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First wave of the influenza A/H1N1v pandemic in Switzerland

Real threat or just media "hype"?

Christian H. Nickel[a], Frank P. Stephan[b*], Marc Dangel[b], Katharina Blume[a], Rainer Gehrisch[a], Alexis Dumoulin[c], Sarah Tschudin[b], Dagmar I. Keller[a], Hans H. Hirsch[b,c], Andreas F. Widmer[b], Roland Bingisser[a]*

[a] Emergency Department, University Hospital, Basel, Switzerland
[b] Department of Infectious Diseases, Hospital Epidemiology, University Hospital, Basel, Switzerland
[c] Institute for Medical Microbiology, University of Basel, Switzerland

Summary

Aim: To describe the disease burden, clinical pattern and outcome of influenza-related cases presenting to a Swiss Emergency Department (ED), during the first wave of the 2009 pandemic.

Methods: Retrospective analysis of prospectively collected data at the University Hospital of Basel, Switzerland. All patients presenting to the ED with influenza-like symptoms from June 1 to October 23, 2009, were studied. Rate of hospitalisation, demographic characteristics, symptoms, microbiological diagnoses and complications of influenza infection were analysed.

Results: One tenth (808 of 8356 patients) of all non-trauma ED presentations, during the study period, were a result of suspected influenza-related illness. Influenza A/H1N1v infection accounted for 5% of these presentations. Patients aged 50 years or less accounted for 87% of these presentations and for 100% of A/H1N1v infection.

The highest detection rate of A/H1N1v-infection occurred in July, and the highest rate of clinical presentations occurred in August 2009. Underlying medical disease was observed in 14% of all patients. The presence of fever, cough and myalgia was the prime clinical predictor for the presence of A/H1N1v infection. 16% of patients with this triad suffered from A/H1N1v.

Conclusion: Suspected A/H1N1v infection contributed to a considerable health care burden in Switzerland. However, the rate of true positivity was low (5%), hospitalisations rare (5%), and mortality did not occur. Therefore, the first wave of the A/H1N1v pandemic in Switzerland was rather media "hype" than real threat.

Key words: A/H1N1v; comorbidities; PCR testing; risk; Oseltamivir; pandemic

Introduction

In April 2009, a novel influenza A/H1N1 virus was detected in two specimens independently collected in Southern California, and was subsequently recognized to be the cause of an outbreak of respiratory disease in Mexico that had been ongoing since February [1, 2]. This new influenza A strain is a result of genome reassortment with segments found in porcine, avian, and human influenza [3]. It is currently spreading in humans, giving rise to the first pandemic in 40 years, as defined by the criteria of the World Health Organization (WHO). It represents the first influenza A virus pandemic since the emergence of H3N2 (Hong Kong Flu) in 1968. It is believed that the pandemic H1N1/09 virus, such as other influenza A viruses, is transmitted from infected individuals through droplets by coughs or sneezes, creating virus-containing aerosols [4]. Its transmissibility is thought to be equal or higher to that known from seasonal influenza [5]. The incubation time of influenza A has been estimated to range between 1 and 4 days [6]. The novel H1N1/09 influenza A virus has generally been affecting young and middle-aged people, including pregnant women who seem to be at an increased risk for complications from A/H1N1 virus infection, including a higher estimated rate of hospital admission [7]. Furthermore, patients who are immuno-compromised or who have chronic underlying diseases are considered to be at high risk for influenza-related

* equal contribution

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complications. There is recent evidence that an IgG2 deficiency predisposes patients to an unfavourable outcome due to A/H1N1v infection [8]. However, the case fatality rate appears to vary significantly between countries [1, 9]. In a previous study, severe illness resulting from A/H1N1v infection among young, healthy persons was identified. The only variable that was significantly associated with a positive outcome was the receipt of antiviral drugs within 2 days after the onset of illness [10]. In Australia and New Zealand, several Intensive Care Units (ICUs) had to provide mechanical ventilation for 201 patients from June to August 2009 for A/H1N1v–associated respiratory failure. Of those, approximately one third even received extracorporeal membrane oxygenation (ECMO). Mainly young patients suffered from severe hypoxemia and had a mortality rate of 21% at the end of the study period [11].

