Danish Pharmacovigilance Update Year 4 #3
21 March 2013

Depressive and suicidal thoughts following discontinuation of varenicline (Champix®)

In January, the Danish Health and Medicines Authority (DHMA) received an adverse reaction report concerning a patient who developed marked fatigue and pressing depressive and suicidal thoughts in association with discontinuation of Champix®.

The patient had been treated with Champix® for 3.5 months, and the above-mentioned symptoms emerged a few days after treatment discontinuation. The symptoms lasted for five days.

The DHMA's adverse reaction database contains a total of 14 reports of patients who developed depressive – and in some cases suicidal – thoughts in association with discontinuation of Champix®. These adverse reactions are known. Some of the reports describe that the symptoms required medical treatment.

As a doctor you should be aware of the following:
At the end of treatment, some patients may experience increased irritability, an urge to smoke, depression and/or insomnia. You should inform the patient about this and consider whether it is necessary to taper the treatment over time.

Indication for Champix®
Used for smoking cessation in adults.

All cases referred to in the articles in the Danish Pharmacovigilance Update originate from the Danish Health and Medicines Authority's adverse reaction database. The cases have been forwarded to all relevant pharmaceutical companies and to the EudraVigilance database. Therefore, pharmaceutical companies should not report these cases to the Danish Health and Medicines Authority.

Risk of femoral fracture during treatment with Prolia® (denosumab)

In the EU, there has been reports of rare cases of atypical femoral fractures in patients receiving Prolia® (denosumab) for the treatment of postmenopausal osteoporosis. Such fractures are normally not seen in this group of patients. In osteoporosis patients, fractures are most often seen in the back or hip regions and may also occur in other bones such as the distal forearm, proximal humerus, pelvis and ankle. Therefore, a correlation with the medical treatment is suspected. There are no reports of such cases in Denmark.

As a doctor you should be aware of the following:

- Patients should be advised to contact their doctor, if they experience new or unusual thigh, hip, or groin pain during treatment with Prolia®.
- Patients having such symptoms must be examined for femoral fractures, including atypical femoral fractures.
- The contralateral femur should be examined in patients with a prior fracture of the femoral shaft.
- Discontinuation of Prolia should be considered while evaluating the patient for atypical femoral fractures.

The product information will be updated. Furthermore, a letter has been sent to doctors and other healthcare professionals to inform them about the risk of atypical femoral fractures during the use of Prolia® (see the letter *here*, in Danish only).

Indication for Prolia®
Used for the treatment of osteoporosis in postmenopausal women with an increased risk of fractures and the treatment of bone loss associated with hormone ablation in men with prostate cancer with an increased risk of fractures.

The European Medicines Agency (EMA) is reviewing benefits and risks of the nicotinic acid analogue acipimox (Olbetam®) for the treatment of elevated cholesterol levels

In January 2013, the drug Tredaptive®, which contains a combination of nicotinic acid and laropiprant, was withdrawn from the European market due to an assessment that the risks of this product for the treatment of elevated cholesterol levels outweigh the benefits.

The assessment was based on the results from a large, long-term study with more than 25,000 patients comparing the effects of adding Tredaptive® to statins. The results showed that adding Tredaptive® did not provide any additional benefit in reducing the risk of serious vascular events compared with statins alone. Furthermore, a higher frequency of various serious, but non-fatal adverse reactions was seen in patients taking Tredaptive® in addition to statins. The adverse reactions included bleedings, muscle weakness, infections and diabetes, among others. In the study, the adverse reactions were assessed to be caused primarily by the nicotinic acid component in Tredaptive®.

In the light of these data, assessment of the benefits and risks of mono-component drugs containing nicotinic acid (or analogues thereof) for the treatment of elevated cholesterol levels is also relevant. Therefore, Denmark has asked the European Pharmacovigilance Risk Assessment Committee (PRAC) to assess the benefit/risk ratio for these products. On the Danish market, Olbetam® is the only drug containing the nicotinic acid analogue acipimox.

Read more about the *withdrawal of Tredaptive®* (in Danish only).

Read also *the news of the review of nicotinic acid* on the EMA's website.

Furthermore, the EMA will start reviewing:

Domperidone (Motilium® etc.), a propulsive, antiemetic drug, in order to assess the potential risk of cardiac disorders

Read the *news of the review* on the EMA's website.

