Protecting the Warfighter from Malaria

Antimalarial Drugs and Vaccines

UNCLASSIFIED

LTC NORMAN C. WATERS
Military Malaria Research Program
Walter Reed Army Institute of Research
US Army Medical Research and Materiel Command
24 MARCH 2015

Purpose

To increase understanding of technology gaps in the development of antimalarial products to protect the Warfighter

Targeted Objectives

- *Antimalarial Drugs*
- *Malaria Vaccines*
- *Vivax Malaria*
- *Malaria diagnostics*

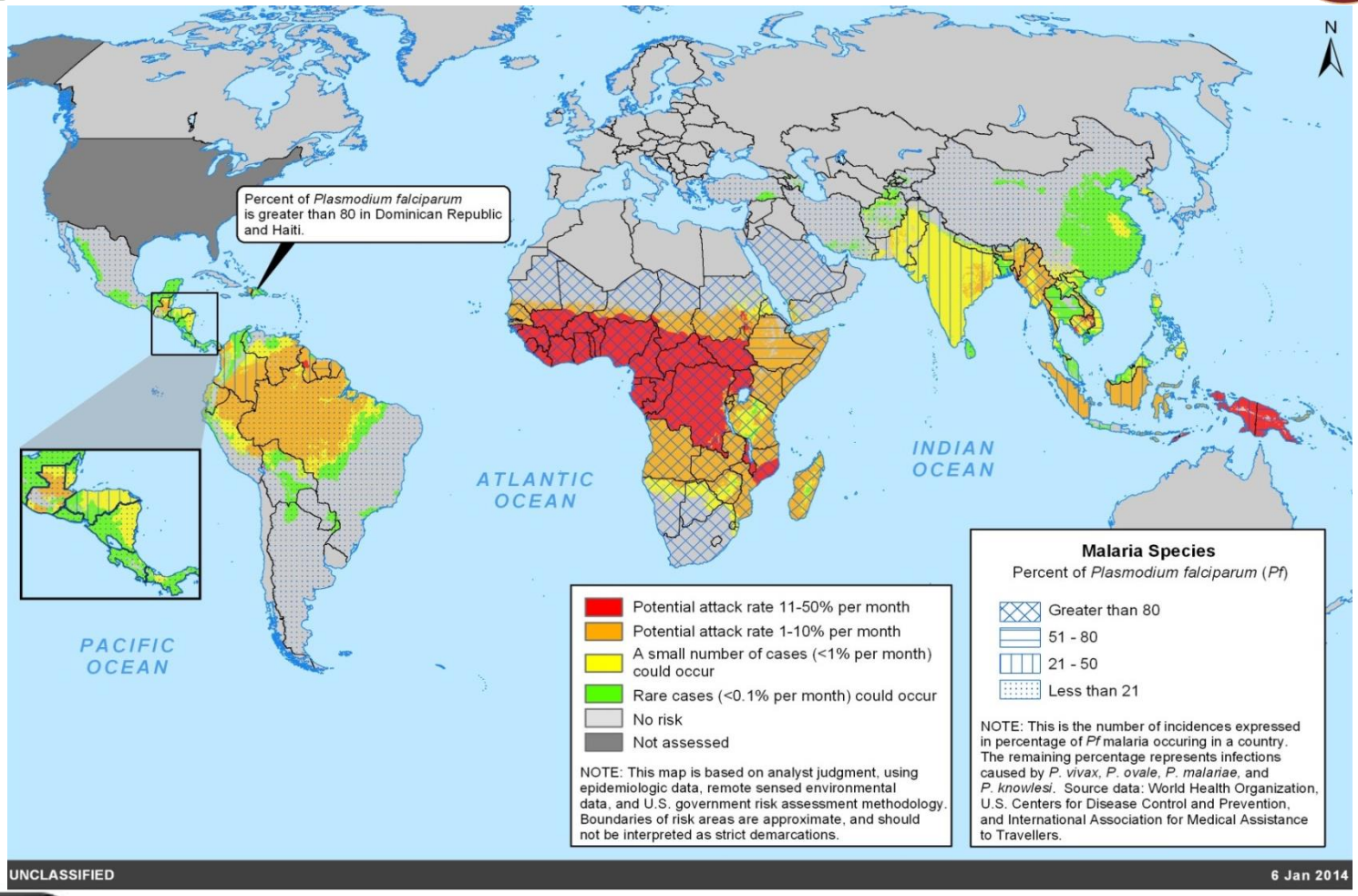
Malaria and Military Operations

Conflict/Deployment	Year	Morbidity and Mortality
WWII	1939–1945	600,000 cases mostly in Pacific theater. In some areas of South Pacific malaria rates were 4 cases per person per year
Korean War	1950–1953	Malaria rate 611/1000/year; 3000 cases in troops returning to US
Vietnam War	1962–1975	100,000 cases, Hospital admissions 27/1000/year 1970: 2222 cases (mostly *P. vivax*) treated in United States
Somalia	1992–1994	48 cases; 243 cases in forces on return home (*P. vivax*)
Nigeria	2001	Special forces 7/300 (2 deaths)
Afghanistan (OEF)	2001-	Over 400 cases since 2005

"Doctor, this will be a long war if for every division I have facing the enemy I must count on a second division in hospital and a third division convalescing from this debilitating disease!"

