Differential use of antivirals for treatment of patients with influenza A(H1N1)pdm09 in Germany

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Background   The World Health Organization recommends early antiviral treatment for patients with severe influenza illness or those at increased risk for severe illness.

Objectives   The aim of this study was to determine the proportion of cases with laboratory-confirmed A(H1N1)pdm09 infection that have been treated with antivirals in Germany during the pandemic (H1N1) 2009 and to investigate factors associated with the use of antivirals.

Methods   We analyzed cases with laboratory-confirmed A(H1N1)pdm09 infection notified to national health authorities in Germany between week 29/2009 and week 17/2010 using multivariable logistic regression. Severity of disease was defined by pneumonia or death.

Results and conclusions   Of 160 804 cases with laboratory-confirmed A(H1N1)pdm09 infection, 22% were treated with antivirals. Cases with severe disease were more likely to be treated with antivirals than cases without severe disease (odds ratio = 1·66; 95% confidence interval: 1·46–1·89). In the group with at least one underlying medical condition, only children aged between 1 and 4 years had significant lower odds for receiving antiviral treatment compared with cases in the age group 15 to 49 years (odds ratio = 0·75; 95% confidence interval: 0·6–0·94). In conclusion, the implementation of international recommendations on use of antivirals differed according to the age of patients in Germany during the pandemic (H1N1) 2009. This indicates that the potential of antivirals to prevent severe influenza might not have been fully exhausted. The reasons leading to the observed differences in patient management need to be investigated.

Keywords   A(H1N1)pdm09, age groups, antiviral agents, H1N1 subtype, influenza A virus.

Introduction

Early antiviral treatment for patients with severe influenza illness or those at increased risk for more severe illness during a pandemic is recommended by the World Health Organization (WHO).[1,2] Even after 48 hours since the onset of influenza illness, treatment with oseltamivir was associated with reduced mortality among hospitalized patients.[3,4]

Infants and young children, in particular those less than 2 years of age, are regarded as a risk group for severe, complicated illness. When the A(H1N1)pdm09 virus emerged in 2009, it caused morbidity and mortality worldwide, especially in children and young adults.[4] In Germany, the majority of cases with laboratory-confirmed A(H1N1)pdm09 infection occurred between October 2009 and February 2010 when population-wide transmission of the virus resulted in a single pandemic wave.[5]

International guidance is available recommending the use of antivirals in case of a pandemic. Based on this, stockpiling of antivirals is arranged for the vast majority of national pandemic preparedness plans.[6–8] However, little is known about the use of antivirals in patients with laboratory-confirmed A(H1N1)pdm09 infection during the influenza A (H1N1) 2009 pandemic at a population level. The studies published to date report on the use of neuraminidase inhibitors (NAIs) in patients with severe influenza (i.e. hospitalized patients and patients admitted to intensive care units).[9–13]

We therefore performed a study using the data from the enhanced surveillance of A(H1N1)pdm09 that was carried out during the influenza A(H1N1) 2009 pandemic on the basis of the International Health Regulations (IHR). The analysis of case-based information including risk factors and antiviral treatment provided a unique opportunity to investigate whether WHO guidelines on antiviral use were followed at the population level.

The aim of this study was to determine the proportion of cases with laboratory-confirmed A(H1N1)pdm09 infection

that have been treated with antivirals in Germany during the pandemic (H1N1) 2009 and to investigate factors associated with the use of antivirals.

Methods

Study population

We identified cases with laboratory-confirmed A(H1N1) pdm09 infection in Germany between week 29/2009 and 17/2010 through the enhanced surveillance of A(H1N1)pdm09 during the influenza A(H1N1) 2009 pandemic. These surveillance data were analyzed. Laboratory methods for confirmation of influenza virus infection comprise molecular identification by polymerase chain reaction, cell culture isolation, rapid antigen tests, and other antigen test systems.

