

Meningococcal ACWY vaccine (Nimenrix®) and convulsions

Introduction

Meningococcal disease refers to conditions that are caused by infection with *Neisseria meningitidis* (meningococcus). Among others, these bacteria can lead to sepsis and meningitis which are potentially life-threatening. Since 2015, an increase is seen in the number of Dutch patients that become ill due to infection with meningococcus serotype W. Because of this, the Dutch government decided to adjust the National Immunisation Programme by replacing the meningococcal type C vaccine, that children receive at the age of 14 months, with the meningococcal type ACWY vaccine. This adjustment was carried out in May 2018. Because teenagers in the age group of 13 to 18 years are also considered more at risk for meningococcal infection, the vaccine was also offered to this group through vaccination campaigns in 2018 and [1,2]. In the Netherlands, the meningococcal ACWY vaccine 'Nimenrix®' is used in the National Immunisation Programme and the vaccination campaign [3].

Nimenrix® is a non-adjuvanted quadrivalent meningococcal ACWY tetanus toxoid conjugated polysaccharide vaccine. Because this vaccine does not contain live pathogens, it cannot cause the diseases to which it offers protection. Before Nimenrix® was approved for use, it has been investigated thoroughly in clinical trials. In these trials the most frequently reported adverse events were pyrexia, fatigue, syncope and headache, and swelling, erythema and pain at the injection site [4].

Up to the first of May 2019, Pharmacovigilance Centre Lareb has received 699 reports of adverse events following immunisation (AEFIs) with Nimenrix®. 14 Reports were reported via marketing authorisation holders and the remaining 685 were directly reported to Lareb.

A febrile convulsion looks similar to an epileptic seizure. However, an epileptic seizure does not involve pyrexia in contrary to a febrile convulsion. During the fit, a short-circuit occurs in the electrical function of the brains, followed by loss of consciousness and jerky movements during several minutes. There are several causes for a febrile convulsion namely fast elevating body temperature, viral infection (influenza, rhinovirus, adenovirus, enterovirus etc), and it can indirectly be caused by vaccination due to development of pyrexia after vaccination. Predisposition of febrile convulsions is probably hereditary or due to a chromosomal defect [1].

Reports

Between July 2018 and April 2019, Lareb received 15 reports of febrile convulsion/febrile seizure associated with the administration of Men ACW135Y vaccine.

For 8 reports of febrile convulsion, the latency of the pyrexia and the febrile convulsion was matching with what is expected for a simultaneously administered MMR Vaccine. Since the MMR vaccine is a live attenuated vaccine, adverse events such a pyrexia leading to febrile seizure are expected to have a longer latency (i.e. five to twelve days after vaccination) [4-6].

Table 1: Cases of Meningococcal ACW135Y and febrile convulsion in the Lareb database

Worldwide Case ID, Primary Source, Sex, Age	Suspect, IA drug	Latency after start	Outcome	Duration	All reported LLTs
A NL-LRB-00330002, Consumer or other non health professional, male, 1-2 years	MMRVAXPRO -- ----- NIMENRIX	8 Days 8 Days ----- 9 Days 9 Days	Recovered ----- Unknown	3 Days -----	Pyrexia ----- Febrile seizure
B NL-LRB-00327378, Physician, female, 1-2 years	MMRVAXPRO -- ----- NIMENRIX	4 Hours 4 Hours ----- 1 Days 1 Days	Recovered ----- Recovered	5 Hours ----- 1 Hours	Pyrexia ----- Febrile convulsion
C NL-LRB-00319202, Consumer or other non health	MMRVAXPRO -- ----- NIMENRIX	9 Days 9 Days ----- 15 Days	Recovered ----- Recovered	1 Days ----- 3 Days	Pyrexia ----- Febrile convulsion

