



**Infectious Diseases Clinical Research Program at  
Uniformed Services University  
Department of Preventive Medicine and Biostatistics**

# **IDCRP Program Overview For the Defense Health Board**

**Public Meeting 2 June 2016**

***A USU/DOD - NIAID Partnership***

National Institute of Allergy and Infectious Diseases  
Uniformed Services University, 'America's Medical School'



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# IDCRP overview

Proven model for multi-center clinical research in MHS

## **Vision:**

To substantially reduce the impact of infectious disease in the military population through collaborative clinical research.

## **Mission:**

To conduct multicenter infectious diseases clinical research, focusing on high-impact cohort and interventional trials, to inform and improve care of the Warfighter.

- Collaboration between USU, MTFs, DoD Biomedical R&D commands, NIAID, other partners
- Chartered by ASD(HA) as a Tri-Service DoD research center at USU



# IDCRP overview

Defining characteristics as an MHS clinical research platform

Groundbreaker in

1. Coordinating research from numerous & geographically diverse entities/locations
2. Standardizing and simplifying the IRB process for multicenter studies
3. Leading the way in innovative, collaborative, impactful research



# IDCRP Research Areas

- HIV
- Deployment / Travel-Associated Infections
- Skin and Soft Tissue Infections (SSTI)
- Sexually Transmitted Infection (STI)
- Emerging Infectious Diseases and Antimicrobial Resistance
- Acute Respiratory Infections
- Trauma-Related Infections

# IDCRP Platform Evolution

2006



2016

## Tertiary care MTFs

## Overseas Troop Clinics

Nanyuki Training Ground (U.K.), Kenya  
Camp Soto Cano, Honduras  
Camp Lemonnier, Djibouti  
Camp Bastion (U.K.), Afghanistan

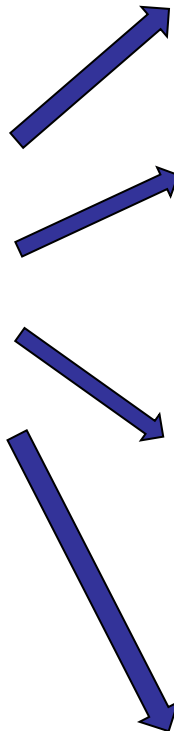
## Operational Forces Settings:

Fort Benning, GA; Fort Bragg, NC; Fort Lewis, WA; Fort Carson, CO; Fort Sam Houston, TX; Naval Station Norfolk; *Ft. Hood TX; Lackland AFB, TX; Camp Lejeune, NC*

## Shipboard and submarine platforms:

San Diego, Portsmouth

**Major  
Tertiary  
Care  
Centers**



# 17

military treatment facilities

# 125+

employees

# 57

active protocols



PARTNER MILITARY COMMANDS

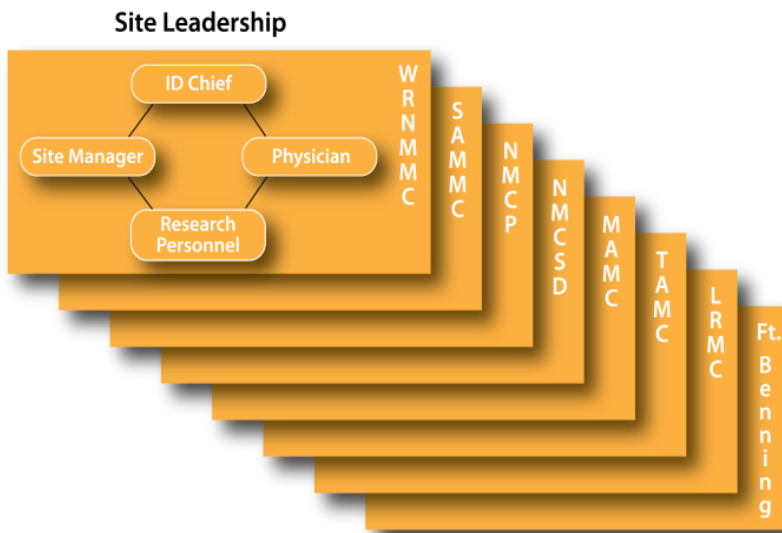
# IDCRP Sites in the MTFs

WRNMMC, SAMMC, NMCS D, NMCP, MAMC

TAMC, LRM C, MACH

WAMC, NHCL

- *IDCRP Staff Embedded in Clinic under direction of Clinic Chief*



- Research Physician
  - 80% research/ 20% clinical and education
- Site manager
  - Oversee all non-physician staff
  - Coordinate all research activities
- Coordinators, Associates and Regulatory Staff





# The Network ID IRB at USU

## A Unique and Critical Aspect of the IDCRP

- ❑ With support of Asst Sec'y of Defense for Health Affairs, MOU was signed in 2008 by Service Surgeons General and USU President
- ❑ Comprised of members and alternates selected by each of the major clinical research partners' commands
  - Ensures unique service and command concerns are addressed
- ❑ Independent of the IDCRP and administered at USU via Office of VPR
- ❑ HQ Admin review performed by Tri-Service Panel at DoD Health Affairs
- ❑ Command level approval before study initiation
- ❑ MOU renewal in process to reflect that DHA is operational



## Executive Steering Committee (ESC)

- Chief, Division of Clinical Research (DCR), National Institute of Allergy and Infectious Diseases (NIAID)
- Dean, School of Medicine, Uniformed Services University of the Health Sciences (USU)
- Director, Research, Development and Acquisition, Defense Health Agency

## Operational Steering Committee (OSC)

- Surgeon General Infectious Disease Consultants—Army, Navy, Air Force
- Director, Armed Forces Health Surveillance Center
- Director, Military Infectious Diseases Research Program, MRMC
- Chief, Collaborative Clinical Research Branch, DCR, NIAID
- Chair, Department of Preventive Medicine and Biometrics, USU
- VA Representative (non-voting)
- HJF Representative (non-voting)

## Program Coordination Center (PCC)

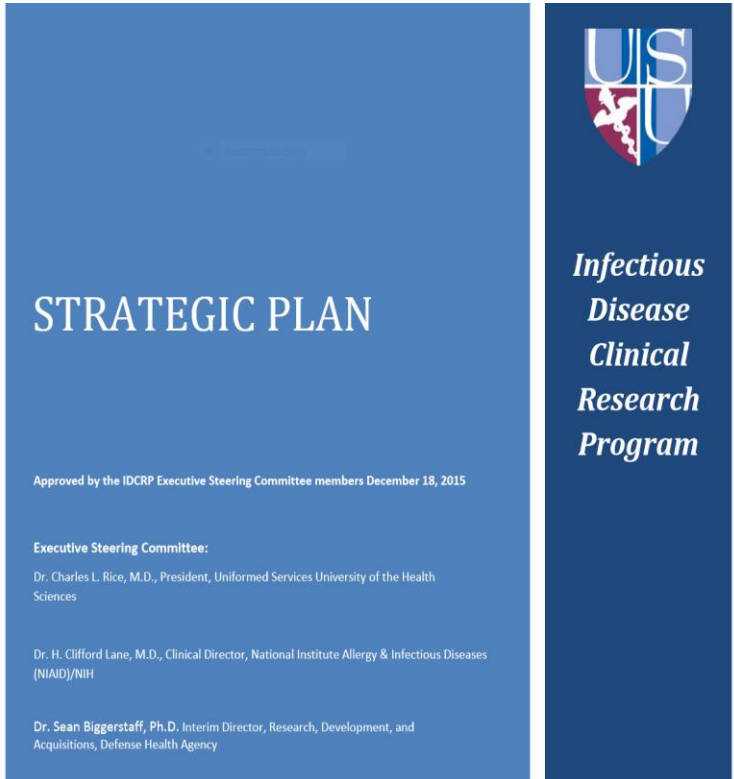
- DIRECTOR**
- Scientific Directorate**
    - Science Director
    - Science Deputy Director
    - Research areas
      - Research area directors and lead clinical research managers
    - Data Coordination Center
      - Data configuration
      - Data management
      - SAS programming
      - Oracle programming
    - Education
  - NIAID Liaison**
    - Chair, Scientific Review Board
  - Deputy Director**
    - Research Administration
    - Regulatory Affairs

## Partnering Networks

- Military Hospitals
- Military Research and Development Commands
- Military Public Health Commands
- Non-DoD Partners



# Strategic Plan



Approved by Executive Steering Committee  
Dec 2015

Program chartered as a DoD Center, based  
at USU, by ASD(HA) in Dec 2015

Core values: Collaboration, Innovation,  
Quality, Adaptability, Dedication

Success is Defined By:

- ❑ Informing military health policy and practice through translation of research findings
- ❑ Publications and presentations within impactful and relevant peer-reviewed journals/forums
- ❑ Capability to respond to emergent infection threats and/or high-priority research initiatives
- ❑ Key stakeholder satisfaction



# IDCRP Strategic Plan Specific Aims

**SP Aim 1:** Plan, execute, and disseminate findings of clinical infectious disease research of relevance and impact for the US military.

