1.1. Reports associated with vaccination against Influenza A (H1N1)

Background

In November 2009, the vaccination campaign against Influenza A (H1N1) started in the Netherlands. Patients with risk factors for asthma, cardiovascular diseases, diabetes mellitus, renal disease as well as immune compromised patients, pregnant women in the 2nd or 3rd trimester and people aged over 60 years, were vaccinated by their general practitioner with the influenza vaccine Focetria®. With the exception of pregnant women, the group of people vaccinated with Focetria® also had an indication to be vaccinated with the seasonal flu vaccine in early October. Health care workers with direct patient involvement were vaccinated by health institution and arbo doctors, who also used Focetria®. For the vaccination of children from the age of 6 months to 5 years, and the close relatives of children aged less than 6 months the influenza vaccine Pandemrix® was used.
Focetria contains Influenza virus surface antigens (haemagglutinin and neuraminidase)* of A/California/7/2009 (H1N1)v like strain (X-181). In this vaccine MF59C.1 was used as adjuvant. [1] 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. [2]
Next to processing and analysing the spontaneous reports concerning Focetria® and Pandemrix®, Lareb also conducted a prospective cohort study among patients vaccinated with Focetria® by their general practitioners.
The aim of this report is to provide an overview of the data Lareb received on both vaccines during this vaccination campaign.

Process

Health Care professionals and patients were advised to use a dedicated reporting form on the Lareb website in order to submit reports on both vaccines used for vaccination against Influenza A (H1N1).
Adverse events could be selected from a predefined list of events, which was based on all events previously submitted to Lareb on vaccines. In addition it was possible to describe the event as free text.
Batch numbers were provided by the RIVM together with the town and venue where vaccinations took place. This enabled a correct, automatic selection of the batch number of the vaccines in the majority of the cases.
All reports were individually assessed and the causal relationship between vaccine and event was assessed. For serious reports and reports concerning events for which EMEA expressed special interest in (Adverse Events of Special Interest – AESI) [3], the reporter was contacted to obtain additional information about the event.
All incoming reports were checked on a daily basis for seriousness and the presence of AESIs. Both groups were handled with priority. On a weekly basis all serious reports were discussed together with a representative of the RIVM.

Number of reports

From 1 November 2009 till January 5th 2010, Lareb received 7,156 reports of adverse events possibly related to the administration of the vaccine. 2,667 reports were related to the vaccine Focetria®, 4,489 reports to the vaccine Pandemrix®. The number of reports on both vaccines received on a daily basis is shown in figure 1.

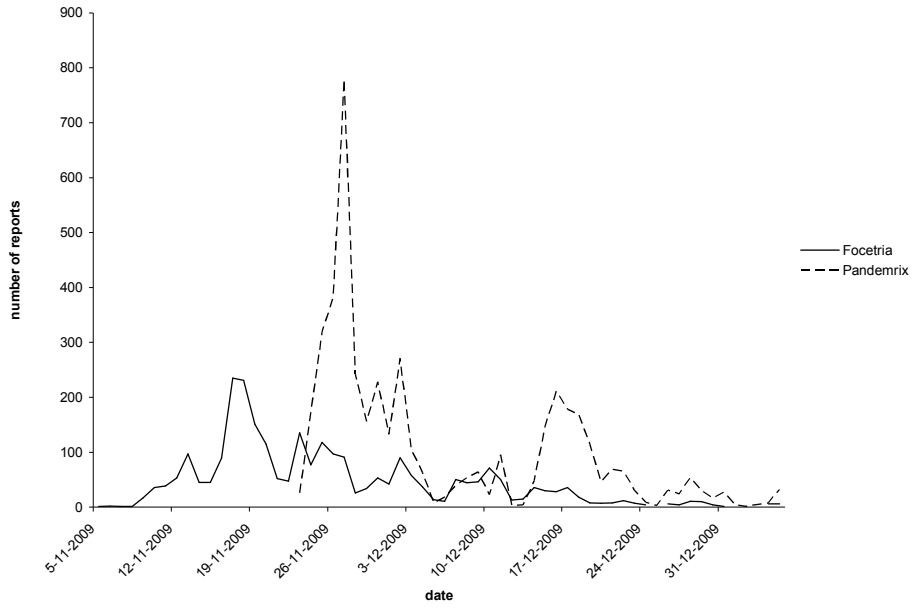

Figure 1. Number of reports on both Pandemrix® and Focetria® over time.

