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Population estimates of persons presenting to general practitioners with influenza-like illness, 1987-96: a study of the demography of influenza-like illness in sentinel practice networks in England and Wales, and in The Netherlands

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SUMMARY

Incidence data by age of new episodes of influenza-like illness reported by sentinel general practice networks in England and Wales and in The Netherlands over a 10-year period were examined to provide estimates of the consulting population during influenza epidemic periods. Baseline levels of recording in each age group were calculated from weeks in which influenza viruses were not circulating and the excess over baseline calculated to provide the population estimates during influenza epidemics. Influenza A/H_3N_2 epidemics were associated with higher population estimates for consultations than influenza B, especially in the age groups 0-4 and 65 years and over. In the intervening age groups, population estimates were more consistent regardless of the virus type. Both networks reported simultaneous peaking of incidence rates in all of the age groups. There were substantial increases in the number of persons reporting other respiratory illnesses during influenza epidemics. Population estimates of the consulting population provide the only secure basis for which health services resource utilization during influenza epidemics can be estimated.

INTRODUCTION

Influenza is responsible for much morbidity [1, 2], hospitalization [3], and mortality [4, 5]. Changes in the antigenic properties of the virus (antigenic drift) mean that the immunity acquired after infection may have only limited long-term benefit, hence annual vaccination is required for an effective immunization programme.

Epidemics of influenza vary in their clinical impact according to age of those infected. Many of the published studies are confined to comparisons based on laboratory-confirmed influenza. However, in the extensive literature on deaths due to influenza, mortality from all causes during the influenza epidemics are used to define the excess attributable to influenza: excess being derived from

comparison with non-epidemic periods [4]. In this report we adopt similar methods to examine the age distribution of patients presenting with influenza-like illnesses during epidemic periods in England and Wales and The Netherlands over the 10 winters since 1987. Knowledge of the age distribution associated with virus (sub)types is of particular value for evaluating therapeutic alternatives for the management of influenza and for focusing surveillance programmes.

METHODS

The study was undertaken using data collected in the sentinel general practice networks in England and Wales (Weekly Returns Service of the Royal College of General Practitioners - WRS [6]), and the Dutch sentinel practice network (DSN) [7] over the 10 winters - 1987/8-1996/7, week 37 in one year to week 20 in the next.

Although we recognize the term epidemic is reserved for particularly severe outbreaks when used for providing information for the public in the United Kingdom [8], it is commonly used to describe the usual winter pattern of occurrence in many European countries and we shall use it in that context in this paper. Based on information gathered in the two networks we have previously defined epidemic periods and background levels of reporting influenza-like illness (all ages) during the 10 winter periods [9]. The background level is the average reported incidence of influenza-like illness when there are almost no influenza viruses circulating in the community. The levels in each age group (0-4, 5-14, 15-44, 45-64 and over 64 years) were derived by averaging weekly incidence rates from the 10 winter periods after excluding rates observed in influenza epidemic periods.

Clinical incidence rates in each age group, during each epidemic period and in each network were accumulated. From these values the accumulated background incidence rates were subtracted to provide estimates of the age-specific populations reported with influenza-like illnesses in each epidemic.

Comparisons of the estimates in the two networks were made in relation to available virological information from the relevant epidemic periods. Since 1992, the virological information has come largely from samples submitted by the sentinel networks, although prior to that, other sources (mainly from hospitalized patients) have been used. (There can be differences between the proportions of virus (sub)types circulating in the community and those isolated from hospitalized patients [10].) For presentation purposes the age-specific population estimates in each year have been related to the average over the 10 winter periods.

We also examined the timing of peak incidence of influenza like illness in each of the age groups, in particular, to determine if incidence in one age group consistently preceded others. Finally we used similar methods to examine incidence rates for acute bronchitis, acute otitis media and all acute respiratory infections (including common cold, influenza-like illness, acute sinusitis, acute laryngitis, acute bronchitis, acute tonsillitis, pleurisy, pneumonia - ARI) in all ages combined in the WRS. (These additional data are not available in the DSN.) Background incidence levels of these conditions in non-epidemic influenza periods were calculated and the differences between observed and background levels provided estimates of the excess population consulting with these conditions during influenza epidemic periods.

RESULTS

Epidemic periods and the predominant influenza viruses circulating at the time are given for each country in Table 1. There were four winters in which influenza A/H_3N_2 viruses were predominant in both countries (1989/90, 1991/2, 1993/4, 1995/6) and three in which B viruses predominated (1990/1, 1992/3, 1994/5). There was a tendency for influenza A/H_3N_2 and B epidemics to alternate during the 10- year period. Influenza A/H_3N_2 epidemics generally peaked before the new year and B epidemics in February or March.