Media coverage of A/H1N1v has been considerable, particularly when the WHO declared pandemic alert phases 4, 5 and 6. There are significant regional differences in public perceptions of illness severity and risk of A/H1N1v infection [12]. An increase in anxiety can lead to behavioural changes to the pandemic, such as reduced public transport use, purchase of materials for self-protection, and can even result in shortages of medication, apart from a substantial economic impact, deriving from the costs of prevention and treatment, work absenteeism and hospitalisations.

Due to factors, such as extensive media coverage, flu clinics were established in many Emergency Departments (ED), because of a suddenly increasing number of, mainly, younger patients presenting with flu-like symptoms. For reasons regarding prevention of disease transmission, the resources used for these flu clinics were considerable. The aim of the present study was to describe the disease burden, clinical pattern and outcome of influenza-related ED presentations, and finally to discuss the usefulness and cost of widespread polymerase chain reaction (PCR)-testing and flu clinics during the first wave of the 2009 A/H1N1v-pandemic in Northwest Switzerland.

Methods

We prospectively included all patients presenting to our ED with flu-like symptoms from June 1 to October 23, 2009. The study took place at the University Hospital of Basel, a 700-bed primary and tertiary care centre. Over 41 000 patients are seen in the ED every year. Patients with flu-like symptoms presenting to the ED were evaluated in a specialised and separate flu clinic, after triage in the ED according to the Emergency Severity Index (ESI), extended by an additional protocol for A/H1N1v infection [13]: ESI 3 patients received their examination in the ED, ESI 4 patients were evaluated by the flu clinic, and ESI 5 patients were triaged according to the "see-and-treat" pathway, immediately discharged and not further analysed. The flu clinic provided a 7-days-a-week, 2-shift service of previously trained nurses and physicians during the entire study period. Standardised protocols for the identification of patients to be tested with naso-pharyngeal swabs, and for patients to be treated with oseltamivir, were introduced prior to the start of the study period [13]. Briefly, patients meeting the WHO criteria, modified by the Swiss Health Authorities (BAG), for A/H1N1v infection were tested, and patients with risk factors for severe disease, and those with more severe symptoms were treated. It is noteworthy, that the case definition from the WHO changed during the study period. This change was adapted by the BAG and introduced to our ED on August 3, 2009, after personal information, written instructions, and a change in ED protocols [13] were implemented. Specifically, testing criteria before August 3, were fever, respiratory symptoms, and a travel history to high incidence countries (weekly changes by the BAG were followed). Testing criteria were changed on August 3: patients with no fever, no high risk features, no hospitalisation, no severe course of disease, no employment factors (hospital or school employees), no contact to persons with high risk features, no contact to geriatric or child care facilities, and finally no mass incidents (>3 suspected cases from one single institution, such as a school) were not tested after August 3.

Study design

This study was a prospective, observational, monocentric cohort study of patients presenting to the ED of the University Hospital Basel with flu-like symptoms. The study was approved by the local ethics committee (EKBB 311/09).

Data collection

A standardised IT-based form that included demographic data, underlying medical conditions, clinical signs, symptoms, and treatment, was filled out by physicians. Additional retrospective data on hospitalised patients were obtained by the Department of Infectious Diseases. For A/H1N1v testing, a PCR-based diagnostic NAT-testing specific for A/H1N1 was used, as previously described [14, 15]. The robustness of the assay was confirmed by bi-weekly comparison with A/H1N1v sequences available in the NCBI database.

Descriptive analyses were performed to summarise the baseline characteristics of the study population. PCR testing was done according to predefined criteria during the surveillance period. From this approach, we obtained an estimate of disease prevalence and its change over time. The data were transferred into a Microsoft Excel 2007 spreadsheet and validated before being transferred into the statistical analysis package SPSS software, version 15.0 for Windows. Categorical variables were compared using chi-square and Fisher's exact tests as appropriate. A p-value of <0.05 (two-tailed) was considered to indicate statistical significance.

