# Military Infectious Diseases Update on Vaccine Development

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**Abstract:**  

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To conduct for the Department of Defense, a focused and responsive world class infectious diseases research and development program leading to **fielding of effective, improved means of protection and treatment** to maintain maximal global operational capability with minimal morbidity and mortality
- Force Health Protection
- Naturally Occurring Infectious Diseases
Infectious diseases adversely impact military operations. Vaccines are the long-term solution.

New drugs are continually required to overcome evolving drug resistance.

Early diagnosis facilitates prompt, appropriate treatment and aids commanders in the field.

Most militarily relevant infectious diseases are transmitted by biting insects and other arthropods.
Naturally Occurring Infectious Diseases Impact U.S. Military Operations

**Infectious Diseases...**
- Can cause more casualties than enemy fire
- Are present wherever the military is deployed
- Require new tools to combat emerging diseases and evolving drug resistance

**Risk Areas for Travelers’ Diarrhea**

**Military Cost...**
- Lost duty time
- Decreased combat effectiveness
- Morbidity due to drug-related side effects
- Medical logistical burden

**Global Distribution of HIV-1 Strains**
# US Military Infectious Disease Products

<table>
<thead>
<tr>
<th>Research Effort</th>
<th>Advanced Development</th>
<th>Fielded Products</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiparasitic Drugs</strong></td>
<td></td>
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<tr>
<td>Leishmaniasis</td>
<td>Pentostam Topical drug</td>
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<td><strong>Vaccines</strong></td>
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<tr>
<td>Diarrhea</td>
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<tr>
<td>Dengue</td>
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<tr>
<td>Hemorrhagic fevers</td>
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<td>Scrub Typhus</td>
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<tr>
<td>Meningitis</td>
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<td>HIV</td>
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<tr>
<td><strong>Protectants</strong></td>
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<tr>
<td>Sand fly control</td>
<td></td>
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<tr>
<td>Insect identification</td>
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<tr>
<td><strong>Diagnostics</strong></td>
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<tr>
<td>Laboratory-based assays</td>
<td>Leishmania PCR Leishmania Skin Test</td>
<td>Malaria Rapid Diagnostic Test (2007)</td>
</tr>
<tr>
<td>Point-of-care devices</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
What Makes the MIDRP Unique?

- Focused on FDA/EPA approved products for the warfighter (adult indication)
  - Enhance global operational capability
  - Enhance Stability operations

- MRMC organized like a pharmaceutical company
  - Product development oriented organizational structure and processes
  - Decision Gate System integrates best industry business practices
  - Historical success of vaccines/therapeutics

- Core research program embedded in Military labs with uniformed researchers
  - Discipline and mission focus (requirements)
  - Global research platform – Host nation partners
  - Unique OCONUS clinical trial sites

"Because, if we fail to protect them, who will protect us?"
CAPT Meg Ryan

2011 MHS Conference
Critical Resource in Global Research

USAMRIID, Fort Detrick

WRAIR/NMRC, Silver Spring

NMRC-D, Lima

USAMRU-K, Nairobi

NAMRU-3, Cairo

AFRIMS, Bangkok

NAMRU-2, Jakarta

2011 MHS Conference
Other Assets

Accredited Lab Animal Facilities

Pilot Vaccine Production Facility

Biosafety Level 4 Containment

Clinical Trials Units
26% of top 100 authors are Army and Navy Investigators
Vaccine Development Update

- Malaria
- Dengue
- Bacterial Diarrheal Pathogens
  - ETEC
  - Shigella
  - Campylobacter
- Top 3 Infectious Disease Threats
  - April 2010 ID Threat Prioritization Panel
A little about Malaria

- Four Major Human Species: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae* and *Plasmodium ovale*.
- Sporozoite stage injected in bite of female *Anopheles* mosquito, invades liver, matures/multiplies producing blood stages that invade host erythrocytes to cause disease, further matures and is ingested by another mosquito to complete life cycle.
- Acute febrile illness characterized by periodic fevers occurring every 48-72 hours
  - *Plasmodium falciparum*- severe disease can cause coma and death
  - *Plasmodium vivax*- relapse or recrudesce over months or years
- Illness easily misdiagnosed
Burden of Malaria for Endemic Countries

