

# Risk of Guillain–Barré syndrome following pandemic influenza A (H1N1) 2009 vaccination in Germany<sup>†</sup>

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## ABSTRACT

**Purpose** A prospective, epidemiologic study was conducted to assess whether the 2009 pandemic influenza A(H1N1) vaccination in Germany almost exclusively using an AS03-adjuvanted vaccine (Pandemrix) impacts the risk of Guillain–Barré syndrome (GBS) and its variant Fisher syndrome (FS).

**Methods** Potential cases of GBS/FS were reported by 351 participating hospitals throughout Germany. The self-controlled case series methodology was applied to all GBS/FS cases fulfilling the Brighton Collaboration (BC) case definition (levels 1–3 of diagnostic certainty) with symptom onset between 1 November 2009 and 30 September 2010 reported until end of December 2010.

**Results** Out of 676 GBS/FS reports, in 30 cases, GBS/FS (BC levels 1–3) occurred within 150 days following influenza A(H1N1) vaccination. The relative incidence of GBS/FS within the primary risk period (days 5–42 post-vaccination) compared with the control period (days 43–150 post-vaccination) was 4.65 (95%CI [2.17, 9.98]). Similar results were found when stratifying for infections within 3 weeks prior to onset of GBS/FS and when excluding cases with additional seasonal influenza vaccination. The overall result of temporally adjusted analyses supported the primary finding of an increased relative incidence of GBS/FS following influenza A(H1N1) vaccination.

**Conclusions** The results indicate an increased risk of GBS/FS in temporal association with pandemic influenza A(H1N1) vaccination in Germany. © 2014 The Authors. *Pharmacoepidemiology and Drug Safety* published by John Wiley & Sons, Ltd.

KEY WORDS—Guillain–Barré syndrome; pandemic influenza vaccination; self-controlled case series; pharmacoepidemiology

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## INTRODUCTION

Guillain–Barré syndrome (GBS) is an acute, immune-mediated polyradiculoneuropathy.<sup>1</sup> Typically, it is clinically characterized by bilateral limb paresis and hyporeflexia/areflexia. Fisher syndrome (FS) is considered as a rare variant of GBS presenting with ataxia,

ophthalmoplegia, and areflexia. The overall GBS incidence was estimated to be between 1.1 and 1.8/100 000/year.<sup>2,3</sup> GBS is deemed to be an autoimmune disease.<sup>1,4</sup> Frequently, GBS is preceded by a gastrointestinal or respiratory infection. Antecedent pathogens include *Campylobacter jejuni*, *Mycoplasma pneumoniae*, *Haemophilus influenzae*, Epstein–Barr virus, cytomegalovirus, or varicella zoster virus.<sup>4</sup> Some recent studies and reports suggest that influenza virus infection may also act as a relevant trigger for GBS.<sup>5–9</sup>

In 1976, a US vaccination campaign against swine influenza had to be stopped prematurely because of an increased number of GBS reports following immunization. Several studies<sup>10–12</sup> found a temporal association between the 1976 swine influenza vaccines and GBS. Subsequent studies on seasonal influenza vaccines<sup>5,12</sup>

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<sup>†</sup>Prior postings and presentations: This study was presented as a poster at the 29th International Conference on Pharmacoepidemiology & Therapeutic Risk Management 2013 in Montréal (abstract number 876). A summary of the study (written in German) is posted on the website of the Paul-Ehrlich-Institut as the German national competent authority responsible for vaccines (www.pei.de/gbs-studie). There were no other public presentations/postings of the study.

found no<sup>13–17</sup> or only a slightly elevated risk of GBS after immunization.<sup>18,19</sup> The increased risk of GBS after the 1976 swine influenza vaccination raised concerns that the pandemic swine influenza vaccines of 2009 might also be associated with GBS. Therefore, a prospective study was conducted by the Paul-Ehrlich-Institut (PEI), the German national competent authority, to evaluate whether there was a temporal association between the 2009 pandemic influenza A(H1N1) vaccination and GBS/FS.

