



# Conducting Human Use Research in the Military Recruit Training Environment: Challenges and Rewards

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**Kevin L. Russell, MD, MTM&H, FIDSA**  
**CAPT, Medical Corps, US Navy**  
**Director, DoD-GEIS**  
**Deputy Director, AFHSC**  
[kevin.russll4@us.army.mil](mailto:kevin.russll4@us.army.mil)

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**Achieving Excellence in DoD Human Research Protection  
Programs: The Role of the Institutional Official: WORKSHOP**  
**Washington Marriot Metro Center**





## Disclaimer

**The ideas and opinions expressed in this presentation are mine and do not represent the views of the U.S. Army, Navy, or the Department of Defense**





# Outline



**PURPOSE:** Discuss the conduct of human use research in the military recruit training environment

1. Surveillance and research in the recruit setting
  - a) Examples and information provided
2. Human Use Issues
3. Conduct of a Phase 3 Trial
  - a) Challenges
  - b) Rewards
4. Conclusions





# Global Emerging Infections Surveillance and Response



AFIP



“A Global Network”

WRAIR



Navy Hub

Air Force Hub

Peru

Germany

Egypt

Kenya

Korea

Thailand

Indonesia



DoD's Unique Assets – Overseas Presence with OCONUS Labs





# DoD-GEIS



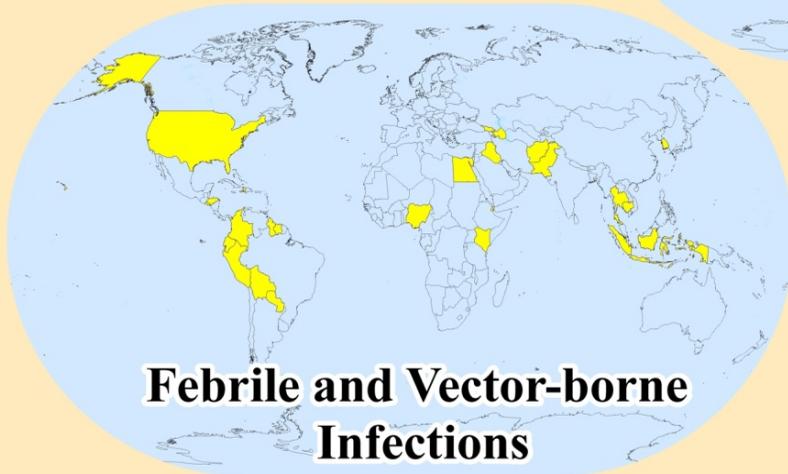
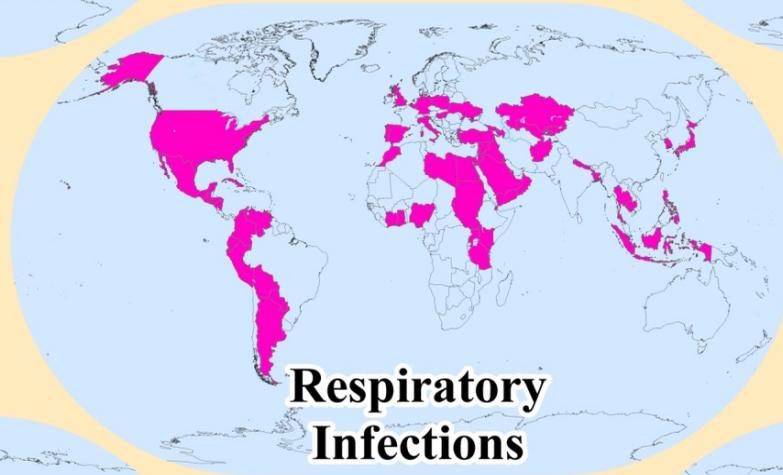
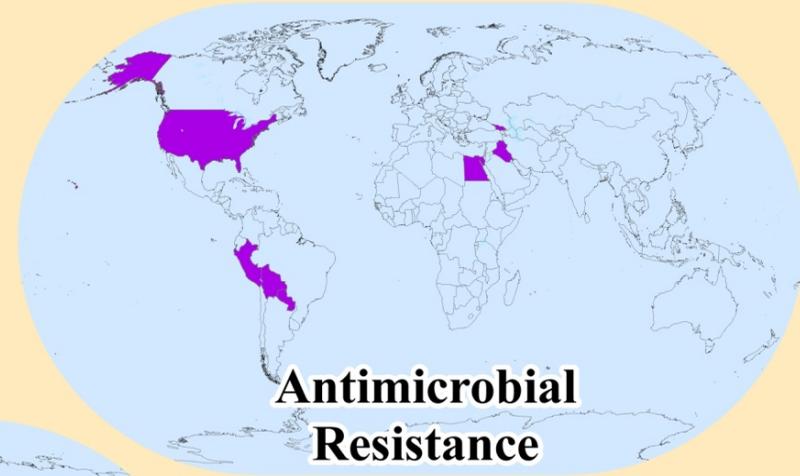
## Strategic Goals and Priority Pillars



RI = Respiratory Infection  
GI = Gastrointestinal Infection  
FVBI = Febrile and Vector-borne Infection  
AR = Antimicrobial Resistance  
STI = Sexually Transmitted Infection



# GEIS Supported Surveillance Programs





# Research with Trainees: WHY?



- **Vulnerable population**
- **Unique setting**
  - Crowding
  - Stress
  - Emotional and physical challenges
- **Unique burden of illnesses/injuries**
  - Respiratory pathogens
  - Skin infections
  - Musculoskeletal injuries/strains
- **Our ethical responsibility to protect and keep as healthy as possible**
  - Surveillance and Research = successful intervention programs







