Pandemic Influenza Virus 2009 H1N1 and Adenovirus in a High Risk Population of Young Adults: Epidemiology, Comparison of Clinical Presentations, and Coinfection

Heather C. Yun1,4*, William H. Fugate2, Clinton K. Murray1,4, Thomas L. Cropper3, Lisa Lott2, J. Matthew McDonald2

1 San Antonio Military Medical Center, Joint Base San Antonio Fort Sam Houston, Texas, United States of America, 2 Center for Advanced Molecular Detection, 59th MDW/ST, Joint Base San Antonio-Lackland, Texas, United States of America, 3 Trainee Health Surveillance, Joint Base San Antonio-Lackland, Texas, United States of America, 4 Uniformed Services University of the Health Sciences, Bethesda, Maryland, United States of America

Abstract

Background: In 2009, pandemic H1N1 influenza virus (2009 H1N1) emerged worldwide, causing morbidity and mortality that disproportionately affected young adults. Upper respiratory infection (URI), largely due to adenovirus, is an endemic cause of morbidity in military training. Whether clinical presentations differ or excess morbidity results from coinfection is unclear.

Methods: The Center for Advanced Molecular Detection evaluates epidemiology and rapid diagnostics of respiratory pathogens in trainees with URI. From May 1, 2009, to November 30, 2009, demographic, clinical, and PCR data from throat and nasal specimens for adenovirus and 2009 H1N1 were prospectively collected.

Results: 375 trainees with URI enrolled and were tested for both adenovirus and 2009 H1N1 by PCR (median age 20; 89% male). Adenovirus PCR was positive in 72% (96% serotype E-4) and 2009 H1N1 in 20%. Males were more likely to have adenovirus and females more likely to have 2009 H1N1 (p = 0.047). Subjects with 2009 H1N1 presented an average of 1 week earlier in training, had shorter illness duration before enrollment, less sore throat, diarrhea, and fewer abnormal findings on throat exam. Coryza and cough were more common with 2009 H1N1 compared to adenovirus. Subjects with 2009 H1N1 were less likely to have adenovirus than those without, despite persistently high frequencies of adenovirus detections during peak 2009 H1N1 weeks (15% vs. 83%, p < 0.01). Coinfection with adenovirus and 2009 H1N1 was rare (4%). Rates of hospitalization and pneumonia did not differ between the adenovirus, 2009 H1N1, or coinfected groups.

Conclusion: Military trainees with 2009 H1N1 vs. adenovirus have differing clinical presentations, and males are more likely to have adenovirus. Despite high frequencies of adenovirus infection, coinfection with adenovirus and 2009 H1N1 is rare and apparently does not result in increased morbidity.

Introduction

Non-influenza related upper respiratory infections (URI) are universally experienced illnesses that, despite their typically self-limited nature, lead to billions of dollars of lost income, and predispose to serious illnesses including pneumonia.[1] When influenza is responsible, pandemics can result and cause millions of deaths. In 2009, a novel H1N1 influenza virus (2009 H1N1) emerged and rapidly spread worldwide, causing excess mortality in children and young adults. Although the global estimate of deaths has been lower than seen in several previous pandemics, the number of life years lost is estimated to be five times higher than those lost to seasonal H1N1 viruses and comparable to the number lost during the 1968 pandemic.[2,3] Military trainees, along with other groups of crowded, stressed individuals, are disproportionately affected by respiratory illnesses due to a variety of pathogens. With the exception of the prior adenovirus vaccine era from 1980–1996, adenoviruses have historically been the most common causes of febrile URI in this population, and have also led to serious illness and fatalities.[4–7] In one large study of transmission dynamics of adenovirus in a military training setting, approximately one-third of incoming trainees were already immune, one-third developed a febrile URI due to adenovirus, and the remainder seroconverted with subclinical or asymptomatic infection.[8] Large influenza outbreaks are less common, given the universal immunization of basic trainees and routine use of ring antiviral chemoprophylaxis in training units with known influenza cases, if cases occur within the first two weeks after immunization.[9,10] However, in 2009, type-specific influenza vaccine was
not widely available until well into the full wave of illness.[11] With large numbers of concurrently circulating respiratory pathogens occurring year round in this diverse group of individuals, coming from a variety of geographic locations and backgrounds, and living in close contact for months, coinfection with multiple organisms would be expected to be a regular occurrence. However, whether coinfection contributes to differing clinical presentations or outcomes in this young, healthy adult population is unknown. While coinfections with viral pathogens including 2009 H1N1 have been described in patients with respiratory infections, few prospective studies have related these to clinical presentation and outcomes in adults since molecular diagnostics became available, and none in the setting of high background rates of adenovirus.[12–17]