## METHODS

In Germany, the influenza A(H1N1) vaccination campaign started on 26 October 2009, almost exclusively using an inactivated, monovalent, AS03-adjuvanted vaccine (Pandemrix, GlaxoSmithKline Biologicals, Rixensart, Belgium). A self-controlled case series (SCCS) design was applied.<sup>20–23</sup> The study protocol was approved by the Ethics Committee of the Hessian Medical Association in Frankfurt, Germany. The study period ran from 1 November 2009 to 30 September 2010. A(H1N1) vaccination had practically stopped by the end of December 2009 in Germany with only a few vaccinations at the beginning of 2010.<sup>24</sup>

### *Participating hospitals*

Initially, 316 neurologic and 346 pediatric acute hospitals in Germany were asked to participate in the study. A total of 351 hospitals (227 neurologic and 124 pediatric hospitals) participated in the study. In each hospital, a physician was nominated as a contact person. The hospitals were asked to report all GBS/FS cases occurring during the study period, regardless of whether any influenza vaccine had been administered or not. In addition, the PEI requested each participating hospital on a regular basis to declare whether a case of GBS/FS had occurred in the meantime.

### *Case ascertainment*

Guillain–Barré syndrome/FS cases were documented on a pseudonymized and standardized reporting form. The following information was collected: year of birth; sex; region of residence; date of symptom onset; clinical details required for classification according to the Brighton Collaboration (BC) case definition<sup>25</sup>; therapy; outcome; gastrointestinal, respiratory, or other infections within 3 weeks prior to symptom onset; pathogen proof concerning preceding infection; immunization status regarding A(H1N1) vaccination and seasonal influenza vaccination including vaccination date, vaccine brand, batch number, and dose (first or second). Hospitals

had to verify the immunization status by reviewing the vaccination certificate or contacting the vaccinating physician/general practitioner. Missing essential information was queried by PEI.

Reports were included in the study only if the subjects were residents of Germany. All reports of a GBS/FS following A(H1N1) vaccination or seasonal influenza vaccination were independently assessed against the BC case definition of GBS/FS by a neurologist from PEI (J.P.) and by an external neurologist (H. C. L.), who was blinded to the immunization status of cases. Reported events that met the case definition were classified into level 1, 2, or 3 of diagnostic certainty. If the evidence available for an event was insufficient to permit classification at any level of diagnostic certainty, it was categorized as level 4. Level 5 reflects the exclusion of GBS/FS according to the case definition.

For the statistical analysis, a case was defined as GBS or FS according to the BC case definition (levels 1–3) within 150 days following A(H1N1) vaccination or seasonal influenza vaccination. Cases were included in the analysis only if the date of the first A(H1N1) vaccination (or seasonal influenza vaccination) and the date of GBS/FS onset fell into the study period.

### *Statistical analysis*

Relative incidence (RI) estimates for GBS/FS following A(H1N1) vaccination/seasonal influenza vaccination were calculated by means of conditional Poisson regression. The null hypothesis of no increased RI of GBS/FS in a predefined risk period compared with a control period was tested. To account for an interim analysis, a critical *p*-value of 0.046 was applied in the final analysis, and 95% CIs were calculated using the repeated confidence interval approach.<sup>26</sup> Unvaccinated GBS/FS cases contributed to the estimation of temporal effects. For the primary analysis, the risk period was defined as days 5–42 after vaccination and the control period as days 43–150 after vaccination (day 1 refers to the day of vaccination). The risk period chosen for the primary analysis extends to day 42 after vaccination because the period of increased risk of GBS after the 1976 swine influenza vaccination campaign was concentrated primarily within 6 weeks following vaccination.<sup>11</sup> Additional analyses were performed, assessing the impact of different definitions of risk and control periods as well as the impact that possible confounders (e.g., age, sex, and previous infections) might have on the RI of GBS/FS following A(H1N1) vaccination. In order to control for confounding by contraindication to A(H1N1) vaccination, pre-vaccination time intervals were not included in the control periods.<sup>27,28</sup>

Statistical analyses were performed using the SAS software, version 9.2 (SAS Institute Inc., Cary, NC, USA).

### *Control for confounding*

In Germany, the A(H1N1) vaccination period<sup>24</sup> and the pandemic peak period<sup>29</sup> were roughly identical (i.e., November 2009–January 2010). Adjusted analyses were performed *post hoc* in an attempt to account for possible seasonal effects on the risk of GBS/FS.<sup>20,27</sup> An adjustment for calendar months and an adjustment for A(H1N1) influenza season (November 2009–January 2010 and February–September 2010) were conducted. The temporal adjustment was performed for the primary analysis population of A(H1N1)-vaccinated cases as well as for an “enriched population” combining information from the primary population and unvaccinated subjects with GBS/FS onset (BC levels 1–3) during the study period. Unvaccinated subjects were included in the “enriched population” with no risk period and a control period identical to the study period.

