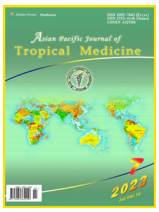

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Hearing loss and tinnitus associated with COVID-19 vaccines: An analysis from the national pharmacovigilance database in Malaysia

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ABSTRACT

Objective: To compare the reporting pattern of hearing loss and tinnitus across different vaccines brands used in Malaysia (BNT162b2, CoronaVac, ChAdOx1, Ad5.CoV2-S and BBIBP-CorV).

Methods: This retrospective study included all reports of hearing loss and tinnitus occurring after COVID-19 vaccination that were received in the national pharmacovigilance database, QUEST, from February 24, 2021 through July 31, 2022. Reports given causality consistent or indeterminate were included.

Results: There were 21 cases of hearing loss, with overall reporting rate of 0.29 cases per million doses. The rate was similar across BNT162b2, CoronaVac and ChAdOx1. For tinnitus, 35 cases were reported, with the overall reporting rate of 0.49 cases per million doses, and the highest rate was reported for ChAdOx1. For both events, most cases aged 30 to 49 years. No gender disparity was observed. Both events were mainly reported to have occurred after the primary doses, with a median time-to-onset of two days. There were no statistically significant differences in the reporting patterns for both events across BNT162b2, CoronaVac and ChAdOx1 by age group, gender, race, and dose number.

Conclusions: Despite the low reporting rates and insufficient evidence to confirm its relationship, hearing loss and tinnitus following vaccinations should not be ignored due to its disabling potential and impact on one's quality of life. Continual reporting is encouraged for better signal characterization in the future.

Keywords: COVID-19 vaccines; Hearing loss; Tinnitus; Adverse events following immunization

1. Introduction

Since the roll-out of COVID-19 vaccines, reports on adverse event following immunization (AEFI) have been flooding into the national databases worldwide. These voluntary reports were valuable for regulatory agencies to quickly identify potential risks associated with the vaccines. By applying the commonly used tool called disproportionality analysis, regulatory agencies are able to detect AEFIs which are reported more frequently than expected that warrant further attention. Safety topics such as thrombosis with thrombocytopenia syndrome and myocarditis/pericarditis have become the center of discussion following similar trigger route.

In early 2021, the World Health Organization-Uppsala Monitoring

Significance

The reporting rates of hearing loss across mRNA vaccine (BNT162b2), inactivated vaccine (CoronaVac), and adenoviral vector vaccine (ChAdOx1) were similar, whereas for tinnitus, ChAdOx1 had approximately two times higher reporting rates compared to the other two vaccines. The reporting pattern of hearing loss and tinnitus by age, gender, race, and dose number was similar for all vaccines.

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Centre (WHO-UMC) has detected disproportional reporting for COVID-19 vaccine-associated hearing loss and tinnitus[1]. The analysis was performed based on data collected in VigiBase, the WHO global database of individual case safety reports (ICSRs). A total of 164 cases of hearing loss and 367 cases of tinnitus reported from ten countries were found up to 22 February 2022. Around the same time, anecdotal reports of sudden sensorineural hearing loss following COVID-19 vaccination had emerged in the scientific literature, and the number of such reports has steadily increased since then[2,3].

In general, hearing loss refers to the partial or total disability to hear in one or both ears[4]. It includes hard of hearing that refers to mild to severe hearing loss where an auditory device may still be beneficial, as well as deafness that refers to profound hearing loss with very little or no hearing. Sensorineural hearing loss (SNHL) is defined as hearing loss of at least 30 dB in three sequential frequencies in the standard pure tone audiogram[5]. It occurs due to damage to the inner ear, the auditory nerves, or the central processing centres in brain. Tinnitus is the sensation of hearing sound, such as ringing, hissing or buzzing sound, despite absence of an external acoustic stimulus[6]. It can be constant or intermittent. Tinnitus has been described to be localized to one or both ears, or also from within the head.

Currently, the causal relationship between hearing loss and COVID-19 vaccines has yet to be established and confirmed. It remains as a potential signal and has not been included in the product information of vaccines. On the other hand, tinnitus has recently been included as an uncommon adverse reaction of the coronavirus vaccine ChAdOx1 (AstraZeneca) by the European Medicines Agency (EMA) and Australian Therapeutic Goods Administration (TGA)[7,8]. The frequency 'uncommon' indicates that it can occur in less than 1 in 100 persons who receive ChAdox1. The update was based on post-marketing reports and new data from an ongoing clinical trial. In Malaysia, both hearing loss and tinnitus are not described in the local package inserts of COVID-19 vaccines.

