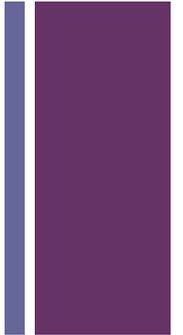


Infectious Diarrhea in Military Settings

+ Outline



- **Take Home Lessons**
- **Epidemiology of Infectious Diarrhea in the Military**
- **Causative Agents**
- **Clinical Presentation and Differential Diagnosis**
- **Diagnostic Considerations**
- **Treatment and Control**

+ Take Home Lessons

- Acute diarrhea/dysentery in deployed military personnel (like travelers' diarrhea) is predominantly caused by bacterial enteropathogens
- Treatment of moderate to severe illness with antibiotics should be the rule (not the exception)
- The U.S. military does not send its forces on overseas vacation
- Population-wide morbidity from acute illness is significant, and greatly compounded by growing evidence of associated post-infectious sequelae

+ Definition of Travelers' Diarrhea

- Three or more unformed bowel movements occurring within a 24-hour period
- Often accompanied by other symptoms
 - cramps
 - nausea, vomiting
 - fever
 - blood in stools
- Typically acquired within first few weeks of travel/ deployment
- Ingestion of contaminated foods or less often drinks

+ Impact of Diarrheal Diseases in Modern Military Campaigns

- **World War II:** 'A few months of the year, malaria would cause more man-days lost, but on the calendar-year average, gastrointestinal infections were well ahead.'¹
- **Vietnam War:** Diarrhea/dysentery largest single disease threat, leading to 4 times more hospitalizations than malaria²
- **OIF:** Acute enteric illness was leading cause of hospital admission among British forces during first 12 months of operations in Iraq³

(1) Ward TG: *History of Preventive Medicine*, US Army Forces in the Middle East, 19Oct41 - 23Jun44, Vol. 111. [Official record.]

(2) Wells RF: GI Diseases: Background and Buildup. In: *Internal Medicine in Vietnam Vol II: General Medicine and ID*, US Army Medical Dept 0:345-354.

(3) Grange, C: *J Royal Army Medical Corps*, 2005;151(2):101-104.

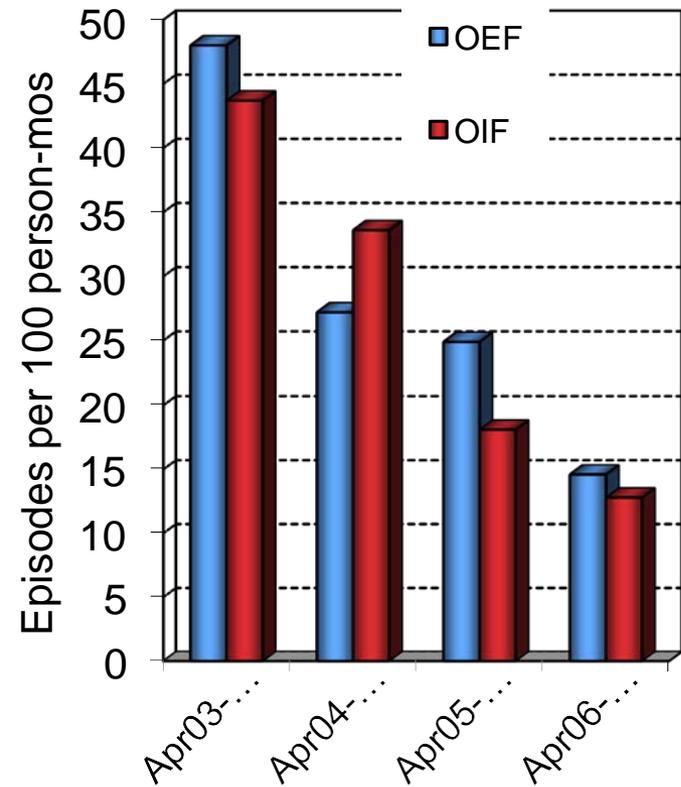
+ OEF/OIF, 2001-2007

Disease Burden 'By the Numbers'



Cumulative deployments and disease burden

2,134,578	No. deployments (\bar{x} , 183 d)
145,871	No. deployments (\bar{x} , 19 d)
3,857,002	Cases of diarrhea
11,478,270	Diarrhea days
850,444	Ambulatory Medical Visits
17,356	Hospitalizations
1,114,208	Duty days lost
162,279	Liters of IV fluids infused



+ Force Health Impacts

Diarrhea with fever	9-25%
Dysentery	2-8%
Severe diarrhea	
Iraq	21-27%
Afghanistan	13-14%
Vomiting only	5-15%

clinical presentations



operational impact

↓ Job performance	45%
Confined to bedrest	13%
Hospitalized	2%
IV fluids	15-17%
Missed patrol	9-13%
Back-fill needed	12%
Grounded	6-12%
Fecal incontinence	32%

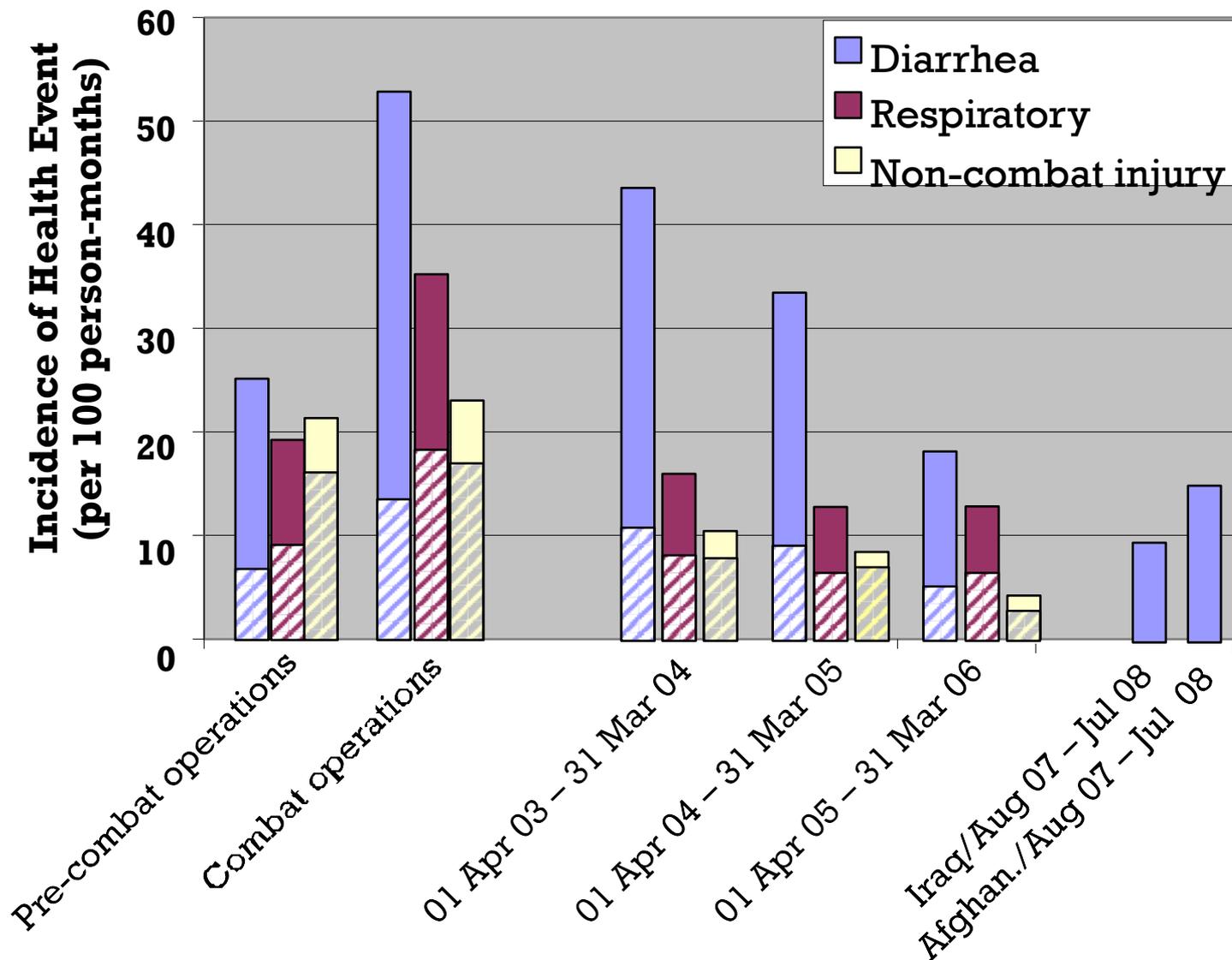


I expect that our imaginations cannot fathom the problems attendant from the absolute urgency for relief from explosive vomiting and diarrhea when experienced within an armored vehicle under fire and at ambient temperature of $>104^{\circ}\text{F}$.

