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# Web-based intensive monitoring of adverse events following influenza vaccination in general practice

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## 1. Introduction

Q4 Annually around 3 million individuals are vaccinated with influenza vaccine in the Netherlands. Since the beginning of the Dutch National Influenza Prevention Program (NPG) in 1997, individuals older than 60 (until 2008 older than 65) and patients with a risk-elevating medical condition including cardiovascular diseases, pulmonary diseases, diabetes mellitus, chronic renal diseases and immune-related diseases and patients in nursing homes are eligible for vaccination with influenza vaccine [1]. This target population is identified and invited by their general practitioner and vaccination is conducted mostly at the general practice.

Influenza vaccines usually differ each year based on the circulating strains of the virus. Therefore, the vaccine is 'updated' every year [2]. The time between development of the vaccine and registration is approximately 8 months, which is relatively short. In addition, in clinical trials mostly healthy people are vaccinated. Before registration it is mandatory to monitor Adverse Events Following Immunisation (AEFI). Nevertheless, possible safety issues may not always be detected before registration. The Netherlands Pharmacovigilance Centre Lareb receives about 200 spontaneous reports of AEFI with an influenza vaccine every year. Based on approximately 3 million administrated vaccines, this number is relatively low. Spontaneous reporting is a valuable tool to detect new signals of unknown AEFI [3]. However, it is not an appropriate method to provide insight into profiles of AEFI such as incidence rates, time course and possible risk factors for developing an AEFI.

In 2006, an intensive monitoring program started at the Netherlands Pharmacovigilance Centre Lareb. This program, named Lareb Intensive Monitoring (LIM), is a non-interventional prospective observational cohort study that follows users of certain drugs during a period of time, collecting information through web-based questionnaires. The aim of LIM is to obtain real time data during the use of a certain drugs and provide insight into profiles of reported adverse drug reactions. This method has proven useful as a complement to spontaneous reporting [4].

During the H1N1 vaccination campaign in 2009, LIM was used to identify and quantify AEFI of the vaccine. The study concluded that LIM methodology could be used to monitor AEFIs in almost real time and collect information about frequency and latency of the AEFIs. Because patients were followed for a couple of weeks it was also possible to collect information of recovery time [5].

Except for the H1N1 vaccination campaign, LIM has not yet been used to monitor the safety of vaccines in the Netherlands. The LIM system has focused so far on new drugs and inclusion of patients in community pharmacies. This method makes it unsuitable for monitoring the safety of vaccines since they are mostly administered through other health professionals for instance general practitioners.

To include participants LIM collaboration with health care professionals is essential [6]. The aim of this study is the evaluation of the feasibility of the LIM system in general practice during the annual influenza vaccination. In addition, the contribution of the LIM method to provide insight into the pattern, time course, risk factors and impact of AEFI after influenza vaccination will be examined.

## 2. Method

### 2.1. LIM method

In this LIM study eligible patients were identified by their general practitioner. General practitioners were asked to invite

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patients, who received an influenza vaccination, to participate in the study. Patient participation consisted of answering three web-based questionnaires concerning the influenza vaccination and, if they occurred, information about AEFI. General practitioners were not involved in filling the web-based questionnaires.

### 2.2. General practitioners

Two groups of general practitioners were approached: a group who had reported ADRs to Lareb in the past two years, and a group of general practitioners from a commercial database that had not reported to Lareb in the past two years. General practitioners were informed by e-mail about the LIM system and the intention of Lareb to use this system to follow patients vaccinated with influenza vaccine and invited to participate. After 2 weeks, a reminder was sent. After 4 weeks, general practitioners could no longer participate in the study. If willing to participate in the study, information concerning the general practitioners name, address, ordered numbers of influenza vaccine and the expected date of vaccination were collected. General practitioners received flyers with information for their patients before the expected date of vaccination. They were asked to inform patients about the study after vaccination, and to distribute the flyers.