[TABLE 1]

The proportion of the population consulting with influenza-like illness in excess of the background recording level is given for each of the networks, for each group and for each of the 10 winter epidemic periods in Table 2. The average in the DSN was higher than that in the WRS in all age groups, but most especially in children 0-4 years. Reports from both networks show that the estimates are relatively greater in children 0-4 and 5-14 years.

[TABLE 2]

There were four winters in which A/H_3N_2 viruses were predominant and for these, age-specific estimates of the excess consulting population with influenza like illness are presented in Figure 1(*a*) (WRS) and 1(*b*) (DSN). In three winters, influenza B viruses predominated and for these, age specific incidence rates are described in Figure 1(*c*) (WRS) and 1(*d*) (DSN). In all figures, incidence rates are presented against the background average experience over the 10 winters. The all age estimate in the winter 1989/90 was the highest in both countries: estimates were particularly high in the youngest and oldest age groups.

[FIGURE 1]

In 1991/2 A/H_3N_2 viruses again predominated in both countries. Population estimates of the excess population reported with influenza like illness in The Netherlands were above average in all age groups, whereas in England and Wales they were well below average in children but there was a trend of increase with age. In the winter of 1993/4 influenza A/H_3N_2 predominated in both countries causing more than the average recognizable influenza-like illness in all age groups. In 1995/6 the age specific profile was similar to that of 1993/4 though slightly less in magnitude. For persons aged 15-44 years there was less variation from year to year in the population estimates than for persons in the other age groups: variation was maximal in the youngest and oldest age groups.

Influenza B epidemics occurred in both countries in 1990/1, 1992/3 and 1994/5. (During the 1994/5 epidemic in The Netherlands many A/H_3N_2 viruses were also isolated.) The age specific profiles of the excess consulting populations with influenza-like illness were generally similar in both countries [Fig.1(*c*), WRS; 1(*d*), DSN]. In the WRS, estimates were highest in the age group 5-14 years. Though this was not the case in the DSN, nevertheless the relative impact of influenza B in this age group was greater and closer to the 10 year average than that in the age group 0-4 years. Estimates in the age groups 45-64 and 65 years and over were consistently below the 10- year average in both networks.

Data for the remaining three winters are not presented because there was no clearly predominant virus. In 1988/9, influenza A/H_1N_1 and A/H_3N_2 circulated in both countries and in 1996/7 influenza A/H_3N_2 viruses circulated in the first part of the winter and B viruses in the latter part. In 1988/9 percentage population estimates decreased with age in both countries though the estimates in the DSN were substantially greater than those in the WRS. In 1996/7 there was an increased impact with age in the WRS with excess populations in the age groups 15-44, 45-64 and 65 years and over similar to those in the winter of 1989/90. In the DSN, the 1996/7 experience was similar to the 10 years average except in children.

Taking a general view of estimates of the excess population with influenza-like illness reported over the 10 winters disclosed in both countries, there was a similarity in the age related trends in the majority of years, though there were differences in relative magnitude. Population estimates were usually higher in winters when A/H_3N_2 viruses rather than when B viruses were circulating. The population estimates varied least in the age group 15-44 years regardless of the predominant virus (sub)type.

Peak incidence

Clinical incidence of influenza-like illness by week and age group in each of the networks during the A/H_3N_2 epidemic of 1989/90 and in the mixed A/H_3N_2 and B epidemic in 1996/7 is described in Figure 2(*a-d*). In 1989/90 in the WRS, increasing incidence was first evident in the age groups 0-4 and 5-14 years with older age groups lagging approx. 1 week behind. In the DSN incidence in the 0-4

years age group preceded the others, including the 5-14 years age group, all of which were about 1 week behind. Incidence peaked more or less simultaneously in all age groups with maximum incidence in children 0-4 years. In 1996/7 in the WRS, increasing incidence was first evident in the age group 15-44 years and rose to a higher level to that in all other age groups. The other age groups were about 1 week behind at the commencement though peak incidence occurred roughly at the same time in all age groups except 5-14 years, in which incidence increased more slowly and a comparatively low peak was reached 4 weeks behind at a time when B viruses rather than A/H_3N_2 viruses were circulating. In the DSN, a hesitant increase was evident in children 0-4 years before that in the other age groups, and in children 5-14 years increasing incidence occurred later than in all other age groups. Incidence peaked in all age groups simultaneously. In an examination of the distribution of the week of peak incidence in the various age groups over the 10 winters studied, there was no evidence to suggest that incidence peaked in one group consistently before or after that applicable to all ages.

