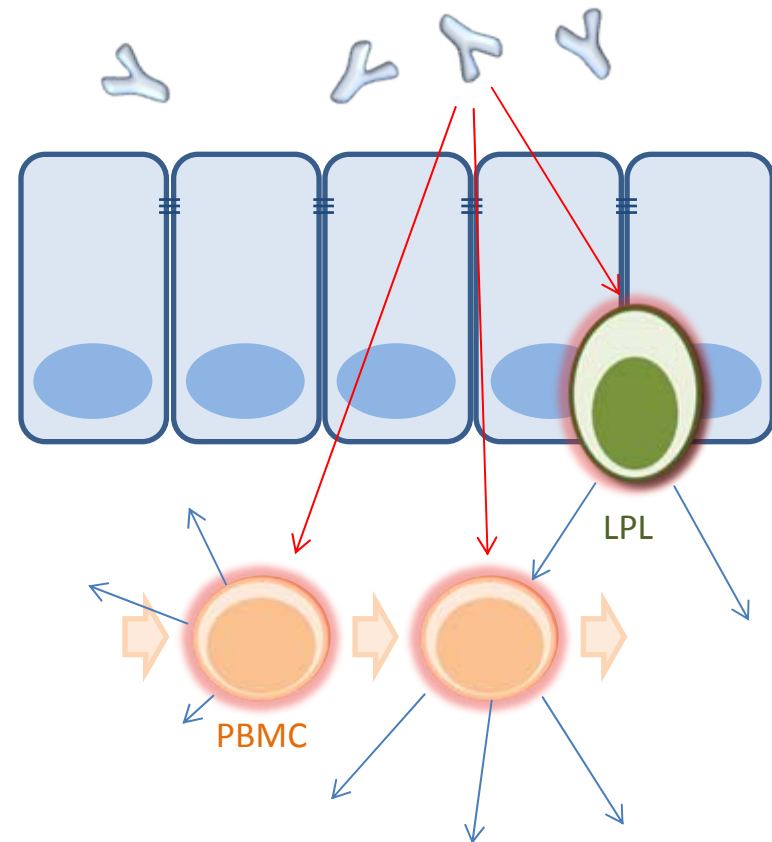
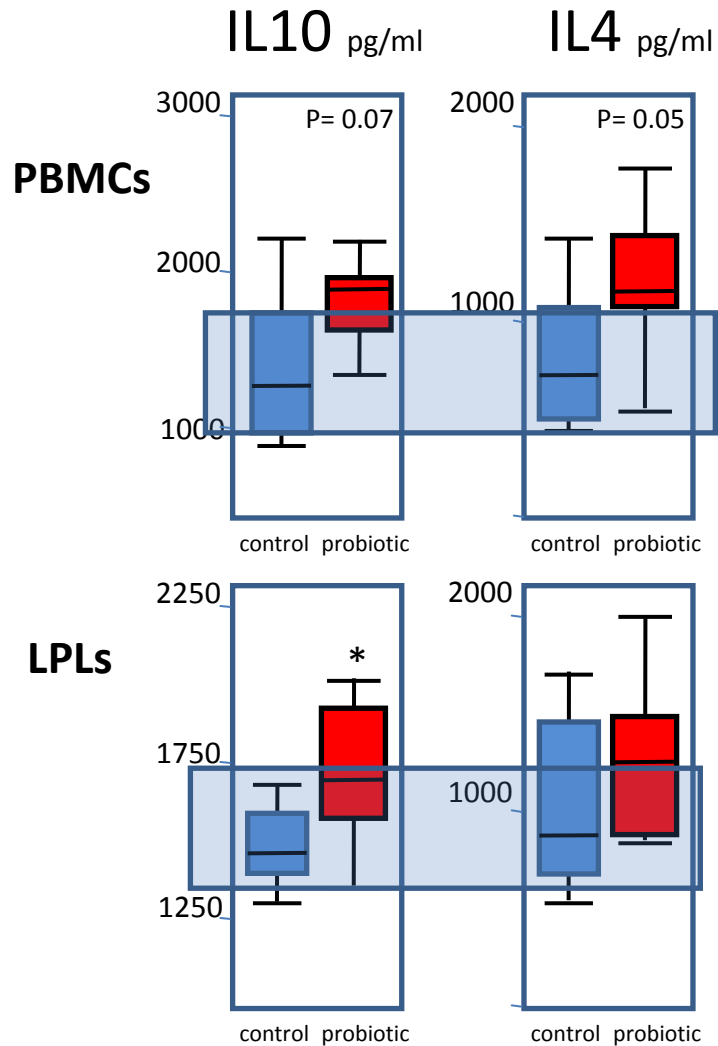
Evidence - I