- 243 million cases
  - 85% Africa
  - 10% SE Asia
- 863,000 deaths
  - 89% Africa
  - 6% E. Mediterranean
  - 5% SE Asia
- Risk groups
  - Infants & young children
  - Pregnant women
  - Travelers
Worldwide Malaria Distribution

Worldwide malaria distribution in 2002

Areas where malaria transmission occurs
Areas with limited risk
No malaria
The image contains a map titled "Africa: Malaria Risk to U.S. Forces." The map is color-coded to indicate different risk levels:

- **Red**: Potential attack rate 11-50% per month
- **Orange**: Potential attack rate 1-10% per month
- **Yellow**: Potential attack rate <1% per month
- **Green**: Rare cases (<0.1% per month)
- **White**: No risk
- **Gray**: Administrative boundary

The map notes that the boundaries of the risk area should not be interpreted as strict demarcations; risk area varies with multiple ecological factors.

Additionally, the map includes a legend with the following details:

- **Datum**: WGS84
- **Coordinate System**: Geographic
- **Updated**: November 2009

The map is credited to the National Geospatial-Intelligence Agency (NGA) and the National Center for Medical Intelligence (NCMI).

The map is part of the 2011 MHS Conference materials.
Afghanistan: Malaria Risk to U.S. Forces

- Potential attack rate 11-50% per month
- Potential attack rate 1-10% per month
- Potential attack rate <1% per month
- Rare cases (< 0.1 % per month)
- No risk

NOTE: Boundaries of the risk area should not be interpreted as strict demarcations; risk area varies with multiple ecological factors.
The Threat:

- Historically the most feared and disabling epidemic disease for deployed forces.
- 80-100% attack rates experienced by US forces in WWII in Guadalcanal and New Guinea.
- Relapsing *Plasmodium vivax* malaria emerged in US forces following Korean war.
- Chloroquine-resistant malaria afflicted US forces during Vietnam war.
<table>
<thead>
<tr>
<th>Country</th>
<th>Forces</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haiti-2010</td>
<td>US Army/Navy</td>
<td>13 Cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 Evacuations</td>
</tr>
<tr>
<td>Liberia-2003</td>
<td>US Marines ~225 for 2 Weeks</td>
<td>80 Cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44 evacuation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 Severe &amp; Complicated</td>
</tr>
<tr>
<td>Afghanistan-2002</td>
<td>US Army Rangers 725 man force</td>
<td>38 cases</td>
</tr>
<tr>
<td></td>
<td>4 months</td>
<td></td>
</tr>
<tr>
<td>Nigeria-2001</td>
<td>US Special Forces 300 for Short Term Deployment</td>
<td>7 Cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 Severe and Complicated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 Death</td>
</tr>
</tbody>
</table>
Naturally Acquired Immunity (model for preventing disease & death)

- No deaths or severe disease after 10 yr age
- > 95% of children < 5 y/o parasitemic
  - Deaths
    - Severe anemia (0-2 y/o)
    - Cerebral malaria (3-5 y/o)
- Decreased incidence, prevalence, and density of infection with age
- Mechanism: Antibodies? Cellular?
- Antigenic targets: parasite proteins expressed on surface?
Approaches to Malaria Vaccine Development

Individual antigens delivered as subunit vaccine
- Hep B SAg, Tet toxoid
  - RTS,S/AS0 (protein-based)
  - NMRC-M3V-D/Ad-PfCA (gene-based)

Many antigens delivered as whole organism
- Licensed live vaccines (polio, MMR)
  - Radiation-attenuated sporozoites
  - Genetically-attenuated sporozoites
Whole Organism Approach- Irradiated Sporozoite vaccine

- Irradiated sporozoite vaccine gives greater than 70% sterile protection when administered by mosquito bite in man.
  - Not strain specific, duration at least 9 months
- Process developed to harvest sporozoites from mosquito salivary glands to allow needle delivery
- 2010 Clinical Trial
  - Mosquito Derived Vaccine safe and well tolerated
  - Protection was substantially less than prior study (2/44)
  - Problem likely the dose, route of delivery and/or administration schedule

Sanaria, MVI/Gates Foundation, NIAID and USMMVP.
Whole Organism Approach- Attenuation of Sporozoite via Genetic Knock-out

- Parasite genetically engineered to lack two genes essential for maturation from liver stage to blood stage parasites.