Two recent studies investigating the association between sudden sensorineural hearing loss (SSNHL) and COVID-19 vaccines concluded with conflicting results[9,10]. Vaccination was linked to a slightly increased risk of SSNHL in a large Israel population, but no association was found in another study that was based on reports in the Vaccine Adverse Events Reporting System (VAERS) in the United States. These studies, as well as most case reports currently available, focused on mRNA vaccines (BNT162b2, Pfizer BioNTech; mRNA-1274, Moderna), or adenoviral vector vaccines (ChAdOx1, AstraZeneca; Ad26.COV2.S, Janssen; Ad5.CoV2-S, Cansino)[2,3,9-12]. There is limited information on hearing disorders following vaccination with inactivated vaccine (CoronaVac, Sinovac; BBIBP-CorV, Sinopharm).

Since Malaysia administered a diverse portfolio of vaccines, predominantly BNT162b2, CoronaVac and ChAdOx1, this study may fill in the gaps particularly regarding hearing disorders that occurred after CoronaVac vaccination. We aimed to describe the reports of hearing disorders, including hearing loss and tinnitus, and to compare its reporting rates across different vaccine brands used in Malaysia (BNT162b2, CoronaVac, ChAdox1, BBIBP-CorV, Ad5.CoV2-S). We also assessed the differences in the reporting characteristics (age, gender, race, dose number) among the vaccines.

2. Subjects and methods

2.1. Data source

This retrospective study was based on data in the Malaysian national pharmacovigilance database, QUEST. Located within the National Pharmaceutical Regulatory Agency (NPRA), QUEST database contains individual voluntary reports of adverse drug reaction (ADR) and AEFI received from healthcare professionals, product registration holders, and consumers throughout the country[13-15]. Every AEFI report received would be carefully processed and assessed by trained pharmacists. Cases classified as serious were investigated at institutional level and reviewed at national level by the COVID-19 Vaccine Special Pharmacovigilance Committee (JFK) to determine the causality between the vaccines and events. All reports followed the revised WHO classification for AEFI causality assessment — consistent, indeterminate, inconsistent (coincidental), and unclassifiable[16]. Subsequently, reviewed reports were submitted to the VigiBase. For the information on total vaccine doses administered during the study period, *i.e.*, the denominator for reporting rate calculation, we retrieved it from the open dataset of the COVID-19 Immunization Task Force (CITF)[17].

2.2. Study design and population

We extracted all reports of hearing loss and tinnitus associated with COVID-19 vaccines in QUEST database that were received since the vaccines rollout on February 24, 2021 until July 31, 2022. The search terms for hearing loss included Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) deafness neurosensory, deafness, and hypoacusis. For tinnitus, PTs tinnitus were included. We screened the reports to exclude possible duplication. Reports given causality inconsistent and unclassifiable were also excluded. The relevant demographic and clinical characteristics of hearing loss and tinnitus incidents were retrieved. All information was recorded as reported.

Table 1. Overall reporting rates of hearing loss and tinnitus after COVID-19 vaccination by vaccine brands, February 24, 2021 through July 31, 2022 in Malaysia.

Variables	All vaccines	BNT162b2	CoronaVac	ChAdOx1	BBIBP-CorV
Hearing loss					
No. of reports	21	12	7	2	NA
Reporting rate*, per million doses	0.29	0.27	0.33	0.35	NA
Tinnitus					
No. of reports	35	20	5	7	1
Reporting rate, per million doses*	0.49	0.45	0.23	1.23	22.80

NA, not available or not applicable. *Denominator is the total vaccine dose administered up until July 31, 2022: All vaccines (71 843 829), BNT162b2 (44 325 076 doses), CoronaVac (21 524 960 doses), ChAdOx1 (5 704 774 doses), BBIBP-CorV (43 854 doses). Numbers may not add up to the total due to the missing value.

2.3. Statistical analysis

Simple descriptive analyses (means, medians, ranges, and percentages) were performed by using Excel software 2016 (Microsoft Corporation). We calculated the reporting rate by dividing the number of reports with the total vaccination doses administered. We also performed Fisher's exact test to assess whether there were any significant differences in the reporting characteristics (age, gender, race, dose number) across vaccine brands in the study.