PBMC's and LPL's are activated by the probiotic



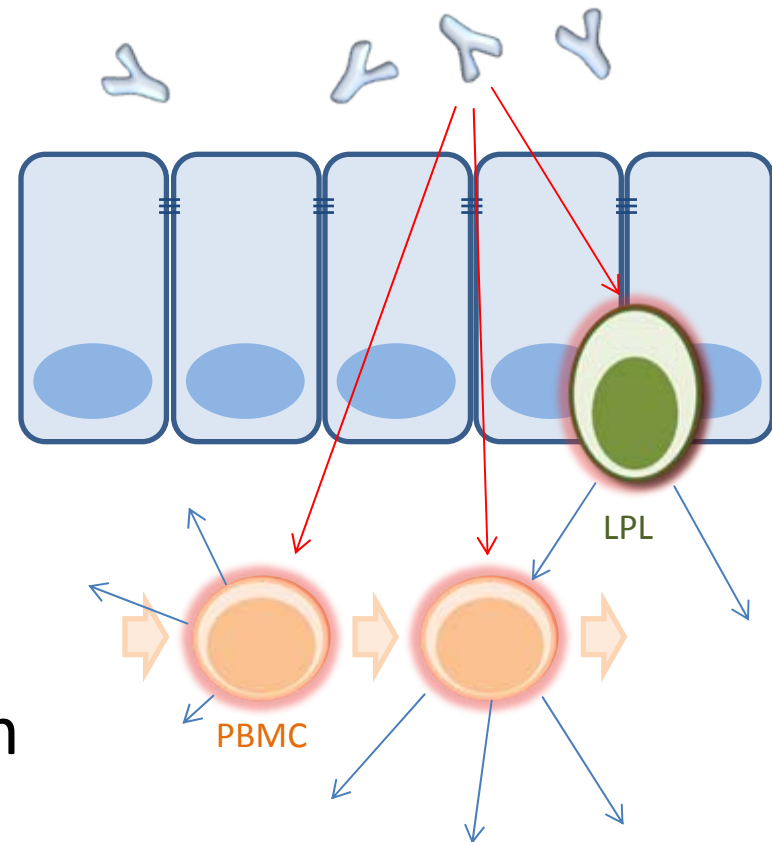
Evidence - II

Increased production of cytokines when the probiotic is present



Working model

- Probiotics increase the activity of immune cells
- Increased immune signalling
- Probiotic strains can 'boost' the immune system and can limit infection

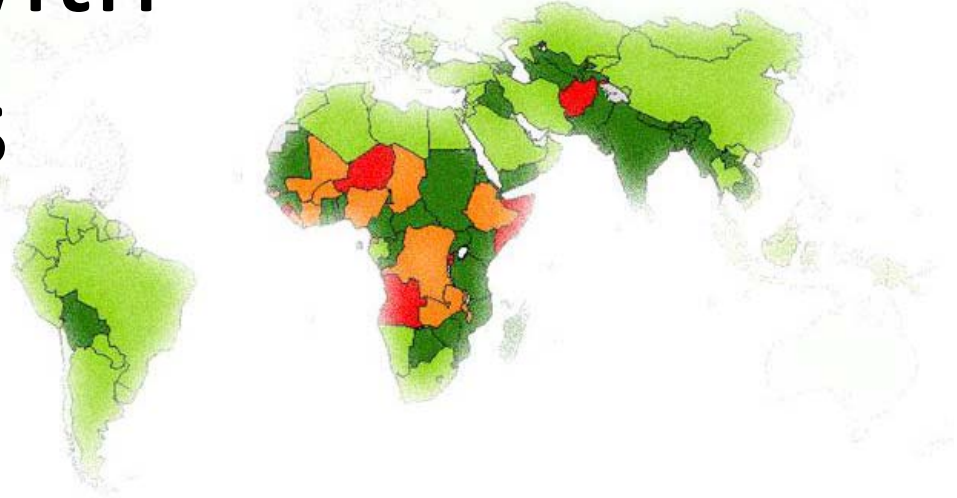


Advantages of probiotics



- Natural
- Greater scope for delivery (Third World)
 - Cheap, can be grown close to, or on site?
- Can work through immune system
- Resistance less likely to develop
- Can be combined with nutritional solutions
 - Oral rehydration, Zinc, sanitation, etc.