- 2010 Clinical Trial at WRAIR
  - Delivery via infected mosquito bite
  - Breakthrough clinical infections
    - Not sufficiently attenuated

Seattle Biomedical, Gates Foundation, WEHI and USMMVP
RTS,S is expressed in yeast

PfCSP + Hepatitis B S Ag

Repeats T epitopes S antigen

RTS,S particles assemble during purification
A PRELIMINARY EVALUATION OF A RECOMBINANT CIRCUMSPOROZOITE PROTEIN VACCINE AGAINST PLASMODIUM FALCIPARUM MALARIA

José A. Stoute, M.D., Moncef Slaoui, Ph.D., D. Gray Hippner, M.D., Patricia Momin, Ph.D., Kent E. Kester, M.D., Pierre Desmons, Ph.D., Bruce T. Welle, Ph.D., Nathalie Garçon, Ph.D., Urszula Krycz, Ph.D., Martine Marichand, W. Ripley Ballou, M.D., and Joe D. Cohen, Ph.D., for the RTS,S Malaria Vaccine Evaluation Group

ABSTRACT

Background: The candidate vaccines against malaria are poorly immunogenic and thus have been ineffective in preventing infection. We developed a vaccine based on the circumsporozoite protein of Plasmodium falciparum that incorporates adjuvants selected to enhance the immune response.

Methods: The antigen consists of a hybrid in which the circumsporozoite protein fused to hepatitis B surface antigen (HBsAg) is expressed together with an unrelated protein. We evaluated three formulations of this antigen in an unblinded trial in 46 subjects who had never been exposed to malaria.

Results: Two of the vaccine formulations were highly immunogenic. Four subjects had adverse systemic reactions that may have resulted from the intensity of the immune response after the second dose, which led us to reduce the third dose. Twenty-two vaccinated subjects and six unvaccinated controls underwent a challenge consisting of bites from mosquitoes infected with P. falciparum. Malaria developed in all six control subjects, seven of eight subjects who received vaccine 1, and five of seven subjects who received vaccine 2. In contrast, only one of seven subjects who received vaccine 3 became infected (relative risk of infection, 0.14; 95% confidence interval, 0.02 to 0.88; P<0.005).

Conclusions: A recombinant vaccine based on fusion of the circumsporozoite protein and HBsAg plus a potent adjuvant can protect against experimental challenge with P. falciparum sporozoites. After additional studies of protective immunity and the vaccine schedule, clinical trials are indicated for this new vaccine against P. falciparum malaria. (N Engl J Med 1997;336:86-91.)

RTS,S Protects 1-4 yo Children in Mozambique

Alonso, Lancet 2005:
- Efficacy against clinical malaria 30% (CI: 8-45%)
- Efficacy against severe malaria 49% (CI: 12-71%)
Sites across Africa where RTS,S is being tested in Phase 3

Subunit approach - RTS,S Vaccine

- Licensure anticipated in ~2015 in Europe
  - Expected to be available in high endemic settings as a pediatric vaccine
  - Anticipate significant public health impact
  - Funded by MVI/Gates Foundation, EU, USAID and GSK with USMMVP support
- Efficacy insufficient for travelers’ (thus military) vaccine
- Current studies in planning to improve efficacy through combination with other immunogen in a heterologous prime-boost approach
Subunit approach - DNA Prime/Ad Boost

- DNA plasmids [Prime]
  - Encoding malaria proteins CSP and AMA1
- Adenovirus 5 (attenuated)[Boost]
  - Encoding malaria proteins CSP and AMA1

- Schedule of administration
  - 3x DNA
  - 1x Ad5
- Elicits strong cellular immunity (CD8>CD4)

Uses host cell machinery to produce the malaria proteins
Subunit approach- DNA Prime/Ad Boost

- **Clinical Results 2010- Proof of Principle**
  - 4/15 immunized volunteers sterilely protected (27%)

Day Post Challenge

- Major challenges to overcome to make this a viable product:
  - Improve protection
  - Require new Adenovirus-Malaria antigen construct
  - Regulatory requirements
  - Business complexity
Dengue Vaccines
Dengue Background

- **Dengue viruses**
  - Single-stranded RNA viruses
  - 4 *antigenically distinct serotypes*
    - (DENV-1, -2, -3 and -4)