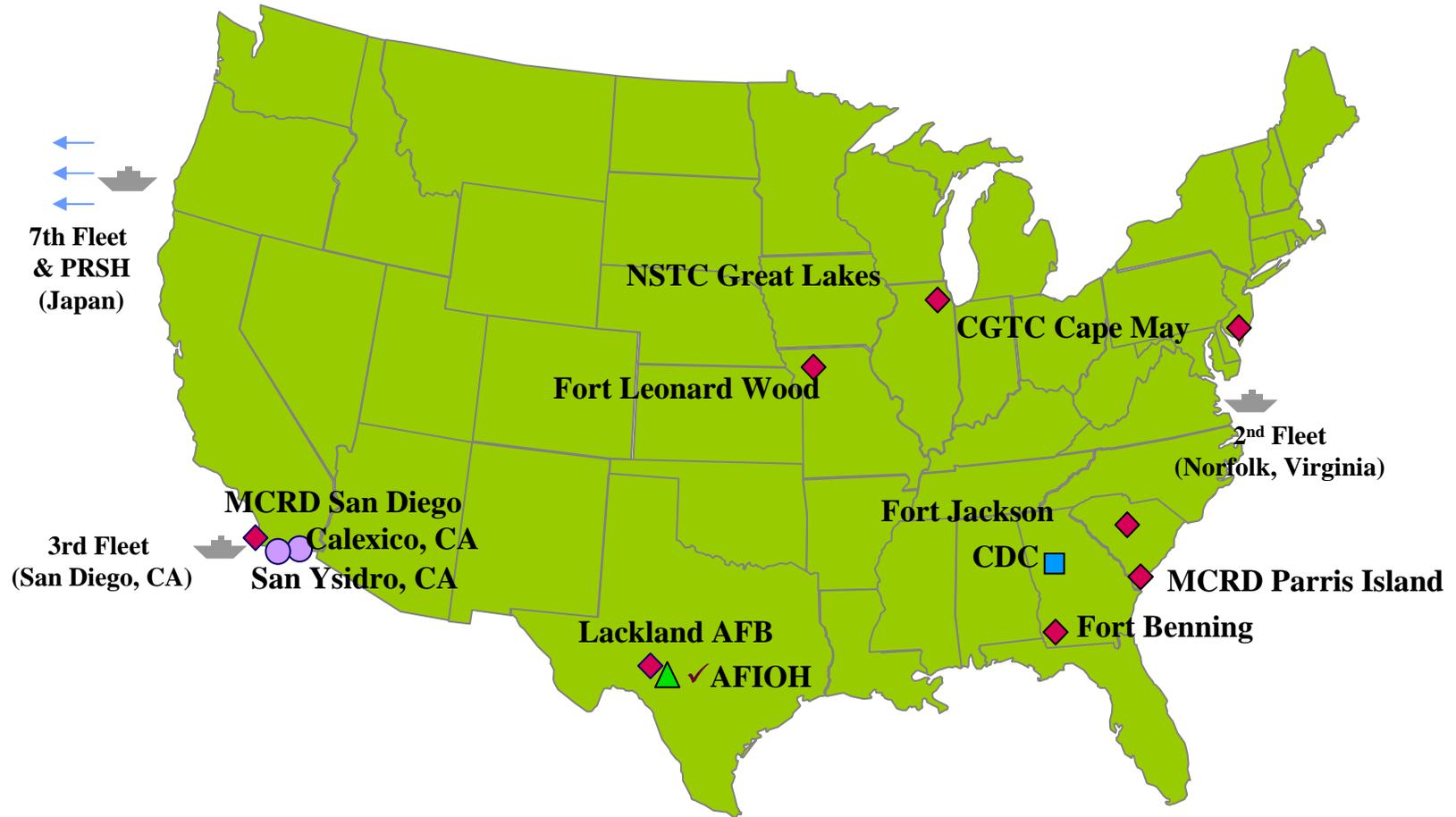
# Research with Trainees: Products



- **Reports**
  - Wide and varied customers
  - Policy-makers
- **Understanding**
  - Data for decision making
  - Further research in an informed manner
- **Collaborative relationship**
  - Work with the line, establish rapport
  - Enable needed work in future



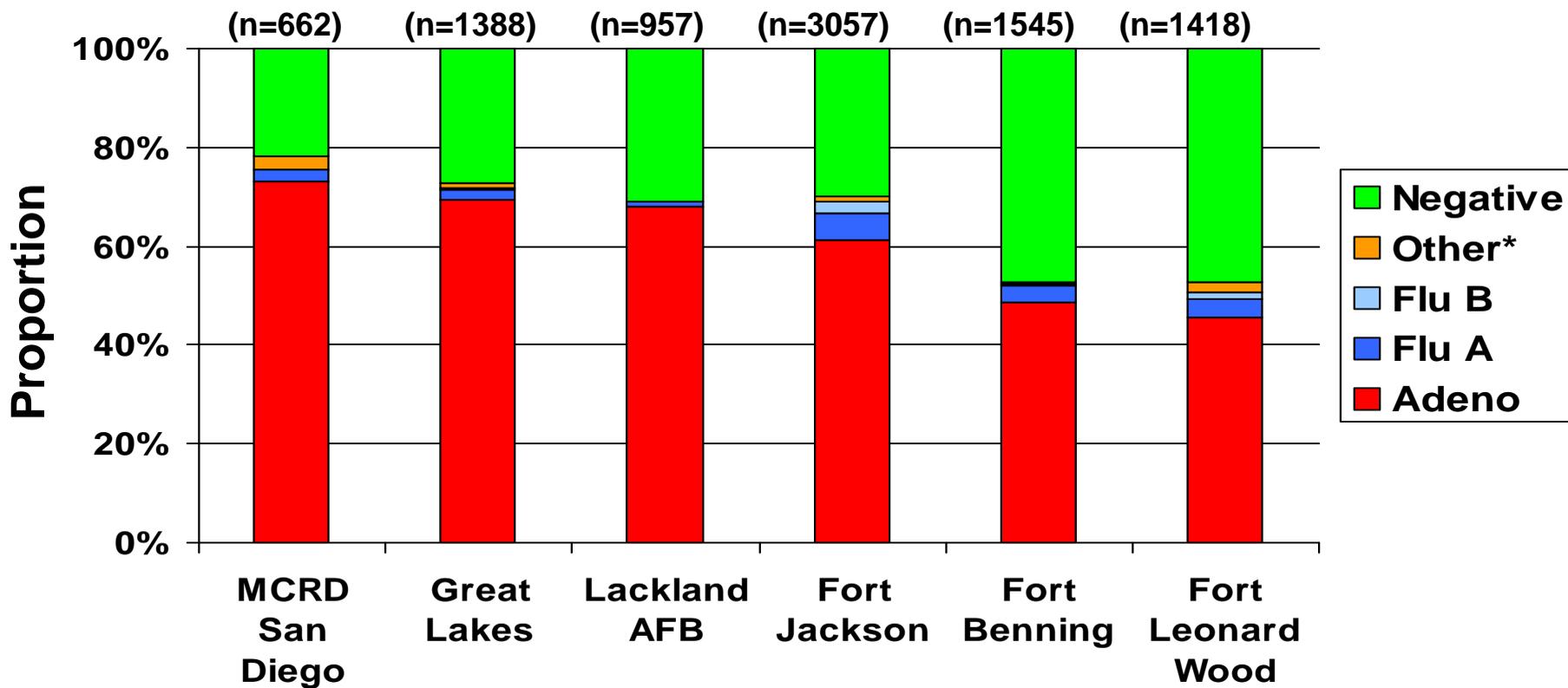
# Naval Health Research Center Surveillance Sites



