



# ETEC Diarrhea: Global Health Problem for LDCs

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**Chief Scientific Officer**  
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*Intercell* develops *vaccines*   
for the  *prevention and treatment*  
of *infectious diseases* .

For more information be invited to: [www.intercell.com](http://www.intercell.com)



# Conflicts of Interest

Intercell is developing a vaccine patch for travelers' diarrhea  
Gregory Glenn is an employee and stockholder of Intercell



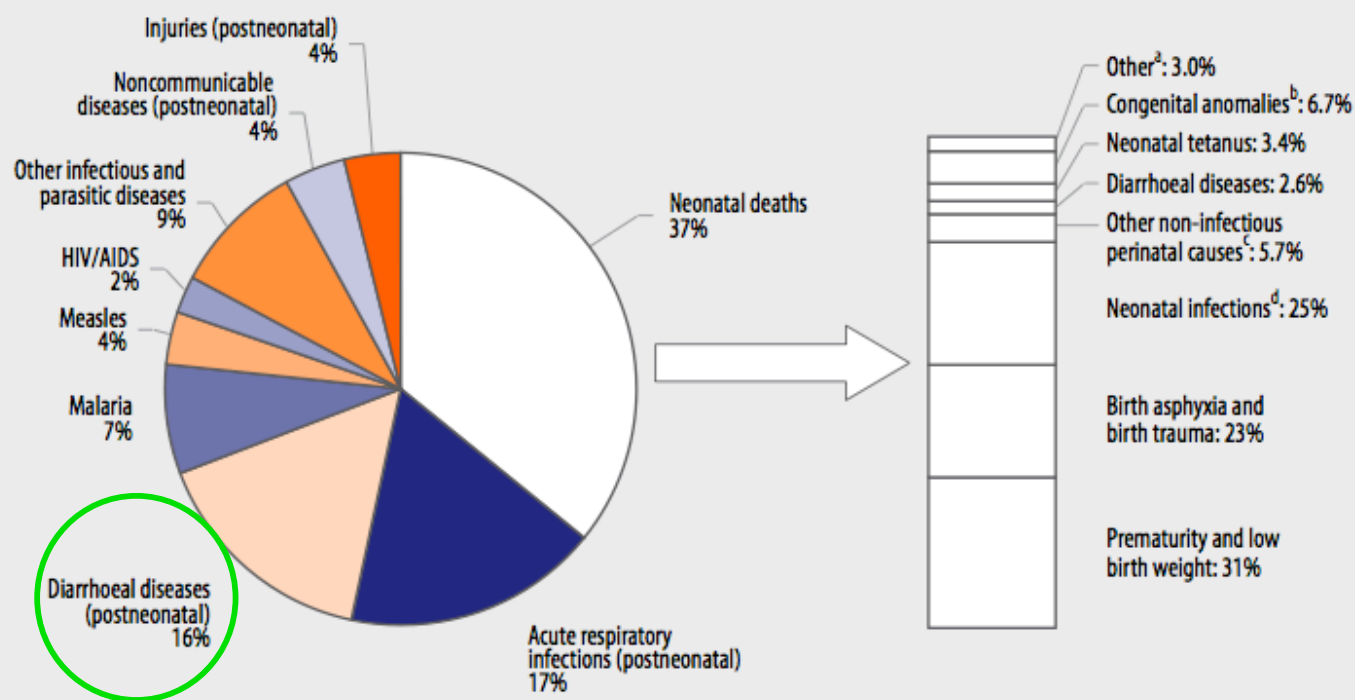
## Qualifying criteria for tropical disease applications under section 524

Product for prevention or treatment of listed neglected tropical diseases or other infectious disease for which:

- » There is no significant market in developed nations
- » That disproportionately affects poor and marginalized populations

# Diarrheal Disease: A Major Burden and Unmet Need in Global Child Health

**Figure 5 : Distribution of causes of death among children aged under five years and within the neonatal period, 2004**



[http://www.who.int/healthinfo/global\\_burden\\_disease/GBD\\_report\\_2004update\\_part2.pdf](http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_part2.pdf)

## 5. Causes of death among children aged under five years

Six causes of death account for 73% of the 10.4 million deaths among children under the age of five years worldwide (**Figure 5**):

- acute respiratory infections, mainly pneumonia (17%)
- diarrhoeal diseases (17%)
- prematurity and low birth weight (11%)
- neonatal infections such as sepsis (9%)
- birth asphyxia and trauma (8%)
- malaria (7%).

