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Comparison of hospitalised children with pandemic human swine influenza A H1N1 and seasonal human influenza A H1N1/H3N2 infections at a regional hospital in Hong Kong

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Abstract

Objective: To compare the demographics and medical course of pandemic human swine influenza A H1N1 and seasonal human influenza A H1N1/ H3N2 infected paediatric patients and determine clinically differentiating features. ***Methods:*** Retrospective case analysis of confirmed human swine influenza (HSI) and seasonal influenza A (FLU) children ≤17 years admitted to a regional hospital in Hong Kong from 1st April to 31st December 2009. ***Results:*** 505 children were recruited, with 73% (M:F=1.5) and 27% (M:F=1) in the HSI and FLU groups, respectively. HSI children were older (median age HSI 6 years vs FLU 2.6 years, p<0.001), had higher incidences of sore throat (HSI 34.4% vs FLU 19.9%, p=0.002) and less vomiting (2.5% vs 39%, p=0.003). More FLU children presented with fever ≥38°C (HSI 80% vs FLU 97.1%, p<0.001) and had higher mean peak temperatures (HSI 39.2°C vs 39.8°C, p<0.001), but mean fever duration was the same (both 3 days, p=0.001). HSI group showed lower leukocyte counts (mean HSI $6.3x10^9$/L vs $7.3x10^9$/L, p<0.001), and more neutropenia (HSI 7.3% vs FLU 3.9%), lymphopenia (HSI 10.1% vs FLU 7%) and thrombocytopenia (HSI 20.8% vs FLU 7%). Viral and bacterial co-infection rates were similar (HSI 2.4% vs FLU 2.2%, p=NS). Nasopharyngeal aspirates performed in 80% of admitted patients showed RT-PCR having 92% sensitivity and 90% specificity in detection of human swine influenza. ***Conclusions:*** Pandemic human swine influenza H1N1 or seasonal human influenza A H1N1/H3N2 infection showed no clinically significant differences in presenting features, disease manifestations, laboratory findings, morbidity or mortality and differentiation is reliant on RT-PCR.

Keywords: H1N1, H3N2, Human swine influenza, Influenza A

Background

Influenza has been described as "an unvarying disease caused by a varying virus".[1] In March 2009, a new strain of human swine influenza A H1N1 virus was identified in Mexico with initial mortality rates up to 41% especially in young patients.[2] Genomic study of the novel H1N1 virus shows a triple-reassortant influenza virus containing genes from human, swine, and avian influenza A viruses isolates originating from Europe, North America, and Asia.[3] On 28th April 2009, human infection with this novel virus was first reported in Hong Kong. Persons in whom infection was confirmed were hospitalised and quarantined with close observation of the disease nature. The impact of human swine influenza locally was unknown, whereas disease burden of seasonal human influenza A in Hong Kong children had already been well described.[4] In our retrospective study, we compared the paediatric clinical presentations and outcome of pandemic human swine influenza A H1N1 (HSI) and seasonal human influenza A H1N1 and H3N2 (FLU) infected patients who were hospitalised in a Hong Kong regional hospital during the period from April 2009 to December 2009.

Materials and methods

Setting: United Christian Hospital is an acute general hospital with approximately 1400 total patient beds (120 paediatric beds) that serve the population of East Kowloon region in the Hong Kong Administrative Region.

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Patients and definitions: All paediatric patients (aged 17 or below) who were admitted to United Christian Hospital within the period of April to December 2009 with a diagnosis of human swine influenza H1N1 or seasonal human influenza A (H1N1 / H3N2) confirmed via antigen rapid tests, RT-PCR, or viral culture were included in the initial patient sample.

Data source: Retrospective data was retrieved from the Clinical Data Analysis and Reporting System (CDARS) of the Hospital Authority of Hong Kong. This is a computerised database of inpatient hospital admissions with details on patient demographics and discharge diagnoses. The patient list was generated using diagnostic codes 487 (Influenza) of the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) AND discharge date between 1st April 2009 and 31st December 2009 AND age ≤17 years. Every patient's medical record was traced and completely reviewed from admission to discharge with details on their demographic and clinical features, laboratory results, pharmacological treatment, and admission duration, entered into a computerised database.

