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Pandemic Influenza H1N1 2009 in north Queensland – risk factors for admission in a region with a large Indigenous population

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Abstract

This study describes the epidemiology of laboratory-confirmed pandemic influenza H1N1 within north Queensland, Australia. We collected data on all specimens tested for influenza (including H1N1) by polymerase chain reaction between May and August 2009 at Townsville Hospital. Patients requiring admission to hospital and a proportion of non-admitted patients had clinical characteristics recorded. Multi-variable logistic regression analysis was used to identify independent predictors for admission. Patients requiring admission were on average older, less likely to be of Aboriginal or Torres Strait Islander descent and more likely to be pregnant, female or suffer from diabetes mellitus. Oseltamivir provision was significantly higher within the Aboriginal or Torres Strait Islander patient population. However, when the relative sizes of the local Indigenous and non-Indigenous populations were considered, the relative risk of hospital admission for Indigenous people was found to be 7.9 (4.7–13.2) in comparison to non-Indigenous. *Commun Dis Intell* 2010;34(2):102–109.

Keywords: influenza A virus, H1N1 subtype; Indigenous health services; pregnancy; diabetes mellitus; Queensland

Introduction

A novel swine-origin influenza A virus (pandemic influenza H1N1 2009, herein referred to as pandemic H1N1) was first described from Mexico in April 2009.[1,2] This was associated with reports of patients requiring hospitalisation for pneumonia with an unexpected increase in mortality and a marked shift in age distribution to the 5–59 year age range. This contrasted to past epidemics of seasonal influenza whereby the greatest morbidity occurred in both those under 5 years of age and those older than 65 years.[3] By mid October 2009, more than 414,000 laboratory confirmed cases of pandemic H1N1 had been recorded worldwide and nearly 5,000 deaths reported to the World Health Organization, with these figures significantly under-representing the true totals.[4]

Early surveillance data from the pandemic in Australia indicated that the median age of patients tested for pandemic H1N1 in Western Australia was 22 years and in Victoria 21 years, again confirming a lower age distribution than that encountered in seasonal influenza epidemics.[5] However, it has been suggested that seasonal H1N1 and influenza B exhibit a tendency to infect those with a younger median age when compared with seasonal H3N2.[6] Attack rates of seasonal influenza in Australia may be as low as 1%.[7] Case fatality ratios have been modelled for seasonal influenza and range from 0.14% (attack rate of 10%) to 1.4% (attack rate of 1%).[5]

Obesity and various co-morbidities may also be risk factors for severe disease with pandemic H1N1. A small subgroup of patients requiring intensive care support was described during the early phase of the pandemic, with obesity appearing to be associated with poor outcome and death.[8] Similar studies from Australia have described the small but significant risk of respiratory failure in relatively young individuals with co-morbidities.[9] By October 2009, 183 deaths have been attributed to pandemic H1N1 in Australia with a median age of 53 years in confirmed cases who died, compared with 83 years for seasonal influenza in the period 2001–2008.[10] The burden on intensive care units in the region has also been substantial.[11]

Queensland, Australia, has a unique population mix with around 3.3% of the population being of Aboriginal and Torres Strait Islander origin, with figures of 7.2% seen in the district served by Townsville Hospital.[12] Indigenous Australians are over-represented statistically for a variety of co-morbid conditions, with an increasing contribution from chronic non-communicable disease.[13] Indigenous communities from several parts of the world appear to have been disproportionately affected by the pandemic H1N1 outbreak.[14,15] In particular, Indigenous Canadians appear to have experienced higher rates of severe H1N1.[16,17] This population is similar to the Australian Aboriginal population in that rates of chronic disease are between 1.5 and 6.9 times that of non-Indigenous Canadians.[16,18] In New Zealand, rates of notifications and hospital admissions for pandemic H1N1

are significantly higher in Maori and Pacific Islander groups compared with those of European or other ethnicities.[19]

