

## Pandemic influenza A (H1N1) 2009: a case series from intensive care units in Port Shepstone, South Africa

<sup>a</sup>Blakemore SP, MBChB(UCT), DCH(SA), DA(SA), FCA(SA)

<sup>b</sup>Gopalan PD, MBChB(Natal), FCA(SA), Crit Care(SA)

<sup>a</sup>Principal Anaesthesiologist, Port Shepstone Regional Hospital

<sup>b</sup>Department of Anaesthesiology and Critical Care, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa

Correspondence to: Dr P Gopalan, e-mail: gopalan@ukzn.ac.za

Keywords: pandemic influenza A (H1N1) 2009; intensive care; critical care; influenza swine flu

### Abstract

This article presents a series of seven ventilator-dependent patients with pandemic influenza A (H1N1) 2009 and one with seasonal influenza at two hospitals – a government regional hospital and a private hospital – in the Ugu District, KwaZulu-Natal. The clinical features of these patients are described, and an attempt is made to highlight the problems encountered in managing such patients in a regional South African setting.

### Introduction

Influenza A (H1N1) 2009 'swine flu' variant is currently a global pandemic.<sup>1</sup> The infection associated with this virus is usually a mild, self-limiting illness. However, it may progress to severe pneumonia requiring intensive care unit (ICU) therapy in 31% of patients.<sup>2</sup> This may happen unpredictably in healthy, young patients as well as older patients with no co-morbidities.

The South African clinical experience with managing the pandemic has not been clearly documented. By 2 November 2009, the National Institute for Communicable Diseases (NICD) had reported 12 619 laboratory-confirmed cases in South Africa with 91 attributable deaths.<sup>3</sup>

A case series of seven patients with pandemic influenza A (H1N1) 2009 who developed ventilator-dependent respiratory failure is presented. One case of seasonal influenza-associated pneumonia is also presented for comparison. All cases occurred between mid-August and mid-September 2009.

### Case reports

Institutional consent to publish this report was obtained from all relevant hospitals. The clinical features of each patient are described below. Bi-level positive airway pressure (BIPAP) or synchronised intermittent mandatory ventilation (SIMV) was used

in all patients, with a protective lung ventilation strategy using tidal volumes of 6–8 ml/kg and titrated positive end-expiratory pressure (PEEP). Permissive hypercapnoea was accepted where appropriate. Sedation was achieved using morphine and midazolam, and, where needed, cisatracurium was used for muscle relaxation. The Surviving Sepsis Campaign Guidelines were followed where possible,<sup>4</sup> targeting mixed venous oxygen saturation and haemodynamic goals. In all patients, unless otherwise contra-indicated, glucose levels were controlled between 8–10 mmol/l, enoxaparin was used as thromboprophylaxis and ranitidine was used as ulcer prophylaxis. Fluid management was generally restrictive. The Vigileo Generation 3<sup>®</sup> Cardiac Output monitor (Edwards Lifesciences, Irvine, California) was used, where appropriate, to guide fluid and inotrope therapy. All patients had an arterial line and a central venous pressure (CVP) line inserted. Percutaneous tracheostomies were inserted on day seven of their ICU stay if further ventilation was anticipated. Blood cultures, urine cultures and sputum/tracheal aspirates were routinely taken, including testing for tuberculosis (TB) and *Pneumocystis jirovecii* pneumonia (PCP). Multiple antibiotics were used in all patients, either empirically or targeting specific organisms cultured. PJP and anti-TB therapy was commenced where appropriate. All patients had nasal and pharyngeal swabs on day one of their ICU admission. These

were reported positive for pandemic influenza A (H1N1) 2009 'swine flu' variant by the NICD or a private laboratory in Durban. Both laboratories tested samples using the reverse transcriptase polymerase chain reaction (PCR). Features are summarised in Table I. Both patients managed in the private sector received oseltamivir (Tamiflu® Roche Laboratories Inc). Only one state patient received oseltamivir.

