Respiratory Diseases in the US Military: Respiratory Epidemiology & Control

COL Stephen J. Thomas, MD
COL James F. Cummings, MD

WRAIR-GEIS OCID
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Most burdensome infection in humans, 2nd overall behind CHD

Morbidity & mortality especially significant in children (2010 data)
- Worldwide, ~4.25 million deaths (mortality rate ~41 per 100K)
- In the US, ~85K deaths (mortality rate ~27 per 100K)

In adults, high incidence & subsequent disability associated with economic loss

As a group are the leading cause of morbidity from any infectious disease
- Children: 6-10 upper respiratory infections/year
- Adults: 2-4 upper respiratory infections/year

At highest risk for complications – very young (< 5yo) & old (> 65yo)

In US military, a significant health care burden (2012 data)
- > 350K cases diagnosed, affecting ~250K personnel each year
- Estimated to be responsible for 25-30% of ID-related hospitalizations

Sources:
Murray CJL & Lopez AD, Global health: measuring the global burden of disease, NEJM 2013; 369(5):448-457, 1 August 2013
Military trainees at increased risk:

- Those with <1 year of service are 5 times more likely to be hospitalized
- New recruits are 29 times more likely

Risk may be related to:

- Stresses of training
- Environmental (seasonal) factors
- Mixing of young adults in close contact settings
- Crowding > determinant than seasonal factors

Impact on Military Training

Upwards of 45,000-66,000 medical visits with 29,000-38,000 recruits affected, ~15,000-27,000 days lost work-time & ~2,000-3,000 hospital bed days

Respiratory Infections
Deployed Military in SW Asia (2003-04)

- Self-reported illnesses; 2nd most common illness (after acute diarrheal disease)
- As high as 70% of deployed; incidence ~15% per month
- Impacted individual performance ~ 14% of time
- Required medical care in ~ 17% of cases

| Impact of respiratory illness among U.S. military personnel deployed to Iraq or Afghanistan, 2003–2004* |
|---|---|---|
| % | 95 CI |
| Number of respiratory infections (cough or cold) during deployment |
| None | 30.9 | 27.6–34.4 |
| 1 | 19.1 | 16.4–22.2 |
| 2–3 | 35.6 | 32.3–39.2 |
| > 3 | 14.4 | 12.0–17.2 |
| Sought medical care for a respiratory infection | 17.0 | 14.2–19.8 |
| Received medicine from a provider for a respiratory infection | 17.8 | 14.9–20.7 |
| Self-medicated for respiratory infection | 29.3 | 26.2–32.5 |

Respiratory Infections

Pathogens of major concern to the military:

- Adenoviruses
- Influenza viruses
  - Respiratory syncytial virus (RSV)
  - Human metapneumoviruses
  - Coronaviruses, MERS-CoV and SARS
  - *Streptococcus pneumoniae*
  - *Streptococcus pyogenes* (Group A strep)
  - *Mycoplasma & Chlamydophila pneumoniae*
  - *Bordetella pertussis*
  - *Mycobacterium tuberculosis*
Respiratory Tract & Infections

Transmission & Shedding

Transmission Modes:
- Person-to-Person (close contacts)
  - Large droplets: coughing, sneezing
  - Highly contagious
  - Hand hygiene is important
- Airborne Spread (same room)
- Fomites (direct contact)

Viral Shedding:
- Can begin before symptom onset
- Peak viral shedding on first 1-2 days of symptoms
- Adults may shed viruses for 5-7 days (weeks to months for Strep/Tb)
- Children shed viruses for longer periods (up to 2 weeks)
## Respiratory Infections
### Presentations during Military Epidemics

<table>
<thead>
<tr>
<th>Incubation period (days)</th>
<th>Pathogen</th>
<th>Clinical presentation and epidemiologic clues</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-12</td>
<td>Adenoviruses</td>
<td>Acute onset with non-suppurative pharyngitis &amp; fever; may be associated with secondary viral (but not bacterial) pneumonia with certain strains; associated with clusters among non-immune recruits, much less of a problem after recruit vaccination began in October 2011</td>
</tr>
<tr>
<td>1-3</td>
<td>Influenza &amp; Parainfluenza viruses</td>
<td>Acute onset of headaches fever &amp; malaise (ILI); may be complicated by secondary bacterial infections in 20 to 30% of cases; associated with clusters among non-immune recruits (early in basic training prior to development of vaccine-induced immunity) &amp; older veterans</td>
</tr>
<tr>
<td>1-3</td>
<td>Respiratory Syncytial virus (RSV)</td>
<td>Acute onset of non-productive cough, sore throat, nasal congestion &amp; wheezing in &gt; 60% of cases reflecting lower respiratory tract involvement; often detected in association with influenza &amp;/or adenovirus among non-immune recruits</td>
</tr>
<tr>
<td>3-5</td>
<td>Human Metapneumoviruses (hMPV)</td>
<td>Acute onset of ILI &amp; common cold syndromes (fever, cough &amp; rhinorrhea), may be associated with community clusters of cases with asthma, conjunctivitis, pharyngitis, laryngitis &amp;/or pneumonia; infrequently associated with CAP (&lt; 5% of cases)</td>
</tr>
<tr>
<td>2-5</td>
<td>Human Coronaviruses (CoV)</td>
<td>Acute onset of a common cold syndrome (non-SARS CoV) lasting 3 to 18 days, severe acute respiratory syndrome (SARS) with onset of pneumonia as long as 10 to 14 days after exposure (SARS &amp; MERS-CoV)</td>
</tr>
<tr>
<td>1-3</td>
<td>Streptococcus pneumoniae</td>
<td>Acute onset with high fever, rigors, productive cough and shortness of breath due to pneumonia; often seen in conjunction with other viral infections; affects non-immune recruits &amp; other highly-stressed, very fatigued, older military trainees (such as Navy Seals, Army Rangers)</td>
</tr>
<tr>
<td>1-3</td>
<td>Streptococcus pyogenes</td>
<td>Acute onset of fever &amp; suppurative, patchy sore throat among non-immune recruits &amp; other highly-stressed, very fatigued, older military trainees (such as Navy Seals, Army Rangers)</td>
</tr>
<tr>
<td>6-32</td>
<td>Mycoplasma pneumoniae</td>
<td>Gradual onset of dry, non-productive cough, malaise &amp; chills (with low-grade fever) &amp; secondary pneumonia; under-recognized cause of illness among trainees &amp; service-related cadets/students; ~50% with positive cold agglutinins</td>
</tr>
<tr>
<td>10-30</td>
<td>Chlamydia pneumoniae</td>
<td>Acute or gradual onset of pharyngitis, dry, non-productive cough, hoarseness &amp; low-grade fever, illness is generally milder than for other pathogens; under-recognized cause of illness among trainees &amp; service-related cadets/students</td>
</tr>
<tr>
<td>6-20</td>
<td>Bordetella pertussis</td>
<td>Gradual onset of unrelenting, hacking cough with paroxysms, whoop or post-cough vomiting, nasal congestion &amp;/or headaches, lasting for 1 to 8 weeks in deployed personnel exposed to local nationals; uncommon in recruits due to effective immunization upon arrival</td>
</tr>
<tr>
<td>Weeks-months</td>
<td>Mycobacterium tuberculosis</td>
<td>Over 90% of cases are pulmonary with persistent cough (&gt; 3 weeks) with subsequent spiking fever, sputum production &amp; shortness of breath, often mis-diagnosed as bronchitis or “atypical pneumonia”, secondary cases in up to 2-3% of those exposed, 6-12 months post-exposure</td>
</tr>
</tbody>
</table>

