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Comparison of different collection methods for reported adverse events following pandemic and seasonal influenza vaccination

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ABSTRACT

Background: During the 2009/2010 season, information on adverse events after administration of seasonal and pandemic influenza vaccines was collected by different active surveys in the Netherlands. In the present paper, we compared data from a paper-based questionnaire with data from a web-based questionnaire with respect to outcomes and target population, in order to guide future influenza vaccine safety monitoring.

Methods: The paper-based survey collected data from patients who attended primary care practices in the province of Utrecht for influenza vaccination. The web-based survey recruited participants from the general population all provinces of the Netherlands. To analyze the association between study approach and the reported local and systemic adverse events, a generalized estimation equation model was applied. We adjusted for age, gender, comorbidity, previous vaccination and socio-economic status score.

Results: No significant differences were found between the two studies approaches in reporting local reactions (OR: 0.98, 95% CI 0.88–1.10) and systemic AEs (OR: 1.12, 95% CI 0.99–1.27). There were important differences in the age groups that responded. The elderly were more represented in the paper-based survey where participants were recruited via GPs (79% $\geqslant$ 60 years) compared to 37% in the web-based survey where participants were recruited via internet.

Conclusion: The paper-based survey with recruitment of participants through GPs is more representative for the target group of influenza vaccination compared to the web-based survey with recruitment of participants via internet. A web-based approach with recruitment of participants via internet seems more suitable for situations where information about adverse events on a national level is desirable. We recommend to recruit participants for a web-based survey during mass vaccinations sessions by GPs to comply with the recommendations of the European Centre for Disease Prevention Control.

1. Introduction

During the influenza season of 2009/2010, a new vaccine had to be used to prevent infection by the novel type A (H1N1) pdm09 influenza virus. Although extensive knowledge was available about adverse events (AEs) after administration of unadjuvanted seasonal influenza vaccines, little was known about the reactogenicity and safety of the new generation adjuvanted influenza vaccines, such as the pandemic vaccine. The pandemic vaccine used in the Netherlands was approved for use by the European Commission in September 2009 upon the recommendations of the European Medicines Agency [1,2]. The vaccine was only approved for use when an H1N1 influenza pandemic had been officially declared by the World Health Organization or European Union [3]. Although initial results in October 2009 for 356 subjects demonstrated a good tolerability profile for this vaccine [4], one of the recommendations of the Health Council of the Netherlands was to collect specific and detail information about the efficacy and safety of the pandemic vaccine [5].

Following this advice, the Ministry of Health commissioned to collect information about AEs after the administration of the pandemic influenza vaccinations. Information on AEs after administration of seasonal and pandemic influenza vaccines was actively collected by the National Institute for Public Health and the Environment (RIVM) by a paper-based questionnaire. In the RIVM

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study, participants were recruited from the province of Utrecht through general practitioners [6]. A second study was commissioned by a private company that operates Influenzanet in the Netherlands. Influenzanet monitors the activity of influenza-like illnesses (ILI) in a dynamic cohort of participants in several countries in Europe. Influenzanet has approximately 20,000 participants in the Netherlands each season [7]. Influenzanet is a web-based system and during the influenza season of 2009/2010, this system was also used for an online questionnaire targeting AEs of the seasonal and pandemic vaccines among existing and new participants from the Netherlands and Belgium. A third study was done by the National Centre for Pharmacovigilance Lareb. Lareb is the designated national pharmacovigilance agency and sends reports of AE's anonymously to the governmental Medicines Evaluation Board and also to the European Medicines Agency and the World Health Organization. In addition to their routine passive surveillance (i.e. a system that collect and analyze individual case reports of adverse events voluntarily sent by physicians and patients), they studied with a web-based approach the occurrence of AEs related to pandemic vaccination among the population immunized in general practice [8,9].

To date, information about the influence of different approaches in collecting information on AEs following vaccination is lacking. In addition, one of the 2014 recommendations of the European Medicines Agency [10], is to have next to the routine passive surveillance, a rapid active pharmacovigilance tool available for detection of AEs after the administration of (novel) influenza vaccines for monitoring the safety of these novel vaccines. Even if AEs are minor, they can have important public health implications, especially when this affects acceptance of vaccination. Therefore, in the present paper, the studies conducted by the RIVM and Influenzanet are compared with respect to frequency of reported AEs and groups targeted for vaccination in order to evaluate the effect of different methods in data collection and guide future influenza vaccine safety monitoring in the Netherlands. Unfortunately, from the study conducted by Lareb only aggregated data were available, so their results could not be included in our analyses.