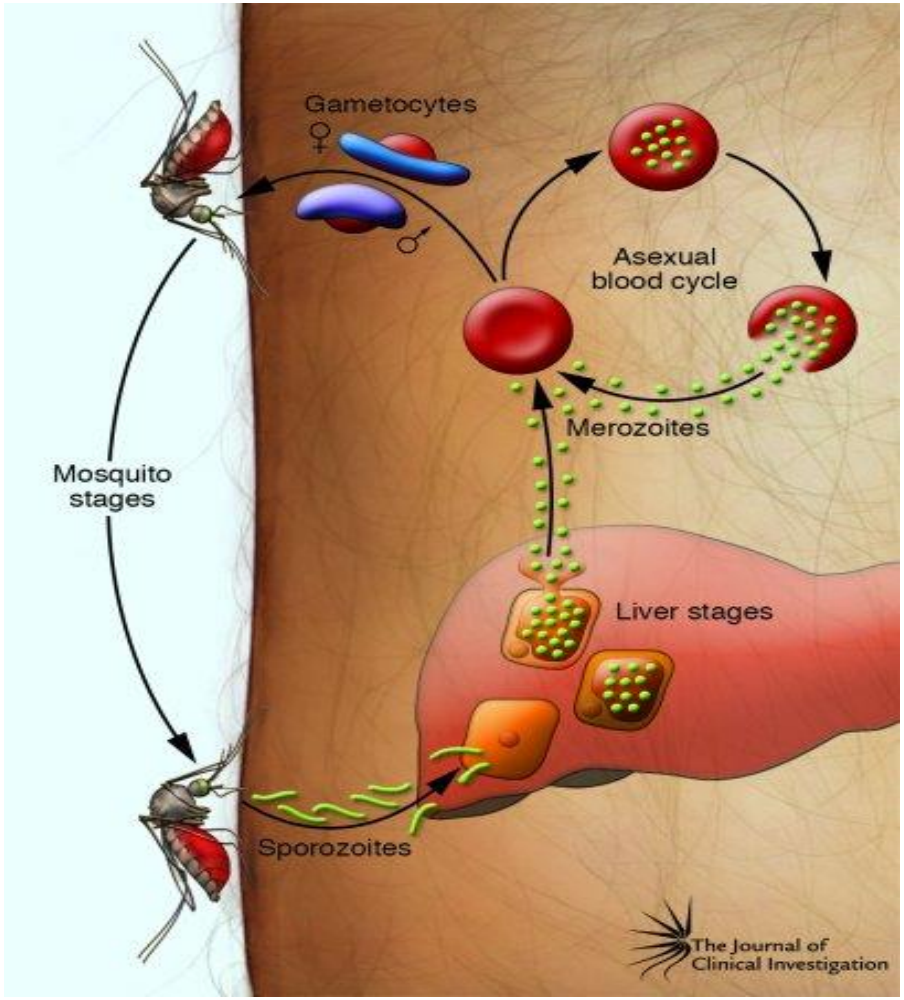
General Douglas MacArthur, May 1943

Malaria Risk to US Forces



Malaria Parasite Life Cycle

Multiple targets: multiple opportunities

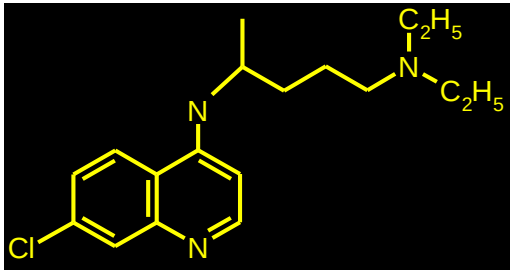


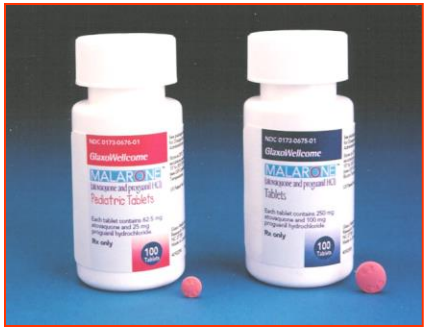
Antimalarial Drugs

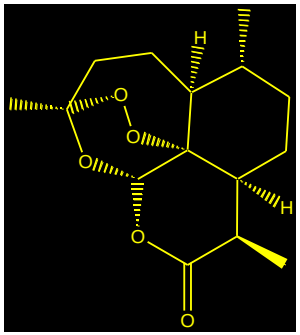
THE CHALLENGE

Drug resistance outpaces drug development

1. Unknown mechanisms of action
   - *Parasite vulnerabilities*
   - *Rapid drug resistance*
2. Novel Chemotypes
3. Compliance and Safety
   - *Weekly dosing*
   - *Lariam® (mefloquine)*
4. Pharmaceutical Partnership
   - *Prophylaxis vs treatment*
   - *Early engagement*



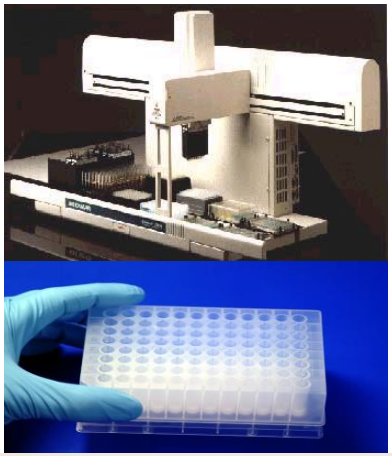


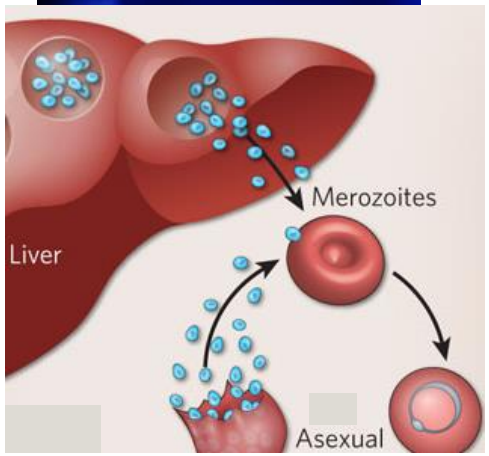


Antimalarial Drugs

GAPS AND SOLUTIONS

1. Acceleration of early lead down-selection
   - Library expansion
     - Expand structural diversity
     - Novel delivery methods
   - Discordance between *in vitro* and *in vivo* activity
     - Multiparameter optimization
     - High content assays
2. Validated inhibitor screens
   - HTS drug combination
     - Blood-stage suppressive versus causal activity
   - *In vitro* hepatocyte assay
   - Hypnozoite characterization (*P. vivax*)



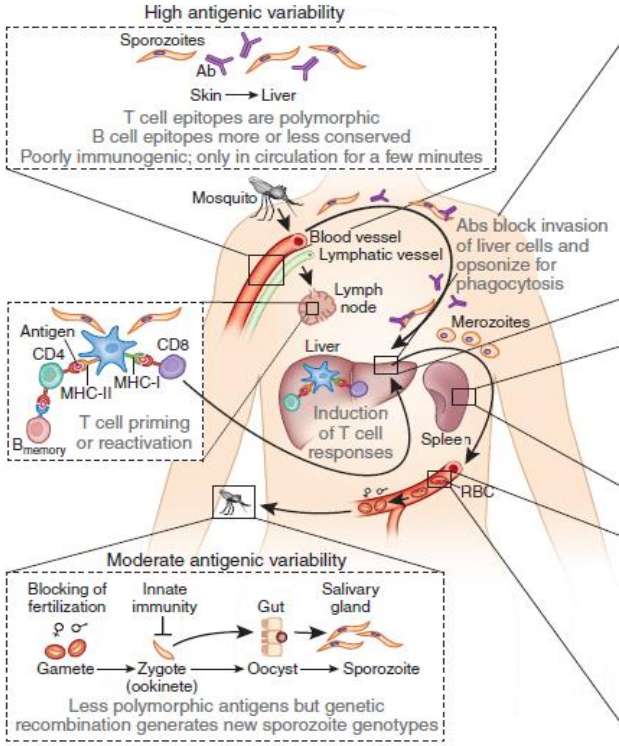


Malaria Vaccines

THE CHALLENGE

Repeated infection does not lead to long lasting immunity
• Natural Immunity is not understood •

1. No immune correlate of protection to compare vaccines
   - Unreliable animal models
   - Results in poorly defined Go/No Go criteria
2. Antigenic variation and heterogeneity
   - No "silver bullet"
   - Vivax versus/and falciparum malaria
3. Access to safe and effective adjuvants
4. Pharmaceutical Partnership
   - *Semi-immune children versus non-immune adults*