Adenoviruses, 1950s & 60s

- Isolated in 1953 by Rowe and Hilleman
- Before vaccines, adenovirus:
  - Caused 10% of all recruits to be hospitalized in 1958
  - Explained up to three-fourths of acute respiratory illnesses
  - Was mostly a problem during winter months
  - Caused outbreaks with very high (50-80%) attack rates
  - Up to 20% of recruits hospitalized for an average of 10 days

Adenovirus-related Disease
Presentations in the Military

- Acute onset with non-suppurative pharyngitis & fever
- May be associated with secondary viral (but not bacterial) pneumonia with certain strains (not common, less than 5% of cases)
- Presents as large clusters among non-immune recruits
- May occur at any time during the year among recruits who are crowded-in close quarters
- Much less of a problem after recruit vaccination restarted in October 2011

Sources:
• Seroconversion (e.g., infection) rate ~60-80% (MN titer > 1:4 - 1:8)
• Greatest risk factor is lack of immunity at entrance
  • High baseline immunity, MN titer > 1:32, AOR ~0.02 (95% CI, 0.005 – 0.06)
• Other notable risk factors examined:
  • Predisposition with younger age (< 20 years), AOR ~3.6 (95% CI, 1.2 – 11.0)
  • Predisposition with male gender, AOR ~3.6 (95% CI, 1.8 – 7.5)
  • Protection in those born/raised in tropical regions, OR ~2.8 (higher immunity)
  • No clear association with race/ethnicity or prior smoking history

ADV-14 Acute Respiratory Disease
“Emerging Threat”

- Adenovirus 14 was first discovered during an ARD outbreak among Dutch recruits in 1955, termed “agent de Wit”
- Sporadic reports between 1960s and 2006, mostly in Europe
- Emergence in USA in Mar-Apr 2006, rapid spread east
- Eventually involved all US military recruit training centers (2006-2009)

Source: Kajon AE, et al, J Infect Dis, 1 Jul 10
“Phase 3 Adenovirus Vaccine Trial”

Vaccine Efficacy

<table>
<thead>
<tr>
<th>ARD Type</th>
<th>ADV Vaccine (N=3031)</th>
<th>Placebo (N=1009)</th>
<th>Vaccine Efficacy (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile, - no. cases (AR%) *</td>
<td>1 (0.03)</td>
<td>48 (4.76)</td>
<td>99.3 (96.0, 99.9)</td>
</tr>
<tr>
<td>Afebrile - no. cases (AR%)</td>
<td>2 (0.06)</td>
<td>17 (1.68)</td>
<td>96.1 (84.8, 98.9)</td>
</tr>
<tr>
<td>Febrile and Afebrile - no. cases (AR%)</td>
<td>3 (0.10)</td>
<td>65 (6.44)</td>
<td>98.5 (95.4, 99.5)</td>
</tr>
</tbody>
</table>

* AR(%) is the attack rate defined as (no. cases /N)100

- US military recruits at Great Lakes & Ft Jackson, Sep 06-Nov 07
- Over 4,000 randomized to vaccine (3,000) or placebo (1,000)
- VE ~ 99% for FRI, ~ 96% for afebrile infection, versus type 4

Source: Kuschner RK & Russell KL, A phase 3, randomized, double-blind, placebo-controlled study of the safety and efficacy of the live, oral adenovirus type 4 and type 7 vaccine in U.S. military recruits, Vaccine 2013; 31:2963-2971
Immunogenicity equivalent to that seen with natural infection (~95%)

Similar for both serotypes 4 and 7, thus, assume VE vs type 7 will be similar

Vaccination at beginning of training reduced infection rates among placebo recipients to ~5-10% (compared with ~60% in same setting in 1998)
ADV Vaccination - All Recruits

“Restart of Program-on/after 24 October 2011”

Impact of Adenovirus type 4 & 7 Vaccination Among Recruits at Eight Training Centers

- Ad vaccination instituted fully by mid-November 2011 (week 45)
- FRI rates decreased by ~80% compared to pre-vaccination period
- Ad isolation rates among FRI recruits decreased over 95% compared to pre-vaccination period
- Sporadic cases of Ad14 (non-vaccine type), will it emerge?

Based on FRI surveillance data by NHRC, it is estimated that ADV vaccine has prevented:

- 15,000 cases of febrile respiratory illnesses per year
- 1,500 hospitalizations (6,000 hospitalizations days) per year
- 50,000 trainee-days of lost training per year
- Over 99% of ADV-associated FRIs (~15,000/year vs 49 in Jan-Aug 12)

Sources:  
USAMMDA, Clifford E. Snyder, 5 October 2012, personal communication  
AFHSC, Angelia Eick-Cost, 5 October 2012, personal communication  
NHRC, Anthony Hawksworth, 9 October 2012, personal communication
Based on follow-up safety data of vaccinated (~78,000) vs unvaccinated (~78,000) cohorts & ICD-9 diagnoses on DMSS data by AFHSC, it is estimated that ADV vaccination has resulted in:

- Prevention of all ADV-associated pneumonias (9 cases in Oct 10-Sep 11 non-vaccination year vs 0 in vaccination year)
- Prevention of all viral-associated pneumonias (20 cases in Oct 10-Sep 11 non-vaccination year vs 0 in vaccination year)
- Prevention of 50% other unspecified pneumonias (2,034 cases in Oct 10-Sep 11 non-vaccination year compared to 1,014 in Oct 11-Sep 12)

USAMMDA, Clifford E. Snyder, 5 October 2012, personal communication
AFHSC, Angelia Eick-Cost, 5 October 2012, personal communication
NHRC, Anthony Hawksworth, 9 October 2012, personal communication
Influenza
Impact in the Military, WWI, 1918

• 25% of military caught the flu
  • 1 million soldiers
  • Mortality from flu ~ 5% (CFR)
  • Mortality from pneumonia 20-50%

• Flu impact as great as bullets/gas
  • 791,907 soldiers hospitalized in US/France
  • 57,460 died of flu/pneumonia (compared to 50,280 combat-related deaths)
  • 1 in 67 American soldiers died of flu/pneumonia

• War Department estimated that it lost 8,743,102 days among enlisted men

Sources:
Vaughan VC, Palmer GT. Communicable disease in the United States Army during the summer and autumn of 1918, J Clin Med 1918;3:587–623, 647–86

Soldier receives throat spray for Spanish Flu
Illness rates highest in children & young adults (red line)

Mortality rates highest in young adults – military age!

Deaths caused mostly by 2ndary bacterial pneumonia

“W-shaped Mortality Curve”

Influenza
Military’s Impact Back Home, 1918

- Highest transmission at end of WWI, October-November 1918
- Spread from US military training camps in the US (Fall)
- Armistice of Compiegne signed on 11 November 1918
- Return of expeditionary forces back to US & Great Britain (Winter)

Source: DoD’s Military Vaccine Agency (MILVAX), http://www.vaccines.mil/Influenza_-_Pandemic, 2 January 2014
Pandemic Flu (pH1N1)

“First two cases identified in California”

- **Case 1:**
  - 10 yo male asthmatic, San Diego
  - Enrolled in a clinical dx study
  - No swine contact
  - Onset 3/30/09
  - NMCSD clinic visit 4/1/09
  - Influenza A unsubtypable at NHRC
  - Confirmed at CDC

- **Case 2:**
  - 9 yo female, Imperial Co., CA
  - Enrolled in DoD-CDC BIDS initiative
  - Onset 3/27/09: influenza-like illness
  - Clinic visit 3/30/09
  - No swine contact
  - Identified at NHRC as swine flu virus
  - Confirmed at CDC

Sources:
- CDR Patrick Blair, Naval Health Research Center, FHP 2009 Conference (19 Aug 09)
Influenza Hospitalizations
US Armed Forces, 5 Sep 09-23 Jan 10

- Reportable medical events system, weekly reports
- Increased burden & severity of influenza in the Fall 2009
- ~1:2 ratio of hospitalizations between active duty vs dependents

Pneumonia/Influenza Cases
US Military & Non-Service Members
July 2007-June 2012

- Pneumonia & Influenza account for up to 16,000-25,000 cases/yr
- Greater burden during the Fall 2009 (pandemic virus)

Novel A/H3N2 viruses – A(H3N2)v - USA
Geographic Distribution, Swine-origin Viruses in Humans
9 July-7 September 2012 (n=306)

Novel A/H3N2 viruses – A(H3N2)v - USA

Where did these A(H3N2)v come from?