### 2.3. Patients

Patients who were vaccinated and had access to internet and were literate in Dutch, were eligible for this study. Patients were informed by their general practitioner and given a flyer with information about the LIM study, website and a log-in code. With the log-in code, the patient could register on the website as participant. To complete the registration, the patient had to actively agree with the privacy statement and informed consent. Patients could register for the study until 4 days after vaccination.

### 2.4. Questionnaires

During registration, information about patient demographics, indication for use, vaccination date and the use of concomitant medication was collected. On day 5 after vaccination, patients received the first questionnaire by e-mail. This questionnaire contained questions about the occurrence of AEFIs. Some common AEFIs were actively asked (injection site reactions, pyrexia, myalgia, rash and headache) but the possibility to report an AEFI as free text was also present. In case of a reported AEFI, more information about the AEFI was inquired, including: time between vaccination and the occurrence of the AEFI, treatment, duration, outcome and severity. In addition, it was requested whether or not an AEFI was serious (according to the CIOMS criteria of seriousness): death, life threatening, (prolongation of) hospitalization, disabling, congenital abnormalities or another medical important condition, and willingness to vaccinate with influenza vaccine in future. Finally, it was asked whether this was the first influenza vaccination and the presence of allergies.

The second and third questionnaires were sent on respectively day 15 and day 30 after vaccination. These questionnaires differed slightly from the first questionnaire. The outcome of AEFIs reported in a previous questionnaire that were not yet recovered was asked. Thereafter, the occurrence of other AEFI was asked, however the predefined AEFI were not listed in the second and third questionnaire. If a patient did not fill in a questionnaire a reminder was sent. The patients were considered lost to follow up when they did not complete the first questionnaire after 11 days and the second and third after respectively 25 and 40 days. Patients could withdraw from the study at any time for any reason. The data obtained from the patients who were lost to follow up was used for analysis.

### 2.5. Data handling

The data was captured in the LIM database of the Netherlands Pharmacovigilance Centre Lareb. The reported indication and AEFI were coded using the MedDRA terminology (version 15) by qualified assessors using the Brighton collaboration definitions where applicable [7,8]. When Brighton collaboration criteria were absent, Lareb used her own definitions. Injection site inflammation, for instance, sometimes extends over the joint or around the vaccinated limb. In such cases these local reactions were coded as 'extensive swelling of vaccinated limb' [9]. In the event of a reported and confirmed serious AEFI, a copy was made and forwarded to the database for spontaneous reports. Subsequently, serious reports were assessed and handled as a regular report to the Marketing Authorisation Holder and the European Medicines Agency. The influenza vaccine and concomitant medication were coded using the Z-index; the drug dictionary of the Netherlands.

## 3. Data analyses

### 3.1. Feasibility of the LIM method in general practice

The proportion of participating general practitioners who reported ADRs to Lareb and the general practitioners who did not report any ADR to Lareb in the past 2 years were calculated based on the sent invitations. In addition, the proportion of participating patients (inclusion rate) of these two groups were calculated.

Descriptive analysis was performed on patient age, gender and indication for influenza vaccination. The proportion of age and indication for influenza vaccination was compared with the national numbers of vaccinated patients. The response rate after registration and after each questionnaire was calculated. In order to see if selection bias occurred, the reporting of AEFI/no AEFI was examined in relation to the time of registration.

### 3.2. Reported AEFI

The total number of all AEFI reported in all three questionnaires was calculated, expressed as the number AEFI versus the number of included patients who completed a questionnaire. In the case a reported AEFI appeared in a subsequent questionnaire it was not counted again. Exact time to onset, duration, outcome and the severity of AEFI were calculated and categorized for all reported AEFI. The number and type of the serious AEFI were summarized.

A multiple logistic regression was performed to identify possible risk factors for developing at least one AEFI. Potential risk factors in the model were age, chronic diseases, previous influenza vaccination and presence of allergy. Both backward and forward procedures were performed.

Finally, the frequency of patients who refused further vaccinations with influenza vaccine was described. And a comparison with the nature of AEFI of spontaneous reports of influenza vaccination during the same season was made.

Data extraction and analysis were performed with SQL, SPSS 17 and Access for Windows.