Viral diagnosis: Routine nasopharyngeal aspirates (NPA) for viral investigation were collected from all children admitted with acute respiratory disease. Secretions were aspirated from each nostril via a specialised suction catheter and then dipped into viral transport medium (Earle's balanced salt solution with bovine serum albumin and antibiotics). Approximately 2 µl of solution was aspirated into the catheter to wash the secretions into the mucus extractor and transported promptly to the laboratory at ambient temperature. Specimens collected were refrigerated at 4°C if immediate transportation to the laboratory was not feasible. An aliquot of the NPA suspension was tested by Directigen Flu A+B assay, RSV Antigen immunofluorescence, and H1 Swine RT-PCR in our hospital microbiology laboratory. Additional aliquots were sent to Government Virus Unit, Department of Health for viral culture.

Directigen Flu A+B immunofluorescence

The assay was carried out according to the manufacturer's guidelines. 200 ml of the NPA suspension was mixed with eight drops extraction buffer into specialised tubes. Four drops of the specimen extract was then added to each well of a test device followed by instillation of specific conjugate, washing buffer, and substrate solutions within a 10-min period. Results were first read at 5 minutes from the device and then stop solution was added. The test result was read again and a purple triangle was required for a positive result. The control dot also needed to be visible for a valid test, and if absent, the result was deemed equivocal.

H1 swine RT-PCR

This one step in-house developed RT-PCR assay employs a pair of specific primers and one TaqMan probe for targeting at the hemagglutinin region of Influenza A virus subtype H1 (swine). One-step RT-PCR includes all components of the RT and PCR therefore the two steps are carried out sequentially in one tube. RNA from *Influenza A* virus subtype H1 (swine) is used as positive control. Water is used as negative control (no template control). Using the NucliSENS easy MAG system, 5µl of RNA extracted from NPA respiratory specimens is required for the reaction. Reaction buffer, RNA primers and probes mix, enzyme blend, PCR grade H_2O, and 5 µl RNA is placed into specialised capillaries and centrifuged by the LightCycler Carousel Centrifuge for 10 seconds at 400xg (2000 rpm). All data is analysed by the LightCycler software. The results are reported as the following manner: "RT-PCR for Influenza A virus subtype H1 (swine): Negative" or "RT-PCR for Influenza A virus subtype H1 (swine): Positive"

Viral culture

For respiratory virus isolation and identification, NPA specimens inoculated into test tubes containing Madin-Darby canine kidney (MDCK) cells and maintenance medium were sent to the Government Virus Unit of the Department of Health. The medium was replaced every 2 days and the cultures were incubated at temperatures of 33-34°C on a roller drum at 12 rpm. The tubes were reviewed daily for cytopathic effect or hemadsorption activity on guinea pig red blood cells, for up to 10 to 14 days.

Statistics: Descriptive statistics were performed on data regarding patient demographics, clinical features, and inpatient parameters. Comparison of the continuous variables in the human influenza A and human swine influenza groups were performed using the Mann Whitney U test. The Chi-squared test or Fisher's exact test was used to compare the categorical variables between those two groups where appropriate. P values <0.05 was considered statistically significant. The data was analysed by using the Statistical Package for Social Science version 15.0 (SPSS Chicago, IL, US).

Results

A total of 1956 children were admitted to our paediatric

department over the study period from 1st April to 31st December 2009. Diagnosis of influenza A infection accounted for 25.8% (505/1956) of admissions in these children and recruited into our study (Table 1). Among patients with influenza A infection, human swine influenza A H1N1 (HSI) accounted for 73% (369/505, M:F=1.5) and FLU patient sample was 27% (H1N1 34/505, H3N2 132/505, M:F=1) in the pandemic human swine influenza A H1N1 (HSI) group and seasonal human influenza A (FLU) group, respectively. Median age of admitted children with HSI ranged from 0.5 month to 17.9 years and FLU ranged from 1 month to 16.7 years (median age HSI 6 years vs FLU 2.5 years, p<0.001). A history of pre-existing medical conditions (Table 2) were present in HSI 7% vs FLU 6% patients.

