



# **Bioconjugate vaccine preventing shigellosis: bridge from HCT to field studies**

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**on behalf of**

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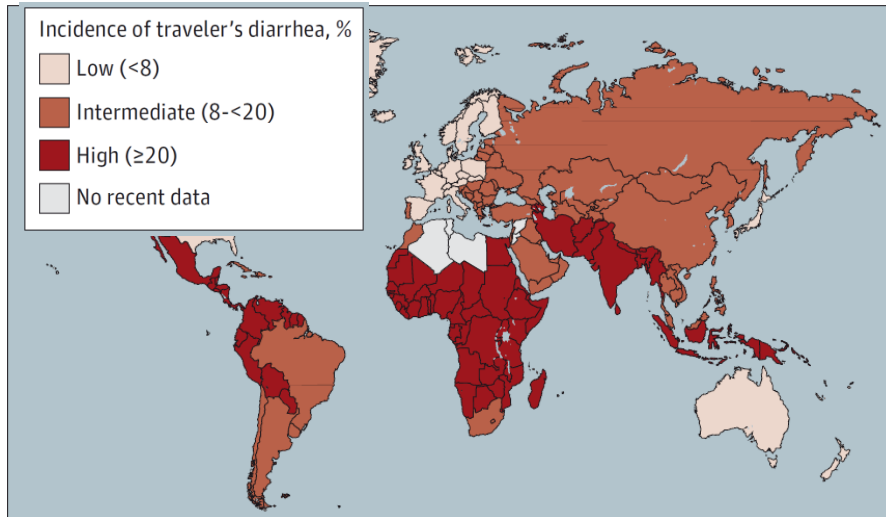
**4 Walter Reed Army Institute of Research, Silver Spring, MD**

**2<sup>nd</sup> Human Challenge Trials in Vaccine Development**  
**September 28, 2017**

# Overview

- Shigella burden of disease in travelers
- A brief review of the status of the shigella bioconjugate vaccine
- Feasibility of an efficacy field trial in travelers
- Suitability for endemic populations to support licensure in travelers
- Suitability of the shigella controlled human challenge model to support licensure
- Summary and discussion of way(s) forward

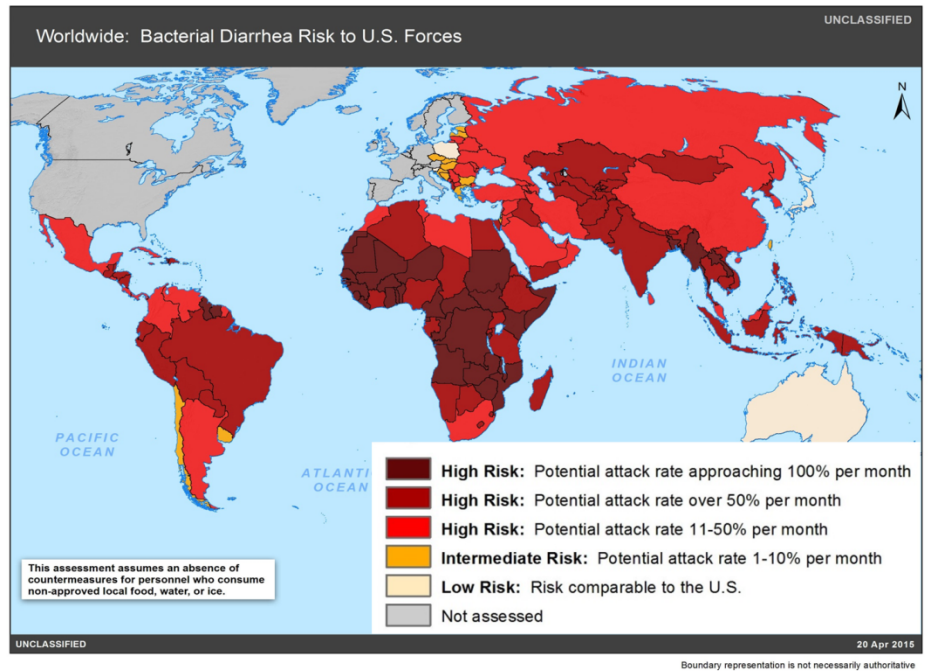
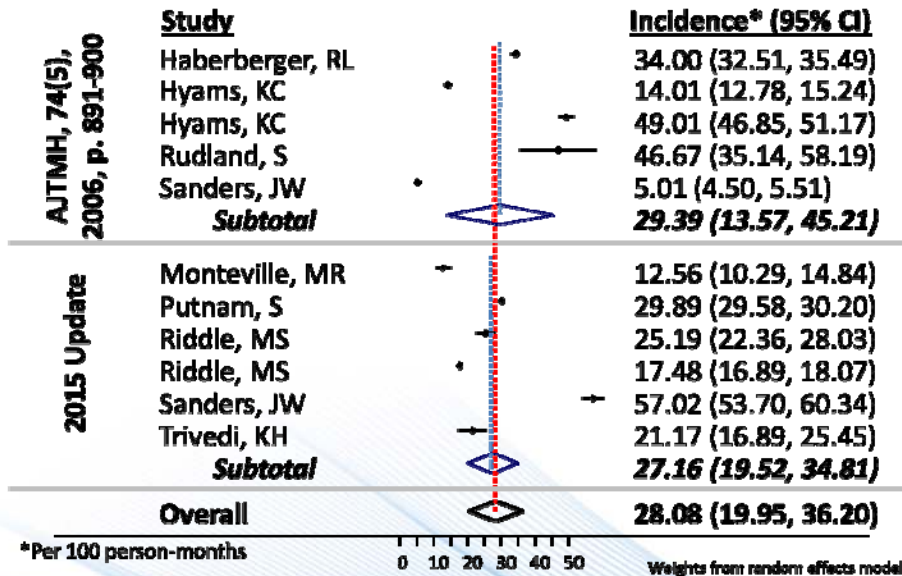
# Traveler Diarrhea: Disease Burden



