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ORIGINAL RESEARCH ARTICLE

Early Detection of Hearing Impairment Signals Post-mRNA COVID-19 Vaccination: A Disproportionality Analysis Study on French Pharmacovigilance Database

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Abstract

Introduction Improving adverse events following immunisation (AEFI) detection is vital for vaccine safety surveillance, as an early safety signal can help minimize risks. In February 2022, the World Health Organization reported a preliminary signal on sudden sensorineural hearing loss (SSNHL) following coronavirus disease 2019 (COVID-19) vaccination, 54 million persons in France received at least one dose, covering 78.8% of the population within a year.

Objective The primary objective of this study was to identify a method of disproportionality analysis capable to detect a safety signal for hearing impairment (HI) as early as possible during the initial phases of the COVID-19 vaccination campaign. Secondly, we described all cases of SSNHL reported during vaccine booster campaigns in France.

Methods Data from January 2011 to February 2022 were extracted from the French pharmacovigilance database. Cases were all spontaneous reports of AEFI for elasomeran and tozinameran, while non-cases were AEFI reported for other vaccines. Disproportionality analysis for HI was performed monthly during 2021, to estimate a reporting odds ratio (ROR). Four different methods were used for ROR estimation. Furthermore, we reviewed cases of SSNHL following messenger RNA COVID-19 vaccinations reported during booster campaigns, from 2 February 2022 to 1 March 2023, based on a comprehensive medical evaluation.

Results Using a standard methodology, we identified a signal on 31 July 2021 (ROR 1.50, 95% confidence interval [CI] [1.06–2.18]). Multivariate analysis adjusted for sex, age, ototoxic drugs and excluding reference reports of common AEFI for vaccines allowed us to detect the HI signal as early as 31 March 2021 (ROR 2.67, 95% CI [1.36–5.57]). The SSNHL reporting rate was estimated to be 0.83/1,000,000 doses for tozinameran and 4.3/1,000,000 for elasomeran during the booster campaigns.

Conclusion Using a well-structured disproportionality analysis could have enhanced early detection of safety signals and contribute to risk minimizing measures. According to descriptive data, HI following mRNA COVID-19 vaccines remains rare.

1 Introduction

Severe acute respiratory syndrome coronavirus 2019 (SARS-CoV-2) has spread rapidly, causing a global pandemic since early 2020 leading to a rapid and extensive vaccination campaign. The scale of the COVID-19 health crisis required a rapid and widespread vaccination campaign. By February 2022, 54 million persons in France received at least one dose of a COVID-19 vaccine, achieving a vaccination coverage of 78.8% of the total population within a year [1]. Monitoring COVID-19 vaccines has been a critical challenge in verifying their efficacy in the general population and detecting any adverse event following immunisation (AEFIs) not yet identified in clinical trials. Spontaneous post-marketing pharmacovigilance systems are a valuable source of data for drug safety monitoring. They are well-designed to identify arising signals using multi-source data. A closer monitoring system was deployed for the COVID-19 vaccination campaign [2, 3]. In this pandemic context, enhancing the detection

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Key Points

Case series and pharmacoepidemiological studies have suggested an association between hearing impairment and mRNA COVID-19 vaccines following the widespread exposure of individuals to these vaccines.

Compared with the standard method, a well-structured disproportionality analysis could have improved the early detection of safety signals by adjusting for age, co-reporting of known ototoxic drugs and excluding common adverse events following immunisation.

In the context of the extensive use of a drug over a short period, a suitable disproportionality analysis would be valuable in generating a safety signal as early as possible, allowing for the implementation of appropriate risk minimisation measures.

mechanism for AEFIs is crucial for strengthening post-marketing vaccine safety surveillance. An early validated safety signal could contribute to risk minimizing. For example, the higher frequency of myocarditis in young adults (< 30 years) with elasomeran compared with tozinameran in 2021, led to a preference for tozinameran in this population [4].

In February 2022, the World Health Organization (WHO) issued a preliminary signal about sudden sensorineural hearing loss (SSNHL) cases following COVID-19 vaccination through an observed/expected analysis, requiring further assessment and found a disproportionate number of SSNHL reports for COVID-19 vaccines compared to other medicines [5]. As of 18 November 2021, there were 1290 observed cases while 284 cases were expected and as early as February 2021, 24 cases were observed while 8 cases were expected. However, the authors advise cautious interpretation of these figures due to mandatory reporting under emergency use authorizations for COVID-19 vaccines, particularly in the USA, urging further investigations by individual countries.

SSNHL is defined as a sensorineural hearing loss of > 30 dB over at least three consecutive audiometric frequencies occurring within < 72 h [6]. SSNHL has an incidence of five to 20 cases per 100,000 people per year [7, 8]. It is unilateral in 98% of cases [9] and mainly affects subjects aged between 40 and 54 years old [8, 10, 11]. SSNHL has recently emerged as a possible adverse effect of COVID-19 vaccines. There have been sporadic reports of unilateral SSNHL occurring shortly after the administration of adenoviral vector or messenger RNA vaccines, either alone or in association with other cochleovestibular symptoms (tinnitus, dizziness, and vertigo), in patients of both sexes with or without a history of audiovestibular, autoimmune, or cardiovascular disease [12–14].

Recently, we carried out a retrospective study on spontaneous reporting of SSNHL after mRNA COVID-19 vaccination in France between January 2021 and February 2022, based on a full medical assessment including the patient's medical history. The reporting rate was similar for tozinameran and elasomeran vaccines, estimated at 1.5 cases per million injections, with a median age of around 50 years old and a very wide range from 13 to 83 years old. At the end of the follow-up period, a complete recovery was observed in less than a quarter of cases. Moreover, seven positive rechallenge cases suggested a strong likelihood of a causal relationship [15].

Our primary objective was to identify a relevant method for early safety signal generation during a pandemic by performing disproportionality analysis on the French pharmacovigilance database (FPVDB), addressing the need for more sensitive tools in AEFI signal detection.

Concurrently, to supplement our previous study reviewing French SSNHL reports from January 2021 to February 2022 [15], we conducted a descriptive analysis of SSNHL cases reported between 2 February 2022 and 1 March 2023, coinciding with the period of the first and second vaccine booster campaigns in France.