2. Methods

2.1. Study population and setting

In 2009, vaccination by the General Practitioner (GP) against the pandemic strain was offered by general practitioners (GPs) to all people eligible for routine seasonal influenza vaccination, i.e. people with predefined chronic medical conditions of all ages and all people of 60 years and older. Furthermore, several risk groups, e.g. healthy pregnant women in their second and third trimester and household members of high-risk patients were defined for pandemic vaccination by their GP. Health care workers were offered vaccination by occupational health services whereas children between the ages of 6 months and 5 years, and caretakers of babies between 0 and 6 years were offered pandemic vaccine only from the municipal health services. Seasonal vaccination was given first, followed after two weeks by the two consecutive doses of pandemic vaccine, three weeks apart, as stipulated in the national guidelines [11]. The pandemic vaccination campaign started on November 2, 2009 and ended before Christmas 209 in almost all GP-practices. The seasonal vaccination campaign started late September 2009. GPs promoted influenza vaccination by sending all eligible persons a personalized invitation letter. Information leaflets were available at the GP-office. Vaccinations were administered during mass vaccination sessions.

In the RIVM study, people from the province of Utrecht who visited their GP ($n = 5$) for the administration of seasonal and/or pandemic vaccine were recruited. At each mass vaccination session, three employees of the RIVM were present at the GP offices and asked vaccinees to participate in a survey about adverse events after administration of the influenza vaccine. Vaccinees who agreed to participate, were handed a questionnaire to fill in and return to RIVM in a pre-stamped envelope within one week. Thus in this paper-based survey (PB-survey), a participant could fill in up to three questionnaires, one for each vaccination. During successive mass vaccination sessions, people were reminded to send in their questionnaire.

Influenzanet recruited persons from all provinces of the Netherlands and Belgium. In the present study, only participants from the Netherlands were included. In addition to ILI reporting, participants of Influenzanet who received the seasonal and/or one both pandemic vaccines were recruited to fill in an extra online questionnaire regarding predefined AEs (i.e. web-based survey; WB-survey). In addition, new participants were recruited through general advertisement by a press release in November 2009 which was published in many local and national newspapers and on websites [12]. New participants could register at the website of Influenzanet and complete the extra questionnaire. Data were collected between November 12, 2009 and January 28, 2010 [13].

2.2. Vaccines

The two seasonal influenza vaccines, used in the Netherlands in 2009, i.e. Vaxigrip® (split virion; Sanofi Pasteur MSD) and Influvac® (subunit surface antigens; Abbott), were both trivalent inactivated vaccines without adjuvants or thiomersal, given intramuscularly or subcutaneously. The pandemic vaccine used by all GPs, was Focetria® (Novartis). This vaccine contained the adjuvant MF59C.1 and was supplied in multi-dose containers with thiomersal as preservative. The vaccine was given intramuscularly.

2.3. Exclusion criteria for comparison analysis

The two studies differed with regard to study population and setting. Due to the categorization of age in blocks of ten years in the Influenzanet study (i.e. 6 months–4 y, 5–14 y, 15–24 y, etc.) and data collection of only adults in the RIVM study, we excluded participants aged 24 years or younger from the analysis of both PB- and WB survey to ensure a valid comparison. Pregnant women, health care workers and respondents for whom information on vaccine type were missing were also excluded. The PB-survey intended to assess the tolerability of pandemic vaccination after a dose of seasonal vaccine. In the Netherlands, healthy pregnant women are not eligible for seasonal influenza vaccination and health care workers are not vaccinated by their GPs but by personnel of the occupational health services. Therefore, those groups were excluded in the PB-survey [14,15].

2.4. Questionnaires

Both surveys included questions about the occurrence of local adverse reactions like redness, swelling and/or pain at the injection site (dichotomized yes/no), and systemic AEs, defined as fever, dizziness, myalgia and fatigue (dichotomized yes/no). Furthermore, information was collected about potential confounders (i.e. gender, age, comorbidity, postal code for calculating SES score and previous vaccination [16–25]).

Receipt of previous vaccination was dichotomized for both the PB- and WB-survey, and was defined as a received seasonal influenza vaccination before 2009. Previous vaccination was included in the analyses because people who have been previously vaccinated against seasonal influence are possibly less prone to adverse events. Comorbidity was defined as having one or more of the following underlying medical conditions: diabetes, heart