- **Transmission primarily by peridomestic mosquito species *Aedes aegypti***
  - Daytime feeding
  - Domestic/Peridomestic habits
    - Breeds in freshwater containers
    - Thrives in urban environment
Dengue: Epidemiology

- Leading vector-borne viral disease globally
  - 2.5 billion people at risk for infection
  - Transmission in ~120 countries
    - Tropics and sub-tropics
    - *Humans are the reservoir*
  - 50 to 100 million infections annually
    - Undifferentiated Fever
    - Dengue Fever
    - Dengue Hemorrhagic Fever (DHF)/ Dengue Shock Syndrome (DSS) *secondary infections*
  - Up to 25,000 deaths annually
Global Resurgence of Dengue

- Unprecedented global population growth
- Unplanned and uncontrolled urbanization
- Numerous man-made breeding grounds (trash)
- Lack of effective mosquito vector control
- Decay in public health infrastructure
- Increased international air travel
Global distribution of dengue virus serotypes, 1970
Air Traffic Global Flight Patterns
Global distribution of dengue virus serotypes, 2004

Cases (x10^3)

- DEN-3
- DEN-2
- DEN-1
- DEN-1,2,4
- DEN-2,3
- DEN-3
- DEN-4

Cases - Rate/1000 - Laboratory-Confirmed DHF Cases

CDC

2011 MHS Conference
Dengue Risk

Worldwide: Dengue Risk to U.S. Forces
February 2010

Potential attack rate 11-50% per month
Potential attack rate 1-10% per month
Potential attack rate <1% per month
Rare cases
Sporadic cases could occur. Under some conditions, limited focal outbreaks could develop among the local population. Attack rates could approach 1 percent per month among personnel exposed to mosquito bites.

Rare cases
Sporadic cases could occur. Under some conditions, limited focal outbreaks could develop among the local population. Attack rates could approach 1 percent per month among personnel exposed to mosquito bites.

Risk present, level unknown
Dengue has not been reported. Because of proximity to known transmission areas and suitable environmental conditions, a low risk of dengue cannot be excluded.

No risk

NOTE: This map is based on analyst judgment, using epidemiologic data, remote sensed environmental data, geospatial population density data, and National Center for Medical Intelligence (NCMI) risk assessment methodology. Boundaries of risk areas are approximate, and should not be interpreted as strict demarcations.

Datum: WGS84, Coordinate System: World_Robinson

Boundary representation is not necessarily authoritative.
Dengue Impact on the U.S. Military

- Philippines
- World War II
- Vietnam
- Philippines
- Haiti
- Somalia
Dengue Outbreak: July – November 1906
~1/3 of troops infected

<table>
<thead>
<tr>
<th>Unit</th>
<th>Strength</th>
<th>No. Cases</th>
<th>% Infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>13th U.S. Infantry</td>
<td>727</td>
<td>240</td>
<td>33</td>
</tr>
<tr>
<td>16th U.S. Infantry</td>
<td>613</td>
<td>162</td>
<td>26</td>
</tr>
<tr>
<td>8th U.S. Cavalry</td>
<td>378</td>
<td>89</td>
<td>24</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1718</strong></td>
<td><strong>491</strong></td>
<td><strong>29</strong></td>
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</tbody>
</table>
Philippine Islands: 1902-1928

• Hospital admission rates
  - Decreases for all diseases
  - Consistent for dengue

• Average loss to Army of 7,715 days per year
Dengue appears after 15 June island assault
- By 11 Aug, Aedes species numerous (rainy season)
- Combat operations created numerous breeding habitats (trash, tire ruts in roads…)

**Table 12:** Daily report of new cases of dengue at height of the epidemic in Saipan, 14 September to 6 October 1944

<table>
<thead>
<tr>
<th>Date</th>
<th>Number</th>
<th>Date</th>
<th>Number</th>
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<tbody>
<tr>
<td>September</td>
<td></td>
<td>October</td>
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</tr>
<tr>
<td>14</td>
<td>393</td>
<td>1944—Continued</td>
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<tr>
<td>15</td>
<td>426</td>
<td>27</td>
<td>62</td>
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<td>294</td>
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<td>306</td>
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<td>289</td>
<td>30</td>
<td>71</td>
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<tr>
<td>19</td>
<td>275</td>
<td>October</td>
<td>44</td>
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<tr>
<td>20</td>
<td>230</td>
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<td>112</td>
<td>4</td>
<td>28</td>
</tr>
<tr>
<td>24</td>
<td>93</td>
<td>5</td>
<td>32</td>
</tr>
<tr>
<td>25</td>
<td>81</td>
<td>6</td>
<td>23</td>
</tr>
</tbody>
</table>