David O. Matson, MD, *Clin Infect Diseases* Editorial, 2005

Infectious Diseases Section, Center for Pediatric Research, Norfolk, Virginia

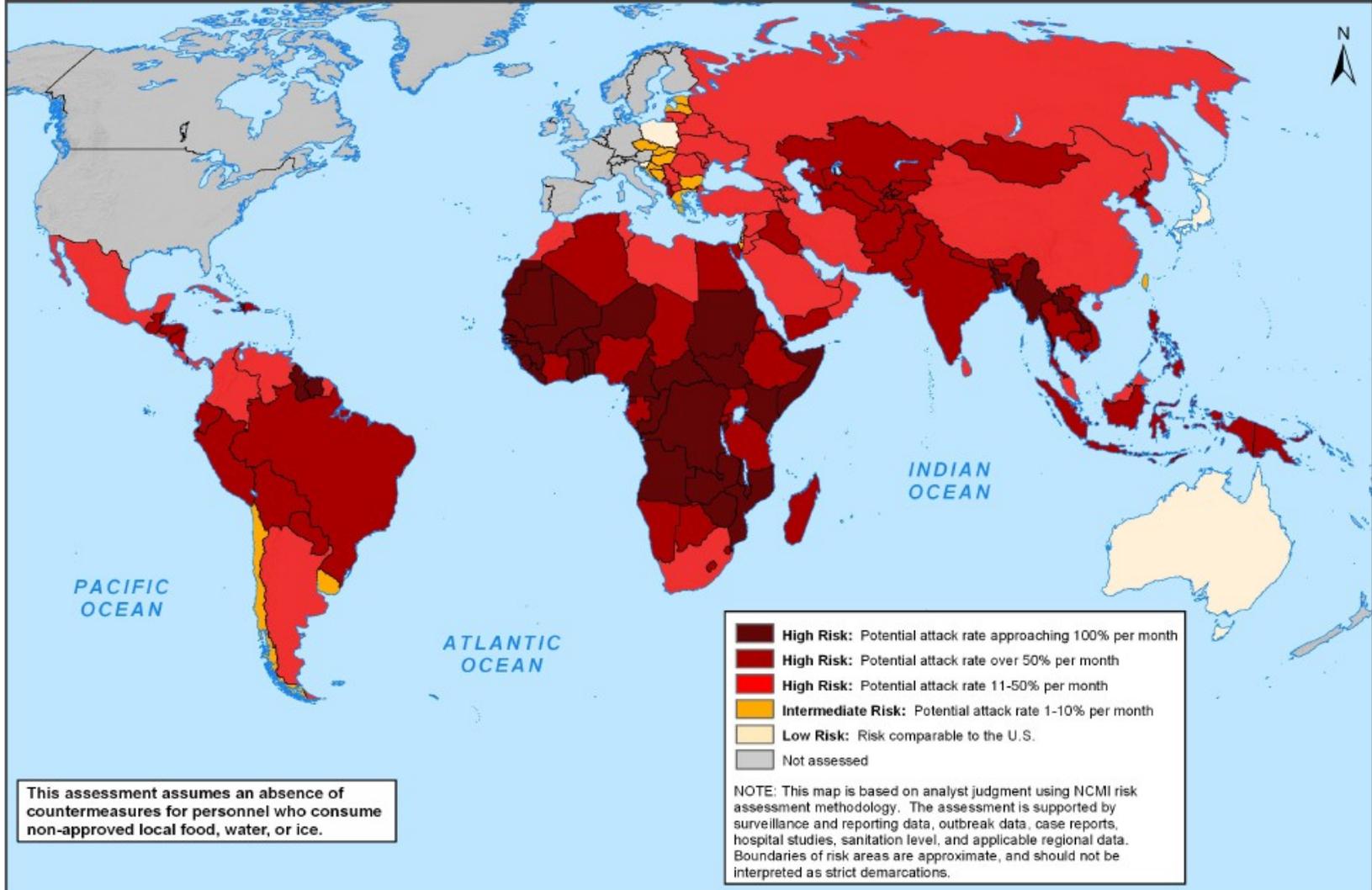
Incidence of Illness based on Self-Reporting vs. DNBI





Worldwide: Bacterial Diarrhea Risk to US Forces (Nov 2013)

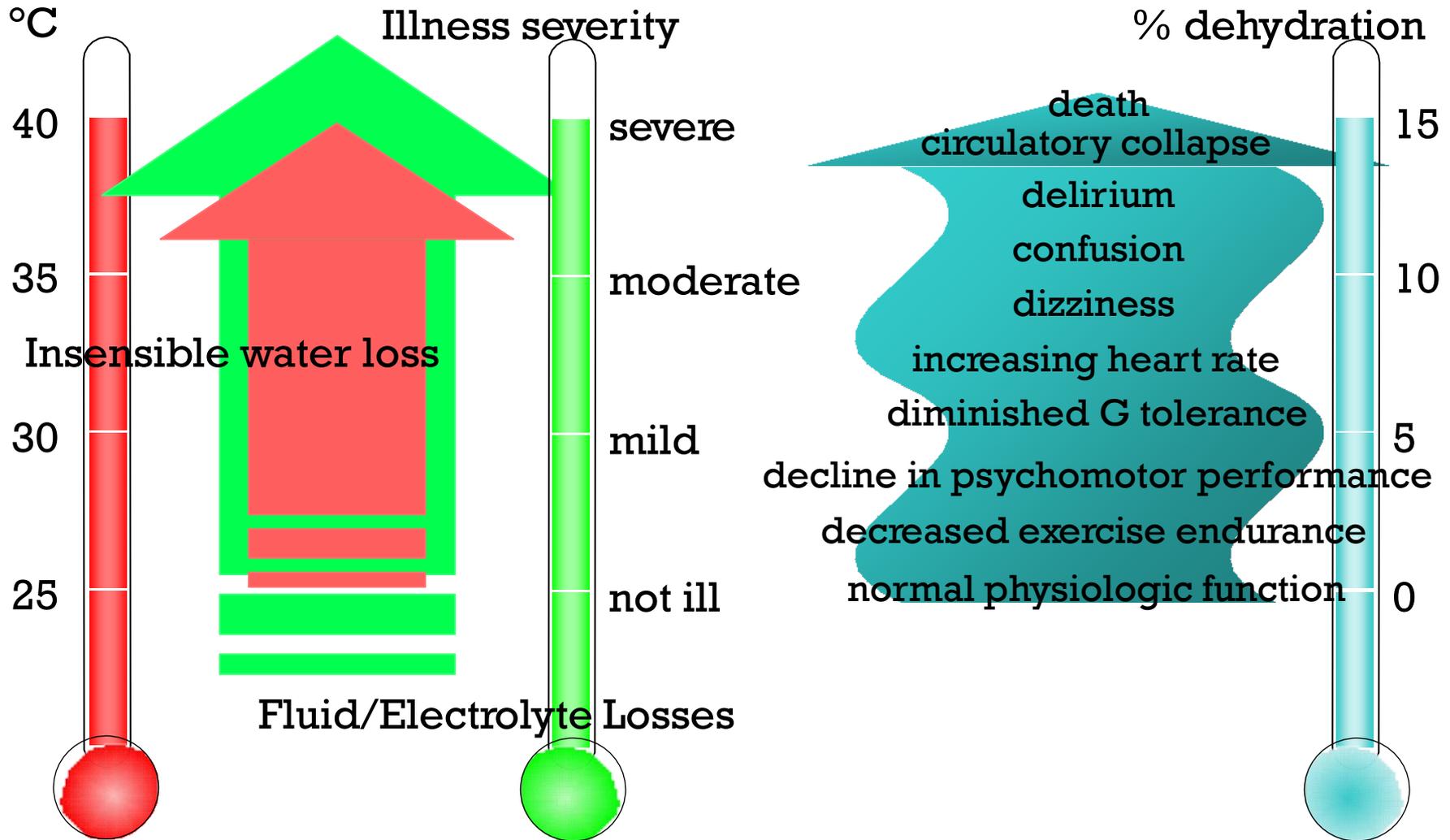
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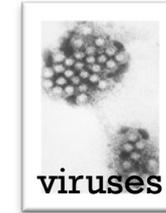
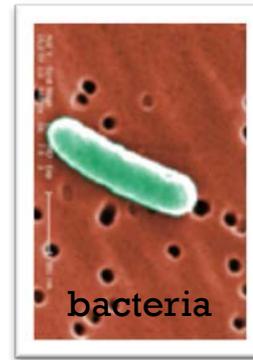
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1 Nov 2013 • DIA-NCMI

Stressors in Extreme Conditions Amplify Diarrhea Morbidity



+ Causative Agents



■ Bacterial agents (80-90%)

■ Common

- Enterotoxigenic *E coli* (ETEC)
- Enteroaggregative *E coli* (EAEC)
- *Campylobacter*
- *Shigella*
- *Salmonella*

■ Less common

- Enteroinvasive *E coli* (EIEC)
- *Aeromonas*
- *Plesiomonas*
- *Vibrio cholerae*

■ Viral agents (5-10%)

