

Mortality of 2009 pandemic influenza A(H1N1) in Germany

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Citation style for this article:

Wilking H, Buda S, von der Lippe E, Altmann D, Krause G, Eckmanns T, Haas W. Mortality of 2009 pandemic influenza A(H1N1) in Germany. *Euro Surveill.* 2010;15(49):pii=19741. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19741>

Article published on 9 December 2010

The mortality in Germany caused by the 2009 pandemic influenza A(H1N1) seems to have been one of the lowest in Europe. We provide a detailed analysis of all 252 fatal cases of confirmed infection with the pandemic virus notified between 29 April 2009 and 31 March 2010. The overall mortality was 3.1 (95% confidence interval (CI): 2.7 to 3.5) per one million inhabitants. We observed an increase in the case fatality rate of notified cases over time; notified cases aged 60 years or older had the highest case fatality rate (2.16%; 95% CI: 1.61 to 2.83; odds ratio: 5.4; $p < 0.001$; reference group: 35–59 years). The median delay of four days (interquartile range (IQR): 2–7) between symptom onset and antiviral treatment was significantly longer in fatal cases than for non-fatal cases (median: two days (IQR: 1–3; $p < 0.001$). Analysis of the underlying medical conditions of fatal cases, based on the observed frequency of the conditions in the general population, confirms the risk for fatal outcome, which is most notably due to immunosuppression, diabetes and respiratory diseases. Our results suggest that early treatment might have had an impact on overall mortality. Identification of risk groups for targeted intervention to prevent fatalities needs to take into account the distribution of underlying conditions in the population.

Introduction

Based on initial reports from Mexico, the case fatality rate (CFR) of 2009 pandemic influenza A(H1N1) was estimated to be 0.09% (range: 0.07–0.4) and there was considerable uncertainty over what could be expected in other countries [1]. Since March 2009, various countries in Europe and worldwide have experienced one or more pandemic waves, with remarkable differences in the number of reported deaths between countries [2–9]. On 27 April 2009 the first symptomatic cases positive for the pandemic virus were notified in Germany [10]. The first death associated with laboratory-confirmed pandemic influenza was reported on 25 September 2009 from North Rhine-Westphalia, just before the

number of autochthonous cases started to rise exponentially in week 42 [11,12]. Despite more than 200,000 cases of laboratory-confirmed pandemic influenza, the overall mortality in Germany based on the notified cases is one of the lowest in Europe. However, an intriguing number of deaths occurred after the incidence of influenza at the population level had already subsided at the end of 2009.

This article presents a detailed analysis of all 252 notified fatal cases in Germany, from the first detection of pandemic cases in April 2009 up to 31 March 2010. We focused on the course of disease, antiviral treatment and the risk factors involved in order to better understand how the situation in Germany differed from that in other countries and to identify groups at risk of severe disease and fatal outcome, in preparation for potential subsequent waves.

Methods

In Germany, in accordance with the protection against infection act, every laboratory-confirmed case of influenza has to be notified by the laboratory to the local health authority and additional clinical information is actively retrieved from the physician [13]. Additionally, on 2 May 2009, a special legal ordinance for pandemic influenza came into force. German physicians had to notify suspected cases of pandemic influenza to the local health authorities. For this the case ascertainment followed the recommendations given by the professional medical societies [12,14]. Suspected cases were tested for presence of the pandemic virus and only laboratory-confirmed cases or clinical cases with an epidemiological link to a laboratory-confirmed case were transmitted for whole Germany from the local health authorities via the federal states to the Robert Koch Institute in Berlin, Germany. These cases are included in this study.

A fatal case is defined as a person whose death was in temporal relation to an infection with pandemic

influenza confirmed by direct identification tests using standard laboratory methods (polymerase chain reaction (PCR) or viral culture) irrespective of other diagnoses. Laboratory confirmation could be ante- or post-mortem. Proof of a causal relationship between death and laboratory-confirmed influenza was not established. All cases (fatal and non-fatal) are transmitted using the official electronic notifying system in Germany (SurvNet) [15]. The system includes information on age, date of onset of illness, hospitalisation and fatal outcome. It allows the update of information including additions and corrections.

