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Monitoring Adverse Events of the Vaccination Campaign Against Influenza A (H1N1) in the Netherlands

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Abstract

Background: In November 2009, a vaccination campaign against Influenza A (H1N1) was started in the Netherlands. The accelerated registration procedure of the vaccines used in this campaign and the use of these vaccines on a large scale indicated a need for real-time safety monitoring.

Objective: To describe the processing, analysing and performing of signal detection by the Netherlands Pharmacovigilance Centre (Lareb) on reports of adverse events following immunization (AEFI) with respect to the two pandemic influenza vaccines, Focetria® and Pandemrix®, used in the Netherlands. The secondary aim is to provide a summary of the results of the safety monitoring of both vaccines.

Study Design: Description of the process of collecting information and analysis of the safety monitoring of the pandemic vaccines during the vaccination campaign against H1N1 in the Netherlands. An observational study on adverse events following immunization (AEFIs) associated with vaccines used in this campaign was conducted.

Results: The use of a dedicated web form with predefined AEFIs enabled an efficient way of processing and analysing the reports, resulting in a close to real-time monitoring of the safety of the vaccines.

From 1 November 2009 until 1 March 2010, 7534 reports concerning one or more AEFIs possibly related to the administration of both vaccines were received. 2788 of the reports related to Focetria® and 4746 of the reports related to Pandemrix®. The total time between receiving the reports and completion was longer for the serious reports (average 2.8 days) compared with the non-serious reports (average 0.8 days).

The profile of the reported adverse events is comparable with the information provided in the Summary of Product Characteristics (SPC). Differences in reported AEFIs between both vaccines may be caused by bias and confounding due to the different populations for which these vaccines have been used. No signals of possible batch-related problems were detected for either vaccine.

Conclusions: The method applied allowed for real-time monitoring for AEFIs during the mass vaccination campaign. The use of web-based forms, preferably with information on venue and used batch numbers, enabled an efficient monitoring of possible batch-related problems. No major safety issues occurred with respect to the type of reported AEFIs, or with the batches of either vaccine.

Background

The influenza pandemic that became apparent in April 2009 raised concern about possible severe implications of this viral infection when large amounts of people would be infected. Various countries decided to vaccinate people at risk for complications due to Influenza A (H1N1), and some countries considered vaccinating the whole population.[1]

In the Netherlands, the vaccination campaign against Influenza A (H1N1) started in November 2009. Patients with risk factors for asthma, cardiovascular diseases, diabetes mellitus and renal disease, as well as immune compromised patients, pregnant women in the second or third trimester and people aged over 60 years, were vaccinated by their general practitioner (GP) with the influenza vaccine Focetria®. This vaccine contains influenza virus surface antigens (haemagglutinin and neuraminidase) of A/California/7/2009 (H1N1)v-like strain (X-181). In this vaccine MF59C.1 is used as an adjuvant.[2] People with possible risk factors for complications due to influenza received an invitation to be vaccinated with Focetria® by their GP. Healthcare workers were also invited to be vaccinated with Focetria®. Vaccination of the latter group was carried out via the occupational medicine doctor involved. Focetria® was administered twice, with a recommended time of 3 weeks between the separate administrations, as recommended at that time. A total of 5 million people belonging to the first group were eligible for vaccination with Focetria.[3] Approximately 70% of these people were vaccinated.[4]

For the vaccination of children aged from 6 months to 4 years, and close relatives of children aged <6 months, the influenza vaccine Pandemrix® was used. This vaccine 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 in this vaccine.[5] This vaccine was also administered twice, with a recommended time interval of 3 weeks between the two dosages. Vaccination for this group was carried out in sport and congress centres by the Community Health Services. A total of 588 750 children received the first dosage and 490 584 children received a second dosage. Of the relatives of the children involved, 124 096 received one dosage and 101 765 received the recommended two dosages.[6,7]

The accelerated development and registration procedure of vaccines used in this campaign urged the need for close monitoring of the safety of the products used. Although tested before registration in a small population, the vaccines involved were, in this vaccination campaign, used in a population with multiple risk factors for complications due to influenza. This may give rise to a different pattern of adverse events compared with those from the preregistration trials.[8] In addition, there was considerable concern in the population about the safety of the vaccines. Because of this, a high number of reports was expected in the Netherlands, and this mass vaccination against Influenza A (H1N1) required an efficient way of processing and analysing large numbers of reports and signal detection processes. The monitoring of voluntary reports of adverse events following immunization (AEFIs) of this campaign was carried out by the Netherlands Pharmacovigilance Centre (Lareb). Lareb maintains the spontaneous reporting scheme for drugs and vaccines on behalf of the Dutch Medicines Evaluation Board.