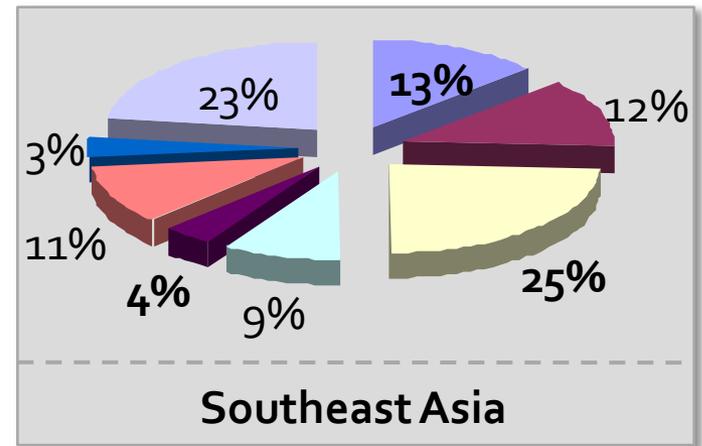
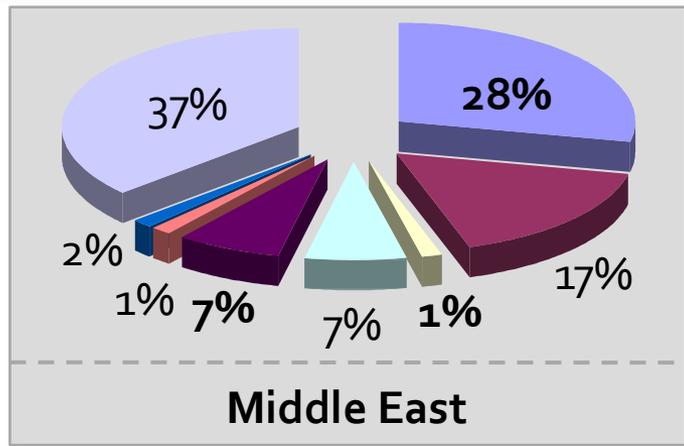
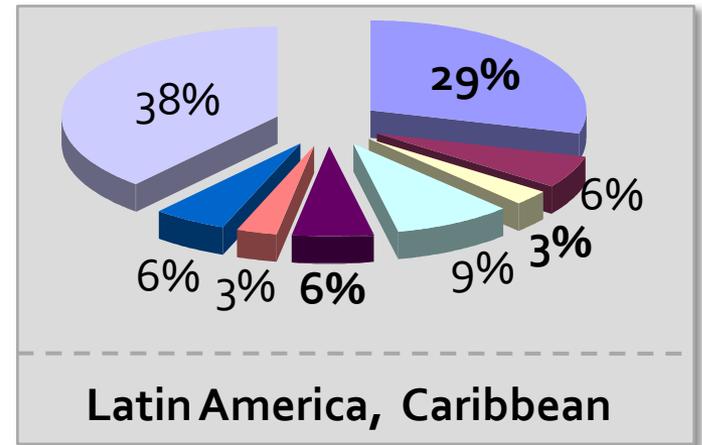
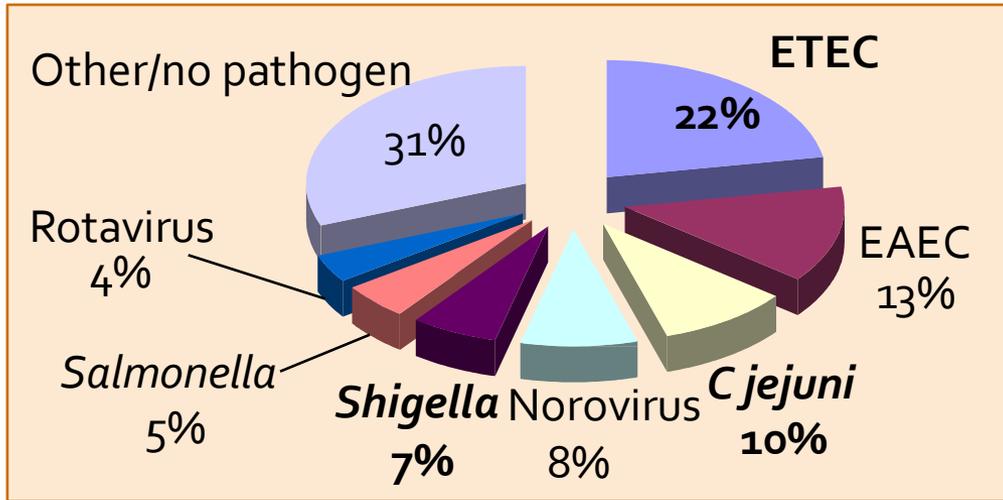
- Norovirus
- Rotavirus
- Astrovirus

■ Parasites (uncommon)

- *Giardia lamblia*
- *Cryptosporidium* spp.
- *Cyclospora cayatanensis*
- *Entamoeba histolytica*



Etiology of Diarrheal Diseases: *U.S. Military on Deployment*

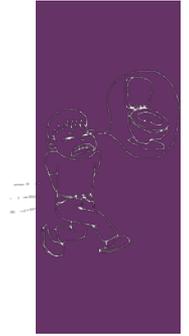


+ Common Etiological Agents of Diarrhea in Iraq and Afghanistan

Study	Year	Area	Pathogens (top 3)	Comments
Thornton <i>et al</i> <u>CID</u> 2005	2003	Diwaniyah (South of Baghdad)	Norovirus 23% <i>Shigella</i> spp. 20% <i>Campylobacter</i> 4%	Sampling favored epidemics, diarrheagenic <i>E. coli</i> not assessed
Monteville <i>et al</i> <u>AJTMH</u> 2006	2004	Kuwait, Qatar, Iraq, Afghanistan	ETEC 32% EAEC 12% <i>Salmonella</i> spp. 6%	Case series out of TMC in Doha, Qatar
Sanders (unpublished)	2004	Anbar Province, Iraq	ETEC 23% EAEC 12% EIEC 7%	Systematic cross-sectional study
Faix (unpublished)	2005	Anbar Province, Iraq	<i>Salmonella</i> spp. 38% Cryptosporidium 38% ETEC 15%	Outbreak in food vendors run by FSNs



Clinical Presentations



■ Watery diarrhea (80%)

- ± Abdominal cramps
- ± Nausea
- ± Vomiting
- ± Fecal urgency
- ± Low-grade fever

■ Dysentery (1-5%)

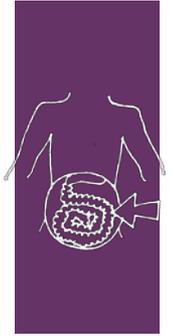
- Fever
- Tenesmus
- Mucoid stools
- Grossly bloody stools

■ Acute gastroenteritis ($\leq 10\%$)

- Recurrent vomiting

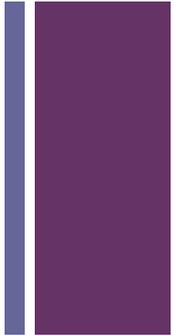


Clinico-pathological Considerations: Acute Travelers' Diarrhea



	Watery diarrhea	Dysentery	Gastroenteritis
Mechanism	Non-inflammatory (enterotoxin)	Inflammatory (invasion or cytotoxin)	Villus blunting (delayed gastric emptying)
Location	Proximal small bowel	Colon or distal small bowel	Small bowel
Usual Pathogens	All causative pathogens; most commonly ETEC, EAEC	<i>C. jejuni</i> <i>Shigella</i> spp. <i>Salmonella</i> (non-typhi) EIEC	Norovirus Rotavirus

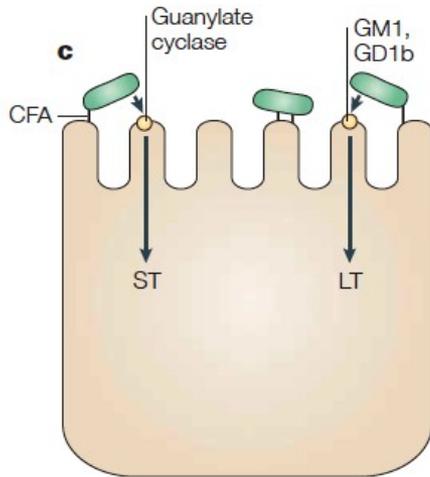
+ Persistent Travelers' Diarrhea



- Travelers' diarrhea is often self-limited, resolving in the majority of cases after several days
- Illness lasting >1 week: 10% of cases
- Illness lasting >1 month: 2% of cases
- Etiological considerations with persistent diarrhea
 - EAEC (occasionally, *Campylobacter*, *Salmonella*)
 - Parasitic diarrhea
 - *Giardia lamblia*
 - *Cryptosporidium parvum*
 - *Cyclospora cayatanensis*

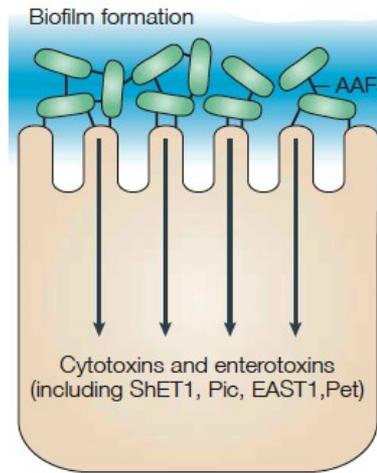
+ Diarrheagenic *Escherichia coli*

Common in Travelers: Pathogenesis



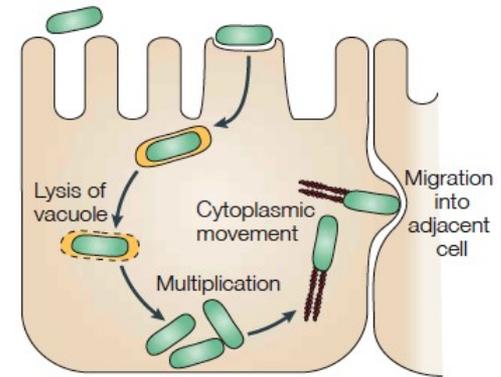
ETEC

- **Fimbrial colonization factors** mediate enterocyte adherence
- Elaboration of secretory heat-labile (LT), heat-stable (ST) **enterotoxins**



