Disproportionate impact of pandemic (H1N1) 2009 influenza on Indigenous people in the Top End of Australia’s Northern Territory

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Objective: To describe the impact of pandemic (H1N1) 2009 influenza (nH1N1) on Indigenous people in the Top End of the Northern Territory at community, hospital and intensive care unit (ICU) levels.

Design, setting and participants: We analysed influenza notifications for the Top End from 1 June to 31 August 2009, as well as data on patients admitted through Top End emergency departments with an influenza-like illness. In addition, data on patients with nH1N1 who were admitted to Royal Darwin Hospital (RDH) and the RDH ICU were prospectively collected and analysed.

Main outcome measures: Age-adjusted notification rates for nH1N1 cases, Top End hospital admission rates for patients with nH1N1 and RDH ICU admission rates for patients with nH1N1, stratified by Indigenous status.

Results: There were 918 nH1N1 notifications during the study period. The age-adjusted hospital admission rate for nH1N1 was 82 per 100 000 (95% CI, 68–95) estimated resident population (ERP) overall, with a markedly higher rate in the Indigenous population compared with the non-Indigenous population (269 per 100 000 versus 29 per 100 000 ERP; adjusted incidence rate ratio, 12 [95% CI, 7.8–18]). Independent predictors of ICU admission compared with hospitalisation were hypoxia (adjusted odds ratio [aOR], 4.5; CI, 1.5–13.1) and chest x-ray infiltrates (aOR, 4.3; CI, 1.5–12.6) on hospital admission.

Conclusions: Pandemic (H1N1) 2009 influenza had a disproportionate impact on Indigenous Australians in the Top End, with hospitalisation rates higher than those reported elsewhere in Australia and overseas. These findings have implications for planning hospital and ICU capacity during an influenza pandemic in regions with large Indigenous populations. They also confirm the need to improve health and living circumstances and to prioritise vaccination in this population.

METHODS

Design and setting

The Top End of the NT encompasses the administrative regions of Darwin, Katherine and East Arnhem and is served by the Royal Darwin Hospital (RDH), a 350-bed tertiary referral centre containing the region’s only ICU, and two small regional hospitals. During the study period — 1 June 2009 to 31 August 2009 — all of these hospitals implemented a consistent policy of influenza screening for all patients presenting with an influenza-like illness (ILI).

We collected and analysed data on: all Top End nH1N1 notifications (notification analysis); all patients admitted through Top End emergency departments with an ILI (ILI analysis); all patients admitted to the RDH with nH1N1 (RDH admission analysis); and all patients admitted to the RDH ICU with nH1N1 (ICU analysis).

Definitions

An ILI was defined as a fever (temperature ≥38°C or a documented fever history) with a cough and/or sore throat. Influenza A was diagnosed by polymerase chain reaction (PCR) analysis of combined nose and throat swabs, and nH1N1 was diagnosed by PCR analysis using primers specific for the nH1N1 haemagglutinin gene.

Remote dwelling was defined using the Australian Bureau of Statistics remoteness area (RA) classification, with urban defined as RA code 2 and remote as RA code 3 or 4.

Data collection

For the notification analysis, population-level notification data were provided by the NT Centre for Disease Control. Before 18 June 2009, testing of anyone presenting to a health care facility with an ILI was encouraged; after this time, only those with severe disease or underlying risk factors were tested — in line with national policy.

For the ILI analysis, hospital admission records were linked with influenza testing data obtained from the RDH microbiology laboratory. We included all patients who were admitted through an emergency department or maternity ward of a hospital in the region during the study period and had a specimen taken for influenza A PCR analysis within 48 hours of admission (before or after). In cases where a person had multiple admissions fulfilling these criteria, the first influenza A-positive admission was included; if none were influenza A positive, the first admission was included.
Data including patient demographics, ICU admission and in-hospital mortality were obtained from hospital databases.

For the RDH admission analysis, the admitting hospital team prospectively collected detailed clinical data on standardised case record forms for all patients admitted non-electively to RDH from the community with nH1N1. Completeness of the dataset was ensured by cross-checking with the ILI analysis dataset, and missing data were obtained retrospectively. Symptoms, initial vital signs, laboratory results and comorbidities were recorded. Obesity was based on a clinical estimate of body mass index of more than 30 kg/m². Patients categorised as pregnant included those diagnosed with nH1N1 within 5 days after giving birth.

