Febrile Respiratory Illness Surveillance and Research at Naval Health Research Center: Evaluating Unique Populations

Navy Respiratory Disease Laboratory
DoD Center for Deployment Health Research
Naval Health Research Center
San Diego, CA

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Overview

- **History of Naval Respiratory Disease Laboratory**
- **Febrile Respiratory Illness Surveillance**
  - Basic Trainees
  - Border
  - Shipboard
  - Fatal Cases
- **Laboratory Capabilities**
  - Sequencing of Influenza/Adenovirus
  - PCR to Distinguish between Vaccine and Wild-type Influenza/Adenovirus
  - Shipboard LightCycler PCR
  - Ambient Temperature Specimens
- **Avian Influenza / Pandemic Influenza Program**
- **Summary / Accomplishments**

Naval Respiratory Disease Laboratory

- **Established in Summer 1995**
- **Began adenovirus surveillance at 5 basic training sites in October 1996**
- **Expanded testing to include other viral pathogens in June 1998:**
  - Influenza A & B, RSV, PIV 1-3
  - 8 basic training sites
- **PCR incorporated into routine testing protocol Aug 2004**
- **Received C.A.P. certification in 1999, 2001, 2003, and 2005**

NHRC Testing Capabilities

Pathogen	Culture	Molecular	Serology
Adenovirus	✔	✔	✔
▪ serotyping		✔	✔
Influenza A/B	✔	✔	✔
▪ subtyping	✔	✔	✔
Human metapneumovirus	✔	✔	
Coronavirus		✔	
Respiratory Syncytial Virus	✔	✔	
Herpes Simplex Virus 1/2	✔		
Enterovirus	✔		
Parainfluenza 1/2/3	✔	✔	
Rhinovirus	✔	✔	
Neisseria meningitidis	✔	✔	
Streptococcus pneumoniae	✔	✔	✔
▪ serotyping	✔	✔	
▪ sensitivity testing	✔		
Streptococcus pyogenes	✔	✔	
▪ *emm* typing	✔	✔	
▪ sensitivity testing	✔		
Staphylococcus aureus	✔	✔	
▪ sensitivity testing	✔		
Haemophilus influenzae	✔	✔	
▪ sensitivity testing	✔		
Bordetella pertussis	✔	✔	✔
Mycoplasma pneumoniae	✔	✔	✔
Chlamydia pneumoniae		✔	✔

Febrile Respiratory Illness
Surveillance Sites

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

Influenza Diagnostic Collaborators:

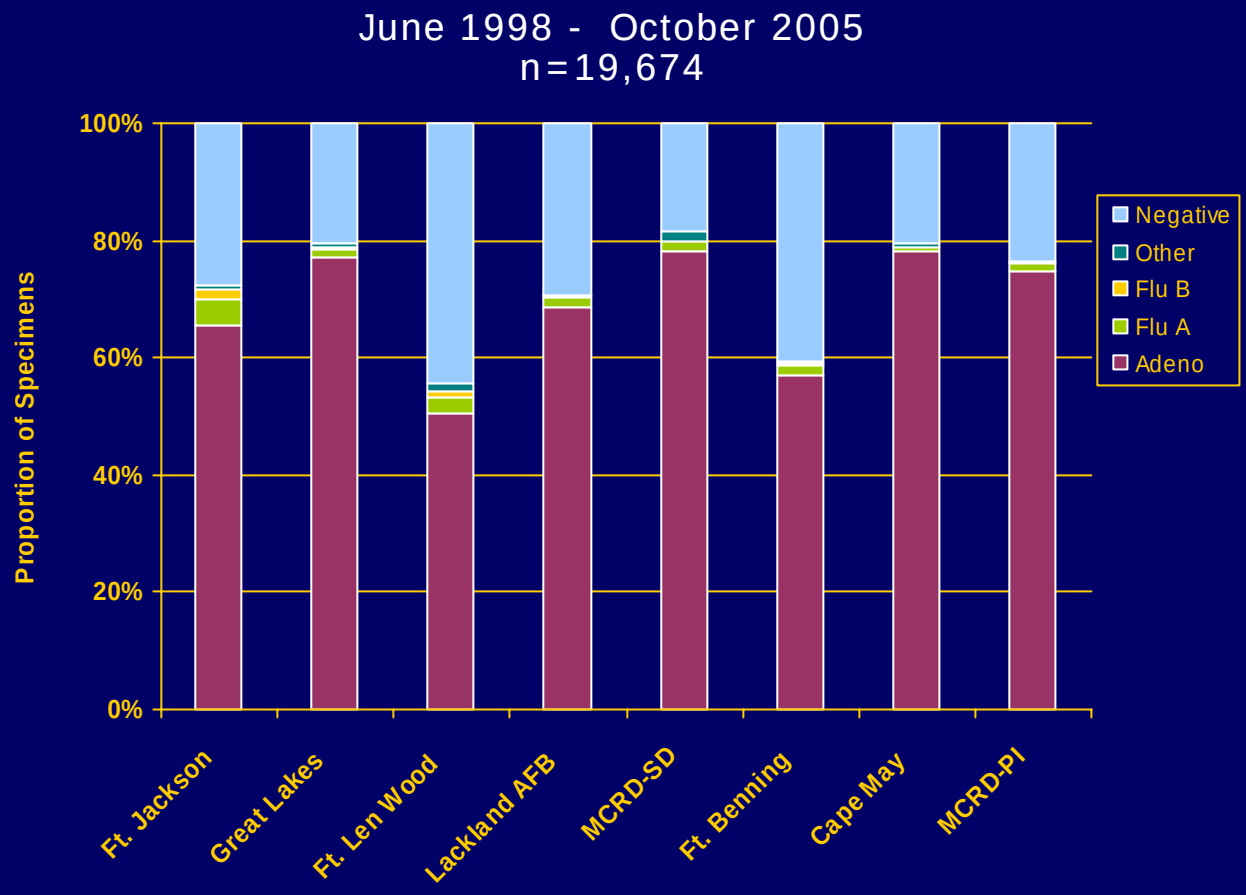
- Center for Disease Control and Prevention (CDC)
- Armed Forces Institute of Operational Health (AFIOH)