Starting on 17 July 2009, the following additional case-based information was included for all notified and transmitted cases, using a standardised free-text format: antiviral treatment (none; oseltamivir; zanamivir), date of start of treatment, reason for hospitalisation (Influenza; other disease, unknown), pneumonia (yes; no) and underlying chronic medical disease conditions (none; diabetes mellitus; impairment of the cardiovascular system including hypertension; impairment of the respiratory system; obesity defined as a body mass index (BMI) ≥ 30 ; pregnancy; immunosuppression; other specified). Data sets of fatal cases in the central database at the Robert Koch Institute were additionally checked for possible inconsistencies and only validated data sets were included in the analysis. A more detailed description of the special issues concerning German data acquisition during the pandemic has been published recently [12].

Cross-sectional data on the 12-monthly prevalence for chronic disease conditions in Germany was collected via a telephone-based self-reported survey – Gesundheit in Deutschland Aktuell [German Health Update]. For detailed information on the method, see reference 16. The target population was the German-speaking resident population aged 18 years and above. The current survey was conducted from July 2008 to June 2009, covering the start of the pandemic.

The overall mortality for Germany is based on the total population in 2009 reported by the Federal Statistical Office (82,200,000) and we calculated cumulative mortality stratified by age group. For the comparison of mortality between different countries, data provided by the European Centre for Disease Prevention and Control (ECDC) were used [5]. As denominator, estimates for the total populations of European countries were obtained from Eurostat, the United States Census Bureau and Statistics Canada (all 2009 estimates).

All calculations were based on cases with available information as denominator. To calculate the case fatality, we used the number of laboratory-confirmed or epidemiologically confirmed pandemic influenza cases notified in Germany for each week as the denominator. Odds ratios (ORs) were given for the influence of age group on the incidence of fatal outcome in all notified influenza cases. Relative risks (RRs) were calculated as

risk of death in persons with underlying chronic conditions divided by the risk of death in persons without these reported risk factors; sex and 10 age strata were used for adjustment, except for pregnancy. We included the exact binomial 95% confidence intervals (CIs) for proportions and the test on the equality of medians if appropriate. For time spans, the median and interquartile range (IQR) as measure of statistical dispersion were given. Stata was used for calculations.

Results

Disease frequency

In Germany 252 fatal cases associated with laboratory-confirmed 2009 pandemic influenza A(H1N1) were reported, starting with the first case on 25 September 2009. The first increase in the number of fatal cases occurred in week 44 of 2009 and within one month the notification of fatal cases rose to a maximum of 37 (in week 47) (Figure 1). A second peak was observed, with 20 fatal cases per week from week 52 of 2009 to week 1 of 2010. Taking all notified and transmitted cases as the denominator ($n=226,075$), the overall CFR of notified cases (nCFR) was calculated to be 0.11% (95% CI: 0.10 to 0.13). The cumulative mortality by 31 March 2010 was 3.1 (95% CI: 2.7 to 3.5) per million inhabitants. The majority (58%; 95% CI: 52 to 64) of fatal cases was male. In cases aged below 15 years a high proportion (66%; 95% CI: 46 to 82) of fatal cases was female.

During the pandemic wave, the weekly nCFR changed with a period with low values before the calendar week 52 and high thereafter (Figure 1). Taking week 52 as a cut-off date we divided the fatal cases into early ($n=189$) and late cases ($n=63$). In a univariate analysis there was a significant association of the late cases with advanced age (≥ 60 years; $p=0.016$) and being male ($p=0.038$). Underlying medical risk factors ($p=0.17$), interval between the onset of symptoms and death ($p=0.56$) and the time from onset of symptoms to the start of antiviral treatment ($p=0.34$) were not associated with late cases. The multivariate model with the above independent variables failed to achieve statistical significance, but this is probably due to small numbers of cases.