Evidence seems to implicate previous human H3N2 viruses from mid-late 1990’s

Introduced into swine populations in the USA in past decade, probably from southern China

Swine-origin human infections have probably been happening for some time now (undetected)


Closest strain, 5.5% divergence
Novel A/H7N9 viruses - China

“Origin as East Asian Influenza viruses”

- First cases in China o/a 19 February 2013, it is like H5N1 a triple reassortant causing severe disease in humans
- Closely related to H9N2 viruses which are endemic in poultry in the Far East (6 of 8 gene segments are same)
- H7N9 viruses are more readily transmissible to humans than H5N1 viruses (eg, greater pandemic risk)

Novel A/H7N9 viruses - China
“Status of Epidemic in the Far East”

- A total of 290 human cases (64 deaths) reported as of 3 February 2014, > 60% visited LPMs
- Large initial wave in February-May 2013 (weeks 8-21) involving 133 lab-confirmed cases
- Only 2 cases over Summer timeframe (weeks 28 & 31)
- Larger wave in Fall-Winter 2013-14 (weeks 41-5), so far, involving >150 lab-confirmed cases
- No reported cases among DoD populations, risk deemed to be low, so far...

Sources:
AFHSC, Influenza A (H7N9) Surveillance Summary #38, 3 Feb 14, and updated information on 4 Feb 14, available from Division of Integrated Biosurveillance staff
CDC, Avian influenza A (H7N9) virus website, 22 January 2013, http://www.cdc.gov/flu/avianflu/h7n9-virus.htm
### Novel A/H7N9 viruses - China

**“Case Fatality Risk in Comparison Other A Viruses Affecting Man”**

<table>
<thead>
<tr>
<th></th>
<th>Case fatality risk in patients admitted to hospital</th>
<th>Case fatality risk in symptomatic patients</th>
<th>Case fatality risk in individuals with serological evidence of infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza A H7N9, 2013</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yu et al (China)</td>
<td>36% (26-45)</td>
<td>0.16-2.8% (0.06-9.4)</td>
<td></td>
</tr>
<tr>
<td>Influenza A H5N1, 2003-13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cowling et al (China)</td>
<td>70% (56-83)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fiebig et al (12 countries)*</td>
<td>56% (28-87%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1957 and 1968 pandemics</td>
<td></td>
<td>0.1%</td>
<td></td>
</tr>
<tr>
<td>1918 pandemic</td>
<td></td>
<td>2.4%</td>
<td></td>
</tr>
<tr>
<td>2009 pandemic</td>
<td></td>
<td>4%</td>
<td>0.4% (0.03-1.8)</td>
</tr>
</tbody>
</table>

|                          |                                                    |                                           |                                                                          |
| Early estimates: first 1100 laboratory-confirmed cases (Mexico)* |                                           |                                           |                                                                          |
| Fraser et al (Mexico; June, 2009) |                                           |                                           |                                                                          |
| Garske et al (15 countries; July, 2009)* |                                           |                                           |                                                                          |
| Baker et al (New Zealand; August, 2009)* |                                           |                                           |                                                                          |
| Presanis et al (USA; December, 2009) |                                           |                                           |                                                                          |
| Echevarria-Zuno et. al (Mexico; December, 2009)* |                                           |                                           |                                                                          |
| Wu et al (Hong Kong; November, 2010) |                                           |                                           |                                                                          |
| Yu et al (China; February, 2011) |                                           |                                           |                                                                          |
| Riley et al (Hong Kong; June, 2011) |                                           |                                           |                                                                          |
| Presanis et al (UK, summer wave; September, 2011) |                                           |                                           |                                                                          |
| Presanis et al (UK, autumn wave; September, 2011) |                                           |                                           |                                                                          |

Data in parentheses are 95% CIs, unless otherwise stated. Note the sharp reduction in estimates of case fatality risk in symptomatic patients for the 2009 pandemic as more information became available. By contrast, estimates of case fatality risk in infected individuals are more consistent, although these estimates were not available in the early stages of the 2009 pandemic or the Influenza A H7N9 outbreak, and no comparable information for the historical pandemics of 1918, 1957, and 1968 is available.

No estimate is available for seasonal influenza. *Range depends on assumptions about number of symptomatic cases of infection with avian influenza A H7N9 virus.*

| Range across 12 countries. Estimates sorted by publication date. | Range across five regions surveyed. | Limited to individuals aged 5-59 years. |

### Observations:

- **H7N9 viruses appear to be milder in presentation than bad viruses of 1918 H1N1 & H5N1 viruses**
- **Somewhat more severe than other pandemic viruses in 1957, 1968 & 2009 (except for Mexico-Spring 2009)**
- **Bias—Underreporting of milder cases, CFR will probably continue be less in the future...who knows...**

**Sources:**
Novel A/H7N9 viruses - China
“Risk Factors & Clinical Course in Comparison to Other A Viruses Affecting Man”

- Comparison of H7N9-(n=123), H5N1- (n=119) & pH1N1-(n=3,486) infected patients in China/Vietnam
- Analysis of endpoints adjusted for age and gender prevalence in general Chinese population
- H7N9 patients much older (mean~63 yrs); CHD a predisposing factor for hospitalization (RR~9.7)
- H7N9 patients had longer duration of hospitalization & median time from onset to death (~18 days)
- Host factors may be an important contributor to H7N9-associated disease severity

Novel A/H7N9 viruses - China

“Importance of Live Poultry Markets (LPMs)”

- Rapid action by Chinese health authorities in April 2013 in/around reported cases
- Found to be clearly correlated with cessation of cases after April 16, 2013
- Routine environmental surveillance for H7N9 used to close LPMs & bird culling

Sources:
AFHSC, Influenza A (H7N9) Surveillance Summary #36, 13 Jan 14, available from Division of Integrated Biosurveillance staff
China - H10N8 in December-January 2014:
- First two report of this subtype in humans, has been isolated from wild waterfowl throughout N America, Europe & Asia as well as ducks & environmental samples from LPMs in Guangdong & Hunan provinces
- Severe pneumonia-73 yo female (Dec 2013) & 55 yo female (Jan 2014) in Jiangxi Province
  - 1st case illness onset-27 Nov 13, hosp-30 Nov 13, died-6 Dec 13, co-morbidities (HTN, DM, thymectomy for treatment of myasthenia gravis), visited local LPM on 23 Nov 13, no other family members sick
  - 2nd case illness onset-8 Jan 14, hosp-15 Jan 14, no co-morbidities, history of shopping in bazaars