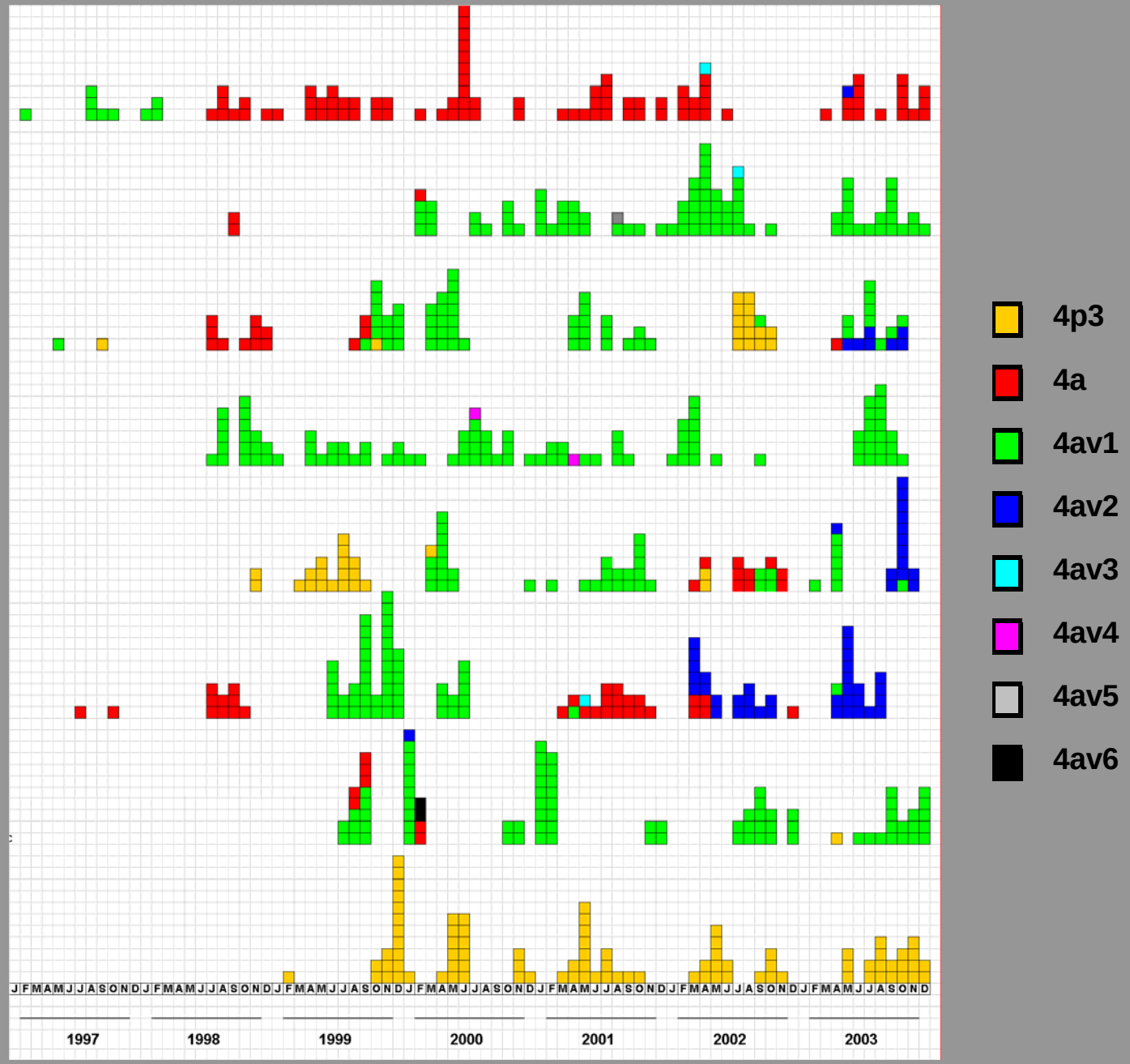
Febrile Respiratory Illness (FRI) Surveillance Programs