### Case report 1

A pregnant 21-year-old black woman at 35 weeks gestation with problems of pre-eclampsia and obesity and in acute pulmonary oedema was referred to Port Shepstone Regional Hospital (PSRH) from a peripheral hospital. A chest radiograph (CXR) revealed an enlarged heart and features consistent with pulmonary oedema. Initial white cell count (WCC) was  $12 \times 10^9$  cells/l. She responded to anti-failure therapy and was referred to Inkosi Albert Luthuli Central Hospital (IALCH) for further management. Echocardiography confirmed the presence of cardiomyopathy. A Caesarean section was performed, after which the patient immediately developed acute respiratory distress and was admitted to the ICU for ventilation. Pharyngeal swabs were taken on day one in the ICU and oseltamivir was started at 75 mg twice daily for five days. A positive pandemic influenza A (H1N1) 2009 result was received on day five. She was ventilated for one week but continued to deteriorate, developed acute respiratory distress syndrome and died of multi-organ failure.

### Case report 2

A 48-year-old white man with problems of chronic obstructive pulmonary disease, congestive cardiac failure and obesity presented to PSRH with a five-day history of an influenza-like illness and acute respiratory failure. He was hypoxic and hypercarbic and had high airway pressures on ventilation. A CXR showed extensive bilateral pneumonia and features of pulmonary oedema. He was febrile, had a WCC of  $10 \times 10^9$  cells/l (predominant neutrophilia) and was inotrope dependent. No oseltamivir was used. Pharyngeal swabs were taken on day one in the ICU. A positive pandemic influenza A (H1N1) 2009 result was received 29 days later. He was ventilated for 23 days, developed renal failure and eventually died from multi-organ failure. Renal replacement therapy (RRT) was not offered.

### Case report 3

A 63-year-old black man, known to have asthma requiring multiple previous admissions, was referred to PSRH from a peripheral hospital in status asthmaticus. A CXR revealed patchy infiltrates on both lung fields. He was febrile and had a WCC of  $12 \times 10^9$

cells/l (predominant neutrophilia). Bronchospasm was treated with hydrocortisone,  $MgSO_4$  and continuous nebulisation with bronchodilators. No oseltamivir was used. Pharyngeal swabs were taken on day three in the ICU and a positive pandemic influenza A (H1N1) 2009 result was received 25 days later. He was ventilated in the ICU for 10 days then extubated and sent to the high care unit (HCU) for a further two days. He was discharged from the HCU in good condition. We were informed of his death in the General Medical ward one week later. Details of his condition in the ward are unknown.

### Case report 4

A pregnant 17-year-old black woman with no co-morbidities presented to PSRH with eclampsia and an intra-uterine death. She was taken to the theatre for a hysterotomy and became hypoxic ( $P_{aO_2}$  of 50 mmHg) post-operatively, necessitating further ventilation. A CXR revealed left patchy opacification, right-sided alveolar infiltrates and an area of right upper lobe consolidation. She was febrile with a WCC of  $12 \times 10^9$  cells/l (predominant neutrophilia). No oseltamivir was used. Pharyngeal swabs were taken on day one in the ICU and a positive pandemic influenza A (H1N1) 2009 result was received 22 days later. No other culture results were received. She was ventilated for five days, her pneumonia resolved and she was easily weaned. She was later discharged to the ward and remained stable.

### Case report 5

A four-year-old black human immunodeficiency virus (HIV)-positive female child with a history of an influenza-like illness presented to a district hospital in respiratory failure. She was then referred to PSRH. A CXR revealed patchy infiltrates on both lung fields, right upper lobe pneumonia and right pleural effusion. She was febrile with a WCC of  $4 \times 10^9$  cells/l and developed septic shock, needing an intravenous adrenalin infusion. No oseltamivir was used. She was ventilated at PSRH for three days then referred to IALCH where she was ventilated for a further 15 days. Pharyngeal swabs were taken on day one at PSRH and came back positive for pandemic influenza A (H1N1) 2009 25 days later. *Klebsiella pneumoniae* and *pseudomonas aeruginosa* were cultured from tracheal aspirates and appropriately treated. She recovered well and was discharged back to the district hospital.

