Allergic reactions after administration of Nimenrix®

Introduction

Nimenrix®, a conjugated meningococcal vaccine containing four meningococcal groups, is indicated for *active immunization against invasive meningococcal disease caused by Neisseria meningitidis-groups A,C, W-135 and Y (MenACWY), for people from six weeks old.* The vaccine induces the production of bactericidal antibodies against capsular polysaccharides of the A, C W-135 and Y groups. Nimenrix® has received marketing authorization in the EU in 2012(1).

The place of Nimenrix® in the Dutch National Immunization programme (NIP) has changed throughout the years. In 2002, a meningococcal C vaccine, NeisVac-C®, was introduced in the NIP for toddlers aged 14 months, which was replaced in 2018 by Nimenrix®. A second vaccination moment with Nimenrix® at 14 years was added to the NIP in 2020. Since August 2022, the vaccine at 14 months was changed from Nimenrix® to MenQuadfi®, also a conjugated MenACWY vaccine. As of right now, MenQuadfi® is administered concomitantly with MMRVaxPro® at 14 months. No concomitant vaccine is given with Nimenrix® at 14 years(2, 3). A third conjugated MenACWY vaccine, Menveo®, has been registered in the Netherlands, but has not been used in the NIP so far(2).

Allergic reactions

An allergic reaction is an exaggerated response from the immune system to a (harmless) substance. This is also known as a hypersensitivity reaction, and its intensity can vary from a mild reaction, such as urticaria, a medium reaction such as angioedema, to a severe multi-organ reaction, such as anaphylaxis, which is rare, but can be life-threatening(4, 5). It is thought that vaccine additives are usually the culprit of allergic reaction after vaccination, such as stabilizers, adjuvants and preservatives, or residual contaminants from the production process such as ovalbumin or antibiotics. Allergic reaction to the vaccine antigens itself are also possible but are rarer(6).

Allergic reactions can occur immediately or delayed(7), and the majority of acute onset allergic reactions are IgE type I reactions. These reactions typically occur within minutes, ranging up to four hours. Delayed reactions occur within hours or days after exposure, even up to two to three weeks, with rash as most common symptom(8). Delayed reactions are often self-limiting and are seldom a contra-indication for future vaccination(5).

Reports

Until August 25th 2023, The Netherlands Pharmacovigilance Center Lareb has received 12 reports categorized as allergic reactions after sole vaccination with Nimenrix®. To identify hypersensitivity reactions, the following MedDRA® terms have been selected:

- Higher Level Terms (HLTs): Oral soft tissue swelling and oedema, Allergic conditions NEC, Anaphylactic and anaphylactoid responses, Urticarias, Angioedemas
- Preferred Terms (PTs): Eye swelling, Dyspnoea and Paraesthesia.

This yielded 134 reports with Nimenrix® as suspect vaccine. Reports with urticaria as only hypersensitivity reaction were filtered out. Upon review of the report summaries, 44 reports contained one or multiple hypersensitivity reactions, out of which 32 reports had both Nimenrix® and MMRVaxPro® as suspects, and 12 reports had Nimenrix® as sole suspect. The latter 12 reports, with reporting date between 2018-2023 are summarized in chronological order in Table 1.

Table 1: Reports of allergic reactions with Nimenrix® as sole suspect from the Lareb database.

