Revisiting traveller’s diarrhoea

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19 Nov 2015

Q 1: On a given trip, traveller's diarrhoea is causing disability for an average of …?

- <1 day
- 1 day
- 2 days
- 3 days
- 4-5 days

Q 2: What is the overall percentage of returning travellers colonised with ESBL-Enterobacteriaceae?

- <1%
- <5%
- 5-10%
- 10-20%
- 20-30%
- >30%

Traveller’s diarrhoea

- Definition
- Epidemiology
- Microbiology
- Prevention
- Treatment

- Impact of diarrhoea on the traveller

- TD in perspective

TD Definitions

- WHO definition
- 3+ unformed stools in 24 hours, with 1+ :
  - Nausea, vomiting, abdominal pain, fever, faecal urgency

- Mild:
  - acute watery diarrhoea (AWD) of mild severity (normal level of activity)
- Moderate/severe:
  - AWD with decreased level of activiy
  - or dysentry
  - or acute febrile watery diarrhoea (subjective fever)

Hill Curr Opin Infect Dis 2010; Lalani J Travel Med 2015

TD…Definitions?

- Heterogeneity of population (age, host risk factors,…)
- …of travel destinations/itineraries
- …of pre-travel advice
- Recall bias
- Selection bias eg travel clinic-based studies

- …global epidemiology of enteropathogens

→ variety of data, and cannot look at TD from the sole point of view of the visitor anymore

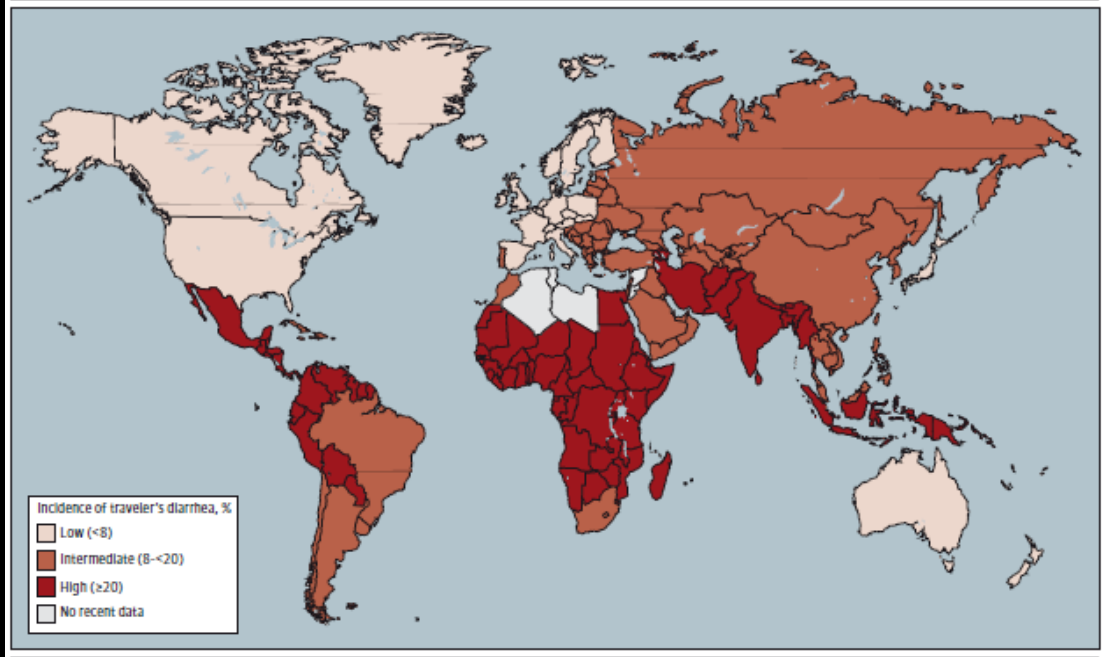
TD Epidemiology

- 100 – 300 million international travellers to ‘high risk areas’ = high burden areas
  - tropical or semitropical areas of Latin America, the Caribbean (Haiti and the Dominican Republic), southern Asia, and Africa
- 335/1000 medical visits by returned travellers
- 10-40% incidence for a 2-week stay

Okeke J Infect Dev Ctries 2009; Kantele CID 2015; http://www.who.int/topics/diarrhoea/en;
de la Cabada 2011; Freedman NEJM 2006

TD Epidemiology: incidence rates

Figure. Incidence Rates of Traveler's Diarrhea in the Initial 2 Weeks of Stay in Various Regions of the World Among Visitors Residing in Industrialized Countries, 1996-2008



Adapted from Greenwood et al,[15] Pitzurra et al,[16] Belderok et al,[18] Soonawala et al,[19] and Mues et al.[21]

Steffen JAMA 2015

TD Risk factors

Factors	Mechanism
Adventure travel, visiting friends and relatives	Varying exposure to contaminated food and beverages
Age	Unknown; possibly more pathogens ingested (crawling infants, larger appetite in adolescents)
Lack of caution in beverage and food selection	Varying exposure to contaminated food and beverages
Use of proton pump inhibitor therapy	Altered killing of enteric pathogens from gastric hydrochloric acid
Certain genetic factors (mostly polymorphism associations)	Interleukin 8 AA: high producers leading to greater intestinal inflammation
	Lactoferrin: high producers leading to greater intestinal inflammation
	High producers of interleukin 10 are more susceptible to TD, which may reflect immunomodulatory effects of heat-labile toxin of enterotoxigenic *E coli* stimulating increases in interleukin 10
	Osteoprotegerin: immunoregulatory member of tumor necrosis factor receptor superfamily that may function as an anti-inflammatory modulator that increases susceptibility to traveler's diarrhea
	CD14: receptor for bacterial lipopolysaccharide binding associated with the innate immune response to enteric infection and inflammation; different SNPs may increase susceptibility to traveler's diarrhea; others may lead to protection
	Type O blood may influence enteric infection through uncertain mechanisms
	Not possessing the nonsense mutation in *FUT2* gene that provides resistance to infection related to virus attachment and internalization

Steffen 2015; Ashley J Travel Med 2004

TD Risk factors

- Study of TD with trips < 6months; 2010-2013
- 24% (270/1120) returning travellers had TD:
  - Rate Ratio = 1,74-1,88 Africa > Asia/South America
  - Rate Ratio = 1,32 female > male
  - No difference if: ate poorly cooked, from vendors, unsafe water or ice, history of H2-blockers
- More related to the level of sanitation in the country visited than interventions by the traveller

Lalani J Travel Med 2015; Steffen 2015; Freedman NEJM 2006

TD Risk factors

- Other study from Swizerland; 2006-2008
  - 962/2800 = 34% had TD
  - 26% within 2 weeks
  - 17,3 had dysentry

  - Independant risk factors identified:
    - Longer stay
    - Allergic asthma
    - Psychiatric co-medication
    - Diarrhoea pre-travel
    - Fever (independent of TD)
    - BMI
    - Malaria prophylaxis

Pitzurra R BMC Infec Dis 2010

TD Microbiology

- When look for a cause: 50-94% identified pathogen

- ETEC (enterotoxigenic)
- EAEC (enteroaggregative)
- DAEC (diffusely adherent)
- Norovirus
- Rotavirus
- Salmonalla spp
- Campylobacter jejuni
- Shigella sp
- Aeromonas sp
- Plesiomonas shigelloides

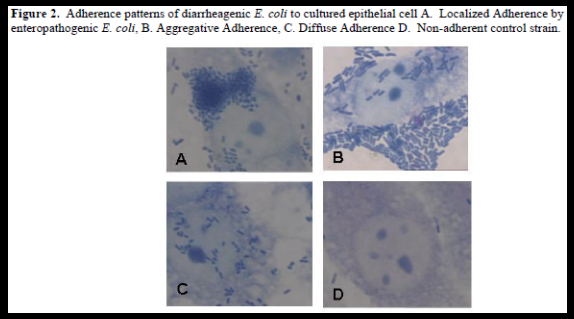


Figure 2. Adherence patterns of diarrheagenic *E. coli* to cultured epithelial cell A. Localized Adherence by enteropathogenic *E. coli*, B. Aggregative Adherence, C. Diffuse Adherence D. Non-adherent control strain.