### Case report 6

A 36-year-old black woman, HIV positive with a  $CD_4$  count of 78, presented to a peripheral hospital for a normal vaginal delivery. On day three post-delivery she developed respiratory failure and was referred to PSRH for ventilation. A CXR revealed left patchy infiltrates, right-sided consolidation and a pleural

effusion. She was afebrile, had a WCC of  $8 \times 10^9$  cells/l (predominant neutrophilia) and needed an adrenalin infusion for the first three days in the ICU due to septic shock. An evacuation of the uterus was done on day two in the ICU, revealing no septic products. No oseltamivir was used. She was ventilated for five days, during which the pneumonia resolved. Pharyngeal swabs were taken on day one in the ICU. A positive pandemic influenza A (H1N1) 2009 result was received 10 days later. Culture results showed no other growth. She was later discharged to the ward and remained stable.

### Case report 7

A 54-year-old white woman with no co-morbidities presented to a local private hospital with bronchitis and a two-week history of an influenza-like illness. A CXR showed bilateral diffuse alveolar infiltration in keeping with an atypical pneumonia. She was febrile and had a WCC of  $3 \times 10^9$  cells/l on admission, which subsequently increased. Procalcitonin levels measured two days apart were elevated to 7.49 and 5.52 ng/ml (reference range 0–0.05 ng/ml) respectively. She developed septic shock and acute renal failure, needing an adrenalin infusion and RRT. Oseltamivir

was started on day one at 75 mg twice daily for 10 days. Pharyngeal swabs taken on day one in the ICU came back positive for pandemic influenza A (H1N1) 2009 within four days. Culture results showed no other growth. She was ventilated for 16 days and eventually died of multi-organ failure.

### Case report 8

A 21-year-old Indian man with a one-week history of an influenza-like illness and no co-morbidities presented to a local private hospital in respiratory failure. A CXR showed left lobar pneumonia and right-sided alveolar infiltrates. He had a WCC of  $4 \times 10^9$  cells/l on admission, which subsequently increased, procalcitonin levels of 0.34 and 0.16 ng/ml (reference range 0–0.05 ng/ml) measured two days apart, and high airway pressures on ventilation. Oseltamivir was commenced on the day prior to ICU admission at 75 mg twice daily for 10 days. Pharyngeal swabs taken on day one in the ICU came back positive for influenza A (H3N2) ‘seasonal influenza’ variant within four days. *Acinetobacter baumannii* and *klebsiella pneumoniae* were cultured later and treated appropriately. He was ventilated for 27 days and was eventually discharged in a stable condition.

**Table 1:** Summary of clinical characteristics of patients

Patient	Age (years)	Sex	Co-morbidity	WCC ( $\times 10^9$ cells/l)	Onset to ventilation (days)	Ventilation time (days)	Oseltamivir therapy	CXR findings	Outcome
1	21	F	Pregnancy Obesity	12	7	5	Yes (late) 75 mg b.d. x 5 days	↑ CTR Pulmonary oedema	Death
2	48	M	CCF COPD	10	5	23	No	Extensive bilateral pneumonia, pulmonary oedema	Death
3	63	M	Asthma	14	5	10	No	Bilateral patchy infiltrates	Death
4	17	F	Pregnancy	12	3	5	No	Bilateral patchy infiltrates, RUL consolidation	Survival
5	4	F	HIV + ve	4	Unknown	18	No	Bilateral patchy infiltrates, RUL pneumonia, R pleural effusion	Survival
6	36	F	Pregnancy HIV + ve	8	3	5	No	L patchy infiltrates, R consolidation, R pleural effusion	Survival
7	54	F	Nil noted	3	14	16	Yes (late) 75 mg b.d. x 10 days	Bilateral diffuse alveolar infiltrates	Death
8*	21	M	Nil noted	4	7	27	Yes (late) 75 mg b.d. x 10 days	L lobar pneumonia, R patchy infiltrates	Survival

WCC – white cell count; CXR – chest radiograph; F – female; M – male; CTR – cardiothoracic ratio; CCF – congestive cardiac failure; COPD – chronic obstructive pulmonary disease; RUL – right upper lobe; R – right; L – left; HIV – human immunodeficiency virus.