We sought to describe the epidemiology of 2009 H1N1 and adenovirus in a basic training population, and to correlate differences in clinical presentations and outcomes with each respective pathogen and in coinfections.

**Methods**

**Setting**

Joint Base San Antonio-Lackland is the only Air Force location for basic military training with approximately 43,000 recruits per year, 6,000–7,000 recruits training at any given time, and a training period lasting 8.5 weeks. Basic military trainees (BMTs) are assigned to training units called “flights” of 50–60 individuals, with whom they train and reside in bay dormitories; tobacco product use is not allowed. Ill trainees present for care at an outpatient clinic; if they are febrile with a respiratory illness they are then cohorted to a “fever flight” where they recover until they are afebrile and able to return to training. Trainees who require hospitalization are admitted to the tertiary care hospital on base. Trainees routinely receive chemoprophylaxis against Streptococcus pneumoniae during their first week of training; this consists of benzathine penicillin or azithromycin for penicillin allergic recruits. Immunizations against meningococcus, hepatitis A and B, and measles, mumps and rubella are also administered during the first week of training. Trivalent seasonal influenza vaccine was administered during the first week of training throughout the study period, but 2009 H1N1 vaccine was not available until December 1, 2009. During the study period, oseltamivir was routinely used for treatment of ill trainees with confirmed 2009 H1N1 infection. Oseltamivir was also routinely used for chemoprophylaxis of well trainees in close contact with a confirmed case.

**Study design**

The Center for Advanced Molecular Detection (59th Medical Wing/Science and Technology, Air Education and Training Command) was established in 2003 for prospective evaluation of epidemiology and novel technologies to rapidly detect respiratory pathogens in trainees with URI. Subjects were approached for enrollment at the point of care for their URI, and met inclusion criteria if they were BMTs 17 years of age or older and had any symptom of upper respiratory tract infection or pneumonia. Demographic data, including age, race, gender, week of training, city/state of previous residence, and smoking history, were recorded. Additionally, a symptom questionnaire (including respiratory and gastrointestinal symptoms), perceived stress level on a 10-point Likert scale, and clinical signs, including vital signs, height and weight, physical exam findings, and physician diagnosis were recorded, as was the ward of hospital admission (intensive care unit vs. ward) where applicable. For this substudy, cases were included if they enrolled in the study and were tested for both adenovirus (using study methodology) and 2009 H1N1 (as part of clinical care). Duplicate cases (for numerous presentations for URI

| Table 1. Demographic information of trainees presenting with respiratory illness. |
|-----------------------------------------------|
| **Total population** |
| Gender | 375 |
| Male | 93.9% |
| Female | 10.7% |
| Age | 374 | 20 (IQR 19–22) |
| Race-Ethnicity | 358 |
| White | 69.3% |
| Black | 15.4% |
| Hispanic | 10.3% |
| Asian | 2.5% |
| Native American | 0.3% |
| Other/Multiple | 2.2% |
| Week of Training | 371 | 6 (IQR, 4–7) |
| Body Mass Index (kg/m²) | 374 | 23.6 (IQR, 21.7–25.1) |
| Perceived Stress Level* | 373 | 4 (IQR 3–5) |
| History of smoking | 375 | 13.9% |