Data are lacking on the real impact of laboratory-confirmed seasonal and pandemic H1N1 amongst Indigenous Australians. Anecdotal local clinical experience in north Queensland would suggest that this group is numerically over-represented in patients presenting with an influenza like illness (ILI). During the 1918 pandemic, Indigenous Australian populations were severely affected, with some remote communities reportedly experiencing high mortality rates.[20] Initial national estimates suggest that Indigenous Australians are approximately 10 times more likely than non-Indigenous Australians to be hospitalised with H1N1, and account for 20% of all influenza-related admissions during the initial months of the current pandemic.[10] One study estimated the relative risk for hospital admission, intensive care requirement and death as 6.6, 6.2 and 5.2 respectively for Indigenous Australians.[21]

The aim of this study was to prospectively look at all cases of influenza A (pandemic H1N1 and seasonal) confirmed at the Townsville Hospital laboratory between May and August 2009. The investigation aimed to compare admitted and non-admitted patients with confirmed H1N1 in order to identify risk factors for hospital admission, morbidity and mortality, particularly within the local Indigenous population.

Methods

This was a prospective study of all laboratory confirmed cases of influenza A who were tested at Pathology Queensland, Townsville Hospital, between April and August 2009. Ethics approval was granted by the Human Ethics Committee, Townsville Health Service District.

Location

Townsville Hospital is located within the tropical region of north Queensland. During the study period it remained the only local facility to offer on-site molecular diagnostic services for influenza. The laboratory receives specimens from hospitals and clinics over a large and diverse geographical area, covering a population of approximately 216,480.[22]

Subjects and design

All subjects who presented with an influenza-like illness between May and August 2009 and who subsequently had a respiratory specimen (nose and throat swab, endotracheal aspirate, bronchoscopic aspirate or nasopharyngeal aspirate) that tested positive for influenza A by nucleic acid amplification were included in the primary analysis. Subsequently, all admitted patients and a proportion of non-admitted H1N1 positive control patients were included in a comparative analysis. The number of non-admitted control subjects with clinical data collected was intended to match those admitted at a ratio of approximately 2:1. Data representing non-admitted patients with H1N1 were obtained from those tested and discharged from the Townsville emergency department, district hospitals (mainly Charters Towers and Palm Island) and a local general practitioner practice. Data could not be obtained for all non-admitted H1N1 positive patients, primarily as a result of the practical difficulties in accessing clinical notes from a diverse group of geographically isolated testing facilities.

Data collection

Demographic and laboratory data were collected on all patients tested. This included age, sex, indigenous status, need for admission and sub-typing of influenza A. Self-reported indigenous status is routinely collected at the time of registration in the laboratory database. For the comparative analysis, clinical data were ascertained by chart review of all admitted and a selection of non-admitted patients. The following variables were collected from both groups: pregnancy, the presence of co-morbid medical conditions (obesity, chronic lung, renal or cardiovascular disease, diabetes mellitus, malignancy or immunosuppression), commencement of antiviral agents, need for intensive care unit (ICU) admission and clinical outcome. Obesity was defined as a body mass index of above 30 kg/m^2. The term 'chronic lung disease' incorporated the diagnoses of asthma, chronic obstructive pulmonary disease and other conditions leading to significant respiratory compromise. Chronic renal failure was defined as an estimated glomerular filtration rate (GFR) of less than 60 mL per minute over a period of 3 months or longer. The definition of immunosuppression included the administration of long term systemic corticosteroids or immunosuppressive medications or HIV infection.

Laboratory diagnosis

Detection of influenza A was performed as previously described.[23] Briefly, this was a 5'-nuclease real-time polymerase chain reaction (RT-PCR) (WhSl-FluA-5N), which had been developed for the detection of influenza type A. This test utilised conserved primer and probe targets on the matrix protein genes of a broad range of influenza A subtypes, including avian influenza subtypes. Using this information, 2 primers and one 5'-nuclease probe were designed. By testing 10-fold dilutions of H1N1 and H3N2 strains, the detection limit of the WhSl-FluA-5N assay

was determined to be 1 TCID50 per millilitre for both viral types. Subsequent typing as pandemic H1N1 was performed as described by Whiley et al.[24] Two assays were used. These were H1-PCR and N1-PCR, targeting the novel influenza A (H1N1) virus haemagglutinin and neuraminidase genes, respectively.

