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DANISH PHARMACOVIGILANCE UPDATE

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Short news

SGLT2 (sodium-glucose co-transporter 2) inhibitors and development of atypical ketoacidosis in patients with type 2 diabetes

The European Medicines Agency (EMA) has initiated a thorough review and assessment of SGLT2 inhibitors following the receipt of several reports of ketoacidosis in type 2 diabetes patients who received treatment.

Diabetic ketoacidosis is a serious and often life-threatening condition usually developing in patients with type 1 diabetes.

Background leading to the EMA review

Diabetic ketoacidosis has been reported as an adverse reaction in a considerable share of patients with type 2 diabetes receiving SGLT2 inhibitors. Some of these patients had an atypical presentation of ketoacidosis and blood sugar levels were only moderately increased. This uncharacteristic progression of diabetic ketoacidosis in patients with type 2 diabetes may potentially delay the diagnosis and thus treatment.

The following products will be covered in the EMA's review. INVOKANA (canagliflozin), FORXIGA (dapagliflozin), JARDIANCE (empagliflozin), VOKANAMET (canagliflozin / metformin), XIGDUO (dapagliflozin / metformin) and SYNJARDY (empagliflozin / metformin).

Also see the warning on the FDA's website

The U.S. Food and Drug Administration (FDA) has issued a warning against potential development of ketoacidosis in treatment of type 2 diabetes with SGLT2: *SGLT2 inhibitors: Drug Safety Communication - FDA Warns Medicines May Result in a Serious Condition of Too Much Acid in the Blood.*

Indication
Sodium-glucose co-transporter 2 (SGLT2) inhibitors are used in combination with diet and exercise in the treatment of patients with type 2 diabetes, either alone or in combination with other antidiabetic medicines.

EU's list of recommendations on safety signals

As part of routine surveillance of medicines in the EU, the Pharmacovigilance Risk Assessment Committee (PRAC) assesses signals of possible adverse reactions every month to determine whether further measures are needed to improve medicines safety.

The list of signals leading the PRAC to recommend further measures is published on the website of the European Medicines Agency (EMA) every month.

The most important safety signals discussed on the PRAC meeting in May 2015 concern the following products:

- Fingolimod – progressive multifocal leukoencephalopathy
- Latanoprost (Xalatan) – increased reporting of eye disorders, in particular eye irritation, after change of formulation
- Leflunomid – colitis
- Natalizumab – anaemia

See EU's list of recommendations on safety signals: *PRAC recommendations on signals.*

Childhood vaccinations and reported suspected adverse reactions in Q1 of 2015

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

Here are the results of the review for Q1 2015.

Since adverse reactions to the HPV vaccine has attracted a lot of attention over the last years, we present our review in two sections:

1. A review of the ADR reports related to vaccines in the childhood immunisation programme – excluding the HPV vaccine.

2. A review of the ADR reports related to the HPV vaccine.

The review covers primary vaccines in the childhood immunisation programme as well as booster vaccines (re-vaccination).

Reports of adverse reactions to vaccines in the childhood immunisation programme (excluding the HPV vaccine) Q1 of 2015

In the first quarter of 2015, the DHMA received a total of 81 reports of suspected adverse reactions to vaccines in the childhood immunisation programme (excluding the HPV vaccine). Seven of them were classified as serious[1].

Table 1a shows the number of ADR reports classified as serious and non-serious.

Vaccine	Non-serious	Serious	Total
DT booster	0	1	1
DTaP Booster / imovax polio	1	0	1
DTaP-IPV Booster	6	1	7
DTaP-IPV /Act-Hib	32	1	33
DTaP-IPV /Act-Hib / MMR vaxpro	1	0	1
DTaP-IPV /Act-Hib / MMR vaxpro / Prevenar 13	3	0	3
DTaP-IPV/ Act-Hib / Prevenar	2	0	2
DTaP-IPV /Act-Hib / Prevenar 13	7	2	9
Infanrix Hexa / Prevenar 13	1	0	1

[1] A report is serious when one or more of the adverse reactions are serious. A serious adverse reaction caused by a medicine for human use is a reaction that results in death, is life-threatening, requires hospitalisation or prolongation of hospitalisation, or which results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Infanrix Hexa	4	0	4
Infanrix Hexa / Prevenar 13	1	0	1
MMR	1	1	2
MMR Vaxpro	9	1	10
Prevenar	1	0	1
Prevenar 13	2	0	2
Priorix	3	0	3
Total	**74**	**7**	**81**

Table 1a. Reports by severity.

Review and assessment of the serious reports

When we assess the serious ADR reports, we investigate whether it is likely that there is a causal link to the vaccine.

As of 1 January 2015, our causality assessment is based on four categories:

- Possible
- Less likely
- Insufficient documentation
- Unclassifiable

Vaccine	ADR description	Assessment and causality
DTaP-IPV Act-Hib	The patient developed a troublesome and itching vaccination granuloma with a cyst formation (sterile abscess?) after vaccination.	The temporal relationship is consistent, and granuloma are known to develop after vaccination with this vaccine. Causality is therefore considered **possible**.
DT-IPV Booster	One month after vaccination, a patient had an epileptic seizure (petit mal).	Petit mal epilepsy is a relatively common form of epilepsy (1 % of the Danish population has epilepsy)[2]. This adverse reaction is not known, and there is no evidence in the literature to support a connection. Therefore, causality is considered **less likely**.
MMR	The patient had, for an unknown period of time, experienced spasms, poor memory and depression, etc. He had the measles three years ago.	This is an adult man who was vaccinated in childhood. He had the measles three years ago. This could be a case of vaccine failure, since it is known that no vaccine offers 100 % protection. Causality is therefore considered **possible**.

