1.1. Seasonal Influenza Vaccines and Extensive Limb Swelling (ELS)

Introduction

Seasonal influenza vaccination is indicated for individuals over sixty years of age and for individuals with an otherwise increased risk of morbidity due to medical conditions like diabetes mellitus, asthma, COPD, cardiac failure, hepatic insufficiency and impaired immune status [1]. In total, about 3.7 million persons are vaccinated annually in the Netherlands.

Two inactivated non-adjuvanted seasonal influenza vaccines are used in the Netherlands Seasonal Influenza Vaccination Programme, Influvac and Vaxigrip. Due to antigenic drift and shift, the contents of seasonal influenza vaccines differs per year. In 2011 and 2010, these vaccines contained A/California/7/2009 (H1N1), A/Perth/16/2009 (H3N2) and B/Brisbane/60/2008 influenza virus strains (prod info) [2;3]. Vaxigrip is a split virion vaccine, whereas Influvac is a surface antigen vaccine. Furthermore, differences may exist between the strains used in both vaccines and additives used for stabilisation or preservation of the vaccine. Some characteristics of both seasonal influenza vaccines are shown in table 1, contents of seasonal influenza vaccines.

Table 1. Contents of seasonal influenza vaccines used in the Dutch seasonal influenza prevention programme for 2010-11 and 2011-12 seasons [2;3].

Vaccine	**Vaxigrip**	**Influvac**
Strains	A/California 7/2009 NYMC X-179A	A/California 7/2009 NYMC X-181
	A/Perth/16/2009 NYMC X-187 B/Brisbane/60 2008	A/Perth/16/2009 NYMC X-187 B/Brisbane/60 2008
Additional contents, including substances used in the production process	NaCl KCl Na2PO42*H2O KH2PO4	NaCl KCl KH2 PO4, Na2PO42*H2O CaCl2*H20 MgCl6*H20 polysorbate 80
	Neomycin Formaldehyde octoxynol-9	Gentamicin formaldehyde cetyltrimethyl ammoniumbromide

Extensive inflammatory reactions at the limb of administration are a known adverse reaction of several vaccines, most notably in 4-year-old children after receiving DPTaP vaccine [4-6]. Extensive limb swelling (ELS) is an adverse reaction specific to vaccination and may concern an extended injection site inflammation. Several definitions for ELS exist In this report, the Vaccine Adverse Event Reporting System (VAERS) criteria as described in Woo are used [7]. In this definition, ELS is defined as a swelling of the vaccination limb extending from the joint proximal to the joint distal to the injection site or resulting in circumference entirely around the limb. Rarely, an entire limb may be involved. Symptoms often present 24-48 hours after vaccination and may persist for several days up to limited weeks. A majority of ELS is not painful, not leading to significant impairment of the use of the affected limb. No indications of bacterial infection or allergic hypersensitivity exist. It is unclear whether ELS can be considered as an extended variant of a local injection site inflammation or that this condition can be considered as a separate entity. ELS is not mentioned in the SmPCs for both Vaxigrip and Influvac [2;3].

The current observation describes the cases of extensive limb swelling that Lareb received associated with vaccination with seasonal influenza vaccines.

Reports

The Netherlands Pharmacovigilance Centre database was screened for reports suspect for ELS. In case of lacking information, the reporter and vaccinee or the vaccinee's parents were asked for additional information on the reaction, vaccine history and contributing medical history. Due to this approach, more cases of ELS were identified than initially coded. Information concerning the type of vaccine and batch were retrieved from 'Stichting Nationaal Programma Grieppreventie' (SNPG, *National Influenza Prevention Program Foundation*) data concerning delivery to GP practices. Reports from prior seasons were screened retrospectively for terms suspect for ELS since ELS was not coded specifically.

Since October 1st 2011, Lareb received 10 reports of ELS associated with administration of seasonal influenza vaccines. Nine reports concerned 2011/2012 seasonal influenza vaccines. One report concerned a vaccine administered in the 2009/2010 influenza season. Details of these reports are shown in table 2 . Reports of ELS associated with the use of seasonal influenza vaccines.

