

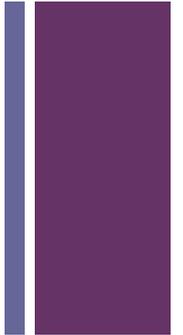
# Infectious Diarrhea in Military Settings



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# + Outline

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

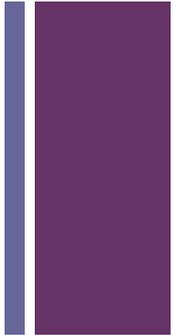


# + Take Home Lessons

- 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

# + Travelers' Diarrhea

- 30-60% travelers affected
  - 20% bed-ridden days
  - 60% change travel plans
- Risk for acquisition may or may not reflect “adventurous” habits
- 70% of all early OEF, OIF affected
  - 30% had 3+ episodes

Steffen, CID 2005

Putnam, J Travel Med 2006

## Nothing but the tooth! Steven Tyler reveals post fall injuries as he insists he has NOT fallen off the wagon

By SOPHIE FORBES and HOLLY THOMAS  
Last updated at 8:04 PM on 27th October 2011

Comments (89) | Share | Tweet | Like

He has struggled with addiction problems for most of his life but this morning Steven Tyler spoke out to refute claims that his horrific fall on Tuesday was caused by intoxication.

The 63-year-old Aerosmith front man called in to The Today Show to discuss the issue with host Matt Lauer and revealed an image of himself taken shortly after the fall in which he sported broken teeth and a nasty black eye.

Tyler, who fell whilst taking a shower, first entered rehab back in 1984 but insists that this time he was completely sober.

Scroll down to see the video....



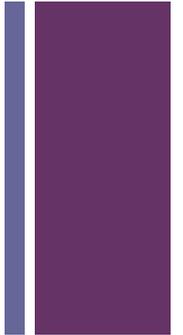
© NBC Today

Not drunk: Steven Tyler shows his post fall picture with The Today Show whilst insisting he was completely sober when he fell

I went in looking like Baryshnikov, and walked out looking like [poor] Leon



# Impact of Diarrheal Diseases in Modern Military Campaigns



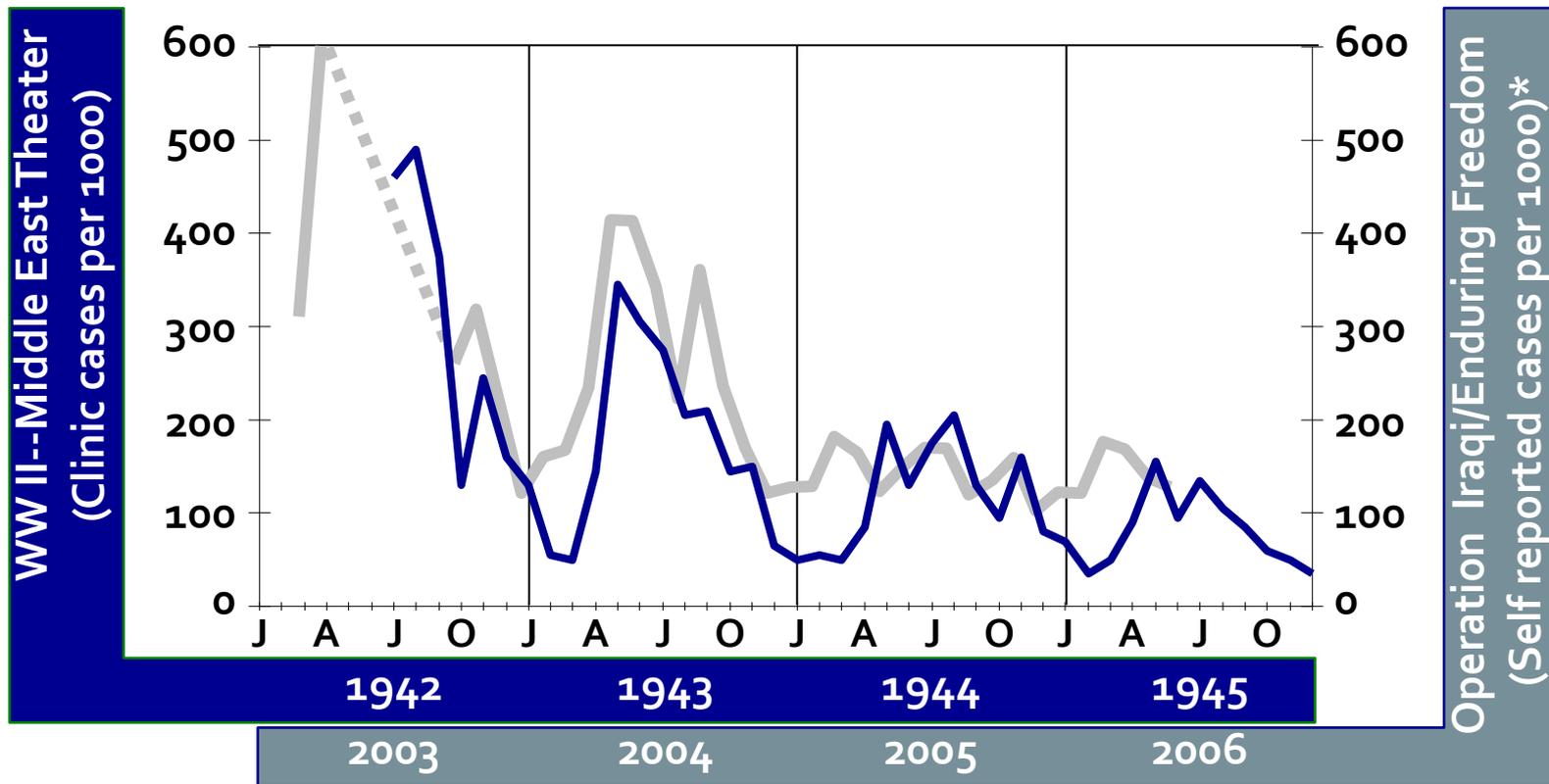
- **World War II:** ‘A few months of the year, malaria would cause more man-days lost, but on the calendar-year average, gastrointestinal infections were well ahead.’<sup>1</sup>
- **Vietnam War:** Diarrhea/dysentery largest single disease threat, leading to 4 times more hospitalizations than malaria<sup>2</sup>
- **OIF:** Acute enteric illness was leading cause of hospital admission among British forces during first 12 months of operations in Iraq<sup>3</sup>

(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.

# + Diarrheal Diseases: A Perennial Disease Risk for Deployed Military Forces



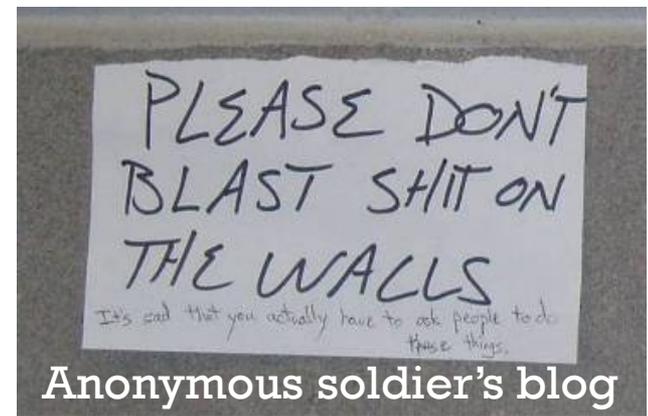
Diarrhea incidence in the Middle East Theater  
World War II vs. Recent Operations SWA