Age distribution

The median age of the fatal cases was 47 years (IQR: 29–57), which is significantly higher than for the non-fatal cases (median: 16 years; IQR: 10–28; $p<0.001$). Generally, all age groups were affected: the age group with the highest mortality was children aged less than 1 year with a cumulative mortality of 4.4 (95% CI: 1.6 to 9.5) per one million children of this age group (Table 1), followed by the age group 35–59 years with 4.2 (95% CI: 3.5 to 5.0) per one million people of this age. However, the 95% CIs and the Kruskal–Wallis rank test ($p=0.41$) indicate that differences in mortality between the age groups was not pronounced and did not achieve statistical significance.

In contrast, the nCFR was highest in elderly people (≥ 60 years), at 2.16%, with an OR of 5.4 (95% CI: 3.9 to 7.6) in comparison with the age group 35–59 years. Schoolchildren (5–14 years) showed the lowest nCFR of 0.03% (95% CI: 0.02 to 0.04) with an OR of 0.07 (95% CI: 0.04 to 0.12).

Course of disease

The median interval between the onset of symptoms and death was 13 days (IQR: 6–22). Symptom onset in adult cases was reported to have occurred more than 14 days before the date of death for 91 of 233 (39%) cases and more than 28 days for 44 of 233 (19%) cases. However, this was observed only for adult cases. In children (<15 years), this interval was significantly

shorter, with a median of six days (IQR: 3–13), than in the other age groups ($p=0.01$).

The majority of notified fatal cases (211 of 233, 90.6%) had been admitted to a hospital. In 125 of 164 (76.2%) cases, the influenza infection was indicated as the cause for hospitalisation. The median length of hospitalisation overall was 12 days (IQR: 4–23); in children (<15 years), the median (five days; IQR: 3–12) was significantly shorter than that in the other age groups ($p=0.04$). Pneumonia was diagnosed in 200 of 220 (90.9%) cases.

Antiviral treatment

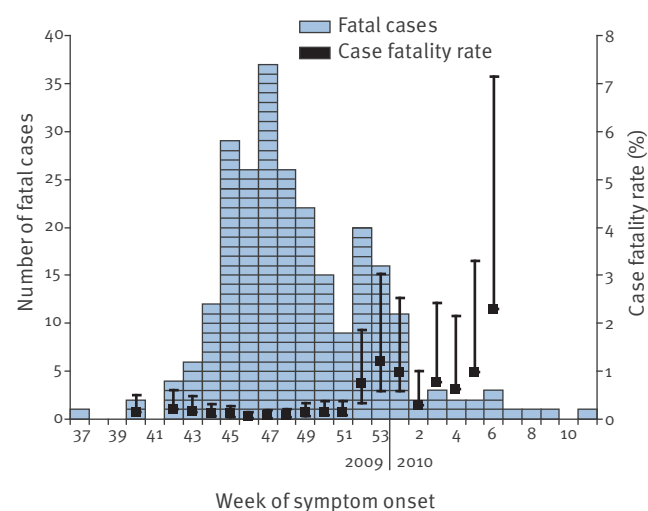
Antiviral therapy was started in more than half of the fatal cases (148 of 230; 64.3%), with oseltamivir in 141 cases and zanamivir in seven cases. In those patients with available data, the median time from onset of symptoms to the start of antiviral treatment was four days (IQR: 2–7) (Figure 2). This interval was significantly longer than that for non-fatal cases (two days; IQR: 1–3; $p<0.001$). In 11 of 15 (73.3%) fatal cases below 15 years of age and in 93 of 125 (74.4%) of the adult fatal cases, treatment was not carried out within 48 hours of the onset of symptoms as recommended [14]. The median time from the start of antiviral treatment to death was five days (IQR: 2–12).

Risk factors

At least one risk factor for severe influenza illness was present in 200 of the 252 fatal cases (79.4%). More than one underlying medical condition was reported for 61 (24.2%) of the patients. For 34 (13.5%) of the fatal cases, no underlying condition regarded as a risk factor was reported. Of these 34 cases, four were aged below 15 years and 13 were female. Half of these cases (16 of 32 with available information) had received antiviral treatment, which was significantly less often than in cases with reported risk factors ($p=0.039$).

FIGURE 1

Notified fatal cases of 2009 pandemic influenza A(H1N1) and case fatality rate, by week of symptom onset in 2009 and 2010, Germany (n=252)



Black bars represent 95% confidence intervals.