[http://www.who.int/healthinfo/global\\_burden\\_disease/GBD\\_report\\_2004update\\_part2.pdf](http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_part2.pdf)

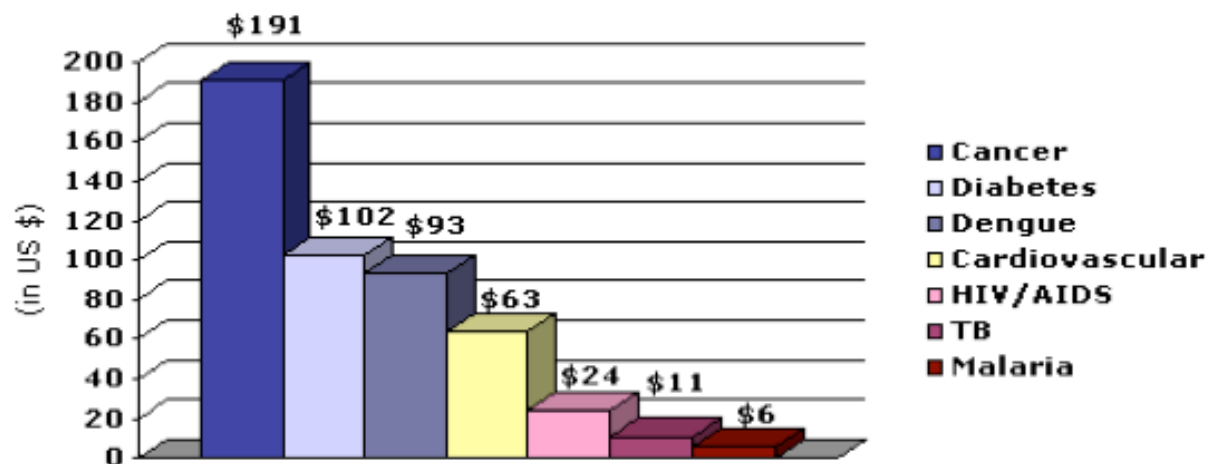
# Investment in Diarrheal Disease Research in LDCs

## Disease Burden vs. Health Care Investment

*Limited developing world health care expenditures highlight global inequities*

- The burden of disease in developing countries outstrips budgets for health care.
- Despite a pressing global burden, R&D spending on neglected diseases is far less than for Western diseases with similar mortality and morbidity profiles.

R&D Spending per DALY



DALY: Disability Adjusted Life Year

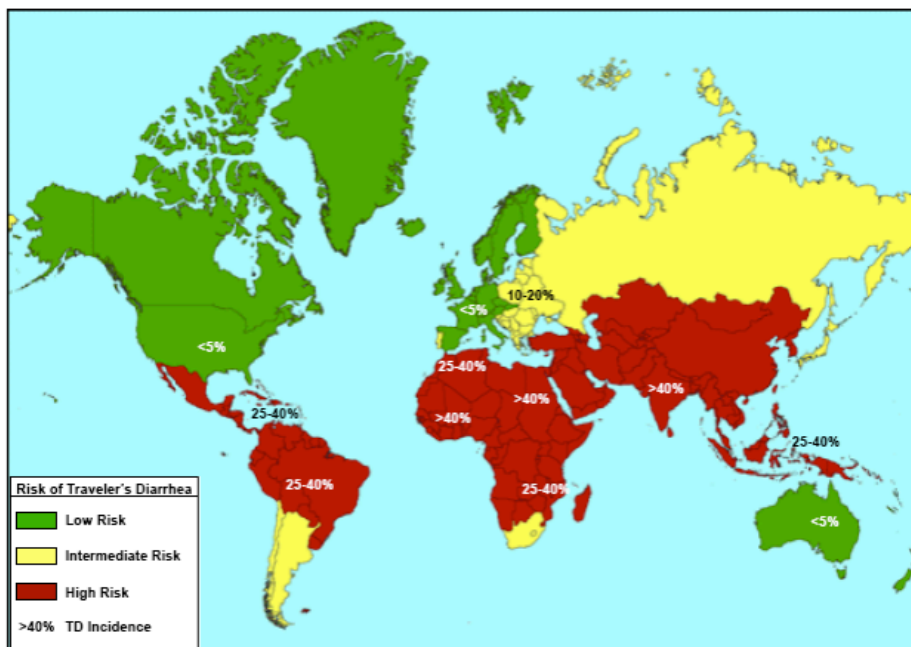
The number of healthy years of life lost due to premature death and disability