Table 2. Reports of ELS associated with the use of seasonal influenza vaccines.

Patient, Report Number, Sex, Age, Source	**Vaccine, batch Indication for use**	**Accompanying symptoms Concomitant Medication, vaccine history**	**Suspected adverse drug reaction, extent**	**Time to onset, outcome**
A 129748 M, 2 – 4 years specialist doctor	Vaxigrip 2011/ 2012 unknown batch or Influvac 2011/2012 X18 Severe allergy	first year of seasonal influenza vaccination, uncomplicated administration of H1N1 2009 pandemic influenza vaccine (Focetria) or regular childhood vaccines.	extensive swelling of vaccinated limb upper arm extending in neck exacerbated eczema	2 days recovered after an unspecified number of days
B 129170 F, 31 – 40 years consumer	Vaxigrip 2011/2012 E3474 allergic asthma, unexplained fever syndrome being examined in a tertiary medical centre. No fever while being vaccinated	seasonal influenza vaccines since 2000, associated with injection site reactions. 2009 H1N1 pandemic influenza: Focetria	extensive swelling of vaccinated limb entire arm, including fingers.	6 hours recovered, eight days persisting. day 10 inguinal lymphadenitis with secondary to bacterial infection.

C 129223 M, 5 – 7 years parents	Influvac 2011/2012 X18 allergic rhinitis, pneumonia in medical history	seasonal influenza vaccination since 2009/2010. 2009 H1N1 pandemic influenza: Focetria. 2010/2011 a seven cm diameter injection site inflammation , regular childhood vaccination: no abnormalities	extensive swelling of vaccinated limb entire arm	1 day recovered after ten days persistence
D 129415 F, 2 – 4 years parents	Vaxigrip 2011/2012 , H7109-5 or Influvac 2011/2012, X18 asthma	seasonal influenza vaccination since 2010, Pandemrix, no abnormalities associated regular childhood vaccination: discoloured leg syndrome associated with DPTaPHib/pneumococcal vaccination (2nd administration)	fever, extensive swelling of vaccinated limb, upper arm, scapula region	6 hours, urticaria at second day swelling recovered after three days duration, however remaining erythema and pain at injection arm.
E 129495 F, 2 – 4 years specialist doctor	Influvac 2011/2012 X18 bronchial hyperreactivity	No information on seasonal influenza vaccination history unspecified pandemic influenza vaccine and regular childhood vaccination without complications	extensive swelling of vaccinated limb, extending distally to elbow generalised urticaria at second day influenza like illness, intercurrent respiratory tract infection, spiking fever up to 40C	25 hours recovered after unknown duration
F 129897 M, 2 – 4 years general practitioner	Influvac 2011/2012 X18 atopy, bronchial hyperreactivity	Seasonal influenza vaccine since 2010 first year uncomplicated, pandemic influenza (Pandemrix) vaccine and regular childhood vaccination without complications	extensive swelling of vaccinated limb shoulder to elbow joint (circumference)	15 hours recovered after days duration

G 130158 F, 2 – 4 years parents	Influvac 2011/2012 X18 pyrexia of unknown origin later diagnosed as chronic recurrent urinary tract infection	first year, second administration, Pandemrix not associated with abnormalities regular childhood vaccination: no abnormalities	extensive swelling of vaccinated limb upper arm	24 hours recovered after five days duration
H 130641 M, 2 – 4 years specialist doctor	Vaxigrip 2011/2012 H7109-5 bronchial hyperreactivity	seasonal influenza vaccination since 2009, no complications regular childhood vaccination uncomplicated) formeterole/ beclamethasone aerosol 100/6mcg/dosis	extensive swelling of vaccinated limb, sore throat upper arm extending over shoulder	36 hours Recovered after days duration
I 130262 F, 51 – 60 years consumer	Vaxigrip 2011/2012 H8235-1 late onset type I diabetes mellitus (LADA), asthma	insulin glargine seasonal influenza vaccination since 2000, injection site inflammation since 2005 both seasonal and 2009 H1N1 pandemic influenza vaccination	extensive swelling of vaccinated limb upper arm extending over elbow	3 hours not fully recovered while contacted 25 days after administration
J 128575 F, 51 – 60 years general practitioner	Influvac 2009/2010 profession-related indication	five years seasonal influenza vaccination, 2008/2009: 5cm injection site reaction, 2007/2008: prominent injection site pain 2009 H1N1 influenza vaccine not administered	extensive swelling of vaccinated limb entire arm, diffuse, pruritic, erythematous swelling	5 minutes Recovered after one week duration