+

# 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%



# *Clinical Infectious Diseases* 2005

## EDITORIAL COMMENTARY

**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  $> 40^{\circ}\text{C}$ .

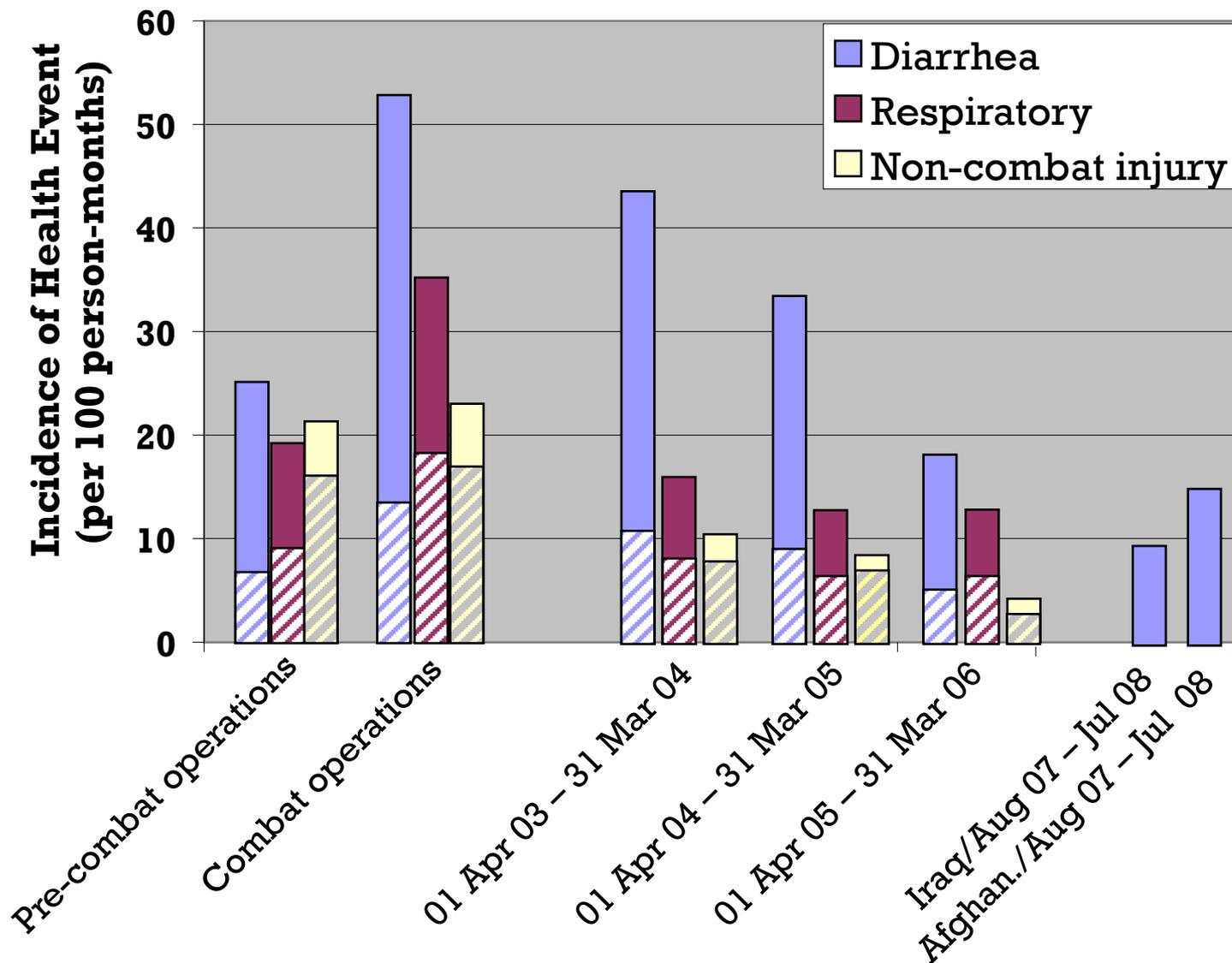
David O. Matson, MD

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

# Complications of Bacterial Diarrhea

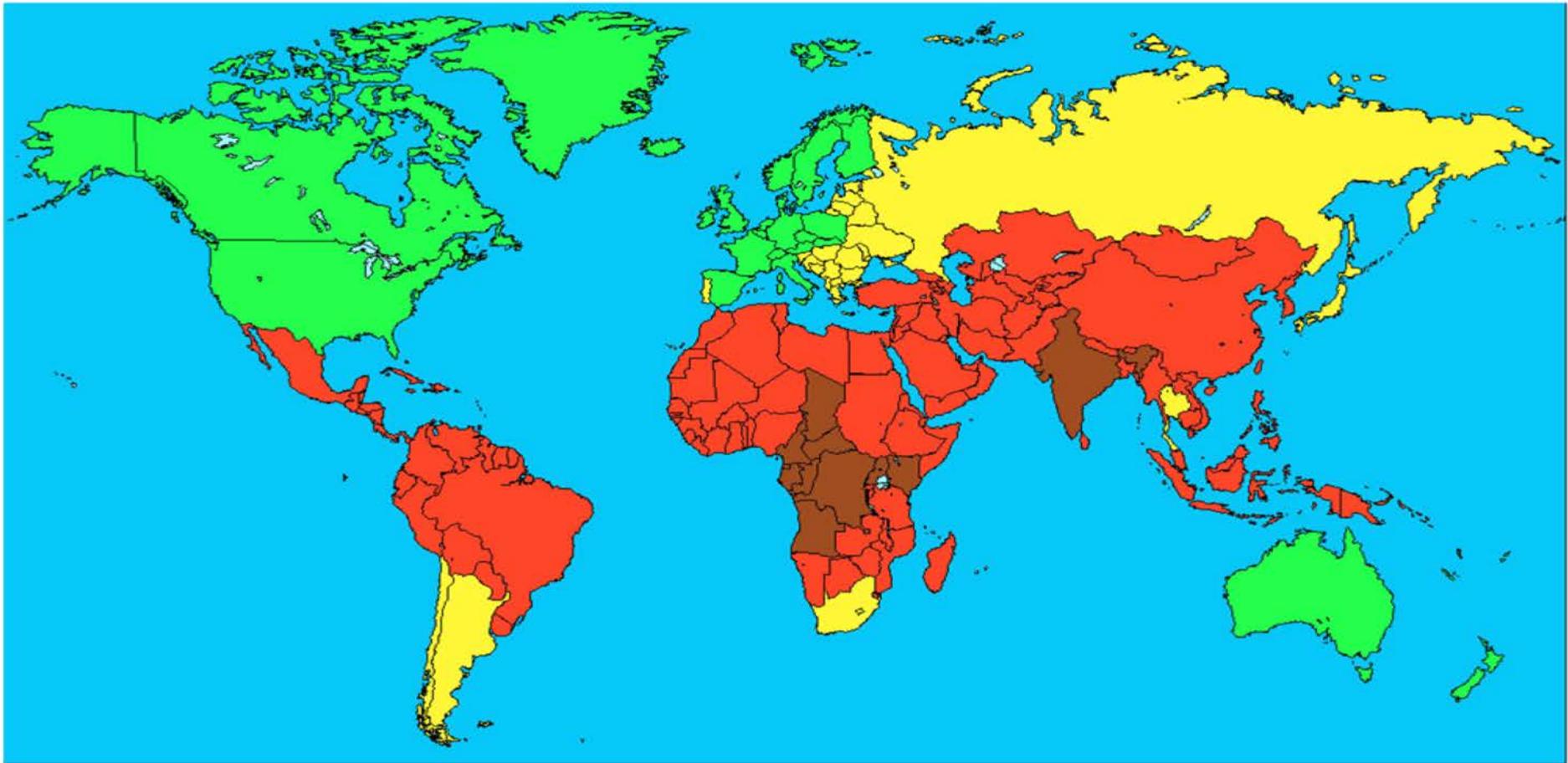
Complication	Associated Bacterial Agents	Clinical Considerations
Dehydration	Any bacterial pathogen	Most important complication of watery diarrhea
Bacteremia	<i>Salmonella</i> spp., <i>C. fetus</i>	Certain conditions predispose to systemic <i>Salmonella</i> infection
Hemolytic-uremic syndrome (HUS)	STEC, <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

# Incidence of Illness based on Self-Reporting vs. DNBI



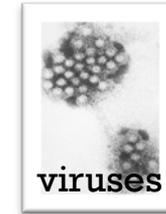
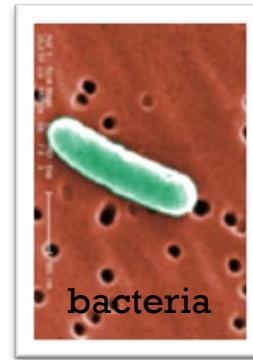
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# Incidence Rates of Travelers' Diarrhea per 2-week Stay



Risk: ■ Low <8% ■ Intermediate 8-20% ■ High 20-50% ■ Very high >50%

# + 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%)

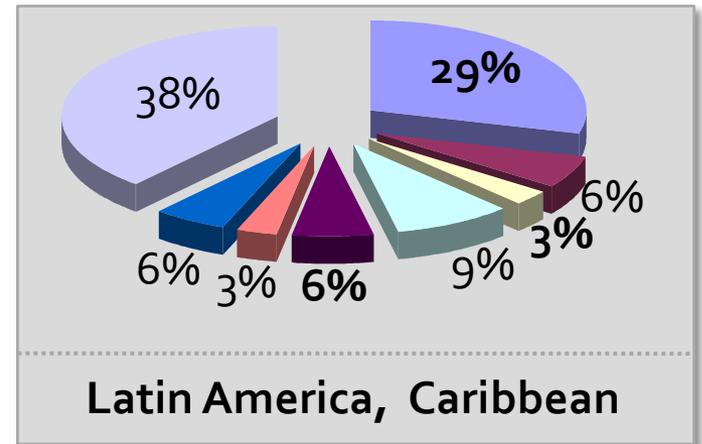
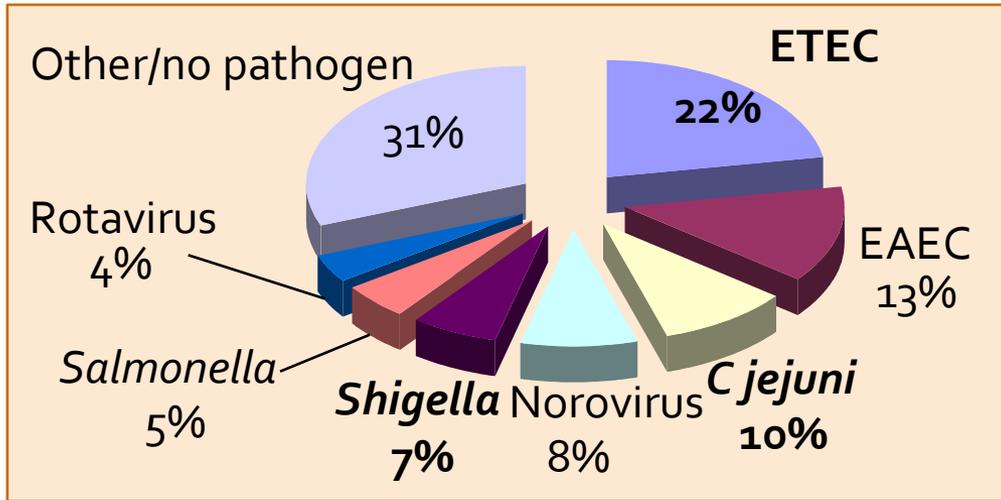
- Norovirus
- Rotavirus
- Astrovirus