EAEC

- Enterocyte adherence and **biofilm formation**
- Elaboration of secretory enterotoxins and cytotoxins

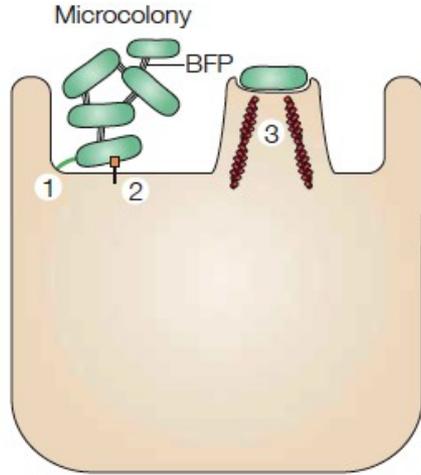


EIEC

- Colonic epithelial cell invasion
- Lysis of phagosome
- Cell-to-cell spread via actin microfilament nucleation

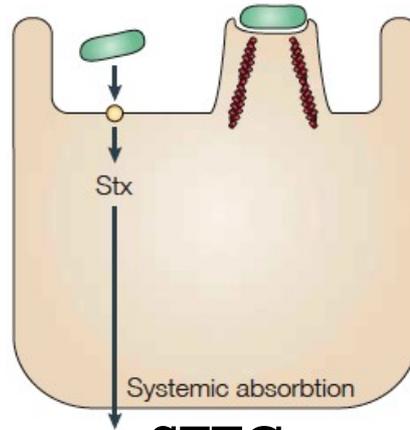
+ Diarrheagenic *Escherichia coli*

Uncommon in Travelers: Pathogenesis



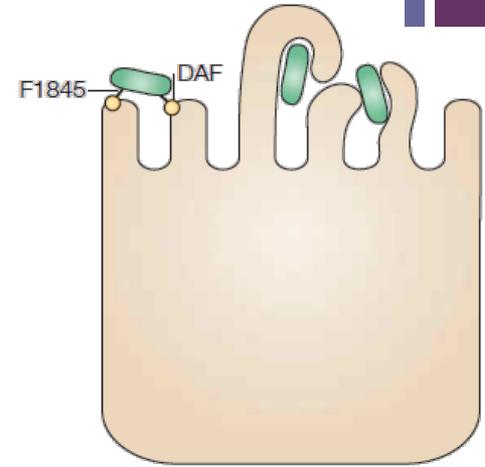
EPEC

- Intimate adherence to small bowel enterocytes
- Attaching and effacing lesion, with cytoskeletal derangement
- Induction of



STEC

- Induction of **attaching and effacing (AE)** lesions in the colonic epithelium
- Elaboration and absorption of **Shiga toxin (STx)**



DAEC

- Signal transduction effects
- Cellular projections induced that enwrap bacteria

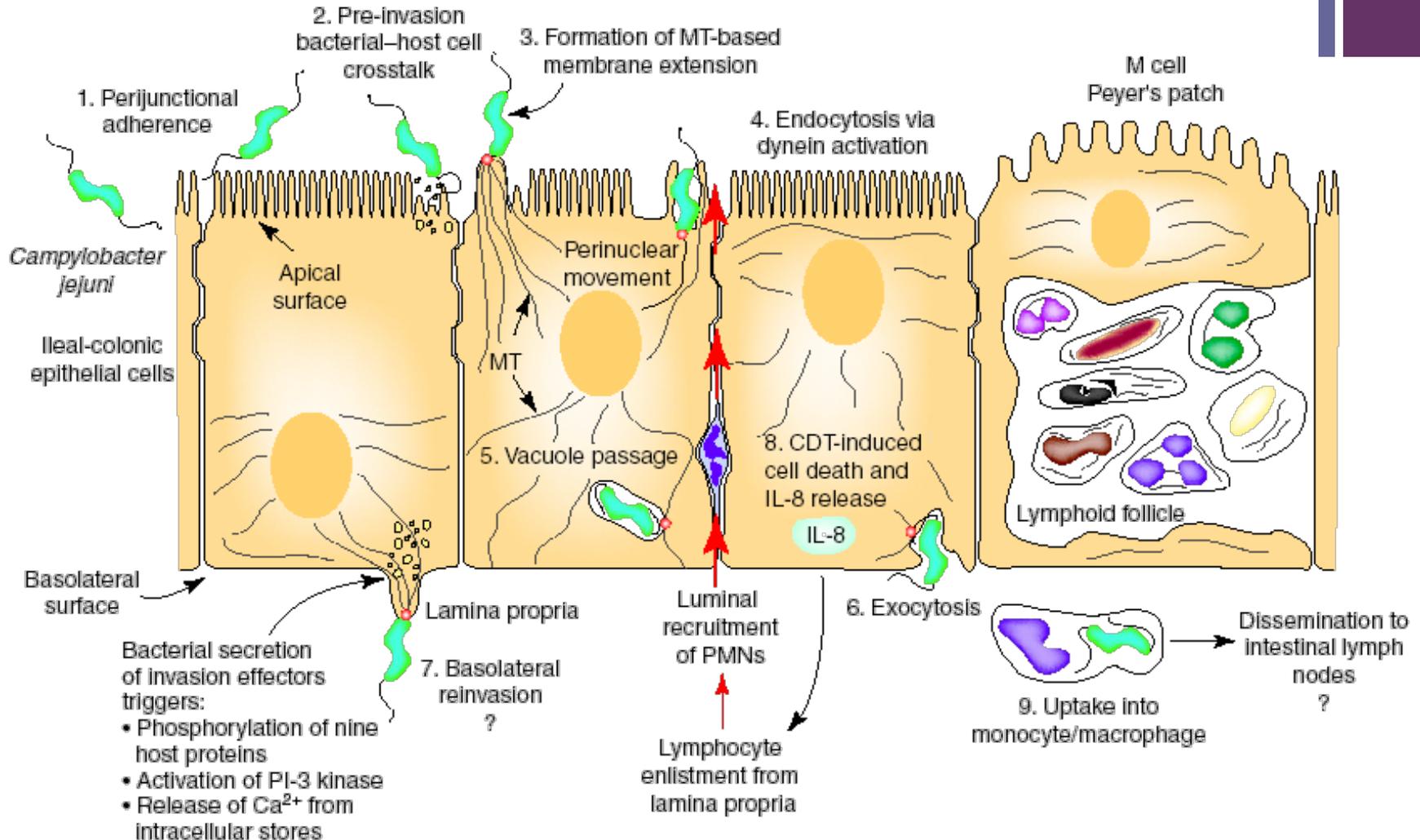
Enterotoxigenic *E. coli* (ETEC): Features



<i>Transmission</i>	foodborne (food, water)
<i>inoculum size</i>	High ($\geq 5 \times 10^6$ organisms)
<i>populations at risk</i>	infants, LDC; travelers to endemic regions
<i>Estimated no. cases annually</i>	200 million worldwide; > 500,000 under five death per year
<i>typical clinical syndrome</i>	watery diarrhea; dehydration in moderate-severe disease
<i>phenotypic diversity</i>	2 enterotoxins; > 20 fimbrial types
<i>sequelae</i>	physical and cognitive retardation; malnutrition



Campylobacter jejuni Pathogenesis



Campylobacter jejuni: Features



Transmission foodborne (food, water)

inoculum size low ($\geq 5 \times 10^2$ organisms)

populations at risk infants, LDC; travelers to hyperendemic regions; young people, HDC

