Pandemic influenza A(H1N1) 2009 breakthrough infections and estimates of vaccine effectiveness in Germany 2009-2010

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During the 2009 influenza pandemic, a monovalent AS03-adjuvanted vaccine was almost exclusively used in Germany for immunisation against the 2009 pandemic influenza A(H1N1) virus. One-dose vaccination was recommended for all age groups. We applied the screening method for the rapid assessment of vaccine effectiveness (VE) based on reported data of vaccinated and unvaccinated pandemic influenza cases and vaccination coverage estimates. Preliminary results demonstrate excellent VE in persons aged 14-59 years (96.8%; 95% confidence interval (CI): 95.2-97.9) and moderately high VE in those 60 years or older (83.3%; 95% CI: 71.0-90.5).

Introduction

In Germany, vaccination against pandemic influenza A(H1N1) 2009 was initiated on 26 October (calendar week 44) with the monovalent AS03-adjuvanted H1N1-vaccine Pandemrix® containing 3,25 µg haemagglutinin. At the onset of the vaccination campaign, the number of reported pandemic influenza cases had just begun to rise rapidly and eventually peaked in week 47 (Figure 1).

A non-adjuvanted vaccine was introduced seven weeks later but was restricted to pregnant women. In a randomised clinical trial a higher dose of the AS03-adjuvanted vaccine (5.25 µg haemagglutinin) showed seroconversion and seroprotection rates over 96% after one shot [1]. Based on these data, the German regulatory authority recommended that one dose was sufficient for immunisation against 2009 pandemic influenza A(H1N1). While immunogenicity data remain the basis for licensure of these vaccines, it is unknown how well they correlate with protection [2]. Therefore, it is essential to estimate vaccine effectiveness (VE) from post-marketing surveillance data to confirm that the one-dose vaccination regimen induces sufficient protection in different age and risk groups [3]. Here we present results from the analysis of breakthrough infections reported through the statutory disease notification system in Germany and report VE estimated using the screening method [4,5].

Methods

With onset of the pandemic, influenza surveillance in Germany was intensified. Notified 2009 pandemic influenza A(H1N1) cases were interviewed by local public health officials for underlying chronic diseases, hospitalisation, and influenza vaccination status. Data from studies on seasonal influenza vaccines showed that protective antibodies are present in over 90% of persons 14 days after vaccination [6]. Therefore we defined vaccine failure as laboratory-confirmed pandemic influenza in a person vaccinated more than 14 days prior to illness onset. Potential risk factors for vaccine failure were assessed by comparing vaccine failure cases with persons vaccinated during the seven days prior to disease onset. The latter group was considered as representative of vaccinated persons in general and, assuming reasonably high VE it should have included only a small proportion of individuals who would have shown true vaccine failure had the infection occurred at a later point in time. For multivariate analysis, logistic regression models were applied using stepwise backward removal with inclusion of age, sex, and all variables with a p-value of ≤0.2 in univariate analysis in the first step.

To monitor pandemic influenza vaccine uptake in Germany, a computer-assisted telephone survey was carried out during the vaccination campaign starting in calendar week 47. A randomly selected representative sample of 1,000 individuals of 14 years or older was interviewed at two week intervals. Demographic information, influenza vaccination status (receipt of 2009-10 seasonal influenza vaccine or 2009 pandemic influenza vaccine, including month of vaccination), as well as knowledge of and attitude towards pandemic influenza vaccination were elicited using a standardised questionnaire. Average vaccination coverage and 95% confidence interval (CI) were weighted for representativeness of the target population. We estimated VE by using the following formula:

VE = (PPV-PCV) / PPV(1-PCV) x 100%

where PPV is the proportion vaccinated in the population and PCV the proportion of vaccinated cases [4]. Laboratory-confirmed pandemic influenza cases notified in all German federal states from week 47 in 2009 (the week when first vaccination coverage data were available, i.e. three weeks after initiation of the vaccination campaign) to week four in 2010 were included in the analysis. Since the exact date of vaccination and symptom onset were not available for all vaccinated cases, an expansion factor was calculated by dividing the total number of cases vaccinated against pandemic influenza by the number of vaccinated cases with available information (Table).
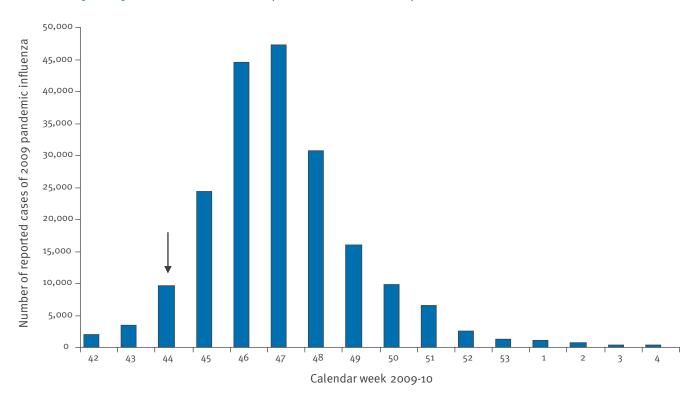
Results

From week 47 in 2009 to week four in 2010, a total of 71,315 laboratory-confirmed pandemic influenza cases were notified. Of 45,733 cases with information available, 425 (0.93%) were reported to be vaccinated against pandemic influenza. Figure 2 shows the distribution of vaccinated cases by number of days between date of vaccination and disease onset: 180 were vaccinated seven days or less, 48 cases 8-14 days, and 61 cases more than 14 days prior to disease onset (136 cases with missing data on vaccination date or symptom onset).

In univariate analysis, age (proportion of cases 60 years or older: 11.4% among vaccine failures versus 3.6% among cases vaccinated seven days or less prior

Number of reported pandemic influenza cases by calendar week, Germany, week 42, 2009 - week 4, 2010

The vaccination campaign was initiated in week 44, 2009 (indicated by the black arrow).

Table

Pandemic influenza 2009 A(H1N1) vaccine effectiveness for individuals ≥14 years of age, estimated by the proportion of pandemic influenza cases with vaccine failure reported among all laboratory-confirmed cases in routine surveillance and the proportion vaccinated in the general population, Germany, week 47, 2009 – week 4, 2010

Age groups (years)	H1N1 cases (total)	H1N1 cases with vaccination status available		Vaccine failures (cases with disease >14 days after vaccination)	Expansion factor (total vaccinated cases / vaccinated cases with information on date of vaccination and symptom onset)	Vaccine failures (after applying expansion factors)	Proportion H1N1 cases with vaccine failure among H1N1 cases with available vaccination status	Proportion vaccinated in the general population (95%CI)	Vaccine effectiveness (95%CI)
		Cases not vaccinated against H1N1	Cases vaccinated against H1N1						
14-59	37,756	23,853	219	35	1.52 (219 / 144)	53.2	0.0022	0.064 (0.044-0.093)	96.8% (95.2-97.9)
≥60	1430	923	25	7	1.92 (25 / 13)	13.4	0.0141	0.079 (0.047-0.131)	83.3% (71.0-90.5)

to symptom onset, p=0.027) and previous seasonal influenza vaccination (61.8% versus 41.0%, p=0.008) were associated with 2009 pandemic influenza vaccine failure. Underlying chronic disease (40.0% versus 28.1%, p=0.093) and hospitalisation (9.8% vs. 12.7%, p=0.53) were not significantly associated with vaccine failure. In multivariate logistic regression only age remained independently associated with vaccine failure (odds ratio (OR)= 1.82; 95% CI 1.03-3.21). Immunosuppression was reported for two (3.3%) cases in the vaccine failure group and five (3.0%) in the control group. None of the vaccine failure cases were pregnant.