## ■ Parasites (uncommon)

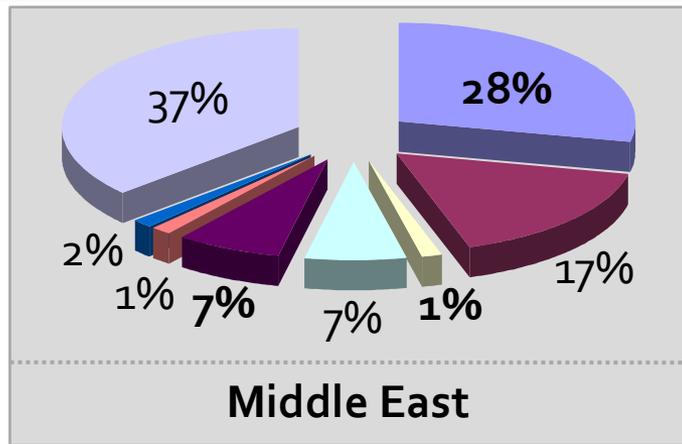
- *Giardia lamblia*
- *Cryptosporidium* spp.
- *Cyclospora cayetanensis*
- *Entamoeba histolytica*



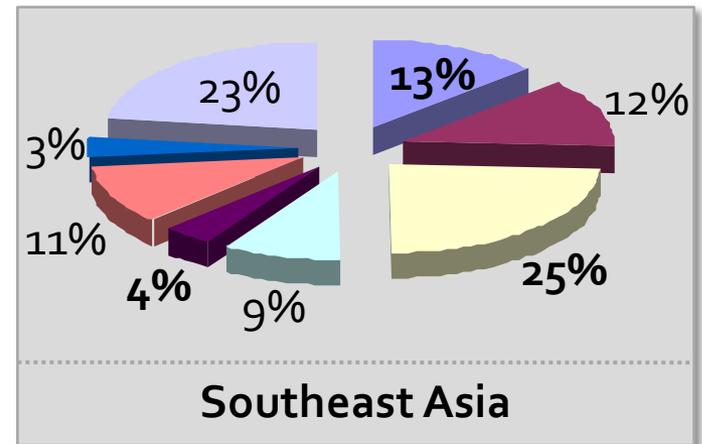
# Etiology of Diarrheal Diseases: *U.S. Military on Deployment*



Latin America, Caribbean



Middle East



Southeast Asia



# Clinical Presentations



## ■ Watery diarrhea (~80%)

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

## ■ Dysentery (1-5%)

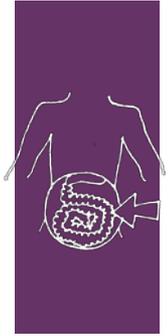
- Fever
- Tenesmus
- Mucoid stools
- Grossly bloody stools

## ■ Acute gastroenteritis ( $\leq 10\%$ )

- Recurrent vomiting



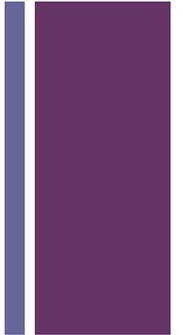
# Clinico-pathological Considerations: Acute Travelers' Diarrhea



	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



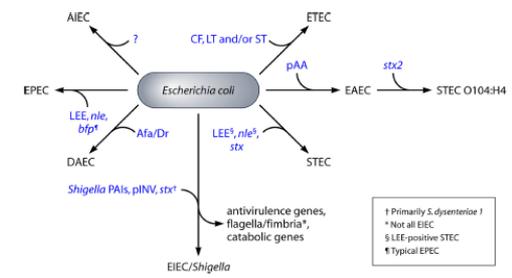
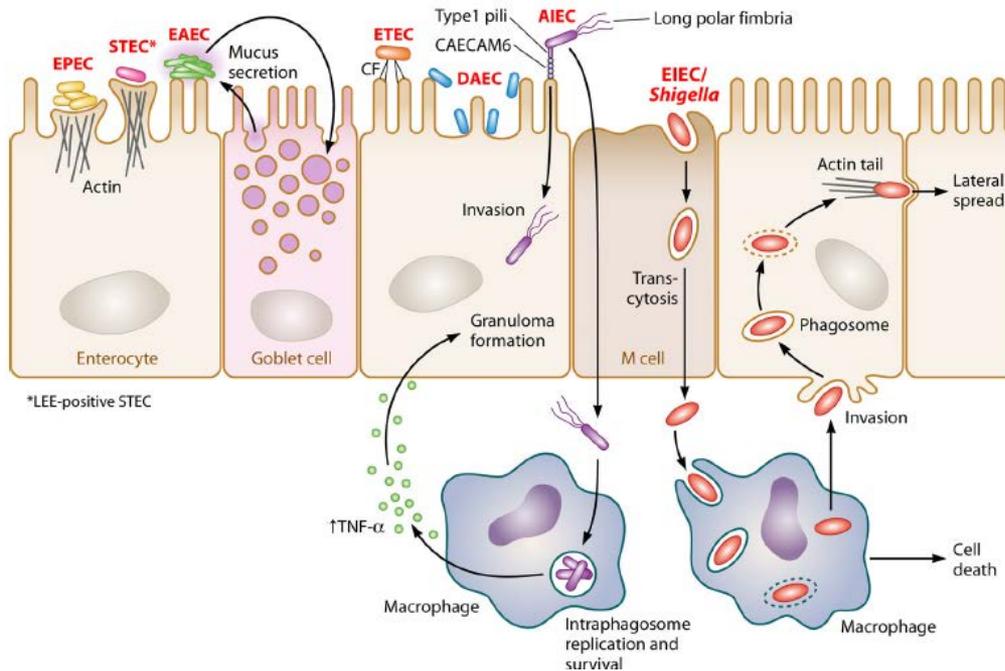
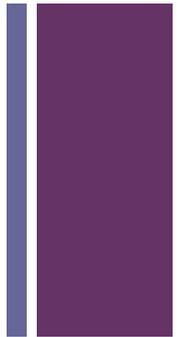
# Persistent Travelers' Diarrhea



- 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 cayetanensis*



# Diarrheagenic E.coli: One bug, many diseases



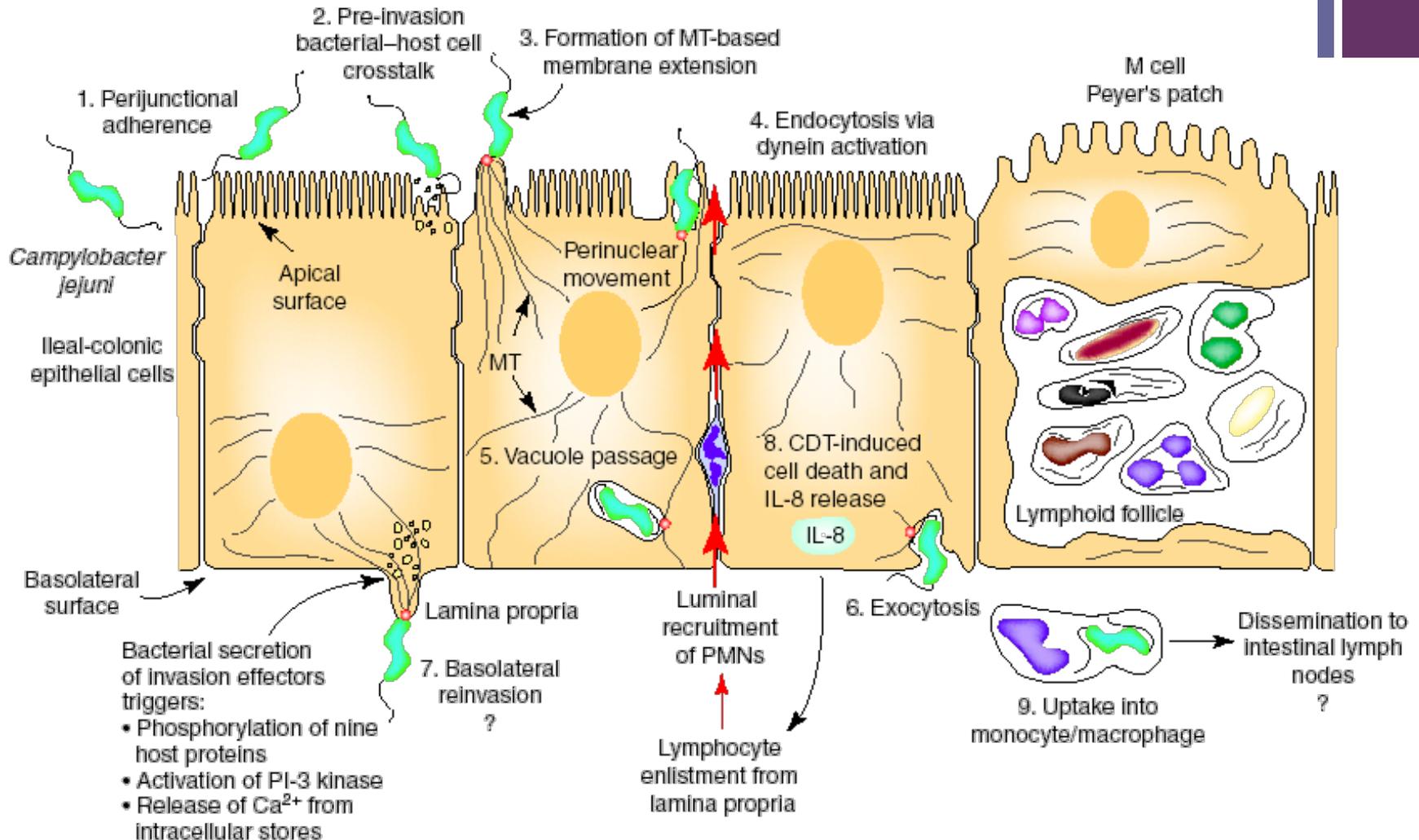
- ETEC – Enterotoxigenic E.coli
- STEC (includes O7:H157) – Shiga toxin producing E.coli
- EAEC, EPEC, AIEC
- EIEC – Essentially Shigella