To investigate possible selective reporting of GBS/FS cases, the hospitals were asked retrospectively to provide the total number of cases with International Classification of Diseases (ICD) discharge diagnosis GBS/FS (according to their ICD hospital database), which occurred during the study period, and the month of hospital admission in each case. The number of GBS/FS study reports was compared with the number of cases with ICD discharge diagnosis GBS/FS for each hospital that participated in both the study and the additional survey. SCCS analyses were performed, restricted to A(H1N1)-vaccinated cases from hospitals that participated in the additional survey with comparable number of reports in the study and survey.

## RESULTS

### *Characteristics of the study population*

A total of 732 reports were transmitted to PEI. Fifty-six of these reports were excluded (Figure 1). As diagnosed by the reporting physicians, 617/676 reports (91.3%) referred to GBS, 54/676 reports (8.0%) referred to FS, and in 5/676 reports (0.7%), both GBS and FS were diagnosed. Four hundred eighty-six of these 676 reports fulfilled the BC case definition (levels 1–3). In 30 cases, a GBS/FS (levels 1–3) occurred within 150 days following A(H1N1) vaccination (all Pandemrix), and 15 patients developed GBS/FS (levels 1–3) within 150 days following vaccination against 2009/2010 seasonal influenza (Table 1). Ten of the 19 GBS/FS cases that occurred within 42 days after A(H1N1) vaccination

occurred during days 6–10 (median 9 days). The demographic and clinical characteristics of the different patient populations are shown in Table 2. In 36.7% of A(H1N1)-vaccinated cases—in contrast to reports without vaccination (50.0%)—a preceding gastrointestinal and/or respiratory infection was reported within 3 weeks prior to the first GBS/FS symptoms (not significant, Fisher test). Proof of a bacterial or viral pathogen concerning an antecedent infection was reported in 6.7% of A(H1N1)-vaccinated cases compared with 14.5% in reports without vaccination (not significant, Fisher test).

### *Unadjusted self-controlled case series analyses*

The unadjusted RI estimate for GBS/FS after A(H1N1) vaccination comparing the primary risk period (days 5–42 post-vaccination) with the control period (days 43–150 post-vaccination) was 4.65 (95%CI [2.17, 9.98]). An increased RI of GBS/FS following A(H1N1) vaccination was also seen when applying different definitions of risk and control periods (Table 3) and when stratifying for infections within 3 weeks prior to the first GBS/FS symptoms (Table 4). None of the other factors (age, sex, and BC level) was identified as an effect modifier (Table 4). The increased risk of GBS/FS following A(H1N1) vaccination was also seen when excluding cases with additional seasonal influenza vaccination (RI, 4.83; 95%CI [2.18, 10.7], regarding primary risk/control period) and in a further sensitivity analysis including level 4/level 5 reports, which may also reflect cases of (atypical) GBS/FS upon review by a neurologist (RI, 4.59; 95%CI [2.27, 9.28]).

### *Self-controlled case series analyses with temporal adjustment*

The results of the temporally adjusted analyses depend on the periods accounted for as well as on the patient population considered for adjustment (Table 3). By restricting temporal adjustment to the primary population of A(H1N1)-vaccinated cases, the adjustment for A(H1N1) season resulted in a less pronounced but still significantly increased RI of GBS/FS following A(H1N1) vaccination (adjusted RI, 2.96; 95%CI [1.06, 8.25]), whereas the adjustment for months did not indicate an increased RI (adjusted RI, 1.12; 95%CI [0.27, 4.64]). When level 1–3 GBS/FS reports in unvaccinated subjects were included in the analysis model for temporal effects (“enriched population”), the resulting estimates for the RI of GBS/FS following A(H1N1) vaccination were similar to the unadjusted effects estimate (RI, 5.35; 95%CI [2.40, 11.9] in case of monthly adjustment; RI, 4.56; 95%CI [2.09, 9.96]

