High mortality from respiratory failure secondary to swine-origin influenza A (H1N1) in South Africa


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Summary

Background: The novel influenza A (H1N1) pandemic affected South Africa late during the 2009 Southern hemisphere winter and placed an extra burden on a health care system already dealing with a high prevalence of chronic lung diseases and human immunodeficiency virus (HIV) infection.

Aim: The aim of this study was to describe the epidemiological characteristics, clinical features, management and outcomes of patients with confirmed influenza A (H1N1) infection complicated by respiratory failure.

Methods: We included all adult patients with confirmed influenza A (H1N1) infection that were referred to the medical intensive care unit of a large academic hospital in Cape Town for ventilatory support in this prospective observational study.

Results: A total of 19 patients (39.5 ± 14.8 years) needed ventilatory support over a 6-week period. Of these, 15 were female and 16 had identifiable risk factors for severe disease, including pregnancy (n = 6), type 2 diabetes mellitus (n = 6), obesity (n = 4), HIV infection (n = 3), immunosuppressive therapy (n = 3) and active pulmonary tuberculosis (n = 2). The most frequent complications were acute renal failure (n = 13), acute respiratory distress syndrome (n = 12) and ventilator associated pneumonia (n = 10). Thirteen patients died (mortality: 68.4%). Fatal cases were significantly associated with an APACHE II score ≥ 20 (P = 0.034), but not with a P/O2/FiO2 < 200 (P = 0.085) and a chest radiograph score ≥ 12 (P = 0.134).

Conclusions: The majority of patients with respiratory failure secondary to influenza A (H1N1) infection were young females and had an underlying risk factor for severe disease. The condition had a high mortality, particularly amongst patients with an APACHE II score ≥ 20.

Introduction

March 2009 saw the dawn of a much anticipated influenza pandemic. The causative agent, a novel strain of influenza A virus (subtype H1N1), referred to as the ‘novel swine-origin influenza A (H1N1) virus (S-OIV)’ was first identified by the Centers for Disease Control and Prevention (CDC) in North America. The outbreak spread rapidly and within 3 months the World Health Organization (WHO) raised the pandemic alert to the highest level (Phase 6).
While the pandemic seemed to decrease in intensity in the Northern hemisphere during the late spring and early summer, it soon spread to Australia and New Zealand during the start of the Southern hemisphere winter, causing much higher numbers of confirmed cases per head of population than in the USA.5,9 Southern Africa was initially spared, but the first case was reported in South Africa in June 2009.9 Within 2 months, there were almost 8000 confirmed cases and at least 31 laboratory-confirmed deaths in South Africa.10 Genomic analysis of this new 2009 virus indicated it to be a reassorted virus containing genes from influenza A virus strains endemic in (mainly Eurasian) swine, avian species and humans.11 The transmissibility of the strain is substantially higher than that seen in seasonal influenza strains.11

An unknown proportion of patients with 2009 influenza A (H1N1) infection develop acute respiratory failure.1,12 although recent epidemiological studies from the USA found that 40% of all hospitalized patients on admission had findings consistent with pneumonia on chest radiographs.12 Pregnancy, obesity and diabetes have been identified as potential risk factors for severe disease.1,12,13 A recent Canadian study also revealed that patients with confirmed infection were significantly younger, had a longer duration of mechanical ventilation and intensive care unit (ICU) stay and higher mortality than patients with suspected disease.14

The emergence of the pandemic in South Africa raised concerns, particularly with regard to the impact the existing disease burden may have on the influenza A (H1N1) infection and vice versa. The country comprises only —0.7% of the world’s population, but carries 17% of the global HIV burden.14 The incidence of pulmonary tuberculosis (TB) in the Western Cape Province is 940 cases per 100,000 population, which is the highest recorded incidence.15 Furthermore, a significant percentage of patients treated for TB are left with sequelae of the disease, including bronchiectasis, which may predispose to life-threatening influenza A (H1N1) infection. The TB and HIV pandemics are compounded by the high prevalence of chronic obstructive pulmonary disease (COPD). In fact, a recent study found that the overall prevalence of COPD in Cape Town was as high as 23.8%.16

The aim of this observational study was to describe the epidemiological characteristics, clinical features, management and outcomes of the first patients with confirmed influenza A (H1N1) infection complicated by respiratory failure and requiring either invasive or non-invasive ventilatory support at a large academic hospital in Cape Town, South Africa. Furthermore, we aimed to identify potential poor prognostic indicators.