# 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

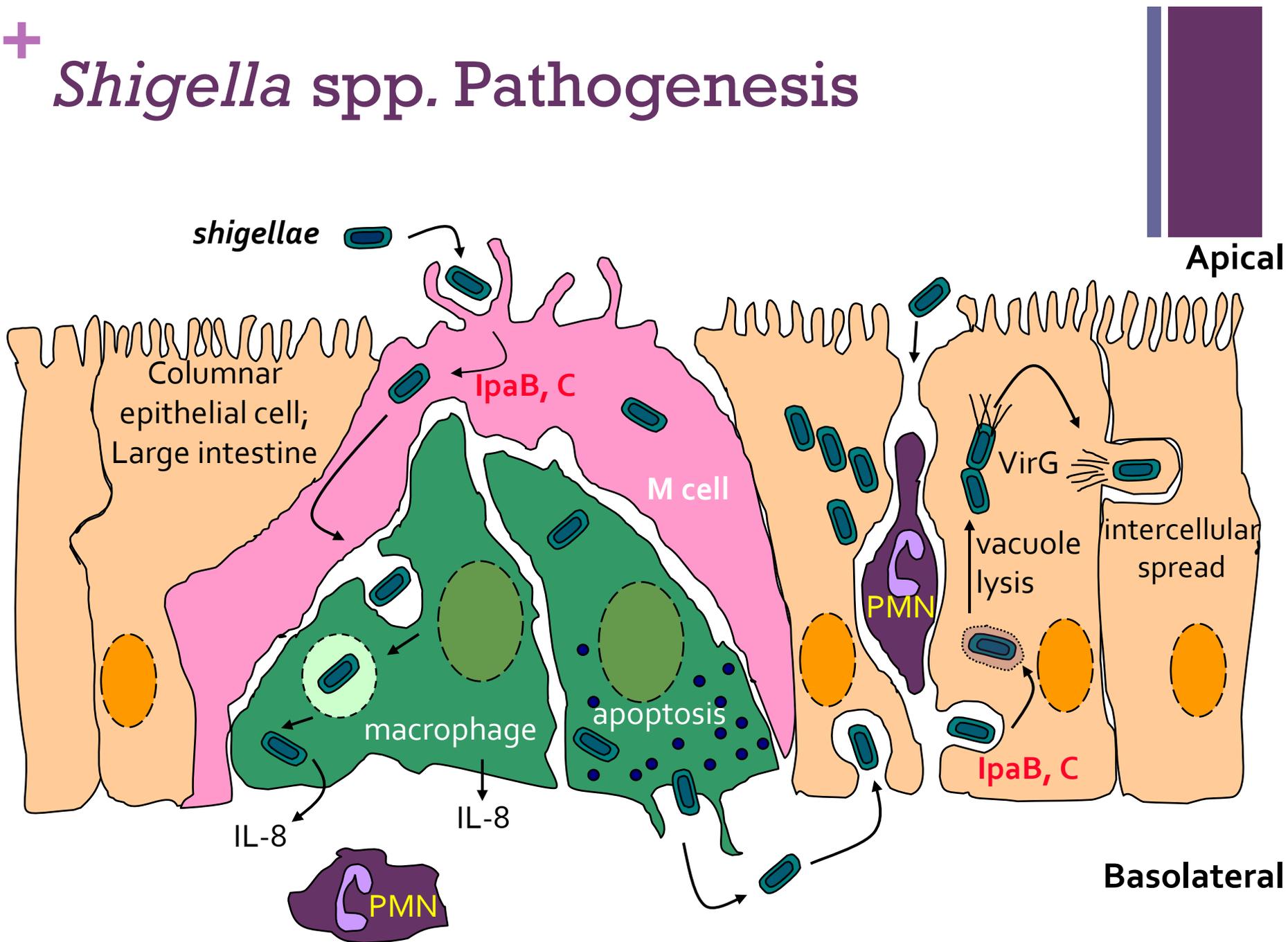
*geographic 'hotspots'* SE Asia, North Africa (Morocco)

*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>	<b>humans</b> 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>	<b>dysentery</b> (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

LDC, less developed countries



## 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

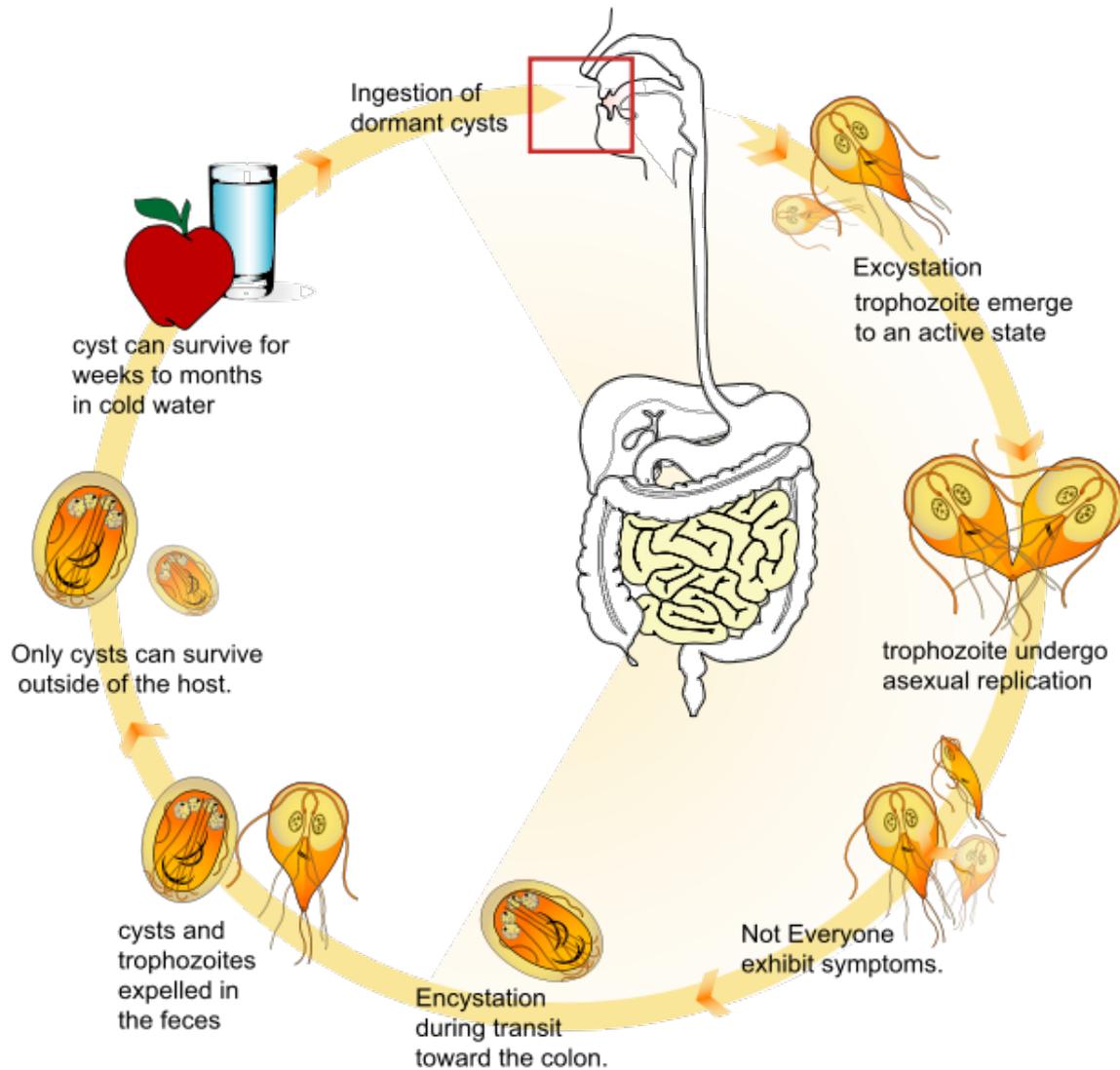


<i>transmission</i>	foodborne (food, water); person-to-person (crowding)
<i>inoculum size</i>	low (as few as 10 viral particles)
<i>reservoirs</i>	<b>humans</b> only; hardy virus, persists on fomites
<i>populations at high risk</i>	All age groups; outbreak potential in semi-closed populations – military populations, including ships
<i>genotypic diversity</i>	3 genogroups, and $\geq 25$ 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 $\leq 72$ 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

