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Hearing disorder following COVID-19 vaccination: A pharmacovigilance analysis using the Vaccine Adverse Event Reporting System

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Abstract

What is known and objective: Evidence on whether the coronavirus disease 2019 (COVID-19) vaccination could cause hearing-related adverse events is still conflicting. This study aims to access the association between COVID-19 vaccine and hearing disorder.

Methods: The Vaccine Adverse Event Reporting System (VAERS) was queried between January 2020 to November 2021. The disproportionality pattern for hearing impairment of COVID-19 vaccine was accessed by calculating the reporting odds ratio (ROR) and proportional reporting ratio (PRR). A further subgroup analysis based on the type of COVID-19 vaccine and the doses administered was performed. In addition, the disproportionalities for hearing dysfunction between COVID-19 and influenza vaccines were compared.

Results and discussion: A total of 14,956 reports of hearing-related adverse events were identified with COVID-19 vaccination and 151 with influenza vaccine during the analytic period in VAERS. The incidence of hearing disorder following COVID-19 vaccination was 6.66 per 100,000. The results of disproportionality analysis revealed that the adverse events of hearing impairment, after administration of COVID-19 vaccine, was significantly highly reported (ROR 2.38, 95% confidence interval [CI] 2.20–2.56; PRR: 2.35, χ^2 537.58), for both mRNA (ROR 2.37, 95% CI 2.20–2.55; PRR 2.34, χ^2 529.75) and virus vector vaccines (ROR 2.50, 95% CI 2.28–2.73; PRR 2.56, χ^2 418.57). While the disproportional level for hearing dysfunction was quite lower in influenza vaccine (ROR 0.36, 95% CI 0.30–0.42; PRR 0.36, χ^2 172.24).

What is new and conclusion: This study identified increased risk for hearing disorder following administration of both mRNA and virus vector COVID-19 vaccines compared to influenza vaccination in real-world settings.

KEYWORDS
COVID-19 vaccine, hearing disorder, influenza vaccine, pharmacovigilance analysis, VAERS

Congqin Chen and Fang Fu contributed equally to this work.

1 | WHAT IS KNOWN AND OBJECTIVE

The spread of Coronavirus Disease 2019 (COVID-19) has imposed a heavy burden on public health as well as global economies.[1,2] Vaccination is significantly essential to manage the COVID-19 pandemic.[3,4] As of January 10, 2022, 9.43 billion doses of COVID-19 vaccine have been administered globally.[5] With the increasing number of COVID-19 vaccine given, there are some reports of new-onset otologic symptoms, which were not listed as common potential Adverse Events following Immunization (AEFIs) during clinical trials. Shortly after vaccination against COVID-19 become available, some physicians have noticed an increased frequency of AEFI with hearing impairment, especially sudden sensorineural hearing loss (SSNHL), aural fullness and tinnitus.[6] Although there are some published case reports regarding hearing loss after COVID-19 vaccination,[7,8] the correlation between hearing impairment with COVID-19 vaccine is still unclear. Thus, to further evaluate the association between COVID-19 vaccine and hearing disorder, we performed a disproportionality analysis based on the Vaccines Adverse Event Reporting System (VAERS), which is a pharmacovigilance database used to monitor safety signals of vaccines.

2 | METHODS

2.1 | Data source

VAERS is a US spontaneous reporting system for AEFIs that is co-administered by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA).[9,10] VAERS accepts reports from vaccine manufacturers, health-care providers, vaccine recipients and others. The VAERS reports include information on age, sex, vaccines administered, dose and lot number, the AEFI experienced, and health history. Signs and symptoms of AEFI are coded by trained personnel using the Medical Dictionary for Regulatory Activities (MedDRA), a clinically validated, internationally standardized terminology.[9,11] VAERS could be applied to detect unexpected patterns of AEFI, which are unlikely to be detected in clinical trials because of the limited number of vaccine recipients involved.[12–16]

2.2 | Data extraction

Reports for individuals receiving any type of vaccine against the COVID-19 or influenza virus categorized as suspect AEFI submitted to VAERS (from January 2020 to November 2021) were selected. Cases of hearing impairment were extracted through specific preferred terms (PTs) according to the MedDRA version 20.1. The standardized MedDRA Queries (SMQ) are groupings of MedDRA terms, ordinarily at the PT level that relate to a defined medical condition or area of interest. We utilized 51 terms that matched the SMQ for "hearing impairment" (SMQ code: 20000171) (Table S1). Data such as age, sex, recovery, and onset interval (from vaccination date [day 0] to the reported onset of first symptom) were also collected.