2 Materials and Methods

2.1 Data Source

The French pharmacovigilance system was instituted in the late 1970s, with a network of 30 regional pharmacovigilance centres (RPVCs) whose mission is to identify, assess, and prevent adverse drug reactions (ADRs) following marketing authorisation. This network is committed to the continuous monitoring and assessment of AEFIs involving COVID-19 vaccines, through the daily evaluation of spontaneous notifications. Healthcare professionals and patients can report suspected AEFIs involving COVID-19 vaccines (as they would for other drugs) directly to the RPVC or via a dedicated website [16]. Each report of a potential adverse reaction is assessed via a careful clinical, chronological, semiotic, and pharmacological analysis before being registered anonymously in the FPVDB. Additionally, it is worth noting that AEFIs and ADR are collected in a single database in France. From 2011 to 2023, more than 1,000,000 ADR reports were registered in the FPVDB, of which approximately 200,000 cases were AEFIs. Each RPVC anonymously registers a spontaneous report with a unique identifier, including Medical Dictionary for Regulatory Activities (MedDRA®)-coded terms that describe adverse drug reactions, suspected and concomitant medications, MedDRA®-coded medical history

and demographic data such as age, sex, weight, height and body mass index (when available). MedDRA® is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Additionally, each case includes a summary of the adverse effect, detailing the event's chronology, clinical context, and supporting biological or paraclinical findings. Anonymized supplementary files, such as hospitalization reports or specific medical examination results, may also be included. For cases with missing data on the degree of hearing loss, we contacted the RPVC that registered the case, requesting the audiometric medical reports from the case reporter (whether a health professional or patient), and these were sent to us if available. The degree of hearing loss was indicated in all standardized audiometric examination reports.

2.2 Disproportionality Analysis

Disproportionality analysis is a set of methods widely used by researchers, health agencies and pharmaceutical companies to generate disproportionality signals, i.e. suspected links between drugs and ADRs. We have chosen to measure disproportionality through reporting odds ratio (ROR) calculation, as this method has demonstrated higher sensitivity compared with other frequentist and Bayesian calculations and allows the use of multivariate logistic regression thus the recognition of confounding and interaction effects [17–20]. We considered that a signal was identified when the following conditions were met: the lower limit of the 95% confidence interval (CI) of the ROR is > 1 and the number of individual cases is ≥ 3 [21, 22].

In our analysis, the cases were the AEFI reports for which mRNA COVID-19 vaccines elasomeran—Spikevax® (Moderna) and tozinameran—Comirnaty® (Pfizer & BioNTech), were suspected, while non-cases were AEFI reports for which all other vaccines listed in Supplementary Table 1 (excluding non-mRNA COVID-19 vaccines) were suspected. The index reports were identified using the narrow standardised MedDRA® query (SMQ) "hearing impairment", excluding the preferred term (PT) "tinnitus", which was the focus of a distinct signal, as they are listed in Supplementary Table 2. SMQ are predefined groups of MedDRA® terms created to help identify and analyse potential drug safety concerns in pharmacovigilance and clinical research. Regularly updated, these validated tools provide a standardized approach for investigating specific medical conditions or adverse events across large datasets. Reference reports were notifications of all other PTs.

All FPVDB reports registered between 1 January 2011 and 31 January 2022 were collected. The choice of year of 2011 for the beginning of the period of study was due to the possibility of reporting of ADRs by patients/consumers without medical confirmation and registration in the FPVDB. The end of our study period (31 January 2022) corresponds to the date of the WHO issuing the preliminary signal for an association between SSNHL and COVID-19 vaccines [5]. Disproportionality analysis was performed monthly during 2021 (at the end of each month).

This first analysis was used as a reference, with a standard methodology as described above. Secondly, we took into account patient characteristics, adjusting the analysis for age, sex and concomitant well-known ototoxic drugs (OD) (Supplementary Table 3) in a multivariate analysis. Thirdly, we excluded reference reports of PTs reported in more than 5% of mRNA vaccine notifications (RRPT5) from the reference reports of COVID-19 vaccines and from the references reports of other vaccines (Supplementary Table 4). We chose to omit commonly reported AEFIs from mRNA vaccine reports to enhance sensitivity in detecting rare adverse events. This choice was supported by the very high number of well-known AEFI cases reported during the COVID vaccination campaign. As suggested by Salvo et al, those events compete with rare AEFIs and mask signals, particularly in the early stages of surveillance [23, 24]. Finally, we pooled the second and third method in a sex, age, and OD-adjusted multivariate analysis, from which we excluded RRPT5. Reports with missing values for gender and age were not excluded from the analysis. Duplicates were identified by comparing the following criteria between reports: sex, age, type of AEFI, concomitant medications and medical history.

Moreover, two other sensitivity analysis were performed excluding reference reports of PTs reported in more than 10% (RRPT10) of mRNA vaccine notifications and the other excluding reference reports of PTs reported in more than 2.5% (RRPT2.5) (Supplementary Table 5). Finally, we performed a sensitivity analysis excluding cases with missing age and sex data.

In a post hoc analysis, we evaluated the persistence of the signal throughout the year 2022. The ROR was calculated at the end of each month from 28 February 2021 to 31 December 2022 using a standard disproportionality method. All disproportionality analyses were performed using RStudio software (version 2022.02.3+492).

2.3 Case Series

All AEFIs recorded in the FPVDB occurring after administration of mRNA COVID-19 vaccines between 2 February 2022 and 1 March 2023 were collected, which corresponds to the period following our previous case review (28 December 2020 to 2 February 2022)—covering the booster vaccination campaign [15]. Eligible cases of SSNHL were extracted using PT chosen from the "Hearing Impairment"

SMQ (Supplementary Table 6), when the suspected drugs were elasomeran and tozinameran.

An audiology expert provided guidelines and reviewed all audiograms and controversial cases. Otologic conditions other than clinically-documented SSNHL (e.g. otitis externa or media, hyperacusis, diplacusis, auditory distortion, vertigo and/or tinnitus without hearing loss) were identified and excluded. Presbycusis and slow-onset hearing loss were excluded. Cases were included only if they corresponded to SSNHL, and if they were diagnosed by an ear, nose, and throat (ENT) specialist on the basis of audiograms and the medical records of the patient concerned. In addition, only cases occurring within 21 days of vaccination were taken into account, as recommended by the Safety Platform for Emergency Vaccines and the Brighton Collaboration guidelines for sensorineural hearing loss [25], with the exception of cases for which a full aetiological investigation (brain and ear computed tomography [CT] scans or magnetic resonance imaging [MRI] imaging, audiometric measurements and at least one recent COVID-19 PCR test) had been carried out and no other cause was found.

