Leibniz Institute for Prevention Research and Epidemiology - BIPS

Short Report - Version 1.0

Evaluation of the Impact of Excluding Individuals with a History of Febrile Convulsions on the Attributable Risk of Febrile Convulsions of MMRV compared to MMR, MMR+V, or MMR/MMR+V.

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Abbreviations

AR	Attributable risk
BIPS	Leibniz Institute for Prevention Research and Epidemiology - BIPS GmbH
CumI	Cumulative incidence
FC	Febrile convulsion
MMR	Measles-mumps-rubella
MMRV	Measles-mumps-rubella-varicella
MMR+V	Measles-mumps-rubella and varicella (“+” indicates that vaccination against MMR is administered separately from the varicella (V) vaccine)
V	Varicella

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1 Introduction

1.1 Background

In a previous study (in the following referred to as 'MMRV 1st dose'), we examined the risk of febrile convulsions (FC) after 1st dose immunization with the quadrivalent measles-mumps-rubella-varicella (MMRV) vaccine compared to immunization with the trivalent measles-mumps-rubella (MMR) vaccine or the separate immunization with MMR and V vaccines on the same day (MMR+V).

The 'MMRV 1st dose' study was designed as matched cohort study. That is all children in the study who received a 1st immunization with the MMRV vaccine were matched one-to-one to children who received a 1st immunization with MMR (MMR matched cohort), MMR+V (MMR+V matched cohort) and MMR or MMR+V (MMR/MMR+V matched cohort) vaccines, respectively. Matching was performed by statutory health insurance provider, sex, age in months (tolerance range: ± 1 month) and calendar month of cohort entry (tolerance range: ± 1 month).

Two main endpoints were defined in the 'MMRV 1st dose' study. The endpoint 'FC Jacobsen' was defined as closely as possible to the outcome used in the study by Jacobsen et al.[1] That is, all hospitalizations with a main discharge diagnosis of FC, all hospitalizations with a (main) admission diagnosis of FC that had no main discharge diagnosis referring to a neurological condition that might be responsible for the FC, and all hospitalizations with a secondary or ancillary diagnosis of FC with a (main) discharge diagnosis coded as complication following immunization were included. The endpoint 'FC narrow' 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. That is, all hospitalizations with FC as main discharge diagnosis, all hospitalizations with a main admission diagnosis of FC without a main discharge diagnosis coded as infectious disease or neurological condition, and all hospitalizations with a secondary or ancillary diagnosis of FC with a (main) discharge diagnosis coded as complication following immunization were included. FC narrow as the more restrict definition probably underestimated the number of FCs and FC Jacobsen as the more sensitive endpoint yielded more reliable estimates of the attributable risk than FC Narrow.

The attributable risks of MMRV compared to MMR, MMR+V and MMR/MMR+V based on FC Jacobsen, was in this study in the main risk period 5 to 12 days after immunization 34.85, 21.77, and 36.40 per 100,000 children, respectively.

As the risk of FC is strongly associated with either personal or family history of FC[2-6], restricting the use of MMRV to children without a personal or family history of FC might be an interesting option to avoid excess cases of FC.

1.2 Study Objective

The objective of this study was to evaluate the impact of excluding children with a history of FC on the attributable risk of FC of MMRV compared to MMR, MMR+V or the mixed exposure group MMR/MMR+V.

2 Source of Data

This study is based on the results of the 'MMRV 1st dose' study, particularly, the estimated cumulative incidences of FC Jacobsen in the main risk period 5 to 12 days after immunization, stratified by personal history of FC. Please refer to the report on this study for a description of the database and the methods used to estimate the risks, as well as a comprehensive discussion of the results.

3 Methods

3.1 Attributable Risks

The attributable risk of MMRV was defined as the difference of the cumulative incidence in the MMRV group and the cumulative incidence in the comparison group (MMR, MMR+V, or MMR/MMR+V). Attributable risks were only calculated based on FC Jacobsen as this is the more sensitive endpoint and thus yields more reliable estimates of the attributable risk than FC Narrow.