Cost estimates were based on wages for one nurse and one physician of average experience in our hospital, working two daily shifts during the entire study period. Additionally, the insurance reimbursement cost of $ 205 for one A/H1N1v-PCR test was used without considering costs for materials and transport.

Results

From June 1 to October 23, 2009, a total of 808 patients (10% of all non-trauma ED patients) presented to the ED with flu-like symptoms, of which 43 (5%) were tested positive for A/H1N1v. Oseltamivir therapy was administered to 132 patients, of which 119 patients were tested negative.

Table 1

Demographics of ED patients with flu-like symptoms.

All patients, No.	808
Age	
Median age, y (IQR)	32 (24, 42)
Gender	
Females, No. (%)	419 (52)
Travel, No. (%)	207 (26)
Spain/Portugal	64 (8)
USA/Canada	22 (3)
Great Britain	17 (2)
Other countries	104 (13)
Professional contact, No. (%)[$]	163 (20)
Time to presentation, No. (%)	622 (77)
Median time (d), (IQR)	2 (1, 4)
PCR performed, No. (%)	521 (65)
Positive PCR	43 (5)
Initiation of Oseltamivir therapy, No. (%)	132 (16)
Patients at risk for unfavourable outcome, No. (%)	110 (14)
Age ≥65 y*	31 (4)
Chronic pulmonary disease*	24 (3)
Cardiovascular disease*	20 (2)
Diabetes mellitus*	20 (3)
Pregnancy*	17 (2)
Immunosuppression*#	10 (1)
Patients with other medical condition	14 (2)

[$] including health care providers and patients in education system
* several answers may apply
# including solid organ, stem cell and bone marrow transplantation, HIV infection/AIDS and drug dependence

Table 2

Symptoms and vital signs of ED patients with flu-like symptoms.

Patients, total No.	808
History of fever, No. (%)	426 (53)
Cough, No. (%)	389 (48)
Throat pain, No. (%)	432 (54)
Myalgia, No. (%)	400 (50)
Headache, No. (%)	361 (45)
Sneezing, No. (%)	354 (44)
Diarrhea, No. %	83 (10)
Oxygen saturation (%)*, n = 522, Median (IQR)	98 (97, 99)
<95%, No. (%)	21 (4)
Systolic blood pressure (mm Hg)*, n =568, Median (IQR)	125 (117, 140)
<90 mm Hg, No. (%)	2 (<1%)
Heart rate (f/min)*, n = 590, Median (IQR)	87 (76, 98)
>90/min, No. (%)	222 (38)
Temperature (°C)*, n = 620, Median (IQR)	37.8 (37.3, 38.6)
>38 °C, No. (%)	297 (48)
Respiratory rate (f/min)*, n = 327, Median (IQR)	12 (11, 16)
>20/min, No. (%)	29 (9)

* where data available

The demographical data are summarised in table 1. The median age of the patients was 32 years (Interquartile Range [IQR] 24, 34 years). Fifty-two percent of the patients were female. 110 patients (14%) were considered at increased risk for influenza-related complications on the basis of age (≥65 years) or the presence of an underlying medical condition. Among these 110 patients, 31 (4%) were 65 years of age or older; and 35 (4%) had at least two such conditions. Similar to patients with seasonal influenza, asthma and chronic obstructive pulmonary disease (COPD) were the two most common comorbidities in the patients we studied. Among the 110 patients of the high-risk group, 90 patients were tested. Of these, only 4 patients were tested A/H1N1v–positive. Among patients 65 years of age or older, 15 patients had an underlying medical condition. However, no patient older than 50 years was identified to be A/H1N1v-positive. A total of 17 patients (2%) were pregnant (see table 1), three of whom had another underlying medical condition.

