

2011 Military Health System Conference

Military Infectious Diseases Update on Vaccine Development

The Quadruple Aim: Working Together, Achieving Success

COL Julia Lynch, MD

24 January, 2011



Medical Research and Materiel
Command

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Military Infectious Diseases Research Program (MIDRP)



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



WRAIR/NMRC



Military Infectious Diseases Research Program (MIDRP)



Prevention



Infectious diseases adversely impact military operations. Vaccines are the long-term solution.

Treatment



New drugs are continually required to overcome evolving drug resistance.

Diagnostics



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

Insect Vector Control



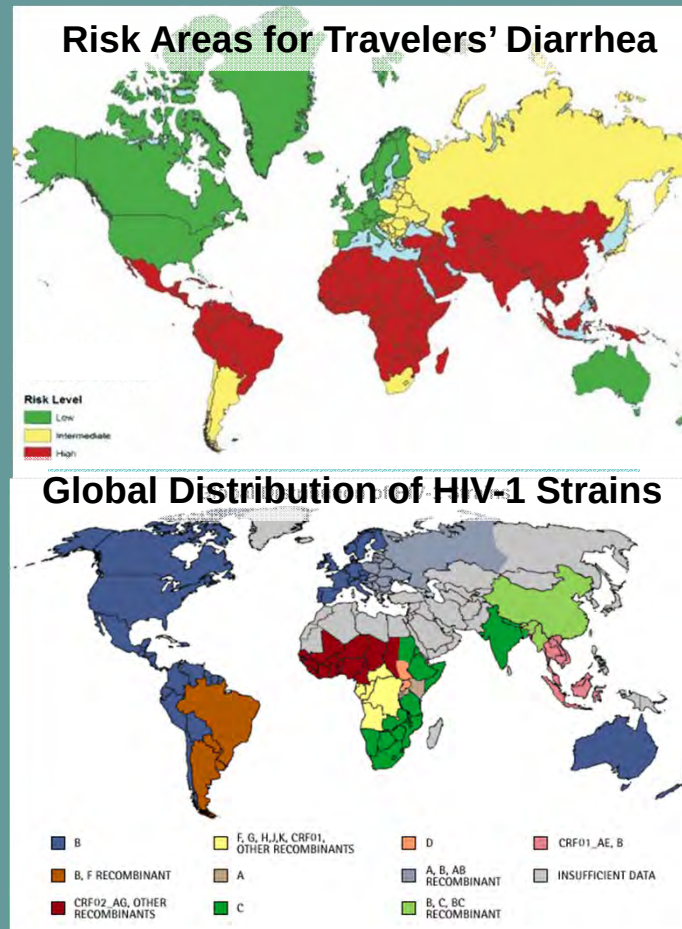
Most militarily relevant infectious diseases are transmitted by biting insects and other arthropods.

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



Military Cost...

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



US Military Infectious Disease Products

Research Effort		Advanced Development	Fielded Products
Antiparasitic Drugs	Malaria	Intravenous Artesunate Tafenoquine	Atovaquone/Proguanil (Malarone, 2000) Doxycycline (Vibramycin®, 1992) Halofantrine (Halfan®, 1992) Mefloquine (Lariam®, 1989) Sulfadoxine-Pyrimethamine (1983) Chloroquine-Primaquine Tablets (1969) Primaquine (1952) Chloroquine (1949)
	Leishmaniasis	Pentostam Topical drug	
Vaccines	Malaria Diarrhea Dengue Hemorrhagic fevers Scrub Typhus Meningitis HIV	New Adenovirus Dengue Tetravalent HIV	Japanese Encephalitis - cell based (2009) Hepatitis A (1995) Japanese Encephalitis (1992) Oral Live Typhoid Ty21A (1989) Hepatitis B (1981) Meningococcus (A, C, Y, W-135) (1981) Adenovirus 4 & 7 (1980) (2011)
Protectants	Repellents Sand fly control Insect identification	Combined Camouflage Face Paint	Walter Reed Biosystematics Unit (2004) West Nile Virus Diagnostic Kit (2001) Scrub Typhus Diagnostic Kit (1998) Malaria Diagnostic Kit (1996) DEET-based Insect Repellent (1946)
Diagnostics	Laboratory-based assays Point-of-care devices	Leishmania PCR Leishmania Skin Test	Malaria Rapid Diagnostic Test (2007)



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

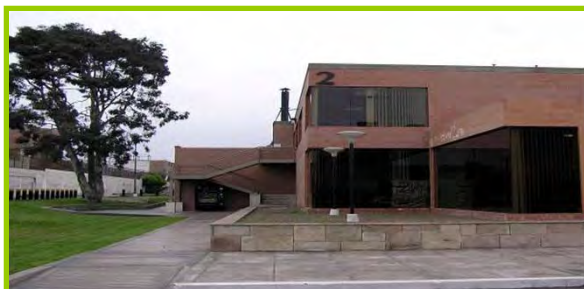
Critical Resource in Global Research



USAMRIID, Fort Detrick

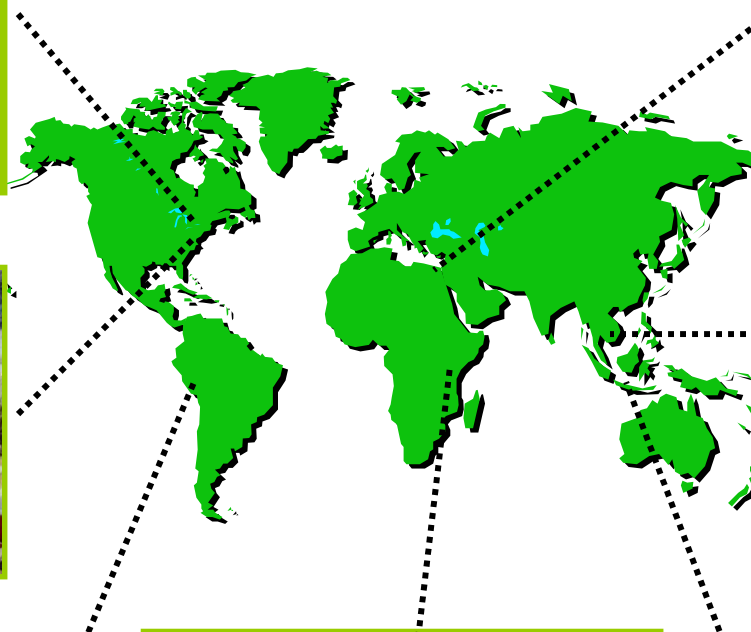


WRAIR/NMRC, Silver Spring



NMRC-D, Lima

2011 MHS Conference



NAMRU-3, Cairo



AFRIMS, Bangkok



USAMRU-K, Nairobi



NAMRU-2, Jakarta

Other Assets



Accredited Lab Animal Facilities



Pilot Vaccine Production Facility



Biosafety Level 4 Containment



Clinical Trials Units

HIGH Research Quality

WEB OF SCIENCE Malaria Vaccine Research



26% of top 100 authors are Army and Navy Investigators

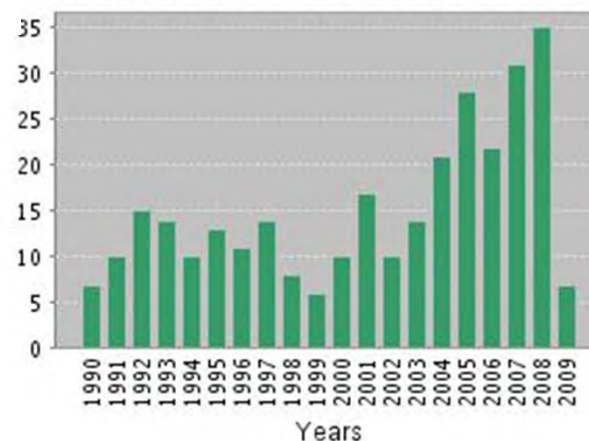
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Authors Sort these by:

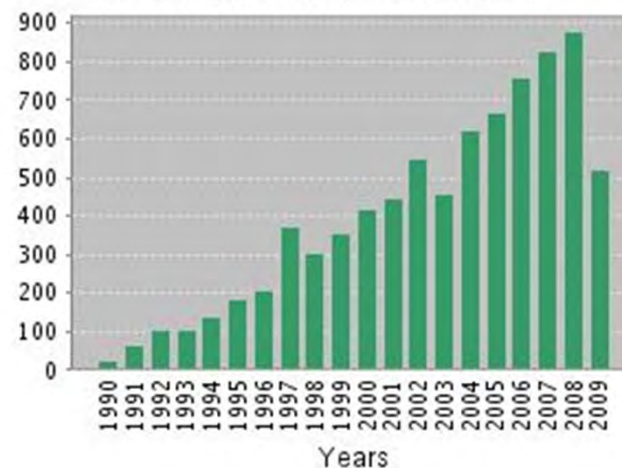
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☐ MARSH, K (38)	☐ GENTON, B (24)	☐ NARDIN, EH (20)	☒ RICHIE, TL (17)
☐ NUSSENZWEIG, RS (36)	☐ HVIID, L (24)	☐ SOARES, IS (20)	☒ SATTABONGKOT, J (17)

Published Items in Each Year



Citations in Each Year



Vaccine Development Update

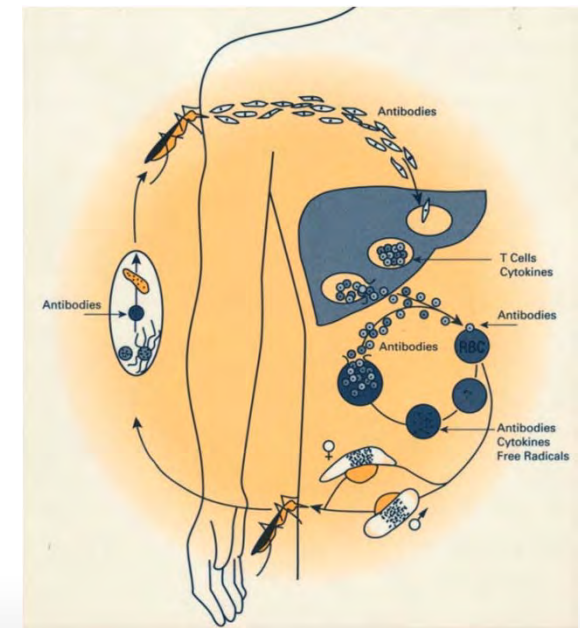


- Malaria
- Dengue
- Bacterial Diarrheal Pathogens
 - ETEC
 - Shigella
 - Campylobacter
- Top 3 Infectious Disease Threats
 - April 2010 ID Threat Prioritization Panel

A little about Malaria



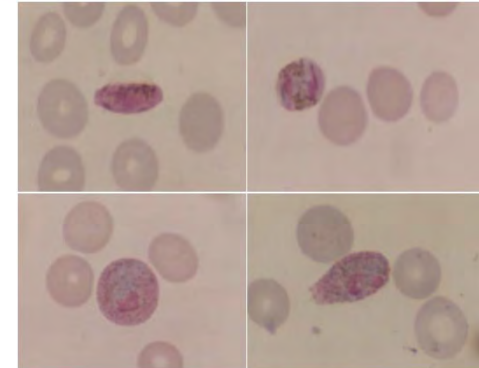
- Four Major Human Species: *Plasmodium falciparum* , *Plasmodium vivax*, *Plasmodium malariae* and *Plasmodium ovale*.
- Sporozoite stage injected in bite of female *Anopheles* mosquito, invades liver, matures/multiplies producing blood stages that invade host erythrocytes to cause disease, further 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