***“The incidence of TD has decreased in countries with increasing economies and in some previously high-risk destinations with improved tourism infrastructure. Overall, the incidence of TD is declining, with current rates ranging from 10% to 40% compared with 65% two decades ago.”***

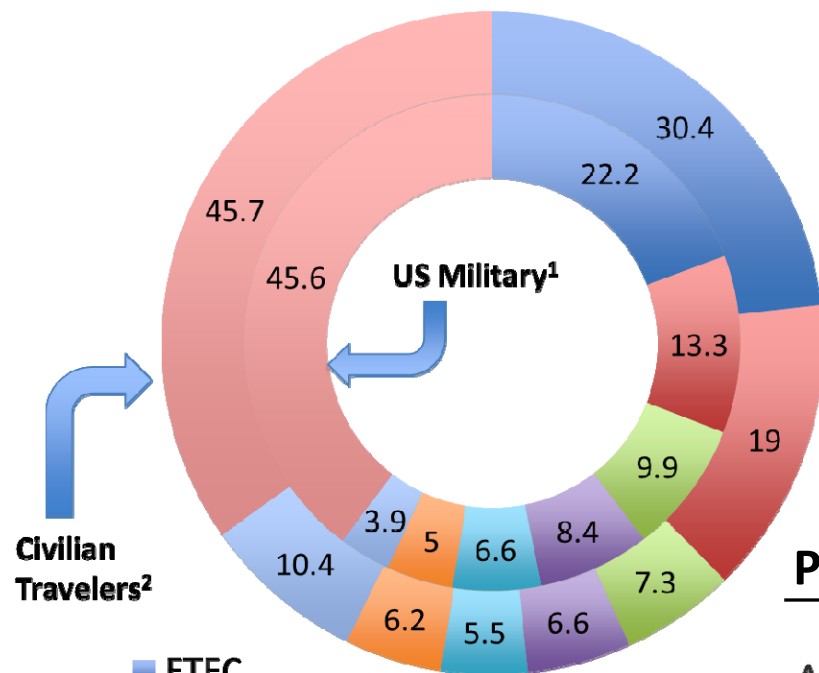
--Steffen et al JAMA 2015

## TD incidence: Middle East; ≥1M duration

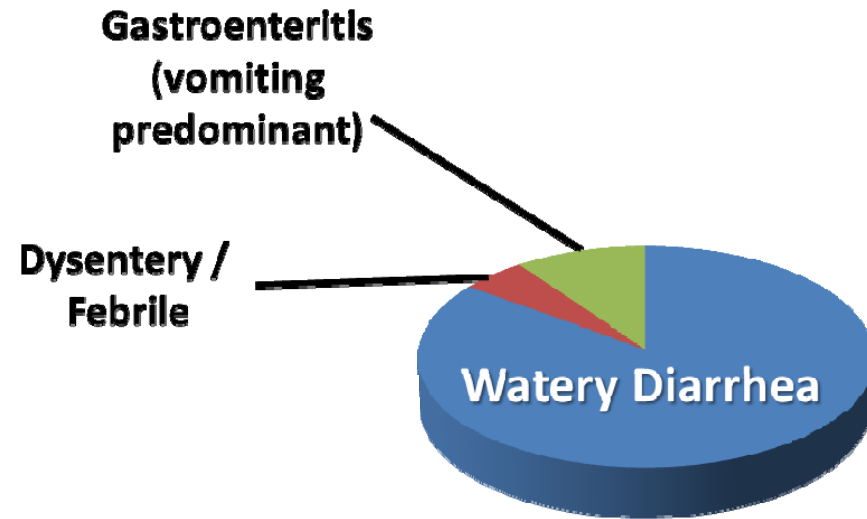


Porter & Riddle, unpublished data

# Syndromic presentation, pathogen attribution (“traditional”), & differential impact of acute TD



- ETEC
- EAEC
- Campy
- Norovirus
- Shigella
- Salmonella
- Rotavirus
- Non identified



