ORIGINAL ARTICLE

Early Clinical Experiences With the New Influenza A (H1N1/09)

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SUMMARY

Background: Because of ongoing person-to-person transmission of the disease, the World Health Organization has declared a phase 6 pandemic alert for the new type of influenza A (H1N1/09). This means that the spread of the disease must be closely monitored.

Methods: At the Düsseldorf University Hospital, patients with flu-like symptoms and their contacts have been tested for the new type of influenza A since April 2009.

Results: The first patients that tested positive for H1N1/09 were treated on 20 May 2009. By mid-September, 3372 persons underwent PCR testing of a sample obtained by deep nasal swabbing, and the results were positive in 450 (13.3%). 379 of these 450 infections, or 84.2%, had been contracted abroad. Most patients came to the hospital with flu-like symptoms within three days of becoming ill. An analysis of the first 60 patients revealed a median core temperature of 37.8°C and a mildly elevated C-reactive protein concentration. All patients were treated with oseltamivir. Most of the initially symptomatic patients were asymptomatic again within 3 days; the median duration of treatment was 5 days. The median time to the first negative deep nasal swab was 4 days. No oseltamivir resistance has been found to date in our patient collective.

Conclusion: The clinical manifestations of the new type of influenza were still mild in the patient population that we studied up to mid-September 2009. At that time, the second wave of the pandemic had not yet begun in Germany. At present, however, the number of cases acquired within the country is on the rise.

Key words: influenza, swine flu, epidemiology, diagnosis, oseltamivir

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On 24 April 2009, the World Health Organization (WHO) reported that seven patients in the USA (five in California and two in Texas) and three patients in Mexico had become infected with a new strain of influenza, subsequently designated the new influenza A virus (H1N1/09) (1).

Molecular biological testing revealed that the new influenza A virus (H1N1/09) possesses the following genes: two genes derived from the strain of avian influenza that infected the Eurasian swine population in 1979; three corresponding to classical influenza A (H1N1) from the North American swine population; two representing a triple reassortment (recombination of various gene segments present in the gene pool) from the North American swine population; and one gene homologous to the strain of human influenza A that reached the human population in 1968 with avian influenza (2).

Thus, the new influenza A virus (H1N1/09) contains only a single gene segment (PB1) corresponding to the two seasonal influenza strains (H1N1 and H3N2), namely, a gene segment that entered the H3N2 virus in 1968 from an avian source and has been circulating since then. Its remaining gene segments come from swine influenza viruses of Eurasian and North American origin and from avian influenza viruses of recent decades.

On 5 May 2009, 1124 cases had already been reported worldwide. In view of ongoing human-to-human transmission in multiple regions of the world, the WHO declared a phase 6 pandemic on 11 June 2009. This was the start of the new influenza A virus (H1N1/09) pandemic (3). By this time, nearly 30 000 persons had become ill with the new virus worldwide, and 144 had died in 74 countries. In Germany, the virus was found in more than 160 persons up to 13 June 2009. About half of all cases were in the state of North Rhine–Westphalia.

Physicians in the Department of Gastroenterology, Hepatology, and Infectious Disease and the Department of General Pediatrics at the Düsseldorf University Hospital tested persons with suspected H1N1/09 infection for the presence of the virus. In this article, we report our experience with the new influenza virus during the first wave of the pandemic in the summer of 2009.

Methods

Testing for the new influenza A virus (H1N1/09) began in late April 2009 (calendar week 18). The persons tested included patients with flu-like symptoms and contacts of persons who had become ill because of the new influenza A virus (H1N1/09) and who had been referred to us for testing by the Düsseldorf Health Department after screening at the Düsseldorf Airport and the bus terminal, by medical colleagues in private practice, and by other hospitals. Some of the patients came on their own initiative.

All patients were clinically examined in a treatment area that was separate from the hospital's Emergency Department, and in which anti-infectious precautions for the medical staff were observed in accordance with Directive 609 of the Committee for Biological Agents of the German Federal Institute for Occupational Safety and Health. These precautions included disposable gowns, protective gloves, a tightly fitting surgical mask (FFP-2), and, if needed, an eye shield.

Initially, various types of biological sample, including nasal swabs, throat-rinsing fluid, and pharyngeal swabs, were tested with the polymerase chain reaction (PCR) in parallel with a rapid influenza test. The rapid test used is said to be 94% sensitive and 90% specific for influenza A (4). The PCR tests were performed with the technique recommended by the Robert Koch Institute (5), which can reportedly detect concentrations as low as 384 RNA copies per mL (95% confidence interval, 273 to 876 RNA copies per mL) with 100% specificity (6). The first positive test was on 20 May 2009: a family of three returning from a trip to the USA tested positive for the new influenza A virus (H1N1/09) with the PCR test, but the rapid influenza test was negative. Thereafter, false negative results were repeatedly obtained with rapid influenza tests despite the presence of a verified H1N1 test, and the rapid test was dropped from further testing. The authors found that, among all sample types, the virus was most reliably demonstrated with deep nasal swabs.