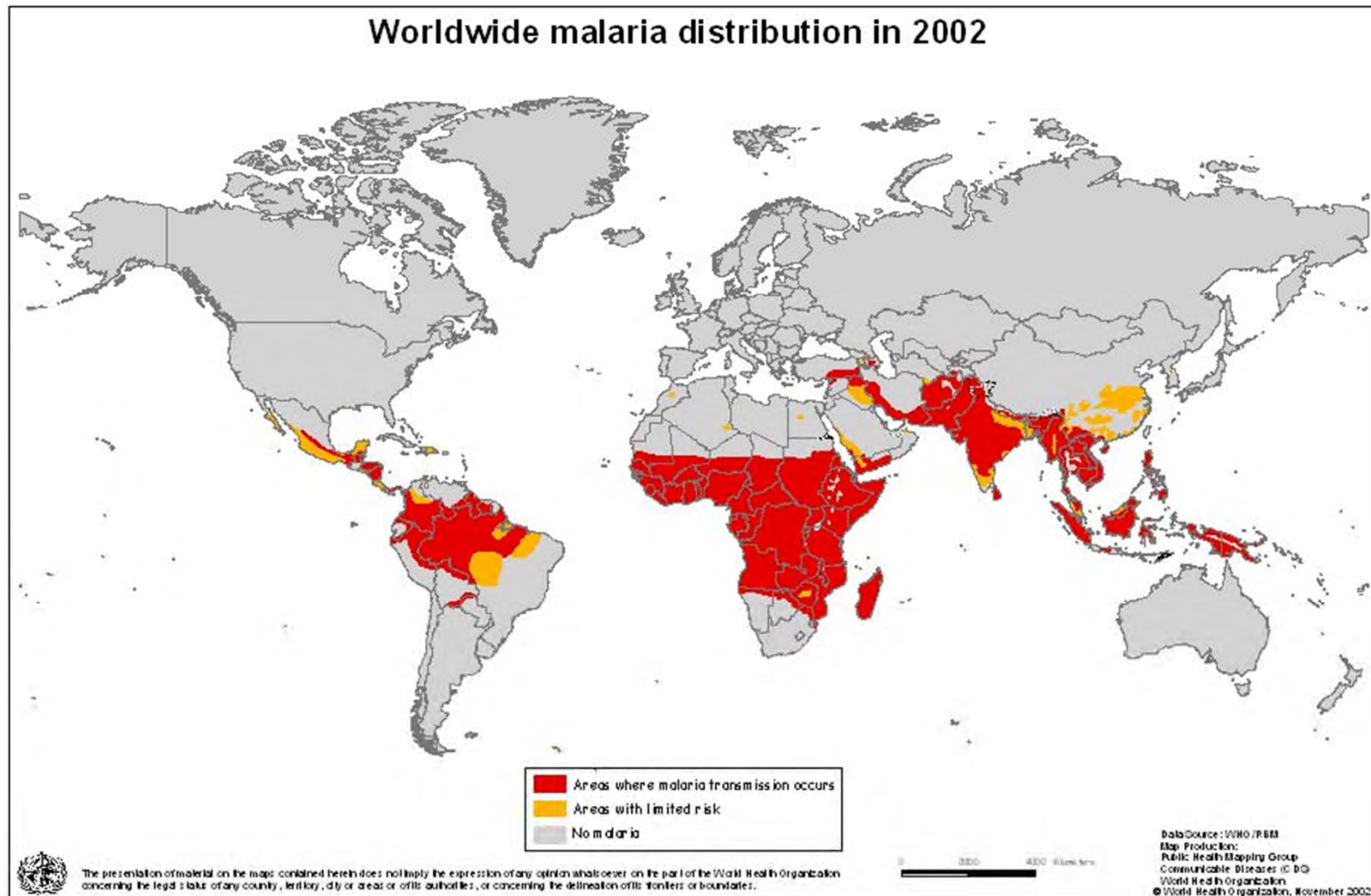
Burden of Malaria for Endemic Countries



- | **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

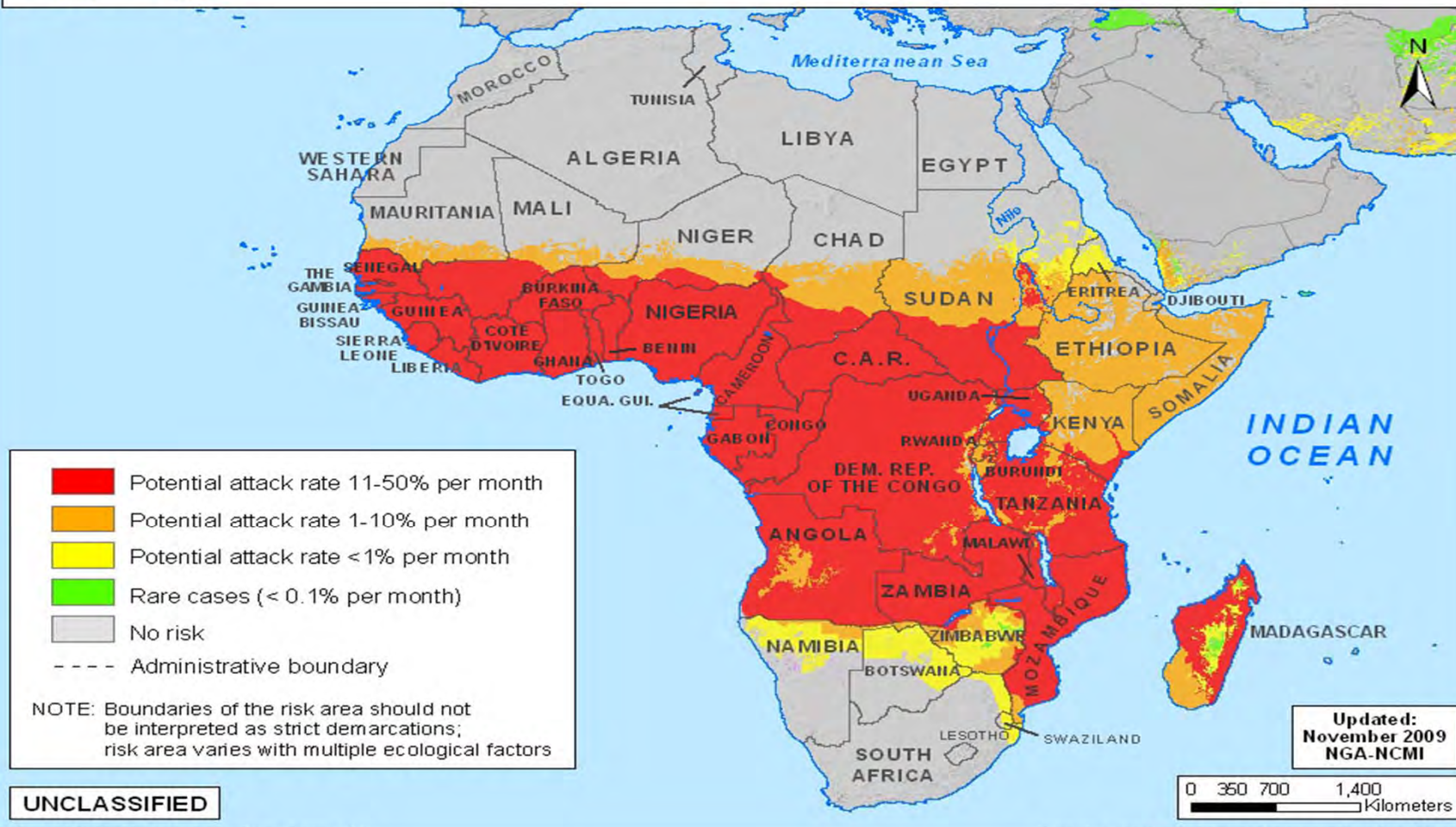


Malaria Risk Map



Africa: Malaria Risk to U.S. Forces

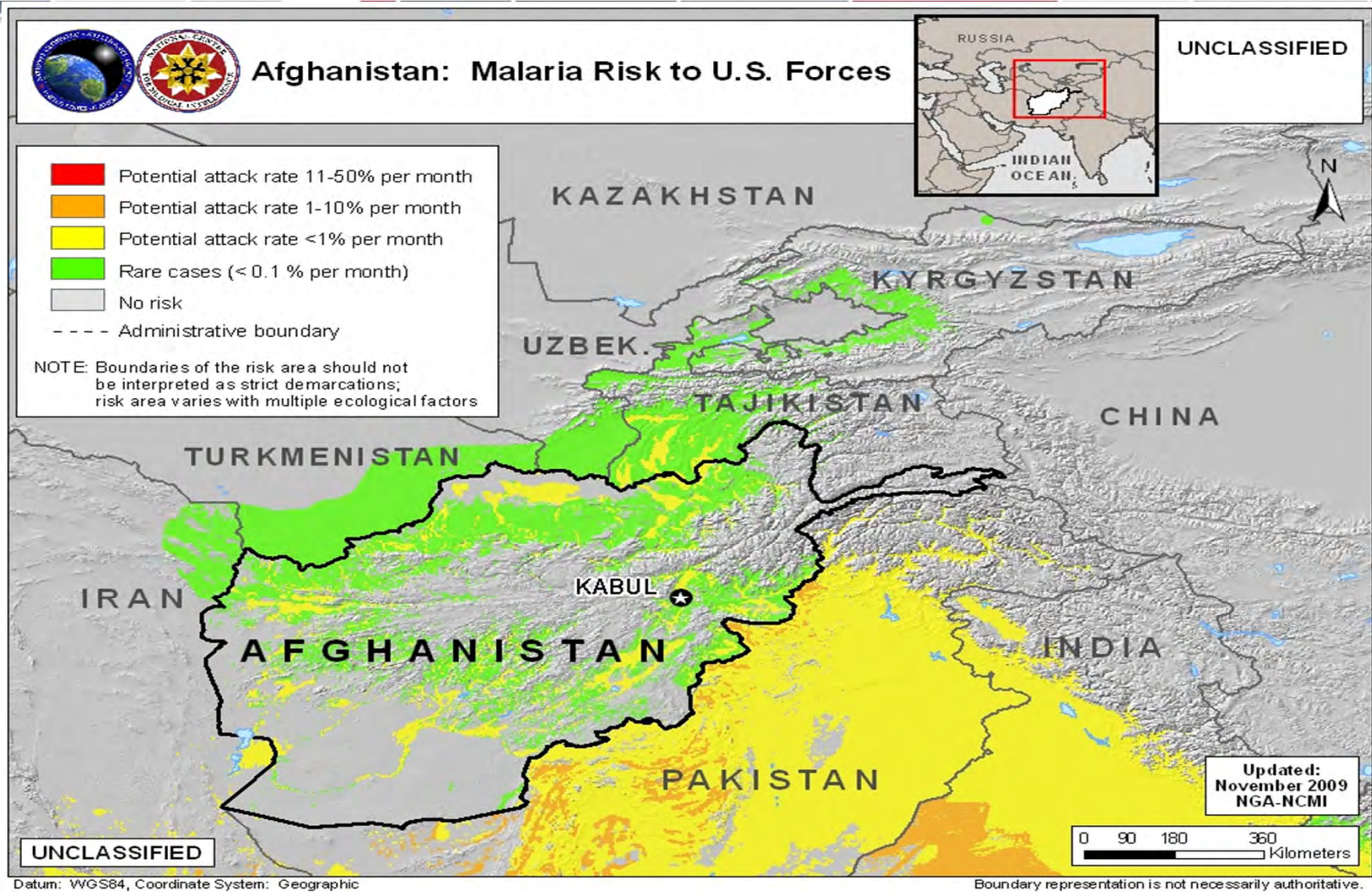
UNCLASSIFIED



Datum: WGS84, Coordinate System: Geographic

Boundary representation is not necessarily authoritative.

Malaria Risk Map



The Threat:



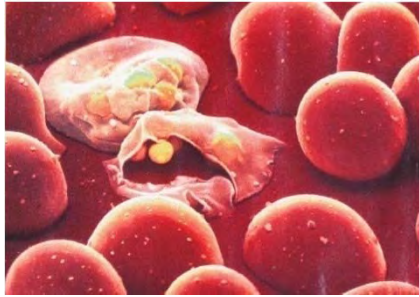
- Historically the most feared and disabling epidemic disease for deployed forces.
- 80-100% attack rates experienced by US forces in WWII in Guadalcanal and New Guinea.
- Relapsing *Plasmodium vivax* malaria emerged in US forces following Korean war.
- Chloroquine-resistant malaria afflicted US forces during Vietnam war.

History of Recent Military Deployments

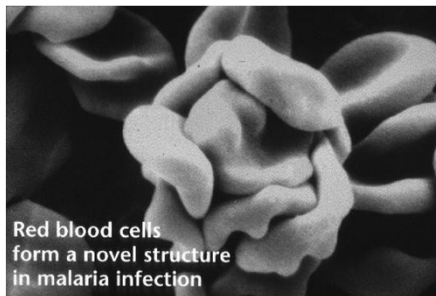


Country	Forces	Outcomes
Haiti-2010	US Army/Navy	13 Cases 6 Evacuations
Liberia-2003	US Marines ~225 for 2 Weeks	80 Cases 44 evacuation 4 Severe & Complicated
Afghanistan-2002	US Army Rangers 725 man force 4 months	38 cases
Nigeria-2001	US Special Forces 300 for Short Term Deployment	7 Cases 2 Severe and Complicated 1 Death

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

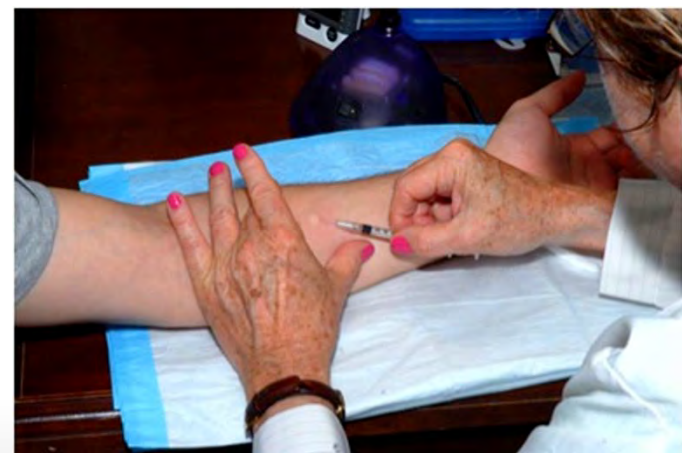
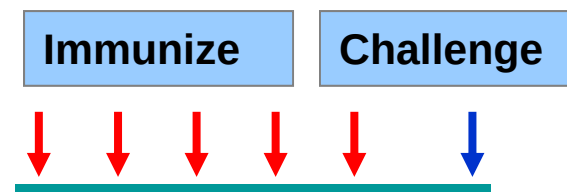
- Licensed live vaccines (polio, MMR)
- **Radiation-attenuated sporozoites**
- **Genetically-attenuated sporozoites**

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.