Worldwide Case ID, sex, age	Primary source tekst (translated)	All reported LLTs	Latency after start	Outcome	Duration	Treatment	Medical history/tests
NL-LRB-00304247, consumer, female, 10-20 years	swollen tongue --- swollen lips --- swollen cheek --- red ear --- stinging left side neck --- nausea --- At first, her left ear became warm and red. She felt stinging at the left side of her neck and became nauseated. After half an hour she had swollen tongue, cheeks and lips.	Swollen tongue --- Lip swelling --- Cheek swelling --- Redness of external ear --- Neck discomfort --- Nausea --- Allergic reaction	60 Minutes --- 60 Minutes --- 60 Minutes --- - --- - --- - --- -	Recovered --- Recovered --- Recovered --- Recovered --- Recovered --- Recovered --- Recovered	2 Hours --- 2 Hours --- 2 Hours --- --- --- --- --- --- ---	antihistamine	cashew nut allergy, grass allergy and dust mite allergy
NL-LRB-00308552, consumer, male, 10-20 years	according to the GP they are urticaria, but very severe --- dyspnoea	Urticaria --- Dyspnoea	4 Days --- 4 Days	Recovering --- Recovering	---	unspecified medication	
NL-LRB-00324327, consumer, male, 4-7 years	2 days after vaccination swollen eyes --- urticaria	Swollen eyes --- Urticaria	2 Days --- 2 Days	Unknown --- Unknown	---	no	allergy to house dust mite, cats and rabbits

NL-LRB-00325079, consumer, female, 10-20 years	on the same day my daughter had myalgia that spread from the arm to the back and legs --- swollen face the next day --- She suffered heavily from nausea. --- Her eyes very wide open and staring. Her whole body was cramped and her limbs were stiff. --- She did not breathe for a bit and collapsed. She was unconscious with fecal incontinence. --- When she regained consciousness she felt hot and tired. --- Sometimes during the day she was a bit confused. --- Her eyes very wide open and staring. Her whole body was cramped and her limbs were stiff.	Myalgia --- Swelling of face --- Nausea --- Eye abnormality --- Fainting --- Feeling hot --- Confusion --- Muscle cramps	1 Day --- 2 Days --- 2 Days --- 2 Days --- 2 Days --- 2 Days --- 2 Days --- 2 Days	Recovering --- Recovered --- Recovering --- Recovered --- Recovered --- Recovering --- Recovering --- Recovered	 --- 2 Days --- --- --- --- --- --- 	no	

NL-LRB-00328479, consumer, male, 10-20 years	he woke up in the morning with swollen face and swelling around the eyes --- Around 19.00h in the evening he got an extreme rash on the legs, arms and trunk with flat spots that were very itchy. A rash behind his ear also developed. He is feeling OK otherwise, but he is suffering from his swollen feet and the pruritus. --- feet became swollen, his heels in particular. There was a lot of fluid retention. swelling of hands --- and his lips were swollen.	Swelling face --- Urticaria --- Peripheral swelling --- Lip swelling	3 Days --- 3 Days --- 3 Days --- 3 Days	Recovered --- Recovered --- Recovered --- Recovered	5 Days --- 5 Days --- 5 Days --- 5 Days	unspecified treatment for pruritus	
NL-LRB-00507715, consumer, male, 10-20 years	Itchy rash on back --- Upper lip was swollen (like a mosquito bite) --- Light swelling around the eyes. Eyes were a bit closed.	Pruritic rash --- Lip swelling --- Eye swelling	4 Days --- 5 Days --- 5 Days	Recovered --- Recovered --- Recovered	--- 3 Days --- 3 Days	desloratadine	
NL-LRB-00622901, consumer, female, 10-20 years	facial eczema, flare up --- swollen eyelids, left more than right	Eczema aggravated --- Swollen eyelid	1 Days --- 5 Days	Recovered --- Recovered	1 Weeks --- 1 Weeks	no	
NL-LRB-00780177, health professional, female, 10-20 years	Edema of eyelids --- Very sleepy	Eyelid oedema --- Somnolence	15 Hours --- -	Recovering --- Unknown	---	no	