2.3 | Disproportionality analysis

Disproportionality analysis is largely used to identify statistical associations between drugs/vaccines and events in their respective databases of safety reports.[17] If there is no link between a vaccine and an AEFI, the frequency of such AEFI will be uniformly distributed in reports listing and in those not listing the specific vaccine as suspect, thus without disproportionality. On the contrary, AEFIs that are caused by a vaccine will occur more frequently in reports listing than in those not listing the vaccine as suspect, thus generating disproportionality.[18] Proportional Reporting Ratio (PRR) is a simple way to measure the strength of the statistical association between a specific vaccine and a specific AE. This concept of disproportionality may be displayed by means of a 2×2 contingency table where: "a" is all reports for a specific adverse event ("Event Y") for Product (e.g., a vaccine) X, "b" is all reports for all other adverse events for Product X, "a + b" are all the reports for Product X, "c" is all reports for all other products for Event Y, "d" is all reports for all other products for all other adverse event, and "c + d" is all reports for all other products. The PRR = [a/(a + b)]/[c/(c + d)]. If the ratio of [a/(a + b)] is greater than the ratio of [c/(c + d)], then Event Y is "disproportionately reported" for Product X. A signal was defined as a PRR of at least 2, χ^2 of at least 4 in three or more cases.[19] The Reporting Odds Ratio (ROR) is the odds of a certain event occurring with a specific vaccine, compared to the odds of the same event occurring with all other vaccines. The ROR = (ad/cb).[20] A signal emerged if the lower limits of the 95% confidence intervals (95% CI) of ROR exceeded 1 in at least three records.[21]

2.4 | Study design

This study was determined to be exempt from institutional review board approval by Xiamen Cardiovascular Hospital because it used publicly available, deidentified data. A pharmacovigilance analysis was conducted to access the association between COVID-19 vaccine and hearing disorder. The disproportionality pattern of hearing impairment for COVID-19 vaccine within VAERS was accessed by calculating ROR and PRR. We performed a further subgroup analysis based on the type of COVID-19 vaccine (mRNA vs. virus vector) and the doses administered. In addition, to better understand the association of COVID-19 vaccination and hearing impairment, we compared the disproportionality between COVID-19 vaccine and influenza vaccine.

3 | RESULTS

3.1 | Descriptive analysis

As of November 10, at least 224,660,453 people or 68.44% of the population in U.S. have received at least one dose of COVID-19 vaccine.[22] Overall, 654,413 AEFIs related to COVID-19 vaccine and 15,670 reports related to hearing impairment were documented in

TABLE 1 Characteristics of reports to the VAERS following COVID-19 vaccination by hearing impairment