The subject is also covered in *Danish Pharmacovigilance Update from November 2011*.

Benefits and risks of the octocog alpha products Kogenate® and Helixate® in previously untreated children with haemophilia A
The review is based on the results from a new study: Gouw S et al.: Factor VIII products and inhibitor development in severe Hemophilia A, N Engl J Med 2013;368:231-9. Read the article *here*.

Read the news of the review on the *EMA's website*.

Nulojix® (belatacept) and increased incidence of acute graft rejection in certain specific cases

Following marketing of Nulojix® (belatacept), an increased incidence of acute graft rejection has been observed after use of Nulojix® when corticosteroids are tapered quickly in patients with a high immunological risk of acute rejection. There are no reports of such cases in Denmark.

Use of Nulojix® in conjunction with basiliximab induction, mycophenolate mofetil and corticosteroid taper to 5 mg/day by week 6 post-transplant has been associated with an increased incidence of acute rejection, particularly grade III rejection. These grade III rejections occurred in patients with 4-6 human leukocyte antigen (HLA) mismatches. The corticosteroids were tapered faster than in the clinical studies supporting the approval of Nulojix®.

As a doctor you should be aware of the following:
Corticosteroid tapering should be implemented slowly and cautiously, particularly in patients with 4-6 HLA mismatches.

Updating of the summary of product characteristics
The product information for Nulojix® will be updated with a warning of the risk of acute graft rejection when corticosteroids are tapered quickly. Also, information about the corticosteroid doses used and the populations participating in the clinical studies supporting the approval of Nulojix® will be added.

Furthermore, a letter (DHPC, Direct Healthcare Professional Communication) with the above-mentioned information has been sent to the relevant hospital departments.

Indication for Nulojix®
Nulojix, in combination with corticosteroids and a mycophenolic acid (MPA), is indicated for the prophylaxis of graft rejection in adult renal transplant patients (see section 5.1 in the summary of product characteristics for data on renal function). It is recommended to add an interleukin (IL)-2 receptor antagonist for induction therapy to the belatacept-based regimen.

Risks associated with off-label use of NeuroBloc® (botulinum toxin type B)

Rare cases of toxin spread far from the injection site following treatment with NeuroBloc® (botulinum toxin type B) have been reported in the EU. There are no reports of such cases in Denmark.

As a doctor you should be aware of the following:

- NeuroBloc® is approved only for the treatment of cervical dystonia (torticollis) in adults. It should be used in accordance with the approved indication.
- In case of use outside the indication, the safety profile for NeuroBloc® has not been established. All patients should be warned of the signs and symptoms of toxin spread and advised to seek medical attention immediately if they experience breathing difficulties, choking, or swallowing difficulties.
- NeuroBloc® should not be used in children.
- NeuroBloc® is contraindicated in patients known to have a neuromuscular disease (e.g. amyotrophic lateral sclerosis or peripheral neuropathy) or neuromuscular transmission disorders (e.g. myasthenia gravis or Lambert-Eaton syndrome).

When NeuroBloc® is used for the approved indication and according to the recommendations for administration in the product information, the majority of the adverse reactions attributable to toxin spread are of a self-limiting and less serious nature, such as dry mouth, dysphagia, blurred vision and abnormal accomodation.

In February this year, a letter was sent to doctors and other healthcare professionals to inform them about the risk of toxin spread associated with the use of NeuroBloc® (see the letter *here*, in Danish only).

There are also reports of toxin spread far from the injection site following treatment with other types of botulinum toxins.

Indication for NeuroBloc®
Used for the treatment of cervical dystonia (torticollis) in adults.

Childhood vaccinations and suspected adverse reactions in the third and fourth quarter of 2012

One of the Danish Health and Medicines Authority's focus areas is potential adverse reactions (ADRs) from vaccinations. A vaccination panel has been established. The panel meets quarterly to assess the suspected ADRs reported.