Statistical analysis

Numerical variables were described using median values, inter-quartile ranges (IQR) and ranges, because their distribution was skewed. Only patients with complete clinical data recorded were included in the analysis. Patients admitted to hospital were compared with patients who were not admitted regarding patient characteristics using non-parametric Wilcoxon tests, Chi-square tests, Fisher's exact test, and Spearman rank correlation coefficient.

Multi-variable logistic regression analysis was used to identify independent predictors of being admitted to hospital. For this analysis, all variables were dummy coded. Age was categorised using the quartiles of the distribution. Stepwise forward and backward selection procedures were used. After a stable model was identified all remaining characteristics were considered as potential confounders. A characteristic was considered a confounder if the estimate changed by 5% or more. Results are presented as odds ratios and 95% confidence intervals. This analysis was repeated for female patients only. Throughout the analysis a significance level of 0.05 was assumed. Statistical analysis was conducted using SPSS for Windows, version 17.0 (SPSS Inc., Chicago, Illinois). We estimated the cumulative incidence of outcomes relating to hospital admissions, intensive care and death during the study period. To calculate the relative risk (RR) for both Indigenous and non-Indigenous groups we compared the cumulative incidence of the outcomes for each group with the same outcome in the total population minus the population at risk. The proportion of Indigenous people within the local population was estimated as 7.2% from Australian census data.[22]

Results

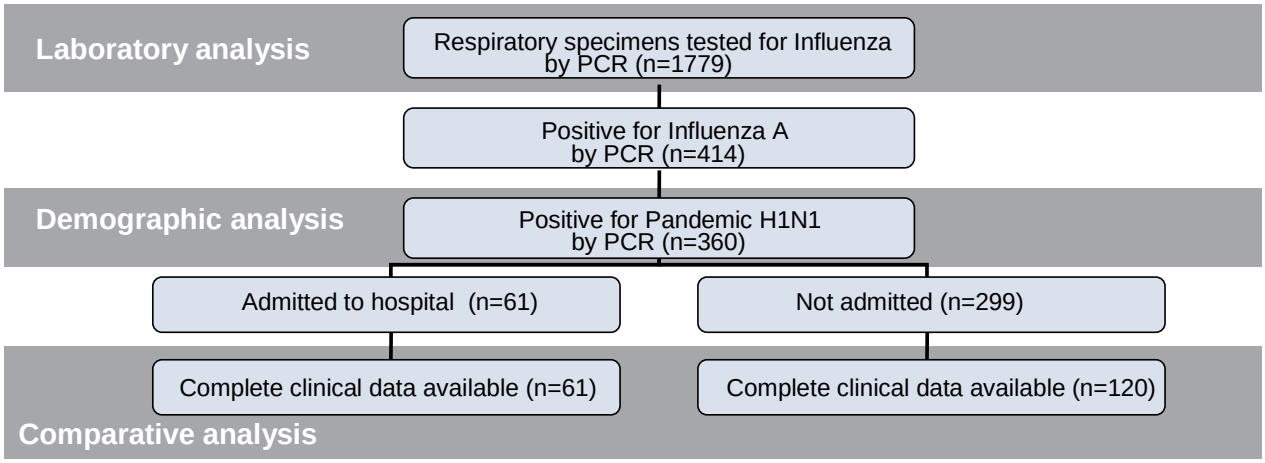
During May to August 2009, 1,779 respiratory specimens were tested for influenza A from subjects with an ILI. A total of 414 (23.3%) tested positive for influenza A by PCR. Of these, 360 (87%) were positive for pandemic H1N1. A total of 61 (17%) patients required admission to hospital with 5 deaths (1.4%). Complete clinical data were available for 181 (50.3%) H1N1 positive subjects (Figure 1).

