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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 $\geqslant 20$ ($P = 0.034$), but not with a P_aO_2/F_IO_2 <200 ($P = 0.085$) and a chest radiograph score $\geqslant 12$ ($P = 0.134$).
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 $\geqslant 20$.

Introduction

March 2009 saw the dawn of a much anticipated influenza pandemic.[1–5] 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.[2,3] The outbreak spread rapidly and within 3 months the World Health Organization (WHO) raised the pandemic alert to the highest level (Phase 6).[6]

While the pandemic seemingly decreased 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.[7,8] 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.[2] 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,[11] although a recent epidemiological study from the USA found that 40% of all hospitalized patients on admission had findings consistent with pneumonia on chest radiography.[12] Pregnancy, obesity and diabetes have been identified as potential risk factors for severe disease.[7,11,12] 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.[13]

The emergence of the pandemic in South Africa raised concerns, particularly with regards 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 N09/09/228). 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 haemodynamic 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/m^2], 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_aO_2/F_IO_2 (partial pressure of arterial O_2 to the fraction of inspired 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

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.[19] 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 6 h were documented.

Complications and death

We specifically documented the development of acute respiratory distress syndrome (ARDS),[20] septic shock,[21] acute renal failure[22] and ventilator associated pneumonia,[23] 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 P_aO_2/F_IO_2 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 9.78×10^9/l (range $4.41–39.41 \times 10^9$/l), only four patients had a WCC $> 11 \times 10^9$/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 (>48 h after admission) were diagnosed in 10 cases. The most common secondary isolates

Table 1 Overview of individual baseline characteristics, risk factors, disease severity, management, complications and outcome

No	Age	Sex	Risk factors	Other co-morbidities	APACHE II	P_aO_2/F_IO_2	CXR score	Oseltamivir: SD or DD (days)	Ventilation (mode)	Complications (S=Septic shock)	Length of ICU stay (days)	Outcome
1	25	F	HIV, Pregnant (40/40)		15	112.8	6	SD (5)	NIPPV	—	12	Survived
2	34	F	Pregnant (31/40)		21	176.3	15	SD (5)	SIMV	ARDS, VAP, S, ARF	18	Died
3	43	F	SLE, Renal transplant[a]		23	186.3	24	SD (5)	NIPPV,SIMV	ARDS, S, ARF	5	Died
4	45	F	Type 2 DM		12	268.5	2	SD (5)	SIMV	VAP, S	5	Survived
5	19	F	Pregnant (30/40)		11	127.8	20	SD (5)	SIMV	ARDS, ARF	12	Died
6	36	F	Type 2 DM, Obesity		23	65.4	14	SD (10)	SIMV	ARDS, VAP, S, ARF	17	Died
7	51	M	Type 2 DM, Renal transplant[a]		18	270.8	19	SD (5)	SIMV	—	13	Survived
8	48	F	HIV, Active PTB, RA	Previous PTB, MTX	23	287.5	11	SD (5)	NIPPV, SIMV	ARDS, ARF	13	Died
9	29	F	HIV, Pregnant (27/40)		22	97.7	23	SD (5)	SIMV	ARDS, ARF	7	Died
10	20	F	—		10	298.3	9	SD (5)	NIPPV	—	10	Survived
11	46	F	Type 2 DM, COPD, Obesity	Previous PTB, Smoker	19	75.9	23	DD (4)	SIMV	ARDS, ARF	6	Died
12	39	F	Obesity	Dyslipidaemia	18	268.8	12	SD (5)	NIPPV, SIMV	—	3	Survived
13	69	M	—		20	146.6	16	SD (2); DD (3)	SIMV	VAP, S, ARF	7	Died
14	19	F	Pregnant (38/40)	Smoker	10	103.8	11	DD (5)	SIMV	ARDS, VAP	22	Died
15	68	F	—	Smoker	18	195.4	20	SD (5)	SIMV	ARDS, VAP, ARF	25	Died
16	42	F	Active PTB, Obesity	Idiopathic PAH	30	125.0	16	DD (10)	SIMV	VAP, S, ARF	30	Died
17	43	M	Type 2 DM		17	131.8	20	DD (5)	SIMV	ARDS, VAP, S, ARF	12	Died
18	24	F	Pregnant (27/40)		16	150.9	24	DD (5)	SIMV	ARDS, VAP, ARF	47	Survived
19	50	M	Type 2 DM		19	163.5	16	DD (5)	NIPPV, SIMV	ARDS, VAP, S, ARF	30	Died
Mean	39.5				18.2	171.2	15.8				15.5	
SD	14.8				5.1	74.4	6.2				11.2	

Note: APACHE II, acute physiology and chronic health evaluation (APACHE) II score; P_aO_2/F_IO_2: partial pressure of arterial O_2 to the fraction of inspired O_2; CXR: chest X-ray; SD: single dose (75 mg twice daily); DD: double dose (150 mg twice daily); ICU: intensive care unit; F: female; M: male; HIV: human immunodeficiency virus; SLE: systemic lupus erythematosus; DM: diabetes mellitus; PTB: pulmonary tuberculosis; RA: rheumatoid arthritis; COPD: chronic obstructive pulmonary disease; MTX methotrexate therapy; PAH: pulmonary arterial hypertension; NIPPV: non-invasive positive pressure ventilation; SIMV 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.
[a]Patient on immunosuppression following renal transplant.

