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Validation of the French national health insurance information system as a tool in vaccine safety assessment: Application to febrile convulsions after pediatric measles/mumps/rubella immunization

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ABSTRACT

In the French national health insurance information system (SNIIR-AM), routine records of health claimed reimbursements are linked to hospital admissions for the whole French population. The main focus of this work is the usability of this system for vaccine safety assessment programme. Self-controlled case series analyses were performed using an exhaustive SNIIR-AM extraction of French children aged less than 3 years, to investigate the relationship between MMR immunization and children hospitalizations for febrile convulsions, a well-documented rare adverse event, over 2009–2010. The results suggest a significant increase of febrile convulsions during the 6–11 days period following any MMR immunization (IRR = 1.49, 95% CI = 1.22, 1.83; $p = 0.0001$) and no increase 15–35 days post any MMR immunization (IRR = 1.03, 95% CI = 0.89, 1.18; $p = 0.72$). These results are in accordance with other results obtained from large epidemiologic studies, which suggest the usability of the SNIIR-AM as a relevant database to study the occurrence of adverse events associated with immunization. For future use, results associated with risk of convulsion during the day of vaccination should nevertheless be considered with particular caution.

1. Introduction

Vaccines are one of the most cost-effective public health measures and are currently a cornerstone of preventive medicine [1]. Routine vaccination campaigns have an almost world-wide coverage [2]. However, due to their particularity of being administered to healthy people, notably children, their safety must be carefully monitored [3,4].

Vaccines undergo extensive testing for safety in clinical trials before they are licensed. Such trials usually have sample sizes that are insufficient to detect rare adverse events and are often carried out in homogeneous populations with relatively short follow-up periods limiting their generalizability [5]. Currently, much information on vaccine safety is based on data coming from passive surveillance of adverse events. Such systems are more practical and less expensive than controlled trials. Unfortunately, they also suffer two limitations which are their underreporting of adverse events and their inability to establish causal relationships between immunization and a specific adverse event [6]. Since the early 1990s, record-linkage methodology has been successfully used to better assess vaccine safety [7]. Record linkage refers to the merging of information (records) on the same person which may have been recorded on different occasions and been part of different data collections [8]. Simultaneously, efficient statistical methods in pharmaco-epidemiology, as the self-controlled case series (SCCS) method, were also developed and successfully applied to vaccine

Abbreviations: MMR, measles/mumps/rubella; PCV, pneumococcal conjugate vaccine; SCCS, self-controlled case series; FC, febrile convulsion; SNIIR-AM, French national health insurance information system; IRR, incidence rate ratio; ICD-10, International Statistical Classification of Diseases, Tenth Revision; GP, general practitioner.

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safety assessment [9]. The SCCS is conducted on cases only and has the advantage of implicitly adjusting for constant confounding factors.

In France, routine records of health claimed reimbursements and hospital admissions for the French population are kept and linked by the National Health Insurance in a database: the French national health insurance information system (SNIIR-AM) [10]. This database could serve as a powerful tool for investigating possible vaccine-associated adverse events and has recently been made available for research purposes. Although previous studies in pharmacoepidemiology have been done from the SNIIR-AM [11], vaccine safety assessment has not yet been undertaken.

The aim of this study was to assess the feasibility of using SNIIR-AM data for vaccine safety assessment: a well documented adverse event in vaccine safety, the occurrence of febrile convulsions (FCs) in children after immunization for measles/mumps/rubella (MMR), was investigated using the SCCS method.

2. Materials and methods

2.1. Current knowledge on febrile convulsions after MMR immunization

Because MMR is a live vaccine, it may cause adverse events but serious reactions are extremely rare [12]. Nevertheless, FCs were shown to be associated with MMR vaccines containing the mumps Urabe strain around 15–35 days after immunization. These vaccines have now been removed from the market and replaced by vaccines with non-reactogenic mumps strains in most European countries (including France). Additionally, at least 5 large epidemiologic studies have suggested that the measles component of MMR vaccines increased by two to three-fold the risk of FCs [9,13–16] 1–2 weeks after immunization (Table 1).

2.2. Standard vaccine schedule and practices in France for MMR

The French vaccine calendar recommends a two MMR doses regimen at age 12 months (9 months for children in nursery) and between 13 and 24 months with at least one month interval between the two doses [17]. In 2007, about 85% of French children were fully immunized at 24 months of age for MMR [18].