# Parasitic Causes of Acute Diarrhea

- Look for prolonged course of diarrhea not responding to antibiotic therapy
  - Patients *usually* not acutely ill
- *Cryptosporidium parvum*
- *Entamoeba histolytica*
- *Giardia lamblia*
- *Cyclospora, Isospora*
- *Shistosomiasis* – rare cases of dysentery
- *Plasmodium* species can cause diarrhea in acute infection

# Giardiasis: *Life Cycle*

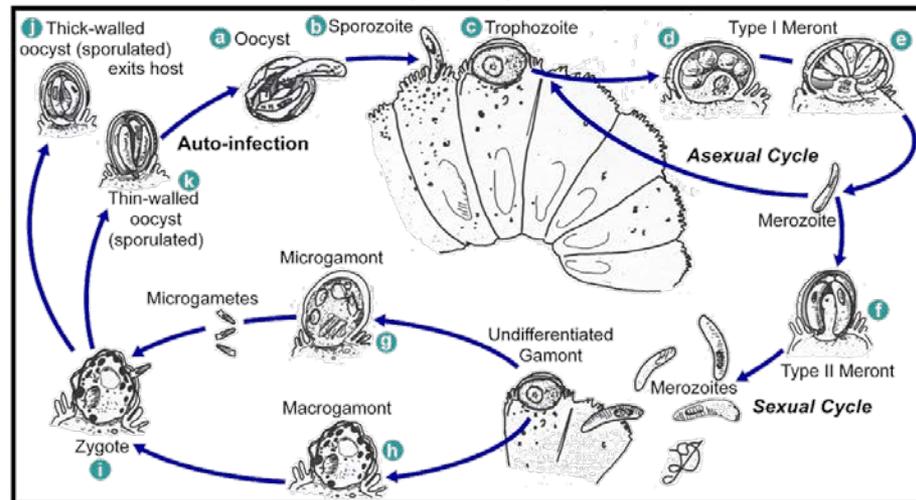
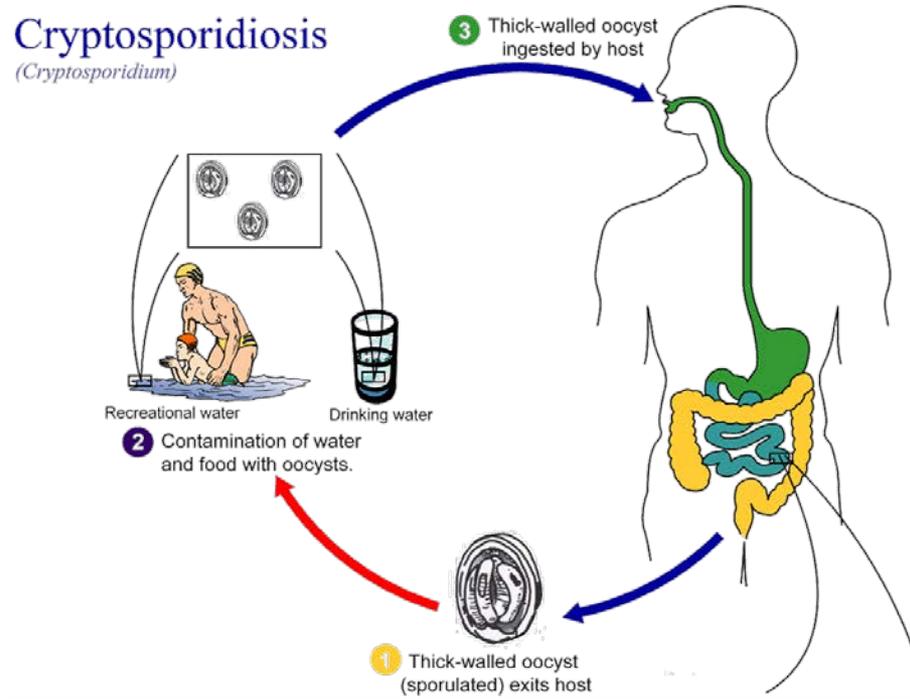


# Giardiasis: Features



<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>Treatments</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*

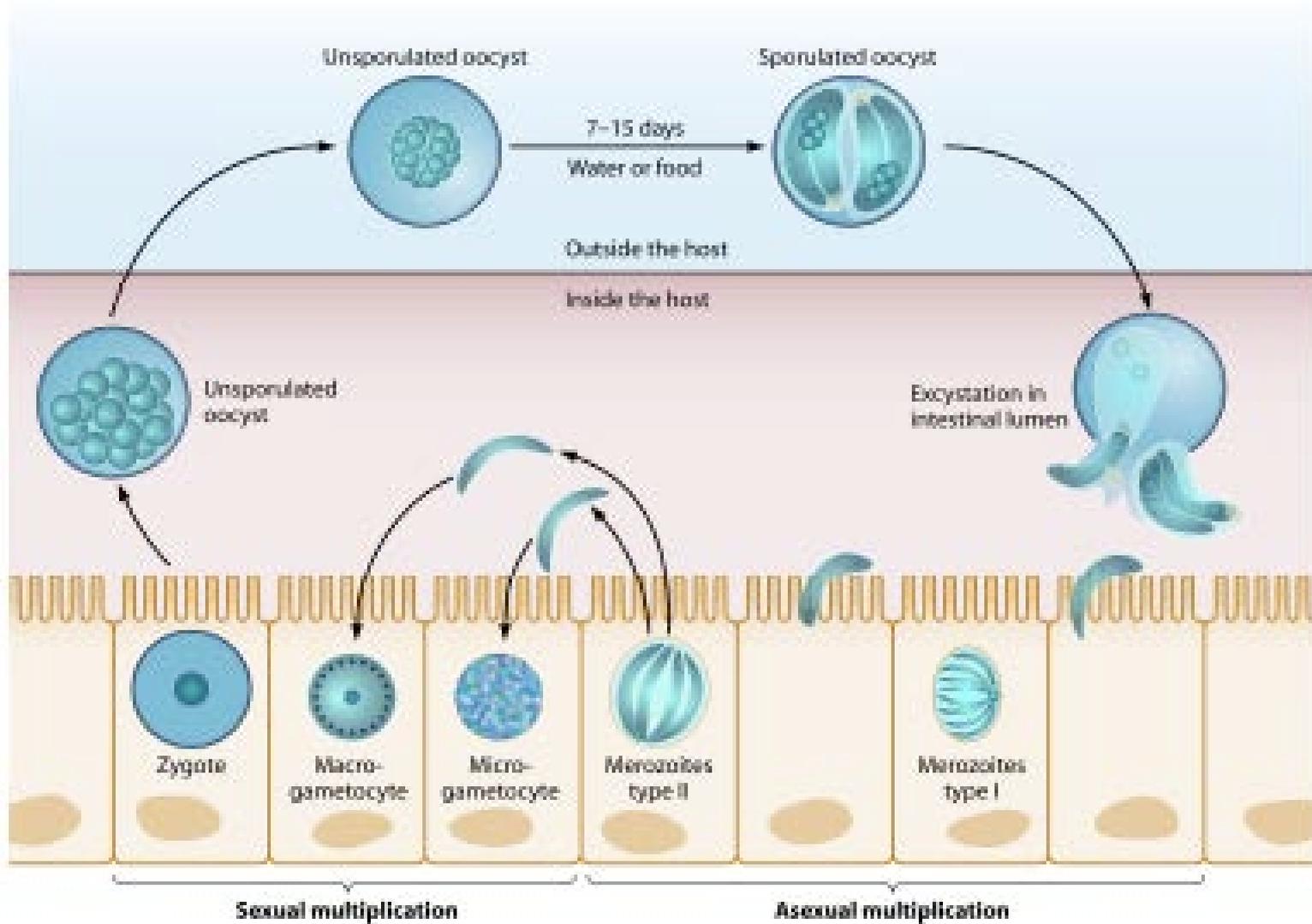
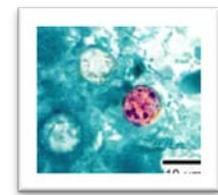


# Cryptosporidium: Features

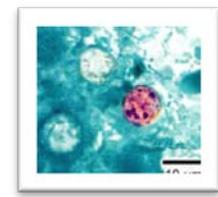


<i>transmission</i>	contaminated water and food; person-to-person
<i>inoculum size</i>	low (as few as 10 oocysts)
<i>reservoirs</i>	humans and other mammals (including livestock)
<i>populations at high risk</i>	HIV/AIDS; urban populations, municipal water contamination; children in LDC; travelers
<i>species 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*



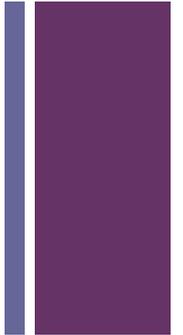
# Cyclosporiasis: Features



<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. cayetanensis</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