[FIGURE 2]

Other respiratory illnesses

The incidence rates (all ages) reported in the WRS of influenza-like illness, acute otitis media, acute bronchitis and all acute respiratory infections (ARI) are presented graphically compared with the background incidence rate for the respective conditions over the period covering the influenza A/H_3N_2 epidemic from weeks 42-51 at the end of 1993 (Fig. 3). The increased incidence of the three individual conditions (Figs 3*a*-3*c*) can be compared directly ; however, for ARI (Fig. 3*d*) a fourfold incremental scale has been used for presentation. The excess consulting population estimates were for influenza-like illness 1-14%, for acute bronchitis 0-66%, for acute otitis media 0-21%, and for ARI 3-25%. The equivalent average excesses over the 10 winter epidemics were: 0-85, 0-45, 0-10 and 2-09%respectively. For ARI there was a considerable range from year to year but the highest excess population was reported in the winter of 1994/5 (3-81%) and not in the 1989/90 epidemic in which the highest estimate of excess cases of influenza-like illness was reported. There was also considerable variation in the estimates for acute bronchitis and acute otitis media. The magnitude of the estimates was not consistently related between the diagnostic groups, which is not surprising given that these estimates are not age specific.

[FIGURE 3]

DISCUSSION

The average population consulting with influenza-like illness over the 10 winters was estimated at 0-85% in the WRS, and 1-39% in the DSN. This difference has been discussed elsewhere [9]. General practitioners reporting in the WRS have the option to enter persons with respiratory infections under the most appropriate diagnostic label. Thus, for this report we have also considered conditions such as acute otitis media and acute brochitis during influenza epidemic periods. General practitioners reporting in the DSN have been given a case definition and they do not report other respiratory conditions. The case definition includes the specification of a temperature exceeding 38 °C. Whilst this may increase the specificity of clinical diagnosis if strictly observed, it nevertheless excludes many persons with illnesses due to influenza virus infections and we think it likely that general practitioners relax this criterion when epidemic conditions are obvious. We have already shown that the background level of reporting influenza-like illness when there are no influenza viruses circulating, is very similar in both networks [9]. The relative increase in the DSN results over those of the WRS is likely explained by these differences in recording arrangements and a possibility that once epidemic conditions are obviously established in their area, general practitioners may be less rigorous in the observance of strict diagnostic criteria. Influenza vaccination uptake rates vary between countries though in the 10 years covered by this study the differences in uptake in The Netherlands and United Kingdom were small [11]. Since 1996, vaccination policy in The Netherlands has included persons

aged 65 years and over whereas in the United Kingdom we included persons aged 75 years and over for the first time in 1998. Differences in vaccination policy and uptake rates are not likely to bias the comparison between the incidence rates of influenza-like illness reported in the two countries.

Accurate estimates of the incidence of influenza are difficult to obtain because of the lack of a specific clinical diagnosis. Are the estimates reported in this study from the two networks under- or over-estimates of the burden of influenza virus infections in the community? They are certainly under-estimates of the population who become infected as measured by antibody seroconversion. In a systematic review of the literature concerned with the economic aspects of influenza vaccination, Jefferson identified 22 studies and the interquartile range of attack rates (mostly based on seroconversion) was given as 4-25-21-3% [12]. Monto and Sullivan in a series of studies between the winters of 1976/7 and 1980/1 estimated average seroconversion rates to influenza A/H_3N_2 at 7-4 per 100 population, to influenza H_1N_1 at 7-7 and influenza B at 7-1 [13]. Rates of seroconversion varied with age. For influenza A/H_3N_2, rates were highest in preschool children, showed a gradually decreasing trend with age but were equivalent to more than 10 per 100 population in the age group 60 years and over. For A/H_1N_1 and B viruses, seroconversion rates were highest in the 5-9 years age group and decreased thereafter. In general, rates were low in the age group 60 years and over with the exception of the B epidemic in 1979/80. The community population estimates based on persons consulting with influenza-like illness and reported here show age specific trends consistent with those reported by Monto in respect of the A/H_3N_2 and B epidemic periods. However, the analyses presented here are population estimates of influenza-like illness linked to predominant circulating virus strains and comparisons between epidemics due to differing virus (sub)types are limited. A pure epidemic involving only one strain is a rarity.