FRI among Basic Trainees

- **Surveillance at 8 sites:**
  - Fort Jackson
  - Fort Leonard Wood
  - Fort Benning
  - NTC Great Lakes
  - CGTC Cape May
  - MCRD San Diego
  - MCRD Parris Island
  - Lackland AFB
- **Case Definition**
  - oral temp of ≥ 100.5°F and cough or sore throat
  - also any case of nonbacterial pneumonia
- **Population-based**
  - FRI and pathogen-specific incidence
- **Collect throat swabs for viral testing**
  - systematic sample of FRI cases
  - PCR for adenovirus and influenza A
  - viral culture for adenovirus, influenza A & B, respiratory syncytial virus, parainfluenza 1-3
  - case data collected

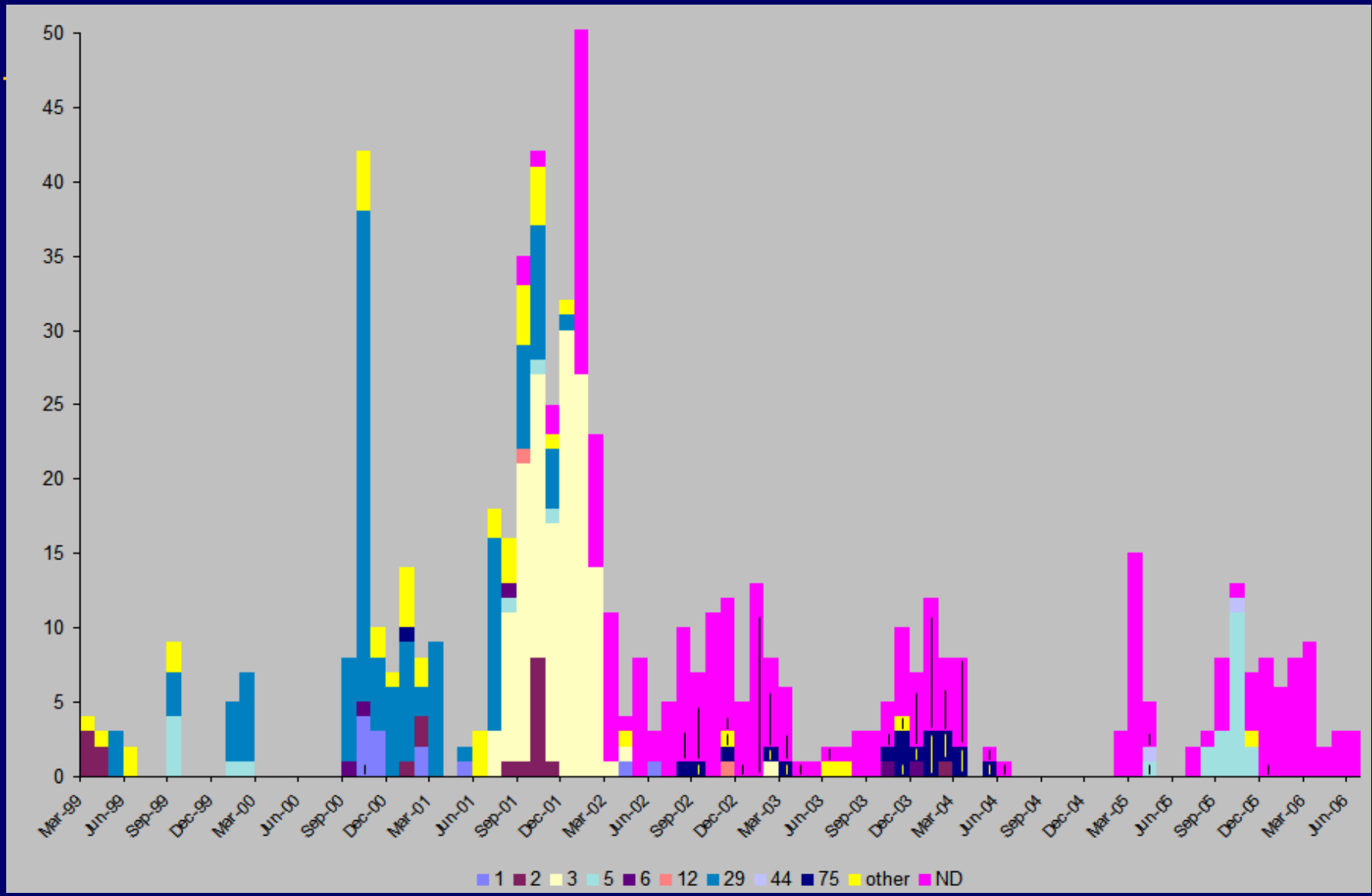
Distribution of Viral Test Results by Site