Within the group of patients for which complete clinical data were available (n = 181), the median duration of stay in hospital was 3 days (IQR = 2 to 7 days; range 1 to 30 days). A majority (77.8%) of cases were Townsville residents, including 34 patients from Palm Island. Single cases came from Mackay, Ayr and Cairns, while 17 patients were resident in Charters Towers. The Townsville Hospital Emergency Department was the primary testing site in most cases (43.6%). The median age of recorded cases was 21 years (IQR = 9.5 to 39.5 years; range 0.2 to 90 years), 47.5% were male and 52.5% were Indigenous (Table 1).

Associations with being admitted to hospital

H1N1 positive cases admitted to hospital were on average older (median age 33 versus 15.5 years), less likely to be Indigenous (37.7% versus 60.3%), and more likely to have diabetes mellitus (24.6% versus 4.2%) compared with cases who were not admitted (Table 2). Multi-variable logistic regression analysis showed that patients with diabetes mellitus were 6.6 times more likely to be admitted to hospital than people without diabetes ($P = 0.005$) (Table 2). Patients of Indigenous descent were 0.3 times likely (that is, non-

Figure 1: Summary of study design and patient selection



Indigenous patients were 3.2 times more likely) to be admitted to hospital than non-Indigenous patients ($P = 0.003$).

Multi-variable regression analysis for female patients only, showed that pregnant women were 5.8 times more likely to be admitted to hospital compared with women who were not pregnant ($P = 0.007$) (Table 3). Women with diabetes mellitus were 9.1 times more likely to be admitted to hospital compared with women without diabetes ($P = 0.016$).

There was a linear trend towards higher admission rates for older patients (Spearman's correlation coefficient = 0.68; $P = 0.021$) (Figure 2). Of the 27 patients aged 5 years or younger, 33.3% were admitted to hospital; while of the 16 patients aged 41 to 50 years, 25% were admitted to hospital.

Indigenous patients

Indigenous subjects were significantly more likely than non-Indigenous, to have at least 1 significant clinical co-morbidity (74.4% vs. 53.8%; OR 2.501 (1.51-4.16); $P = 0.0003$), as might be expected for this population. This was particularly so with diabetes where 12% of H1N1 positive Indigenous subjects had diabetes compared with 3% of non-Indigenous (OR 4.23 (1.49-11.98); $P = 0.0045$).

Table 1: Basic characteristics overall and stratified by admission of 181 H1N1 positive cases

	Total (n=181)	Not admitted (n=120)	Admitted (n=61)	*P*-value
Median age (IQR); range (years)	21 (9.5, 39.5); range 0.2 to 90	15.5 (8.25, 26.75); range 0.75 to 61	33 (15.5, 53.0); range 0.2 to 90	*P*<0.001
% Male	47.5	46.7	49.2	*P*=0.749
% Aboriginal and Torres Strait Islander	52.5	60.3	37.7	*P*=0.004
% Townsville resident	77.8	78.2	77.0	*P*=0.866
% Females who were pregnant	15.1 (n=93)	8.1 (n=62)	29.0 (n=31)	*P*=0.013
Median gestation week of pregnant females (IQR); range (weeks)	33 (22.75, 37.25); range 12 to 40; (n=14)	32 (14, 36); range 12 to 38; (n=5)	36 (27, 38); range 22 to 40; (n=9)	*P*=0.298
% Diabetes mellitus	11.0	4.2	24.6	*P*<0.001
% Lung disease	29.8	27.5	34.4	*P*=0.336
% Renal disease	8.3	3.3	18.0	*P*=0.001
% Cardiac disease	14.4	8.3	26.2	*P*=0.001
% With malignancy	2.8	0.8	6.6	*P*=0.045
% Immunosuppressed	5.0	2.5	9.8	*P*=0.063
% Obese	16.1	10.0	28.3	*P*=0.002