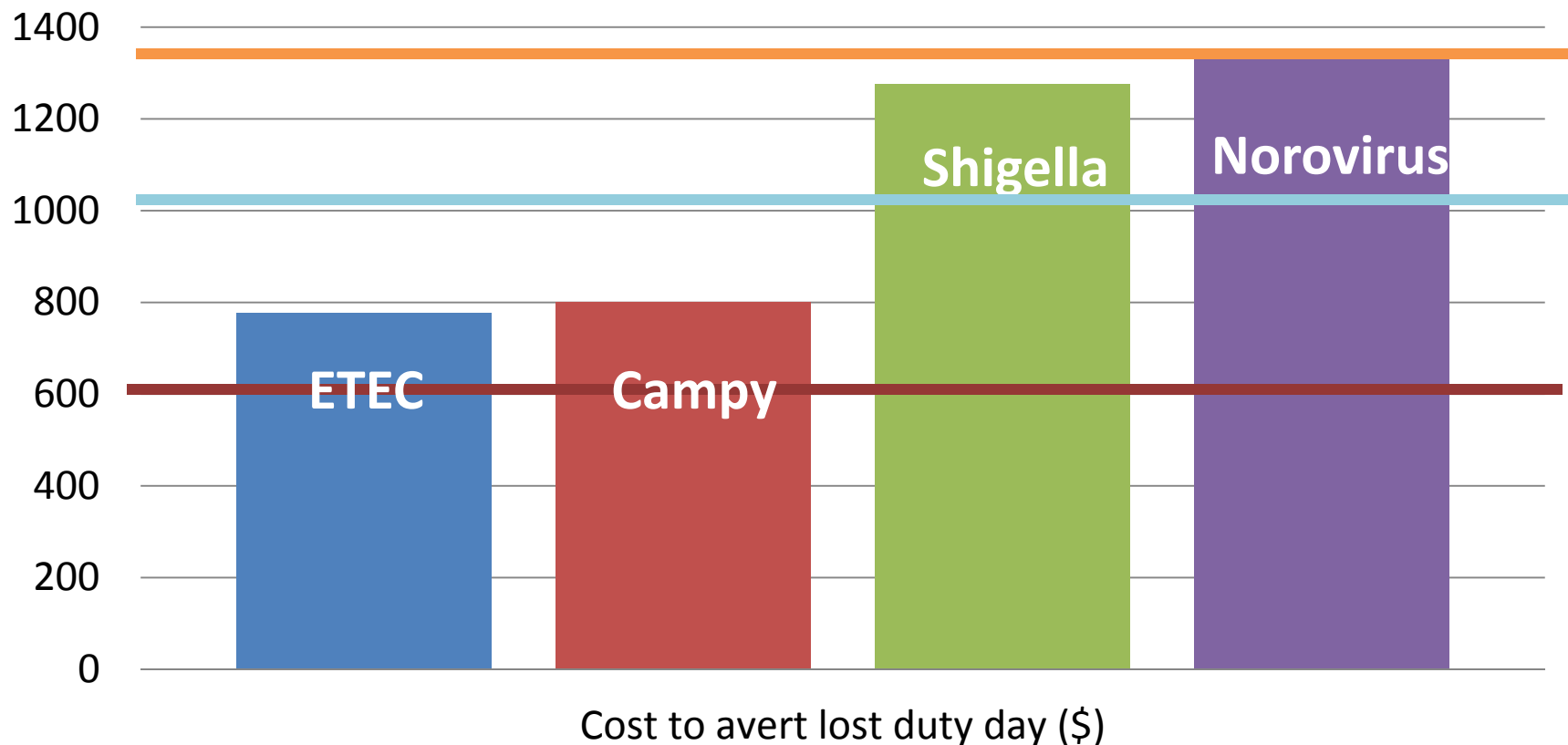
**Percent troops sick in quarters or incapacitated**

Author (year)	<i>Campylobacter</i>	ETEC	<i>Shigella</i>	Other
Hyams (1991)	--	21%	64%	--
Cohen (2001)	--	--	56%	27%
Walz (2001)	--	--	92%	46%
Sanders (2002)	47%	--	--	27%
Monteville (2006)	--	26%	--	--
Porter (2010)	50%	18%	--	20%

<sup>1</sup>Riddle M , *Am J Trop Med Hyg*, 74;2006:891-900.

<sup>2</sup>Shah N *Am J Trop Med Hyg*, 80;2009:609–614.