Around 85% of infant immunizations are performed by private practitioners, either paediatricians or general practitioners [19]. The National Health Insurance reimburses 100% of the cost of such MMR vaccines and 70% of the consultations during which the vaccinations are administered. The remaining 15% of infant immunizations are performed in public maternal and child health (MCH) clinics, covering children up to six years of age where MMR vaccines are provided and administered free of charge. No data are available in the SNIIR-AM for these vaccinations.

In the private sector, the choice of vaccine is left to the prescribing physicians. Two MMR vaccines were used during the study period. The first (Priorix^{TM} – GlaxoSmithKline) contained the attenuated measles virus (Schwarz strain), RIT 4385 strain of mumps virus (derived from the Jeryl Lynn strain) and the Wistar RA 27/3 rubella virus strain. The second (M-M-RVAXPRO^{TM}, Sanofi Pasteur) contained the attenuated measles virus (Edmonston Enders strain), Jeryl Lynn strain of mumps virus and the Wistar RA 27/3 rubella virus strain.

2.3. Datasets

Associations between MMR immunizations and occurrences of FCs in children were investigated from an exhaustive extraction of the SNIIR-AM concerning French children less than 3 years of age at event having had at least one hospitalization for FCs between 2009 and 2010.

The National Health Insurance covers the whole French population. Its information system, the SNIIR-AM, contains individualized, anonymous, and exhaustive data on all health spending reimbursements for more than 80% of the population [10]. In this database, data are only available for a period of two years plus the current year. It contains anonymous sociodemographic, medical characteristics and records of health care reimbursements. Thus, only drugs which are in part reimbursed (such as MMR vaccines) can be studied. Since 2009, SNIIR-AM data are completed by hospital admissions data contained in the National hospital discharge database (PMSI). Due to the impossibility to distinguish same sex twins in the PMSI database, twins were excluded from the analyses.

The SNIIR-AM received approval from the Commission nationale de l'informatique et des libertés (CNIL). In this study, data access was based on special permissions given by the National Health Insurance. All data were completely anonymous. This study was approved by the CNIL.

2.4. Ascertainment of febrile convulsion occurrences

The practice in France is to hospitalize children with FCs. Information on hospitalized FCs was obtained from the PMSI in which diseases were recorded according to the French version of the International Statistical Classification of Diseases, Tenth Revision (ICD-10). FC events were identified by using the ICD-10 code R560 as the main diagnosis. Re-admissions within 72 h with the same diagnosis were counted as a single episode.

2.5. Ascertainment of vaccination dates

Because dates of vaccination are not held in the SNIIR-AM database, they must be inferred. It is important to understand how paediatric vaccines are typically delivered in France. The parent or guardian first obtains a prescription for the child's vaccine from their general practitioner (GP) or paediatrician (the date at which the prescription is issued will be referred to as the date of prescription). The parent then takes the prescription to a pharmacist, who supplies the vaccine to the parent (the date at which this occurs is the delivery date). The parent then arranges to have the child vaccinated by the GP or paediatrician (the date at which this occurs is the date of consultation; these are distinct from dates of hospitalization). Most often, therefore, the date of vaccination is the first date of consultation with the GP or paediatrician following the date of vaccine delivery.

For MMR vaccine, only the dates of prescription and delivery are recorded in the SNIIR-AM, along with consultation dates. We extracted all prescriptions and deliveries of vaccines using the French standard drug identification code. The following algorithm was implemented to calculate the likely date of vaccination for each child in the study. For each child and each vaccine delivered for that child, the vaccination date was taken to be the first consultation date with the GP or paediatrician on or after the delivery date, excluding the date of prescription (if this was the same as the date of delivery) and any consultation at which an antibiotic was prescribed.

The reason for excluding the date of prescription if this was the same as the date of delivery is that a consultation on that date was likely to have been booked to obtain the prescription, not to administer the vaccine. Consultations at which antibiotics were prescribed were excluded, as they indicate that the child had become ill and that vaccination would most likely be deferred. Due to the inability to reconstruct their likely vaccination schedule, children with a delivery of more than one dose of a particular MMR vaccine on the same day were excluded from the analyses.