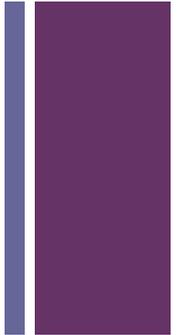


- Assess for dehydration
  - Mild (3-5%): dry mouth, decreased sweat and urine output
  - Moderate (6-9%): orthostasis, skin tenting, sunken eyes
  - Severe (>10%): hypotension, tachycardia, confusion, shock
- Consider setting of illness
  - Host factors
  - Environment, geographic region
  - Pathogen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



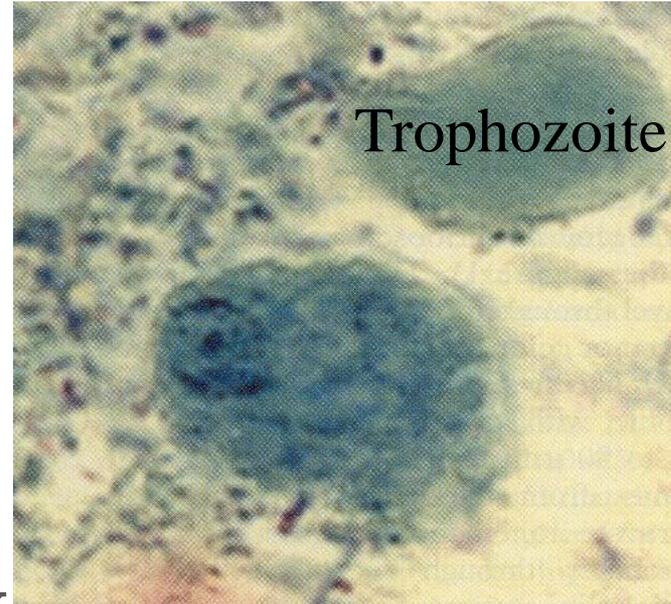
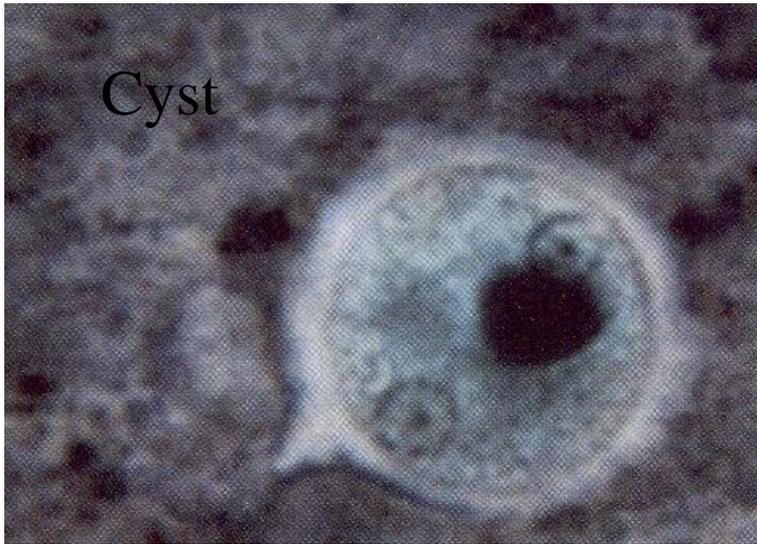
# Considerations for Laboratory Work-up

- 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



# + Diagnosis and Treatment

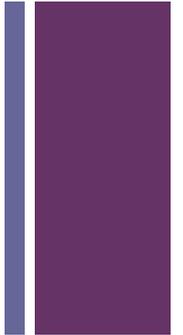
- Stool examination
- Stool Antigen *E histolytica* vs *E dispar*
- Amoebic serology for liver abscess



- Metronidazole 750mg PO TID x 10 days
- + Paromomycin (luminal agent)



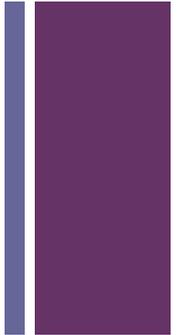
# Considerations for Laboratory Work-up



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



# 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  $\text{Na}^+$  (plus  $\text{H}_2\text{O}$  and other electrolytes) with glucose or amino acids
  - Effective in majority of patients
- Intravenous rehydration
  - Severe dehydration
  - Altered sensorium
  - Intractable vomiting

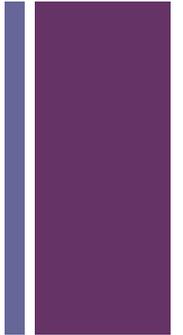
# + Oral Rehydration Therapy

- 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
<b>Rehydration Formulas</b>					
<b>WHO ORS</b>	<b>13.5</b>	<b>75</b>	<b>1.2</b>	<b>20</b>	<b>245</b>
Pedialyte	25	45	3.1	20	250
<b>Sports Drinks</b>					
Gatorade	45	20	13	3	330
Powerade	60-80	~10	~6	~3	346-391
<b>Other fluids</b>					
Red Bull	108	35	~3	0	601
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
<b>Fluoroquinolones</b>		
Norfloxacin	800 mg once or 400 mg bid	Re-evaluate 12-24 h after single dose. Continue for up to 3 d if diarrhea not resolved
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**

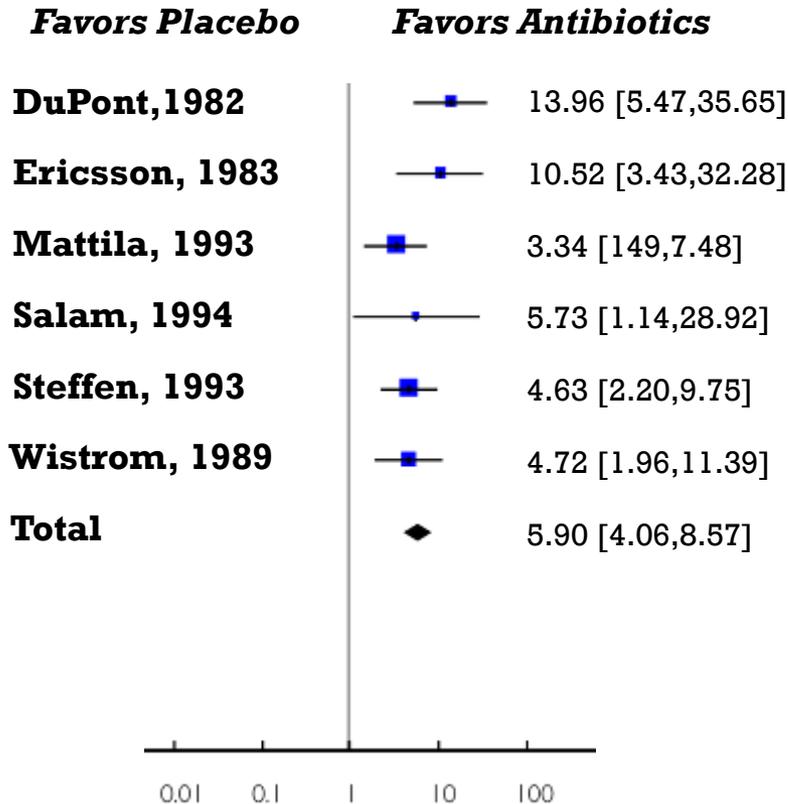
Region	1994-2000			2001-2006		
	No. isolates	No. resistant isolates	Resistance rate (%)	No. isolates	No. resistant isolates	Resistance rate (%)
Africa	162	22	13.6	114	36	31.6
Asia	208	74	35.6	95	67	70.5
Caribbean, Central & So. America	36	10	27.8	33	20	60.6

- 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)

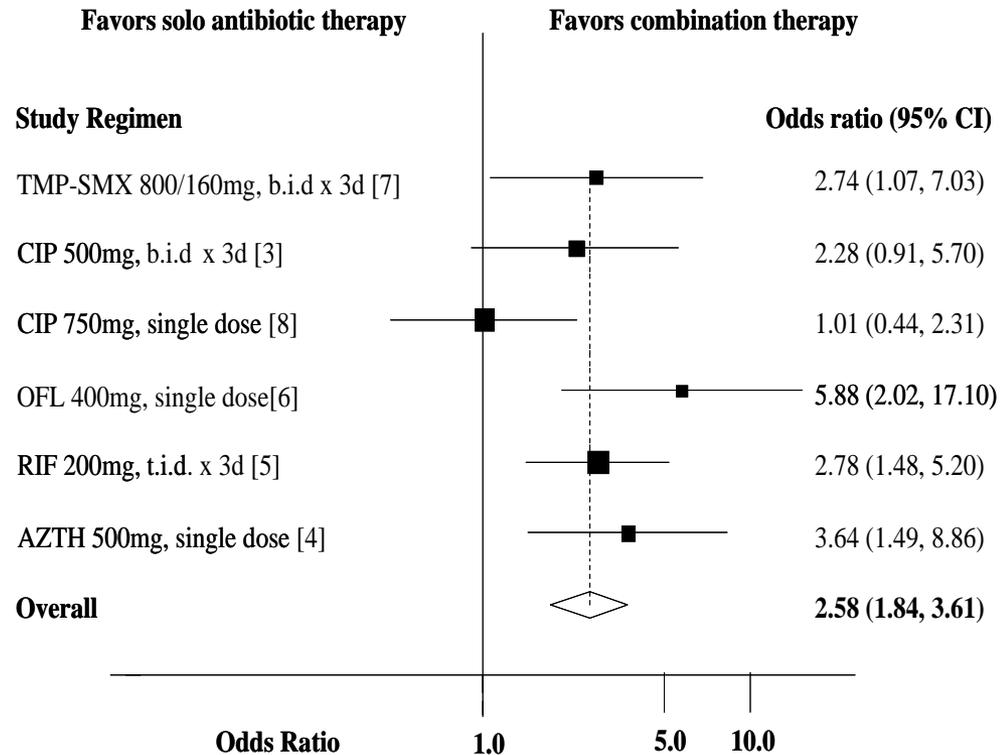


Placebo vs antibiotics alone  
(outcome: cure at 72 hours)  
Bruyn G et al Cochrane Collab 2004