\* Patient influenza A (H3N2) positive

## Discussion

Novel influenza A (H1N1) ('swine flu') virus, first reported in Mexico in March/April 2009 and in the United States of America in April 2009, progressed to being declared a pandemic by the World Health Organization (WHO) on 11 June 2009.<sup>5</sup> More than 482 300 laboratory-confirmed cases of pandemic influenza A (H1N1) 2009 have been reported worldwide, and over 6 071 deaths were reported to the WHO from April to 1 November 2009.<sup>1</sup> A second wave of the pandemic seems to be developing with a new outbreak in the USA. Many other northern hemisphere countries are reporting a similar situation with an expected worsening due to their upcoming winter.<sup>6</sup>

In August 2009, the southern coast of Kwa-Zulu Natal in South Africa experienced an influenza A (H1N1) 2009 outbreak. Similar outbreaks occurred in all provinces of South Africa. Data initially emerged slowly but by the end of September 2009, the NICD reported 11 729 laboratory-confirmed cases with 84 deaths.<sup>7</sup> Two large private laboratories also reported large numbers of positive cases (personal communication). The pandemic influenza A (H1N1) 2009 virus had replaced the seasonal influenza A (H3N2) virus that had peaked in mid-June. Between mid-August and mid-September the two private hospitals in Port Shepstone admitted 27 and 18 confirmed cases of influenza A (H1N1) 2009, respectively (personal communication).

The exact extent of the problem has been difficult to quantify. Many patients with self-limiting influenza-like symptoms did not present to doctors. Patients who did present to health care facilities were not routinely tested, due to either financial constraints or unavailability of testing at many institutions. The NICD and Centers for Disease Control (Atlanta, USA) recommendations were to test only severe cases.<sup>7,8</sup> Consequently underreporting of cases was a major problem.

In keeping with reports from other countries, most cases in the Port Shepstone region appeared mild and resolved spontaneously within a few days.<sup>1,6,9,10,11,12</sup> Initially patients were tested according to the NICD recommendations, but a long delay in return of results made subsequent testing sporadic to the point where all that was used was a high index of suspicion. The mean (range) delay in return of results of the patient series was 15.5 (4–29) days.

General practitioners in the area adopted a diversified approach to the problem: Some of them used oseltamivir on every patient with influenza-like symptoms, others only treated patients with severe

symptoms, a few treated only hospitalised patients and some opted not to treat at all. In the series from California, 21% of patients with severe infections received no anti-viral therapy.<sup>2</sup> Most physicians in Port Shepstone treated high-risk patients according to the NICD guidelines, which were undergoing constant revision at the time.

## The ICU experience

From mid-August 2009 to mid-September 2009, the ICU at PSRH received increased referrals of patients with pneumonia requiring respiratory support. PSRH is a state hospital with four ICU and four high-dependency unit (HDU) beds serving one million people of the Ugu District. Attempts at securing additional beds in other state hospitals or the private sector are usually unsuccessful. Patients needing a higher level of care are referred to IALCH. Consequently, the limited critical care services are quickly overwhelmed.

Six patients were managed at PSRH and two at a local private hospital. Two of the six patients from PSRH were referred to IALCH. The mean (range) age of the seven patients who were influenza A (H1N1) positive was 34.7 (4–63) years with their mean (range) period of ventilation being 13.6 (5–27) days. Four of the eight patients had a fatal outcome. Three died of multi-organ failure, and the fourth died days later in the ward under unclear circumstances. The mortality rate in our series is 57% (4/7). Other published data describe a mortality rate of 11%, with the highest rate (18%–20%) in persons aged 50 years or older.<sup>2</sup> Although our case series is too small to draw clear statistical conclusions, factors such as delayed presentations and anti-viral therapy, lack of appropriate support modalities such as RRT and ECMO, and the presence of significant co-morbid conditions should all be considered as potential contributors to such a mortality.

