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The predictive value of influenza symptomatology in elderly people

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Objective. We aimed to determine the complex of symptoms which has the highest predictive value for the diagnosis of influenza.

Method. A questionnaire study with questions regarding the symptomatology of influenza among patients aged 60 and older (n = 1838). Thirty-four participating GPs recorded the symptomatology of patients who came to their general practice with influenza-like complaints. The validity of the diagnostic conclusion of the GP, as well as the diagnostic validity of the criteria of the International Classification of Health Problems in Primary Care (ICHPPC-2) and the Sentinel Stations in The Netherlands, was determined with the help of the predictive value and odds ratio, using serologically confirmed influenza as the gold standard. The same method was used to determine which complex of symptoms has the highest predictive value for influenza. The results were verified using logistic regression analysis.

Results. The predictive value of the diagnostics of the GP amounted to 35%. The predictive values of the diagnostics according to the criteria of the two classification methods were 24% (Sentinel Stations) and 18% (ICHPPC-2). Of the individual symptoms, the combination of fever, coughing and acute onset had the highest predictive value (30.3%) for the diagnosis of influenza.

Conclusion. It is recommended that the criteria of the Sentinel Stations in The Netherlands and the ICHPPC-2 be adapted in the following way: influenza is likely if, out of the entire complex of symptoms, at least fever, coughing and an acute onset occur.

Keywords. Diagnostics, influenza, predictive value.

Introduction

As long as there is no reliable, fast and simple laboratory test for the diagnosis of influenza the GP has to rely on the clinical symptomatology of influenza.[1] However, the diagnostic criteria are not uniform.[2,3] According to the criteria of the Sentinel Stations in The Netherlands, an acute onset (with a prodromal stage of no more than 3–4 days) and a temperature of at least 38°C, measured rectally, are obligatory for influenza or an influenza-like illness (Table 1).[2] According to the criteria of the International Classification of Health Problems in Primary Care (ICHPPC-2),[3] the diagnosis of influenza can be made if six of the nine symptoms occur (Table 1). A total of 102 GPs participating in the influenza surveillance in England reported that they considered the symptoms chills, malaise, myalgia and the presence of an influenza epidemic the most important criteria.[4] An Australian investigation from 1968 to 1972 showed that of the symptoms listed in the ICHPPC-2 definitions, only the complaint coughing is obligatory for the serologically confirmed diagnosis.[5] In addition, there is an inter-doctor variation in the interpretation of the different criteria. For this reason, doctors in France are advised to use their own criteria and to keep them consistent for the entire season.[6] It is important to differentiate between influenza and influenza-like illnesses as much as possible. Influenza leads to a shorter duration of illness than influenza-like illnesses,[7] but results in more serious complications, especially among the elderly and high-risk patients.[8,9]

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TABLE 1 *Criteria for diagnosing influenza and influenza-like illness*

According to the Sentinel Stations	(1) An acute onset, i.e. a prodromal stage of at most 3–4 days (including pre-existing infection of the airways at a non-symptomatic level).
	(2) The infection must be accompanied by a fever of at least 38°C, measured rectally.
	(3) At least one of the following symptoms must be present: coughing, coryza, sore throat, frontal headache, retrosternal pain, myalgia.
According to the ICHPPC-2	Inclusion requires *one* of the following:
	(a) Viral culture or serological evidence of influenza virus infection
	(b) Influenza epidemic, plus *four* of the criteria in (c)
	(c) *Six* of the following:
	Sudden onset (within 12 hours)
	Cough
	Rigors or chills
	Fever
	Prostration and weakness
	Headache
	Myalgia, widespread aches and pains
	No significant physical signs other than redness of nasal mucous membrane and throat
	Influenza in close contacts

We conducted a randomized, double-blind, placebo-controlled study into the predictive value of the complex of symptoms on which the diagnosis influenza is made. Serologically confirmed influenza was used as the gold standard. This research was assessed as part of a large study evaluating the incidence of influenza, the duration of illness as a result of influenza, side effects following vaccination, the immune response after vaccination and the efficacy of vaccination on preventing influenza.[7,10–13] Since 95% of the deaths due to influenza occur among people aged 60 years and older[8,9] these studies were done in elderly individuals.

