bijwerkingen centrumlareb

Meningococcal ACWY vaccine (Nimenrix®) and lymphadenopathy

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.

Lymphadenopathy is an enlargement or abnormal consistency of a lymph node. A normal lymph node is usually less than 1 cm in diameter. In most patients, lymphadenopathy is benign and self-limiting. Lymphadenopathy can have many potential causes, like infection, auto-immune disorder, malignancy, medication and an iatrogenic cause. The location is often helpful in identifying specific etiologies. Lymphadenopathy is classified as localized when it involves one region (e.g. the neck or axilla). The etiology is typically associated with the lymphatic drainage pattern. Generalized lymphadenopathy is defined as two or more involved regions and is more often associated with systemic diseases [5].

Reports

From 1 July 2017 until 1 May 2019 the Netherlands Pharmacovigilance Centre Lareb received eighteen reports concerning lymphadenopathy associated with the Nimenrix® vaccine. In five reports, also a second vaccine was reported as suspect drug.

Table 1. Reports of lymphadenopathy associated with Nimenrix® vaccine in the Lareb database

Worldwide Case ID	Primary Source Sex, Age	Suspect, Indication for use	Latency after start	Outcome	All reported LLTs	Concomitant medication
A NL-LRB-244923	Physician male, 30-40 years	NIMENRIX INJPDR FLACON + SOLVENS IN WWSP + TOEBEH óf MENVEO Prophylaxis	4 Days ---------- 6 Days	Recovering (6 days after vaccination) ---------- Recovering	Lymphadenopathy axillary ---------- Lymphadenopathy cervical	
B NL-LRB-00283040	Consumer or other non health professional female, 1-2 years	MMRVAXPRO INJPDR FLACON + SOLVENS 0,5ML Routine childhood immunisation ---------- NIMENRIX INJPDR FLACON + SOLVENS IN WWSP + TOEBEH Routine childhood immunisation	- - ---------- 1 Days 1 Days	Unknown ---------- Not Recovered (2 days after start symptoms)	Feeling unwell ---------- Lymphadenopathy	

C NL-LRB-00286522	Consumer or other non health professional female, 1-2 years	MMRVAXPRO INJPDR FLACON + SOLVENS 0,5ML Routine childhood immunisation --- NIMENRIX INJPDR FLACON + SOLVENS IN WWSP + TOEBEH Routine childhood immunisation	4 Days 4 Days --- 6 Days 6 Days --- 6 Days 6 Days --- 6 Days 6 Days --- - - --- days days	Recovered --- Recovered --- Recovered --- Recovered --- Recovered --- Recovered (after one week)	Localised rash --- Localized erythema --- Swelling --- Localised feeling of warmth --- Red blotches --- Lymphadenopathy	
D NL-LRB-00296348	Consumer or other non health professional male, 1-2 years	MMRVAXPRO INJPDR FLACON + SOLVENS 0,5ML Routine childhood immunisation --- NIMENRIX INJPDR FLACON + SOLVENS IN WWSP + TOEBEH Routine childhood immunisation	3 Days 3 Days --- 3 Days 3 Days --- 3 Days 3 Days --- 3 Days 3 Days --- 3 Days 3 Days --- 9 Days 9 Days --- 3 Days 3 Days --- 3 Days 3 Days --- 12 Days 12 Days --- 12 Days 12 Days	Recovered --- Recovered --- Recovered --- Recovered --- Recovered --- Recovered --- Recovered --- Unknown --- Unknown	Pyrexia --- Rash morbilliform --- Respiration abnormal --- Myalgia --- Decreased appetite --- Rash morbilliform --- Heart rate irregular --- Arthralgia --- Lymphadenopathy --- Otitis	
E NL-LRB-00299719	Consumer or other non health professional male, 10-20 years	NIMENRIX INJPDR FLACON + SOLVENS IN WWSP + TOEBEH Prophylaxis	24 Hours	Recovering (12 days after vaccination)	Lymphadenopathy	
F NL-LRB-00302441	Consumer or other non health professional male, 10-20 years	NIMENRIX INJPDR FLACON + SOLVENS IN WWSP + TOEBEH Routine childhood immunisation	1 day --- -	Not Recovered (6 days after start lymphadenopathy) --- Unknown	Lymphadenopathy --- Pain in arm	
G NL-LRB-00304848	Consumer or other non health professional female, 10-20 years	NIMENRIX INJPDR FLACON + SOLVENS IN WWSP + TOEBEH Routine childhood immunisation	4 Days	Not Recovered (reported the day the symptoms started)	Lymphadenopathy	