Malaria Vaccines

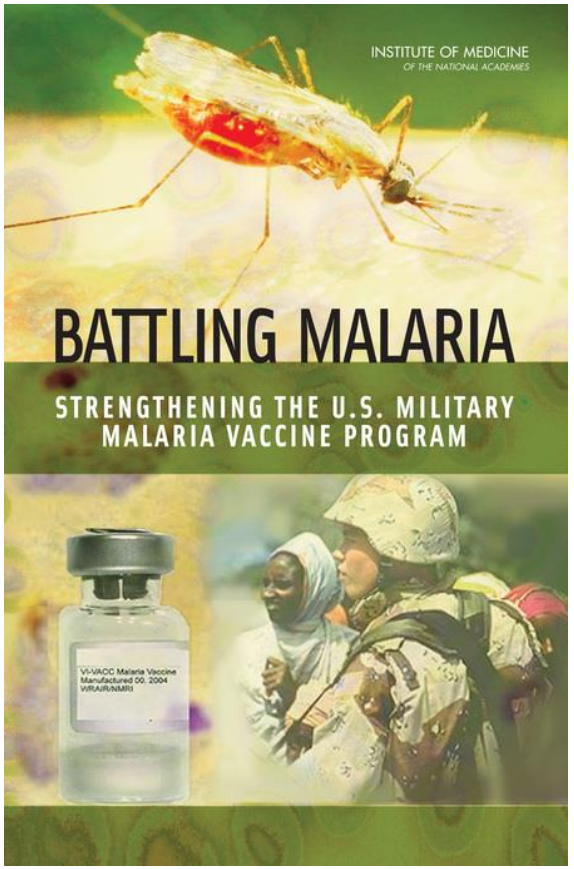
GAPS AND SOLUTIONS

1. Validation of novel antigens
   - Testable vaccine platforms
   - Multivalent vaccines

2. System Biology
   - Host-parasite relationship
   - Semi-immune vs non-immune

3. Immune modulation
   - Adjuvants
   - Expression platforms
   - Boosting strategies

4. Correlates of protection
   - Bridge animal models
   - Controlled Human Malaria Infection (CHMI)



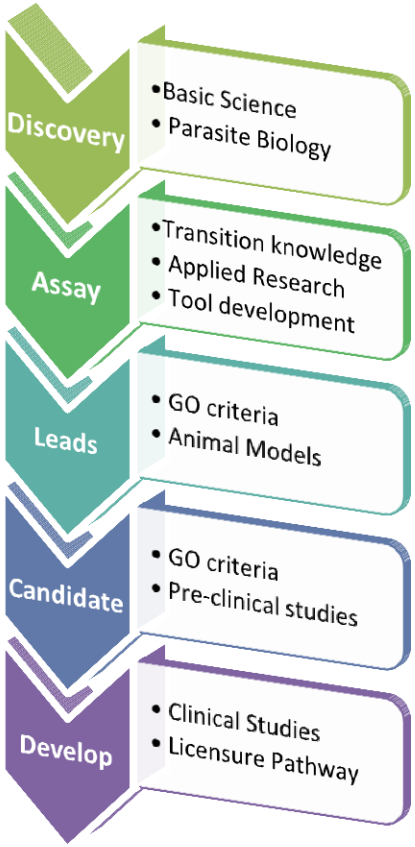
Technology Transfer

Pull from Academia: Push to Industry

A rush to develop antimalarial products without understanding parasite biology and the pharmaceutical landscape

1. Academic Partnerships
   - How do parasites respond to drug pressure?
   - Host-parasite interactions?
   - How do parasites respond to immune pressure?
   - Immune-escape mechanisms?

2. Industry Partnerships
   - Align Target Product Profiles (TPPs) with Global Health Initiatives
     - WHO Preferred Product Characteristics (PPC) for malaria Vaccines
   - Identify relationships early
   - Ensure clinical data fosters advancement of the DoD Product pipeline
     - Most valuable data since animal and *in vitro* models are not reliable



Questions?

For additional questions after the conclusion of the conference, send an email message to usarmy.detrick.medcom-usamrmc.mbx.mmpd@mail.mil

Gaps in Enteric Disease Research and Development

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CAPT Stephen J. Savarino, MD, MPH

Enteric Diseases Department

Naval Medical Research Center

24 March 2015

Purpose

To increase understanding of current requirements and technology gaps for protecting the warfighter against acute and chronic consequences of gastrointestinal infections.

- *A robust program for vaccine development exists for partnership*
- *Needs and opportunities for point of care diagnostics have been identified*
- *Understanding the role of the human microbiome in gut resiliance to infection and consequences and potential applications are a major need*