-  Febrile Respiratory Illness (FRI) Surveillance
-  FRI Surveillance in a U.S.-Mexico Border Population
-  Shipboard FRI Surveillance

**Influenza Diagnostic Collaborators:**

-  Center for Disease Control and Prevention (CDC)
-  Armed Forces Institute of Operational Health (AFIOH)

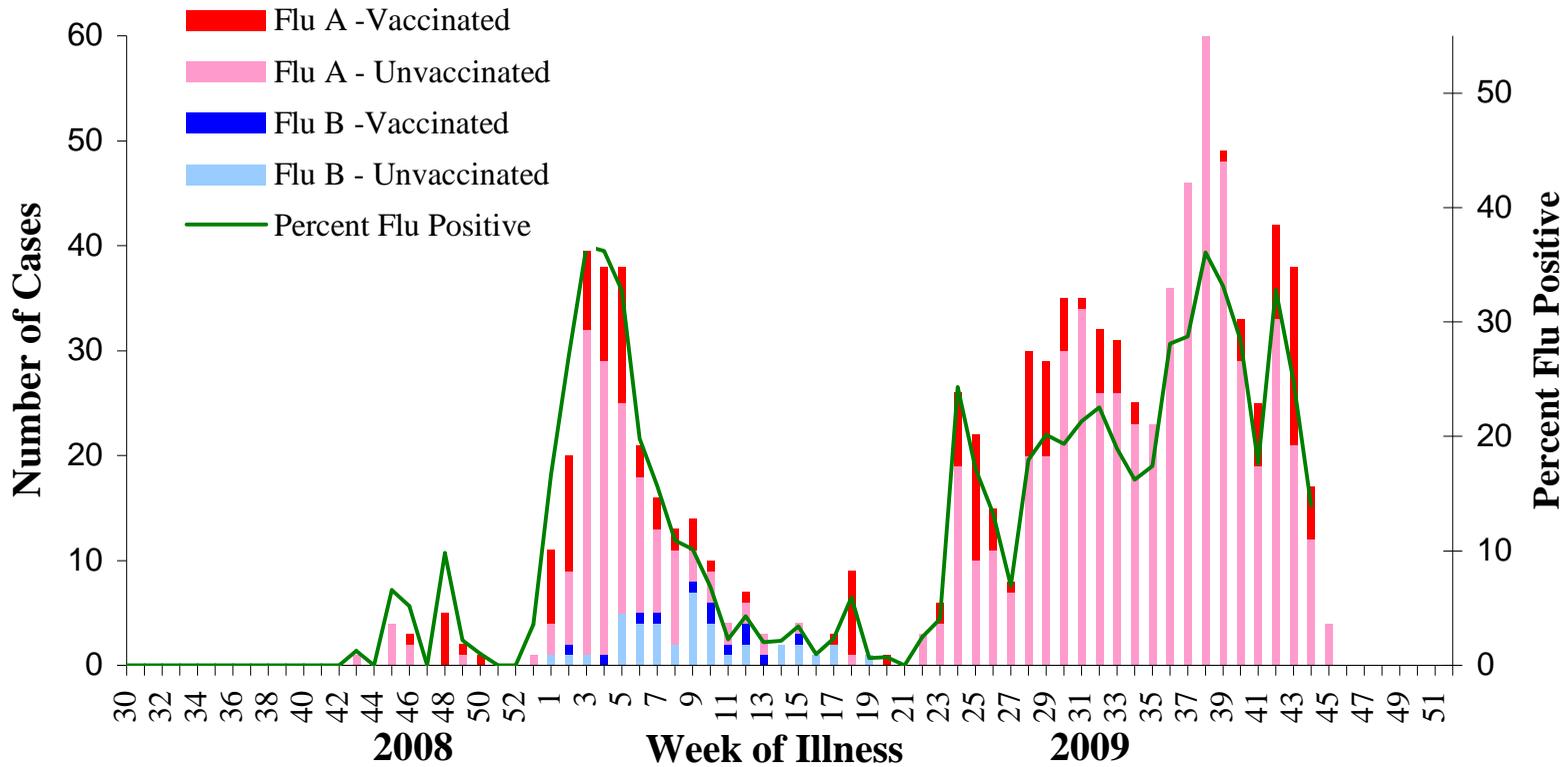


\*Other pathogens include parainfluenza and RSV





## Vaccination Status of Confirmed Influenza Cases Among Military Basic Trainees, 2008-09

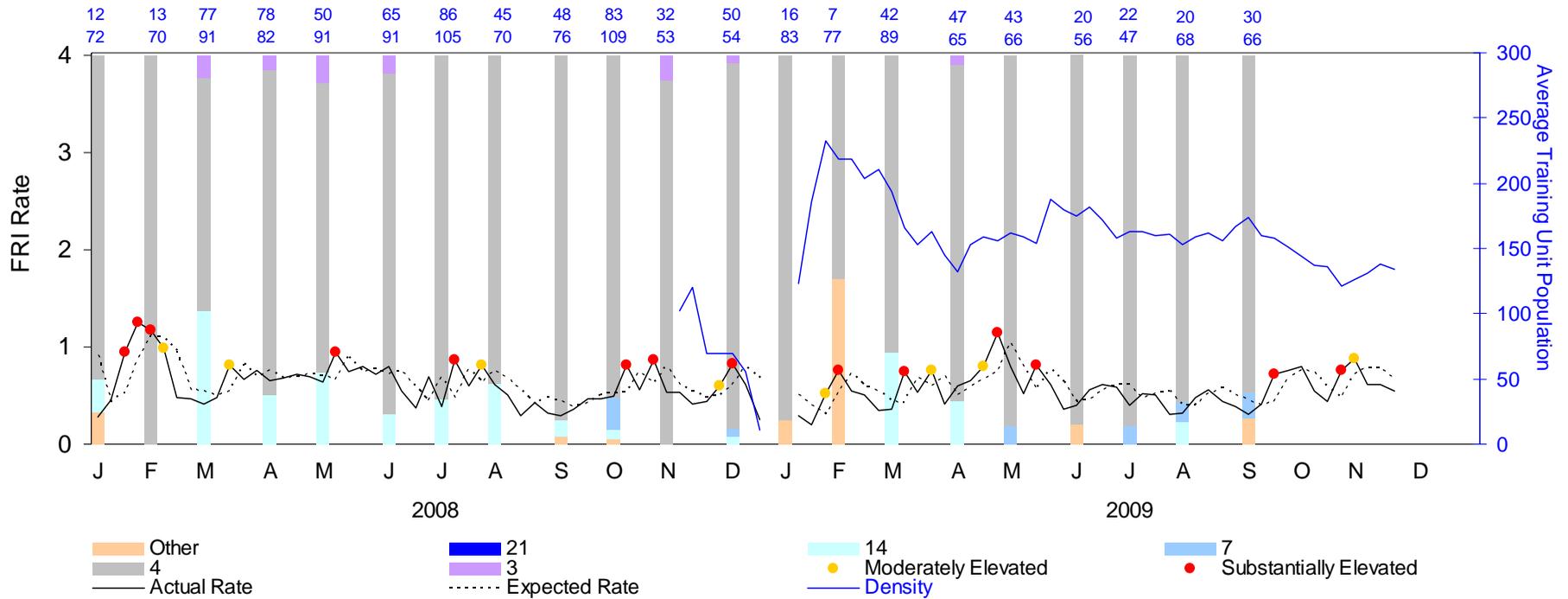




Total Serotyped  
Total Received

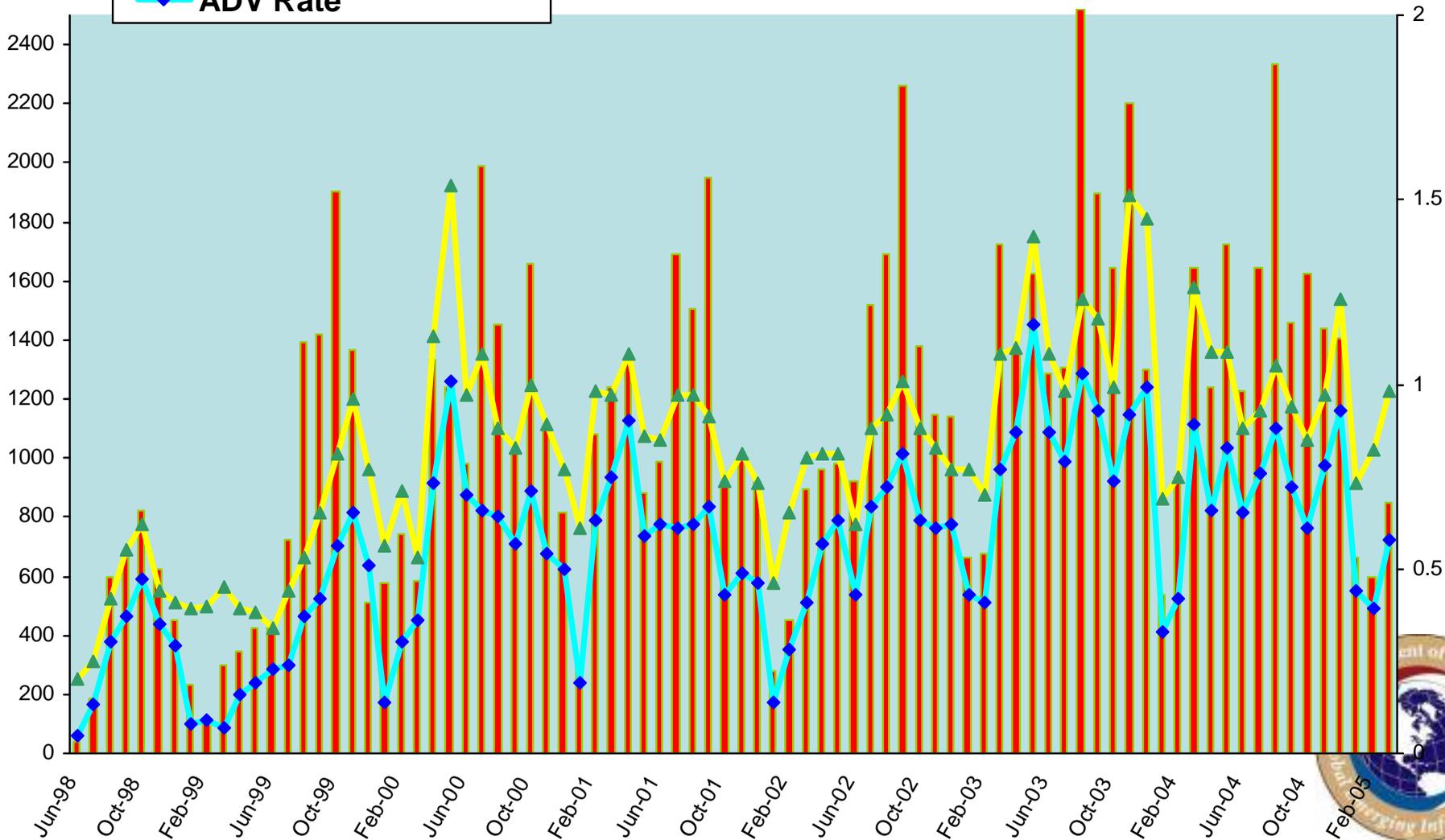
### Ft. Leonard Wood FRI Rates and Adenovirus Serotype Distributions

Serotyping performed for all adenovirus positive cases





# History: Trends in Illness Rates





# Recruit Research: Challenges



- **“Vulnerable Subjects”**
- **Minimize coercion**
- **Command objectives are NOT ours**
- **Multiple IRB reviews**
- **Timing**
- **Follow-ups**





# International Council on Harmonization



## E6 Good Clinical Practice – clinical trials

### 1.61 Vulnerable Subjects:

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, **of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate.**

Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing **students**, subordinate hospital and laboratory personnel, **employees** of the pharmaceutical industry, **members of the armed forces**, and persons kept in detention.

Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.



\*\*courtesy of COL (ret) Laura Brosch, AN, PhD



## **Students, Employees, Military Service Members as Competent Adults, who...**

- **Benefit from the outcomes of research**
- **Have the right to participate in research if they so desire**
- **Are able to decide for themselves –make competent, rational and voluntary choices**

**So what's the problem?**





# What constitutes “coercion” and “undue influence” in recruitment when there is a hierarchical relationship?

- **Coercion**
  - Use of threat
- **Undue Influence**
  - Use of enticement (alone...insufficient)
  - trading on power in one sphere to influence outcomes in another—is often associated with dependency relationships
  - occurs “when an incentive is attractive enough to tempt people to participate in a research study ‘against’ their better judgment.” (Grant & Sugarman, 2004, p. 733-734)

\*\*courtesy of COL (ret) Laura Brosch, AN, PhD



# It's about Relationships...



- **Students – Faculty**
- **Employees – Employers**
- **Military Service Members – Chain of Command**





# Issues



- **Exploitation of relationships**
- **Positive and negative consequences of consent/declination**
- **Loss of Privacy**





# Military Service Members



- **Available**
- **Convenient**
- **Educated**
- **Trained to think, consider options, decide and act in stressful situations**
- **Trained to be independent**
- **Moral courage as a core value**
- **Organized and predictable**
- **Universal access to health care**
- **Ideal “healthy volunteer” population**
- **Follow directions**
- **Limited compensation options**





# Military Service Members



- **Serve in a strict hierarchical culture**
- **Trained to respect rank differentials**
- **Implicitly agree to subordinate their autonomy for the sake of accomplishing the military mission**
- **Obligated to obey all lawful orders from superiors**
- **Agree to risk personal injury or loss of life if need be in compliance with lawful orders of their superiors**
- **Are susceptible to directives/requests from senior officials**
- **Potential disqualifying consequences to disclosure of sensitive information**





# Potential Consequences of Military Participation/Non-participation

- **Perceived Negative**
  - Perception of adverse performance appraisal
  - Loss of favor from supervisor
  - Threat of exclusion by peers
  - Disclosure of disqualifying information
- **Perceived Positive**
  - Promise of positive performance appraisal and assignment opportunities
  - Extra favors from supervisor
  - Selection for desirable work projects





## Institutional Policies – Military Service Members as Subjects

- Department of Defense Directive (DODD) 3216.2  
March 25, 2002 – “Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research”
- Special protections for military personnel
  - Chain of command may not influence participation
    - Supervisors and unit leaders may not be present for recruitment, enrollment or consent processes





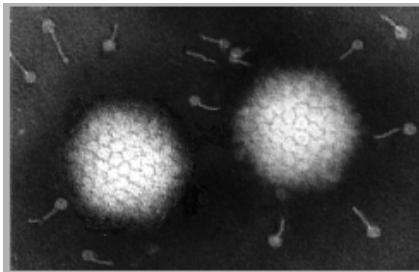
# Adenovirus in Recruits: History



**“The Armed Forces Epidemiological Board and the Institute of Medicine of the National Academy of Sciences have unequivocally, forcefully, and repeatedly recommended the replacement of these vaccines”**

**--Honorable William Winkenwerder, Jr., MD  
Assistant Secretary of Defense for Health Affairs**

- Barr-Duramed awarded contract for resumed vaccine production in 2001**





# Clinical Trial Phases



- **Phase I**

- small group of people for the first time to evaluate its **safety**, determine a safe **dosage range**, and identify **side effects**

- **Phase II**

- **larger group** of people to see if it is **effective** and to further evaluate its **safety**

- **Phase III**

- **large groups** of people to confirm its **effectiveness**, monitor **side effects**, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used **safely**

- **Phase IV**

- **after** the drug or treatment has been **marketed** to gather information on the drug's effect in various populations and any **side effects** associated with **long-term use**

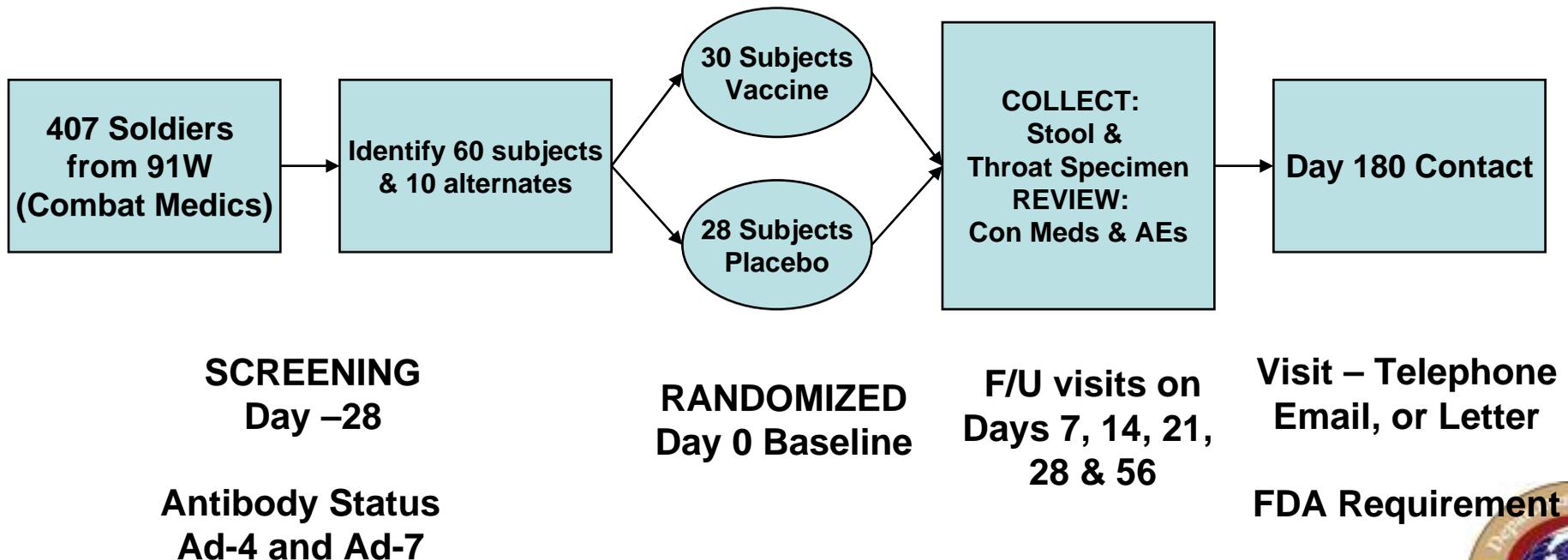




# Phase 1 Trials



**A Phase I, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Immunogenicity of the Live, Oral Type-4 and Type-7 Adenovirus Vaccines**