Table 1
Characteristics and results of main large epidemiologic studies having found that MMR vaccines increase the Incidence Rate Ratio (IRR) of febrile convulsions in children.

Author	Year	Country	Design	Studied periods	Incidence rate ratio [95% CI[a]]	References
Farrington et al.	1995	United Kingdom	SCCS	[6, 11] [15, 35]	3.04 [2.27–4.07] 1.51 [1.21–1.90]	[9]
Barlow et al.	2001	USA	Cohort	[0] [1, 7] [8, 14] [15, 30]	(No cases in the period) 1.73 [0.72–4.15] 2.83 [1.44–5.55] 0.97 [0.49–1.95]	[9,13]
Vestergaard et al.	2004	Denmark	Cohort	[1, 14]	2.74 [2.55–2.97]	[13,14]
Miller et al.	2007	United Kingdom	SCCS	[−14, −1] [6, 11] [15, 35]	0.38 [0.22–0.64] 4.09 [3.14–5.33] 1.13 [0.87–1.48]	[14,15]
Gold et al.	2010	Australia	SCCS	[−14, −1] [6, 11] [15, 35]	0.58 [0.33–1.02] 2.11 [1.43–3.10] 0.90 [0.65–1.25]	[15,16]

[a] CI: confidence interval.

Furthermore, owing to vaccinations for which no reimbursements are available (MCH clinics), all children with no MMR vaccination histories during the first 205–730 days of life were excluded from the analyses. Children with their two first MMR doses separated by less than one month were also excluded because of a lack of confidence in these estimated dates.

2.6. Study hypotheses

This study estimated the association between MMR vaccinations and risk of FCs. The hypotheses tested were that there was an increase in the incidence of hospitalizations for FCs within 0, 1–5, 6–11, or 15–35 days from a MMR vaccination in the children aged between 240 days and 730 days compared to the incidence in unexposed. A pre-vaccination period of 14 days was also defined to account for possible delayed vaccination due to FCs. Based on the literature, the 6–11 days risk period served as a positive control and the 15–35 days risk period as a negative one (Table 1). All other times were regarded as unexposed. We examined the risk after the first, second and all MMR doses separately. Here, "first" and "second" doses meant the first and second vaccination dates recorded in the data. Separate analyses were also performed for each vaccine (PRIORIX^{TM} and M-M-RVAXPRO^{TM}).

2.7. Statistical methods

The relative risks (IRRs) of events occurring during the defined risk periods and their 95% confidence intervals were estimated using the SCCS method [5]. This method, which uses only information from individuals with an adverse event, was developed specifically for vaccine safety studies [6]. It provides an alternative to more established cohort or case–control methods. Only individuals who were admitted to hospital within the time period of interest were included in the analysis. Each individual is regarded as a fixed effect and only within-subject time varying effects, i.e. the exposure and age effects (categorized into 8 periods of approximately 60 days) are estimated. IRRs for the exposure periods were obtained using a within subjects conditional Poisson regression model, conditionally on the total number of events experienced by each individual.

3. Results

3.1. Total number of individuals, hospitalizations and vaccinations

In the SNIIR-AM database, a total of 8045 children less than 3 years of age were hospitalized for at least one episode of FC between 2009 and 2010 (Fig. 1). 5124 children had their first FC between 240 and 730 days of age. Among these children, 2913 (56.9%) had at least one available date of MMR immunization between 205 and 730 days of age with a minimum interval of 1 month between the two possible MMR doses (if applicable), and received delivery of a single pack of vaccine on each occasion (individuals to whom two packs of vaccine were delivered on the same date were excluded). Among them, 2376 (81.6%) had only one episode of FCs, 430 (14.8%) two episodes and 107 (3.6%) three or more episodes. The maximum number of episodes per children was 9. The SCCS analyses were performed from these 2913 children and all their episodes of febrile convulsions. For this population, histograms of age at first hospitalizations for FCs, and first and second MMR vaccinations (1357 children from the 2913) are shown in Fig. 2. In this figure, a peak around 1 year of age was observable for the first MMR vaccinations (as expected with the French vaccination schedule). In these 2913 children, 2162 (74.2%) were exclusively immunized with PRIORIX^{TM} and 649 (22.3%) with M-M-RVAXPRO^{TM}.