## 4. Results

### 4.1. Participating general practitioners

A total of 628 general practices were invited and 83 general practitioners participated in the study. Of the participating general



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**Table 1**
Participating general practitioners and registered patients (inclusion rate).

| General practitioner | Invitation | Participants | Ordered vaccines | Patients registered |
|---|---|---|---|---|
| Report to Lareb in past 2 years | 335 | 53 (15.8%) | 58450 | 737 (1.3%) |
| No report to Lareb in the past 2 years | 293 | 30 (10.2%) | 29680 | 728 (2.5%) |
| Unspecified general practitioner | | | | 42 |
| Total | 628 | 83 (13.2%) | 83100 | 1507 (1.8%) |

practitioners 64% (53/83) had reported ADRs to Lareb in the past two years. The general practitioners ordered a total of 88130 influenza vaccines, and based on this number the overall patient inclusion rate was 1.8%, see Table 1.

### 4.2. Characteristics of the participating patients

A total of 1507 patients completed the registration for participating in this study. 97% of these patients were informed after vaccination in a participating general practice. In addition, a small group of 42 patients wanted to participate in this study, after they became aware of it in the media. Of all included patients, 52.7% were female. Table 2 presents the indication for vaccination of the participants compared to representative population sample. Of the participants 71.1% patients were aged above 60 years. And 43.3% had no other indication for the vaccination than their age. The percentage of vaccinated patients above 60 years in a population sample was calculated to be 75.2%, see Table 2.

### 4.3. Response rates and occurrence of AEFI

After registration a total of 1367 (90.7%) patients completed the first questionnaire. The second and third questionnaires were completed by respectively 1273 (84.5%) and 1182 (78.4%) patients. Of the 1367 patients who completed the first questionnaire, 451 (33%) registered on the day of vaccination. Most of them (73.2%) reported no AEFI, see Fig. 1.

### 4.4. Reported AEFI

Of the patients who responded to the first questionnaire, 490 (35.8%) reported at least one AEFI. Patients without an AEFI in the first questionnaire reported no AEFI in subsequent questionnaires. The patients reported a total of 849 AEFI. The most reported AEFI, their time to onset, outcome and time to recovery are shown in Table 3. In addition, the severity of these AEFI is summarized in Table 4. Three of the patients who reported an AEFI met the criteria for seriousness.

Of the 490 patients who had experienced an AEFI, 5.7% was unwilling to vaccinate again with the influenza vaccine in future.

**Table 2**
Indication for influenza vaccination of the participants ($n = 1507$) in this study compared with a representative sample of vaccinated patients in the Netherlands during season 2013/2014. Patients might have filled in more than one indication.

| Indication | Number of patients ($n$) | Percentage of patients (%) | Reference population from the Netherlands (%)[a] |
|---|---|---|---|
| Age >60 | 1072 | 71.13 | 75.24 |
| *Age >60 without any other indication* | *653* | *43.33* | *19.39* |
| *Age >60 with at least one other indication* | *419* | *27.80* | *55.85* |
| Cardic disorder | 163 | 10.82 | 54.88 |
| Diabetes mellitis | 132 | 8.76 | 28.37 |
| Pulmonary disorder | 269 | 17.85 | 20.56 |
| Immunodeficiency | 51 | 3.38 | 5.72 |
| Kidney disease | 13 | 0.86 | 3.40 |
| Other | 280 | 18.58 | Unknown |

[a] Numbers received from the monitor of degree of vaccination in the Netherlands during the season 2013/2014. This sample is representative for the total population [10].

### 4.5. Possible risk factors

Women younger than 60 and men older than 60 years reported respectively most (67.0%) and the least (19.3%) AEFI. The logistic prediction model (LR forward), see Table 5, shows an increased risk for patients younger than 60 (OR 2.85; CI 95 2.19–3.72) and females (OR 2.55; CI 95 1.98–3.27). Furthermore, presence of an allergy or immunodeficiency increased the risk of occurrence of at least one AEFI.