- Enterotoxigen Bacteroides fragilis
- Vibrio sp
- Parasites: Giardia duodenalis, Cyrptosporidium sp, Entamoeba histolytica, Microsoridium sp
- Arcobacter emerging

- Remember the STEC outbreak in Germany

TD Microbiology: regional differences

Table 1. Causative Agents in Traveler's Diarrhea

Etiologic agent	Estimated importance in Latin America (%)	Estimated importance in Africa (%)	Estimated importance in South Asia (Indian subcontinent; %)
ETEC	34	31	31
EAEC	24	2	16
Shigella	7	9	8
Salmonella	4	6	7
Campylobacter	3	5	8
Aeromonas	1	3	3
Plesiomonas	1	3	5
Noroviruses	17	13	Unknown
Protozoa*	3	3	9
No pathogen	49	45	39

EAEC–enteroaggregative *Escherichia coli*; ETEC–enterotoxigenic *E. coli*.

*Protozoa include *Giardia*, *Cryptosporidium*, *Cyclospora*, and *Entamoeba histolytica*.

Data obtained from Shah N, DuPont HL, Ramsey DJ.[6]

De la Cabada 2011

Table 2. Estimated Regional Differences in the Etiology of Traveler's Diarrhea[a]

Organism	Reported Pathogens, %			
	Latin America and Caribbean	Africa	South Asia	Southeast Asia
Enterotoxigenic *Escherichia coli*	≥35	25-35	15-25	5-15
Enteroaggregative *E coli*	25-35	<5	15-25	No data
Campylobacter	<5	<5	15-25	25-35
Salmonella	<5	5-15	<5	5-15
Shigella	5-15	5-15	5-15	<5
Norovirus	15-25	15-25	5-15	<5
Rotavirus	15-25	5-15	5-15	<5
Giardia	<5	<5	5-15	5-15

* Compilation of data from several studies conducted in 2002-2011.[8,60-64] Studies do not uniformly report on all pathogens; no pathogen is identified in up to 50% of cases.

Steffen 2015

TD…Microbiology?

- Data from
  - Travel clinics
  - Local surveillance data: bias towards easy to detect pathogens: eg don't test or know some E.coli, if they are also part of the commensals
- How intersecting are the types of infections between kids with severe diarrhoae and TD?
- Could use PCR as multiplex assays to increase sensitivity
  - Risk false pos – colonisation, commensals?
  - Mixed infections?
- Regional differences

Table 2. Detection Methods for Enteropathogens That Cause Traveler's Diarrhea

Enteropathogen	Laboratory detection methods
ETEC	Standard microbiology isolation of *Escherichia coli* followed by tests for LT and ST by PCR, DNA hybridization, or ELISA
EAEC	HEp-2 cell assay or PCR for definable EAEC virulence property (eg, *aggR*)
DAEC	HEp-2 cell assay or PCR for DAEC virulence factor
EIEC	Standard microbiology isolation of *E. coli* followed by PCR for *Shigella*-like invasion genes (*ipaH*, *invE*)
Shigella, *Salmonella*, *Aeromonas*, *Plesiomonas*	Standard microbiology isolation
ETBF	Anaerobic culture and testing for *Bacteroides fragilis* toxin gene by PCR in suspicious colonies
Campylobacter	Standard microbiology isolation
Noroviruses	Reverse transcriptase PCR
Giardia	Commercial EIA
Cryptosporidium	Commercial EIA
Cyclospora	Modified acid-fast stain (modified safranin technique and Kinyoun staining) and fluorescence microscopy
Microsporidium	Modified trichrome stains and fluorescence microscopy (Uvitex 2B, Calcofluor White M2R)
Blastocystis hominis	Stained smears or wet mounts (formol-ethyl acetate sedimentation concentration technique or trichrome stains)

DAEC–diffusely adherent *E. coli*; EAEC–enteroaggregative *E. coli*; EIA–enzyme immunoassay; EIEC–enteroinvasive *E. coli*; ELISA–enzyme linked immunoassay; ETBF–enterotoxigenic *B. fragilis*; ETEC–enterotoxigenic *E. coli*; LT–heat-labile toxin of ETEC; PCR–polymerase chain reaction; ST–heat-stable toxin of ETEC.

Okeke J Infect Dev Ctries 2009; De la Cabada 2011

TD Prevention

- Dietary precautions

- ‘boil it, cook it, peel it or forget it’ may not reduce the risk of TD
- May reduce massive or parasitic infections such as helminths

- 14% of travellers fully compliant with directives (Lalani 2014) -
- …after all…’the purpose of travelling is also to taste new things’…

- Give advice anyway

Shlim CID 2005; Lalani 2014

TD Prevention

- Synbiotics, prebiotics, probiotics – no consistent data
- Bismuth subsalicylate
  - Up to 65% reduction in TD if take it 4/day (USA)
- Antibiotics !!??
- Rifaximin
  - Poorly absorbed, gut-selective antibiotic
  - Reduces non-invasive TD: 48% effectiveness in s + se asia
  - Unclear for invasive pathogens!
- Vaccines:
  - typhoid fever vaccine
  - Oral cholera vaccine offers cross-reaction for heat-labile toxin-producing ETEC – at best would protect a small proportion of travellers
  - Oral cholera vaccine for those travelling to affected areas.

Table 3. Chemoprophylaxis and Chemotherapy for Traveler's Diarrhea in Adults[a]

Pharmacologic Agent	Recommended Dosage	Effectiveness and Adverse Events
Chemoprophylaxis of traveler's diarrhea for trips ≤14 d		
Bismuth subsalicylate[82]	2 tablets chewed well 4 times daily	Only moderately effective Turns stool and tongue black from harmless hydrogen sulfide May cause tinnitus from systemic salicylate levels
Ciprofloxacin[83]	500 mg once or twice daily	Many fluoroquinolones are effective against most bacterial enteropathogens other than *Campylobacter jejuni* Adverse effects can include Achilles tendon damage or *Clostridium difficile* infection
Rifaximin[84]	200 mg once or twice daily with meals	Only moderately effective; uncertain if prevents invasive forms of traveler's diarrhea like *Campylobacter* or *Salmonella* Considered safe as it is not absorbed

Steffen J Trav Med 2014 + JAMA 2015; Du Pont J Travel Med 2009; Roa G J Travel Med 2004; DuPont Ann Intern Med 2005; Hu Y J Travel Med 2012;

TD Treatment

- Aims of therapy:

- Avoid dehydration
- Mitigate the symptoms of diarrhoea, abdominal cramps and nausea
- Prevent interruption of travel plans

- Self treatment

TD Self-treatment recommendations

- Mild TD = 1-3 loose stools/24hours and activities not affected
  - Non-antibiotic agent or antimotility agent (not if <2yrs or temps>38,5)
  - Anti-emetic agent

- Moderate to severe TD = signs of dysentry: add
  - Fluoroquinones in Africa/South America (500mgx2/dag; 750mgx1/day)
  - Azithromycine in Asia: as Campylobacter spp resistent to FQ (500mg/day or 1000mg single dose)
  - Single dose or 3-day treatment

  - Rifaximin non-inferior to ciprofloxacin in non-invasive infections: 200mgx3/day

  →Combination of an antibiotic with loperamide: normalisation of bowel habit within 17 hours (range 2-23 hours) = Antibiotics shorten the duration of symptoms to 1,5 days