A dedicated campaign was initiated in order to stimulate reporting of AEFIs. The goal of this campaign was to inform both health professionals and consumers about the possibility and method of reporting AEFIs. The information campaign did not only focus on health professionals. Because information from consumers has been accepted since 2003, this group was also invited to report their experiences.[9,10] On a dedicated section of the Lareb website, information was provided about the vaccination campaign and the safety of the vaccines involved. Health professionals were also informed about the procedure of reporting in an article published in the journal of the Royal Dutch Medical Association (KNMG).[11] Finally, information leaflets about the occurrence of possible AEFIs and the method of reporting for consumers were distributed to all those being vaccinated. Together with other parties involved, a protocol was drawn up describing the processes and ways of communicating the information about possible signals to the general public before the start of the vaccination campaign.

The goal of this article is to describe the methods of processing, analysing and performing signal detection on the reports of AEFIs in relation to the pandemic influenza vaccines. The secondary aim is to provide a summary of the results of safety monitoring of both vaccines involved in the vaccination campaign against Influenza A (H1N1).

Methods

Processing Reports

Given the large population that needed to be vaccinated in a short period of time, a system for fast processing and analysing AEFI reports had to be developed to be able to deal with the anticipated large number of reports. To achieve this and to guarantee adequate safety monitoring in case staff became sick and required time off work due to the influenza pandemic, part of this system was automated. A flow diagram of the various steps in this process is shown in figure 1.

In order to submit reports on the vaccines used to vaccinate against Influenza A (H1N1), healthcare professionals and patients were advised to use dedicated reporting forms on Lareb's website. On these forms, adverse events could be selected from a predefined list of events to accomplish automatic encoding of the reactions. This list comprised all events previously submitted on vaccines to this pharmacovigilance centre. When a certain term was not available in the list, it was possible to describe the event as free text. When selecting a town/venue combination, possible batch numbers were provided. In the majority of cases, this enabled a correct, automatic selection of the administered batch number of the vaccines. These batch numbers, together with the town and venue where vaccinations took place, were provided by the institutions responsible for the distribution of the vaccines.

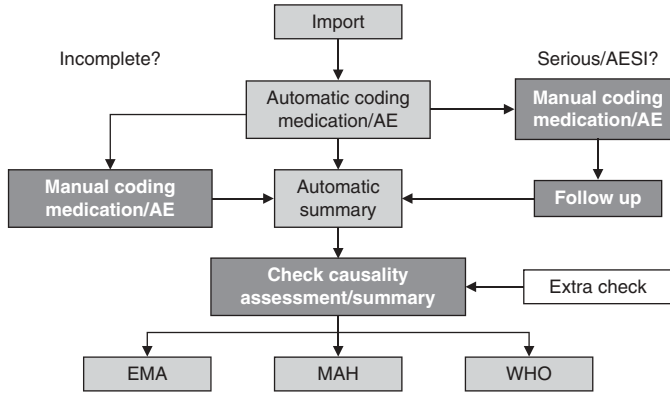

Fig. 1. Flow of reports during the vaccination campaign. Automatic processes are shown in light grey, manual processes in dark grey. **AE** = adverse event; **AESI** = adverse events of special interest; **EMA** = European Medicines Agency; **MAH** = Marketing Authorization Holder.