The median time from the onset of illness to presentation was 2 days (IQR 2, 4). Table 2 shows symptoms and vital signs of the study population. Symptoms at presentation included a history of fever in 426 (53%), coughing in 389 (48%), throat pain in 432 (54%), myalgia in 400 (50%), headache in 361 (45%), sneezing in 354 (44%), and diarrhoea in 83 (10%) cases.

Vital signs were recorded (table 2). In very few cases, they were markedly out of range. An oxygen saturation rate below 95% was reported in 21 (4%) patients, a systolic blood pressure below 90 mmHg in 2 (1%), a heart rate greater than 90/min in 222 (38%), and a respiratory rate of greater than 20/min in 29 cases. Body temperature was recorded in 620 cases, and was higher than 38 degrees Celsius in 297 (48%) cases.

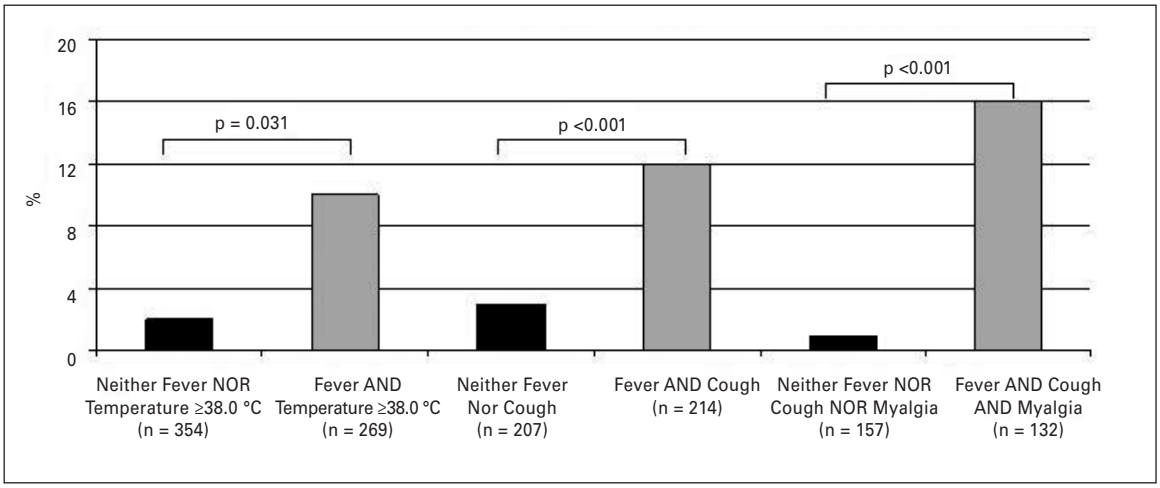
Risk factors (table 3) for positive A/H1N1v-PCR testing were an age of 50 years or younger, male sex, recent travel, initiation of Oseltamivir therapy, a history of fever, a documented body temperature of 38 degrees Celsius or higher, coughing, myalgia and sneezing. The analysis of the combinations of flu-like symptoms is shown in figure 1. If fever, cough and myalgia were reported by the patient, the likelihood of A/H1N1v positivity significantly increased to 16%.

Weekly presented cases were analysed and compared: While the prevalence of A/H1N1v infection was higher in July, the number of presented cases rapidly increased in August (figure 2).

Due to the fundamental change of testing practise triggered by decisions of the WHO, our cohort was separately analysed for the period before this change (June 1 to August 2) and the period after this change (August 3 to October 23).

Figure 1

Symptoms and prediction of A/H1N1v-positivity.



While in the first period the proportion of positive tests was 24%, it declined to 4% in the second period. The test rates were comparable with 56% and 67%.

Forty-two patients (5%) presenting to the ED with ESI 3 were admitted to the hospital. None of these patients were tested positive for A/H1N1v.

