

Travellers' diarrhoea

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A Global Health perspective



Image sourced from Brit Med J 2009; 338: 1467

When is diarrhoea diarrhoea?

- acute

- an increase of 3 or more loose or watery stools per day lasting up to 2 weeks

- chronic

- ditto for more than 4 weeks
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What is diarrhoea – Bristol stool form scale



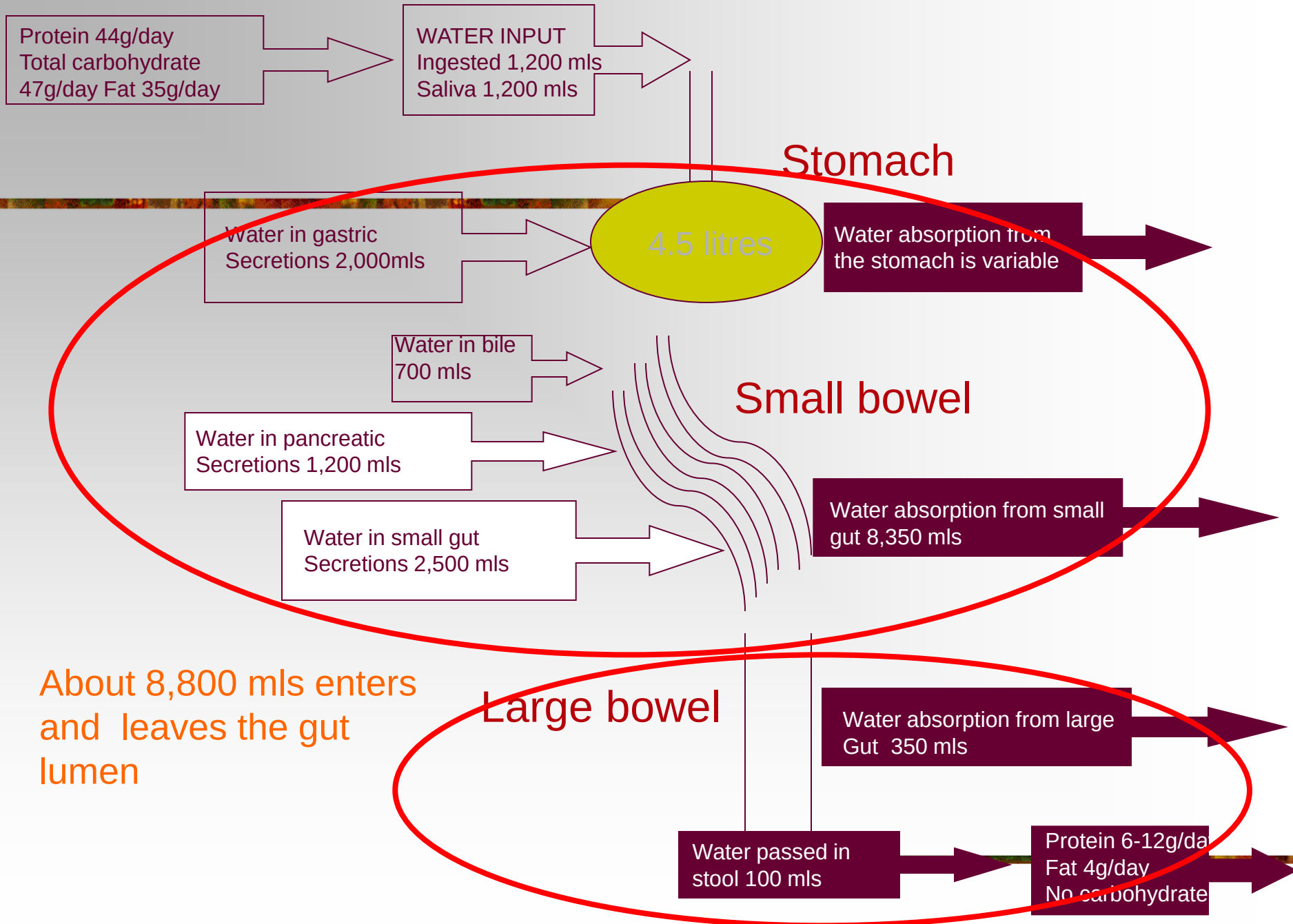
The Bristol Stool Form Scale



- Type 1 - separate hard lumps, like nuts
- Type 2 - sausage-like but lumpy
- Type 3 - like a sausage but with cracks in the surface
- Type 4 - like a sausage or snake, smooth and soft
- Type 5 – soft blobs with clear cut edges
- Type 6 - fluffy pieces with ragged edges, a mushy stool
- Type 7 - watery, no solid pieces

Mechanisms of infection related diarrhoea

- toxin production
 - invasion of bowel wall
 - immunological effects
 - bacterial overgrowth
 - parasite invasion
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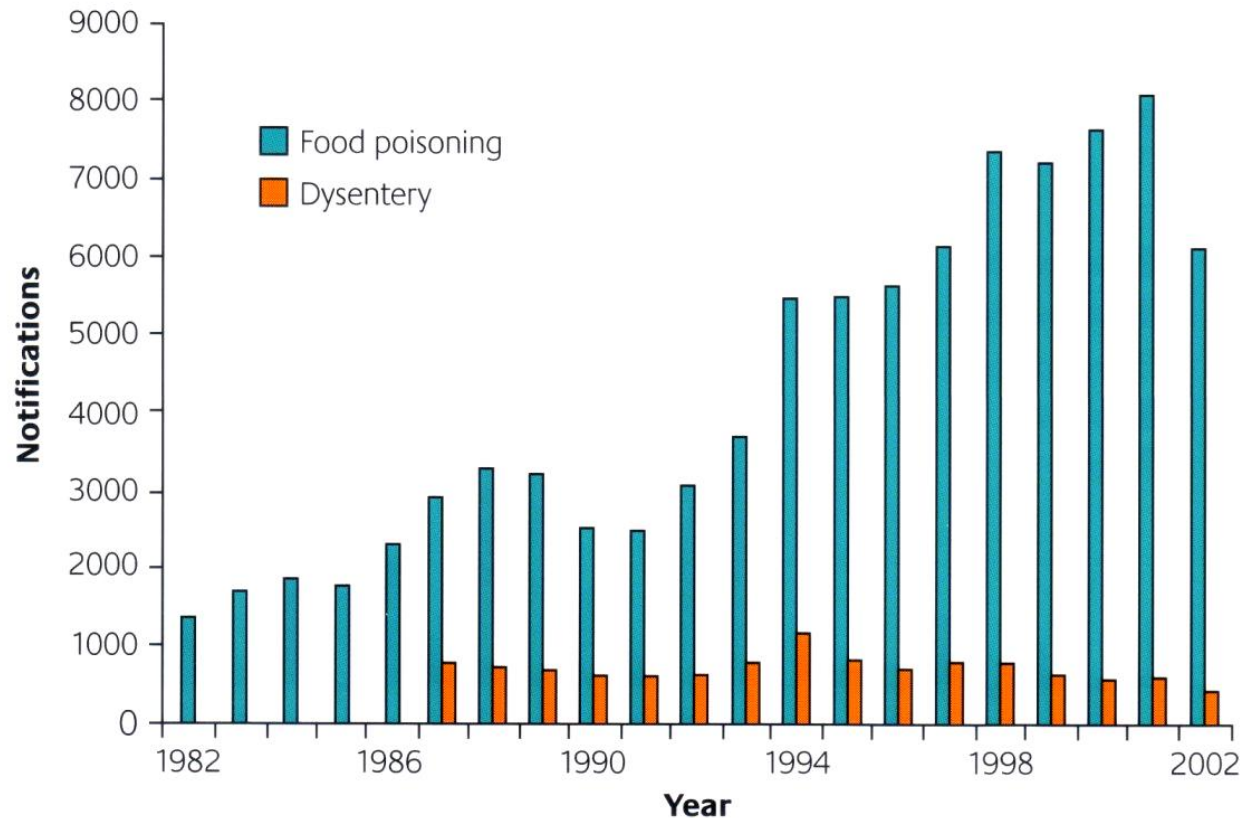