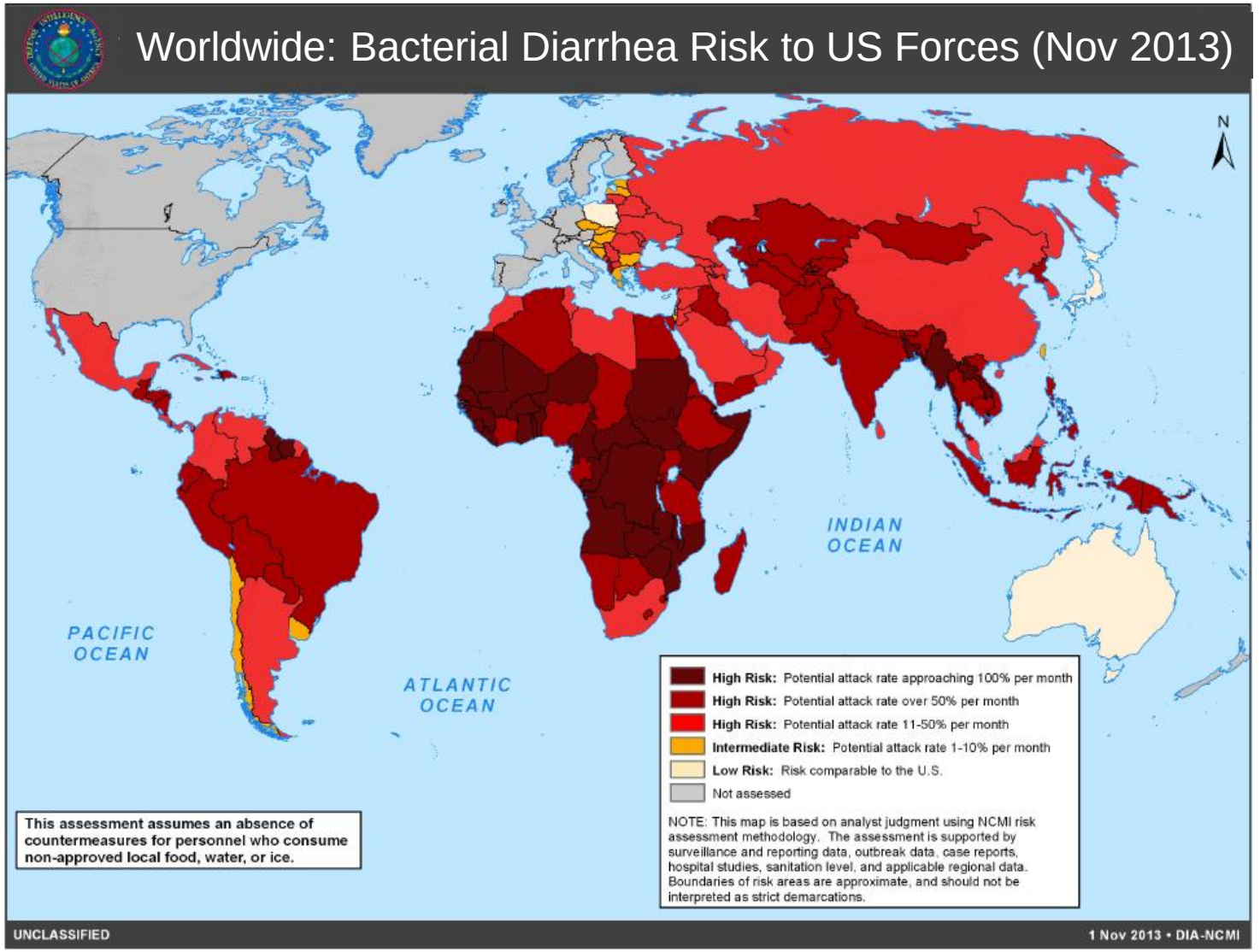
THESE ARE NOT MILITARY UNIQUE PROBLEMS

Background (1)

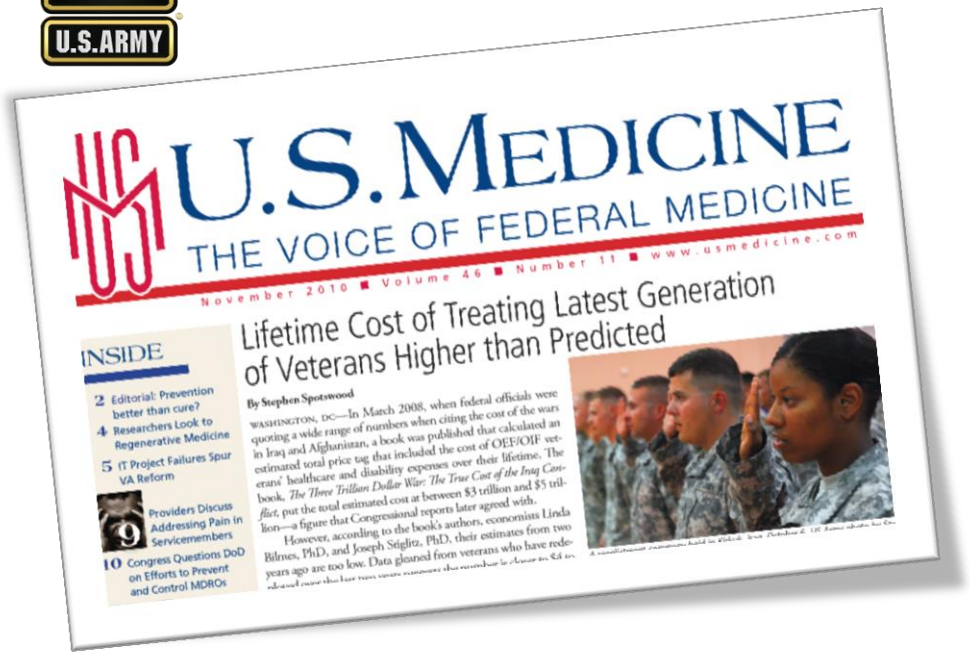
'I expect that our imaginations cannot fathom the problems attendant from the absolute urgency for relief from explosive vomiting and diarrhea when experienced within an armored vehicle under fire and at ambient temperature of >40°C.'

D.O. Matson, Infectious Diseases Section, Center for Pediatric Research, Norfolk, VA. *Clin Infect Dis* (editorial) 2005;40:526-7.

Background (2)



Background (3)



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Lifetime Cost of Treating Latest Generation of Veterans Higher than Predicted

By Stephen Spotswood

WASHINGTON, DC—In March 2008, when federal officials were quoting a wide range of numbers when citing the cost of the wars in Iraq and Afghanistan, a book was published that calculated an estimated total price tag that included the cost of OEF/OIF veterans' healthcare and disability expenses over their lifetime. The book, *The Three Trillion Dollar War: The True Cost of the Iraq Conflict*, put the total estimated cost at between $3 trillion and $5 trillion—a figure that Congressional reports later agreed with.

However, according to the book's authors, economists Linda Bilmes, PhD, and Joseph Stiglitz, PhD, their estimates from two years ago are too low. Data gleaned from veterans who have rede-

"Looking at long-term costs for wars is important, because the costs last so long."

"…compelling is the emerging evidence for exposure to enteric pathogens during deployment leading to the development of post-infectious IBS." *--Institute of Medicine, 2010*

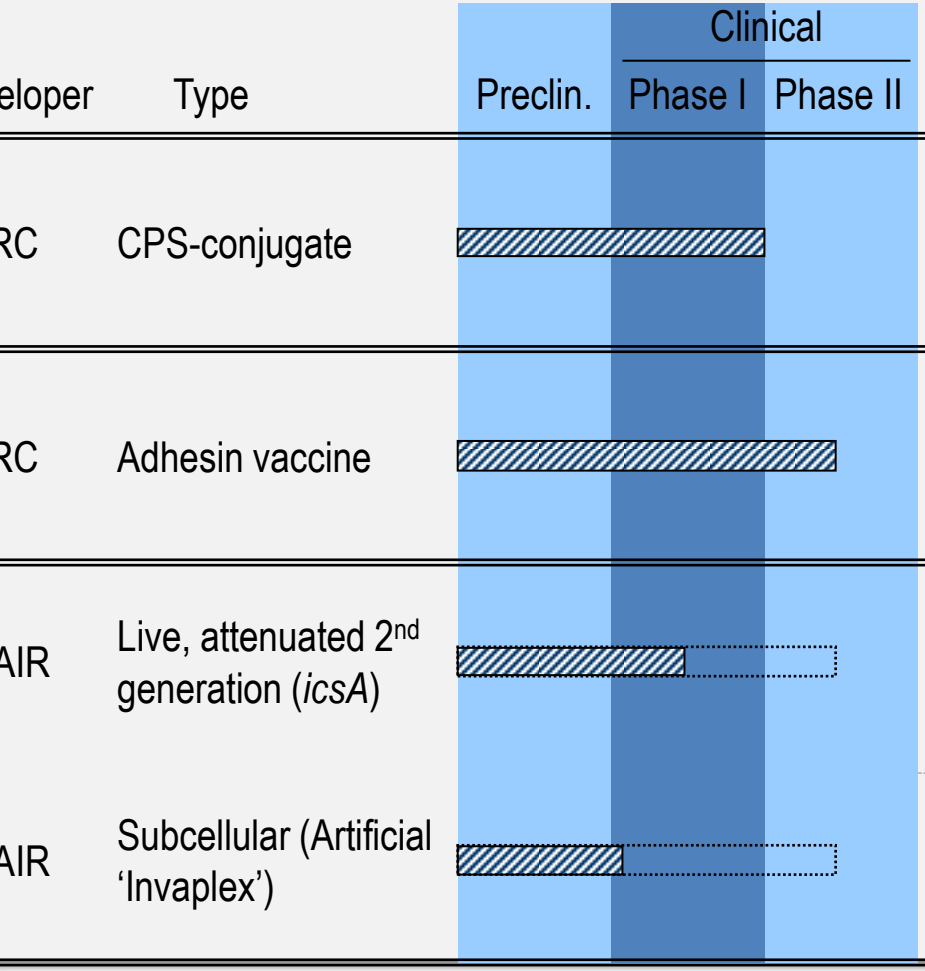
AUTHENTICATED U.S. GOVERNMENT INFORMATION GPO