TD Self treatment

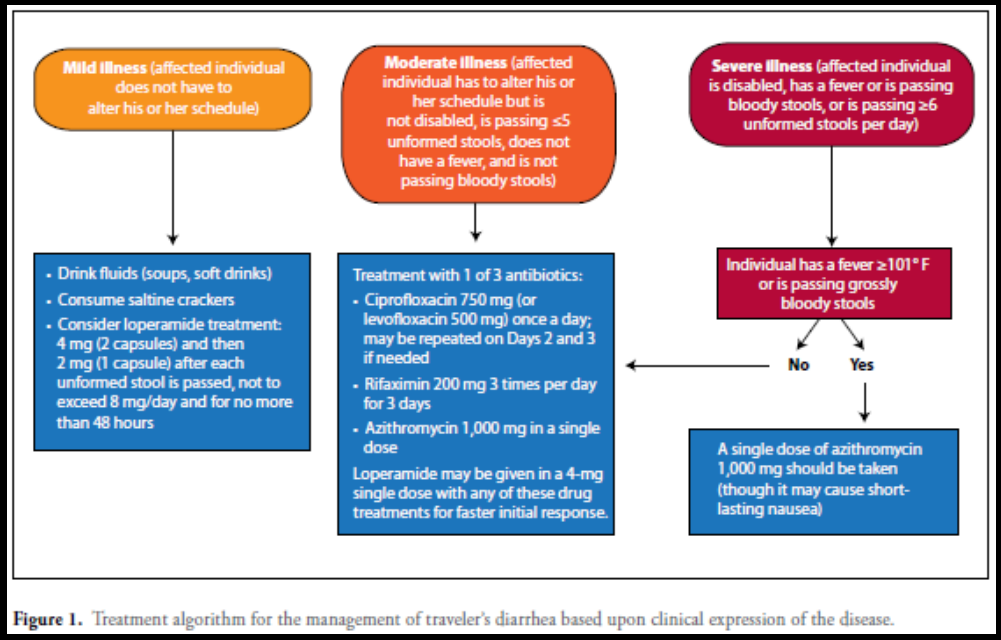


Figure 1. Treatment algorithm for the management of traveler's diarrhea based upon clinical expression of the disease.

De la cabada Gastro and Hep 2011

TD The impact on the traveller?

- Diarrhoea itself
- average duration of untreated TD very variable, up to 4-5 d
- only 3% have >10 unformed stools/day; or 4% severe diarrhoea

- Consequences of TD
- 12-46% of patients have short-term disability: on average disability is for < 1 day!
- Long(er)-term complications:
  - Post Infectious-Inflammatory Bowel Syndrome (PI-IBS): 3-17% of patients
  - R Factors: severity of TD, pretravel diarrhoea, pre-travel adverse events, infection with heat-labile toxin producing ETEC

Belderok BMC InfDis 2011 Soonawala D BMC Infect Dis 2011; Steffen 2004; Hill Am J Trop Med Hyg 2000; Sebeny 2012

TD Adequate self-treatment and effectiveness?

- 1120 US travellers, 17 days
- 24% (270) had TD
  - Of which 23% with febrile TD or dysentry, 10% sought medical help/hosp
  - Overall: TD lasted only a median of 8,5 hours
  - 52% had incapacitation for 1 day (reported as significant impact)
- Suboptimal self-treatment analysis (n= 212):
  - if had moderate/severe TD: OR 10,4 (4,92-22)- more likely to suboptimally self treat
  - only 42% took treatment optimally if mod/severe
- Effectiveness analysis (n=124):
  - did not observe a benefit when took antibiotics (limitation ? small sample; or milder forms of TD?)
- IBS occurred in 3,4%
  - not associated with TD; found more if had more severe diarrhoea (7% vs 1,4%) or if TD during >1day (NS); also more if had not taken an antibiotic (NS)

Lalani J Travel Med 2015

TD The view of the traveller

- Dutch study: 160/390 (41%) travellers contracted TD

Table 3 Characteristics of the episode of travelers' diarrhea for 160 Dutch travelers, stratified by the objective degree of inconvenience.

Objective degree of inconvenience - *n* (%)	Conducted program as planned 107/160 (67%)	Forced to alter program 33/160 (21%)	Confined to accommodation 20/160 (13%)	Total 160 (100%)
Subjective degree of inconvenience - *n* (%)				
None/Minor	58 (54)	5 (15)	-	63 (39)
Moderate	33 (31)	13 (39)	8 (40)	54 (34)
Large/Severe	16 (15)	15 (46)	12 (60)	43 (27)

- Considered it less of a problem in retrospect than they had thought it would be before departure

Table 5 How did an episode of travelers' diarrhea (TD) influence travelers' perception of TD? The expected amount of subjective inconvenience due to travelers'' diarrhea before and after travel is stratified by whether travelers had TD.*

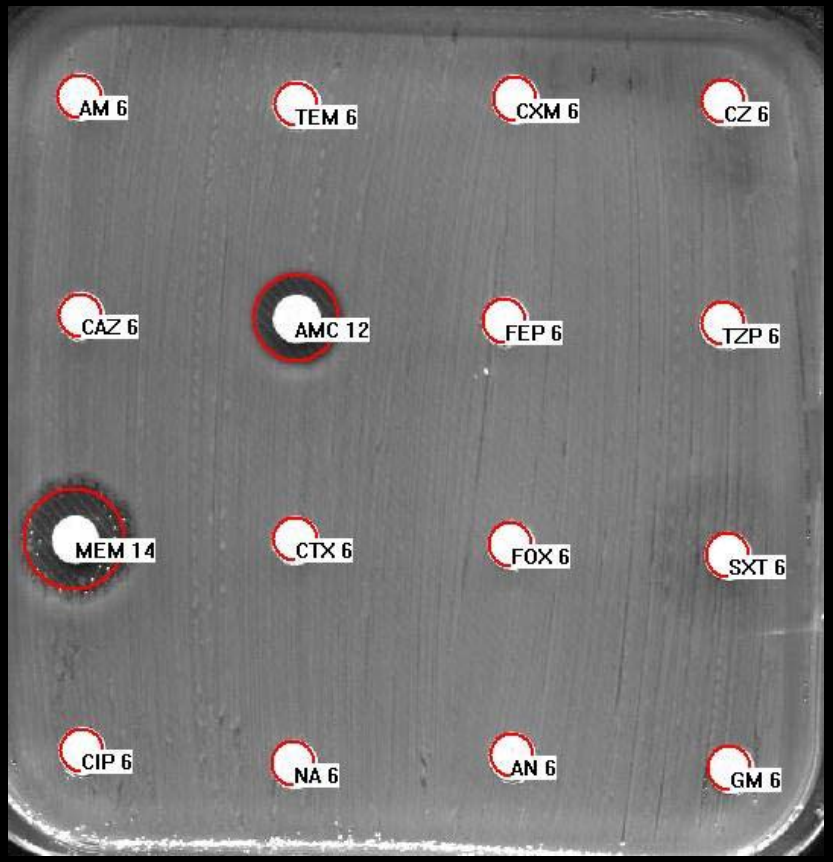
	Travelers who had TD n = 160		Travelers who did not have TD n = 230	
	Before departure	After returning	Before departure	After returning
No problem - *n* (%)	1 (1)	11 (7)	1 (0.4)	3 (1)
A small problem - *n* (%)	22 (14)	42 (26)	50 (22)	53 (23)
Neither a small nor a large problem - *n* (%)	51 (32)	56 (35)	61 (27)	57 (25)
A large problem - *n* (%)	69 (43)	49 (31)	99 (43)	99 (43)
A very large problem - *n* (%)	17 (11)	2 (1)	19 (8)	18 (8)

*Participants were presented the following scenarios: *Before departure:* If you were to contract travelers' diarrhea during the coming journey, with a duration of three days accompanied by urgency and abdominal cramps, how large a problem do you think this would be for you? *After returning*: If you were to make the exact same journey in the future and you were to contract travelers' diarrhea with a duration of three days accompanied by urgency and abdominal cramps, how large a problem do you think this would be for you?.