The scale of the problem

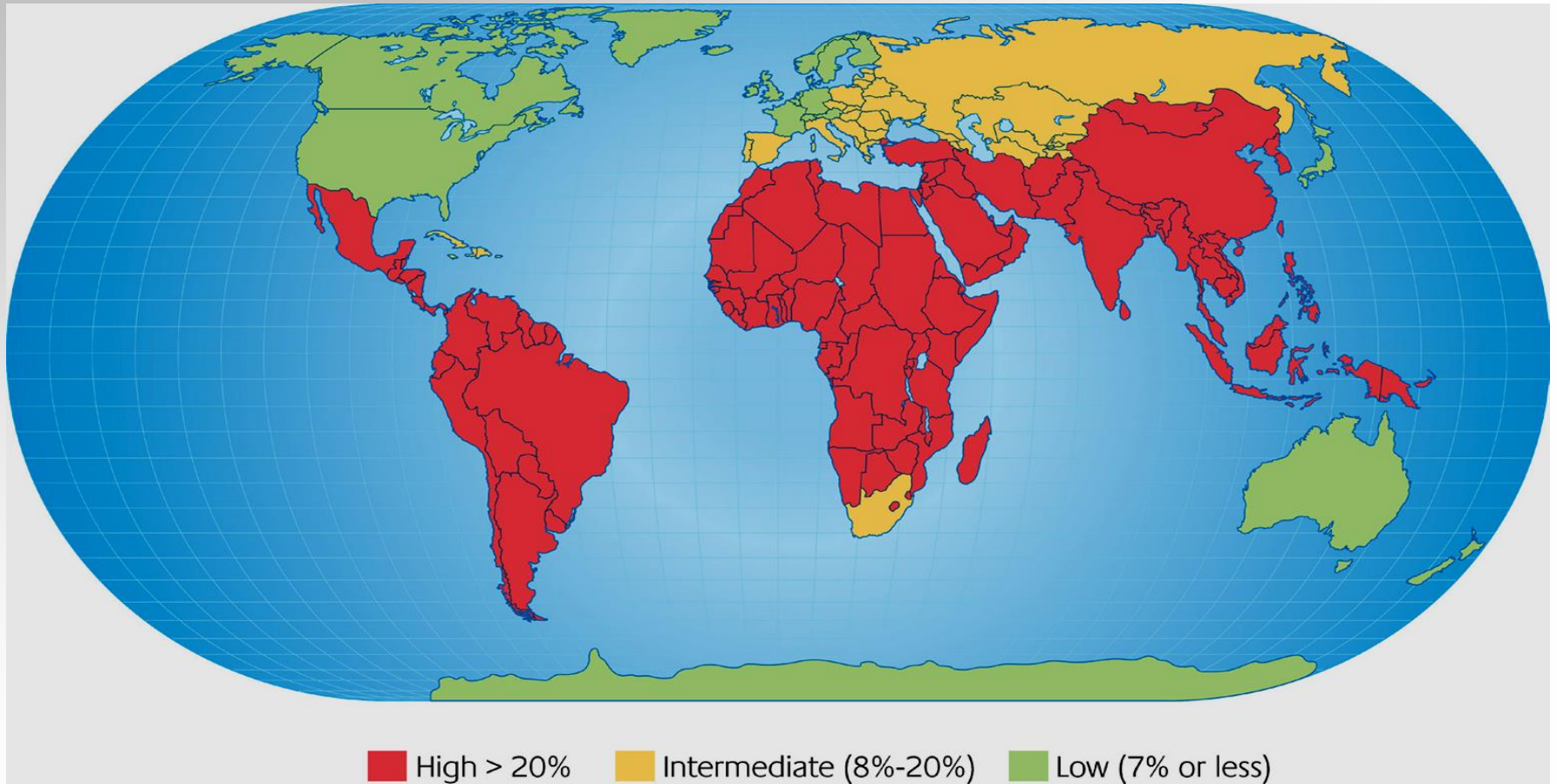
- 1 billion people travelled internationally in 2011
- 100 million people travel to developing countries annually of whom 50% get diarrhoea
- one third of travellers seeking medical attention had significant pathogens

Travellers' diarrhoea

Figure 2 *Notifications of food poisoning and dysentery presumed to be contracted abroad, England and Wales: 1982 - 2002*



Global epidemiology



Foreign travel-associated illness: a focus on travellers' diarrhoea - 2010 report, HPA

