Risk of Febrile Convulsions after a Second Immunization against Measles, Mumps and Rubella with MMRV as compared to MMR or MMR+V

Background: The German Standing Vaccination Committee (STIKO) recommends vaccination against measles, mumps, rubella (MMR), and varicella (V) 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. After licensure of the MMRV vaccine, studies on the safety of the vaccine have suggested an elevated risk for febrile convulsions (FC) in children vaccinated with MMRV as compared to children vaccinated with separately administered MMR and V vaccines. Against this background, the Leibniz Institute for Prevention Research and Epidemiology – BIPS (previously BIPS - Institute for Epidemiology and Prevention Research) conducted a safety study on the risk of FC after a 1st dose of MMRV as compared to MMR and MMR and V given on the same day (MMR+V based on data from the German Pharmacoepidemiological Research Database (GePaRD). This study revealed an elevated risk for FC in the time period of 5 to 12 days after MMRV vaccination as compared to vaccination with MMR only, while as compared with MMR+V no significant effect was found in this risk interval.

Concerning the risk of FC after the 2nd dose of MMRV as compared with a 2nd dose of MMR or MMR+V, data is generally limited. For Germany, where the 2nd dose is recommended for relatively young children as compared to e.g. the US (recommendation for 2nd dose at the age 4 to 6 years), no data at all is available to date.

Objective: The objective of this study is to estimate the risk of FC after a 2nd immunization against measles, mumps and rubella with MMRV (Priorix-Tetra®) in comparison to MMR or MMR+V in the pre-specified risk intervals: 0 to 4 days after immunization, 5 to 12 days after immunization (main risk interval), 13 to 30 days after immunization and the entire risk period of 0 to 30 days after administration of the 2nd dose.

Methods: A retrospective matched cohort study was performed to provide confounder adjusted risk estimates of FC after a 2nd dose of MMRV compared to MMR and MMR+V in the pre-defined risk intervals. Analyses were based on a cohort of all insurants born during the study period from January 1st, 2004 through December 31st, 2008, with available date of birth who received a 2nd vaccination with one of the index vaccines MMRV, MMR+V, or

MMR. 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 31st, 2008, or 31 days after cohort entry, or interruption/end of insurance. Vaccinations were identified using so called EBM-codes, which are used for reimbursement of outpatient treatments.

The primary endpoint 'FC Jacobsen' was defined as all hospitalizations with a diagnosis of FC that had no main discharge diagnosis referring to a neurological condition. The secondary endpoint 'FC narrow' basically consisted of a subgroup of the 'FC Jacobsen' cases. It was defined as a hospitalization where no plausible cause of FC other than the immunization, e.g. an infection or a neurological condition, was coded as main discharge diagnosis.

Cumulative incidences (=risks) of the primary and the secondary endpoint with 95% CIs were calculated for all exposure groups within each risk interval (0-4, 5-12, 13-30 and 0-30 days after cohort entry). Relative risks (RRs) and risk differences (RDs) for the comparison of exposure groups were calculated with 95% CIs.

All children who received a 2nd immunization with the MMRV vaccine were matched one-to-one to children who received a 2nd immunization with MMR or MMR+V between January 01st, 2006 and December 31st, 2008, respectively. Three matched cohorts (MMRV vs. MMR, MMRV vs. MMR+V, and MMRV vs. MMR/MMR+V) were created. Matching was performed by statutory health insurance (SHI), sex, age in months (tolerance range: ± 1 month) and calendar month of cohort entry (tolerance range: ± 1 month).

A multivariable analysis based on the matched cohorts was performed to compare the occurrence of FC within each risk interval between exposure groups, adjusted for FC history, hospitalization for an infectious disease between the 15 days before and 30 days after 2nd dose, administration of other vaccines between the 30 days before and 30 days after 2nd dose, type of vaccine used as 1st dose, time between 1st and 2nd dose. 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 every risk interval.

Results: Cumulative incidences for the primary endpoint 'FC Jacobsen' in the main risk period of 5 to 12 days after immunization were lower in the MMRV group than in the matched MMR (RR=0.36; 95% CI 0.12–1.14) or MMR/MMR+V group (RR=0.40; 95% CI 0.13–1.28). No RRs could be calculated for the matched MMR+V cohort due to missing cases in this cohort within the main risk interval. The same can be said for the endpoint 'FC Narrow'. In the matched MMR and in the matched MMR/MMR+V group RRs were 2.00 (95% CI 0.18–22.06) in both cohorts.

The multivariable analysis yielded no statistically significantly increased risk of FC as defined by 'FC Jacobsen' after the administration of MMRV as compared to MMR or MMR/MMR+V in the main risk interval (MMRV vs. MMR: OR=1.14; 95% CI 0.24 – 5.38; MMRV vs. MMR/MMR+V: OR=1.31; 95% CI 0.28 – 6.25). With regard to 'FC Narrow', ORs of 9.61 (95% CI 1.46 – 63.08) and of 9.98 (95% CI 1.51 – 65.94) were observed in the main risk period in the matched MMR and the matched MMR/MMR+V cohorts. No estimations were possible for the matched MMR+V cohort for any of the outcomes under investigation, since no cases were captured in this cohort during the main risk period. Analyses stratified by the type of vaccine used for the 1st dose showed generally higher estimates for children who had not received MMRV as the 1st dose vaccine.

Discussion: Cumulative incidences of 'FC Jacobsen' within the risk period were extremely low (with a maximum of 0.02%, and even lower for 'FC Narrow'), which was in line with results from a meta-analysis based on clinical data from GSK studies. As shown also in the available literature, no relevant difference in the incidences of FC in the respective vaccine groups and no time pattern for the time to onset of FC after the 2nd dose of any of the index vaccines could be observed.

This study does not suggest an elevated risk of FC as defined by the primary outcome 'FC Jacobsen' after the 2nd dose of MMRV as compared to MMR or MMR+V in the main risk interval 5 to 12 days after vaccination or in any other of the investigated risk periods. However, the power of these analyses was very limited and e.g. only 37% for the comparison against MMR/MMR+V to detect an OR of 2.0 due to the low incidence of FC. For the secondary outcome 'FC Narrow' multivariable analysis yielded a statistically significant risk of FC for children immunized with MMRV as compared to MMR or MMR/MMR+V in the main risk interval, but this risk is uninterpretable due to its even lower power. There was no indication for relevant misclassification of exposure or outcome. The point estimates of the risk of FC ('FC Jacobsen') after MMRV were increased in children who did not receive MMRV as the 1st dose vaccine in comparison to children who had received MMRV as first dose vaccine, but this was not statistically significant and might be a chance finding. Confirmatory investigations should conduct stratified analyses to further evaluate this finding. Generally, the limited power of the analyses does not allow for definite conclusions on the risk of FC after the 2nd dose of MMRV as compared to MMR, MMR+V or the combined group of MMR/MMR+V. Further analyses based on sufficiently large sample sizes are needed.