# Cost-effectiveness of a vaccine in the DoD (today)



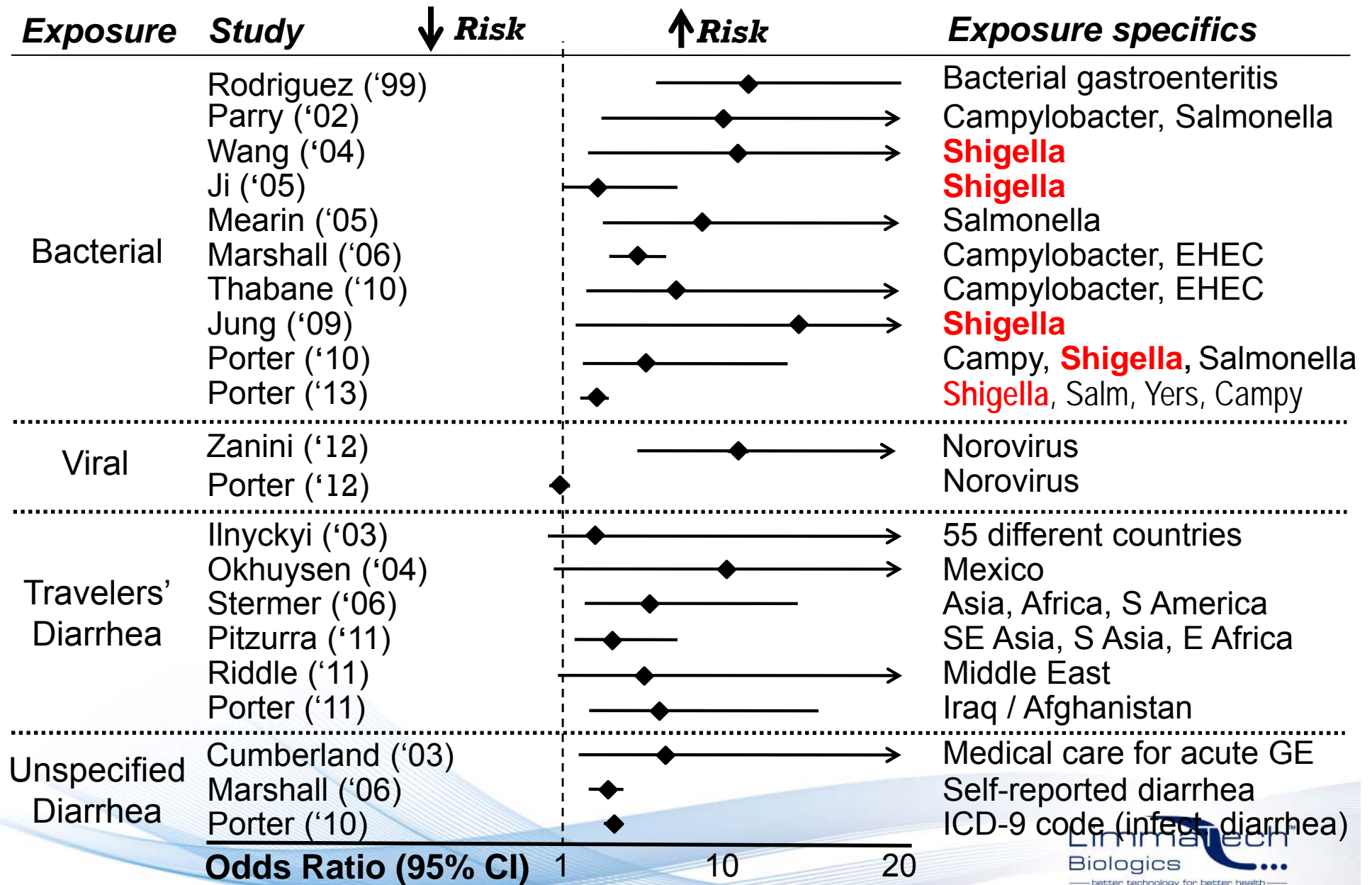
**Cost Per Soldier-Day of a Potential Conflict with Iraq, CBO, 2002**

**Cost Per Soldier-Day of Conflict in Iraq, CRS, 2006**

**Cost Per Soldier-Day of a Potential Conflict in Afghanistan, Pentagon Comptroller, 2009**

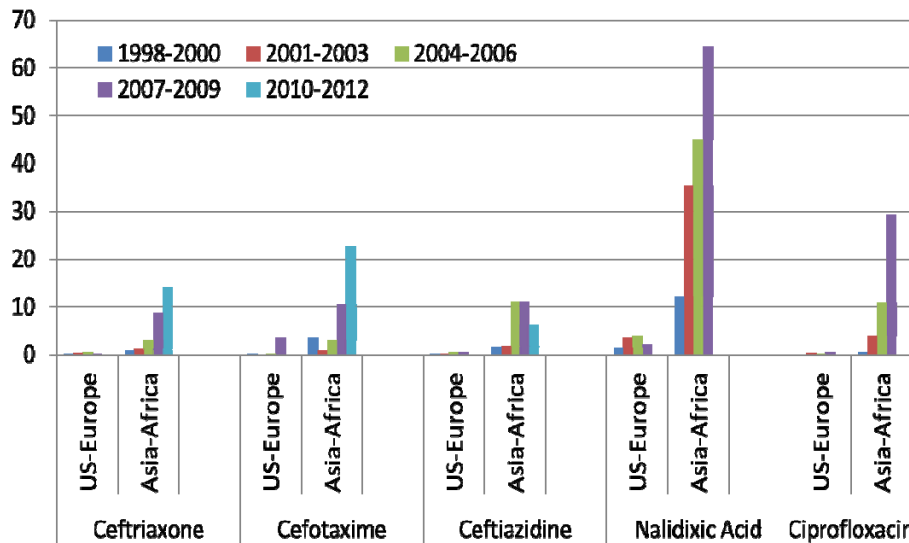
*A Tallant, Vaccine, 2014*

# Potential impacts and vaccine value goes beyond acute disease (case in point: IBS)



# Emerging concern of antibiotic resistance raises importance of vaccine and vulnerable populations

## Multi-drug resistance a global concern




Gu B, Int J of Antimicrobial Agents (2012)  
Gu B, Epi & Infect (2015)




