Published in final edited form as:

Otolaryngol Head Neck Surg. 2016 July ; 155(1): 81–86. doi:10.1177/0194599816639043.

Sudden-Onset Sensorineural Hearing Loss after Immunization: A Case-Centered Analysis

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Abstract

Objective.—Case reports of sudden sensorineural hearing loss (SSHL) following vaccines have led to concerns that vaccines may rarely cause hearing loss. Because of this concern, we analyzed for an association between SSHL and vaccinations.

Study Design.—We used a case-centered method, equivalent to a case control design using immunization dates from all matched members of the population to calculate exposure to vaccines, rather than sampling.

Setting.—Kaiser Permanente Northern California (KPNC), 2007 to 2013.

Subjects and Methods.—We searched KPNC databases from 2007 to 2013 for all first-time diagnoses of SSHL. We used the date of any hearing-or ear-related visit in the 60 days prior to the first SSHL diagnosis as the onset date. Using only SSHL cases immunized in the prior 9 months, we compared the vaccine exposure in several risk intervals prior to onset with the exposure to the same vaccine during the same time period in all KPNC membership, matched to sex and age.

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Author Contributions

Roger Baxter, conception and design, interpretation of data, drafting the manuscript and revising it, final approval, agreement to be accountable for all aspects of the work; **Ned Lewis**, initial conception and design, acquisition and analysis of data, revising the work critically, final approval, agreement to be accountable for all aspects of the work; **Pamela Bohrer**, substantial contributions to the conception of the work and the interpretation of results, reviewing and revising the draft, approving the final draft, agreement to be accountable for all aspects of the work; **Theresa Harrington**, substantial contributions to the interpretation of data for the work, revising the draft critically, final approval of the version to be published, agreement to be accountable for all aspects of the work; **Laurie Aukes**, substantial contributions to acquisition and interpretation of data, critical review of the draft, final approval of the version to be published, agreement to be accountable for all aspects of the work; **Nicola P. Klein**, conception and design of the work, interpretation of data for the work, revising the work critically, final approval of the version to be published, agreement to be accountable for all aspects of the work.

Disclosures

Competing interests: Roger Baxter and Nicola P. Klein have received research grants for unrelated studies from GSK, Sanofi Pasteur, Pfizer, Merck, MedImmune, Novartis, Nuron, and Protein Sciences. Theresa Harrington is an employee of the CDC.

Supplemental Material

Additional supporting information may be found at <http://otojour-nal.org/supplemental>.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Results.—During the study period, >20 million vaccines were administered at KPNC. In all risk intervals prior to onset of SSHL, we found no evidence of increased risk of immunization compared with matched controls. The odds ratios for vaccination 1 week prior to SSHL were 0.965 (95% confidence interval, 0.61–1.50) for trivalent inactivated influenza vaccine (TIV); 0.842 (0.39–1.62) for tetanus, reduced diphtheria, and reduced acellular pertussis; and 0.454 (0.08–1.53) for zoster vaccine.

Conclusion.—A large-scale analysis applying a case-centered method did not detect any association between SSHL and previous receipt of TIV or other vaccines.

Keywords

vaccine; immunization; adverse event; hearing loss; sensorineural; influenza vaccine

Background

Sudden sensorineural hearing loss (SSHL) is generally idio-pathic but in some cases may be associated with infections, vasculitides, tumors, certain genetic conditions, and cardiovascular risk factors.^{1,2} Anecdotal case reports of SSHL following vaccines have speculated that vaccines might be the cause of hearing loss in some cases.^{3–7}