The surveillance of influenza and the enhanced surveillance of A(H1N1)pdm09 based on the IHR in Germany have been described in detail elsewhere.[14] In brief, case-based information on antiviral treatment was collected in a standardized way via the electronic notification system (Surv*Net*) from week 29/2009 (July) to week 17/2010 (April). Data included anonymized information on demographic characteristics, pregnancy, underlying chronic medical conditions (diabetes mellitus, respiratory and/or cardiovascular disease including hypertension, obesity [body mass index, BMI>30], immunosuppression, other underlying chronic medical conditions), vaccination against A(H1N1)pdm09, date of symptom onset, antiviral treatment (oseltamivir, zanamivir), date of start of antiviral therapy, pneumonia, hospitalization, and fatal outcome.

Statistical analyses

Demographic and clinical characteristics of cases were described by absolute and relative frequencies. The following age strata were analyzed: <1 year, 1 to 4 years, 5 to 9 years, 10 to 14 years, 15 to 49 years, and 50 years and older. The time between onset of symptoms and start of antiviral treatment (in days) was described by median, 25% percentile, and 75% percentile (interquartile range; IQR). The Kruskal–Wallis test was applied to assess differences in the time from onset of symptoms to start of antiviral treatment between age groups. The Cochran-Armitage test for trend was used to investigate the association between ordered categorical variables and antiviral treatment. To estimate the strengths of association, we derived odds ratios (OR) and 95% confidence intervals (CI) by univariable and multivariable logistic regression. Investigated possible risk factors comprised gender, age group, having at least one underlying medical condition, pneumonia, and death, where pneumonia or death was used as an indicator for severe disease. Hospitalization was not included in the logistic regression models because of the collinearity to having pneumonia. We chose age group 15 to 49 years as a reference group because

this age group has the lowest risk of developing severe influenza disease. Male gender was chosen as a reference group because of the initial coding of the data. Possible risk factors with a *P*-value <0·2 in the univariable analysis were considered in the multivariable model. The presence of two-way interactions between underlying medical conditions and severe disease, underlying medical conditions and age groups, and severe disease and age groups were investigated in the multivariable model. Interactions with a *P*-value<0·05 were considered in the multivariable model. All reported *P*-values are two-sided and $P < 0.05$ was considered significant. Calculations and statistical analyses were performed using STATA 12.

Results

Case characteristics

Of 160 804 cases with laboratory-confirmed A(H1N1)pdm09 infection notified between week 29/2009 and 17/2010 in Germany, the majority of cases (93·5%) was less than 50 years old (Table 1). 71 354 cases were children less than 15 years old (43·4%). For those with information available, 7·9% of cases were reported to have at least one underlying medical condition, 1·2% of cases had pneumonia, and 0·2% of cases died.

Use of antivirals

Information on antiviral treatment was available for 70% of cases. Of those, 21·6% received antiviral treatment (Table 1). The vast majority of cases received oseltamivir (99·7%), the

Table 1. Demographic and clinical characteristics of notified cases with laboratory-confirmed A(H1N1)pdm09 infection in Germany, week 29/2009 to 17/2010

Characteristic (*n* = 160 804 unless otherwise specified)	No. of cases (%)
Female Gender (*n* = 159 703)	77 845 (48·7)
Male Gender (*n* = 159 703)	81 858 (51·3)
Age group	
< 1 year	1519 (0·9)
1 to 4 years	9226 (5·7)
5 to 9 years	24 871 (15·5)
10 to 14 years	35 738 (22·2)
15 to 49 years	79 000 (49·1)
≥50 years	10 450 (6·5)
Any underlying medical condition* (*n* = 112 714)	8920 (7·9)
Pneumonia (*n* = 115 842)	1389 (1·2)
Hospitalization (*n* = 153 421)	7590 (5·0)
Death (*n* = 157 163)	249 (0·2)
Antiviral treatment (*n* = 109 651)	23 634 (21·6)
Vaccination (*n* = 80 451)	523 (0·7)

*Including pregnancy.

remaining received zanamivir (0·3%). Seventeen per cent of children <15 years of age were treated with antivirals, whereas 25% of cases in the age group 15 to 49 years and 28% of cases ≥50 years of age received antivirals. Among hospitalized cases, 19·5% of children <15 years of age, 35% of cases in the age group 15 to 49 years, and 41% of cases ≥50 years of age received antivirals. There was no difference in the use of antivirals between the vaccinated and non-vaccinated patients. The proportion of cases with underlying medical conditions that received antiviral treatment ranged from 28% (age <1 year) to 45% (age ≥50 years) (Figure 1). Among cases with severe disease, the proportion of cases with antiviral treatment ranged from 20% (age <1 year) to 51% (age ≥50 years) (Figure 2).