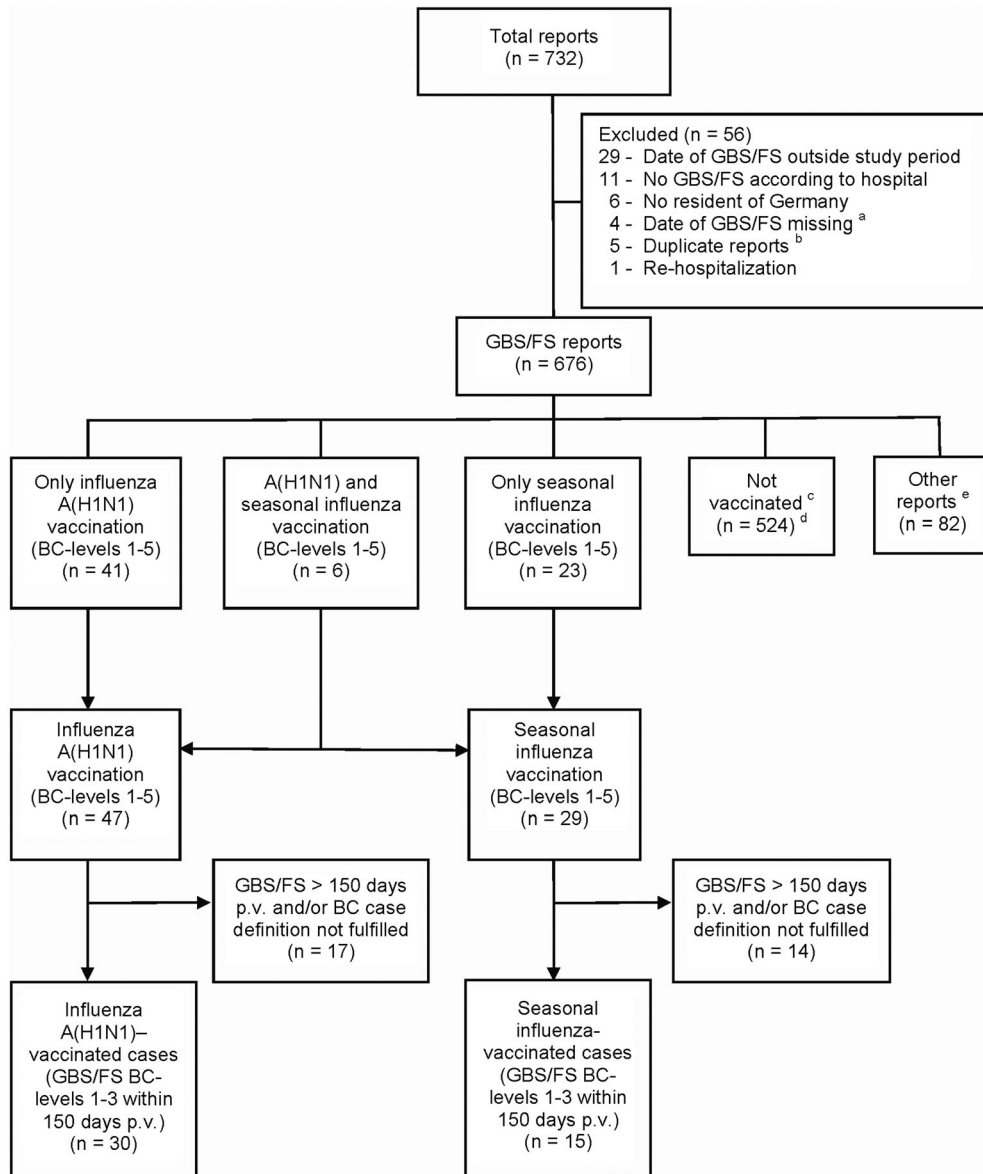


Figure 1. Patient flow. <sup>a</sup>Among four reports that were excluded from the study because of missing date of GBS/FS, one report referred to A(H1N1) vaccination. Including this report in a sensitivity SCCS analysis altered the result only marginally. <sup>b</sup>Duplicate reports: Five patients with onset of GBS/FS during the study period were reported twice, each by different participating hospitals. For these patients, the report from the initially treating hospital was included in the analysis. <sup>c</sup>The “not vaccinated” population contains only reports without A(H1N1) vaccination and without seasonal influenza vaccination in the season 2009/2010. Reports with A(H1N1) and/or seasonal influenza vaccination in 2009/2010 prior to 1 November 2009 were included in the population of “other reports.” <sup>d</sup>Out of these, 362 reports fulfilled the BC case definition (levels 1–3). <sup>e</sup>“Other reports” include one report with A(H1N1) vaccination prior to 1 November 2009, 54 reports with seasonal influenza vaccination prior to 1 November 2009, one report with GBS onset before seasonal influenza vaccination, three reports with unknown month of seasonal influenza vaccination, 20 reports (3.0% of all 676 GBS/FS reports) with unknown vaccination status regarding A(H1N1) and seasonal influenza vaccination, and three reports with unknown vaccination status regarding seasonal influenza vaccination. BC, Brighton Collaboration; FS, Fisher syndrome; GBS, Guillain–Barré syndrome; p.v., post-vaccination

in case of adjustment for A(H1N1) season) (Table 3). When including all unvaccinated subjects with BC levels 1–4 in the analysis, only marginal changes for the adjusted estimates were observed (RI, 5.47; 95% CI [2.47, 12.1] in case of monthly adjustment; RI, 4.48; 95% CI [2.06, 9.74] in case of adjustment for A(H1N1) season).

