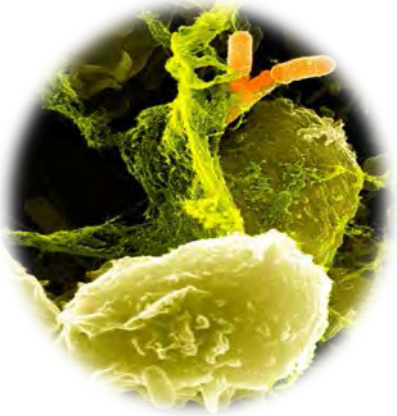
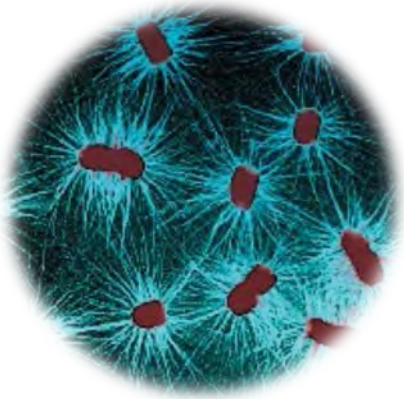

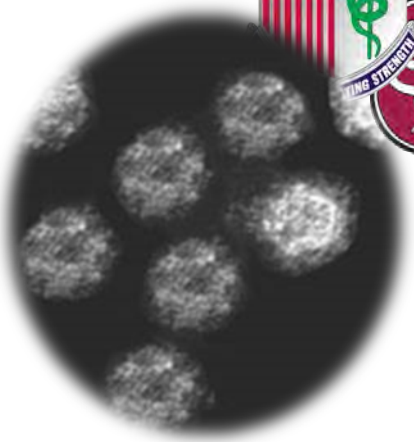

Diarrheal Diseases

WRAIR- GEIS 'Operational Clinical Infectious Disease' Course

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Disclaimer

The views expressed in this presentation are those of the speaker and authors, and do not reflect the official policy of the Department of Army, Department of Defense, or U.S. Government

Acknowledgements

- CDR Ramiro Gutierrez
- CDR Mark Riddle

Enteric Diseases Department
Naval Medical Research Center

Learning Objectives

1. Understand the epidemiology, including burden of disease, etiology and risk factors associated with diarrhea during deployment
2. Describe the evidence for preventive interventions including personal protective measures and chemoprophylaxis.
3. Discuss diagnostic algorithms and strategies for acute and chronic diarrheal infections associated with deployment
4. List the treatment strategies, antibiotic and non-antibiotic, for management of acute and chronic diarrheal illness associated with deployment.

Bottom Line Up Front

- Travelers' diarrhea is predominantly caused by bacterial enteropathogens
- Field diagnostics (norovirus, Shigella, Salmonella, Campy) are needed
- Treatment of moderate to severe illness with antibiotics should be the rule (not the exception)
- Morbidity from acute illness is significant, and greatly compounded by growing evidence of associated post-infectious sequelae
- Chemoprophylaxis may have a role – more study is needed

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
- Ingestion of contaminated foods or less often drinks
- Usually self-limited, but morbidity common
  - 40% of affected travelers have to alter planned activities (e.g. business meetings, change itinerary)
  - 20% have to stay in bed for at least one day

Steffen R *Journal of Travel Medicine*. 2005;12(2):102-107.
Grahek 2008 (unpublished data)

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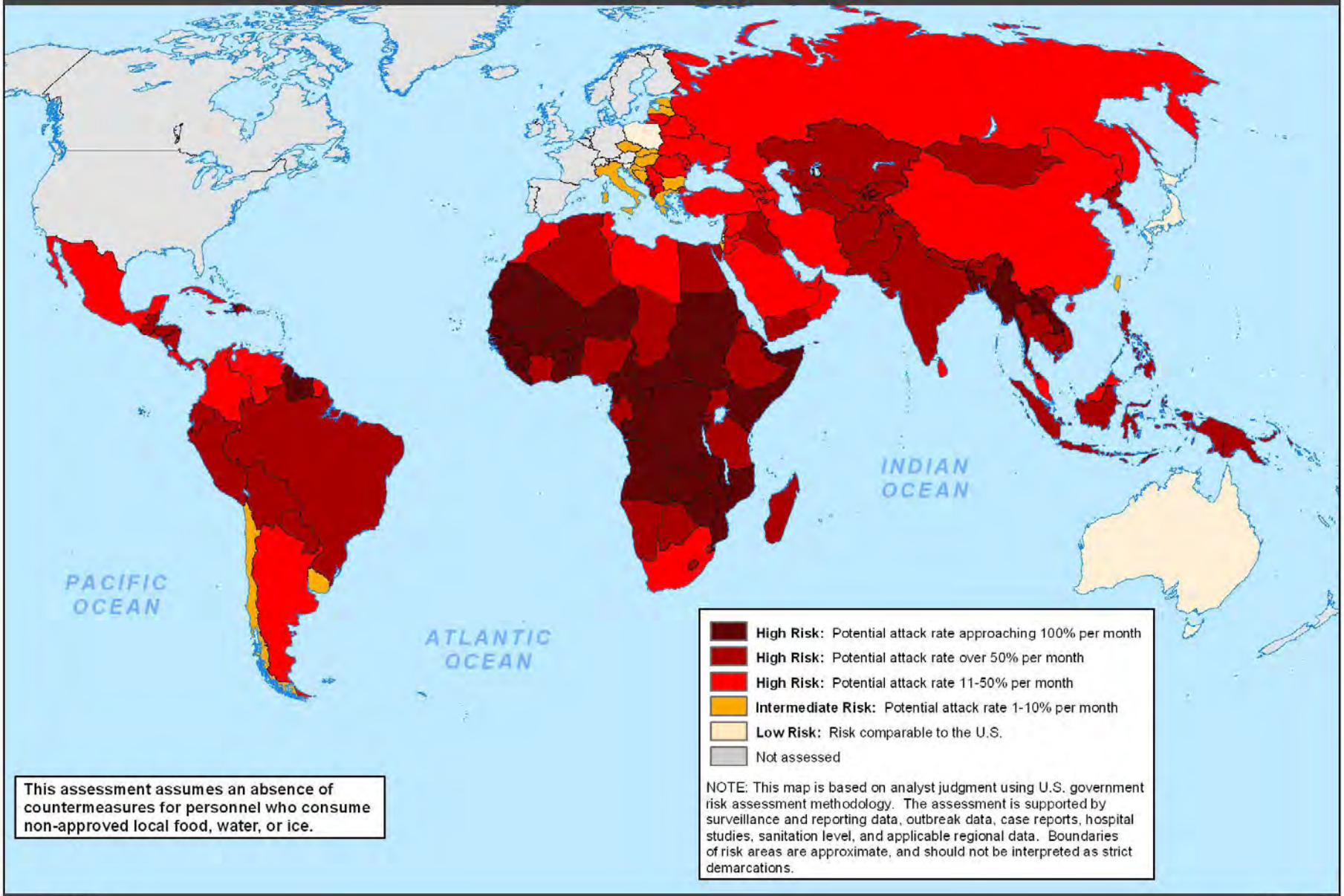
Worldwide: Bacterial Diarrhea Risk to U.S. Forces



This assessment assumes an absence of countermeasures for personnel who consume non-approved local food, water, or ice.