Methods

Study population
All adult patients (≥18 years) with laboratory-confirmed 2009 H1N1 influenza A infection that were referred to the medical ICU of Tygerberg Academic Hospital for either invasive or non-invasive ventilatory support were included in this prospective observational study. The Stellenbosch University Research Ethics Committee approved the study (study number 09/05/228). Our institution is a 1200-bed academic hospital in Cape Town, South Africa. It is one of two academic referral centres in the city and renders a tertiary service to a population of ~1.5 million. During the course of the pandemic all cases of respiratory failure due to suspected or confirmed of H1N1 influenza A were isolated in the medical ICU of our institution, where infection prevention and control measures were implemented. At the time, all unrelated ICU admissions were diverted to other units and the medical ICU had the capacity to offer full invasive ventilation to eight patients, and non-invasive ventilation to a further four patients. All patients were continuously monitored (including invasive hemodynamic monitoring where appropriate), and managed by experienced intensive care specialists and chest physicians.

Clinical information

Apart from the general epidemiological characteristics, we specifically documented the presence or absence of co-morbid diseases and other potential risk factors, including current or recent pregnancy, HIV infection, active or previous pulmonary TB, COPD, obesity (body mass index (BMI) > 30 kg/ m²), known malignancies and the use of immunosuppressive drugs.

Disease severity

The severity of illness was assessed by means of the acute physiology and chronic health evaluation (APACHE) II score,17 which was calculated 24 h after admission to ICU, as well as the \( P_{\text{aO2}}/F_{\text{O2}} \) (partial pressure of arterial \( \text{O}_2 \) to the fraction of inspired \( \text{O}_2 \)), which was calculated on admission to ICU. We adapted a scoring system described by Opravil et al.18 to grade the severity of pulmonary infiltrates: each lung was divided into four equal quadrants and each quadrant was scored on a

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scale of 0-3 (0: normal; 1: subtle increased interstitial markings; 2: prominent interstitial opacities; 3: confluent interstitial and acinar opacities), giving a maximum score of 24 for both lungs. White cell counts and C-reactive protein (CRP) levels were performed on admission.

**Microbiological specimens**
Nasopharyngeal-swab specimens were collected on all patients (prior to enrolment), and influenza A (H1N1) infection was confirmed by means of real-time reverse transcriptase PCR in accordance with CDC guidelines. Blood cultures, tracheal aspirates and other microbiological specimens were obtained at the discretion of the attending physician. HIV status was tested by means of a third generation ELISA test.

**Medical treatment**
The dose and duration of Oseltamivir treatment were documented in all cases, as well as use of corticosteroids and other antimicrobials. All modes of ventilation that were utilized for at least 6h were documented.

**Complications and death**
We specifically documented the development of acute respiratory distress syndrome (ARDS), septic shock, acute renal failure and ventilator associated pneumonia, all defined according to accepted criteria. All patients who survived their ICU admission were followed up daily until hospital discharge. In the absence of a post-mortem investigation, we accepted the opinion of the unit’s morbidity and mortality committee regarding the cause of death.

**Statistical aspects**
Descriptive statistics and Fisher’s exact test were performed on dichotomous categorical variables. Reported *P* values were not adjusted for multiple testing. Odds ratios (OR) with 95% confidence intervals (given in brackets unless otherwise stated) were calculated for the various binary risk factors. Unless stated otherwise, data are displayed as means ± standard deviation (SD).