Estimated coverage in Denmark of each individual vaccine[1]:

DTaP-IPV booster vaccination	85.1-86.3%
DTaP-IPV/Hib1	94.1%
DTaP-IPV/Hib2	90.6%
DTaP-IPV/Hib3	90.7%
MMR1	90.7%

The participation in the PCV (pneumococcal vaccination), HPV (human papilloma virus) vaccination, DTaP-IPV/Hib vaccination and MMR vaccination, respectively[2]:

a. During the period 2007-2010, the participation was 92% for the first PCV, 81-92% for the second PCV and 79-90% for the third PCV.
b. For HPV, the participation for girls born in 1996, 1997 and 1998 was 88-90%, 83-86% and 76-82% for the first, second and third vaccinations, respectively.
c. For DTaP-IPV/Hib, the coverage for the years of birth 2002-2010 has been calculated to be 89-94%, 88-93% and 87-91% for the first, second and third vaccinations, respectively.
d. For the first MMR vaccination, the participation for the years of birth 2007-2009 is 88%, whereas the participation for the second MMR vaccination is lower. However, since the immunisation programme has been changed to offer the second MMR vaccination at the age of 12 instead of the age of four, the participation per year of birth varies from 69-88%. This is below the target of 95%.

At present, there are no data on the number of persons receiving vaccines from the immunisation programme later in life.

Third quarter of 2012

In the third quarter, the Danish Health and Medicines Authority (DHMA) received a total of 45 reports comprising a total of 138 suspected ADRs and with an increasing trend as compared to the 36 reports comprising 100 suspected ADRs received in the second quarter. Of the reports received by the DHMA in the third quarter of 2012, 17 comprised suspected ADRs classified as serious[3].

The majority of the suspected ADRs reported are well-known, such as local reactions at the injection site and general malaise. General symptoms such as fatigue, fever, pain, local irritation, rash and temporary changes of the skin accounted for approx. 50% of the suspected ADRs reported.
The vaccines were given to persons aged 0-53 years, and 17 (37%) of the reports concerned persons over the age of 18.
Table 1a below shows the distribution according to seriousness of the reports submitted. A report may comprise more than one suspected ADR, and Table 1b shows the number of suspected ADRs reported for each individual vaccine.

Reported suspected unexpected ADRs classified as non-serious include, e.g., hyperhidrosis, elevated liver values and nodules.

Table 1a. Distribution of the reports according to seriousness.

Vaccine	Serious	Non-serious	Total
DTaP-IPV booster	1	2	3
DTaP-IPV/Act-Hib	1	0	1
Prevenar13 and DTaP-IPV/Act-Hib	6	4	10
Prevenar	0	2	2
Gardasil	6	16	22
Gardasil and Priorix	0	1	1
Priorix	3	3	6
Total	**17**	**28**	**45**

1) The Statens Serum Institut, National Institute for Health Data and Disease Control, EPI-NEWS, No. 20, 2012.
2) The Statens Serum Institut, National Institute for Health Data and Disease Control, EPI-NEWS, No. 21, 22, 23a and 23b, 2012.
3) A 'serious adverse reaction' is defined as an adverse reaction which is fatal, life-threatening, causes or prolongs hospitalisation, or causes permanent or significant disability or inability to work, or which is a congenital anomaly or birth defect. This means that any person who has, e.g., been briefly hospitalised (e.g., in a paediatric admission ward) with an adverse reaction will have been classified as a patient with a serious adverse reaction.

Table 1b. The number of suspected ADRs reported for each individual vaccine.

Vaccine	Number of ADRs
DTaP-IPV booster	8
DTaP-IPV/Act-Hib	21
Prevenar13	15
Prevenar	4
Gardasil	72
Priorix	18
Total	**138**

Below are detailed descriptions of the reports comprising suspected serious ADRs.

DTaP-IPV/Act-Hib and Prevenar13

1. A boy developed fever on the day of the vaccination. He developed febrile convulsions, a known ADR, and due to the temporal association between the convulsions and the vaccination, a correlation is deemed possible.
2. A girl developed fever and febrile convulsions on the day of the vaccination. Due to the temporal association between the convulsions and the vaccination, a correlation is deemed possible.
3. An expremature girl developed fever and a susceptibility to apnoea on the day of the vaccination. This has been described earlier in prematures (J Pediatrics; 153(3); 2008:429-431). Therefore, a correlation is deemed possible.
4. A girl developed febrile convulsions on the day after vaccination. Due to the temporal association between the convulsions and the vaccination, a correlation is deemed possible.
5. A girl developed granulomas on both thighs after vaccination. An epicutaneous patch test was positive for aluminium, and the Danish Patient Insurance Association has awarded a compensation corresponding to a 5% degree of permanent injury. Aluminium sensitisation is theoretically possible, as the vaccine contains aluminium. Therefore, a correlation with the vaccination is deemed possible.
6. A girl developed petechia symmetrically around both knees and around the malleoli and foot soles. The reporting doctor agrees that this is a case of discoloured leg syndrome after reading the article: Kemmeren et al: Discolored leg syndrome after vaccination (Eur J Pediatr 2009; 168: 43-50). Thus, a correlation is deemed possible.