At the start of the wave of infection, all patients that tested positive (n = 60) were kept in the hospital under quarantine, in view of the lack of clinical experience at that time and in accordance with the instructions of the health authorities. This is a reasonable strategy to slow the spread of disease at the beginning of a first wave of infection (7). All these patients were treated with oseltamivir until their first nasal swab tested negative, as recommended by the guidelines. Oseltamivir has not been approved for children under one year old; nevertheless, because infants are particularly at risk, the WHO has now published a recommendation that oseltamivir should be used (8). Thus, after meticulous consideration of the benefits and risks, infants that have tested positive for H1N1 infection during a pandemic can be treated with oseltamivir, as long as their parents have given informed consent. Later on in the period of time covered by this article, the number of cases rose markedly, and hospitalization was reserved for severely ill patients

FIGURE 1

Overall depiction of the number of tests performed for the new influenza A virus (H1N1/09) by calendar week

FIGURE 2

Age distribution of persons testing positive for the new influenza A virus (H1N1/09) who had probably contracted the infection abroad (n=379) or in Germany (n=63)

TABLE

Characteristics of patients that tested positive for the new influenza A virus (H1N1/09) according to the place where they contracted the infection (figures as of 20 September 2009)

	Overall	North America	Germany	Japanese community in Düsseldorf	England	Spain	Other
Number	450	25	63	8	18	310	26
Females	216	11	27	4	5	145	16
Males	234	14	23	4	13	165	10
Age (median, years)	19.0	31.0	25.0	13.4	17.1	18.6	21.7
Age, minimum	0.7	1.7	0.7	8.5	11.1	1.0	14.3
Age, maximum	89.4	61.1	89.4	15.2	62.5	58.8	57.9
Age, females (median, years)	18.7	29.1	37.4	11.5	17.3	18.2	20.6
Age, minimum	0.7	1.7	0.7	8.5	13.1	2.0	15.3
Age, maximum	61.1	61.1	52.6	15.2	32.6	58.8	57.9
Age, males (median, years)	19.2	31.0	23.5	13.7	16.8	19.1	20.8
Age, minimum	1.0	18.1	7.1	10.7	11.1	1.0	14.3
Age, maximum	89.4	55.9	89.4	14.6	62.5	49.0	53.5

for whom quarantine at home would have been inadequate medical treatment.

The criteria for suspected infection with the new influenza A virus (H1N1/09) were changed as of 24 August 2009 (calendar week 35): since that date, the suspicion of infection requires that the patient suffer from otherwise unexplained fever ($>38.0^{\circ}\text{C}$) and cough (9). Because of this change in criteria, the clinical manifestations were evaluated only up to 24 August 2009 ($n = 411$). Fewer patients were tested for the new influenza A virus (H1N1/09) afterward.

Results

The number of samples that tested positive and negative for the new influenza A virus (H1N1/09) in each calendar week is shown in *Figure 1*. There is a clearly recognizable, sharp increase in positive samples that began in week 29 and reached a peak in week 31. 3372 tests were performed up to and including week 38; 450 persons had a positive test for the new influenza A virus (H1N1/09) during this time. Aside from the detection of the new influenza A virus (H1N1/09), testing also revealed an influenza A (H3N2) infection in four patients and a seasonal influenza A (H1N1) infection in two patients. Three of the tested patients were also tested for HIV, with their informed consent, on the basis of their history. This testing led to the initial diagnosis of HIV infection in all three cases.

eFigure 1 shows the age of persons testing positive for the new influenza A virus (H1N1/09) and the countries in which they contracted the infection, as a function of time. The graph clearly reflects the fact that nearly all cases in the first few weeks were among

business travelers and tourists returning from North America ($n = 25$). In calendar week 24, there was an outbreak of infection among members of the Japanese community in Düsseldorf. The disease had been transmitted to pupils of the Düsseldorf International School during a class trip; the Düsseldorf Health Department reports that, in all, about 80 members of the Düsseldorf Japanese community were infected. The outbreak was rapidly and successfully controlled within that community. As a result of the quarantine measures that were put into effect, no further cases with a proven connection to this outbreak were diagnosed from calendar week 26 onward.

