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Abstract

BACKGROUND: After the introduction of an inactivated intranasal influenza vaccine that was used only in Switzerland, 46 cases of Bell's palsy were reported. METHODS: We conducted a matched case-control study and a case-series analysis. All primary care physicians, ear, nose, and throat specialists, and neurologists in German-speaking regions of Switzerland were requested to identify cases of Bell's palsy diagnosed in adults between October 1, 2000, and April 30, 2001. Each physician was invited to select three control patients for each patient with Bell's palsy, with matching according to age, date of the clinic visit, and physician. Vaccination information was provided by the physicians. RESULTS: A total of 773 patients with Bell's palsy were identified. Of the 412 (53.3 percent) who could be evaluated, 250 (60.7 percent) were enrolled and matched with 722 control patients; the other 162 patients had no controls. In the case-control study, we found that 68 patients with Bell's palsy (27.2 percent) and 8 controls (1.1 percent) had received the intranasal vaccine (P<0.001). In contrast to parenteral vaccines, the intranasal vaccine significantly increased the risk of Bell's palsy (adjusted odds ratio, 84.0; 95 percent confidence interval, 20.1 to 351.9). Even according to conservative assumptions, the relative risk of Bell's palsy was estimated to be 19 times the risk in the controls, corresponding to 13 excess cases per 10,000 vaccinees within 1 to 91 days after vaccination. In the case-series analysis, the period of highest risk was 31 to 60 days after vaccination. CONCLUSIONS: This study suggests a strong association between the inactivated intranasal influenza vaccine used in Switzerland and Bell's palsy. This vaccine is no longer in clinical use.

ORIGINAL ARTICLE

Use of the Inactivated Intranasal Influenza Vaccine and the Risk of Bell's Palsy in Switzerland

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ABSTRACT

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BACKGROUND

After the introduction of an inactivated intranasal influenza vaccine that was used only in Switzerland, 46 cases of Bell's palsy were reported.

METHODS

We conducted a matched case–control study and a case-series analysis. All primary care physicians, ear, nose, and throat specialists, and neurologists in German-speaking regions of Switzerland were requested to identify cases of Bell's palsy diagnosed in adults between October 1, 2000, and April 30, 2001. Each physician was invited to select three control patients for each patient with Bell's palsy, with matching according to age, date of the clinic visit, and physician. Vaccination information was provided by the physicians.

RESULTS

A total of 773 patients with Bell's palsy were identified. Of the 412 (53.3 percent) who could be evaluated, 250 (60.7 percent) were enrolled and matched with 722 control patients; the other 162 patients had no controls. In the case–control study, we found that 68 patients with Bell's palsy (27.2 percent) and 8 controls (1.1 percent) had received the intranasal vaccine (P<0.001). In contrast to parenteral vaccines, the intranasal vaccine significantly increased the risk of Bell's palsy (adjusted odds ratio, 84.0; 95 percent confidence interval, 20.1 to 351.9). Even according to conservative assumptions, the relative risk of Bell's palsy was estimated to be 19 times the risk in the controls, corresponding to 13 excess cases per 10,000 vaccinees within 1 to 91 days after vaccination. In the case-series analysis, the period of highest risk was 31 to 60 days after vaccination.

CONCLUSIONS

This study suggests a strong association between the inactivated intranasal influenza vaccine used in Switzerland and Bell's palsy. This vaccine is no longer in clinical use.

INFLUENZA IS A LEADING CAUSE OF ILL-ness and death.[1] Annual vaccination is recommended for certain age groups and high-risk populations. However, the acceptance of parenteral influenza vaccines has frequently been unsatisfactory, in part because of the fear of injections.[2] Intranasal administration of influenza vaccines is an attractive alternative. It might also reduce the transmission of influenza more efficiently than parenteral administration by stimulating both mucosal and systemic immune responses.[2,3] To date, two trivalent intranasal influenza vaccines have been developed. An inactivated virosomal-subunit influenza vaccine licensed in Switzerland (Nasalflu, Berna Biotech) was available for the 2000–2001 influenza season; it contained *Escherichia coli* heat-labile toxin as a mucosal adjuvant. A different live attenuated, cold-adapted influenza vaccine was recently licensed in the United States.[4]

No serious adverse events were reported with the Swiss vaccine in the prelicensure trials conducted among 1218 volunteers during four winter seasons (1996 to 1999).[5-9] It was introduced to the Swiss market in October 2000 as the first licensed intranasal influenza vaccine in the world.