3.2 Personal History of FC

Personal history of FC was one of the potential confounders assessed in the 'MMRV 1st dose' study. Thus, cumulative incidences of FC in the main risk interval 5 to 12 days after vaccination in each of the three matched cohorts could easily be stratified by personal history of FC .

3.3 Family History of FC

Family history of FC was defined as a first degree relative history of FC, that is having at least one parent or sibling with a history of FC.

Data on the conditional probabilities of a previous family history of FC given that a child had or didn't have a FC, that is P(family history of FC | FC) and P(family history of FC | no FC) should be obtained from literature. Despite a comprehensive literature research only one study[3] could be found that presented data on both P(family history of FC | FC) and P(family history of FC | no FC). Several studies[7-10] presented data on P(family history of FC | FC), but not on P(family history of FC | no FC) and could thus not be used. Some studies[11-14] examined the genetics of FC, but most studies[2-6, 15] focused on the risk factors of FC, that is the probability of FC given that the child has a (family) history of FC.

Thus the analyses could only be based on the numbers provided by Berg et al.[3] who conducted a matched case-control study and estimated P(family history of FC | FC) = 17/69 and P(family history of FC | no FC) = 5/99.

3.4 Exclusion Scenarios

- **Scenario 0:** No exclusion of children with a personal or family history of FC

- **Scenario 1:** Exclusion of children with a personal history of FC
    - only from MMRV immunization (scenario 1A)
    - from all immunizations (scenario 1B)

- **Scenario 2:** Exclusion of children with a personal or family history of FC
    - only from MMRV immunization (scenario 2A)
    - from all immunizations (scenario 2B)

4 Results

4.1 Matched MMR Cohort

Table 14c from the 'MMRV 1st dose' study report displays that in the matched MMR cohort, 45 out of 74,631 children who received MMRV vaccine and 19 out of 74,654 children who received MMR had a FC Jacobsen in the main risk period 5 to 12 days after immunization. The slightly different numbers of children at risk resulted from differences in the occurrence of FC in the previous risk window 0 to 4 days after immunization and different dropout rates up to day 5.

Stratification of this table by personal history of FC yielded **Figure 4-1**.

	personal FC history		
	FC	no FC	
MMRV	6	571	577
MMR	3	566	569
	no personal FC history		
	FC	no FC	
MMRV	39	74015	74054
MMR	16	74069	74085

Figure 4-1: *Stratification of table 14c of the 'MMRV 1st dose' study report based on the matched MMR cohort by personal history of FC*

In the baseline **scenario 0,** no child would be excluded from immunization. Thus, the cumulative incidence of FC in the MMRV exposed would be $cumI_{MMRV,0}$ = 45/74,631 = 0.0006 and the respective cumulative incidence in the MMR exposed would be $cumI_{MMR,0}$ = 19/74,654 = 0,0003. The resulting attributable risk would be $AR_{MMR,0}$ = $cumI_{MMRV,0}$ - $cumI_{MMR,0}$ = (45/74,631 - 19/74,654)*100,000 = 34,85 per 100,000 children.

In **scenario 1A,** 577 children with a personal history of FC would be excluded from receiving MMRV, which would reduce the cumulative incidence in the MMRV exposed to $cumI_{MMRV,1A}$ = 39/74,054 = 0.0005. The resulting attributable risk would be $AR_{MMR,1A}$ = (39/74,054 - 19/74,654)*100,000 = 27,21 per 100,000 children.

In **scenario 1B,** additionally 569 children with a personal history of FC would be excluded from receiving MMR. This would reduce the cumulative incidence in the MMRV exposed to

$cumI_{MMR,\ 1B}$ = 16/74,085 = 0,0002. The resulting attributable risk would be $AR_{MMR,1B}$ = (39/74,054 - 16/74,085)*100,000 = 31,07 per 100,000 children.

