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Study Summary (version 1.0)

Risk of Febrile Convulsions after MMRV Vaccination in Comparison to MMR or MMR+V Vaccination

Main Study: Assessment of the Risk of Febrile Convulsions after MMRV Vaccination in Comparison to MMR or MMR+V Vaccination

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Summary

Background: The German Standing Vaccination Committee (STIKO) recommends vaccination against measles, mumps, rubella, and varicella in all children at 11 to 14 months of age (1st dose) and revaccination at 15 to 23 months of age (2nd dose). In July 2006, the combined measles-mumps-rubella-varicella (MMRV) vaccine Priorix-Tetra® (GlaxoSmithKline) was licensed in Germany, which made simultaneous vaccination against all four infectious diseases possible. Before the MMRV vaccine was available, measles, mumps and rubella (MMR) vaccines were usually administered separately from the varicella (V) vaccine or children were only vaccinated against MMR. Several months before Priorix-Tetra® was licensed in Germany, the first combined MMRV vaccine worldwide (ProQuad®) was launched by Merck in the USA. Post-marketing observations revealed an elevated risk of febrile convulsions (FC) in children, who received a first dose vaccination with ProQuad® in comparison to children vaccinated with MMR and V vaccine separately on the same day. Due to the analogy of ProQuad® and Priorix-Tetra® an elevated risk of FC cannot be excluded for Priorix-Tetra® vaccination. A meta-analysis of clinical trials showed an elevated but statistically not significant increased relative risk (RR) of FC in children, who received a first dose vaccination of Priorix-Tetra® compared to children who received a first immunization against MMR or against MMR and V (MMR+V) separately on the same day.

As German infants are routinely vaccinated against measles, mumps, rubella and varicella, it is of high public interest to further investigate the risk of FC after vaccination with Priorix-Tetra® in comparison to MMR vaccination or the separate injection scheme (MMR+V) under routine care conditions.

Objective: The objective of this study was to estimate the risk of FC after vaccination with Priorix-Tetra® in comparison to vaccination with MMR or MMR+V vaccines in pre-specified time-windows.

Methods: Analyses were based on a cohort of all insurants born during the study period from January 01, 2004 through December 31, 2008, with available date of birth who received a first vaccination with one of the index vaccines MMRV, MMR+V, MMR, unspecified trivalent (U3), or unspecified quadrivalent (U4) vaccine. Cohort entry was defined as the date of the first immunization with one of the index vaccines if inclusion criteria were fulfilled. Cohort exit was defined as the first of the following dates: December 31, 2008; 91 days after cohort entry; or interruption, end of insurance or death.

Vaccinations were identified using EBM-codes, which are used for reimbursement of ambulatory treatments including administration of vaccines. Prescription data could not be

considered for the identification of vaccinations, as physicians generally use vaccines deposited in their own medical practices ("Sprechstundenbedarf").

The primary outcome 'FC narrow' was defined as a hospitalization with a diagnosis of FC where no plausible cause of FC, e.g. an infection or neurological condition, was coded as main discharge diagnosis. Among the secondary outcomes, "FC Jacobsen" was defined as in the study by Jacobsen et al.(1) that is, all hospitalizations with a diagnosis of FC that had no main discharge diagnosis referring to a neurological condition were included, "FC broad" included all hospitalizations with a diagnosis of FC, irrespective of the possible cause, and "seizures" included all hospitalizations with a main discharge diagnosis indicating seizures and convulsions (including FC and epilepsy).

Cumulative incidences (=risks) of primary and secondary outcomes with 95% confidence intervals (CIs) were calculated for all exposure groups within each risk interval (0-4, 5-12, 13-30 and 0-30 days after cohort entry). RRs and risk differences of primary and secondary outcomes for the comparison of exposure groups were calculated with 95% CIs. Additionally, RRs and risk differences and their 95% CIs were calculated for the pre- or post-vaccination self-comparison periods 60 to 30 days before immunization and 60 to 90 days after immunization.

Children who received an immunization with MMRV vaccine were matched one-to-one on sex, age at vaccination in months (tolerance range: ± 1 month), statutory health insurance (SHI) and calendar month of cohort entry (tolerance range: ± 1 month) to children who received an immunization with MMR vaccine or MMR+V vaccine between 1.1.2006 and 31.12.2008, respectively.

A multivariate analysis based on the matched cohorts considering history of FC, hospitalizations for infectious diseases or administration of other vaccinations as possible confounders was performed to compare the occurrence of FC within each risk interval between exposure groups. That is, confounder adjusted ORs with corresponding 95% CIs were estimated to compare the MMRV exposure group with each of the comparison exposure groups using a separate binary logistic regression model for each risk interval.