[2] sundhed.dk

		There is very little information about the other symptoms, and causality is **unclassifiable** on the available basis.
MMR Vaxpro	Four to five weeks after vaccination, the patient developed thrombocytopenia.	Thrombocytopenia is a known adverse reaction to the vaccine. There is a temporal relationship to vaccination, and causality is considered **possible**.
DTaP-IPV /Act-Hib / Prevenar 13	About one month after vaccination, a 3-month-old baby developed bullous pemphigoid.	Bullous pemphigoid is a rare autoimmune condition. For this patient, there was a temporal relationship to vaccination. However, there is **insufficient documentation** in the literature to determine causality.
DTaP-IPV/Act-Hib and Prevenar13	A 1-year-old child experienced febrile seizures and muscle pain on the day of vaccination.	Febrile seizure is a known adverse reaction to the vaccine, and causality is therefore considered **possible**. Seizures may result in secondary muscle pain.
DT Booster-Stamaril-Twinrix	A 46 year-old man had left axillary lymphadenitis a few weeks after vaccination.	Temporal relationship is consistent. Lymphadenitis is a known adverse reaction to both Twinrix® and Stamaril®. Since Stamaril® was the vaccine administered in the left upper arm, it is most likely this vaccine which caused lymphadenitis. Causality is considered **possible**.

Table 1b: Description of the suspected adverse reactions described in the serious ADR reports and subsequent causality assessment.

Review of the non-serious ADR reports

A total of 74 ADR reports were classified as non-serious.

Local reactions at the injection site is the most common suspected adverse reaction among the non-serious ADR reports. Most often these are granuloma[3] and/or nodules (47 ADR reports) as well as itching. Metal allergy was also reported relatively frequently in the ADR reports.

[3] The formation of granuloma has long been a known, yet relatively rare, adverse reaction of vaccination with aluminium-containing vaccines. In recent years, aluminium allergy has also been reported after vaccination with aluminium-containing vaccines. The DHMA has previously written about granuloma formation and aluminium allergy from aluminium adjuvant vaccines in *Danish Pharmacovigilance Update, October 2013*. The Department of Dermatology and Allergy at Gentofte Hospital has published an article, which elaborates on the issue: *Aluminium allergy and granuloma in children induced by vaccinations for children (in Danish only).* The article gives information about causes, diagnostics and treatment of vaccination granuloma and aluminium allergy and considerations made about revaccination. The article is in keeping with the DHMA's previous article in Danish Pharmacovigilance Update.

Unknown adverse reactions not described in the vaccines' product information
Among the suspected adverse reactions classified as non-serious, we received one ADR report describing mouth blisters and one report describing affected vision.

Conclusion
In the first quarter of 2015, we received a total of 81 ADR reports that concerned vaccines in the childhood immunisation programme (excluding the HPV vaccine).

Seven were classified as serious. In five of these reports, a causal link to the vaccine was assessed as possible. The majority of suspected adverse reactions described in the non-serious ADR reports were local reactions at the injection site. These adverse reactions are known. In the past years, the number of ADR reports submitted for the childhood immunisation programme is more or less the same.

There are no new data shifting the benefit-risk balance, and therefore the DHMA assesses that the benefits of the vaccines still outweigh the possible risks.

ADR reports about the HPV vaccine received in Q1 2015

In the first quarter of 2015, the DHMA received a total of 77 reports of suspected adverse reactions related to the HPV vaccine, of which 41 were classified as serious.

Table 2a shows the number of ADR reports related to the HPV vaccine classified as serious and non-serious.

Vaccine	Serious	Non-serious	Total
HPV vaccine	41	36	77

Table 2a. Reports by severity

Number of doses sold and number of ADR reports from 2009 to Q1 of 2015*

HPV vaccine	2009	2010	2011	2012	2013	2014	Q1 2015	Total
Number of reports	288	66	43	96	511	224	77	1305
– of which serious	25	5	6	18	177	91	41	363
Number of doses sold	347,690	151,476	163,374	349,730	488,224	114,457	20,817	1,635,768

Table 2b. Number of ADR reports related to the HPV vaccine received from 2009 to 31 March 2015, broken down by serious and non-serious reports. The number of doses sold in Denmark is also shown. (Please be aware that when the DHMA receives additional information, this may imply changes. Consequently, there may be small variations between previously published figures and the figures reported here.)

*The figures in the table cover only reported adverse reactions received by the DHMA after the HPV vaccine became part of the Danish childhood immunisation programme in 2009. The DHMA has also received ADR reports of suspected adverse reactions to the HPV vaccine before 2009. From 2006, when the HPV vaccine was marketed, up until 2009, the DHMA received a total of 83 ADR reports about the HPV vaccine, of which 11 were classified as serious.

Age distribution

The HPV vaccine is the only vaccine included in the Danish childhood immunisation programme that is also offered free of charge to women outside the childhood programme.

From August 2012 until end-2013, the HPV vaccine was offered free of charge to women from the 1985-1992 birth cohorts. Since 1 January 2014, the HPV vaccine has been offered to women from the 1993-1997 birth cohorts. These birth cohorts have previously been offered the HPV vaccine. The offer is available until the end of 2015.