41696 **Federal Register** / Vol. 76, No. 136 / Friday, July 15, 2011 / Rules and Regulations

DEPARTMENT OF VETERANS AFFAIRS
38 CFR Part 3
Presumptive Service Connection for Diseases Assoc. With Service: Functional GI Disorders

DoD Vaccines in Development

Pathogen	Developer	Type	Comments
C jejuni	NMRC	CPS-conjugate	▪ Positive proof-of-efficacy in NHP ▪ Phase 1 first-in-human (FIH) complete ▪ ***Seeking industry partnership***
ETEC	NMRC	Adhesin vaccine	▪ Positive proof-of-efficacy in NHP ▪ Two Phase 1 and Phase 2b trials of prototype adhesin performed 2011-14
Shigella	WRAIR	Live, attenuated 2nd generation (*icsA*)	▪ 1st gen. SC602 protective in humans ▪ Phase 1 FIH trial 2nd underway ▪ ***Seeking industry partnership***
	WRAIR	Subcellular (Artificial 'Invaplex')	▪ 1st gen. not protective in humans ▪ Phase 1 FIH trial with AI prototype vaccine to begin mid-FY15



Status of current generation

Status of 1st generation

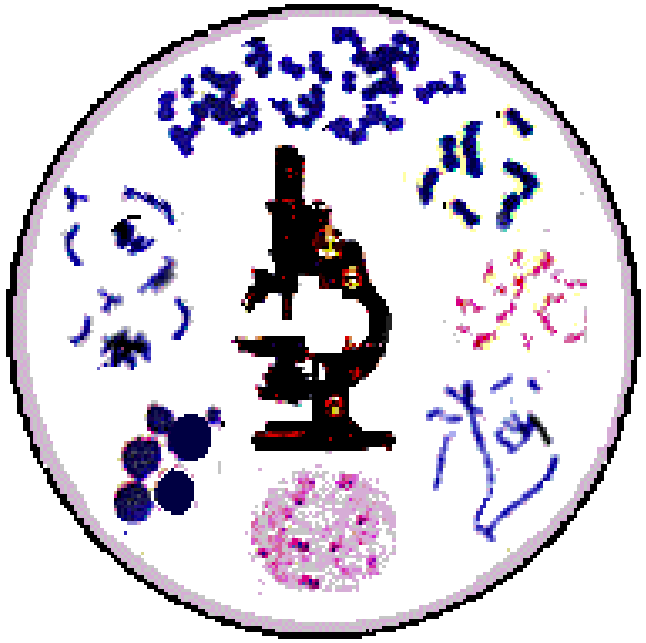
Technology Gaps in Diagnostics

- ***FICTIONAL "REAL WORLD" SCENARIO***: A 23 year old US Navy Lab Tech (microbiologist) has been working in the Liberian EBV mobile lab in support of Operation Unified Assistance. About a week ago he shared a meal with a local Liberian family in their home who he helped during the humanitarian effort.

- Presents worsening symptoms over the past 72 hours including:
  - Fever
  - Severe headache
  - Muscle pain
  - Weakness and fatigue
  - Diarrhea with blood in stools
  - Vomiting
  - Abdominal (stomach) pain

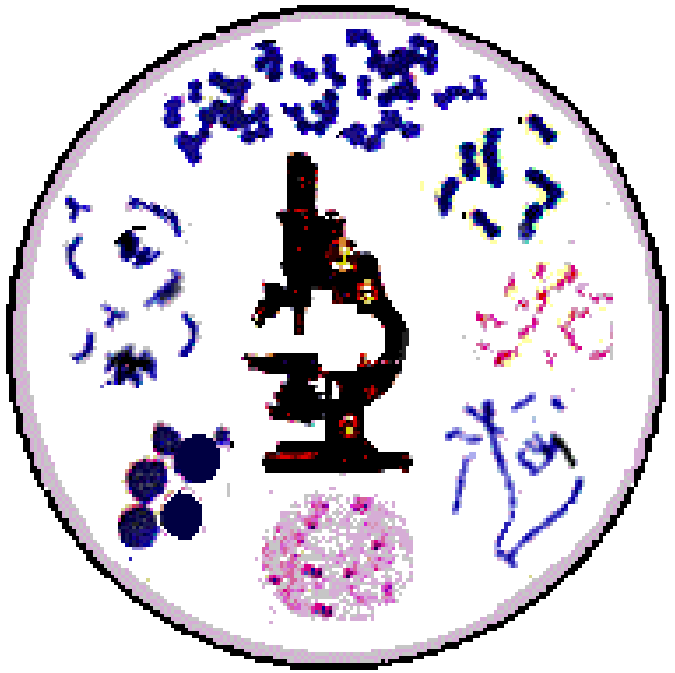
Diagnostics: state of the art

TODAY



"Pretty much the same."

WWII



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

Source: Mark Riddle

Source: Preventive Medicine in World War II-Volume IV: Communicable Diseases

Overview: Diagnostics Program

Task

- **Priority**: Rapid and convenient identification and diagnosis of infectious diseases of military interest
- **Problem:** Few FDA-cleared diagnostic devices for target pathogens
- **Objective:** FDA-cleared devices or platforms that are easily transportable, self contained, easy-to-use, and provide the rapid diagnosis capability (≤ 2 hours) for infectious diseases at point-of-need

Current Portfolios/Priorities

Rapid diagnostic devices

1. Dengue (virus and anti-dengue antibody)
2. Bacterial diarrheal diseases
3. Norovirus and other viral diarrheal diseases

Reagent repository preparation

- Support the development of multiple diagnostics

Innovative technologies

- Sample stabilization, biomarker detection, multiplex

Technical Barriers

- Lack of efficient, field-capable sample-processing technology
- Limited genetic and biological markers for infectivity and virulence
- Lack of reference strains and positive human samples to validate assays

Future Opportunities/Follow-on Research

- Expanded biomarker discovery
- Multiplexed assays
- Miniaturization and nanotechnology
- Automated processing (sample in/answer out)
- Expanded reagent and sample repositories

Gut Resilience

- *Acute infection may impact human performance beyond localized GI effects.*
- *Evidence linking acute enteric infections with chronic health outcomes is strong and growing*
- *Improvement in gut health may mitigate these consequences*

Questions?

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The views expressed in this presentation are those of the presenter and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the U.S. Government.