2.4. Ethical approval

This study has obtained approval from the Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR-21-555-59135). Informed consent was waived as the study used secondary data for analysis.

3. Results

During the study period, a total of 71 843 829 doses of COVID-19 vaccines have been administered in Malaysia. The total AEFI reports received was 26 051, with the reporting rate of 362 reports per million doses.

3.1. Hearing loss

For hearing loss, a total of 21 reports were retrieved, with no duplications found. All cases were given causality indeterminate and were included in the analysis. These 21 reports involved BNT162b2 (12, 57.1%), CoronaVac (7, 33.3%), and ChAdOx1 (2, 9.5%), and none were received for Ad5.CoV2-S and BBIBP-CorV (Table 1). The reporting rate was similar across these three vaccines with the range of 0.27 to 0.35 cases per million doses, with an overall rate of 0.29 cases per million doses. The reports were received from healthcare professionals (14, 66.7%) and consumers (7, 33.3%).

Table 2. Reporting rates of hearing loss and tinnitus after COVID-19 vaccination by age, gender, race, and dose number, February 24, 2021 through July 31, 2022.

Characteristics	Hearing loss, *n*=21			Tinnitus, *n*=35		
	Number of reports (%)	Number of doses, *n*	Reporting rate, per million doses	Number of reports (%)	Number of doses, *n*	Reporting rate, per million doses
Age, year						
5< age ≤17	1 (4.8)	9 157 130	<0.01	1 (2.9)	9 157 130	0.17
17< age ≤29	3 (14.3)	17 944 896	0.17	3 (8.6)	17 944 896	0.17
29< age ≤39	9 (42.9)	14 139 909	0.64	15 (42.9)	14 139 909	1.06
39< age ≤49	5 (23.8)	10 705 657	0.47	10 (42.9)	10 705 657	0.93
49< age ≤59	2 (9.5)	8 372 029	0.24	3 (8.6)	8 372 029	0.36
59< age ≤69	NA	5 991 751	NA	3 (8.6)	5 991 751	0.50
69< age ≤79	1 (4.8)	2 711 804	0.37	NA	2 711 804	NA
Gender						
Male	10 (47.6)	32 788 491	0.30	17 (48.6)	32 788 491	0.52
Female	11 (52.4)	30 985 359	0.36	18 (51.4)	30 985 359	0.58
Race						
Malay	7 (33.3)	34 120 522	0.21	21 (60.0)	34 120 522	0.62
Chinese	8 (38.1)	16 189 655	0.49	7 (20.0)	16 189 655	0.43
Indian	1 (4.8)	4 120 891	0.24	2 (5.7)	4 120 891	0.49
Others	5 (23.8)	16 834 658	0.30	5 (14.3)	16 834 658	0.30
Dose number						
First dose	9 (42.9)	27 857 336	0.32	19 (54.3)	27 857 336	0.68
Second dose	9 (42.9)	27 451 938	0.33	11 (31.4)	27 451 938	0.40
Booster dose	1 (4.8)	16 534 555	0.06	3 (8.6)	16 534 555	0.18
Not specified	2 (9.5)	NA	NA	2 (5.7)	NA	NA

NA: no case in this category or not applicable.

Table 3. Comparison of reporting characteristics of hearing loss and tinnitus after COVID-19 vaccination across vaccine brands.