1 Cases include Army, Navy, and Marine Corps personnel.
Recent Experience

- **1966 - Long Binh, Vietnam**
  - 110 Cases of FUO at 93rd Evacuation Hospital
  - **28%** were determined to be dengue by viral isolation or serology

- **1992 - Operation Restore Hope, Somalia**
  - 129 hospitalized with FUO
  - **60%** were determined to be dengue by viral isolation or serology

- **1997 - Haiti**
  - 103 hospitalized with FUO
  - **29%** were determined to be dengue by viral isolation or serology
Dengue

- Currently no U.S. FDA approved vaccine or pharmaceutical to protect or treat the Warfighter

- Current standard of care:
  - Supportive care
    - Careful fluid management and other supportive measures (10-14 LDD per episode)
  - Prevention
    - Effective vector control proven very difficult (requires sustained usage of products)
    - Personal Protective Measures (PPM) (repellents, bed nets, treated uniforms) difficult to sustain
Dengue and the US Military

- Mission-stopping disease threat to U.S. forces deployed throughout the tropics/sub-tropics
- #2 on US Military Infectious Disease Threat list
Target Product Profile

- **Safety**
  - Well tolerated injection
  - Does not cause dengue
  - Does not risk of disease severe disease with secondary infection

- **Efficacy**
  - Vaccine Efficacy ≥ 80%
  - Durable immune response (>2 years)
  - 1-3 doses
Challenges in Dengue Vaccine Development

- Multiple (4) serotypes (4 vaccines in one)
  - Each capable of producing DF and DHF
  - Disease enhancement: Risk of DHF enhanced by pre-existing immune response to another serotype
- Lack of an animal model of disease
- Unknown Surrogate marker of protection
- Incomplete understanding of pathophysiology
Sanofi pasteur/Acambis-Chimerivax®
WRAIR/GSK DTV LAV
NIH/JHU - Δ30 mut
NMRC - DNA
Merck – r80E
WRAIR/GSK - PIV
CDC/Inviragen –
DEN/DEN chimeric/Tetra
GenVec –
Adenovectored DNA
Carolina Vaccine
Inst/Global Vaccines –
VEE dengue replicon
VaxInnate –DENV TLR5 Ligand (Flagellin)
Tetravalent Dengue Virus (TDV) Vaccine – Landscape

– Chimerivax®
  • Chimeric of yellow fever vaccine backbone with Dengue membrane proteins
  • Safe, well tolerated and immunogenic in clinical studies
  • Dosing schedule: 0, 6, 12-month
  • Starting Phase 3 clinical trials FY11
    – AFRIMS
      » Thailand, Philippines
  • Uncertain whether dosing schedule or level of efficacy will meet DoD needs
Virology Field Site Kamphaeng Phet Province

Pivotal Trials Conducted by MRMC/Thai MoPH

Japanese encephalitis Virus (JE-VAX®) 1980’s
- Biken

Hepatitis A Vaccine (Havrix) 1990’s
- GSK

Dengue vaccine (Chimerivax) (2011)
- Sanofi Pasteur
Tetravalent Dengue Virus (TDV)
Vaccine - Landscape

- Live attenuated vaccine (LAV)
  • Viruses (classically) attenuated through serial passage in non-human cell line
  • Tetravalent formulation required balancing
  • 2 doses : 0, 6 months
  • 100% protection in animal models
  • Safe and immunogenic in human trials
    - Phase 2 study Puerto Rico
      » 700 subjects
      » 2-50y
      » Safe and immunogenic
    - Phase 3
Tetravalent Dengue Virus (TDV) Vaccine - Landscape