Case Report

A healthy man in his 30s presented with sudden onset of right-sided tinnitus and hearing loss 6 days after receiving a trivalent inactivated influenza vaccine (TIV). The patient reported slight, intermittent dizziness but denied fever, congestion, or headache, and he had no known risk factors for hearing loss. His head and neck examination was normal. The patient had taken an appropriate dosage of ibuprofen for 2 days after TIV for self-limited, non-ear-related pain but stopped 2 days before the onset of hearing loss. His primary care provider advised decongestants, but these provided no relief of symptoms. The patient was referred to otolaryngology for further evaluation. Audiogram revealed normal hearing in the right ear to 2000 Hz, then a precipitous drop to profound hearing loss in the higher frequencies. Pure tones in the left ear were normal. Word recognition scores were 100% in both ears, and tympanograms were type A. Audiology testing performed 6 years earlier was normal bilaterally. Magnetic resonance imaging (MRI) of the brain with and without gadolinium, focused on the internal auditory canal, was normal. He was diagnosed with SSHL and treated with a prednisone taper. At the time this case occurred, intratympanic steroids were not commonly used; oral steroids alone were the standard of care. His hearing did not improve. Because of the temporal association between the SSHL and immunization, the patient's otolaryngologist brought the case to the attention of Centers for Disease Control and Prevention's (CDC's) Clinical Immunization Safety Assessment (CISA) Project to assess whether there might be a causal association between receipt of TIV and onset of SSHL. The CISA Project is a national network of vaccine safety experts from the CDC's Immunization Safety Office (ISO), 7 medical research centers, and other partners that conducts vaccine safety research and provides comprehensive clinical consultations for US health care providers regarding complex or unusual vaccine adverse events in their patients (<http://www.cdcgov/vaccinesafety/ensuringsafety/momonitoring/cisa/index.html>). In 2014,

CISA contracted with Kaiser Permanente Northern California (KPNC) to pilot application of case-centered analytic methods to assess whether specific vaccine adverse events might be associated with an increased likelihood of receipt of one of more vaccines during a risk interval. A risk interval is the biologically plausible time period during which an adverse event following an immunization might occur.⁸ Results of these analyses have supplemented other information reviewed during CISA clinical case consultations, including medical records, scientific literature, manufacturer package inserts, similar adverse event reports from the Vaccine Adverse Event Reporting System (VAERS),⁹ and expert opinion.

To assess for an epidemiological association between immunizations and SSHL, we performed a case-centered analysis within KPNC. Here we report the findings of this analysis.

Methods

Our analysis used a case-centered risk interval design, as has been used in multiple vaccine studies.^{10–17} Case-centered analyses look back from the date of onset of the case to determine whether vaccinations cluster in the risk interval prior to the onset. In this method, the observed odds of exposure (immunization) during the risk interval prior to the outcome are compared with the expected odds of exposure during the same risk interval, based on vaccination times in the population of all similar persons vaccinated with the same vaccine of interest. The method is equivalent to a matched case-control study, which uses all matched controls (no sampling) and is anchored to an index date for each case. Each case of SSHL, from the electronic search, was matched by age and sex to all KPNC members who, as of the onset date of the case SSHL, received the same vaccine as the case in the 9 months prior to the onset date of the index case. The onset date was set to the first hearing-related diagnosis in the 2 months prior to the SSHL diagnosis, as noted in Cases below. All cases and matched comparison KPNC members were vaccinated in the 9-month period prior to the onset of SSHL in the cases, and we determined the proportion of cases vaccinated within predetermined risk intervals compared with the rest of the 9 months prior to vaccination (29 days through 9 months), as well as the proportion of matched controls vaccinated in the same risk interval time period, with the same vaccine, using Cox regression. Stratified exact methods were used, with a mid-*P* adjustment for the 2-sided tests and test-based confidence intervals, as previously described.¹⁸

Study Population

This study used electronic medical records from KPNC, which provides integrated medical services to over 3.5 million members. For this study, we used data including all the years from 2007 through 2013 and required 1 year of membership prior to the diagnosis.

Cases

We searched internal KPNC databases for all first-ever (within all available data) diagnoses of SSHL, using internal electronic medical record text codes, which are more detailed and specific than *International Classification of Diseases, Ninth Revision (ICD-9)* codes. As illustrated in the presenting case, a diagnosis of SSHL is often delayed until the patient is

seen by an otolaryngologist. For this reason, to better identify the date of symptom onset, we first searched for all diagnoses during the 60 days prior to the diagnosis of SSHL and chose from among those the diagnoses that could possibly have been related or been a precursor to an SSHL diagnosis. These diagnoses included deafness, hearing loss, tinnitus, ear pain, otitis, and dizziness. We used the first date for these diagnoses as the index date for the case.

