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ORIGINAL RESEARCH ARTICLE

Facial Paralysis Following Influenza Vaccination: A Disproportionality Analysis Using the Vaccine Adverse Event Reporting System Database

Ashwin Kamath[1] · **Nivedita Maity**[2] · **Manel Arjun Nayak**[3]

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Abstract

Background and Objective Several cases of facial paralysis have been reported following influenza vaccination; however, recent surveillance studies have not shown an increased risk. In this study, we analyzed the vaccine adverse event reporting system (VAERS) data to determine whether the facial paralysis reporting rate is higher in those who received influenza vaccination compared with those who received other vaccines.

Methods We evaluated reports of facial paralysis in people who received influenza vaccination during January 2015 to October 2019 using Medical Dictionary for Regulatory Activities Preferred Terms. A disproportionality analysis was performed to determine the proportional reporting ratio (PRR), Chi-square statistic, and reporting odds ratio (ROR) with 95% confidence interval (CI). The demographic and clinical characteristics of the cases were also analyzed.

Results Two hundred fifty cases of facial paralysis following influenza vaccination were reported during the study period. The median age of the patients was 45 (interquartile range, 30–57) years; 132 (52.8%) patients were females. The majority of the patients received the injected trivalent or quadrivalent seasonal influenza vaccine by intramuscular route. The PRR, Chi-square statistic, and ROR (95% CI) was 2.44, 122.32, and 2.44 (2.08–2.88), respectively; on excluding cases involving concomitant paresis/paralysis of limbs or Guillain–Barre syndrome, the disproportionality statistics were 2.30, 89.37, and 2.30 (1.93–2.75), respectively.

Conclusions Our study shows increased reporting of facial paralysis following influenza vaccination as compared with other vaccines. Considering the inherent limitations of the VAERS database analysis, and the fact that disproportionality measures only indicate the presence of a signal, our study findings need to be explored in well-designed prospective pharmacoepidemiologic studies.

1 Introduction

Influenza is a seasonal viral infection. The outbreaks usually occur in winter months in areas with a temperate climate and during rainy season in tropical regions, although there may not be a distinct pattern in all geographical areas [1]. Worldwide, approximately 2–5 million cases of severe influenza infection and up to 500,000 deaths are estimated to be caused by the virus epidemic annually; the annual infection rates are 5–10% in adults and 20–30% in children [2]. Pandemics of influenza are highly unpredictable and

Key Points

Evidence for facial paralysis following influenza vaccination is conflicting

Disproportionality analysis of recent 5-year vaccine adverse event data was performed

A signal of increased likelihood of reporting of facial paralysis following influenza vaccination was found

✉ Ashwin Kamath
ashwin.kamath@manipal.edu

1 Department of Pharmacology, Kasturba Medical College, Mangalore, Manipal Academy of Higher Education, Manipal, Karnataka, India

2 Department of Pharmacology, M.S. Ramaiah Medical College, Bengaluru, Karnataka, India

3 Department of General Medicine, Kasturba Medical College, Mangalore, Manipal Academy of Higher Education, Manipal, Karnataka, India

have resulted in significant mortality globally [3]. Despite the high disease burden, the currently marketed vaccines provide only partial protection against seasonal influenza, typically ranging from 10 to 60%, and there is a need for the vaccines to be updated each year in view of the antigenic change that occurs in the virus [4]. Also, the production of a strain-specific vaccine is time-consuming and provides little or no protection against the newer pandemic influenza strains [5].

The World Health Organization recommends vaccination of high-risk groups with yearly seasonal influenza vaccine. As per the guidelines, the vaccine should be recommended to healthcare workers, pregnant woman, and people with chronic disease conditions like chronic obstructive pulmonary disease, asthma, heart disease, liver disease, etc.[6]. However, concerns about the adverse effects of the influenza vaccine have been a reason for its underutilization [7]. The influenza vaccine, which can be an inactivated or live attenuated vaccine, is generally associated with minor adverse effects such as fever, malaise, myalgia, and injection site soreness [8]. Though uncommon, several neurological complications have been reported following influenza vaccination, such as Guillain–Barre syndrome [9] and chronic inflammatory demyelinating polyneuropathy [10], although the association with the vaccine has not been adequately established [11, 12]. One of the neurological adverse effects of concern has been facial paralysis, particularly Bell's palsy.