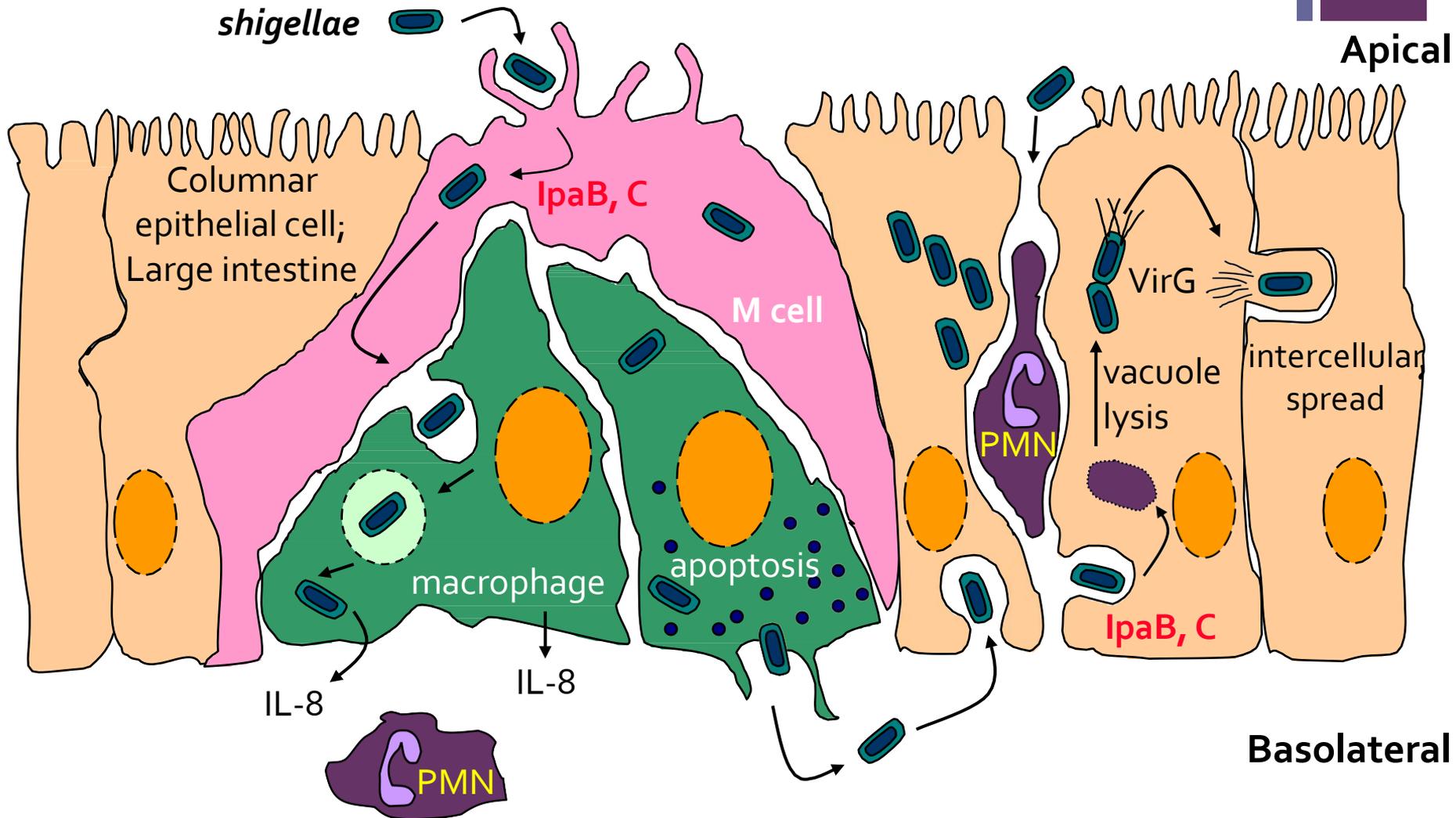
geographic 'hotspots' SE Asia, North Africa (Morocco)

typical clinical syndrome acute inflammatory enteritis

serotypic diversity multiple (108 Lior, 47 Penner serotypes)

sequelae reactive arthritis; Guillain-Barré syndrome; irritable bowel syndrome

+ *Shigella* spp. Pathogenesis



Shigellosis: Features

<i>transmission</i>	person-to-person; foodborne (food, water)
<i>inoculum size</i>	low (10-200 organisms)
<i>reservoirs</i>	humans only
<i>populations at high risk</i>	toddlers living in and travelers to LDC; crowding, poor sanitation (e.g., day care, institutions)
<i>serotypic diversity</i>	Over 50 different serotypes (determinant, LPS)
<i>key pathogenic processes</i>	invasion, spread, inflammatory response; cytotoxicity (<i>S. dysenteriae</i> type 1, Shiga toxin)
<i>typical clinical syndrome</i>	dysentery (most commonly, acute watery diarrhea)
<i>natural immunity</i>	Medium-term, serotype-specific immunity
<i>sequelae</i>	Reiter's syndrome; reactive arthropathy; hemolytic uremic syndrome

+ Differential Morbidity Associated with Major Bacterial Pathogens of Travelers' Diarrhea



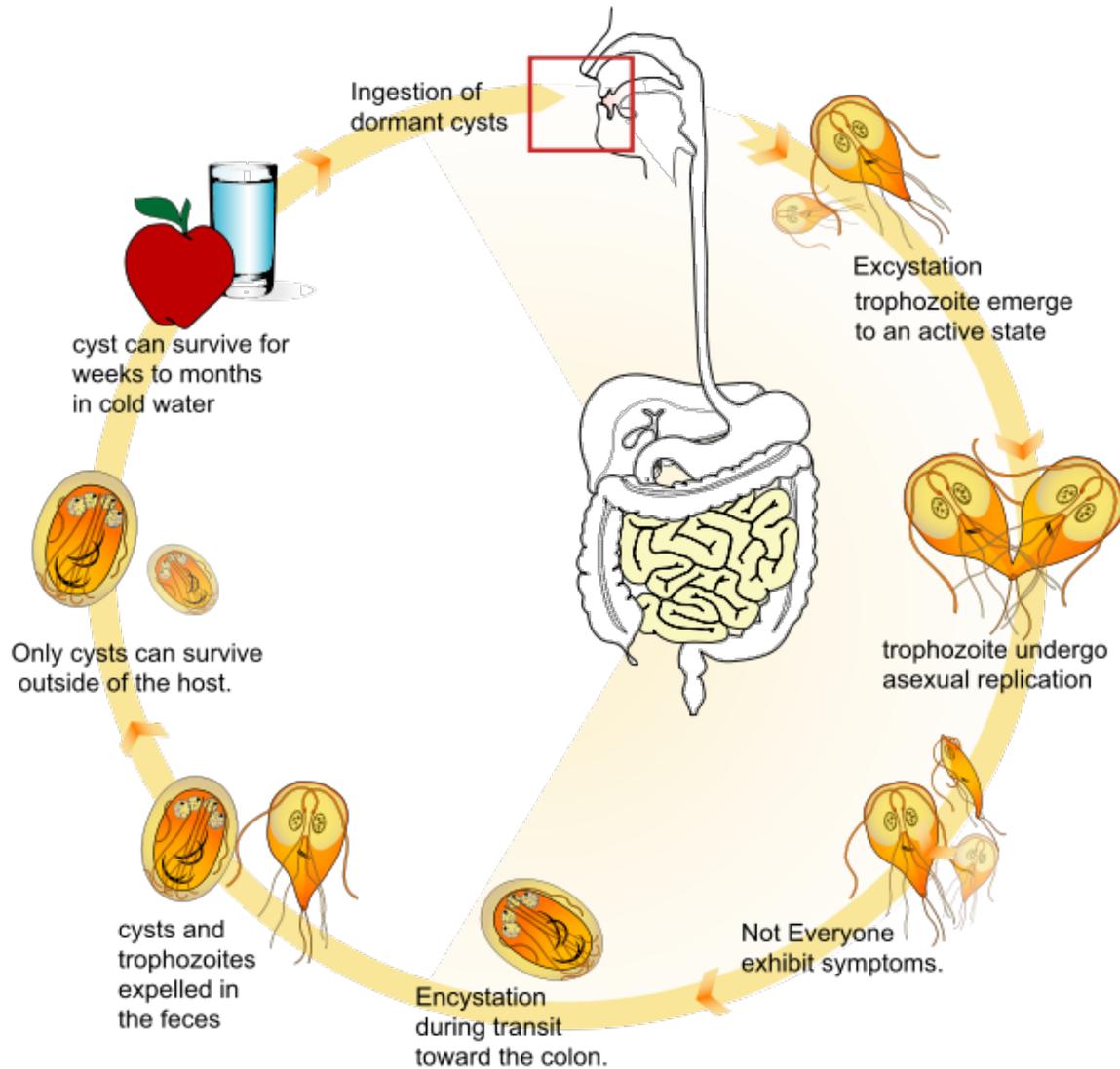
Pathogen profile	ETEC	<i>C jejuni</i>	<i>Shigella</i>
Global prevalence (%)	22 (17-28)	10 (5-15)	7 (3-10)
Illness duration w/o treatment (mean, d)	3.6	8.0	7.1
Probability of causing incapacitation (%)	21-27	47	56-92
Illness duration after treatment (mean, d)	1.0	2.5	1.2

Noroviruses: Features



<i>transmission</i>	foodborne (food, water); person-to-person (crowding)
<i>inoculum size</i>	low (as few as 10 viral particles)
<i>reservoirs</i>	humans only; hardy virus, persists on fomites
<i>populations at high risk</i>	All age groups; outbreak potential in semi-closed populations – military populations, including ships
<i>genotypic diversity</i>	3 genogroups, and ≥ 25 genotypes
<i>key pathogenic processes</i>	Limited to small intestine, broadening/blunting of proximal intestinal villi; transient malabsorption
<i>typical clinical syndrome</i>	Sudden onset of vomiting and non-inflammatory diarrhea; duration typically ≤ 72 hours
<i>natural immunity</i>	Short-term homologous immunity; possible long-term immunity with repeated exposure
<i>sequelae</i>	No evidence of serious long-term sequelae