For the ICU analysis additional ICU-specific data were collected prospectively by RDH ICU staff for the Australian and New Zealand Intensive Care Society registry. Daily ICU bed occupancy was defined as the proportion of the eight beds staffed for ventilated patients occupied each day, and could exceed 100%.

The study was approved by the Human Research Ethics Committee of the Menzies School of Health Research and the NT Department of Health and Families (DHF) as a quality assurance activity.

Statistical analysis
Continuous variables were compared using the Mann–Whitney U test. Categorical variables were compared using the χ², Fisher exact or Wilcoxon rank sum tests as appropriate. Non-annualised incidence rates were calculated for the region using 2008 NT population data provided by the Health Gains Unit of the NT DHF. These were standardised to the 2001 Australian standard population using the direct method. Adjusted incidence rate ratios (IRRs) were derived using a Poisson regression model. A univariate analysis was performed for the ILI analysis. In the RDH admission analysis, patients requiring ICU care were compared with those not requiring ICU care. Clinically important variables and those with P<0.25 in the univariate analysis were included in an initial logistic regression model with backwards stepwise elimination of variables. Further univariate analyses were performed comparing Indigenous patients with non-Indigenous patients. Statistical analyses were performed using STATA version 11 (StataCorp, College Station, Tex, USA). Two-sided P values of <0.05 were considered significant.

RESULTS
The numbers and categories of notifications and patients included in the four parts of this study are summarised in Box 1.

Notification analysis
A total of 918 cases of nH1N1 in the Top End were notified during the study period. This corresponds to an age-adjusted notification rate of 497 (95% CI, 494–500) per 100 000 estimated resident population (ERP). There were 473 female (51.5%) and 445 male (48.5%) cases. The number of notifications increased sharply in Week 5 (25 June – 1 July) and peaked in Week 7 (9–15 July) (Box 2). The median age (interquartile range [IQR]) for notifications was 25 (15–40) years. Indigenous people accounted for 72% of those who tested positive for nH1N1. There was no significant difference in either the need for ICU admission or in-hospital mortality between the three groups.

The overall age-adjusted incidence of admission with an ILI was 361 per 100 000 ERP over the study period. The corresponding incidence rate for nH1N1 was 82 per 100 000 ERP overall, with stark differences between Indigenous and non-Indigenous populations (269 [95% CI, 214–324]) v 29 [95% CI, 20–39] per 100 000 ERP). The adjusted IRR for nH1N1 admission was 12 (95% CI, 7.8–18; adjusted for age and remoteness) and the IRR for ICU admission was 5.2 (95% CI, 2.3–12) — both calculated for Indigenous versus non-Indigenous patients (Box 4). For the Indigenous population alone, the IRR of hospital admission for remote compared with urban dwelling was 0.63 (95% CI, 0.43–0.92).
For the 643 patients who were admitted through Top End emergency departments with an ILI, hospital admissions for nH1N1 and non-influenza ILI peaked in Weeks 7 and 8 (9–22 July), whereas those for seasonal influenza A peaked in Week 6 (2–8 July).

**RDH admission analysis**

Of the 161 patients who were positive for nH1N1, 131 were admitted to RDH from the community; 21 of these patients (16%) required ICU admission, and two died. Within the group admitted from the community, there were 24 women aged 15–45 years, of whom 11 (46%) were classified as pregnant. Three of those 11 were admitted to ICU. Nosocomial acquisition was noted in 10 patients who were admitted to RDH and subsequently tested positive for nH1N1 at greater than 48 hours after admission; these patients were not considered in the RDH admission analysis.

Unusual presenting symptoms in patients admitted to RDH with community-acquired nH1N1 included chest pain in 20 patients (15%) and seizures in five patients (of whom three were children with febrile convulsions). The median (IQR) duration of symptoms before admission was 3 (1–5) days. Oseltamivir or zanamivir were administered to 107 patients (82%), including 99 of 109 (91%) of those aged ≥5 years, but only eight of 22 (36%) of those aged <5 years.