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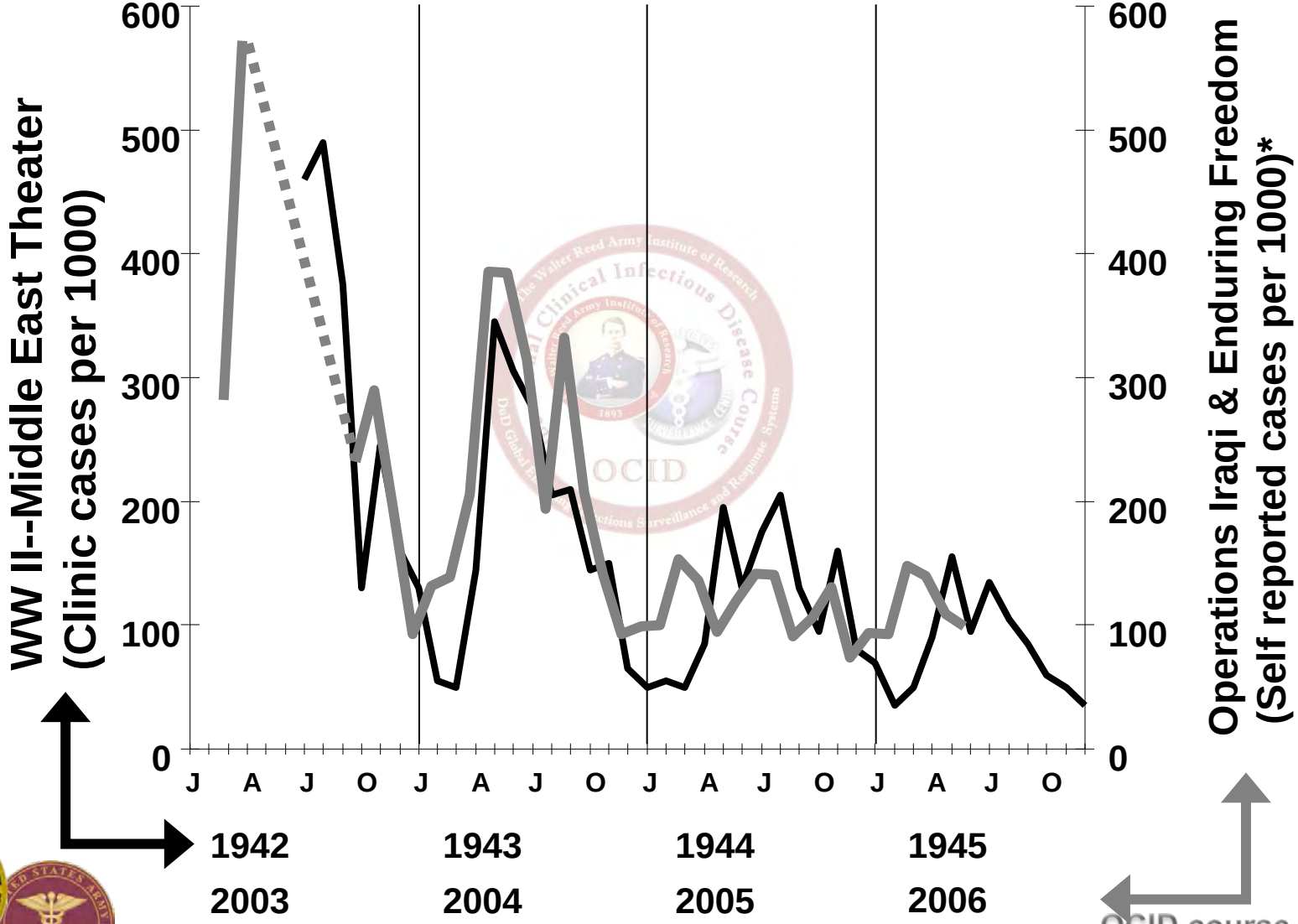
7 Feb 2013

Boundary representation is not necessarily authoritative

WWII-Middle East vs. OIF/OEF



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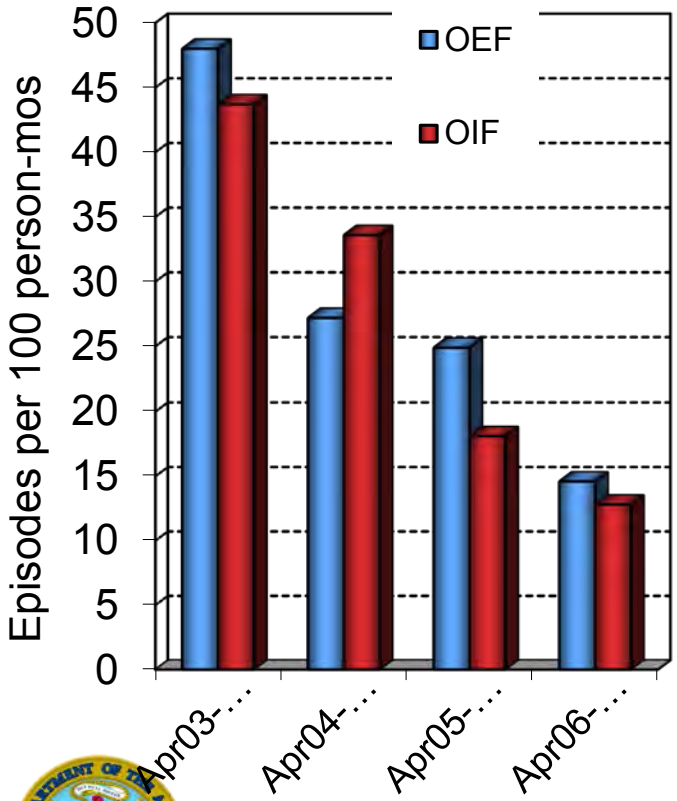
*JW Sanders et al. AJTMH 2005; MS Riddle et al. AJPH 2008; extrapolation (dotted line)

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 malaria[2]
- **OIF**: Acute enteric illness was leading cause of hospital admission among British forces during first 12 months of operations in Iraq[3]

(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

Anonymous soldier's blog

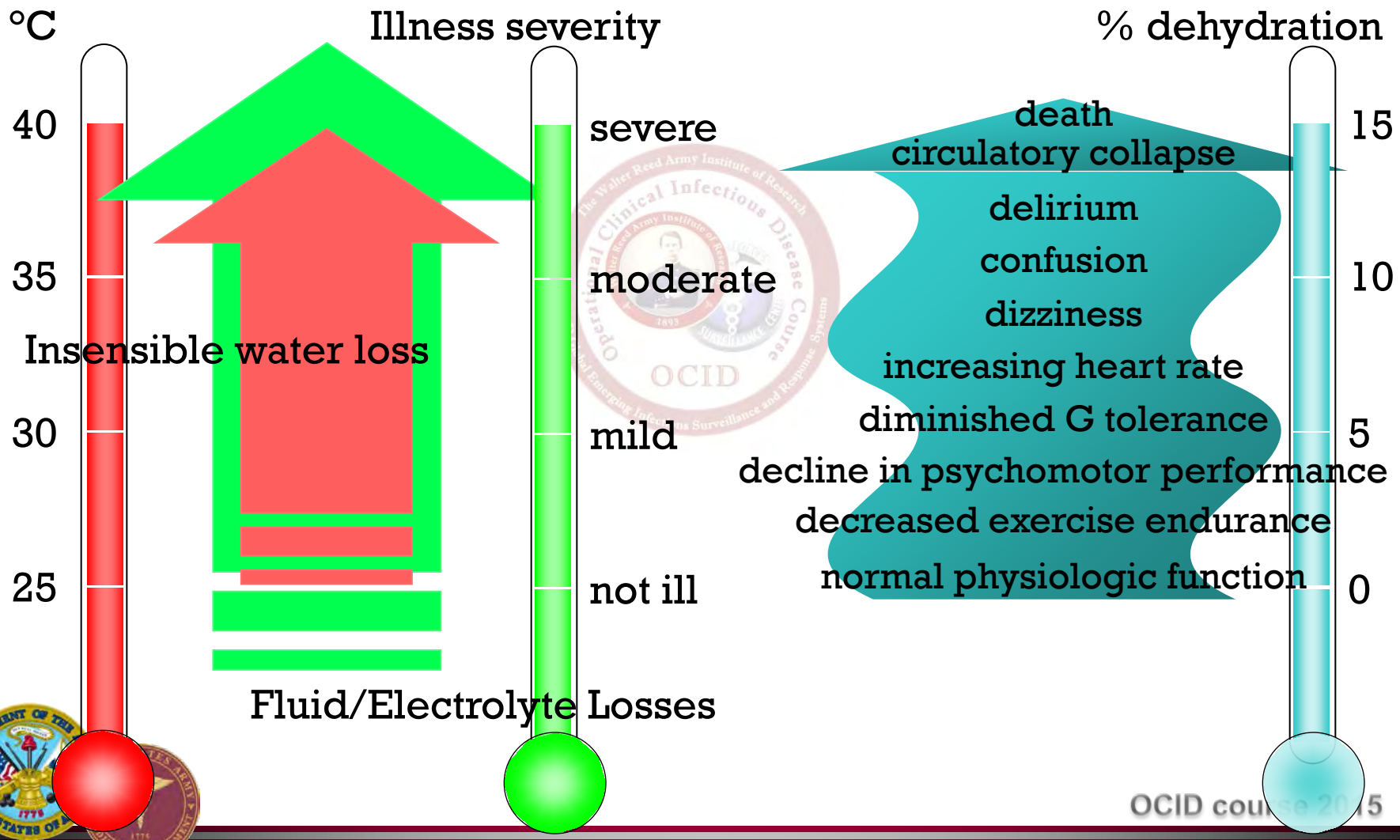
Diarrhea with fever	9-25%
Dysentery	2-8%
Severe diarrhea	
Iraq	21-27%
Afghanistan	13-14%
Vomiting only	5-15%

