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Monitoring the safety of influenza A (H1N1) vaccine using web-based intensive monitoring

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ABSTRACT

Background: When adjuvant vaccines against the pandemic influenza A (H1N1) virus became available after an accelerated registration process, safety issues dominated the public debate. As part of the immunisation campaign, the Dutch government installed an active monitoring of possible adverse events following immunisation (AEFIs). As part of the monitoring we conducted an anonymous prospective cohort study to identify and quantify the occurrence of AEFIs related to pandemic vaccination among the population immunised in general practice.
Method: Adults aged 60 years and older or persons with a risk-elevating medical condition recommended for vaccination in general practice were eligible for participation. After receipt of the first pandemic vaccine the administrator handed over an information flyer of the web-based monitoring program. The patient could sign up for study participation online. Within one week, three weeks and three months after the first immunisation questions were asked about demographics and health, immunisations, injections site reactions and labeled reactions as well as other possible new AEFIs.
Results: In all, 3569 participants filled in the first questionnaire. Corresponding figures for the second and third questionnaires were 3395 (95.1%) and 3162 (88.6%). Mean age was 58 years (SD 15) and 50.1% was female. Main indication was 60 years or older followed by presence of pulmonary or cardiovascular disease. Of all participants, 1311 (37%) reported an AEFI. Unexpected serious reactions were not reported nor were there signals of possible new AEFIs. The occurrence of an AEFI was determined by gender, age and type of co-morbidity.
Conclusion: The web-based intensive monitoring system among patients immunised in general practice revealed AEFIs due to pandemic vaccination in one-third of participants. There were no unexpected serious adverse events in this population. This advanced methodology can be further developed to monitor real-time use and AEFIs of vaccines.

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1. Introduction

In March and early April 2009, Mexico experienced outbreaks of respiratory illness and increased reports of patients with influenza-like illness. On April 23 several cases of severe respiratory illness were confirmed as swine origin influenza A (H1N1) [1]. The virus spread throughout the world and on June 11, 2009, the World Health Organization declared an influenza pandemic [2].

Vaccination is the most effective measure to control the spread of influenza virus and reduces associated morbidity and mortality. The development of vaccines against the influenza A (H1N1) virus became a high priority for vaccine manufacturers. In the European Union special registration procedures were put in place in order to speed up the availability of vaccines. These procedures managed by the European Medicines Agency allowed an influenza vaccine to be authorised more quickly than the 18–24 months usually required [3]. By the end of September and beginning of October 2009, three influenza vaccines were approved for marketing in the European Union, Focetria®, Pandemrix® and Celvapan® [3]. When the vaccines became available a fierce public debate about their safety started in the Netherlands as well as in the rest of the world. Because the new influenza vaccines only had been tested in a small population and had been approved through an accelerated registration process, the public was concerned about the

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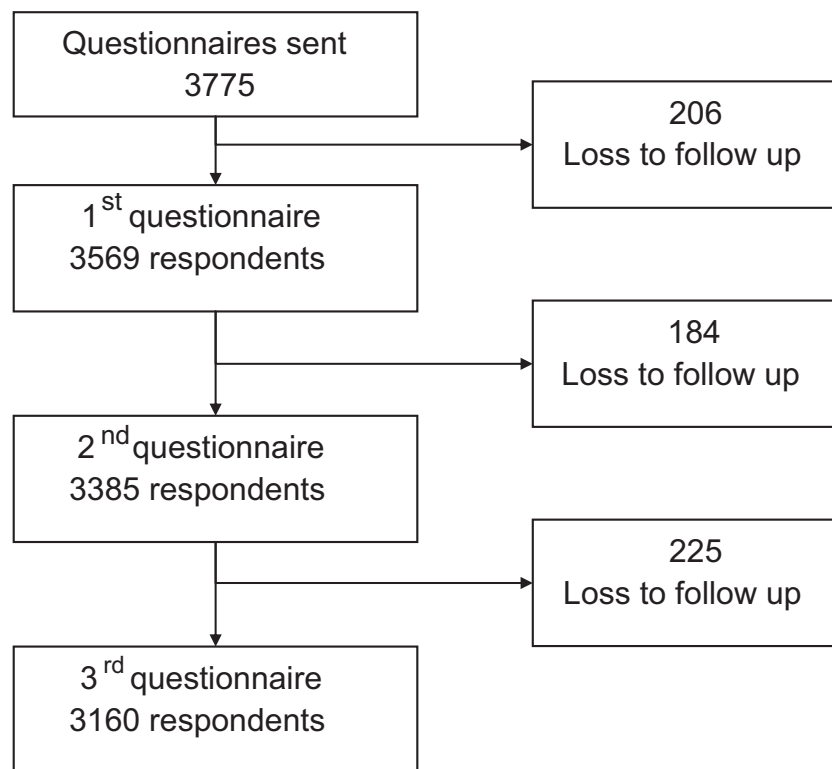
Fig. 1. Response rate of the different questionnaires.