Factors associated with antiviral treatment

In the univariable analysis, female influenza cases were less likely to receive antiviral treatment than male cases
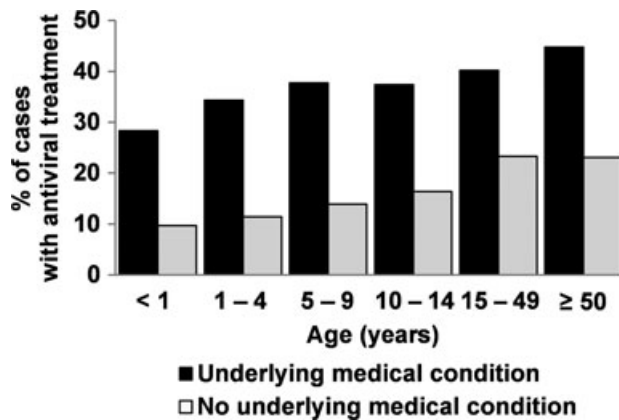

Figure 1. Antiviral treatment in notified cases with laboratory confirmed A(H1N1)pdm09 infection in Germany, week 29/2009 to 17/2010, stratified by underlying medical conditions.
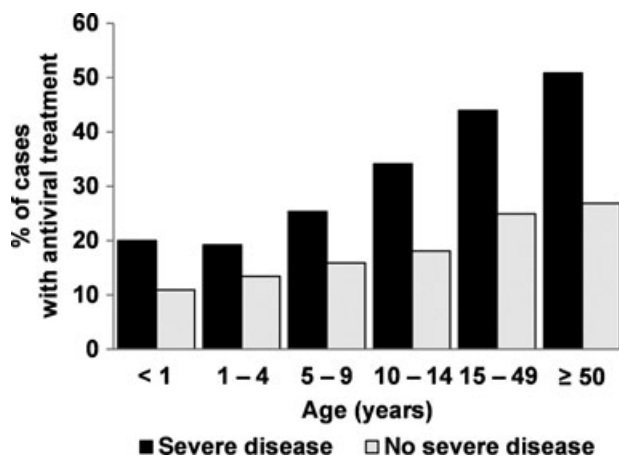

Figure 2. Antiviral treatment in notified cases with laboratory confirmed A(H1N1)pdm09 infection in Germany, week 29/2009 to 17/2010, stratified by severity of disease.

(Table 2). The chance for being treated with antivirals increased with age ($P < 0·001$). Having at least one underlying medical condition resulted in a 2·7 higher odds of being treated with antivirals than having no underlying medical condition. Likewise, cases with severe disease had 2·4 higher odds to receive antiviral treatment than cases without severe disease. All factors from the univariable analysis were included in the multivariable model.

In the multivariable analysis, the odds of antiviral treatment were lower in female patients compared with male patients. Patients with severe disease were more likely to be treated with antivirals than patients without severe disease. In addition, we found significant two-way interactions between having at least one underlying medical condition and age groups ($P < 0·001$), which were included in the final model. In the group with no underlying medical condition, children in the younger age groups remained to be less likely to receive antiviral treatment than cases in the age group 15 to 49 years (reference group) (Table 3). In particular, the odds for being treated with antivirals increased with age. There was no difference in odds between cases over 50 years of age and the reference group. In the group with at least one underlying medical condition, only children with age between 1 and 4 years had significant lower odds for receiving antiviral treatment compared with the reference group. Cases over 50 years of age had slightly higher odds to be treated with antivirals than the reference group. Exclusion of children <1 year of age from the model did not change the results.