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%

Stressors in Extreme Conditions Amplify Diarrhea Morbidity



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°C.

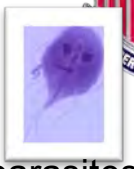
David O. Matson, MD

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	*Salmonella* spp., *C. fetus*	Certain conditions predispose to systemic *Salmonella* infection
Hemolytic-uremic syndrome (HUS)	STEC, *S. dysenteriae* type 1	Pathogenesis due to shiga toxin absorption and damage
Guillain-Barré syndrome	*Campylobacter jejuni*	40% cases of GBS caused by *C. jejuni;* molecular mimicry LOS
Reactive arthritis	*C. jejuni, Salmonella, S. flexneri*	Occurs in 2.1 per 100 000 *Campylobacter* infections
Irritable bowel syndrome	Most bacterial pathogens	≤ 10% incidence following bacterial enteric infection

Causative Agents



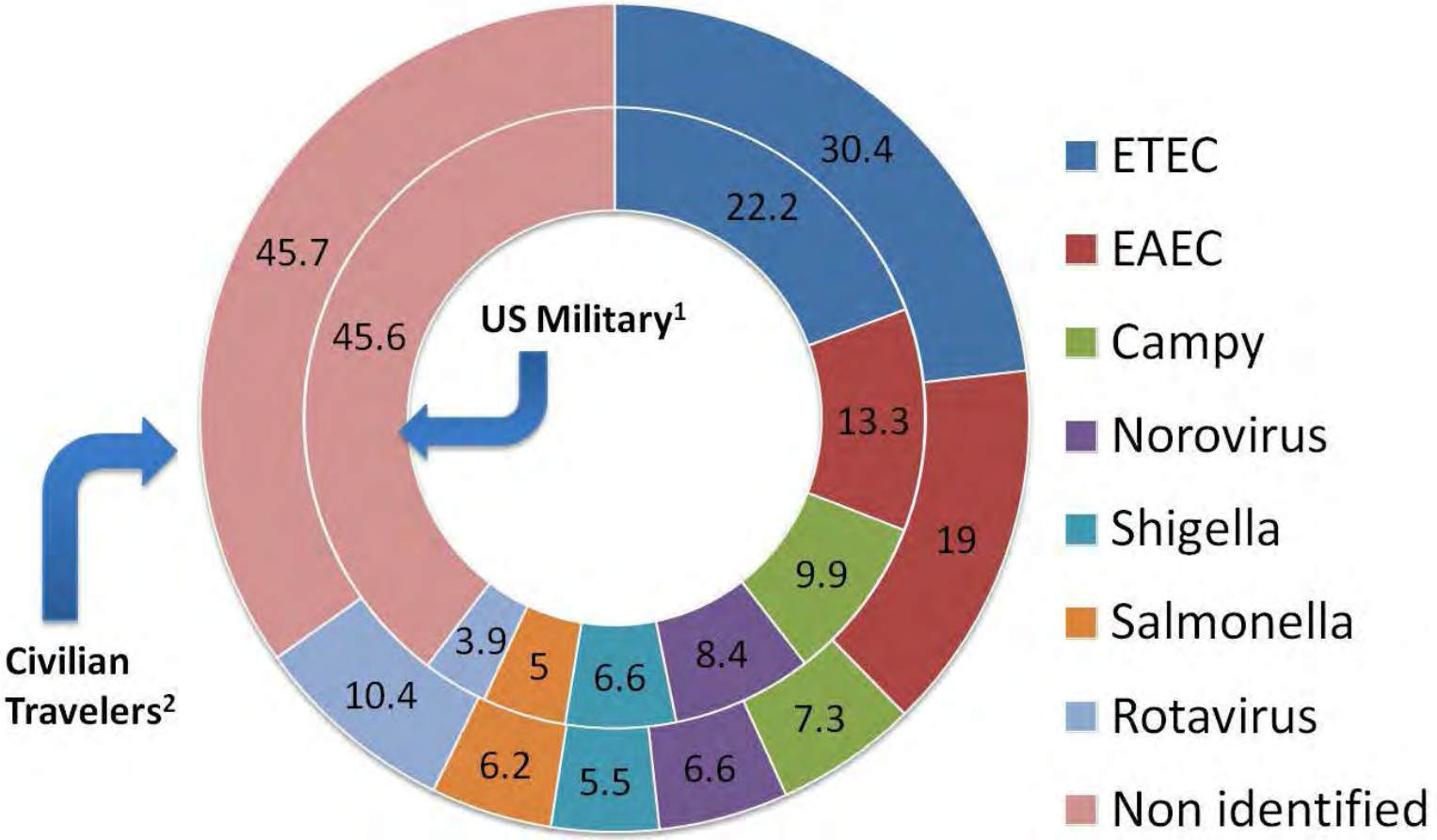
- Bacterial agents (80-90%)
- **Common**
  - Enterotoxigenic *E coli* (ETEC)
  - Enteroaggregative *E coli* (EAEC)
  - *Campylobacter*
  - *Shigella*
  - *Salmonella*
- **Less common**
  - Enteroinvasive *E coli* (EIEC)
  - *Aeromonas*
  - *Plesiomonas*
  - *Vibrio cholerae*

- Viral agents (5-10%)
  - Norovirus
  - Rotavirus
  - Astrovirus
- Parasites (uncommon)
  - *Giardia lamblia*
  - *Cryptosporidium* spp.
  - *Cyclospora cayatanensis*
  - *Entamoeba histolytica*

Clinico-pathological Considerations: Acute Travelers' Diarrhea

	Watery diarrhea (80%)	Dysentery (1-5%)	Gastroenteritis (<10%)
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	*C. jejuni* *Shigella* spp. *Salmonella* (non-typhi) EIEC	Norovirus Rotavirus

Common Etiological Agents of Travelers Diarrhea



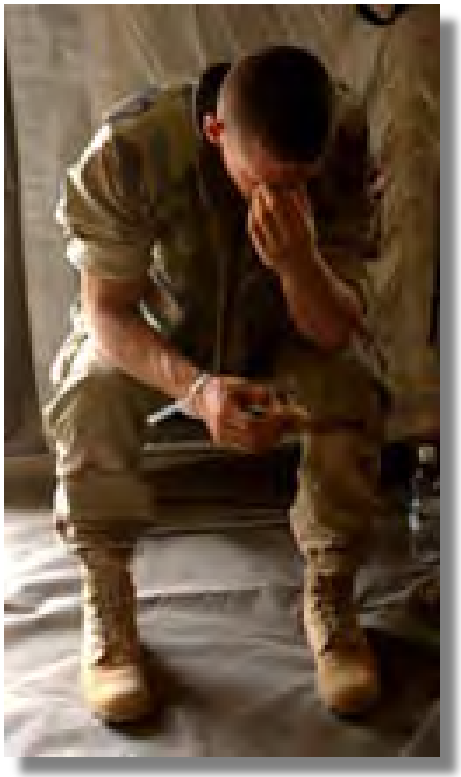
[1]Riddle M et al, *Am J Trop Med Hyg*, 74;2006:891-900.
[2]Shah N et al, *Am J Trop Med Hyg*, 80;2009:609–614.