Method

Patients

The study was conducted in the 1991–1992 influenza season and involved 34 GPs in 15 practices in the southern region of The Netherlands. All persons aged 60 or older not known as belonging to those high-risk groups in which vaccination had previously been given were invited to enter into the trial. High-risk groups were patients with heart or lung conditions, diabetes mellitus, chronic renal insufficiency, or chronic staphylococcal infections.[14] Of the people invited (n = 9907) to enrol in the trial, 1838 (19%) agreed (Table 2). The following reasons were given for non-participation: not understanding the letter of invitation; hesitation about participating in an investigation; fear of receiving an injection and having blood samples taken; and being pressed for time. In conclusion, there was no evidence that participants were untypical of the population as a whole. Of those who enrolled, histories of cardiological, pulmonary or metabolic problems were still reported by 490 participants. The GPs appear to have had different interpretations of being at high risk for influenza. These patients were treated in the analysis as having a potential risk status.

Procedure

The vaccine used was a purified split-virus vaccine. Each dose (0.5 ml) contained A/Singapore /6/86 (H1N1), A/Beijing /353/89 (H3N2), B/Beijing /1/87, and B/Panama /45/90, all at a strength of 15 mg haemagglutinin. Physiological saline solution was used as placebo. Between 1 and 15 November 1991, the participants received an injection with either placebo or

TABLE 2 *Characteristics of the study population*

Subgroup	*n*	%
Vaccination status		
Vaccine	927	50.4
Placebo	911	49.6
Potential risk status		
Yes	490	26.7
No	1348	73.3
Sex		
Male	869	47.3
Female	969	52.7
Age (years)		
60–64	764	41.6
65–69	530	28.8
70–74	353	19.2
75–79	127	6.9
80–84	48	2.6
85–91	16	0.9

vaccine, according to a stratified randomization schedule. A venous blood sample was taken from the participants prior to the injection (S1), 3 weeks later (S2) and at the end of the trial period (April 1992) (S3).

The participating GPs were asked to register the relevant symptoms of those patients presenting with influenza-like complaints. The participants were asked to fill out and return a questionnaire asking about possible influenza episodes and the symptoms experienced. In addition, a comparable questionnaire was sent to all participants after 10 weeks and after 23 weeks.

The antibody titre in the serum samples was measured by means of the haemagglutinin inhibition test at the end of the trial period.[15–17]

Diagnostic criteria

A titre ≥ 38 in S3 and a four-fold titre increase in S3 relative to S2 were considered as meeting the criterion of influenza infection.[18]

The GPs were asked to apply the criteria of the ICHPPC-2 to patients with signs of influenza who consulted them.

The criteria of the Sentinel Stations in The Netherlands[2] and the criteria supported by the ICHPPC-2[3] were used to evaluate the questionnaires filled in by the participants for the diagnosis influenza or influenza-like illness.

Data analysis

Of the patients who recorded symptoms of influenza on more than one questionnaire, only the questionnaire for which the period of illness was closest to the epidemic peak within the trial period was used in the analysis.

The validity of the diagnosis influenza or influenza-like illness according to the GP, the criteria of the ICHPPC-2 and the criteria of the Sentinel Stations were studied using serology as the gold standard for the diagnosis of influenza. By determining the sensitivity, specificity, predictive value and odds ratio, the differentiating capacities of individual symptoms and various complexes of symptoms for the diagnosis of influenza were determined. The results were verified by means of a multiple logistic regression analysis, using all relevant influenza symptoms, vaccination and potential risk status, age and gender as independent variables and serological influenza as a dependent variable. The analyses were conducted on a VAX-mainframe computer, using the BMDP program.

Approval by the medical ethics committee

The protocol was approved by the medical ethics committee of the University of Maastricht and the University Hospital, Maastricht. All participants gave informed consent.

Results

The composition of the trial population is shown in Table 2. In total, 927 participants received vaccine (420 men) and 911 participants received placebo (449 men). The numbers of vaccinated and non-vaccinated participants were almost equally distributed over the different subgroups.

Influenza was serologically confirmed in 121 cases (41 vaccinated). The GPs reported 48 cases (17 vaccinated) of influenza-like illness of which 17 cases were serologically confirmed. According to them the following symptoms were most important: malaise (45 times), fever (43 times), coughing (42 times) and acute onset (38 times).

The participants returned 1806 questionnaires at the end of the first trial period. At the end of the second trial period 1756 questionnaires were returned. Sixty-two participants reported symptoms of an influenza episode twice and 11 participants three times. In total, 645 questionnaires in which participants reported influenza symptoms were used in the analysis. Using the criteria of the ICHPPC-2, 233 cases (108 vaccinated) of influenza or an influenza-like illness were found. Of these cases, 41 were serologically confirmed. According to the criteria of the Sentinel Stations, 144 cases (62 vaccinated) of influenza or an influenza-like illness were found, of which 35 cases were serologically confirmed.