**SP Aim 2:** Align and support infectious disease product development for the warfighter through partnership with MIDRP and Navy Advanced Development.

**SP Aim 3:** Align and support infectious disease military public health surveillance through partnership with the Armed Forces Health Surveillance Branch (AFHSB) and other military surveillance activities/centers.

**SP Aim 4:** Develop integrated research plans in the area of clinical infectious diseases in collaboration with Veterans Affairs (VA) Health Systems to provide improved outcomes research across the active duty-veteran lifecycle.

**SP Aim 5:** Sustain and enhance NIAID/NIH collaborations, yielding greater generalizability of research impact to both the DoD and the US civilian population.

**SP Aim 6:** Align and support clinical research along with investigator education and training within DoD.

**SP Aim 7:** Develop and sustain a robust military clinical research network, with capability to execute FDA-regulated clinical trials.



# HIV Research Area Scientific Strategic Plan

**Research Area Director: Brian Agan, MD**

**Aim 1:** To understand the epidemiology and pathogenesis of specific complications of HIV and HAART among military HIV infected patients.

**Aim 2:** To develop and employ predictive models allowing targeted care to optimize individualized management of HIV.

**Aim 3:** To improve therapeutic outcomes with the ultimate goal of functional cure of HIV.

**Aim 4:** To understand HIV acquisition among active duty service members and how to effectively prevent new infections.



# HIV Research Area Overview



## HIV Natural History Study

- Non-AIDS/ Non-Communicable Disease diagnoses
- Many active analyses including Risk Behavior analyses underway
- Manuscripts (since April 2015): **Total 18** (8 published, 3 accepted, 1 in revision, 6 submitted)
- Meeting Presentations (since April 2015): **Total 12**
- Continued efforts to increase repository-based science
  - Nine currently active analyses, several more in development
  - 4 new NHSR requests filled/in process 2016
- Strong productivity and extramural collaborations

Hist-HTLV 28 April 1988

1. TITLE:  
The Natural History of HIV Infection and Disease in United States Military Beneficiaries. - REVISION of Protocol WU#1943

2. INVESTIGATORS:

PRINCIPAL INVESTIGATOR

Edmund C. Tramont, MD  
COL, MC  
OTSG Consultant Infectious Diseases  
Chief, Infectious Disease Service  
Director, HIV Research  
Walter Reed Army Medical Center  
Washington, DC 20307-5001  
(202) 576-0584

CO-INVESTIGATORS

Charles N. Oster, MD  
COL, MC  
Chief, Clinical Infectious Disease Service  
Walter Reed Army Medical Center  
Washington, DC 20307-5001  
(202) 576-1740

Donald Burke,  
COL, MC  
Chief, Dept. of Virus Diseases  
Walter Reed Army Institute of Research  
Washington, DC 20307-5001  
(202) 576-3757

John W. Boslego, MD  
LTC, MC  
Dept of Medicine  
Walter Reed Army Medical Center  
Washington, DC 20307-5001  
(202) 576-3303

Robert R. Redfield, MD  
MAJ (P), MC  
Dept. of Virus Diseases  
Walter Reed Army Institute of Research  
Washington, DC 20307-5001  
(202) 576-3655



# The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

AUGUST 27, 2015

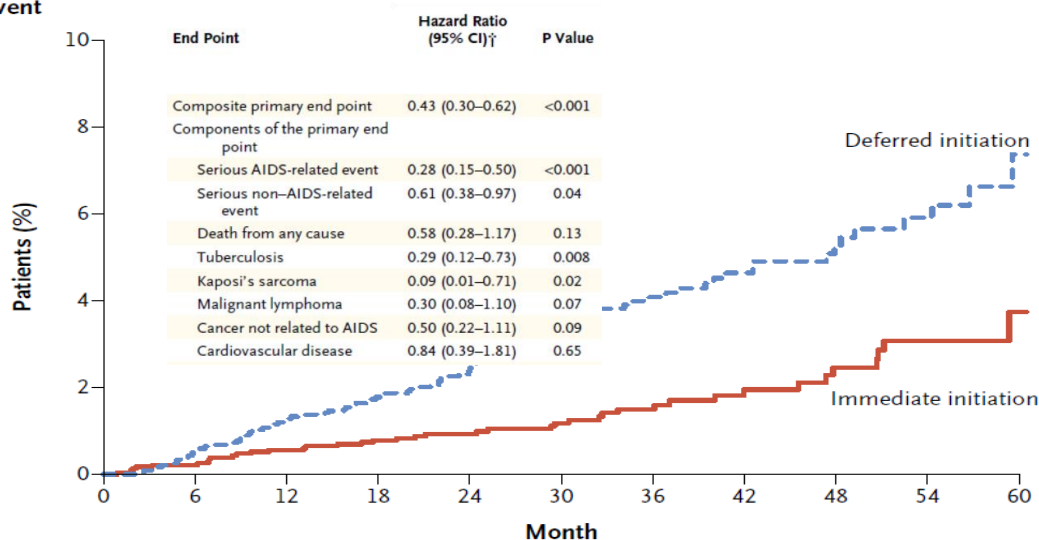
VOL. 373 NO. 9



## Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group\*

### A Time to First Primary Event



#### No. at Risk

Immediate initiation	2326	2302	2279	2163	1801	1437	1031	757	541	336	110
Deferred initiation	2359	2326	2281	2135	1803	1417	1021	729	520	334	103

#### Estimated Percentage

Immediate initiation	0.2	0.6	0.8	0.9	1.2	1.5	2.0	2.5	3.1	3.7
Deferred initiation	0.5	1.2	1.8	2.4	3.3	4.1	4.6	5.3	5.9	7.4





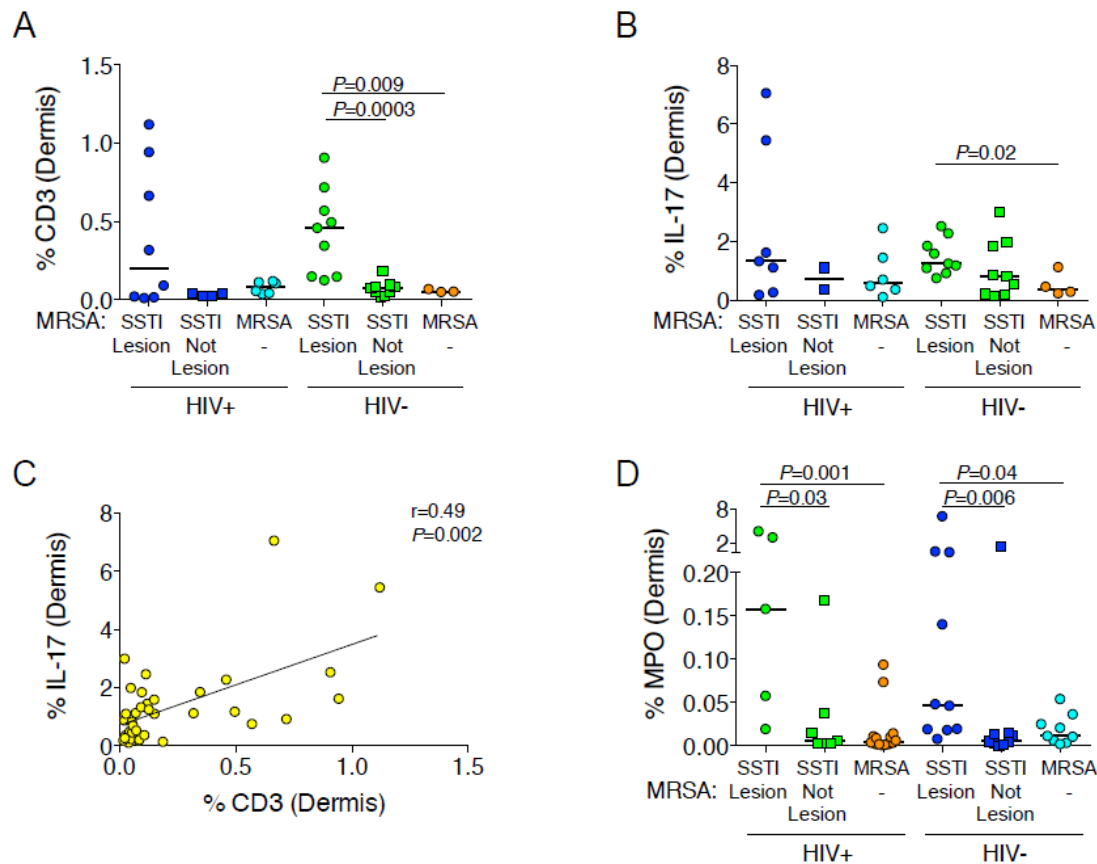
# MRSA Infections in HIV-Infected People Are Associated with Decreased MRSA-Specific Th1 Immunity

