DOI:10.1111/j.1750-2659.2012.00404.x
www.influenzajournal.com

Original Article

Pandemic influenza A(H1)pdm09 in hospitals and intensive care units – results from a new hospital surveillance, Germany 2009/2010

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Accepted 29 May 2012. Published online 9 July 2012.

Objectives The pandemic influenza A(H1)pdm09 (PI) was introduced to Germany in April 2009. The Robert Koch Institute (RKI) implemented a nationwide voluntary hospital sentinel surveillance for to assess the burden and severity of PI.

Setting Three modules were offered: a hospital module collected aggregated data from all hospital units on admissions and fatalities with and without PI; an intensive care module data on admissions, patient-days, and ventilated patient-days with and without PI; and a case-based module retrieved clinical patient data of PI cases. A in-patient with a PCR confirmation was defined as a PI case. Descriptive, trend, uni-, and multivariable analysis were performed.

Results Between week 49/2009 and 13/2010, the hospitals reported 103 (0·07%) PI cases among 159 181 admissions and 59/16 728 (0·35%) PI-related admissions in intensive care units (ICUs). The weekly average incidence decreased in hospitals by 21·5% and in ICUs by 19·2%. In ICUs, 1848/85 559 (2·2%) patient-days were PI-related, 94·8% of those with mechanical ventilation. Case-based data on 43 recovered and 16 fatal PI cases were reported. Among recovered, 61% were admitted to ICUs, 51% were mechanically ventilated, and 16% received extracorporeal membrane oxygenation (ECMO). All fatal cases were admitted to ICUs and received mechanical ventilation, 75% ECMO. Fatal outcome was rather associated with complications than with underlying medical conditions.

Conclusion The surveillance started shortly after the PI peak, which explains the small number of PI cases. The burden of PI disease was low, but higher in ICUs with a high proportion of severe cases needing ventilation and ECMO treatment. A continuous hospital surveillance system could be helpful to measure the burden of severe community-acquired infections.

Keywords Germany, hospital, intensive care unit, pandemic influenza A(H1)pdm09, surveillance system.

Please cite this paper as: Adlhoch *et al.* (2012) Pandemic influenza A(H1)pdm09 in hospitals and intensive care units – results from a new hospital surveillance, Germany 2009/2010. Influenza and Other Respiratory Viruses 6(601), e162–e168.

Introduction

The pandemic influenza A(H1)pdm09 (PI) was imported to Germany in April 2009.[1–3] The number of pandemic influenza infections registered in the mandatory notification system peaked in week 47/2009.[4] Important indicators to assess the severity of an influenza wave are the proportions of influenza-associated patients and fatalities in hospitals.[5] The number and proportion of influenza-related admissions mirror the burden of the disease for the hospitals and the general health system. Cases needing intensive care and disease-associated fatalities are important for the estimation of disease severity and the analysis of especially affected risk groups. In Germany, laboratory-confirmed influenza infections have to be notified by law.[6] Additionally, there are a number of surveillance systems in place to monitor influenza disease focusing on different settings and risk groups. However, a systematic nation-wide sentinel surveillance in hospitals to monitor the mentioned indicators was not established before. With the emergence of more autochthonous cases in September 2009, the RKI decided to initiate the implementation of a new hospital surveillance of in-patients to assess and describe the burden and severity of PI disease in hospitals and intensive care units (ICUs).

Methods

Definitions

A hospitalized patient with a laboratory-confirmed pandemic influenza (by any PCR-based method) was defined as a PI case. A nosocomial PI case was defined as a PI case with influenza-specific disease (influenza-like illness symptoms) onset more than 72 hours after hospitalization.[7] Mechanical ventilation was defined as temporary (minimum 6 hours) or time-independent ventilation. A decision to refer a patient's sample for laboratory testing was made by treating physicians; no specific guidelines on the testing indications or the type of the PCR test to be used were given within the framework of the newly introduced surveillance system.

Data collection

The hospital surveillance of the influenza cases was initiated when the rise of autochthonous cases in Germany in late September was observed. It was conducted between the week 49 in 2009 (30 November) and the week 13 in 2010 (31 March). Detailed information (study protocol, questionnaires, presentations, etc.) was distributed to all hospitals in Germany before the implementation using several platforms, for example the health authorities of the German Federal States, the RKI homepage, and the electronic surveillance platform of the National Reference Center for Nosocomial Infections ''webKess''.[8] Participation was voluntary for the hospitals.