**Results**
Between 17 August 2009 and 24 September 2009, a total of 19 patients (age 39.5 ± 14.8 years) with laboratory confirmed influenza A (H1N1) infection were referred to the medical ICU for ventilatory support (Tables 1 and 2). Fifteen (78.9%) were females (age 32.1 ± 10.6 years) and four males (age 53.0 ± 11.0 years). Sixteen patients had an underlying risk factor (Table 3), which included pregnancy (n=6), type 2 diabetes mellitus (n=6) and obesity (n=4). Three patients were on immunosuppressive therapy: two had undergone cadaveric renal transplants in 1998 and 2007, respectively, and were on methylprednisolone, azathioprine and cyclosporine, or on methylprednisolone, azathioprine and tacrolimus, respectively. One patient was known with severe rheumatoid arthritis, and was on methotrexate and prednisone at the time of admission.

The HIV-status of all patients was either known on admission or confirmed shortly thereafter. Only three patients were HIV positive. Two were females that were known with the diagnosis prior to influenza A (H1N1) infection and their CD4 counts were 477 cells/mm^3 (on combination anti-retroviral therapy) and 497 cells/mm^3 (no anti-retrovirals), respectively. The third patient was diagnosed with HIV infection on admission and had a CD4 count of 128 cells/mm^3. No patient had clinical features of acquired immune deficiency syndrome (AIDS). Only single cases of COPD and TB bronchiectasis were observed. No clear risk factor could be identified in three patients. Of note is the fact that one of them was a 68-year-old female, not known with overt lung disease, but with >40 pack-years of smoking.

All patients reported a viral prodrome prior to onset of overt respiratory failure. Symptoms preceded ICU admission by 4.4 ± 2.4 days (range: 0-7 days). All patients had PaO2/FiO2 ratios below 300 at the time of their ICU admission (mean: 171.2 ± 74.4) and in 12 cases this value was below 200. Ten of these patients died (*P* = 0.085, OR = 6.67) (Table 3). The APACHE scores ranged from 10 to 30 and all patients with a score ≥ 20 died (*P* = 0.034). The initial chest radiographs varied from almost no infiltrates (score of 2) to confluent acinar opacities (score 24).