Antimicrobial Agents  
and Chemotherapy

A waterborne outbreak of *Shigella sonnei* with resistance to azithromycin and third-generation cephalosporins in China, 2015

Ma et al, April 2017, ahead of print



**Centers for Disease Control and Prevention**  
CDC 24/7: Saving Lives. Protecting People™



**HAN**  
HEALTH ALERT NETWORK

April 18, 2017, 16:00 ET,  
CDCHAN-00401

**CDC Recommendations for Diagnosing and Managing *Shigella* Strains with Possible Reduced Susceptibility to Cipro**

- *Shigella* can cause a severe life-threatening illness among the young, old and immunocompromised
- Antibiotics are important to treat such cases and prevent death
- Resistance (and treatment failures) disproportionately affect vulnerable populations
  - Children under 5 in developing world
  - MSM populations

# Shigella Bioconjugate Vaccine

## ➤ CPOC with monovalent vaccine



- Safety
- Immunogenicity
- Indication of protection

*S. flexneri* 2a-EPA  
phase 1(2015)

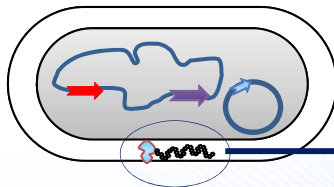
*S. flexneri* 2a-EPA phase 2b  
challenge study (2016-2017)

Development  
multivalent  
vaccine

  
**Multivalent  
Shigella  
Bioconjugate  
Vaccine**



**Recombinant *E. coli***

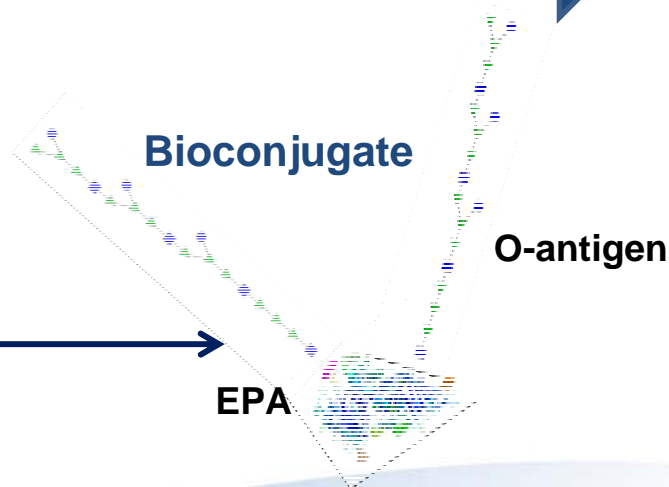


**Purification**

**Bioconjugate**

**EPA**

**O-antigen**



Phase 2b Shigella  
CHIM (2457T)  
with Flexyn2a:  
Placebo subjects  
(n=29)

**PI: Kawsar Talaat,**  
*Johns Hopkins University*  
ClinicalTrials.gov Identifier:  
NCT02646371

Approx dose (cfu)	1500
Diarrhea (any)	72.4%
Diarrhea (severe)	44.8%
Dysentery	24.1%
Vomiting	24.1%
Nausea	37.9%
Abd pain/cramps	62.1%
Fever	48.3%
Early antibiotics	62.1%

## Phase 2b Shigella-CHIM with Flexyn2a: Shigellosis Attack Rate in Placebo

	Cohort 1		Cohort 2		Total	
	Placebo		Placebo		Placebo	
	N=15		N=14		N=29	
Shigellosis PP	9	60%	9	64%	18	62%

### Shigellosis PP primary endpoint

- Severe Diarrhea, or
- $\geq$  Moderate Diarrhea & fever/moderate enteric symptom, or
- Dysentery

➤ **Consistent attack rate between cohorts**

# Phase 2b Shigella-CHIM with Flexyn2a: Vaccine efficacy

	Attack Rate (%)		Vaccine Efficacy	
	Flexyn2a N=30	Placebo N=29	(%)	p-value
<b>Shigellosis (PP primary endpoint)</b>				
<ul style="list-style-type: none"> <li>• Severe Diarrhea, or</li> <li>• ≥ Moderate Diarrhea &amp; fever/moderate enteric symptom, or</li> <li>• Dysentery (≥ 2 gross blood/h'occult + &amp; sympt)</li> </ul>	<b>13 (43.3)</b>	<b>18 (62.1)</b>	<b>30.2</b>	<b>0.1123</b>
≥ More Severe Diarrhea	2 (6.7)	7 (24.1)	<b>72.4</b>	<b>0.0651</b>
Received Early Administration of Antibiotics	9 (30.0)	18 (62.1)	<b>51.7</b>	<b>0.0093</b>
Received IV Fluids	7 (23.3)	13 (44.8)	<b>47.9</b>	<b>0.0525</b>
<b>More Severe Shigellosis (post hoc analysis)</b>				
<ul style="list-style-type: none"> <li>• ≥ Moderate diarrhea &amp; fever/<b>severe</b> enteric symptom, or</li> <li>• Dysentery &amp; ≥ 1 <b>severe</b> enteric symptom</li> </ul>	<b>8 (27.6)</b>	<b>16 (53.3)</b>	<b>51.7</b>	<b>0.0151</b>