# Adverse Events



5% or More Occurrence Rate  
Day 0 to Day 56 All Treated Subjects

Preferred Term	Vaccine N = 30	Placebo N = 28
Nasal Congestion	10 (33.3)	16 (57.1)
Cough	10 (33.3)	10 (35.7)
Pharyngeal Pain	8(26.7)	8 (28.6)
Abdominal Pain	5 (16.7)	1 (3.6)
Diarrhea	4 (13.3)	2 (7.1)
Nausea	4 (13.3)	6 (21.4)
Pneumonia	1 (3.3)	3 (10.7)
Sinusitis	3 (10.0)	2 (7.1)
Arthralgia	4 (13.3)	0 (0.0)
Headache	6 (20.0)	6 (21.4)
Pyrexia (fever)	2 (6.7)	6 (21.4)
WBC Count Increased	0 (0.0)	3 (10.7)

- **Immunogenicity and Safety felt adequate to proceed**





# Perform a Phase 3



## IRB Hurdles

- **Great Lakes Naval Health Clinic CPHS**
  - Approval: 06 Sept 2006
- **Naval Health Research Center IRB**
  - Approval: 11 Sept 2006
- **Bethesda Naval Hospital IRB**
  - Approval: 04 Oct 2006
- **US Army HSRRB**
  - Approval: 04 Oct 2006





# Study Design: Phase 3



- **Where?**
- Objectives?
- Sample Size?
- Randomization?
- Inclusion/Exclusion criteria?
- Capture of cases?
- Follow-up periodicity?



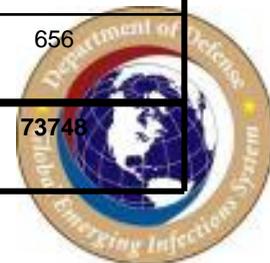


# Burden of Adenovirus at Recruit Training Centers



## 1999-2004

Training center	No. FRI	Trainee-weeks	FRI rate	No. specimens collected	Percent ADV positive	Estimated no. adenovirus cases
Ft Leonard Wood	14355	1619864	0.89	2022	52.3	7742
<b>Ft Jackson</b>	<b>23122</b>	<b>2617350</b>	<b>0.88</b>	<b>3326</b>	<b>68.1</b>	<b>17553</b>
Ft. Benning	18687	1916087	0.98	2009	55.4	9169
<b>Great Lakes</b>	<b>28237</b>	<b>2359105</b>	<b>1.20</b>	<b>1791</b>	<b>72.6</b>	<b>20833</b>
MCRD San Diego	3465	1021264	0.34	1053	74.4	2500
MCRD Parris Isl.	4274	989053	0.43	999	71.8	2533
Lackland AFB	17101	1268259	1.35	1816	75.7	12762
Cape May	931	187103	0.50	867	76.4	656
<b>Total</b>	<b>110172</b>	<b>11978085</b>	<b>0.92</b>	<b>13883</b>	<b>66.8</b>	<b>73748</b>





# Study Design: Phase 3



- Where?
- **Objectives?**
- Sample Size?
- Randomization?
- Inclusion/Exclusion criteria?
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# Study Design



## Objectives:

### – Primary:

- To determine the efficacy of the oral Type-4 ADV vaccine in reducing the attack rate of wild Type-4 ADV-associated febrile ARD.
- To determine the antibody response to the oral Type-7 ADV vaccine.

### – Secondary:

- To determine the antibody response to the oral Type-4 ADV vaccine.
- To evaluate the safety and tolerability of the oral Type-4 and Type-7 ADV vaccines.





# Study Design: Phase 3



- Where?
- Objectives?
- **Sample Size?**
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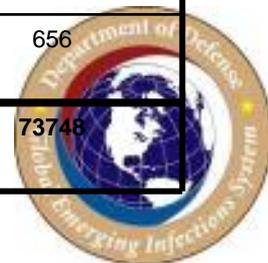


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# Study Design



- **Sample size determination**

- 1-10% attack rate in placebo recipients
- 80% vaccine efficacy
- 95% C.I. no lower than 60%
- 3:1 randomization
- Type 1 error = 0.05
- Power = 80%
- 2-sided

Placebo Rate	Vaccine N	Placebo N	Total N	Total N Adjusted for 15% Dropout
1%	12721	4240	16962	19955
2%	6325	2108	8434	9922
3%	4193	1398	5591	6578
4%	3127	1042	4170	4906
<b>5%</b>	<b>2488</b>	<b>829</b>	<b>3317</b>	<b>3902</b>
10%	1208	403	1611	1896

Note: Calculation based on likelihood score method (Blackwelder 1993).





# Study Design: Phase 3



- Where?
- Objectives?
- Sample Size?
- **Randomization**
- Inclusion/Exclusion criteria?
- Capture of cases?
- Follow-up periodicity?





# Study Design



- **3:1 Randomization**

- Placebo:Vaccine
- 1 lot of vaccine for the “safety cohort”
- 3 lots of vaccine for the remainder
- Blocks of 8
  - Safety (first 780):
    - n=6; Lot 1 of each vaccine (ADV Type-4 and Type-7)
    - n=2; Placebos (ADV Type-4 and Type-7)
  - Remainder:
    - n=2; Lot 1 of each vaccine (ADV Type-4 and Type-7)
    - n=2; Lot 2 of each vaccine (ADV Type-4 and Type-7)
    - n=2; Lot 3 of each vaccine (ADV Type-4 and Type-7)
    - n=2; Placebos (ADV Type-4 and Type-7)





# Study Design: Phase 3



- Where?
- Objectives?
- Sample Size?
- Randomization?
- **Inclusion/Exclusion criteria?**
- Capture of cases?
- Follow-up periodicity?