The NICD describes HIV infection, pregnancy/ puerperium, diabetes, obesity, cardiac disease and active tuberculosis as risk factors for serious infection and/or death.<sup>3</sup> Of the seven patients, three were pregnant, two were HIV positive, two were obese and two had chronic medical illnesses. Both HIV-positive patients had good outcomes. None of the survivors with influenza A (H1N1) received oseltamivir. In the series described by Louie et al, 68% had risk factors for seasonal influenza complications.<sup>2</sup>

Patient eight described in the series has been included to emphasise the difficulty in distinguishing between influenza A (H1N1) and seasonal influenza (H3N2) infections. This patient was treated with oseltamivir and had a good outcome.

Many other features were in keeping with other case series described.<sup>1,6,9,10,11,12,13</sup> White cell counts were not markedly raised, no lymphocytosis was noted and fever was common. Hypoxaemia was a constant feature. Other organisms were cultured in only one of the patients who were influenza A (H1N1) positive.

Radiographic features have been variably described in the literature. Louie et al describe 66% abnormal radiographs while Agarwal et al note 42% of initial radiographs to be abnormal.<sup>2,14</sup> In the Agarwal series, all patients requiring ICU admission and advanced mechanical ventilation had extensive disease on radiographs. All patients in our series demonstrated changes on the CXR. The CXR showed mainly alveolar infiltrates bilaterally with some patients having areas of consolidation and pleural effusions.

Thromboembolism, previously reported in Michigan and Ontario, was not described as serial D-dimers and spiral computerised axial tomography were not performed.<sup>10</sup> Extracorporeal membrane oxygenation (ECMO) and RRT, widely used in other series, are not readily available for use in our resource-limited setting.<sup>6,10,15</sup>

Two patients deteriorated post-operatively. The role of anaesthesia, surgery, and immune depression associated with concurrent pandemic influenza A (H1N1) 2009 has not been explored.

During the period reported 7/12 doctors and 10 other health workers in the theatre/ICU at PSRH developed mild influenza-like illnesses. None were tested, none received oseltamivir and all recovered. A Mexican case series showed similar outcomes with their health care workers, although all were treated with oseltamivir.<sup>16</sup>

### Treatment

Oseltamivir and zanamivir, both of which inhibit the neuraminidase protein and block cell-to-cell transmission early in the course of the disease, have been used. Although the literature in general shows only modest benefit from the use of antiviral medications, some studies showed a reduction in influenza mortality in high-risk hospitalised patients after the use of neuraminidase inhibitors.<sup>17,18</sup> Some studies have suggested a large reduction in pneumonia and mortality. These studies, however, have been conducted on patients with seasonal influenza and avian influenza.<sup>17,19,20</sup>

Various side effects of these drugs have been described. Common adverse drug reactions (occurring in over 1% of clinical trial participants) include nausea, vomiting, diarrhoea, abdominal pain

and headache. Rare reactions include hepatitis and elevated liver enzymes, rash and allergic reactions. There are concerns that oseltamivir may cause dangerous psychological and neuropsychiatric side effects including self-harm in some users.

Some patients treated with oseltamivir for confirmed influenza A (H1N1) 2009 have tested positive again a month later. This leads to the speculation that if treated early, a viraemia may not occur; hence, immunity may not develop. A further problem with using oseltamivir inappropriately is the possibility of the development of resistance.

The initial guidelines for treatment and prophylaxis using anti-viral agents were unclear. The selection of appropriate groups of patients was controversial. This was compounded by the limited availability of oseltamivir at PSRH and the delayed return of results. A decision was made to treat patients only if their symptomology was of less than 72 hours duration. Oseltamivir should be used only for severe and high-risk cases, as recommended by the NICD and CDC.<sup>7,21</sup> It should be commenced early at a dose of 75 mg twice daily for five days. Initiation of therapy within 72 hours is most effective.<sup>17</sup> All pregnant women should be treated empirically as the delay in obtaining results in our setting is far too long.<sup>7,21</sup> The limited availability of oseltamivir makes empirical treatment for low-risk patients in our setting impossible. There is some evidence for commencement of therapy in patients in the ICU, the suggested dosing schedule being 150 mg twice daily for 10 days or longer.<sup>1,6,21</sup>

An influenza A (H1N1) vaccine is currently available in some countries. Recommendations are currently evolving.<sup>22</sup> The vaccine is not currently readily available in South Africa. The role of other therapies needs further definition. The thromboembolic basis for pulmonary complications may allow a potential role for agents such as activated protein C and heparins.