vaccine actually causing influenza, Guillain-Barré syndrome and other neurological syndromes and adjuvants being harmful [4]. As part of the large-scale immunisation campaigns careful monitoring of the adverse events following immunisation (AEFIs) was therefore urgently needed [5,6]. An adverse event following immunization is defined by the WHO as a medical incident that takes place after an immunization, causes concern and is believed to be caused by the immunization [7].

The Netherlands Pharmacovigilance Centre Lareb was appointed by the Dutch Ministry of Health to monitor the safety of the pandemic vaccines. In addition to the spontaneous reporting system, Lareb was asked to conduct a prospective cohort study using a modified form of the intensive monitoring methodology to follow people who had been vaccinated with Focetria® in general practice during a three month period [8–10].The aim of this study was to identify and quantify AEFIs associated with the pandemic vaccine Focetria®. Secondly, we investigated risk factors for the occurrence of AEFIs.

2. Method

2.1. Setting and study population

In the Netherlands, the Health Council, which acts as an advisor to the Minister of Health, recommended vaccination to all persons with a medical indication which warrants the seasonal flu vaccination (persons with pulmonary-, cardiovascular- and renal disease, diabetes and immunodeficiency), healthy persons above the age of 60, pregnant women in the 2nd or 3rd trimester, health care personnel with direct patient contact and family members and care givers of patients with a high risk of serious complications following an influenza infection were offered the vaccine [11,12] The vaccination of all the above mentioned groups except the health care personnel would be carried out by the general practitioner. Specific software to search for these patients in general practice has been

in use since 1995 and has been updated according to the guidelines [13].

GPs who had reported an ADR to Lareb in the past two years and all GPs living in the Northern provinces of the Netherlands (duplicate addresses were identified), in total 989 practices, were sent an invitation letter with information about the study. Of those practices 117 responded that they wanted to participate in the study. 100,000 flyers were sent to these practices to hand out to the patients during their first pandemic vaccination in November 2009. The flyer contained information about the aim of the study and instruction on how to sign up for the study via a dedicated and password safeguarded website. Eligible participants were those who were enlisted at the general practice who met the eligibility criteria for such immunisation according to the guidelines of the Dutch Health Council as described above.