Table 2c shows the age distribution of the girls/women described in the ADR reports we received in the first quarter of 2015.

Number of ADR reports about persons under 18	Number of ADR reports about persons aged 18 or over	Number of ADR reports, age unknown
33	41	3

Table 2c. Age of the girls/women for whom adverse reactions have been reported.

ADR reports by year of adverse reaction onset

Table 2d shows the distribution of the ADR reports according to the year when the adverse reactions[4] began.

Year	2008	2009	2010	2011	2012	2013	2014	2015	Year not provided	Total
Number	1	5	2	3	25	13	13	8	7	77

Table 2d. Distribution according to the year the adverse reactions started.

Review and assessment of the serious ADR reports about the HPV vaccine

ADR description	Assessment and causality
Pain in arms, knees and shoulder, dizziness, migraine.	A patient experienced pain in the arm immediately after vaccination. This is a known adverse reaction, and causality is therefore considered **possible**. The other symptoms, which occurred a couple of months after the last vaccine dose, are described only in case reports in the literature, and therefore there is **insufficient documentation** to confirm a causal link to the vaccine.
POTS with syncope, etc.	There is some uncertainty as to the temporal relationship between vaccination and symptoms, but symptom onset is assessed to be months after the last vaccine dose. Regarding a potential causal link between POTS and the HPV vaccine, many cases have been described in the literature by several groups[5],[6]; and even though there are no controlled studies that confirm such causality, causality is considered **possible** due to the number of case reports, the temporal relationship and lack of alternative explanations.
Haemolytic anaemia, POTS, dyssomnia, nausea, headache, fatigue, etc.	Two reports have been received about the same patient, and slightly diverging medical histories are provided in the two reports. The patient first had infections, then onset of haemolytic anaemia with neutropenia about two months after the third vaccine dose. Other symptoms occurred later on. The patient has subsequently been diagnosed with POTS. Haemolytic anaemia is not a known adverse reaction to the HPV vaccine, and there is **insufficient documentation** to assess a causal link to the vaccine. Regarding a potential causal link between POTS and the HPV vaccine, many cases have been described in the literature by several groups[7],[8]; and even though there are no controlled studies that confirm such causality, causality is considered **possible** due to the number of case reports, the temporal relationship and lack of alternative explanations.

[4] One report may describe several different adverse reactions. The adverse reactions of one report may have different start dates. In the table above, the ADR report is counted in the year when the first adverse reaction occurred.
[5] Brinth LS, Pors K, Theibel AC, MehlsenJ: Orthostatic intolerance and postural tachycardia syndrome as suspected adverse effects of vaccination against human papillomavirus Vaccine 33 (2015) 2602–5.
[6] Blitshteyn S: Postural tachycardia syndrome following human papillomavirus vaccination. European Journal of Neurology 2014:21(1):135-9
[7] Brinth LS, Pors K, Theibel AC, MehlsenJ: Orthostatic intolerance and postural tachycardia syndrome as suspected adverse effects of vaccination against human papillomavirus Vaccine 33 (2015) 2602–5
[8] Blitshteyn S: Postural tachycardia syndrome following human papillomavirus vaccination. European Journal of Neurology 2014:21(1):135-9

Radiating pain, sensory disturbances, dizziness, etc.	The symptoms occurred after the third dose of Gardasil®. There is a temporal relationship to vaccination. However, since similar symptoms are only described in case reports there is **insufficient documentation** to assess a causal link to the vaccine.
Influenza symptoms, headache, joint pain etc.	Symptom onset occurred before the third Gardasil® vaccine dose, presenting as influenza-like symptoms. Two years after vaccination, the patient developed neurological symptoms and was tested for Guillain-Barré syndrome, but all tests were normal. It is considered most likely that the initial influenza infection was unrelated to the vaccine. There is no temporal relationship between the subsequent neurological symptoms and the vaccinations, and therefore causality is considered **less likely**.
Headache, dizziness, fatigue etc.	The symptoms occurred before the third dose of Gardasil®. The symptoms were long-term and thus are not known adverse reactions, and there is **insufficient documentation** to assess a causal link to the vaccine.
Headache and muscle weakness	Symptoms started before vaccination. The patient has been examined, and no diagnosis other than tension headache and a virus on the acoustic nerve has been made. Long-term headache is not a known adverse reaction to the HPV vaccine. Since the symptoms had already started one month before the first vaccine dose, and it is not a known adverse reaction, causality is considered **less likely**.
POTS with dizziness and visual disturbances	There is a temporal relationship between symptom onset and the vaccinations. The patient has been diagnosed with POTS. Regarding a potential causal link between POTS and the HPV vaccine, many cases have been described in the literature by several groups[9],[10]; and even though there are no controlled studies that confirm such causality, causality is considered **possible** due to the number of case reports, the temporal relationship and lack of alternative explanations.
Autonomic dysfunction, fatigue, headache, nausea, orthostatic intolerance	There is a temporal relationship between symptoms and vaccination. The patient has been tested for POTS, but the test results were negative. Persistent symptoms are not known adverse reactions, and in the literature there is **insufficient documentation** to assess a causal link to the vaccine.
Multiple symptoms with dizziness, pain, complaints, rash, etc.	Symptoms started one year after the last vaccine dose, and causality is therefore considered **less likely**.
Headache, joint/muscle pain, fatigue, autonomic dysfunction, etc.	There is a temporal relationship between the symptoms and the vaccinations, but the results from a tilt table tests/POTS tests were negative. Persistent symptoms are not known adverse reactions, and in the literature there is **insufficient documentation** to assess a causal link to the vaccine.
Chronic fatigue syndrome	The patient was tired, had abdominal pain, etc. after the last vaccine dose A British study disproves a causal relationship between another HPV vaccine and chronic fatigue syndrome[11]. In the case at hand, the temporal relationship was, however, consistent, but since there is limited literature on the subject, the case is categorised under **insufficient documentation.**