Evaluation of scenarios 2A and 2B requires further stratification on family history of FC for children without a personal history of FC. Given the probabilities from Berg et al.[3] 17/69 of the 39 children of the MMRV group who had a FC would have had a family history of FC (n=10, see **Figure 4-2**) and 5/99 of the 74,015 children of the MMRV group who did not have a FC would have had a family history of FC (n = 3,738). Accordingly, 16 * 17/69 = 4 children of the MMR group who had a FC would have had a family history of FC and 74,069 * 5/99 = 3,741 children of the MMR group who did not have a FC would have had a family history of FC.

	family history of FC		
	FC	no FC	
MMRV	10	3738	3748
MMR	4	3741	3745
	no personal or familiy history of FC		
	FC	no FC	
MMRV	29	70277	70306
MMR	12	70328	70340

Figure 4-2: *Further stratification of the matched MMR cohort by family history of FC for children without a personal history of FC*

Thus, in **scenario 2A** further 3,748 children with a family history of FC would be excluded from receiving MMRV, which would reduce the cumulative incidence to $cumI_{MMRV,2A}$ = 29/70,306 = 0.0004. The resulting attributable risk would be $AR_{MMR,2A}$ = (29/70,306 - 19/74,654)*100,000 = 16,35 per 100,000 children.

In **scenario 2B** additionally 569 children with a personal history of FC and 3,745 children with a family history of FC would be excluded from receiving MMR. This would yield a cumulative incidence of $cumI_{MMR,2B}$ = 12/70,340 = 0,0002. The resulting attributable risk would be $AR_{MMR,2B}$ = (29/70,306 - 12/70,340) 100,000 = 24,66 per 100,000 children.

4.2 Matched MMR+V Cohort

Table 18c from the 'MMRV 1st dose' study report displays that in the matched MMR+V cohort, 21 out of 32,148 children who received MMRV vaccine and 14 out of 32,145 children who received MMR+V had a FC in the main risk period 5 to 12 days after immunization. Again, the slightly different numbers of children at risk resulted from differences in the occurrence of FC in the previous risk window 0 to 4 days after immunization and different dropout rates up to day 5.

Figure 4-3 displays these numbers stratified by personal history of FC which is the basis for the calculation of the attributable risk in the scenarios 1A and 1B.

	personal FC history		
	FC	no FC	
MMRV	2	219	221
MMR+V	2	184	186
	no personal FC history		
	FC	no FC	
MMRV	19	31908	31927
MMR+V	12	31947	31959

Figure 4-3: *Stratification of table 18c of the 'MMRV 1st dose' study report based on the matched MMR+V cohort by personal history of FC*

In the baseline **scenario 0,** no child would be excluded from immunization. Thus, the cumulative incidence of FC in the MMRV exposed would be $cumI_{MMRV,0}$ = 21/32,148 = 0.0007 and the respective cumulative incidence in the MMR+V exposed would be $cumI_{MMR+V,0}$ = 14/32,145 = 0,0004. The resulting attributable risk would be $AR_{MMR+V,0}$ = (21/32,148 - 14/32,145)*100,000 = 21,77 per 100,000 children.

In **scenario 1A,** 221 children with a personal history of FC would be excluded from receiving MMRV, which would reduce the cumulative incidence in the MMRV exposed to $cumI_{MMRV,1A}$ = 19/31,927 = 0.0006. The resulting attributable risk would be $AR_{MMR+V,1A}$ = (19/31,927 - 14/32,145)*100,000 = 15,96 per 100,000 children.

In **scenario 1B,** additionally 186 children with a personal history of FC would be excluded from receiving MMR+V. This would change the cumulative incidence in the MMR+V exposed to $cumI_{MMR+V,1B}$ = 12/31,959 = 0,0004. The resulting attributable risk would be $AR_{MMR+V,1B}$ = (19/31,927 - 12/31,959)*100,000 = 21,96 per 100,000 children.