2.2. Data collection

Data were collected between November 16, 2009 and March 3, 2010. After online registration, patients received a questionnaire via e-mail within a week after the first immunisation. In the vaccination schedule an interval of at least two weeks was recommended between the first and second immunisation. The second questionnaire in which AEFIs attributed to the second immunisation were reported, were sent three weeks later. The third questionnaire was sent three months after the first questionnaire to monitor AEFIs with a late onset. If the participant failed to fill out one questionnaire, a reminder was sent after 7 days. Non-responders were considered to be lost to follow up and did not receive any further questionnaires (see participant flow, Figs. 1 and 2). In the questionnaires, questions were asked about personal characteristics that could be potential risk factors for developing AEFIs, the received vaccinations and possible AEFIs (see Appendix A). In order to increase the response rate and make the questionnaire more user friendly, we actively asked for injections site reactions and labeled
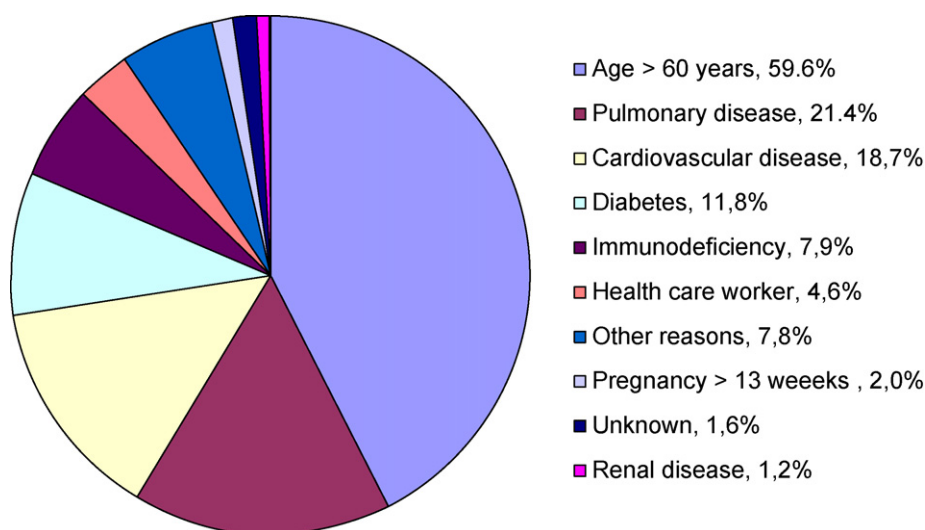
Fig. 2. Indication for vaccination. Age is the main indication followed by pulmonary and cardiovascular disease. Since the patient could choose one or more indications the percentages add up to more than 100%.

reactions such as fatigue, influenza-like illness, headache, myalgia, arthralgia, pyrexia and enlarged lymph nodes through multiple choice questions [14]. Other possible AEFIs could be filled in as free text. If the patient reported an AEFI which was considered to be serious according to the Council for International Organizations of Medical Sciences, CIOMS, criteria, the seriousness of the event was first assessed by two assessors. If deemed serious, the report was exported to the Lareb database and handled according to the European regulations for serious adverse drug reaction reports [15,16]. Questionnaires were designed and data were collected using the commercially available software Survey Monkey with secure entry [17]. Before finalising and sending the questionnaire, it was tested by a test panel for comprehensibility.

2.3. Sample size and data analysis

Since no data were available on the occurrence of AEFIs, we conservatively assumed a prevalence of potential AEFIs after one week of 10% based on data from seasonal influenza vaccines. The sample size calculation was done for the risk factor analysis. According to the rule of thumb to have adequate statistical power to develop a multivariable model with at least 10 cases for each determinant, we needed at least 2000 participants. We used descriptive statistics to describe response rate, gender, age, indication for vaccination, administration of seasonal vaccination, injection site reactions and labeled reactions. The latency, outcome and duration of the AEFIs were analysed as well as action taken when experiencing an AEFI, if the patient had experienced the reaction in association with the seasonal influenza vaccine in the past and other reasons for the AEFI. AEFIs reported as free text were coded by a qualified assessor using the the Medical Dictionary for Regulatory Activities, MedDRA, Lower Level Term, LLT [18]. Reactions were grouped per MedDRA Preferred Term, PT. The reported reactions were divided into labeled and not labeled according to the EPAR. Reactions that were not labeled and considered to be potential signals were analysed on a case by case basis. In the case by case analysis causality was assessed by looking at the temporal relationship between the drug and the reaction and to exclude other causes for the reaction.

Multivariable logistic regression was carried out to develop a prediction model of risk factors for developing an AEFI encoded as a dichotomous outcome variable (yes/no). Potential risk factors were age (in four equally sized categories, the youngest group was used as reference category), gender and the different indications for

the vaccination (dichotomous). Both backward and forward selection procedures were used with a significance level of <0.05 to develop the model. Odds ratio's and their 95% confidence interval (95% CI) were estimated as measures of relative risks. The Hosmer–Lemeshow goodness of fit was assessed as a measure of calibration of the final model. Data were analysed using SPSS 17 for Windows.

3. Results

In total, 3775 persons registered as potential participants (see Fig. 1). Of these persons, 3569 (94.5%) filled in the first questionnaire. Mean age of the respondents was 58.4 years (standard deviation (SD) 14.8 years) and 1789 (50.1%) were female. The main indication for use was age above 60, followed by pulmonary- and cardiovascular disease (Fig. 2). Of the respondents 85.1% reported to have received the second immunisation. The majority had also received the seasonal flu vaccination a few weeks earlier (84%).