Characteristics	Reports, *n* (%)				
	mRNA (PfizerBioNTech+Moderna)	Virus vector (Johnson & Johnson's Janssen)	Mixed vaccination	Not specified	Total
N (%)	13,520 (90.40)	1414 (9.45)	1 (0.01)	21 (0.14)	14,956
Age (years)					
<18	283 (2.09)	0 (0)	0 (0)	0 (0)	283 (1.89)
18–44	3884 (28.73)	530 (37.48)	0 (0)	7 (33.33)	4421 (29.56)
45–64	6180 (45.71)	648 (45.83)	1 (100)	11 (52.38)	6840 (45.73)
≥65	2618 (19.36)	140 (9.90)	0 (0)	3 (14.29)	2761 (18.46)
Not specified	555 (4.11)	96 (6.79)	0 (0)	0 (0)	651 (4.35)
Sex					
Male	5115 (37.83)	548 (38.76)	0 (0)	7 (33.33)	5670 (37.91)
Female	8231 (60.88)	820 (57.99)	1 (100)	14 (66.67)	9066 (60.62)
Not specified	174 (1.29)	46 (3.25)	0 (0)	0 (0)	220 (1.47)
Dose					
First	6772 (50.09)	943 (66.69)	1 (100)	14 (66.67)	7730 (51.68)
Second	4707 (34.82)	3 (0.21)	0 (0)	0 (0)	4710 (31.49)
Third	221 (1.63)	–	0 (0)	0 (0)	221 (1.48)
Not specified	1820 (13.46)	468 (33.10)	0 (0)	7 (33.33)	2295 (15.35)
Recovering					
Recovered	1761 (13.03)	270 (19.09)	0 (0)	6 (28.57)	2037 (13.62)
Not recovered	9892 (73.17)	942 (66.62)	1 (100)	14 (66.67)	10,849 (72.54)
Not specified	1867 (13.81)	202 (14.29)	0 (0)	1 (4.76)	2070 (13.84)

the VAERS database during the analytic period. Among them, COVID-19 vaccination was identified as the suspected vaccine causing hearing impairment in 14,956 reports and the clinical characteristics of these vaccine recipients are presented in Table 1. AEFI of hearing impairment following COVID-19 vaccination was found with an incidence rate of 6.66 per 100,000. Most of the reports were from administration of mRNA vaccine (90.40%). Females accounted for 9066 (60.62%) reports, males accounted for 5670 (37.91%) reports, and in 220 (1.47%) reports, sex was unknown or not reported. In reports in which age was documented ($n = 14{,}305$), most ($n = 6840$, 47.82%) described persons aged 45 to 64 years. Notably, cases of hearing impairment were more common after the administration of the first dose of vaccine (51.68%). Most of the reports (72.54%) did not recover from hearing-related AEFI in time.

TABLE 2 Results of disproportionality analysis

Vaccines	Cases	ROR (95%CI)	PRR (χ^2)
COVID-19 vaccines	14,956	2.38 (2.20–2.56)	2.35 (537.58)
mRNA	13,520	2.37 (2.20–2.55)	2.34 (529.75)
1st dose	6772	2.37 (2.19–2.56)	2.34 (506.07)
2nd dose	4707	2.50 (2.31–2.71)	2.47 (551.20)
3rd dose	221	1.30 (1.12–1.52)	1.30 (11.86)
Unspecified dose	1820	2.26 (2.07–2.47)	2.24 (356.05)
Virus vector	1414	2.50 (2.28–2.73)	2.56 (418.57)
1st dose	943	2.99 (2.71–3.30)	2.93 (525.20)
2nd dose	3	0.80 (0.26–2.51)	0.81 (0.14)
Unspecified dose	468	1.90 (1.69–2.13)	1.88 (117.86)
Influenza vaccines	151	0.36 (0.30–0.42)	0.36 (172.24)

Abbreviations: 95%CI, 95% confidence interval; COVID-19, coronavirus disease 2019; PRR, proportional reporting ratio; ROR, reporting odds ratio.

3.2 | Disproportionality analysis

The results of disproportionality analysis are summarized in Table 2. These revealed significantly high reporting of hearing impairment following the administration of COVID-19 vaccine (ROR 2.38, 95% CI 2.20–2.56; PRR: 2.35, chi-square 537.58). Influenza vaccine showed a lower ROR of 0.36 (95% CI 0.30–0.42) and a lower PRR of 0.36 (χ^2 172.24), demonstrating that in comparison to COVID-19 vaccine, influenza vaccine was not associated with signal of hearing impairment. We conducted separate sub-analysis based on the type of COVID-19 vaccine and the dose administered. Both mRNA and virus vector vaccines were significantly associated with increased risk for hearing disorder compared to all other vaccines from VAERS (mRNA: ROR 2.37 95% CI 2.20–2.55, PRR 2.34 χ^2 529.75; virus vector:

TABLE 3 Time to event onset of hearing impairment following different types COVID-19 vaccine

Onset time (day)	Reports *n* (%)								
	mRNA vaccine					Virus vector vaccine			
	1st dose	2nd dose	3rd dose	Unspecified dose	Overall	1st dose	2nd dose	Unspecified dose	Overall
0–3	4196 (61.96)	2653 (56.36)	160 (72.40)	1038 (57.03)	8047 (59.52)	662 (70.20)	2 (66.67)	170 (36.32)	834 (58.98)
4–7	793 (11.71)	474 (10.07)	26 (11.76)	216 (11.87)	1509 (11.16)	93 (9.86)	1 (33.33)	36 (7.69)	130 (9.19)
8–14	500 (7.38)	379 (8.05)	16 (7.24)	162 (8.90)	1057 (7.82)	64 (6.79)	0 (0)	26 (5.56)	90 (6.36)
15–30	502 (7.41)	459 (9.75)	14 (6.33)	133 (7.31)	1108 (8.20)	71 (7.53)	0 (0)	17 (3.63)	88 (6.22)
31–60	208 (3.07)	276 (5.86)	2 (0.90)	82 (4.51)	568 (4.20)	30 (3.18)	0 (0)	10 (2.14)	40 (2.83)
61–90	44 (0.65)	75 (1.59)	1 (0.45)	16 (0.88)	136 (1.01)	9 (0.95)	0 (0)	2 (0.43)	11 (0.78)
>90	42 (0.62)	108 (2.29)	1 (0.45)	19 (1.04)	170 (1.26)	8 (0.85)	0 (0)	5 (1.07)	13 (0.92)
Unspecified	487 (7.19)	283 (6.01)	1 (0.45)	154 (8.46)	925 (6.84)	6 (0.64)	0 (0)	202 (43.16)	208 (14.71)

ROR 2.50 95% CI 2.28–2.73, PRR 2.56 χ^2 418.57). For mRNA vaccines, the ROR was highest in dose 2 (2.50, 95% CI 2.31–2.71), then it decreased to 2.37 (95% CI 2.19–2.56) in dose 1 and 1.30 (95% CI 1.12–1.52) in dose 3. The PRR reached peack in dose 2 (2.47, χ^2 551.20), then it decreased to 2.34 (χ^2 506.07) in dose 1 and 1.30 (χ^2 11.86) in dose 3. For virus vector vaccines, dose 1 was disproportionately associated with AEs of hearing loss with ROR of 2.99 (95%CI 2.71–3.30) and PRR of 2.93 (χ^2 525.20), while the disproportional values were quite lower in dose 2 (ROR 0.80, 95%CI 0.26–2.51; PRR 0.81, χ^2 0.14).

3.3 | Time to onset of COVID-19 vaccine-associated hearing impairment

The times to onset following each type and dose of COVID-19 vaccines are shown in Table 3. Interestingly, it can be seen from the data that the AEFIs of hearing impairment occurred as soon as after administration of all types of COVID-19 vaccination and all doses. For mRNA vaccines, 8047 (59.52%) cases of hearing impairment occurred within 3 days and 1509 (11.16%) cases on day 4–7 after vaccination. For virus vector vaccines, 58.98% of the cases occurred within 3 days and 9.19% on day 4–7 following administration.

4 | DISCUSSION

To the best of our knowledge, this is the first real-world disproportionality study investigating the risk of hearing impairment following COVID-19 vaccination by assessing spontaneous reports submitted to the VAERS. This post-marketing safety study stems from recent conflicting evidence surrounding the possible sudden-onset hearing loss after immunization especially COVID-19 vaccination,[6–8,23] thus joining in the wider debate on the relationship between COVID-19 vaccination and hearing impairment.

Three major findings emerged from our study: (a) Hearing impairment represented a very rare AEFI, based on the low reporting frequency retrieved in VAERS and the COVID-19 vaccination coverage rate in U.S. (b) Comparing to influenza virus vaccine, COVID-19 vaccination had higher ROR and PRR of hearing impairment. The disproportionality results showed that both mRNA and virus vector COVID-19 vaccines were associated with hearing impairment. (c) Most of the AEFIs with hearing impairment occurred within 3 days after administration of COVID-19 vaccine.