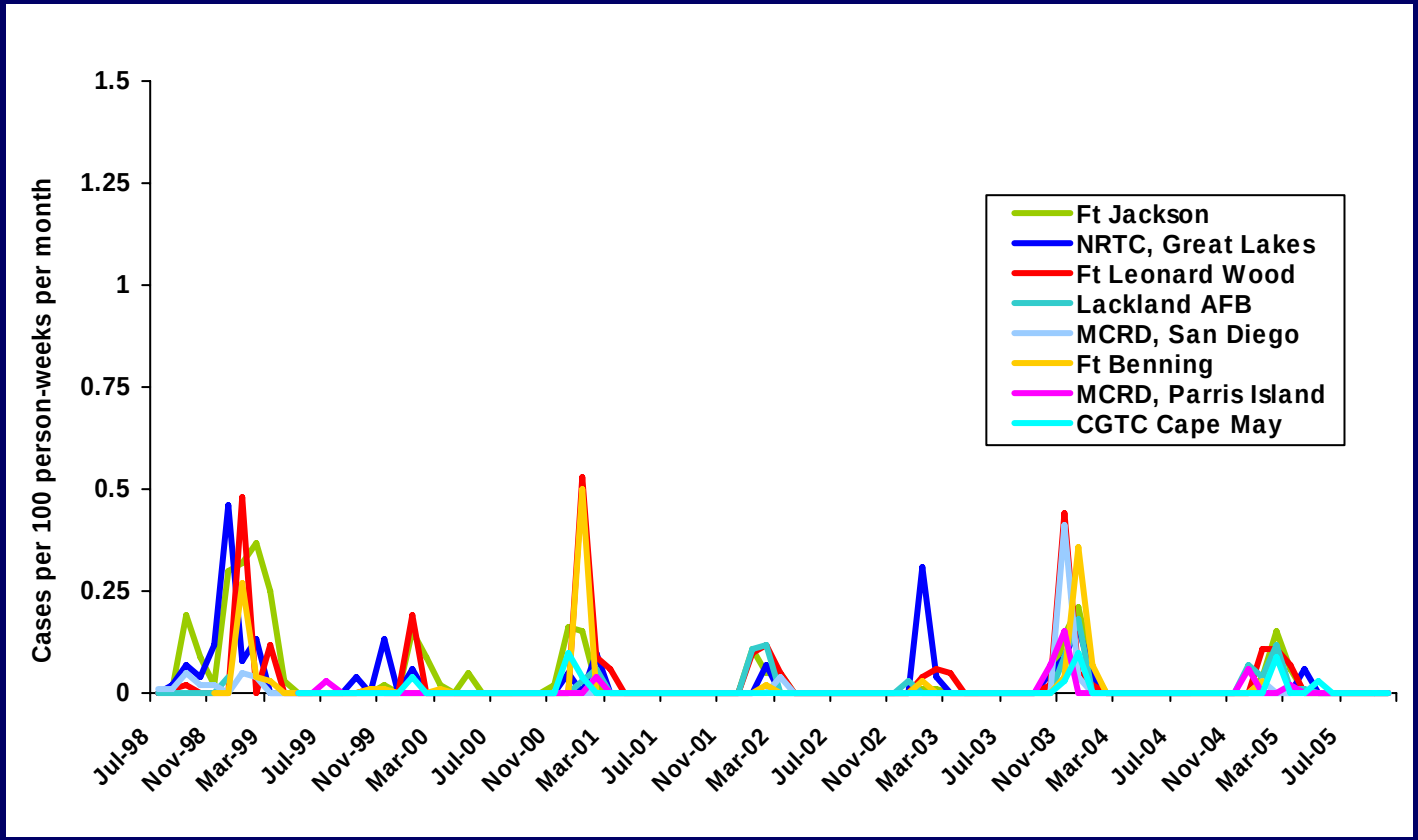

MCRDSD, CA
LUSAF, TX
FLW, MO
NTCGL, IL
FB, GA
FJ, NC
MCRDPI, SC
CGTCCM, NJ
J F M A M J J A S O N D J F M A M J J A S O N D J F M A M J J A S O N D J F M A M J J A S O N D J F M A M J J A S O N D J F M A M J J A S O N D J F M A M J J A S O N D J F M A M J J A S O N D
1997
1998
1999
2000
2001
2002
2003
4p3
4a
4av1
4av2
4av3
4av4
4av5
4av6

GAS Isolates MCRD-PI

with Antibiotic Sensitivities



Influenza Infection Rates at Basic Training Centers



Influenza Vaccine Effectiveness Against Lab-Confirmed Influenza, 2005-06

Site	Proportion Vaccinated	Person-weeks	Cases Vax	Cases Unvax*	Rate Vax	Rate Unvax	Effectiveness
Ft. Jackson	0.75	103832	7	13	0.00008989	0.00050081	82.1
Ft. Len Wood	0.75	90017	2	11	0.00002962	0.00048880	93.9
Ft. Benning	0.75	91536	3	0	0.00004370	0.00000000	N/A
Lackland AFB	0.667	56125	1	10	0.00002671	0.00053506	95.0
Great Lakes	0.75	90351	0	13	0.00000000	0.00057553	100.0
MCRD San Diego	0.75	47320	0	10	0.00000000	0.00084531	100.0
Totals		**479181**	**13**	**57**	**0.00003101**	**0.00045800**	**92.0**