A minimum follow-up period of 3 months was established for each SSNHL case to gather missing data and evaluate potential hearing recovery. We requested that each pharmacovigilance centre that registered the spontaneous report send us any available audiometric examinations or relevant medical reports. The degree of hearing loss was documented in all standardised audiometric examination reports.

A clinical analysis was carried out on the basis of patient demographics (sex, age) and risk factors (autoimmune, cardiovascular or audiovestibular), the side (either unilateral or bilateral) of the hearing loss, the presence of tinnitus and/or balance disorders, the onset of SSNHL, the vaccination status (first, second or booster injections), the hearing loss grade according to Modified Siegel's criteria (Supplementary Table 7) and recovery (total, absent, possible need for hearing aids). Particular attention was paid to any positive rechallenge cases.

A descriptive analysis was performed for mRNA COVID-19 vaccines, for all factors listed above. We also estimated the rate of reporting of SSNHL after the administration of mRNA COVID-19 vaccines per 1,000,000 doses. This was calculated using the total number of doses of mRNA COVID-19 vaccines administered during the study period as the denominator [26].

Patient characteristics were expressed as a number (percentage) for categorical variables and a median (range) for quantitative variables, according to the vaccine administered and for all cases. The reporting rate was expressed as cases per 1,000,000 vaccine injections.

3 Results

3.1 Disproportionality Analysis

Between 1 January 2011, and 31 January 2022, a total of 134,853 notifications for AEFIs were recorded. Among these, 120,395 reports were associated with mRNA COVID-19 vaccines, elasomeran (Spikevax®) or tozinameran (Comirnaty®), while 14,458 reports were associated with other vaccines. We found 0.32% missing values for sex and 1.75% missing values for age, and no duplicate reports. All reports were included for the disproportionality analysis even if the age or sex was missing. The PTs reported in more than 5% of cases were influenza-like illness, asthenia, headache, vaccination site pain and lymphadenopathy. Consequently, 34,453 RRPT5 cases and 2314 RRPT5 non-cases were excluded from the third and final analysis (Fig. 1).

The first cases of hearing impairment recorded in the FPVDB were registered in February 2021, with an ROR of 0.92, 95% CI [0.52–1.58] on the 28 February 2021, with 20 HI cases. Disproportionality reporting was significant on 31 July 2021 (ROR 1.50, 95% CI [1.06–2.18], 215 HI cases), as shown in Fig. 2a, and it remains significant until the end of 2021. The signal remains constant during 2022, according to post hoc analyses, with an ROR increasing to 2.58, 95% CI [1.90–3.61] at the end of 2022 and 997 HI cases (Supplementary Fig. 1)

When the ROR estimate was adjusted for age, sex and OD, a signal appears 2 months earlier, at the end of May 2021 (ROR 1.83, 95% CI [1.09–3.23], 116 HI cases) (Figure 2a). Furthermore, excluding RRPT5, a signal appears in April 2021 (ROR 1.61, 95% CI [1.07–2.47], 63 HI cases) as shown in Figure 2b. Finally, the combination of adjusting for age, sex and OD and exclusion of RRPT5 identified the earliest signal in March 2021 (ROR 2.67, 95% CI [1.36–5.56], 35 cases), and increased to 2.88, 95% CI [1.88–4.66] by the end of 2021 (Fig. 2b).

The RRPT10 corresponds to the PT "influenza-like syndrome". The exclusion of RRPT10 reveals a signal at the end of May, 2 months earlier compared to the standard method (ROR 1.66, 95% CI [1.15–2.46]). In contrast, the exclusion of RRPT2.5 including a total of 15 PTs, with "paraesthesia", "herpes zoster" and "menstrual disorder" led to a significant signal in March with an ROR of 1.74, 95% CI [1.10–2.76] (Fig. 3).

Detailed monthly ROR are provided in Supplementary Table 7 and detailed numbers of cases and non-cases are available for each of these analyses in the Supplementary Table 8.