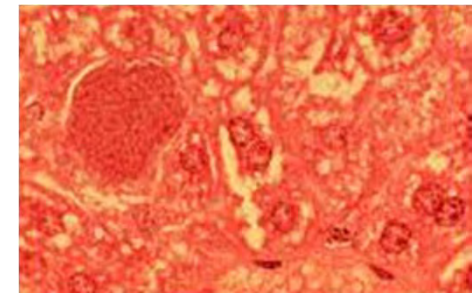
Whole Organism Approach- Attenuation of Sporozoite via Genetic Knock-out



- 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

Subunit approach- RTS,S Vaccine



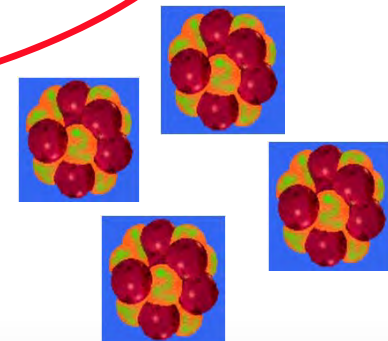
RTS,S is expressed
In yeast

PfCSP + Hepatitis B S Ag

Repeats **T** epitopes **S** antigen



RTS,S particles assemble
during purification



Subunit approach- RTS,S Vaccine



6/7 subjects receiving
RTS,S/AS02B were
completely protected

The New England Journal of Medicine
Established in 1812 as THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY
VOLUME 336 JANUARY 9, 1997 NUMBER 2

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A PRELIMINARY EVALUATION OF A RECOMBINANT CIRCUMSPOROZOITE PROTEIN VACCINE AGAINST *PLASMODIUM FALCIPARUM* MALARIA

JOSÉ A. STOUTE, M.D., MONCEF SLAQUI, PH.D., D. GRAY HEPPNER, M.D., PATRICIA MOMIN, PH.D., KENT E. KESTER, M.D., PIERRE DESMONS, PH.D., BRUCE T. WELDE, PH.D., NATHALIE GARÇON, PH.D., URSZULA KRZYCH, PH.D., MARTINE MARCHAND, 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 unfused HBsAg. 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 unimmunized 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 percent 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 vaccination schedule, field trials are indicated for this new vaccine against *P. falciparum* malaria. (N Engl J Med 1997;336:86-91.)

that inhibit the invasion of hepatocytes by sporozoites and induce cellular responses that kill sporozoite-infected liver cells.² Complete immunity against infection rarely develops from natural exposure, but immunization with radiation-attenuated sporozoites affords full protection.³ This vaccine strategy is not practical, since it requires repeated exposure to hundreds of infected, irradiated mosquitoes over a period of 6 to 10 months, and sporozoites cannot be cultured in vitro. Nonetheless, these findings revealed a critical role for the circumsporozoite protein in the development of immunity against sporozoite challenge and led to its development as a candidate vaccine.^{4,5} In clinical trials, however, the circumsporozoite protein is poorly immunogenic, and few subjects have been protected.⁶ To address these issues, we created a hybrid in which the circumsporozoite protein fused to hepatitis B surface antigen (HBsAg) was expressed together with unfused HBsAg. The resulting hybrid was significantly more potent than previous circumsporozoite-protein formulations.⁷ We hypothesized that more potent adjuvants could improve the efficacy of the vaccine. We therefore conducted a clinical trial to determine the safety and efficacy of three formulations of circumsporozoite-protein vaccines against *P. falciparum*.

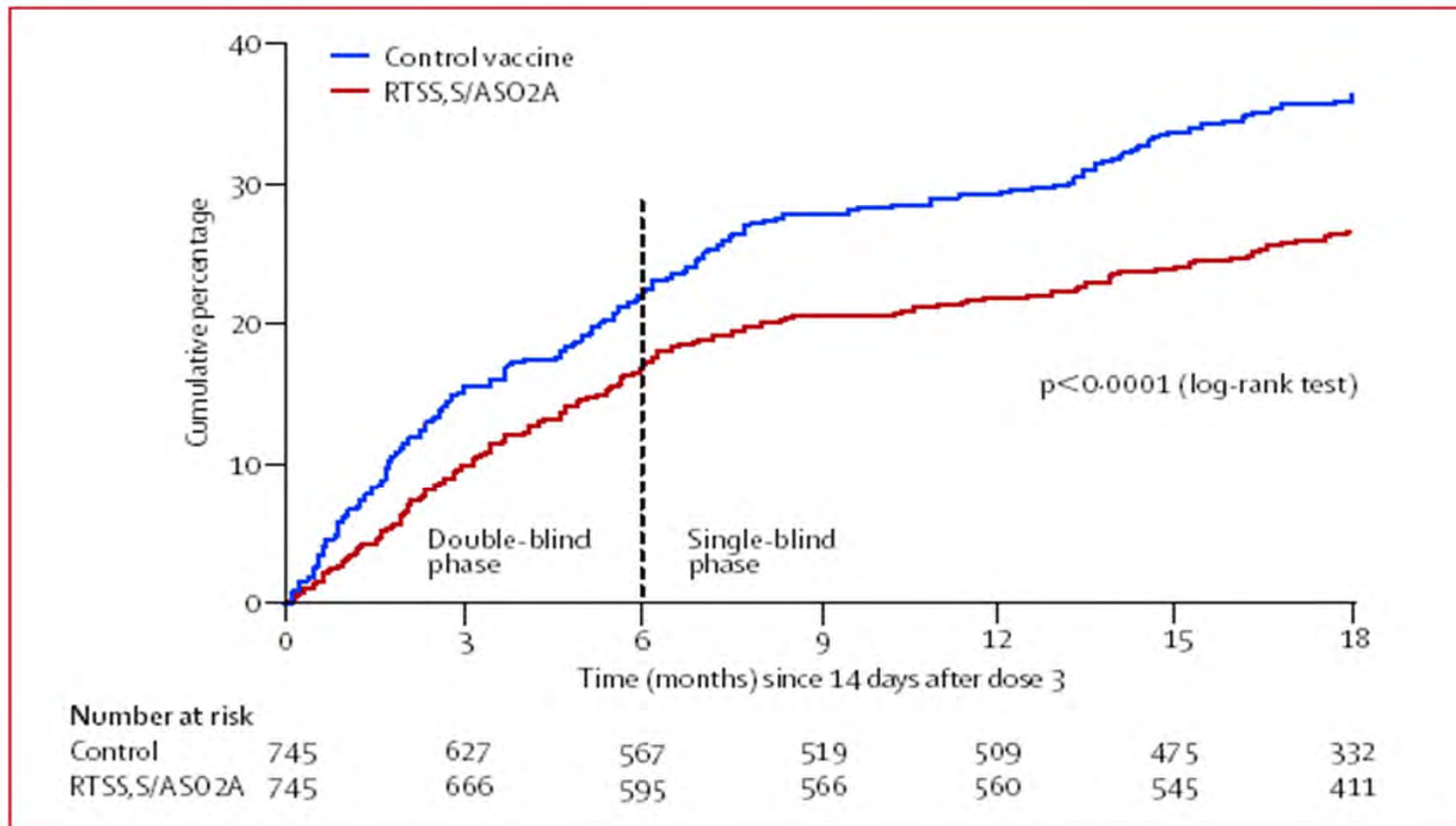
METHODS

Subjects

Forty-six subjects who had not been exposed to malaria (age, 18 to 45 years) were recruited by noncoercive means under a protocol approved by an institutional review board. Potential risks associated with participation in the study, including those associ-

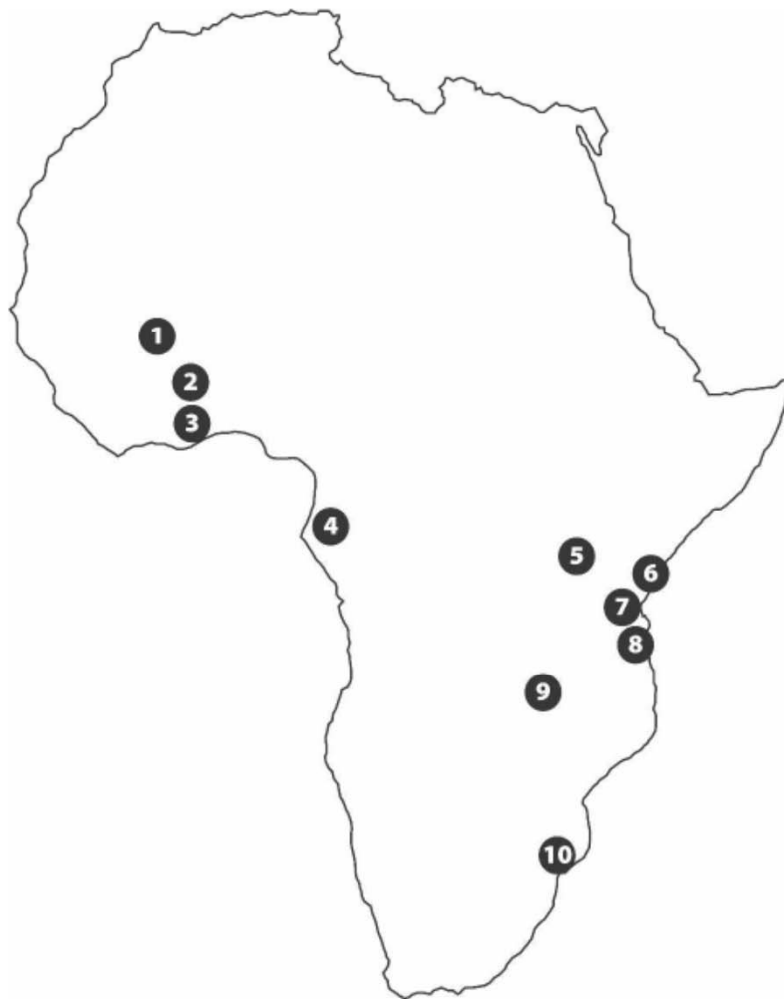
Stoute JA et al. *N Engl J Med* 1997; 336(2):86-91

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%)

Subunit approach- RTS,S Vaccine



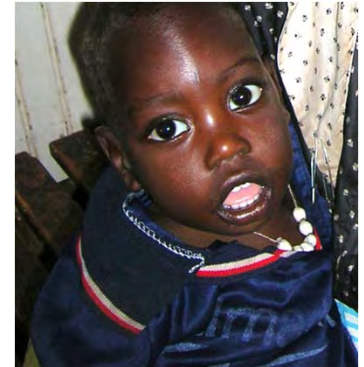
Sites across Africa where RTS,S is being tested in Phase 3

FIGURE 1. 1, Institut de Recherche en Science de la Santé, Nanoro, Burkina Faso. 2, Kintampo Health Research Center (KHRC), Kintampo, Ghana. 3, Kumasi Center for Collaborative Research (KCCR)/School of Medical Sciences (SMS), Kumasi, Ghana. 4, Albert Schweitzer Hospital, Medical Research Unit Lambaréné, Gabon. 5, Kenya Medical Research Institute (KEMRI), Kisumu, Kenya. 6, KEMRI Wellcome Collaborative Research Program, Kilifi, Kenya. 7, Joint Malaria Program (JMP) Korogwe, Tanzania. 8, Ifakara Health Research and Development Center (IHRDC), Bagamoyo, Tanzania. 9, University of North Carolina Project, Lilongwe, Malawi. 10, Centro de Investigação em Saúde da Manhica, Mozambique.

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

*Uses host cell
machinery to
produce the
malaria proteins*

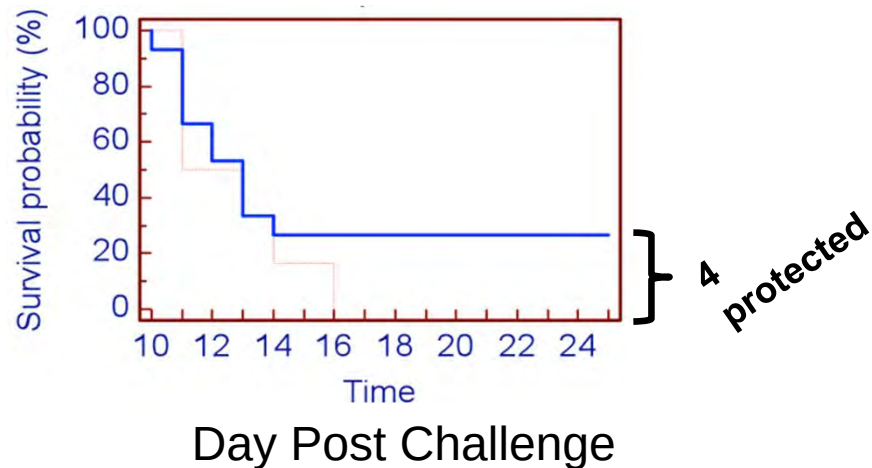
- Schedule of administration
 - 3x DNA
 - 1x Ad5
- Elicits strong cellular immunity (CD8>CD4)

Subunit approach- DNA Prime/Ad Boost



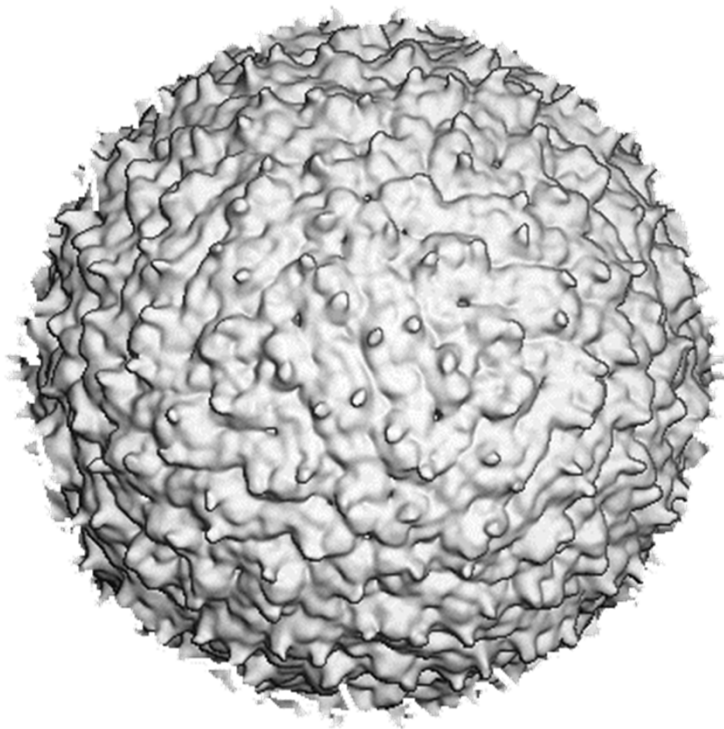
■ Clinical Results 2010- Proof of Principle