- Purified inactivated virus (PIV)
  - Formalin inactivated, purified virus
  - Combined with adjuvants
    - Alum adjuvant
    - Novel adjuvants (GSK)
  - 100% protection in animal models
  - Shorter administration schedule
  - Phase 1 clinical trials begin in FY11
– DNA Vaccine
  • DENV DNA vaccine – closed circular double-stranded plasmid DNA
  • Full length genes encoding membrane proteins for DENV
  • Initial Phase 1 clinical study with DENV-1 DNA vaccine safe and immunogenic
  • TDV DNA Phase 1 clinical trial planned in 2011/12
Heterologous Prime Boost Strategy

- Assess sequentially delivered combinations of different immunogens
  - Increase and broaden immune response
  - Shorten time to development of protective response
- Live attenuated (replicating) immunogen combined with non-replicating
  - PIV
  - DNA

- More complex business development
- More complex logistics
- Suitable for DoD
Vaccines Against Bacterial Diarrhea and Dysentery

- Prevention of Diarrheal Diseases
  - Develop effective vaccines and other countermeasures against leading causes of infectious diarrhea and dysentery in deployed U.S. military personnel
  - Major research and development thrusts
    - Enterotoxigenic *Escherichia coli* (ETEC) vaccines
    - *Shigella* vaccines
    - *Campylobacter jejuni* vaccines
### Vaccines Against Bacterial Diarrhea and Dysentery - Burden

- **Cumulative deployments and diarrhea/dysentery burden OEF/OIF ’01-’07**
  - # of deployments (mean 183 d) 2,134,578
  - # of deployments (mean 19 d) 145,871
  - Cases of diarrhea 3,857,002
  - Diarrhea days 11,478,270
  - Visits to medical 850,444
  - Hospitalizations 17,356
  - Duty days lost 1,114,208

*Data provided by AFHSC; Riddle et al Vaccine, 2008*
Vaccines Against Bacterial Diarrhea and Dysentery - Prevalence

- Other/no pathogen: 31%
- Rotavirus: 4%
- Salmonella: 5%
- *Shigella*: 7%
- Norovirus: 8%
- *ETEC*: 22%
- EAEC: 13%

Latin America:
- 38%: 6%
- 29%: 6%
- 12%: 9%
- 25%: 3%

Middle East:
- 37%: 2%
- 28%: 7%
- 17%: 1%

Southeast Asia:
- 23%: 3%
- 13%: 11%
- 12%: 4%

# Vaccines Against Bacterial Diarrhea and Dysentery

<table>
<thead>
<tr>
<th>Developer</th>
<th>Type</th>
<th>Clinical Phase I</th>
<th>Clinical Phase II</th>
<th>Clinical Phase III</th>
<th>Comments</th>
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<tbody>
<tr>
<td>ACE BioScience</td>
<td>Subunit (ACE393)</td>
<td></td>
<td>×</td>
<td>×</td>
<td>Failed to show protection</td>
</tr>
<tr>
<td>Intercell USA</td>
<td>LT, TCI (skin patch)</td>
<td></td>
<td>×</td>
<td>×</td>
<td>Failed to show protection</td>
</tr>
<tr>
<td>TD Vaccines</td>
<td>LA (ACE527)</td>
<td></td>
<td>×</td>
<td></td>
<td>Failed to show protection</td>
</tr>
<tr>
<td>NICHD</td>
<td>PS conjugate</td>
<td>×</td>
<td></td>
<td></td>
<td>S. sonnei vaccine efficacious (Cohen ‘97); No pharm partner</td>
</tr>
<tr>
<td>Glycovaxyn</td>
<td>Bioconjugate, Sd1</td>
<td>×</td>
<td></td>
<td></td>
<td>FIH Trial started Feb 2010</td>
</tr>
<tr>
<td>Institut Pasteur</td>
<td>LA (SC599), Sd1</td>
<td></td>
<td></td>
<td></td>
<td>Safe, modest immunogenicity</td>
</tr>
<tr>
<td>Univ MD CVD</td>
<td>LA (CVD1208S), Sf2a</td>
<td>×</td>
<td></td>
<td></td>
<td>Currently on FDA clinical hold</td>
</tr>
<tr>
<td>PATH/EVI</td>
<td>Killed whole cell, Sf2a</td>
<td>×</td>
<td></td>
<td></td>
<td>Phase 1 trial projected to start in FY11 under EVI</td>
</tr>
</tbody>
</table>
Vaccines Against Bacterial Diarrhea and Dysentery - ETEC