[9] Brinth LS, Pors K, Theibel AC, MehlsenJ: Orthostatic intolerance and postural tachycardia syndrome as suspected adverse effects of vaccination against human papillomavirus Vaccine 33 (2015) 2602–5

[10] Blitshteyn S: Postural tachycardia syndrome following human papillomavirus vaccination. European Journal of Neurology 2014:21(1):135-9

[11] Donegan K et al: Bivalent human Papillomavirus vaccine and the risk of fatigue syndromes in girls in the UK, Vaccine 2013 31(43):4961-7.

Aplastic anaemia	The patient developed aplastic anaemia (AA) about three years after vaccination. Received a bone marrow transplant. Preceding long-term fatigue. No definite temporal relationship, and no evidence in the literature of aplastic anaemia as suspected adverse reaction to the vaccine. AA is most common in young people (10-25 years) and older people (>60 years)[12], and normally the disease triggers are not identified (idiopathic). Causality is considered **less likely**.
POTS	There is a temporal relationship between symptom onset and the vaccinations. The patient has been diagnosed with POTS. Regarding a potential causal link between POTS and the HPV vaccine, many cases have been described in the literature by several groups[13],[14]; and even though there are no controlled studies that confirm such causality, causality is considered **possible** due to the number of case reports, the temporal relationship and lack of alternative explanations.
Chronic dizziness, bloody stools, shortness of breath, etc.	It is considered less likely that bloody stools should be related to the vaccination. The information is very limited, and it has not been possible to obtain a medical confirmation. Causality is assessed to be **unclassifiable**.
Autonomic dysfunction, orthostatic intolerance, chronic headache, etc.	The temporal relationship between symptoms and vaccination is uncertain because the patient and doctor have indicated different dates of symptom onset. The patient was vaccinated seven years ago. Besides a negative tilt table test, there was no other information about examinations performed. It is indicated that the patient has symptoms of autonomic dysfunction. On the available basis, causality is **unclassifiable**.
Autonomic dysfunction, fatigue, nausea, orthostatic intolerance, dyssomnia	The patient had a prior history of headache and fatigability. These symptoms got worse after the first vaccination, and she developed chronic headache, dizziness, fatigue, etc. There is **insufficient documentation** in the literature to suggest a causal link between the vaccine and long-term, chronic headache.
Chronic headache, dizziness, cognitive dysfunction, sleepiness	The patient had a history of meningitis and was prone to headaches. After the vaccination, these symptoms got worse, and she developed chronic headache, dizziness, fatigue, etc. There is **insufficient documentation** in the literature to suggest a causal link between these symptoms.
Chronic fatigue, muscle pain, headache	It was known that the patient had an uncontrolled metabolic disorder before vaccination. The doctor believed the symptoms to be caused by this disorder. Thus, there is another explanation which more likely can explain the symptoms, and therefore a causal link to the vaccine is considered **less likely**.
Dizziness, syncopes, bladder symptoms	There is a temporal relationship between the vaccinations and onset of dizziness and syncope. The patient has been examined by tests, including a tilt table test, which showed no signs of POTS.

[12] www.sundhed.dk.
[13] Brinth LS, Pors K, Theibel AC, MehlsenJ: Orthostatic intolerance and postural tachycardia syndrome as suspected adverse effects of vaccination against human papillomavirus Vaccine 33 (2015) 2602–5
[14] Blitshteyn S: Postural tachycardia syndrome following human papillomavirus vaccination. European Journal of Neurology 2014:21(1):135-9