TABLE 1

Age distribution of fatal cases of 2009 pandemic influenza A(H1N1), Germany, 29 April 2009 to 31 March 2010 (n=252)

Age group (years)	Number of cases	Percentage male	Cumulative mortality in one million population (95% CI) ^a	Notified case-fatality rate as percentage ^b	Odds ratio (95% CI) ^c	P value
0–1	6	66	4.4 (1.6–9.5)	0.18	0.47 (0.21–1.06)	0.07
2–4	4	50	1.9 (0.5–4.9)	0.05	0.13 (0.05–0.35)	<0.001
5–14	19	21	2.5 (1.5–3.9)	0.03	0.07 (0.04–0.12)	<0.001
15–34	42	57	2.2 (1.6–3.0)	0.07	0.18 (0.13–0.26)	<0.001
35–59	130	62	4.2 (3.5–5.0)	0.40	Reference group	Reference group
≥ 60	51	63	2.4 (1.8–3.2)	2.16	5.4 (3.86–7.56)	<0.001
Total	252	58	3.1 (2.7–3.5)	0.15 0.11^d	–	–

CI: confidence interval.

^a Based on the German population of 2008. The output of the Kruskal–Wallis rank test was $p=0.41$, which indicates that there were no significant differences in cumulative mortality between the age groups.

^b Denominator: all notified and transmitted pandemic influenza cases with detailed information on age, unless otherwise indicated.

^c Odds ratio for the influence of the age group on the incidence of fatal outcome in all pandemic cases. The age group 35–59 years was set as the reference group.

^d Denominator: all notified and transmitted pandemic influenza cases.

Measures of disease frequency and association with underlying medical conditions among adult (≥ 18 years) fatal cases are given in Table 2. The relative risk of death of infected individuals with underlying chronic disease conditions in comparison with that for infected individuals without any reported risk factors was 10.0 (95% CI: 6.7 to 15.0). Immunosuppression was most frequently notified, with a proportion of 26.0% (95% CI: 20.0% to 32.7%) fatal cases. This is in keeping with the fact that immunosuppression was notified in 34 of 138 (24.6%) of the fatal cases with only one underlying

disease as a risk factor. This is by far the highest proportion in this group of patients, indicating a strong association to severe cases of pandemic influenza. However, no population-based survey data are available to calculate the relative risk.

Diseases of the cardiovascular system were reported, with a proportion of 23.5% (95% CI: 16.7 to 29.3), which is in the same range as the sum of self-reported population-based 12-month prevalences of hypertension: 21.4% (95% CI: 20.9 to 22.0), angina pectoris: 1.7% (95% CI: 1.5 to 1.9) and heart failure: 2.4% (95% CI: 2.2 to 2.6). Obesity was notified with a proportion of 19.9% (95% CI: 14.5 to 26.2) and showed a slight association with fatal outcome RR: 1.2 (95% CI: 0.8 to 1.8). Underlying chronic respiratory disease was notified, with a proportion of 19.9% (95% CI: 14.5 to 26.2). This proportion was twice as high as the combined prevalence of asthma: 5.2% (95% CI: 4.9 to 5.5) and chronic (obstructive) bronchitis: 4.5% (95% CI: 4.3 to 4.8) in the German population. Furthermore, diabetes was frequently reported for the fatal cases (17.2%) and doubled the risk of a fatal outcome (RR: 2.3; 95% CI: 1.5 to 3.6).

Two of the fatal cases were pregnant. One presented no other additional risk factor; the other was reported to be obese. Considering all pregnant women of

FIGURE 2

Notified fatal cases of 2009 pandemic influenza A(H1N1) by time between symptom onset and start of antiviral treatment, by age group, Germany, 29 April 2009 to 31 March 2010 (n=140)