The vaccination coverage assessment included a total of 6,009 household interviews and revealed an average pandemic influenza vaccination coverage of 6.8% (95% CI 5.0-9.2) for Germany in persons 14 years and older. VE was estimated at 96.8% (95% CI 95.2-97.9) for all persons aged 14-59 years and at 83.3% (95% CI 71.0-90.5) for persons 60 years or older (Table).
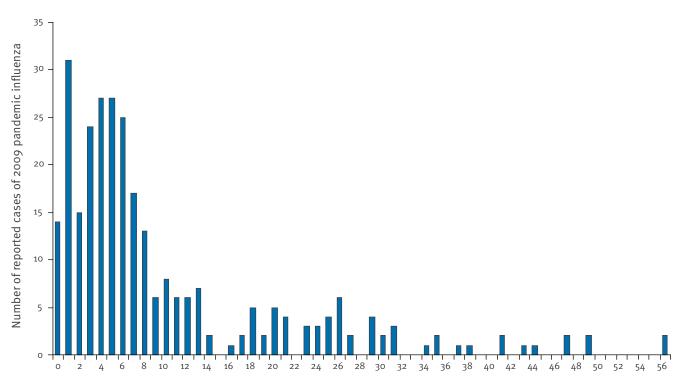
Conclusions

A comparison of the prevalence of potential risk factors for vaccine failure in the group of cases vaccinated in the seven days before disease onset (proxy for successfully vaccinated persons) with that in the group of vaccine failure cases revealed only older age to be significantly associated with vaccine failure, in keeping with the findings from the screening analysis. A

Cochrane review has shown high VE of seasonal influenza vaccines up to 80% against laboratory-confirmed seasonal influenza in healthy adults aged 16 to 65 years in seasons in which the vaccine matched circulating strains [7]. In contrast, reviews on the effectiveness of seasonal influenza vaccination in the elderly have shown low or uncertain effectiveness [8, 9]. These reviews identified a lack of high quality, unbiased studies using the specific end-point of laboratory-confirmed influenza. A few studies on the effectiveness of adjuvanted seasonal influenza vaccine were included in the Cochrane review on VE in the elderly [8] and all used non-specific end-points such as preventing influenza-like illness (ILI), hospitalisation, or emergency admissions for pneumonia. However, use of adjuvanted vaccines seems to be a promising approach leading to improved immune responses compared with the conventional vaccines [10]. While lower than in younger adults, our results also suggest an acceptable effectiveness of the AS03-adjuvanted pandemic influenza vaccine in preventing laboratory-confirmed pandemic influenza in the elderly, which should be confirmed in further analytical studies.

A statistically significant association of vaccine failure with underlying chronic disease was not found, suggesting that on the whole, the vaccine is effective in chronically ill persons. However, as this group is rather inhomogeneous, an association of vaccine failure with

Time from pandemic influenza vaccination to date of symptom onset in 298 reported cases with laboratory-confirmed 2009 pandemic influenza A(H1N1) and information on exact date of vaccination and symptom onset, Germany , calendar week 47, 2009 - 4, 2010

certain diagnoses or therapies cannot entirely be ruled out.

The screening method is a quick and simple tool to assess VE in a population with known vaccination coverage. With reasonably accurate estimates of vaccination coverage, this technique can provide a rough guide as to whether further evaluation is necessary [5]. Strengths of our study were the statutory notification of infections with the 2009 pandemic influenza A(H1N1) virus in Germany, the occurrence of more than 70,000 laboratory-confirmed pandemic influenza cases after the implementation of the vaccination campaign, and the availability of only one vaccine type against pandemic influenza. However, it is possible that vaccinated patients with ILI might have been less frequently tested for pandemic influenza compared with unvaccinated persons, thereby potentially leading to VE overestimation. Thus, our results must be regarded as an upper-limit estimate. They nevertheless suggest excellent VE of the AS03-adjuvanted pandemic vaccine after one dose with lower but still acceptable VE in elderly persons.

Acknowledgements

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