Fever ≥38°C (Table 3) was present in 79.9% of HSI children and 97.1% of FLU children (p<0.001). Children with seasonal influenza also had slightly higher mean peak temperatures (HSI 39.2 vs FLU 39.8°C, p-value <0.001), although the mean duration of fever of 3 days was the same in both (Table 4). Presenting respiratory symptoms of rhinorrhea and cough were found not to be different between the two groups, but HSI children had a higher incidence of sore throat (HSI 34% vs FLU 20%, p=0.002). Patients in the FLU group presented more frequently with vomiting (39% vs 25.5%, p=0.003), but there was no difference in diarrheal complaints (watery stool >3 per day). Of the total 40 children who presented with seizures (HSI 6.8% vs FLU 11%, p=NS), 100% were associated with fever, HSI 40% vs FLU 60% had a prior history of epilepsy or febrile seizures, HSI 10% vs FLU 20% were atypical with focal features or repeated episodes within the same admission. Symptoms of myalgia, arthritis or chills and rigors were not routinely asked on admission and were excluded from this analysis.

Pneumonia (Table 5) was characterised as chest radiograph abnormalities or clinical signs compatible with consolidation, and diagnosed in 11.1% and 14% of HSI and FLU children, respectively. Other major

Table 1. Demographics and admission data of 136 children admitted with human influenza infection compared with 369 children with human swine influenza infection

	Human influenza A (H1N1/H3N2) (n=136)	Human swine influenza (H1N1) (n=369)	p value Human influenza A (H1N1/H3N2) vs. human swine influenza (H1N1)
Admission age in months (range)	31 (1-200)	72 (0.5-215)	<0.001[M]
Gender			
Male	67 (48.9%)	150 (40.8%)	0.1[C]
Female	70 (51.1%)	218 (59.2%)	
Pre-existing medical conditions#	8 (5.9%)	26 (7%)	0.54[C]
Days of hospitalisation (range)*	3 (2-4)	3 (2-5)	0.82[M]

p values performed using analysed by Chi-square test[C] and Mann-Whitney U test[M]

*Continuous variables are expressed as median (10th - 90th percentile)

#Refer to Table 2

Table 2. Summary of co-morbidities and/or risk conditions in the study sample (N=505)*

Co-morbidity and/or risk condition	Number of patients (%)
Chronic respiratory disease (chronic lung disease of prematurity / asthma)	15 (3.0)
Congenital heart disease (Non-cyanotic)	2 (0.4)
Musculoskeletal deformities	2 (0.4)
Renal disease (IgA nephropathy)	2 (0.4)
Gastrointestinal disease (inflammatory bowel disease)	1 (0.2)
Haematological (Haemoglobin H disease)	1 (0.2)
Inborn errors of metabolism (mucopolysaccharidosis type II / glutaric aciduria type I)	2 (0.4)
Neurological conditions (epilepsy / developmental delay / brain malformations	8 (1.6)
Morbid obesity (BMI >35)	1 (0.2)

*Multiple risk factors were possible for the same patient

Table 3. Clinical presenting features of 136 children admitted with human influenza infection compared with 369 children with human swine influenza infection

	Human influenza A (H1N1/H3N2) No. positive / total (%)	Human swine influenza (H1N1) No. positive / total (%)	p value Human influenza A (H1N1/H3N2) vs. Human swine influenza (H1N1)
Fever (≥38°C)*	132 (97.1)	295 (80)	<0.001[C]
Rhinorrhoea	108 (79.4)	263 (71.3)	0.07[C]
Cough	118 (86.8)	333 (90.2)	0.26[C]
Sore throat	27 (19.9)	127 (34.4)	0.002[C]
Vomiting	53 (39)	94 (25.5)	0.003[C]
Diarrhoea	4 (2.9)	7 (1.9)	0.5[F]
Rash	5 (3.7)	18 (4.9)	0.57[C]
Headache	5 (3.7)	25 (6.8)	0.19[C]
Dizziness	4 (2.9)	25 (6.8)	0.1[C]
Syncope	1 (0.7)	6 (1.6)	0.68[F]
Altered mental state	2 (1.5)	15 (4.1)	0.58[F]
Seizures	15 (11)	25 (6.8)	0.12[C]
Myositis	0 (0)	3 (0.8)	0.58[F]

p values performed using analysed by Chi-square test[C] or Fisher's Exact test[F]

*Children that were afebrile in hospital were excluded

Table 4. Fever trends and laboratory findings of 136 children admitted with human influenza A infection compared with 369 children with human swine influenza