Table 2: Independent factors associated with admission to hospital. Results of multi-variable logistic regression analysis based on 177* H1N1 positive cases

	Not admitted (n=116)	Admitted (n=61)	Odds-ratio (95% CI)†	*P*-value
Age	Continuous		1.02 (1.00, 1.04)	*P*=0.042
Being Aboriginal or Torres Strait Islander				
No	46	38	1	*P*=0.003
Yes	70	23	0.31 (0.14, 0.68)	
Diabetes mellitus				
No	111	46	1	
Yes	5	15	6.6 (1.8, 25.0)	*P*=0.005

* Four cases had missing values for ethnicity.

† 95% confidence interval; the model was adjusted for the confounding effects of gender.

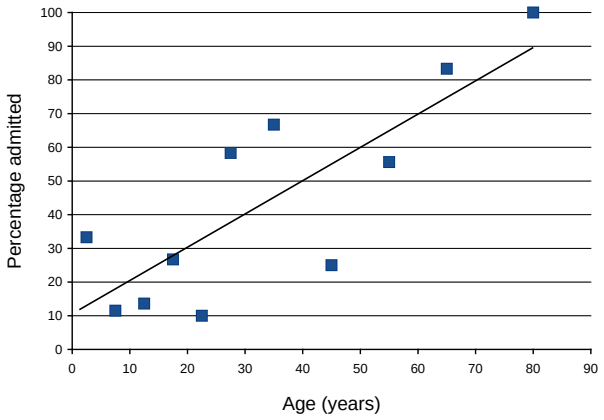
Table 3: Independent factors associated with admission to hospital. Results of multi-variable logistic regression analysis based on 93* female H1N1 positive cases

	Not admitted (n=62)	Admitted (n=31)	Odds ratio (95% CI)†	*P*-value
Being pregnant				
No	57	22	1	*P*=0.007
Yes	5	9	5.8 (1.6, 20.6)	
Diabetes mellitus				
No	59	23	1	*P*=0.016
Yes	3	8	9.1 (1.5, 55.0)	

* Two cases had missing values for being pregnant.

† 95% confidence interval; the model was adjusted for the confounding effects of age and ethnicity.

Figure 2: Association between age and percentage of cases admitted to hospital for pandemic H1N1



Of the 91 pregnant women with H1N1, 11 (12%) were Indigenous, of which four were admitted. Of the admissions to ICU, only two were Indigenous and neither of these died. There was a single death within the Indigenous group, in an elderly patient with multiple co-morbidities.

Neuraminidase inhibitor use

Oseltamivir was the only recorded anti-viral agent prescribed. Rates of oseltamivir provision were significantly greater in Indigenous patients. Seventy-nine per cent (n = 81) of non-Indigenous patients received antiviral drugs compared with 93.5% of those of Aboriginal and Torres Strait Island origin (n = 93) (OR 3.9 (1.4- 10.3); *P* = 0.005).

Outcome

Overall, 9 cases (5.0%) were treated in ICU and 8 cases (4.4%) required ventilation for a median time of 7 days (range 4–12 days). Five cases died, 2 cases required extracorporeal membrane oxygenation (ECMO), 1 case developed encephalitis, 1 pregnant woman lost her foetus but recovered herself, 2 pregnant women required a lower segment Caesarian section at term and 2 cases were still in ICU when data were retrieved. There was also one death from seasonal influenza A and *Staphylococcus aureus* pneumonia in a young non-Indigenous patient with a history of intravenous drug use.

Cumulative incidence of hospitalisation, intensive care admission and death for Indigenous populations

Estimations of the RR for hospital admission, intensive care and death for Indigenous Australians were 7.85 (4.7-13.2), 3.7 (0.8-17.8) and 3.24 (0.4-29.0) respectively in comparison with the non-Indigenous population. The wide confidence intervals for the latter 2 figures reflect the small numbers involved (Table 4).