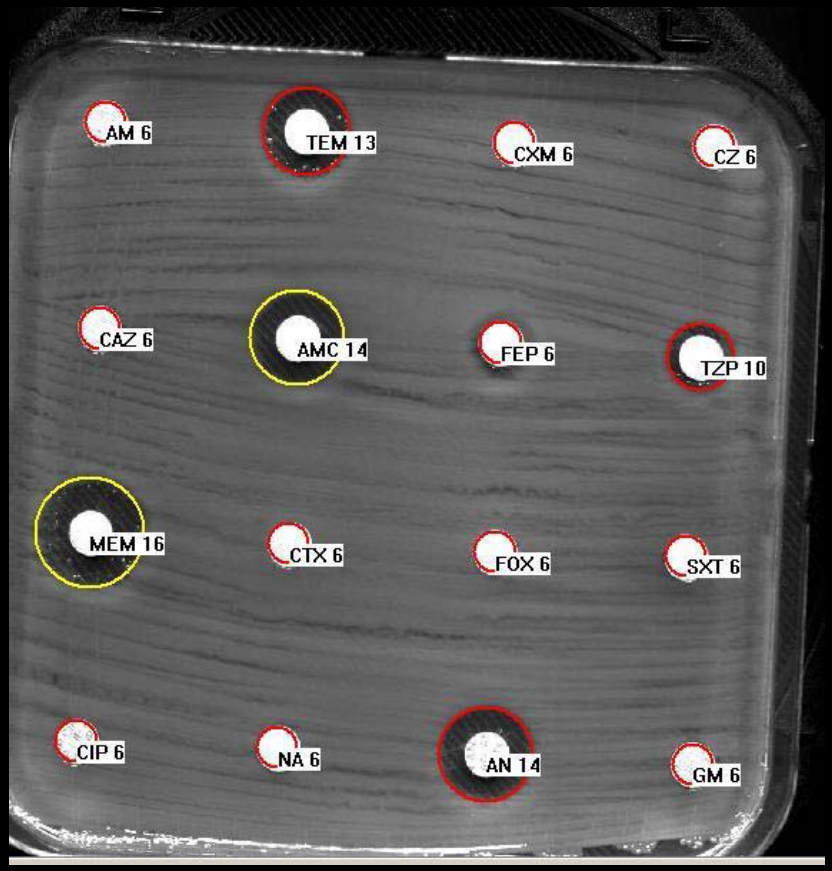
Soonawal BMC Infectious Dis 2011

TD In perspective…

Enterobacteriaceae isolates



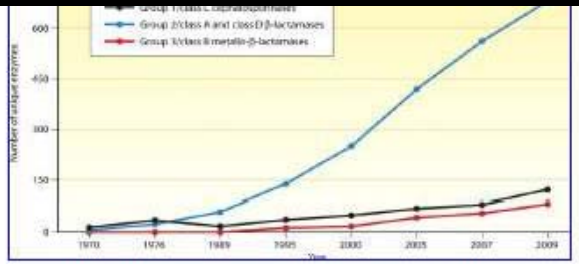
NDM-1 + CTX-M-15 + CMY-58 (AmpC) + TEM-1 + RmtB (aminoglycosides) + QnrS1 (quinolones)



NDM-1 + CTX-M-15 + SHV-12 + OXA-9 + OXA-30 + TEM-1 + RmtB (aminoglycosides) + QnrB quinolones + …

Courtesy of Glupczynski

Evolving resistance in Enterobacteriaceae

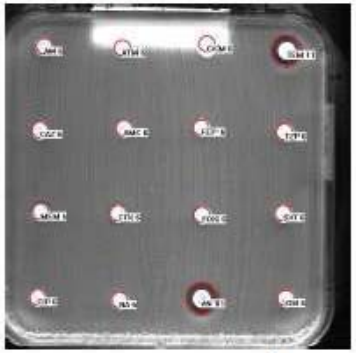


Wild-type

Penicillinases (TEM-1, SHV-1)

ESBLs (CTX-M >>SHV,TEM)

Carbapenemases

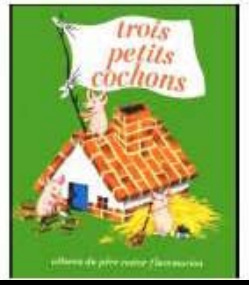


1940

1970

1990

2000

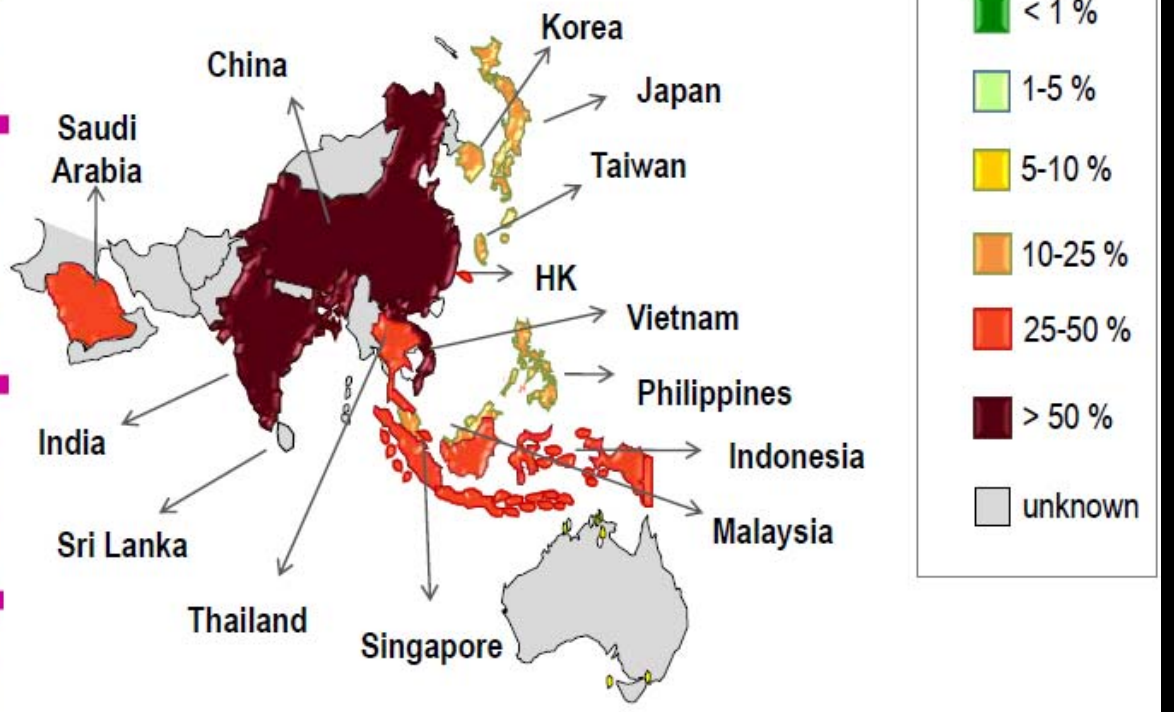


Courtesy of Glupczynski

Current Status of Antimicrobial Resistance in Asia

	Resistance %
Korea	10-25%
Japan	10-25%
China	>50%
Hong Kong	25-50%
Taiwan	10-25%
Philippines	10-25%
Thailand	25-50%
Vietnam	>50%
Malaysia	10-25%
Singapore	25-50%
Indonesia	25-50%
India	>50%
Sri Lanka	?
Saudi Arabia	25-50%