H NL-LRB-00310097	Consumer or other non health professional female, 1-2 years	MMRVAXPRO INJPDR FLACON + SOLVENS 0,5ML Routine childhood immunisation --- NIMENRIX INJPDR FLACON + SOLVENS IN WWSP + TOEBEH Routine childhood immunisation	4 Days 4 Days --- 5 Days 5 Days --- 6 Days 6 Days --- 2 Days 2 Days	Not Recovered --- Not Recovered --- Not Recovered (1 week after vaccination) --- Not Recovered	Common cold --- Eye inflammation --- Lymphadenopathy --- Breath odour	
I NL-LRB-00317794	Consumer or other non health professional male, 2-4 years	NIMENRIX INJPDR FLACON + SOLVENS IN WWSP Routine childhood immunisation --- BOOSTRIX POLIO INJSUSP WWSP 0,5ML Routine childhood immunisation	1 Days 1 Days --- 1 Days 1 Days --- 1 Days 1 Days	Recovered --- Recovering --- Recovering (3 weeks after start)	Pyrexia (max 39) --- Throat pain --- Lymphadenopathy	
J NL-LRB-00323197	Physician male, 10-20 years	NIMENRIX INJPDR FLACON + SOLVENS IN WWSP Routine childhood immunisation	4 Days	Recovering (9 days after vaccination)	Lymphadenopathy	
K NL-LRB-00323579	Consumer or other non health professional male, 10-20 years	NIMENRIX INJPDR FLACON + SOLVENS IN WWSP Routine childhood immunisation	2 Hours --- 2 Hours	Recovered --- Recovered (after several days)	Headache --- Lymphadenopathy	
L NL-LRB-00324656	Consumer or other non health professional female, 10-20 years	NIMENRIX INJPDR FLACON + SOLVENS IN WWSP Routine childhood immunisation	1 Days --- 1 Days	Not Recovered (2 days after start symptoms) --- Recovered	Lymphadenopathy cervical --- Fever	
M NL-LRB-00323188	Consumer or other non health professional male, 10-20 years	NIMENRIX INJPDR FLACON + SOLVENS IN WWSP Routine childhood immunisation	8 Hours	Not Recovered (1 day after start symptoms)	Lymphadenopathy axillary	
N NL-LRB-00330515	Consumer or other non health professional female, 10-20 years	NIMENRIX INJPDR FLACON + SOLVENS IN WWSP Routine childhood immunisation	6 Days --- 6 Days --- 6 Days	Not Recovered --- Not Recovered --- Not Recovered (6 days after vaccination)	Haematoma --- Headache --- Lymphadenopathy	
O NL-LRB-00330685	Consumer or other non health professional female, 10-20 years	NIMENRIX INJPDR FLACON + SOLVENS IN WWSP Routine childhood immunisation	24 Hours	Recovering (12 days after vaccination)	Lymphadenopathy axillary	

P NL-LRB-00325569	Consumer or other non health professional female, 10-20 years	NIMENRIX INJPDR FLACON + SOLVENS IN WWSP Routine childhood immunisation	1 Days ---------- 1 Days ---------- 1 Days ---------- -	Not Recovered ---------- Not Recovered (3 days after vaccination) ---------- Not Recovered ---------- Not Recovered	Throat pain ---------- Lymphadenopathy ---------- Malaise ---------- Dizziness	
Q NL-LRB-00327272	Consumer or other non health professional male, 10-20 years	NIMENRIX INJPDR FLACON + SOLVENS IN WWSP Routine childhood immunisation	16 Hours ---------- 16 Hours ---------- 16 Hours	Not Recovered ---------- Not Recovered ---------- Not Recovered	Lymphadenopathy axillary ---------- Swelling ---------- Axillary pain	Dexamphetamine
R NL-LRB-00329813	Physician female, 10-20 years	NIMENRIX INJPDR FLACON + SOLVENS IN WWSP Routine childhood immunisation	7 Days ---------- 7 Days ---------- 7 Days	Recovering ---------- Recovering (12 days after vaccination) ---------- Recovering	Pyrexia (max 39.7) ---------- Lymphadenopathy ---------- Headache	

Additional information on reports:

The vaccines were administered in the arm, unless otherwise specified.
A: it was unknown whether Nimenrix® or Menveo® was administered. The lymphadenopathy appeared on the same side as the vaccine was administered.
B: reported as 'swelling around left cheek/ear/jaw'.
C: vaccines administered in both legs. Lymphadenopathy in neck and jaw, approximately one week after vaccination.
D: vaccines administered in both legs. Lymphadenopathy cervical (throat) 12 days after vaccination. The patient also had an otitis at that time.
E: swollen and painful node behind the clavicle. The lymphadenopathy appeared on the same side as the vaccine was administered.
F: painful lymphadenopathy on the clavicle. Confirmed with an ultrasound.
G: lymphadenopathy in the neck.
H: swelling behind the left ear.
I: vaccines administered in arm and leg. Lymphadenopathy cervical (throat). Parents had a feeling that the boy had a slight flu the time of vaccination.
J: lymphadenopathy below the left clavicle, the same side as the vaccine was administered.
K: painful swelling in the left axilla, the same side as the vaccine was administered.
L: painful, cervical lymphadenopathy (throat).
M: painful lymphadenopathy left axilla. The lymphadenopathy appeared on the same side as the vaccine was administered.
N: lymphadenopathy neck and occipital.
O: axillary lymphadenopathy. A few days before the vaccination, the patient had fever.
Q: vaccine administered left side (unknown body part). Painful swelling left axilla.
R: cervical lymphadenopathy