- 4/15 immunized volunteers sterilely protected (27%)

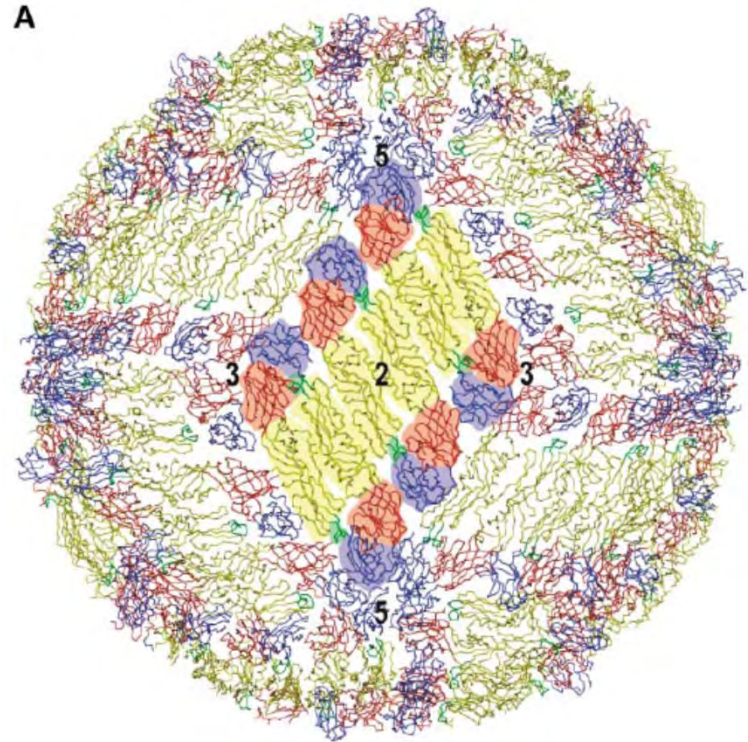


- Major challenges to overcome to make this a viable product:
 - Improve protection
 - Require new Adenovirus-Malaria antigen construct
 - Regulatory requirements
 - Business complexity

Dengue Vaccines



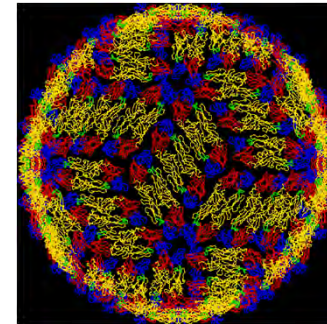
A



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

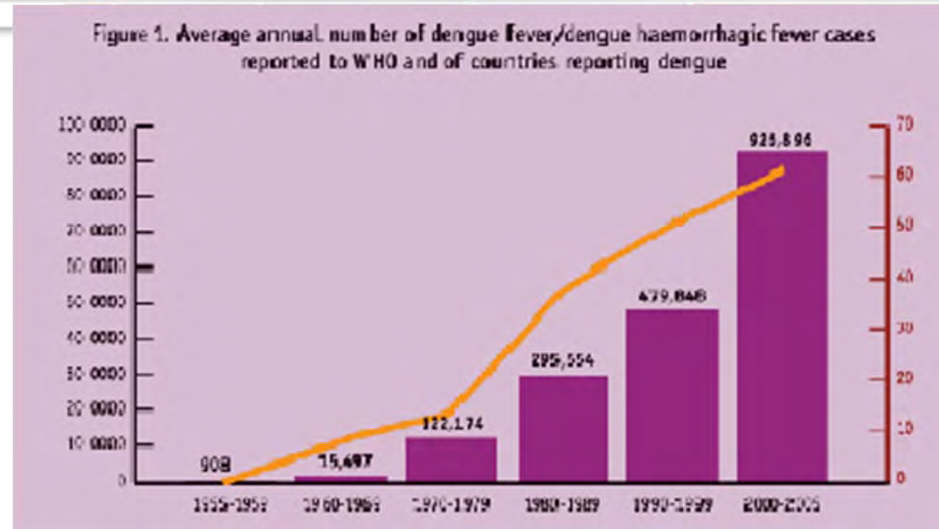




Dengue: Epidemiology

- 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

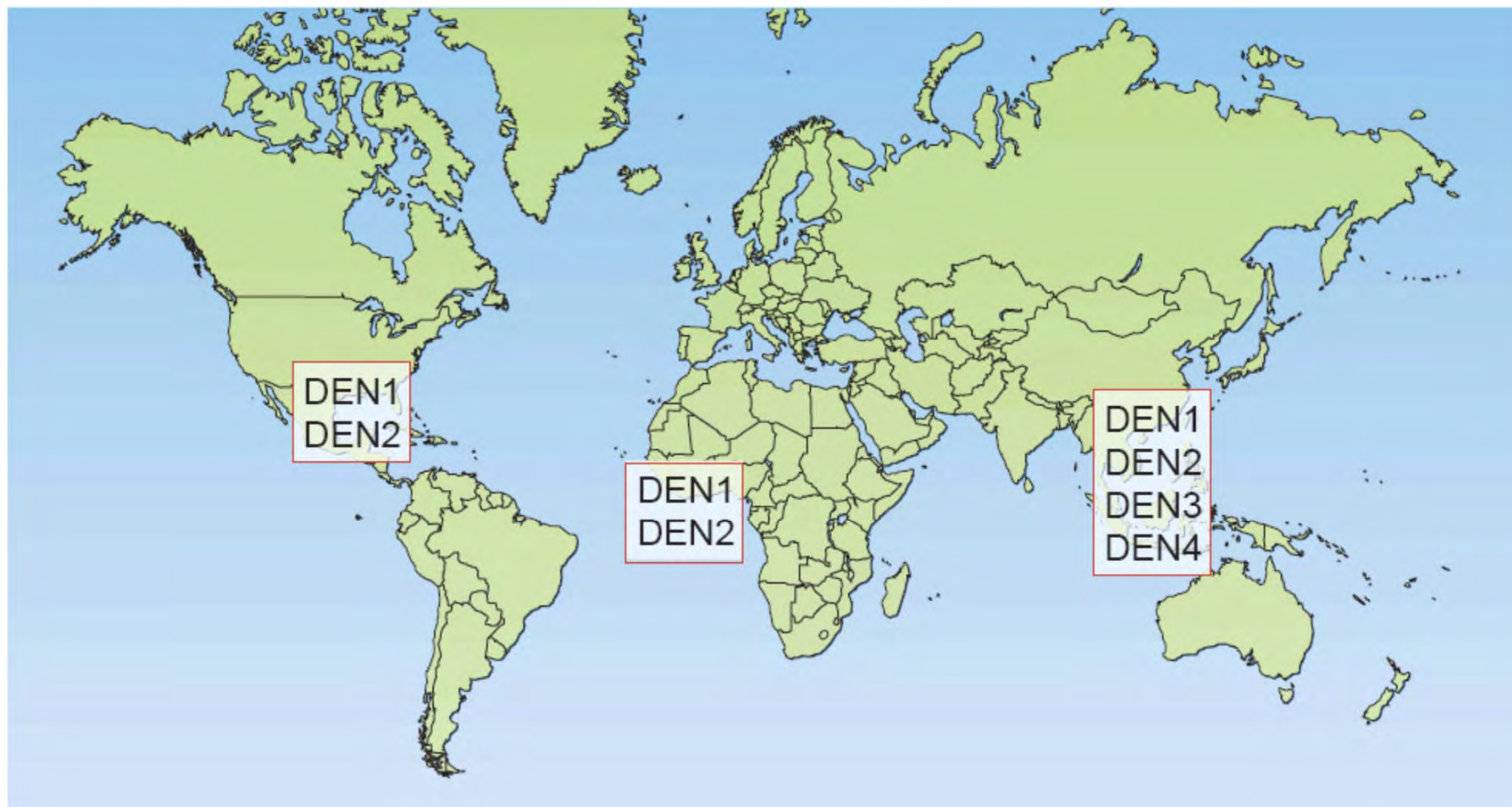
Global Resurgence of Dengue



- 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



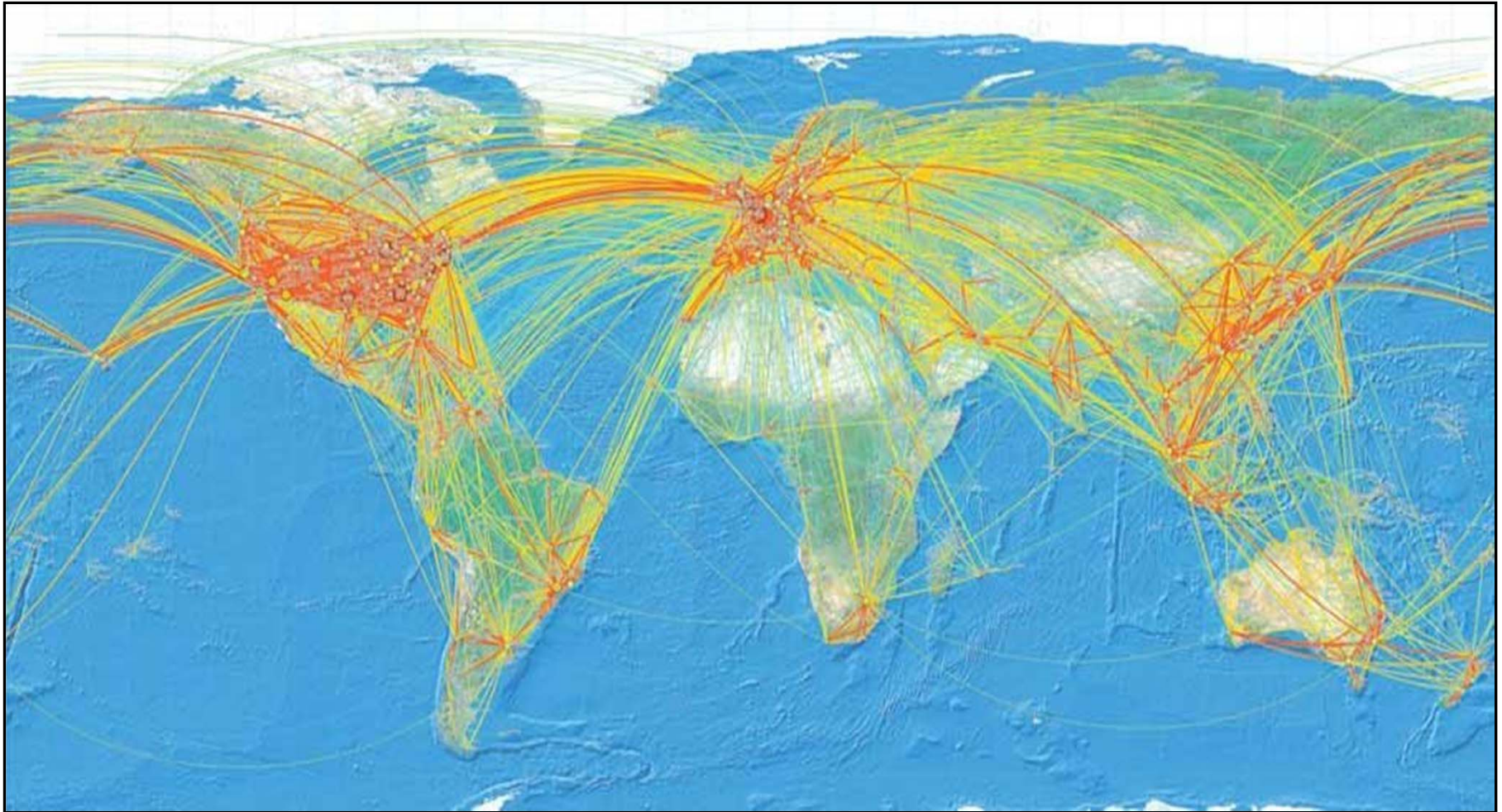
Global distribution of dengue virus serotypes, 1970