<http://www.bvgh.org/innovation/crisis/GlobalHealthChallenge.asp>

# ETEC Diarrhea in Infants and Children in LDCs

- Enterotoxigenic *E. coli* (ETEC) diarrhea
  - Follows ingestion of contaminated food or water
    - 1.1 billion have no access to safe drinking water\*
  - Leads to profuse, watery diarrhea lasting several days
  - Can lead to dehydration in young children in LDCs
- ETEC Distribution: risk distribution similar to traveler's diarrhea

Risk Areas for Traveler's Diarrhea



\*I. Mara, D.D. 2003. Water, sanitation and hygiene for the health of developing nations. *Public Health*. 117:452-456.

# ETEC and Global Diarrhea Mortality

- Enterotoxigenic E. coli (ETEC) diarrhea mortality
    - Overall global mortality has declined from 4.6 to 1.6 due to ORS in past decade
    - Currently estimated 200 million cases of ETEC in LDC children <5 years of age
      - Leading cause of diarrhea
      - Second only to rotavirus in dehydrating diarrhea
    - Estimated 380-500,000 deaths annually due to ETEC
- [http://www.who.int/vaccine\\_research/diseases/e\\_e\\_coli/en/](http://www.who.int/vaccine_research/diseases/e_e_coli/en/)



**Figure 1**

Worldwide distribution of deaths caused by diarrhea in children under 5 years of age in 2000. Although global mortality from diarrhea has declined in recent years, from approximately 4.6 million deaths during the mid-1980s to the current estimate of 1.6-2.1 million, most of these deaths occur in children in developing countries under the age of 5 years. Data are from the year 2000 (2).