PLOS Pathogens April 19, 2016

Netanya S. Utay, Annelys Roque, J. Katherina Timmer, David R. Morcock, Amy C. Weintrob, Brian K. Agan, Jacob D. Estes, Nancy F. Crum-Cianflone, Daniel C. Douek

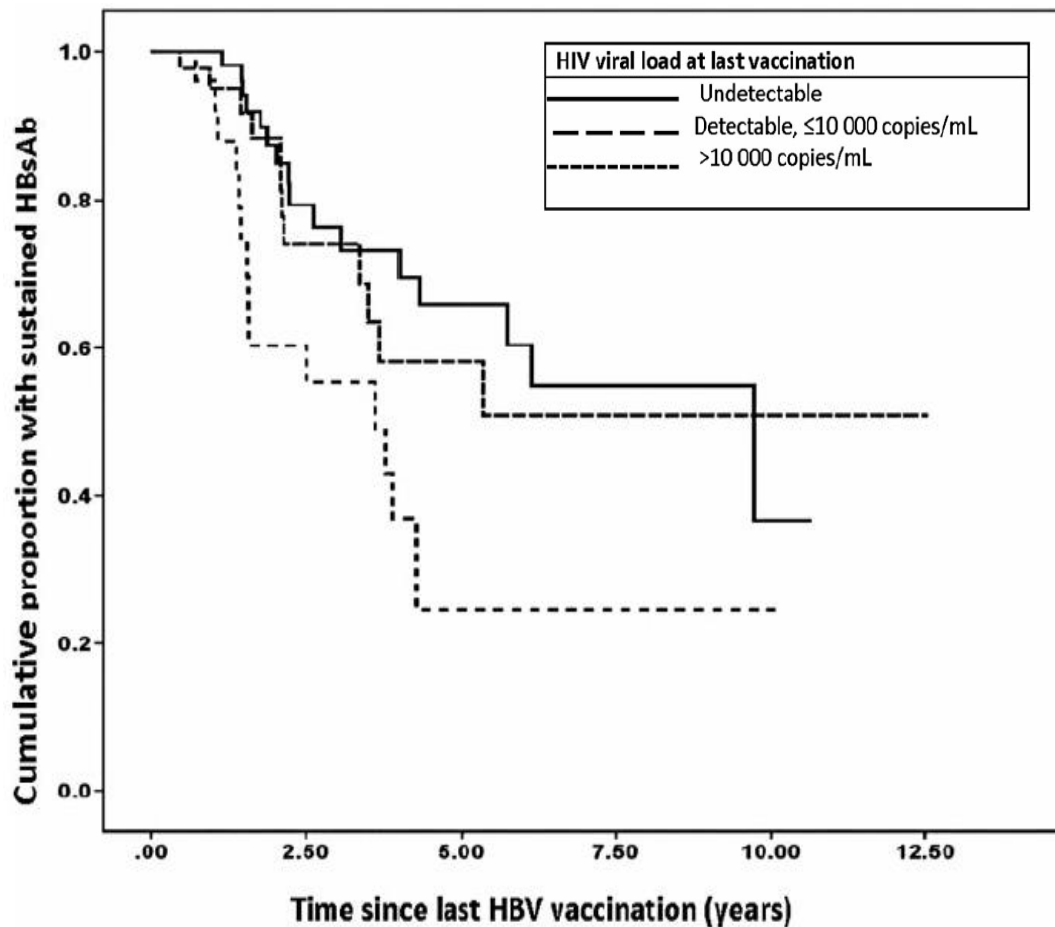


Figure 3



## ORIGINAL RESEARCH

## HIV viraemia during hepatitis B vaccination shortens the duration of protective antibody levels

TA O'Bryan,<sup>1,2</sup> EA Rini,<sup>2</sup> JF Okulicz,<sup>2</sup> O Messner,<sup>1</sup> A Ganesan,<sup>1,3</sup> T Lalani,<sup>1,4</sup> MF Bavaro,<sup>5</sup> RJ O'Connell,<sup>6</sup> BK Agan<sup>1</sup> and ML Landrum<sup>1,2</sup>

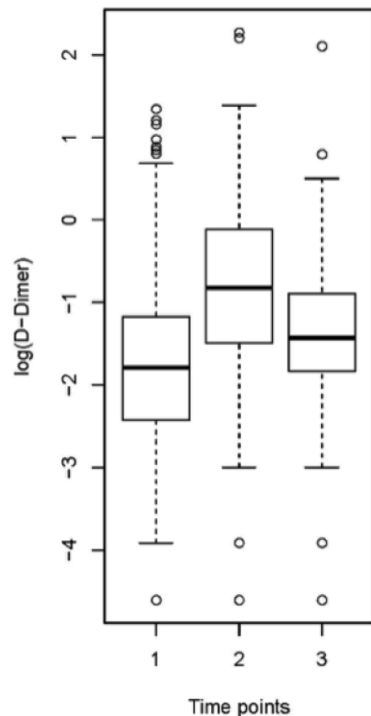
Characteristic	n	Univariate HR (95% CI)	P
<b>Age</b>			
< 33 years	89	0.78 (0.45–1.36)	0.38
≥ 33 years	97	Reference	
<b>Gender</b>			
Male	158	1.46 (0.62–3.42)	0.39
Female	28	Reference	
<b>Race</b>			
African-American	82	1.66 (0.68–4.08)	0.27
Caucasian	75	1.82 (0.73–4.49)	0.20
Other	29	Reference	
<b>HIV diagnosis era</b>			
Before 1996	81	1.49 (0.82–2.71)	0.19
During or after 1996	105	Reference	
<b>Number of HBV vaccinations</b>			
1 or 2	51	0.83 (0.39–1.76)	0.63
3	64	1.18 (0.63–2.20)	0.61
4 or more	71	Reference	
<b>CD4 count at last vaccination (n = 185)</b>			
< 500 cells/μL	57	1.09 (0.54–2.18)	0.81
500–699 cells/μL	76	1.18 (0.60–2.32)	0.64
> 700 cells/μL	52	Reference	
<b>HIV viral load at last vaccination (n = 162)</b>			
Undetectable by assay	81	0.37 (0.18–0.76)	<0.01*
≤ 10 000 copies/mL	49	0.46 (0.21–1.00)	0.05†
> 10 000 copies/mL	32	Reference	
<b>Receipt of HAART</b>			
Yes	96	Reference	
No	90	1.29 (0.73–2.27)	0.38
<b>Hepatitis C virus serology</b>			
Positive	6	3.37 (0.46–24.46)	0.14
Negative	180	Reference	

RESEARCH ARTICLE

# D-Dimer Levels before HIV Seroconversion Remain Elevated Even after Viral Suppression and Are Associated with an Increased Risk of Non-AIDS Events

Matthew S. Freiberg , Ionut Bebu, Russell Tracy, Kaku So-Armah, Jason Okulicz, Anuradha Ganesan, Adam Armstrong, Thomas O'Bryan, David Rimland, Amy C. Justice, Brian K. Agan, Infectious Disease Clinical Research Program HIV Working Group 

Published: April 18, 2016 • <http://dx.doi.org/10.1371/journal.pone.0152588>



## NEJM Journal Watch

HOME SPECIALTIES & TOPICS NEWS BLOGS CME

SUMMARY AND COMMENT | INFECTIOUS DISEASES, HIV/AIDS

INFORMING PRACTICE

May 3, 2016

### D-Dimer Levels Remain Elevated After Starting ART, Linked to Increased Risk for Non-AIDS Events

Keith Henry, MD reviewing Freiberg MS et al. PLoS One 2016 Apr 18.

RA Overview – Aim 2  
Targeted HIV Care

# Deployment & Travel-related Infections Research Area Scientific Strategic Plan

**Research Area Director: Tahanyat Lalani, MBBS, MHS**

**Aim 1:** To describe the clinical features of infectious diseases among deployed military personnel and other DoD beneficiaries.

**Aim 2:** To evaluate the knowledge of infectious disease threats and prevention methods as well as counseling and prescription practices of providers in the pre-deployment setting.

**Aim 3:** To assess novel diagnostic test platforms to improve infection exposure ascertainment used in clinical outcomes assessment.

**Aim 4:** Inform optimal prevention strategies to limit the high rates of infection during military deployments (e.g. TD, particularly due to uncontrolled food sources).