IQR, interquartile range. * Ten point Likert scale where 10 represents maximal subjective stress and 0 is no stress at all.

doi:10.1371/journal.pone.0085094.t001

| Table 2. Pathogens recovered, by specimen source. |
|-----------------------------------------------|
| **N tested** | **N positive** |
| **Viral culture** | 375 |
| Adenovirus (Ad) | 224 (59.7%) |
| Influenza virus | 73 (19.5%) |
| Parainfluenza type 3 | 1 (0.3%) |
| **2009 H1N1 PCR** | 375 |
| 2009 H1N1 PCR | 74 (19.7%) |
| **Ad Pan PCR** | 375 |
| Nasal Wash | 365 | 242 (66.3%) |
| Throat Swab | 367 | 254 (69.2%) |
| **Ad B-14 PCR** | 373 |
| Nasal Wash | 3 | 0 (0.8%) |
| Throat Swab | 375 | 4 (1.1%) |
| **Ad E-4 PCR** | 375 |
| Nasal Wash | 373 | 254 (68.1%) |
| Throat Swab | 375 | 260 (69.3%) |
| **Ad B-7 PCR** | 63 |
| Nasal Wash | 1 (1.6%) |
| Throat Swab | 65 | 1 (1.5%) |
| Any Ad PCR | 375 | 271 (72.3%) |
| **Coinfected: Any Ad PCR** | 375 |
| 2009 H1N1 PCR | 16 (4.3%) |

doi:10.1371/journal.pone.0085094.t002
in the same subject) were excluded; all cases represent unique subjects.

**Clinical laboratory data**

Respiratory viral culture data (Wilford Hall Medical Center) and 2009 H1N1 influenza virus PCR data (United States Air Force School of Aerospace Medicine reference laboratory) obtained during clinical care were prospectively collected from May 1, 2009, to November 30, 2009. Both respiratory viral culture and 2009 H1N1 PCR were performed on predominantly nasal wash specimens as part of routine clinical care. Respiratory viral culture was performed using standard methods and 2009 H1N1 PCR using the CDC protocol of real-time RT-PCR for influenza A (H1N1) (World Health Organization Collaboration Center for Influenza at the Centers for Disease Control and Prevention, Atlanta, GA, USA).[18]

**Nucleic acid extraction**

Nasal wash and throat swabs for adenovirus PCR were collected in parallel in approximately 3 ml of saline and viral transport medium, respectively. Total nucleic acid was extracted from 400μl of each sample using the MagNA Pure Compact Nucleic Acid Isolation Kit I (Roche Diagnostics, Mannheim, Germany, MagNA Pure Kit 03 730 964 001) with the MagNA Pure Compact instrument (Roche Applied Science Mannheim, Germany).

**Real-time adenovirus PCR and data interpretation**

Primers and probes used have been reported for adenovirus by Heim et al.[19] All qPCR was conducted using Applied Biosystems 7900 and 7500 real-time PCR instruments (Applied Biosystems, CA).

For adenovirus testing, cycling was conducted with 500 nM concentrations of both forward and reverse primers and 300 nM concentration of probe. Reaction conditions included an initial 10 min denaturation at 95°C, followed by 45 cycles of 95°C for 15 sec and 60°C for 1 min. A specimen was considered positive if its cycle of threshold (Ct value) was equal to or less than 40, as described previously.[19,20].

**Protection of human subjects/Ethics Statement**

All subjects provided written, voluntary informed consent in the presence of an ombudsman. The study was approved by Wilford Hall Medical Center/Brooke Army Medical Center Institutional Review Board (IRB). Gender and ethnicity were self-reported. Per Department of Defense (DoD) Directive 3216.02, for purposes of legal capacity to participate in DoD-conducted or -supported research involving human subjects, all active duty service members in a federal duty status are considered to be adults. The participation of such members is not subject to requirements regarding research involving children or minors. When service members are under 18 years of age, students at service academies, or trainees, the IRB shall carefully consider the recruitment process and the necessity to include such members as human subjects.

