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

LCDR Dennis Faix, MC, USN
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
## NHRC Testing Capabilities

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Culture</th>
<th>Molecular</th>
<th>Serology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenovirus</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>• serotyping</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza A/B</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>• subtyping</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human metapneumovirus</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronavirus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory Syncytial Virus</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpes Simplex Virus 1/2</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterovirus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parainfluenza 1/2/3</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinovirus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>• serotyping</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>• emm typing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• sensitivity testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>• sensitivity testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• sensitivity testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bordetella pertussis</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Chlamydia pneumoniae</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>
Febrile Respiratory Illness Surveillance Sites

7th Fleet (Japan)
- Fort Benning
- Fort Jackson
- Lackland AFB
- CGTC Cape May
- MCRD San Diego
- MCRD Parris Island
- Fort Leonard Wood
- NSTC Great Lakes

2nd Fleet (Norfolk, Virginia)
- San Ysidro, CA
- Calexico, CA

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

June 1998 - October 2005
n=19,674

Ft. Jackson
Great Lakes
Ft. Len Wood
Lackland AFB
MCRD-SD
Ft. Benning
Cape May
MCRD-PI

Proportion of Specimens

Negative
Other
Flu B
Flu A
Adeno
GAS Isolates MCRD-PI
with Antibiotic Sensitivities
Influenza Infection Rates at Basic Training Centers

![Graph showing influenza infection rates at various basic training centers from July 1998 to July 2005. The x-axis represents months from Jul-98 to Jul-05, and the y-axis represents cases per 100 person-weeks per month. The graph includes data for Ft Jackson, NRTC, Great Lakes, Ft Leonard Wood, Lackland AFB, MCRD, San Diego, Ft Benning, MCRD, Parris Island, and CGTC Cape May.]
# Influenza Vaccine Effectiveness Against Lab-Confirmed Influenza, 2005-06

<table>
<thead>
<tr>
<th>Site</th>
<th>Proportion Vaccinated</th>
<th>Person-weeks</th>
<th>Cases Vax</th>
<th>Cases Unvax*</th>
<th>Rate Vax</th>
<th>Rate Unvax</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ft. Jackson</td>
<td>0.75</td>
<td>103832</td>
<td>7</td>
<td>13</td>
<td>0.00008989</td>
<td>0.00050081</td>
<td>82.1</td>
</tr>
<tr>
<td>Ft. Len Wood</td>
<td>0.75</td>
<td>90017</td>
<td>2</td>
<td>11</td>
<td>0.00002962</td>
<td>0.00048880</td>
<td>93.9</td>
</tr>
<tr>
<td>Ft. Benning</td>
<td>0.75</td>
<td>91536</td>
<td>3</td>
<td>0</td>
<td>0.00004370</td>
<td>0.00000000</td>
<td>N/A</td>
</tr>
<tr>
<td>Lackland AFB</td>
<td>0.667</td>
<td>56125</td>
<td>1</td>
<td>10</td>
<td>0.00002671</td>
<td>0.00053506</td>
<td>95.0</td>
</tr>
<tr>
<td>Great Lakes</td>
<td>0.75</td>
<td>90351</td>
<td>0</td>
<td>13</td>
<td>0.00000000</td>
<td>0.00057553</td>
<td>100.0</td>
</tr>
<tr>
<td>MCRD San Diego</td>
<td>0.75</td>
<td>47320</td>
<td>0</td>
<td>10</td>
<td>0.00000000</td>
<td>0.00084531</td>
<td>100.0</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>479181</strong></td>
<td><strong>13</strong></td>
<td><strong>57</strong></td>
<td><strong>0.0003101</strong></td>
<td><strong>0.00045800</strong></td>
<td></td>
<td><strong>92.0</strong></td>
</tr>
</tbody>
</table>

*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

n=223

- Negative
- Influenza A
- Influenza A & Adenovirus
- Influenza A & RSV
- Influenza B
- Adenovirus
- Enterovirus
- Enterovirus & Group C Strep
- Group C Strep
- Group A Strep
- N. meningitidis
- PIV 1
- PIV 2
- RSV
Summary of Rapid Influenza Test Performance, 2005-06

Rapid test Negative, but had Influenza!
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

Number of Specimens

- USS Nimitz
- USS Belleau Wood
- USS Boxer
- USS Peleliu
- USS Stennis
- USS Tarawa
- USS Rushmore
- USS Bonhomme-Richard

- Negative
- Influenza A
- Influenza B
- Adenovirus
- Other
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)

- 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 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.
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