In the event of a pregnancy, an additional question about its duration was included. Information was requested about possible prior administration of seasonal influenza vaccination 2009/2010 because this vaccination campaign had been previously carried out. Finally, in the event that people reported a serious AEFI, additional questions were asked about current treatment, additional risk factors and complaints with previous vaccinations. A report is considered to be serious in the event of death, a life-threatening situation, (prolonged) hospital admission, disability or congenital abnormalities. These questions were also included when one of the adverse events of special interest (AESIs) was selected. These are a set of possible events for which the European Medicines Agency have expressed special interest.[10]

All incoming reports were checked on a daily basis for seriousness. Serious reports and AESIs were handled with priority. All reports were individually assessed by a doctor or pharmacist and the causal relationship between vaccine and event was assessed, based on the global introspection method.[12] These reports, including the causality assessments, were discussed in a weekly meeting, where all assessors involved took part in order to make the final assessment and quality check.

For serious reports and reports concerning AESIs, the reporter was contacted either by telephone or by e-mail to obtain additional information about the event. All serious reports were shared anonymously, on a weekly basis, with governmental parties involved. These consist of representatives from the Dutch Medicines Evaluation Board and the Dutch Centre for Disease Control.

Signal Detection

Since the vaccines were administered in a relatively short period of time, possible actions on safety issues needed to be taken immediately to be effective. The aim of signal detection was the identification of signals that became apparent after marketing of the vaccines. These signals may refer to individual AEFIs, but also to batch-related safety issues that may warrant immediate action. Several systems for signal detection were in place during this campaign. First, all serious reports were discussed on a daily basis with the assessors involved to decide which additional information was needed and to get an impression of the type of reports received previously.

On a weekly basis, serious reports were discussed with all assessors involved, together with a representative of the Dutch Centre for Disease Control to check retrospectively the causality assessment and completeness of the reports in this category. Disproportionality analysis of all reported associations on the influenza vaccines were carried out on a weekly basis by providing lists with all reported associations of both vaccines. These lists were reviewed by one of the staff members.

As Lareb received information about the batch numbers of the administered vaccines, it was possible to continuously monitor for differences in reported AEFIs between the individual batches. The number of reports per batch were compared with all other reports received on the influenza vaccines present in the Lareb database and expressed as a reporting odds ratio with 95% confidence interval.[13-15] A list of the strength of these associations and its graphical representation was continuously monitored in order to detect possible batch-related problems. We focused on four possible aspects. First, we monitored for AEFIs possibly related to the reactogenicity of the batches. Reactogenicity refers to signs of effective immunization, such as local reactions or fever. Adverse events were considered to be a sign of reactogenicity if they had been coded with the Medical Dictionary for Regulatory Activities (MedDRA®) preferred terms referring to either injection site reactions or fever. Because a high number of reports of fever were received, batches were also compared for the number of reports of hyperpyrexia, defined as a temperature above 39°C, in a separate analysis. Second, batches were monitored for AEFIs related to possible infections, since this may have pointed towards a possible contamination of a specific batch. A report was considered to be an indication of a possible infection if the event was coded with a MedDRA® term from the primary System