Seven of the 2011/2012 seasonal influenza vaccine reports concern children, six of whom were four years or younger at administration. All children had a medical history consisting of an immune-mediated disorder, asthma, or symptoms of severe allergies as well as fever syndromes or infectious comorbidity. In two children the ELS extended over the entire vaccination-arm, in two additional reports, ELS extended significantly over the shoulder joint (neck and scapula-region). In two reports no information on the extent could be retrieved.
The two reports concerning adults, consisted of ELS affecting the entire vaccination arm in a female aged 31-40 years who was vaccinated because of asthma and a female aged 51-60 years with late onset type I diabetes and asthma. In the 2011/2012 seasonal vaccine reports, latencies varied from 6 hours to two days. One patient (130262) experienced ELS associated with 2010/2011 seasonal influenza vaccination. In general the reports correspond to ELS associated with DPTaP vaccines.

Other sources of information

SmPC

ELS is not addressed in the Vaxigrip or Influvac SmPCs in addition to injection site reactions [2-3].

Literature

No publications of seasonal influenza vaccination associated ELS are presented through Medline. However in an analysis concerning spontaneous reports of ELS in the VAERS database by Woo et al. [7], 31 cases of seasonal influenza vaccine associated ELS are mentioned.

Databases

Eudravigilance

The Eudravigilance database contains 6 reports of ELS associated with seasonal influenza, providing limited additional information.

WHO-UMC

As of January 17th the WHO-UMC database contains 129 reports of influenza vaccine associated ELS. 109 reports were of Australian origin, 79 concern 2010 or 2011 cases. A specification per country of origin is shown in table 3. All reports concern inactivated, non-adjuvanted influenza vaccines. In one report a intradermally administered vaccine (Intanza) was involved. A specification per vaccine is shown in table 4.

Table 3. WHO reports of ELS per country per Influenza season

Vaccine	Influenza Season	Number
Australia	2004	1
	2005	-
	2006	1
	2007	6
	2008	15
	2009	5
	2010	39
	2011	40
	Unknown	2
United States	2009/2010	7
	2010/2011	3
Netherlands	2009/2010	
	2011/2012	6
Croatia	2008/2009	1
	2009/2010	1
Germany	2006/2007	1
Italy	2009/2010	1

Table 4. specification of vaccines associated with ELS in WHO-UMC reports

Vaccine	Number
Fluvax	56
Vaxigrip	17
Influvac	7
Fluarix	4
Fluzone	3
Fluimin	1
Intanza	1
Unknown	21

Mechanism

ELS is considered a non-infectious, non-allergic reaction. An exact pathophysiological mechanism has not been elucidated. However, an immune complex mediated hypersensitivity has been postulated but remains controversial, since no association with antibody levels has been found [6].

Discussion and conclusion

Since October 2011, Lareb received ten reports of ELS associated with seasonal influenza vaccination, with nine reports concerning 2011/2012 vaccines. One patient experienced ELS associated with 2010/2011 vaccination previously. One additional report concerns 2009/2010 vaccination. All reports met VAERS criteria for ELS. The reports concern ELS associated with both vaccines used in the Netherlands seasonal influenza vaccination. ELS is a well-known adverse effect of vaccination in general [7], related to a wide array of vaccines. Information on influenza vaccine-associated ELS however is limited to 31 cases in Woo's analysis of 497 spontaneous reports of vaccine-associated ELS, received from January 1990 to July 2003 to the VAERS database [7]. A vast majority of cases reported to the UMC-WHO database concern Australian cases (109/129). 79 of these cases concern cases in which 2010 or 2011 seasonal influenza vaccines were involved. These cases can be related to increased attention towards seasonal influenza vaccines after a 2010 seasonal influenza safety issue concerning febrile seizures in children vaccinated with seasonal influenza vaccines [8]. It may well be conceivable that additional cases of ELS are coded as injection site inflammation and are not retractable as ELS in both international databases.

