Epidemiology of Severe Infection due to Influenza A (H1N1) and A (H3N2): Are There Differences?

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ABSTRACT

Background: **Recent influenza seasons have been mixed, with isolates of influenza B, A (H1N1) and A (H3N2). The emergence of differing antiviral resistance in different FLU types/subtypes has made appropriate antiviral selection increasingly difficult. We asked whether the epidemiology and clinical features of Flu associated hospitalization due to A(H1N1) and A(H3N2) are different.**

Methods: **Since 1/1/2005, TIBDN has performed population-based surveillance for FLU associated with hospital admission. Consenting patients hospitalized for illness associated with FLU from rapid test, culture or PCR are enrolled. For the 2006/7, 2007/8 and 2008/9 seasons, all available influenza A isolates were sub-typed.**

Results: ***776 FLUA infections causing hospitalization have been identified; to date 428*** **(55%) have been sub-typed: 289 H3 and 139 H1. Of the H1 isolates, 16/127 (12%) contained the H275Y mutation conferring oseltamivir resistance. The proportion of hospitalizations associated with H1 isolates was 56% (68/122) in children, 37%(33/90) in adults aged 15-64, and 15%(30/200) in older adults.11/16 infections due to strains with the H275Y mutation (69%) occurred in children. Children with H1 infections were less likely to be vaccinated (4/64, 6% vs 14/50, 28%; P=.007), less likely to be treated with antibiotics (36/68, 53% vs. 42/54, 78%, P=.005), and had shorter length of stay (median 1 vs. 2d, P=.06) than children with H3 infections. Among adults, H1 infections were associated with younger age (median age 62 vs 79y, P<.001), and absence of underlying illness (10/45, 45% vs 47/247, 19%, P=.01).Otherwise, there were no differences in risk factors, clinical features, or outcomes.**

Conclusions: **Influenza A (H1N1) infections severe enough to require hospitalization are more common in children than adults, and are rare in older adults. H1N1 infections may be less severe than H3N2 infections in children.**

INTRODUCTION

Annual influenza outbreaks contribute to high morbidity and mortality, especially among extreme ages, people with chronic underlying illnesess, and the immunocompromised. While infants are vulnerable to influenza because of the immaturity of their immune systems and lack of previous exposure, older adults (>65 yrs old) suffer more consequences of influenza such as pneumonia, secondary bacterial infections, exacerbation of asthma and COPD, and cardiac complications) because of their aging immune response and chronic medical conditions. The emergence of anti-viral resistant Influenza A has highlighted the urgent need to understand the epidemiology infection in severe cases in order to inform clinical management and therapy. Surveillance of hospitalized patients offers the opportunity to dissect the underlying factors associated with severe outcomes due to Influenza A infection by different circulating subtypes. The purpose of this study was to 1) examine the distribution of Influenza subtypes in hospitalized cases, 2) identify associations with H1N1 or H3N2 infection in hospitalized patients and 3) detect differences in risk factors, clinical features or outcomes between H1N1 and H3N2 Influenza infection.

METHODS

Surveillance Framework: A population-based surveillance study of laboratory-confirmed influenza requiring hospitalization in Metropolitan Toronto and Peel Region, Ontario, Canada, conducted by the Toronto Invasive Bacterial Diseases Network (TIBDN), began on January 1 2005. TIBDN is a network comprising all hospitals and microbiology laboratories serving the population of Metropolitan Toronto and Peel region (pop. 4.5 million in 2006).

All influenza cases were reported to the TIBDN study office where a study number was assigned and initial clinical and microbiology information was collected. All hospitalized cases were forwarded to study nurses to obtain consent, to collect clinical and laboratory data from patient charts and family doctors, and to conduct a short interview with patients. Nasopharyngeal swabs were taken in ER, ICU and medical departments and were processed in site microbiology labs using rapid tests (EIA, DFA) or culturing. Subsequent testing and subtyping was performed at the Toronto Public Health Laboratory at the Ontario Agency for Health Protection and Promotion. During the 2006-2007 flu season we did active surveillance in the ICU departments of 6 TIBDN hospitals, and during the 2007-2008 flu season we added to this surveillance all medical admissions at 4 of these hospitals. At the end of the flu season an audit was conducted to better capture all influenza cases. We have used Charlson Index as a prognostic indicator for clinical outcomes of adult patients with comorbid conditions since it correlates significantly with mortality, disability, readmission and length of hospital stay. We have looked as well at bacterial co-infections, rate of flu vaccination, use of antibiotics and time of initiation of antivirals.