In total 1311 (37%) of the participants reported an AEFI. After the first vaccination, 963 (27%) participants reported to have experienced 2401 AEFIs. After the second immunisation 746 (24.6%) patients reported 2479 AEFIs. 420 patients reported an AEFI after both the first and the second immunisation. 43 patients reported 69 AEFIs, which were not possible to attribute with certainty to nor the first nor the second immunisation.

There were no differences in loss to follow up between the first and second questionnaire between patients who had reported an AEFI and patient who did not report AEFIs (chi-squared test, $p = 0.52$).

3.1. Injection site reactions

After the first immunisation, 562 patients reported 1065 injection site reactions (1.9 events/patient). After the second immunisation 472 patients reported 1240 injection site reactions (2.6 events/patient). See Table 1 for an overview of the type of reactions. Table 3 provides additional information about the injection site reactions.

3.2. Labeled AEFIs

494 patients experienced 1077 labeled AEFIs (2.2 events/patient) after the first immunisation. After the second

Table 1
Injections site reactions reported after the first and second immunization. In total 562 patients reported an injection site reaction after the first immunization and 472 patient reported such a reaction after the second immunization. The patients could report one or more injection site reactions, therefore the total number of reactions per immunization exceeds the number of patients reporting an injection site reaction. The percentages are calculated using the total number of respondents per questionnaire as a denominator.

	Total number of patients	%
1st immunisation		
Injection site pain	445	12.5
Injection site swelling	231	6.5
Injection site erythema	153	4.3
Injection site warmth	122	3.4
Injection site bruising	61	1.7
Injection site itching	53	1.5
2nd immunisation		
Injection site pain	469	13.9
Injection site swelling	289	8.5
Injection site erythema	187	5.5
Injection site warmth	129	3.8
Injection site bruising	87	2.6
Injection site itching	79	2.3

Table 2
Labeled AEFIs reported after the first and second immunization. In total 494 patients reported a labeled AEFI after the first immunization and 472 patient reported such a reaction after the second immunization. The patients could report one or more labeled AEFIs, therefore the total number of reactions per immunization exceeds the number of patients reporting an injection site reaction. The percentages are calculated using the total number of respondents per questionnaire as a denominator.

	Total number of patients	%
1st immunisation		
Fatigue	246	6.9
Headache	243	6.8
Influenza-like symptoms	216	6.1
Myalgia	191	5.4
Arthralgia	76	2.1
Pyrexia	69	1.9
Lymph nodes enlarged	36	1.0
2nd immunisation		
Fatigue	244	7.2
Headache	226	6.7
Influenza-like symptoms	221	6.5
Myalgia	205	6.1
Arthralgia	107	3.2
Pyrexia	88	2.6
Lymph nodes enlarged	30	0.9

immunisation 1121 labeled AEFIs were reported by 389 patients (2.9 events/patient). See Table 2 for an overview of the type of reactions. Table 4 provides additional information about the frequently occurring AEFIs. Because some of the frequently occurring AEFIs are similar to influenza symptoms, the question was asked if there were any other factors contributing to the occurrence of the reaction. Nasopharyngitis was the most commonly reported other factor followed by influenza, increased infections susceptibility, fatigue and stress.

3.3. Other AEFIs

190 patients reported 264 other AEFI after the first immunisation (1.4 events/patient). After the second immunisation 83 patients reported 118 AEFIs (1.4 events/patient). In the third questionnaire which was filled in after three months 43 patients reported 69 AEFIs (1.6 events/person). For an overview of reported reactions see Table 5. None of the reported AEFIs were considered to be potential signals. In total 3 reports (incidence of 1/1000) were received concerning serious AEFIs leading to one of the CIOMS cri-

Table 3
Information about injections site reactions grouped per immunisation. The time to onset is given as a latency and the duration of the reaction is described as well.

Injection site reactions	1st immunisation	2nd immunisation
Time to onset	Less than 1 day	Less than 1 day
Duration of AEFI	3 days	3 days
Contact general practitioner	2.3%	2.8%
Treatment	0.2%	0.0%
Recovering/resolving	95.6%	95.6%
Similar reaction in the past when receiving the seasonal flu vaccination	37.0%	83.2%

Table 4
Information about frequently occurring AEFIs grouped per immunization.