NL-LRB-00850997, health professional, female, 10-20 years	rash all over body like stinging nettle rash --- Fainted --- Nausea --- Angio edema of tongue, face --- swollen face and tongue, rash all over body like stinging nettle rash, nausea --- Vomiting	Urticarial rash --- Syncope --- Nausea --- Angio edema --- Allergic reaction --- Vomiting	1 Days --- 2 Days --- 1 Days --- 1 Days --- 1 Days --- 1 Days	Recovered --- Recovering --- Recovering --- Recovered --- Recovered --- Recovering	1 Days --- --- --- 1 Days --- 1 Days --- --- 1 Days	prednison and antihistamine	no known allergies
NL-LRB-00868598, consumer, female, 10-20 years	red rash in face --- swollen face	Erythema facial --- Swelling face	1 Days --- 1 Days	Recovered --- Recovered	3 Days --- 3 Days	no	
NL-LRB-00871079, consumer, male, 10-20 years	Swollen eyelids --- Pruritis neck and face --- red rash especially on neck and face	Swelling of eyelid --- Pruritus --- Rash erythematous	4 Days --- 4 Days --- 4 Days	Recovered --- Recovered --- Recovered	6 Days --- 6 Days --- 6 Days	Cetirizine	Dust allergy
NL-LRB-00871682, consumer, male, 10-20 years	Throat tingling --- less air --- rash on chest --- allergy	Tingling throat --- Dyspnoea --- Rash --- Allergic reaction	5 Minutes --- 5 Minutes --- 5 Minutes --- 5 Minutes	Recovered --- Recovered --- Recovered --- Recovered	3 Hours --- 3 Hours --- 3 Hours --- 3 Hours	Unspecified injection (against allergic reactions)	blood pressure and saturation: no results reported

None of the reports were serious according to the CIOMS criteria for seriousness(9), and most of the children were 10-20 years old. There were two cases (NL-LRB-00304247 and NL-LRB-00871682) with reactions within an hour, such as difficulty breathing, nausea, swelling of face/lip/eye and/or rash. The reactions were treated with antihistamine, possibly one of them with epinephrine as well. One of the children was allergic to nuts, grass and dust mite. They recovered within a few hours. The time to onset (TTO) and the treatments were typical for acute, IgE mediated allergic reactions.

There were five cases (NL-LRB-00308552, NL-LRB-00328479, NL-LRB-00507715, NL-LRB-00850997 and NL-LRB-00871079) with a delayed TTO and with treatment. These reactions consisted mostly of urticaria with swelling in the face (especially eyes and lips) and sometimes dyspnoea and/or nausea. There was one report with a TTO of one day and the others had a TTO of four to five days. The reactions were treated with antihistamines and anti-inflammatory drugs, and recovery took place between one and six days. One patient had dust mite allergy. The delayed TTOs, in combination with the anti-allergic treatments, are typical for delayed allergic reactions.

There were also five cases with a delayed TTO but without treatment (NL-LRB-00324327, NL-LRB-00325079, NL-LRB-00622901, NL-LRB-00780177, NL-LRB-00868598). These reactions consisted of swelling of eyes/lips/face, and in one of the cases urticaria also occurred. The reactions started between one to five days and resolved within one week (if reported). One patient had dust mite, cat and rabbit allergy. A delayed TTO and no treatment means that these cases are a bit less convincing than the other cases, in terms of causality and allergic nature of the reactions.

MenQuadfi® and Menveo®

The same query was executed for MenQuadfi® and Menveo®. MenQuadfi® yielded eight reports at first, but three of them had urticaria only. Upon further review, four reports were not typical for an allergic reaction, so one report remained, but MMRVaxPro® was given concomitantly. Menveo® yielded one report, but it was only with urticaria, so it was excluded.

Other sources of information

SmPC

Nimenrix® has urticaria, rash and pruritus labeled in the Summary of Product Characterics (SmPC) under section 4.8. In section 4.4 there is a description of hypersensitivity: “Adequate medical treatment and supervision should be available immediately in case a rare anaphylactic reaction occurs after administration of the vaccine”. There is no mention of allergic or anaphylactic reaction in section 4.8(1).

MenQuadfi® has the same messages in its SmPC as above, in the same sections, with similar wording(10).