Giardiasis: *Life Cycle*

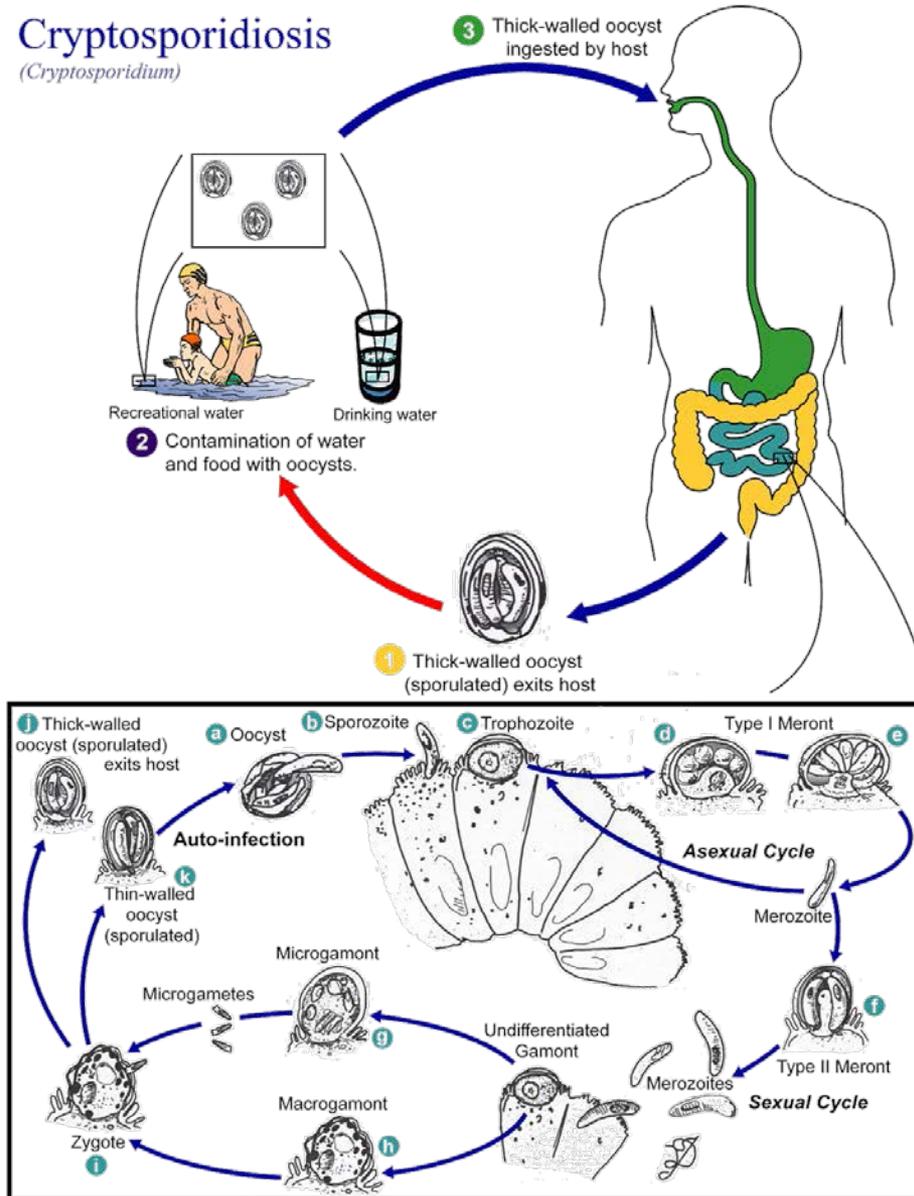


Giardiasis: Features

<i>transmission</i>	contaminated water; infected food handlers
<i>inoculum size</i>	low (as few as 10-25 cysts)
<i>reservoirs</i>	Humans and other mammals
<i>populations at high risk</i>	backpackers; young children LDC; higher risk with travel to Russia, Mexico, SE Asia, South America
<i>antigenic variation</i>	on-off switch of variant specific surface proteins (VSP)
<i>key pathogenic processes</i>	Attachment to intestinal epithelium via ventral disc; flagellar motility; VSP switching evades IgA
<i>typical clinical syndrome</i>	watery diarrhea; epigastric abdominal pain, bloating, malabsorption, nausea, vomiting, weight loss
<i>natural immunity</i>	both humoral and cell mediated immunity play a role in clearance; specific mechanisms poorly understood
<i>sequelae</i>	Functional gastrointestinal disorders (IBS)

Cryptosporidium: *Life Cycle*

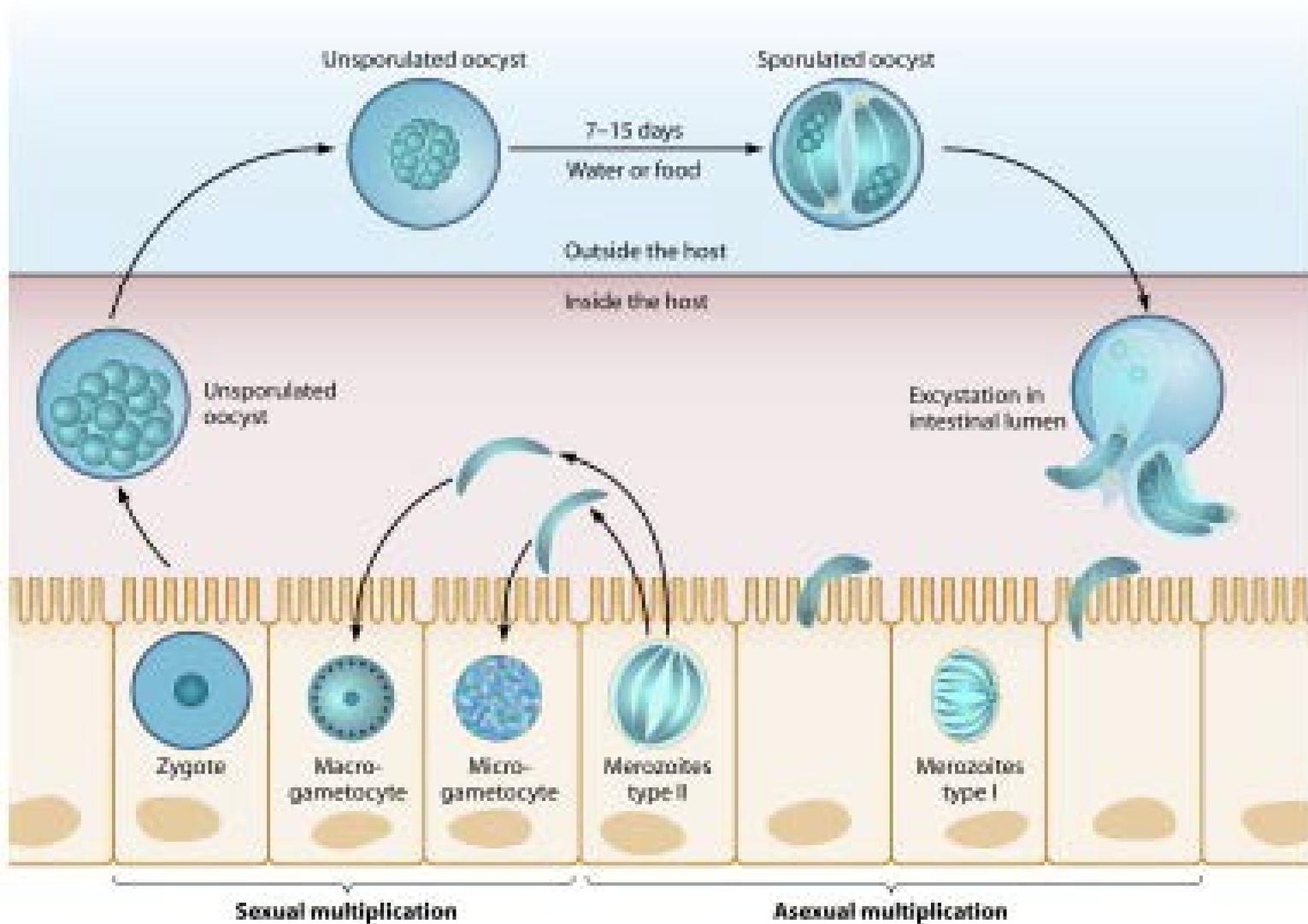
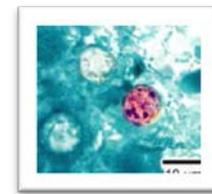
Cryptosporidiosis (*Cryptosporidium*)



Cryptosporidium: Features

<i>transmission</i>	contaminated water and food; person-to-person
<i>inoculum size</i>	low (as few as 10 oocysts)
<i>reservoirs</i>	humans and other mammals (including livestock)
<i>populations at high risk</i>	HIV/AIDS; urban populations, municipal water contamination; children in LDC; travelers
<i>species diversity</i>	majority of human cases due to <i>C. hominis</i> , <i>C. parvum</i>
<i>key pathogenic processes</i>	Localizes in parasitophorous vacuoles in intestinal epithelium; distal small intestine; villous atrophy
<i>typical clinical syndrome</i>	watery diarrhea, abdominal cramps, vomiting, mild fever, and loss of appetite
<i>natural immunity</i>	Acquisition of natural immunity inferred from human challenge studies and age-related incidence in LDC
<i>sequelae</i>	intractable diarrhea in immunocompromised patients

Cyclosporiasis: *Life Cycle*



Cyclosporiasis: Features



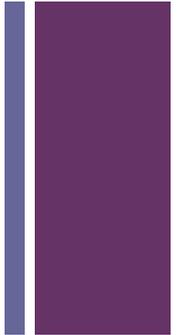
<i>transmission</i>	contaminated food and water; no person-to-person
<i>inoculum size</i>	undefined
<i>reservoirs</i>	environmental; may be host species-specific types
<i>populations at high risk</i>	young children in LDC; travelers (especially Peru, Nepal, Haiti, Guatemala (*)); immunocompromised
<i>species diversity</i>	<i>C. cayatanensis</i> found only in humans
<i>key pathogenic processes</i>	not well understood; localizes to small intestinal epithelium, partial villous atrophy, crypt hyperplasia
<i>typical clinical syndrome</i>	persistent diarrhea, anorexia, nausea/vomiting, abd cramps, flatulence, low grade fever, weight loss
<i>natural immunity</i>	decreased incidence with increasing age in high endemic areas of LDC;
<i>sequelae</i>	Chronic diarrhea in immunocompromised patients