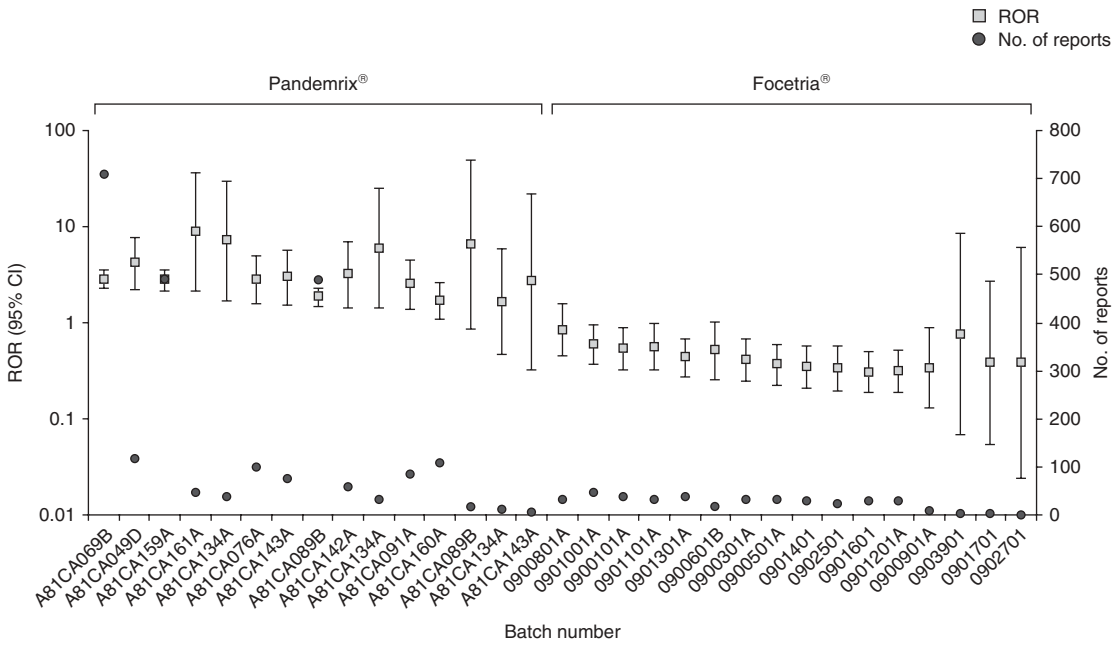

Fig. 2. Comparison between the batches of Pandemrix® (left) and Focetria® (right) with respect to reports on adverse events following immunization related to the reactogenicity of the vaccines. For both vaccines the confidence interval (CI) of the reporting odds ratios (RORs) overlapped.

Organ Class 'Infections and infestations'. Third, we monitored the number of reports in each batch indicating a lack of efficacy. Finally, the number of serious events in each batch was monitored.

In circumstances where a batch-related problem would have occurred, immediate action would have been required. Therefore, the above-mentioned analysis was carried out automatically and the resulting reports were forwarded by e-mail to one of the assessors. An example of the graphical representation of these analyses is shown in figure 2. Statistical analysis was conducted using the software package SPSS 16.0 (SPSS Software, Chicago, IL, USA).

Results

Processing Reports

From 1 November 2009 until 1 March 2010, Lareb received 7534 reports concerning one or more adverse events possibly related to the administration of one of the two vaccines. 2788 reports were for Focetria® and 4746 reports for Pandemrix®. The number of reports on both vaccines received on a daily basis is shown in figure 3.

The contribution from consumers was high. They sent 2226 (79.8%) of the reports on Focetria® and 3889 (81.9%) of the reports on Pandemrix®.

Figure 4 shows the total time between the date and time on which the reports were received and completed. Since the reporters of all serious reports were contacted, the total time to completion was longer for the serious reports (average 2.8 days) compared with the non-serious reports (average 0.8 days). All serious reports were forwarded to the European Medicines Agency and the Marketing Authorization Holders within 15 days after receipt.

With regard to the batch-related monitoring of the vaccines, in 4845 (91.6%) of 5290 venues where vaccination with Focetria® took place, only one batch number was used for the first vaccination. This involved only 2016 (32.8%) of

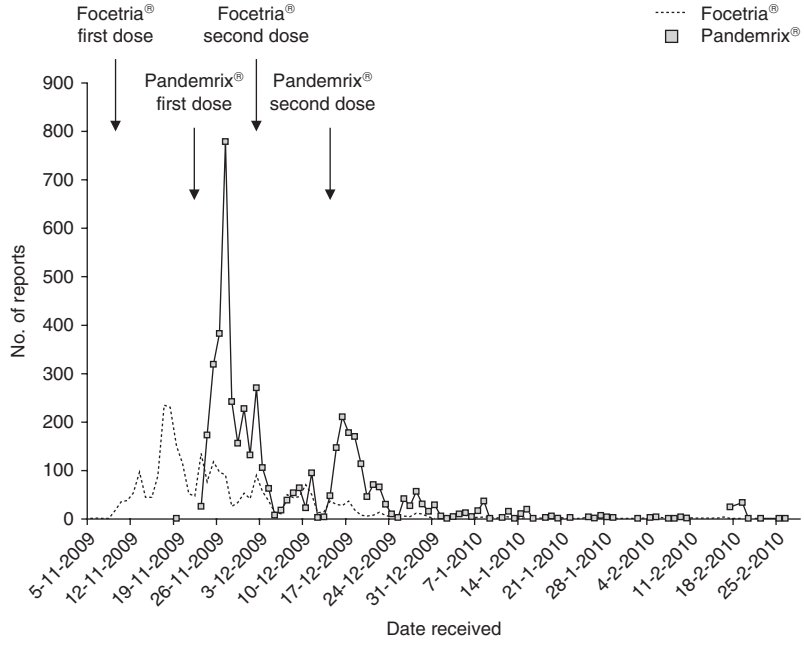

Fig. 3. No. of reports received on a daily basis for both Pandemrix® and Focetria® over time. The arrows refer to the first date on which the first and second dosages were administered. The majority of individuals were vaccinated in the subsequent days.