Although the median white cell count upon ICU admission was 9.76 x 10^9/l (range 4.41-39.41 x 10^9/l), only four patients had a WCC ≥ 11 x 10^9/l on admission. The CRP values ranged from 37.4 to 285.8 mg/l, with a mean of 177.1 mg. Lactate dehydrogenase (LDH) values were recorded in 14 cases and were raised in all (mean: 722.3 IU/l). No patient had evidence of a secondary pathogen on admission, but nosocomial infections (≥ 48h after admission) were diagnosed in 10 cases. The most common secondary isolates...
<table>
<thead>
<tr>
<th>No</th>
<th>Sex</th>
<th>Age</th>
<th>Risk factors</th>
<th>APACHE II</th>
<th>P(Fio2/FiO2)</th>
<th>Curr score</th>
<th>Other co-morbidities</th>
<th>Ventilation (mode)</th>
<th>Complications (Sepsis, shock)</th>
<th>Length of ICU stay (days)</th>
<th>Outcome</th>
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<td>1</td>
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<td>6 (SD)</td>
<td>NPPV</td>
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<td>ARDS, VAP, S, ARF</td>
<td>12</td>
<td>Survived</td>
</tr>
<tr>
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</tr>
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<td>Survived</td>
</tr>
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<tr>
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<td>14 (SD)</td>
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<td>17</td>
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</tr>
<tr>
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<td>M</td>
<td>51</td>
<td>Type 2 DM, Renal transplant*</td>
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<td>270.0</td>
<td>19 (SD)</td>
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<td>—</td>
<td>ARDS, VAP, S, ARF</td>
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<td>—</td>
<td>ARDS, VAP, S, ARF</td>
<td>13</td>
<td>Died</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>29</td>
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<td>23 (SD)</td>
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<tr>
<td>10</td>
<td>F</td>
<td>20</td>
<td>Type 2 DM, COPD, Obesity</td>
<td>10</td>
<td>296.3</td>
<td>9 (SD)</td>
<td>NPPV</td>
<td>—</td>
<td>ARDS, VAP, S, ARF</td>
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<td>Survived</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>46</td>
<td>Type 2 DM, COPD, Obesity</td>
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<tr>
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<td>39</td>
<td>Obesity</td>
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<td>248.9</td>
<td>12 (SD)</td>
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<td>ARDS, VAP, S, ARF</td>
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<td>Died</td>
</tr>
<tr>
<td>13</td>
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<td>69</td>
<td>—</td>
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<td>146.6</td>
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<td>ARDS, VAP, S, ARF</td>
<td>5</td>
<td>Survived</td>
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<td>14</td>
<td>F</td>
<td>19</td>
<td>Pregnant (38W)</td>
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<td>103.0</td>
<td>11 (DO)</td>
<td>NPPV</td>
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<td>ARDS, VAP</td>
<td>22</td>
<td>Died</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>66</td>
<td>—</td>
<td>18</td>
<td>195.4</td>
<td>20 (SD)</td>
<td>NPPV</td>
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<td>ARDS, VAP, S, ARF</td>
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<td>16</td>
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<td>42</td>
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<td>123.0</td>
<td>16 (DO)</td>
<td>NPPV</td>
<td>—</td>
<td>ARDS, VAP, S, ARF</td>
<td>30</td>
<td>Died</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>43</td>
<td>Type 2 DM</td>
<td>17</td>
<td>131.6</td>
<td>20 (DO)</td>
<td>NPPV</td>
<td>—</td>
<td>ARDS, VAP, S, ARF</td>
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<td>Died</td>
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<tr>
<td>18</td>
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<td>24</td>
<td>Pregnant (37W)</td>
<td>16</td>
<td>330.9</td>
<td>24 (DO)</td>
<td>NPPV</td>
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<td>50</td>
<td>Type 2 DM</td>
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<td>163.5</td>
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<td>—</td>
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<tr>
<td>Mean</td>
<td>35.5</td>
<td>18.2</td>
<td>171.2</td>
<td>13.0</td>
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<td>5.5</td>
<td>74.4</td>
<td>6.2</td>
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</table>

Note: APACHE II, acute physiology and chronic health evaluation; P(Fio2/FiO2) partial pressure of arterial O2 to the fraction of inspired O2; Curr score, current score; SD: single dose (75 mg twice daily); DO: double dose (150 mg twice daily); ICU: intensive care unit; F: female; M: male; HIV: human immunodeficiency virus; SE: systemic lupus erythematosus; DM: diabetes mellitus; PTH: pulmonary tuberculosis; RA: rheumatoid arthritis; COPD: chronic obstructive pulmonary disease; MX: methotrexate therapy; PHT: pulmonary arterial hypertension; NPPV: non-invasive positive pressure ventilation; SMV: pressure control synchronised intermittent mandatory ventilation (with pressure support ventilation); ARDS: acute respiratory distress syndrome; VAP: ventilator-associated pneumonia; ARF: acute renal failure; S: septic shock.

*Patient on immunosuppression following renal transplant.
Mortality from respiratory failure secondary to H1N1 were Acinetobacter baumannii (n = 6) and Candida albicans (n = 5).

Only one patient failed to complete at least 5 days of oral oseltamivir (died 4 days after the drug was commenced), and in all but five cases (Patients 1, 2, 3, 9, and 14) was the drug commenced within 48 h of the onset of symptoms (Table 1). The initial patients were given single-dose (75 mg twice daily) therapy, but the majority of the last nine patients received double-dose Oseltamivir (150 mg, twice daily). Six patients received at least two doses of corticosteroids, the indications being septic shock (intravenous hydrocortisone 50 mg, six hourly; n = 4) and preterm labour (intramuscular betamethasone 12 mg, 12 hourly; n = 2).

Non-invasive positive pressure ventilation (NIPPV) was commenced on six patients upon their ICU admission. This failed in four patients, who were subsequently intubated. Most patients (17) were ventilated by means of pressure control synchronized intermittent mandatory ventilation (SIMV), backed up by pressure support ventilation (PSV) and in accordance with ARDS network guidelines.