Not all persons who seroconvert experience clinical illness, not all those who are ill consult a doctor, not all those consulting are correctly diagnosed. Monto and Sullivan estimated 1 in 4 respiratory illnesses were reported to physicians in the Tecumseh study [13]. Govaert and colleagues reported the results of a randomized double-blind placebo-controlled trial of influenza vaccination in persons aged 60 years and over who did not belong to risk groups, conducted in The Netherlands in the Winter of 1991/2 (a winter in which there was an influenza A/H_3N_2 epidemic with above average consulting rates) [14]. The incidence of serological influenza during that winter was 4%in the vaccinated group, and 9% in the control group, and of clinical influenza 2 and 3%, respectively. In this study, the average excess population consulting with any new episode of respiratory illness over the 10 influenza epidemic periods was 2-1% of the population ; and the maximum in any one year 3-8%. Given the methods used in this study to define the baseline recording level, these estimates represent the maximum estimate of the population that could be consulting with true influenza virus infection unless we assume that many persons consulting outside epidemic periods are actually experiencing true influenza illness. Undoubtedly some true influenza virus illnesses occurred outside the epidemic periods but we believe these were uncommon since virological tests on specimens from patients in the sentinel surveillance networks are likely to have identified some of them.

From the opposite perspective - over-estimating the proportion; what proportion of persons reported with influenza-like illness actually have an influenza infection ? In both the networks, selected practices within the sentinel networks submit specimens from suspected cases for virological examination. Whilst there is some variation from year to year, both networks currently find between 30 and 40% positivity and in excess of 50% during epidemic periods [16, 17].

Both systems also report higher positivity in samples from school children and young adults than from babies and the elderly. There are several possible reasons why estimates based on virus isolation are likely to be under-estimates. Some cases have swabs taken for virological examination at a stage in the illness when virus shedding is minimal or may be influenced by prior antibody status [13]. In clinical experience several members of one family can suffer an influenza-like illness at the same time but not all necessarily yield positive virus isolates. Some specimens are of poor quality or deteriorate with transport and are thus unsuitable for virus isolation, though hopefully recent advances in the use of polymerase chain reaction will improve identification rates [17]. Laboratory investigation is variable in quality both over time and between laboratories: in general increased experience yields increased proportions of positive specimens.

Theoretically, over-estimation from clinical data for influenza-like illness is likely to be greatest in the most elderly where rates of positive isolation of influenza viruses are lowest. However, clinical incidence of epidemics of influenza-like illness are similar in timing in all age groups, consistent in timing with the isolation of influenza viruses and contemporaneous with increased mortality and, as has been shown here contemporaneous with increased incidences of other morbidities. The clear link between all these parameters suggest a common causal pathway. The outstanding question therefore concerns the possibility that other micro-organisms are at least partly responsible and may themselves be more prevalent at times of influenza epidemics, whether encouraged by the presence of influenza or simply present at particular times which favour the spread of epidemic respiratory diseases. There is some evidence suggesting that respiratory syncytial virus (RSV) is a likely contributor [18-20], and possibly also rhinoviruses [21]. Clinically, illness due to RSV is indistinguishable from that due to influenza virus in the elderly [22].

If epidemics of influenza-like illness are not solely due to influenza viruses, what are the other causative organisms? This question is in urgent need of resolution. The influenza vaccination programme in most countries is based on the assumption that excess mortality during influenza epidemics is due to influenza and not to some other organism. There is good evidence of protective effects from influenza vaccination. Nicholson estimated that RSV may be responsible for more deaths than influenza [20]. However, the evidence that either influenza or RSV is directly responsible for a large excess mortality during epidemics of influenza-like illness is circumstantial and not yet conclusive.

The onset of an epidemic impacts on the workload in all health-care sectors. It is often felt most acutely in increased demand for hospital admission. Nationally, epidemics last about 8-10 weeks but once influenza has arrived in a local area it will stay there for at least 4 weeks. With knowledge of the prevailing virus and age-specific incidence data, the information provided in this report can be used to gauge the likely impact of an epidemic in the different age groups. There is also a need to consider the impact in healthcare workers. Whilst vaccination once an epidemic has arrived is clearly a second best option, any vaccine still available should be offered to high risk individuals and possibly also to health-care workers, particularly nurses. Sickness absence amongst health-care workers creates great difficulties during influenza epidemics. There is a margin of about 10 days between administration and useful response [23].