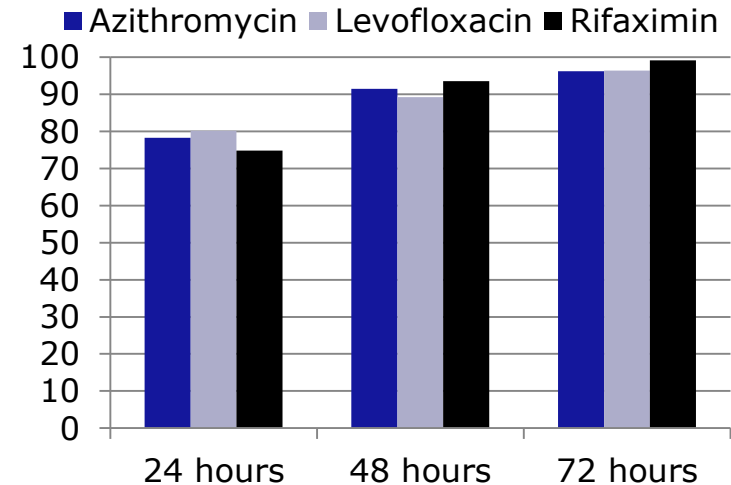
**Aim 5:** To evaluate the safety and effectiveness of treatment strategies for TD and vector-borne febrile illnesses optimized for military application.



# Recent data from D/T Research Area

## ■ TrEAT-TD clinical trial:

- No difference in cure rates observed in the watery diarrhea arm (figure)
- Utilized a novel platform for storage and detection of diarrheal enteropathogens:
  - Stool smears stored at room temp >2 years on Whatman FTA Elute cards, had comparable detection rates to frozen stool via quantitative PCR assay



## ■ TravMil (observational study):

- Low compliance with use of personal protective measures noted among travelers to regions with risk of falciparum malaria or arboviral infection:
  - 53% (95% CI: 48%-57%) were compliant with skin repellent use
  - 16% (95% CI: 12%-19%) used permethrin on clothing
  - 39% (95% CI: 35% -43%) used a bed net
- Moderate or severe TD is independently associated with suboptimal self-treatment (OR 10.4 [95% CI: 4.92-22.0]) i.e. self-treatment without an antibiotic
  - IBS occurred in 4.5% (7/154) of TD cases and 3.1% (16/516) of patients without TD (p=0.39)

# Skin & Soft Tissue Infections

## Research Area Scientific Strategic Plan

Research Area Director: Eugene Millar, PhD

**Aim 1:** To describe the clinical characteristics and outcomes of SSTI, and MRSA SSTI, in military settings at high risk for overall and MRSA SSTI in order to inform prevention strategies (specifically recruit training and submarine deployments)

**Aim 2:** To determine the impact of *S. aureus* SSTI on military training and determine the direct medical and indirect costs of these infections

**Aim 3:** To determine the etiology of non-purulent SSTI in a high-risk setting to inform prevention and treatment strategies

**Aim 4:** To determine the *S. aureus*- specific humoral and cellular immune responses associated with colonization, infection, protection against disease, and favorable clinical response

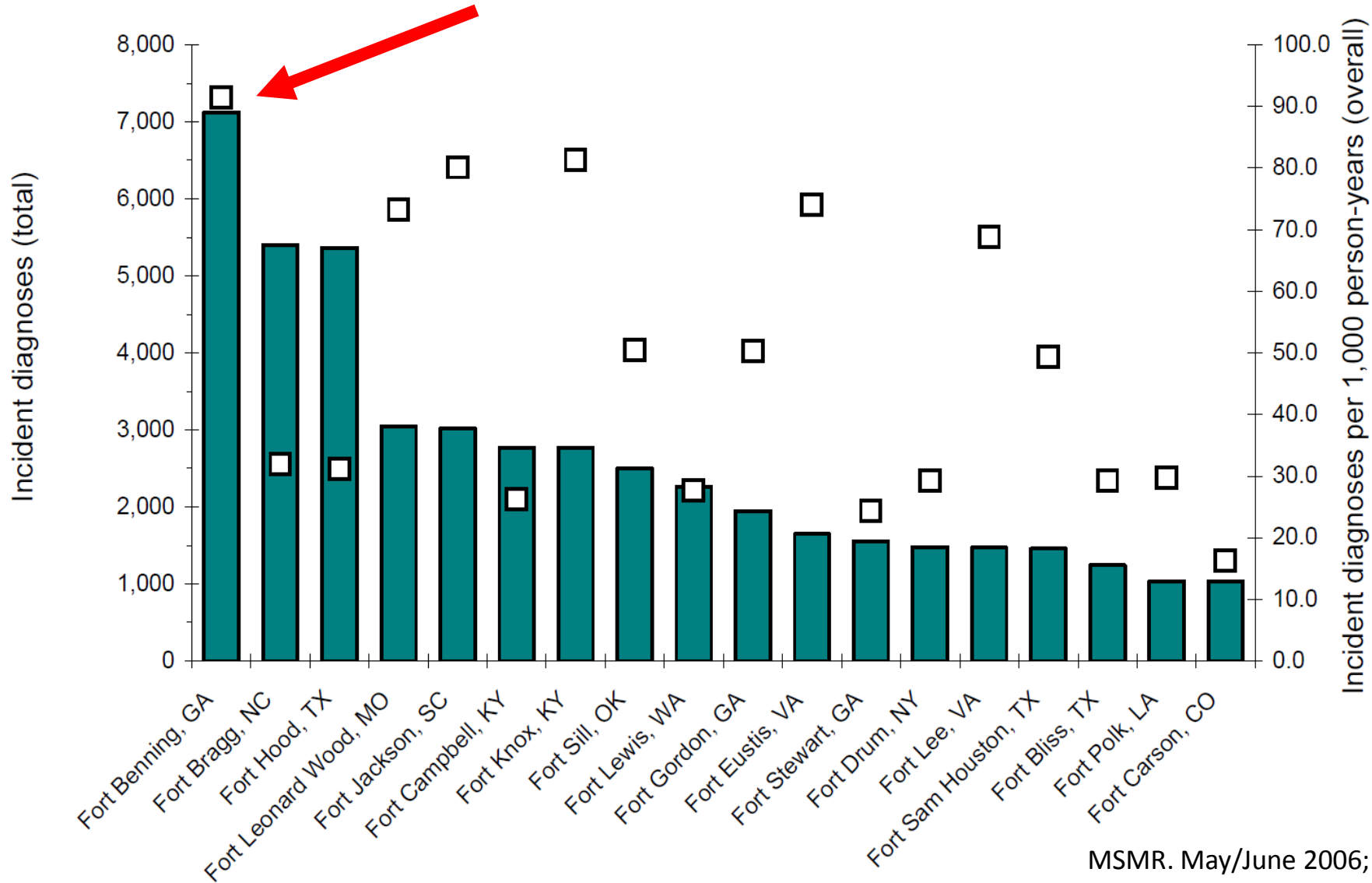
**Aim 5:** To describe the microbiome of military personnel with and without *S. aureus* SSTI and determine whether it is associated with infection risk, disease manifestation, or clinical outcome

**Aim 6:** To determine optimal treatment duration and explore novel strategies for treating SSTI in a high-risk setting

**Aim 7:** To evaluate hygiene and vaccine-based strategies for preventing *S. aureus* SSTI

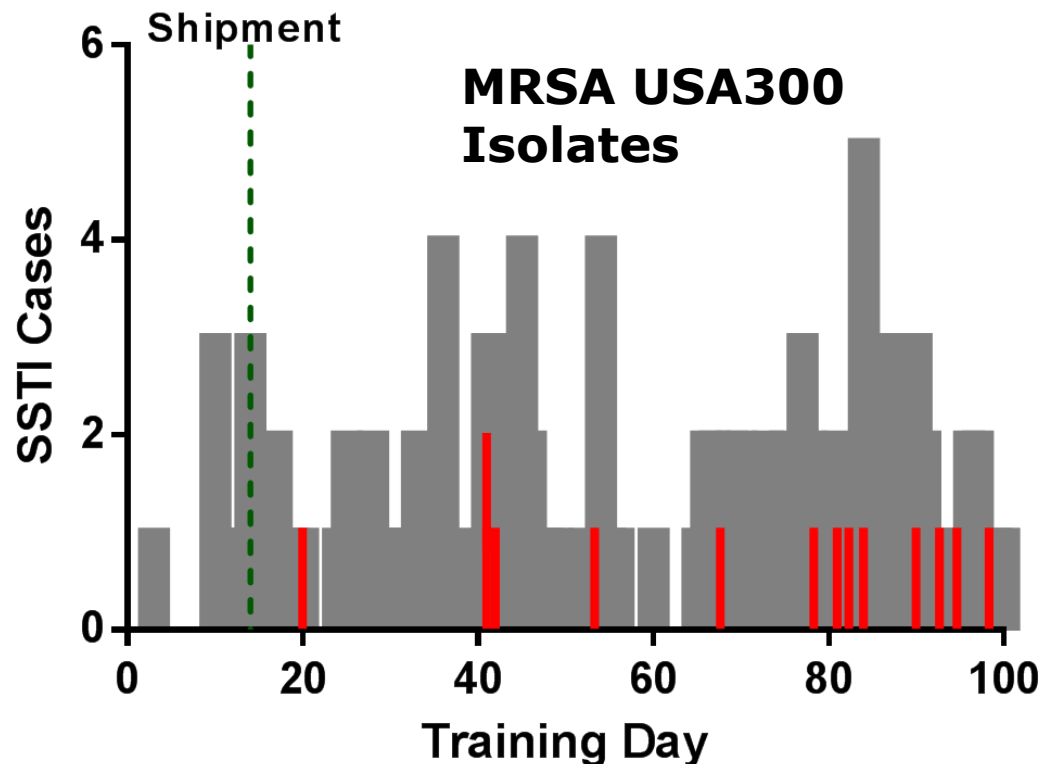


# Rates of SSTI at US Army Bases



# IDCRP-074: SSTI Epidemiology Study

Describe the epidemiology of SSTI in a high CA-MRSA setting- determine incidence rates, clinical presentations, outcomes, recurrence rates, and risk factors