High risk destinations

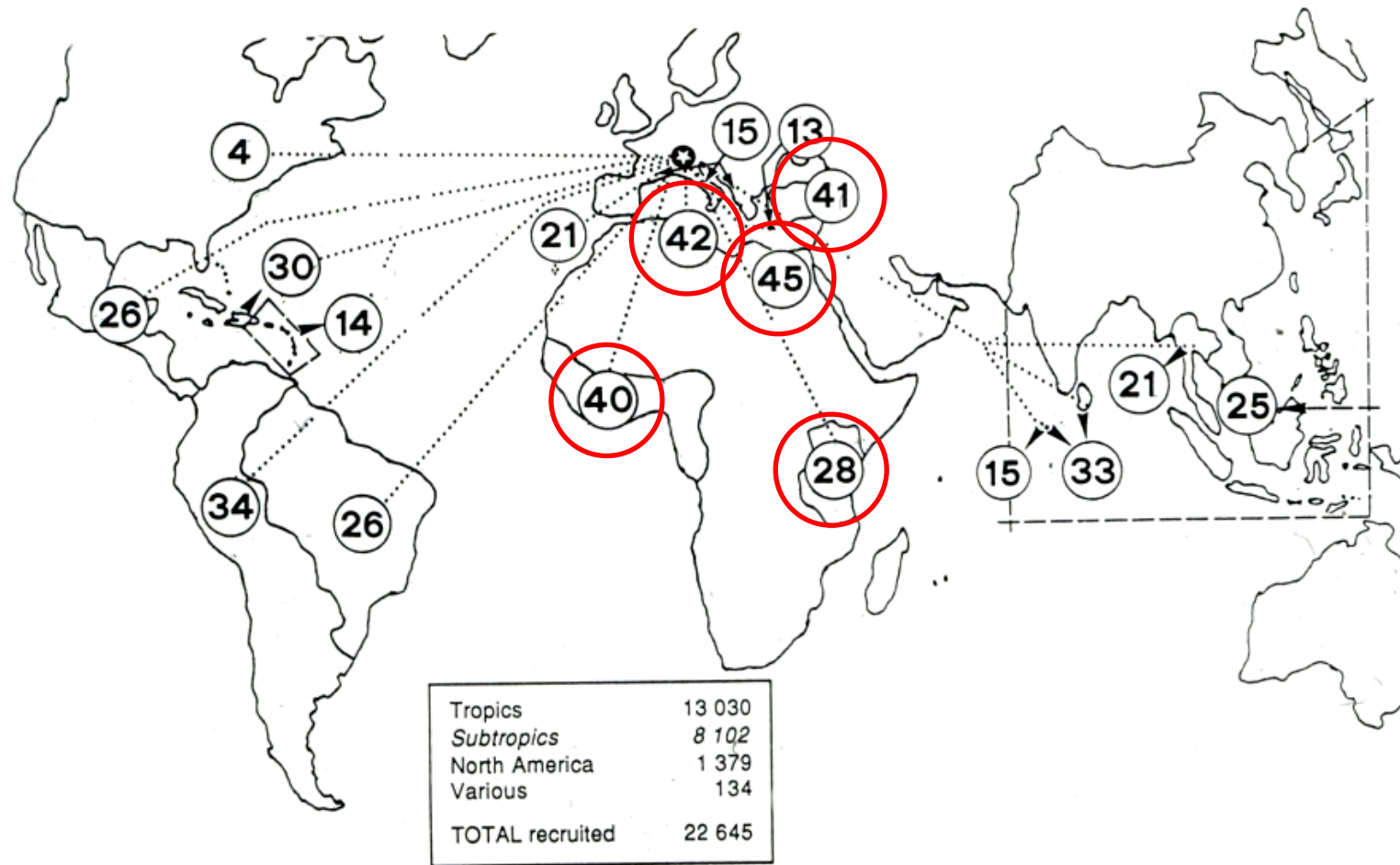


Fig. 2 Incidence of traveller's diarrhoea per 14 days of stay in 22,645 European tourists to various destinations

Causal pathogens identified in 40-60%

■ Bacteria >80%

- *Esch. coli* - enterotoxigenic and enteroaggregative
- *Campylobacter jejuni*
- Shigella
- Salmonella
- *Vibrio cholerae* (rare)
- Campylobacter more likely in SE Asia
- Yersinia underestimated
- Aeromonas and Plesiomonas may have localised importance

■ Viruses 5-10%

- Rota, noro and sapovirus

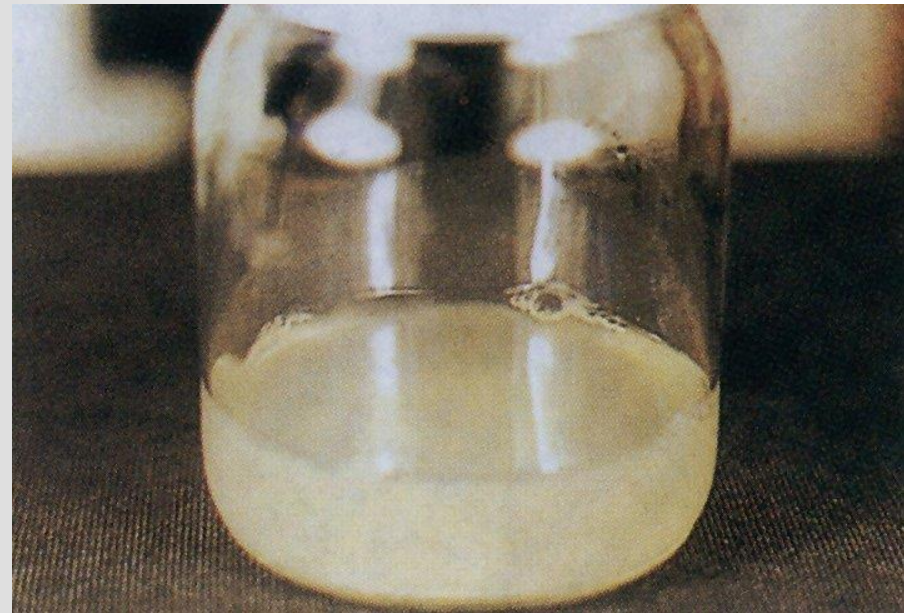
■ Protozoa (2-10%)

- *Giardia intestinalis*
- *Entamoeba histolytica*
- *Cryptosporidia*
- *Cyclospora*

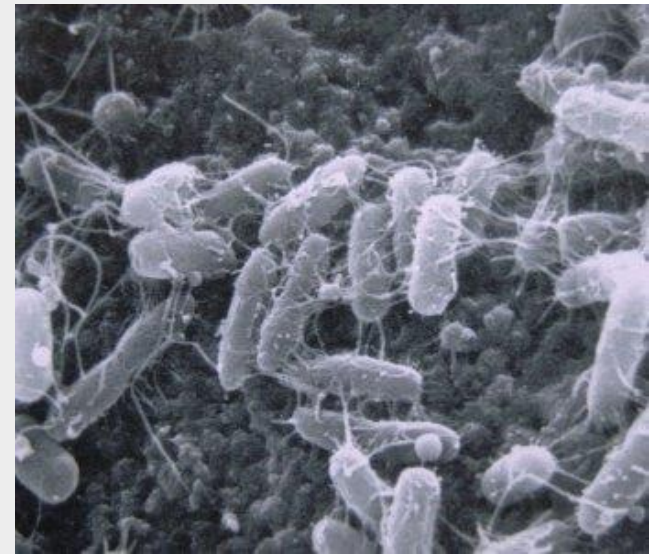
■ Helminths and Flukes

Cholera

- incubation 12-72 hours
- toxin mediated
- fever unusual
- worse in *H. pylori* infected persons
- small bowel diarrhoea
 - rice water typically but diarrhoea may be moderate in travellers



Escherichia coli



- enterotoxigenic
 - abrupt onset diarrhoea usually without vomiting
 - usually no fever
- Enteropathogenic
 - Infantile diarrhoea in developing countries
- Enterohaemorrhagic
 - Shiga toxin producing
- Enteroaggregative
 - adherent to intestinal mucosa
 - associated with TD at similar rates to ETEC
- Enteroinvasive
 - Watery diarrhoea progressing to dysentery behaving like Shigella