Characteristics	Human influenza A (H1N1/H3N2) (Range)*	Human swine influenza A (H1N1) (Range)*	p value[M]
Highest temperature in hospital (°C)	39.8 (37-42)	39.2 (37-41)	<0.001
Duration of fever (days)	3 (2-7)	3 (0-6)	0.001
White blood cell count (10^9/L)	7.3 (4.2-12.76)	6.3 (3.61-11.9)	<0.001
Mean neutrophil count (10^9/L)	5 (1.86-9)	3.8 (1.2-8.23)	<0.001
Number of patients with neutropenia <1x10^9/L	3.9%	17.3%	
Mean lymphocyte count (10^9/L)	1.4 (0.5-4.53)	1.5 (0.5-5.43)	0.62
Number of patients with lymphopenia <0.5x10^9/L	7%	10.1%	
Mean platelet count (10^9/L)	226 (167.6-318.4)	208 (146-305.1)	0.06
Number of patients with thrombocytopenia <150x10^9/L	7%	20.8%	
Mean C-reactive protein level (mg/L)	5.95 (1-25.94)	5.2 (1-27.24)	0.86
Mean ALT level (IU/L)	17 (12-38)	15 (10-35)	0.02
Number of patients with ALT >60 IU/L	2.4%	2.3%	
Mean urea level (mmol/L)	4 (2.54-5.4)	4 (2.7-5.4)	0.52
Mean creatinine level (micromol/L)	36 (25.4-54)	41 (27-70.7)	<0.001
Mean sodium level	138 (136-141)	139 (136-142)	<0.001
Mean potassium level	4.1 (3.6-4.9)	4.2 (3.7-4.8)	0.34

p values performed using Mann-Whitney U test[M]

*Continuous variables are expressed as median (10th-90th percentile)

Table 5. Disease manifestations of 136 children admitted with human influenza A infection compared with 369 children with human swine influenza infection

Clinical diagnoses	Human influenza A (H1N1/H3N2) No. positive / total (%)		Human swine influenza (H1N1) No. positive / total (%)		p value Human influenza A (H1N1/H3N2) vs. Human swine influenza (H1N1)
Myositis	0	(0)	3	(1.1)	0.57[F]
Pneumonia	19	(14)	41	(11.1)	0.38[C]
Acute bronchiolitis	3	(2.2)	3	(0.8)	0.35[F]
Asthmatic attack	3	(2.2)	11	(3)	0.77[F]
Croup	2	(1.5)	8	(2.2)	1[F]
Acute otitis media	1	(0.7)	2	(0.5)	1[F]
Repeated febrile seizures	3	(2.2)	2	(0.5)	0.12[F]
Clinical sepsis	5	(3.7)	13	(3.5)	1[F]
Bacteraemia	0	(0)	0	(0)	
Co-infection (viral or bacterial)	3	(2.2)	9	(2.4)	1[F]

p values performed using analyzed by Chi-square test[C] or Fisher's Exact test[F]

infective complications included otitis media (HSI 0.5% vs FLU 0.7%, p=NS), Croup (HSI 2.2% vs FLU 1.5%, p=NS), acute bronchiolitis (HSI 0.8% vs FLU 2.2%, p=NS), asthmatic attack (HSI 3% vs FLU 2.2%, p=NS), and atypical febrile seizures (HSI 0.5% vs FLU 2.2%, p=NS). Clinical sepsis, was defined as examination features suspecting of bacteraemia (extreme dullness, extensive petichiael rash, skin mottling, poor peripheral perfusion) and/or left shift with toxic granules formation in the complete blood picture. This occurred similarly in the two groups (HSI 3.5% vs FLU 3.7%, p=NS), and there were no confirmed cases of bacteraemia or meningitis. Three children solely in the HSI group with acute muscle tenderness and weakness were diagnosed with viral myositis (creatine phosphokinase 2018-18199 IU/L).