Discussion

The current pandemic of H1N1 influenza was first reported to disproportionately affect Indigenous populations in Canada.[16] The Indigenous Australian population is similar in relation to the presence of co-morbidities such as diabetes, chronic renal, respiratory and cardiac disease. The study reported here, is the first to describe the impact of pandemic H1N1 influenza on the Indigenous population of north Queensland. The co-morbidities described conform to those expected throughout Indigenous populations in Australia. Despite making up approximately 7% of the local population, 34.7% (125/360) of all H1N1 positive specimens were from Indigenous subjects.

Patients admitted for pandemic H1N1 appeared less likely to be Indigenous in the comparative analysis. This finding appeared counter-intuitive given the well-described burden of co-morbidity within this population.[13] This result may reflect

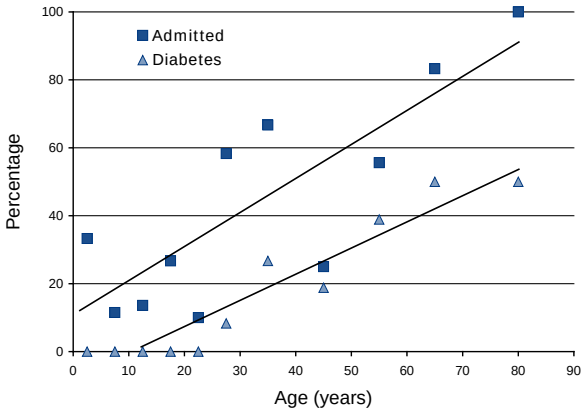
Table 4: Estimated relative risk of the cumulative incidence of hospitalisation, Intensive Care Unit (ICU) admission or death in relation to pandemic H1N1 for Aboriginal and Torres Strait Islander and non-Indigenous populations within the Townsville Health Services district

Outcome measure	Number	Population at risk	Rate per 100,000	RR	95% confidence interval
Hospitalisation total	61	216,480	28.2		
ICU admission total	9	216,480	4.2		
Death total	5	216,480	2.3		
Hospitalised Indigenous	23	15,500	148.4	7.85	4.7–13.2
Hospitalised non-Indigenous	38	200,980	18.9		
ICU Indigenous	2	15,500	12.9	3.70	0.8–17.8
ICU non-Indigenous	7	200,980	3.5		
Death Indigenous	1	15,500	6.5	3.24	0.4–29.0
Death non-Indigenous	4	200,980	2.0		

bias within the data whereby a greater proportion of Indigenous patients were represented within the non-admitted group. This could have resulted from the overuse of emergency services (the primary point of testing in most cases), the public health emphasis for testing in Indigenous populations (during the 'Protect' phase of the pandemic introduced locally on 22 June 2009[25]) and the predominance of clinical data available (and therefore inclusion in the study) from certain health services such as Palm Island. When the relative population sizes are taken into account a cumulative incidence of 148.4 per 100,000 for admission within the Aboriginal and Torres Strait Island group can be estimated and compared with a rate of 18.9 per 100,000 in the non-Aboriginal and Torres Strait Island group. These figures then translate into a significantly elevated relative risk of admission for Indigenous patients with H1N1. These results are broadly in agreement with previously published data analysed in a similar way.[21]

Despite the relatively young age of patients admitted in comparison with previous influenza seasons, increasing age remains a predictor of admission with a linear relationship seen in comparison with the proportion of those admitted. Equally, the under 5 year group were more likely to be admitted (33% admitted in this age range). In Australia, an average of 3,000 excess deaths a year may be attributable to influenza in people who are at least 50 years of age, with at least 85% of these occurring in people 65 years of age or older. Many of these would have underlying medical conditions.[26] Increasing age was associated with increasing co-morbid conditions and may account for the relationships seen (Figure 3). The presence of diabetes mellitus provided a strong predictor of requirement for admission. Diabetes has been described as occurring in up to 15% of hospitalised patients with H1N1 in the United States,[27] second