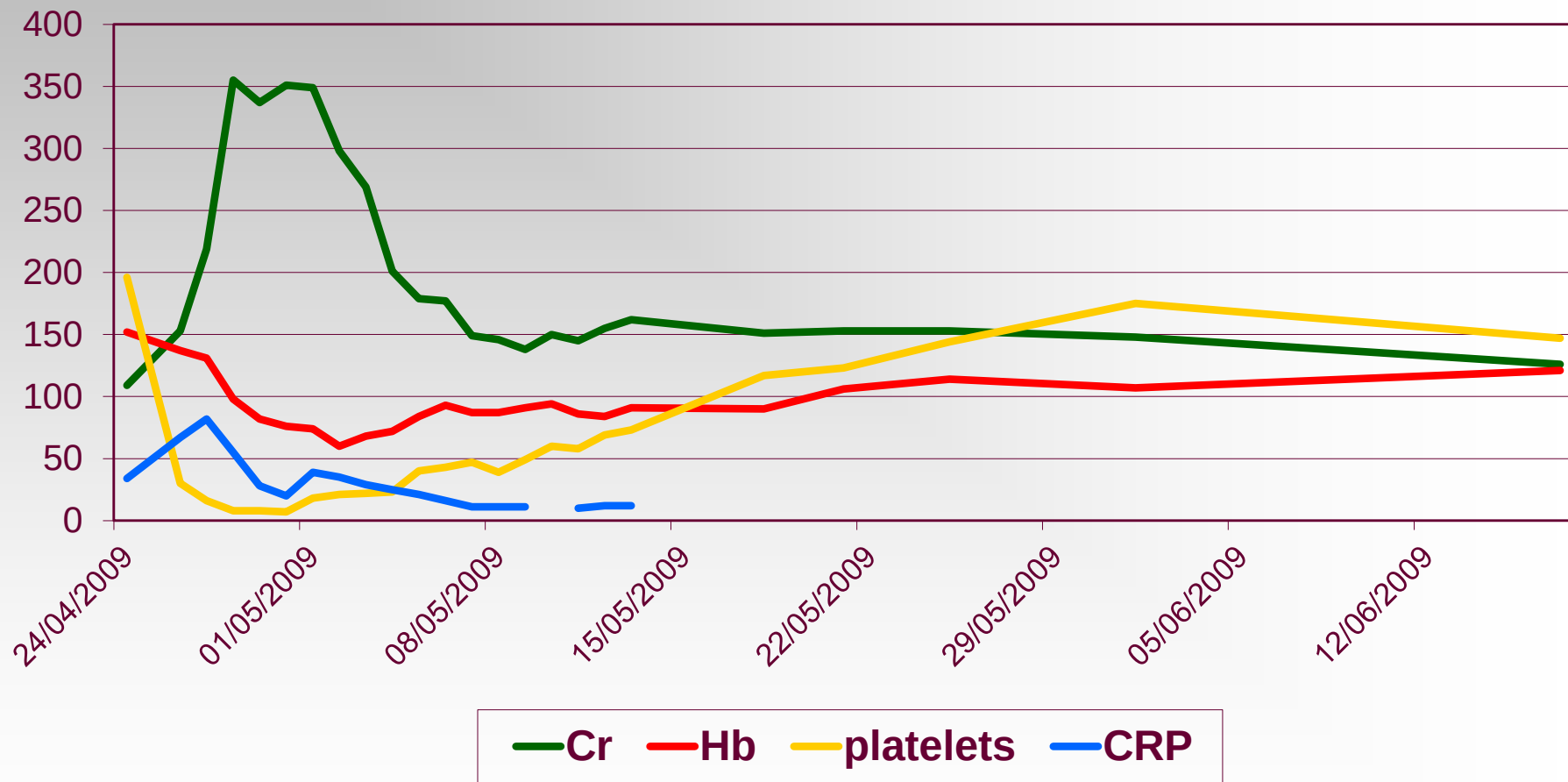
Entero-haemorrhagic *Esch. coli*

0157:H7 and 0104:H4 (2011 in Germany)

- large gut diarrhoea, bloody in 7%
- no fever
- risk of haemolytic-uraemic syndrome or thrombotic thrombocytopenic purpura
 - 6% in 0157
 - 20% in 0104
- some antibiotics contraindicated
 - ciprofloxacin increases expression of Shiga toxins
 - azithromycin, meropenem and rifaximin reduce expression

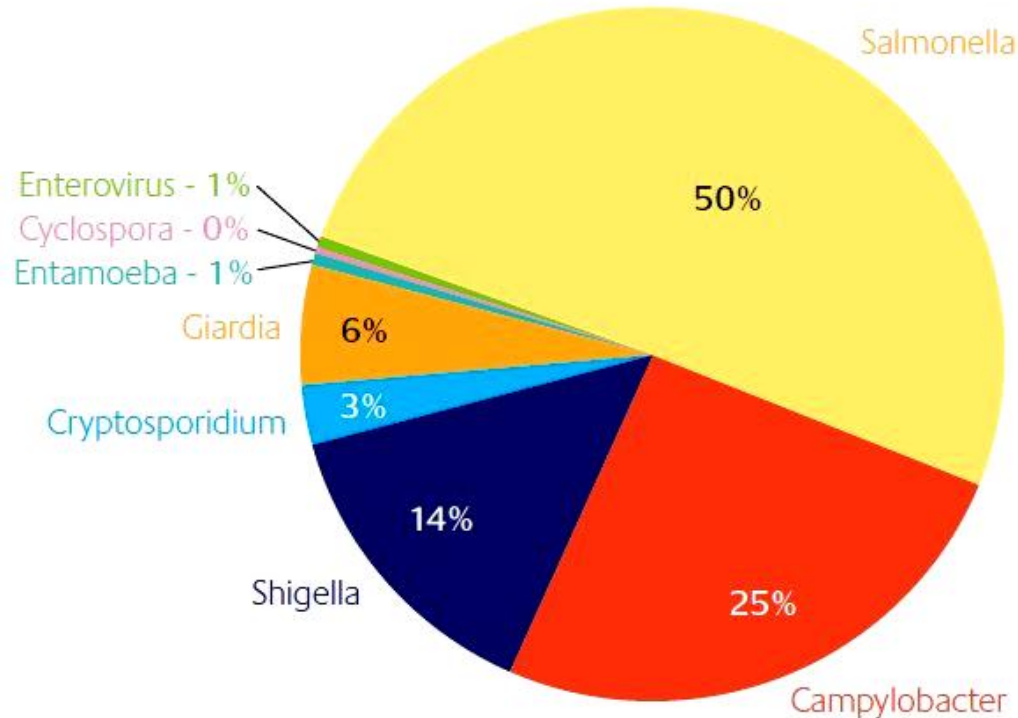


HIV +ve patient admitted with bloody diarrhoea



When ETEC is excluded

Figure 3. Travel-associated GI illness reported in England, Wales and Northern Ireland: 2004 - 2008 (N=24,332)



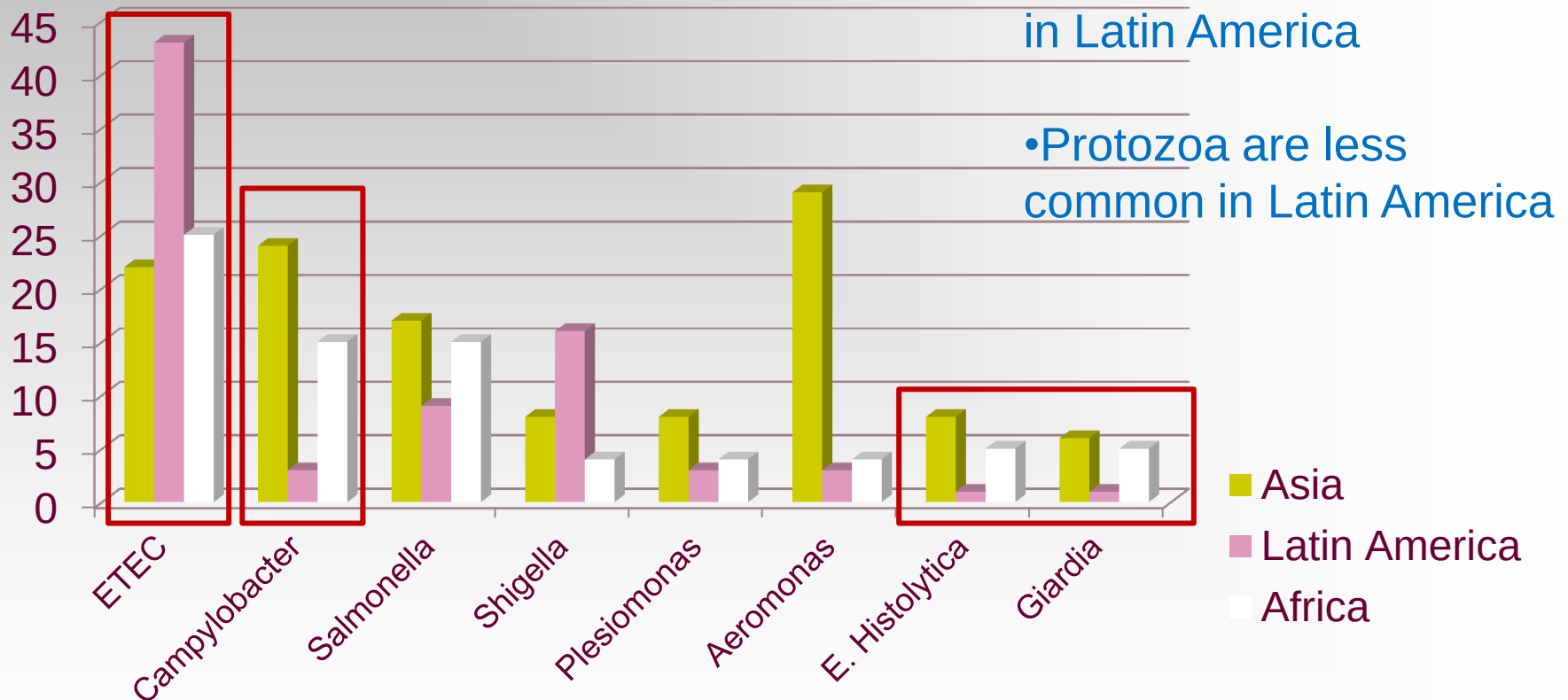
Risk factors for TD (1)