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, 5, 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.[24]

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 3 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.

Table 2 Gender and age distribution

Age categories (years)	<20	20–39	40–59	≥60
Female	2	7	5	1
Male	0	0	3	1

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 $P_aO_2/F_IO_2 < 200$ [OR 6.67 (0.87–50.8), $P=0.085$] and a CXR score ⩾12 [OR 5.50 (0.67–44.82), $P=0.134$].

Unlike seasonal influenza, respiratory failure secondary to influenza A (H1N1) more frequently effects relatively young adults.[2] Kumar *et al.*[13] found a mean age of 32.3 years when they reported on the characteristics, treatment and outcomes of

Table 3 Individual risk factors and disease severity indices

	Frequency amongst all cases ($n=19$) (%)	Frequency amongst survivors ($n=6$)	Frequency amongst non-survivors ($n=13$)	OR (95% CI)	*P*-value
HIV infection	3 (15.8)	1	2	1.10 (0.08–15.14)	0.483
Immunosuppressive therapy	3 (15.8)	1	2	1.10 (0.08–15.14)	0.483
Pregnancy	6 (31.6)	2	4	1.13 (0.14–8.88)	0.395
Type 2 diabetes mellitus	6 (31.6)	2	4	1.13 (0.14–8.88)	0.395
Obesity	4 (21.1)	1	3	1.50 (0.12–18.17)	0.443
Active pulmonary TB	2 (10.5)	0	2	NA	0.456
Previous pulmonary TB	2 (10.5)	0	2	NA	0.456
APACHE II score ≥20	7 (36.8)	0	7	NA	0.034
P_aO_2/F_IO_2 <200	12 (63.2)	2	10	6.67 (0.87–50.80)	0.085
CXR score ≥12	14 (73.7)	3	11	5.50 (0.67–44.82)	0.134

CI: confidence intervals; HIV: human immunodeficiency virus; TB: tuberculosis; NA: not applicable; APACHE II: acute physiology and chronic health evaluation (APACHE) II score; P_aO_2/F_IO_2: partial pressure of arterial O_2 to the fraction of inspired O_2; CXR: chest X-ray.

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.[1,7,26] 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.[1,7,25]

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 obesity[7,13,25,27], clearly outnumbered these afflictions. Although three patients were HIV positive, none of these individuals had clinical features of AIDS (as defined by the WHO),[28] and all three had significant other risk factors. The prevalence of HIV infection at present amongst females of childbearing 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 $\geqslant$20 was found to significantly predict mortality. In fact, no patient with a score above 20 survived ($P = 0.034$). Kumar also found previously that a higher APACHE II score predicted mortality.[13] In their study, non-survivors had a mean score of 26 (± 8) as opposed to survivors who had a mean score of 18 (± 8) ($P < 0.01$).[13] All patients fulfilled the criteria for acute lung injury, namely a P_aO_2/F_IO_2 <300.[20] Those with a P_aO_2/F_IO_2 <200 tended to have a higher mortality [OR 6.67 (0.87–50.8), $P = 0.085$]. We also attempted to validate a chest radiograph scoring system described by Opravil *et al.*[18] and observed a tendency towards a higher mortality with a score $\geqslant$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.[3] Louie *et al.*[25] 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,[13] whereas the Australia and New Zealand extracorporeal membrane oxygenation (ANZ ECMO) influenza investigators reported a mortality rate of 21.0%.[7] We observed the highest reported mortality rate to date, even exceeding the rate reported from the original Mexico City outbreak.[3] A potential explication may be a pure selection bias with regards to the population reported, as our ICU offers a referral service to many secondary and districts 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.[7]

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 $\geqslant$20. We could not corroborate HIV infection as a risk factor for respiratory failure secondary to influenza A (N1H1) infection.

Conflict of interest: None declared.

References

1. Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. *N Engl J Med* 2009; **360**:2605–15.
2. Trifonov V, Khiabanian H, Rabadan R. Geographic dependence, surveillance, and origins of the 2009 influenza A (H1N1) virus. *N Engl J Med* 2009; **361**:115–9.
3. Perez-Padilla R, de la Rosa-Zamboni D, Cordova-Villabois JA, Hernandez M, Quiñones-Falconi F, Bautista E, *et al.* Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. *N Engl J Med* 2009; **361**:680–9.