Figure 1. TIBDN Surveillance Area

Statistical Analysis: All data were entered, processed and analyzed using SAS version 9.1. Research ethics board was obtained from all participating hospitals.

Laboratory Testing Algorithm:

Viral RNA Extraction: Nucleic acid was extracted from 200µl of primary specimen by the easyMag NucliSense magnetic extraction method (bioMerieux).

Influenza A detection: Nucleic acid was tested for the presence of the Influenza A matrix gene by the CDC real-time reverse transcriptase polymerase chain reaction (rRT-PCR) protocol (reference method).

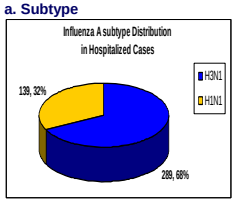
Subtyping: Influenza A-positive specimens were assayed with H1N1 and H3N2 primer sets with rRT-PCR to determine FluA subtype.

Oseltamivir Resistance Detection: Pyrosequencing was performed on FluA H1N1+ isolates to determine whether Histidine 275 on the neuraminidase gene was mutated to Tyrosine (H275Y).

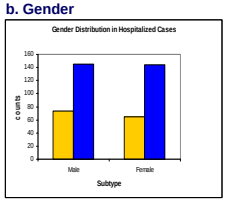
RESULTS

Figure 2. Distribution of Influenza Subtypes

a. Subtype



b. Gender



c. Age

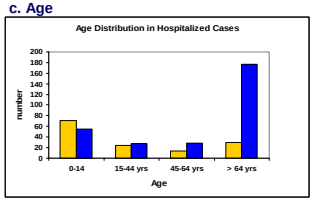
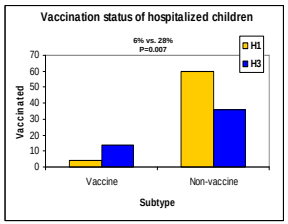
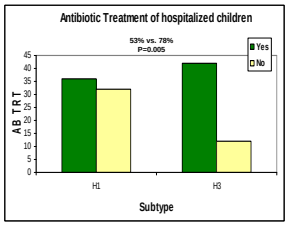


Figure 3. Associations of H1N1 Influenza Infection in Children under 14 yrs of age.

a. Vaccination Status



b. Antibiotic Treatment



c. Hospital stay

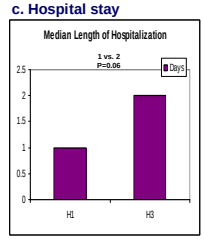
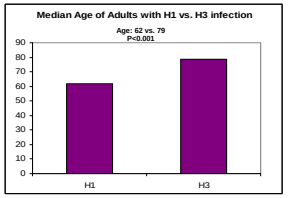
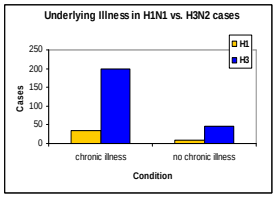


Figure 4. Associations of H1N1 Influenza Infection in Adults and median age (a) and underlying illness (b).





Overall cases with H3N2 infection had higher rates of underlying illness than H1N1 infected cases: bacterial co-infection (70% vs. 30%), chronic cardiac conditions (81% vs. 19%), chronic pulmonary conditions (74% vs. 26%), diabetes (78% vs. 22%), chronic renal disease (85% vs. 15%), malignancy (86% vs. 14%) and smoking (71% vs. 29%). This may be attributed to the higher proportion of older adults (>64yrs) in the H3N2 group.

CONCLUSIONS

❖Higher rates of H1N1 infection are found in children under the age of 14 years. However Influenza H1N1 infections in children may be less severe.

❖H3N2 infection was more common in older hospitalized adults (>64 yrs). Chronic underlying conditions were also more common in patients with H3N2 infection.