Formeister et al. conducted a preliminary analysis of incidence of SSNHL that occurred after vaccination of COVID-19 using VAERS database.[24] The incidence was estimated to be 0.3–4.1 per 100,000, which is slightly lower than our result. Narrow PTs (sudden hearing loss, deafness, deafness unilateral, deafness neurosensory, and hypoacusis) were utilized to identify AEFIs of hearing loss in this study. As the number of COVID-19 vaccine given increased, more and more reports of other otologic manifestations such as tinnitus, aural fullness, and dysacusis were noticed.[6–8,25] With this correspondence, we

performed a broad SMQ search for "hearing impairment" with 51 related PTs, which identified more reports and resulted in a slightly higher incidence. To be noted, hearing impairment represented a very rare AEFI in both studies with an incidence of <0.01% according to the CIOMS criteria.[26] Still, the pattern of "very rare" does not by itself prove no association.

During clinical trials, otologic symptoms such as hearing loss were not listed as common potential AEFIs for COVID-19 vaccine.[27,28] Due to the known limitations of clinical trials to detect particularly rare adverse events and an increase in patients present with hearing loss noticed in otologic practice,[6] we utilized VAERS, a post-marketing safety database of vaccine, to detect signals of hearing impairment. Long before COVID-19 vaccine, anecdotal case reports of SSNHL following other vaccines have led to a speculation that vaccination might be the cause of hearing loss in some cases.[29,30] Baxer and colleagues performed a large-scale case control study to analyse for an association between SSNHL and vaccinations.[21] The odds ratios for vaccination to SSNHL were 0.965 (95% CI, 0.61–1.50) for influenza vaccine, 0.842 (95% CI 0.39–1.62) for tetanus, and 0.454 (95% CI 0.08–1.53) for zoster vaccine, demonstrating no association between these vaccination and the rate of SSNHL. Given the fact that influenza vaccine has been deemed acceptably safe since they have undergone thorough safety evaluations in the form of continued population-based post-market surveillance,[31,32] we set it as the control group to compare the disproportionality pattern. Similarly, our results showed a lower ROR of 0.36 (95% CI: 0.30–0.42) and PRR of 0.36 (χ^2) for influenza vaccine, demonstrating no association with signal of hearing related disorder, while signal of disproportionate reporting for COVID-19 vaccine was found, indicating there might be a risk of hearing impairment following vaccination of COVID-19.

As of today, there are currently three COVID-19 vaccines available in US, Pfizer-BioNTech, Moderna and Janssen COVID-19 vaccine.[33] Among them, Janssen is a virus vector vaccine, while Pfizer-BioNTech and Moderna are mRNA vaccines based on new technologies that have not been deployed to the general population. So far, there have been several case reports of hearing loss following vaccination of Pfizer-BioNTech vaccine published.[7,23] Wichova et al.[6] reported 30 patients who had new or significantly exacerbated otologic symptoms that began shortly after COVID-19 vaccination, among them, 18 patients received Moderna and 12 patients received Pfizer vaccine. To specify whether the technique of vaccine play a role in hearing risk, we conducted a sub-group analysis based on the vaccine type, which showed both mRNA and virus vector COVID-19 vaccines were associated with adverse event of hearing impairment.

The hearing disorder is more common in female and middle-aged people (45–64 years) in our study. The pattern is different from the demographic characteristics in wider population based on a cross-sectional analysis, in which hearing loss was more pronounced in male and the elderly.[34] The influence of sex and age deserves further studies. Time to onset of COVID-19 vaccine-associated hearing impairment was explored too. Results showed that >50% of the reports experienced hearing-related symptoms within 3 days after vaccination. Oddly, most of the reports did not recover in time.