Frequently occurring AEFIs	1st immunisation	2nd immunisation
Latency	1 day	1 day
Duration	2 days	3 days
Contact general practitioner	11.5%	15.8%
Treatment	3.5%	4.5%
Recovering/resolving	83.6%	8480.0%
Similar reaction in the past when receiving the seasonal flu vaccination	22.7%	38.3%

teria. The reactions reported were atrial fibrillation, aggravation of MS and influenza-like illness persisting for over a month.

3.4. Logistic regression

Male patients experienced less AEFIs than females and the risk of AEFIs decreases with age (see Table 6). Cardiovascular disease, pulmonary disease, immunodeficiency and pregnancy increased the risk of an AEFI.

4. Discussion

4.1. Principal findings

Prior to the large-scale immunisation campaign against the influenza A (H1N1) virus a fierce public debate about the safety of adjuvanted pandemic vaccines. Our study shows that the incidence of AEFIs in the population who were vaccinated by the general practitioners in the Netherlands was 36.7%. The results of the current study do not raise any concerns about the safety of the used vaccine in The Netherlands. The reactions reported were expected and non-serious. Injection site reactions and labeled AEFIs have a short latency, a short duration and are in most cases self-limited. The occurrence of an AEFI was determined by gender, age and type of co-morbidity.

4.2. Strengths and weaknesses

Since we did not control how many of the 100,000 flyers were actually handed out at the GPs office we do not know if there is a selection bias in who was given a flyer for participation or not. Because the lack of denominator data it is also not possible to calculate an over all response rate (numbers of patients participating/number of patients receiving a folder).

In order to check if the population of this cohort was representative for the patients receiving the pandemic influenza vaccine in general practice, the population was compared to vaccination data from a sample of 72 general practices, believed to be representative for the Dutch population as described in the report 'Monitoring Vaccination rate, Dutch National Influenza Prevention Program 2009'. When comparing the characteristics between these two cohorts the percentage of men is slightly higher in our cohort (49.9% com-

Table 5
AEFIs reported as free text grouped per Meddra PT and per immunisation. For each immunisation the 10 most reported events are shown.

1st immunisation	
Dizziness	63
Nausea	22
Diarrhoea	22
Nasopharyngitis	18
Pain in extremity	16
Dyspnoea	14
Oropharyngeal pain	14
Palpitations	12
Abdominal pain	11
Injection site pain	10
Cough	10
2nd immunisation	
Dizziness	42
Nasopharyngitis	24
Oropharyngeal pain	10
Palpitations	10
Diarrhoea	8
Nausea	6
Oedema peripheral	6
Oral herpes	6
Dyspnoea	6
Flank pain	4
Pain in extremity	4
Feeling hot	4
Cough decreased	4
Muscular weakness	4
Abdominal pain upper	4
Agitation	4
3 months	
Nasopharyngitis	24
Dizziness	15
Cough	7
Dysphonia	6
Palpitations	6
Oropharyngeal pain	6
Rhinorrhoea	4
Dyspnoea	4
Eructation	4
Cough decreased	4
Pain in extremity	4

another adjuvanted vaccine (Pandemrix®), so comparisons are difficult.

Injection site reactions and labelled reactions were actively asked for, other reactions could be reported as free text. Because it might be easier for a patient to answer a question with a multiple choice option than filling in AEFIs as free text, there might be an overestimation of the AEFIs where multiple choice questions were used.

For injection site reactions the causality is strong since there is a very clear link between the injection and the reaction. For the labeled AEFIs and the reactions that were reported as free text, it is more difficult to assess causality, most of the symptoms can also be due to influenza itself. In order to see to what extent patients were aware of other factors playing a role in the occurrence of the AEFI, patients were asked to name other factors. Nasopharyngitis was the most commonly reported other factor followed by influenza, increased infections susceptibility, fatigue and stress. These factors were only reported by a small proportion of all patients reporting a labeled AEFI.

In this study it was assumed that all reactions reported in the first questionnaire were attributed to the first vaccination an all reactions in questionnaire two, plus the injection site reactions and frequently occurring AEFIs in the third questionnaire were attributed to the second vaccination if the second vaccination had been taken. Since this division between the first and second immunisation is done after collecting the data, there is a possibility that reactions, which were considered to be attributed to the second vaccination actually were caused by the first vaccination.