- where you go
 - destination is the single most powerful predictor
- season of the year
 - summer
- where you stay
 - room only or B & B
 - self arranged
 - expensive hotels and cruise ships are not protective



Continental variations

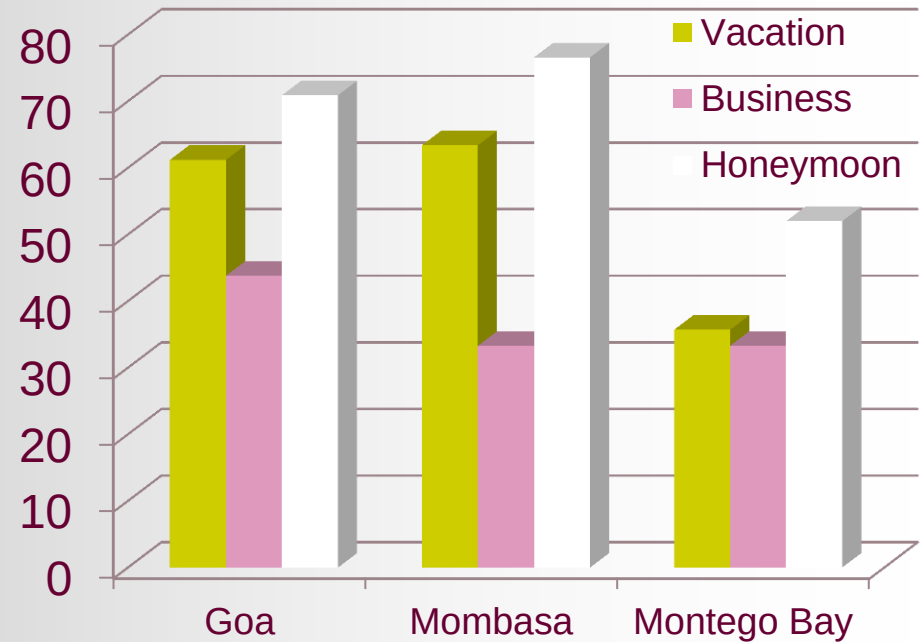
- In general risks in Asia and Africa are similar with campylobacter more common in Asia



- ETEC is more common in Latin America

- Protozoa are less common in Latin America

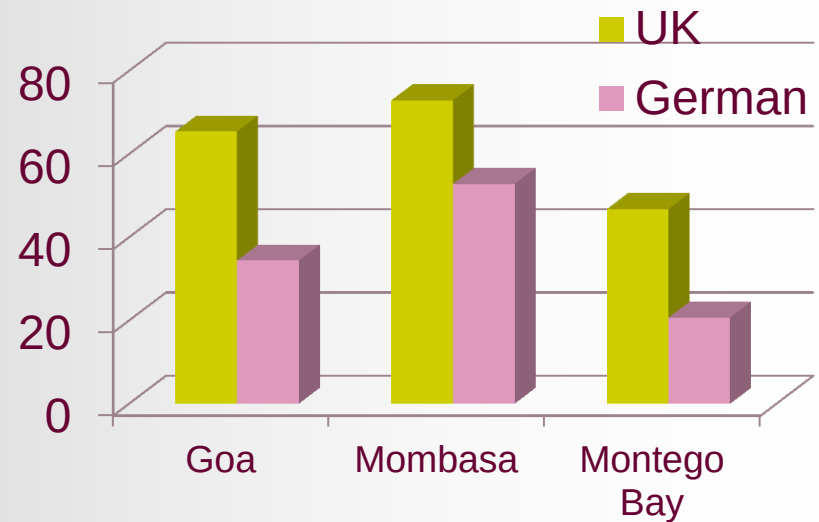
Risk factors (2)



- who you travel with
 - friends are worse than family
 - a new wife is worse than an old one
- what you eat and drink
 - shellfish concentrate bacterial and viral pathogens

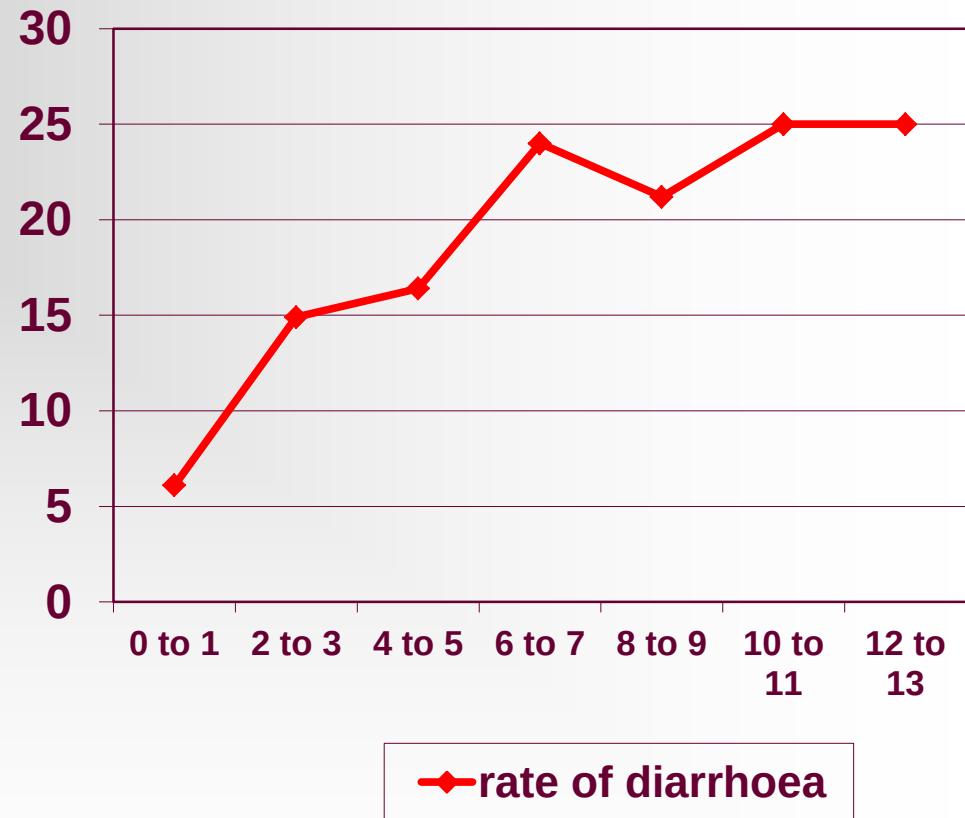
Host factors

- Nationality
- Blood group O susceptible to shigella
- Interleukin 8 promotor gene a/w enteroaggregative *Esch. coli*
- Gastric hypochlorhydria – PPIs and *Helicobacter pylori*
- HIV – low CD4 predisposing to protozoa and salmonella
- Immunosuppressive and common IgA deficiency



