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Risk of febrile convulsions after MMRV vaccination in comparison to MMR or MMR+V vaccination

Tania Schink[a,1], Jakob Holstiege[a,2], Frank Kowalzik[b,3], Fred Zepp[b,4], Edeltraut Garbe[a,*]

[a] Leibniz Institute for Prevention Research and Epidemiology – BIPS, Achterstraße 30, 28359 Bremen, Germany
[b] Center for Children and Adolescent Medicine of the Johannes Gutenberg-Universität, Langenbeckstraße 1, 55131 Mainz, Germany

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ABSTRACT

Background: In July 2006, Priorix-Tetra™, a combined measles-mumps-rubella-varicella (MMRV) vaccine, was licensed in Germany. Since a postlicensure study had shown a more than twofold elevated risk of febrile convulsions (FC) after first dose vaccination with the combined MMRV vaccine ProQuad® compared to separately administered MMR and V vaccines (MMR+V), the Paul-Ehrlich-Institute, the German regulatory agency for vaccine licensing and safety, requested a study investigating the risk of FC for Priorix-Tetra™.

Methods: We performed a matched cohort study based on claims data of more than 17 million insurees in the German Pharmacoepidemiological Research Database. All children born between 01.01.2004 and 31.12.2008 who received a 1st dose of MMRV vaccine were matched to children vaccinated with MMR, MMR+V and MMR or MMR+V (combined group), respectively, by sex, age, month of vaccination and statutory health insurance. The primary outcome was defined as hospitalization with a diagnosis of FC without any alternative plausible cause of FC, e.g. an infection or neurological condition, coded as main discharge diagnosis. The secondary outcome excluded only neurological conditions to provide a more comparable outcome definition to the one used in the ProQuad® study. Numbers needed to harm (NNH), risk ratios and confounder adjusted odds ratios (ORs) with 95% CIs were estimated to compare the exposure groups.

Results: In the main risk period 5–12 days after immunization, the adjusted ORs of the primary endpoint for immunization with MMRV vaccine relative to the comparator vaccine indicated in brackets were 4.1 [95% CI 1.3–12.7; MMR], 3.5 [0.7–19.0; MMR+V], and 4.1 [1.5–11.1; MMR and MMR+V]. The corresponding ORs for the secondary outcome were 2.3 [1.4–3.9; MMR], 1.5 [0.8–2.9; MMR+V] and 2.4 [1.5–3.9; MMR and MMR+V].

Conclusions: This study in children younger than 5 years, 90% of them between 11 and 23 months, shows a risk of FC similar in magnitude for Priorix-Tetra™ as has previously been reported for ProQuad® suggesting a class effect for these quadrivalent vaccines.

1. Introduction

In July 2006, the quadrivalent measles-mumps-rubella-varicella (MMRV) vaccine Priorix-Tetra™ (GlaxoSmithKline) was licensed in Germany. Before, measles, mumps and rubella (MMR) vaccines were administered separately from varicella (V) vaccines or children were only vaccinated against MMR. The MMRV vaccine was developed to reduce the number of injections and to increase acceptance and coverage of the V vaccine. The German Standing Vaccination Committee (STIKO) recommends vaccination against measles, mumps, rubella, and varicella in all children at 11–14 months of age (1st dose) and revaccination at 15–23 months of age (2nd dose).

Several months before Priorix-Tetra™ was licensed in Germany, the first quadrivalent MMRV vaccine worldwide (ProQuad®) was launched by Merck in the USA and was recommended for both the first and second dose over separately administered MMR and V vaccines (MMR+V) [1]. In 2009, an observational post-licensure study among 12–23 months old children found a more than 2-fold significantly elevated relative risk (RR) of febrile convulsions (FC) in children in the time window 5–12 days after a first dose of

* Corresponding author. Tel.: +49 421 218 56862; fax: +49 421 218 56861.
E-mail addresses: schink@bips.uni-bremen.de (T. Schink), holstiege@bips.uni-bremen.de, jakob.holstiege@uni-ulm.de (J. Holstiege), frank.kowalzik@unimedizin-mainz.de (F. Kowalzik), Fred.Zepp@unimedizin-mainz.de (F. Zepp), garbe@bips.uni-bremen.de (E. Garbe).
[1] Tel.: +49 421 218 56865; fax: +49 421 218 56941.
[2] Present address: Institute of Research in Rehabilitation Medicine at Ulm University, Wuhrstraße 2/1, 88422 Bad Buchau, Germany.
[3] Tel.: +49 6131 17 59 22; fax: +49 6131 17 34 82.
[4] Tel.: +49 6131 17 73 26; fax: +49 6131 17 39 18.

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ProQuad® compared to separately administered MMR+V [2]. The timing of the peak in FC corresponded to the peak in fever rates which were shown to be 1.5 to 2-fold elevated after MMRV compared to MMR vaccination [3–5]. Another US study using data from the Vaccine Safety Datalink found a statistically elevated RR of 1.98 of FC in the time window 7–10 days after first dose immunization with ProQuad® in comparison to MMR+V [6]. Due to the similar composition of ProQuad® and Priorix-Tetra™ and the similar pattern of post-vaccination fever [3,7], an elevated risk of FC was also of concern for Priorix-Tetra™ and a study investigating this risk was requested by the Paul-Ehrlich-Institute in Germany.