Further stratification on family history of FC for children without a personal history of FC based on the probabilities from Berg et al.[3] yields **Figure 4-4**.

	family history of FC		
	FC	no FC	
MMRV	5	1612	1616
MMR+V	3	1613	1616
	no personal or familiy history of FC		
	FC	no FC	
MMRV	14	30296	30311
MMR+V	9	30334	30343

Figure 4-4: *Further stratification of the matched MMR+V cohort by family history of FC for children without a personal history of FC*

In **scenario 2A** further 1,616 children with a family history of FC would be excluded from receiving MMRV, which would result in a cumulative incidence of $cumI_{MMRV,2A}$ = 14/30,311 = 0.0005. The resulting attributable risk would be $AR_{MMR+V,2A}$ = (14/30,311 - 14/32,145)*100,000 = 3,69 per 100,000 children.

In **scenario 2B** additionally 186 children with a personal and 1,616 children with a family history of FC would be excluded from receiving MMR. This would yield a cumulative incidence of $cumI_{MMR+V,2B}$ = 9/30,343 = 0,0004. The resulting attributable risk would be $AR_{MMR+V,2B}$ = (14/30,311 - 9/30,343)*100,000 = 17,44 per 100,000 children.

4.3 Matched MMR/MMR+V Cohort

Table 97c from the 'MMRV 1st dose' study report displays that in the matched MMR/MMR+V cohort, 51 out of 82,436 children who received MMRV vaccine and 21 out of 82,469 children who received MMR or MMR+V had a FC in the main risk period 5 to 12 days after immunization. Again, the slightly different numbers of children at risk resulted from differences in the occurrence of FC in the previous risk window 0 to 4 days after immunization and different dropout rates up to day 5.

Figure 4-5 displays these numbers stratified by personal history of FC which is the basis for the calculation of the attributable risk in the scenarios 1A and 1B.

	own FC history		
	FC	no FC	
MMRV	7	594	601
MMR/MMR+V	4	590	594
	no own FC history		
	FC	no FC	
MMRV	44	81791	81835
MMR/MMR+V	17	81858	81875

Figure 4-5: *Stratification of table 97c of the 'MMRV 1st dose' study report based on the matched MMR/MMR+V cohort by personal history of FC*

In the baseline **scenario 0,** no child would be excluded from immunization. Thus, the cumulative incidence of FC in the MMRV exposed would be $cumI_{MMRV,0}$ = 51/82,436 = 0.0006 and the respective cumulative incidence in the MMR/MMR+V exposed would be $cumI_{MMR/MMR+V,0}$ = 21/82,469 = 0,0003. The resulting attributable risk would be $AR_{MMR/MMR+V,0}$ = (51/82,436 - 21/82,469)*100,000 = 36,40 per 100,000 children.

In **scenario 1A,** 601 children with a personal history of FC would be excluded from receiving MMRV, which would reduce the cumulative incidence in the MMRV exposed to $cumI_{MMRV,1A}$ = 44/81,835 = 0.0005. The resulting attributable risk would be $AR_{MMR/MMR+V,1A}$ = (44/81,835 - 21/82,469)*100,000 = 28,30 per 100,000 children.

In **scenario 1B,** additionally 594 children with a personal history of FC would be excluded from receiving MMR or MMR+V. This would result in a cumulative incidence in the MMR/MMR+V exposed of $cumI_{MMR/MMR+V,1B}$ = 17/81,875 = 0,0002. The resulting attributable risk would be $AR_{MMR/MMR+V,1B}$ = (44/81,835- 17/81,875)*100,000 = 33,00 per 100,000 children.