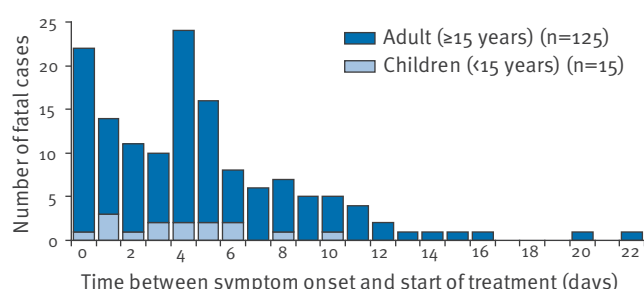


TABLE 2

Underlying medical conditions of the first fatal cases of 2009 pandemic influenza A(H1N1) in adults ≥ 18 years, Germany, 29 April 2009 to 31 March 2010 (n=196)

Underlying conditions ^a	Number of notifications in fatal cases (%)	Proportion in fatal cases as percentage (95% CI)	12-month prevalence as percentage (95% CI) ^b	Relative risk (95% CI) ^c
Yes	169 (100)	86.2 (80.6–90.7)	37.4 (36.8–38.1)	10.0 (6.7–15.0)
Immunosuppression ^d	51 (30)	26.0 (20–32.7)	NA ^e	NA
Cardiovascular disease	46 (27.2)	23.5 (16.7–29.3)	NA	NA
Hypertension	NA	NA	21.4 (20.9–22.0)	NA
Angina pectoris	NA	NA	1.7 (1.5–1.9)	NA
Heart failure	NA	NA	2.4 (2.2–2.6)	NA
Obesity ^f	39 (23.1)	19.9 (14.5–26.2)	13.4 (12.9–13.9)	1.2 (0.8–1.8)
Respiratory disease	39 (23.1)	19.9 (14.5–26.2)	NA	NA
Asthma	NA	NA	5.2 (4.9–5.5)	NA
Chronic bronchitis	NA	NA	4.5 (4.3–4.8)	NA
Diabetes	29 (17.2)	14.8 (10.1–20.6)	5.7 (5.4–6.0)	2.3 (1.5–3.6)
Pregnancy	2 (1.2)	1.0 (0.1–3.6)	NA	2.2 (0.5–9.4) ^g
Other	50 (29.6)	25.5	NA	NA
None	27	13.8 (9.3–19.4)	NA	NA
Total	196	100.0	NA	NA

CI: confidence interval.

^a Multiple answers possible.

^b German Health Update - Telephone Health Survey 2008/2009 (Germany) [16].

^c Age- and sex-adjusted relative risk: risk in the exposed divided by the risk in the unexposed.

^d Including three reported cases with leukaemia.

^e NA= Not available

^f Body mass index (BMI) > 30 or being treated for obesity or international statistical classification of disease (ICD-10) Code E66 obesity (self-reported).

^g Estimate for the relative risk of pregnancy: number of births in 2009: 682,514; population based on the female general population in women of child-bearing age (15–45 years): 16,129,518; corrected for the duration of pregnancy: 267 days and the days of the risk period: 338 days. Relative risk = $2 / 682,514 / 365 \times 267 / 365 \times 338 / 27 / 16,129,518$.

childbearing age in the general population at risk of infection, a rough estimate of the relative risk is possible. Taking 27 April 2009 as the start of the risk period, the relative risk was 2.2 (95% CI: 0.5 to 9.4).

Discussion

Disease frequency

The detailed analysis of notification data and risk factors in the general population of Germany presented in this paper gives insight into what might play a role in the differences between countries. Based on reported cases, the overall mortality in Germany of 3.1 (95% CI: 2.7 to 3.5) per one million inhabitants is lower than that in North America – United States: 7.0 (95% CI: 6.7 to 7.3) and Canada: 13.7 (95% CI: 12.4 to 15.1) and shows more similarities to that in other European countries. However, while in some neighbouring countries such as the Netherlands 3.7 (95% CI: 2.8 to 4.7), Belgium 1.8 (95% CI: 1.1 to 2.8) and Austria: 4.8 (95% CI: 3.4 to 6.5), the reported mortality was in the same range, Spain 6.3 (95% CI: 5.6 to 7.1), the United Kingdom 7.6 (95% CI: 6.9 to 8.3) and France 5.1 (95% CI: 4.6 to 5.7) reported a substantial higher overall mortality than that observed in Germany. Special care should be taken when comparing and interpreting CFRs as the number of cases in the denominator is often difficult to estimate [3]. A right shift of the epidemic curve for fatal cases when compared with the non-fatal cases contributing to an increase in CFR might suggest that the risk of severe outcome changed during the pandemic (Figure 1). We consider it more likely, however, that the affected age groups as well as the probability of laboratory confirmation and reporting might have varied during the course of the pandemic wave.