- Jul 2012-Dec 2014, 2008 cases of SSTI enrolled among ~52,000 trainees
- SSTI rate of 4%
  - 84% *S. aureus*
  - 54% MRSA
- Approximately 10% of trainees get recurrent infections during infantry basic combat training



# Emerging ID and Antimicrobial Resistance Research Area Scientific Strategic Plan

**Research Area Director: MD, PhD  
PhD**

**AIM 1:** To determine what emerging infections are affecting military health and to what extent, risk factors, and whether future research should be pursued.

**AIM 2:** To improve understanding of the natural history, clinical features, pathogenesis, and immune responses to emerging infectious diseases affecting military health.

**AIM 3:** To improve understanding of treatment and outcome differences of emerging infectious diseases affecting military health.

**AIM 4:** To evaluate new diagnostics for emerging infectious diseases affecting military health.

**AIM 5:** To evaluate preventive measures against emerging infectious disease affecting military health.



# Emerging ID and Antimicrobial Resistance Research Area Scientific Strategic Plan

**AIM 6:** To compare clinical outcomes and antibiotic exposure to specific microbiologic pathogenicity factors such as clonal patterns, resistance mechanisms, and/or additional genotypic/phenotypic characteristics in colonizing or infecting organisms isolated from trauma patients (also listed as part of Trauma Conditional Aim 5 using the TIDOS dataset).

**AIM 7:** Evaluate novel antibiotics for MDRO in multicenter drug trials.

**AIM 8:** To evaluate epidemiology, risk factors and natural history of carriage of MDR Enterobacteriaceae in the gut microbiome in healthy military personnel.

**PROVISIONAL AIM 9:** Assess the impact of antibiotic administration on MICs of all antibiotics, not only the drug in use, and evaluate effectiveness of the new DoD antibiotic stewardship program.



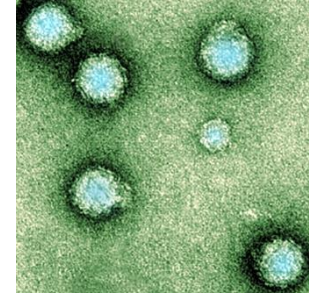
# Ebola Treatment

## PREVAIL

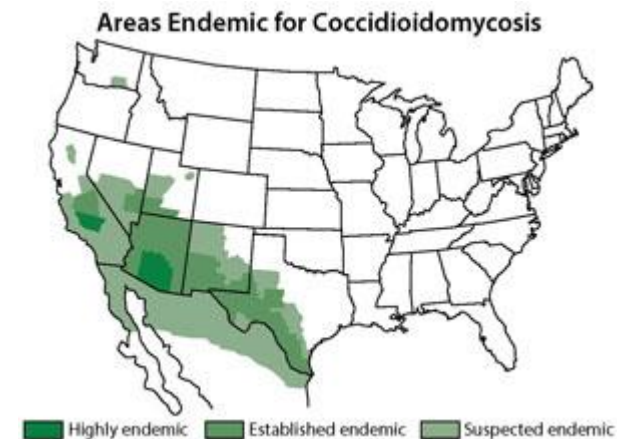


- NIAID-sponsored RCT protocol. 1 Chair
  - To evaluate optimized supportive care compared to intervention with Zmapp™
- 4 Participating US sites and West Africa sites
  - NIH, U Nebraska, Emory, WRNMMC
  - Liberia, Sierra Leone, Guinea
- IDCRP partnered in joint scientific/ethical review
  - Access to major DoD medical centers through research infrastructure
  - Potential to stand up new sites within MHS rapidly
  - Provide service members access to state-of-the-art products through research protocols
- Overall 28 day mortality 21/72 (29.6%)
  - CFR Rate – 8/36 (22.2%) vs Control 13/35 (37.1%)
  - 91.2% posterior probability that ZMapp™ arm superior
    - Not statistically significant (short of 97.5% predefined cutoff)
    - Supports a trend suggesting beneficial effect of ZMapp™

# Upcoming EIDAR Studies



- Virtual cohort to evaluate the impact of short and long term disability associated with Chikungunya
- Impact of bacterial resistance and patient comorbidities on outcomes in MDRO bloodstream infections
- Impact of Coccidioidomycosis on US military
  - Expansion of Naval Air Station Lemoore – in the heart of endemic zone
- Impact of *Borrelia miyamotoi* in service members stationed in the Northeast/Midwest
- Contingency protocols for EID syndromes – EPICC-SARI, EPICC-VHF



# Sexually-Transmitted Infections Research Area Scientific Strategic Plan

## Research Area Director: PhD

**Aim 1:** To evaluate the military impact of multi-drug resistant gonorrhea (MDR-GC) among active duty members.

**Aim 2:** To evaluate the military impact of other high-risk/high prevalence STIs among active duty members.

**Aim 3:** To develop and test STI prevention efforts among active duty members to inform DoD policy and impact STI clinical practice.

**Aim 4:** To evaluate novel strategies to improve STI treatment outcomes and practices in the military.



# Current STI portfolio

## ❑ **GC resistance study**

- ❑ Prospective study of military beneficiaries at risk for GC/CT
- ❑ Clinical sites: NMCP, SAMMC, MAMC, NMCS D

## ❑ **Social networks study**

- ❑ To understand racial differences in social networks among military members
- ❑ To understand social networks and its association with risk behaviors and STIs
- ❑ Clinical sites: NMCP, SAMC, MAMC, NMCS D

## ❑ **STI Serosurvey**

- ❑ Secondary data analyses of MHS data from 100,000 active duty members from 15 year accession cohorts with 2:1 oversampling of women

## ❑ **HIV Natural History Study—STI epi sub study**

- ❑ Risk behavior and prospective STI screening data from an HIV+ beneficiary cohort

## ❑ **Planned Analyses**

- ❑ Short- and long-term outcomes associated with STIs (MHS data)
- ❑ Remnant specimen STI surveillance



# Acute Respiratory Infections Research Area Scientific Strategic Plan

**Research Area Director: PhD**

**Aim 1:** To describe the clinical features, course and outcomes of ILI among DoD active duty and beneficiaries.

**Aim 2:** To utilize novel diagnostic platforms for the determination of ILI etiology among active duty and related populations, and to correlate etiology with host immune response and clinical outcomes.

**Aim 3:** To explore novel strategies for the prevention and treatment of influenza and other respiratory viruses.

**Aim 4:** To investigate severe, epidemic, or emerging respiratory threats, and undiagnosed ILI to identify etiology, evaluate diagnostics, describe epidemiology and clinical characteristics, course and outcomes, and to study therapeutic and preventive measures.