	Persistent symptoms are not known adverse reactions, and in the literature there is **insufficient documentation** to assess a causal link to the vaccine.
Dizziness and syncopes	There is insufficient information about the temporal relationship between symptoms and vaccination (although occurring within the same year). The patient has been examined, including by tilt table test, which was normal. Persistent symptoms are not known adverse reactions, and in the literature there is **insufficient documentation** to assess a causal link to the vaccine.
Constipation, sleepiness, migraine, etc.	There is very little information in the report, including no indication of time between symptom onset and vaccination. On the available basis, causality is **unclassifiable**.
Tiredness, headache, etc.	Little information about examination and medical history. However, many of the symptoms occurred up to five years after the vaccinations. On the available basis, causality is **unclassifiable**.
Headache, concentration problems, fainting, etc.	The symptoms are described as having occurred in connection with the vaccinations, but there is no additional information about tests or examinations performed. On the available basis, causality is **unclassifiable**.
Joint symptoms with swelling/pain	There is a close temporal relationship (a few days) between the vaccination and the symptoms. Joint symptoms are among the known adverse reactions. Causality is considered **likely**.
Fatigue, joint and muscle pain	The report contains very little information, and it is not indicated if there is a consistent temporal relationship. On the available basis, causality is **unclassifiable**.
Anxiety attacks, headache and fatigue, etc.	The ADR report's time indications are not precise, but the symptoms are estimated to have occurred within one year after vaccination. Persistent symptoms are not known adverse reactions, and in the literature there is **insufficient documentation** to assess a causal link to the vaccine.
Dizziness, sensory disturbances, paresthesia, headache, etc.	The symptoms occurred about six weeks after the last vaccination, and the temporal relationship is thus consistent. Persistent symptoms are not known adverse reactions, and in the literature there is **insufficient documentation** to assess a causal link to the vaccine.
Acute glomerulonephritis, various other symptoms such as fatigue	The diagnosis of acute glomerulonephritis was made four years after vaccination, and therefore causality with the vaccine is considered **less likely**. The other symptoms (light sensitivity, fatigue) occurred in closer temporal relation to vaccination, but given the available, limited details about these symptoms, causality is **unclassifiable**.
Discolouration of legs, fatigue, dizziness	Discolouration of the lower extremities occurred about two months after the last vaccine dose. The other symptoms occurred several years later. There is very little information, and neither examination results nor diagnoses are described in the report. On the available basis, causality is **unclassifiable**.
Headache, dizziness, abdominal pain, etc.	The symptoms occurred after the third dose of Gardasil®. The patient has since undergone surgery for ovarian cysts. This is neither a known adverse reaction, nor is it described in follow-up studies, and causality is therefore considered **less likely**. As for the other symptoms, persistent symptoms are not known adverse reactions, and in the literature there is **insufficient documentation** to assess a causal link to the vaccine.
Anxiety, abdominal pain, rash, etc.	The symptoms occurred within months after vaccination. No medical confirmation has been obtained. It is not known adverse reactions when the

	symptoms are persistent, and there is **insufficient documentation** to confirm causality with the vaccine.
Migraine-like headache, fainting, nausea, abdominal pain, etc.	The symptoms occurred within a year after vaccination. There is very little information, and on the available basis, causality is **unclassifiable**.
Nausea, headache, fainting, elevated rates of infection, etc.	The report describes many symptoms having occurred after vaccination at a time unknown. No medical confirmation has been obtained. On the available basis, causality is **unclassifiable**.
Pernicious anaemia, shortness of breath, insomnia, digestive problems, etc.	The symptoms occurred two years after vaccination. The temporal relationship is thus inconsistent, and a causal link to the vaccine is considered **less likely**.
Sensory disturbances and loss of strength	The symptoms occurred about three weeks after the first vaccination. Thus, there is a temporal relationship between symptoms and vaccination. In the literature, there are case reports describing paraesthesias after vaccination, but there is no evidence. On the available basis, there is **insufficient documentation** to assess causality.
Chronic headache	The symptoms occurred 24 days after the first vaccine dose, and there is thus a temporal relationship between symptoms and vaccination. In the literature, there are case reports of chronic headache after vaccination, but there is no conclusive evidence. The condition is common in the general population (4 %)[15]. On the available basis, there is **insufficient documentation** to assess causality.
Joint pain, headache, dizziness, etc.	There is insufficient information about a possible temporal relationship between vaccination and symptoms. However, there is a minimum of six months between vaccination and symptom onset. There is no information about examinations or other, and causality is assessed as **unclassifiable**.
Fatigue, muscle spasms, nausea, stiffness, etc.	There is insufficient information about the temporal relationship between symptoms and vaccination, and there is no information about examinations or other, and causality is therefore assessed as **unclassifiable**.
Fatigue, headache, etc.	Symptom onset with headache and dizziness, etc. about one year after the vaccinations ended. Since there is no consistent temporal relationship between vaccinations and symptoms, causality is considered **less likely**.
Seizures, headache, nausea in a 15-year-old boy	Eight days after the second vaccine dose, the patient had a seizure and was later diagnosed with epilepsy. There is a consistent temporal relationship between symptoms and vaccination, but epidemiological studies[16] did not find epilepsy to be more prevalent in HPV vaccinated people. Epilepsy is a relatively common condition (affecting 1 % of the population), which is why causality is considered **less likely**.

Table 2d. Description of the adverse reactions in the serious ADR reports and subsequent causality assessment.

[15] www.sundhed.dk.

[16] Arnheim-Dahlstrøn L et al: Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study. BMJ. 2013 Oct 9;347:f5906.

Summary
Unfortunately, some of the ADR reports contained very limited information, and it has not been possible to obtain exhaustive information. In these reports causality is therefore **unclassifiable**. Especially the temporal relationship between vaccination and symptom onset as well as tests and examinations have not been described in adequate detail.

Among the ADR reports for which causality is assessed as possible, there is one case of joint symptoms and four cases of POTS. One of the cases in which POTS had been diagnosed described a patient whose symptom onset was haemolytic anaemia. At present, there is insufficient documentation for causality between haemolytic anaemia and HPV vaccine.

There are still many ADR reports of long-term headache, dizziness, fatigue and various neurological symptoms. In the literature, only case reports describe causality between the HPV vaccine and these symptoms, and a controlled study with the aim of investigating a possible causal link has not yet been carried out. These ADR reports are grouped under the category of "insufficient documentation".

When considering the temporal relationship between vaccine and adverse reaction, it should be noted that most acknowledged autoimmune adverse reactions of vaccines occur within months after vaccination. In general, adverse reactions with onset more than a year after vaccination are considered less likely to be caused by vaccination.