Menveo® has hypersensitivity labeled in the SmPC of as follows: ‘Frequency unknown: hypersensitivity, including anaphylaxis’. Rash and immune system disorder are also mentioned with frequency ‘often’. Section 4.4 of Menveo® contains the same suggestion as the other two SPCs: to have adequate measures in case of allergy/anaphylaxis(11).

Literature

A PubMed(12) search with Nimenrix/meningococcal ACWY vaccine AND allergy/allergic reaction/ hypersensitivity, retrieved no results. Meningococcal vaccine AND allergy did retrieve a relevant result from the USA, with Menveo® as subject, which has other excipients such as: non-toxic diphtheria cross reacting material 197 carrier protein (CRM197)(13), so they are not directly comparable. The Vaccine Adverse Event Reporting System in the USA registered 2614 adverse events after administration of Menveo® (including concomitant vaccinations) between 2010 and 2015, of which 74% were from adolescents aged 11-18 years. Among the 67 serious cases, the second most common MedDRA System Organ Class (SOC) was Immune system disorders, with ten reports: out of which seven were anaphylaxes and two were non-anaphylactic allergic reactions (and one was drug eruption). There were also two possible anaphylaxes that were non-serious. Out of these nine possible anaphylaxes, only one had Menveo® as single suspect(14).

Other databases

Due to the nature of the query used in the Lareb database, a direct comparison with World Health Organisation’s VigiBase(15) cannot be made. However, to estimate the global occurrence of these types of reactions, a search has been done for Nimenrix® and the MedDRA Lower Level Term (LLT) Allergic reaction, which yielded 38 reports globally. Twelve of these reports had Nimenrix® as only suspect, and out of these reports, three were from the Lareb database. The LLT Anaphylaxis yielded 21 reports globally, with Nimenrix® as only suspect six times. None of these were from the Lareb database. There is no overlap in

reports between the two LLTs.

Prescription data

From 2018-2022, Nimenrix® was administered to 14-month-olds in the NIP. In 2020 another vaccination moment was added for the 14-year-olds, which is still fulfilled with Nimenrix®(3). In 2022, the vaccination rates for MenACWY were 88,3% for the 14-month-olds (Nimenrix® + MenQuadfi®) and 80,3% for the 14-year-olds (Nimenrix®) (16).

Mechanism

As stated earlier, it is believed that an allergy to a vaccine is usually caused by one of its excipients, and rarely caused by the antigens. For the complete ingredient list of Nimenrix®, see the addendum. In this vaccine, the tetanus toxoid carrier protein is of interest, because it's an antigen conjugated to the active substances to induce a stronger immune response. Another ingredient of interest is trometamol, because allergic reactions to it have been described, albeit very rarely(17). And finally, the meningococcal antigens could also be involved, but the chances are slim.

Discussion and conclusion

Lareb has received 12 reports of possible allergic reaction following immunization with Nimenrix® only, up until August 25th 2023. Out of the 12 reports, two possibly had an IgE mediated reaction. A delayed response also seems possible, with urticaria, swelling of the face (lips/eyes) and dyspnoea or nausea. Other causes for the reactions have not been mentioned in the reports, even though three patients already had other allergies. Globally there have been reports with similar reactions as the reports in the Lareb database.

It is difficult to impossible in these cases to determine by the individual pre-existing allergies which vaccine antigens, excipients or residuals caused the allergic reactions. Even though the exact cause of the reactions may not be known, attention for allergic reactions in association with Nimenrix® is warranted.

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This signal has been raised on October 9, 2023. 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.cbg-meb.nl

Addendum

List of Nimenrix® ingredients (1):

After reconstitution, 1 dose (0.5 ml) contains:
Neisseria meningitidis group A polysaccharide, 5 micrograms
Neisseria meningitidis group C polysaccharide, 5 micrograms
Neisseria meningitidis group W-135 polysaccharide, 5 micrograms
Neisseria meningitidis group Y polysaccharide, 5 micrograms
All are conjugated to tetanus toxoid carrier protein, 44 micrograms
Powder: sucrose, trometamol
Solvent: sodium chloride, water for injections