# Intensive care patients with influenza A (H1N1) infection in Iceland 2009

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## ABSTRACT

**Purpose:** To describe the main symptoms and outcome of patients admitted to intensive care units in Iceland due to an infection with influenza A (H1N1) during the outbreak in the autumn/winter of 2009.

**Methods:** Retrospective and prospective medical record analysis of patients with positive RT-PCR for influenza A (H1N1) that were admitted to intensive care units in Iceland.

**Results:** During a six week period in the autumn/winter of 2009, sixteen patients with a confirmed influenza A (H1N1) infection were admitted to the intensive care units in Iceland. Prior to infection most of them were reasonably healthy, but 13 had a history of smoking, obesity or hypertension. Excepting one, they all had fever, cough, dyspnea and bilateral infiltrates on chest X-ray and many developed multiorgan failure. All received anti-viral medication, 12 needed mechanical ventilation and two required extra corporeal membrane oxygenation (ECMO). Mean APACHE II score was 20. No patient died in ICU, but one elderly patient, with many co-morbidities, died a few days after being discharged to a general ward.

**Conclusions:** (1) The incidence of severe influenza A (H1N1) in Iceland leading to intensive care unit admission was high during the epidemic. (2) As well as diverse organ dysfunctions, the majority of admitted patients developed acute respiratory distress syndrome that did not always yield to conventional mechanical ventilation. (3). Twenty-eight day mortality was low. (4) This study is potentially valuable to health authorities in planning for a possible future outbreak of this life-threatening disease.

## Introduction.

The influenza virus is an orthomyxovirus of three types, A, B and C. A and B infect humans. This virus has a great mutating capacity, playing a major role in its epidemiology and pathogenicity. The frequent mutation has two basic causes, one being the error prone RNA polymerase, constantly creating new mutated versions. If the new viruses are different enough to evade an immune response to the prior viruses and are pathogenic enough to cause disease, it can turn into the next annual epidemic. These changes are caused by a molecular alteration in the surface proteins, hemagglutinin (H) and/or neuraminidase (N). Another method for radical genetic alteration is the exchange of 1-8 gene segments with genes from waterfowl or pigs, thus creating a brand new virus. This is thought to be the basis for the pandemic strains of influenza A.[1,2] In that case the new virus carries an H and/or N surface protein which are previously unknown to the human immune system, and no one has any protective antibodies against.

During the last century four global influenza pandemics raged, all caused by the influenza A virus.[3,4] The most virulent was the Spanish Flu (H1A1) of 1918 killing tens of millions. During that pandemic in Iceland approximately 500 people died during six weeks and mortality is thought to have been around 2,6%.[5] Less potent were the Asian Flu of 1957 (H2N2) and the Hong Kong Flu of 1968 (H3N2).[5] The main characteristic of these pandemics was the young age of their victims[6]. The discovery of the so-called Swine Flu in March of 2009 followed an outbreak of serious lung infections in Mexico and in two children in the United States. This is a new strain of the influenza A virus that turned out to have originated in pigs where two pig strains of the virus had combined, both being related to the strain causing the Spanish Flu in 1918[9,10] creating a new virus. It quickly spread across the globe and on 11 June 2009 WHO declared it a world pandemic.

In Iceland the first infection with influenza A (H1N1) was diagnosed on 23 May 2009. Exactly three months later on 23 September the first patients were admitted to hospital. Initially, the epidemic was slow-moving, with the infection in most cases originating abroad. During August and September it gradually picked up the pace, peaked in mid-October, and thereafter gradually subsided[11].