# Guatemala: Example of Diarrhea as a Global Health Problem in an LDC

## Causes of death in children under-5

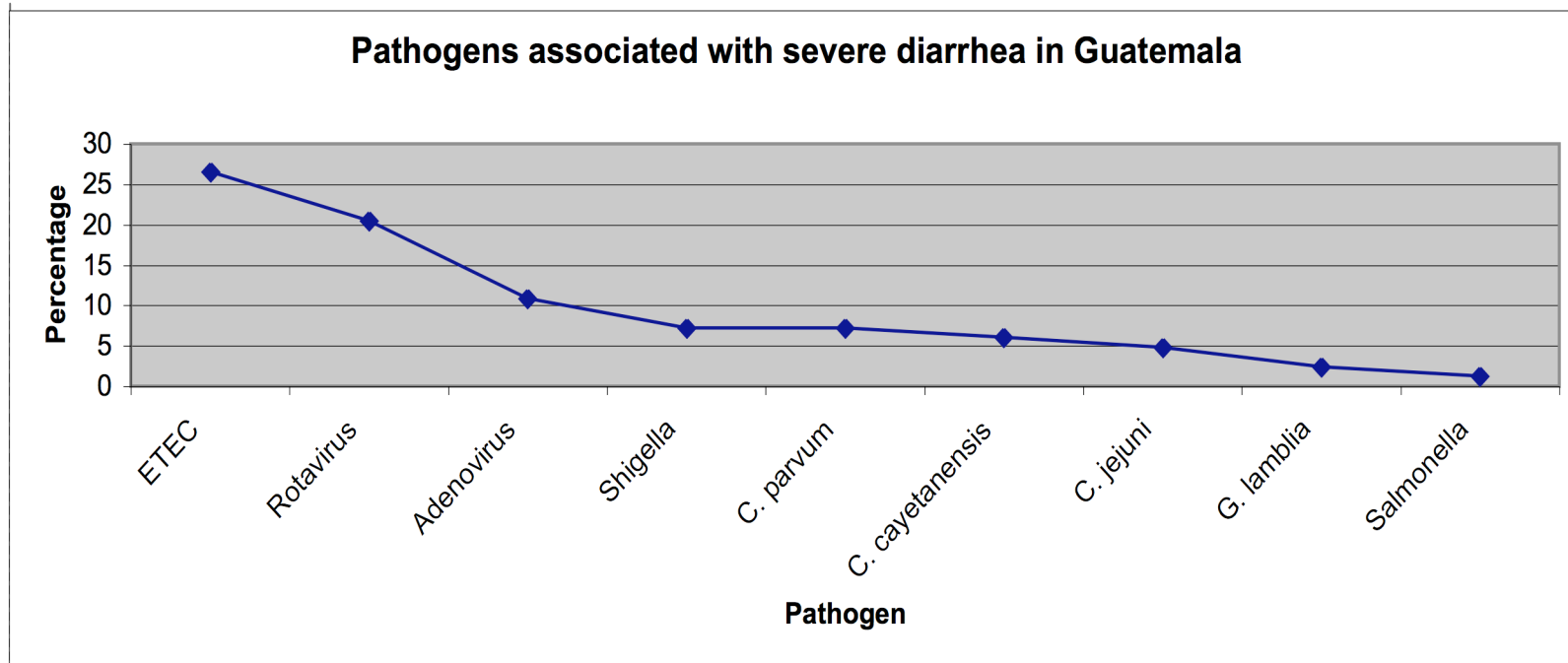
Distribution of causes of death  
among children under 5 years of age  
Guatemala, 2000-2003

Causes	Deaths <sup>b</sup>	Regional average
	(%)	(%)
Total neonatal deaths	100	100
Neonatal causes <sup>a</sup>	37	44
HIV/AIDS	3	1
Diarrhoeal diseases	13	10
Measles	0	0
Malaria	0	0
Pneumonia	15	12
Injuries	2	5
Others	30	28

a. Includes diarrhoea during neonatal period  
b. Sum of individual proportions may not add up to 100% due to rounding.

[http://www.who.int/whosis/mort/profiles/mort\\_amro\\_gtm\\_guatemala.pdf](http://www.who.int/whosis/mort/profiles/mort_amro_gtm_guatemala.pdf)

# Etiology of Severe Diarrhea in Guatemalan Children



Olga Torres (Guatemala) presented to WHO working group, October 2006 Gothenburg,

# Morbidity Due to Diarrhea

- Enterotoxigenic *E. coli* (ETEC) diarrhea morbidity
  - Overall global morbidity from diarrhea unchanged in past decades
    - Diarrheal bout in the first 2 years of life:
      - Disrupts absorptive function of GI tract
      - Brain and synapse development occurs in first 2 years of life
    - Growth stunting, IQ loss, fitness for schooling, other effects
  - Estimated 200 million cases of ETEC in children <5 years of age
    - ETEC most common etiology in many settings
    - Repeat bouts common



... [www.umich.edu/.../img/Cholera-Babies-&-Diet.j](http://www.umich.edu/.../img/Cholera-Babies-&-Diet.j)



Review series

## Enteric infections, diarrhea, and their impact on function and development

William A. Petri Jr.,<sup>1</sup> Mark Miller,<sup>2</sup> Henry J. Binder,<sup>3</sup> Myron M. Levine,<sup>4</sup>  
Rebecca Dillingham,<sup>1</sup> and Richard L. Guerrant<sup>1</sup>

<sup>1</sup>Center for Global Health, Division of International Health, University of Virginia, USA. <sup>2</sup>Fogarty International Center, USA. <sup>3</sup>Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, Maryland, USA. <sup>4</sup>Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, Maryland, USA.

*J. Clin. Invest.* **118**:1277–1290 (2008)

University of Virginia, Charlottesville, Virginia, USA.