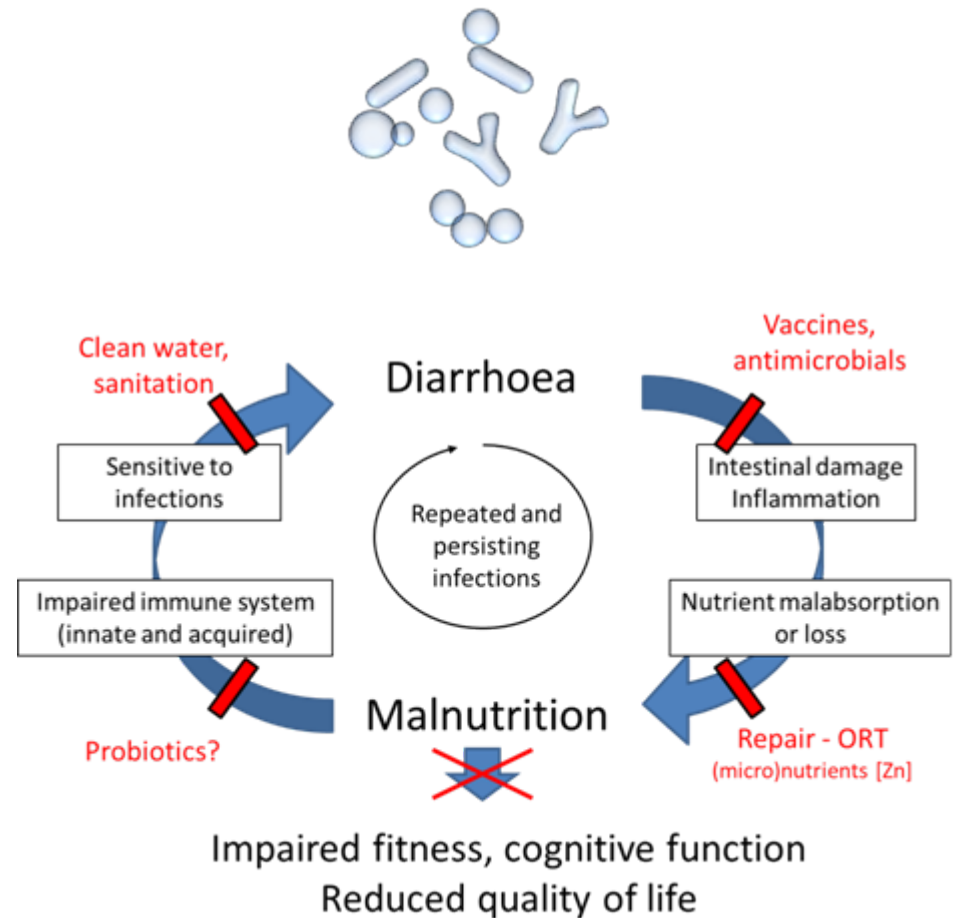
Challenges with probiotics



- Which probiotic?
- What is the best delivery method?
- Can safety of probiotics be assured?
- Can probiotics be afforded?
 - Average daily income in Sub Sahara is \$1.50

Conclusions

Probiotics will prove a useful additional weapon in the fight to break the infection-malnutrition cycle of disease



Thanks



Gerald Fitzgerald
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(APC & Teagasc)

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(University of Virginia)

Gillian Gardiner, Garret Casey, Pat Casey, Orla Hart, Peadar Lawlor, Maria Walsh



Alimentary Pharmabiotic Centre
Mining Microbes for Mankind



Germany

Deaths

15

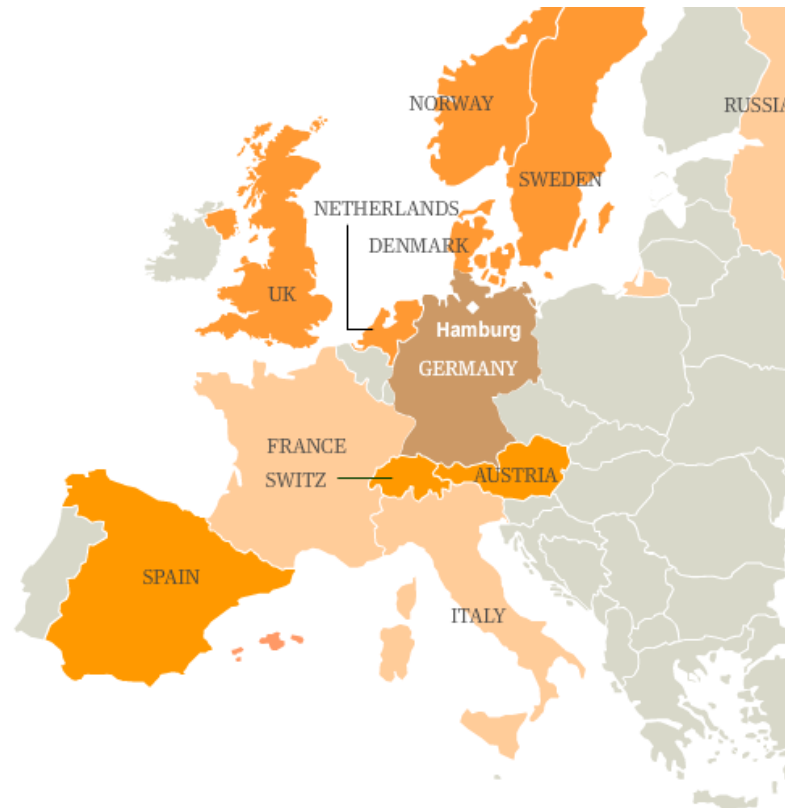
Suspected cases of E coli infection:

1,250

Germany's national health agency said 470 people are now suffering from haemolytic uremic syndrome (HUS), in which E coli infection attacks the kidneys, sometimes causing seizures, strokes and comas. That figure is up from 373 reported Tuesday. Germany typically sees a maximum of 50 to 60 HUS cases in a year.

Key

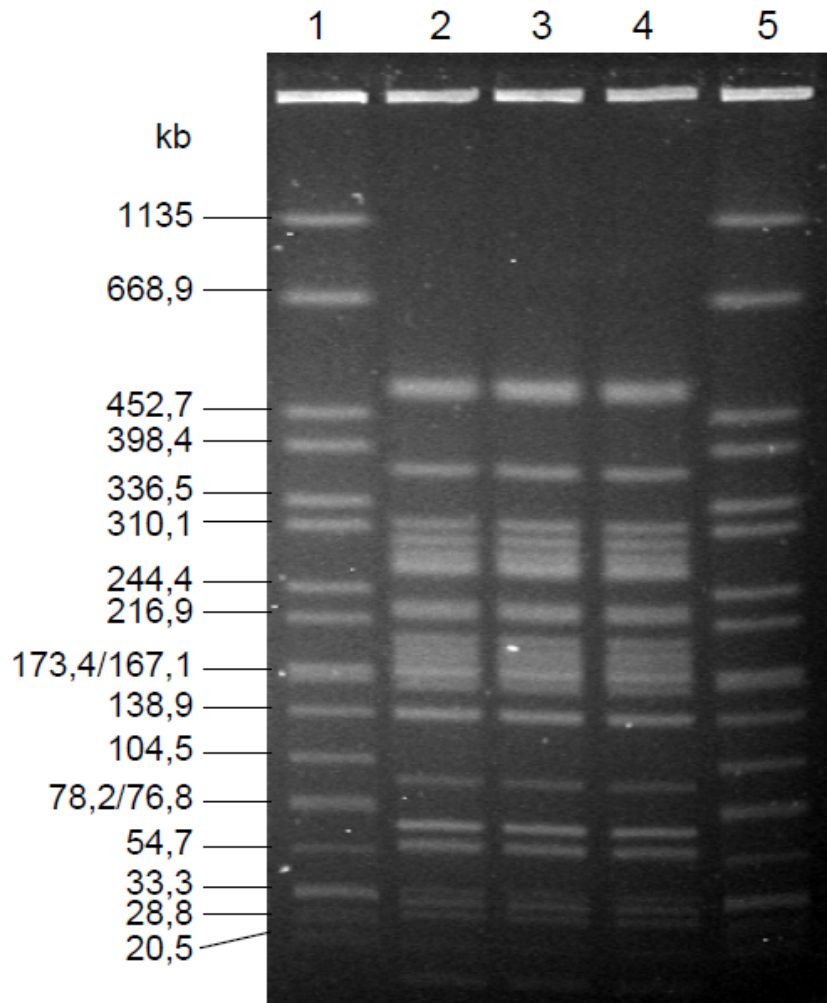
- Outbreak centre
- Suspected cases
- Other countries affected



Food Safety Authority of Ireland (June 1, 2011)

- *E. coli* O104:H4 multi drug resistant - bloody diarrhoea - HUS - death
- Epidemiology suggests cucumbers, lettuce, tomatoes (Hamburg, ~25 cases)
- Spanish cucumbers contaminated, but **not** with the outbreak strain
- No evidence of contaminated foods in Ireland

Macrorestriction pattern (*Xba*I) from human *E. coli* O104:H4 isolates from the current outbreak



PFGE according to Prager et al. (2011) IJMM 301:181-191.

Lanes 1 and 5 MW-Standard *Salmonella* Braenderup H9812. Lane 2: RKI-11-02027 (HUS), Lane 3: RKI-11-02034 (diarrhea), Lane 4: RKI-11-02060 (bloody diarrhea).