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In this issue

Childhood vaccinations and reported suspected adverse reactions in Q2 of 2016

Every three months, the reports of suspected adverse reactions to vaccines in the Danish childhood immunisation programme are reviewed and assessed by the Danish Medicines Agency (DKMA) and a vaccination panel composed of a number of experts.

Here are the results of the review for Q2 2016. The review covers primary vaccines in the childhood immunisation programme as well as booster vaccines (re-vaccination).

ADR reports related to vaccines in the childhood immunisation programme

Vaccine	Serious	Non-serious	Total
DT booster	0	6	6
DTaP Booster	1	0	1
DTaP-IPV Booster	0	9	9
DTaP-IPV Booster / DTaP-IPV/Act-Hib	1	1	2
DTaP-IPV Booster / DTaP-IPV/Act-Hib / Prevenar 13	0	1	1
DTaP-IPV Booster / MMR vaxpro	0	1	1
DTaP-IPV /Act-Hib	6	39	45
DTaP-IPV /Act-Hib / Infanrix Hexa	0	2	2
DTaP-IPV /Act-Hib / Infanrix Hexa / Prevenar 13	0	3	3
DTaP-IPV /Act-Hib / MMR vaxpro	0	2	2
DTaP-IPV /Act-Hib / MMR Vaxpro / Prevenar 13	0	3	3
DTaP-IPV /Act-Hib / Measles and mumps and rubella / Prevenar 13	0	1	1
DTaP-IPV /Act-Hib / Prevenar	1	4	5
DTaP-IPV /Act-Hib / Prevenar 13	2	48	50
DTaP-IPV /Act-Hib / Prevenar 13 / Priorix	0	1	1
Hexaxim	0	2	2

Hexyon	0	1	1
Hexyon / Prevenar 13	0	2	2
Infanrix Hexa	0	2	2
Infanrix Hexa / Prevenar 13	1	9	10
MMR Vaxpro	1	18	19
M-M-RVaxpro /Prevenar 13	0	1	1
Pneumovax	1	6	7
Prevenar 13	0	3	3
Priorix	2	3	5
Gardasil	77	41	118
Cervarix	1	3	4
Main total	**94**	**212**	**306**

Summary of the Q2 ADR reports

In this quarter, we note the following:

- Compared to the last quarter, we received a corresponding number of reports related to vaccines in the childhood immunisation programme (excluding the HPV vaccine). The non-serious ADR reports primarily described vaccination granulomas.
- Among the 16 serious ADR reports (excluding reports about HPV vaccines), two described surgical removal of granulomas under general anaesthetic. Normally, this is not recommended since granulomas are expected to resolve spontaneously.
- In addition, well-known adverse reactions or symptoms have been reported. It is not considered likely that these are linked to the vaccines. Among them were two cases of idiopathic thrombocytopenia, one of which described onset less than 24 hours after vaccination with MMR Vaxpro. It is considered most likely to have occurred randomly (1). In the other case, the child was diagnosed less than a month after vaccination with Priorix – in this case, it is considered possible that there is an association with the vaccine. Furthermore, three cases of pertussis were reported in children aged 1, 4 and 8 years, although they had received all DTaP-IPV/Act-Hib vaccine doses.
- In the second quarter, we received a total of five non-serious ADR reports about the new vaccines Hexaxim and Hexyon. The five reports described various forms of rash, which all resolved spontaneously.
- Compared to the last quarter, we received more reports of suspected adverse reactions related to the HPV vaccines. In this quarter, we received 78 ADR reports classified as serious. Similar to our previous statements, most of these ADR reports describe suspected adverse reactions in girls who had been given the HPV vaccine several years ago.
- The following specific diagnoses suspected to be caused by the HPV vaccine were reported: two cases of epilepsy, eight cases of POTS, two cases of narcolepsy, two cases of optic neuritis, one case of asthma as well as one case each of manic depressive psychosis, lupus, Sjögren's syndrome and rheumatoid arthritis. No studies point to increased incidence rates for any of these diseases after HPV vaccination (6,7).
- We continue to receive many ADR reports about the HPV vaccines that lack important information, e.g. about current examinations and/or the results thereof. It is not possible to assess causality for any such reports (reports are unclassifiable).