6153 venues for the second vaccination. Automatic determination of the administered batch number was only possible where one batch was used per venue. The batch number was retrieved in 812 (29.1%) reports where Focetria® had been used.

For the first vaccination with Pandemrix® only one batch number was used in 212 (77.9%) of 271 venues were vaccination took place. For the second vaccination, this was the case in 209 (76.8%) of these venues. Information about the batch number was available in 3305 (69.6%) of the reports on Pandemrix®.

Reports of Adverse Events on Focetria®

Most of the reports concerned adverse events directly related to the administration or reactogenicity of the vaccine. A total of 419 (15.0%) reports involved fever and 436 (15.6%) reports involved local reactions. In 155 (5.6%) cases Lareb received reports on Focetria® concerning events that have led to a serious reaction. Multiple reasons may be present for labelling a report as serious. In 86 cases the patient involved was admitted to a hospital, and in 20 cases the reported event was considered to be 'life threatening' by the reporter. In 51 of the cases the reported event was labelled as an 'other medically imported condition'.

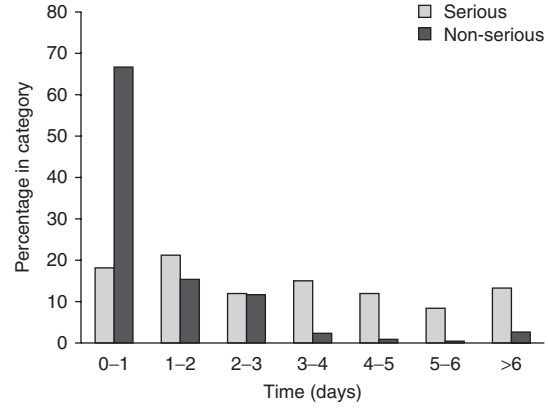

Fig. 4. Time between receiving reports and completion of analysis of the report.

Table I. Overview of adverse events of special interest of Focetria®. No reports were received on vaccination failure

Adverse event	n	Age		Latency	Causal relationship				Outcome			Remarks
		range (y)	mean (y)		certain/likely	probable	possible	unlikely/inconclusive	recovered	not (yet) recovered	unknown	
Neuritis	4	30–71	54.3	6 h–2 wk	0	0	3	1	1	2	1	
Convulsions	18	1–63	23.1	1 h–30 days	0	3	8	7	9	6	3	3 hospitalized
Anaphylactic reaction	7	14–83	47.1	12 min–2 days	0	3	4	0	6	1	0	2 hospitalized
Anaphylactic shock	2	1–35	18	4–15 min	0	2	0	0	2	0	0	1 hospitalized
Encephalitis	3	26–74	57	4–30 days	0	0	2	1	0	1	2	All hospitalized
Vasculitis	5	40–79	54.2	2 days–1 wk	0	2	2	1	0	4	1	
Guillain-Barré syndrome	15	36–80	57.8	3 days–2 mo	0	2	7	6	0	2	13	9 reports originated from VAESCO study[17]
Aggravated multiple sclerosis	3	32–98	55.7	1 day	0	0	3	0	1	2	0	Causality assessment difficult due to fluctuating illness
Bell's Palsy	5	37–58	47.4	1 day–6 wk	0	1	3	1	1	3	1	
Intrauterine death	10	21–41	32.4	1 day–6 wk	0	0	0	10	0	0	0	

A total of 16 reports recorded the death of a patient shortly after vaccination with Focetria®. The time between vaccination and death varied from several hours to 2 days. The age of the patients varied from 28 years to 90 years. In all these patients, an underlying illness was present that most probably caused the death. Although a possible relationship cannot be excluded, the causal relationship between administration of the vaccine and death is improbable on the basis of what is currently known about these reports. Given the high number of the Dutch population being vaccinated, especially elderly and people with risk factors for complications due to influenza, it could be expected that sudden death occurred in this group, which may not necessarily be related to the vaccination.