Characteristics	Hearing loss, *n* (%)				Tinnitus, *n* (%)				
	BNT162b2	CoronaVac	ChAdOx1	*P*-value*	BNT162b2	CoronaVac	ChAdOx1	BBIBP-CorV	*P*-value*
Age, year†									
5< age ≤17	1 (8.3)	NA	NA	0.906	NA	NA	1 (14.3)	NA	0.861
17< age ≤29	2 (16.7)	1 (14.3)	NA		2 (10.0)	NA	1 (14.3)	NA	
29< age ≤39	4 (33.3)	2 (28.6)	2 (100.0)		8 (40.0)	4 (80.0)	2 (28.6)	1 (100.0)	
39< age ≤49	2 (16.7)	3 (42.9)	NA		6 (30.0)	1 (20.0)	1 (14.3)	NA	
49< age ≤59	2 (16.7)	NA	NA		2 (10.0)	NA	1 (14.3)	NA	
59< age ≤69	NA	NA	NA		2 (10.0)	NA	1 (14.3)	NA	
69< age ≤79	1 (8.3)	NA	NA		NA	NA	NA	NA	
Gender									
Male	4 (33.3)	5 (71.4)	1 (50.0)	0.316	11 (55.0)	2 (40.0)	2 (28.6)	1 (100.0)	0.561
Female	8 (66.7)	2 (28.6)	1 (50.0)		9 (45.0)	3 (60.0)	5 (71.4)	NA	
Race									
Malay	4 (33.3)	3 (42.9)	NA	0.810	13 (65.0)	3 (60.0)	3 (42.9)	NA	0.080
Chinese	4 (33.3)	2 (28.6)	2 (100.0)		3 (15.0)	NA	4 (57.1)	NA	
Indian	1 (8.3)	NA	NA		2 (10.0)	NA	NA	NA	
Others	3 (25.0)	2 (28.6)	NA		2 (10.0)	2 (40.0)	NA	1 (100.0)	
Dose number									
First dose	5 (41.7)	3 (42.9)	1 (50.0)	>0.950	11 (55.0)	3 (60.0)	2 (28.6)	1 (100.0)	0.400
Second dose	4 (33.3)	4 (57.1)	1 (50.0)		8 (40.0)	1 (20.0)	2 (28.6)	NA	
Booster dose	1 (8.3)	NA	NA		1 (5.0)	NA	2 (28.6)	NA	
Not specified	2 (16.7)	NA	NA		NA	1 (20.0)	1 (14.3)	NA	

NA, no case in this category or not applicable; *Fisher's exact test; †Numbers may not add up to the total due to the missing value.

Hearing loss occurred in both males and females almost equally, with comparable reporting rates (0.30-0.36 cases per million doses) (Table 2 and Supplementary Table 1). Their age ranged from 8 to 74 years, with a mean of 37.4 years. Most of them (66.7%) aged 30-49 years, with the highest reporting rate among those aged 30-39 years, followed by those aged 40-49 years (0.64 and 0.47 cases per million doses, respectively). The individuals were comprised of mainly Chinese (38.1%) and Malay (33.3%) but the reporting rate for Chinese was two times higher than Malay (0.49 versus 0.21 cases per million doses). Similar reporting rates of hearing loss were observed following the first and second dose (0.32 and 0.33 cases per million doses, respectively). Time-to-onset varied vastly from the same day, *i.e.* within hours to seven months, with the median of two days. Excluding few outliers with longer time-to-onset, hearing loss typically occurred within four days after vaccination.

Of all 21 reports, the most commonly co-reported terms were vertigo (6, 28.6%), tinnitus and dizziness (5, 23.8% each) (Supplementary Table 1). Other terms including headache, nausea and chest pain were also mentioned, with three reports each. Concomitant medications were not reported except in one case in which the patient took a health supplement evening primrose oil and an unregistered traditional product. Underlying diseases including hypertension, hyperlipidemia and hyperthyroidism were reported in two cases without mentioning on the medications used. Notably, neither a clear audio-vestibular diagnosis nor details of a clinical evaluation were described in most of the reports, except for four cases which reported a diagnosis of sensorineural hearing loss and another case with the diagnosis of Meniere's disease.

While most cases were reported as non-serious (12, 57.1%), nine cases (42.9%) were serious. The seriousness criteria reported were caused/prolonged hospitalization (4), disabling/incapacitating (4) and death (1). Of note, the cause of death for the fatal case was not related to hearing loss, but due to severe sepsis. Outcome were reported in 15 cases, of which six (28.6%) were recovering or recovered from their symptoms and nine (42.9%) had not recovered at the time of reporting.

Based on Fisher's exact test performed, the reporting pattern by age group (P=0.906), gender (P=0.316), race (P=0.810), and dose number (P>0.950) was similar across all vaccine brands (Table 3).

3.2. Tinnitus

The analysis included 35 reports on tinnitus associated with COVID-19 vaccines that were given causality indeterminate, of which five were overlapped with the reports on hearing loss. Most reports involved BNT162b2 (20, 57.1%), followed by ChAdOx1 (7, 20.0%), CoronaVac (5, 14.3%), and BBIBP-CorV (1, 2.9%) (Table 1). While none were received for Ad5.CoV2-S, a vaccine brand not mentioned in two reports. The overall reporting rate for tinnitus was higher than hearing loss, at 0.49 cases per million doses. It ranged from 0.23 to 22.80 cases per million doses across all vaccine brands. The reports were received from healthcare professionals (20, 57.1%), consumers (14, 40.0%) and pharmaceutical company (1, 2.9%).

