USING SENTINEL SURVEILLANCE TO MONITOR EFFECTIVENESS OF INFLUENZA VACCINE IS FEASIBLE: A PILOT STUDY IN DENMARK

A Mazick[1,2], AH Christiansen[2], S Samuelsson[2], K Mølbak[2]

The influenza vaccine for the season 2003/04 did not contain the circulating A(H3N2)/Fujian virus strain. Vaccine effectiveness (VE) estimates were needed but unavailable. We explored whether or not laboratory based influenza surveillance can be used to estimate VE. We carried out a case-control study nested within Danish sentinel surveillance. A case was defined as a person aged 25 or above with A(H3N2)/Fujian/411/02 influenza. Four controls per case, matched on age groups and time, were selected from clients of sentinel practitioners (SP) who reported cases. SPs collected the following data in structured one-page questionnaires: vaccination status, chronic illness and previous pneumococcal vaccination. We sent postal survey questionnaires to participating SPs to assess acceptability and simplicity of data collection.

Twenty four cases were identified. Data from 19 case-control sets were analysed. One control was excluded because information on vaccination status was missing. Two of the 19 cases and 11 of 75 controls had been vaccinated against influenza. The VE adjusted for chronic illness was 33% (95% CI 0%–88%) and 37% (95% CI 0%–89%) when excluding 5 controls with influenza-like illness. Twenty two SPs returned survey questionnaires. Fifteen of 17 SPs reported that it was easy to find controls. SPs collected data through interviews and clinical notes, spending 1 to 5 minutes per case and 5 to 15 minutes for all four controls. Nineteen of 22 SPs considered the amount of time they spent on the study to be acceptable, 17 said that they would like to participate again, and none ruled out further participation.

Monitoring VE within sentinel surveillance systems is feasible. The small numbers in our study limit interpretation of VE. Expansion to a European multicountry study could overcome this limitation and provide VE estimates earlier in the season, for different age groups and emerging virus strains, including new and pandemic subtypes.

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Introduction

Influenza is a major cause of morbidity and mortality in Europe[1]. Surveillance of influenza, usually designed as sentinel surveillance, is crucial to early detect epidemics and changes in circulating virus strains. With this objective in mind, Danish sentinel surveillance for influenza was implemented in 1994. The system is based on voluntary participation of up to 150 general practitioners, distributed nationwide. Between week 40 and week 20 of the following year, sentinel practitioners (SP) report weekly the number of consultations for influenza-like illness (ILI, defined as acute onset of fever, myalgia and respiratory symptoms) by age group and the number of total consultations in their practice. For surveillance of circulating virus strains, 50 SPs collect throat swabs from the first five ILI patients seen on three occasions during the influenza season (beginning, peak and end). These swabs are analysed and typed by PCR, virus isolation and haemagglutination inhibition assay at the National Influenza Reference Laboratory at the Statens Serum Institut (SSI). In Denmark, annual influenza vaccination is recommended for people aged 65 years or over and for people with chronic medical conditions.

During the 2003/04 season, the influenza vaccine recommended by the World Health Organization did not contain the circulating A(H3N2)/Fujian virus strain, and reports of severe illness and paediatric deaths associated with Fujian alarmed the public [2-4]. Vaccine effectiveness (VE) estimates were needed, but were unavailable.

The objective of the study reported here was to explore whether it is feasible to use sentinel surveillance to monitor the effectiveness of seasonal influenza vaccination, with the perspective of using a similar methodology to rapidly estimate effectiveness of a vaccine against pandemic influenza.

Methods

The study was designed as a case-control study nested within the Danish sentinel surveillance, in order to estimate effectiveness of the seasonal influenza vaccine during the influenza season 2003/04. A case was defined as a person aged 25 years or older, from whom a specimen taken by the SP was found to be positive for influenza A/Fujian/411/02 (H3N2). Younger patients were initially included in the study but were later excluded after preliminary analysis showed low vaccination coverage in this population. Cases were identified based on test results received from the National Influenza Laboratory. SPs who reported a case selected as controls four patients attending the clinic two weeks afterwards a particular case. Controls were matched to cases by age groups that corresponded to those used in ILI surveillance (25 – 64 years and ≥ 65 years).

SPs used one-page questionnaires to collect information on influenza vaccination, severity of illness, underlying chronic illness (cardiovascular and chronic pulmonary disease, diabetes mellitus, immunodeficiency and other chronic diseases), previous pneumococcal vaccination, residence and presence of ILI in controls at the time of selection. Case questionnaires were sent to SPs together with the laboratory sampling kits, and were completed by SPs when they collected specimens from ILI patients. As soon as a case was identified, we sent four control questionnaires to the SP reporting the case. Cases who had received influenza vaccine more than one week before specimen collection were coded as vaccinated. Controls were considered vaccinated if they had received vaccine more than one week before selection. To estimate vaccine effectiveness, case-control sets were analysed by conditional logistic regression using two different control groups: Control group 1 included all controls regardless of whether or not they had symptoms of ILI at the time of selection (case–cohort approach) [5,6]. In control group 2, people reporting ILI at the time of selection were excluded.