Further stratification on family history of FC for children without a personal history of FC based on the probabilities from Berg et al.[3] yields **Figure 4-6**.

	family history of FC		
	FC	no FC	
MMRV	11	4131	4142
MMR/MMR+V	4	4134	4138
	no personal or familiy history of FC		
	FC	no FC	
MMRV	33	77660	77693
MMR/MMR+V	13	77724	77737

Figure 4-6: *Further stratification of the matched MMR/MMR+V cohort by family history of FC for children without a personal history of FC*

In **scenario 2A** further 4,142 children with a family history of FC would be excluded from receiving MMRV, which would result in a cumulative incidence of $cumI_{MMRV,2A}$ = 33/77,693 = 0.0004. The resulting attributable risk would be $AR_{MMR/MMR+V,2A}$ = (33/77,693 - 21/82,469)*100,000 = 17,22 per 100,000 children.

In **scenario 2B** additionally 594 children with a personal and 4,138 children with a family history of FC would be excluded from receiving MMR or MMR+V. This would yield a cumulative incidence of $cumI_{MMR/MMR+V,2B}$ = 13/77,737 = 0,0002. The resulting attributable risk would be $AR_{MMR/MMR+V,2B}$ = (33/77,693 - 13/77,737)*100,000 = 26,20 per 100,000 children.

4.4 Summary of Results

Table 4-1 gives an overview of the attributable risks per 100,000 children in the different scenarios and the absolute (Δ) and relative change (Δ%) of the AR for the respective scenario compared to the baseline scenario 0.

Table 4-1: *Overview of the attributable risks in the different scenarios and the absolute (Δ) and relative change (Δ%) of the AR for the respective scenario compared to the baseline scenario 0.*

		MMR cohort	MMR+V cohort	MMR/MMR+V cohort
Scenario 0	AR	34.85	21.77	36.40
Scenario 1A	AR	27.21	15.96	28.30
	Δ	7.63	5.81	8.10
	Δ%	21.90%	26.70%	22.25%
Scenario 1B	AR	31,07	21.96	33.00
	Δ	3.78	-0.19	3.40
	Δ%	10.84%	-0.88	9.34%
Scenario 2A	AR	16.35	3.69	17.22
	Δ	18.49	18.08	19.19
	Δ%	53.07%	83.06%	52.71%
Scenario 2B	AR	24.66	17.44	26.20
	Δ	10.18	4.33	10.20
	Δ%	29.22%	19.91%	28.03%

5 Discussion

This short study evaluated the impact of excluding children with a history of FC on the attributable risk of FC of MMRV compared to MMR, MMR+V or the mixed exposure group MMR/MMR+V. Depending on the scenario attributable risks ranged from 3.69 (matched MMR+V cohort, scenario 2A) to 36.40 (matched MMR/MMR+V cohort, scenario 0, see **Table 4-1**). The absolute change in the attributable risks compared to the baseline scenario 0 ranged between 0.19 (matched MMR+V cohort, scenario 1B) to 19.19 (matched

MMR/MMR+V cohort cohort, scenario 2A) and the relative change ranged between -0.88 (matched MMR+V cohort, scenario 1B) to 83.06% (matched MRR+V cohort, scenario 2A).

The major limitation of the study is that the underlying database did not contain information on family history of FC. The conditional probabilities had to be obtained from literature. Despite a comprehensive literature research, only one study[3] could be found that presented data on both P(family history of FC | FC) and P(family history of FC | no FC). Thus, the planned sensitivity analyses based on varying the conditional probabilities could not be performed. The validity of the results depends on the generalizability of the results from Berg et al. to our setting and the assumption that the conditional probabilities are not influenced by immunizations. Additionally, personal history and family history of FC are both estimates and therefore random numbers. This study did not take the variability of these estimates into account.

However, this study was an exploratory study, given a first impression on the impact of excluding children with a history of FC on the attribuatable risks. Further studies should use Markov-Chain- Monte-Carlo (MCMC) methods to address the variability of the conditional probabilities of personal history and family history of FC. These analyses might use a decision analytic approach, using the different scenarios as decision options. In this context, the conditional probabilities would be interchanged, that is P(FC | family history of FC) and P(FC | no family history of FC). As most studies focus on risk factors of FC, this would enlarge the number of data on which the study is based. This method would also allow for threshold analyses to examine how large a conditional probability would need to be to change the decision.

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