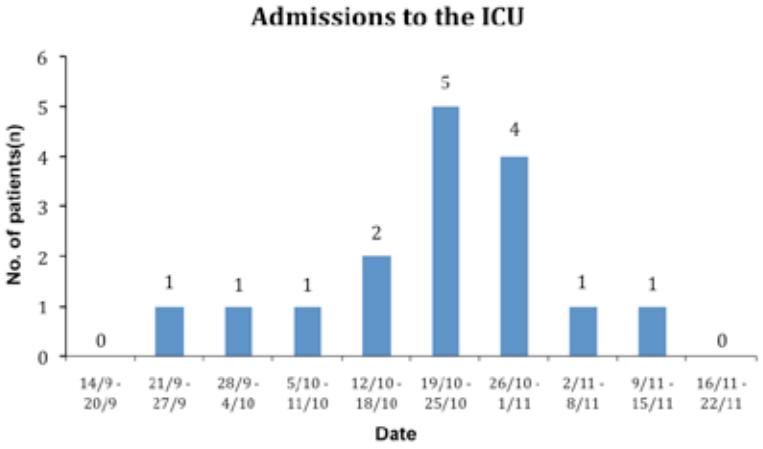


**Figure 1:** *Admissions due to H1N1 influenza to all three intensive care units in Iceland.*

Several scientific papers about the influenza A (H1N1) pandemic have already been published, from Mexico, [12] Australia and New Zealand[13] and Canada[14], to name a few. These papers describe the most severe cases, i.e. those admitted to the ICU units. Their conclusions indicate the predominance of infections occurring in young patients, most developing severe pneumonia and acute respiratory distress syndrome, (ARDS) and that many additionally suffered multi organ failure. Mortality among ICU patients was high, in Mexico 40%,[12], 14% in Australia and New Zealand[13] and 14% in Canada.[14].

The purpose of this study was to review patient data on ICU admissions due to influenza in Iceland during the pandemic in the autumn/winter of 2009 as well as mortality 28 days after diagnosis.

### Material and methods.

We were granted appropriate permissions from the National Bioethics Committee, the Data Protection Authority and the Executive Directors of Medicine at Landspitali University Hospital and the District Hospital in Akureyri. An informed consent was not deemed necessary as there was no intervention in treatment. The study was carried out in all three ICUs in Iceland, two in Landspitali and one in the District Hospital of Akureyri, 25 beds altogether. All patients admitted to any of these units (children and adults) due to confirmed influenza A (H1N1) during the period 23 May until 1 December 2009 were included. The diagnosis of influenza A (H1N1) was confirmed in all cases by reverse transcriptase-polymerase chain reaction, RT-PCR.

The following data was collected from medical records: age, sex, height, weight, hospital, diagnosis, underlying diseases, body temperature, blood pressure, heart rate, respiratory rate, other flu symptoms, oxygen supplementation, arterial blood gases, electrolytes, renal function, serum hemoglobin, other infections during the ICU stay, results from microbial cultures, time from initial symptoms to admission, ICU length of stay, hospital length of stay, cause of death, date of death, secondary disorders (multiorgan failure, septic shock, bleeding) and treatment with anti viral medication (oseltamivir or zanamivir), other antibiotics, nutritional support, mechanical ventilation, vasoactive drugs and renal supportive therapy. To assess severity of illness we used APACHE II score (acute physiology and chronic health score), SAPS II score (simplified acute physiology score), RIFLE score (risk, injury, failure, loss of kidney function, end stage kidney disease score) and SOFA score (sequential organ failure assessment).

In this study the following were considered underlying diseases: a severe coronary heart disease, chronic heart failure, chronic obstructive pulmonary disease, liver failure or kidney failure, cerebrovascular disease, diabetes mellitus, obesity (body mass index >30), malignancy or immunosuppressive therapy. In addition the presence of arterial hypertension, smoking, pregnancy or child birth within 30 days of initial symptoms was recorded.

The primary end-point of the study was death within 28 days of diagnosis, but secondary endpoints were time on mechanical ventilation, ICU- and hospital length of stay.

Statistics and interpretation of data: We used basic and descriptive statistics; mean value and standard distribution for variables with normal distribution and median value and range for other variables.