During the seven-month period beginning that month (i.e., October 2000 to April 2001), the Swiss Drug Monitoring Center and various University of Zurich institutions received 46 sentinel case reports of Bell's palsy among recipients of the vaccine, including 43 from German-speaking parts of Switzerland. The media reported these events in March 2001. Subsequently, Berna Biotech suspended distribution of the vaccine and invited our institutions at the University of Zurich to investigate whether the inactivated intranasal vaccine was associated with an increased risk of Bell's palsy. The Centers for Disease Control and Prevention joined the investigation in November 2001. The Swiss intranasal vaccine is now no longer in clinical use.

There has been no systematic survey of Bell's palsy in Switzerland. The reported incidence of Bell's palsy in other countries has ranged from 15 to 40 cases per 100,000 population per year.[10-16]

METHODS

STUDY DESIGN

We conducted a matched case–control study in which patients with Bell's palsy (case patients) and control patients were matched according to age, date of their clinic visit, and physician. Since about 74,000 doses of the intranasal vaccine, or more than 80 percent of the intranasal-vaccine supply, were distributed in the 19 German-speaking regions of Switzerland, this region was defined as the study area. To gain a better understanding of the timing of the risk for Bell's palsy after administration of the intranasal vaccine, we assessed the onset intervals (i.e., the intervals from the date of the first dose of the vaccine to the date of the first visit to a physician for Bell's palsy) in a larger series of patients, a method referred to as case-series analysis.

The study protocol was approved by the ethics committees of the regions involved in the study. All the patients gave written informed consent, except for a small minority with additional cases reported by physicians anonymously. The academic investigators had access to all the study data, took responsibility for designing and conducting the analysis, and had authority over the manuscript preparation and the decisions concerning publication.

SELECTION OF CASE PATIENTS AND CONTROLS

All 4891 primary care physicians, ear, nose, and throat specialists, and neurologists in the study area were invited twice to report cases of Bell's palsy first diagnosed between October 1, 2000, and April 30, 2001. The overall response rate was 81.1 percent. Subsequently, the physicians who had reported cases of Bell's palsy were asked to document the date of the visit and information pertinent to the study's inclusion and exclusion criteria and to select, from among their patients without Bell's palsy, three controls sequentially from their registration log. The controls were matched with the case patients according to age (within five years), date of the clinic visit (within four days), and physician. Trained study monitors contacted the physicians and reviewed the selection forms regularly to ensure consistency in the selection of controls. At this point, participating physicians had not been made aware of the exposure to be investigated (influenza vaccination). Thereafter, questionnaires requesting clinical information about the case patients and controls were sent together with informed-consent forms to both the physicians and their patients. The patients' questionnaires were used primarily for validation of the information provided by the physicians. When there was a discrepancy, both the patient and the physician were contacted for clarification.

Patients with Bell's palsy were eligible for the

study if they were at least 18 years of age and if they had complete or incomplete unilateral weakness of the facial muscles. The onset of weakness had to be sudden, and the progression of facial palsy had to reach a maximum within one week after the onset of the first symptoms. Exclusion criteria were head trauma within two months before enrollment and a history of brain tumor, cerebrovascular accident, ipsilateral ear disease or surgery, or the Guillain–Barré syndrome. Patients were not selected as controls if they met the same exclusion criteria or if they received a clinical diagnosis of influenza at the index visit. The exclusion of patients with influenza as controls was a measure taken in an effort to prevent an overrepresentation of patients with influenza as controls during the winter season. Physicians who were unwilling to select controls were still asked to document any cases.