There were significant differences between Indigenous and non-Indigenous patients admitted with nH1N1 (Box 5). Indigenous patients were more likely to live remotely and were younger, with lower haemoglobin and serum albumin levels, and higher white cell counts and C-reactive protein (CRP) levels than non-Indigenous patients. The proportions of patients who reported being a current smoker and patients who reported hazardous alcohol use were also higher in Indigenous patients.

On univariate analysis, serum albumin <35g/L (odds ratio, 3.5), elevated CRP levels, infiltrates on chest x-ray and hypoxia were significantly associated with ICU admission. Obesity was associated with an odds ratio of 2.4, which was not statistically significant. Details of the univariate analysis are available from the authors. On multivariate logistic regression, only hypoxia (adjusted odds ratio [aOR], 4.5; 95% CI, 1.5–13.1) and chest x-ray infiltrates (aOR, 4.3; 95% CI, 1.5–12.6) on initial hospital admission were significantly associated with ICU admission. Indigenous status and pregnancy were not significant in either of these analyses.

### 3 Characteristics of patients admitted for acute care to Top End hospitals with an influenza-like illness (ILI), by result of influenza testing (1 June to 31 August 2009)*

<table>
<thead>
<tr>
<th>Pandemic (H1N1) 2009 influenza (n = 161)</th>
<th>Seasonal influenza A (n = 50)</th>
<th>Non-influenza A febrile respiratory illness (n = 432)</th>
<th>Total (n = 643)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (52%)</td>
<td>29 (58%)</td>
<td>198 (46%)</td>
<td>311 (48%)</td>
<td>0.70f</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 (19–51)</td>
<td>38 (2–58)</td>
<td>40 (11–57)</td>
<td>40 (12–55)</td>
<td>0.13f</td>
</tr>
<tr>
<td>Age ≥60 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23 (14%)</td>
<td>12 (24%)</td>
<td>98 (23%)</td>
<td>133 (21%)</td>
<td>0.07f</td>
</tr>
<tr>
<td>Indigenous (72%)</td>
<td>30 (60%)</td>
<td>236 (55%)</td>
<td>382 (59%)</td>
<td>0.11f</td>
</tr>
<tr>
<td>Remoteness**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remote (49%)</td>
<td>30 (64%)</td>
<td>182 (47%)</td>
<td>286 (49%)</td>
<td>0.09f</td>
</tr>
<tr>
<td>Non-remote (51%)</td>
<td>17 (36%)</td>
<td>208 (53%)</td>
<td>301 (51%)</td>
<td></td>
</tr>
<tr>
<td>Intensive care unit</td>
<td>27 (17%)</td>
<td>5 (10%)</td>
<td>46 (11%)</td>
<td>0.26f</td>
</tr>
<tr>
<td>Died (2%)</td>
<td>1 (2%)</td>
<td>9 (2%)</td>
<td>14 (2%)</td>
<td>0.95f</td>
</tr>
</tbody>
</table>

* Data are number (%) or median (interquartile range) unless otherwise indicated. † χ² test on 3×2 table. ‡ Kruskal–Wallis rank test. § χ² test on pandemic (H1N1) 2009 influenza × non-influenza A. ¶ χ² test on pandemic (H1N1) 2009 influenza × influenza A. ** Remoteness data do not include 56 people with usual place of residence outside of the Top End.
ICU analysis

Twenty-eight of the 161 patients in the Top End who were positive for nH1N1 (17%) were admitted to the RDH ICU; this included six interhospital transfers and one nosocomial acquisition. The median (IQR) APACHE (Acute Physiology and Chronic Health Evaluation) II score for these patients was 16 (14–23), and four patients died. The average daily ICU bed occupancy was 110% and nH1N1 admissions contributed 23% of this load. The median (IQR) length of stay was 4.5 (1.0–6.7) days. Admission of patients positive for nH1N1 to the RDH ICU peaked in Week 8 (16–22 July) (Box 2).