*Unvaccinated or vaccinated < 14 days

FRI Surveillance in a Border Population

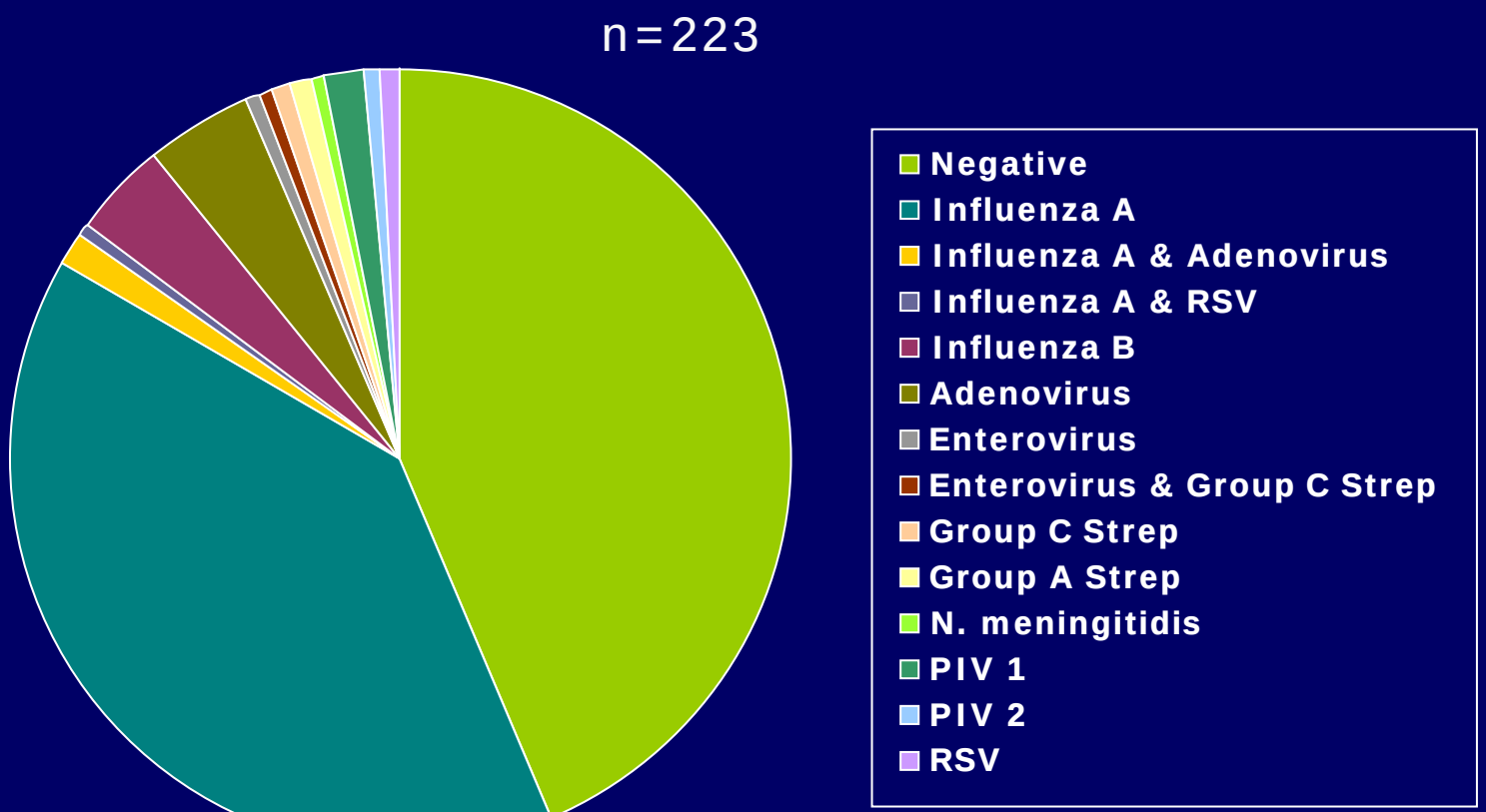
FRI Surveillance in a Border Population

- **Collaboration among:**
  - Naval Health Research Center
  - CDC Border Infectious Disease Surveillance (BIDS)
  - San Ysidro Health Center (SYHC) and Clínicas de Salúd del Pueblo, Caléxico, CA (CSPC)
    - Community health clinics near the U.S.-México border
    - Viral testing not routinely performed