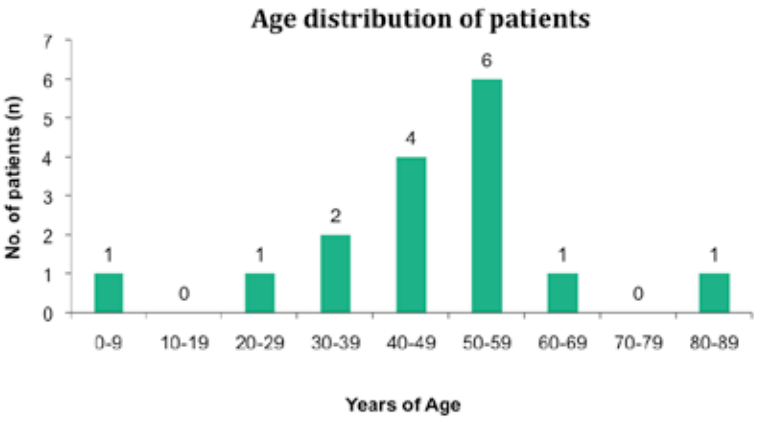


**Figure 2.** *Age distribution of patients admitted to icelandic intensive care units due to H1N1 influenza.*

**Results.**

Sixteen patients were admitted to the intensive care units in Iceland during the period 25 September to 8 November 2009 because of pneumonia and confirmed influenza A (H1N1) infection (fig 1 and table I). On average the patients had been symptomatic for three and a half days prior to hospital admission. Average time to ICU admission was 24 hrs (table I) but six patients went directly to the ICU on admission. Median age was 47.5 years (1-81), but the majority was between 30 and 60 years of age (fig.2). During the study period 170 patients were admitted to hospital in Iceland with symptoms of Swine Flu, half of whom had confirmed influenza A (H1N1). Patients with confirmed influenza needing intensive care were thus about 20% of all patients admitted with confirmed influenza, or 10% of all admissions, a similar percentage to that described in other countries.[12,13] During the study period 8650 individuals with flu-like symptoms or positive RT-PCR visited health care facilities, but the estimated number of nation-wide infections was between 60-100.000[16].

Most of those admitted to ICU were believed to have been in previous good health, but 81% had some underlying risk factors. Most common were smoking, obesity and hypertension (table II). No pregnant woman needed ICU admission due to influenza.

With the exception of one, all the patients (15/16) had fever, cough, dyspnea and bilateral infiltrates on chest X-ray, but one was admitted following convulsions (fig.3). A significant characteristic was a considerable amount of very thick bronchial secretions, increasing as the disease progressed. The majority of patients (11/16) received treatment for circulatory shock; four had acute renal failure or other characteristics of multiorgan failure (table III). Abnormal blood chemistry was common on admission. Creatinine kinase was analysed in 7 patients and was elevated in all (125-2988 U/L).

All the patients received either oseltamir or zanamivir during their hospital stay (table IV). A total of 12 patients needed full mechanical ventilatory support. Non-invasive ventilation was tried in four patients (BiPAP, Bi-level Positive Airway Pressure, Respironics©). In three cases this was insufficient and they were eventually endotracheally intubated and received full ventilatory support. Many patients had pulmonary infiltrates so severe that their lung consolidation on chest X-ray or ultrasound was similar to that of the liver (fig.3). Three were treated in a prone position, one with nitric oxide inhalation and two with extra corporeal membrane oxygenation (ECMO) (table IV). One patient with no prior history of epilepsy suffered convulsions.

The mean APACHE II score was 20, showing the severity of illness (table I) and accordingly an

**Table I.** Patient information, severity scores and length of stay. Data presented as mean (±SD) or median (range).

| Baseline characteristics of patients and time course of illness | value |
|---|---|
| Total number of patients (n) | 16 |
| male | 12 (75%) |
| Age (median) | 48 (1-81) |
| Body mass index (mean) | 31,3 ± 6,48 |
| APACHE II* (mean) | 20 ,0 ± 10,8 |
| SAPS II** (mean) | 33,9 ± 22,4 |
| Time from first symptoms to hospitalization, d (median) | 3,5 (0-11) |
| Time from hospitalization to ICU admission, d (median) | 1 (0-6) |
| ICU length of stay, d (median) | 9,5 (1-57) |
| Hospital length of stay, d (median) | 15,5 (3-72) |

* APACHE II = Acute Physiology and Chronic Health Evaluation II
** SAPS II = Simplified Acute Physiology Score II

**Table II.** Risk factors and underlying diseases.

| Risk factors | n | % |
|---|---|---|
| Ever smoker | 9 | 56% |
| Obesity (≥30 BMI) | 8 | 50% |
| Hypertension | 7 | 44% |
| Using anti-depressant drug | 6 | 38% |
| Heart disease | 3 | 19% |
| Asthma or Chronic pulmonary disease | 3 | 19% |
| Diabetes | 2 | 13% |
| No predisposing factors | 3 | 19% |

**Table III.** Complications

| Complications | n (%) |
|---|---|
| SOFA* score | 6,9 ±3,3 |
| Acute kidney injury according to RIFLE** classification | 4 (25%) |
| Risk | 1 (6,25%) |
| Injury | 0 |
| Failure | 1 (6,25%) |
| Loss | 2 (12,5%) |
| Shock | 11 (69%) |
| Secondary pneumonia | 3 (19%) |
| Laboratory finding | |
| Thrombocytopenia (<150 x $10^9$/L) | 8 (50%) |
| Lymphocytopenia (<1,1 x $10^9$/L) | 13 (81%) |

*SOFA = Sequential Organ Failure Assessment score.
**RIFLE = Risk, Injury, Failure, Loss, and End-stage Kidney (RIFLE) classification.