EXPOSURE TO INFLUENZA VACCINES

Physicians were asked to document the dates of administration and the brand name and type of influenza vaccine (parenteral or intranasal) used during the study period. Other vaccine exposures during the study period and the preceding two months were also documented. Since in all 43 sentinel cases reported in the study area the onset of Bell's palsy occurred within 91 days after intranasal vaccination, we defined the period of 1 to 91 days as the postexposure risk period.

For 10 exposed case patients and 1 exposed control, we were unable to calculate the onset interval because the date of vaccination was unknown. We decided to include them in the conditional logistic-regression analysis on the assumption that they had an onset interval of 1 to 91 days, because including them would provide a more conservative estimate of the adjusted odds ratio for Bell's palsy with use of the intranasal vaccine than would excluding them.

COVARIATES

Additional information, including potential risk factors for Bell's palsy,[11-21] was obtained from physicians and patients. Documented information at the time of enrollment included sex, nationality, pregnancy status, smoking status, current infectious diseases (upper respiratory infections, influenza, herpes simplex, other herpes infections, borreliosis, human immunodeficiency virus infection, and *Mycoplasma pneumoniae* infection), chronic diseases (di-abetes, cardiovascular diseases, hypertension, asthma, allergies, and neoplasm), and a personal or family history of Bell's palsy.

STATISTICAL ANALYSIS

Matched Case–Control Study

The date of the first visit to a physician for Bell's palsy was used as the index date and was documented for all the case patients. The date of administration of the first dose of the intranasal vaccine was defined as the exposure date. Conditional logistic regression (SAS version 8, SAS Institute) was performed to estimate the risk of Bell's palsy during the period from 1 to 91 days after vaccination (the predefined risk period), with adjustment for the potential risk factors defined as covariates.

Case-Series Analysis

To determine which exposure periods after vaccination were associated with the highest risk of Bell's palsy, we performed a case-series analysis.[22,23] The case series included 412 case patients (250 from the case–control study and 162 from the group of case patients without controls). We compared the risk of Bell's palsy during various periods after intranasal or parenteral vaccination (1 to 30, 31 to 60, and 61 to 91 days, as compared with 92 or more days).

Risk Assessment after Adjustment for Biases

To assess the presence and the magnitude of selection bias, we compared the number of case patients who had been exposed to the intranasal vaccine during the case–control study with the number of the sentinel case patients and with the series of case patients for whom there were no matched controls. In addition, we estimated the relative and excess risks based on the risk in the adult population and the number of doses of the intranasal vaccine distributed in the study area.

RESULTS

STUDY POPULATION

A total of 1291 cases of Bell's palsy were reported during the seven-month period in the study area. Eighty-one (6.3 percent) represented duplicate cases, 187 (14.5 percent) involved patients who were not identifiable in the medical records, and 250 (19.4 percent) involved patients who were ineligible for the study because they were younger than 18 years of age (34 patients), had an onset of Bell's

palsy before or after the study period (101), did not have Bell's palsy (31), or met one or more exclusion criteria (84).

Of the remaining 773 patients with Bell's palsy, 361 (46.7 percent) were not enrolled because their providers declined to participate; the other 412 (53.3 percent) were enrolled. The diagnosis was confirmed by a specialist in 298 patients (72.3 percent) and by a primary care physician in 114 (27.7 percent). Of the 412 case patients, 250 (60.7 percent) were matched with 722 controls; the providers of the remaining 162 case patients declined to enroll controls.

CASE–CONTROL STUDY

Table 1 summarizes the characteristics of the case patients, controls, and all vaccinees. Sixty-eight of the 250 patients with Bell's palsy (27.2 percent)

and 8 of the 722 controls (1.1 percent) had received the inactivated intranasal vaccine (P<0.001). Of the patients who had not received the intranasal vaccine, 27 of the 182 patients with Bell's palsy (14.8 percent) and 90 of the 714 controls (12.6 percent) had been immunized with parenteral influenza vaccine before the index date (Table 2).