DNA Vaccines Hantaviruses, Alphaviruses, Filoviruses

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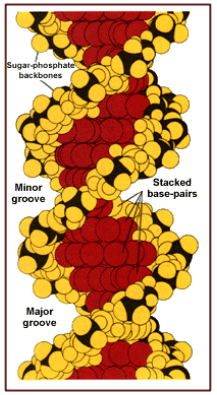
Connie Schmaljohn, Ph.D.
US Army Medical Research Institute of Infectious Diseases
US Army Medical Research and Materiel Command
24 March, 2015

DNA Vaccines

- **Easily Manufactured**
  - Can be quickly designed and produced in response to emerging or genetically engineered threats
  - DNA has established and approved manufacturing procedures
- **Safe**
  - Plasmids are replication defective
  - Not transmissible person to person or into the environment
- **No Pre-existing Vector Immunity**
- **Flexible Platform**
  - Easily combined to form multivalent vaccines
  - Can be delivered by a variety methods



DNA Vaccines

BSL-3

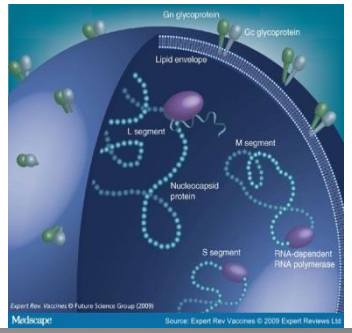
- **Alphaviruses**
  - Venezuelan equine encephalitis virus
  - eastern equine encephalitis virus
  - western equine encephalitis virus
- **Bunyaviruses**
  - Hantaan virus
  - Puumala virus
  - Sin Nombre virus
  - Andes virus
  - Rift Valley fever virus

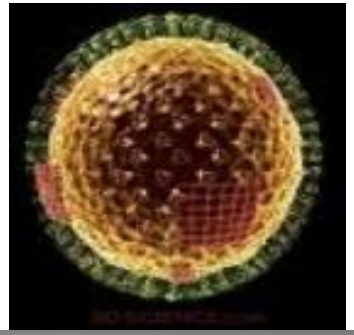
BSL-4

- **Filoviruses**
  - Ebola virus
  - Marburg virus
- **Flaviviruses**
  - Tick-borne encephalitis virus
- **Arenaviruses**
  - Lassa virus
- **Bunyaviruses**
  - Crimean-Congo hemorrhagic fever virus

Summary: HFRS DNA Vaccines

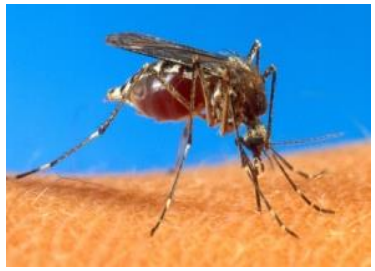
- Four hantaviruses cause HFRS in Europe and/or Asia: Hantaan, Puumala, Dobrava, and Seoul viruses
- Bivalent DNA vaccine (Hantaan and Puumala virus genes) protects animals against all four HFRS-causing hantaviruses
- Two Phase 1 studies (27 subjects each) completed
  - gene gun or intramuscular (IM) electroporation (EP) delivery
- Phase 2a dose ranging (120 subjects, IM-EP) in progress
- Phase 1 comparison of IM vs intradermal (ID) -EP delivery planned
- Orphan drug status granted by FDA





Summary: VEEV, EEEV, WEEV DNA Vaccines

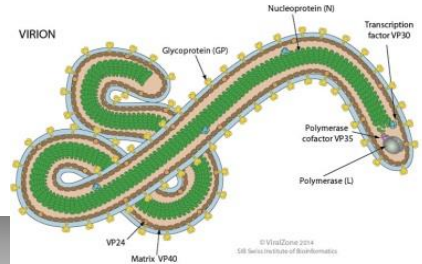
- Venezuelan (VEEV), eastern (EEEV) and western (WEEV) equine encephalitis viruses are endemic in the Americas, and are biological warfare threats
- DNA vaccines for VEEV, EEEV, and WEEV delivered by IM- or ID-EP protect nonhuman primates from aerosol challenge
- Phase 1 Study of VEEV vaccine delivered by IM vs ID-EP completed
- GMP lots of all three vaccines produced and nonclinical testing in progress
- GMP lots of all three vaccines are available for clinical testing





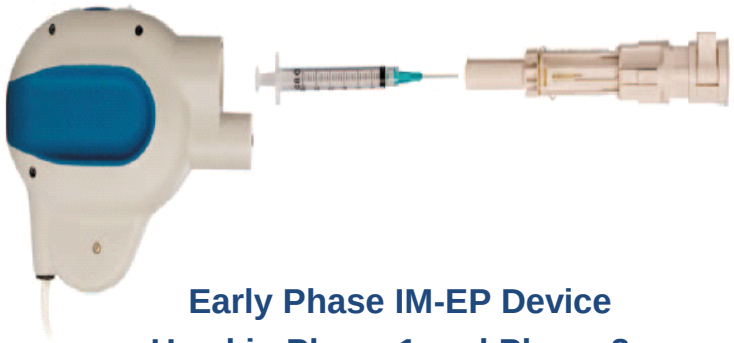
Summary: Filovirus DNA vaccines

- DNA vaccines expressing genes of Ebola (EBOV), Sudan (SUDV), Marburg (MARV) and Ravn (RAVV) viruses tested in mice and NHP
- 5/6 NHP vaccinated by IM-EP with EBOV or MARV DNA vaccines survived challenge with homologous virus
- 6/6 NHP vaccinated with quadrivalent vaccine survived MARV challenge
- 1/6 NHP vaccinated with quadrivalent vaccine survived EBOV challenge, suggesting immunological interference
- EBOV survivors had significantly higher neutralizing antibody titers than non-survivors



Electroporation

Ichor Medical Systems intramuscular (IM) and Intradermal (ID) Electroporation (EP) Device(s)



Early Phase IM-EP Device
Used in Phase 1 and Phase 2a

ID-EP Device
Jet injection, needle free
Used in Phase 1

Device Features

- Electroporation increases DNA uptake by cells
- Early phase device uses “off the shelf” syringe
- Automated, user independent administration
- Single button activation
- Controlled rate, site, and timing of injection
- Good tolerability scores
- Deployable electrodes
- Total duration ~5-10 seconds (EP < 1 second)
- Multiple redundant safety features
- Commercial device nearing completion

Questions?

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Opinions, interpretations, conclusions, and recommendations are those of the author and are not necessarily endorsed by the U.S. Army. All clinical research was conducted under Investiigational New Drug Protocols reviewed by a the FDA. Animal research was conducted under an IACUC approved protocol in compliance with the Animal Welfare Act, PHS Policy, and other Federal statutes and regulations relating to animals and experiments involving animals. The facility where this research was conducted is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care, International and adheres to principles stated in the Guide for the Care and Use of Laboratory Animals, National Research Council, 2011. This research was funded by the Military Infectious Diseases Research Program and the Defense Threat Reduction Agency.