AESIs that required special attention were neuritis, convulsions, severe allergic reactions, encephalitis, vasculitis, Guillain-Barré syndrome, Bell's Palsy, demyelination and vaccination failure.[16] In addition, during the vaccination campaign, the European Medicines Agency drew special attention to the occurrence of intrauterine death following vaccination. The reports received on these adverse events are shown in table I.

Reports of Adverse Events on Pandemrix®

Also with this vaccine, the majority of the reports concerned AEFIs directly related to the administration or reactogenicity of the vaccine. A total of 1107 (23.3%) reports concerned local reactions. Fever was the most reported adverse event after vaccination with Pandemrix®. Among the reports of this vaccine, 3392 (71.5%) mentioned fever and 1621 (47.9%) of these concerned hyperpyrexia (defined as a body temperature above 39°C). This adverse event is mentioned in the Summary of Product Characteristics (SPC) of the vaccine,[3] but was apparently a point of concern for the parents of the children who were vaccinated.

A total of 96 (2.0%) cases were related to events that have led to a serious reaction according to the CIOMS criteria. Seventy-six patients using this vaccine reported an AEFI that has led to observation in or admission to a hospital; seven times the reported event was considered to be 'life

Table II. Overview of adverse events of special interest of Pandemrix®. No reports were received on neuritis, anaphylactic shock, encephalitis, vasculitis, multiple sclerosis, Bell's Palsy, vaccination failure or intrauterine fetal death

Adverse event	n	Age		Latency	Causal relationship				Outcome			Remarks
		range (y)	mean (y)		certain/ likely	probable	possible	unlikely/ inconclusive	recovered	not (yet) recovered	unknown	
Convulsions	80	0–24	4.8	30 min–4 days	0	47	23	10	58	12	10	39 hospitalized
Anaphylactic reaction	3	2–63	22.7	1 min–2 days	0	1	1	1	2	1	0	
Guillain-Barré syndrome	1	72	NA	7 days	0	0	1	0	0	0	1	Hospitalized

NA = not applicable.

threatening' by the reporter and in 13 cases the reported event was labelled as an 'other medically imported condition'.

Two reports concerned the death of a child in the days following vaccination with Pandemrix®. A 2-year-old boy died 1.5 days after vaccination. The night before he died, the boy had a fever and was vomiting. Although the polymerase chain reaction (PCR) for H1N1 was positive, a clear cause of death could not be established. The second case concerned a report of a 3-year-old boy who died 5 days after vaccination. During hospital admission, a dilated cardiomyopathy was found which, according to the treating physician, must have been present before vaccination. In both children, a causal relationship between their death and the administered vaccine was improbable based on the currently known information, although a possible relationship or contributive factor cannot definitely be excluded.

An overview of the AESIs received on Pandemrix® is presented in table II.

Batch-Related Problems

In respect to the various batches used, no signals of possible batch-related problems have been detected for either vaccine.

Discussion

More than 7500 reports of AEFIs of the Influenza A (H1N1) vaccine have been processed and analysed in a short period of time. The time needed to correctly file the reports in the database was, on average, less than 1 day after they were received. The use of a dedicated web form with predefined AEFIs enabled an efficient way of analysing the reports, resulting in almost real-time safety monitoring. In the event of a pandemic, there is an increased risk that some staff will become sick, requiring time off work. Therefore, it was necessary to ensure that processing the reports and signal detection would still be possible with a minimum number of employees. The use of automatic processes allowed for a reduction in the number of manual interventions and enabled the continuation of the process in the event that offices would have to be closed. Although face-to-face meetings were held on a regular basis as described, theoretically the entire process would not have been hampered when additional techniques were applied, e.g. desktop virtualization, allowing staff to access the computer systems from home just as they do in their offices, or having teleconferences instead of face-to-face meetings.