Conditional logistic-regression analysis showed that the adjusted odds ratio for a diagnosis of Bell's palsy during the 91-day exposure period among recipients of intranasal vaccine, as compared with controls, was 84.0 (95 percent confidence interval, 20.1 to 351.9) (Table 2). In contrast, there was essentially no risk of Bell's palsy after receipt of the traditional, parenteral influenza vaccine (adjusted odds ratio, 1.1; 95 percent confidence interval, 0.6 to 2.0). The only risk factor for Bell's palsy other than receipt of the intranasal vaccine was a nation-

Variable	Case–Control Study			All Vaccine Recipients (Case Patients and Controls)		
	Case Patients (N=250)	Controls (N=722)	Additional Patients with Bell's Palsy (N=162)	Intranasal Vaccine (N=99)	Parenteral Vaccine (N=130)	Crude Odds Ratio (95% CI)*
Demographic characteristic						
Age — yr						
Mean	49.9	50.3	49.7	50.0	54.8	
Median	49.7	50.3	48.1	49.0	57.0	
Sex — no. (%)						
Female	136 (54.4)	389 (53.9)	76 (46.9)	60 (60.6)	73 (56.2)	1.0
Male	114 (45.6)	328 (45.4)	85 (52.5)	38 (38.4)	57 (43.8)	0.8 (0.5–1.4)
Unknown	0	5 (0.7)	1 (0.6)	1 (1.0)	0	
Nationality — no. (%)						
German-speaking countries	203 (81.2)	569 (78.8)	129 (79.6)	92 (92.9)	114 (87.7)	1.0
Other countries	21 (8.4)	54 (7.5)	30 (18.5)	1 (1.0)	6 (4.6)	0.2 (0–1.3)
Unknown	26 (10.4)	99 (13.7)	3 (1.9)	6 (6.1)	10 (7.7)	0.7 (0.3–2.1)
Relevant diagnosis or intervention — no. (%)						
Type 2 diabetes	21 (8.4)	51 (7.0)	17 (10.5)	6 (6.1)	32 (24.6)	0.2 (0.1–0.5)
Hypertension	61 (24.4)	173 (24.0)	40 (24.7)	28 (28.3)	67 (51.5)	0.4 (0.2–0.7)
Asthma	6 (2.4)	41 (5.7)	6 (3.7)	7 (7.1)	11 (8.5)	0.8 (0.3–2.4)
Infectious disease	47 (18.8)	205 (28.4)	32 (19.8)	21 (21.2)	45 (34.6)	0.5 (0.3–1.0)
Upper respiratory infection	35 (14.0)	123 (17.0)	21 (13.0)	13 (13.1)	29 (22.3)	0.5 (0.1–1.1)
Other vaccination	5 (2.0)	27 (3.7)	2 (1.2)	3 (3.0)	4 (3.1)	1.0 (0.2–5.4)

Table 1. Demographic Characteristics and Underlying Conditions of the Patients with Bell's Palsy and the Controls.

* The crude odds ratio was calculated to assess differences between the intranasally and the parenterally vaccinated patients. CI denotes confidence interval.

ality within southern Europe (adjusted odds ratio, 2.4; 95 percent confidence interval, 1.3 to 4.7). In addition, controls were more likely than case patients to have an infectious disease, although the difference was barely significant (adjusted odds ratio, 0.47; 95 percent confidence interval, 0.23 to 0.98).