Monitoring for differences between batches

Since Lareb received information about the batch numbers of the administered vaccines, possible differences between the different batches involved was continuously monitored for. We focused on four possible aspects:

- Adverse events related to the reactogenicity of the vaccines.
- Reports of infections (in cases of a possible contamination of one of the batches)
- Seriousness of the events
- Given the large number of reports on fever, batches were also compared for this adverse event

The number of reports related per batch were compared to all other reports received on the influenza vaccines present in the Lareb database and expressed as a reporting odds ratio with 95% confidence interval. An example of the comparison on the batches is shown in figure 2.

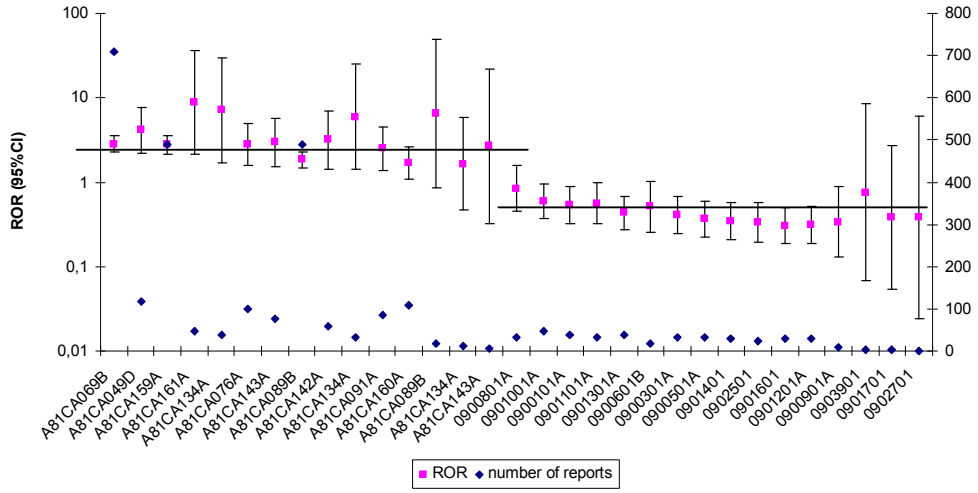

Figure 2. Comparison between the batches of Pandemrix® (left) and Focetria® (right) in respect to number of reports on adverse events related tot the reactogenicity of the vaccines. On the left axis the extent of the ROR is displayed, on the right axis the total number of reports.

Reports of adverse events on Focetria

Lareb received 2,667 reports of suspected adverse events to the vaccine Focetria®. This vaccine is in the vaccination campaign mainly used by doctors, health institutions and company doctors. 77 of these reports led to admission or observation in a hospital.
The European Medicines Agency EMEA required special attention for a number of possible adverse reactions of the pandemic vaccines. Among these, special attention was asked for neuritis, convulsions, severe allergic reactions, encephalitis, vasculitis, Guillain Barré syndrome, Bell's Palsy, demyelination and vaccination failure. For this reason, these effects are separately discussed below. During the vaccination campaign the EMEA drew special attention on the occurrence of intra-uterine death following vaccination. Therefore the reports received on this adverse event are mentioned below as well.

Neuritis
Three reports of neuritis possibly associated with Focetria® were reported. The age of the patients varied from 30 to 70 years. The latency times were six hours, 12 hours and six days. The causal relation was considered 'unlikely' in one patient and possible in the two others. Two patients had not yet recovered at the time of reporting. The outcome is unknown for the third patient.

Convulsions
Lareb received 23 reports of (febrile) convulsions after vaccination with Focetria®. In seven cases this was reason for hospitalization. Among these cases there were three children in the age 2 to 4 and 5 to 7 (two children) who were admitted to hospital due to febrile convulsions. The time between administration of the vaccine and the occurrence of the convulsion varied from two hours to four days

Severe allergic reactions
Lareb received six reports of a possible anaphylactic reaction. The time between administration of the vaccine and the occurrence of the reaction varied from 12 minutes to one day. One of these patients had an anaphylactic shock; the causal

relationship between the vaccine and the adverse event in this patient was assessed as 'probable'.

Encephalitis
Lareb received one report of encephalitis and subsequent cerebral edema following administration of Focetria® in a female in the age category 21-30. Headache occurred two days after vaccination, the collapse and hospital admission four days after administration. Another report of encephalitis was received from the registration holder of Focetria®. This report concerned a man in the age category 70 and older with herpes encephalitis and pyrexia eight days after administration of the vaccine. A causal relationship was considered unlikely due to positive herpes simplex serology.