**More severe diarrhea:** ≥10 loose (grade 3-5) stools within 24h or ≥1000 gr loose (grade 3-5) stools / 24h

**Severe diarrhea:** ≥6 loose (grade 3-5) stools within 24h or >800gr loose (grade 3-5) stools within 24h

**Moderate diarrhea:** 4-5 loose (grade 3-5) stools within 24h or 401-800gr loose (grade 3-5) stools / 24h

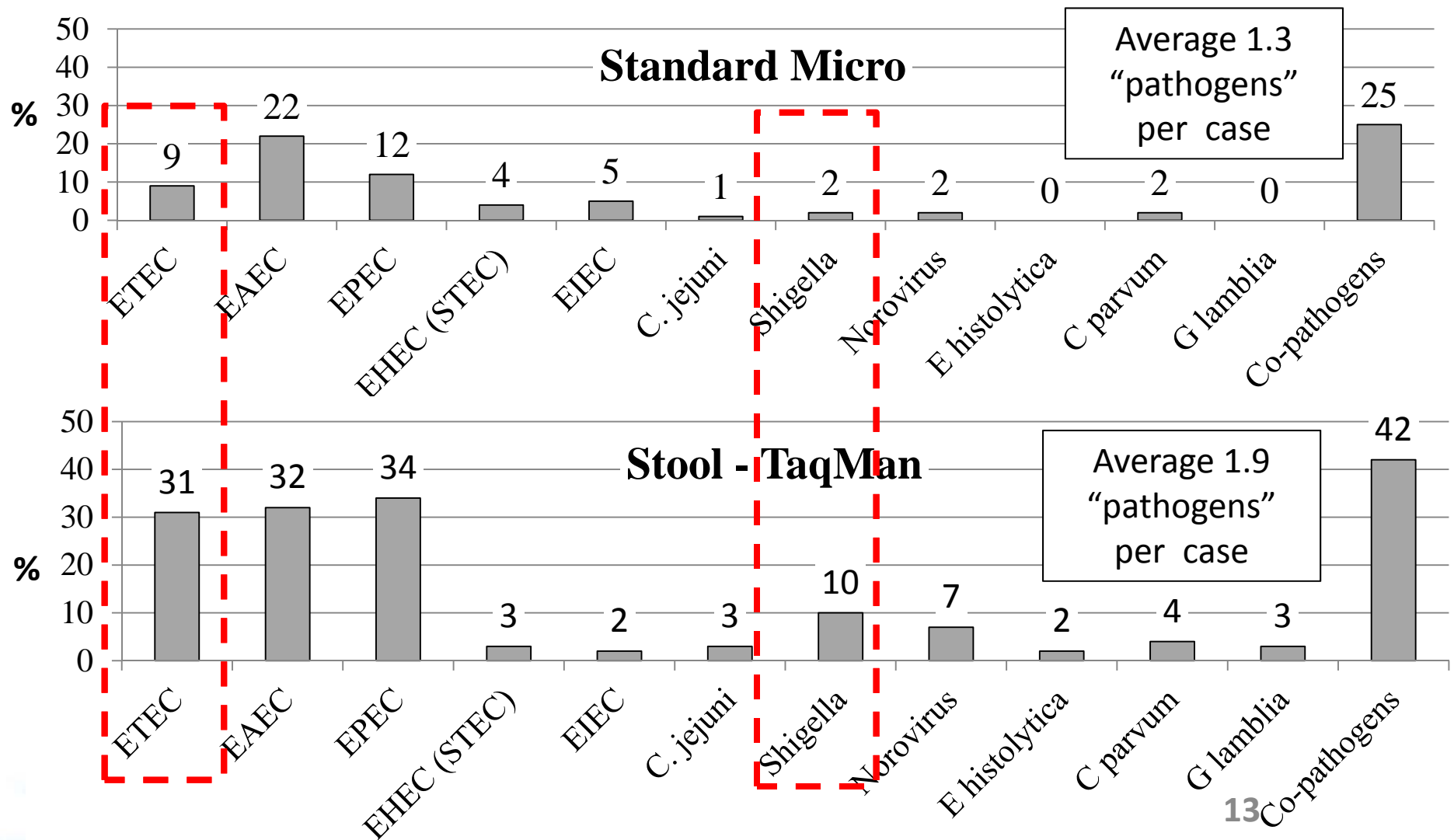
# Feasibility of an efficacy trial in travelers (back of the envelope)