# Study Design



- **Inclusion Criteria:**

- At the Enrollment Visit (Visit 0) and day of study medication administration (Visit 1), a subject must meet the following criteria to participate in this study:
- Age 18 or older;
- Written informed consent obtained from the subject;
- Military recruit in training;
- Willing to meet the specimen-collection schedule;
- If the subject is female, she must be of non-childbearing potential, i.e., surgically sterilized: or, if of childbearing potential, she must have a documented negative  $\beta$ -HCG pregnancy test  $\leq 72$  hours prior to study medication administration and must agree not to become pregnant during the study and for at least 90 days after the Study Medication Administration Visit (Visit 1). Effective ways to avoid pregnancy include: abstinence, hysterectomy, bilateral oophorectomy or tubal ligation; or current use of oral contraceptives or accepted barrier methods (i.e., condoms, diaphragms, and sponges);
- If the subject is male, he must agree to avoid unprotected sexual intercourse for at least 90 days after the Study Medication Administration Visit (Visit 1). Effective ways to avoid unprotected sexual intercourse include: abstinence; vasectomy; accepted barrier methods (i.e., condoms).
- Exclusion Criteria: At the Enrollment Visit (Visit 0) and day of study medication administration (Visit 1), a subject will be excluded from participating in the study for any of the following reasons:





# Study Design



- **Exclusion Criteria:**

- At the Enrollment Visit (Visit 0) and day of study medication administration (Visit 1), a subject will be excluded from participating in the study for any of the following reasons:
- If the subject is female, nursing an infant or planning on nursing during the study and/or at anytime during the 90 days after the Study Medication Administration Visit (Visit 1);
- Immunosuppressed for any reason, including past (within last 6 months) or current treatment with systemic immunosuppressive therapy (systemic corticosteroids, chemotherapy or radiation therapy);
- Known allergy to any component of the vaccines and/or placebo tablets;[\[1\]](#)
- Use of any investigational new or non-registered drug or vaccine other than the study medication planned during the study period or within 30 days preceding the study medication administration; however, subjects will be allowed to receive routine vaccinations associated with basic training and any other prescribed medications not in the exclusion criteria;
- Unable or unwilling to return for follow-up visits;
- If the subject appears to be too ill for participation in the study as determined by the Principal Investigator, or designated qualified sub-investigator;
- Any condition that would make volunteer unsuitable for the study as determined by the Principal Investigator or designated qualified sub-investigator;
- Presence of immunocompromised individuals (e.g., HIV, recent or current chemotherapy), children under 2 years of age, or pregnant female in home of record.





# Study Design: Phase 3



- Where?
- Objectives?
- Sample Size?
- Randomization?
- Inclusion/Exclusion criteria?
- **Capture of cases?**
- Follow-up periodicity?





# Study Design



## Case Capture

- **Site specific issues**
- **Active or passive?**
- **Locations for medical care?**
- **Staffing issues?**





# Informed Consent



- **Group or one-on-one?**
- **Who performs?**
- **Ombudsmen**
  - How to avoid conflict of interest?
- **Coercion DURING CONDUCT**
  - Continued ombudsmen use





# Conduct of the Trial



## Informed Consent





# Conduct of the Trial



## Informed Consent





# Adequate Staffing



- **Core, Full-time: 13**
- **Temporary, Part-time (weekends only): 100 +**





# Conduct of the Trial



## Study Medication Administration





# Study Design: Phase 3

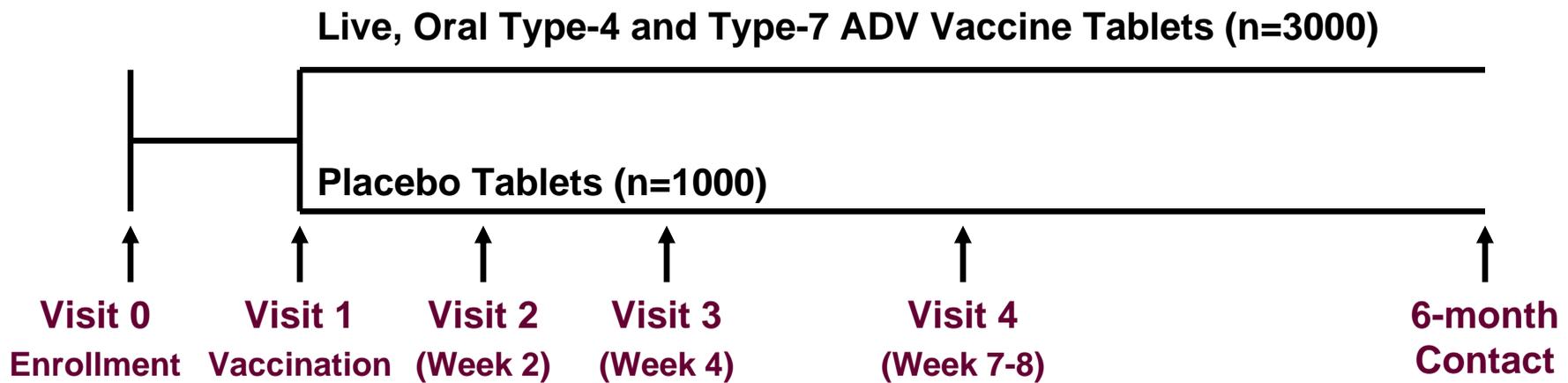


- Where?
- Objectives?
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## Study Flow Diagram

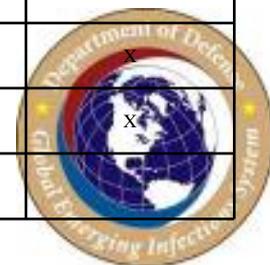




# Study Design: follow-up



Study Procedures	Visit 0*	Visit 1*	Visit 2	Visit 3	Visit 4	6-Month Contact	Early Term Visit
		Day 0	Week 2 (Day 12 ± 4 days)	Week 4 (Day 26 ± 4 days)	Week 8 (Day 56 ± 14 days)	(Day 180 ± 30 days)	
Consent	x						
Inclusion criteria	x						
Exclusion criteria	x						
Collection of subject demographics	x						
Pregnancy test**(β-HCG)		x					
Blood sample for ADV Type-4/7 serology†	x		x	x	x		x§
Study medication administration		x					
Distribute 2-Week Diary	x#						
Distribute 1-Week Diary	x##						
Collect & Review Diary			x				x§
Record AEs	x		x	x	x	xv	x
Record concomitant medications			x	x	x		x
Randomization		x					