## 5. Discussion

In this study we evaluated the feasibility of the LIM method in general practice. The response rates of general practitioners who reported to Lareb in the past two years and the general practitioners who did not report was respectively 15.8% and 10.2%. This small difference could possibly be explained by more awareness of, or commitment to pharmacovigilance by general practitioners who had previously reported to Lareb. Notable is the difference in inclusion rates of patients between general practitioners who previously reported and did not report to Lareb in the past two years; respectively 1.3% and 2.5%. Both groups of general practitioners covered a total 83,100 patients eligible for vaccination. However, it should be noted that the number of patients was based on the ordered vaccines. As the degree of vaccinated patients decreases each year, the ordered vaccines could have been a slight overestimation of actually vaccinated patients. The overall number of patients who registered for the study, based on the number of ordered vaccines, was low (1.8%). The overestimation of vaccinated patients cannot explain this low inclusion rate. Unfortunately, the inclusion rate of the patients for each general practice could not be calculated since the exact numbers of vaccinated patients were not available. In addition, the methods used in general practice to inform patients and efforts made for the recruitment to participate are unknown. Consequential, we cannot determine whether there was a problem with distribution of the flyers or unwillingness of the patients to participate. Therefore, it is difficult to draw conclusions from the number of patients who were invited and how many registered for this study. On the contrary, the response rate to the questionnaires of the patients who actually registered was very high: 90.7% completed the first and 78.4% participants completed all questionnaires.

The frequency of participants aged above 60 years in this study (71.13%) was comparable with a representative population sample (75.24%). However, our study sample represented relatively more patients above 60 years without any risk elevating medical condition (43.33%) compared to the population sample (19.39%). This indicates that probably healthy elderly were more able to or willing to participate in the study. These healthy elderly were possibly because of their physical and mental condition more able to work with a computer. Another explanation could be that these elderly are more concerned about the risks of vaccination. In the past years

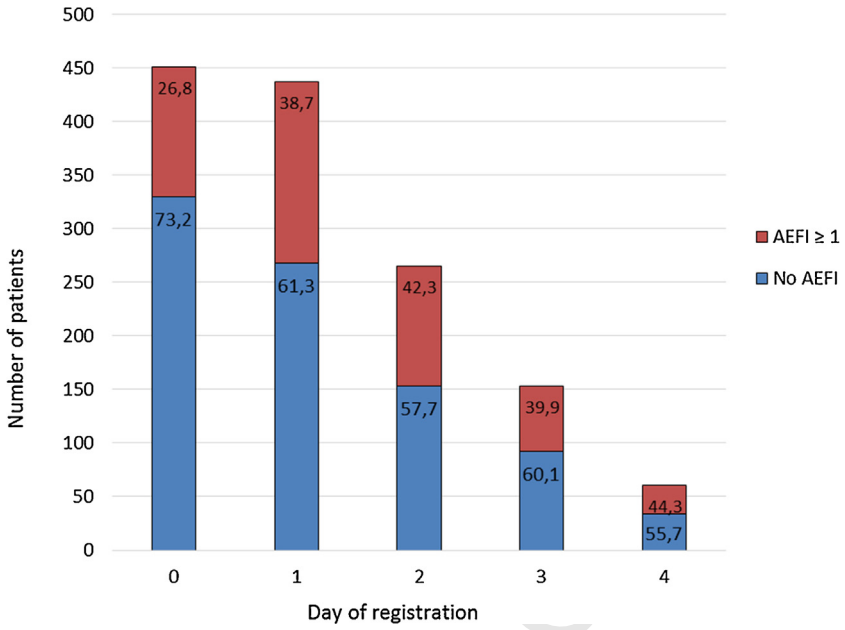


**Fig. 1.** The number of patients who registered on the day of vaccination or subsequent days and the distribution (%) of no or at least one AEFI reported in the questionnaires per day of registration.