We randomly selected 25 SSHL cases from the electronic medical records that were seen within 2 weeks of immunization and 25 cases that were vaccinated outside the 2-week period but within 9 months prior to onset, for medical records review, to determine whether the case was new (not a “history of”) and whether the clinician truly made the diagnosis.

Exposure

We examined all vaccines for which over 20,000 doses were given at KPNC in the 7-year study period.

Risk and Comparison Intervals

To guide our selection of the appropriate risk intervals, we reviewed the literature, obtained expert opinion, and used database searches. We searched the Vaccine Adverse Event Reporting System (VAERS) downloadable data (<https://vaers.hhs.gov/data/data>) among reports received from June 1, 1990, through February 4, 2015, for hearing-related diagnoses in patients who received TIV alone (no concomitant vaccines). Among the 13 reports of adults diagnosed with sensorineural hearing loss, the median onset from receipt of TIV to onset of tinnitus and/or hearing loss was 2 days (mean, 3 days; range, 0–12 days). On the basis of this search and our other criteria, we selected risk intervals of 1 to 7 and 1 to 14 days for our primary analyses. To address concerns that SSHL onset might be delayed in some cases beyond the 1- to 14-day primary risk interval, we performed secondary analyses using risk intervals of days 1 to 28 and days 15 to 28 prior to onset. As a comparison interval, we used all observation time outside the 28-day risk interval in the 9 months prior to immunization (day 29 through 9 months). Nine months was selected to minimize flu vaccine receipt over successive seasons.

Given the number of vaccines administered and the incidence of SSHL, we had 80% power to detect, in the 1- to 7-day risk interval, a relative risk of 1.88 for TIV, 2.57 for tetanus reduced diphtheria acellular pertussis (Tdap), 4.3 for pneumococcal polysaccharide (Pneumovax), and 1.52 for any vaccine.

This study was approved by the KPNC Institutional Review Board.

Results

In the KPNC databases, we detected a total of 1929 cases of SSHL within 9 months of any vaccine. Of these, 57 (3.0%) were within 1 week of a vaccine. All 50 randomly selected SSHL cases were verified by chart review as new incident cases.

During the course of the study, over 20 million vaccines were given. The frequency and distribution of the vaccines are shown in Table 1.

Influenza Vaccines

We found no increased risk of prior TIV vaccination in patients with SSHL in any of the prespecified risk intervals (Table 2). The odds ratio point estimates ranged from 0.87 to 1.235, all upper 95% confidence bounds were less than 1.7, and none of the risk intervals for TIV were statistically significantly elevated.

Other Vaccines

Among the noninfluenza vaccines, there were no vaccines with a statistically significant elevated odds ratio of prior immunization in any risk interval compared with the rest of the prior 9 months (Table 3). Although the quadrivalent human papillomavirus (HPV4) vaccine had an odds ratio point estimate of 4.155, this finding was based on only 1 case in the risk interval and had wide confidence intervals (CIs).

Analyses evaluating all noninfluenza vaccines during the different risk intervals (1–14 days, 1–28 days, and 15–28 days) demonstrated similar results in that there were no statistically significant increases in the odds of vaccination in any of the risk intervals prior to the onset of SSHL (see Supplemental Material at www.otojournal.org/supplemental).

Discussion

The etiology of most cases of SSHL is unknown.² Cardiovascular risk factors may play a role, as may hypercoagulable states,¹ tumors, autoimmune diseases,¹⁹ and diet.²⁰ Viral and bacterial infectious diseases² have also been postulated as causes of SSHL, and this has led to speculation that vaccines may also potentially play a role.

Review of the 13 VAERS reports of SSHL following TIV seemed to indicate the possibility of clustering in time of SSHL with respect to TIV vaccination; however, temporal association does not prove causation when assessing the association of vaccine adverse events. Our application of case-based statistical methods clearly demonstrated no clustering of either TIV or any other vaccine prior to the outcome of SSHL.