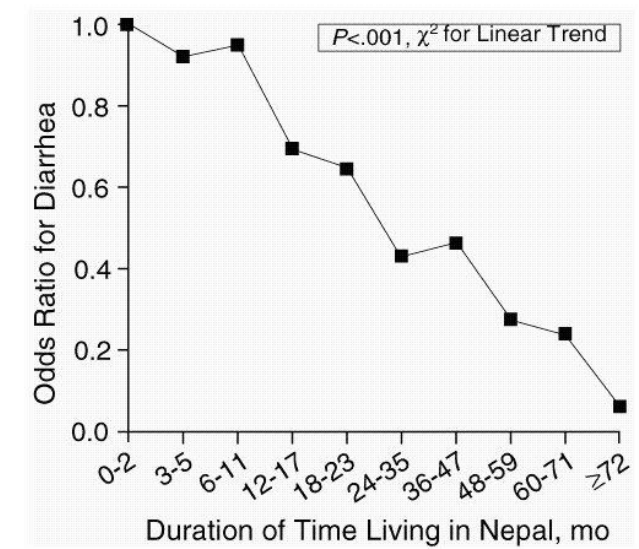
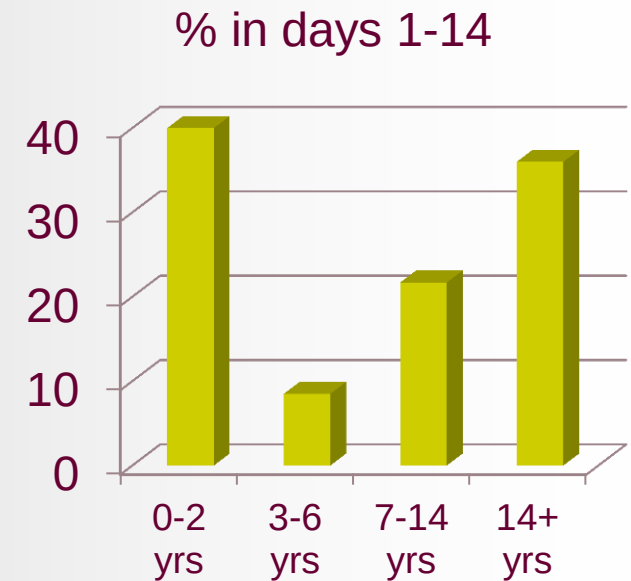
Rates of diarrhoea compared to dietetic errors

- 700 Swiss travellers to Kenya
- 98% had accepted food or beverages that would not be recommended
- diarrhoea incidence 19.5% was proportionate to the number of dietetic errors



Bowel Immunity

- risk factors for expatriates
 - younger age
 - shorter duration of stay
 - by the end of 6 years diarrhoea frequency is very low
 - eating in restaurants
 - dietary errors become less important



Syndromes

- short lived watery diarrhoea without significant fever
 - caused by both invasive pathogens and secretory diarrhoea
- fever, bloody diarrhoea or features of invasive disease
 - bacteria more likely
 - *Campylobacter*, Enteroinvasive *Esch coli*, *Shigella*, *Salmonella*
- chronic diarrhoea lasting >1 month in 1-3%
 - protozoa more likely

Social and occupational consequences

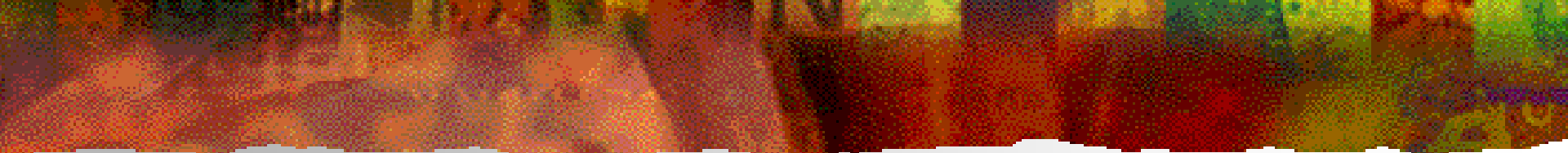
- impairs quality of life
- disrupts travel itineraries
 - one fifth confined to bed
 - two fifths have to change their itinerary
 - 1% admitted to hospital
- interferes with business opportunities.
- decreases combat effectiveness in soldiers

Medical consequences

- may progress to chronic diarrhoea
 - 5-10% lasts longer than 2 weeks
- in 10% (4-32) may be associated with development of irritable bowel syndrome
- reactive arthritis may be a/w prolonged diarrhoea and be persistent and is more common in HLA-B27 positive individuals
- Guillain-Barré syndrome 1:1000 in Campylobacter
- long term effects on bowel flora

Tropical sprue

- Predisposition
 - *H. pylori*
 - Infective aetiology suggested by
 - frequent initiation by acute diarrhoeal episode
 - epidemic and seasonal pattern
 - response to treatment with antibiotics and nutritional supplements
 - Pathogenesis
 - gram negative rods appear in SB
 - probable secretory syndrome
 - malabsorption of bile acids → fat malabsorption
 - Vitamin B12 malabsorption
-



Management

Oral fluid rehydration

- tell travellers that this:
 - will **not** reduce the frequency or volume of stools
 - will replace fluid loss and ensure metabolic stability
- what to use?
 - sugar and salt powder sachets (use sterile water) available from most UK chemists and may not be available abroad
 - make up rehydration solution with
 - finger pinch of salt plus teaspoon of sugar in mug of sterile water plus squeeze of orange juice
 - one cupful for each loose stool



Antibiotics? What does the NHS advise?

- Treatment with antibiotics is not recommended for diarrhoea if the cause is unknown
 - it will not work if the cause is a virus
 - it may cause unpleasant side effects
- can become less effective at treating more serious conditions if they are used to treat mild conditions

What does Travax advise?

- Antibiotic self treatment is unnecessary for the majority of travellers and should NOT be recommended routinely
- Travellers suitable for self treatment may include:
 - Travellers to remote areas
 - Travellers with pre-existing bowel problems such as IBD where infection may trigger a relapse
 - Travellers with pre-existing medical conditions
 - Travellers with a tendency to severe TD

What does CDC advise?

- 'Empiric therapy for TD remains the best therapy'
 - benefit proven in numerous studies
 - first line quinolone
 - Single dose or one day therapy
 - second line azithromycin
 - Single dose of 1G (limited by nausea) or 500mg daily for 1-3 days
 - third line rifaximin
 - 200mg tds for 3 days

What accelerates the emergence and spread of anti-microbial resistance?