During the influenza period general practitioners will have increased number of persons presenting with a variety of respiratory illness. From the analysis made here we estimate that in an A/H_3N_2 epidemic this number equates to an excess of between 2 and 3% of the practice population seen over a period of 4 weeks. The increase is most evident in young children presenting with acute febrile illness, often involving out-of-hours consultation and home visits. Fever and cough are likely to be obvious, but young children do not complain of muscle aches. They may present with earache and have signs of acute otitis media. An increase in consultation by older persons can be expected except in most influenza B epidemics, and many of these are likely to present clinically as acute bronchitis. Older persons often delay consultation and only present because their cough is not getting better.

Once the first few cases are seen, especially where it is known from surveillance programmes that influenza viruses are circulating, practices should recognize that there will be a significant increase in workload and particularly out-of-hours calls over the following 4 weeks. Wherever possible, appointment schedules should be adjusted to cater for a high demand for urgent appointments because of acute illness.

Influenza A/H_3N_2 epidemics were associated with high population estimates of influenza-like illness in young children. There is good evidence of the efficacy of vaccination against influenza in older age groups. Should immunization of young children be reconsidered [24, 25]?

The differing patterns of incidence of influenza like illness by age, emphasizes the need to maintain surveillance in all age groups. Fleming and Cohen reported on the timing of epidemics in European countries in the 1993 epidemic and found no bias towards earlier onset in any particular age group [25].

Because influenza infection is so common (judged by seroconversion) rational prevention and management programmes must be based on evidence of benefit among persons with significant clinical illness. The decision of a person to consult represents a proxy measure of clinically significant

illness, though we recognize its limitations given the lack of a specific clinical syndrome and the limitations of virological investigation.

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TABLES AND FIGURES

Table 1. *Epidemic periods by week number and predominant virus subtypes (secondary subtypes given where identified in 25% or more of isolations)*

	England and Wales		The Netherlands	
1987/8	04–11	H_3N_2 (H_1N_1)	41–14	H_3N_2
1988/9	48–04	H_1N_1 (H_3N_2)	45–06	H_1N_1 (H_3N_2)
1989/90	46–03	H_3N_2	47–05	H_3N_2
1990/1	51–10	B	03–14	B
1991/2	51–09	H_3N_2	49–09	H_3N_2 (H_1N_1)
1992/3	08–16	B	04–17	B
1993/4	42–51	H_3N_2	45–01	H_3N_2
1994/5	01–14	B	08–17	B(H_3N_2)
1995/6	45–03	H_3N_2	48–05	H_3N_2
1996/7	49–09	H_3N_2 (B)	52–10	H_3N_2(B)

Table 2. *Average percentage of the population in each age group consulting with influenza-like illness during 10 winter epidemic periods*

Age (years)	0–4	5–14	15–44	45–64	65+	All ages
WRS	1·17	1·07	0·85	0·75	0·60	0·85
DSN	2·96	1·85	1·25	1·27	1·23	1·39