Review of the non-serious ADR reports

The most frequently reported symptoms in the 36 non-serious ADR reports on HPV vaccine were headache (sometimes long-term), dizziness, nausea and fatigue. Whereas these symptoms are known adverse reactions described in the vaccine's product information if short-termed and occurring in immediate relation to the vaccine, long-term symptoms are not known adverse reactions. Other reported suspected adverse reactions in this segment included increased appetite and cough. Only a few ADR reports described local reactions.

Conclusion

We received a total of 77 ADR reports concerning the HPV vaccine in the first quarter of 2015. 41 of them were classified as serious.

There were a few new cases of POTS, and there are still many cases that describe a syndrome with long-term headache, fatigue, dizziness and various neurological symptoms. There is no knowledge that these symptoms can be long-term. The new classification subject to which these ADR reports are categorised as "Insufficient documentation" makes it clear that it is necessary to investigate a causal link to the vaccine.

In this regard, it is crucial to make sure that ADR reports are as complete as possible. In this review, there are no new data shifting the benefit-risk balance, and the DHMA assesses that the benefits of the vaccines still outweigh the possible risks.

DHMA maintains focus on ADR reports related to the HPV vaccine

The DHMA takes it very seriously that an increasing number of suspected adverse reactions keeps being reported about the HPV vaccine, and we are continuing work to investigate the problem.

At present, there are no scientific studies that can establish whether or not there is a causal link between many of the serious ADR reports and the vaccine.

Investigating the connection can be difficult, especially because the ADR reports often describe a complex of symptoms with no clear diagnosis. It is therefore difficult to use the Danish registers, which are based on diagnoses, to determine if the complex of symptoms occurs more often than in the general population.

We have initiated a project to re-examine the ADR reports of suspected adverse reactions to the HPV vaccine classified as serious. We will be investigating if it is possible to identify new unifying features in the ADR reports through an examination with focus on reported symptoms rather than diagnoses. During the review of the ADR reports, it will also be investigated if it is possible to identify any underlying features that the vaccinees may have in common through which to pinpoint possible causes or possible risk factors.

The review will primarily be conducted by a paediatrician who has extensive clinical experience coupled with data-handling experience. The WHO[17] contributes to the project with expert knowledge and searches in their database of adverse reactions reported globally for the HPV vaccine.

Furthermore, the DHMA is collaborating with the SSI and other experts to look at new potential aspects of possible adverse reactions, including the possibilities of adding new registry studies to the review.

The DHMA intends for the results of the evaluation to be included in the European Pharmacovigilance Risk Assessment Committee's next review of the safety of the HPV vaccine in autumn 2015.

All cases referred to in this article originate from the Danish Health and Medicines Authority's database of adverse drug reactions. The cases have been forwarded to all relevant pharmaceutical companies and to the EudraVigilance database. Therefore, the pharmaceutical companies are not to report these cases to the Danish Health and Medicines Authority.

[17] Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring.

Important notes
Always remember to record the vaccine batch number in connection with vaccination as well as the specific location on the body where the vaccine was injected. Batch number and product name are important details when you report suspected adverse reactions to the DHMA as it can significantly impact the evaluation of adverse reactions.

Aripiprazole, amisulpride, risperidone and ADR reports of deaths

As part of our pharmacovigilance activities, we have focus on antipsychotic drugs among other products.

We have received 19 ADR reports that describe deaths suspected as adverse reactions to, respectively, aripiprazole, amisulpride and risperidone – including aripiprazole (7 deaths), amisulpride (1 death) and risperidone (11 deaths). We have received eight of the 19 ADR reports in the last five years – the most recent one is from November 2014.

In this issue of Danish Pharmacovigilance Update, we provide a brief overview of the ADR reports of deaths of patients treated with the three antipsychotic medicines aripiprazole, amisulpride and risperidone.

Review of the 19 reported deaths related to treatment with aripiprazole, amisulpride and risperidone

Age and gender distribution

Gender

- Women (11)
- Men (6)
- Gender undisclosed (2)

Age

- Age unknown (3)
- Age 19-40 (6)
- Age 41-60 (6)
- Age over 61 (4)

Reported causes of death in the 19 patients

Cause of death	Aripiprazole	Amisulpride	Risperidone
Sudden unexpected death (cause unknown)	2		3*
Drug intoxication	2		2
Pulmonary embolism			2
Malignant neuroleptic syndrome			1
Generalised tonic-clonic seizures			1*
Cardiac arrest possibly caused by bronchopneumonia			1
Cerebellar haemorrhage and sepsis (prescribed overdose)			1*
Acute heart failure due to blood clot in the heart		1	
Suicide	1		
Unknown	2		

*Since the patients are treated with several different antipsychotics, including clozapine, quetiapine, olanzapine and risperidone, four of the above ADR reports are also mentioned in the articles on Cloazapine and deaths, Olanzapine and deaths and Quetiapine and deaths.