- weak or absent anti-microbial resistance surveillance and monitoring systems
- inadequate systems to ensure quality and uninterrupted supply of medicines
- inappropriate use of anti-microbials, including animal husbandry
- poor infection and control practices
- insufficient diagnostic, prevention and therapeutic tools
- *‘single isolated interventions have little impact’*

Preventing emergence of resistance

- *‘Have all patients treated with the most effective, least toxic, and least costly antibiotic for the precise duration of time needed to cure or prevent an infection’*

Arguments for & against antibiotics for TD

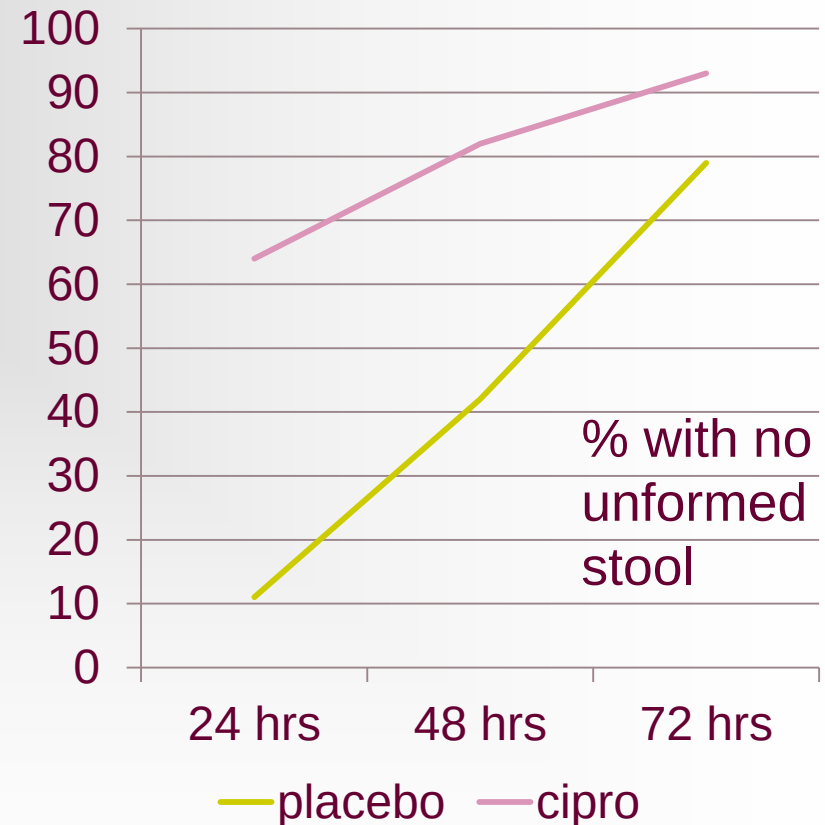
- we don't know the causative organism
 - we may stimulate antibiotic resistant organisms
 - ciprofloxacin increases expression of Shiga toxins in O157
 - already the case for most UTI treated in GP
 - few patients have a viral or parasitic cause – most will have a sensitive organism
 - spillover from agricultural use for growth enhancement is much more important
 - countries with poor anti-microbial stewardship tend to have more resistance
 - antibiotic resistance is most likely where exposure to the agent is long and sustained
-

What are the potential benefits of antibiotics?

- shorter duration of intestinal infection
 - potentially less risk of invasive phase with some organisms
 - reduced risk of transmission to others
 - *may* reduce frequency of post infectious complications
-

Placebo controlled RCT in British soldiers

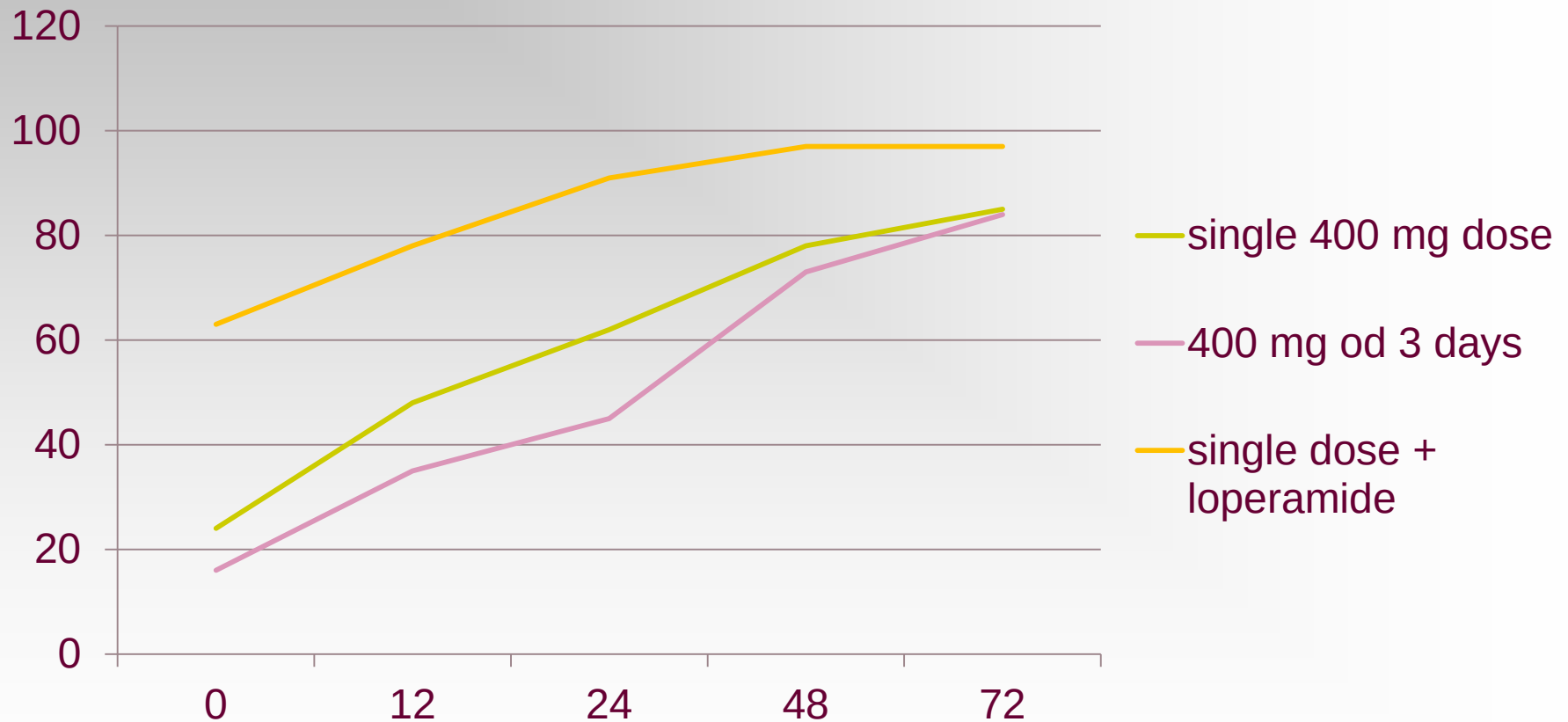
- 88 subjects with 45 on ciprofloxacin 500mg single dose
- mean time to last unformed stool reduced from 53.5 hours to 24.8 hours ($p < 0.0001$)
- mean no. of liquid stools reduced from 11.4 to 5.0 ($p < 0.0001$)



Lancet Editorial

- *‘All travellers from the developed to the developing world, especially those taking short trips , are advised to carry a quinolone antibiotic and an anti-motility agent; one of them should be taken at the first sign of diarrhoea’*

% of 166 subjects passing last unformed stool during the 72 hours after start of treatment