# IRC005 influenza convalescent plasma RCT

- **Study Aim:** Evaluate efficacy of rx w/ high-titer vs. low-titer anti-flu immune plasma + standard care in subjects hospitalized with severe flu A by clinical status at Day 7
- **Design:** Multicenter, double-blinded, phase 3 RCT. Target enrollment: 150 subjects
- **Sites:** 25 centers (including 5 IDCRP ARIC NHS sites)
- **Status:** 2 IDCRP sites activated in April 2016, 3 more IDCRP sites to be activated for 2016-2017 flu season

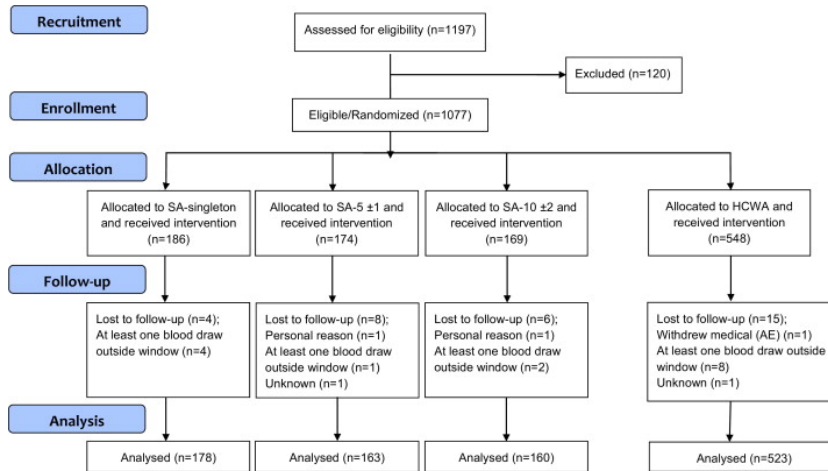




# Self-administration of intranasal influenza vaccine: Immunogenicity and volunteer acceptance

Burgess TH, Murray CK, Bavaro MF, Landrum ML, O'Bryan TA, Rosas JG, Cammarata SM, Martin NJ, Ewing D, Raviprakash K, Mor D, Zell ER, Wilkins KJ, Millar EV

*Vaccine*. 2015 Jul 31;33(32):3894-9. doi: 10.1016/j.vaccine.2015.06.061



- Study Aim:** Evaluate feasibility of self-administration of LAIV. Solicited by US Military Vaccines Agency.
- Design:** 2-site, block-randomized RCT: self-administration vs HCW-administration of LAIV. Enrolled 1077 volunteers over two vaccination seasons. Assessed acceptance, feasibility, immunogenicity.
- Results:** Post-administration, more volunteers expressed preference for self-administration vs HCW. No difference in immunogenicity.

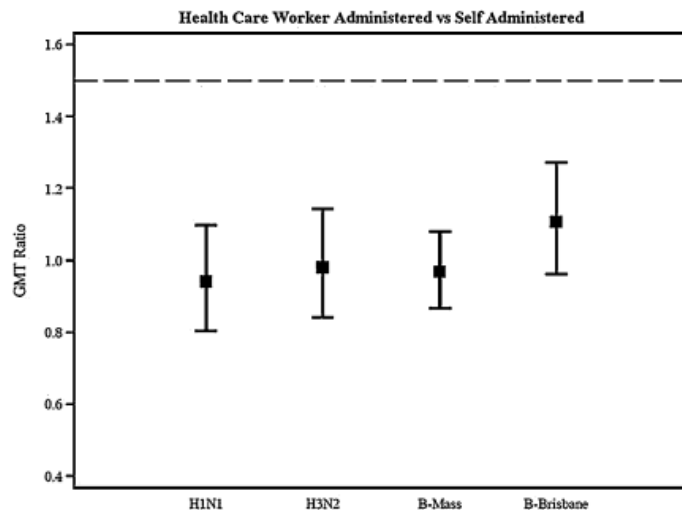


Fig. 2. Immunologic non-inferiority of health care worker-administered versus self-administered live attenuated influenza vaccine.

# Durability of naïve, amnestic immune response to inactivated monovalent influenza vaccine

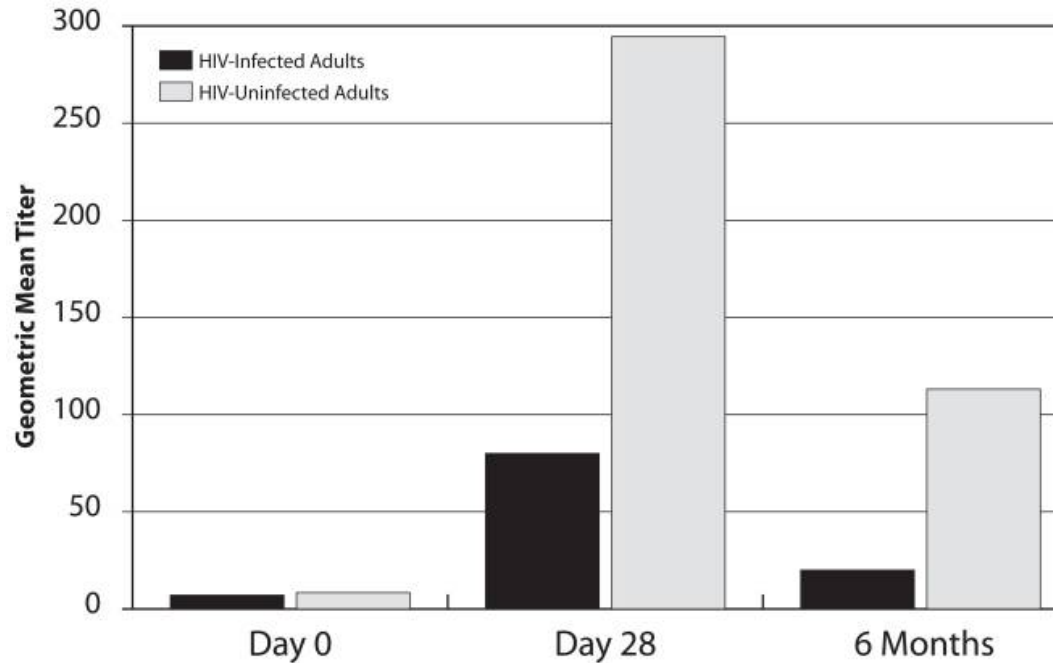


Fig. 1 Median of geometric mean titers to 2009 H1N1 pandemic strain pre- and post-vaccination among HIV-infected and HIV-uninfected participants.

Crum-Cianflone NF, Iverson E, Defang G, Blair PJ, Eberly LE, Maguire J, Ganesan A, Faix D, Duplessis C, Lalani T, Whitman T, Brandt C, Macalino G, Millar EV, Burgess T.

**Durability of antibody responses after receipt of the monovalent 2009 pandemic influenza A (H1N1) vaccine among HIV-infected and HIV-uninfected adults**

# Prior vaccination with LAIV enhanced the response to the novel (pandemic) inactivated vaccine

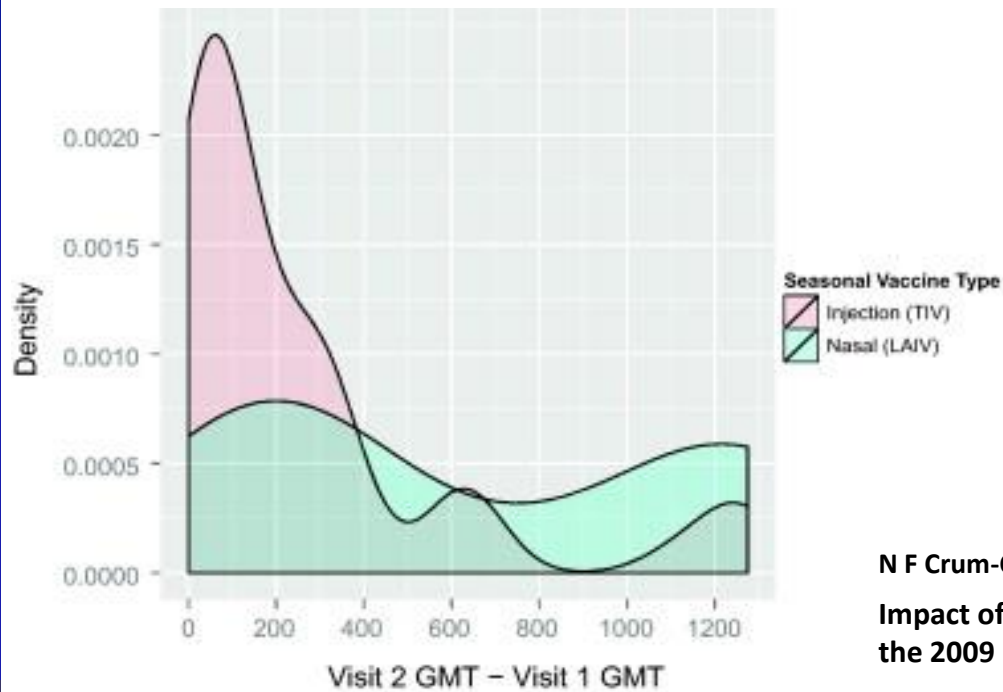


Fig. 1 Change in GMT for Antibody Responses to Pandemic H1N1 Influenza by prior Seasonal Vaccine Type

Density plots of the difference in GMT between Visit 1 (Day 0) and Visit 2 (Day 28) to the pandemic H1N1 influenza virus by type of prior seasonal vaccine “prime”:

LAIV (shaded green) or TIV (shaded red)

Median change in GMT H1N1 antibodies was higher for LAIV (313, IQR 213–1240) compared to TIV (108, IQR 35–315) ( $p = 0.004$ )

N F Crum-Cianflone, E Iverson, G Defang, IDCRP Influenza Working Group

Impact of the type of seasonal influenza vaccine on immune responses to the 2009 pandemic influenza A (H1N1) vaccine

Possible strategy for enhanced vaccine immunogenicity:  
Heterologous, heterotypic prime – boost?