Zhou et al. analyzed the Vaccine Adverse Event Reporting System (VAERS) for reports of Bell's palsy following vaccination with intranasal inactivated influenza vaccine in Switzerland during 1991–2001 [13]. They found an increased proportional reporting ratio (PRR) in all age groups, with the maximum reports being in the elderly. However, based on the findings of two subsequent well-conducted studies, the Institute of Medicine's Committee to Review Adverse Effects of Vaccines concluded that there was no causal relationship of inactivated influenza vaccine with Bell's palsy [14]. Subsequent studies have shown conflicting results [15, 16], with most of the recent follow-up studies showing no increased risk [17–22].

In light of the above findings, we intended to determine whether a current analysis of the VAERS database for reports of facial paralysis over the past 5 years would reveal a signal and describe the clinical characteristics of the cases. In order to account for the different types of influenza vaccines available and the difficulties involved in identifying Bell's palsy from a user-reported passive surveillance system [23], in our study, we included reports of facial paralysis following vaccination with any of the currently marketed influenza vaccine.

2 Methods

We searched the VAERS database for reports of facial paralysis in people who received influenza vaccination alone or in combination with any other vaccine from January 2015 to October 2019. VAERS is a passive reporting system, maintained by the Center for Disease Control and Prevention and the United States Food and Drug Administration (FDA) [24]. The adverse events are limited to those reported by the US population. The study protocol was approved by the Institutional Ethics Committee.

In the VAERS database, the adverse event data of each case are present in three sets of files: VAERSDATA.CSV, VAERSVAX.CSV, and VAERSSYMPTOMS.CSV [24]. We searched the VAERSSYMPTOMS.CSV for cases of facial paralysis using the following Preferred Terms of Medical Dictionary for Regulatory Activities (MedDRA) terminologies: Bell's phenomenon, Facial asymmetry, Facial palsy, Facial paralysis, Facial paresis, Facial nerve disorder, VIIth nerve injury, and VIIth nerve paralysis. Reports for all influenza vaccines, irrespective of the type of vaccine, the route of administration, or the manufacturer were included. The reports included in the analysis had to fulfil the following three criteria: reported during the time period January 2015 to October 2019; the report should list any of the influenza vaccines as being administered prior to the adverse event, irrespective of the presence or absence of any other vaccine; at least one of the symptoms or signs reported should be one of the preferred terms for facial paralysis mentioned above. For all the reports of facial paralysis identified following influenza vaccination, two authors read the adverse event description to determine whether the facial paralysis was likely to be Bell's palsy or isolated facial paralysis, or was part of a more widespread paresis/paralysis (for example, hemiplegia), so as to avoid overestimation of the adverse event; any discrepancy in the results was resolved by consensus.

We also recorded the number of adverse events other than facial paralysis that were reported with influenza vaccine for the disproportionality analysis. We also searched the database for reports of facial paralysis reported with all the other vaccines listed in the VAERS database and the total number of other adverse events reported with the same.

2.1 Disproportionality Analysis

A disproportionality analysis was performed to determine the PRR, Chi-square statistic, and reporting odds ratio (ROR) with 95% confidence interval (CI) [25]; these frequentist data mining approaches are reliable and relatively easier to compute and understand compared with the Bayesian approaches [26]. PRR and ROR are akin to the

calculation of relative risk and odds ratio, respectively, based on a two-by-two contingency table (Table 1), except that the disproportionality measures help in identifying potential signals of an adverse event occurring due to a drug; such signals are not confirmatory [27]. The analysis was performed twice; first, by including all cases of facial paralysis identified by the database search; second, by excluding events where the facial paralysis was associated with more widespread paralysis or Guillain–Barre syndrome (unlikely to be Bell's palsy/isolated facial paralysis). A PRR > 2, Chi-square statistic > 4, and ROR > 2 with the lower bound 95% CI > 1 were considered significant [28, 29].