Pre-travel consultation

- Prevention Counseling
  - Avoid exposure to pathogens transmitted by soiled food and drink ('boil it, cook it, peel it, or forget it!')
  - Stay hydrated
  - Use empiric therapy
  - Cruise ship outbreaks
- Administer appropriate enteric vaccines
  - No 'travelers diarrhea' vaccine
  - Typhoid, Hepatitis A vaccines
- Antibiotic chemoprophylaxis
  - Currently not recommended for routine travel
  - More on this later

Clinical Case (part 1): 26 y/o male with history of "cast iron stomach" presents to sick call after return from recent 3 day patrol in

- In past 24 hours he reports 4 liquid bowel movements without gross blood
  - Nausea w/o vomiting, cramping, and HA
  - Denies fever/chills/night-sweats
- Physical exam: ill-appearing, afebrile
  - Seated BP (HR): 128/82 (84)
  - Standing BP (HR): 110/75 (101)
  - Mucus membranes were slightly dry
  - Abdomen: benign except for mild diffuse tenderness.
- How would you treat this?

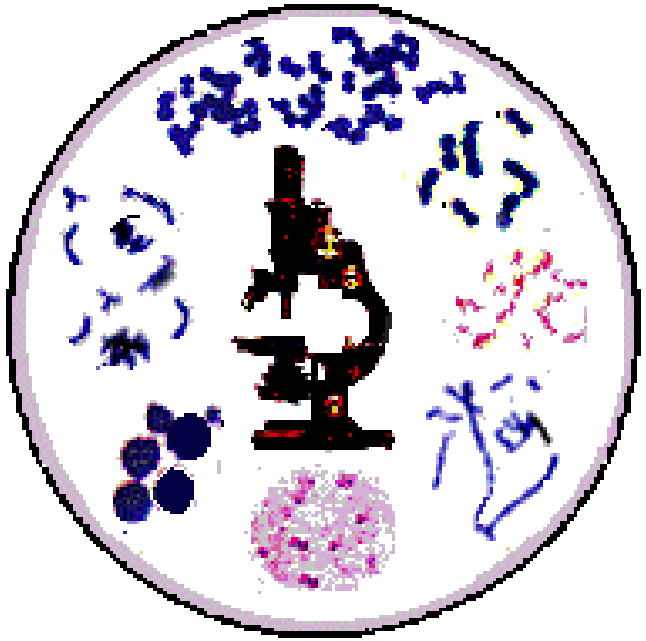


Clinical and Diagnostic Evaluation

- 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

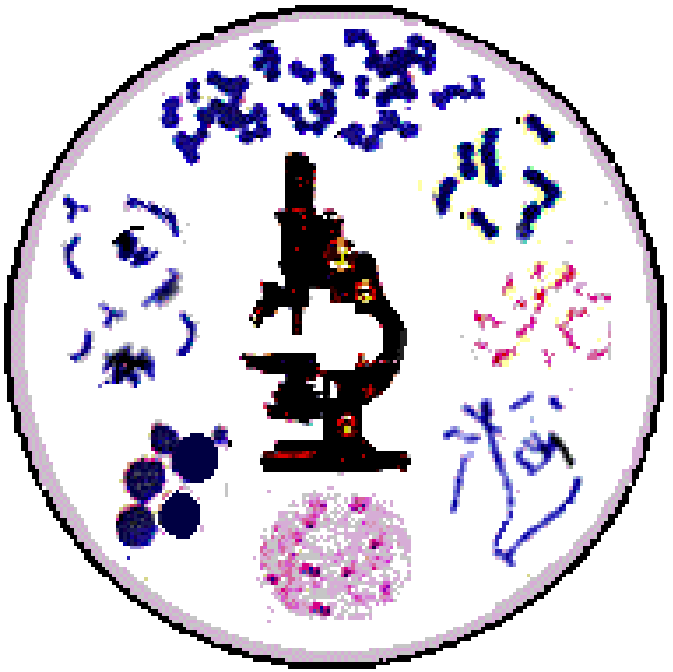
Enteric Field Diagnostics

OIF/OEF



Pretty much the same

WWII



"Laboratory capacity in working up diagnoses of diarrheas and dysenteries, particularly in the first 2 years, was limited or more often not attempted."

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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 (others difficult to identify)
  - Diarrheagenic *E. coli* (ETEC, EAEC, EIEC)
  - Norovirus
  - Campylobacter
- 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

Therapeutics: Water and Electrolyte Replacement

- Cornerstone of diarrhea treatment
- Mild dehydration: Potable water or appropriate ORS
- Moderate-severe disease: ORS/IV fluids

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

"Traveler ORT"

- Add to 1 Liter of water
  - One teaspoon of salt
  - 2 to 3 tablespoons of sugar or honey
- Mix 8 ounce cup of orange juice with 3 cups of water; add 1 teaspoon of salt
- Another option: Mix sports drink with water (~50% - 50% mixture) to lower osmolarity

CDC Yellowbook; Chapter 5, Travelers' Diarrhea

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)

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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		
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 *C. jejuni* suspected
Rifaximin	200 mg tid	Effective for non-invasive *E coli*

Hawk D. Military Medicine, 2010

Increasing Fluoroquinolone Resistance among *Campylobacter* in Travelers

Norfloxacin resistance rates

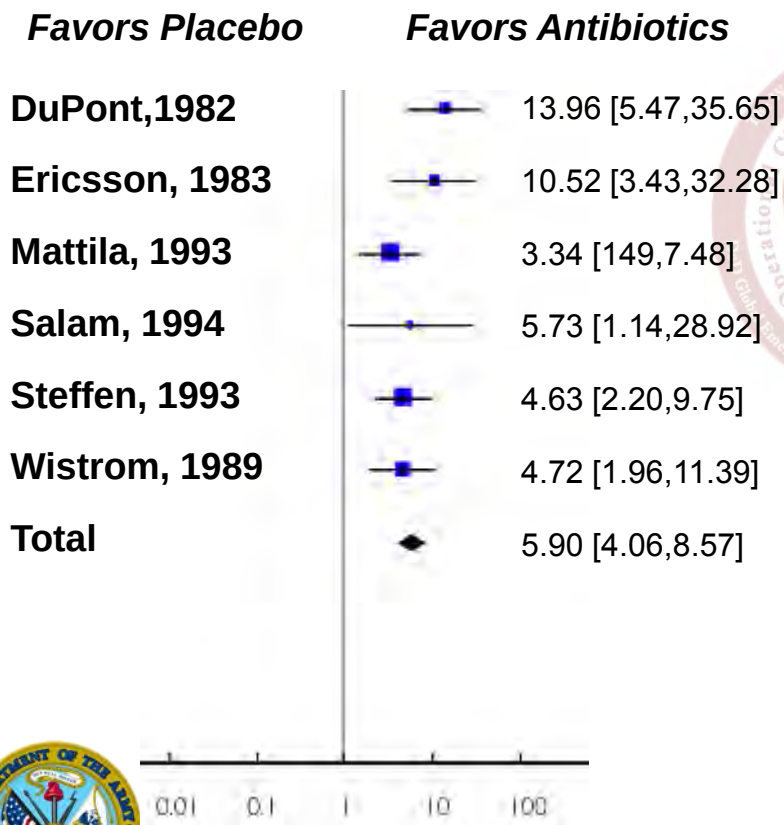
	1994-2000			2001-2006		
Region	No. isolates	No. resistant isolates	Resistance rate (%)	No. isolates	No. resistant isolates	Resistance rate (%)
Africa	162	22	13.6	114	36	31.6
Asia	208	74	35.6	95	67	70.5
Caribbean, Central & So. America	36	10	27.8	33	20	60.6