In recent years the patient has become an important player in pharmacovigilance and in a number of countries patients are allowed to submit reports to a spontaneous reporting system [20]. Patients do not have a professional filter in what to report; therefore the chance of finding new associations is high. A disadvantage often mentioned with patient reports is that they are not medically confirmed. For the type of reactions reported in this study, medical conformation is not necessary. In the cases where AEFIs were reported which were considered to be serious, follow up information was asked in order to confirm the diagnosis.

This study was performed using web-based questionnaires. With web based questionnaires, it is possible to structure the data received so that they will be more complete than data received on paper. Through the web based character of the study, interim analysis could be performed at any time, making it possible to monitor the AEFIs in real time. Older people might be underrepresented in the cohort since they are not familiar with using internet. Recent statistics show that 86% of Dutch households have access to internet, however persons aged above 75 and persons living in an institution were not included [21].

In this study the patient was followed over time making it possible to collect information about latency, recovery and duration of the AEFI. This type of information is important, since it can reassure the patient who will be immunized. This type of information

pared to 49.6%). The main indication for vaccination in this cohort which is assumed to be representative for the Dutch population was, except age, cardiovascular disease, followed by pulmonary disease and diabetes mellitus. This is similar with the indications in our cohort [19].

Only patients with a medical indication which warrants the seasonal flu vaccination, healthy persons above the age of 60, pregnant women in the 2nd or 3rd trimester, and family members and care givers of patients with a high risk of serious complications following an influenza infection were vaccinated in general practice. How these results apply to children and healthy adults is uncertain, notably since young age seems to be associated with more AEFIs. In The Netherlands, children were vaccinated with

Table 6
Logistic prediction model for the occurrence of an AEFI.

	OR	p	AEFI+	AEFI−
Gender	0.6 (0.50–0.70)	<0.001	Male 344,Female 636	Male 1431,Female 1140
Age (0–52.5 years)			414	462
Age (52.5–61.9 years)	0.54 (0.44–0.67)	<0.001	248	628
Age (61.9–67.2 years)	0.4 (0.32–0.50)	<0.001	177	699
Age (67.2–90.0 years)	0.3 (0.23–0.38)	<0.001	135	740
Cardiovascular disease	1.32 (1.08–1.62)	0.008	181	484
Pulmonary disease	1.36 (1.13–1.65)	0.001	298	980
Immunodeficiency	1.5 (1.15–1.95)	0.003	115	166
Pregnancy	2.61 (1.55–4.40)	<0.001	48	24

Hosmer and Lemeshow test chi-square 4.593, df 7, $p = 0.709$.

is rarely presented in the SmPC and spontaneous reporting might not be able to capture it, therefore web-based cohort monitoring can be a valuable addition.

4.3. Strengths and weaknesses in relation to other studies

The SmPC of Focetria reports a study conducted with 131 adults and 123 elderly. In this study most of the AEFIs were mild and of short duration. The incidence of symptoms observed in subjects over 60 years of age was generally lower as compared to subjects aged 18–60 years [14]. In a study done by Clark et al. the vaccine was tested in 176 adults 18–50 years of age. 80% of subjects reported adverse reactions after either dose (73% after the first and 60% after the second). The frequency or severity did not increase after the second dose was administered. The reported reactions were graded as mild or moderate and were generally self limiting resolving within a 72 h period. The most frequent local and systemic reactions were pain at the injection site and muscle aches [22]. The incidence of AEFIs in these studies is much higher compared to the incidences in our study. A possible explanation might be that the data collection methods differs between our study and this study. In this study self completed diaries where used where patients could report both solicited an unsolicited symptoms. The study by Clarke et al. was performed in a group aged 18–50 years, in our study the median age was 58 years. It has also been clear both from clinical trials as well through the logistic regression in this study, that young age is associated with more AEFIs than older age, this might be another explanation for the higher incidence rate.

Also for the labeled AEFIs the incidencies in the SmPC for headache, myalgia and fatigue are higher than in our cohort whereas the incidence of arthralgia and pyrexia are consistent with out findings. The incidence of influenza like illness is much higher in our cohort than mentioned in the SmPC. A possible explanation for this is that the patients in our cohort were vaccinated during the influenza season and it is possible that the symptoms they report are actually due to influenza itself instead of the vaccine.