This study was reassuring with regard to all vaccines studied. With 7 years of follow-up, monitoring over 23 million vaccines, we found no indication of an increased risk of immunization with any vaccine prior to the development of SSHL. Reassurance of vaccine safety is critical to maintain high levels of immunization and protect the public's health, particularly in these times of increasing vaccine hesitancy.

By using only cases and controls that are vaccinated with the same vaccine at some time in the past 9 months, the case-centered method controls very well for inherent differences between vaccinated and unvaccinated persons. Case-centered methods are anchored to the calendar date of the outcome onset (ie, controls are matched to cases based on calendar date) and, hence, control extremely well for time-varying confounding, such as seasonality. The method also controls very well for age, with cases matched very finely to controls by age and vaccine.

Members of KPNC are similar in race and socioeconomic status to the rest of the state of California, although as an insured population, they underrepresent the very poor.²¹ The health plan covers all routine medical care, and patients receive essentially all care within KPNC facilities. Vaccines are provided at no additional cost and are easy to obtain, so most vaccines, including influenza, are administered within the health plan. Diagnoses from hospital stays, outpatient and emergency department visits, medications, laboratory tests, immunizations, imaging, and other ancillary tests are all linked via a unique medical record number that stays with each member throughout his or her life.

Our study has some limitations. Cases were not all individually reviewed to confirm the diagnosis, so there could be some misclassification of diagnosis or onset date; however, our review of 50 random cases verified that the electronic diagnosis was highly specific. Power was dependent on the number of vaccines given. For vaccines such as TIV, with over 8 million doses, we are able to provide strong evidence against an association with SSHL, whereas with some vaccines, such as yellow fever, our confidence intervals are wide. In addition, since SSHL is often transient or mild, many affected persons may not present for care. Our study only speaks to those with medically attended SSHL. In addition, the risk intervals were selected through literature and VAERS review as well as consultation with experts. If the interval selected does not match the timing of increased risk, an association may be missed.

Conclusions

Many people, physicians and patients alike, make the presumption that if an event follows immunization, it is due to immunization. This study illustrates the fallacy in that thinking and reminds us that, since we are often giving vaccines, some adverse events are bound to happen shortly after immunization, due to random chance alone. However, when we consider millions of people and millions of vaccines, we see that SSHL was not significantly increased after immunization; hence, sporadic cases are very unlikely to be caused by vaccines. Through this study, we are appreciating how the application of case-based statistical methods can be an effective tool for helping to guide expert clinical and epidemiological assessment of vaccine adverse event causality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sponsorships: Collaborators of this CDC project were active in providing guidance on study design and conduct, as well as expert opinion. The CDC reviewed and approved the manuscript.

Funding source: This work was supported by the Clinical Immunization Safety Assessment (CISA) Project under contract 200–2012-53662 from the CDC.