U.S. Military HIV Research Program

Overview and Opportunities

UNCLASSIFIED

Dr. Robert A. Gramzinski

U.S. Military HIV Research Program

US Army Medical Research and Materiel Command

24 March 2015

Disclaimer

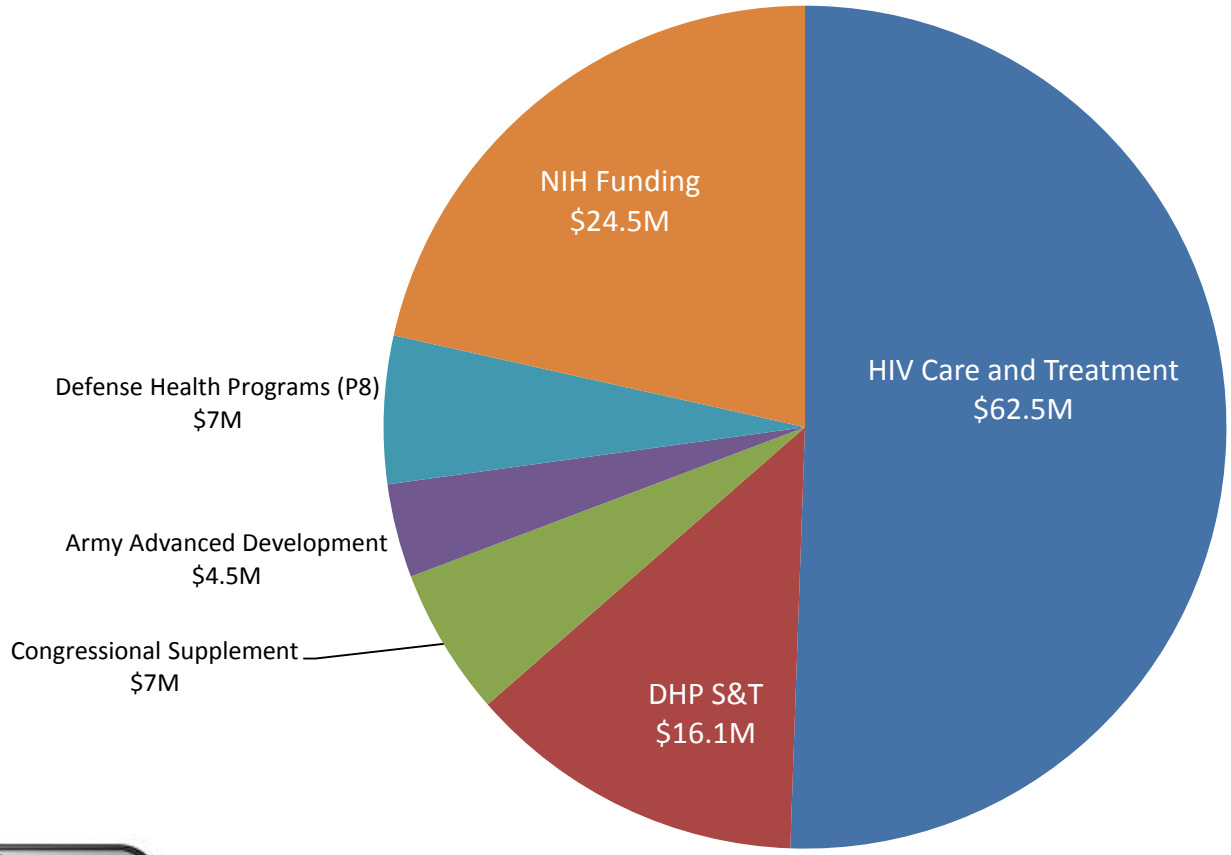
Material has been reviewed by the Walter Reed Army Institute of Research. There is no objection to its presentation and/or publication. The opinions or assertions contained herein are the private views of the author, and are not to be construed as official, or as reflecting true views of the Department of the Army or the Department of Defense.

Mission and Manpower

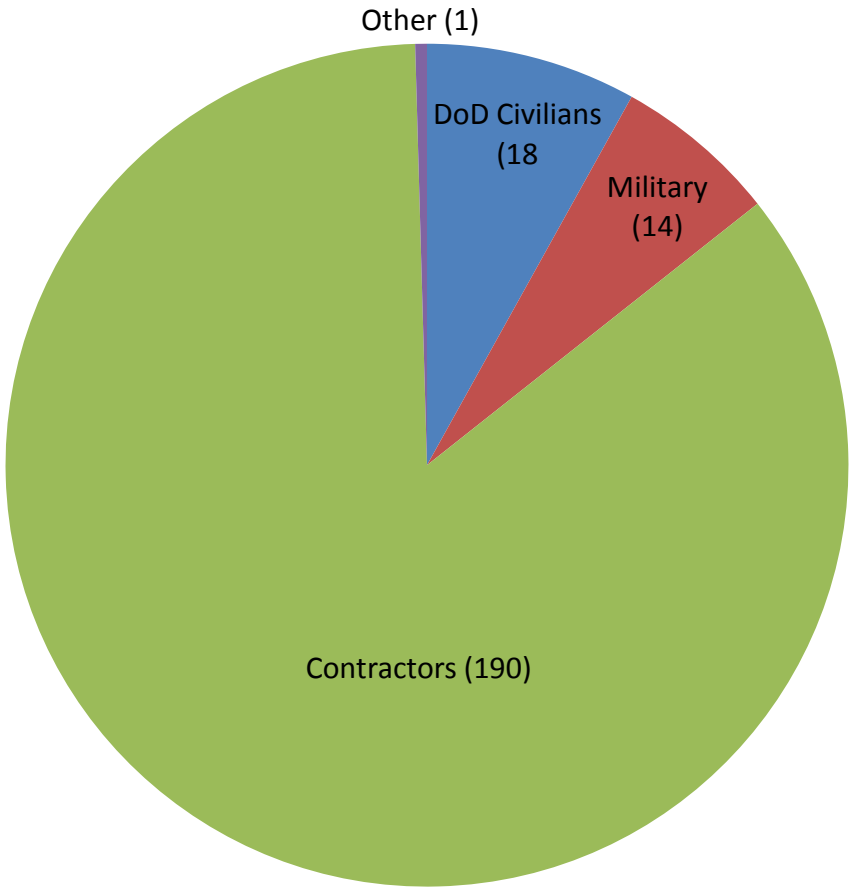
- US Military HIV Research Program is based at the Walter Reed Army Institute of Research in Silver Spring, Maryland
  - International Research Program executing:
    - HIV Basic, Translational, and Clinical Research
    - HIV Diagnostics
    - HIV Epidemiology and Threat Assessment
    - HIV Care and Treatment
  - Diversified workforce
    - Military
    - Department of Army Civilians
    - Contractors

MHRP FY15 Funding Breakdown

Total FY15 Funding = $121.4M



Workforce Composition



A Closer Look

- Since 1988 MHRP partnered with a Congressionally established non-profit organization to execute its mission

- Recent Cooperative Agreement Awards
  - Jun 1998: $173M 5 year award/1yr extension
  - Apr 2004: $183M 5 year award
  - Sep 2007: $437M 5 year award
  - Sep 2011: $817M 5 year award

- **Opportunities** in 2015 thru 2016
  - Expect new awards:
    - 2015
      - RFP/Contract Award for HIV Diagnostics
      - RFP/Contract Award for HIV Vaccine Advanced Development
    - 2016
      - PA/Cooperative Agreement for HIV Basic/Translational Research, Epidemiology, HIV Care & Treatment

DoD: Why HIV Research?