Intubation and mechanical ventilation was required for 17 of the 28 ICU patients, with a median (IQR) duration of 121 (47–293) hours. Inhaled nitric oxide was used in three patients, high frequency oscillatory ventilation in two patients, and prone positioning in one patient. Extracorporeal membrane oxygenation (ECMO) was not available at RDH and no patients were transferred elsewhere for ECMO. Two patients had rhabdomyolysis (peak creatine kinase levels, 82 000 IU/L and 42 000 IU/L [reference range, 0–220 IU/L]), of whom one died.

**DISCUSSION**

In the Top End of northern Australia, nH1N1 had a disproportionate impact on the Indigenous population at community, hospital and ICU levels. Rates of notification, hospital admission and ICU admission were 3.5 times, 12 times and 5 times higher, respectively, than for the non-Indigenous population. In contrast, hospital and ICU admission rates for the non-Indigenous population in this region were equivalent to admission rates for the non-Indigenous population. In contrast, hospital and ICU admission rates for the non-Indigenous population in this region were equivalent to admission rates for the non-Indigenous population. The median (IQR) length of stay was 4.5 (1.0–6.7) days. Admission of patients positive for nH1N1 to the RDH ICU peaked in Week 8 (16–22 July) (Box 2).

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Second, Indigenous populations worldwide have a high prevalence of risk factors for severe influenza. Among Indigenous people living in the Top End, the population-based prevalence of chronic lung disease has been estimated at eight per cent, four times higher than the comparable age-adjusted Australian rate, and a similar excess has been shown for the other major comorbidities. Given this substantial underlying disparity, it is noteworthy that there were few differences in risk factors between Indigenous and non-Indigenous hospitalised patients in our study. This suggests that excess comorbidities contributed to the high hospitalisation rates among Indigenous people (otherwise the differences in risk factors would have been preserved).

Reports to date have consistently found that Indigenous people with nH1N1 are over-represented in ICUs. Our data sug-
### 5 Characteristics of patients admitted to Royal Darwin Hospital with pandemic (H1N1) 2009 influenza, by Indigenous status (1 June to 31 August 2009)*

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Non-Indigenous (n = 39)</th>
<th>Indigenous (n = 92)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>23 (58%)</td>
<td>40 (47%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Female</td>
<td>14 (36%)</td>
<td>49 (53%)</td>
<td>0.07†</td>
</tr>
<tr>
<td>Age (years)</td>
<td>46 (19–61)</td>
<td>39 (15.5–49)</td>
<td>0.04†</td>
</tr>
<tr>
<td>Duration of symptoms (days)</td>
<td>3 (2–7)</td>
<td>3 (1–4)</td>
<td>0.27‡</td>
</tr>
<tr>
<td>Remote dwelling§</td>
<td>2/32 (6%)</td>
<td>43/88 (49%)</td>
<td>&lt;0.01‖</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>2 (5%)</td>
<td>10 (11%)</td>
<td>0.30†</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>2 (5%)</td>
<td>18 (20%)</td>
<td>0.04‖</td>
</tr>
<tr>
<td>Neurological disease</td>
<td>4 (10%)</td>
<td>5 (5%)</td>
<td>0.45‖</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>3 (8%)</td>
<td>3 (3%)</td>
<td>0.36‖</td>
</tr>
<tr>
<td>Current smoker</td>
<td>5 (13%)</td>
<td>38 (41%)</td>
<td>&lt;0.01‖</td>
</tr>
<tr>
<td>Pregnant</td>
<td>3 (8%)</td>
<td>8 (9%)</td>
<td>1.00‖</td>
</tr>
<tr>
<td>≥ 1 comorbidity</td>
<td>28 (72%)</td>
<td>68 (74%)</td>
<td>0.80‖</td>
</tr>
</tbody>
</table>

#### Initial vital signs on hospital admission

<table>
<thead>
<tr>
<th>Vital sign</th>
<th>Non-Indigenous (n = 39)</th>
<th>Indigenous (n = 92)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)**</td>
<td>100 (84–120)</td>
<td>105 (88–118)</td>
<td>0.64|</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)**</td>
<td>24 (20–28)</td>
<td>24 (22–32)</td>
<td>0.24|</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>37.8 (36.8–38.6)</td>
<td>37.4 (36.7–38.4)</td>
<td>0.29|</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)**</td>
<td>130 (112–145)</td>
<td>125 (105–148)</td>
<td>0.50|</td>
</tr>
<tr>
<td>Hypoxia††</td>
<td>16/38 (42%)</td>
<td>31/86 (36%)</td>
<td>0.52|</td>
</tr>
</tbody>
</table>