References

1. Lin RJ, Krall R, Westerberg BD, Chadha NK, Chau JK. Systematic review and meta-analysis of the risk factors for sudden sensorineural hearing loss in adults. *Laryngoscope*. 2012;122:624–635. [PubMed: 22252719]
2. Chau JK, Lin JR, Atashband S, Irvine RA, Westerberg BD. Systematic review of the evidence for the etiology of adult sudden sensorineural hearing loss. *Laryngoscope*. 2010;120: 1011–1021. [PubMed: 20422698]
3. Huang HH, Huang CC, Hsueh PY, Lee TJ. Bilateral sudden deafness following H1N1 vaccination. *Otolaryngol Head Neck Surg*. 2010;143:849–850. [PubMed: 21109091]
4. Orlando MP, Masieri S, Pascarella MA, Ciofalo A, Filiaci F. Sudden hearing loss in childhood consequent to hepatitis B vaccination: a case report. *Ann N Y Acad Sci*. 1997;830:319–321. [PubMed: 9616691]
5. Mair IW, Elverland HH. Sudden deafness and vaccination. *J Laryngol Otol*. 1977;91:323–329. [PubMed: 856923]
6. Kaga K, Ichimura K, Ihara M. Unilateral total loss of auditory and vestibular function as a complication of mumps vaccination. *Int JPediatr Otorhinolaryngol*. 1998;43:73–75. [PubMed: 9596372]
7. Jayarajan V, Sedler PA. Hearing loss following measles vaccination. *J Infect*. 1995;30:184–185. [PubMed: 7636291]
8. Rowhani-Rahbar A, Klein NP, Dekker CL, et al. Biologically plausible and evidence-based risk intervals in immunization safety research. *Vaccine*. 2012;31:271–277. [PubMed: 22835735]
9. Shimabukuro TT, Nguyen M, Martin D, DeStefano F. Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS). *Vaccine*. 2015;33:4398–4405. [PubMed: 26209838]
10. Klein NP, Lewis E, Fireman B, et al. Safety of measles-containing vaccines in 1-year-old children. *Pediatrics*. 2015; 135:e321–e329. [PubMed: 25560438]
11. Fireman B, Lee J, Lewis N, Bembom O, van der Laan M, Baxter R. Influenza vaccination and mortality: differentiating vaccine effects from bias. *Am J Epidemiol*. 2009;170:650–656. [PubMed: 19625341]
12. Baxter R, Bakshi N, Fireman B, et al. Lack of association of Guillain-Barre syndrome with vaccinations. *Clin Infect Dis*. 2013;57:197–204. [PubMed: 23580737]
13. Baxter R, Ray GT, Fireman BH. Effect of influenza vaccination on hospitalizations in persons aged 50 years and older. *Vaccine*. 2010;28:7267–7272. [PubMed: 20832494]
14. Rowhani-Rahbar A, Klein NP, Lewis N, et al. Immunization and Bell's palsy in children: a case-centered analysis. *Am J Epidemiol*. 2012;175:878–885. [PubMed: 22411861]
15. Greene SK, Rett MD, Vellozzi C, et al. Guillain-Barre syndrome, influenza vaccination, and antecedent respiratory and gastrointestinal infections: a case-centered analysis in the Vaccine Safety Datalink, 2009–2011. *PLoS One*. 2013;8: e67185.
16. Klein NP, Fireman B, Yih WK, et al. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. *Pediatrics*. 2010;126:e1–e8. [PubMed: 20587679]
17. Baker MA, Lieu TA, Li L, et al. A vaccine study design selection framework for the postlicensure rapid immunization safety monitoring program. *Am J Epidemiol*. 2015;181:608–618. [PubMed: 25769306]
18. Guess HA, Thomas JE. A rapidly converging algorithm for exact binomial confidence intervals about the relative risk in follow-up studies with stratified incidence-density data. *Epidemiology*. 1990;1:75–77. [PubMed: 2081244]
19. Toubi E, Ben-David J, Kessel A, Halas K, Sabo E, Luntz M. Immune-mediated disorders associated with idiopathic sudden sensorineural hearing loss. *Ann Otol Rhinol Laryngol*. 2004; 113:445–459. [PubMed: 15224826]
20. Nakashima T, Tanabe T, Yanagita N, Wakai K, Ohno Y. Risk factors for sudden deafness: a case-control study. *Auris Nasus Larynx*. 1997;24:265–270. [PubMed: 9251855]
21. Gordon NP, Gordon NP. Similarity of the adult Kaiser Permanente membership in Northern California to the insured and general population in Northern California: statistics from the 2011–

12 California Health Interview Survey. Oakland, CA: Kaiser Permanente Division of Research, 1
1, 2012 http://www.dor.kaiser.org/external/chis_non_kp_2011/ . Accessed February 13, 2015.

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Table 1.
Vaccines Given at Kaiser Permanente Northern California (KPNC) from 2007 through 2013.^a