+ Clinical and Diagnostic Evaluation

- Assess for dehydration
 - Mild (3-5%): dry mouth, decreased sweat and urine output
 - Moderate (6-9%): orthostasis, skin tenting, sunken eyes
 - Severe (>10%): hypotension, tachycardia, confusion, shock
- Consider setting of illness
 - Host factors
 - Environment, geographic region
 - Pathogen
- Define the clinical syndrome
 - Watery diarrhea
 - Dysentery
 - Gastroenteritis with recurrent vomiting
 - Persistent diarrhea



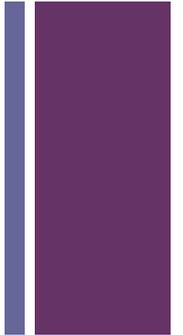
Considerations for Laboratory Work-up



- With military deployments, available laboratory capabilities may be austere
- Several common pathogens are not detectable with routine laboratory diagnostic tests
 - Diarrheagenic *E. coli* (ETEC, EAEC, EIEC)
 - Norovirus
- Differentiate inflammatory vs. non-inflammatory diarrhea
 - Clinical indicators of inflammatory disease include fever, tenesmus, visible blood in stool
 - Gross and microscopic examination of stool for blood and fecal leucocytes

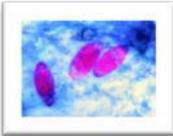
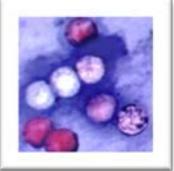
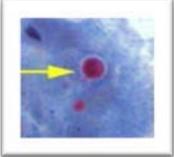
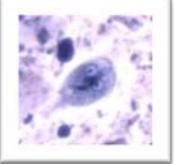


Considerations for Laboratory Work-up



- **Stool culture: clinical indications**
 - Severe diarrhea (≥ 6 loose/liquid stools/24 hrs, incapacitating illness)
 - Febrile enteritis and/or dysentery
 - Persistent diarrhea (≥ 14 days duration)
 - Bloody diarrhea (at risk for Shigella, STEC)
 - Inflammatory enteritis (by stool diagnostics)
- **Stool parasitology: clinical indications**
 - Persistent diarrhea (≥ 14 days duration)
 - Diarrhea in traveler returning from known high risk region

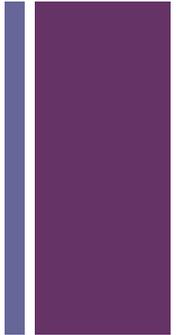
+ Stool O&P Testing

	Isospora	Cyclospora	Cryptosporidium	Giardia
Size (µm)	20-30	8-10	4-6	12-15
				
Modified AFB	positive	positive	positive	negative
Treatment	tmp-smx ¹ Cipro pyrimeth. ²	tmp-smx Cipro	HAART ³ paramomycin nitazoxinide	Flagyl
Antigen detection test	not available	not available	available	available

¹tmp-smx, trimethoprim-sulfamethoxazole. ²pyrimethamine.

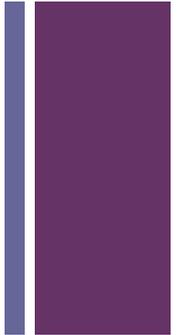
³HAART, for patients with HIV infection/AIDS.

+ Therapeutics: Water and Electrolyte Replacement



- Cornerstone of diarrhea treatment
- Military settings, insensible fluid losses increased with high ambient temperature, intense physical activity
- Oral rehydration
 - Physiological principle: Integrity of coupled transport of Na^+ (plus H_2O and other electrolytes) with glucose or amino acids
 - Effective in majority of patients
- Intravenous rehydration
 - Severe dehydration
 - Altered sensorium
 - Intractable vomiting

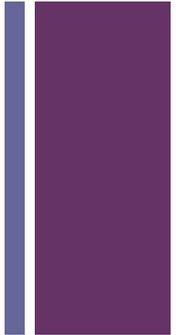
+ Oral Rehydration Therapy



- Mild dehydration
 - Potable water or appropriate ORS
- Moderate-severe disease
 - ORS

	CHO g/L	Na mmol/L	CHO:Na	K mmol/L	OSM mOsm/kg
Rehydration Formulas	13.5	75	1.2	20	245
WHO ORS					
Pedialyte	25	45	3.1	20	250
Sports Drinks	45	20	13	3	330
Gatorade					
Powerade	60-80	~10	~6	~3	346-391
Other fluids	108	35	~3	0	601
Red Bull					
Apple Juice	690	3	230	32	694-773
Chicken Broth	0	250	-	8	500

+ Non-Antibiotic Therapy



- Consider with mild diarrhea for symptomatic relief
- Loperamide: antimotility agent of choice
 - Slows down peristalsis, intestinal transit
 - Increased fluid and salt absorption
 - 4 mg by mouth, then 2 mg after each liquid movement (up to 16 mg per day)
- Bismuth subsalicylate (Pepto Bismol)
 - Reduces number of passes stools
 - Does not limit duration of disease
 - 525 mg (2 tabs) every 30 min for 8 doses
 - Contraindicated in persons on salicylates, warfarin
 - Can interfere with doxycycline absorption (malaria prophylaxis)

+ Empiric Antibiotic Therapy

- Indicated for patients with moderate to severe diarrhea/dysentery
- Combination of antibiotic plus loperamide leads to rapid resolution of illness
- Re-evaluate patient if no improvement after 1 wk

Antibiotic (po)	Dosage (adult)	Considerations
Fluoroquinolones		Re-evaluate 12-24 h after single dose. Continue for up to 3 d if diarrhea not resolved
Norfloxacin	800 mg once or 400 mg bid	
Ciprofloxacin	750 mg once or 500 mg bid	
Ofloxacin	400 mg once or 200 mg bid	
Levofloxacin	500 mg once or 500 qd	
Azithromycin	1000 mg once or 500 mg bid x 3d	Use when <i>C. jejuni</i> suspected
Rifaximin	200 mg tid	Effective for non-invasive <i>E coli</i>

+ Increasing Fluoroquinolone Resistance among *Campylobacter* in Travelers

norfloxacin resistance rates

Region	1994-2000			2001-2006		
	No. isolates	No. resistant isolates	Resistance rate (%)	No. isolates	No. resistant isolates	Resistance rate (%)
Africa	162	22	13.6	114	36	31.6
Asia	208	74	35.6	95	67	70.5
Caribbean, Central & So. America	36	10	27.8	33	20	60.6

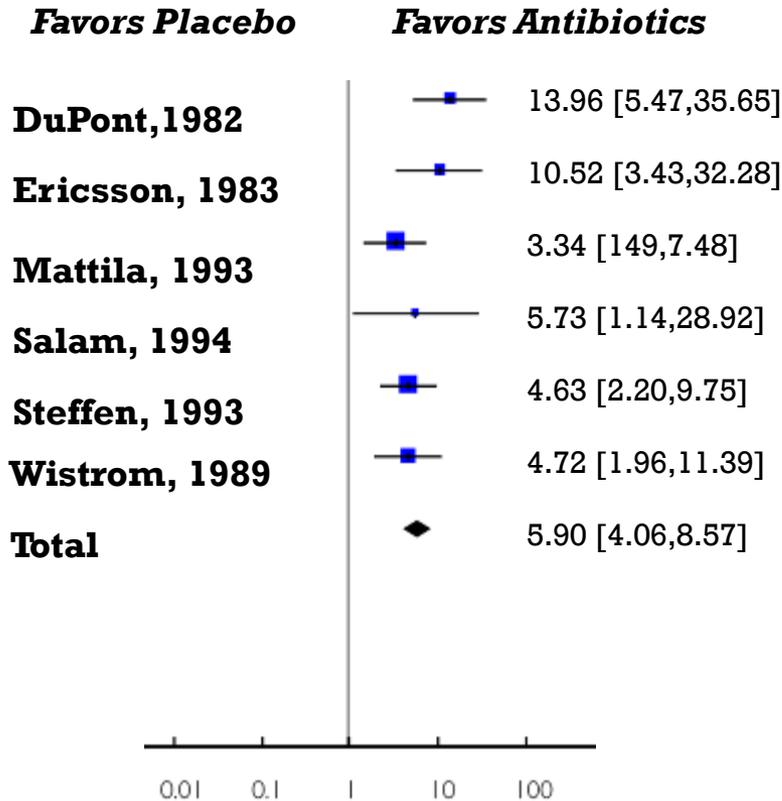
- Study site: Travel clinic, Antwerp, Belgium
- Erythromycin resistance showed modest increase over same period to 8.6% resistance in 2006

Effectiveness of Antibiotics, and Additive Effect of Loperamide)