Rates of co-infections were similar in both groups (HSI 2.4% vs FLU 2.2%, p=NS). Viral co-infections were determined by blood antibody titres or NPA specific antigen tests and/or viral cultures positive for multiple viruses. Bacterial co-infections were determined by direct cultures or acute and convalescent phase serums. The HSI group had viral respiratory tract co-infections comprising of two patients with adenovirus and two patients with respiratory syntycial virus (RSV). Gastroenteritis and concomitant HSI was seen in two cases of rotavirus and one case of norovirus. Two cases of Mycoplasma bacterial co-infection was also seen solely in this group, one presenting with pneumonia and the other with erythema multiforme. For those infected with influenza A H3N2, one child had RSV co-infection and another with streptococcal infection associated with scarlet fever. Multiple co-infections were present in one child with human influenza A H1N1 pneumonia consisting of RSV and *S. pneumoniae*.

Comparison of C-reactive protein levels showed same ranges 1-27.2 mg/L (mean HSI 5.2 vs FLU 5.95, p=NS) for both groups. Total white cell counts of admitted children with HSI ranged from 3.61-11.9x10^9/L and FLU from 4.2-12.8x10^9/L (mean HSI 7.3 vs FLU 6.3x10^9/L, p<0.001). Differential white cell counts were performed in 38% of HSI and 26% of FLU study patients. Neutrophil counts ranged from HSI 1.2-8.23x10^9/L and FLU 1.86-9x10^9/L (mean HSI 5 vs FLU 3.8x10^9/L, p<0.001), with neutropenia (<1x10^9/L) detected in HSI 7.3% vs FLU 3.9% patients. Lymphocyte counts ranged from HSI 0.5-5.43x10^9/L and FLU 0.5-4.53x10^9/L (mean HSI 1.5 vs FLU 1.4x10^9/L, p=NS), with lymphopenia (<0.5x10^9/L) present in HSI 10.1% vs FLU 7% patients. Platelet counts ranged from HSI 146-305x10^9/L and FLU 168-318x10^9/L (mean HSI 208 vs FLU 226x10^9/L, p=NS), with HSI 20.8% vs FLU 7% patients having thrombocytopenia (<150x10^9/L).

Renal and liver function tests (Table 4) were checked in 91% of admitted patients in both groups. Blood ranges for sodium (HSI 136-142 mmol/L and FLU 136-142 mmol/L) and potassium (HSI 3.7-4.8 mmol/L and FLU 3.6-4.9 mmol/L) were similar. Mean values were for serum sodium (HSI 139 vs FLU 138 mmol/L, p<0.001) and potassium (HSI 4.1 vs FLU 4.2 mmol/L, p=NS). Serum urea varied from HSI 2.7-5.4 mmol/L and from FLU 2.54-5.4 mmol/L (both mean 4 mmol/L, p=NS) and serum creatinine ranged from HSI 27-70.7 micromol/L

and FLU from 25.4-54 micromol/L (mean HSI 41 vs FLU 36 micromol/L, p<0.001). Alanine aminotransferase (ALT) levels ranged from HSI 10-35 IU/L and FLU 12-38 IU/L (mean HSI 15 vs FLU 17 IU/L, p=0.02), with the proportion of patients with ALT >60 IU/L being HSI 2.3% vs FLU 2.4%.

Nasopharyngeal aspirates (NPA) were respectively performed in 73% and 99% of admitted HSI and FLU patients. The remainder had nasopharyngeal swabs previously taken at an outpatient clinic or emergency department. For children with seasonal influenza infection, discrepancies between the NPA influenza A antigen IF result and viral culture were noted in 22% of cases. In the HSI group, discrepancies between RT-PCR and viral culture were only 11.5%. Using viral culture results as the standard for comparison, the sensitivity of NPA rapid influenza antigen tests (Flu A IF) for detecting HSI was 72%, whereas for RT-PCR the sensitivity was 92% and specificity 90%.

There was no mortality in our study and only one patient required intubation and intensive care for status febrile seizures. Lengths of stay ranged from 2-5 days in HSI children and from 2-4 days in FLU children, both with a mean of 3 days.