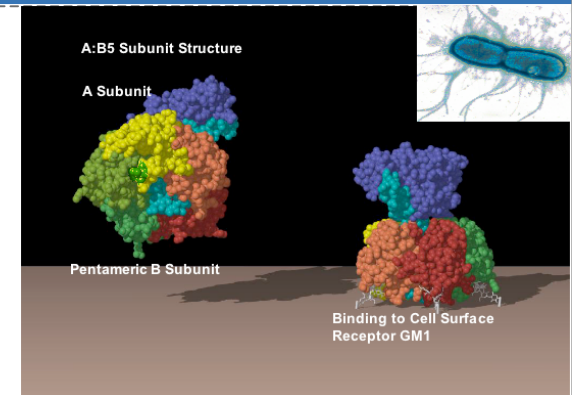
# Intercell Vaccine Approach to Traveler's Diarrhea

## •Vaccine Antigen

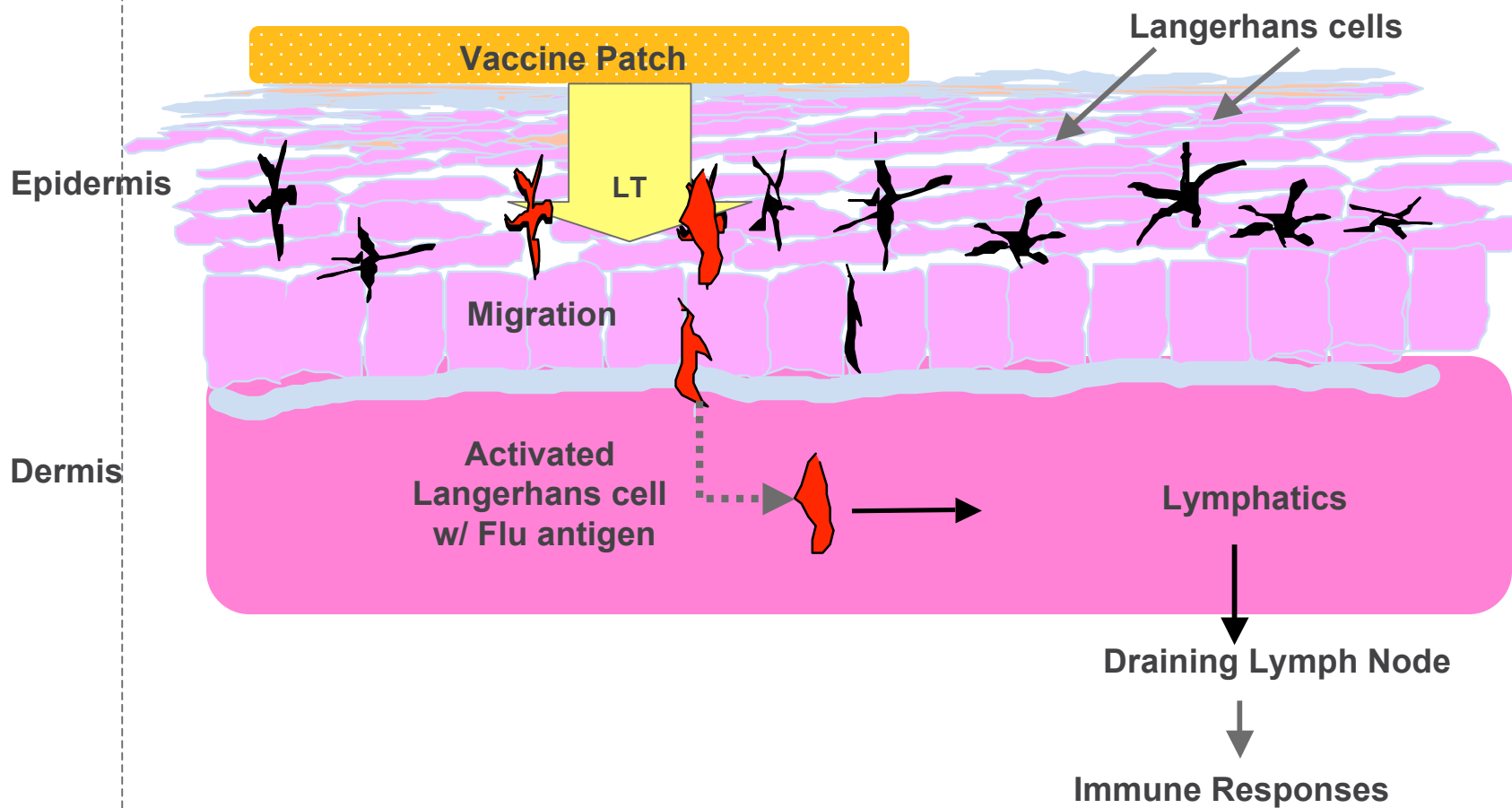
- LT, the heat labile toxin from *E. coli*