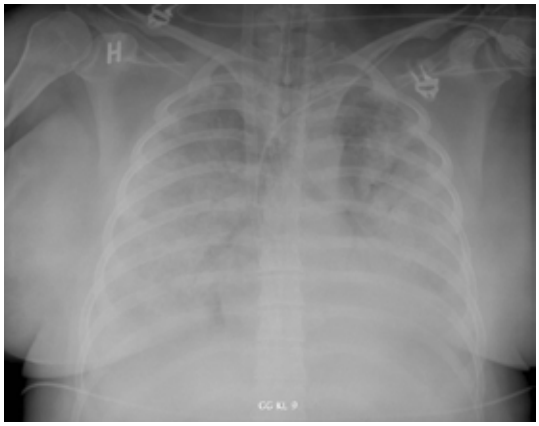

**Figure 3.** *Dense bilateral pulmonary infiltrates in a patient with influenza pneumonitis (a) that progress to severe acute respiratory distress syndrome (b).*

estimated 35% mortality. No patient, however, died in ICU, but one patient in his eighties with multiple severe underlying diseases died on a general ward after discharge from the ICU. At the time of writing all the other patients have been discharged from hospital. The longest stay in ICU was seven weeks; this patient spent four weeks on ECMO and stayed 12 weeks in hospital.

## Discussion

We have now witnessed the first pandemic influenza in 41 years. It first came to notice in Mexico and the United States in March of 2009.

**Table IV.** Management of intensive care patients with H1N1 infection. The usual doseage of oseltamivir was 150mg/day but 4 patients received 300mg/day. Dosage of zanamivir was 20mg/day

| Treatment | No. of patients, n (%) |
|---|---|
| BiPAP ventilation (non-invasive) | 4 (25%) |
| Later required mechanical ventilation % | 3 (75%) |
| Mechanical ventilation (invasive) | 12 (75%) |
| Prone position | 3 (25%) |
| Nitric oxide | 1 (6%) |
| Duration of ventilation, d | 12,5 (1-52) |
| Extracorporeal membrane oxygenation (ECMO) | 2 (12%) |
| Renal replacement techniques | 3 (19%) |
| Vasopressor drugs | 11 (69%) |
| Antiviral treatment | 16 (100%) |
| Oseltamivir | 14 (88%) |
| Zanamivir | 2 (12%) |
| Duration of treatment, d | 10 (5-24) |
| Antibiotics | 16 (100%) |
| Ceftriaxone | 7 (44%) |
| Azithromycin | 5 (31%) |
| Amoxicillin/clavulanic acid | 3 (19%) |
| Meropenem | 3 (19%) |
| Cefuroxime | 2 (13%) |
| Corticosteroids | 7 (44% |

It quickly spread around a large part of the globe despite appearing in the Northern hemisphere at the time of year when the annual flu period was almost over. In Iceland the first case, a rather mild one, turned up on 23 May 2009. The pandemic caused quite severe illness e.g. in Canada and the United States and in the Southern hemisphere when winter closed in. This pandemic clearly highlights how world pandemics may vary. On the whole this one has, despite everything, been relatively mild, but differing, however, from the seasonal epidemics in being harder on the young and previously healthy. Intensive care doctors in this country have hardly ever before seen so many patients in the prime of life with such severe viral pneumonia and certainly never had 16 such patients in intensive care during such a short period of time.

This pandemic was characterised by the high proportion of patients admitted to hospital needing intensive care treatment, or between 10-20%. On the other hand, assuming that 60-100.000 people became ill, 170 hospital admissions is a relatively small proportion, lower, in fact, than can be expected in a seasonal epidemic.[17] Mortality is also lower than in seasonal epidemics when 0.1% is usually expected.[18] What differentiates this pandemic from the annual flu epidemic is that for the most part it was the young and middle-aged that were stricken, not the old afflicted with various other diseases.