Later, there were sporadic cases among persons returning from travel to England ($n = 18$) and a small number of imported infections ($n = 26$) from other countries (Bulgaria: $n = 9$, Greece: $n = 3$, Italy: $n = 3$, Malta: $n = 2$, Egypt: $n = 1$, Brazil: $n = 1$, Denmark: $n = 1$, Corsica: $n = 1$, Mexico: $n = 1$, the Netherlands: $n = 3$; Singapore: $n = 1$), as well as 63 infections contracted in Germany, most of which could be traced to contact with persons who had already tested positive for the new influenza A virus (H1N1/09).

The largest group of infected persons consisted of returning travelers from Spain ($n = 310$), most of them adolescents. Most cases were diagnosed during the first half (calendar weeks 28 through 30) of the official summer vacation from school in the State of North Rhine–Westphalia (2 July to 14 August 2009) (see *eFigure 2*). This explains the age distribution of infected persons, as shown in *Figure 2* and *eFigure 3*: there is a peak in the number of cases among 15- to 25-year-olds. The style of travel and other behavioral

patterns specific to this age group are likely to have promoted the rapid dissemination of the new influenza A virus (H1N1/09) within it. Among the cases acquired in Germany, the age distribution was broader. Only two infants (8 and 12 months old) tested positive for the new influenza A virus (H1N1/09); treatment with oseltamivir was discussed with their parents, but we do not know whether such treatment was actually provided. The *Table* shows the age distribution of patients that tested positive as well as the place (Germany or another country) in which the infection was contracted.

Figure 3 provides an overview of the clinical manifestations of persons testing positive for the new influenza A virus (H1N1/09) at the time of their presentation to the authors' hospital. Patient data were evaluated up to and including calendar week 34 ($n = 411$), because the criteria for suspected infection with the new influenza A virus (H1N1/09) were changed on 24 August 2009: after this date, only patients with otherwise unexplained fever ($>38.0^{\circ}\text{C}$) and cough were considered potentially infected with the new virus (9). While some patients manifested nearly the entire clinical spectrum of all of the listed manifestations, there were others who were only mildly affected and then rapidly recovered. Only about one-third of all patients had a temperature above 38.0°C on presentation, but about two-thirds had at least a history of fever. Most patients, including pediatric patients, presented to the hospital within the first three days of illness (*Figure 4*).

At the start of the wave of infection, all persons testing positive for the new influenza A virus (H1N1/09) were admitted to the hospital and kept under quarantine. This was done in accordance with a directive of the health authorities as a strict containment measure to minimize the spread of the disease, whose severity could not yet be judged in this early period (7).

Later on, as the number of cases rapidly increased, hospital admission was reserved for severely ill persons who could not be cared for adequately under quarantine at home. Two of these persons additionally suffered from mycoplasma pneumonia. Detailed clinical data are only available for the hospitalized patients, and an analysis of all the available data would have created a statistical bias toward more severe illness. To circumvent this problem, we restricted the analysis of laboratory parameters to the first 60 patients who tested positive for the new influenza A virus (H1N1/09), because all of these patients were hospitalized regardless of the severity of their illness.

The clinical manifestations in most patients included fever, myalgia, arthralgia, headache, and respiratory symptoms such as cough, runny nose, and sore throat. The median core temperature on admission to the hospital was 37.8°C (range, 36.4 to 39.4°C). The C-reactive protein (CRP) concentration was generally only mildly elevated (median, 1.0 mg/dL; range, <0.3 to 23.9 mg/dL). The normal CRP value is under 0.5 mg/dL.

The measured leukocyte counts were in the low normal range (median, $5.8 \times 1000/\mu\text{L}$; range, 2.7 to $19.6 \times 1000/\mu\text{L}$). Patients with markedly elevated CRP

FIGURE 3

Clinical manifestations on presentation of patients testing positive for the new influenza A virus (H1N1/09) ($n=411$)

FIGURE 4

Information given by patients on presentation about the duration of symptoms to date (e.g., fever, headache, sore throat, and pain in the limbs)

FIGURE 5

Body temperature on admission of the first 60 patients that tested positive for the new influenza A virus (H1N1/09)

C-reactive protein (CRP) on admission (normal value <0.5 mg/dL). Data from the first 60 patients that tested positive for the new influenza A virus (H1N1/09).

concentrations and leukocytosis generally had an additional bacterial focus of infection, e.g., a urinary tract infection or purulent tonsillitis (*Figures 5, 6, and 7*). All patients were treated with oseltamivir. Most of the initially symptomatic patients were free of symptoms within 3 days. The median duration of treatment with oseltamivir was 5 days. Most patients had mild side effects, such as headache and gastrointestinal complaints (nausea, vomiting), which were easily controlled with symptomatic treatment. No serious side effects were observed. The median interval to the first PCR-negative deep nasal swab was 4 days (range, 1 to 10 days). There has not yet been any evidence of oseltamivir resistance.