## •Toxin-The Key Pathogenic Factor

- Binds to, and activates mucosal epithelial cells
  - Causes fluid dysregulation via chloride channels
    - Results in fluid secretion in the gut
  - Disrupts the mucosal barrier, aids colonization by *E. coli* and other organisms
- Toxins are the classic approach to vaccination with a historic impact on disease**
- Hypothesis: Immunity to LT neutralizes the toxin effects, will prevent and ameliorate diarrhea**



# Transcutaneous Immunization: Vaccine Delivery to the Skin



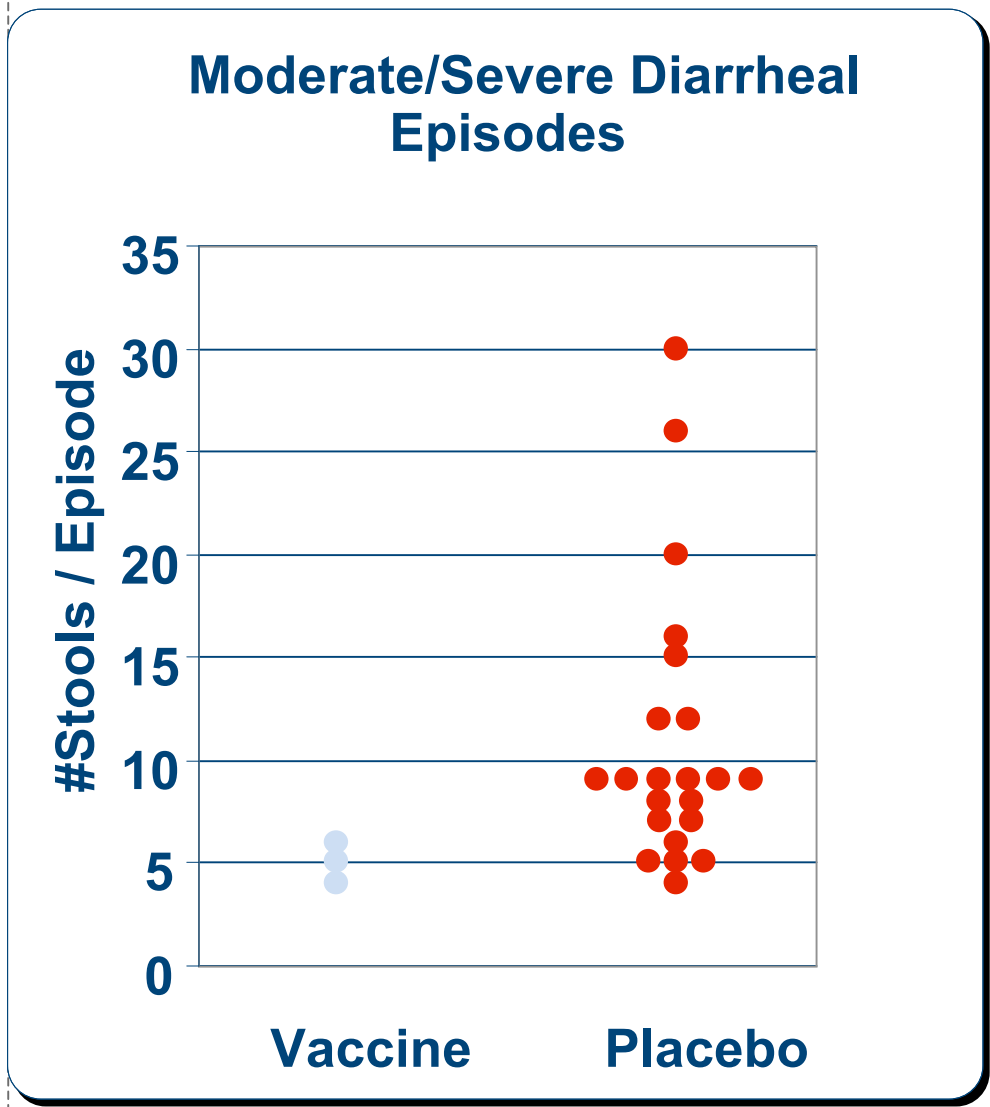
# Intercell TD Patch System

## LT Patch

- » Needle-free
- » Simple to apply, flexible for addition to EPI schedule
- » Dry, with stabilizing excipient formulation
  - Stable under harsh conditions,  
ie for shipping, shelf storage
- » Process scaled for manufacturing



# LT Patch Efficacy Against Clinically Significant Diarrheal Episodes in Travelers



Use of a patch containing heat-labile toxin from *Escherichia coli* against travellers' diarrhoea: a phase II, randomised, double-blind, placebo-controlled field trial

Sarah A Frech, Herbert L DuPont, A Louis Bourgeois, Robin McKenzie, Jaime Belkind-Genson, Jose F Figueroa, Pablo C Okhuysen, Norma H Guerrero, Francisco G Martinez-Sandoval, Juan H M Meléndez-Romero, Zhi-Dong Jiang, Edwin J Asturias, Jane Halpern, Olga R Torres, Ana S Hoffman, Christina P Villar, Ranjya N Kassem, David C Flyer, Bo H Andersen, Kazem Kazempour, Sally A Breisch, Gregory M Glenn

Frech et al: Lancet 371, 2008

## ETEC Vaccine Patch

- Potentially efficacious vaccine against ETEC for children
  - » Protection extending beyond ETEC
- Needle-free, ambient temperature stable patch vaccine
- Benefits of pediatric vaccine extend to decreased mortality and morbidity