ESBL-producing *E. coli*



Source: Hsueh PR, 2012

Courtesy of Vlieghe

Global dissemination

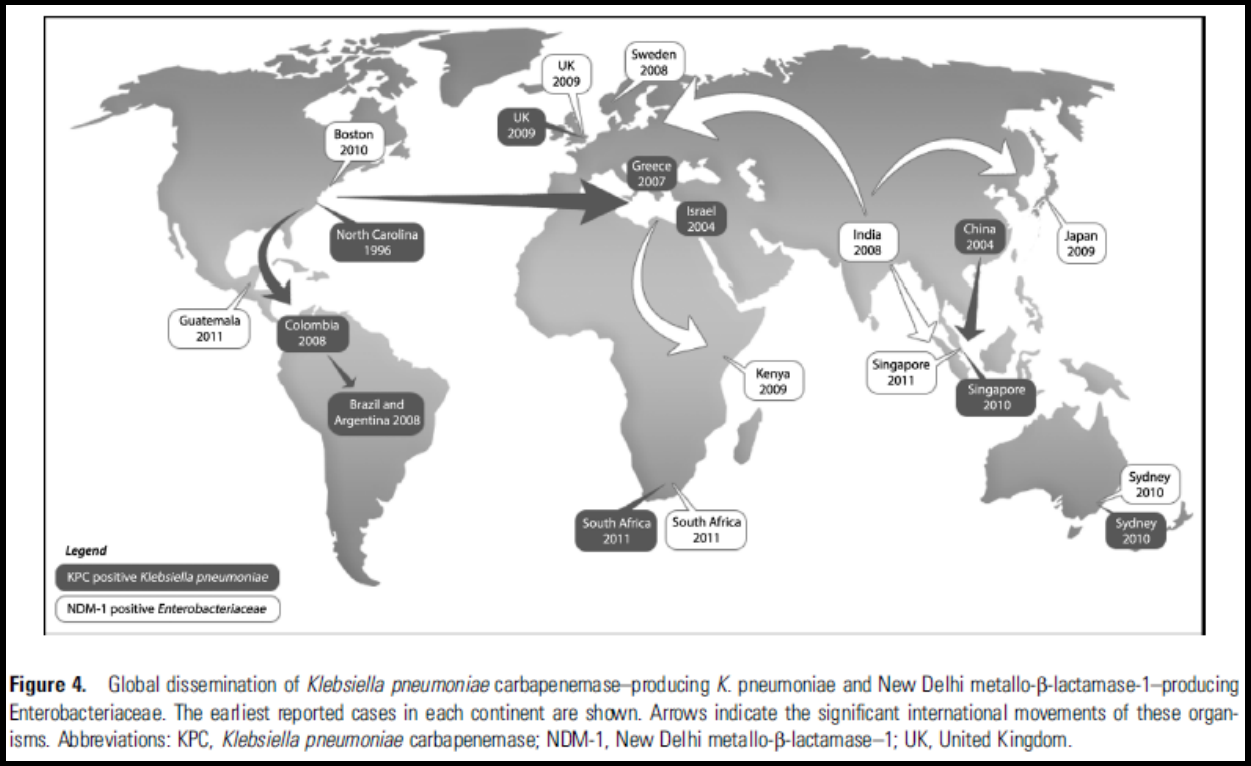
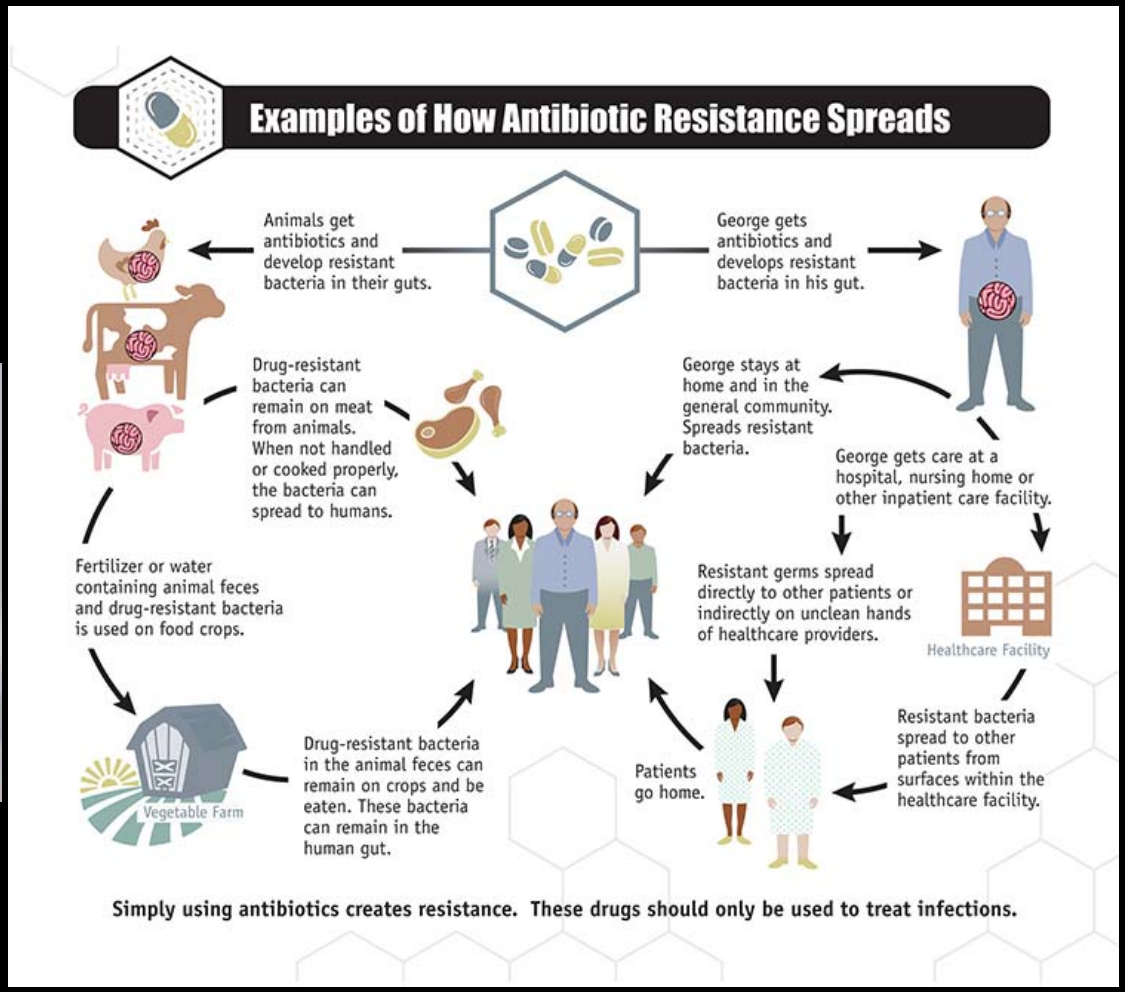


Figure 4. Global dissemination of *Klebsiella pneumoniae* carbapenemase–producing *K.* pneumoniae and New Delhi metallo-β-lactamase-1–producing Enterobacteriaceae. The earliest reported cases in each continent are shown. Arrows indicate the significant international movements of these organisms. Abbreviations: KPC, *Klebsiella pneumoniae* carbapenemase; NDM-1, New Delhi metallo-β-lactamase–1; UK, United Kingdom.

Molton JS CID 2013

Overlapping resistance with animals



WHO

TD In perspective…using local data

Some islands of good news…

- Madagascar:
- Kids with diarrhoea + samples to the Pasteur inst:
  - mainly Campylobacter, DEC, Shigella, Salmonella
  - most were sensitive to FQ (O to 3,1% (DEC))
  - →Campylobacter – not very resistent to FQ or tetracyclines because antibiotics are too expensive for local farmers

- Australia:
- Only cooked chicken is imported, and FQ not approved for use in food-producing animals, low res. to Campylobacter (2%)