- At risk populations
  - Military / Civilian travelers
    - Leading cause of travelers’ diarrhea
  - Endemically exposed individuals
    - 500K deaths annually in young children
  - Major disease in young farm animals (calves, piglets)
    - Characterized by different colonization factors

Vaccines Against Bacterial Diarrhea and Dysentery - ETEC

- Live, attenuated vaccines
- Killed whole-cell vaccine
- Subunit vaccines
- LT toxoid ± colonization factors [fimbriae]

Clear, clinical proof has yet to accrue for any ETEC vaccine
Vaccines Against Bacterial Diarrhea and Dysentery - ETEC

- Adhesin-based vaccine
  - Tip-localized adhesin ascribed role in intestinal binding
  - Adhesins exhibit greater antigenic conservation than major pilus-forming subunit
  - Recombinant adhesin variants developed, which are
    - Stabilized in native conformation
    - Highly immunogenic when given by mucosal and skin vaccination with adjuvant
    - Prototype adhesin (dscCfaE) proven as protective antigen
Vaccines Against Bacterial Diarrhea and Dysentery - ETEC

- ETEC:

  - Whole-cell ETEC
  - CFA/I Fimbria
  - dscCfaE Adhesin
Vaccines Against Bacterial Diarrhea and Dysentery - ETEC

- NHP Model: Proof of efficacy for ETEC adhesin-based vaccine
  - Nonhuman primate ETEC diarrhea model established in *A. nancy maae* that mimics human disease
    - Challenge models established with CFA/-ETEC type strain
    - Intranasal vaccination with dscCfaE alone or with LTB (CTB) elicits significant protection
    - Result: 83% protective efficacy using dscCfaE with LTB
Vaccines Against Bacterial Diarrhea and Dysentery – ETEC

- Oral, passive protection with bovine milk IgG
  - Vaccinate pregnant cows with dscCfaE to get hyperimmune colostrum
  - Isolate hyperimmune bovine IgG (BlgG)
  - Two days before challenge take 3 oral doses/day BlgG at meals
  - Challenge with ETEC (homologous strain 1 x 10^9 cfu)
  - 10 human subjects, ----7 fully protected, 2 with mild diarrhea, 1 with moderate diarrhea, 0 with severe
  - 11 placebo subjects, ---- 9 with diarrhea, (6 severe, 1 moderate, 2 mild)
Vaccines Against Bacterial Diarrhea and Dysentery - ETEC

- A first-in-human Phase 1 clinical trial of the prototype ETEC adhesin (dscCfaE)
  - scheduled to begin in 2011,
    - active, skin patch vaccination
    - Challenge
- The adhesin-based vaccine IP has been licensed to sanofi pasteur (sp) vaccines
  - expanded preclinical evaluation of the components of a pentavalent adhesin-based ETEC vaccine
- US Army, NMRC, sanofi pasteur, PATH (nonprofit)
Vaccines Against Bacterial Diarrhea and Dysentery - *Shigella*

- **Shigellosis / Dysentery**
  - Person-to-person, foodborne (food, water)
  - Inoculum size --- 10-200 organisms
  - Serotype diversity --- >50 different serotypes (LPS)
  - Pathogenesis --- invasion, spread, inflammatory response with cytotoxicity
  - Clinical syndrome --- dysentery
Vaccines Against Bacterial Diarrhea and Dysentery – *Shigella*

**shigellae** → Columnar epithelial cell; Large intestine

IpaB, C → M cell

Macrophage → Apical

IL-8 → Basolateral

Vaccines

Against

Bacterial Diarrhea and Dysentery – *Shigella*

IL-8

Macrophage apoptosis

PMN vacuole lysis

Intercellular spread

VirG

IpaB, C

Live-attenuated: Mutate “VirG” and do not get further spread of infection
Shigella vaccine strategies

- Live, attenuated Shigella vaccines (LASV)
  - Virulence-based mutations (virG) in Shigella (WRSS1) and further mutate toxins and immunomodulators (shET and msb) for less reactogenicity to create second generation vaccines (WRSs2 and WRSs3)
- Recombinant
  - Invasion plasmid antigen (Ipa) proteins of Type Three Secretion System (TTSS) cloned, expressed and purified and added to Shigella LPS to create the “Invaplex” vaccine
Live attenuated *Shigella* vaccines
- WRSS1 given to more than 100 volunteers, found to be safe and highly immunogenic but some side effects
- WRSs2 and WRSs3 in phase 1 clinical trial to be conducted in April, FY11
- To determine safety and immunogenicity
- US Army, NIH funded
**Vaccines Against Bacterial Diarrhea and Dysentery - Shigella**