# Trauma Related Infections

## Research Area Scientific Strategic Plan

### Research Area Director: MD, DrPH

**Aim 1:** Describe the clinical characteristics, risk factors, and clinical outcomes among infections complicating deployment-related injuries, particularly associated with combat trauma.

**Aim 2:** Evaluate short and long term health impacts (quality of life, healthcare utilization, and cost) of combat-related infections.

**Aim 3:** Assess novel diagnostic modalities and biomarkers for traumatic wound-related infection.

**Aim 4:** Evaluate existing and new therapies for treatment or prevention of trauma-related infections with focus on emerging and multidrug resistant organisms (IFI therapy objectives under Aim 3).

**Aim 5:** Compare clinical outcomes and antibiotic exposure to specific microbiologic pathogenicity factors such as clonal patterns, resistance mechanisms, and/or additional genotypic/phenotypic characteristics in colonizing or infecting organisms isolated from trauma patients.



# Combat-related Extremity Wound Infections (CEWI)

**CEWI Epidemiology & Clinical Outcomes**

**CEWI Management and Practice Guidance**

**CEWI Practice Patterns, HC Utilization, and Costs**

**New Collaboration**

➤ *Military Orthopaedic Trauma Registry (USAISR/DoDTR)*

## Combat Trauma-Associated Osteomyelitis

**Epidemiology, Clinical Outcomes, HC Costs**

**Management and Practice Guidance**

Focus on healthcare utilization and costs [VA Health Services Research & Development grant; USU PMB/HSA collaboration]

**Comorbidities (mental health and social factors) and QOL Assessment**



# Invasive Fungal Wound Infections (IFI)

## IFI Epidemiology & Clinical Outcomes

- Larger more complete patient registry from the Afghanistan Theater [reassess epidemiology, risk factors, surgical/medical management, and outcomes]

## IFI Molecular Diagnosis

- Retrospective analysis of tissue specimens from cases in IFI registry
- Expanded opportunities to investigate etiology and relative impact on treatment response and clinical outcome

# Combat Trauma Wound Microbiology: Multidrug Resistant and Virulent Organisms

## Wound microbiology–Clinical Correlation

## Wound microbiology–Phenotypic/Genotypic Analyses

- Microbial colonization and infection of combat extremity wounds
- Evaluation of the interactions of wound bacteria with focus on Enterococci
- Evaluation of biofilm formation in *Enterococcus* and other species
- *Stenotrophomonas maltophilia* among trauma-related infections



# IDCRP's Impact on Military Clinical Practice and Policy

- ❑ Latent Tuberculosis Infection Screening Comparative Study
  - changed policy on screening for Army accession
- ❑ Polytrauma wound infections
  - clinical expertise contributed to antibiotic stewardship practices and CPGs
- ❑ Wound Invasive Fungal Infection outbreak investigation
  - recommendations for evaluation and management leading to JTS CPG
- ❑ DoD HIV cohort
  - Cited by IOM for new Social Security HIV disability ratings
- ❑ RCT prevention trial in skin and soft tissue infection
  - Change in prevention policy to de-emphasize chlorhexidine based strategies
- ❑ Travelers' Diarrhea treatment strategies
  - TREAT-TD; consensus conference for CPG development

# DoD Priority/Clinical Question: LTBI screening at military accessioning

- ❑ CDC guidance to perform targeted testing since 2000
- ❑ Pseudo-outbreaks of false-positive TB skin tests in military populations
- ❑ Needed evidence-based guidance to evaluate proposed changes in DoD tuberculosis screening policy at accession<sup>1,2</sup>
  - Targeted testing vs. universal testing (status quo)
  - Interferon-Gamma Release Assays (IGRAs) vs. Tuberculin skin test (TST)

1. Armed Forces Epidemiological Board. Recommendations regarding risk-based tuberculosis screening policies and new technologies. Washington, DC: Department of Defense; 2000.
2. Armed Forces Epidemiological Board. Quantiferon-TB's Application in the US Military. Washington, DC: Department of Defense; 2003.





# IDCRP Response and Findings

## LTBI screening

- ❑ Collaborative team: USUHS, USAPHC, Fort Jackson, Army OTSG, FDA, Aeras Foundation
- ❑ Cross-sectional study of 2,017 recruits
- ❑ Equivalent specificity of the TST and IGRAs
- ❑ Discordant positive TST/negative IGRA associated with sensitization to non-tuberculous mycobacteria

<i>Factor</i>	<i>Positive RFQ responses (n=1783)</i>	<i># with positive TST (n=38)</i>	<i>Sensitivity</i>	<i>Specificity</i>	<i>AUC</i>
1. Close Contact of TB Case	20 (1.1%)	3	7.9%	99.0%	0.535
2. TB Prevalence $\geq$ 20 per 100,000 in Country of Birth	96 (5.4%)	19	50.0%	95.6%	0.730
3. Lived with Parent Not Born in the US	79 (4.4%)	13	34.2%	96.2%	0.652
4. Prior TST positive	21 (1.2%)	12	31.6%	99.5%	0.655
<b>1,2,3, and 4 (selected model)</b>	<b>166 (9.3%)</b>	<b>30</b>	<b>79.0%</b>	<b>92.2%</b>	<b>0.871</b>

Mancuso JD et al. *Clin Infect Dis* 2011;53(3):234-44.

Mancuso JD et al. *Am J Resp Crit Care Med* 2012;185(4):427-434.



# Study Impact

## LTBI screening

- ▣ Targeted approach reduces testing by > 90%
- ▣ Save 50,000+ recruit-hours and over \$2 million annually
- ▣ DoD/ASD(HA) Memorandum: Guideline for Tuberculosis Screening and Testing. 20 Apr 2012
- ▣ MEDCOM Regulation 40-64: *The Tuberculosis Surveillance and Control Program*. 26 Nov 2013

**Table 4** Cost-effectiveness

Screening strategy	Incremental cost per case prevented US\$*
None	
Targeted strategies	
RFQ followed by TST	285 777
RFQ followed by QFT	D (strong) <sup>†</sup>
RFQ followed by T-Spot	369 273
Sequential strategies	
TST followed by QFT	D (weak) <sup>‡</sup>
TST followed by T-Spot	D (weak) <sup>‡</sup>
Universal strategies	
Universal TST	711 363
Universal QFT	D (strong) <sup>†</sup>
Universal T-Spot	3 347 268

# IDCRP's Impact on Military Clinical Practice and Policy



## THE ASSISTANT SECRETARY OF DEFENSE

1200 DEFENSE PENTAGON  
WASHINGTON, DC 20301-1200

### HEALTH AFFAIRS

MEMORANDUM FOR ASSISTANT SECRETARY OF THE ARMY (M&RA)  
ASSISTANT SECRETARY OF THE NAVY (M&RA)  
ASSISTANT SECRETARY OF THE AIR FORCE (M&RA)  
DIRECTOR OF THE JOINT STAFF

SUBJECT: Guideline for Tuberculosis Screening and Testing

- References: (a) Department of Defense (DoD) Instruction (DoDI) 6130.03, "Medical Standards for Appointment, Enlistment, or Induction in the Military Services," April 28, 2010
- (b) DoDI 6490.03, "Deployment Health," August 11, 2006
- (c) DoD 6055.05-M, "Occupational Medical Surveillance Manual," May 2, 2007
- (d) Centers for Disease Control and Prevention (CDC) Morbidity and Mortality Weekly Report (MMWR) Recommendations and Reports (RR) 59 RR-05, "2010 Jun 25—Updated Guidelines for Using Interferon Gamma Release Assays to Detect *Mycobacterium tuberculosis* Infection," United States, 2010
- (e) CDC MMWR 54 RR-17, "2005 Dec 30—Guidelines for Preventing the Transmission of *Mycobacterium tuberculosis* in Health Care Settings," 2005
- (f) CDC Publication, "2010—Latent Tuberculosis Infection: A Guide for Primary Health Care Providers"

Tuberculosis (TB) is an infection with *Mycobacterium tuberculosis*. TB is uncommon in the United States; in 2010, the incidence of active TB was 3.6 per 100,000 person-years, the lowest ever recorded. The prevalence of latent tuberculosis infection (LTBI) in the U.S. is estimated at 4 percent overall, but is 1 percent in military-aged groups. The principal risk factors for acquiring TB infection are birth or prolonged community residence in a TB endemic country, exposure to a known active TB case, residence with someone from a TB endemic country, and residence in an institutional or congregate setting such as prison, drug treatment center, or homeless shelter. As the prevalence of TB in most military members is quite low, testing persons at low risk of disease should be avoided and be replaced with targeted testing based on risk assessment, usually with a simple questionnaire (see attached sample questionnaire).