professional, male, 1-2 years		15 Days ----- 14 Days 14 Days	----- Recovered -----	----- 3 Days -----	----- Hyperpyrexia -----
D NL-LRB-00318799, Consumer or other non health professional, male, 1-2 years	MMRVAXPRO -- ----- NIMENRIX	4 Days 4 Days ----- 4 Days 4 Days	Recovered ----- Recovered -----	36 Hours ----- -----	Fever ----- Febrile convulsion -----
E NL-LRB-00311714, Consumer or other non health professional, male, 1-2 years	MMRVAXPRO -- ----- NIMENRIX	8 Hours 8 Hours ----- 32 Hours 32 Hours	Recovered ----- Recovered -----	3 Days ----- -----	Pyrexia ----- Febrile convulsion -----
F NL-LRB-00302546, Consumer or other non health professional, male, 1-2 years	MMRVAXPRO -- ----- NIMENRIX	24 Hours 24 Hours ----- 24 Hours 24 Hours	Recovered ----- Recovered -----	2 Hours ----- -----	Pyrexia ----- Febrile convulsion -----
G NL-LRB-00302097, Consumer or other non health professional, male, 1-2 years	MMRVAXPRO -- ----- NIMENRIX	10 Days 10 Days ----- 10 Days 10 Days ----- 10 Days 10 Days	Recovering ----- Recovered ----- Recovering -----	5 Days ----- 2 Minutes ----- 5 Days -----	Pyrexia ----- Febrile convulsion ----- Erythematous rash -----
H NL-LRB-00297732, other health professional male, 1-2 years	MMRVAXPRO -- ----- NIMENRIX	----- 10 Days 10 Days	Unknown----- Recovered -----	4 Minutes ----- -----	Otitis----- Febrile convulsion (pyrexia 40.2 degrees celcius) -----
I NL-LRB-00297457, Consumer or other non health professional, male, 1-2 years	MMRVAXPRO -- ----- NIMENRIX	3 Days 3 Days ----- 3 Days 3 Days ----- 3 Days 3 Days	Recovered ----- Recovered ----- Recovered -----	4 Days ----- 4 Days ----- 4 Days -----	Injection site warmth ----- Pyrexia (multiple days, temperature above 40 degrees celcius) ----- Febrile convulsion -----
J NL-LRB-00296554, Consumer or other non health professional, male, 1-2 years	MMRVAXPRO -- ----- NIMENRIX	21 Hours 21 Hours ----- 21 Hours 21 Hours	Recovered with squelae ----- Recovered with squelae -----	----- ----- -----	Fever ----- Febrile convulsion -----
K NL-LRB-00295971, Other health professional (arts JGZ), male, 1-2 years	MMRVAXPRO -- ----- NIMENRIX	8 Days 8 Days ----- 8 Days 8 Days ----- 8 Days 8 Days	Recovered ----- Recovering ----- Recovered -----	3 Days ----- ----- -----	Fever ----- Hepatic function abnormal ----- Febrile convulsion -----
L NL-LRB-00295896, Consumer or other non health professional, female, 1-2 years	MMRVAXPRO -- ----- NIMENRIX	1 Weeks 1 Weeks ----- 1 Weeks 1 Weeks	Recovered ----- Recovered -----	20 Minutes ----- 20 Minutes -----	Pyrexia ----- Febrile convulsion -----
M NL-LRB-00293975, Consumer or other non health professional, female, 1-2 years	MMRVAXPRO -- ----- NIMENRIX	7 Days 7 Days ----- 8 Days 8 Days	Recovered ----- Recovered -----	----- ----- -----	Pyrexia ----- Febrile convulsion -----
N NL-LRB- 00293330,Consumer or other non health professional, male, 1-2 years	MMRVAXPRO -- ----- NIMENRIX	8 Hours8 Hours	Recovering -----	----- -----	Febrile convulsion -----
O NL-LRB-00291156, Consumer or other non health professional, male, 1-2 years	MMRVAXPRO -- ----- NIMENRIX	7 Days 7 Days ----- 8 Days 8 Days	Recovered ----- Recovered -----	4 Days ----- 5 Minutes -----	Pyrexia ----- Febrile convulsion -----

Additional information on the cases with a latency period more likely related to vaccination with Nimenrix® is given below:

Case B

A girl aged 1-2 years developed pyrexia after administration of meningococcal ACW135Y and MMR vaccine. The day after vaccination, she had an incident with jerky movement of the arms and cyanosis around the mouth. Maximum measured body temperature was 40.2 degrees Celsius. The child was hospitalised for observation during 5 hours. She had never experienced a febrile convulsion before although she had high fever previously.

Case D

A boy aged 1-2 years who experienced fever 4 days after administration of meningococcal ACW135Y and MMR vaccine. The fever was treated with paracetamol. The sister of the boy was also ill. One day later in the afternoon the boy experienced a febrile convulsion and he was taken to the hospital by ambulance. His body temperature was not measured. He spent several hours in hospital. The boy had never experienced a febrile convulsion before.

Case E

A boy aged 1-2 years experienced pyrexia 8 hours after administration of meningococcal ACW135Y and MMR vaccine (maximum body temperature was 39.6 degrees Celsius). 32 hours after vaccination he experienced a febrile convulsion. The boy was given paracetamol suppository half an hour before the convulsion. He had short but powerful jerky movements. The boy was not known with febrile convulsions and did not have any after this episode (as of 6 months after the febrile convulsion).

Case F

A boy aged 1-2 years experienced a febrile convulsion one day after administration of meningococcal ACW135Y and MMR vaccine (latency 24 hours). Maximum body temperature was 39.6 degrees Celsius. The body temperature decreased after approximately 2 hours. He was taken to the hospital by ambulance. Paracetamol was administered in the ambulance and at the hospital. He had never experienced a febrile convulsion before.

Case I

A boy aged 1-2 years who experienced an injection site reaction and pyrexia after administration of meningococcal ACW135Y and MMR vaccine. He developed pyrexia and a convulsion 3 days after vaccination. Maximum body temperature was over 40 degrees Celsius. He experienced pyrexia for several days. He was treated with paracetamol for 4 days.

Case J

A boy aged 1-2 years with pyrexia (body temperature not measured) and a febrile convulsion 21 hours after administration of meningococcal ACW135Y and MMR vaccine. Pyrexia was treated with paracetamol. Physical examination by the general practitioner did not reveal any other possible cause.