Table 2. Risk of Bell's Palsy among Participants in the Case–Control Study.*

Vaccine and Bell's Palsy Onset Interval	Case Patients (N=250)	Controls (N=722)	Adjusted Odds Ratio (95% CI)
	no. (%)		
Intranasal vaccine†			
Onset interval ≤91 days	63 (25.2)	7 (1.0)	84.0 (20.1–351.9)
Onset interval >91 days	5 (2.0)	1 (0.1)	
Parenteral vaccine			
Onset interval ≤91 days	10 (4.0)	41 (5.7)	1.1 (0.6–2.0)
Onset interval >91 days	17 (6.8)	49 (6.8)	

* The date of vaccination (the date of the first dose in the case of intranasal vaccine) and the date of the first visit to a physician for Bell's palsy (the index date) were used to determine the onset interval. This information was obtained from the medical records. Case patients and controls were matched according to age, date of the clinic visit, and physician. The odds ratios for Bell's palsy were estimated by conditional logistic-regression analysis. CI denotes confidence interval.
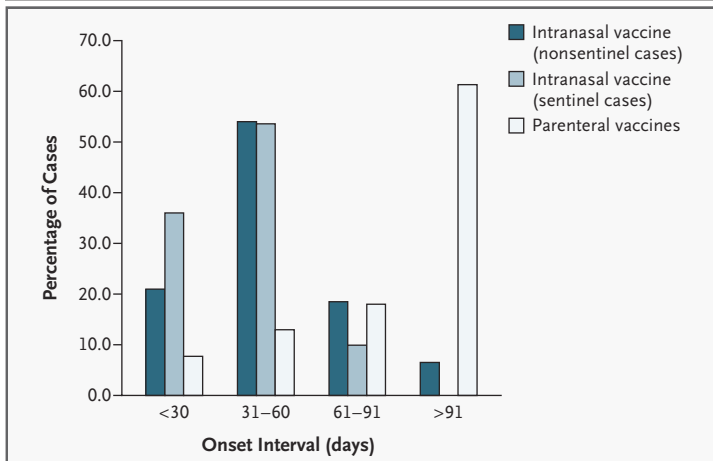† For 10 case patients and 1 control, the onset interval was unknown.

Figure 1. Onset Intervals among the Patients with Bell's Palsy.
Among nonsentinel cases of Bell's palsy in which the intranasal vaccine had been administered, the onset interval was defined as the period from the first dose of the intranasal vaccine to the first visit to a physician for Bell's palsy; among sentinel cases, the onset interval was defined as the period from the first dose of the intranasal vaccine to the onset of Bell's palsy. Among cases of Bell's palsy in which a parenteral vaccine had been administered, the onset interval was defined as the period from vaccination to the first visit to a physician for Bell's palsy.

CASE-SERIES ANALYSIS AND RISK PERIODS
In our case-series analysis of 412 patients, we identified 91 intranasally vaccinated patients with Bell's palsy, 81 of whom had adequate data for calculating onset intervals. Forty-four of these 81 patients (54.3 percent) first visited a physician because of symptoms 31 to 60 days after intranasal vaccination (relative incidence of Bell's palsy after intranasal vaccination, 35.6; 95 percent confidence interval, 14.1 to 89.8), 17 (21.0 percent) had an onset interval of 1 to 30 days (relative incidence, 14.0; 95 percent confidence interval, 5.2 to 37.9), 15 (18.5 percent) had an onset interval of 61 to 91 days (relative incidence, 11.8; 95 percent confidence interval, 4.3 to 32.3), and 5 (6.2 percent) had an onset interval exceeding 91 days (Fig. 1). The onset intervals in sentinel cases had a similar distribution, although in more than one third of the sentinel cases the onset interval was 1 to 30 days. In contrast, 61.5 percent of parenterally vaccinated case patients had an onset interval of more than 91 days. Table 3 provides data on the neurologic outcome in these patients.

RISK ASSESSMENT AFTER ADJUSTMENT FOR BIASES
We were concerned that in our case–control study we may have overestimated the risk of Bell's palsy after intranasal vaccination, for the following two reasons. First, sentinel cases had a higher probability of being included in the case–control study (22 of 43 cases [51.2 percent]) than nonsentinel cases (228 of 730 [31.2 percent]) (Table 4). Second, the proportion of patients with Bell's palsy who had been exposed to the vaccine was 27.2 percent (68 of 250 patients) in the case–control study but only 14.2 percent (23 of 162 patients) in the series of case patients without controls (Table 4). We used two approaches to estimate the total number of exposed case patients in the entire group of 773 patients with Bell's palsy in order to adjust for this likely overestimation.