Randrianirina et al. BMC Infectious Diseases 2014; Smith NEJM 1999

Vietnam 1995-2008: shift in species and resistance patterns

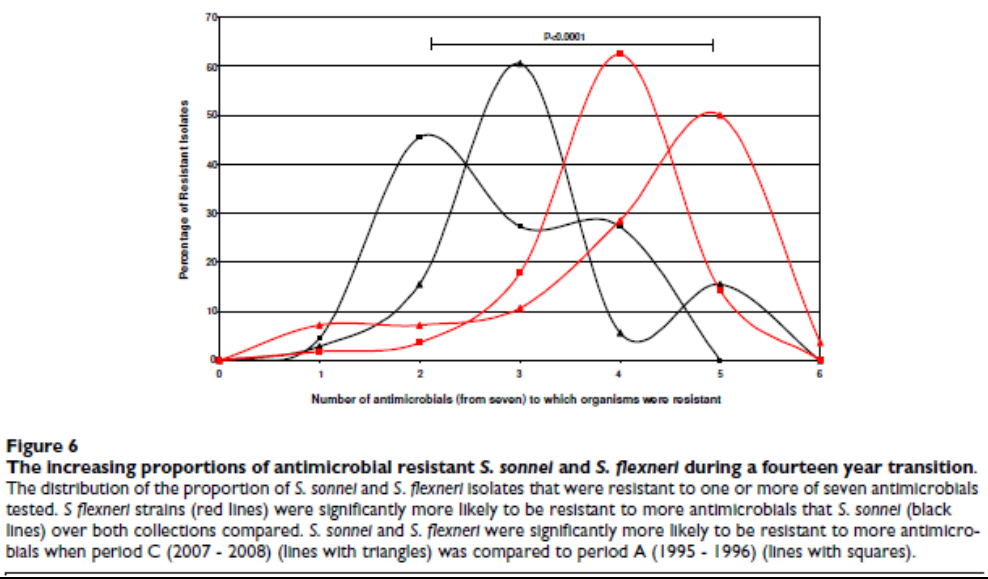


Figure 6
The increasing proportions of antimicrobial resistant *S. sonnei* and *S. flexneri* during a fourteen year transition. The distribution of the proportion of *S. sonnei* and *S. flexneri* isolates that were resistant to one or more of seven antimicrobials tested. *S flexneri* strains (red lines) were significantly more likely to be resistant to more antimicrobials that *S. sonnei* (black lines) over both collections compared. *S. sonnei* and *S. flexneri* were significantly more likely to be resistant to more antimicrobials when period C (2007 - 2008) (lines with triangles) was compared to period A (1995 - 1996) (lines with squares).

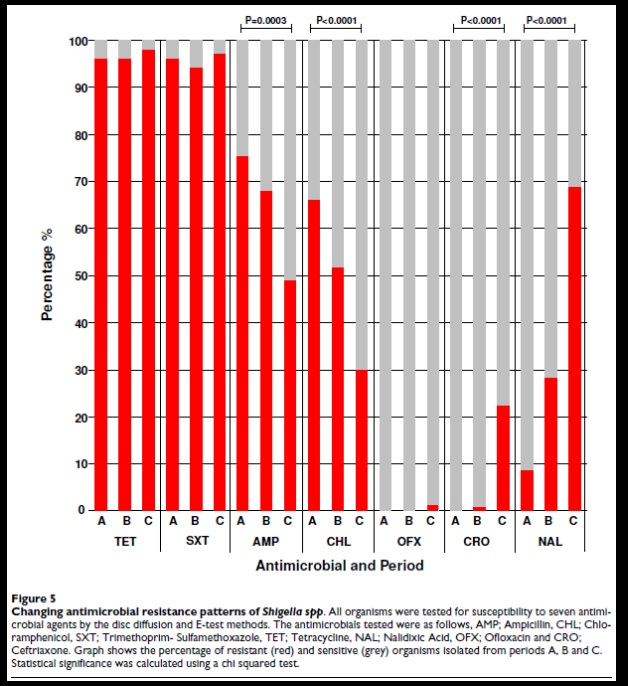


Figure 5
Changing antimicrobial resistance patterns of *Shigella spp*. All organisms were tested for susceptibility to seven antimicrobial agents by the disc diffusion and E-test methods. The antimicrobials tested were as follows, AMP; Ampicillin, CHL; Chloramphenicol, SXT; Trimethoprim- Sulfamethoxazole, TET; Tetracycline, NAL; Nalidixic Acid, OFX; Ofloxacin and CRO; Ceftriaxone. Graph shows the percentage of resistant (red) and sensitive (grey) organisms isolated from periods A, B and C. Statistical significance was calculated using a chi squared test.

Vinh BMC Infect Dis 2009

Diarrhoeagenic E.coli in China

- Sentinel hospitals
- Oupatients with acute diarrhoea

	All DEC (n = 347)	EAggEC (n = 214)	ETEC (n = 61)
Ciprofloxacin R	25.4%	31.8%	6.6%
ESBL	34.5%	40.7%	11.5%
MDR	70.2%	77.1%	34.4%

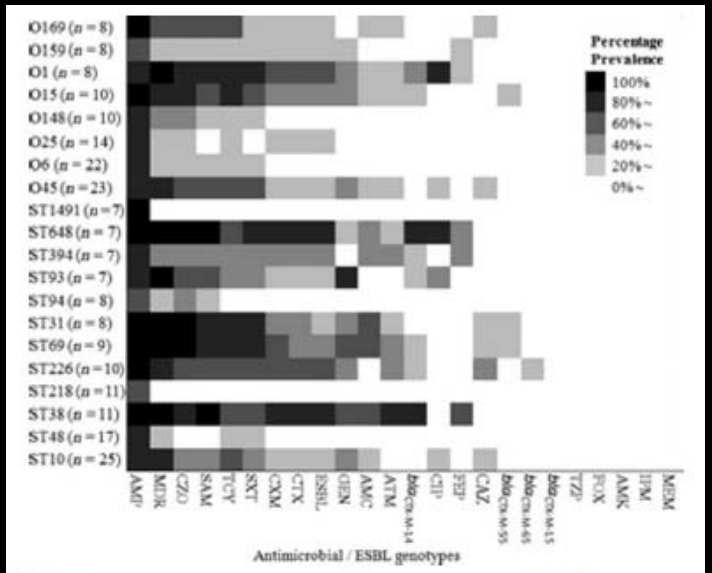


FIG. 2. Heat map of antimicrobial resistance and ESBL genotype

gene; CIP, ciprofloxacin; FEP, cefepime; CAZ, ceftazidime; TZP, piperacillin-tazobactam; FOX, cefoxitin; AMK, amikacin; IPM, imipenem; MEM, meropenem.

Chen CMI 2014

TD in perspective …using data from travellers

In Vitro Antimicrobial Susceptibility of Bacterial Enteropathogens Isolated from International Travelers to Mexico, Guatemala, and India from 2006 to 2008[▽]

Jeannette Ouyang-Latimer,[1,2] Syed Jafri,[2] Audrey VanTassel,[2] Zhi-Dong Jiang,[2] Kaur Gurleen,[3] Savio Rodriguez,[3] Ranjan K. Nandy,[4] Thandavaryan Ramamurthy,[4] Santanu Chatterjee,[5] Robin McKenzie,[6] Robert Steffen,[7] and Herbert L. DuPont[1,2,8]*

TABLE 1. Bacterial enteropathogens isolated from subjects with travelers' diarrhea in Mexico, Guatemala, and India and studied for *in vitro* susceptibility to antimicrobial agents, 2006 and 2008

Pathogen	No. of strains				% of total no. of isolates
	Mexico	Guatemala	India	Total	
ETEC	245	25	98	368	81
EAEC	17	3	3	23	5
Aeromonas spp.	1	0	3	4	1
Campylobacter spp.	5	1	17	23	5
Plesiomonas spp.	2	0	8	10	2
Salmonella spp.	10	0	5	15	3
Shigella spp.	2	0	11	13	3
Total	282	29	145	456	

Antibiotic	BP[a] (μg/ml)	% R[b]
AMP	≥32	45.2
NAL	≥32	41.8
TET	≥16	55.3
DOX	≥16	50.2
T/S	≥8/152	50
CFO	≥32	4.4
RIF	≥32	15.3
CIP	≥4	17.2
LEV	≥8	21
AZM	≥8[c]	16.7

Antibiotic	India		Mexico and Guatemala	
	ETEC (n = 98)		ETEC (n = 270)	
	MIC_{90} (μg/ml)	% R	MIC_{90} (μg/ml)	% R
AMP	>1,024	49.4	>1,024	52.8
NAL	>1,024	71.1	>1,024	38.5
TET	256	52.5	256	59.2
DOX	128	48.5	64	51.9
T/S	64	58.9	128	46
CFO	0.5	6.2	0.25	4.8
RIF	32	19.6	32	15.5
CIP	256	27.8	64	17.5
LEV	8	40.8	8	20.1
AZM	32	24.5	32	16.1