- ◆ **TD incidence: 8.8 - 20%**
  - ◆ **Attribution to Shigella: 2.2 – 8.6%**
  - ◆ **Target efficacy (hypothetical): 70%**
- } Not adjusted for mod-severe disease

TD Rate	Shigella-attributable proportion	Shigella-TD rate	Shigella rate if VE=70%	Total Analyzable Sample Size	Allow for 17% dropout
20.00%	8.60%	1.72%	0.52%	3,230	3,892
	7.30%	1.46%	0.44%	3,798	4,576
	2.20%	0.44%	0.13%	12,426	14,971
14.00%	8.60%	1.20%	0.36%	4,606	5,549
	7.30%	1.02%	0.31%	5,706	6,875
	2.20%	0.31%	0.09%	17,330	20,880
8.80%	8.60%	0.76%	0.23%	7,366	8,875
	7.30%	0.64%	0.19%	8,574	10,330
	2.20%	0.19%	0.06%	31,046	37,405

- ◆ **Critical assumptions: suitable field sites available; efficacy against individual serotypes not powered**

# Sample size reduction possible *if* culture-independent testing could be used (Riddle, unpublished)



\***SUBSET**: limited to subjects with paired culture and frozen stool and filter paper available at time of comparison (Clinicaltrials.gov: NCT01618591)

# What about use of endemic populations to support efficacy licensure in travelers?

- Epidemiological data of shigellosis in children in LMICs show higher incidence than in travelers
  - Differential serotype is likely between populations
- Exhibit A: Shigella chemical conjugate vaccine in Israeli soldiers and children
  - *S. sonnei* conjugate showed 74% VE in military, yet no efficacy in children below 3 years of age.
- Exhibit B: Vaxchora example
  - failed to show efficacy when tested in the field in endemic population in Indonesia (under the name CVD 103-HgR), whereas strong immunogenicity and efficacy were obtained in US travelers
- Under-performing in endemic settings is common, compared with the immune-response achieved when tested in developed countries (i.e. polio, cholera, salmonella and rotavirus vaccines)
- Suggest that formulation, adjuvant, dosing and schedule needs to be optimized in the target population.