22 October 2007
2011 MHS Conference

FOUO

Air Traffic Global Flight Patterns

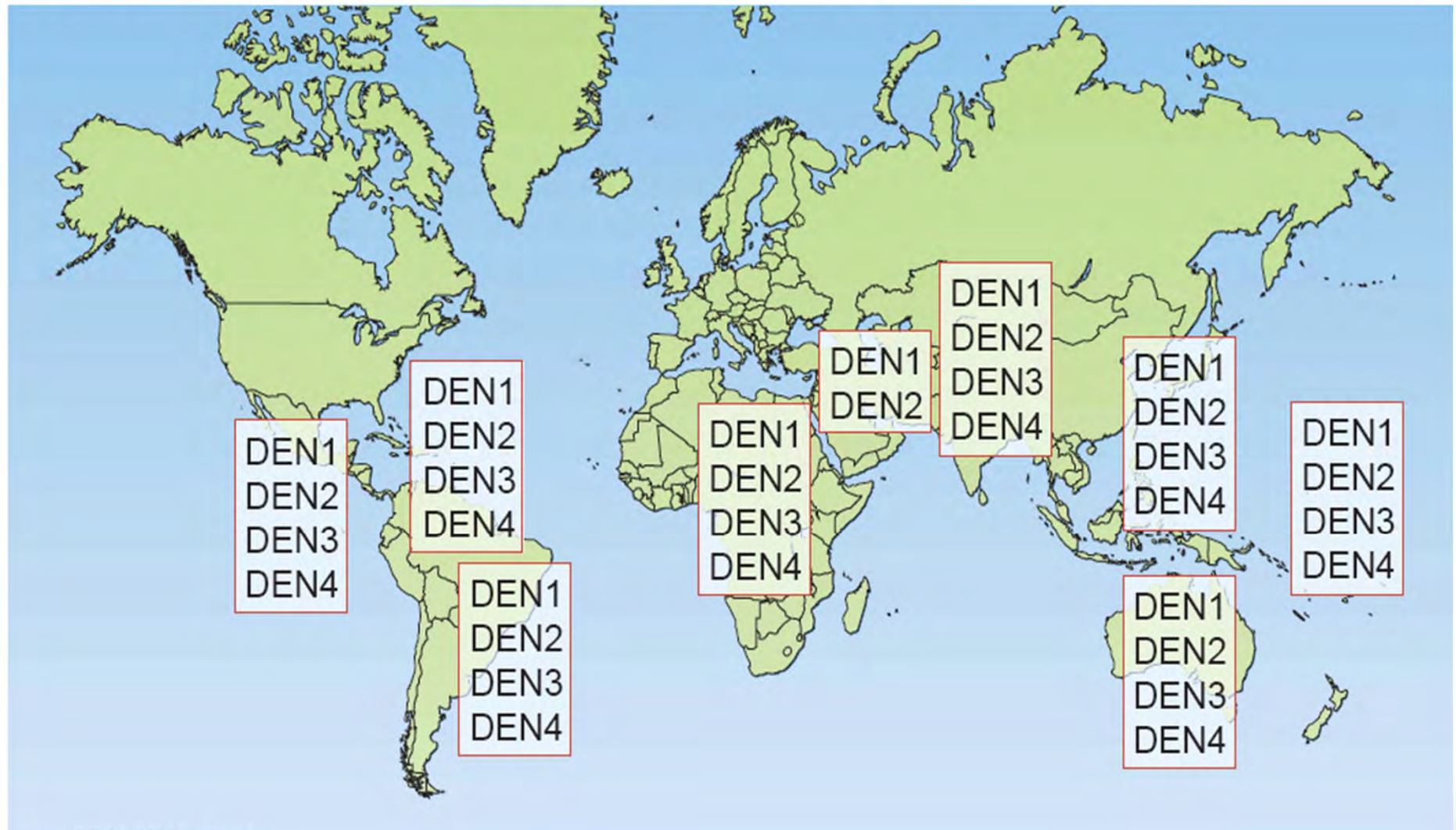


FOUO

2011 MHS Conference

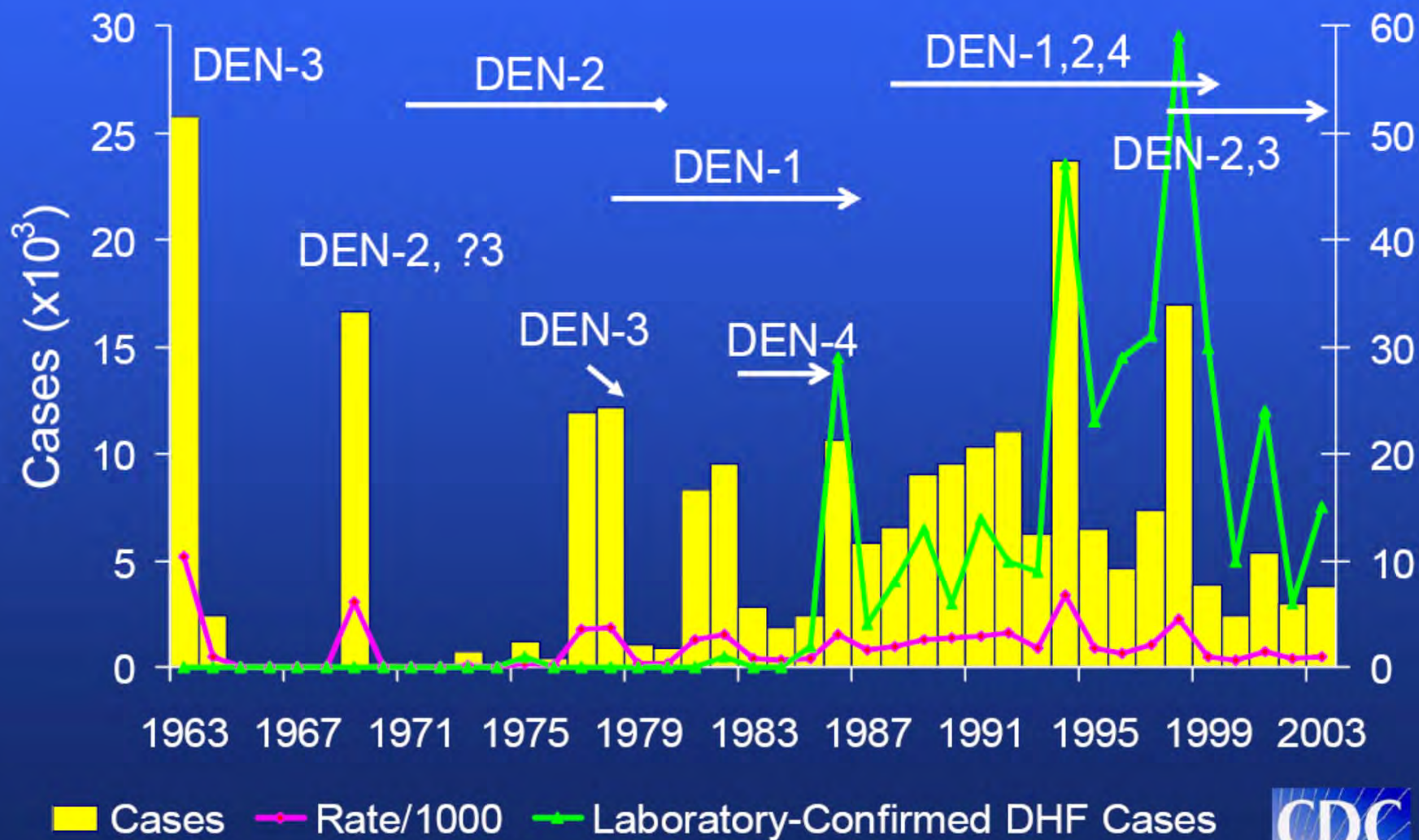


Global distribution of dengue virus serotypes, 2004





Dengue in Puerto Rico: 1963-2003



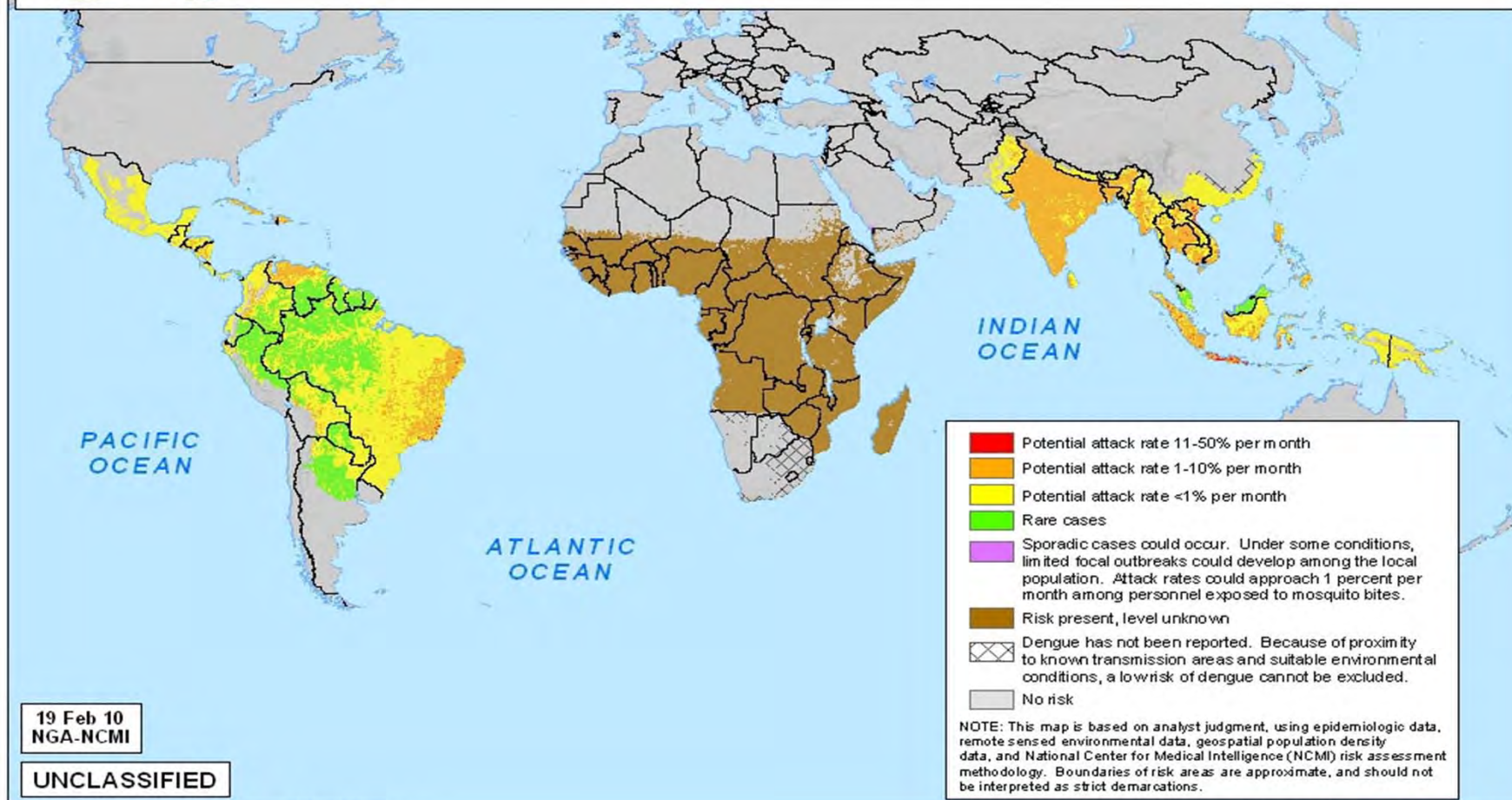
Dengue Risk



Worldwide: Dengue Risk to U.S. Forces

February 2010

UNCLASSIFIED



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



Fort McKinley, Philippines



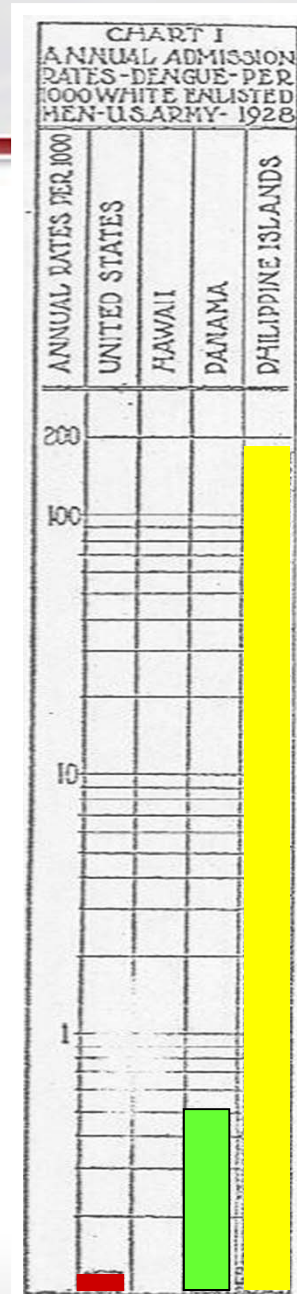
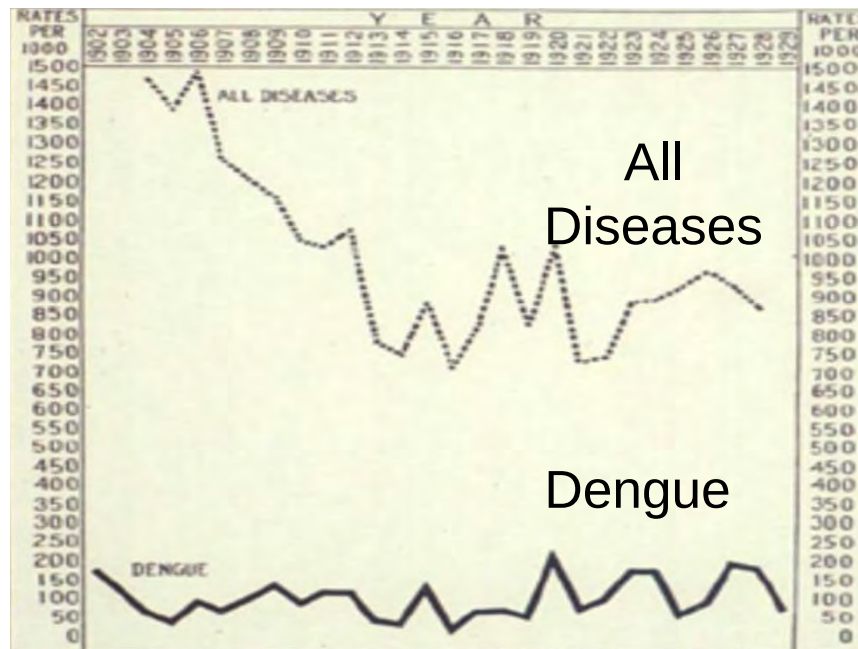
Dengue Outbreak: July – November 1906
~1/3 of troops infected