2.2 Statistical Analysis

We analyzed the adverse event data to determine the various patient and adverse event characteristics such as age, gender, presence or absence of paralysis of limbs, severity, time of onset of adverse event following vaccination, history of allergies, and co-administration of other vaccines. Continuous variables have been reported as median and interquartile range since the data were not normally distributed, as determined using Shapiro–Wilk test ($p < 0.05$); categorical variables have been reported as proportion and percentage. Kruskal–Wallis test was used to compare the continuous variables between groups. Categorical variables were compared using Chi-square test. The data were analyzed using Statistical Package for Social Sciences, version 11.5 (SPSS Inc., Chicago, IL, USA). A p value < 0.05 was considered statistically significant.

Table 1 Contingency table for disproportionality analysis

	Adverse event of interest	All other adverse events	Total
Vaccine of interest	P	Q	P + Q
All other vaccines	R	S	R + S

Proportional reporting ratio = (P/P + Q)/(R/R + S)

Reporting odds ratio = (P/Q)/(R/S)

3 Results

From January 2015 to October 2019, 253 reports of facial paralysis in patients who received influenza vaccine were reported. Of these, three reports were not included in the analysis; one patient did not receive influenza vaccine, and two reports were repetitions. During the same time period, 51,383 adverse events, other than the target adverse event, were reported with influenza vaccine. Similarly, 346 reports of facial paralysis were available for all the other vaccines and 173,858 other adverse events. On excluding facial paralysis adverse events associated with more widespread paralysis or Guillain–Barre syndrome, the number of target adverse events were 207 in those who received influenza vaccine and 304 in those who received other vaccines. These numbers formed the inputs for the contingency table for the calculation of the disproportionality measures. Of the 263 facial paralysis adverse event terms reported, the preferred term facial paralysis constituted 168 (63.9%), VIIth nerve paralysis constituted 65 (24.7%), facial paresis 27 (10.3%), and facial asymmetry 3 (1.1%). Table 2 shows the disproportionality analysis results for facial paralysis adverse events following immunization.

For influenza vaccines, the probability of reporting facial paralysis, rather than any other adverse event, was approximately two times higher compared to the probability for other vaccines. The lower limit of 95% CI of ROR was more than one. On excluding reports of facial paralysis associated with limb paralysis/Guillain–Barre syndrome, the PRR and ROR, along with the Chi-square statistic, remained above the threshold of significance, suggesting the presence of a signal of increased reporting of facial paralysis following influenza vaccination.

Table 3 shows the number of cases of facial paralysis reported each year. The median age (interquartile range) of the patients was 45 (30–57) years; 132 (52.8%) patients were female, and the gender was not recorded for 9 (3.6%) patients; 26 (10.4%) patients were ≥ 65 years of age, and age was not recorded in 22 (8.8%) patients. There was

Table 2 Disproportionality analysis of facial paralysis reported following influenza vaccination

Disproportionality measure	Results		Criteria for significance
	Including all reports of facial paralysis	Excluding those associated with paralysis of limbs/Guillain–Barre syndrome	
Proportional reporting ratio	2.44	2.30	PRR ≥ 2
Chi-square statistic[a]	122.32 ($p < 0.001$)	89.37 ($p < 0.001$)	$\chi^2 \geq 4$
Reporting odds ratio	2.44	2.30	ROR > 2
ROR 95% CI	2.08–2.88	1.93–2.75	95% CI > 1

CI confidence interval, *PRR* proportional reporting ratio, *ROR* reporting odds ratio

[a]With Yate's correction

Table 3 Age and gender distribution of patients with facial paralysis following influenza vaccination during the study period

Year (number of facial paralysis adverse events)	Age in years Median (IQR)	Females *N* (%)	Elderly[a,b] *N* (%)
2015 (62)	42 (28–52)	30 (48.4)	7 (11.9)
2016 (59)	44 (32–56)	33 (55.9)	5 (8.9)
2017 (52)	51 (34–57)	28 (53.8)	6 (12.8)
2018 (58)	44 (28–58)	29 (50)	4 (8.2)
2019 (19)	50 (44–64)	12 (63.2)	4 (23.5)

IQR interquartile range (25th–75th percentile)

[a]Does not include missing data

[b]≥ 65 years of age

Table 4 Characteristics of facial paralysis adverse events following immunization with influenza vaccine