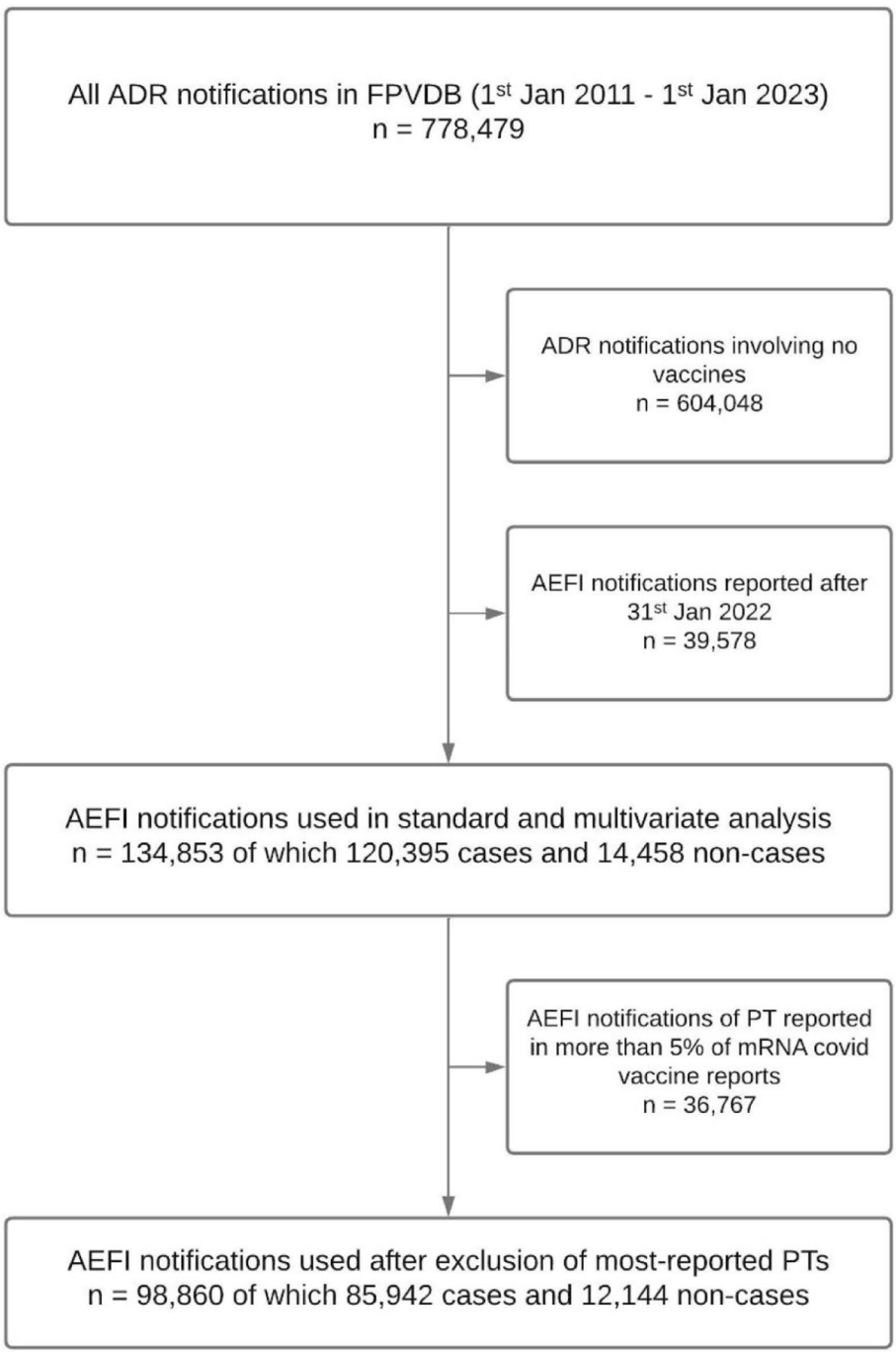


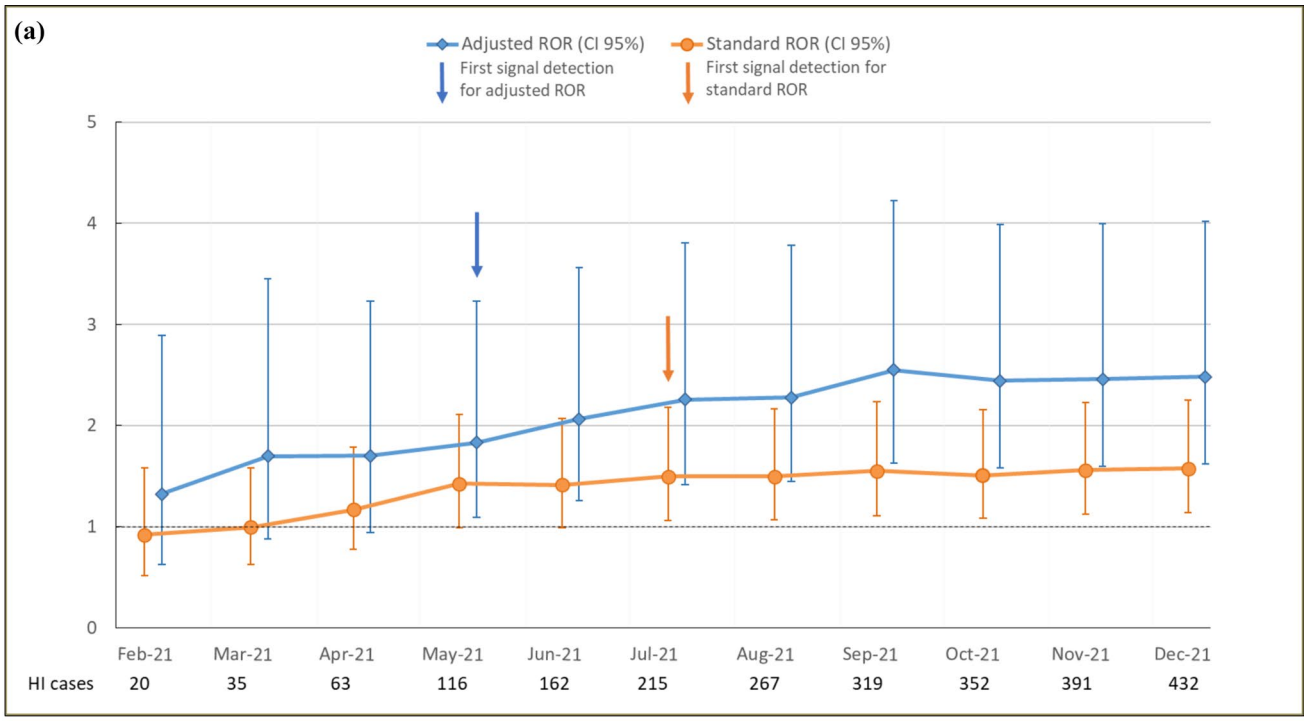
Fig. 1 Cases and non-cases selection flow chart

3.2 Case Review

During the study period, 120 cases of hearing loss were recorded in the FPVDB: 80 cases concerned tozinameran and 40 cases concerned elasomeran. Of these, 92 cases were excluded and 28 cases of SSNHL were included for analysis: 18 cases involved the tozinameran vaccine and 10 involved the elasomeran vaccine (Fig. 4). Of these, 17 cases occurred within 21 days post vaccination (11 cases for tozinameran and 6 cases for elasomeran).

3.2.1 Description of SSNHL Cases for the Tozinameran Vaccine

When SSNHL occured within 21 days, the median time to onset was 7 (1–19) days. The median age was 60.5 (26–87) years old, and 39% of cases concerned the 50–64-year-old age group, 12 (67%) were women. Twelve cases occurred after the first booster and four cases after the second booster (Table 1).