![Figure 1. Number of detections of adenovirus, 2009 H1N1 influenza virus, and coinfected from May 1, 2009- November 30, 2009. doi:10.1371/journal.pone.0085094.g001](/images/figure1.png)
Results

Statistical analyses

Data were entered in duplicate for quality control. Analysis was performed using existing software (SPSS, version 19.0; SPSS). Continuous variables were analyzed by Student’s t-test or Mann-Whitney U test for parametric and nonparametric data, respectively. Categorical variables were evaluated by chi-squared, Fisher’s exact test, or Spearman correlation. Multiple nonparametric groups of continuous variables were analyzed by Kruskal-Wallis testing. All p-values are two-tailed and statistical significance at p < 0.05.

Discussion

This large, prospective cohort study describes otherwise healthy, young adult patients presenting with acute febrile respiratory illness during basic military training and evaluated, through PCR amplification of respiratory specimens, for 2009 H1N1 infection, adenovirus, or both. These data illustrate the scarcity of coinfections with 2009 H1N1 and adenovirus, despite high endemic frequencies of adenovirus in this population during peak 2009 H1N1 months. This study also represents the largest clinical evaluation of adenovirus and 2009 H1N1 coinfected patients to date, to our knowledge. In the wake of 2009 H1N1 emergence, a number of studies have investigated the role of coinfection with viral pathogens with 2009 H1N1. One evaluation of non-influenza viruses in influenza-like illness during the 2009 H1N1 epidemic in France demonstrated a 5% incidence of adenovirus; only 1 patient was coinfected with adenovirus and 2009 H1N1, limiting clinical
evaluation of this particular combination.[17] Several additional studies have sought to examine whether clinical presentations vary with 2009 H1N1 infection in the presence of other respiratory viruses, with at least one suggesting increased clinical severity among some non-rhinovirus coinfections, but these have included few adenovirus coinfections.[16,21].

A number of studies have also evaluated whether 2009 H1N1 was associated with either negative or positive effects (predominantly in terms of acquisition rather than severity) on other respiratory viruses, and, taken together with reference to adenovirus, the results of these are inconclusive. One study performed in the United Kingdom in 2009–2010 suggested negative associations between 2009 H1N1 and human metapneumovirus as well as rhinovirus, though not adenovirus. However, few adenovirus detections were found compared to our population (5%), and most of these were in young children.[22] A South African study of respiratory viruses in hospitalized patients found only six patients with adenovirus and 2009 H1N1 coinfection out of over 8000 subjects enrolled.[23] To our knowledge, negative associations between adenovirus and influenza A virus (either seasonal or 2009 H1N1) detection have not been demonstrated. It is also unclear, if there is a negative association between the two viruses, whether adenovirus is protective against influenza infection or vice versa. In this data set, influenza patients presented earlier, although not after excluding those presenting during the first week of training, who likely would have arrived with their infection. The policy of cohorting together all BMTs with fever and URI, regardless of the causative pathogen, would seem to increase the likelihood of coinfection, rather than skewing the data towards the appearance of a negative association. It will also be worthwhile to see whether influenza epidemiology will change since the late 2011 reintroduction of adenovirus serotypes 4 and 7 vaccines in military trainees, or whether issues arise with concurrent administration of both live attenuated influenza and adenovirus vaccines, which could affect current trainee vaccine policies. In the meantime, concerns about cohorting patients that may have either adenovirus or 2009 H1N1 on the basis of syndromic presentation can be alleviated on the relative scarcity of coinfection and on the absence of any evidence of increased illness severity among coinfected subjects.