### Seasonal influenza vaccination

The SCCS analyses regarding seasonal influenza vaccination did not indicate a significantly increased risk of GBS/FS. The unadjusted RI was 1.89 (95% CI [0.66, 5.42]) for the primary risk and control period and did not substantially change when temporal



Table 1. Time interval between vaccination with influenza A(H1N1) vaccine and/or seasonal influenza vaccines and first symptoms of GBS/FS

Days of exposure	Reports of influenza A(H1N1) vaccination		Reports of seasonal influenza vaccination	
	BC levels 1–5	BC levels 1–3	BC levels 1–5	BC levels 1–3
1–4	3	1	1	-
5–21	15	12	5	5
22–42	6	6	3	1
43–62	5	5	1	1
63–150	8	6	10	8
Total within 150 days p.v.	37	30*	20	15*
>150	10	8	9	7

BC, Brighton Collaboration; GBS, Guillain-Barré syndrome; FS, Fisher syndrome; p.v., post-vaccination.

\*Out of these GBS/FS cases (BC levels 1–3), three patients received both influenza A(H1N1) vaccination and seasonal influenza vaccination during the study period within 150 days prior to the first symptoms of GBS/FS. None of these three patients were vaccinated with both vaccines on the same day.

Table 2. Demographic and clinical characteristics of patients

	GBS/FS reports (n = 676)	Influenza A(H1N1)-vaccinated cases* (n = 30)	Seasonal influenza-vaccinated cases* (n = 15)	Not vaccinated (n = 524)
Sex, n (%)				
Female	302 (44.7)	10 (33.3)	5 (33.3)	239 (45.6)
Male	374 (55.3)	20 (66.7)	10 (66.7)	285 (54.4)
Age				
Median (range)	58.5 (1–90)	62.0 (4–82)	66.0 (14–88)	56.0 (1–90)
<10 years, n (%)	21 (3.1)	1 (3.3)	—	18 (3.4)
10–60 years, n (%)	344 (50.9)	12 (40.0)	4 (26.7)	290 (55.3)
>60 years, n (%)	311 (46.0)	17 (56.7)	11 (73.3)	216 (41.3)
Patients with infections within 3 weeks prior to the first GBS/FS symptoms, n (%)				
GI	175 (25.9)	7 (23.3)	1 (6.7)	140 (26.7)
Respiratory	173 (25.6)	5 (16.7)	4 (26.7)	135 (25.8)
GI and/or respiratory	333 (49.3)	11 (36.7)	5 (33.3)	262 (50.0)
Others	42 (6.2)	2 (6.7)	—	31 (5.9)
Any infection	371 (54.9)	13 (43.3)	5 (33.3)	290 (55.3)
Laboratory confirmation of pathogen (per patient), n (%)				
No	463 (68.5)	28 (93.3)	11 (73.3)	344 (65.6)
Yes	101 (14.9)	2 (6.7)	4 (26.7)	76 (14.5)
Missing	112 (16.6)	—	—	104 (19.8)
Confirmed pathogen <sup>†</sup>				
<i>Campylobacter jejuni</i>	45	1	1	36
<i>Mycoplasma pneumoniae</i>	18	0	2	14
Epstein-Barr virus	14	0	1	10
Cytomegalovirus	5	0	0	3
Varicella zoster virus	3	0	0	3
<i>Haemophilus influenza</i>	2	0	0	0
Others	22	1	0	17
BC levels 1–3, n (%)	486 (71.9)	30 (100)	15 (100)	362 (69.1)

BC, Brighton Collaboration; GBS, Guillain-Barré syndrome; GI, gastrointestinal; FS, Fisher syndrome.

\*Within 150 days post-vaccination, BC levels 1–3.

<sup>†</sup>Laboratory-confirmed pathogen regarding infections within 3 weeks prior to the first symptoms of GBS/FS; multiple entries possible.

adjustment was performed (RI adjusted for A(H1N1) season, 1.62; 95%CI [0.44, 5.89]).