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

Vlieghe ER et al, *J Travel Med* 2008;15:419-25

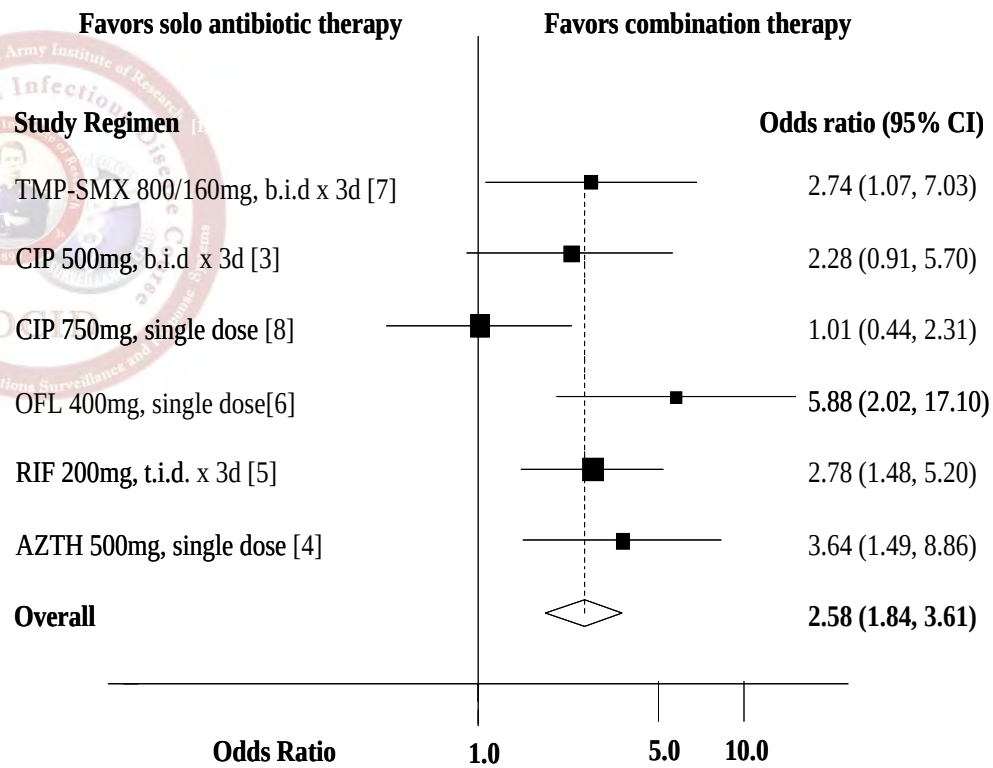
Effectiveness of Antibiotics, and Additive Effect of Loperamide)

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



TLUS = 24 – 36 hours

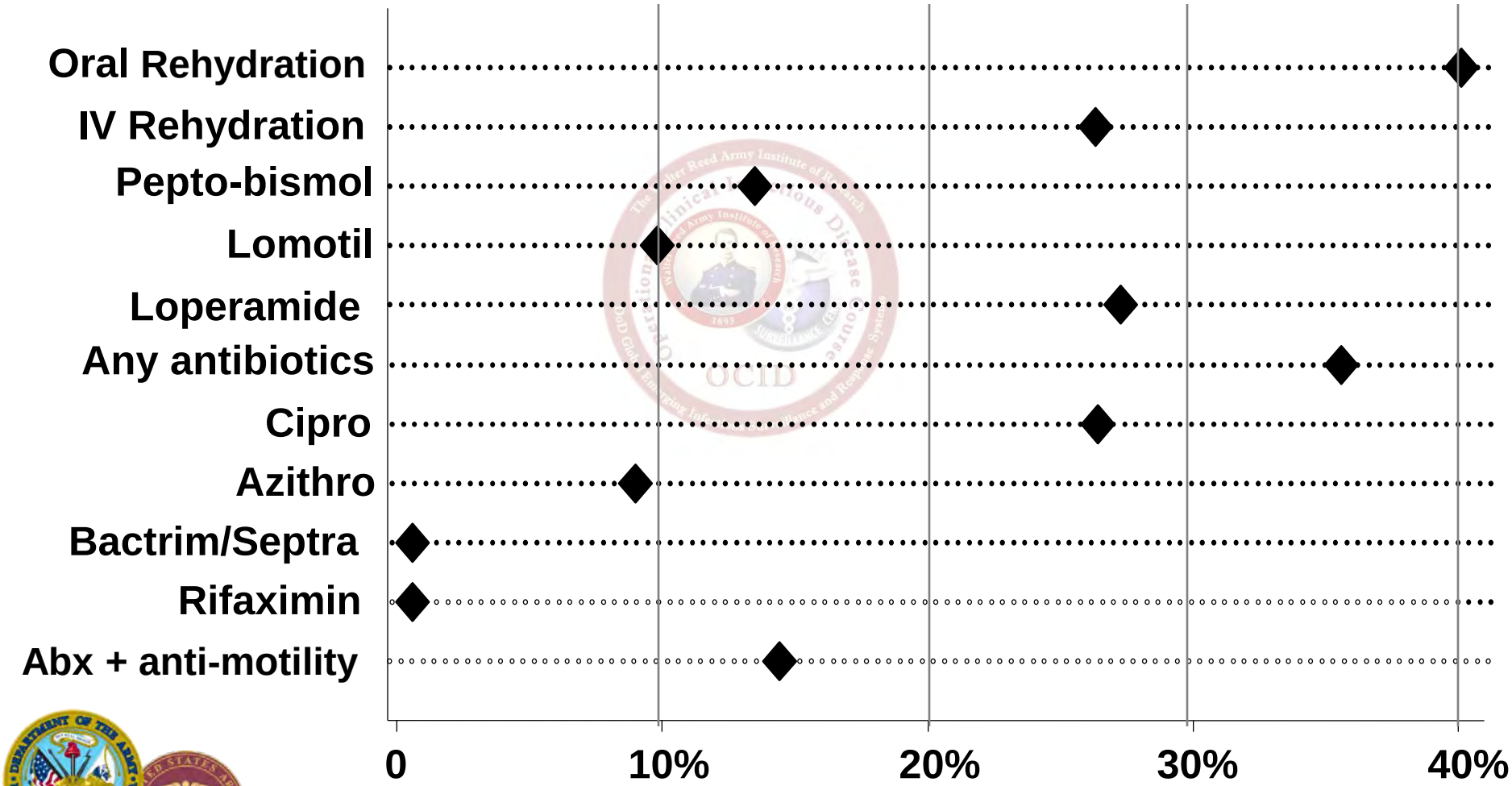
Antibiotics alone or plus **loperamide**
(outcome: cure at 24 hours)
Riddle MS et al, CID 2008



TLUS ~ 12 hours

How are we actually treating it?