Hong Kong – H9N2 in December-January 2014
- Two cases reported, an 86 yo man & a 7 yo boy with ILI who recovered
- No exposure to poultry, other animals or ill individuals
- Previous cases have been reported in 1999, 2003, 2007-2009
- As opposed to H7N9 & H5N1, cases have had mild illness & have recovered
- Commonly found in LPMs in Hong Kong, may be transmitted by sparrows/crows
- Co-circulating in poultry at LPMs with H7N9 (probably contributed internal genes to H7N9)

Airline Traveler to Canada – H5N1 in January 2014
- First report of a human H5N1 infection in the Americas!!!
- ILI illness in a 28 yo flight attendant who was symptomatic on 27 December while flying Beijing-Vancouver-Edmonton
- Developed severe pneumonia, hospitalized on 1 January & died on 3 January
- No exposure to poultry, other animals or ill individuals
- No other close contacts found to be symptomatic to-date (within 10-days of onset)

Sources: AFHSC Executive Summary, Influenza A (H10N8), 18 December 2013, available from Division of Integrated Biosurveillance staff
WHO IHR, Influenza due to identified avian or animal influenza virus, 18 December 2013, http://www.wpro.who.int/sites/ihr/
AFHSC All-Hands Health Surveillance Update, 7 January 2014, available from Division of Integrated Biosurveillance staff
Yu X, et al, Coexistence of influenza H7N9 and H9N2 in poultry linked to human H7N9 infection & their genome characteristics, J Virol online, 8 January 2014
AFHSC Executive Summary, Influenza A (H5N1), 9 January 2014, available from Division of Integrated Biosurveillance staff
DoD Influenza Surveillance: Role in Vaccine Development

- Sentinel Sites
- Participating Non-sentinel Sites
- National Respiratory & Enteric Virus Surveillance System Labs (U.S.)
- WHO Influenza Labs
- USAFSAM DoD Global Lab-Based Sentinel Surveillance
- CDC/Viral Surveillance
- FDA’s VRBPAC* Committee meets to decide strains for annual flu vaccine
- SEASONAL INFLUENZA VACCINE PRODUCED

*Food and Drug Administration, Vaccines & Related Biological Products Advisory Committee

Respiratory Syncytial Virus (RSV)

Background Information

• Commonly presents with fever & upper respiratory symptoms
• In severe cases lower respiratory tract symptoms may be present (bronchitis, wheezing)
• Can be life-threatening in young children (< 5 yo) where wheezing and lower tract symptoms are more common
• Occurs in late fall, winter and early spring
• Usually precedes influenza peak by 4-8 weeks
• Could predispose military recruits to acquire adenovirus &/or influenza infections
• Morbidity/Mortality: ~ 90,000 hosp/5000 deaths yearly

Sources: Breese Hall C, Respiratory Syncytial Virus (Chapter 158), In: Mandell GL, Bennett JE & Dolin R, eds, Principles and Practice of Infectious Diseases 2010 (7th edition), pp 2207-2221
RSV-related Disease
Presentations in the Military

- Affects mainly recruits in basic military training, less so more “seasoned” troops given their higher level of immunity
- Acute onset of non-productive cough, sore throat & nasal congestion
- Associated with wheezing in ~60-70% of cases reflecting lower respiratory tract involvement
- Often detected in association with influenza &/or adenovirus among non-immune recruits
- May occur at any time during the year, as opposed to fall/winter in civilian populations
- May occur among non-immune personnel deployed to SW Asia (contact with locals)
  - In OEF in 2004-2007 RSV infections were common among non-immune (~46% infection rate)

• 1959: Significant proportion of respiratory disease "probably due to unidentified respiratory viruses" Fort Ord, CA
• 1961: Serological evidence of RSV infection among Marine recruits at Camp Lejeune, NC. Evidence for occurrence of natural re-infection with RSV
• 1967-68: RSV infection identified by serology in 11% of Dutch military recruits admitted with respiratory tract infections (mostly pneumonia)
• 1965-70: Among US Army troops in Vietnam, RSV was 2\textsuperscript{nd} most prevalent virus isolated in Special Forces Troops (10%)

Respiratory Syncytial Virus
Military Experience—"Recent Past"

- ~10-11% of febrile respiratory illnesses are due to RSV among recruit populations at Fort Benning, GA, and HMS Raleigh (Royal Navy Basic Training Center), UK (2005)
- ~14% of FRIs in Royal Navy recruits due to RSV (2007)
  - RSV was 3rd most prevalent virus identified (by PCR/serology)
  - ADV in 35% and influenza in 19%
  - Lower respiratory tract (wheezing) noted in 60% of RSV-infected
- Very challenging to diagnose given low yield by viral culture; PCR-based detection more reliable
- Additional studies among US military recruits needed

RSV Infection Rates in Afghanistan
OEF, 2004-07

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Pre-deployment seroprevalence</th>
<th>Seroconversion rates^</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td><strong>Bordetella pertussis</strong></td>
<td>142</td>
<td>14.2 (12.0-16.4)</td>
</tr>
<tr>
<td><strong>Chlamydia pneumoniae</strong></td>
<td>651</td>
<td>65.1 (62.2-68.1)</td>
</tr>
<tr>
<td><strong>Mycoplasma pneumoniae</strong></td>
<td>219</td>
<td>21.9 (19.4-24.5)</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>987</td>
<td>98.7 (98.0-99.4)</td>
</tr>
<tr>
<td>Parainfluenza Viruses (PIV)</td>
<td>799*</td>
<td>81.6 (79.2-84.0)</td>
</tr>
<tr>
<td><strong>Respiratory syncytial virus</strong></td>
<td>978</td>
<td>97.8 (96.9-98.7)</td>
</tr>
</tbody>
</table>

^Only includes individuals who were seronegative on the pre-deployment specimen

* Total starting sample size for PIV testing was 979 due to insufficient volume for testing in 21 samples

- Infection rates as high as 46% among those non-immune (n=22)
- Very large number (98%) of previously immune personnel

Ribavirin aerosol only FDA-approved antiviral

Monthly polyclonal RSV-IGIV (RespiGam, MedImmune) reduced rates of hospitalization from RSV in children <24 months with chronic lung disease or premature birth (developed at USUHS by Dr’s Val Hemming, Gerald Fisher)
  — RespiGam reduced hospitalizations by 41% (PREVENT trial)
  — Not marketed anymore in the USA (better IM Synagis developed)

Humanized monoclonal Ab, Palivizumab (Synagis, MedImmune) since 2009
  — Reduced hospitalizations by 45-55% (Impact-RSV trial)
  — Very expensive!!! (est at $6,000 per season)

Vaccines are under early development
  — Hindered by lack of strong/robust protective immune response with inactivated vaccines
  — Enhanced pulmonary disease due to immune complex activation with FI vaccine

Sources: Ottolini MG, Burnett MW, History of U.S. military contributions to the study of respiratory infections, Mil Med 2005; 170:66-70
Human metapneumovirus (hMPV)

- Paramyxoviridae
- Presentation and epidemiology similar to RSV
- Mild illness appears to be common in adults
- May cause upwards of 1-2% of febrile respiratory illnesses among non-immune military recruits

Sources: Falsey AR, Human Metapneumovirus (Chapter 159), In: Mandell GL, Bennett JE & Dolin R, Principles and Practice of Infectious Diseases 2010 (7th edition), pp 2223-2227
hMPV-associated Disease
Presentations in the Military

• Affects mainly non-immune recruits in basic military training
• Acute onset of ILI &/or common cold syndromes (symptoms such as fever, cough & rhinorrhea)
• May be associated with community clusters of cases with asthma, conjunctivitis, pharyngitis, laryngitis &/or pneumonia
• Infrequently associated with CAP (< 5% of cases)
• May occur at any time during the year
• Impact in operational forces worldwide is largely unknown at this time