The current approach has now been used for the influenza campaign, but it can also be applied to other mass vaccination campaigns.

Signal Detection

One of the goals of this campaign was to ensure adequate signal detection. Since every case required checking for the MedDRA® coding, causality assessment and the content of the summary, these interventions were also used to check for possible signals. For this reason, signal detection was still dominated by the case-by-case review. All signals detected by this case-by-case

review were also highlighted by disproportionality analysis. In the event of an even larger number of reports, disproportionality analysis on this dataset would have been a possible alternative approach to replace the case-by-case analysis.

Given the nature of the events and the comorbidity of the people involved, it is difficult to make an estimate of the actual incidence of the reported events. Many of the vaccinated people had additional risk factors, which carries the risk for confounding by indication. In addition, long-term effects will be difficult to monitor for. Additional prospective studies are needed to study these data. For this reason, we launched an additional prospective web-based cohort study among 3000 people being vaccinated with Focetria®. The results of this study will be published elsewhere.

Consumer Reporting

Since 2003, both health professionals and consumers can report to Lareb.[9,18] Previous experiences with consumer reporting have shown that the information from both sources of report is generally similar with respect to the type of reported events and concomitant medication, but the type and quality of clinical information in patient reports differs from that in reports from health professionals. In addition, reporting by consumers may relieve healthcare professionals of an administrative task during a very demanding period. The value of consumer reports is reflected in the type of reported events. These are a reflection of the way the AEFIs are experienced by those being vaccinated and their relatives. An example is the high proportion of reports of fever associated with the use of Pandemrix®. Although this event is mentioned in the SPC, it was not mentioned in the information leaflet that was handed out at the time of vaccination. This was a cause of concern among parents of vaccinated children.

The number of reports by consumers regarding both vaccines during this campaign was significantly higher compared with other reports in the Lareb database (two-sided Chi-square; $p < 0.001$). This may be due to the fact that consumers in particular were invited to a government-supported information campaign to report AEFIs. In cases where serious reports were received, the reporter was contacted to verify the reported events and to retrieve additional information when needed. When necessary, permission of the consumers was requested to contact their healthcare professional in order to retrieve additional information.

Differences in the quality of the reports from health professionals and consumers may exist in respect to the level of clinical documentation; however, all reports were checked by qualified assessors and additional follow-up was requested if needed.

Bias, Confounding and Misclassification

Reporting AEFIs associated with both vaccines may have been subject to bias, confounding or misclassification.

Because vaccines are being administered as a prophylactic measure, a high level of safety is generally expected compared with other medical interventions. Less serious reactions are more likely to be reported compared with drugs administered for the treatment of, for instance, life-threatening disorders. The amount of selection bias involved is difficult to estimate. Shortly after introduction of a drug, the number of reports is relatively high.[19] This so-called Weber effect might have also been present in this campaign since both vaccines were newly introduced on the market.

Particularly at the beginning of the vaccination campaign, much media attention was focused on the safety of the vaccines involved. Many people were worried about the vaccine safety. An example is the concern about the use of adjuvants present in the vaccines, which was rumoured to cause a number of alleged severe adverse reactions. Other examples were the assumed risk of stillbirth and an increased risk of Guillain-Barré syndrome. It is likely that because of attention drawn to these adverse events, notoriety bias may have occurred.[20] As a result, a selective increase in the number of reports of these AEFIs might have occurred.

For Focetria® in particular, most of the vaccinated people had additional medical risk factors.

Confounding by indication may have occurred for the reports on this vaccine, giving rise to a relatively high number of serious reports. Another confounding factor may be the differences in age between those vaccinated with Focetria® and those vaccinated with Pandemrix®, which may be a possible contributing factor to the high number of reports of fever associated with the use of the latter vaccine. Differences in reactogenicity may also be explained by differences in the adjuvant present in both vaccines. However, the number of reports of fever was especially high in children. It is therefore less likely that differences in reactogenicity could only be attributed to the adjuvant in vaccines.

Misclassification may have occurred when reporters chose the wrong predefined AEFIs on the dedicated web form in cases where the most appropriate term was not present. By offering the additional possibility of entering an event as free text, the chance for misclassification was reduced. Another approach to reduce misclassification is to contact the reporter in the event a serious report or AESI had been reported. In exceptional cases, the original reported diagnosis had to be refuted after the reporter was contacted by telephone.