In order to compare the cohort of all 808 ED patients with all hospitalised patients under suspicion of A/H1N1v infection, we retrospectively analysed the prevalence of A/H1N1v in the different Departments of the University Hospital Basel during the study period (table 4). The highest prevalence was among the patients tested in the ICU: Two of seven suspected cases (29%) tested positive. The total number of patients tested in all Departments other than the ED was 57. Six patients were tested positive (table 4). Among the 51 patients tested negative, 16 suffered from bacterial pneumonia (of which one Legionella and one Mycoplasma could be identified), seven suffered from bronchitis, asthma, or COPD, seven from abdominal sepsis, five from other infections (of which one HIV and one osteomyelitis), four from cancer, and another four from different immunological causes. Of the remaining eight, five were newborn infants and three were their mothers in fear of an influenza infection.

Table 3

Risk factors for positive A/H1N1v-PCR.

		A/H1N1v-PCR +	*p*-Value
Age (y)	13–50 (n = 699)	43	$p = 0.002$
	51–90 (n = 109)	0	
Gender	Female (n = 419)	16	
	Male (n = 389)	27	$p = 0.034$
Travel	Yes (n = 207)	33	$p < 0.001$
	No (n = 601)	10	
Professional contact	Yes (n = 163)	6	n.s.*
	No (n = 645)	37	
Initiation of Oseltamivir therapy	Yes (n = 132)	13	$p = 0.014$
	No (n = 676)	30	
History of fever	Yes (n = 426)	35	$p < 0.001$
	No (n = 382)	8	
Temperature (n = 620)#	≥38.0 °C (n = 297)	27	$p = 0.031$
	<38.0 °C (n = 323)	16	
Cough	Yes (n = 389)	32	$p < 0.001$
	No (n = 419)	11	
Throat pain	Yes (n = 432)	25	n.s.*
	No (n = 376)	18	
Myalgia	Yes (n = 400)	33	$p < 0.001$
	No (n = 408)	10	
Headache	Yes (n = 361)	24	n.s.*
	No (n = 447)	19	
Sneezing	Yes (n = 354)	27	$p = 0.008$
	No (n = 454)	16	
Diarrhea	Yes (n = 83)	6	n.s.*
	No (n = 725)	37	

* not significant; # where data available

Discussion

We report on a case series of patients with flu-like symptoms during the first wave of the A/H1N1v pandemic in Northwest Switzerland. Consistent to previous reports, our population had a median age of 32 years, possibly due to the fact that younger adults are exposed to the virus first, since they are the most active travelling population. In contrast, media coverage seemed to heighten insecurity about morbidity and mortality of this illness, especially in younger adults. Interestingly, as the prevalence of the disease in patients presenting with flu-like symptoms dropped in late July, the number of presentations sharply increased in August. Therefore, it could be debated that the first wave of the pandemic was rather media-"hype" than real threat, especially when considering that the low prevalence of 5% dropped even lower in August 2009 (figure 2).

As all patients were triaged according to the ESI, and ESI 5 patients were not even triaged to the flu clinic, other viruses must have been responsible for the flu-like symptoms in the vast majority of these patients. A previous, smaller study in Northwestern Switzerland from this summer detected respiratory viruses in 65% of the pa-

Figure 2

Epidemiology of patients presenting to the ED with flu-like symptoms.

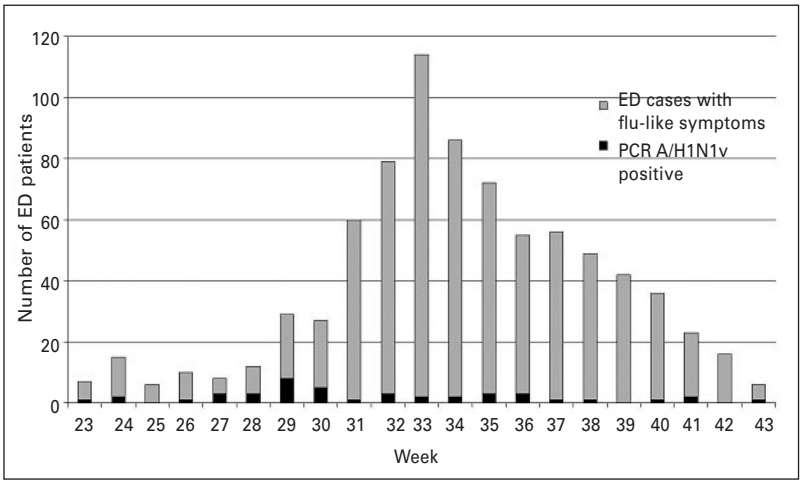


Table 4

A/H1N1v-PCR-Positive Patients in the University Hospital of Basel.