Force Health Protection

- Protect US and Allied Troops
- Walking blood bank
- Data-driven policy and prevention
- Long term care: quality and cost

National Security

- HIV as warstarter - societal destablization, economic impact
- CIA assessment, President's National Security Strategy
- Theater security / cooperation

Global Health

- Army has international focus and product development expertise
- Strong collaboration with NIH helps drives progress
- DoD provides NIH with access to clinical sites in endemic areas

An effective HIV vaccine is needed to end the pandemic, protect deployed American and allied troops, and stabilize key partners impacted by AIDS

Leveraged Resources

Builds partnerships and secures financial and in-kind support.

Gates Foundation, Sanofi Pasteur, Crucell, Global Solutions for Infectious Diseases, Novartis, Harvard, University of Washington, Duke, International NGOs, WHO, UNAIDS, Global HIV Vaccine Enterprise

- Strategic partnership with NIAID/NIH
- Broad pharmaceutical company partnerships (Sanofi, J&J, Crucell, Novartis, GSK)
- Collaborative relationship with the Bill & Melinda Gates Foundation
- Extensive engagements with international normative bodies (WHO, UNAIDS) and Non Government Organizations

MHRP: Force Readiness

HIV Epidemiology and Threat Assessment

- Develop knowledge products help public health leaders:
  - Identify gaps in service delivery
  - Address barriers that limit access to care
  - Provide services and education that promotes responsible sexual behavior.
  - inform force policy and develop and implement strategies

MHRP Diagnostics

- Accelerate and drive diagnostic research and product acquisitions
  - Industry partnerships ensure DoD acquires best products to support the warfighter
    - *MHRP conducted 50% of all pre-market applications for FDA clearance for HIV assays*
- Effective Clinical Monitoring for optimal patient care

MHRP Research in Developing Countries

DoD/MHRP

- Longstanding presence and strong relationships internationally
- Developed scientific infrastructures needed for sustainable research efforts
- Can conduct targeted research in parts of the world hit hardest by epidemics

Int'l Partners

- Improved scientific infrastructures
- Expanded human capacity to conduct research and provide effective care and prevention
- New technologies

Building Capacity and Infrastructure in Africa

- Develop scientific infrastructures needed for sustainable research efforts:
  - Build laboratory infrastructure and capacity
  - Expand human capacity to conduct research
  - Transfer new technologies
- Strong partnerships with local researchers, health care services and NGOs

International Research Network

Nigeria	• HIV vaccine cohort expansion • HIV rapid test algorithm study • Avian influenza/Pandemic influenza (GEIS)
Tanzania	• Vaccine Phase I/II trials • Pandemic Influenza (GEIS-TPDF) • Malaria studies (AFRICOM, PMI)
Uganda	• Vaccine Phase I/II trials • Ebola-Marburg vaccine development (VRC, DCR, IDCRP) • Avian influenza/Pandemic influenza (GEIS)
Kenya	• Vaccine Phase I/II trials - small clinical studies building on RV144 - planned follow-up to RV144 in MSM • AIDS Clinical Trial Group studies • HIV-Malaria initiative (DAIDS) • IRIS Study (IDCRP) • Pandemic influenza (GEIS, TPDF)
Mozambique	• Vaccine Phase I trials • Cohort studies
Thailand	• Vaccine Phase I/III trials • High risk cohort studies • Acute Infection studies • Therapeutics research • Laboratory - mucosal immunology and vaccine immuno-monitoring

Interagency Success

- Strong collaboration with National Institute of Allergy and Infectious Diseases (NIAID/NIH) helps drives progress
  - Jointly identify and address key research areas that will help speed progress in the quest for an effective HIV vaccine
  - NIAID depends upon MHRP's international clinical network to study diseases in endemic areas
- Interagency Agreement since 2003
  - Peer review of research proposals
  - Collaborative framework for publications, communications
  - RV144 trial was led by MHRP, funded by DoD (20%) and NIAID (80%)

Military HIV Research Program ROI

Force Readiness

- First demonstration that an HIV vaccine is p[illegible]
- Defined peri-deployment period as highest risk for HIV transmission
- Improved emergent whole blood screening
- Improved HIV testing algorithm
- Characterization of Army installation-specific HIV epidemics to inform outbreak investigations and delivery of preventive interventions
- Rapid influenza detection capability

National Security

- Strengthened health of foreign militaries (Africa, SW/SE Asia, South America)
- Provide key support of COCOM TSP via PEPFAR and PMI
- Improved US defense engagement with counterparts in sub-Saharan Africa and Thailand

Leveraged Resources

- Strategic partnership with NIAID/NIH
- Broad pharmaceutical company partnerships (Sanofi, J&J, Crucell, Novartis GSK)
- Strong Bill & Melinda Gates Foundation partnership
- Extensive engagements with international normative bodies (WHO, UNAIDS) and NGOs

International Infrastructure

- Expanded platforms for defense related clinical research in six countries or three continents
- Execution of IND research for both HIV and Ebola-Marburg countermeasures
- Embedded in US Embassies with close working relationships with DAO, ODC, and CDC/AID

$27.6 M
DoD funding

MIDRP/POM	$16.1 M
Adv Dev POM	$4.5 M
P8	$7.0 M

$94.0 M
Other Funding

PEPFAR	$62.5 M
DAIDS/NIAID/NIH	$24.5 M
CSI	$7 M

2015 Total Funding
$121.4 M

www.hivresearch.org

Soldier Health.
World Health.

The MHRP is centered at the Division of Retrovirology, Walter Reed Army Institute of Research (WRAIR), U.S. Army Medical Research and Materiel Command. MHRP works closely with a not-for-profit research support organization, the Henry M. Jackson Foundation for the Advancement of Military Medicine (HJF), through a cooperative agreement.

Strategic Gaps in the Pharmaceutical Systems PMO ID Portfolio

UNCLASSIFIED

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Pharmaceutical Systems Program Management Office

US Army Medical Research and Materiel Command

24 March 2015

Purpose

To increase understanding of strategic gaps with the PSPMO.

- Top priority ID efforts in PSPMO
  - *Malaria countermeasures (drugs and vaccines)*
  - *Dengue vaccine*
  - *Leishmaniasis countermeasures (diagnostics and treatments)*
  - *Future: Chikungunya??*

Leishmaniasis

Status of Leishmaniasis countermeasures:

1. Diagnostic Capability Gap
   - Fulfilled. Leishmaniasis Rapid Dx Device FDA cleared.
2. Treatment for Cutaneous Leishmaniasis (CL) in development
   - Phase 3 studies nearing completion (FY16)
   - Gap: Long-term commercial/co-development partner and final product manufacturer not yet identified

Chikungunya

Status of Chikungunya countermeasures:

- Chikungunya program beginning
- 2010 COCOM Rank = 16 / 20
  - Priority is likely to increase.

- MRMC possesses a live, attenuated candidate
- MRMC actively seeking commercial partners for development of Chikungunya vaccine candidates
- Key challenge = Efficacy studies
  - MRMC has clinical sites in endemic areas

Questions?

For additional questions after the conclusion of the conference, send an email message to usarmy.detrick.medcom-usamrmc.mbx.mmpd@mail.mil