Timeliness of antiviral treatment

Overall, median start of antiviral treatment was 1 day after onset of symptoms (IQR: 1 to 2 days). There was no difference between male and female cases and between cases

Table 2. Antiviral treatment of notified cases with laboratory-confirmed A(H1N1)pdm09 infection in Germany, week 29/2009 to 17/2010, univariable analysis

Factor	Category	OR (95% CI)	P-value
Gender	Male	Reference	
	Female	0·93 (0·91–0·96)	<0·001
Age group	<1 year	0·37 (0·31–0·45)	<0·001
	1 to 4 years	0·47 (0·43–0·50)	<0·001
	5 to 9 years	0·57 (0·54–0·59)	<0·001
	10 to 14 years	0·66 (0·64–0·69)	<0·001
	15 to 49 years	Reference	
	≥50 years	1·15 (1·09–1·22)	<0·001
At least one underlying medical condition	No	Reference	
	Yes	2·73 (2·60–2·86)	<0·001
Severe disease (pneumonia or death)	No	Reference	
	Yes	2·40 (2·14–2·69)	<0·001

Table 3. Antiviral treatment of notified cases with laboratory-confirmed A(H1N1)pdm09 infection in Germany, week 29/2009 to 17/2010, multivariable analysis

Factor	Category	Adjusted OR (95% CI)	*P*-value
Gender	Male	Reference	
	Female	0·91 (0·88–0·93)	<0·001
Severe disease (pneumonia or death)	No	Reference	
	Yes	1·66 (1·46–1·89)	<0·001
At least one underlying medical condition			
No			
Age group	< 1 year	0·35 (0·28–0·44)	<0·001
	1 to 4 years	0·42 (0·38–0·45)	<0·001
	5 to 9 years	0·53 (0·50–0·56)	<0·001
	10 to 14 years	0·64 (0·62–0·67)	<0·001
	15 to 49 years	Reference	
	≥50 years	0·99 (0·92–1·05)	0·701
Yes			
Age group	<1 year	0·58 (0·33–1·02)	0·060
	1 to 4 years	0·75 (0·60–0·94)	0·012
	5 to 9 years	0·90 (0·78–1·03)	0·118
	10 to 14 years	0·88 (0·78–1·00)	0·052
	15 to 49 years	Reference	
	≥50 years	1·15 (1·02–1·31)	0·028

with and cases without underlying medical conditions (IQR: 1 to 2 days). Median start of antiviral treatment was later in cases with severe disease (2 days; IQR: 1 to 5 days) than in cases without severe disease (1 day; IQR: 1 to 2 days, $P < 0·0001$). The median time elapsed between onset of symptoms and start of antiviral therapy was 1 day across all age groups, the IQR ranging from <1 to 2 days in children <1 year to 1 to 3 days in patients ≥50 years ($P < 0·0001$).

Discussion

Our study revealed that NAIs were used less frequently in children with laboratory-confirmed A(H1N1)pdm09 infection than in adults in Germany during the pandemic (H1N1) 2009. Of those children who were hospitalized, 19·5% were treated with antivirals. Furthermore, less than 50% of the patients with underlying medical conditions or severe disease received antiviral treatment. Almost exclusively oseltamivir was used.

In contrast, over 70% of hospitalized patients in the US and Austria were treated with antivirals[10,13] Population-based surveillance data on influenza-related hospitalizations in the US showed that 77% of children and 82% of adults received antiviral treatment during the pandemic (H1N1) 2009 and that these numbers were lower in the post-pandemic season 2010/11 (children 56% and adults 77%).[9]

Patients admitted to intensive care units were more frequently treated with antivirals: 91% in Canada and 90% in California.[11,12] In comparison, a nationwide hospital-based study in Germany showed that only 62% of children <15 years admitted to pediatric intensive care units were treated with oseltamivir both during the pandemic (H1N1) 2009 and the post-pandemic season 2010/11.[15,16]