DTaP-IPV/Act-Hib

7. A boy developed complex convulsions on the day after vaccination. It has not been possible to obtain additional information. Provided the convulsions occurred in association with fever, a correlation is deemed likely, since this is a known ADR. Afebrile convulsions are not immediately attributable to the vaccination.

DTaP-IPV booster

8. A boy developed an antibiotic-requiring infection at the vaccine injection site. The report specifies that this is a case of overdose. However, that has subsequently been disconfirmed. A correlation is deemed possible.

Gardasil®

9. A girl experienced a gradual onset of depression following the first vaccination with Gardasil®. The literature does not support a correlation between onset of depression and vaccination with Gardasil, and depression is relatively frequent (2-8%) in teenagers. Therefore, a correlation is deemed less likely.
10. A young woman developed swelling of the mouth, throat and tongue immediately after vaccination. She was treated for anaphylaxis in an emergency room. A correlation is deemed possible.
11. A young woman developed dizziness and breathing difficulties five minutes after vaccination. She was treated for anaphylaxis, and a correlation is deemed possible.
12. A young woman became unwell and dizzy immediately after vaccination. She was treated for anaphylaxis. Based on the medical history, it cannot be ruled out that this woman had a vasovagal reaction. A correlation with the vaccination is deemed possible.
13. A young woman was vaccinated and fainted a few minutes later. She developed a grand mal seizure. Assessment did not provide an explanation. According to the summary of product characteristics, fainting followed by convulsions occurs as an ADR of unknown incidence. Therefore, a correlation is deemed possible.
14. A young woman developed sensory disturbances in hands and feet, which were initially suspected to be the first symptoms of Guillain-Barré syndrome. However, this was subsequently disconfirmed, and she received her second dose of Gardasil® without problems. A correlation is deemed less likely.

Priorix®

15. A girl developed long-lasting febrile convulsions four days after vaccination. The summary of product characteristics lists febrile convulsions as a rare ADR of the vaccine. Therefore, a correlation is deemed possible.
16. A boy developed febrile convulsions nine days after vaccination. The summary of product characteristics lists febrile convulsions as a rare ADR of the vaccine. Therefore, a correlation is deemed possible.
17. A girl developed nodules and subsequently tested positive for aluminium allergy. The Danish Patient Insurance Association has awarded a compensation. It cannot be ruled out that use of Priorix® may lead to nodules. However, since Priorix® does not contain aluminium, a correlation between use of this vaccine and the allergy is deemed less likely.

Conclusion for the third quarter of 2012

There has been a moderate rise in the number of reports received in the third quarter as compared to the 36 reports comprising 100 suspected ADRs in the second quarter.

As of 1 April and the rest of 2012, vaccination against measles was available free of charge in Denmark. The offer applied to adults born in 1974 or later and comprised persons above 18 years of age who had not had measles and had not previously been vaccinated against measles. There are no reports of ADRs in association with vaccination with Priorix® in young adults who were offered free vaccination during this period. This was also the case in the second quarter.

Table 2a. Distribution of the reports according to seriousness.

Vaccine	Serious	Non-serious	Total
Td booster	3	2	5
Td booster and Gardasil		1	1
DTaP-IPV booster	0	7	7
DTaP-IPV/Act-Hib	16	5	21
Prevenar13 and DTaP-IPV/Act-Hib	5	4	9
Prevenar	0	1	1
Gardasil	3	36	39
Gardasil and Priorix	1		1
Priorix	4	6	10
The tetanus vaccine SSI	1	0	1
Pneumovax	0	4	4
Total	**33**	**66**	**99**

As of 27 August 2012, HPV vaccination (cervical cancer vaccination) has been offered free of charge to all girls born in 1985-1992. All free HPV vaccinations must be given before the end of 2013. The rise in the number of reports may be due to the receipt of more ADR reports for Gardasil® in adults. Of these, there are reports of serious ADRs in five patients, including two anaphylaxis-like reactions.