### Recommendations

We make the following recommendations:

- i. Programmes focusing on public and health care worker awareness should continue.
- ii. Contingencies should be created for laboratory services to function efficiently.
- iii. Infection control practices at all health care facilities need to be emphasised.
- iv. All health care facilities should ensure that appropriate records are completed and forwarded to the NICD for central co-ordination.
- v. A clinical database should be created to allow better analysis of clinical data.
- vi. Anti-viral agents should be made more

readily available but need to be administered appropriately.

- vii. The vaccine should be made available and only used as per yet-to-be-determined guidelines for South Africa.

These can only be achieved by a better co-ordinated effort among clinicians, laboratory services and health administrators. The formation of a steering committee consisting of these key role-players should be considered.

### Conclusion

Pandemic influenza A (H1N1) 2009 remains a concern. The large numbers of affected patients and the heavy load on limited critical care resources are likely to worsen with the anticipated second wave of the pandemic. Such resources in countries such as ours are severely limited and are likely to place health care services under immense strain. Preparation is thus of paramount importance. Normal seasonal influenza causing severe pneumonia should also be considered. The higher number of influenza-related pneumonia patients identified in 2009 is due to increased vigilance. The clinical patterns and controversies in management of pandemic influenza A (H1N1) 2009 continue to evolve. This has perhaps been best described by Dr Heath Kelly (Head of Epidemiology at Victoria State Infectious Disease Laboratory, Melbourne) and other health care workers as the 'swine flu paradox'. In the ICU it looks worse, but everywhere else it looks better than seasonal influenza.<sup>23</sup>

### Acknowledgements

The assistance of Dr J Steyn, Dr S Jithoo, Dr N Parouk, Ms M Cranzi, Ampath Laboratories and ICU personnel at Port Shepstone Hospital and Margate Private Hospital is acknowledged.

### Conflicts of interest

The authors have no conflicts of interest to declare.