Case N

A boy aged 1-2 years who experienced febrile convulsion and pyrexia (40 degrees Celsius, measured directly after convulsion by the ambulance personnel) 8 hours after administration of meningococcal ACW135Y and MMR vaccine. The boy was treated with paracetamol. According to the parent, the physician concluded a relationship between the vaccination and the febrile convulsion. The boy was hospitalised for 1 night. He had never had a febrile convulsion after vaccination before.

Other sources of information*SmPC*

The SmPC of the currently used Meningococcal ACW135Y vaccine in the Dutch routine childhood immunisation programme Nimenrix® does not mention febrile convulsion nor does it mention convulsion in general as an adverse drug reaction [7].

The SmPC of another Meningococcal ACW135Y vaccine that is available in the Netherlands (Menveo®) does mention tonic convulsion and febrile convulsion as an adverse event that was seen during post marketing experience [8].

Literature

Febrile seizures are generalized in nature and are associated with high body temperatures. They affect up to 5% of children, most commonly between the ages of 6 months and 5 years. Most children who experience febrile seizures do not develop seizures without fever after the age of 5 years. The risk of a febrile seizure depends, among others, on the type of administered vaccine, the age of the child, and the sensitivity towards developing a febrile seizure. The sensitivity is often hereditary [9,10]

Immunization can induce inflammation and fever, which could theoretically trigger a febrile seizure. Duffy *et al.* found that vaccination in children aged three to five months was associated with a large relative risk of febrile seizure on the day of and the day after vaccination, but the risk was small in absolute terms [11].

Databases

Table 2. Reports of convulsions associated with Nimenrix®, in the Lareb and WHO [12] database on 19 June 2019.

Database	MedDRA PT	Number of reports	ROR (95% CI)
Lareb	Febrile convulsion	15	1.3 (0,8-2,1)*
WHO (based on J07AH08)	Febrile convulsion	1233	**

* The Reporting Odds Ratio was not calculated based on the complete database, but on the fraction of vaccine reports in the Lareb database (ATC J07).

** Lareb is not able to determine disproportionality for Nimenrix® specifically, this can only be calculated on substance level by Lareb.

Prescription data

According to data from Stichting Farmaceutische Kengetallen (SFK) 75660 Nimenrix vaccines were issued from January 2018 to May 2019 from public Pharmacies, with a peak in September 2018 (20809 vaccines) and 3118 in May. These vaccines are probably given by the general practitioner. This were issued for all age groups, but the large majority was given to children (0-18 years). SFK has also published on meningococcal vaccines issued in earlier years [13].

From 1 May 2018 the Men C vaccination in the National Immunisation Programme was replaced by a Men ACWY vaccination (Nimenrix®. The RIVM published on the vaccination rate for children of the birth cohort 2016; 1.4% were found to have had a Men ACWY vaccination and 91.2% a Men C vaccination. Data for later birth cohorts are not yet published [14].

In the last months of 2018, adolescents born between 1 May and 31 December 2004 were offered a Men ACWY vaccination. The provisional vaccination rate for this group is 87.1%; in 2019 they will receive another reminder call. In 2019, the rest of the birth cohort 2004 and the cohorts 2001, 2002, 2003 and 2005 (catch-up campaign) will be offered a ACWY vaccination. Only then can the final vaccination rate for 2004 birth cohort be calculated [14].

Mechanism

Pyrexia induced by a vaccination can lead to a febrile seizure. This relationship is also depending on other factors, such as age, genetic inheritance, type of vaccine, combination of different types of vaccines and the timing of vaccination [15, 16]. For MMRV (measles–mumps–rubella–varicella) vaccination it is described that the risk of seizure or febrile seizure for children aged 10–24 months is elevated, but not for children aged 4–6 years [15].

Discussion and Conclusion

The Netherlands Pharmacovigilance Centre Lareb received 15 reports of febrile convulsion associated with the administration of meningococcal ACW135Y and MMR vaccine. For 8 reports of febrile convulsion, the latency of the pyrexia and the febrile convulsion was matching with a simultaneously administered MMR Vaccine. Since the MMR vaccine is a live attenuated vaccine, adverse events such a pyrexia leading to febrile seizure are expected to have a longer latency (i.e.

five to twelve days after vaccination). For the other 7 reports, the latency in the described reports varied from eight hours to four days. In 2 reports, the reaction is also likely to be caused by an infection, since the latency was 4 days (case D) and 3 days (case I), In six reports, it concerns a male, in one report a female. The body temperature was not measured in two reports, whereas in five reports, the highest measured body temperature was 39.6 degrees Celsius or higher. In four out of seven cases, the child was hospitalised for observation, for a duration varying of several hours to one day. In all cases the child recovered. Pyrexia is a well-known adverse event after immunisation, and febrile convulsion is mentioned in several other SmPCs of vaccines (including the Menveo®). In conclusion, attention is warranted for the association between febrile convulsions and Nimenrix®.

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This signal has been raised on July 4, 2019. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbq-meb.nl