The other suspected ADRs reported were largely well-known, primarily with local reactions at the injection site, general malaise, fever and pain.

Fourth quarter of 2012

In the fourth quarter, the Danish Health and Medicines Authority (DHMA) received a total of 99 reports including a total of 325 suspected ADRs, which is a rise as compared to the third quarter (45/138).

Of the reports received by the DHMA in the fourth quarter of 2012, 33 comprised suspected ADRs classified as serious[4]. Among these were cases of vaccine failure (pertussis) in 11 children.

The majority of the suspected ADRs reported were well-known, such as local reactions at the injection site and general malaise. Thus, general symptoms such as fatigue, fever, pain, local irritation, rash and temporary changes of the skin accounted for approx. 50% of the ADRs reported.

The vaccines were given to persons aged 0-86 years, and 43% (43/99) of the reports concerned persons over the age of 18. The adults had most frequently received Gardasil®. Also, one of these adults had been vaccinated with Td booster. Furthermore, four had received Td booster only, one had received Priorix®, and four others had received Pneumovax.

4) A 'serious adverse reaction' is defined as an adverse reaction which is fatal, life-threatening, causes or prolongs hospitalisation, or causes permanent or significant disability or inability to work, or which is a congenital anomaly or birth defect. This means that any person who has, e.g., been briefly hospitalised (e.g., in a paediatric admission ward) with an adverse reaction will have been classified as a patient with a serious adverse reaction.

Table 2a shows the distribution according to seriousness of the reports submitted. A report may comprise more than one suspected ADR, and Table 2b shows the number of suspected ADRs reported for each individual vaccine.

Reported suspected unexpected ADRs classified as non-serious include, e.g., acne, alopecia and discoloured teeth.

A total of 16 children had suspected ADRs in the form of nodules or granuloma at the injection site, including eight following vaccination with DTaP-IPV/Act-Hib. Aluminium allergy was reported in a total of five children.

Below are detailed descriptions of the reports comprising suspected serious ADRs.

DTaP-IPV/Act-Hib and Prevenar13

1. A patient developed aluminium allergy and granuloma formation. The Danish Patient Insurance Association has awarded a compensation.
2. A girl developed fever and a rash and became 'unresponsive to stimuli'. Based on the medical history, non-convulsive fever cramps must be suspected. A correlation is deemed possible.
3. A girl developed apnoea, altered state of consciousness and paleness approx. five hours after vaccination. A hypotonic-hyporesponsive episode must be suspected, and a correlation is deemed possible.
4. A girl developed a high fever and a rash on the day of the vaccination. Both of these suspected ADRs disappeared within a few hours.
5. A boy developed febrile convulsions approx. 12 hours after vaccination. A correlation is deemed possible.
6. A girl developed fever and febrile convulsions on the day of the vaccination. The convulsions followed an erroneous administration of a 20 mg Primperan suppository (adult dose). Primperan may cause neurological symptoms, but rarely convulsions. A correlation with the vaccination is deemed possible.

DTaP-IPV/Act-Hib

7. A total of 11 cases of pertussis in vaccinated children have been reported. It is known that DTaP-IPV/Act-Hib does not provide full protection against pertussis (approx. 70-80%). The vaccine failures occurred in 2010, 2011 and 2012 (1, 5 and 5 cases, respectively).
8. A boy developed idiopathic thrombocytopenic purpura (ITP) one week after vaccination. There are reports of rare cases of ITP following DTaP-IPV/Act-Hib vaccination, and a correlation is deemed possible.
9. Two girls developed granulomas after vaccination. An epicutaneous patch test was positive for aluminium allergy in both girls, and a correlation is deemed possible.
10. A boy developed a rash/eczema at the injection site. He had a positive skin test for aluminium allergy, and the Danish Patient Insurance Association has awarded a compensation. A correlation is deemed possible.

DTaP-IPV booster, Gammagard, Havrix

11. An immune system disease of unknown nature and a mucosal disease were reported after vaccination. The vaccinee suspected the cause to be the aluminium content of the vaccine. Data are limited, but based on the documentation available, a correlation is deemed less likely.