Three surveillance modules were offered for use: a hospital module for the collection of aggregated data from all hospital units; an ICU module to collect aggregated data from the ICUs; and a case-based module to receive detailed patient data. The modules were independent and hospitals were free to take part in all or just one or two of them. The participating hospitals and ICUs collected the data and entered them into ''webKess'' on a weekly basis. Anonymous data on hospital and patient level were accessible for the RKI. The RKI performed the analysis of received data on a weekly basis and published the results on the RKI homepage, in the ''Weekly influenza letter'' and once in the ''Epidemiological Bulletin.''[1,9] Data security and protection were warranted by the ''webKess'' platform.

Aggregated data

In the hospital module, participating hospitals collected the following aggregated data on a weekly basis: the total number of all admissions in the hospital, the number of admissions of PI cases, the number of nosocomial PI cases, the total number of fatalities, and the number of influenza-related fatalities.

Hospitals within the ICU module collected the following aggregated data every week: the total number of all admissions in the ICU, the number of admissions of PI cases, the total number of patient-days, and the number of patient-days of PI cases with or without mechanical ventilation.

Case-based data

In the case-based module, the participating hospitals were asked to collect case-based data of the first three PI cases of every week to minimize the workload for the hospitals during the pandemic. Furthermore, the hospitals collected case-based data of all fatal PI cases between 30 November 2009 and 31 March 2010. Additionally, data of cases with date of discharge or dead between 1 and 30 November 2009 were collected retrospectively. Cases with missing information on the outcome (recovery or death) or date of discharge were excluded from the analysis. Collected information contained demographic data, date of symptom onset, date of hospital admission and discharge, length of hospitalization, ICU stay, use of mechanical ventilation or extracorporeal membrane oxygenation (ECMO), secondary infections, underlying medical conditions, complications, Pandemrix®-vaccination (GlaxoSmithKline Biologicals S.A, Rixensart, Belgium), therapy, and outcome (recovery or death).

Statistical analysis

We analyzed the aggregated and case-based data separately, because the three modules were offered as independent modules. The collection of case-based data from only the first three PI cases per week and all fatal cases was stratified by recovered and fatal cases. Means, medians, and ranges were calculated for continuous variables, proportions for categorical variables. We used the total number of 82 million inhabitants in Germany to calculate the hospitals' estimated catchment area. For each 100 000 inhabitants, an average number of 613 hospital beds was used to determine the percentage of the population covered by the participating hospitals (Source: Federal Statistical Office, Germany).

To quantify an increasing or decreasing trend during the surveillance period for PI admissions in hospitals and ICUs and PI patient-days in ICUs, we applied a mixed Poisson regression model with the total number of admissions as an offset variable, the reporting week as continuous variable, and hospital identification number as a random effect. This model can also be viewed as a two-level model that allows us to account for correlations between the admissions of the same hospital.

For the statistical analysis of the case-based data, we used Wilcoxon rank-sum test, Fisher's exact test, and chi-square test as well as exact logistic regression. Univariable and multivariable analyses using logistic regression were applied to determine risk factors regarding the outcome death. P-values $<0{\cdot}05$ were considered as statistically

significant. We analyzed the data with stata ic 11.1 (College Station, TX, USA).

Results

Aggregated data

In total 29 hospitals participated in the surveillance, 13 of them had up to 299 beds, eight had 300 to 599 beds, and eight had more than 600 beds. Eleven of these hospitals had ICU wards, three had up to 25 beds for intensive care, five between 26 and 100, and three hospitals more than 100 ICU beds. The participating hospitals were located in eight of the 16 German Federal States. One hospital participated only in the ICU module. Within the surveillance period, hospital-based aggregated data were reported weekly from 8–25 hospitals and 9–26 hospitals collected weekly ICU-based aggregated data (Table 1). Small hospitals (<299 beds) were responsible for 44% (165/372) of all reports during the surveillance, and big hospitals (>600 beds) reported 30% of the aggregated data in the hospital module.

For the hospital module, the mean estimated catchment area of the participating hospitals covered the average of 2·3% of the German population, with a mean number of 11 432 beds per week. Overall, the hospitals reported 103 PI-related admissions representing 0·07% of all admissions and four nosocomial PI infections. From the start of the surveillance, the number of admitted PI cases decreased weekly on average by 21·5% using the Poisson model [incidence rate ratio (IRR): 0·79; 95% confidence interval (CI): 0·74–0·83]. The 18 influenza-related fatalities comprised 0·6% of all deaths in the hospitals and did not show any time dependency within the surveillance period. The highest numbers of fatalities were reported in weeks 1/2010 (January) and 9/2010 (March).