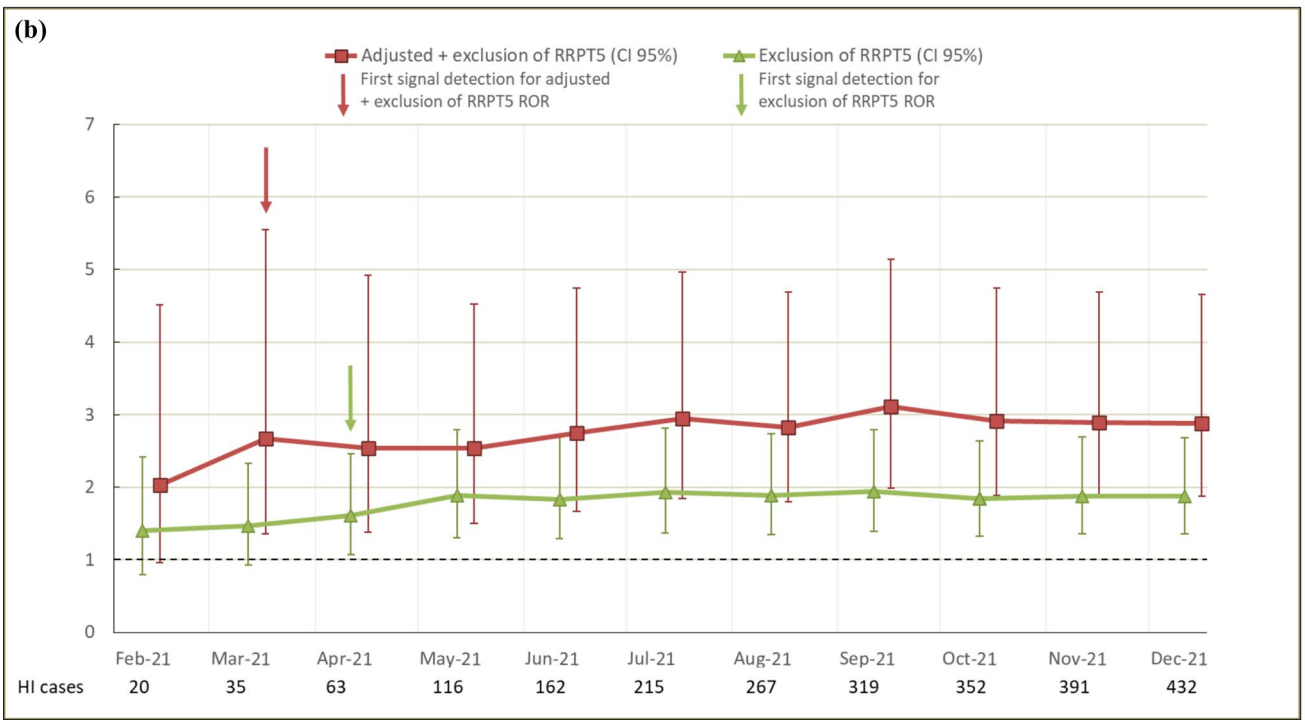


Fig. 2 **a** Trends in the ROR for hearing impairment standard and adjusted for age, sex and ototoxic drugs. *ROR* reported odd ratio, *95% CI* 95% confidence interval, *HI cases* number of "hearing impairment" cases. **b** Trends in the ROR for hearing impairment with the exclusion of RRPT5 and adjusted for age, sex and ototoxic drugs. *RRPT5* reference reports of preferred term reported in more than 5% of mRNA vaccine notifications, *ROR* reporting odd ratio, *95% CI* 95% confidence interval, *HI cases* number of "hearing impairment" cases

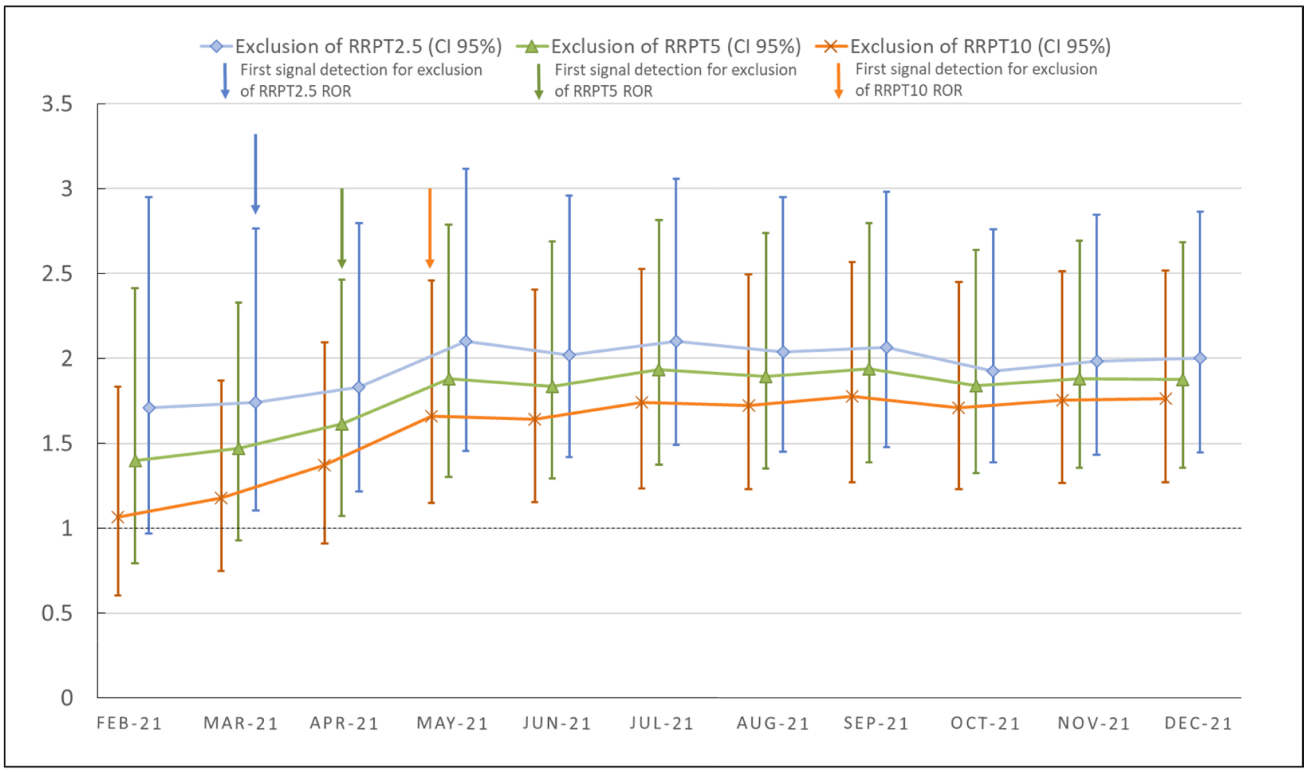


Fig. 3 Trends in the ROR for hearing impairment with the exclusion of RRPT2.5, RRPT5 or RRPT10. *RRPT* reference reports of preferred term reported in more than 2.5%, 5% or 10% of mRNA vaccine notifications, *ROR* reporting odd ratio, *95% CI* 95%, confidence interval

Among the SSNHL cases, 13 (72%) had a medical history considered as a risk factor for SSNHL, of which five (28%) were cardiovascular and three (17%) were otoneurological (Table 1).