# Status and suitability of the Shigella CHIM

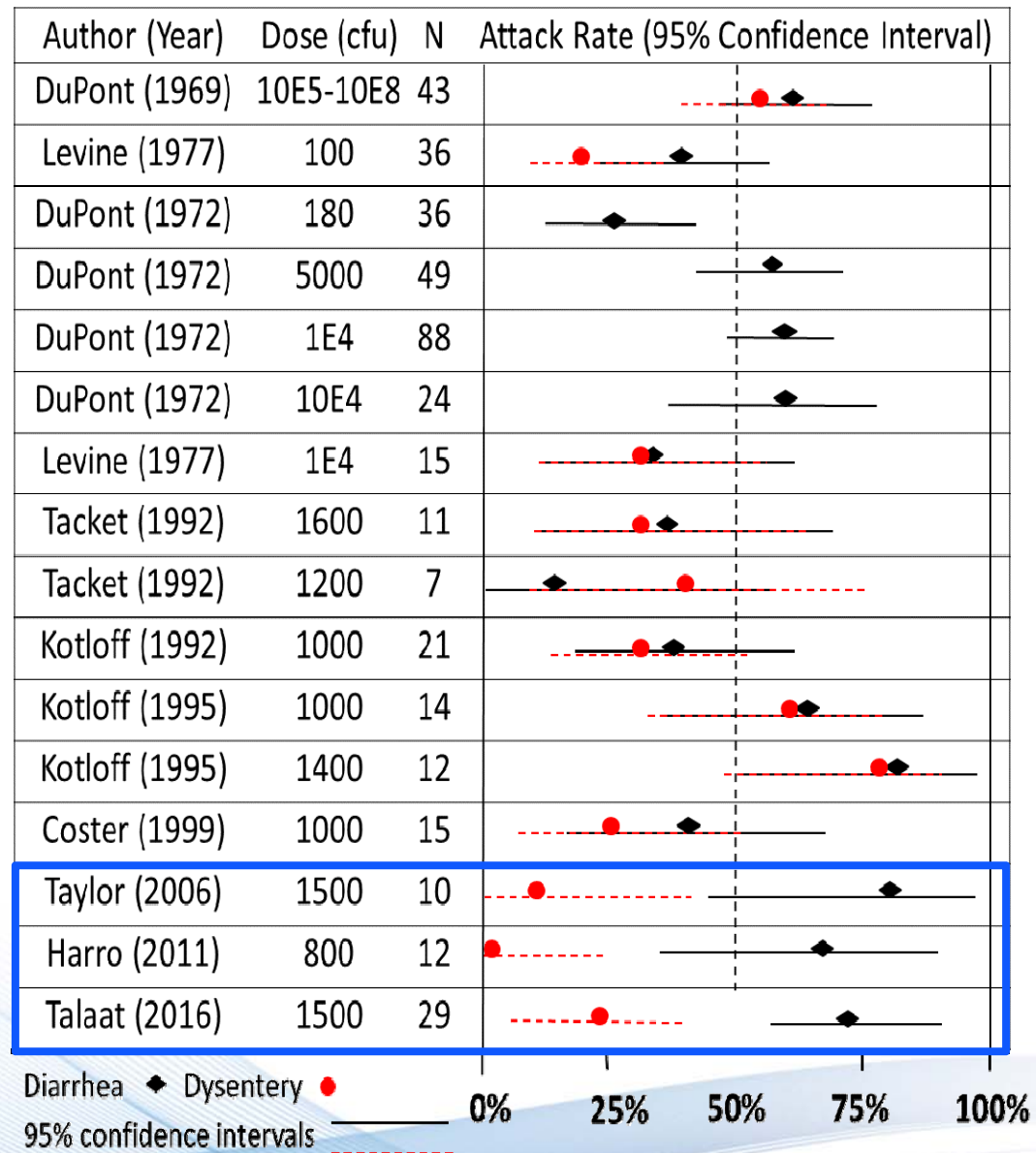
## ❖ *S. flexneri* 2a

- Isolated from a patient with clinical illness in Japan in early 1950s
- Administered to ~500 naïve subjects
- GMP lot 1617, WRAIR Pilot Bioproduction Facility (27 Jan '10)
- Vials:  $1.8 \times 10^8$  cfu/vial
  - Freshly harvest cells brought to fixed dilution and administered in  $\text{HCO}_3$

## ❖ *S. sonnei*

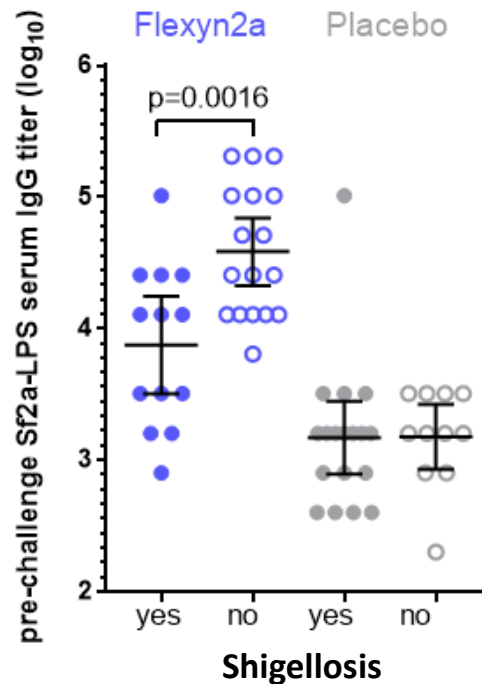
- Isolated in Tokyo, Japan (24 Aug 1954) from a 5 year-old boy hospitalized with diarrhea
- Administered to ~300 naïve subjects
- GMP Lot 1794, WRAIR Pilot Bioproduction Facility (25 Feb '13)
- Multi-dose vials:  $1.9 \times 10^9$  cfu/vial
  - Lyophilized cells re-suspended, diluted to appropriate dose, administered in  $\text{HCO}_3$
- Model refinement ongoing (BB-IND 17,015; PATH sponsor)

# *S. flexneri* 2a 2457T Attack Rates



Updated from CK Porter. Epidemiol Infect (2012): 1-10

# Shigella-CHIM with Flexyn2a: Correlation immune response and protection against shigellosis



Optimal cutpoint analysis: Serum IgG Day 56 $\geq$ 6400 ( $\log_{10}$ 3.8)									
Num of vaccinees meeting endpoint			Num of vaccinees not meeting endpoint			Relative risk	p value	Efficacy	p value
With shigellosis	Without shigellosis	Tot	With shigellosis	Without shigellosis	Tot				
7	17	24	6	0	6	0.292	0.003	53	0.03

Analysis kindly provided by C. Porter (NMRC)

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# Which way do you go?

Traditional  
Traveler Vaccine  
Field Trial

CHIM Model

## Strengths

- Most relevant to target population (adults)
- Mimics natural exposure

## Limitations

- Low incidence, ↑sample size
- Adequate field sites not available (2 sites in different geographical location)
- Inadequate epidemiology

## Strengths

- Homologous/heterologous protection can be assessed
- Evaluable duration of protection
- Potential shortens timeline to licensure

## Limitations

- Artificial exposure, high inoculum
- Causes severe disease which may be harder to protect (too stringent?)

# *The way forward...*

- ✓ Rational for shigella CHIM for licensure needs validation
- ✓ Paxvax with licensure of Vaxchora as precedent
  - ✓ Though situation with Vaxchora a little different
- ✓ Prior conjugate demonstrated effective in “traditional field trial” and relevant population (Israeli military)
  - ✓ Field trial sites at present do not exist to support large studies
- ✓ Correlation with serological endpoints is possible
- ✓ Phase IV immunological bridging studies and phase 2 supportive field studies are feasible

*The need for a shigella vaccine in travelers (and military) is sorely needed, the road to get there needs to be paved and the CHIM may present a path*



**NMRC**



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**Wellcome<sup>Trust</sup> Global  
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*Thank you*



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