Td booster, Havrix, Meningovax A+C, Stamaril

12. Six months after vaccination, a person developed general neurological complaints (pain, palpitations) and chronic urticaria. A correlation is deemed less likely by the Danish Patient Insurance Association due to lack of temporal association. This conclusion is maintained.

Td booster, Twinrix

13. Four days after vaccination, a man developed muscle pain and paraclinically elevated creatinine

Table 2b. The number of suspected ADRs reported for each individual vaccine.

Vaccine	Number of ADRs
Td booster	21
DTaP-IPV booster	15
DTaP-IPV/Act-Hib	94
Prevenar13	40
Prevenar	6
Gardasil	107
Priorix	23
The tetanus vaccine SSI	1
Pneumovax	12
Total	**325**

kinase.He was diagnosed with myositis. The literature describes case reports following use of both DTa-IPV vaccine and hepatitis B vaccine. Due to the temporal association with the vaccination, a correlation is deemed possible.

The tetanus vaccine SSI

14. A person reportedly developed a systemic allergic reaction after tetanus vaccination. The person has a known latex allergy, and a correlation is deemed possible.

Gardasil®

15. A pregnant woman – around ten days pregnant – was vaccinated and then had a miscarriage in week six. Approx. 10-20% of clinically acknowledged pregnancies result in spontaneous miscarriage. The literature describes no reports of an increased incidence of miscarriages after HPV vaccination. Therefore, a correlation is deemed less likely.
16. Five hours after the second HPV vaccination, a woman developed dizziness and malaise and then fainted. It was interpreted as a case of anaphylaxis, and a correlation is deemed possible.
17. A woman developed diarrhoea and vomiting with hypokalaemia and altered liver values. Diarrhoea is not a known ADR, and it is deemed most likely that the temporal association with the vaccination is coincidental.

Gardasil® and Priorix®

18. On day 12 and 19 after vaccination, respectively, a girl developed a petechial rash in her face and on her shoulders. Her haematology was normal. On day 25 after vaccination, she developed a local severe swelling at the injection site. A correlation is deemed possible – most likely with Priorix®.

Priorix®

19. A girl developed febrile convulsions eight days after vaccination, and a correlation is deemed possible.
20. A girl developed febrile convulsions seven days after vaccination, and a correlation is deemed possible.
21. A girl developed a granuloma after vaccination and subsequently tested positive for aluminium allergy. It cannot be ruled out that use of Priorix® may lead to nodules. However, since Priorix® does not contain aluminium, a correlation between use of this vaccine and the allergy is deemed less likely.
22. A boy developed reactive arthritis two days after vaccination. According to the summary of product characteristics, arthritis may occur after vaccination. Therefore, a correlation is considered possible.

Conclusion for the fourth quarter of 2012

There has been a rise in the number of reports received in the fourth quarter as compared to the third quarter of 2012.

As of 3 August 2012, if a marketing authorisation holder for a medicinal product for human use becomes aware of a suspected ADR observed in Denmark, the marketing authorisation holder is obliged to report the ADR to the DHMA. Prior to that date, the marketing authorisation holder only had to report suspected serious ADRs.

The changed rules for reporting to the DHMA, together with the rise in the number of reports of ADRs for Gardasil® in adults and the reports concerning pertussis in vaccinated children, can explain the rise in the number of reports received in the fourth quarter of 2012.

The DHMA has received reports of five cases of aluminium allergy, a number of which were reported via the Danish Patient Insurance Association. The children were vaccinated during the period 2008 to 2011.

The DHMA has not received reports of suspected ADRs in adults vaccinated with Priorix® during this period. As of 1 April and the rest of 2012, vaccination against measles was available free of charge in Denmark. The offer applied to adults born in 1974 or later and comprised persons above 18 years of age who had not had measles and had not previously been vaccinated against measles.

The other suspected ADRs reported were largely well-known, primarily with local reactions at the injection site, general malaise, fever and pain.

The DHMA has contacted the marketing authorisation holder for the DTaP-IPV/Act-Hib vaccine and asked for a report on the subject 'Granuloma formation and aluminium sensitisation due to vaccination with aluminium adjuvant vaccines' and a suggestion for an update of summaries of product characteristics for aluminium adjuvant vaccines. The DHMA has taken this initiative based on decisions received from the Danish Patient Insurance Association describing that aluminium allergy is a known ADR of the above-mentioned vaccine.

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