### References

1. World Health Organization. Global Alert and Response (GAR). Pandemic H1N1 (2009) – update 73. Laboratory-confirmed cases of new influenza A (H1N1) as officially reported to WHO by States Parties to the International Health Regulations (2005). Available from [http://www.who.int/csr/don/2009\\_11\\_06/en/index.html](http://www.who.int/csr/don/2009_11_06/en/index.html) (Accessed 07/11/2009).
2. Louie JK, Acosta M, Winter K, et al (for the California Pandemic (H1N1) Working Group). Factors associated with death or hospitalization due to pandemic 2009 influenza A (H1N1) infection in California. *JAMA* 2009;302(17):1896–902.
3. National Institute of Communicable Diseases. Influenza A/H1N1. Situation report as at 17h00 on 10 November 2009. Available from <http://www.nicd.ac.za/outbreaks/h1n1/h1n1.htm> (Accessed 12/11/2009).
4. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Intensive Care Medicine* 2008;34:17–60.
5. World Health Organization. Influenza-like illness in the United States and Mexico. Available from [http://www.who.int/csr/don/2009\\_04\\_24/en/index.html](http://www.who.int/csr/don/2009_04_24/en/index.html) (Accessed 10/10/2009).
6. Centers for Disease Control and Prevention. Hospitalized patients with novel influenza A (H1N1) virus infection – California, April–August 2009. *MMWR Morb Mortal Wkly Rep.* 2009;58:1009–12.
7. National Institute of Communicable Diseases. Communicable diseases communiqué. Available from [http://www.nicd.ac.za/pubs/communique/2009/NICDCommSept09Vol08\\_09.pdf](http://www.nicd.ac.za/pubs/communique/2009/NICDCommSept09Vol08_09.pdf) (Accessed 10/10/2009).
8. Centers for Disease Control and Prevention. Interim recommendations for clinical use of influenza diagnostic tests during the 2009–10 influenza season. Available from [http://www.cdc.gov/h1n1flu/guidance/diagnostic\\_tests.htm](http://www.cdc.gov/h1n1flu/guidance/diagnostic_tests.htm) (Accessed 29/09/2009).
9. Kumar A, Zarychanski R, Pinto R, et al for the Canadian Critical Care Trials Group H1N1 Collaborative. Critically ill patients with 2009 influenza A (H1N1) infection in Canada [published online October 12, 2009]. *JAMA* 2009;302(17):1872–9.
10. Napolitano LM, Park PJ, Sihler KC, et al. Intensive care patients with severe novel influenza A (H1N1) virus infection – Michigan, June 2009. *MMWR Morb Mortal Wkly Rep* 2009;58:749.
11. ANZIC Influenza Investigators. Critical care services and 2009 H1N1 influenza in Australia and New Zealand [published online October 8, 2009]. *N Engl J Med.* Available from <http://content.nejm.org/cgi/content/full/NEJMoa0908481?query=TOC> (Accessed 14/11/2009).
12. Jain S, Aminmoto L, Bramley AM, et al. Hospitalized patients with 2009 H1N1 influenza in the United States, April–June 2009 [published online October 8, 2009]. *N Engl J Med.* <http://content.nejm.org/cgi/content/full/NEJMoa0906695?resourcetype=HWCIT> (Accessed 14/11/2009).
13. Patel M, Dennis A, Flutter C, et al. Pandemic (H1N1) 2009 influenza: experience from the critical care unit. *Anaesthesia* 2009;64:1241–5.
14. Agarwal PP, Cinti S, Kazerooni EA. Chest radiographic and CT findings in novel swine-origin influenza A (H1N1) virus (S-OIV) infection. *AJR* 2009;193:1–6.
15. The Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators. Extracorporeal membrane oxygenation for 2009 influenza A (H1N1) acute respiratory distress syndrome. *JAMA* 2009;302(17):1888–95.
16. Perez-Padilla R, De la Rosa-Zamboni D, Ponce de Leon S. Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. *NEJM* 2009;361(7):680–9.
17. McGeer A, Green KA, Plevneshi A, et al. Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. *Clin Infect Dis.* 2007;45:1568–75.
18. Fiore AE, Shay DK, Broder K, et al. Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP). Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008. *MMWR Recomm Rep.* 2008;57:1–60.
19. Writing Committee of the Second World Health Organization Consultation on Clinical Aspects of Human Infection with Avian Influenza A (H5N1) Virus. Update on avian influenza A (H5N1) virus infection in humans. *N Engl J Med.* 2008;358(3):261–73.
20. Treanor JJ, Hayden FG, Vrooman PS, et al. Efficacy and safety of oral neuramidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. *US Oral Neuramidase Study Group.* *JAMA* 2000;283(8):1057–9.
21. Centers for Disease Control and Prevention. Updated interim recommendations for the use of antiviral medications in the treatment and prevention of influenza for the 2009–2010 season. Available from <http://www.cdc.gov/h1n1flu/recommendations.htm> (Accessed 14/11/2009).
22. World Health Organization. Global Alert and Response (GAR). Vaccines for pandemic influenza H1N1 (2009). Available from [http://www.who.int/csr/disease/swineflu/frequently\\_asked\\_questions/vaccine\\_preparedness/en/index.html](http://www.who.int/csr/disease/swineflu/frequently_asked_questions/vaccine_preparedness/en/index.html) (Accessed 12/11/2009).
23. Gale, J. Swine flu pandemic paradox kills few, overwhelms hospital ICUs. Available from <http://www.bloomberg.com/apps/news?pid=20601081&sid=a9vKlznnyeQ4> (Accessed 02/09/2009).