- In this quarter, an association with the HPV vaccine was considered less likely for nearly half of the serious ADR reports describing suspected adverse reactions to the HPV vaccine. Another known disease or other factors are more likely to explain the symptoms.
- We received five ADR reports with insufficient documentation to perform a causality assessment. These ADR reports carry descriptions of symptoms/ examinations, and there is a temporal relationship with the vaccine, but the adverse reactions are not known, and there is no evidence in the literature confirming or disproving an association between the suspected adverse reactions and the HPV vaccine. In this quarter, no ADR reports involving the HPV vaccine received the causality assessment "possible".

Conclusion

In the second quarter of 2016, the DKMA received a total of 306 reports of suspected adverse reactions to vaccines in the childhood immunisation programme

Like previous quarters, we received many ADR reports about vaccination granulomas in connection with DTaP-IPV/Act-Hib possibly co-administered with a Prevenar (13) vaccine – most of the symptoms occurred earlier, but were not reported until now. This likely reflects the public's increased awareness of vaccination granulomas and not a real increase in numbers. The development of granulomas is a well-known adverse reaction, and for most of them, symptom onset occurred years back. In this quarter, surgical removal of granulomas was once again reported in two children although the literature states that granulomas should dissolve spontaneously.

The number of HPV vaccine ADR reports has once again risen, but the reports still describe girls/women who were vaccinated several years back, and most of them still describe symptoms of fatigue, headache and dizziness. We continue to receive quite many ADR reports with inadequate details about examination and results.

We maintain our focus on HPV vaccine safety, looking also at reported symptoms not appearing in the summary of product characteristics.

None of the new ADR reports shift the benefit-risk balance of the childhood vaccines.

Focus in Q2

In recent years, the DKMA has received increasing numbers of ADR reports describing sleep disorders as suspected adverse reactions to the HPV vaccines. This is therefore the focus of this quarter.

Sleep disorders and frequency

Sleep disorders are common in the Danish population. Prevalence of chronic insomnia in the adult population is about 6-10% (2). Fatigue is a symptom described in about 10% of all GP consultations (3). Fatigue is often associated with an increased need for sleep. There are many aetiologies of both insomnia and an increased need for sleep.

The diagnosis of narcolepsy has spurred particular interest after Sweden and Finland in 2009 perceived it as an adverse reaction to Pandemrix (the H1N1 influenza vaccine) especially in people with tissue type HLA DQB1*0602 (4).

Narcolepsy is a disorder with excessive daytime sleepiness, and there are two major types: narcolepsy type 1 often with cataplexy (loss of muscle tone) and low cerebrospinal fluid hypocretin, and narcolepsy type 2 with normal cerebrospinal fluid hypocretin (5).

Narcolepsy is one of the most common causes of chronic sleepiness and is found in about 1 in 2000 people. The first symptoms commonly appear between the ages of 10 and 20. The sleepiness is severe and makes everyday activities difficult and can lead to road accidents for example.

In the article by Arnheim-Dahlstrøm L et al from 2013 (6), no excess incidence of narcolepsy was found among HPV-vaccinated girls and women under the age of 18.

Danish ADR reports of sleep disorders after HPV vaccination
The DKMA has received 227 ADR reports in total (as at 27 June 2016) describing the "sleep disorder" adverse reaction.

Most of the ADR reports concern "poor sleep" and "increased need for sleep" related to general fatigue. Often, the ADR reports describe many other symptoms with no actual diagnosis being made.

Among the ADR reports, there are a total of 12 cases with the diagnosis of narcolepsy with or without cataplexy, and a further two ADR reports describe ”sudden onset of sleep”. The time from vaccination to symptom onset differs significantly between these reports.