Source: Falsey AR, Human Metapneumovirus (Chapter 159), In: Mandell GL, Bennett JE & Dolin R, Principles and Practice of Infectious Diseases 2010 (7th edition), pp 2223-2227
Human Coronaviruses (HCoVs) and SARS

- Coronaviruses OC43 and 229E types historically recognized as human respiratory pathogens of low virulence
- Common (~30%) cause of the “common cold”
- May cause 1-2% of febrile respiratory illnesses in recruits

SARS = Severe Acute Respiratory Syndrome
- Caused by a previously unrecognized, phylogenetically-distinct more virulent family of coronaviruses (see inset graph)
- Transmission by close person-to-person contact
- February 2003 – April 2004 (affected 26 countries & 5 continents)
- 10% case-fatality rate among ~8,098 recognized infections (774 deaths)
- Main animal host – Palm Civet cats in Guangdong, southern China
- No SARS cases detected among US military

Sources:  
Poon LLM, et al, TLID 2004; 4:663-71  
Mandell, Douglas & Bennett’s Principles & Practice of Infectious Diseases, 2010, 7th edition
● SARS spreads via respiratory droplets (primary) and fomites (secondary)

● Presentation includes insidious onset, but peak viral load (optimal transmission) follows onset of symptoms by several days (*Note contrast to influenza, where viral load peaks before symptoms)

● Isolation, rather than true quarantine, proved effective in interrupting transmission
Recent cluster of novel coronavirus cases from the Middle East & Europe, termed Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV)

- As of end of January 2014, there have been 179 confirmed cases (77 deaths) identified since April 2012
- Limited person-to-person transmission (20 clusters to-date)
- CFR ~43%; in 1stary cases estimated at ~74%; in 2ndary cases estimated at ~20%
- Unknown future impact to the military at-large

AFHSC, MERS Coronavirus Surveillance Summary #30, 24 January 2014 & updated information, Dr. Orville (Stic) Harris, 24 January 2014
• A total of 10 countries involved (n=179), ~80% in KSA
• At least 61 (62%) of 98 2ndary cases thought to have been infected in a health care setting
• Probably greatly underestimated & underdiagnosed
• Bias towards reporting of severe cases, estimate many more mildly sx
• Estimated ~1,000 symptomatic infections (as of end-December 2013)

Sources:  
AFHSC, MERS Coronavirus Surveillance Summary #30, 24 January 2014 & updated information, Dr. Orville (Stic) Harris, 24 January 2014  
MERS-CoV - Origins

- Phylogenetic analyses place its origin back in late 2010 (Oct-Nov 2010) - mid-2011 (Jun-Jul 2011)
- Geographically disperse origin for at least 3 genotypes in KSA, both human-human transmission as well as sporadic zoonotic events
- Potential role of *Taphozous perforatus* bats & dromedary camels as MERS-CoV reservoir in KSA (not present in other domestic livestock, sheep, goats or chickens)
- Camels in Qatari farm found PCR+ with similar sequences as in 2 human cases (Oct 2013, who came first?)
- Evidence of long-term prior infections among camelids in UAE (~97% seropositive) dating back to 2003 - 2005

**Rambaut**

**Cotten**

Sources:  
Eurosurveillance editorial team, Note from the editors: MERS-CoV – the quest for the reservoir continues, Eurosurveillance, 12 December 2013  
Alexandersen S, et al, Middle East Respiratory Syndrome Coronavirus antibody reactors among camels in Dubai, UAE, in 2005, Influenza & Other Respiratory Diseases, 24 January 2014
One in five cases has reported exposure to animals, principally dromedary camels, may have occurred in several separate occasions, hard to say if camel is true animal reservoir or some other species (such as bats)

- Intensive investigation of Qatari farm where 2 human cases detected in October 2013
- Evidence of MERS-CoV among camels in Saudi Arabia & Qatar as well as MERS-CoV Ab in camels in the Canary Islands, Oman and Egypt

**MERS-CoV Transmission Scenarios**

**Zoonotic-limited transmission to humans**

**Zoonotic-sustained human-to-human**

**Sources:**
Streptococcus pneumoniae

• A leading cause of morbidity and mortality:
  — 1.3 Million pneumonia deaths (< 5 yo) worldwide each year
  — 500,000 cases of pneumonia per year in the US
  — Outbreaks common in South Africa and Papua New Guinea

• In the military, the pneumococcus:
  — Leading cause of pneumonia hospitalization in US military
  — Caused ~12% of Navy pneumonia hospitalizations 1981-1991
  — Caused large epidemics among overcrowded & stressed at training facilities

Balicer RD, et al, Control of Streptococcus pneumoniae serotype 5 epidemic of severe pneumonia among young army recruits by mass antibiotic treatment & vaccination, Vaccine 2010; 28:5591-5596
Dawood FS, et al, Outbreak of pneumonia in the setting of fatal pneumococcal meningitis among US Army trainees: potential role of Chlamydia pneumoniae infection
BMC Infectious Diseases 2011; 11:157-165
Acute onset with high fever, rigors, productive cough and shortness of breath due to pneumonia

May also present with chest pain as well as occasional nausea, vomiting & diarrhea

Historically seen in conjunction with other viral infections, especially following influenza outbreaks, such as in 1919 in US military

Affects non-immune recruits & other highly-stressed, very fatigued, older military trainees (such as Navy Seals, Army Rangers)

Predominantly occurs during wintertime when recruits/trainees and other groups are crowded-in close quarters

May occur in other crowded institutional settings, such as disciplinary barracks, service-specific & advanced military training schools

Sources: Gray GC, et al, Diseases Spread by Close Contact: Respiratory Pathogens (Chapter 38), In: Military Preventive Medicine: Mobilization and Deployment, Textbooks of Military Medicine 2005, Vol 2, pp 1117-1146
Ash SY, Sheffield JVL, Pneumococcus, Med Clin N Am 2013; 97:647-666
Hirsch EF & McKinney M, An epidemic of pneumococcus bronchopneumonia, J Infect Dis 1919; 24:594-617
O'Shea MK & Wilson D, Respiratory infections in the military, J R Army Med Corps 2013; 159:181-189
Streptococcus pneumoniae

Elements of Prevention

- Provide routine Bicillin prophylaxis
  - 2 doses, 4 wks apart (for susceptible strains)
  - During high-risk period (Oct-Mar)
- Erithromycin to be used in case of allergic history
- Provide routine PV (1 dose) upon arrival (only for certain high-risk groups); PCV13 preferred over PPSV23 (as of 3 Feb 2014, per ACIP)
- Use of azithromycin (500 mg weekly) remains a useful option for prophylaxis in the future
  - Expensive but covers non-bacterial agents
- Need for subsequent studies with larger # cases and evaluation of non-bacterial etiologies
- **Stop smoking!!**

Sources:
- CDC, ACIP Recommended Immunization Schedule for Adults Aged 19 Years or Older – United States, MMWR Early Release 2014; 63:1-4 (3 February 2014)
Streptococcus pneumoniae
PV Study-Trainees

- A double-blind placebo-controlled trial of 23-valent pneumococcal vaccine for military trainees
- Enrollment at four BCT sites, 4-year follow-up (Parris Island, Great Lakes, Ft Leonard Wood, Ft Jackson)
- Largest vaccine trial in military history
- Enrollment began October 2000, completed June 2003 (152,000 recruits enrolled)
- After 4 yrs, lack of efficacy of 23-valent PV (compared to placebo) in preventing:
  - Acute Respiratory Distress Syndrome (ARDS)
  - Pneumonia associated hospitalization rates