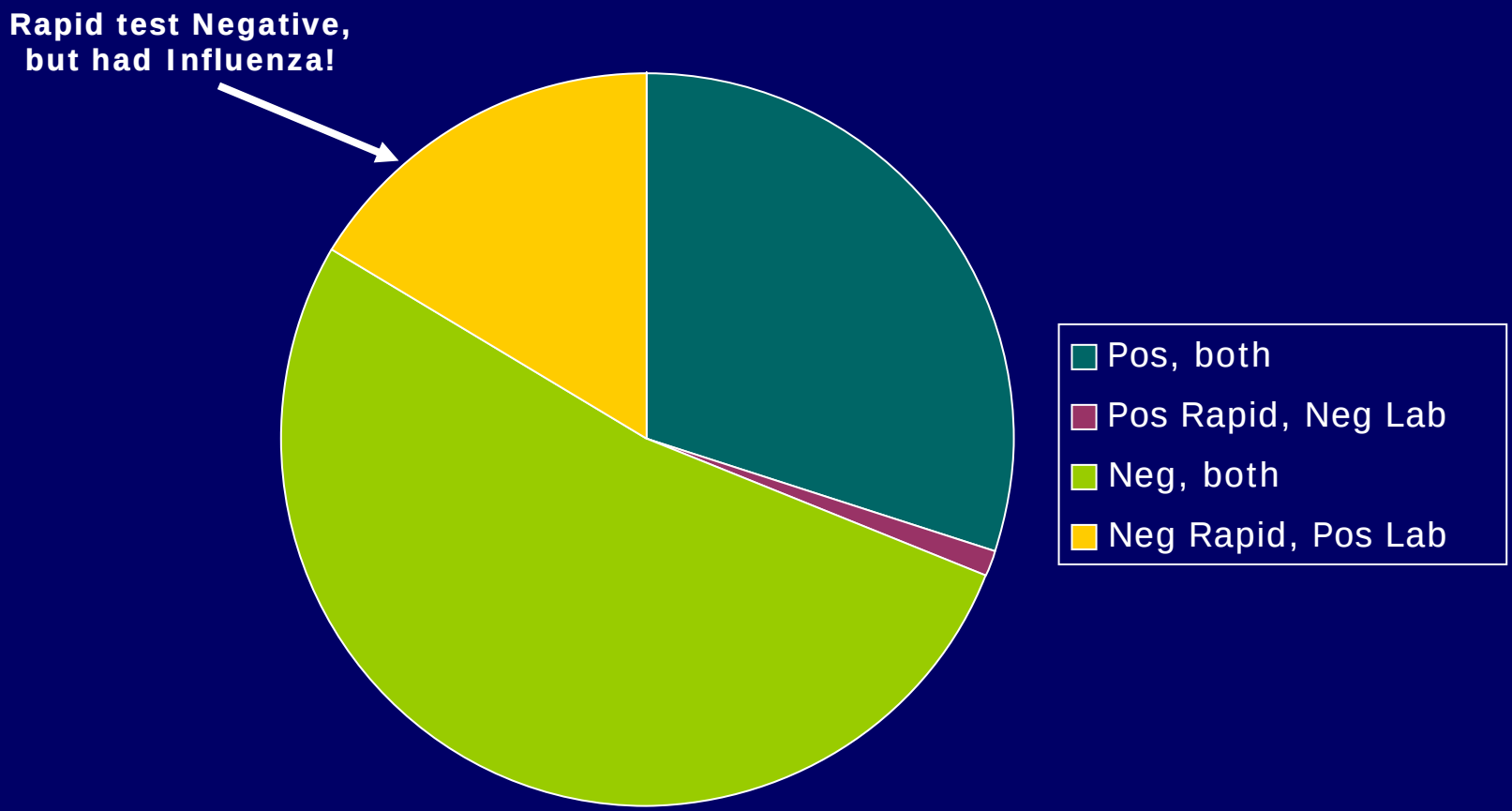
- **Influenza was the primary focus, but testing for other viral pathogens was also performed**
  - Adenovirus, RSV, PIV 1-3
  - Rapid influenza test also performed on all cases