Approach 1
We assumed that nonsentinel cases of Bell's palsy with vaccine exposure had the same probability of being included in either the case–control study or the case series as did sentinel cases. According to Table 4, this assumption forces the following equation: $(22+5)\div43=(46+18)\div(64+x)$, which is solved when x=38 and which yields an estimate of 145 total (sentinel and nonsentinel) cases with vaccine exposure.

Approach 2

The proportion of cases with vaccine exposure was higher in the case–control study than in the case series, with an odds ratio of 2.25 (27.2 percent vs. 14.2 percent). We assumed that the odds of exposure in the case series was also 2.25 times the odds of exposure in the remaining, unreported cases. This assumption forces the following equation: $[0.142 \div (1-0.142)] \div [(16+x) \div (361-[16+x])] = 2.25$, which is solved when $x=9$ and which yields an estimate of 116 total exposed cases (Table 4).

The more conservative estimate of 116 cases of Bell's palsy with vaccine exposure, as calculated with the second approach, yields an overall risk associated with exposure of 15.0 percent (116 of 773 cases overall). Thus, among 250 cases in the case–control study, one would have expected 38 cases with exposure, rather than the observed 68. This suggests that the adjusted odds ratio in the case–control study may have been overestimated by a factor of $(0.272 \div [1-0.272]) \div (0.150 \div [1-0.150])$, or 2.1. When we accounted for the overestimation, the estimate of the adjusted odds ratio was reduced to 40.0 ($84.0 \div 2.1$).

We identified 107 cases of Bell's palsy with vaccine exposure from all sources of information (Table 4). We assumed that they constituted all the exposed cases (and that there were no additional instances of exposure among the 361 nonparticipating patients with Bell's palsy). We also had information on the size of the adult population in the study area (4.056 million) and on the doses of intranasal vaccine that were distributed for 74,000 vaccinees. The estimated 666 cases of Bell's palsy without exposure (773 cases overall, minus 107 cases with exposure) over a seven-month period in a population of 3.982 million adults (4.056 million overall, minus 0.074 million vaccinees) yields a rate of 29 cases per 100,000 population per year.

On the basis of the available onset intervals among the cases of Bell's palsy with vaccine exposure, we estimated that in 93.8 percent of these cases the palsy developed 1 to 91 days after vaccination. Combining this result with the minimum number of 107 for all cases of Bell's palsy with exposure would yield 100 as the number of intranasally vaccinated patients in whom the palsy developed within 1 to 91 days. This would yield an estimated rate of 541 cases of Bell's palsy per 100,000 vaccinees per year, with a relative risk of 19 for the three months after intranasal vaccination and a corresponding excess risk of 13 cases per 10,000 vaccinees.

DISCUSSION

We found that the intranasal influenza vaccine used in Switzerland during the 2000–2001 influenza season greatly increased the risk of Bell's palsy among vaccinees. The association was strong, temporal, and specific. The risk was highest during the second month after intranasal vaccination. In contrast, no significant risk of Bell's palsy was found to be associated with the parenteral influenza vaccines.

We faced substantial challenges in the process of collecting data. Because of strict medical-privacy standards in Switzerland, few physicians would allow us to review the medical records on site or off site, in the form of photocopies. The time required for physicians to enroll both cases and controls became a formidable burden. Consequently, we were able to enroll only about one third of the identified cases in the case–control study. Our data suggested that patients with Bell's palsy who had received the intranasal vaccine were overrepresented in the case–control study, probably because of the regional media coverage of this problem. Furthermore, the exact magnitude of the risk associated with use of the intranasal vaccine was difficult to quantify because of the small number of controls who had received it.