3.2. Risk of febrile convulsions with MMR vaccination

The results of the SCCS analysis for all MMR doses and all events of FCs are detailed in Table 2. There was a significant increase in IRR of FCs the day of MMR immunizations (IRR = 2.66, 95% CI = 1.85, 3.85; $p < 0.0001$) and 6–11 days post any MMR doses (IRR = 1.49, 95% CI = 1.22, 1.83; $p = 0.0001$). A similar result was observed the day of first MMR doses (IRR = 2.99, 95% CI = 1. 2.02, 4.44; $p < 0.0001$) and 6–11 days post first MMR doses (IRR = 1.50, 95% CI = 1.20, 1.89; $p = 0.0005$). No increase in IRR of FCs was observed 15–35 days post all MMR doses (IRR = 1.03, 95% CI = 0.89, 1.18; $p = 0.7181$) and post first MMR doses (IRR = 1.06, 95% CI = 0.91, 1.23; $p = 0.4818$). For second MMR doses analysis, whatever the risk period, no significant increase in IRR of FCs was observed. Furthermore, whatever the dose and the risk period, the same results were obtained for PRIORIX^{TM} or M-M-RVAXPRO^{TM} vaccines separately.

Concomitant vaccination with pneumococcal conjugate vaccine (PCV) may have occurred, since the first MMR dose and third PCV dose are both recommended at 12 months. We estimated dates of PCV immunizations using the same algorithm as for MMR vaccination. A total of 893 children had an identical MMR and PCV date. Exclusion of these children did not modify substantially the results presented above.

4. Discussion

In this study, the SNIIR-AM, a French administrative database containing all health claimed reimbursements and hospital

Table 2
Estimation of incidence risk ratio of hospitalisation for febrile convulsions post MMR vaccinations, following defined exposure periods with the SCCS method.

Parameter	No of cases	IRR	SE (β)	P value	95% CI
All vaccines (*N* = 2913)					
First MMR dose					
Unexposed		1.00	–	–	–
−14 to −1 days	121	1.06	0.09	0.5614	[0.88–1.27]
0 day	25	2.99	0.20	<0.0001	[2.02–4.44]
1–5 days	44	1.05	0.15	0.7497	[0.78–1.42]
6–11 days	76	1.50	0.12	0.0005	[1.20–1.89]
15–35 days	184	1.06	0.08	0.4818	[0.91–1.23]
Second MMR dose					
Unexposed		1.00	–	–	–
−14 to −1 days	34	0.87	0.18	0.4333	[0.61–1.24]
0 day	4	1.57	0.50	0.3654	[0.59–4.20]
1–5 days	12	0.64	0.36	0.2101	[0.32–1.29]
6–11 days	22	1.44	0.22	0.1007	[0.93–2.22]
15–35 days	45	0.91	0.16	0.5497	[0.67–1.24]
All MMR doses					
Unexposed		1.00	–	–	–
−14 to −1 days	155	1.01	0.08	0.8885	[0.86–1.19]
0 day	29	2.66	0.19	<0.0001	[1.85–3.85]
1–5 days	56	0.96	0.14	0.7543	[0.73–1.26]
6–11 days	98	1.49	0.10	0.0001	[1.22–1.83]
15–35 days	229	1.03	0.07	0.7181	[0.89–1.18]
Priorix vaccine (*N* = 2162)					
First MMR dose					
Unexposed		1.00	–	–	–
−14 to −1 days	90	1.06	0.11	0.6026	[0.85–1.31]
0 day	20	3.22	0.23	<0.0001	[2.07–5.01]
1–5 days	31	0.99	0.18	0.9720	[0.70–1.42]
6–11 days	56	1.49	0.14	0.0036	[1.14–1.95]
15–35 days	137	1.07	0.09	0.4704	[0.89–1.27]
Second MMR dose					
Unexposed		1.00	–	–	–
−14 to −1 days	27	0.95	0.20	0.7888	[0.63–1.41]
0 day	3	1.65	0.58	0.3860	[0.53–5.14]
1–5 days	11	0.78	0.38	0.5208	[0.37–1.65]
6–11 days	15	1.34	0.27	0.2783	[0.79–2.28]
15–35 days	29	0.80	0.20	0.2597	[0.54–1.18]
All MMR doses					
Unexposed		1.00	–	–	–
−14 to −1 days	117	1.03	0.10	0.7332	[0.85–1.25]
0 day	23	2.87	0.21	<0.0001	[1.90–4.33]
1–5 days	42	0.95	0.16	0.7446	[0.69–1.31]
6–11 days	71	1.46	0.12	0.0021	[1.15–1.86]
15–35 days	166	1.02	0.08	0.8385	[0.86–1.20]
M-M-RVAXPRO vaccine (*N* = 649)					
First MMR dose					
Unexposed		1.00	–	–	–
−14 to −1 days	26	0.98	0.20	0.9228	[0.66–1.46]
0 day	5	2.61	0.45	0.0328	[1.08–6.32]
1–5 days	12	1.26	0.29	0.4361	[0.71–2.23]
6–11 days	20	1.73	0.23	0.0163	[1.11–2.72]
15–35 days	43	1.06	0.16	0.7083	[0.78–1.45]
Second MMR dose					
Unexposed		1.00	–	–	–
−14 to −1 days	5	0.81	0.45	0.6366	[0.33–1.97]
0 day	1	2.37	1.00	0.3894	[0.33–16.96]
1–5 days	1	0.48	1.00	0.4668	[0.07–3.44]
6–11 days	3	1.23	0.58	0.7209	[0.39–3.87]
15–35 days	8	1.03	0.37	0.9413	[0.50–2.10]
All MMR doses					
Unexposed		1.00	–	–	–
−14 to −1 days	31	0.95	0.19	0.7726	[0.66–1.36]
0 day	6	2.57	0.41	0.0217	[1.15–5.75]
1–5 days	13	1.12	0.28	0.6917	[0.64–1.94]
6–11 days	23	1.65	0.21	0.0199	[1.08–2.51]
15–35 days	51	1.04	0.15	0.7990	[0.77–1.39]