**TLUS = 24 – 36 hours**

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



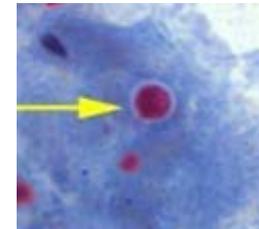
**TLUS ~ 12 hours**

# + Management of Persistent Diarrhea

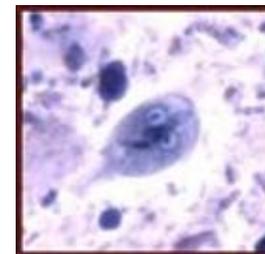
- Search for red-flag symptoms
- Diagnostic evaluation
  - O&P w/mod AFB stain
  - Stool Antigen Tests (Giardia, Crypto, Entamoeba)
    - Sens. 80-88%, Spec >98%
- Therapeutic Options
  - Azithromycin (Campylobacter)
  - Metronidazole (Giardia, Entamoeba)
  - TMP-SMX (Cyclospora, Isospora)
  - Cryptosporidium (Nitazoxanide)



Cyclospora  
6-8 um



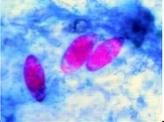
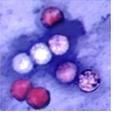
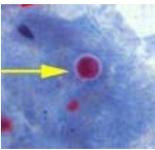
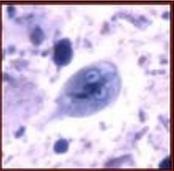
Cryptosporidium  
4-6 um



Giardia  
12 um



# Stool O&P Testing

	Isospora	Cyclospora	Cryptospor.	Giardia
Size (µm)	20-30 	8-10 	4-6 	12-15 
Mod AFB	Positive	Positive	Positive	Negative
Therapy	Tmp-smx, cipro, pyrimethamine	Tmp-smx, cipro	HAART**, paromomyn Nitazoxinid	Metronidazole
Ag test	None	None	+	+

# Post-dysenteric colitis (a.k.a irritable bowel syndrome)

## MEDICAL DISEASES OF THE WAR

BY  
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SECOND EDITION  
SECOND IMPRESSION

LONDON  
EDWARD ARNOLD

1918

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### (vi) Colitis and Irritability of the Colon following Dysentery

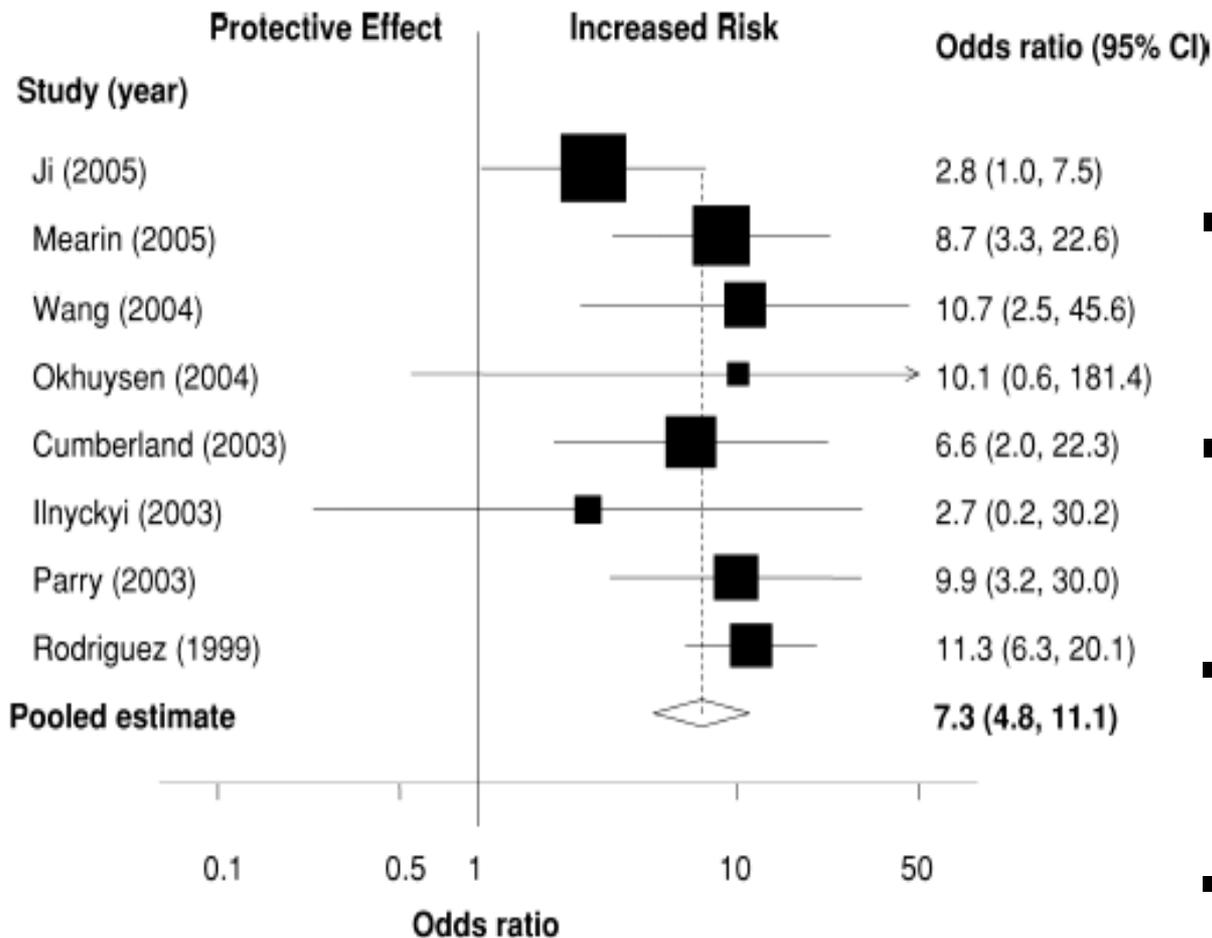
Patients who have recovered from an acute attack of dysentery frequently remain unfit for a considerable period, which may even extend to years. The symptoms are due to the chronic colitis, which may follow either amœbic or bacillary dysentery after the specific infection has died out, but the possibility that amœbic cysts or even dysentery bacilli may still be present can only be excluded by frequent expert examinations of the stools. In most cases the patient suffers from alternating attacks of constipation and diarrhoea, the latter often being brought on by aperients taken for the relief of the former, or it may follow an

infection was amœbic. The tongue is dirty and the patient complains of discomfort and fulness immediately after meals. There is no fever, but the pulse is often rapid and symptoms of "soldier's heart" may be present. The patient gets quickly tired

Dr. T. G. Moorhead observed a number of cases in Egypt, most of which came from Gallipoli, in which severe abdominal distension developed from four to eight months after the patient had apparently recovered from an attack of dysentery. They complained of a feeling of fulness in the abdomen, with dyspnoea and general dyspeptic symptoms. The bowels were regular, and nothing

147000  
13/9/18

# 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, Aavaxim]; Hepatitis B vaccine [Engerix-B]
- Antibiotic chemoprophylaxis
  - Not recommended for routine travel or deployment



# Rifaximin and Chemoprophylaxis of Travelers' Diarrhea

## Pros

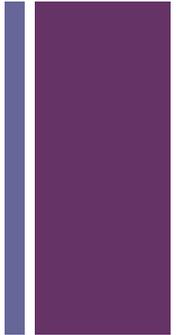
- Poorly adsorbed oral antibiotic
  - Absent side effects
- Low levels of rifaximin resistance among enteric pathogens
- Prophylaxis against travelers' diarrhea for short-term travelers
  - ETEC predominant regions
  - $\geq 70\%$  protection conferred

## 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

# + Q&A

- Risk of HUS and treatment with antibiotics after TD?
  - The role of antibiotics increasing the risk of HUS was demonstrated in a few pediatric studies with Shiga toxin producing E.coli strains. For healthy adult deploying forces the risk appears to be not as great and not a strong reason to avoid treatment.
- Vaccine efficacy of oral (whole cell) vs. IM Typhoid vaccine?
  - The efficacy may be slightly better with the whole cell vaccines but estimates of efficacy vary greatly (50-96%) and probably have to do with the setting. There is an ongoing military study that may shed some light in the comparative efficacy of these vaccines in among US military serve members.
- Role of Vibrio infections in TD and association with seafood?
  - Absolutely, Vibrio strains normally live in brackish/estuarial waters where oyster beds and other filter feeders also live and can concentrate the pathogen. Ingestion of raw oysters is a risk factor for Vibrio infection as well as other enteric pathogens (Hep A, Norovirus) especially when oyster beds are near human waste drainage. Vibrio cholera is a contaminated water pathogen.