#### Initial investigations

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Non-Indigenous (n = 39)</th>
<th>Indigenous (n = 92)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g/L) (RR, 115–165g/L)</td>
<td>139 (120–148)</td>
<td>126 (109–143)</td>
<td>0.02|</td>
</tr>
<tr>
<td>White cell count × 10⁹/L (RR, 4.0–11.0 × 10⁹/L)</td>
<td>8.7 (6.1–10.9)</td>
<td>11.4 (8.1–14.5)</td>
<td>&lt;0.01|</td>
</tr>
<tr>
<td>Serum albumin (g/L) (RR, 35–45g/L)</td>
<td>41 (38–45)</td>
<td>37 (31–41)</td>
<td>&lt;0.01|</td>
</tr>
<tr>
<td>C-reactive protein (mg/L) (RR, 0.0–5.0 mg/L)</td>
<td>31.5 (11–82)</td>
<td>50.8 (25.6–97.2)</td>
<td>0.02|</td>
</tr>
<tr>
<td>Infiltrates on chest x-ray</td>
<td>16/39 (41%)</td>
<td>34/87 (39%)</td>
<td>0.84|</td>
</tr>
</tbody>
</table>

COPD = chronic obstructive pulmonary disease. RR = reference range. * Data are number (%) or median (interquartile range) unless otherwise indicated. Where data are missing or excluded, denominators are specified. †χ² test. † Wilcoxon rank sum test. § 11 people with usual place of residence outside of the Top End were not included in the remoteness classification. ¶ Fisher’s exact test. ** Children < 16 years are excluded due to different normal values. †† Hypoxia defined as either SaO₂ < 93% on room air or PaO₂/FiO₂ < 300 mmHg.

**gest that this over-representation flows from an excess of community and hospital cases, rather than an environmentally or genetically determined susceptibility to severe disease as has been hypothesised.** We observed a similar pattern with pregnant women, who were over-represented in the hospital admissions (46% of women of child-bearing age) but not the ICU admissions. A previous study showed that 23% of all women admitted with nH1N1 in Melbourne were pregnant. However, by restricting the denominator to women of child-bearing age this figure becomes a more comparable 38% (Justin Denholm, Infectious Diseases Physician, Victorian Infectious Diseases Service, personal communication).

Risk factors that were associated with ICU admission on multivariate analysis were hypoxia and chest x-ray infiltrates. Although both obesity and hypoalbuminaemia were more than twice as common in ICU patients on univariate analysis, neither were significant on multivariate analysis. A high prevalence of obesity in ICU patients with nH1N1 has been reported elsewhere and hypoalbuminaemia has been shown to be associated with severe nH1N1 infection and ICU admission in Top End patients with community-acquired pneumonia. The absence of associations between severe nH1N1 disease and obesity and hypoalbuminaemia on multivariate analysis may be due to a small sample size.

The consistently high ICU bed occupancy observed during the study period was due to the substantial burden of nH1N1 on critical care resources. The nH1N1-related bed occupancy of 23% was higher than the 5.2% reported across Australasia, and directly affected the capacity of the RDH as both a remote regional ICU and as the National Critical Care and Trauma Response Centre. The mortality rate of 14% for patients who were admitted to the RDH ICU (four deaths among 28 patients) was comparable to national figures. We noted two cases of severe hyperthermia and rhabdomyolysis with nH1N1; to date, this brings the total number of rhabdomyolysis cases reported worldwide to four. Lack of access to ECMO did not appear to adversely affect outcomes, which is reassuring for other jurisdictions without access to ECMO.

In conclusion, pandemic (H1N1) 2009 influenza has disproportionately affected the Indigenous population of the NT. This is likely to be due to a combination of increased attack rates and a high prevalence of comorbidities in this population.
findings have significant implications for planning hospital and ICU capacity during an influenza pandemic in regions with large Indigenous populations. They also confirm the need to improve health and living circumstances and prioritise vaccination in this population.

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COMPETING INTERESTS
None identified.

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