Clinical pattern of lymphadenopathy in the reports

Times to onset of lymphadenopathy varied from less than one day in three reports (2, 8 and 16 hours after vaccination), to approximately one day in seven reports and four or more days in eight reports. In two reports the patient recovered from lymphadenopathy after several days to one week. In six reports, the patient is recovering or has not recovered at the time of reporting, which is more than one week after start of the lymphadenopathy.
The reported location of the lymphadenopathy is diverse (axilla 5x, clavicle 3x, cervical 8x and surrounding the jaw/ear 3x). It is not always clear if the reported location matches with the lymphatic

drainage pattern of the vaccinated body part. In at least 5 reports, the lymphadenopathy appeared on the same body side as the vaccine was administered (cases A, E, J, K and M).
In five reports another vaccine was co-administered: in four reports the combined live attenuated mumps-measles-rubella virus vaccine and in one report the combined diphtheria-acellular pertussis-poliomyelitis-tetanus-vaccine.
In two reports other reported adverse reactions are suspicious for a co-incident (viral) infection (case D and H). In two reports, the reporter mentioned that the patient was ill before or at the time of vaccination (case I and O).

Other sources of information

SmPC

The Summary of Product Characteristics (SmPC) of non-adjuvanted quadrivalent meningococcal ACWY tetanus toxoid conjugated polysaccharide vaccine (Nimenrix®) does not mention lymphadenopathy as an adverse drug reaction [4].

Lymphadenopathy is listed as an adverse event following immunisation in the SmPC of aluminum adjuvanted tetanus toxoid conjugated meningococcal group C vaccine (NeisVac-C®) [6], which was formerly administered in the Dutch National Immunisation Programme.

Literature

In the literature, postvaccinational lymphadenopathy is mainly described following immunisation of live attenuated vaccines. For example, following MMR (Mumps, Measles, Rubella) immunisation and BCG (Bacille Calmette–Guérin) immunisation [7,8]. Live vaccines produce a low-grade infection which can cause lymphadenopathy [9].

Postvaccinational lymphadenopathy following inactivated vaccines is described in a few case reports following pertussis, diphtheria, tetanus toxoids and human papilloma virus immunisation [10,11]. No case reports describing the occurrence of lymphadenopathy following meningococcal vaccination were found. However, recent immunisation and the immunisation status are important factors that should be considered in the evaluation of lymphadenopathy, suggesting a causative relation between immunisation and lymphadenopathy [12,13].

Databases

Table 2. Reports of lymphadenopathy associated with Nimenrix®, in the Lareb and WHO [14] database on 19 June 2019.

Database	MedDRA PT	Number of reports	ROR (95% CI)
Lareb	Lymphadenopathy	22	2.8 (1.8-4.4)*
WHO	Lymphadenopathy	68	**

* 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.

Mechanism

Lymphadenopathy develops as a reaction to inflammation in the lymphatic drainage-area of the involved lymphnodes. When the lymph contains antigens, an immune response starts. Enlargement of the lymph node is particularly caused by proliferation of plasma cells in the medulla. Fast growth of the lymph node can cause pain because of stretch of the lymph node capsule [15].
Lymphadenopathy following immunisation is therefore logically explained by this mechanism. With active immunisation, weakened or dead microorganisms, or proteins or toxins of the microorganisms are administered to the body. These antigens stimulate an immune response [16]. A vigorous immune response can cause lymphadenopathy following the lymphatic drainage pattern of the vaccination site.

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 [17].

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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 [18].

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 [18].

Discussion and conclusion

From 1 July 2017 until 1 May 2019 the Netherlands Pharmacovigilance Centre Lareb received eighteen reports concerning lymphadenopathy associated with the Nimenrix® vaccine. In five reports also another vaccine was co-administered, the combined live attenuated mumps-measles-rubella virus vaccine in four reports and the combined diphtheria-acellular pertussis-poliomyelitis-tetanus-vaccine in one report. Three reports were from healthcare professionals, the other reports from consumers and not medically confirmed. The location of the lymphadenopathy varied from axilla to clavicle, cervical and surrounding the jaw/ear. In five reports, the reported location matches with the lymphatic drainage pattern of the vaccinated body part. In four casus the reported symptoms and additional information is suggestive for a co-incident infection as a cause for the lymphadenopathy.
In the Lareb database the association Nimenrix® and lymphadenopathy is disproportionally present, with a reporting odds ratio calculated on vaccine reports only.

Although literature is very scarce about the occurrence of lymphadenopathy after immunisation of inactivated vaccines, it is likely that active immunisation can cause lymphadenopathy. Mechanistically, lymphadenopathy can be explained by activation of the immune system, which is caused by the administration of antigens from the vaccine, especially in the lymphatic drainage area of the injected body part. Also, lymphadenopathy is already mentioned as an adverse event in the SmPC of meningococcal group C vaccine (NeisVac-C®). Despite several reports where another cause for the lymphadenopathy is more plausible, the Lareb reports in this signal call for attention for an association between Nimenrix® and lymphadenopathy.

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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.cbg-meb.nl