**Table 3**
Reported frequencies, latency and recovery time of the ten most reported AEFI ($n = 1367$; 490 patients reported at least one AEFI; total reported AEFIs was 849).

| Reported AEFI | Patients ($n$) | Time to onset | | Recovered ($n$) | Time to recover | |
|---|---|---|---|---|---|---|
| | | Median (hour) | Average (hour) | | Median (hour) | Average (hour) |
| Injection site inflammation | 227 | 3 | 11 | 181 | 96 | 115 |
| Headache | 109 | 24 | 41 | 97 | 48 | 62 |
| Myalgia | 80 | 24 | 53 | 62 | 72 | 92 |
| Injection site pain | 59 | 3 | 8 | 50 | 72 | 73 |
| Pyrexia | 47 | 24 | 50 | 43 | 48 | 56 |
| Nasopharyngitis | 41 | 72 | 158 | 20 | 173 | 132 |
| Extensive swelling of vaccinated limb | 33 | 3 | 9 | 26 | 156 | 195 |
| Malaise | 31 | 48 | 77 | 22 | 48 | 107 |
| Fatigue | 18 | 48 | 161 | 8 | 84 | 162 |
| Oropharyngeal pain | 18 | 84 | 180 | 11 | 48 | 113 |
| Influenza like illness | 14 | 120 | 174 | 9 | 96 | 115 |

there is a decrease in the vaccination rate. Since age is the only indication for vaccination in healthy elderly they could doubt whether they are at an increased risk in case of an influenza infection. If that is the case the balance between benefit and risk becomes more important. Consequently, AEFI will be less accepted by this group.

### 5.1. Selection- and reporting bias

Of the patients who registered on the day of vaccination, 26.8% reported eventually one or more AEFI in the questionnaires sent from day 5. The percentage of patients who reported an AEFI

**Table 4**
Severity[a] of the 10 most reported AEFI.

| Reported AEFI | No impact | Slightly impact | Moderately impact | Severe impact |
|---|---|---|---|---|
| Injection site inflammation | 68 (30.0%) | 142 (62.6%) | 17 (7.5%) | 0 (0.0%) |
| Headache | 13 (11.9%) | 78 (71.6%) | 18 (16.5%) | 0 (0.0%) |
| Myalgia | 12 (15.0%) | 46 (57.5%) | 20 (25.0%) | 2 (2.5%) |
| Injection site pain | 32 (54.2%) | 24 (40.7%) | 3 (5.1%) | 0 (0.0%) |
| Pyrexia | 5 (10.6%) | 27 (57.4%) | 13 (27.7%) | 2 (4.3%) |
| Nasopharyngitis | 6 (14.6%) | 22 (53.7%) | 12 (29.3%) | 1 (2.4%) |
| Extensive swelling of vaccinated limb | 5 (15.2%) | 13 (39.4%) | 13 (39.3%) | 2 (6.1%) |
| Malaise | 4 (12.9%) | 21 (67.7%) | 6 (19.4%) | 0 (0.0%) |
| Fatigue | 2 (11.1%) | 10 (55.6%) | 4 (22.2%) | 2 (11.1%) |
| Oropharyngeal pain | 3 (16.7%) | 13 (72.2%) | 2 (11.1%) | 0 (0.0%) |
| Influenza like illness | 1 (7.1%) | 9 (64.3%) | 4 (28.6%) | 0 (0.0%) |

[a] Severity was asked out in a question: How stressful/burdensome was this AEFI for you? Patients could answer: no, slightly, moderately or severe impact.

**Table 5**
Logistic prediction model for the occurrence of at least one AEFI ($n = 1348$).

| | OR | $p$ | AEFI ≥ 1 | No AEFI |
|---|---|---|---|---|
| Age | 2.85 (2.19–3.72) | <0.001 | <60 231<br>>=60 254 | <60 159<br>>=60 704 |
| Gender | 2.55 (1.98–3.27) | <0.001 | F 346<br>M 139 | F 366<br>M 497 |
| Allergy | 1.64 (1.25-2.15) | <0.001 | 178 | 172 |
| Immunodeficiency | 2.60 (1.31–5.18) | 0.007 | 31 | 14 |

increased after subsequent registration days. Eventually, of the patients who registered on the fourth day 44.3% reported the occurrence of an AEFI in the questionnaires. A plausible explanation could be selection bias, patients tend to be more concerned and willing to participate when they actually have experienced an AEFI. There were three questionnaires sent over a period of 45 days. Therefore the chance of occurrence and reporting of not related events increases when the time between vaccination and reporting is longer. Additionally, the frequency of reported AEFI can be an overestimation of the actually incidence rates. The high number of healthy elderly participants could also have caused selection bias, although this group reported relatively less AEFI.