In Iceland men became more seriously ill than women, unlike that seen in other studies, e.g. in Canada where the incidence was higher among women.[14] Still, this high incidence in Iceland among men is in accordance with reports from Spain[19]. It is for instance well-known from other serious infections that males are more likely than females to develop septic shock and die as a result.[20,21]

Obesity seems to be a significant risk factor for Icelandic ICU patients with influenza A (H1N1), similar to that in other countries, [12,14] The average BMI was 31. The reason for this increased risk from obesity is not clear, but many factors have been mentioned, such as the commonly worse prognosis of the obese in serious illness and changes in the immune response.[22-24] It is also possible that the smaller lung volume of the obese results in their lungs being more vulnerable to this infection.[24] On the other hand it has been shown that moderate obesity as such is not a risk factor for mortality in intensive care patients. In fact it appears to reduce risk of death in these cases.[25]

In addition to obesity a high proportion of those admitted to ICU had a history of smoking

**Table V.** Comparison of Icelandic data with data from other countries.

| Comparison of studies on H1N1 | | | | | | | |
|---|---|---|---|---|---|---|---|
| Reference (number) | Iceland | Australia and New Zealand (13) | Spain (19) | Canada (14) | Mexico (34) | Mexico (12) | Chíle (35) |
| Total no. of patients in study, n | 16 | 722 | 32 | 168 | 58 | 18 | 75 |
| Age | | | | | | | |
| median | 48 | 40 | 36 | | 44 | 38 | 45 |
| mean | 46 | | | 32 | | | |
| APACHE II (mean) | 20 | | 14 | 20 | 20 | 15 | 14 |
| Male sex | 75% | 48% | 73% | 33% | 47% | 50% | 59% |
| Children | 6% | | | 30% | | 28% | |
| Ratio of hospitalizations requiring ICU admission | 10-20% | | | 19% | 6,5% | | 5% |
| Time course | | | | | | | |
| First symptoms to hospitalization, d (median) | 4 | 4 | 4 | 4 | | 6 | 5 |
| Length of ICU stay, d (median) | 10 | 7 | | 12 | 14* | | |
| Length of hospital stay, d (median) | 16 | 12 | | 12 | | | |
| Ratio of pregnant women | 0% | 9% | 6% | 8% | | | 9 |
| Mechanical ventilation (invasive) | 75% | 65% | 69% | 81% | 83% | 67% | 75% |
| Duration of ventilation, d (median) | 13 | 8 | 10 | 12 | 15* | | |
| Extracorporeal membrane oxygenation (ECMO) | 12% | 12% | 0 | 4% | 0 | | 6% |
| Renal replacement techniques | 19% | | 22% | | | | 9% |
| Mortality | 6% | 14% | 19% | 14% | 40% | 39% | |

and hypertension (table II). What seems to clearly differentiate Icelandic ICU patients from those in other countries is their age. Most were between 30 and 60 years old while incidence in other countries is similar in all age-groups from infancy to about sixty.[14] It is possible that easy access to anti-viral drugs played a shielding role here. The incidence of ICU admissions seems somewhat higher than in other countries that have already published such statistics.[12-14]

Most patients needing hospital admission had been symptomatic for 3-4 days and those admitted to ICU had on average stayed in hospital for 24 hrs prior to transfer to ICU. However, the condition of six patients was serious enough to warrant direct admission to ICU. Most of those needing ICU therapy were seriously ill and many stayed in the ICU for 2-3 weeks, some considerably longer. Most evident was respiratory failure due to widespread pneumonia and acute respiratory distress syndrome, (ARDS) and most of the patients needed extensive respiratory treatment measures. When conventional lung protective ventilation to maintain acceptable oxygenation was not sufficient, additional treatment was used such as prone position, muscle relaxants, nitric oxide inhalation or extra corporeal membrane oxygenation (ECMO). The goal of lung protective ventilation is to avoid high inspiratory pressures (<30 cm $H_2O$), limit the tidal volume (<6 ml/kg), using appropriate end expiratory pressure (PEEP) and avoid the use of more than 80% inspired oxygen. A significant problem in these patients was the production of extensive thick bronchial secretions requiring frequent, even daily, bronchial lavage with bronchoscopy.

Although respiratory failure was the most prominent characteristic in ICU patients many showed signs of dysfunction of other organs such as the gastrointestinal tract tract, acute renal failure, septic shock or coagulopathy.[23,24] Three patients suffering from renal failure needed hemofiltration. One recovered, but in the other two cases the renal damage was chronic (loss class according to RIFLE criteria). Unlike patients with renal failure due to septicaemia the influenza patients seemed in most cases not to have been dehydrated or hypotensive. Abnormalities in renal function are well known in influenza infections and may be caused[26] at least partly by rhabdomyolysis with concomitant elevation of creatinine kinase and serum myoglobin. Another characteristic of this particular pandemic has been considerable muscle and bone aches and high creatinine kinase levels have been described in cases of influenza A.[27, 28] Serum myoglobin was measured in one patient and was elevated and creatinine kinase was measured in seven patients, elevated in all cases.