Hearing loss grade was reported in 11 cases. We counted seven (63%) cases of mild to moderately severe hearing loss (grades 1–3), and four (36%) cases of severe to total deafness (grades 4 and 5). Hearing loss was unilateral in 83% of cases, and these symptoms were associated with tinnitus for ten (55%) patients and vertigo for three (17%) patients (Table 1).

Of the 18 cases selected, data were available for 16 cases about the symptomatic treatment: corticosteroids were prescribed for 13 patients (81%), one of whom reported complete resolution a few days later and one partial resolution. For the other 11 patients, the deafness persisted for more than 3 months (the end of follow-up). Four of these patients received hearing aids.

A case of positive rechallenge was documented in an 87-year-old patient who had been wearing hearing aids since 2006 and had previously suffered a stroke. The patient suffered a first episode of total right-sided hearing loss in December 2021, a few weeks after the first tozinameran booster dose. The second tozinameran booster was administered in March 2022 leading to another episode of SSNHL four days later, in the form of a total left-sided deafness. The patient was prescribed corticosteroids without improvement. A brain scan found no evident aetiology, apart from ischaemic lesions already present before the two events.

From February 2022 to March 2023, 21,598,558 doses of the tozinameran vaccine were injected in France [26]. Over this period, the rate of reported SSNHL was 0.83/1,000,000 doses.

3.2.2 Description of SSNHL Cases for the Elasomeran Vaccine

When SSNHL occured within 21 days, the median time to onset was 12 (1–18) days. The median age was 57.5 (32–85) years old, 50% of cases concerned the 50-to-64 year old age group, and seven (70%) were women. Nine cases occurred after the first booster and one case after the second booster (Table 1).

Among the SSNHL cases, four (40%) had a medical history considered as a risk factor for SSNHL, of which three (30%) were cardiovascular and one (10%) was COVID-19 (Table 1).

Hearing loss grade was reported in seven cases. There were four (56%) cases of mild to moderately severe hearing loss (grades 1–3), and three (42%) cases of total deafness

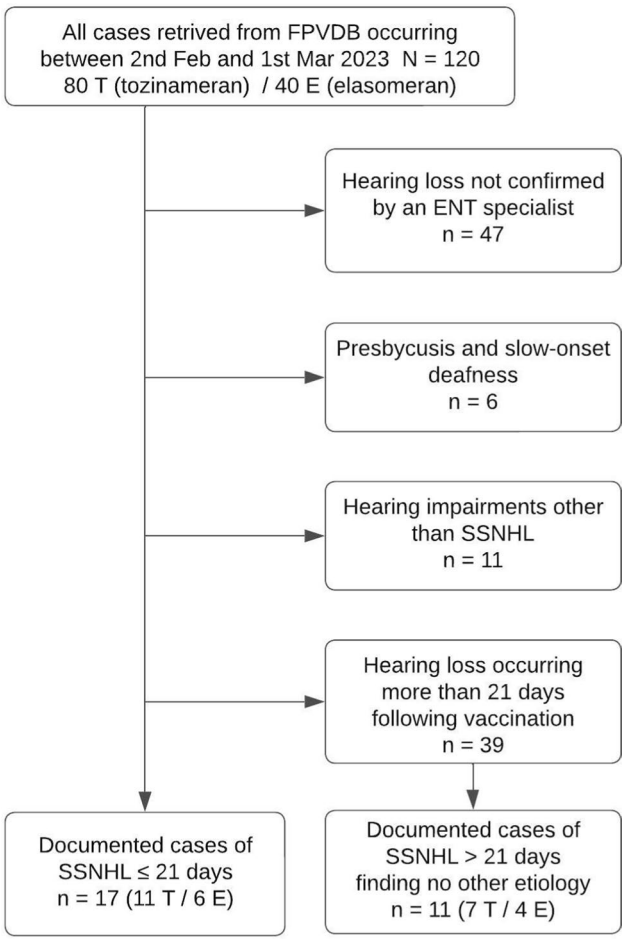


Fig. 4 SSNHL case selection flowchart. *T* tozinameran, *E* elasomeran

Table 1 Characteristics of sudden sensorineural hearing loss cases

	Tozinameran	Elasomeran
N, (%)	18 (64)	10 (36)
Gender, *n* (%)		
Female	12 (67)	7 (70)
Age (years)		
Median (range)	60.5 (26-87)	57.5 (32-85)
19–29, *n* (%)	1 (5)	
30–49, *n* (%)	4 (22)	2 (20)
50–64, *n* (%)	7 (39)	5 (50)
65–74, *n* (%)	3 (17)	1 (10)
≥ 75, *n* (%)	3 (17)	2 (20)
Medical history, *n* (%)		
n (%)	13 (72)	4 (40)
Cardiovascular (CV)	5 (28)	3 (30)
Otoneurological (ON)	3 (17)	
CV and ON	2 (11)	
COVID-19	3 (17)	1 (10)
Vaccination rank, *n* (%)		
First dose	1 (5)	
Second dose	1 (5)	1 (10)
First booster	12 (67)	9 (90)
Second booster	4 (22)	
Laterality, *n* (%)		
Unilateral	15 (83)	10 (100)
Bilateral	3 (17)	
Hearing loss grades, *n* (%)		
N, (%)	11 (61)	7 (70)
Grade 1	1 (9)	2 (28)
Grade 2	2 (18)	2 (28)
Grade 3	4 (36)	
Grade 4	1 (9)	
Grade 5	3 (27)	3 (42)
Symptomatic treatment, *n* (%)		
n (%)	16 (89)	6 (60)
Oral corticosteroids	13 (81)	3 (50)
Intratepanic injection of corticosteroids	2 (12)	1 (16)
Hearing aids	4 (25)	3 (50)
Associated cochleovestibular disorders, *n* (%)		
Tinnitus	10 (55)	4 (40)
Vertigo and balance disorders	3 (17)	3 (30)

(grade 5). Hearing loss was unilateral in all the cases, and these symptoms were associated with tinnitus for four (40%) patients, and vertigo for three (30%) patients (Table 1).