Age distribution of fatal cases

The population-based cumulative mortality in elderly people (≥ 60 years) was lower than that in adults aged 35 to 59 years. However, this contrasts with the highest nCFR in the age group above 60 years and older. Serology data for pre-existing immunity from the United States, United Kingdom and Finland suggest that this might be the result of lower susceptibility of the oldest age group to an infection with the newly emerged influenza viral genotype, thus causing fewer cases [17–19]. Alternatively, age-dependent contact frequency can become the driving force for an age-related distribution of cases, as studies on contact patterns show that the main contacts occur mostly within the same age strata [20].

Disease course

An intriguing observation has been the difference in the interval between onset of symptoms and death between children younger than 15 years and adults. This might suggest a frequent fulminant course of disease in children, despite the same frequency of hospitalisation and pneumonia in both groups.

Antiviral treatment

In two thirds of the fatal cases, antiviral treatment was started after the 48-hour window following the onset

of symptoms (Figure 2) and in half of the patients only after four days. This shows that some patients may not be treated optimally, according to the recommendations for antiviral treatment [14]. On the other hand, the earlier treatment start reported for non-fatal cases suggests that specific antiviral treatment can reduce untoward outcome. Similar observations have been made in other countries [3,21].

Risk factors

It can be assumed that acute infection interacting with underlying chronic diseases plays a pivotal role in the outcome, as has been described by a number of studies on disease severity of pandemic influenza. Old and newly suggested risk factors, such as obesity, might also impair physiological mechanisms of compensation [22]. This is why it is important to report fatal cases of influenza virus infection even when the contribution of the infection to the detrimental course of disease cannot be quantified precisely.

Most (86.2%) of the reported fatal cases in Germany had an increased likelihood of a severe disease course because of chronic illnesses, including a quarter of patients with more than one underlying disease condition. The proportions of specific underlying conditions vary between different countries or regions, with obesity most frequently observed in California (United States), neurological disorders in England and human immunodeficiency virus (HIV) infections in South Africa [2,3,7]. In our analysis we could show that the relative risk calculated on the basis of population data allows a more precise definition and ranking of risk groups, which might also allow for better comparison between countries. The fifth most frequent underlying disease, showing the highest estimate of risk in our study, was diabetes. As this condition is widely distributed in the European population it has probably been underestimated as a risk factor, so far and further research seems to be warranted. Other studies identified pregnancy as an important risk factor [23,24]. However, due to the small number of deaths in pregnant cases, our results are neither able to confirm nor exclude this for Germany.

Study limitations

Given the high disease awareness during the pandemic in the general population, among medical staff and the reporting authorities, it can be assumed that notified fatal cases with laboratory-confirmed pandemic influenza present a good source of data for the elucidation of underlying medical conditions and other factors related with severe cases of this infection. Nevertheless, artefacts such as underreporting and misclassification of outcome or risk factors are possible and might conceal the real disease burden. Even though case-based information on risk factors was also available for non-fatal cases, analysis showed that reporting was much more complete for patients who died. Therefore, we calculated the relative risk based on a self-reported population survey. In addition, as notification of deaths is mandatory for laboratory-confirmed cases only, such deaths might represent only the tip of the iceberg,

since in the course of the pandemic wave it is estimated that fewer than every tenth case seen by a physician will be laboratory confirmed [25]. Information on other factors for the development of severe illness, such as infectious dose, general immune status (pre-existing immunity), nutrition, access to healthcare or unrecognised comorbidity is lacking and might also influence the risk of death from pandemic influenza.

Acknowledgements

We wish to thank all the physicians who notified their cases to the health authorities and provided adequate information. We also want to thank all German local and regional health authorities, who investigated these cases and submitted the information to the Robert Koch Institute. In addition, we thank the PAE training programme coordinator for her comments on the manuscript and Christina Rafehi for checking and improving the English.

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