Discussion

Our retrospective study showed the burden of influenza A accounting for 25.8% of hospital admissions in children <18 years with fever and acute respiratory disease to our regional Hong Kong hospital over the period from 1st April to 31st December 2009. This varied significantly compared to previous local data by Chiu et al who reported influenza related admission rates of 7.7-13% for children <15 years from 1997 to 1999.[4] Within the literature, the greatest impact of influenza was said to be amongst children under the age of two years, and rates of hospitalisation may exceed even older children with high risk conditions.[4-6] However, when comparing admitted children infected with pandemic human swine influenza A H1N1 (HSI) and with seasonal influenza A H1N1 or H3N2 (FLU), our study found a higher median age of admission for the former. This may be explained by the public health measures of strict admission and quarantine for all HSI cases during the initial outbreak and early mitigation phase. As a result, older or institutionalised children with relatively mild symptoms that may usually not have presented were hospitalised. Even so, the common presenting signs and symptoms of upper respiratory tract infection were only mildly distinguishable between the two viral groups. HSI children presented with more sore throat complaints, less vomiting, and fewer incidence of fever on admission. For those patients that had fever, lower hospital mean peak temperatures were also found compared to Flu children. Again this may be due to bias towards an older age of admission.

Reports in the literature also describe children with chronic medical conditions having higher mortality and were more likely to be hospitalised for an acute respiratory disease during seasonal influenza peaks.[6,7] A history of pre-existing medical conditions was present in approximately 7% of our study (Table 2). Comparing the HSI and FLU groups, we did not observe any adverse outcome or significant difference in rates of admission for children with underlying medical conditions. Hospitalised children with seasonal influenza A (H1N1/H3N2) was previously reported to be associated with a higher incidence of febrile seizures and of repeated seizures in the same febrile episode than are adenovirus or parainfluenza infections.[8] However, in our study comparing this group with pandemic HSI, there appeared to be no statistically important variation in terms of seizures or repeated seizures. Analysing our study groups in terms of respiratory manifestations including acute bronchiolitis, asthma, croup, and acute otitis media also showed no statistically important variation. There were no cases of bacteraemia in either group. Viral myositis was diagnosed in three children solely in the HSI group with acute muscle tenderness and weakness (creatine phosphokinase 2018-18199 IU/L). All were discharged without complications within two days of admission.

Historically, the major cause of morbidity and mortality attributable to influenza A virus pandemics has always been superimposed bacterial pneumonia, usually occurring 7 to 10 days after initial influenza infection.[9,10] Common bacterial co-infections included *Streptococcus pneumoniae*, *Staphylococcus aureus (including MRSA), Streptococcus pyogenes, Haemophilus influenzae, Moraxella catarrhalis, Klebsiella* species, and *Mycoplasma pneumoniae* with multi-pathogenic pneumonia associated with a higher rate of fatality.[11,12] In our study, rates of co-infection were similar in both the HSI and FLU groups, all occurring in non-institutionalised children without pre-existing medical conditions and all with good outcome.

For both the HSI and FLU groups, respiratory and/or gastrointestinal viral co-infections were without significant complications. In our series, we did not find

any patients having evidence of co-infection with pandemic human swine influenza A H1N1 together with seasonal human influenza A. This may potentially be due to technical limitations in the viral culture and cross-reactivity in the NPA specific antigen tests. In ferret models, such a co-infection is implicated to result in more severe clinical manifestations and earlier viral shedding.[13]

Bacterial co-infection was evident seen both groups. One child with influenza A H3N2 and RSV respiratory infection had superimposed *S. pyogenes* co-infection associated with scarlet fever. Multiple co-infections were present in another child with human influenza A H1N1 pneumonia with RSV and *S. pneumoniae*. Co-infection with *Mycoplasma* was present in two children with human swine influenza infection, one with pneumonia and another with erythema multiforme. Nevertheless, all the above children did not have any major complications and responded well antibiotics. In recommendations by Wright et al., patients with respiratory distress having human swine H1N1 influenza pneumonia should be treated empirically with an intravenous second or third generation cephalosporin and additional agents to cover MRSA if rapid deterioration or gram stains are suggestive of staphylococci.[14] Based on our study findings, there is indication to consider synergistic co-infection of human swine influenza with Mycoplasma pneumoniae and the addition of macrolide antibiotics for treatment in both the out-patient and intensive care setting.