Discussion

The clinical data reported here indicate that infection with the new influenza A virus (H1N1/09) during the period of investigation (up to mid-September 2009) was a rather mild disease that was usually acquired outside the country. This observation holds for children with the disease as well. The authors' experience with

the new influenza A virus (H1N1/09) is comparable to the data published to date from other countries (10–17, e1–e3). More and more patients, however, are contracting the disease within Germany, and the average age of these patients is higher. If the number of cases continues to rise, it is highly likely that severe disease courses and fatal cases will be seen in Germany as well as in other European countries (18). As of 1 November 2009, 6 deaths in Germany had been causally connected to the new influenza A virus (H1N1/09) (19–24); as of 10 November 2009, this number had risen to 9.

Treatment of the new influenza A virus (H1N1/09) with oseltamivir is relatively well tolerated, but it causes side effects including headache, gastrointestinal complaints (nausea, vomiting), and disturbed concentration, as was recently found in a study of school-children in England (25). In the present study, we found that the median duration of treatment until the first negative nasal swab was four days. According to data presented at this year's Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) (presentations K-1918a and V-1269c), 8 of 100 patients studied were still PCR- and culture-positive for the new influenza A virus (H1N1/09) a week after the beginning of their illness. In our patient collective, there has not yet been any evidence of oseltamivir resistance; 28 cases of oseltamivir resistance have been reported thus far around the world (e4). The infection-control measures undertaken to date have enabled us to withstand the first wave of infection with the new influenza A virus (H1N1/09). The Robert Koch Institute reports a total of 20 068 cases of infection with the new influenza A virus (H1N1/09) in Germany up to 25 September 2009, of which 6073 had been acquired within the country (e5). Studies in the Southern Hemisphere have shown that the new influenza A virus (H1N1/09) is now the main cause of influenza infection, having taken the lead over seasonal influenza A (H1N1), seasonal influenza A (H2N3), and influenza B (e6). Vaccination against the new influenza A virus (H1N1/09) throughout the Federal Republic of Germany began in late October 2009.

In summary, the new influenza A virus (H1N1/09) characteristically caused mild illness up to mid-September 2009. This article describes the beginning of the pandemic. The number of infections acquired within Germany, and the number of resulting deaths, can be expected to rise markedly over its further course. The infection-control measures undertaken to date have enabled us to withstand the first wave of the pandemic with good success. There is no evidence yet of any development of oseltamivir resistance in Germany.

Conflict of interest statement

Dr. Jensen is a member of an advisory board for HIV therapy for the Glaxo-SmithKline company. Prof. Adams is conducting a study on the prevalence of HCV infection with support from Roche. Prof. Häussinger receives support from Roche for research and residency training projects. Dr. Winzer, Dr. Kanig, Dr. Schneitter, PD Dr. Reuter, Dr. Müller-Stöver, Dr. Oh, Prof. Mayatepek, Prof. Hengel, and Prof. Schneitter state that they have no conflict of interest as defined by the guidelines of the International Committee of Medical Journal Editors.

Interval of time to the first PCR-negative nasal swab. Data from the first 60 patients that tested positive for the new influenza A virus (H1N1/09).

KEY MESSAGES

- The new type of influenza A virus (H1N1/09) caused relatively mild disease over the period of time covered by this study, i.e., up to mid-September 2009 (the initial phase of the pandemic).
- Most cases documented in this report were acquired outside Germany.
- The number of cases acquired within the country is rising sharply.
- If the number of cases continues to rise, it seems likely that cases with a complicated course, as well as deaths, will be encountered in Germany as in other European countries.
- There was no evidence of oseltamivir resistance in Germany as of 5 November 2009.

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ORIGINAL ARTICLE

Early Clinical Experiences With the New Influenza A (H1N1/09)

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eFIGURE 1

Epidemiological data of persons that tested positive for the new influenza A virus (H1N1/09). The figure shows the age of each patient plotted against the date of the positive test. The color of each data point indicates the place in which the infection was presumably contracted.

eFIGURE 2

Number of persons testing positive for the new influenza A virus (H1N1/09) per calendar week. A separate plot is shown for each place in which the infection was presumably contracted.

eFIGURE 3

Overall depiction of the age distribution of persons testing positive for the new influenza A virus (H1N1/09) (n=450) with a separate plot for each place in which the infection was presumably contracted