	No.	Age: Median, (IQR)	Female Gender: No. (%)	PCR Performed: No. (%)	A/H1N1v-PCR +: No. (%)
ED*	808	32 (24, 42)	419 (52)	521 (65)	43 (5)
Medical Ward	23	55 (35; 68)	12 (52)	20 (87)	2 (9)
Obstetrics[§]	16	30 (0; 37)	12 (75)	16 (100)	1 (6)
ICU[#]	7	45 (39; 65)	3 (43)	7 (100)	2 (29)
Others	11	32 (26; 56)	5 (46)	9 (82)	1 (9)

* Emergency Department; [#] Intensive Care Unit; [§] including 5 newborn infants

tients, with the three leading pathogens being rhinoviruses in 36%, followed by adenovirus in 6%, and human metapneumovirus in 5% [15]. In the present study, the prevalence of A/H1N1v infection in the high risk group was also very low (4%). Of note, no patient older than 50 years was tested A/H1N1v-positive.

This low prevalence raises two questions: the first addresses PCR testing strategies during the first wave of a pandemic, especially when a media-"hype" is driving hundreds of patients to their family physicians, hospitals, or even EDs. For example, cost-efficiency should be considered; as in our cohort, the cost for PCR testing amounted to $ 2483 per case identified.

In a disease in which, according to the last update of the WHO from October 16, 2009, the overwhelming majority of patients continue to experience an uncomplicated course, and in an environment where the prevalence is only 5%, testing should possibly be restrained to patients with certain presentations, such as the combination of fever, cough, and myalgia (see figure 1). However, there is rising concern on the clinical course and management of a small subgroup that rapidly develops very severe progressive pneumonia, which is often associated with organ failure, or a worsening of underlying pulmonary disease [16]. Of note, two patients with a severe course were not admitted via the flu clinic, but were transferred to our ICU. As of now, one patient is still being treated by extracorporeal membrane oxygenation (ECMO) due to respiratory failure. A second patient has been taken off the ECMO and is in a stable condition. This raises the second question about the usefulness of flu clinics in low-prevalence areas or in decreasing prevalence. The cost of human resources for our flu clinic during the study period per case identified amounted to $ 6900, with the vast majority of infected patients leaving the ED untreated. For the cost of identifying a single A/H1N1v-positive patient in our flu clinic, 188 patients could have been treated with Oseltamivir.

Limitations

Since this study was performed at a single urban tertiary care centre serving Northwestern Switzerland, the generalisability of the results to other communities is limited. One issue was that the range of interpretation of the criteria given by the BAG for testing was rather broad, leading to over 500 tests in a city of 180 000 inhabitants in a period of 144 days. This liberal practice may not be representative for Switzerland and Europe and may lead to a bias in the interpretation of the data.

However, there were no other flu clinics in Northwestern Switzerland (population >500 000), so a concentration of patients with flu-like symptoms can be expected. Secondly, there was no follow-up on the population seen. As the only public hospital in the city of Basel is the University Hospital, it would be highly likely that patients with clinical deteriorations occurring later would have been hospitalized and retested by the same institution that they initially presented to. A possible bias in favour of underreported hospitalisation therefore seems unlikely. Thirdly, as not every patient was PCR-tested, the real prevalence of A/H1N1v could be biased. This possible bias, however, would most probably not have increased the prevalence, but rather decreased, because testing would rather be omitted in less severely symptomatic patients. Finally, we followed the recommendation of the BAG to omit testing in the less severely ill patients after August 3 (except for the random sample of the first five patients each day), possibly explaining the lower prevalence of positive tests for A/H1N1v in the second part of the study period.