Deployment to TB endemic countries, even for periods in excess of a year, has not been shown to be a risk factor for TB for most average risk Service members (including the Korean War, Vietnam War, and the current conflicts of Operation Enduring Freedom and Operation Iraqi Freedom). Prisoners of War are the only group to demonstrate higher rates of active TB after military deployment. Based on civilian studies, other groups assumed to be at increased risk are health care workers (HCW) caring for TB patients at hospitals and individuals working at prisons and detainee facilities where TB may be present. Nearly all military medical treatment facilities (MTFs) in the military healthcare system are considered low risk according to

MEDCOM Reg 40-64

DEPARTMENT OF THE ARMY  
HEADQUARTERS, UNITED STATES ARMY MEDICAL COMMAND  
2748 Worth Road  
JBSA Fort Sam Houston, Texas 78234-6000

MEDCOM Regulation  
No. 40-64

26 November 2013

### Medical Services THE TUBERCULOSIS SURVEILLANCE AND CONTROL PROGRAM

Supplementation of this regulation and establishment of forms other than MEDCOM forms are prohibited without prior approval from HQ MEDCOM, ATTN: MCPO-SA.

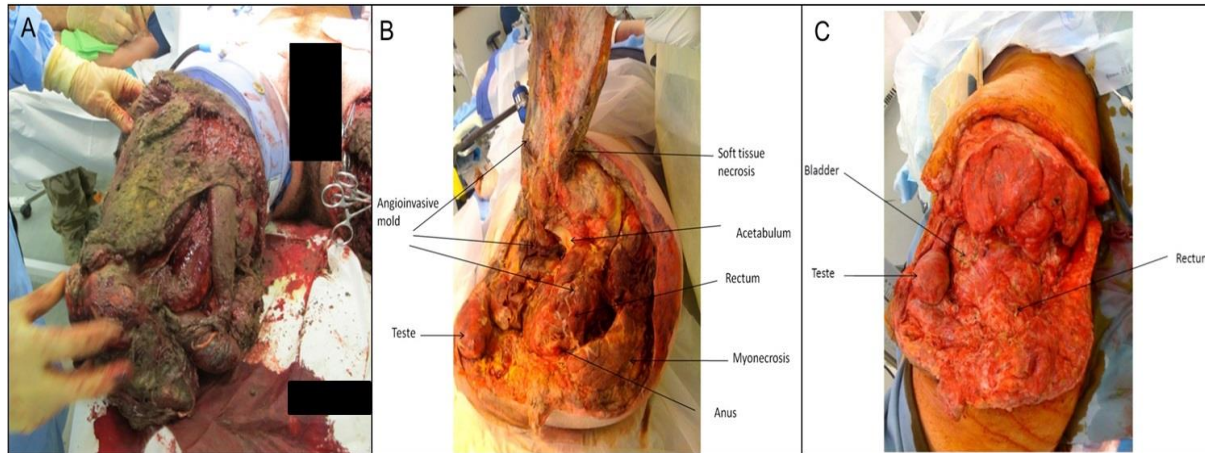
- 1. History.** This issue publishes a new regulation.
- 2. Purpose.** The purpose of the Tuberculosis (TB) Surveillance and Control Program is to prevent new cases of TB through prompt identification and treatment of both TB infection and disease. This regulation prescribes policy and procedures for testing, evaluating, treating, monitoring, referring, documenting, and tracking Army personnel and beneficiaries at risk for TB. It also assigns responsibilities applicable to key personnel working with this program.
- 3. Applicability.** This regulation applies to personnel in all U.S. Army Medical Command (MEDCOM) installations and activities.
- 4. References.** References are listed at appendix A. (See *Note* at appendix A for information specific to references in this regulation.)
- 5. Responsibilities**
  - a. The Office of The Surgeon General/MEDCOM G-3/5/7 Health & Wellness is responsible for the oversight of practice standards and providing regulation updates as applicable.
  - b. The U.S. Army Public Health Command (PHC) will provide disease and epidemiology surveillance, relevant training, and resources that support the TB Surveillance and Control Program.
  - c. Regional medical command preventive medicine (PM) physicians will ensure subordinate military treatment facilities (MTFs) maintain effective TB control programs.
  - d. MTF Commanders are responsible for ensuring that PM personnel have sufficient staffing, resources, and training to implement the TB Surveillance and Control Program.



# Combat-Related Invasive Fungal Wound Infections

## IFI Outbreak and Response Timeline

- 2009-2010: Clinician recognition & evolving efforts to respond to emergent IFI outbreak among personnel with blast injuries



**Progression of IFI wound. (A) Wound immediately following blast. (B) After surgical debridement; mold angioinvasion noted. (C) Clean wound after serial debridements and antifungal therapy. (Tribble and Rodriguez, 2014)**

- Feb-Apr 2011: TIDOS led outbreak investigation
- May/June 2011: TIDOS IFI Technical Pentagon Report briefing (SMMAC / COCOM surgeons) providing detailed diagnosis and treatment recommendations

Joint Theater Trauma System Clinical Practice Guideline

### Treatment of Suspected Invasive Fungal Infection in War Wounds

Original Release/Approval	26 Oct 2012	Note: This CPG requires an annual review.	
Reviewed:	Oct 2012	Approved:	1 Nov 2012



# IDCRP Trauma Infections Research

## TIDOS IFI Research Initiatives

- ❑ TIDOS analysis confirmed risk factors used for JTS CPG (*Rodriguez et al., Surg Infect 2014*)
  - ❖ Blast injuries sustained while dismounted (on foot patrol)
  - ❖ Above knee amputations
  - ❖ Massive (>20 units) of blood transfused w/i 24 hrs of injury
- ❑ Effectiveness of LRMC Blast Protocol assessed (*Lloyd et al., Surg Infect 2014*)
  - ❖ Earlier diagnosis achieved (time to diagnosis went from 9 to 3 days post-injury)
  - ❖ Earlier initiation of antifungal therapy
  - ❖ However, no difference in clinical outcomes
- ❑ Environmental factors assessed with modeling to predict mold wound contamination risk in other locations (*Tribble et al, Emerging Infect Dis 2015*)



Example of 'Green Zone' combat environment

# IDCRP Trauma Infections Research

## TIDOS IFI Research Initiatives

- ❑ Case-control analysis confirmed increased morbidity of IFIs and effect on wound healing and clinical outcomes (*Lewandowski et al J Ortho Trauma 2015 under review*)
  - ❖ IFI wounds had significantly greater residual limb shortening, changes in amputation level, a higher number of operative procedures, and a longer time (days) from injury to initial wound closure
- ❑ Clinical relevance of mold without wound necrosis (does not require directed antifungal therapy) (*Weintrob et al Epidem Infect 2014*)
- ❑ Major initiative underway to assess PCR-based molecular diagnostics related to fungal identification, which could support early diagnosis and empiric treatment at DoD hospitals.
- ❑ Collaboration with the United Kingdom Defence Medical Services Wound Infection Surveillance Programme (WISP) to examine characteristics and management approaches between US and UK IFI patients



# Other recent program milestones

- ❑ Successful integration of Infectious Diseases into the MHS Research Symposium
  - 2014: two dedicated IDCRP sessions
  - 2015: 16 abstracts across the Program
  - 2016: Three separate tracks directly relevant to IDCRP
- ❑ Increased synergy with VA
  - Joint research in Trauma Infections and HIV
  - OSC representation
- ❑ DoD programmatic funding for infrastructure support FY 14-18



# Building and Retaining the Bench: Mentored Training Numbers (2014-2015)

**31 trainees** involved in 24 active research projects and 7 overseas clinical research rotations

- ❑ Infectious Diseases – 9 fellows in all three DoD programs
- ❑ Internal Medicine – 10 residents in three programs
- ❑ Pathology – 1 resident
- ❑ Surgery – 3 residents (2 Ortho, 1 Gen Surg)
- ❑ Preventive Medicine – 2 residents
- ❑ USU Graduate Programs – 1 MPH, 1 MTM&H, 2 DrPH, 1 PhD
- ❑ Graduate Program at Baylor – 1 MS (Nutrition Med)





# IDCRP overview

Defining characteristics as an MHS clinical research platform

Groundbreaker in

1. Coordinating research from numerous & geographically diverse entities/locations
2. Standardizing and simplifying the IRB process for multicenter studies
3. Leading the way in innovative, collaborative, impactful research



# Summary and future direction

- ❑ IDCRP is robust at 10 years; numerous accomplishments, poised for future success
- ❑ To maintain relevance and effectiveness, IDCRP as a core function will identify the current disease burden encountered in the MHS specific to each Program Research Area
- ❑ Programmatic shift emphasizing interventional studies needed to effect positive outcomes; observational studies support interventional trials
- ❑ IDCRP studies military-relevant ID threats where and in whom those threats are encountered, to mitigate those threats

