What are the complications of influenza and can they be prevented? Experience from the 1989 epidemic of H3N2 influenza A in general practice

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Abstract

Objective—To compare the incidence and risk of complications of influenza; to determine the effects of pre-existing disease on complications; to estimate vaccine uptake and efficacy.

Design—Case-control study.

Setting—Primary care: two group practices.

Subjects—342 of the 395 cases of clinically diagnosed influenza reported to the general practice surveillance of infectious diseases scheme of the Public Health Laboratory Service during the 1989 epidemic, and 342 age and sex matched controls.

Interventions—None.

Main outcome measures—Documented recognised complications; hospital admission; previous vaccination.

Results—Of the 15 recognised complications, bronchitis was the commonest (rate 190/1000 cases) and significantly commoner in cases (summary odds ratio 9-7) after adjusting for higher consultation rates (mean 6·1 per annum v 4·2 among controls; p < 0·0001). No deaths were recorded. The risk of bronchitis complicating influenza was higher in patients with pre-existing illnesses regarded as an indication for vaccination (odds ratio 3·3; p < 0·0001). Observed vaccination efficacy in those with pre-existing illnesses and in elderly subjects was high (63% and 77% respectively) but uptake was low (4·5% and 6·1% respectively).

Conclusions—Bronchitis complicates about one fifth of all cases of influenza presenting to general practitioners. Patients with pre-existing illnesses regarded as an indication for vaccination are particularly at risk. Vaccine uptake is extremely low, precluding an unequivocal demonstration of a protective effect.

Introduction

Influenza is the most important viral infection of the respiratory tract, partly because of the scale of epidemics and partly because of complications, which include excess mortality, several medical conditions, and exacerbations of pre-existing diseases. However, little is known about the expected incidence of these complications. Knowledge tends to be based on complications observed in hospital. Of 237 English language reports since 1966 on influenza and complications cited in Medline, none measure the incidence of complications in the community.

In 1989 there was the first epidemic of influenza A in the United Kingdom since 1975. We studied the epidemic in Wales in order (a) to measure the incidence and risk of complications, (b) to identify the rate of hospitalisation, (c) to determine the extent of pre-existing disease on the development of complications, and (d) to estimate vaccine uptake and efficacy.

Subjects and methods

Influenza in Wales is monitored as part of the general practice surveillance of infectious diseases scheme of the Public Health Laboratory Service Communicable Disease Surveillance Centre (Welsh Unit). This scheme comprises 34 spotter practices that provide weekly returns of cases of eight infectious diseases seen
by them. Influenza is defined clinically as upper respiratory tract symptoms, fever, chills, myalgia, and cough. Two practices with a list size of 22,076 patients which had kept complete registers identifying the cases of influenza reported to the scheme during the eight weeks of the epidemic took part.

Cases were patients reported as having influenza between weeks 45 and 52 of 1989. Controls, one per case, matched for sex and age (within one year for ages 0-4, 2 years for ages 5-14, and five years for ages 15 plus) were chosen as the next patient, at least three places from the case, on the practice age-sex register fulfilling the matching criteria. Those who had influenza within three months before or after the date of onset in the case or who had registered with the practice after the epidemic were excluded. An alternative control 10 places or more away from the case was chosen. Patients' notes were examined for details of illness, influenza vaccination, admissions to hospital, and recognised complications defined by criteria which could be identified in practice records (table I). Details of previous chronic illnesses and of numbers of consultations in the previous year were documented.

**Stats**—Complication rates were calculated with 95% confidence intervals by using standard error of proportion or, where observed proportions were less than 0.1, the Poisson distribution. The rates in cases and controls were compared by matched univariate and multivariate analysis performed in Epi Info version 5 by using the Mantel-Haenszel version of the χ² test. Vaccine efficacy was determined overall and for the subgroups of cases and controls with conditions for which vaccination was indicated in the chief medical officers' annual guidelines by using the Mantel-Haenszel test (unmatched). Complication rates in cases with and without conditions for which vaccination was indicated were compared by using the Mantel-Haenszel test and by logistic regression, MULTREET, to allow for the effect of age as a continuous variable.

**Results**

Three hundred and ninety five cases were on the register, all occurring over the epidemic period (figure). Records of 43 cases could not be located. Of these, three had died after the study period (one of ischaemic heart disease and one of cerebrovascular event, both over a year after the epidemic, and one in a road accident eight months after) and 31 had moved away. Ten controls' records could not be located. Analysis was performed on 342 case-control pairs.

There were no (upper 95% confidence limit 3-7) cases of myocarditis, pericarditis, hyperpyrexia, febrile convolution, encephalitis, ataxia, myositis, toxic shock syndrome, Reye's syndrome, or death. An upper 95% confidence limit of 3-7 was equivalent to an incidence of these complications of 10-8/1000 cases and a population incidence of 16-8/10000. Only two cases were admitted to hospital—equivalent to a rate of 9/110000 population (upper 95% confidence limit 32/7100000). The incidence of complications is given in table II. Bronchitis (odds ratio 12.8; p < 0-0001) and pneumonia (odds ratio 9.0; p < 0-05) were significantly commoner in cases. The mean number of consultations in the preceding year among cases was 6.1 and among controls was 4.2 (p < 0-0001). When this was allowed for only bronchitis occurred significantly more frequently in cases (summary odds ratio 9.7; p < 0-0001).