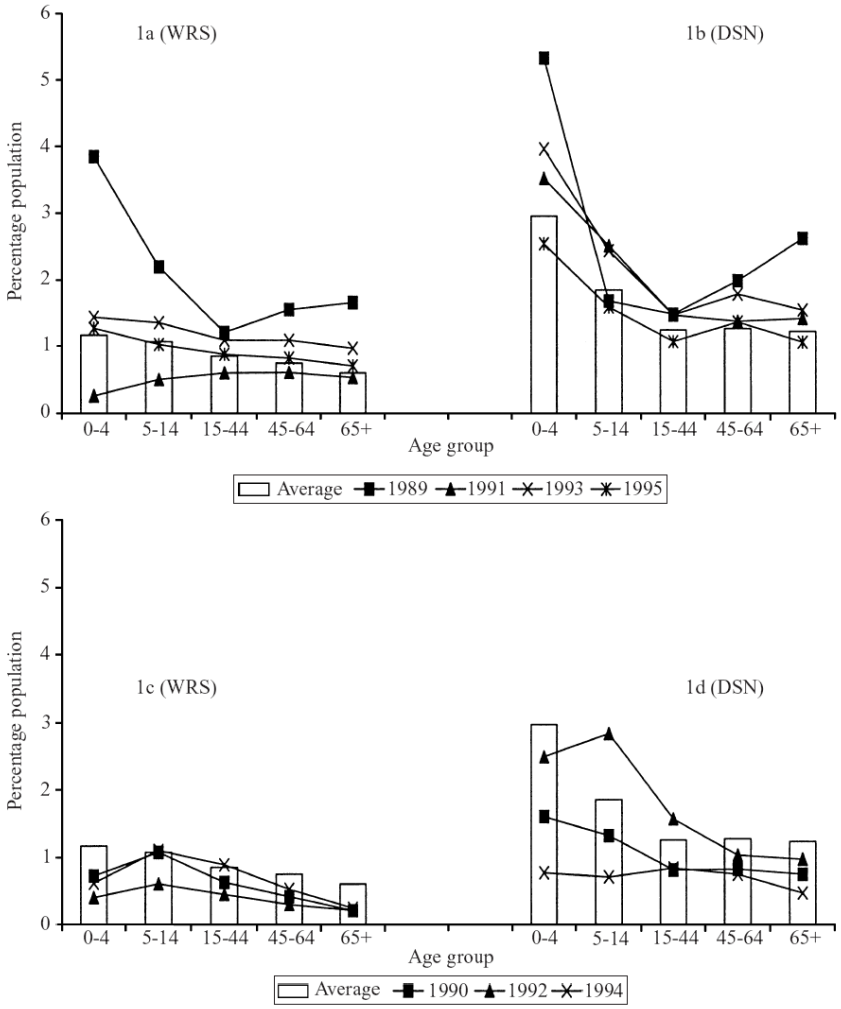

Fig. 1. Influenza-like illness: Estimates of excess consulting in each network in winters in which H_3N_2 viruses predominated (Fig 1a WRS, 1b DSN) and in which B viruses predominated (Fig 1c WRS, 1d DSN) compared with the average over 10 winters (1987/8 to 1996/7) presented as a histogram.

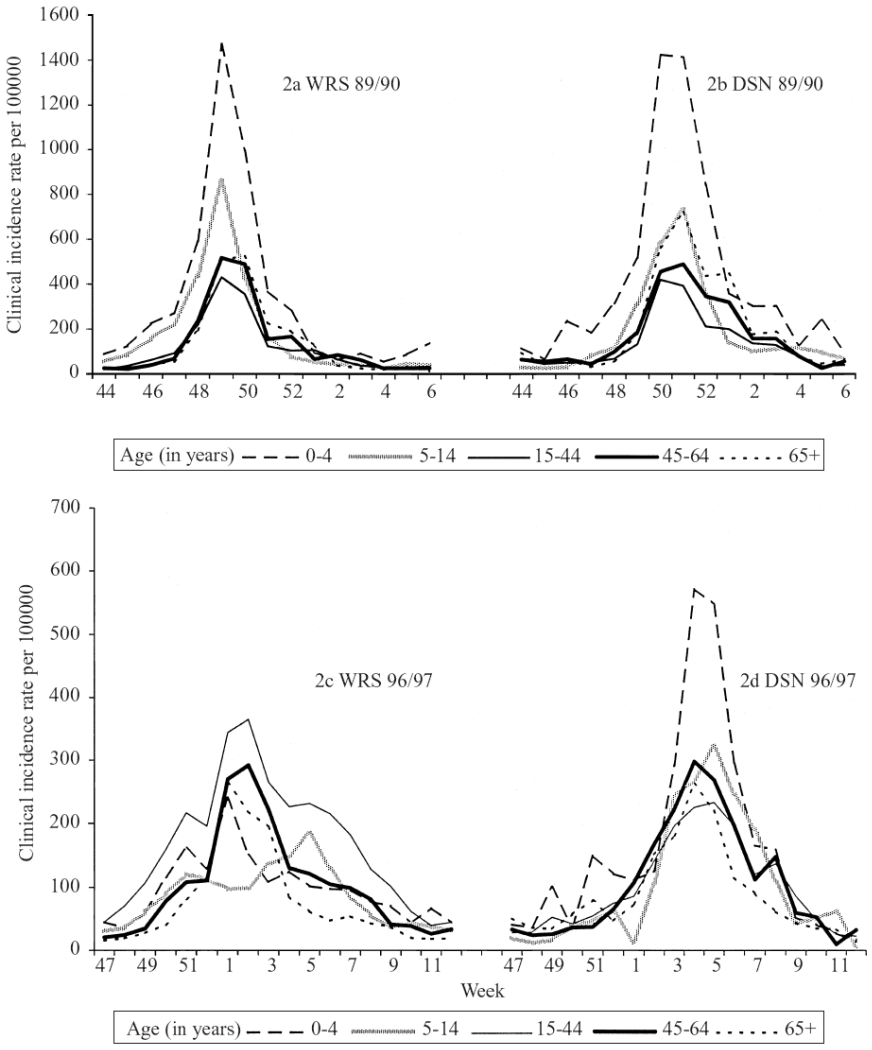

Fig. 2. Influenza-like illness 1989/90 and 1996/7. Incidence per 100000 by age group during influenza epidemic periods in WRS and DSN networks.