In the ICU module, aggregated data of 16 728 admissions including 59 (0·35%) PI cases were provided with the highest number in week 49/2009 (November/December). The proportion of PI-related ICU admissions was fivefold higher than the hospital admissions. We estimated a weekly average decrease of 19·2% (IRR: 0·81; 95% CI: 0·76–0·86) for the admissions of PI cases in the ICUs. In total, 1848 (2·2%) of all patient-days were PI-associated with a weekly decrease of PI-related patient-days on average by 11·3% (IRR: 0·89; 95% CI: 0·88–0·90). PI-related patient-days accounted for a maximum of 5% of all patient-days in the ICUs. Compared to the proportion of PI case admissions, the higher proportion of PI-related patient-days indicated that PI cases stayed longer in the ICUs than non-PI patients. Mechanical ventilation was required in 94·8% (66·7–100%) of all patient-days with PI infection (Table 1).

Case-based data

Case-based data of 67 hospitalized PI cases were collected; of those, eight cases were excluded from analysis. Of the 59 analyzed PI cases, 43 recovered and 16 died (Table 2). The onset of symptoms of five cases was registered after hospital admission (4, 5, 8, 14, and 30 days); hence, they were

Table 1. Aggregated weekly data from hospitals and intensive care unit (ICU) wards participating in the pandemic influenza hospital surveillance, Germany, 2009–2010

	Hospital module	ICU module
Sentinel hospitals (mean; range per week)	20; 8–25	21; 9–26
Beds (mean; range per week)	11432; 3321–14029	773; 307–932
Catchment area* (mean; range per week)	2·28; 0·66–2·79	–
Admissions, total (total sum; range per week)	159181; 1991–11395	16728; 342–1127
Admissions with PI (total sum; range per week)	103; 0–18	59; 0–14;
% of admissions with PI on total (total; range per week)	0·07; 0·0–0·36	0·35; 0·0–1·8
Nosocomial PI infections (total)	4	–
Deaths, total (total sum; range per week)	2835; 46–201	–
Influenza-related fatalities (total sum; range per week)	18; 0–4	–
% Influenza-related fatalities on total (total; range peer week)	0·6; 0·0–2·1	–
Patient-days, total (total sum; range per week)	–	85559; 1435–5767
PI patient-days (total sum; range per week)	–	1848; 5–185
% PI patient-days on total (total; range per week)	–	2·2;0·4–5·2
PI patient-days with mechanical ventilation (total sum; range per week)	–	1752; 5–177
% mechanical ventilation of PI patient-days (total; range per week)	–	94·8; 66·7–100

–: not collected.
*Catchment area: estimation using the mean number of 613 beds per 100 000 inhabitants and 82 002 360 inhabitants in Germany in 2008, Source: Federal Statistical Office, Germany.

Table 2. Descriptive analysis of case-based data collected in the case-based module from participating hospitals in the pandemic influenza hospital surveillance, Germany, 2009–2010

	Recovered PI cases *n* = 43		Fatal PI cases *n* = 16		
	n	%	*n*	%	*P*
Age (years in median; range)	41; 1–81		49; 14–58		0·35
Men	27	63	12	75	0·38
Length of stay in hospital (days in mean; range)	17; 0–69		18; 2–37		0·31
ICU stay	26	61	16	100	0·003
Length of stay in ICU (days in mean; range)	23; 1–58		18; 2–38		0·58
Mechanical ventilation	22	51	16	100	<0·001
ECMO	7	16	12	75	0·008
One or more underlying medical conditions	31	72	14	88	0·31
One or more complications	28	65	16	100	0·006
Pandemrix®-vaccination	1		3		
Oseltamivir therapy	22*	51	12	75	0·21
Start of Oseltamivir therapy after the onset of symptoms (days in mean; range)	4; 0–17*		8; 0–22		0·04
Zanamivir therapy	8	19	9	56	0·009
Start of Zanamivir therapy after the onset of symptoms (days in mean; range)	12; 0–21		15; 3–36		0·7
Antibiotic therapy	28	65	15	94	0·012

*Two patients excluded: treatment 6 and 22 days before the onset of symptoms.

regarded as nosocomial infections. All fatal cases were reported from large hospitals with more than 600 beds.

Recovered PI cases

Overall, the 43 recovered PI cases had a median age of 41 years, 27 (63%) were men (Table 2). An ICU stay was recorded for 26 (61%) cases: of those, 85% were mechanically ventilated and 27% received ECMO treatment. At least one underlying medical condition was specified in 31 (72%) of all recovered patients. Most of them (15 cases) had only one underlying medical condition, nine cases showed two different underlying conditions, three cases were diagnosed with three, each two cases with four or five underlying medical conditions. The most frequently indicated underlying medical condition was chronic respiratory disease (Table 3).