When cases were considered on their own, out of the total of 342, there were 38 for whom vaccine was recommended. Fifteen developed bronchitis compared with 50 of the remaining 304 cases for whom vaccine was not recommended (odds ratio 3.3; p < 0-0001). When age was allowed for the odds ratio became 2.4 (p < 0.05). Considering the conditions for which vaccination is recommended individually, there were five cases with pre-existing diabetes mellitus. Bronchitis, as a complication of influenza, occurred in all five compared with 60 of 337 cases without diabetes mellitus (odds ratio undefined; p < 0.001). There were 26 cases with pre-existing ischaemic heart disease. Ten developed bronchitis as a complication of influenza compared with 55 of 316 cases without ischaemic heart disease (odds ratio 2.9; p < 0.01). Of nine cases with pre-existing chronic obstructive airways disease, two developed bronchitis as a complication of influenza compared with 63 of 333 without chronic obstructive airways disease (odds ratio 1.2; p = NS). Being elderly (>65 years) was a risk factor for bronchitis (16/41 v 49/301; odds ratio 3.3; p < 0.001) even after allowing for intercurrent conditions for which vaccination is recommended (summary odds ratio 2.38; p < 0.001).

Eight cases and seven controls had been vaccinated—an overall rate in the subjects studied of 2.2%. Among those at risk, according to chief medical officer guidelines, 45% were vaccinated and observed vaccine efficacy was 63% (1/38 cases v 2/28 controls; NS). Altogether 6.1% of those aged over 65 were vaccinated with an efficacy of 77% (1/41 cases v 4/41 controls; NS). For those both over 65 and at risk, efficacy was 100% (0/16 cases v 0/16 controls; NS).

**Discussion**

This was a community based study of influenza as it presents to general practitioners. It could not tell us about patients who stayed at home and did not consult. Nevertheless, although validation of case reporting during an influenza A outbreak in Wales in 1988-9 showed such underreporting to be of the order of tenfold, probably those experiencing more severe symptoms and complications would have contacted...
their doctor. The study should therefore have ascertained more serious cases and provided an accurate picture of the more serious community morbidity associated with the 1989-90 epidemic. With regard to the accuracy of the diagnoses and the completeness of reporting, although no systematic laboratory confirmation of the diagnoses was made, general practitioners are well able to discriminate between any flu-like illness and true influenza during an epidemic.1 H3N2 influenza A was shown to be circulating in the communities at the time.

Many recognised complications, including death, were not seen. In Wales (population 2,870 million) there was an estimated excess of registered deaths of 1,627 during the epidemic, of which only one in 10 were assigned to influenza.2 This would equate with an incidence of death ascribed to influenza of 5-66/100,000 total population and is within the 95% confidence interval of the zero incidence observed in the study.

The rate of hospital admission would equate with a demand for some 20-30 beds in a "typical" 250,000 population health district in Britain over the epidemic period. It was much less than the rate of 160/100,000 observed in the United States,3 which may reflect the greater availability and use of hospital inpatient care there. There was no suggestion from clinicians that the British epidemic was unusually mild.

Bronchitis was the only complication of influenza occurring more commonly in cases than controls. The incidence of bronchitis and pneumonia together was 219-3/1000 (95% confidence interval 175-4 to 263-2) compared with a previous study in Britain which found rates of lower respiratory tract infections (laryngitis, tracheitis, bronchitis, pneumonia) in laboratory confirmed cases of 253/6/1000.4

Pre-existing chronic illness, particularly those conditions for which vaccination is recommended in the United Kingdom, was associated with significantly raised levels of bronchitis as a complication of influenza. In effect that vindicated the relevant part of the guidance. Of the conditions individually present in the sample, ischaemic heart disease, diabetes mellitus, and chronic obstructive airways disease all showed a heightened risk of bronchitis, although the numbers for chronic obstructive airways disease were too small to achieve statistical significance. Being elderly (over 65), which is not generally regarded as an indication for vaccination in the United Kingdom, was also associated with a significantly increased risk of bronchitis.

The vaccine efficacy observed was consistent with the 60-80% reported when vaccine and epidemic strain were closely matched.5 Nevertheless, uptake was too low at 4-5% for those with an indication for vaccination to exhibit this efficacy with confidence. Why is vaccine apparently not getting to those who would benefit from it? Professional workers may harbour doubts about efficacy and indications. They may also find it difficult in a general practice setting to identify patients for whom it is indicated as, unlike with childhood vaccinations, no single convenient register may exist. Similarly patients may well be unaware of the need for annual vaccination, not perceive the risk as serious, and ultimately not come forward.

In the 1989 influenza A epidemic a significant excess of cases in two general practices were complicated by lower respiratory tract infection. Vaccine did not apparently reach those identified as appropriate recipients in official policy. Does this matter? Is vaccination worth while, given the relative infrequency of many of the commonly listed complications. We found 15 cases of acute bronchitis complicating influenza in 38 patients with conditions for which vaccination is recommended by the chief medical officer from a total list of 22,076. If our experience is typical of the United Kingdom as a whole over 30,000 cases of acute bronchitis must have occurred over the seven weeks of the epidemic, a large proportion of which were potentially preventable by vaccination. This would have been without extending the criteria on which vaccination is currently recommended to, for example, all elderly people. On the limited evidence from this study this should also be further considered. While vaccination coverage is so extremely low unequivocal evidence of benefit cannot be proved. This also means that most of any such benefit is not being obtained.

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