Ouyang-Latimer AAC 2011

In Vitro Antimicrobial Susceptibility of Bacterial Enteropathogens Isolated from International Travelers to Mexico, Guatemala, and India from 2006 to 2008[▽]

Jeannette Ouyang-Latimer,[1,2] Syed Jafri,[2] Audrey VanTassel,[2] Zhi-Dong Jiang,[2] Kaur Gurleen,[3] Savio Rodriguez,[3] Ranjan K. Nandy,[4] Thandavaryan Ramamurthy,[4] Santanu Chatterjee,[5] Robin McKenzie,[6] Robert Steffen,[7] and Herbert L. DuPont[1,2,8]*

- 10 year trend: MICs are increasing 10-20x
- Issues:
  - Are blood MICs the appropriate to use? Probably not as intestinal concentrations of FQ have been shown to be much higher than the BP used in blood
  - EAEC is emerging as more resistent straight off
  - Background:
    - countries use the drugs as treatment and for different types of infections (respi/UTI)
    - drugs available w/o prescriptions
    - TD self-treatment could play a role in those treads, but probably more so animal use.
  - Authors argue: use non-absorbable antibiotics such as rifaximin

Ouyang-Latimer AAC 2011

Trends of Norfloxacin and Erythromycin Resistance of *Campylobacter jejuni/Campylobacter coli* Isolates Recovered From International Travelers, 1994 to 2006

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- Norfloxacin:

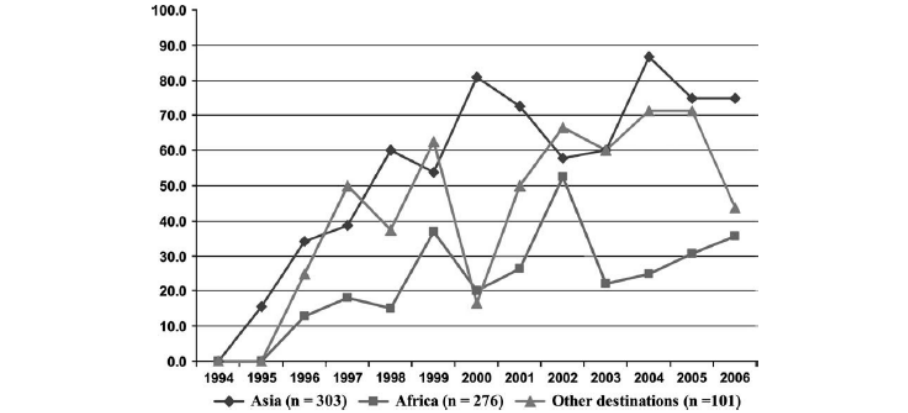
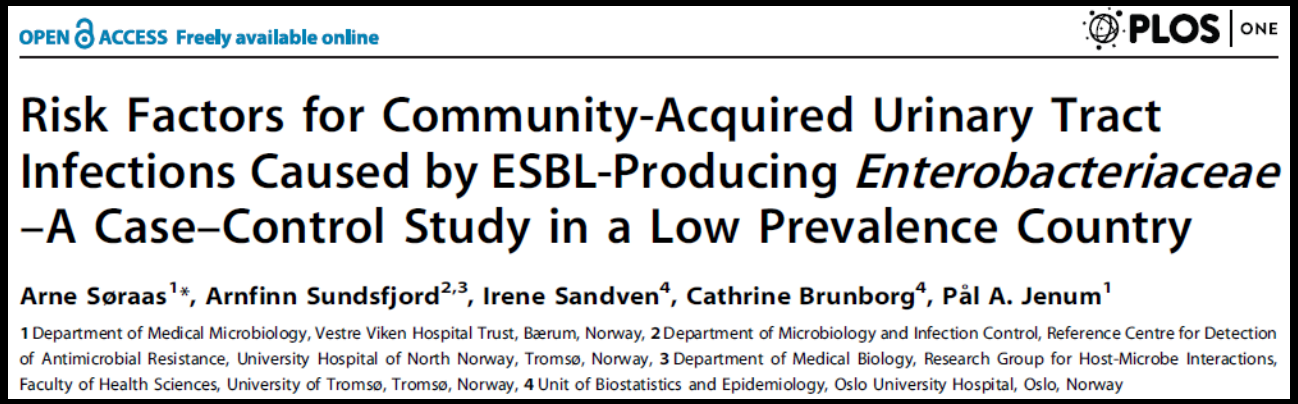


Figure 1 Annual rates of norfloxacin resistance in *Campylobacter* isolates recovered from travelers on their return from Asia, Africa, and other travel destinations (the Caribbean, Central and South America, Europe without Belgium and Australia) combined, $p < 0.001$ for the three groups.

- Erythromycin: mean annual resistance rate = 3,1% and increased over time to 7,5% (2004) - 8,6% (2006)

Vlieghe J Trav Med 2008



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PLOS ONE

Risk Factors for Community-Acquired Urinary Tract Infections Caused by ESBL-Producing *Enterobacteriaceae* –A Case–Control Study in a Low Prevalence Country

Arne Søraas[1]*, Arnfinn Sundsfjord[2,3], Irene Sandven[4], Cathrine Brunborg[4], Pål A. Jenum[1]

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- Not in travellers but the most imp risk factors were:
  - Travel to Asia, Middle East or Africa
  - OR 21 *in past 6 weeks*
  - OR 2,3 *past 6w-24month*
  - Recent use of FQ (OR 16), b-lactam use (OR 5), diabetes, fresh water swimming.

- Associated with decreased risk: number of fish meals per week (0,68)

Soraas Plos One 2013

Case studies

JOURNAL OF CLINICAL MICROBIOLOGY, June 2008, p. 2147–2148 Vol. 46, No. 6
0095-1137/08/$08.00+0 doi:10.1128/JCM.00427-08

CTX-M-15-Producing *Shigella sonnei* Strain from a Czech Patient Who Traveled in Asia[▽]

Diarrhoea Risk associated with taking an antibiotic

- Prior antibiotics and risk of getting Campylobacteriosis

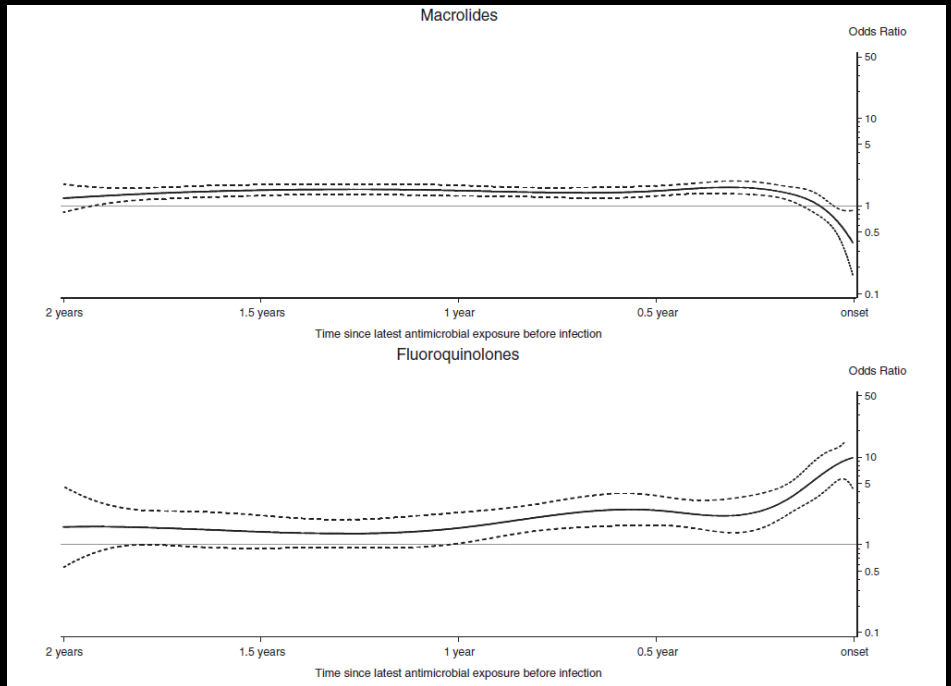


Figure 1. Cubic spline plots of the odds ratio (OR) of being exposed to macrolides and fluoroquinolones 0–2 years before infection with *Campylobacter*, 1997–2005 Denmark. The ORs are adjusted for sex, age, county of residence, population density, income, and schooling..