Published studies of pandemic H1N1 infection in the United States reported lymphopenia ($<0.5x10^9$/L) to be present in around 20% of hospitalised patients in all ages.[15] A recent Chinese study, where blood counts were measured every day of admission, showed the incidence of lymphopenia ($<0.3x10^9$/L) eventually occurring in up to 92% of children.[16] The majority of subjects in our study only had one blood count taken upon time of admission and the incidence of lymphopenia ($<0.5x10^9$/L) was 10%. When comparing between the HSI and FLU groups (Table 4) no significant disparity was found for the mean lymphocyte counts, but the former did have slightly more lymphopenic patients in the sample. HSI children also had statistically lower mean neutrophil counts and mean platelet counts, as well as higher proportion of neutropenia and thrombocytopenia compared to FLU children. However, similar to the Chinese study, our mean values for these two parameters still fell within normal laboratory ranges and may not have clinical significance. The fraction of cases with thrombocytopenia $<150x10^9$/L in our pandemic influenza H1N1 patients were 20.8%, compared to the 33% reported in the US study, although that study included both adults and children.[15]

Reports of acute renal failure in association with influenza A in the literature were mainly in relation to myoglobinuria or disseminated intravascular coagulation.[17] Similar to the Chinese study by Cao et al, the mean values for sodium, potassium and creatinine on admission in our pandemic influenza H1N1 patients were all within normal laboratory ranges.[16] Comparison between renal function test mean values in the HSI and FLU groups in our series, showed no *clinically* important variation between. Mild liver dysfunction with slightly elevated alanine aminotransferase (ALT) levels in HSI patients were reported in a number of international studies, but no cases of Reye's syndrome.[15,16,18] Our comparisons in this study between pandemic human swine or seasonal influenza A infected children showed no significant difference in mean ALT levels or the proportion of patients with ALT >60 IU/L (twice normal range).

Overall morbidity is low and there is no mortality when comparing between human swine influenza and seasonal influenza in our study. Intubation and intensive care was required in only one patient in the series, a previously healthy 20 month old girl with influenza H3N2 infection presenting with febrile status epilepticus. Median period of hospitalisation was 3 days in both groups. However, public health issues may yet again have skewed the HSI data either by admission of infected but relatively well children (shorter stays), or mandatory quarantine of affected institutionalised patients until complete course of oseltamivir was taken (longer stays).

Comparison of presenting features, disease manifestations and blood laboratory findings has thus far, revealed no prominent features that allow clinical differentiation between human swine influenza and seasonal influenza infection. Definitive diagnosis must then be reliant on nasopharyngeal studies. Within our series, every admitted patient either had nasopharyngeal swabs were taken from an outpatient clinic or emergency department prior to hospitalisation or had nasopharyngeal aspirates (NPA) done upon arrival to the triage ward. Reports of the sensitivity of rapid influenza antigen testing for HSI virus infection in the literature ranges from 10 to 69%, but is generally regarded as poor.[19] On the other hand, RT-PCR methods for detecting HSI were highly accurate in our study and had high sensitivity and specificity of 92% and 90%, respectively. Therefore, clinicians need to exercise wariness when relying solely upon rapid influenza

antigen tests as evaluation of patients suspected of infection with pandemic H1N1 influenza A. These rapid influenza antigen tests are more useful in distinguishing between influenza A and B viruses, but are less useful in differentiating between influenza A subtypes (e.g. seasonal human influenza A H3N2 / H1N1 vs pandemic human swine influenza A H1N1). Confirmation of the latter is best made via RT-PCR or viral culture.

Nevertheless, our study has several limitations. During the public health early mitigation phase, a large proportion of patients with human swine influenza infection were referred to hospital for mandatory quarantine, so our data may not necessarily reflect true patient demographics. No standardised format was set for obtaining histories or for investigation of patients upon admission, thus all relevant clinical information may not have been collected. The patient sample also represents only a small fraction of total hospitalisations for both pandemic influenza A H1N1 infection and seasonal human influenza A in Hong Kong during the study period.

Conclusion

The effect of different strains of influenza can vary considerably from season to season, from interpandemic to pandemic. Very high mortality in Mexico was associated with the novel human swine influenza A H1N1, but was not similarly reported in other countries during pandemic spread. Our retrospective study during the peak infection period from April to December 2009 at a regional Hong Kong hospital also showed low paediatric morbidity and no mortality for this virus. Comparisons of children infected with pandemic human swine influenza A or seasonal human influenza strains (H3N2 and H1N1) showed no clinically significant variation in the presenting symptoms, disease manifestations, or blood laboratory parameters that may allow differentiation between them. Thus, diagnosis of HSI infection is reliant on NPA RT-PCR tests which are both sensitive and specific.

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