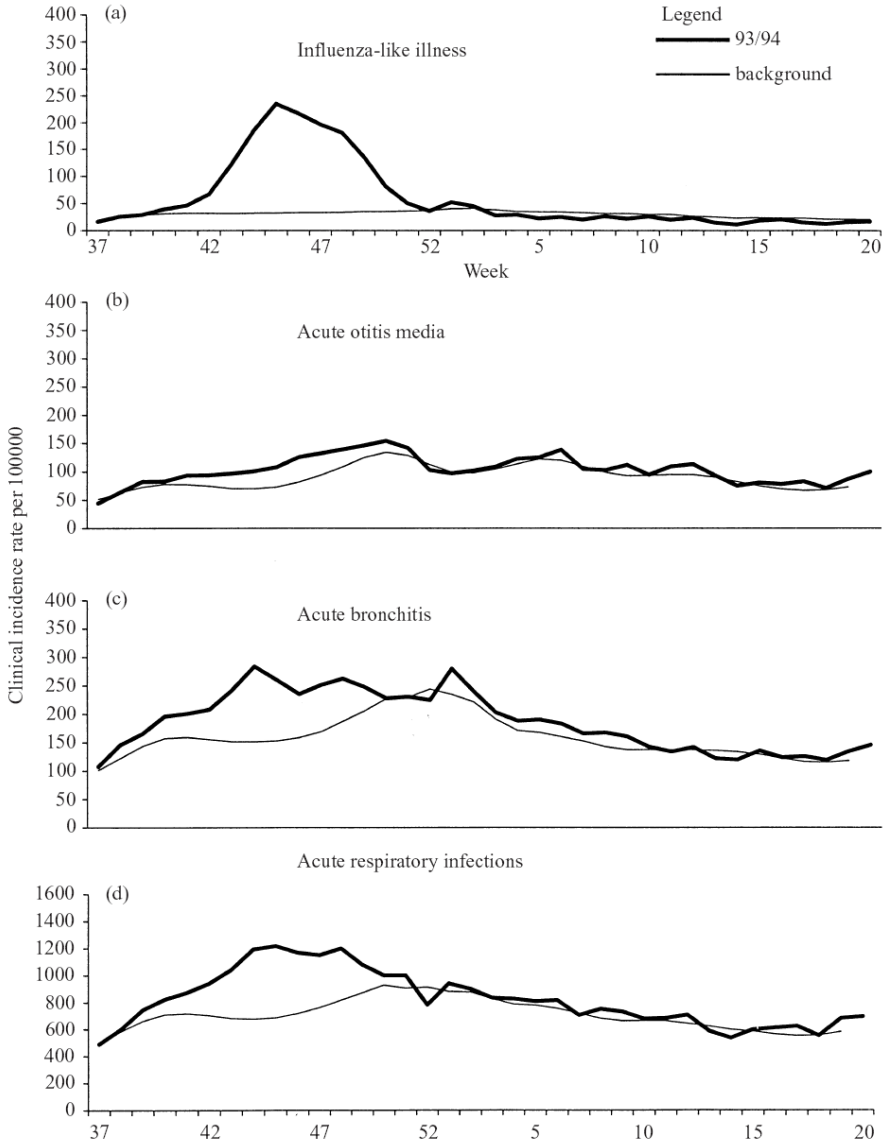

Fig. 3. Incidence of (a) influenza-like illness (b) acute otitis media (c) acute bronchitis and (d) acute respiratory infections during influenza epidemic period for 1993/4 set against background recording rate over the winters 1987/8 to 1996/7 observed when flu viruses were not circulating. (WRS data only).