Characteristic[a]	Value [*n* (%)]
Adverse event severity (*N* = 168)	
Life-threatening/death	5 (2)
Required emergency room visit	95 (38)
Required hospitalization	51 (20.4)
Prolongation of hospital stay	0 (0)
Resulted in disability	17 (6.8)
Time (in days) to symptom onset following vaccination, median (interquartile range) (*N* = 220)	3 (1–10)
Adverse event characteristic (*N* = 250)	
Likely to be facial paralysis	207 (82.8)
Associated with weakness/paralysis of limbs	24 (9.6)
Associated with Guillain–Barre syndrome	19 (7.6)

[a]*N* is not uniform for all the characteristics due to missing data in the adverse event database

no significant difference in age ($\chi^2(4) = 5.029$, $p = 0.284$) or gender ($\chi^2(8) = 3.648$, $p = 0.887$) or number of elderly ($\chi^2(4) = 3.422$, $p = 0.490$) based on the year of reporting. The adverse event characteristics are shown in Table 4. There was no significant gender difference in the time to symptom onset following vaccination ($Z = -0.584$, $p = 0.559$). Similarly, no significant gender difference was seen with regard to the type of influenza vaccine received ($p = 0.115$) and presence of weakness/paralysis of limbs or Guillain–Barre syndrome ($p = 0.143$). Approximately 5% of the facial paralysis events, following influenza as well as other vaccine administration, were associated with Guillain–Barre syndrome.

The type of influenza vaccine used, and the routes of administration, are shown in Table 5. Majority of the patients received the injected trivalent or quadrivalent seasonal influenza vaccine. Intramuscular route was most commonly (62.8%) used to administer the vaccines.

4 Discussion

Our study shows that the likelihood of reporting facial paralysis following influenza vaccination is higher compared with other vaccines. In spite of the close association between influenza vaccine and Bell's palsy shown in some earlier studies, literature is sparse regarding the specific mechanism. The appearance of Bell's palsy after the vaccination supports the immunological hypothesis; intranasal immunization may be more commonly associated, as it stimulates both mucosal and systemic immune responses compared to parenteral administration of influenza vaccine [30]. The higher rate of Bell's palsy for the intranasal administered vaccine-population is speculated to be due to the mucosal adjuvant, *Escherichia coli* heat-labile toxin. *E. coli* heat-labile toxin is one of the most powerful mucosal adjuvants [31]. But subsequent research did not support the above [32]. In view of the delayed occurrence of Bell's palsy, i.e. 30–60 days post-vaccination, Couch proposed that it may be due to induced response (e.g. reactivation of a herpes virus infection), rather than by a direct toxic effect of the toxin [31].

Since the adverse events reported to VAERS are not of the same data quality as in cases of a clinical trial or a prospective study, there is a likelihood of duplication of cases, misdiagnosis due to inadequate information or lack of adequate knowledge in the reporter, all of which can overestimate the risk. We tried to avoid overestimation by screening the adverse event description of individual reports of facial paralysis following influenza vaccination. All reports where there was associated weakness or paralysis of limbs or the presence of Guillain–Barre syndrome were excluded during the second round of disproportionality analysis; although there was a decrease in the disproportionality measures, PRR and ROR (and its 95% CI) remained above the criteria for significance. Since a significant score indicates only increased likelihood of reporting, rather than an actual increased risk of the adverse event, the clinical significance of these scores needs to be interpreted with caution [25].

The recent passive surveillance and cohort studies have failed to show an increased risk of facial paralysis [18–22]. Apart from the study by Zhou et al. [13], the VAERS database has not been specifically studied for facial paralysis possibly due to influenza vaccine, although the adverse effects of influenza vaccine, in general, have been studied [28]. Similar to the findings of Zhou et al. [13], Mutsch et al. found a strong association between intranasal inactivated influenza vaccine (which is no longer available) and Bell's palsy, but not parenteral vaccines, in their matched case–control study and case series analysis [33].