Both clinical trials as our study are prospective cohort studies. The difference between them is that with our study we did not have any additional inclusion or exclusion criteria, making it possible to collect data from the actual users of the vaccine. Furthermore because of its observational character it is possible to follow a greater number of patients as compared to clinical trials which makes it possible to gather more data. Because we worked with three questionnaires it was also possible to follow the time course of the AEFIs and report information about time to onset, duration of AEFI and action taken when experiencing an AEFI, data which are rarely published as a result of RCT whose main focus is to investigate efficacy and not report on AEFIs.

4.4. Meaning of the study and future research

This study show the ADR spectrum in the population immunised in general practice in the Netherlands. In order to get a complete picture of the AEFIs from this vaccine, research has to be done also in other populations since it both from our study as well as other studies has been indicated that for example age might influence the AEFI pattern. Secondly, our study monitored the vaccine and its effects during three months. In order to be sure that there are no unforeseen late onset effects, a longer follow up period might be warranted. Thirdly our cohort size was not large enough to identify any rare AEFIs. In order to detect new rare signals spontaneous reporting would probably be a more suitable mean, and a case control study could verify that signal. Cohort studies are inefficient in finding these types of reactions because you need to follow a very large cohort in order to identify these kind of events for example cases of Guillain Barre syndrome. In Europe the VAESCO consortium initiated a study to look at the association between the pandemic influenza vaccines using a case control approach [23].

Funding

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Ethical approval

No ethical approval was necessary in order to conduct this study.

Conflict of interest: All the authors declare that they do not have any conflict of interest.

Appendix A.

Questions asked in the questionnaires.

1. Gender
2. Date of birth
3. On which date did you receive your Influenza A H1N1 immunisation?
4. Is this your first or second immunisation?
   1st
   2nd
5. Did you receive the seasonal flu immunisation earlier this year?
   Yes
   No
6. What is the reason for receiving the influenza A H1NI immunisation? (multiple answers possible)
   Pulmonary disease
   Cardiovascular disease
   Diabetes
   Pregnancy
   Age above 60
   Renal disease
   Immunodeficiency
   I work in health care
   Do not know/unknown
   Other reasons than above mentioned
7. Did you experience any AEFIs from the influenza A H1N1 vaccine?
   Yes
   No
   If No, end of questionnaire
8. If Yes, did it concern an injection site reaction?
   Yes
   No
   If No, skip to question 18
9. If Yes, please tick the appropriate reaction (multiple answers possible)
   Pain
   Erythema
   Swelling or induration
   Feeling of warmth
   Pruritus
   Hematoma
10. Since when do you have this reaction?
11. Has the reaction lead to one of the following serious situations?
    Hospitalization
    Disability
    Life threatening situation
    Congenital abnormality
    Death
    No, none of the above
12. If one of the above situations occurred, do you give us permission to contact you for further information?
    Yes
    No
13. Have you recovered from the AEFI?
    Yes, I have
    The AEFI is getting less severe but I am not fully recovered yet
    No, I have not recovered
14. If yes, when did you recover?
15. Which action did you undertake when experiencing the AEFI?
    I have discussed the AEFI with a doctor but have not yet received treatment
    I have been treated by the doctor
    I have not undertaken any of the actions above.

Questions asked in the questionnaires.

16. Did you experience similar complaints by seasonal flu vaccination?
    Yes
    No
17. Are there other explanations for the reactions, if yes, which ones
18. Have you experienced any other AEFIs?
No, end of questionnaire
19. If yes, have you had any of the below described, frequently occurring AEFI?
    Yes
    No, skip to question 21
20. If yes, which ones?
    Headache
    Fatigue
    Pyrexia
    Myalgia
    Arthralgia
    Sweating, chills and influenza like illness
    Lymphadenopathy
Repetition of questions 10–17
21. Have you experienced any other AEFIs?
No, end of questionnaire
22. Yes, free text field to write the AEFI. For each AEFI reported questions 10–17 were repeated.
Question 21 and 22 was repeated until the patient had filled in all the experienced AEFIs.

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