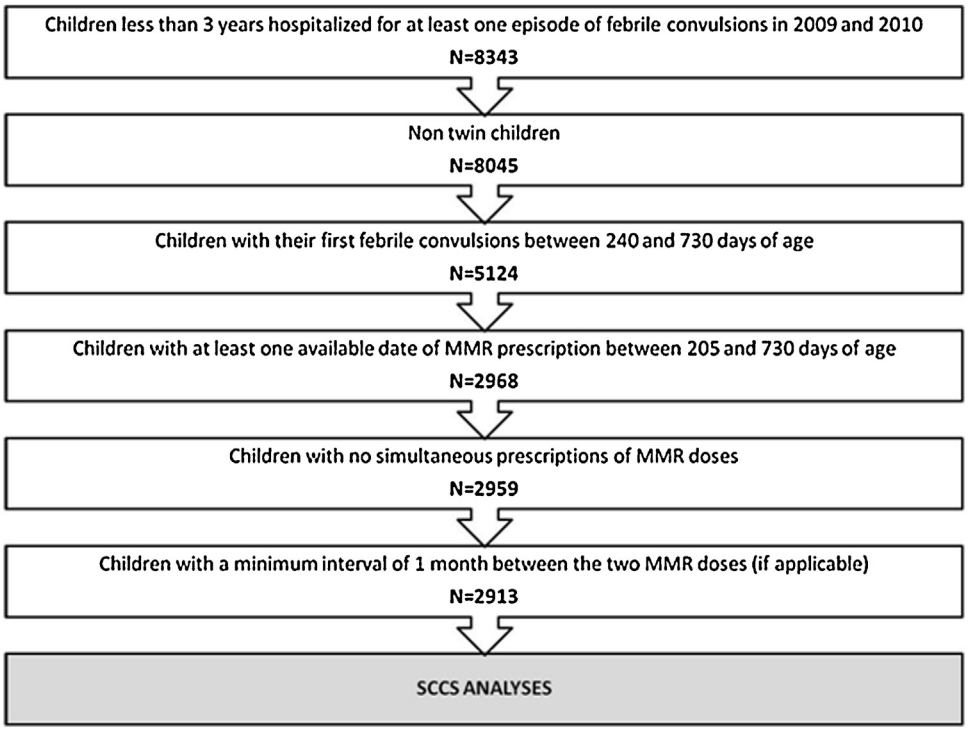

Fig. 1. Flow chart of children selection for the SCCS analyses from the initial SNIIR-AM dataset.

admissions for around 85% of the French population, was evaluated for the first time as an active tool for post-market vaccine safety assessment. From data concerning children less than 3 years old between 2009 and 2010, its usability was demonstrated with a documented adverse event, the occurrence of FCs after MMR immunization.