Figure 3: Relationships between age, diabetes mellitus and hospital admission for pandemic H1N1



only to asthma in frequency. Diabetes has long been thought to increase the risk of complications in seasonal influenza.[28] Whether this occurs as a product of diabetes itself, from increased risk of secondary bacterial infection, through co-existing cardiovascular mortality or via other factors remains to be clarified. There has been increasing awareness of the potential links between influenza and cardiovascular disease and cardiac death.[29]

Pregnancy was overrepresented in admitted patients with no significant difference being seen between Indigenous and non-Indigenous women. A total of 12 pregnant women required admission to hospital for H1N1 in this period (16% of all H1N1 admissions). Two of these subsequently required ICU management and, although neither died, one suffered a stillbirth. However, whether higher rates of admission in pregnancy reflect the presence of more severe respiratory disease or greater vigilance by clinicians (given the publicised concerns within this group) cannot be concluded from this study.

Whether older patients, those that were pregnant or those with diabetes developed more severe disease or were more likely to be admitted as a result of their co-morbid conditions alone is not clear. However, the pandemic response team within the hospital maintained a policy of encouraging medical staff to only admit patients with clear evidence of complicated disease (e.g. hypoxia, tachypnoea, abnormal chest signs, etc) rather than admitting due to the presence of co-morbidities alone. Patients not demonstrating these adverse clinical features were usually tested, started on oseltamivir and discharged with advice to return if symptoms deteriorated. As such, admission to hospital should remain a reasonable, although imperfect, surrogate marker of disease severity.

There were a total of 6 deaths in hospitalised patients attributable to influenza A during this period, of which five were confirmed H1N1 and one seasonal influenza A. Given that the number testing positive for H1N1 at our laboratory would grossly underestimate the total number infected in the community as a whole, the overall number of deaths and ICU admissions attributable to H1N1 was relatively low.

The early use of oseltamivir had initially been encouraged, on the basis of published papers, to reduce the duration of symptoms, transmissibility and possibly the likelihood of severe lower respiratory tract infection.[30] Oseltamivir use was significantly higher within the Aboriginal and Torres Strait Island group in comparison to non-Indigenous patients. Taken in conjunction with the relatively low rates of adverse outcomes in this group, the possibility is raised that widespread antiviral use ameliorated the anticipated impact of pandemic H1N1. However, this conclusion cannot be drawn with confidence from the data presented here.

Limitations of this study are acknowledged. Firstly only patients tested for influenza were included, but not all patients with ILI. With the progression of the pandemic, national and state protocols defined testing to be restricted to 'at risk' groups or those with severe disease manifestations. As such, numbers tested will greatly underestimate the true incidence of H1N1 within the community and 'at-risk groups' will be over-represented. However, we maintained a relatively liberal testing protocol during this time and continued to receive and process specimens from 'low-risk' individuals. Complete clinical data were not available for approximately 50% of non-admitted H1N1 positive patients. We attempted to obtain a representative sample of these, however, we cannot be certain that significant clinical differences exist between these included patients and those for whom data were not available. Furthermore this study only described the experience from a single centre, with relatively small numbers involved. Nonetheless, given these caveats, we believe that the findings presented here provide some insight into the effects of pandemic influenza H1N1 on Indigenous communities of north Queensland, especially given the paucity of accurate data in this area.

In summary, we describe the basic epidemiology of laboratory-confirmed pandemic H1N1 cases from north Queensland. Comparison with non-admitted patients with H1N1 suggested that those admitted were older, more likely to have diabetes mellitus and be non-Indigenous. Pregnancy also appeared to be strongly associated with probability of admission. However, the robustness of these findings are tempered by the possibility that significant ascertainment bias may exist within the data. Estimations of the cumulative incidence for H1N1 within the respective populations demonstrated that the relative risk for admission within the Aboriginal and Torres Strait Island group was higher (RR = 7.9 (4.7-13.2)) than for the non-Aboriginal and Torres Strait Island group. However, the overall numbers within the Aboriginal and Torres Strait Island group of ICU admission and death were small.

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