In ELS associated with other vaccines, most notably DPTaP, the incidence of ELS increases with the number of administered doses [6]. The 2011/2012 vaccine is identical to the 2010/2011 vaccine which may have been a factor in the increased incidence of ELS, furthermore one of the strains used in both vaccines is identical to the strain administered in the 2009 H1N1pandemic influenza vaccines to which all affected children were eligible. It is common that individual strains are used multiple seasons, however in the last ten seasons, only in the 2003/2004 influenza vaccine all strains were identical to the strains used during the previous influenza season.

It must be noted that a majority (7/10) of patients involved is of child age and that six are aged four years or younger. All but one patient had an immune-mediated indication (as asthma, severe allergic hypersensitivity, or a fever syndrome) for seasonal influenza vaccination, which may lead to the assumption that a subset of the population is prone to seasonal influenza vaccine related ELS. This notion may be supported by the fact that in at least five reports injection site reaction related to previous influenza vaccine administration were noticed. Two reactions

concerned first-year administration, all other reports concerned second or later administration, which is in line with the dose- number related character of ELS. In four vaccinees an infectious disease was active the immediate days prior or after vaccine administration, which may have led to stimulation of the immune system and may have acted as a cofactor for the manifestation of ELS. It is unclear whether ELS is particularly linked with this 2011/2012 influenza vaccination.
The Netherlands Pharmacovigilance Centre Lareb database lacks reports of ELS received before 2011. This may be attributed to underreporting but may in part reflect earlier practice at Lareb. Screening for potential reports of ELS revealed eight cases in which symptoms highly specific for ELS were reported and an additional nine cases in which a firm suspicion of ELS exists (reports concern the period from Jan 1st 1996-to Jan 1st 2011 with exclusion of both 2009 H1N1 pandemic influenza vaccines). Notably, four of the specific cases concern the 2010/2011 seasonal influenza vaccines, identical to the vaccines used in the 2011/2012 season.

Ten reports of seasonal influenza vaccine related ELS reports warrants addition of ELS in the SmPCs for seasonal influenza vaccines.

- Consider to mention Extensive Limb Swelling in the SmPC of both seasonal influenza vaccines (Influvac and Vaxigrip)

References

1. Dutch National Program influenza prevention (access date 9-3-2012) http://www.snpg.nl/index.htm
2. Dutch SmPC Influvac® 2011/2012 . (version date: 19-7-2011, access date: 9-3-2012) http://db.cbg-meb.nl/IB-teksten/h22289.pdf
3. Dutch SmPC Vaxigrip® 2011/2012. (version date: 10-6-2011, access date: 9-3-2012) http://db.cbg-meb.nl/IB-teksten/h22306.pdf
4. Dutch SmPC Infanrix IPV®. (version date: 10-6-2011, access date: 9-3-2012) http://db.cbg-meb.nl/IB-teksten/h34568.pdf
5. Vermeer-de Bondt PE, Moorer-Lanser N, PHaff TAJ, Oostvogels B, Wesselo C, van der Maas NAT Adverse events in the Netherlands vaccination programme. Reports 2010 and Review 1994-2010 RIVM report 205051004/2011, (access date 9-3-2012) http://www.rivm.nl/bibliotheek/rapporten/205051004.html
6. Casey JR, Pichichero ME. Acellular pertussis vaccine safety and efficacy in children, adolescents and adults. Drugs. 2005;65:1367-89.
7. Woo EJ, Burwen DR, Gatumu SN, Ball R; Extensive limb swelling after immunization: reports to the Vaccine Adverse Event Reporting System. Clin Infect Dis. 2003 Aug 1;37(3):351-8.
8. Gold MS, Effler P, Kelly H, Richmond PC, Buttery JP; Febrile convulsions after 2010 seasonal trivalent influenza vaccine: implications for vaccine safety surveillance in Australia. Med J Aust 2010; 193 (9): 492-493

This signal has been raised on April 2012. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).