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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.