Koningstein CID 2011

Travellers' colonisation

- 90/430 = 21% became colonised with ESBL-PE

- Overall
- TD-AB- : 11%
- TD+AB- : 21%
- TD+/AB+ : 37%

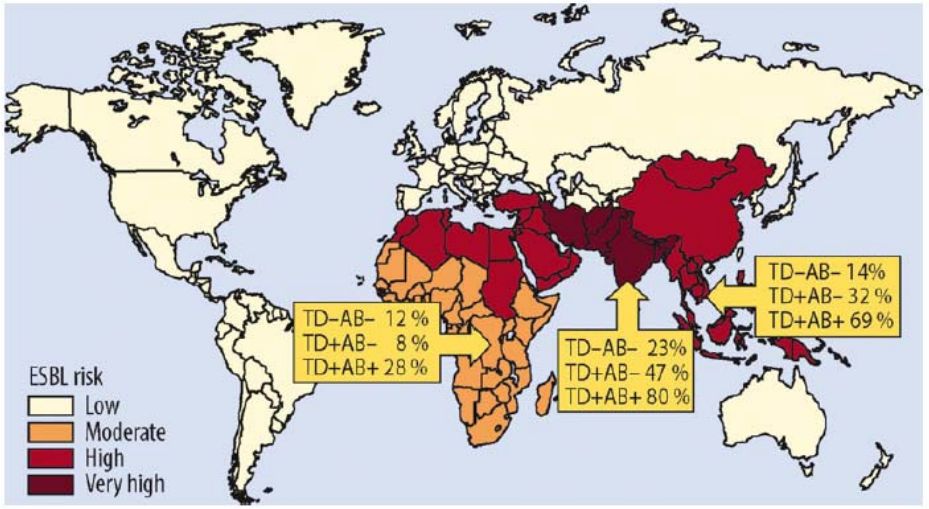


Figure 2. World map indicating the risk levels of contracting extended-spectrum beta-lactamase–producing *Enterobacteriaceae* (ESBL-PE) in different geographic regions as established in the present investigation. In the entire study population, 21% of the travelers contracted ESBL-PE; 11% in subgroup TD–AB– (travelers' diarrhea/antimicrobials), 21% in TD+AB–, and 37% in TD+AB+ contracted ESBL-PE. The respective subgroup analyses for the regions with highest risk (Africa, South Asia, and Southeast Asia) are given in the boxes with arrows. The ESBL-PE strains contracted were all *Escherichia coli*, except for 2 *Klebsiella oxytoca* and 1 *Escherichia hermannii*.

Kantele CID 2015

Given…

- …the extent and types of discomfort from TD
- …the potentially poor effectiveness of anbibiotic in most cases
- …the plausible (best case) scenario that out of 300 million travellers: if no-one took AB 53 million returning travellers with ESBL carriage (if all TD took abx: 85million/year)
- …data that macrolides disrupt the gut microbiota even more than FQ (Cho et al animal studies)
- …we do have a responsibility to fight the global spread, by trying not to contribute to the spread to low-prevalence countries

- …Why should we give AB to patients at travel clinics?

The Belgian consensus

2015

Selftreatmemt Travelers' Diarrhea in Belgian travellers ?

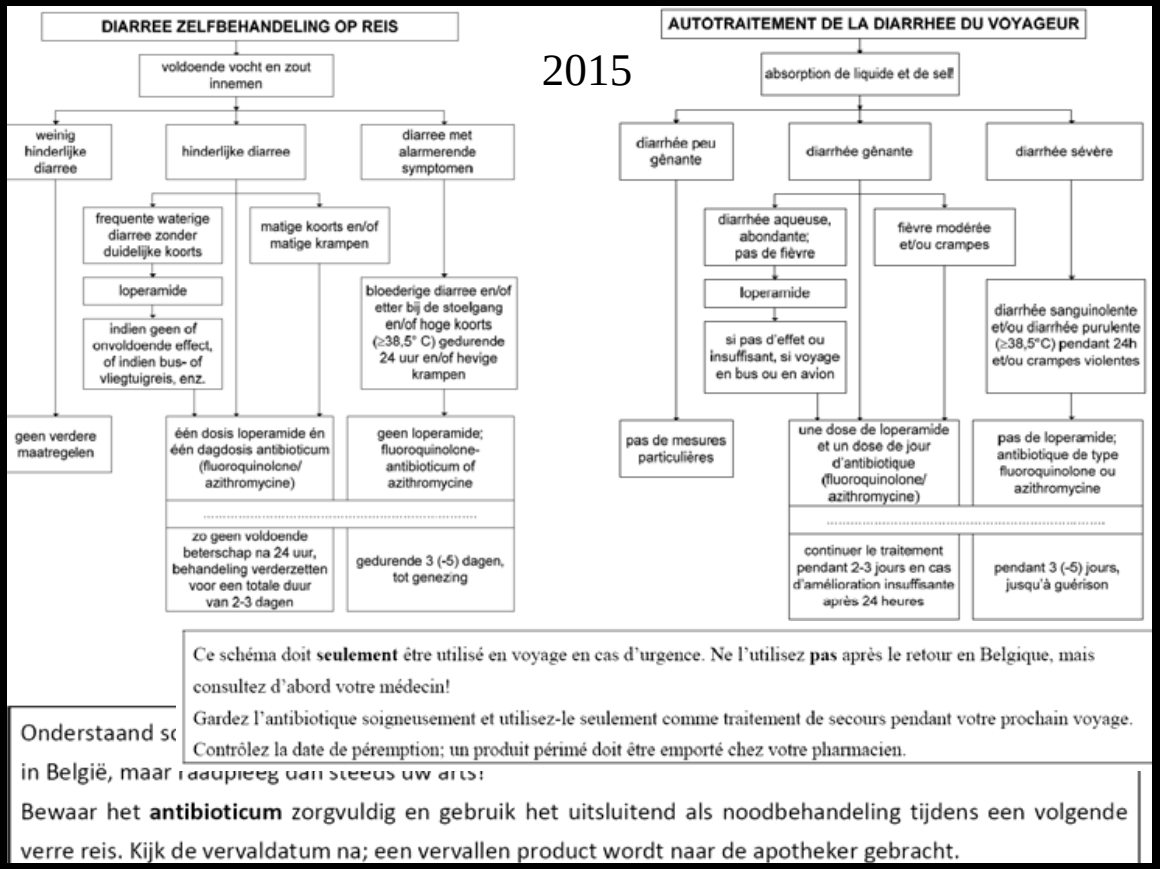
Belgium does not follow the recommendations to treat TD with antibiotics as liberally as the US does,

but the treatment policy is not as restrictive as in Scandinavia and in the Netherlands.

The present Belgian recommendations have been drawn up **years ago by infectiologists after intense discussions**. The recent publication of Kantele et al. has however forced us **to rethink in 2016** the recommendations, and asks for a balanced discussion, taking into account the following:

- What is the impact of a one-day antibiotic treatment, the schedule most often advised for (uncomplicated) diarrhea,
- In which circumstances? To prevent ruining the trip?
- Clinical evidence suggests that the Belgian traveler sparsely takes antibiotic treatment rather than overusing it.
- Restricting antibiotic self-treatment may increase (avoidable) hospitalization in low income country setting (& wrong antibiotic use)
- Reviewing the TD treatment policy would preferentially be based on prospective study data, that are not yet available…..

The Belgian consensus



Q 1: On a given trip, traveller's diarrhoea is causing disability for an average of …?

- <1 day
- 1 day
- 2 days
- 3 days
- 4-5 days

Q 2: What is the overall percentage of returning travellers colonised with ESBL-Enterobacteriaceae?

- <1%
- <5%
- 5-10%
- 10-20%
- 20-30%
- >30%

Thank you