To assess workload and acceptability of the VE study we sent anonymous questionnaires to all SPs, who had cases, at the end of the influenza season. Information collected included time spent participating in the study, ease of control selection and data collection, reasons for non-response and willingness to participate again.

1. European Programme for Intervention Epidemiology Training (EPIET)
2. Department of Epidemiology, Statens Serum Institut, Denmark

Results

In the 2003/04 influenza season, 79 SPs submitted a total of 219 specimens from ILI patients; of these, 55 specimens (submitted by 34 SPs) tested influenza virus positive [TABLE 1].

Table 1

Number of throat swab specimens submitted by sentinel practitioners by laboratory result and age group, influenza season 2003/2004, Denmark

Age group (years)	Sentinel specimens			
	A(H3N2)[a]	B[b]	Negative	Total
0-24	30		33	63
25-64	21	1	117	139
65+	3		14	17
Total	**54**	**1**	**164**	**219**

a A(H3N2): Influenza virus A(H3N2), all with Fujian/411/02 characteristics.

b B: Influenza B virus

Among 54 patients with A/Fujian positive influenza, 24 were in the relevant age groups for this study. Control data was obtained for 19 of these cases (79%) and consequently 19 case-control sets were analysed. One control was excluded because information on influenza vaccination status was missing. Cases and controls did not significantly differ with regards to age, sex and presence of underlying chronic illness [TABLE 2]. None of the cases or controls lived in a residential home. Of all cases and controls with underlying chronic illness 31.3% (10/32) had been vaccinated with seasonal influenza vaccine.

Table 2

Characteristics of A(H3N2)/Fujian influenza infected study cases and controls, influenza season 2003/04, Denmark

Characteristics	Cases (n =19) (%)	Control group 1 (n=75) (%)	P value*
Age in years: median (range)	36 (25-68)	46 (25-82)	0.14†
Female	13/19 (68.4)	46/73 (63)	0.66
Underlying chronic illness	6/18 (33.3)	26/75 (34.7)	0.92
Previous pneumococcal vaccination	0/15	3/72 (4.2)	0.42
Living in institution	0/19	0/75	
ILI at time of selection	19/19	4/75 (5.3)	

* Pearson χ^2

† Kruskal-Wallis rank test

Of 75 controls, four (5.3%) had symptoms of ILI and were excluded from analysis in control group 2.

Factors related to A(H3N2)/Fujian influenza were analysed in a conditional logistic regression model. Chronic disease was introduced as confounding variable; other variables did not alter the model [TABLE 3]. The vaccine effectiveness (1-OR) adjusted for chronic illness was 33% (95% CI 0%–88%) in the model including control group 1 and 37% (95% CI 0%–89%) in the model including control group 2.

Twenty two of 30 SPs returned survey questionnaires, and of these, 17 had returned control questionnaires and 15 of these 17 reported that they had found it easy to find controls. SPs collected data through interviews and clinical notes, spending 1 to 5 minutes per case and 5 to 15 minutes for all four controls. Nineteen of 22 SPs considered the amount of time they spent on the study to be acceptable, 17 of 22 said that they would like to participate again, and none ruled out further participation. Inadequate briefing was mentioned a reason for non-participation

The additional costs for the national coordination of the VE study were calculated based on direct and indirect costs shown in table 4, and totalled approximately 2000 Euro.

Table 4

Operational costs of influenza vaccine effectiveness study at national level, 2003/04, Denmark

Indirect costs (at SSI*)	Hours	Euro
Epidemiologist	32	1176
Nurse	12	364
Laboratory technician, secretary	20	558
Total	**64**	**2098**

Direct costs	Euro
Postage	94
Stationary	13
Telephone	13
Total	**120**

* SSI: Statens Serum Institute

Discussion

The results suggest that monitoring the effectiveness of influenza vaccines within sentinel surveillance systems is generally feasible. However, the small numbers of positive specimens collected by the Danish sentinel system limit the interpretation of the vaccine effectiveness estimate and therefore the value of the method for ongoing monitoring of VE in Denmark. Expansion to a European multicountry study could overcome this limitation and provide VE estimates earlier in the season, for different age groups and for emerging virus strains.