The recent studies, which did not find a risk for facial paralysis, followed up the patients for 7 days

Table 5 Types of influenza vaccines used and the routes of administration

Variable		*N (%)*
Type of vaccine		
FLU (H1N1)	Influenza (H1N1) monovalent (injected)	1 (0.4)
FLUX (seasonal)	Influenza virus vaccine, no brand name	30 (12.0)
FLUX (H1N1)	Influenza (H1N1) monovalent, unknown manufacturer	1 (0.4)
FLU3 (seasonal)	Influenza virus vaccine, trivalent (injected)	71 (28.4)
FLU4 (seasonal)	Influenza virus vaccine, quadrivalent (injected)	108 (43.2)
FLUA3 (seasonal)	Influenza virus vaccine, trivalent, adjuvant (injected)	4 (1.6)
FLUC4 (seasonal)	Influenza virus vaccine, quadrivalent, cell culture-derived (injected)	14 (5.6)
FLUN (H1N1)	Influenza (H1N1) monovalent (intranasal spray)	1 (0.4)
FLUN3 (seasonal)	Influenza (H1N1) trivalent (intranasal spray)	6 (2.4)
FLUN4 (seasonal)	Influenza (H1N1) quadrivalent (intranasal spray)	7 (2.8)
FLUR4 (seasonal)	Influenza virus vaccine, quadrivalent, recombinant (injected)	3 (1.2)
FLUC3 (seasonal)	Influenza virus vaccine, trivalent, cell culture-derived (injected)	4 (1.6)
Route of administration		
Intradermal		1 (0.4)
Intramuscular		157 (62.8)
Intranasal		14 (5.6)
Other		2 (0.8)
Subcutaneous		5 (2.0)
Needle and syringe (not specified further)		11 (4.4)
Unknown		41 (16.4)
Not recorded		19 (7.6)

post-vaccination, and one study for 6 weeks. The time to onset of adverse event following vaccination in our study was a median of 3 (1–10) days. Zhou et al. reported increased PRR in the 1–3 days and 1–30 days post-vaccination periods [13]. Our study did not find significant late occurrence cases, although the number of patients for whom the time of onset data were recorded was limited. The time of occurrence of the adverse event is unlikely to have significantly influenced the results, and in general, most cases occur within 6 weeks [16].

The finding of our study needs to be interpreted in light of the recent surveillance studies, considering the limitations inherent in data generated from VAERS, which is exploratory rather than confirmatory [25]. Our study found a signal of potentially increased risk of reporting based on the standard significance criteria for disproportionality analysis. A similar pattern has also been seen for Guillain–Barre syndrome, wherein VAERS database analysis has shown possible association [9], but not a recent nested case–control study [12]. Also, the data from the surveillance studies differ from our study data [19–22]. While about 5% of the facial paralysis events were associated with Guillain–Barre syndrome in our study, no cases of Guillain–Barre syndrome were reported in the surveillance studies. Most of these studies were conducted in the United Kingdom, but a recent surveillance study of 1060 vaccinated individuals from Belgium, Germany and Spain also showed similar findings [22]. Hence, if an association between facial paralysis and influenza vaccine does actually exist, the risk is likely to be very low. The annual incidence of facial paralysis is reported to be about 15–50 cases per 100,000 population [18]. However, no direct comparisons could be made with our study data since not all adverse events are reported to VAERS.

Our study has limitations. It is based on analysis of a passive surveillance system, which has inherent limitations, such as underreporting, lack of adequate data quality, absence of adequate clinical data to confirm the diagnosis, and absence of all the data for all the cases reported. We tried to avoid overestimation of the adverse event in those who received influenza vaccine by screening the adverse event description to detect associated limb paralysis or Guillain–Barre syndrome; however, due to the lack of adequate description in many of the adverse event reports, the results are approximate at best. We used the widely adopted disproportionality threshold of > 2 (for

PRR and ROR). This threshold level is used to identify signals in safety databases, and hence, an above threshold estimate does not always mean the presence of an association between the adverse event of interest and the suspect drug.

5 Conclusions

A large number of cases of facial paralysis have been reported following influenza vaccination; most of these cases occur within the first 2 weeks following vaccination with the seasonal trivalent or quadrivalent intramuscular influenza vaccine. The risk of reporting of facial paralysis following influenza vaccination seems to be higher compared with that following the administration of other vaccines. Considering the inherent limitations of the VAERS database analysis and the fact that disproportionality measures only indicate the presence of a signal, our study findings need to be explored in well-designed prospective pharmacoepidemiologic studies.

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Declarations

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Conflict of interest The authors have no conflicts of interest to declare.

Ethics approval The study protocol was approved by Kasturba Medical College Institutional Ethics Committee.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material All data pertaining to this study is available in the CDC and US FDA-managed Vaccine Adverse Event Reporting System, a public database.

Code availability Not applicable.

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