Complications such as pneumonia, acute respiratory distress syndrome (ARDS), or sepsis were reported for 29 (67%) cases. The 15 PI cases without complications stayed on average shorter (6 days; range 1–18 days) in hospital than the 28 cases with at least one complication (24 days; range 0–69 days; $P = 0{\cdot}02$).

In 11 patients out of 25 cases diagnosed with pneumonia, a culture isolated from respiratory material was positive for: *Staphylococcus aureus* (two cases), *Candida albicans* (2), *Proteus* spp. (1), *Streptococcus pyogenes* (A-*Streptococci*) (1), ESBL-*Escherichia coli* (1), and MRSA (1); Three patients had multiple infections of *C. albicans/Enterobacter* spp./MRSA (1), *Aspergillus* spp./*Enterobacter* spp./*S. aureus* (1), and ESBL-*Klebsiella pneumoniae/Pseudomonas aeruginosa/Proteus* spp. (1).

One case had been vaccinated against PI 5 days before onset of symptoms with Pandemrix®. All patients receiving Zanamivir were also treated with Oseltamivir. Oseltamivir treatment was recorded for 22 patients, and Oseltamivir prophylaxis was given to two patients (Table 2).

Fatal PI cases

The median age of the 16 fatal PI cases was 49 years, 12 (75%) were men. Recorded primary causes of death were as follows: PI-related pneumonia (seven cases), sepsis (three cases), ARDS with kidney failure, hypoxic respiratory failure, colon necrosis, lung perforation, retinal, and spleen bleeding. All fatal PI cases stayed in ICUs and received mechanical ventilation, most of them ECMO treatment (Table 2).

An underlying medical condition was present in 14 fatal PI cases (Table 3). Four patients were diagnosed with only one underlying medical condition, eight with two, and each one case with three or four different conditions.

All fatal cases were diagnosed with at least one complication (pneumonia, ARDS or sepsis; Table 3). Pneumonia as single complication was present in one case. Co-occurrence of multiple complications was seen in most cases. Pneumonia was diagnosed in 15 cases, seven patients with pneumonia had bacterial mono-infection diagnosis from

Table 3. Univariable analysis of case-based data from participating hospitals in the pandemic influenza hospital surveillance, Germany, 2009–2010

Underlying medical conditions and clinical complications	Recovered PI cases *n* = 43	Fatal PI cases *n* = 16	Univariable analysis outcome death	
			OR (95% CI)	*P*
Kidney disease	3	4	8·2 (1·4–47·1)	0·016
Diabetes	5	4	2·9 (0·6–13·4)	0·179
Immune suppression	7	4	2·6 (0·6–11·4)	0·194
Obesity*	9	5	2·3 (0·6–8·9)	0·229
Liver disease	1	1	4·4 (0·3–56·9)	0·230
Chronic respiratory disease	12	1	0·5 (0·1–2·0)	0·300
Pregnancy	1	0	2·5 (0–97·5)	0·400
Neurologic disorders	4	2	1·7 (0·3–9·3)	0·539
Health care worker	1	0	1·6 (0·1–22·3)	0·707
Chronic heart disease	9	3	1·2 (0·3–4·8)	0·822
Other	8	3	1·5 (0·5–4·8)	0·456
No underlying medical condition	12	2	2·7 (0·5–13·6)	0·229
Sepsis	5	11	27·2 (5·6–132·0)	<0·001
Acute respiratory distress syndrome	12	13	15·8 (3·1–80·5)	<0·001
Pneumonia	25	15	10·3 (1·3–84·4)	0·004

*Obesity: BMI > 30 kg/m^2.

respiratory material: *Enterococcus* spp. (two cases), *Citrobacter* spp. (1), *E. coli* (1), ESBL-*E. coli* (1), *Proteus* spp. (1), and *Serratia* spp. (1).

Three cases have been vaccinated against PI with Pandemrix®; a vaccination date was recorded for two of them – it was 5 and 33 days before the onset of symptoms. Oseltamivir treatment started earlier after the onset of symptoms than Zanamivir therapy (mean 8 versus 15 days, Table 2).

Analysis of case-based data comparing recovered and fatal cases

The time span from symptom onset to hospital admission among cases with community-acquired infection was longer for recovered than for fatal cases (mean 11 versus 6 days; $P = 0{\cdot}02$). The period from symptom onset until hospital discharge or death was longer for fatal cases (mean 21 versus 28 days; $P = 0{\cdot}03$). Therapy with Oseltamivir was initiated more rapidly following the onset of symptoms in patients who recovered compared to the fatal cases.