Sources: McKeehan et al. Mil Med 2001;166(12):1087-90; Russell KL, unpublished data, 10 Sep 2009
Pharyngitis

- Estimate ~616 million GAS pharyngitis cases/yr worldwide
- Acute onset of fever & suppurative, patchy sore throat
- May be followed by more severe acute necrotizing fasciitis & sepsis (invasive GAS)
- May follow primary viral infection such as varicella (induces a relative state of immune deficiency)
- Affects non-immune recruits & other highly-stressed, very fatigued, older military trainees (such as Navy Seals, Army Rangers)
- Predominantly occurs during wintertime when recruits/trainees are crowded-in close quarters

Sources:
Invasive Disease

- Emerged with increased incidence in 1980s
- Estimate ~10,000 cases/yr in US, ~663,000 cases/yr worldwide
- Severe, toxin-mediated illness, associated with specific emm gene (mucoid morphology) types
- May be necrotizing (“flesh-eating”) & may be associated with toxic shock syndrome (TSS)
- May be associated with fulminant fatal hemorrhagic pneumonia in healthy adults (virulent GAS clones)
- Case-fatality rate ~15-25% (~163,000 deaths/yr worldwide)
- May not have obvious preceding strep infection; may follow primary varicella

Sources:
- Wong CJ, Stevens DL. Serious Group A streptococcal infections, Med Clin N Am 2013; 97:721-736
**Streptococcus pyogenes**  
*(Group A Strep-GAS)*

**Bicillin Prophylaxis – Recruit Training Camps**

- Routinely used at 7 of 9 locations, 3 give a 2\textsuperscript{nd}/3\textsuperscript{rd} dose at 5/9 wks
- Surveillance for high streptococcal pharyngitis (SASI) rates for 2\textsuperscript{nd} dose

### Table: Recruit Training Site Prophylaxis

<table>
<thead>
<tr>
<th>Recruit Training Site</th>
<th>Automatic Accession Prophylaxis?</th>
<th>All Non PCN-Allergic?</th>
<th>Day of Administration</th>
<th>Follow-Up Administration?</th>
<th>How Long Protocol in Place?</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCRD-SD</td>
<td>Yes</td>
<td>Yes</td>
<td>Day 1-3</td>
<td>Weeks 5 &amp; 9</td>
<td>&gt;10 yrs w break in 2006</td>
</tr>
<tr>
<td>MCRD-PI</td>
<td>Yes</td>
<td>Yes</td>
<td>Day 1-3</td>
<td>Week 5, only in Oct-Apr timeframe</td>
<td>5 yrs, &gt;10 yrs w variations</td>
</tr>
<tr>
<td>Lackland AFB</td>
<td>Yes</td>
<td>Yes</td>
<td>Day 1-3</td>
<td>No</td>
<td>&lt;10 yrs w occasional variations</td>
</tr>
<tr>
<td>Great Lakes NTC</td>
<td>Yes</td>
<td>Yes</td>
<td>Day 4</td>
<td>Week 5, only if high strept rates</td>
<td>&gt;10 yrs w break in 2006</td>
</tr>
<tr>
<td>Fort Benning</td>
<td>Yes</td>
<td>Yes</td>
<td>Day 1-3</td>
<td>No</td>
<td>&gt;10 yrs w break in 2006</td>
</tr>
<tr>
<td>Fort Jackson</td>
<td>No, only in case of outbreak</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>&gt;10 yrs</td>
</tr>
<tr>
<td>Fort Leonard Wood</td>
<td>Yes</td>
<td>Yes</td>
<td>Day 1-3</td>
<td>No, surveillance based</td>
<td>&gt;10 yrs w break in 2006</td>
</tr>
<tr>
<td>Fort Sill</td>
<td>Yes</td>
<td>Yes</td>
<td>Day 1-3</td>
<td>No</td>
<td>&gt;10 yrs w break in 2006-07</td>
</tr>
<tr>
<td>USCG-Cape May</td>
<td>No, only in case of outbreak</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>&gt;10 yrs</td>
</tr>
</tbody>
</table>

Source: Anthony Hawksworth, NHRC, unpublished data, 20 December 2012
Mycoplasma and Chlamydophila
Past Military History

- *M. pneumoniae* infected as many as 44% of recruits over 3-month period (known as Eaton agent, in WWII, 1944-45, Fort Bragg, NC)
- Mycoplasma infections identified by serology in 25% of Dutch military recruits with respiratory tract infections (mostly pneumonias admitted to Military Observation Centre for Diseases of the Chest (Miloc), Amersfoort
- Advanced trainees (such as US Navy Seals) may be more often affected than basic military trainees
- Frequent cause (over 50%) of pneumonias among US Marines in southern California (MCRD-San Diego)
- Frequent cause of clusters of pneumonia and ARD among shipboard personnel

Sources:
- Committee on Acute Respiratory Diseases (CARD), Am J Publ Health;1944;34:335-346
Mycoplasma and Chlamydophila Disease Presentations in the Military

- Gradual onset of dry, non-productive cough, malaise & chills (with low-grade fever) & secondary pneumonia
- Under-recognized cause of illness among trainees & service-related cadets/students
- Lab finding of ~50% with positive cold agglutinins
- These bacterial pathogens are emerging as more common causes of pneumonia in both civilian and military communities

Sources:
**Mycoplasma and Chlamydophila**

Basic Underwater Demolition School (BUDS) SEAL School, July-August 2008

- Have had high rates of severe bacterial infections, including pneumonia illnesses caused by *Mycoplasma* and *C. pneumoniae*

- Well documented outbreak, 10 cases (7-pneumonia) due to *C. pneumoniae* among 100 BUDS trainees in July 2008

- A clinical trial of azithromycin vs. penicillin prophylaxis showed a clinical advantage (64% efficacy) with azithromycin use (1gm/week)

Sources:  
Mycoplasma & Chlamydia in Korea, 1997-98

Clinical Findings

- Associated with afebrile ARD among US military personnel
- Non-productive, persistent dry cough (pertussis-like illness without paroxysms)
- ~ 63% of cases lost some duty due to illness
- Majority (~ 74%) shown to sustain *M. pneumonia* &/or *C. pneumoniae* infection

Serology

Table 1. Clinical findings for 54 afebrile US soldiers with non-productive coughs of ≥2 weeks’ duration.

<table>
<thead>
<tr>
<th>Finding</th>
<th>% of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of cough, d</td>
<td></td>
</tr>
<tr>
<td>≥21</td>
<td>69</td>
</tr>
<tr>
<td>≥35</td>
<td>26</td>
</tr>
<tr>
<td>≥49</td>
<td>13</td>
</tr>
<tr>
<td>Characteristics of cough</td>
<td></td>
</tr>
<tr>
<td>Worse at night</td>
<td>54</td>
</tr>
<tr>
<td>Wakes subject from sleep</td>
<td>31</td>
</tr>
<tr>
<td>Prevents sleep</td>
<td>26</td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>83</td>
</tr>
<tr>
<td>Posttussive emesis</td>
<td>46</td>
</tr>
<tr>
<td>Affected military readiness*</td>
<td>63</td>
</tr>
</tbody>
</table>

Table 4. Proportions of case patients (n = 54) and control subjects (n = 55) with combinations of high antibody values that correlated with illness.