### Retrospective survey

One hundred eighteen of the 227 neurologic hospitals (52.0%) and 76 of the 124 pediatric hospitals (61.3%) participating in the study also participated in the additional survey. Unadjusted SCCS analyses restricted to

A(H1N1)-vaccinated cases from hospitals that transmitted a comparable number of reports in study and survey also indicated an increased risk of GBS/FS following A(H1N1) vaccination: The RI was 5.68 (95%CI [1.91, 16.96]) when solely A(H1N1)-vaccinated cases from those hospitals were included where the number of study reports was either greater or at most one report less than the number of ICD-coded GBS/FS cases during the study period. When including solely A(H1N1)-

Table 3. Relative incidence of GBS/FS cases (BC levels 1–3) following influenza A(H1N1) vaccination: SCCS analyses

Risk/control period (days p.v.)	Number of cases (risk/control)	Unadjusted analysis		Adjusted analysis restricted to A(H1N1)-vaccinated cases only		Adjusted analysis including information from unvaccinated subjects	
		RI [95%CI]	<i>p</i> -value	Monthly adjustment*	Adjustment for A(H1N1) season†	Monthly adjustment	Adjustment for A(H1N1) season†
5–42/43–150	18/11	4.65 [2.17, 9.98]	<0.001	1.12 [0.27, 4.64]	2.96 [1.06, 8.25]	5.35 [2.40, 11.9]	4.56 [2.09, 9.96]
1–42/43–150	19/11	4.44 [2.09, 9.46]	<0.001	1.19 [0.28, 5.01]	2.85 [1.03, 7.90]	5.13 [2.32, 11.3]	4.36 [2.01, 9.44]
5–42/1–4 and 43–150	18/12	4.42 [2.10, 9.30]	<0.001	1.67 [0.56, 4.95]	2.80 [1.08, 7.26]	5.03 [2.31, 11.0]	4.33 [2.03, 9.25]
1–42/43–84	19/6	3.17 [1.24, 8.06]	0.014	0.95 [0.21, 4.36]	2.71 [0.98, 7.54]	3.32 [1.27, 8.71]	3.16 [1.24, 8.05]
1–58/59–150	21/9	3.70 [1.67, 8.20]	0.001	0.45 [0.07, 2.93]	1.92 [0.61, 6.06]	4.27 [1.87, 9.79]	3.62 [1.60, 8.17]

BC, Brighton Collaboration; GBS, Guillain-Barré syndrome; FS, Fisher syndrome; p.v., post-vaccination; RI, relative incidence; SCCS, self-controlled case series.

\*Not considered reliable owing to problems regarding identifiability: The likelihood ratio test rejected the global null hypothesis, but none of the model parameters (i.e., risk and months) was statistically significant. The parameter estimates for the monthly components had huge standard errors and were highly correlated.

†A(H1N1) influenza season: time intervals, November 2009–January 2010 and February 2010–September 2010.

vaccinated cases from those hospitals where the number of study reports was either greater than or equal to the number of ICD-coded cases, the RI was 4.97 (95%CI [1.42, 17.37]).

## DISCUSSION

We performed a prospective SCCS study with a robust case ascertainment. The unadjusted SCCS analysis indicated an elevated risk of GBS/FS in close temporal relation to A(H1N1) vaccination in Germany. The increased risk was also seen in various unadjusted sensitivity analyses. Stratification by preceding gastrointestinal and/or respiratory infection did not alter the results.

In 2009/2010, the influenza A(H1N1) vaccination period<sup>24</sup> and the pandemic peak period<sup>29</sup> in Germany roughly overlapped. This impacts the separation of the vaccination effect from temporal effects on the occurrence of GBS/FS. To account for possible temporal effects, adjusted analyses were performed *post hoc*. Adjusting for months in the primary population of A(H1N1)-vaccinated cases did not indicate an elevated RI. However, this analysis revealed severe problems regarding identifiability (which might be partly due to the time pattern of vaccination and GBS/FS cases and partly due to the restricted sample size), questioning the validity of the results of this specific analysis. The temporal adjustment for A(H1N1) season in the primary population as well as the temporally adjusted analyses including the unvaccinated GBS/FS cases resulted in a reliable estimation of all model parameters including seasonality. The results of these analyses supported the findings from the unadjusted analyses.

The reason for including unvaccinated GBS/FS cases to estimate seasonal components was to increase the precision of the corresponding estimates. One might argue that the inclusion of unvaccinated cases might introduce bias; however, it should be noted that—in case there had been temporal effects—these effects would be similar in A(H1N1)-vaccinated cases and unvaccinated cases. This assumption seems to be plausible, because both vaccinated and unvaccinated cases occurred in the same geographic area (Germany). Furthermore, neither the temporal distribution of the unvaccinated GBS/FS cases in our study nor the temporal distribution of hospitalization due to GBS/FS in Germany according to data from the German Federal Statistical Office<sup>30</sup> indicates an increased incidence of GBS/FS for the time interval November 2009–January 2010.