The differing demographics and clinical presentations of adenovirus vs. 2009 H1N1 infection in this study are also of

### Table 4. Clinical characteristics of total study population, and comparison of clinical variables: Adenovirus (Ad) vs. 2009 H1N1, and coinfection vs. Ad alone.

|                      | Total study population (n = 375) | Ad + (n = 255) | 2009 H1N1 + (n = 58) | p-value | Ad/2009 H1N1+ (n = 16) | p-value |
|----------------------|---------------------------------|---------------|---------------------|---------|-----------------------|---------|
| **Symptoms**         |                                 |               |                     |         |                       |         |
| Subjective fever     | 373 (99.5%)                     | 253 (99.2%)   | 58 (100%)           | 1.0     | 16 (100%)             | 1.0     |
| Cough                | 336 (89.6%)                     | 226 (88.6%)   | 56 (96.6%)          | 0.01    | 15 (93.8%)            | 1.0     |
| Sore throat          | 326 (86.9%)                     | 236 (92.5%)   | 43 (74.1%)          | <0.01   | 11 (68.8%)            | <0.01   |
| Sinus congestion     | 301 (80.3%)                     | 206 (80.8%)   | 44 (75.9%)          | 0.34    | 13 (81.3%)            | 0.26    |
| Myalgia              | 295 (78.7%)                     | 196 (76.9%)   | 47 (81.0%)          | 0.49    | 15 (93.8%)            | 0.21    |
| Coryza               | 241 (64.3%)                     | 155 (60.8%)   | 45 (77.6%)          | 0.02    | 12 (75.0%)            | 0.12    |
| Malaise              | 198 (52.8%)                     | 132 (51.8%)   | 35 (60.3%)          | 0.25    | 8 (50.0%)             | 0.88    |
| Vomiting             | 45 (12.0%)                      | 32 (12.5%)    | 6 (10.3%)           | 0.64    | 3 (18.8%)             | 0.44    |
| Diarrhea             | 21 (5.6%)                       | 20 (7.8%)     | 0                   | 0.03    | 0                     | 0.62    |
| **Duration of symptoms (days; IQR*)** | 3 (2–4) | 3 (2–5) | 2 (2–3) | <0.01 | 2.5 (2–3) | 0.09 |
| **Vital Signs**      |                                 |               |                     |         |                       |         |
| Heart Rate           | 94.1 (14.1)                     | 93 (15)       | 97 (12)             | 0.08    | 95 (10)               | 0.71    |
| Respiratory Rate     | 17.0 (1.8)                      | 17 (2)        | 17 (1)              | 0.92    | 17 (2)                | 0.37    |
| Systolic BP**        | 119.6 (9.3)                     | 120 (9)       | 119 (11)            | 0.67    | 120 (11)              | 0.92    |
| Diastolic BP**       | 71.9 (7.5)                      | 72 (7)        | 71 (9)              | 0.13    | 71 (3)                | 0.61    |
| Oral temperature (°F) | 101.5 (0.9)                     | 101.5 (0.8)   | 101.7 (1.0)         | 0.07    | 101.9 (0.9)           | 0.03    |
| **Physical exam**    |                                 |               |                     |         |                       |         |
| Pharyngitis          | 283 (75.5%)                     | 203 (79.6%)   | 38 (65.5%)          | <0.01   | 9 (56.2%)             | <0.01   |
| Exudative pharyngitis| 22 (5.9%)                       | 21 (8.2%)     | 1 (1.7%)            | 0.045   | 0                     | 0.24    |
| Lymphadenopathy      | 189 (50.4%)                     | 131 (51.4%)   | 32 (55.2%)          | 0.78    | 5 (31.3%)             | 0.08    |
| Tonsillitis          | 64 (17.1%)                      | 53 (20.8%)    | 2 (3.4%)            | <0.01   | 0                     | 0.02    |
| Abnormal lung exam   | 11 (2.9%)                       | 7 (2.7%)      | 2 (3.4%)            | 0.30    | 0                     | 0.63    |
| Pneumonia            | 6 (1.6%)                        | 4 (1.6%)      | 1 (1.7%)            | 1.00    | 0                     | 0.78    |
| Hospitalized         | 3 (0.8%)                        | 2 (0.8%)      | 0                   | 1.00    | 0                     | 1.00    |