Military Provider Responses (n=101, Nov 05 – Nov 06)

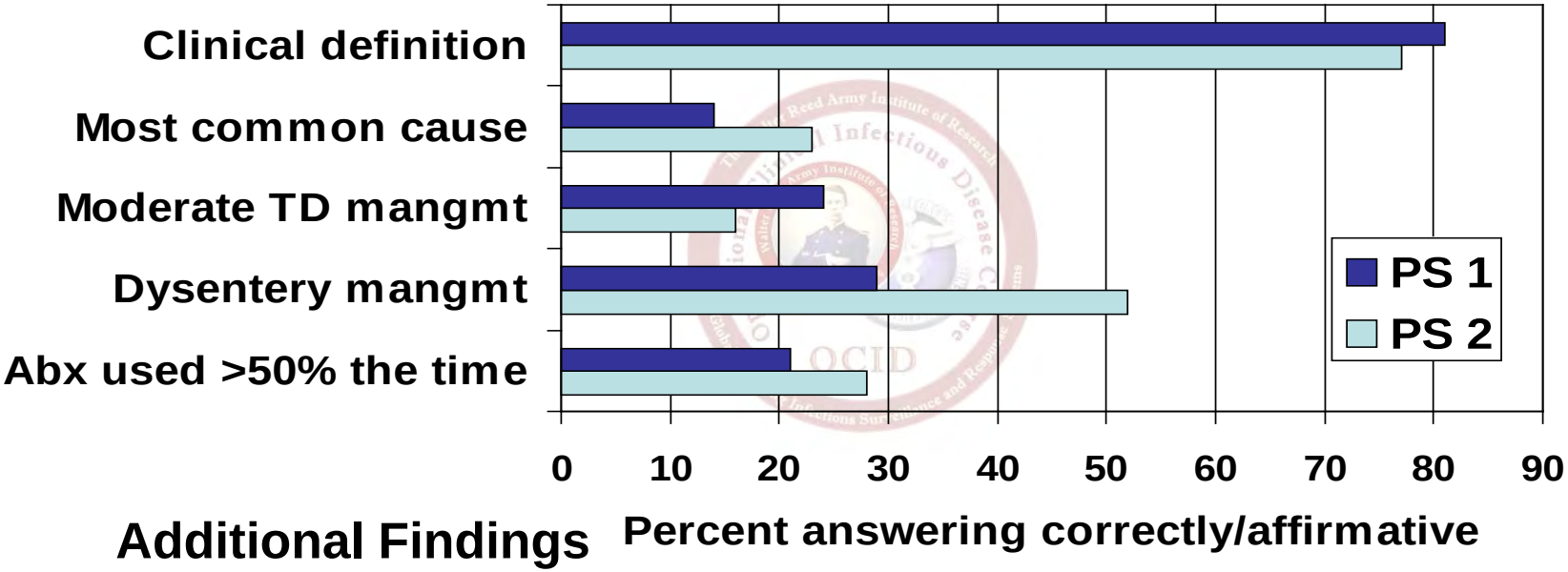


Riddle et al., Military Medicine, 2005

Additional data from provider surveys
(Riddle 2005; Hayat 2011)

Provider Survey 1 (PS1): CENTCOM PA Conference, Doha, Qatar, DEC 03

Provider Survey 2 (PS2): Web-based convenience sample, NOV 05 – NOV 06



Additional Findings

- **43% Agree/Strongly Agree that antimotility agents keep toxins in where they do more damage to the gut**
- **38% Agree/Strongly Agree antimotility agents prolong illness by delaying pathogen excretion**
- **21% Agree/Strongly Agree antibiotics should not be used in most cases so individual can develop immunity**

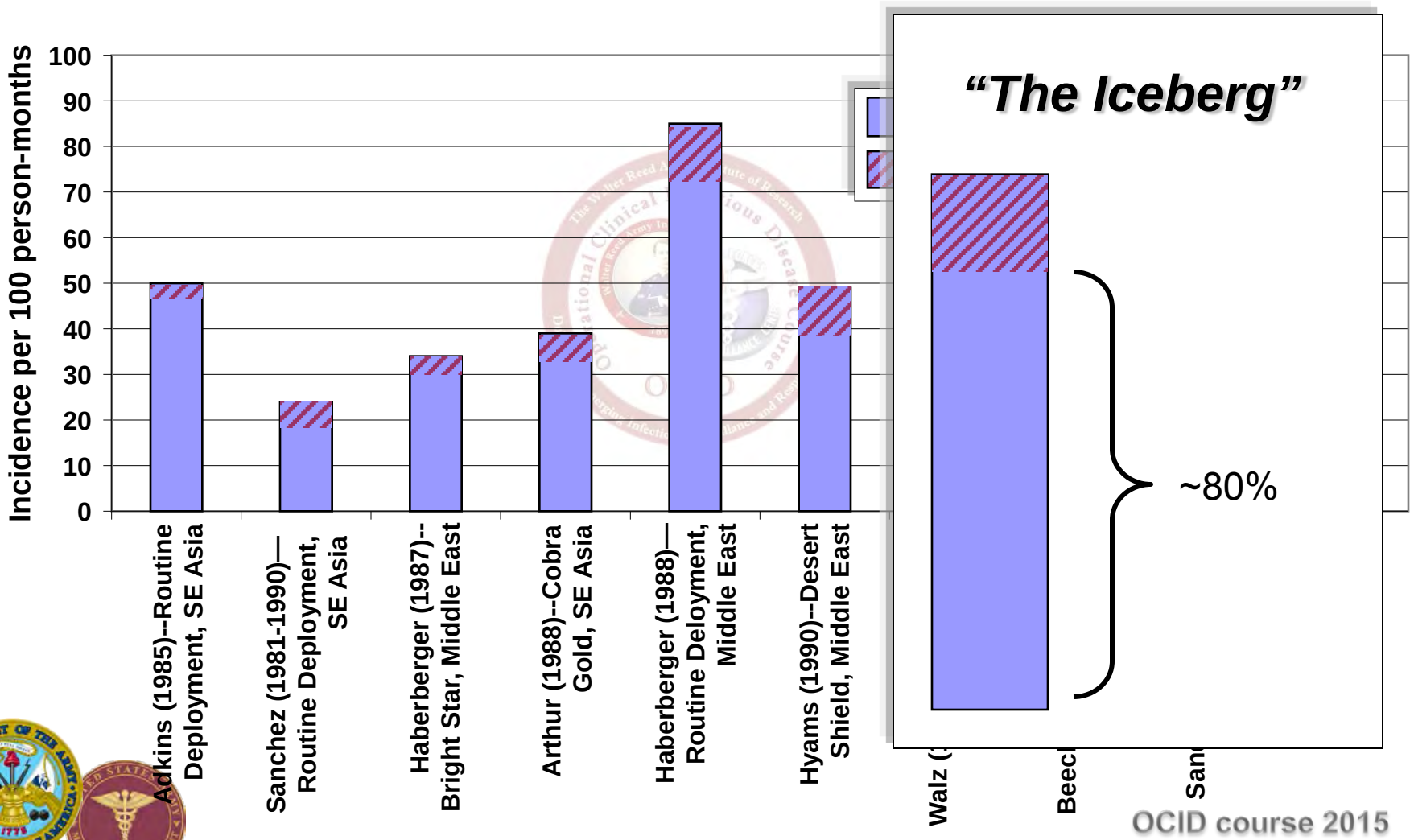
The boots on the ground perspective

- 51% sought care from “Medic,” who provided medicine 58% of time
- 30% sought care from “Sick Call,” who provided medicine 41% of time

Management approach	Percent (95% CI)
Increase fluids only (oral)	15.3 (12.3 – 18.3)
Pepto-Bismol	13.0 (10.2 – 15.9)
Loperamide (Imodium)	37.1 (33.0 – 41.2)
Antibiotics	26.8 (23.0 – 30.5)
Intravenous fluids	16.5 (13.4 – 19.6)

SD Putnam *et al.*, Journal of Travel Medicine, Volume 13, Issue 2, 2006, 92–99

What about those that don't seek care?