Overall, we concluded that the discrepancy between the unadjusted analysis and the temporally adjusted analysis restricted to A(H1N1)-vaccinated cases was due to the lack of reliability of the statistical model when adjusting for months, whereas the other temporal adjustments resulted in reliable RI estimates, which supported the findings from the unadjusted analysis.

We did not identify any plausible biologic reason for a temporal effect in this study such as preceding infections. In A(H1N1)-vaccinated cases, a clinically apparent infection within 3 weeks prior to the first GBS/FS symptoms as well as a pathogen proof concerning the preceding infection was reported less frequently than in GBS/FS reports without vaccination. This does not support the hypothesis that concomitant pathogens circulating in the population during the vaccination campaign (e.g., influenza A(H1N1) infection itself) caused the increased number of GBS/FS cases

Table 4. Influenza A(H1N1)-vaccinated cases (BC levels 1–3): unadjusted SCCS analyses stratified for age, sex, preceding infection, and BC level

Factor	Influenza A(H1N1)- vaccinated cases in risk period (days 5–42)	Influenza A(H1N1)- vaccinated cases in control period (days 43–150)	Unadjusted RI [95%CI]
Age group			
<10 years	1	0	NA*
10–60 years	7	5	3.98 [1.24, 12.8]
>60 years	10	6	4.74 [1.69, 13.3]
Sex			
Male	12	8	4.26 [1.72, 10.6]
Female	6	3	5.68 [1.39, 23.3]
Any infection <sup>†</sup>			
Yes	8	5	4.55 [1.46, 14.2]
No	10	6	4.74 [1.69, 13.3]
Gastrointestinal and/or respiratory infection <sup>†</sup>			
Yes	7	4	4.97 [1.42, 17.4]
No	11	7	4.47 [1.70, 11.7]
Gastrointestinal infection <sup>†</sup>			
Yes	4	3	3.78 [0.83, 17.4]
No	14	8	4.97 [2.05, 12.0]
Respiratory infection <sup>†</sup>			
Yes	4	1	11.4 [1.22, 106]
No	14	10	3.98 [1.74, 9.09]
BC level <sup>‡</sup>			
BC level 1	7	4	3.55 [1.38, 9.15]
BC level 2	11	7	7.58 [1.96, 29.3]

BC, Brighton Collaboration; NA, not applicable; RI, relative incidence; SCCS, self-controlled case series.

\*Not evaluable as there were no cases in the control period.

<sup>†</sup>Within 3 weeks prior to onset of GBS/FS.

<sup>‡</sup>No influenza A(H1N1)-vaccinated case was classified in BC level 3.

following A(H1N1) vaccination. Furthermore, the significantly increased risk of GBS/FS in A(H1N1)-vaccinated cases in the unadjusted analysis was not substantially altered by excluding patients with preceding gastrointestinal and/or respiratory infection. However, for each individual patient, we cannot prove that the physician has taken the infection history thoroughly and that the patient has given complete and correct information. Thus, regarding infection history, confounding cannot totally be excluded. Besides, A(H1N1) infections—for example—can occur with inconspicuous or without clinical symptoms, and testing for A(H1N1) infection was not routinely conducted in study patients.

Our study design is sensitive toward a potential reporting bias. Theoretically, stimulated reporting during the vaccination campaign and underreporting thereafter might have led to selective reporting by hospitals. However, various analyses did not indicate such selective reporting. As A(H1N1) vaccination had practically stopped by the end of December 2009 in Germany with only a few vaccinations at the beginning of 2010,<sup>24</sup> it is assumed that by the middle of February 2010, nearly all GBS/FS cases in the risk period would have occurred, and by the end of May 2010, nearly all cases in the control period would have occurred. There was no statistically significant difference in the number of study reports of

unvaccinated cases in the period from February to May 2010 compared with the period from November 2009 to January 2010 (referring to date of GBS/FS onset). This finding does not support the hypothesis of differential reporting of A(H1N1)-vaccinated cases, either. Furthermore, in an additional retrospective survey, the number of cases with ICD discharge diagnosis GBS/FS was determined according to hospital databases. From the result of the survey, it seems unlikely that selective reporting would have occurred to such an extent that the results of the SCCS analyses would have been substantially impacted.

The vaccination status regarding A(H1N1) vaccination could be determined in 656 of all 676 GBS/FS study reports (97.0%). It seems unlikely that the small proportion of reports with unknown vaccination status would have notably affected the study result.