*median, interquartile range.  **mean, standard deviation.  ***BP = blood pressure (mmHg).  acompared to Ad alone.
interest. First, the gender differences seen for each virus are intriguing. Males represented 89% of the study population, enrolled after presenting with respiratory illness. However, males generally represent only 90% of the Air Force basic training population, so the study population was already disproportionately male. Adenovirus has long been suggested to be predominantly an illness of men in this population, and this study is no exception to this trend.[24,25] 2009 H1N1, like all influenza A viruses, has similar mechanisms of transmission, yet in this study population disproportionately affected females. The reasons for this gender difference are unclear. Both of these infections as captured in this study population would meet the CDC definition for influenza-like illness (fever plus cough or sore throat), used for surveillance and cohorting purposes, but had differences in presentation of statistical and arguably clinical significance.[26] Adenovirus was consistently more likely to produce signs and symptoms referable to the throat, while 2009 H1N1 produced a predominance of cough, as well as shorter illness duration prior to presentation for care, potentially reflecting more rapid development of uncomfortable symptoms. These findings may have importance for both infection control and empiric therapy.

The strengths of this study include the molecular characterization of respiratory pathogens together with capture of detailed clinical data in a large cohort of otherwise healthy adult patients with few complicating comorbidities, as well as the closed nature of the population, which lends itself to capture of events such as hospital admissions and pneumonia diagnoses. Limitations include the absence of serologic data, or the ability to serially characterize pathogens from the same cohort of individuals, which would provide more granular detail about the time course of developing each infection. Subject enrollment was variable throughout the study period, depending on rates of clinical illness within the training population, as well as availability of study personnel to enroll trainees, and given that 2009 H1N1 influenza virus PCR was done as part of clinical care, there could have been some differences in those who enrolled vs. did not enroll, or those who received 2009 H1N1 testing (and thus were included in this study) and those who did not. Due to this variability in total enrollment, and because 2009 H1N1 testing became infrequent clinically after November 2009, inferences about the impact of H1N1 towards the end of 2009 are limited. However, data from the Naval Health Research Center’s Febrile Respiratory Illness Surveillance Update show a rate of febrile respiratory infection that increased in December of 2009, 82% of which was associated with adenovirus, with no influenza virus detected.[27] Additionally, the use of oseltamivir, both for prophylaxis and for treatment, would have impacted both epidemiology and severity of illness. Finally, without inclusion of asymptomatic or minimally symptomatic individuals, conclusions can only be drawn about the scarcity of coinfections with individuals at the point of presentation to care.

In summary, this epidemiologic survey of young adults in military training presenting with fever and URI demonstrated significant differences in 2009 H1N1 vs. adenovirus in terms of gender predilection and presenting symptoms. In addition, coinfections with 2009 H1N1 and adenovirus were rare despite high endemicity of adenovirus before and during the 2009 H1N1 epidemic, and, beyond a higher temperature on presentation, coinfections were not associated with increased clinical severity compared with adenovirus alone.

Acknowledgments

We appreciate the administrative assistance of Francine Stoler with the execution of this study.

Disclaimer: The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or reflecting the views of the Department of the Army, Department of the Air Force, Department of Defense or the US government. This work was prepared as part of their official duties and, as such, there is no copyright to be transferred.

Author Contributions

Conceived and designed the experiments: HCY CKM TLC LL JMM. Performed the experiments: HCY WHF. Analyzed the data: HCY. Contributed reagents/materials/analysis tools: WHF LL JMM. Wrote the paper: HCY JMM.