- **Surveillance ongoing since 2004**

2005-06 Border FRI Laboratory Results



Summary of Rapid Influenza Test Performance, 2005-06

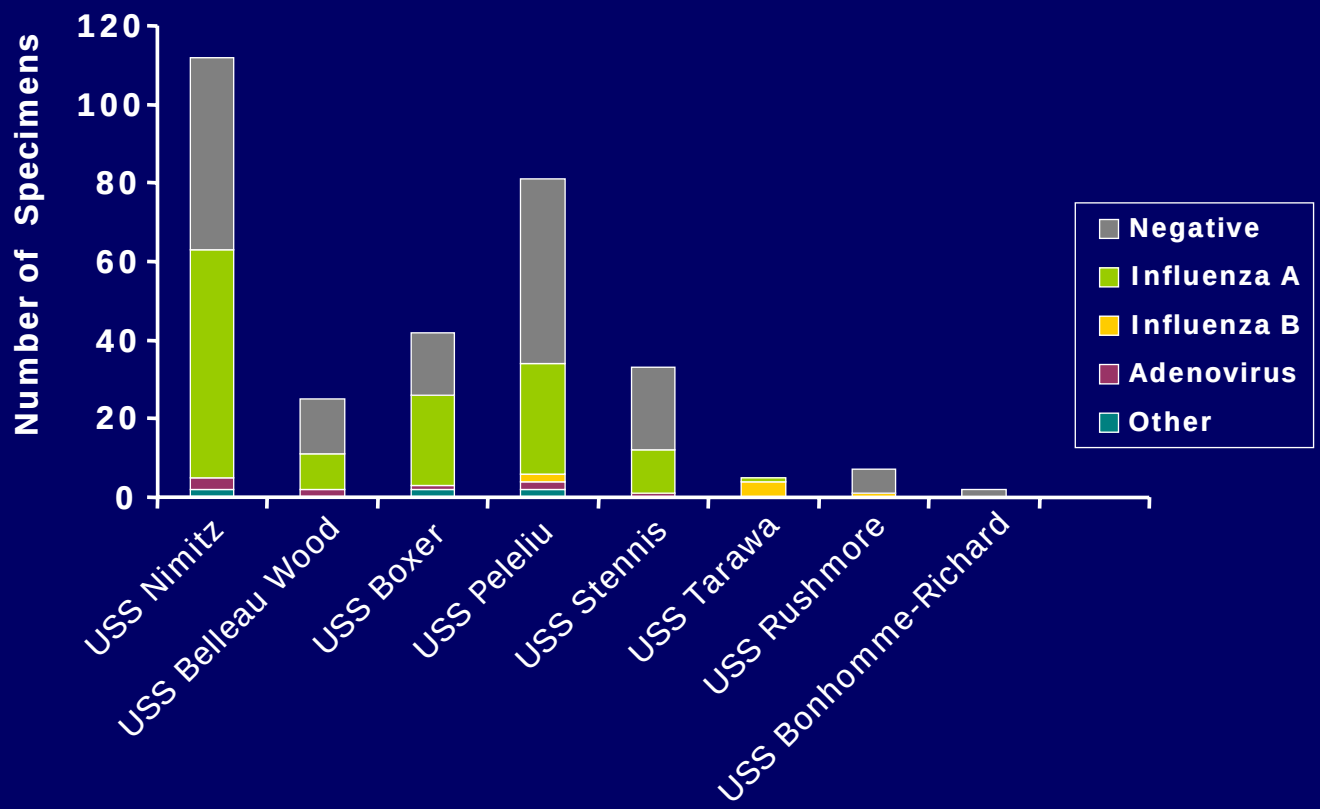


Shipboard FRI Surveillance

Shipboard FRI Surveillance: Objectives

- **Expand and strengthen the ongoing population-based surveillance**
  - Aboard ships of the 3rd Fleet (San Diego) since 2002/3
  - 2nd Fleet (Virginia) and 7th Fleet (Japan) now engaged
- **U.S. Naval Fleet offers an attractive platform**
  - Improved worldwide surveillance
  - Highly vaccinated population – an influenza outbreak could signal new strain
- **Determine viral pathogen distribution aboard floating platforms and document emerging pathogens in this population**
  - Influenza
  - Adenovirus
  - Other??
- **Obtain influenza isolates from unique locations**

Shipboard FRI Surveillance: Results



Shipboard FRI Surveillance: Results

- **Ships collect and store specimens during their deployment, samples are tested upon their return to port (or sooner if indicated/desired)**

- **Influenza A clusters occurred after port stops in past seasons:**
  - Pearl Harbor, HI (USS Nimitz, March 03)
  - Sydney, Australia (USS Boxer, July 03)
  - Singapore (USS Peleliu, October 03)
  - Port Kalang, Malaysia (USS Stennis, August 04)
  - San Diego, CA (USS Nimitz, January 05)
  - Astoria, OR (USCGC Fir, February 05)
  - Victoria, Canada (USS Belleau Wood, April 05)
  - Townsville, Australia (USS Boxer, June 05)
  - Honolulu, HI (USS Peleliu, Mar/Aug 06)
  - Phuket, Thailand (USS Peleliu, Jul 06)

- **Invaluable collection of influenza samples affecting our operational troops**

- **Adenovirus morbidity rare**
  - “Non-recruit” strains seen (ADV groups B, C, and D)

Molecular Influenza Projects

Sequencing of 2004-2006 Isolates

- Influenza
  - Sequencing of the HA/NA genes
  - Isolates from various sources
    - Shipboard
    - Basic training centers
    - Border FRI surveillance
  - Sequence data and isolates shared with CDC
- Adenovirus
  - Sequence Hexon and Fiber genes

PCR to Distinguish between Vaccine and Wild-type Strains

- **Influenza**
  - **FluMist has been used in recruits in recent years**
    - Concern about false positive influenza results
  - **PCR developed at NHRC to distinguish between FluMist and wild-type influenza**
  - **PCR positive, culture negative samples are tested to rule-out FluMist false positives**
- **Adenovirus**
  - **Adenovirus vaccine trial ongoing**
  - **Differentiate vaccine strain from wildtype**

Congressional Supplemental Avian/Pandemic Influenza Projects

Congressional Supplemental Avian/Pandemic Influenza Projects

- **Funding received late March 2006**
- **Objectives:**
  - Add surge capacity
  - Increase molecular capability
  - Incorporate TIGER
  - BSL-3 laboratory
  - Pacific Rim Surveillance Center
  - US Navy ship surveillance
  - Shipboard PCR diagnostic capability
  - Field PCR diagnostic capability
  - Surveillance strategies

Recent Products (2005/6 Only)