Vaccine	Number Given
Inactivated influenza vaccines (trivalent)	8,354,237
Tetanus, reduced diphtheria, reduced acellular pertussis (Tdap)	2,317,610
Hepatitis A	1,280,568
<i>Haemophilus influenzae</i> type b	1,162,675
Varicella	813,499
Diphtheria, tetanus, acellular pertussis, polio, hepatitis B (Pediarix)	784,457
7-Valent pneumococcal conjugate	748,325
Hepatitis B	731,201
Quadrivalent human papillomavirus (Gardasil—HPV4)	719,278
H1N1 inactivated monovalent	681,737
I3-Valent pneumococcal conjugate	647,057
Diphtheria, tetanus, acellular pertussis	622,973
Meningococcal quadrivalent conjugate (MCV4)	597,324
Live attenuated influenza (trivalent)	577,651
23-Valent pneumococcal polysaccharide (Pneumovax)	551,520
Measles, mumps, rubella (MMR)	548,983
Rotavirus (pentavalent)	465,324
Injectable polio	381,920
Zoster vaccine	376,531
Tetanus diphtheria toxoid	235,261
Measles, mumps, rubella, varicella (MMR-V)	225,546
Injectable typhoid	201,527
Rotavirus (monovalent)	173,548
Diphtheria, tetanus, acellular pertussis, polio (Kinrix)	153,175
Hepatitis A and B (Twinrix)	107,575
Pentacel (DTaP-IPV-Hib)	99,318
Yellow fever	38,484
Rabies	23,484

^aOnly vaccines with more than 20,000 doses were studied.

Number Given	
Total	23,620,788

Vaccine

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Risk of Inactivated Influenza Vaccination Prior to Onset of Sudden-Onset Hearing Loss, Kaiser Permanente Northern California, 2007 through 2013.

Table 2.

Risk Interval	Odds Ratio of Vaccination in the Risk vs Control Interval		95% Confidence Interval	P Value	Cases in Risk Interval		Cases in 9-Month Control Interval ^a	
	Risk	Control			Risk	Control	Risk	Control
1–7 days	0.965		0.61–1.50	.892	41		1286	
1–14 days	1.235		0.89–1.69	.201	92		1398	
1–28 days	1.026		0.80–1.31	.829	167		1519	
15–28 days	0.870		0.63–1.18	.377	75		1463	

^aThe control interval is the 9 months prior to immunization, excluding the 28-day risk interval.

Table 3.

Risk of Vaccination in the 1 Week Prior to Onset of Sudden-Onset Sensorineural Hearing Loss.^a

Vaccine	Odds Ratio of Vaccination in the Risk vs Control Interval	95% Confidence Interval	P Value	Cases in 1-Week Risk Interval	Cases in 9-Month Control Interval ^b
Measles, mumps, rubella (MMR)	0	0.00–33.29	.873	0	4
Injectable polio	0	0.00–92.95	.928	0	2
Hepatitis A/B (Twinrix)	2.388	0.37–9.14	.285	2	16
MCV4	0	0.00–21.06	.822	0	5
Tdap	0.842	0.39–1.62	.665	8	319
Zostavax	0.454	0.08–1.53	.258	2	124
Rabies	0	0.00–152.00	.889	0	1
DTaP	0	0.00–36.61	.874	0	4
Varicella	0	0.00–155.27	.957	0	2
Oral typhoid	0	0.00–48.96	.912	0	4
Pneumovax	0.813	0.20–2.26	.784	3	128
Yellow fever	0	0.00–44.78	.901	0	4
Injectable typhoid	1.244	0.06–6.74	.757	1	28
HPV	4.155	0.17–29.13	.273	1	6
H1N1 inactivated monovalent	1.065	0.20–3.88	.879	3	99
Hepatitis A	0	0.00–3.42	.400	0	28
Hepatitis B	0.667	0.03–3.51	.783	1	32
LAIV	0	0.00–214.66	.971	0	3
Td	0	0.00–2.67	.317	0	43
Any	0.911	0.67–1.22	.546	57	1872

Abbreviations: DTaP, diphtheria, tetanus, acellular pertussis; HPV, human papillomavirus; LAIV live attenuated influenza; MCV4, meningococcal quadrivalent conjugate; Td, tetanus, diphtheria; Tdap, tetanus, reduced diphtheria, reduced acellular pertussis.

^a All vaccines other than inactivated influenza vaccine at Kaiser Permanente Northern California, 2007 through 2013. Only vaccines that had at least 1 case of sudden-onset sensorineural hearing loss were included.

^b The control interval is the 9 months prior to immunization, excluding the 28-day risk interval.