The proportions of cases occurred among males and females were similar (Table 2 and Supplementary Table 2). The average age was 40 years, ranging from 17 to 66 years. Similar with hearing loss,

majority (71.4%) aged 30 to 49 years, with the highest rate among those aged 30 to 39 years, followed by those aged 40 to 49 years (1.06 and 0.93 cases per million doses, respectively). More than half (60.0%) of the cases involved Malays. Tinnitus was mainly reported to have occurred after the primary doses – first dose (54.3%) and second dose (31.4%). However, the reporting rate was slightly higher for the former (0.68 versus 0.40 cases per million doses). The median time-to-onset was two days, ranging from 10 minutes to 16 days, with the majority occurring within the first five days after vaccination.

The most commonly co-reported terms were dizziness and headache (6, 17.1% each), followed by nausea (5, 14.3%), as well as pruritus (3, 8.6%) (Supplementary Table 2). Few reports included information on concomitant medications, of which mostly were antihypertensives, antihyperlipidemics, antidiabetics, and statins. One of the case reported smoking and vaping history. All except five cases were reported as non-serious (85.7%). The seriousness criteria for the five serious cases included disabling/incapacitating (3) and caused/prolonged hospitalization (2). At the time of reporting, tinnitus had resolved or resolving in 12 (34.3%) cases and had not resolved in 15 (42.9%) cases.

There were no statistically significant differences in the reporting pattern of tinnitus across BNT162b2, CoronaVac and ChAdOx1 by age group (P=0.861), gender (P=0.561), race (P=0.080), and dose number (P=0.400) (Table 3).

4. Discussion

Our study found that the reporting rate for hearing loss were similar across all three COVID-19 vaccines used in the COVID-19 Immunization Programme in Malaysia, namely the BNT162b2, CoronaVac and ChAdOx1, whereas the reporting rate for tinnitus was higher following vaccination with ChAdOx1 compared to BNT162b2 and CoronaVac. Since only one report was received for BBIBP-CorV, it will not be discussed thereafter. Although most cases, particularly those reported by consumers, were not medically-confirmed, they do help in visualizing the first puzzle piece of these potential signals.

Approximately 466 million (5%) individuals worldwide live with disabling hearing loss, and the prevalence rises with age, becoming prevalent beyond the age of 65 years[4,5,18]. However, in our study, the reporting rate was the highest among those aged 30 to 49 years. Moreover, as opposed to its higher prevalence in males in the general population[5,18], gender disparity was not observed in this study. Similarly, the reporting pattern of tinnitus by age and gender in our study differed from epidemiological studies. Our study observed the highest reporting rate of tinnitus among those aged 30 to 49 years, with no differences between males and females; whereas in the general population, tinnitus prevalence increased with age, and was higher among males than females[19,20]. While these pattern differences may add to the suspicion of its association with COVID-19 vaccines, we could not exclude the possibility of over-reporting of hearing disorders due to the absence of audiometric assessment in most of our cases[21].

The time-to-onset is an additional significant piece of information that may help in assessing the relationship between these potential signals and COVID-19 vaccines. Most of our cases reported an onset of event within four to five days after vaccination. For tinnitus, the vast majority occurred within the same day of vaccination, a time frame where the events are likely to be associated with anxiety as part of immunization stress-related responses[6], instead of COVID-19 vaccines. This is supported by the co-reported terms in our cases that included dizziness, headache, nausea, vertigo, and presyncope. In addition, this short time-to-onset does not coincide with the onset of immunoglobulin G (IgG) production. IgG antibodies against the specific vaccine protein antigens first appear 10 to 14 days after vaccination[2]. Considering the autoimmune theory of its pathophysiology, the time-to-onset is expected to be longer.