Indications reported for aripiprazole, amisulpride and risperidone use in the 19 patients:

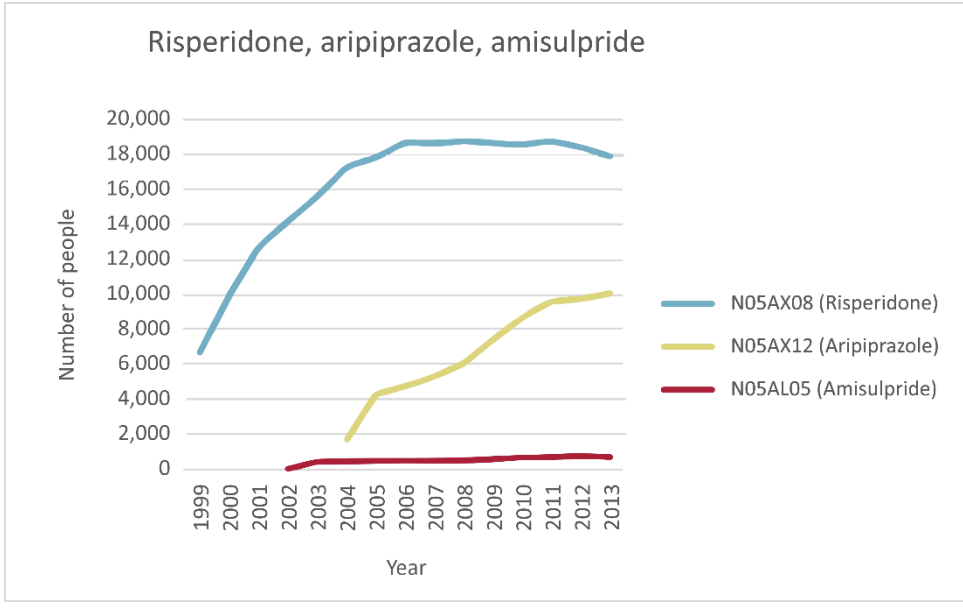
- Schizophrenia (10)
- Psychoses (2)
- Manias (1)
- Bipolar disorder (1)
- Hallucinations (1)
- Personality disorders (1)
- Not provided (3)

Co-medication/polypharmacy/treatment with several antipsychotics

Seven of the 19 patients who died were treated with several different medicinal products. Seven of the patients were treated concomitantly with two or more antipsychotics, and six were treated concomitantly with a benzodiazepine.

Number of aripiprazole, amisulpride and risperidone users

The number of people treated with risperidone in the primary sector has since 2005 remained relatively stable at around 18,000 (17,921 individuals in 2005 and 17,937 in 2013). The number of people on aripiprazole medication has risen from 1,743 in 2004 to 10,093 in 2013. Although the number of people on amisulpride medication is limited compared to the two other antipsychotics, the number of people treated nonetheless increased from 475 persons in 2004 to 755 persons in 2013.



Number of persons treated with aripiprazole, amisulpride and risperidone from 1999-2013 (Medstat, primary sector).

Conclusion

More than one third of the patients who died in connection with aripiprazole, amisulpride or risperidone treatment were treated concomitantly with one or several other antipsychotic medicines. Some patients were also being treated with benzodiazepines at the same time. This is inconsistent with the current guideline on antipsychotic treatment, and it is a known problem which was addressed in the DHMA's report about medical treatment of adults diagnosed with schizophrenia (in Danish only): *Medicinsk behandling af voksne diagnosticeret med skizofreni, Sundhedsstyrelsen, 8 October 2014*. The report was prepared based on a comprehensive investigation, which showed that many of the patients were treated with more than one antipsychotic medicine. The scientific evidence on antipsychotic polypharmacy is limited, and for most combinations, polypharmacy does not provide improved effects compared to monopharmacy. Antipsychotic polypharmacy may be associated with an increased risk of adverse reactions.

In compliance with the DHMA's present guideline "Behandling med antipsykotiske lægemidler til personer over 18 år med psykotiske lidelser *no. 9276 of 6 May 2014" (in Danish only)*, doctors should, among other things, be aware of the following:

- Avoid concomitant treatment with antipsychotics and benzodiazepines after the acute phase (1-2 weeks) as combination treatment increases the risk of serious adverse reactions.
- There is no evidence that concomitant treatment with several antipsychotics increases efficacy. On the contrary, polypharmacy causes more adverse reactions.

The patient should be monitored with respect to the tests below at the start of treatment and after 2, 4, 8, and 12 weeks. In long-term treatment, at least once a year.

Prescribers should ensure the following are performed:

- Height and weight measurement
- BMI calculation
- Waist measurement
- Blood pressure measurement
- Hba1c and lipid measurements
- ECG monitoring

After each monitoring, the doctor treating the patient must decide on the continued medical treatment based on the guideline's criteria. The Danish Society of Cardiology and the Danish Psychiatric Society have developed an algorithm that is to reduce the risk of cardiac arrhythmia and sudden death induced by psychoactive drugs (in Danish only): *Arytmi-risiko ved anvendelse af psykofarmaka.*

Indication for risperidone

- Indicated for the treatment of schizophrenia.
- Indicated for the treatment of moderate to severe manic episodes associated with bipolar disorders.
- Indicated for the short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others.
- Indicated for the short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with subaverage intellectual functioning or mental retardation diagnosed according to DSM-IV criteria, in whom the severity of aggressive or other disruptive behaviours require pharmacologic treatment.

Indication for aripiprazole

- Indicated for the treatment of schizophrenia in adults and in adolescents aged 15 years and older.
- Indicated for the treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment.

  Indicated for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.