A significant increase in IRR of FCs 6–11 days post any MMR vaccinations was identified. This result is in accordance with other large epidemiologic studies which were done on this subject. It is now accepted that the excess risk of FCs in this period is attributable to the measles component of MMR vaccines [20]. The estimated IRR was 1.49 95%CI [1.22–1.83] and seemed to be mainly related to the first MMR dose. There were 1357 children with a second dose of MMR, and the power to detect an IRR of 1.5 for dose 2 was approximately 0.44. Thus lack of statistical power could affect the second dose analyses. During this period, no large difference in IRR estimations was found between PRIORIX^{TM} and M-M-RVAXPRO^{TM}, in accordance with Miller et al. [15] who underlined that both vaccines are derived from the measles Edmonston strain, so major differences in reactogenicity seem unlikely. Furthermore, no increase in IRR of FCs was observed 15–35 days post any MMR doses. This confirms the non reactogenicity of non-Urabe mumps strains [15,16].

Our study was restricted to FCs serious enough to warrant hospitalization. An advantage of this restriction is that it enables a direct comparison to be made between our results and those obtained in other studies involving hospitalized cases [9,15]. A disadvantage is that we are unable to comment on the association, if any, between vaccination and less serious events.

An apparent increase in risk on the day of MMR immunization was also observed. A selection bias linked to the algorithm calculating the vaccination dates is strongly suspected here. In our sample, there was a large number of consultations on the day of hospitalization for FCs (plausibly consultations confirming the need for hospitalization). Thus our algorithm was more prone to select the date of these consultations as the vaccination date, leading to an overestimation of the risk associated with the day of hospitalization. It has thus to be interpreted with caution (Appendix 1). No significant clustering of events in the 14 days preceding vaccination was observed, suggesting there is no major 'healthy vaccine' effect.

All these results seem to confirm the capability of the SNIIR-AM database to efficiently detect adverse events associated with vaccine immunization. However, the estimated IRRs 6–11 days post MMR vaccinations are lower than those found in studies using a similar methodology. Indeed, the latter have identified a two to four-fold increase in IRR of FCs, around twice the value we estimated. Possible explanations are as follows.

First, SNIIR-AM data are reimbursement data and reimbursed vaccines may differ from administered ones. If some reimbursed vaccines are not administered, the IRR will be biased towards 1. Conversely, some vaccines can be administered but not reimbursed, particularly the least expensive. In that case the IRR are also biased towards 1. Despite the generalized use in France of an electronic card automating reimbursement of drugs which should limit this effect, such bias could not be excluded.

Second, in the French health insurance scheme, every child could be entitled to the health insurance of his/her two parents. However, if a parent is affiliated to the general health insurance regime and the second one to another health insurance regime, vaccines administered to the child may alternatively be reimbursed under the general regime and the other regime. If a vaccine is reimbursed by another regime than the general one, it will not appear in the SNIIR-AM, which will lead this study to bias IRR towards 1. Although the SNIIR-AM database covered more than 80% of the French population during the period studied and no more than 9% of under-five children are entitled to the health insurance of more than one person, this bias may have an impact on the study results.

Third, the estimated dates of vaccination may not all be correct, leading to bias towards 1 in the IRR estimations, though the use of alternative algorithms to calculate vaccination dates suggest that the bias persisted whatever the method employed (Appendix 2).