Of the ten cases selected, data were available for six cases concerning the symptomatic treatment: corticosteroids were prescribed for three patients (50%). For all patients, the hearing loss persisted for more than 3 months. Three patients received hearing aids.

From February 2022 to March 2023, 2,323,190 doses of the elasomeran vaccine were administered in France [26]. Over this period, the rate of reported sudden sensorineural hearing loss was 4.3/1,000,000 doses.

4 Discussion

The main objective of our study was to investigate the appropriate disproportionality analysis to detect hearing impairment after mRNA COVID-19 vaccines as soon as possible during the COVID-19 primary vaccination campaign. Using a standard method, the ROR values showed a signal in July 2021, about 4 months after the beginning of the vaccination campaign in France, remaining constant during the second half of 2021 and 2022. Taking into account demographic factors such as age and sex, as well as the co-reporting of known ODs, the signal emerged 2 months earlier (May 2021). Finally, signal detection was brought forward 2 months (March 2021) when we added the exclusion

of RRPT5 in the analysis. We assume that the exclusion of frequent and then well-known reported AEFIs enabled us to target rare AEFIs in the disproportionality assessments, thereby reducing event-competition bias. Salvo et al. suggested that event competition bias may be observed when other ADRs are reported with a much higher rate than the ADRs of interest: the removal of known and frequent ADRs for some drugs, such as statins and rhabdomyolysis/myopathy or oral anticoagulants and haemorrhages, revealed new signals of disproportionate reporting of which 12% appeared related to potential safety signals and were later confirmed [23, 24]. In fact, in 1 year, the RPVC Network collected, analysed and registered more than 120,000 AEFI reports associated with tozinameran and elasomeran vaccines alone. In contrast, over a 10-year period, from 2011 to 2022, the FPVDB recorded around 620,000 ADR and AEFI reports. Non-serious adverse reactions to COVID-19 vaccines were very frequently reported in 2021. This is most likely due the extensive media coverage of the vaccination campaign in France [27–32]. In particular, influenza-like illness emerged as the most frequently reported adverse event following COVID-19 mRNA vaccination, reported in 11% of cases.

According to our data, the choice of the threshold for excluding frequently and well-known reported AEFIs could have an impact on signal detection. Setting the threshold at 10% leads the exclusion of PT "influenza-like illness" from the reference reports, and a signal emerging in May, i.e. 1 month later than those detected with 5% threshold. Conversely, lowering the threshold to 2.5% leads to a signal emerging one month earlier, in March and excluded 15 PTs, corresponding to terms not known as AEFIs, such as "menstrual disorder", "Herpes zoster", and "arthralgia". A 5% threshold appears consistent for mRNA COVID vaccines, considering terms like "influenza-like illness", "asthenia", "headache", "vaccination site pain" and "lymphadenopathy". The appropriate threshold depends on the specific drug studied and the database used and should be determined with careful consideration.

Finally, the most effective approach for early signal detection by ROR value estimation was to exclude RRPT5s combined to adjust for gender, age and OD. This approach led to an estimate ROR with a large confidence interval due to a reduction in the statistical power of the analysis. However, the high number of reports registered in the first few months of the vaccination campaign allows to have enough statistical power. The media and social attention given to the COVID-19 pandemic and the vaccination campaign has underlined the importance of pharmacovigilance. It can be assumed that this heightened awareness has encouraged the reporting of serious AEFIs that might not have been reported in another context.

This method of signal detection could be applied during public health crises similar to COVID-19. However, its application in routine pharmacovigilance practice requires further investigation. As suggested by Fusaroli et al., due to the lack of exposure data and the unquantified under and selective reporting, signals of disproportionate reporting cannot on their own be interpreted as conclusive scientific evidence of a causal relationship between a drug and an ADR [33]. We conducted this disproportionate reporting analysis following our previous study [15], which included an exhaustive, case-by-case assessment of all cases and contextualization within the knowledge already accrued from other sources, such as fundamental data, case series, literature and observational studies.

Concerning the previous and current cases review, despite oral or intra-tympanic corticosteroid therapy, deafness persisted for more than 3 months. The irreversible nature of the deafness reported is a cause for concern, since there is no treatment that can restore hearing apart from hearing aids. It is possible that the most severe SSNHL are over-represented in our case review. This may be due to reporting bias, with practitioners and patients tending to report the most severe cases more often. Also, the lack of medical confirmation of deafness led to the exclusion of the largest number of cases in our study. It is possible that patients with mild hearing loss did not consult an ear, nose and throat (ENT) specialist, explaining the higher rate of severe cases. It also implies that the reporting rate is underestimated for less severe cases. As expected, we gathered mainly cases occurring after booster doses, and most importantly, there was one positive rechallenge case. A patient developed SSNHL a few days after the first and second booster doses of tozinameran, suggesting the strong likelihood of a causal relationship [34]. Patients who had tolerated their primary COVID-19 vaccination well may still suffer from SSNHL following a booster dose. It seems important to take this risk into account during booster campaigns, particularly for patients who have already suffered from this AEFI.

Hearing disorders have also been observed in patients following COVID-19 infection. The effects of SARS-CoV-2 on neuronal tissue could be due to direct infection of the central nervous system, or linked to vascular damage caused by vasculitis or vasculopathy, in the same manner as the mechanism described for the varicella-zoster virus and human immunodeficiency virus [35]. The SARS-CoV-2 spike glycoprotein is known to exhibit tropism for human angiotensin-converting enzyme 2 [36], which is expressed not only in pulmonary respiratory epithelium and vascular endothelium, but also in olfactory neuroepithelium [37]. Indeed, the COVID-19 virus exhibits tropism for the central nervous system. Several studies have demonstrated the infection of neurons by COVID-19, causing characteristic metabolic changes, both in the animal model and in human neurons in vitro [38, 39], which explains the neurological symptoms observed in some patients, but does not explain

the AEFIs related to hearing. The pathophysiological mechanisms that might explain post-vaccination SSNHL are those already suspected of causing idiopathic SSNHL. Vaccination could induce an immunological response leading to the release of antibodies and cytokines. The formation of immune complexes could trigger an autoimmune response directing antibodies to the cochlea. As a result, immunological and inflammatory responses lead to vasculitis and vascular ischaemia of the cochlea [40].