Unit	Strength	No. Cases	% Infected
13 th U.S. Infantry	727	240	33
16 th U.S. Infantry	613	162	26
8 th U.S. Cavalry	378	89	24
Total	1718	491	29

Philippine Islands: 1902-1928



- Hospital admission rates
 - Decreases for all diseases
 - Consistent for dengue
- Average loss to Army of 7,715 days per year



Daily Reported Cases During the Saipan Dengue Epidemic, Sep - Oct 1944



- 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 cases¹ of dengue at height of the epidemic in Saipan, 14 September to 6 October 1944

Date	Number	Date	Number
<i>1944</i>		<i>1944—Continued</i>	
September 14.....	393	September 26.....	62
15.....	426	27.....	87
16.....	294	28.....	79
17.....	306	29.....	71
18.....	289	30.....	44
19.....	275	October 1.....	36
20.....	230	2.....	33
21.....	137	3.....	27
22.....	137	4.....	28
23.....	112	5.....	32
24.....	93	6.....	23
25.....	81		

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 $\geq 80\%$
 - Durable immune response (>2 years)
 - 1-3 doses



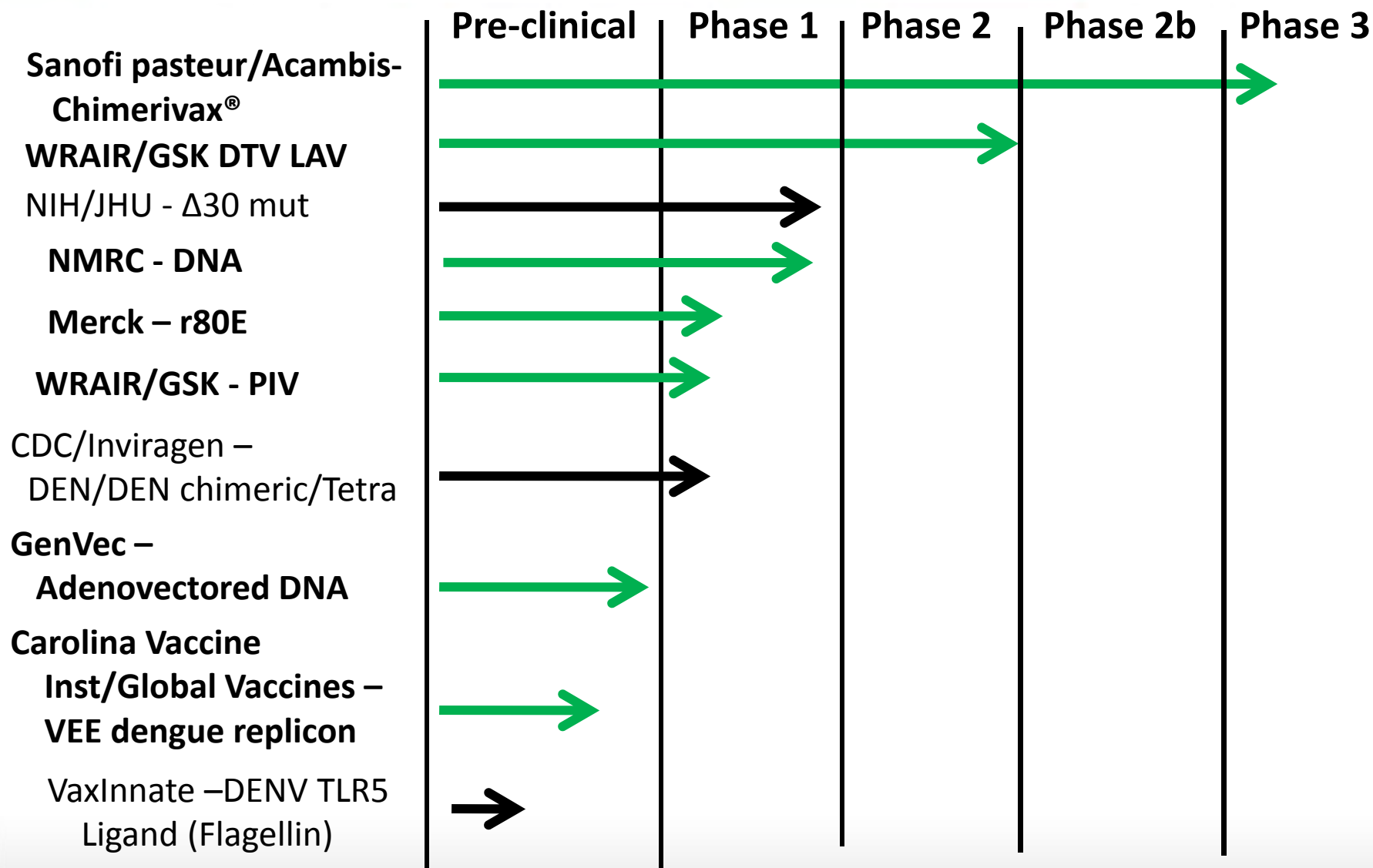
Challenges in Dengue Vaccine Development



- 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



Dengue Vaccine Landscape



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



Virology Field Site Kamphaeng Phet Province



Pivotal Trials Conducted by MRMC/Thai MoPH

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

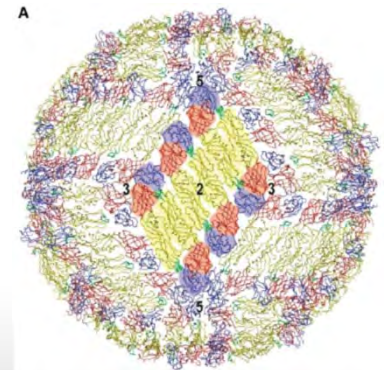
Hepatitis A Vaccine
(Havrix) 1990's
-GSK

Dengue vaccine
(Chimerivax) (2011)
-Sanofi Pasteur

Tetravalent Dengue Virus (TDV) Vaccine - Landscape



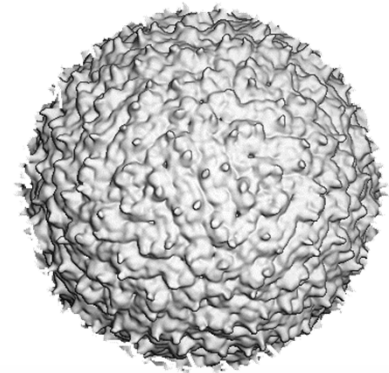
- Live attenuated vaccine (LAV)
 - Viruses (classically) attenuated through serial passage in non-human cell line
 - Tetravalent formulation required balancing
 - 2 doses : 0, 6 months
 - 100% protection in animal models
 - Safe and immunogenic in human trials
 - Phase 2 study Puerto Rico
 - » 700 subjects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

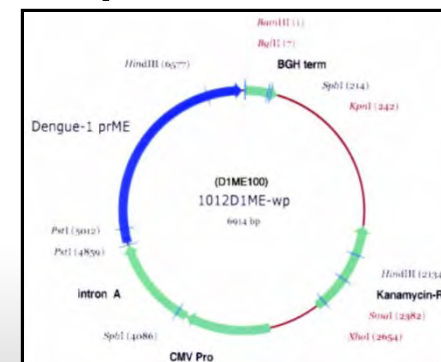


Tetravalent Dengue Virus (TDV) Vaccine - Landscape



– 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



Tetravalent Dengue Virus (TDV) Vaccine – Landscape



- 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



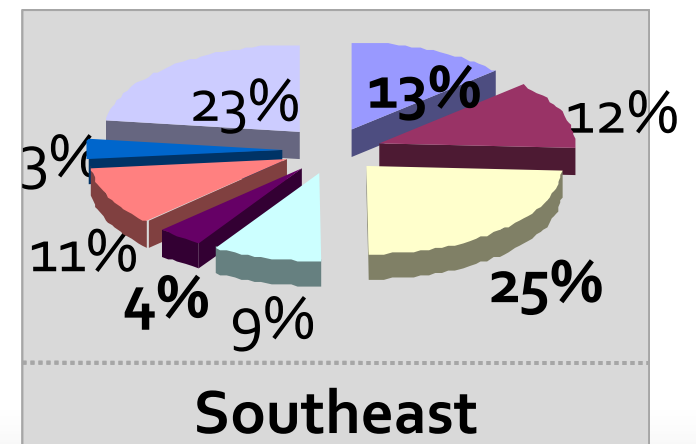
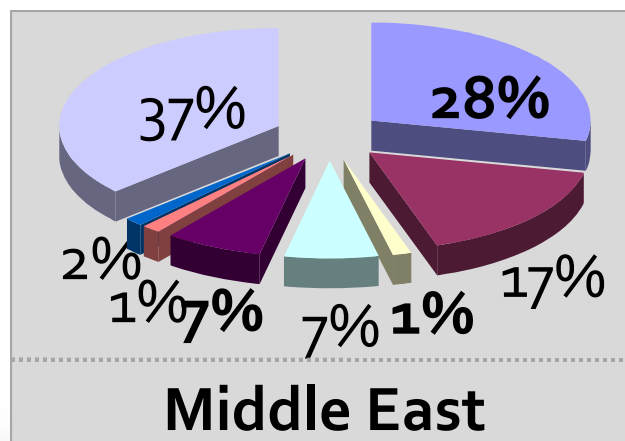
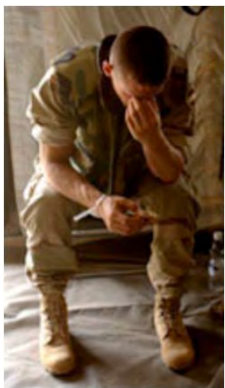
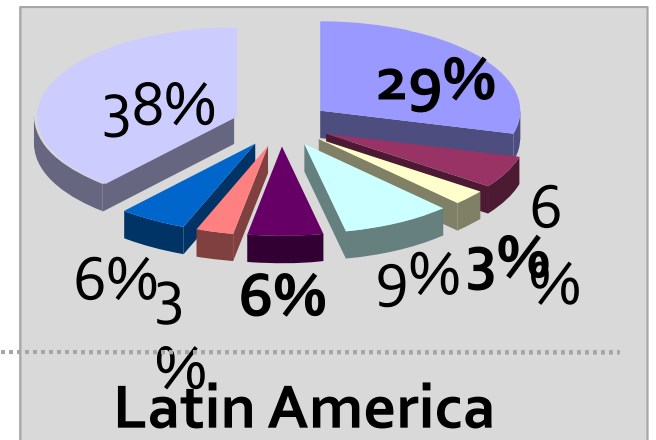
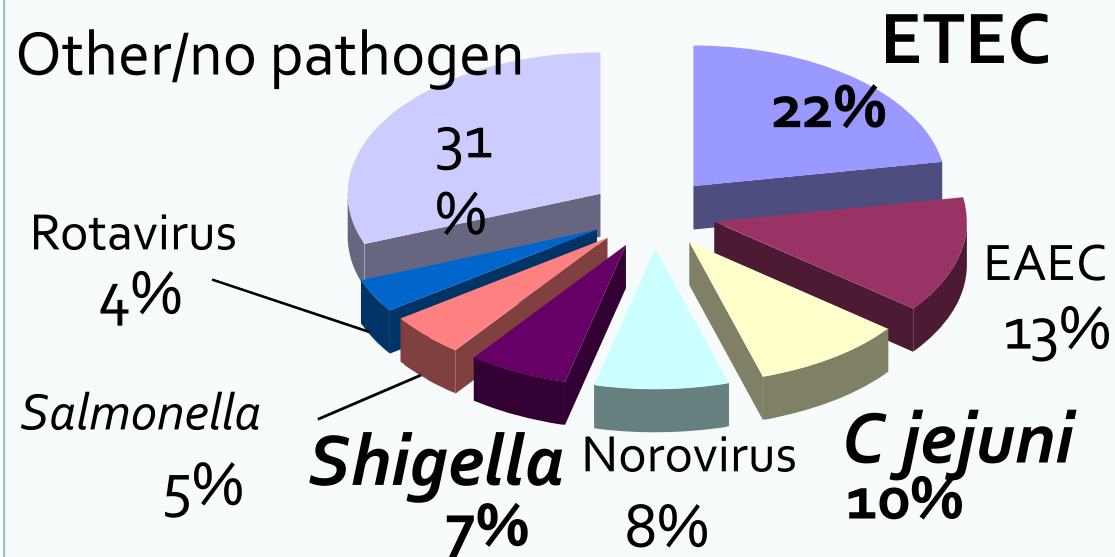
- Prevention of Diarrheal Diseases
 - Develop effective vaccines and other counter-measures against leading causes of infectious diarrhea and dysentery in deployed U.S. military personnel
 - Major research and development thrusts
 - Enterotoxigenic *Escherichia coli* (ETEC) vaccines
 - *Shigella* vaccines
 - *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