The FDA has issued Emergency Use Authorization (EUA) for a booster dose of the Janssen, Pfizer-BioNTech and Moderna COVID-19 vaccine months ago. There have been concerns for the safety of the booster dose due to the limited data at the moment.[35] We analysed the frequency of hearing impairment after each dose. For mRNA vaccine, the disproportional value of hearing dysfunction was highest in dose 2, and lowest in dose 3. Similarly, only three vaccines had hearing-impaired symptoms after the booster dose of virus vector vaccine. Even though limited reports of hearing impairment adverse events after booster dose were detected in our study, further pharmacovigilance research is still needed to investigate the risk when the application of booster dose in larger populations is achieved.

There are several hypotheses for the potential mechanisms of COVID-19 vaccination-induced hearing disorder.[7] Previous studies indicated an association between COVID-19 infection and audiovestibular symptoms.[36–39] Viral infection is one of the known suspicious causes of SSNHL regardless of vaccination. One hypothesis is that adenovirus vector vaccine may result in causing possible reactivation of previous latent viruses.[6] Yet in our study, despite virus vector vaccine, mRNA vaccine was also proved to be associated with hearing dysfunction. Wichova et al.[6] suggested that a potential systemic immune response induced by Immunoglobulin G (IgG) might play a role in both COVID-19 infection and vaccination-associated hearing dysfunction. Skarzynska and colleagues[40] reviewed potential audiovestibular side-effects as an ototoxic adverse reaction for COVID-19 vaccines. According to the results of clinical trials, dizziness as an ototoxic effect occurred only in hypersensitive people as part of anaphylactic shock with unknown frequency for Moderna and Pfizer-BioNTech vaccines. As for the Janssen vaccine, the most important side effects in the audiology and otorhinolaryngology field reported in the clinical trials were dizziness (of uncommon frequency) and tinnitus (rare). These conclusions may further support the hypothesis that immune response might be the potential mechanism for COVID-19 vaccine associated hearing impairing. Our analysis based on the symptoms showed that among all the 1414 reports in which virus vector COVID-19 vaccination was identified as the suspected vaccine causing hearing impairment, 253 reports were combined with dizziness, while only two cases with anaphylactic reaction. There were 13,520 mRNA hearing-impairment-related AEFIs following mRNA COVID-19 vaccination in our study, 16.64% of which were combined with symptoms of dizziness, and 20 reports with combination of anaphylactic reaction. In this real-world study, not all cases of otologic dizziness were combined with anaphylactic reaction. Sample sizes might be the reason for this difference since at least 224,660,453 people in U.S. have received at least one dose of COVID-19 vaccine during the study period. Deep investigations are needed to clarify the issues.

We acknowledge the limitations of our study, mainly inherent to the nature of self-reporting database.[41] First, cases in VAERS might contain information that is incomplete and inaccurate, especially the lack of information on concomitant medications or medical histories. Second, adverse events are usually under-reported in VAERS, which may lead to an underestimation of the associated risks. Last, previous studies have indicated an association between COVID-19 infection

and audio-vestibular symptoms.[34–37] For those reports combined with confirmed or suspect COVID-19 infection, it was hard to distinguish whether the side effects were caused by vaccines or COVID-19 itself. Eighty-eight out of 14,956 reports were with combination of COVID-19 infection in our study, this proportion may not be significant to affect the disproportional pattern of hearing impairment to COVID-19 vaccine. Still, all reports are submitted to VAERS without specific causality assessed considering the events may be coincidental and related to other causes. The inability to make causal inference is a limitation of all pharmacovigilance studies. Notwithstanding these limitations, disproportionality analysis still represents an invaluable method to monitor vaccine safety and identify novel rare signals. Many initial warnings about vaccine safety are primed by a disproportionality in the VAERS.[12–16]

5 | WHAT IS NEW AND CONCLUSION

In conclusion, this study found increased risk for hearing disorder following administration of both mRNA and virus vector COVID-19 vaccines. Further observational studies are required to verify the causality. Health care providers are urged to rigorously report all possible otologic adverse events to VAERS to allow identification of systematic vaccine safety studies and sentinel trends.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data supporting the conclusion of this article will be made available from the corresponding authors upon on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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