TABLE 3 *Sensitivity (Se), specificity (Sp), positive (PV^+) and negative (PV^-) predictive value and odds ratio (OR), including the CI of the clinical diagnosis of influenza or influenza-like illnesses according to the GP, the criteria of the Sentinel Stations and the International Classification of Health Problems in Primary Care (ICHPPC-2), using serologically confirmed influenza (n = 121) as the gold standard*

Influenza or influenza-like illness	n[a]	Se	Sp	PV^+	PV^-	OR	95% CI
GPs	48	na[b]	na[b]	35	na[b]	na[b]	
Sentinel Stations	144	29	94	24	95	5.8	3.8–9.1
ICHPPC-2	233	35	89	18	95	4.1	2.8–6.2

[a] number of cases of influenza or influenza-like illnesses according to various criteria.
[b] not applicable (the GP evaluates only the population that comes for consultation).

TABLE 4 *Sensitivity (Se), specificity (Sp), positive (PV^+) and negative (PV^-) predictive value and odds ratio (OR), including the CI, of the symptoms for the serologically confirmed diagnosis influenza (n = 121)*

Symptoms	n[a]	Se	Sp	PV^+	PV^-	OR	95% CI
Coughing	456	66	76	17	97	6.2	4.15–9.23
Fever	187	34	91	21	95	5.0	3.28–7.63
Acute onset	335	51	81	16	96	4.2	2.83–6.31
Malaise	428	57	77	16	96	4.6	3.13–6.75
Rigors or chills	358	47	81	15	95	3.7	2.52–5.46
Myalgia	374	45	80	14	95	3.3	2.25–4.84
Headache	399	44	78	13	95	2.9	1.97–4.24
Sore throat	365	40	80	13	95	2.7	1.83–3.99

[a] total number of reports of the symptom.

The differentiating capacity of the conclusions of the GPs, and those based on the criteria of the ICHPPC-2 and the Sentinel Stations are shown in Table 3. The criteria of the Sentinel Stations score better than those of the ICHPPC-2. The sensitivity, specificity, predictive value and odds ratio of the various symptoms belonging to the diagnosis influenza are shown in Table 4. The predictive value of the symptoms fever and coughing stand out here. Logistic regression analysis showed the same symptoms as significant predictors of serologically confirmed influenza (Table 5). The table shows also that apart from coughing and having fever, not being vaccinated is an important predictor of influenza. Belonging to a risk group did not influence the predictive value of symptomatology. Table 6 shows that as more symptoms are present, the predictive value of the complex increases. Moreover, specific combinations of symptoms (fever and coughing; fever, coughing and acute onset; fever, coughing, acute onset and malaise) have a higher predictive value than the presence of all symptoms. If the combination fever, coughing and acute onset was to have been used by the GPs in diagnosing influenza, this complex of symptoms would have achieved a predictive value of 44% (CI 30–58%).

Discussion

A relatively low positive predictive value of the symptom complex fever, coughing and acute onset (30%)

TABLE 5 *Multiple logistic regression analysis with all symptoms relevant to influenza, vaccination and potential risk status, age and gender as independent variables, and confirmed serological influenza as the dependent variable. The complete model and the reduced model with only statistically significant results are shown*

	Full model				Reduced model		
Variable	Code	OR	(95% CI)	*P*-value	OR	(95% CI)	*P*-value
Coughing	yes = 1 no = 0	7.29	(3.31–16. 1)	0.001	5.25	(3.28–8.39)	0.001
Fever	yes = 1 no = 0	2.30	(1.31–4.04)	0.005	2.18	(1.33–3.57)	0.002
Acute onset	yes = 1 no = 0	0.95	(0.51–1.77)	0.881			
Malaise	yes = 1 no = 0	1.27	(0.57–2.82)	0.571			
Rigor or chills	yes = 1 no = 0	1.05	(0.57–1.93)	0.880			
Myalgia	yes = 1 no = 0	0.90	(0.48–1.69)	0.745			
Headache	yes = 1 no = 0	0.66	(0.36–1.20)	0.178			
Sore throat	yes = 1 no = 0	0.74	(0.43–1.30)	0.312			
Risk status	yes = 1 no = 0	0.88	(0.54–1.44)	0.619			
Vaccine/placebo	yes = 1 no = 0	0.56	(0.36–0.86)	0.009	0.56	(0.36–0.86)	0.009
Sex	male = 1 female = 0	0.97	(0.63–1.51)	0.908			
Age	per year	1.01	(0.7–1.05)	0.702			
Constant		0.026	(0.0018–0.37)	0.008	0.041	(0.028–0.059)	0.001