- Recombinant *Shigella* “Invaplex” vaccine
  - Cloned and purified proteins from the Type Three Secretion System (TTSS) mixed with *Shigella* LPS
  - Produces protective immune response in mice and guinea pig
  - Phase 1 clinical trial scheduled for FY13
  - US Army, sanofi pasteur

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*Injectisome extending from Shigella*  
*Injectisome*  
*Injectisome graphic*
Campylobacter jejuni

- Transmission: Foodborne
- Inoculum size: low (> 5 x10^2 orgs)
- Reservoirs: animals (poultry)
- Serotype diversity: 48 Penner serotypes
- Pathogenic process: adherence, invasion, inflammatory response
- Clinical syndrome: acute inflammatory response
- Sequelae: reactive arthritis, Guillain-Barre, irritable bowel syndrome
Vaccines Against Bacterial Diarrhea and Dysentery - *Campylobacter*

- *C. jejuni* polysaccharide capsules (CPS) first identified by genomics
- Major determinant of Penner serotype
- Proven *C. jejuni* virulence factor
- Polysaccharide antigens have required protein conjugation to be efficiently immunogenic as vaccines
  - Pneumococcus (Prevnar) *H. influenzae* B (HiB)
- Conjugate by reductive amination to CRM197 protein to elicit T-cell dependent response
Vaccines Against Bacterial Diarrhea and Dysentery - *Campylobacter*

- NHP model to prove efficacy for *C. jejuni* CPS-CRM197 conjugate vaccine
  - *C. jejuni* diarrhea model established in *Aotus nancymaae* that mimics human disease
  - SC vaccination with CPS81-76-CRM197 conjugate + alum
  - 100% protection from homologous (same serotype) challenge
- IND submission in FY11 for capsule-conjugate vaccine, phase 1 clinical trial beginning of FY13
Challenges

- ETEC, *Shigella* and *Campylobacter* all have numerous serotypes
- Each vaccine will have to be multivalent to cover relevant serotypes and to afford broad protection
- The “Ideal” Diarrhea Vaccine will be multivalent, multi-pathogen
Summary

- Malaria
- Dengue
- Bacterial Diarrheal pathogens
- Challenges
  - Technical
  - Business
  - Cost
  - Time
Asia: Dengue Risk to U.S. Forces

February 2010

INDIAN OCEAN

Bay of Bengal

INDIA

PAKISTAN

NEPAL

BHUTAN

INDIAN OCEAN

SRI LANKA

MALAYSIA

MALARIA

THAILAND

VIETNAM

PHILIPPINES

SOUTH KOREA

NORTH KOREA

JAPAN

NOTE: This map is based on analyst judgment, using epidemiologic data, remote sensed environmental data, geospatial population density data, and National Center for Medical Intelligence (NCMI) risk assessment methodology. Boundaries of risk areas are approximate, and should not be interpreted as strict demarcations.

Potential attack rate 11-50% per month
Potential attack rate 1-10% per month
Potential attack rate < 1% per month
Rare cases
No risk

Dengue has not been reported. Because of proximity to known transmission areas and suitable environmental conditions, a low risk of dengue cannot be excluded.

Datum: WGS84, Coordinate System: Geographic
Middle East: Dengue Risk to U.S. Forces
February 2010

Potential attack rate 1-10% per month
Potential attack rate <1% per month
Sporadic cases could occur. Under some conditions, limited focal outbreaks could develop among the local population. Attack rates could approach 1 percent per month among personnel exposed to mosquito bites.

NOTE: This map is based on analyst judgment using epidemiologic data, remote sensed environmental data, geospatial population density data, and National Center for Medical Intelligence (NCMI) risk assessment methodology. Boundaries of risk areas are approximate, and should not be interpreted as strict demarcations.

Boundary representation is not necessarily authoritative.
South America: Dengue Risk to U.S. Forces
February 2010

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Dengue Vaccinologist