Vasculitis
Two cases of leucocytoclastic vasculitis were reported in association with Focetria®. Both patients were male with an age in the category 51-60 and older than 70 years. The time between administration of the vaccine and the occurrence of the vasculitis was two and four days. Both causal relations were rated as probable.

Guillain Barré syndrome
Six cases of Guillain Barré syndrome (GBS) following vaccination with Focetria® were reported to Lareb. Three of these were received through a study on GBS performed by the Erasmus Medical Centre in cooperation with the Dutch Centre for Disease Control (RIVM) and Dutch Medicines Agency (CBG). The time between vaccination and the occurrence of the first symptoms of GBS varied from one day to three weeks. In two cases a possible other cause than the vaccine was reported. Two patients needed mechanical ventilation.

Demyelination
Besides the reports of Guillain Barré syndrome, Lareb received three reports of aggravated multiple sclerosis with latencies between two hours and one day after vaccination. Causality assessment is difficult in these cases due to the natural fluctuation of multiple sclerosis.

Bell's Palsy
Three cases of suspected Bell's Palsy were reported to Lareb. The latency period in these patients was twice one day and once 11 days after administration of Focetria®.

Vaccination failure
No reports of confirmed vaccination failure were reported.

Intra-uterine death
Eight reports of intra-uterine fetal death (IUFD) following vaccination with Focetria® were reported to Lareb. The age of the women varied from 21 to 41 years (average: 33 years). The gestational period ranged from 13 to 38 weeks. A causal relationship was considered unlikely in all these women. According to the Teratology Information Service of the RIVM the incidence of IUVD in the Netherlands is 7 of 1000 pregnancies, which could be higher due to underreporting. In most cases no cause for the IUFD is found.

Reports of death
Till January 5th, Lareb received 14 reports of the death of a patient shortly after vaccination with Focetria®. The time between vaccination and death varied from several hours to two days. The age of the patients varied from 28 to 90 years; ten people were older than 60 years. In all these patients, an underlying illness or risk

factors were present that most probably has caused the death. On what is currently known about these reports, the causal relation between administration of the vaccine and death is unlikely.
Given the large number of the Dutch population, especially elderly and people with risk factors, that was vaccinated, it could be expected that sudden death occurred in this group, which is not related to the vaccination.

Reports concerning people that died are mentioned in table 1.

Table 1. Reports of death after vaccination with Focetria.

Patient, Number, Sex, Age category, Source	**Suspected Drug**	**Concomitant Medication**	**Suspected adverse drug event**	**Time to onset, Medical history**
A 92928 M, 61 to 70 General Practitioner	focetria	lisinopril diazepam hydrochlorothiazide	sudden death	12 hours hypertension smoker alcohol abuse adipositas
B 92946 F, 21 to 30 General Practitioner	focetria lacosamide tablet epilepsy	oxcarbazepine risperidone desogestrel oxazepam hydrochlorothiazide levetirazetam triamterene desloratidine clonazepam lactulose	cardiac death	2 days congenital anomaly NOS Down's syndrome Fallot's tetralogy Pulmonary artery stenosis congenital
C 92984 M, Physician	focetria	furosemide	coughing blood sudden death	5 hours alcohol abuse cardiac disorder NOS
D 93026 F, 70 and older General Practitioner	focetria	spironolactone, simvastatin pantozole bumetanide temazepam gliclazide epoetin acenocoumarol atenolol	sudden death	8 hours aortic valve replacement depression hypertension diabetes mellitus heart failure impaired renal function
E 93084 M, 70 and older General Practitioner	focetria	salmeterol/fluticasone tiotriopium acetylcysteine	sudden death	2 days syncope chronic obstructive pulmonary disease
F 93120 M, 70 and older General Practitioner	focetria acenocoumarol 1mg	sotalol metformin pantoprazole gliclazide nifedipine peridopril	cerebral hemorrhage death	2 days diabetes mellitus myocardial infarction cerebrovascular accident malignant neoplasm of sigmoid colon hypertension
G 93255 M, 51 to 60 General Practitioner	focetria	atorvastatin, metoprolol acetylsalicylic acid	myocardial infarction death	4 hours percutaneous transluminal coronary angioplasty backache
H 94177 F, 70 and	focetria	metformin	ventricular fibrillation	1 hour diabetes mellitus