Fifteen patients experienced ICU complications that included ARDS (n = 12), VAP (n = 10), acute renal failure (n = 13) and septic shock (n = 8). Three patients required temporary renal replacement therapy in the form of intermittent haemodialysis.

The total length of ICU stay varied from 5 to 47 days, and 13 patients (68.4%) died in ICU. The causes of death included severe respiratory failure secondary to primary viral pneumonia (n = 1), ventilator associated pneumonia (n = 1), ARDS (n = 7) and refractory septic shock (n = 4). No patient died in hospital after ICU discharge. All the six survivors had a relatively uneventful stay following their discharge from ICU, and were all eventually discharged home.

Discussion

In this prospective observational study, we found respiratory failure secondary to influenza A (H1N1) to have a high mortality rate of 68.4% and to affect mostly young females with a mean age of 32.1 years. The vast majority of patients had identifiable risk factors for severe infection, the most frequently observed being pregnancy, type 2 diabetes mellitus and obesity. Only an APACHE II score >20 (P = 0.034) was significantly associated with death, although trends towards a higher mortality were observed with a PaO₂/FiO₂ < 200 (OR = 6.67, 95% CI: 0.87-50.80, P = 0.085) and a CXR score >12 (OR = 5.50, 95% CI: 0.67-44.82, P = 0.134).

Unlike seasonal influenza, respiratory failure secondary to influenza A (H1N1) more frequently affects relatively young adults. Kumar et al. found a mean age of 32.3 years when they reported on the characteristics, treatment and outcomes of inpatients. Most patients were ventilated on the characterisation ward, treatment and outcomes.

Table 1: Gender and age distribution

<table>
<thead>
<tr>
<th>Age categories</th>
<th>Female (n=12)</th>
<th>Male (n=10)</th>
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<tbody>
<tr>
<td>&lt;20</td>
<td>2</td>
<td>0</td>
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<tr>
<td>20-39</td>
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<td>2</td>
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<td>40-59</td>
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<td>≥60</td>
<td>1</td>
<td>3</td>
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Table 2: Individual risk factors and disease severity indices

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Frequency amongst all cases (n=19)</th>
<th>Frequency amongst survivors (n=6)</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>HIV infection</td>
<td>1 (5.3)</td>
<td>1</td>
<td>1.10 (0.08-15.14)</td>
<td>0.483</td>
</tr>
<tr>
<td>Immunosuppressive therapy</td>
<td>1 (5.3)</td>
<td>1</td>
<td>1.10 (0.08-15.14)</td>
<td>0.483</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>6 (31.6)</td>
<td>2</td>
<td>1.33 (0.14-44.08)</td>
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<tr>
<td>Type 2 diabetes mellitus</td>
<td>6 (31.6)</td>
<td>2</td>
<td>1.13 (0.14-44.08)</td>
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<tr>
<td>Obesity</td>
<td>4 (21.1)</td>
<td>1</td>
<td>1.30 (0.12-18.17)</td>
<td>0.441</td>
</tr>
<tr>
<td>Active pulmonary TB</td>
<td>2 (10.5)</td>
<td>0</td>
<td>NA</td>
<td>0.456</td>
</tr>
<tr>
<td>Previous pulmonary TB</td>
<td>2 (10.5)</td>
<td>0</td>
<td>NA</td>
<td>0.456</td>
</tr>
<tr>
<td>APACHE II score &gt;20</td>
<td>12 (63.2)</td>
<td>2</td>
<td>6.67 (0.67-50.80)</td>
<td>0.085</td>
</tr>
<tr>
<td>PaO₂/FiO₂ &lt;200</td>
<td>14 (73.7)</td>
<td>3</td>
<td>5.30 (0.67-44.82)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

CI: confidence intervals; HIV: human immunodeficiency virus; TB: tuberculosis; NA: not applicable; APACHE II: acute physiology and chronic health evaluation (APACHE) II score; PaO₂/FiO₂: partial pressure of arterial O₂ to the fraction of inspired O₂; CXR: chest X-ray.