nonetheless provides, in comparison with the prior chance of serologically confirmed influenza (prevalence) of 7% (121/1838), a net increase in diagnostic confidence of 23% (30–7%) and a percentage increase in confidence of 328% (23%/7%).[19] This means that if a patient thinks he has influenza, his suspicion becomes four times (30%/7%) more reliable if he has fever, coughs and complains of an acute onset. The predictive value will be even higher in the subpopulation that consults a GP with these complaints. This is illustrated by the difference between the positive predictive value of the complex of symptoms based on questionnaire data (30%) and the positive predictive value of the same complex when patients consulted their GP (44%).

Many influenza-like illnesses, caused for example by the adenovirus, rhinovirus, respiratory syncytial virus, para-influenza virus, herpes simplex virus or mycoplasma pneumoniae, are clinically indistinguishable from influenza. Furthermore, a wide range of unrelated pyrexial illnesses can mimic influenza, for example malaria, pyelitis, tonsillitis, psittacosis and acute bacterial endocarditis. However, when influenza is suspected and an influenza outbreak exists, and when clinical findings do not explicately relate to another viral disease, the trias fever, coughing and acute onset will

TABLE 6 *Positive predictive value (represented as the percentage of positive serology) and the odds ratio (OR), with the CI, of various combinations of symptoms reported by the trial population (n = 1791), using serologically confirmed influenza (n = 121) as the gold standard*

Combination of symptoms	n[a]	% positive serology	OR	95% CI
0	1155	3.2[b]		
1	75	6.7	0.99	0.39–2.49
2	70	5.7	0.83	0.30–2.32
3	52	15.4	2.62	1.20–5.69
4	92	10.8	1.74	0.88–3.46
5	112	13.4	2.29	1.29–4.09
6	89	16.9	3.05	1.69–5.50
7	99	15.2	2.76	1.49–4.79
8	47	25.5	5.14	2.60–10.20
Fever and acute onset	144	24.3	5.83	3.76–9.03
Fever and coughing	137	26.3	5.68	4.24–10.20
Fever, coughing and acute onset	109	30.3	7.87	4.96–12.50
Fever, coughing, acute onset and malaise	105	29.5	7.43	4.64–11.90
Total population	1791	6.8[b]		

[a] Total number of people with that/those particular symptom(s).
[b] In the total population, with respect to the subgroup serological influenza without symptoms, this percentage reflects the prior chance of getting influenza.

be helpful in further confirming the diagnosis influenza. In those circumstances smaller CIs for the predictive values and odds ratios of the symptomatology will result.

That the predictive value of the combination fever, coughing and acute onset is higher than that of all the symptoms together has the consequence that for all symptoms together there is a greater chance of diagnosing an influenza-like illness than influenza.

The predictive value of the diagnostic conclusion of the GP is of course higher than the predictive values of the conclusions drawn from the questionnaires, using the criteria of the ICHPPC-2 and the Sentinel Stations. After all, the GP, unlike the unselected population to which participants who filled in a questionnaire belong, has the advantage of a greater prior chance of influenza with patients who consult him on account of the suspicion of influenza. Moreover, on the grounds of his experience, the GP is likely to interpret better the weight of symptoms. Confounding of the findings, which may occur because patients have to fill in a questionnaire at the middle and the end of the trial period, cannot be excluded. However, other, somewhat similar studies show that information provided by patients is on the whole reliable.[20,21] Moreover, the direction of the confounding is not entirely clear in advance. Patients can forget which symptoms bothered them, while at the same time they may wrongly score symptoms.

The external validity could have been affected by the number of people (81%) who declined to participate

in this investigation. However, the reasons given for not participating are unlikely to affect the results, since the subjects were randomized after enrolment. Also it does not seem likely that these reasons are related to age, gender or state of health. Moreover, after comparing the composition of age and the distribution of gender to the random sample data of the University of Maastricht Registration Network of General Practitioners and to Dutch population data, the trial population proved sufficiently representative of an average population of 60 and older.[22]

The symptom complex fever, coughing and acute onset achieves a higher predictive value in our trial population than the criteria of the Sentinel Stations and the ICHPPC-2, and should consequently be preferred for clinical diagnosis.

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