Randomized clinical trials and observational studies showed the benefit of antiviral treatment such as a reduced risk of lower respiratory tract complications requiring antibiotic treatment, a reduction in the median duration of illness, and a reduction in mortality.[17–20] Based on these finding, international and national guidelines recommend the use of antivirals to prevent severe illness.[1,21–24] In May 2009, the European Medicines Agency approved the use of Tamiflu® (F. Hoffmann-La Roche) for children below 1 year of age under medical supervision during the influenza A (H1N1) 2009 pandemic.[25] The decision was based on a retrospective study showing that the efficacy and safety in children less than 1 year of age was similar to that in older children.[26] The national recommendations by the German Society for Paediatric Infectious Diseases also included the treatment of children less than 1 year of age.[21] In December 2012, the U.S. Food and Drug Administration (FDA) expanded its approval for Tamiflu® to treat children 2 weeks of age and older who have been symptomatic for no longer than 2 days.[27]

From the national surveillance data, we cannot deduce why NAIs were used less often in Germany than in other countries during the influenza A(H1N1) 2009 pandemic, in particular in children. One reason may be the critical discussions about the efficacy and safety of antivirals, particularly of oseltamivir, in the media before and during the influenza A(H1N1) 2009 pandemic.[28–30] Additionally, since 2008, the product label of Tamiflu® includes information that neuropsychiatric events had been observed in children and that the contribution of Tamiflu® to this is unclear.[27] Physicians may have hesitated because of these concerns or because of the fear for emergence of resistance. Noteworthy, Tamiflu prescriptions increased in the USA during the influenza A(H1N1) 2009 pandemic.[31] In hindsight, cases with antiviral resistance occurred only sporadically during the pandemic.[32] Information on the proportion of patients treated with antivirals in Germany is not available for seasonal influenza. Thus, we do not know whether the proportion of patients treated with antivirals was higher during the influenza A(H1N1) 2009 pandemic than during seasonal influenza as it has been published for the United States.[33]

To our knowledge, the present study is the first study demonstrating that female patients were less likely to be treated with antivirals during the pandemic (H1N1) 2009 than male patients. Possible hypotheses may include a greater

demand for antivirals in male patients or a gender-specific prescription practice of physicians because studies have shown that the immune response and the pharmacological reaction are different in females and males and that female gender is associated with a lower clinical response for oseltamivir than male gender (hazard ratio = 0·53; 95% CI: 0·36–0·79; $P = 0.002$).[34,35] We have not the possibility to test these hypotheses with our data. Further research is needed to further elaborate on this finding and its implications.

Overall, antiviral treatment was given one day after onset of symptoms. For cases with severe disease, median start of antiviral treatment was one day later than for cases without severe disease. These findings were in line with recommendations during the influenza A(H1N1) 2009 pandemic.[1–4] Our study expands on previous results of a study on fatal cases in Germany.[36]

Our study has several strengths. We investigated the use of antivirals in the largest number of patients with laboratory-confirmed A(H1N1)pdm09 infection (more than 160·000) reported to date. Furthermore, the data collected consist of detailed case-based information on in- and outpatients of all age groups from all Federal States in Germany.

This study also has potential limitations. Information on antiviral treatment is missing for a third of notified cases. Information on antiviral treatment was more often available when patients were hospitalized, had pneumonia, or died. There were no differences between cases with and without available information on antiviral treatment with regard to gender, age, underlying medical conditions, and vaccination. The results of our logistic models did not change when we assumed that all patients with missing information on antiviral use either had received antivirals or not received antivirals. Due to the high work load during the pandemic, local health authorities might not have updated the information for each case when it became available. Thus, our results may underestimate the true number of patients with antiviral treatment and the true number of patients with underlying medical conditions.

In conclusion, this study provides insight that recommendations on antiviral use were followed differently by physicians in Germany with regard to the age and gender of patients with laboratory-confirmed A(H1N1)pdm09 infection. This indicates that the potential of antivirals to prevent severe influenza might not have been fully exhausted. The reasons leading to the observed differences in patient management urgently remain to be investigated with regard to pandemic influenza and seasonal influenza.

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