The objective of this study was to estimate the risk of FC after vaccination with Priorix-Tetra™ compared to vaccination with MMR or MMR+V vaccines in the time-windows specified in the study by Jacobsen et al. [2].

2. Methods

2.1. Source of data

The study was carried out using data from the German Pharmacoepidemiological Research Database (GePaRD). This database consists of claims data from four German statutory health insurances (SHIs) and includes more than 17 million insurees covering all regions in Germany. It provides demographic information as well as information on hospital admissions, outpatient physician visits, and outpatient prescriptions.

Hospital data include admission and discharge dates, information on in-hospital procedures and on four different types of hospital diagnoses: the main discharge diagnosis which codes the disease requiring the hospital stay, the admission diagnosis, which is a tentative diagnosis at hospital admission, diagnoses secondary to an admission or discharge diagnosis, and ancillary diagnoses (co-morbidities).

Outpatient data include diagnoses, diagnostic procedures and non-drug treatments. Since outpatient physician visits are reimbursed on a quarterly basis, outpatient diagnoses can only be allocated to a quarter and not to an exact date. All diagnoses are coded according to the German modification of the 10th International Classification of Diseases (ICD-10 GM). Preliminary evaluations regarding the age and sex distribution, number of hospital admissions and drug use have shown that the database is representative for Germany [8–10].

In Germany, the utilization of health insurance data for scientific research is regulated by the Code of Social Law. The Federal Ministry of Health and the regulatory authority in Bremen approved the use of the data for this study. Informed consent was not required by law, since the necessary permissions were granted.

2.2. Study design

A matched cohort study was conducted among insurees who received a first vaccination with one of the index vaccines MMRV, MMR, or MMR+V during the study period from January 1 2006 to December 31 2008. During the study period, the STIKO gave equal preference to the use of the MMRV vaccine and the separate administration of MMR and V vaccines. Eligible were insurees born between January 1 2004 and December 31 2008 for whom the insurance started no later than 180 days after the date of birth. Cohort entry was defined as the date of first immunization with one of the index vaccines. Cohort exit was defined as the first of the following dates: 91 days after cohort entry, interruption/end of insurance, death or December 31 2008.

Children who received an immunization with MMRV vaccine were matched to each of the other vaccine exposure groups. Matching was conducted one-to-one on sex, age at vaccination in months (±1 month), SHI and calendar month of vaccination (±1 month) to children who received an immunization with MMR vaccine (matched MMR cohort), MMR+V vaccine (matched MMR+V cohort) or to children who received either MMR or MMR+V vaccine (matched MMR/MMR+V cohort).

2.3. Exposure assessment

Vaccinations were identified by outpatient codes used for reimbursement of administration of vaccines. For MMR and V vaccines these codes cover all brands available in Germany from different manufacturers. Vaccine dispensations in the pharmacy could not be considered, as physicians generally use vaccines kept in their own medical practices.

2.4. Outcome definition

Cases were defined as hospitalizations with a diagnosis of FC, i.e. an ICD-10-GM code R56.0 in any of the hospital diagnoses. Two outcome definitions were used based on their presumed different sensitivity and specificity. The primary outcome “FC narrow” was defined as hospitalization where no alternative plausible cause of FC, e.g. an infection or a neurological condition, was coded as main discharge diagnosis. In detail, this endpoint included: (i) all hospitalizations with FC as main discharge diagnosis; (ii) all hospitalizations with FC as main admission diagnosis and without a main discharge diagnosis of an infectious disease (except measles, mumps, rubella, or chickenpox) or a neurological condition; and (iii) all hospitalizations with FC as secondary or ancillary diagnosis and a main discharge diagnosis coded as complication following immunization (ICD-10-GM code “T88.0 infection following immunization” or “T88.1 other complications following immunization, not elsewhere classified”). Due to exclusion of alternative causes of FC in this outcome definition, it was assumed that it would have higher specificity, but lower sensitivity.

The secondary outcome “FC Jacobsen” was defined as closely as possible to the outcome-criteria specified by Jacobsen et al. [2]. That is, only hospitalizations for FC with a neurological condition coded as main discharge diagnosis were excluded. In consequence, “FC Jacobsen” included (i) all hospitalizations with FC as main discharge diagnosis; (ii) all hospitalizations with FC as main admission diagnosis and without a main discharge diagnosis of a neurological condition; and (iii) all hospitalizations with FC as secondary or ancillary diagnosis and with a main discharge diagnosis coded as complication following immunization. Due to inclusion of cases with an infection coded as main discharge diagnosis in this outcome definition, it was assumed to have lower specificity, but higher sensitivity.

By definition, “FC narrow” cases are a subset of “FC Jacobsen” cases. To assess whether our assumptions regarding the specificity of these two outcome definitions based on coding guidelines [11] in Germany were empirically confirmed, an additional investigation was conducted to ascertain the time window in which the endpoints “FC narrow” and “FC Jacobsen” occurred after vaccine administration.

2.5. Assessment of potential confounders

Potential confounders included age, sex, a prior FC, hospitalization for an infectious disease 15 days before until 30 days after vaccination, administration of other vaccines 30 days prior to 30 days after immunization with MMRV, MMR or MMR+V vaccine, and calendar month of vaccination to take into account the seasonality of infectious diseases. For FC cases, confounder assessment regarding hospitalizations for an infectious disease