older General Practitioner			death	
I 94273 M, 70 and older General Practitioner	focetria		death	2 days COPD GOLD IV/IV rheumatoid arthritis meningioma bladder cancer cardiac failure atrial fibrillation pulmonary embolism coronary artery bypass
M 98812 M, 70 and older General Practitioner	focetria		death	12 hours no medical history
N,99261 M, 61 to 70, General Practitioner	focetria glimepiride 3 mg 1dd1	not reported	sudden death	6 days end stage kidney disease, diabetes mellitus acute coronary syndrome coronary artery bypass
O,100826 M,51 to 60, General Practitioner	focetria	metformin simvastatin	sudden death	21 hours diabetes mellitus
P,101077 F,70 and older, General Practitioner	focetria	temazepam simvastatin dextran/hypromellose diltiazem valsartan/hydrochlorothiazide metoprol	sudden death	12 hours hypertension angina pectoris hyperlipidemia claudication intermittent triple vessel disease third degree AV block
Q,101330 F,51 to 60, General Practitioner	focetria	lactulose fenoterol/ipratropium oxazepam morphine ipratropium fentanyl	sudden death	5 days end stage COPD

Other reports

Most of the other reports concern adverse events directly related to the administration or the reactogenicity of the vaccine. The top 10 of reported adverse events on Focetria® is shown in table 2.

Table 2. Most reported adverse events associated with the use of Focertria®

Reported adverse event	Number of reports
Headache	536
Pyrexia	364
Injection site pain	341
Myalgia	291
Nausea	275
Fatigue	246
Flu like illness	213

Dizziness	204
Diarrhoea	169
Vomiting	139

Prospective cohort study Focetria®

During the vaccination campaign, Lareb followed 3,780 people who had been vaccinated by their general practitioner with Focetria®. In this study (called 'Vaccinmonitor'), the vaccinated people received surveys over a three month period of time to examine the possible adverse events and the course of these complaints. 3,570 surveys were completed as part of this study, which is 94.4% of the people that were asked to complete a survey. 27.6% of the vaccinated people indicate that they experienced a mild adverse event. This figure has remained stable since the beginning of the study.

A second survey has been sent to 3,551 people who completed the first survey. This second survey has been completed by 3,373 persons (95.0%). 90.8% of these people indicated they took the second vaccination. One reported adverse event in this study was considered as serious. A third survey is scheduled three months after the first survey.

Up to January 5t two reported adverse events in this study were considered as serious. One patient suffered from an aggravation of MS, the other patient from atrial fibrillation. Both events led to hospitalization of the patient. The patients have recovered. Both patients gave permission in the survey to be contacted for follow-up information.

Reports of adverse events on Pandemrix®

Till January 5th, Lareb received 4,489 reports of suspected adverse events on this vaccine. In 69 patients the adverse event led to observation or admission in a hospital.

Neuritis
No cases of neuritis in association with the use of Pandemrix® were received by Lareb.

Convulsions
In 77 cases, convulsions (of which 59 were febrile convulsions) have been reported; 38 patients were admitted to hospital for observation, in 27 cases this was because of a febrile convulsion. Based on the current available information, all children have recovered.

Severe allergic reactions
Lareb received four reports of anaphylactic reaction after vaccination with Pandemrix. All patients have recovered. One of the patients was admitted to hospital for 24 hours for observation.

Encephalitis
No reports of encephalitis in association with Pandemrix® were received by Lareb.

Vasculitis
No reports of vasculitis in association with Pandemrix® were received by Lareb.

Guillain Barré syndrome
One case of Guillain Barré Syndrome (GBS) following seven days after administration of Pandemrix® was reported to Lareb. It concerned a female in the age category 70 and older with no GBS in the past. No other causes for the GBS were found. The patient was treated with immunoglobulines and needed mechanical ventilation. It was confirmed that this patient used Pandemrix®.

Demyelination
Except for the case of GBS, no other demyelinating diseases were reported to Lareb following administration of Pandemrix®.

Bell's Palsy
Bell's Palsy was not reported to Lareb in association with this vaccine.

Vaccination failure
No reports of confirmed vaccination failure were reported.

Intra-uterine death
No reports of intra-uterine fetal death (IUFD) following vaccination with Pandemrix® were reported to Lareb.

Reports of death
Lareb received two reports of death of a child in the days after vaccination with Pandemrix®. In both children a causal relationship with the vaccine was improbable based on the currently known information. A boy in the age category 2 to 4 died one and a half day after vaccination. At that time he had a fever and vomited. He was confirmed with an Influenza A (H1N1) infection. In addition, Lareb received a report of a boy in the age category 2 to 4, who died five days after vaccination. During hospital admission, a dilated cardiomyopathy was found, which must have been present before vaccination, according to the treating physician.