All these factors raised concern about the ability of the case–control study to provide unbiased results. However, even after we adjusted for possible biases, our risk assessment provided strong evidence supporting our findings. Even with the most conservative assumption — that the 107 documented cases with exposure were the only such cases — the association of Bell's palsy and intranasal vaccination was still overwhelming, with a relative risk of at least 19 and an excess risk of 13 cases per 10,000 vaccinees. The population-based risk esti-

Table 3. Outcome of Patients with Bell's Palsy.*

Cranial-Nerve Function†	Intranasal Vaccine (N=91)	Parenteral Vaccine (N=40)	No Vaccine (N=281)
	number (percent)		
Complete (100%)	73 (80.2)	27 (67.5)	180 (64.1)
Incomplete	15 (16.5)	7 (17.5)	62 (22.1)
≥95%	7 (7.7)	4 (10.0)	18 (6.4)
<95%	8 (8.8)	3 (7.5)	44 (15.7)
Unknown	3 (3.3)	6 (15.0)	39 (13.9)

* Because of rounding, not all percentages total 100.
† Cranial-nerve function (the function of the seventh cranial nerve) was documented by the patients' physicians.

Table 4. Distribution of Cases of Bell's Palsy According to the Data-Collection Process and Exposure to the Intranasal Vaccine.*

Case Patients	Cases with Vaccine Exposure		Cases without Vaccine Exposure	All Cases	Percentage of Cases with Vaccine Exposure
	Sentinel	Nonsentinel			
			number		
Enrolled in case–control study†	22	46	182	250	27.2
Enrolled without controls‡	5	18	139	162	14.2
Not enrolled	16	x	361−[16+x]	361	≥4.4
Total	43	64+x	321+[361−(16+x)]	773	

* Values for the variable x were found in each of two methods used to evaluate the probable overestimation of the risk of Bell's palsy after intranasal vaccination.
† These case patients were enrolled in both the case–control study and the case-series analysis.
‡ These case patients were enrolled only in the case-series analysis because controls were not made available by the participating physicians.

mate for the cases of Bell's palsy without exposure was within the ranges reported in the literature.[10-16] The relatively high risk of Bell's palsy among southern Europeans has been reported previously.[24,25] We cannot explain the finding that controls were more likely than case patients to have infectious diseases, since this variable included multiple diseases, each of which affected only a small number of patients.

The clinical features of the Bell's palsy affecting the patients in this study were consistent with those described in the literature.[21] About one in five patients in all the groups had an incomplete recovery; loss to follow-up was more common among parenterally vaccinated or unvaccinated patients than among intranasally vaccinated patients.

The causes and pathogenesis of Bell's palsy remain unclear. Herpes simplex has been suspected,[26-28] but autoimmune processes have also been considered.[21] The results of studies in animals have raised concern that the adjuvant *Escherichia coli* heat-labile toxin may be an inflammatory mediator,[3,29] but preclinical research on its toxicologic characteristics and biologic distribution did not support this idea,[30] and neurologic toxicity of this substance in humans has never been described. Further studies are needed to investigate the pathogenesis of Bell's palsy after use of the inactivated intranasal influenza vaccine. Adverse neurologic events, such as Bell's

palsy, should be monitored for at least 60 days when any intranasal influenza vaccine is tested.

In the prelicensure trials of the intranasal influenza vaccine, no cases of Bell's palsy were reported among 1218 recipients (Spyr C, Berna Biotech: personal communication). However, 46 cases of Bell's palsy were reported shortly after licensure. Historically, the sample sizes for even the largest phase 3 trials before licensure have been based on efficacy, not on safety considerations. Unfortunately, as with the experience with the rotavirus vaccine and intussusception,[31] the risk of Bell's palsy found after licensure of the intranasal influenza vaccine could not have been detected beforehand, given the sample size in the prelicensure trials. These experiences may reinforce the arguments both for larger prelicensure safety trials[32] and for enhanced postlicensure surveillance.[33]

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