Adapted from Riddle *et al*. AJTMH (2006)

Do those who show up in the clinic with TD differ than those who don't?

- What is known:
  - Only 23% of troops report seeking care from military health provider for illness (MS Riddle, *AJTMH* 2005)
  - ~31% attempt self-treatment, 8% use antibiotics (various reports)
- What is <u>not</u> known: How do those that seek differ from those who don't seek?
- Al Asad, Iraq, Case-finding Study (used with permission from CAPT John W. Sanders)
  - Enrolled 537 volunteers (~8,000 base population) in randomly selected areas of the base
  - 66% reported a prior episode of diarrhea during this deployment (over half reported multiple episodes)
  - 120 were acutely ill at time of interview, 21% reported having sought care

Case-finding Study Findings
(Sanders JW, unpublished)

- Top three reasons for not seeking care included:
  - "symptoms not severe enough" (52%)
  - "fear of appearance of shirking duty" (14%)
  - "low expectation of treatment effect" (7%)
- Those who sought care reported vomiting, HA more frequently.
- Similar in terms of duration of symptoms and frequency of stools in past 24 hours.
- Those seeking care more often resulted in back-up personnel being called in to cover (17% vs 2%, p=0.007)
- Those who did not seek medical care at the time of interview reported more decreased days in job performance (3 versus 2 days, p = 0.02).

Take home on Treatment of Acute TD

- Current DoD treatment guidelines outdated, not optimized, and **not utilized**
- Specific infectious diarrhea syndrome consideration not well-configured into practice guidance
- Most diarrhea (with impact) is left untreated
- Questions remain:
  - What is the optimal first-line agent by most common acute infectious diarrhea syndromic presentation?
  - How effective do people self treat TD?
  - How effective are regimens in Africa/SW Asia.

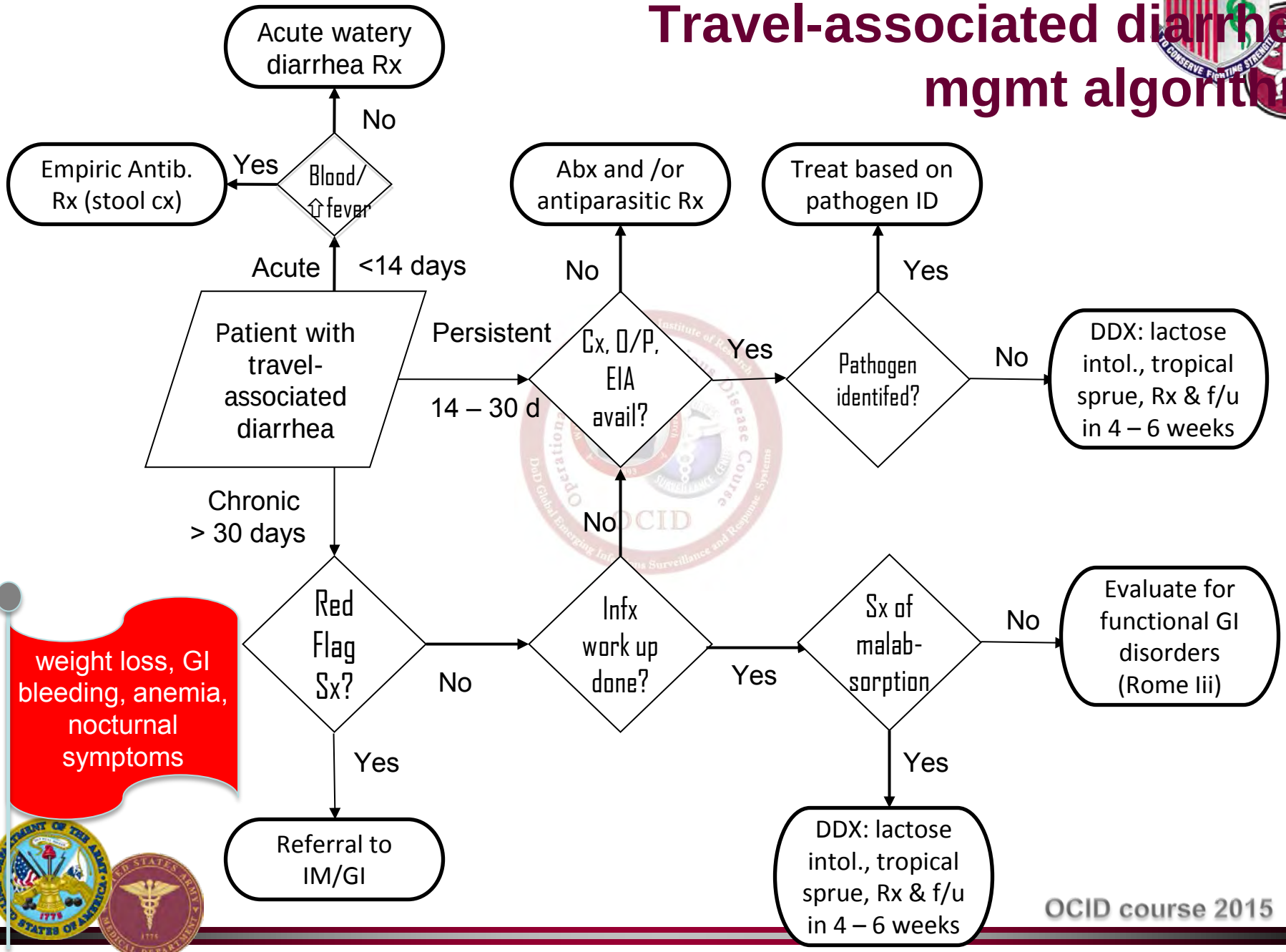
Clinical Case (part 2): 26 y/o male presents to your clinic with 3 weeks of diarrhea.

- Has been on a year long tour in Afghanistan
- He has frequent abdominal discomfort (bloating), cramping and loose stools 3 or more times a day for over two weeks.
- Took a dose of cipro and a couple of imodium during the first couple days in which “things sort of got better, but not really. “
- Stools are soft and sometimes associated w/ urgency.
- No fevers, chills, or night sweats. Reports mild weight loss but denies nighttime awakenings to defecate or bloody stools.

Persistent / Chronic Diarrhea in Returning Traveler

- Persistent Diarrhea: Illness lasting > 2 weeks
  - 10% of cases, likely infectious
    - EAEC (occasionally, *Campylobacter*, *Salmonella*)
    - Parasitic diarrhea
      - *Giardia lamblia*
      - *Cryptosporidium parvum*
      - *Cyclospora cayatanensis*
  - Post-infectious lactose intolerance
- Chronic Diarrhea: Illness lasting > 4 weeks
  - Could still be infectious
  - DDx includes non-infectious etiologies
    - Tropical malabsorption
    - Functional gastrointestinal disorders
    - New onset or unmasked organic disease (celiac dz, IBD)

Travel-associated diarrhea mgmt algorithm



So how do we prevent it?

- More than just the acute effects of TD on the traveler must be considered
- Must also consider:
  - Economic, societal, disability impacts of chronic sequelae
  - Lost work days of personnel
- Boil it, cook it, peel it, or forget it – the evidence
  - Loewenstein, 1973
  - Steffen,1983

These considerations suggest <u>primary prevention strategies remain a priority</u>!