Finally, misclassification might have occurred due to previous vaccination with the seasonal flu vaccine. Most people vaccinated with Focetria® also had, because of the presence of risk factors for complications that may occur due to the onset of an influenza infection, an indication for vaccination with the seasonal flu vaccine. Although vaccination took place approximately 1 month earlier, possible AEFIs may erroneously have been attributed to Focetria®.

During the vaccination campaign, no batch-related issues were detected. A good collaboration with the institutions responsible for the distribution of the vaccines was needed to ensure reliable information about the batch numbers of the vaccines was incorporated in the web-based reporting forms. In the event two or more different batch numbers of Focetria® had been used in the same venue, selection of the correct batch number was not always possible. This was the case for several venues at the time the second vaccination was administered. Many GPs ordered new dosages for the second vaccination (with a new batch number), whereas it could not be ruled out that all dosages from the first vaccination were already administered. In addition, in the first days after the start of the first and second vaccination, the batch numbers for Focetria® were not yet available. This hampered the selection of the correct number and, for this reason, the percentage of reports with the administered batch number is lower than the percentage of venues with a single batch number where vaccination took place.

Since the possibility of selecting the option 'batch number unknown' was available on the web form, the risk for misclassification was reduced. However, in the event a wrong batch number was chosen, it is unlikely that a relationship with the selected AEFI would exist. Since this might have caused a non-differential misclassification, it is unlikely to have affected the height of the reporting odds ratio.[21] For this reason, monitoring the batch-related safety issues is not likely to have been jeopardized by possible misclassification.

Reports Received on Both Vaccines

Compared with the number of reports received in previous years regarding the seasonal influenza vaccines, the number of reports received during this campaign was relatively high; however, these reports did not give rise to concern about the safety of the vaccines. There were a high number of reports of fever associated with Pandemrix® and because of this, we conducted a separate survey-based descriptive study among parents or caregivers of vaccinated children who reported fever following the first immunization with this vaccine to Lareb. The results of this study are published in this issue of *Drug Safety*.[22]

The absolute number of reports for Pandemrix® was higher than those for Focetria® despite the lower number of individuals being vaccinated. This may have been caused by a selection bias due to high notoriety bias in the days before vaccination. The number of serious reports was higher for Focetria®, which may have been caused by the

previously mentioned confounding by indication. Another possible explanation for the relatively low number of reports on Focetria® is the fact that reporting via the Internet may be more bothersome for the elderly. Finally, people at risk due to medical conditions may be more accustomed to receiving medical treatment and/or experiencing adverse events and may therefore have a higher threshold for reporting.

The number of AESIs on both vaccines was lower than expected based on the reported incidence in the population. For reports on Guillain-Barré syndrome, the VAESCO consortium initiated an international study to investigate the actual incidence of these reactions.[17]

Dissemination of Information

Since vaccination on a large scale was almost simultaneously carried out in various countries, an efficient exchange of information about the safety of the vaccines involved was needed to share experiences all over the world.

During the vaccination campaign, various parties showed interest in the results of the analysis of the reports received so far. On a weekly basis, overviews of the reports, together with an interpretation of the findings, were available both in English and Dutch on the Lareb website and forwarded to the mailing list Vigimed.[23] A weekly press bulletin was issued to focus attention on these overviews. As with all other reports that are received, the anonymized reports on the pandemic influenza vaccines were available for the general public on the Internet site of Lareb. The reports on the website were updated on a weekly basis.

Conclusions

Differences in reported AEFIs between both vaccines used in the Netherlands may be caused by bias and confounding due to the different populations for which these vaccines were used. The reports received on both vaccines showed that the profile of the reported adverse events is comparable with the information provided in the SPCs.

Although interpretation of the results and selection of the signals involved require human intervention, automated processes may help in processing and condensing the information needed. The method applied has proven to be an efficient way of processing reports in the event of a pandemic. The use of web-based forms, preferably with information on venue/batch number, allows for efficient monitoring of possible batch-related problems.

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