More than 600,000 Danish women have been vaccinated with the HPV vaccine since 2009. Compared to the prevalence of narcolepsy in the general population, it is estimated that 300 of them could suffer from narcolepsy (5).

The vast majority of ADR reports indicating ”sleep disorder” describe, as mentioned, unspecific symptoms with increased fatigue/need for sleep. Even though some of these vaccinated girls have narcolepsy, the prevalence is not higher than estimated. Nor has the epidemiological study Arnheim-Dahlstrøm L et al (7) found any evidence indicating that narcolepsy is more common in the HPV-vaccinated population.

Conclusion

Based on the Danish ADR reports, there is no ADR signal of narcolepsy related to HPV vaccination.

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Prevent mix-ups of vaccines in the childhood immunisation programme

The DKMA has received two reports of adverse reactions occurring after mix-up of two vaccines in the childhood immunisation programme; the child was given the wrong vaccine by mistake.

- The one report is about a boy who was vaccinated with Cervarix by mistake. He developed fever afterwards. It does not appear which vaccine the boy was to have received, but the boy's age makes it likely that he should have been given the MMR vaccine. The reporter indicates new vaccine and new procedures as causing the mistake.
- The other report is also about a boy who was vaccinated with Cervarix by mistake together with Prevenar 13. After vaccination, the boy was tired, whimpered and had a mild fever. The reporting doctor indicates that these adverse reactions could be related to both vaccines. It does not appear which vaccine the boy was to have received instead of Cervarix, but the boy's age and co-administration with Prevenar 13 suggest that it should have been the DTaP-IPV/Act-Hib vaccine.

The Danish Patient Safety Authority has extracted data from the Danish Patient Safety Database from which it appears that from January 2015 to September 2016, 117 adverse events have been reported involving mix-ups of vaccines in the childhood immunisation programme.

Of the 117 events, the four most common mix-ups are:

- Mix-ups of the Gardasil and the MFR vaccine (22 events) and mix-ups of the HPV vaccine and the MMR vaccine (4 events).
- Mix-up of Infanrix and DTaP-IPV/Act-Hib (15 events)
- Mix-up of DTaP-IPV Booster and the MMR vaccine (8 events)
- Mix-up of DTaP Booster and DTaP-IPV Booster (7 events)

The events describe non-serious adverse reactions in the children, but the mix-ups imply that the children have been exposed to unnecessary vaccines.

A string of reasons have been given to explain why the mix-ups occurred. The most common explanations are that mistakes are made as a result of changes in the immunisation programme. Packaging mix-ups are often given as the reason why the Gardasil vaccine and the MMR vaccine were confused (the two vaccines are from the same manufacturer). Moreover, missing or inadequate control before vaccine administration as well as the placement/marking in the refrigerator are indicated as error sources.

To prevent mix-ups and ensure administration of the right vaccine, some simple measures can be taken:

- Talk to the parents about which vaccine is to be given
- Keep vaccines apart in the refrigerator, and mark them clearly and unambiguously
- Always verify the vaccine before administration
- Always consult the vaccination card and medical record before administration

Please also see the theme about adverse events in the childhood immunisation programme, including mix-ups of childhood vaccines, in EPI-NEWS, Week 46, issued by Statens Serum Institut, SSI: *Patient safety incidents in the childhood vaccination programme*.

Most recent Direct Healthcare Professional Communications (DHPCs)

Below is a list of the most recent DHPCs that have been sent out to relevant doctors and healthcare professionals with safety information and updated recommendations about medicines:

- **Contraceptive etonogestrel implant (Implanon (NXT), Nexplanon):** Risk of migration with etonogestrel implants as well as updated recommendations on insertion, localisation and removal. Sent out 2 September 2016.
- **Agent inhibiting peristalsis, Opium NMI 10 mg/ml, oral drops:** Change of composition and change of the bottle's dropper insert alter the number of drops in a dose. Sent out 19 September 2016.

The DHPCs are available at the DKMA website – most of them in Danish only: *Direct Healthcare Professional Communication (DHPC) sent to healthcare professionals*.

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