Recently, a study compared the SSNHL incidence rate in a university hospital in southern Israel over the COVID-19 outbreak and the COVID-19 vaccination campaign periods with pre-COVID-19 periods [41]. The authors found a low but significant increase of SSNHL incidence during the COVID-19 vaccination campaign, but the adjusted annual incidence rate of SSNHL for tozinameran-vaccinated patients was not significantly different compared with unvaccinated patients. This study is limited by the small sample size (single hospital, small number of patients), given the rarity of the event investigated. However, another study, through a very large retrospective cohort study of 2,602,557 patients in Israel, suggested an increase in the incidence of SSNHL within 21 days after the first or second dose of tozinameran compared with the incidence observed previously in 2018 and 2019 [42].

Damkier et al. carried out a study on the Danish national health register which failed to find an increased risk of SSNHL or vestibular neuritis following mRNA COVID-19 vaccination [43]. However, it did show that mRNA COVID-19 vaccination may be associated with a slight excess risk of a visit to an ENT specialist followed by a prescription for moderate to high doses of prednisolone, used as a proxy. This highlights the difficulty of identification of patients suffering from SSNHL in medico-administrative data. In practice, this event could be diagnosed and treated without requiring hospitalisation. Thus, SSNHL diagnostic codes are not sufficiently reliable to detect the event. Here, the authors attempted to measure the occurrence of the event indirectly by hypothesising that the initiation of high-dose corticosteroid therapy following an auditory procedure was most likely related to SSNHL. Recently, Shetty et al. adopted a multisource data approach with, [44] on the one hand, a retrospective observational analysis of spontaneous reports of audiovestibular events and, on the other, a self-controlled case series analysis using general practice data. Certain aetiologies such as intracranial lesions, neck pathologies, Meniere's disease, hydrops or ischemic stroke were excluded, but case reports were not evaluated on the basis of a full medical analysis. The authors found a significant increase in vertigo and tinnitus following Vaxzevria® and tozinameran, but not in hearing loss. The difference in results could be due to the small number of cases of hearing loss selected (n = 76) compared with vertigo (n = 415) or tinnitus (n = 226), making it difficult to reach a threshold of significance, and to the subjectivity of the diagnosis of vertigo and tinnitus, whereas hearing loss is objectively diagnosable.

Several strengths could be highlighted in our study. First, the original approach to find a sensitive and reproducible method for early signal detection. Our data suggested the necessity of applying different methods of estimation in disproportionality analysis to identify those allowing an early detection of signals related to rare ADRs during pandemic or public health crisis. Secondly, to reduce the influence of notoriety bias, we included in the disproportionality analysis the cases of hearing impairment occurring before 1 February 2022, the date of WHO signals [5]. Consequently, all cases occurring prior to this date but reported between February 2022 and March 2023 were excluded. In fact, the impact of media is known on quantitative reporting of ADR [45–47]. Furthermore, the French pharmacovigilance system relies on a network of pharmacovigilance centres and ADR reports from healthcare professionals and patients are carefully reviewed by pharmacovigilance experts as well as clinicians, with this medical data making it possible to select a high-quality dataset. In contrast to epidemiological studies based on administrative databases, our case review is supported by application of strict diagnostic criteria, which reduces the risk of including false positives. In our first study, the reporting rate was similar for both mRNA vaccines, estimated at 1.5 cases per million injections [15]. The difference of the reporting rate in this study (0.83/1,000,000 doses for tozinameran and 4.3/1,000,000 for elasomeran) could be explained by the few cases selected (18 cases for tozinameran and 10 cases for elasomeran).

This study has some limitations, as disproportionality analysis can be affected by a variety of biases, since they are based on declarative data and under-reporting. However, regarding the context of intensive pharmacovigilance for COVID-19 vaccination campaign in France, the under-reporting rate could be considered as low. Moreover, few patient characteristics were taken into account by adjusting the analysis (age, gender and OD drugs). Other relevant criteria such as cardiovascular, autoimmune and otoneurological history were not considered.

An important step in the evaluation of vaccine-related ADRs is to compare their rates in vaccinated and unvaccinated populations, as was done for myocarditis [48]. As the adverse event studied is very rare, a case-control study appropriate to rare events is needed to better explore the association of mRNA COVID-19 vaccination with hearing impairment, as has been done for menstrual cycle [49]. We compared the rate of reporting of hearing impairment between mRNA vaccines and other vaccines, and not to the population not exposed to mRNA vaccines in the same period. Furthermore, we excluded non mRNA vaccines for COVID-19 considering the lower exposure of the population

to these vaccines and in order to focus the analysis on mRNA vaccines.

5 Conclusion

Hearing impairment/SSNHL occurring after mRNA COVID-19 vaccination seems to be a rare adverse event, which does not call into question the benefits of mRNA vaccines. Regardless, these AEFI deserve to be known, given the potentially disabling impact of sudden deafness, and the occurrence of SSNHL after booster doses of the tozinameran and elasomeran vaccines. The use of a well-designed disproportionality analysis could have revealed an early signal during the 2021 vaccination campaign.

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Declarations

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Conflict of interest No commercial organizations had any role in the writing of this paper for publication**.** All authors declare they have no conflicts of interest.

Ethics approval The study was conducted in accordance with the principles of the Declaration of Helsinki. Patient consent was not required because the analysis was carried out on the French Pharmacovigilance DataBase, an anonymized database.

Consent to participate Patient consent was waived as the French Pharmacovigilance database contains anonymised data that cannot allow patients' identification.

Consent for publication Not applicable.

Availability of data and material Data sharing is not applicable to this article, as the datasets used are based on anonymised data that are protected by agreements with the French Data Protection Commission (CNIL; Commission Nationale de l'Informatique et Liberté).

Code availability The code will be made available upon reasonable request to the corresponding author.

Authors' contributions D.B., H.B. and H.T.-V. contributed equally to this study. They had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. D.B. and H.B. conceptualized the study. D.B., H.B. and F.S. designed the study. All authors were involved in acquisition, analysis, and interpretation of the data. M.B.R., H.G., M.L., F.R., J.M. and A.G. provided administrative, technical or material support. D.B., H.B. and H.T.-V. drafted the manuscript. All authors read and approved the final version.

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