A number of patients had considerable thrombocytopenia, anemia and low white blood cell count on arrival. These were not investigated further, but were most likely direct consequences of the viral infection and bone marrow suppression. A few patients had increased bleeding tendency, despite normal or nearly normal coagulation tests. Bleeding from needle marks, subcutaneously, in the lungs, from the gastrointestinal- and urinary tract were common.

Symptoms from the gastrointestinal tract were mainly long-standing bowel paralysis, lack of stools for up to 2-3 weeks. There were also gastrointestinal bleedings despite stress ulcer prophylaxis and enteral nutrition, something rarely seen in our usual ICU patients.

No patient died in the ICU, but one elderly patient with many co-morbidities died a few days after discharge from the ICU. In view of the high mean APACHE II score (20) which gives an expected mortality of 35% the patients were severely ill. At the time of writing all the patients have been discharged from hospital.

It is not clear why the incidence of severe symptoms is higher in Iceland than in Australia, New Zealand and Canada. A possible explanation may be a relatively more wide-spread epidemic, but genetic factors may also play a part.

Typically for infectious respiratory diseases this one spreads rapidly as described in previous epidemics both within and between countries. In Mexico, Australia, New Zealand and Canada the period of greatest severity was 8-10 weeks [12-14], similar to our 8 week experience in this study.

All the patients included in this study had classic symptoms and tested positive for influenza A (H1N1). An interesting detail is that some patients' initial throat cultures tested negative for influenza A (H1N1) while subsequent cultures from their bronchial secretions following bronchoscopy tested positive. Of further interest also was how long some patients tested positive despite treatment with anti-viral medication. Because of this a few patients were kept in isolation for up to 14 days and their anti-viral medication continued for 10-14 days.

In this influenza A pandemic intensive care treatment was very costly as many of the patients were so severely ill that all available intensive care resources were required to pull them through. In some cases the expense per patient came to between 10 and 20 million Icelandic kronur. This high cost was however justified by the relatively low median age of the patients and good prognosis. In fact, it appears that most of the patients have recovered completely.

In recent years there has been some discussion concerning possible reluctance of health care personnel to care for infected patients during pandemics.[30-33] No such problems appeared among the ICU personnel of the Landspítali ICU units nor the Akureyri hospital unit. In fact, quite the opposite happened, the staff showed dedication and calmness and worked hard to solve any problems that occurred. Clinical guidelines about isolation were followed, protective clothing worn and any treatment methods avoided that could increase risk of infection. Personnel were vaccinated as soon as vaccine was available. As far as we know, no member of ICU staff fell seriously ill.

Considering ICU admissions, the pandemic seems to have been shorter and harder in this country than in others. ICU admissions peaked in five weeks, whereas in Australia and New Zealand time to peak number of admissions was 7-8 weeks.[13]. Treating 16 patients so critically ill in an intensive care unit in addition to other patients is a complex problem, particularly as their stay was long. Early on it became clear that additional equipment was needed and relevant ministries responded quickly granting money for what was needed e.g. infusion pumps and two additional heart and lung machines used in the ECMO treatment of the most critically ill patients.

At the time of the SARS pandemic our ICU mechanical ventilation equipment was renewed, something which came in useful during the influenza pandemic. This clearly reveals how crucial it is to be far-sighted, continually renewing and improving medical equipment.

The main strength of this study is its inclusion of all patients admitted to all intensive care units in the whole country due to influenza A (H1N1) during the autumn/winter of 2009 making it unique. It is also the first study describing the main characteristics of the illness, which in this country seem rather different from those described elsewhere. The study's main weakness is the small number of patients diminishing the soundness of its conclusions and their fitness for deductions.

## Conclusion

1. During the recent pandemic 16 patients with confirmed influenza A (H1N1) needed intensive care treatment in Iceland.
2. In addition to functional disorders in many organ groups, most patients admitted to ICU in Iceland suffered from severe respiratory failure, in many cases not yielding to conventional lung protective ventilation.

3. Nevertheless, by using all additional means available in Icelandic ICUs the result of treatment in these most severely affected cases has until now been good; the relatively young age of the patients justifying the huge cost of their complex treatment.
4. Our conclusions ought to be of use to health authorities in assessing the need for continuing preventive measures in vaccinating against this life-threatening disease.
5. Our conclusions should also be of use in the treatment of patients infected in subsequent waves of this H1N1 pandemic which might possibly be upon us in a few months time.
6. Our conclusions will be of use in planning for future pandemics.

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