Other reports
Besides the above mentioned reports, most of the other received reports concern non-serious adverse events. The top 10 of reported adverse events on Pandemrix® is shown in table 3.

Table 3. Most reported adverse events associated with the use of Pandemrix

Reported adverse event	Number of reports
Pyrexia	3189
Injection site pain	825
Vomiting	556
Headache	379
Diarrhoea	275
Fatigue	232
Myalgia	223
Cough	199
Decreased appetite	178
Nausea	177

Reports of Pyrexia
Pyrexia is the most reported adverse drug event after vaccination with Pandemrix®. Among the reports of Pandemrix® Lareb received until January 5th, 71.0% of the reports concerned pyrexia. Slightly less than half of the reports concern a body temperature above 39 degrees Celsius. This adverse event is mentioned in the summary of product characteristics of the vaccine, but was

apparently a point of concern for the parents. Based on the high number of reports a questionnaire was sent to 896 people who reported pyrexia after the first vaccination with Pandemrix®. The response to this questionnaire was 83.1%. The time to onset of the fever was in 90.6% of the cases within one day, in 61.0% of the cases within 12 hours. The average temperature reported was 39-39.5 C. In 74.0% of the cases, the temperature normalized within two days.
724 people gave permission to send an additional questionnaire after the second vaccination. The response of this second questionnaire was 74.7%. The majority (71.5%) of those reporting pyrexia after the first vaccination decided to have their child vaccinated a second time. Of those who decided not to have their child vaccinated a second time, 67.3% stated that the adverse events encountered during the first vaccination were the reason for this.
Pyrexia during the second vaccination occurred in 57.5% of the cases. The average temperature was lower compared to the first vaccination (see figure 2). Increase in body temperature is a known side effect of this type of vaccines. Given the fact that Lareb did not follow a cohort of vaccinated children in for this vaccine, estimation of the incidence of fever was not possible. Although labeled in the SPC, the large number of reports of fever following immunisation indicates that this effect is considered bothersome by the parents.

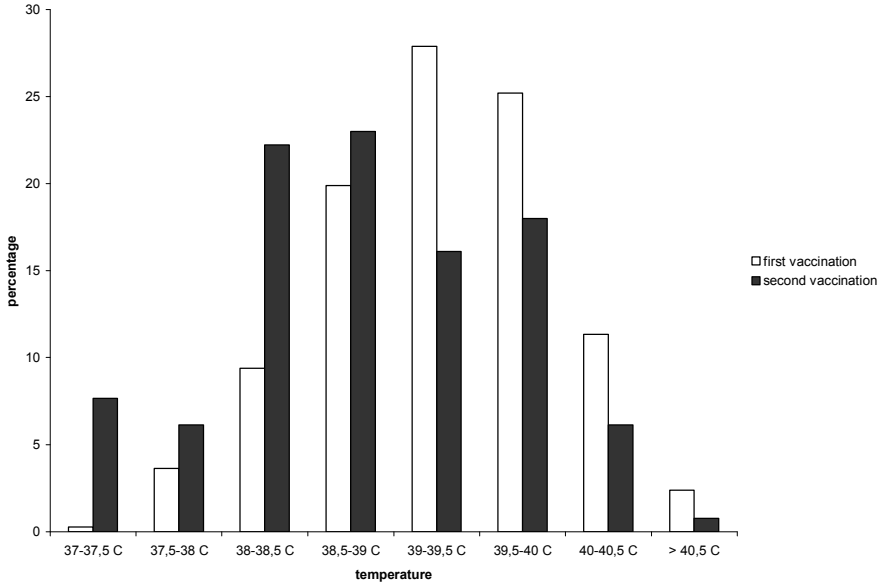

Figure 2. Highest measures body temperature during the first and second vaccination with Pandemrix®.

Conclusion

The reports received on both vaccines showed that the profile of the reported adverse events is comparable with the information provided in the SPC. The number of reports received on pyrexia indicated that this adverse event was perceived as bothersome by patients and their parents involved.

References
1. EPAR Focetria. (version date: 2009, access date: 18-12-2009) European Medicines Evaluation Agency.
2. EPAR Pandemrix. (version date: 2009, access date: 18-12-2009) European Medicines Evaluation Agency.
3. CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccine Revision 1.0. (version date: 25-6-2009, access date: 17-7-2009). (version date: 17-7-2009, access date: European Medicines Agency.

This signal has been raised on February 2010. 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).