Vaccines Against Bacterial Diarrhea and Dysentery



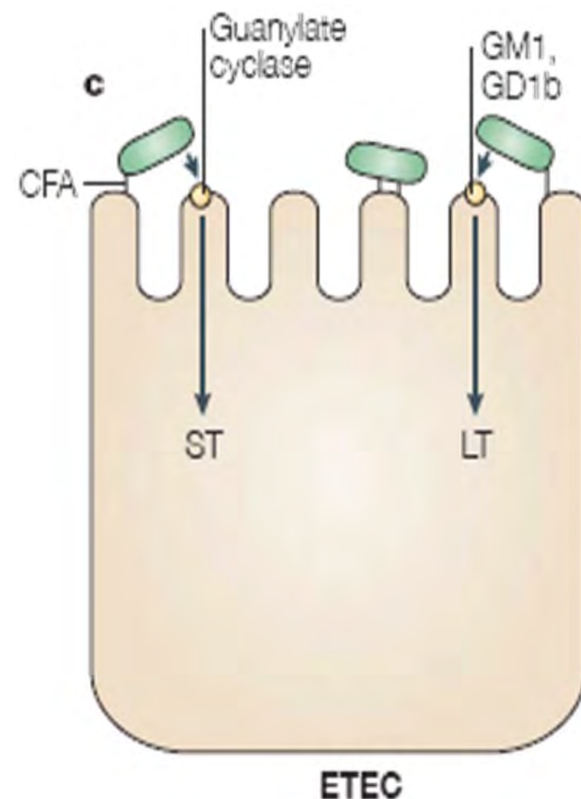
	Developer	Type	Clinical Phase I	Clinical Phase II	Clinical Phase III	Comments
Campy	ACE Bioscience	Subunit (ACE393)				Failed to show protection
	Intercell USA	LT, TCI (skin patch)				Failed to show protection
ETEC	TD Vaccines	LA (ACE527)				Failed to show protection
	NICHD	PS conjugate				<i>S sonnei</i> vaccine efficacious (Cohen '97); No pharm partner
Shigella	Glycovaxyn	Bioconjugate, <i>Sd1</i>				FIH Trial started Feb 2010
	Institut Pasteur	LA (SC599), <i>Sd1</i>				Safe, modest immunogenicity
	Univ MD CVD	LA (CVD1208S), <i>Sf2a</i>				Currently on FDA clinical hold
	PATH/EVI	Killed whole cell, <i>Sf2a</i>				Phase 1 trial projected to start in FY11 under EVI

Vaccines Against Bacterial Diarrhea and Dysentery - ETEC



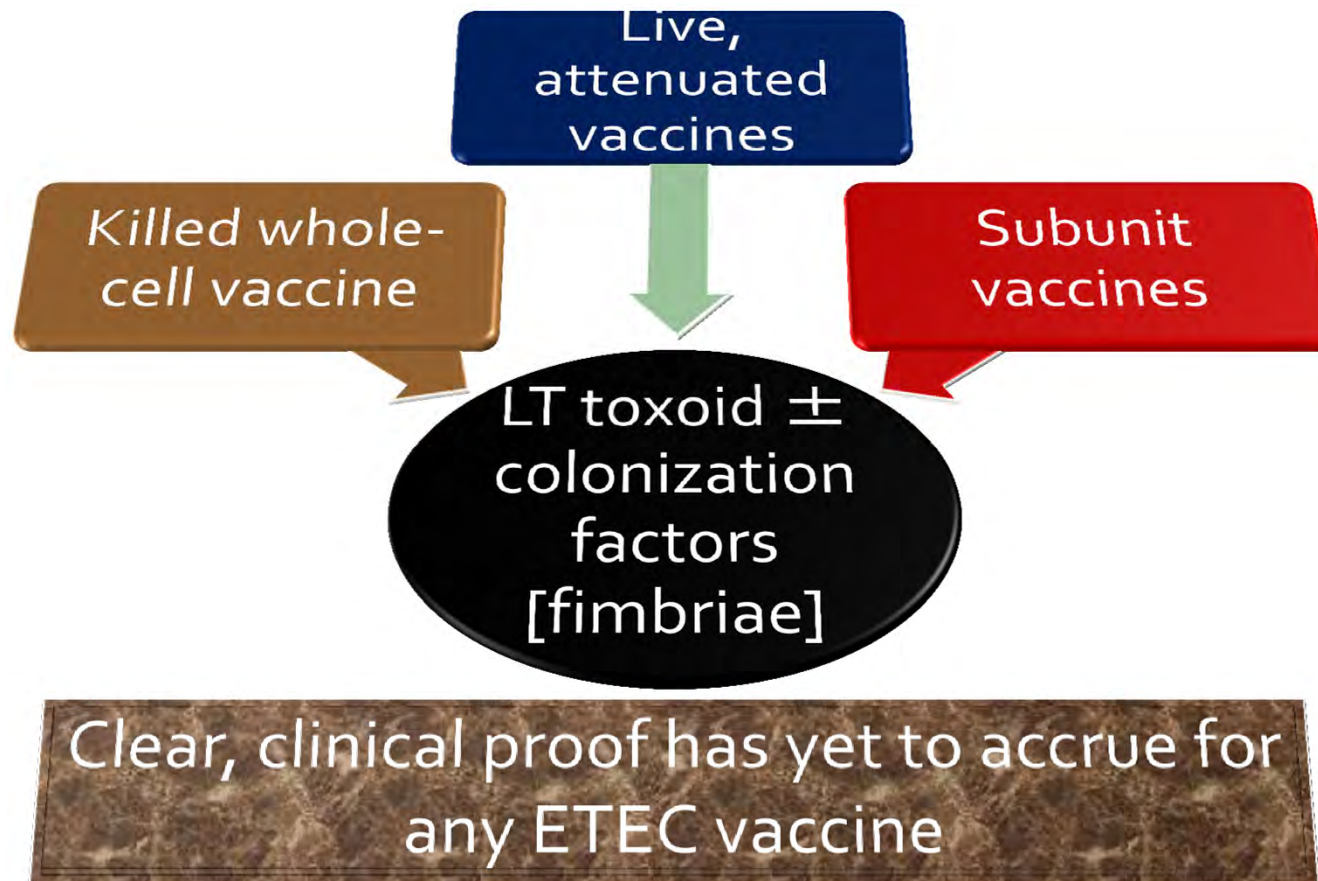
- At risk populations
 - Military / Civilian travelers
 - Leading cause of travelers' diarrhea
 - Endemically exposed individuals
 - 500K deaths annually in young children
 - Major disease in young farm animals (calves, piglets)
 - Characterized by different colonization factors

Pathogenesis



*from JB Kaper et al *Nature Rev Microbiol*
2004;2:123.

Vaccines Against Bacterial Diarrhea and Dysentery - ETEC



Vaccines Against Bacterial Diarrhea and Dysentery - ETEC



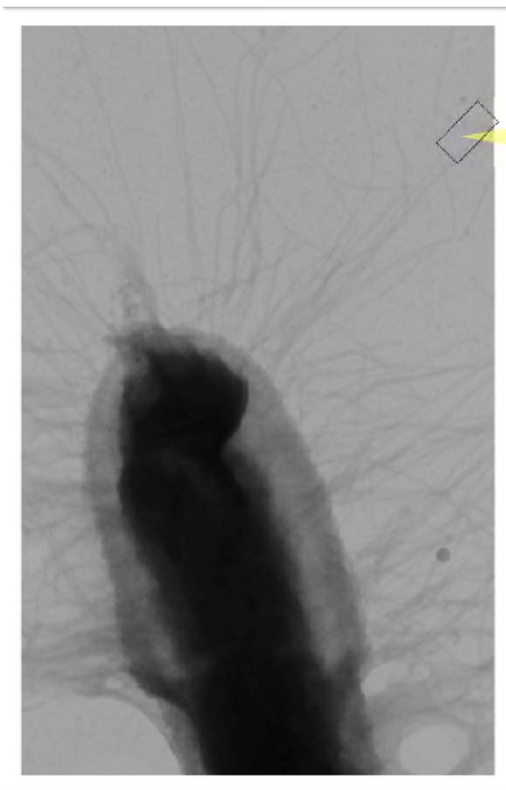
- Adhesin-based vaccine
 - Tip-localized adhesin ascribed role in intestinal binding
 - Adhesins exhibit greater antigenic conservation than major pilus-forming subunit
 - Recombinant adhesin variants developed, which are
 - Stabilized in native conformation
 - Highly immunogenic when given by mucosal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



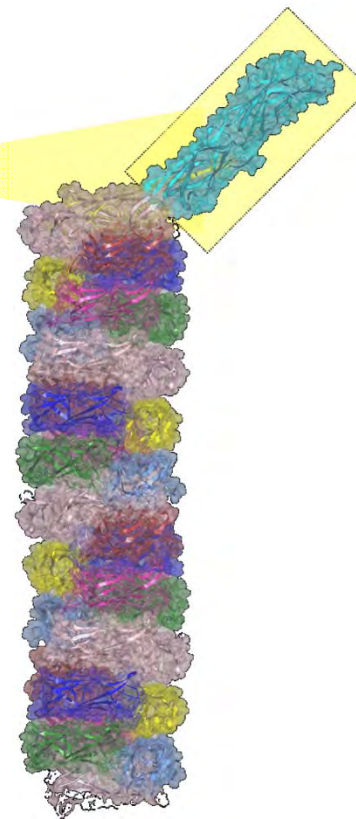
Vaccines Against Bacterial Diarrhea and Dysentery - ETEC



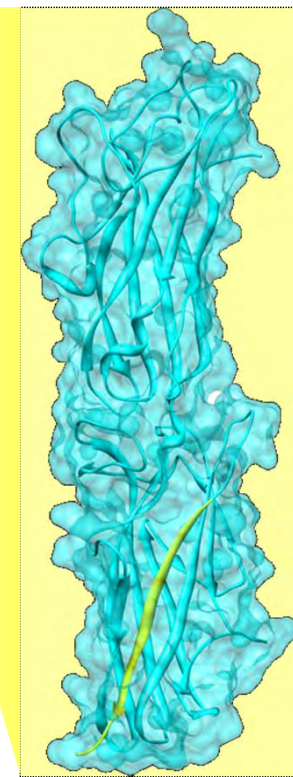
- ETEC:



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. nancymae* 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 (BIgG)
 - Two days before challenge take 3 oral doses/day BIgG at meals
 - Challenge with ETEC (homologous strain 1×10^9 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



sanofi pasteur
The vaccines division of sanofi-aventis Group

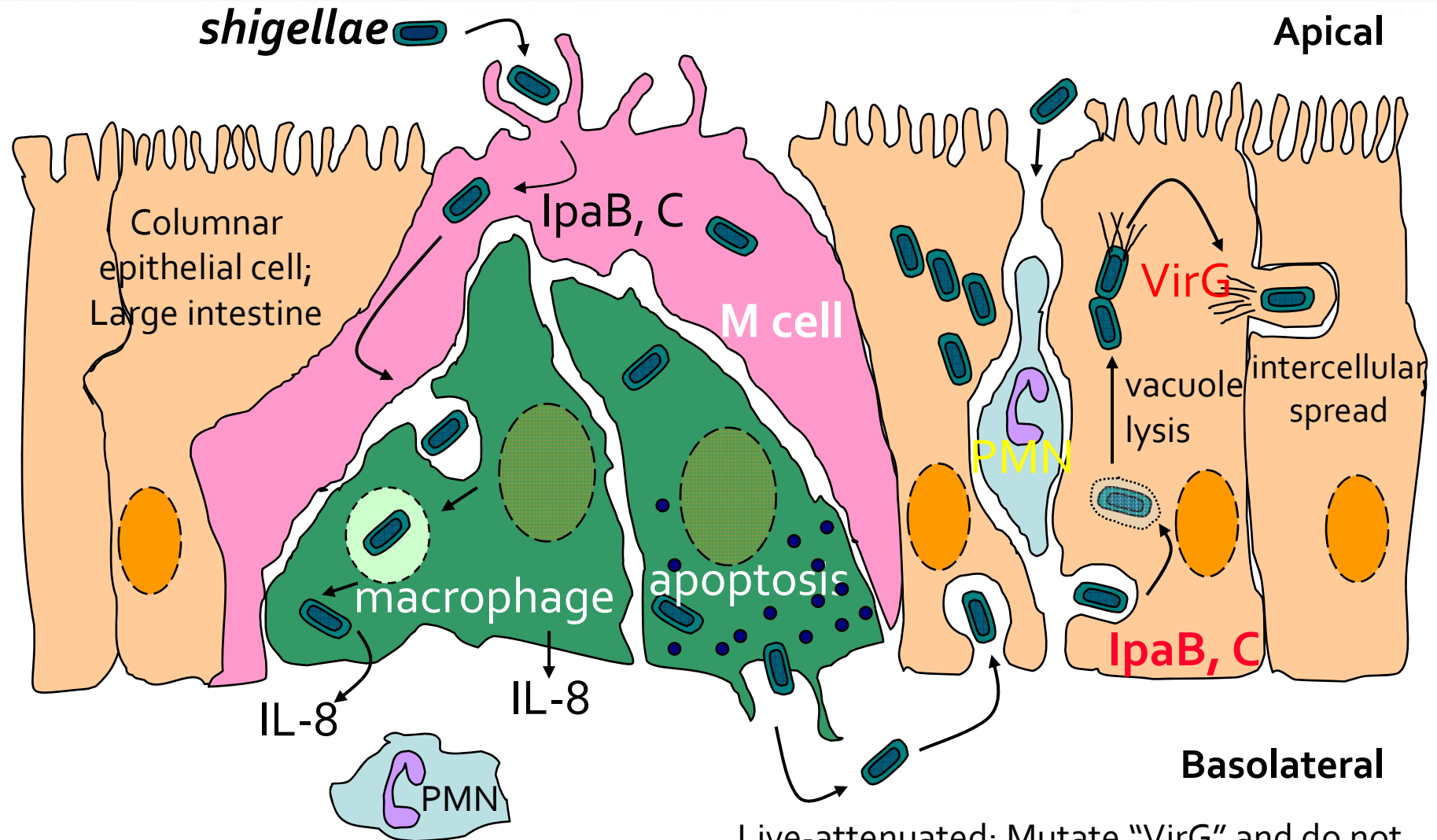
- A first-in-human Phase 1 clinical trial of the prototype ETEC adhesin (dscCfaE)
 - scheduled to begin in 2011,
 - active, skin patch vaccination
 - Challenge
- The adhesin-based vaccine IP has been licensed to sanofi pasteur (sp) vaccines
 - expanded preclinical evaluation of the components of a pentavalent 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*