# 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

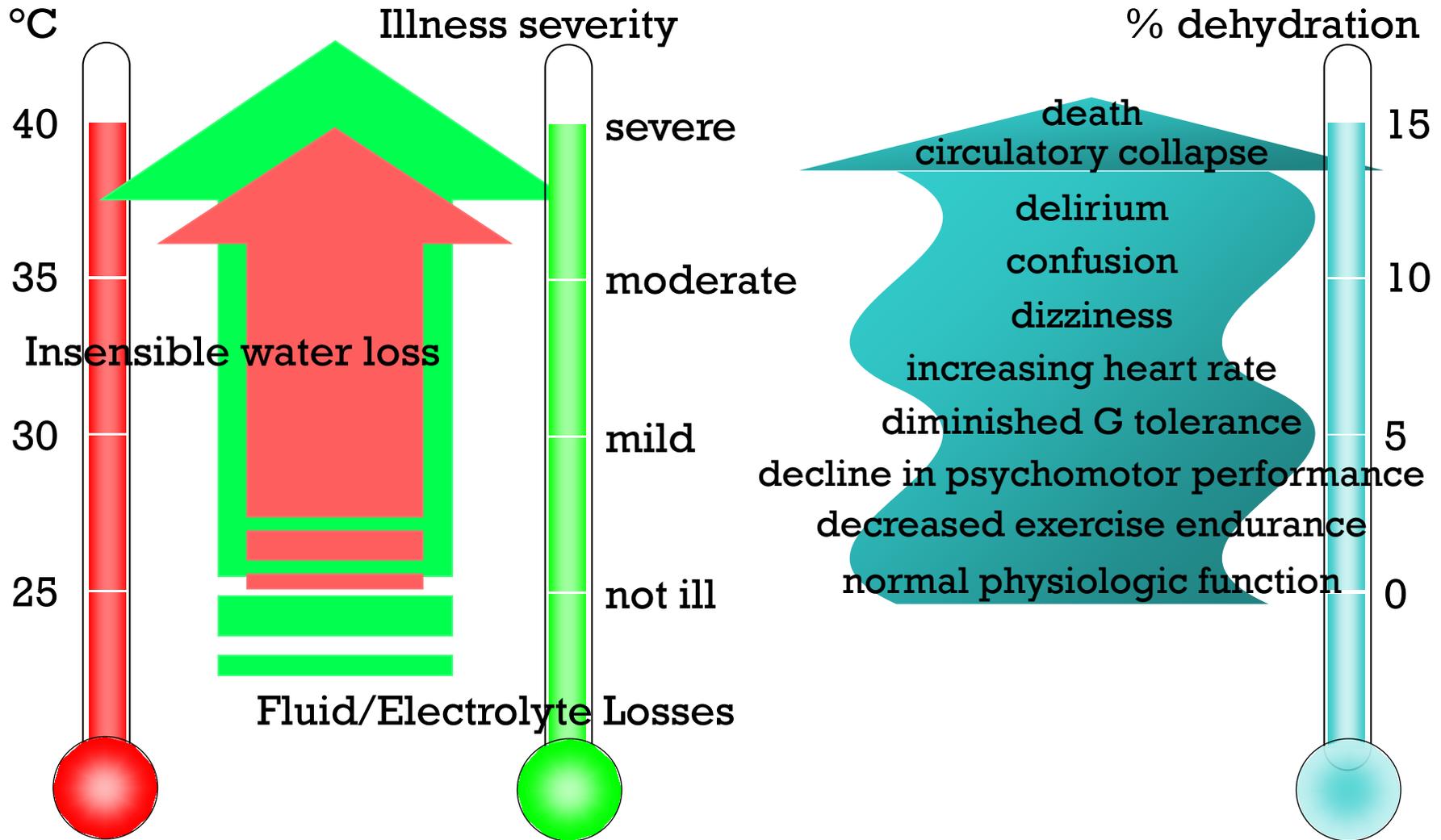
## Deployed Military

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

# + Common Etiological Agents of Diarrhea in Iraq and Afghanistan

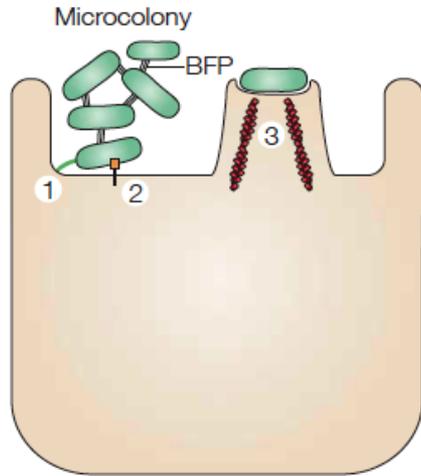
Study	Year	Area	Pathogens (top 3)	Comments
Thornton <i>et al</i> <u>CID</u> 2005	2003	Diwaniyah (South of Baghdad)	Norovirus 23% <i>Shigella</i> spp. 20% <i>Campylobacter</i> 4%	Sampling favored epidemics, diarrheagenic <i>E. coli</i> not assessed
Monteville <i>et al</i> <u>AJTMH</u> 2006	2004	Kuwait, 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

# Stressors in Extreme Conditions Amplify Diarrhea Morbidity



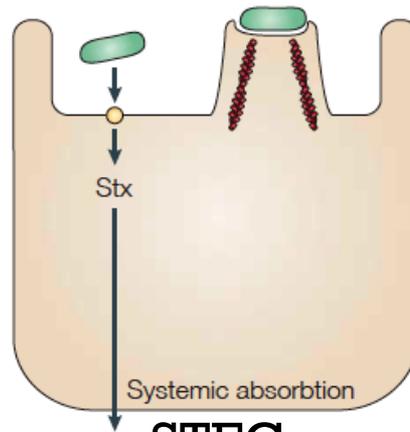
# + Diarrheagenic *Escherichia coli*

## Uncommon in Travelers: Pathogenesis



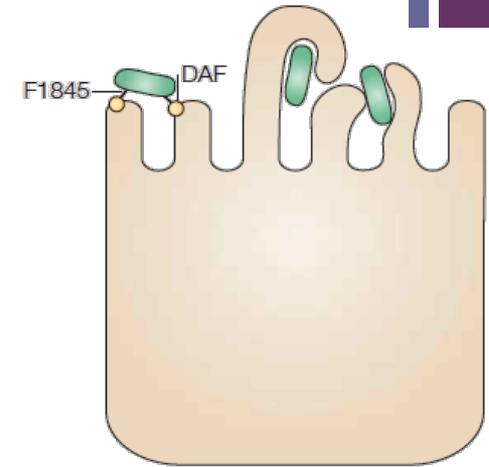
**EPEC**

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



**STEC**

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

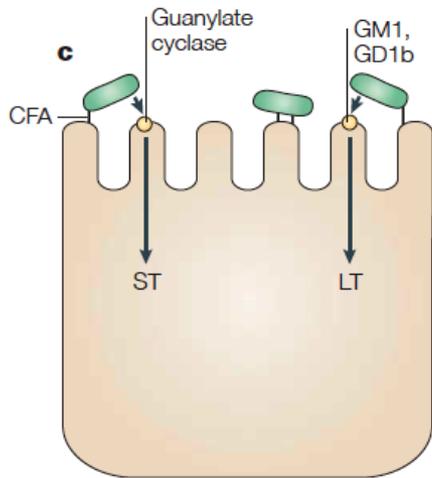


**DAEC**

- Signal transduction effects
- Cellular projections induced that enwrap bacteria

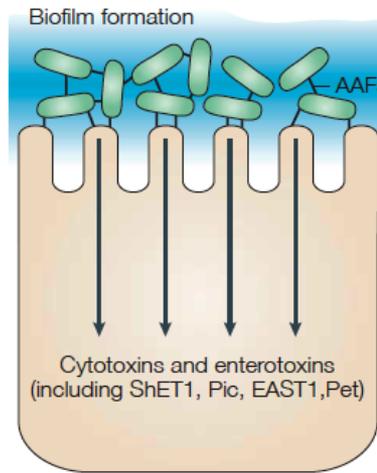
# + Diarrheagenic *Escherichia coli*

## Common in Travelers: Pathogenesis



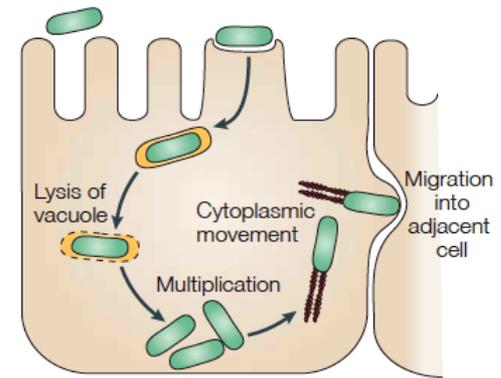
**ETEC**

- **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

# 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