<table>
<thead>
<tr>
<th>Antibody values</th>
<th>Case patients</th>
<th>Control subjects</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Mycoplasma pneumoniae</em> IgM antibody plus high titer</td>
<td>13 (24)</td>
<td>2 (4)</td>
<td>.002</td>
</tr>
<tr>
<td>of IgG or IgA antibody to FHA*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>M. pneumoniae</em> IgM antibody plus <em>Chlamydia pneumoniae</em> IgG titer ≥512 or IgM positivity</td>
<td>13 (24)</td>
<td>4 (7)</td>
<td>.016</td>
</tr>
<tr>
<td><em>C. pneumoniae</em> IgG titer ≥512 or IgM positivity plus high titer of IgG or IgA antibody to FHA*</td>
<td>8 (15)</td>
<td>0</td>
<td>.0027</td>
</tr>
<tr>
<td><em>M. pneumoniae</em> IgM antibody plus <em>C. pneumoniae</em> IgG titer ≥512 or IgM positivity plus high titer of IgG or IgA antibody to FHA*</td>
<td>6 (11)</td>
<td>0</td>
<td>.01</td>
</tr>
</tbody>
</table>

NOTE. Data are no (%) of patients. FHS, filamentous hemagglutinin.
* >95th percentile for control subjects.

Mycoplasma & Chlamydociphila pneumoniae
OEF, 2004-07 (n=1,000 personnel)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Pre-deployment seroprevalence</th>
<th>Seroconversion rates^</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td><strong>Bordetella pertussis</strong></td>
<td>142</td>
<td>14.2 (12.0-16.4)</td>
</tr>
<tr>
<td><strong>Chlamydia pneumoniae</strong></td>
<td>651</td>
<td>65.1 (62.2-68.1)</td>
</tr>
<tr>
<td><strong>Mycoplasma pneumoniae</strong></td>
<td>219</td>
<td>21.9 (19.4-24.5)</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>987</td>
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<tr>
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<td>81.6 (79.2-84.0)</td>
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<td>Respiratory syncytial virus</td>
<td>978</td>
<td>97.8 (96.9-98.7)</td>
</tr>
</tbody>
</table>

^Only includes individuals who were seronegative on the pre-deployment specimen

* Total starting sample size for PIV testing was 979 due to insufficient volume for testing in 21 samples

- Infection rates as high as 4 to 10%
- Close contact with host nationals a factor

**Mycoplasma pneumoniae**

Race-related Risk, OEF, 2004-07

- **M. pneumoniae** rates much higher among blacks & others
- Underlying reason for increased risk is unknown

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Variable</th>
<th>% positive</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Mycoplasma pneumoniae</em></td>
<td>Race</td>
<td>White</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Black</td>
<td>11.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other/unknown</td>
<td>5.4</td>
</tr>
</tbody>
</table>

Bordetella pertussis

“Resurgence in the USA, 1990-2011”

Since mid-2011, over 3,000 cases of pertussis reported in Washington state; over 2,500 reported just in 1 Jan-16 Jun 12 period

- Highest incidence in over 30 years, overall rate of 38 cases per 100,000
- Incidence highest in infants (150 per 100,000) and those 8-15 yo (100-220 per 100,000)
- Increased rates of pertussis among adolescents aged 13–14 years who were fully vaccinated with acellular vaccines in childhood suggests early waning of immunity after vaccination with Tdap vaccine

Gradual onset of unrelenting, hacking cough with paroxysms, whoop or post-cough vomiting, nasal congestion &/or headaches

Long-lasting symptoms for 1 to 8 weeks, may be complicated by secondary bacterial pneumonia

Uncommon in recruits due to effective immunization prior to/upon arrival

IDF recruits & French military boarding school students who are not immunized upon arrival have had large outbreaks in past

Greatly under-recognized pathogen among military personnel deployed in Korea or Afghanistan

Sources:
**Bordetella pertussis in DoD, Jan 07-Jun 12**

- Cases (ICD-9-CM: 033) reported from DoD MTFs (eg, most severe cases)
- Clear increase in 2010-2012 timeframe (over 100 cases per month)
- Total of 476 confirmed & 3,073 probable cases, 81% & 90% in dependents
- Over one-half of all confirmed cases in children ≤ 15 yo
- Large clusters (12 or more cases) at 7 military installations, mostly in West Coast

Source: AFHSC, Pertussis diagnoses among service members and other beneficiaries of the U.S. Military Health System, January 2005-June 2012, MSMR 2012; 19(8), 14-17
Bordetella pertussis
OEF, 2004-07 (n=1,000 personnel)

- B. pertussis rates are 2-4x that among comparable US adults
- Low level of immunity due to waning vaccine-induced immunity

Bordetella pertussis Infection Risk
OEF, 2004-07

- B. pertussis rates much higher in later deployment
- Closer contact with local nationals is an issue

Vaccines

- Whole Cell pertussis vaccines historically approved for children, under 7 years old; no vaccine initially approved for those 7-10 yo
- Initial acellular vaccines reduced rare severe side effects (DTaP), however, are associated with a shorter-lasting immune response
- In 2005, FDA approved reduced pertussis-antigen containing vaccines (Tdap) for use in adolescents/adults (11-64 yo, to improve population immunity)
- In October 2010, based on safety & immunogenicity data, ACIP recommended expansion to those 7-10 yo (to complete 4-5 doses) & adults ≥ 65 yo at high-risk
- In February 2011, based on increased threat & outbreaks/resurgence in USA, ACIP recommended that all nurses & other HCWs have Tdap
- In October 2011, based on continuing cases in infants, ACIP recommended expansion of Tdap vaccination in pregnant women & those in close contact with infants
- Tdap = tetanus toxoid, reduced diphtheria toxoid and acellular pertussis
  - Boostrix (GSK) for 10-64 yo
  - Adacel (Sanofi Pasteur) for 11-64 yo
- Impact of newer vaccines on military service members not yet known

Sources: CDC, MMWR, Vol. 60, No. 1, 14 January 2011
CDC’s ACIP statement, 21 October 2011, Updated recommendations for use of Tdap, http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6041a4.htm?s_cid=mm6041a4_e%0D%0A
Respiratory Infections

“How to Reduce Risk”

<table>
<thead>
<tr>
<th>Physical Intervention</th>
<th>Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handwashing (“Hand hygiene”)</td>
<td>55%</td>
</tr>
<tr>
<td>Wearing Surgical Masks</td>
<td>68%</td>
</tr>
<tr>
<td>Wearing N-95 Masks</td>
<td>91%</td>
</tr>
<tr>
<td>Wearing Gloves</td>
<td>57%</td>
</tr>
<tr>
<td>Wearing Gowns</td>
<td>77%</td>
</tr>
<tr>
<td>All of the above (surgical mask)</td>
<td>91%</td>
</tr>
</tbody>
</table>

Influenza Survivability in Hands

“No Hand Hygiene”

- Influenza A viruses in droplets have potential to easily survive on hand surfaces
- Marked reduction in infectious virus after 5-30 min
- Rapid decrease in infectiousness when droplet integrity was disrupted (not shown)
- Role of self-inoculation from environmental surfaces is biologically plausible, but, probably of lesser relevance than direct droplet spread (eg, person-to person)
- Hand hygiene may be of greatest relevance within 10-15 min after inoculation

Handwashing

“Effect on Influenza & Acute Respiratory Infections”

- Most marked effect in decreasing transmission in school settings (explained by good opportunity for implementation & follow-up)
- Less impact on intra-household transmission (eg, hard to limit transmission early on after index case)
- Small reduction in transmission child care center settings (eg, too many other opportunities for transmission taking place)


![Influenza](image1)

![ARI](image2)
Handwashing
“Effect on Influenza Virus Surface Contamination”

- Trial of non-pharmaceutical interventions (control, HW, HW + face masks) in urban Bangkok in 2009-2010, children 1-15 yo with an ILI, 191 households

- Comparison of surface sampling testing for influenza (by RT-PCR)
  - Control households (n=96) RT-PCR-positive (17.7%)
  - Intervention HW households (n=95) RT-PCR-positive (7.4%)

Handwashing
What is the Right Way to Wash your Hands?