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215 critically ill patients in Canada with 2009 influenza A (H1N1) infection. In California, most hospitalized patients fell in the age group of 20–39 years. 25 Other investigators reported similar findings.1,2,26 We found a mean age of 32.1 years and that almost half were younger than 40 years. In fact, only two patients in our study were older than 60 years. It has been suggested that older persons may have some level of cross-protection against S-OIV infection from pre-existing antibodies against other influenza A (H1N1) viruses.1 Another potential explanation may be the fact that pregnant females contributed a large proportion in our study and most other studies.7,13,25,26 Almost 79% of our study population were female. A female predominance was also observed by Kumar, but at least three other authors reported an almost equal gender distribution.1,2,25

In a population with a high burden of chronic pulmonary disease, we identified two patients with active pulmonary TB, one with COPD and one with post-TB bronchiectasis. Of note is the fact that the risk factors already described amongst more affluent and developed societies, namely pregnancy, diabetes and obesity13,25,26, clearly outnumbered these afflictions. Although three patients were HIV positive, none of these individuals had clinical features of AIDS (as defined by the WH-O),28 and all three had significant other risk factors. The prevalence of HIV infection at present amongst females of child-bearing age in South Africa is ~25%.29 The exact prevalence of HIV infection amongst all patients admitted to our medical ICU is however unknown, as routine testing is not performed. We therefore could not corroborate a role for HIV infection as an independent risk factor for respiratory failure secondary to influenza A (H1N1) infection.

With regards to disease severity, only an APACHE II score ≥20 was found to significantly predict mortality. In fact, no patient with a score above 20 survived (P=0.034). Kumar also found previously that a higher APACHE II score predicted mortality.13 In their study, non-survivors had a mean score of 26 (± 8) as opposed to survivors who had a mean score of 16 (± 5) (P < 0.01).13 All patients fulfilled the criteria for acute lung injury, namely a Pao2/Fio2 <300.20 Those with a Pao2/Fio2 <200 tended to have a higher mortality (OR 6.67 (0.87–50.8), P=0.065). We also attempted to validate a chest radiograph scoring system described by Opravil et al.28 and observed a tendency towards a higher mortality with a score ≥12 (OR 5.50 (0.67–44.82), P=0.134). The relatively small sample size caused a wide variation in the OR for these parameters and probably resulted in the failure of either of these parameters to reach statistical significance.

There is significant variation in the reported mortality rates of serious influenza A (H1N1) infection. Seven of the 12 (58.3%) patients ventilated during the initial outbreak in Mexico died.1 Louie et al.13 analysed 1088 cases of hospitalization or death due to pandemic 2009 influenza A (H1N1) infection reported in California. They found an overall mortality of 11%. The highest mortality was seen in patients aged 50 years or older (18–20%). The most common causes of death were viral pneumonia and ARDS.25 Kumar reported a 90-day mortality of 17.3% in their Canadian multicentre study,1 whereas the Australia and New Zealand extracorporeal membrane oxygenation (ANZ ECMO) influenza investigators reported a mortality rate of 21.0%.27 We observed the highest reported mortality rate to date, even exceeding the rate reported from the original Mexico City outbreak.2 A potential explanation may be a pure selection bias with regards to the population reported, as our ICU offers a referral service to many secondary and district hospitals, and our study population therefore represented the more serious end of the spectrum of affected individuals. Moreover, PCR and viral cultures for influenza A (H1N1) and other seasonal influenza strains were not uniformly performed at all institutions at the time of the study and milder cases may not have been detected. We also do not have access to certain modalities that have been utilized in the management of severe influenza A (H1N1) infections elsewhere, e.g. ECMO.2

In conclusion, the majority of patients with respiratory failure secondary to 2009 influenza A (H1N1) were young females and had an underlying risk factor for severe disease. The condition had a high mortality, particularly amongst patients with an APACHE II score ≥20. We could not corroborate HIV infection as a risk factor for respiratory failure secondary to influenza A (H1N1) infection.

Conflict of interest: None declared.

References