### 5.2. Profiles of AEFI

The 10 most reported AEFI were mostly well-known expected AEFI. Only the rash did not appear in the ten most reported AEFI. The time to onset of AEFI with inactivated vaccines, such as the influenza vaccines in the Netherlands, is usually within 48 h [1]. The results of time to onset of the local reactions fit into this profile. Actually, it can be seen from our results that these local reactions have a relatively short time to onset (median and average) compared to well-known possible systematic reactions such as headache, myalgia and malaise. Nasopharyngitis and oropharyngeal pain are not expected AEFI. The time to onset differs from the expected profile suggesting these reactions could also have been coincidental events or, as described above, possible reporting bias. In addition, the composition of the vaccine cannot explain these reactions, because these are possibly caused by a viral or bacterial infection. In case of 'influenza like illness' it is sometimes seen that patients are convinced they can be infected by the vaccine causing these symptoms. The average recovery time of the patients is longer than expected [11,12]. Most of the patients reported that the experienced AEFI had a slight impact on their wellbeing and they have the intention to vaccinate again in future. The highest percentages of moderate and severe impact was seen in patients who experienced an extensive swelling of vaccinated limb. In the past years this reaction was seen more often and these numbers underlines the need for further investigation of this reaction and possible risk factors [9,13]

The pattern of AEFI was comparable with the reported AEFI in spontaneous reports [14]. However, one strength of intensive monitoring is obtaining real time data and the possibility to calculate the occurrence of AEFI more accurately. Additionally, intensive monitoring provided more detailed information about the course, outcome, severity and possible risk factors of the reported AEFI. Although this information was not medically confirmed, studies suggest that the nature of ADR reporting of patients is similar to that of health professionals [15]. Our data showed a third of all patients experienced one or more AEFI. This percentage is higher than expected from studies [11,12]. As mentioned before, selection bias and reporting bias could have occurred.

Three reports of the total of 490 patients who reported an AEFI were assessed as serious. In spontaneous reporting the number of reports considered serious is around 8%. The frequency in our study (0.6%; 3/490) however, is much lower. Serious AEFI reporting by health care professionals is mandatory in the Netherlands. In addition, patients are possibly more concerned and willing to report when they have experienced a serious AEFI. These factors together probably cause a shift between the balance of non-serious and serious reports in spontaneous reporting. And probably the frequency calculated of serious reports in our data is a more accurate approach.

The logistic regression showed an increased risk for occurrence of at least one AEFI for women, age 60 years or younger, allergy and immunodeficiency. Age is well known to be a risk factor, because it is assumed that older patients do have more pre-existing antibodies which could neutralize reactogenicity [16]. One review, concerning sex differences in local reactions after vaccination, found that local pain was reported more in women. In addition, it was recommended to analyse data of AEFI by sex [17]. In the case of allergy or immunodeficiency, more frequently occurrence of AEFI could be biological plausible. However it has not been examined whether or not which specific AEFI these patients experienced. And there is no data available to support our finding.

## 6. Conclusion

Intensive monitoring of AEFI after influenza vaccination in general practice is a feasible method based on willingness and possibility of participants to complete the questionnaires. The overall inclusion rate of patients was relatively low. However, there was a high response rate of registered patients. Information of completed questionnaires provided us more information about the frequency of occurrence of AEFI, serious case reports and the course and severity of experienced AEFI and risk factors compared to spontaneous reporting. Possible selection bias and reporting bias could not be ruled out completely.

## Conflict of interest

The authors declare they have no conflict of interest.

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