References

1. Fendrick AM, Monto AS, Nightengale B, Barnes M (2003) The economic burden of non-influenza-related viral respiratory tract infection in the United States. Arch Intern Med 163: 487–494.
2. Butler D (2010) Portrait of a year-old pandemic. Nature 464: 1112–1113.
3. Viboud C, Miller M, Olson D, Ostroholm M, Simonsen L (2010) Preliminary Estimates of Mortality and Years of Life Lost Associated with the 2009 A/H1N1 Pandemic in the US and Comparison with Past Influenza Seasons. PLoS Curr 2: RNN1153.
4. Gray GC, Goswami PR, Malaisig MD, Hawksworth AW, Trump DH, et al. (2000) Adult adenovirus infections: loss of orphaned vaccines precipitates military respiratory disease epidemics. For the Adenovirus Surveillance Group. Clin Infect Dis 31: 663-670.
5. Budding BA, Top FH Jr, Winter PE, Buescher EL, Lamson TH, et al. (1973) Acute respiratory disease in military trainees: the adenovirus surveillance program, 1966-1971. Am J Epidemiol 97: 187–198.
6. Gray GC, McCarthy T, Lebeck MG, Schnurr DP, Russell KL, et al. (2007) Genotype prevalence and risk factors for severe clinical adenovirus infection, United States 2004–2006. Clin Infect Dis 43: 1120–1131.
7. Potter RN, Cantrell JA, Mallak CT, Gaydos JC (2012) Adenovirus-associated deaths in US military during postvaccination period, 1999-2010. Emerg Infect Dis 18: 507–509.
8. Russell KL, Broderick MP, Franklin SE, Blay LB, Freed NE, et al. (2006) Transmission dynamics and prospective environmental sampling of adenovirus in a military recruit setting J Infect Dis 194: 877–885.
9. Gray GC, Callahan JD, Hawksworth AW, Fisher CA, Gaydos JC (1999) Respiratory diseases among U.S. military personnel: counteracting emerging threats. Emerg Infect Dis 5: 379–383.
10. Rowles DM, Walter EA, Dolan DM, Canas LC, Meier PA (2000) Influenza A in a basic training population: implications for directly observed therapy. Mil Med 165: 941–945.
20. Metzgar D, Skochko G, Gibbins C, Hudson N, Lott L, et al. (2009) Evaluation and validation of a real-time PCR assay for detection and quantitation of human adenovirus 14 from clinical samples. PLoS One 4: e7081.

21. Camargo C, Guatura SB, Bellei N (2012) Respiratory viral coinfection among hospitalized patients with H1N1 2009 during the first pandemic wave in Brazil. Braz J Infect Dis 16: 180-183.

22. Tanner H, Boxall E, Osman H (2012) Respiratory viral infections during the 2009-2010 winter season in Central England, UK: incidence and patterns of multiple virus co-infections. Eur J Clin Microbiol Infect Dis 31: 3001-3006.

23. Pretorius MA, Madhi SA, Cohen C, Naidoo D, Groome M, et al. (2012) Respiratory viral coinfections identified by a 10-plex real-time reverse-transcription polymerase chain reaction assay in patients hospitalized with severe acute respiratory illness—South Africa, 2009-2010. J Infect Dis 206 Suppl 1: S159–165.

24. Tate JE, Running ML, Lott L, Lu X, Su J, et al. (2009) Outbreak of severe respiratory disease associated with emergent human adenovirus serotype 14 at a US air force training facility in 2007. J Infect Dis 199: 1419–1426.

25. Sanchez JL, Binn LN, Innis BL, Reynolds RD, Lee T, et al. (2001) Epidemic of adenovirus-induced respiratory illness among US military recruits: epidemiologic and immunologic risk factors in healthy, young adults. J Med Virol 65: 710–716.

26. (2011) Self-reported influenza-like illness during the 2009 H1N1 influenza pandemic—United States, September 2009 - March 2010. MMWR Morb Mortal Wkly Rep 60: 37–41.

27. (2011) Febrile Respiratory Illness (FRI) Surveillance Update, Department of Respiratory Diseases Research, Naval Health Research Center, San Diego, CA. Available at http://www.med.navy.mil/sites/nhrc/gris/Documents/FRIupdate.pdf. Accessed 12 March 2011.