While the pathophysiology of hearing loss and tinnitus remains unclear, a few hypotheses have been postulated, including one involving the phenomenon of molecular mimicry. The principle is that because there is a certain level of molecular structure resemblance between a SARS-CoV-2 spike protein and human proteins, the immune response generated against the pathogen could cross-react with human proteins, leading to autoimmunity[22,23]. Besides, the formation and precipitation of immune complexes in various tissues, including the ear, may also trigger a series of immune response cascades that could insult the structure of the ear, leading to SNHL. For mRNA vaccines, it was also suggested that both the mRNA strand and the encapsulating lipid nanoparticle are immunogenic and could play a role in the pathogenesis of SNHL[10]. The mechanism for tinnitus is associated with the lesions that occur following hearing loss, medications, and noise trauma. These initial lesions can cause abnormal neuronal activity in central auditory pathways, which is then perceived as tinnitus[6].

From previous studies, hearing loss and tinnitus is linked to vascular risk factors including hypertension, dyslipidaemia and diabetes[24–27], as well as smoking[28]. It was suggested that as blood viscosity increases, capillary blood flow decreases, resulting in reduced oxygen transport and tissue hypoxia, thus causing hearing loss[28]. Besides, people with underlying autoimmune diseases, such as systemic lupus erythematosus which was also reported in one of our cases, are also at risk of developing SNHL. There is possibility that the occurrence of SNHL in these people are due to exacerbation of existing symptoms in autoimmune inner ear disease or Menière's disease, instead of COVID-19 vaccines[2,10]. While

there were only few cases in our study that reported underlying medical conditions, there could have been more because underlying diseases are frequently not reported in spontaneous reporting system. Besides, information such as underlying ear problems or other illnesses, concomitant medication, and COVID-19 infection status, all of which are important for causality assessment, were missing in our study. Nonetheless, despite the lack of existing evidence to support the causal relationship, the fact that several reports have been received should be an impetus for healthcare professionals to investigate future cases in greater depth when such potential association is suspected.

Further hearing assessment and case investigation is particularly recommended if tinnitus is severe or persistent, especially when it occurs after vaccination with ChAdOx1, because its reporting rate was the highest among all vaccines. This result concurs with the reporting patterns in Australia and European Union countries[7,8]. Of note, because tinnitus is a self-perceived symptom with no standard diagnostic criterion, the comparison with the prevalence determined from studies using varying tinnitus definitions needs to be cautiously done[20]. Although tinnitus does not cause disability, it could be severely bothersome that it affects one's daily functioning and quality of life. Furthermore, it is commonly associated with hearing loss[6,8], as demonstrated in a few cases in our study.

Based on real-world data, our study showed that the reporting characteristics of both hearing loss and tinnitus were similar across different vaccine brands. Our work fills a knowledge gap concerning hearing loss and tinnitus associated with inactivated vaccinations, specifically CoronaVac, by adding to the existing body of knowledge, which is primarily focused on mRNA vaccines and adenovector viral vaccines. Furthermore, our study provided a new insight on the reporting of hearing loss and tinnitus in Asian population, complementing the existing evidence that is mainly based on studies conducted in Western countries.

The main limitation of our study is consistent with the known limitation of passive reporting system, which is underreporting. Without a national electronic medical record system, the lack of information on underlying illnesses, concomitant medications, COVID-19 infection status, follow-up and the final outcome is inevitable. We could therefore unable to rule out the possibility that these factors contributed to the reporting of hearing loss and tinnitus. However, we used the most comprehensive national data that is available from a variety of sources. While a reported adverse event does not necessarily mean a causal relationship, we recommend continuous reporting and a prompt investigation including audiometric evaluation for better characterization of these potential signals in the future.

Even though the low reporting rate of less than one case in a million doses in our study may indicate a low public health impact, and the current available evidence is insufficient to suggest that COVID-19 vaccines have played a role, hearing loss and tinnitus following vaccinations should not be ignored due to its disabling potential and impact on one's quality of life. Our findings on similar reporting rates across BNT162b2, CoronaVac and ChAdOx1 suggest that all hearing loss following vaccination, regardless of vaccine brand, requires further investigations. Equal attention should be given to tinnitus that occurs after COVID-19 vaccination, particularly after ChAdOx1. Close monitoring of these potential signals is ongoing.

Conflict of interest statement

The authors declare that they have no potential conflicts of interest that might be relevant to the content of this article.

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Authors' contributions

SCL and AR conceived and designed the research. AR supervised the research. SCL performed the data extraction. SCL and SMC performed the data analysis. All authors contributed to the interpretation of the results. The manuscript was written by SCL, WKW and HSY. All authors reviewed, edited, and approved the final version of the manuscript.

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