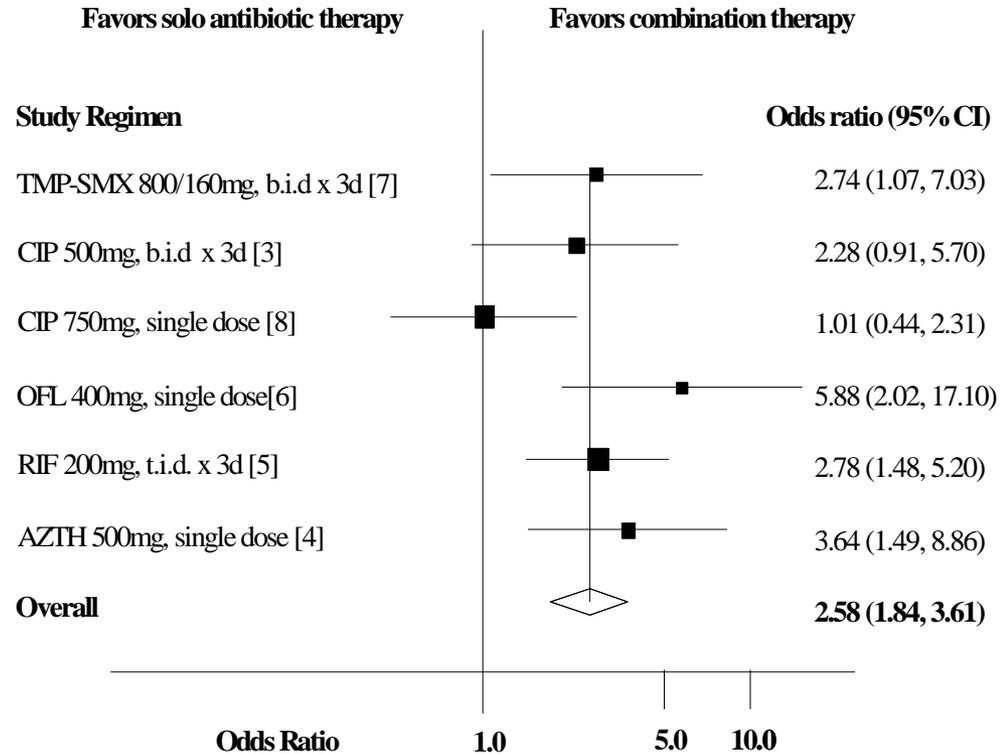


Placebo vs antibiotics alone
(outcome: cure at 72 hours)
Bruyn G et al Cochrane Collab 2004

Antibiotics alone or plus loperamide
(outcome: cure at 24 hours)
Riddle MS et al, CID 2008



TLUS = 24 – 36 hours

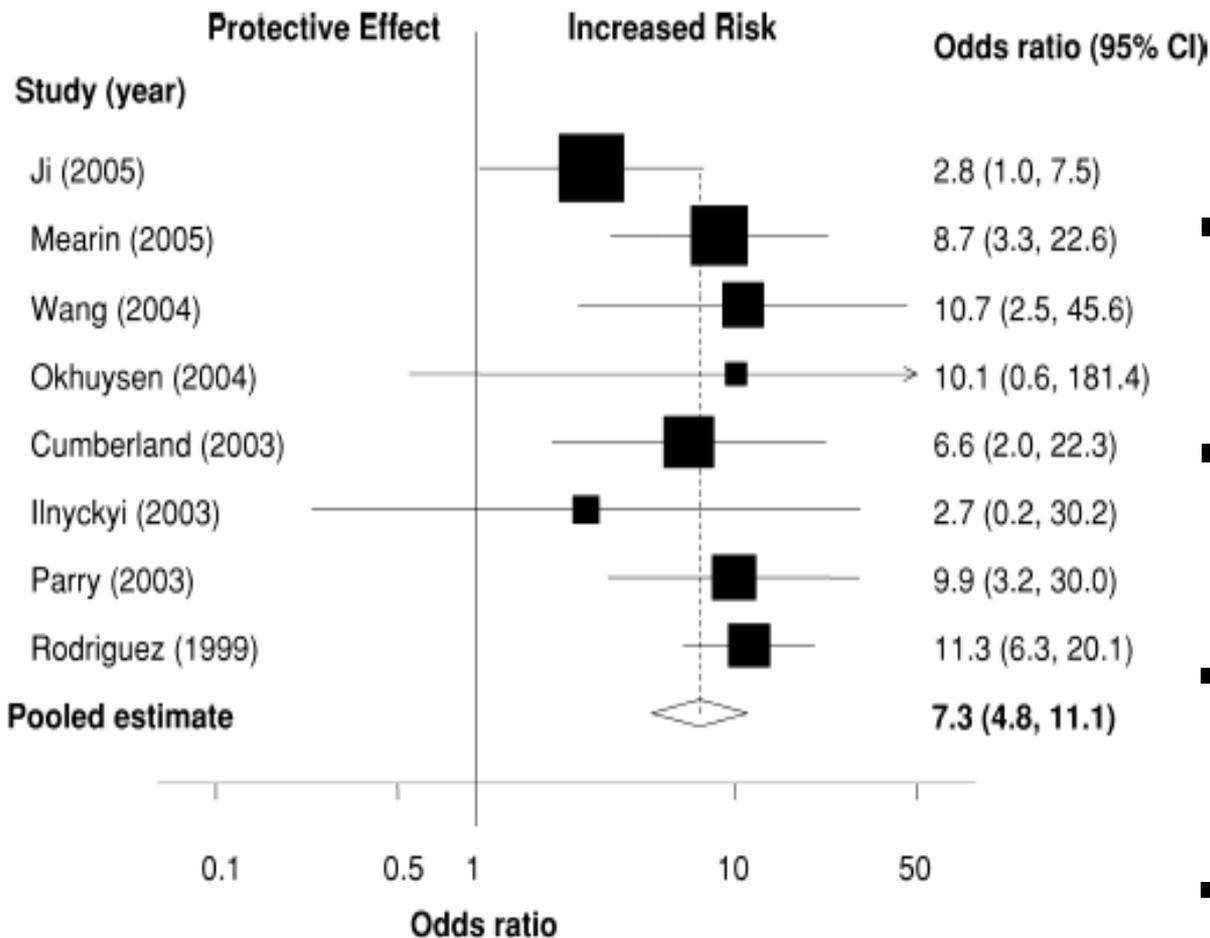


TLUS ~ 12 hours

Complications of Bacterial Diarrhea

Complication	Associated Bacterial Agents	Clinical Considerations
Dehydration	Any bacterial pathogen	Most important complication of watery diarrhea
Bacteremia	<i>Salmonella</i> spp., <i>C. fetus</i>	Certain conditions predispose to systemic <i>Salmonella</i> infection
Hemolytic-uremic syndrome (HUS)	STEC, <i>S. dysenteriae</i> type 1	Pathogenesis due to shiga toxin absorption and damage
Guillain-Barré syndrome	<i>Campylobacter jejuni</i>	40% cases of GBS caused by <i>C. jejuni</i> ; molecular mimicry LOS
Reactive arthritis	<i>C. jejuni</i> , <i>Salmonella</i> , <i>S. flexneri</i>	Occurs in 2.1 per 100 000 <i>Campylobacter</i> infections
Irritable bowel syndrome	Most bacterial pathogens	≤ 10% incidence following bacterial enteric infection

Postinfectious Irritable Bowel Syndrome (PI-IBS)



- First described among British Forces during WWII (Stewart. *Br Med J* 1950; 1(4650):405-9)
- Approx. 1 in 12 people develop PI-IBS after infectious diarrhea
- Higher risk associated with prolonged illness and invasive pathogens
- Onset usually occurs within 6 months after infection
- Can persists 5-6 years in 60 - 70% of people

+ Prevention of Enteric Diseases in Deployed Personnel

- Pre-deployment counseling of troops
 - Avoid exposure to pathogens transmitted by soiled food and drink ('boil it, cook it, peel it, or forget it!')
 - Seek early treatment with diarrhea
- Administer appropriate enteric vaccines
 - Typhoid vaccines (Ty21a [Vivotif]; Vi CPS [Typhim V])
 - Hepatitis A vaccine [Havrix, Avaxim]; Hepatitis B vaccine [Engerix-B]
- Antibiotic chemoprophylaxis
 - Not recommended for routine travel or deployment

+ Rifaximin and Chemoprophylaxis of Travelers' Diarrhea

Pros

- Poorly adsorbed oral antibiotic
 - Absent side effects
- Low levels of rifaximin resistance among enteric pathogens
- Prophylaxis against travelers' diarrhea for short-term travelers
 - ETEC predominant regions
 - $\geq 70\%$ protection conferred

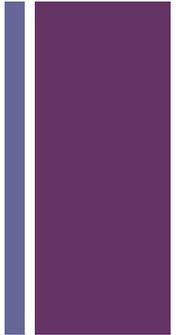
Cons

- Limited studies to date
 - Geographically delimited
 - Predominance of ETEC/EAEC
 - Short duration travel
- Impact of widespread usage for prophylaxis unknown



Take Home Lessons

- Acute diarrhea/dysentery in deployed military personnel (like travelers' diarrhea) is predominantly caused by bacterial enteropathogens
- Treatment of moderate to severe illness with antibiotics should be the rule (not the exception)
- The U.S. military does not send its forces on overseas vacation
- Population-wide morbidity from acute illness is significant, and greatly compounded by growing evidence of associated post-infectious sequelae





Back-Up Slides



+ Comparison of Civilian Travelers vs. Deployed Military

Civilian Travelers

- Short-term trip (days-wks)
- Less crowding (cruise ship)
- Leisure trips
- Eating on economy
- Varied exertion level
- Typically poor access to medical facilities
- Self-treatment of diarrhea

Deployed Military

- Long deployment (wks-mos)
- Crowded housing is norm
- Intensive work demand
- Availability of MREs
- Typically high exertion
- Embedded medical assets
- Encourage early care seeking