Monitoring of seasonal influenza vaccine effectiveness within surveillance systems is, in addition to the Danish pilot study presented here, also carried out in France [7,8] and in Canada[9]. All three approaches use a case-control method, and identify cases from sentinel surveillance (study outcome either ILI (France) or laboratory confirmed influenza (Canada, Denmark)), but they differ in the selection of the control group [FIGURE]. The Canadian controls are sentinel patients with ILI that test negative for influenza, while in France, the control group is the study population of an annual vaccine uptake survey of the preceding influenza season.

Table 3

Factors related to A(H3N2)/Fujian influenza among study cases and controls, influenza season 2003/04, Denmark

		Control group 1			Control group 2		
		n/total	Crude OR*	Adjusted matched OR[a] (95% CI[b])	*n*/total	Crude OR	Adjusted matched OR (95% CI)
Influenza vaccination	Cases	2/19	0.7	0.67 (0.1-3.7)	2/19	0.64	0.63 (0.1-3.4)
	Controls	11/75			11/71		
Chronic disease	Cases	6/18	0.98	1.11 (0.3-4.1)	6/18	0.92	1.08 (0.3-4.0)
	Controls	26/75			25/71		

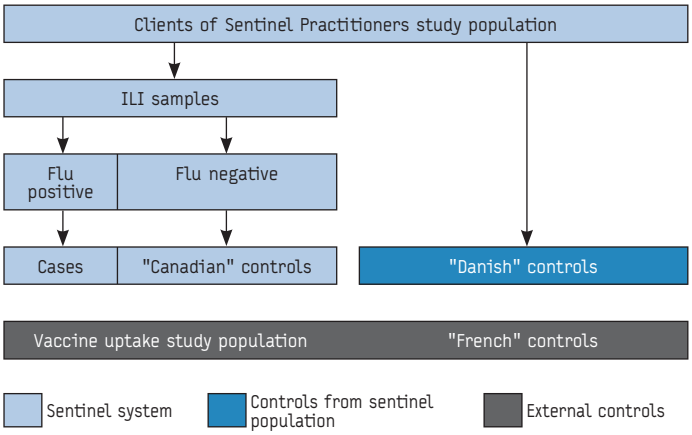
* Crude OR were estimated on matched sets by Mantel Hænszel method

a Odds ratio,

b Confidence interval

FIGURE

Framework for case-control studies to monitor influenza vaccine effectiveness within surveillance systems: three different control groups as used in the Danish, French and Canadian study designs



As observational studies with rather simple designs, all three approaches are subject to potential bias and confounding. Particular methodological limitations include: in Canada, the limiting or the study population to patients with ILI who consult sentinel practitioners, and it is not known how far these VE estimates can be generalised to the general population. Furthermore, the approach is very sensitive to misclassification of outcome, as demonstrated in the Canadian study and in a simulation with German data [10]. The screening method used in France is limited its adjustability for confounding, for example for underlying chronic illness, and the validity of the VE estimate depends on a valid external vaccine uptake estimate for relevant age groups in a comparable population [10,11]. Both the Danish and the Canadian approaches use laboratory confirmed influenza as an outcome measure, allowing the study to distinguish between co-circulating virus (sub-)types and to estimate VE for the different influenza vaccine components. An operational limitation of both approaches is, however, the requirement that SPs collect a limited set of additional information.

A further weakness of all approaches is the inability to ensure susceptibility of controls such as would be required to derive a valid estimate on the strength of an association when the outcome is common [5].

In spite of these limitations, the approaches may well be suitable for monitoring changes over time by comparing VE estimates between influenza seasons, as the estimates will be comparable. The validity of the seasonal estimates may be studied by triangulating the results of the three methods by additional registry (i.e. population or GP) based VE studies in countries where these are feasible or by rigorous focused studies in particular risk groups as required.

Integrating VE monitoring into existing sentinel surveillance has a number of advantages. It builds on already well established networks and capitalises on routinely collected information. It further means that most European Influenza Surveillance Scheme (EISS) member countries already have the minimum capability requirements for participation already in place, although one particular method may be more suitable for some countries than for others. In Denmark the study was considered a surveillance project and did not require ethical approval. However, requirements for scientific ethical clearance and for financial issues may vary from country to country. These aspects would need to be considered in a European study.

Timeliness is a priority consideration in choosing a suitable methodology, so that a first VE estimate can be obtained early in the influenza season, with precision continuing to increase as the season progresses

In the Danish VE study, data on controls were available already 14 days after the occurrence of the case, and an external vaccine uptake, which may only be available later in the influenza season, is not required.

In a pandemic there will be an urgent need to determine the effectiveness of the pandemic vaccine, as only limited or no trial data on the protective vaccine efficacy will be available prior to licensure of a pandemic vaccine [12,13]. The present designs offer an attractive and feasible approach for a rough estimate of the effectiveness of a pandemic vaccine but the methods must be trialled and be in place prior to the pandemic.

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