• Use soap & water, rub hands well for at least 15 seconds
• Rinse well & dry with paper towel
• Turn off water faucet with paper towel, not hands!

Handwashing

When Should You Wash your Hands?

- Before, during, and after preparing food
- Before eating food
- Before and after caring for someone who is sick
- Before and after treating a cut or wound
- After using the toilet
- After changing diapers or cleaning up a child who has used the toilet
- After blowing your nose, coughing, or sneezing
- After touching an animal or animal waste
- After handling pet food or pet treats
- After touching garbage

Source: CDC, Seasonal Flu Website, 3 January 2014, http://www.cdc.gov/handwashing/
Alcohol-based Hand Sanitizers

- Reduce markedly viral counts on hands (by several logs)
- Foam, gel and wipes worked equally well (~3 log reductions)
- Assumed that transmission to patients would be reduced

<table>
<thead>
<tr>
<th>Product</th>
<th>Mean ± SD</th>
<th>Range</th>
<th>95% CI</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foam</td>
<td>3.27 ± 0.31</td>
<td>2.88-3.80</td>
<td>3.05-3.49</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gel</td>
<td>3.35 ± 0.79</td>
<td>2.15-4.78</td>
<td>2.78-3.91</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hand wipes</td>
<td>3.25 ± 0.45</td>
<td>2.53-3.98</td>
<td>2.93-3.58</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Paired t test comparing before and after reductions in viral counts.

Source: Larson EL, Columbia University, Analysis of Et-OH based hand sanitizer delivery systems, Am J Infect Control, 21 Feb 12
Alcohol-based Hand Sanitizers vs Soap & Water

- Markedly viral counts on hands with any of four measures (Et-OH 70% only, Et-OH 70% + 0.5% chlorhexidine, Isopropanol 70% + 0.5% chlorhexidine, Soap & Water)
- Little difference between measures (only 1-100 virus copies/uL)
- Alcohol-based sanitizers may be preferred given ease-of-use

Table 2. Assessment, by PCR and culture, of the efficacy of various hand hygiene (HH) protocols against live H1N1 influenza virus on the hands of 14 human volunteers who were culture-positive at baseline.

<table>
<thead>
<tr>
<th>HH product</th>
<th>Palm</th>
<th>Glove juice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>24.0 ± 3.4&lt;sup&gt;b&lt;/sup&gt; (19.8–32.2)</td>
<td>24.3 ± 3.8&lt;sup&gt;b&lt;/sup&gt; (18.6–32.4)</td>
</tr>
<tr>
<td>SW</td>
<td>37.6 ± 3.2&lt;sup&gt;c&lt;/sup&gt; (30.9–40.1)</td>
<td>39.4 ± 1.1&lt;sup&gt;d&lt;/sup&gt; (37.0–40.1)</td>
</tr>
<tr>
<td>ETOH only</td>
<td>34.8 ± 2.6&lt;sup&gt;c&lt;/sup&gt; (30.4–40.1)</td>
<td>33.3 ± 2.1&lt;sup&gt;d&lt;/sup&gt; (30.1–36.3)</td>
</tr>
<tr>
<td>ISOP-CHX</td>
<td>35.7 ± 2.2&lt;sup&gt;c&lt;/sup&gt; (32.8–40.1)</td>
<td>33.5 ± 2.5&lt;sup&gt;d&lt;/sup&gt; (30.5–39.8)</td>
</tr>
<tr>
<td>ETOH-CHX</td>
<td>34.4 ± 2.9&lt;sup&gt;c&lt;/sup&gt; (28.3–38.2)</td>
<td>33.3 ± 3.0&lt;sup&gt;d&lt;/sup&gt; (28.9–38.6)</td>
</tr>
</tbody>
</table>

<p>| Culture TCID&lt;sub&gt;50&lt;/sub&gt;/0.1 mL level, mean ± SD (range) |</p>
<table>
<thead>
<tr>
<th>Palm</th>
<th>Glove juice</th>
</tr>
</thead>
<tbody>
<tr>
<td>3325 ± 8352&lt;sup&gt;e&lt;/sup&gt; (0–32,000)</td>
<td>1041 ± 1701&lt;sup&gt;f&lt;/sup&gt; (0–5600)</td>
</tr>
<tr>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
</tr>
<tr>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
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<td>0 (0–0)</td>
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<tr>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
</tr>
</tbody>
</table>

NOTE: Control, no product was used; Ct, cycle threshold; ETOH-CHX, ethanol 70% plus 0.5% chlorhexidine solution; ETOH only, ethanol 61.5% gel; glove juice, right hand glove juice; ISOP-CHX, isopropanol 70% plus 0.5% chlorhexidine solution; palm, right palm; SW, soap and water.

Alcohol-based Hand Sanitizers

General Points & How to Use Them

- Alcohol-based hand sanitizers can quickly reduce the number of germs on hands in some situations
- Sanitizers do not eliminate all types of germs
- Hand sanitizers are not as effective when hands are visibly dirty

- Apply the product to the palm of one hand
- Rub your hands together
- Rub the product over all surfaces of your hands and fingers until your hands are dry

Source: CDC, Seasonal Flu Website, 3 January 2014, [http://www.cdc.gov/handwashing/](http://www.cdc.gov/handwashing/)
Masks & N95 Respirators in Influenza

What is the Verdict?

• Jury is still out, none of 17 studies established conclusive evidence
  • Only 2 of 8 RCTs showed suggested efficacy in preventing influenza
    – One household trial found mask + hand sanitizer reduced secondary transmission
    – One household trial found no effect of mask and/or hand washing (Bangkok)
    – One hospital-based trial (Beijing) showed reduction for N95, but not face masks

• Eight of 9 retrospective studies found efficacy in preventing SARS
  – No definitive evidence in the prevention of influenza
  – Most of these studies were suboptimal, compliance not well determined

• Some studies suggest mask use is best undertaken as a package with hand washing, sanitizer, gloves and/or hand wipes

• Effectiveness is probably linked to early, consistent & correct usage

Respiratory Infections
Containment Measures

- Other than Vaccine, best interventions are non-pharmaceutical in nature (referred to as “NPIs”)
  (also known as “personal & community mitigation strategies”)
  - Sneeze and cough etiquette
  - Handwashing & Hand sanitizers
  - Daily temperature monitoring
  - Staying home when sick
  - Social Distancing (“increase space between people”)
    - Tele-commuting or remote-meeting options
    - Closing schools (keep kids at home), Mexico, 2009
    - Limit or cancel social gatherings, St Louis, 1918
  - Cleaning surfaces & objects routinely
  - Flu hot lines, triage, off-site clinics
  - Risk communication (“talk to your patients”)

“A Final Note”

• Prevention programs must be supported by sound epidemiologic data and the constant attention of public health professionals

• The adenovirus vaccine story may be a cautionary tale. Effective prevention programs (especially immunization programs?) may be lost without our strong advocacy
Questions?

COL James F. Cummings, MD FACP FIDSA
Director, GEIS
Tel: 301-319-3268
E-mail: james.f.cummings6.mil@mail.mil

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