Results: Regarding the entire 30-day risk period, the cumulative incidence of the primary outcome 'FC narrow' was 1.29 times higher (95% CI 0.69 – 2.44) in the MMRV group than in the matched MMR group and 4.50 times higher (95% CI 0.97 – 20.83) than in the matched MMR+V group. In the main risk period 5 to 12 days after immunization, the cumulative incidence was 4.67 times higher (95% CI 134 – 16.24) in the MMRV group than in the matched MMR group and 5.00 times higher (95% CI 0.58 – 42.79) than in the matched MMR+V group. For the comparison of MMRV and the pooled exposure group of children vaccinated against MMR or MMR+V, the unadjusted RR was 1.63 (95% CI 0.87 – 3.03) for

the entire risk period and 4.50 (95% CI 1.52 – 13.30) for the main risk period 5 to 12 days after immunization.

The unadjusted RRs regarding the secondary outcome ‘FC Jacobsen’ showed a similar pattern. In the entire 30-day risk period, the cumulative incidence was 1.38 times higher (95% CI 1.00 – 1.91) in the MMRV group than in the matched MMR group and 1.47 times higher (95% CI 0.92 – 2.33) than in the matched MMR+V group. In the main risk period 5 to 12 days after immunization, the cumulative incidence was 2.37 times higher (95% CI 1.39 – 4.05) in the MMRV group than in the matched MMR group and 1.50 times higher (95% CI 0.76 – 2.95) than in the matched MMR+V group. The corresponding unadjusted RRs for the comparison with the pooled exposure group of children vaccinated against MMR or MMR+V were 1.48 (95% CI 1.08 – 2.01) for the entire risk period and 2.43 (95% CI 1.46 – 4.04) for the main risk period 5 to 12 days after immunization.

In the main risk period 5 to 12 days after immunization, the adjusted OR regarding the primary outcome ‘FC narrow’ was 4.13 (95% CI 1.34 – 12.68) for immunization with MMRV vaccine compared to immunization with MMR alone, 3.53 (95% CI 0.66 – 18.98) for immunization with MMRV compared to immunization with MMR+V and 4.10 (95% CI 1.51 – 11.12) compared to the pooled exposure group of children vaccinated against MMR or MMR+V. The corresponding ORs for the secondary outcome ‘FC Jacobsen’ were 2.30 (95% CI 1.36 – 3.88), 1.52 (95% CI 0.79 – 2.93) and 2.38 (95% CI 1.45 – 3.92).

For the entire risk period 0 to 30 days the adjusted OR regarding the primary outcome ‘FC narrow’ was 1.28 (95% CI 0.70 – 2.37) for immunization with MMRV vaccine compared to immunization with MMR alone, 3.85 (95% CI 1.02 – 14.53) for immunization with MMRV compared to immunization with MMR+V and 1.62 (95% CI 0.88 – 2.96) compared to the pooled exposure group of children vaccinated against MMR or MMR+V.. The corresponding ORs for the secondary outcome ‘FC Jacobsen’ were 1.37 (95% CI 0.99 – 1.89), 1.54 (95% CI 0.98 – 2.44) and 1.48 (95% CI 1.09 – 2.02).

Discussion: The strengths of the study are its size and the representativeness of the data. There was no strong indication for important misclassification of exposure or outcome. The results were robust to sensitivity analyses and comparable with literature.

Cumulative incidences of FC were in our study lower than reported in comparable studies. This is most probably due to the inclusion of cases that occurred in the outpatient setting in the other studies. We did not include outpatient cases in our study, since no date of diagnosis was available for the ambulatory diagnoses.

In conclusion, this study suggests an fourfold increase in the cumulative incidence of the main outcome ‘FC narrow’ in the main risk interval 5 days to 12 days after a first dose

immunization with MMRV vaccine compared to MMR vaccine and 3.5-fold increase in the cumulative incidence of FC in this risk period compared to MMR+V immunization.

In contrast to Jacobsen et al. we saw for the primary outcome 'FC narrow' for the comparison of MMRV and MMR+V immunization also for the entire risk period 0 to 30 days after immunization an elevated unadjusted RR of 4.50 (95% CI 0.97 – 20.83.42) and a statistically significantly elevated adjusted OR of 3.85 (95% CI 1.02 – 14.53).

The observed risk difference of 0.67 per 10,000 children for the entire risk period results in one excess case of FC per 14,925 children receiving an immunization with MMRV vaccine compared to MMR. For the comparison of MMRV and MMR+V the observed risk difference for the entire risk period was 2.18 per 10,000, resulting in one excess case of FC per 4,587 children receiving an immunization with MMRV vaccine compared to MMR+V.

These excess cases have to be weighted against the advantages of one versus two injections regarding complications and compliance and the benefits of a high coverage of immunization against V.

(1) Jacobsen SJ, Ackerson BK, Sy LS, Tran TN, Jones TL, Yao JF et al. Observational safety study of febrile convulsion following first dose MMRV vaccination in a managed care setting. Vaccine 2009 July 23;27(34):4656-61.