In univariable analysis, fatal PI cases were 8·2 (95% CI: 1·4–47·1) times more likely to suffer from kidney disease than recovered PI cases. The occurrence of any complication like sepsis, pneumonia, or ARDS during PI disease progression was significantly associated with a fatal outcome (Table 3). The multivariable analysis included underlying chronic diseases with $P < 0{\cdot}25$ as well as age and sex. The results showed no significant association between any risk factor and death.

Discussion

In the first weeks of the surveillance period, when the pandemic influenza wave was ongoing, <1% and 2% of all admissions to the hospital and ICUs were PI-related, respectively. Based on our previous experience of handling comparable situations, for example outbreaks, we therefore assessed the hospital burden of PI-related disease to be low to moderate and it declined during the surveillance period. The high proportion of severe PI cases in the ICUs needing mechanical ventilation or ECMO treatment suggests a higher impact for the ICUs but did not yield in an overload of the capacities.

Even though only a few German hospitals took part in the surveillance, the participation of big hospitals accounted for an average coverage of 2·3% of the German population. However, the results of this surveillance illustrate the situation of severe PI cases in hospitals and ICUs during the pandemic in Germany. Compared to PI cases notified in the German mandatory reporting system during the surveillance period (30 November 2009–30 March 2010), PI cases of the aggregated data represented 3·8% of all hospitalized PI cases and 11·8% of all PI-associated fatalities; the case-based data accounted for 2·2% of all hospitalized and for 10·5% of all fatal PI cases.[4,10] Although we collected more data on severe cases because of the participation of big hospitals with large ICU wards, the findings are comparable to international data. The mostly affected age group was 40 and 60 year olds, which

corresponds to the findings of other studies.[11,12] The high proportion of PI cases with ICU admission is also in line with other studies.[13–16] In Australia, 65% of ICU PI patients received mechanical ventilation.[17] This is comparable to the findings of the case-based data in this surveillance where 85% of the recovered PI cases in ICUs received mechanical ventilation. In our data, 14 of 16 fatal patients had at least one underlying medical condition. A high proportion of all analyzed PI cases with underlying medical conditions was shown in other countries;[13,18–20] for example in the UK, chronic renal disease was also associated with fatal outcome as shown in our study.[12] Other studies also described that complications like sepsis, pneumonia, or ARDS influenced the length of hospital stay as well as the outcome.[12–14] We failed to identify any risk factors associated with the fatal outcome, possibly due to a relatively low sample size.

The delayed start of antiviral treatment after the onset of symptoms seemed to be a critical factor for fatal outcome, which was also shown in the analysis of the German fatal PI cases reported within the notification system as well as in other studies.[10,11] The mean time span between symptom onset and start of Oseltamivir application differed between recovered and fatal PI cases and was started later than recommended (max. after 48 hours). This underlines that the prevention and early treatment play a key factor in the prevention of complications leading to severe clinical presentation and fatal outcome.

Potential limitations were first, the restriction to patients with PCR confirmation only. The indication for testing laid in the decision of the treating physician and reflects a potential selection bias. Severe cases might have been tested more frequently, which leads to an underestimation of the case numbers with moderate infections and an overestimation of cases with severe infections. Second, the high proportion of big hospitals (>600 beds) participating in this surveillance might have introduced a bias: severe cases tend to be transferred from small to big hospitals because the latter have a higher number of intensive care beds and specialized facilities. This might be reflected in the high number of severe clinical presentations seen in the case-based data. Additionally, the selection of only the first three cases per week might introduce a bias, although no further selection criteria were given and therefore the respective case was chosen randomly. In the German notification system PI fatalities need to have a timely relatedness between influenza infection and death. The adoption of this criterion in this surveillance might have introduced an underestimation of the true number of PI fatalities. The low number of PI cases and the weekly decreasing proportions of hospitalized PI patients during the surveillance period can be explained by the fact that the start of the surveillance in week 49/2009 was shortly after the peak of the PI wave in Germany in week 47/2009 (November). The generated data represented the burden of severe PI cases in the participating hospitals but were not representative for Germany, because of the small number of voluntary participants.

The implementation of a hospital surveillance system for the continuous and timely monitoring of community-acquired infections in Germany could be helpful to measure the yearly burden of severe infections.

Acknowledgements

The authors wish to thank all persons in the participating hospitals and ICUs who supported the surveillance or carried out data collection and reporting. We are grateful to Katharina Alpers, Manuel Dehnert, and other EPIET coordinators for critical reading and helpful comments as well as Matthias an der Heiden for statistical support.

Conflict of interest

The authors declare no conflict of interest.

Financial support

None reported.

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