4. CDC. Swine influenza A (H1N1) infection in two children—Southern California, March-April 2009. *MMWR Morb Mortal Wkly Rep* 2009; **58**:400–2.
5. CDC. Outbreak of swine-origin influenza A (H1N1) virus infection—Mexico, March-April 2009. *MMWR Morb Mortal Wkly Rep* 2009; **58**:463–6.
6. World Health Organization report. Global influenza surveillance network: laboratory surveillance and response to pandemic H1N1 2009. *World Health Organization Weekly Epidemiological Record* 2009; **84**:361–72.
7. 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**:1888–95.
8. The ANZIC Influenza Investigators. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. *N Engl J Med* 2009; **361**:1925–34.
9. South African Department of Health. First case of H1N1 confirmed in South Africa. (Accessed 6 September 2009 http://www.doh.gov.za/swineflu/swineflu-f.html).
10. National Institute of Communicable Diseases. Situation update pandemic Influenza A (H1N1), South Africa. September 2009 Communiqué. (Accessed 8 September 2009http://www.nicd.ac.za).
11. Jain S, Kamimoto L, Bramley AM, Schmitz AM, Benoit SR, Louie J, *et al.* Hospitalized patients with 2009 H1N1 influenza in the United States, April–June 2009. *N Engl J Med* 2009; **361**:1935–44.
12. Fraser C, Donnelly CA, Cauchemez S, Hanage WP, Van Kerkhove MD, Hollingsworth TD, *et al.* Pandemic potential of a strain of influenza A (H1N1): early findings. *Science* 2009; **324**:1557–61.
13. Kumar A, Zarychanski R, Pinto R, Cook DJ, Marshall J, Lacroix J, *et al.* Critically Ill patients with 2009 influenza A (H1N1) infection in Canada. *JAMA* 2009; **302**:1872–9.
14. Karim SS, Churchyard GJ, Karim QA, Lawn SD. HIV infection and tuberculosis in South Africa: an urgent need to escalate the public health response. *Lancet* 2009; **374**:921–33.
15. World Health Organization report 2008. Global tuberculosis control- surveillance, planning, financing. Geneva; 2008:19 (Accessed September 12, 2009, at http://www.who.int/tb/publications/global_report/2008/en/index.html).
16. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, *et al.* International variation in the prevalence of COPD (The BOLD study): a population-based prevalence study. *Lancet* 2007; **370**:741–50.
17. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; **13**:818–29.
18. Opravil M, Marincek B, Fuchs WA, Weber R, Speich R, Battegay M, *et al.* Shortcomings of chest radiography in detecting Pneumocystis carinii pneumonia. *J Acquir Immune Defic Syndr* 1994; **7**:39–45.
19. CDC. CDC protocol of realtime RTPCR for influenza A (H1N1). Geneva, World Health Organization, 2009. (Accessed 15 October 2009. http://www.who.int/csr/resources/publications/swineflu/CDCRealtimeRTPCR_SwineH1Assay-2009_20090430.pdf).
20. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, *et al.* The American-European consensus conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; **149**:818–24.
21. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, *et al.* Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest* 1992; **101**:1644–55.
22. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004; **8**:R204–12.
23. Koenig SM, Truwit JD. Ventilator-associated pneumonia: diagnosis, treatment, and prevention. *Clin Microbiol Rev* 2006; **19**:637–57.
24. Fessler HE, Brower RG. Protocols for lung protective ventilation. *Crit Care Med* 2005; **33**:S223–7.
25. Louie JK, Acosta M, Winter K, Jean C, Gavali S, Schechter R, *et al.* Factors associated With death or hospitalization due to pandemic 2009 influenza A(H1N1) infection in California. *JAMA* 2009; **302**:1896–902.
26. Langenegger E, Coetzee A, Jacobs A, le Roux A, Theron G. Severe acute respiratory infection with influenza A (H1N1) during pregnancy. *S Afr Med J* 2009; **99**:713–6.
27. Domínguez-Cherit G, Lapinsky SE, Macias AE, Pinto R, Espinosa-Perez L, de la Torre A, *et al.* Critically Ill patients with 2009 influenza A(H1N1) in Mexico. *JAMA* 2009; **302**:1880–7.
28. World Health Organization. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. Geneva, WHO Press, 2006 (Accessed 5 November 2009. http://www.who.int/hiv/pub/guidelines/hivstaging/en/index.html).
29. UNAIDS. 2008 Report on the Global AIDS Epidemic. Geneva, UNAIDS, 2008:8.