# Study Design: follow-up



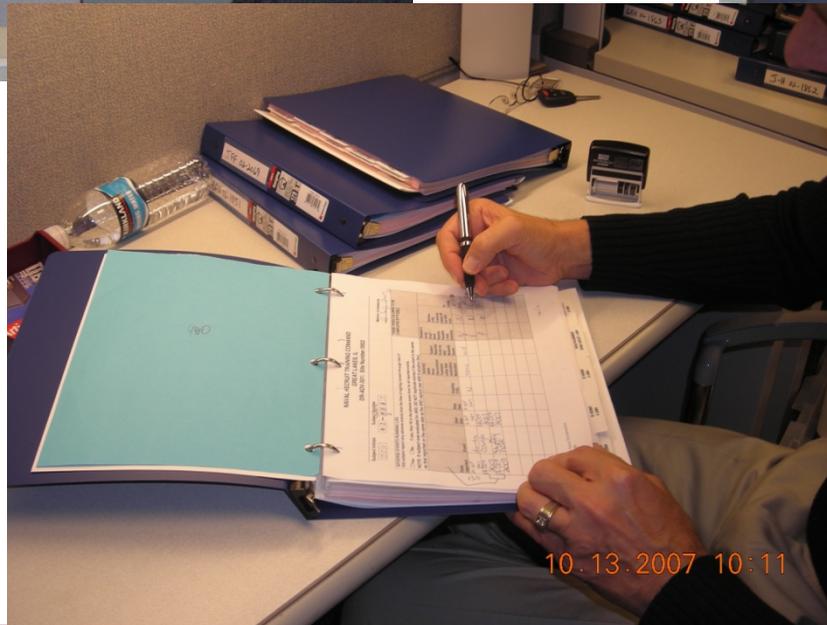
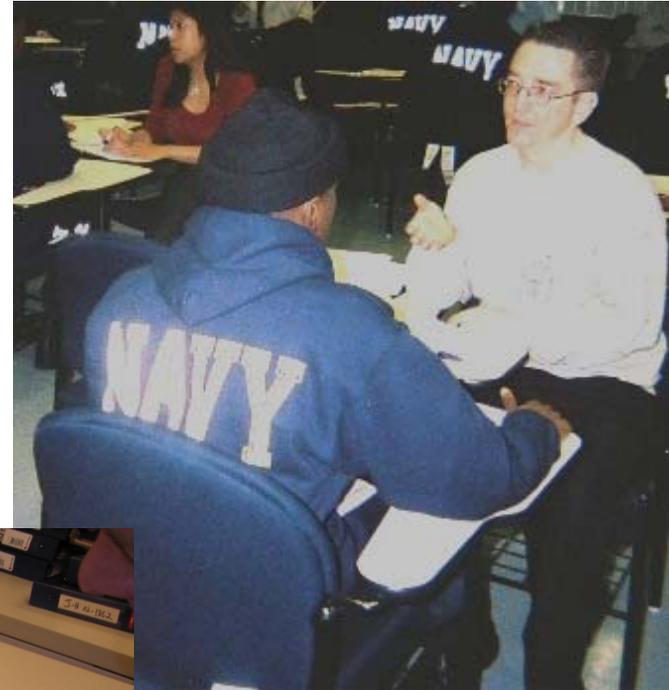
	2007 Saturday Schedule								
DATE	6-Jan	13-Jan	20-Jan	27-Jan	3-Feb	10-Feb	17-Feb	24-Feb	3-Mar
Cohort 1	Enroll		Visit 2		Visit 3			Visit 4	
Cohort 2		Enroll		Visit 2		Visit 3			Visit 4
Cohort 3			Enroll		Visit 2		Visit 3		
Cohort 4				Enroll		Visit 2		Visit 3	
Cohort 5					Enroll		Visit 2		Visit 3
Cohort 6						Enroll		Visit 2	
Cohort 7							Enroll		Visit 2
Cohort 8								Enroll	
Cohort 9									Enroll



# Conduct of the Trial



## Follow-ups





# Institutional Policies – Military Service Members as Subjects

- **Ombudsman**

- Not affiliated with military unit or research team
- Monitors the voluntary nature of participation
- Ensures information provided is adequate, accurate and appropriate

- **Additional Safeguard - Medical Monitor**

- Required for all greater than minimal risk research
- Independent of research team
- Assesses individual subject management and safety
- Serves as subject advocate





# IRB Considerations



- **Same as those for all human subjects research**
- **With autonomy, beneficence and justice as guiding principles, consider the following:**
  - Is there a dependency relationship between the researcher and subject?
  - How are subjects recruited?
  - What are the incentives for participation?
  - What are the implications of consent/refusal?
  - What are the implications of the researcher possessing a subordinate's identified data in the research topic areas?
  - How will confidentiality of data be maintained?
  - Will the research be conducted during class/work time?
  - Should there be process modifications based on the researcher-subject relationship?
    - Disallow enrollment of subordinates
    - Honest broker/blinding of researcher
    - Ombudsmen/advocate
  - Is special post-approval monitoring indicated?





# Conclusions



- **Discussions began 2+ years before on-site and beginning**
- **Logistics can be overwhelming**
- **IRB issues must be a priority**
- **Extremely rewarding**
- **Military a unique environment for conduct**
  - Pros and cons
  - MUST minimize impact
- **RELATIONSHIPS**
  - With Command
  - With Subjects





**\*\*Marine Photos, by MCRD-SD**



# *QUESTIONS?*

**CAPT Kevin L. Russell, MD, MTMH**

**Director, DoD-GEIS**

**Deputy-Director, AFHSC**

*Tel: 301-319-3041*

*E-mail: [Kevin.Russell4@us.army.mil](mailto:Kevin.Russell4@us.army.mil)*