Cochrane review 2000

- 12 placebo controlled trials
- various antibiotics
- in a variety of dosages prior to 2000
 - 'antibiotic treatment is associated with shorter duration of diarrhoea but a higher incidence of side effects. Trials generally do not report duration of post treatment diarrhoea using time to event analyses and should do'

Expert Reviews

■ Al Abri 2005

- ciprofloxacin 750mg/norfloxacin 800 mg/
levofloxacin 500mg as a single dose or 500mg
twice daily for 3 days
- none of the references cited used these doses

■ 2008 Hill & Ryan

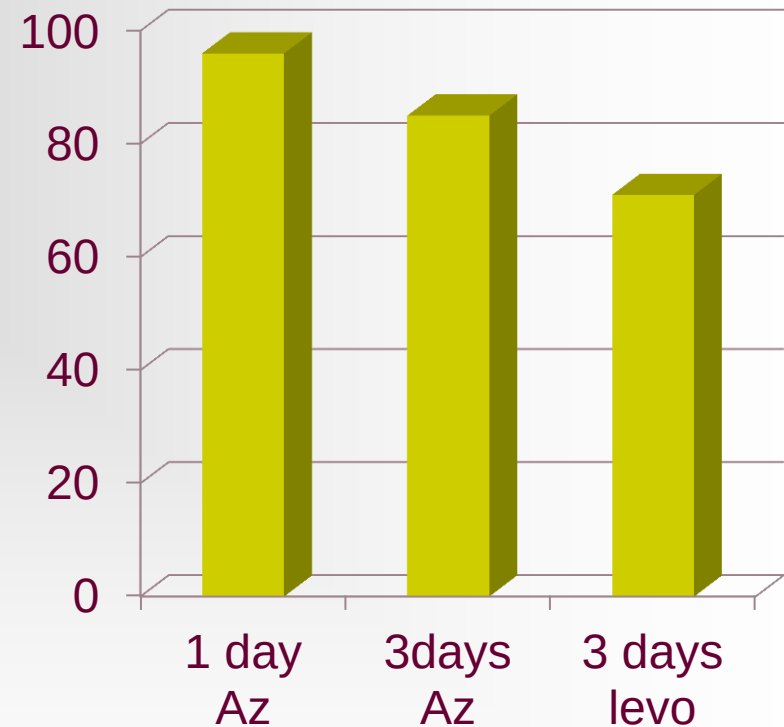
- Similar recommendations with no references

What do we know?

- single dose quinolones at moderate (e.g ciprofloxacin single dose 500mg) reduce the duration and severity of TD
 - single dose quinolone at enhanced dosage (e.g. ciprofloxacin 750mg) is also effective
 - two doses of quinolone in one day is effective
 - clearance of some organisms may be incomplete with smaller single doses but there is no evidence of adverse outcomes with moderate doses of single dose quinolones
 - we know that in SE Asia single dose azithromycin at 1G is more effective than 3 days of quinolone
-

US servicemen in Thailand

- RCT of 156 personnel
 - azithromycin 1G single dose
 - v azithromycin 500mg od for 3 days
 - v levofloxacin 500mg daily for 3 days
- *'Single dose azithromycin is attractive in areas where invasive pathogens are common and quinolone resistance is increasing. Elsewhere a quinolone in a single dose of 500mg remains adequate'*



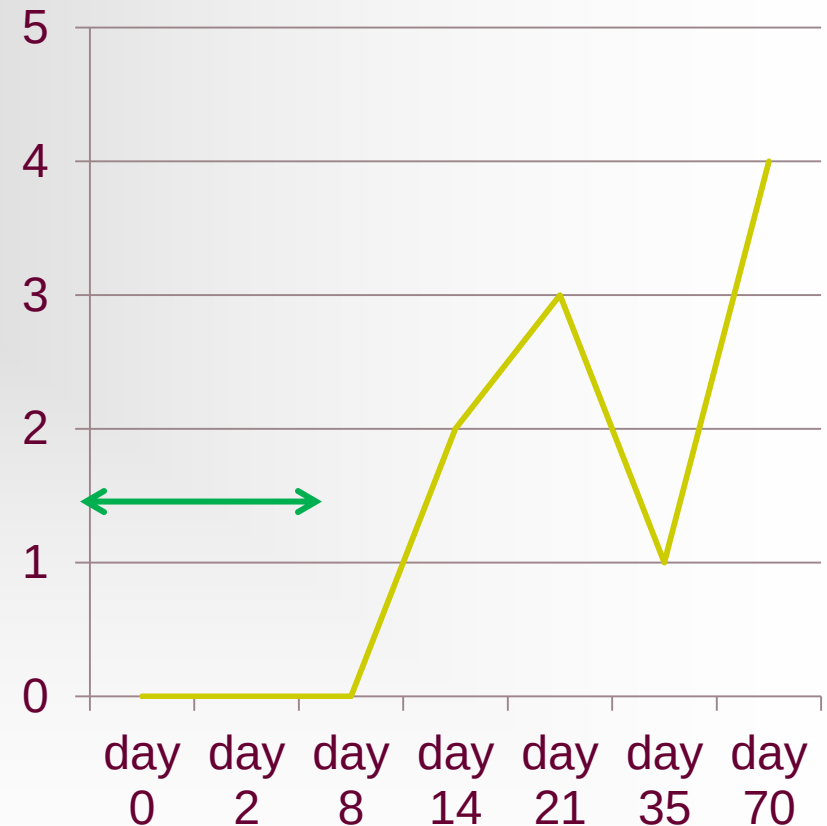
■ Clinical cure at 72 hrs

Antibiotic prophylaxis

- prophylaxis usually reserved for
 - when a trip is vitally important
 - the consequences of watery diarrhoea would be difficult to manage e.g. colostomy or ileostomy
- antibiotic choice
 - fluoroquinolone (ciprofloxacin 500mg daily)
 - azithromycin for SE Asia (no data to guide on dosage)
 - rifaximin 200mg once or twice daily but not where campylobacter risk is high

Potential problems with rifaximin

- not absorbed and is not useful for invasive organisms
- uncontrolled study on a 7 day course of rifaximin at 400mg BD in 12 volunteers
 - *higher than prophylactic dose*
 - *Staph. aureus* resistance to rifampicin induced in >50%



Other preventative modalities

- Oral cholera vaccine
 - heat labile toxin of ETEC is very similar to cholera toxin
 - 67% fewer ETEC diarrhoeas in Bangladesh with a precursor vaccine
 - 23% reduction in TD of all causes in Finnish travellers in Morocco with a precursor vaccine
 - protective efficacy of 50% claimed for ETEC diarrhoea in US students in Mexico after subset analysis on the timing of diarrhoea but Cochrane assessed as no significant effects on ETEC, or all cause diarrhoea
 - overall marginal benefit against all cause TD
 - benefit has no implications for anti-microbial resistance



My personal practice

- I will continue to prescribe single dose anti-microbials for self treatment of TD
 - there appears to be no advantage for 3 days or higher doses than 500 mg for ciprofloxacin and 1G for azithromycin
 - resistance induction is probably minimal
 - I have concerns about the potential for rifampicin resistance in staph exposed to rifaximin
 - onus is on the company to fund a placebo controlled study to settle concerns about treatment courses
 - I rarely prescribe prophylaxis with any agent
-

Avoiding disasters

- always
 - perform rectal exam in patients with persistent diarrhoea
 - investigate patients who complain of rectal bleeding
 - look for a reasonable explanation for iron deficiency
 - retain a low threshold for sigmoidoscopy/colonoscopy
-