Indication for amisulpride

- Indicated for the treatment of acute and chronic schizophrenic disorders
  - positive symptoms such as delusions, hallucinations, thought disorders, hostility and paranoid delusions.
  - negative symptoms such as blunted affect, emotional and social withdrawal.
- Amisulpride also regulates secondary negative symptoms and affective disorders such as depression.

All cases referred to in this article originate from the Danish Health and Medicines Authority's database of adverse drug reactions. The cases have been forwarded to all relevant pharmaceutical companies and to the EudraVigilance database. Therefore, the pharmaceutical companies are not to report these cases to the Danish Health and Medicines Authority.

Still fewer women get 3rd and 4th generation contraceptive pills

The DHMA recommends 2nd generation contraceptive pills as first choice to reduce the risk of blood clots.

A new report from the SSI on the consumption of contraceptive pills shows that doctors comply with the DHMA's recommendation, and that the consumption of 3rd and 4th generation pills keeps falling (figure 1).

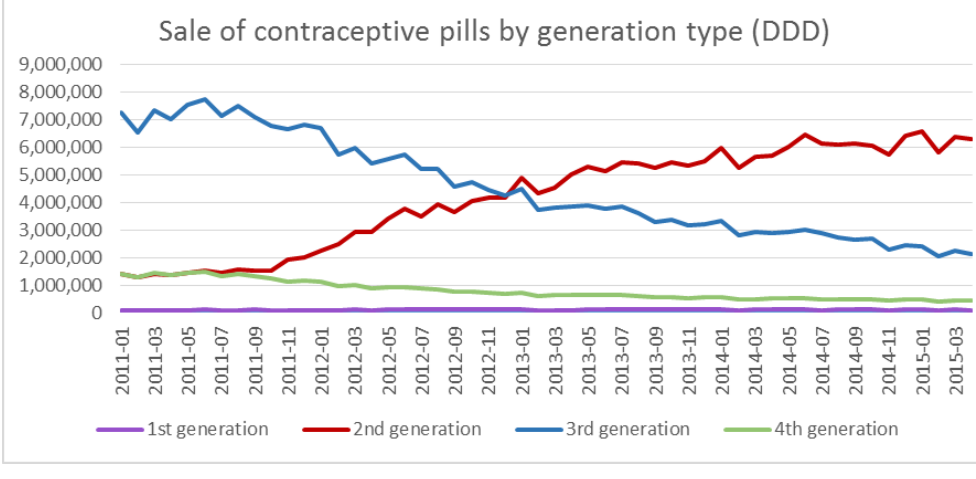


Figure 1. Development in the sale of contraceptive pills by generation

Contraceptive pills and the risk of blood clots

It is known that contraceptive pills increase the risk of blood clots, and several studies have shown that 3rd and 4th generation contraceptive pills are associated with a higher risk of blood clots compared to the older 2nd generation contraceptive pills (Table 1).

Women not using contraceptive pills who are not pregnant	Approx. 2 out of 10,000 women
Women using 2nd generation contraceptive pills	Approx. 5-7 out of 10,000 women
Women using 3rd and 4th generation contraceptive pills	Approx. 6-12 out of 10,000 women

Table 1. Absolute risk of developing venous blood clot in a year.

The relative risk is up to twice as big for the new contraceptive pills compared to 2nd generation contraceptive pills. In all cases, the risk is small and it depends highly on what other risk factors the women may have, not only on the type of contraceptive pill used.

In 2013, the European Pharmacovigilance Risk Assessment Committee, PRAC, assessed the risk of venous blood clots of contraceptive pills and other combination products with oestrogen and progesterone. It concluded that the risk of venous blood clots is small for all types of contraceptive pills and other contraception with hormone combinations. The risk differs slightly between products depending on the type of hormone contained in the contraceptive pills. Therefore, it was decided not to recommend any type of contraceptive pills over others.

A new British study published in the British Medical Journal from May 2015 has now also confirmed the previous conclusions.

Advice for prescribers

- 2nd generation contraceptive pills should generally be prescribed as first choice.
- The woman's risk factors for venous blood clots should be evaluated prior to the prescription of the first contraceptive pills or other hormone-containing contraception and regularly thereafter as the risk factors change over time. The risk factors for venous blood clots include overweight, age above 35 years, migraine, family history of blood clots, or use of contraceptive pills few weeks after delivery.
- Doctors should always weigh the benefits and risks for women who have used 3rd and 4th generation pills for a long period of time without problems. If a woman has never tried low-risk hormones, it is advisable to make a product switch at the next prescription renewal and then be guided by the woman's experience with the new product. Either way, doctors should always ensure that the so-called precautions for use are observed.
- It is important to inform the woman about the risk of blood clots and the symptoms she needs to pay attention to, e.g. strong pain or swelling in the legs, sudden unexplainable shortness of breath, faster breathing or cough, chest pain and numbness in face, arms or legs. If any of these symptoms occur, a doctor should be consulted immediately.

See the DHMA's *Guidance material for doctors and users of contraceptive pills*.

Most recent Direct Healthcare Professional Communications (DHPCs)

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

- Anakinra, Kineret 100 mg and 100 mg/0.67 ml solution for injection, in a pre-filled syringe – product complaints about the presence of a visible solid substance on the surface of the needle.

The DHPCs are available in Danish at the DHMA website: *Direct Healthcare Professional Communication (DHPC) sent to healthcare professionals.*

The next Danish Pharmacovigilance Update will be out in August

Have a nice summer!

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