## No Significant Market

- » Little or no ETEC disease in developed countries
- » TD market is for travelers, typically 18 years of age and up, running the range from retirees down to students studying languages, taking Spring breaks, or participating in service projects
- » Developing an ETEC vaccine for children in endemic countries means targeting children at weaning age and up (from 3 to 5 months of age)
  - Product likely to be different from the adult TD vaccine in dose, formulation and size.
- » No significant market for a pediatric formulation in developed nations

“Any other infectious disease for which there is no significant market in developing nations  
And that disproportionately affects poor and marginalized populations...”

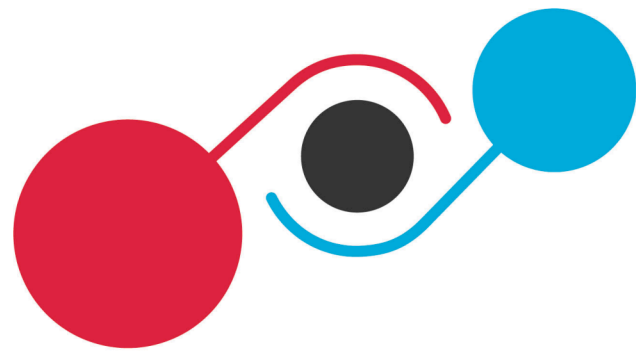
## Qualifying criteria for tropical disease applications under section 524 – ETEC

Product for prevention or treatment of listed neglected tropical diseases or other infectious disease for which:

- » There is no significant market in developed nations
  - No current ETEC vaccine for infants
  - No market opportunity for infants from developed world
- » That disproportionately affects poor and marginalized populations
  - ETEC is major child global health problem in the LDCs
    - Mortality
    - Morbidity
  - No current product addresses ETEC

## Conclusions

- » ETEC diarrhea is a global health problem affecting the most vulnerable and marginalized populations
- » No significant market for a pediatric ETEC patch
- » Intercell requests that ETEC diarrhea will be added to the list of Designated Tropical Diseases to the FDA



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SMART VACCINES

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