Conclusions

At present, it seems that the first wave of A/H1N1v in Switzerland was rather media "hype" than real threat. However, it remains to be observed, whether the virus will mutate into a more virulent or dangerous form, perhaps as early as of now [17]. Thus, careful monitoring of A/H1N1v infection during the upcoming winter season is of critical importance to detect more virulent virus variants. Also, historically, the second wave of an influenza pandemic is usually more severe than the first wave.

In conclusion, our data suggest that testing

could be restricted to patients with more severe symptoms, such as fever, coughing, and myalgia, in order to save resources for later stages of the present pandemic.

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Correspondence:
Roland Bingisser, MD, FCCP
Department of Emergency Medicine
University Hospital Basel
Petersgraben 2
CH-4031 Basel
Switzerland
E-Mail: BingisserR@uhbs.ch

References

1 Neumann G, Noda T, Kawaoka Y. Emergence and pandemic potential of swine-origin H1N1 influenza virus. Nature. 2009; 459(7249):931–9.
2 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(5934):1557–61.
3 Smith GJ, Vijaykrishna D, Bahl J, Lycett SJ, Worobey M, Pybus OG, et al. Origins and evolutionary genomics of the 2009 swine-origin H1N1 influenza A epidemic. Nature. 2009;459(7250): 1122–5.
4 Brankston G, Gitterman L, Hirji Z, Lemieux C, Gardam M. Transmission of influenza A in human beings. Lancet Infect Dis. 2007;7 (4):257–65.
5 Yang Y, Sugimoto JD, Halloran ME, Basta NE, Chao DL, Matrajt L, et al. The Transmissibility and Control of Pandemic Influenza A (H1N1) Virus. Science 2009.
6 Lessler J, Reich NG, Brookmeyer R, Perl TM, Nelson KE, Cummings DA. Incubation periods of acute respiratory viral infections: a systematic review. Lancet Infect Dis. 2009;9 (5):291–300.
7 Jamieson DJ, Honein MA, Rasmussen SA, Williams JL, Swerdlow DL, Biggerstaff MS, et al. H1N1 2009 influenza virus infection during pregnancy in the USA. Lancet. 2009;374 (9688):451–8.
8 Gordon CL, Johnson PDR, Permezel M, Holmes N, Gutteridge G, McDonald C, et al. Association between Severe Swine-origin Influenza A Virus (S-OIV) Infection and Immunoglobulin G2 Subclass Deficiency. Book of Abstracts ICCAC/ 49th Interscience Conference on Antimicrobial Agents and Chemotherapy, September 12–15, 2009, San Francisco, CA. 2009. V-1269a
9 Dawood FS, Jain S, Finelli L, Shaw MW, Lindstrom S, Garten RJ et al. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med. 2009;360(25):2605–15.
10 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. Oct 8. [Epub ahead of print]
11 Davies A, Jones D, Bailey M, Beca J, Bellomo R, Blackwell N, et al. Extracorporeal Membrane Oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome. JAMA. 2009;302(17):1888–95.
12 Goodwin R, Haque S, Neto F, Myers LB. Initial psychological responses to Influenza A, H1N1 ("Swine flu"). BMC Infect Dis. 2009;9:166.
13 http://www.notfallstandards.ch.
14 Richt JA, Lager KM, Clouser DF, Spackman E, Suarez DL, Yoon KJ. Real-time reverse transcription-polymerase chain reaction assays for the detection and differentiation of North American swine influenza viruses. J Vet Diagn Invest. 2004;16(5): 367–73.
15 Dumoulin A, Widmer AF, Hirsch HH. Comprehensive diagnostics for respiratory virus infections after transplantation or after potential exposure to swine flu A/H1N1: what else is out there? Transpl Infect Dis. 2009;11(4):287–9.
16 WHO. http://www.who.int/csr/disease/swineflu/en/.
17 Watson R. Swine flu could come back in more virulent form after summer, European experts say. BMJ. 2009;338:b1792.