Prophylaxis for TD

Year, Location	Antibiotic regimen	PE %
1976, Kenya	Doxycycline 100 mg qd	86
1977, Morocco	Doxycycline 100 mg qd	83
1977, Mexico	BSS (QID)	62
1979, Mexico	TMP/SMX 160 mg of 800 mg bid	71
1980, Mexico	TMP/SMX 160 mg of 800 mg qd	94
1980, Honduras	Doxycycline 100 mg qd	68
1982, Mexico	Bicozamycin 500 mg qid	100
1984, Mexico	Norfloxacin 400 mg qd	88
1985, Mexico	BSS (QID)	65
1986, Multiple	Norfloxacin 200 mg bid	75
1988, Egypt	Norfloxacin 400 mg qd	93
1988, Tunisia	Ciprofloxacin 500 mg qd	94
2003, Mexico	Rifaximin 200 mg/qd, bid, or tid	72 – 77
2005, Mexico	Rifaximin 600 mg once per day	58

Adapted from: DuPont et al. J Travel Med 2009; 16: 149–160

Antibiotic Prophylaxis for TD

- Consensus Conference held at the NIH in JAN 1985
  - Recommended AGAINST prophylactic use of antibiotics for TD
- Consensus Conference Reasons
  - Potential drug adverse events
  - Widespread use may facilitate resistance
  - Self-treatment had high efficacy
  - No documented evidence of disease entities worsened sufficiently by episode of TD
  - No basis for recommending prophylactic abx use for any special groups of travelers

Rifaximin: a potential solution?

- Antimicrobial chemoprophylaxis has the potential to address a number of the current concerns associated with the burden and management of infectious diarrhea in specific deployment settings/populations:
  - initial period of combat operations/exercises
  - port visits / short exercises
  - special forces or those who cannot tolerate becoming ill
- Rifaximin is a non-absorbable antibiotic with a strong safety profile.
- Chemoprophylaxis with rifaximin may have benefits which outweigh the costs.

Systematic Review of Rifaxmin (Alajbegovic et al. Systematic Reviews 2012, 1:39)

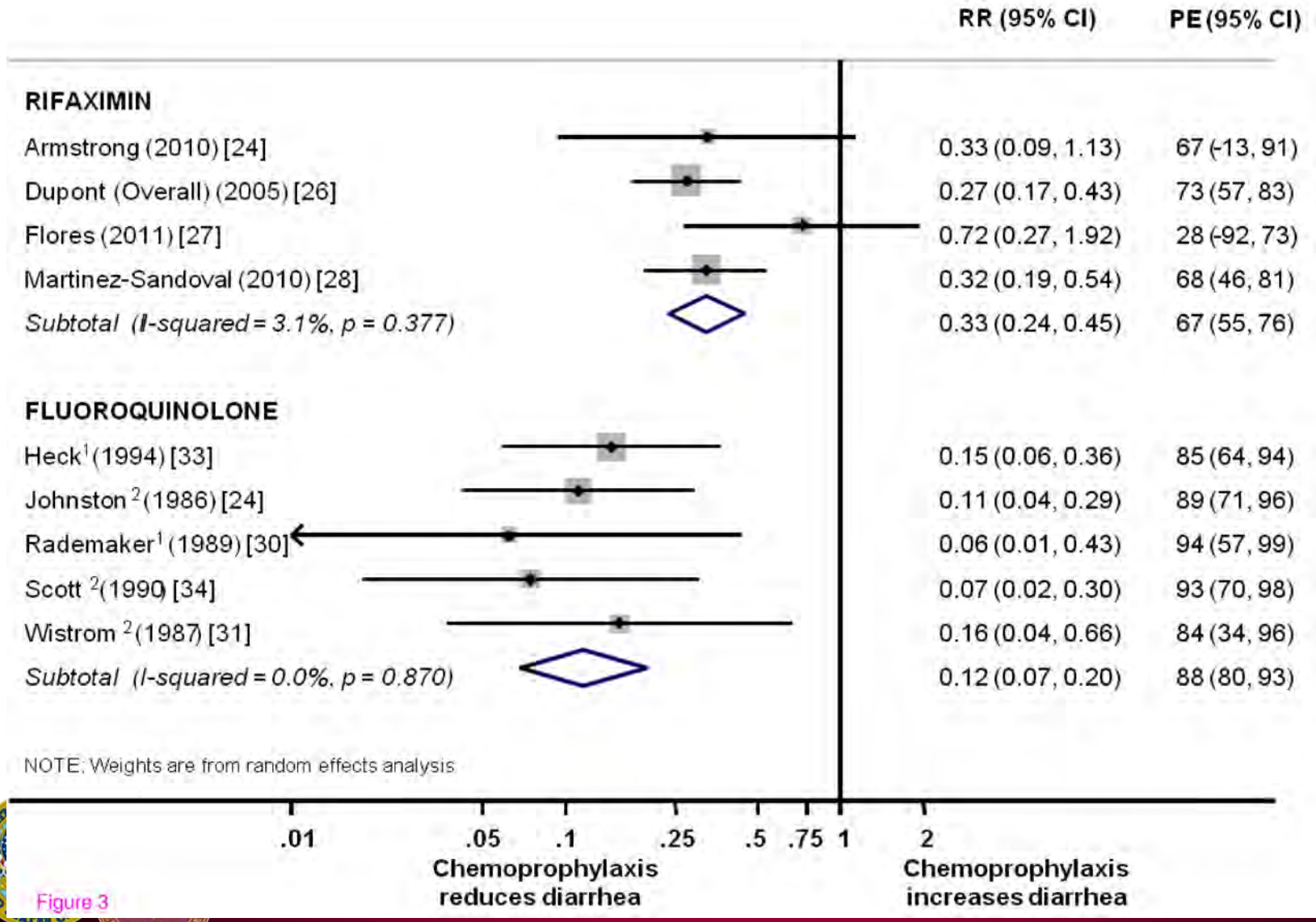


Figure 3

"Back of the Envelope Cost-effectiveness analysis" Alajbegovic et al. Systematic Reviews 2012, 1:39

- **TD Event Cost[1]**: $1,460 / $1,996
  - leisure / business traveler
  - includes value of travel, value of time, and medical costs)
- **PI-IBS Cost[2]**: $700 and $12,000 per year
- **NNT with chemoprophylaxis to prevent TD**
  - 2.8 (95% CI = 2.0 to 4.7) for fluoroquinolones
  - 4.5 (95% CI = 2.6 to 15.9) for rifaximin
- **Single-dose, 14-day rifaximin 550 mg:** $317
- **Rifaximin Prophylaxis Net Benefit**: $35 for a leisure traveler, $571 business traveler to an average-risk region.

1. Lundkvist, J. J Travel Med 2009. 16(1): p. 28-34.
2. Maxion-Bergemann S. Pharmacoeconomics 2006, 24:21–37.

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
    - ≥70% protection conferred
  - Potential to prevent important acute and chronic complications in deployment setting

- Cons
  - Limited studies to date
    - Geographically delimited
    - Predominance of ETEC/EAEC
    - Short duration travel
  - Impact of widespread usage for prophylaxis unknown
  - May not be most active against invasive pathogens
  - Ability to prevent chronic sequelae unproven

* * Bonus Clinical Case * *

- A 23 year old US Navy Lab Tech (microbiologist) has been working in the Liberian EBV mobile lab in support of Operation Unified Assistance. About a week ago he shared a meal with a local Liberian family in their home who he helped during the humanitarian effort.
- He presents worsening symptoms over the past 72 hours including:
  - Fever
  - Severe headache
  - Muscle pain
  - Weakness and fatigue
  - Diarrhea with blood in stools
  - Vomiting
  - Abdominal (stomach) pain

- Clinical questions:
  - What's your differential diagnosis?
  - What other information would be useful?
  - What would you do?

Take Home Lessons

- Travelers' diarrhea is predominantly caused by bacterial enteropathogens
- Field diagnostics (norovirus, Shigella, Salmonella, Campy) are needed
- Treatment of moderate to severe illness with antibiotics should be the rule (not the exception)
- Morbidity from acute illness is significant, and greatly compounded by growing evidence of associated post-infectious sequelae
- Chemoprophylaxis may have a role – more study is needed

Questions?