Live-attenuated: Mutate "VirG" and do not get further spread of infection

Vaccines Against Bacterial Diarrhea and Dysentery - *Shigella*



- *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

Vaccines Against Bacterial Diarrhea and Dysentery - *Shigella*



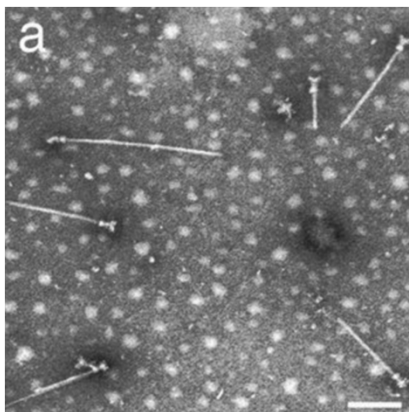
- Live attenuated *Shigella* vaccines
 - WRSS1 given to more than 100 volunteers, found to be safe and highly immunogenic but some side effects
 - WRSs2 and WRSs3 in phase 1 clinical trial to be conducted in April, FY11
 - To determine safety and immunogenicity
 - US Army, NIH funded

Vaccines Against Bacterial Diarrhea and Dysentery - *Shigella*

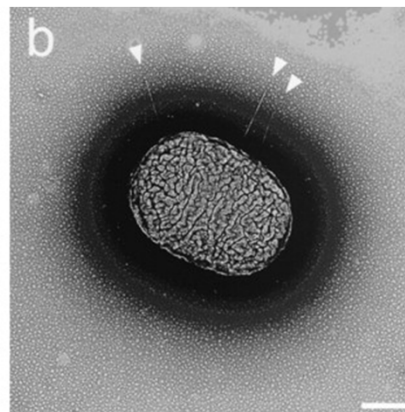


- Recombinant *Shigella* “Invaplex” vaccine
 - Cloned and purified proteins from the Type Three Secretion System (TTSS) mixed with *Shigella* LPS
 - Produces protective immune response in mice and guinea pig
 - Phase 1 clinical trial scheduled for FY13
 - US Army, sanofi pasteur

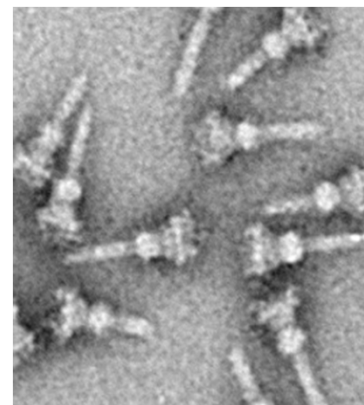
sanofi pasteur
The vaccines division of sanofi-aventis Group



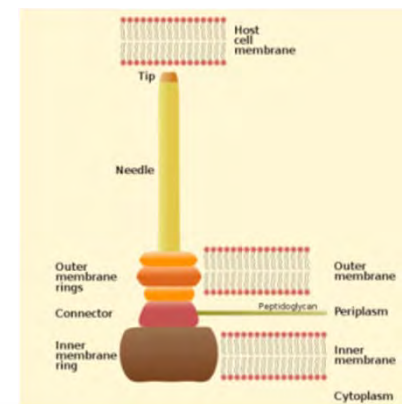
2011 MHS Conference



Injectisome extending from *Shigella*



Injectisome



Injectisome graphic

Vaccines Against Bacterial Diarrhea and Dysentery - *Campylobacter*

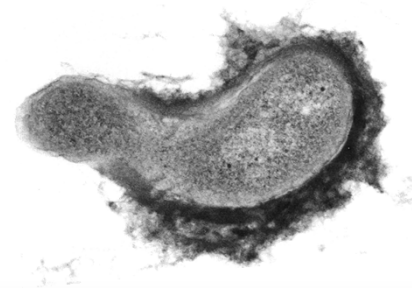


- *Campylobacter jejuni*
 - Transmission: Foodborne
 - Inoculum size: low ($\geq 5 \times 10^2$ orgs)
 - Reservoirs: animals (poultry)
 - Serotype diversity: 48 Penner serotypes
 - Pathogenic process: adherence, invasion, inflammatory response
 - clinical syndrome: acute inflammatory response
 - sequelae: reactive arthritis, Guillian-Barre, irritable bowl 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 nancymae* 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

Vaccines Against Bacterial Diarrhea and Dysentery



- 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

Tetravalent Dengue Virus (TDV) Vaccine



Back-up Slides



Asia: Dengue Risk to U.S. Forces

February 2010

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Datum: WGS84, Coordinate System: Geographic

Boundary representation is not necessarily authoritative.

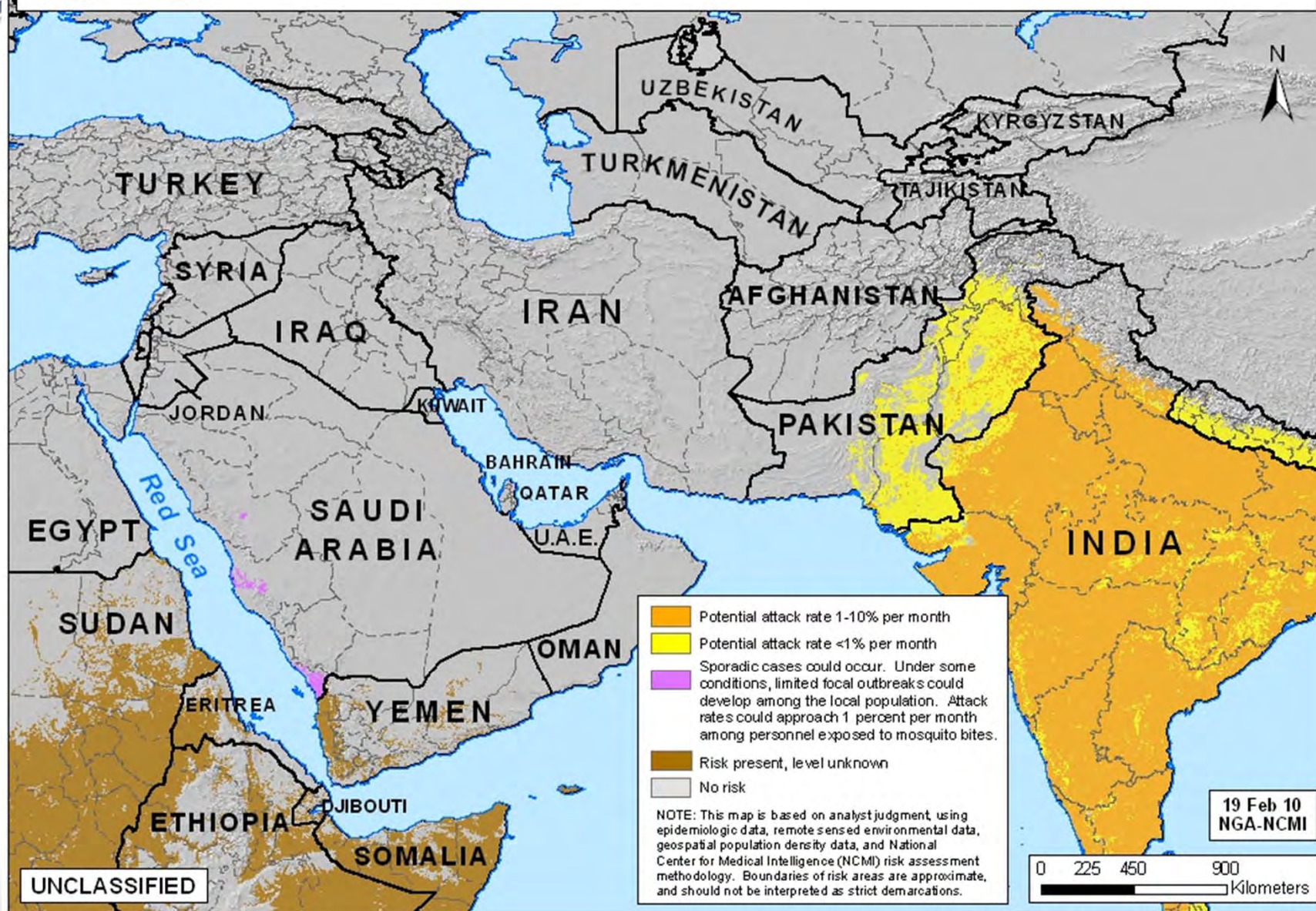
19 Feb 10
NGA-NCMI



Middle East: Dengue Risk to U.S. Forces

February 2010

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Datum: WGS84, Coordinate System: Geographic

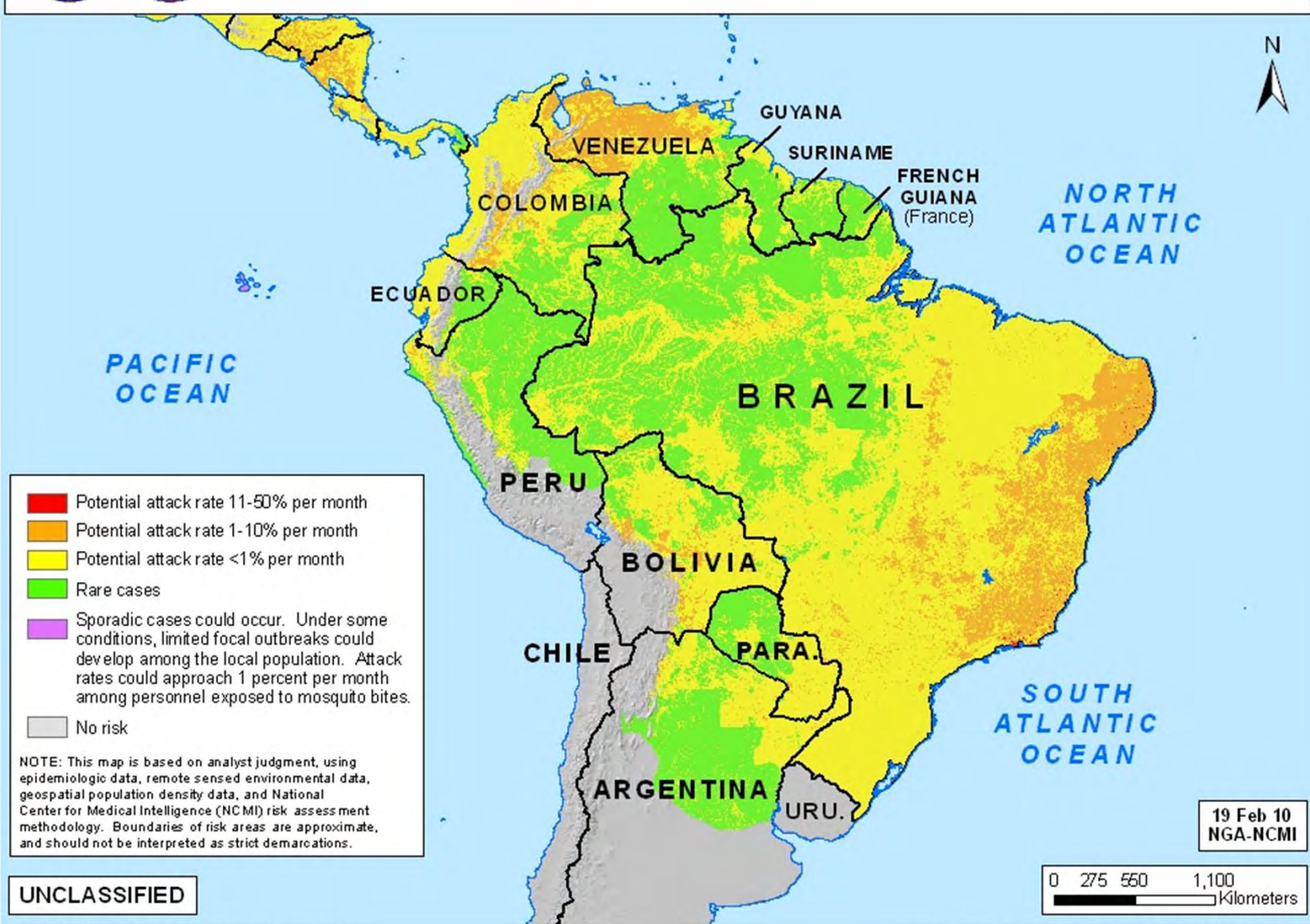
Boundary representation is not necessarily authoritative.



South America: Dengue Risk to U.S. Forces

February 2010

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Datum: WGS84, Coordinate System: Geographic

Boundary representation is not necessarily authoritative.

Dengue Vaccinologist

