1.1. Pandemic influenza vaccine (Pandemrix®) and injection site discolouration

Introduction

In November 2009, a mass vaccination against Influenza A (H1N1) was performed in the Netherlands. Pandemrix® was used in children in the age of 6 months to 5 years, and the close relatives of children aged less than 6 months. Vaccination took place twice (with an interval of three weeks).
Pandemrix® contains a split, inactivated, influenza virus, containing antigen equivalent to A/California/7/2009 (H1N1)v-like strain (X-179A). AS03 is used as an adjuvant. Most common dermal adverse events consisted of induration, swelling, pain and redness at the injection site [1]. The current report however describes a more specific discolouration, consisting of a persistent grey to black small spotty or point-like lesion limited to the injection site.

Reports

On 20 November 2010, the Netherlands Pharmacovigilance Centre Lareb had received five reports of injection site discolouration after administration of Pandemrix®. Reporters included parents and physicians involved in the vaccinations.
All reporters emphasize the local character of the lesion as well as persistence of discolouration. Report A concerns a cluster of children, aged 0 to five years whereas in Case D, the reporting parent mentions occurrence in both his two children as well as occurrence in children in his social network. In reports C and D, the discolouration presented after administration of both first and second vaccine. Reported latencies varied from minutes to days. Two reports B and D were reported six and nine months after vaccination. In both reports, the discolouration did not resolve. Follow up was suggestive for a lasting effect.

Table 1. Reports of injection site discolouration associated with the administration of pandemic influenza vaccine (Pandemrix®)

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 105364 M, 2 – 4 years	pandemic influenza vaccine (Pandemrix) batch: A81CA142A prophylaxis	none	injection site discolouration	within minutes not applicable not recovered
B 108156 M, 0 – 1 years	pandemic influenza vaccine (Pandemrix) batch: A81CA069B prophylaxis	none	injection site discolouration	within minutes not applicable not recovered
C 109018 M, 2 – 4 years	pandemic influenza vaccine (Pandemrix) batch: A81CA069B prophylaxis	none	injection site discolouration	5 days not applicable recovered with sequelae
D 102247 F, 2 – 4 years Multiple persons	pandemic influenza vaccine (Pandemrix) batch unspecified prophylaxis	none	injection site discolouration	within days not applicable not recovered multiple persons involved

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
E, 94557 multiple persons	pandemic influenza vaccine (Pandemrix) Batch unspecified prophylaxis	none	injection site discolouration	within minutes not applicable unknown

Other sources of information

Literature

No additional published cases were accessible through a Medline search using Mesh terms influenza vaccine and skin pigmentation.

Databases

On November 29, the Eudravigilance database did not contain any reports of localised skin discolouration associated with administration of Pandemrix® or other A/California/7/2009 (H1N1) v-like virus vaccines. Given then non-serious nature of the reported events, these reports are unlikely to be forwarded to the Eudravigilance database.

On December 24, the UMC-WHO database contained 28 reports of pandemic influenza vaccine associated skin discolouration. These reports originated from the United States, Norway and Belgium. In contrast to the reports Lareb received, in these cases the discolouration had resolved.

Discussion

Lareb received five reports, involving one or multiple patients (D, E, numbers unspecified), of localised greyish or dark skin discolouration, confined to the injection site and in some cases to localisations of first and second administration (A,C). With all reservations, it is curious that Pandemrix® is linked with this localised skin discolouration, in contrary to other vaccines.
The reported latencies (presentation minutes after administration) do not fit into hyper pigmentation secondary to an injection site reaction and could only be explained because of deposition of elements present in the administered vaccine. It is however hard to conceive how macroscopic elements could have contaminated vaccines during the production process.
Reporters were asked for further clarification; however response was limited and insufficient to discriminate between a deposit and hyper pigmentation after initial skin inflammatory reaction and later pigmentation. The reported cases do not support a batch related issue because of different batches used and the limited number of cases.
Lareb received one report of skin discolouration associated with vaccination of the other H1N1 vaccine used in the Netherlands, Focetria® which was reported through a hospital-linked organisation specialised travellers vaccination. Although reported as a reaction concerning a female aged 41 – 50 years, multiple vaccinated persons were reported to have been involved. The reported event concerned an injection site discolouration (metallish) shortly after vaccination. The outcome is unknown.

Conclusion:

Five reports of a skin discolouration confined to administration site, not explained by a plausible mechanisms, however, latencies are in five cases consistent with an acute event. Given the nature of these events, a possible signal on the level of the Eudravigilance database is not likely. Therefore screening for similar cases in PSURs could be considered.

- Possible signal of unexplained skin discolouration at injection site after Pandemrix administration

References
1. European Product information Pandemrix®. (version date: 2010, access date: 25-11-2010) http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000710/WC500023749.pdf.

This signal has been raised on April 2011. 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).