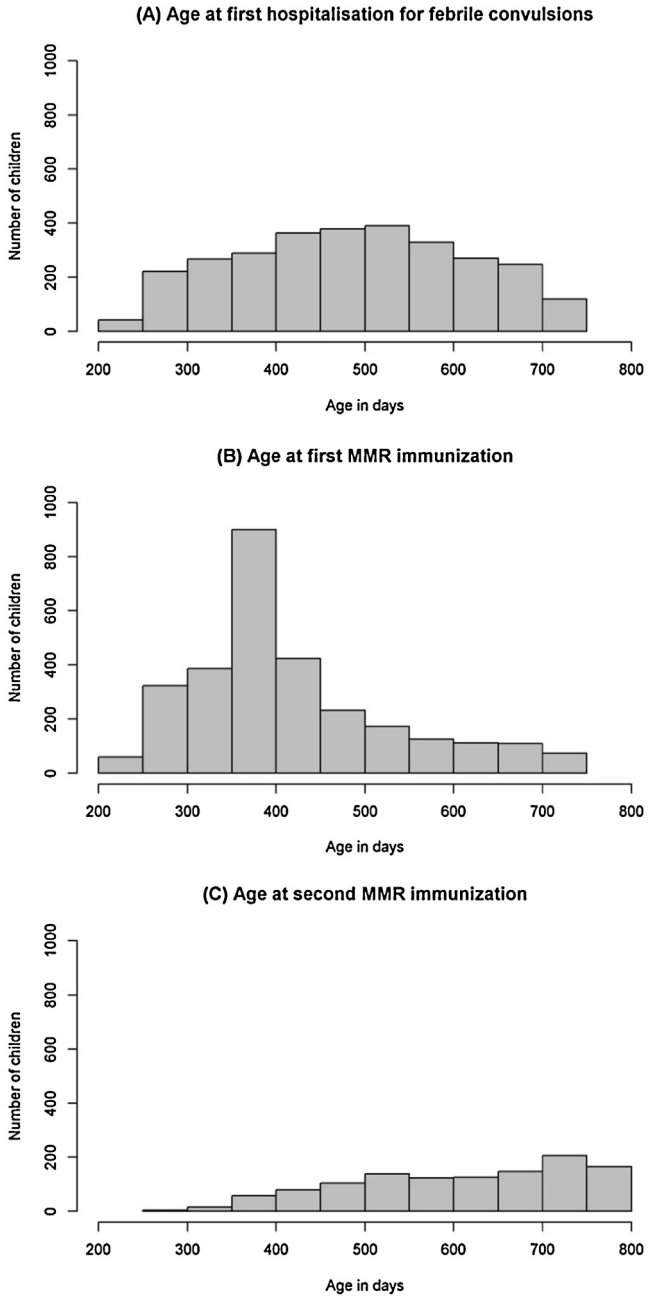

Fig. 2. Age distributions at (A) first hospitalization for febrile convulsions ($n = 2913$), (B) first MMR immunization ($n = 2913$) and (C) second MMR immunization ($n = 1357$) for the children included in the SCCS analyses.

5. Conclusions

The present analysis has shown that although bias towards the null inherent in the nature of the data exist, the study of rare events associated with vaccination is possible in France through the SNIIRAM database. For future use, results associated with the day of vaccination should nevertheless be considered with caution. The number of novel vaccines which have recently been introduced or are being developed underlines the need for rapid and efficient methods to assess possible associations between vaccines and adverse events in France. This study shows that the SNIIRAM database is a promising tool in vaccine safety evaluation which ought to be fully exploited in the next few years.

Ethical approval

This study was approved by the Commission nationale de l'informatique et des libertés (CNIL).

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Contributors: MaH participed in the study design, analyzed the data, participated in the interpretation of results and drafted the article. CQ participated in the conception and design of the study, the acquisition of data, the interpretation of results, and revised critically the article. PF, SE, and PTB participated in the conception and design of the study, the acquisition of data, the interpretation of results, provided guidance on statistical analysis and revised critically the article. EB participated in the acquisition of data, the design of the study, the interpretation of results, and revised critically the article. MoH participated in the interpretation of the results, provided guidance on statistical analysis and revised critically the article. MV participated in the interpretation of the results, and revised critically the article. All authors approved the final version of the article. *Conflict of interest statement:* None declared. *Funding:* This work was supported by grants from the Agence Nationale pour la Recherche (ANR), the Institut National de la Santé et de la Recherche Médicale (Inserm, Réseau de recherche clinique et en santé des populations), the Programme Hospitalier de Recherche Clinique (PHRC) and by a Royal Society Wolfson research Merit Award to PF. The funders had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2013.09.052.

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