- Vaccine-preventable adenoviral respiratory illness in US military recruits, 1999-2004. Vaccine 2006;24(15):2835-42.
- 15-Year retrospective study of the changing epidemiology of methicillin-resistant Staphylococcus aureus (MRSA). Am J Med 2005. IN PRESS
- PCR analysis of Egyptian respiratory adenovirus isolates: Species, Serotypes, and Coinfections. J Clin Microbiol 2005;43(11):5743-5752.
- Surveillance for febrile respiratory infections during Cobra Gold 2003. Mil Med 2006, IN PRESS.
- Many Faces of Meningococcal Disease: a Case Series and Review of Presentations and Treatment Options, IDCP, IN PRESS.
- Mycotic pseudoaneurysm and purulent pericarditis due to methicillin-resistant Staphylococcus aureus. Mil Med 2006, IN PRESS.
- Emergence of a new human Adenovirus type 4 (Ad4) genotype: Identification of a novel inverted terminal repeated (ITR) sequence from majority of Ad4 isolates from US military recruits. J of Clin Vir. IN PRESS.
- Respiratory infections in military recruits, Chapter 11, Textbooks of Military Medicine, IN PRESS
- Genomic and Bioinformatics Analysis of HAdV-4vac and HAdV-7vac, Two Human Adenovirus Strains that Constituted Original Prophylaxis Against HAdV-related Acute Respiratory Disease (ARD), a Reemerging Epidemic Disease. 2005. JCM, Jul;43(7):3083-94.
- Effectiveness of the 2003-04 Influenza Vaccine Among U.S. Military Basic Trainees. 2005. Vaccine, Vol 23(16), pp 1981-1985.
- A multiplex PCR for detection of Mycoplasma pneumoniae, Chlamydophila pneumoniae, Legionella pneumophila, and Bordetella pertussis in clinical specimens. 2005. Molecular and Cellular Probes, Oct;19(5):314-22 .
- Fatal meningitis caused by Streptococcus pneumoniae Serotype 38. 2005. BMC-Inf Dis, 5(38).
- Rapid identification and strain-typing of respiratory pathogens. 2005. PNAS, 102(22), p8012-8017.
- Antimicrobial Susceptibility and Serotype Distribution of Streptococcus pneumoniae Causing Meningitis in Egypt, 1998 – 2003. 2005. JAC, 55(6):958-64.
- Evaluation of PCR Testing on Ethanol-Fixed Nasal Swab Specimens as an Augmented Surveillance Strategy for Influenza and Adenoviruses. 2005. CID, Vol 40, pp 511-8.
- Pneumonia Outbreak Associated with Group A Streptococcus at a Military Training Facility. 2005. CID, Vol 40, pp 511-518.

Questions / Discussion

www.nhrc.navy.mil/geis

Email: FRI@nhrc.navy.mil

Add Surge Capacity

- **FRI**
  - Double number of samples from recruit camps
  - More frequent shipments to NHRC
- **Improved methodologies for molecular high-throughput**
  - Equipment/validations
- **Laboratory upgrades ongoing**

Increase Molecular Capability

- **Influenza**
  - Full H, N, M gene sequencing
  - Strongly advocated by CDC
    - They take our sequences and look for interesting variations/drifts

- **Avian Influenza PCR capabilities**
  - Leveraging overseas collaborations
  - Strong interest

Incorporate TIGER

- **Many strong applications identified**
  - Influenza
  - Respiratory pathogens
  - Adenovirus
  - Group A streptococcus

- **Influenza plate**
  - One pass identification of ANY H or N type
  - High Through-put
  - Useful for our surveillance, as well as an asset for the DoD
    - Overseas laboratories and increasing demands/sample processing
    - We could do first pass, then they could pick and choose what they do culture on
    - CDC permit obtained

BSL-3E

- **Much ground work already performed**
  - Expected to be operational by Spring 2007
  - Construction to begin this month

- **External building; inner core—BSL-3 Enhanced**
  - High priority for HA
  - Allow us to assist with pandemic influenza workups

Pacific Rim Surveillance Center

- **Yokosuka Naval Hospital**
  - Strong support; CAPT Hoeksema
  - Office space identified; 2-3 personnel, HMJ hired (I hired now)
  - Oversee shipboard surveillance, Pacific Rim deployments, facilitate AFIOH sentinel site surveillance
- **Facilitate diagnostics at NH Yokosuka**
  - Assist in becoming an LRN (CDC, Laboratory Reference Network)
  - Assist with the Real-Time PCR training/capability
- **Training also provided to NH Okinawa**

U.S. Navy Ship Surveillance

- **Initiated in late 2002**
  - Discussed earlier…
- **Expanded to 7th and 2nd Fleet**
  - Agreement obtained from 7th Fleet, Yokosuka, Japan, May 2006
  - Agreement obtained from 2nd Fleet, Norfolk, Virginia, July 2006
- **Proven useful in obtaining influenza isolates**
  - Optimal specimens will be collected at the most opportune time
  - Strengthens global pandemic influenza surveillance
- **High Interest/facilitation**

Shipboard PCR Capability

- **LightCyclers currently onboard**
  - Biological Defense Research Directorate (BDRD), NMRC, Dr. Mateczun
  - Biological Warfare agent detection
- **Have engaged in past, little use**
- **Recent interactions with CAPT (ret) Mateczun has led to modifications in methodologies**
- **Interest rapidly increasing**
- **Current pathogens:**
  - Influenza A
  - Influenza B
  - H5 Avian influenza
  - *Mycoplasma pneumoniae*
  - *Chlamydia pneumoniae*
  - Adenovirus

Field PCR Capability

- **Given current pandemic influenza concerns, need for a field deployable testing unit for avian influenza needed**

- **Many companies in development stages**
  - Real time RT-PCR
    - Quiagen/Artus
    - Eiken LAMP
    - TIB Light Mix
    - Arbor Vita
  - Self-contained kits
    - Response Biomedical
    - Cepheid
    - GeneXpert

Syndromic Surveillance

- **Information-aggregation system to predict influenza vaccine effectiveness during the season**
  - Internet based
  - People in field often have perceptions early
  - Opinions of vaccine performance will be solicited and consensus probabilities generated
  - Monitor for indications of poor vaccine effectiveness