Our results are comparable with results of five studies from the USA,<sup>31–35</sup> in which the risk of GBS after receipt of monovalent, inactivated, non-adjuvanted A(H1N1) 2009 vaccine or additionally live-attenuated A(H1N1) vaccine was investigated. The results ranged from a rate ratio of 1.57 (95%CI [1.02, 2.21]) corresponding to 0.74 excess GBS cases per million doses (95%CI [0.04, 1.56])<sup>32</sup> to a relative risk of 4.7 (95%CI [1.2, 18.3]) corresponding to 3.9 excess cases per million doses (95%CI [0.0, 7.9]).<sup>33</sup> A meta-analysis of A(H1N1) 2009 monovalent inactivated

vaccines in the USA found an incidence rate ratio of 2.35 (95%CI [1.42, 4.01]).<sup>36</sup> In Quebec where a mono-valent, AS03-adjuvanted A(H1N1) vaccine (Arepanrix) was used, the relative risk of GBS during a 4-week post-vaccination period was 2.33 (95%CI [1.19, 4.57]) in an SCCS study and 2.26 (95%CI [1.24, 4.09]) in a cohort study with an attributable risk of approximately two GBS cases per million doses.<sup>37</sup> An international SCCS study found an RI of GBS of 2.42 (95%CI [1.58, 3.72]) following A(H1N1) vaccination in a pooled data analysis and 2.09 (95%CI [1.28, 3.42]) using a meta-analytic approach. RI estimates were higher in analyses of unadjuvanted vaccines than in adjuvanted vaccines without a statistically significant difference.<sup>38</sup>

In contrast to these studies, an SCCS study conducted in the UK found no increased risk of GBS in the 6 weeks following Pandemrix vaccination.<sup>39</sup> In a case-control study<sup>40</sup> and an SCCS study<sup>41</sup> from several European countries, no elevated<sup>40</sup> or no significantly elevated risk of GBS<sup>41</sup> was observed in adjusted analyses. A retrospective cohort study in Stockholm county,<sup>42</sup> a French case-control study,<sup>43</sup> and an Australian SCCS study<sup>44</sup> found no increased<sup>42,43</sup> or no significantly increased risk of GBS following A(H1N1) vaccination.<sup>44</sup> However, these three studies were not powered to detect a small risk increase.

Our SCCS analysis regarding seasonal influenza vaccination did not indicate a significantly increased risk of GBS/FS. This corresponds to the results of other studies of seasonal influenza vaccines.<sup>5,12-17</sup> Because of the low number of case reports that may be related to the fact that the vaccination campaign already started in September 2009, several weeks prior to the study, the results regarding seasonal influenza vaccination must be interpreted with caution.

In conclusion, our data indicate an increased risk of GBS/FS in temporal association with influenza A (H1N1) vaccination (Pandemrix) in Germany. Because of the study design, confounding by temporal effects and by selective reporting cannot totally be excluded. However, several analyses suggest that possible confounding by temporal effects and possible reporting bias were unlikely to have a major impact on the study results. Our results are compatible with other active surveillance studies of both adjuvanted and unadjuvanted pandemic influenza 2009 vaccines.

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## CONFLICT OF INTEREST

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## KEY POINTS

- The results of our SCCS study indicate an increased risk of GBS/FS in temporal association with adjuvanted pandemic influenza A(H1N1) 2009 vaccination in Germany.
- Sensitivity analyses suggest that possible confounding by temporal effects and possible reporting bias were unlikely to have a major impact on the study results.
- The risk of GBS observed in our study is lower than that observed following the 1976 swine influenza vaccination campaign in the USA.
- Although not all studies of pandemic influenza 2009 vaccines have shown an elevated risk of GBS, our results are in line with the outcome of several other active surveillance studies of both adjuvanted and unadjuvanted pandemic influenza 2009 vaccines.

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## AUTHOR CONTRIBUTIONS

J. Prestel contributed to drafting of the manuscript, study concept or design, analysis and interpretation of data, acquisition of data, and study coordination. P. Volkers contributed to drafting of the manuscript, study concept or design, analysis and interpretation of data, and statistical analysis. D. Mentzer contributed to the revision of the manuscript, study concept or design, analysis of data, and acquisition of data. H.C.



Lehmann contributed to the revision of the manuscript, analysis of data, and acquisition of data. H.-P. Hartung contributed to the revision of the manuscript, study concept or design, interpretation of data, and study supervision. B. Keller-Stanislawski contributed to drafting of the manuscript, study concept or design, analysis and interpretation of data, acquisition of data, and study supervision and coordination. All authors approved this version of the manuscript.

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