REFERENCES

1. Sullivan KM, Monto AS, Longine IM. Estimates of the US health impact of influenza. Am J Publ Hlth 1993; 83: 12 1713.
2. Fleming DM. The impact of three influenza epidemics on primary care in England and Wales. Pharmaco- Economics 1996; 9: 38-45.
3. McBean AM, Babish JD, Warren JL, Melson EA. The effect of influenza epidemics on the hospitalisation of persons 65 years and older. In: Options for the control of influenza, II. Hannoun C, Kendall AP, Klenk HP, Rueben FL, eds. 1993. Amsterdam: Elsevier Science Publishers, BV International Congress Series 1019: 25-37.
4. Clifford RE, Smith JWG, Tillett HE, Wherry PJ. Excess mortality associated with influenza in England and Wales. Int J Epidemiol 1977; 6: 115-28.
5. Glezen WP. Serious morbidity and mortality associated with influenza epidemics. Epidemiol Rev 1982; 4: 25-44.
6. Fleming DM. Weekly returns service of the Royal College of General Practitioners. Commun Dis Public Health 1999; 2: 96-100.
7. Sprenger MJW, Naelten AMG van, Mulder PGH, Masurel N. Influenza mortality and excess deaths in the elderly, 1967-82. Epidemiol Infect 1989; 103: 633-41.

8. Dedman DJ, Watson JM. The use of thresholds to describe levels of influenza activity. PHLS Microbiol Dig 1997; 14: 206-8.
9. Fleming DM, Zambon M, Bartelds AIM, De Jong J. The duration and magnitude of influenza epidemics. Eur J Epidemiol 1999; 15: 467-73.
10. Claas J, de Jong JC, Bartelds AIM, et al. Infuenza types and patient population. Lancet 1995; 346: 180.
11. Fedson DS. National immunisation policies and vaccine distribution. In: Textbook of influenza. Nicholson KG, Webster RG, Hay AJ, eds. Oxford: Blackwell Science 1998: 445-53.
12. Jefferson TD, Demicheli V. A systematic review of world literature on the economics of influenza. Influenza ESW1 1997; 7: 6.
13. Monto AS, Sullivan KM. Acute respiratory illness in the community. Frequency of illness and the agents involved. Epidemiol Infect 1993; 110: 145-60.
14. Govaert TME, Thijs CT, Masurel N, Sprenger MJ, Dinant GJ, Knottner JA. The efficiency of influenza vaccination in elderly individuals. JAMA 1994; 272: 1661-5.
15. Hutchinson EJ, Joseph CA, Zambon M, Fleming DM, Watson JM. Influenza surveillance in England and Wales: October 1995 to June 1996. CDR Rev 1996; 6: 163-9.
16. Bestebroer TM, Bartelds AIM, Andeweg AC, et al. Virologische NIVEL/RIVM-surveillance van respiratoire virusinfecties in het seizoen 1995/96. Report National Institute of Public Health and the Environment, Bilthoven, December 1996.
17. Ellis JS, Fleming DM, Zambon MC. Multiplex reverse transcription PCR for surveillance for influenza A and B viruses in England and Wales in 1995 and 1996. J Clin Micro 1997; 35: 2076-82.
18. Fleming DM, Cross KW. Respiratory syncytial virus or influenza? Lancet 1993; 342: 1507-9.
19. Dowell SF, Anderson LJ, Gary Jr. HE, et al. Respiratory syncytial virus is an important cause of community-acquired lower respiratory infection among hospitalized adults. J Infect Dis 1966; 174: 456-62.
20. Nicholson KG. Impact of influenza and respiratory syncytial virus on mortality in England and Wales from January 1975 to December 1990. Epidemiol Infect 1996; 116: 51-63.
21. Nicholson KG, Kent J, Hammersley V. Cancio Esperanza. Acute viral infections of upper respiratory tract in elderly people living in the community: comparative, prospective, population based study of disease burden. BMJ 1997; 315: 1060-4.
22. Falsey AR, Cunningham CK, Barker WH, et al. Respiratory syncytial virus and influenza A infections in the hospitalized elderly. J Infect Dis 1995; 172: 389-94.
23. Lambkin R, Oxford JS, Biao L, Al-Jabri A, Fleming DM. Rapid antibody response to influenza vaccination in `at risk ' groups. Vaccine 1999. In press.
24. Barnett ED. Influenza immunization for children. N Engl J Med 1998; 338: 1459-61.
25. Belshe RB, Mendelman PM, Treanor J, et al. The efficacy of live attenuated, cold-adapted, trivalent intranasal, influenzavirus vaccine in children. N Engl J Med 1998; 338: 1405-12.
26. Fleming DM, Cohen J-M. Experience of European collaboration in influenza surveillance in the winter of 1993-1994. J Publ Hlth Med 1996; 18: 133-42.